EXPERT REVIEWS

Interventions to reduce mortality in sub-Saharan Africa among HIV-infected adults not yet on antiretroviral therapy

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Where antiretroviral therapy is available, the primary source of mortality among HIV-infected people is the delay in starting treatment. Many of these delays occur in the context of care and are modifiable through changes in the protocols followed by healthcare providers for HIV testing, staging and preparation of patients for antiretroviral therapy. A number of potential evidence-based interventions are discussed in the context of sub-Saharan Africa. Included are decentralizing services, initiating counseling on antiretroviral therapy without delay, tracing patients that miss appointments, protecting patient confidentiality, reducing user fees, and providing point-of-care tests for CD4 cell counts, cryptococcal antigen, and for the diagnosis of TB.

Keywords: adherence • antiretroviral therapy • clinical staging • counseling • HIV • HIV testing • lost to follow-up • mortality • opportunistic infection • sub-Saharan Africa

HIV is one of the major causes of mortality in sub-Saharan Africa (sSA), responsible for 1.3 million deaths in 2009 [101]. Decreasing mortality should be addressed through a combination of interventions: HIV prevention, expanding testing, in particular provider initiated testing, antiretroviral treatment (ART), and the prevention and management of opportunistic infections (OIs), in particular TB. The period between HIV diagnosis and initiating ART is critical for the overall HIV program success [1–3]. More than two-thirds of people with a positive HIV test are estimated to be lost to follow-up (LTFU) temporarily or definitively during this time [4]. Delays starting ART increase mortality even in those not LTFU. People with a low CD4 cell count that defer ART prolong the period during which they are at increased risk of getting OIs or malignancies. When they do initiate ART it is at a lower CD4 cell count which is associated with a smaller chance of achieving viral suppression [5] and higher rates of ART side effects, including immune reconstitution inflammatory syndrome [6]. Delaying ART initiation as CD4 cell counts continue to decline below 350 cells/µl also increases the costs of medical care around the time of ART initiation [7]. In this paper we review opportunities for improving HIV care during this key period to reduce HIV-related adult deaths in sSA.

HIV testing & counseling

HIV testing in sSA is typically at the point of care (POC), with a combination of rapid tests. Only in certain situations is laboratory-based HIV testing required, for example, when the rapid test results are inconclusive, or when there is a suspicion of an HIV-2 infection. Following HIV diagnosis and clinical staging, ideally supplemented by CD4 cell count testing, care should include screening, prophylaxis, and treatment of OIs and other comorbidities, such as sexually transmitted infections [8]. At this point it is also essential to provide counseling that allows patients to understand their infection and its treatment to prepare them for optimal adherence to their antiviral regimen once such treatment is initiated. Specifics of each of these steps will vary by clinic and program; unnecessary delays in these processes should be avoided [3]. A generic overview of this period is provided in Figure 1, emphasizing two key strategic points: later care builds on earlier care,

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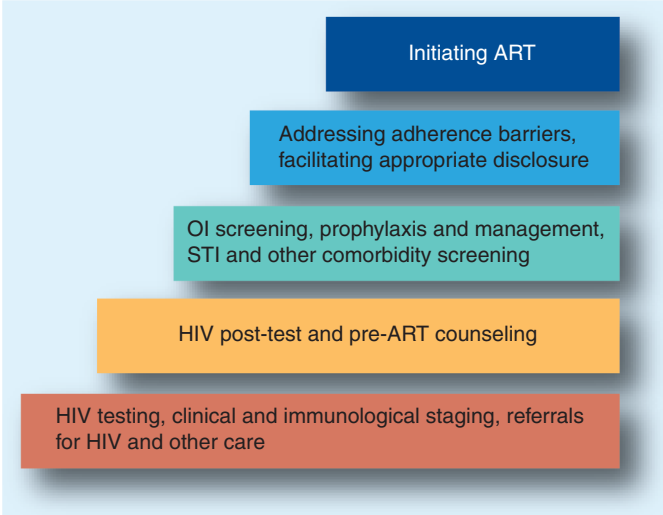

Figure 1. Building towards antiretroviral treatment.
ART: Antiretroviral treatment; OI: Opportunistic infection; STI: Sexually transmitted infection.

and access to ART is accelerated by simultaneously addressing multiple aspects of care.

