

Utility of Tuberculosis Directly Observed Therapy Programs as Sites for Access to and Provision of Antiretroviral Therapy in Resource-Limited Countries

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The overwhelming share of the global human immunodeficiency virus (HIV) infection and disease burden is borne by resource-limited countries. The explosive spread of HIV infection and growing burden of disease in these countries has intensified the need to find solutions to improved access to treatment for HIV infection. The epidemic of HIV infection and acquired immune deficiency syndrome (AIDS) has been accompanied by a severe epidemic of tuberculosis. Tuberculosis has become the major cause of morbidity and mortality in patients with HIV disease worldwide. Among the various models of provision of HIV/AIDS care, one logical but unexplored strategy is to integrate HIV/AIDS and tuberculosis care and treatment, including highly active antiretroviral therapy, through existing tuberculosis directly observed therapy programs. This strategy could address the related issues of inadequate access and infrastructure and need for enhanced adherence to medication and thereby potentially improve the outcome for both diseases.

The overwhelming share of the global burden of HIV infection and disease is borne by resource-limited countries. Of the worldwide total of >42 million people living with HIV/AIDS at the end of 2002, close to 30 million were in sub-Saharan Africa and >6 million in Southeast Asia [1]. In South Africa alone, >5.3 million persons, or 1 in 4 adults, are currently thought to be living with HIV/AIDS. The explosive spread of HIV infection and growing burden of disease in Africa and other resource-poor areas has intensified the need to find solutions to improved access to treatment for HIV infection.

Treatment of HIV infection with HAART has dra-

matically altered the natural history of HIV disease among those in resource-rich countries, for whom potent combinations of antiretroviral agents have been available. Of the millions of people worldwide eligible for treatment, it is estimated that only 300,000 people in resource-limited countries are receiving HAART, and one-half of these are in Brazil, where universal access has been established. Excessive cost and lack of infrastructure and political will have limited access to HAART in resource-poor countries. Requirements for successful treatment of HIV infection with HAART include the existence of an HIV/AIDS care infrastructure capable of identifying and caring for those with HIV infection, providing a reliable source of medication, maintaining support for adherence to probable lifelong treatment, and monitoring of drug toxicities, side effects, and treatment response [2]. Recent reductions in the prices of antiretroviral agents will make their availability more widespread. But even if drugs became universally available, the health care infrastructure needed for their successful use is limited and must be rapidly

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expanded and put into place, lest the great potential benefit of therapy be wasted [3]. The need to develop simple and sustainable strategies for delivery of HIV/AIDS care and therapy to large numbers of patients in the context of the existing underdeveloped health care delivery systems is a matter of great urgency. Among the various models of provision of HIV/AIDS care, one proposed strategy is to integrate HIV/AIDS and tuberculosis care [3–5]. Further expansion of this strategy to include the provision of HAART through existing tuberculosis directly observed therapy (DOT) programs is logical and appealing and warrants rapid and careful evaluation. Here we explore the rationale and potential benefits and limitations of such a strategy for resource-poor countries.

HIV/AIDS AND TUBERCULOSIS

Worldwide, the HIV/AIDS epidemic has been accompanied by a severe epidemic of tuberculosis. It is estimated that there were ~8 million new cases and 16 million prevalent cases of tuberculosis in 2000 [6]. The interaction between HIV and *Mycobacterium tuberculosis* has profoundly influenced the epidemiology and clinical outcome of both diseases. HIV infection markedly increases the risk of reactivation of latent tuberculosis and of progression of primary disease after initial infection. The lifetime risk for progressing to active tuberculosis among HIV-negative persons latently infected with *M. tuberculosis* is estimated to be 10% [7]. In contrast, among HIV-infected persons, the risk is ~10% per year. The risk for progressive primary disease after recent infection with *M. tuberculosis* approaches 40% [8]. The global estimate of HIV coinfection in patients with tuberculosis increased during the 1990s and reached 10% by the end of the decade [6]. Although India has the greatest absolute number of persons coinfecting with HIV and *M. tuberculosis*, sub-Saharan Africa carries the greatest burden of the global epidemic of tuberculosis associated with HIV infection, with the highest proportion (32%) of patients with new cases of tuberculosis who are coinfecting with HIV [6]. An estimated 2 million adults are coinfecting with HIV and *M. tuberculosis* in South Africa alone [6], and in the province of KwaZulu Natal, two-thirds of patients with newly diagnosed cases of tuberculosis are coinfecting with HIV [9].

