

ABSTRACT

Paediatric HIV care has lagged behind that for adults in South Africa. It is estimated that almost 300 000 children are HIV-infected. HIV is responsible for an upswing of child mortality in the country, reversing improvements in child survival. Despite the implementation of a perinatal prevention programme in 2003 and the increasing availability of antiretroviral therapy for children since early 2004, facilities still admit significantly large numbers of HIV-infected children. Little data exist evaluating the outcomes of the prevention of mother-to-child transmission of HIV programme. Postnatal transmission of HIV is elevated despite the availability of replacement feeds as part of the national prevention of mother-to-child transmission of HIV programme. Infant diagnosis rates are low even though guidelines recommend diagnosing infants from 6 weeks of age. Cotrimoxazole prophylaxis is not widely available, this contributes to high morbidity and mortality in HIV-infected infants. The number of children receiving antiretroviral therapy has increased over the past year from roughly 3 000 to more than 14 000, however inequalities exist across the provinces. Challenges for paediatric antiretroviral therapy include lack of sufficiently trained health care personnel, inadequate facilities, complexity of treatment recommendations, as well as drug regimens and formulations. Children are made particularly vulnerable by their circumstances and by frequent change of caregivers. Lack of integration of services results in attrition of patients at each step from prior to delivery through to the initiation of ART. Still relatively few children are benefiting from the services which should be available through the Comprehensive HIV and AIDS, Care, Management and Treatment Plan.

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INTRODUCTION

There is mounting global concern regarding the lack of urgency in response to the plight of children affected by the HIV pandemic. Every day an estimated 1 800 children under-15 years of age become infected and 1 400 children die from the disease, with the majority of these in sub-Saharan Africa.¹ UNICEF in its 'Unite for Children, Unite against AIDS' campaign of 2005 urges countries to take 'urgent account of the specific impact of AIDS on children'.²

South Africa (SA) faces many challenges in rolling out the Comprehensive HIV and AIDS, Care, Management and Treatment Plan (CCMT) due to lack of sufficiently trained staff, laboratory capacity, drug procurement and distribution problems as well as integration of services.

This chapter uses the available data to review the epidemiology of paediatric HIV and focuses on prevention of paediatric infection, early diagnosis and medical care for infected children. It uses, wherever possible, information from peer-reviewed publications. Other sources of information include several reports produced by various organisations. Although these reports contain limited data, they have been helpful in providing snapshot information on various aspects of the programme.

Palliative care, psychosocial and traditional medicine issues, while important components of the programme are not addressed here. Other components of comprehensive paediatric HIV care such as child nutrition receive attention elsewhere in this Review.

HIV INCIDENCE, PREVALENCE AND MORTALITY IN CHILDREN

In 2004, 29.5 % of women attending public antenatal facilities were HIV positive.³ The lack of data on the national coverage and efficacy of the prevention of mother-to-child transmission of HIV (PMTCT) programme makes the HIV infection incidence in children difficult to quantify.

The Actuarial Society of South Africa AIDS and Demographic Model (ASSA2003) assumes that with no intervention, 20% of infants born to HIV-infected mothers are infected in utero, at birth or within the first 4-6 weeks postpartum and that another 16% of

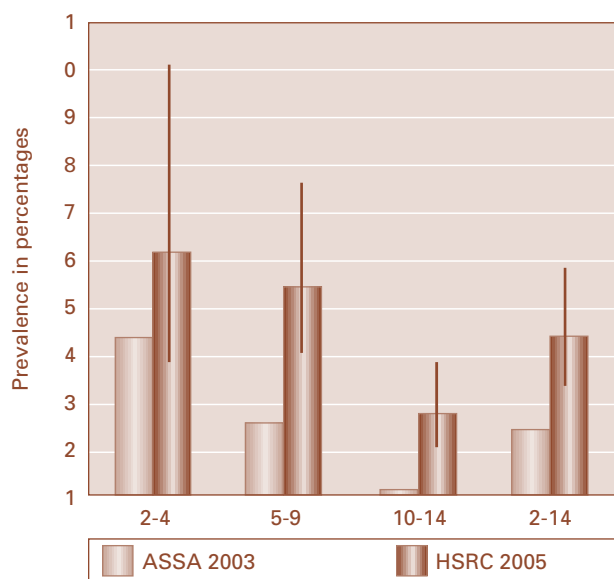
those initially negative are assumed to acquire the virus through breastfeeding up to 18-24 months. The model also assumes that 80% of pregnant women in 2004 had access to PMTCT services with 80% agreeing to VCT and 100% of those tested receiving nevirapine and 50.3% opting to formula feed. Using these assumptions, the ASSA2003 model estimates that, in the calendar year commencing 1st January 2004, 41 000 babies were infected within the first 4-6 weeks of life with an additional 28 000 infected through breast milk.^{4,a} In comparison the national Department of Health (DoH), assuming a flat mother-to-child HIV transmission (MTCT) rate of 30% and utilising mid-point population estimates based on a 'with AIDS' scenario from Statistics South Africa (StatsSA), estimated that 105 000 babies (95%CI: 98 347-111 403) were infected in 2004.³ Since the DoH makes no allowance for the PMTCT programme and uses the StatsSA mid-point population estimates, their figures are likely to be an overestimate; whereas the ASSA2003 model appears to overestimate PMTCT uptake (see PMTCT section) and thus underestimate incidence. The true incidence of paediatric HIV in SA is therefore likely to lie somewhere between these two estimates.

In older children, ASSA2003 estimates that 1.4% of children aged 2-14 years were HIV-infected in mid-2005. In comparison, the 2005 Human Sciences Research Council (HSRC) household HIV prevalence and behaviour survey estimated that 3.3% (95%CI: 2.3-4.8%) of children in SA were HIV positive in mid-2005.⁵ The reasons for the lower prevalence found in the HSRC's 2005 survey compared with its 2002 survey (5.6%; 95%CI: 3.7-7.4%)⁶ are unknown, but are probably partly due to an increase in sample size and the use of a more accurate test in the 2005 survey. The 2005 HSRC survey was limited by the exclusion of children <2 years and children in institutions, assumptions regarding South Africa's demographic profile and a testing rate of only 54.6% of eligible children.

a Figures rounded to nearest 1 000 to avoid spurious accuracy. If the PMTCT uptake rates for all population groups in the ASSA2003 model are decreased to 60% of pregnant women tested and 90% of these receiving nevirapine, ASSA2003 generates estimates of 45 000 infected in the first few weeks of life and 30 000 through breast milk in the calendar year starting 1st of July 2004. Because of the change in assumptions the figures in this footnote do not represent the views of the ASSA.