CD4 cell count testing & clinical staging

Treatment eligibility is based on the individual's CD4 cell count and his or her current clinical status, as indicators for near-term risk of disease progression and HIV-related morbidity and mortality. From the perspective of increasing timely initiation of ART the primary role of CD4 cell counts is to permit those with WHO clinical Stage [9] 1 or 2 disease to receive ART if their CD4 cell count is found to be under the program's threshold for CD4 cell count-guided initiation. The WHO currently recommends a threshold of 350 cells/µl [9], and expanding access by adopting that guideline should be a priority for programs. All patients with WHO Stage 3 or 4 disease need ART and should be referred for pre-ART counseling without waiting for their CD4 cell count results. At a threshold of 350 cells/µl a large proportion of ART-eligible people will have minimal or no symptoms. To identify them will require expanding the use of CD4 cell count testing. This will require POC CD4 cell count rapid tests that do not require capital-intensive equipment. Such tests will also eliminate the delays arising from reliance on off-site laboratories. Several such tests have already been described [10–12]. POC CD4 cell counts should be done at the same time a person is having their HIV diagnosed, as this has been shown to reduce LTFU and accelerate ART initiation [4,13]. Key interventions to improve HIV testing and counseling procedures are summarized in Box 1.

Loss to follow-up

Delays between testing and ART initiation are associated with patients becoming LTFU [14], especially when their CD4 cell count is too high to qualify for ART in the short term [4,15,16]. For ART-ineligible patients, who should be regularly followed and reassessed for ART, provision of trimethoprim–sulfamethoxazole (TMP–SMX) appears to reduce LTFU [17]; medical indications for TMP–SMX prophylaxis are summarized later under the 'Opportunistic infections' section. A number of patient and program factors have been associated with LTFU. For patients these include male gender [16,18], limited knowledge about HIV treatment [19], reliance on traditional healers [19,20], and less perceived control over one's own healthcare and outcomes [21]. High costs to patients increase LTFU, regardless of patients' financial dependence on others to afford their care [20,22,23].

Task shifting may be one way to reduce the cost of care to the patient. Task shifting is the use of specifically trained staff to carry out functions traditionally performed by more extensively trained individuals, for example, having nurses provide routine care instead of doctors. Several studies have demonstrated the feasibility and challenges of this in HIV care in sSA [24]. Task shifting has the potential to reduce operating costs directly and permits more widely dispersed HIV care, thus reducing patient's travel and indirect costs as well.

At program level, low staff-to-patient ratios, lack of adherence support in the form of counseling, reminders, treatment supporters and so on, and not tracing pre-ART patients that miss their appointments are also associated with LTFU [25]. Although challenging where staffing levels are inadequate to workload, several recent reports suggest that appointment tracking is feasible and beneficial in sSA both with and without an electronic database [26,27].

Disclosure & LTFU

Fear of inadvertent disclosure of one's HIV status has been cited as a reason for LTFU, for example, by healthcare workers failing to maintain patient confidentiality [19,22]. Some LTFU and ART delay results from a requirement to disclose one's HIV status to a spouse and/or treatment supporter. Non-disclosure to spouses is associated with worse adherence [28,29], and requiring patients to disclose their HIV status to a treatment supporter and/or to their spouse/sexual partner(s) prior to accessing ART has been part of several successful programs [30,102]. Nonetheless, the evidence supporting mandatory disclosure is weak, while the hazard of delaying ART for required disclosure has been suggested by one study [18]. Risks and benefits of disclosure depend on the type/method of disclosure, community norms, gender, and a patient's dependence on others in order to be able to afford ART [31,32].

