

DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, & IMMUNE-BASED & GENE THERAPIES

2016

PIPELINE REPORT

HIV & TB

IN DEVELOPMENT

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2016 PIPELINE REPORT

HIV AND TUBERCULOSIS (TB)
DRUGS, DIAGNOSTICS, VACCINES, PREVENTIVE TECHNOLOGIES,
RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES
IN DEVELOPMENT

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HIV i-BASE/TREATMENT ACTION GROUP

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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organization.
HIV i-Base works in the United Kingdom and internationally to ensure that people living with HIV are
actively engaged in their own treatment and medical care and
are included in policy discussions about HIV treatment recommendations and access.

ABOUT TAG

Treatment Action Group is an independent AIDS research and policy think tank
fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

We are science-based treatment activists working to expand and accelerate vital research and
effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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THIS REPORT IS DEDICATED TO

Margie Garber-Steinberg
April 7, 1949 – April 14, 2016



This edition of the *Pipeline Report* is dedicated to Margie Garber-Steinberg, mother of long-time board member Jason Osher. Margie was a steadfast TAG supporter for well over a dozen years, and not only fought against the HIV/AIDS pandemic through her support and philanthropy, but also fought her own battle with cancer for ten years, undergoing two stem cell transplants and countless chemotherapies and drug combinations.

She was a much adored wife, mother, grandmother, and friend. She was also a strong warrior, and showed us all how to continue to fight, despite the obstacles. Her love for TAG and its leaders, her humor, and her voice to end HIV/AIDS will be sorely missed.

THIS REPORT IS DEDICATED TO

Paul Blanchard
1964 – 2016



The 2016 *Pipeline Report* is dedicated to i-Base co-founder Paul Blanchard (1964 -2016). Paul played a unique role in establishing treatment activism in the UK, challenging doctors to continually update their views and practice with evidence from rapidly evolving research.

Like many HIV activists Paul experienced the dramatic benefits of ART first hand when antiretroviral therapy was very new. He was one of the leading activists to recognize the need to use triple combination therapy to achieve optimal and sustained viral suppression and to avoid drug resistance, when UK guidelines – and many other UK HIV organizations – suggested fewer drugs might be sufficient.

Paul had a tremendous and steady intellect and a unique critical view that enabled him to comment on new advances and current practice with such masterly understatement that would make disagreeing with his conclusions extremely difficult.

He also had a wicked sense of humor, writing an article on the increases in “internet-related STIs” with a chuckle “because doctors love reading about this sort of thing” or commenting proudly on his own 7-drug salvage regimen in the late 90s that “none of them are made by Glaxo Welcome”.

Paul will be deeply missed.

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Executive Summary - HIV

By Mark Harrington

THE ANTIRETROVIRAL TREATMENT PIPELINE

In their chapter on Antiretroviral Treatment in this year's *Pipeline Report* [9], Tim Horn and Simon Collins provide a sweeping overview of developments in the past twenty years to put those of the past year into context.

The first decade after the advent of effective combination antiretroviral treatment (ART) was marked by improving safety, tolerability, and ease of administration among ART regimens. This was accompanied by growing awareness of the side effects of the earlier regimens, concerns about the evolution of acquired drug resistance, and outstanding questions about when to start ART and whether structured treatment interruptions (STIs) were safe. Subsequent research culminating in the Strategic Management of ART (SMART) study showed definitively that STIs had serious risks due to a host of inflammatory complications of untreated HIV – including cardiovascular, liver, and kidney disease – which had previously been seen as side effects of ART [1].

In the meantime, with when-to-start guidelines swinging back to later initiation of ART, the International AIDS Conference in Durban in 2000 provided the impetus for an enormous, unprecedented global effort to combat a chronic, incurable infectious disease with life-long ART. This effort encompassed the launch of affordable generic combination ART [2]; the establishment of a number of new institutions such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) [3], the President's Emergency Plan for AIDS Relief (PEPFAR) [4], and new initiatives such as the WHO '3x5' strategy [5], the U.S. Food and Drug Administration (FDA) program for tentative approval for generic ART combinations for use in developing countries, the tax-funded UNITAID, and others. Over the subsequent 16 years, more than 17 million people have been able to use ART; AIDS death rates dropped; and there are emerging signs that HIV incidence rates are going down at least in some parts of the world.

After SMART, it became imperative to define with a randomized controlled trial whether the benefits of immediate HIV treatment outweighed any risk, partly enabled by easier to use ART, which increasingly came in the form of fixed-dose combinations (FDCs) and single-tablet regimens (STRs). Thus the U.S. NIH and other partners launched the START study [6] and France's ANRS launched TEMPRANO [10]. Both studies, released in 2015, showed that immediate ART led to better clinical outcomes. Several other studies, including HPTN 052 [11] and early results from the PARTNER study [12] demonstrated that virologic suppression dramatically reduced the risk of HIV transmission, and that perhaps this effectively is zero. These advances set the stage for the WHO's revised 2015 "treat all" guidelines," which mean that in the coming years we must continue treating the 17 million people already on ART [7] and add to them the 20 million who are not yet receiving it, while simultaneously scaling up ART-based prevention such as PrEP. Together, if scaled up rapidly, these converging approaches hold out the promise of bringing down new HIV infection rates to very low levels, while enabling people with HIV to live long and healthy lives.

Activists, providers, and program managers are concerned that prevalent austerity policies worldwide – coupled with the Global Fund's narrowing focus which excludes most middle-income countries where millions of people living with HIV, TB, or malaria live [8] will make it harder to secure and sustain the resources required to achieve the promise of these gains, and at the same time the shrinking number of innovator companies in the ART discovery and development space leads to fears that too few players will diminish the fruitfulness of the pipeline while possibly creating unacceptably high prices through limited voluntary licenses which will diminish access for those whose countries cannot pay for their treatment – as is already occurring with direct-acting antivirals (DAAs) in the global hepatitis C virus (HCV) pandemic.

Advancing in the clinical development pipeline this year are a number of new drugs, combinations, and formulations such as long-acting injectable ART, and new strategies such as reduced drug ART using dolutegravir – either alone or with lamivudine (3TC). It's too soon yet to assess whether this approach will prove as durable as initial studies suggest and whether it will work in the diverse settings in developing countries where it has the potential to both increase quality of life (with reduced side effects) and save considerable resources.

Reviewed elsewhere in this year's pipeline are other approaches to optimize ART using lower doses, e.g., of efavirenz at 400mg, or combinations with lower molecular weight, that would reduce the cost of the active pharmaceutical ingredient (API); particularly attractive are combinations of dolutegravir with TAF and 3TC; see Polly Clayden's "Fit for Purpose: Antiretroviral Treatment Optimization".

To validate a new first-line regimen with dolutegravir, additional studies are already underway to get more data for use in women, during pregnancy, and in TB coinfection.

The 2016 ART chapter summarizes the status of twelve drugs and combination therapies in clinical development – seven in phase III, four in phase II, and two in phase I (see Table 1: Summary of Pipeline Compounds in 2016).

FIT FOR PURPOSE: ANTIRETROVIRAL TREATMENT OPTIMIZATION

Polly Clayden leads us on a brisk, bracing walk through the changing landscape of ART optimization in her 2016 "Fit for Purpose: Antiretroviral Treatment Optimization" chapter. [13]

"Since the 2015 *Pipeline Report* global antiretroviral treatment (ART) guidelines have moved to recommending "treat all" HIV positive people. With this recommendation comes the massive task of starting and keeping everyone with HIV on ART. ART optimization is one of many critical steps to universal access to HIV treatment that is: safe, effective, tolerable, durable, simple and affordable. Antiretrovirals can sometimes be optimized by dose reduction. [14, 15] Reducing an approved dose of a drug might be possible, because when new ones are developed, the highest tolerated doses in phase II are usually selected for phase III and approval. In some cases lower doses might have equivalent efficacy and better tolerability – as has been shown with efavirenz (EFV). [16] But since discussions on treatment optimization began the field has evolved and newer, better, and lower dose antiretrovirals have been approved. [17, 18] With a couple of exceptions, treatment optimization has shifted away from making older drugs more efficient. Speeding up the introduction of generic versions of newer drugs – in appropriate regimens and formulations – into low-and middle-income countries (LMIC) – is now the main focus of ART optimization. [19]

"Experts now agree on a short list of antiretrovirals that have shown superior or non-inferior efficacy compared to existing recommended ones. These drugs offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for fewer side effects. [20, 21] The antiretrovirals are: dolutegravir (DTG), tenofovir alafenamide (TAF), efavirenz (EFV) 400 mg, and darunavir/ritonavir (DRV/r)." [13]

As Clayden points out, the 2015 WHO guidelines now include dolutegravir and efavirenz 400mg; generic formulations of dolutegravir are on the way; and the FDA has begun to approve TAF-containing regimens to replace those with tenofovir disoproxil fumarate (TDF). WHO second-line recommended alternative regimens now "include ritonavir-boosted darunavir (DRV/r) or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r)." [13]

New generic formulations of dolutegravir (DTG), DTG/TDF/3TC, efavirenz 400mg/TDF/3TC, and DRV/r will come on-line in the next year; see Table 3: New generic antiretrovirals available 2016/2017 for adults. "By the end of 2025 the introduction of TAF, EFV 400 mg, and DTG into ART programs in LMIC could mean

savings up to a whopping US \$3 billion” – please see Table 5: Market share and cumulative savings 2025. [22]

Clayden reviews studies investigating dolutegravir or efavirenz at 400mg as global first-line ART anchor drugs (see Table 6: New first-line regimen studies), first-line pregnancy studies (see Table 7: First-line pregnancy studies), reviews the urgent case of first-line ART in combination with tuberculosis co-treatment (see Table 8: First-line HIV/TB co-treatment studies), and considers the potential use of darunavir/r/dolutegravir in second-line therapy (see Table 9: Low dose DRV/r studies).

This chapter provides a long view of what to expect in the coming decade and how research can provide answers which will make it easier to treat all of the world’s 37 million HIV-infected persons.

THE PEDIATRIC ANTIRETROVIRAL PIPELINE

In the Pediatric Antiretroviral Pipeline [51] Polly Clayden shows us that developing “new antiretroviral drugs and appropriate formulations for children continues to be far too slow;” and that 40% of children on ART are on suboptimal regimens. Among noteworthy steps forward are the inclusion in the new WHO guidelines of integrase inhibitors, efavirenz 400mg and dolutegravir as alternatives for adolescents, raltegravir as recommended second-line for children, and dolutegravir and darunavir/ritonavir for third-line [52], and FDA approval of dolutegravir tablets for children aged 6 to 12 [53]. New solid lopinavir/ritonavir pellets are now approved for infants and young children [54, 55], but apparently don’t taste very good [56]. Priority formulations identified back in 2013 remain lacking, including AZT or abacavir (ABC) plus 3TC and lopinavir/r and ABC with 3TC and efavirenz [57]. Additional priority formulations from 2014 remain unavailable. [7] Clayden reviews ongoing and planned trials to address gaps in treatment options for newborns [see Table 3: Newborn treatment options (or lack of options to date): including ongoing and planned IMPAACT trials], children, and adolescents. The current pediatric ARV pipeline is shown in Table 4: The pediatric antiretroviral pipeline.

PREVENTIVE TECHNOLOGIES: ANTIRETROVIRAL AND VACCINE DEVELOPMENT

Tim Horn and Richard Jefferys present an overview of developments in their “Preventive Technologies: Antiretroviral and Vaccine Development” chapter [23].

The current paradigm is shifting not only to universal immediate ART among those living with HIV, but to intensified biomedical prevention efforts focusing on pre- and post-exposure prophylaxis (PrEP, PEP), as well as increased use of other prevention modalities such as harm reduction, syringe exchange, opiate substitution therapy, and voluntary male medical circumcision. As Horn and Jefferys write, [this] “fierce commitment to primary biomedical prevention... isn’t simply rhetoric, but rather a public health mandate that is supported by a growing body of epidemiological and other scientific data. [24, 25, 26, 27]

In the U.S., where tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) were first approved for use as PrEP in mid-2012, just 4% of the estimated 1.2 million U.S. residents who might benefit from its use are or have used it. [28, 29] To make a public health impact, however, PrEP will have to be scaled up to reach almost half of high-risk MSM, as well as at least 10% of people who inject drugs and among high-risk heterosexual persons, who may not even realize they are at risk for contracting HIV. [30]

In the U.S., failure to expand Medicaid in states where HIV is infecting the most people today – such as young MSM of color, particularly in the South, creates often-insuperable obstacles for those who need PrEP the most. [31] Elsewhere, PrEP has only been approved in a handful of countries and, even where it is approved and

subsidized, high levels of provider stigma or ignorance plus lack of HIV prevention education among at-risk individuals impedes its successful uptake at the requisite scale. [32] Other potential PrEP approaches now under study include oral maraviroc (MVC) or TAF instead of TDF, but these are in early stages still.

Long-acting (LA) injectable ART such as cabotegravir, if shown safe and effective, could potentially be used as PrEP.

A variety of genital gels, rings, tablets, and films are also being investigated for potential preventive therapy indications in both women and men. There is also tremendous interest in multi-purpose biomedical prevention technologies, notably ring and other extended-release delivery systems that can provide broad-spectrum protection against multiple viral infections—HIV, herpes simplex virus 2 (HSV-2), and human papillomavirus (HPV)—as well hormonal contraception.

NIH is launching large-scale efficacy trials to see whether infusions of broadly-neutralizing HIV antibodies such as VRC01 can be used as a durable HIV prevention intervention[33]; but – as with treatment – it’s possible that combinations of antibodies will be more effective both in protecting from infection and in preventing the rapid emergence of resistance among those exposed. [34, 35]

The long-awaited successor study to RV144, the only HIV vaccine trial that has shown even a marginal level of statistically-significant protection, is finally close to being launched. [36]. “The trial, HIV Vaccine Trials Network (HVTN) 702, is designed to try and duplicate or improve on the 31.2% reduction in risk of HIV acquisition that was observed in RV144, a large-scale evaluation of a prime-boost vaccine regimen that was conducted in Thailand. [37] HVTN 702 will take place in South Africa and, if all goes according to plan, results are anticipated by 2020.” [23]

In the vaccine field, a whopping 52 candidate vaccines are in various stages of clinical trials, as well as three studies of passive immunization with the NIH’s VRC01 and one antibody gene transfer study; see Table 4: HIV vaccines, passive immunization, and antibody gene transfer pipeline. The contrast with the TB vaccine field – with only 14 candidates in clinical trials (see Table 1: TB Vaccines in Development, in Mike Frick’s TB Prevention Pipeline chapter – is stark, though both fields face analogous challenges trying to develop protective immunity against tough and complex intracellular pathogens.

RESEARCH TOWARD A CURE AND IMMUNE-BASED AND GENE THERAPIES

Once again, Richard Jefferys effortlessly guides us through the challenging landscape of “Research Toward a Cure and Immune-Based and Gene Therapies” [39].

HIV cure research is now acknowledged as a central goal of U.S. NIH-funded AIDS research [40, 41] Meanwhile, it is expected that the currently-underway renewal of the Martin Delaney Cure Collaboratories may result in the funding of five or six consortia compared with the current three. amfAR has established a new Institute for HIV Cure Research at U.C. San Francisco. [42]

In Durban the International AIDS Society expects to release an updated global scientific strategy towards an HIV-1 cure. [43]

Currently ongoing and planned cure-related clinical trials are not expected to lead directly to a cure, but rather to define pathways which when further developed and possibly combined may lead to sterilizing or functional cure. The only possible exception to this would be if researchers were able to replicate the one documented case of a cure for HIV-1 in a human being, the case of Timothy Brown. This approach would involve giving stem-cell or bone marrow transplants from a CCR5-delta32 homozygous mutant immune system to an HIV-infected person whose cancer therapy requires such a transplant. [44, 45]

According to Jefferys, “at least six individuals have since been reported who underwent similar procedures, but all of them died due to either the underlying cancers or complications from the transplantation procedure. [46] One new case was described in a poster at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), and the preliminary signs appear encouraging: the cancer is in remission and HIV cannot be detected by multiple techniques. [47] However ART had not yet been interrupted at the time of the presentation, so it is too early to know if this may represent a second example of an HIV cure.”

Research on putative immune-based therapies for HIV infection seems to be in decline, aside from a few studies such as one of pitavastatin to reduce cardiovascular disease incidence among people on ART. [48]

However there is still a clinical need for therapies for people who in spite of successful virologic suppression on ART fail to reconstitute their immune systems to healthy and safe levels.[49] Late initiation of ART – simultaneous with the diagnosis of AIDS, as is the case with 23.6% of newly-diagnosed HIV in the U.S. as recently as 2013) [50] – greatly increases the risk of becoming an immunologic non-responder (INR). Jefferys states that “TAG is currently collaborating with other activists to explore whether candidate treatments for INRs might be considered orphan drugs, a U.S. Food and Drug Administration (FDA) designation intended to spur the development of treatments for disorders that are relatively rare.” [39]

The 2016 immune-based therapy pipeline (see table 2) includes fifteen agents with a broad variety of putative therapeutic mechanisms; all are languishing or at best moving forward slowly in phase I or II studies.

2016 HIV PIPELINE RECOMMENDATIONS

Antiretroviral Therapy Recommendations

- “With some major pharmaceutical manufacturers retreating from the ARV research and development space, the industry partners that remain should strengthen their resolve to meet the ARV safety, efficacy, acceptability, and affordability challenges that remain in low-, middle-, and high-income countries.
- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers must also commit to meet the treatment access needs in middle-income countries, which will be home to 70% of people living with HIV before the end of this decade and are facing both funding losses from donor agencies as well as crippling intellectual property rules that will block access to affordable generics.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- The development of new drugs for treatment of cross-class-resistant HIV should remain a priority. It is very encouraging to see progress in this area. For drugs with limited indications, including those without clear marketing potential for treatment-naïve individuals, the Orphan Drug Designation program should be explored and engaged.
- Manufacturers should continue to closely collaborate with, and invest heavily in, evidence-based research, implementation science, policy advocacy, and service delivery aimed at improving HIV diagnosis and clinical care engagement rates. Their efforts should aim to maximize virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.” [9]

Antiretroviral Treatment Optimization Recommendations

- **“Upgrade the new first-line regimen.** Sufficient evidence to change WHO guidelines to recommend DTG and TAF as part of the preferred first-line regimen (replacing EFV and TDF) needs to be generated in order to convince generic manufacturers to invest in new production for the new regimens. A recommendation from WHO is the strongest signal to generic manufacturers to take the risk and produce new FDCs. Such WHO recommendations will require results from the studies discussed here.
- **Originators donate drugs to strategy studies for LMIC.** Originator manufacturers must take responsibility and supply prioritized antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate data to support their use in LMIC. And not after several years of deliberation. The lack of information on use of new regimens in pregnancy and with TB treatment – that is critical to treating populations in LMIC – will continue to be a barrier to their universal recommendation however impressive the results from the phase III trials are.
- **Countries get ready to switch.** Countries with high volume ART programs such as South Africa, Kenya, and Uganda, need their guideline committees briefed as results are generated (even before they are publically released), so that they can make new recommendations, hopefully before final WHO decisions.
- **Donors must support switch to new drugs and regimens.** Donors can play a huge part in changing standard of care in countries. UNITAID bought large volumes of TDF and helped to bring down the price and speed up the switch from d4T – so called market dynamics.
- **Timely approval.** Regulatory agencies in LMIC, such as the South African Medicines Control Council, need to register new originator and generic formulations, as swiftly as possible. Ideally this should happen before new WHO and national recommendations.
- **Generic companies need time to plan for high volume manufacture.** Generic manufacturers need to be briefed on when data from key studies are expected to be released, guideline changes, and tender timing in countries, so that they can start planning to compete to supply the newly recommended regimens.
- **Pre-empt possible chaos.** Before introducing new drugs, issues such as stockpiling (and stock outs) need to be discussed and planned, so that hitches with switching from old to new regimens are kept to a minimum.
- **Second-line needs more consideration.** Although there is consensus on the likely best optimized first-line regimen, second-line is not quite there yet and requires more discussion and research and development to ensure best regimens and formulations.” [13]

Pediatric Antiretroviral Recommendations

- **Speed up development.** The gap needs to be narrowed between approval of new drugs for adults, children, and neonates. An evidence base to support not always taking a de-escalated age band approach when studying new drugs is needed. Optimize use of pharmacokinetic data and modelling.
- **Speed up approval.** Harmonization of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is needed to help speed up approval.
- **Implement WHO recommendations.** As simpler formulations identified to implement the guidelines become available (most topically LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

- **Coordinate Procurement.** Guidance on optimal formulations needs to be easily available to countries and updated as better ones become available. Companies need to be informed of the priority formulations. Plans need to be in place to phase out suboptimal formulations and phase in new ones. Donors need to ensure the availability of low volume products in a diminishing market.

Preventive Technologies: Antiretroviral and Vaccine Recommendations

- Consider “how to incorporate PrEP into background standard-of-care options in vaccine and prevention-based immunotherapy clinical trials. In HVTN 702, for example, South African study participants will receive referrals to local programs where they may obtain TDF/FTC, as opposed to active provision of PrEP as a component of prevention services (e.g., free condoms and lubricant, counseling, and access to STI testing and treatment). This is similar to the standard-of-care approach being employed in the VRC01 AMP Study (HVTN 704/HPTN 085), although in that case US participants have access to a specific referral program that allows their primary care provider to offer TDF/FTC PrEP free of charge. It has been argued that TDF/FTC should be offered through these trials themselves.⁸² This is, however, a difficult issue to wrestle with, as active provision of PrEP may substantially increase the person-years of followup required—and, with it, the study’s population size and expense—to reach the statistically sound number of seroconversion events needed for efficacy analyses. Indeed, the local Institutional Review Boards and both local and global Community Advisory Boards responsible for reviewing and approving both HVTN 702 and the AMP Study appear to have found the practice of referring participants to external sources of PrEP to be acceptable, at least at the current time.”
- Promote “registrational trial methodologies that are necessarily rigorous in their design, yet feasible for the sponsors of new biomedical prevention candidates—a large number of which are not-for-profit programs that are dependent on finite public and philanthropic support. A major factor influencing study designs is the ethical principle of beneficence, which requires the abandonment of placebo comparisons and the inclusion of proven interventions, such as oral TDF/FTC, in control groups. Regulatory agencies, however, still want proof that an experimental PrEP regimen is more effective than placebo. This in turn requires reliable background incidence estimates, which have repeatedly proven to be difficult to come by in PrEP clinical trials. Also required are many person-years of follow up—and, by extension, extremely large, long, and expensive clinical trials—to yield the number of seroconversions necessary for standard non-inferiority comparisons, particularly with a highly efficacious regimen such as TDF/FTC.”
- “Close attention to these issues, particularly as an increasing number of products enter phase II and III stages of development, is critical. A stringent, but amenable, regulatory climate is necessary to ensure the availability of necessary safety, efficacy, and acceptability data, without being prohibitively costly and ultimately deterring critical investments by product sponsors, particularly those heavily dependent on limited public and philanthropic funding.” [23]

Research Toward A Cure and Immune-Based and Gene Therapies Recommendations

- Continue to increase funding for cure-related research.
- Promote dialogue between regulators, researchers, funders and community stakeholders on trial design issues, with a particular view to smoothing the pathway toward the evaluation of combination approaches
- Support efforts to develop novel means to make potentially complex interventions such as gene therapy more convenient, accessible and affordable.
- Improve communication on concepts of HIV remission, and be clear that the maintenance of low viral

load in the absence of ART may not necessarily be equivalent to suppression of HIV by ART in terms of long-term health outcomes.

- Broaden community education efforts on HIV cure research and promote and facilitate participation of diverse populations in clinical trials.
- Invest in webcasting for all cure-related scientific conferences in order to facilitate greater global sharing of information.
- Be vigilant for any evidence that interventions could benefit immunologic non-responders (INRs) even if they fail in the cure research context, and conduct studies in this population when appropriate.
- Convene a scientific workshop (or workshops) on drug development and trial design for the INR population.
- Develop a research agenda to resolve outstanding uncertainties on the value of probiotics as an adjunctive therapy for individuals on ART.

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Executive Summary – Tuberculosis

TUBERCULOSIS DIAGNOSTICS

The year 2015–2016 saw more concrete progress in moving new TB diagnostic tests from research to recommendation by the World Health Organization (WHO) than any year since 2010, when the WHO recommended GeneXpert MTB/RIF. As Erica Lessem shows in this year's "Tuberculosis Diagnostics Pipeline," in the past year, the WHO "approved Alere's lipoarabinomannan (LAM) test – a very affordable, simple, rapid, noninvasive, point-of-care (POC) rule-in test for people with HIV with very low CD4 counts... New versions of line-probe assays [LPAs] – Hain's MTBDR_{plus} and MTBDR_{sl} and a product from Nipro [NTM+MDR-TB Detection Kit 2] – received WHO recommendations... Improvements on nucleic acid amplification tests such as GeneXpert Omni and Ultra and Molbio's TrueNAT are being validated... Further upstream, encouraging research into gene sets that can predict active TB disease and reliably distinguish it from latent TB and other infections may eventually underpin new blood tests... Incremental advances are being made to improve the detection of pediatric TB." [1]

Lessem cautions, however, the deployment of new TB diagnostic tests remains abysmal, with 3.6 million of the world's estimated 9.6 million new TB cases in 2014 undiagnosed; "59% of cases of multidrug-resistant (MDR-TB) undetected... [and] a mere US \$65 million in 2014 funding out of an estimated annual need of \$340 million in research investment in new TB diagnostics tests." Furthermore, WHO guidance on how to implement recently-approved tests remains in development, while the funds to scale-up their use remain elusive. Disappointingly, fourteen TB diagnostic test candidates are in later stages of development or already marketed (in some countries) without any new published data since the 2015 Pipeline Report [see table 2].

An implementation science study carried out in South Africa, Tanzania, Zambia, and Zimbabwe showed that "among 578 people with HIV... using LAM was associated with an absolute reduction of all-cause mortality at eight weeks of four percent, and a relative risk reduction of 17 percent... [apparently] attributable to the test's allowing earlier initiation of ... anti-TB therapy." [2] The LAM test should be deployed rapidly in hospitals and clinics in high-HIV burden settings so that this benefit may help to prevent some of the hundreds of thousands of cases of TB disease and death among people with HIV.

The newer line probe assays (LPAs) are a step forward in making drug-susceptibility testing (DST) more available, but their drawbacks include technical difficulty, requirement for separate rooms for each stage of the process, and the possibility of contamination, which could yield inaccurate results. The newer innovations with Xpert platforms such as Xpert XDR, Omni, and Ultra, will each be a step forward, and less difficult to carry out than the LPAs, but suffer from incomplete penetration of the health care sector, maintenance issues, and the high cost of the machine itself.

As Lindsay McKenna points out in a special section on diagnosing pediatric TB, in the past year, WHO doubled the estimated annual number of TB cases among children to one million. TB diagnosis among infants and children is more difficult than in adolescents or adults. Research to improve the situation remains insufficient and lags behind the advances mentioned above. The next-generation Xpert tests are expected to have increased sensitivity and ability to diagnose paucibacillary disease common in children. The LAM urine dipstick was not particularly sensitive or specific in pediatric studies to date, but the WHO recommendation to use the test includes HIV-positive children with CD4 counts below 100/mm³ along with adults. As with all aspects of pediatric tuberculosis, more research, program implementation, resources, and political will are needed to move forward. [3]

TUBERCULOSIS PREVENTION – VACCINES AND PREVENTIVE THERAPY

After two-and-a-half decades when efforts to contain tuberculosis focused principally on treating the disease – especially in its drug-sensitive form – the TB policy and research world has recently begun to expand its focus to include greater emphasis on prevention, as Mike Frick demonstrates in “The Tuberculosis Prevention Pipeline.” [4]

Last year the WHO released its first-ever *Guidelines on the Management of Latent Tuberculosis Infection* [5]. Earlier this year UNITAID adopted TB prevention as a new area of emphasis for intervention [6]. In spite of the flatlined infectious diseases research agenda at the U.S. National Institutes of Health (NIH), the White House issued an (unfunded) *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* last December [7]. (The President’s proposed fiscal year 2017 budget, proposed in January of this year, recommended cutting global TB control funding by \$45 million, or 19% [8, 9].) WHO’s new “End TB Strategy” concludes that reaching the proposed elimination targets will require intensified efforts to prevent TB transmission through chemoprophylaxis and – when available – a vaccine. [10]

Frick discusses a number of high-priority questions in TB prevention research, including efforts to identify genetic signatures of risk for progression of TB infection – whose discovery and validation could help speed up research in both TB vaccines and preventive therapy – disparities between measurable immune responses in the blood and in the lung where most TB disease occurs, the mystery of the mycobacterial granuloma, and the perennial question of MTB persistence in the face of a partially-effective immune response and sometimes-curative chemotherapy.

The TB vaccine field is experiencing a move back towards basic and early-phase clinical research, one reminiscent of what happened with the HIV vaccine field after the setback of the STEP trial, in which the adenovirus-5 vector in which the HIV immunogens were delivered actually caused increased HIV infection as compared to the study’s placebo arm [11, 12]. Just one trial is in phase III, one in phase IIb, six in phase IIa, and five in phase I. The predominant approaches include whole-cell preparations of *M. vaccae*, genetically attenuated MTB, recombinant BCG, whole-cell *M. obuense*, and ‘fragmented’ MTB; prime-boost studies of various TB antigens with various adjuvants; while the phase I studies are all prime-boost approaches using viral vectors and TB proteins [see Table 1. TB Vaccines in Development].

TB vaccine R&D is massively underfunded – investments in 2014 totaled just \$111.3 million, less than one-third of the Global Plan-recommended \$380 million annual target [13] – and it is difficult to see how the TB vaccine field will produce a safe, effective vaccine by the 2025 target required by The End TB Strategy [10: Figure 2. Projected acceleration in the decline of global tuberculosis incidence rates to target levels; p. 5]. The field is moving towards earlier-stage translational studies and novel clinical trial designs targeting TB incidence rather than prevention of disease as a primary endpoint. The problem here is that diagnosing TB infection definitively is even harder than diagnosing TB disease. We already know that 3.6 million of the world’s annual 9.6 million cases of active disease already go unreported. Proving that TB infection has been prevented would require a test better than the currently-used tools of tuberculin skin testing (TST) and interferon gamma release assays (IGRAs), which are all too unspecific, insensitive, and likely to give contradictory results in different hands or in different settings. Other approaches such as targeting TB reactivation or reinfection suffer from the same lack of a definitive measurement tool, except for genetic fingerprinting in cases of active TB disease when reactivation can be distinguished from reinfection by a different molecular fingerprint, in cases where the original disease-causing strain is still on hand for comparison.

Lack of resources is leading to excessive caution in the populations prioritized for research, as Frick points out: “[b]y conducting fewer clinical trials in children and people with HIV, TB vaccine developers are effectively making the decision to direct research away from the two groups most vulnerable to TB... developers should acknowledge that the current strategy risks leaving behind two key TB-affected populations with greatly enhanced risks of disease and death that rightly draw significant attention from global health actors.” [4]

Luckily, this is not the case in TB preventive therapy research, where “children and people with HIV still occupy the center of efforts to develop new or improved preventive therapies.” [4]. According to Frick, “Eight studies are underway or in late development, six of which are examining different dosing schedules of rifapentine, administered either in combination with other drugs such as isoniazid or alone. Two studies are investigating preventive therapy for individuals exposed to DR-TB, one looking at daily delamanid vs. INH and the second comparing 6 months daily levofloxacin vs. placebo.” (See Table 2, Clinical trials of TB treatments to prevent tuberculosis disease; and Lindsay McKenna’s Table 1: Ongoing and Planned TB Prevention and Treatment Studies in Children.)

TUBERCULOSIS TREATMENT

TB treatment remained largely unchanged in 2015 with five new drugs at various stages of clinical development. Of these, two – bedaquiline and delamanid – have approved accelerated approval from the US FDA (in 2012 for bedaquiline) and conditional approval from the European Medicines Agency (EMA, in 2014 for delamanid) as additive therapies to use with background regimens to treat multidrug resistant (MDR) TB. Pretomanid, formerly PA-824, a drug similar to delamanid but further behind in clinical trials, is being studied in various combinations for drug-sensitive, MDR, and extensively-drug resistant (XDR) TB. Sutezolid, a drug which spent the first decade on the shelf after the acquisition of Pharmacia and Upjohn by Pfizer, then came to life briefly when an early bactericidal activity (EBA)/phase IIa study showed anti-TB activity in the clinic, and is now paralyzed due to the inaction and lack of resources of Sequella, Inc., which bought the drug from Pfizer when the latter abandoned infectious disease research. The past year saw the abandonment of AstraZeneca’s AZD5847 due to lack of anti-TB activity and the emergence into the clinic of Qurient’s Q203, a new drug from a new class developed by a company in South Korea.

As Erica Lessem shows in “The Tuberculosis Treatment Pipeline: Activity, but No Answers,” the rollout of both bedaquiline (BDQ) and delamanid (DLM) has been painfully slow. Safety concerns following the apparent excess of late deaths in the phase IIb study of bedaquiline, along with the general and pervasive delays of TB programs in adopting new technologies, have slowed its uptake. It took almost four years for the sponsor, Janssen, to start its phase III study following accelerated approval in December 2012 – surely a massive abuse of the accelerated approval system. Similar delays afflicted a long-agreed-to drug-drug interaction study of BDQ and DLM to determine if their QTc-prolonging activity (a marker of cardiac toxicity) was additive and compromised safety, or whether the two drugs could safely be co-administered; legal foot-dragging by Janssen means that the study still has not begun today, even though both sponsors agreed to conduct it in December 2012.

Increasing amounts of programmatic data, particularly from South Africa, indicate that the addition of BDQ to background treatment appears to be increasing cure rates for pre-XDR and XDR-TB, without an excess of cardiac deaths. Otsuka, the maker of delamanid, has been so tardy in registering the drug or even allowing its compassionate use, that few safety and no additional efficacy data are yet available. The ongoing phase III study is expected to be reported out in 2018. Meanwhile, the company has an ethical obligation to register the drug in the many high-TB-burden countries where it carried out its phase II studies, and in places with high burdens of DR-TB. The soon-to-launch ACTG/IMPAACT PHOENIX study, which will compare 6 months of DLM to INH among household contacts of people with MDR-TB, will provide considerable new safety data on the drug, as well as showing whether it can prevent MDR-TB acquisition or disease among these high-risk individuals.

Ambitious plans for pretomanid came to a standstill last fall when the ongoing STAND study of pretomanid-moxifloxacin-pyrazinamide (PaMZ) among people with DS and DR-TB was put on clinical hold because of three sudden hepatic deaths among people in the DS-arm who were receiving PaMZ. Nine months later the study’s data safety monitoring board has signaled that the study can proceed with additional safeguards.

Sutezolid remains paralyzed by the sponsor's lack of funds or willingness to cooperate with other players. However, the drug's patent status suggests that outside manufacturers could make the drug, and it is hoped that this will allow phase IIb studies to begin in the next 18 months.

A number of studies are looking at repurposed older drugs in new indications or at new dosing levels. High-dose studies of rifampin and rifapentine are ongoing. One study, TRUNCATE-TB, seeks to accelerate the validation of a super-short-course two-month regimen for DS-TB by comparing four two-month regimens. It's understood that failure levels will be higher than with six months of the current regimen, but it is hoped that the majority of people would be cured in two months and that the others would still respond to standard therapy.

Other studies continue to look at, and sometimes to compare, fluoroquinolones such as levofloxacin and moxifloxacin in drug-resistant disease. (and – controversially, – gatifloxacin, which was removed from developed-world markets for toxicity some years ago, has also been re-recommended by the WHO for the treatment of MDR-TB) in drug-resistant disease.

Dose-ranging studies are being planned at last for two old drugs whose importance in TB treatment has recently become clearer, clofazimine and linezolid.

An EBA study presented at the 2016 CROI showed that the carbapenem meropenem, given with amoxicillin/clavulunate intravenously [IV] three times a day, had measurable anti-TB activity without grade 3/4 toxicity. Another drug in the class, ertapenem, may also have activity, though it too requires IV administration. [14]

Pediatric TB treatment research is one of the brighter spots in the overall clinical TB research landscape, as Lindsay McKenna shows in "The Pediatric Tuberculosis Treatment Pipeline: Beyond Pharmacokinetics and Safety Data" [15]. Long-neglected formulations suitable for children have finally advanced towards market and new studies in preventive therapy, dose optimization, and treatment for drug-resistant disease are finally beginning to be carried out. McKenna shows five studies are planned or underway for TB prevention, five for treatment using new drugs (3 DLM, 2 BDQ), and fourteen studies of various existing drugs, combinations, and interaction studies with commonly-used antiretrovirals (see Table 1: Ongoing and planned TB prevention and treatment studies in children). Researchers continue to try and optimize dose-levels for first-line therapy in young children, where achieving pharmacokinetic levels similar to those of adults has proven challenging. Co-treatment for HIV and TB remains an issue for children, again because of the lack of previous drug-drug-interaction studies and necessary formulations. Meanwhile, research on second-line drugs and how to shorten and simplify treatment for drug-resistant disease in children is even further behind.

Otsuka has completed pediatric dosing studies of delamanid for 12-to-17-year-olds and 6-to-11-year-olds; a study using the DLM pediatric formulation in children aged 5 and younger is expected to be complete in time for the launch of PHOENIX, which will compare delamanid to INH among household contacts – including children 5 years and under, TST-positive persons, and those living with HIV – of MDR-TB cases, to see whether six months of DLM can better prevent transmission and progression to active disease of MDR-TB.

Janssen has been further behind in its pediatric research on BDQ, principally because the FDA – unlike the EMA – lacks the power to mandate pediatric studies, even of drugs where there is such a high global burden of pediatric disease. Its first PK/safety study in HIV-negative children opened in May 2016, 3.5 years after FDA approval in adults – another unacceptable delay by Janssen.

McKenna highlights the importance of conducting TB treatment research in pregnant women, where data are lacking not only on drug safety and activity, but even on TB incidence, though it is estimated that almost a quarter-million women may develop active TB each year. The IMPAACT network is conducting two studies of TB prevention and one TB treatment study in pregnant women. (See Table 2: Ongoing and planned TB

prevention and treatment studies in pregnant women.) McKenna recommends the establishment of a TB Pregnancy Registry, similar to the Antiretroviral Pregnancy Registry which that has been underway since 1989.

Finally, McKenna reviews current progress on pediatric formulations for first-line therapy (several fixed-dose combinations of HRZ, HR, or HP from five companies; four single-drug dispersible tablet forms of E, H, Z, and P from Macleods and Sanofi; and 7 second-line drugs in dispersible tablets or mini-capsules; see Table 3: Pediatric formulations in development). [15]

2016 TUBERCULOSIS PIPELINE RECOMMENDATIONS

TB Diagnostics Recommendations

- “Both R&D on and access to evidence-based TB diagnostic tests need dramatic infusions of funding and political will.
- National governments and donors must substantially increase funding for TB programs to allow for best diagnostic practices. This includes the widespread scale-up of NAAT to supplant microscopy, universal DST using liquid culture or LPAs, digital X-ray, and the rapid adoption of LAM testing in areas with high HIV burdens.
- National governments, donors, and the private sector must invest far more in TB R&D to advance better tests, including those for children. This should include a commitment to rapidly and rigorously evaluating new technologies and to publishing peer-reviewed results.
- National governments and donors should work closely with the nonprofit and private sectors to ensure only quality and affordable tests are used. In countries with large proportions of care-seeking in the private sector, access to appropriate diagnostics is extremely limited and can be catastrophically expensive.
- Developers must commit to timely and rigorous validations of their tests prior to marketing, and health and regulatory authorities and private practitioners should hold them accountable for doing so. Epistem and other companies who market ineffective or as-yet-unproven tests must cease doing so immediately. National governments should ban the import and use of inappropriate tests and enforce those bans. Those working in TB globally should call to task companies such as Epistem that inappropriately market them.” [1]
- “Greater efforts to identify children at risk for TB – especially within maternal and child health programs, where sick children often first present for care – and referral systems and decentralized capacity to diagnose childhood TB, clinically or with available tools, are urgently needed.
- Developers should validate tests in adults and children in parallel to expedite access to improved diagnostic technologies for children. These evaluations should include a variety of sample types in children with and without HIV and should assess age-related performance.
- Developers and donors should increase investments in research to discover and validate biomarkers and innovation to translate these biomarkers into simple and affordable tests that can rapidly and accurately diagnose TB, monitor treatment, and predict disease progression in children. In 2014, less than \$2.3 million and \$2.8 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively;

- Developers and research networks should establish and support harmonized and collaborative pediatric biorepositories important for biomarker discovery and development.
- Developers and researchers should support and create networks of sites that support rigorous evaluation of new diagnostics and can pool data to more rapidly demonstrate the impact of new tools.
- Programs should scale up and decentralize the use of existing technologies and strategies to diagnose pediatric TB infection and disease, especially within maternal and child health programs.
- Programs should train health care workers to improve their ability and confidence to clinically diagnose children with TB when tests are unavailable or come back negative.” [2]

TB Prevention Recommendations

“For funders: Ensure financing mechanisms are sufficiently flexible and durable to support the multi-year, collaborative research endeavors that will be required to make progress against a challenge as complex and intractable as MTB infection. For example, nearly ten years passed between when the South African adolescent cohort enrolled its first participant in 2005 and when it published results announcing the discovery of a risk signature of disease progression in *The Lancet* in 2016. This was not time wasted, and the cohort will likely yield publications and results for years to come. Further advancing our knowledge of MTB infection and TB disease may require larger cohorts with even longer periods of follow-up. In addition, funding agencies should support translational work to bridge advancements in basic science with clinical development and maintain openness to a wide range of approaches that probe the nature of MTB infection from the perspective of both host and pathogen, and through the application of new assays and imaging technologies in both humans and animal models.

For vaccine researchers and developers: Continue to explore a greater diversity of approaches to TB vaccine development through the use of experimental medicine studies and trials designed around novel endpoints. Ultimately, this will likely require developers to introduce wholly new vaccine candidates whose designs look beyond the narrow focus on cell-mediated immunity that has dominated past efforts. The development and introduction of new assays that are able to translate signals of immunogenicity between lung and blood (or capable of safely measuring vaccine responses directly in the lung itself) should also be a priority. Developers and their sponsors should not foreclose on clinical trials among infants and people with HIV, two of the groups most in need of a new TB vaccine. Although previous trials in these two populations have fallen short of expectations, there is much that can be learned from past failures. Rather than wholly abandon vaccine concepts and constructs that did not work, vaccine researchers and developers should more forthrightly interrogate the reasons behind disappointing results.

For drug researchers and developers: Accelerate research to understand MTB persistence and the nature of latency to develop new drugs targeting latent infection. Efforts to understand MTB persistence would benefit from initiating a dialogue with researchers involved in vaccine development about differences in how the TB drug and vaccine fields approach preclinical testing. Each field is confronting challenges related to MTB persistence and the nature of latency, but vaccine and drug developers do not always measure the same pathology or immunological events using relatable endpoints or definitions of scale in the animal models in which much of this work will be conducted. Closer collaboration with their vaccine counterparts might also open the door for drug developers to use vaccines as adjuncts to shorten therapy or reduce the risk of relapse. In the meantime, ongoing efforts to shorten and simplify TB preventive therapy for children, people with HIV, pregnant women, and household contacts of people with DR-TB should continue. The advanced stage of many of TB prevention trials obligates pharmaceutical companies involved in this research – namely, Sanofi and Otsuka – to take steps to register their products more widely and facilitate equitable access through measures such as affordable pricing.

For all researchers and developers: Recognize community engagement in research as the ethical complement to good clinical practice and take steps to involve representatives from TB-affected communities in all stages of R&D. The potential of ongoing or planned TB preventive therapy and vaccine studies to refashion clinical practice in ways that could render many more people with asymptomatic MTB infection eligible for medical intervention makes it imperative that developers create meaningful spaces for community voices, concerns, and priorities to enter the research process. Communities must become true partners in TB prevention research, and not merely its silent beneficiaries.

For activists: Take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes. With the exception of TB PROOF – a South African advocacy group founded by doctors who contracted TB that is dedicated to preventing MTB infection among healthcare workers – activist voices in TB prevention have been few in number and modest in volume. This absence does not reflect a lack of need. A global shortage of BCG continues into its third year, needlessly endangering the lives of millions of infants. Rifapentine, the cornerstone of TB preventive therapy research, is registered for the treatment of MTB infection in just one country, despite being studied in at least a dozen more. Individuals exposed to MDR-TB have few evidence-based options to treat probable drug-resistant infection. And countries remain slow to rollout proven interventions such as IPT to people with HIV, 400,000 of whom died from TB in 2014. We are one year closer to 2025, the year WHO says new prevention tools must be introduced to reach the End TB Strategy’s goal of eliminating TB by 2035, and there is no new vaccine or transformative preventive drug regimen on the immediate horizon. The clock is ticking.” [4]

TB Treatment Recommendations

- “1. Government agencies, pharmaceutical companies, and foundations must dramatically scale up funding for TB R&D. In line with the third pillar of the WHO’s End TB strategy, which calls for R&D, countries must commit more resources to TB drug development.⁷⁷ The U.S. government, which is the leading funder of TB R&D, should increase funding levels to \$300 million by 2018 to keep its critical investments at pace with inflation. TAG suggests that this should entail an additional \$17 million from the NIH, \$15 million from USAID, \$16 million from the U.S. Centers for Disease Control and Prevention, and \$5 million from the FDA for TB R&D.⁷⁸ European Union countries, particularly Germany, should double their TB R&D funding, and Brazil, China, India, Russia, and South Africa should each triple their funding for TB R&D.⁷⁹ Activists in other countries should call for commensurate increases in their own settings. Companies such as Otsuka and Sanofi should maintain strong levels of investment, and Janssen needs to recommit to further developing bedaquiline, as significant work remains despite bedaquiline’s conditional approval, and to moving the most promising of its pipeline of bedaquiline analogues further toward clinical study. Other pharmaceutical companies and philanthropic organizations should also begin to invest in TB R&D.
2. Donor and high-TB-burden governments should create and invest in mechanisms that build access to TB drug development, and drug developers should participate in them. The inability to access data hampers collaborative TB drug development, which is essential because TB must be treated with a combination of drugs to prevent the development of resistance. The inability to access drugs hampers TB treatment and cure and threatens to render the limited R&D that is occurring less useful. Fortunately, members of the TB community have proposed feasible and appealing solutions that should be actively pursued. These include remedying loopholes in the FDA’s priority review voucher system to ensure innovation and drug availability and fair pricing and should also entail product developers licensing their compounds to and sharing data with the MPP, which recently received a mandate to work on TB drug development and could possibly play a key role in brokering combination drug development.⁸¹ MSF’s proposed 3P (“Push, Pull, Pool”) project may also provide an interesting, innovative, and potentially transformative approach to spur the

development of regimens and ensure their availability post-approval, though the devil here will lie in the details of how it is actually executed.

3. Drug and trial sponsors must expedite the development of preclinical and clinical candidates. Delays in TB research and development are widespread and atrocious. The TB drug development pipeline remains frighteningly sparse, pointing to the urgent need to advance preclinical work to allow viable candidates into clinical studies. Clinical development for the few products in the pipeline has been unacceptably slow, with drugs taking over five years to advance from one stage to the next. In particular, Janssen's and Sequella's failures to rapidly move bedaquiline and sutezolid, respectively, through important studies are deplorable.
4. Ministries of health, regulatory authorities, and ministries of finance should prioritize the timely introduction of evidence-based TB treatment, and donors and providers of technical assistance should ensure they are supporting rather than hindering scale-up. Drug development will not affect the TB epidemic and improve the lives of people affected by TB unless new interventions are available to communities and people who need them. Unfortunately, country-level demand for important new products such as delamanid and bedaquiline has been weak, and implementation slow. USAID, which has partnered with Janssen to make bedaquiline available via a donation program, literally cannot give the drug away for free to enough people. Poor advice from technical assistance providers has worsened the situation and excused complacency. All parties, national and global, must be much more ambitious and supportive of new ways to find and treat TB.

Pediatric TB Treatment Recommendations

"For researchers:

- Consider children when planning adult studies. Building PK investigations into studies that evaluate higher doses of TB drugs in adults is necessary to inform future PK targets in children.
- Determine which PK value(s) correlate best with efficacy for TB drugs in children and establish PK targets based on adult data, taking into consideration the variability in severity and type of TB disease among, and challenges defining efficacy in, children.
- Enroll children two years of age and younger in pediatric studies, as this is the period during which drug disposition changes the most for children, increasing risk for high or low drug exposures.
- Include HIV-positive children in studies of new TB drugs and regimens.
- Include pregnant women in studies of new TB drugs and regimens.

For policy makers:

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children.

For regulatory authorities:

- Enforce more thoughtful requirements to ensure comprehensive and timely investigations of TB drugs
- in children. Mandatory and time-bound pediatric investigational plans that also require studies in HIV-positive children will help to shrink the persisting evidence and access gaps that exist between adults and children for new TB drugs.

- Follow the important precedent set by the EMA and allow parallel enrollment of pediatric cohorts in PK and safety studies.
- Be transparent and clear about requirements to register pediatric formulations for both existing and new drugs.
- When possible and appropriate, consider waived requirements and registration fees to facilitate access.” [15]

For donors:

- Maintain and adequately fund momentum in pediatric TB drug R&D, for which global investments totaled \$11.6 million in 2014. Recent attacks on the budget for and AIDS research priorities of the NIH are particularly concerning for pediatric TB R&D. Not only is the NIH the leading funder, but its investments support studies that are critical to improving treatment of pediatric TB and to filling both long-standing and new gaps in pediatric PK and safety data, especially for HIV-positive children taking ARVs.
- Further attention to and investments in pediatric TB trial infrastructure and site capacity development are urgently needed to support the increasingly full research agenda for prevention and treatment of TB in children.
- UNITAID, whose investments have led to the market introduction of appropriately dosed FDCs of first-line TB drugs for children, and whose planned investments will ensure global uptake of these new formulations, should invest in a project modeled after STEP-TB that is focused on expediting development and market introduction of pediatric formulations of second-line TB drugs.

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The Antiretroviral Pipeline

By Tim Horn and Simon Collins

INTRODUCTION

The year 2016 marks 20 years since combination-based antiretroviral therapy (ART) first demonstrated durable, effective and sustained HIV control. An unprecedented period of drug discovery followed, and advances in viral load and resistance technology made HIV, in high-income countries, one of the most individualized infections to manage.

Within a decade of the advent of ART, from 1996 to 2006, competition between at least eight major companies steadily improved regimens that initially required handfuls of daily pills with complex dosing, to an option of a three-in-one fixed dose combination that simplified adherence to a daily pill.

The significant side effects of early treatment led to widespread use of CD4 guided treatment breaks – until the results from the Strategies for Management of Antiretroviral Therapy (SMART) study, also in 2006, reported that ongoing viral replication (rather than just a reduced CD4 count) was associated with an increased risk of serious AIDS- and non-AIDS-related events.¹ Until SMART, numerous small underpowered studies had suggested intermittent treatment might be safe.

The development of an affordable generic regimen in 2001;² the formation of the Global Fund to Fight AIDS, TB and Malaria in 2002;³ the establishment of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in 2003;⁴ and the World Health Organization's (WHO's) 3 by 5 initiative and subsequent efforts enabled greater access to ART on a global scale.⁵

During the second decade of ART, additional single-pill formulations became available, and treatment became sufficiently safe and effective for the international START study to conclusively show that the benefits of starting ART, regardless of CD4 cell count, outweighed the risks of waiting until the CD4 count dropped to 350.⁶ These results contributed to WHO guidelines recommending universal access to ART, and were also supported by new evidence showing the dramatic impact of ART on reducing onward transmission. Globally, there are now approximately 17 million people using ART.⁷

But as treatment became more effective and guidelines selected only the few best combinations, many of the original large manufacturers—Roche, Boehringer Ingelheim, and, most recently, Bristol-Myers Squibb—withdraw from HIV research and development. It is unclear how this diminishing competition will affect innovative research and drug development in the long run.

Drug pricing in high-income countries has become increasingly important, just as patents are ending for many well-established antiretrovirals (ARVs). There are also growing treatment access concerns in many middle-income countries, where support is being phased out from the Global Fund, which is calling for lower funding targets than predicted in previous years.⁸

Looking forward, the next ten years will need drug development to become ever more advanced—and here we report on compounds that hint at these possibilities. The first generation of long-acting formulations might enable ART to be reduced to only six injectable treatments a year. At an earlier stage of development, another pipeline compound might deliver a slow-release drug from a depot for up to a year. Also on the horizon are promising monoclonal antibodies, along with a new oral attachment inhibitor and maturation inhibitor, which show immediate promise for treatment-experienced individuals in need of new regimen components.

Added to this overview of new drugs are tentative data on potentially new, simplified approaches to using existing drugs. Emerging data from studies of dolutegravir as monotherapy (or in a two-drug combination with lamivudine [3TC]) suggest that we may be over-treating millions of people (see sidebar). This has global implications, as the price for generic dolutegravir is likely to match generic efavirenz, enabling the poorest and the richest countries to offer the same first-line combinations. Many middle-income countries, unfortunately, will be left using older drugs.

The timeline for future World Health Organization treatment guidelines to recommend dolutegravir instead of efavirenz is dependent on additional data in women, during pregnancy, and in TB coinfection (see “Fit for Purpose: Treatment Optimization,” on page 43).

For all of the optimism and hope behind the efforts to dramatically reduce new HIV infections and minimize HIV-related mortality, HIV remains a significant health challenge in all countries. Effective ARVs are a cornerstone of every plan to reduce and contain the epidemic, for treatment and for prevention.

The pipeline over the third decade of ART therefore needs to have ambitious targets that push the science of drug discovery and drug delivery. The previous two decades have shown that such advances are possible.

SUMMARY OF PIPELINE PROGRESS

A summary of key developments since the *2015 Pipeline Report* is included in Table 1. Study details, references, and timelines for compounds with significant advances over the past year are discussed in greater detail in the text below.

