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Strategies to Optimize HIV Treatment Outcomes in Resource-Limited Settings

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Abstract

Although the availability of antiretroviral therapy has increased rapidly to reach over three million people in low- and middle-income countries, coverage remains low as only 31% of people in need were receiving antiretroviral therapy in sub-Saharan Africa. Antiretroviral therapy scale-up needs to continue to grow exponentially to meet the need for universal access and keep pace with or exceed the new HIV infections. This calls for strategies that will have the greatest impact on the reduction of opportunistic infections, toxicities, and early mortality after antiretroviral therapy initiation as well improve adherence, clinical, immunological, and virologic responses, patient retention in antiretroviral therapy programs, and overall quality of life of people living with HIV/AIDS. Expanding antiretroviral therapy to all those eligible requires evidence-based decisions about how, when, and where expansion should occur.

In this article we highlight some of the strategies that have optimized HIV treatment outcomes within the constraints of limited resources in sub-Saharan Africa.

Key strategies to optimize HIV treatment outcomes include, i) scaling up HIV testing to identify all in need of HIV treatment, ii) strengthening the links between HIV diagnosis and comprehensive HIV/AIDS care, iii) timely initiation of antiretroviral therapy, iv) optimal diagnosis and treatment of opportunistic infections and comorbidities, v) investing in laboratory tests to support clinical monitoring of patients on antiretroviral therapy, vi) maximizing adherence to antiretroviral medication and retention of patients in HIV/AIDS care, viii) improving the health infrastructure, and increasing the human resources to handle the growing numbers of people in need of HIV treatment. **(AIDS Rev. 2009;11:179-89)**

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Introduction

Since the launch of the "3 by 5" initiative by the World Health Organisation (WHO) in 2003, the number of patients on antiretroviral therapy (ART) has increased rapidly in sub-Saharan Africa. Antiretroviral therapy was reaching over three million people in low- and middle-income countries at end of 2007, a tenfold increase during the previous six years. Despite progress, ART coverage remains low as only 31% of people in need were receiving ART in sub-Saharan Africa by the end of 2007[1]. Antiretroviral therapy scale-up needs to continue to grow exponentially to meet the need for universal access and keep pace with or exceed the new HIV infections. This calls for strategies that will have the greatest impact on the reduction of opportunistic infections, toxicities, and early mortality after ART initiation as well improving adherence, clinical, immunological, and virologic responses, patient retention in ART programs, and overall quality of life of people living with HIV/AIDS (PLWA).

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Antiretroviral therapy has had a dramatic impact on mortality rates among those infected with HIV in both the developed[2,3] and developing world[4-6] with comparable rates of adherence and virologic suppression. However, individuals continue to die as a result of late presentation (Table 1) and delayed uptake of ART[7,8]. In addition, many patients continue to have undiagnosed HIV disease; only 10% of the adult population in sub-Saharan Africa is aware of their HIV serostatus. There is a need for innovative and evidence-based models of care to inform decisions about how, when, and where the expansion of HIV treatment should occur and to penetrate the hard to reach populations.

The effectiveness of HIV treatment could be affected by several factors that include (i) patients often starting ART with advanced HIV infection, e.g. CD4 T-cell counts < 100 cells/μl)[1], (ii) a high prevalence of coinfections, including tuberculosis, cryptococcal meningitis, and bacterial diseases, and difficulties to diagnose and treat these conditions[9,10], (iii) interruptions in HIV treatment[11-13], and (iv) limited laboratory facilities to conduct tests such as CD4 T-cell counts and viral loads that are essential in monitoring the efficacy and safety of antiretroviral treatment[14,15].

In this article we highlight some of the strategies that are able to optimize HIV treatment outcomes within the constraints of limited resources in sub-Saharan Africa. We consider issues related to access to HIV testing, initiation of HIV treatment for all in need of it, choice of first-line ART regimens, and integration of management of opportunistic infections into HIV treatment programs. We also highlight the important aspects in the follow-up of patients on HIV treatment that include clinical and laboratory monitoring of individuals on ART, immune reconstitution inflammatory syndrome (IRIS), retention of patients in HIV/AIDS care programs, adherence to medication, and HIV prevention among PLWA. We do not review the healthcare system issues that include HIV/AIDS care in the work place, community education, health workers' motivation and attitude, logistics of procurement and management, and training as well as task sharing in HIV care.

