Eur Respir J 2012; 39: 1064–1075
DOI: 10.1183/09031936.00116611

PERSPECTIVE

Unmasking tuberculosis in the era of antiretroviral treatment

Giuseppe Lapadula*, Alessandro Soria*, Alessandra Bandera*, Nicola Squillace*, Francesca Sabbatini*, Fabio Franzetti#, Giovanni Battista Migliori¶ and Andrea Gori*

ABSTRACT: Tuberculosis (TB) can develop soon after antiretroviral treatment initiation, as the result of restoration of the anti-TB specific immune response. This form of the disease is often defined as ''unmasked TB'', and it represents a major challenge for severely immune-suppressed HIV-infected subjects initiating treatment. Emergence of previously unrecognised TB disease occurs frequently in countries where TB/HIV co-infection is common, and where antiretroviral treatment has become increasingly accessible. The challenges posed by unmasked TB, such as its high incidence, the lack of reliable diagnostic tools and the uncertainties on its optimal management, may hamper our ability to face the TB/HIV epidemic. Therefore, unmasked TB appears a major threat to global health and poses additional barriers to successful HIV/AIDS care and treatment programmes.

This review focuses on the epidemiology, immunopathogenesis and clinical manifestations of unmasked TB, and provides evidence-based recommendations for management and care of the disease.

KEYWORDS: Antiretroviral therapy, HIV/AIDS, immune reconstitution inflammatory syndrome, unmasked tuberculosis

Tuberculosis (TB) is the most common opportunistic infection worldwide, and it is a major contributor to the mortality of people living with HIV/AIDS [1]. It is currently estimated that over one million people worldwide have TB/HIV co-infection and the burden of the diseases is particularly high in sub-Saharan Africa. The risk of developing active TB is greatly increased in HIV-infected compared with HIV-negative subjects [2]. Although combination antiretroviral therapy (cART) reduces this risk, TB incidence among treated HIV-infected patients remains higher than that among HIV-negative subjects in the same community [3, 4].

The rapid expansion of antiretroviral roll-out programmes in high TB burden areas, mainly in southern Africa, has been associated with an unexpectedly high occurrence of TB during the first 3 months of cART, suggesting a potential role of cART-driven immune restoration in ''unmasking'' subclinical TB [3]. The underlying mechanisms through which TB is unmasked have yet to be fully explained. A growing body of indirect evidence suggests that the phenomenon is the result of a complex interaction between cART-driven immune restoration and *Mycobacterium* antigen load. The resulting disease spectrum may range from typical TB presentations to TB presenting as an exaggerated inflammatory response due to dysregulated immune restoration, commonly referred to as immune reconstitution inflammatory syndrome (IRIS) [5].

The clinical management of this peculiar manifestation of TB/HIV co-infection can be particularly challenging, due to the difficulties in its diagnosis and the uncertainties regarding its optimal management. Therefore, unmasked TB appears a major threat to global health and poses additional barriers to successful HIV/AIDS care and treatment programmes. Notwithstanding, to our knowledge, no recent review has addressed these topics in major journals.

AIM

Aim of the present perspective article is to highlight the burden of TB unmasked by cART in HIV/TB epidemics and its individual and public health implications, either in low- or high-income settings.

AFFILIATIONS
*Clinic of Infectious Diseases, ''San Gerardo de' Tintori'' Hospital, University of Milano-Bicocca, Monza, #Clinic of Infectious Diseases, ''Luigi Sacco'' Hospital, University of Milan, Milan, and ¶WHO Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy.

CORRESPONDENCE
G. Lapadula
Clinic of Infectious Diseases
''San Gerardo de' Tintori'' Hospital
via Pergolesi 33
20900 Monza
Italy
E-mail: g.lapadula@hsgerardo.org

Received:
July 08 2011
Accepted after revision:
Oct 04 2011
First published online:
Oct 17 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

We discuss the available evidence on the different aspects of unmasked TB, starting from the definitions proposed, then analysing the incidence of TB soon after cART initiation, risk factors and mortality, immunopathogenesis, clinical features, prevention and treatment.

METHODS

The present article is based on a comprehensive review of peer-reviewed studies published on TB unmasked by cART. Literature searches of the PubMed/MEDLINE databases were undertaken to identify pertinent articles. The searches were first performed in September 2009 and then repeated in September 2010 and May 2011, in order to update the reference list. The following search string was used to identify articles focusing on or mentioning unmasked TB: (HIV OR AIDS) AND (TUBERCULOSIS OR TB) AND (UNMASK* OR IRIS OR ''IMMUNE RECONSTITUTION''). A second, wider search was conducted in order to identify all studies on TB occurring during antiretroviral treatment. The following search string was used: (HIV OR AIDS) AND (TUBERCULOSIS OR TB) AND (HAART OR ARV OR ANTIRETROVIRAL). All searches were limited to English language. In addition, the websites of the major international congresses on HIV were browsed in order to identify relevant unpublished studies. Conference abstracts more than 1 yr old were discarded, if full data were still unpublished.

The articles were then independently sifted by two authors (G. Lapadula and A. Bandera), based on abstract and, if deemed to be necessary, by reading the full paper. Articles judged to be irrelevant by both authors were discarded, while disagreements were resolved through discussion. Eventually, the reference lists of the selected articles were browsed to identify further papers of interest.

Each article was then categorised by its relevance to one or more of the following subtopics: 1) definition of unmasked TB; 2) incidence, risk factors and mortality of TB during cART; 3) immunopathogenesis; 4) clinical presentation; 5) prevention and treatment.

Overview of the different definitions of unmasked TB

Due to lack of diagnostic tests, diagnosis of unmasked TB relies solely on case definition. However, that definition is not standardised, and varies from study to study. Table 1 shows the definitions proposed to date.

During an expert meeting held in Kampala (Uganda) in 2006, a provisional case definition was proposed by the International Network for the Study of HIV-associated IRIS (INSHI) [6]. The authors define any new presentation of TB occurring within the first 3 months of cART as ''cART-associated TB'', while the term ''unmasking TB-IRIS'' is reserved for a subset of cART-associated TB whose clinical course is either characterised by heightened intensity or has been complicated by a paradoxical reaction. ''Unmasking TB-IRIS'' is distinguished from TB-IRIS (in the paper termed ''paradoxical tuberculosis-associated IRIS''), defined as a paradoxical reaction and/or a deterioration of an already diagnosed TB, which occurs after the start of cART in a patient receiving anti-TB treatment.

The foremost advantage of this definition is its clinical validity, which has been documented. In a prospective cohort of 498 HIV-infected adults initiating cART in South Africa, the INSHI definition was, in fact, in good agreement with the opinion of an expert panel [10]. Nonetheless, the definition failed to identify about one-third of the cases that had been classified as unmasked TB by the experts. The main reasons for the discrepancy were delayed presentation (more than 3 months after cART initiation), or absence of a ''heightened intensity of clinical manifestation'' in cases where, according to expert opinion, immune reconstitution

TABLE 1 Unmasked tuberculosis (TB) definitions

Study	Definition
MEINTJES *et al.* [6]	**Unmasking TB-associated IRIS** 1) Patient is not receiving treatment for TB when cART is initiated AND 2) Active TB within 3 months of cART initiation AND 3) Either one of the following: a) Heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component to the presentation OR b) Once established on TB treatment, a clinical course that is complicated by a paradoxical reaction
MANABE *et al.* [7]	**Unmasked TB** 1) Latent TB before the development of HIV-induced immunosuppression AND 2) TB occurring as a consequence of the up-regulation of memory immune response during immune reconstitution induced by cART
LAWN *et al.* [8]	**Unmasking TB** TB presenting during the initial months of immune recovery (''ART-associated TB'') whereby immune recovery triggers the presentation of TB
HADDOW *et al.* [9]	**Unmasking IRIS** Clinical criteria 1) Temporal relationship: cART initiation must precede clinical deterioration 2) New onset of symptoms of an infectious or inflammatory condition after initiation of cART 3) Consistent with the presence of pre-existing causative pathogen or antigen at the time of starting cART 4) Either of the following a) Onset within 3 months of initiating cART b) Atypical or exaggerated clinical, histological or radiological findings Exclusion of other causes Event not explained by 1) Expected clinical course of another condition 2) Drug toxicity 3) Newly acquired infection Failure of ART treatment

IRIS: immune reconstitution inflammatory syndrome; (c)ART: (combination) antiretroviral treatment.

had played an important role in the clinical presentation of the disease. Criteria regarding the clinical characteristics of the disease can indeed be quite subjective, due to the wide spectrum of TB manifestations. For this reason, clinical differentiation between incident TB and TB elicited by cART remains difficult in practice.