FIGURE 1:
HIV prevalence in children 2-14 years of age, mid 2005



Source: AIDS Committee of the Actuarial Society of South Africa.⁷

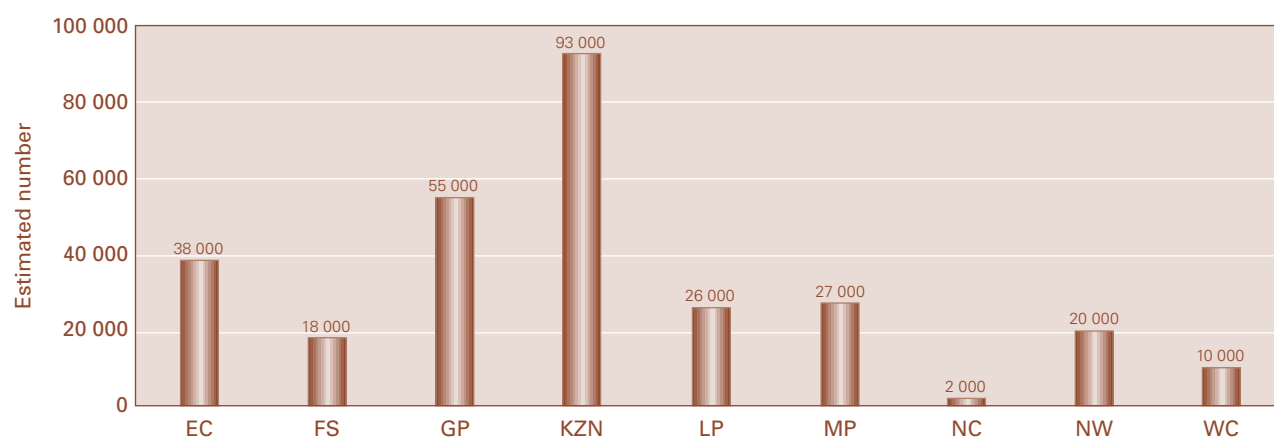
A comparison between the ASSA2003 model and the 2005 HSRC survey is shown in Figure 1.⁷ The higher prevalence rates found in the 2005 survey are difficult to explain. The authors suggest some of the discrepancy would potentially be explained by non-vertical transmission or by a higher proportion of late transmission with concomitant longer survival, but

note that the higher prevalence rate is not corroborated by cause of death data, particularly in older children. Recently Shisana et al.⁸ found only seven (1.4%) of 484 HIV-infected children in the Free State had HIV negative mothers which is too low to explain the large discrepancy between the ASSA2003 model and the 2005 HSRC survey. While high rates of late transmission through breast milk recently reported in SA⁹ could account for some of the discrepancy in younger children, the most plausible explanation for the higher prevalence reported in older children in the 2005 survey are due to the methodological limitations of the survey exacerbated by the likely overestimate of PMTCT uptake in the ASSA2003 model.

The ASSA2003 model would, however, appear to provide the most reliable estimates available of HIV-infected children in SA. In mid 2005 the ASSA2003 model estimates that there were 275 000 HIV-infected children, increasing to 293 000 in mid-2006.^{10,b} It should be noted that because of the methodology employed, these estimates do not have confidence intervals or probability bounds and would be increased should the PMTCT coverage rate prove to be lower than assumed by the model.

Figure 2 shows the estimated distribution of HIV-infected children by province.¹¹

FIGURE 2:
Estimated number of HIV-infected children under-15 years by province, 2005



Source: ASSA 2003 Provincial Output Tables.^{11,c}

b Figures rounded to nearest 1 000 to avoid spurious accuracy. If the PMTCT uptake rates for all population groups in the ASSA2003 model are decreased to 60% of pregnant women tested and 90% of these receiving nevirapine, ASSA2003 generates estimates of 287 000 infected in July 2005 and 309 000 in mid-2006. Because of the change in assumptions, the figures in this footnote do not represent the views of the ASSA.

c Numbers rounded to nearest 1 000 to avoid spurious accuracy. The sum of provincial figures will not equal those provided for South Africa because of differences in the provincial and national models.

The proportion of HIV-infected children requiring antiretroviral therapy (ART) is unknown. However, pro-gression to AIDS is more rapid in children than adults. ASSA2003 estimates that a total of 41 000 children had clinical AIDS in mid-2005. However, the high mortality rate in children with AIDS means that many more children would have progressed through to AIDS at some point during the year. Furthermore, antiretroviral therapy guidelines recommend initiation of ART for children with WHO stage 3 clinical disease and low CD4 counts or percentages.¹² The authors roughly estimate that at least 40% (110 000 children) of all HIV-infected children in SA require ART.

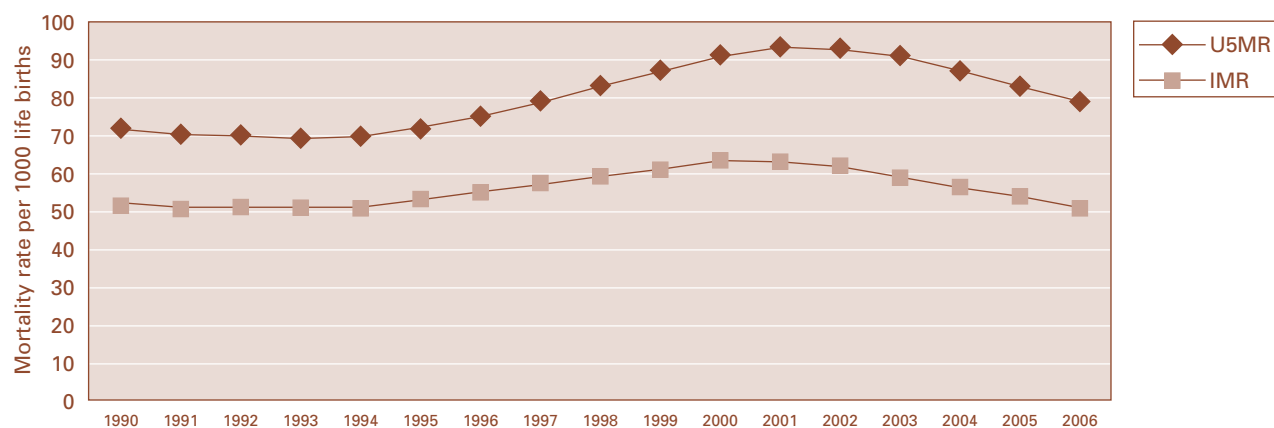
MORTALITY

SA adopted the Millennium Development Goals (MDG) in 2000, committing the country to reducing under-5 mortality rate by $\frac{2}{3}$ by 2015.¹³ Under-5 (U5MR) and infant mortality rate (IMR) in SA had decreased from 1975 through to 1994.^{14,15} In 1998, the South African Demographic and Health Survey (SADHS) reported an IMR of 45.5 and U5MR of 59.4.¹⁶ The 2001 census data were too flawed to provide any credible childhood mortality rates.¹⁷ All childhood mortality data provided for SA since 1998 have incorporated some degree of modelling.

The estimates produced by Dorrington et al. (Figure 3) using the ASSA2002 model suggest an upswing in the IMR and U5MR until 2001; and estimated that 42% of deaths in children under-15 in 2004 were due to HIV.¹⁸ Their model, which predicts a decline in childhood mortality rates from 2002 onwards, assumes an increase in national PMTCT coverage from 10% in 2001 to 90% in 2005 with a constant uptake rate of 80% of women who had access to a PMTCT service which has not been borne out by the most recent estimates of PMTCT coverage (see PMTCT later in this chapter).

The provincial U5MR estimates (Figure 4) produced by Bradshaw et al.¹⁹ from analysis of the National Burden of Disease data reveal large differences between provinces, with KwaZulu-Natal having a rate 2.5 times that of the Western Cape.

