Published in final edited form as:
J Acquir Immune Defic Syndr. 2012 August 15; 60(5): 503–510. doi:10.1097/QAI.0b013e318256b4f8.

Changes in paediatric HIV-related hospital admissions and mortality in Soweto, South Africa 1996–2011: light at the end of the tunnel?

Tammy Meyers, MD[1], **Angela Dramowski, MD**[2], **Helen Schneider, MD**[3], **Nicolene Gardiner, MD**[4], **Louise Kuhn, MPH, PHD**[5], and **David Moore, MD**[6]

[1]Harriet Shezi Clinic, Department of Paediatrics, Chris Hani Baragwanath Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[2]Academic Unit for Infection Prevention and Control, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa

[3]School of Public Health, University of the Western Cape, Cape Town, South Africa

[4]AURUM Institute, Johannesburg, South Africa

[5]Gertrude H. Sergievsky Center, College of Physicians and Surgeons; and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

[6]Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases & Medical Research Council: Respiratory & Meningeal Pathogens Research Unit, University of the Witwatersrand, Soweto, South Africa

Abstract

Background—With widespread availability of paediatric ART and improved access to PMTCT, it is important to monitor the impact on paediatric HIV-related hospital admissions and in-hospital mortality in South Africa.

Methods—Over a 15 year period, 4 independant surveillance studies were conducted in the paediatric wards at Chris Hani Baragwanath Hospital in Soweto, South Africa (1996, 2005, 2007 and late 2010 to early 2011). Trends in HIV prevalence and HIV-related mortality were evaluated.

Results—HIV prevalence was similar during the first 3 time periods: 26.2% (1996), 31.7% (2005) and 29.5% (2007) p>0.10, but was lower in 2010–11 (19.3%; p=0.0005). Median age of the children admitted with HIV increased in the latter time periods from 9.13 (IQR 3.6 – 28.8), to 10.0 (3.0 – 44.5) (p>0.10) and 18.0 (6.2 – 69.8) months (p=0.048). Median admission WAZ-scores were similar (<−3 SD) for the latter 3 time periods. Admission CD4 percentage increased from 0.0% (0.0 – 9.4) 2005, to 15.0% (8.2 – 22.8) 2007 (p<0.0001) and was 18.7% (9.6 – 24.7) in 2010–11 (p>0.10). Mortality among all vs. HIV-infected admissions was 63/565 (11.2%) and 43/179 (24.0%) in 2005, 91/1510 (6.0%) and 53/440 (12.0%) in 2007 and 18/429 (4.2%) and 9/73 (12.3%) in 2010–11.

Corresponding author: Tammy Meyers, Department of Paediatrics, Chris Hani Baragwanath Hospital, PO Bertsham 2013, Johannesburg, South Africa, tammy@meyers.net, Phone: +2711938 8000, Mobile: +27833270066.

Conflicts of Interest: The authors have no conflict of interest.

Conclusion—HIV-prevalence and mortality among paediatric admissions is decreasing. This is likely a result of improved PMTCT and wider ART coverage. Continued effort to improve PMTCT coverage and identify and treat younger and older HIV-infected children is required to further reduce HIV-related morbidity and mortality.

Introduction

By the end of 2009 there were an estimated 330,000 children infected with HIV in South Africa, accounting for 13.2% of the world's HIV-infected children[1]. In the same year it was estimated that up to 35% of deaths among South African children under 5 years of age were HIV-related.[2]

Prevalence of HIV among admissions to paediatric wards has been tracked and used as a marker of the impact of HIV on health services for children. At Chris Hani Baragwanath Hospital (CHB), in Soweto, South Africa, the trends in HIV prevalence among paediatric admissions have been intermittently evaluated over a 20 year period. Between May 1989 and April 1990, 23 children were diagnosed with HIV at the hospital (the first cases described at this institution).[3] Following a rapid rise in HIV prevalence among pregnant women,[4] Zwi et al reported that HIV-related paediatric admissions climbed from 1% to almost 30% of all admissions from 1990 until 1996.[5] In-hospital mortality increased by 42% during this time period, attributable to HIV.[6]

Provision of antiretroviral therapy (ART) for adults and children by the South African National Department of Health began in 2004. Prior to this few children had access to ART. Uptake among children was initially slow, but South Africa now has the largest ART programme globally with an estimated paediatric ART coverage of 54% in 2010.[7] Despite lengthy delays in implementing HIV prevention of mother-to-child transmission (PMTCT) programmes in South Africa, there is now evidence that vertical transmission of HIV is decreasing. Data from the National Health Laboratory Services on HIV DNA polymerase chain reaction (PCR) test positivity rates for HIV-exposed children attending government clinics show a decline among HIV-exposed infants under 2 months of age from 8.2% to 4.3%, and estimated coverage of early infant testing (within 2 months of birth) improved from 31.4% to 54.7%.[8] A study evaluating the effectiveness in 2010 of the national PMTCT program showed that, among 9,915 infants attending government clinics across the country for first immunization, 31.4% were HIV-exposed and the HIV transmission rate from mother-to-child was 3.5% in these infants aged 4–8 weeks.[9]

Based on these programmatic improvements, with declining vertical HIV transmission and increasing paediatric ART coverage, we describe the impact on HIV prevalence and inpatient mortality among children admitted to the paediatric wards at Chris Hani Baragwanath hospital.

