Perinatal tuberculosis and HIV-1: considerations for resource-limited settings

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Tuberculosis is the commonest HIV-1-related disease and the most frequent cause of mortality in young women in endemic regions. Tuberculosis and HIV-1 are independent risk factors for maternal mortality and adverse perinatal outcomes, and in combination have a greater impact on these parameters than their individual effects. In referral health centres in southern Africa around one-sixth of all maternal deaths are due to tuberculosis/HIV-1 coinfection. One-third (37%) of HIV-1-infected mothers with tuberculosis are severely immunocompromised, with CD4 counts of fewer than 200 cells/μL compared with 14–19% in mothers recruited into major mother-to-child intervention trials in Europe. Babies born to mothers with tuberculosis/HIV-1 also have higher rates of prematurity, low birthweight, and intrauterine growth restriction. Transmission rates of HIV-1 from mother to infant are around 25–45% in resource-limited settings, while that for mother-to-child-transmission of tuberculosis is 15% within 3 weeks of birth. We highlight this emergent problem, and discuss the dilemmas associated with diagnosis and management of pregnant HIV-1-infected mothers with tuberculosis, and their newborn babies.

Globally, tuberculosis has increased over the past two decades, with the largest burden of disease borne by impoverished communities in Africa and Asia.[1–5] Although factors such as a deterioration in socioeconomic conditions, within-country and cross-border conflicts and migrations, poorly functioning national tuberculosis-control programmes, and multidrug resistance have to varying extents contributed to the resurgence of tuberculosis, the main driving force has been the pandemic of HIV-1 infection.[1,6]

In developing countries there is considerable overlap in the age periods during which tuberculosis and HIV are most prevalent. Tuberculosis has been a leading cause of morbidity and mortality in women in their childbearing prime.[7,8] This period is also the peak age during which women are infected with HIV-1. Much of the recent increase in tuberculosis has been associated with the increase in HIV-1 coinfection.[1] Consequently, tuberculosis is the commonest HIV-1-related illness and cause of mortality in young women in these regions.[1,9]

HIV-1 infection and tuberculosis are independent risk factors for maternal mortality (deaths within 1 year of parturition, according to the World Health Organization). For example, 3–4%[10] of HIV-1-infected mothers die within 1 year of delivery in sub-Saharan Africa. Reports of maternal mortality associated with tuberculosis are limited, but in regions with high maternal death rates such as India, less than 6% of maternal mortality (grouped with other associated causes of death such as meningitis) was due to tuberculosis in the pre HIV-1 era.[11] In the early 1990s in Mexico, 6·6% of mothers with tuberculosis in pregnancy died (one death in 15 mothers studied).[12] In combination, the effects of tuberculosis and HIV-1 seem to be accentuated. Tuberculosis/HIV-1-associated deaths have accounted for 14–15%[13,14] of maternal mortality in teaching hospitals in southern Africa. In dually endemic regions this fact is gradually being appreciated by health professionals[13–19] along with its effect on the exposed fetus and neonate, including the perinatal transmission of tuberculosis from mother to newborn.[20–22] Dual disease does seem to be associated with adverse pregnancy outcomes (table 1), but it is not clear whether pregnancy itself exaggerates this dual disease, thereby producing a mutually reinforcing negative effect on maternal health. This review presents the important clinical and management issues, and draws attention to the dilemmas associated with the care of mothers and their newborn babies who are exposed to and/or infected with tuberculosis and HIV-1. In this review and in general, infection refers to acquisition of *Mycobacterium tuberculosis* without clinical signs and symptoms of disease—ie, latent—whereas active tuberculosis refers to the manifestation with signs and symptoms of tuberculosis, with supporting microbiological and/or radiological evidence. In areas of high tuberculosis endemicity infection with *M tuberculosis* occurs early and widely.

Clinical features in mothers

Pregnancy can mask the clinical manifestations of tuberculosis; women may be symptom-free,[37] have limited symptoms including cough, fever, and fatigue, or severe symptoms such as haemoptysis and weight loss.[29,38–40] As in the non-pregnant adult,[41] pulmonary tuberculosis is by far the commonest detected form of the disease; changes

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Table 1. Selected outcomes of infected pregnant women in developing countries with tuberculosis and/or HIV-1

Outcome	Tuberculosis only	Tuberculosis and HIV-1	HIV-1 infection
Maternal mortality	0% of maternal mortalities due to tuberculosis in pre HIV-1 era in Zambia[13] Less than 6% of all maternal mortality in India[11] 6·6% case fatality rate in Mexico[12] 3·9% case fatality rate in Durban[14]	36/251 (14%) maternal deaths, Zambia, 1996–97[13] 14·9% of maternal deaths in Durban, with case fatality rate of 12·2%[14] Increase in indirect deaths due to tuberculosis, pneumonia, and meningitis in Zimbabwe[15] 4/73 (5·4%) in Malawi 1990[27]	3–4% in rural Malawi[23] 0·5% within 8 weeks of birth[24] 0·9–5·6% 2-year mortality[25,26]
Maternal CD4 <200 cells/μL	0% (0/19)[28]*	36·5% (23/63)[29]	13·9–18·6%[24] 12·3%[25]
Perinatal death	0·0[28]–10·1%[30]	8·5% (8/82)[28]	1·7[24]†–3·9% (47/1196)[31]
Prematurity	14·3[32]–50%[28]	45·7%[28]	9·6[26]–18·1% (738/4067)[31]
Low birthweight <2·5 kg	34·2[30]–53%[28]	60·4%[28]	11·1[33]–20·5%[31]
Mean birthweight (kg)	2·4[28]–2·85 kg[32]‡	2·3 kg[28]	3·1–3·2;[24] 2·7–2·9[31]
SGA	20·2[30]–50%[28]	67·9%[28]	11·5%[33]
Detectable transfer of *Mycobacterium tuberculosis*	20·0% (5/25)[28]	13·4% (11/82)[28]	
Overall vertical transmission of HIV-1	··	40·2%[35]	15–45%[36]

