Scaling Up Antiretroviral Therapy in Africa: Are We There Yet?

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(See the Major Article HIV/AIDS by Scarsi et al on pages 512–8.)

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Antiretroviral therapy (ART) as a compact regimen of 3 coformulated reverse transcriptase inhibitors is saving millions of lives through public health programs in low- and middle-income countries (LMICs) over the last decade. Evidence from treatment as prevention, early treatment, Strategic Timing of AntiRetroviral Therapy study, and pre-exposure prophylaxis (PrEP) studies have led to a call to augment and sustain universal treatment, building on the momentum of the first 2 decades of ART [1–3]. New World Health Organization (WHO) guidelines recommend detection of 90% of those infected and engagement of 90% in care to achieve virologic suppression among 90% of those treated. The effectiveness of 90-90-90 and models of universal treatment to eliminate AIDS and human immunodeficiency virus (HIV) depends on lower-cost compact fixed-dose combinations (FDCs) with minimal toxicity. However, in LMICs, the current options for affordable treatment are regimens of generic FDCs of agents developed in the 1990s and deployed over the last decade.

Access to affordable high-quality potent and compact ART is the barrier to achieve the recommended scale-up of ART to >10 million newly diagnosed people living with HIV/AIDS (PLWHA) in Africa. Current first-line reverse transcriptase inhibitor therapy recommendations are efavirenz (EFV), lamivudine (3TC) or emtricitabine (FTC), and tenofovir (TDF). Nevirapine (NVP) and zidovudine (ZDV) + 3TC are considered alternative nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitor (NRTI) FDCs. A systematic review comparing combinations of reverse transcriptase inhibitors provides evidence that EFV is more effective virologically than NVP [4], and TDF is widely recommended over thymidine analogue nucleosides and ZDV based on tolerability and safety (Table 1).

Assessment of NVP-based ART from 2006 to 2008 in Nigeria by Scarsi et al, in this issue of Clinical Infectious Diseases [5], provides a timely reminder of the complexity and importance of evaluating lower-cost generic full-dose combinations in LMICs for public health ART. Nevirapine was the recommended NNRTI owing to its success in prevention of mother-to-child transmission, as well as its safety among women with lower CD4 counts and the higher cost and potential teratogenicity of EFV [6]. A systematic review from Tang et al in 2012 showed the paucity of evidence for the effectiveness of 3TC, TDF, and NVP compared with the other recommended TDF-based regimens [7]. The accompanying commentary noted that new ART combinations may be less than the sum of their parts, and characterized the NVP + TDF regimen as (at best) the least among equals [8]. Tang et al cited the DAUFIN study [9], Lapadula [13], and early data from the US President’s Emergency Plan for AIDS Relief (PEPFAR) ART programme in Nigeria (APIN) presented in 2010 [10], which raised questions about NVP, 3TC, and TDF as a 3-drug combination. The virologic effectiveness of EFV formulations in LMICs is supported by postmarketing studies and systematic reviews of published studies [4, 11, 12].

The combined use of TDF + 3TC + NVP was assessed in only 1 controlled trial. The DAUFIN study, a European open-label, multicenter, noninferiority trial, compared NVP with ZDV, 3TC twice daily, or TDF + 3TC once daily. Begun in 2005, the study was stopped in 2006 when unexpected study discontinuations were observed after 71 of the planned 250 subjects had been enrolled. The study authors cautioned: “Whatever the mechanism that led to the high viral failure rate, we deem it essential to alert that the once-daily combination of TDF, 3TC and NVP should not be given as a first-line [antiretroviral] therapy” [9]. A letter in 2008 noted that the “use of TDF-FTC + NVP was associated with unexplained early virological failure” [13]. An adverse pharmacologic interaction was demonstrated...
in vitro by Liptrott et al [14]. Subsequent observations show that K65R, a TDF-associated NRTI drug resistance mutation, was significantly more common following TDF or stavudine in HIV-1 subtypes C and CRF01_AE [15, 16]. A lower barrier to resistance in non–subtype B may be another factor in the relatively higher risk of virologic failure of NVP and TDF/FTC vs ZDV/3TC in APIN.

The analysis of clinical and virologic data from the scale-up of ART to improve and sustain treatment effectiveness faces many challenges including late presentation, diverse HIV subtypes, tuberculosis coinfection, and limited monitoring and treatment infrastructure. The APIN program in Nigeria in 2006 faced challenges in the treatment of a population that, like many PEPFAR programs in Africa, recruited a majority of women with AIDS (nearly half at stage 3 or 4) with low CD4 cell count, high viral load, and high rates of tuberculosis (14%), hepatitis B (25%), and hepatitis C (7%). In that setting, the virologic success rate of twice-daily NVP with ZDV/3TC or once-daily TDF and 3TC/FTC (93% and 89%, respectively) as-treated is remarkable. This was achieved despite higher rates of treatment change and discontinuation in the TDF arm in a predominantly female population where tuberculosis coinfection, low CD4 cell count, and high viral load challenge the scale-up of ART in Africa.

Treatment is now recommended to >30 million PLWHA through “test and treat,” treatment as prevention, and PrEP to high-risk populations. Rapid point-of-care and provider-initiated HIV testing and lower-cost CD4 count and viral load testing have increased access to first- and second-line therapies. Evidence that universal treatment, treatment as prevention, and PrEP could end the epidemic in 20–30 years is quickening the pace of drug access and implementation. However, there is a wide gap between first-line regimens recently recommended by the US Department of Health and Human Services and International AIDS Society–USA (integrase strand transfer inhibitors) and the WHO (NNRTI) [3, 17, 18]. How will new affordable generic combinations and formulations including integrase inhibitors be evaluated in LMICs as early treatment and treatment as prevention are implemented? Resources for comparative clinical trials are limited, but better data collection and outcomes research across treatment programs, hopefully in near–real time, can measure effectiveness of new combinations and identify regimens that are more and less effective. Minding the gap between the aspirational and the possible and acting to reduce these disparities will require the acquisition and analysis of “big data” from national programs in parallel with the allocation of resources for comparative clinical trials to optimize safe, effective, and affordable ART. Lack of access to resources, infrastructure, new formulations, and strategies in the most severely affected LMICs challenges the “beginning of the end of the AIDS epidemic” (http://www.globe-network.org/en/beginning-end-aids-epidemic).

Note

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