Intensified Case Finding for Tuberculosis in Prevention of Mother-to-Child Transmission Programs: A Simple and Potentially Vital Addition for Maternal and Child Health

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The intersection of HIV and tuberculosis (TB) poses a serious threat to HIV-infected women and their children.[1,2] The majority of patients with TB in sub-Saharan Africa are infected with HIV, and together the overlapping epidemics synergistically accelerate illness and death.[3,4] Escalating case rates, increased mortality, and the recent emergence of extensively drug-resistant TB highlights how catastrophic a once preventable and curable disease has become among people with HIV/AIDS.[5] The HIV epidemic requires new strategies to control TB in high-burden areas[6] especially as women of reproductive age are disproportionately affected by the epidemic. Intensified case finding for TB has the potential to reduce morbidity and mortality for people living with HIV, especially pregnant women, their families, and infants.[7,8]

Women of reproductive age bear a disproportionate burden of TB case notification rates in sub-Saharan Africa relative to their population, and pregnant HIV-infected women who have active TB disease are at higher risk for mortality.[9,10] Khan et al[11] documented a more than 3-fold increase in maternal mortality for mothers with both TB and HIV infection. Among African women in the early reproductive years, case detection rates of sputum smear-positive TB are 1.6–2.4 times higher than in women aged 44 and older (Fig. 1).[10] In 15- to 24-year olds, there is marked gender disparity; women experience TB rates 1.5–2 times higher than men in the same age group in areas of high HIV prevalence (Fig. 2).[10] At all ages, women have a higher prevalence of HIV compared with men in many African and Asian countries[12–14] (Table 1). This disproportionate impact of HIV on women affects maternal mortality rates, a sensitive indicator of women's health; HIV-infected mothers are at 1.5–2 times greater risk of dying during or after pregnancy compared with uninfected women.[17–19]

The impact of TB and HIV on maternal health is dramatic. In Durban, South Africa, Pillay et al[20] assessed the difference between rates of TB and death amongst 50,000 deliveries. Of women who were HIV negative at the time of delivery, the incidence of TB was 72.9 of 100,000 compared with a rate of 774.5 of 100,000 in those HIV seropositive at the time of delivery, a more than 10-fold increased incidence. Another recent study from Pune, India, by Gupta et al[21] showed that 22 of 627 HIV-infected women who had recently delivered developed active TB or 4.6 of 100 postpartum person-years (4600/100,000). The median time for development of active TB postpartum was 3 months.

In addition, women with TB have a high probability of transmitting TB infection to their infants, increasing the risk of child mortality, especially in children who are HIV infected. In the Pune study, TB increased the probability of death 2.2-fold for HIV-infected women and 3.4-fold for their infants compared with HIV-infected women who did not develop TB.[21] Infants born to women with TB face the threat of both vertical and horizontal transmission of TB and higher rates of intrauterine growth retardation, premature birth, and low birth weight.

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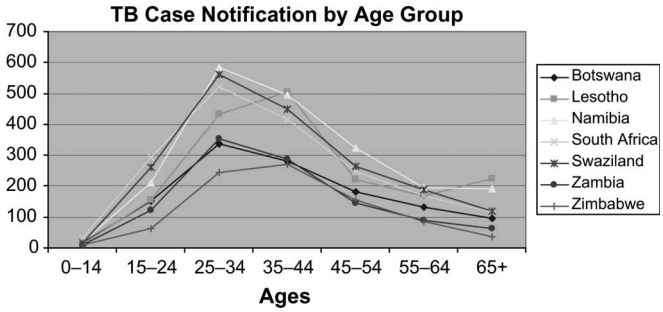

FIGURE 1. Total TB case detection rates among women by age in selected African countries.[10]

TABLE 1. HIV Prevalence, Sex, Fertility, and HIV-Related TB in Selected African Countries[15,16]

	HIV Prevalence in Women ≥15 Years of Age (% of Total)	Total Fertility Rate (Births per Woman)	HIV Prevalence in Incident TB Cases (Men and Women) (%)
Botswana	54	3.2	54
Malawi	59	6.0	70
Mozambique	60	5.5	30
South Africa	58	2.8	44
Swaziland	57	3.9	54
Zimbabwe	59	3.6	43