Table 1. Summary of Pipeline Compounds in 2016

Compound	Class/Type	Company	Status	Comments
Tenofovir alafenamide fumarate (TAF)	NtRTI (tenofovir prodrug)	Gilead	Phase III	Three coformulations approved over the past year. Two phase III trials of FDC containing darunavir/cobicistat/FTC/TAF (D/C/F/TAF) under way. Also in phase III trials of FDC containing GS-9883/F/TAF.
Doravirine (MK-1439)	NNRTI	Merck	Phase III	Phase III studies include evaluation of an FDC with generic TDF and 3TC
GS-9883	INSTI	Gilead	Phase III	Two phase III trials of FDC containing GS-9883/F/TAF compared with dolutegravir-based regimens
Fostemsavir (BMS-663068)	Attachment inhibitor (gp120)	ViiV Healthcare/BMS	Phase III	Phase III safety and efficacy evaluation in heavily treatment-experienced patients currently under way
Raltegravir (once-daily formulation, 2 x 600 mg tablets)	INSTI	Merck	Phase III	Phase III non-inferiority study comparing once- vs. twice-daily raltegravir; primary outcome results expected in 2016
Dolutegravir plus rilpivirine (coformulation)	INSTI plus NNRTI	ViiV Healthcare, Janssen	Phase III	In parallel with FDC development, standalone versions of both drugs are being combined for use as maintenance therapy in the phase III SWORD-1 and SWORD-2 trials
Ibalizumab (TMB-355; formerly known as TNX-355)	CD4-specific humanized IgG4 monoclonal antibody	TaiMed Biologics	Phase III	Open-label phase III program to support orphan drug indication for heavily treatment-experienced patients under way

Compound	Class/Type	Company	Status	Comments
PRO 140	CCR5-specific humanized monoclonal antibody	CytoDyn	Phase II/III	Phase II/III trial in treatment-experienced patients under way
BMS-955176	Maturation inhibitor	ViiV Healthcare	Phase IIb	Phase IIb trial in treatment-experienced patients under way. Phase III evaluations in treatment-naïve and treatment-experienced patients planned
Cabotegravir oral and long-acting (LA) formulations	INSTI	ViiV Healthcare	Phase IIb	32-week results from phase II LATTE-2 trial evaluating IM injections of LA cabotegravir plus rilpivirine every four or eight weeks reported in February
Rilpivirine-LA (long-acting formulation)	NNRTI	Janssen	Phase II	32-week results from phase II LATTE-2 trial evaluating IM injections of LA cabotegravir plus rilpivirine every four or eight weeks reported in February
MK-8591 (formerly EFdA)	NRTI	Merck	Phase I	PK and antiviral activity data presented at CROI; potential for once-weekly oral dosing, prolonged injectable dosing
BMS-986197	Entry Inhibitor	ViiV Healthcare	Preclinical/Phase I	Preclinical data presented at CROI

BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; EU: European Union; FDA: Food and Drug Administration (U.S.); FDC: fixed-dose combination; FTC: emtricitabine; IM: intramuscular; INSTI: integrase strand transfer inhibitor (integrase inhibitor); NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PK: pharmacokinetics; TDF: tenofovir disoproxil fumarate.

APPROVALS SINCE JULY 2015

Three new ARV coformulations have been granted marketing clearance since the last *Pipeline Report* was published in July 2015. Genvoya, Odefsey, and Descovy are for all intents and purposes updated versions of Stribild, Complera, and Truvada, with Gilead's nucleotide reverse transcriptase inhibitor tenofovir alafenamide fumarate (TAF) replacing the company's tenofovir disoproxil fumarate (TDF).

TAF was originally positioned as a potentially more potent tenofovir prodrug, but virologic and immunologic responses in trials comparing TAF with TDF have been indistinguishable. However, there are three advantages of the low milligram dose needed for TAF: 1) smaller size tablets for fix-dose combinations (FDCs), 2) lower generic equivalent production costs and prices for low-income countries, and 3) reduced kidney and bone toxicity.

Although there are no data confirming that TAF-based regimens are associated with a reduced risk of significant renal disease or frailty fractures compared with TDF, TAF is likely to be a safer drug, both over many decades of use and for those with pre-existing conditions resulting in declines in kidney function and bone mineral density. Unfortunately, however, TDF's safety concerns have not been sufficiently pressing for Gilead to rush TAF to market: development was shelved for at least ten years, with coformulation approval timelines curiously tied to TDF's patent expiry in December 2017.⁹

As the new TAF-based coformulations become available, Gilead has been undercutting the prices for its own TDF-based products. This is not generosity, but is instead likely a strategy to retain market share before TDF goes off patent, as it will be more difficult to switch patients back to a generic version of a drug that they were previously tolerating well.

People living with HIV should have better drugs. But the strategy for this particular advance threatens to tie drug purchasers and insurance providers, whether public or private, into higher cost ART for at least the next decade. This can potentially result in two-tier access to low- and high-cost treatment for people living with HIV.

Elvitegravir/Cobicistat/Emtricitabine/TAF (E/C/F/TAF)

A coformulation of elvitegravir (150 mg), cobicistat (150 mg), FTC (200 mg), and TAF (10 mg) was approved by the FDA on November 5, 2015, with marketing authorization being granted by the European Commission on November 23, 2015.^{10,11}

The U.S. indication is either as initial therapy in treatment-naïve patients, or as a switch option for patients who have had an undetectable viral load for >6 months on their current ART and no history of virologic treatment failure on previous combinations.

Regulatory approvals were based on noninferiority findings in two phase III randomized and blinded studies in treatment-naïve patients with estimated glomerular rates ≥ 50 mL/min (studies 104 and 111) comparing E/C/F/TAF with E/C/F/TDF (Stribild), with E/C/F/TAF being associated with more favorable renal and bone laboratory parameters in both clinical trials.¹²

Additional data supporting E/C/F/TAF's approval include 96-week results from a phase III randomized, open-label trial (study 109) that found noninferiority and improvements in bone and renal markers in virologically suppressed adults that were switched to E/C/F/TAF compared with those remaining on TDF-inclusive regimens.¹³ Data from phase III open-label studies evaluating the safety of E/C/F/TAF in virologically suppressed adults with mild-to-moderate renal impairment (study 112) and treatment-naïve adolescents 12–17 years of age (study 106) have also been reported.^{14,15}

Whereas E/C/F/TDF is typically reserved for patients with creatinine clearance (CrCl) of at least 70 mL/min, E/C/F/TAF can be used with a pre-treatment estimated CrCl of >30 mL/min.

Rilpivirine/Emtricitabine/TAF (R/F/TAF)

An FDC containing rilpivirine (25 mg), TAF (10 mg), and FTC (200 mg) was approved for use in the U.S. on March 1, 2016, following a truncated nine-month FDA new drug application (NDA) review that was made possible with Gilead's US\$125 million purchase of a priority review voucher from Knight Therapeutics.^{16,17}

Approval of R/F/TAF was based almost entirely on a bioequivalence study that evaluated the components of R/F/TAF, using rilpivirine (25 mg) and E/C/F/TAF as references, in 96 HIV-negative volunteers.¹⁸ The 90% confidence intervals (CIs) for the ratios of key pharmacokinetic (PK) parameters, including the area under the curve up to the last measurable concentration (AUC_{last} ; 250 ng hr/mL for TAF 25 mg in R/F/TAF versus 238 ng hr/mL for TAF 10 mg in E/C/F/TAF), were within the protocol-specified bioequivalence boundary of 80%–125%. As with E/C/F/TAF, the R/F/TAF plasma tenofovir exposure was 90% less than that associated with TDF-inclusive regimens, which was used to explain the renal and bone biomarker differences reported in the various phase III evaluations of TAF.

Phase 3 randomized, double-blind clinical trial evaluating the safety and efficacy of switching to R/F/TAF in HIV-positive individuals who are virologically suppressed on either R/F/TDF (Complera) or efavirenz/F/TDF (Atripla) are under way.^{19,20}

Emtricitabine/TAF (F/TAF)

F/TAF FDC was approved by the FDA and the European Commission on April 4th and April 25th, 2016, respectively, for adults and adolescents 12 years of age and older.^{21,22}

Although an NDA for two formulations was submitted to the FDA—the first containing 25 mg TAF for use in combination with unboosted third agents, and the second containing 10 mg TAF for use in combination with third drugs that require boosting (tenofovir plasma levels can fluctuate when combined with either inhibitors or inducers of p-glycoprotein)—only the 25 mg formulation was ultimately approved. According to Gilead, this decision was based on FDA determinations that there were no significant drug-drug interactions with any commonly prescribed third drugs. Even when plasma tenofovir exposures were increased, when 25 mg TAF was used with ritonavir- or cobicistat-boosted protease inhibitors, the tenofovir mean AUC was still significantly lower than those seen with F/TDF. The FDA decision to approve a single formulation is apparently meant to prevent prescribing confusion.

April 2016 saw the publication of 48-week data from a phase III trial (GS-1089) evaluating the safety and efficacy associated with switching to F/TAF from F/TDF as a regimen backbone.²³ The trial randomly assigned 663 HIV-positive individuals, all virologically suppressed while using an F/TDF-inclusive regimen and having an estimated glomerular filtration rate of >50 mL/min at study entry, to either switch to F/TAF (200/10 or 200/25 mg, depending on the continued third agent) or remain on their F/TDF-inclusive regimen.

The median age at study entry was 48 years; approximately 15% were female and 73% were white. The median baseline eGFR was 100 mL/min, and slightly more than half ($n = 358$) of the participants continued non-boosted third drugs in the trial and would therefore be using F/TAF 200/25 mg (or matching placebo).

By week 48—the study is ongoing—94% in the F/TAF group, compared with 93% in the F/TDF group, had maintained virologic suppression (HIV RNA <50 copies/mL), for a treatment difference of 1.3% (95% CI: -2.5% to +5.1%). Virologic suppression rates were similar across age and race; virologic success was also similar among men (94% versus 95% in the F/TAF versus F/TDF groups, respectively), with a trend toward better virologic suppression among women receiving F/TAF (94%) compared with those continuing F/TDF (83%).

Among study participants using a boosted protease inhibitor as their third agent (darunavir/r [~46%], atazanavir/r [~25%], or lopinavir/r [~15%]), 92% in the F/TAF group, compared with 93% in the F/TDF group, maintained viral loads below 50 copies/mL. Among those using unboosted third drugs (nevirapine [~21%], raltegravir [~21%], or dolutegravir [~8%]), 97% in the F/TAF group, compared with 93% in the F/TDF group, were virologically suppressed at week 48.

Changes in renal toxicity markers were reported at week 48. Median increases in eGFR were documented in both groups: +8.4 mL/min versus +2.8 mL/min in the F/TAF and F/TDF groups, respectively. Also documented were differences in the median percentage changes in the urine protein-to-creatinine ratio (-14.6% versus +7.7%), urine albumin-to-creatinine ratio (-7.7% versus +12.3%), urine retinol binding protein-to-creatinine ratio (-16.3% versus +18.2%), and urine beta-2-microglobulin-to-creatinine ratio (-39.6% versus +22.0%). All differences between the two groups were statistically significant ($P < 0.001$).

There were no study drug discontinuations because of renal adverse events in the F/TAF group and only one in the F/TDF group. No cases of proximal tubulopathy or Fanconi syndrome were documented in either group.

Statistically significant differences in bone mineral density (BMD) through week 48 were also reported. Mean BMD measurements of the hip increased 1.14% in the F/TAF group, as compared with a 0.15% decrease in the F/TDF group ($P < 0.001$). Mean BMD measurements of the spine increased 1.53% among those receiving F/TAF, as compared with a -0.21% decrease among those in the F/TDF group ($P < 0.001$). More

study participants in the F/TAF group also experienced a >3% improvement in BMD from baseline to week 48, as compared with those who remained on F/TDF (hip: 17% versus 9%, respectively, $P = 0.003$; spine: 30% versus 14%, respectively, $P < 0.001$).

Bone fractures were uncommon in both groups: one patient in the F/TAF group and two patients in the F/TDF group. The study investigators conclude that all fractures were related to trauma, not to the study drugs. The investigators also rightly comment that longer term data from observational cohort studies are necessary to establish whether the use of TAF, as compared with TDF and independent of other risk factors, is associated with a reduction in frailty fracture risk.

Notably, fasting lipid levels increased in the F/TAF group, whereas they remained stable in the F/TDF group: a 14 mg/dL total cholesterol increase in the F/TAF group, as compared with a 1 mg/dL increase in the F/TDF group; a 13 mg/dL increase in LDL cholesterol versus a 4 mg/dL increase; a 2 mg/dL HDL cholesterol increase versus a 1 mg/dL decrease; and a 10 mg/dL increase in triglycerides versus a 2 mg/dL decrease. However, changes in total cholesterol to HDL ratio were minimal (0.1 versus 0.0; $P = 0.073$). Approximately 4% of participants in both groups began a lipid-lowering agent through week 48.

SELECT DRUGS AND COFORMULATIONS IN PHASE III DEVELOPMENT

Doravirine (MK-1439)

Data from 48 weeks of a phase II clinical trial evaluating doravirine (MK-1439) were presented at CROI.²⁴ Doravirine is Merck's once-daily NNRTI, which can be taken with or without food. Its potential for fewer drug-drug interactions compared with other NNRTIs is notable, as it is neither an inducer nor an inhibitor of CYP3A4.

This was a two-part study. Part 1 was a dose-ranging evaluation of 25, 50, 100, and 200 mg of doravirine, with the 100-mg dose being ultimately selected for further safety and efficacy evaluation in part 2. Combined results were presented at CROI for the 42 participants randomized to doravirine 100 mg in part 1 of the study, 66 additional participants who received doravirine in part 2 of the study, and 109 participants who received efavirenz. Both doravirine and efavirenz were combined with TDF/FTC.

Approximately 90% of the study participants were men, 75% were white, and the mean age at entry was 35 years. The median CD4⁺ cell count and viral load at baseline were 425 cells/mm³ and 2.6 log copies/mL, respectively.

At week 48, there were slightly fewer discontinuations in the doravirine group compared with the efavirenz group (12% versus 14.7%), which included fewer discontinuations because of side effects (2.8% versus 5%). Virologic suppression (<40 copies/mL) rates were 77.8% and 78.7% in the doravirine and efavirenz groups, respectively (difference: -1.1%; 95% CI: -12.2 to +10.0). Although virologic suppression rates were also comparable in patients with baseline viral loads <100,000 copies/mL, with approximately 87% of the patients having viral loads <40 copies/mL at week 48, rates appeared to be greater in the efavirenz group among those starting therapy with viral loads $\geq 100,000$ copies/mL: 84% versus 74% among those receiving doravirine.

Drug-related adverse events, including diarrhea, dizziness, and abnormal dreams, were less common in the doravirine group than the efavirenz group (56.5% versus 31.5%, for a difference of -25.0%; 95% CI: -37.3 to -11.8). Laboratory abnormalities were generally grade 1 or 2, with lipid, liver enzyme, and lipase data generally favoring the doravirine group, and grade 2 fasting glucose abnormalities being slightly more common in the doravirine group (3.2% versus 1.1%).

Merck is continuing its phase II/III clinical development program evaluating the safety and efficacy of a single-tablet regimen (MK-1439A) containing doravirine, TDF, and 3TC.^{25,26,27,28} The company is also conducting a phase II trial enrolling treatment-naïve individuals with transmitted NNRTI-resistant HIV, based on doravirine's in vitro activity against common NNRTI resistance mutations.^{29,30} Also in development are nanoformulations of doravirine for potential long-acting dosing.³¹

Fostemsavir (BMS-663068)

Fostemsavir is an oral prodrug of the HIV attachment inhibitor temsavir (BMS-626529), which prevents attachment to host CD4 cells by binding to HIV gp120. It is currently in a phase III clinical development program that is focused on heavily treatment-experienced patients and is one of several compounds included in ViiV Healthcare's acquisition of BMS's HIV portfolio of HIV research and development assets.³² BMS will, however, continue to be responsible for the ongoing phase III clinical trial until completion.

Open-label continuation data from an international phase IIb dose-ranging study were reported at CROI 2016.³³ These data follow 24-week primary endpoint and 48-week follow-up results that were published earlier this year and at CROI 2015, respectively.^{34,35}

The trial randomized 254 treatment-experienced participants, all of whom had virus susceptible to raltegravir, TDF, and atazanavir, to receive fostemsavir at doses of 400 mg twice daily, 800 mg twice daily, 600 mg once daily, or 1,200 mg once daily, compared with ritonavir-boosted atazanavir (ATV/r), all in combination with raltegravir and TDF. Sensitivity to temsavir was also an entry requirement (IC50 < 100 nM).

The median age at baseline was 39 years, 60% of the participants were male, and 38% were white. The median pretreatment viral load was 4.85 log copies/mL (43% had viral loads >100,000 copies/mL), and CD4 count was 230 cells/mm³ (38% with <200 CD4 cells/mm³).

Given that fostemsavir 1,200 mg once daily was selected as the open-label continuation dose after week 48, the results reported at CROI 2016 were the pooled efficacy and safety data through week 96.

At week 96 in the modified intent-to-treat analysis, 61% in the fostemsavir group, compared with 53% in the ATV/r group, had viral loads <50 copies/mL. In the observed analysis, the proportion of patients with viral loads <50 copies/mL was 90% in both groups, with comparable efficacy regardless of baseline temsavir sensitivity (<0.1 nM versus ≥0.1 nM, <1 nM versus ≥1 nM, and <10 nM versus ≥10 nM).

CD4 count gains were similar across all groups, with mean increases of 219 cells/mm³ in the fostemsavir group and 250 cells/mm³ in the ATV/r group, according to an observed analysis of the pooled 96-week data.

Ten participants discontinued treatment as a result of adverse events: five (10%) in the atazanavir group and five (2.5%) in the fostemsavir group. Abdominal pain, nausea, and headache were among the most common side effects, although most occurred in the atazanavir group. Similarly, elevations in bilirubin occurred in 31 of 51 (62%) participants in the atazanavir group, compared with no cases of hyperbilirubinemia or jaundice in the fostemsavir group. Laboratory abnormalities were uncommon among those receiving fostemsavir, with grade 3–4 ALT, AST, creatinine kinase, fasting glucose, and uric acid abnormalities occurring in less than 5%.

A phase III trial of fostemsavir in treatment-experienced patients was started in February 2015 (study A1438-047).³⁶ Approximately 410 participants will be enrolled. Entry criteria include detectable viral load of >400 copies/mL on current ART and resistance, intolerance, or contraindications to drugs in at least three classes. Participants must be taking at least one, but no more than two, active approved drugs to be eligible for the randomized, placebo-controlled eight-day monotherapy arm of the study. Optimized background therapy is added after day 8, with all participants receiving open-label fostemsavir (600 mg twice daily) for at least 48 weeks.

Participants without any remaining fully active approved ARVs may enroll in an open-label cohort. This arm includes the option of using the experimental monoclonal antibody ibalizumab to prevent functional monotherapy, although ibalizumab has to be procured by the individual participant and is not provided as part of the study.

The difficulty in enrolling such an experienced patient group has led to this international study having 168 trial sites in multiple countries.

GS-9883

GS-9883 is a Gilead INSTI that, unlike its predecessor elvitegravir, does not require boosting. It is currently being studied in a single-tablet regimen that also contains TAF and FTC.

Although the 9883/F/TAF coformulation is currently in the phase III stage of development, little to no data from phase I evaluations or ongoing phase II trials have been reported. Phase II data are, however, anticipated at the 21st International AIDS Conference (IAC) in July.

Phase III trials of 9883/F/TAF include two head-to-head comparisons with dolutegravir plus F/TAF in treatment-naïve adults, with each study enrolling 600 participants in the U.S., Canada, Belgium, France, Italy, Germany, United Kingdom, Spain, Australia, and the Dominican Republic.^{37,38} Three phase III switch studies are also under way: one evaluating the safety and efficacy of switching from dolutegravir plus abacavir/lamivudine (ABC/3TC) to 9883/F/TAF; the second evaluating a switch from boosted atazanavir or darunavir plus either F/TDF or ABC/3TC; and the third evaluating a switch in a cohort comprised of HIV-positive women—all in virologically suppressed participants.^{39,40,41}

Raltegravir

Merck has announced via press release that the company's investigational once-daily formulation of raltegravir (needing two 600 mg tablets for the single dose) was statistically non-inferior to the currently approved formulation requiring a 400 mg BID dosing schedule.⁴² Results from the phase III ONCEMRK trial, which Merck says also met its secondary endpoints of tolerability and changes in CD4 cell counts, are anticipated at the 21st IAC. Applications for licensure will also be filed with the FDA and the European Medicines Agency (EMA) later this year.

Darunavir/Cobicistat/Emtricitabine/TAF (D/C/F/TAF)

Janssen's D/C/F/TAF coformulation is currently in phase III trials. Because of initial concerns about three-way drug-drug interactions involving TAF, darunavir, and cobicistat, FDA approval based solely on bioequivalence data—similar to those used to support the NDAs for Odefsey and Descovy—was not possible. Fully powered non-inferiority registrational trials were required by the agency.

One trial is evaluating the efficacy of safety of D/C/F/TAF compared with coformulated darunavir/cobicistat plus coformulated F/TDF in treatment-naïve individuals.⁴³ The second trial is comparing safety and rates of maintained virologic suppression in individuals switching to D/F/TAF compared with those remaining on a boosted protease inhibitor plus F/TDF.⁴⁴

SELECT DRUGS AND COFORMULATIONS IN PHASE II DEVELOPMENT

Long-acting Cabotegravir and Rilpivirine

Long-acting formulations of ARVs have the potential to improve clinical outcomes, particularly for individuals for whom adherence continues to be difficult or infrequent injectable dosing is preferable to daily pills. These slow-release formulations might also have better tolerability, including fewer gastrointestinal-related adverse effects. In addition, they may be cheaper than oral formulations to produce, given that they use less API and packaging and generate fewer distribution costs, and could potentially help overcome a key global concern of stock-outs in low-income countries.

Although many people are excited to have this option, a potential disadvantage, compared with daily oral drugs, involves the difficulty of withdrawing drug in case of adverse reactions or drug interactions. An additional concern is the move to less-frequent (perhaps annual) CD4 and viral load monitoring and, with it, the risk of drug resistance accumulating for many months in the case of viral rebound.

Similar concerns relate to missed injections, whether from adherence or supply issues.

Nanoformulations of the INSTI cabotegravir (CAB) and the NNRTI rilpivirine (RPV) are furthest along the pipeline, both of which extend drug exposure and are delivered by intramuscular (IM) injections. As a two-drug maintenance therapy, coadministered oral versions of both drugs had comparable efficacy to a three-drug, efavirenz-based regimen over 96 weeks of follow-up in the phase IIb LATTE-1 study.⁴⁵

Results from LATTE-2, a phase IIb trial evaluating the long-acting versions of CAB and RPV as maintenance therapy, were reported at CROI 2016.⁴⁶ The study began with oral CAB plus abacavir/lamivudine (ABC/3TC) treatment for 20 weeks, with oral RPV being used for the last 4 weeks of the induction phase. The study enrolled 309 treatment-naïve patients; 91% had undetectable viral loads at week 20 and were randomized 2:2:1 to one of three open-label arms: CAB 400 mg plus RPV IM every four weeks (Q4W), CAB 600 mg plus RPV 900 mg IM every eight weeks (Q8W), or oral CAB 30 mg plus ABC/3TC.

Baseline CD4 and viral load were 489 cells/mm³ and 4.3 log copies/mL (with 18% >5 logs). Only 8% of participants were women and 15% were black/African American.

At week 32 of the trial's maintenance period, viral suppression was documented in 94% (treatment difference versus the oral regimen: 2.8%; 95% CI: -5.8% to +11.5%), 95% (difference: 3.7%; 95% CI: -4.8% to +12.2%), and 91% of participants in the Q4W, Q8W, and oral groups, respectively. These findings met the pre-specified threshold for concluding that the long-acting regimen is comparable to the oral regimen. Virologic non-response rates were slightly lower in the Q4W group (<1% versus 4% in the other groups), with lower non-virologic reasons (e.g., adverse events) for discontinuation in the Q8W arm (<1% versus 5% in each of the other two groups).

There were two protocol-defined virologic failures (confirmed viral load >200 copies/mL), one in the Q8W group and the other in the oral regimen group, with no evidence of INSTI, NRTI, or NNRTI resistance.

Excluding injection site reactions (ISRs), tolerability was good, but higher rates of fever (3%), fatigue (3%), and flu-like illness (2%) were observed in a combined analysis of the injection groups, as compared with a single report of fatigue in the oral regimen group. None of the grade 3–4 side effects were judged to be related to the study drug, including a single death that was related to epilepsy.

Reports of ISRs were common, but decreased over the 32-week follow-up period: 86% in the combined IM groups at day 1 and 33% at week 32. Most ISRs were grade 1 (80%) or grade 2 (19%) and lasted for a median duration of three days (with 90% lasting less than seven days). The most common ISR manifestations were pain (67%), swelling (7%), and nodules (6%). Only two participants stopped as a result of ISRs.

In a patient satisfaction survey, more than 95% of participants reported injections were preferable to the daily oral induction phase and that they would be willing to continue injection in the future.

In the PK analysis, mean plasma cabotegravir levels stayed between the 10–30-mg target concentrations established in LATTE-1, with troughs that were well above the protein-adjusted IC₉₀ (PA-IC₉₀). Although rilpivirine levels also remained well above the PA-IC₉₀, levels were lower over the first 16 weeks of IM dosing than with what was seen with 25-mg oral dosing. This was highlighted as an area that will require further study in the final dose selections for phase III trials.

BMS-955176

BMS-955176 is a second-generation maturation inhibitor that targets the final stage of HIV Gag processing, resulting in the production of immature, non-infectious virions. It is one of the products in the pipeline portfolio sold by BMS to ViiV Healthcare, along with a back-up maturation inhibitor candidate, BMS-986173.

In part A of a proof-of-concept study reported at CROI 2015, ten days of BMS-955176 monotherapy led to maximum median viral load declines that plateaued at roughly 1.64 log copies/mL at doses of 20–120 mg once daily.⁴⁷ BMS-176 showed similar antiviral activity in subjects with either wild-type HIV or HIV with Gag polymorphisms, and in subjects with either HIV-1 subtype B or subtype C, unlike its first-generation predecessor bevirimat. Data from part B of the study, evaluating BMS-176 in combination with atazanavir (with or without ritonavir boosting) in an expanded cohort of 28 subtype B and protease inhibitor- and maturation inhibitor-naïve HIV-positive volunteers, were reported at the 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in July 2015. Patients were randomized to one of four treatment groups: BMS-176 40 mg plus r/ATV 100/300 mg, 40 mg BMS-176 plus ATV 400 mg, BMS-176 80 mg plus ATV 400 mg, or r/ATV plus TDF/FTC.

Median age at baseline was 32 years, 100% of the 28 participants were male, and 90% were white. Median baseline CD4 T cells and viral loads ranged from 430 to 580 cells/mm³ and 4.0 to 4.4 log copies/mL across arms.

Median viral load changes at day 29, the study's primary endpoint, ranged from –1.6 to –2.2 logs in the BMS-176 groups, compared with –2.2 in the standard-of-care group. Study participants in the BMS-176 groups also had similar maximum median declines in viral loads through day 42 of the study, compared with those in the standard-of-care arm (–1.86 to –2.23 versus –2.39 log copies/mL, respectively).

BMS-176 was generally well tolerated, with no adverse events leading to discontinuation. BMS-176 plus unboosted ATV was associated with lower median changes from baseline in bilirubin levels compared with the arms with boosted ATV (41.8 to 60 mmol/L versus 7.7 to 11.8 mmol/L, respectively).

Phase II studies that are underway include a safety and efficacy comparison with efavirenz (with both BMS-176 and efavirenz combined with TDF/FTC) and an open-label evaluation of BMS-176 combined with dolutegravir and atazanavir in treatment-experienced adults. Pharmacokinetics and additional safety trials are also ongoing.^{48,49,50}

SELECT DRUGS AND COFORMULATIONS IN PHASE I DEVELOPMENT

MK-8591

Merck's MK-8591, formerly known as EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine), is an NRTI acquired by Merck from the Chōshi, Japan-based Yamasa Corporation.⁵¹ Preclinical data have established that the properties of MK-8591 are ideal for long-acting administration, both as treatment and pre-exposure prophylaxis (PrEP).

Latest reports include data from a dose-ranging study in SIV-infected macaques that were given MK-8591 once a week. Viral load and PK results were then used to determine oral doses in a phase I evaluation that involved HIV-negative individuals, as well as dose selections for the development of long-acting injectable formulations.⁵²

Baseline SIV viral load ranged from six to eight log copies/mL. Following single doses ranging from 3.9 to 18.2 mg/kg, viral load dropped by approximately 1.5 logs (maximal 2-log drops) and was sustained for at least seven days.

PK data from the multiple-dose study in HIV-negative adults (using 10 mg, 30 mg, and 100 mg once-weekly for three weeks) revealed that, with the 10 mg dose, target intracellular drug concentrations were exceeded for more than seven days.

Early data on a solid-state slow release parenteral injection formulation that has an option for removability showed sustained release for more than 180 days in rat studies, with the potential to provide coverage for up to one year.

Also available are early results from a phase Ib evaluation of MK-8591 in HIV-positive, treatment-naïve individuals receiving a single dose across a range of doses, with safety, PK, and viral load data from the 10 mg dosing group reported at CROI 2016.⁵³ At seven days (168 hours) post-dose, the mean viral load reduction was 1.67 log copies/mL (95% CI: 1.47–1.87), with a mean reduction of 1.78 log copies/mL (95% CI: 1.59–1.98) through day 10. The 10 mg dose was generally well tolerated with a limited number of mild-to-moderate side effects: headaches in all six study volunteers.

Phase II evaluations of MK-8591 are planned, but have not yet been announced.

SELECT BIOLOGICS IN DEVELOPMENT

A number of biologic agents are being studied for their potential in treatment, prevention, and cure research. These are gene- and cellular-based products that are composed of sugars, proteins, and/or nucleic acids that differ from conventional ARV drugs. Notable candidates include the Adnectins-based entry inhibitor BMS-986197 and the monoclonal antibodies PRO 140 and ibalizumab, which are discussed briefly below. The broadly neutralizing antibody VRC01 is currently undergoing extensive clinical evaluation for primary HIV prevention (see "Preventive Technologies," page 83) and as a potential strategy for controlling HIV without ARVs (see "Research Toward a Cure," page 109).

Ibalizumab (TMB-355)

As a monoclonal antibody, ibalizumab binds to CD4 and blocks HIV entry post-attachment. It is being developed, albeit slowly, by TaiMed Biologics and has been granted orphan designation by the FDA due to its

limited, but important, treatment potential as a regimen component for people with cross-class-resistant HIV. If approved, it will be marketed and distributed in the U.S. and Canada by Theratechnologies.⁵⁴

For treatment-experienced patients requiring ibalizumab to construct a viable or tolerable ARV regimen, two open-label phase III trials have been initiated by TaiMed to help satisfy FDA registrational requirements, along with a compassionate use program.^{55,56,57} In addition, heavily treatment-experienced patients have been enrolled in the nonrandomized arm of the phase III evaluation of the ViiV Healthcare attachment inhibitor fostemsavir to use ibalizumab to help optimize treatment outcomes.³⁷

Ibalizumab requires intravenous infusion and is currently being evaluated using doses administered once every two or four weeks.

PRO 140

PRO 140, originally developed by Progenics and now owned by CytoDyn, is a monoclonal antibody targeting CCR5. Though no new data have been published or presented for peer review since 2010, the company will present data from a 16-patient extension stage of a phase IIb study at the June 2016 American Society for Microbiology conference (taking place as this chapter goes to press).⁵⁸ According to the published abstract, 15 patients were included in the analysis – all of whom had suppressed viral loads before switching to stand-alone PRO 140 (350 mg) self-administered subcutaneously once a week – with 11 patients remaining on PRO 140 maintenance therapy for at least one year. Three of the 15 (20%) evaluable study volunteers experienced virologic failure with a median time of 169 days; all were successfully restarted on standard ARV regimens.

Additional phase II and III trials are planned or under way. These include CD02, a phase IIb/III two-part study evaluating the safety and efficacy of PRO 140 used in conjunction with a failing regimen for one week in treatment-experienced patients with CCR5-tropic virus, followed by PRO 140 combined with an optimized background regimen for 24 weeks.⁵⁹ Data from this study will be used to support an initial indication for treatment-experienced individuals, potentially through the FDA's accelerated approval mechanism.

A second phase III study is planned that will explore PRO 140 as maintenance treatment administered once weekly without ARVs. It is also being studied as a potential prophylaxis in transplant patients that are at risk for graft-versus-host disease.⁶⁰

BMS-986197

Adnectins are engineered versions of proteins that possess antibody-like binding characteristics. Using a combination of Adnectins targeting CD4 and a region of gp41, as well as a peptide fusion inhibitor that also targets gp41, BMS developed the Combnectin BMS-197, a long-acting biologic with three independent and synergistic modes of HIV entry inhibition that could potentially be self-administered as a long-acting subcutaneous injection.

Preclinical data were presented at CROI 2016.⁶¹ The independent EC50s of the anti-CD4 Adnectin, anti-gp41 Adnectin, and fusion inhibitor peptide were 8.5 nM, 5.4 nM, and 0.4 nM, respectively. Combining the two Adnectins increased potency over 100-fold to ~30 pM; adding the fusion inhibitor peptide increased the barrier to resistance. Adding a fourth element to the mix, human serum albumin (HSA), decreased potency to 0.27 nM, but improved PK—a half-life of 30 hours was documented when a combination of all four biologics were administered subcutaneously to cynomolgus monkeys.

In addition to in vitro findings of antiviral activity against a range of clinical HIV isolates, data from evaluations of BMS-197's efficacy in a mouse model of infection were also reported. Three doses of BMS-197 were

administered to the HIV-infected mice and compared with those treated with a placebo or a standard ARV regimen (raltegravir plus TDF/FTC). Dose-dependent decreases in viral load were reported, and efficacy at the highest BMS-197 dose was similar to that of ART. Adding to the potential for long-acting administration were data indicating that receptor occupancy and PK were consistent over 36 days in the mice.

BMS-197 is now a part of ViiV Healthcare's portfolio of pipeline products; additional preclinical and human studies are anticipated.

SIDEBAR: Dolutegravir: Mono and Dual Therapy

A group of studies presented at the 15th European AIDS Conference in October 2015—some of which have since been published—showed remarkable results using dolutegravir either as monotherapy or in dual therapy with 3TC.

These were mostly small, observational, uncontrolled studies, but the results would not have been possible with any other drug. Dolutegravir has demonstrated a very high barrier to resistance in vitro and treatment-naïve studies. One proposed mechanism relates to both a longer half-life and a deeper binding site. Another is that dolutegravir targets an essential and highly conserved region of the viral genome and that any mutations make the virus incapable of further replication. At least six independent research groups recognized these properties and, together with a clinical need in some patients, believed that this strategy was worth studying.

This need for reduced treatment included study participants, now in their 50s and 60s, who had limited HIV treatment options as a result of side effects, drug interactions, or other contraindications. Many trial volunteers had been HIV positive for more than 20 years and most were highly treatment experienced. For the majority, however, viral suppression below 50 copies/mL was sustained for more than six months on dolutegravir monotherapy.

Unlike maintenance therapy using boosted protease inhibitor (PI) monotherapy, there was no evidence of viral load blips or even changes in low-level viremia below 50 copies/mL when switching to dolutegravir as the only drug. Also unlike boosted-PI studies, however, the few patients with viral rebound did develop mutations associated with dolutegravir resistance. These cases tended to be people with previous integrase inhibitor experience (although no integrase mutations were detected at baseline). Poor adherence was a factor in at least two cases, but not in all of them. Switching back to triple therapy re-suppressed viral load in participants in which adherence was good.

Similar results were reported when dolutegravir was used as dual therapy with 3TC in people starting their first treatment. Viral load became undetectable within eight weeks in all participants, including those with baseline viral load >100,000 copies/mL.

Longer follow-up is essential, as the duration of previous viral suppression on ART might be a factor in the good outcomes. However, if viral suppression is sustained with longer follow-up, this has the potential to radically change the management of HIV globally.

Tables 2 and 3 summarize the current data and planned studies for dolutegravir monotherapy and dual therapy with 3TC. All monotherapy studies are switching people with undetectable viral loads on their current treatment regimens.

Crucially, thanks to negotiations by the Clinton Health Access Initiative (CHAI) and others, generic dolutegravir is expected to be available in low-income countries by 2017 at less than US\$50 a year, which is comparable to generic efavirenz.⁶² This makes the results of these studies compelling for the way ART will be prescribed globally.

Even if these strategies can only be guaranteed for shorter periods—effective for up to a year, for example—they have the potential to improve the quality of life for people in all countries who are struggling with the complexities of ART with other comorbidities.

Table 2. Summary of Studies Using Dolutegravir (DTG) Monotherapy

Study	Details	Results	Comment
Retrospective analysis of treatment-experienced patients who switched to DTG monotherapy ⁶³	N = 33; median age, 56 years; median HIV duration, 19 years (IQR: 17–23); median HIV suppression, 8 years (IQR: 4–13); 40% with history of AIDS	32/33 <37 copies/mL at 24 weeks; no change in viral dynamics at levels <37 copies/mL	One case of viral rebound in complex patient with integrase inhibitor (INSTI)-experience and poor adherence; included INSTI mutation I18R at week 24
Single-arm observational pilot switch in treatment-experienced patients ⁶⁴	N = 28; median age, 48 years; median HIV duration, 20 years; median HIV suppression, 6 years (IQR: 3–8)	25/28 <50 copies/mL at 24 weeks; 24/25 <20 copies/mL	Three cases of viral rebound in patients with prior INSTI experience, but with good adherence. All <50 copies/mL with triple therapy
Retrospective data from case notes in treatment-experienced patients switched to DTG monotherapy ⁶⁵	N = 52 (N = 21 monotherapy); median follow-up, 27 weeks (IQR: 24–40)	21/21 remained <50 copies/mL	No cases of viral rebound
Single-arm observational pilot study ⁶⁶	N = 5	4/5 remained undetectable	Viral rebound included possible drug interaction with multivitamins. A larger randomized study has started based on these results
Single-arm, open label, retrospective case notes ⁶⁷	N = 9 (7 men, 2 women); treatment naïve; baseline viral load (VL), 16,000–90,000 copies/mL; median age, 45 years; median duration of infection, 8 years	All VL <50 by week 4 and <20 copies/mL by week 24	Patient group who refused ART and only started because of the simplicity of DTG monotherapy
Randomized, controlled, 48-week switch study in treatment-experienced patients (DOMONO) ⁶⁸	N = 104; randomized to immediate switch to DTG monotherapy or deferred switch after 24 weeks	Currently enrolling in the Netherlands	Final results after January 2017
Randomized, controlled study in treatment experienced patients with VL <50 copies/mL on current ART (DOLAM) ⁶⁹	N = 450; randomized 1:1:1 to DTG, DTG + 3TC, or current treatment (control)	Currently enrolling in Spain. Phase 1 was judged safe in March 2016 based on three-month results, allowing rollout to 450 patients	Largest randomized study to date; results expected after October 2017
Randomized, controlled switch study in patients treated for primary HIV infection with VL <50 copies/mL for at least 48 weeks ⁷⁰	N = 138; randomize 2:1 to DTG mono vs. current treatment (control).	Currently enrolling in Switzerland.	
Single-arm, open-label switch study in patients with VL <50 copies/mL ⁷¹	N = 10	Enrolling expected to start in June 2016 (in Switzerland)	Results expected 2017
Randomized, controlled switch study in patients with suppressed VL on DTG/abacavir/3TC ⁷²	N = 160	Enrolling in France	Final results expected after April 2018

Table 3. Summary of Studies Using Dolutegravir Dual Therapy with 3TC*

Study	Details	Results	Comment
Single-arm, open-label, 96-week study in treatment-naïve patients with VL <100,000 copies/mL ⁷³	N = 20; baseline VL was >100,000 copies/mL in four patients	Interim results: 20/20 <400 copies/mL by week 3 and 20/20 <50 copies/mL by week 8, sustained to week 24	Study ongoing for longer follow-up to 96 weeks
Retrospective data from case notes of treatment-experienced patients switched to DTG + another drug ⁶⁶	N = 31; median follow-up, 45 weeks (IQR 25 to 70)	30/31 maintained VL <50 copies/mL	One case of viral rebound in person using DTG + maraviroc
48-week switch study in virologically suppressed patients with intolerance to NRTIs (DOLBI) ⁷⁴	N = 100	Currently enrolling	Results expected after December 2016
Open-label, single-arm 48-week ACTG study in treatment-naïve patients ⁷⁵	N = 120	Currently enrolling	Results expected after November 2016
56-week ANRS switch study in virologically suppressed patients (LAMIDOL) ⁷⁶	N = 110; includes semen substudy	Fully enrolled	Results expected after April 2017
Randomized, controlled, 48-week switch to open-label dual therapy vs. current ART (ASPIRE) ⁷⁷	N = 90	Currently enrolling in U.S. sites	Sponsored by ViiV

*Several dual therapy studies are also ongoing using dolutegravir plus a boosted PI. These are of less interest because, compared with 3TC, boosted PI therapy is associated with a higher rate of side effects, potential drug interactions, and a requirement to take with food.

CONCLUSION

A number of compounds with potentially significant value to people living with HIV continue to make their way through the development pipeline.

The approvals of three TAF-inclusive coformulations are welcomed additions, particularly after being priced in parity with their TDF-inclusive predecessors. Gilead's strategy to maximize the number of people switching from the older TDF coformulations before its 2017 patent expiry may provide only short-term financial benefits, however, particularly if regimens containing generic TDF end up being considerably cheaper than those containing TAF. Not only should generic versions of remarkably safe and effective products themselves provide some relief to cash-strapped payers, they should rightly be considered as price and cost benchmarks with which new and innovative products with unclear clinical safety or efficacy advantages must be compared.⁷⁸

The price of Merck's single-tablet regimen containing doravirine in combination with off-patent TDF and 3TC (MK-1439A) will be crucial for whether the company is able to compete against the FDC market dominance of Gilead and ViiV.

For treatment-experienced individuals, the advancement of fostemsavir and the continued development of BMS-955176 illustrate exciting and encouraging options for the small group of people with cross-class resistance. The slow, but steady, advancements of ibalizumab and PRO 140 may also help this population.

The clinical advancement of long-acting cabotegravir and rilpivirine continues to show great promise as an alternative to daily oral therapy.

Finally, if additional evaluations of simplified treatment using dolutegravir monotherapy or dual therapy with 3TC sustain the promise in early studies—we will have the first randomized data within a year—the pressure for cheaper treatment⁷⁹ will only intensify and potentially usher in significant changes in ART prescribing practices within three years.

RECOMMENDATIONS

- With some major pharmaceutical manufacturers retreating from the ARV research and development space, the industry partners that remain should strengthen their resolve to meet the ARV safety, efficacy, acceptability, and affordability challenges that remain in low-, middle-, and high-income countries.
- Manufacturers must commit to the drug prices required to achieve cost-contained HIV care and service delivery in high-income countries.
- Manufacturers must also commit to meet the treatment access needs in middle-income countries, which will be home to 70% of people living with HIV before the end of this decade and are facing both funding losses from donor agencies as well as crippling intellectual property rules that will block access to affordable generics.
- Manufacturers developing new oral drugs are strongly encouraged to follow the emerging trend of evaluating coformulations with historically potent and safe generic ARVs, notably TDF and 3TC. However, these fixed-dose combinations must be priced accordingly.
- The development of new drugs for treatment of cross-class-resistant HIV should remain a priority. It is very encouraging to see progress in this area. For drugs with limited indications, including those without clear marketing potential for treatment-naïve individuals, the Orphan Drug Designation program should be explored and engaged.
- Manufacturers should continue to closely collaborate with, and invest heavily in, evidence-based research, implementation science, policy advocacy, and service delivery aimed at improving HIV diagnosis and clinical care engagement rates. Their efforts should aim to maximize virologic suppression rates required to improve disease-free mortality and prevent ongoing transmission of the virus.

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EACS: European Conference on AIDS

IAS: IAS Conference on HIV Pathogenesis, Treatment and Prevention

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Fit for Purpose: Antiretroviral Treatment Optimization

By Polly Clayden

INTRODUCTION

Since the 2015 *Pipeline Report* global antiretroviral treatment (ART) guidelines have moved to recommending “treat all” HIV positive people. With this recommendation comes the massive task of starting and keeping everyone with HIV on ART.

ART optimization is one of many critical steps to universal access to HIV treatment that is: safe, effective, tolerable, durable, simple and affordable.

Antiretrovirals can sometimes be optimized by dose reduction.^{1,2} Reducing an approved dose of a drug might be possible, because when new ones are developed, the highest tolerated doses in phase II are usually selected for phase III and approval. In some cases lower doses might have equivalent efficacy and better tolerability – as has been shown with efavirenz (EFV).³

But since discussions on treatment optimization began the field has evolved and newer, better, and lower dose antiretrovirals have been approved.^{4,5} With a couple of exceptions, treatment optimization has shifted away from making older drugs more efficient. Speeding up the introduction of generic versions of newer drugs – in appropriate regimens and formulations – into low-and middle-income countries (LMIC) – is now the main focus of ART optimization.⁶

Experts now agree on a short list of antiretrovirals that have shown superior or non-inferior efficacy compared to existing recommended ones. These drugs offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for fewer side effects.^{7,8} The antiretrovirals are: dolutegravir (DTG), tenofovir alafenamide (TAF), efavirenz (EFV) 400 mg, and darunavir/ritonavir (DRV/r).

Over the past year there have been several important steps towards optimized treatment using these drugs:

- DTG and EFV 400 mg are now included in 2015 World Health Organization (WHO) guidelines as alternative first-line options.⁹
- The first generic version of DTG was submitted to the US Food and Drug Administration (FDA) for tentative approval and should be approved anytime soon.¹⁰
- The US FDA approved the originator manufacturer’s 25 mg TAF-containing co-formulation.¹¹
- Several important ART optimization studies, that will provide evidence for future first- and second-line recommendations, have been designed and funded or are seeking funding.^{12,13}

This commentary gives an update on adult antiretroviral treatment optimization trials and strategies – both ongoing and planned – and pipeline products for LMIC. It also looks at missing evidence that is needed to change current recommendations.

WHO 2015 Guidelines

The newly published WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV*¹⁴ – for which there have already been a couple of sneak previews and a policy brief^{15,16,17} – include 10 new recommendations. Universal eligibility for ART (treat all) is the most important of these – so more people will start ART earlier.

The preferred and alternative first-line ART regimens are shown in Table 1. The preferred regimens remain the same as 2013 recommendations. This is unsurprising: at a WHO Think Tank convened in February 2015,¹⁸ the expert group recognized that a greater body of evidence supports the use of EFV 600 mg first-line (an estimated 15 million patient years when combined with tenofovir disoproxil fumarate [TDF] and XTC – meaning either emtricitabine [FTC] or lamivudine [3TC]). The group suggested that this evidence provides a level of confidence that is not currently there with the alternatives. A year later the same group arrived at much the same conclusion.¹⁹

For adults and adolescents the alternatives include the introduction of EFV 400 mg and DTG. More information is needed on how they are likely to perform in real world, LMIC settings for these two alternatives to be recommended in WHO guidelines without restriction. Populations in such settings include larger proportions of women of childbearing age, children, and people with tuberculosis (TB), malaria, and other coinfections.²⁰

Table 1: WHO 2015 preferred and alternative first-line adult ART regimens

First line ART	Preferred regimens	Alternative regimens
Adults	TDF+3TC (or FTC)+EFV	AZT+3TC+EFV (or NVP) TDF+3TC (or FTC)+DTG TDF+3TC (or FTC)+EFV400 TDF+3TC (or FTC)+NVP
Pregnant/breastfeeding women	TDF+3TC (or FTC)+EFV	AZT+3TC+EFV (or NVP) TDF+3TC (or FTC)+NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

New recommendations for second-line ART are shown in Table 2. Those include DRV/r or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r).

Similarly to the 2013 guidelines, third-line includes new drugs (if available) with the least risk of cross-resistance to those used already.

Table 2: WHO 2015 preferred and alternative second- and third-line adult ART regimens

First line ART	Preferred regimens	2nd-line regimens	3rd-line regimens
Adults	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r + 2 NRTIs + NNRTI
		2 NRTIs + DRV/r	Optimize regimen using genotype profile
Pregnant/breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	

Key: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NRTI, nucleoside/nucleotide reverse, transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir.

New drugs and formulations will support the guidelines and drive the next major drop in ART costs

EFV 400 mg, DTG and TAF (the later not yet recommended by WHO but studies in LMIC are on the way) are expected to make up a large chunk of the adult first-line market over the next five years, and contribute to ART cost reductions, according to recent projections by The Clinton Health Access Initiative (CHAI).²¹

CHAI's ARV Market Report – now in its 6th year – provides a global perspective on the antiretroviral marketplace in LMIC each year and describes the organization's expectations of the market's evolution over the subsequent five years.

By the end of 2014, 13.5 million people were receiving ART in LMIC. ART coverage grew from 15% in 2009 to 40% in 2014 (including all HIV positive people at all CD4 counts) – coverage rates that year were 29% of children and 41% of adults. The pace of scale up in 2014 (another 1.8 million additional people on ART since 2013) was similar to that seen in the previous year (2 million more people on ART from 2012 to 2013). By 2018 several countries are projected to approach universal coverage, including Rwanda, Uganda and Swaziland for adults, and Vietnam for children.

WHO guideline changes will increase the overall antiretroviral market size. Most importantly, the adoption of treat all, so all 36.9 million HIV positive people are eligible for treatment. And the recommendation of oral PrEP for people at risk of HIV, once implemented, will lead to more demand for TDF.

Brazil announced its adoption of treat all in 2013 and saw a 27% increase in people receiving ART in 2014 (coverage went from 39% to 48% by the end of 2014). Brazil's domestic manufacturing capacity distinguishes it from other LMIC and might allow faster ART scale up than elsewhere. Since the WHO recommendation several LMIC, including South Africa, have announced they will adopt treat all.²²

CHAI says that the immediate effect of the treat all recommendation on ART scale up is unclear but as a "conservative" projection 23 million people are likely to be on ART in LMIC by 2019 (95% adults and 5% children).

The report shows how the price of recommended generic antiretrovirals has stabilized and well-established drugs reached the minimum prices at which they can feasibly be produced. Pipeline products are expected to drive the next major drop in ART cost.

Generic accessible LMIC can look forward to several new drugs and formulations for adults, including DTG, EFV 400 mg, and TAF, which are expected to significantly reduce the cost of first-line treatment.

EFV 400 mg and DTG will have a substantial impact on the first-line market by 2019. By this time DTG is predicted to gain 37% and EFV 400 mg 19% of the adult first-line non-nucleoside reverse transcription inhibitor/integrase inhibitor (NNRTI/INSTI) market – respectively 7.2 million and 3.8 million people.

TDF made up 72% of the first-line nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) market in generic accessible LMIC in 2014 – 8.3 million people received this drug as part of adult first-line regimens by the end of that year.

The US FDA first approved TAF as part of an FDC in November 2015,²³ and the dual co-formulation TAF/FTC in April 2016.²⁴ A generic TAF-based FDC is expected mid-2018. With the caveat that various active product ingredients (API) production steps need to be optimized by generic manufacturers, TAF will cost a lot less than TDF as its dose is about 10-fold lower.

Uptake of TAF is likely to begin in the latter half of 2018. In the first year that it is available, TAF is likely to capture up to 22% of the first-line NRTI market in generic accessible LMIC. Eventually TAF is projected to almost entirely replace TDF.

Three new agreements were announced by CHAI, UNAIDS, and UNITAID on World AIDS Day 2015.²⁵ Table 3 shows the generic ART pipeline associated with these agreements.

Table 3: New generic antiretrovirals available 2016/2017 for adults

ARV, co-formulation or FDC	Generic manufacturer	FDA filing
DTG	Aurobindo	May 2015
DTG/TDF/3TC	Aurobindo	Q3 2016
EFV400/TDF/3TC	Mylan	Q1 2016
DRV/r	Hetero	Q3 2016

Key: 3TC, lamivudine; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV400, efavirenz 400 mg, TDF, tenofovir disoproxil fumarate

Under the first, Aurobindo will make generic DTG available for US \$44 per patient per year (pppy), once it has been approved. CHAI and colleagues say the leadership of the government of Kenya partly made this launch price possible. Kenya will include DTG in its national guidelines and start providing it to suitable patients as soon as it is approved. ViiV Healthcare licensed Aurobindo for generic DTG and the single formulation is filed with the US FDA for tentative approval.²⁶

This is the first Abbreviated New Drug Application (ANDA) for a generic version of DTG and has been made within two years from FDA approval of originator DTG for the US. ViiV has provided a selective waiver to the FDA for the five-year period of New Chemical Entity (NCE) exclusivity, which would have prevented tentative approval of Aurobindo's ANDA. This product is expected to gain tentative approval in the first quarter of 2016.

ViiV has also licensed DTG to the Medicines Patent Pool (MPP).²⁷ The first agreements for both adult and pediatric treatment were signed just two months after DTG was approved by the EMA and eight months after FDA approval. The adult agreement was recently extended to include all lower middle-income countries.²⁸

Aurobindo will file a DTG-based FDC with the US FDA by the third quarter of 2016. Several generic manufacturers are working on FDCs of DTG/TDF/3TC.

Secondly, Mylan will file for US FDA tentative approval of an EFV 400 mg-based FDC in the first quarter of 2016. This alternative FDC regimen will be available for US \$99 once approved. This price represents an 8% decrease from current ones, which could mean potential savings of US \$80-100 million globally through 2020.

The third agreement is a partnership between Janssen (the originator manufacturer of DRV) and CHAI to develop and deliver a heat-stable version of DRV/r in LMIC. This boosted protease inhibitor is finally included in WHO guidelines as part of alternative second- and third-line regimens. One reason for this delay was the lack of a generic heat-stable version of DRV/r. As ritonavir is tricky to make in a heat-stable formulation there have been technical hitches with this product development. CHAI is partnering with Hetero to develop the co-formulation – and they seem to have overcome the obstacles. They plan to file for regulatory approval by the third quarter of 2016.

Providing all the work goes according to plan, there should be generic FDCs available to implement WHO first-line recommendations and a new generic option for second- or third-line for adults and adolescents by the end of 2017. CHAI and UNITAID are also committed to supporting other generic manufacturers who can develop these products for stringent regulatory approval and/or WHO pre-qualification. The manufacturers included above are closest to such approval.

By the end of 2025 the introduction of TAF, EFV 400 mg, and DTG into ART programs in LMIC could mean savings up to a whopping US \$3 billion.²⁹

Using their forecast for currently available products as baseline, CHAI modelled differences in prices of new and current products. Their assumptions were: TAF would displace TDF and zidovudine (AZT), and EFV 400 mg and DTG would displace EFV 600 mg and nevirapine (NVP) in first-line; and DTG would replace TDF and AZT-based backbones in second-line.

They estimated price discounts of new products over time using: costs of raw material (either directly from manufacturers or from the India Import/Export database); API process costs (from patents or literature; and formulation costs (assumed API accounts for 70-90% of the cost of formulation and packaging); volumes needed for economies of scale (chemistry inputs based on patents/scientific literature); and manufacturer profit margins (assumed approximately 25%).

The estimated pppy price savings at launch and scaled up with new products are shown in Table 4. Market share of new products and cumulative savings to 2025 are shown in Table 5.

Table 4: Estimated pppy savings with new products

ARV	vs	At launch	At scale
TAF	TDF	\$0-2	\$20-24
EFV400	EFV600	\$10-11	\$10-14
	NVP	<\$1	\$0-2
DTG	EFV600	Parity-slight premium	\$17-21
	NVP	Parity-slight premium	\$1-2

Key: DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV400, efavirenz 400 mg; EFV600, efavirenz 600 mg; NVP, nevirapine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

Table 5: Market share and cumulative savings 2025

ARV	Market share	Saving
TAF	95% of first-line	\$1.8 billion
DTG	80-90% of first-line and second line	\$1.1 billion
EFV400	10-15% of first-line	\$0.3 billion

Key: DTG, dolutegravir; EFV400, efavirenz 400 mg; TAF, tenofovir alafenamide

CHAI expect EFV 400 mg to peak at approximately 25% market share in 2021 before DTG takes over.

After all this good news on potential price savings, one important concern for access to Indian generic products is that the department within the Indian Central Drugs Standard Organization of the Ministry of Health, responsible for regulating medical devices and drugs, the Drug Controller General of India (DCGI), requests clinical trials in India for all new drugs.³⁰ This request can also affect the export of new drugs.

