Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment

Elizabeth L Corbett, Barbara Marston, Gavin J Churchyard, Kevin M De Cock

Rapid scale-up of antiretroviral treatment programmes is happening in Africa, driven by international advocacy and policy directives and supported by unprecedented donor funding and technical assistance. This welcome development offers hope to millions of HIV-infected Africans, among whom tuberculosis is the major cause of serious illness and death. Little in the way of HIV diagnosis or care was previously offered to patients with tuberculosis, by either national tuberculosis or AIDS control programmes, with tuberculosis services focused exclusively on diagnosis and treatment of rising numbers of patients. Tuberculosis control in Africa has yet to adapt to the new climate of antiretroviral availability. Many barriers exist, from drug interactions to historic differences in the way that tuberculosis and HIV are perceived, but failure to successfully integrate HIV and tuberculosis control will threaten the viability of both programmes. Here, we review tuberculosis epidemiology in Africa and policy implications of HIV/AIDS treatment scale-up.

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HIV and epidemiology of tuberculosis in Africa

Burden of HIV/AIDS and tuberculosis

Figure 2 summarises the disproportionate burden of HIV and tuberculosis infection and disease in Africa at the start of the new millennium. In 2003, an estimated 8.8 million new cases of tuberculosis resulted in 1.7 million deaths. 27% of these cases and 31% of these deaths arose in Africa, home to only 11% of the world’s population. HIV prevalence in tuberculosis patients is less than 1% in the Western Pacific region but 38% in Africa. In countries with the highest HIV prevalence, more than 75% of cases of tuberculosis are HIV-associated.

In Africa, tuberculosis is often the first manifestation of HIV infection, and it is the leading cause of death among HIV-infected patients. In hospital-based series, 40–65% of HIV-infected African patients with respiratory disease had tuberculosis. In primary health and chest clinic settings, tuberculosis was confirmed in 43–70% of adults with cough for 3 weeks or longer (chronic cough) in Zimbabwe, Kenya, and Malawi. Patients with tuberculosis now commonly present with atypical symptoms: *M. tuberculosis* was isolated from 9% of adults with acute pneumonia in Kenya, 35% of people with cough for less than 3 weeks in Malawi, 23% of febrile HIV-infected inpatients in Tanzania, and 13% of HIV-infected patients with chronic diarrhoea in Kenya. In Cote d’Ivoire, the Democratic Republic of Congo, and Kenya, 18–47% of autopsies in HIV-positive adults indicated tuberculosis as the cause of death, although tuberculosis had been diagnosed during life in only about half of those with autopsy-proven disease.

Increased risk for tuberculosis from HIV infection in Africa

Comparison of HIV prevalence in general populations and tuberculosis patients shows that tuberculosis incidence was 8–3 times higher in HIV-positive than HIV-negative African people in 2003 (figure 3). In 2000, similar methods led to an estimated relative rate of 5.9, whereas estimates from individual cohort studies range from less than 5 to more than 20. Tuberculosis incidence increases with worsening immunosuppression, so that relative rates rise during the course of an HIV epidemic.

Tuberculosis incidence in African countries with high HIV prevalence

Reported tuberculosis case rates rose by 6.4% per year in the WHO African region in the late 1990s, but with up to five-fold increases since 1990 in some countries. Incidence might have peaked in some countries (figure 4) but at very high rates. The high case rate in Africa contributed to a global rise in tuberculosis incidence of 1% in 2003, despite stable or declining rates in the rest of the world.

Southern Africa has the highest prevalence of HIV infection and had the highest incidence of tuberculosis before the HIV/AIDS era. In the six southern African countries with adult HIV prevalence of more than 20%, tuberculosis case-notification rates are 461–719 per 100 000 per year; by comparison, the notification rate in the USA was 5 per 100 000 per year. True yearly rates in Africa are likely to be even higher because of under-diagnosis and under-reporting.

