SERIES "UPDATE ON TUBERCULOSIS"
Edited by C. Lange, M. Raviglione, W.W. Yew and G.B. Migliori
Number 3 in this Series

Clinical management of tuberculosis and HIV-1 co-infection

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ABSTRACT: In many parts of the world the commonest serious opportunistic infection that occurs in HIV-1 infected persons is tuberculosis (TB). HIV-1 co-infection modifies the natural history and clinical presentation, and adversely affects the outcome of TB. Severe disseminated disease is well-recognised but it is increasingly appreciated that early disease characterised by very few or no symptoms is also common. Immunodiagnostic methods to ascertain latent TB in HIV-1 infected persons are compromised in sensitivity.

Chemoprevention of HIV-1-associated TB is effective, its benefits are restricted to those which have evidence of immune sensitisation and appear short-lived in areas of high TB burden. Although promising advances in the microbiological diagnosis of TB have recently occurred, the diagnosis of HIV-1-associated TB remains difficult because of more frequent presentation as sputum negative or extrapulmonary disease.

Management of co-infected patients can be complex because of overlapping drug toxicities and interactions. Nevertheless consensus is developing that antiretroviral therapy should be provided as soon as practicable after starting TB treatment in HIV-1 co-infected persons. This has the consequence of increasing the frequency of immune reconstitution inflammatory syndrome, the pathogenesis and management of which is poorly defined.

KEYWORDS: Complications, diagnosis, HIV-1, management, *Mycobacterium tuberculosis*

In the 30 yrs since the progressive immuno-suppressive effects of HIV-1 were first recognised, tuberculosis (TB) has emerged as the most common serious opportunistic infection. This is especially the case in Sub-Saharan Africa where the advent of the HIV-1 pandemic has seriously derailed TB control. The remit of this article is to describe the modifying effect of HIV-1 infection on the clinical presentation and management of TB in HIV-1 infected persons.

CLINICAL FEATURES OF HIV-1 ASSOCIATED TB

Persons with HIV-1 infection are at increased risk of active TB due to reactivation of latent TB and more rapid progression to disease after TB infection. In TB endemic settings an annual risk of active TB of up to 30% in those with advanced HIV-1 has been documented [1]. The clinical presentation and course of active TB in HIV-1 infected persons are altered, particularly in those with advanced immunosuppression (CD4 counts <200 cells·mm^{-3}): active pulmonary TB can initially be asymptomatic; extrapulmonary TB is more common; the clinical course is accelerated; it is more difficult to diagnose; and mortality is higher.

In Europe and North America active TB predominantly occurs in HIV-1 infected patients with low CD4 counts (<200 cells·mm^{-3}) [2] whereas in TB endemic settings, such as sub-Saharan Africa, it occurs across the spectrum of CD4 counts [3]. In a study conducted in the South African gold mines, the risk of TB doubled even in the first year after HIV-1 seroconversion [4]. The clinical presentation in HIV-1 infection is influenced by degree of immunodeficiency [5–7]. In patients with CD4 >350 cells·mm^{-3}, there are few differences in the clinical presentation compared with HIV-1 uninfected patients, whereas in

Previous articles in this series: No. 1: .Erkens CGM, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. Eur Respir J 2010; 36: 925–949. No. 2: Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2010; 36: 1185–1206.

those with CD4 counts <200 cells·mm^{-3} atypical clinical and radiographic features and more rapid progression are far more common [5, 6, 8, 9]. Multidrug-resistant (MDR)- and extensively drug-resistant (XDR)-TB are also emerging problems. MDR- and XDR-TB are associated with a high early mortality in the context of HIV-1 infection [10] and HIV-1 infection is an independent risk factor for death from drug-resistant TB [11].

PRESENTATION OF PULMONARY TB

Pulmonary TB remains the most frequent form of active TB in HIV-1 infected persons, even those with low CD4 counts. Although the clinical presentation of pulmonary TB is different to the presentation of pulmonary TB in HIV-1 uninfected patients, the most common symptoms remain cough, fever, night sweats and significant weight loss [12, 13]. Relative to HIV-1 uninfected patients, weight loss and fever are more common, whereas haemoptysis is less common and some studies have reported a decreased proportion of patients with cough [14, 15]. The latter observations relate to a reduced inflammatory response resulting in less pulmonary cavitation and endobronchial involvement [8, 9].

Whereas many case detection algorithms for TB include cough of ⩾2–3 weeks duration in their criteria, it is important to note that cough of <3 weeks can be a presenting feature in HIV-1 infected patients. In Brazil, a third of patients with pulmonary TB were diagnosed when cough had been present for ⩽3 weeks [16]. In Malawi, amongst patients (53% of whom were HIV-1 co-infected) with a cough of <3 weeks duration and no response to oral antibiotics, 35% were found to have pulmonary TB. [17]. In regions with a high incidence of TB, persistent cough even for <3 weeks is suspicious for active TB in HIV-1-infected individuals.

Significant weight loss is observed in up to 85% of patients from Africa at the diagnosis of TB [8]. In a large study in Thailand looking at screening for TB in HIV-1 infected patients, weight loss occurred in 50% of patients who were screened and had a negative predictive value of 92% [18]. Weight loss was reported more frequently in patients with a CD4 <200 cells·mm^{-3} when compared to patients with higher CD4 counts in Brazil [16]. This has also been observed in Africa where weight loss >10% was strongly correlated with a CD4 <200 cells·mm^{-3} [3]. Weight loss was found to discriminate between pulmonary TB and other pulmonary infections (*Pneumocystis jiroveci* pneumonia and bacterial pneumonia) in HIV-1-infected patients (OR 3.6) in one study [14]. In the same study, fever for >7 days was also strongly associated with a TB diagnosis (OR 3.9) [14].

ASYMPTOMATIC ACTIVE PULMONARY TB

Prevalence surveys and intensified case finding studies that rely on sputum culture have brought to prominence the phenomenon of HIV-1 infected patients having sputum culture-positive TB in the absence of symptoms [19–21]. SWAMINATHAN *et al.* [20] described 10 such patients (CD4 count range 72–552). During an active case finding study in a high TB and HIV-1 prevalence community in South Africa, among 762 adults enrolled investigators found 12 cases of previously undiagnosed, sputum culture-positive TB, nine of whom were HIV-1 infected. Symptoms were not a useful screen for TB in these patients [21]. Four out of 14 Tanzanian HIV-1 infected

patients with CD4 ⩽200 diagnosed with pulmonary TB (positive sputum microscopy or culture) during screening for a vaccine study were asymptomatic with a normal chest radiograph [19]. This phenomenon is one of the reasons why symptoms screens have reduced sensitivity in HIV-1 infected patients [19–21]. In South Africa one or more of cough for ⩾2 weeks, night sweats, fever or significant recent weight loss were reported in only 79% of patients diagnosed with TB on the basis of a positive sputum culture. Importantly, 62% of patients without TB had one or more of these symptoms, suggesting suboptimal sensitivity and specificity of this symptom screen [22]. In contrast, a recent study in South East Asia found that a screening tool requiring any one of three symptoms (cough of any duration, fever of any duration and night sweats for ⩾3 weeks duration in the preceding 4 weeks) performed well with a sensitivity of 93% among 1,748 HIV-1 infected patients, 15% of whom had culture proven TB. The study included extrapulmonary TB cases [18]. This suggests screening for TB in HIV-1 infected persons in the setting of a high TB burden, the best approach is to use symptom screen in conjunction with induced sputum culture. However, this poses significant programmatic challenges and laboratory cross contamination is also a problem in areas of high TB incidence [23, 24]. Symptom screen could be repeated at each follow-up visit.

EXTRAPULMONARY TB

Extrapulmonary TB and disseminated TB (active TB at more than one non-contiguous anatomical location) are more common in HIV-1 infected persons, especially as the CD4 count declines [25–28]. Wide dissemination of TB in advanced HIV-1 may occur [29]. There may or may not be coexistent pulmonary TB. In Zambia, amongst HIV-1 uninfected TB patients, 72% had pulmonary TB alone, 16% extrapulmonary TB alone and 12% had both. Among HIV-1 infected patients, 40% had pulmonary disease alone, 34% extrapulmonary disease alone and 26% both [30]. More striking differences between HIV-1 uninfected and infected patients have been reported in a review combining data from several studies: pulmonary TB alone was present in 80% *versus* 30%, extrapulmonary TB alone in 15% *versus* 20% and both in 5% *versus* 50% [31]. In the USA, HIV-1 infected TB patients with CD4 >300 had overt evidence of extrapulmonary involvement in 28% of cases, 44% in those with a CD4 count 201–300, 50% in those with a CD4 count 101–200 and 70% in those with a CD4 count ⩽100 [7].

