Commentary: Antiretroviral therapy initiation criteria in low resource settings – from 'when to start' to 'when not to start'

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AIDS 2014, **28** (Suppl 2):S101–S104

By the end of 2012, the number of people receiving antiretroviral treatment (ART) in low and middle-income countries reached 9.7 million, including 7.2 million in sub-Saharan Africa. The bad news is that these figures represent only 65% of the global target of 15 million people on ART set for 2015, and 63% of those in need of ART, therefore, excluding nearly one-third of eligible persons from a life-saving treatment [1]. The good news is that this 2012 ART coverage figure represents an 11% increase since 2011, and a three-fold increase since 2007. As a result of government efforts and international funds, the gap between ART needs and resources is steadily decreasing.

Progress in access to ART should be measured not only in terms of eligible patients who have not yet started ART, but also based on mortality among patients who actually started ART. In resource-constrained settings, early mortality in adults who start ART ranges from 7 to 16%, a rate considerably higher than that observed in high-income countries [2–5]. The main factors associated with early mortality on ART are male sex, anemia, low body mass index (BMI), positive serum cryptococcal antigen, having to pay for the drugs, advanced clinical stage, ongoing active tuberculosis at ART initiation, and advanced immunosuppression [2–6]. It is because of the latter three reasons that WHO immunological and clinical criteria for starting ART have been revised twice in the past 3 years.

Before 2010, WHO guidelines recommended that ART should be started in adolescents and adults with less than 200 $CD4^+$ T-cells/μl irrespective of their clinical stage, in those at WHO clinical stage 4 irrespective of their $CD4^+$ T-cell count, and in those at WHO clinical stage 3 as soon as their $CD4^+$ T-cell count decreased bellow 350 $CD4^+$ T-cells/μl [7]. In 2010, WHO recommended that not only clinical stage 4 but also stage 3 patients should start ART irrespective of their $CD4^+$ T-cell count, and raised the $CD4^+$ T-cells threshold to start ART in asymptomatic adolescents and adults from 200 to 350 cells/μl [8]. Three years later, the 2013 WHO guidelines have now raised the $CD4^+$ T-cells threshold to start ART to 500 cells/μl (Table 1) [9]. This accelerating trend towards earlier ART initiation in low-resource settings is spectacular, making some people speculate about the future WHO 2015 guidelines recommending that ART should be given to all patients irrespective of their $CD4^+$ T-cell count, as already recommended in France, Brazil or in the United States [10–13]. It is noteworthy, though, that the most recent European AIDS Clinical Society (EACS) [14] and UK [15] guidelines still recommend to start below 350 $CD4^+$ T-cells/μl, and consider starting ART below 500 $CD4^+$ T-cells/μl (Table 2).

WHO guidelines are evidence-based and use the GRADE methodology. Initiating ART earlier – that is, at higher $CD4^+$ T-cell counts or less advanced clinical stage – may entail individual benefits, consisting of a reduction in early mortality and severe morbidity [16–19], and population benefits, consisting of preventing HIV transmission to non-HIV-infected partners [20–22]. In 2010, raising the $CD4^+$ T-cells threshold from 200 to 350/μl was a strong recommendation based on high-quality evidence of individual benefits [8]. In 2013, raising the $CD4^+$ T-cell threshold to 500/μl was a strong recommendation based on a systematic review of 24 studies [23], of which three were randomized trials and the remainder observational studies. There was high-quality evidence of population benefits in reducing transmission, but only low-quality evidence for individual benefits (reduced risk of mortality, progression to AIDS or death, and diagnosis of an AIDS defining

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DOI:10.1097/QAD.0000000000000237

Table 1. Summary of recommendations on when to start in the 2013 WHO guidelines [9].

Population	Recommendation	Strength of recommendation and quality of evidence
Adults and adolescents (≥10 years)	Initiate ART if $CD4^+$ T-cell count ≤500 cells/μl	*Strong recommendation, moderate quality evidence*
	As a priority, initiate ART in all individuals with severe/advanced HIV disease (WHO clinical stage 3 or 4) or $CD4^+$ T-cell count ≤350 cells/μl	*Strong recommendation, moderate quality evidence*
	Initiate ART regardless of WHO clinical stage and $CD4^+$ T-cells in those with:	*Strong recommendation, low quality evidence*
	Active TB disease	*Strong recommendation, low quality evidence*
	HBV coinfection with severe chronic liver disease	*Strong recommendation, low quality evidence*
	Pregnant and breastfeeding women with HIV	*Strong recommendation, moderate quality evidence*
	HIV-positive individual in a serodiscordant partnership (to reduce HIV transmission risk)	*Strong recommendation, high quality evidence*
Children ≥5 years old	Initiate ART if $CD4^+$ T-cell count is ≤500 cells/μl	*Conditional recommendation, very low quality evidence*
	As a priority, initiate ART in all children with severe/advanced HIV disease (WHO clinical stage 3 or 4) or $CD4^+$ T-cell count ≤350 cells/μl	*Strong recommendation, moderate quality evidence*
	Initiate ART regardless of $CD4^+$ T-cell count WHO clinical stage 3 or 4 Active TB disease	*Strong recommendation, moderate quality evidence*
Children 1–5 years old[a]	Initiate ART in all regardless of WHO clinical stage and $CD4^+$ T-cell count	*Conditional recommendation, very low quality evidence*
	As a priority, initiate ART in all HIV-infected children 1–2 years old or with severe/advanced HIV disease (WHO clinical stage 3 or 4) or with $CD4^+$ T-cell count ≤750 cells/μl or <25%, whichever is lower	*Strong recommendation, very low quality evidence*
Infants <1 year old[a]	Initiate ART in all infants regardless of WHO clinical stage and $CD4^+$ T-cell count	*Strong recommendation, moderate quality evidence*