The use of Indian generics to treat HIV is global: Mylan has 30% of the most recent South African tender, covering the three-year period from 1 April 2015 to 31 March 2018.³¹

But the DCGI can waive the local clinical trial requirement for drugs, where the need is considered sufficiently urgent or important. This occurred with sofosbuvir for hepatitis C,³² for example. The generic formulations described here, particularly DTG-based, represent clear cases for such an exception.

TAF, EFV 400 mg, and DTG will enable programs in LMIC to put more people on ART. These findings support advocacy for accelerated availability of these products, and the swift uptake of new antiretrovirals to realize their savings potential.

THE ONES TO WATCH

Efavirenz 400 mg

EFV 600 mg – the currently approved dose – fulfils many of the characteristics in the target product profile as part of an ideal ART regimen. For those who tolerate the drug, it is safe and effective, can be used in pregnancy and in people also receiving TB treatment and needs minimal laboratory monitoring.

But it has a low genetic barrier to resistance. It is also associated with central nervous system (CNS) side effects, which can lead to drug discontinuation, reported in as many as half the people receiving it in settings with access to alternatives.³³ There is also an interaction between EFV and some hormonal contraceptives that can reduce their efficacy.³⁴

A meta-analysis found that over 90% of treatment-naïve people remained on an EFV-based first-line regimen after an average follow up of 78 weeks.³⁵ But CNS side effects were more frequent with this antiretroviral compared to a number of others. HIV positive people and activists have reported these adverse events as flaws of EFV since it was first approved.³⁶

The ENCORE 1 study, showing 400 mg EFV to be non-inferior to 600 mg (both plus TDF/FTC), was completed in July 2013. The 48-week results were published in *The Lancet* in April 2014.³⁷ There were no surprises at 96 weeks.³⁸ The researchers recommend replacing the current EFV dose with the lower one.

The study was conducted in 636 treatment-naïve participants in Europe, Australasia, Latin America, Asia, and Africa.

A very high proportion (approximately 90%) of participants had an undetectable viral load in ENCORE1. Extended follow up to 96-weeks continued to demonstrate non-inferiority of 400 mg EFV.

Significantly fewer participants (2% versus 6%, $p=0.01$) discontinued treatment due to EFV-related side effects (rash, CNS, gastrointestinal, but not psychiatric) in the 400 mg arm compared to the 600 mg arm and 10% fewer reported these side effects.

Results from a pharmacokinetic substudy of ENCORE1 suggest that although 400 mg gives cerebrospinal fluid (CSF) exposure of EFV above that needed to suppress HIV exposure of metabolites might still be within the concentration range associated with toxicities.³⁹ Although statistically significant, the reduction in EFV-associated side effects was modest in ENCORE1 and the pharmacokinetic study suggests this possible explanation.

Questions about whether or not 400 mg would be robust in the third trimester of pregnancy and with TB treatment have delayed recommendations from WHO and national guidelines.

There are six studies that include 235 women treated with 600 mg EFV in pregnancy in which drug concentrations were not significantly affected and there were high rates of viral load suppression in the mothers at the time of delivery.⁴⁰ The results suggest that pregnancy has slight if any clinically important effects on EFV pharmacokinetics.

A South African study of 97 pregnant women (44 with TB) found that pregnancy increased the rate of low EFV plasma concentrations, but vertical transmission was rare.⁴¹ A detectable viral load at delivery was more common among pregnant women with TB, but ART was generally started later in this group. Another small study also found lower EFV plasma concentrations during pregnancy but the authors suggested that the clinical implications are unknown.⁴²

Pharmacokinetic modelling, conducted to simulate EFV exposure using 600 mg and 400 mg during the third trimester of pregnancy, suggested that although pregnancy decreases total exposure of EFV the unbound fraction is predicted to be unchanged.⁴³ This study indicates that a dose reduction to 400 mg might be feasible in pregnancy.

For rifampicin, there have been seven short-term pharmacokinetic studies with EFV 600 mg (less than two weeks) showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Five longer-term studies in HIV positive people have shown increased C_{min} or no effect.⁴⁴

Three leading HIV doctors suggested that the dominant role of EFV in first-line ART should be reconsidered,⁴⁵ and wrote: “this should not only happen in high-income countries but ideally also in low-income settings, if alternative drugs are available, and this recommendation should be reflected in the treatment guidelines of the WHO and both governmental and nongovernmental organizations.”

But EFV is likely to remain a recommended first-line antiretroviral for a while. In countries where generics are not accessible until a drug is off patent this is likely to be for some time. The EFV/TDF/3TC regimen will be generic in most countries worldwide by 2017,⁴⁶ but DTG and TAF patents extend for at least another 10 years.⁴⁷ This will mean many middle-income countries that do not qualify for minimum prices – including swathes of South America, South East Asia, and Eastern Europe, where countries can pay four times as much for antiretrovirals than African ones with similar Gross National Incomes⁴⁸ – will encounter significantly higher (likely prohibitive) ones.

While EFV remains an option, it is important that the pharmacokinetic studies to look at the lower dose with TB treatment and in pregnancy are conducted to ensure that people receive the most optimized version.

Dolutegravir

With a low 50 mg once daily dose that does not require boosting, a very high barrier to resistance, good efficacy, minimal toxicity, pregnancy category B, and the potential to be low-cost and co-formulated, DTG looks like it will be an important potential option for use in LMIC. It is expected to replace EFV first-line.

DTG was superior to EFV at 48 weeks in antiretroviral naive participants in phase III trials (and remained so at 96 weeks).^{49, 50} At 48 weeks the proportion of participants who discontinued treatment due to adverse events was lower in the DTG group than in the EFV group (2% vs 10%). Rash and CNS events frequently associated with EFV were significantly more common in the EFV group.

Data from this comparison and from studies comparing DTG to RAL and in people with resistance to other integrase inhibitors^{51, 52} were used to gain approval for a broad indication in adults and adolescents aged 12 and above.⁵³ The indication for 12 to 18 year olds is based on a 24-week open-label study in integrase inhibitor-naïve adolescents.

DTG studies have not yet included significant numbers of people who would be treated in LMIC. The registrational trials for DTG comprised approximately 80% men and few non-white participants and hardly anyone co-infected with other diseases (a few with hepatitis B and none with TB or malaria). People with baseline NRTI resistance were not included.

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. A phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin.⁵⁴ The study suggested that 50 mg twice daily dosing is likely to be required when it is co-administered with rifampicin to overcome UGT1A/CYP3A induction by this drug, which is used in standard first-line TB treatment.

To date information about DTG in pregnant women is also scarce. Although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies.

The following need to be considered when new drugs are evaluated for pregnancy: pharmacokinetic differences, possible increased risk and viral suppression in pregnant women; safety for infant (teratogenicity, birth outcomes and longer term toxicities); and prevention of vertical transmission.

In the DTG registrational trials and compassionate use programs, among 38 pregnancies, there were: one congenital anomaly; 18 live births without anomalies; nine elective terminations without anomalies; 13 spontaneous abortions without anomalies, and three ectopic pregnancies. Post marketing surveillance of 74 pregnancies to January 2016 reported: 18 live births any anomalies, two live births with congenital anomalies; four spontaneous abortions without anomaly; one spontaneous abortion with anomaly; one stillbirth without anomaly and 39 pregnancies ongoing or lost to follow up.⁵⁵

So far only 10 first trimester and 18 second/third trimester exposures have been reported to the Antiretroviral Pregnancy Registry (APR) to 31 July 2015, with none and one congenital defect respectively.⁵⁶

Preliminary pharmacokinetic data from 15 women enrolled in IMPAACT P1026s suggests DTG exposures in pregnancy are similar to that in non-pregnant adults but lower compared with postpartum.⁵⁷

DTG AUC was 25-30% lower in the second and third trimester compared with paired postpartum – the differences were not significant. DTG Cmax was significantly lower in the third trimester compared with postpartum. C24 was 41% lower in the second and third trimester but differences were not significant. In this evaluation, 6/9 (67%) women in the second trimester, 12/15 (80%) in the third trimester and 8/9 (89%) postpartum had an AUC above the 10th percentile (37.5 mcg*hr/mL) of non-pregnant adults (historical controls).

All 15 women had viral load <50 copies/mL at delivery.

DTG infant elimination half-life was more than twice that of the mothers in the study and historical non-pregnant adult controls. All evaluable infants were HIV negative.

This evaluation reported four infant congenital anomalies: total anomalous pulmonary venous return; polycystic right kidney and cystic fibrosis; congenital chin tremor; filum terminale and sacral dimple. At the time of analysis data were not available showing how long the women in the study were on treatment. The investigators will also look into the family history of the infant with polycystic right kidney and cystic fibrosis. The congenital chin tremor resolved and the study sites did not consider the other two anomalies to be related to DTG.

The DTG arm of IMPAACT 1026s now has 30 mother-infant pairs enrolled and is closed to new enrolments. The protocol takes up to eight months to complete for each mother-infant pair and in turn more data from the study to be presented. More information about the four infants will be released as the sites provide it.

Tenofovir alafenamide

TAF is a newly approved prodrug of tenofovir. TAF doses are one tenth or less than that of TDF and give intracellular levels of the active metabolite, tenofovir diphosphate, which are four to seven times higher and plasma concentrations that are 90% lower than those with TDF.⁵⁸

The reduction in plasma concentrations with TAF could mean less tenofovir accumulation in bone and kidneys and, in turn, fewer bone and kidney associated toxicities compared with TDF.

There were no significant differences in efficacy or clinical side effects between TAF and TDF across phase II and III studies at 48 and 96 weeks. At 48 weeks, participants receiving TAF had statistically significant less renal toxicity and reduced bone mineral density compared to those receiving TDF. But TAF was also associated with increases in low-density lipoprotein (LDL) cholesterol and total cholesterol plasma levels. It is unclear whether or not these differences will have clinical significance long-term.

As with DTG, TAF needs to be evaluated in pregnancy and in the presence of rifampicin-based TB treatment.

TAF is a minor CYP3A4 substrate and a substrate of p-glycoprotein, both of which are induced by rifampicin, so there might be an interaction. Gilead has not conducted any interaction studies with TAF and rifampicin. Co-administration with carbamazepine leads to a 55% decrease in TAF in plasma⁵⁹; results from modelling to predict the interaction with rifampicin predict this reduction will be 73% in plasma.⁶⁰ But the intracellular concentrations of tenofovir-diphosphate when TAF is co-administered with rifampicin need to be investigated clinically.

TAF might give safety benefits over TDF and it could offer considerable benefits in price to generic accessible LMIC.

Darunavir/ritonavir

WHO has finally recommended DRV/r for second-line treatment. DRV/r is generally considered to be the most potent and tolerable protease inhibitor, but the generic formulation has taken its time, and cost has been a barrier to its wide use.

No dose-finding studies have ever been conducted with DRV/r in treatment-naïve populations. The original studies were conducted in people that were highly protease inhibitor-experienced.^{61, 62} The approved doses are DRV/r 800/100 mg once daily and 600/100 mg twice daily for people with no protease inhibitor resistance and with protease inhibitor resistance respectively.

Results from the dose finding studies and two with 600/100 mg once daily,^{63, 64} plus one showing the recommended dose of cobicistat results in a significantly lower DRV C_{min} than when it is boosted with ritonavir^{65, 66} (in which the investigators say a reduction of up to 50% in C_{min} should not make a difference to efficacy), suggest that a dose reduction to DRV/r 400/100 mg might be feasible.

WHAT IS PLANNED OR ONGOING?

First-line

Experts agree that a DTG-based preferred first-line regimen is the current goal. As well as offering the advantages described earlier, in combination with TAF and FTC the total daily dose would be 275 mg (375 mg with 3TC) compared to 1200 mg with the current WHO preferred first-line: EFV 600 mg/TDF/3TC.

For people who cannot access (or tolerate) DTG, EFV 400 mg based regimens should be an alternative first-line.

Table 6: New first-line regimen studies

Study	Sponsor (collaborators)	Design	Status	Purpose
ADVANCE	Wits RHI	DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority 1050 treatment naive adult participants (350 per arm) 60 treatment naive 12-15 year olds (20 per arm) Johannesburg	Phase III Start September 2016	Establish non-inferior efficacy for DTG/FTC/TAF compared to other study arms Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 96 weeks, CD4 changes, tolerability, safety and efficacy
NAMSAL ANRS 12313	Inserm-ANRS (Institute de Recherche pour le developement)	DTG/3TC/TDF vs EFV 400 /3TC/TDF 606 treatment naive participants Cameroon	Phase III Start June 2016	Establish non-inferior efficacy for DTG/3TC/TDF compared to EFV 400 mg/3TC/TDF Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy

Key: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; Inserm-ANRS, French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis; NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PK, pharmacokinetic; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

Two investigator-led studies are planned to look at these regimens in closer-to-real-life African settings. The studies are: ADVANCE, a three arm randomized comparison between two DTG-based regimens (one with TDF/FTC and the other with TAF/FTC) and EFV 600 mg (with TDF/FTC); and NAMSAL comparing DTG-based to EFV 400 mg-based regimens.⁶⁷ See table 6.

There are a number of ongoing or planned studies to help to address some of the evidence gaps associated with use in pregnant women and people receiving TB treatment.

Pregnancy

TABLE 7: First-line pregnancy studies

Study	Sponsor (collaborators)	Design	Status	Purpose
Dolutegravir				
DoIPHIN1 (dolutegravir in pregnant HIV mothers and neonates)	University of Liverpool (University of Cape Town/ University of Makerere/ViiV)	DTG PK in pregnant women in third trimester and post partum during 2 weeks breastfeeding 60 late presenting women (28 to 36 weeks gestation) Women randomized 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs Sites in South Africa and Uganda	Phase II Start May 2016 Completion July 2017	PK 3rd trimester Secondary outcomes include: safety and tolerability of DTG up to 2 weeks post partum and VL at delivery
ING200336 PK and safety study in pregnant women with HIV	ViiV Healthcare	PK and safety single arm study of women with unintended pregnancies while participating in ARIA study of DTG/ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women (NCT01910402) to be completed 2018 Estimated enrolment 25 (approx 237 receive study drug in ARIA) Multinational	Phase III Start October 2014 Completion February 2019	PK 2nd/3rd trimester PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes
DoIPHIN2	University of Liverpool	DTG PK in pregnant women in third trimester and post partum during breastfeeding until weaning or 18 months 250 late presenting women (28 weeks gestation to delivery) Women randomized 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs	Phase III	Primary endpoints: viral load at delivery, safety and tolerability Secondary endpoints include breast milk sterilisation
Tenofovir alafenamide				
WAVES (OLE)	Gilead Sciences	EVG/COBI/FTC/TDF vs TDF/FTC + ATV/r in treatment nave women with OLE with women in ATV/r arm rerandomized to remain or switch to EVG/COBI/FTC/ TAF 583 women and those that become pregnant can remain on study regimen	Phase III Ongoing Completion June 2017	Safety and efficacy of EVG/COBI/FTC/TDF vs TDF/FTC + ATV/r
Dolutegravir and tenofovir alafenamide fumarate				
IMPAACT P1026s PK properties of antiretroviral and related drugs during pregnancy and postpartum	US National Institutes of Health	PK Pregnant women > 20 weeks gestation receiving DTG or TAF as part of clinical care Each study arm 12 to 25 (target) women with evaluable 3rd trimester PK data Open to all IMPAACT sites	Phase IV Start September 2014 Completion May 2016	PK 2nd/3rd trimester PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes

Study	Sponsor (collaborators)	Design	Status	Purpose
Dolutegravir and tenofovir alafenamide fumarate (continued)				
PANNA study	Radboud University	PK Pregnant women < 33 weeks gestation receiving DTG or TAF as part of clinical care Each study arm 16 with evaluable 33 week data Open to all PANNA sites	Phase IV	PK at 33 weeks and 4-6 weeks after delivery PK in neonate, safety, VL and transmission
IMPAACT P2010*	US National Institutes of Health	DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/XTC in 550 mother/infant pairs Treatment-naïve women starting ART at 14-28 weeks gestation Randomized 1:1:1 open label Open to all IMPAACT sites	Phase III Planning stage	Superiority (virologic endpoint); non inferiority (adverse pregnancy outcome, toxicity endpoints) VL < 200 copies/mL at delivery; adverse pregnancy outcome (SGA and, separately, PTD); and maternal toxicity Rates of virologic failure or switch; VL <50 at delivery and 50 weeks postpartum; renal toxicity (mothers and infants); bone toxicity by DXA (infants); rates of SAB, foetal death; infant AEs; mother-infant ARV transfer at birth and from breast milk
Efavirenz 400mg				
PK of EFV 400 mg once daily during pregnancy in HIV positive women (SSAT063)	St Stephens AIDS Trust/Mylan Inc.	PK single arm 25 women stable on 2 NRTI plus EFV 600 mg for > 12 weeks, switch to EFV 400 mg at gestational age 28 weeks Sites in London	Phase I Start August 2015 Completion June 2017	PK (AUC 24h and Ctrough) EFV 400 mg during 3rd trimester pregnancy and post partum Safety and tolerability, genetic influences on EFV PK

* Only study that evaluates DTG/TAF/3TC in pregnancy together

Key: AE, adverse event; ABC, abacavir; ATV/r, atazanavir/ritonavir; BF, breast feeding; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Trials Network; NRTI, nucleos(t)ide reverse transcriptase inhibitor; OLE, open label extension; PANNA, Study on Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-infected pregnant Women; PK, pharmacokinetic; PTD, preterm delivery; SGA, small for gestational age; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

A ViiV-sponsored study is enrolling ART-naïve women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.⁶⁸ Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.⁶⁹

DOLPHIN 1 and 2 will look at DTG pharmacokinetics in pregnancy and post-partum, the pilot study is just starting to enrol and the larger one is in the planning stage.⁷⁰

The women-only Gilead study WAVES includes an open label extension in which women are re-randomized to remain on a boosted atazanavir-based regimen or switch to one that includes TAF. Women who become pregnant in the study can stay on their ART regimen.⁷¹

IMPAACT P1026s (which has presented preliminary data for DTG described earlier)^{72, 73} and PANNA⁷⁴ – the respective American and European studies that look at pharmacokinetics of antiretrovirals in pregnancy and post-partum include women receiving DTG and TAF.

IMPAACT P2010 will make the three arm same comparison as ADVANCE but in pregnant women.

ADVANCE and NAMSAL will give women who become pregnant during the study the option to continue on their study drugs.

And for EFV 400 mg – for which the safety concerns were resolved with wide use of EFV 600 mg – a pharmacokinetic study in pregnant women is ongoing.⁷⁵

Tuberculosis

Table 8: First-line HIV/TB co-treatment studies

Study	Sponsor (collaborators)	Design	Status	Purpose
Open label study of DTG vs EFV for HIV/TB coinfection	ViiV	50 mg DTG twice daily vs 600 mg EFV (randomized 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) 125 treatment naive participants Multinational sites including South Africa	Phase IIIb Ongoing Primary completion July 2017	Establish antiviral activity of DTG or EFV containing regimens with TB treatment Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy
EFV 400 mg	SSAT/Mylan	Sequential: 98 days (stage 1) and 28 days (stage 2) open label PK study Stage 1 (London) PK in 25 HIV positive participants on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 12 weeks (2 weeks after reduced EFV dose) Stage 2 (Kampala) PK in 10 participants with HIV and TB on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 28 weeks (2 weeks after reduced EFV dose)	Phase I Planning stage	Evaluate steady state PK of EFV 400 mg during co-administration with rifampicin and isoniazid Secondary endpoints: safety and tolerability; relationship between genetic polymorphisms and EFV exposure
TAF	SSAT	TFV-DP after 28 days of TAF/FTC followed by 14 days of TAF/FTC/rifampicin followed by 28 days of TDF with PK on days 28, 42, and 70 in HIV negative participants	Phase I Planning stage	Establish potential decrease in TFV-DP when TAF is given with rifampicin compared to TAF alone and TDF

Key: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; PK, pharmacokinetic; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate

ViiV is sponsoring an open label study of regimens containing 50 mg DTG twice daily or EFV 600 mg once daily during first-line TB treatment, which begun enrolling early 2015.⁷⁶

A study is planned to investigate the pharmacokinetics of EFV 400 mg in HIV positive people in the presence of rifampicin and isoniazid in London and in HIV and TB coinfecting participants receiving full anti-TB treatment in Kampala.

For TAF the key pharmacokinetic parameter is intracellular tenofovir diphosphate in plasma and peripheral blood mononuclear cells. A study to measure this in the presence of rifampicin is planned in HIV negative people. Once this has been established then studies can be conducted in HIV/TB coinfecting people.

It might be that EFV/TDF/3TC remains the recommended regimen during TB co-treatment if studies suggest that adjusting the dose of DTG (and possibly TAF) is necessary, as this can get a bit too complicated.

If DTG/TAF/XTC fulfils its early promise, is recommended, and generic FDCs are made available, there will be questions to be answered on the pros and cons of a wholesale switch from the current EFV-based first-line versus a gradual transition.

Two drugs first-line

There is currently interest, including from the AIDS Clinical Trial Group (ACTG) in looking at DTG/3TC dual therapy, as a potential new strategy to reduce ART cost and toxicity.⁷⁷ Planned and ongoing research on this is described earlier in the Antiretroviral Pipeline chapter.

In order for this strategy to be considered for LMIC there would need to be robust data from large pragmatic studies in unselected African populations, including TB and pregnancy. Both TB and pregnancy occur at incidence rates around 5% on ART in Southern Africa, so it is critical that the preferred first-line regimen is effective in these populations.

Although preliminary data from IMPAACT P1026s suggests DTG exposures in pregnancy will be sufficient (in three drug regimens), some pharmacokinetic parameters are reduced in the third trimester.⁷⁸ There is also considerable reduction in DTG exposure with rifampicin. Using it with only 3TC would likely scupper the possibility that DTG might still be effective at the standard dose with TB co-treatment, despite this reduction, which will be investigated further along the line.

When DTG/3TC was raised at the WHO Think-Tank meeting earlier this year, only a minority were in favour.⁷⁹ The other concerns were lack of coverage for people co-infected with hepatitis B, and baseline antiretroviral resistance.

Although every rand, pound or dollar saved in ART programs is important at scale, the projected annual difference adding TAF to the regimen is about US \$10–15 per patient, which would have to be considered against the cost impact of potential first-line failure.

At the moment it seems that the potential benefits outweigh the potential risks. The studies would need to be designed to make sure these potential risks could be ruled out, before this regimen could be considered for global guidelines.

Second-line

For people failing EFV-based first-line treatment – and this population is expected to grow with greater access to viral load testing – there have been discussions about a second-line regimen with low dose DRV/r.⁸⁰

A regimen of DRV/r plus DTG has the potential to be once daily, heat-stable, co-formulated second-line option with no cross-resistance to an EFV/TDF/3TC first-line. Making recommendations for DTG first- and second-line depending on the initial regimen is not mutually exclusive.

Studies to investigate this regimen are under discussion. There is also the potential for a dose reduction of to DRV/r 400/100 mg.

Table 9: Low dose DRV/r studies

Study	Sponsor (collaborators)	Design	Status	Purpose
DRV/r 400/100 mg vs LPV/r WRH1052	Wits RHI	300 participants stable on LPV/r + 2 NRTI twice daily randomized to stay or switch to DRV/r 400/100 mg once daily 48 weeks Johannesburg	Phase IIIb Starting July 2016	Primary endpoint VL <50 copies/mL at 48 weeks Secondary endpoints include clinical and laboratory markers
Low dose DRV/r pilot	SSAT	120 treatment naive participants randomized to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC London, Kampala, Chennai	Phase IIb pilot Funding application stage	PK and VL
Low dose DRV/r	SSAT	600 1st line treatment experienced participants randomized to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC 96 weeks London, Kampala, Chennai	Phase III Funding application stage	PK and VL

Key: DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; PK, pharmacokinetic; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load

If DTG becomes preferred first-line, research into the best option for second-line after this regimen is needed. Early discussions have included using NRTIs again or combining DRV/r with rilpivirine or doravirine.

WHAT NEEDS TO BE DONE?

- **Upgrade to the new first-line regimen.** Sufficient evidence to change WHO guidelines to recommend DTG and TAF as part of the preferred first-line regimen (replacing EFV and TDF) needs to be generated in order to convince generic manufacturers to invest in new production for the new regimens. A recommendation from WHO is the strongest signal to generic manufacturers to take the risk and produce new FDCs. Such WHO recommendations will require results from the studies discussed here.
- **Originators donate drugs to strategy studies for LMIC.** Originator manufacturers must take responsibility and supply prioritized antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate data to support their use in LMIC. And not after several years of deliberation. The lack of information on use of new regimens in pregnancy and with TB treatment – that is critical to treating populations in LMIC – will continue to be a barrier to their universal recommendation however impressive the results from the phase III trials are.

- **Countries get ready to switch.** Countries with high volume ART programmes such as South Africa, Kenya, and Uganda, need their guideline committees briefed as results are generated (even before they are publically released), so that they can make new recommendations, hopefully before final WHO decisions.
- **Donors must support switch to new drugs and regimens.** Donors can play a huge part in changing standard of care in countries. UNITAID bought large volumes of TDF and helped to bring down the price and speed up the switch from d4T – so called market dynamics.
- **Timely approval.** Regulatory agencies in LMIC, such as the South African Medicines Control Council, need to register new originator and generic formulations, as swiftly as possible. The DCGI in India needs to waive the request for Indian trials before prioritized antiretrovirals products can be exported. Ideally this should happen before new WHO and national recommendations.
- **Generic companies need time to plan for high volume manufacture.** Generic manufacturers need to be briefed on when data from key studies are expected to be released, guideline changes, and tender timing in countries, so that they can start planning to compete to supply the newly recommended regimens.
- **Pre-empt possible chaos.** Before introducing new drugs, issues such as stockpiling (and stock outs) need to be discussed and planned, so that hitches with switching from old to new regimens are kept to a minimum.
- **Second-line needs more consideration.** Although there is consensus on the likely best optimised first-line regimen, second-line is not quite there yet and requires more discussion and research and development to ensure best regimens and formulations.

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The Pediatric Antiretroviral Pipeline

By Polly Clayden

INTRODUCTION

The development of new antiretroviral drugs and appropriate formulations for children continues to be far too slow. There are now 2.6 million children in need of antiretroviral treatment (ART) globally. Of those treated, more than 40% are on a suboptimal regimen.¹ What is on offer to treat them has been described as: “too much of what we don’t need”.

This means limited options for newborns, still too few appropriate fixed dose combinations (FDCs), and pediatric regimens that cannot harmonize with those recommended for adults.

Since the 2015 *Pipeline Report*, there has been little change. But a few steps in the past year are noteworthy:

- World Health Organization (WHO), The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children (IATT) and UNICEF published a policy brief and factsheet on the lopinavir/ritonavir (LPV/r) oral pellets, that provide program managers, implementers, procurement and supply chain managers, important points to consider before and during the introduction of the new formulation.²
- The updated WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection now include integrase inhibitors – a new antiretroviral class for children.³
- The US Food and Drug Administration (FDA) approved dolutegravir (DTG) 25 mg and 10 mg tablets for children weighing at least 30 kg in ages six to less than 12 years old.⁴

This commentary gives an update on the pediatric antiretroviral pipeline, with a focus on low- and middle-income countries (LMIC). Sharp-eyed regular readers will note that not much has moved on from last year’s report (so some of the summaries remain the same) as unfortunately recent developments have not been very speedy.

WHO 2015 Guidelines

In line with adult first-line recommendations, there are two new alternative regimens for adolescents: DTG or efavirenz (EFV) 400 mg based. Raltegravir (RAL) is now recommended second-line for younger children and DTG and darunavir/ritonavir (DRV/r) is recommended for third-line.

As with the 2013 recommendations, there are no suitable generic formulations yet to support this guidance (although for adolescents DTG and EFV 400 mg based ones are on the way for adults. See *Fit for Purpose: antiretroviral treatment optimization* chapter).

Only one regimen (that is not preferred), zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP) is currently available as an FDC. There is still some way to go with formulations and regimens appropriate to children. Despite some advances in the last few years, innovation and access in antiretrovirals for children still lags behind that for adults.

Table 1: WHO recommended first-line ART for children and adolescents

First line ART	Preferred regimens	Alternative regimens
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV 400 mg TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

Table 2. WHO recommended second- and third-line ART for children and adolescents

First line ART	Preferred regimens	2nd-line regimens	3rd-line regimens
Children	2 NRTIs + LPV/r	Less than 3 years: 2 NRTIs + RAL	DTG + 2 NRTIs DRV/r + 2 NRTIs DRV/r + DTG + 1-2 NRTIs
		Older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	

Key: ATV/r, atazanavir/ritonavir; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir

Lopinavir/ritonavir pellets

In 2015 the big news for pediatric HIV in LMIC was that there is finally a solid form of LPV/r suitable for infants and young children. On 21 May 2015, the US FDA tentatively approved LPV/r pellets, manufactured by Cipla (working in collaboration with the Drugs for Neglected Diseases Initiative [DNDi]) for infants and young children less than three years old.^{5, 6}

A few months before, in December 2014, the Medicine Patent Pool (MPP) signed a licensing agreement with AbbVie – that holds the patent for LPV/r.⁷ The agreement should help to make the new formulation available for children in LMIC. The next hurdles are getting it approved by regulatory agencies and used in programs in these countries.

WHO has recommended LPV/r-based regimens as preferred for infants and young children since the 2013 guidelines.⁸ Following this recommendation has been hard as this boosted protease inhibitor was previously only available as syrups, which are too complicated to use for most programs in LMIC. The solid formulation consists of a finite number of LPV/r 40/10 mg pellets in a capsule, which is opened and sprinkled on soft food.

Although it is quite a step forward from syrup, the new formulation of LPV/r is still not ideal. The pellets are much easier to transport and store (no cold chain), and for this reason programs are keen to start using them. But acceptability data from the CHAPAS-2 trial⁹ – that showed similar LPV/r exposure with pellets and syrups – revealed that pellets were not more acceptable than syrups by 48 weeks.¹⁰ For infants and young children

overall, the trial found pellets were more acceptable than syrups at week 12 but not by week 48. The main problem was taste.

Infants less than three months old have not yet been treated with the pellets. As they cannot be stirred, dissolved/dispersed or crushed in liquids it is important to make sure that infants can swallow them. For the youngest infants (three to six months old) in CHAPAS-2, the pellets were either added to a small amount of expressed breast milk in a spoon and given to the infant, or put on the infant's tongue before breastfeeding.

The LIVING study is an implementation study using the new formulation ongoing in Kenya and starting soon in several other sub-Saharan African countries.¹¹ DNDi is also working on an improved taste masked granule formulation of LPV/r (as part of a fixed dose combination [FDC] 4-in-1 regimen).

Missing pediatric formulations

Several gaps remain in available products for children that need to be filled before even the 2013 WHO guidelines (you read that right) can be implemented in most LMIC.

Where possible these should be FDC dispersible tablets. For compounds that cannot be formulated in this way (large and/or insoluble molecules like LPV/r) pellets are preferable to liquids. Liquid formulations are expensive, have short shelf lives, and often require a cold chain, making them hard to store and transport and inappropriate for most LMIC.¹²

The two priority formulations needed to treat children according to the 2013 guidelines remain notable by their absence:¹³

AZT or abacavir (ABC) plus 3TC plus LPV/r. These formulations are still in development and are needed to make it possible to give FDCs to children younger than three. Better solid forms could overcome palatability issues with the currently available nasty tasting LPV/r syrup (although taste masking is complicated and can limit drug absorption and the LPV/r pellets still need improving). Many barriers with supply chain – transport, storage and distribution – could be addressed by these formulations.

Supported by UNITAID, DNDi is working on a more palatable version of LPV/r – which will be produced in combined 4-in-1 granule formulations (finer than the 0.8mm pellets and more sand-like in texture).¹⁴

ABC plus 3TC plus efavirenz (EFV). Currently this regimen can only be given by using ABC/3TC co-formulated tablets with EFV tablets. A one-pill, once-daily regimen for children aged three to 10 years (less than 35 kg) would be useful. There is some discussion as to what dosing ratios for the FDC best facilitate recommendations for the individual agents across weight bands. Optimal doses need to avoid under- and overdosing of children at either end of each weight band, as far as possible, and be most suitable from a regulatory standpoint.

These two formulations have been a priority for quite some time now and are still unavailable.

Recommendations from PADO2: more missing formulations

The first Pediatric Antiretroviral Drug Optimization (PADO1) meeting, held in Dakar in 2013, brought together researchers, clinicians, activists and other experts to identify medium- and long-term priority drugs and formulations for children. The recommendations from this meeting were summarized in a WHO 2014 supplement,¹⁵ and the priority formulations are still missing.

The Second Pediatric Antiretroviral Drug Optimization (PADO2) meeting,¹⁶ held in December 2014 was conducted to build on the PADO1 agenda and provide technical advice to the WHO 2015 guidelines development group. Among the topics discussed at the meeting were the needs for children at both ends of the age spectrum: newborns and adolescents.

Newborns

For newborns, less than four weeks, the participants noted that there was currently no alternative to NVP plus 3TC plus AZT. Although very early treatment is being explored for infants, data for this very young age group are scarce. See Table 3. Data from population modelling can help to predict dosing regimens in this age group.

NVP clearance is low immediately after birth and increases dramatically over the first months of life. Since PADO2 the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) have presented population modelling and pharmacokinetic simulations predicting dosing regimens to achieve target NVP treatment concentrations in term and late preterm infants.¹⁷

NVP clearance is low in term neonates, and lower still in preterm ones, because of immaturity in CYP2B6 and CYP3A4 activity. Clearance is also autoinduced in proportion to the size of the NVP dose in the first years of life.

Pharmacokinetic data are available to guide NVP dosing for treatment of HIV in infants after one month of life: trough concentration target 3.0 ug/mL. But NVP pharmacokinetic studies in infants less than one month old are limited to evaluations of dosing regimens for prevention of vertical transmission: trough concentration target 0.1 ug/mL.

Increasing evidence for early treatment and trends on early infant diagnosis – as well as a paucity of other antiretroviral options in this age group – has led to considerable interest in the use of NVP as part of ART regimens for neonates.

IMPAACT used population modelling to evaluate proposed NVP dosing regimens to meet target concentrations in term and late preterm infants (34-37 weeks gestation) from birth to 6 months old. The model included data from 192 infants (1121 plasma NVP concentrations) from US, Africa and Brazil.

CYP2B6 metaboliser status, rate of autoinduction, and preterm effects were estimated from published literature. Dosing regimens from birth through 6 months of age were evaluated using simulations. Simulations were used to evaluate proposed NVP doses of 6 mg/kg twice daily for term infants and 4mg/kg twice daily for one week followed by 6 mg/kg twice daily for late preterm infants. The target was to meet trough concentrations of > 3.0 ug/mL.

Clearance was scaled allometrically and volume of distribution scaled linearly for weight. It was modelled to mature with age and autoinduction as a linear function of dose. Effects of prematurity and maturation of CYP2B6 and CYP3A4 activity on NVP clearance from published data were included.

The model revealed that typical NVP clearance (L/hr/kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and by an additional 79% due to induction. The final simulations used term infant doses of 6 mg/kg twice daily and late preterm infant doses of 4mg/kg twice daily for one week followed by 6 mg/kg twice daily. In these simulations, the dosing regimens achieved NVP targets.

The study concluded that NVP dosing regimens in neonates must take into account the impact of maturation, auto-induction and prematurity on NVP clearance.

More missing data for priority antiretrovirals will be provided by ongoing IMPAACT trials:

P1026s – phase IV, prospective, pharmacokinetic study in pregnancy and post partum, that obtains infant antiretroviral washout data.¹⁸

P1093 – phase I/II, open label, non-comparative, intensive pharmacokinetics and safety study of DTG down to four weeks.¹⁹

P1097 – washout pharmacokinetic study of RAL including in low birth weight (<2500 g) infants.²⁰

P1106 – phase IV prospective pharmacokinetic study in low birth weight infants receiving NVP prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or LPV/r-containing ART.²¹

P1110 – phase I open label, non-comparative pharmacokinetic dose-finding study of RAL in high risk, HIV-exposed neonates.²²

P1115 – phase I/II proof of concept study of very early intensive antiretroviral therapy (ART) in infants to achieve HIV remission.²³

Table 3: Newborn treatment options (or lack of options to date): including ongoing and planned IMPAACT trials

Compound	Preterm	Term	2 weeks
Nucleos(t)ide Reverse Transcriptase Inhibitor			
ABC	P1106 < 2500 g		
AZT	✓	✓	✓
ddl			✓
d4T	P1106 < 2500 g	✓	✓
FTC		✓	✓
TAF	P1026s washout	P1026s washout	
3TC	P1106 < 2500 g	✓	✓
Non-nucleoside Reverse Transcriptase Inhibitor			
Doravirine	P1026s washout	P1026s washout	
EFV	P1026s washout	P1026s washout	
ETR	P1026s washout	P1026s washout	
NVP	P1106 < 2500 g	P1115 >34 weeks GA	✓
RPV			
Protease Inhibitors			
ATV			
DRV	P1026s washout	P1026s washout	
LPV	P1026s washout P1106 <2500 g	P1026s washout	✓

Compound	Preterm	Term	2 weeks
Integrase Inhibitors			
DTG	P1026s washout	P1026s washout P1093 dosing (in development)	P1093 dosing (in development)
EVG	P1026s washout	P1026s washout	
RAL	P1097 washout	P1097 washout P1110 dosing	
CCR5 Receptor Antagonist			
Maraviroc		In development	

Adapted from Ruel T. IMPAACT 2015.

Key: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; ddl, didanosine; DTG, dolutegravir; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; ETR, etravirine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; 3TC, lamivudine. GA, gestational age.

Infants and children

For infants two weeks and above, the immediate priority first-line is still LPV/r-based regimens and for older children EFV-based FDCs. An alternative to the liquid formulation of ritonavir (RTV) is needed to make double boosting (adding extra RTV to overcome pharmacokinetic interactions with TB drugs during co-treatment) easier with LPV/r.

Adolescents

Discussion about adolescents at PADO2 focused on adherence and more tolerable alternatives to EFV.

Priority antiretrovirals

For second-line treatment a generic, co-formulated, heat stable version of darunavir/ritonavir (DRV/r) is a priority. Children who fail on LPV/r-based first-line regimens particularly need a robust option second-line. Current dosing recommendations for DRV/r (approved by FDA and EMA) need to be simplified to reduce the number of different formulations and minimize pill burden for children in LMIC. A 240/40 mg DRV/r tablet for twice daily dosing is a priority for children in weight bands 10 kg and above. DRV/r is not approved for children less than three years old and will not be investigated in this age group due to toxic levels in pre-clinical studies.

Approved pediatric dosing regimens for DRV/r are different from WHO-recommended ones because different weight bands have been used. When considering a co-formulation for children, generic manufacturers will likely use a darunavir:ritonavir (DRV:RTV) fixed ratio and the WHO pediatric weight bands.

To simplify administration, WHO recommends five weight bands from 10 kg to > 35 kg and a 6:1 ratio of DRV:RTV. US approved dosing uses eight weight bands from 10 kg to >40 kg, and varying DRV:RTV ratios that range from 7.5:1 to 5.8:1.

Janssen, the originator manufacturer of DRV, conducted a pharmacokinetic simulation to look at a regimen that conforms with the WHO weight bands and 6:1 ratio, and reaches DRV exposures comparable to

those in adults.²⁴ These simulations suggest that DRV dosing according to current WHO weight band recommendations might lead to either under-dosing in a lower weight band or over-dosing in a higher weight one. The study suggested that simple changes to the current WHO dosing schedule could improve DRV exposure in children while still keeping to the number of weight bands and a standard DRV/r dosing ratio.

The priority antiretrovirals identified by PADO2 participants in the medium-term (five years) are: DTG, RAL and tenofovir alafenamide (TAF), which are discussed below. The meeting participants did not expect RAL to be used widely when DTG comes to the market (and it has not been identified as a priority for adults) a better formulation of RAL might offer an alternative for infants. A pediatric first-line regimen of DTG/TAF/3TC has the potential to harmonize with that planned for adults.

The Pipeline

Pediatric investigation plans (PIPs) will be in place or under discussion for all compounds in early phases of development by originator manufacturers (described in the adult antiretroviral chapter). Although a generic company and DNDi are developing the LPV/r-based 4-in-1 FDC, and the list of pipeline pediatric drugs and regimens also includes this.

There are considerable incentives and/or penalties from regulatory agencies to ensure that any new drug that might benefit children must be studied in this population. Pediatric research and development of new drugs is mandatory. The European Medicines Agency (EMA) enforces penalties for companies that do not provide a PIP as part of their application (or request a waiver). The FDA also extends six-month patent protection to companies that perform the requested pediatric studies – though companies are not required to do this.

A PIP can be waived for specific drugs or classes of drugs that are likely to be ineffective or unsafe in all or some pediatric age groups. A waiver can also be obtained for products that are intended for conditions that only occur in adults, or that do not represent a benefit over existing pediatric treatments. In some cases, studies can be deferred until after the adult studies have been conducted.

Manufacturers must include pharmacokinetic data for all age groups of children, efficacy, tolerability, and differences in side effects. They must have stability and palatability data for formulations and demonstrate that they are able to achieve pharmacokinetic targets associated with efficacy in adults.

Studies are conducted in children as soon as there are sufficient data from those in adults. Most pediatric development programs take an age staggered approach, starting with the older cohorts of children and working in de-escalated age bands: 12 to 18 years; six to 12 years; two to six years; six months to two years and less than six months. Data are required in the youngest age groups – down to newborns – unless a regulatory waiver is obtained. As the youngest age group is last to be studied and approved there are considerable delays in availability of new drugs for this population.

The problems with the age-staggered approach that results in delays in approval and availability of new drugs, particularly in the youngest age group where options are lacking, have been much discussed. WHO uses a weight band dosing approach and it would make sense to investigate weight band dosing in pediatric antiretroviral development from the beginning, optimizing the use of pharmacokinetic data and modelling. The DTG development program, IMPAACT P1093 (see below), will try to capture enough data to inform weight band dosing, with the dispersible tablet in the younger cohorts.

Moving away from the age-staggered approach to weight bands could also make it possible to open multiple cohorts simultaneously, if formulations are available, which would speed up availability of new drugs for infants and children considerably.

It would be interesting to see if doses for younger children have changed dramatically from predicted milligrams per kilogram ones due to pharmacokinetic data from older cohorts.

If work on aligning age bands with WHO weight bands could be done as originator manufacturers conduct their pediatric development programs, this would help generic manufacturers develop co-formulations and FDCs that allow dosing aligned with recommendations across the weight bands. It could help close the gap between when new drugs and regimens are available in LMIC for adults and children.

The current pediatric antiretroviral pipeline is shown in Table 4.

Table 4. The pediatric antiretroviral pipeline

Compound	Sponsor	Formulation/s and dose	Status and comments
Nucleotide reverse transcriptase inhibitor and combinations			
Tenofovir alafenamide f (TAF)/ emtricitabine (FTC) elvitegravir (EVG)/cobicistat (COBI) (E/C/F/TAF)	Gilead	Reduced dose FDC tablets in development	Phase II/III singlearm, open label E/C/F/TAF treatment-naïve children and adolescents 6 to <18 years PK within adult range at 24 weeks in 12 to <18 years Waiver <6 years
FTC/TAF (F/TAF)	Gilead	Reduced dose, co-formulated tablets and non-solid formulation in development	Switch study in children and adolescents stable on FTC/TDF plus 3rd agent Study in infants and children 4 weeks to <6 years planned
Rilpivirine (RPV)/FTC/TAF	Gilead/Janssen	Reduced dose, FDC tablets planned	Dependent on development of RPV and F/TAF Initial indication adolescents >12 years
Non-nucleoside reverse transcriptase inhibitors			
Etravirine (ETR)	Janssen	Dispersible tablets 25 (scored), 100 mg	FDA/EMA approval for children and adolescents 6 to <18 years Phase I /II treatment-experienced infants and children 2 months to <6 years and treatment-naïve 2 months to <2 years enrolling Waiver <2 months
Rilpivirine (RPV)	Janssen	Tablet 25mg Granules 2.5 mg /g	Submitted to FDA and EMA for adolescents 12 and above with viral load < 100,000 copies/mL 2 to <12 years planned
Doravirine	Merck	Single agent and FDC with TDF/3TC planned	Pediatric plans under discussion with EMA and FDA
Protease inhibitor and combinations			
Lopinavir/ritonavir/ lamivudine/abacavir or zidovudine (LPV/r/3TC/ABC or AZT)	DNDi/Cipla	4-in-1 FDC granules	Formulation work ongoing

Compound	Sponsor	Formulation/s and dose	Status and comments
Booster			
Cobicistat (COBI)	Gilead	75 mg tablets 20 mg dispersible tablets for oral suspension	Booster with ATV, DRV and as part of E/C/F/TDF and E/C/F/TAF
Atazanavir/cobicistat (ATV/c)	Gilead/BMS	Reduced dose and dispersible tablets planned	Phase II/III treatment experienced children 3 months to <18 years (ATV/c)
Darunavir/cobicistat (DRV/c)	Gilead/Janssen		3 to < 18 years (DRV/c)
Integrase inhibitors and combinations			
Raltegravir (RAL)	Merck	Granules for suspension 6mg/kg (100 mg sachet)	FDA-approval for use in children 4 weeks and older Passive PK study ongoing: neonates born to women who received RAL in pregnancy and during labor Neonates PK and safety study for prophylaxis ongoing in high-risk HIV-exposed neonates from birth to six weeks
Elvitegravir (EVG)	Gilead	Reduced dose tablets and suspension in development	EVG PK completed, RTV boosted 12 to <18 years RTV-boosted EVG to be studied in all age groups
E/C/F/TDF (Stribild)	Gilead	Reduced dose tablets in development	Studies underway in treatment-naïve 12 to <18 years 6 to <12 years planned Waiver <6 years
E/C/F/TAF See TAF above	Gilead	Reduced dose tablets in development	Studies underway in treatment naïve 12 to <18 years 6 to <12 years planned Waiver <6 years
Dolutegravir (DTG)	ViiV Healthcare	Granule formulation (for studies) Dispersible tablets in development 10 mg and 25 mg tablets	10 and 25 mg tablets approved for children and adolescents 6 years and above weighing >30kg in US Phase I/II study, 6 weeks to <18 years treatment-naïve and -experienced children, ongoing
DTG/ABC/3TC (572-Trii)	ViiV	Pediatric formulation development planned	FDA/EMA approval for adolescents >12 years and >40 kg Dependent on ongoing studies confirming DTG dose in children and ability to establish appropriate dosing ratios for components
DTG/RPV	ViiV/Jansen	Reduced dose co-formulation	PIP in development Studies planned in children and adolescents 6 to <18 years
Cabotegravir/RPV long acting (LA)	ViiV/Janssen	Age appropriate liquid formulation for induction Intramuscular nanosuspension as for adults	PIP approved October 2014 (to be completed by 2018) Waiver <2 years Deferral 2 to <18 years
CCR5 Receptor Antagonist			
Maraviroc (MVC)	ViiV	Suspension 20 mg/mL	Phase IV, Treatment-experienced CCR5 tropic 2 to <18 years

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR

Tenofovir alafenamide

TAF is considered to be a priority for future generic FDCs for children. Early data in adults suggests that it might have a better safety profile than TDF. This has yet to be confirmed in children. TAF also has a low milligram adult dose: 25 mg without a boosting agent and 10 mg boosted.

For children TAF might be an alternative to ABC. It could help to harmonize pediatric and adult ART regimens, particularly if it could be co-formulated with DTG and 3TC or FTC.

The development of an FDC of elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (E/C/F/TAF) is the originator company, Gilead Science's priority. Gilead is also investigating a co-formulation with FTC (F/TAF) – recently approved for adults.^{25, 26}

F/TAF

TAF is being investigated co-formulated with FTC in a phase II/III switch study will enroll children down to six years of age.²⁷

Adolescents aged 12 to 18 years will switch their current two nucleoside reverse transcriptase inhibitor (NRTI) containing regimen to F/TAF (while continuing on their third antiretroviral agent) for 96 weeks. After review of the pharmacokinetic and safety data from the older cohort, children aged six to 12 years will be randomized to receive either F/TAF or FTC/TDF (continuing on their third agent) for 96 weeks.

A study in infants and children aged four weeks to six years is planned. Reduced dose tablets and a non-solid formulation are in development. As with the pediatric formulation of TDF, the taste of TAF is bitter and will need masking. Because of TAF's low milligram dose, taste masking might be easier than it was for TDF.

E/C/F/TAF

A phase II/III, single arm, open label study of once-daily E/C/F/TAF in treatment-naïve children and adolescents aged six to 18 years is ongoing.²⁸ There is a waiver for children less than six years old.

In the phase II/III study in 12 to 18 year olds with a median age of 15 years receiving E/C/F/TAF, steady-state pharmacokinetic parameters of EVG, COBI, FTC, TAF and tenofovir (TFV) were compared to adult exposures. The study found TAF (as well as TFV, EVG, COBI, and FTC) pharmacokinetic parameters in adolescents to be consistent with those associated with safety and efficacy in adults.²⁹

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Etravirine

A scored 25 mg etravirine (ETR) tablet with dosing recommendations for treatment-experienced children and adolescents aged six to 18 years and weighing at least 16 kg is currently approved.³⁰ The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naïve and -experienced children aged two months to six years.³¹ Phase I/II studies in the younger age groups are currently enrolling treatment-experienced children. There is a waiver for infants less than two months.

Rilpivirine

Rilpivirine (RPV) is approved for treatment of adults 18 years old and above with viral load less than 100,000 copies/mL. The originator company Janssen has submitted applications for an adolescent indication (12 to 18 years) to the FDA and EMA.

PAINT (Pediatric study in Adolescents Investigating a New NNRTI TMC278), is an ongoing, open label, 48-week phase II trial looking at RPV pharmacokinetics, safety and efficacy in treatment-naïve adolescents aged 12 to 18 years.³²

Based on pharmacokinetics, tolerability and efficacy data at four weeks, a dose of 25mg RPV once daily with food was selected³³ – providing comparable exposure to that in adults. This dose was effective and generally well tolerated over 24 weeks for the treatment of ART-naïve adolescents with viral load less than 100,000 copies/mL.³⁴ PAINT is ongoing.

IMPAACT P1111 is planned in children from two weeks to less than 12 years of age.³⁵ A granule formulation of RPV is in development.

RPV is also being developed as an intramuscular long acting formulation for treatment and prevention (see cabotegravir below).

Doravirine

Once-daily 100 mg doravirine looks promising in adults (see antiretroviral pipeline chapter).

The originator company Merck has submitted pediatric plans to FDA and EMA for doravirine as a single agent and as an FDC: doravirine plus TDF plus 3TC. The studies will enroll populations similar to those in adult phase III studies: treatment-naïve and stable experienced patients for switch studies.

PROTEASE INHIBITOR

Lopinavir/ritonavir

As described above, the FDA has tentatively approved LPV/r pellets for young children. DNDi and Cipla are continuing to develop a more palatable version of LPV/r granules in 4-in-1 FDCs with two NRTIs, ABC or AZT, plus 3TC. The granule formulation of LPV/r will be tested in HIV-negative adults soon.

INTEGRASE INHIBITORS

Raltegravir

RAL is approved for infants and children from four weeks of age.³⁶ For the youngest age group (four weeks to less than two year olds, weighing 3 kg to 20 kg) it is formulated as granules for oral suspension. The formulation comes in single-use packets of banana-flavored granules containing 100 mg of RAL, which is suspended in 5 mL of water giving a final concentration of 20 mg/mL. Giving RAL to neonates currently requires a complex dosing regimen.

For older children there is an orange-banana flavored, chewable pediatric formulation. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and

have specific guidance. There have been discussions about the possibility of using the chewable formulation in younger age groups, as the granules for oral suspension are complicated to use.

A comprehensive development plan is ongoing with the IMPAACT Network including in neonates less than four weeks of age (both HIV-infected and exposed) infants.^{37,38, 39, 40, 41, 42} This development plan is excellent and deserves detailed review. It will provide comprehensive data to inform dosing of young infants for both treatment and prophylaxis. IMPAACT are following a similar plan with DTG.

IMPAACT P1097 was conducted to look at washout PK in neonates born to mothers receiving RAL in late pregnancy. This study showed that RAL crosses the placenta well. There was variable and prolonged elimination of RAL in the first days of life compared with older infants and children. P1097 is now assessing washout PK in a cohort of low birth weight (including preterm) neonates.

IMPAACT P1110 is an ongoing two-part PK and safety study of RAL in term neonates at high risk of vertical HIV infection, informed by P1097 results.

RAL has the potential for use in prophylaxis and treatment of neonates at high risk of vertical HIV infection. The drug is primarily metabolized by UGT1A1, which has low activity at birth but increases over the first weeks of life and will influence neonatal dosing.

IMPAACT P1110 aims to evaluate the pharmacokinetics and safety of RAL and find an appropriate dose for neonates and infants up to six weeks of age. The study has a two cohort adaptive design: pharmacokinetic data from cohort 1 are included in pharmacokinetic modelling to inform dosing in cohort 2. It is a phase I multicentre pharmacokinetic study of in full-term, HIV-exposed, high-risk neonates.

Data from P1110 were presented last year.⁴³ Cohort 1 participants received a single oral dose of RAL within 48 hours of birth added to standard of care antiretrovirals for PMTCT prophylaxis, and a second dose at 7-10 days old. The initial dose was 3 mg/kg and doses were adjusted as the study progressed. RAL-exposed infants born to mothers receiving the drug during pregnancy and delivery were excluded at the beginning of the study. Later their enrollment was permitted with a lower initial dose.

An intensive pharmacokinetic sampling was performed around the initial dose: pre-dose and 1-2 hours, 4-8 hours, 12 hours, 24 hours post-dose and a random sample at 3-4 days old. Sampling was at three time points around the second dose: pre-dose and 1-2 hours and 24 hours post-dose. A validated HPLC-MS-MS method with a lower limit of quantification of 22.5 nM was used to analyse the samples. Protocol specified exposure limits from non-compartmental analysis for each participant were: $C_{max} < 19.6 \mu M$ and $AUC_{12} < 63 \mu M \cdot hr$.

Cohort 1 comprised 13 neonates: 10 were born to mothers who did not receive RAL before delivery (RAL-naive) and 3 to mothers who received RAL before and during delivery (RAL-exposed). Neonates were 54% female with a median gestational age of 39.0 weeks (range 36.0 to 39.6) and birth weight of 3.02 kg (2.39 to 4.20). Evaluable initial dose and week 1 dose concentration data were available for 12/13 neonates.

The interim analysis of pharmacokinetic data from the first six RAL-naive neonates who received 3 mg/kg initial doses found none exceeded the C_{max} upper limit but two exceeded the AUC_{12} upper limit. Following this analysis, the initial dose was reduced to 2 mg/kg for RAL-naive and 1.5 mg/kg for RAL-exposed neonates.

All neonates received 3 mg/kg for the second dose at 7-10 days old. All 12 evaluable neonates had a $C_{max} < 19.6 \mu M$. But, 3/6 infants who received 3 mg/kg; 2/3 infants who received 2 mg/kg; and 1/3 RAL-exposed infants who received 1.5 mg/kg initial dose exceeded $AUC_{12} < 63 \mu M \cdot hr$.