Specialization, integration & LTFU

HIV care is specialized in many parts of sSA, often supported by HIV-specific funding streams. In the USA specialized HIV care was superior to care by generalists relatively early in the HAART era, specifically with regards to the appropriateness of the prescribed ART combinations [33]. This may not apply in sSA where regimens are typically protocol driven [34] and where nurses and physician extenders have been shown to be similarly effective within defined practice limits. Moreover, care at specialty centers generally increases the distance patients must travel as well, creating a significant financial burden as mentioned above. Paradoxically, specialized HIV care within one's community may also be associated with increased rates of LTFU [35]. It is

conceivable that additional barriers to follow-up more than offset advantages of specially trained personnel [34], especially for individuals stabilized on ART with adequate immune reconstitution [36]. In comparing rural and urban HIV primary care, it appears that uptake is similar [37] and LTFU may be less [38].

Box 1. Key interventions to improve HIV testing and counseling procedures.

- Minimize interval between screening and provision of confirmatory test results.
- Initiate pre-ART counseling during post-test counseling and continue it in parallel with other care.
- Accelerate pre-ART counseling to reduce delays in ART initiation.
- Obtain CD4 cell counts in parallel with confirmatory testing.
- Implement surveillance for primary resistance.
- Screen/address adherence barriers.

ART: Antiretroviral treatment.

Communication, referral & LTFU

Individuals with an HIV infection enter healthcare through a variety of channels, including hospitals and diverse clinics, including antenatal, primary, sexually transmitted infection and TB clinics. Weak integration between specialist HIV units and other elements of the healthcare system contributes to poor outcomes through miscommunication and delays in care [39]. This has been specifically demonstrated in hospital [40], TB clinic [41] and peripheral care [42] settings. When patients are referred out for a specific form of care from another provider, this necessarily delays their receiving that care. When the patient being referred has not been instructed well on the importance of that care or lacks the means to access it, they may become LTFU, or as Lubega describes it 'lost in transition' [19]. Studies have repeatedly shown a benefit from additional counseling and testing at the point of first contact, whether that be for inpatients or patients with TB referred for HIV care, or patients with HIV referred for TB care [25,39,40,43]. More detailed guidance for monitoring and evaluation of TB–HIV program integration has been published by the WHO [44]. Mechanisms for integrating HIV care across multiple provider locations require negotiation among stakeholders at clinic, community, regional and national levels, and should target hospitals, TB clinics and antenatal programs. Where sufficient organizational capacity exists, systems for confirming referrals from either the referring, receiving, or both sites should further minimize LTFU. A summary of recommendations to reduce LTFU is given in **Box 2**.

Opportunistic infections

The incidence of selected OIs and their contributions to mortality in sSA has been reviewed elsewhere [45,46]. TB and cryptococcal meningitis management and prophylaxis with TMP–SMX, are the three areas where optimization of care is likely to have the greatest impact on mortality. Treatment of HSV-2 infection with oral aciclovir appears to slow HIV disease progression [47,48], however, it remains to be demonstrated that this will affect mortality [48]. Screening, prevention and management of other comorbidities are not reviewed here in detail.

TB

The most important OI in HIV-infected adults in sSA is TB [45,46], and the most important tool to screen for TB remains the clinical history. Every patient with HIV infection should be queried about key TB symptoms such as cough, fever, night sweats and weight loss [49,50].

In patients known to be HIV positive, with suspected pulmonary TB, the WHO recommends examination of sputum with a single Xpert® MTB/Rif diagnostic test [51,52]. Use of Xpert will reduce treatment delay in smear-negative pulmonary TB [53] and lead to rapid diagnosis of multidrug-resistant TB. More work needs to be done on the impact of Xpert testing on program costs, work flow and treatment outcomes in settings with diverse TB and multidrug-resistant TB prevalences. Its application to extrapulmonary TB also remains to be explored [52].

Where Xpert MTB/Rif diagnostic tests are unavailable, specimens should be stained for acid-fast bacteria and cultured. Yet even under ideal conditions staining has poor sensitivity (50% compared with culture in HIV-uninfected pulmonary TB [49]) and results from culture take too long. People infected with HIV often present with disseminated, life-threatening infections, and the decision to treat must often be made on clinical grounds [54]. As an example of a low threshold for presumptive treatment, a trial is currently underway of using weight loss alone (BMI <18) as the sole criteria for the diagnosis of TB in HIV-infected people with a CD4 cell count under 50 cells/µl [103].