*Study of 107 mothers with tuberculosis during pregnancy in Durban, of whom 82 were HIV-1 coinfected. †4 stillbirths, 7 neonatal deaths. ‡Study of 35 (1 HIV-1 coinfected) mothers with tuberculosis disease during pregnancy in Mexico, 1990–1998. SGA=small for gestational age.

include bronchopneumonia, cavitation, bronchiectasis, and interstitial pneumonitis. Extrapulmonary tuberculosis occurs in 5–10% of pregnant women who are not infected with HIV but who have tuberculosis.[42] It is more common in adults who are HIV-1 infected than those who are not;[43] data in HIV-1-coinfected pregnant women is limited, although early evidence suggests that these women also have more extrapulmonary disease.[28] In a study of 82 HIV-1-infected pregnant women and 25 HIV-1-uninfected women with tuberculosis from South Africa, pleural effusions were more common in HIV-infected mothers (27 *vs* 3, p=0·05) as was generalised lymphadenopathy (13 *vs* 0, p=0·04), although the last clinical sign may have been due to HIV-1 or other related causes. But tuberculosis is notoriously difficult to identify in routine antenatal care services and therefore these findings are to some degree dependent on the intensity of the investigations undertaken. In resource-limited settings investigations of tuberculosis among pregnant women are often incomplete or absent. For example, maternal tuberculosis of the hip was undiagnosed in an HIV-1-infected mother until her newborn baby manifested with disseminated tuberculosis.[44] In a review of 26 cases of congenital tuberculosis,[45] 15 (57·7%) cases of disease in the mother only became apparent after diagnosis in the infant.

In HIV-1 coinfected pregnant women, the gestational stage at presentation with tuberculosis, the proportion who are sputum smear-positive, and the fraction with multidrug resistant tuberculosis (MDR-TB), do not seem to differ from tuberculosis in HIV-uninfected pregnant women.[28] Clearance rates of tubercle bacilli from sputum-positive HIV-1-infected pregnant women treated for tuberculosis are not known. In non-pregnant HIV-1-infected women, these rates may be similar to those in HIV-uninfected adults. No substantial antenatal differences emerge between pregnant women who have combined tuberculosis and HIV-1 and those who have tuberculosis alone; however, much maternal and perinatal adversity accompanies the dually affected pregnancies.

Pregnancy outcomes
Maternal mortality
With HIV-1 coinfection, increasing maternal deaths associated with tuberculosis have been reported from endemic areas. In Lusaka, Zambia, tuberculosis-associated deaths in pregnancy increased from 0% in the 1970s to 14% (36/251) by 1997. 92% of this escalation was HIV-1 associated.[13] More importantly, increased maternal mortality due to tuberculosis has been documented in some of the 22 highest-burdened countries responsible for 80% of the global tuberculosis incidence.[46] In a South African study,[14] tuberculosis was the third leading disease (14·9%) associated with maternal mortality after sepsis (34%) and hypertensive disorders of pregnancy (25%); in Zimbabwe[15] a steady increase in maternal mortality from 1988 was coupled with, among other causes, a significant increase in indirect deaths due to maternal tuberculosis. In these highly endemic southern African environments it remains uncertain whether the deaths are the result of the added biological and metabolic costs of pregnancy, indicate the rates of death for HIV-1/tuberculosis independent of pregnancy, or indicate the sociomedical burden of pregnancy (such as access to antenatal services, availability of appropriate care during pregnancy, and health-professional-attended deliveries).

Obstetric outcomes
Early data did not show a striking effect of tuberculosis on the type of delivery or course of the pregnancy.[38,42] More recently, different obstetric outcomes based on the site of the

extrapulmonary disease in HIV-uninfected women have been described. In a study of 33 pregnant women with extrapulmonary tuberculosis disease in India, those without lymph-node involvement (21/33: intestinal tuberculosis 9, skeletal tuberculosis 7, renal tuberculosis 2, meningeal tuberculosis 2, endometrial tuberculosis 1) had higher rates of antenatal hospitalisation[34] when compared with 132 healthy pregnant women from the same region. This study did not compare outcomes between women in whom pulmonary tuberculosis was principally detected and those with extrapulmonary tuberculosis. Such comparative data for tuberculosis/HIV-1-infected pregnancies are not recorded.

Perinatal outcomes

Earlier reports suggested either no effect of maternal tuberculosis on neonatal and fetal outcome, or an increase in fetal deaths, prematurity, and congenital malformations.[38,29] More recent studies have documented significant differences in neonatal outcomes of women with tuberculosis during pregnancy compared with women with no obvious disease during pregnancy. In a study of 35 consecutive pregnancies complicated by tuberculosis in Mexico,[32] babies were significantly smaller than babies from 105 apparently healthy pregnancies (2·8 vs 3·1 kg, p=0·03). These diseased women had a relative risk (RR) of 2·1 (95% CI 1–4·3) for having a premature baby, and RR of 3·1 (95% CI 1·6–6) for perinatal death when compared with the control group. These adverse perinatal outcomes were more pronounced in those with advanced pulmonary lesions where treatment was either incomplete or delayed into late pregnancy.[47] Only one of these 35 diseased women was HIV-1 coinfected. In India[30] 79 perinatal outcomes of women with tuberculosis in pregnancy were compared with 316 apparently healthy pregnant women matched for age, parity, and socioeconomic status. Acute fetal distress (15·2% vs 6·3%, p<0·01), prematurity (22·8% vs 11·1%, p<0·01), small for gestational age (20·2% vs 7·9%, p<0·005), low birthweight (34·2% vs 16·5%, p<0·001), and perinatal deaths (10·1% vs 6·4%, p<0·001) were significantly more common in babies born to women with tuberculosis. Whether these events occurred in HIV-1-infected or uninfected pregnant women is not clear. Where the mother had extrapulmonary tuberculosis disease, the risks of delivering a baby with low Apgars scores(<6/10) and low birthweight (<2·5 kg) were also higher than for the mother with a presumed healthy pregnancy in India.[34]

