INT J TUBERC LUNG DIS 15(11):1436–1444

http://dx.doi.org/10.5588/ijtld.11.0503
Published online 6 September 2011

The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis

A. D. Harries,*† Y. Lin,‡ S. Satyanarayana,§ K. Lönnroth,¶ L. Li,# N. Wilson,§ L. S. Chauhan, R. Zachariah,†† M. A. Baker,‡‡,§§ C. Y. Jeon,¶¶ M. B. Murray,‡‡,## D. Maher,† I. C. Bygbjerg,*** D. A. Enarson,* N. E. Billo,* A. Kapur†††**

***International Union Against Tuberculosis and Lung Disease, Paris, France; †London School of Hygiene & Tropical Medicine, London, UK; ‡China Office, International Union Against Tuberculosis and Lung Disease, Beijing, China; §South-East Asia Office, International Union Against Tuberculosis and Lung Disease, Delhi, India; ¶Stop TB Department, World Health Organization, Geneva, Switzerland; #Clinical Center on Tuberculosis, Chinese Centers for Disease Control and Prevention, Beijing, China; **National Centre for Disease Control, Ministry of Health and Family Welfare, Government of India, Delhi, India; ††Medical Department, Médecins Sans Frontières, Operational Research Unit, Brussels Operational Center, Luxembourg; ‡‡Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, §§Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts, ¶¶School of Nursing, Columbia University, New York, New York, ##Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, USA; ***Department of International Health, Immunology and Microbiology, University of Copenhagen, Copenhagen, †††World Diabetes Foundation, Gentofte, Denmark**

SUMMARY

The prevalence of diabetes mellitus is increasing at a dramatic rate, and countries in Asia, particularly India and China, will bear the brunt of this epidemic. Persons with diabetes have a significantly increased risk of active tuberculosis (TB), which is two to three times higher than in persons without diabetes. In this article, we argue that the epidemiological interactions and the effects on clinical presentation and treatment resulting from the interaction between diabetes and TB are similar to those observed for human immunodeficiency virus (HIV) and TB. The lessons learned from approaches to reduce the dual burden of HIV and TB, and especially the modes of screening for the two diseases, can be adapted and applied to the screening, diagnosis, treatment and prevention of diabetes and TB. The new World Health Organization (WHO) and The Union Collaborative Framework for care and control of TB and diabetes has many similarities to the WHO Policy on Collaborative Activities to reduce the dual burden of TB and HIV, and aims to guide policy makers and implementers on how to move forward and combat this looming dual epidemic. The response to the growing HIV-associated TB epidemic in the 1980s and 1990s was slow and uncoordinated, despite clearly articulated warnings about the scale of the forthcoming problem. We must not make the same mistake with diabetes and TB. The Framework provides a template for action, and it is now up to donors, policy makers and implementers to apply the recommendations in the field and to 'learn by doing'.

KEY WORDS: diabetes mellitus; tuberculosis; screening; HIV; treatment outcomes; framework

Nothing will ever be attempted if all possible objections must first be overcome.
—Samuel Johnson

WHEN the acquired immune-deficiency syndrome (AIDS) was first reported in 1981, there was little realisation at the time of the impending scale of the forthcoming epidemic or that the epicentre would be in sub-Saharan Africa. Thirty years on, the statistics make grim reading: 60 million infections, more than 25 million deaths and more than 33 million persons currently living with human immunodeficiency virus (HIV) infection or AIDS.[1] Sub-Saharan Africa has borne the brunt of this epidemic: the latest estimates are that 22.5 million persons are living with HIV/AIDS, of whom an estimated 50% live in southern Africa.[2] In 2009, about one third of all persons living with HIV (PLWH), one third of all new infections and one third of all AIDS-related deaths occurred in just 10 countries in southern Africa.[2]

Chronic, non-communicable diseases such as cardiovascular disease, diabetes mellitus (DM), cancer and chronic obstructive pulmonary disease have insidiously emerged as the next twenty-first century global epidemic. These diseases have become the leading causes of death and disability worldwide, and are predicted to be the cause of over three quarters of global deaths by 2030.[3] In parts of rural Africa, there is already an epidemiological transition, with chronic

Correspondence to: A D Harries, Old Inn Cottage, Vears Lane, Colden Common, Winchester SO21 1TQ, UK. Tel: (+44) 1962 714 297. e-mail: adharries@theunion.org
Article submitted 22 July 2011. Final version accepted 15 August 2011.

care illness as a result of communicable (HIV/AIDS) and non-communicable diseases contributing more to mortality than acute care illness.[4] The fact that chronic diseases are becoming increasingly important in the setting of economic development and a threat to health in low- and middle-income countries has been recognised by the United Nations General Assembly, and a high-level meeting with the participation of heads of state is to be hosted on the topic in September 2011.[5]

Tuberculosis (TB) emerged early in the HIV epidemic as one of the most important and serious opportunistic infections to be associated with HIV, and has become the leading cause of death in HIV-infected persons.[6] Nowhere is this more starkly apparent than in sub-Saharan Africa, where HIV has been responsible for an unprecedented increase in TB case notifications and for derailing TB control efforts.[7] In this article, we argue that there is an important interaction between DM and TB, the effects of which may be similar to those observed between HIV and TB. Although at the individual level the risk of developing TB is considerably lower in persons with DM than in HIV patients, the much larger, and rapidly growing, pool of DM patients makes the global and population attributable fraction of TB due to DM very similar to that seen with HIV.[8]

We believe that DM-associated TB is the next looming challenge for global TB control, with the battleground being focused in Asia, and particularly India and China. We compare and contrast the interactions, interventions and framework for collaborative activities between HIV and TB and DM and TB, and believe that if we are forewarned and prepared we stand a better chance of reducing the dual burden of disease of DM and TB than was the case with HIV and TB.