HIV and infectiousness and transmission of tuberculosis

The critical period with respect to infectiousness is before diagnosis, because most patients become non-infectious soon after starting treatment, even if they are HIV-infected. Both intensity and duration of infectiousness are highly variable, with some individuals remaining very infectious for prolonged periods, sometimes with apparently minor symptoms. HIV-positive individuals with tuberculosis are less infectious than HIV-negative patients since they are less often and...
less intensely smear-positive and because they remain infectious for a much shorter average duration.23,24

The average duration of smear positivity for HIV-negative individuals in resource-poor settings is estimated to be between 1 and 3 years.3,23,24,31 In two African studies in high HIV settings,23,24 mean durations of smear-positivity of only 6 and 8 weeks were estimated for HIV-positive patients with smear-positive tuberculosis, indicating fast progression to symptomatic disease.32 In both studies, most infectious individuals at any given point in time—the driving force for tuberculosis transmission in the community—were HIV-negative, because of their fairly long duration of infectiousness (figure 5).23,24 Thus, HIV-associated tuberculosis contributes greatly to incidence of tuberculosis and deaths, but it might contribute much less to disease transmission because of early diagnosis or death.33 This combination of exquisite vulnerability to disease by HIV-positive individuals and prolonged transmission from HIV-negative patients with tuberculosis together fuel escalating tuberculosis incidence in areas of high HIV prevalence. This fundamental observation has important implications for tuberculosis control in Africa.

Tuberculosis control in Africa before antiretroviral treatment

Tuberculosis control has been based on the WHO-promoted DOTS strategy, whose philosophical basis is prompt diagnosis and effective treatment of individuals with smear-positive tuberculosis to interrupt continuing transmission.1 In the face of rising tuberculosis incidence in Africa, international guidance during the 1990s emphasised the need for tuberculosis programmes to focus on diagnosis and treatment of self-presenting patients and to improve adherence and cure rates. HIV services, such as HIV-testing, were only deemed appropriate when priority tuberculosis objectives had been met.24-26 While understandable under the circumstances and funding of the time, this approach did not serve the overall medical needs of HIV-infected patients with tuberculosis.

The HIV epidemic has challenged DOTS as a sole tuberculosis control strategy for Africa, because even rigorous programmes cannot adequately compensate for the rising susceptibility to tuberculosis at the population level that occurs as HIV prevalence increases.27-41 As an example, despite well-funded control programmes in the South African gold mining industry that adhere to all elements of WHO’s DOTS strategy and screen miners every year, tuberculosis case rates have risen four-fold since 1990, driven by an increase in population HIV prevalence from less than 1% to almost 30%.42

Containing tuberculosis transmission and preventing drug resistance might be realistic and important goals for conventional DOTS programmes, but they are not routinely evaluated.43-49 Evidence that strong tuberculosis control programmes can control disease transmission is provided by analysis of incidence data stratified by HIV status.46-49 Figure 6 shows two possible scenarios of an epidemic of HIV.

In part A, an epidemic of HIV is shown, during which slowly falling tuberculosis transmission rates (from 1%
in 1985 to 0.7% per year in 2010) are maintained despite a rising burden of HIV-related tuberculosis. Disease incidence continues to decline in the HIV-negative subpopulation, but rises in the HIV-positive subpopulation as the proportion of patients with moderate-to-severe immunosuppression increases (maturation of the HIV epidemic). Overall tuberculosis incidence rises to a plateau soon after peak HIV prevalence in 2000. This scenario might describe the course of HIV and tuberculosis in countries with fairly strong tuberculosis control programmes such as Malawi and Tanzania, where peak tuberculosis incidence might already have been reached. In part B, an identical HIV epidemic to that in part A is shown, with the same assumptions about the effect of HIV on susceptibility to tuberculosis disease. However, in this scenario, the potential for HIV-related tuberculosis to increase disease transmission rates is not contained. Tuberculosis incidence rises to very high levels among HIV-positive individuals and increases substantially in the HIV-negative subpopulation as well, because of a rise in yearly risk of infection from 1% in 1985 to 2.7% in 2010. Tuberculosis incidence continues to rise after HIV prevalence peaks. Several countries, including Kenya, Uganda, and Swaziland, might be following a course intermediate between these two scenarios. Uganda and Kenya have reported continuing rises in tuberculosis case rates despite falling HIV prevalence, associated with a noted rise in yearly risk of *M tuberculosis* infection in Kenya. Data for Cote d’Ivoire, South Africa, Malawi, and Thailand, however, show stable or declining tuberculosis incidence among HIV-negative individuals despite increasing burdens and incidence of HIV-related tuberculosis. Similarly, in Tanzania, tuberculosis transmission rates have continued to decline while case-notifications have quadrupled. Within the same environment, therefore, strong orthodox tuberculosis control approaches can limit or reduce HIV-negative tuberculosis but not that associated with HIV.

