

Potential utility of empirical tuberculosis treatment for HIV-infected patients with advanced immunodeficiency in high TB-HIV burden settings

S. D. Lawn,^{*†} H. Ayles,^{**} S. Egwaga,[§] B. Williams,[¶] Y. D. Mukadi,[#] E. D. Santos Filho,^{**}
P. Godfrey-Faussett,^{*} R. M. Granich,^{††} A. D. Harries^{**††}

^{*}Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK;

[†]Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; [‡]Zambia AIDS Related Tuberculosis Project, University of Zambia Ridgeway Campus, Lusaka, Zambia; [§]National Tuberculosis Programme, Dar Es Salaam, Tanzania; [¶]South African

Centre for Epidemiological Modelling and Analysis (SACEMA), Stellenbosch, South Africa; [#]Family Health International, Washington, DC, USA; ^{**}Grupo Pela VIDA–Rio de Janeiro, Parceria Brasileira Contra a Tuberculose (Stop TB Brazil), Rio de Janeiro, Rio de Janeiro, Brazil; ^{††}Department of HIV/AIDS, World Health Organization, Geneva, Switzerland; ^{†††}International Union Against Tuberculosis and Lung Disease, Paris, France

^{†††}International Union Against Tuberculosis and Lung Disease, Paris, France

SUMMARY

The human immunodeficiency virus (HIV) and HIV-associated tuberculosis (TB-HIV) epidemics remain uncontrolled in many resource-limited regions, especially in sub-Saharan Africa. The scale of these epidemics requires the consideration of innovative bold interventions and ‘out-of-the-box’ thinking. To this end, a symposium entitled ‘Controversies in HIV’ was held at the 40th Union World Conference on Lung Health in Cancun, Mexico, in December 2009. The first topic debated, entitled ‘Annual HIV testing and immediate start of antiretroviral therapy for all HIV-infected persons’, received much attention at international conferences and in the literature in 2009. The second topic forms the subject of this article. The rationale for the use of empirical TB treatment is premised on the hypothesis that in settings worst affected by the TB-HIV epidemic, a subset of HIV-infected patients have such a high risk of undiagnosed TB and of

associated mortality that their prognosis may be improved by immediate initiation of empirical TB treatment used in conjunction with antiretroviral therapy. In addition to morbidity and mortality reduction, additional benefits may include prevention of nosocomial TB transmission and TB preventive effect. Potential adverse consequences, however, may include failure to consider other non-TB diagnoses, drug co-toxicity, compromised treatment adherence, and logistical and resource challenges. There may also be general reluctance among national TB programmes to endorse such a strategy. Following fruitful debate, the conclusion that this strategy should be carefully evaluated in randomised controlled trials was strongly supported. This paper provides an in-depth consideration of this proposed intervention.

KEY WORDS: empirical treatment; tuberculosis; HIV; Africa; mortality

IF CURRENT TRENDS CONTINUE, the Millennium Development Goals (MDGs) and associated World Health Organization (WHO) Stop TB targets for tuberculosis (TB) control will not be achieved by 2015.^{1,2} One of the key obstacles to progress is the human immunodeficiency virus (HIV) associated TB (TB-HIV) epidemic, with more than 1.4 million new cases and almost half a million deaths in 2008.² In particular, it is unlikely that the Stop TB target of halving the 1990 TB mortality rates by 2015 will be achieved in high TB-HIV settings.² TB is a leading cause of HIV/AIDS (acquired immune-deficiency syndrome) related mortality worldwide, although these are routinely classified as ‘HIV deaths’ in the Inter-

national Statistical Classification of Diseases (ICD-10). An integrated package of both HIV and TB interventions is clearly needed to prevent these deaths.³

Ideally, the TB-HIV epidemic should be tackled through widespread scale-up of preventive measures to enhance the WHO DOTS strategy for TB control. Frequent widespread HIV testing with early HIV diagnosis would permit implementation of the ‘Three Is’ strategy (intensified case finding, isoniazid preventive treatment and infection control) used in combination with a package of HIV care that includes timely initiation of antiretroviral treatment (ART).^{4–6} These interventions would reduce TB-HIV incidence rates.

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

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

However, for the many patients who currently present with TB-HIV, optimal case management is needed to enhance their chances of survival. In the era prior to ART, patients with a known TB-HIV diagnosis had case-fatality rates of approximately 16–35% during the course of TB treatment compared to 4–9% among non-HIV-infected patients.⁷ Mortality is highest for those with the lowest CD4 cell counts,⁸ and may be due to TB or to another HIV-associated pathology.^{7,9} Use of cotrimoxazole prophylaxis^{10,11} and ART^{5,12,13} in combination with TB treatment substantially reduces mortality risk.

Many TB-HIV deaths, however, occur among HIV-infected patients who first present to clinical services with advanced immunodeficiency and in whom a diagnosis of TB is never established, i.e., the patient dies without receiving anti-tuberculosis treatment. In this paper, we speculate that such deaths may contribute to the high early mortality rates observed in ART programmes in resource-limited settings. We proceed to discuss the rationale for the potential use of empirical anti-tuberculosis treatment for a defined group of HIV-infected patients with advanced immunodeficiency and who have a high prevalence of undiagnosed TB and associated mortality. The arguments for and against such a strategy are explored.

Many of the data highlighted are from southern Africa, which bears a large proportion of the burden of TB-HIV and where such an intervention is therefore most likely to have a beneficial impact. However, this strategy may also be applicable in other high TB-HIV burden settings.

MAIN HYPOTHESIS

In settings worst affected by the TB-HIV epidemic, a sub-set of HIV-infected patients with advanced im-

munodeficiency have such a high risk of undiagnosed TB and of associated mortality that their prognosis may be improved by immediate initiation of empirical TB treatment used in conjunction with ART.

