Published in final edited form as:

AIDS. 2012 November 13; 26(17): . doi:10.1097/QAD.0b013e3283565dd1.

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

Stephen D. Lawn^{a,b}, Anthony D. Harries^{b,c}, Graeme Meintjes^{d,e}, Haileyesus Getahun^f, Diane V. Havlir^g, and Robin Wood^a

^aThe Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa ^bDepartment of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK ^cInternational Union Against Tuberculosis and Lung Disease, Paris, France ^dInstitute of Infectious Diseases and Molecular Medicine and Department of Medicine, University of Cape Town, Cape Town South Africa ^eDepartment of Medicine, Imperial College London, UK ^fStop TB Department, WHO, Geneva, Switzerland ^gDepartment of Medicine, University of California, San Francisco, California, USA

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.

Correspondence: Stephen D. Lawn, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, Cape Town, South Africa. Tel +27 21 650 6970, Fax +27 21 650 6963, stevelawn@yahoo.co.uk.

Conflicts of interest

The authors have no conflicts of interest to declare

Disclaimer

The views and opinions expressed in this article are those of the individual authors and do not necessarily reflect those of their organizations.

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/ μ L [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/ μ L, 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/ μ L) 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/ μ L 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/ μ L [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/ μ L 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/ μ L [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/ μ L, 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.

Acknowledgments

SDL was funded by the Wellcome Trust, London, UK. RW was funded in part by the International Epidemiologic Database to Evaluate Aids with a grant from the National Institute of Allergy and Infectious Diseases (NIAID: 5U01AI069924-02); Cost-Effectiveness of Preventing AIDS Complications (CEPAC) funded by the National Institutes of Health (NIH, 5 R01AI058736-02); USAID Right to Care (CA 674 A 00 08 0000 700) and the South African Centre for Epidemiological Modeling and Analysis (SACEMA). GM was funded in part through a Fogarty International Center South African TB/AIDS Training Award (NIH/FIC 1U2RTW007373-01A1, U2RTW007370 ICORTA). DH received funding from the NIH/NIAID (A151982). We thank Dr. A. Gupta for Figure 1.

References

1. WHO / UNAIDS. [Accessed 29 Feb 2012] Global HIV/AIDS response. Epidemic update and health sector progress towards universal access. Progress report. 2011. at: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20111130_UA_Report_en.pdf
2. World Health Organization. [Accessed on 21.12.11] Global tuberculosis control. 2011. at: http://www.who.int/tb/publications/global_report/en/index.html
3. Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbichi JM, et al. The mortality and pathology of HIV infection in a west African city. *AIDS*. 1993; 7:1569–1579. [PubMed: 7904450]
4. Rana FS, Hawken MP, Mwachari C, Bhatt SM, Abdullah F, Ng'ang'a LW, et al. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. *J Acquir Immune Defic Syndr*. 2000; 24:23–29. [PubMed: 10877491]
5. Ansari NA, Kombe AH, Kenyon TA, Hone NM, Tappero JW, Nyirenda ST, et al. Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana, 1997–1998. *Int J Tuberc Lung Dis*. 2002; 6:55–63. [PubMed: 11931402]
6. Cohen T, Murray M, Wallengren K, Alvarez GG, Samuel EY, Wilson D. The prevalence and drug sensitivity of tuberculosis among patients dying in hospital in KwaZulu-Natal, South Africa: a postmortem study. *PLoS Med*. 2010; 7:e1000296. [PubMed: 20582324]
7. World Health Organization. Interim policy on collaborative TB/HIV activities. WHO; Geneva, Switzerland: 2004. WHO/HTM/TB/2004.330 WHO/HTM/HIV/2004.1 http://whqlibdoc.who.int/hq/2004/WHO_HTM_TB_2004.330_eng.pdf
8. World Health Organization. Guidelines for national programmes and stakeholders. World Health Organization; Geneva: 2012. WHO policy on collaborative TB/HIV activities. WHO/HTM/TB/2012.1at: http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf [Accessed on 10th April 2012]
9. Ivers LC, Kendrick D, Doucette K. Efficacy of antiretroviral therapy programs in resource-poor settings: a meta-analysis of the published literature. *Clin Infect Dis*. 2005; 41:217–224. [PubMed: 15983918]
10. Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boule A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006; 367:817–824. [PubMed: 16530575]
11. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS*. 2008; 22:1897–1908. [PubMed: 18784453]
12. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*. 2005; 19:2141–2148. [PubMed: 16284464]
13. Bassett IV, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. *J Acquir Immune Defic Syndr*. 2009; 51:135–139. [PubMed: 19504725]
14. Zachariah R, Tayler-Smith K, Manzi M, Massaquoi M, Mwagomba B, van GJ, et al. Retention and attrition during the preparation phase and after start of antiretroviral treatment in Thyolo, Malawi, and Kibera, Kenya: implications for programmes? *Trans R Soc Trop Med Hyg*. 2011; 105:421–430. [PubMed: 21724219]
15. Lawn SD, Little F, Bekker LG, Kaplan R, Campbell E, Orrell C, et al. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS*. 2009; 23:335–342. [PubMed: 19114870]
16. Moore D, Liechty C, Ekwaru P, Were W, Mwima G, Solberg P, et al. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. *AIDS*. 2007; 21:713–719. [PubMed: 17413692]
17. Westreich D, MacPhail P, Van RA, Malope-Kgokong B, Ive P, Rubel D, et al. Effect of pulmonary tuberculosis on mortality in patients receiving HAART. *AIDS*. 2009; 23:707–715. [PubMed: 19279444]

18. Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. *AIDS*. 2006; 20:2355–2360. [PubMed: 17117022]
19. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA*. 2006; 296:782–793. [PubMed: 16905784]
20. Boule A, Van CG, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *AIDS*. 2010; 24:563–572. [PubMed: 20057311]
21. Lawn SD, Fraenzel A, Kranzer K, Caldwell J, Bekker LG, Wood R. Provider-initiated HIV testing increases access of patients with HIV-associated tuberculosis to antiretroviral treatment. *S Afr Med J*. 2011; 101:258–262. [PubMed: 21786731]
22. Van Rie A, Westreich D, Sanne I. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors, and prevention strategies. *J Acquir Immune Defic Syndr*. 2011; 56:349–355. [PubMed: 20926954]
23. Komati S, Shaw PA, Stubbs N, Mathibedi MJ, Malan L, Sangweni P, et al. Tuberculosis risk factors and mortality for HIV-infected persons receiving antiretroviral therapy in South Africa. *AIDS*. 2010; 24:1849–1855. [PubMed: 20622529]
24. Kranzer K, Houben RM, Glynn JR, Bekker LG, Wood R, Lawn SD. Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010; 10:93–102. [PubMed: 20113978]
25. Lawn SD, Wood R. Tuberculosis in antiretroviral treatment services in resource-limited settings: addressing the challenges of screening and diagnosis. *J Infect Dis*. 2011; 204 (Suppl 4):S1159–S1167. [PubMed: 21996698]
26. Lawn SD, Edwards DJ, Kranzer K, Vogt M, Bekker LG, Wood R. Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. *AIDS*. 2009; 23:1875–1880. [PubMed: 20108382]
27. Bassett IV, Wang B, Chetty S, Giddy J, Losina E, Mazibuko M, et al. Intensive tuberculosis screening for HIV-infected patients starting antiretroviral therapy in Durban, South Africa. *Clin Infect Dis*. 2010; 51:823–829. [PubMed: 20735240]
28. Lawn SD, Brooks SV, Kranzer K, Nicol MP, Whitelaw A, Vogt M, et al. Screening for HIV-Associated Tuberculosis and Rifampicin Resistance before Antiretroviral Therapy Using the Xpert MTB/RIF Assay: A Prospective Study. *PLoS Med*. 2011; 8:e1001067. [PubMed: 21818180]
29. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS*. 2009; 23:1717–1725. [PubMed: 19461502]
30. Houlihan CF, Mutevedzi PC, Lessells RJ, Cooke GS, Tanser FC, Newell ML. The tuberculosis challenge in a rural South African HIV programme. *BMC Infect Dis*. 2010; 10:23. [PubMed: 20146818]
31. Nicholas S, Sabapathy K, Ferreyra C, Varaine F, Pujades-Rodriguez M. Incidence of tuberculosis in HIV-infected patients before and after starting combined antiretroviral therapy in 8 sub-Saharan African HIV programs. *J Acquir Immune Defic Syndr*. 2011; 57:311–318. [PubMed: 21423023]
32. Lawn SD, Wilkinson RJ, Lipman MC, Wood R. Immune reconstitution and “unmasking” of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med*. 2008; 177:680–685. [PubMed: 18202347]
33. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis Incidence Rates during 8 Years of Follow-Up of an Antiretroviral Treatment Cohort in South Africa: Comparison with Rates in the Community. *PLoS One*. 2012; 7:e34156. [PubMed: 22479548]
34. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS*. 2006; 20:1605–1612. [PubMed: 16868441]
35. Lawn SD, Bekker LG, Wood R. How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. *AIDS*. 2005; 19:1113–1124. [PubMed: 15990564]