The most frequent extrapulmonary sites in HIV-1 infected and uninfected persons have been reported to be lymphadenitis (35%) and pleural effusion (20%) [31], other sites include other serosal surfaces (pericardial and peritoneal), abdominal (involving liver, spleen, peritoneal surface and/or lymph nodes) and neurological [8, 32]. Splenic hypodensities reflecting multiple microabscesses and abdominal lymphadenopathy are common ultrasound findings in HIV-1-infected patients with disseminated TB [33]. Mycobacteraemia is more common in HIV-1 [20, 34]. In South Africa, 28% of HIV-1 infected patients with smear-negative TB had positive mycobacterial blood cultures [35]. Mycobacteraemia has been reported to be more common as the CD4 count declines and in patients with CD4 ⩽100 mycobacteraemia has been reported in up to 49% [7]. Patients with advanced HIV-1 and mycobacteraemia may present with

sepsis syndrome and septic shock [36, 37]. Severe wasting illness with or without associated diarrhoea may be the only clinical feature of disseminated TB in HIV-1 [6, 29]; although, in such patients it is important to investigate for other HIV-1 related opportunistic infections that may account for over half of such presentations rather than TB (table 1) [38].

Like HIV-1 uninfected patients, HIV-1 infected patients can present with a range of neurological manifestations: tuberculous meningitis (TBM), tuberculomas, radiculomyelitis and tuberculous brain abscess [39]. In patients with TB, meningeal involvement is more common in HIV-1-infected patients [40, 41]. One study of 3,710 TB cases demonstrated meningeal involvement in 6.4% of HIV-1-infected patients compared to 1.2% of HIV-1-uninfected patients [41]. TBM generally presents with similar clinical and cerebrospinal fluid (CSF) findings in the HIV-1-infected compared to the HIV-1-uninfected patients [42]. Acellular and completely normal CSF examinations have, however, been described in HIV-1-infected patients with TBM [40, 43, 44]. HIV-1-infected TBM patients more frequently also have extra-meningeal TB [41, 42, 44].

While most extrapulmonary manifestations are more common in HIV-1, extraspinal tuberculous arthritis appears to occur less frequently [45]. Clinical features of disseminated TB depend upon anatomical location [32, 46] and systemic symptoms can be nonspecific. Given that 40–60% of cases of disseminated TB have co-existent pulmonary TB [8], patients presenting with features of disseminated TB should always have sputum sent for TB microscopy and culture. HIV-1 may modulate the complications of extrapulmonary TB. For example, HIV-1 infected patients are reported to be less prone to developing constriction as a complication of pericardial TB [47].

TABLE 1	Disorders that occur commonly in HIV-1 infected patients and should be considered in the differential diagnoses for tuberculosis (TB)[#]

Pulmonary TB
  Bacterial pneumonia
  Pneumocystis pneumonia
  Bacterial infection exacerbating bronchiectasis
  Pulmonary Kaposi's sarcoma
  Lymphoid interstitial pneumonitis
  Pulmonary nocardiosis or cryptococcosis
  Heart failure

Disseminated TB
  Bacterial sepsis, *e.g.* non-salmonella typhi infection
  Disseminated fungal infection, *e.g.* cryptococcosis, histoplasmosis and
    penicilliosis
  Non-tuberculous mycobacterial infection, *e.g. Mycobacterium avium* complex
  Kaposi's sarcoma, Lymphoma or Castleman's disease
  Disseminated cytomegalovirus infection
  Enteric pathogens, *e.g.* isosporiasis, cryptosporidiosis
  Visceral leishmaniasis
  Bacillary angiomatosis

[#]: considerations will depend on clinical presentation and which opportunistic infections are endemic.

RAPID PROGRESSION AND HIGHER MORTALITY

TB tends to progress more rapidly in HIV-1 infected persons and may present as an acute illness [6, 48]. Amongst South-African gold miners who were diagnosed with TB the mean duration of smear positivity before diagnosis was substantially shorter for HIV-1-infected compared to uninfected TB patients (0.17 and 1.15 yrs, respectively) [48]. This indicates more rapid progression of disease and subsequent diagnosis of TB in HIV-1 infected patients compared to TB patients who were not HIV-1 infected. Similar findings were noted in a community-based study in Zimbabwe: duration of infectiousness prior to TB diagnosis was 18 weeks for HIV-1 infected *versus* 1 yr for HIV-1 uninfected patients [49]. TB may also present as an acute community acquired pneumonia and needs to be considered in any HIV-1 infected patient presenting with acute respiratory illness (table 1) [50, 51].

Several studies from sub-Saharan Africa have demonstrated that TB is present in approximately half of HIV-1 infected persons at *post mortem* and in many TB was not diagnosed *ante mortem*. Therefore, it is critical to investigate, diagnose and start TB treatment rapidly in HIV-1 infected patients, to reduce morbidity, the need for hospitalisation and mortality which may result from rapid deterioration [29, 52]. The rapidity of deterioration in HIV-1 patients with TB, as well as difficulties in diagnosis (discussed below), contributes to this. During treatment, mortality is higher for HIV-1 infected patients [53–55] due to both advanced TB disease at diagnosis and other opportunistic infections. Amongst South African gold miners 6-month mortality in HIV-1 infected patients with TB was 13% compared to 0.5% in HIV-1 uninfected patients [53]. In Brazil the mortality rate in HIV-1 infected TB patients was 24.7 per 100 patient yrs compared to 2.5 per 100 patient yrs amongst HIV-1 uninfected patients. Although mortality was substantially reduced amongst patients on antiretroviral therapy (ART), it was still significantly higher than HIV-1 uninfected TB patients (HR 6.6) [54].

DIAGNOSIS OF TB IN HIV-1 INFECTED PERSONS

Latent TB in HIV-1 infected persons

Latent TB is inferred solely by evidence of immunological sensitisation to mycobacterial proteins by a positive tuberculin skin test (TST) or a positive interferon-gamma release assay (IGRA) in the absence of symptoms or signs of active disease [56, 57]. The evidence for latency arises from historical studies in which *Mycobacterium tuberculosis* was isolated *post mortem* from lesions in otherwise disease-free persons [56]. From TST surveys it is inferred that one third of the world's population has latent TB infection. This presents an enormous reservoir of infected persons who could potentially develop active disease. However, several features of the epidemiology of HIV-1-associated TB require modification of the concept of latency [58]. First, HIV-1 infected persons more often and rapidly progress to disease following infection than the often-quoted 5–10% life-time risk [4, 59–61]. The annual risk of active TB is up to 30% in HIV-1 infected individuals [1]. Secondly, in cases of recurrent TB, it has become clear that this often represents re-infection rather than endogenous reactivation: this is particularly the case in high-incidence environments [62, 63]. Thirdly, the existence of a substantial prevalence of asymptomatic early HIV-1-associated TB, as outlined above, indicates

that bacterial replication is a feature of minimally symptomatic disease [21, 48, 49, 59]. Indeed this has always been inferred because the most tested treatment for latent infection, isoniazid (INH), kills replicating bacilli.

DIAGNOSIS OF LATENT TB IN HIV-1 INFECTED PERSONS

Despite flaws, the TST remains the best-validated method of inferring latent TB infection, and predicting risk of progression and benefit from INH preventive therapy (IPT). The flaws of the TST have been extensively discussed: false positives occur because the purified protein derivative reagent contains many antigens present in bacille Calmette–Guérin (BCG) and non-pathogenic mycobacteria, and false negatives occur in the immunocompromised, early in primary TB and in disseminated TB [64]. The test cannot distinguish active infection from latent infection. Administration and reading require two clinic visits and occasionally the reaction may scar.

Early studies established that in HIV-1 infected persons the sensitivity of the TST is markedly diminished especially as the CD4 count declines [65–67]. In a comparison of similar HIV-1 infected and uninfected persons in a high-incidence area of South Africa, 52% of HIV-1 infected persons had a reaction >5 mm, whereas 86% of those uninfected had reactions >5 mm. The corresponding figures for the 10 mm cut-off were 49% and 83%, respectively [68].

In recognition of these deficiencies of the TST, in the last 10 yrs *in vitro* IGRAs have been developed and commercialised as a potential replacement. IGRAs depend on *in vitro* restimulation of lymphocytes by antigens that are either deleted from the genome of all BCG strains (early secreted antigenic target 6 KDa protein and culture filtrate protein-10 [69, 70]) or encoded on an evolutionarily recent prophage insertion into the genome of modern pathogenic *M. tuberculosis* strains (TB7.7 encoded by Rv2654c [71]). Although a laboratory capable of cell culture and ELISA is required, IGRA tests have operational advantages over the TST as they require a single patient visit and render a quantitative result that may remain relevant for some time whereas a missed TST reading means the test can only be repeated. IGRA have relatively low inter-observer variability and, providing no TST is simultaneously administered [72], repeat testing does not boost the response. There is consensus that IGRA are of higher specificity for diagnosing TB infection in BCG vaccinated persons [73]. Like the TST, they have limited ability to differentiate between active disease and latent infection.

