

Commentary

Preferred antiretroviral drugs for the next decade of scale up

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Abstract

Global commitments aim to provide antiretroviral therapy (ART) to 15 million people living with HIV by 2015, and recent studies have demonstrated the potential for widespread ART to prevent HIV transmission. Increasingly, countries are adapting their national guidelines to start ART earlier, for both clinical and preventive benefits. To maximize the benefits of ART in resource-limited settings, six key principles need to guide ART choice: simplicity, tolerability and safety, durability, universal applicability, affordability and heat stability. Currently available drugs, combined with those in late-stage clinical development, hold great promise to simplify treatment in the short term. Over the longer term, newer technologies, such as long-acting formulations and nanotechnology, could radically alter the treatment paradigm. This commentary reviews recommendations made in an expert consultation on treatment scale up in resource-limited settings.

Keywords: Antiretroviral therapy; regimen sequencing; treatment optimization.

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Introduction

Recent global commitments aim to provide antiretroviral therapy (ART) to 15 million people living with HIV by 2015, but with current coverage at around 50%, and with international funding for HIV/AIDS on the decline, there is an enormous task ahead [1].

Yet, expectations of antiretroviral (ARV) medications have never been higher. The massive scale up of access to ART over the last decade has demonstrated the feasibility of delivering ART as a public health intervention, with an estimated 2.5 million deaths averted since 1995 [2]. More recent studies have demonstrated the potential for widespread ART use to reduce HIV transmission at the population level, findings that offer enormous opportunities to reverse the epidemic. Similarly, options for ART have never been greater: there are now 27 US FDA-approved ARVs collectively targeting five different points in the HIV life cycle [3].

The need to diagnose more people earlier in their disease progression, ensure rapid linkage to care, and improve strategies for retention in care and adherence to ART continue to be important challenges. Improvements in uptake and long-term adherence to treatment will likely depend on improved access to the best available ART regimens [4]. To direct clinical research, future guidelines and advocacy efforts, it is critical to develop priority treatment options, particularly for resource-limited settings. In September 2011, Médecins Sans Frontières, SOLTHIS (Solidarity Thérapeutique & Initiatives contre le SIDA) and Esther (Ensemble pour une solidarité Thérapeutique Hospitalière en Réseau) organized an expert consultation to

provide recommendations on ARV regimens and strategies to support further scale-up of treatment in resource-limited settings [5].

This workshop took place as part of a broader set of initiatives aiming to develop a vision for the further simplification of ART in the medium and long term. Of particular note are two meetings on the strategic use of ARVs for treatment and prevention of HIV, convened by the World Health Organization (WHO) under the *Treatment 2.0 Strategy* [6]: a conference on short-term priorities for ART optimization that took place in April 2011 [7] and two consultations on the strategic use of ARVs for treatment and prevention held in November 2011 and May 2012 [8].

This viewpoint summarizes the main consensus recommendations from the workshop. The most important research questions relating to priority ARV drugs and research questions for resource-limited settings emerging from the meeting are summarized in Table 1.

Target characteristics of future treatment regimens

Clinical drug development aims primarily to achieve therapeutic efficacy. Efficacy is an important precondition for any successful regimen and is particularly important in developing countries where access to viral load monitoring and genotyping remain limited. Nevertheless, delivering ART in resource-limited settings requires more than efficacious drugs. With effective therapy, people living with HIV can expect a near normal lifespan [9,10]. Therefore, long-term

Table 1. Priority ARV drugs and research questions

H	Issue	Research agenda
Efavirenz	Safety in pregnancy Cost	Prospective birth registries Dose optimization
Tenofovir	Toxicity (renal and bone) Cost	Long-term cohort reporting Dose optimization
Lopinavir/ritonavir	Poor palatability for infants Cold chain	Development of other pro-drugs Development of sprinkles Heat stable formulations
Darunavir, raltegravir, etravirine	High cost	Preferential pricing Market competition
Long-acting formulations	Long-acting regimens required	Dose optimization Prioritize development of molecules that can be combined to form a regimen
Nanotechnology	Poor linkage between science and clinical need	Priority research agenda to be established
Novel delivery systems	Not yet developed	Long-acting formulations, patches, injections and implants

treatment strategies, including a sequence of regimens that will provide effective treatment over decades, are required.