THE DIABETES EPIDEMIC

According to a global analysis involving 199 countries and 2.7 million persons, the number of adults with DM increased alarmingly from 153 million in 1980 to 347 million in 2008.[9] Numbers are predicted to rise to 472 million by 2030, with almost 80% of DM patients living in low- and middle-income countries.[10] Although much of this increase in DM is attributed to population growth and aging, it also reflects a global shift towards a western lifestyle of unhealthy eating and physical inactivity.

Although this is a global epidemic, Asia is the epicentre of the escalating burden of disease.[9,11] Estimates based on population growth, aging and urbanisation indicate that India and China are, and will be, the two countries with the highest numbers of DM patients: the 199-country analysis estimated that 40% of DM patients (138 million in 2008) live in China and India. Among the next top eight countries, four more are in Asia: Indonesia, Pakistan, Bangladesh and the Philippines.[11] As with HIV/AIDS in the early years, the scale of the epidemic is probably underestimated. A national representative survey in China involving over 46 000 adults between 2007 and 2008 showed, when extrapolated to the total population, that an estimated 92 million adults had DM, in contrast to a previous estimation of approximately 42 million.[12] Of note, and similar to the global situation with HIV, is the observation that in over 60% of adults with DM in China, the disease was undiagnosed at the time of the survey.[12]

Morbidity and mortality accompany this rise in case burden. A hospital-based study in China, for example, showed that more than half of persons with known DM experience chronic complications and exhibit poor glucose control.[13] In 2010, there were an estimated 3.5 million deaths due to DM worldwide.[14]

EPIDEMIOLOGICAL INTERACTIONS BETWEEN HIV, DM AND TB

From the mid-1980s, TB programmes in countries with high HIV prevalence rates, particularly in sub-Saharan Africa, saw rising TB case notifications, and over a period of 10–15 years these increased up to 500% in some countries. A number of recent literature reviews, which have included systematic reviews and meta-analyses of previous studies, have shown that DM patients have a significantly increased risk of developing active TB, which is two to three times higher than in persons without DM.[15–18] Previous studies have tended to be secondary analyses of usually health facility-based data, and are subject to confounding and other limitations. Nevertheless, there has been a consistency in the findings, and prospective studies are currently underway. On the Texas-Mexico border, for example, it was shown prospectively that DM contributed 25% of TB cases, whereas HIV infection contributed ⩽5%.[19] To date, little information has been published on whether DM has any effect on TB case notifications or estimated case numbers at country level. However, an ecological association between changes in DM and TB prevalence has been observed across 46 countries.[20] Furthermore, an analysis of nutrition and DM changes in India suggests that increased DM prevalence between 1998 and 2008 contributed to an increase in the total number of TB cases, which exceeded the rate of population growth in the same time period.[21] It will be important to further focus on and monitor this association, especially in countries in Asia with escalating DM epidemics.

MECHANISMS OF ASSOCIATION BETWEEN HIV, DM AND TB

HIV causes disease by destroying cells of the immune system, with the gradual decrease and dysfunction of

naive and memory CD4+ T-lymphocyte populations (which control the body's defences against infection) being the hallmark of infection.[22] The association between HIV and TB stems from two distinct processes: HIV increases the risk of reactivation in those who already have latent TB infection by up to 100 times; in those who acquire new TB infection, HIV increases the risk of progression to active disease.[7] While the risk of active TB in an individual is related to the prevailing socio-economic conditions and pressure of exogenous TB infection in the community, the critical determinant is the degree of immunodeficiency, as measured by the CD4-lymphocyte count, with the lower counts and the amount of time accrued at low counts being significantly associated with increasing risk of TB.[23]

DM increases the general risk of infection, but the precise mechanisms by which DM predisposes to TB are still not clear. DM does not reduce CD4+ T-lymphocyte populations, but rather impairs the function and activation of macrophages, monocytes and lymphocytes which play a pivotal role in combating the TB pathogen.[15,17,24,25] The relative contribution of other factors such as pulmonary microangiopathy, renal dysfunction and vitamin deficiencies remains to be established.[15] DM patients with poorer glycaemic control appear to be at higher risk for TB,[26,27] demonstrating a dose-response relationship between the degree and duration of hyperglycaemia and vulnerability to TB, rather similar to that observed with HIV and TB.

EFFECT ON CLINICAL MANIFESTATIONS OF TB BY HIV AND DM

In PLWH, the clinical pattern of TB correlates with the host immune status. As the immune system becomes more compromised, granuloma formation decreases and the pattern of TB shifts from typical sputum smear-positive, cavitary, upper-lobe pulmonary disease to atypical smear-negative, infiltrative, lower-lobe pulmonary disease or extra-pulmonary disseminated disease. As CD4-counts decline to levels below 100 cells/μl, the proportions of PLWH with culture-confirmed pulmonary TB who have negative sputum smears, who are without radiographic cavities and who have normal chest radiographs, increase.[28]

A similar, although not always consistent, picture may be found in DM patients.[17] Nearly 90 years ago, it was reported that a large proportion of DM patients had lower lung involvement, in contrast to non-DM patients, who usually had upper lobe infiltrates.[29] While the predominance of lower-lobe infiltrates in DM patients has been confirmed in more recent studies,[30,31] these findings are not consistent,[17,32] and higher quality, prospective research in this area is needed. As is the case with HIV, it is likely that clinical and radiographic manifestations of TB are a feature of host immune status, and poorly controlled DM patients with hyperglycaemia may have a higher frequency of atypical features of TB.