Other authors refer to ''unmasked TB'' as a wide spectrum of TB clinical presentations, triggered by cART-induced immune recovery [5]. In a recent review, MANABE *et al*. [7] proposed a new way of classifying the different forms of TB occurring during cART. According to the authors, ''primary TB'' is only temporally associated with cART and is not associated with a rapid recall of TB antigen-specific memory immune response. Conversely, ''unmasked TB'' occurs in the subset of patients who develop clinically recognisable TB after the initiation of cART because of the restoration of TB antigen-specific functional immune responses. Among them, only a proportion of individuals develops an exaggerated inflammatory response, defined as ''unmasked TB-IRIS''. The authors speculate that these three clinical presentations are part of a disease spectrum in which interaction between the TB antigen burden and degree of immune restoration determines the magnitude of clinical symptoms.

Similarly, LAWN *et al*. [8] used the term ''unmasking'' TB in reference to subclinical TB that is present but unrecognised before treatment initiation and whose early onset after cART introduction is determined by the restoration of TB-specific immune response. Both definitions, while theoretically intriguing and biologically plausible, are limited by the absence of objective criteria able to distinguish between pre-existing subclinical TB and incident TB that occurs early during cART as a result of persistent immune deficiency. The practical utility of such distinction in the clinical practice is, anyhow, questionable.

HADDOW *et al*. [9] recently proposed a new general definition of ''unmasking IRIS''. Its application to TB may resolve some of the problems with previous definitions, by classifying most of the events occurring soon after cART introduction as unmasked TB. According to the authors, the diagnosis of unmasked TB can be made when a strict temporal correlation exists between antiretroviral treatment and TB (*i.e.* TB presentation within 3 months of initiating cART), even in settings of typical disease progression. Conversely, an atypical or exaggerated course could be considered to be consistent with unmasked TB, even in cases presenting more than 3 months after cART initiation (table 1). This comprehensive definition is likely to prove more sensitive than the INSHI definition, but will probably lack in specificity in settings where TB is highly prevalent. Further evaluation in clinical practice is, therefore, required.

As available clinical and immunological markers are as yet unable to differentiate pre-existing from incident TB, a margin of uncertainty and arbitrariness is unavoidable in any definition. Meanwhile, current data support the adoption of the INSHI definition in research practice.

Incidence of TB and unmasked TB during cART

Several observational studies have been conducted to assess the burden of TB among individuals receiving cART [3, 4, 8, 11–32]. Estimates of TB incidence, however, differ greatly among the published studies. Differences in TB case definitions, length of follow-up, degree of immune suppression prior to cART initiation or rate of TB infection in the studied populations are all plausible explanations for the apparent discrepancies. Nonetheless, all the studies consistently report that TB incidence is higher early in the course of cART than at later time points during treatment and, in many cases, more than half of TB cases occurring during cART are diagnosed within the first 3 months of treatment [11, 13, 23–25, 29, 30, 32]. LAWN *et al*. [8] observed that the risk of TB occurrence during the first months of cART, among patients with a CD4+ T-cell counts <200 cells per μL, was 40% (95% CI 6–61%) higher than among those with the same CD4+ T-cell counts during long-term treatment. The authors suggested that this excess rate of TB is directly attributable to the ''unveiling'' effect of cART-induced immune restoration. Consistent with this hypothesis, TB rates were reported to remain high soon after cART initiation and, in some cohorts, were even higher than pre-cART rates. In an observational cohort study conducted in the USA, incidence of TB during the first 6 months of cART was almost double than that in persons not on cART (0.4 *versus* 0.21 per 100 person-yrs of follow-up), although the difference was not statistically significant adjusting for CD4+ T-cell count [17]. Similarly, in a South African cohort, TB incidence before and within 3 months of cART was 10.5 and 13 per 100 person-yrs of follow-up, respectively [32].

Table 2 shows the incidence of TB occurring during cART and shortly after cART initiation in various studies, conducted both in high- and low-income settings.

The introduction of cART has dramatically reduced TB incidence among the resident HIV-infected population of high-income countries. The incidence of TB in the Swiss cohort decreased from 0.78 per 100 person-years before cART to 0.22 per 100 person-yrs during cART. In this study, the incidence during the first trimester was similar to pre-cART levels, whereas it significantly decreased from month 3 onwards [11]. Two large collaborative cohort studies, conducted in Europe and North America, consistently demonstrated that 0.9–1% of patients beginning cART develop TB during treatment over an extended follow-up and that incidence of unmasked TB during the first months of treatment is three to four times higher than incidence of TB during later time-points (1.3–1.7 per 100 person-yrs in the first trimester, compared with 0.3–0.62 per 100 person-yrs after month 6) [14, 15]. This means that, in settings with low prevalence of TB in the general population and high (and early) accessibility of antiretroviral drugs, a significant proportion of TB cases is, in fact, seen in patients receiving cART, with most of these cases occurring soon after cART introduction (up to 15% of all cases of TB in HIV-infected individuals in a British case series) [13].

In studies conducted in low-income countries, 3–14% of HIV-infected patients developed TB during cART (table 2). In these cohorts, the estimated incidence of unmasked TB was 10- to 40-fold higher than in high-income settings, ranging from 5.6 per 100 patient-yrs [20] to 22.1 per 100 patient-yrs of follow-up [22]. In other words, while in high-income countries approximately one out of every 300 to 1,000 patients is diagnosed with TB within 3 months of starting cART, the proportion of patients diagnosed with unmasked TB in low-income countries ranged from a minimum of one case per 80 patients in a South African cohort [3] to a maximum of one case per 11 patients in a Cambodian cohort [23], meaning that unmasked TB, while a

clinical and diagnostic challenge worldwide, is a particularly heavy burden in resource-constrained settings.

Risk factors for unmasked TB upon receipt of antiretroviral treatment

Two factors contribute primarily to the risk of unmasked TB disease after cART initiation: frequency of TB infection in the asymptomatic HIV-infected population and degree of immune suppression before cART.

In a study comparing TB incidence in five different low-income countries, risk of unmasked TB was higher in countries with higher TB burden, such as Senegal and Malawi, than in countries where overall TB incidence was lower, such as Cameroon [23]. In high-income countries, low rates of unmasked TB largely reflect the lower incidence of TB, either in the general population or among HIV-infected subjects, compared with resource-limited countries. Notably, HIV-infected immigrants from countries with high TB incidence may run risks of unmasked TB comparable those run in their country of origin. For instance, in a case-series of 267 individuals who immigrated into the UK from Sub-Saharan Africa, eight (3%) patients developed TB within 3 months of cART [13]. Similarly, Sub-Saharan country of origin and being foreign born were demonstrated to be risk factors for unmasking TB-IRIS in a French case–control study and in a US observational cohort study, respectively [16, 17].