Six key principles guide ART choice: simplicity, tolerability and safety, durability, universal applicability, affordability and heat stability.

Simplicity

To expand access, many countries have simplified HIV care so that it can be delivered at primary health care centres by nurses or community health workers. In such decentralized settings, simple regimens, prioritizing fixed-dose combinations (FDCs), once-daily formulations, drugs that can be given weekly or monthly and regimens with minimal laboratory monitoring, food or fluid requirements, are required [11].

Tolerability and safety

Side effects are a major driver of poor adherence, drug substitution and treatment discontinuation, all of which undermine treatment and prevention efforts [12,13]. In particular, providing ART as prevention implies giving ART to people who may not yet have experienced clinical illness and may therefore be more reluctant to adhere to drugs with side effects.

Durability

With effective therapy, people living with HIV are likely to take ART for several decades after HIV diagnosis, far longer than the average life span of most older-generation ARVs. To maximize durability, drugs must have a high genetic barrier to resistance mutations. ART must continue to be provided with an appropriate amount of adherence education and counselling, long-term support and follow up. Nevertheless, to cope with the increasing caseload, models of care that rely on less frequent clinic visits for stable patients are likely to become increasingly popular [14], and in these contexts durability becomes more important.

Universal applicability

Current regimens require frequent substitutions according to age, pregnancy presence of comorbidities and interactions with other drugs. The ideal regimen would be one that is safe and effective, irrespective of disease stage, usable throughout pregnancy, appropriate for infants, children and adults, and can be taken together with drugs for co-infections, notably tuberculosis and viral hepatitis [15].

Affordability

Strategies that lower treatment costs should be prioritized. These include dose reduction, improved drug bioavailability, cost reduction of active pharmaceutical ingredient through improved chemistry process and novel drug delivery systems.

Heat stability

Finally, drug formulations need to be stable without the need for refrigeration.

Short-term recommendations (One–three years)

First line antiretroviral therapy

Considering the above six key principles, the preferred first-line regimen for adults and adolescents is the WHO-recommended combination of tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV), available as a once-daily FDC [7]. However, three issues must be overcome to further expand its use: safety of efavirenz in pregnancy, tenofovir toxicity and cost reduction.

EFV has been associated with potential teratogenicity following data from animal models and case reports. To date, however, rates of congenital abnormalities associated with EFV are no greater than the background rate [16]. A pragmatic approach has recently been put forward by WHO recognizing the important advantages of EFV within a once-daily regimen and the consequences of switching to potentially less safe and efficacious alternatives, such as nevirapine [17]. TDF is associated with long-term renal and bone toxicities and increased risk of fracture [18], but the clinical

significance of these toxicities remains unclear [16] and the overall risk–benefit equation favours prioritization of this drug with ongoing monitoring and reporting of adverse events [19].

The recent approval of TDF for children over two years of age creates possibilities to align recommendations for adults and children. An ideal formulation for first-line treatment of children over three years would be a scored, adult-strength, dispersible FDC tablet of TDF/3TC/EFV. Treatment programmes could then use the same pill for almost all patients. For children below three years of age, protease inhibitors will remain the preferred strategy given the lack of safety data for EFV and TDF in infants, non-nucleoside reverse transcription inhibitor (NNRTI) exposure from prevention of mother to child transmission and the potential failure of a NNRTI-based regimen in the HIV-positive mother. To overcome this issue, better co-formulations of lopinavir/ritonavir (LPV/r) are needed. A strategy for transitioning children from paediatric regimens to adult regimens once they reach the age of three needs to be defined.

Several ongoing studies could potentially lead to lower costs for EFV and TDF. These include an EFV dose reduction trial, reformulation and clinical evaluation of tenofovir pro-drugs CMX157 and GS 7340 [20]. These studies may also demonstrate reduced drug-related side effects.