ART, antiretroviral treatment; HBV, hepatitis B virus; TB, tuberculosis.
[a]Initiate ART in all HIV-infected children below 18 months of age with presumptive clinical diagnosis of HIV infection.

illness) [9]. Even if strong recommendations based on low-quality evidence are not unusual in WHO HIV/AIDS guidelines [24], recommendations mainly based on evidence of population benefits, with low evidence of individual benefits, are less common. If recommending ART in all patients irrespective of their $CD4^+$ T-cell count was to be the next step, one may expect it to be taken based on strong evidence of individual benefits. It is hoped that, the two ongoing 'when to start' randomized controlled trials – TEMPRANO and Strategic Timing of

Table 2. Current recommendations for initiation of ART in major guidelines.

Guideline	AIDS or HIV-related symptoms	$CD4^+$ T-cell count <200/μl	$CD4^+$ T-cell count 200–350/μl	$CD4^+$ T-cell count 350–500/μl	$CD4^+$ T-cell count >500 cells/μl
DHHS, 2012 [11]	Yes	Yes	Yes	Yes	Yes
International Antiviral Society, USA, 2012 [12]	Yes	Yes	Yes	Yes	Yes
European AIDS Clinical Society, 2013 [14]	Yes	Yes	Yes	'Consider'	Defer
French Guidelines, 2013 [10]	Yes	Yes	Yes	Yes	Yes
British HIV Association, 2012 [15]	Yes	Yes	Yes	Defer	Defer
WHO, 2010 [8]	Yes	Yes	Yes prioritize	Yes	Defer

ART, antiretroviral treatment.

Antiretroviral Treatment (START), may provide such evidence [25,26].

Meanwhile, the 2013 WHO guidelines highlight four priorities.

First, HIV-infected persons should be diagnosed and referred to care much earlier than is currently done. The current mean pre-ART $CD4^+$ T-cell count in most low-resource settings, remains close to 150/μl [27]. This is not only related to HIV testing occurring too late, but also to weak linkages to of care in people who have been HIV-tested [28]. Causes of late testing include insufficient willingness to undergo voluntary testing and caregivers' reluctance to offer the test, especially in asymptomatic individuals [29]. Recommending earlier ART initiation will entail benefits only if we can strengthen the cascade between people being HIV tested earlier and treatment being started in patients eligible for ART [1].

Second, earlier ART initiation should not impair the efforts to increase ART coverage first in patients who need it most, that is, those with advanced stages of the disease. This raises equity issues, and in some settings, the need for prioritization. Similarly, the workload involved with changing international recommendations needs to be recognized. Task shifting from doctors to nurses prescribing ART may be part of the solution in countries that have not yet adopted earlier ART initiation [30]. However, increasing health care worker recruitment is also imperative. This includes nurses, social workers, counselors, but also pharmacists who not only deliver the drugs but also advise patients on their treatment and may sometimes manage several hundreds of drug deliveries per health center per day [31,32]

Third, earlier ART initiation is facilitated through access to safer and easier-to-take ART. This translates in terms of good tolerance, fixed-drug combination availability, cost-effectiveness, and, in a context of task shifting, prescriber friendliness [33,34]. In most resource-limited settings, this also implies that ART drugs should be easily combined with antituberculosis drugs, be active against hepatitis B virus (HBV), and be well tolerated in pregnant women. From 2003 to 2010, the WHO recommended first-line ART regimens were reduced from eight to four options, combining two nucleoside reverse transcriptase inhibitors with efavirenz or nevirapine [7,8]. In 2013, one single regimen was considered to meet all the above criteria: tenofovir + lamivudine/emtricitabine + efavirenz [9]. This is currently the preferred first-line option for adoption in low-resource settings.

Finally, there remains a tension between individual and population benefits of starting ART earlier, as illustrated by the 2013 WHO consolidated guidelines. This has prompted speculation about the nature of the evidence that will be provided from the ongoing 'when to start' trials. There are two possible scenarios. The first is that high-quality evidence will demonstrate that ART should be prescribed to all HIV-infected individuals, irrespective of their $CD4^+$ T-cell counts, with no exception. In that case, 'when to start ART' would no longer be a question. The second one would be that ART at any $CD4^+$ T-cell count is proven to have strong benefits globally, with some doubts remaining about whether these benefits outweigh the risks in some groups of patients. In that situation, the relevant question for HIV-infected patients in low-resource settings might then shift to 'when not to start ART'.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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