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Reducing deaths from tuberculosis in antiretroviral treatment programmes in sub-Saharan Africa

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Abstract

Mortality rates are high in antiretroviral therapy (ART) programmes in sub-Saharan Africa, especially during the first few months of treatment. Tuberculosis (TB) has been identified as a major underlying cause. Under routine programme conditions, between 5% and 40% of adult patients enrolling in ART services have a baseline diagnosis of TB. There is also a high TB incidence during the first few months of ART (much of which is prevalent disease missed by baseline screening) and long-term rates remain several-fold higher than background. We identify three groups of patients entering ART programmes for which different interventions are required to reduce TB-related deaths. First, diagnostic screening is needed in patients who have undiagnosed active TB so that timely anti-tuberculosis treatment can be started. This may be greatly facilitated by new diagnostic assays such as the Xpert MTB/RIF assay. Second, patients with a diagnosis of active TB need optimised case management, which includes early initiation of ART (with timing now defined by randomised controlled trials), trimethoprim-sulphamethoxazole prophylaxis and treatment of co-morbidity. Third, all remaining patients who are TB-free at enrolment have high ongoing risk of developing TB and require optimised immune recovery (with ART ideally started early in the course of HIV infection), isoniazid preventive therapy and infection control to reduce infection risk. Further specific measures are needed to address multi-drug resistant TB (MDR-TB). Finally, scale-up of all these interventions requires nationally and locally tailored models of care that are patient-centred and provide integrated health care delivery for TB, HIV and other co-morbidities.

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Keywords

HIV; tuberculosis; antiretroviral; death; mortality; Africa

Introduction

The HIV/AIDS epidemic has had a devastating impact in sub-Saharan Africa over the past 25 years. With just 12% of the global population, sub-Saharan Africa nevertheless accounts for two-thirds of the world's HIV-infected people [1]. HIV has fuelled the tuberculosis (TB) epidemic and in 2010 an estimated 39% of new TB cases in sub-Saharan Africa were HIV-coinfected and this proportion exceeded 50% in the ten countries of southern Africa where HIV prevalence is highest [2]. Overall, sub-Saharan Africa accounted for a staggering 82% of the global burden of HIV-associated TB and 71% of resulting deaths. Moreover, the extremely high frequency of undiagnosed disseminated TB in post-mortem studies of HIV/AIDS patients in the region indicates that the contribution of TB to mortality is very likely to be substantially underestimated [3–6]. Not surprisingly, diagnosed and undiagnosed TB have been identified as key factors underlying the high mortality rates characteristic of ART programmes in sub-Saharan Africa.

The World Health Organization (WHO) first developed the framework outlining interventions to address the HIV-associated TB epidemic as an interim policy in 2004 [7] and this was updated in 2012 [8]. Important developments in recent years include the rapid ART scale-up across Africa, emergence of data from treatment strategy trials and the development of new diagnostic tools for TB. We aim to highlight these and other key developments that are specifically relevant to TB-related mortality reduction among adult patients in ART programmes.

We identify three key groups of patients entering ART programmes for which different interventions are required. These include: (i) patients with undiagnosed active TB who need diagnostic screening and timely anti-tuberculosis treatment; (ii) patients with diagnosed active TB who need optimised case management, and (iii) all remaining patients who are TB-free nevertheless have high ongoing risk of developing active disease and require preventive interventions. We highlight further specific measures that are needed to address the specific challenges of multi-drug resistant TB (MDR-TB) and finally we discuss the need to deliver all these interventions within the context of optimally structured and integrated health services.

Mortality and tuberculosis in ART services

Mortality before and during ART

Despite similar immunological and virological responses to ART [9], patients starting ART in sub-Saharan Africa have a substantially higher mortality risk compared to those treated in industrialized nations even after adjustment for baseline characteristics [10]. Between 8% and 26% of patients die in the first year of ART, with a majority of deaths reported within the first few months [11]. Substantial mortality also accrues while eligible patients prepare for treatment [12–14], but mortality rates fall rapidly once ART has been started [11]. Cumulative mortality is directly related to patient time spent at low CD4 counts [15].

Burden of TB

The proportion of patients with TB diagnoses at baseline in ART services in sub-Saharan Africa is extremely variable, ranging between 5% and 40% [16–23]. This includes two groups of patients: (i) those who first present to health services with TB and are

subsequently referred to ART services following HIV diagnosis and (ii) HIV-infected patients enrolling in ART services who are found to have active TB during baseline screening. The variability in the overall proportion with a TB diagnosis depends on many factors, including local TB rates, the proportion of TB patients tested for HIV, the efficiency of referrals between TB and ART services, and the rigour of pre-ART TB screening.