Methods

Chris Hani Baragwanath Hospital (CHB), one of the largest public hospitals on the African continent, serves a population of 1.4 million in Soweto, Johannesburg in the Gauteng Province of South Africa. The hospital is a referral centre for local primary health care clinics, regional hospitals in Gauteng and neighbouring provinces. Approximately 6,000 children up to age 15 years are admitted annually. PMTCT services are widespread in the Soweto area and the Harriet Shezi Children's clinic at CHB provides outpatient paediatric HIV services for children from the Soweto area and surrounds. Almost 5,000 children have initiated ART since 2004, of whom more than 1,200 have been out-referred to district services for ongoing care and treatment.

Table 1 summarizes study design, study population, timing and HIV diagnostic criteria applied for four surveillance studies included in this analysis and conducted in the paediatric wards of CHB between 1996 and 2011. Approval to conduct each surveillance study and to compare them over time was obtained from the Human Research Ethics Committee of the University of the Witwatersrand.

During this time period the HIV/AIDS programme in South Africa underwent several changes. In 2003, a constitutional court order compelled the government to provide single-dose nevirapine as part of a national PMTCT programme. In early 2004, a government-led programme providing universal access to ART was introduced in South Africa. Initially WHO ART guidelines were used but these had scant guidance for treatment of children, especially for the care of young infants. By 2008 it became evident from the Children with HIV Early Antiretroviral Therapy (CHER) study that HIV-related deaths in infants and young children could be dramatically reduced by early ART.[10] As a result, WHO revised guidelines recommending that all infants with HIV infection start ART early in the first year of life. During this period, the South African Expanded Programme on Immunization (EPI) introduced new vaccines (Haemophilus *Influenzae* type b in 1999, and pneumococcal and rotavirus vaccines in 2009). In the earlier time periods, HIV testing was mainly offered to children presenting for admission with signs and symptoms of HIV-disease. The practice of provider-initiated counselling and testing (PICT) was formally implemented in 2010 when a government policy document on counselling and testing was published, stipulating that all adults and children presenting at health services should be offered HIV testing.[11]

Methodology of the most recent study (2010/2011)

From 1 August 2010 through 31 January 2011, children were enrolled prospectively from one of four general paediatric wards. Admissions to one ward are representative of paediatric admissions to the hospital since patients are admitted to each of 4 wards on a cyclical basis. PICT for all paediatric admissions is part of routine care. Where HIV status was unknown, parental consent for testing was obtained. Only data from children whose caregivers (parents or guardians) consented to use of hospital data were included in the analysis.

HIV infection was defined as HIV antibody positive in children ≥18 months of age, or HIV PCR positive in children < 18 months of age. HIV-uninfected was defined as HIV antibody negative for children ≥18 months and DNA PCR negative in children <18 months, or HIV antibody negative in children <18 months or their mothers, indicating lack of HIV exposure. HIV status was recorded as unknown if the test result was not found.

Data were collected from hospital discharge and death summary forms which are routinely completed by hospital staff. Each admission was regarded as a separate event. However to assess the number of unique patients admitted and calculate mortality rates, patients readmitted during the study period were only counted once.

Methodology for previous studies

2007—A cross-sectional retrospective review of all children (from birth to 14 years of age) admitted to all four general paediatric wards at CHB between 1 October 2007 and 31 December 2007 was performed. HIV status was determined by review of laboratory and/or hospital records. HIV diagnosis was established using the criteria as described above for 2010/11. HIV period prevalence was calculated using all admissions in the study sampling timeframe as the denominator and in-hospital mortality rates using hospital records and routinely-collected paediatric ward mortality data. In-depth data on the profile of HIV-

infected paediatric admissions were extracted from individual patient records that were available for 440 of the 446 HIV-infected children.[12]

2005—As part of a larger sentinel surveillance study to monitor the impact of HIV on health services in Gauteng Province, information was collected on all patients admitted to the medical and paediatric wards of four selected hospitals over a 4–6 week period in April and May 2005. The CHB hospital paediatric wards were included among the sites targeted for surveillance, and children were enrolled from all general paediatric wards at CHB. Consent for recording of clinical and demographic information into structured study case report forms, and HIV testing (if status was not already known), was obtained from caregivers. Discharge summaries were completed by ward doctors.