**Effect of antiretroviral treatment on tuberculosis epidemiology**

**Mortality in HIV-infected tuberculosis patients**

Antiretroviral treatment scale-up mainly aims to reduce HIV-associated morbidity and mortality. Tuberculosis case-fatality rates (proportion of patients dying while on antituberculous treatment) in Africa are 16–35% in HIV-positive individuals not receiving antiretroviral treatment and 4–9% in HIV-negative patients.

Increased mortality in the first month of treatment seems largely attributable to tuberculosis itself, whereas other HIV-associated pathologies predominate thereafter. The highest death rates are present for people with the lowest CD4+ T-lymphocyte counts (CD4 count). In a 7-year follow-up in Malawi before HIV/AIDS treatment initiatives, only 11% of individuals who were HIV-infected at tuberculosis diagnosis were known to be still living. About a quarter of known deaths arose within 1 month of tuberculosis diagnosis.
Case-fatality rates can be reduced by diagnosis of HIV infection linked to co-trimoxazole prophylaxis and antiretroviral treatment. Mortality in tuberculosis patients in London (UK) fell by 72% after introduction of highly active antiretroviral drugs. Mortality in African people with HIV-associated tuberculosis is similar to that in patients with tuberculosis before effective antituberculous treatment, and provision of antiretroviral drugs could have as revolutionary an effect as anti-tuberculous drugs themselves did when first introduced.

Tuberculosis incidence and recurrence in HIV-infected people
Findings of several studies from different countries show that antiretroviral drugs reduce the incidence of tuberculosis in HIV-infected people by 80% or more, with the greatest effect at the lowest CD4 counts. However, clinically important immune dysfunction persists even during successful antiretroviral treatment, and tuberculosis incidence remains well above HIV-negative rates, even at high CD4 counts. Rates of recurrent disease in patients with previous HIV-related tuberculosis are also high, suggesting a need for secondary preventive treatment.

Tuberculosis is an aggressive opportunistic infection that arises at higher median CD4 counts than do most other AIDS-defining disorders. For example, median CD4 counts were 257 per μL for smear-positive patients in Cote d’Ivoire. Current guidelines for resource-poor settings recommend treatment for patients with symptomatic HIV or a CD4 count of 200 per μL or less. The potential effect of antiretroviral treatment on tuberculosis incidence, therefore, is lessened because many HIV-infected patients with tuberculosis present before antiretroviral drugs are prescribed.

Theoretically, even well-functioning antiretroviral programmes could worsen the HIV-associated tuberculosis epidemic if an expanding cohort of patients remains highly susceptible and capable of transmitting tuberculosis for long periods. Mathematical and statistical modelling suggests antiretroviral drug coverage would have to be high, start early, and be combined with tuberculosis preventive treatment to contain disease incidence and reduce mortality.