The trends of infection, morbidity, and mortality attributable to TB in children for the most part follow those of adults but are compounded by the complexity of confirming a diagnosis of TB in infants born to HIV-infected mothers.[22] In a study of 126 children with TB in the Democratic Republic of Congo, 65% had HIV coinfection.[23] Mortality and relapse rates are higher among HIV-infected children who have active TB than in HIV-uninfected children.[24] Anti-TB drugs are not specifically formulated for children, making treatment challenging. A recent review concludes that in most developing countries, there are few TB medications designed for children; using tablets in place of stable syrups increases the potential for inaccurate dosing, resulting in toxicity or the emergence of drug resistance.[25] In a cohort of 213 HIV-infected children from the West Indies (all of whom were on combination antiretroviral therapy), there were 24 cases of culture-confirmed TB. Among this group, 3 of 24 had drug-resistant TB and 20% (5/24) of children died.[26] These data underscore the imperative of finding TB in women of childbearing age as a way to protect their children and prevent mortality.

There is a strong evidence base for screening pregnant HIV-infected women for TB as part of antenatal care. Intensified case finding for TB can reduce morbidity and mortality and prevent transmission of TB in families, the community, and health care settings. Delaying the diagnosis of active TB significantly increases the proportion of infected contacts.[27] By finding existing TB that would otherwise go undetected or only be detected by passive case finding at a later time, spread of TB is interrupted. If the cycle of transmission of TB from adults to children is to be interrupted, those with active TB, particularly parents, need to be detected and treated as early in the course of their illness as possible.

Active, intensified TB case finding is a powerful tool for TB control even without new drugs and diagnostic tests. As documented in a 2005 review, case finding in conjunction with a strong directly observed therapy, short course (DOTS) program has the potential to significantly reduce TB incidence.[27] Active case finding through house-to-house surveys and enhanced case-finding strategies in clinical settings that focus on increasing TB awareness have been demonstrated as effective in diverse settings.

By utilizing existing points of care, such as antenatal, family planning, or immunization clinics, large numbers of women could be opportunistically screened both for HIV and for TB as they receive routine health services, making active TB case finding cost effective and sustainable. Pregnant women are tested for HIV at antenatal clinics with prevention

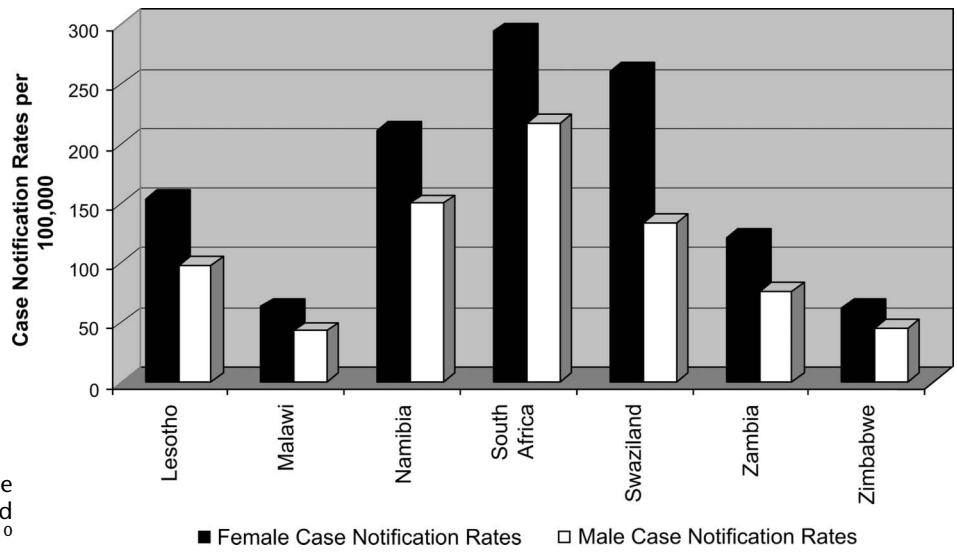

FIGURE 2. New smear-positive case notification rates by gender in selected sub-Saharan African Countries, 2006.[10]

of mother-to-child transmission (PMTCT) programs, and many offer CD4 counts at the time of initial HIV diagnosis to identify women who would benefit from combination antiretroviral therapy rather than single or dual therapy for PMTCT. These programs offer a unique opportunity to evaluate women who are at increased risk of TB.