Early HIV diagnosis and linkage to comprehensive HIV care

Despite the widespread availability of voluntary counseling and testing centers in sub-Saharan Africa, the unmet need for HIV testing is great. Only 10% of adults in sub-Saharan Africa know their HIV serostatus[16]. In Uganda, data from a national sero-behavioral survey showed that only 15% of the adult population is aware of their HIV serostatus[17]. Most people living with HIV remain undiagnosed and lack opportunities to access adequate prevention, treatment, care, and support services. Lack of routine HIV testing in hospital settings has contributed to this gap since many patients are treated and discharged from health units with undiagnosed HIV infections[18]. Until recently, most low- and middle-income countries used a client-initiated approach to HIV testing and counseling through stand-alone facilities, facilities integrated in health settings, mobile services, and community-based settings. However, evidence indicates that the uptake of client-initiated approaches has remained largely limited due to reasons such as fear, stigma, underestimation of personal risk, negative reactions to disclosure, limited access to treatment and care services, and gender inequality[16]. HIV testing has expanded as a result of innovative approaches including home-based testing, which provides the HIV test, test results, and counseling services to people in their homes[19,20]. With the availability of ART, countries should adopt innovative ways like routine HIV testing to scale-up HIV testing, the gateway to treatment and prevention (Table 2).

High acceptance rates of routine HIV testing (> 90%) have been documented in two large hospitals in Uganda where HIV testing and counseling is routinely offered free of charge[21,22], and the use of rapid tests has increased the proportion of tested people who receive their test results within 30 minutes of testing[23]. In a hospital setting, routine HIV testing was shown to identify over 70% of the patients in need of ART that had not yet received any specific HIV/AIDS care[23]. Therefore, strategies to increase HIV diagnoses must be coupled with increased opportunities for timely linkage to HIV treatment.

Similarly, early diagnosis is particularly crucial for pregnant mothers in order to reduce new infections through prevention of mother-to-child transmission (PMTCT) interventions, as well as identification of the HIV-infected mothers and infants in need of HIV treatment. However, despite the improved quality and access to PMTCT interventions in Africa[24-28], only 4-12% of HIV-positive mothers access PMTCT services[29,30], and continuity of comprehensive HIV/AIDS care, for both the mother and baby, beyond the peripartum PMTCT interventions is limited. One-third of the mothers that receive perinatal PMTCT interventions