ANTI-TUBERCULOSIS TREATMENT AND EFFECT ON TREATMENT OUTCOMES BY HIV AND DM

International guidelines disseminated by the World Health Organization (WHO) recommend that treatment for TB be standardised with 6-month rifampicin (RMP) based regimens.[33] TB patients who are HIV-infected should receive anti-tuberculosis treatment of the same duration as HIV-negative TB patients.[33] However, in industrialised countries, the optimal duration of treatment for HIV-infected TB patients is still controversial. For example, in the United States it is recommended that 6-month regimens be given, but this should be extended by 3 months if the patient presents with cavitary lung disease or is still sputum culture positive for *Mycobacterium tuberculosis* 2 months after the start of treatment.[34] In DM patients, the same recommendations for a standardised 6-month anti-tuberculosis regimen apply, although clinicians in industrialised countries may take a more individualised approach and consider the possibility of longer treatment as a result of the associated immune dysfunction.[35] Whether longer treatment in TB patients with DM has a beneficial effect on treatment outcomes and in reducing the risk of recurrent disease is not known and needs prospective research.[36]

PLWH respond as well to anti-tuberculosis treatment as non-HIV-infected patients, with similar rates of sputum conversion and radiographic improvement. However, there are two major problems: in the absence of cotrimoxazole adjunctive therapy or antiretroviral therapy (ART), TB case-fatality rates are high, and are related, in sub-Saharan Africa at least, to the degree of HIV-related immune suppression.[37] If a patient completes treatment satisfactorily, the rates of recurrent TB are much higher in HIV-infected than in HIV-negative patients.[38,39] Low initial CD4 counts are a risk factor for recurrence,[39] with most second episodes of TB being a result of re-infection with a new strain of *M. tuberculosis*.[40] Standard anti-tuberculosis treatment on its own is not enough to reduce TB case fatality or recurrence.[41] Interventions for both of these adverse events require timely initiation of cotrimoxazole preventive therapy, ART and consideration of secondary isoniazid (INH) prophylaxis.[42]

DM appears to have a similar effect on treatment outcomes (Table 1). A systematic review of studies, papers and reports from 1980 to December 2010 assessed the results of sputum culture conversion at 2–3 months of anti-tuberculosis treatment, death during treatment and relapse of TB after successful completion of treatment.[43] Nine studies analysed culture positivity at 2–3 months of treatment, with six reporting

Table 1 Main adverse outcomes in HIV-infected patients and patients with diabetes who are being treated for TB

Adverse outcomes	Patients with HIV	Patents with diabetes
Case fatality during anti-tuberculosis treatment	Increased	Increased
Recurrence of TB after successful completion of anti-tuberculosis treatment	Increased	Increased

HIV = human immunodeficiency virus; TB = tuberculosis.

relative risks of >2, and three reporting relative risks of <1.[43] However, all but one of the studies reported a delay in sputum culture conversion at some point during the course of anti-tuberculosis treatment. A total of 23 studies assessed risk of death during TB treatment, with a pooled and significantly higher relative risk of 1.89 in DM patients.[43] Four of these studies adjusted for age and other potential confounders, finding a pooled odds ratio of 4.95; this suggests that patients who die during anti-tuberculosis treatment have other strong risk factors for death, such as HIV and comorbidities, which reduce the impact of DM in unadjusted analyses. Five studies assessed the risk of TB relapse, with a pooled and increased significant relative risk of 3.89 in DM patients.[43] Whether these patients experienced a recurrence of the former infection (true relapse) or re-infection with a new strain of *M. tuberculosis* is not known.

There are many unanswered questions, including the influence of poor DM control on death and recurrent TB, the timing and aetiology of death in DM patients, the reasons for recurrent disease, and interventions that may reduce the frequency of these adverse events. These questions are best answered through prospective rather than retrospective studies. DM impairs innate and adaptive immune responses, and poor DM control, as measured by glycosylated haemoglobin (HbA_{1c}) levels, affects in vitro innate and cell-mediated immune cytokine responses.[44] TB disease per se and the drugs used to treat TB, such as RMP, can all worsen DM control, particularly the use of RMP as a result of direct and indirect interactions with oral hypoglycaemic drugs.[45] Uncontrolled DM can eventually lead to impaired renal function and an increased risk of drug toxicities. Hepatic toxicity due to anti-tuberculosis drugs may also be increased in DM patients, potentially increasing the risk of adverse treatment outcomes.[46]

SCREENING TB PATIENTS FOR HIV AND DM AND REFERRAL TO CARE

The crucial first step for ensuring access to HIV prevention and care in TB patients in high TB-HIV burden countries is to ensure that they are counselled and tested for HIV. The WHO recommends that provider-initiated HIV testing and counselling (PITC) be offered as a routine service,[47] and this has been shown to be both feasible and acceptable in various settings.[48,49] Rates of HIV testing have increased dramatically in the last 5 years, probably as a consequence of the advent of ART. In 2009, over 50% of TB patients in sub-Saharan Africa were tested for HIV.[49] HIV testing establishes the diagnosis of HIV and serves as the gateway to HIV-related prevention and care interventions.

