



FORUM

Tuberculosis prevention in HIV-infected pregnant women in South Africa

C E Martin, V Black

WITS Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg

C E Martin, MB ChB, Dip HIV Man, DTM&H

V Black, BSc, MB ChB, Dip HIV Man, DTM&H

Corresponding author: C E Martin (cmartin@wrhi.ac.za)

The high burden of HIV and tuberculosis (TB) among pregnant women in South Africa contributes to a high maternal mortality rate. Isoniazid preventive therapy (IPT) is recommended for the prevention of active TB in HIV-infected individuals, including pregnant women. However, there are few data regarding IPT use in the latter, with concern regarding the concurrent use of IPT with nevirapine in pregnancy, as both treatments are hepatotoxic. The benefit and safety of IPT in HIV-infected pregnant women has not been established. We recommend a simplification of HIV and TB interventions by providing triple antiretroviral therapy to all HIV-infected pregnant women.

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Maternal deaths in South Africa (SA) continue to rise, despite the target of the fifth Millennium Development Goal (MDG) of a 75% reduction in maternal mortality by 2015. This target cannot be addressed without an appreciation of the effect of HIV and tuberculosis (TB) on maternal mortality in the country: the antenatal HIV sero-prevalence stands at 29.4%,¹ and HIV is the most common contributory condition to maternal mortality.² A number of studies have confirmed the contribution of HIV in maternal mortality and morbidity.³⁻⁵

The prevalence of TB in HIV-infected pregnant women in SA is similar to that of the general population: approximately 795/100 000.⁶ In 2009, the prevalence of active TB in HIV-infected women attending antenatal care in Soweto, Gauteng Province, was found to be 688/100 000; higher than the prevalence in HIV-uninfected women (201/100 000).⁷ These findings were comparable with data from Durban, KwaZulu-Natal, where prevalence rates of active TB between 1996 and 1998 were 774/100 000 HIV-infected pregnant women; 10 times higher than the prevalence for HIV-uninfected pregnant women.⁸

It is well established that TB and HIV are closely linked. An estimated 70% of adults presenting with new cases of TB in SA are co-infected with HIV, with TB being the most common cause of morbidity and mortality in HIV-infected individuals.⁹ TB is a leading cause of maternal mortality and morbidity, causing 15% of all maternal mortality in high HIV prevalence settings, and 15 - 34% of indirect obstetric maternal mortality.¹⁰ In SA between 2008 and 2010, TB accounted for 27% of deaths in women who died of AIDS-related complications during pregnancy, childbirth or the puerperium.² The findings of a study in Durban revealed a 3-fold higher maternal mortality ratio (MMR) among HIV-infected women with TB (12 170/100 000 live births) compared with TB-infected HIV-

uninfected women (3 850/100 000 live births) in the absence of antiretroviral therapy (ART).¹¹ Of the women diagnosed with TB, 79% were co-infected with HIV.¹¹ Similarly high MMRs in TB/HIV-co-infected women have been observed in a number of studies in sub-Saharan Africa.^{4,12-14}

The challenge of TB diagnosis in HIV-infected pregnant women

Although diagnostic approaches to TB are similar for HIV-infected pregnant women as they are for HIV-uninfected and non-pregnant women, there are major challenges to the diagnosis of TB in the former. The symptoms of TB may be non-specific in pregnancy, or even absent, mimicking physiological changes. Weight loss associated with TB disease may be masked by normal weight gain in pregnancy.¹⁵ The disease may only present post delivery in either the mother or infant.¹⁶ Furthermore, clinical signs of HIV may overlap with those of TB and there may be a wide differential diagnosis.¹⁶ HIV-infected adults may also have a high prevalence of subclinical TB disease,¹⁷ with HIV-infected pregnant women also less likely to be sputum acid-fast bacilli smear-positive than HIV-uninfected pregnant women with TB disease.^{7,18} Barriers to accessing care may contribute further to the under-diagnosis of TB in these women.⁷