THE SCALE OF THE TB-HIV EPIDEMIC

Since 1990, the incidence of TB globally has risen dramatically, particularly in parts of the world where there is significant overlap between the HIV and TB epidemics. In 2008, an estimated 33 million people worldwide were living with HIV, of whom 1.4 million developed TB.² In the same year, TB was responsible for approximately one quarter of the 2 million HIV/AIDS-associated deaths worldwide.

Sub-Saharan Africa

The epicentre of the TB-HIV co-epidemic lies in sub-Saharan Africa, which accounted for 79% of the disease burden in 2007, with South-East Asia accounting for a further 11%.¹⁴ The countries towards the south of the African continent have the highest HIV prevalence and thus have been hit hardest by rising TB incidence rates (Figure 1). Collectively, the nine countries in Figure 1 accounted for approximately half of the global burden of TB-HIV in 2007.¹⁴ In the worst-affected countries of South Africa and Swaziland, approximately 1% of the population develops TB each year (Figure 1), and South Africa alone accounts for approximately 25% of the global burden of TB-HIV.¹⁴

The estimated mortality rate (deaths per unit of the general population) attributable to TB-HIV in the WHO African region was between 20- and 60-fold higher than the rate in the five other WHO regions in 2007 (Figure 2). Rates are highest in the countries to the south of the continent (Figure 3A), and South Africa alone accounts for more than half of the

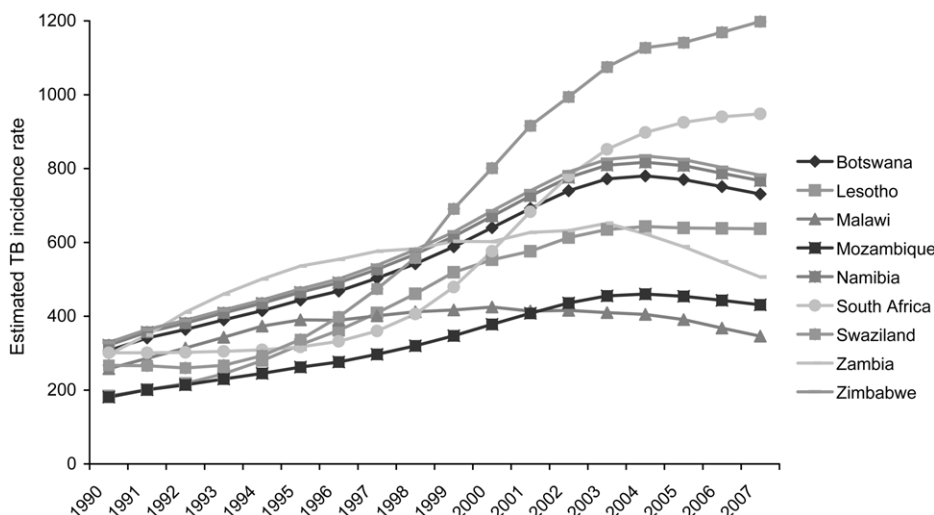


Figure 1 Changes in estimated TB incidence rates in nine high HIV prevalence countries in southern Africa, 1990–2007. Data from World Health Organization, 2009.¹⁴ In all but one of these countries, over two thirds of new TB cases are co-infected with HIV. TB = tuberculosis; HIV = human immunodeficiency virus.

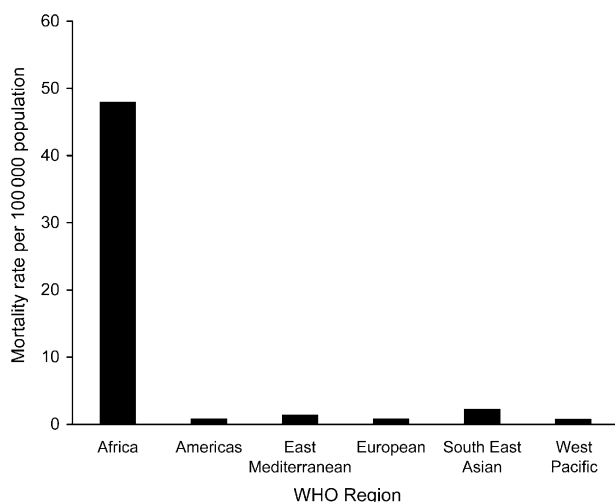


Figure 2 Estimated annual HIV-associated TB mortality rates per 100 000 population in the six WHO regions in 2007. Data from WHO, 2009.¹⁴ WHO = World Health Organization; HIV = human immunodeficiency virus; TB = tuberculosis.

TB-HIV deaths in the southern African region (Figure 3B). WHO declared this to be a regional emergency in 2005.¹⁵

Communities with the highest TB-HIV rates

Within individual countries, TB rates may vary substantially between communities. In impoverished black African townships in Cape Town, South Africa, antenatal HIV seroprevalence rates of approximately 30% have fuelled extraordinary increases in TB notification rates over the past 15 years. Rates in one such community have increased steadily from 580 cases per 100 000 population in 1996 to reach a rate of 2140/100 000 in 2005–2006.^{16,17} Thus, approximately 2% of this community developed TB each year despite a well functioning DOTS programme, as defined by treatment outcomes and case detection rates in non-HIV-infected individuals. A cross-sectional survey of the same community found a TB prevalence of approximately 9% in HIV-infected individuals, of which 5% were previously undiagnosed.¹⁸ At a population level, much HIV-associated TB may thus remain undiagnosed, and this may be a key factor contributing to the major increases in mortality rates among young adults in South Africa.¹⁹

Clinical populations with the highest TB-HIV risk

Not only is the burden of TB-HIV highly variable between countries and communities, it also differs substantially between clinical populations.²⁰ The highest rates occur among symptomatic patients attending voluntary counselling and testing services, those enrolling in ART services²⁰ and symptomatic HIV-infected patients requiring hospital admission. The burden of TB among patients accessing some ART programmes in the highest burden communities in South Africa is staggering, with as many as 67% of patients having a