At the time of conduct of this study, the cut-off for ELISA positivity as an indicator of vertical acquisition of maternally-derived antibody was 15 months. HIV infection was defined as being confirmed in children ≥15 months of age with positive antibody tests or in children <15 months if a positive PCR result was obtained. Children <15 months of age with a positive antibody test and clinical evidence of HIV infection but no confirmatory PCR (exposed with clinical evidence) or children of any age without any evidence of an HIV test result but who were suspected of having HIV infection on clinical grounds were deemed to be HIV-infected.[13]

1996—From 1 July to 31 December 1996, children under the age of 5 years admitted to one ward at CHB were enrolled. Parental consent for testing was sought. HIV antibody testing was used to screen patients. Children with positive results had confirmatory serologic tests performed if they were ≥15 months and DNA PCR testing if <15 months of age and asymptomatic for HIV. Children < 15 months of age with positive HIV serology and clinical features of HIV infection were deemed to be HIV-infected. Each admission was regarded as a separate event for most of the analyses however to assess the number of first admissions and mortality rates patients readmitted during the study period were only counted once. Patients were enrolled from one ward over a 6-month period. This study only included children up to 5 years of age.[14]

Statistical methods

Proportions and descriptive statistics were calculated for each survey. Groups were compared within surveys and between surveys using Chi-squared tests for categorical outcomes and Wilcoxon tests for continuous outcomes.

Results

From 1996 until 2007, HIV prevalence among children hospitalised at CHB remained relatively constant; 26.2% (1996; children under 5 years old), 31.7% (2005) and 29.5% (2007) p>0.10, but was significantly lower 19.3% by 2010–11 (p=0.0005) (Table 2).

Of the children admitted in 2010–11, 429 (76.1%) of 564 children had caregiver consent to use their hospital information for study purposes. In this period, there were 397 unique children admitted, (32 of 429 had repeat admissions), 308 (77.6%) HIV-uninfected, 73 (18.4%) HIV-infected and 16 (4.0%) of unknown HIV status.

The median age of the HIV-infected children in the 2010–11 study was significantly older than the HIV-uninfected group: 18.0 vs 7.3 months (p<0.0001) with 20/73 (27.4%) vs. 51/308 (16.6%) (p=0.002) older than 60 months (Table 3). HIV-infected children were significantly more malnourished than their HIV-uninfected counterparts with median WAZ-score −3.48 vs. −1.26 (p<0.0001). Pneumonia 23/73 (31.5%), tuberculosis 18/73 (24.7%),

urinary tract infections 15/73 (20.5%) and gastroenteritis 14/73 (19.2%) were the commonest diagnoses among HIV-infected children, who had longer duration of hospitalisation than HIV-uninfected children (10 vs. 6 days, p<0.0001) and higher in-hospital case fatality rates (9/73 [12.3%] vs. 7/308 [2.3%], p=0.0001).

Among HIV-infected admissions during the 2005, 2007 and 2010–11 studies, the age profiles of children changed with 40.1% (2005), 37.7% (2007) and 24.7% (2010–11) of children being <6 months of age when admitted (Table 4). The proportion of children admitted over 5 years of age also increased from 15.9% (2005) to 22.3% (2007) and 27.4% (2010–11). Median WAZ score was similar over the 3 periods. Median CD4% increased from 0.0% (IQR: 0.0 – 9.4) (2005) to 15.0% (IQR: 8.2 – 22.8) (2007) (p<0.0001) and 18.7% (IQR 9.6 – 24.7) (2010–11) (p>0.10). The proportion of HIV-infected children already established on ART at the time of hospitalisation increased steadily, from 22/182 (12.1%) (2005) to 76/440 (17.3%) (2007) and 26/73 (35.6%) (2010–11). Between 2007 and 2010–11, the frequency of in-hospital ART initiation increased from 15/364 (4.1%) to 11/47 (23.4%) (p<0.0001). There are no data indicating whether children were initiated on ART in the 2005 period.

Mortality rates decreased over the latter 3 time periods (Table 5). Among HIV-infected children, mortality rates declined from 24.0% (2005) to 12.0% (2007) and 12.3% (2010–11). There was no significant change in mortality among HIV-uninfected children over the different study periods. HIV-attributable deaths among infants <6 months of age, were 66.7% (18/27; 2005), 70.0% (28/40; 2007) decreasing to 44.4% (4/9; 2010–11). HIV prevalence among children who died ranged from 68.3% (2005) and 58.2% (2007) to 50.0% in the 2010–11 study.

Infectious diseases were the most common diagnoses among those who died, with pneumonia being the most common cause of death in all study periods. Death was attributed to tuberculosis (TB) in 18.0%, 26.3% and 44.0% of children in 2005, 2007 and 2010–11, respectively (data not shown).