The proportion of patients enrolling in ART services with TB has increased following successful provider initiated testing and counselling (PITC) in TB clinics. In two South African townships, for example, this proportion increased from 15% to approximately 30–40% of patients [20,21]. The yield of intensified case finding among the remaining patients who enrol in ART clinics without a TB diagnosis varies substantially [24] and is highly dependent upon the screening strategy used. Restricting sputum smear microscopy and chest radiology to only those with a positive symptom screen results in considerable under-diagnosis [24,25]. Three studies in South African communities with very high TB rates found the prevalence of sputum culture-positive TB was approximately 15–25% in those with no pre-existing diagnosis when undergoing systematic microbiological screening [26–28].

A substantial burden of incident TB also presents during ART. In the first few months of treatment [16,22,29–31], much of the TB burden is due to ‘unmasking’ of asymptomatic or minimally symptomatic disease that was present at baseline but missed during screening [29,32]. Rates rapidly decrease within the first 6–12 months of ART, being strongly associated with the magnitude of immune recovery as reflected by time-updated CD4 count measurements [22,29,33]. However, long-term incidence rates remain at approximately 1.0 to 5.0 cases/100 person-years [16,22,29,30], several-fold higher than rates in non-HIV-infected people living in the same communities [29,33,34]. This may reflect incomplete restoration of anti-mycobacterial immune responses and high ongoing TB transmission risk [35,36].

TB and mortality risk

Although determining causes of death is difficult and multiple pathology is common [37], many data indicate that HIV-infected patients with either diagnosed or undiagnosed TB have high mortality risk. Post-mortem studies from across Africa of hospital in-patients dying with HIV/AIDS in the pre-ART and ART eras have all reported that active TB was extremely common, being found in 30%–50% of cadavers [3–6]. Most disease was disseminated and frequently remained undiagnosed before death. In the ART era, TB is reported as a leading cause of death in ART services [11,12,18,38–40] and a post-mortem study found disseminated TB in the majority of patients in South Africa who died during hospital admission within the first 6 months of ART [41].

Studies have inconsistent findings regarding whether TB is a risk factor for mortality in ART services. Some [17,34,38,42] but not all [18,19] studies report that patients with a TB diagnosis at baseline have an approximately 2–3-fold greater crude mortality risk. One study concluded that high mortality was simply the result of more advanced immunodeficiency [17] whereas others have found prevalent TB is a strong independent risk factor for mortality [43] or for mortality and loss to follow-up combined [42]. Incident TB diagnosed during ART was reported to be associated with a 2–3-fold greater mortality risk in crude and adjusted analyses [23,34,44]. A more recent study from Cape Town (in which 73% of TB cases were culture-confirmed) found substantially increased mortality risk during the 6 month period following diagnoses of both prevalent and incident TB in multivariate analyses (Figure 1) [45].

These inconsistencies in study findings are likely to be explained by a number of factors. With lack of accurate TB diagnostics in many settings, considerable misclassification of TB status may occur under routine programme conditions, with much under-diagnosis as well as some over-diagnosis. Further misclassification occurs in studies of prevalent TB if patients with incident disease are not excluded from the 'TB-free' comparison group. Also much TB may remain unascertained among patients who die or who are lost to follow-up [41]. In some studies, ART is only started after completion of the intensive phase of treatment for prevalent TB, inevitably leading to major survival bias. The rest of this review is written from the perspective that TB is a key cause of mortality in ART services in sub-Saharan Africa and that mortality risk can be reduced by early diagnosis, treatment and prevention.

Addressing the burden of undiagnosed TB

Potential impact of intensified TB case finding

The goal of intensified case finding in ART programmes is to rapidly diagnose TB both at baseline and during follow-up visits, thereby potentially reducing morbidity, mortality and nosocomial TB transmission. Effective baseline screening reduces the risk of 'unmasking' TB immune reconstitution disease in the early weeks of ART [32,46], which is occasionally life-threatening [47,48]. Moreover, rapid effective screening may reduce diagnostic uncertainty, potentially shortening the time to initiation of ART. However, studies demonstrating the benefits of intensified case finding in ART services are few since randomisation to either receive screening or no screening would clearly not have equipoise. One observational study from South Africa reported that intensive baseline TB screening pre-ART was associated with a halving in the TB incidence rate during the first few months of ART compared to historical data [46].

How frequently patients should undergo symptomatic or microbiological screening for TB during ART is unknown, and may vary between settings with different TB burdens and different resources. TB risk is strongly related to incomplete or poor immune recovery [29] [49] and therefore serial screening might best be targeted in those starting ART or those with poor immune recovery. Studies of cost and the added burden to laboratory services will be needed.

Symptom screening

WHO previously recommended screening for cough of more than 2–3 weeks duration to identify those who might have TB [50,51]. This, however, has poor sensitivity (<50%) for HIV-associated TB [27,28,52,53] and is lower still (<25%) among patients with sputum culture-positive TB pre-ART [54]. Screening for multiple symptoms increases sensitivity but lowers specificity [53]. A meta-analysis of nearly 10,000 HIV-infected patients found that reporting at least one of four common symptoms (current cough, night sweats, weight loss or fever) had an overall sensitivity of 79% and a specificity of 50% during active screening for TB [55].