Second-line antiretroviral therapy

While improving first-line therapy should improve long-term adherence to treatment at scale, some patients will develop treatment failure and will need a directed sequence of safe, independent (in terms of resistance) and convenient regimens.

In the short term, the preferred regimen will likely remain protease inhibitor-based: heat stable co-formulated atazanavir plus ritonavir low dose (ATV/r) or darunavir/ritonavir (DRV/r), which should lower the pill burden and permit once-daily doses. Incompatibility of these drugs with rifampicin in tuberculosis regimens is a limitation, but this could be resolved by replacing rifampicin with rifabutin [21].

As an immediate priority, the price of new drugs currently used in third-line line regimen, notably darunavir (DRV), etravirine (ETV) and raltegravir (RAL) needs to decrease substantially so that second-line treatment can be improved and become widely available. Dolutegravir (DTG), a pipeline once-daily integrase inhibitor, is a promising future option, with the relatively low cost of its active pharmaceutical ingredient raising the potential for inexpensive manufacture [22]. Finally, to support adherence to first-line treatment and detect timely treatment failure, increased access to simple, affordable viral load measurement is a high priority.

Mid- to long-term recommendations (three–ten years)

For patients initiating antiretroviral treatment

TDF (or alternative pro-drugs of TDF)/3TC/EFV may remain the preferred option for resource-limited settings for the medium term. Newer FDCs, including the recently FDA-approved QUAD[®] (elvitegravir, cobicistat, tenofovir and emtricitabine) or rilpivirine-based regimen also available in

once-daily FDC will need careful assessment for use in resource-limited settings. DTG co-formulated with abacavir and 3TC is likely to become another single daily co-formulated pill, although cost may remain an issue. A first-line regimen with a high genetic barrier to resistance is preferable, and once-daily ATV/r or DRV/r could be options as first-line anchor drugs, but these drugs need to be developed as affordable FDCs. An FDC of darunavir, cobicistat, tenofovir and emtricitabine is currently under development, but the price is yet to be determined [23].

Subsequent treatment options

Regimens that have minimal cross-resistance after first-line failure, and therefore limit the need for virus genotyping, are a priority. A DRV/r- or DTG-based regimen co-formulated with a PI (assuming continued successful development of DTG) for adults, and hopefully also for children failing PI regimens, meets this requirement. Implementation will require a strategic decision on when to use DRV and DTG for optimal benefit (as first- or second-line option).

In the longer term, a number of emerging new technologies have the potential to revolutionize ART. Long-acting formulations offer the promise of weekly or even monthly therapy, which could improve patient adherence and health service efficiencies, such as prescriptions, drug supply and pharmacy management. Numerous drugs, including rilpivirine, S/GSK 744 and CMX 157, are already in clinical development as long-acting drugs, although the potential for combining several drugs into a single long-acting combination therapy remains unexplored [22]. Novel delivery systems, including patches, implants and injections, are also under development and could potentially improve adherence. Finally, nanotechnology holds promise for better treatments by enhancing drug activity, improving toxicity profiles and reducing cost (by reducing the amount of active ingredient). A nanosuspension of rilpivirine is currently in development. The clinical challenges related to the implementation of these delivery systems will require careful assessment.

Conclusions

Countries are increasingly adapting their national guidelines to start ART earlier, for both clinical and preventive benefits. Providing people with affordable medicines, combined into effective regimens with as few side effects as possible and in a form that is practical to take and easy to adhere to, remains a challenge. But this challenge must be met in order to improve patient outcomes and reap the preventive benefits of widespread ART coverage.

These considerations raise the stakes for the ongoing WHO-facilitated discussions on implementation of the *Treatment 2.0* strategy [6] and the update process of WHO ART guidelines (planned for release in 2013), which will define the optimized choices of ART management in a public health approach. This implies prioritizing ART regimens to ensure that patient treatment, programme management and drug procurement are all simplified as far as possible. These issues are particularly critical to the policy environment in which decisions are made about key levers (such as local drug

production and generic competition) for driving down the price of drugs.