The potential advantages of IGRA testing have encouraged evaluation of these tests in HIV-1 infected persons with three aims being pertinent. First, is the sensitivity of IGRA to detect TB infection in HIV-1 infection less impaired than the TST? Secondly, do IGRA tests better predict subsequent active TB and thus better guide the prescribing of preventive therapy? Thirdly, can IGRA tests aide the diagnosis of active HIV-1 associated TB? With respect to latent TB these aims are, however, confounded by the following factors. First, there is no 'gold-standard' for latent TB and so studies have tended to use the sensitivity to detect active culture proven TB (see below) as a proxy. This is likely to lead to an overestimate of sensitivity because it is recognised experimentally and in humans that

there is a relationship between bacillary counts and the peripheral response to ESAT-6 and CFP-10 proteins [74–78]. As HIV-1 infected persons with latent TB presumably have relatively low bacillary counts and an impaired immune response it follows that a lower frequency of positive results would be expected in the profoundly immunosuppressed. A second factor must also be considered when interpreting variable findings on this subject. Whilst the term IGRA is catchy, it implies that tests are generic and interchangeable which they are not. Importantly, the laboratory base for the ELISpot based T-Spot.TB test is a fixed number of peripheral blood mononuclear cells whereas the QuantiFERON tests use whole blood. As numbers of CD4+ T-cells decline, isolation of peripheral blood mononuclear cell might tend to partially offset that decrease whereas the absolute numbers of CD4 cells (upon which both tests rely) will obviously decrease in whole blood [79, 80].

Only a minority of studies of IGRA have included HIV-1 infected persons who may have latent TB. Study design is markedly heterogeneous and very few studies have encompassed latent infection in a high incidence environment. The T-Spot.TB test has less frequently been studied than the QuantiFERON tests. However, several conclusions can be made from existing studies. First, it is commonly observed that the rate of indeterminate assays (due a negative response in the positive control well or tube) increases as the CD4 count declines [81–86]. In the few studies in which 'head to head' three-way comparisons have been made, data are conflicting as to whether this effect is greater with QuantiFERON tests [68, 85] or for the T-Spot.TB [86, 87]. It is certainly the case that the T-Spot.TB test requires greater laboratory sophistication. Almost all studies of HIV-1 infected persons report that agreement between the IGRAs and TST is sometimes poor and rarely better than fair with kappa values in the range 0.3–0.5 [68, 83–87]. This disconcordance might feasibly be of prognostic significance but it is very difficult to evaluate which is best at predicting subsequent TB. Only a single study has reported the predictive value of a baseline positive IGRA test for subsequent TB in HIV-1 infected persons. AICHELBERG *et al.* [81] performed QuantiFERON Gold-in tube testing on 830 HIV-1 infected persons attending a clinic in Austria. 44 were found to be positive of whom seven had prevalent TB. Three of the remaining 37 (and none of those negative) developed bacteriologically unproven TB during follow-up. It is difficult to avoid the frequently made conclusion that further studies would be required, especially in high incidence environments, to determine whether these tests could become a routine part of care in HIV-1 infected persons without evidence of active TB.

DIAGNOSIS OF ACTIVE TB

TB diagnostics have benefited considerable innovation in the last 10–15 yrs and there is now optimism that some new tests can be implemented that will hopefully translate into better health outcomes. An important distinction needs to be made between tests applicable at national and regional reference laboratories and those intended for point of care, which is the most demanding scenario. Benchmarking new techniques to diagnose active TB is guided by the diagnostic gold standard for active TB, which is microbiological isolation of *M. tuberculosis*. However, the detection of acid-fast bacilli by microscopy

remains the only available laboratory test to diagnose active TB in most resource-limited settings. Sputum microscopy is inexpensive, of high specificity and detects the most infectious patients [88]. However, sputum microscopy is insensitive: a feature exacerbated by HIV-1 co-infection because the frequency of smear-negative and culture-positive cases is increased (fig. 1) [64, 88, 103]. Fluorescence microscopy appears more sensitive than conventional microscopy and has similar specificity [104], but has not been as widely studied in HIV-1-infected persons. The advent of light emitting diode fluorescent microscopes that appear to equal the performance of the more complex mercury vapour lamp based devices is also an advance [105]. Sputum induction has been referenced in medical research literature since the 1960s as an effective tool for the diagnosis of TB in patients who are smear-negative or unable to produce sputum [106]. Studies in HIV-1 infected persons are relatively few. HARTUNG et al. [107] demonstrated that sputum induction performed on smear-negative patients or those unable to expectorate increased their diagnosis of TB by 29%. Similarly, PARRY et al. [108] observed a 19% increase in TB diagnoses when sputum induction was evaluated in Malawi.

In the absence of a positive smear the chest radiograph may play an important role in the diagnosis of HIV-1 patients with suspected TB. There are several chest radiograph features that are highly suggestive of TB, but none are diagnostic [17, 26, 38]. The degree of immunosuppression plays a critical role in the radiographic pattern [8, 9]. Persons with relatively well-preserved immunity (CD4 cell count >200 cells·μL^{-1}) can present with a typical adult pattern with upper lobe predominance and cavitation. In patients with more advanced immunosuppression (CD4 cell count <200 cells·μL^{-1}) the radiological features tend to be more atypical with mid- or lower-zone infiltrates and hilar and mediastinal lymphadenopathy [8, 9, 16, 27, 109]. Pleural effusions can occur irrespective of immune

status [16]. A miliary pattern occurs commonly with more advanced immunosuppression [8]. It is also well described that HIV-1 infected patients with active TB proven on sputum culture can have normal chest radiographs [16, 19, 26].

In the absence of any microbiological evidence of TB, guidelines for diagnosis exist [110]. Expanded case definitions have performed well but should be combined with follow-up and objective assessment of response to treatment [38]. HIV-1 infected patients with smear-negative TB have a higher mortality than smear positive patients [9, 38, 111, 112]. Therefore, it is important that patients who fail to respond to treatment for smear-negative TB should be referred for further investigation as they may have drug-resistant disease or an alternative diagnosis (table 1) [38].

Culture of M. tuberculosis on solid media may be prolonged. Liquid culture media significantly reduces the time and effort of obtaining a positive culture [6, 26, 113] but is not infrequently associated with contamination (up to 17%) [114]. It is also expensive to establish and thereby not routinely available in many resource-limited settings [64]. An alternative lower cost liquid-based culture technique is the microscopic observation drug sensitivity (MODS) assay in which tangles of mycobacteria are directly visualised via an inverted microscope [115]. An additional advantage is the ability to simultaneously determine drug resistance. Several subsequent evaluations of MODS have found it to be equivalent or slightly superior to automated liquid culture for the diagnosis of both pulmonary and extrapulmonary TB [116, 117]. However, no commercially available form of the test exists.

Present commercially available and several 'in house' nucleic-acid amplification (NAAT) tests have a high specificity for M. tuberculosis, and high sensitivity in smear-positive sputum. However, sensitivity in smear-negative TB and disseminated
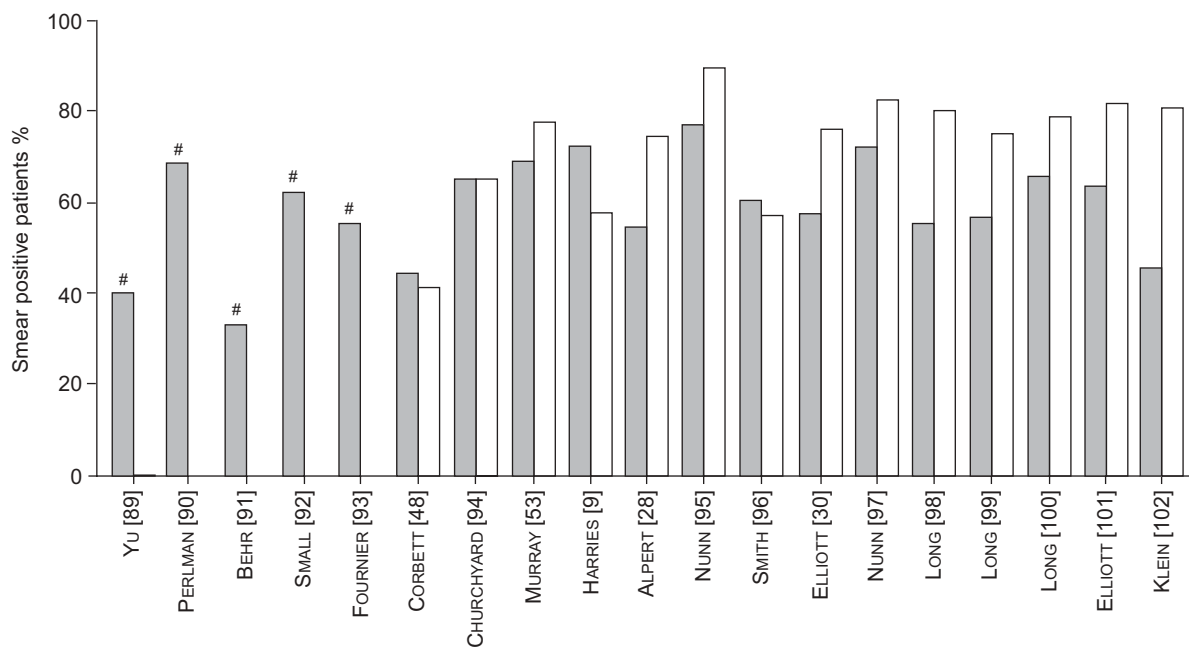

FIGURE 1. Comparison of smear positivity in HIV-1 infected and HIV-1 uninfected patients. □: HIV negative, smear positive; ■: HIV positive, smear positive. #: no HIV-negative comparison groups in these studies.