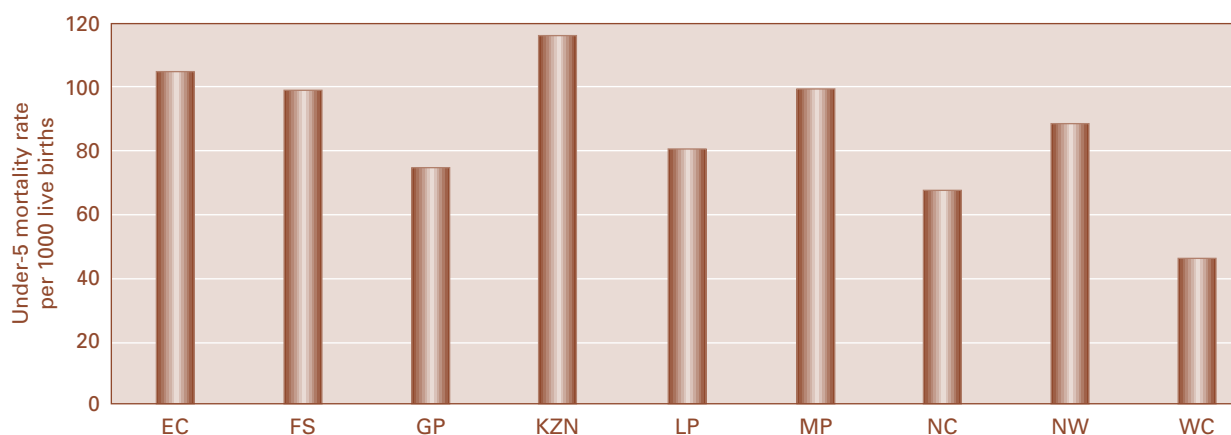
FIGURE 3:
Childhood mortality in South Africa 1990-2006



Source: Adapted from Dorrington et al.¹⁸



FIGURE 4:
Provincial estimates of under-5 mortality by province, 2000



Source: Bradshaw et al.¹⁹

Reported deaths in children under-15 increased by 72.9% between 1997 and 2004 (Table 1).²⁰ While some of this increase could be attributed to improved death reporting and increased total population, much of the increase in mortality is attributable to HIV. Analysis of cause-specific mortality rates in 2000 and 2001 revealed that HIV related mortality was significantly under-reported with 49.2% of under-5 deaths from nine specific causes being misclassified as non-HIV related.²¹ The study estimated 40 727 children under-5 years died in 2000-2001 from HIV which was similar to the ASSA2000 estimate.

TABLE 1:
Increase in reported deaths in children <15 years of age in South Africa 1997-2004

Year of Death	Reported Deaths
1997	38 194
1998	44 169
1999	44 810
2000	45 861
2001	48 090
2002	54 101
2003	60 231
2004	66 072
Increase 1997-2004	72.9%

Source: Statistics South Africa.²⁰

Mortality in HIV-infected children in the first year of life is very high with estimates of 30-39%.^{22,23} Recent and unpublished data emerging from the School of Public Health at the University of Cape Town and the Burden of Disease Research Unit at the Medical Research Council (MRC) indicate a peak in mortality at around 3 months of age contributing significantly to infant and under-5 mortality rates. It is likely that this peak of mortality is predominantly in peripartum HIV-infected infants.^c

Hospital mortality data from 2003/2004 from the Child Problem Identification Programme (Child-PIP) Group show an overall case fatality rate of 7.8% with 60% of deaths being HIV-related.²⁴ At Chris Hani Baragwanath Hospital (CHB), Soweto, inpatient mortality increased from 4.3% to 5.2% and the HIV contribution to inpatient deaths rose from 6.7% to 46.1% between 1992 and 1996.²⁵ In 2005 overall inpatient paediatric mortality at CHB had risen further to 10.9%.²⁶

Of concern, although beyond the scope of this chapter, is emerging data indicating that mortality in HIV-exposed infants is related to maternal mortality, irrespective of the HIV status of the child.²⁷

c Personal communication, D. Bourne, UCT School of Public Health, July 2006.

HIV-RELATED PAEDIATRIC HOSPITAL ADMISSIONS – BURDEN ON THE HEALTH SECTOR

Hospital admission data have been published from CHB Hospital reflecting patterns of paediatric admissions over the last 15 years. This provides snapshot information about the burden of disease on hospitals in the most densely populated province in the country. Similar information from other provinces is not available.

Annual paediatric admissions to CHB increased by 23.6% from 1992 to 1997.²⁸ In 1996, 29.2% of admissions to CHB were HIV positive.²⁹ In 2005, a sentinel surveillance system showed 31.5% of admissions to CHB were HIV positive and as can be seen in Figure 5 HIV prevalence in other hospitals was also high.²⁶ The similarity between the 1996 and 2005 seroprevalence rates is interesting given the doubling of antenatal clinic (ANC) seroprevalence rates during this period. Dorrington et al. estimates,¹⁸ however, suggest that the HIV seroprevalence rate might have peaked between 1996 and 2001. The implementation of the PMTCT programme has probably contributed to the apparent plateau, although other factors such as changes in health care workers' decision making processes on whether to admit patients or not, in health seeking behaviour, and in the provision of ART could also have contributed.

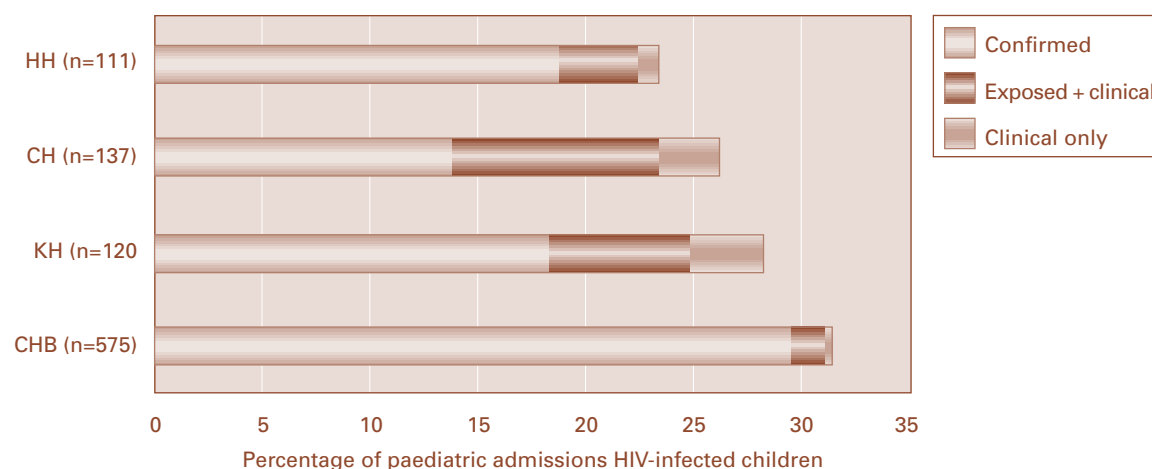
CHALLENGES AND RECOMMENDATIONS REGARDING THE EPIDEMIOLOGY OF PAEDIATRIC HIV

The ASSA2003 model is able to provide fairly robust HIV prevalence, incidence and mortality estimates which are adequate for planning purposes, particularly since service delivery is limited by capacity. However, further research into the causes of discrepancies between the ASSA2003 model and the second household survey is required.