36. Middelkoop K, Bekker LG, Liang H, Aquino LD, Sebastian E, Myer L, et al. Force of tuberculosis infection among adolescents in a high HIV and TB prevalence community: a cross-sectional observation study. *BMC Infect Dis.* 2011; 11:156. [PubMed: 21631918]
37. Martinson NA, Karstaedt A, Venter WD, Omar T, King P, Mbengo T, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. *AIDS.* 2007; 21:2043–2050. [PubMed: 17885294]
38. Moore, D.; Yiannoutsos, C.; Musick, B.; Downing, R.; Were, W.; Degerman, R., et al. Determinants of mortality among HIV-infected individuals receiving home-based ART in rural Uganda. Abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA. Feb. 2007; p. Abstract #34
39. Etard JF, Ndiaye I, Thierry-Mieg M, Gueye NF, Gueye PM, Laniece I, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS.* 2006; 20:1181–1189. [PubMed: 16691070]
40. Kouanda S, Meda IB, Nikiema L, Tiendrebeogo S, Doulougou B, Kabore I, et al. Determinants and causes of mortality in HIV-infected patients receiving antiretroviral therapy in Burkina Faso: a five-year retrospective cohort study. *AIDS Care.* 2012; 24:478–90. [PubMed: 22148973]
41. Wong, EB.; Omar, T.; Setlhako, G.; Osih, R.; Murdoch, D.; Martinson, N., et al. Causes of death in ART-treated adults: a post-mortem study from Johannesburg. Abstracts of the XVIII International AIDS Conference. International AIDS Society; Vienna, Austria. 2010. p. Abstract #WEPE0154
42. Bassett IV, Chetty S, Wang B, Mazibuko M, Giddy J, Lu Z, et al. Loss to follow-up and mortality among HIV-infected people co-infected with TB at ART initiation in Durban, South Africa. *J Acquir Immune Defic Syndr.* 2012; 59:25–30. [PubMed: 22027877]
43. Moore DM, Yiannoutsos CT, Musick BS, Tappero J, Degerman R, Campbell J, et al. Determinants of early and late mortality among HIV-infected individuals receiving home-based antiretroviral therapy in rural Uganda. *J Acquir Immune Defic Syndr.* 2011; 58:289–296. [PubMed: 21857358]
44. Yu JK, Bong CN, Chen SC, Dzimidzi R, Lu DY, Makombe SD, et al. Outcomes in HIV-infected patients who develop tuberculosis after starting antiretroviral treatment in Malawi. *Int J Tuberc Lung Dis.* 2008; 12:692–694. [PubMed: 18492340]
45. Gupta, A.; Wood, R.; Kaplan, R.; Bekker, L-G.; Lawn, SD. Mortality associated with tuberculosis in patients receiving antiretroviral therapy in South Africa. Abstracts of the International AIDS Society XIX International AIDS Conference; July 2012; p. Abstract #
46. Lawn SD, Kranzer K, Edwards DJ, McNally M, Bekker LG, Wood R. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy. *AIDS.* 2010; 24:1323–1328. [PubMed: 20386425]
47. Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS.* 2009; 23:143–145. [PubMed: 19050399]
48. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect.* 2003; 79:337–338. [PubMed: 12902592]
49. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS.* 2005; 19:2109–2116. [PubMed: 16284460]
50. World Health Organization. Recommendations for HIV-prevalent and resource-constrained settings. WHO; Geneva: 2007. Improving the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents. WHO/HTM/2007.379 & WHO/HIV/2007.1 http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.379_eng.pdf
51. World Health Organisation. Treatment of tuberculosis. Guidelines for national programmes. 3. WHO; Geneva: WHO/CDS/TB 2003.313
52. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis.* 2009; 9:173–184. [PubMed: 19246021]
53. Cain KP, McCarthy KD, Heilig CM, Monkongdee P, Tasaneeyapan T, Kanara N, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med.* 2010; 362:707–716. [PubMed: 20181972]