TB prevention strategies in the context of HIV

TB prevention, diagnosis and treatment in HIV-infected pregnant women should be integrated into routine maternal healthcare services. Key strategies adopted by the World Health Organization (WHO) to decrease the effect of TB on people living with HIV include the 3 I's: intensified TB case finding,

isoniazid preventative therapy (IPT); and infection control for TB.¹⁹

It has been established that the use of IPT reduces the risk of active TB in HIV-infected individuals. However, this is more pronounced in those with a positive tuberculin skin test (TST).^{20,21} The most recent meta-analysis of the treatment of latent TB infection (LTBI) in HIV-infected individuals encompassed 12 trials and 8 578 HIV-infected participants.²⁰ Overall, the treatment of LTBI reduced the risk of active TB by 32% (risk ratio (RR) 0.68; 95% confidence interval (CI) 0.54 - 0.85). This benefit was stronger in TST-positive individuals (RR 0.38; 95% CI 0.25 - 0.57) than in TST-negative individuals (RR 0.89; 95% CI 0.64 - 1.24). Isoniazid (INH) monotherapy was found to reduce mortality only in those who were TST-positive. However, overall, there was no evidence that preventive therapy reduced all-cause mortality.²⁰ A randomised controlled trial (RCT) of 6- v. 36-month IPT for TB in HIV-infected adults in Botswana also found a benefit of IPT in TST-positive individuals, but no benefit for those who were TST-negative.²¹

The use of ART in HIV-infected adults also reduces the incidence of TB. In a meta-analysis of 9 observational cohort studies, a 67% reduction in TB incidence across a range of CD4 cell counts and WHO disease stages was reported.²² TB risk reductions with ART occur irrespective of TST reactions.^{22,23} Although the greatest absolute risk reduction of TB is observed in individuals with the most advanced immunodeficiency at baseline,²² patients starting ART earlier, at higher CD4 cell counts, have a 2-fold lower risk of TB compared with those initiating ART at lower CD4 cell counts.^{23,24} HIV-infected individuals starting ART with low CD4 cell counts remain at high risk of TB until CD4 cell count recovery has occurred.²³

Studies have suggested that there may be additional benefit to concurrent IPT and ART.^{21,25,26} In a recent RCT in Khayelitsha, a 37% reduction in the risk of TB was evident in individuals receiving IPT and ART compared with patients receiving ART only (RR 0.63; 95% CI 0.41 - 0.94). However, the risk of stopping INH or placebo due to grade 3 or 4 elevation of alanine transaminase (ALT) was twice as high in the patients receiving IPT compared with those receiving placebo and, overall, there was no evidence of mortality benefit.²⁷ The effect of timing of IPT v. ART initiation has not been determined. Experts recommend not initiating IPT at the same

time as ART, but rather delaying initiation until stabilisation on ART, at approximately 3 months.^{22,28}

The safety of IPT in pregnant women

Current national and international guidelines recommend the use of IPT for 6 months for all HIV-infected adults asymptomatic for TB, including pregnant women.^{9,29} WHO advises that, although not a requirement for IPT initiation in HIV-infected individuals, TSTs may identify those who would benefit most from IPT. The American Thoracic Society (ATS) recommends a TST for the diagnosis of LTBI in pregnant women with a specific risk factor for LTBI or who are at risk for progression to TB disease. This includes women who are HIV-infected or who have a recent TB case contact. Although ATS acknowledge that treatment for LTBI in pregnancy is controversial, they do recommend such treatment for cases of recent TB or HIV infection where there is an increased risk of haematogenous spread of organisms to the placenta, as well as in situations with a high risk of progression of LTBI to disease.³⁰ Guidelines do indicate that IPT can be administered during pregnancy, but it is unclear when and if IPT should be given if the pregnant woman is receiving ART.

There is little evidence available on IPT use in HIV-uninfected pregnant women in general. Furthermore, to our knowledge, there is no evidence available of the effectiveness of IPT in reducing TB risk in HIV-infected pregnant women.