Towards a coordinated public-health response to tuberculosis and HIV/AIDS
One strategy alone is unlikely to succeed: different approaches based on serostatus need to address the vulnerability to tuberculosis disease of HIV-infected individuals and reduce disease transmission from all affected people, including those who are HIV-negative. The need for a coordinated approach towards tuberculosis and HIV control is now stressed at the highest levels. There is understandable reluctance to relinquish the traditional disease model for tuberculosis control: past experience, notably in Zambia, shows that well-intentioned reform can disrupt essential tuberculosis control activities. However, different programme models are now emerging that retain DOTS as the essential but insufficient minimum, while additional elements discussed below are implemented or investigated in collaboration with HIV/AIDS control programmes. Essential outcomes are reduced transmission, disease, and death for both HIV and tuberculosis (panel). Seamless collaboration between tuberculosis and HIV/AIDS treatment programmes is needed, along with a unified public-health vision towards the prevention and treatment of these interacting infectious diseases.

One barrier to closer collaboration is the philosophical difference historically in how HIV/AIDS and tuberculosis surveillance, diagnosis, and treatment have been approached. Tuberculosis control programmes have epitomised the public-health approach of case finding, name-based case notification, and, when possible, screening of contacts. Control of tuberculosis transmission and prevention of drug resistance have been paramount aims, with less emphasis on patient-centred goals such as reduction of deaths. By contrast, HIV/AIDS programmes have focused on an individual approach to HIV testing that is private, confidential, and voluntary, but which has little emphasis on interrupting chains of transmission.

Currently, fewer than 10% of African patients with tuberculosis are tested for HIV, although HIV testing is acceptable to most people when provided in a convenient and confidential way. The major difficulty is that testing is still not routinely offered in most tuberculosis clinics. WHO and UNAIDS guidelines now lend support to diagnostic HIV testing of individuals with HIV-associated disorders, including known and suspected tuberculosis patients, using an opt-out approach, and these organisations have requested routine reporting of the uptake of HIV testing along with the numbers of notified tuberculosis cases.

There are three goals of coordinated tuberculosis and HIV interventions: (1) to optimise diagnosis and treatment to improve outcome for all tuberculosis patients; (2) to reduce HIV-associated tuberculosis incidence and recurrence; and (3) to improve HIV and tuberculosis control overall.

Optimisation of tuberculosis diagnosis and treatment
Tuberculosis diagnosis in Africa relies on sputum microscopy followed by broad-spectrum antibiotics and chest radiography if smears are negative. Although specificity is high, major concerns include low sensitivity and delayed diagnosis of smear-negative disease. The accuracy of both microscopy and radiography is reduced by HIV, and so assessment of diagnostic approaches with existing methods and continuing research into new diagnostics are necessary.
Panel: Key interventions for improving tuberculosis and HIV control in Africa

1) Better implementation of existing policies
   - Universal HIV testing of patients with confirmed or suspected tuberculosis
   - Universal access to high-quality sputum microscopy for individuals with suspected tuberculosis
   - Universal directly observed treatment while taking rifampicin-containing tuberculosis regimen
   - Antiretroviral treatment according to national guidelines for all HIV-infected individuals, including tuberculosis patients
   - Ready access to voluntary counselling and testing for HIV and condoms to prevent HIV transmission

2) More widespread implementation of additional interventions known to be effective
   - Use of the most effective short-course chemotherapy for all tuberculosis patients
   - Co-trimoxazole prophylaxis for all HIV-infected tuberculosis patients not taking antiretroviral drugs
   - Screening of all HIV-infected individuals for tuberculosis infection and disease
   - Primary isoniazid preventive treatment for all HIV-infected individuals
   - Environmental measures to prevent nosocomial transmission of M tuberculosis

3) Rapid assessment of promising new approaches
   - More sensitive sputum smear microscopy
   - More rapid and sensitive diagnostic algorithms for smear-negative individuals with suspected tuberculosis
   - Expanded access to tuberculosis culture with rapid liquid culture systems
   - Secondary preventive treatment for HIV-infected individuals after successful treatment of active tuberculosis
   - Early initiation of antiretroviral treatment in newly diagnosed HIV-infected tuberculosis patients
   - Co-trimoxazole prophylaxis for HIV-infected tuberculosis patients taking antiretroviral drugs
   - Active case-finding for tuberculosis in the community
   - Promotion of universal knowledge of HIV serostatus, with emphasis on prevention of transmission from HIV-infected individuals
   - Novel HIV prevention interventions