Table 1. A summary of studies showing the benefits of ART in sub-Saharan Africa

Author and year	Study description	Baseline CD4 counts (cells/μl)/ WHO Stage of HIV disease	Outcomes
Lawn, et al. 2009	Prospective observational cohort of 2,423 patients on ART in South Africa Follow-up: 5 years	Median baseline CD4 cell count 101 (48-157) cells/μl; 104 (52-159) for survivors and 104 (52-159) for deaths 77% WHO clinical stage 3 & 4 for survivors and 83% for deaths	Patients with baseline CD4 cell counts < 100 cells/μl had much higher cumulative mortality estimates at 1 and 4 years (11.6 and 16.7%) compared with those of patients with baseline counts of at least 100 cells/ul (5.2 and 9.5%).
Bussmann, et al. 2008	Prospective observational cohort of 633 patients on ART in Botswana Follow-up: 5 years	Median CD4 cell count of 67 (28-127) cells/μl 81% WHO clinical stage 3 & 4	Median CD4 cell count increases were 169, 302, and 337 cells/μl at 1, 3, and 5 years, respectively. The percentages of patients with viral suppression at 1, 3, and 5 years were 91.3, 90.1, and 98.3%, respectively. Low mortality among those surviving into the second year of ART.
Marazzi, et al. 2008	Retrospective cohort of 3,456 patients on ART for > 6 months in outpatient HIV clinics in Mozambique, Malawi and Tanzania Follow-up: 1 year	Median CD4 166 (80-256) cells/μl 62% CD4 < 200 cells/μl 72% WHO clinical stage 3 & 4	16.4 deaths/100 person-years in the first 3 months to 1.34 deaths/100 person-years. 93% of deaths had CD4 < 200 cells/μl.
Moore, et al. 2007	Prospective cohort of 1,044 patients initiating ART in Uganda Follow-up: 1.4 years	Median CD4 127 cells/μl 84% < 200 cells/μl	17.9 deaths/100 person-years among patients with TB. 3.8/100 person-years among those without TB. ART resulted in a 61% reduction of TB incidence and 52% reduction in TB-associated mortality after the first 6 months of therapy.
Ferradini, et al. 2006	Prospective observational cohort of 1,308 patients initiating ART in Malawi Follow-up: 8.3 months	21% had CD4 < 200 cells/μl 27% had WHO stage IV	19% died. Median CD4 gain was 165 (67-259) cells/μl.
Lawn, et al. 2005	Prospective community-based ART cohort of 712 patients in South Africa Follow-up: 1 year	Median CD4 94 cells/μl	Mortality reduced from 35.6 deaths/100 person years (pre-ART) to 2.5 deaths/100 person-years (post-ART).
Palella, et al. 2006	Prospective multicenter observational cohort of 6,945 patients from 12 outpatient clinics in the USA Follow-up: 8 years	71% of those who died had CD4 < 200 cells/μl	Mortality fell from 7.0/100 person-years in 1996 to 1.3/100 person-years in 2004; AIDS related deaths fell from 3.79/100 person-years to 0.32/100 person-years. Mean CD4 closest to death rose from 42 in 1996 to 130 in 2004.
Crum, et al. 2006	4,241 patients from a prospective continuous enrollment cohort in the USA Follow-up: 13 years	Median CD4 count 122 cells/μl	93% of death had CD4 < 200 cells/μl in pre-ART era; fell to 77% in early ART era (first 2 years); fell to 61% in late ART era (year 2-4). Median CD4 count prior to death rose from 122 to 316 cells/μl.

ART: antiretroviral therapy; TB: tuberculosis.

Table 2. Summary of the key strategies to optimize HIV treatment outcomes in resource-limited settings

Scale-up HIV testing in various settings
- Routine HIV testing in hospital settings.
- Community-based models of HIV testing.
- Family-based approach to HIV testing.

Active linkage of HIV-positive individuals to comprehensive HIV care
- Provide the basic care package at HIV testing sites i.e. co-trimoxazole prophylaxis, safe drinking water, insecticide-treated bed nets, condoms, counseling HIV testing for other family members.
- Routine assessment for ART eligibility for all HIV- positive individuals.
- Integration of HIV treatment into routine medical care.

Improve diagnosis and treatment opportunistic infections
- Routine screening for tuberculosis and cryptococcal meningitis.
- Increase availability of drugs for treatment of opportunistic infections.

Early initiation of ART
- Reduce the numbers of patients eligible for ART but not receiving it (ART waiting lists).
- Integrate treatment of comorbidities with ART.

Reduce early mortality on ART
- Active screening and management of opportunistic infections.
- Improve diagnosis and management of immune reconstitution inflammatory syndrome (IRIS).
- Active monitoring for toxicities.
- Better tracking systems for patients in HIV care (ART and non-ART patients).

Follow-up of patients on ART
- Combine clinical and laboratory monitoring.
- Minimize treatment interruptions.
- On-going adherence support through health facility and community based approaches.
- Maximize the time spent on first-line regimen.

Integrate prevention in HIV care programs
- Prevention with positives.
- Scale-up access and utilization of prevention of mother-to-child transmission.