While it is acknowledged that TB patients would merit being screened for DM,[50] especially in high DM burden areas, how this is best done and carried out in routine settings is not known. Possible screening tests might include measurement of urine glucose, random blood glucose, fasting blood glucose, oral glucose tolerance testing and HbA_{1c}. HbA_{1c} has recently been endorsed by the WHO as a diagnostic test for DM,[51] although its sole use as a diagnostic test is still controversial.[52] Despite its obvious attraction, urine testing for glucose is sub-optimal for early case finding of DM at the primary health care level.[53]

In high-burden countries, action is already being taken. In Kerala State, India, the Revised National TB Control Programme has already initiated screening of TB patients for DM and is assessing its effect on TB treatment outcomes under routine programme conditions (L S Chauhan, personal communication). A recent stakeholders' meeting in China agreed that a feasible and potentially affordable working strategy would be to screen TB patients at registration and start of anti-tuberculosis treatment by random blood glucose (RBG) tests; if RBG was >6.1 mmol/l, patients could be asked to return at the next visit for a fasting blood glucose (FBG) test; an FBG > 7.0 mmol/l would indicate a diagnosis of DM[54] and the need for referral to DM care for confirmation of diagnosis and optimal blood glucose management, particularly as blood glucose levels may be elevated in the setting of acute TB infection[50] (A D Harries and L Yan, personal communication).

PREVENTING AND REDUCING THE BURDEN OF TB IN PLWH AND DM

In PLWH, early initiation of ART through immune reconstitution reduces the risk of TB,[55] and this has led the WHO to recommend that ART should be initiated at CD4 count thresholds of 350 cells/μl rather than 200 cells/μl.[56] Mathematical modelling using the case reproduction number, long-term dynamics of the HIV epidemic, data from South Africa and the known effects of HIV on TB incidence, suggests that a strategy of HIV testing and immediate start of ART could, in a short period of time, significantly reduce the incidence of HIV-associated TB;[23] this approach needs to be evaluated and tested. Further reduction in the risk of TB could be achieved through implementation of the 'Three I's': intensified case finding,

Quarter and year	TB registration no.	Name	TB type and category*	Date of TB registration	Known DM (Y/N)	Family history DM (Y/N)	Date of RBG screening	RBG results	Date of FBG screening	FBG results	Diagnosis DM (Y/N)	Date of referral to DM care	Date of confirmation with DM and entry into DM care

*Smear-positive PTB (SPPTB), smear-negative PTB (SNPTB), extra-pulmonary TB (EPTB), new (N) or re-treatment (R).

Figure 1 DM screening register for TB patients. Ten rows per page (therefore 10 patients per page). If RBG > 6.1 mmol/l (110 mg/dl), do second screen with FBG at next visit. If FBG > 7.0 mmol/l (126 mg/dl), diagnosis = DM and refer to diabetes care. TB = tuberculosis; DM = diabetes mellitus; Y = yes; N = no; RBG = random blood glucose; FBG = fasting blood glucose.

infection control and INH preventive therapy (IPT).[42] Symptom screening for TB using cough of any duration, weight loss, night sweats and fever now has a sound evidence base for policy recommendations.[57,58] There are good guidelines on what to do and how to implement TB infection control in health care facilities.[59] The efficacy of IPT in reducing the risk of active TB in PLWH with latent TB infection has been well established through clinical trials.[60] Evidence has recently shown that 36 months of IPT is more effective than 6 months at reducing the risk of TB among PLWH.[61] What remains now is implementation of policy recommendations in HIV care clinics in high HIV and TB burden countries.

In a similar vein, good DM control should reduce the risk of TB, as evidenced by a higher risk of TB in people with poorly controlled DM compared to those with well controlled DM.[26,27] Although no data are available from recent intervention studies to support the use of IPT, two observational studies conducted in Germany in the 1950s and Russia in the 1960s showed that chemoprophylaxis with either INH or an INH analogue respectively reduced the primary and secondary risk of TB in DM patients.[62,63] However, the absence of randomisation and the lack of details of the interventions in these two studies limit the evidence base to support IPT in DM patients.

While it is acknowledged that DM patients living in high TB burden countries might merit active screening for TB,[50] experience in routine health settings about how to do this is limited. TB screening should be performed at each visit using a simple symptom screen similar to what has been adopted for intensified case finding in PLWH.[58] Screening by chest X-ray could also be considered at the time of DM diagnosis, and possibly at regular intervals thereafter. If screening identifies a significant number of previously undiagnosed TB cases, the issue of infection control should not be forgotten, and guidelines to prevent nosocomial TB transmission within HIV care facilities should be considered for DM clinics. The concept of the Three I's for PLWH should be considered, adapted and evaluated in DM patients as a way of reducing the dual disease burden.

MONITORING, RECORDING AND REPORTING

Effective collaboration between TB and HIV programmes demands that each reliably monitor and report on one another's parameters. This has been an iterative process, guided by intuition and experience, resulting in a revised international guide that spells out the data required for denominators, numerators and indicators to monitor progress in HIV care in TB patients and TB preventive efforts in PLWH.[64] Treatment cards, registers and cohort reporting forms have required modification and revision to accommodate such collaboration on the ground.

At present little is known on how to conduct such monitoring in DM and TB, and operational research will be needed to test out different modalities. The recent stakeholders' meeting in China agreed on some ways forward (A D Harries and L Yan, personal communication). A register similar to that shown in Figure 1 might be a useful tool to be used alongside the Patient TB Register to monitor DM screening in TB patients, with a template for the cohort reporting shown in Table 2. A treatment card similar to that shown in Figure 2 might be a useful tool to monitor TB screening in DM patients when they attend the DM clinic, with a template for the cohort reporting shown in Table 3. These suggested tools need to be piloted and evaluated in field conditions in various settings.