On its own, pregnancies in HIV-1-infected women are also more likely to result in low-birthweight premature babies,[31] especially in those women with advanced HIV-1,[48] but the combined effect of tuberculosis and HIV-1 on perinatal outcome has not been widely described. In the same South African clinical study described above, seven perinatal deaths occurred in mothers with dual disease and none in those with tuberculosis alone. This perinatal mortality rate was 1·6-fold higher than that for the hospital and region. The neonates were also significantly smaller than the general births at this tertiary hospital (birthweight

rate <2·5 kg for the hospital was 21·8%, compared with a low birthweight rate of 49% for pregnancies complicated by tuberculosis disease; p=<0·01; OR 4·8, 95%, CI 3·2–7·0).[28] Although the exact contribution of each disease to this process is difficult to establish, the mean birthweight (2·3 kg vs 2·4 kg), mean gestational age (36 vs 37 weeks), and growth-restriction rates (68% vs 50%) were similarly negatively affected between mothers who had tuberculosis with HIV-1 coinfection, and those with tuberculosis alone. This finding suggests that the net negative effect on perinatal health is affected by maternal tuberculosis. But confounding this finding, babies born to dually diseased mothers were more likely to have CD4 suppression than their counterparts who were exposed to maternal tuberculosis but not HIV-1. This outcome was most likely due to HIV-1 infection. In brief, the very limited data suggest a dual effect of maternal HIV-1 and tuberculosis on perinatal health.

Vertical transmission of tuberculosis and/or HIV-1

Perinatal transmission of Mycobacterium tuberculosis

Little is known about the epidemiology of perinatal exposure of the fetus and newborn to tubercle bacilli, since both are difficult to establish quantitatively.[49] Assuming that the mother is the source of infection for congenitally or perinatally acquired tuberculosis in the newborn, the materno-fetal model provides a tight window for quantifying the dynamics of exposure, infection, and disease. The greatest limitation to this quantification is the lack of a gold standard for diagnosis of neonatal infection (as opposed to disease). Hence, while the risks for conversion from infection to disease are highest in the 1st year of life, the exact risks of transfer of infection from mother to baby are poorly defined. Tuberculin skin testing is unreliable in the newborn period; recently described cellular assays[50] have not yet been validated as a diagnostic tool for wild-type infection in newborn babies at high risk, and microscopy and culture of M $tuberculosis$ is dependent on appropriate sampling of the sites involved. In perinatal tuberculosis these sites are often hard to access. Although microbiological methods are the most robust, they always provide an underestimate of perinatal infection rates.

Of the 107 mothers with tuberculosis during pregnancy studied in South Africa, mother-to-child transmission of tuberculosis bacilli was detected in 15% of neonates sampled within the first 3 weeks of life (in the 1st week where maternal tuberculosis was diagnosed antenatally and by the 3rd week where maternal tuberculosis was diagnosed in the immediate postpartum period).[28] This transfer of M $tuberculosis$ correlated with untreated tuberculosis (late diagnosis). Maternal CD4 category, HIV-1 status, sputum-smear positivity, and obstetric comorbidity did not affect transmission of the mycobacteria. Although four mothers with MDR-TB were studied in this cohort, none of their babies had detectable M $tuberculosis$ infection. Additionally, there did not seem to be select mycobacterial strains preferentially transmitted from mother to baby.[51]

Perinatal transmission of HIV-1

Mothers with high viral loads have a higher risk of transmitting HIV-1 to their newborn babies, and those transmitting mothers with category C disease are more likely to have infants with rapidly progressive disease.[52] Silent placental inflammation and/or rampant viral replication leading to high viral loads, caused by active tuberculosis in the pregnant women, may facilitate intrauterine and/or intrapartum transmission of HIV-1. Preliminary and limited data suggests that, whatever the mechanism, vertical transfer of HIV-1 is increased in-utero.[53] In a subgroup of 42 HIV-1-infected women with tuberculosis during pregnancy eight (19%) exposed babies acquired in-utero HIV-1 infection (ie, a positive PCR within the first 3 days of birth). Although the numbers are small, this is the highest rate of in-utero transmission of HIV-1 documented; intrauterine transmission is generally in the range of 5–10%.[36]

Tuberculosis/HIV-1 disease progression due to pregnancy

Women between the ages of 15 and 49 years carry the greatest risk of converting from tuberculosis infection to disease.[54] In the pre-chemotherapeutic era, pregnancy was believed to aggravate tuberculosis but evidence has since shown that pregnancy has few adverse effects on the course of tuberculosis.[29,38,40] This debate on the effects of pregnancy on tuberculosis resurfaces within the context of the HIV-1 epidemic, considering its dramatic effects on the immune system. The CD4 lymphocyte is the key cell involved in control of tuberculosis infection.[55] Animal models suggest that immune homeostasis in pregnancy, which underpins tolerance of the non-self antigens of the fetus, and which favours a Th2 as opposed to a Th1 response,[56] could provide a milieu in which tuberculosis might progress, since control of tuberculosis requires a predominant cell-mediated or Th1 reaction.[57] This idea has not been substantiated in clinical studies.

Recent pregnancy was a risk factor for the development of active tuberculosis in HIV-1-infected women in Africa,[58,59] but these findings have not been confirmed in other regions.[60,61] *M tuberculosis* increases the rate of replication of HIV-1 in vitro; a direct extrapolation of these results to clinical circumstances cannot be made. A link between tuberculosis disease and progressive HIV-1 disease has been described in adults,[62,63] but the association is tenuous[64] and difficult to substantiate. For example, studies from resource-limited settings have been confounded by unknown HIV-1 seroconversion times, delays in diagnosis, and treatment of tuberculosis. The added effect of pregnancy on this process is unknown, especially since it is difficult to standardise and quantify the extent of HIV-1 and tuberculosis disease before the onset of pregnancy. Despite theoretical and experimental animal models and some clinical data that would argue for and anticipate more severe tuberculosis in pregnant women coinfected with HIV-1, they are not consistent or convincing enough to prove such an hypothesis.

