HIV and Tuberculosis Coinfection: Inextricably Linked Liaison

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In sub-Saharan Africa, human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB) are among the leading causes of morbidity and mortality. Sub-Saharan Africa has seen the woeful failure of World Health Organization (WHO) targets of detecting 70% of the infectious cases of tuberculosis and curing ≥85%. Current treatment of *Mycobacterium tuberculosis* in most resource limited settings is comprised of a four-drug initial antituberculosis regimen for two months, followed by either a two-drug continuation phase of antituberculosis regimen for four months or six months depending on the medications. Many countries in sub-Saharan Africa are scaling up with highly active antiretroviral therapy (HAART), using one of the first-line regimens that consist of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). Our current HAART regimen and antituberculosis drugs continue to give us a therapeutic challenge in terms of adverse effects, drug–drug interactions and immune reconstitution inflammatory syndromes. Scientific research is needed in the areas of diagnosis, treatment and prevention of tuberculosis in sub-Saharan Africa. Such research could be facilitated due to greater availability of funding than a decade ago.

Key words: HIV/AIDS ■ tuberculosis ■ drugs

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GLOBAL HIV AND TUBERCULOSIS COINFECTION

Forty million people are infected with HIV globally, with about 28 million deaths in total. Every year, there are about 5 million new HIV infections and about 3 million deaths. For *Mycobacterium tuberculosis* (TB), there are almost 9 million new cases every year, half of which are infectious, with about 2 million deaths from TB annually.[1] Despite all the efforts, the global TB incidence rate continues to grow at 1% per annum. The Millennium Development Goals set a target of halting the spread and reversing HIV and TB infection rates by 2015. With TB, the goal is to reduce the prevalence and mortality by 50%.

With the prevalence levels of these infections, it is not surprising that there is an overlap. In 2003, Corbett and her colleagues estimated that >60% of TB patients in South Africa have HIV-1 coinfection.[2] For those coinfected people, the annual risk of active TB is 5–15% considerably higher than those who are not infected. Among persons who are dually infected, the risk of active TB increases as the immune deficiency progresses.

HIV AND TB COINFECTION IN SUB-SAHARAN AFRICA

Sub-Saharan Africa, which is home to about 10% of the world population, bears the brunt of the dual epidemic, although HIV infection rates vary widely among the sub-Saharan countries. In 2006, there were about 28 million individuals with HIV/AIDS in this region. Sub-Saharan Africa has both the highest TB incidence rate and the highest annual rate of increase of TB cases in the world.

HIV complicates TB infection and is associated with a more rapid clinical decline. Infection with HIV increases the risk of reactivating latent TB infection, and HIV-infected individuals who acquire new TB infections have high rates of disease progression.[3] However, HIV-positive individuals with TB may be less infectious than HIV-negative individuals with TB because HIV-positive individuals are less smear positive than HIV-negative individuals.[4-7]

TB can also affect HIV infection and is now the most common opportunistic infection in individuals being treated with antiretroviral therapy in the developing world. It may present as the first manifestation of HIV infection. Also, paradoxical reactions from immune reconstitution syndrome continue to pose challenges for clinicians and scientists.

In the more northern part of this region, >30% of TB cases are HIV seropositive. As one moves towards

the southern part of the continent, that prevalence rises to 60–80%. Between 30–40% of deaths in HIV-positive adults in sub-Saharan Africa are due to TB.[8-10] Because few countries with high incidence and prevalence of TB compile reliable statistics on the cause of death, the regional trends in TB deaths are uncertain.

TB Control in Sub-Saharan Africa

In sub-Saharan Africa, TB is often the first manifestation of HIV disease and is the leading cause of death among HIV-infected individuals.[8-11]

TB control in Africa is generally based on the WHO-promoted Directly Observed Therapy Strategy (DOTS) program. The aim of DOTS is to diagnose and immediately provide effective treatment for those with smear-positive TB. However, the HIV pandemic has challenged the DOTS concept as the sole TB control strategy in sub-Saharan Africa. For example, the well-funded South-African gold-mining industry DOTS project continue to experience an increase in the population's HIV prevalence rate.[12]

TB is an aggressive opportunistic infection that can manifest at higher median CD4+ lymphocyte count.[13] Current guidelines for resource-poor settings recommend treatment for individuals with symptomatic HIV or a CD4+ lymphocyte of ≤200/μL.[14] Due to these criteria for starting treatment, many HIV-infected individuals present with TB before antiretroviral therapy is started. A clear definition of the best time to start antiretroviral therapy in individuals with TB awaits results from controlled trials.