FRAMEWORK FOR COLLABORATION

One of the important milestones in the fight against HIV and TB was the publication and dissemination in 2004 of the WHO Interim Policy of Collaborative

Table 2 Quarterly report of diabetes screening in TB patients*

Number of TB patients registered
Number already known with DM
Number screened with RBG
Number with RBG > 6.1 mmol/l (110 mg/dl)
Number screened with FBG
Number with FBG < 6.1 mmol/l (110 mg/dl)
Number with FBG 6.1–7.0 mmol/l (110–126 mg/dl)
Number with FBG > 7.0 mmol/l (126 mg/dl)
Number newly diagnosed with DM (FBG > 7.0 or 126 mg/dl)
Number with known DM + number with new DM
Number referred to diabetes care
Number confirmed with DM in diabetes clinic and entered to DM care

*Quarterly report completed 1 month after end of the quarter.
TB = tuberculosis; DM = diabetes mellitus; RBG = random blood glucose; FBG = fasting blood glucose.

Table 3 Quarterly report of TB screening in diabetes patients*

Number of DM patients ever registered up to end of the quarter
Number of DM patients seen in the clinic in the quarter
Number of DM patients screened for TB symptoms in quarter (screened at least once)
Number of DM patients with a positive TB symptom screen
Number of DM patients referred for TB investigations
Status of DM patients referred for TB investigations
Number referred for TB investigations in quarter
Number diagnosed with TB
Number registered with TB
Type of TB
Smear-positive PTB
Smear-negative PTB
EPTB
Category of TB
New or recurrent
Number started on anti-tuberculosis treatment

*Quarterly report completed 1 month after end of the quarter.
TB = tuberculosis; DM = diabetes mellitus; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis.

HIV and TB Activities to reduce the joint burden of the two diseases (Table 4).[65] As the evidence base for policy recommendations was weak at that time, the guidance was promoted as interim in nature. New evidence and experience has since become available, and as a result the policy has been updated and should be published in 2011.

An important step in the fight against DM and TB has been the development of a WHO-Union Framework for Collaborative activities to guide policy makers and implementers in reducing the dual burden of DM and TB (Table 5).[66] This was developed through an iterative process,[67] with the WHO giving clearance to develop a Framework rather than Guidelines due to lack of strong evidence to support some of the suggested interventions. The Framework was printed in August 2011,[66] and will serve as a guide to help policy makers and implementers move forward to combat the looming epidemic. It will be important to ensure that interventions are delivered within the context of general health systems, that they take into account other chronic non-communicable diseases, and that engagement is sought both with and from civil society.

CONCLUSION

The global and national response to the HIV-associated TB epidemic was slow and uncoordinated. The first reports of the association between HIV/AIDS and TB were published in the late 1980s,[68,69] and warnings were clearly articulated in the early 1990s about the impending scale of the forthcoming dual

Diabetes registration no._____

DIABETES TREATMENT CARD AND TUBERCULOSIS SCREENING: YEAR_____

Name: _____ Age: _____ Sex: _____

Date of diagnosis of DM: _____ Type of DM: _____ Current medication: _____

Quarter	Month	Date	Weight kg	Fasting blood glucose mmol/l	Outcome*	Medication†	TB symptom screening performed (Y/N)	Positive TB screening (Y/N)	Referred for TB tests (Y/N)	Diagnosed with TB (Y/N)	TB details
Q1	January										Date of diagnosis
	February										
	March										TB: type and category
Q2	April										
	May										TB register no.
	June										
Q3	July										Date of TB treatment
	August										
	September										
Q4	October										
	November										
	December										

*A = alive in care, DIED = dead, LTFU = lost to follow-up, TO = transferred out.
†Diet; oral hypoglycaemic drugs; insulin.

Figure 2 Diabetes treatment card and TB screening. DM = diabetes mellitus; TB = tuberculosis; Y = yes; N = no.

Table 4 WHO Interim Policy on collaborative TB-HIV activities[65]

A Establish the mechanisms for collaboration
1 Set up a co-ordinating body for TB-HIV activities effective at all levels
2 Conduct surveillance of HIV prevalence in TB patients
3 Carry out joint TB-HIV planning for resources, capacity building, communication, community participation and operational research
4 Conduct monitoring and evaluation
B Reduce TB burden in persons living with HIV/AIDS
1 Establish intensified TB case finding
2 Introduce isoniazid preventive therapy
3 Ensure TB infection control in health care and congregate settings
C Reduce HIV burden in TB patients
1 Provide HIV testing and counselling
2 Introduce HIV prevention methods
3 Introduce cotrimoxazole preventive therapy
4 Ensure HIV/AIDS care and support
5 Introduce antiretroviral therapy

WHO = World Health Organization; TB = tuberculosis; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

epidemic.[70,71] Little action was taken, and HIV and TB programmes barely interacted at global, national or district levels. It was not until 2004, with the release of the WHO interim policy,[42] that collaborative HIV and TB activities got under way and progress was made in the fight against the two diseases. We cannot afford to make the same mistake with DM and TB.