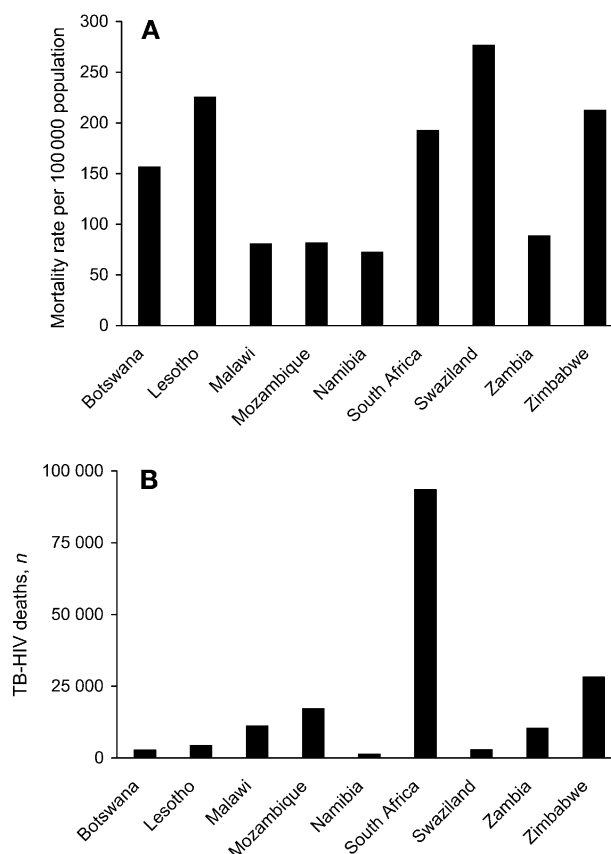


Figure 3 Estimates of **A**) annual HIV-associated TB mortality rates per 100 000 population and **B**) absolute numbers of HIV-associated TB deaths in nine high HIV prevalence countries in southern Africa in 2007. Data from World Health Organization, 2009.¹⁴ TB = tuberculosis; HIV = human immunodeficiency virus.

history of previous TB or a current diagnosis of TB prior to initiating ART.²¹

Very high rates of incident TB also persist during early ART.^{21–23} However, one study estimated that approximately 40% of incident TB diagnoses during the first 4 months of ART results from ART-mediated ‘unmasking’ of sub-clinical disease that was present at baseline, but which remained undetected.²⁴ This is consistent with subsequent data showing that systematic screening for TB pre-ART using high-sensitivity TB diagnostics detects a far greater burden of prevalent disease at baseline and was associated with a corresponding reduction in the TB incidence rate during early ART.²⁵

In two studies from South Africa, use of sputum induction and automated liquid culture detected culture-proven disease among 20–25% of patients pre-ART.^{26,27} An additional 5% of patients had disease (largely extra-pulmonary) diagnosed using other investigational modalities.^{25,26} This very high prevalence of active disease may be an important driver of high mortality rates around the time of treatment initiation in ART programmes, especially as much of this TB remains undiagnosed under routine programme conditions.

These observations are also consistent with post-mortem studies conducted in sub-Saharan Africa in the pre-ART era. Despite considerable regional variation in TB-HIV rates, studies conducted in West, East and Southern Africa have remarkably consistent findings, each showing TB to be the most common HIV-associated pathology among patients dying in hospital with HIV/AIDS.^{28–31} TB was present in over one third of cadavers, and in approximately half of those with AIDS-defining pathology. In the vast majority of cases, disease was disseminated.

High rates of Mycobacterium tuberculosis infection

Rates of infection with *M. tuberculosis* and of re-exposure are also extremely high in the sub-region. Studies from South Africa and Zambia have documented annual risks of tuberculous infection of up to approximately 4% per annum.^{17,32–35} In the worst-affected communities as many as 50% of 15-year-olds and 77–89% of adults have evidence of latent TB infection (LTBI). As a result, most young adults are likely to already have *M. tuberculosis* infection at the time of HIV acquisition, fuelling the high rates of TB in this age group.¹⁶ Such high annual risks of infection mean that patients are also continually re-exposed to TB in the long term, further fuelling TB incidence rates, especially in those with advanced immunodeficiency. Tuberculin skin testing in such patients, however, is likely to markedly underestimate the true burden of infection due to cutaneous anergy.

TB-HIV AND MORTALITY IN ART PROGRAMMES

Despite having similar immunological and virological responses to patients receiving ART in high-income settings, patients treated in resource-limited settings have a much higher risk of mortality during the initial months of ART, even after adjustment for baseline immunodeficiency.³⁶ In sub-Saharan Africa, between 8% and 26% of patients die during the first year of ART.³⁷ Most of these deaths occur in the initial months of treatment, and a substantial proportion also die in the weeks just prior to ART.^{38,39}

Post-mortem studies from these ART programmes are lacking and causes of death are often either unknown or speculative. TB-HIV is nevertheless frequently reported as a leading cause of death,³⁷ and as TB-HIV is so difficult to diagnose in this patient group, it may well be under-reported. In a study from South Africa, for example, six of eight patients who died just prior to starting ART were later found to have culture-positive TB identified from sputum samples obtained before death.²⁵

CHALLENGES OF TB-HIV DIAGNOSIS

The fact that much TB-HIV remains undiagnosed among HIV-infected patients dying in Africa reflects

the huge challenges of diagnosis. Both the identification of suspects through symptom screening and subsequent diagnosis using currently available diagnostic tools are problematic.

