Serge-Paul Eholié et al. *Journal of the International AIDS Society* 2012, **15**:17334
http://www.jiasociety.org/index.php/jias/article/view/17334 | http://dx.doi.org/10.7448/IAS.15.2.17334

JIAS Journal of the International AIDS Society

Commentary

HIV treatment and care in resource-constrained environments: challenges for the next decade

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Abstract

Many successes have been achieved in HIV care in low- and middle-income countries (LMIC): increased number of HIV-infected individuals receiving antiretroviral treatment (ART), wide decentralization, reduction in morbidity and mortality and accessibility to cheapest drugs. However, these successes should not hide existing failures and difficulties. In this paper, we underline several key challenges. First, ensure long-term financing, increase available resources, in order to meet the increasing needs, and redistribute the overall budget in a concerted way amongst donors. Second, increase ART coverage and treat the many eligible patients who have not yet started ART. Competition amongst countries is expected to become a strong driving force in encouraging the least efficient to join better performing countries. Third, decrease early mortality on ART, by improving access to prevention, case-finding and treatment of tuberculosis and invasive bacterial diseases and by getting people to start ART much earlier. Fourth, move on from WHO 2006 to WHO 2010 guidelines. Raising the cut-off point for starting ART to 350 CD4/mm^3 needs changing paradigm, adopting opt-out approach, facilitating pro-active testing, facilitating task shifting and increasing staff recruitments. Phasing out stavudine needs acting for a drastic reduction in the costs of other drugs. Scaling up routine viral load needs a mobilization for lower prices of reagents and equipments, as well as efforts in relation to point-of-care automation and to maintenance. The latter is a key step to boost the utilization of second-line regimens, which are currently dramatically under prescribed. Finally, other challenges are to reduce lost-to-follow-up rates; manage lifelong treatment and care for long-term morbidity, including drug toxicity, residual AIDS and HIV-non-AIDS morbidity and aging-related morbidity; and be able to face unforeseen events such as socio-political and military crisis. An old African proverb states that the growth of a deep-rooted tree cannot be stopped. Our tree is well rooted in existing field experience and is, therefore, expected to grow. In order for us to let it grow, long-term cost-effectiveness approach and life-saving evidence-based programming should replace short-term budgeting approach.

Keywords: HIV; antiretroviral therapy; resources-constrained environments.

Received 17 April 2012; **Revised** 16 May 2012; **Accepted** 11 July 2012; **Published** 22 August 2012

Introduction

National government initiatives sometimes supported by UNAIDS, and programmes implemented by non-governmental organizations clearly demonstrated in the late 1990s and early 2000s that programmes addressing access to antiretroviral treatment (ART) in low- and middle-income countries (LMIC) were feasible [1–5].

The findings of these pilot projects were widely confirmed in larger national and international programmes which proliferated worldwide in the following decade. Successes achieved over those 10 years were impressive: rapidly increasing number of patients receiving ART in LMIC, from 0.7 million in 2004 to 6.6 millions in 2010 [6,7]; wide decentralization of care, with services extended from urban settings to increasingly remote rural areas, where it is estimated that 22 400 medical centres currently offer ART [6,7]; dramatic reduction in morbidity and mortality in people receiving ART [6,7]; reduction of the cost of antiretroviral drugs, related to the availability of generics as well as to international financial mobilization, which allows access to free ART in the majority of LMIC [6,7]. However, these successes should not hide existing failures and difficulties faced in consolidating these results as well as in scaling them up in the long term. The objective of this paper is to examine these challenges.

First challenge: ensuring long-term financing

Dependence on international assistance is the Achilles heel of the fight against HIV in LMIC where half of this funding is provided by external international donors, including the ''US President's Emergency Plan for AIDS Relief'', the Global Fund to fight AIDS, Tuberculosis and Malaria, UNITAID and others. If one only considers low-income countries, this share of international donors' funding reaches 88% [6,7]. This reality is of great concern considering the following observations: (1) a persistent gap between

estimated needs and the resources actually available: resources allocated to the fight against HIV in LMIC in 2010 were US$ 15 billion with needs estimated at US$ 24 billion [6,7]; (2) a decrease in international aid in 2010 compared to 2009 and 2008, whereas it had previously increased every year since 2004 [6,7]; (3) the recent plans by the Global Fund to Fight AIDS, Tuberculosis and Malaria to replace its next call for country proposals (Round 11) with a new transitional funding mechanism, making new funding available only in 2014 [8].