This new 4-symptom screening tool is incorporated within the WHO 2011 guidelines on intensified case finding and isoniazid preventive therapy [56] with a primary role to rule-out TB and identify those who may be eligible for IPT. However, poor specificity means that large numbers of identified patients may require further diagnostic evaluation. Moreover, since sensitivity is sub-optimal, 10%–20% of asymptomatic patients with active TB are missed [24,27,28]. Thus, where the prevalence of undiagnosed active TB may be as high as 20% among patients entering ART programmes as in South Africa [26–28], there is a strong argument for microbiological screening of all patients regardless of symptoms.

Limitations of existing diagnostic tools

The lack of simple, accurate, low-cost, point-of-care diagnostic tests for TB has crucially undermined the response to the HIV-associated TB epidemic. Diagnoses are often missed or delayed as a result of the non-specific clinical presentation and high rates of sputum smear-negative, extrapulmonary and disseminated disease [25,52]. Fluorescence microscopy is increasingly used but its sensitivity during pre-ART screening remains less than 30% compared to sputum liquid culture [26,27,54]. Chest radiology marginally increases the sensitivity of symptom-based screening [55], but overall diagnostic accuracy in this clinical setting is very poor [52,57]. Culture-based diagnosis has much higher sensitivity but is slow. For smear-negative samples, the mean time to positivity in liquid culture may be three weeks [26,28]. Moreover, the technical requirements for culture preclude its use on a large scale in most of Africa.

New diagnostic tools

A range of new TB diagnostics has emerged over the past few years [58] and two in particular may potentially play important roles within ART services as alternatives to microscopy and culture (Table 1). The Xpert MTB/RIF assay (Cepheid Inc, Sunnyvale, CA, USA) is a key breakthrough and was endorsed by the WHO in December 2010 as a replacement for sputum smear microscopy in settings with high prevalence of HIV-associated TB and/or MDR-TB [59,60]. This rapid molecular assay uses real-time polymerase chain reaction technology to detect *Mycobacterium tuberculosis* and mutations associated with rifampicin resistance. Testing a single sputum sample detects 98%–100% of smear-positive pulmonary TB and between 57% and 83% of sputum smear-negative disease with high specificity in adults presenting with suspected TB [60]. Testing fine needle aspirates of lymph nodes and other extrapulmonary clinical samples using Xpert might be used to further increase diagnostic yield in HIV-infected patients [60–63].

In a South African study, Xpert MTB/RIF increased TB case finding by 45% compared to smear microscopy during pre-ART screening [28]. However, in view of the very low bacillary burden in patients with early smear-negative disease, the sensitivity for smear-negative culture-positive TB was just 43% testing one sample and 62% testing two. Despite this diagnostic short-fall, follow-up studies found that, compared to Xpert-positive TB cases, Xpert-negative cases had less advanced immunodeficiency, less severe TB and had much better prognosis despite the associated delays in starting TB treatment [64]. No studies have yet directly assessed the impact of Xpert screening on mortality or on nosocomial TB transmission. However, modelling analyses suggest that routine pre-ART screening of all patients is a highly cost-effective intervention in South Africa [65].

Cost and technical constraints mean that Xpert MTB/RIF may not be widely used in sub-Saharan Africa [66], although it is being implemented country-wide in South Africa. When used at the district or sub-district level, Xpert has been found to substantially increase case finding and reduce time to starting treatment [67]. However, current implementation within a centralised laboratory system in South Africa threatens to undermine this impact as separation of this technology from the site of patient care inevitably means that some patients testing positive never start treatment and others only start after prolonged delays [64]. Rapid point-of-care assays that can be used during a clinic visit are needed to bridge this gap.

In this regard, a simple assay that detects mycobacterial lipoarabinomannan (LAM) antigen present in urine of some TB patients regardless of the anatomic site of disease is promising [68]. Initially developed as a laboratory-based enzyme-linked immunosorbent assay (ELISA), this was found to have useful diagnostic accuracy in HIV-infected patients who

had CD4 cell counts <200 cells/μL [26,69–71]. In ambulatory patients screened prior to ART and in hospitalised HIV-infected TB suspects, the sensitivities of the assay were 67% and 85%, respectively, in those with CD4 cell counts <50 cells/μL, greatly out-performing smear microscopy [26,70]. Very high specificity was observed in both studies but the utility of the assay is greatly limited by very low sensitivity at higher CD4 cell counts [71].

