

## Review article

# HIV and tuberculosis — science and implementation to turn the tide and reduce deaths

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### Abstract

**Introduction:** Every year, HIV-associated tuberculosis (TB) deprives 350,000 mainly young people of productive and healthy lives. People die because TB is not diagnosed and treated in those with known HIV infection and HIV infection is not diagnosed in those with TB. Even in those in whom both HIV and TB are diagnosed and treated, this often happens far too late. These deficiencies can be addressed through the application of new scientific evidence and diagnostic tools.

**Discussion:** A strategy of starting antiretroviral therapy (ART) early in the course of HIV infection has the potential to considerably reduce both individual and community burden of TB and needs urgent evaluation for efficacy, feasibility and broader social and economic impact. Isoniazid preventive therapy can reduce the risk of TB and, if given strategically in addition to ART, provides synergistic benefit. Intensified TB screening as part of the “Three I’s” strategy should be conducted at every clinic, home or community-based attendance using a symptoms-based algorithm, and new diagnostic tools should increasingly be used to confirm or refute TB diagnoses. Until such time when more sensitive and specific TB diagnostic assays are widely available, bolder approaches such as empirical anti-TB treatment need to be considered and evaluated. Patients with suspected or diagnosed TB must be screened for HIV and given cotrimoxazole preventive therapy and ART if HIV-positive. Three large randomized trials provide conclusive evidence that ART initiated within two to four weeks of start of anti-TB treatment saves lives, particularly in those with severe immunosuppression. The key to ensuring that these collaborative activities are delivered is the co-location and integration of TB and HIV services within the health system and the community.

**Conclusions:** Progress towards reducing HIV-associated TB deaths can be achieved through attention to simple and deliverable actions on the ground.

*John Donne, Meditation XVII, Devotions upon Emergent Occasions:*

... any mans death diminishes me because I am involved in Mankinde; And therefore never send to know for whom the bell tolls; it tolls for thee ...

**Keywords:** HIV; tuberculosis; antiretroviral therapy; intensified case finding; isoniazid preventive therapy; mortality.

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### Introduction

In 2010, an estimated 34 million adults and children were living with HIV/AIDS [persons living with HIV (PLHIV)] worldwide: 1.1 million had HIV-associated tuberculosis (TB) and 350,000 with HIV-associated TB died [1]. Given that TB is a curable disease and that HIV/AIDS can now be treated, albeit with life-long drug therapy, why did this high mortality occur? People died for three main reasons: (i) TB was not diagnosed in those known to have HIV infection and who were accessing antiretroviral therapy (ART); (ii) HIV was not diagnosed in those with TB and therefore these patients were not offered HIV care and treatment, and (iii) when the two diseases were diagnosed and treated, these interventions happened far too late. The application of new scientific evidence and strategic use of new diagnostic tools make it possible to address these gaps and dramatically reduce the mortality caused by HIV-associated TB.

### Discussion

#### Epidemiology

In 2010, 82% of the global burden of HIV-associated TB and 71% of the associated deaths occurred in sub-Saharan Africa, with 10 countries in the southern region of Africa accounting for more than 50% of cases [1]. Although HIV-associated TB is a global problem, other focal points are South Asia (India, Thailand, Indonesia and Myanmar) and Eastern Europe (Ukraine and the Russian Federation) where intravenous drug use drives the co-epidemic.

The scale up of ART over the last seven years has been a remarkable, and deservedly applauded, success, with over 6.6 million people (5.1 million in sub-Saharan Africa) estimated to be receiving treatment in low- and middle-income countries [2]. However, between 8% and 26% of patients die in the first year of treatment [3], and both diagnosed and undiagnosed TB are recognized as major

causes of this mortality. Autopsy studies conducted in sub-Saharan Africa before and during the ART era in adult HIV-infected hospitalized patients found that TB, particularly disseminated disease, was responsible for 40% to 50% of deaths (Table 1) [4–7]. A more recent study in South Africa in HIV-positive adults also showed that high proportion of patients who died in the first six months of receiving ART had disseminated TB [8].

Similarly, TB patients diagnosed with HIV and not receiving HIV treatment have a high case fatality, which occurs early during the course of anti-TB treatment [9], is generally higher in smear-negative TB [10] and increases as the CD4 count decreases (Table 2) [1,11,12]. Early diagnosis, treatment and prevention of TB in PLHIV and early diagnosis and treatment of HIV in TB patients are essential if these deaths are to be avoided [13].