Discussion

The results presented here demonstrate an encouraging trend in the pattern of HIV-related paediatric admissions and overall mortality at one of the busiest public hospitals in South Africa. Despite wide availability of PMTCT and ART services in South Africa since the early part of this century, it is only in the most recent study at CHB hospital, that HIV-related admissions have decreased. HIV prevalence amongst paediatric admissions appears to have peaked (31.7%) in 2005, decreasing to 19.3% (2010/2011).

Previous reports on child health in South Africa have painted a bleak picture of the effect HIV has had on childhood morbidity and mortality. Over the last two decades, with the burden of HIV increasing sharply among pregnant women, paediatric hospitalisations increased simultaneously, mirrored by rising paediatric mortality. South Africa's under-5 mortality (U5M) rate in 1990 was 56 per 1,000 live births, rising to 73 and 67 per 1,000 live births in 2000 and 2008 respectively.[15] This reversal in downward U5M trends was attributable to the paediatric HIV epidemic.[16]

The results of our study reflect progress due to several factors. Nationwide, vertical HIV transmission rates have declined consequent upon recent improvements to the PMTCT programmes.[8,9] Thousands of HIV-infected children are now accessing ART, with excellent outcomes reported at the HIV outpatient service at CHB,[17] and from pooled data from multicentre sites in South Africa.[18] In a recent report on Sowetan children admitted to CHB, a significant reduction in invasive pneumococcal disease (IPD) among HIV-infected

children over the period 2003–2008 was described. Since this was prior to pneumococcal conjugate vaccine (PCV) being introduced, the authors attribute this to increasing ART coverage among children.[19] Together, reduction in perinatal HIV transmission and wider ART coverage likely account for the reduction in HIV-related admissions and for some of the improvement in mortality rates among children admitted to the hospital.

Coverage of adult antiretroviral treatment services has also improved. One report from rural South Africa suggests that maternal antiretroviral therapy improves outcomes in their offspring.[20] This may also be a potential explanation for the improving child outcomes that we observed.

During the period spanned by the surveys reported here, new vaccines were introduced into the South African immunization programme. Introduction of *Haemophilus influenzae* type b vaccine in 1999 was associated with a significant reduction in the number of cases of invasive *H. influenzae* type b disease,[21] and despite the vaccine being reportedly less immunogenic in HIV-infected children in South Africa, it was still estimated to be 83.2% effective.[19] In April 2009, PCV was introduced into the EPI, significant reductions in morbidity and mortality attributable to *Streptococcus pneumoniae* have been reported.[22,23] Although PCV is less effective in HIV-infected children, the vaccine has effected a marked reduction in IPD because of the disproportionate burden of pneumococcal disease encountered in this immunosupressed group of children.[24] Additionally, oral rotavirus vaccine was introduced into the EPI in 2009. Rotavirus infection is considered to be the leading cause of dehydrating diarrhoeal diseases globaly. Oral rotavirus vaccine has demonstrated efficacy in reducing the burden of diarrhoeal disease and although less effective, has demonstrated immunogenicity and is well tolerated in HIV-infected children.[25]

The contribution of tuberculosis (TB) to morbidity and mortality among HIV-infected children increased during the time period. This may partly reflect a proportional decrease in illness from vaccine-preventable acute respiratory infections, prevented by introduction of new vaccines. It is however plausible that this trend may reflect an absolute increase in TB prevalence, possibly through increased household exposure or through increased risk for the development of TB immune reconstitution inflammatory syndrome (IRIS) in the latter time periods. TB IRIS was diagnosed in 10/296 children starting ARV in Cape Town 2003–2005.[26] In the NEVEREST study (2005–2006), 34/162 children with IRIS included 24 with BCG and 12 TB IRIS.[27] With rising numbers of children starting ART in South Africa, increased vigilance for TB IRIS is warranted. We did not have data on the proportion of deaths attributable to culture-confirmed TB in the various studies, although culture-confirmed disease in children is rare. Improved tools for TB diagnosis (GeneXpert) were unavailable and only subsequently introduced in the hospital. Since there was no change in diagnostic methods for paediatric TB, this is unlikely to explain the rise in TB-related mortality in the later periods. Empiric diagnosis of TB may have been more frequently considered in children subsequent to the publication of the WHO TB guidance document in 2006.[28] it has been demonstrated that there is a high prevalence of drug-resistant *Mycobacterium tuberculosis* amongst children diagnosed with culture-confirmed TB at CHB,[29] which may have contributed to more severe illness as a consequence of poor response to first-line anti-tuberculosis therapy. Our findings emphasise that TB remains an important co-infection in children with HIV. Efforts to prevent TB disease and death should focus on the use of isoniazid preventive therapy, early diagnosis and treatment of TB.