In 2004, a cross-sectional study was carried out in 2 community antenatal clinics in Soweto, South Africa, a setting of high HIV seroprevalence where 30,000 women receive antenatal voluntary counseling and testing (VCT) each year.[7] In Soweto, more than 97% of pregnant women accept VCT and receive posttest counseling, 31% are HIV seropositive, and 90% of seropositive women are given treatment to prevent mother-to-child transmission of HIV. HIV-infected pregnant women enrolled during their posttest counseling session, and lay counselors screened patients for TB symptoms using a simple questionnaire with symptomatic patients referred to a primary health care nurse. The symptom screen was positive if there was 1 or more major TB symptoms (cough longer than 2 weeks, cough producing sputum, blood in sputum, and night sweats) or 2 or more minor symptoms (shortness of breath, fever, chest pain, weight loss, loss of appetite, or fatigue). Of 370 participants screened, 120 (32%) had symptoms and 8 (2.1%) patients were diagnosed with active TB by sputum culture; all cases were sputum smear negative.[7] As sputum smear is the most common method of diagnosis in South Africa, none of these patients would have been detected if smear was used alone. The TB screening survey—which was performed by lay VCT counselors—added an average of just 3 additional minutes to the VCT session. Early detection of active TB resulted in earlier treatment and prevented exposure to infectious TB in the infants subsequently born to these women. Other studies have documented the benefit of using a symptom screen to diagnose TB, though sensitivity and specificity vary.[28–31]

Another South African study in a group of HIV-infected postpartum women used tuberculin skin tests to screen for TB. Four hundred thirty-eight women were enrolled, 72% returned for a skin test reading, and 49% had reactions $\geq$5 mm.[8] Active TB was found in 11% of those completing screening (3% of the total), including 9 with extrapulmonary TB.

Although there is a wealth of evidence suggesting that screening for active TB during routine antenatal care would be a beneficial intervention, especially in places with efficient PMTCT program, no country programs have implemented this strategy as part of best practices. Finding TB in patients who are the most vulnerable, such as HIV-infected women in reproductive ages, is an urgent priority. Because PMTCT services are widely utilized and promoted, they can serve as an excellent venue to enhance TB screening services in both HIV-infected and HIV-uninfected women.

Operational research on case-finding strategies should be performed to develop best and most cost-effective practices for women, their children, and communities. In addition, serious consideration should be given to prevention of TB in women for whom active TB has been excluded by use of isoniazid preventive therapy (IPT). Guidelines in the United States recommend the use of IPT for HIV-infected pregnant women.[32] Few if any PMTCT programs in developing settings offer IPT.

A research agenda for TB screening and prevention in antenatal settings must include studying alternative PMTCT regimens for pregnant women on TB treatment, examining the sensitivity and specificity of symptom-based screening for early TB, active case finding at every pretest counseling session and early antenatal visit, and IPT for pregnant women with latent TB infection. Although the reality of the existing situation must be taken in to consideration—including low coverage of PMTCT services focused on preventing transmission of HIV and the limits of antenatal clinics—targeted TB interventions should be incorporated into comprehensive women's health services.