### The 2012 WHO policy on collaborative TB/HIV activities

In March 2012, the World Health Organization (WHO) released an updated policy on collaborative TB/HIV activities, which consolidates evidence collated over the last six years from randomized controlled trials, observational studies, operational research and best practices from programme implementation [14]. It follows the same framework as the 2004 interim policy document [15], structuring 12 activities under three distinct objectives (Table 3), but with some important differences. These include (i) recognition of the crucial role of early ART initiation in preventing TB in PLHIV, (ii) expanded use of HIV testing and HIV prevention to include patients with presumptive TB as well as partners and family members of patients with TB and (iii) more guidance for the integration of HIV and TB services in time and place and with other health programmes.

It is estimated that one million lives have been saved between 2005 and 2010 as a result of implementing key activities of the 2004 interim policy [16], and adoption of the new policy should bring even greater benefit. Five important spheres of work are needed to reduce HIV-TB mortality: (i) preventing TB in PLHIV by early ART and isoniazid preventive therapy (IPT); (ii) finding, diagnosing and treating tuberculosis in PLHIV; (iii) diagnosing and treating HIV in people with presumptive and diagnosed TB, including drug-resistant TB; (iv) addressing these challenges in children; and (v) ensuring

that HIV/TB services are co-located and/or integrated within health facilities and the community.

### Preventing TB in PLHIV: early ART and IPT

#### *Antiretroviral therapy*

There is now compelling evidence that ART is a powerful preventive agent for TB in PLHIV. A systematic review and meta-analysis of studies in cohorts of PLHIV from around the world have shown that ART significantly reduces rates of TB, with effects most apparent in patients with more advanced HIV-disease or with the lowest CD4 counts (Table 4) [17]. At the individual level, these beneficial effects increase with length of time on ART, although they never decrease to a level that approaches the rates of TB seen in patients without HIV-infection [18,19]. At the programme level, it has also been shown in rural Malawi [20] and Cape Town, South Africa [21], that when ART coverage in a population reaches a high level of coverage, TB notification rates in that population decrease, and in Malawi, this reduction was noted for both new and recurrent TB (Table 5) [20].

Definitive evidence of the protective effect of ART at higher baseline CD4 counts is provided in randomized controlled trials. In a study in Haiti, TB incidence was reduced by 50% in patients starting ART at CD4 counts between 200 and 350 cells/ $\mu$ L compared with those starting ART when the CD4 count dropped to below 200 cells/ $\mu$ L or when treatment was deferred until the onset of AIDS [22]. This reduction in TB incidence was matched by a 75% reduction in the risk of death for those starting ART early. These data informed the 2010 revision of the WHO ART Guidelines [23] that recommend starting ART at CD4 counts < 350 cells/ $\mu$ L. Evidence for the TB protective effect of ART at even higher CD4 counts came from a recent HIV Prevention Trials Network (HPTN 052) study [24] in which there was a 40% reduction in serious HIV-related clinical events or death in PLHIV starting ART at CD4 counts from 350 to 550 cells/ $\mu$ L compared with those initiating ART at CD4 counts  $\leq$  250 cells/ $\mu$ L or when AIDS had developed. The difference in incidence of clinical events was driven mainly by extrapulmonary TB (EPTB), which developed in three patients in the early-therapy group and 17 in the delayed-therapy group.

Mathematical models predict the enormous benefit that early ART initiation might have on TB prevention [25].

**Table 1. Causes of death in HIV-infected patients on medical wards – autopsy studies from sub-Saharan Africa**

Country	Condition and/or diagnosis at death	Number with autopsies	Number (%) with TB found at autopsy	Number (%) with disseminated TB
Cote d'Ivoire [4]	HIV wasting syndrome diagnosed on medical wards	93	41 (44)	41 (44)
Kenya [5]	HIV-positive diagnosed on medical wards	75	38 (51)	31 (41)
Botswana [6]	HIV-positive diagnosed on medical wards	104	42 (40)	37 (36)
South Africa [7]	HIV-positive diagnosed on medical wards	96	40 (42)	No data

TB, tuberculosis.

**Table 2. Case fatality in HIV-infected smear-positive pulmonary TB patients before the era of antiretroviral therapy**

Country	Mortality rates at different CD4 counts (cells/ $\mu$ L) in HIV-positive PTB patients			HIV-negative PTB patients
	< 200	200 to 499	500 or >	
Zaire at 24 months [11]	67%	22%	8%	~ 2%
Cote d'Ivoire at 6 months [12]	10%	4%	3%	< 1%

PTB, pulmonary tuberculosis.