4) Increased resources and support
   - Training and retention of health-care workers in joint HIV and tuberculosis management
   - Increased funding for integrated tuberculosis and HIV activities
   - Increased funding for tuberculosis control programmes to support HIV diagnosis and initiation of HIV care, and more rapid diagnosis and effective treatment of both HIV-positive and HIV-negative patients with tuberculosis

DOTS programmes have focused on smear-positive disease because it is the most infectious type, but much of the increased tuberculosis caseload in Africa is reported as smear-negative. HIV-related tuberculosis is more usually smear-negative, extrapulmonary, or disseminated than tuberculosis among HIV-negative individuals. Worsening immunosuppression correlates with increased mycobacterial load and atypical radiological findings: smear-negative tuberculosis has a worse prognosis than smear-positive disease in HIV-positive patients. In studies based on blood culture, disseminated tuberculosis typically presents as a non-specific febrile disorder that progresses rapidly to death, and in autopsy studies, up to 50% of HIV-related tuberculosis deaths go undiagnosed; these findings indicate the diagnostic challenge. In programmes, a commitment must be made to prioritise smear-negative disease and lower the threshold for starting antituberculous treatment, with appropriate follow-up and outcome assessment.

Major initiatives to increase culture facilities in Africa are underway but without any consensus about their probable effect. Culture outperforms other investigations for early HIV-related tuberculosis and could be ideal for screening at HIV diagnosis and before starting tuberculosis preventive treatment. For routine investigation of ambulant individuals with suspected tuberculosis, however, the potential gain over sensitive microscopy and radiology is not clear. Logistic constraints to decentralisation of culture to primary health-care level are considerable, and culture might be too slow to contribute much to clinical decision-making. Expert groups have prioritised sensitive microscopy over expanded access to culture.

Active case finding for tuberculosis and HIV
Up to 10% of HIV-infected individuals have active tuberculosis when first seeking knowledge of their HIV status. Symptom screening detects most, but not all, active cases, with culture but not radiology seeming to add substantially to sensitivity. Every opportunity should be taken to screen HIV-infected African people for active tuberculosis, just as every patient with tuberculosis should be screened for HIV. To increase access to life-prolonging interventions, active case finding for HIV will have to be developed in a way that is acceptable to communities.

Optimisation of antituberculous chemotherapy
The most frequently used treatment for newly diagnosed tuberculosis in Africa is an 8-month regimen introduced in the 1990s to replace thioacetazone-based strategies that were poorly tolerated in patients with HIV infection. The 8-month regimen includes rifampicin for 2 months only, but it is inferior to an alternative 6-month regimen containing rifampicin throughout. Using rifampicin for 6 months rather than 2 months...
extends direct supervision of treatment, which is recommended to prevent rifampicin resistance developing, and it makes treatment choices difficult because of drug interactions between rifamycins and antiretroviral drugs.\textsuperscript{108} However, to strive for antiretroviral drug access while tolerating suboptimum tuberculosis treatment is inconsistent, and the 8-month regimen should be phased out as soon as possible.