The framework of a TB control program must have a clear explicit target. WHO defines targets of 70% case detection in the community and an 85% cure rate of new smear-positive pulmonary TB.[15,16] Despite intensified efforts, these targets are not being met. In the absence of HIV, many African countries believe they might have been able to meet the Millennium Development Goals but, unfortunately, HIV muddles the plan. For example, the country of Malawi with a good DOTS TB control program is negatively impacted by HIV. HIV negatively impacts the TB control program indirectly at the program level and directly at the patient level. In 1999, a survey was conducted among 2,979 healthcare workers from 40 Malawian hospitals.[17] In their findings, Harries and colleagues reported that chronic illness due to AIDS and TB was the most common cause of death.[17] At the end of that year, 60 of the 2,979 healthcare workers died. The authors observed that the high death rates from AIDS and TB will have a crippling toll on the health sector, and effective methods of reducing these deaths need to be put in place. The cumulative effect of staff absences from illness, death and attendance at funerals ultimately cripples the healthcare delivery system, the authors concluded.

At the direct patient effect level, HIV-positive pulmonary TB individuals' presentation depends on the status of the immune system. If the patient's immunity is good, the TB tends to be upper lobe, cavitatory and smear positive. If the immunity is poor, the TB tends to be infiltrative, lymphadenopathic and sputum smears negative.

In resource-limited settings, the diagnosis of smear-negative pulmonary TB is very difficult. The core diagnostic test in the current method of detection is sputum microscopy. According to Perkins and colleagues,[18]

> *Microscopy is an attractive technology for public-health programmes: it requires one piece of equipment, can be used for more than one purpose, provides visual evidence not only for tuberculosis, but of bacterial burden, and in most instances is specific enough that no confirmatory testing is needed.*

They further stated, however, that only tiny amounts of the material are examined even when viewing >100 microscopic fields so bacteria must be present in high concentrations to be visible.[18] The low sensitivity of this test compounds its complexity in the developing world since bacteria must typically be present at ≥10,000 acid-fast bacilli/mm for this particular diagnostic to be useful. Additionally, the interpretation of the test is highly dependent on the training and diligence of the microscopist.[18]

Some of the challenges in diagnosing TB are seen in an audit of diagnostic practice in 37 hospitals in Malawi that was designed to look at a cross-sectional survey of adults receiving treatment for smear-negative pulmonary TB by Harries and colleagues.[19] The recommended diagnostic guidelines were cough >3 weeks, no response to antibiotics, negative sputum smears and a chest radiograph compatible with pulmonary TB. However, it is the chest radiograph that occasionally creates difficulties. If the CD4+ lymphocyte count is good, there will be a typical-looking pulmonary TB chest radiograph. However, in a small percentage of the cases, the chest radiographs can be completely normal and sputum smears are negative, thereby creating a difficult diagnosis challenge for radiologists and clinicians.

Additional challenges present in the correct diagnosis of TB in children and disseminated TB. Pediatric TB is difficult to detect with microscopy in children, a problem that has not been adequately addressed even though TB threatens the lives of millions of infants and children in sub-Saharan Africa.[20]

Some Coinfection Studies

Some studies show a relatively high level of coinfection where as many as 40% of the patients with HIV wasting syndrome have disseminated TB at autopsy.[3,21]

Lewis and colleagues[22] in Malawi found out up to 10% of HIV-positive patients with severe anemia have disseminated TB. The diagnosis was made on the basis

of bone marrow mycobacterium culture, a methodology not typically found in African hospitals.

Among individuals completing TB treatment successfully, there are high rates of recurrent TB in HIV-infected individuals as compared to those who are HIV negative. This is largely due to reinfection with some cases due to reactivation.[23-25]

TB is also the most common opportunistic infection in individuals being treated with antiretroviral therapy in the advance world. Recently, outbreaks of multidrug-resistant and extensively drug-resistant TB have been reported in resource-rich nations with access to modern HIV care.[26]

Increased mortality among HIV-infected individuals with TB coinfection, including those starting antiretroviral therapy, has been reported in sub-Saharan Africa. Martinson and colleagues evaluated the causes of death in 47 HIV-infected adults with TB admitted to two hospitals in Soweto, South Africa.[27] These investigators obtained complete autopsies for the 47 patients who died during hospitalization for HIV and TB coinfection in Soweto. Pulmonary TB was identified as the immediate cause of death in 19 patients and bacterial pneumonia in four. Among 28 patients, disseminated TB was considered a contributory cause of death. This study suggests an urgent need for the availability of methods, materials, equipment and training that will permit earlier diagnosis of both HIV and TB to a much greater degree than currently available in the developing world.