A potentially major step forward is the development of a point-of-care version of the assay [54]. Determine TB-LAM Ag (Alere, Waltham, MA, USA) is a simple lateral-flow (strip-test) assay providing a qualitative (yes/no) visual read-out after 25–35 minutes (Table 1). This has similar performance to the ELISA and could potentially be used by health-care workers within the out-patient clinic or at the bed-side. This is not a stand-alone assay but provides 'added value' when combined with existing diagnostics. There is substantial incremental sensitivity when combined with smear microscopy; the positive predictive value is high in patients with abnormal chest radiographs, and it provides accelerated point-of-care diagnosis when the results of laboratory-based Xpert testing are not immediately available [54]. The assay may have specific utility in reducing mortality by rapid TB diagnosis in HIV-infected patients with those with the most advanced immunodeficiency and highest mortality risk [68,72]. Studies of the impact on clinical outcomes, especially mortality, are needed.

Presumptive or empirical TB treatment prior to starting ART

In the absence of appropriate diagnostic tools, diagnosis of smear-negative and extrapulmonary TB in sub-Saharan Africa has often relied upon algorithms with repeated clinical assessments over a period of time. WHO guidance was revised in 2007, recognising patients' high mortality risk from untreated TB and complications of advanced immunodeficiency [50]. Case definitions for HIV-associated TB were simplified and diagnostic algorithms were stream-lined, including an algorithm for the management of a subgroup of seriously ill patients [50]. This permitted presumptive TB therapy to be started within 3–5 days following lack of response to parenteral antibiotics in patients with danger signs and suspected but unconfirmed TB. This algorithm has been associated with improved outcomes in observational studies from South Africa and Uganda [73,74].

Extending this rationale, it has been suggested that empiric TB treatment may also benefit a broader spectrum of patients who have high risk of undiagnosed TB, including ambulatory HIV-infected patients with very low CD4 cell counts (eg <50 cells/μL) attending ART clinics [75]. Empirical TB treatment used in combination with ART may reduce TB-related morbidity and mortality in those with unrecognised active TB and may provide a prevention benefit in those who do not [75]. A potential drawback would be the failure to identify and treat other (non-TB) underlying conditions. Trials assessing such a strategy in Africa include the AIDS Clinical Trial Group REMEMBER trial (NCT01380080) and the PROMPT study (NCT01417988) funded by the European Developing Countries Clinical Trials Programme. Implementation of new diagnostic tools such as Xpert MTB/RIF and the Determine TB-LAM Ag point-of-care test may supersede the need for presumptive and empiric TB treatment but clinical trials are needed to compare different approaches [76].

Optimised case management for those with active TB

Optimised case management for HIV-associated TB requires rifampicin-containing TB treatment (if drug susceptible), trimethoprim-sulphamethoxazole prophylaxis and timely initiation of ART [77]. Assessment of HIV status is the absolutely critical step to enable this package of care to be implemented. Although testing rates have been improving in sub-Saharan Africa, reaching 59% in 2010 [2], these remain inadequate in many countries. The huge opportunity to save lives through use of ART and trimethoprim-sulphamethoxazole

prophylaxis is currently being squandered simply as a result of patients not being tested. Adopting provider-initiated testing and counselling (PITC) is an important means of achieving this [21,78].

In two randomised controlled trials from Zambia and Cote D'Ivoire, trimethoprim-sulphamethoxazole prophylaxis among patients with HIV-associated TB reduced mortality by 45% – 48% in the absence of ART [79,80]. This may well reflect the high rate of concurrent sepsis among these patients [37,41]. Implementation has increased substantially in recent years in sub-Saharan Africa, being received by an estimated 76% of those with known HIV-associated TB in 2010 [2].

In view of poor long-term prognosis, revised WHO (2010) guidelines recommend that all patients with HIV-associated TB should receive ART regardless of CD4 count [81]. ART reduces mortality risk by between 64% and 95% [82]. Efavirenz-based regimens are recommended in preference to regimens including nevirapine or protease inhibitors in view of less significant pharmacokinetic interactions with rifampicin, high rates of virological suppression and lower risk of co-toxicity [77,81].

The critical question regarding the optimum time to start ART in patients with HIV-associated TB is subject to multiple competing risks [83] but has now been addressed by three strategy trials [84–87]. These studies show that ART should be given concurrently with TB treatment regardless of CD4 cell count, and that risk of AIDS and death in those with CD4 cell counts <50 cells/μL was minimised by starting treatment within the first 4 weeks of TB treatment (Table 2). Two of the three studies showed that start of ART could be deferred until the end of the 2-month intensive phase of TB treatment in those with CD4 cell counts >50 cells/μL [86,87]. A meta-analysis of these data may provide additional information in due course. A further randomised trial, however, found no survival benefit from early ART in patients with TB meningitis [88], which may simply reflect the awful prognosis of such patients and the dire consequences of TB immune reconstitution disease (TB-IRD) within the central nervous system [89,90].