A population pharmacokinetic model including the initial cohort 1 pharmacokinetic data from 6 neonates and

RAL concentration data from 24 infants and children ages 4 weeks to <2 years from IMPAACT P1066 – a phase 1/2, multi-centre, open-label, non-comparative intensive pharmacokinetic study in infants and children – was developed. And population modelling of the combined data was performed.

This revealed a change in absorption rate from 16% of maximum at birth to 90% within 2 weeks. Clearance changed from almost nil to a maximum at approximately 6 months of age.

Pharmacokinetic parameters including absorption and clearance were estimated using this population model, and simulations of various dosing regimens in the first 6 weeks of life were run.

In the final model the dosing regimen through 6 weeks of age that best met the following revised PK exposure targets (defined for safety and efficacy from recent studies in older infants, children and adults) was selected for use in cohort 2: $C_{max} < 19.63 \mu\text{M}$, $C_{min} > 75\text{nM}$, AUC_{12} (twice a day) $< 45 \mu\text{M}\cdot\text{hr}$ and AUC_{24} (one a day) $< 90 \mu\text{M}\cdot\text{hr}$.

Cohort 2 will begin enrolling RAL-naïve neonates with the dose selected from the pharmacokinetic modelling and simulations: 1.5 mg/kg once a day from birth to day 7, followed by 3 mg/kg twice a day until 4 weeks of age, then 6 mg/kg twice a day to age 6 weeks.

Additional pharmacokinetic data need to be obtained before RAL-exposed neonates are enrolled. Pharmacokinetic results for cohort 2 will be evaluated on a rolling basis and dosing adjusted based on these results.

Neonates exposed to RAL in utero might require a different dosing strategy and are also being studied in P1110.

Elvitegravir

Elvitegravir (EVG) is an integrase inhibitor given with a booster and mostly used for adults in the FDC containing EVG/COBI/FTC/TDF (E/C/F/TDF). It is also being developed as part of E/C/F/TAF.

Exposures in adolescents 12 to 18 years old receiving 150 mg once daily EVG plus a RTV-boosted protease inhibitor-optimized background regimen, showed comparable exposures to those seen in adults.⁴⁴

Two pediatric formulations are in development: a 50 mg tablet and a 5 mg/mL suspension. Single-dose pharmacokinetics evaluations compared two formulations to the 150 mg adult formulation (all boosted by RTV) in a crossover study in HIV-negative adults.⁴⁵

In this study, both pediatric formulations were bioequivalent to the adult formulation. The RTV-boosted formulations are being evaluated in children in an ongoing phase II/III study in children aged 4 weeks to 18 years of age.⁴⁶

PENTA 17 will evaluate EVG with DRV/r in stable, virologically suppressed children.

E/C/F/TDF

EVG is also being studied in treatment-naïve adolescents aged 12 to 18 years as part of the adult FDC, E/C/F/TDF containing EVG 150 mg, COBI 150 mg, FTC 200 mg and TDF 300 mg.⁴⁷ Early data has shown similar exposures of all the individual agents to adults and good virologic suppression.⁴⁸ Study of E/C/F/TDF in adolescents and children continues.

Dolutegravir

DTG is currently under investigation for use in all age groups from birth. DTG has shown good safety, efficacy

and tolerability so far, does not require boosting and has a low milligram dose.

DTG is being studied in infants (down to 4 weeks of age), children and adolescents in IMPAACT P1093.⁴⁹ The estimated primary completion date for the whole study is May 2018.

Expert groups have identified DTG as a priority for children (as well as adults) in LMIC. The development of generic formulations of DTG for children should follow as swiftly as the originator company ViiV Healthcare and regulators allow.

The US FDA recently approved a supplemental new drug application (sNDA) for DTG 10 mg and 25 mg oral tablets, reducing the weight limit from at least 40 kg to at least 30 kg in ages 6 to less than 12 years old.⁵⁰ The indication is for treatment naive and experienced but not INSTI experienced children and based on 24-week data from IMPAACT P1093.

IMPAACT P1093 is an ongoing, phase I/II, open label pharmacokinetic, safety and efficacy study in children and adolescents in age de-escalated cohorts of DTG plus optimized background regimen.⁵¹

The dose is 1 mg/kg once daily (based on weight bands). Forty-eight week data have been presented for children aged 6 to 12 years and children and adolescents aged 12 to 18 years.^{52, 53, 54, 55} Both age groups showed good short-term safety and tolerability. IMPAACT P1093 is continuing to evaluate infants and young children 4 weeks of age and above.

ViiV has developed a 5 mg dispersible tablet formulation of DTG as an alternative to the granule formulation (which was originally developed and used in early studies) for infants and young children. The dispersible tablet and granule formulations are bioequivalent.⁵⁶

The oral bioavailability of DTG is affected by metal cation-containing supplements. The originator company has compared DTG pharmacokinetics when tablets are dispersed in either low mineral content or high mineral content water in a randomized, open-label, 5-way, single-dose crossover study in HIV negative adults with DTG administered at 20 mg.

ViiV have also evaluated whether or not consuming the dispersed in water tablet immediately or after the suspension had been standing for 30 minutes made a difference.

The study showed equivalent exposure with the two DTG formulations, so found the dispersible tablet to be bioequivalent to the granule formulation. DTG PK was not affected by water mineral content or 30-minute delay in dispersed tablet consumption. The dispersible tablet can be given under these conditions.

In the limited data collected on palatability, the majority of participants described the taste and mouth feel of the dispersible tablet as acceptable. But the granule formulation appeared to be more acceptable than the dispersible tablet.

The dispersible tablet is undergoing further development and the formulation is being adjusted to improve the taste. Taste masking work on the dispersible tablets is also ongoing. The tablets will be strawberry cream flavored.

The two cohorts in the youngest age groups (6 months-2 years and 4 weeks-6 months) started with the granules in suspension formulation but use of this will stop once the 5 mg dispersible tablet formulation is available on site. Only the dispersible tablets will be available commercially.

A treatment strategy trial ODYSSEY (PENTA 20) of DTG in all age groups of children is also planned.

DTG/ABC/3TC

Development of a pediatric formulation of the FDC of DTG/ABC/3TC – currently approved for adults and adolescents aged 12 years and above^{57, 58} - is also planned.

The DTG/ABC/3TC PIP requires data from IMPAACT P1093 in two to 12 year old children to inform DTG dosing. Results from the ARROW trial⁵⁹ (that found once-daily dosing of ABC and 3TC non-inferior to twice-daily in children) will provide data for ABC/3TC once-daily dosing.

The investigation plan also requires the completion of a DTG/ABC/3TC FDC pediatric study in two to 12 year olds. This will be an open-label, switch design and enroll children who are fully suppressed on ART and integrase inhibitor-naïve.

DTG/RPV

The current plan for a pediatric DTG/RPV FDC is as a maintenance regimen in children and adolescents aged six to 18 years and virologically suppressed.

Data from planned adult phase III studies and existing adolescent data from single agents will be used for the 12 to 18 years age group. Providing the adult data supports the maintenance strategy, dosing studies and pediatric FDC development will then go ahead in the 6 to 12 age group.

Cabotegravir and rilpivirine long-acting

Cabotegravir is under investigation as a long-acting formulation with RPV. An age appropriate formulation will be developed for induction and the intramuscular nanosuspension will be the same as for adults.

The final PIP was approved October 2014 and includes pharmacokinetics, safety, tolerability, durability, acceptability and maintenance of cabotegravir and rilpivirine in two to 18 year olds.

There is a waiver for children less than two and a deferral for two to 18 year olds. The PIP will be completed by 2018, so although the idea of long acting formulations might be appealing for children and adults, it is some way off.

PHARMACOKINETIC BOOSTER

Cobicistat

COBI is a CYP3A inhibitor with no antiretroviral activity. COBI 150 mg is approved for adults as a booster of atazanavir (ATV) 300 mg or DRV 800 mg, including in co-formulated tablets.^{60, 61} It is also under investigation for children and adolescents aged at least six years as a part of the FDCs: E/C/F/TDF and E/C/F/TAF.

A 50 mg pediatric immediate-release tablet and a 20 mg pediatric dispersible tablet are in development.

COBI is being studied in treatment-experienced children aged three months to 18 years who are suppressed and on RTV boosted ATV- or DRV-containing regimens.⁶² The study will switch children from RTV to COBI and look at steady state pharmacokinetics and confirm the dose. It will also evaluate the safety, tolerability, and efficacy of ATV/COBI or DRV/COBI. Reduced dose co-formulations are planned.

CCR5 RECEPTOR ANTAGONIST

Maraviroc

The pediatric maraviroc (MVC) study is still ongoing in children aged two to 18 years who are infected with CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). This drug will not work for people with CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.⁶³

Dosing of MVC is complex and determined by body surface area and concomitant medications.⁶⁴ Wide use of MVC is not expected.

WHAT NEEDS TO BE DONE?

Speed up development. The gap needs to be narrowed between approval of new drugs for adults, children, and neonates. An evidence base to support not always taking a de-escalated age band approach when studying new drugs is needed. Optimize use of pharmacokinetic data and modelling.

Speed up approval. Harmonization of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is needed to help speed up approval.

Implement WHO recommendations. As simpler formulations identified to implement the guidelines become available (most typically LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers.

Coordinate Procurement. Guidance on optimal formulations needs to be easily available to countries and updated as better ones become available. Companies need to be informed of the priority formulations. Plans need to be in place to phase out suboptimal formulations and phase in new ones. Donors need to ensure the availability of low volume products in a diminishing market.

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Preventive Technologies: Antiretroviral and Vaccine Development

By Tim Horn and Richard Jefferys

With the continued rollout and implementation of global, national, and regional HIV incidence targets and timelines, one thing has become abundantly clear: reducing HIV rates below endemic and epidemic levels in all vulnerable populations and subpopulations everywhere in the world will require not only a monumental scale-up of care and antiretroviral therapy for those living with the virus, but also fierce commitment to primary biomedical prevention. This isn't simply rhetoric, but rather a public health mandate that is supported by a growing body of epidemiological and other scientific data.^{1,2,3,4}

However, only a fraction of adolescents and adults vulnerable to HIV are accessing one of the most important evidence-based additions to the prevention toolbox: coformulated tenofovir disoproxil fumarate and emtricitabine (Truvada; TDF/FTC) as a pre-exposure prophylaxis (PrEP). In the U.S. alone, where TDF/FTC has been approved as PrEP since July 2012, of the 1.2 million adults with indications for PrEP—a likely conservative estimate from the U.S. Centers for Disease Control and Prevention (CDC)—only an estimated 4% have used it, even briefly.^{5,6} For PrEP to have a population-level effect in the U.S., however, a substantial increase in PrEP uptake will be required: 40% use among high-risk men who have sex with men, 10% use among people who inject drugs, and 10% use among high-risk heterosexuals would be in the absence of any improvements in clinical care engagement and viral load suppression rates among people living with HIV, necessary to prevent approximately 48,000 new infections between 2015 and 2020.⁷

Significant barriers to PrEP uptake exist, with the most egregious examples being achingly slow product registration and national health plan inclusion—the high cost of TDF/FTC, along with limited cost-effectiveness data, are considerable factors⁸—in many high-, middle-, and low-income countries. Even where PrEP has been approved, myriad access challenges exist. Examples in the U.S. include restrictions in CDC and other federal agency funds to pay for TDF/FTC; reluctance to expand Medicaid in many states, particularly those with high HIV prevalence and incidence estimates; and lags in awareness of PrEP and best screening, prescribing, and monitoring practices among primary care providers. Implementation strategies to overcome these structural hindrances, on top of myriad social and behavioral barriers, will be critical for PrEP's success.

Success also depends on expanding the toolbox of biomedical prevention modalities that can extend the very high level of adherence-dependent protection associated with oral TDF/FTC to individuals and populations with unique safety, dosing, and affordability needs.⁹ Additional oral antiretroviral regimens, including maraviroc (MVC)- and tenofovir alafenamide (TAF)-based combinations, are in various stages of development. Although no generic contenders have yet entered clinical trials, the scientific and economic basis for fast-track evaluations of TDF (which loses its patent at the end of 2017) and 3TC can potentially hasten global scale-up of oral PrEP before coformulated TDF/FTC's patent expires in 2021.

Interest in long-acting (LA) products also continues to grow. An injectable nanoformulation of cabotegravir is now entering its efficacy phase of development. Another intriguing contender, much further back in the pipeline, is MK-8591, Merck's nucleoside reverse transcriptase inhibitor, which may allow for injectable dosing separated by several months (see "The Antiretroviral Pipeline," page 21).

Researchers and advocates for women's health are also working to wrap their heads around long-awaited data from ASPIRE and the Ring Study, two phase III investigations of the dapivirine intravaginal ring reported at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI) earlier this year in Boston and

reviewed in detail below. Both trials suggest that the dapivirine ring has the potential to be at least moderately effective, but that significant utilization challenges exist, particularly for young sub-Saharan African women—a highly vulnerable population in dire need of an acceptable primary prevention option.

Also inching forward is a cache of other products for vaginal and rectal administration: gels, tablets, and films, along with an array of other intravaginal rings that combine drug and hormonal products for broad-spectrum antiviral and contraceptive protection.

Passive immunization involves the infusion of antibodies that are capable of inhibiting a large swathe of HIV variants, and represents another potential biomedical prevention option that is now being vigorously pursued. The launching of the first efficacy trials of the approach in adults was announced recently.¹⁰ Known as the antibody-mediated prevention (AMP) studies, they will test bimonthly infusions of the VRC01 antibody in populations that are at high risk of HIV infection.

Inducing protective antibody responses with a vaccine remains a stubborn challenge for researchers, but progress continues in the pre-clinical realm, and there is hope that candidates capable of leading the immune system down the road toward the generation of effective antibodies will enter clinical trials in the next year or two.^{11,12}

In the interim, the major news for the HIV vaccine field is that the first efficacy trial in nearly a decade will begin later this year.¹³ The trial, HIV Vaccine Trials Network (HVTN) 702, is designed to try and duplicate or improve on the slight, but statistically significant, 31.2% reduction in risk of HIV acquisition that was observed in RV144, a large-scale evaluation of a prime-boost vaccine regimen that was conducted in Thailand and reported results in 2009.¹⁴ HVTN 702 will take place in South Africa and, if all goes according to plan, results are anticipated by 2020.

ANTIRETROVIRALS FOR PREVENTION

Table 1. Antiretroviral-based PrEP and Microbicides Pipeline 2016

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
ORAL FORMULATIONS				
TAF + FTC	NtRTI/NRTI	Gilead Sciences	Oral	Phase III (planned)
MVC	EI	HPTN/ACTG	Oral	Phase II
LONG-ACTING FORMULATIONS				
Cabotegravir	INSTI	ViiV Healthcare	IM	Phase IIb/III
Rilpivirine	NNRTI	PATH	IM	Phase II
MICROBICIDE RINGS, GELS, FILMS, AND OTHER INSERTABLES				
Dapivirine	NNRTI	IPM	Vaginal ring	Phase IIIb
			Vaginal gel	Phase II
			Rectal gel	Phase II
			Vaginal film	Phase I
Tenofovir	NtRTI	CONRAD	Vaginal gel	Phase IIIb
			Rectal gel	Phase II
			Vaginal ring	Phase I
			Vaginal tablet	Phase I

Agent	Class/Type	Manufacturer/Sponsor	Delivery	Status
MICROBICIDE RINGS, GELS, FILMS, AND OTHER INSERTABLES (continued)				
PC-1005	NNRTI, ZA, CGN	Population Council	Vaginal and rectal gel	Phase I
MVC	EI	IPM	Vaginal and rectal gel	Phase I
MVC + dapivirine	EI/NNRTI	IPM	Vaginal ring	Phase I
Dapivirine + darunavir	NNRTI/PI	IPM	Vaginal gel	Phase I
DS003	EI	IPM	Vaginal tablet	Phase I
MULTI-PURPOSE TECHNOLOGIES				
Tenofovir + levonorgestrel	NtRTI/HC	CONRAD	Vaginal ring	Phase I
Dapivirine + levonorgestrel	NNRTI/HC	IPM	Vaginal ring	Phase I

ACTG, AIDS Clinical Trials Group; CGN, carrageenan; EI, entry inhibitor; FTC, emtricitabine; HC, hormonal contraceptive; HPTN, HIV Prevention Trials Network; IM, intramuscular; IPM, International Partnership for Microbicides; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide fumarate; ZA, zinc acetate

ORAL FORMULATIONS

With scale-up initiatives to bolster TDF/FTC awareness and utilization where it is approved as PrEP under way—along with ongoing efforts to see that the coformulation is registered and covered by national health programs in other countries—two additional oral products continue to make their way down the biomedical prevention pipeline.

The advantages of these compounds—which include ViiV’s MVC and Gilead’s TAF plus FTC—as PrEP remain unclear. Possibilities include improved markers of renal and bone safety relative to TDF-inclusive regimens. Although kidney and bone problems remain uncommon and mild, and are almost always reversible following drug cessation among long-term TDF/FTC PrEP users in clinical trial and demonstration project cohorts, new oral compounds may prove to be useful for those with other risk factors (e.g., underlying renal insufficiency, baseline bone mineral deficiency, concomitant use of nephrotoxic or bone mineral-depleting medications, and advancing age).^{15,16,17,18,19,20}

MVC (Selzentry)

CCR5-tropic HIV—HIV that utilizes the CCR5 coreceptor on CD4 cells to gain entry and establish infection—is responsible for more than 95% of new sexually transmitted infections of the virus.^{21,22} Thus, there has been interest in studying the CCR5 antagonist MVC for its potential use as PrEP. Not only might MVC be associated with a reduced risk of adverse events, its unique mechanism of blocking cellular rather than viral protein function may also be associated with a reduced risk of developing drug resistance.

Preliminary data from the phase II NEXT-PrEP study (HPTN 069/ACTG A5305) suggest that MVC is well tolerated and is potentially efficacious as PrEP in transgender women and men who have sex with men (TG/MSM), although it is likely more effective as a component of a multi-drug regimen.²³ Results from the study’s cohort of 200 women vulnerable to HIV infection enrolled in NEXT-PrEP will be reported at the 2016 International AIDS Conference in Durban.

The TG/MSM cohort comprises 406 participants randomized to receive either MVC alone, MVC plus FTC, MVC plus TDF, or standard-of-care TDF/FTC. All participants had a history of condomless anal intercourse

with at least one HIV-positive or unknown serostatus man within 90 days of study entry. The median age at baseline was 30 years; 2% were transgender, 28% black/African American, 22% Latino, and 62% white.

There were 34 sexually transmitted infections (STIs) diagnosed among 31 participants (8%) at study entry. During the 48-week follow-up period, 115 additional STIs were diagnosed.

Adherence rates, based on plasma drug concentrations in a random subset of 160 participants across the four study groups, were 83% at week 24 and 77% at week 48.

There were 67 grade 3–4 adverse events, with no differences in occurrence rates or severity among the four study arms. Hypophosphatemia (17%) and upper respiratory tract infections (11%) were the most common grade 2 or higher adverse events. Other than increased creatinine being documented in 1% of study volunteers in the MVC/FTC group, renal safety results were limited. Additional safety data, including bone mineral density findings, are forthcoming.

Five new HIV infections were documented during the study, for an annual incidence rate of 1.4% (95% confidence interval (CI): 0.8%–2.3%). Four of the five infections occurred in participants in the MVC monotherapy group; one occurred in the MVC/TDF group, but this participant had undetectable plasma drug concentrations at every study visit.

One of the participants in the MVC monotherapy group who became infected had a plasma drug concentration at the time of seroconversion (145 ng/mL) that was significantly above the median pre-dose state of 32 ng/mL expected in individuals with 100% adherence. His MVC plasma concentrations were highly variable prior to HIV detection at week 16, however, indicating that adherence was inconsistent. The second and third participant in the MVC monotherapy group to become infected had suboptimal drug concentrations on their documented seroconversion dates: 6.7 and 0.7 ng/mL; both individuals also had a history of drug concentrations consistent with poor adherence. The fourth participant in the MVC group to become infected had undetectable drug concentrations at the time of seroconversion and throughout the duration of the study.

Adherence observations aside, the imbalance in new infections among those in the MVC monotherapy group raises questions about the potential for stand-alone MVC as PrEP and the likely need for MVC-inclusive combinations to ensure efficacy.

A substudy of NEXT-PrEP underscores this concern.²⁴ It was conducted to explore MVC's association with increased gut-associated lymphoid tissue (GALT) T cell activation as well as increased CCR5 expression^{25,26}—observations in HIV-positive people that would be undesirable in HIV-negative individuals who are already vulnerable to the virus—and to determine whether MVC is associated with suppression of colorectal explant HIV infection.

There were no significant differences in CD4+ cell activation phenotypes between baseline and week 24 or 48 samples collected from the 55 TG/MSM participants selected at random from the four study groups. Nor were there increases in CCR5 phenotype in the substudy. And although significant viral suppression was seen between baseline and week 24 with all of the PrEP study regimens in the explant infection study, no significant suppression was seen at week 48 in samples from substudy participants receiving MVC alone.

The reason(s) for MVC's diminished suppression of explant HIV infection are not clear. The study investigators noted that a limitation of explant research is that MVC disassociates, or loses its affinity for, tissue in culture—findings that don't necessarily mirror what happens in vivo. Pharmacokinetic (PK) and pharmacodynamics (PD) data are pending and may help to explain the lack of efficacy.

The next steps for MVC's development as oral PrEP, or a component thereof, are currently being discussed.

TAF and FTC

Like TDF, TAF is a prodrug formulation of tenofovir. Unlike TDF, which is converted in the blood to the active drug tenofovir diphosphate (TFV-DP) and then taken up into cells, TAF is primarily metabolized and converted to TFV-DP inside of cells. Using a much lower dose (25 mg), TAF achieves plasma tenofovir levels that are roughly 90% lower, but intracellular concentrations that are approximately four- to sevenfold higher.^{27,28} The reduced systemic exposure has the potential for fewer renal- and bone-related toxicities compared with TDF. TAF's low-milligram dosing also has the potential for reduced generic production costs and, ultimately, greater affordability versus TDF/FTC in low-income countries. Hence, TAF coformulated with FTC—approved as Descovy in the U.S. and other countries, but indicated only for the treatment of HIV infection—is also being eyed as an alternative to Truvada.

Results from CDC evaluations of TAF plus FTC in rhesus macaques that were rectally challenged with simian-human immunodeficiency virus (SHIV)—a model and methodology that were used previously to establish the potential efficacy of TDF and TDF/FTC as PrEP—were reported at CROI 2016.²⁹ The first of the two-part study established TAF 1.5 mg/kg as the macaque dose required to achieve intracellular concentrations that were comparable to those typically seen in humans receiving TAF 25 mg. The second part of the study treated 12 macaques with either TAF or placebo and then challenged them weekly for up to 19 weeks.

None of the TAF-treated macaques were infected after 19 exposures—100% protection, whereas the previous macaque studies of TDF/FTC suggested 94% protection after 14 SHIV exposures—and all six of the placebo-treated macaques were infected by their tenth exposure to the virus. Of note, macaque rectal concentrations of TFV-DP were lower with TAF than those of the macaques previously treated with TDF.

Some questions about the interchangeability of TAF for TDF as PrEP have arisen following a second report at CROI 2016, this time from a study evaluating concentrations of TFV and TFV-DP in mucosal tissues from eight HIV-negative women who received a single dose of TAF 25 mg.³⁰ Consistent with PK data used to support TAF's use as a treatment, the plasma levels of TFV were 19-fold lower and peripheral blood mononuclear cell (PBMC) levels of TFV-DP were ninefold higher than those seen following single-dose TDF 300 mg dosing in an earlier study.

The investigators hypothesized that TFV-DP levels following TAF administration would also be significantly higher in cervical, vaginal, and rectal cells compared with TDF. Conversely, intracellular concentrations in biopsied tissues proved to be significantly lower: twofold in cervicovaginal samples and 13-fold in rectal samples. And, compared with TDF, TAF administration resulted in a higher percentage of tissue samples with undetectable drug levels: 63% of the rectal and 75% of genital tract samples had TFV and TFV-DP concentrations below the level of detection.

Making heads or tails of the macaque and human tissue studies is especially difficult in light of the fact that pharmacologic correlates of protection and surrogate/biologic markers of prophylactic efficacy have not yet been fully validated. The research teams from both studies agree that additional study will be necessary before any conclusions about the efficacy of F/TAF can be made, particularly in comparison with a coformulated regimen that has not only been proven to be highly effective and well tolerated as PrEP, but will be coming off of patent in five years.

Additional investigations aimed at determining the pharmacology of TAF in mucosal tissues are expected, as are large-scale registrational trials conducted by Gilead Sciences.

Of additional interest are extended-release implants containing TAF. The Oak Crest Institute for Science (Monrovia, California) published encouraging animal PK data from a study of a subdermal delivery system similar to that used for removable contraceptive rods (e.g., Norplant).³¹ Also in early development is a biodegradable thin-film polymer device containing TAF that can be administered subcutaneously.³²

LONG-ACTING (LA) FORMULATIONS

Improving the acceptability of PrEP is one approach to strengthening adherence rates among populations at risk for HIV infection. Particular focus is being placed on the development of LA nanosuspension formulations of antiretrovirals with PrEP potential, which may allow for doses that are separated by weeks or months. The drug furthest along the development path is LA cabotegravir (CAB LA), ViiV Healthcare's integrase strand transfer inhibitor (and dolutegravir analog) entering phase III trials. On a less certain course is a LA injectable version of rilpivirine (RPV LA), Janssen's NNRTI.

Cabotegravir LA

Long-awaited preliminary data from the phase IIa ÉCLAIR trial were reported at CROI 2016.³³ The study, designed to assess safety and tolerability, randomized 127 HIV-negative men between 18 and 65 years of age and at low risk of acquiring HIV at screening to either CAB (N = 106) or placebo (N = 21). For the first four weeks of the trial, oral CAB (30 mg) or placebo were administered, followed by a seven-day washout period. The injection phase began at week five and ended at week 41, with CAB LA 800 mg or saline being administered via IM injections during visits on weeks 5, 17, and 29. The study also included a follow-up phase, for a total of 81 weeks.

The median age at baseline was 30 years. Approximately 57% were white, 33% were black/African American, and 14% were Hispanic/Latino. Approximately 76% in the placebo group, compared with 85% in the CAB group, listed sex with other men as their risk factor for HIV (compared with heterosexual contact for 29% and 21%, and occupational exposure for 5% and 2%, respectively).

Adverse events leading to withdrawal during the oral phase (N = 7) included three events of neutropenia, three events of increasing creatine phosphokinase (CPK), and one event of fatigue—all of which occurred in the CAB group. For participants who entered the injection phase, a similar proportion (93% for CAB LA, 95% for placebo) completed all three injection cycles. Injection intolerability led to withdrawal in 4% of CAB LA participants. One participant in the placebo group seroconverted and subsequently withdrew from the study.

The number of grade 2–4 adverse events in the CAB group was higher than in the placebo group during the injection phase (80% for CAB LA, 48% for placebo). Grade 2 events in the injection phase that were not related to injection site pain included fever (7% versus 0%, respectively), injection site itching (6% versus 0%, respectively), and injection site swelling (6% versus 0%, respectively).

CAB PK data throughout each 12-week dosing interval were reported. Results showed trough concentrations to be lower than the prespecified ideal (fourfold higher than the protein-adjusted 90% inhibitory concentration [$4 \times \text{PA-IC}_{90}$] of 0.664 mg/mL) at the end of the dosing intervals in approximately two-thirds of participants; 15% to 31% had trough concentrations below $1 \times \text{PA-IC}_{90}$ at the end of the dosing intervals. On the basis of these findings, a new dosing strategy of 600 mg IM injections every eight weeks has been selected for CAB LA's continued development.

Two seroconversions were reported: one in the placebo group at week 23 and one in the CAB LA group at week 53—24 weeks after the participant's final injection. The participant in the CAB group who ultimately seroconverted had no detectable CAB in blood plasma at week 53 and was one of the individuals who had CAB trough concentrations below $1 \times \text{PA-IC}_{90}$ on two occasions during the injection phase of the study.

A second phase IIa trial, HIV Prevention Trials Network study 077 (HPTN 077), is currently enrolling approximately 176 HIV-negative volunteers—60% of the participants will be women—in the U.S., South America, and sub-Saharan Africa.³⁴ It is designed similarly to ÉCLAIR, with its primary objectives being safety, tolerability, and acceptability assessments in participants at low-to-minimal risk of HIV infection.

Currently in the final stages of development is HPTN 083, a phase IIb/III head-to-head safety and efficacy trial of CAB LA versus oral TDF/FTC.³⁵ In step 1 of the trial, lasting five weeks, participants will receive oral TDF/FTC or oral CAB 30 mg daily, depending on the randomization. In step 2, participants will receive a daily oral placebo plus active CAB LA 3 mL injections at two time points four weeks apart and every eight weeks thereafter, or active daily oral TDF/FTC plus placebo injections, for up to 180 weeks. In step 3, to cover the prolonged PK “tail” associated with CAB LA dosing, all participants will receive daily oral TDF/FTC for approximately one year, starting no later than eight weeks after the last injection.

HPTN 083 trial has a planned enrollment of 4,500 TG/MSM individuals 18 years of age and older who are at high risk for sexually acquiring HIV infection. The estimated study completion date is June 2020.

Rilpivirine LA

Encouraging phase I results from the SSAT 040 study evaluating the PK of RPV LA in plasma, the genital tract in women, and the rectum in men were published in 2014.³⁶ Later that year, however, preliminary data from the MWRI-01 phase I study suggested that RPV LA’s activity in rectal versus cervicovaginal tissues may differ considerably.³⁷ Although RPV levels following single 600 mg and 1,200 mg (2×600 mg) doses were higher in vaginal fluids versus rectal fluids, rectal tissues were found to have twice the concentration of RPV compared with vaginal tissues. In fact, rectal cell explants were fully resistant to HIV nearly two months after the 1,200 mg RPV LA injections were given, whereas vaginal and cervical cell explants appeared to be no better protected from HIV following either dose of the drug.

A more recent study characterized the concentrations of RPV needed to prevent HIV infection in mucosal tissue.³⁸ Although rectal tissue RPV PK appeared to be sufficient to block HIV infection—concentrations were approximately fivefold higher than what would be required to suppress viral infection—2.5-fold more drug was needed in female genital tissue to demonstrate similar inhibition. These data, the authors noted, support the explant findings from MWRI-01, in which HIV infection was suppressed in rectal tissue, but not in cervicovaginal tissues.

Still under way, with an expected completion date of October 2017, is HPTN 076, a phase II safety and acceptability evaluation of RPV LA, compared with placebo, in approximately 132 HIV-negative women between 18 and 45 years of age in Cape Town, South Africa; Harare, Zimbabwe; Newark, New Jersey; and Bronx, New York.³⁹ The women have been randomized (2:1) to receive either daily oral rilpivirine 25 mg or placebo for four weeks. In the absence of any safety signals, the participants will receive either 1,200 mg RPV LA (2 mL IM injections in both gluteal muscles) or placebo every eight weeks for a total of six injections.

Based on the conflicting PK and explant infection data reported to date, compounded by the formulation’s need for cold-chain storage, RPV LA is not expected to move into phase III trials for PrEP.⁴⁰

MICROBICIDES: INTRAVAGINAL RINGS

With a growing body of data suggesting that antiretroviral-based prevention modalities are effective for women who are vulnerable to HIV infection, provided that adherence levels that are consistent with protection can be achieved, there has been considerable interest in more user-friendly and longer acting technologies. Polymeric intravaginal rings (IVRs), similar to those used to control the release of estrogens or progestogens that provide contraceptive protection, are one such technology and are currently in various stages of development.

Dapivirine

The most clinically advanced candidate is a silicone elastomer IVR containing 25 mg dapivirine (TMC120), a NNRTI licensed to the International Partnership for Microbicides (IPM) by Janssen Sciences Ireland UC. Data from two registrational trials, the Microbicide Trials Network's ASPIRE study (MTN-020) and the International Partnership for Microbicides' Ring Study (IPM 027), were reported at CROI 2016, with the final ASPIRE results being simultaneously published in the New England Journal of Medicine.^{41,42,43}

ASPIRE, a phase III trial conducted at sites in Malawi, South Africa, Uganda, and Zimbabwe, randomized 2,629 HIV-negative women between 18 and 45 years of age to receive the dapivirine IVR or a matching placebo IVR, which were self-inserted and removed once a month for a year. The Ring Study, a phase II/III evaluation at six South African and one Ugandan site, compared the dapivirine IVR to a placebo IVR, inserted once every month over 24 months, in 1,959 HIV-negative women between 18 and 45.

Results from both studies, highlighted in table 2, suggest that the dapivirine IVR is safe and moderately effective at reducing incident HIV in African women. HIV infection rates were reduced by approximately one-third overall, with greater protection occurring in both trials among women 22 years of age and older: 56% in ASPIRE and 37% in the Ring Study, with little to no protection among women 21 years of age and younger.

In ASPIRE, women 22 years of age and older appeared to use the ring more consistently. In the Ring Study, there was a trend toward higher efficacy with more consistent use. In discussing the ASPIRE results, principal investigator Jared Baeten, MD, of the University of Washington reiterated that strong relationships between adherence and HIV protection are expected in all biomedical prevention studies. However, unlike post hoc PK analyses from oral TDF/FTC PrEP trials, which have demonstrated strong adherence is associated with protection approaching 100%, inferences regarding maximum possible protection using the dapivirine IVR are not yet possible. Further analyses are required to define whether there is a threshold of dapivirine IVR use for protection against HIV, and to ferret out both behavioral and possible biologic effects that may have contributed to the lack of HIV protection in the youngest women in both studies.

Table 2. ASPIRE and The Ring Study

	ASPIRE (MTN 020)		Ring Study (IPM 027)	
	Dapivirine IVR (N = 1,313)	Placebo IVR (N = 1,316)	Dapivirine IVR (N = 1,300)	Placebo IVR (N = 650)
Median age	26 years		26 years	
Married	41%		11%	
Primary sex partner	>99%		>98%	
RETENTION AND ADHERENCE				
Person-years follow-up	4,280		2,805	
Expected protocol-specified visits	91%		82%	
Ring adherence	82% to 84%		83%	
HIV-1 PROTECTION				
Number of seroconversions, overall	71	97	77 (5.9%)	56 (8.9%)
Number of seroconversions, sites exclude**	54	85		
HIV-1 incidence, overall (per 100 patient-years [P/Y])	3.3	4.5	4.1	6.1
HIV-1 incidence, sites excluded (per 100 P/Y)**	2.8	4.4		

	ASPIRE (MTN 020)		Ring Study (IPM 027)	
	Dapivirine IVR	Placebo IVR	Dapivirine IVR	Placebo IVR
HIV-1 PROTECTION (continued)				
Protection effectiveness, overall, all ages	27% (95% CI: 1% to 46%); P = 0.007		31% (95% CI: 0.9% to 51%); P = 0.040	
Protection effectiveness, sites excluded, all ages**	37% (95% CI: 12% to 56%); P = 0.007			
Protection effectiveness, <21 years of age	−27% (95% CI: −133% to 31%)		15% (95% CI: −60% to 55%)	
Protection effectiveness, ≥22 years of age	56% (95% CI: 31% to 71%); P < 0.001		37% (95% CI: 3% to 59%)	
SAFETY				
Serious adverse events	4%	4%	3%	1%
Metrorrhagia			26%	28%
Genital infection			22%	18%
Menorrhagia			20%	10%
NNRTI mutations	12%	10%	18%	16%

*Dapivirine plasma concentrations >95 pg/mL (indicating at least 8 hours of continuous use); residual dapivirine <23.5 mg in returned rings (indicating at least some use during the month)

**Excluding data from two sites with recruitment and monitoring difficulties

Additional dapivirine IVR results reported at CROI 2016 included data from a phase IIa PK, safety, adherence, and acceptability study in 96 postmenopausal women in the U.S (MTN-024/IMP 031).^{44,45} The women—the mean age at baseline was 56.8 years; 66% were white and 31% were black/African American, 61% had a primary sexual partner, and 66% were sexually active—were randomized 3:1 to monthly IVRs containing dapivirine 25 mg or placebo for 12 weeks.

IVRs were safe and well tolerated. Only two women chose not to continue using the rings as a result of adverse events. There was no difference in the number of women with related grade 2 or higher adverse events in the two groups (8% versus 13% in the dapivirine and placebo groups, respectively), and no statistical significantly differences in grade 3 or higher adverse events (6% versus 0%, respectively). One grade 3 adverse event (vaginal pain) was deemed to be related to study product. Adherence rates were also high, with most women (99%) saying the IVR was very easy/easy to use, 96% indicating that it never interfered with daily activities, 91% reporting they either liked or very much liked the IVR, and 65% preferring VR to condoms.

Two cost-effectiveness analyses were also reported at CROI 2016.^{46,47} According to one analysis using a deterministic HIV transmission model of South Africa, the dapivirine IVR could avert 125,000–175,000, 265,000–364,000, or 427,000–588,000 infections at 25%, 50%, and 75% efficacy, respectively, from 2017–2050 under the different counterfactual scenarios.⁴⁶ This represents 1.1% to 7.0% of total HIV infections in this period at corresponding cost-effectiveness of US\$1,000 to US\$1,300, US\$370 to US\$520, and US\$160 to US\$260 per disability-adjusted life year (DALY) averted.

As for next steps, two open-level evaluations of the dapivirine IVR are planned. MTN-025, the HIV Open-Label Prevention Extension (HOPE) trial, is an ASPIRE follow-on study to assess continued safety and adherence, and is scheduled to begin this summer. IPM hopes to conduct its own open-label extension follow-on study to provide former Ring Study participants with the dapivirine IVR.

IPM plans to submit the dossier of dapivirine IVR evidence—ASPIRE and the Ring Study are only a part of an extensive research portfolio (table 3)—required for licensure to regulatory agencies beginning in early 2017.

Table 3. Dapivirine IVR Study Portfolio

Study	Description	N	Status
IPM 007	Seroconverter protocol	n/a	Ongoing
IPM 013	IVR safety & PK	48	Completed
IPM 015	IVR safety	280	Completed
IPM 024	IVR safety & PK	16	Completed
IPM 027	The Ring Study	1,959	To be completed 12/2016; preliminary data reported at CROI 2016
IPM 028	Drug-drug interaction	36	Completed
IPM 029	Male condom functionality	70 couples	Completed
MTN-020	Phase III ASPIRE trial	2,629	Completed; reported at CROI 2016 and published
MTN-023/IPM 030	IVR safety (adolescent girls)	96	Ongoing
MTN-024/IPM 031	IVR safety & acceptability (postmenopausal women)	96	Reported at CROI 2016
IPM 033	Female condom functionality	80 couples	Data analysis
IPM 034	IVR extended PK	40	Completed
IPM 035	Menses & tampon use	32	Ongoing
IPM 036	Drug-drug interactions	36	Ongoing
MTN-029/IPM 039	PK (lactating women)	16	Enrolling
MTN-031/IPM 043	Financial Incentives and ring adherence	450	In development
MTN-034/IPM 045	IVR and oral TDF/FTC crossover in adolescent girls	300	In development
MTN-036/IPM 047	PK & safety of three dapivirine ring formulations	36	In development
MTN-025	Phase IIIb open-label (HOPE) ASPIRE follow-on trial		Planned

Source: Microbicide Trials Network, International Partnership for Microbicides

MICROBICIDE GELS

The future of vaginal microbicides remains uncertain following the disappointing data from both the FACTS 001 and VOICE studies evaluating 1% tenofovir gel.^{48,49} Additional data are anticipated, however. These include results from the phase IIIb CAPRISA 008—currently being analyzed by CONRAD investigators—an open-label follow-on study of the phase IIb CAPRISA 004 trial to collect additional safety and data and to evaluate the feasibility and effectiveness of providing 1% tenofovir gel to HIV-negative women through family planning clinics in KwaZulu-Natal, South Africa.⁵⁰

Although adherence, rather than potency, was believed to be the primary factor associated with poor efficacy in the FACTS 001 and VOICE studies, a number of gel-based microbicides containing alternative compounds—dapivirine, MVC, and a broad-spectrum coformulation of MIV-150, zinc acetate, and carrageenan (see below)—are at various stages of early development. Several of these products, in addition to a reduced-glycerin 1% tenofovir gel, are also being evaluated for rectal use and protection.

Reduced-Glycerin 1% Tenofovir Gel

The reduced-glycerin 1% tenofovir gel (RG 1% TFV), developed by CONRAD, has an improved osmolality profile, meaning that it contains fewer sugars and salts relative to epithelial cells, and therefore prevents tissues from purging too much water. This may in turn prevent damage to the structural integrity of the rectum's lining and help to minimize the gastrointestinal side effects documented in earlier 1% tenofovir gel studies.^{51,52}

MTN-017 is a phase II safety and acceptability study of RG 1% TFV in 195 HIV-negative MSM and transgender women in the U.S., Peru, Thailand, and South Africa.⁵³ It was designed as a follow-up trial to the phase I MTN-007 rectal study, the data from which were published last year.⁵⁴

The study employed a crossover design that required all study participants to cycle through three eight-week regimens: RG 1% TFV used daily, RG 1% TFV used episodically before and after receptive anal intercourse, and TDF/FTC taken orally daily.

Most side effects from study products in MTN-017 were minor, with roughly a third of participants experiencing grade 2 or higher adverse events using the three regimens: 34% for TDF/FTC, 33% for daily RG 1% TFV, and 30% for episodic RG 1% TFV.

Overall, participants were highly adherent in MTN-017, which was defined as >80% of expected doses taken and assessed by convergence scoring of daily texts and study product returns. Episodic RG 1% TFV and daily oral TDF/FTC dosing were associated with >80% adherence among 93% and 94% of study participants, respectively, compared with 83% adherence to daily RG 1% TFV dosing. Using qualitative plasma PK testing, the investigators also noted that 94.3% TFV-positive samples were associated with oral TDF/FTC, compared with 80.2% with daily RG 1% TFV dosing.

With respect to acceptability, participants reported they would be less likely to use the daily RG 1% TFV regimen (odds ratio [OR]: 0.38, $P < 0.001$), but would be just as likely to use the episodic RG 1% TFV regimen (OR: 0.70, $P = 0.23$), for HIV protection compared with oral TDF/FTC dosing. Overall liking of the regimens also favored oral TDF/FTC compared with either daily (OR: 0.28, $P < 0.28$) or episodic (OR: 0.37, $P < 0.002$) RG 1% TFV dosing.

Additional data from MTN-017, including quantitative PK testing data to shed additional light on adherence in the trial, are forthcoming.

PC-1005

The Population Council is developing PC-1005, a combination gel containing the NNRTI MIV-150, zinc acetate, and carrageenan. PC-1005 potentially offers protection not just against HIV, but also against herpes simplex virus-2 (HSV-2) and human papillomavirus.

Phase I safety, PK, acceptability, and adherence data were presented at CROI 2016.⁵⁵ The trial enrolled 25 HIV-negative women between 19 and 44 years of age. Following a three-day open label evaluation of PC-1005 in five participants, 20 women were randomized to apply PC-1005 4 mL or placebo once daily for 14 days.

Seventeen women completed the randomized phase of the trial (two were lost to follow up and one withdrew before dosing). There were no severe adverse events or early discontinuations because of adverse events. MIV-150 was absorbed systemically at low levels and there was measurable HIV and HPV activity in cervicovaginal lavages (CVLs). Acceptability was also high: 94% of participants reported a willingness to use the gel in the future.

Additional data presented at CROI 2016 indicate that PC-1005 inhibits HIV and HSV-2 infection in cervical explants in a dose-dependent manner.⁵⁶

CONTRACEPTIVE-INCLUSIVE MULTIPURPOSE PREVENTION TECHNOLOGIES

As has been well documented in the development of oral PrEP and microbicides, there is a need for biomedical prevention options that protect against not just HIV (and other STIs), but also unwanted pregnancies. For women vulnerable to both, the development of multipurpose prevention technologies (MPTs) is of tremendous interest.

Products currently in preclinical development can be categorized as either LA or on-demand. LA MPTs include IVRs, and on-demand products include gels that can be used around the time of intercourse.

LA MPTs that are currently in phase I studies include IVRs containing levonorgestrel—a synthetic progestogen that has been studied and used extensively, and is therefore considered to be suitable for formulation in matrix IVRs—combined with either tenofovir or dapivirine. Data from CONRAD’s phase I evaluation of the safety, PK, and acceptability of its IVR containing tenofovir and levonorgestrel are being analyzed.⁵⁷ A phase I safety and PK study of IPM’s matrix IVR containing dapivirine and levorgestrel is still being finalized in partnership with the Microbicide Trials Network.

PREVENTIVE VACCINES, PASSIVE IMMUNIZATION, AND ANTIBODY GENE TRANSFER

Table 4. HIV Vaccines, Passive Immunization, and Antibody Gene Transfer Pipeline

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES			
ALVAC-HIV (vCP2438) + bivalent clade C gp120/MF59	Canarypox vector encoding HIV-1 clade C gp120, clade B gp41, Gag, and protease + protein boost comprising two clade C Env proteins (TV1.Cgp120 and 1086.Cgp120)	NIAID/HIV Vaccine Trials Network (HVTN)/Bill & Melinda Gates Foundation/South African Medical Research Council/Sanofi Pasteur/Novartis Vaccines	Phase IIb/III
pGA2/JS7 DNA + MVA/HIV62	Prime: DNA vaccine Boost: Modified vaccinia Ankara strain (MVA) vector Both encoding Gag, Pol, and Env proteins from HIV-1 clade B	GeoVax/NIAID	Phase IIa
ALVAC-HIV vCP1521	Canarypox vector encoding HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol protein, and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. HIV Military HIV Research Program (MHRP)/NIAID	Phase II
AIDSVAX B/E	AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	U.S. Army Medical Research and Materiel Command	Phase II
HIVIS 03 DNA + MVA-CMDR	Prime: HIVIS DNA encoding Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) proteins Boost: MVA-CMDR encoding Env (E), Gag (A), and Pol (E) proteins	Vectura/Karolinska Institutet/Swedish Institute for Infectious Disease Control (SMI)/MHRP	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
VICHREPOL	Chimeric recombinant protein composed of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/ Russian Federation Ministry of Education and Science	Phase II
Ad26.Mos.HIV MVA-Mosaic gp140 protein	Adenovirus serotype 26 (Ad26) vectors encoding mosaic Env, Gag, and Pol MVA vectors encoding mosaic Env, Gag, and Pol gp140 protein boost	Crucell/NIAID/MHRP/IAVI/Beth Israel Deaconess Medical Center	Phase I/IIa
DNA-C + NYVAC-C	Prime: DNA vaccine encoding clade C Env, Gag, Pol, and Nef proteins Boost: NYVAC-C attenuated vaccinia vector encoding clade C Env, Gag, Pol, and Nef proteins	GENEART/Sanofi Pasteur/Collabo- ration for AIDS Vaccine Discovery (CAVD)	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics	Phase I/II
DNA-HIV-PT123 + AIDSVAX B/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID	Phase Ib
Ad26.ENVA.01	Adenovirus serotype 26 vector encoding the HIV-1 clade A Env protein	Crucell/International AIDS Vaccine Initiative (IAVI)/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost Phase I w/ Ad35-ENVA
Ad35-ENVA	Adenovirus serotype 35 vector encoding the HIV-1 clade A Env protein	Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I w/ Ad26.ENVA.01
Ad35-GRIN/ENV	Two adenovirus serotype 35 vectors, one encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, the other encoding HIV-1 clade A Env (gp140)	IAVI/University of Rochester	Phase I Prime-boost Phase I w/ GSK HIV vaccine 732461 (F4)
Ad5HVR48.ENVA.01	Hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; encodes HIV-1 clade A Env	Crucell/NIAID	Phase I
Cervicovaginal CN54gp140-Hsp70 conju- gate (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (Hsp70) adjuvant, delivered intravaginally	St George's, University of London/ European Union	Phase I
DCVax + poly ICLC	Recombinant protein vaccine including a fusion protein comprising a human monoclonal antibody specific for the dendritic cell receptor DEC-205 and the HIV Gag p24 protein, plus poly ICLC (Hiltonol) adjuvant	Rockefeller University	Phase I
DNA-HIV-PT123, NYVAC- HIV-PT1, NYVAC-HIV-PT4, AIDSVAX B/E	DNA and NYVAC vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	NIAID/IPPOX/EuroVacc/HVTN	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
DNA + Tiantan vaccinia vector	Prime: DNA vector, with or without electroporation Boost: Replication-competent recombinant Tiantan vaccinia strain vector Both encoding Gag, Pol, and Env proteins from HIV-1 CN54	Chinese Center for Disease Control and Prevention/National Vaccine and Serum Institute/Peking Union Medical College	Phase I
EN41-FPA2	Gp41-based vaccine delivered intranasally and intramuscularly	PXTherapeutics/European Commission	Phase I
GEO-D03 DNA + MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines encode Gag, Pol, and Env proteins from HIV-1 clade B and produce virus-like particles (VLPs)	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461 (F4)	Gag, Pol, and Nef fusion protein in proprietary adjuvant AS01	GlaxoSmithKline	Phase I Prime-boost Phase I w/ Ad35-GRIN
HIV-1 Tat/delta-V2 Env	Tat and oligomeric ΔV2 Env proteins	Istituto Superiore di Sanità/Novartis Vaccines	Phase I
MAG-pDNA, Ad35-GRIN/ENV	Multi-antigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system + two adenovirus serotype 35 vectors, one encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef, and the other encoding HIV-1 clade A Env (gp140)	IAVI/Profectus Biosciences/Ichor Medical Systems	Phase I
MAG-pDNA, rVSV _M , HIV-1 Gag	Multiantigen DNA vaccine encoding the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector encoding HIV-1 clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector encoding HIV-1 clade A Gag protein and 25 CD8 T-cell epitopes	Impfstoffwerk Dessau-Tornau (IDT)/University of Oxford/Medical Research Council/University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-positive (PedVacc002) and HIV-negative mothers (PedVacc001)
MVA HIV-B	MVA vector encoding HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
PENNVAX-G DNA + MVA-CMDR	Prime: DNA vaccine encoding HIV-1 clade A, C, and D Env proteins and consensus Gag protein Boost: MVA-CMDR live attenuated MVA vector encoding HIV-1 clade CRF _{01_AE} -01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/MHRP/Walter Reed Army Institute of Research	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
PolyEnv1 EnvDNA	Vaccinia viruses encoding 23 different Env proteins and DNA vaccine encoding multiple Env proteins	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA + ChAdV63.HIVconsv, or MVA.HIVconsv	Prime : DNA vaccine pSG2 Boost : chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
Ad35-ENVA	Adenovirus serotype 35 vector encoding HIV-1 clade A Env	Vaccine Research Center/NIAID	Phase I
rVSV _{IN} HIV-1 Gag	Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector encoding HIV-1 Gag	Profectus Biosciences/HVTN	Phase I
SAAVI DNA-C2, SAAVI MVA-C, clade C gp140/ MF59	SAAVI DNA and MVA vectors encoding an HIV-1 clade C polyprotein including Gag-reverse transcriptase-Tat-Nef and an HIV-1 clade C truncated Env + Novartis protein subunit vaccine comprising a clade C oligomeric V2-loop-deleted gp140 given with MF59 adjuvant	South Africa AIDS Vaccine Initiative/ HVTN/Novartis	Phase I
SeV-G(NP), Ad35-GRIN	Sendai virus vector encoding HIV-1 Gag protein delivered intramuscularly or intranasally, adenovirus serotype 35 vector encoding HIV-1 clade A Gag, reverse transcriptase, integrase, and Nef	IAVI/DNAVEC	Phase I
LIPO-5, MVA HIV-B, GTU-MultiHIV	Five lipopeptides comprising CTL epitopes from Gag, Pol, and Nef proteins MVA vector encoding Env, Gag, Pol, and Nef proteins from HIV clade B DNA vector encoding fusion protein comprising elements from six different HIV proteins Given in four different prime-boost combinations	INSERM-ANRS	Phase I Phase II
Ad4-mgag, Ad4-EnvC150	Live, replication-competent recombinant adenovirus serotype 4 vectors encoding HIV-1 clade C Env and HIV-1 mosaic Gag proteins Formulated either as enteric-coated capsules for oral administration or as an aqueous formulation for tonsillar administration	NIAID/PaxVax	Phase I
DNA Nat-B Env, NYVAC Nat-B Env DNA CON-S Env, NYVAC CON-S Env DNA mosaic Env, NYVAC mosaic Env	Prime: DNA vector encoding Nat-B, CON-S or mosaic Env proteins Boost: NYVAC vectors encoding Nat-B, CON-S or mosaic Env proteins	HVTN/IPPOX/Center for HIV/AIDS Vaccine Immunology (CHAVI)	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
CN54gp140 + GLA-AF	HIV-1 clade C gp140 protein and glucopyranosyl lipid adjuvant (aqueous formulation [GLA-AF]), delivered intramuscularly	Imperial College London/Wellcome Trust/National Institute for Health Research, U.K.	Phase I
DNA, MVA-C, CN54rgp140 + GLA-AF	DNA vectors encoding a Gag-Pol-Nef polypeptide and gp140 Env protein, both from clade C MVA-C vector encoding Gag-Pol-Nef and gp120 Env protein from clade C HIV-1 clade C gp140 protein and glucopyranosyl lipid adjuvant (aqueous formulation [GLA-AF]), delivered intramuscularly	Imperial College London/Medical Research Council/Wellcome Trust	Phase I
GTU-MultiHIV	DNA vector encoding fusion protein comprising elements from six different HIV proteins, administered by intramuscular, intradermal or transcutaneous routes	Imperial College London/European Commission- CUT'HIVAC Consortium	Phase I
DNA Nat-B Env DNA CON-S Env DNA mosaic Env MVA-CMDR	Prime: DNA vector encoding Nat-B, CON-S, or mosaic Env proteins Boost: MVA vector encoding Env (E), Gag (A), and Pol (E) proteins	NIAID/ CHAVI/IPPOX/MHRP/HVTN	Phase I
Trimeric glycoprotein140 (gp140)	Protein vaccine consisting of a trimeric gp120	Crucell/NIAID/Beth Israel Deaconess Medical Center	Phase I
MVA mosaic	MVA vectors encoding HIV-1 mosaic proteins	Crucell/MHRP/NIAID/Beth Israel Deaconess Medical Center	Phase I
DNA-HIV-PT123 AIDSVAXB/E	DNA vectors encoding HIV-1 clade C Gag, gp140, and Pol-Nef AIDSVAX B/E recombinant protein vaccine containing gp120 from HIV-1 clades B and CRF01_AE	EuroVacc/IAVI/Uganda Medical Research Council/UVRI Uganda Research Unit on AIDS/Centre Hospitalier Universitaire Vaudois	Phase I
Oral Ad26	Orally administered, replicating adenovirus serotype 26 vector encoding mosaic Env protein	IAVI/University of Rochester/Beth Israel Deaconess Medical Center	Phase I
PENNVAX-GP HIV-1 DNA vaccine Interleukin-12 (IL-12) DNA adjuvant	DNA vector encoding Gag, Pol, and Env proteins + DNA vector encoding IL-12 adjuvant, delivered via intradermal or intramuscular electroporation	NIAID	Phase I
IHV01 (FLSC-001)	Full-length single-chain gp120-CD4 complex vaccine	University of Maryland/Bill and Melinda Gates Foundation/Profectus BioSciences, Inc.	Phase I
HIV DNA-C CN54ENV + recombinant HIV CN54gp140	DNA vector encoding HIV-1 clade C Env delivered intramuscularly and intradermally Clade C Env protein boost	Imperial College London	Phase I
Ad26.Mos.HIV + clade C gp140	Adenovirus serotype 26 (Ad26) vectors encoding mosaic HIV-1 Env, Gag, and Pol + clade C HIV Env protein boost	Crucell Holland BV	Phase I

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
HIV VACCINES (continued)			
HIV-1 Nef/Tat/Vif, Env pDNA + HIV-1 rVSV envC	DNA vector encoding HIV-1 Nef/Tat/Vif and Env Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector encoding HIV-1 clade C Env	NIAID	Phase I
Ad4-mgag, Ad4-EnvC150 + AIDSVAX	Orally administered replication-competent adenovirus serotype-4 HIV vaccine in combination with an AIDSVAX B/E boost	PaxVax, Inc./NIAID	Phase I
Trivalent Ad26.Mos.HIV, tetravalent Ad26.Mos4.HIV + clade C gp140	Adenovirus serotype 26 (Ad26) vectors encoding mosaic HIV-1 Env, Gag, and Pol or Ad26 vectors encoding two mosaic HIV-1 Envs, and mosaic Gag, and Pol + clade C HIV Env protein boost	Crucell Holland BV	Phase I
PASSIVE IMMUNIZATION			
VRC01	Monoclonal broadly neutralizing antibody (bNAb) administered intravenously	NIAID/HVTN/HPTN	Phase IIb
VRC01	Monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I (adults and HIV-exposed infants)
VRC01LS	LA monoclonal bNAb administered subcutaneously or intravenously	NIAID	Phase I
ANTIBODY GENE TRANSFER			
rAAV1-PG9DP	Recombinant AAV vector encoding the PG9 broadly neutralizing antibody	IAVI/NIAID/Children's Hospital of Philadelphia (CHOP)	Phase I

PASSIVE IMMUNIZATION/ANTIBODY GENE TRANSFER

HIV is notorious for its ability to evade antibody responses, and for a long period the number of antibodies known to be capable of significantly inhibiting the virus could be counted on one hand. But the landscape has changed dramatically in recent years as a result of technological advances that have allowed the identification of an ever-growing list of antibodies that can neutralize a broad array of HIV isolates from multiple different clades. Many of these broadly neutralizing antibodies (bNAbs) are extremely potent, meaning that they can neutralize the virus even when present at relatively low concentrations.⁵⁸

The burgeoning armamentarium of bNAbs has spurred researchers to develop and manufacture candidates for testing in people, both in the prevention and treatment contexts. The furthest along is VRC01, a bNAb that was discovered toward the end of the last decade by scientists at the Dale & Betty Bumpers Vaccine Research Center (VRC) at the U.S. National Institutes of Health.⁵⁹ Phase I trials showed favorable safety and pharmacokinetic profiles,⁶⁰ leading to the recent initiation of the AMP studies, two large-scale phase IIb efficacy evaluations that represent collaborations between the HVTN and the HPTN:

- HVTN 704/HPTN 085 will enroll approximately 2,700 men and transgender people who have sex with men at sites in Brazil, Peru, and the U.S.
- HVTN 703/HPTN 081 will enroll approximately 1,500 sexually active women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe.