Highly Active Antiretroviral Therapy and TB Treatment

In terms of mortality, HIV and TB have their largest effects in sub-Saharan African countries. Treatment of TB in most sub-Saharan countries comprises a four-drug initial phase of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by a two-drug continuation phase of rifampicin and isoniazid for four months or, alternatively, followed by six months of isoniazid and ethambutol.[28]

HIV-positive individuals with pulmonary TB are classified in WHO clinical stage 3, and HIV-positive individuals with extrapulmonary TB are classified in WHO clinical stage 4. In many countries with adequate resources, highly active antiretroviral therapy (HAART) is started early in TB-infected individuals with advanced HIV disease (CD4 <100 cells/μL) but is deferred until the continuation phase of TB therapy (i.e., after two months) for individuals with CD4 lymphocyte counts of >100 cells/μL.[29]

In sub-Saharan Africa, the question of when to start HAART is still unresolved. However, Badri and colleagues, in their South African study, reported that HAART reduces the risk of TB in individuals with WHO stages 3 or 4 and in those with CD4+ lymphocyte counts of <200 cells/μL.[30] If HAART is started early enough, it should reduce mortality and reduce the recurrent rates of TB. If we have massive coverage, HAART should decrease the incidence and prevalence of TB. In the South African study,[30] the risk of TB for the HIV-positive individuals on HAART was 2.4%, compared to almost 10% for those not on HAART.

As of December 2006, almost 5 million people in sub-Saharan Africa are in need of HAART, and about 1 million were placed on HAART. This is treatment of only 20% of those in need; however, in a relative sense, it represents progress.

The first-line HIV regimen in many African countries consists of two nucleoside reverse transcriptase inhibitors (NRTI)—namely, stavudine and lamivudine; and one non-nucleoside reverse transcriptase inhibitor (NNRTI)—namely, nevirapine. Because there is a generic combination of these products in a fixed-dose tablet available, to be taken twice a day, it is commonly used. Other options at the time of this writing include substitution of zidovudine for stavudine and efavirenz for nevirapine.

Treatment Questions

There are many questions surrounding the use of HAART and anti-TB treatment: Should we treat all HIV-positive TB patients? How do we manage the additive adverse reactions; for example, stavudine and isoniazid causing peripheral neuropathy? What do we do about drug–drug interactions of rifampicin with NNRTIs and with protease inhibitors (PIs)? Should we add/continue trimethoprim-sulfamethoxazole (cotrimoxazole) with antiretroviral therapy? Should we add/continue isoniazid with antiretroviral therapy with the hope of really knocking down the recurrence of TB?

Drug interactions between current HAART and anti-TB medications are a problem. The majorities of the clinically significant drug interactions are pharmacokinetically based,[31] and are due to induction or inhibition of metabolic enzymes in the liver and extrahepatic tissues. The NNRTIs and the PIs are metabolized through the cytochrome P450 (CYP450) enzyme system. Rifampicin induces CYP450, thereby reducing nevirapine serum concentration by 30%.[32] However, Manosuthi and colleagues reported no difference in long-term virological and immunological outcomes in nevirapine-based HAART in HIV/TB-coinfected individuals receiving rifampicin as compared to when nevirapine-based HAART was given to HIV-infected individuals who are not coinfected with TB and did not receive rifampicin.[33] Since nevirapine increases the risk of hepatitis and both nevirapine and rifampicin may be hepatoxic,[34] some clinicians prefer to use efavirenz because the probability of a drug interaction with rifampicin is lower. However, there is an additional problem of efavirenz teratogenicity.

When Should We Start HAART in TB Treatment?

Should we start early in the first two weeks? It is recommended to start when the CD4+ lymphocyte count

is <100 cells/μL.[29] If we do that, we may reduce early death. However, there will be a high bill burden and a rifampicin drug interaction with antiretroviral therapy. Lawn and colleagues evaluated the predictors of outcome among 213 HIV-infected individuals with TB and 675 HIV-infected individuals without TB recently.[35] In a multivariate analysis, a CD4+ lymphocyte count <100 cells/μL and WHO stage-4 disease were the only independent predictors of death. Among the HIV-infected individuals with TB, 70% of them died before HAART were initiated, suggesting again a need to consider initiating HAART earlier in HIV/TB coinfected individuals.

The high death rate in the first two months after infection with TB suggests that antiretroviral therapy should be started as soon as possible.

WHO guidelines[14] suggest that individuals with TB who have CD4+ lymphocyte count <200 cells/mm^3 should initiate HAART 2–8 weeks after starting TB treatment therapy. Those with CD4+ lymphocyte count >200 cells/mm^3 should delay HAART until the initial intensive phase of TB treatment is complete. Additionally, the initiation of HAART during TB treatment can lead to immune reconstitution syndrome in an already sick individual. Immune reconstitution syndrome in HIV-infected individuals is an adverse consequence of the restoration of pathogen-specific immune responses during the initial months of HAART and is generally presented as worsening of the TB symptomatology.[36] The risk is higher if the CD4 lymphocyte count is low, and the most common features are fever, lymphadenopathy, and worsening respiratory signs and symptoms.[36]

Lawn and colleagues looked at a retrospective analysis of detailed data from a study cohort in 160 individuals enrolled over three years within a community-based service in South Africa.[37] HAART was initiated after a median of 105 days from TB diagnosis. Starting HAART earlier after TB treatment was associated with a higher risk of immune reconstitution disease. However, most cases were self-limiting, and hospitalizations and mortality were rare. There is a need for randomized trials to address the optimal timing of antiretroviral therapy initiation in these settings.