The earlier ART is started and the lower the baseline CD4 cell count, the greater the risk of paradoxical TB-IRD [91, 92]. Although deaths from TB-IRD occur [91,93], they do so in those who have a high pre-existing mortality risk and overall are relatively infrequent. A meta-analysis reported that TB-IRD develops in 15.7% (95%CI, 9.7–24.5) of people at risk and that 3.2% (95%CI, 0.7–9.2) of these died [94], representing approximately 1 in 200 patients overall. Revised 2010 WHO guidelines recommend ART is started within 2 and 8 weeks of TB treatment [81] to reduce mortality risk. Clinical care programs will need to ensure adequate provider training in the management of TB-IRD. Corticosteroids have a role in reducing morbidity and duration of in-patient stay in those with TB-IRD requiring hospital admission [95]. A number of prevention trials are also underway or planned [96].

The contribution of other opportunistic infections such as cryptococcal disease and cytomegalovirus and bacterial infections to mortality in patients with HIV-associated TB may be substantial [41,97,98]. Some gram-negative sepsis is not prevented by co-trimoxazole prophylaxis and may be particularly important in hospitalised patients [98]. Improved diagnostics (such as blood cultures or cryptococcal antigen screening), treatment options for co-infections and empirical antibiotics all need to be considered, evaluated and applied.

TB prevention in those who are TB-free

TB prevention in ART services

Patients accessing ART programmes who do not have TB require an optimized package of preventive interventions using ART, isoniazid preventive therapy (IPT) and infection control measures. Both isoniazid preventive therapy and infection control are heavily dependent upon intensified case finding and collectively this triad of interventions is called the 'three I's strategy' [99].

ART itself is the key long-term intervention, reducing TB risk by 67% (95%CI, 61–73%) regardless of tuberculin skin test (TST) status [100]. TB risk is directly related to the current CD4 count and is increased by virological failure [22,29,33] and so optimisation of adherence and immune recovery are important as is rapid detection of virological failure and timely switching to second line ART. However, even in those with optimum immune recovery, TB risk does not reduce to background [29,33,34]. Observational data strongly suggest that IPT given either before or during ART has an additive effect [101, 102]. Further data are awaited from two randomized placebo-controlled trials, the HAART-IPT trial in South Africa (NCT00463086) and the ANRS TEMPRANO trial in Cote D'Ivoire (NCT00495651), in 2012 and 2013, respectively.

Patients testing tuberculin skin test (TST) positive derive significant benefit from IPT and ideally all such patients should receive IPT early in the course of HIV infection before becoming eligible for ART. This, however, requires early HIV diagnosis and linkage to a system of pre-ART care, which is all too often lacking. Starting IPT at the same time as ART in patients with advanced immunodeficiency is challenging and may have limited impact for several reasons. First, WHO symptom screening excludes up to 70% of patients as being ineligible for IPT [28]. Second, in a large study in Botswana only 1 in 8 patients with CD4 cell counts <200 cells/μL tested TST-positive with potential to benefit from IPT [102]. Third, the negative predictive value of a negative symptom screen is insufficient to rule out active TB in settings with a TB prevalence >10% [55]. It has therefore been suggested that IPT might be started several months after initiating ART when active TB might be more easily excluded and when TST responses may have been restored [100,103]. Empiric data are needed. Increasing evidence from studies in southern Africa reveal that the benefit of IPT is largely limited to the period that IPT is taken [102,104,105], probably because of high reinfection risk after treatment cessation. The rationale for using long-term courses (rather than 6 or 9 months) of IPT in TST-positive individuals is therefore increasing.

Observational data from South African gold mines suggested that IPT started around the time of ART initiation might reduce early mortality [106]. However, since IPT was given to people in whom TB had been carefully excluded, it seems likely that any early reduction in mortality additional to that derived from ART was due to the intensified case finding component of the intervention [107]. A phased implementation study from Brazil in which IPT was widely introduced to HIV/ART clinics found no significant benefit from IPT in the primary intention-to-treat analysis, but risk of TB and a combined end-point of TB or death were reduced in a sub-analysis of those who remained within the clinic at least for 12 months [108].

In view of the very high burden of undiagnosed TB among patients accessing ART clinics, nosocomial TB transmission is a major hazard requiring rigorous implementation of administrative and environmental interventions and use of personal protection [109]. This might be greatly enhanced by systematic screening of patients enrolling in ART programmes using Xpert MTB/RIF where available. The limit of detection of this assay is

131 bacilli per ml of sputum [110], suggesting that TB cases undetected by this assay have low bacillary burdens in sputum and pose low infectious risk [60].

TB prevention up-stream of ART services

While this review has largely focussed on interventions within ART programmes, TB preventive interventions are clearly needed throughout the HIV care pathway. Longitudinal care pre-ART is typically weak within African health systems [111–113]. This is needed so that patients might enrol within ART programmes TB-free and with higher CD4 cell counts so that their cumulative risk of TB and TB-related death thereafter remains low.