The predictive value of baseline CD4+ T-cell count has been convincingly demonstrated in several studies: the lower the CD4+ T-cell count before cART, the higher the risk of TB during cART [3, 8, 14, 15, 17, 27–29, 32]. LAWN *et al*. [8] estimated that the risk of unmasked TB among patients who had a CD4+ T-cell count <200 cells per mm^3 and <100 cells per mm^3 was approximately three and four times higher than among those with $\geqslant 200$ CD4+ per mm^3, respectively. CD4+ T-cell counts also contribute to the high incidence of unmasked TB recorded in low-income countries, where treatment is generally initiated in the lowest CD4+ strata. One study also suggested that unmasking-TB IRIS is associated with steeper CD4% increases, and more rapid HIV-RNA decline subsequent to cART introduction, compared to non-IRIS-like cART-associated TB [16].

In developing countries, other factors have been independently associated with increased risk of TB during cART. Most of them, such as low body mass index (BMI), anaemia, World Health Organization stage and weight for age, may themselves be indirect measurements of immune suppression and disease advancement, independent of CD4+ count [3, 4, 22, 23, 26, 30]. Moreover, low BMI and recent weight loss may also reflect undiagnosed TB before treatment initiation [30].

Past history of TB has been linked to risk of recurrence upon cART initiation in two studies conducted in Abidjan (Ivory Coast) and in one conducted in South Africa [20, 24, 32]. However, this association has not been confirmed by other studies and, by contrast, LAWN *et al*. [3] suggested that past treatment for TB, particularly if recently completed, may exert a protective effect against risk of active TB after cART initiation. Given the possible implications in terms of secondary prophylaxis, further studies are needed in order to clarify whether a previous episode of TB poses patients at additional risk of TB disease during cART.

Unmasked TB and risk of death

Unmasked TB is an important cause of mortality and has been associated with a high risk of death. When assessed, the mortality of the patients diagnosed with unmasked TB exceeded 25% [4, 22, 29]. While the occurrence of TB following initiation of cART has been consistently associated with significant higher mortality compared with TB-free patients [4, 22], it is unclear whether the occurrence of unmasked TB early during the course of cART may put patients at additional risk of death, compared with TB occurring at later time-points. In one study, the subjects diagnosed with TB within the first 3 months of cART did not experience an excess mortality risk compared with subjects who were diagnosed with TB later [4]. Conversely, in a study conducted in Haiti, patients who received a diagnosis of TB during the first 3 months of cART were three times more likely to die than other patients with AIDS and TB [29]. As the authors recognised, in this study, delayed diagnosis and treatment of TB already present at baseline (almost 50% of patients were symptomatic at the time that cART was started) is likely to have greatly contributed to the high mortality. Moreover, despite an attempt to correct for baseline CD4+ T-cell strata, the deepest immune suppression of patients with unmasked TB may also have influenced their prognosis. Although it cannot be ruled out that exaggerated response due to unmasking-TB IRIS may also have contributed to high mortality, the overall contribution of TB-IRIS events to TB mortality is generally low [25, 33].

Anyway, irrespective of its causes, unmasked TB has been associated with high risk of death and, therefore, represents an important burden in low-income countries, leading to a substantial increase of avoidable mortality in antiretroviral roll-out programmes.

Immunopathogenesis of unmasked TB

Following initiation of antiretroviral treatment, restoration of CD4+ T-cells is documented to occur and is associated with augmentation of bactericidal effector function (cytotoxicity and macrophage-activating cytokine production) with respect to the pre-antiretroviral treatment phase [34]. This is reflected in the restoration of a delayed type hypersensitivity reaction to mycobacterial antigens administered intradermally to HIV-infected patients [35, 36]. Several studies have demonstrated that recovery of a protein purified derivative (PPD)-specific response is specific for immune reconstitution with cART [37–40]. Tuberculin-specific T-cells are known to recover rapidly, both qualitatively and quantitatively, within 3–6 months of cART initiation and successful HIV control. Among HIV/TB co-infected patients, these cells have been shown to reach proportions of up to 33% of the peripheral CD4+ T-cells after 9 months of cART and to have an effector memory CD45RA-CD62L+ phenotype. Moreover, a recent study showed that HIV-infected patients with low CD4+ T-cell counts (<200 per μL) had a significantly higher proportion of interferon (IFN)-γ+ cells after PPD stimulation than either patients with high CD4+ T-cell counts (>500 per μL) or HIV-negative controls. However, analysis of interleukin (IL)-2 and tumour necrosis factor-α production in response to TB antigens, alongside IFN-γ, showed that patients with high CD4+ T-counts had significantly more T-cells co-expressing more than one cytokine than patients with low CD4+ T-cell counts, indicating that a polyfunctional CD4+ T-cell profile could be protective against TB in HIV-infection [41].

TABLE 2 Studies reporting incidence and risk factors for tuberculosis (TB) during antiretroviral treatment

Location	Study	Population characteristics	Patients on cART n	Incidence rates of TB during cART	Incidence rates of TB within 3 months of cART	Early/any TB	CD4+ before cART	Factors associated with TB during cART
High-income countries								
Switzerland	Ledergerber *et al*. [11]	HIV+ starting PI-containing cART	2410	6 (0.2%) (0.22 per 100 person-yrs)	3 (0.1%) (~0.5 per 100 person-yrs)	50%	Median 188 per μL	
Italy	Girardi *et al*. [12]	HIV+ starting cART	387	1 (0.2%)	0			
UK	Breen *et al*. [13]	HIV/TB during cART		19	16	84%	Median 112 per μL	
UK	Breen *et al*. [13]	Sub-Saharan Africans starting cART	267	11 (4.1%)	8 (3%)	73%		
Europe and North America	Girardi *et al*. [14]	Asymptomatic HIV+ starting cART	17142	173 (1%) (0.46 per 100 person-yrs)	55 (0.3%) (1.3 per 100 person-yrs)	32%	55% <200 per μL	cART duration, calendar year, CD4+ nadir, risk factor for HIV (IVDU, heterosexuality)
Europe and North America	Brinkhof *et al*. [15]	HIV+ starting cART observed over 1 yr	22217	205 (0.9%) (1 per 100 person-yrs)	1.7 per 100 person-yrs		Median 234 per μL	CD4+ nadir, risk factor for HIV (heterosexuality)
France	Valin *et al*. [16]	HIV+ starting cART		11 unmasking TB-IRIS			Median 116 per μL	Sub-Saharan African, baseline HIV-RNA, CD4% increase, HIV-RNA decline
USA	Pettit *et al*. [17]	HIV+ starting cART	3492	17 (0.5%) (0.13 per 100 person-yrs)	7 (0.2%) (0.4 per 100 person-yrs within 6 months of cART)	41%	Median 242 per μL	Male sex, black ethnicity, place of birth (foreign born), risk factor for HIV (heterosexuality), CD4+ nadir, baseline HIV-RNA
Low-income countries								
Thailand	Sungkanuparph *et al*. [18]	AIDS patients starting cART	60	8 (13.3%)			Median 9 per μL	
Uganda	John *et al*. [19]	HIV/TB during cART		131	29	22%		
Ivory Coast	Seyler *et al*. [20]	HIV+ starting cART	129	12 (9.3%) (4.8 per 100 person-yrs)	3 (2.3%)	25%	Median 129 per μL	Previous TB diagnosis
South Africa	Lawn *et al*. [3]	HIV+ starting cART	346	27 (7.8%) (2.4 per 100 person-yrs)	4 (1.2%) (3.35 per 100 person-yrs within 1 yr of cART)	15%	Median 242 per μL	Age, CD4+ nadir, WHO stage
Uganda	Baalwa *et al*. [21]	HIV+ without TB starting cART	271	26 (9.6%)	8 (2.8%)	31%		
South Africa	Lawn *et al*. [22]	HIV+ without TB starting cART	756	81 (10.7%) (10.5 per 100 person-yrs)	40 (5.3%) (22.1 per 100 person-yrs)	49%	Median 96 per μL	Current CD4+
Cambodia	Bonnet *et al*. [23]	HIV+ starting cART	717	100 (13.9%) (7.6, 12.7 per 100 person-yrs)#	63 (8.8%)	63%	66% <50 per μL	
Thailand	Bonnet *et al*. [23]	HIV+ starting cART	500	57 (11.4%) (10.4, 4.3 per 100 person-yrs)#	30 (6%)	53%	72% <50 per μL	
Kenya	Bonnet *et al*. [23]	HIV+ starting cART	654	73 (11.2%) (17.6, 6.9 per 100 person-yrs)#	41 (6.3%)	56%	36% <50 per μL	
Malawi	Bonnet *et al*. [23]	HIV+ starting cART	1064	80 (7.5%) (14.3, 2.1 per 100 person-yrs)#	50 (4.7%)	62%	21% <50 per μL	
Cameroon	Bonnet *et al*. [23]	HIV+ starting cART	216	10 (4.6%) (4.8, 0 per 100 person-yrs)#	8 (3.7%)	80%	25% <50 per μL	
Africa, Asia and South America	Brinkhof *et al*. [15]	HIV+ starting cART	4540	258 (5.7%) (7.4 per 100 person-yrs)	10.7 per 100 person-yrs		Median 107 per μL	CD4+ nadir, sex, age