Governments of LMIC, for their part, have announced efforts which are, however, struggling to take shape on the ground. There is, therefore, a double challenge for the years ahead: (1) to further increase available resources in order to fill the gap and to meet the increasing needs and (2) to redistribute the overall budget in a concerted and progressive way amongst donors. If one stakeholder stabilizes or decreases its share whilst the other does not increase his/hers, the gap between needs and resources will continue to increase and the success of the decade 2000 will not be confirmed in the next decade [9–10].

Second challenge: increasing ART coverage

Only 47% of patients requiring ART in LMIC according to WHO 2010 criteria had initiated this treatment at the end of 2010, therefore, excluding nearly one out of two eligible persons from life-saving treatment [6,7].

These estimates hide wide regional and in-country variations in the percentage of those in need of ART who actually initiated treatment: 10% in North Africa and the Middle East; 30% in Western and Central Africa; and 56% in eastern and southern Africa, including 55% in South Africa and 93% in Botswana [6,7]. This disparity illustrates two facts: (1) universal treatment is a realistic goal, since some low-income countries heavily affected by the HIV epidemic have reached or are about to reach this goal; (2) treatment coverage rate is a complex phenomenon where both funding and socio-political climate (national and international) play important roles.

Universal access to ART may not only be cost-effective, but also cost-saving. Controlling the virus at the individual level not only decreases mortality: it also decreases HIV transmission [11], thus leading to dramatically decrease the need for new treatments [6,7,12,13].

Third challenge: decreasing early mortality on ART

Cumulative mortality at 12 months in adults initiating ART in low-income countries ranges between 8% and 26% [14,15], a much higher rate than that observed in high-income countries. The most frequently reported specific causes of death include tuberculosis, severe bacterial diseases and cryptococcal meningitis, suggesting that most of these deaths could be avoided [14,16–18]. The main factors associated with a risk of early mortality are immuno-suppression, late-stage disease, presence of active tuberculosis when ART is initiated, male gender, anaemia, low Body Mass Index, positivity to serum cryptococcal antigen and having to pay for treatment [14].

Two messages may be drawn from this data:

(1) Expanding case finding for tuberculosis, invasive bacterial diseases and cryptococcosis and integrating care for these diseases within HIV care are key to reducing early mortality on ART [19–24].

As for diseases prevention, this is the place to remind us of two points: first, although the effectiveness of tuberculosis chemoprophylaxis has been clearly established, this intervention is still very seldom applied [24]. Second, cotrimoxazole prophylaxis has proven efficacy against invasive bacterial diseases [25,26].

(2) Early initiation of ART – that is with higher CD4 counts or less advanced clinical stage – could reduce initial mortality, regardless of local conditions of access to diagnosis and treatment of concurrent diseases [11,21,23].

One could argue that it is precisely where conditions for access to diagnosis and treatment of concurrent conditions are bad that earlier start of ART is most necessary to avoid early death, as is, for example, the case in rural areas and in poor settings with limited healthcare facilities [27].

Fourth challenge: moving on from WHO 2006 to WHO 2010 guidelines

In 2010, the revision of WHO guidelines on ART for HIV Infection in adults and adolescents led to experts' agreement over three major decisions: raising the cut-off point for starting ART, stopping stavudine and using viral load in routine monitoring [28]. These recommendations are scientifically indisputable, and could have been made earlier considering standards of care applied in rich countries. The problem, therefore, is not related to the evidence sustaining the recommendations but lies with their application on the ground: from international conference rooms to the field realities change, and sometimes motivations too.

Earlier start of ART

The 2010 WHO guidelines recommend that all adolescents and adults with HIV infection and CD4 counts $\leq$350 cells/mm^3 should be started on ART similarly to those with WHO clinical stage 3 or 4. Previous WHO guidance was to start ART at CD4 counts $<$200 cells/mm^3 irrespective of the clinical stage, at WHO clinical stage 4 irrespective of the CD4 count, or with 200 to 350 cells/mm^3 and WHO clinical stage 3.