The key to successful integration of TB and HIV treatment is early co-treatment. Current WHO guidelines recommend starting ART as soon as possible, within 8 weeks, for all HIV-coinfected patients tolerating their TB medications [9]. More recent data argues for starting ART within 2 weeks for those with a CD4 cell count under 50 [55,56] or 100 cells/µl [57], with the possible exception of CNS TB infections [58,59]. Early treatment with

Box 2. Key interventions to avoid loss to follow-up.

- Decentralize HIV care.
- Reduce costs to patients.
- Avoid delays initiating ART, provide OI prophylaxis and other services pending ART initiation.
- Ensure sufficient staff to provide good care without excessive waiting times.
- Structure health services to preserve confidentiality.
- Obtain patients' numbers and/or addresses and trace them in case of missed visits, including referrals.
- Adapt disclosure requirements on a case-by-case basis to avoid delaying ART initiation.

ART: Antiretroviral treatment; OI: Opportunistic infection.

ART increases the risk of immune reconstitution inflammatory syndrome (IRIS), however, the mortality of IRIS is less than the mortality of deferring ART. This could perhaps be further mitigated by closer follow-up [60].

Where active TB can be confidently excluded, isoniazid preventive therapy should be provided to people with HIV infection. The WHO guidelines propose at least 6 months of isoniazid monotherapy (emphasis added) [61], yet this recommendation remains poorly implemented in sSA [62]. Nine months of isoniazid monotherapy is probably superior [63]. While it reduces active TB disease risk, the impact of isoniazid preventive therapy on mortality in HIV is less clear [61,64].

Cryptococcus neoformans

Cryptococcosis, most often presenting in the form of cryptococcal meningitis, rivals TB as one of the most important causes of death in persons with HIV infection in sSA [45]. Fluconazole prophylaxis in those with CD4 cell counts less than 100 cells/µl is not universally recommended, although the case has been made to reconsider this given the higher incidence and case fatality rates in sSA compared with well resourced settings [65]. Screening for cryptococcal infection using cryptococcal antigen (CrAg) tests in HIV-infected adults in sSA with CD4 cell counts under 100 cells/µl followed by fluconazole treatment has been suggested by others [3] and shown to be very cost effective [66], although early ART initiation is probably more important [67]. Recently a POC CrAg lateral flow immunoassay was shown to be reliable on urine as well as blood [68,69], making screening potentially even more practical. Where available on site, CrAg, preferably on CSF, is also the test of choice in symptomatic patients [70,71], as the sensitivity of India ink staining is only 60% that of CrAg by latex agglutination [71].

As is the case with TB, untreated or partially treated cryptococcal infections are associated with IRIS when ART is started. In contrast to TB infections in general, it appears that the risk of death is substantially higher with earlier ART initiation in the setting of cryptococcal meningitis. In a recent study in Zimbabwe, patients receiving ART within 3 days of starting fluconazole for cryptococcal meningitis had a nearly threefold increased risk of mortality compared with patients starting ART after 10 weeks of fluconazole [72]. Intermediate delay intervals were not tested. Compared with fluconazole monotherapy, combination regimens with flucytosine plus either fluconazole or amphotericin have been shown to clear CrAg faster [73,74], therefore the optimal delay might be shorter in people treated with one of those regimens.

TMP–SMX

Early initiation of routine OI prophylaxis with TMP–SMX is possibly the single most important intervention for the reduction of HIV-associated mortality from all causes prior to initiating ART. It is recommended for every patient with an HIV infection in WHO stage 2–4, including all those with active TB regardless of the community TB prevalence, and/or those with a CD4 cell count under 350 cells/µl [9]. TMP–SMX has been shown to reduce death and hospitalization [75] and prevent not only *Pneumocystis jirovecii* (formerly carinii) pneumonia and disease from *Toxoplasma gondii*, but also other HIV-related infections and malaria as well [76]. The benefit for protection against *T. gondii* applies to those with a CD4 cell count below 100 cells/µl, and against *P. jirovecii* for those with a CD4 cell count below 200 cells/µl, while the benefit from reduced rates of other infections, including malaria, may apply to all regardless of CD4 cell count. For patients with a mild-to-moderate allergy to TMP–SMX, desensitization appears a reasonable alternative [77], although this has not been studied in sSA. Interventions to reduce mortality related to OIs are listed in **Box 3**.