54. Lawn SD, Kerkhoff AD, Vogt M, Wood R. Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. *Lancet Infect Dis.* 2012; 12:201–209. [PubMed: 22015305]
55. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med.* 2011; 8:e1000391. [PubMed: 21267059]
56. WHO. Guidelines for intensified case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. World Health Organization; Geneva: 2010. at http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf [Accessed on 15 Jan 2011]
57. Dawson R, Masuka P, Edwards DJ, Bateman ED, Bekker LG, Wood R, et al. Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV. *Int J Tuberc Lung Dis.* 2010; 14:52–58. [PubMed: 20003695]
58. Pai M, Minion J, Sohn H, Zwerling A, Perkins MD. Novel and improved technologies for tuberculosis diagnosis: progress and challenges. *Clin Chest Med.* 2009; 30:701–16. [PubMed: 19925962]
59. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. *N Engl J Med.* 2010; 363:1005–1015. [PubMed: 20825313]
60. Lawn SD, Nicol MP. Xpert(R) MTB/RIF assay: development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. *Future Microbiol.* 2011; 6:1067–1082. [PubMed: 21958145]
61. Ligthelm LJ, Nicol MP, Hoek KG, Jacobson R, van Helden PD, Marais BJ, et al. Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle-aspiration biopsy specimens. *J Clin Microbiol.* 2011; 49:3967–3970. [PubMed: 21880965]
62. Hillemann D, Rusch-Gerdes S, Boehme C, Richter E. Rapid Molecular Detection of Extrapulmonary Tuberculosis by the Automated GeneXpert MTB/RIF System. *J Clin Microbiol.* 2011; 49:1202–1205. [PubMed: 21270230]
63. Lawn SD, Kerkhoff AD, Vogt M, Wood R. High diagnostic yield of tuberculosis from screening urine samples from HIV-infected patients with advanced immunodeficiency using the Xpert MTB/RIF assay. *J Acquir Immune Defic Syndr.* 2012 Epub ahead of print.
64. Lawn SD, Kerkhoff AD, Vogt M, Ghebrekristos Y, Whitelaw A, Wood R. Characteristics and Early Outcomes of Patients With Xpert MTB/RIF-Negative Pulmonary Tuberculosis Diagnosed During Screening Before Antiretroviral Therapy. *Clin Infect Dis.* 2012; 54:1071–1079. [PubMed: 22318975]
65. Andrews JR, Lawn SD, Rusu C, Wood R, Noubary F, Bender MA, et al. The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis. *AIDS.* 2012; 26:987–995. [PubMed: 22333751]
66. Trebucq A, Enarson DA, Chiang CY, Van DA, Harries AD, Boillot F, et al. Xpert(R) MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? *Int J Tuberc Lung Dis.* 2011; 15:1567–1572. [PubMed: 22005110]
67. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet.* 2011; 377:1495–1505. [PubMed: 21507477]
68. Lawn SD. Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. *BMC Infect Dis.* 2012; 12:103. [PubMed: 22536883]
69. Achkar JM, Lawn SD, Moosa MY, Wright CA, Kasproicz VO. Adjunctive Tests for Diagnosis of Tuberculosis: Serology, ELISPOT for Site-Specific Lymphocytes, Urinary Lipoarabinomannan, String Test, and Fine Needle Aspiration. *J Infect Dis.* 2011; 204 (Suppl 4):S1130–S1141. [PubMed: 21996695]