An earlier start of ART has clear advantages in terms of reducing morbidity and mortality as well as in preventing HIV transmission [11,21,29,30].

However, early initiation of ART raises two questions:

(1) How can HIV-positive persons be identified early – i.e. when their CD4 counts are still relatively high – in order to treat them earlier? The current mean pre-ART CD4 count in LMIC is close to 150/mm^3 [31], and is not only related to HIV screening which occurs way too late but also to weak linkages in the continuum of care of people who have been tested for HIV infection [31,32]. Causes of late screening include insufficient willingness from clients to undergo voluntary testing [33], reluctance from caregivers to offer the test [32,34] and/or an offer of the test often mostly directed at symptomatic individuals [32]. Changing paradigm, adopting an opt-out approach, facilitating pro-active testing,

targeting not only symptomatic ones, but also asymptomatic patients (''target HIV-negative to find HIV-positive''), making rapid tests available and finally making HIV testing every healthcare professional's business – and not HIV specialists' one – are the necessary steps for active case finding of people requiring ART treatment without waiting for them to become too ill [32,35].

(2) How can we succeed in early initiation of ART and at the same time adequately respond to increasing ART coverage rates for people in the most advanced stages of disease? First of all, by being aware of the workload involved with changed recommendations. For example, stakeholders in Uganda estimated a 60% increase in health-seeking behaviour as a result of the adoption of the new WHO guidelines [36]. Task shifting from doctors to nurses prescribing ART is one solution whose effectiveness has been demonstrated [37]. However, increases in staff recruitments among paramedics is also imperative: nurses, social workers, counsellors 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 centre per day [38].

Stop using stavudine and identify the best first-line regimen

Although evidence that stavudine is more toxic than zidovudine or tenofovir and should be removed from routine prescriptions is strong [39], its application at field level remains challenging. In late 2009, 30 countries had implemented a plan to phase stavudine out yet 60% of first-line ART regimens in LMIC were still based on stavudine [6,7]. The main reason for continued stavudine use is budget constraints since first-line stavudine-based ART combinations cost two to three times less than those based on zidovudine or tenofovir [40]. We, therefore, witness a perfect vicious circle: ART coverage is low, funding needs are growing, international aid decrease and we know that we must abandon the cheapest antiretroviral drug. To break the circle there are two solutions: acting for a drastic reduction in the costs of other drugs [41]; and demonstrate cost-effectiveness of non-stavudine-based regimens to donors and policy-makers [42,43]. When stavudine is withdrawn, recommended first line ART include zidovudine, tenofovir, 3TC/FTC, nevirapine and efavirenz [28]. The choice of one specific drugs versus another primarily depends on tolerance: hematologic and renal toxicity guiding the choice between zidovudine and tenofovir; and skin toxicity, hepatotoxicity, fetotoxicity and interaction with rifampicin guiding the choice between efavirenz and nevirapine [44–46]. In recent years, evidence was specifically lacking in relation to the renal toxicity of tenofovir in a context of high prevalence of chronic kidney disease [47,48], as well as on efavirenz' fetotoxicity. There is now stronger evidence on tenofovir's use in LMIC which clearly shows that (1) renal toxicity exists, justifying existing recommendations on monitoring creatinine clearance and/or dipstick screening for proteinuria [28]; (2) only a small percentage of patients exposed to tenofovir for at least 12 months developed severe renal intolerance, which does not make this drug more toxic than zidovudine, abacavir or nevirapine [28,49–51]. The real kidney killer in HIV infected adults d in LMIC is, therefore, HIV itself, not tenofovir [47]. There is still suspicion of superimposed fetotoxicity linked with efavirenz and no data from large scale studies are yet available although evidence from small studies seems reassuring [52,53]. In the absence of hard data, balancing superimposed fetotoxicity with clinical benefits in comparing efavirenz with nevirapine remains challenging, and the option to only offer efavirenz to women using contraception is of difficult application in the field [51,54,55].

Ensure availability of plasma HIV-1 RNA testing

Measurement of plasma viral load in routine monitoring and diagnosis of treatment failure is only available to a minority of patients [6,7,56]. Arguments in support of a wide access to viral load testing include the following: (1) in the first 12 months of treatment, 30–50% of people diagnosed with virological failure have not yet selected a resistance to specific antiretroviral drugs [57,58].