How Do We Decrease the Joint Burden of HIV and TB?

An option available to address this issue is to establish mechanisms for collaboration between the respective groups working on HIV and the groups working on TB through an interdisciplinary approach that does the following:

A. Set up coordinating bodies;
B. Conduct surveillance of HIV prevalence in TB patients;
C. Carry out joint TB and HIV planning;
D. Conduct joint monitoring and evaluation.

Strengthening basic TB programs and infection control measures are crucial in decreasing the joint burden of HIV and TB.

How Do We Decrease the TB Burden with People with HIV Disease?

We decrease the burden by intensifying the TB case finding where we are actively looking for cases where HIV/TB often presents as a coinfection. By finding these cases, diagnosing them and quickly treating them, we thereby prevent transmission of infection. This approach works well in the research arena but may not work as well in a routine health system arena in sub-Saharan Africa.

Isoniazid preventative therapy (IPT) in HIV-infected individuals has also been tested and published by few trials.[38,39] In both of these studies, isoniazid for about 12 months in HIV-infected individuals who have completed TB treatment successfully reduced the recurrence of TB by >50%. Unfortunately, feasibility is difficult in most routine treatment situations. There are also concerns about the risk for the development of isoniazid-resistant TB. A recent mathematical model evaluating HIV/TB coepidemics concluded that community-wide IPT will reduce the incidence of TB in the short-term but may also speed the emergence of drug-resistant TB.[40] IPT is hardly implemented anywhere, but there are a few documented exceptions. Additionally, continued monitoring and drug susceptibility testing are necessary to evaluate the long-term effects of IPT.

Trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis for HIV-positive TB individuals in developing countries is also being advocated. Cotrimoxazole is inexpensive, reduces diarrhea, reduces malaria, reduces hospital admissions and also reduces mortality. There have been very good studies in the last five years testifying the above.[41-43] Cotrimoxazole prophylaxis is feasible to implement in HIV-positive TB individuals, and we should be ready to scale up. Unfortunately, despite provisional recommendations from the WHO and UNAIDS that cotrimoxazole prophylaxis be offered to all individuals living with HIV disease, including HIV-positive individuals with TB, routine use of cotrimoxazole prophylaxis in sub-Saharan Africa has been minimal.[44]

Drug-Resistant TB

Multidrug-resistant TB (MDR-TB) is now being transmitted among the HIV-1 seropositive population in sub-Saharan Africa. MDR-TB is resistant to both isoniazid and rifampicin with or without resistance to other drugs. According to Weyer,[45]

> *South Africa faces one of the most devastating TB epidemics in the world with more than 400,000 cases per annum, compounded by a large burden of some 10,000 incident cases of MDR-TB.*

Weyer further stressed that public health concerns have been amplified by the emergence of extensively drug-resistant TB (XDR-TB) in South Africa, where community and nosocomial transmission are occurring.[45] XDR-TB case definition specifies resistance to at least isoniazid and rifampicin among first-line anti-TB drugs, resistance to any fluoroquinolone and resistance to ≥1 second-line injectable drug (amikacin, capreomycin or kanamycin).[46] These XDR-TB strains are associated with exceptionally high mortality in HIV- and TB-co-infected individuals, so further investigation will likely continue in the sub-Saharan African region.

CONCLUSIONS

In areas where people are at risk of coinfection with HIV and TB, there is an urgent need to identify ways to jointly treat these two diseases. HIV infection is a significant impediment to TB control. Our current HAART regimen and anti-TB drugs continue to give us a therapeutic challenge in terms of adverse effects, drug–drug interactions and immune reconstitution inflammatory syndromes. There are also concerns about adherence because of the long duration of treatment and the potential for emergence of drug resistance.

In many African countries, the healthcare systems are in a state of collapse. There is often a large-scale health-related impact on the workforce. Sub-Saharan African countries have a very poor infrastructure and a poor health information system. Also, the financial control system is inadequate, and it is a challenging arena in which to deliver services. Sub-Saharan Africa has seen the woeful failure of the WHO targets of detecting 70% of the infectious cases of TB and curing ≥85%.

More funds are now available as compared to a decade ago, and this could help prioritization of scientific research in the areas of diagnosis, treatment and prevention of TB. We still have some learning in HIV and TB coinfections, especially in the diagnosis of smear-negative TB in adults and children. However, we are also learning quickly how to use HAART with anti-TB medications. To confront these issues, a holistic and interdisciplinary approach is needed at the facility, local and national levels in sub-Saharan African countries.

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