TB has tended to be moderate, which limits their diagnostic role [1118, 119]. The Cepheid GeneXpert system has, however, recently been reported as having 71.7% sensitivity in smear-negative, culture-positive cases [120] and is under extensive evaluation. This system has two operational advantages: simplicity of sputum processing and the ability to simultaneously detect drug resistance. Rapid detection of rifampicin resistance is also possible on culture or smear-positive specimens with high sensitivity (~98%) and specificity (97%) by the use of line probe assays: two of which are commercially available [121]. The accuracy for INH is more variable, with lower sensitivity (84.3%). However, these tests require extensive laboratory support and infrastructure: the generation of amplicon by nested NAAT that is subsequently hybridised to a membrane create conditions in which cross-contamination can be problematic.

An encouraging initial report of 90% sensitivity of RD1 specific ELISpot in active HIV-1-associated TB [122] prompted a number of evaluations of commercial tests. A wide range of sensitivities have been observed from 23% to 81% [74, 123–128]. Indeterminate rates increase as CD4 count declines. Relating the quantitative ELISpot count to CD4 increases the specificity and sensitivity of the diagnosis of active TB in HIV-1 infected persons [74, 129, 130]. However, overall specificity remains poor at 62%, although it could be argued that the finding of a positive IGRA in a HIV-1 infected person should prompt consideration of treating latent infection even if active disease is not found [74].

Commercial and in house serological testing continues to be researched although the consensus is that where adequate sensitivity is achieved this is always at the loss of specificity and few studies have included HIV-1 infected patients [131, 132]. There has been recent interest in the detection of the urinary lipoarabinomannan antigen, particularly in HIV-1 infected persons, as test sensitivity tends to improve with advancing immunosuppression [22] and may, therefore, serve as a potentially useful 'rule-in' tool.

MANAGEMENT OF TB IN HIV-1 INFECTED PERSONS
TB therapy
Duration and effectiveness of TB treatment
The optimal length and type of TB treatment in patients co-infected with HIV-1 is unknown and long-term randomised trials are needed to address this question. Some trials suggest that a 6-month short-course therapy is appropriate in HIV-1 [133–135], whilst others suggest prolonging the duration to 9 months. A retrospective review from the US showed no treatment failures in HIV-1 infected patients administered a 6 month standard rifampicin-based regimen but relapse rates were four-times higher in those treated for 6 months compared to those treated for longer [136]. However, re-infection could not be distinguished from relapse and the dataset was from a small subset of patients as only 17% of the HIV-1 infected patients (compared to 37% of the HIV-1 uninfected/unknown group) were given the standard 6-month regimen. Directly observed therapy (DOT) was only prescribed to 57% of the cases and there were no formal adherence assessments in those not on DOT. Interestingly, HIV-1 infected patients were significantly more likely to experience adverse drug reactions and to acquire drug-resistant TB than the HIV-1-uninfected/

unknown group. A conclusion to be drawn from these data is that when adherence is suboptimal, 6 months of therapy is insufficient.

Further insight comes from a review of six studies of HIV-1 infected patients and three studies of patients without HIV-1 infection given treatment for ≥6 months. Unfortunately, there was variability in study design, eligibility criteria, site of TB disease, frequency and method of treatment, and outcome definitions [137]. Although the relapse rates appeared higher in some studies of co-infected patients, other outcomes such as cure rates and successful treatment rates were comparable when 6-month regimens were used. In Brazil, TB recurrence rates were high in HIV-1 infected persons but if there was completion of initial TB therapy, use of ART and subsequent increases in CD4 cell counts then recurrence rates were low, suggesting re-infection may have been the reason for recurrence [138]. Overall, most studies concur that standard TB treatment should be given to HIV-1 infected patients whenever possible [134, 135, 139, 140]. A 6-month treatment regimen that includes rifampicin and INH throughout should be given for drug-sensitive TB (outside of the central nervous system). This is usually a regimen of four drugs for 2 months, followed by INH and rifampicin for a further 4 months (at least 182 doses of INH and rifampicin and 56 doses of pyrazinamide and ethambutol in total). Daily TB treatment should be given whenever possible. A recently published systematic review and meta-analysis of treatment studies of active TB in HIV-1 co-infected patients suggested that ≥8 months of rifamycin containing treatment with initial daily dosing might be required for optimal treatment outcomes, but concluded that further randomised controlled trials were required to confirm this [141]. In drug-sensitive TB affecting the central nervous system, data supports 9–12 months of treatment. This usually consists of four drugs for 2 months, followed by 7–10 months of INH and rifampicin. MDR- or XDR-TB should be treated by practitioners with experience in such cases and requires prolonged treatment [142, 143].

DIRECTLY OBSERVED THERAPY
DOT is recommended by the World Health Organization for the treatment of HIV-1/TB, especially if dosing is intermittent. DOT/supervised therapy for ART has been used in some patients but ART has to be administered daily [144]. There have been no randomised controlled trials or systematic reviews on the usefulness of combined ART/TB DOT in treating HIV-1/TB co-infection.

In some circumstances, intermittent therapy can be given three times per week with dose modification [133, 145] but it must be *via* DOT. However, this has caused concern as in one study there was an increased risk of acquired rifamycin resistance in HIV-1-infected patients given three times per week. However, in that study although DOT was used for all doses during the intensive phase, only one dose of three per week was supervised during the continuation phase [146]. Two other DOT strategies used in HIV-1-negative patients have been associated with unacceptably high relapse rates and acquired rifampicin resistance in HIV-1-infected patients and should not be used in this population: these are, once-weekly INH-rifapentine in the continuation phase, and twice weekly INH-rifampicin or INH-rifabutin in patients with CD4 counts

<100 cells$\cdot\mu L^{-1}$ [139, 147–150]. In the case of MDR-TB a systematic review and meta-analysis showed higher treatment success when treatment duration was at least 18 months and there was DOT throughout treatment [143].

ROLE OF CORTICOSTEROIDS

In HIV-1-infected adults with pulmonary or pleural TB, corticosteroids do not improve survival or reduce TB recurrence [151–153]. A sub study of HIV-1 infected persons within a randomised controlled trial of dexamethasone for TBM in Vietnam showed a trend towards increased survival in the dexamethasone arm [154]. Most physicians, therefore, give steroids to patients with TB meningitis and use dexamethasone 12–16 mg$\cdot$day^{-1} intravenously until the patient begins taking medicines orally. An alternative is prednisolone 1.5 mg$\cdot$kg$^{-1}\cdot$day^{-1} for 3 weeks and tapered over the next 3 weeks [155]. A randomised controlled trial of adjunctive prednisolone in HIV-1-infected patients with effusive tuberculous pericarditis demonstrated reduction in mortality among patients who received prednisolone despite the relatively small sample size (n=58) [153].

DRUG–DRUG INTERACTIONS

Drug–drug interactions between HIV-1 and TB therapy are common and the mechanism is mainly through induction or inhibition of the metabolic family of enzymes in the liver, cytochrome P450 (CYP450). The isoform CYP3A4 is particularly important as it is the main enzyme responsible for the metabolism of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI). Amongst the most potent inducers of CYP3A4 [156, 157] are the rifamycin family and rifampicin (table 2) is the most powerful inducer of CYP3A4 known, with rifabutin less so (table 3) [158]. Rifampicin also induces other cytochromes such as CYP2C19 and CYP2D6 and increases activity of the drug transporter P-glycoprotein that contributes to the absorption, distribution and elimination of PI [159, 160]. Rifabutin, unlike rifampicin, is also a substrate of the CYP3A4 enzyme [156] thus CYP3A4 inhibitors will increase the concentration of rifabutin but have no effect on rifampicin metabolism. As HIV-1 PI are inhibitors of CYP3A4, plasma concentrations of rifabutin and its metabolites may increase and cause toxicity when used with PI [161]. Rifabutin has successfully substituted rifampicin in treating TB in HIV-1-negative patients [162, 163]. It can be used as an alternative to rifampicin to avoid drug interactions. Rifabutin showed similar efficacy to rifampicin in a single-blind, randomised study of 50 HIV-1-positive patients in Uganda [164] and a cohort of 25 patients in the US [165]. However, there is a lack of long-term data with rifabutin in HIV-1 infected adults. Rifabutin is expensive though a generic version may soon be developed. Its toxicities include bone marrow suppression, uveitis and arthralgia.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) are mostly metabolised by glucuronidation and are free of clinically significant interactions with rifamycins. Few data are available for the newer antiretroviral agents. Newer drugs such as the CCR5-inhibitors maraviroc and vicriviroc are metabolised by CYP3A4 and thus interact with rifamycins, as does the integrase inhibitor elvitegravir. Raltegravir is metabolised by UGT1A1, which is induced by rifampicin, and studies are underway to clarify the interaction.