Symptom screening for TB-HIV suspects

Traditional TB control strategies have relied on passive case-finding, in which TB suspects were defined as patients reporting cough of ≥ 2 or 3 weeks' duration. However, this has a sensitivity of approximately 50% for TB-HIV.⁴⁰ Using a meta-analysis of 12 studies, representing almost 10 000 patients, a screening tool with a much higher sensitivity for TB-HIV has been developed by the Centers for Disease Control and Prevention and the WHO.⁴⁰ This algorithm defines patients as either symptom-free and likely to be eligible for isoniazid preventive treatment, or symptomatic and requiring diagnostic evaluation for TB. The latter group are patients with one or more of the following four symptoms: current cough (regardless of duration), fever, night sweats and weight loss. Despite having much higher sensitivity for TB-HIV (79%), the algorithm nevertheless misses one in five cases, and specificity is also low (56%).⁴⁰

Limitations in diagnostics for TB-HIV

In addition to the challenges of defining TB-HIV suspects, the tools for diagnosis are limited, especially in those with advanced immunodeficiency.⁴¹ There is a greater proportion of extra-pulmonary and disseminated disease. Pulmonary radiographic appearances are often atypical or absent; a study from South Africa that screened for TB in patients about to start ART found that one third of patients with sputum culture-positive TB had entirely normal chest radiographs.⁴²

Most disease is sputum smear-negative, with positive microscopy typically in only 20–50% of cases.^{41,43,44} In two separate South African studies of patients with advanced HIV being screened for TB before starting ART, fluorescence microscopy had a sensitivity of approximately 15% compared to automated liquid culture.^{26,27} Despite the high sensitivity of culture, the time to diagnosis is prolonged, as sputum specimens typically have very low bacillary numbers. Even using automated liquid culture, the mean time to positivity may exceed 3 weeks.²⁶ Moreover, a proportion of cultures is lost due to bacterial contamination, further frustrating diagnostic efforts.

Liquid culture is the most effective means for TB-HIV diagnosis at present, but, despite WHO policy initiatives for expansion,⁴⁵ availability within sub-Saharan Africa remains extremely limited. Thus, in the absence of culture and ongoing heavy reliance on smear microscopy as the primary diagnostic tool, TB diagnosis in those with advanced HIV remains extremely difficult in the vast majority of settings.

The time between TB-HIV patients entering clinical care, the diagnosis being suspected, investigations

being ordered and a diagnosis being finally made (if at all) is often very prolonged. This can be very costly for the patient in terms of time and indirect costs for recurrent clinic visits. Moreover, in those with advanced immunodeficiency, clinical deterioration and death may occur before a diagnosis can be made. Thus, with the diagnostic facilities currently available, a large proportion of diagnoses will continue to be missed and mortality rates will remain high.

RAPID AND SENSITIVE NEW DIAGNOSTICS: THE IDEAL SOLUTION

There are two main alternative approaches to the problem of high rates of undiagnosed prevalent TB-HIV. The ideal solution would be the development of a high-sensitivity point-of-care diagnostic assay, with good performance characteristics even among patients with advanced HIV and sputum smear-negative disease. While still some way off, progress is being made towards this goal. For example, an enzyme-linked immunosorbent assay that detects mycobacterial liparabinomannan in urine provides a diagnosis of TB with high specificity in approximately two thirds of TB-HIV patients with very low CD4 cell counts.^{26,46} Limited sensitivity of the assay at CD4 cell counts > 100 cells/ μ l and current lack of a validated point-of-care version of the assay limit its utility at present, however.

New rapid molecular diagnostics also show promise,⁴⁴ including the GeneXpert MTB assay (Cepheid, Sunnyvale, CA, USA), which has very high sensitivity and provides a TB diagnosis and assessment of rifampicin resistance within 2 h in those with smear-positive disease. However, although simple to use, the current assay is costly, multiple specimens may be required to achieve adequate sensitivity in those with smear-negative TB, it is not in a high throughput format and it requires high-technology hardware. It is at present unclear how widespread the availability of this technology will become in sub-Saharan Africa.

EMPIRICAL TB TREATMENT: A POTENTIAL PRAGMATIC SOLUTION?

Rationale

The current severe limitations in diagnostic capacity for TB-HIV require alternative solutions to be considered. One such approach would be to use empirical TB treatment. This could only be considered for carefully defined patient groups in whom the risk-benefit analysis was favourable. The rationale for such an approach is largely two-fold. First, patients with active prevalent TB would receive appropriate treatment without any diagnostic delay. Second, the subset of patients who did not actually have active TB may nevertheless derive benefit from a preventive effect, reducing incident TB as a result of treating *M. tubercu-*

losis infection and preventing exogenous re-infection during the course of treatment.

This strategy could be viewed as an extension of the existing WHO algorithm for the management of seriously ill patients with confirmed HIV infection living in HIV-prevalent settings.⁴⁷ This algorithm recommends empirical TB treatment for those with cough for 2–3 weeks and danger signs, but who have negative sputum smears and fail to respond to parenteral antibiotics for bacterial infection or other specific treatments, such as for *Pneumocystis jirovecii* pneumonia, within 3–5 days.⁴⁷ The potential advantages of routine empirical TB treatment are the elimination of the 2–3 week cough screen (which has very limited sensitivity for TB in this patient group), expediting the start of TB treatment by excluding the need for a prior trial of 3–5 days antibiotic treatment and including many other patients who may also benefit.