While the impact of HIV on IMR and U5MR in SA can be estimated, better census data collection, increased HIV testing of children, improved death registration and the completion of 'cause-of-death' on death certificates would facilitate ongoing monitoring of paediatric HIV-related mortality trends. This is increasingly important as the provision of ART to children is scaled up.

Sentinel surveillance at health care facilities and population-based prevalence surveys which include children less than 2 years of age are required from all provinces to monitor and evaluate the coverage and impact of the PMTCT programme and the roll-out of ART, as routine data are currently inadequate. Improving the tracking and follow-up of infants at and between primary health care facilities is necessary to obtain better routine data of the coverage and impact of the PMTCT programme.

FIGURE 5:
HIV related admissions at four Gauteng Hospitals (paediatric wards)



Source: Schneider et al., 2005.^{26,d}

d HH – Heidelberg Hospital, CH – Carltonville Hospital, KH – Kalafong Hospital and CHB – Chris Hani Baragwanath Hospital.



PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV

HIV infection in children is preventable. In Europe and the United States, MTCT rates have been reduced to under 2% and few HIV-infected babies are born in these countries.^{30,31} In 2002, SA set a goal to reduce the proportion of infants infected with HIV by 20% by 2005.³² There are no reliable data to assess whether this has been achieved.

PMTCT involves providing information, education and counselling on primary prevention of infection and unintended pregnancy in women; identification of HIV-positive pregnant women; and ART prevention of perinatal transmission, as well as feeding options.

PREVENTION OF HIV INFECTION OF WOMEN AND OF UNINTENDED PREGNANCY

The primary prevention of HIV infection and of unintended pregnancies in women is essential to the prevention of vertical transmission to children. Sweat et al. demonstrate through modelling, that the impact of small reductions in HIV prevalence among young women and in unintended pregnancy, is equivalent to that of antiretroviral interventions on reducing HIV incidence in children.³³

VOLUNTARY COUNSELLING AND TESTING

The uptake of Voluntary Counselling and Testing (VCT) at antenatal services is reportedly low, with some indication that less than 50% of women attending PMTCT sites agree to be tested.³⁴ Current approaches to VCT adhere to 'opt-in' principles although opt-out strategies appear to dramatically increase uptake of testing.³⁵

REPEAT TESTING OF WOMEN IN LATE PREGNANCY

Pregnant women have a higher risk of acquiring HIV than non-pregnant women³⁶ and the risk of transmission is increased in women with high viral loads³⁷ which are found in patients with acute primary HIV infection. A second test at or around the time of delivery, would allow for the provision of post-exposure prophylaxis which has been shown to reduce

transmission of HIV to infants of untreated mothers.³⁸ The incidence rate of HIV infection in women 15-49 years of age in SA was recently reported to be 6.3% with an even higher incidence of 7.9% in women who had been pregnant in the past 24 months.⁵ The methodology used in this study to determine incidence is thought to significantly over-estimate incidence, possibly by as much as 2-3 fold.⁷ A seroconversion rate of 5% in pregnant women attending CHB Hospital has been cited elsewhere,³⁹ and a seroconversion rate of 2% was reported in rural KwaZulu-Natal in 2000.⁴⁰ However, a study in the Western Cape utilising repeat HIV-Elisa tests in late pregnancy found no late seroconversion during pregnancy in 532 women.⁴¹ An American study concluded that re-testing, together with the provision of triple therapy to newly identified HIV positive women in late pregnancy, would be cost-effective in a population with an incidence rate of 1.2 per 1 000 person-years.⁴² The local feasibility, programmatic effectiveness and cost-effectiveness of implementing a repeat testing strategy needs to be studied with reference to the type of test (Elisa versus Ribonucleic acid [RNA] Polymerase Chain Reaction[PCR]) and intervention (triple therapy versus single dose nevirapine) before a recommendation on repeat testing can be made.

FEEDING OPTIONS

HIV transmission to infants can occur through breastfeeding, although exclusive breastfeeding for the first few months of life is associated with lower transmission rates than mixed feeding.^{43,44} Replacement feeding is available as an option for women through the national PMTCT programme. Counselling on risks to the infant anticipated by either choice should ensure that women make an informed decision around feeding options most suitable to their circumstances. Chopra et al. have illustrated that late transmission of HIV to children through mixed feeding is occurring, reversing some of the effects of antiretroviral intervention and that this is likely due to inadequate counselling, support and education of women.⁹ (Refer to the HIV and Infant Feeding chapter for a more detailed discussion of the debate around feeding options and programme outcomes for HIV-exposed infants in this Review.)

ANTIRETROVIRAL PREVENTION OF PERINATAL TRANSMISSION

Single-dose nevirapine to mothers and babies has been standard of PMTCT care in SA since 2003. Although simple and cost-effective, its efficacy is at best around 50%.⁴⁵ The national DoH's report to the United Nations General Assembly Special Session on HIV and AIDS (UNGASS) indicates three widely different nevirapine coverage rates of 15%, 55% and 78% within the same document.⁴⁶ The authors believe that nevirapine coverage for HIV-infected pregnant women is no more than 30%, based on PMTCT task team reports.³⁴

No routine information on MTCT rates in SA exists. However, in some urban facilities where more women choose to formula feed, HIV perinatal transmission rates with single-dose nevirapine have been reported to be about 9%.^{47,48}

Nevirapine resistance has been documented in high proportions of mothers and babies following the provision of single-dose nevirapine.^{49,50} The implications for future treatment regimens for mothers and babies are currently being investigated. Evidence suggests that nevirapine-containing regimens for the treatment of women recently receiving nevirapine for PMTCT or with known resistance mutations may not be as efficacious as in women never previously exposed to nevirapine.⁵¹ However, this does not appear to be the case when treatment is commenced after delayed periods of time.^{52,53} Prior single dose nevirapine exposure also does not appear to have an impact on the efficacy of the drug when used to prevent transmission in future pregnancies.^{54,55}

The addition of zidovudine to single-dose nevirapine significantly reduces transmission to less than 2% in non-breast-feeding populations.⁵⁶⁻⁵⁸ The WHO, in the 2005 updated guidelines, recommends and advocates that countries consider implementing combination therapy where feasible.⁵⁹ The Western Cape has implemented this approach. Sweat et al. show that it is more cost-effective for programmes to implement more expensive regimens when these are likely to significantly reduce transmission of HIV beyond that achievable with nevirapine alone.³³ The addition of zidovudine and zidovudine plus lamivudine to single-

dose nevirapine appears to decrease the emergence of resistance.^{60,61}

Women testing HIV positive in early pregnancy should have a CD4 count performed immediately in order to assess whether they require triple ART which would both improve their own outcome and decrease perinatal HIV transmission to their infants. Anecdotal evidence suggests that very few pregnant women with CD4 counts under 200 are receiving triple therapy.