RIFAMYCINS AND NNRTIS

Rifampicin and efavirenz

There is no consensus about what is the appropriate dose of efavirenz to administer with rifampicin. Several pharmacokinetic studies have found a 20–30% reduction in efavirenz levels when administered with rifampicin [166, 167] and that, in general, increasing the efavirenz dose from 600 mg to 800 mg is effective and safe [166, 168]. Conversely in cohort studies standard dose efavirenz has been given with rifampicin without compromised clinical efficacy [169–171]. A large cohort study conducted in South Africa showed no difference in rates of virological suppression when comparing patients on efavirenz-containing ART alone and those on efavirenz-containing ART and rifampicin-based TB treatment concurrently. Efavirenz was used at a dose of 600 mg daily irrespective of weight in this cohort [172]. In contrast, an observational cohort looking at pharmacokinetic and clinical outcomes and weight suggested that for patients weighing >60 kg a dose of 800 mg efavirenz should be prescribed [173]. One problem is the large interpatient variability in efavirenz levels [174] and this is compounded by the fact that efavirenz levels and toxicity are increased in individuals with polymorphisms in CYP2B6, present in 20% of the black population compared with 3% of whites [175, 176]. This may explain some of the variability and high rates of clinical toxicity in some studies [177]. Based on available data, standard doses of efavirenz can be given to patients weighing <60 kg, but in patients weighing >60 kg an increase to 800 mg daily can be considered although may be unnecessary [159, 178]. Trough drug level monitoring where available can be performed 2 weeks after starting efavirenz to check adequacy.

Rifampicin and nevirapine

Rifampicin and nevirapine are both widely used in resource poor countries. Pharmacokinetic data show that nevirapine levels are reduced by 20–55% by rifampicin [179–183]. As with efavirenz there has been a debate about whether this has any clinical impact. Studies from South Africa and Thailand have found nevirapine levels were significantly reduced by rifampicin in up to a third of patients [182, 183]. One study aimed to address this issue with patients prescribed 200 mg nevirapine as lead-in dose every 12 h (rather than the standard 200 mg daily), increasing to 300 mg every 12 h at 2 weeks (rather than the standard 200 mg every 12 h) [184]. The pharmacokinetics was improved in this high-dose group but there was an unacceptably high rate of nevirapine hypersensitivity during the early dosing period. Two studies of clinical outcome have shown high rates of HIV-1 viral suppression with standard dose nevirapine and rifampicin [180, 185]. However, in a large study of 1,283 patients starting ART while on rifampicin (209 people on nevirapine and 1,074 on efavirenz), virological failure rates were almost three times higher in the nevirapine arm compared to the efavirenz or not-on-TB-treatment arms [172]. Interestingly, in a sub-analysis of those patients already on nevirapine who developed incident TB and then started rifampicin-based TB treatment, virological suppression rates were not compromised [172]. Overall, the data to date suggest that if rifampicin and an NNRTI are to be used then efavirenz is preferred.

TABLE 2	Pharmacokinetic drug interactions between rifampicin and antiretroviral drugs	
Drug	**Rifampicin**	
	Interaction with rifampicin	**Recommended antiretroviral therapy dose**
Non-nucleoside reverse transcriptase		
inhibitor		
Efavirenz	Efavirenz[#] ↓ 20–30%	Can consider increasing the dose to 800 mg once daily if weight >60 kg
Nevirapine	Nevirapine[¶] ↓ 20–55%	Not recommended[+]
Etravirine	No data	Do not use
Rilpivirine	Rilpivirine[¶] ↓ 90%	Do not use
Protease inhibitors		
Ritonavir-boosted atazanavir	Atazanavir[¶] ↓	Do not use
Ritonavir-boosted darunavir	No data[¶]	Do not use
Indinavir	Indinavir[¶] ↓ 89%	Do not use
Ritonavir-boosted lopinavir	Lopinavir[¶] ↓ 75%	Add high dose ritonavir (300 mg every 12 h) or double lopinavir/ ritonavir dose but do not use in case of hepatotoxicity
Nelfinavir	Nelfinavir[¶] ↓ 75%	Do not use
Ritonavir	Ritonavir[#] ↓ 35%	Poorly tolerated and only used as booster for other PIs
Ritonavir-boosted saquinavir	Saquinavir[¶] ↓ 80%	Can add high dose ritonavir but do not use in case of hepatotoxicity
Integrase inhibitors		
Raltegravir	Raltegravir[¶] ↓ 60%	Use with caution, even with 800 mg *b.i.d.*
Elvitegravir	Elvitegravir[¶] ↓ level	Do not use
CCR5 antagonist		
Maraviroc	Maraviroc[#] ↓ level	Double the dose
Enfuvirtide	No interaction	Same dose

Data for interaction with rifampicin are presented as % of changes in area under the plasma concentration time curve. [#]: potential interaction; [¶]: definite interaction, do not combine; [+]: if nevirapine needs to be used, start at 200 mg twice daily (no lead-in dose).

Rifampicin and etravirine or rilpivirine

No data are available for etravirine and to our knowledge no studies are planned. Based on pharmacokinetic properties they should not be co-administered. Rifampicin reduces plasma concentrations of rilpivirine by up to 90% so these drugs should also not be used together [186].

RIFABUTIN AND NNRTI

Efavirenz reduces the area under the plasma concentration time curve (AUC) of rifabutin by 38% and so the rifabutin dose should be increased to 450 mg daily. Concomitant administration of nevirapine results in nonsignificant changes in nevirapine pharmacokinetics and, based on limited data, rifabutin and nevirapine can probably be given together with no adjustment in either of their doses. Rifabutin and etravirine can be co-prescribed with no dose adjustment. Rifabutin decreases plasma levels of rilpivirine by 50%, and so the dose of rilpivirine should be doubled [186].

RIFAMYCINS AND RITONAVIR-BOOSTED PI

Most patients are prescribed PI with low dose ritonavir (100 mg or 200 mg daily) to take advantage of ritonavir's CYP3A4 enzyme-inhibiting properties. Ritonavir boosts the concentration of the other PI allowing easier dosing. This property is in contrast to rifampicin's inducing activity which can only be "neutralised" by giving large doses of ritonavir 400 mg *b.i.d.*

LOPINAVIR/RITONAVIR

Standard dose ritonavir, as used in the usual dose of lopinavir/ritonavir combination tablets, is not enough to compensate for the inducing effect of rifampicin on lopinavir metabolism [187]. One strategy is to give lopinavir/ritonavir with increased dose ritonavir. In one study when the ritonavir dose was increased to 400 mg twice daily then lopinavir trough concentrations were adequate in nine out of 10 subjects. However, high rates of elevated transaminases, lipid changes and gastrointestinal toxicity were observed [187]. A pharmacokinetic study in healthy volunteers of such a strategy was terminated early because of high rates of severe increase of liver enzymes/transaminases [188]. Another strategy is to double the dose of lopinavir/ritonavir which also overcomes the effect of rifampicin induction [187].

OTHER RITONAVIR-BOOSTED PI

Saquinavir, atazanavir and tipranavir all have unfavourable pharmacokinetics with rifampicin and should not be administered together. The interaction between darunavir and rifampicin has not been investigated but based on pharmacokinetic properties it should not be co-administered with rifampicin [189–196].

RIFABUTIN AND PI

Ritonavir boosted PI

When low-dose ritonavir boosted PI are used with rifabutin there is a complex drug–drug interaction. Rifabutin induces

TABLE 3	Pharmacokinetic drug interactions between rifabutin and antiretroviral drugs		
Drug	**Rifabutin**		
	Interaction with rifabutin	**Antiretroviral therapy dose**	**Rifabutin dose**
Non-nucleoside reverse transcriptase inhibitor			
Efavirenz	Rifabutin[#] ↓ 38%	Standard dose	Increase to 450 mg once daily
Nevirapine	Nevirapine[¶] ↓ 16%	Standard dose	Standard dose
Etravirine		Standard dose with caution	Standard dose
Rilpivirine	Rilpivirine[#] ↓ 50%	Double dose	Standard dose
Protease inhibitors			
Ritonavir- boosted atazanavir	#	Standard dose	↓ 150 mg three times per week or 150 mg daily
Ritonavir-boosted darunavir	#	Standard dose	↓ 150 mg three times per week or 150 mg daily
Indinavir	Indinavir[+] ↓ AUC 32% Rifabutin ↑ AUC 204%	Do not use	Do not use
Ritonavir-boosted lopinavir	Rifabutin[#] ↑ AUC 303%	Standard dose	↓ 150 mg three times per week or 150 mg daily
Nelfinavir	Nelfinavir[#] 1250 mg *b.i.d.* rifabutin ↑ AUC 207%	Nelfinavir 1250 mg twice daily	↓ 150 mg daily or 150 mg three times per week
Ritonavir	#	Rifabutin ↑ 435%	↓ 150 mg three times per week or 150 mg daily
Ritonavir-boosted saquinavir	#	Monitor liver function	↓ 150 mg three times per week or 150 mg daily
Integrase inhibitors			
Raltegravir			Standard dose
Elvitegravir	No data		
CCR5 antagonist			
Maraviroc	No interaction[¶]	Standard dose	Standard dose
Enfuvirtide	No interaction[¶]	Standard dose	Standard dose

Data for interaction with ributin are presented as % changes in area under the plasma concentration time curve. AUC: area under the plasma concentration time curve. [#]: potential interaction; [¶]: no interaction, use standard doses.

the metabolism of the PI but this induction is countered by the inhibitory effects of ritonavir which also inhibit the metabolism of rifabutin. Consequently, the dose of the ritonavir-boosted PI remains unchanged but the dose of rifabutin should be reduced to 150 mg three times per week. There are no clinical outcome data for either HIV-1 or TB using this strategy and, where available, drug levels of the PI should be measured. A recent pharmacokinetic study has raised concerns regarding the current dosing recommendations for rifabutin when used with lopinavir/ritonavir, because of sub therapeutic rifabutin concentrations in the majority of subjects. The authors of that study suggested therapeutic drug monitoring [197]. If physicians consider measuring rifabutin levels this should include determination of the active metabolite, 25-0-desacetyl rifabutin.