Target patient group

As CD4 cell counts progressively decline, TB risk increases, especially at counts < 100 cells/ μ l (Figure 4).^{48–50} Patients with very low CD4 cell counts enrolling in ART services or who have required hospital admission are those patients most likely to have prevalent TB and to benefit from empirical treatment. In a study of patients systematically screened for TB prior to ART initiation in South Africa, regardless of the presence or absence of symptoms, the prevalence of sputum culture-positive TB was 38% in those with CD4 cell counts < 100 cells/ μ l compared to 16% among those with counts > 100 cells/ μ l.²⁶ In these, the sensitivity of sputum smear microscopy was just 14%. If empirical TB treatment were given to all those with CD4 < 100 cells/ μ l in this cohort, approximately

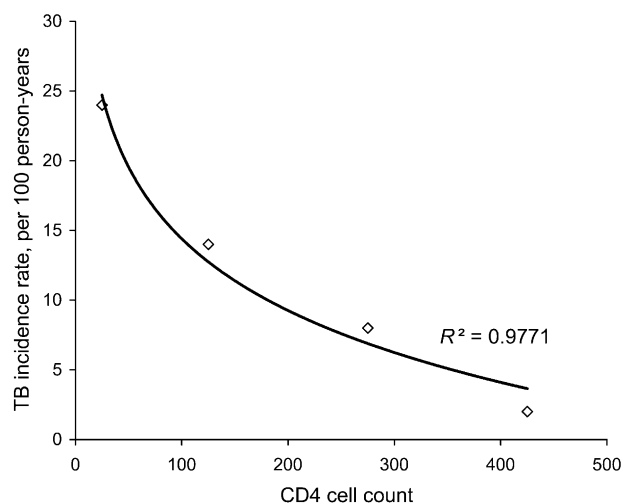


Figure 4 Graph showing the relationship between blood CD4 cell count and TB incidence rates (cases per 100 person-years) in a natural history cohort of patients in the pre-ART era living in Cape Town, South Africa. Data adapted from Holmes et al. 2006;⁴⁸ a best-fit logarithmic trend line has been added. TB = tuberculosis; ART = antiretroviral treatment.

one third of patients treated would actually have active TB that would not have been detected using standard screening with sputum smear microscopy. This would represent approximately one in six patients referred to the cohort without a pre-existing TB diagnosis. The proportion potentially deriving benefit may differ between settings, depending on the prevalence of TB.

In the same ART cohort, the cumulative mortality risk of patients from enrolment to completion of the first year of ART was 11.6% among those with baseline CD4 cell counts < 100 cells/ μ l compared to 5.2% among those with counts > 100 cells/ μ l.⁵¹ Thus, a CD4 cell count threshold of <100 cells/ μ l or <50 cells/ μ l, for example, would be useful to identify a patient group with a high risk of active prevalent TB and of mortality. Such patients might be expected to be most likely to benefit and would therefore be targeted first in randomised controlled trials of this intervention.

Both symptomatic and asymptomatic patients would be eligible. However, patients who have previously been treated for TB should be excluded from the initial evaluation of such a strategy, for two reasons. First, a study from South Africa reported that those patients who had completed treatment within the previous 3 years were found to have a much lower prevalence of active TB on enrolment with an ART service and would therefore be much less likely to benefit.²¹ Second, such patients are at higher risk of having drug-resistant TB, for which standard TB treatment would be inappropriate. In addition, patients with known active hepatic disease and at heightened risk of drug-induced hepatotoxicity would also be excluded.

Practical implementation

Such a strategy would employ standard first-line rifampicin-containing TB treatment, as those with a previous history of TB would be excluded. In keeping with current WHO guidelines, TB treatment should be started prior to ART, but ART should be initiated as soon as possible, ideally within the first 1–2 weeks of TB treatment. It would be important to minimise delays in ART initiation. Any patients without proven TB who were receiving empirical treatment should have their treatment discontinued if it is poorly tolerated and causing a delay in ART.

Baseline investigations for TB using front-loaded sputum microscopy should be performed, but there would be no need to await results before starting treatment. Confirmation of diagnoses in some patients by this means would assist in reporting, assessment of treatment response, triggering contact tracing among children in the household and decision making in the event of drug toxicity. In settings where mycobacterial sputum culture is available, a potential strategy would be to discontinue empirical TB treatment after the 2-month intensive phase among those with negative sputum cultures and with no other evidence of TB. Such patients would have received adequate TB

preventive effect by 2 months. Conversely, those developing signs and symptoms suggesting worsening TB during empirical treatment should be investigated for possible drug-resistant disease.

Implementation of this intervention would increase the workload and be a challenge to integrate into busy ART services. Integrated delivery of TB treatment and ART within the same health clinics would be essential, rather than patients having to attend separate clinics and pharmacy pick-ups. Detailed operational research would be required to develop optimal models of implementation.

Potential benefits of empirical TB treatment

The potential benefits of empirical treatment include the following:

- 1 Mortality reduction: this would be the primary goal of the intervention. This is supported from observational data from South Africa, suggesting that initiation of isoniazid preventive treatment at the same time as ART may be associated with a significant reduction in mortality.⁵²
- 2 Reduced morbidity: empirical TB treatment would diminish TB-associated morbidity and may thereby reduce hospital admissions. Due to earlier clearance of mycobacterial antigen load, empirical TB treatment may also reduce the risks and severity of both paradoxical and ‘unmasking’ forms of TB immune reconstitution disease occurring during the initial months of ART.^{53–55}
- 3 Reduced risk of nosocomial TB transmission: ART services in Africa are sites associated with high risk of nosocomial transmission^{56,57} due to the high susceptibility of this patient group to infection and to the very high prevalence of undiagnosed disease. While implementation of adequate infection control measures (administrative measures, environmental controls and respiratory protection) should be rapidly scaled up, empirical TB treatment could further reduce transmission risk by rapidly rendering patients with TB non-infectious.
- 4 TB prevention: empirical use of TB treatment would entail the treatment of a proportion of individuals who did not have active TB at baseline. However, many of these patients are likely to have *M. tuberculosis* infection and also remain at risk from ongoing exogenous re-exposure. Empirical TB treatment would treat LTBI and prevent exogenous re-infection, thereby leading to a reduction in TB incidence. Thus, the benefits of empirical treatment are unlikely to be confined only to those with active TB at baseline.
- 5 Prevention or treatment of bacterial sepsis: rifampicin has useful antimicrobial activity against a spectrum of organisms other than mycobacteria, but especially gram-positive bacteria.⁵⁸ This includes activity against many strains of *Streptococcus pneu-*

moniae, which is one of the common pathogens that causes breakthrough sepsis in HIV-infected patients receiving trimethoprim-sulphamethoxazole (cotrimoxazole) prophylaxis.⁵⁹ The magnitude of any such effect is unknown, however, and may vary according to the regional spectrum of opportunistic bacterial infections and drug resistance patterns.