Tuberculosis is the major medical complication of HIV disease and the major cause of death among people with AIDS in resource-poor countries [4–6, 10]. HIV infection has a substantial deleterious impact on tuberculosis outcomes, and the development of tuberculosis has been shown to accelerate the course of HIV disease [11]. In the presence of HIV infection, tuberculosis is associated with substantially higher case-fatality rates regardless of use of effective tuberculosis chemotherapy [12, 13]. Even though tuberculosis is treatable, the tuberculosis case-fatality rate in some areas is very high, approaching 40%

at 1 year [14]. Among patients with tuberculosis who have received antituberculosis therapy, most of the increased mortality is directly attributable to untreated HIV infection and associated opportunistic diseases and not to tuberculosis itself.

In addition to high mortality rates, the burden of HIV-associated tuberculosis on already weak health care facilities has been immense. Tuberculosis programs are often unable to manage the increased numbers of HIV-related tuberculosis cases and ensure completion of tuberculosis therapy, and inpatient facilities are overwhelmed with patients with HIV infection and tuberculosis. For example, a survey at the King Edward VIII Hospital in Durban, KwaZulu Natal, South Africa, in 1998 reported that 54% of adult inpatients have an AIDS-related illness, the majority of whom have pulmonary or extrapulmonary tuberculosis [15].

DOT FOR TUBERCULOSIS

The importance of adherence to tuberculosis medications is fundamental to treatment success. Poor adherence affects both individual and public health and results in an increased morbidity and mortality and the emergence and potential transmission of multidrug resistance. DOT for tuberculosis was introduced >40 years ago as a method of ensuring adherence to medication, completion of treatment, and decreasing the risk of development of drug-resistant tuberculosis, and it is the most successful and well-studied of adherence interventions. This strategy has become one of the central components of the DOTS (directly observed therapy, short-course) strategy recommended by the World Health Organization (WHO) for treatment of tuberculosis [16, 17]. DOT for tuberculosis is usually carried out with once-daily administration of 4 antituberculous drugs (isoniazid, rifampin, pyrazinamide, and ethambutol), usually 5 days per week for 2 months, followed by once-daily treatment with isoniazid and rifampin, 3–5 days per week, for a total of 6–9 months of therapy. Although treatment success rates are variable, available data indicate that, compared with self-administered tuberculosis therapy, DOT is associated with decreased incidence of tuberculosis and rates of drug resistance and with increased rates of sputum conversion and completion of therapy [18–20]. Among persons infected with HIV, DOT has also been associated with improved survival [20].

By 2001, there were 155 of a total of 210 countries that had implemented the DOTS strategy for tuberculosis, and an estimated 61% of the world's population lived in parts of countries providing DOTS programs [21]. WHO and national guidelines exist to guide and monitor tuberculosis treatment and its outcomes [16, 17]. Programmatic success is generally defined as a treatment completion rate of >85%, but this is often not achieved, and there is wide variability in the success

in implementing DOTS [16, 17, 22–26]. Some studies even indicate that observed pill-taking is not superior to self-administration. The lack of success is often related to how well DOTS is implemented. Constraints most commonly identified that impede successful implementation include lack of qualified staff, insufficient preparation for program development and decentralization, lack of contribution of the private sector, inadequate health infrastructure, lack of stable drug supplies, and lack of political commitment. Furthermore, these impediments have become even more problematic as a consequence of the HIV/AIDS epidemic [5]. These constraints notwithstanding, in many developing countries, an established, acceptable, and familiar DOT infrastructure is available to provide diagnosis and treatment for patients with tuberculosis. In these programs, tuberculosis patients receive ongoing clinical care, have secure access to medications, and are monitored by staff and community supporters for adherence, side effects, and treatment outcome. Furthermore, the most successful DOT programs have supplemented observation of taking of medication with several other components, including enhanced staff motivation and patient-centered supportive program elements and enhancements [16, 17, 22, 23]. These are often essential for treatment success.