In low- and middle-income countries, the DM epidemic is growing quickly. In sub-Saharan Africa, the absolute numbers of DM patients are predicted to grow from 12 million in 2010 to 24 million by 2030, with most cases undiagnosed and untreated.[72] However, it is Asia, as we have said earlier, that will bear the brunt of this epidemic, with the number of DM patients in South-East Asia and the Western Pacific predicted to reach over 210 million by 2030.[14] Epidemiological models using 2000 data in India have already shown the important interaction between DM and TB in that country, with DM accounting for 20% of smear-positive pulmonary TB cases,[73] and recent analyses have indicated that the increase in DM prevalence in India has been a significant impediment to reducing TB incidence in that country.[21]

Table 5 Collaborative activities to reduce the dual burden of diabetes and TB (adapted from reference 66)

A Establish the mechanisms for collaboration
1 Set up means of co-ordinating DM and TB activities
2 Conduct surveillance of TB disease prevalence in DM patients in medium and high TB burden settings
3 Conduct surveillance of DM prevalence in TB patients in all countries
4 Conduct monitoring and evaluation of collaborative DM and TB activities
B Detect and manage TB in DM patients
1 Intensify detection of TB disease among DM patients
2 Ensure TB infection control in health care settings where DM is managed
3 Ensure high quality TB treatment and management in people with DM
C Detect and manage DM in patients with TB
1 Screen TB patients for DM
2 Ensure high quality DM management among TB patients

TB = tuberculosis; DM = diabetes mellitus.

We must learn from the TB-HIV epidemic. One of the important keys to controlling the TB-HIV epidemic lies in preventing new HIV infections, and a milestone in this regard has been the recent recognition of the important TB preventive role of ART.[42] With a global DM epidemic that is escalating rapidly, the prevention and control of DM is likely to be an equally important intervention in controlling the DM-TB epidemic. Primary prevention of DM through attention to unhealthy diets, sedentary lifestyles and childhood and adult obesity must be included in broad prevention strategies for non-communicable diseases. Better integration of communicable and non-communicable disease prevention and care strategies that are focused on the patient rather than the disease is required. As with TB-HIV, we must adapt and apply similar methods of preventing, screening and treating the two diseases together, and ensure that we have secure pipelines for drugs, that we develop mechanisms of working together, that we undertake relevant operational and other kinds of research,[36] and that we adopt the philosophy of 'learning by doing'. We may then stand a good chance of winning this war.

Disclaimer

The views expressed in this article are the sole responsibility of the authors and may not necessarily reflect the positions and views of their affiliated institutions.

References

1 Dieffenbach C W, Fauci A S. Thirty years of HIV and AIDS: future challenges and opportunities. Ann Intern Med 2011; 154: 766–771.
2 Joint United Nations Programme on HIV/AIDS. Global report. UNAIDS report on the global AIDS epidemic 2010. Geneva, Switzerland: UNAIDS, 2010.
3 Geneau R, Stuckler D, Stachenko S, et al. Chronic diseases: chronic diseases and development 1. Raising the priority of preventing chronic diseases: a political process. Lancet 2010; 376: 1689–1698.
4 Tollman S M, Kahn K, Sartorius B, Collinson M A, Clark S J, Garenne M L. Implications of mortality transition for primary health care in rural South Africa: a population-based surveillance study. Lancet 2008; 372: 893–901.
5 Beaglehole R, Horton R. Chronic diseases: global action must match global evidence. Lancet 2010; 376: 1619–1620.
6 Crunch time for tuberculosis control [Editorial]. Lancet 2009; 373: 1145.
7 Chaisson R E, Martinson N A. Tuberculosis in Africa—combating an HIV-driven crisis. N Engl J Med 2008; 358: 1089–1092.
8 Lönnroth K, Castro K G, Chakaya J M, et al. Tuberculosis control and elimination 2010–2050: cure, care and social development. Lancet 2010; 375: 1814–1829.
9 Danaei G, Finucane M M, Lu Y, et al. National, regional and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys

and epidemiological studies with 370 country-years and 2.7 million participants. Lancet 2011; 378: 31–40.
10 The diabetes epidemic. Lancet 2011; 378: 99. [Editorial]
11 Ramachandran A, Wan Ma R C, Snehalatha C. Diabetes in Asia. Lancet 2010; 375: 408–418.
12 Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362: 1090–1101.
13 Liu Z, Fu C, Wang W, Xu B. Prevalence of chronic complications of type 2 diabetes mellitus in outpatients—a cross-sectional hospital based survey in urban China. Health Qual Life Outcomes 2010; 8: 62.
14 International Diabetes Federation. IDF diabetes atlas. 4th ed. Brussels, Belgium: International Diabetes Federation, 2009. http://www.eatlas.idf.org Accessed August 2011.
15 Stevenson C R, Critchley J A, Forouhi N G, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health. Chronic Illness 2007; 3: 228–245.
16 Jeon C Y, Murray M B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008; 5: e152.
17 Dooley K E, Chaisson R E. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis 2009; 9: 737–746.
18 Ruslami R, Aarnoutse R E, Alisjahbana B, van der Ven A J A M, van Crevel R. Implications of the global increase of diabetes for tuberculosis control and patient care. Trop Med Int Health 2010; 15: 1289–1299.
19 Restrepo B I, Camerlin A J, Rahbar M H, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. Bull World Health Organ 2011; 89: 352–359.
20 Goldhaber-Fiebert J D, Jeon C Y, Cohen T, Murray M B. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. Int J Epidemiol 2011; 40: 417–428.
21 Dye C, Trunz B B, Lönnroth K, Roglic G, Williams B G. Nutrition, diabetes and tuberculosis in the epidemiological transition. PLoS One 2011; 6: e21161.
22 Simon V, Ho D D, Karim Q A. HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. Lancet 2006; 368: 489–504.
23 Lawn S D, Harries A D, Williams B G, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis 2011; 15: 571–581.
24 Moutschen M P, Scheen A J, Lefebvre P J. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab 1992; 18: 187–201.
25 Chang F Y, Shaio M F. Decreased cell-mediated immunity in patients with non-insulin-dependent diabetes mellitus. Diabetes Res Clin Pract 1995; 28: 137–146.
26 Leung C C, Lam T H, Chan W M, et al. Diabetic control and risk of tuberculosis: a cohort study. Am J Epidemiol 2008; 167: 1486–1494.
27 Pablos-Mendez A, Blustein J, Knirsch C A. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health 1997; 87: 574–579.
28 Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis 2010; 14: 1295–1302.
29 Sosman M C, Steidl J H. Diabetic tuberculosis. Am J Roentgenol 1927; 17: 625–629.
30 Weaver R A. Unusual radiographic presentation of pulmonary tuberculosis in diabetic patients. Am Rev Respir Dis 1974; 109: 162–163.
31 Marais R M. Diabetes mellitus in black and coloured tuberculosis patients. S Afr Med J 1980; 57: 483–484.
32 Nissapatorn V, Kuppusamy I, Jamaiah I, Fong M Y, Rohela M, Anuar A K. Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Health 2005; 36 (Suppl 4): S213–S220.
33 World Health Organization. Treatment of tuberculosis. Guidelines. 4th ed. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO, 2010.
34 Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. MMWR Early Release 2009; 58: 1–206.
35 Centers for Disease Control and Prevention. Treatment of tuberculosis. MMWR 2003; 52 (RR-11): 1–77.
36 Harries A D, Murray M B, Jeon C Y, et al. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. Trop Med Int Health 2010; 15: 659–663.
37 Diul M Y, Maher D, Harries A D. Tuberculosis case fatality rates in HIV prevalence populations in sub-Saharan Africa. AIDS 2001; 15: 143–152.
38 Korenromp E L, Scano F, Williams B G, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. Clin Infect Dis 2003; 37: 101–112.
39 Panjabi R, Comstock G W, Golub J E. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. Int J Tuberc Lung Dis 2007; 11: 828–837.
40 Sonnenberg P, Murray J, Glynn J R, et al. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. Lancet 2001; 358: 1687–1693.
41 De Cock K M, Chaisson R E. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. Int J Tuberc Lung Dis 1999; 3: 457–465.
42 Harries A D, Zachariah R, Corbett E L, et al. The HIV-associated tuberculosis epidemic—when will we act? Lancet 2010; 375: 1906–1919.
43 Baker M A, Harries A D, Jeon C Y, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. BMC Med 2011; 9: 81.
44 Restrepo B I, Fisher-Hoch S P, Pino P A, et al. Tuberculosis in poorly controlled type 2 diabetes: altered cytokine expression in peripheral white blood cells. Clin Infect Dis 2008; 47: 634–641.
45 Niemi M, Backman J T, Fromm M F, Neuvonen P J, Kivisto K T. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 2003; 42: 819–850.
46 Xiao Q H, Deng Z Z, Liu J X, Mao C G, Li Q A. Risk factor analysis of hepatic toxicity of antituberculosis agents. Chinese J Antibiotics 2004; 29: 760–761.
47 World Health Organization. Guidance on provider-initiated HIV testing and counselling in health facilities. Geneva, Switzerland: WHO, 2007.
48 Odhiambo J, Kizito W, Njoroge A, et al. Provider-initiated HIV testing and counselling for TB patients and suspects in Nairobi, Kenya. Int J Tuberc Lung Dis 2008; 12: 63–68.
49 World Health Organization. WHO report 2010. Global tuberculosis control 2010. WHO/HTM/TB/2010.7. Geneva, Switzerland: WHO, 2010.
50 Jeon C Y, Harries A D, Baker M A, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health 2010; 15: 1300–1314.
51 World Health Organization. Use of glycated haemoglobin (HbA_{1c}) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. WHO/NMH/CHP/CPM/11.1. Geneva, Switzerland: WHO, 2011. http://www.who.int/cardiovascular_diseases/report-hba1c_2011_edited.pdf Accessed August 2011.
52 Misra A, Garg S. HbA_{1c} and blood glucose for the diagnosis of diabetes. Lancet 2011; 378: 104–106.