\textit{Prevention of the emergence of multidrug-resistant tuberculosis}

Multidrug-resistant strains of \textit{M tuberculosis} (resistant to at least isoniazid and rifampicin) arise from inadequate treatment of active tuberculosis, and can then be further transmitted. Treatment outcomes are poor for both HIV-positive and HIV-negative patients, with high case-fatality and treatment failure rates.\textsuperscript{103–106} Treatment for multidrug-resistant tuberculosis is expensive, toxic, difficult to combine with antiretroviral drugs, and unavailable in most of Africa.\textsuperscript{62} HIV-care settings are prone to outbreaks of nosocomial multidrug-resistant tuberculosis, which can persist for years without intervention.\textsuperscript{102,105} Lack of diagnostic capacity would make early recognition difficult in most of Africa. Data indicate a growing problem, with primary multidrug resistance in more than 2% of patients in parts of South Africa, and a rise in Botswana from 0.2% to 0.8%.\textsuperscript{106,107} Continued commitment, more comprehensive surveillance, better access to drug-sensitivity testing, implementation of fixed-drug combination tablets, and policies for management of multidrug-resistant tuberculosis in HIV care settings are needed. The DOTS strategy focuses on standard treatment regimens and direct observation and extends direct supervision of treatment, which is recommended to prevent rifampicin resistance developing, and it makes treatment choices difficult because of drug interactions between rifamycins and antiretroviral drugs.\textsuperscript{108} However, to strive for antiretroviral drug access while tolerating suboptimum tuberculosis treatment is inconsistent, and the 8-month regimen should be phased out as soon as possible.

\textit{Optimisation of antiretroviral therapy in HIV-infected patients with tuberculosis}

The high death rate in the first 2 months of tuberculosis treatment provides an argument for antiretroviral drugs to be started as soon as possible. However, challenges favouring a delayed start include drug interactions, combined toxic effects, and non-adherence to treatment.\textsuperscript{71,108,109} Clear definition of the best time to initiate antiretroviral treatment in patients with tuberculosis awaits results from controlled trials.

Detailed discussions of antiretroviral treatment for tuberculosis patients are available elsewhere.\textsuperscript{72,108,109} In brief, enzyme induction by rifampicin causes many interactions, with additional concerns of combined toxic effects, especially for nevirapine. Nevirapine-containing antiretroviral regimens are first-line in all African countries apart from South Africa, since the drug is cheap, effective, available in various fixed-drug combinations, and safe in pregnancy.\textsuperscript{71} Rifampicin reduces nevirapine concentrations by about a third,\textsuperscript{108} and both drugs can cause severe hepatitis.\textsuperscript{110} Women with a CD4 count greater than 250 per \(\mu L\)—a substantial subgroup of African patients with tuberculosis—are at highest risk of nevirapine-associated hepatitis.\textsuperscript{71,109,111–113} Clinical experience of concurrent use of nevirapine and antituberculosis treatment is accruing, but at the time of writing the risks remain unclear.\textsuperscript{71}

Patients who start antiretroviral drugs early in their tuberculosis treatment can be predisposed to immune reconstitution inflammatory syndrome, which is frequent, has symptoms overlapping with worsening tuberculosis and drug reactions, and can be life-threatening.\textsuperscript{114,115} WHO guidelines suggest starting antiretroviral drugs within 2 months of tuberculosis treatment at a CD4 count of 200 per \(\mu L\), or less and for extrapulmonary tuberculosis or other manifestations of severe immunosuppression.\textsuperscript{71} for patients with CD4 counts less than 50 per \(\mu L\), treatment initiation is advised within 2 weeks. In such cases, efavirenz-containing regimens are recommended unless contraindicated by pregnancy or the potential to conceive.\textsuperscript{71} Use of protease inhibitors other than full-dose ritonavir is not recommended. Nevirapine can be used “in the absence of other options”.\textsuperscript{71}

Rifabutin is a less potent enzyme inducer than rifampicin; it can effectively treat tuberculosis and is compatible with antiretroviral drugs, but it is prohibitively expensive at present.\textsuperscript{109} Triple nucleoside or nucleotide regimens, such as zidovudine, lamivudine, and tenofovir, have potential as tuberculosis-compatible antiretroviral regimens if shown to be sufficiently potent.\textsuperscript{115}