Early diagnosis of treatment failure can, therefore, support strategies for treatment adherence, and transform treatment failure into successful treatment prior to the establishment of a resistance [59]; (2) the currently practiced diagnosis of treatment failure based on immuno-clinical results is responsible for excess switches in treatment regimens since its specificity is low [60,61]; generalizing viral load measurements would, therefore, prevent unnecessary decisions to switch to second-line regimens [58,62]; (3) virological failure precedes immuno-clinical failure; using immuno-clinical criteria for switching treatment regimens implies continuation of ineffective treatment for a longer period of time and, therefore, an accumulation of nucleosides reverse transcriptase inhibitors (NRTI) resistance which affects the remainant choices for NRTI use in second-line regimens [62]; (4) existing cost-effectiveness models suggest that monitoring viral load in routine may be cost-effective [63]. Although cost-effective, plasma viral load comes with a cost. Similarly to the case made for antiretroviral drugs, if the revised 2010 WHO guidelines are not to remain wishful thinking, a real mobilization for lower prices of reagents and equipment needed to measure viral load is clearly necessary. Technological and logistical challenges linked to viral load testing make its decentralization complex, especially in rural areas and based on previous experience with CD4 counts few years ago, efforts in relation to point-of-care automation, and to maintenance will be key [64,65].

Second-line regimens: we must do better now

In 2009, only 1.4–5.2% of adults receiving ART in LMIC were on second-line antiretroviral therapy [6,7,41], a figure well below what one would expect more than five years into the implementation of large international ART programmes [41]. Second-line regimens are clearly under prescribed, and, at the time we wrote this paper, hundreds of thousands of patients have already failed first-line ART without receiving adequate second-line treatment. There are two main reasons for this: (1) the inability to measure viral load: one can decide to switch to second-line regimens on the basis of clinical or immune-clinical criteria [28]; however, prescribers are suspicious of these criteria and rightly question their reliability. In a context where the availability of second-line treatment

is in itself uncertain and finding the second-line treatment often requires important efforts, uncertainty in the diagnosis of treatment failure is a discouraging element for prescribers [6,7,58,66]; (2) second-line regimens are still 4–5 times more expensive than first line ones [41].

Second-line regimens recommended by the WHO include protease inhibitors: ritonavir-boosted atazanavir as first choice but ritonavir-boosted lopinavir remaining a valid option too [28].

Heat-resistant lopinavir/ritonavir dry-tablets remain the most commonly prescribed protease inhibitors in second-line regimens. In the absence of genotypic testing and considering the amount of time spent under a failing first-line regimen, optimizing the choice of the NRTI backbone associated with the protease inhibitor remains a challenge [67,68].

It is highly likely that many second-line treatments currently offered in LMIC are sub-optimal in relation to an NRTI backbone which is not coherent with the resistance profile [66–71].

Evaluations of second-line treatment in LMIC are presently very rare [59,67,70,72], a pressing gap to fill.

Third-line regimens: an uneasy but necessary step

Similarly to second-line regimens, needs for third-line regimens are expected to grow and will be closely related to the monitoring of second-line regimens. Therefore, the challenges documented above – access to routine viral load and genotypic testing as well as of course, cost – will be faced with third-line regimens as they presently are with second line ones [40].

Designing and implementing specific studies in relation to third-line regimens – needs assessment studies, efficacy, resistance and tolerance studies; and feasibility of multi-level modification of treatment without the guidance of viral loads and resistance testing – are, therefore, an important priorities [28]. The WHO guidelines recommend ritonavir-boosted darunavir, raltegravir or etravirine as third-line regimens [28]. At current prices, their cost would be 8 to 10 times that of second-line regimens [40]. Again, depending on resistances previously accumulated, the choice of drugs for the NRTI backbone will be difficult. Moreover, resistance to new drugs is a particular challenge for third-line regimens: resistance to etravirine could be more frequent than expected in settings where patients remain with non nucleosides reverse transcriptase inhibitors (NNRTI)-based potentially failing first-line regimens for long period of time [73]; resistance to protease inhibitors, although potentially less frequent, could be an important issue in view of recycling protease inhibitors and saving darunavir [73].