RECOMMENDATIONS

Information on the coverage and efficacy of the PMTCT programme is urgently needed. The following represent practical suggestions from the Concerned Child Health Workers' forum³⁴ as well as Chopra et al.⁶²

- ◆ Incorporate VCT into family planning activities and family planning into VCT services;
- ◆ Implement an opt-out approach to VCT at antenatal clinics;
- ◆ Train all nursing staff who come into contact with pregnant women or mothers of young infants to provide information on PMTCT and infant feeding choices;
- ◆ Improve counsellor training:
 - Provide counsellors with prompt cards reminding them of key issues to be discussed with pregnant women;
 - Include a checklist of counselling topics covered by counsellors in patient files; and
 - Monitor counsellors' competency in delivering key messages.
- ◆ Pregnant women testing HIV positive should immediately have a CD4 count performed to assess whether triple therapy is indicated. Point of service CD4 count machines should be introduced at PMTCT sites;
- ◆ Pregnant women with a CD4 count <200 should access ART as a matter of urgency and systems should be put in place to expedite this at all facilities;
- ◆ Assist health care workers to easily identify exposed children by recording maternal HIV status on the child's Road to Health Chart, the mother's



antenatal clinic card or alternatively on a separate form/smart card which should be presented at Expanded Programme on Immunisation (EPI) visits. However, the potential for negative impact on EPI uptake would need to be evaluated first; and

- ◆ Include zidovudine (ZDV) together with nevirapine for PMTCT (follow WHO recommendations⁶³ ZDV from 28 weeks, single dose nevirapine to mother and baby and ZDV one week to baby postpartum).

HIV DIAGNOSIS OF INFANTS AND CHILDREN

EARLY INFANT DIAGNOSIS

Early identification of HIV-infected children is vital for a child's entry into comprehensive care and to monitor the efficacy of the PMTCT programme. HIV Deoxyribonucleic acid (DNA) PCR testing was introduced in 2004 for early diagnosis of infants from 6 weeks of age.^{12,64} More than 1 million babies were born in SA in 2005 and about 300 000 of these are estimated to have been exposed to HIV, requiring a laboratory capacity to perform 300 000 PCR tests per annum. In January 2006, approximately 5 500 PCR tests were performed nationally, equating to 22% of the total capacity required. Only three laboratories, one in Western Cape, KwaZulu-Natal and Gauteng respectively, are currently processing substantial volumes of HIV DNA PCR tests in SA. The NHLS plans to have 11 HIV DNA PCR laboratories nationally by end of 2006 to improve equity and accessibility.^c

Capacity to perform HIV DNA PCR testing on infants at health care services, particularly outside the major cities is limited. Facilities are poorly staffed and many have no skills required for paediatric venesection. However, dried blood spots (DBS) have been shown to be as accurate as those performed on liquid blood.⁶⁵⁻⁶⁷ DBS from heel pricks are thought to be easier to obtain than liquid blood as many health care workers have been trained to obtain a drop of blood by pricking the heel of infants for evaluation of neonatal jaundice or blood glucose levels. Efforts are underway

to massively scale up DBS nationally to improve the rate of diagnosis in the field,^f despite the fact that it is less complicated to process liquid blood at the laboratory.

It is appropriate to perform HIV antibody tests from birth if the mother's HIV status is unknown in order to establish whether the child is HIV-exposed or not. Research on the feasibility of rapid HIV tests in young children is ongoing. Preliminary data suggest the less sensitive rapid tests are highly accurate in excluding infection between 9 and 12 months of age and may be useful as early as 6 months of age as waning maternal antibodies in an HIV uninfected child are less likely to be detected. A negative test in this instance is helpful in confirming lack of infection without requiring repeat testing or an HIV PCR test. False negative rapid HIV test results have been noted. These usually occur in infants with AIDS-defining illnesses making it essential that the HIV test results are interpreted in conjunction with clinical findings. Since false negative rapid HIV results have occurred in asymptomatic, HIV-infected infants it is recommended that rapid HIV tests are performed in parallel (two tests used simultaneously) until further data become available. Oral fluid tests in addition to rapid HIV tests have the potential for excluding HIV infection in HIV-exposed children at less than 9 months of age, further reducing the need for PCR tests. However, further operational research is required.⁶⁸

Since diagnostic PCR is still being phased in, there are many older HIV-infected children who have yet to be identified. The clinical features of HIV in children are too non-specific to enable health care workers to reliably diagnose HIV on clinical grounds alone.²² Laboratory testing is recommended by WHO if it is available prior to the commencement of antiretroviral (ARV).⁶⁹

Opportunities for testing and diagnosing children attending EPI, TB or in- and out-patient paediatric services, and children of adults attending VCT services, are being missed. Only 63% of children admitted to Kalafong, a regional hospital in Gauteng, were tested for HIV.²⁶ In the Problem Identification Programme (PIP) study, in 22% of the deaths reported as being HIV-related, patients were clinically suspected to have had HIV but had not been formally tested.⁷⁰

^c Personal communication, T Marshal, National Health Laboratory Service, September 2005.

^f Personal communication, G Sherman, National Health Laboratory Service, June 2006.

CHALLENGES FOR SCALING UP DIAGNOSIS

- ◆ Knowledge and skills are required by health care workers to perform testing and interpret and act on results speedily;
- ◆ Health workers are anxious about taking blood in infants and children;
- ◆ Scaling up diagnostic services in both clinics and laboratories requires space, human resources and training;
- ◆ Breastfeeding populations present a particular challenge to infant diagnosis because of ongoing exposure to the virus through breast milk and the need to repeat testing after breastfeeding is stopped; and
- ◆ There is a lack of systems in place for health care personnel to easily identify participants of the PMTCT programme who bring their infants for immunisation or other well-baby programmes.

RECOMMENDATIONS

Widespread improvement in the identification of HIV-infected children from 4-6 weeks of age must be urgently implemented.

Early diagnosis with HIV DNA PCR (particularly with DBS) requires that the scale up of laboratory and clinical capacity be synchronised.

At the clinical level, a diagnostic service has to be commenced. This will require:

- ◆ Identifying facilities (e.g. PMTCT programmes, immunisation clinics, etc.);
- ◆ Providing appropriate staffing at these facilities (e.g. phlebotomists, counsellors); and
- ◆ Training staff in blood sampling, laboratory logistics, record keeping, tracking and interpretation of test results.

At the laboratory level:

- ◆ Space has to be found for new instruments that need to be procured;
- ◆ Staff require training;
- ◆ Research and development is needed to improve laboratory capacity e.g. increase automation with careful quality control; and

- ◆ Procurement and distribution of consumables is required to enable DBS testing.

Routine HIV testing of children of all ages needs to be established at all health services, e.g. TB services, in-patient and out-patient, and adult HIV services where parents should be encouraged to bring their children for testing.

Key indicators must be documented to assess service, and monthly HIV DNA PCR test statistics should be made available. A system for feedback from clinics for central monitoring of, for instance, service issues and quality control, should be established.

PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS

COTRIMOXAZOLE PROPHYLAXIS

Cotrimoxazole (CTZ) prophylaxis for prevention of *Pneumocystis jirovecii* pneumonia (PCP) and other commonly acquired infections reduces mortality in HIV-infected children by as much as 43%.⁷¹ PCP has a peak incidence in children between 3 and 6 months of age carrying a very high mortality.⁷² SA follows WHO guidelines in advising CTZ prophylaxis from 4-6 weeks of age for all HIV-exposed infants, continuing in those with a definitive diagnosis of HIV until such time as demonstrated CD4 response has occurred on ART.¹²

Boerma et al. recently estimated that the number of children requiring CTZ prophylaxis in sub-Saharan Africa would be reduced from 3.5 million to 1.9 million through the implementation of early infant diagnosis, as, once a definitive diagnosis has been made, HIV negative infants may have their CTZ stopped.⁷³

In 2001, only a third of clinics in SA reported routine administration of CTZ to HIV-exposed children and the majority of those providing CTZ were administering inappropriate doses.⁷⁴ In 2005, 85% of HIV-exposed infants at Community Health Centres (CHC) in the Cape Town Metropole received CTZ. There are few data from elsewhere, but anecdotal reports indicate that this coverage is inadequate with occasional stock-outs of CTZ occurring at CHC facilities in Soweto.^g

g Personal communication, L Obidike, Wits Paediatric HIV Clinics, March 2006.



TUBERCULOSIS PROPHYLAXIS

Tuberculosis (TB) and HIV co-infection is common in South African children.⁷⁵⁻⁷⁸ At Harriet Shezi Children's Clinic, 38% of children less than three years of age were on TB treatment at the time of starting ART, despite the fact that bacteriological confirmation of TB was rare.⁷⁹ There is no guidance regarding TB prophylaxis for HIV-exposed or infected children in the South African Guidelines.¹² Children under five years of age (both HIV infected and uninfected), where TB has reasonably been excluded and there is an open TB contact, should receive isoniazid (INH) prophylaxis.¹² Routine INH prophylaxis for HIV-infected children has raised concern because of the potential for children with undiagnosed TB to receive INH monotherapy which would result in inadequate treatment and possible resistance to INH.

Zar et al. have reported that routine INH prophylaxis for HIV-infected children has early and significant survival benefit.⁸⁰ Further data are awaited to verify this finding.

RECOMMENDATIONS

Cotrimoxazole prophylaxis is simple and cheap enough to implement widely. A media campaign targeted at HIV-infected women explaining the benefits of CTZ prophylaxis should be implemented to increase client awareness and demand for this service. Health workers should educate expectant mothers about the benefits of CTZ prophylaxis for their infants at early postnatal contact with mothers e.g. visits for fetching formula, 6 week postnatal check-ups or EPI visits.

Pharmacy control systems need to be in place to ensure that stock-outs of this essential drug do not occur and that it is widely available at primary health care levels.

ANTIRETROVIRAL TREATMENT

ACCESS OF CHILDREN TO ANTIRETROVIRAL THERAPY

Highly active antiretroviral therapy (HAART) has been responsible for converting HIV disease into a chronic, manageable disorder in adults and children for more than a decade. This life-sparing therapy has become widely available through the CCMT since early 2004. Early in the programme very few children were accessing this care, although paediatric numbers have increased from fewer than 3 000⁸¹ at the beginning of 2005 to more than 14 000 (Table 2) by early 2006. The total number of children on treatment through private medical aids and other treatment projects outside of the public health system is unknown. However, in one of the largest such programmes, Aid for AIDS, there were, in May 2006, 1 233 children under-12 years of age on treatment, of whom 34% were under-2 years of age.^h

h Personal communication, L Regensberg, C Whitelaw and M Hislop, Aid for AIDS, May 26th 2006.

TABLE 2:
Provincial breakdown of children on ART, early 2006 (public sector)

Province	Children on ARV	Total Number of People on ART	Percentage patients on ART <14 years	Month in 2006
EC	1 523	21 511	7.1	March
FS	605	4 928	12.3	March
GP	4 217	39 165	10.8	February
KZN	3 522	34 205	10.3	March
LP	680	6 679	10.2	March
MP	387	4 796	8.1	March
NC	408	2 320	17.6	February
NW	896	14 821	6.0	March
WC	2 009	16 300	12.3	March
South Africa	14 247	14 4725	9.8	February/March

Source: Statistics provided to authors by provincial CCMT directorates and provincial health care workers.

The rapid increase in absolute numbers of children on treatment is in part, driven by the increase in the number of accredited facilities, with a total of 204 facilities having been accredited by the end of 2005.⁴⁶

The publication of the Guidelines for the Management of HIV-infected Children in 2005 removed a barrier to the provision of ART to children. Nine thousand copies have been disseminated and the guidelines are available on the DoH's web site.¹² Experience in other health programmes, however, suggests that the dissemination of guidelines is unlikely to have had a large impact on care.⁸²

WHO has recently released updated Guidelines for the Management of Children.⁶⁹ Decisions around which recommendations will need to be adopted for South African programme and how these updates should be disseminated will need to be made.

In early 2005, the DoH responded positively to the concerns of health care workers and civil society members about the limited access to care for children provided through the CCMT. Six task teams were formed (PMTCT, infant diagnosis, training and guidelines, integration of services and improvement of health systems, adolescent care and pharmacological issues) to identify barriers and develop specific recommendations. The task teams' recommendations were finalised in November 2005 and tabled to the

DoH. The national DoH has called upon provincial HIV/AIDS, STI and Tuberculosis (HAST) directorates to ensure that children comprise at least 15% of patients on ART.ⁱ

Despite the successful scaling up of ART access for children, marked inequities in care exist. Most provinces have not achieved the targeted proportions. In the Eastern Cape, Mpumalanga and North West provinces, children make up considerably less than 10% of all patients on ART (Table 2). Inequalities in access to paediatric ART exist even within provinces (Table 3) where, for instance in KwaZulu-Natal, children comprise between 5.7% and 20% of patients on ART in the different districts. While KwaZulu-Natal has successfully increased the proportion of children from less than 5% in November 2004⁸³ to more than 10% in 2006, the large differences in absolute numbers and percentages of children on ART by district is cause for concern. The rural district of Umkhanyakude has as many children on ART as eThekweni which has nearly double the number of accredited facilities and incorporates the large hospitals in Durban. ART sites such as Manguzi Hospital, where children comprise 28% of patients on ART, have succeeded in scaling up paediatric ART in very remote, rural areas.

i Personal communication, D Kalumbo, National Department of Health, June 2006.