Investigating the HIV-1-infected mother with suspected tuberculosis

The high-risk mother may be identified by her history of contact with recent tuberculosis (family or other), and/or suspicious clinical signs or symptoms. Other high-risk groups include the malnourished, homeless, socio-economically impoverished mother, the alcoholic/drug-abusing mother, or mother with immunosuppressive illnesses such as diabetes mellitus. Since tuberculosis is the commonest chronic infection in Africans with HIV-1, all mothers who are HIV-1 positive should be carefully screened for tuberculosis. Equally, mothers with tuberculosis disease must be screened for HIV-1 coinfection, because 37–77% of 15–49 year olds with tuberculosis in Africa may have associated HIV infection.[1] However, since "casual" contact may also be associated with tuberculosis in adults, as shown in the Western Cape (a region with very high tuberculosis rates),[65] it is prudent in areas of high endemicity to always consider tuberculosis disease as a differential diagnosis in the mother with suspicious clinical signs.

Where clinically suspected, as in the case of the high-risk mother with suggestive clinical signs,[41] the mother should have a thorough clinical examination coupled with a shielded chest radiograph and sputum investigation for both smear microscopy (acid-fast bacilli) and culture of *M tuberculosis*. Additional investigations such as lymph-node or skin, bone-marrow biopsy and cerebrospinal fluid assay, are indicated where extrapulmonary sites of disease are suspected.

In tuberculosis non-endemic areas, a tuberculin skin test may be indicated and interpreted accordingly. However, the use of tuberculin tests in endemic regions is of limited value. With a prevalence of latent tuberculosis in sub-Saharan Africa of 35–42% and a yearly increase in incidence of 3·4–9·0%,[1] the skin test, which does not distinguish infection from disease, may not be interpretable. Other tests such as the ELISpot assay,[66] which detects T lymphocyte γ interferon release in response to antigens also present in wild-type *M tuberculosis*, might be of value in the diagnosis and tracking of individuals with new infection. The use of these tests in the diagnosis of reactivating or new tuberculosis disease in endemic settings has not been established, because they do not distinguish infection from disease.

Management of tuberculosis in HIV-1-infected pregnant women

The attending physician may be faced with three different clinical scenarios in HIV-1-infected women with tuberculosis during pregnancy. Firstly, the mother may be symptomatic. Secondly, symptoms and signs may emerge only during the peripartum or postpartum periods. And thirdly, the mother may be symptom-free or mildly symptomatic with the detection of tuberculosis in their infants the first and only clue to maternal disease.

Once tuberculosis is diagnosed or highly suspected, treatment with antituberculosis therapy should begin immediately to reduce the risks of an adverse perinatal and maternal outcome, associated with disease progression.[28,47]

Treatment can begin even while awaiting culture results. Regimens that are recommended in pregnancy include combination therapy with rifampicin, isoniazid (together with pyridoxine), ethambutol, and pyrazinamide.[67] Although the fetal effects and breast-milk excretion data on pyrazinamide is sparse, it is generally considered safe to use in pregnancy. Strictly defined regimens minimise confusion and contribute to a degree of uniformity of care for such patients; easy-to-follow guidelines are especially helpful to highly stressed staff working in under-resourced health-care centres. In an endemic area such treatment should be administered through directly observed treatment, short course (DOTS) programmes. An integral part of managing the mother is the appropriate notification of tuberculosis disease, which would initiate investigation and treatment of close household contacts. Such follow-on investigation is especially important for the mother's new baby since the risk of acquiring postnatal tuberculosis through exposure from another close household source can be minimised. Other children in the family should also be screened.

Antiretroviral therapy
To improve maternal health
One-third of the HIV-1-infected adults with tuberculosis have a CD4 concentration of fewer than 200 cells/μL.[28,68] For HIV-1-infected pregnant women without tuberculosis this figure is 13·6–18·6%.[69] Local guidelines for therapy in developing countries are often based on CD4 suppression below 200 cells/μL or clinical stage IV disease;[70] as a result not all mothers will necessarily qualify for antiretroviral therapy.

To reduce vertical transmission of HIV-1
Apart from the direct issues of antiretroviral therapy affecting maternal health, regimens that require consideration are those that reduce mother-to-child transmission of HIV-1. If the risk of vertical transfer of HIV-1 is high in mothers with advanced HIV-1 disease (which includes the subgroup with coexistent tuberculosis), with possible higher risks for intra-uterine transfer of HIV-1,[53] the

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Panel 1. Possible mechanisms of altered drug pharmacokinetics in mothers with tuberculosis–HIV

Disease interactions
Malabsorption
Diarrhoea or vomiting
HIV enteropathy
HIV-related achlorhydria
Coadministration with antacids for upper gastrointestinal tract pathology
Coexistent hepatic pathology

Drug–disease interactions[75]
Altered expression of proteins—eg, P-glycoprotein. This efflux membrane transporter, which binds protease inhibitors, is increasingly expressed in CD4+ and CD8+ T cells in advanced disease, resulting in decreased concentrations of drugs in specific areas, such as in CD4 cells and in cerebrospinal fluid.
Altered phenotype of enzymes—eg, N acetyl transferase type 2 phenotype may change from fast to slow phenotype in advanced HIV, resulting in decreased acetylation of isoniazid.

Drug–drug interactions[67,76]
Induction of CYP3A4—eg, rifampicin, rifabutin, rifapentine, non-nucleoside reverse transcriptase inhibitors (NRTI). These drugs induce this enzyme system. Coadministered drugs, which are normally metabolised by this system (eg, protease inhibitors, aminophylline), are more rapidly metabolised resulting in decreased circulating concentrations of the drug, and decreased efficacy.
Inhibition of CYP 3A4—eg, the antiretrovirals: ritonivir, indinivir, or saquinavir. antifungal: ketoconazole. These drugs inhibit the CYP3A4 system and may result in slower metabolism of drugs using this system (eg, rifabutin, ethionamide) than normal. This could lead to increased toxicity.
Induction of glucuronosyl-transferase enzymes. Drugs such as rifamycins can induce these enzymes which are responsible for metabolism of–eg, NRTI, zidovudine.