In a model using data from the South African HIV/AIDS epidemic, universal and annual HIV testing of adults linked to immediate start of ART in those HIV-positive could lead to a halving in incidence of HIV-associated TB within five years and a reduction by 95% within 40 years [26]. The strategy works in two ways: a direct effect for the individual through immune reconstitution and an indirect effect for the community by reducing HIV transmission, resulting in fewer people infected with HIV and, therefore, being at risk of HIV-associated TB.

Identification of HIV infection early in the course of disease when CD4 counts are still high is essential for maximizing the protective effect of ART for TB. In sub-Saharan Africa, most patients are diagnosed with HIV and start ART at low CD4 counts of 100 to 150 cells/ $\mu$ L, while the majority of HIV-associated TB patients are diagnosed at higher CD4 counts of 150 to 200 cells/ $\mu$ L [13,18]. Thus, HIV diagnosis and initiation of ART are generally too late to prevent TB, and the TB preventive role of ART is largely squandered. Further and urgent research is now needed to assess efficacy, feasibility, safety, cost, social and population uptake and effect of the "Test and Treat" approach where the linkage of HIV testing

to CD4 count measurements, a barrier to ART access in many low-income countries, is removed. Several randomized controlled trials are underway [27], and in some countries like Malawi, the strategy is already being implemented at country level for pregnant women [28].

#### *Isoniazid preventive therapy*

IPT is another essential intervention for TB prevention. Given daily for six months, it reduces the overall risk of TB in PLHIV by 33%, with the protective effect confined to those with a positive tuberculin skin test (TST) in whom the risk reduction is 64% [29]. Based on this evidence, WHO guidelines between 1998 and 2009 emphasized that IPT should be used as prophylaxis in PLHIV who are TST-positive [30].

However, implementation has been poor with the two major stumbling blocks being the process of TST assessment and reliable exclusion of active TB. To overcome this inertia, the revised WHO IPT guidelines made a strong explicit recommendation that "TST is not a requirement for initiating IPT in people living with HIV" although it "can be used where feasible" [31]. Implementation is improving, and by the end of 2010, about one-quarter of PLHIV enrolled

**Table 3. WHO policy on recommended collaborative TB/HIV activities, 2012**

#### **A. Establish and strengthen the mechanisms for delivering integrated TB and HIV services**

- A.1. Set up and strengthen a coordinating body for collaborative TB/HIV activities functional at all levels
- A.2. Determine HIV prevalence among TB patients and TB prevalence among people living with HIV
- A.3. Carry out joint TB/HIV planning to integrate the delivery of TB and HIV services
- A.4. Monitor and evaluate collaborative TB/HIV activities

#### **B. Reduce the burden of TB in people living with HIV and initiate early antiretroviral therapy (the Three I's for HIV/TB)**

- B.1. Intensify TB case-finding and ensure high quality antituberculosis treatment
- B.2. Initiate TB prevention with isoniazid preventive therapy and early antiretroviral therapy
- B.3. Ensure control of TB infection control in healthcare facilities and congregate settings

#### **C. Reduce the burden of HIV in patients with presumptive and diagnosed TB**

- C.1. Provide HIV testing and counselling to patients with presumptive and diagnosed TB
- C.2. Provide HIV prevention interventions for patients with presumptive and diagnosed TB
- C.3. Provide cotrimoxazole preventive therapy for TB patients living with HIV
- C.4. Ensure HIV prevention interventions, treatment and care for TB patients living with HIV
- C.5. Provide antiretroviral therapy for TB patients living with HIV

TB, tuberculosis.

Adapted from Ref. [14].

**Table 4. Reduction in the incidence rate ratio of TB in people living with HIV and started on ART**

Baseline CD4 count at the time of starting ART	TB incidence rate ratio (95% confidence intervals)
Less than 200 cells/ $\mu$ L	0.16 (0.07 to 0.36)
200 to 350 cells/ $\mu$ L	0.34 (0.19 to 0.60)
More than 350 cells/ $\mu$ L	0.43 (0.30 to 0.63)
Any CD4 count	0.35 (0.28 to 0.44)

TB, tuberculosis; ART, antiretroviral therapy.

Adapted from Ref. [17]: in the systematic review, data were abstracted from 11 studies that met the inclusion criteria of the systematic review – the intervention was ART, the comparator was no ARV drugs and the outcome was an incident case of TB.

in care and eligible for IPT on the basis of negative symptom screening were started on TB preventive therapy [1].