The observation that in some regions up to 40% of patients entering ART programmes have a TB diagnosis at baseline indicates that up-stream prevention is sorely lacking and that ART is being started far too late, effectively squandering the TB preventive potential of ART [114]. Evidence is accumulating that ART prevents TB among patients with CD4 cell counts >350 cells/μL [101,115,116] and modelling analyses suggest that initiation of ART at much higher CD4 cell counts (using the ‘test and treat’ strategy) would have a far greater TB preventive effect [114,117]. This would be mediated by not only improved community ‘CD4 health’ but also by reduced HIV incidence [114,117].

Addressing drug resistant TB

The outbreak of extensively drug resistant TB (XDR-TB) among patients accessing ART at a rural district hospital in KwaZulu Natal in South Africa in which 52 out of 53 patients affected died after a median of 16 days was an extraordinary wake-up call to the dangers of drug resistant TB in HIV care settings [118]. Delays in the diagnosis of TB and detection of drug resistance were critical factors contributing to the high rates of mortality and transmission [119]. Prevention of outbreaks of MDR- and XDR-TB in ART services is dependent upon rapid diagnosis and rigorous implementation of comprehensive infection control measures [109,120].

Molecular line-probe assays were endorsed by the WHO in 2008 to speed up diagnosis of MDR-TB [121]. However, these assays are costly, technically complex and can only be applied to smear-positive sputum samples or culture isolates. Implementation has therefore been limited. However, the Xpert MTB/RIF assay endorsed by WHO in 2010 has high sensitivity for rifampicin resistance [59,60]. When used to screen patients pre-ART in South Africa, all cases of MDR-TB were diagnosed after a mean of 2 days compared to 21 days using culture and line-probe assay and 43 days using culture and phenotypic drug susceptibility testing [28]. This is potentially a major step forward. However, a significant rate of false-positive rifampicin resistance results associated with the original assay cartridges [28,122] require that follow-up testing is done with another assay. A version of Xpert MTB/RIF cartridge (version G4) modified to address this problem was released in December 2011 and field data are awaited.

It is likely that the number of MDR-TB cases that are diagnosed will increase dramatically through implementation of Xpert MTB/RIF, and programmes will need to ensure that appropriate second-line treatment is available. ART improves survival of HIV-infected patients with drug resistant TB [123] and should be started as early as possible in combination with an optimised TB treatment regimen and trimethoprim-sulphamethoxazole. Such patients may be prone to more frequent TB-IRD due to persisting bacillary burden [124] as well as frequent drug interactions and co-toxicity [125]. In the longer term, it is essential that HIV-infected patients receiving ART are included in drug development studies for emerging new TB compounds for MDR-TB treatment [126].

Integrated delivery of TB and HIV services

The quality of care received by patients with HIV-associated TB may be greatly compromised if health care services are not coordinated and provided in an integrated fashion. In a study from a township in South Africa, delays in starting ART among TB patients were prolonged [127] but were almost three-fold greater for patients who were referred between non-integrated TB services and ART clinics compared to those in whom TB was diagnosed in the ART clinic [128]. Thus, of TB clinic referrals with CD4 counts <50 cells/μL, only 11% started ART within 4 weeks of TB diagnosis. This illustrates how lack of integration of TB and ART services compromises patient care and potentially increases mortality risk.

People living with HIV should receive integrated prevention, diagnostic and treatment services for both TB and HIV at a single location with effective TB infection control measures [129]. This entails a patient-centred approach that is tailored according to national and local health infrastructure issues delivered in a coordinated and integrated manner. Evidence based and locally tailored models of integrated service delivery have to be defined and scaled up.

Research Priorities

Despite the major advances in our knowledge since the first interim policy on collaborative activities for addressing the HIV-associated TB epidemic was published in 2004 [7], there remains an extensive research agenda to further advance the field (Table 3). While in the long term, new diagnostics and new TB drugs are sorely needed, much of the research agenda requires operational research to address how best to implement recent gains in knowledge and current international policy.

Conclusions

TB represents a major challenge to the scale-up of ART in sub-Saharan Africa and must be addressed to reduce the high early mortality in these programmes. The huge burden of TB among patients enrolling in ART services indicates that treatment is being started far too late and this remains a fundamental issue that needs to be addressed. In addition, the opportunity must be taken to harness new diagnostic assays that are able to rapidly and accurately detect sputum smear-negative TB and to rapidly screen for rifampicin resistance. These and other diagnostic tools within the developmental pipeline undoubtedly have the potential to revolutionize our capacity to address the challenge of TB and to reduce mortality. Important data have now accumulated regarding case management, including the optimum time to start ART during TB treatment, and prevention. The challenge remains to operationalize these findings and to shape our health systems appropriately to deliver these packages of care. In addition, the much bolder approach to ART scale-up using the ‘test and treat’ strategy potentially offers a much more radical solution to this devastating co-epidemic.