REFERENCES

1. Mashego M, Johnson D, Frohlich J, et al. High AIDS-related mortality among young women in rural KwaZulu-Natal. *S Afr Med J*. 2007;97:587–592.
2. Mofenson L, Laughon B. Human immunodeficiency virus, *Mycobacterium Tuberculosis*, and pregnancy: a deadly combination. *Clin Infect Dis*. 2007;45:250–253.
3. Corbett EL, Marston B, Churchyard GJ, et al. Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. *Lancet*. 2006;267:926–937.
4. Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. *Trop Med Int Health*. 2005;10:734–742.
5. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients coinfected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368:1575–1580.
6. De Cock KM, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int J Tuberc Lung Dis*. 1999;3:457–465.
7. Kail PB, Gray GE, Violari A, et al. Combining PMTCT with active case finding for tuberculosis. *J Acquir Immune Defic Syndr*. 2006;42:379–381.
8. Nachega J, Coetzee J, Adendorff T, et al. Tuberculosis active case-finding in a mother-to-child transmission prevention programme in Soweto, South Africa. *AIDS*. 2003;17:1398–1400.
9. Pillay T, Khan M, Moodley J, et al. Perinatal tuberculosis and HIV-1: considerations for resource-limited settings. *Lancet Infect Dis*. 2004;4:155–159.
10. World Health Organization. *Global Tuberculosis Control*: Surveillance, planning, financing. WHO Report. 2008. Geneva, World Health Organization, WHO/HTM/2008. 393. Available at: http://www.who.int/tb/publications/global_report/2008/pdf/annex3_afr.pdf. Accessed April 11, 2008.
11. Khan M, Pillay T, Moodley JM, et al, and Durban Perinatal TB HIV-1 Study Group. Maternal mortality associated with tuberculosis-HIV-1 co-infection in Durban, South Africa. *AIDS*. 2001;15:1857–1863.
12. National Institute on Allergy and Infectious Diseases. Fact Sheet: HIV infection in women. Available at: http://www.niaid.nih.gov/factsheets/womenhiv.htm. Accessed December 8, 2006.
13. Auvert B, Buve A, Ferry B, et al. Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. *AIDS*. 2001;15:S15–S30.
14. Espinaoza L, Hall I, Hardnett F, et al. Characteristics of persons with heterosexually acquired HIV infection, United States 1999–2004. *Am J Public Health*. 2007;97:144–149.
15. Joint United Nations Programme on HIV/AIDS, World Health Organization. AIDS Epidemic Update, December 2006. Geneva. UNAIDS/06.29E. Available at: http://www.who.int/hiv/mediacentre/2006_GR_ANN1A-L_en.pdf. Accessed November 26, 2008.
16. United Nations Development Reports. *World Population Prospects 1950–2050: The 2006 Revision. Database*. New York, NY: Department of Economic and Social Affairs, Population Division; 2007. Available at: http://hdrstats.undp.org/indicators/48.html. Accessed May 23, 2008.
17. Hill K, Thomas K, AbouZahr C, et al. Estimates of maternal mortality worldwide between 1990 and 2005: an assessment of available data. *Lancet*. 2007;370:1311–1319.

18. McIntyre J. Maternal health and HIV. *Reprod Health Matters*. 2005;13:129–135.
19. Mataka E. Maternal health and HIV: bridging the gap. *Lancet*. 2007;370:1290–1291.
20. Pillay T, Khan M, Moodley J, et al. The increasing burden of tuberculosis in pregnant women, newborns, and infants under 6 months of age in Durban, KwaZulu-Natal. *S Afr Med J*. 2001;91:983–987.
21. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002–2005. *Clin Infect Dis*. 2007;45:241–249.
22. Edwards DJ, Kitetele F, Van Rie A. Agreement between clinical scoring systems used for the diagnosis of pediatric tuberculosis in the HIV era. *Int J Tuberc Lung Dis*. 2007;11:263–269.
23. M'Pemba Loufoua Lemay AB, Mabiala Babela JR, Bantsimba T, et al. Tuberculosis and HIV/AIDS co-infection in children: experience carried out in a paediatric service of the teaching hospital of Brazzaville, Republic of Congo (1995–2004). *Bull Soc Pathol Exot*. 2007;100:51–52.
24. Marais BJ, Graham SM, Cotton MF, et al. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. *J Infect Dis*. 2007;196:S76–S85.
25. Chintu C. Tuberculosis and human immunodeficiency virus co-infection in children: management challenges. *Paediatr Respir Rev*. 2007;8:142–147.
26. Kumar A, Upadhyay S, Kumari G. Clinical presentation, treatment outcome and survival among the HIV infected children with culture confirmed tuberculosis. *Curr HIV Res*. 2007;5:299–504.
27. Golub J, Mohan CI, Comstock GW, et al. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis*. 2005;9:1183–1203.
28. Kruk A, Gie RP, Schaaf HS, et al. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. *Pediatrics*. 2008;121:e1646–e1652.
29. Day JH, Charalambous S, Fielding KL, et al. Screening for tuberculosis prior to isoniazid preventive therapy among HIV-infected gold miners in South Africa. *Int J Tuberc Lung Dis*. 2006;10:523–529.
30. Kimerling ME, Schuchter J, Chanthol E, et al. Prevalence of pulmonary tuberculosis among HIV-infected persons in a home care program in Phnom Penh, Cambodia. *Int J Tuberc Lung Dis*. 2002;6:988–994.
31. Mohammed A, Ehrlich R, Wood R, et al. Screening for tuberculosis in adults with advanced HIV infection prior to preventive therapy. *Int J Lung Dis*. 2004;8:792–795.
32. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. ATS/CDC statement committee on latent tuberculosis infection, June 2000. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm. Accessed July 11, 2008.

