HIV, TB and child health

Brian Eley (Paediatric Infectious Diseases Unit, Red Cross Children's Hospital
and School of Child and Adolescent Health, University of Cape Town)

HIV infection and tuberculosis (TB) are common diseases that adversely affect the health and survival of many children in South Africa. HIV/AIDS-related complications are the main cause of death in children under five.[1] Children acquire HIV infection mainly through mother-to-child transmission during pregnancy, at the time of birth, or after birth from infected breast milk.

Children are largely infected with TB by airborne spread of the TB bacteria, usually from close contact with an adult with active TB. Adults are often highly infectious, coughing up large numbers of TB organisms from open cavities in the lungs. In contrast, children rarely pass the infection on to others when they first become infected with TB because they seldom develop cavities that can release large numbers of organisms.

HIV infection and TB in children are strongly linked to the pandemics in adults. More than 95% of HIV-infected children contract the virus through mother-to-child transmission and there is a strong correlation between childhood TB and adult TB contacts, emphasising the family context in which children frequently acquire both HIV and TB.

There is a strong relationship between HIV and TB. HIV-infected children have weakened immune systems, which substantially increase their risk of becoming infected with TB. As both HIV infection and TB are very common in South Africa, a high proportion of HIV-infected patients will develop TB. Children infected with both HIV and TB are regarded as having HIV-TB co-infection.

This essay focuses on five key questions:

- What is the current situation in South Africa?
- What are the national strategic objectives for HIV, AIDS and TB?
- What is needed to ensure the integration of HIV and TB services?
- What are the latest treatment guidelines for children?
- What are the recommendations for improving South Africa's response to the dual pandemics?

What is the current situation in South Africa?

HIV

South Africa has been disproportionately affected by the HIV/AIDS and TB pandemics. Although the country has a relatively small population, it has one of the largest HIV pandemics and the biggest paediatric HIV pandemic in the world.

In 2009, 5.21 million people were HIV positive in South Africa; of these, 280,000 were children under 15 years. Despite 83% of HIV-infected pregnant women receiving antiretroviral therapy (ART) in 2009 to prevent HIV transmission to newborns, the annual number of newly infected children (59,000 in 2009) remains very high and contributes substantially to under-five mortality.[2]

In 2006, the World Health Organisation (WHO) estimated that 57% of under-five mortality in South Africa was associated with HIV infection, and recent information from the Child Healthcare Problem Identification Programme showed that HIV/AIDS causes at least 30% of all child deaths in South Africa.[3] In recent years access to ART has escalated for both mothers and children. At the end of 2008, South Africa had the largest paediatric ART programme in the world: More than 57,000 children were receiving ART, with an estimated coverage of 61%.[4]

Despite intensive ongoing research, no vaccine is yet available to prevent HIV infection.

Tuberculosis

South Africa also has one of the world's largest TB pandemics. In 2008, South Africa was ranked third after India and China in terms of the burden of new cases of TB, with an estimated 480,000 new cases, and second after Swaziland in terms of TB incidence, with an incidence rate of 960 cases per 100,000 population per year.[5] The cure rates for all new (74%) and re-treated TB cases (67%) remain low – below the 2005 global target of 85%.[6]

Table 4: TB rates in a Cape Town community

Setting	Period	Rates
Prospective surveillance of children under 15 years in a single peri-urban township (population: 13,000).	1997 – 2007	• Child TB-notification rate ranged from 315 per 100,000 to 1,105 per 100,000. • Adult rates increased from 629 per 100,000 to 2,106 per 100,000. • Childhood TB was statistically linked to adult TB prevalence.

Source: Middelkoop K, Bekker L-G, Morrow C, Zwane E & Wood R (2009) Childhood tuberculosis infection and disease: A spatial and temporal transmission analysis in a South African township. *South African Medical Journal*, 99: 738-743.

The emergence of multi-drug resistant TB (MDR-TB) and extreme drug resistant TB (XDR-TB) is of particular concern. South Africa ranks among the top five countries with the highest number of MDR-TB cases. Amongst new TB cases, 1.8% had MDR-TB. In patients who were previously treated for TB, the proportion with MDR-TB (6.7%) was more than three times higher.[7] These resistant forms of TB are associated with major treatment and infection control challenges. As standard TB drugs are not effective, treatment consists of specialised drugs which are expensive and associated with many side-effects. The treatment of drug-resistant TB is less successful than that of drug-susceptible TB.