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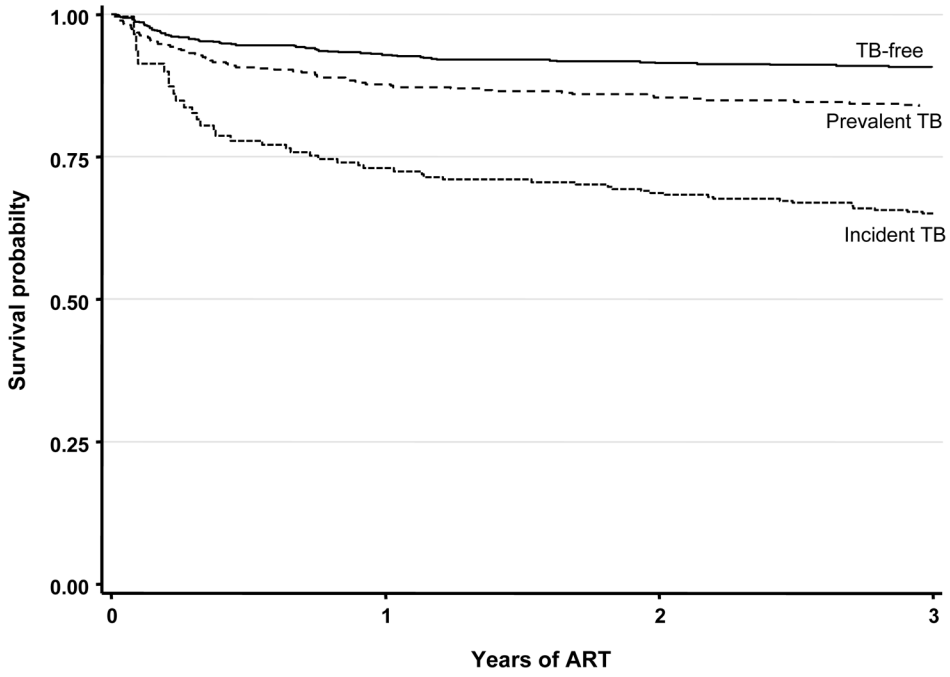

Figure 1.

Kaplan-Meier plots showing survival proportions during the first 3 years of antiretroviral therapy (ART) in a cohort in Cape Town, South Africa. Patients who remain tuberculosis (TB)-free throughout follow-up are compared with those with prevalent TB present at baseline and with those with incident TB developing at any time-point during ART. Data from [45].

Table 1

Comparison of the diagnostic accuracy and utility of smear microscopy, mycobacterial culture, Xpert MTB/RIF and Determine TB-LAM Ag assays for diagnostic screening for tuberculosis (TB) in patients in antiretroviral treatment services in sub-Saharan Africa.

	Diagnostic accuracy	Advantages	Disadvantages	References
Sputum smear microscopy	Low sensitivity (approx 10%- 30%); high specificity	Current widespread availability and low cost. Detects most infectious cases	Low sensitivity. Laboratory requirements and technician dependent.	[26–28, 54]
Sputum culture	Liquid culture has highest sensitivity of all assays (gold standard).	High sensitivity and specificity and enables speciation and drug susceptibility testing.	Too slow. High cost and infrastructure requirements. Cross contamination and laboratory biohazard risks.	[26–28, 54]
Xpert MTB/RIF	Diagnoses all smear-positive cases and approximately 40%–70% of smear-negative culture- positive cases (depends on number of tests). Very high specificity.	Greatly increased case finding compared to smear microscopy. Rapid TB diagnosis and detection of rifampicin resistance. Diagnoses 'sicker' patients whereas Xpert- negative cases have more favourable prognostic characteristics. Can be used at district and sub-district level without need for laboratory-trained staff.	High cost (approx. $15 per cartridge). Not true point-of-care. Some false-positive rifampicin resistance requires confirmatory testing. Infrastructure requirements (electricity supply, linked computer, annual calibration).	[28, 60, 64, 66, 67, 130]
Determine TB- LAM Ag	Only useful at CD4 cell counts <200 cells/μL. Sensitivity highest at lowest CD4 cell counts (eg. 67% at CD4 <50 cells/μL). Studies overall are inconsistent regarding specificity. More data awaited.	True point-of-care assay providing results within 30 minutes at first consultation. Urine samples easy to obtain. Low cost. Simple to use without additional equipment. Diagnoses TB in the 'sickest' patients with highest mortality risk. Provides incremental value when combined with other tests.	Use restricted to patients with very low CD4 cell counts. Urine contamination or non-tuberculous mycobacteria may potentially cause false-positive results. Not a stand- alone test.	[54, 68, 72, 131]