TABLE 3:
Children on ART by district in KwaZulu-Natal, March 2006

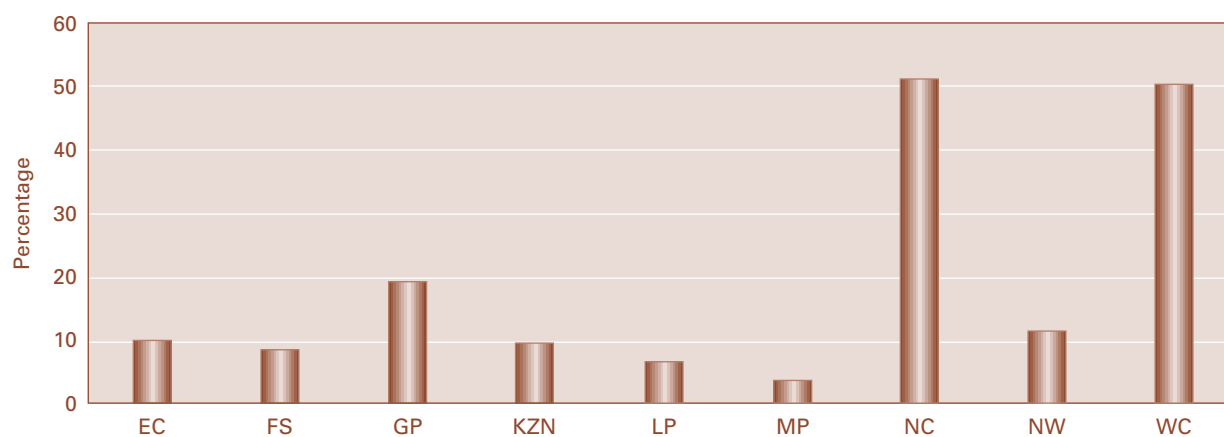
District	Accredited ARV Facilities	Children on ART	Adults on ART	Percentage of patients on ART <14 years of age
Amajuba	3	148	1 530	8.8
eThekweni	9	542	4 769	10.2
iLembe	4	234	1 745	11.8
Sisonke	4	139	1 932	6.7
Ugu	4	127	2 107	5.7
Umgungundlovu	5	816	3 272	20.0
Umkhanyakude	5	548	3 701	12.9
Umzinyathi	4	247	2 784	8.1
Uthukela	3	265	2 613	9.2
Uthungulu	8	329	3 074	9.7
Zululand	6	127	1 896	6.3
TOTAL KZN	55	3 522	29 423	10.7

Source: Weekly Report on ARV Roll-Out, KZN, DoH March 2006.

The provinces where the estimated number of infected children is low, most notably the Western Cape and Northern Cape, are faring much better in meeting the demand for paediatric ART. As noted earlier, it is not known what proportion of HIV-infected children require ART. However, for purposes of comparison, in Figure 6 below, it has been assumed that 40% of all

HIV-infected children require ART. While the percentage of coverage for each province is a very rough estimate, it is clear that there are very large inequities among the provinces, with a child with advanced disease living in the Western Cape having approximately a 14 fold higher chance of being on ART than a similar child in Mpumalanga.

FIGURE 6:
Estimated percentage of children with advanced HIV who are receiving ART^j

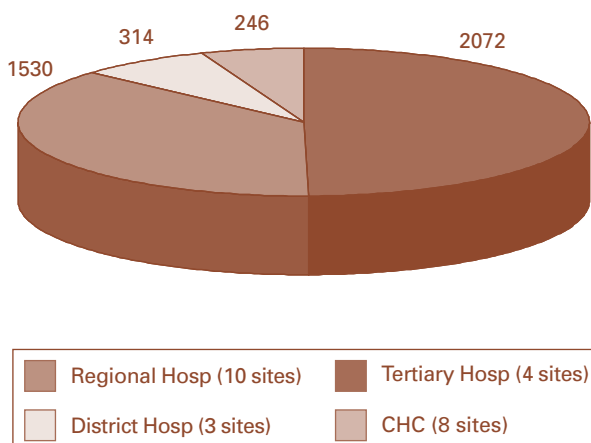


Source: Data compiled from ASSA2003 (provincial output) mid-2005 estimates¹¹ and Table 3 above.

^j These are rough estimates and the dates of the numerator and denominator differ.

As shown in Figure 7, almost half of all children on treatment in Gauteng are receiving ART from tertiary hospitals and only 6% at Community Health Centres (CHCs). The scale up of ART at primary and secondary level facilities in Gauteng has been hampered by a lack of human resources together with inadequate skills to provide appropriate medical care for children. Many facilities lack doctors and primary health care nurses have not been trained to manage HIV-infected patients on ART. However, at CHB Hospital, primary health care nurses have been trained and successfully initiate and manage children on ART with the support of medical officers.

FIGURE 7:
Breakdown of children on ART by health facility level in Gauteng



Source: Compiled from data provided by Gauteng DoH.

The Western Cape has made some progress in decentralising paediatric ART, having decreased the proportion of children receiving ART in the province at three referral hospitals from 78.4% to 49.5% between March 2004 and 2006.^k

HEALTH SYSTEMS CHALLENGES OF SCALING UP PAEDIATRIC ART

IMPACT OF THE VERTICAL NATURE OF ART SERVICES ON THE CARE OF CHILDREN

While the CCMT intended to integrate the component services into the primary health care (PHC) framework, integration of ART with PHC services has been very limited. The current vertical nature of ART poses specific challenges to the provision of care to children. The functional and frequently structural separation of the ART services from other components of the CCMT precludes continuity of care for children and results in high leakage rates between the component services. This is particularly true for children as the PMTCT programme is generally independent from the HIV infant diagnosis services, which in turn are frequently removed from the ART services.

Furthermore, the basket of HIV-related services are delivered independently from the Expanded Programme of Immunisation (EPI), Integrated Management of Childhood Illnesses (IMCI) and Tuberculosis programmes, resulting in missed opportunities. Despite the vast majority of children acquiring HIV from their mothers, ART services for adults and children are separated, with very few family-based clinic services known to the authors.

Staff appointed to the smaller accredited ART facilities, where there is frequently only one ART doctor, are isolated from colleagues in the general services. Experience suggests that ART health care providers frequently do not have the skills or knowledge to adequately manage general paediatric conditions, resulting in a lack of confidence.⁸⁴ Doctors working in ART facilities report 'fear' of taking blood from children.⁸⁵ Guidelines for the management of HIV-infected children were only distributed in late 2005. This delayed distribution of guidelines has been compounded by the lack of a nationally standardised training programme in paediatric ART. In addition, practical on-site case-based training is believed to be necessary to improve health care workers' confidence. Furthermore, health care providers working in small ART services have difficulty in attending training programmes, or even taking leave, as this can result in interruption of service to their patients. The lack of

^k Personal communication, B Eley, University of Cape Town, June 2006.



human resource capacity to provide treatment to all those who need it potentially results in indirect rationing of treatment to those who are informed, geographically close to treatment sites, have time to wait in queues every month to collect medicines and have higher socio-economic status.^{85,86} The lack of family-based services and the geographical concentration of children in the larger ART facilities results in inequity of access and indirectly rations treatment for children. The concentration of children on ART in tertiary/regional facilities also results in inappropriate utilisation of highly skilled staff to manage stable children on ART. These experienced staff will be increasingly needed to attend to more complicated cases related to adverse reactions and treatment failure as the provision of ART matures.

RECOMMENDATIONS

The differences in infrastructure, disease burden and access to resources across provinces and districts requires that local solutions tailored to local conditions are tested and if successful, implemented. District-level networks of all service providers with community representation should be formed to coordinate services and test strategies to improve the functional integration of services. Appointing CCMT staff to a district-based cluster of ART facilities where appropriate could provide staff flexibility, facilitate outreach training and support from the larger ART sites, and improve communication and referrals between ART sites and related services. This cluster strategy needs to be tested.