Specific childhood TB frequencies were not included in the global reports from which these statistics were extracted.

Case 1: The South African Tuberculosis Vaccine Initiative

Linda Rhoda, SATVI, University of Cape Town

Research into finding new and more effective TB vaccines is gathering momentum globally. At the forefront of TB vaccine research is the South African Tuberculosis Vaccine Initiative (SATVI) of the University of Cape Town. Established in 2001, SATVI has grown into the most advanced and experienced TB-vaccine research site in the world, having conducted a number of large-scale epidemiological as well as TB-vaccine trials involving thousands of participants.

SATVI is currently conducting clinical trials on four potential new TB vaccines, including a preliminary efficacy trial of a new TB vaccine for infants. The research site is in the Boland district of the Western Cape, which has one of the highest TB rates in the world, and where SATVI enjoys an effective partnership with the Department of Health, non-governmental organisations and the community.

Table 4 captures the results of a recent study that calculated the frequency of TB in children in a Cape Town community. It shows a strong association between childhood TB and contact with adult cases of smear-positive TB. Another study from Cape Town recorded a progressive increase in prevalence of MDR-TB, from 2.3% in 2005 to 6.7% in 2007.[8] While these studies show that childhood TB is a significant public health problem in Cape Town, an accurate assessment of the impact of TB on children in South Africa requires regular surveillance in all nine provinces, with adequate rural representation.

The BCG vaccine, which is currently administered to all infants after birth, is only partially effective in lessening the risk of invasive forms of TB, and does not prevent primary infection. Following BCG vaccination, there is an added risk of HIV-infected children developing disseminated BCG infection, which may be difficult to treat.[9] Case x describes the promising development of new vaccines to prevent more invasive forms of TB.

HIV-TB co-infection

South African paediatric studies have reported TB infection to be present in more than 40% of HIV-infected children, and that these children are 24 times more likely to develop TB than children not infected with HIV during the first year of life.[10] Predictably, ART significantly reduces susceptibility to TB in HIV-infected children. A recent paediatric study reported that ART reduces the risk of developing TB by 70%.[11]

Recent evidence suggests that isoniazid[i] administration does not reduce the risk of TB in HIV-infected children younger than 12 months as it does in older children. Therefore, the WHO now recommends that all HIV-infected children over 12 months should receive routine isoniazid therapy for six months. However, infants younger than 12 months should not receive routine isoniazid as part of a comprehensive package of HIV care.[12] This is a recent recommendation and still has to be considered for implementation in South Africa.[13]

i An antibiotic used to prevent TB in adults and children.

Table 5: Progress towards child-specific targets set by the HIV and AIDS and STI National Strategic Plan (2007 – 2011)

Objective/indicator	2008 target	2011 target	2008 progress and comments
Proportion of pregnant women in need of PMTCT interventions who received these services	70%	95%	86%
Increase in the number of children starting ART for the first time	24,000	40,000	25,168
Proportion of HIV-positive or exposed children receiving cotrimoxazole	75%	100%	No estimate for South Africa in 2008 global report

Sources: Republic of South Africa (2010) *Country progress report on the declaration of commitment on HIV/AIDS. 2010 report.* Pretoria: Republic of South Africa; UNICEF (2009) *Children and AIDS: Fourth stocktaking report. November 2009.* New York: UNICEF; World Health Organisation (2008) *Towards universal access – Scaling up priority HIV/AIDS interventions in the health sector: Progress report.* Geneva: WHO.

What are the national strategic objectives for HIV and AIDS?

South Africa's response to the dual HIV/AIDS and TB pandemics is described in two strategic plans which cover the period 2007 – 2011.[14] The HIV and AIDS and STI[ii] National Strategic Plan 2007 – 2011 (NSP) defines four priority areas (prevention; treatment, care and support; research, monitoring and surveillance; and human rights and access to justice) and 19 goals. Fifteen of these goals have objectives that mention or affect children. Annual targets are specified for each objective for the period 2007 – 2011.