70. Shah M, Variava E, Holmes CB, Coppin A, Golub JE, McCallum J, et al. Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a High HIV prevalence setting. *J Acquir Immune Defic Syndr*. 2009; 52:145–151. [PubMed: 19692904]
71. Minion J, Leung E, Talbot E, Dheda K, Pai M, Menzies D. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. *Eur Respir J*. 2011; 38:1398–1405. [PubMed: 21700601]
72. Lawn SD, Kerkhoff AD, Vogt M, Wood R. Clinical significance of lipoarabinomannan (LAM) detection in urine using a low-cost point-of-care diagnostic assay for HIV-associated tuberculosis. *AIDS*. 2012
73. Holtz TH, Kabera G, Mthiyane T, Zingoni T, Nadesan S, Ross D, et al. Use of a WHO-recommended algorithm to reduce mortality in seriously ill patients with HIV infection and smear-negative pulmonary tuberculosis in South Africa: an observational cohort study. *Lancet Infect Dis*. 2011; 11:533–540. [PubMed: 21514234]
74. Alamo ST, Kunutsor S, Walley J, Thoullass J, Evans M, Muchuro S, et al. Performance of the new WHO diagnostic algorithm for smear-negative pulmonary tuberculosis in HIV prevalent settings: a multisite study in Uganda. *Trop Med Int Health*. 2012 Epub ahead of print.
75. Lawn SD, Ayles H, Egwaga S, Williams B, Mukadi YD, Santos Filho ED, et al. Potential utility of empirical tuberculosis treatment for HIV-infected patients with advanced immunodeficiency in high TB-HIV burden settings. *Int J Tuberc Lung Dis*. 2011; 15:287–295. [PubMed: 21333094]
76. Lawn SD, Harries AD. In reply to 'Empirical tuberculosis treatment or improved diagnostics?'. *Int J Tuberc Lung Dis*. 2012; 16:280–281. [PubMed: 22236934]
77. Harries AD, Zachariah R, Lawn SD. Providing HIV care for co-infected tuberculosis patients: a perspective from sub-Saharan Africa. *Int J Tuberc Lung Dis*. 2009; 13:6–16. [PubMed: 19105873]
78. Odhiambo J, Kizito W, Njoroge A, Wambua N, Nganga L, Mburu M, et al. Provider-initiated HIV testing and counselling for TB patients and suspects in Nairobi, Kenya. *Int J Tuberc Lung Dis*. 2008; 12:63–68. [PubMed: 18302825]
79. Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet*. 1999; 353:1469–1475. [PubMed: 10232312]
80. Nunn AJ, Mwaba P, Chintu C, Mwinga A, Darbyshire JH, Zumla A. Role of co-trimoxazole prophylaxis in reducing mortality in HIV infected adults being treated for tuberculosis: randomised clinical trial. *BMJ*. 2008; 337:a257. [PubMed: 18617486]
81. World Health Organization. Recommendations for a public health approach (2010 revision). World Health Organization; Geneva: Antiretroviral therapy for HIV infection in adults and adolescents. at the following URL: <http://www.who.int/hiv/pub/arv/adult/en/index.html> [Accessed on 19.12.10]
82. Lawn SD, Kranzer K, Wood R. Antiretroviral Therapy for Control of the HIV-associated Tuberculosis Epidemic in Resource-Limited Settings. *Clin Chest Med*. 2009; 30:685–699. [PubMed: 19925961]
83. Lawn SD, Torok ME, Wood R. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. *Curr Opin Infect Dis*. 2011; 24:34–42. [PubMed: 21150593]
84. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010; 362:697–706. [PubMed: 20181971]
85. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011; 365:1471–1481. [PubMed: 22010913]
86. Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011; 365:1482–1491. [PubMed: 22010914]
87. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011; 365:1492–1501. [PubMed: 22010915]