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Table 2

Randomized Controlled studies of the timing of starting antiretroviral therapy (ART) during tuberculosis (TB) treatment

	Study Population				Methods		Results			
Study	**N**	**Location**	**TB**	**Median CD4+ cells/mm^3 (IQR)**	**Timing of ART in Weeks "Earlier" vs "Later"**	**Primary Endpoint**	**Follow-up in Months**	**Primary Endpoint "Earlier" vs "Later"[b]**	**Primary Endpoint in CD4 <50 cells/μL [c]**	**TB Immune Reconstitution**
CAMELIA [85]	660	Cambodia	Smear-positive TB	25 (11–56)	2 vs 8	Death	25	18% vs 27%, p=0.006	Not reported[e]	33.1% vs 13.7% p<0.001
SAPIT [87]	429	South Africa	Smear-positive pulmonary TB	150 (77–254)	4 vs 8–12	AIDS or Death	17.7	6.9 vs 7.8[d] p=0.73	8.5 vs 26.3[d] p=0.06	20.1% vs 7.7% p<0.001
STRIDE [86]	809	Multicontinent[a]	Confirmed or presumed pulmonary or extrapulmonary TB	77 (36–145)	2 vs 8–12	AIDS or Death	12	12.9% vs 16.1% p=0.45	15.5% vs 26.6% p=0.02	11% vs 5% p=0.02
TB Meningitis [88]	253	Vietnam	TB Meningitis	39 (18–116)	2 vs 8	Death[e]	12	59.8% vs 55.6% p=0.50	63.3% vs 65.1% p=0.84	not reported

[a] North America, South America, Asia, Africa

[b] Presented as cumulative incidence of primary endpoint in early vs. later arm

[c] Prespecified analysis

[d] Expressed per 100 person-years

[e] Lower CD4 was not associated with an increased risk for the primary endpoint. Primary endpoint was all cause mortality at 9 months.

Table 3

Research priorities to address tuberculosis (TB) mortality in antiretroviral treatment (ART) programmes in sub-Saharan Africa[1]

1. Causes of mortality

- Post-mortem and clinical studies need to better define the contribution of diagnosed and undiagnosed TB to overall mortality, including among HIV-infected children
- Define the contribution of multi-drug resistant TB (MDR-TB) and TB immune reconstitution disease (TB-IRD)
- Define the contribution of co-infections (bacterial sepsis, cryptococcosis and other opportunists) and other co-morbidities in patients with TB

2. Intensified TB case finding and diagnosis

- New diagnostic tests for use among adults and children, particularly a point-of-care test for smear negative and Xpert negative cases
- Operational research of implementation, impact and yield of intensified case finding in different geographical settings and with different diagnostic tests
- Implementation, impact and cost-effectiveness of new diagnostics / algorithms in programmatic settings
- Clinical trials of outcomes, feasibility and cost-effectiveness comparing different diagnostic and empiric TB treatment strategies

3. Case management of HIV-associated TB

- Research to ‘fine-tune’ the optimal timing of ART in relation to CD4 count strata and clinical parameters
- Implementation of early ART initiated during TB treatment in programmatic settings
- Novel strategies to improve acute management and reduce mortality in patients with HIV-associated TB requiring hospital admission
- Choice of empiric antibiotic in those with presumed concurrent sepsis or with severe immune deficiency
- Prevention of TB-IRD, especially neurological TB-IRD
- New TB drugs and regimens, including use of rifabutin with protease inhibitors

4. Prevention of HIV-associated TB

- Best infection control interventions in resource-limited settings, particularly in health care facilities.
- Monitoring of infection control practices within ART and pre-ART clinics
- TB preventive therapy in adults and children receiving ART: efficacy above ART alone, optimal timing, drugs, duration and cost-effectiveness
- Operational research of delivery of TB preventive therapy in pre-ART care pathway and ART clinics
- Community interventions to reduce TB transmission and incidence
- ART initiation at CD4 counts >350 cells/mm^3: effect on TB incidence, mortality and cost-effectiveness

5. Drug resistant TB

- Algorithms to direct use of drug-susceptibility testing in HIV-associated TB cases
- Impact of Xpert MTB/RIF assay on outcomes in HIV-infected patients with MDR TB
- Additional rapid drug susceptibility tests (including for second-line drugs)

- New TB drugs and regimens
- Optimal ART timing in MDR TB
- Drug interactions of new TB drugs with ART

6. Health systems research concerning integration of TB and HIV care

- Best models for integrating HIV and TB care to facilitate rapid ART initiation
- Infection control issues in integration models
- Barriers in the pathway of HIV-TB care from patient and provider perspectives
- Knowledge translation of research findings into routine practice

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[1] Reference sources [130, 131]