TABLE 2 Continued

Location	Study	Population characteristics	Patients on cART n	Incidence rates of TB during cART	Incidence rates of TB within 3 months of cART	Early/any TB	CD4+ before cART	Factors associated with TB during cART
Uganda	Moore *et al*. [4]	HIV+ without TB starting cART	969	53 (5.5%) (3.9 per 100 person-yrs)	23 (2.4%) (7.5 per 100 person-yrs within 6 months of cART)	43%	Median 127 per μL	Low BMI
Ivory Coast	Moh *et al*. [24]	HIV+ without TB starting cART	792	23 (2.9%) (3.3 per 100 person-yrs)	5.6 per 100 person-yrs	~50%	Median 252 per μL	Previous TB diagnosis, haemoglobin, current CD4+
South Africa	Murdoch *et al*. [25]	HIV+ without TB starting cART	338	16 (4.7%)	11 (3.2%)	69%	Median 115 per μL	
Ethiopia	Huruy *et al*. [26]	HIV+ without TB starting cART	178	20 (11.2%)			Mean 123 per μL	
Senegal	Etard *et al*. [27]	HIV+ without TB starting cART	352	42 (11.9%) (2.3 per 100 person-yrs)	4.5 per 100 person-yrs within 1 yr of cART		Median 128 per μL	Haemoglobin, CD4+ nadir
South Africa	Smith *et al*. [28]	Children <2 yrs of age starting cART	169	12 (7.1%)	11 (6.5%)	92%	39% <15 CD4%	Age <6 months, CD4%, HIV-RNA, weight for age
Haiti	Koenig *et al*. [29]	HIV/TB during cART		97	49	50.5%		CD4+
Malawi	Bedell *et al*. [30]	HIV+ without TB starting cART	2281		67 (2.9%)			Weight loss >10%, WHO clinical stage 4
South Africa	Lawn *et al*. [8]	HIV+ without TB starting cART	1032	171 (16.6%) (7.3 per 100 person-yrs)	18.8 per 100 person-yrs		Median 97 per μL	Current CD4+
Burkina Faso	Dembelé *et al*. [31]	HIV+ starting cART	2383	70 (2.9%)	33 (1.4%) (5.77 per 100 person-yrs)	47.1%	Mean 128 per μL	Low BMI, CD4+ nadir
South Africa	Nicholas *et al*. [32]	HIV+ without TB starting cART	19325	933 (4.8%) (5.4 per 100 person-yrs)	470 (2.4%) (13 per 100 person-yrs)	50.4%	Median 142 per μL	Urban sites, male sex, calendar year, low BMI, previous TB diagnosis, CD4+ nadir

cART: combination antiretroviral treatment; PI: protease inhibitor; IVDU: intravenous drug user; IRIS: immune reconstitution inflammatory syndrome; WHO: World Health Organization; BMI: body mass index. Note that data may not directly reflect those reported in the cited papers, because patients with a diagnosis of TB before cART initiation have been excluded from the table. Data for incidence rates are given for the first 3 months of antiretroviral treatment, unless otherwise specified. #: incidence rates for pulmonary and extrapulmonary TB, respectively.

Taken together, these findings suggest that the relatively sudden and rapid restoration of functional CD4+ T-cells specific for *Mycobacterium tuberculosis* may be massively involved in the pathophysiology of unmasked TB disease after cART initiation. Observations that unmasked TB disease is more common among formerly naïve patients with very low CD4+ cell counts (<200 cells per μL) and with strong response to cART support this hypothesis [16].

Expansion of tuberculin-specific T-cells has also been cited as a possible cause of IRIS, a complex phenomenon which likely shares a common immunological pathway with unmasked TB. Amplification of IFN-γ producing T-cells has been reported among patients with TB-IRIS and has been associated with an acute burst of other T-helper type 1 (Th1) and pro-inflammatory cytokines/chemokines, which provokes conditions favouring deregulated immune activation [42]. Similarly, rapid increases in IFN-γ responses to RD1 antigens and to PPD have been found among patients with unmasked TB, suggesting that unmasked TB and TB-IRIS are both associated with restoration of immune response against *M. tuberculosis* antigens [43]. However, increases in IFN-γ responses during TB-IRIS were shown to be relatively slow, compared with unmasked TB, hinting that additional immune defects may play important roles in TB-IRIS. Dysregulation of IFN-γ activity, manifested by higher levels of IL-18 (an inducer of IFN-γ production) and CXCL10 (a marker of IFN-γ production), has indeed been demonstrated during TB-IRIS, but not during unmasked TB [44]. Moreover, circulating IL-10 has been reported to be lower during TB-IRIS events than during non-IRIS events, whereas no differences in IL-10 levels were found between unmasked TB and control events [45]. IL-10 is produced by monocytes and T-regulatory (T-reg) cells and down-regulates many immune functions, including Th1 cytokines and killing of mycobacteria. A defect in T-reg function and a reduction in its ability to downregulate immune response are likely to be among the mechanisms underlying the exaggerated inflammatory response observed during TB-IRIS [46]. In contrast, the role of the T-reg subset would appear to be less important in determining unmasked TB, which is apparently driven by a restoration of effector T-cell responses, in the absence

of proper dysregulation between the effector and the regulatory functions of immune response [45].

Further studies, however, are needed to clarify the role of T-reg cells in the pathogenesis of TB IRIS and unmasked TB. It is likely that exploration of the frequency and the function of these cells, not only in the peripheral blood, but also in the site of disease, could elucidate their exact function.

Figure 1 summarises the hypothetical immunopathogenesis of unmasked TB manifesting with and without IRIS.