88. Torok ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. 2011; 52:1374–1383. [PubMed: 21596680]
89. Lawn SD, Wood R. Poor Prognosis of HIV-Associated Tuberculous Meningitis Regardless of the Timing of Antiretroviral Therapy. *Clin Infect Dis*. 2011; 52:1384–1387. [PubMed: 21596681]
90. Pepper DJ, Marais S, Maartens G, Rebe K, Morroni C, Rangaka MX, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. 2009; 48:e96–107. [PubMed: 19405867]
91. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007; 21:335–341. [PubMed: 17255740]
92. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008; 8:516–523. [PubMed: 18652998]
93. Worodria W, Massinga-Loembe M, Mazakpwe D, Luzinda K, Menten J, van LF, et al. Incidence and predictors of mortality and the effect of tuberculosis immune reconstitution inflammatory syndrome in a cohort of TB/HIV patients commencing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2011; 58:32–37. [PubMed: 21654499]
94. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010; 10:251–261. [PubMed: 20334848]
95. Meintjes G, Wilkinson RJ, Morroni C, Pepper DJ, Rebe K, Rangaka MX, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010; 24:2381–2390. [PubMed: 20808204]
96. Lawn SD, Meintjes G. Pathogenesis and prevention of immune reconstitution disease during antiretroviral therapy. *Expert Rev Anti Infect Ther*. 2011; 9:415–430. [PubMed: 21504399]
97. Martinson NA, Karstaedt A, Venter WD, Omar T, King P, Mbengo T, et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. *AIDS*. 2007; 21:2043–2050. [PubMed: 17885294]
98. Pepper DJ, Rebe K, Morroni C, Wilkinson RJ, Meintjes G. Clinical deterioration during antitubercular treatment at a district hospital in South Africa: the importance of drug resistance and AIDS defining illnesses. *PLoS One*. 2009; 4:e4520. [PubMed: 19229341]
99. World Health Organization. Report of a joint WHO HIV/AIDS and TB Department Meeting 2008. WHO; Geneva: 2008. WHO three I's meeting. http://www.who.int/hiv/pub/meetingreports/WHO_3Is_meeting_report.pdf
100. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. 2010; 10:489–498. [PubMed: 20610331]
101. Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007; 21:1441–1448. [PubMed: 17589190]
102. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011; 377:1588–1598. [PubMed: 21492926]
103. Girardi E, Palmieri F, Zaccarelli M, Tozzi V, Trotta MP, Selva C, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS*. 2002; 16:1976–1979. [PubMed: 12351964]
104. Samandari, T.; Agizew, T.; Nyirenda, S.; Tedla, Z.; Sibanda, T.; Mosimaneotsile, B., et al. TB incidence increase after cessation of 36 months isoniazid prophylaxis in HIV+ adults in Botswana. Abstracts of the 19th Conference on Retroviruses and Opportunistic Infections; March 2012; Seattle, WA, USA. p. Abstract #147

105. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011; 365:11–20. [PubMed: 21732833]
106. Charalambous S, Grant AD, Innes C, Hoffmann CJ, Dowdeswell R, Pienaar J, et al. Association of isoniazid preventive therapy with lower early mortality in individuals on antiretroviral therapy in a workplace programme. *AIDS*. 2010; 24 (Suppl 5):S5–13. [PubMed: 21079429]
107. Lawn SD, Harries AD. Reducing tuberculosis-associated early mortality in antiretroviral treatment programmes in sub-Saharan Africa. *AIDS*. 2011; 25:1554–1555. [PubMed: 21747238]
108. Durovni, B.; Saraceni, V.; Pacheco, A.; Cavalcante, S.; Cohn, S.; King, B., et al. Impact of tuberculosis (TB) screening and isoniazid preventive therapy (IPT) on incidence of TB and death in the TB/HIV in Rio de Janeiro (THRio) study. Abstracts of the 6th IAS Conference on HIV Pathogenesis, treatment and prevention. International AIDS Society; July 2011; Rome, Italy. p. WELBB18
109. Bock NN, Jensen PA, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. *J Infect Dis*. 2007; 196 (Suppl 1):S108–S113. [PubMed: 17624819]
110. Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. *J Clin Microbiol*. 2010; 48:229–237. [PubMed: 19864480]
111. Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, et al. Early loss to follow up after enrolment in pre-ART care at a large public clinic in Johannesburg, South Africa. *Trop Med Int Health*. 2010; 15 (Suppl 1):43–47. [PubMed: 20586959]
112. Lessells RJ, Mutevedzi PC, Cooke GS, Newell ML. Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. *J Acquir Immune Defic Syndr*. 2011; 56:e79–e86. [PubMed: 21157360]
113. Tayler-Smith K, Zachariah R, Massaquoi M, Manzi M, Pasulani O, Van den AT, et al. Unacceptable attrition among WHO stages 1 and 2 patients in a hospital-based setting in rural Malawi: can we retain such patients within the general health system? *Trans R Soc Trop Med Hyg*. 2010; 104:313–319. [PubMed: 20138323]
114. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis*. 2011; 15:571–581. [PubMed: 21756508]
115. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet*. 2002; 359:2059–2064. [PubMed: 12086758]
116. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011; 365:493–505. [PubMed: 21767103]
117. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. *Proc Natl Acad Sci U S A*. 2010; 107:19485–19489. [PubMed: 20974976]
118. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006; 368:1575–1580. [PubMed: 17084757]
119. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010; 181:80–86. [PubMed: 19833824]
120. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis*. 2007; 196 (Suppl 1):S86–107. [PubMed: 17624830]
121. World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Policy statement. Jun. 2008 www.who.int/entity/tb/dots/laboratory/lpa_policy.pdf
122. Marlowe EM, Novak-Weekley SM, Cumpio J, Sharp SE, Momeny MA, Babst A, et al. Evaluation of the Cepheid Xpert MTB/RIF Assay for Direct Detection of *Mycobacterium*