- 6 Reducing the diagnostic dilemma: deciding whether or not patients with very low CD4 cell counts have active TB is often a diagnostic dilemma for health care workers in primary care. The decision-making process may require multiple consultations and investigations, ultimately leading to delays in ART initiation and associated mortality risk. Empirical treatment may actually simplify the decision-making process.
- 7 Integration of TB-HIV care: a further beneficial consequence of such a strategy is that it may promote the integration of TB and HIV care.

Potential adverse consequences of empirical TB treatment

- 1 Missing other diagnoses: there is a danger that health care workers might overlook other potential diagnoses such as bacterial and *Pneumocystis jirovecii* pneumonia that may mimic TB. Empirical treatment should not be used as a substitute for proper evaluation and investigation of patients at baseline and during follow-up visits.
- 2 Co-toxicity and pill-burden: concurrent use of ART and TB treatment is associated with co-toxicity, such as hepatotoxicity and neuropathy.^{60,61} Increasing use of efavirenz rather than nevirapine^{60,62} and the planned phasing out of d4T (stavudine) containing regimens⁶³ may reduce the risk of these toxicities. Increased pill burden and toxicities could also compromise adherence to ART, but may be minimised by using fixed-dose combinations.
- 3 Delays in ART initiation: as TB treatment would be started before ART, ART initiation may be delayed in some patients, especially those with poor medication tolerance. Any delays in ART may adversely affect outcomes.
- 4 Logistical and resource challenges: empirical TB treatment would ultimately lead to many more patients being treated for TB. This would contribute to increased clinical workload, record-keeping and reporting in already overstretched health facilities and increase costs and logistical demands on drug forecasting and supply. National TB Programmes would also need guidance on how to register and report on such cases.

CONCLUSIONS

The TB-HIV co-epidemic is taking an unprecedented toll on the countries of sub-Saharan Africa, and there

is little evidence that public health interventions to date have made much impact. While TB preventive interventions of ART and the WHO Three Is strategy are being scaled up, additional bold, innovative strategies should also be considered. We have proposed that a subset of patients with advanced immunodeficiency living in very high TB burden communities have risks of active TB and of death that are sufficiently high as to warrant use of empirical TB treatment to be used in tandem with ART.

We have considered the pros and cons for such a strategy. The cost-benefit ratio will depend strongly on whether treatment is associated with any mortality reduction. Empirical treatment is also anathema to National TB Programmes, and sound evidence is needed before implementation of such a strategy. We therefore conclude that a randomised trial to determine the efficacy of this strategy is warranted to determine whether such a strategy is associated with a reduction in mortality. Such a trial is being planned by the AIDS Clinical Treatment Group (ACTG5274 REMEMBER trial; Amita Gupta, personal communication), and should provide invaluable data to guide the way forward with this potentially important intervention.

Acknowledgements

All authors contributed to the symposium debate at the 40th Union World Conference on Lung Health in Cancun, Mexico, in December 2009 that gave rise to this manuscript. SDL is funded by the Wellcome Trust, London, UK.

References

- 1 United Nations. The Millennium Development Goals report 2008. New York, NY, USA: United Nations, 2008. <http://www.un.org/millenniumgoals/> Accessed February 2010.
- 2 World Health Organization. Global tuberculosis control. A short update to the 2009 report. Geneva, Switzerland: WHO, 2009. http://www.who.int/tb/publications/global_report/2009/update/tbu_9.pdf Accessed March 2010.
- 3 World Health Organization. Strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296 WHO/HIV/AIDS/2002.2. Geneva, Switzerland: WHO, 2002. http://www.who.int/tb/publications/who_cds_tb_2002_296/en/index.html Accessed February 2010.
- 4 World Health Organization. WHO Three Is meeting. Report of a joint WHO HIV/AIDS and TB Department meeting. Geneva, Switzerland: WHO, 2008. http://www.who.int/hiv/pub/meeting_reports/WHO_3Is_meeting_report.pdf Accessed February 2010.
- 5 Lawn S D, Kranzer K, Wood R. Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. *Clin Chest Med* 2009; 30: 685–699.
- 6 Harries A D, Zachariah R, Corbett E L, et al. Confronting the HIV-associated tuberculosis epidemic—when will we act? *Lancet* 2010; 375: 1906–1919.
- 7 Mukadi Y D, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001; 15: 143–152.
- 8 Ackah A N, Coulibaly D, Digbeu H, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet* 1995; 345: 607–610.