Clinical features of unmasked TB

Unmasked TB can vary widely in the degree of its clinical presentation, and there is no clear evidence that unmasked TB is clinically distinguishable from other HIV-associated TB or that unmasking TB has different features from paradoxical TB-IRIS. Restoration of immune function following cART introduction can simply elicit or exacerbate symptoms of TB, or it can be responsible for exaggerated inflammatory response, similar to TB-IRIS. Table 3 shows the clinical features of unmasked TB cases as reported in published cohort studies, case series and case reports.

Data from larger cohorts show that roughly two-thirds of unmasked TB cases present with lung involvement as primitive and exclusive localisation [22, 23, 31, 32]. This contrasts to some extent with data from cohorts of untreated patients with advanced HIV infection, among whom extrapulmonary involvement accounts for 50% of cases or more [59, 60]. Of note, the high rate of pulmonary TB observed in the first trimester of cART has been associated in particular with a higher incidence of sputum smear-negative forms, as compared with TB occurring later during cART [31, 32]. This observation, although potentially influenced by diagnostic capacities, deserves attention, because it can delay diagnosis and treatment of unmasked TB.

Similar diagnostic problems are posed by extrapulmonary TB, which accounted for 30 to 40% of all unmasked TB, in various cohorts. The most common areas of extrapulmonary localisation of unmasked TB are lymphatic, gastrointestinal and central nervous system [16, 21, 33, 47, 51, 52]. Other, less frequent, manifestations include glaucomatous hepatitis, genito-urinary TB, splenic abscesses and hypercalcaemia. Unusual and extremely severe presentation of unmasked TB have been reported, encompassing adult respiratory distress syndrome [48], bronchiolitis obliterans organising pneumonia [55], pyomiositis [57], multiple cerebral tuberculomas [52] and haemophagocytic syndrome [58]. These manifestations are likely to be due to an IRIS-like inflammatory reaction, as a consequence of cART-induced restoration of specific TB immune response.

Prevention of unmasked TB

Given the high disease burden and mortality of HIV-infected subjects diagnosed with unmasked TB, all possible efforts should be made to prevent it, particularly in developing countries. In the present paper, we will use the term ''primary prevention'' to indicate interventions aimed at reducing the risk of TB among HIV-infected patients initiating cART. Those interventions aimed at identifying patients at risk of unmasked TB and/or at increasing the yield of early unmasked TB diagnosis will be referred to as ''secondary prevention''.

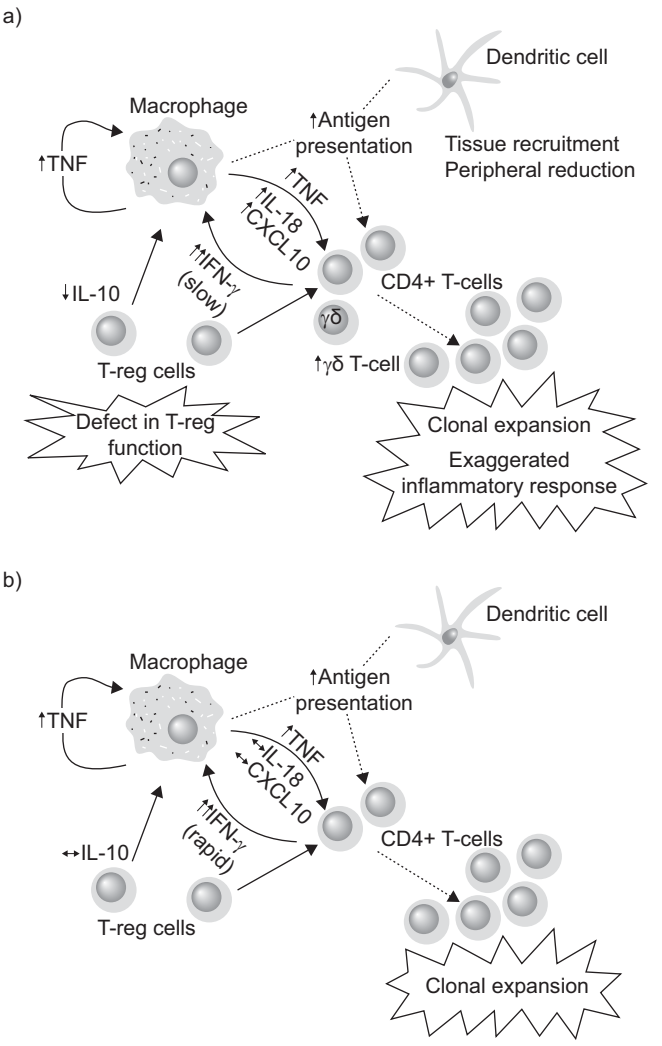

FIGURE 1. Postulated immunopathogenesis of a) unmasking tuberculosis (TB)-immune reconstitution inflammatory syndrome (IRIS) and b) unmasked TB without IRIS. Both conditions are associated with restoration of immune response against *Mycobacterium tuberculosis* antigens due to antiretroviral treatment. Unmasking TB-IRIS (a) is characterised by slow increases in interferon (IFN)-γ responses, dysregulation of IFN-γ activity, increasing levels of interleukin (IL)-18 and CXCL10 and defect in T-regulatory (T-reg) cell function, leading to exaggerated inflammatory response. Tissue recruitment of dendritic cells and increase in peripheral γδ T-cells contribute to IRIS manifestations. Unmasked TB with no IRIS manifestation (b) is associated with a more rapid IFN-γ increase in absence of T-reg functional defects. TNF: tumour necrosis factor. Adapted from the Wikimedia Commons files "Image:Macrophage.png" and ''Image: Dendritic cell.png'' available from http://commons.wikimedia.org/wiki.

Two different, and possibly complementary, strategies are prime candidates for primary prevention: early cART introduction and preventive treatment with isoniazid.

As previously mentioned, unmasked TB is strictly dependent on CD4+ T-cell count: the lower the count, the higher the risk. Timely cART is therefore a potent intervention for unmasked TB prevention, provided that it is initiated before significant immune depletion. The exact risk reduction associated with different CD4+ T-cell strata, however, is yet to be determined. While it has

been convincingly demonstrated that the elevation of the CD4+ threshold for cART eligibility from 200 to 350 cells per μL (or even more) significantly reduces TB among patients awaiting cART [61], indirect evidence suggests that the benefit of this shift in terms of prevention of unmasking TB is likely to be low. In fact, LAWN *et al*. [8] showed that, among patients with CD4+ T-cell counts >200 per mm^3, TB incidence rates during early cART were comparable to rates during long-term treatment. This suggests that, under these circumstances, the role of immune recovery in unmasking subclinical TB is less important.

Therefore, in terms of unmasked TB prevention, promoting early HIV diagnosis and minimising health system delays in cART initiation are likely to be more cost-effective than further anticipating cART debut among patients already on longitudinal care.

Isoniazid preventive treatment (IPT) is a second strategy that could be effective in reducing the risk of developing active TB and, subsequently, unmasked TB upon cART initiation.

Integration of IPT programmes in HIV care has been demonstrated to be both feasible and practical, and IPT used concomitantly with cART among the common scenario of patients with advanced HIV infection is likely to have great benefit in terms of preventing unmasked TB. A recent study offered new insights about the benefits of concomitant IPT and cART treatment. Among previously cART-naïve patients with symptomatic disease and/or low CD4+ T-cell counts, a significantly lower mortality rate was observed among those receiving IPT together with cART, compared with those receiving cART alone [62]. Whether this effect is driven, at least in part, by a reduced incidence of unmasked TB is unknown and further study is needed to specifically address the impact of concurrent IPT and cART on unmasked TB among formerly naïve patients with advanced HIV disease.