Table x draws on recent global reports to illustrate progress towards three of the NSP objectives. It seems that South Africa is meeting or exceeding its targets for the prevention of mother-to-child transmission (PMTCT) and the initiation of ART. However, progress in the use of cotrimoxazole prophylaxis[iii] in HIV-exposed and -infected children in South Africa was not reported on in 2008. The NSP was drafted before the extreme vulnerability of HIV-infected infants (0 – 12 months) in resource-limited settings was fully appreciated, and therefore it does not include objectives and targets that specifically address the care needs of these infants. Specific care targets and monitoring indicators should be developed to track the national response to this important patient sub-group.

Recent research indicates that HIV-infected children are at a high risk of progressing to advanced HIV infection or death during the first two years of life, and that early intervention with ART can prevent these adverse outcomes.[15] Consequently, the WHO recommends that all HIV-positive children younger than 12 months should commence ART as soon as possible following diagnosis, irrespective of clinical severity or CD4[iv] count.[16]

The guidelines for the management of HIV-infected children, published in 2005, do not prioritise the care needs of HIV-infected infants.[17] A recent review of seven large paediatric treatment programmes in the country showed that the median age of children starting ART before March 2008 was 42.7 months, and only 28.9% were less than 18 months old.[18] These results confirm that young children have not been adequately prioritised for ART in South Africa.

On World AIDS Day 2009, President Jacob Zuma announced that children under 12 months will be prioritised for ART, and the treatment guidelines for HIV-infected children were updated accordingly.[19] To give greater effect to this important decision, which will hopefully lead to a greater proportion of young, HIV-infected children accessing ART, it is urgent to:

- communicate this policy shift to all child health professionals;
- implement appropriate training for front-line health professionals;
- develop care indicators for HIV-infected infants; and
- revise ART targets for infants and children within the context of the NSP.

What are the national strategic objectives for TB?

Both the NSP and the draft Tuberculosis Strategic Plan for South Africa, 2007 – 2011 (TBSP) describe aspects of the national response to the TB pandemic. The NSP includes objectives for the effective management of HIV-TB co-infection, while the TBSP provides a comprehensive description of the national TB strategy. The TBSP acknowledges the importance of treatment guidelines, political and managerial support, adequate resources and effective programme management.

ii Sexually transmitted infections.

iii Treatment with cotrimoxazole prevents *pneumocystis jiroveci* pneumonia (PCP) – a leading cause of death in HIV-infected children.

iv CD4-positive cells bind to the HI-virus and a diminished number of these cells indicate severe HIV infection – hence the term 'CD4 count'.

The listed indicators and targets address TB diagnosis, treatment (including MDR-TB and XDR-TB), HIV-TB co-infection, and cure rates. Although the TBSP provides "standards of care" for childhood TB, drug regimens for mild and severe forms of childhood TB are not clearly differentiated. The plan also acknowledges the need to strengthen collaboration between TB and HIV/AIDS programmes to ensure better management of co-infected patients, and recommends the integration of HIV/AIDS and TB activities at health facilities.

What is needed to ensure the integration of HIV/AIDS and TB services?

Integration of HIV/AIDS and TB services should be an essential component of the overall response to the dual pandemics. In 2006, the WHO published a framework for integration, which included objectives for reducing the burden of TB in people with HIV/AIDS, and the burden of HIV in TB patients.[20] Currently, HIV/AIDS and TB are largely managed as separate vertical programmes in South Africa. Consequently, patients infected with either disease and dual-infected patients are often treated in separate HIV/AIDS and TB clinics. This system has created inherent inefficiencies. For example, only 15 – 49% of TB patients in South Africa are screened for HIV infection.[21]

Integration should improve the management of both conditions. As ART services are relatively new in South Africa, the Department of Health implemented an accreditation system in 2004 to ensure that clinics deliver an acceptable standard of care. This has limited the number of ART treatment centres in the country. The HIV-site accreditation system has recently been withdrawn, permitting the extension of ART services to many more primary health care clinics. This may in future facilitate the functional integration of HIV/AIDS and TB services. However, joint national and provincial HIV-TB co-ordinating committees are needed to drive integration at health facilities.

What are the latest treatment guidelines for children?