In a study which modelled the cost-effectiveness and outcomes of different treatment strategies for LTBI in pregnancy, antepartum IPT was anticipated to result in the fewest cases of TB and be more cost-effective than no treatment or delaying treatment until postpartum.³¹ Ante- and postpartum IPT was predicted to be less costly and result in a higher life expectancy than no treatment, despite a higher mortality rate due to hepatitis in the antepartum group.³¹ However, HIV infection and the use of ART were not taken into account.

INH is not teratogenic, even if given during the first trimester,³² but it has a number of known adverse effects which include neurological toxicity, skin rash and hepatotoxicity. Reported rates of INH-associated clinical and biochemical hepatitis range from 0% to 5%.²⁸ In a systematic review of the risk of age-related hepatotoxicity in LTBI

treatment, a median hepatotoxicity rate of 1.8% was reported. Studies with close monitoring of hepatotoxicity reported lower rates of hepatotoxicity than those without monitoring. In studies with available information, there was only one reported case of hospitalisation and no reported cases of mortality.³³ A comparison of treatment with rifampicin for 4 months v. INH for 9 months found rates of hepatotoxicity of 1.4 - 5.2% in the latter.³⁴

Although it is not conclusive whether the side-effects of INH are worsened by pregnancy, 2 studies have suggested that pregnant or postpartum women may be at higher risk of hepatotoxicity.³⁰ Pyridoxine supplementation is recommended in HIV-infected and pregnant individuals taking INH to prevent neurological toxicity.³⁰

The rate of INH-associated hepatitis in HIV-infected individuals appears to be similar to that of the general population.³⁵ In a Brazilian study of HIV-infected patients receiving IPT (with or without ART), 1.2% of participants had adverse reactions leading to discontinuation of IPT.³⁶ In a study of 1 762 HIV-infected individuals receiving IPT in Botswana, 1.1% developed hepatitis, and one death was reported.²⁸ In Khayelitsha, a hepatitis risk of 2.9% was reported in patients receiving IPT and ART.²⁷

Some antiretroviral drugs are known to be associated with significant adverse effects, including hepatotoxicity. A 4.4% prevalence of grade 3 - 4 hepatotoxicity and 7% prevalence of grade 1 - 2 hepatotoxicity have been associated with nevirapine (NVP) use in HIV-infected pregnant women. The rate of NVP side-effects is higher in women with CD4 counts >250 cells/mm³.³⁷ NVP is part of the first-line regimens used to treat HIV-infected pregnant women with CD4 counts ≤350 cells/mm³ or WHO clinical stage 3 or 4 conditions in SA.

Increased rates of INH-associated hepatitis have been reported in patients receiving NVP-containing ART regimens compared with those receiving efavirenz (EFV)-containing regimens. In a previous study, the use of ART by 480 patients was not associated with INH-hepatitis, although those receiving NVP had a higher rate of hepatitis (2%) than those receiving EFV (0.9%). Interestingly, a CD4 cell count <200 cells/mm³ was associated with INH hepatitis (RR 2.80; 95% CI 1.13 - 6.84).²⁸

Conclusion

There is a high burden of HIV and TB among pregnant women in SA, contributing to a high

MMR. Despite ART availability in the country, the recent maternal mortality survey showed that the majority of women who died from HIV did not access ART. If we are to progress towards the MDG targets, interventions need to be safe, easy to implement and simplified to maximise early nurse initiation of ART. IPT initiation after ART in pregnancy adds additional steps to antenatal care, which is currently under-resourced. This may further burden the programme and compromise other areas of care, for a benefit apparently limited to TST-positive individuals and that, to date, has no evidence of efficacy in pregnancy.

Screening all pregnant women for TB and HIV is imperative. Those with TB disease should be treated accordingly, with contact tracing and screening of household contacts. Although not currently stipulated in guidelines, all HIV-infected pregnant women should be considered for initiation onto combination ART. With this approach, IPT initiation may be better deferred until the postpartum period. Triple ART for all HIV-infected pregnant women will reduce mother-to-child HIV transmission, adverse pregnancy outcomes, maternal mortality, horizontal transmission to uninfected partners and, specifically, the incidence of TB disease.

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