The identification of the patients who are more likely to develop unmasked TB after cART initiation is a mainstay of secondary prevention. Nonspecific markers of inflammation, such as D-dimer [63], C-reactive protein and plasma IFN-γ [64], have been demonstrated to be higher before cART initiation among those who subsequently develop unmasked TB. Their utility as diagnostic markers is, however, very limited. ELLIOTT *et al*. [43] proposed that IFN-γ release assays prior to cART might help in predicting unmasked TB and in stratifying patients in low- and high-risk groups. Nonetheless, IFN-γ release assays are generally unable to distinguish between active disease and latent infection. Moreover, the need for advanced infrastructure means these tests are of little or no use in resource-constrained settings. A more interesting marker is lipoarabinomannan (LAM), a major component of *M. tuberculosis* cell wall, which can be detected in the urine of TB patients, using a relatively easy and inexpensive procedure. Urine LAM assay was demonstrated to be specific and substantially more sensitive than sputum microscopy as a routine diagnostic TB screening test among patients with CD4+ T-cell counts <100 cells per μL [65].

Treatment of unmasked TB

Most unmasked TB has a clinical presentation similar to that of incident TB. Since therapy for susceptible TB is typically as effective in the HIV-infected patient as it is in the general population, prompt initiation of appropriate chemotherapeutic regimen is the only effective therapeutic measure available. Treatment of unmasked TB must be integrated with close follow-up and with immediate revision of cART, in order to minimise adverse interactions between anti-tubercular and antiretroviral drugs, keeping in mind that the use of rifamycins is essential, and that rifabutin is an acceptable alternative to rifampin if this choice is required by drug interaction issues. The response to treatment of unmasked TB is comparable to that of other TB/HIV co-infections, as demonstrated by the low rate of recurrence after TB treatment [32].

Occasionally, unmasked TB can present with a marked inflammatory component and/or with a clinical course complicated by paradoxical reactions. Management of unmasked TB with a paradoxical presentation has not been extensively studied. However, since the underlying immunopathogenetic mechanism is likely to be similar to that of TB-IRIS, the therapeutic approach is similar. Published cases and clinical experience suggest that continuation of cART is reasonable in the majority of cases. Paradoxical reactions are self-limiting in most patients, and treatment is usually reserved for severe manifestations, such as life-threatening conditions or in patients at risk of permanent sequelae. Discontinuation of cART should be considered only as a last resort, given the higher mortality rate of patients with HIV/TB not receiving concomitant antiretroviral treatment [66, 67]. Only in cases ''resistant'' to corticosteroids should cART interruption be considered [68].

In general, symptomatic agents, such as corticosteroids or non-steroidal anti-inflammatory drugs, are effective in obtaining symptom relief and in controlling inflammatory response. Corticosteroid treatment, although widely used, has yet to be standardised, and published studies and case series report varying choices of dosing and treatment duration. Severe IRIS-like reactions can be managed with prednisone at a starting dosage of 1 to 2 $mg \cdot kg^{-1} \cdot day^{-1}$. In cases with central nervous system involvement, dexamethasone use (8 mg twice daily) could be preferred. Steroids were also demonstrated to be safe and effective when used in not life-threatening TB-IRIS. In a recent randomised placebo controlled trial, a 4-week course of prednisone reduced hospitalisation and hastened the improvement in signs and symptoms associated with TB-IRIS [69]. The risk of adverse reactions attributable to corticosteroids, however, should be carefully evaluated before initiating therapy, because more side-effects were reported in the prednisone than in the placebo arm, although the difference did not reach statistical significance.

Occasionally, corticosteroid treatment has been reported to be ineffective in controlling severe cases of TB-IRIS. Where maximal dosages of corticosteroids fail to control a life-threatening inflammatory reaction, alternative drugs can be considered as salvage treatment. Leukotriene antagonists, such as montelukast and zafirlukast, have been considered in a few reports as treatment for IRIS [70].

CONCLUSIONS

All these challenges make unmasked TB a dangerous threat in antiretroviral roll-out and TB control programmes, particularly in resource-limited countries, and limit global and national capacities to curb the HIV/TB epidemic. Delays in diagnosis and treatment and, in some cases, exaggerated inflammatory response, are causes of a high attributable mortality and put other

TABLE 3 Clinical features of published cohort studies, case series and case reports of unmasked tuberculosis (TB)

Study	Location	Cases	Symptoms before cART initiation	Clinical features	Sputum smear/culture
Shelburne *et al*. [47]	USA	1	Not reported	Fever, weight loss, abdominal pain due to bowel (cecal) TB	Culture-positive
Goldsack *et al*. [48]	UK	1	Asymptomatic; normal chest radiograph	Fever, night sweats, shortness of breath rapidly evolving in respiratory failure due to ARDS	Smear- and culture-positive
John *et al*. [19]	Uganda	1	Malaise, weight loss, low-grade fever, intermittent cough; normal chest radiograph	Fever, dry cough, miliary pulmonary infiltrates	Smear- and culture-negative
Seyler *et al*. [20]	Sub-Saharan Africa	3	Not reported	1 pulmonary, 2 disseminated	2 smear-positive, culture-positive
Breen *et al*. [13]	England	13	60% symptomatic (5 fever, 4 weight loss, 2 cough, 2 night sweats)	38% pulmonary, 24% extrapulmonary, 38% miliary, 61% ''paradoxical reactions''	85% culture-positive
Miller *et al*. [49]	UK	1	Weight loss, minimal productive cough, fever	Pulmonary TB	Smear- and culture-negative
Bonnet *et al*. [23]	Cambodia, Thailand, Kenya, Malawi, Cameroon	192	Not reported	68% pulmonary, 32% extrapulmonary	Not reported
Lawn *et al*. [22]	Sub-Saharan Africa	40	Not reported	78% pulmonary, 22% extrapulmonary	41% smear-positive, 81% culture-positive
Zampoli *et al*. [50]	South Africa	7 children	Not reported	6 pulmonary TB, 1 disseminate TB (pulmonary+lymphoadenitis+meningitis)	4/6 smear- and culture-positive (1 MDR), 1/6 smear-negative and culture-positive, 2/6 smear- and culture-negative
Park *et al*. [51]	South Korea	5	Not reported	3 pulmonary, 2 extrapulmonary (1 cerebral); lymphadenitis in 3/5 cases	Not reported
Moh *et al*. [24]	Ivory Coast	23	Not reported	64% pulmonary, 24% extrapulmonary, 12% disseminated	Not reported
Dautremer *et al*. [52]	France	1	Not reported	Tuberculous meningitis (acute onset), multiple cerebral tuberculomas	Culture-positive CSF
Tuon *et al*. [53]	Brazil	1	Not reported	Hepatosplenic abscesses and granulomatous hepatitis	Culture of liver biopsy negative
Meintjes *et al*. [6]	Not reported	1	Low-grade fever, retrosternal chest pain, dry cough; normal chest radiograph	Fever and respiratory distress due to pulmonary TB	Smear-positive
Ocama *et al*. [54]	Uganda	7	Not reported	Suspected TB hepatitis	Not reported
Baalwa *et al*. [21]	Uganda	8	Not reported	1 pulmonary, 7 extrapulmonary (2 meningitis, 1 lymphadenitis, 1 abdominal), 3 disseminated	1 smear-positive
Murdoch *et al*. [25]	South Africa	18	Not reported	50% pulmonary, 25% extrapulmonary, 25% disseminated	69% smear- or culture-positive
Lawn *et al*. [55]	South Africa	1	Asymptomatic	Bronchiolitis obliterans organising pneumonia, death	Smear- negative
Lawn *et al*. [8]	South Africa	203	Not reported	74% pulmonary, 26% extrapulmonary	Not reported
Manabe *et al*. [7]	USA	1	Chronic watery diarrhoea, subjective fevers, chills, weight loss; normal chest radiograph; PPD negative	Fever and cough due to upper lobe cavitary TB	Smear-negative, culture-positive
Castelnuovo *et al*. [33]	Uganda	2	Asymptomatic	1 extrapulmonary TB, 1 TB meningitis	Not reported
Tsao *et al*. [56]	Taiwan	1	Weight loss	Hypercalcaemia, splenic abscess	Not reported
Chen *et al*. [57]	Taiwan	1	Weight loss	Gluteal pyomiositis	Not reported
Soria *et al*. [58]	Italy	1	Not reported	Haemophagocytic syndrome due to disseminated TB	Smear- and culture-negative
Valin *et al*. [16]	France	11	Not reported	4 pulmonary, 3 extrapulmonary, 4 disseminated (2 CNS involvement)	All culture-confirmed