The duration of treatment is currently recommended for at least six months [31]. New data on the optimal duration of IPT could improve the overall effectiveness of this intervention, although this will raise additional challenges for IPT delivery. In Botswana, 36 months of IPT reduced TB incidence by 43% compared with six months of IPT, the effects again being most apparent in TST-positive persons [32]. After cessation of IPT, TB incidence increased [33], even in the presence of ART, suggesting that continued isoniazid in these settings with high TB burden and transmission is necessary to maintain a TB preventive effect. Based on these and other data, the new WHO Guidelines recommend that, in countries with high rates of community TB transmission, such as in southern Africa, consideration should be given to extended treatment for 36 months or longer [31], and evidence is beginning to suggest that IPT should be life long.

An area of ongoing research and debate is the optimal timing and use of IPT and ART. Observational studies from Brazil [34] and South Africa [35] and the data from Botswana [32] suggest that sequential or concurrent use of ART and IPT results in a synergistic decline in risk of active TB. Randomized placebo-controlled data regarding the additive beneficial effects of this combined approach are awaited from the ANRS TEMPRANO trial in Core d'Ivoire [NCT00495651] and the HAART-IPT trial in South Africa [NCT00463086] [27]. However, in the interim and within the structured set up

of an ART clinic, an implementable strategy could be the introduction and continuation of IPT once patients are stable, asymptomatic and prevalent TB has been unmasked [36].

#### Finding, diagnosing and treating TB in PLHIV

##### *Intensified TB case finding*

Linked to the prevention of TB with use of IPT is the need to reliably find and diagnose active TB disease, and this is packaged together under the acronym “The Three I’s” (intensified case finding, isoniazid preventive therapy and infection control). Good progress has been made with intensified TB case finding (ICF) in terms of the development of a standardized screening tool [37] and indicators for monitoring progress [38]. A standardized screening tool, developed as a result of meta-analysis of available data, focusses on four key questions: current cough of any duration and a history of unintentional weight loss, night sweats and fever in the last four weeks [37]. This is being used in the field, and for example, in one study amongst HIV-infected pregnant women, these questions were found to be acceptable, feasible and associated with a high negative predictive value [39]. In patient groups with the very highest TB prevalence rates exceeding 10%, the negative predictive value would be somewhat lower.

Available data show that about 50% of PLHIV being screened have one or more positive symptoms, and 10% of those with a positive screen may be subsequently diagnosed with TB [37], with the numbers needed to screen and the yield of active TB being dependent on prevalence of endemic TB, the setting and the diagnostic methods used [40]. A small proportion (1% to 2%) of asymptomatic PLHIV have microbiologically confirmed TB [37], although between 50% and 75% of such patients develop symptoms over the subsequent few months [41,42].

These findings have implications for the programme setting. In 2010, an estimated 2.3 million PLHIV (58% of those enrolled in care) were screened for TB [1]. With the new and simpler screening recommendations, these numbers will undoubtedly increase. Symptom screening must be done at baseline in all PLHIV attending pre-ART or ART clinics. Screening should also not be a one-off event but performed serially when PLHIV come to the clinic to prevent the small proportion of asymptomatic patients with TB from slipping through the net as well as to detect the high ongoing incidence of new disease that persists long-term during ART.

**Table 5. Effect of ART scale up on TB case notification rates in a rural district, Malawi**

Year	Population Thyolo District, Malawi	PLHIV ever started on ART	New TB cases per 100,000	Recurrent TB cases per 100,000
2004	539,610	1550	253	18
2005	556,700	3145	259	20
2006	574,384	6216	255	20
2007	592,630	11,525	227	18
2008	611,424	16,106	191	14
2009	630,756	21,064	173	15

PLHIV, people living with HIV; ART, antiretroviral therapy; TB, tuberculosis. Adapted from Ref. [20].

In the busy, understaffed ART clinics of sub-Saharan Africa, it is important to address simple operational questions about how often and when best to do this symptom screening so as not to overwhelm the already high workload. Laboratory capacity and appropriate quality assurance must also develop in parallel to manage the increase in referrals.

The usual method of investigating for TB is with sputum smear microscopy followed by chest radiography in those with negative sputum smears. While this system has been the mainstay for TB diagnosis for years, it is time consuming, costly for the patient who needs to make multiple journeys to the clinic and diagnostically insensitive [43,44]. This is especially true for HIV-infected TB patients in whom a significant proportion have negative sputum smears and a normal chest x-ray at very low CD4 counts < 50 cells/ $\mu$ L [45]. Without facilities for culture of *Mycobacterium tuberculosis* (MTB), and this is the case in most resource-poor settings, it is easy to miss the diagnosis of TB. There is an urgent need for more accurate, inexpensive, quick point-of-care tests for diagnosing TB.