Participants will be randomly assigned to receive either placebo or VRC01 at one of two doses: 30 mg/kg or 10 mg/kg. Infusions are scheduled every eight weeks. The primary endpoints are safety and efficacy, with secondary analyses including assessments of VRC01 levels, markers of protection, and antibody effector functions. If the trials proceed as expected, results are likely to become available around 2022.

It is currently unclear whether VRC01 might be developed commercially if significant efficacy is demonstrated. Since VRC01 was discovered, several other broader and more potent bNAbs have been identified, and certain dual combinations have been reported to neutralize over 98% of circulating HIV isolates from multiple clades⁶¹—theoretically, at least, these newer bNAbs may be better candidates for advancing toward possible licensure.

Delivery is another issue for passive immunization approaches, and ongoing work is aiming to produce LA bNAb formulations that would be amenable to subcutaneous injection (as opposed to the inconvenient method of inpatient intravenous infusion being used in the AMP studies). A phase I trial of a LA version of VRC01, VRC01LS, was started earlier this year.⁶²

The question of whether the expense of manufacturing bNAb may be an impediment to making passive immunization a real-world prevention option has been the subject of some debate. In a presentation at the Cent Gardes HIV vaccine conference last October, John Mascola from the VRC noted that the current cost to manufacture a bNAb is about US\$100 per gram, which equates to US\$1,200 per year for a bimonthly 30 mg/kg dose administered to a 70 kg adult. However, according to Mascola, progress in improving potency, half-life, and manufacturing efficiency could conceivably bring this figure down to as low as US\$10 per person per year.⁶³

Antibody gene transfer, also known as vectored immunoprophylaxis, is a potential alternate method of bNAb delivery that is similar to gene therapy. The approach utilizes adeno-associated virus (AAV) vectors that are modified to encode genes for producing bNAbs. When injected into muscle tissue, the AAV vectors can act as factories for the persistent generation of bNAbs. A first human trial of an AAV vector encoding the bNAb PG9 began in the UK in 2014, but results have not yet been published.⁶⁴ The VRC is aiming to start a trial of an AAV vector encoding another bNAb, VRC07, before the end of the year.^{65,66}

HIV VACCINES

For the past several years, TAG's annual *Pipeline Report* has been covering the incremental progress toward the next round of HIV vaccine efficacy trials. This year represents a milestone because, on May 18, it was announced that the first of these trials, HVTN 702, is scheduled to begin before the end of the year.

HVTN 702 is the culmination of a huge amount of work conducted by the Pox-Protein Public-Private Partnership (P5), a collaboration involving the HVTN, the Bill & Melinda Gates Foundation, Novartis Vaccines and Diagnostics, Sanofi Pasteur, the South African Medical Research Council, the U.S. Military HIV Research Program, and the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS.

The goal of P5 is to duplicate or improve on the results of the RV144 trial in Thailand, which demonstrated a significant 31.2% reduction in the risk of HIV acquisition being associated with receipt of a prime-boost vaccine regimen consisting of a canarypox vector encoding HIV antigens (vCP1521) and an HIV envelope protein (AIDSVAX). Notably, vaccine efficacy appeared to be higher after one year of follow up in RV144, at around 60%, but subsequently waned—this has led to the incorporation of additional booster immunizations in the design of HVTN 702. Versions of the vaccines used in RV144 have also been developed and tailored to the prevalent clade C HIV that is circulating in South Africa, where HVTN 702 will take place.

The trial will enroll a total of approximately 5,400 men and women between the ages of 18 and 35 years who are at risk for HIV infection at 15 sites in South Africa. Participants will be randomized to receive placebo immunizations or ALVAC vCP2438 plus a boost consisting of two clade C HIV gp120 proteins in MF59 adjuvant. The ALVAC vector is administered alone at baseline and after one month, and then in combination with the gp120 boost at months 3, 6, and 12 (in RV144, the final boost was at month 6).

The decision to begin HVTN 702 was based on results from an ongoing study in South Africa, HVTN 100, which tested the same vaccine regimen to establish whether it induced HIV-specific antibody and CD4+ T cell immune responses comparable or superior to those that were associated with protection from HIV infection in RV144. The specific criteria included:

- Prevalence of binding antibodies to clade C gp120 antigens in the vaccine that approach 90%
- Prevalence of V1V2 antibodies to clade gp70 scaffold antigens of >57% at week 28
- CD4+ T cell responses to HIV Env of ~60%

Based on the results of RV144, the above immune responses would predict vaccine efficacy of at least 50% at two years of follow up.⁶⁷ The data from HVTN 100 have not yet been presented publicly, but the announcement that HVTN 702 has been given the green light indicates that all of the immune response criteria were met.

In terms of anticipating results, three interim analyses of HVTN 702 are planned, two in 2018 and one in 2019, which will assess whether the trial should continue or be stopped early as a result of either evidence of efficacy or futility (a finding that, if the trial were to proceed, it would not be able show a difference between vaccines and placebo). If the trial proceeds, the final efficacy analysis will take place in 2020.

Although it is hoped that HVTN 702 may confirm and extend the results of RV144, there are also some reasons to be cautious about expectations. The study population in South Africa is at a higher risk for HIV infection than was the case for the Thai participants in RV144, and there is evidence in the original trial that higher HIV risk is associated with lower or absent vaccine efficacy.

In addition, background levels of immune activation and inflammation have been reported to be higher on the African continent than other geographic locales,^{68,69} and this is likely linked to higher rates of HIV transmission as a result of the virus's predilection for targeting activated immune cells. In a microbicide trial conducted in South African women, genital tract inflammation was found to be a significant correlate of risk for HIV acquisition.^{70,71} It is not known whether inflammation or other factors (such as coinfections) could act as countervailing forces capable of undermining otherwise protective vaccine-induced immune responses, but this is one of the questions that HVTN 702 has the potential to address.

In addition to the P5 program, another large collaborative effort (involving the International AIDS Vaccine Initiative, the Beth Israel Deaconess Medical Center, the U.S. Military HIV Research Program, the Ragon Institute, NIAID, and Crucell Holland B.V., one of the Janssen Pharmaceutical Companies of Johnson & Johnson) is continuing to test various adenovirus and modified Vaccinia Ankara strain (MVA) vectors, as well as HIV Env protein boosts, with the goal of starting efficacy trials of selected vector/protein prime-boost combinations toward the end of this decade.^{72,73,74,75}

An array of other HIV vaccine candidates loiter in the waiting room of early-stage clinical testing, uncertain whether they'll ever be called on to pass through the doorway to further development. Results from efficacy trials such as HVTN 702 should help to shed additional light on what types of immune responses are associated with protection against HIV infection, which in turn should help to identify which of the various vaccine concepts in the pipeline have promise.

Relatively few clinical trials of new experimental HIV vaccines have begun over the past year, but among them is a candidate that has been in the works for many years. The creation of George Lewis and colleagues at Robert Gallo's Institute for Human Virology in Maryland, the vaccine is comprised of elements of both the HIV gp120 protein and the human CD4 protein. The goal is to generate immune responses to HIV antigens that are typically only briefly exposed as the virus binds to the CD4 protein on target cells, and the vaccine has shown some success in macaque challenge studies.⁷⁶ There have been concerns that including parts of CD4 could result in the induction of autoimmune responses, but this was not observed in a recently published macaque study⁷⁷, and a dose-escalation trial is now underway in humans.

The 2015 *Pipeline Report* mentioned plans to study a new oral, probiotic-based HIV vaccine developed by Jean-Marie Andrieu, which had shown a surprising degree of protective efficacy in the SIV/macaque model⁷⁸ and drawn considerable press coverage.⁷⁹ Unfortunately, an attempt to confirm the macaque results by the laboratory of Guido Silvestri at Emory University produced very disparate findings, with no evidence of protection documented.⁸⁰ Andrieu and colleagues believe that the use of macaques of Indian rather than Chinese origin may explain the divergent outcomes because of differing immune response genes,⁸¹ but it seems likely that further research will be needed before the candidate can advance into clinical trials.

CONCLUSION

Several antiretroviral-based modalities, along with numerous active and passive immunization strategies, continue to make their way down the HIV biomedical prevention pipeline. Although there have been no registrational approval filings for any primary prevention products other than coformulated TDF/FTC anywhere in the world, immunologic, antiviral activity, PK/PD, safety, and efficacy data from clinical trials of new products continue to accumulate.

Testaments to this include entire abstract sessions dedicated to biomedical prevention at longstanding HIV congresses. In fact, the bulk of data reported in this year's *Pipeline Report* chapter come from standing-room-only presentations at CROI in Boston earlier this year. There is also the biennial HIV Research for Prevention (HIVR4P) conference, the second of which will be held in Chicago in October.

However, with the advancement of several antiretroviral compounds, biologics, and vaccines, as well as new delivery technologies—compounded by the real-world scale up of TDF/FTC PrEP as a cornerstone of primary prevention services—a number of product registration challenges are becoming increasingly apparent.

One issue is how to incorporate PrEP into background standard-of-care options in vaccine and prevention-based immunotherapy clinical trials. In HVTN 702, for example, South African study participants will receive referrals to local programs where they may obtain TDF/FTC, as opposed to active provision of PrEP as a component of prevention services (e.g., free condoms and lubricant, counseling, and access to STI testing and treatment). This is similar to the standard-of-care approach being employed in the VRC01 AMP Study (HVTN 704/HPTN 085), although in that case U.S. participants have access to a specific referral program that allows their primary care provider to offer TDF/FTC PrEP free of charge.

It has been argued that TDF/FTC should be offered through these trials themselves.⁸² This is, however, a difficult issue to wrestle with, as active provision of PrEP may substantially increase the person-years of follow-up required—and, with it, the study's population size and expense—to reach the statistically sound number of seroconversion events needed for efficacy analyses. Indeed, the local Institutional Review Boards and both local and global Community Advisory Boards responsible for reviewing and approving both HVTN 702 and the AMP Study appear to have found the practice of referring participants to external sources of PrEP to be acceptable, at least at the current time.

A second related issue involves registrational trial methodologies that are necessarily rigorous in their design, yet feasible for the sponsors of new biomedical prevention candidates—a large number of which are not-for-profit programs that are dependent on finite public and philanthropic support. A major factor influencing study designs is the ethical principle of beneficence, which requires the abandonment of placebo comparisons and the inclusion of proven interventions, such as oral TDF/FTC, in control groups. Regulatory agencies, however, still want proof that an experimental PrEP regimen is more effective than placebo. This in turn requires reliable background incidence estimates, which have repeatedly proven to be difficult to come by in PrEP clinical trials. Also required are many person-years of follow up—and, by extension, extremely large, long, and expensive clinical trials—to yield the number of seroconversions necessary for standard non-inferiority comparisons, particularly with a highly efficacious regimen such as TDF/FTC.^{83,84}

Close attention to these issues, particularly as an increasing number of products enter phase II and III stages of development, is critical. A stringent, but amenable, regulatory climate is necessary to ensure the availability of necessary safety, efficacy, and acceptability data, without being prohibitively costly and ultimately deterring critical investments by product sponsors, particularly those heavily dependent on limited public and philanthropic funding.

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Research Toward a Cure and Immune-Based and Gene Therapies

By Richard Jefferys

INTRODUCTION

The pursuit of a cure for HIV infection has become a central plank of the overall research portfolio, and this has been officially underpinned by the revised HIV/AIDS priorities announced by the U.S. National Institutes of Health (NIH) in 2015.^{1,2} The NIH has cited the goal of developing a cure for HIV/AIDS as one of five high-priority areas for HIV/AIDS research, and only grant applications that address these priorities will be considered for funding from 2016 onwards.

The NIH will soon announce the funding of several new Martin Delaney Collaboratorships, which are research collaborations specifically focused on discovering a cure (the total number that will be supported is unknown, but may be as many as five or six). The grants for the current Martin Delaney Collaboratorships—the Collaboratory of AIDS Researchers for Eradication (CARE), Delaney AIDS Research Enterprise (DARE), and the Delaney Cell and Genome Engineering Initiative (defeatHIV)—expire in mid-2016. The non-profit organization amfAR continues to invest heavily in cure research, announcing last December the creation of the amfAR Institute for HIV Cure Research, which is based at the University of California, San Francisco (UCSF).³

At the global level, the International AIDS Society (IAS) has embraced cure research as a key element of their mission with the long-running Towards an HIV Cure initiative. At the upcoming AIDS 2016 conference in Durban, IAS will issue an update to the Towards an HIV Cure: Global Scientific Strategy Recommendations that were originally published in 2012.⁴

The number of clinical trials and observational studies related to the effort to cure HIV has expanded further over the past year (see table 1). However, this work remains largely exploratory; among the main lines of research being pursued, investigators are probing a variety of possible means to try and diminish the reservoir of HIV that persists in the body despite antiretroviral therapy (ART). Strategies for inducing containment of the virus when ART is interrupted are also being explored, including gene therapies and immune-based therapies (particularly therapeutic vaccines). These are early-stage tests, and it is important to appreciate that there is no prospect of study participants being cured; the hope is that the information gleaned will guide scientists toward curative approaches.

The one current area of research where there might be a slim possibility of a cure being achieved is limited to HIV-positive individuals with life-threatening cancers requiring stem cell transplantation. Several projects are looking to treat people in this situation using stem cells from donors who are homozygous for the CCR5-Δ32 mutation (which abrogates expression of the CCR5 co-receptor that most forms of HIV use to enter target cells), in hopes of recapitulating the experience of Timothy Brown, who remains the lone individual considered to be cured of HIV infection.⁵

Brown received stem cell transplants from a CCR5-Δ32 homozygote as part of a grueling series of treatments for acute myelogenous leukemia nearly a decade ago, and no trace of replication-competent HIV has been detected in his body since that time, despite the discontinuation of ART.⁶ At least six individuals have since been reported who underwent similar procedures, but all of them died as a result of either the underlying cancers or complications from the transplantation procedure.⁷ One new case was described in a poster at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), and the preliminary signs appear

encouraging: the cancer is in remission and HIV cannot be detected using multiple techniques.⁸ However, ART had not yet been interrupted at the time of the presentation, so it is too early to know whether this may represent a second example of an HIV cure.

Research into therapies that might offer benefits as adjuncts to ART is dwindling, and it would be a stretch to describe the candidates in this area as moving through a pipeline. Academic investigators have initiated the clinical trials that are being conducted, and there are currently no pharmaceutical companies attempting to usher interventions along a pathway toward approval. The only trial of sufficient size to assess the efficacy of an adjunctive approach is the NIH-sponsored REPRIEVE study, which is evaluating whether pitavastatin can reduce the incidence of cardiovascular disease in people on ART.⁹

Despite the fallowness of this field, there does remain a need for therapies capable of addressing the elevated risk of morbidity and mortality faced by individuals who experience a poor immunologic response to ART.¹⁰ The single most important risk factor for becoming an immunologic non-responder (INR) is late initiation of ART, and the most recently available surveillance data from the U.S. Centers for Disease Control and Prevention indicate that this remains a problem despite efforts to promote early diagnosis: in 2013, 41,661 individuals were newly diagnosed with HIV infection, and 23.6% had progressed to AIDS at the time of diagnosis.¹¹ TAG is currently collaborating with other activists to explore whether candidate treatments for INRs might be considered as orphan drugs, a U.S. Food and Drug Administration (FDA) designation intended to spur the development of treatments for disorders that are relatively rare.

Table 1. Research Toward a Cure 2016: Current Clinical Trials and Observational Studies

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ADOPTIVE IMMUNOTHERAPY				
Early ART in combination with autologous HIV-specific cytotoxic T lymphocyte (CTL) infusion	T cell therapy	NCT02231281	Yongtao Sun, MD, PhD, Tangdu Hospital, the Fourth Military Medical University	Phase III
Reconstitution of HIV-specific immunity against HIV	T cell therapy	NCT02563509	Guangzhou 8th People's Hospital	Phase I/II
HXTC: HIV 1 antigen expanded specific T cell therapy	HIV 1 antigen expanded specific T cell therapy	NCT02208167	University of North Carolina, Chapel Hill	Phase I
ANTIBODIES				
VRC01	Broadly neutralizing monoclonal antibody	NCT02664415 (not yet open for enrollment)	National Institute of Allergy and Infectious Diseases (NIAID)	Phase II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02446847	Rockefeller University	Phase I/II
3BNC117	Broadly neutralizing monoclonal antibody	NCT02588586	Rockefeller University	Phase I/II
10-1074	Broadly neutralizing monoclonal antibody	NCT02511990	Rockefeller University	Phase I
Vedolizumab	Anti- $\alpha 4\beta 7$ integrin antibody	NCT02788175 (not yet open for enrollment)	NIAID	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
ANTIBODIES (continued)				
VRC01	Broadly neutralizing monoclonal antibody in acute HIV infection	NCT02591420 (not yet open for enrollment)	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02471326 (closed to enrollment)	NIAID	Phase I
VRC01	Broadly neutralizing monoclonal antibody	NCT02411539 (closed to enrollment)	NIAID	Phase I
CHERUB 001	Intravenous immunoglobulin in primary HIV infection	No clinicaltrials.gov entry	CHERUB (Collaborative HIV Eradication of viral Reservoirs: UK BRC)	N/A
ANTI-FIBROTIC				
Losartan	Angiotensin receptor blocker	NCT01852942	University of Minnesota	Phase II
Telmisartan	Angiotensin receptor blocker	NCT02170246	Yale University	Phase I
ANTI-INFLAMMATORY				
Canakinumab	IL-1 β inhibitor	NCT02272946	University of California, San Francisco	Phase II
CC-11050	Phosphodiesterase-4 inhibitor	NCT02652546	NIAID	Phase I
Metformin	Antidiabetic	NCT02659306 (not yet open for enrollment)	McGill University Health Center	Phase I
ANTIRETROVIRAL THERAPY				
HIV reservoir dynamics after switching to dolutegravir in patients on a PI/r based regimen		NCT02513147	Hospital Universitari Vall d'Hebron Research Institute	Phase IV
ANTIRETROVIRAL THERAPY IN HIV CONTROLLERS				
Emtricitabine + Rilpivirine + Tenofovir		NCT01777997 (closed to enrollment)	AIDS Clinical Trials Group/ NIAID	Phase IV
COMBINATIONS				
Perturbing of HIV reservoir with immune stimulation: Fluarix, Pneumovax vaccines		NCT02707692 (not yet open for enrollment)	University of California, San Diego	Not listed
Panobinostat + pegylated interferon-alpha2a	HDAC inhibitor + cytokine	NCT02471430	Massachusetts General Hospital	Phase II
Research In Viral Eradication of HIV Reservoirs (RIVER): ART, ChAdV63. HIVconsV and MVA.HIVconsV vaccines, vorinostat	Therapeutic vaccines + HDAC inhibitor	NCT02336074 UK CPMS18010	Imperial College London	Phase II
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02225665 (closed to enrollment)	Sangamo BioSciences	Phase I/II

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
COMBINATIONS (continued)				
SB-728-T + cyclophosphamide	Autologous CD4 T cells gene-modified via adenovirus vector to inhibit CCR5 expression + transient chemotherapy	NCT01543152 (closed to enrollment)	Sangamo BioSciences	Phase I/II
Vacc-4x + romidepsin	HDAC inhibitor + peptide-based therapeutic vaccine	NCT02092116 (closed to enrollment)	Bionor Immuno AS/Celgene	Phase I/II
AGS-004 + vorinostat	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens + HDAC inhibitor	NCT02707900 (not yet open for enrollment)	NIAID	Phase I
DCV3 + pegylated interferon	Dendritic-cell-based vaccine pulsed with autologous heat-inactivated HIV + cytokine	NCT02767193 (not yet open for enrollment)	Judit Pich Martínez, Fundació Clínic per la Recerca Biomèdica	Phase I
MVA.HIVconsv + romidepsin	Therapeutic vaccine + HDAC inhibitor	NCT02616874	IrsiCaixa	Phase I
SB-728mR-T + cyclophosphamide	Autologous CD4 T cells gene-modified via messenger RNA to inhibit CCR5 expression + transient chemotherapy	NCT02388594	University of Pennsylvania	Phase I
CD4-ZETA ± interleukin-2 (IL-2)	Gene-modified T cells + cytokine	NCT01013415 (closed to enrollment)	University of Pennsylvania	Phase I
GENE THERAPIES				
Cal-1: Dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46)	ACTRN12615000763549	Calimmune	Phase I/II
Cal-1: Dual anti-HIV gene transfer construct	Lentiviral vector encoding a short hairpin RNA that inhibits expression of CCR5 and a fusion inhibitor (C46)	NCT01734850 NCT02390297 (long term safety phase)	Calimmune	Phase I/II
VRX496	Autologous CD4 T cells—modified with an antisense gene targeting the HIV envelope	NCT00295477 (closed to enrollment)	University of Pennsylvania	Phase I/II
SB-728mR-HSPC	Autologous hematopoietic stem/progenitor cells gene-modified to inhibit CCR5 expression	NCT02500849	City of Hope Medical Center	Phase I
MazF-T	Autologous CD4 T cells gene-modified with MazF endoribonuclease gene to inhibit HIV	NCT01787994 (closed to enrollment)	Takara Bio/University of Pennsylvania	Phase I

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
GENE THERAPIES FOR HIV-POSITIVE PEOPLE WITH CANCERS				
High-dose chemotherapy with transplantation of gene-modified stem cells for high-risk AIDS-related lymphoma	Stem cells gene-modified to express an HIV entry inhibitor C46	NCT00858793 (suspended)	Universitätsklinikum Hamburg-Eppendorf	Phase I/II
HIV-resistant gene-modified stem cells and chemotherapy in treating patients with lymphoma and HIV infection	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02343666	Fred Hutchinson Cancer Research Center	Phase I
Gene-modified HIV-protected stem cell transplant in treating patients with HIV-associated lymphoma	Stem cells gene-modified to abrogate CCR5 expression and encode an HIV entry inhibitor C46	NCT02378922 (not yet open for enrollment)	Fred Hutchinson Cancer Research Center	Phase I
Gene therapy and combination chemotherapy in treating patients with AIDS-related non-Hodgkin lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-sh1-TAR-CCR5RZ)	NCT02337985	City of Hope Medical Center	Not listed
Busulfan and gene therapy after frontline chemotherapy in patients with AIDS-related non-Hodgkin's lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-sh1-TAR-CCR5RZ) + cyclophosphamide conditioning	NCT01961063	City of Hope Medical Center	Not listed
Gene-therapy-treated stem cells in patients undergoing stem cell transplant for intermediate-grade or high-grade AIDS-related lymphoma	Stem cells gene-modified with a lentivirus vector encoding three forms of anti-HIV RNA (pHIV7-sh1-TAR-CCR5RZ)	NCT00569985 (closed to enrollment)	City of Hope Medical Center	Not listed
IMMUNE CHECKPOINT INHIBITORS				
Pembrolizumab	Anti-PD-1 antibody in people with HIV and relapsed, refractory, or disseminated malignant neoplasms	NCT02595866	National Cancer Institute (NCI)	Phase I
Nivolumab + Ipilimumab	Anti-PD-1 antibody + anti-CTLA-4 antibody in people with advanced HIV-associated solid tumors	NCT02408861	National Cancer Institute (NCI)	Phase I
IRON CHELATORS				
Deferiprone		NCT02456558 (closed to enrollment)	ApoPharma	Phase I
JANUS KINASE INHIBITORS				
Ruxolitinib		NCT02475655	NIAID	Phase II
LATENCY-REVERSING AGENTS				
MGN1703	Toll-like receptor 9 (TLR-9) agonist	NCT02443935 (enrolling by invitation only)	University of Aarhus	Phase Ib/IIa

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
LATENCY-REVERSING AGENTS (continued)				
Chidamide	HDAC inhibitor	NCT02513901	Tang-Du Hospital	Phase I/II
Poly-ICLC	TLR-3 agonist	NCT02071095 (closed to enrollment)	Nina Bhardwaj, MD/Campbell Foundation/Oncovir, Inc.	Phase I/II
Romidepsin	HDAC inhibitor	NCT01933594	AIDS Clinical Trials Group/ NIAID/Gilead	Phase I/II
GS-9620	TLR-7 agonist	No clinicaltrials.gov entry	Gilead Sciences	Phase Ib
ALT-803	Recombinant human super agonist interleukin-15 complex	NCT02191098	University of Minnesota - Clinical and Translational Science Institute	Phase I
Kansui	Traditional Chinese medicine containing ingenols	NCT02531295 (not yet open for enrollment)	UCSF	Phase I
OBSERVATIONAL STUDIES				
ACTG A5321	Decay of HIV-1 reservoirs in subjects on long-term antiretroviral therapy: The ACTG HIV reservoirs cohort (AHRC) study	Not listed yet, see ACTG website entry for information	AIDS Clinical Trials Group	N/A
Analytic treatment interruption (ATI) to assess HIV cure	Antiretroviral treatment interruption	NCT02437526 (enrolling by invitation only)	Mayo Clinic	N/A
CLEAC	Comparison of late versus early antiretroviral therapy in HIV-infected children	NCT02674867 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
CODEX (the “Extreme” cohort)	Long-term non-progressors and HIV controllers	NCT01520844	French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	N/A
Effects of Dolutegravir based regimen on HIV-1 reservoir and immune activation		NCT02557997	University Hospital, Strasbourg, France	N/A
EPIC4	Early pediatric treatment initiation cohort study	CTN S 281	Canadian Institutes of Health Research (CIHR)/ Canadian Foundation for AIDS Research (CANFAR)/ International AIDS Society (IAS)	N/A
Establish and characterize an acute HIV infection cohort in a high-risk population		NCT00796146	Southeast Asia Research Collaboration with Hawaii/ Armed Forces Research Institute of Medical Sciences/ Thai Red Cross AIDS Research Centre	N/A
HEATHER	HIV reservoir targeting with early antiretroviral therapy	UK CPMS17589	University of Oxford/Medical Research Council/British HIV Association	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
OBSERVATIONAL STUDIES (continued)				
HIV-STAR	HIV sequencing after treatment interruption to identify the clinically relevant anatomical reservoir	NCT02641756 (enrolling by invitation only)	University Hospital, Ghent	N/A
Host and viral factors associated with HIV elite control		UK CPMS16146	University College London Hospitals NHS Foundation Trust	N/A
HSCT-HIV	Allogeneic hematopoietic stem cell transplantation in HIV-1-infected patients	NCT02732457	Kirby Institute	N/A
ISALA	Analytical treatment interruption in HIV-positive patients	NCT02590354	Institute of Tropical Medicine, Belgium	N/A
Post analytic treatment interruption study		NCT02761200 (closed to enrollment)	South East Asia Research Collaboration with Hawaii	N/A
Quantitative measurement and correlates of the latent HIV reservoir in virally suppressed Ugandans		NCT02154035	NIAID	N/A
The use of leukapheresis to support HIV pathogenesis studies		NCT01161199	University of California, San Francisco	N/A
Tat protein vaccine	Roll-over observational study for extended follow-up of volunteers in the ISS T-003 trial	NCT02712489 (closed to enrollment)	Barbara Ensoli, MD, Istituto Superiore di Sanità/Italian Ministry of Foreign Affairs	N/A
mTOR INHIBITORS				
Everolimus	Impact of everolimus on HIV persistence post kidney or liver transplant	NCT02429869	UCSF	Phase IV
Sirolimus	Safety and efficacy of sirolimus for HIV reservoir reduction in individuals on suppressive ART	NCT02440789	ACTG	Phase I/II
STEM CELL TRANSPLANTATION				
BMT CTN 0903	Allogeneic transplant in individuals with chemotherapy-sensitive hematologic malignancies and coincident HIV infection	NCT01410344 (closed to enrollment)	National Heart, Lung, and Blood Institute (NHLBI)/ National Cancer Institute (NCI)/ Blood and Marrow Transplant Clinical Trials Network	Phase II
Immune response after stem cell transplant in HIV-positive patients with hematologic cancer		NCT00968630	Fred Hutchinson Cancer Research Center	Phase II
IMPAACT P1107	Cord blood transplantation using CCR5-Δ32 donor cells for the treatment of HIV and underlying disease	NCT02140944	IMPAACT/NIAID/Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)	N/A

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
THERAPEUTIC VACCINES				
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT01069809 (closed to enrollment)	Argos Therapeutics	Phase II
GTU-multiHIV + LIPO-5	DNA + lipopeptide vaccines	NCT01492985 (closed to enrollment)	French National Institute for Health and Medical Research/ French National Agency for Research on AIDS and Viral Hepatitis (Inserm/ANRS)	Phase II
VAC-3S	Peptide-based vaccine	NCT02041247 (closed to enrollment)	InnaVirVax	Phase II
VAC-3S	Peptide-based vaccine	NCT02390466 (closed to enrollment)	InnaVirVax	Phase I/ IIa
GTU-MultiHIV B Clade Vaccine	DNA vaccine	NCT02457689	Imperial College London	Phase I/II
AGS-004	Personalized therapeutic vaccine utilizing patient-derived dendritic cells and HIV antigens	NCT02042248	University of North Carolina at Chapel Hill/Argos Therapeutics/U.S. National Institutes of Health (NIH)	Phase I/II
Tat Oyi	Tat protein vaccine	NCT01793818 (closed to enrollment)	Biosantech	Phase I/II
THV01	Lentiviral-vector-based therapeutic vaccine	NCT02054286 (closed to enrollment)	Theravectys S.A.	Phase I/II
Recombinant adenovirus type 5 vaccine	Viral vector vaccine	NCT02762045	Centers for Disease Control and Prevention, China	Phase I
iHIVARNA-01	TriMix and HIV antigen naked messenger RNA vaccine	NCT02413645	Biomedical Research Institute August Pi i Sunyer (IDIBAPS)	Phase I
HIVAX	Lentiviral-vector-based therapeutic vaccine	NCT01428596	GeneCure Biotechnologies	Phase I
MAG-pDNA + rVSV_{ΔM} HIV-1 Gag	DNA + viral vector vaccines	NCT01859325 (closed to enrollment)	NIAID/Profectus Biosciences, Inc.	Phase I
TRADITIONAL CHINESE MEDICINE				
<i>Triptolide wilfordii</i>		NCT02219672	Peking Union Medical College	Phase III
TREATMENT INTENSIFICATION/EARLY TREATMENT				
LEOPARD: Latency and Early Neonatal Provision of Antiretroviral Drugs Clinical Trial	Combination antiretroviral therapy	NCT02431975	Columbia University	Not listed
New Era Study: Treatment with multi-drug class (MDC) HAART	Combination antiretroviral therapy	NCT00908544 (closed to enrollment)	MUC Research GmbH	Not listed

Trial	Additional Description	Trial Registry Identifier(s)	Manufacturer/Sponsor(s)	Phase
TREATMENT INTENSIFICATION/EARLY TREATMENT (continued)				
Antiretroviral regime for viral eradication in newborns	Combination antiretroviral therapy	NCT02712801 (not yet open for enrollment)	National Center for Women and Children's Health, China CDC	Phase IV
DGVTRU: Immediate initiation of antiretroviral therapy during "hyperacute" HIV infection	Combination antiretroviral therapy	NCT02656511	UCSF	Phase IV
DIORR: Dolutegravir Impact on Residual Replication	Combination antiretroviral therapy	NCT02500446	University of Melbourne	Phase IV
DRONE: Impact of starting a dolutegravir-based regimen on HIV-1 proviral DNA reservoir of treatment naïve and experienced patients	Combination antiretroviral therapy	NCT02370979	University Hospital, Strasbourg, France	Phase IV
AAHIV: antiretroviral therapy for acute HIV infection	Combination antiretroviral therapy	NCT00796263	South East Asia Research Collaboration with Hawaii	Phase III
VIRECURE: Impact of extremely early ART to reduce viral reservoir and induce functional cure of HIV infection	Combination antiretroviral therapy	NCT02588820	David Garcia Cinca, Hospital Clinic of Barcelona	Phase III
EIT: Early Infant HIV Treatment in Botswana	Combination antiretroviral therapy	NCT02369406	Harvard School of Public Health	Phase II/III
Viral suppression after analytic treatment interruption in Thai patients who initiated HAART during acute HIV infection		NCT02614950	South East Asia Research Collaboration with Hawaii	Phase II
Peginterferon alfa-2b	Cytokine	NCT02227277	The Wistar Institute	Phase II
Peginterferon alfa-2b	Cytokine	NCT01935089 (closed to enrollment)	University of Pennsylvania/ Wistar Institute	Phase II
Alpha interferon intensification	Cytokine	NCT01295515	NIAID	Phase I/II
IMPAACT P1115: Very early intensive treatment of HIV-infected infants to achieve HIV remission	Combination antiretroviral therapy	NCT02140255	IMPAACT/NIAID/NICHD	Phase I/II

For a listing including completed trials related to cure research, with links to published and presented results where available, see TAG's research toward a cure clinical trials web page at: <http://www.treatmentactiongroup.org/cure/trials>.

Combination Approaches

The number of trials combining agents to target the HIV reservoir has increased since 2015. A leading strategy is known as "kick and kill" and combines drugs that may have the potential to reverse HIV latency (latency-reversing agents or LRAs) with immune-based interventions intended to facilitate the elimination of latently infected cells that have been prompted to express viral proteins by LRAs. At CROI 2016, Ole Søgaaard from the University of Aarhus in Denmark presented preliminary data from an ongoing trial of this type of

two-pronged approach, involving a combination of the HDAC inhibitor romidepsin with Vacc-4x, a therapeutic vaccine comprised of several epitopes from the HIV Gag protein delivered with a GM-CSF adjuvant.¹²

In a previous pilot study, Søgaaard and colleagues administered romidepsin alone to six individuals on ART with suppressed viral loads; as covered in last year's *Pipeline Report*, evidence of latency-reversing activity was documented in the form of detectable increases in HIV RNA after drug administration. There were no significant changes in the size of the HIV reservoir. These results were presented at the 2014 International AIDS Conference and subsequently published in *PLoS Pathogens* in September 2015.¹³

In the new trial, a series of six immunizations with Vacc-4x and GM-CSF adjuvant were administered, followed by three infusions of romidepsin, to 17 participants on ART. Levels of total HIV DNA, one possible surrogate measure of the reservoir, showed a statistically significant decline of 39.7%. An alternate assay measuring HIV DNA that is integrated into the genome of CD4 T cells also documented a slight reduction, but this did not reach statistical significance. Replication-competent HIV was detectable in six participants at baseline using a viral outgrowth assay, and levels fell significantly after the interventions by around 38%.

In the final stage of the study, 16 participants underwent an ART interruption. Despite the evidence of a small decline in HIV reservoir size, there was no delay in viral load rebound in any participant. In his CROI presentation, Søgaaard concluded that the data offer some support for the idea of combining LRAs with therapeutic vaccines, but improvements are needed to enhance the magnitude of the effect.

Additional insights into the potential of kick and kill strategies should emerge from other ongoing trials of different combinations of HDAC inhibitors and therapeutic vaccines (see table 1). These include:

- The multicenter RIVER trial in the UK, investigating vorinostat together with two viral-vector-based HIV vaccines derived from chimpanzee adenovirus and a modified Vaccinia Ankara strain (MVA).
- A study at the IrsiCaixa institute in Spain looking at romidepsin and an MVA-based HIV vaccine.
- A combination of vorinostat with AGS-004, a dendritic-cell-based vaccine that is personalized to present HIV antigens obtained by sampling viral sequences from each intended recipient, which is being tested at the University of North Carolina.

Other types of combinations are also being explored, with several new protocols being launched or imminent since last year. Among them is a trial of the HDAC inhibitor panobinostat and the cytokine pegylated interferon- α 2a that is being conducted at Massachusetts General Hospital by Dan Kuritzkes, Mathias Lichterfeld, and Rajesh Gandhi. The rationale derives from a previously published study of panobinostat that reported that a small subset of participants appeared to experience a diminution of the HIV reservoir that correlated with a delay in viral rebound after ART interruption.¹⁴ An analysis led by Mathias Lichterfeld found that this response was partly linked to interferon-stimulated genes,¹⁵ suggesting that interferon may be able to potentiate the effects of panobinostat on the HIV reservoir.

Pegylated interferon is also being assessed as a means to enhance responses to a dendritic-cell-based HIV vaccine in an upcoming trial in Spain. Felipe García's research group has conducted two previous trials with the vaccine, which uses heat-inactivated HIV isolated from each participant as the source of antigens. The results demonstrated induction of HIV-specific T cell responses and a significant, albeit transient, lowering of HIV viral load during an ART interruption.¹⁶ An inverse correlation was also reported between HIV-specific T cell responses and measures of integrated HIV DNA, suggesting a possible effect on the HIV reservoir.¹⁷

David Smith and colleagues at the University of California, San Diego are exploring whether influenza and pneumococcus vaccines can perturb the HIV reservoir in individuals on ART. Latent HIV resides in resting memory CD4 T cells, and vaccination might be a means of stimulating these cells and awakening the virus,

particularly if the latently infected CD4 T cells recognize antigens contained in the vaccines. At least one published study has reported the presence of latent HIV infection in influenza-specific CD4 T cells.¹⁸

Immune Checkpoint Inhibitors

Over the past decade or so, scientists have discovered a family of receptors that are involved in dampening or switching off immune responses; examples include PD-1 and CTLA-4. These “immune checkpoint” receptors have an important role in restraining immune responses that might otherwise attack body tissues causing autoimmune disease (the immunological equivalent of friendly fire). Sometimes, however, immune checkpoint receptors can curtail responses to viruses or cancerous tissues, impeding activities of the immune system that would be helpful rather than harmful. This has led to the development of immune checkpoint inhibitors that aim to revive beneficial immune responses, particularly against cancers. Several immune checkpoint inhibitors are now FDA approved, having shown significant efficacy against a variety of cancers, including the anti-PD-1 antibodies nivolumab (trade name Opdivo) and pembrolizumab (Keytruda) and the anti-CTLA-4 antibody ipilimumab (Yervoy).¹⁹

There is longstanding interest in studying immune checkpoint inhibitors in the context of HIV cure research, stemming from evidence that expression of the receptors PD-1, CTLA-4, and TIGIT increases as disease progresses and is associated with exhaustion of HIV-specific T cell immunity.^{20,21,22} Furthermore, latently infected CD4 T cells preferentially express several immune checkpoint receptors, including PD-1, LAG-3, and TIGIT^{23,24}, and antibodies against PD-1 have been reported to reverse HIV latency in laboratory studies.²⁵ The major hurdle to evaluating the approach is the potential for the induction of autoimmunity, which has occurred in a minority of participants in cancer trials and, in rare cases, can be fatal.²⁶

Earlier this year, Joe Eron from the University of North Carolina debuted data from the first trial of an antibody targeting the PD-1 pathway in people with HIV. The antibody in question is manufactured by Bristol-Myers Squibb and does not bind to PD-1, but rather to a ligand that it interacts with, PD-L1. The original intent was to study single infusions of various, escalating doses in people on suppressive ART; however, only the lowest dose (0.3 mg/kg) was administered due to an unexpected concern about the potential for retinal toxicity that emerged from animal experiments.

A total of six individuals received the antibody, and two showed clear evidence of increased HIV Gag-specific CD8 T cell responses (measured both by interferon gamma production and expression of CD107a, a marker of cytotoxicity), but the overall average change compared to a control group of two placebo recipients did not reach statistical significance. An assay that can measure HIV RNA levels down to a single copy did not reveal significant changes associated with the treatment, but one individual experienced a tenfold decline in levels of cell-associated HIV RNA, and Eron noted that this was the person who experienced the greatest increase in Gag-specific CD8 T cell responses. This individual also had the highest baseline expression of PD-1, hinting that perhaps they had started with the most exhausted HIV-specific T cell response and were therefore best able to respond to the antibody.

In terms of safety, no evidence of the retinal toxicity that stymied plans to escalate dosing was observed. However, one person developed autoimmune pituitary insufficiency nine months after the infusion, and, although the relationship to the anti-PD-L1 antibody is uncertain, the fact that it was an autoimmune phenomenon raises serious concerns about whether further studies of antibodies targeting the PD-1 pathway will be possible in otherwise healthy HIV-positive people.

An alternate approach to investigating immune checkpoint inhibition in HIV is to conduct trials limited to HIV-positive individuals with cancers that are unresponsive to standard therapies, and this is the tack that has been taken by Thomas Uldrick at the National Cancer Institute. The primary goal of Uldrick’s phase I study of the

anti-PD-1 antibody pembrolizumab is to assess whether the cancers can be successfully treated, but secondary analyses will measure the effect on the HIV reservoir and HIV-specific immune responses.

Lakshmi Rajdev of the AIDS Malignancy Consortium at the National Cancer Institute is conducting a multicenter trial of a combination of the anti-CTLA-4 antibody ipilimumab with the anti-PD-1 antibody nivolumab in HIV-positive people with advanced, HIV-associated solid tumors that are refractory to standard care. The primary endpoint is safety, but the study will also look at efficacy against cancer and several HIV-related parameters, including viral load and HIV-specific T cell immunity.

Another potential source of information is case reports on HIV-positive people with cancer who have received approved immune checkpoint inhibitors as part of their medical care. One such report has been published on an individual with HIV and metastatic melanoma who received the anti-CTLA-4 antibody ipilimumab and, interestingly, there was evidence of transient increases in cell-associated HIV RNA after infusions, suggestive of latency-reversing activity.²⁷ In parallel, HIV RNA levels measured by a single copy assay declined over time, from 60 to 5 copies/ml. The report has spurred interest in conducting further research, but it is currently uncertain whether ipilimumab can be studied outside of the cancer setting; results from other ongoing trials and experiments in animal models should help to ascertain if this will be possible.

Gene Therapies

Two new gene therapy trials were initiated last summer. At the City of Hope Medical Center in Los Angeles, enrollment began in a study that is extracting stem cells from participants, genetically modifying them with a zinc finger nuclease technology that is designed to abrogate expression of the CCR5 coreceptor, then reinfusing them with the aim of generating new immune cells that are resistant to HIV. The research represents a collaboration between Sangamo BioSciences (the developer of the zinc finger nuclease technology), City of Hope, and the Keck School of Medicine at the University of Southern California, supported by the California Institute for Regenerative Medicine (CIRM). As discussed in a plenary presentation at CROI 2016 by Paula Cannon (available online via webcast), Sangamo's approach has shown some promise when applied to CD4 T cells, with a subset of recipients displaying evidence of lowered viral loads after ART interruption.²⁸

The company Calimmune is also pursuing a strategy involving gene modification of stem cells. Their approach uses a lentiviral vector designed to both downregulate CCR5 expression and introduce a gene that encodes an HIV fusion inhibitor, designated C46.²⁹ Results are pending from an ongoing phase I trial in the U.S., and recruitment began earlier this year for another small study in Australia that is being conducted by Anthony Kelleher at the Kirby Institute.

A possible gene therapy candidate that has generated intense interest recently involves the use of the gene-editing tool CRISPR/Cas9 to try and excise the HIV genome from latently infected cells. CRISPR/Cas9 is derived from bacteria, where it evolved as a defense mechanism against invading viruses. Researchers have reported some success in using CRISPR/Cas9 to delete HIV genes from cells³⁰ and small animals³¹ in laboratory studies, but it has also emerged that viruses can rapidly become resistant to its effects.^{32,33,34} Although some scientists have made optimistic predictions that human trials may begin in the next few years, it is not yet known whether it will be feasible to deliver CRISPR/Cas9 into the human body.

Ruxolitinib

Ruxolitinib is an FDA-approved treatment for myelofibrosis (a type of bone marrow cancer) that targets a cellular signaling pathway with a complicated name: the Janus activating kinase–signal transducer and activator of transcription (JAK-STAT) pathway. Studies have shown that this pathway is activated in HIV-infected

macrophages and lymphocytes, creating an inflammatory environment that favors viral replication and persistence.^{35,36} In laboratory experiments, ruxolitinib countered this environment and inhibited HIV,³⁷ leading researchers at the National Institute of Allergy and Infectious Diseases (NIAID) to launch a clinical trial of the drug in individuals on ART. Endpoints include safety, anti-inflammatory activity, and impact on the HIV reservoir.

Anti-inflammatories

The question of whether suppressing inflammation can reduce the HIV reservoir is being probed in several other studies. At the University of California, San Francisco, Priscilla Hsue and colleagues are testing canakinumab, an antibody that blocks the inflammatory cytokine interleukin-1 β (IL-1 β), primarily to assess whether it can beneficially modulate markers of cardiovascular disease risk, but measures of the HIV reservoir are among the secondary endpoints.

CC-11050 is a novel compound that inhibits phosphodiesterase-4; other drugs in this class have been found to be useful against inflammatory diseases such as asthma and psoriasis.³⁸ Researchers at NIAID have initiated a study to evaluate CC-11050 in HIV-positive individuals on ART, including any effects on HIV persistence.

Jean-Pierre Routy and colleagues at McGill University in Canada are investigating the antidiabetic drug metformin, which has recently been shown to also have an anti-inflammatory mechanism of action.³⁹ The primary goal of the trial, named the Lilac Study, is to measure if the drug reduces the size of the HIV reservoir.

Vedolizumab

The monoclonal antibody vedolizumab is an FDA-approved treatment for ulcerative colitis and Crohn's disease. It binds to a molecule expressed on CD4 T cells, $\alpha 4\beta 7$ integrin, that is involved in the trafficking of cells to the gut. As there is evidence that HIV can interact with the $\alpha 4\beta 7$ integrin in a manner that enhances transmission and viral replication,^{40,41} researchers at NIAID are on the verge of initiating a trial that will evaluate whether vedolizumab administration can suppress viral load during an ART interruption. The approach has shown activity in the SIV/macaque model,⁴² but some laboratory experiments have suggested that the capacity to bind to the $\alpha 4\beta 7$ integrin is uncommon among HIV isolates;⁴³ the NIAID study should reveal whether there is a relationship between HIV and $\alpha 4\beta 7$ integrins that can be targeted therapeutically.

Protein Kinase C (PKC) Agonists

Many laboratory studies have identified PKC agonists as having the potential to reverse HIV latency.^{44,45} Recently, results of the first human trial of the PKC agonist bryostatin-1 were published, demonstrating that a single, low dose of the drug appears to be safe in individuals on ART, but the study did not show activity against the latent HIV reservoir.⁴⁶ The researchers now aim to explore the effects of multiple doses and combinations with other candidate LRAs.

Sulggi Lee and colleagues at the University of California, San Francisco are hoping to soon launch a trial of a plant extract used in traditional Chinese medicine, kansui, on the basis that it contains PKC agonists with latency-reversing activity known as ingenols.⁴⁷ The product is delivered as a tea made from powder extracted from the plant *Euphorbia kansui*.

Broadly Neutralizing Antibodies

An increasing number of highly potent antibodies that are capable of neutralizing a broad array of differing HIV isolates (broadly neutralizing antibodies, or bNAbs) are becoming available for use in both prevention and cure research. In the latter context, there is interest in investigating whether bNAbs can promote clearance of HIV-infected cells via effector functions such as antibody-mediated cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP).^{48,49}

At CROI 2016, two presentations debuted data from trials of the bNAb VRC01 in HIV-positive people undergoing ART interruptions. Katherine Bar from the University of Pennsylvania described results from a trial involving three infusions of VRC01, given before and after an interruption of ART to assess whether viral load rebound would be delayed.⁵⁰ The antibody was safe and well tolerated, but there was only a slight hint of a short-term delay in the return of detectable viral load compared with historical controls, which evanesced by eight weeks of post-interruption follow up. Bar highlighted the need to better understand the relationship between HIV neutralization measured in laboratory assays and antibody potency in people, and suggested that combinations of different bNAbs will likely be required to improve results. Another similar trial conducted by Tae-Wook Chun at the NIAID was presented at CROI 2016 as a poster, reporting broadly consistent findings.⁵¹ Results from several trials of newer bNAbs that appear to be more potent than VRC01 are pending.

Deferiprone

Several years ago there was a wave of media coverage regarding a study suggesting that ciclopirox, an antifungal drug, or deferiprone, an iron chelator that is used to treat thalassemia, might be able to promote the apoptotic death of HIV-infected cells.⁵² In May of 2016, results of a small pilot trial of deferiprone in ART-naïve HIV-positive people in South Africa were published, claiming evidence of mild antiretroviral activity in a small number of individuals with deferiprone levels above a certain threshold.⁵³ A variety of side effects were also reported, including elevations in transaminases and serum liver enzymes, and over a third of participants assigned to the highest dose did not complete the study. The researchers nevertheless continue to investigate the approach, and a second, larger trial—also conducted in South Africa—is now in follow up.

Table 2. Immune-Based Therapy Pipeline 2016

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Losartan	Angiotensin II receptor antagonist, anti-inflammatory	Minneapolis Medical Research Foundation	Phase II
Lubiprostone	Apical lumen ClC-2 chloride channel activator	Ruth M. Rothstein CORE Center/Chicago Developmental Center for AIDS Research	Phase II
Methotrexate (low dose)	Anti-inflammatory	NIAID	Phase II
Metformin	Biguanide antidiabetic	University of Hawaii/National Institute of General Medical Sciences	Phase II
Niacin	Vitamin B3	McGill University Health Center/Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network	Phase II
VSL#3	Probiotic	Virginia Commonwealth University/ Bill & Melinda Gates Foundation University Health Network, Toronto/ CIHR Canadian HIV Trials Network	Phase II

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Lactobacillus casei shirota	Probiotic	University of Sao Paulo General Hospital	Phase II
Isotretinoin	13-cis retinoic acid	NIAID	Phase II
Dipyridamole	Phosphodiesterase type 5 inhibitor, anti-inflammatory	Sharon Riddler, University of Pittsburgh/NIAID	Phase I/II
Mesenchymal stem cells	Allogenic adult mesenchymal stem cells from adipose tissue	Iniciativa Andaluza en Terapias Avanzadas – Fundación Pública Andaluza Progreso y Salud	Phase I//II
<i>Tripterygium wilfordii</i> Hook F	Traditional Chinese medicine, anti-inflammatory	Beijing 302 Hospital Peking Union Medical College	Phase I/II
Umbilical cord mesenchymal stem cells	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
Vorapaxar	Thrombin receptor (PAR-1) antagonist	Kirby Institute/NIAID/University of Minnesota – Clinical and Translational Science Institute/ University of Melbourne/Merck	Phase I/II
Aprepitant	Neurokinin 1 receptor antagonist	University of Pennsylvania	Phase I
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I

As explained in the introduction, the pursuit of immune-based adjuncts to ART now represents a small niche in the HIV research portfolio with essentially no significant industry interest. Much of the work in this area involves probiotic supplements, which are available over the counter, but are typically expensive, and, despite some evidence of beneficial effects, the data are unfortunately insufficient to offer a great deal of guidance as to how best they might be used.

Over the past year, two additional probiotic studies have been published that appear somewhat consistent with findings from a randomized trial of *Saccharomyces boulardii*⁵⁴ that was described in the 2015 *Pipeline Report*. Birgitte Stiksrud and colleagues from Oslo University Hospital in Norway conducted a small trial of multistrain probiotics delivered in the form of fermented skimmed milk supplemented with *Lactobacillus rhamnosus* GG, *Bifidobacterium animalis* subsp. *lactis* B-12 and *Lactobacillus acidophilus*. A total of 32 HIV-positive people on ART with CD4 T cell counts below 500 participated and were randomly assigned to receive the intervention (15), placebo (9), or to serve as untreated controls (8). After eight weeks, a significant 33% decline in levels of D-dimer—a coagulation biomarker that is associated with risk of mortality⁵⁵—was observed, along with falls in levels of the inflammatory biomarkers C-reactive protein and IL-6, which did not quite crest the threshold for statistical significance.

The second study was performed by Gabriella d’Ettorre and colleagues from the University of Rome, and administered a probiotic containing *Streptococcus salivarius* ssp. *Termophilus*, *Bifidobacteria* represented by *B. breve*, *B. infantis*, and *B. longum*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus delbrueckii* ssp. *Bulgaricus*, and *Streptococcus faecium*. The supplement was taken for 48 weeks, twice a day. A total of 20 HIV-positive participants on suppressive ART were enrolled together with 11 HIV-negative controls. The researchers documented significant declines in levels of immune activation markers on CD4 T cells, high-sensitivity C-reactive protein and lipopolysaccharide binding protein (LBP). In contrast to the Norwegian study, D-dimer levels did not change significantly.