Historically, tuberculosis treatment programs have been separated from the mainstream of medical care and practice and have focused specifically on the diagnosis and treatment of tuberculosis. In the context of the rapidly growing HIV/AIDS and tuberculosis epidemics, these programs as currently constituted cannot fully address either tuberculosis or HIV disease [5, 17]. The common ground between tuberculosis and HIV/AIDS care is being increasingly recognized. At the third meeting of the WHO Tuberculosis/HIV Working Group in June 2003, it was concluded that there was clear and achievable benefit of tuberculosis and HIV/AIDS programs working together to integrate the care of both diseases [21]. It was noted that program collaboration was essential and more efficient than completely separate approaches and that care should be “patient- and not disease-focused.” Five key points of collaboration emerged from the meeting: (1) strengthen DOTS and HIV/AIDS care and prevention, (2) establish national-level tuberculosis/HIV disease coordination committees, (3) offer HIV testing and counseling to all patients with tuberculosis, (4) screen all people attending HIV/AIDS services for tuberculosis, and (5) offer preventive therapy for opportunistic infections to those coinfecting with *M. tuberculosis* and HIV.

Although they are a laudable, essential, and major step forward toward integrating diagnosis and treatment of HIV infection and tuberculosis, these recommendations still fall short of addressing the need for treatment of both diseases through the coordinated administration of tuberculosis and antiretroviral therapy. To accomplish this, DOT programs for tuber-

culosis could provide an existing, ready-made infrastructure for the treatment of both tuberculosis and HIV infection and the concomitant administration of HAART and tuberculosis medications.

HAART AND DOT

As access to HAART begins to widen in resource-poor countries, concern exists about the long-term effectiveness of these regimens, given the potential for inadequate adherence and subsequent emergence of drug resistance. Issues raised have included concern that HAART may be problematic in countries where the costs associated with treatment remain prohibitive for most and where well-developed health care infrastructures capable of treatment administration and monitoring are often limited or nonexistent. These concerns, coupled with undocumented stereotypes about the ability of patients in resource-poor countries to take antiretroviral medication reliably and consistently, have been used as arguments to limit the availability of HAART. Such views ignore the heterogeneity of African and other populations and the great desire for treatment for HIV disease. Indeed, available evidence indicates that rates of adherence to HIV treatment and therapeutic outcomes do not differ significantly from those seen in developed countries [27]. Nevertheless, as therapy becomes more widely available, difficulties with inadequate adherence to lifelong antiretroviral therapies can be expected, as has been the experience in developed countries. It is critically important to anticipate this and develop and implement strategies for enhancement and support of adherence. This need has been much too slowly appreciated in developed countries, with resultant blunting of therapeutic benefit of HAART and associated rise in the prevalence of HIV resistance.

The previously available, more-complicated and more-frequent dosing regimens of antiretrovirals and the need for lifelong treatment have resulted in appropriate concerns that DOT, as an adherence support measure, although successful for tuberculosis treatment, might be unsuitable for treatment of HIV infection [28, 29]. However, existing preliminary information supports the utility of DOT for administration of HIV/AIDS therapy in special settings. In one study, incarcerated, treatment-naive patients enrolled in 4 clinical trials received HAART by DOT and were compared with patients who received HAART by self-administration in the community and who were enrolled in the same trials. The proportion of patients with declines in HIV RNA levels was significantly higher in the incarcerated DOT group, an indication of both the importance of adherence and the value of this intervention to improve adherence and therapeutic outcome [30]. The administration of HAART by DOT has shown very promising results in special community-based programs as well in developed countries [29,