The most important and revolutionary diagnostic development to date is a sensitive and specific fully automated and commercially available nucleic acid amplification test, the Xpert MTB/RIF assay (Cepheid, Inc., Sunnyvale, CA, USA) for use with sputum and other body specimens [46]. Xpert MTB/RIF uses a common platform to detect TB and rifampicin resistance. The cartridge-based system dispenses with the need for prior sputum processing, requires minimal laboratory expertise and results are provided in an automated manner in less than two hours. Sensitivity for one sputum specimen for smear-positive PTB is high at 98%, and for smear-negative PTB in whom sputum bacillary numbers are low, sensitivities are 72%, 85% and 90% for one, two or three specimens, respectively [46]. When used to investigate suspected EPTB using samples from a wide range of anatomic locations, Xpert MTB/RIF provides a rapid TB diagnosis in over two-thirds of cases but with a wide range of sensitivity (25% to 97%). Sensitivity is notably lower from body fluids in which mycobacterial load is likely to be very low such as pleural, pericardial and peritoneal fluid [47].

In December 2010, WHO strongly recommended that Xpert MTB/RIF be used as the initial diagnostic test in persons suspected of HIV-associated TB. By early 2012, over 450 Xpert instruments had been placed in 47 countries, and work is ongoing to assess feasibility, accuracy and effectiveness at district and sub-district health facilities [48]. The machine's functionality in these settings will depend on various operational factors that include cost, temperatures, shelf-life of cartridges, electricity supplies, maintenance and the need for annual calibration of the machine. The machine's impact will depend on how effective and timely is the linkage between the patient, the diagnosis and subsequent treatment. Data from South Africa illustrate that, when the technology is separated from the patient because of distance or related factors, the resulting gap significantly undermines the potential to improve patient outcomes [49].

Another promising test that might be useful in severe immune suppression, which is often associated with

disseminated MTB, is the measurement of urine lipoarabinomannan (LAM), one of the cell wall lipopolysaccharide components of MTB. This can be measured either with an ELISA or more easily with a Determine TB-LAM test strip (Alere, Waltham, MA, USA), the latter costing \$3.50 per test strip and producing a result in 30 minutes. This offers the real possibility of point-of-care testing. In HIV-infected patients, specificity is high at over 95% for all CD4 strata. Useful sensitivity is observed in those with CD4 counts < 200 cells/ $\mu$ L, but progressively increases as the CD4 count decreases, reaching over two-thirds in those with CD4 counts < 50 to 100 cells/ $\mu$ L [50,51].

Further work will determine the most feasible screening and diagnostic algorithm for PLHIV in these clinic settings. This will most probably be a combination of tests that include sputum smears (to identify those with infectious TB), urine LAM (to identify TB patients with the most advanced immune suppression) and Xpert MTB/RIF, for which operational research is urgently needed to determine how far peripherally the test can be decentralized to bring it as close to the patient as possible. Accurate and timely diagnosis of TB in the setting of HIV clinics has, and continues to be, the Achilles heel of the Three I's where it is important not only to diagnose and treat TB but also exclude TB so that TB preventive therapy can be safely implemented.

#### *Empirical anti-TB treatment*

Faced with the current difficulties of implementing ICF and IPT and of diagnosing TB in PLHIV with low CD4 counts, it is reasonable to consider the option of empirical anti-TB treatment in high HIV-TB burden settings [52]. The rationale is that as the CD4 count decreases, the risk of TB exponentially increases, and at a certain point, there is more to gain than lose in treating empirically for TB (Table 6). Two randomized controlled trials [PROMPT (NCT01417988) and REMEMBER (NCT01380080)] [27] are currently underway to test whether this strategy has a high benefit-to-risk ratio in PLHIV about to start ART and whether the intervention is associated with a reduction in early and long-term mortality. A final caveat is that empirical anti-TB treatment in settings where drug resistance is high adds complexity to this approach and to subsequent research study designs if the two trials underway show positive benefit.