The reason for listing the multifarious species of bacteria used in these trials is to highlight the daunting complexity that lies behind the deceptively simple term probiotic. With relatively little else on offer to address

the residual inflammation and immune activation that can persist despite ART, there is a need to try and pull together the scattered data suggesting that probiotics could be helpful and to design research that could provide clear guidance as to how best they might be used. TAG's recommendation is that a research funder—perhaps the Bill & Melinda Gates Foundation, who are co-sponsoring an ongoing trial of the probiotic VSL#3 in HIV-positive individuals—convene a workshop for investigators to generate a scientific agenda for resolving uncertainties about the value of probiotics as adjuncts to ART.

CONCLUSION

The expansion of clinical research into curing HIV infection continues in 2016; seen in light of Mao's view on the benefits of many blooming flowers, this offers reasons for optimism that encouraging data is likely to emerge from at least some trials. A counterbalancing cause for caution is that, thus far, the HIV reservoir that persists despite ART is proving stubbornly difficult to reduce. The latest news on the state of the field can be expected to emerge from the IAS Towards an HIV Cure Symposium that will take place in Durban, South Africa, July 16–17, and the NIH-sponsored Strategies for an HIV Cure workshop, which is scheduled for November 14–16 in Bethesda, Maryland, U.S.A.

Efforts to develop immune-based enhancements to ART remain on the backburner, at least relatively speaking. But activists and researchers are seeking ways to ensure that the work carries on, as there is evidence that an effective intervention could address residual risks of morbidity and mortality, particularly in immunologic non-responders. It is possible that the strategies being studied in the context of curing HIV will turn out to have potential as additions to ART, and it is important that results from trials are viewed with this possibility in mind to avoid potential therapies being discarded prematurely.

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The Tuberculosis Diagnostics Pipeline

By Erica Lessem

INTRODUCTION

Over the past decade, several new options for improving TB diagnosis have become available. The past year saw considerably more progress than the previous one. However, the reality of how most TB is diagnosed—or not—remains largely unchanged. The world failed to detect 3.6 million of the estimated 9.6 million new cases of TB in 2014.¹ Sputum smear microscopy—which misses over half of TB cases² and gives no indication of drug susceptibility to guide appropriate treatment—is still the diagnostic standard in most of the world, despite the availability of the far more sensitive GeneXpert MTB/RIF for six years.³ Late in 2015, the World Health Organization (WHO) approved Alere's TB lipoarabinomannan (LAM) test—a very affordable, simple, rapid, noninvasive, point-of-care (POC) rule-in test for people with HIV with very low CD4 counts—but no country has begun to implement it yet. New versions of line probe assays—Hain's MTBDR*plus* and MTBDR*s*/ and a product from Nipro—received WHO recommendation, facilitating rapid drug susceptibility testing (DST), but the world is still a long way from universal DST, with an estimated 59 percent of cases of multidrug-resistant TB (MDR-TB) undetected.⁴

Research and development (R&D) for TB diagnostics features some promising developments since last year (see table 1). Improvements on nucleic acid amplification tests (NAATs) such as GeneXpert Omni and Ultra and Molbio's TrueNAT are being validated, positioning them for possible WHO recommendation. Further upstream, encouraging research into gene sets that can predict active TB disease and reliably distinguish it from latent TB and other infections may eventually underpin new blood tests (currently, there is no effective serological test for active TB). Incremental advances are being made to improve detection of pediatric TB (see "Extending quality," page 133).

Yet, overall, with a mere US\$65 million in 2014 funding out of an estimated annual need of \$340 million,⁵ the pipeline for evidence-based new diagnostics has largely remained stagnant (see table 2). Dismayingly, some companies continue to move forward with marketing for their products when the data are unavailable or scream that they should not, as is the case with Epistem, which is marketing GeneDrive in India despite the test's having flopped in studies.

With use of poor tests predominating, poor uptake of good extant options, poor evidence bases to support the introduction of new tests, and poor funding to support the development of better tests, it's no wonder we've made little headway in diagnosing TB.

Table 1. 2016 Tuberculosis Diagnostics Pipeline: Products in Later-Stage Development or on Track for Evaluation by the WHO with New Published Data or Policy Updates Since the 2015 Pipeline Report

Test	Type	Sponsor	Status	Comments
MOLECULAR/NAAT				
BD MAX MTB assay	qPCR for MTB in automated BD MAX	BD	In 16 <i>M. tuberculosis</i> samples, 100% sensitivity, 97.1% specificity ⁶	
Genedrive MTB/RIF	Portable RT-PCR for MTB + RIF resistance	Epistem	Worse sensitivity than smear [!] in 2016 study ⁷	Marketed in India
GenoType MTBDR _{plus}	Line probe assay for RIF + INH resistance	Hain Lifescience	WHO now recommends based on FIND evaluation ⁸	WHO guidance pending
GenoType MTBDR _s /	Line probe assay for FQ + SLID resistance	Hain Lifescience	WHO now recommends ⁹	FIND's multicountry evaluation of MTBDR _s / version 2.0 from 2015 still unpublished
MeltPro	Closed-tube RT-PCR	Zeesan Biotech	New study from China of 2,057 smear-positive TB patients shows sensitivity of detecting resistance to rifampin 94.2%, isoniazid 84.9%, ofloxacin 83.3%, amikacin 75.0%, kanamycin 63.5% ¹⁰	
NTM+MDR-TB Detection Kit 2	Line probe assay for RIF + INH resistance	Nipro	WHO now recommends based on FIND evaluation ¹¹	WHO guidance pending
RealTime MTB/ TB MDx m2000	Automated RT-PCR for MTB; can be added to HIV RNA platform	Abbott	Sensitivity 100%, 95% CI: 98.6–99.9 in smear-positive samples, similar to GeneXpert MTB/RIF ¹²	
Truenat MTB	Chip-based NAAT with RT-PCR on handheld device for MTB	Molbio Diagnostics, Bigtec Labs	FIND and ICMR studies underway	
Xpert MTB/RIF Ultra	Next-generation cartridge-based detection of MTB + RIF resistance	Cepheid	FIND study results anticipated end 2016	
Xpert Omni	Single-cartridge mobile platform that can use single MTB/RIF or Ultra cartridge	Cepheid	FIND study pending but delayed	
Xpert XDR	NAAT	Cepheid	FIND study anticipated 2018	
ANTIBODY/ANTIGEN DETECTION				
Determine TB LAM Ag	Urine dipstick for TB LAM protein	Alere	WHO recommended use in people with HIV with CD4 count ≤ 100 ¹³	

CI: confidence interval

FLD: first-line drugs (isoniazid, rifampin, ethambutol, pyrazinamide)

FQ: fluoroquinolone

ICMR: Indian Council of Medical Research

INH: isoniazid

LAM: lipoarabinomannan

MDR-TB: multidrug-resistant tuberculosis

MTB: *Mycobacterium tuberculosis*

NAAT: nucleic-acid amplification test

qPCR: quantitative polymerase chain reaction

RIF: rifampin

RT-PCR: real-time polymerase chain reaction

SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)

WHO: World Health Organization

Table 2. Later-Stage or Marketed TB Diagnostic Test Candidates with No New Published Evaluation Data

Test	Type	Sponsor	Status
MOLECULAR/NAAT			
EasyNAT	Isothermal DNA amplification/lateral flow to detect MTB	Ustar	No new data since poor in Tanzanian field study ¹⁴
FluoroType MTB	Semiautomated direct MTB detection; PCR in a closed system; results in 3 hours	Hain Lifescience	Marketed
FluoroType MTB RNA	MTB RNA for monitoring of anti-TB therapy	Hain Lifescience	No published data
GeneChip	RT-PCR for RIF + INH DR	CapitalBio	Marketed
LATE-PCR with Lights-On/Lights-Off Probes + PrimeSafe	Single-tube PCR to detect MTB, resistance to INH, RIF, EMB, SLID	Hain Lifescience/Brandeis University, Stellenbosch University	No published data
LiPA pyrazinamide	Line probe assay for PZA resistance	Nipro	Marketed
PureLamp	Manual NAAT by loop-mediated isothermal amplification for MTB detection	Eiken	WHO June 2015 review impeded by data quality issues; guidelines development group reexamined evidence January 2016; recommendations expected June 2016
REBA MTB-MDR	Line probe assay for RIF + INH resistance	YD Diagnostics	No new data; marketed
REBA MTB-XDR	Line probe assay for FQ + SLID DR	YD Diagnostics	No new data; marketed
TREK Sensititre MYCOTB MIC plate	Dry microdilution plate to detect MICs for FLD + SLD (except PZA)	TREK Diagnostic Systems, Thermo Fisher Scientific	No new evaluation data but used in study in Cameroon ¹⁵
TRC Rapid MTB	Automated rapid rRNA to detect MTB	Tosoh	No new data
VOLATILE ORGANIC COMPOUNDS			
Giant African pouched rats (<i>Cricetomys gambianus</i>)	Trained sniffer rats to detect MTB in sputum	Apopo Foundation	No new data
AUTOMATED IMAGING			
CAD 4TB	Digital CXR for TB screening	Delft Imaging Systems	Marketed; in 2016 WHO to review available evidence on computer-aided radiographic TB detection and organize a scoping meeting to determine research needs and if guidelines should be developed ¹⁶
ANTIBODY/ANTIGEN DETECTION			
MBio Array System	POC cartridge to measure ~57 simultaneous MTB antigen-antibody reactions	MBio Diagnostics, FIND	No new data

CXR: chest x-ray

DR: drug resistance

EMB: ethambutol

FLD: first-line drugs (isoniazid, rifampin, ethambutol, pyrazinamide)

FQ: fluoroquinolone

INH: isoniazid

MDR-TB: multidrug-resistant TB

MIC: minimum inhibitory concentration

MTB: *Mycobacterium tuberculosis*

NAAT: nucleic-acid amplification test

PCR: polymerase chain reaction

POC: point of care

PZA: pyrazinamide

RIF: rifampin

RT-PCR: real-time polymerase chain reaction

SLD: second-line drug

SLID: second-line injectable drug (e.g., amikacin, capreomycin, or kanamycin)

TB: tuberculosis

WHO: World Health Organization

TROT, TROT TO MARKET

Perhaps the most exciting advance in TB diagnostics came in late 2015, when the WHO recommended Alere's Determine LAM Ag simple urine dipstick test for ruling in TB in people with HIV with CD4 counts below 100/mm³ or who are seriously ill.¹⁷ The test's imperfect sensitivity (56% pooled sensitivity based on five studies of people with CD4 counts below 100/mm³) means that a negative test must still be followed up with other testing to rule out TB.¹⁸ However, given the extremely high mortality of people with TB and HIV (TB is thought to be the cause of death in nearly 40% of HIV-positive patients, half of which is undiagnosed)¹⁹ and challenges in diagnosing TB in people with low CD4 counts, having an inexpensive (\$2.26 per test), simple, and noninvasive test to use in this very high-risk population is a major advance. In fact, the LAM test is the first TB test to ever demonstrate a mortality benefit in a randomized controlled clinical trial: among 578 people with HIV in hospitals in South Africa, Tanzania, Zambia, and Zimbabwe, using LAM was associated with an absolute reduction of all-cause mortality at eight weeks of 4% (95% confidence interval [CI]: 1%–7%) from 25% to 21%, and a relative risk reduction of 17% (95% CI: 4%–28%).²⁰ This difference appeared to be attributable to the test's allowing earlier initiation (by one day on average) of anti-TB therapy.²¹ Countries with large burdens of TB/HIV, including many countries in sub-Saharan Africa, should roll out LAM testing immediately, along with proper accompanying training to ensure the test is used only in the recommended population and that follow-up tests are done as necessary.²² Whoever ends up with the rights to the test—Abbott is trying to pull out of a putative acquisition of Alere—should ensure its continued manufacture as well as marketing.²³ Further upstream, funding from the Global Health Innovative Technology Fund (GHIT Fund, which is itself funded by the Japanese government, pharmaceutical companies, the Bill & Melinda Gates Foundation, and the Wellcome Trust) to FIND and Fujifilm will support the development of what is hoped to be a more sensitive LAM test.^{24,25,26}

Other policy advances can help improve timely detection of drug-resistant TB. In late 2015, the WHO extended its 2008 guidance, which recommended the use of the Hain version 1 line probe assay (LPA), to recommend the use of two alternative LPAs with the capability to detect TB and rifampin resistance: the Hain version 2 LPA (also called the GenoType MTBDR_{plus} assay) and the Nipro Assay.²⁷ The WHO still does not recommend using LPAs on smear-negative samples. In 2014 and 2015, FIND conducted a cross-sectional noninferiority study to compare the accuracy of these two tests to that of Hain Version 1 assay, evaluating their performance both on clinical isolates and on sputum specimens from people with pulmonary TB; both tests showed comparable performance in detecting *Mycobacterium tuberculosis* (the bacterium that causes TB infection and disease) and rifampin resistance in smear-positive samples: on clinical isolates, sensitivity and specificity compared with the phenotypic reference standard for Hain V1, HainV2, and Nipro were 90.3%/98.5%, 90.3%/98.5% and 92.0%/98.5%, respectively, for detection of rifampin resistance and 89.1%/99.4%, 89.1%/99.4%, and 89.6%/100.0%, respectively, for detecting isoniazid resistance. In sputum testing, sensitivity and specificity were 97.1%/97.1%, 98.2%/97.8%, and 96.5%/97.5% for rifampin resistance and 94.4%/96.4%, 95.4%/98.8%, and 94.9%/97.6% for isoniazid resistance.²⁸ The WHO will update its guidance on LPAs later in 2016. While this certainly reflects progress, Hain and Nipro launched these assays in 2011; it's taken five years to optimize and fully evaluate them.

In May 2016, the WHO also recommended and issued guidance on Hain's MTBDR_{sl}, an LPA capable of detecting resistance to fluoroquinolones and second-line injectables.²⁹ LPAs can produce results in 24–48 hours, much quicker than the two weeks that liquid culture or two to three months that solid culture take. As such, the MTBDR_{sl} LPA can guide appropriate treatment selection. The announcement of the WHO's MTBDR_{sl} recommendation accompanied its recommendation of the shortened or "modified Bangladesh" regimen, whose introduction the test can help facilitate, as the shortened (9- to 12-month) regimen is not suitable for fluoroquinolone- or injectable-resistant TB (pre-XDR-TB; see "Tuberculosis Treatment," page 163).³⁰ Countries and donors must scale up the introduction of this test and work with Hain to further reduce the price. FIND negotiated a public sector price of €7.50 (approximately \$10) per test strip in 138 countries; however, the total cost of running a test (which requires other laboratory supplies) can result in costs of \$20–\$30. The test equipment itself can cost \$8,000–\$40,000, depending on its size and whether it automatically reads results or not.³¹

Newer iterations of GeneXpert are moving closer to market. Recent investments may make it more suitable for use in a variety of settings and more sensitive. GeneXpert Omni, a smaller and more rugged single-cartridge version of the test that is dustproof and runs on batteries could be a point-of-care test for TB. The test device's anticipated cost is \$2,895.³² Cepheid claims that another new product, the GeneXpert Ultra cartridge, is more sensitive than the MTB/RIF, approximating the sensitivity of culture, and has a shorter processing time.³³ FIND is currently validating both the Ultra cartridge and Omni platform: Ultra results are expected at the end of 2016; Omni results have been further delayed. If studies show them to indeed be as promising as the company claims, the WHO will issue recommendations and formulate guidance accordingly. Data on the use of Ultra in smear-negative specimens are expected in 2017, which could inform recommendations on whether Ultra can be used to replace culture. Cartridge prices are expected to remain consistently high at \$9.99, as even though MTB/RIF sales volumes have increased,³⁴ those profits are said (by Cepheid) to have been reinvested in R&D. In 2017, Cepheid plans to release the XDR assay, designed to genotype resistance to isoniazid, fluoroquinolones, and second-line injectables when MTB/RIF (or Ultra) indicates rifampin-resistant TB, though no peer-reviewed data yet exist on this product.³⁵ A FIND evaluation is expected in 2018.

Molbio's TrueNAT, an Indian GeneXpert competitor that has been on the market since 2013, is finally being validated by outside parties (FIND and the Indian Council on Medical Research).³⁶ A recent study compared TrueNAT to Xpert MTB/RIF on 274 patient specimens, using culture as the reference standard. The assays had similar sensitivity on sputum-smear-positive samples: TrueNAT had 99% sensitivity (95% CI: 94.2%–99.95%) versus MTB/RIF's 100% (95% CI: 96.5–100.0%, respectively). With sputum-smear-negative, culture-positive samples, the sensitivity of the TrueNAT was 86.2% (95% CI: 74.1%–93.4%) as compared with 90.1% (95% CI: 88.7%–94.35%) for Xpert MTB/RIF.³⁷ The cartridge-based sample preparation extraction tool, TruePrep—which is rugged and portable—costs \$7,000, and each assay costs \$14; the public sector will receive a further discount.³⁸

Other products without the data to back them up continue to be marketed by unscrupulous manufacturers. Epistem's Genedrive performed dismally in a recent clinical study of 336 participants: sensitivity was 45.4% (95%CI: 35.2%–55.8%) versus 91.8% (95% CI: 84.4%–96.4%) for Xpert MTB/RIF and 77.3% (95% CI: 67.7%–85.2%) for smear microscopy. In smear-negative cases, sensitivity of GeneDrive was 0% (95% CI: 0, 15.4) versus 68.2% (95% CI: 45.1%–86.1%) for Xpert.³⁹ Yet just after those data were published, Epistem announced full commercial launch of Genedrive TB tests in India, claiming it “enables early detection of TB and antibiotic resistance without need for central laboratory facilities.”⁴⁰ The regulatory authority in India should ban the marketing of this test, and private providers should be extremely wary and not waste patients' time, money, and effort by subjecting them to it (see box).

Extending Quality and Affordability to the Private Sector

Many countries, including 12 of the 22 countries with the highest TB burdens (India, Pakistan, the Philippines, Bangladesh, Afghanistan, Kenya, Uganda, Vietnam, Indonesia, Myanmar, Nigeria, and Cambodia) have large private-sector markets for TB diagnosis and care.⁴¹ Ensuring access to affordable, quality diagnosis is both critical and challenging. The use of unvalidated tests, or using tests off-label, can endanger patients and their communities and, at best, wastes their money and time. Important tests, such as GeneXpert, are not commercially available in the private sector in Burma, Cambodia, Indonesia, Nigeria, Uganda, or Vietnam.⁴² But even when good tests are available in the private sector, patients pay dearly, as concessional prices are normally available only to the public sector, and some private practitioners are aiming to maximize profit. For example, in Afghanistan, Bangladesh, India, Kenya, Pakistan, and the Philippines, GeneXpert is available, but the average price charged by private laboratories is \$68.73 (range \$30.26–\$155.44).⁴³ Private diagnosis without case notification to the public program also impedes getting a true picture of local, national, and global TB epidemiology.

In India, where about half of patients seek TB diagnosis and care in the private sector, the Indian government and other actors have taken steps to mitigate the inappropriate use of TB diagnostics, such as banning the use of serological tests and discouraging the use of Quantiferon TB Gold (a test for latent TB that was being inappropriately marketed and used in India to screen for active TB).^{44,45} Efforts are underway to ensure best TB diagnostic practices among private-sector providers in India at an affordable price. The Initiative for Promoting Affordable and Quality TB Tests (IPAQT) offers WHO-recommended TB diagnostics to laboratories who agree to pass on these price reductions to patients by agreeing to a maximum ceiling price, participating in quality assurance programs, and notifying cases to the public program.⁴⁶

To date, IPAQT has involved 116 laboratories across India, with over 250,000 presumptive TB cases tested, and volumes climbing. IPAQT has notified 23,000 cases in five cities under a pilot program and plans to further involve more decentralized laboratories and to streamline notification, as well as to look into expanding into cross-disease diagnostic support, such as including the HIV1 viral load GeneXpert cartridge in the IPAQT framework. Other countries with robust private-sector activity in TB should follow suit. The Clinton Health Access Initiative's Nigeria team recently conducted an analysis to determine feasibility there.

IN DEVELOPMENT

Back in the lab, a promising development came from a team at Stanford University that identified a three-gene set indicative of active TB (*GBP5*, *DUSP3*, and *KLF2*) in whole blood across eight data sets containing over 1,000 samples from both adult and pediatric patients in ten countries. This gene signature could accurately separate people with active TB from healthy controls, from people with latent TB, and from people with other diseases. HIV status, bacillus Calmette-Guérin (BCG) vaccination, and drug resistance did not confound expression of the three-gene set. The gene set may be of use in monitoring treatment, as its expression increases with disease severity and decreases with time of treatment, though this must be validated prospectively. Further validation and development are required.⁴⁷

Researchers from the University of Washington and the University of Cape Town have received funding to further study a simple oral swab to test for TB DNA, and it detected TB well in 18 of 20 patients in a proof-of-concept study (90.0% sensitivity compared with GeneXpert MTB/RIF; 95% CI: 66.9%–98.2%).^{48,49}

Several researchers are exploring the value of immune activation markers such as C-reactive protein (CRP) to indicate active TB disease or to identify good responses to TB therapy. One small study pre- and post-treatment in Gambia showed that CRP levels showed the most significant decrease by two months of treatment ($P < .0001$), whereas two other markers, beta2 microglobulin and neopterin, showed little change by two months but a significant decrease by six months of treatment ($P = .0002$ and $P < .0001$, respectively).⁵⁰ A larger prospective study identified a seven-marker biosignature including CRP as well as transthyretin, interferon- γ , complement factor H, apolipoprotein-A1, inducible protein 10, and serum amyloid A that identified TB disease in the test set ($N = 210$) with a sensitivity of 93.8% (95% CI: 84.0%–98.0%) and a specificity of 73.3% (95% CI: 65.2%–80.1%), regardless of HIV infection status.⁵¹ CRP may be of particular interest for pediatric development (see “Tuberculosis Diagnostics Research for Children,” page 135).

DST research saw some developments. Development of a rapid colorimetric method for detection of resistance to pyrazinamide—one of the most important drugs to treat TB, for which DST development remains challenging due to the enormous number of resistance-associated mutations in the *M. tuberculosis* *pncA* gene—using a dye called 5-cyano-2,3-ditolyl tetrazolium chloride (CTC) progressed when initial testing in a small test of 50 isolates showed DST results could be available in four to six days with 97.1% sensitivity

and 81.3% specificity, in comparison with liquid culture.⁵² Unfortunately, research that could underpin DST development for bedaquiline has not yet been as successful—examining the 12 cases who had developed over fourfold increases in bedaquiline minimum inhibitory concentrations (MICs) in study C209 revealed that all had *M. tuberculosis* with mutations in the *Rv0678* gene, but there was no correlation between MIC change and treatment response, making it unclear what might be a clinically meaningful breakpoint.⁵³ Developing DST for bedaquiline will be important, as resistance to it has already started to develop.⁵⁴

RECOMMENDATIONS

With new products moving forward and interesting new leads to pursue, we are pleased to report progress with the TB diagnostics pipeline. But the world is still far from ensuring all those with TB get appropriate diagnostics. Both R&D and access need dramatic infusions of funding and political will. In particular:

- **National governments and donors must substantially increase funding for TB programs to allow for best diagnostic practices.** This includes the widespread scale-up of NAAT to supplant microscopy, universal DST using liquid culture or LPAs, digital X-ray, and the rapid adoption of LAM testing in areas with high HIV burdens.
- **National governments, donors, and the private sector must invest far more in TB R&D to advance better tests, including those for children.** This should include a commitment to rapidly and rigorously evaluating new technologies and to publishing peer-reviewed results. Greater resources are necessary to achieve the requirements set out in Target Product Profiles (TPPs).⁵⁵
- **National governments and donors should work closely with the nonprofit and private sectors to ensure only quality and affordable tests are used.** In countries with large proportions of care-seeking in the private sector, access to appropriate diagnostics is extremely limited and can be catastrophically expensive. Good programs such as IPAQT to address this exist and should be expanded and replicated.
- **Developers must commit to timely and rigorous validations of their tests prior to marketing, and health and regulatory authorities and private practitioners should hold them accountable for doing so.** Epistem and other companies who market ineffective or as-yet-unproven tests must cease doing so immediately. National governments should ban the import and use of inappropriate tests and enforce those bans. Those working in TB globally should call to task companies such as Epistem that inappropriately market them.

Tuberculosis Diagnostics Research for Children

By Lindsay McKenna

The ability to confirm the presence of tuberculosis (TB) bacteria in the body (microbiological diagnosis) underpins much of the existing technology and paradigm for diagnosing TB in adults, but this approach is problematic for children. An estimated 60 percent of children with TB go undiagnosed: in 2014, national TB programs reported 358,521 cases of TB among children to the World Health Organization (WHO),⁵⁶ yet credible models estimate that one million cases of incident TB occur among children each year.⁵⁷ TB is also likely a major unrecognized co-morbidity or cause of illness and death among children affected by pneumonia, meningitis, HIV, and malnutrition.⁵⁸ Children with the disease have fewer TB bacteria in their bodies (paucibacillary disease), difficulty producing sputum, and high rates of extrapulmonary TB. As a result, diagnosis is often empirical (presumed, rather than confirmed) and based on a combination of clinical and epidemiologic information.

The gold standard for diagnosing TB, microbiological confirmation using culture, is only obtained in 15–20% of children with clinically diagnosed TB disease.⁵⁹ Compared with culture, Xpert MTB/RIF has 62% pooled sensitivity when performed on induced or expectorated sputum (36% more sensitive than smear microscopy) and 66% pooled sensitivity when performed on gastric aspirate or lavage (44% more sensitive than smear microscopy).⁶⁰ Xpert MTB/RIF sensitivity in culture-negative children clinically diagnosed with TB is just 2% for induced or expectorated sputum.⁶¹ The WHO recommends Xpert MTB/RIF as the initial diagnostic test in children suspected of having multidrug-resistant TB (MDR-TB) or HIV-associated TB or, where resources allow, as the initial diagnostic test in all children suspected of having TB.⁶² These recommendations apply to both pulmonary and extrapulmonary specimens, with the exception of stool, urine, and blood, given the lack of data for the utility of Xpert MTB/RIF for these specimen types.⁶³ It is important to note that a majority of studies evaluating Xpert MTB/RIF's performance have been conducted at higher-level health facilities, where it is likely that sicker children with higher rates of smear-positive TB are present for evaluation. How Xpert MTB/RIF performs among children in an outpatient setting, and with different levels of TB disease severity, has not been well studied. That said, while Xpert MTB/RIF is superior to smear microscopy and helps provide rapid confirmation of disease, it should not be used as a rule-out test for TB in children: clinical evaluation remains important in diagnosing TB in children.

Research is ongoing to determine the most feasible and sensitive combinations of tests and specimen types (including urine and stool) for diagnosing TB in children⁶⁴; to compare the performance of smear, culture, and Xpert at baseline and during treatment; and to optimize specimen sample collection and processing to improve diagnostic yields in children. In addition to efforts to optimize existing tools, new technologies in the pipeline might also improve our ability to detect TB in children in the future. The WHO recently recommended molecular line probe assays (LPAs) for the rapid detection of resistance to second-line TB drugs, including fluoroquinolones and injectable agents in children with confirmed rifampin-resistant TB or MDR-TB, based on extrapolation from data in adults.⁶⁵ Xpert MTB/RIF Ultra, currently under evaluation in adults, is expected to have increased sensitivity and ability to detect paucibacillary TB disease, which is common in young children. Xpert XDR is expected to improve our ability to quickly diagnose resistance to first- and second-line TB drugs. These advances, though extremely important, are incremental. To radically improve diagnosis of all forms of pediatric TB, a rapid biomarker-based test that does not rely on sputum and can be used at the point of care is necessary.⁶⁶

The discovery and validation of biomarkers for TB diagnosis and treatment monitoring in children is an urgent research priority. A blueprint for pediatric TB biomarker identification and development, resulting from a 2014 U.S. National Institutes of Health (NIH)-convened workshop, is a call to action. The blueprint identifies critical research needs, including enhancing the detection of pathogen biomarkers and identifying host biomarkers, and calls for collaboration to advance the field.⁶⁷ Efforts by an NIH-organized working group are underway to harmonize pediatric biorepositories (specimen collection methods and clinical data collection) to optimize their use for the future discovery and development of TB biomarkers in children.

Compared with adults, children have increased risk of progression from infection to active disease.⁶⁸ While it is possible to diagnose TB infection in children using biomarker-based tuberculin skin testing (TST) and interferon-gamma release assays (IGRAs), these tests have shortcomings, including their inability to differentiate between TB infection and disease, cross-reactivity with other mycobacteria, particularly for TST, and increased false-negative tests among immune-compromised children. The ability to differentiate between infection and disease and to identify children at increased risk of progression to active disease would improve feasibility and make more efficient the targeted provision of preventive therapy to child contacts of TB patients in high-burden settings.

Efforts to identify and validate biomarkers of TB disease and risk of progression in adults and children are ongoing and, if proven, will greatly improve the reliability and ease of TB diagnosis. However, drug-susceptibility tests rely on microbiological samples. Where a microbiological sample cannot be obtained, biomarkers that enable treatment monitoring in children could provide an interesting opportunity to improve access to appropriate treatment. Select pediatric biomarker research highlights are presented below.

PEDIATRIC BIOMARKER RESEARCH HIGHLIGHTS

LAM

Because both children and people with HIV tend to have higher rates of extrapulmonary TB, it was expected that the lateral flow urine LAM assay (currently recommended in HIV-positive adults who have low CD4 counts or are seriously ill) would work well in children, too. However, the LAM test demonstrated poor sensitivity (48.3%) and specificity (60.8%) compared with culture in HIV-positive and HIV-negative children with TB.⁶⁹ The WHO recommendation for LAM in people with CD4 counts <100 (or with advanced HIV disease) does extend to children, based on the generalization of data from adults, while acknowledging very limited data in children.

C-reactive protein

C-reactive protein (CRP), a nonspecific marker of inflammation detectable in blood and measurable with existing assays at the point of care, has shown potential for screening for TB disease and indicating response to TB treatment in adults (see “In Development” in this chapter, page 134). In one study, CRP demonstrated 98% sensitivity and 59% specificity for TB among South African adults with smear-negative, culture-positive TB with or without HIV.⁷⁰ A study to identify the expression patterns of biomarkers in the plasma of HIV-negative children in India with pulmonary and extrapulmonary TB compared with healthy controls found that children with active TB showed significantly elevated levels of CRP. These findings are not surprising, as a detectable difference in inflammation can be expected when comparing healthy and sick children. As such, CRP should be evaluated as a marker of active TB and for use in TB diagnostic algorithms in larger pediatric cohorts, inclusive of children with latent TB and other pulmonary infections and HIV.⁷¹

TAM-TB

Encouragingly, a novel T-cell activation marker-tuberculosis assay (TAM-TB) demonstrated 83.3% sensitivity and 96.8% specificity among children with TB symptoms compared with culture. The pediatric cohort (N = 113) in this prospective proof-of-concept study included HIV-positive and HIV-negative children 6 months to 16 years old. The combined use of the TAM-TB assay and Xpert MTB/RIF demonstrated 94% sensitivity compared with culture. TAM-TB is a rapid blood-based test with the potential to improve the detection of active TB in children; further refinement and testing, especially in HIV-positive children with low CD4 cell counts, are necessary.⁷²

RNA expression signatures

A genome-wide analysis of RNA expression in blood among children undergoing evaluation for TB, including those with HIV, identified a 51-transcript signature capable of distinguishing TB from other diseases and from latent TB infection. The 51-transcript signature demonstrated 82.9% sensitivity and 83.6% specificity for culture-confirmed TB (Xpert MTB/RIF sensitivity was 54.3%). For culture-negative TB where children are deemed to have highly probable, probable, or possible TB, the 51-transcript signature had an estimated sensitivity of 62.5–82.3%, 42.1–80.8%, and 35.3–79.6%, respectively (estimated

sensitivity for Xpert MTB/RIF was 25%–35.7%, 5.3%–13.3%, and 0%, respectively). The 51-transcript signature distinguished TB from latent infection with a sensitivity of 94% and a specificity of 100%. The 51-transcript signature identified higher proportions of culture-confirmed and culture-negative cases of TB than Xpert MTB/RIF; however, innovation is needed to translate transcriptional signatures into diagnostic tools for resource-poor settings—current methods used to detect RNA transcripts are complex and costly.⁷³

Gene expression signatures

A multicohort analysis of data sets available in two public gene expression microarray repositories identified a three-gene signature (*GBP5*, *DUSP3*, and *KLF2*) capable of diagnosing active TB in adults and children, irrespective of bacillus Calmette-Guérin (BCG) vaccination or HIV status. The TB score derived from the three-gene signature demonstrated 85 percent sensitivity and 93% specificity in a cohort made up of both healthy people and those with active TB, 80% sensitivity and 86% specificity in a cohort made up of people with latent or active TB, and 81% sensitivity and 74% specificity in a cohort made up of people with other diseases or active TB. The TB score showed a significant decreasing trend with progression of treatment, suggesting its potential as a biomarker of clinical response to treatment. However, TB scores in children with culture-negative TB were significantly lower than those in children with culture-positive TB. The TB score demonstrated 86% sensitivity and specificity for latent TB versus culture-positive active TB in children.⁷⁴ A blood-based test offers much advantage over what currently exists, but the ability to detect TB in culture-negative children is extremely important, limiting the potential utility of this three-gene signature for children with culture-negative TB, who account for 80% of children with TB.

RECOMMENDATIONS FOR PEDIATRIC TB DIAGNOSTICS

Much work remains to develop novel diagnostic technologies to accurately detect TB infection and disease; to predict disease progression in healthy, infected children; and to monitor treatment in children. The few tests that have been validated and recommended for use in children, including Xpert MTB/RIF, are sub-optimal and underutilized, partly due to difficulties with specimen collection. At the same time, efforts to identify children at risk for TB—especially within maternal and child health programs, where sick children often first present for care—and referral systems and decentralized capacity to diagnose childhood TB, clinically or with available tools, are urgently needed. We also need:

- To validate tests in adults and children in parallel to expedite access to improved diagnostic technologies for children. These evaluations should include a variety of sample types in children with and without HIV and should assess age-related performance;
- Increased investments in research to discover and validate biomarkers and innovation to translate these biomarkers into simple and affordable tests that can rapidly and accurately diagnose TB, monitor treatment, and predict disease progression in children. In 2014, less than \$2.3 million and \$2.8 million was spent globally on research and development for pediatric TB diagnostics and basic science, respectively;⁷⁵
- To establish and support harmonized and collaborative pediatric biorepositories important for biomarker discovery and development;
- To support and create networks of sites that support field evaluation of new diagnostics and can pool data to more rapidly demonstrate the impact of new tools;
- To scale up and decentralize the use of existing technologies and strategies to diagnose pediatric TB infection and disease, especially within maternal and child health programs; and
- To train health care workers to improve their ability and confidence to clinically diagnose children with TB when tests are unavailable or come back negative.

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The Tuberculosis Prevention Pipeline

By Mike Frick

After decades of receiving short shrift from most national TB programs and international organizations, tuberculosis (TB) prevention is finally coming into the mainstream. In 2015, the World Health Organization (WHO) published its first-ever *Guidelines on the Management of Latent Tuberculosis Infection*.¹ The launch of these guidelines has awakened countries and donors to the idea that TB prevention is an area ripe for intervention—and for intensified research. In March 2016, the executive board of the global health financing mechanism UNITAID endorsed TB prevention as one of three “areas for intervention” that should be prioritized for targeted investments in its TB portfolio.² This support will likely include funding for research projects seeking to shorten and simplify preventive therapy for the groups that are most at risk of developing active TB disease: children and people with HIV. On the other side of the Atlantic, the U.S. White House’s *National Action Plan for Combatting Multidrug-Resistant Tuberculosis* lists TB prevention—specifically, “increasing options for preventing active TB, latent TB infection, and TB transmission”—as the first objective toward its goal of accelerating basic and applied research to overcome the threat of drug resistance.³

As exemplified by these new guidelines and plans, a more focused TB prevention research agenda is beginning to take shape. This agenda involves tackling TB infection from two angles. First, preventive therapy is used to keep asymptomatic infection with *Mycobacterium tuberculosis* (MTB) from progressing to active, symptomatic TB disease. Second, vaccination is administered either pre-exposure to prevent infection with MTB altogether, or post-exposure to prevent infection from developing into disease. To date, research and development (R&D) on TB preventive therapies and vaccines have progressed with little interaction, despite the common goal of using new preventive therapies and vaccines to greatly hasten the decline in TB incidence by reducing the number of people with MTB infection who may one day develop transmissible disease. Indeed, mathematical modeling shows that the dramatic reductions in TB incidence required to meet the TB elimination targets of the WHO’s End TB Strategy will require addressing TB infection—first through preventive therapy and then through vaccination.⁴

To acknowledge the momentum building behind TB prevention as a unified field of research, this year’s *Pipeline Report* jointly reviews progress in the clinical development of TB preventive therapy and TB vaccines. (Advances in infection control—the administrative, environmental, and personal protective measures that reduce the risk of TB transmission in the built environment—fall outside of the biomedical focus of this chapter.) There is much to be gained from breaking the habitual thinking that has placed TB drug development in one camp and vaccines in another. For one, a joint discussion reveals that initiatives to develop new TB preventive therapies and vaccines face a shared thicket of thorny scientific issues, whose lack of resolution has snarled progress toward both ends. Approaching TB preventive therapy and vaccines as related endeavors may also jumpstart an advocacy movement for TB prevention that is more forceful than disjointed efforts to hold public and political attention on separate technological fixes (an approach that can sometimes be misinterpreted by politicians as an either/or choice between treatment and prevention). Finally, prevention research raises a number of unique ethical considerations, with corresponding implications for engaging communities in TB research that both drug and vaccine developers will need to address.

PROGRESS IN TB PREVENTION SCIENCE

Developing new tools to prevent TB will require an intensification of basic science research that can inform product development, so it is fitting that some of the most notable achievements over the past year have

come from the laboratory. Scientists are employing a range of tools to shine new light on how MTB interacts with its human host—sometimes literally, as with the application of positron emission tomography (PET) and X-ray computed tomography (CT) to visualize and map inflammation-based immune activity to MTB as it unfolds across the geography of the lung.⁵ An array of studies—some in animals, others in humans; some observational, others experimental—are illuminating the hidden corners of genome, blood, and lung to improve our understanding of the dynamic nature of MTB infection, how it progresses over time, and why it sometimes spills over into active TB disease.

Predicting Disease Progression through Gene-based Signatures of Risk

The central challenge in TB prevention research is that scientists have yet to establish a firm link between the appearance of any specific biomarker in individuals with asymptomatic MTB infection and progression to active TB disease. Biomarkers are measurable characteristics, such as gene activity, biological processes, or clinical phenotypes, whose presence signifies either a particular disease state or the body's response to vaccination or drug therapy.⁶ The quest to identify biomarkers that act as prospective signatures of risk for developing TB disease among individuals infected with MTB has animated much of TB prevention research.^{7,8} Current methods for diagnosing MTB infection—the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)—cannot predict whether individuals with MTB infection will develop TB disease. (An estimated 10% of MTB-infected people will develop active TB at some point in their lifetimes.⁹)

Once validated in late-stage clinical trials, a biomarker that could reliably predict disease progression or distinguish between individuals with high or low risk would be a powerful tool for guiding public health intervention efforts by identifying individuals most in need of preventive therapy, thereby creating opportunities to interrupt transmission by preempting disease progression. Biomarker-guided interventions might require fewer resources than less-targeted approaches by placing only those people most likely to progress to disease on treatment. More immediately, a biomarker of prospective risk could streamline the clinical development of new TB vaccines and preventive therapies by allowing clinical trials to enroll persons with the greatest risk of developing active TB disease. This targeted approach would reduce the costs of research by allowing investigators to conduct smaller, more quickly enrolling studies.¹⁰

Biomarker identification efforts took a significant step forward in 2016 with the publication of a prospective cohort study of over 6,000 South African adolescents with MTB infection.¹¹ Investigators reported discovering a blood-based RNA signature comprised of 16 genes that predicted the risk of TB disease progression over a two-year period. These 16 genes, collectively referred to as a gene signature, appeared to be more active in 46 adolescents who developed TB than in 107 matched controls who remained healthy. Notably, the gene signature's predictive power increased when measured at time points closer to TB diagnosis (sensitivity of 71.2% at 6 months before diagnosis compared with 62.9% at 6 to 12 months and 47.7% at 12 to 18 months, reported at a specificity of 80%).¹²

To validate these results, researchers tested the gene signature in two separate cohorts of HIV-negative adult household contacts of people with pulmonary TB: one from South Africa and the other from The Gambia. Successful validation in these cohorts led the investigators to ask two additional questions. First, given that sensitivity increased closer to diagnosis, could this signature of risk discriminate between MTB infection and active TB disease? When applied to published data from other adult cohorts in the United Kingdom, South Africa, and Malawi, the gene signature distinguished active TB from both MTB infection and other pulmonary diseases, including in people coinfecting with TB and HIV (a population that usually presents more diagnostic challenges).¹³ Second, could a risk signature found in adolescents perform well in younger children? Here, too, the researchers found that the signature could distinguish between MTB infection and culture-confirmed TB disease in children (but not culture-negative TB). Children with culture-positive TB have more bacteria in

their lungs than those with culture-negative disease; thus, the signature's discriminatory capability in this group suggests that activity in these 16 genes might be related to the number of replicating bacteria in the lung (i.e., bacterial load). Consistent with this idea, the gene signature gradually disappeared when researchers looked for it in patients receiving treatment for drug-sensitive TB.¹⁴

Discovery of this 16-gene risk signature was made possible by the kind of collaborative team science that requires time and sustained financial support. The cohort of South African adolescents that provided data for the primary analysis enrolled its first participant in 2005 and completed follow-up in 2009.¹⁵ That means that the adolescents who participated in the study are now adults. No doubt many have since fallen sick from TB, and some may even have died from it. To build on the contribution of these then-teenagers, investigators should continue to follow them into adulthood to understand how risk of disease progression changes over the life cycle. Evaluating how well this risk signature performs in a larger number of participants drawn from a more general population with less exposure to TB is also important, as biomarker identification studies may have cohort biases that limit their generalizability across different populations.¹⁶ This cohort drew adolescents from an area with an extraordinarily high TB incidence rate (1,400 per 100,000 people), where the lifetime risk of progressing from MTB infection to TB disease far exceeds the 10% risk observed in any given population.¹⁷

Failures of Translation between Markers in the Blood and Events in the Lung

One lingering question from this genetic risk signature study is the extent to which a signature identified from the blood reflects concurrent pathogenesis in the lung. Scientists are increasingly recognizing how the initial lung environment encountered by MTB is important for determining the outcome of infection, but these processes may not be well represented by immune cells circulating in peripheral blood.^{18,19} Acknowledging this limitation, investigators countered that circulating white blood cells "can serve as sentinels of lung pathophysiology."²⁰ However, the fidelity with which measurements taken from peripheral blood mirror disease processes unfolding in the lung remains far from settled.²¹ Long-held assumptions about the relationship between lung and blood in TB are being rethought on the basis of evidence from a range of studies (many in nonhuman primates) that is rewriting the script on the classic symbol of TB pathology, the granuloma, and its role in disease progression.

Granulomas (TB's signature pulmonary lesions) are organized collections of macrophages and other immune cells that flock to sites of MTB infection in the lung. Traditional thinking has likened granulomas to immune fortresses that serve an essential protective function by containing MTB in a quiescent state. In the canonical view, people who develop active TB mount a less-effective immune response than individuals who maintain MTB infection without falling ill. This implies that different granulomas in a given individual all behave similarly, and that differences in granuloma activity between individuals result in one of two divergent clinical outcomes: latent infection or active disease.²²

Nothing seems so simple anymore. As one recent review put it, "the clinical hallmark of TB is the granuloma....[Yet] the field is even at a loss as to whether granuloma formation ultimately benefits host or bacterium, and which is the master of the situation."²³ Under certain conditions, granulomas appear to offer MTB a niche in which it can replicate and persist, whereas the granuloma at other times becomes the focal point at which immune cells marshal a coordinated response to control MTB.²⁴ Whether a granuloma becomes a site of vulnerability or protection appears to depend on the nature of the local CD4+ T-cell response, particularly the ratio of pro- and anti-inflammatory cytokines present in the granuloma.²⁵ CD4+ T cells are critical for immunity against TB, and TB vaccine research has focused on achieving protection through cell-mediated immunity by developing vaccines that trigger CD4+ T cells to release type 1 helper (TH1) cytokines such as interferon-gamma (IFN γ), tumor necrosis factor-alpha (TNF α), and

interleukin-2 (IL-2).²⁶ (Cytokines are small proteins that call and direct the behavior of other immune cells.) However, because immune responses to TB are usually measured in blood—which is easier to collect from humans than lung tissue—not much is known about the profile of local T-cell responses in the granuloma itself.²⁷

A clearer picture is starting to form from a series of studies in cynomolgus macaques, which have become an important animal model for TB prevention research, as they can develop either clinically active TB disease or latent TB infection with granulomas similar to those seen in humans.²⁸ In addition, the MTB epitopes recognized by human CD4 T cells overlap substantially with those in macaques.²⁹ (Epitopes, or small cell-surface proteins, are the parts of antigens that are recognized by immune cells). Research summarized in last year's *Pipeline Report* shows that a spectrum of lesion activity exists in individual macaques with either active disease or latent infection. Animals with active TB disease can have sterilized lesions, but, critically, they also contain a number of granulomas in which infection is not controlled, resulting in disease progression.³⁰ This spectrum of activity in an individual suggests that the outcome of MTB infection is determined locally at the level of the granuloma and not systemically, where the immune response is more conveniently sampled from circulating blood. What controls infection at the granuloma level, and to what extent is this local response represented by immune readouts taken from the blood?

One recent study in MTB-infected macaques sought to answer this question by comparing the T cells and cytokines found in granulomas to those observed in circulating blood.³¹ Investigators used PET/CT imaging to track granuloma formation in 28 cynomolgus macaques, 13 of which developed active TB disease and 15 of which remained latently infected. After macaques were necropsied (killed), granulomas identified by PET/CT underwent histological examination, quantification of bacterial burden, and immunological analysis to measure the presence of pro-inflammatory cytokines (IFN γ , IL-2, TNF, and IL-17) and the anti-inflammatory cytokine IL-10.³² The results add several layers of complexity to our understanding of how cell-mediated immunity operates locally in TB. In a particular macaque, different granulomas exhibited highly variable cytokine profiles. Most T cells in granulomas produced a single type of cytokine (i.e., were monofunctional), but granulomas themselves contained a mix of T cells that produced different cytokines.³³ (This stands in contrast with the stated intention of many TB vaccine studies, which judged the immunogenicity of vaccine candidates by looking for polyfunctional T cells in blood.³⁴) Granulomas in which T cells produced both pro- and anti-inflammatory cytokines were more likely to be sterile or have lower bacterial burdens.³⁵ This is consistent with an emerging consensus that stimulation of pro-inflammatory cytokines such as IFN γ is necessary, but not sufficient, for protection; there must be a counterpoint to inflammatory activity, as too much can damage the lung and impair protection.³⁶ Finally, in most of the macaques, T-cell responses measured in circulating blood (the systemic immune response) did not closely mirror T-cell responses observed in granulomas (the local immune response).³⁷

A related study in macaques probed the differential fates of granulomas from the perspective of MTB itself.³⁸ Investigators added genetic barcodes to individual MTB isolates, tracked the formation of lesions using PET/CT, and, after necropsy, quantified the relative frequency of each MTB barcode in different lesions. They observed that most granulomas were founded by a single bacterium and that bacterial burden varied greatly across lesions, even in the same animal.³⁹ Differences in bacterial burden may reflect variability in the killing efficacy of the immune response at the level of the individual lesion, as animals with active disease also had sterilized granulomas. Given this heterogeneity, the investigators commented that “it is not surprising that relevant predictors of disease outcome have been hard to identify from peripheral measures of immune response.”⁴⁰

The combination of PET/CT, genetic barcoding, and histopathology has revealed that, so long as TB vaccine developers continue to measure success through blood-based immune assays, they risk overlooking important details of what effective immunity against MTB looks like at sites of infection in the lung.⁴¹ Although it is now

possible to closely examine lung responses in nonhuman primates, investigators working in the clinic have few alternatives at hand. Some have predicted that PET/CT may one day be used in clinical trials to track biological signals of an effective vaccine. These signals might include observing fewer granulomas form early in infection, no dissemination of granulomas after infection, or lower levels of lung inflammation—as indicated by radiological markers picked up by PET/CT (e.g., 18-F fluorodeoxyglucose). However, due to concerns about exposing humans to repeated radiation without clear therapeutic necessity, PET/CT cannot be applied for routine monitoring in large clinical trials, and, even if the technique could, the composite vision of inflammation produced by PET/CT is not yet well enough defined to serve as a reliable surrogate of protection, much less a clinical trial endpoint. Other sampling methods, such as bronchoalveolar lavage (BAL)—a technique used to sample cells from the airway—yield closer approximations of the lung environment than blood, but there may be important differences between T cell responses in the airway and lung that make BAL an imperfect alternative.⁴² In addition, given that BAL requires passing a bronchoscope through the mouth or nose into the lung, it may be too invasive to perform on the scale of a clinical trial. Although formidable, these limitations should not inspire a sense of futility among vaccine developers. Work to develop blood-based assays that provide indications of vaccine-induced immunity in the lung should be a priority for the field. Using assays that measure more than IFN γ and other TH1 cytokines may also yield a more complete picture of vaccine-driven immune responses for guiding clinical development.