- 9 Greenberg A E, Lucas S, Tossou O, et al. Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Cote d'Ivoire. *AIDS* 1995; 9: 1251–1254.
- 10 Wiktor S Z, Sassin-Morokro M, Grant A D, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999; 353: 1469–1475.
- 11 Grimwade K, Sturm A W, Nunn A J, Mbatha D, Zungu D, Gilks C F. Effectiveness of cotrimoxazole prophylaxis on mortality in adults with tuberculosis in rural South Africa. *AIDS* 2005; 19: 163–168.
- 12 Dheda K, Lampe F C, Johnson M A, Lipman M C. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis* 2004; 190: 1670–1676.
- 13 Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr* 2006; 43: 42–46.
- 14 World Health Organization. Global tuberculosis control 2009. Epidemiology, strategy, financing. WHO/HTM/TB/2009.411. Geneva, Switzerland: World Health Organization, 2009. http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf Accessed January 2010.
- 15 World Health Organization. WHO declares TB an emergency in Africa. Call for 'urgent and extraordinary actions' to halt a worsening epidemic. Geneva, Switzerland: WHO, 2005. http://www.who.int/mediacentre/news/2005/africa_emergency/en/ Accessed September 2005.
- 16 Lawn S D, Bekker L G, Middelkoop K, Myer L, Wood R. Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions. *Clin Infect Dis* 2006; 42: 1040–1047.
- 17 Middelkoop K, Bekker L G, Myer L, Dawson R, Wood R. Rates of tuberculosis transmission to children and adolescents in a community with a high prevalence of HIV infection among adults. *Clin Infect Dis* 2008; 47: 349–355.
- 18 Wood R, Middelkoop K, Myer L, et al. Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. *Am J Respir Crit Care Med* 2007; 175: 87–93.
- 19 Bradshaw D, Laubscher R, Dorrington R, Bourne D E, Timaeus I M. Unabated rise in number of adult deaths in South Africa. *S Afr Med J* 2004; 94: 278–279.
- 20 Kranzer K, Houben R M, Glynn J R, Bekker L G, Wood R, Lawn S D. Yield of HIV-associated tuberculosis during intensified case finding in resource-limited settings: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; 10: 93–102.
- 21 Lawn S D, Myer L, Bekker L G, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *AIDS* 2006; 20: 1605–1612.
- 22 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.
- 23 Bonnet M M, Pinoges L L, Varaine F F, et al. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. *AIDS* 2006; 20: 1275–1279.
- 24 Lawn S D, Myer L, Edwards D, Bekker L G, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS* 2009; 23: 1717–1725.
- 25 Lawn S D, Kranzer K, Edwards D J, McNally M, Bekker L G, Wood R. Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pre-treatment screening strategy. *AIDS* 2010; 24: 1323–1328.
- 26 Lawn S D, Edwards D J, Kranzer K, Vogt M, Bekker L G, Wood R. Urine lipoarabinomannan assay for tuberculosis screening before antiretroviral therapy diagnostic yield and association with immune reconstitution disease. *AIDS* 2009; 23: 1875–1880.
- 27 Bassett I, Chetty S, Wang B, et al. Intensive TB screening for HIV-infected patients ready to start ART in Durban, South Africa: limitations of WHO guidelines. Program and Abstracts of the 16th Conference on Retroviruses and Opportunistic Infections. Montreal, Canada: CRIO, February 2009. [Abstract #779]
- 28 Lucas S B, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a West African city. *AIDS* 1993; 7: 1569–1579.
- 29 Lucas S B, De Cock K M, Hounnou A, et al. Contribution of tuberculosis to slim disease in Africa. *BMJ* 1994; 308: 1531–1533.
- 30 Rana F S, Hawken M P, Mwachari C, et al. Autopsy study of HIV-1-positive and HIV-1-negative adult medical patients in Nairobi, Kenya. *J Acquir Immune Defic Syndr* 2000; 24: 23–29.
- 31 Ansari N A, Kombe A H, Kenyon T A, et al. Pathology and causes of death in a group of 128 predominantly HIV-positive patients in Botswana, 1997–1998. *Int J Tuberc Lung Dis* 2002; 6: 55–63.
- 32 Kritzinger F E, Den B S, Verver S, et al. No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa. *Trop Med Int Health* 2009; 14: 136–142.
- 33 Chapman A L, Munkanta M, Wilkinson K A, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *AIDS* 2002; 16: 2285–2293.
- 34 Wood R, Liang H, Wu H, et al. Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. *Int J Tuberc Lung Dis* 2010; 14: 406–412.
- 35 Shanaube K, Sismanidis C, Ayles H, et al. Annual risk of tuberculosis infection using different methods in communities with a high prevalence of TB and HIV in Zambia and South Africa. *PLoS One* 2009; 4: e7749.
- 36 Braitstein P, Brinkhof M W, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006; 367: 817–824.
- 37 Lawn S D, Harries A D, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008; 22: 1897–1908.
- 38 Lawn S D, Myer L, Orrell C, Bekker L G, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* 2005; 19: 2141–2148.
- 39 Bassett I V, Wang B, Chetty S, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. *J Acquir Immune Defic Syndr* 2009; 51: 135–139.
- 40 Getahun H, Kittikraisak W, Heilig C M, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med* 2011; 8(1): e1000391.
- 41 Reid M J, Shah N S. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis* 2009; 9: 173–184.
- 42 Dawson R, Masuka P, Edwards D J, et al. Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV. *Int J Tuberc Lung Dis* 2010; 14: 52–58.
- 43 Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet* 2007; 369: 2042–2049.
- 44 Perkins M D, Cunningham J. Facing the crisis: improving the