\textit{Co-trimoxazole prophylaxis in HIV-infected people with tuberculosis}

Results from a placebo-controlled trial of co-trimoxazole in Cote d’Ivoire, showing a 46% reduction in mortality in HIV-infected tuberculosis patients, have been lent support by research in other parts of Africa.\textsuperscript{74–76} Since 1999, WHO and UNAIDS have recommended co-trimoxazole prophylaxis for all individuals with symptomatic HIV disease or CD4 counts less than 500 per \(\mu L\), but uptake was estimated as only 3% of HIV-infected adults in 2003. The current drive towards roll-out of antiretroviral treatment might greatly enhance co-trimoxazole uptake as systems are put into place for delivery of chronic HIV care. An important question is whether co-trimoxazole benefits patients with tuberculosis who are taking antiretroviral treatment. In the industrialised world, co-trimoxazole can safely be withdrawn when CD4 count is greater than 200 per \(\mu L\), but in the African environment, benefit could extend to higher CD4 cell counts.\textsuperscript{117,118}

\textit{Reduction of tuberculosis incidence and recurrence in HIV-infected individuals}

Risk of new tuberculosis disease in HIV-infected individuals can be lowered, but not eliminated, by
isoniazid preventive treatment,68 antiretroviral drugs,120–121 and reducing exposure to *M tuberculosis*. The benefits of antiretroviral drugs68 and secondary isoniazid preventive treatment69 for recurrent tuberculosis disease have not yet been clearly defined, but the rate of recurrence remains very high even for patients on antiretroviral drugs.29

Isoniazid preventive treatment for 6–9 months reduces tuberculosis prevalence by about 60% in HIV-infected individuals with a positive tuberculin skin test, and by about 40% when used irrespective of skin-test results.120,121 However, this low-cost intervention has been little used in Africa, with only Botswana attempting widespread implementation.29 In part, this low use relates to concerns about possible promotion of drug resistance and past absence of additional funding, but it also exemplifies limited commitment to date to joint tuberculosis and HIV interventions. Definition of screening procedures needed in operational settings remains an important research question.92,97 Other unresolved issues include the best duration of preventive treatment, since protection wanes with time in HIV-infected individuals not receiving antiretroviral drugs,120,121 and the role and safety of primary and secondary preventive treatment and antiretroviral regimens.

Epidemics of nosocomial tuberculosis have been well documented in industrialised countries, where they stand out against low background rates.122 In Africa, the potential for nosocomial transmission affecting patients and staff is much higher, and facilities are ill-equipped. In two cohort studies in a goldmining workforce, a rise in the incidence of HIV-related recurrent tuberculosis, from 8.2 to 19.1 per 100 person-years, coinciding with the introduction of HIV clinics.77 Integrated care needs planning, retraining, and considerable expansion of tuberculosis programme personnel, but it is more patient-orientated and efficient than current systems.77

Models for delivery of coordinated tuberculosis and HIV treatment services

Rapid scale-up of antiretroviral programmes dominates public-health interventions in Africa, but with only limited attention to coordination with tuberculosis programmes.125 Coordination can mean referral between services, some provision of joint services, or complete integration of tuberculosis and HIV/AIDS clinics. Important experience has been gained in Malawi, where the national tuberculosis control programme provides a model for scaling-up delivery of antiretroviral drugs.126 First-line treatment is with stavudine, lamivudine, and nevirapine (provided free of charge); clinical staging is used to define eligibility after a positive HIV test. Uptake of routine (opt-out) HIV testing among tuberculosis patients has reached 70%, with high uptake and adherence to co-trimoxazole but with success rates for starting antiretroviral treatment of 20% or less.126 The main constraints seem to be the 8-week delay between starting tuberculosis treatment and becoming eligible for nevirapine-containing antiretroviral regimens (during which time patients are discharged) and logistic difficulties for patients in accessing centralised antiretroviral services when they also have to attend local health clinics for continued management of antiretroviral drugs.76,77,127}

Good uptake rates for antiretroviral treatment have been reported from programmes that offer tuberculosis and antiretroviral drugs from the same clinic, with transfer of care once tuberculosis treatment has been completed (partial integration) or continued treatment as a fully integrated HIV and tuberculosis service.77,127 Timely investigation and improved management of patients who develop tuberculosis while on antiretroviral drugs might be a further benefit of completely integrated clinics.77 Integrated care needs planning, retraining, and considerable expansion of tuberculosis programme personnel, but it is more patient-orientated and efficient than current systems.77