31, 32]. In a randomized clinical trial of modified DOT (in which not all medication doses were administered via DOT), preliminary results indicate significantly greater decreases in viral load and increases in CD4⁺ cells among those randomized to the DOT arm than among those in the control arm who received self-administered therapy [32]. Of further and particular relevance for resource-limited countries, the strategy of DOT HAART has been successfully used in an innovative community-based program in Haiti among patients with advanced HIV disease, although without active tuberculosis [33, 34].

Although the utility of administration of HAART by DOT requires further study and validation, the availability of potent once-daily regimens makes this strategy more practical, particularly because there are existing DOT once-daily regimens for tuberculosis. Simpler and more easily tolerated antiretroviral agents and regimens have provided an appealing, direct, and generalizable intervention to improve adherence. Simpler regimens, including those requiring administration only once daily, have been associated with equivalent or better therapeutic outcomes [35, 36]. Recently, more complete understanding of the pharmacokinetic properties of available NRTIs and the more favorable pharmacological properties of newer agents has made once-daily dosing of selected antiretrovirals possible. Although plasma levels and half-lives of the nucleoside reverse-transcriptase inhibitors (NRTIs) appear too short for once-daily dosing, the intracellular half-lives of these agents—a more important measurement of dosing intervals for this class of drugs—are substantially prolonged. Once-daily dosing is now possible with many antiretroviral drugs, including the NRTIs didanosine, stavudine, lamivudine, abacavir, and emtricitabine and for the nucleotide reverse-transcriptase inhibitor tenofovir. The nonnucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine and the protease inhibitor atazanavir are administered once daily, and low-dose, ritonavir-boosted protease inhibitor regimens (saquinavir, amprenavir, lopinavir, and fosamprenavir) can be given once daily. Potent combinations of these individual agents are now possible to construct—creating a broad therapeutic armamentarium of once-daily regimens. However, the need for use of rifampin-based antituberculosis regimens limits the antiretroviral options because of drug interactions. Nonetheless, once-daily HAART regimens that could be used concomitantly with tuberculosis therapy include efavirenz plus 2-drug combinations of didanosine, lamivudine, emtricitabine, tenofovir, and stavudine in extended-release formulation.

Several examples of successful once-daily regimens of relevance for combined therapy with tuberculosis medications have been reported [37, 38]. In a pilot study among patients with tuberculosis and HIV infection, once-daily HAART has been given with tuberculosis medications in a tuberculosis DOT program [39]. This study has been successfully carried out in a

large urban tuberculosis clinic in Durban, South Africa. Patients who were smear-positive for pulmonary tuberculosis and were receiving tuberculosis treatment were offered HIV testing and counseling. For those found to be coinfecting, a once-daily regimen of 400 mg of didanosine, 300 mg of lamivudine, and 600 mg of efavirenz was provided concomitantly with standard tuberculosis therapy. Tuberculosis and HIV medications were given under observation 5 days per week, and HIV medications were self-administered on weekends. Of the 20 patients, 17 completed combined standard tuberculosis and anti-HIV therapy. With regard to outcomes of anti-HIV therapy, 16 (80%) of 20 patients enrolled and 15 (88%) of 17 completing standard tuberculosis therapy achieved a viral load of <50 copies/mL and mean increase in CD4⁺ cell count of 148 cells/mm³. With regard to tuberculosis outcome, tuberculosis cure was achieved in 17 (89%) of 19 with drug-susceptible tuberculosis. Treatment was well tolerated, with frequent but mild gastrointestinal, hepatic, skin, or transient neurological toxicity. A number of important lessons have emerged from this pilot study that should inform further evaluation and expansion of this strategy. First, with careful preparation, the addition of antiretroviral therapy to the tuberculosis DOT program can be feasible, well-accepted by staff, and integrated into the daily tuberculosis clinic functions. Second, a relatively small investment in additional staff and training is necessary. Third, counseling and testing for HIV infection can be accomplished within a tuberculosis program, and concerns about patient confidentiality can be successfully managed. Finally, it seems clear that the introduction of HAART through an existing tuberculosis DOT program can be safe and effective. These preliminary findings are encouraging and warrant rigorous comparison with existing practices, verification in other settings, and ultimately, with proper attention to the challenges and opportunities that they raise, consideration of more widespread implementation.