People living with HIV, treatment providers and high-prevalence communities have a stake in these decisions about how HIV will be managed in the coming years. A key challenge is how much (and at what cost) to optimize treatment for individuals while expanding it to as many people as possible. Currently, constrained budgets should not lead to compromising the quality of treatments that achieve and maintain viral suppression that will benefit the health of both individuals and communities.

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Authors' contributions

NF and IAM wrote the first draft of the article. All authors contributed to subsequent drafts and approved the final version. The views expressed in this article are those of the authors and not necessarily their affiliated organizations.

References

1. United Nations General Assembly. Political declaration on HIV/AIDS: intensifying our efforts to eliminate HIV/AIDS – United Nations General Assembly Resolution 65/277. New York, United Nations; 2011.
2. Progress report 2011. Global HIV/AIDS response Epidemic update and health sector progress towards universal access. WHO, UNICEF, UNAIDS. Geneva, Switzerland: December 2011.
3. US Food and Drugs Administration. Antiretroviral drugs used in the treatment of HIV infection, 2012. Available from: <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm>
4. Lynch S, Ford N, van Cutsem G, Bygrave H, Janssens B, Decroo T. Getting HIV treatment to the most people. *Science* 2012;337(6092):298–300.

5. Antiretroviral Sequencing Meeting Report. MSF. Geneva, 2011. Available from: <http://www.msfast.org/content/antiretroviral-sequencing-meeting-report>
6. WHO/UNAIDS. The treatment 2.0 framework for action: catalyzing the next phase of treatment, care and support. Geneva, Switzerland: World Health Organization; 2011.
7. WHO. Short-term priorities for antiretroviral drug optimization: meeting report. Geneva, Switzerland: World Health Organization; 2011.
8. WHO. Consultation: the strategic use of antiretrovirals for treatment and prevention of HIV. Geneva, Switzerland: WHO; 2011.
9. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372:293–9.
10. Mills E, Bakanda C, Birungi J, Chan K, Ford N, Cooper C, et al. Life expectancy of individuals on combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. *Ann Intern Med*. 2011;155:209–16.
11. Calmy A, Klement E, Teck R, Berman D, Pécoul B, Ferradini L, et al. Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling up. *AIDS*. 2004;18:2353–60.
12. Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. *Trop Med Int Health*. 2011;16(10):1297–313
13. Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med*. 2006;3(11):e438.
14. MSF/UNAIDS. Closer to home: delivering antiretroviral therapy in the community. Experience from four countries in Southern Africa. Geneva, Switzerland: MSF/UNAIDS; 2012.
15. Ford N, Calmy A. Improving first-line antiretroviral therapy in resource-limited settings. *Curr Opin HIV AIDS*. 2010;1:38–47.
16. Ford N, Calmy A, Mofenson L. Safety of efavirenz in first-trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS*. 2011;25:2301–4.
17. WHO. Technical update on treatment optimization: use of efavirenz during pregnancy in a public health perspective. Geneva, Switzerland: World Health Organization; 2012. Available from: http://extranet.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf
18. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS*. 2012;26(7):825–31.
19. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. 2010;51(5):496–505.
20. Crawford KW, Ripin DH, Levin AD, Campbell JR, Flexner C, participants of Conference on Antiretroviral Drug Optimization. Optimising the manufacture, formulation, and dose of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement. *Lancet Infect Dis*. 2012;12(7):550–60.
21. Loeliger A, Suthar A, Ripin D, Glaziou P, O'Brien M, Renaud-Thery F, et al. Protease inhibitor-containing antiretroviral treatment and tuberculosis: can rifabutin fill the breach? *Int J Tuberc Lung Dis*. 2011;16(1):6–15.
22. Clayden P, Collins S, Daniels C, Geffen N, Harrington M, Jefferys R, et al. 2012 Pipeline report. HIV, HCV and TB, drugs, diagnostics, vaccines, and preventive technologies in development. London, UK: i-Base/Treatment Action Group; 2012.
23. Safety and efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 single tablet regimen versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate fixed dose combination in HIV-1 infected, antiretroviral treatment naive adults. *ClinicalTrials.gov Identifier: NCT01565850*.