TABLE 3 Continued

Study	Location	Cases	Symptoms before cART initiation	Clinical features	Sputum smear/culture
PETTIT *et al.* [17]	USA	7	Not reported	2 not reported, 5 extrapulmonary IRIS (2 lymphadenitis, 1 splenic, 2 disseminated)	Not reported

cART: combination antiretroviral treatment; PPD: protein purified derivative; ARDS: adult respiratory distress syndrome; CNS: central nervous system; IRIS: immune reconstitution inflammatory syndrome; MDR: multidrug resistant; CSF: cerebro-spinal fluid.

HIV-infected patients at risk of TB nosocomial transmission. Given the high disease burden, it is crucial to invest all possible efforts to prevent unmasked TB among patients starting antiretroviral treatment, either by impeding TB disease or by increasing the yield of subclinical TB diagnosis before treatment initiation. The problem deserves urgent attention by researchers and political commitment in order to adopt evidence-based pre-emptive policies. Research priorities include the identification of new rapid, affordable and reliable diagnostic tools. Moreover, further investigation on the optimal timing and duration of IPT, as well as implementation of IPT in HIV/AIDS national programmes, are urgently needed. Prompt anti-TB treatment and management of paradoxical inflammatory reactions are the cornerstones of unmasked TB treatment.

SUPPORT STATEMENT

This work has partially been funded by TB PAN-NET (www.tbpannet.org), which is sponsored by the European Commission's Seventh Framework Programme for Research (FP7-HEALTH-2007-B).

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

We thank D. Iemmi (University of Milano-Bicocca, Monza, Italy) for the help in editing the figure presented in the paper.

REFERENCES

1 Lawn SD, Myer L, Orrell C, *et al.* Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* 2005; 19: 2141–2148.
2 Corbett EL, Watt CJ, Walker N, *et al.* The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009–1021.
3 Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS* 2005; 19: 2109–2116.
4 Moore D, Liechty C, Ekwaru P, *et al.* Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. *AIDS* 2007; 21: 713–719.
5 Lawn SD, Wilkinson RJ, Lipman MC, *et al.* Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med* 2008; 177: 680–685.
6 Meintjes G, Lawn SD, Scano F, *et al.* Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008; 8: 516–523.
7 Manabe YC, Breen R, Perti T, *et al.* Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. *J Infect Dis* 2009; 199: 437–444.
8 Lawn SD, Myer L, Edwards D, *et al.* Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS* 2009; 23: 1717–1725.
9 Haddow LJ, Easterbrook PJ, Mosam A, *et al.* Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion *versus* 2 case definitions in a South African cohort. *Clin Infect Dis* 2009; 49: 1424–1432.
10 Haddow LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010; 24: 103–108.
11 Ledergerber B, Egger M, Erard V, *et al.* AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999; 282: 2220–2226.
12 Girardi E, Antonucci G, Vanacore P, *et al.* Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS* 2000; 14: 1985–1991.
13 Breen RA, Smith CJ, Cropley I, *et al.* Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? *AIDS* 2005; 19: 1201–1206.
14 Girardi E, Sabin CA, d'Arminio MA, *et al.* Incidence of tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clin Infect Dis* 2005; 41: 1772–1782.
15 Brinkhof MW, Egger M, Boulle A, *et al.* Tuberculosis after initiation of antiretroviral therapy in low-income and high-income countries. *Clin Infect Dis* 2007; 45: 1518–1521.
16 Valin N, Pacanowski J, Denoeud L, *et al.* Risk factors for ''unmasking immune reconstitution inflammatory syndrome'' presentation of tuberculosis following combination antiretroviral therapy initiation in HIV-infected patients. *AIDS* 2010; 24: 1519–1525.
17 Pettit AC, Jenkins CA, Stinnette SE, *et al.* Tuberculosis risk before and after highly active antiretroviral therapy initiation: does HAART increase the short-term TB risk in a low incidence TB setting? *J Acquir Immune Defic Syndr* 2011; 57: 305–310.
18 Sungkanuparph S, Vibhagool A, Mootsikapun P, *et al.* Opportunistic infections after the initiation of highly active antiretroviral therapy in advanced AIDS patients in an area with a high prevalence of tuberculosis. *AIDS* 2003; 17: 2129–2131.
19 John L, Baalwa J, Kalimugogo P, *et al.* Response to ''Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?'' *AIDS* 2005; 19: 2049–2050.
20 Seyler C, Toure S, Messou E, *et al.* Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan. *Am J Respir Crit Care Med* 2005; 172: 123–127.
21 Baalwa J, Mayanja-Kizza H, Kamya MR, *et al.* Worsening and unmasking of tuberculosis in HIV-1 infected patients after initiating highly active anti-retroviral therapy in Uganda. *Afr Health Sci* 2008; 8: 190–195.