In addition the following is recommended:

- ◆ The normalisation of HIV, particularly HIV testing, within the health sector is appropriate and necessary, especially since ART has become available.⁸⁷ Removing the exceptionalisation of HIV, however, does not necessarily mean integrating patients on ART into the general queues in PHC clinics.
- ◆ Emphasis should shift away from a doctor-based to a nurse-based service with clinically trained primary health care nurses becoming the key personnel to prescribe treatment to stable patients on ART. Pharmacist assistants should be utilised likewise.
- ◆ Family-orientated services should be aimed at all levels of care where they are feasible, to ensure that families are not inconvenienced by multiple visits. It is recommend that at least one day a week be assigned for family care at ART facilities.
- ◆ Theoretical training for nursing and medical students should be aligned with the DoH treatment guidelines for children.
- ◆ Outreach from sites with experience in treating children should be encouraged to inexperienced sites to provide practical patient-based on-site training.
- ◆ A team needs to be appointed by DoH as technical advisors for regularly updating guidelines and a strategy for dissemination of updated information needs to be developed.
- ◆ A standardised patient management tool to support both the management of patients and the reporting of indicators needs to be developed and piloted. The tool needs to add value to health care workers and facility managers in order to be easily implemented. The system ideally needs to support the tracking of patients across the vertical programmes (VCT, PMTCT, infant diagnosis and ART) and provinces. Programme managers at site level need to be trained to use the data collected to improve the efficiency and effectiveness of their service.

CHALLENGES IN PROVIDING ART TO CHILDREN

Managing children on ART is more complex than in adults because:

- ◆ CD4 percentage rather than absolute count is used in children and the cut-off for initiating therapy differs according to age of child;
- ◆ Drug doses need to be regularly reviewed to keep up with growth;
- ◆ No guidance is provided in DoH guidelines for infants under-6 months of age as few formulations have been studied in this age group and because the mortality is so high, these young infants deserve special attention;

- ◆ Even for older children, fewer formulations exist than for adults and palatability is generally poor; and
- ◆ Elderly caregivers often have practical difficulties dispensing medication e.g. drawing up solutions requires good vision as well as some degree of numeracy.

In addition, as the programme matures, side effects are becoming more evident. In particular, lipoatrophy/lipodystrophy from stavudine is being reported more frequently. Fourteen children at CHB have required regimen changes from stavudine to abacavir because of toxicity.¹

Adherence to ART is enhanced by the simplification of treatment. ART regimens include three separate drugs and sometimes large volumes and/or poorly palatable formulations are prescribed for children. Adequate drug levels and good clinical outcomes have been reported with the use of fixed dose combination (FDC) tablets in children, even when adult strength FDC tablets are broken to approximate paediatric doses.^{88,89} No fixed dose combinations are currently registered for use in children in SA.

The following has been recommended⁹⁰ to address these concerns:

- ◆ The immediate placement of stavudine 15 mg and paediatric strength enteric-coated didanosine on tender and made available in all ART facilities;
- ◆ The fast tracking of the registration of paediatric (i.e. chewable or dispersible) and scored adult FDC formulations by the Medicines Control Council;
- ◆ The even distribution of the active ingredient within adult formulations and the scoring of tablets to facilitate breaking of these for paediatric dosing, where appropriate, by drug manufacturers;
- ◆ The improvement of thermo-stability and palatability of paediatric solutions; and
- ◆ The countrywide standardisation of colour coding of individual antiretroviral agents.

HIGHLY VULNERABLE CHILDREN

INFANTS

HIV-infected infants have a high mortality rate.²³ As described above, limited delivery of infant diagnosis services results in relatively few infants being identified and referred to ART centres. In addition fewer formulations have been studied in young infants and drug dose calculations in the very young require the use of body surface area making treatment more complicated. Obtaining blood samples for monitoring young infants is technically challenging.

ORPHANS AND VULNERABLE CHILDREN

Children are often subject to changing caregivers due to ill-health or death, or adult migration. Child care professionals frequently encounter children with no identifiable or reliable caregiver or family support system. The number of HIV-infected orphans in child-headed households, with unreliable caregivers or who cannot access health services at all, is unknown. There is currently no legislation that addresses this vulnerable group adequately.

ADOLESCENTS

In 2001, the DoH recognised the unique needs of adolescents by formulating a specific health policy which outlines comprehensive and sensitive community-based therapy for all adolescents.⁹¹ ART provision is resulting in more HIV-infected children surviving childhood and entering adolescence, and adolescents are becoming HIV-infected as a result of high-risk behaviour. HIV-infected youth have particular needs which are not addressed by the current policy and few health care workers in SA are skilled at addressing these needs. Adolescent HIV clinics will become increasingly needed.

1 Personal communication, H Moultrie, Wits Paediatric HIV Clinics, May 2006.



DISCLOSURE OF HIV STATUS

Disclosure to other household members and to the child about their own disease is often difficult for caregivers. Children have a right to know their status in an age-appropriate way. Caregivers find it difficult to disclose to children for a number of reasons including fear that the child and family may be stigmatised if the child leaks the information to others. They are also concerned that the information may be overwhelming for the child.⁹² Although disclosure to children is recommended from early ages, as they enter adolescence it becomes more critical that children are aware of their HIV status so that they can make appropriate behavioural choices.

RECOMMENDATIONS

- ◆ Early diagnosis should urgently be scaled up, as discussed above;
- ◆ District Child Care Forums, involving the health sector, social welfare, businesses, non-government organisations and community based organisations, need to be formed or where existing, strengthened. A registry of highly vulnerable children should be kept in each district to coordinate support; and
- ◆ Adolescent-friendly clinic services should be made available in every district by the end of 2006. Adolescent-focused training materials, such as those developed by the National Adolescent-Friendly Clinic Initiative (NAFCI), need to be updated to include information on ART and disseminated.

CHILDRENS' OUTCOMES ON ART

ART in well-resourced countries has resulted in children living healthy, productive lives well into adolescence and early adulthood.^{93,94} Programmes in less resourced countries have also documented good outcomes for children on ART – for instance, in the Ivory Coast, two-year survival rates of 98% in children on ART with CD4 counts of $\geq 5\%$ have been reported.⁹⁵

No routine data on adherence, retention, viral load suppression, clinical status, mortality or side effects are available for children accessing ART through the CCMT. This information is urgently required to assess the impact of the programme. Some sites have, however, published data demonstrating the early benefits of ART

in children enrolled in the programme. In the Northern Cape, 67 of the first 100 children completing at least 6 months of ART achieved viral load suppression (<400 copies/ml).⁹⁶ Significant improvement in CD4 percentages and good clinical outcomes in children have been reported in a cohort in Cape Town.⁹⁷ Significant improvement in weight-for-age z-scores⁹⁸ and viral load suppression rates of more than 80% at 6 months on ART⁹⁹ have been documented in Soweto.

CONCLUSION

Through the CCMT, SA has a programme in place to both prevent children from becoming infected with HIV and to improve the quality of life of those who do become infected. Effort is being placed on the scale-up of paediatric prevention and care, although monitoring processes are not yet sufficiently in place to accurately assess the outcomes of the programme. Focused attention and efficient use of available resources is needed to ensure that the particular needs of children are not overshadowed by the overwhelmingly large adult HIV epidemic. What is evident is that there is marked inequity in access to care in different parts of the country. HIV prevention and care for all children must be addressed urgently and measures should be put in place to track outcomes.

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