Fit for Purpose: Antiretroviral Treatment Optimization

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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 Aurobino'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 waiver 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-naive 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-naive 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 Cmin 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 Incomes[48] – 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 label study in integrase inhibitor-naive 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 plasma[59]; 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-naive 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 Cmin than when it is boosted with ritonavir[65, 66] (in which the investigators say a reduction of up to 50% in Cmin 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 development)	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/TDT 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				
DolPHIN1 (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 Heatlthcare	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
DolPHIN2	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-naive 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-naive 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 PANNA [74] – 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 1 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 coinfected 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 coinfected 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 WRHI052	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 programes 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 waiver 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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