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benefits of long antiretroviral courses that reduce perinatal transmission including intrauterine transfer of HIV-1 must be weighed. In a study of 1437 Thai women, long maternal treatment with zidovudine beginning at 28 weeks' gestation resulted in in-utero transmission of 1·6% compared with short-course therapy (beginning at 35 weeks gestation), which was associated with a 5·1% intrauterine transmission rate.[71] While this regimen may not be practical and cost

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Table 2. Use of antituberculosis drugs in pregnancy, lactation, and in the newborn baby

Drug	Pregnancy	Lactation[77]	Newborn
Rifamycins			
Rifampicin	Safe	0·05% of adult dose can be detected	Safe 10–20 mg/kg/day
Rifabutin	Congenital defects in animal studies	··	Use not established
Rifapentine	Rarely causes bleeding in mother and newborn if administered in last few weeks of pregnancy	··	Use not established
Isoniazid	Safe, supplement with pyridoxine to avoid peripheral neuropathy	0·75–2·3% of adult dose can be detected	Safe 5–10 mg/kg/day
Pyrazinamide	Limited data but recommended	··	Safe 20–30 mg/kg/day
Ethambutol	Safe in human beings, cleft palate, skull and spine defects	Yes, in minute amounts	Retrobulbar neuritis Not recommended
Ethionamide	Premature labour, congenital abnormalities	··	Safe
Aminoglycosides	Ototoxicity in fetus, renal damage	0·05–0·5% of adult dose can be detected, but not well absorbed orally	Use with caution
Quinolones	Bone developmental abnormalities in animals	··	Use with caution

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Table 3. Use of antiretroviral drugs in pregnancy, lactation, and in the newborn baby

Antiretroviral agents	Pregnancy	Placental passage (human)	Lactation	Newborn
Nucleotide/nucleoside reverse transcriptase inhibitors				
Zidovudine	Safe	85%	Passes into breast milk in high concentrations[78]	Safe
Lamivudine	Safe	100%	Passes into breast milk	Safe
Didanosine	Safe. Lactic acidosis in combination with stavudine/ hepatic steatosis	50%	Unknown; excreted in breast milk of lactating rats	Safe in children
Stavudine	Safe. Lactic acidosis/hepatic steatosis in combination with didanosine	76% (in rhesus monkey)	Passes into breast milk	Safe
Abacavir Tenofovir Zalcitabine	No studies in human pregnancy	..	..	..
Non-nucleoside reverse transcriptase inhibitors				
Nevirapine	Safe	100%	76% of maternal blood concentration may be detected in breast milk	Safe
Efavirenz	Neural tube defects in animals Not recommended in pregnancy	..	..	..
Delavirdine	Muscular ventricular septal defect	..	..	..
*Protease inhibitors**				
Amprenavir	No studies in human pregnancies	..	..	..
Lopinavir/ritonavir	No studies in human pregnancies/neonates	..	..	Safe, tolerated in children over 6 months[79]
Indinavir	Limited, safe; studies ongoing	Minimal[80]	Excreted in milk of lactating rats	Possible risk of exacerbating neonatal hyperbilirubinaemia
Nelfinavir	Safe, metabolic induction in pregnancy[83]	Minimal[80]	Excreted in milk of lactating rats	Safe[81], requires higher dosing[82]
Ritonavir	Limited, safe; studies ongoing	Minimal[80]	Excreted in milk of lactating rats	..
Saquinavir	Limited, safe	Minimal[80]	Excreted in milk of lactating rats	..
Fusion inhibitors				
Enfuvirtide	No studies in human pregnancy	..	..	..

Adapted from http://www.Hopkins-aids.edu/guidelines/st/gl_st.pdf and reference 70. This table excludes general side effects of the individual drugs. *Combination therapy with protease inhibitors may be associated with increased rate of prematurity and anaemia, reference 84. Protease inhibitors may be associated with glucose intolerance which may have serious consequences on the fetus.

effective for high antenatal-HIV-1 prevalence resource-limited settings, this and other combination therapies that decrease vertical transmission to 1–3%[72,73] may be selectively beneficial in the mother with tuberculosis.

Effect of combined antiretroviral and antituberculosis therapy

Most tuberculosis regimens have minimum maternal and fetal effects[74] but complexities in combination with antiretrovirals are multiple. Pharmacokinetic, physiological, and disease-mediated mechanisms may affect the absorption, distribution, uptake, and elimination of the drugs used (panel 1). Drugs that are considered safe in pregnancy (table 2, table 3) should be used, administered under the guidance of an experienced clinical team, and tailored to suit the individual patient.

Apart from the toxicities of individual drugs used to treat tuberculosis, control HIV-1 infection, or treat other copathology that frequently accompanies severe HIV-1 infection, specific adverse interactions between the antituberculosis and antiretroviral agents exist. These drug–drug interactions are predominantly described between the rifamycins and antiretroviral agents, which are metabolised via the cytochrome P450 isoform CYP3A4.[76]

Little is known of the effect of pregnancy on drug levels when both antiretroviral and antituberculosis drugs are used in various combinations. The clinical team will need to carefully weigh the risk-benefits of different combinations, taking into consideration available resources, dosage adjustments,[85] clinical, virological, and drug-level monitoring where appropriate and available, and the most recent data.

Breastfeeding advice in resource-limited environments

WHO/UNAIDS/UNICEF recommends[86] that breastfeeding is supported by proper voluntary counselling and testing, to enable mothers to make accurate choices about feeding.

Panel 2. Clinical features in perinatal tuberculosis
Prematurity
Low birthweight
Persistent pneumonia
Lymphadenopathy
Hepatomegaly
Splenomegaly
Jaundice
Seizures
Skin lesions
Ear discharge
Paravertebral abscess
Chorioretinitis
Haematological abnormalities: anaemia, thrombocytopaenia, disseminated intravascular coagulopathy

Alternatives to breast feeding may be adopted in situations where they are feasible, safe, affordable, and sustainable.