Research to provide evidence-based models of HIV/AIDS care

Continued lobbying for funding for HIV/AIDS care both nationally and globally

ART: antiretroviral therapy.

return for continued HIV care[31,32], hence the need to strengthen the linkage of HIV-infected mothers and their children to HIV/AIDS care following the peripartum PMTCT interventions. Therefore, in order to optimize HIV treatment in resource-limited settings, there is a need to integrate HIV testing and ART into routine healthcare, including antenatal care, care for sexually transmitted infections, hospitalization, and general primary care. For late-presenting women, effective strategies to allow safe prolonged breastfeeding include: starting extended infant prophylaxis at birth, rapid identification of women with low CD4 counts, and initiation of ART postpartum as soon as possible, continuing infant prophylaxis for women who do not need ART, bearing in mind the challenges of starting ART in pregnant mothers with CD4 counts above 350 when nevirapine is toxic and efavirenz is not recommended[33]. In addition, creating "one-stop centers" for mothers to provide HIV testing, opportunistic infection prophylaxis and treatment, ART, maternal child health, and general medical care is a strategy that will ensure active linkage to comprehensive HIV care in order to minimize the delays and the lack of continuity caused by repeated appointments for parallel services.

Rapid entry into HIV treatment programs

Despite the rapid scale-up of HIV treatment in the last five years, patients continue to die due to delayed diagnosis of HIV infection coupled with delayed initiation of ART within HIV care programs[7,34]. Optimizing HIV treatment requires active linkage of individuals to comprehensive HIV treatment including ART. In Uganda, about 60% of patients died within three months following discharge from hospital if they were not initiated on ART[18], mainly because they did not honor the referrals to HIV treatment. High mortality

rates are reported among individuals enrolled into care that are awaiting ART as well as those elsewhere in the healthcare system awaiting referral to HIV treatment services[35]. In South Africa, 67-87% of the in-program deaths occurred during the interval between enrollment and initiation of ART, and were due to the difficulties in diagnosis and treatment of comorbidities during advanced HIV disease, delays in referral, and the time taken to prepare patients for the life-long treatment[36,37]. These data imply that identification and treatment of patients earlier in the course of their illness, coupled with the timely use of ART, could improve survival and quality of life of PLWA in resource-limited settings. The basic HIV care package, that includes co-trimoxazole prophylaxis, use of safe water, insecticide-treated bed nets, and condoms, has improved the survival of HIV patients prior to initiation of ART[20,38,39]. Therefore, healthcare workers need to offer the basic HIV care package as soon as patients are diagnosed with HIV disease, and they must be equipped with the clinical skills to determine eligibility for ART at the first contact with an HIV-infected patient[23,40]. In addition, there is need for integration of HIV treatment with routine medical care for hospitalized patients in order to minimize the delays caused by referrals to parallel HIV treatment programs.

Timely initiation of antiretroviral therapy

Early HIV diagnosis that is linked to active follow-up (using CD4 counts) and timely initiation of ART will maximize the impact of HIV treatment in resource-limited settings[41]. In Uganda, about one million people are infected with HIV, at a prevalence of 7% of all adults aged 15-49 years. There were 140,000 individuals on ART by the end of 2008, which constitutes about 45% of those who need it (based on a cutoff of CD4 of 200 cells/μl)[42]. This is, however, an underestimation of the need for ART, considering the evidence that starting therapy earlier, among motivated patients, improves clinical outcomes. The WHO recommends initiation of ART at CD4 counts below 350 cells/μl, whereas the U.S. Department of Health and Human Services guidelines state that ART can be considered at any CD4 counts, depending on the patient's readiness, comorbidities, and likelihood of adherence[43].

At the in Infectious Diseases Clinic, that offers HIV care to over 20,000 patients, raising the CD4 cutoff for initiation of ART from 200 to 350 cells/μl will cause a threefold increase in the number of individuals that are eligible for ART[44]. This is similar to data from a mathematical model showing that frequent monitoring of patients in HIV care and the use of CD4 cutoff of 350 cells/μl will cause a threefold increase in the number of individuals eligible for ART and double the number of life-years saved compared to the model where symptomatic individuals are enrolled into ART programs to initiate ART[41] (Table 3). Similarly, for a country like Uganda, where an estimated 312,000 individuals required ART (using a cutoff of 200 cells/μl), raising the cutoff to 350 cells/μl increases those in need of ART to about 936,000 and drops the ART coverage from the estimated 45% by the end of 2008 to 15%. This has implications on the strategic plan for universal access for those in need of ART in resource-constrained settings.