Bacterial Individuality and Persistence

The ability to attach genetic barcodes to individual bacteria, as described above, has made it possible to speak of bacterial *individuality* and recognize that, just as not all granulomas behave identically, not all MTB cells are homogenous.⁴³ Most MTB cells are susceptible to the bactericidal effects of the immune response or antibiotic therapy, but in any given population of MTB, a few bacteria are able to survive these assaults. Sometimes referred to as *persisters*, these bacterial survivors are slow-growing, nonreplicating, and thought to develop noninheritable resistance to antibiotics and the body's adaptive immune response.⁴⁴ The recalcitrance of these persisters contributes to the lengthy duration of treatment for both TB disease and MTB infection, and likely gives rise to a range of observed phenomena in TB infection and disease, from latency to disease progression to posttreatment relapse.^{45,46}

Understanding the biological mechanisms of persistence and how to overcome them is a major priority for TB drug developers working on prevention. Several TB drug research networks have formed scientific working groups to address the problem of persisters, and the topic has featured prominently in satellite meetings organized by the WHO at the 2014 and 2015 Conference on Retroviruses and Opportunistic Infections.^{47,48} Of immediate concern for the development of new TB preventive therapies, some drugs may be more effective against persisters than others. For example, drugs with sterilizing activity such as rifapentine and pyrazinamide appear to be more capable of killing persistent organisms than bactericidal agents such as isoniazid, which is thought to be more active against replicating bacteria.⁴⁹ Research into MTB persistence has also raised more fundamental questions, leading many scientists to ask, “What is latency anyway?” The initial challenge has been to disentangle terminology that is often conflated in the drug development vernacular—for example, the terms *latency*, *persistence*, and *dormancy*, which likely point to related, yet distinct, concepts.⁵⁰

PROGRESS IN TB VACCINE DEVELOPMENT

The past year has served as the opening chapter in the TB vaccine field's “shift to the left,” a strategy in which major funders such as the Bill & Melinda Gates Foundation are moving resources to basic discovery, preclinical development, and phase I and II trials (events located on the left side of the clinical development pipeline).⁵¹ No new vaccines have entered clinical testing since TAG's 2015 *Pipeline Report*, although many

of the 14 candidates in the pipeline have initiated new trials (see table 1). Thus far, the thrust of activity under this shift to the left has been directed toward two tactics: experimental medicine studies and novel clinical trial designs. Taken together, the intention behind deploying these tactics is to first generate a more diverse stable of vaccine concepts, and then to more efficiently triage these in early-stage trials so that only the most promising candidates advance to larger, costlier efficacy trials.⁵² This strategy aims to correct a glaring weakness in the composition of the TB vaccine pipeline: the viral-vectored and adjuvanted subunit vaccines under development were all designed to play the same notes, just in slightly different combinations. For example, six of the eight subunit vaccines contain an Ag85 antigen (either Ag85A or Ag85B), and the majority of candidates were designed to provoke cell-mediated immunity driven by CD4 and CD8 T cells, resulting in vaccines with little immunologic diversity.⁵³

Table 1. TB Vaccines in Development

Agent	Strategy	Type	Sponsor(s)	Status
<i>M. vaccae</i>	Immunotherapeutic	Whole-cell <i>M. vaccae</i>	AnHui Longcom	Phase III
M72/AS01	Prime-boost	Protein/adjuvant	GlaxoSmithKline, Aeras	Phase IIb
H4 + IC31	Prime-boost	Protein/adjuvant	Statens Serum Institut (SSI), Sanofi Pasteur, Valneva, Aeras	Phase IIa
H56 + IC31	Prime-boost	Protein/adjuvant	SSI, Valneva, Aeras	Phase IIa
MTBVAC	Prime	Live genetically attenuated <i>M. tuberculosis</i> (MTB)	University of Zaragoza, Biofabri, TuBerculosis Vaccine Initiative (TBVI)	Phase IIa
VPM1002	Prime	Live recombinant rBCG	Serum Institute of India, Vakzine Projekt Management, TBVI, Max Planck Institute for Infection Biology	Phase IIa
Dar-901	Prime-boost	Whole-cell <i>M. obuense</i>	Dartmouth University, Aeras	Phase IIa
ID93 + GLA-SE	Prime-boost	Protein/adjuvant	Infectious Disease Research Institute, Aeras	Phase IIa
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase IIa
Ad5Ag85A	Prime-boost	Viral vector	McMaster University, CanSino	Phase I
ChAdOx1.85A + MVA85A	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A (aerosol)	Prime-boost	Viral vector	Oxford University	Phase I
MVA85A-IMX313	Prime-boost	Viral vector	Oxford University, Imaxio	Phase I
TB/FLU-04L	Prime-boost	Viral vector	Research Institute for Biological Safety Problems	Phase I

Experimental Medicine Studies

Experimental medicine refers to studies in humans—usually small and often nested into larger clinical trials—that are intended to ask and answer scientific questions that may inform vaccine discovery and product development.⁵⁴ These studies take advantage of opportunities to work in humans to further our understanding of the biological mechanisms underlying infection and disease. For the purposes of TB vaccine R&D, one major objective of experimental medicine studies is to develop new vaccine concepts by looking beyond immunity mediated through CD4 and CD8 T cells to consider other cell types (e.g., $\gamma\delta$ T cells, mucosal-associated invariant T cells, CD1-restricted T cells, antibodies produced by B cells, etc.).⁵⁵ The overarching goal is to elevate the role of biological investigation in TB vaccine R&D and, in doing so, refashion product development from a strictly linear pathway to an iterative exchange between clinical work in humans, preclinical testing in their animal model counterparts, and basic research in vitro.⁵⁶

Vaccine developers have already responded to the call to incorporate experimental medicine into clinical testing. For example, Aeras is working with the HIV Vaccine Trials Network of the U.S. National Institutes of Health (NIH) on an immunology study that aims to better understand the assays used to assess the immune responses generated by subunit vaccines that are currently in the pipeline.⁵⁷ In this study, South African adolescents will receive either the H4 + IC31 vaccine, the H56 + IC31 vaccine, or revaccination with bacillus Calmette–Guérin (BCG), the existing TB vaccine, which was first licensed in 1921 and used to prevent severe forms of TB in children. This is not a head-to-head trial between H4 + IC31, H56 + IC31, and BCG; rather, blood will be sampled at different time points and analyzed to generate a trove of immunological data on vaccine responses using validated and exploratory assays that may one day be evaluated as possible correlates of risk or protection.^{58,59} There is interest in conducting similar experimental medicine studies involving whole-cell mycobacterial vaccines.⁶⁰ In such studies, the goal would be to refine assays to better distinguish the immune response provoked by whole-cell vaccines from that stimulated by BCG, or to develop assays to measure the activity of unconventional T cell subsets such as $\gamma\delta$ T cells or CD1-restricted T cells. The field aspires to initiate one to two experimental medicine studies per year, and although each will have its own sharp focus, the overarching goal is to probe important scientific questions and increase our understanding of the biology of MTB infection in humans.⁶¹

Novel Clinical Trial Designs

In parallel with experimental medicine studies, vaccine developers are employing novel clinical trial designs in early stages of testing. This has mostly entailed getting creative with clinical trial endpoints by designing phase IIa trials around the primary outcome of prevention of MTB infection as opposed to prevention of TB disease.^{62,63} As with any departure from convention, this strategy offers both risk and reward. Unlike TB disease, which can be microbiologically confirmed through diagnostic tests such as GeneXpert/MTB RIF or mycobacterial culture, MTB infection is difficult to reliably identify with extant tools. Prevention-of-infection trials define infection using blood-based IGRAs such as Qiagen's QuantiFERON Gold In-Tube (QFT-Gold), a test that converts from negative to positive when it detects cell-mediated immune responses (i.e., IFN γ) to MTB antigens.⁶⁴ However, the well-documented variability of IGRA results, and the potential of a positive IGRA to sometimes revert to negative after repeat testing, means that investigators must proceed cautiously.^{65,66,67} Without a gold-standard diagnostic test for MTB infection, and without validated correlates of protective immunity, regulatory authorities are unlikely to license a new TB vaccine that is based on endpoints other than prevention of disease.⁶⁸

As a result, prevention-of-infection is not being pursued as a licensable vaccine indication, but rather as a tool for winnowing vaccine concepts before mounting efficacy studies with traditional prevention of TB disease endpoints. Given that infection with MTB is a more common occurrence than TB disease, prevention-of-

infection trials promise to save money by enrolling fewer participants in less time.⁶⁹ The first results from this approach may be just around the corner. Aeras is conducting a three-arm phase IIa study of H4 + IC31 and BCG revaccination in 990 BCG-vaccinated, HIV-negative adolescents in South Africa's Western Cape province.⁷⁰ The H4 + IC31 candidate pairs MTB antigens Ag85B and TB10.4 with IC31, an adjuvant owned by Valneva. One-third of participants will receive two doses of H4 + IC31, one-third will be revaccinated with a single dose of BCG, and the final third will receive two doses of placebo.⁷¹ The primary outcome is MTB infection, as defined by sustained IGRA conversion (in this case, QFT-Gold), and the primary analysis will occur when the study accrues 64 cases of MTB infection. Aeras reports that it is close to reaching this point and expects to release the results in 2017.⁷²

The subunit vaccine H56 + IC31, developed by the Statens Serum Institut of Denmark (SSI), will soon be used in a prevention-of-infection trial in Tanzania. H56 + IC31 consists of three MTB antigens (Ag85B, ESAT-6, and Rv2660c) paired with Valneva's IC31 adjuvant. Given that the ESAT-6 antigen is present in both the H56 vaccine and the QFT-Gold test, the SSI first had to develop an IGRA without ESAT-6 before it could study H56 in a prevention-of-infection trial.⁷³ (Using QFT-Gold to measure MTB infection in participants vaccinated with H56 could result in false positives, as the ESAT-6 in H56 could prime the antigen-specific T cells that the test looks for as an indication of MTB infection). The resulting ESAT-6-free IGRA contains four antigens (CFP10, QTC6, QTC7, and QTC13) and has been evaluated in studies in Denmark, Egypt, Tanzania, and South Africa; its performance appears to be on par with that of QFT-Gold.⁷⁴ This ESAT-6-free IGRA was developed as a companion diagnostic for the H56 vaccine and is not intended to be a commercial alternative to QFT-Gold.⁷⁵ The trial in Tanzania will contain two arms—one with H56 and the other with placebo—and enroll 1,400 adolescents. Aside from the lack of a third arm looking at BCG revaccination, the major difference between this study and the H4 prevention-of-infection trial is that the incidence of MTB infection in this part of Tanzania is much lower than that in South Africa's Western Cape.⁷⁶

In addition to prevention of infection, TB vaccine developers are designing trials to evaluate prevention of recurrence, defined as either reactivation of disease from latency (i.e., relapse) or reinfection with MTB after treatment completion.⁷⁷ Similar to MTB infection, the incidence of recurrent TB disease is higher in any given population than new cases of TB. Anywhere from 2–8% of treated TB patients will face recurrent disease, and the vast majority of these cases occur in the first 12 months after completing therapy.^{78,79} Consequently, prevention-of-recurrence trials offer similar advantages as prevention-of-infection trials in terms of demonstrating the mettle of vaccine candidates before selecting which ones to move forward to efficacy trials looking at prevention of disease. Successful prevention-of-recurrence trials might also create a pathway for developing therapeutic vaccines to either shorten the duration of treatment or bolster chemotherapy.⁸⁰

Several prevention-of-recurrence studies are under way. A phase IIa prevention-of-recurrence trial was recently begun for the subunit vaccine ID93 + GLA-SE in 60 South African adults who successfully completed therapy for drug-sensitive TB (DS-TB). Developed by the Infectious Disease Research Institute (Seattle, Washington), ID93 + GLA-SE combines the MTB antigens Rv2608, Rv3619, and Rv3620 with the GLA-SE adjuvant. The trial contains four arms and is testing two intramuscular injections of vaccine—given at three different doses—against placebo (saline solution). This safety and dose-ranging study will inform planning for a phase IIb prevention-of-recurrence trial of ID93 + GLA-SE that will enroll up to 450 adults per arm.⁸¹ In addition to ID93 + GLA-SE, H56 recently completed enrollment in a phase I safety, immunogenicity, and dose-escalation study among 24 HIV-negative adults that were previously treated for DS-TB; results are forthcoming.⁸² H56 + IC31 is being studied as an adjunct to TB therapy when paired with COX-2-selective inhibitors (a type of nonsteroidal anti-inflammatory drug).⁸³ The idea is that COX-2 inhibitors will strengthen the vaccine response to H56, and that the two together will shorten the duration of chemotherapy for multidrug-resistant TB. This initial study is recruiting participants in Oslo, Norway and is supported by the Norwegian Research Council.⁸⁴ Despite these interesting applications of H56 during and after TB drug therapy, the SSI has indicated that future development efforts will focus on prevention-of-infection trials rather than prevention-of-recurrence trials.⁸⁵

Other Approaches and Developments

The TB vaccine field's only ongoing phase IIb efficacy trial is evaluating whether two intramuscular doses of M72 + AS01, a subunit vaccine developed by GlaxoSmithKline (GSK) that pairs MTB antigens 32A and 29A with GSK's AS01 adjuvant, protects MTB-infected, HIV-negative adults from TB disease progression compared with placebo.⁸⁶ The trial, which opened in 2014 and is being conducted in South Africa, Kenya, and Zambia, reached its targeted enrollment of 3,500 participants in 2015 and is now in follow-up for the primary outcome analysis, which will be case driven. The analysis will be conducted after investigators detect 21 cases of pulmonary TB; results are expected in late 2018.⁸⁷

Activity also continues on the development of two vaccines designed to replace BCG and be administered to infants soon after birth: VPM1002 and MTBVAC. VPM1002, a live, recombinant form of BCG developed by Vakzine Projekt Management in Germany and licensed to the Serum Institute of India (SII), recently began a phase IIa trial in over 400 South African newborns. The study will compare the safety and immunogenicity of VPM1002 versus BCG in both HIV-exposed and unexposed infants.⁸⁸ The SII is currently in discussions with regulatory authorities in India to take VPM1002 into two larger studies: a phase IIb BCG-replacement trial in newborns (pending a favorable outcome from the South African study), and a phase III prevention-of-recurrence trial in adults.⁸⁹ Work also continues on MTBVAC, a live, genetically attenuated form of MTB that was made less virulent by the deletion of two genes (*phoP* and *fadD26*). A phase IIa safety, dose-escalation, and immunogenicity study of MTBVAC in South Africa is currently recruiting participants in two phases. The first will randomize MTB-negative, BCG-vaccinated adults to receive either MTBVAC or BCG. If safety is demonstrated in this group, the trial will progress to the second stage and randomize infants to receive either BCG or MTBVAC at one of three doses.⁹⁰ A phase IIa study among South African adults is also planned.⁹¹

Efforts to replace BCG will likely receive less financial and intellectual attention in the coming years. In contrast with earlier phase IIa and IIb trials, many of which were conducted in either adults with HIV or infants,^{92,93} vaccine developers are now focusing on HIV-negative adolescents and adults, who account for the majority of MTB transmission globally. (This may be one reason why VPM1002 and MTBVAC—each designed as BCG-replacement vaccines—are also being tested in adult prevention-of-recurrence and prevention-of-infection trials). By conducting fewer clinical trials in children and people with HIV, TB vaccine developers are effectively making the decision to direct research away from the two groups most vulnerable to TB. If focusing testing on adults without comorbidities shortens the clinical development timeline, and if the resulting vaccine averts cases of TB in children and people with HIV through a herd immunity effect by interrupting TB transmission among the adult contacts around them (as modeling suggests could occur),⁹⁴ then this may prove to be a prescient move. But that string of assumptions contains many uncertainties, and developers should acknowledge that the current strategy risks leaving behind two key TB-affected populations with greatly enhanced risks of disease and death that rightly draw significant attention from global health actors.

PROGRESS IN TB PREVENTIVE THERAPY DEVELOPMENT

Although they are no longer the focus of TB vaccine development, children and people with HIV still occupy the center of efforts to develop new or improved TB preventive therapies (see table 2). Research into preventive TB treatment is pursuing answers to two primary questions. First, what are the most effective regimens for treating MTB infection, particularly in high-risk groups, including children, people with HIV, and pregnant women? And second, how should physicians treat probable infection with drug-resistant TB (DR-TB)?

As with the overall TB drug pipeline (see “Tuberculosis Treatment Pipeline,” page 163, for a detailed overview), there are few new drug candidates available for investigators to study. Consequently, much of the activity has focused on optimizing existing drugs for TB prevention (e.g., rifapentine, a rifamycin that is closely related to rifampin and is off-patent and marketed by the French pharmaceutical company Sanofi) or studying

the chemoprophylactic potential of new drugs (e.g., delamanid, a nitroimidazole developed by the Japanese company Otsuka and approved for the treatment of DR-TB). Despite the limited armamentarium, the field is poised to make major strides in coming years with planned or ongoing phase III trials that, if successful, could dramatically refashion treatment guidelines.

Table 2. Clinical Trials to Prevent Tuberculosis Disease

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + isoniazid for 1 month (vs. isoniazid daily for 9 months) NCT01404312*	Fully enrolled	People with HIV either living in high-TB prevalence regions or with a positive TST or IGRA (QFT or T-SPOT TB test)	ACTG
A5300/PHOENIX 6 months daily delamanid (vs. isoniazid)	Beginning enrollment Q4 2016	High-risk (HIV+, TST/IGRA+, or ≤5 years old) household contacts (adults, adolescents, and children 0–5 years old) of individuals with MDR-TB	ACTG, IMPAACT
WHIPP TB 6H versus 3HP (given once) versus p3HP (given once a year for two years)	Beginning enrollment Q3 2016	People with HIV without active TB in high-TB prevalence regions	KNCV, USAID
TBTC Study 37 6 weeks of daily rifapentine (P) versus rifamycin-based standard of care regimens (3HP, 4R, 3HR)	Protocol development	Household contacts, people with HIV, individuals with recent TST or IGRA conversion	TBTC, TBESC, UK MRC, University College London
4R versus 9H 4 months daily rifampin (self-administered) NCT00931736*	Fully enrolled	Adults with positive skin test or QuantiFERON-TB blood test, including people with HIV who are not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR
V-QUIN 6 months daily levofloxacin (vs. placebo) ACTRN12616000215426**	Protocol development	Household contacts (adults, adolescents, and children ≥3 kg) of individuals with MDR-TB	NHMRC, VNTP
P2001 12 weeks of supervised 3HP NCT02651259*	Protocol development	HIV-positive and HIV-negative pregnant and postpartum women with MTB infection	IMPAACT
CORTIS 3HP versus no intervention and active surveillance for TB NCT02735590*	Beginning enrollment Q3 2016	HIV-negative adults with MTB infection in high-risk individuals identified by a gene-based signature of risk	University of Cape Town, Bill & Melinda Gates Foundation

* Clinicaltrials.gov identifier; for more details, see <http://www.clinicaltrials.gov>

** Australian New Zealand Clinical Trials Registry identifier; for more details, see <http://www.anzctr.org.au>

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases (NIAID)

ARVs: antiretrovirals

CIHR: Canadian Institutes of Health Research

IGRA: interferon gamma release assay (QuantiFERON-TB Gold In-Tube (QFT) or T-SPOT TB test)

IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group, NIAID

NHMRC: National Health and Medical Research Council (Australia)

NIAID: National Institute of Allergy and Infectious Diseases (U.S.)

TBESC: Tuberculosis Epidemiologic Studies Consortium, U.S. Centers for Disease Control and Prevention

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

UK MRC: Medical Research Council, United Kingdom

VNTP: Vietnam National Treatment Program

Treating MTB Infection in Household Contacts of People with DR-TB

The question of how to treat MTB infection among individuals exposed to DR-TB is one of the most vexing, and least studied, in TB prevention. To date, no randomized controlled trials have been conducted to guide prophylactic treatment of people exposed to DR-TB, who are often people living in the same household as someone with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). For household contacts of DR-TB patients, MTB infection is an experience fraught with uncertainty, as progression to active disease could entail an MDR-TB or XDR-TB diagnosis. The lack of research on this topic has resulted in wildly divergent guidelines. On one end of the spectrum, the U.S. Centers for Disease Control and Prevention (CDC) outlines a range of treatment options—typically 6–12 months in duration—based on the idea that physicians should treat probable DR-TB infection with two or more drugs to which the infecting organism is believed susceptible.⁹⁵ On the other end, the WHO contends “strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment.”⁹⁶

To help fill this evidence gap, the AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) are collaborating on the PHOENIx study, which will enroll HIV-infected and uninfected child, adolescent, and adult household contacts of adults newly diagnosed with MDR-TB, pre-XDR-TB, and XDR-TB.⁹⁷ Since being described in last year’s *Pipeline Report*, the study has undergone an important modification to the composition of the experimental arm and will now compare the safety and efficacy of delamanid, rather than levofloxacin, to isoniazid—each given daily for six months—for preventing active TB among individuals exposed to DR-TB. Eligible household contacts include people with HIV of any age, children ages 0–5, and anyone older than 5 years who reacts positively to TST or IGRA.⁹⁸ Delamanid has several qualities that make it an attractive potential treatment for probable DR-TB infection. Most importantly, it is effective at treating DR-TB, at least according to the phase IIb data that underpinned its approval by the European Medicines Agency in 2015.⁹⁹ It also appears to be generally safe and well tolerated; has few drug-drug interactions with antiretrovirals that might limit its use among people with HIV; can be given as a single daily dose (thereby promoting adherence); and can be administered safely to children (a safety study of delamanid in children at all age groups is nearing completion).^{100,101}

Given that PHOENIx is the first large MDR-TB household study undertaken by ACTG and IMPAACT, the two networks have been conducting an observational feasibility study to prepare for the larger trial. Clinical trial sites participating in this preparatory study hit the targeted enrollment of 300 adult MDR-TB index cases and over 800 household contacts much faster than investigators had anticipated, suggesting that TB prevention trials among DR-TB patients and their close contacts are feasible despite a lack of experience in this area.¹⁰² In addition to PHOENIx, two other randomized controlled trials are investigating approaches to treating probable DR-TB infection. In Vietnam, the V-QUIN study is testing six months of treatment with levofloxacin versus placebo in Vietnamese adult, adolescent, and child household contacts of MDR-TB patients.¹⁰³ In South Africa, the TB CHAMP study will compare levofloxacin versus placebo in children ages five years and younger (see “Pediatric Tuberculosis Treatment Pipeline,” page 181, for a detailed discussion of pediatric TB drug research).

Treating MTB Infection in People with HIV

Work to develop better TB prevention options for people with HIV is also progressing, and most of this work is revolving around rifapentine. The notion of using rifapentine to prevent TB has amassed considerable interest in the wake of the landmark phase III trial by the Tuberculosis Trials Consortium (TBTC), which demonstrated the safety and efficacy of 12 once-weekly doses of rifapentine and isoniazid (the 3HP regimen).¹⁰⁴ However, most participants in this trial were HIV-negative, raising questions about the effectiveness of the 3HP regimen

in people with HIV. The TBTC recently published the results of a 403-person substudy conducted with the ACTG and IMPAACT under the larger trial that showed 3HP is as safe and effective at preventing TB among people with HIV as nine months of daily isoniazid (9H) and is better tolerated.¹⁰⁵ These findings complement a study among nearly 1,150 adults with HIV and MTB infection in Soweto, South Africa, in which 3HP treatment had similar (although not superior) efficacy in preventing TB disease, fewer side effects, and better treatment completion rates than six months of isoniazid treatment.¹⁰⁶

New research is investigating whether administering multiple courses of 3HP over several years offers people with HIV more durable and long-lasting protection against TB compared with a single round of 3HP in high-TB-burden countries. (Previous *Pipeline Reports* have summarized related work investigating the durability of daily isoniazid preventive therapy, or IPT). The proposed Weekly High-dose Isoniazid and Rifapentine [P] to Protect against TB (WHIPP TB) study will investigate this question using a two-part approach.¹⁰⁷ Part A is an observational, randomized comparison of 3HP versus six months of daily isoniazid (6H) treatment among people with HIV. The primary objective is to compare treatment completion between the two regimens; secondary objectives will compare 3HP to 6H with respect to TB incidence, all-cause mortality, and discontinuation of therapy as a result of adverse events.¹⁰⁸ If 3HP performs favorably in part A, the results could lead the WHO to recommend the provision of 3HP to prevent TB among people with HIV in TB and HIV high-burden countries, offering an alternative to IPT. Part B is a randomized, controlled trial with three arms and will enroll concurrently to part A. Participants in the first arm will receive one course of 6H; those in the second will receive one round of 3HP; and those in the third will receive two rounds of 3HP, one given each year for two years (referred to as pulsing 3HP, or p3HP). The trial will enroll 4,000 participants at 12–14 sites in Ethiopia, Malawi, South Africa, and Mozambique. After two years of follow-up, the primary outcome analysis will compare the effectiveness of a single round of 3HP versus p3HP in preventing TB disease among people with HIV.¹⁰⁹ The study is sponsored by the KNCV Tuberculosis Foundation and funded by the U.S. Agency for International Development (USAID); Sanofi is donating drugs for the study. Investigators have received ethics approval and are awaiting final regulatory go-ahead from the South African Medicines Control Council. They expect to begin enrollment in June 2016.¹¹⁰

The ACTG is also investigating the potential of daily rifapentine and isoniazid (HP) to prevent TB in people with HIV in study A5279. This phase III clinical trial is comparing the effectiveness of daily HP given for 4 weeks to daily isoniazid given for 36 weeks (9H) among 3,000 people with HIV 13 years of age and older who either have MTB infection or live in high-transmission areas. The study reached its targeted enrollment at the end of 2014 and will complete follow-up in November 2017.¹¹¹ Building on this effort, the TBTC, together with the U.S. CDC's Tuberculosis Epidemiological Studies Consortium (TBESC), the U.K. Medical Research Council (MRC), and University College London (UCL), is developing a study of daily rifapentine in settings of low-to-medium TB incidence. The study is still in the early stages of protocol development, but the current plan is to study the safety, tolerability, and efficacy of six weeks of daily rifapentine (P), primarily among HIV-negative individuals.¹¹² As written, the control arm in the study will be a composite of the three rifamycin-based standard-of-care regimens included in the WHO *Guidelines on the Management of Latent Tuberculosis Infection*: 3HP, three months of daily rifampin plus isoniazid (3HR), or four months of daily rifampin (4R).

The considerable potential of rifapentine to improve TB preventive therapy can only be unlocked if the drug becomes more widely available. Currently, rifapentine is approved for the treatment of MTB infection in just a single country, the United States, despite being studied through a series of public-private partnerships in at least a dozen more.¹¹³ Sanofi has made some progress over the past year in broadening access to rifapentine, most notably through its decision to list rifapentine in the catalogue of the Global Drug Facility (GDF).¹¹⁴ This means that, for the first time, TB programs outside of the U.S. will have a direct route for purchasing rifapentine and may even be able to start using the drug while registration is pending by exercising import waivers and other pre-approval access mechanisms.¹¹⁵ Sanofi has also taken steps to register rifapentine in a wide swath of countries, with the most progress seen in East Asia (Taiwan and Hong Kong).¹¹⁶ Still, access to

rifapentine remains far too constrained given its central role in the TB prevention research agenda. For their part, investigators should be asking more of Sanofi in terms of securing commitments to making rifapentine available swiftly and without undue delay after the conclusion of efficacy trials. This is all the more justifiable considering that the lion's share of investment in rifapentine has come from the public sector. In the United States alone, three public agencies (CDC, NIH, and USAID) are footing the bill for trials that may expand the use of rifapentine to a broader array of countries and patient populations.

PROGRESS IN PUBLIC ENGAGEMENT IN TB PREVENTION RESEARCH

The strategies being pursued by developers of TB vaccines and preventive therapies carry a mixture of risk and reward. For clinical trial participants, the decision about whether to enroll in a study involves a more personal risk/benefit calculus. Progress in the clinical research efforts described above will depend on the willingness of people at risk of TB to participate in experiments with uncertain outcomes. A similar bargain is struck by preventive interventions given that, as the writer Eula Biss reminds us, "it is through us, literally through our bodies, that certain public health measures are enacted."¹¹⁷ For prevention, especially, it is important that these measures be safe, effective, and acceptable for the healthy individuals who will be asked to take therapy or undergo vaccination to ward off an event whose occurrence is probabilistic and may never come to pass. Cutting-edge science alone is not enough to guarantee that new TB prevention methods will be acceptable to their intended users—a group that at its largest could include all 2 billion people estimated to be infected with MTB globally. TB prevention science must progress in lockstep with the meaningful engagement of the communities that will be asked to embrace any resulting new technologies and that will be called, time and again, to participate in the research to develop them.

Thoughtful community engagement is an important element of any TB R&D endeavor, but its presence or absence invokes unique considerations for prevention research. The science underlying prevention carries profound implications, not only for its potential to avert suffering resulting from disease, but also for its ability to reshape how individuals imagine themselves as either sick or healthy in relation to new conceptions of risk and susceptibility.¹¹⁸ If validated in clinical trials, correlates of risk, such as the gene signature identified from the South African adolescent cohort study, could create whole new clinical categories of people—the pre-symptomatically ill—that are subject to interventions ranging from treatment to vaccination to repeat testing. It is unclear whether signatures of risk will end up expanding the proportion of people with MTB infection in need of intervention, or whether they will narrow the eligibility for TB preventive services by assigning MTB-infected individuals to a spectrum of risk with interventions reserved for those at the high end. In either case, TB prevention science promises to open many people who consider themselves healthy to new forms of medical action. Engaging communities in TB prevention research, from the laboratory to the clinic, will help to ensure that the development of new TB vaccines and preventive therapies moves forward in parallel with the knowledge, values, concerns, and needs of the communities around the world at risk for TB.

Given these potentially transformative considerations, moves by Aeras in the last year to form a community engagement program come not a moment too soon. As designed, the program contains many of the best practices developed by earlier community engagement initiatives supported by TB drug developers such as the TB Alliance and the TBTC. Community engagement in TB vaccine trials sponsored by Aeras will occur on multiple levels: individual trial sites (e.g., through local initiatives led by community advisory boards), sponsors (e.g., through community reviews of clinical trials protocols), and regional (e.g., through the formation of an Africa TB vaccine advocates network).¹¹⁹ Among the proposed activities, the most important is Aeras's plan to involve community representatives in reviewing clinical trials protocols—a key step for building scientific literacy and for incorporating community feedback into the research agenda. Funders of TB vaccine R&D should commit to funding the Aeras community engagement program and acknowledge this work as the ethical complement to other standards of clinical research, such as Good Clinical Practice.

RECOMMENDATIONS

For funders: Ensure financing mechanisms are sufficiently flexible and durable to support the multi-year, collaborative research endeavors that will be required to make progress against a challenge as complex and intractable as MTB infection.

For example, nearly ten years passed between when the South African adolescent cohort enrolled its first participant in 2005 and when it published results announcing the discovery of a risk signature of disease progression in the *Lancet* in 2016. This was not time wasted, and the cohort will likely yield publications and results for years to come. Further advancing our knowledge of MTB infection and TB disease may require larger cohorts with even longer periods of follow-up. In addition, funding agencies should support translational work to bridge advancements in basic science with clinical development and maintain openness to a wide range of approaches that probe the nature of MTB infection from the perspective of both host and pathogen, and through the application of new assays and imaging technologies in both humans and animal models.

For vaccine researchers and developers: Continue to explore a greater diversity of approaches to TB vaccine development through the use of experimental medicine studies and trials designed around novel endpoints.

Ultimately, this will likely require developers to introduce wholly new vaccine candidates whose designs look beyond the narrow focus on cell-mediated immunity that has dominated past efforts. The development and introduction of new assays that are able to translate signals of immunogenicity between lung and blood (or capable of safely measuring vaccine responses directly in the lung itself) should also be a priority. Developers and their sponsors should not foreclose on clinical trials among infants and people with HIV, two of the groups most in need of a new TB vaccine. Although previous trials in these two populations have fallen short of expectations, there is much that can be learned from past failures. Rather than wholly abandon vaccine concepts and constructs that did not work, vaccine researchers and developers should more forthrightly interrogate the reasons behind disappointing results.

For drug researchers and developers: Accelerate research to understand MTB persistence and the nature of latency to develop new drugs targeting latent infection.

Efforts to understand MTB persistence would benefit from initiating a dialogue with researchers involved in vaccine development about differences in how the TB drug and vaccine fields approach preclinical testing. Each field is confronting challenges related to MTB persistence and the nature of latency, but vaccine and drug developers do not always measure the same pathology or immunological events using relatable endpoints or definitions of scale in the animal models in which much of this work will be conducted. Closer collaboration with their vaccine counterparts might also open the door for drug developers to use vaccines as adjuncts to shorten therapy or reduce the risk of relapse. In the meantime, ongoing efforts to shorten and simplify TB preventive therapy for children, people with HIV, pregnant women, and household contacts of people with DR-TB should continue. The advanced stage of many of TB prevention trials obligates pharmaceutical companies involved in this research—namely, Sanofi and Otsuka—to take steps to register their products more widely and facilitate equitable access through measures such as affordable pricing.

For all researchers and developers: Recognize community engagement in research as the ethical complement to good clinical practice and take steps to involve representatives from TB-affected communities in all stages of R&D.

The potential of ongoing or planned TB preventive therapy and vaccine studies to refashion clinical practice in ways that could render many more people with asymptomatic MTB infection eligible for medical intervention makes it imperative that developers create meaningful spaces for community voices, concerns, and priorities to enter the research process. Communities must become true partners in TB prevention research, and not merely its silent beneficiaries.

For activists: Take up TB prevention as a unified cause and break with the habit of advocating for vaccines, preventive therapy, and infection control as separate and unrelated technological fixes.

With the exception of TB PROOF—a South African advocacy group founded by doctors who contracted TB that is dedicated to preventing MTB infection among healthcare workers—activist voices in TB prevention have been few in number and modest in volume. This absence does not reflect a lack of need. A global shortage of BCG continues into its third year, needlessly endangering the lives of millions of infants.¹²⁰ Rifapentine, the cornerstone of TB preventive therapy research, is registered for the treatment of MTB infection in just one country, despite being studied in at least a dozen more. Individuals exposed to MDR-TB have few evidence-based options to treat probable drug-resistant infection. And countries remain slow to rollout proven interventions such as IPT to people with HIV, 400,000 of whom died from TB in 2014.¹²¹ We are one year closer to 2025, the year WHO says new prevention tools must be introduced to reach the End TB Strategy's goal of eliminating TB by 2035, and there is no new vaccine or transformative preventive drug regimen on the immediate horizon. The clock is ticking.

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The Tuberculosis Treatment Pipeline: Activity, but No Answers

By Erica Lessem

In the past year, the development of new tuberculosis (TB) drug candidates experienced some setbacks as well as some wise pruning, with the unexpected suspension of enrollment in STAND (a phase III combination trial that includes the new drug pretomanid), the discontinuation of candidate TBA-354 (due to signs of toxicity), and the official end of development of AZD5847 (due to lack of anti-TB activity). In a bright spot, QuriEnt's Q203 entered phase I, representing a new drug class and a new sponsor in TB clinical trials. But overall, the new TB drug development landscape remains parched, with just five candidates from four classes in development—including bedaquiline and delamanid, which already have conditional marketing approval in some countries. Most of these drugs have been stalled for years. Delays across the board, from sponsors, from regulators, and from funders, are preventing nascent progress from flourishing. The phase III trial for bedaquiline has finally started enrolling—some five years after the phase IIb trial concluded. Sutezolid is still awaiting entry into phase IIb, nearly five years after showing promise in phase IIa. Delamanid's phase III trial is chugging along dutifully, but, due to the lengthy standard-of-care background treatment and follow-up time required in TB clinical studies, won't give results till 2018.

More activity is ongoing among trials testing combinations of drugs already on the market, often called repurposed drugs. But again, most will not bear fruit for several years. These various trials to optimize therapies point to creativity among researchers but also to the poor existing evidence base for use that has left the TB field reliant upon lengthy, poorly tolerated—and, for drug-resistant TB, marginally effective—regimens. Some exciting advances are being made in preventive therapy for TB—these are now reported in the TB prevention chapter (see page 143)—but this chapter will focus exclusively on the development of treatments for active TB disease.

New guidelines from the World Health Organization (WHO) may help improve the treatment of multidrug-resistant TB (MDR-TB) by updating options for stronger treatments in combination regimens, though the newly recommended putative treatment-shortening approach has yet to be validated in randomized controlled trials. However, the updated WHO guidelines will help increase the use and availability of drugs of greater potency such as delamanid, bedaquiline, clofazimine, and linezolid.¹ MDR-TB treatment is still inadequate, with fewer than 10% of those with the disease successfully treated worldwide, and less than 2% of those who may benefit from new drugs receiving them.^{2,3} Investment in new alternatives is also scandalously low; in 2014, just US\$243 million out of the needed US\$740 million were available for TB drug research and development (R&D).⁴ Recent global and national strategic plans to address antimicrobial resistance and TB, such as those from the Netherlands, the United States, and the United Kingdom, must go beyond lip service and be met with financial commitments to increase support for TB R&D.^{5,6,7,8} Countries with high TB burdens and large economies, such as Brazil, China, India, Indonesia, Russia, and South Africa, must contribute far more to R&D as well as to service scale-up.

UPDATES ON NEW COMPOUNDS IN DEVELOPMENT

Table 1. Drugs in Development for Tuberculosis

Drug	Class	Sponsor(s)	Phase
bedaquiline	diarylquinoline	Janssen (Johnson & Johnson), TB Alliance, NIAID, SAMRC, the Union, UNITAID, USAID	III
delamanid	nitroimidazole	Otsuka, NIAID, UNITAID	III
pretomanid	nitroimidazole	TB Alliance	III
sutezolid	oxazolidinone	Sequella, NIAID	IIa
Q203	imidazopyridine	Qurient, Infectex	I

NIAID: National Institute of Allergy and Infectious Diseases (United States)

SAMRC: South African Medical Research Council

The Union: International Union Against Tuberculosis and Lung Disease

USAID: The U.S. Agency for International Development

Q203

A new compound, Q203, developed by Qurient, entered clinical testing in late 2015.⁹ Q203's phase I, single-dose, dose-escalating study has completed enrollment. Results will be shared in 2017, and phase II trials will likely start then.¹⁰ A member of the imidazopyridine class, Q203 targets the respiratory cytochrome bc₁ complex, inhibiting the synthesis and homeostasis of adenosine triphosphate (ATP), thereby crippling the energy conversion system in both replicating and nonreplicating TB bacteria.¹¹ Q203 brings much-needed diversity to the pipeline and is an important addition to early-stage development as TBA-354 drops out of the running. Qurient is developing Q203 with support from the Korea Drug Development Fund and is partnering with Infectex to develop the drug for Russia and the other Commonwealth of Independent States (CIS) markets.

TBA-354

TBA-354, in the same class of drugs as delamanid and pretomanid (the nitroimidazole class), was the first candidate to enter phase I TB trials in six years, but regrettably, this rising star burned out quickly. After a phase I dose-escalating trial showed an association with mild signs of neurotoxicity (repetitive uncontrolled eye movements and overactive reflexes, from which all affected study participants recovered), the TB Alliance voluntarily placed TBA-354 on hold in January 2016 and announced the discontinuation of its development in March 2016.^{12,13} This unfortunate event nonetheless represents responsible stewardship and communication of results, and it reinforces the need for more investment in TB R&D since—as in all disease areas—the majority of early-stage drug candidates will fail, necessitating a variety of compounds in development at a given time.

Pretomanid

The development of another nitroimidazole, pretomanid, has also been hampered—this time by unexpected fatalities that led to a partial clinical hold on pretomanid and a complete hold for the STAND study.¹⁴ This phase III trial was testing the combination of pretomanid (at different doses) along with moxifloxacin and pyrazinamide (PaMZ) in people with drug-sensitive TB (DS-TB) and some forms of MDR-TB; TAG has previously critiqued the design of this trial, particularly its uncontrolled MDR-TB arm and the regimen's expected vulnerability to resistance.¹⁵ Unfortunately, the experimental regimen was associated with high levels of liver

toxicity, which caused the death of three participants, all in the drug-sensitive PaMZ arms of the study. The study's Data Safety Monitoring Committee (DSMC) promptly recommended a suspension in enrollment in September 2015 and, after further analysis, in November 2015 recommended restart of enrollment with the addition of safety procedures and, at least initially, the exclusion of people with HIV.¹⁶ In May 2016, the DSMC completed its review and concluded that full enrollment could resume regardless of HIV status; in May 2016, the Alliance noted it was preparing all necessary regulatory submissions to prepare for resuming enrollment into the STAND trial.¹⁷

The NiX-TB trial, which is testing pretomanid, bedaquiline, and linezolid in participants with extensively drug-resistant TB (XDR-TB), is faring better—though there is no randomization or control arm in this open-label study. As of March 2016, 37 patients were enrolled, and 14 patients completed treatment. The TB Alliance reports—though data have not yet been peer reviewed or formally presented at a scientific meeting—that four patients have died early on in treatment due to underlying disease, and that all other patients are doing well and showing good clinical response, with the majority having converted their sputum cultures to negative in the first two months of treatment. Linezolid toxicity has been manageable, though some dose interruptions and dose reductions occurred, mainly after week 9. The first formal interim analysis will occur in the third quarter of 2016.¹⁸

NC-005, a phase IIb trial that is testing the efficacy and safety of two months of bedaquiline (in a simpler dosing scheme than the currently recommended one), pretomanid, and pyrazinamide in about 240 patients with either DS- or MDR-TB, completed enrollment at the end of 2015 and will have results at the end of 2016.¹⁹ The PRACTECAL study, a multiarm, open-label, randomized controlled pragmatic trial from Médecins Sans Frontières (MSF) that will examine various combinations of pretomanid, bedaquiline, moxifloxacin, linezolid, and clofazimine given for six months to people with MDR-TB in comparison to the WHO standard of care, has received ethics and regulatory approval; MSF anticipates opening enrollment in the third quarter of 2016.²⁰

Sutezolid

Readers will be dismayed to learn that sutezolid, an oxazolidinone hoped to be a safer alternative to linezolid, is still stuck in phase IIa some three years after Pfizer ended its anti-infectives program and licensed the promising candidate to the small pharmaceutical company Sequella. Sequella has recently called sutezolid a “companion drug” for its probably ineffective compound, SQ109.²¹ Sutezolid is, in fact, a candidate in high demand on its own (unlike SQ109, see more in box “Foul Play in the Federation,” page 169). Fortunately, the U.S. National Institutes of Health (NIH) will sponsor the manufacture of 15,000 doses of a 600 mg tablet, which should be ready within six months after a protocol for an AIDS Clinical Trials Group (ACTG) study is given the green light. ACTG study A5289 is under development and currently features sutezolid replacing ethambutol in the experimental arm of a two-stage, adaptive study design to evaluate the pharmacokinetics, safety, and initial efficacy of sutezolid over two and eight weeks in people with DS-TB. It would determine an ideal dose for sutezolid, as well as evaluate interactions between rifamycins and sutezolid and its main metabolite.

If the study is approved for implementation, A5289 will trigger sutezolid's long-awaited entry into phase IIb.²² Sequella and Johns Hopkins (which owns the intellectual property rights for the development of sutezolid in combinations) should turn over intellectual property rights, and Sequella should also release the toxicity and clinical data on sutezolid to date to the Medicines Patent Pool (MPP). Fortunately, it appears Johns Hopkins has entered into negotiations to do so.²³ If Sequella refuses to turn over early data to facilitate collaboration, it will take other interested parties three to five years and several million dollars to reproduce data to move forward with development—wasted time and money that are simply not available given the scarce resources for TB R&D and the urgent need for new compounds.

Bedaquiline

Bedaquiline's use in programmatic settings is on the rise (see table 2), and data described below support the continued expansion of its use. Indeed, the new WHO MDR-TB guidelines better categorize bedaquiline (and delamanid) as agents that can be added on to an MDR-TB regimen to ensure incorporation of five effective drugs.²⁴

Data from South Africa's incorporation of bedaquiline first into a clinical access program and then into routine programmatic use indicate the drug's safety, effectiveness, and importance in treating MDR-TB. The bedaquiline clinical access program, which started with just five sites while the Medicines Control Council (MCC) was reviewing bedaquiline's dossier for marketing approval, enrolled 221 patients for whom other treatment options had been exhausted. Data from the full cohort of 221 patients with follow-up will be available in 2017, but an interim analysis of the 91 patients with MDR- or XDR-TB enrolled by July 2014 (60 of whom had completed treatment) showed that 70 percent had culture converted or remained culture negative—an impressive result for these patients with intractable forms of TB, many of whom had HIV infection and low CD4 counts (as opposed to carefully screened clinical trial participants, who are generally healthier and have fewer complications). The South African experience showed that participants with HIV on appropriate antiretroviral therapy (ART) did quite well on bedaquiline, and participants could easily be switched to nevirapine- or lopinavir/ritonavir-based regimens for the duration of their treatment with bedaquiline and then be placed back on the preferred efavirenz-based fixed-dose ART (whose use is contraindicated with bedaquiline due to drug-drug interactions).²⁵ Notably, lopinavir/ritonavir does increase bedaquiline exposure compared with no ART (median area under the curve 67,002 vs. 34,730 ng·h/mL, $P = .003$; median time of highest concentration [T_{max}] of 6 vs. 4 hours, $P = .003$; and terminal half-life of 55 vs. 31 hours $P = .004$), though clinical implications are unknown.²⁶

Based on this positive experience, and with the MCC's approval of bedaquiline, the South African Department of Health launched a framework for routine programmatic use of bedaquiline in June 2015.²⁷ Under this framework, bedaquiline can be used in the public sector without review by the national or provincial program in anyone 18 years or older with pre-XDR-TB (TB that is resistant to either a fluoroquinolone or an injectable, as well as isoniazid and rifampin) or XDR-TB, whose TB shows *InhA* and *KatG* mutations (indicating resistance to isoniazid), who has intolerance to second-line drugs (such as drug-induced hearing loss or psychosis), or who has a history of surgery, as long as he or she has no personal or family history of QT prolongation (a potentially dangerous disturbance in the heart's electrical activity, for which bedaquiline increases the risk). The South African treatment program does allow for people who are under 18, who are pregnant, or who have MDR-TB treatment failure without proven second-line drug resistance to receive bedaquiline per individual case review and approval.

Over 1,000 patients from all but one (Mpumalanga) of South Africa's provinces have now received bedaquiline. The vast majority have XDR-TB (39%) or pre-XDR-TB (40%); 12% received bedaquiline due to intolerance of other drugs, 8% due to *InhA* and *KatG* mutations, and 1% because they were surgical candidates. For the first time, a new TB drug has been added to routine management for MDR-TB, and it is going very well.^{28,29} In a separate analysis of the 598 patients who started bedaquiline between March and end of September 2015, the most common reason for denying bedaquiline initiation was having too few potentially effective drugs in the proposed background regimen, pointing to the urgent need for companion drugs such as linezolid and delamanid. Indeed, provinces that quickly scaled up bedaquiline use were those that had linezolid access, as well as those that had tools to detect need for bedaquiline (genotypic second-line drug resistance testing and capacity to detect high-frequency hearing loss).³⁰

More data to inform the optimal use of bedaquiline come from a French cohort of patients started on bedaquiline between 2011 and 2013. In this cohort of 45 patients, 33 patients received bedaquiline for longer than six months (the duration that was studied in phase IIb clinical trials and hence the recommended

duration of treatment under conditional approvals and in WHO guidance);³¹ some patients received bedaquiline for up to 768 days, with a median of 360 days. Patients receiving courses of bedaquiline for more than six months were more likely to have hepatitis C (58% vs. 17%, $P = .020$), to have been previously treated for TB (94% vs. 25%, $P < .001$), and to have sputum culture-positive TB (97% vs. 75%, $P = .048$). In those who received a standard six-month course of bedaquiline, 75% achieved cure, versus 82% of those receiving a longer course. There were no significant differences in adverse events in the two groups. These findings indicate that prolonged bedaquiline use is well tolerated, at least in this small cohort, and that good outcomes may be partially explained by the decision to extend bedaquiline treatment in select challenging cases. The clinicians from the French program therefore recommend extension of bedaquiline in cases that would have fewer than four effective drugs if bedaquiline were stopped, that have delayed microbiological response (i.e., culture positivity after four months of treatment), and risk factors for poor outcomes (e.g., extensive lung disease, low body mass index, high acid-fast bacilli [AFB] positivity, or HIV), as long as prerequisites such as pharmacovigilance, close monitoring, patient consent, treatment tolerability, and expert opinion are in place.

All countries with MDR-TB burdens should follow France's and South Africa's examples and safely incorporate bedaquiline into their treatment programs. Ministries of health in countries such as India and the Philippines have been negligent in making this drug available to their citizens who so desperately need it: despite registration and availability of the drug and guidelines for its use in country, as of May 31, 2016, neither has started a single patient on treatment under routine programmatic conditions.

Indeed, further research supports the increased use of bedaquiline. A new analysis of the phase II, randomized, double-blind C208 stage 2 study of bedaquiline showed that only two out of ten participants receiving bedaquiline who had either converted or relapsed acquired resistance to companion drugs, versus 16 out of 30 in the background regimen plus placebo arm. No participant developed pre-XDR-TB or XDR-TB in the bedaquiline arm, versus six and two participants, respectively, in the placebo arm. Though the number of participants in this analysis is very small, these data point to bedaquiline's potential ability to protect against the amplification of resistance to other drugs. Notably, one out of ten participants in the bedaquiline arm showed a greater than fourfold increase in the minimum inhibitory concentration of bedaquiline, indicating potential acquired resistance to the new drug, though this does not necessarily correlate with clinically observed lack of drug efficacy.³² Some clinical cases of resistance to bedaquiline have been reported.³³

A recent analysis of C209, the phase II single-arm open-label trial of bedaquiline plus background regimen in 233 adults with MDR-TB (including XDR-TB and pre-XDR-TB), showed high rates of culture conversion and good outcomes with bedaquiline, regardless of type of MDR-TB. Of 205 participants included in the modified intention to treat analysis, 40% had pre-XDR-TB or XDR-TB, and 66% had extensive cavitation. Yet outcomes were still good: using a conservative measure of cure (the old WHO definition of five consecutive negative cultures), 61% of participants were cured, and only 16% failed, 7 percent died, and 15% transferred out or were lost to follow-up at 120 weeks after treatment initiation. Of 37 patients with XDR-TB, 23 (62%) culture converted, and all remained culture negative during the trial—though follow-up data were only available for 16 of 23 participants for a median of 5.4 months. In multivariate analysis, cure was associated with newly diagnosed MDR-TB (82% versus 71% cured in previously treated participants, $P < .05$), and with lower AFB score (90% of sputum smear-negative cases had negative cultures by week 120 versus only 52% for participants who had an AFB score of 3, $P < .05$).³⁴

The STREAM-II study, which will test bedaquiline in a nine-month injectable-free regimen, as well as a six-month combination, finally started enrolling in March 2016³⁵—more than three years since the drug's approval from the U.S. Food and Drug Administration (FDA), which was conditional upon the timely conduct of a phase III trial. Mongolia is the first country to start enrollment; significant MDR-TB clinical trial capacity development for STREAM-II should benefit the field of TB R&D overall. The Union, the study's sponsor,

attributes the delay in the study's start to the greater burden required for a registrational trial (versus the pragmatic design of STREAM-I, described in the next section), including the requirement for export permits and couriering study samples when trial host countries do not have registered laboratories.

Despite these challenges, Janssen—bedaquiline's sponsor—could certainly have committed more resources to speed bedaquiline's entry into phase III, as required by the FDA. The gap between bedaquiline finishing phase IIb and entering phase III spans nearly five years; meanwhile, the paucity of data has contributed to the limited use of bedaquiline. Janssen's legal department has been delaying support for another important and long-awaited study, ACTG study A5343, which will test delamanid and bedaquiline in combination to determine if together they cause unsafe levels of QT prolongation, for which each drug individually increases the risk. Some patients have already been treated with a combination of bedaquiline and delamanid without adverse events; one patient from the Democratic Republic of the Congo experienced no QT prolongation, but a Tibetan patient from living in India did experience asymptomatic increases in QTc from <450 to 486 ms after eight doses of the new drugs. This observed increase was manageable, and no harm to the patient occurred, but it does reinforce the need for more information on the impact of the two drugs together.^{36,37} Janssen's lack of urgency on A5343, coupled with its deplorable delays on initiating pediatric research even after receiving public contributions to expedite it (see "Pediatric Tuberculosis Treatment Pipeline," page 181), clearly point to Janssen's plummeting contributions to TB R&D since bedaquiline's approval—for which Janssen received a handsome reward of a priority review voucher as well as substantial tax credits. Janssen is looking into determining a breakpoint for resistance to guide drug susceptibility testing in line with the terms of its conditional FDA approval, though this appears to be scientifically challenging to determine.³⁸

Public resources are furthering bedaquiline's research. The NExT study in South Africa, which is testing the drug in a six-month injectable-free regimen, has started enrolling in Cape Town, but bureaucratic delays from the South African Medical Research Council have meant that only one study site is open.³⁹ Bedaquiline and delamanid will also be tested together and separately as part of nine-month injectable-free regimens in the UNITAID-funded endTB trial, which sponsors MSF and Partners In Health anticipate to begin enrollment in late June or early July 2016.⁴⁰

Delamanid

Delamanid's phase III trial, which started in a much timelier fashion than bedaquiline's (although it was arguably also more urgent, given the poor design of delamanid's phase IIb trial), is in follow-up, with results expected in 2018. These results, though eagerly anticipated for the information they will give about delamanid's safety and efficacy, will not inform the drug's optimal use in combinations, as the study design just adds it to the old WHO-recommended background regimen. The above-noted publicly funded endTB and A5343 trials should provide important information about delamanid's use, as will studies MDR-end (sponsored by the Korean Center for Disease Control to test an injectable-free regimen of delamanid, linezolid, levofloxacin, and pyrazinamide against the current standard of care in people with fluoroquinolone-susceptible MDR-TB, which is currently enrolling⁴¹), A5356 (the ACTG's study of linezolid and delamanid for MDR-TB), and VTEU (sponsored by the NIH Division of Microbiology and Infectious Diseases to test a delamanid-containing, injectable-free MDR-TB regimen against the standard of care).⁴² Otsuka, delamanid's sponsor, which has been the lead private-sector investor in TB R&D for years, is much more advanced than Janssen in terms of its pediatric (see "Pediatric Tuberculosis Treatment Pipeline," page 181) and prevention (see "Tuberculosis Prevention Pipeline," page 143) research.

However, given Otsuka's limited-access strategy (if one can even call it a strategy), only a few hundred people have received delamanid outside of clinical trials, despite the fact that up to two-thirds of people with MDR-TB may benefit from it, according to WHO guidance.⁴³ Otsuka has finally made some much-needed and long-called-for changes, including allowing for the co-administration of bedaquiline and delamanid

under compassionate use, ending a formal blanket exclusion of pregnant women in the compassionate use program, and including delamanid in the Global Drug Facility catalogue. But this is just the tip of the iceberg, with approvals for delamanid still only in low-TB-burden regions of the European Union, Japan, and South Korea. Submissions are in progress for delamanid in China, Hong Kong, Indonesia, the Philippines, and Turkey.⁴⁴ Otsuka has still not filed in the vast majority of high burden countries, including in trial-site countries of Moldova, Peru, and South Africa, and in other countries with large epidemics, such as India. Table 2 provides a direct comparison of how each of the new drugs in phase III is faring on important research and access milestones. Access to bedaquiline and delamanid is particularly important as research continues to highlight the importance of early treatment in interrupting MDR-TB and XDR-TB, given extensive ongoing transmission in households, communities, and hospitals.⁴⁵

Foul Play in the Federation: Unvalidated TB Drugs in Russia

Perchlozone and SQ109—not included in table 1, as there are no peer-reviewed clinical trial data in English to support their efficacy—are bulldozing their way forward into the Russian market. Perchlozone, developed by JSC Pharmasintez, was approved for the treatment of MDR-TB in Russia in 2012, at a different dose and duration than those studied in the two small trials off which approval was based (see the *2013 Pipeline Report* for more details). It has since been added to the List of Vital and Essential Medicines in Russia, and the Russian Association of Pulmonologists recommends it for empiric TB treatment.⁴⁶

In addition to the uncertain safety and efficacy of perchlozone, its clinical value for the treatment of MDR-TB might be limited because of its mode of action. A recent study demonstrated that perchlozone is a prodrug activated by monooxygenase EthA. This same enzyme activates the second-line drugs ethionamide and prothionamide⁴⁷ and is frequently mutated in the dominant MDR clones in Russia, which therefore raises the possibility that significant rates of preexisting resistance to perchlozone might exist due to prior use of ethionamide or prothionamide.⁴⁸ Moreover, the recommendation by JSC Pharmasintez to prescribe perchlozone in combination with prothionamide is questionable.⁴⁹ This underlines the importance of a recent call to require the elucidation of resistance mechanisms as part of the approval of new TB drugs, as is already the case for antivirals.⁵⁰

SQ109 appears to be following an equally troubling path. Developed by Sequella, the same company that has been unable to move promising candidate sutezolid forward for the past three years, SQ109 was found to have no discernable antimicrobial or clinical activity when used in combination therapy for drug-susceptible TB.⁵¹ Sequella licensed SQ109 to Russian company Infectex, which conducted a measly but putatively registrational trial of 80 patients.⁵² Despite the lack of a proper and robust trial, and no generation of peer-reviewed data or plans to do so, Sequella announced that SQ109 will be registered in Russia this year.⁵³

The use of unvalidated drugs carries great costs to the patient, society, and the economy. Perchlozone's safety is unclear, its efficacy is unvalidated and may be impeded by known preexisting drug resistance, and its price tag of US\$1,458 for three months is hefty.⁵⁴ SQ109, though probably safe, has no evidence of efficacy, is likely to also add substantial costs to treatment, and could endanger lives if it is used instead of a more effective drug. The use of these drugs is not only unwarranted but dangerous. Pharmasintez, Infectex, and Sequella are each acting unethically in pursuing marketing approval before clinical evidence supports doing so. Roszdravnadzor, the Russian regulatory authority, is failing to protect public health and urgently needs to change its policies to end, rather than encourage, poor science and indiscriminate marketing. On a troubling note, Qurient, sponsor of the above-mentioned Q203, has also arranged to partner with Infectex for Russia and the other CIS countries and should be extremely careful to ensure an ethical and scientifically rigorous approach to the development of this important new compound.

Table 2. Research and Access for Late-Stage New Compounds

	Bedaquiline	Delamanid	Pretomanid
RESEARCH			
Pediatrics (see Pediatric TB Treatment, page 181)	Enrollment started May 2016	Trial started June 2013; delamanid appears safe in children age 6 and up, with further results from younger age groups expected 2017	Trial not yet started (further toxicology work pending)
Phase III trial	Enrollment started March 2016	Enrollment completed November 2013; results expected 2018	Enrollment in STAND trial started February 2015; on hold since September 2015
Latent TB infection trial (see TB Prevention, page 143)	None	Feasibility study successful; PHOENIX trial expected to start later in 2016	n/a
ACCESS			
Number of patients receiving drug under programmatic conditions	6,000 treatments shipped (as of April 2016)	1,100 treatments shipped (as of May 2016)	None
Pre-approval access programs	Started Q1 2011, ended Q3 2015; >800 patients from 47 countries enrolled	Started Q1 2014; ongoing	None
Expanded access trials	Started 2011 in Lithuania, Russia (application in China denied)	None	None
Approvals	2012: United States 2013: Russia 2014: EU, Peru, Philippines, South Africa, South Korea 2015: Armenia, India, Turkmenistan, Uzbekistan, Macau (import license)	2014: EU, Japan, South Korea 2016: Hong Kong	None (not pursuing accelerated approval; waiting for phase III combination trial completion)
Additional registrations pending	Azerbaijan, Bangladesh, Belarus, Brazil, Burundi, Cameroon, China, Colombia, Ethiopia, Ghana, Hong Kong, Indonesia, Kazakhstan, Kenya, Mexico, Moldova, New Zealand, Rwanda, Switzerland, Taiwan, Tanzania, Thailand, Uganda, Vietnam Note: Kyrgyzstan rejected due to lack of phase III data	Turkey (submissions in progress for China, Philippines, Vietnam)	None
WHO Essential Medicines List inclusion	Included (April 2015)	Included (April 2015)	n/a
Pricing	Tiered pricing by country income level plus donation program (treatment course price: high US\$26,000; middle US\$3,000; low US\$900); 30,000 treatment courses donated to Global Fund–eligible countries	US\$28,000–\$33,000 in Europe; US\$1,700 in Global Fund–eligible countries	n/a (note: nonprofit TB Alliance has affordability commitment)

EU: European Union; WHO: World Health Organization

n/a: not applicable as has not yet received marketing approval

OPTIMIZING THE USE OF APPROVED AND REPURPOSED DRUGS

Rifamycins

The quest for optimizing the use of rifampin, one of the most potent TB drugs and a backbone of DS-TB treatment, continues with several studies planned and underway to test much higher doses than the current standard 10 mg/kg. A two-month study to increase the dose to 15 or 20 mg/kg showed no significant increase in adverse events (no grade 4 liver enzyme increases; rates of grade 3 increases in liver enzymes were 1% in 10 mg/kg arm vs. 2% in the 15 mg/kg arm vs. 4% in the 20 mg/kg arm, $P = .15$).⁵⁵ Increasing the dose of rifampin to correct what is likely current underdosing may help reduce the pervasive resistance to this important drug. A recent interesting, if unvalidated, artificial model has shown rifampin is excellent at penetrating TB lesions, a breeding ground for bugs in people with cavitary TB disease.⁵⁶ If the model and the hypothesis that drug penetration improves outcomes are accurate, this may also help explain the widespread emergence of rifampin resistance, as the lack of penetration of other drugs means rifampin is effectively given as monotherapy.