CHALLENGES AND OPPORTUNITIES

Treating tuberculosis and HIV disease concomitantly by means of the existing tuberculosis DOTS structure may potentially improve the outcome for each disease. There remain special challenges as well as opportunities in wider implementation of this strategy [40, 41]. These include issues related to program and infrastructure development, patient confidentiality, side effects and toxicities, pharmacological considerations, durability of benefit, and array of operational research questions that require attention and resolution (table 1).

Programmatic and infrastructure issues. To accomplish integration of tuberculosis and HIV/AIDS care and use of HAART in the tuberculosis DOT programs, long-held attitudinal and programmatic practices must be altered, because the current system has been organized around the diagnosis and

Table 1. Challenges and opportunities of integrating directly observed therapy (DOT) for HIV infection into existing tuberculosis DOT programs.

Challenge	Opportunity
System organized around diagnosis and treatment of individual diseases	Integrates care for patient, not individual diseases: "two diseases—one patient"
Requires resources for enhancing and strengthening tuberculosis DOT infrastructure and risks potential disruption and overburdening of programs	Uses existing infrastructure, reducing start-up and overall HIV diagnosis and treatment costs and increases efficiency
May compromise patient confidentiality	Provides convenient and efficient site for identifying HIV-positive patients eligible for HAART
Increases pill burden May increase side effects and toxicities May result in problematic pharmacological interactions between tuberculosis drugs and antiretroviral drugs May increase "paradoxical" immune reconstitution reactions	Provides existing structure: —for promoting HIV adherence —for monitoring for side effects and toxicities —for improving HIV therapeutic outcome
Provides only short-term structured HAART because duration of tuberculosis DOT is limited	Provides initial structured and supervised HAART experience, with assistance for transition to self-administration
May result in increased rates of tuberculosis treatment failure and dropout	May have a positive effect on tuberculosis treatment outcomes, reducing treatment failure and dropout
	May improve survival and delay HIV disease progression

treatment of individual diseases. It is well accepted that strengthening and enhancing existing infrastructure is a more efficient and cost-effective approach than is development of entirely new programs and structures. Tuberculosis programs will require the addition of new resources and personnel, as well as training to accommodate the necessary increased program responsibilities. This will be difficult, but the logic and efficiency of establishing a single program to treat individual patients with several comorbid conditions is compelling and likely to be cost-effective. If the strategy of integration of HAART into tuberculosis DOT programs is to work on a large scale, there will be a need for enhanced development and use of community-based resources as well. Many tuberculosis DOT programs have relied on community-based treatment supporters to assist with administration and supervision of tuberculosis medication. This valuable resource should be extended to include supervision and assistance with administration of HIV medications [33, 34]. Community programs and personnel represent an underutilized infrastructure in many resource-limited countries. Although limited in technical and medical expertise, affected communities often have great personal and cultural strength and support that can be mobilized. For the support of long-term administration of medications, this may be as important as the technical laboratory requirements and medical expertise often cited as necessary for HIV care.