Using the WHO recommendation of initiation of ART at WHO clinical stage 3 and 4, in areas where CD4 counts are not available, will miss about half of the patients who are classified as WHO stage 1 and 2, yet they have a CD4 count below 200 cells/μl and are already in need of ART[45,46]. There is therefore a need to increase the availability of CD4 testing among HIV care programs in sub-Saharan Africa in order to deliver HIV treatment to all in need of it[47]. We recommend both clinical and CD4 monitoring for all patients in HIV care in order to correctly identify all individuals that are eligible for ART and initiating the treatment in a timely fashion. However, adjusting the national guidelines for initiation of ART to match the WHO recommendations for initiation of ART should be done in a planned fashion since it will overstretch the current infrastructure for ART delivery.

Reduce early deaths during antiretroviral therapy

It is clear that ART has improved survival among PLWA (Table 1); however, patients continue to die soon after initiation of ART. In an observational database in the UK, about a fifth of all deaths among HIV patients in care occurred among individuals who had first been diagnosed with HIV within the six months prior to death[8]. The majority of patients in the developing world who present for ART have $CD4^+$ T-cell counts far below 200 cells/μl[48]. Most of these patients receive a diagnosis of HIV infection only when they present to the hospital with a life-threatening opportunistic infection[23,49]. Early mortality rates in sub-Saharan Africa are very high; 8-26% of patients on ART die within the first year

Table 3. Models of ART scale up strategies in sub-Saharan Africa

Author	Setting	Criteria for initiation of ART	Estimated number in need of ART	Key areas that require intervention
Hallet, et al. 2008	Model is based on data from Zimbabwe, Uganda, Ethiopia, & Cote d'Ivoire. Cohort of 1,000 hypothetical patients in Africa.	a) Symptomatic patients with CD4 < 350 cells/µl	25% will start ART and 6 life-years will be saved per person treated.	Low rates of HIV testing.
		b) Asymptomatic patients with CD4 counts < 200 cells/µl	3-times as many are expected to be treated and life-years saved increased to 15/patient treated.	Late entry into HIV/AIDS care programs.
Walensky, et al. 2008	Simulation model of HIV infection with South African data. Projected HIV-associated mortality with and without effective ART for an adult cohort in need of therapy (2007) and for adults who became eligible for treatment (2008–2012).	WHO stage 4 AIDS-defining illness and/or symptomatic disease with a CD4 < 200 cells/µl	Compared 5 scale-up scenarios: – Zero growth with 100,000 new Rx slots met 28% coverage. – Constant growth with 600,000 on ART met 52% coverage. – Moderate growth, with 2.1 M on ART met 97% coverage. – Rapid growth, with 2.4 M on ART met 100% coverage. – Full capacity, with 3.2 M.	Lack of access to CD4 monitoring was associated with increased deaths compared with similar scale-up scenarios where CD4 monitoring is available.

ART: antiretroviral therapy.

of antiretroviral treatment[12,36,49], with most deaths occurring in the first few months of treatment, and the leading causes of death include tuberculosis (TB), cryptococcal meningitis (CCM), acute sepsis, chronic diarrhea, and Kaposi's sarcoma[35,50,51]. There are few data to guide the timing of treatment of opportunistic infections versus the initiation of ART, even in industrialized countries. The general practice is to screen and treat active opportunistic infections before the initiation of ART to minimize risk of IRIS[14]. Tuberculosis is the most common serious opportunistic infection in sub-Saharan Africa, accounting for 11% of AIDS-related deaths[52] followed by CCM[35,51]. Screening for active TB and CCM is critical in all situations in which HIV is diagnosed, although concomitant initiation of ART is complicated by the simultaneous introduction of multiple drugs that increase the probability of drug intolerance/toxicity and adherence problems. Cryptococcal antigen screening before initiation of ART in patients with a CD4 cell count ≤ 100 cells/µl is highly effective for identifying those at risk of CCM and death, and might permit implementation of a targeted preemptive treatment strategy[53]. Therefore, strategies to reduce early mortality must include improved facilities for prevention, diagnosis, and treatment of opportunistic infections. Healthcare workers should be equipped with skills to manage severe late-stage HIV disease, assess for eligibility for HIV treatment, and initiate ART using up to date WHO and national guidelines. National HIV programs in resource-limited settings should be designed to minimize the time patients spend with CD4 cell counts less than 200 cells/µl, both before and during ART, to reduce the risk of early mortality on ART[50].