Pre-ART counseling & adherence promotion

Pre-ART counseling builds on HIV test counseling, and may incorporate screening for, and addressing, adherence risks such as depression and alcoholism. Pre-ART counseling is widely implemented and has been shown to be advantageous [78]. The optimal content, format and duration of counseling however remain to be determined and a combination of different forms is often used in practice. Rarely are more than three sessions dedicated to pre-ART counseling [79]. The investment in patient preparation for ART, while it may provide benefits in terms of later adherence, must be balanced against the risks of LTFU and delayed ART initiation. To achieve this balance, ART counseling should take place in parallel with other elements of care and continue after ART initiation. To reduce the burden on clinic staff and avoid adversely impacting clinic flow and patient waiting times it may be in large part conducted in groups, and in some settings possibly managed by peer counselors.

Box 3. Key interventions to optimize the prevention and management of opportunistic infections.

- Initiate TMP–SMX OI prophylaxis at HIV diagnosis.
- Use 3–4 item symptom checklist for TB screening.
- Use Xpert® MTB/Rif as primary diagnostic test for TB.
- Start ART within 2 weeks after the start of TB treatment if CD4 cell count <50–100 cells/µl and within 8 weeks for all.
- Give isoniazid preventive therapy after excluding active TB.
- Screen for cryptococcal infection with CrAg if CD4 cell count <100 cells/µl.

ART: Antiretroviral treatment; CrAg: Cryptococcal antigen; OI: Opportunistic infection; TMP–SMX: Trimethoprim–sulfamethoxazole.

Summary

The primary cause of mortality in adults with HIV in sSA is HIV infection that suppresses immune function, ultimately leading to the OIs or malignancies which are the proximal cause of death; and ART can effectively control HIV. While these statements appear trivial, their value lies in focusing clinicians and program administrators on the importance of reducing delays in starting ART. Unnecessary delay at this stage is

responsible for excess disease, LTFU, and ultimately mortality. On the other hand, crucial tasks for ensuring the success of ART take place at this time. This paper attempts to identify the interventions with the greatest potential to reduce an individual's HIV-associated mortality in sSA prior to initiating his or her ART.

Expert commentary

Despite successful ART roll-out, mortality among those infected with HIV remains high in sSA. Efforts to optimize HIV care should focus more on the period between the initial HIV diagnosis and successful recruitment onto ART. A multidisciplinary approach addressing logistical, social, psychological and medical barriers is needed to improve outcomes at this time.

Five-year view

The core challenges of the coming 5 years will be to increase the numbers of people on ART and to reduce the incidence of new infections. Earlier treatment of HIV infections will support both of those goals, as well as reducing morbidity, mortality and their associated costs. However, extending treatment eligibility and putting more people on ART carries direct costs that will be challenging to meet. Operational research guiding changes in standards and protocols will be needed to improve the cost–effectiveness of HIV care. Clinically, the major development in HIV care in the coming 5 years will be expanded POC testing. Use of POC CD4 cell counts and the Xpert system for TB diagnosis will likely increase rapidly, followed by some form of viral load and genotypic resistance monitoring. Beyond 5 years, growing rates of antiretroviral resistance will be one of the most difficult challenges for the public health approach to ART in sSA, and in the long term this may be compounded by barriers to the production of low-cost generic versions of the next generation of antiretrovirals.

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Key issues

- Testing, staging and preparation for antiretroviral therapy can be done much more swiftly, resulting in less death and loss to follow-up. This can be achieved through implementation of more point-of-care diagnostics and through parallel, rather than sequential, provision of patient care.
- TB remains the number one killer in sub-Saharan Africa among those with HIV; systematic symptom screening, Xpert® MTB/Rif testing, and early co-treatment of HIV and TB should be a priority.
- Presumptive treatment of TB and treatment of latent TB may reduce opportunistic infections and immune reconstitution inflammatory syndrome mortality.

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