#### **Diagnosing and treating HIV in patients with diagnosed and presumptive TB**

If we fail to prevent TB, it is important that PLHIV who develop active TB are diagnosed and treated for HIV/AIDS. The key interventions include the use of cotrimoxazole preventive therapy (CPT) and ART, provided early and promptly in the course of anti-TB treatment. CPT is safe, cheap, easy to administer and associated with significant decreases in mortality of between 25% and 46% [53–58]. CPT can also be used before and in combination with ART, with observational and clinical studies showing 40% reductions in early mortality and overall increases in life expectancy [59–61]. ART is essential to the prognosis of patients with HIV-associated TB: mortality risk is reduced by 64% and 95%, there are excellent immunological/virological responses and a reduction in recurrent TB [62–64].



**Table 6. Potential benefits from empirical antituberculosis treatment in persons living with HIV who are severely immune suppressed**

Benefit	Explanation
Mortality reduction	<ul style="list-style-type: none"> <li>● Treatment of active, undiagnosed TB</li> </ul>
TB prevention	<ul style="list-style-type: none"> <li>● Treatment through rifampin of drug-susceptible gram-positive bacterial sepsis</li> <li>● 6-months treatment of <i>Mycobacterium tuberculosis</i> in those with latent TB infection</li> <li>● 6-months prevention of exogenous TB infection in those with no latent infection</li> </ul>
Reduced nosocomial TB transmission	<ul style="list-style-type: none"> <li>● Treatment of active, undiagnosed TB, which is therefore not transmitted</li> <li>● Prevention of exogenous TB infection in those who might be exposed</li> </ul>
Promotion of integrated HIV-TB care	<ul style="list-style-type: none"> <li>● TB treatment and ART provided either in same clinic or in different clinics within the same health facility</li> </ul>
Reducing the diagnostic dilemma of diagnosing and excluding TB	<ul style="list-style-type: none"> <li>● Empirical treatment provides effective treatment to all those with active TB and prevents TB in all those with no active TB who could benefit from IPT</li> </ul>

TB, tuberculosis; ART, antiretroviral therapy; IPT, isoniazid preventive therapy.  
 Adapted from Ref. [52].

The management algorithm is straightforward (Figure 1), and provider-initiated HIV testing and counseling (PITC), CPT and ART are the basic standard of care.

#### Provider-initiated HIV testing and counselling

The HIV test is the gateway to HIV care and treatment. It establishes the diagnosis and is an important component of efforts to prevent HIV transmission. WHO recommends that PITC is provided on a routine basis [65], and this service, delivered largely through point-of-care HIV diagnostics using dipstick technology, is feasible and acceptable in most settings [66,67]. Good progress has been made in the HIV testing of TB patients, with the proportion of new and retreatment TB cases HIV tested rising from less than 5% in 2004 to 34% in 2010 [1]. Some regions do better than others – in 2010, HIV testing reached 59% of notified TB cases in Africa and 80% in Europe [1].

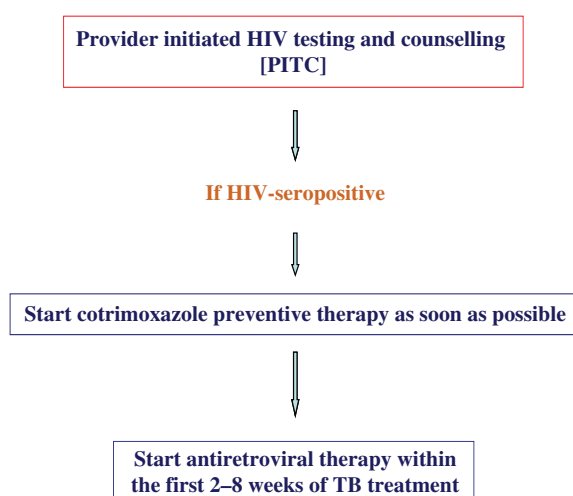
Two additional issues merit comment. First, in the routine programme setting, false-positive and false-negative HIV test results occur, and programmes need to decide on whether they do serial or parallel testing, the need for confirmatory

tests and how to implement quality assurance. Second, studies in East Africa, Guinea-Bissau and Zimbabwe [68–71] indicate the importance of moving HIV testing upstream to include patients with suspected TB and ensuring that those who are smear-negative can be referred for HIV care and consideration of ART. In Zimbabwe, 63% of patients suspected of PTB who were found to be smear-negative were HIV-positive and the majority had CD4 cell counts <350 cells/ $\mu$ L [71]. During 12-month follow-up, 18% were diagnosed as having TB, only 15% were started on ART and 12% of the cohort was known to have died. In line with new WHO recommendations [14], these poor outcomes could be avoided if patients with suspected TB, and this applies to partners and family members, were routinely HIV tested and those found HIV-positive linked to structured HIV care and treatment that included TB screening.