53 Bitzen P O, Schersten B. Assessment of laboratory methods for detection of unsuspected diabetes in primary health care. Scand J Prim Health Care 1986; 4: 85–95.
54 World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF consultation. Geneva, Switzerland: WHO, 2006. http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf Accessed August 2011.
55 Severe P, Jean Juste M A, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. N Engl J Med 2010; 363: 257–265.
56 World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach (2010 revision). Geneva, Switzerland: WHO, 2010. http://www.who.int/hiv/pub/arv/adult/en/index.html Accessed August 2011.
57 Cain K P, McCarthy K D, Heilig C M, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. N Engl J Med 2010; 362: 707–716.
58 Getahun H, Kittikraisak W, Heilig C M, et al. Development of a standardised screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med 2011; 8: e1000391.
59 World Health Organization. WHO policy on TB infection control in health care facilities, congregate settings and households. WHO/HTM/TB/2009.419. Geneva, Switzerland: WHO, 2009. http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf Accessed August 2011.
60 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV-infected persons. Cochrane Database Syst Rev 2010; (1): CD 000171.
61 Samandari T, Agizew T B, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011; 377: 1588–1598.
62 Pfaffenberg R, Jahler H. Isoniazid and recurrence of tuberculosis in diabetics. Zeitschrift fur Tuberkulose 1958; 111; 167–173.
63 Lesnichii A V, Karpina L Z. Experience with the chemoprophylaxis of pulmonary tuberculosis in diabetes mellitus patients. Problemy Tuberkuleza 1969; 47: 1–3.
64 World Health Organization, Joint United Nations Programme on HIV/AIDS. A guide to monitoring and evaluation for collaborative TB/HIV activities. WHO/HTM/TB/2009.414. WHO/HTM/HIV/09.01. Geneva, Switzerland: WHO, 2009. http://www.who.int/hiv/pub/tb/hiv_tb_monitoring_guide. pdf Accessed August 2011.
65 World Health Organization. Interim policy on collaborative TB/HIV activities. WHO/HTM/TB/2004.330. WHO/HTM/HIV/2004.1. Geneva, Switzerland: WHO, 2004. http://whqlibdoc.who.int/hq/2004/WHO_HTM_TB_2004.330_eng.pdf Accessed August 2011.
66 World Health Organization/International Union Against Tuberculosis and Lung Disease. Provisional collaborative framework for care and control of tuberculosis and diabetes. Geneva, Switzerland: WHO, 2011.
67 Ottmani S E, Murray M B, Jeon C Y, et al. Consultation meeting on tuberculosis and diabetes mellitus: meeting summary and recommendations. Int J Tuberc Lung Dis 2010; 14: 1513–1517.
68 Sunderam G, McDonald R J, Maniatis T, Oleske J, Kapila R, Reichman L B. Tuberculosis as a manifestation of the acquired immunodeficiency syndrome (AIDS). JAMA 1986; 256: 362–366.
69 Meeran K. Prevalence of HIV infection among patients with leprosy and tuberculosis in rural Zambia. BMJ 1989; 298: 364–365.
70 Murray J F. Tuberculosis and human immunodeficiency virus infection during the 1990's. Bull Int Union Tuberc Lung Dis 1991; 66 (1): 21–25.
71 Schulzer M, FitzGerald J M, Enarson D A, Grzybowski S. An estimate of the future size of the tuberculosis problem in sub-Saharan Africa resulting from HIV infection. Tubercle Lung Dis 1992; 73: 52–58.
72 Mbanya J C N, Motala A A, Sobngwi E, Assah F K, Enoru S T. Diabetes in sub-Saharan Africa. Lancet 2010; 375: 2254–2266.
73 Stevenson C R, Forouhi N G, Roglic G, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. BMC Public Health 2007; 7: 234.

RÉSUMÉ

La prévalence du diabète sucré augmente à un rythme dramatique et des pays d'Asie, particulièrement l'Inde et la Chine, porteront le choc de cette épidémie. Chez les sujets atteints de diabète, le risque de la tuberculose (TB) active est significativement augmenté et de deux à trois fois supérieur à celui des personnes sans diabète. Dans cet article, nous soutenons que les interactions épidémiologiques et les effets de l'interaction entre le diabète et la TB sur sa présentation clinique et le traitement résultant sont similaires à ceux observés en matière de VIH et de TB. Les leçons retenues des approches visant à réduire le fardeau double du VIH et de la TB, et particulièrement les modes de dépistage des deux maladies, peuvent être adaptées et appliquées au dépistage, au diagnostic, au traitement et à la prévention du diabète associée à la TB. Le nouveau Réseau de Collaboration de l'OMS et L'Union pour les soins et la maîtrise de la TB et du diabète est similaire à beaucoup d'égards à la politique de l'OMS sur les activités de collaboration visant à réduire le double fardeau de la TB et du VIH ; il vise à orienter les concepteurs de politique et ceux qui l'appliquent sur la façon de progresser et de combattre cette double épidémie en extension. La réponse à l'épidémie progressive de TB associée au VIH dans les années 1980 et 1990 a été lente et mal coordonnée en dépit des avertissements clairement articulés concernant l'étendue du problème à venir. Nous ne devons pas commettre la même erreur en ce qui concerne le diabète et la TB. Ce réseau fournit un gabarit pour l'action ; c'est maintenant aux donateurs, aux concepteurs de politique et à ceux qui la mettent en œuvre qu'il revient d'appliquer les recommandations dans ce domaine ainsi que de « se former par l'action ».

RESUMEN

La prevalencia de diabetes sacarina aumenta a un ritmo alarmante y algunos países de Asia, en especial la India y China, soportarán la mayor carga de esta epidemia. Las personas diabéticas presentan un riesgo de padecer tuberculosis (TB) activa que es dos a tres veces más alto que el riesgo de las personas sin diabetes. En el presente artículo se propone que las interacciones epidemiológicas y clínicas con respecto al modo de presentación y al tratamiento son equivalentes a las interacciones que se han observado en la coinfección por el virus de la inmunodeficiencia humana (VIH) y la TB. Las lecciones extraídas de las estrategias encaminadas a disminuir la carga de morbilidad por esas dos enfermedades, sobre todo en materia de métodos de detección sistemática, se pueden aplicar a la detección, el diagnóstico, el tratamiento y la prevención de la diabetes y la TB. El nuevo marco de acción conjunta para la atención y el control de la TB y la diabetes de La Unión y la Organización Mundial de la Salud (OMS) muestra muchas similitudes con la política de la OMS sobre las actividades de colaboración que tienden a aliviar la carga de morbilidad por TB e infección por el VIH; el marco tiene como objetivo guiar a las instancias normativas y ejecutoras en el progreso de la lucha contra esta inminente epidemia doble. En los años 1980 y 1990, la respuesta a la epidemia progresiva de coinfección por el VIH y la TB fue lenta y descoordinada, pese a las alertas que se expresaron claramente sobre la amplitud del problema que se acercaba. No se debe cometer el mismo error con la diabetes y la TB. Este marco ofrece un modelo para la acción y es ahora responsabilidad de los donantes y las instancias normativas y ejecutoras que se apliquen las recomendaciones en el terreno y 'se aprenda actuando'.