The declining proportion of HIV-attributable deaths among the very youngest infants is also heartening. Young infants are most vulnerable to HIV-related death, as demonstrated by Bourne et al, where deaths among young infants caused the sharp spike in South Africa's

infant and U5MR between 1997 and 2002.[30] If, as suggested by our study, mortality in this age group is falling, we cautiously anticipate a reduction in infant and U5 mortality rates and movement in the right direction to attain the fourth Millenium Development Goal (MDG4) of a two thirds reduction in U5M by 2015.[31]

An interesting finding in our study was that median age of children admitted with HIV to the hospital increased in the 2010–11 period. The likely explanation for this is that, as the PMTCT programme expands and fewer infants become infected,[8] the burden of HIV disease among young infants is starting to decrease. HIV infection in women rose rapidly in the late 1990's and early 2000's resulting in HIV transmission to large numbers of infants in the absence of a functional PMTCT programme. Although many infants likely presented and died early, survivors and long term progressors may have remained undiagnosed, becoming sick and requiring admission for the first time at older ages and in the later study periods. A study on temporal trends among children treated at multiple centres in South Africa, demonstrated that between 2004 to 2009, although the proportion of children <18 months starting ART increased, the median age of children starting ART rose.[32] In addition, recent modelling by Marston et al using pooled multicentre data suggests that mortality is significanltly delayed among infants acquiring HIV postnatally through breastfeeding versus infants infected perinatally.[33] Although replacement formula feeding has been available to infants of HIV-infected women, many may not have accessed this intervention and mixed formula and breast feeding occurred commonly.[34] Children being admitted and diagnosed for the first time at older ages may reflect some of these dynamics. It is important for healthcare providers to be vigilant for signs of HIV among older children. Of particular note in this regard, is the relatively high proportion (15%) of children who remained HIV-unknown in the only retrospective survey described in this paper (2007), which possibly reflects the prevailing practice of HIV testing of admitted children at the time of that survey.

There are several limitations to this study. No uniform surveillance system was in place at the hospital and all of the surveys were conducted using different methodologies, making direct comparison of the studies challenging. In the period 2010–11, a larger proportion of caregivers did not sign consent for their children's hospital information to be used as part of the study and the sample size in the latest period was the smallest. The reason for the higher rate of exclusion in the latter period was due to budgetary constraints that precluded having study staff available to obtain consent at all times. Consent for participation was missing not because of active refusals but because caregivers were not available to provide consent at times when study personnel attended the wards. It is unlikely that this resulted in bias to the proportion of HIV admissions or mortality in this latter period. Although reasons for admissions and deaths were available, there was insufficient detail to establish whether these were IRIS related or in any way associated with antiretroviral therapy. The results from this large urban academic hospital in the well-resourced province of Gauteng, may not be directly generalisable to rural or less well-resourced settings. Nevertheless, we believe that each study period is representative of admissions to the hospital during that time, since each survey utilised a representative sample of admissions to the general paediatric wards at the facility. Our results are cause for cautious optimism for both our immediate environment and for other settings in South Africa because the PMTCT programme is widely implemented, there is broader access to ART for HIV-infected children, and the new EPI vaccinations are available nationally.

There is, however, little room for complacency. Nearly one fifth of the estimated 6,000 admissions to the paediatric wards at CHB remain HIV-related in 2010–11. Even though results from the PMTCT programme are reassuring, HIV is a preventable condition in children, and most cases should be successfully prevented. Among HIV-infected infants for whom PMTCT has failed, HIV diagnosis and access to ART is often delayed until the first

episode of hospitalisation. PMTCT and ART coverage needs to continue to grow and expand, to ensure that fewer opportunities for intervention are missed. Mortality remains greater in HIV-infected children than their uninfected counterparts. A high index of suspicion for HIV-infection should be maintained and routine HIV screening of all children presenting at health services should increase in order to diagnose all infants and older children. With continued effort, South Africa can regain some ground in attaining the MDG4 target and substantially reduce new HIV infections and HIV-related deaths among children.

Acknowledgments

Source of Funding: Dr Tammy Meyers is a Fogarty Fellow sponsored by grant no. 5U2RTW007370 and 5U2RTW007373. We are grateful to Chih-Chi Hu of the Gertrude H. Sergievsky Center, College of Physicians and Surgeons; and Department of Epidemiology, Mailman School of Public Health for her insightful assistance with statistical analysis.