PI AND RIFAMYCINS: WHAT TO DO?
PI/ritonavir combinations tend not be given with rifampicin, thus, either the ART regimen should be modified to one containing efavirenz if possible or rifabutin should be used instead of rifampicin. In resource-limited settings where rifabutin is not available additional ritonavir boosting of lopinavir has been used with rifampicin. This is done by either adding high-dose ritonavir (additional 300 mg every 12 h) to lopinavir/ritonavir combination or by doubling the lopinavir/ritonavir dose to overcome the induction by rifampicin. In healthy volunteer and patient studies, high rates of hepatic events and gastro-intestinal intolerance have been reported with such strategies and patients should be carefully monitored for the development of jaundice or hepatitis [188, 198]. Quadruple nucleosides are also a possibility as ART. The choice of any ART regimen depends on baseline and subsequent resistance testing and history of drug exposure if there has been virological failure.

RIFAMYCINS AND NRTI
When NRTI are given with rifampicin the pharmacokinetic interactions do not have a significant clinical impact. Triple NRTI regimens are theoretically as attractive as ART because they are free of interactions with TB treatment and have been used in observational studies in Africa [199–201], but have been shown to be virologically inferior to ART containing an NNRTI in a randomised study [202]. Quadruple NRTI regimens (most commonly abacavir, lamivudine, zidovudine and tenofovir) have also been used in adults taking TB treatment [203].

RIFAMYCINS AND INTEGRASE INHIBITORS

Raltegravir is metabolised by UGT1A1 glucuronidation. Rifampicin is an inducer of this enzyme and reduces drug levels of raltegravir [204]. Because the antiviral activity of raltegravir may depend on its AUC, pharmacokinetic data suggests this is maintained if raltegravir dose is doubled when given with rifampicin. Normal doses of raltegravir and rifabutin can be used based on data to date [204]. Elvitegravir is metabolised by CYP3A4 and should not be given with rifampicin.

RIFAMYCINS AND CCR5-ANTAGONISTS OR ENFURVIRTIDE

As maraviroc is metabolised by CYP3A4 the dose of maraviroc should be doubled to 600 mg *b.i.d.* when administered with rifampicin [205]. Theoretically, maraviroc can be given at standard doses with rifabutin. There are no significant interactions between rifamycins and enfuvirtide [206].

NON-RIFAMYCIN REGIMENS

HIV-1 related TB may sometimes be treated with non-rifamycin-containing regimens but these are inferior in efficacy, with high relapse rates [207, 208]. A review of drug–drug interactions between drugs used in non-rifamycin regimens and antiretrovirals describes the potential interactions of these second-line drugs with antiretrovirals [209].

TOXICITY OF COMBINED ART AND TB THERAPY

Adverse reactions to drugs are common among patients with HIV-1-related TB especially if patients are also taking ART with rash, fever, hepatitis and peripheral neuropathy being common side-effects (table 4). It can be difficult to identify the drug responsible especially if the patient is co-prescribed drugs for opportunistic infection treatment or prophylaxis, such as co-trimoxazole, and the treatments have been started concurrently. High rates of adverse reactions requiring changes in therapy have been reported in HIV-1-infected patients [210, 211]. High rates of discontinuations of either TB or HIV-1 therapy occur [212, 213] and re-introducing drugs can be prolonged and difficult. This may indirectly increase morbidity and mortality by delaying effective treatment of TB and HIV-1.

HEPATOTOXICITY

Hepatotoxicity is caused by many drugs used in the treatment of HIV-1, such as co-trimoxazole, azoles and macrolides. Not all reactions are due to HIV-1 or TB drugs. Patients with chronic liver disease have higher rates of toxicity and need more frequent monitoring of liver function tests. Chronic hepatitis B and C are common in HIV-1 infected persons. Acute drug related liver injury or hepatotoxicity is defined as: a serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than three times the upper limit of normal in the presence of symptoms, or a serum AST or ALT more than five times the upper limit of normal in the absence of symptoms. Hepatotoxicity due to INH in the general population increases with age, and is more likely with heavy alcohol intake, hepatitis C co-infection and in those also on rifampicin.

MANAGEMENT OF HEPATITIS

All potentially hepatotoxic drugs should be stopped immediately, including INH, rifampicin, pyrazinamide, ART and co-trimoxazole, serology for hepatitis A, B and C should be sent and exposure to other hepatotoxins, including alcohol, should be determined. If resolution of the hepatitis is prolonged then it may be necessary to treat TB with two or more anti-TB medications without significant risk of hepatotoxicity, such as ethambutol, streptomycin, amikacin/kanamycin, capreomycin or a fluoroquinolone; but not moxifloxacin as it can cause a severe hepatitis. Once the AST drops to less than twice the upper limit of normal and symptoms have significantly improved, first-line TB medications can be restarted. Many physicians use a re-introduction regimen based on common practice but these have not been investigated in clinical trials. If the drugs cannot be restarted or the initial reaction was life-threatening then an alternative TB regimen should be used. Reintroduction of antivirals has to be with complete regimens as introducing drugs one by one could lead to virological failure. A less hepatotoxic ART regimen may be used when ART is re-introduced.

PERIPHERAL NEUROPATHY

The nucleoside analogues didanosine and stavudine cause peripheral neuropathy: a toxicity that may be additive when INH is used with stavudine [214, 215]. Thus, stavudine is undesirable if concomitant INH is being administered, although this combination by necessity has been used widely. Patients who develop TB when already taking stavudine should be switched to an alternative antiretroviral, such as tenofovir or zidovudine, if available. All HIV-1-infected patients on TB treatment should receive supplementary pyridoxine to prevent neuropathy.

RASH

Rashes are usually mild to moderate and usually occur in the first 2 months of treatment. Mild rashes without mucosal involvement can be treated symptomatically but more widespread or worsening rashes or those with systemic symptoms or mucosal ulceration require drug cessation. In many cases, when the rash has resolved careful drug re-introduction can be performed. There is little prospective data to guide re-challenge. Severe skin reactions to anti-tuberculous therapy should be re-challenged under specialist guidance and aim to re-introduce one drug after the other with gradually escalating doses to aid desensitisation [216]. However, it is not recommended to re-introduce an NNRTI following Stevens–Johnson syndrome attributed to an NNRTI.

RENAL

Tenofovir and aminoglycosides used in the treatment of TB (kanamycin, amikacin and streptomycin) are potentially nephrotoxic [217]. All of these drugs predominantly cause toxicity at the level of the proximal renal tubules [218] and it is plausible that simultaneous prescribing of two drugs sharing the same toxic action would increase the risk of nephrotoxicity. The combination of tenofovir with an aminoglycoside should, therefore, be avoided if possible. In patients on an aminoglycoside for the intensive phase of MDR-TB treatment this is an essential part of their treatment, and an alternative antiretroviral to tenofovir should be used during this period.

TABLE 4	Overlapping or additive toxicities of antiretroviral drugs and anti-tuberculosis (TB) agents	
Toxicity	**Antiretroviral**	**Anti-TB**
Peripheral neuropathy	Stavudine, didanosine	INH, ethionamide and cycloserine
Gastrointestinal intolerance	All	All
Hepatotoxicity	NVP, EFV and PI (especially if additional ritonavir boosting)	INH, rifampin, rifabutin and pyrazinamide and moxifloxacin
Central nervous system toxicity	Efavirenz	INH, cycloserine, quinolones and ethionamide
Bone marrow suppression	Zidovudine	Rifabutin, rifampin and INH
Skin rash	Abacavir, amprenavir, nevirapine, efavirenz, darunavir and fosamprenavir	INH, rifampin and pyrazinamide, ethambutol and streptomycin
Renal toxicity	Tenofovir	Aminoglycosides, capreomycin and rifampicin
Ocular effects	Didanosine (retinal changes and optic neuritis)	Ethambutol (optic neuritis or retrobulbar neuritis) and rifabutin (uveitis)

NVP: nevirapine; EFV: efavirenz; PI: protease inhibitors; INH: isoniazid.