- tuberculosis Complex in Respiratory Specimens. *J Clin Microbiol.* 2011; 49:1621–1623. [PubMed: 21289151]
123. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet.* 2010; 375:1798–1807. [PubMed: 20488525]
 124. Meintjes G, Rangaka MX, Maartens G, Rebe K, Morroni C, Pepper DJ, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis.* 2009; 48:667–676. [PubMed: 19191655]
 125. Scano F, Vitoria M, Burman W, Harries AD, Gilks CF, Havlir D. Management of HIV-infected patients with MDR- and XDR-TB in resource-limited settings. *Int J Tuberc Lung Dis.* 2008; 12:1370–1375. [PubMed: 19017444]
 126. Luetkemeyer AF, Getahun H, Chamie G, Lienhardt C, Havlir DV. Tuberculosis drug development: ensuring people living with HIV are not left behind. *Am J Respir Crit Care Med.* 2011; 184:1107–1113. [PubMed: 21868507]
 127. Lawn SD, Campbell L, Kaplan R, Boule A, Cornell M, Kerschberger B, et al. Time to initiation of antiretroviral therapy among patients with HIV-associated tuberculosis in Cape Town, South Africa. *J Acquir Immune Defic Syndr.* 2011; 57:136–140. [PubMed: 21436714]
 128. Lawn SD, Campbell L, Kaplan R, Little F, Morrow C, Wood R. Delays in starting antiretroviral therapy in patients with HIV-associated tuberculosis accessing non-integrated clinical services in a South African township. *BMC Infect Dis.* 2011; 11:258. [PubMed: 21957868]
 129. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis.* 2010; 50 (Suppl 3):S238–S244. [PubMed: 20397954]
 130. Lawn SD, Kerkhoff AD, Wood R. Location of Xpert(R) MTB/RIF in centralised laboratories in South Africa undermines potential impact. *Int J Tuberc Lung Dis.* 2012; 16:701. [PubMed: 22507934]
 131. Peter JG, Theron G, van Zyl-Smit R, Haripersad A, Mottay L, Kraus S, et al. Diagnostic accuracy of a urine LAM strip-test for TB detection in HIV-infected hospitalised patients. *Eur Respir J.* 2012 Epub ahead of print.

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].

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.

Table 1

	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/ μ L. Sensitivity highest at lowest CD4 cell counts (eg. 67% at CD4 <50 cells/ μ L). 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]

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

Table 2

	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” ^{a,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

^aNorth America, South America, Asia, Africa

^bPresented as cumulative incidence of primary endpoint in early vs. later arm

^cPrespecified analysis

^dExpressed per 100 person-years

^eLower 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 Africa¹

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/mm³: 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

¹Reference sources [130, 131]