References Cited

1. UNICEF. THE STATE OF THE WORLD'S CHILDREN 2011 Adolescence An Age of Opportunity. New York: 2011 Februaru. 2011.
2. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic. 2010. ISBN 978-92-9173-871-7.
3. Friedland IR, Snipelisky M. Vertically transmitted HIV-1 infection in children. A report of 23 cases. S Afr Med J. 1991 Feb 2; 79(3):157–159. [PubMed: 1994487]
4. National Department of Health. National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa 2009. Pretoria: 2010.
5. Zwi KJ, Pettifor JM, Soderlund N. Paediatric hospital admissions at a South African urban regional hospital: the impact of HIV, 1992–1997. Ann Trop Paediatr. 1999 Jun; 19(2):135–142. [PubMed: 10690253]
6. Zwi K, Pettifor J, Soderlund N, Meyers T. HIV infection and in-hospital mortality at an academic hospital in South Africa. Arch Dis Child. 2000 Sep; 83(3):227–230. [PubMed: 10952640]
7. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010.
8. Sherman, G. Report on Early infant diagnosis of HIV infection in South Africa: 2008 to 2010. Johannesburg: National Health Laboratory Service; 2011 Mar.
9. Dinh, T-H. A generic protocol on measuring PMTCT impact through immunization clinic surveys (WHO-CDC). 6th International AIds Society Conference on HIV pathogenesis, treatment and prevention, Elimination of Mother-to-Child Transmission of HIV: Measuring the Effectiveness of National PMTCT Programmes SUSA15; Rome. 2011.
10. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008 Nov 20; 359(21):2233–2244. [PubMed: 19020325]
11. NAtional Department of Health. National HIV Counselling and Testing Policy Guidelines. Pretoria: 2010.
12. Dramowski AC, AH Meyers T, Goga A. Identifying missed opportunities for early intervention among HIV infected paediatric admissions at Chris Hani Baragwanath Hospital, Soweto, South Africa. South African Jounal of HIV Medicine. 2011 Dec; 2011(42):16–23.
13. Schneider H, Kellerman R, Oyedele S. HIV Impact Surveillance System in 2005 Summary Report; Design and Data Collection: Wits School of Public Health Gauteng Department of Health. 2005
14. Meyers TM, Pettifor JM, Gray GE, Crewe-Brown H, Galpin JS. Pediatric admissions with human immunodeficiency virus infection at a regional hospital in Soweto, South Africa. J Trop Pediatr. 2000 Aug; 46(4):224–230. [PubMed: 10996984]
15. Bhutta ZA, Chopra M, Axelson H, et al. Countdown to 2015 decade report (2000–10): taking stock of maternal, newborn, and child survival. Lancet. 2010 Jun 5; 375(9730):2032–2044. [PubMed: 20569843]

16. Bradshaw D, Chopra M, Kerber K, et al. Every death counts: use of mortality audit data for decision making to save the lives of mothers, babies, and children in South Africa. Lancet. 2008 Apr 12; 371(9620):1294–1304. [PubMed: 18406864]

17. Meyers TM, Yotebieng M, Kuhn L, Moultrie H. Antiretroviral Therapy Responses Among Children Attending a Large Public Clinic in Soweto, South Africa. Pediatr Infect Dis J. 2011 Jul 15.

18. Davies MA, Keiser O, Technau K, et al. Outcomes of the South African National Antiretroviral Treatment Programme for children: the IeDEA Southern Africa collaboration. S Afr Med J. 2009 Oct; 99(10):730–737. [PubMed: 20128272]

19. Nunes MC, von Gottberg A, de Gouveia L, et al. The impact of antiretroviral treatment on the burden of invasive pneumococcal disease in South African children: a time series analysis. Aids. 2011 Feb 20; 25(4):453–462. [PubMed: 21178754]

20. Ndirangu J, Newell ML, Thorne C, Bland R. Treating HIV-infected mothers reduces under 5 years of age mortality rates to levels seen in children of HIV-uninfected mothers in rural South Africa. Antivir Ther. 2012; 17(1):81–90. [PubMed: 22267472]

21. von Gottberg A, de Gouveia L, Madhi SA, et al. Impact of conjugate Haemophilus influenzae type b (Hib) vaccine introduction in South Africa. Bull World Health Organ. 2006 Oct; 84(10):811–818. [PubMed: 17128361]

22. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med. 2003 Oct 2; 349(14):1341–1348. [PubMed: 14523142]

23. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet. 2005 Mar 26; Apr 26; 365(9465):1139–1146. [PubMed: 15794968]

24. Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and - uninfected children. Clin Infect Dis. 2005 May 15; 40(10):1511–1518. [PubMed: 15844075]

25. Steele AD, Madhi SA, Louw CE, et al. Safety, Reactogenicity, and Immunogenicity of Human Rotavirus Vaccine RIX4414 in Human Immunodeficiency Virus-positive Infants in South Africa. Pediatr Infect Dis J. 2011 Feb; 30(2):125–130. [PubMed: 20842070]