#### Antiretroviral therapy

ART is an essential intervention for the management of HIV-associated TB. The Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) trial clearly showed that across a range of CD4 counts it was better to start ART during anti-TB treatment than to wait until TB treatment had been completed [72], and these data informed the 2010 WHO ART guidelines recommending that all HIV-positive TB patients are eligible for ART, regardless of CD4 count [23].

The issue of optimal timing of ART in relation to start of anti-TB treatment has been clarified by three randomized controlled studies: CAMELIA, STRIDE and SAPIT [73–75]. While all three trials were slightly different – median CD4 counts at baseline ranged from 25 cells/ $\mu$ L in Cambodia to 150 cells/ $\mu$ L in South Africa, and there were different working definitions of TB – collectively, one clear message emerges, namely that earlier initiation of ART saves lives in HIV-infected patients with TB. These benefits were particularly evident for those with CD4 cell counts <50 cells/ $\mu$ L in whom the risk of HIV infection or death was minimized by starting ART within the first two to four weeks of TB treatment. These and subsequent studies [76,77] show that



**Figure 1. Management algorithm for HIV-associated TB.**

the risk of immune reconstitution inflammatory syndrome (IRIS) is increased, especially in those with low CD4 counts, but this is counterbalanced by improved survival. One exception is in HIV-infected patients with TB meningitis in whom early ART is not associated with improved survival, probably because of the devastating effects of IRIS within the confined space of the central nervous system [78].

In many low-income countries, CD4 count testing remains an obstacle to accessing HIV care and treatment, and insistence on its use will reduce ART uptake. However, where facilities for measurement do exist, knowledge of the CD4 count would allow a more rational guide as to whether ART is started within two weeks or between two and eight weeks of the start of anti-TB treatment.

There are no important drug-drug interactions between first-line ART and standard anti-TB treatment, provided efavirenz is used as the non-nucleoside reverse transcriptase inhibitor. However, protease inhibitors, used in most second-line ART regimens, cannot be administered with rifampicin. Rifabutin has minimal effects on serum levels of protease inhibitors and is therefore a potentially safe and effective agent to maintain rifamycin-based anti-TB treatment with second-line ART [79]. To date, however, issues such as cost, lack of fixed-dose combination pills and lack of registration in many countries preclude its use in current routine management.

#### *ART and drug-resistant TB*

In the absence of ART, HIV-infected patients with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) have high case fatality rates [80–82]. With the rollout of Xpert MTB/RIF assay as the recommended diagnostic test in HIV-infected patients with suspected TB, it is likely that the number of patients diagnosed with MDR-TB will increase dramatically. The earlier detection of MDR-TB should in itself improve prognosis provided there is ready access to appropriate second-line anti-TB treatment, as most MDR-TB patients in low-income countries are diagnosed late, usually only when they fail or relapse on standard anti-TB treatment.

Observational cohort studies have shown that ART improves survival of HIV-infected patients with MDR-TB [83] and XDR-TB [84], and ART should be started as early as possible in combination with CPT [85]. Early ART combined with often advanced clinical disease puts patients at increased risk of TB-IRIS in addition to frequent drug interactions and co-toxicities [86]. With promising new TB drug compounds on the horizon to treat drug-sensitive and drug-resistant TB, it will be essential to include patients with HIV-associated TB in clinical trials to understand and better manage the potential interactions between ART, CPT and the new TB agents.

#### **HIV-associated TB in women and children**

In high HIV-prevalence settings, more women are notified with TB compared with men, especially in the southern part of Africa, and this is due to the feminization of the HIV epidemic in this region [87]. There appears to be no difference in access, treatment or response to treatment between male and female patients. TB in pregnant women living with HIV increases the risk of vertical transmission of HIV and there

is a higher risk of maternal mortality in pregnant women co-infected with HIV and TB compared with pregnant women who just have TB [87].

Although TB is not the great killer in HIV-infected children as it is in adults, it is nonetheless an important cause of their death [88,89]. Because of overlap in clinical features between children with HIV/AIDS and TB, accurate diagnosis of HIV-associated TB is very difficult, even with point scoring systems and diagnostic algorithms, which are anyway rarely used in routine practice [87]. In general, the HIV-TB strategies described for adults are equally applicable to children, but some brief comments are in order.