It has long been anticipated that with large numbers initiating ART in sub-Saharan Africa, IRIS would be a major problem because of the low CD4 cell count at ART initiation and the high underlying prevalence of infections such as *Mycobacterium tuberculosis*, and *Cryptococcus neoformans*. It is, however, reassuring that IRIS has not had a serious impact on the effectiveness of ART programs in resource-limited settings[54]. The majority of IRIS cases are mild and self-limiting with a low IRIS-attributable mortality[54-56]. Healthcare workers should be equipped with skills to evaluate patients, and prevent as well as manage IRIS, drug toxicities, and decision making to antiretroviral drug regimens.

Strengthen laboratory capacity to monitor patients on antiretroviral therapy

As more patients are initiated and maintained on ART, the need to monitor the efficacy and drug resistance patterns is essential to maintain the value of HIV treatment[57]. Without laboratory support, especially in rural settings, clinicians rely on clinical monitoring only, using symptoms and signs to indicate treatment failure or drug toxicity. In assessing treatment failure, clinicians should evaluate the treatment history, adherence, potential drug interactions, clinical evidence of failure, and available laboratory test results (CD4, viral load). Treatment failure should be considered only after ascertaining that poor response is not due to non-adherence. However, using clinical symptoms to assess treatment failure may be inaccurate, especially during the first 3-6 months of ART. Patients may develop symptoms of IRIS[58]. OIS may continue to appear because the patient is still immunocompromised, or an infection/re-infection by a common endemic pathogen such as TB or malaria. Similarly, in a patient who is not doing well clinically, with a decreasing $CD4^+$ T-cell count, it is often unclear whether the latter is due to intercurrent illness, HIV disease progression, or test variation. It is clear that viral load testing is more useful than CD4 counts in monitoring and making treatment decisions for patients on ART[57,59,60]. The CD4 counts, on the other hand, are more useful in making decisions on ART initiation[41].

Virologic monitoring is considered the ideal method for assessing the efficacy of an antiretroviral regimen since it directly assesses the effect of therapy, and virologic failure typically occurs before immunological or clinical failure[59]. Moreover, patients with virologic failure may progress to drug resistance prior to the development of illness. However, viral load testing is still unavailable and unaffordable in developing countries, and there are efforts to find less expensive ways to monitor efficacy of treatment[61,62]. Clinical algorithms have been developed to predict treatment failure in areas where testing of viral loads is unaffordable[63]; however, plans are needed for the development of local laboratory and technical capacity to monitor ART (including viral load and resistance testing)[57] (Table 2). There is a need for operational research to discover more cost-effective methods to deliver high-quality HIV care over the short and long term within the context of limited resources.

Maximize retention of patients in HIV care programs

Since the inception of large-scale ART access early in this decade, ART programs in Africa have retained about 60% of their patients at the end of two years, with loss to follow-up as the major cause of attrition, followed by death[64]. "Lost to follow-up" includes all categories of patients who miss scheduled clinic visits or medication pickups for a specified period of time. The percentage of patients lost to follow-up varies widely across programs and ranges from 3.7 to 44% in resource-limited settings[12,64,65]. Reasons for the high losses to follow-up include transport costs, drug stock-outs, toxicities, food challenges, pill burden, comorbidities, and psychosocial reasons like disclosure, stigma, and fatigue[66]. Unfortunately, most large-scale HIV treatment providers have few resources available to track missing patients[64]. There is a need to identify innovative methods to sustain the provision of long-term care for patients receiving comprehensive HIV care. Better patient tracing procedures, better understanding of loss to follow-up, and earlier initiation of ART to reduce mortality are needed if retention is to be improved. One of the strategies to improve continuity of HIV care is to decentralize the services and encourage patients to receive care at health facilities that are nearest to their homes in order to reduce transport costs. In addition, patients that initiate HIV care at tertiary centers should be transferred to their primary care facilities after stabilizing, and the referral system should be strengthened to refer them back for specialized care as required. Some programs have provided home-based care to enhance continuity of care, although it is an expensive model of care[20,38]. There is a need to evaluate the cost-effectiveness of the various models of HIV care, considering their impact on efficacy, adherence, and drug resistance. Programs that have achieved higher retention rates can serve as models for future improvements since long-term retention of patients in treatment programs is a prerequisite for achieving good adherence[64].