HIV status disclosure and patient confidentiality. Concerns have been raised that the integration of HIV and tuberculosis treatment might create situations in which unanticipated or undesired disclosure of HIV status will occur, with subsequent increased discrimination and stigma. However, if programs are carefully constructed and staff properly trained,

this can be minimized, and the potential benefits should outweigh the dangers. In addition, the availability of treatment is a powerful motivator for acceptance of HIV testing and counseling and may reduce stigma. In the pilot tuberculosis-HIV DOT program mentioned above, HIV testing and counseling was readily accepted, and both tuberculosis and HIV medications were taken in full view of other patients and staff without incident. The use of tuberculosis programs as sites for offering HIV testing and counseling will efficiently identify many who would qualify for and benefit from anti-HIV treatment. It is estimated that >300,000 people with HIV infection are given the diagnosis of tuberculosis each year in Africa alone, and an estimated 400,000 more infected persons are not yet identified or notified by national programs [21]. If these patients were offered HIV testing and counseling, they would likely constitute one of the largest single groups eligible for HAART and provide an opportunity to bring large numbers of coinfecting people into care and HIV treatment.

Overlapping and additive drug toxicities and side effects. The treatment of tuberculosis requires intake of 2–4 medications, and HIV therapy adds an additional 3 medications. Each of these regimens and their constituent drugs may be associated with adverse events. These include gastrointestinal intolerance (associated with isoniazid, rifampin, pyrazinamide, zidovudine, didanosine, and protease inhibitors), hepatitis (associated with isoniazid, rifampin, pyrazinamide, nevirapine, efavirenz, and protease inhibitors), pancreatitis (associated with didanosine), hypersensitivity reactions (associated with isoniazid, rifampin, and abacavir), peripheral neuropathy (associated with isoniazid, didanosine, and stavudine), rash (associated with isoniazid, rifampin, nevirapine, and efavirenz), and neuropsychiatric diffi-

culties (associated with isoniazid and efavirenz). The combination of both regimens may result in additive toxicity and side effects. Some studies suggest that HIV-infected patients have a higher rate of adverse events when treated for tuberculosis, whereas other studies do not support these findings [42]. Retrospective studies suggest high rates of side effects when both tuberculosis and HIV treatment regimens are combined [43]. In the small pilot study of combined tuberculosis and HIV treatment noted above [39], side effects were common, but generally minor, and did not result in interruption of therapy. There is a clear need for prospective and uniform collection of detailed toxicity and side effect data among those receiving separate and concomitant therapy for tuberculosis and HIV infection. The concern about additive side effects and toxicities warrants provider and patient education as well as careful monitoring for toxicity and tolerability but does not, in itself, obviate the potential utility of the combined treatment strategy.

Drug interactions between tuberculosis and antiretroviral therapy. Drug-drug interactions can result in changes in the concentrations of one or both of the drugs involved, with consequent reductions in efficacy or increase in toxicity and side effects. In the case of the antituberculous drugs, the only HAART-induced interaction of concern is the elevation of rifabutin levels as a consequence of inhibition of cytochrome P-450 by ritonavir and other protease inhibitors [15, 16]. In resource-limited countries, rifabutin is rarely used because of expense, and this interaction is not seen with the other rifamycins. Most of the clinically relevant drug-drug interactions involving the antituberculous drugs are due to the effect of the rifamycins (rifampin, rifabutin, and rifapentine) on the metabolism of antiretrovirals [44–46]. The potentially more problematic interactions are those induced by rifampin, the most potent inducer of cytochrome P-450, which is the major pathway of metabolism of both the protease inhibitors and NNRTIs. The NRTIs (zidovudine, didanosine, stavudine, lamivudine, abacavir, and tenofovir) are not metabolized by cytochrome P-450, and drug interactions with rifampin are not expected or reported.