In general, the decision to breastfeed should not be affected by tuberculosis in the mother, with the exception of tuberculosis breast abscess, in which case breastfeeding is discontinued from the affected breast. The risk of transmission of tuberculosis to infants from breastfeeding exists, but is not quantified. Since tuberculosis is an airborne pathogen, unlike HIV, the risks of postnatal transmission from an infectious mother, with open pulmonary tuberculosis, to her baby remain, even if she is not breastfeeding. The extreme option, which is hardly practical in the developing world, is to isolate mother from baby. Although studies are limited, the overall risk of transmission of tuberculosis from HIV-infected mothers to their newborns may not be greater than that from women who are HIV uninfected.[28] Therefore, provided the HIV-infected mother with tuberculosis disease is adequately treated for tuberculosis, and the baby at risk is appropriately given prophylaxis and investigations for tuberculosis, the feeding choice should not be restricted by tuberculosis in the mother. The residual amounts of antituberculosis medication that are passed through the breast milk to the baby do not contribute to toxicity despite ingestion of standard neonatal doses of tuberculosis treatment or prophylaxis by the infant. There is no evidence that this residual breast-milk transfer of antituberculosis therapy supports the emergence of drug-resistant strains of *M tuberculosis* in infants.

The HIV-1-infected mother with MDR-TB

MDR-TB is uncommon in sub-Saharan Africa, and its spread does not generally seem to be aggravated by HIV-1;[87] nor does it appear to be more aggressively transmitted from mother to newborn.[28] A diagnosis of MDR-TB can only be made based on susceptibility testing of cultured samples, and is never made on suspicion. The diagnosis of MDR-TB should be considered in a mother with culture/microscopy-confirmed tuberculosis, who is compliant with antituberculosis therapy, but remains clinically ill and smear/culture positive for mycobacteria.

Importantly, a past history of tuberculosis rather than associated HIV-1 infection may be a marker for MDR-TB in the mother. Once diagnosed, the challenges lie in choice of treatment during pregnancy. The choice of second-line drugs (ie, the aminoglycosides kanamycin and amikacin, capreomycin, para-aminosalicylic acid, cycloserine, clofamizine, ethionamide, and fluoroquinolones) is dictated by the susceptibility results, together with availability, ease, and route of administration, and balanced against teratogenicity of the antibiotic used.

Perinatal tuberculosis in babies

Tuberculosis detected in the newborn may be acquired (a) in utero, through haematogenous dissemination via umbilical vein, aspiration of infected amniotic fluid, or ingestion of infected amniotic fluid; (b) intrapartum, through aspiration or ingestion of tuberculous amniotic fluid or cervicovaginal secretions at birth; or (c) postpartum, through breastfeeding (ingestion of infected milk), inhalation, or ingestion of infected respiratory droplets from an infectious source, usually the mother.[88] Inoculation through traumatised skin and mucous membranes has also been postulated. In-utero and intrapartum spread implies infection through the maternal reproductive system, most likely due to a tuberculous bacillaemia. Distinguishing between congenital[89] and early neonatal tuberculosis is probably not crucial,[90] since the presentation, treatment, and immediate prognosis do not differ, provided the baby and mother are adequately investigated and treated. A more favourable description is "perinatal tuberculosis", which encompasses in-utero, intrapartum, and early neonatal acquisition. Molecular characterisation of the infecting organisms in the mother and baby suggests mother-to-child transmission, but does not distinguish between congenital and postnatal acquisition of tuberculosis. Nor does it exclude transmission to each from a common close contact, such as the baby's father. From data preceding the HIV-1 epidemic, risk factors for increased vertical transmission of *M tuberculosis* have included miliary tuberculosis, untreated tuberculosis, or a sputum smear microscopy positive for acid-fast bacilli in the mother. These risks are likely to be similar in the HIV-1-infected pregnancy.

Clinical features of perinatal tuberculosis

The common clinical features of newborn babies with tuberculosis are described in panel 2. Few cases[21,22,91,92] of congenital tuberculosis in association with HIV-1 coinfection have been described. Clinical signs may be similar to earlier descriptions in the pre HIV-1 era. Where both infections are acquired, the course may be one of rapidly progressive HIV-1 disease.[91] With highly active antiretroviral therapy (HAART) this deterioration may be slowed. Diseases due to immunodeficiency, including other congenital infections (such as congenital syphilis) may present in this period. Due to the long incubation period before signs and symptoms of tuberculosis appear and the overlap of clinical signs with HIV-1 and other congenital infections, it is likely that tuberculosis infection acquired in the perinatal period is under diagnosed. In infants with rapidly progressive HIV-1 coincident with tuberculosis,
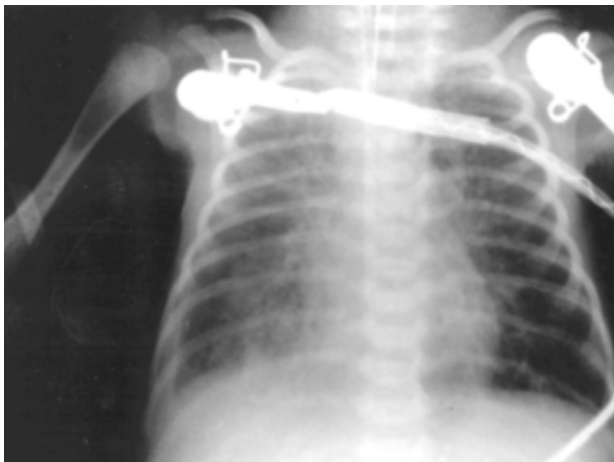
Figure 1. Chest radiograph of neonate with severe bilateral bronchopneumonia requiring mechanical ventilatory support. Endotracheal aspirate grew M tuberculosis.

Figure 2. Tuberculosis granuloma in lung biopsy sample of neonate with culture-proven tuberculosis.

there is a distinct possibility that their mycobacterial infection was acquired perinatally.

Diagnosis of perinatal tuberculosis

Babies at risk for perinatal tuberculosis include those whose mothers have proven or suspected tuberculosis disease during pregnancy. Failure to investigate appropriately may result in a missed diagnosis and contribute to mortality, especially as signs of disease may not appear until several days or weeks later if the infection is transmitted peripartum rather than intrauterine.