Monitoring and assessment

Traditional outcome measures for tuberculosis programmes need cohort analysis of treated patients to establish successful and adverse outcomes. WHO defines targets of 70% case detection (estimated indirectly) and 85% cure rates.126 Collaborative HIV and tuberculosis programmes also need to monitor uptake of HIV testing and antiretroviral treatment, with subsequent measures of adherence, default, and survival. Because antiretroviral regimens, unlike antituberculous treatment, are lifelong, complexity of programmes will be greatly enhanced.126

From a surveillance perspective, universal opt-out HIV testing of tuberculosis patients will provide useful data for HIV prevalence and allow estimation of tuberculosis incidence in HIV-positive and HIV-negative subpopulations (figure 6). HIV-positive tuberculosis trends could usefully be viewed as a surrogate for trends in a country’s overall AIDS epidemic,125 and HIV-negative trends would offer assessment of programme performance in controlling tuberculosis transmission. Demonstration that the incidence of tuberculosis was declining in HIV-negative subpopulations could do much to enhance morale of tuberculosis programmes, whose confidence has been shaken by escalating incidence, as could data showing reduced HIV-positive mortality rates.
Challenges, constraints, and future prospects

Whatever we aim for, limited human resources, weak management and health systems, inadequate clinical and laboratory infrastructure, and absent training programmes for combined tuberculosis and HIV/AIDS care are all formidable barriers to supporting large numbers of patients in long-term care.\(^{72,130–132}\) Despite potential for increased funding, African tuberculosis control programmes remain poor in resources—in absolute terms and relative to those available for HIV/AIDS control.\(^{88,111}\) Few areas of the health sector have seen demand escalate to the degree experienced by tuberculosis programmes, yet support has not greatly increased and sometimes has declined in important areas such as personnel.\(^{110}\) The incidence of AIDS and HIV-associated tuberculosis in Africa is hundreds of times more than that in the industrialised world, but the ratio of health-care workers to population is a tenth of European levels.\(^{112}\) Programmes cannot succeed without increased funding for basic public-health and clinical infrastructure and appropriate personnel.\(^{114}\)

Since the tuberculosis epidemic in Africa has been driven by HIV, activities directed towards HIV-associated disease should logically be the most effective response. Paradoxically, results from mathematical modelling suggest that improvements in tuberculosis case-finding and treatment, and reductions in HIV incidence, have a greater potential than interventions targeted to known HIV-positive individuals.\(^{72}\) Tuberculosis control in Africa remains weak, and large gains can still be made from strengthening basic disease control. Care must be taken to avoid collapse of previously well-functioning tuberculosis control programmes after competition for scarce human resources and to ensure that integration of HIV and tuberculosis services does not compromise core tuberculosis programme functions, such as maintenance of drugs and supplies, prevention of drug resistance, assurance of quality diagnostic microscopy, and cohort analysis of treated patients.\(^{77}\)

In the same way that HIV fundamentally changed tuberculosis and its epidemiology in Africa, so the introduction of antiretroviral treatment poses important challenges to how tuberculosis control should be approached. Rapid scale-up of antiretroviral programmes in Africa in the past 2 years has not adequately taken patients with tuberculosis into account.\(^{113}\) Without sufficient coverage of preventive and therapeutic interventions for both diseases, tuberculosis could yet be the limiting factor to the long-term success of antiretroviral programmes because of uncontrolled incidence, recurrence, and institutional transmission. The advent of antiretroviral treatment in Africa is the most important event for tuberculosis patients since the introduction of antituberculous drugs, and HIV/AIDS and tuberculosis programmes will both have to change greatly to benefit as much as possible from this development.

Conflict of interest statement

We declare that we have no conflict of interest.

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