Maximize adherence to HIV treatment

Once initiated, continuity of HIV treatment is important in order to maximize the efficacy, prolong the period patients spend on the first-line ART regimen, and minimize the negative consequences of treatment interruption that include drug resistance and

treatment failure. Although the choice of first-line regimen is largely influenced by availability and affordability, it should take into consideration factors that have the potential to influence patients' adherence; for example comorbidities, pill burden, and the tolerability of the drugs. Currently, the initial treatment regimens that are widely used in resource-limited settings are: nonnucleoside reverse transcriptase inhibitor (NNRTI): efavirenz (EFV) or nevirapine (NVP) plus a nucleoside reverse transcriptase inhibitor (NRTI) backbone: stavudine (d4T) plus lamivudine (3TC) or zidovudine (ZDV) plus 3TC. These first-line regimens prolong life, have a low pill burden, and have the lowest cost at the present time. However, they are associated with drug toxicities that may be irreversible or lethal[67]. Using the fixed-dose combination (currently the least expensive regimen) of d4T/3TC/NVP poses a complication with regard to starting and stopping treatment. The recommended NVP dosing regimen starts with a lower lead-in dose of 200 mg once daily for two weeks, followed by 200 mg twice daily thereafter[68]. This is based on analyses suggesting that this regimen is less frequently associated with rash[69]. Starting a fixed-dose regimen of combination NNRTI-NRTI treatment without the "lead-in" dose of NVP may be associated with increased toxicity. In addition, NVP has a very long pharmacokinetic tail after discontinuation and a low genetic barrier to resistance. Therefore, stopping use of the fixed-dose combination without continuing the NRTI for an additional five days (lead-out) may lead to NNRTI resistance[70]. This poses a challenge to many ART programs that may not have the single-drug formulations of d4T/3TC that are required to 'lead-in' or 'lead-out' the patient on the fixed combinations. On the other hand, regimens that contain EFV should not be used by women at risk of pregnancy because of the teratogenic potential for the fetus[69]. Zidovudine, on the other hand, is not without problems; ZDV is associated with anemia, which may lead to blood transfusions and rarely to death[71]. Tenofovir (TDF) is co-formulated with emtricitabine (FTC; Truvada) and a single combination pill of EFV/TDF/FTC has been developed. This combination allows for the possibility of a one pill/day regimen, with the obvious potential for improved adherence, although its availability is still limited in resource-limited settings. There is data to suggest that select triple-NRTI regimens are simple to administer, have low pill burden, are associated with acceptable HIV RNA reductions and $CD4^+$ T-cell increases, are relatively safe, have fewer drug-drug interactions, and are less likely than NNRTI-containing regimens to cause antiretroviral drug resistance when treatment is interrupted[72]. These regimens may be good choices for patients with TB or in whom a preferred or alternative NNRTI- or PI-based regimen may be less desirable due to concerns about toxicity, drug interactions, or regimen complexity. Examples of triple-NRTI regimens include ZDV/3TC/TDF and ZDV/3TC/ABC. Therefore, ART programs should continue to lobby for regimens that will maximize adherence and minimize toxicities because patients with clinical AIDS who discontinue ART are likely die within a relatively short time[73]. In addition, patients should be informed about the symptoms of antiretroviral drug toxicities and should be aware of the need to seek care and/or to stop therapy in the interim if the need so arises.