WHEN TO START ART

The World Health Organization 2010 guidelines recommend ART for all HIV-1 infected patients with active TB, irrespective of CD4 cell count. However, the optimal time to start ART in HIV-1/TB patients is incompletely understood and several trials are underway to answer this question [219]. The risk of HIV-1 progression has to be balanced against the hazards of starting ART in patients on anti-TB therapy, which include toxicities, side-effects, immune reconstitution inflammatory syndrome (IRIS) and drug interactions. ART and anti-TB drugs may share similar routes of metabolism and elimination, and extensive drug interactions may also result in sub-therapeutic plasma levels of either or both drugs. Overlapping toxicity may result in the interruption of TB or HIV-1 regimens with subsequent microbiological or virological failure. Deaths may be due to TB especially if occurring early, while late deaths in co-infected persons are usually due to HIV-1 disease progression [53, 96, 220].

A recent study from South Africa showed a clear mortality benefit in HIV-1/TB who started ART during TB treatment compared to deferring ART until TB treatment was completed. There were 5.4 deaths per 100 person-yrs in the integrated treatment arm and 12.1 per 100 person-yrs in the sequential arm (HR in the integrated-therapy group 0.44, p=0.003). The study included HIV-1 infected patients with CD4 counts <500 cells·μL^{-1}. The sequential arm of the study was stopped by the data safety monitoring committee and integrated ART was recommended for all patients. TB-IRIS occurred more in the integrated treatment group but the TB-IRIS events did not require changing ART regimen or cause any fatalities and the grade 3 and 4 adverse events (non-IRIS) were similar in both groups [221]. Another South African study of those with low CD4 cell counts starting ART early also showed rates of IRIS are high but mortality is low [222]. A randomised trial recently completed in Cambodia showed a mortality benefit in patients with TB who have a low CD4 count and start ART early. Patients were randomised to start ART either 2 weeks after TB treatment was initiated or 8 weeks later. There was a mortality rate of 8.25 (95% CI 6.4–10.7) in the early treatment arm and 13.77 (95% CI 11.2–16.9) in the late treatment arm after 712 person-yrs of follow-up. This was statistically significant (p=0.02) [223]. In contrast, a randomised study of HIV-1 co-infected patients in Vietnam, who were mainly male drug users diagnosed clinically with TB meningitis, compared early (same day as TB treatment) *versus* deferred ART (2 months after starting TB treatment). It showed no significant differences in outcomes such as deaths at 12 months or AIDS events. There were a significantly increased number of adverse events in the early ART group [224].

Patients with a preserved CD4 count (>350 cells·μL^{-1}) have a lower risk of HIV-1 progression or death during their TB treatment, depending on their age and viral load. In this group ART could be deferred until completion of short-course TB treatment, provided there is both clinical and CD4 count monitoring. This could prevent toxicity and drug interactions. However, most patients with TB present with a low CD4 count, often <100 cells·μL^{-1}. ART improves survival in these patients and most would advise that ART should be started as soon as practicable [225, 226]. Some physicians prefer to wait for up to 2 weeks before starting ART after commencing patients on TB treatment to allow diagnosis and management of any early toxicity and adherence problems. Although some groups have not found an advantage of starting ART early [227, 228], others have shown that early treatment is associated with decreased mortality and a lowering of the rates of progression [212].

TB-ASSOCIATED IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

After the initiation of ART, HIV-1 replication is greatly reduced and viral load rapidly falls. This results in a CD4 T-lymphocyte count increase and immune function improves. When ART is started in patients who are significantly immunosuppressed during the early period of immune recovery a subset may develop IRIS, also termed immune restoration disease [229]. IRIS manifests with clinical deterioration and features of inflammation due to dysregulated immune responses directed to antigens of opportunistic infections, treated or untreated, present prior to ART initiation. IRIS has been described in association with a wide variety of opportunistic infections, but the form that has been most frequently reported and poses the greatest challenge to clinicians globally

is TB-associated IRIS. TB-IRIS has been reviewed by several authors [230, 231].

TB-IRIS may present as one of two forms. Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB prior to ART, are typically improving on TB treatment and then early during ART develop an immune-mediated paradoxical reaction with new or recurrent clinical and/or radiological manifestations of TB. Less well defined is unmasking TB-IRIS, which occurs in a subset of patients diagnosed with active TB while on ART (ART-associated TB) and who present with unusually accelerated or inflammatory features of TB during the first 3 months of ART [231].

PARADOXICAL TB-IRIS

Paradoxical TB-IRIS has been reported in 8–43% of patients starting ART while on TB treatment [231]. Most cases of paradoxical TB-IRIS develop during the first 4 weeks of ART [222, 232–235]. Common features are recurrence of TB symptoms, fever, lymphadenitis, enlarging serous effusions, new or recurrent infiltrates on chest radiograph and subcutaneous or deep tissue abscesses [236, 237]. Multiple organ systems may be involved. Patients may experience high fevers, persistent tachycardia and weight loss. The liver may be affected by cholestatic hepatitis due to TB-IRIS, presenting with tender hepatomegaly and cholestatic liver function derangement [222, 237]. This is difficult to differentiate from drug-induced liver injury. Neurological features, including new or recurrent tuberculous meningitis or enlarging tuberculomas have been reported in 12% of patients with paradoxical TB-IRIS and may result in death and disability [238].

The major risk factors for paradoxical TB-IRIS are disseminated TB, low CD4 count and shorter interval from start of TB treatment to ART initiation [222, 233–235, 239–241]. The pathogenic mechanism is thought to be an inflammatory reaction to the antigens of mycobacteria still present in tissues despite TB treatment. The duration of paradoxical TB-IRIS is typically 2–3 months [240, 241], but cases lasting >1 yr have been reported [231, 241].

There is no diagnostic test for paradoxical TB-IRIS. The diagnosis is suggested by the following features: improvement on TB treatment prior to ART, deterioration with inflammatory features of TB, a close temporal relationship to ART initiation and exclusion of alternative explanations for deterioration during diagnostic work-up. Alternative diagnoses that need to be considered will depend on the individual case and include: other opportunistic or bacterial infections, malignancy, drug-resistant TB, non-adherence to or malabsorption of TB medication and a drug reaction. In a South African study, the most frequent diagnosis found during work-up was drug-resistant TB. Undiagnosed rifampicin resistance was present in nine out of 100 TB-IRIS suspects [236]. Drug susceptibility testing, preferably with a rapid test, should be performed on all paradoxical TB-IRIS suspects.

In some cases the diagnosis is straightforward, such as a patient with proven tuberculous lymphadenitis responding to TB treatment who experiences recurrent night sweats and enlargement of the same lymph node after starting ART. In other cases considerable diagnostic uncertainty may exist. This is particularly the case in resource limited settings where the initial diagnosis of TB is often not microbiologically proven and diagnostic capacity to investigate for alternative diagnoses and drug resistance is limited. In such situations it may not be clear whether deterioration is due to an incorrect diagnosis of TB or TB-IRIS.

A consensus clinical case definition for paradoxical TB-IRIS has been published by the International Network for the Study of HIV-1-associated IRIS (table 5) [231]. This case definition was developed to promote standardisation of research findings from different settings, but it may also be of practical use for clinicians as it provides a systematic approach to diagnose of paradoxical TB-IRIS. This case definition does not include viral load or CD4 criteria because these tests are frequently not available in resource limited settings. Two research groups have independently validated this case definition [237, 242]. The consensus clinical case definition appears to perform as well as a case definition that includes viral load and CD4 cell count criteria which is important, especially in resource limited settings where these variables are often undetermined at the time of presentation with TB-IRIS [237].

Mild cases may require symptomatic therapy only. Aspiration of large fluctuant lymph nodes or soft tissue abscesses may provide symptomatic relief [241]. It is critical to optimise treatment for TB, particularly in cases with drug-resistant TB. Corticosteroids and non-steroidal anti-inflammatory drugs are the most frequently used adjunctive treatments. In a randomised, placebo-controlled trial of prednisone for the treatment of non-life threatening paradoxical TB-IRIS, a 4-week course of prednisone (1.5 $mg \cdot kg^{-1} \cdot day^{-1}$ for 2 weeks followed by 0.75 $mg \cdot kg^{-1} \cdot day^{-1}$ for 2 weeks) significantly reduced a combined primary end-point of number of days hospitalised and number of out-patient therapeutic procedures performed. There was also more rapid symptom improvement in the prednisone arm [243]. Corticosteroids in HIV-1-infected persons are associated with the risk of Kaposi's sarcoma, herpes virus reactivations, other infections and metabolic side-effects [152, 244, 245] and should only be used when the diagnosis of paradoxical TB-IRIS is certain and alternative diagnoses have been excluded.

In most cases, ART should be continued. ART interruption may be considered in life-threatening TB-IRIS, especially when there is severe neurological involvement. Other immunomodulatory treatments, including thalidomide, leukotriene antagonists and tumour necrosis factor-α inhibitors, have been proposed but only isolated case reports of their efficacy exist [230].

UNMASKING TB-IRIS

High TB incidence rates (5.6–23 TB cases per 100 person-yrs) in the first 3 months of ART have been reported in developing country ART programmes [246, 247]. TB is an important cause of the high mortality observed during early ART in these settings [248].