Confirmation of diagnosis is based on the detection of acid-fast bacilli on smear microscopy, and/or culture of *M tuberculosis* from neonatal samples, or histology (figure 1, figure 2). Delays in diagnosis of smear-negative, culture-positive congenital tuberculosis, may be accounted for by the slow growth of *M tuberculosis,* which may take up to 12 weeks.[21] It is important to note that infection diagnosed in the baby is usually smear-negative, culture-positive.

The use of tuberculin skin testing in the neonatal period is unreliable, since most babies, due to their immunological immaturity (especially if premature), will not mount a delayed hypersensitivity response, even if infected by this stage.[45] Newer T-lymphocyte-based assays[50] are yet to be validated for use in these scenarios. In HIV-1-infected symptomatic newborn babies and infants, the effect of CD4 suppression on the cellular immune response to tuberculosis antigens is unknown. Due to the high risk of contamination resulting in false positives in tuberculosis-endemic areas and the labour-intensive nature and cost of PCR-based diagnosis of tuberculosis, this diagnostic tool may be less practical in resource-limited settings.

Managing the newborn exposed to maternal tuberculosis and HIV during gestation
Investigations
Since tuberculosis develops slowly and it is possible for the recently infected baby to appear well early on, both the apparently well baby and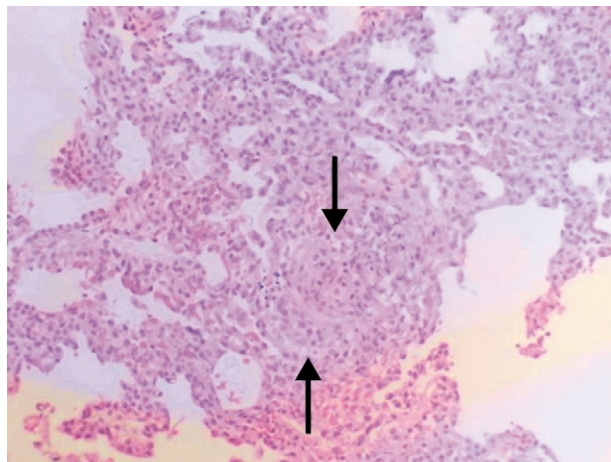 the symptomatic baby should be investigated for vertical transfer of *M tuberculosis* (figure 1). Early-morning prefeed buffered gastric washings and/or nasopharyngeal aspirate,[93] submitted for smear microscopic detection of acid-fast bacilli and *M tuberculosis* culture,[21] should be undertaken, together with a chest radiograph (figure 2). In the symptomatic baby, further sampling as appropriate could be undertaken, such as cerebrospinal fluid,[21] abscess aspirate,[94] liver biopsy, bone marrow aspirate, lymph node biopsy, tracheal aspirate, ear swab,[95] and urine.[45] These investigations may yield a highly suggestive result within a day (if smear microscopy positive for acid-fast bacilli) or take as long as 8–12 weeks to prove a smear-microscopy negative but culture positive case.

Therapy
If the baby is symptomatic, common differential diagnoses for each of the clinical signs elicited should be considered and treated accordingly. These include congenital syphilis, congenital cytomegalovirus infection, congenital herpes virus infection, or non-typical *Mycoplasma pneumoniae* infection. Tuberculosis as a differential diagnosis or a copathology is often difficult to exclude in these circumstances, and antituberculosis therapy is often started on suspicion. This includes a 2-month initiation course of rifampicin, isoniazid, and pyrazinamide, followed by a further 4-month course of rifampicin and isoniazid (figure 3).

If the symptomatic baby is HIV-1 exposed, vertical transmission of HIV-1 should be established by HIV-1 PCR assay. Where the baby is HIV-1 infected, early antiretroviral therapy is likely to be of benefit since these babies are most likely to develop rapidly progressive HIV-1.[52] Drug–drug interactions, described above, apply with the use of rifamycins and antiretroviral drugs in the infant; these babies will need carefully tailored care to limit the toxicity and drug failures that could follow combination antiretroviral and antituberculosis therapy.

In the symptom-free baby careful investigations for tuberculosis infection must be undertaken initially, and tuberculosis prophylaxis administered to the baby while

awaiting culture results. This is done where the mother is considered infectious (ie, poor compliance with antituberculosis therapy, sputum-smear-microscopy positive at time of delivery, and/or start of antituberculous therapy within 3 months of delivery). Protagonists who argue that all newborn babies and mothers with tuberculosis during pregnancy (regardless of duration of tuberculosis therapy before birth) be offered prophylaxis may be justified, since the clearance rate of tuberculosis after therapy may vary, and a negative sputum-smear-microscopy result may not necessarily indicate complete clearance of the organism in the mother. While clearance rates may be similar in HIV-1-infected and non-infected adults, in HIV-1-infected pregnancies these rates are unclear. These uncertainties warrant a cautious approach especially as the prophylactic regimen is not harmful to the baby.

Recommended guidelines for tuberculosis prophylaxis include either a 6-month course of isoniazid, or a 3-month course of rifampicin and isoniazid combination.[96] The 3-month course is preferable where isoniazid resistance profiles are high, and where compliance over 6 months is likely to be poor. Separation of the mother and child is not practical in the developing world.

Where the investigations for *M tuberculosis* infection yield a positive culture a complete course of antituberculosis therapy should be given to the baby regardless of clinical signs or lack thereof. In addition, it has been recommended that babies born to mothers with proven endometrial tuberculosis[89] be started on antituberculosis therapy. Where perinatal tuberculosis (disease or infection) is diagnosed, the case should be notified.

While the at-risk baby is being intensively investigated and managed in the neonatal unit, careful consideration must be given to maternal control of tuberculosis. The risks of acquiring tuberculosis persist after birth, especially if the baby is continually exposed to incompletely treated or recurrent open pulmonary tuberculosis in its mother. Prophylactic therapy administered to the baby in the first 3 months of life does not confer any long-term protection from childhood infection and disease.