Global treatment guidelines have been updated regularly during the past 5 – 10 years, due to the rapid evolution of HIV/AIDS and TB research. This trend is likely to persist during the next decade. Revision of the national Guidelines for the Management of HIV in Children has not kept pace, and many clinicians are still using outdated 2005 guidelines. However, updated guidelines were published in March 2010, which should improve the treatment response to paediatric HIV infection in South Africa. In addition, the 2004 Tuberculosis Control Programme Practical Guidelines remain in use. Although draft HIV and TB Guidelines for Paediatric Practice were produced in 2009, they have not yet been finalised or disseminated nationwide.

The WHO convened a series of meetings during 2009 to update existing global guidelines. These resulted in several new recommendations for improving and refining clinical practice relating to the use of antiretroviral drugs for preventing perinatal[v] transmission; infant feeding practice; ART for children, adolescents and adults; and the treatment of HIV-TB co-infection.[22] The revised ART guidelines for children are in the process of being finalised and are likely to result in further review of the South African guidelines. An efficient system needs to be developed to ensure that research findings and global recommendations are rapidly reviewed and, where appropriate, incorporated into the national clinical response.

What are the recommendations for improving South Africa's response to the dual pandemics?

This overview has raised several recommendations that health professionals and administrators should consider for improving the collective response to the dual paediatric HIV/AIDS and TB pandemics:

- Place greater emphasis on HIV testing and prevention because heterosexual transmission remains the major driver of HIV. Scaling up of care and treatment for HIV-infected patients can be sustained only if the number of new infections is reduced. The development of effective vaccines remains a priority. The Minister of Health recently launched a massive HIV counselling and testing campaign to test 15 million South Africans for HIV over the next year. This is a significant development which should boost prevention initiatives.
- Strengthen PMTCT services. The number of new HIV infections in children remains unacceptably high and an effective PMTCT programme is essential to reverse the HIV pandemic in children.
- Prioritise the care needs of young HIV-infected children because of the increased mortality risk during the first two years of life.
- Evaluate current use of TB medication. Research indicates that current TB-drug dosing instructions are sub-optimal for both HIV-infected and uninfected children, leading to the recent revision of the dosages of antitubercular drugs

v Period immediately before and after the birth of a baby.

by the WHO. Furthermore, some TB-drug formulations are not appropriate for children.

- Clearly define and formalise the process of updating and disseminating treatment guidelines. The Department of Health should be more responsive to clinical advances and ensure that reasonably up-to-date standards of care are practised. This can be done by the prompt revision of treatment guidelines.
- Harmonise HIV/AIDS and TB treatment guidelines to ensure that they promote service integration.
- Establish national and provincial co-ordinating committees in line with the WHO's Stop TB strategy to promote functional integration of HIV/AIDS and TB services at all health care facilities.

Conclusion

This essay has highlighted limitations in the management of childhood HIV/AIDS and TB. A systematic review is required to identify all the prevention, care and treatment gaps, and formulate a comprehensive national response. The response to the dual paediatric HIV/AIDS and TB pandemics should be carefully monitored to ensure that the rights of affected children are protected. Anticipated revisions to global guidelines will include several recommendations for improving the response to childhood HIV infection, including extending early ART to all children younger than two years and simplifying the management of HIV-TB co-infection.

South Africa should not delay adopting these recommendations, which are to the benefit of all affected and infected children.

References

1 World Health Organisation (2006) *Mortality country fact sheet.* Accessed on 19 April 2010: www.who.int/whosis/mort/profiles/mort_afro_zaf_southafrica.pdf.

2 Republic of South Africa (2010) *Country progress report on the declaration of commitment on HIV/AIDS. 2010 report.* Pretoria: Republic of South Africa; Statistics South Africa (2009) *Statistical release P0302: Mid-year population estimates 2009.* Pretoria: StatsSA.

3 See no. 1 above;
South Africa Every Death Counts Writing Group (2008) Every death counts: Use of mortality audit data for decision making to save the lives of mothers, babies and children in South Africa. *The Lancet*, 371: 1294-1304.

4 United Nations Children's Fund (2009) *Children and AIDS: Fourth stocktaking report. November 2009.* New York: UNICEF.

5 World Health Organisation (2009) *Global tuberculosis control: A short update to the 2009 report.* Geneva: WHO.

6 World Health Organisation (2009) *Global tuberculosis control – epidemiology strategy, financing. WHO report 2009.* Geneva: WHO.