Rifampin can reduce therapeutic levels of protease inhibitors by 80%, and therefore these agents are not recommended for coadministration with rifampin. Exceptions, based on preliminary evidence, indicate that ritonavir alone [47] and the combination boosted by ritonavir [48] provide acceptable therapeutic levels and therapeutic benefit. Data are currently available for this ritonavir-boosted protease inhibitor combination only. It may well be that ritonavir-boosted regimens with other protease inhibitors will provide similar therapeutic coverage. Such studies are essential to perform. Rifampin also induces the metabolism of NNRTIs, reducing levels of efavirenz by 25% [49] and nevirapine by up to 40% [15, 16]. The former remains

recommended for use with rifampin, whereas there is insufficient information available to guide proper use of nevirapine. Opinions differ as to whether efavirenz doses should be routinely increased to 800 mg daily to compensate for the rifampin-induced enhanced metabolism of efavirenz. There is wide interpatient variability in efavirenz levels during coadministration of rifampin [49], and subtherapeutic levels may occur and are associated with treatment failure [50]. However, unexpectedly high levels of efavirenz also occur and are associated with undesirable side effects, such as dizziness and neuropsychiatric symptoms. These occur in a substantial proportion of patients receiving efavirenz [38, 39, 50]. If rifampin and efavirenz are concomitantly administered in the morning, as is the likely scenario in a tuberculosis DOT program, these symptoms could interfere with daily activities and result in decreased adherence to treatment. On the basis of available data [50], weight adjustments of efavirenz might be desirable to both provide therapeutic drug levels and help reduce side effects [47]. Consideration should be given to administering an 800-mg dose to persons who weigh >50 kg and a 600-mg dose to those who weigh <50 kg. Finally, it is likely that efavirenz levels may vary over the course of therapy, because the induction mechanisms of both rifampin and efavirenz change over time. Although these pharmacological issues are of concern, it is important to appreciate that available case series regarding coadministration of rifampin and efavirenz in a standard 600-mg dose note excellent therapeutic outcomes [39, 51, 52]. Resolution of this issue requires careful measurement of efavirenz levels over time in larger numbers of patients receiving both rifampin and efavirenz and relating these results to clinical outcome.

Immune reconstitution reactions. The initiation of antiretroviral therapy during tuberculosis treatment has been linked to the development of a “paradoxical” transient worsening of signs and symptoms of tuberculosis, most likely as a result of immune reconstitution. The frequency of such events varies [53–55]. These reactions occur at a median time from the start of antiretroviral therapy of 22.5 days and are more likely to occur in patients with larger reductions in viral load and higher increases in CD4⁺ cell count [54]. The reactions can complicate clinical assessment and treatment and can be confused with adverse drug reactions or the appearance of other opportunistic diseases. Carefully performed prospective studies with precise case definitions and proper control populations receiving tuberculosis therapy alone are necessary to obtain a better understanding of the frequency, severity, and clinical consequences of this entity.

Concerns about durability of benefit. An obvious difference in tuberculosis and HIV therapy is that the former is time-limited, whereas the latter is likely to be lifelong. The coadministration of HIV and tuberculosis therapy through the existing tuberculosis DOT program, although extending to

completion of tuberculosis treatment, does not directly address the requirement for more long-term administration of anti-retroviral therapy. However, this does not obviate the potential utility of the strategy. This strategy can serve as an entry point for identification of patients eligible for HIV treatment and initiation of therapy and the provision of an initial successful structured experience with antiretrovirals, the benefits of which may extend well into the subsequent period of long-term self-administration.

Additional operational research questions. Many additional questions remain regarding the risks and benefits of the proposed strategy, as well as programmatic and structural configurations needed for its successful implementation. Operational research addressing these is crucial and should be directed toward establishing the effect of the strategy on clinical outcome, including HIV disease progression and mortality; the necessary personnel, dose, duration, and location of DOT; and the needed resources to most efficiently implement such a strategy. These important questions are being addressed in KwaZulu Natal, South Africa, in a series of demonstration projects in urban [39] and rural [56] areas and in a large randomized control trial of concomitant versus sequential tuberculosis and HAART [57]. The related dual epidemics of HIV/AIDS and tuberculosis provide the context to explore and answer these questions and to provide expanded and successful access to HAART in resource-poor countries, potentially benefiting large numbers of people living with both diseases.

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