26. Walters E, Cotton MF, Rabie H, Schaaf HS, Walters LO, Marais BJ. Clinical presentation and outcome of tuberculosis in human immunodeficiency virus infected children on anti-retroviral therapy. BMC Pediatr. 2008; 8:1. [PubMed: 18186944]

27. Smith K, Kuhn L, Coovadia A, et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. Aids. 2009 Jun 1; 23(9):1097–1107. [PubMed: 19417581]

28. WHO. Guidance for nationa tuberculosis programmes on the management of tuberculosis in children. Geneva: 2006.

29. Fairlie L, Beylis NC, Reubenson G, Moore DP, Madhi SA. High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study. BMC Infect Dis. 2011; 11:28. [PubMed: 21269475]

30. Bourne DE, Thompson M, Brody LL, et al. Emergence of a peak in early infant mortality due to HIV/AIDS in South Africa. Aids. 2009 Jan 2; 23(1):101–106. [PubMed: 19065753]

31. Lozano R, Wang H, Foreman KJ, et al. Progress towards Millennium Development Goals 4 and on maternal and child mortality: an updated systematic analysis. Lancet. 2011 Sep 24; 378(9797): 1139–1165. [PubMed: 21937100]

32. Fatti G, Bock P, Eley B, Mothibi E, Grimwood A. Temporal Trends in Baseline Characteristics and Treatment Outcomes of Children Starting Antiretroviral Treatment: An Analysis in Four Provinces in South Africa, 2004–2009. J Acquir Immune Defic Syndr. 2011 Sep 8.

33. Marston M, Becquet R, Zaba B, et al. Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa. Int J Epidemiol. 2011 Apr; 40(2):385–396. [PubMed: 21247884]

34. Laher F, Cescon A, Lazarus E, et al. Conversations With Mothers: Exploring Reasons for Prevention of Mother-to-Child Transmission (PMTCT) Failures in the Era of Programmatic Scale-Up in Soweto, South Africa. AIDS Behav. 2011 Jan 1.

Table 1

Summary of 4 surveillance studies conducted at Chris Hani Baragwanath Hospital 1996–2011

Period	PMTCT available	Wards included	Duration	Sample size	Season	Prospective	Age of children	Age at diagnosis of HIV ELISA vs. DNA PCR
1 July–31 Dec 1996[14]	None	One of four	6 months	549	Winter-summer	Yes	< 5years	15 months
18 April–15 May 2005[13]	CD4 <200 → ART start mother CD4 > 200→ Single dose nevirapine for mother and baby	All four	1 month	575	Autumn	Yes	<15 years	15 months
1 Oct–31 Dec 2007[12]	CD4 <200 → ART start mother CD4 >200→ Single dose nevirapine for mother and baby	All four	3 months	1510	Spring-summer	No	<15 years	18 months
1 Aug 2010–31 Jan 2011	CD4<350 → ART start mother CD4>350 → AZT from 14 weeks and single dose nevirapine for mother and baby	One of four	6 months	429	Winter-summer	Yes	<15 years	18 months

Table 2

Prevalence of HIV and mortality rates among paediatric admissions in four surveillance studies conducted at Chris Hani Baragwanath Hospital, Soweto, South Africa 1996–2011

Period	Ward	Age range (years)	Number of children included of total admissions (%)	Number with HIV infection (%)[#]	Percent with unknown HIV status (%)	Mortality rate amongst all admissions (%)
1 June–31 Dec 1996	One of four	0–5	549/549 (100.0)	144/549 (26.2)	56/549 (10.2)	32/493 (6.5)[*]
18 April–15 May 2005	All four	0–15	575/615 (93.5)	182/575 (31.7)	37/575 (6.4)	64/575 (11.1)
1 Oct–31 Dec 2007	All four	0–15	1510/1510 (100.0)	446/1510 (29.5)	227/1510 (15.0)	91/1510 (6.0)
1 Aug 2010–31 Jan 2011	One of four	0–15	429/564 (76.1)	83/429 (19.3)	16/429 (3.7)	18/429 (4.2)

[#]P<0.0001 comparing the HIV prevalence between all four studies and p>0.10 comparing only the first 3 studies

[*]Number of deaths refers to those among the HIV-infected and uninfected children only. Number of deaths among HIV unknown group not reported

Table 3

Profile of 397* children admitted to Chris Hani Baragwanath Hospital during the most recent surveillance study (2010–11) by HIV status