ART is recommended for all children under the age of two years with confirmed HIV infection, regardless of CD4 count [90], and under trial conditions, this is associated with a significant reduction in mortality and disease progression, including a reduction in the burden of active TB [91]. However, despite ART, the risk of TB remains high. Primary IPT in one trial in South Africa amongst children on ART failed to reduce this risk or the risk of death [92], while amongst young children not accessing ART, primary isoniazid prophylaxis in another South African trial was associated with reduced TB incidence and death [93]. The conundrum of how to best prevent TB in HIV-infected infants is still not resolved. Scale up of ART in this population is slow and requires far better access to early infant diagnosis and appropriate paediatric ART formulations. BCG vaccination in these children is potentially dangerous with an attendant risk of local and disseminated TB [89], underscoring the urgent need for a TB vaccine that can be safely given to young children with HIV infection.

TB case finding and diagnosis in children is hampered by the frequent failure to produce sputum and by a high proportion presenting with EPTB. Within these constraints, Xpert MTB/RIF is proving a potentially useful tool in children for the diagnosis of PTB (using induced sputum specimens) and EPTB [94], especially lymphadenitis [95].

#### **Delivering HIV-TB services**

Despite good progress made in HIV care and treatment for TB patients only one third of notified TB patients in 2010 were HIV tested, and of those, only 46% received ART [1]. Co-location and/or integration of TB and ART services are the key to achieving better and timely collaborative activities. In a South African township, for example, only 11% of HIV-infected patients with CD4 cell counts <50 cells/ $\mu$ L who were referred from TB services to separate HIV services started ART within four weeks of their TB diagnosis [96]. Centres for TB diagnosis and treatment and for HIV care and treatment must be integrated, located together or better matched quantitatively and geographically. HIV testing and TB treatment services are already well decentralized in many countries to peripheral sites, so the goal is now to decentralize services for TB diagnosis and ART provision. Innovative approaches are needed – for example, providing comprehensive HIV-TB care and treatment at the TB clinic for the duration of TB treatment with transfer to the HIV programme after TB treatment is completed [97]. Attention must be paid to clinic infrastructure with good natural

cross-ventilation and patient-flow so as to minimize the risk of TB nosocomial transmission.

Current screening and treatment strategies miss large numbers of people who never make it to health facilities, so it is essential to think out of the box and determine whether community diagnostic, treatment and preventive services can be provided through home-based and mobile care teams. For example, in Malawi, oral self-testing for HIV was acceptable and accurate and has the potential for high uptake at community level if it can be supervised and linked to counselling and care [98]. In Zambia, household-based HIV and TB interventions offering HIV testing, easy access to TB diagnosis and linkage to HIV-TB care and treatment were feasible and reduced TB prevalence in the community [99–101]. In Zimbabwe, active TB case finding in the community, particularly with a mobile van approach, was successful in detecting and reducing community prevalence of culture-positive TB [102]. In Thibela, South Africa, community-wide IPT for nine months regardless of HIV status in a gold-mining work force had no effect in reducing community-wide TB incidence or prevalence [103]. Moreover, any individual benefit in reducing TB risk among those who received IPT was limited to the duration of therapy [104], strengthening the argument for long-term therapy when used in countries with high TB transmission rates.

Not everyone identified and diagnosed through a community approach makes it to care, either for TB or HIV treatment [105], so it is essential that these gaps are plugged. As with case detection, integrated care and treatment can also be given through a home-based approach and may be associated with excellent treatment outcomes [106].

## Conclusions

In summary, new scientific evidence shows us what interventions can make a difference and we have new tools to improve TB diagnosis. The job now is to apply this evidence and these new tools within routine healthcare systems and communities in resource-poor countries. Much earlier start of ART combined with IPT, active TB case finding using innovative TB diagnostic technology, quality assured HIV testing of patients with confirmed or suspected TB and timely initiation of CPT and ART to co-infected patients will save many lives and may be augmented by bold initiatives involving empirical TB treatment and community-based interventions. The 2012 World TB statement of “Zero TB deaths” fits well into the bold new vision articulated by UNAIDS of the Three Zeros – zero new HIV infections, zero discrimination and zero AIDS-related deaths [107]. Every year, HIV-associated TB robs 350,000 young men and women of a potentially long, healthy and productive life. As Bo Draser, Editor of the *Transactions of the Royal Society of Tropical Medicine & Hygiene*, once remarked “We need to take death away from these young people and make it the monopoly of the old” [108].

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## Authors’ contributions

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