It has been proposed that a subset of cases of active TB diagnosed on ART represent unmasking TB-IRIS [231, 248]. These are patients who present with heightened inflammatory presentations of TB during the first 3 months of ART. Such patients are assumed to have had undiagnosed or subclinical TB prior to ART. It is hypothesised that the combination of high mycobacterial organism load and rapid immune recovery favour the development of unmasking TB-IRIS [249]. The few cases that are reported in the literature include patients

TABLE 5	International network for the study of HIV-1-associated immune reconstitution inflammatory syndrome (IRIS) consensus: clinical case definition for paradoxical tuberculosis (TB)-IRIS

A: Antecedent requirements

Both the following two requirements must be met:

   1) Diagnosis of TB: the TB diagnosis was made before starting ART and this should fulfil WHO criteria for diagnosis of smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB

   2) Initial response to TB treatment: the patient's condition should have stabilised or improved on appropriate TB treatment before ART initiation, *e.g.* cessation of night sweats, fevers, cough and weight loss. Note: this does not apply to patients starting ART within 2 weeks of starting TB treatment since insufficient time may have elapsed for a clinical response to be reported

B: Clinical criteria

The onset of TB-associated IRIS manifestations should be within 3 months of ART initiation, re-initiation or regimen change because of treatment failure

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

   New or enlarging lymph nodes, cold abscesses or other focal tissue involvement, *e.g.* tuberculous arthritis

   New or worsening radiological features of TB (found by chest radiography, abdominal ultrasonography, CT or MRI)

   New or worsening CNS TB (meningitis or focal neurological deficit, *e.g.* caused by tuberculoma)

   New or worsening serositis (pleural effusion, ascites or pericardial effusion)

Minor criteria

   New or worsening constitutional symptoms such as fever, night sweats or weight loss

   New or worsening respiratory symptoms such as cough, dyspnoea or stridor

   New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly or abdominal adenopathy

C: Alternative explanations for clinical deterioration must be excluded if possible[#]

Failure of TB treatment because of TB drug resistance

Poor adherence to TB treatment

Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary TB and extrapulmonary TB where the initial TB diagnosis has not been microbiologically confirmed)

Drug toxicity or reaction

ART: antiretroviral therapy; WHO: World Health Organization; CT: computed tomography; MRI: magnetic resonance imaging; CNS: central nervous system. [#]: it might be difficult or impossible in resource-poor settings to confirm TB drug resistance and to exclude certain other infections or neoplasia. Cases where alternative diagnoses cannot be fully excluded because of limited diagnostic capacity should be regarded as ''probable paradoxical TB-associated IRIS''. In these probable cases, should resolution of clinical or radiological findings of the suspected IRIS episode occur without a change in TB treatment or ART having been made, they could then be reclassified as ''paradoxical TB-associated IRIS'' cases. Reproduced from [231] with permission from the publisher.

presenting with rapid onset severe pulmonary TB [231, 249, 250], one of whom required mechanical ventilation for adult respiratory distress syndrome associated with miliary TB [250], complicated neurological involvement [251, 252] and pyomyositis [253]. A higher mortality in those diagnosed with TB in the first 3 months of ART (27% mortality) compared to other patients with AIDS and TB (8% mortality) was documented in Haiti [254]. This may have been contributed to by unmasking TB-IRIS.

Clinicians should screen for TB symptoms prior to ART, investigate those with symptoms and be aware that some patients with severe immunosuppression may have subclinical active TB [248]. In patients in TB endemic settings or in immigrants from these regions who deteriorate after ART initiation, the diagnosis of unmasking TB-IRIS should be strongly considered. Cases of unmasking TB-IRIS are treated with standard TB treatment. The role of corticosteroids in unmasking TB-IRIS has not been defined.

PREVENTIVE THERAPY AGAINST TB IN HIV-1 INFECTED PERSONS

Preventive therapy against TB involves treating persons at risk of developing active TB (persons with latent infection with *M. tuberculosis*) with one or more anti-tuberculous drugs with the aim of eradicating *M. tuberculosis* infection before disease occurs. Evidence indicates that treatment for latent TB infection reduces the risk of active TB in all HIV-1 infected persons; however, there are two provisos. First, the benefit is only seen in those who are TST positive (>5 mm) and with a risk ratio of 0.38 compared to those who have a negative tuberculin skin test and a risk ratio of 0.89 [255]. Secondly, the benefits are short-lived in settings of high TB burden. In contrast, IPT is very effective in reducing the risk of TB in countries of low TB incidence [256].

In order to commence a HIV-1 infected person on preventive therapy, active TB needs to be ruled out. This can present difficulties, especially in persons with advanced immunosuppression in areas with high HIV-1 prevalence and TB incidence. Screening for active TB involves symptom screens, microbiological screening, radiological screening or a combination of these tests and, as stated above, all of these may have decreased sensitivity in patients with advanced HIV-1. The yield of intensified case finding in resource-limited settings is predictably associated with the prevalence of HIV-1 in the target population, the local incidence of TB and the screening strategy. When screening only HIV-1 infected populations, substantially higher yields were found when all persons had microbiological screening (sputum test) irrespective of symptoms, consistent

with a substantial proportion of HIV-1 infected patients who have asymptomatic active TB [19–21, 257]. Screening protocols may, therefore, need to be individualised for different settings according to local and national HIV-1 and TB prevalence and available laboratory and treatment resources.

The current recommended treatment for latent TB in HIV-1 infected persons is 6–9 months of INH monotherapy. Several shorter combinations of anti-tuberculous drugs have also been found to be effective. Efficacy is similar for all regimens but the risk of stopping treatment due to adverse events is significantly higher in the short-course combinations of therapy when compared to INH monotherapy [255]. In HIV-1 uninfected patients the protective effect of TB pre-ventive therapy is long lasting [258]. This has not been observed in HIV-1 infected persons. Several studies from high-burden TB settings showed a fairly rapid waning of the protective effect after stopping TB preventive therapy. In one study the protective effect dissipated after 6 months, suggest-ing prolonged treatment might be necessary in HIV-1 infected persons [259–261]. A recent large cohort study in Botswana (2,000 HIV-1 infected patients) compared two arms of TB preventive therapy. One arm received 6 months INH monotherapy followed by placebo and the second arm received 3 yrs of continuous INH monotherapy. The study showed a significant decrease in TB incidence for 36 months in the continuous INH arm compared to the 6-month arm. The protective benefit for the 6-month arm waned 200 days after the INH was stopped. The benefit of INH only occurred in patients who were TST positive

although patients who were TST negative were at high risk of developing TB [262].

These findings suggest that even if TST has poor sensitivity to detect latent TB infection in HIV-1 infected persons, it still plays an important role in identifying those HIV-1 infected persons who benefit from long-term TB preventive treatment. It also suggests that those who are TST positive should be on preventive therapy for longer than the currently recommended 6 months. The short-lived IPT induced protection observed in HIV-1 infected persons can be interpreted to indicate that infection pressure in the settings of trials is greater than was experienced in the Bethel studies [258] and, thus, re-infection may be an important factor. An alternative explanation would be that a residual immune response to TB (as manifest by a positive TST) is necessary for IPT to be effective.

In areas with low TB incidence all HIV-1 infected persons should be screened for latent TB infection using TST. IPT should be offered if the test is positive or if the persons are known to be exposed to TB. The recommendation is 9 months of IPT with INH monotherapy.

In areas with high TB incidence all HIV-1 infected individuals should be screened for latent TB infection with TST and those with a positive test should be offered IPT. Long-term IPT may be most effective but has not been systematically evaluated. Also see tables 6 and 7 for summary statement and recommendations.

SUPPORT STATEMENT

TABLE 6	Recommendations for prevention and diagnosis of HIV-1 associated tuberculosis (TB)	
	Low TB incidence region	**High TB incidence region**
Should all HIV-1 infected individuals be screened for LTBI?	Yes	Yes
Preferred screening method?	TST	TST
Symptom screen at every visit?	Not essential	Strong recommendation
Sputum TB culture on initial screening?	Recommend if symptoms present or abnormal chest radiograph	Recommended in all patients where possible, but this is seldom feasible in resource constrained settings

LTBI: latent TB infection; TST: tuberculin skin test.

TABLE 7	Recommendations for treatment of latent tuberculosis infection (LTBI)
	Recommendation
Should all HIV-1 infected persons who are TST positive be treated with IPT?	Yes, unless there is a contraindication to IPT (e.g. liver disease and alcohol abuse)
Should HIV-1 infected person who are TST negative be treated with IPT?	IPT should be considered regardless of TST result where there has been known exposure to a smear-positive TB case for a significant time period and in high TB incidence areas
What treatment should be given for LTBI?	INH monotherapy
How long should patients be treated for LTBI?	9 months of IPT is adequate in areas with low incidence of TB and high TB incidence areas long-term (up to 36 months) IPT should be considered

TST: tuberculin skin test; IPT: isoniazid preventative therapy; INH: isoniazid.

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