Rifapentine, also in the rifamycin class, is the linchpin of shortened treatment for latent TB infection (see “TB Prevention Pipeline,” page 143), and is now being studied by the Tuberculosis Trials Consortium (TBTC) and ACTG in Study 31/A5349 for its potential—with or without moxifloxacin—to shorten DS-TB treatment to four months.⁵⁷ Study 31 has started enrollment in Fort Worth, Hanoi, Hong Kong, Kampala, Port-au-Prince, and Soweto, but is behind schedule due to bureaucratic and regulatory delays. Additional funding for the TBTC, whose budget has either been cut or flatlined for the past several years, is critical to allow for timely enrollment and important additional activities such as biobanking at TBTC sites to gather as much useful data as possible from the study. In the meantime, additional funding for Study 31/A5349 from the NIH via the ACTG will support enrollment and allow for biobanking at ACTG sites.

One notable study, TRUNCATE-TB, aims to reduce treatment for most people with DS-TB to two months, using combinations of new and repurposed drugs, including the rifamycins. The approach taken in this trial is to allow larger proportions of patients to fail initial therapy than would otherwise be tolerated in conventional trials but treat again those who are not cured. The primary endpoint is the proportion cured at two years, whether or not they required additional treatment following relapse. By definition, this will result in a greater degree of illness in a number of participants but will benefit those who are cured quickly with shorter treatment durations. This is a philosophical shift from historical TB trials, which have aimed to cure as many patients as possible and do not tolerate relapses, which usually require longer treatment durations. The randomized controlled TRUNCATE-TB trial will examine four two-month regimens, compared with the standard DS-TB treatment. Experimental regimens involve an arm with high-dose rifampin (35 mg/kg), linezolid, isoniazid, pyrazinamide, and ethambutol; a second arm that is the same but substituting clofazimine for linezolid; a third arm that uses rifapentine, levofloxacin, linezolid, and pyrazinamide; and a fourth arm that has bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol. TRUNCATE-TB has complete protocol and ethics committee approvals in the United Kingdom and Singapore and should begin enrollment by the end of 2016. Planned trial site countries include Indonesia, the Philippines, Thailand, Vietnam, and China (if regulators allow it).⁵⁸

Fluoroquinolones

Fluoroquinolones are arguably the most important element in MDR-TB treatment; resistance to fluoroquinolones greatly increases the likelihood of a poor outcome.⁵⁹ As such, several studies for MDR-TB continue to use fluoroquinolones. A recent randomized controlled trial in Korea compared treatment outcomes from levofloxacin or moxifloxacin and found they had similar treatment success rates (84.4% vs.

79.7%, $P = .53$ [a nonsignificant difference]), though rates of musculoskeletal adverse events were higher in those receiving levofloxacin (37.7% vs. 14.9%, $P = .001$).⁶⁰ Because moxifloxacin causes higher QT prolongation than levofloxacin, knowing levofloxacin has comparable efficacy is very useful in designing regimens with other QT-prolonging drugs, such as bedaquiline and delamanid. The Opti-Q study, sponsored by Boston University and the U.S. National Institute of Allergy and Infectious Diseases, is exploring the best dose for levofloxacin and should have results in 2018.^{61,62}

Moxifloxacin is being used in the STREAM-I trial, a nine-month regimen for MDR-TB based on the modified Bangladesh regimen of multiple existing drugs (described in previous *Pipeline Reports*), including an injectable and clofazimine. Follow-up is ongoing; in the meantime, this regimen has received WHO endorsement for use in previously untreated patients with rifampicin-resistant TB or MDR-TB.⁶³ The recommendation is based on observational cohort data, with very low certainty in the evidence, calling into question the rationale for and the objectivity of recommending this regimen. Randomized controlled clinical trial data are essential for understanding how well this regimen truly works in the indicated population, and scale-up of drug susceptibility testing (see “TB diagnostics pipeline,” page 129) must accompany shortened regimen rollout. However, given that the brutal 18–24-month standard of care for MDR-TB has also not been validated in randomized controlled clinical trials and is very difficult for patients, many may be eager for access to a shortened regimen.

Also controversially, gatifloxacin, used in the original Bangladesh regimen and then abandoned due to safety concerns, recently received endorsement in the new WHO MDR-TB treatment guidelines.⁶⁴ Like levofloxacin, gatifloxacin has less risk of QT prolongation than moxifloxacin, and observational studies and the OFLOTUB trial did not indicate safety issues (though in the trial the drug was only given for four months).⁶⁵ While more drugs in the arsenal to treat TB are helpful, re-adding gatifloxacin is confusing for countries and further fragments the challenging market for MDR-TB drugs, especially because there is no current quality-assured source of gatifloxacin due to its withdrawal from the market over safety concerns and because supporting evidence is of very low quality.

Because of the fluoroquinolones’ good activity against TB, they continue to be examined for shortening treatment for DS-TB, for example in the above-mentioned TBTC Study 31 and as part of TRUNCATE-TB.

Of note, the FDA has recently recommended against the routine use of fluoroquinolones for more minor infections such as acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections when other treatment options exist, noting that because of serious side effects, the harms outweigh the benefits, so for these conditions, fluoroquinolones should be reserved for those without alternative treatment options.⁶⁶ This does not apply to MDR-TB and DS-TB, which are certainly more serious conditions, but does again point to the need for safer, better treatment options more generally for TB.

Clofazimine

Clofazimine, a riminophenazine long used for the treatment of leprosy and off-label for MDR-TB, is finally moving toward formal evaluation for TB in randomized controlled trials. Novartis has planned study CLAM320B2202, a phase IIb/III randomized, open-label trial to evaluate the efficacy and safety of clofazimine (at 200 mg once daily for six months followed by 100 mg once daily for the remaining 12 to 18 months of treatment) plus background regimen compared with background regimen alone in people with MDR-TB. Enrollment was anticipated to start in March 2016 but is now projected to start in April 2017.⁶⁷ The ACTG is planning a phase IIc study of clofazimine, added to standard therapy with a treatment duration of four months, for DS-TB. Clofazimine also plays an important role in the above-mentioned ongoing and planned PRACTECAL, STREAM-I, STREAM-II, and endTB studies.

The new WHO MDR-TB treatment guidelines recognize clofazimine's and linezolid's importance, elevating them as "core second-line agents" on par with cycloserine/terizidone and ethionamide/prothionamide and preferable to para-aminosalicylic acid for constructing a regimen.⁶⁸

Linezolid

Linezolid, of increasing importance for MDR- and XDR-TB, has manageable but nonetheless challenging side effects, including painful nerve damage. The TB Alliance examined the early bactericidal activity (EBA) of linezolid over two weeks as part of its efforts to determine an ideal dose and dosing schedule for linezolid to support the above-mentioned NiX-TB trial. The study found that all daily doses, from 300 mg to 1,200 mg, given as either once-daily or twice-daily doses, demonstrated EBA, and there was a statistically significant dose response from 300 mg to 1,200 mg daily, indicating that higher doses provided greater activity, with no difference between once- and twice-daily dosing for the same total daily dose. As a result, the TB Alliance has changed the NiX study dosing of linezolid from 600 mg twice to 1,200 mg once a day.⁶⁹ Mouse model data suggest that linezolid may only be needed for one to two months, which might also be worth exploring in clinical trials.

As noted previously, linezolid availability is critical to the successful rollout of bedaquiline. One-year posttreatment outcome data from a small clinical trial of linezolid in South Korea whose four-month sputum-culture conversion data were previously reported further indicate that linezolid is an important drug for treating XDR-TB. Of 38 patients receiving linezolid, 27 had negative results on sputum culture one year after treatment end, 3 were lost to follow-up, and 8 withdrew from the study (including 4 who failed on linezolid treatment, as previously reported). Of the 27 participants completing the study, 4 had a dose reduction from 600 to 300 mg. Among 13 participants assigned to continue receiving 600 mg, 9 had to reduce the dose to 300 mg due to adverse effects. All serious adverse events resolved after the discontinuation of linezolid. Though the study design was questionable, as linezolid was effectively given as monotherapy, only 4 out of 38 participants, or 11% of those receiving linezolid, developed resistance to linezolid. In total, 27 of 38 patients (71%) with chronic XDR-TB were cured at one year after termination of treatment.⁷⁰

To inform the use of linezolid for people with HIV on ART, a retrospective study of linezolid use for the treatment of pre-XDR-TB and XDR-TB in people with HIV in Khayelitsha, South Africa, and Mumbai, India, showed that the rate of culture conversion in patients treated with linezolid is better than previously reported among XDR-TB cohorts and that people with HIV on ART were able to tolerate prolonged linezolid exposure, adding to the body of evidence supporting linezolid's use in challenging cases.⁷¹ Recent efforts to increase generic competition and bring down prices for linezolid in South Africa have been successful thanks to strong advocacy.⁷² The Global Drug Facility has announced a 70% decrease in the price of linezolid.⁷³

Carbapenems

Carbapenems such as meropenem and imipenem are beta-lactams—antibiotics with a good safety profile and low potential for interaction with antiretrovirals. Historically, they have received little attention for TB because of the high intrinsic resistance of mycobacteria to these drugs, although this can be overcome with the addition of amoxicillin/clavulanate.⁷⁴ Carbapenems have been used more frequently due to the need for companion drugs for bedaquiline. A recent proof-of-concept randomized controlled study gave two kinds of carbapenems—orally available faropenem (at 600 mg three times a day) or intravenous meropenem (at 2 g three times a day)—or the standard of care for 14 days to people (15 in each arm) with untreated, DS-TB. This study found that faropenem had no detectable EBA: estimated fall in \log_{10} colony-forming units was 0.00 (95% confidence interval [CI]: -0.002 to 0.002, P value vs. control < .001), likely due to the very low exposures to the drug measured in blood during the trial. In contrast, meropenem had good EBA, with a

fall in log₁₀ colony-forming units of 0.11 (95% CI: 0.009 to 0.13) versus the control's 0.17 (95% CI: 0.15 to 0.19), though the control was still significantly better ($P < .001$).⁷⁵ Meropenem use was not associated with any grade 3 or 4 events (compared with four in the control arm and three in the faropenem arm). Diarrhea was observed frequently in both the meropenem and faropenem arms, likely from the amoxicillin/clavulanate. The study's findings indicate the need for further optimization of the use of this class for TB, including determining whether amoxicillin/clavulanate is necessary, reducing dosing to once or twice daily, prioritizing the development of orally bioavailable carbapenems, and testing faropenem medoxomil (an unapproved formulation that may have higher exposures and EBA against TB than faropenem alone) for use against TB.

Ertapenem, another carbapenem, may merit further study. A recent retrospective study in the Netherlands of 12 patients who received ertapenem as part of their treatment between 2010 and 2013 and in whom drug exposure was evaluated showed that ertapenem was well tolerated and had a favorable pharmacokinetics/pharmacodynamics profile in people with MDR-TB. Though not orally available, ertapenem requires only once-daily dosing, in contrast to meropenem's thrice-daily dosing.⁷⁶

RECOMMENDATIONS

1. **Government agencies, pharmaceutical companies, and foundations must dramatically scale up funding for TB R&D.** In line with the third pillar of the WHO's End TB strategy, which calls for R&D, countries must commit more resources to TB drug development.⁷⁷ The U.S. government, which is the leading funder of TB R&D, should increase funding levels to \$300 million by 2018 to keep its critical investments at pace with inflation. TAG suggests that this should entail an additional \$17 million from the NIH, \$15 million from USAID, \$16 million from the U.S. Centers for Disease Control and Prevention, and \$5 million from the FDA for TB R&D.⁷⁸ European Union countries, particularly Germany, should double their TB R&D funding, and Brazil, China, India, Russia, and South Africa should each triple their funding for TB R&D.⁷⁹ Activists in other countries should call for commensurate increases in their own settings.

Companies such as Otsuka and Sanofi should maintain strong levels of investment, and Janssen needs to recommit to further developing bedaquiline, as significant work remains despite bedaquiline's conditional approval, and to moving the most promising of its pipeline of bedaquiline analogues further toward clinical study. Other pharmaceutical companies and philanthropic organizations should also begin to invest in TB R&D.

2. **Donor and high-TB-burden governments should create and invest in mechanisms that build access to TB drug development, and drug developers should participate in them.** The inability to access data hampers collaborative TB drug development, which is essential because TB must be treated with a combination of drugs to prevent the development of resistance. The inability to access drugs hampers TB treatment and cure and threatens to render the limited R&D that is occurring less useful. Fortunately, members of the TB community have proposed feasible and appealing solutions that should be actively pursued. These include remedying loopholes in the FDA's priority review voucher system to ensure innovation and drug availability and fair pricing⁸⁰ and should also entail product developers licensing their compounds to and sharing data with the MPP, which recently received a mandate to work on TB drug development and could possibly play a key role in brokering combination drug development.⁸¹ MSF's proposed 3P ("Push, Pull, Pool") project may also provide an interesting, innovative, and potentially transformative approach to spur the development of regimens and ensure their availability post-approval, though the devil here will lie in the details of how it is actually executed.⁸²

3. **Drug and trial sponsors must expedite the development of preclinical and clinical candidates.** Delays in TB research and development are widespread and atrocious. The TB drug development pipeline remains frighteningly sparse, pointing to the urgent need to advance preclinical work to allow viable candidates into clinical studies. Clinical development for the few products in the pipeline has been unacceptably slow, with drugs taking over five years to advance from one stage to the next. In particular, Janssen's and Sequella's failures to rapidly move bedaquiline and sutezolid, respectively, through important studies are deplorable.
4. **Ministries of health, regulatory authorities, and ministries of finance should prioritize the timely introduction of evidence-based TB treatment, and donors and providers of technical assistance should ensure they are supporting rather than hindering scale-up.** Drug development will not affect the TB epidemic and improve the lives of people affected by TB unless new interventions are available to communities and people who need them. Unfortunately, country-level demand for important new products such as delamanid and bedaquiline has been weak, and implementation slow. USAID, which has partnered with Janssen to make bedaquiline available via a donation program, literally cannot give the drug away for free to enough people. Poor advice from technical assistance providers has worsened the situation and excused complacency. All parties, national and global, must be much more ambitious and supportive of new ways to find and treat TB.

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The Pediatric Tuberculosis Treatment Pipeline: Beyond Pharmacokinetics and Safety Data

By Lindsay McKenna

INTRODUCTION

The roster of enrolling and planned pediatric tuberculosis (TB) treatment studies is growing. Emerging results from pharmacokinetics (PK) and safety studies continue to inform optimal dosing strategies in children and to highlight areas in need of further investigation. New pediatric formulations continue to advance to market, and consensus has begun to form around the need for efficacy studies of simplified multidrug-resistant TB (MDR-TB) treatment regimens in children.

PEDIATRIC PIPELINE OVERVIEW

Studies that are under way or starting soon will evaluate preventive therapy for children exposed to MDR-TB and treatment shortening for less severe forms of drug-sensitive TB (DS-TB) in children, as well as fill gaps in PK and safety data that are necessary to optimize treatment, including in HIV-positive children and children with MDR-TB. Table 1 provides an overview of ongoing and planned pediatric TB prevention and treatment studies.

Table 1. Ongoing and Planned TB Prevention and Treatment Studies in Children

Study/Regimen	Status	Population(s)	Sponsor(s)
PREVENTION			
P4v9 4 months of self-administered daily rifampin for prevention of TB NCT00170209*	Enrollment complete; results expected 2016	HIV-positive and HIV-negative infants, children, and adolescents 0–17 years old with LTBI	CIHR, McGill University
TBTC 35 PK and safety of rifapentine/isoniazid FDC for prevention of TB	Planned; opening 2017	HIV-positive and HIV-negative infants, children, and adolescents 0–12 years old with LTBI	TBTC, Sanofi
TB-CHAMP 6 months of levofloxacin vs. placebo for prevention of MDR-TB (substudy planned using delamanid for child contacts of FQ-R TB patients)	Planned; opening 2016	HIV-positive or HIV-negative infant and child household contacts 0–5 years old; children ≤5 years old will get new pediatric formulation	BMRC, Wellcome Trust, DFID, SA MRC
ACTG A5300/IMPAACT P2003 (PHOENIX) 6 months of delamanid vs. isoniazid for prevention of MDR-TB	Planned; opening late 2016/early 2017	High-risk (HIV+, TST+, or ≤5 years) infant, child, adolescent, and adult household contacts of index patient with MDR-TB	NIAID
V-QUIN 6 months of levofloxacin vs. placebo for prevention of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative adult household contacts; phased inclusion of infant, child, and adolescent contacts	NHMRC

Study/Regimen	Status	Population(s)	Sponsor(s)
TREATMENT – NEW DRUGS			
232 PK and safety of delamanid; OBR for treatment of MDR-TB NCT01856634*	Enrolling; final results expected 2018	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
233 6 months of delamanid; OBR for treatment of MDR-TB NCT01859923*	Enrolling; final results expected 2020	HIV-negative infants, children, and adolescents 0–17 years old with MDR-TB; children ≤5 years old will get pediatric formulation	Otsuka
IMPAACT P2005 PK and safety of delamanid; all oral OBR for treatment of MDR-TB	Planned	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID
JANSSEN C211 PK and safety of bedaquiline; OBR for treatment of MDR-TB NCT02354014*	Enrolling	HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB; children ≤12 years old will get pediatric formulation	Janssen, UNITAID/TB Alliance (STEP-TB Project)
IMPAACT P1108 PK and safety of bedaquiline; OBR for treatment of MDR-TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–18 years old with MDR-TB	NIAID
TREATMENT – EXISTING DRUGS			
Treat Infant TB PK and safety of FLDs using 2010 WHO dosing guidelines for treatment of TB	Enrollment complete; results presented 2015	HIV-positive or HIV-negative infants <12 months old with TB	UNITAID/TB Alliance (STEP-TB Project)
PK-PTBHIV01 PK of FLDs using 2010 WHO dosing guidelines for treatment of TB NCT01687504*	Enrollment complete; interim results presented 2015; final results expected 2016	HIV-positive or HIV-negative children 3 months to 14 years old with TB	NICHD
OptiRif Kids PK, safety, and dose optimization of rifampin for treatment of TB	Planned; opening 2016	HIV-positive or HIV-negative infants and children ≤5 years old with TB	TB Alliance
SHINE 4 vs. 6 months using 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of minimal TB	Planned; opening 2016	HIV-positive or HIV-negative infants, children, and adolescents 0–16 years old with minimal TB	BMRC, DFID, Wellcome Trust, UCL
TBM-KIDS Safety and efficacy of high-dose rifampin 3 levofloxacin for treatment of TBM	Planned; opening 2016	HIV-positive or HIV-negative infants and children with TBM	NICHD
MDR-PK 1 PK and safety of SLDs for treatment of MDR-TB	Enrollment complete; interim results presented; final results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB or LTBI	NICHD
MDR-PK 2 PK, safety, and dose optimization of SLDs for treatment of MDR-TB	Enrolling; results expected 2020	HIV-positive or HIV-negative infants, children, and adolescents with MDR-TB	NICHD, SA MRC

Study/Regimen	Status	Population(s)	Sponsor(s)
COTREATMENT WITH ARVS			
DATiC PK of FLDs using 2010 WHO dosing guidelines for treatment of TB and interactions with lopinavir/ritonavir and nevirapine NCT01637558*	Enrolling; results expected 2017	HIV-positive or HIV-negative infants, children, and adolescents 0–12 years old with TB	NICHD
IMPAACT P1106 PK of rifampin and isoniazid with nevirapine or lopinavir/ritonavir NCT02383849*	Enrolling; results expected 2018	HIV-positive or HIV-negative low-birth-weight/ premature infants	NIAID, NICHD
PK and safety of nevirapine with rifampin-containing TB treatment NCT01699633*	Enrolling; results expected 2017	HIV-positive children 3 months to 3 years old with TB	NICHD
IMPAACT P1070 PK and safety of efavirenz with rifampin-containing TB treatment NCT00802802*	Enrollment complete; results presented 2016	HIV-positive children 3 months to <3 years old with TB	NIAID, NICHD
PK and safety of efavirenz with rifampin-containing TB treatment NCT01704144*	Enrolling; results expected 2017	HIV-positive children and adolescents 3–14 years old with TB	NICHD
HIVPED001 PK and safety of superboosted lopinavir/ritonavir (1:1) with rifampin-containing TB treatment NCT02348177*	Enrolling; interim results presented 2015; final results expected 2016	HIV-positive infants and children with TB weighing 3–15 kg; DNDi developing stand-alone ritonavir booster formulation	DNDi, AFD, UBS Optimus Foundation, MSF
IMPAACT P1101 PK and safety of raltegravir with rifampin-containing TB treatment NCT01751568*	Enrolling; results expected 2018	ARV-naïve, HIV-positive children and adolescents 2–12 years old with TB	NIAID
*U.S. National Institutes of Health (NIH) clinical trial identifiers; for more information, go to ClinicalTrials.gov .			

AFD: French Development Agency

ART: antiretroviral therapy

ARV: antiretroviral

BMRC: British Medical Research Council

CIHR: Canadian Institutes of Health Research

DFID: Department for International Development (United Kingdom)

DNDi: Drugs for Neglected Diseases

FDC: fixed-dose combination

FLD: first-line drug

FQ-R: fluoroquinolone-resistant

IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, NIH

LTBI: latent tuberculosis infection

MDR-TB: Multidrug-resistant tuberculosis

MSF: Médecins Sans Frontières

NHMRC: National Health and Medical Research Council (Australia)

NIAID: National Institute of Allergy and Infectious Diseases, NIH

NICHD: National Institute of Child Health and Human Development, NIH

OBR: optimized background regimen

PK: pharmacokinetics

SA MRC: South African Medical Research Council

SLD: second-line drug

TB: tuberculosis

TBM: tuberculous meningitis

TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

TST: tuberculin skin test

UBS: Union Bank of Switzerland

UCL: University College London

WHO: World Health Organization

TB drugs and regimens with proven efficacy in adults have long been assumed to work at least equally as well in children. Typically, PK and safety studies are conducted in children only to inform appropriate dosing and to confirm safety and tolerability; efficacy studies are therefore not usually considered to be necessary.

However, given the paucibacillary nature of TB disease in children (characterized by fewer TB bacteria in the body), it might be possible to achieve a cure using shorter, milder regimens than those that are necessary in adults. This logic underpins **SHINE**, a study to evaluate whether it is possible to shorten standard first-line treatment from six to four months for less severe forms of pulmonary and extrapulmonary TB in children. There is an urgent need to conduct a similar evaluation to shorten treatment for children with less severe MDR-TB; conversations about what this regimen and study might look like are ongoing. Regimens for children with more severe forms of TB with higher bacterial loads, such as disseminated or HIV-associated TB, should also be studied.

RESEARCH UPDATES

Data from ongoing pediatric PK and safety studies continue to contribute findings that are important for optimizing TB treatment for children. Here we present recent research updates and discuss remaining research needs for first-line, second-line, and new TB drugs in children. For a comprehensive discussion of available evidence and recommended doses for TB drugs in children, see the review *Antituberculosis Drugs in Children*, from Schaaf, Garcia-Prats, and Donald.¹

First-Line Drugs

A study of first-line treatment in infants in Cape Town, South Africa (**Treat Infant TB**; N = 39), using doses recommended by the WHO, found that 35 mg/kg (recommended range: 30–40 mg/kg) of pyrazinamide and 15 mg/kg (recommended range: 10–20 mg/kg) of isoniazid achieved drug exposures in infants that are comparable to those in adults. Exposures following 15 mg/kg (recommended range: 10–20 mg/kg) of rifampin and 20 mg/kg (recommended range: 15–25 mg/kg) of ethambutol were lower than those achieved in adults. HIV-positive infants taking ARVs (abacavir, lamivudine, and lopinavir/ritonavir) achieved lower pyrazinamide and ethambutol exposures than did HIV-negative infants.^{2,3}

Another study of first-line treatment using WHO-recommended doses in Durban, South Africa, in children 10 years old or younger found exposures for rifampin, isoniazid, and pyrazinamide below those associated with optimal microbiological and clinical outcomes in adults.⁴

A study of first-line treatment in infants and children in Ghana (**PK-PTBHIV01**; N = 62; 47% of children less than five years old), again using WHO-recommended doses, found that 59% of children had low exposures to rifampin and 52% of children had low exposures to ethambutol.^{5,6}

A recent study in Vietnamese children 15 years of age or younger found rifampin concentrations in cerebrospinal fluid below the minimum inhibitory concentration (minimum drug concentration required to inhibit mycobacterial growth) for almost all children treated for TB meningitis using pre-2010 WHO-recommended doses.⁷ These findings support planned work to investigate the use of higher doses of rifampin for TB meningitis (**TBM-KIDS**). Further research is urgently needed to establish optimal drug combinations and doses for the treatment of pediatric TB meningitis.

Despite good treatment outcomes, investigators continue to find lower drug exposures measured by C_{max} (peak drug exposure) and area under the curve (AUC, or total drug exposure) in children compared with adults. It is important to note a recently demonstrated association between low TB drug levels and poor outcomes in children. A study in India comparing PK for rifampin, isoniazid, and pyrazinamide in HIV-

positive and HIV-negative children receiving thrice-weekly TB treatment found that the C_{max} of rifampin and pyrazinamide significantly affected TB treatment outcomes.⁸ These findings support the higher and daily doses recommended by the WHO and underscore the need to identify PK targets that correlate with good outcomes in children and the drug doses that are necessary to achieve them. Low rifampin exposures in children are of special concern for the treatment of more severe forms of TB and in light of plans to evaluate shorter regimens.

Children experience a broad spectrum of TB disease, ranging from severe TB (e.g., TB meningitis) in young children to limited pulmonary disease to cavitary disease in adolescents. Optimal drug doses and treatment durations likely differ by disease type (extent and location). It is critical to determine which PK values correlate most precisely with efficacy for TB drugs in children. This information is necessary to optimize pediatric dosing, which is especially important in the context of simplified and shortened regimens for DS-TB and drug-resistant TB (DR-TB) and in treating more severe forms of TB.

Findings from these studies point to the need for investigations to determine PK targets for children, especially considering differences in bacterial burden and severity and location of disease; to elucidate optimal age- and weight-based dosing schedules in infants and young children; and to optimize dosing for first-line TB drugs in children younger than five years. In addition, as investigators continue to study higher doses of rifampin in adults without finding toxicity (see “Tuberculosis Treatment Pipeline,” page 163), higher doses should be considered in children and evaluated in future PK and safety studies. Some work is already under way or being planned, including a study to evaluate the PK and safety of higher doses of rifampin in children 0–12 years old with severe and nonsevere forms of TB (**OptiRif Kids**). This dose-finding and safety study will explore the drug doses in children necessary to achieve the PK exposures shown to be safe, well tolerated, and associated with improved TB killing activity in recent adult studies.⁹

Cotreatment with ARVs

Rifampin (a rifamycin) induces drug metabolism by increasing the amount of drug-metabolizing enzymes in the liver.¹⁰ As a result, rifampin interacts with many other drugs, including anti-HIV compounds such as the non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine and the protease inhibitors lopinavir and ritonavir. Studies are necessary to characterize these drug-drug interactions and to determine whether dose adjustments are necessary or contraindications exist.

Efavirenz, which has minimal interactions with rifampin, is an important treatment option for people coinfecting with TB and HIV, but PK variability and formulation issues have precluded its use in children younger than three years. A PK study using higher doses of efavirenz (65 mg/kg) in TB/HIV-coinfecting children 3–36 months old (**P1070**) found therapeutic efavirenz concentrations in children with fast metabolism of drugs processed by the cytochrome P450 2B6 enzyme (encoded by the *CYP2B6* gene). The investigators concluded that a lower dose is likely to be necessary for TB/HIV-coinfecting children with slow *CYP2B6* metabolism.¹¹ This study demonstrates that optimal exposure to efavirenz can be achieved in coinfecting children younger than three years but requires pretreatment genotyping with pharmacogenomic assays that are expensive and not widely available.

A study of rifabutin, an alternative to rifampin that is more forgiving in adults on protease inhibitor–based antiretroviral therapy (ART), in HIV-positive children younger than five years receiving lopinavir/ritonavir closed early due to safety concerns. In the six children who completed the study prior to closure, rifabutin dosed at 5 mg/kg three times a week resulted in lower AUC and C_{max} values for rifabutin and its metabolite compared with those in adults receiving the recommended dose of 150 mg rifabutin daily. In addition, high rates of severe transient neutropenia (characterized by low concentrations of white blood cells that are important for fighting infections) were observed.¹² It is unclear whether a safe and effective rifabutin dose exists for TB/HIV-coinfecting children on protease inhibitor–based ART.

Interim results from a study evaluating superboosted lopinavir/ritonavir administered in a ratio of 1:1 (standard lopinavir/ritonavir is administered in a ratio of 4:1) with rifampin-containing TB treatment to infants and young children (**HIVPED001**) found that exposures to lopinavir/ritonavir (1:1) with rifampin were not inferior to exposures to lopinavir/ritonavir (4:1) without rifampin. Virological efficacy and safety were also comparable. However, problems with existing lopinavir/ritonavir formulations and tolerability remain.¹³

Given the challenges presented by interactions between protease inhibitors and rifamycins, integrase inhibitors may provide a good alternative for young TB/HIV-coinfected children. PK and safety studies for integrase inhibitors, notably dolutegravir and raltegravir, are under way for children and infants¹⁴ (see “Pediatric Antiretroviral Pipeline,” in *2016 Pipeline Report*), and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network is planning to evaluate the PK and safety of raltegravir administered with rifampin-containing anti-TB treatment to children 2–12 years old (**P1101**).

Second-Line Drugs

In addition to the preliminary PK and safety data covered by previous reports,^{15,16} further analyses from **MDR-PK 1**, which completed enrollment in 2015, are presented here for ofloxacin, levofloxacin, and amikacin. More data will be disseminated throughout 2016, including those on moxifloxacin and linezolid.

Children given ofloxacin at 15–20 mg/kg as whole or crushed tablets for treatment (N = 55) or prevention (N = 30) of MDR-TB had peak exposures slightly lower than, but comparable to, those achieved in adults. Total exposures were far below the targets achieved in adults—likely because of more rapid drug clearance in children. Higher C_{max} values were observed in children receiving crushed versus whole tablets (statistically insignificant), but AUCs remained unaffected. Peak exposures were higher among younger children, but increased with total exposure and weight. No difference was observed in children coinfecting with HIV. Ofloxacin appeared to be safe, with no grade 3 or 4 adverse events in 46 children followed for a median of 150 days.^{17,18} Of the fluoroquinolones, moxifloxacin and levofloxacin are generally considered to be superior to ofloxacin, but given cost, availability, and formulation constraints, ofloxacin is still used in children in some settings.

Previously published data on levofloxacin dosed at 15 mg/kg in children show low drug exposures compared with those achieved in adults.¹⁹ Using additional PK data from children given levofloxacin at 15 mg/kg and 20 mg/kg (N = 109) and pharmacometric modeling, researchers have determined that the 20 mg/kg dose more closely approximates adult exposures.²⁰ However, there is room to further optimize levofloxacin exposures in children, and studies are under way (**MDR-PK 2**).

Age influenced the AUC, but not the C_{max}, when amikacin was given to children (N = 96) at 15–20 mg/kg (recommended range: 15–30 mg/kg). There was no effect on exposure by HIV status. Based on these and earlier data, to achieve exposures similar to those in adults, the investigators suggest that amikacin be given to children at a dose of 18–20 mg/kg.²¹ Hearing loss (associated with cumulative amikacin exposure) has not yet been analyzed in this cohort, but has been previously reported in up to 24% of children in this setting.²²

Further analyses of the data collected in MDR-PK 1 are planned for high-dose isoniazid, ethionamide, para-aminosalicylic acid, and linezolid. **MDR-PK 2**, which opened in October 2015, will build on the evidence collected in MDR-PK 1 to further optimize the use of key second-line drugs in children, including moxifloxacin, levofloxacin, and linezolid. MDR-PK 2 incorporates a crossover design to allow for the collection of PK data on moxifloxacin and levofloxacin in children across all ages; children younger than eight years are typically only given levofloxacin due to the limitations of the existing formulation of moxifloxacin, a large unscored tablet that is bitter when crushed. MDR-PK 2 will look more closely at bioavailability when moxifloxacin and levofloxacin are administered as whole tablets versus crushed tablets or extemporaneously prepared solutions.²³

The PK and safety data presented here and still being collected are critical to informing dosing for first- and second-line TB drugs in children. However, several ongoing or planned treatment-shortening studies in adults use higher doses of key first- and second-line drugs (see “Tuberculosis Treatment Pipeline,” page 163). It is imperative that these treatment-shortening studies collect data on ideal PK values in adults, as this information is necessary to inform appropriate, evidence-based dosing in children.

In May 2016, the WHO issued an update to its guidelines for treating MDR-TB. Based on data in adults, the guidelines recommend that children with confirmed rifampin-resistant or MDR-TB be given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults.²⁴ However, this recommendation is likely to have limited reach given the challenges of obtaining viable samples for microbiologically confirmed diagnosis of TB in children (see “Tuberculosis Diagnostics Pipeline,” page 129). Another pediatric recommendation that was included in the WHO’s 2016 update to the MDR-TB treatment guidelines and is likely to have much broader implications is for the exclusion of injectable agents from regimens for children with nonsevere disease.²⁵ This recommendation was based on consideration of the potential harms associated with the injectable agents, namely hearing loss and pain with administration, and meta-analysis of individual patient data, which points to insignificant differences in rates of treatment success among children with clinically diagnosed and nonsevere disease treated with or without an injectable agent.²⁶

New Drugs

After one year of follow-up for the first age cohort (12–17 year olds) enrolled in **C232/C233** (a pediatric PK and safety study of delamanid in HIV-negative children), Otsuka found six months of twice-daily delamanid administered at 100 mg to be safe and well tolerated. Delamanid exposures in the adolescent cohort were slightly higher than but comparable to, those achieved in adults, suggesting that the standard adult dose for delamanid is adequate for adolescents.²⁷

Follow-up for the second age cohort (6–11 year olds), who received 50 mg of delamanid twice daily, is ongoing, and enrollment for the third cohort (3–5 year olds), using the pediatric formulation, is half completed. A modification to Otsuka’s Pediatric Investigation Plan, agreed to by the European Medicines Agency (EMA), will allow for the final cohort (0–2 year olds) to enroll in parallel. This sets an important precedent for the parallel enrollment of pediatric cohorts, which is expected to help expedite access to new drugs for younger children.²⁸ Despite the encouraging pace at which Otsuka’s pediatric investigations are progressing and the recent inclusion of delamanid in the Global Drug Facility (GDF) catalogue, delamanid has been registered only in the European Union, Japan, and South Korea. Routine access is likely to be an issue for years to come (see “Tuberculosis Treatment Pipeline,” page 163).

The WHO is planning an update to its guidance on the programmatic use of delamanid before the end of 2016 and will consider the available PK and safety data in children as young as six years.²⁹ Rapid release of its guidelines will be necessary to ensure that policy is not a barrier to access for children. In the meantime, the Sentinel Project on Pediatric Drug-Resistant Tuberculosis has released rapid clinical advice on the use of delamanid and bedaquiline in children.³⁰ Country programs shouldn’t wait, but many programs will not procure or use delamanid for children without formal recommendation from the WHO in the form of updated treatment guidelines. This underscores the importance of WHO processes that allow for more rapid review and incorporation of emerging data into guidelines for children.

In contrast, bedaquiline is much more widely available to adults under programmatic conditions, but children have virtually no access to it due to lack of data. Janssen’s PK and safety study of bedaquiline in HIV-negative children (**C211**), which has been in development for over five years, finally opened to enrollment in May 2016.³¹ Janssen’s lack of experience setting up pediatric MDR-TB studies, the paucity of adequately prepared trial sites independent of those participating in established pediatric research networks like the IMPAACT

Network, and apparent pushback from regulators were among the reported causes of the study's severely delayed start.³² In an effort to expedite the study, Janssen is now exploring additional trial sites in Ethiopia, India, and the Philippines.³³

To further hasten the investigation of bedaquiline in children, Janssen should make its pediatric formulation available free of charge for complementary studies, including **P1108**, a pediatric PK and safety study of bedaquiline that will include HIV-positive and HIV-negative children with MDR-TB.³⁴

Box 1. Inclusion of Pregnant Women in TB Research

An estimated 3.2 million women develop TB each year; conservative models estimate that 216,500 of them are also pregnant, but these data are not collected.³⁵ TB is one of the leading non-obstetric causes of death among pregnant women, accounting for 28% of maternal deaths globally.³⁶ Currently, treatment of TB during pregnancy is done with minimal specific guidance and with a lack of information on the effects of physiological and metabolic changes that occur during pregnancy on drug metabolism and achieved drug exposures. Pregnant women are systematically excluded from TB research, and, as a result, clinicians are forced to use old and sometimes new TB drug regimens in pregnant women with TB without any guidance on safety, efficacy, or dose adjustments—or, even worse, to deny them treatment for lack of options.

An expert panel convened by the NIH recently published a consensus statement advocating for the earlier inclusion of pregnant and postpartum women in TB drug trials and outlining priority research needs.³⁷ The few ongoing or planned TB prevention and treatment studies in pregnant women are presented in table 2.

In line with a 1994 report by the Institute of Medicine, which recommends that pregnant women be “presumed eligible for participation in clinical studies,”³⁸ TB researchers should assume inclusion, and then, on an individual trial basis, think carefully about safety and whether the balance of risks and benefits warrants the exclusion of pregnant women from TB drug trials. In fact, expert consensus statements, regulatory frameworks, and guidance documents already exist to facilitate the appropriate and earlier inclusion of pregnant women in research.

Additionally, a registry, similar to the Antiretroviral Pregnancy Registry, should be established for pregnant women with TB to prospectively monitor birth defects in infants exposed to TB drugs in utero, provide early warning of major teratogenicity (ability to induce congenital malformations), and help estimate risk of birth defects. In the absence of clinical trials data, a TB registry is critical for informing the safe treatment and prevention of TB in pregnant women and their children.³⁹

Table 2. Ongoing and Planned TB Prevention and Treatment Studies in Pregnant Women

Trial	Phase	TB type	Study purpose
PREVENTION			
IMPAACT P1078 (TB APPRISE) NCT01494038*	IV	DS-TBI	To evaluate antepartum vs. postpartum isoniazid preventive therapy in HIV-positive women
IMPAACT P2001 NCT02651259*	I/II	DS-TBI	To evaluate the pharmacokinetics and safety of once-weekly rifapentine and isoniazid in pregnant and postpartum women with and without HIV
TREATMENT			
IMPAACT P1026s NCT00042289*	IV	DS-/DR-TB	To evaluate the pharmacokinetics of first- and second-line TB drugs with and without ARVs in pregnant women
ACTG A5338 NCT02412436*	IV	DS-TB	To evaluate the pharmacokinetic interactions among depo-medroxyprogesterone acetate, rifampin, and efavirenz in women co-infected with HIV and TB
TB pregnancy registry	IV	DS-/DR-TB	To evaluate maternal and infant treatment and safety outcomes from clinical research databases (planned)
*NIH clinical trial identifiers; for more information, go to ClinicalTrials.gov .			

DR-TB: drug-resistant tuberculosis

DS-TB: drug-sensitive tuberculosis

DS-TBI: drug-sensitive tuberculosis infection

PEDIATRIC FORMULATIONS IN THE PIPELINE

In dose or form, preexisting pediatric formulations and preparations of TB drugs have been inadequate.⁴⁰ However, new pediatric fixed-dose combinations (FDCs) provide a rare occasion for celebration. Anticipated additional advances in pediatric formulation development should be approached with tempered optimism, as much remains to be done. Table 3, presented at the end of this section, provides an overview of the pediatric formulations new to market and in development.

First-Line Drugs

Five years after the WHO increased the recommended doses for first-line TB drugs in children, and following significant investments by UNITAID and work by the TB Alliance and partners under the STEP-TB project grant, Macleods has introduced new pediatric FDCs.

Macleods's FDCs of HRZ (isoniazid, rifampin, and pyrazinamide) and HR (isoniazid and rifampin) are now available through the GDF and have been successfully registered in Côte d'Ivoire and India. Registrations are pending in Botswana, Burkina Faso, Cambodia, Cameroon, Congo, Ethiopia, Ghana, Kenya, Mozambique, Nigeria, the Philippines, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe.⁴¹ Registration is stalled in South Africa, as the Medicines Control Council requires bioequivalence work to be conducted in-country.⁴² Rollout of the new pediatric FDCs is anticipated in Kenya and the Philippines before the end of 2016 and as part of a 100-site pilot program in India.⁴³ Macleods has also received orders from Papua New Guinea and Kiribati and an inquiry from Zimbabwe.⁴⁴

Other companies, including Lupin, Sanofi, Sandoz, and Svizera, are working on developing and introducing their own versions, albeit at varying paces and at the mercy of review and approval times of country regulatory authorities and WHO prequalification—a mechanism put in place to ensure and monitor the quality of

medications procured in bulk—and in the absence of approval by a Stringent Regulatory Authority, a requirement of manufacturers to sell medications through the GDF.

Work to increase awareness and facilitate uptake of the new pediatric FDCs is being led by the TB Alliance, the WHO Global TB Program, and the WHO Department of Essential Medicines and Health Products. The UNITAID-funded STEP-TB project will come to an end in 2016, but UNITAID will continue to promote scale-up of the new pediatric treatment options and to support a more sustainable market, and it has issued a call for relevant proposals.⁴⁵

Sanofi, the sponsor of rifapentine (indicated in the United States, in combination with isoniazid, for latent TB infection in children as young as two years), will perform a bioavailability and safety study of the components of its mango-flavored, fixed-dose dispersible of rifapentine and isoniazid and of a rifapentine stand-alone dispersible to facilitate dose adjustments in young children before the end of 2016. The Tuberculosis Trials Consortium will use these formulations in its pediatric PK and safety study of three months of once-weekly rifapentine and isoniazid (3HP) to prevent TB in children. The study (**S35**) is expected to open in 2017, and HIV-positive children on select ARV regimens will be eligible for participation.^{46,47} Unfortunately, rifapentine is still registered only in the United States; Sanofi has a long way to go to ensure wider access for adults and children (see “Tuberculosis Prevention Pipeline,” page 143).

Second-Line TB Drugs

Encouragingly, in August 2015, the WHO Expert Review Panel (ERP) issued an invitation to manufacturers to submit an expression of interest (EOI) to the WHO prequalification team for pediatric formulations of several second-line TB drugs, including cycloserine, levofloxacin, moxifloxacin, linezolid, and ethionamide.⁴⁸ Macleods expects to register pediatric formulations of these second-line drugs before the end of 2016.⁴⁹ A pediatric formulation of clofazimine was not included in the invitation for EOI, but should be immediately added considering its increasingly important role as a component of MDR-TB treatment and trials of shortened regimens. A scored-dispersible or other novel pediatric formulation of clofazimine is urgently needed to facilitate dosing in small children; an invitation for an EOI from the WHO ERP for a pediatric formulation of clofazimine is a necessary first step. It is critical that these new formulations undergo palatability and acceptability evaluations in children and that their quality be assured.

Still, even with the invited EOI and continued investments by Macleods to bring pediatric formulations for second-line TB drugs to market, without updated WHO dosing guidelines, future uptake by country programs is likely to be severely limited. The first time the WHO recommended doses for second-line TB drugs in children was 2006. In 2010, the WHO issued *Rapid Advice: Treatment of Tuberculosis in Children*,⁵⁰ which recommended increased doses of first-line TB drugs in children; in 2014, it updated its *Guidance for National Tuberculosis Programs on the Management of Tuberculosis in Children*.⁵¹ Yet neither of these updates considered data that have emerged for the use of second-line TB drugs in children since 2006. In fact, existing WHO guidelines do not include a recommended pediatric dose for clofazimine at all. The WHO should immediately take the steps necessary to issue updated, comprehensive, and evidence-based dosing guidelines for second-line TB drugs in children.

New Drugs

Otsuka is using 5 mg and 25 mg dispersible tablets of delamanid in strawberry and cherry flavors in its PK and safety study, which is now enrolling children under five years of age (**232; 233**).

The bioavailability study for Janssen's 20 mg dispersible tablet of bedaquiline has long been completed, and Janssen's pediatric study finally opened to enrollment in May 2016. A second bioavailability study to evaluate differences between crushed and whole tablets of the adult formulation of bedaquiline (**bedaquiline-crush**) is under regulatory review in South Africa.⁵² Without access to Janssen's pediatric formulation, these data are necessary to inform IMPAACT's planned PK and safety study of bedaquiline in children, including those with HIV (**P1108**). Data from bedaquiline-crush will also be important to inform use of bedaquiline in children during the time between when evidence from pediatric PK and safety studies is available and when the pediatric formulation enters the market.

Table 3. Pediatric Formulations Newly Marketed and in Development

Drug	Dose	Formulation	Company
First-line drugs			
Fixed-dose combinations H: isoniazid R: rifampin Z: pyrazinamide P: rifapentine	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Macleods
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Lupin
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Sandoz
	HRZ: 50/75/150 mg HR: 50/75 mg HP: 150/150 mg	Dispersible tablets	Sanofi
	HRZ: 50/75/150 mg HR: 50/75 mg	Dispersible tablets	Svizera
Ethambutol	100 mg	Dispersible tablet	Macleods
Isoniazid	100 mg	Dispersible tablet	Macleods
Pyrazinamide	150 mg	Dispersible tablet	Macleods
Rifapentine	100 mg	Dispersible tablet	Sanofi
Second-line and new drugs			
Bedaquiline	20 mg	Dispersible tablet	Janssen
Cycloserine	125 mg	Mini capsule	Macleods
Delamanid	20 mg 5 mg	Dispersible tablets	Otsuka
Ethionamide	125 mg	Scored dispersible tablet	Macleods
Levofloxacin	100 mg	Scored dispersible tablet	Macleods
Linezolid	150 mg	Dispersible tablet	Macleods
Moxifloxacin	100 mg	Scored dispersible tablet	Macleods

RECOMMENDATIONS

In recent years, significant strides have been made in pediatric TB research and development (R&D). Yet much work remains to collect critically important data in children, to increase access to the new pediatric FDCs, and to expedite development of, and access to, pediatric formulations for new and second-line TB drugs.

For researchers

- Consider children when planning adult studies. Building PK investigations into studies that evaluate higher doses of TB drugs in adults is necessary to inform future PK targets in children.
- Determine which PK value(s) correlate best with efficacy for TB drugs in children and establish PK targets based on adult data, taking into consideration the variability in severity and type of TB disease among, and challenges defining efficacy in, children.
- Enroll children two years of age and younger in pediatric studies, as this is the period during which drug disposition changes the most for children, increasing risk for high or low drug exposures.
- Include HIV-positive children in studies of new TB drugs and regimens.
- Include pregnant women in studies of new TB drugs and regimens.

For policy makers

- Incorporate emerging data into guidelines for children more rapidly, especially those for new and second-line TB drugs in children.

For regulatory authorities

- Enforce more thoughtful requirements to ensure comprehensive and timely investigations of TB drugs in children. Mandatory and time-bound pediatric investigational plans that also require studies in HIV-positive children will help to shrink the persisting evidence and access gaps that exist between adults and children for new TB drugs.⁵³
- Follow the important precedent set by the EMA and allow parallel enrollment of pediatric cohorts in PK and safety studies.
- Be transparent and clear about requirements to register pediatric formulations for both existing and new drugs.
- When possible and appropriate, consider waived requirements and registration fees to facilitate access.

For donors

- Maintain and adequately fund momentum in pediatric TB drug R&D, for which global investments totaled \$11.6 million in 2014.⁵⁴ Recent attacks on the budget for and AIDS research priorities of the NIH are particularly concerning for pediatric TB R&D. Not only is the NIH the leading funder, but its investments support studies that are critical to improving treatment of pediatric TB and to filling both long-standing and new gaps in pediatric PK and safety data, especially for HIV-positive children taking ARVs.⁵⁵
- Further attention to and investments in pediatric TB trial infrastructure and site capacity development are urgently needed to support the increasingly full research agenda for prevention and treatment of TB in children.
- UNITAID, whose investments have led to the market introduction of appropriately dosed FDCs of first-line TB drugs for children, and whose planned investments will ensure global uptake of these new formulations, should invest in a project modeled after STEP-TB that is focused on expediting development and market introduction of pediatric formulations of second-line TB drugs.

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2016 Hepatitis C Virus (HCV) Update

By Mark Harrington

Due to recent transitions in the TAG HCV Project [1], we did not complete a comprehensive update on hepatitis C virus (HCV) pipeline. Here are a few highlights in HCV regulation, access, and policy over the past year.

Since the 2015 HCV pipeline, “New Drugs, New Strategies: Conquering Hepatitis C with Direct-Acting Antivirals” by Tracy Swan [2], the U.S. Food and Drug Administration (FDA) has approved several new products, including AbbVie’s Technivie (ombitasvir, paritaprevir + ritonavir tablets) [3], BMS’s Daklinza (daclatasvir) [4, 5], Merck’s Zepatier (elbasvir + grazoprevir) [6], and – most recently – Gilead’s Epclusa (sofosbuvir + velpatasvir) [7], expanded the labeled indication for Harvoni (sofosbuvir/ledipasvir) to include genotypes 4, 5, and 6 [8], and published recommended guidance to industry on development of direct-acting antivirals (DAAs) for treatment of HCV infection. [9]

In February 2016, Médecins du Monde (MdM) and Treatment Action Group (TAG) launched mapCrowd (www.mapCrowd.org), an online resource which includes epidemiological data, HCV diagnostics (viral load and Fibroscan) pricing and availability information, maps showing the extent of Gilead’s and BMS’s voluntary licenses for sofosbuvir and daclatasvir, maps showing annual HCV treatment uptake and the existence of national HCV plans, and links to community-based organizations and some government agencies. The data are available in English, French, Spanish, Russian, Mandarin, and Arabic. [10]

In April 2016 the American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) updated their *Recommendations for Testing, Managing, and Treating Hepatitis C* [11], and the World Health Organization updated its *Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection: Update Version: April 2016*. [12]

At the European Association for the Study of the Liver (EASL) meeting in Barcelona, that same month a global coalition of activists called for “no more treatment rationing: universal access to generic medicines everywhere!” [13]:

Barcelona, Spain – People with hepatitis C virus (HCV) and their allies from Spain and around the world have gathered at the International Liver Congress to protest the outrageous price of lifesaving HCV medicines. They are pushing for generic competition to bring down the price of HCV treatment and ensure universal access.

“New direct-acting antivirals (DAAs) cure nearly everyone from hepatitis C—but Gilead’s greed prevents universal access to their lifesaving medicines. People continue to die needlessly, while Gilead reaps billions in annual profits,” said Damián Caballero of Plataforma de Afectados por Hepatitis C. “They have already earned more than US\$ 32 billion on their HCV DAAs, far more than has been invested in developing them.”

Worldwide, over 150 million people have chronic HCV and need treatment. Some already have cirrhosis and are at risk for liver failure and liver cancer. Each year, approximately 750,000 people die from HCV, although it can be quickly and safely cured with oral DAAs. But DAAs are unaffordable – or unavailable – in most countries.

Patents & exorbitant prices

With sofosbuvir (Sovaldi), Gilead Sciences set the benchmark for scandalous pricing. Sofosbuvir was launched at US \$1,000 per pill, or at least \$84,000 per treatment course. Harvoni, Gilead's fixed-dose combination, is even more expensive. As a result, few countries are able to provide HCV treatment. In places where HCV treatment is available, Gilead's exorbitant prices have led payers to ration. Only the sickest patients are treated, to avoid bankrupting national healthcare systems. "What all these problems, including the lack of access to treatment, show is that the system of research, development and innovation is broken and needs to be transformed," says Vanessa Lopez of Salud por Derecho.

Even in high-income countries, HCV treatment is being rationed. In Spain, more than 500,000 people have HCV, but only 40,000 have been treated. "Due to 20-year patent protection, Gilead was able to set the price for their DAAs and justify it by saying it cost less than a liver transplant. We have to break these illegitimate monopolies," said Chloé Forette of Médecins du Monde. "Gilead's high prices have nothing to do with the actual cost of their research and development."

Most low- and middle-income countries – home to more than 120 million people with hepatitis C – do not have access to Gilead's HCV treatment. Gilead claims that its voluntary licensing program provides access to 103 people million with HCV, but this is not the reality. Sofosbuvir must be registered in each country before it can be sold. Gilead has only registered sofosbuvir in 9 of the 101 so-called access countries where they have offered voluntary licenses. It cannot be sold in the other access countries until Gilead registers it.

The primary purpose of Gilead's voluntary licensing is to control the market by preventing access to generics in countries where it can reap high profits. Gilead did not offer voluntary licenses to many countries with a high burden of HCV. "Without access to generic sofosbuvir, countries are left at Gilead's mercy for drug pricing," said Tracy Swan of Treatment Action Group. "In Brazil, Gilead charges more than US\$ 7,000 for sofosbuvir, though the country's GNI [gross national income] per capital is US\$ 961 per month."

Actions for Universal Access

Unrestricted generic competition is the most effective strategy for reducing the price of medicines. For example, a 12-week course of generic sofosbuvir is currently being sold in India for US \$325. This price will continue to drop as economies of scale are achieved. Generic sofosbuvir could be mass-produced for only US \$1 per pill.

Countries can oppose outrageous pricing policies by invoking legal safeguards to protect public health. They can issue compulsory licenses so that they can provide affordable generic medicines. With HIV, generic competition lowered the price of antiretroviral therapy from US\$ 10,000 per year to less than US\$ 100 per year.

Patients and activists joined forces at the International Liver Congress to protest the lack of access to DAAs and speak out against their outrageous prices. They encourage civil society to oppose illegitimate patents that block access to HCV drugs and demand that:

- Gilead register sofosbuvir NOW, everywhere it is needed.
- Gilead expand their voluntary licenses to include all countries with a high burden of HCV.
- Gilead drop the price of its HCV medications so that universal access can become a reality.

- Our governments overcome patent barriers by using their legal right to issue compulsory licenses so that they can provide access to affordable generic DAAs.

Sofosbuvir is just the tip of the iceberg. New treatments for Alzheimer's disease or cancer are likely to be rationed, due to exorbitant prices. We demand a public debate on price-setting methods for medicines, alternative financing mechanisms for research and development, transparency about the actual cost of drug development, and accountability for the public money that supports research.”[13]

Researchers estimate that the cost of dual-therapy with sofosbuvir and daclatasvir could be brought down to under \$200 per person per treatment course, with the potential to save millions of lives [14, 15]. Domestic and international efforts to reduce the price of DAAs to make them truly accessible and affordable are intensifying. [16, 17, 18]

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