- diagnosis of tuberculosis in the HIV era. *J Infect Dis* 2007; 196 (Suppl 1): S15–S27.
- 45 World Health Organization. The use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Geneva, Switzerland: WHO, 2007. http://www.who.int/tb/dots/laboratory/Use%20of%20Liquid%20TB%20Culture_Summary%20Report.pdf Accessed November 2010.
 - 46 Shah M, Variava E, Holmes C B, et al. Diagnostic accuracy of a urine lipoarabinomannan test for tuberculosis in hospitalized patients in a high HIV prevalence setting. *J Acquir Immune Defic Syndr* 2009; 50: 537–545.
 - 47 World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. WHO/HTM/2007.379 WHO/HIV/2007.1. Geneva, Switzerland: WHO, 2007. http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007_379_eng.pdf Accessed February 2010.
 - 48 Holmes C B, Wood R, Badri M, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; 42: 464–469.
 - 49 Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 359: 2059–2064.
 - 50 Williams B G, Dye C. Antiretroviral drugs for tuberculosis control in the era of HIV/AIDS. *Science* 2003; 301: 1535–1537.
 - 51 Lawn S D, Little F, Bekker L G, et al. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS* 2009; 23: 335–342.
 - 52 Innes C, Charalambous S, Felix M, et al. The effectiveness of isoniazid preventive therapy in reducing mortality in patients on antiretroviral therapy. Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, USA. February 2010. [Abstract no. 102]
 - 53 Lawn S D, Bekker L G, Miller R F. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005; 5: 361–373.
 - 54 Lawn S D, Myer L, Bekker L G, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007; 21: 335–341.
 - 55 Lawn S D, Wilkinson R J, Lipman M C, Wood R. Immune reconstitution and ‘unmasking’ of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med* 2008; 177: 680–685.
 - 56 Bock N N, Jensen P A, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. *J Infect Dis* 2007; 196 (Suppl 1): S108–S113.
 - 57 Gandhi N R, Moll A, Sturm A W, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; 368: 1575–1580.
 - 58 Kucers A, Crowe S M, Grayson M L, Hoy J F. The use of antibiotics: a clinical review of antibacterial, antifungal and antiviral drugs, 5th ed. Oxford, UK: Butterworth-Heinemann, 1997.
 - 59 Anglaret X, Messou E, Ouassa T, et al. Pattern of bacterial diseases in a cohort of HIV-1 infected adults receiving cotrimoxazole prophylaxis in Abidjan, Cote d’Ivoire. *AIDS* 2003; 17: 575–584.
 - 60 Boule A, Van C G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; 300: 530–539.
 - 61 Westreich D J, Sanne I, Maskew M, et al. Tuberculosis treatment and risk of stavudine substitution in first-line antiretroviral therapy. *Clin Infect Dis* 2009; 48: 1617–1623.
 - 62 Hoffmann C J, Charalambous S, Thio C L, et al. Hepatotoxicity in an African antiretroviral therapy cohort: the effect of tuberculosis and hepatitis B. *AIDS* 2007; 21: 1301–1308.
 - 63 World Health Organization. Rapid advice. Antiretroviral therapy for HIV infection in adults and adolescents. Geneva, Switzerland: WHO, 2009. http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf Accessed January 2010.

R É S U M É

La lutte contre les épidémies du virus de l'immuno-déficience humaine (VIH) et de la tuberculose (TB) associée au VIH (VIH-TB) continue à faire défaut dans beaucoup de régions à ressources limitées, mais particulièrement en Afrique sub-saharienne. L'étendue de ces épidémies exige la prise en considération d'interventions courageuses et novatrices ainsi que des réflexions originales. Dans ce but, un symposium intitulé « Controverses au sujet du VIH » a été organisé lors de la 40^{ème} Conférence Mondiale de l'Union sur la Santé Pulmonaire à Cancun, Mexique en décembre 2009. Le premier sujet débattu, intitulé « Test annuel pour le VIH et mise en route immédiate d'un traitement antirétroviral pour toutes les personnes infectées par le VIH », a retenu fortement l'attention dans les conférences internationales et dans la littérature en 2009. Le deuxième sujet débattu fait l'objet de cet article. Le rationnel pour l'utilisation d'un traitement antituberculeux empirique trouve ses prémices dans l'hypothèse que dans les contextes les plus atteints par l'épidémie VIH-TB un sous-groupe de patients infectés par le VIH comporte un risque

tellement élevé de TB non diagnostiquée et de mortalité en relation avec celle-ci, que leur pronostic peut être amélioré par la mise en route immédiate d'un traitement antituberculeux empirique utilisé en même temps que le traitement antirétroviral. A côté d'une réduction de la morbidité et de la mortalité, les avantages complémentaires de cette attitude comportent la prévention d'une transmission nosocomiale de la TB et un effet préventif sur la TB. Toutefois, les conséquences indésirables potentielles peuvent comporter la non-prise en considération de diagnostics autres que la TB, la cytotoxicité des médicaments, une adhésion médiocre au traitement, des défis de logistique et de ressources, et enfin, une réticence générale des Programmes Nationaux contre la TB à appuyer cette stratégie. A la suite d'un débat fructueux, on a conclu que cette stratégie devait faire l'objet d'une évaluation soigneuse dans des essais contrôlés randomisés ; cette option a été largement soutenue. Cet article expose la prise en considération approfondie de l'intervention proposée.

R E S U M E N

Las epidemias de infección por el virus de la inmunodeficiencia humana (VIH) y de tuberculosis (TB) asociada con el VIH continúan sin control en muchas regiones con recursos limitados, pero especialmente en África subsahariana. La amplitud de estas epidemias exige contemplar la posibilidad de intervenciones innovadoras y audaces e ideas creativas. Con este fin se celebró un simposio titulado 'Controversias sobre el VIH' en la 40^a Conferencia mundial sobre salud respiratoria de La Unión que tuvo lugar en Cancún, México, en diciembre del 2009. El título del primer debate, 'Pruebas anuales de detección del VIH y comienzo inmediato del tratamiento antirretrovírico a todas las personas infectadas por el virus', atrajo mucha atención en las conferencias internacionales y en las publicaciones científicas en el 2009. El segundo debate constituye el tema del presente artículo. El uso empírico del tratamiento antituberculoso se fundamenta en esta hipótesis: en medios con una epidemia grave de infección por el VIH y TB, un subgrupo de personas infectadas por el virus presenta un

riesgo tan alto de padecer TB no diagnosticada y de fallecer por la enfermedad, que el comienzo inmediato del tratamiento antituberculoso empírico asociado con el tratamiento antirretrovírico puede mejorar su pronóstico. Además de disminuir la morbilidad y la mortalidad, otras ventajas de esta estrategia serían la prevención de la transmisión intrahospitalaria de la TB y un efecto de prevención de la TB. Sin embargo, entre las consecuencias adversas se podrían contar: propiciar la falta de consideración de otros diagnósticos, la toxicidad concomitante de los medicamentos, una degradación de la adhesión al tratamiento, las dificultades logísticas y de recursos y tal vez la renuencia de los programas nacionales de control de la tuberculosis a aprobar este tipo de intervención. Después de un debate muy fructífero se llegó a la conclusión de respaldar firmemente la evaluación de esta estrategia en estudios comparativos aleatorizados. En el presente artículo se expone un análisis de fondo de la intervención propuesta.