7 See no. 5 above; see no. 6 above.

8 Schaaf HS, Marais BJ, Hesseling AC, Brittle W & Donald PR (2009) Surveillance of antituberculosis drug resistance among children from the Western Cape province of South Africa – An upward trend. *American Journal of Public Health,* 99: 1486-1490.

9 Hesseling AC, Johnson LF, Jaspan H, Cotton MF, Whitelaw A, Schaaf HS, Fine PEM, Eley BS, Marais BJ, Nuttall J, Beyers N & Godfrey-Fausset P (2009) Disseminated bacilli Calmette-Guerin disease in HIV-infected South African infants. *Bulletin of the World Health Organisation*, 87: 505-511.

10 Hesseling AC, Cotton MF, Jennings T, Whitelaw A, Johnson LF, Eley B, Roux P, Godfrey-Fausset P & Schaaf HS (2009) High incidence of tuberculosis among HIV-infected infants: Evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. *Clinical Infectious Diseases*, 48: 108-114;
Jeena PM, Pillay P, Pillay T & Coovadia HM (2002) Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *International Journal of Tuberculosis and Lung Disease*, 6(8): 672-678;
Madhi SA, Huebner RE, Doedens L, Aduc T, Wesley D & Cooper PA (2000) HIV-1 co-infection in children hospitalised with tuberculosis in South Africa. *International Journal of Tuberculosis and Lung Disease*, 4(5): 448-454.

11 Martinson NA, Moultrie H, van Niekerk R, Barry G, Coovadia A, Cotton M, Violari A, Gray GE, Chaisson RE, McIntyre JA & Meyers T (2009) HAART and risk of tuberculosis in HIV-infected South African children: A multi-site retrospective study. *International Journal of Tuberculosis and Lung Disease*, 13(7): 862-867.

12 Madhi SA, Nachman S, Violari A, *et al* (2008) *Lack of efficacy of primary isoniazid (INH) prophylaxis in increasing tuberculosis (TB) free survival in HIV-infected (HIV+) South African children.* 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, 25 – 28 October 2008, Washington, Abstract G2-1346a;
Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf HS, Rabie H & Lombard C (2007) Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: Randomised controlled trial. *British Medical Journal*, 334(7585): 136.

13 WHO & International Union against Tuberculosis and Lung Disease (in press) *Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach, March 2010.*

14 South African National AIDS Council (2007) *HIV and AIDS and STI National Strategic Plan 2007 – 2011.* Pretoria: SANAC;
Department of Health (no date) *Draft Tuberculosis Strategic Plan for South Africa, 2007 – 2011.* Pretoria: DoH.

15 Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, Jean-Phillipe P & McIntyre JA, for the CHER study team (2008) Early antiretroviral therapy and mortality among HIV-infected children. *New England Journal of Medicine*, 359: 2233-2244.

16 World Health Organisation (2008) *Report of the WHO technical reference group, paediatric HIV/ART care guideline group meeting, WHO headquarters, Geneva, Switzerland, 10 – 11 April 2008.* Geneva: WHO.

17 Department of Health (2005) *Guidelines for the management of HIV-infected children.* Pretoria: Jacana Media.

18 Davies M-A, Keiser O, Technau K, Eley B, Rabie H, van Cutsem G, Giddy J, Wood R, Boulle A, Egger M & Moultrie H (2009) Outcomes of the South African national antiretroviral treatment programme for children: The IeDEA Southern Africa collaboration. *South African Medical Journal*, 99: 730-737.

19 Department of Health (2010) *Guidelines for the management of HIV in children.* 2nd edition. Pretoria: DoH.

20 World Health Organisation (2006) *The stop TB strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals.* Geneva: WHO.

21 See no. 6 above.

22 World Health Organisation (2009) *Rapid advice: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants.* Geneva: WHO; World Health Organisation (2009) *HIV and infant feeding: Revised principles and recommendations. Rapid advice.* Geneva: WHO;
WHO (2009) *Rapid advice: Antiretroviral therapy for HIV infection in adults and adolescents.* Geneva: WHO.