Adherence should be reinforced by the entire ART team; doctors, pharmacists, nurses, and counselors should encourage patients to go through multiple adherence-counseling sessions before ART is initiated. Motivation sessions that include presentations by PLWA are particularly useful[14]. Other strategies to improve adherence include: (i) disclosure to spouse, which should be encouraged by testing as couples, (ii) fitting the dosing into a patient's routine, (iii) opting for simpler regimen (once/twice daily) to minimize the pill burden, (iv) using adherence aids such as pill boxes and telephone reminders, and (v) directly-observed therapy using a treatment supporter identified by the patient to motivate and ensure patient compliance with the ART regimen[14]. Follow-up of patients in their homes enables follow-up on adherence and provides an opportunity for family HIV testing and enrollment into HIV care[19,74]. Therefore, HIV/AIDS care programs need to invest in home visiting, especially for patients with adherence problems. Involvement of PLWA and community-based organizations has been used to support adherence and retention of PLWA in HIV care programs[14].

Combine HIV treatment and prevention

The correlation between HIV-1 RNA viral load and transmission has been well established[75] and one benefit of earlier treatment might be the reduction in new infections as a result of larger numbers of people with HIV having suppressed viral load. Analysis of HIV incidence in the Ugandan Home Based AIDS Care (HBAC) cohort showed that an estimated 90% reduction in new infections over three years, when compared with historical controls, was attributable to antiretroviral

therapy[76]. However, this benefit must be weighed against the potential risk of transmission of drug-resistant virus by patients failing therapy. In an adherent population, the benefits of early therapy outweigh the risks[43]. Furthermore, there is evidence that unsafe sex was reduced by 70% in HIV-positive individuals six months after initiation of ART in a prospective cohort study in rural Uganda[77]. Therefore, we recommend that follow-up of patients on HIV treatment should include counseling on HIV prevention practices, promote positive living, and empower PLWA networks to lead the prevention of HIV transmission (Table 2).

Similarly, the risk of mother-to-child transmission (MTCT) of HIV can be reduced to 2% through the combination of several preventive interventions: antiretroviral prophylaxis administered to women during pregnancy and labor and to infants during the first weeks of life, elective caesarean delivery, and the complete avoidance of breastfeeding[25,78]. However, within low-income countries that are able to deliver only a minimal range of antiretroviral drugs and where caesarean delivery is seldom feasible[79], the risk of MTCT HIV ranges from 25 to 48% in the populations that practice prolonged breastfeeding[80]. Thus the need to increase the availability and utilization of PMTCT services and further reduce MTCT that accounts for 95% of pediatric HIV disease[42].

Resources for scaling-up antiretroviral therapy programs in resource-limited settings

Donor dependency of most HIV/AIDS-related services raises concerns related to sustainability and predictability of 100% coverage and continuity of universal HIV care. Comprehensive treatment of opportunistic infections and other pathologies can consume a substantial part of overall resources for a national HIV/AIDS treatment program[81,82]. The costs of ART and management of opportunistic infections were estimated to consume 41-46% and 32-36% of the national HIV/AIDS program costs, respectively; moreover, often inpatient care for treatment of opportunistic infections is paid for by patients. In East Africa, the estimated annual costs of US$ 504 per ART patient and US$ 91 per non-ART are clearly unaffordable for patients in countries where 80% of the population have to live on less than US$ 2 a day[82,83]. There is a need to assess potential financing alternatives to donor funding in the foreseeable future. HIV care providers, patients, politicians, and policy makers should continue to lobby for funding for HIV/AIDS care both nationally and globally.

Conclusions

As we aim at universal access to HIV treatment in resource-limited settings, the key strategies to optimize HIV treatment outcomes include (i) scaling-up HIV testing to identify all in need of HIV treatment, (ii) strengthening the links between HIV diagnosis and comprehensive HIV/AIDS care, (iii) timely initiation of ART, (iv) optimal diagnosis and treatment of opportunistic infections and comorbidities, (v) investing in laboratory tests to support clinical monitoring of patients on ART, (vi) maximizing adherence to antiretroviral medication and retention of patients in HIV/AIDS care, (vii) exploring all potential funding alternatives to improve the healthcare infrastructure and increase the human resources to handle the growing numbers of people in need of HIV treatment. We recommend that HIV treatment programs should engage in operational research to identify and provide cost-effective evidence-based models of HIV care.

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