22 Lawn SD, Myer L, Bekker LG, *et al.* Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS* 2006; 20: 1605–1612.
23 Bonnet MM, Pinoges LL, Varaine FF, *et al.* Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. *AIDS* 2006; 20: 1275–1279.
24 Moh R, Danel C, Messou E, *et al.* Incidence and determinants of mortality and morbidity following early antiretroviral therapy initiation in HIV-infected adults in West Africa. *AIDS* 2007; 21: 2483–2491.
25 Murdoch DM, Venter WD, Feldman C, *et al.* Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. *AIDS* 2008; 22: 601–610.
26 Huruy K, Mulu A, Mengistu G, *et al.* Immune reconstitution inflammatory syndrome among HIV/AIDS patients during highly active antiretroviral therapy in Addis Ababa, Ethiopia. *Jpn J Infect Dis* 2008; 61: 205–209.
27 Etard JF, Diouf A, De BP, *et al.* Short and long-term incidence of tuberculosis and CD4-cell count dynamic on HAART in Senegal. *Open AIDS J* 2009; 3: 63–70.
28 Smith K, Kuhn L, Coovadia A, *et al.* Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS* 2009; 23: 1097–1107.
29 Koenig SP, Riviere C, Leger P, *et al.* High mortality among patients with AIDS who received a diagnosis of tuberculosis in the first 3 months of antiretroviral therapy. *Clin Infect Dis* 2009; 48: 829–831.
30 Bedell R, Chan AK, Bourgeois J, *et al.* Clinical features amongst ART patients who develop suspected TB early after initiation in a district in Southern Malawi, 5th IAS Conference on HIV Pathogenesis and Treatment: Abstract no TUPEB137 2009. Available from: www.iasociety.org/Default.aspx?pageId=12&abstractId=200722060
31 Dembelé M, Saleri N, Carvalho AC, *et al.* Incidence of tuberculosis after HAART initiation in a cohort of HIV-positive patients in Burkina Faso. *Int J Tuberc Lung Dis* 2010; 14: 318–323.
32 Nicholas S, Sabapathy K, Ferreyra C, *et al.* Incidence of tuberculosis in HIV-infected patients before and after starting combined antiretroviral therapy in 8 sub-Saharan African HIV programs. *J Acquir Immune Defic Syndr* 2011; 57: 311–318.
33 Castelnuovo B, Manabe YC, Kiragga A, *et al.* Cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome in the first 3 years after antiretroviral therapy initiation in an urban African cohort. *Clin Infect Dis* 2009; 49: 965–972.
34 Kampmann B, Tena-Coki GN, Nicol MP, *et al.* Reconstitution of antimycobacterial immune responses in HIV-infected children receiving HAART. *AIDS* 2006; 20: 1011–1018.
35 French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. *AIDS* 1992; 6: 1293–1297.
36 Narita M, Ashkin D, Hollender ES, *et al.* Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998; 158: 157–161.
37 Havlir DV, Schrier RD, Torriani FJ, *et al.* Effect of potent antiretroviral therapy on immune responses to *Mycobacterium avium* in human immunodeficiency virus-infected subjects. *J Infect Dis* 2000; 182: 1658–1663.
38 Wendland T, Furrer H, Vernazza PL, *et al.* HAART in HIV-infected patients: restoration of antigen-specific CD4 T-cell responses *in vitro* is correlated with CD4 memory T-cell reconstitution, whereas improvement in delayed type hypersensitivity is related to a decrease in viraemia. *AIDS* 1999; 13: 1857–1862.
39 Hengel RL, Allende MC, Dewar RL, *et al.* Increasing CD4+ T cells specific for tuberculosis correlate with improved clinical immunity after highly active antiretroviral therapy. *AIDS Res Hum Retroviruses* 2002; 18: 969–975.
40 Foudraine NA, Hovenkamp E, Notermans DW, *et al.* Immunopathology as a result of highly active antiretroviral therapy in HIV-1-infected patients. *AIDS* 1999; 13: 177–184.
41 Sutherland JS, Young JM, Peterson KL, *et al.* Polyfunctional CD4+ and CD8+ T cell responses to tuberculosis antigens in HIV-1-infected patients before and after anti-retroviral treatment. *J Immunol* 2010; 184: 6537–6544.
42 Bourgarit A, Carcelain G, Martinez V, *et al.* Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS* 2006; 20: F1–F7.
43 Elliott JH, Vohith K, Saramony S, *et al.* Immunopathogenesis and diagnosis of tuberculosis and tuberculosis-associated immune reconstitution inflammatory syndrome during early antiretroviral therapy. *J Infect Dis* 2009; 200: 1736–1745.
44 Oliver BG, Elliott JH, Price P, *et al.* CXCL10 (IP-10) levels may be a marker of immune dysregulation in tuberculosis-associated immune reconstitution inflammatory syndrome, 5th IAS Conference on HIV Pathogenesis and Treatment: Abstract no TUPEB160 2009. Available from: http://iset.ias2009.org/Abstracts/A200721707.aspx
45 Haddow LJ, Dibben O, Moosa MY, *et al.* Circulating inflammatory biomarkers can predict and characterize tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2011; 25: 1163–1174.
46 Seddiki N, Sasson SC, Santner-Nanan B, *et al.* Proliferation of weakly suppressive regulatory CD4+ T cells is associated with over-active CD4+ T-cell responses in HIV-positive patients with mycobacterial immune restoration disease. *Eur J Immunol* 2009; 39: 391–403.
47 Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, *et al.* Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)* 2002; 81: 213–227.
48 Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect* 2003; 79: 337–338.
49 Miller RF, Shahmanesh M, Talbot MD, *et al.* Progressive symptoms and signs following institution of highly active antiretroviral therapy and subsequent antituberculosis therapy: immune reconstitution syndrome or infection? *Sex Transm Infect* 2006; 82: 111–116.
50 Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. *Int J Tuberc Lung Dis* 2007; 11: 417–423.
51 Park WB, Choe PG, Jo JH, *et al.* Tuberculosis manifested by immune reconstitution inflammatory syndrome during HAART. *AIDS* 2007; 21: 875–877.
52 Dautremer J, Pacanowski J, Girard PM, *et al.* A new presentation of immune reconstitution inflammatory syndrome followed by a severe paradoxical reaction in an HIV-1-infected patient with tuberculous meningitis. *AIDS* 2007; 21: 381–382.
53 Tuon FF, Mulatti GC, Pinto WP, *et al.* Immune reconstitution inflammatory syndrome associated with disseminated mycobacterial infection in patients with AIDS. *AIDS Patient Care STDS* 2007; 21: 527–532.
54 Ocama P, Katwere M, Piloya T, *et al.* The spectrum of liver diseases in HIV infected individuals at an HIV treatment clinic in Kampala, Uganda. *Afr Health Sci* 2008; 8: 8–12.
55 Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS* 2009; 23: 143–145.
56 Tsao YT, Wu YC, Yang CS, *et al.* Immune reconstitution associated hypercalcemia. *Am J Emerg Med* 2009; 27: 629–623.
57 Chen WL, Lin YF, Tsai WC, *et al.* Unveiling tuberculous pyomyositis: an emerging role of immune reconstitution inflammatory syndrome. *Am J Emerg Med* 2009; 27: 251–252.
58 Soria A, Foresti S, Fortuna P, *et al.* Unmasked tuberculosis or lymphoma in late AIDS presenters: a difficult differential diagnosis. *Eur Respir J* 2009; 34: 997–998.

59 Jones BE, Young SM, Antoniskis D, *et al.* Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis* 1993; 148: 1292–1297.

60 Kingkaew N, Sangtong B, Amnuaiphon W, *et al.* HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death. *Int J Infect Dis* 2009; 13: 722–729.

61 Severe P, Juste MA, Ambroise A, *et al.* Early *versus* standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med* 2010; 363: 257–265.

62 Innes C, Charalambous S, Felix M, *et al.* Effectiveness of isoniazid preventive therapy in reducing mortality in patients on ART, Presented at: 17th Conference on Retroviruses and Opportunistic Infections San Francisco (CA): USA; February 16–19, 2010. Abstract 102. Available from: http://retroconference.org/2010/Abstracts/38631.htm

63 Porter B, Ouedraogo L, Hodge J, *et al.* D-dimer levels are elevated in unmasking IRIS cases prior to and 1-month following antiretroviral initiation, 5th IAS Conference on HIV Pathogenesis and Treatment 2009. Abstract TUPEB164. Available from: www.iasociety.org/Abstracts/A200722375.aspx

64 Haddow L, Borrow P, Dibben O, *et al.* Cytokine profiles predict unmasking TB immune reconstitution inflammatory syndrome, and are associated with unmasking and paradoxical presentations of TB immune reconstitution inflammatory syndrome, 16th Conference on Retroviruses and Opportunistic Infections, Montreal (Canada) Abstract #773 2009. Available from: http://retroconference.org/2009/Abstracts/34242.htm

65 Lawn SD, Edwards DJ, Kranzer K, *et al.* Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. *AIDS* 2009; 23: 1875–1880.

66 Dheda K, Lampe FC, Johnson MA, *et al.* Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis* 2004; 190: 1670–1676.

67 Abdool Karim SS, Naidoo K, Grobler A, *et al.* Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; 362: 697–706.

68 French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis* 2009; 48: 101–107.

69 Meintjes G, Wilkinson RJ, Morroni C, *et al.* Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010; 24: 2381–2390.

70 Hardwick C, White D, Morris E, *et al.* Montelukast in the treatment of HIV associated immune reconstitution disease. *Sex Transm Infect* 2006; 82: 513–514.