	HIV-infected (N=73)	**HIV-uninfected (N=308)**	**HIV-unknown (N=16)**	**P-values, (HIV-infected vs. uninfected)***
Median Age (months)	18.0	7.3	23.5	<0.0001
<6 months	18 (24.7)	143 (46.4)	4 (25.0)	
6–<24months	25 (34.3)	67 (21.8)	4 (25.0)	
24–<60 months	10 (13.7)	47 (15.3)	4 (25.0)	
>60 months	20 (27.4)	51 (16.6)	4 (25.0)	0.003
Gender (%female)	27 (37.0)	129 (41.9)	7 (43.8)	>0.10
Median Weight-for age z-score (IQR)**	−3.48 (−4.38 to −1.56; n=67)	−1.26 (−2.47 to −0.20; n=289)	−1.30 (−3.33 to −0.60; n=13)	<0.0001
Most frequent admission diagnosis	Bronchopneumonia 23 (31.5%)	Bacterial sepsis of the newborn 53 (17.2%)	Gastroenteritis 4 (25%)	
2nd most frequent admission diagnosis	Primary pulmonary TB 18 (24.7%)	Bronchopneumonia 47 (15.3%)	Bacterial sepsis of the newborn 3 (18.8%)	
3rd most frequent admission diagnosis	Urinary tract infection 15 (20.5%) Gastroenteritis 14 (19.2%)	Gastroenteritis 45 (14.6%)	Bronchopneumonia 2 (12.5%)	
Median no. days of hospital stay	10	6	5.5	<0.0001
Number Died (%)	9 (12.3)	7 (2.3)	2 (12.5)	0.0001

*Unique children only (32 repeat hospitalizations are excluded)

**Refers to children <10 years: 6 HIV-infected, 18 HIV-uninfected and 3 HIV-unknown children were older than 10 years and were not included in the comparison as WHO Growth Reference Standards software only accommodates analysis up to 10 years of age. One child in the HIV-uninfected group had no recorded weight.

*Categorical variables compared using Chi-squared tests and continuous variables using Wilcoxon test.

Table 4

Comparisons of characteristics of the HIV-infected children admitted to Chris Hani Baragwanath Hospital in 3 surveillance studies; 2005, 2007 and 2010–11

	Children admitted 18 April–15 May 2005 (n=182)	**Children admitted 1 Oct–31 Dec 2007 (n=440)**	**Children admitted 1 Aug 2010–31 Jan 2011 (n=73)**	**p-value * 2005 vs. 2007**	**p-value * 2007 vs. 2010–11**
Gender female (%)	89 (48.9)	206 (46.8)	27 (37.0)	>0.10	>0.10
Median age (months; IQR)	9.13 (3.6 – 28.8)	10.0 (3.0 – 44.5)	18.0 (6.2 – 69.8)	>0.10	0.048
< 6months (%)	73 (40.1)	166 (37.7)	18 (24.7)	0.578	0.031
6 – <24 months (%)	54 (29.7)	116 (26.4)	25 (34.3)	0.400	0.162
24 – <60 months (%)	26 (14.3)	60 (13.6)	10 (13.7)	0.831	0.989
>60 months (%)	29 (15.9)	98 (22.3)	20 (27.4)	0.074	0.335
Median WAZ-score (IQR) *	−3.08 (−4.40 to −1.77;n=173)	−3.05 (−4.15 to −1.68; n=402)	−3.48 (−4.38 to −1.56; n=67)	>0.10	>0.10
Median CD4% (IQR)	0.0 (0.0 – 9.4)	15.0 (8.2 – 22.8)	18.7 (9.6 – 24.7)	<0.0001	>0.10
Number started ART at current visit (%)	Not available	15/364 (4.1)	11/47 (23)		<0.001
Number already on ART (%)	22/182 (12.1)	76 (17.3)	26 (35.6)	>0.1	0.0003

* Refers to children <10 years

* Categorical variables compared using Chi-squared tests and continuous variables using Wilcoxon test.

Table 5

Mortality by surveillance study period among all paediatric admissions (2005–2011), by HIV-infection status, percentage deaths of HIV-infected infants <6 months and percentage HIV-related deaths

	18 April –15 May 2005 (n=565)	**1 Oct – 31 Dec 2007 (n=1510)**	**1 Aug 2010 – 31 Jan 2011 (n=397)**
Mortality rate overall (%)	63/565 (11.2)	91/1510 (6.0)	18/429 (4.2)
Mortality in HIV-uninfected (%)[#]	16/350 (4.6)	38/1064 (3.6)[*]	7/308 (2.3)
Mortality in HIV-infected (%)[##]	43/179 (24.0)	53/440 (12.0)	9/73 (12.3)
Deaths in HIV-infected children <6 months by all deaths <6 months	18/27 (66.7)	28/40 (70.0)	4/9 (44.4)
% of all deaths that were HIV-related	43/63 (68.3)	53/91 (58.2)	9/18 (50.0)

[#]Not significantly different across time (p>0.10)

[##]P=0.001 for difference over time (chi-squared test for trend)

[*]This number includes deaths in HIV-uninfected, HIV-exposed unknown and HIV-unknown children.