BCG vaccination
In resource-limited settings where compliance and follow-up is uncertain, the BCG vaccine should be administered to the newborn for the following reasons. First, failure to administer BCG in the high-risk neonate—ie, exposure to the mother/environment with active tuberculosis—could result in the baby being at greater risk for miliary tuberculosis and tuberculosis

meningitis than the general population. The risk of these forms of disseminated disease are greatest in the 1st years of life, and the protective effects of the BCG vaccine administered in the baby are greatest against these forms of disseminated disease in infants.[97] Second, a uniform policy limits any nursing/medical confusion about who should and should not receive the vaccine (and inadvertent missed vaccines) in busy resource-restricted neonatal units. Third, evidence that isoniazid/rifampicin prophylaxis inhibits the immunogenicity of the BCG vaccine is not conclusive,[98] and the benefits of omitting the vaccine, to use the skin test as a marker for infection, are limited and do not outweigh the risks posed. Finally, in the symptomatic baby, whose mother is considered infectious for *M tuberculosis*, the risks of acquiring wild-type tuberculosis may outweigh the risks of disseminated BCG vaccine tuberculosis. In a recent report of 49 HIV-1-infected children with culture-positive tuberculosis, five cases of Danish BCG vaccine disease were identified, manifesting with ipsilateral axillary adenitis with or without pulmonary disease.[99] Until a controlled study is done to assess the risk-benefits of omitting BCG vaccination in babies exposed to wild-type *M tuberculosis* through their mothers, the vaccine should be administered.

Preventing perinatal tuberculosis in HIV-1-infected pregnant women in the developing world: what could the future hold?
In addition to a high index of suspicion, timely investigations and appropriate treatment of the tuberculosis-diseased pregnant woman and her close contacts, including her baby, are required. This demands awareness by all
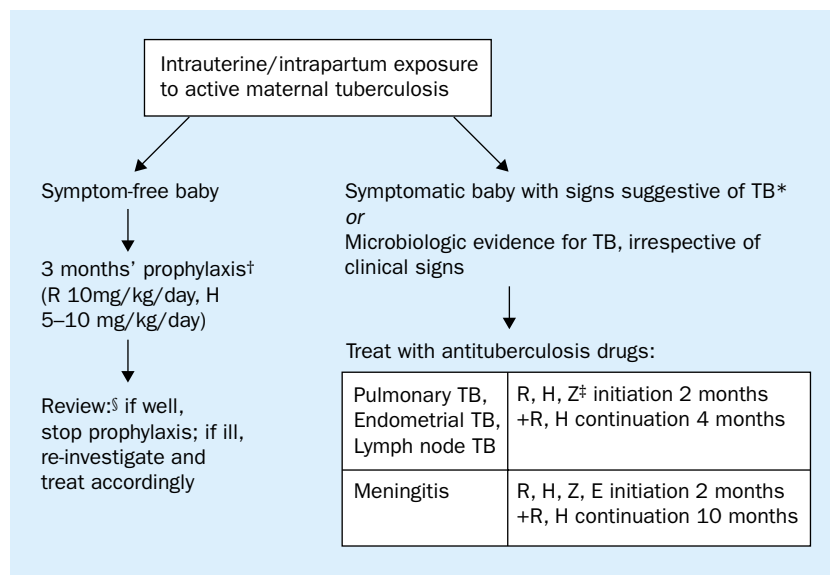
Figure 3. Management of the newborn with intrauterine/intrapartum exposure to active maternal tuberculosis. *Exclude other copathology—eg, congenital syphilis, congenital cytomegalovirus infection. †Where the mother is considered infectious—eg, poor compliance on antituberculosis therapy, sputum-smea microscopy at time of delivery, and/or who have begun antituberculosis therapy within 3 mths of delivery. ‡For dosing schedules see reference 96. §Having administered BCG at birth, care should be taken in interpreting tuberculin skin testing in the infant at this stage. A positive skin test (eg, mantoux >15mm in non-immunocompromised or >5mm in compromised) should be considered grounds for full tuberculosis therapy. TB=tuberculosis, R=rifampicin, H=isoniazid, Z=pyrazinamide, E=ethambutol.

health-care workers, that a newborn infant forms a dyad with its mother, and that investigation and management of recent parturients who are ill must include the newborn.

In addition to optimising established tuberculosis-control strategies,[100,101] one component in reducing the incidence of tuberculosis in developing countries could be preventing active disease through screening at-risk population groups. This principle could apply to the HIV-1-infected pregnant woman in the prevention of perinatal tuberculosis disease. If the yearly risk for tuberculosis (ie, clinical signs and symptoms of tuberculosis) in latently infected (ie, people infected with *M tuberculosis*, but who are symptom-free) HIV-1-infected individuals is 10%,[67] then during the course of an HIV-1-infected pregnancy and the first 3 months after birth, such a risk would be minimally 10%, assuming no effect of the pregnancy state on reactivation or acquisition of tuberculosis. In Soweto, South Africa, as many as 11% of women enrolled in a prevention of mother-to-child-transmission of HIV-1 programme have active tuberculosis disease.[102] This finding could support the case for tuberculosis preventive therapy in pregnant women with latent tuberculosis infection, in areas of high incidence of tuberculosis and HIV-1. A caveat to this proposal must be the careful exclusion of active tuberculosis before the start of a preventive regimen. Since most mothers in resource-limited settings attend antenatal clinics after the first trimester of pregnancy, the teratogenic risks of such a preventive programme will not exist. However, this component will need validation because the effect of such screening on the prevention of active tuberculosis is unproved.

The effect of antiretrovirals on tuberculosis control is also unclear. Antiretroviral therapy could benefit tuberculosis control. In a theoretic model, early institution of antiretroviral was estimated to reduce the number of tuberculosis cases among HIV-1-infected individuals by 70%.[103] But it is unrealistic to expect that it will be possible to implement antiretrovirals to all HIV-1-positive mothers with CD4 counts above 500 cells/μL in the developing world.[103] For now, consolidating national tuberculosis programmes, targeting antenatal visits for early detection of tuberculosis disease and HIV-1 infection, early detection, and appropriate treatment of mother and baby are principal components in the control of perinatal tuberculosis.

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