Fifth challenge: reducing lost-to-follow-up rates

Lost-to-follow-up rates in large ART programmes are very high [74–77].

These figures mask a mixture of unaccounted deaths as well as drop-outs or prolonged interruptions of treatment [78,79]. There is great heterogeneity in treatment retention from one region to another, but also from one country to another and even from one centre to another, suggesting that poorly performing centres could learn from better performing ones [80]. Determinants of treatment retention are complex and multi-factorial. Some factors are individual, and their inclusion will require highly individualized interventions [81,82].

We here intend to insist on potential areas of work for collective action on treatment retention Access to free ART is one such crucial area [83], and a growing number of countries have clearly taken this into account [6,7]. But once the ARV drugs became free, cost of care became more visible. Recent studies show that in households with at least one member infected with HIV, healthcare costs often represent a catastrophic percentage of the household budget, with more than half of these health costs directed at the diagnosis and treatment of concurrent morbidity events (opportunistic diseases, drug toxicity, etc.) [84,85].

Transportation from home to the health centres is another important financial burden linked with care [84,85]. It is very likely that this heavy financial burden on households eventually affects the health of the household's HIV-infected member, and that supporting households in facing the costs of care other than ART would benefit mortality outcomes. A second area of work for collective action on treatment retention is addressing the human resources for health crisis. Trained and experienced human resources are often recruited by international organizations or NGOs offering more attractive salaries. They often migrate to richer countries [86], or participate in multiple training sessions where per diems are offered (''perdiemitis'' is the terminology recently coined on this phenomenon) [87] but where staff is taken away from patients and places of care. High staff turnover and the resulting increase in remaining staff's workload do not facilitate the retention of patients.

Sixth challenge: long-term management of successful ART

Despite the important challenges outlined in previous sections of this article, the majority of the millions of people started on ART since 2004 are now happily alive on successful treatment. For these people, managing lifelong treatment and care including long-term drug toxicity, residual HIV-related morbidity (particularly tuberculosis and bacterial diseases) as well as additional chronic concerns such as cardiovascular diseases, cancers, co-infections (particularly HBV and HCV) and aging [44,88–91] is a clear challenge. In sub-Saharan Africa, 14% of HIV-infected adults are older than 50 [92,93]. Aging with HIV requires the diagnosis and treatment of cardiovascular, metabolic, neurological, bone diseases and malignancies [94], which requires resources often considered unrealistic for LMIC. Let us, however, remind ourselves that 20 years ago, access to ART for patients in LMIC was also considered unrealistic; and that all efforts made to support the management of HIV-related illnesses will contribute to organizing and pulling up the entire system of care.

Seventh challenge: copying with unforeseen events

Low- and middle-income countries (LMIC) face crises caused by natural disasters (earthquakes, floods or drought) [95] or by socio-political events more often than rich countries do.

In a very short period of time, these crises can greatly impact results which took 15 or 20 years to achieve. For natural disasters which cannot be prevented, emergency response mechanisms must ensure continuity in the supply of medicines and the swift re-establishment of an abruptly interrupted care system [95]. Those responsible for socio-political crises should be held accountable. Justice must prevail against those who exploit patients as political weapons and thereby undermine years of human rights progress. Much has been said and written about the need to treat as war crimes all failures to protect civilians during conflict. Obstructing access to needed medical care should rank high among these [96].

Conclusions

An old African proverb states that the growth of a deep-rooted tree cannot be stopped. Our tree – representing care and support for people living with HIV in LMIC – is well rooted in existing field experience and is, therefore, expected to grow. The complexity of the challenges we face is directly related to our successes. The easiness and speed with which we identify these challenges is linked with increasing opportunities to deepen and share experiences [97]. Effectiveness and cost-effectiveness considerations, and a long-term cost saving approach, should replace the current short-term budgeting approach if the real challenges are to be effectively tackled.

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Competing interests
The authors do not have any commercial or other associations that pose a conflict of interest.

Authors' contributions
SPE, FEA, ISO, and XA wrote the paper; ISO contributed to the writing of the manuscript.

Abbreviations
ART, antiretroviral treatment; LMIC, low-and middle-income countries.

Acknowledgement
The authors warmly thank Dr Fatou Mbow for her great help with the English language as well for her careful editing of the manuscript.

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