Challenges to Pediatric HIV Care and Treatment in South Africa

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It is estimated that almost 300,000 children in South Africa have human immunodeficiency virus (HIV) infection. The disease is responsible for reversing decreases in child mortality. Few data exist evaluating the outcomes of the prevention of mother-to-child transmission of HIV (PMTCT) program, although PMTCT coverage appears to be low. Hospitals are still witnessing large numbers of admissions of HIV-infected children. Postnatal transmission of HIV is high, reflecting poor education of and support for women in their infant feeding choices. Too few infants and children are entering care through early diagnosis, which should be widely available. Cotrimoxazole prophylaxis coverage is inadequate, contributing to high morbidity and mortality in infants. The number of children receiving antiretroviral therapy (ART) is increasing steadily. However, significant inequalities in access to ART exist between and within provinces. Challenges for pediatric ART include a lack of sufficiently trained health care personnel and inadequate facilities, as well as the complexity of drug regimens and formulations. The compartmentalization of the ART rollout program hinders PMTCT and makes it difficult for children to be identified and referred into appropriate services. This article delineates the challenges to pediatric HIV care in South Africa and provides some practical recommendations to improve it.

EPIDEMIOLOGY

In 2004, 29.5% (95% confidence interval [CI], 28.5%–30.5%) of women attending public antenatal facilities in South Africa were HIV positive [1]. There are, unfortunately, no reliable data on the national coverage and efficacy of the prevention of mother-to-child transmission of HIV (PMTCT) program, which makes the incidence of HIV infection in children difficult to quantify.

The Actuarial Society of South Africa AIDS and Demographic Model (ASSA2003), which provides the most plausible estimates of the prevalence of HIV infection among children in South Africa, estimates that there were 275,000 HIV-infected children in mid-2005, increasing to 293,000 in mid-2006 [2]. The estimated numbers of HIV-infected children in each province range from <3000 in the Northern Cape to nearly 100,000 in KwaZulu-Natal (figure 1).

The proportion of these HIV-infected children requiring antiretroviral therapy (ART) is unknown. Progression to AIDS is more rapid in children than adults, and it is likely that a large proportion of HIV-infected children are urgently in need of access to ART.

The under-5 mortality rate and the infant mortality

* Figures are rounded to nearest 1000 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 those 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 Actuarial Society of South Africa.
rate in South Africa decreased from 1975 to 1994 [3, 4]. Data from the 1998 South African Demographic and Health Survey suggested reversals of these gains. Indications from other studies are that mortality rates among infants and among children <5 years of age are continuing to rise [4–6]. Reported deaths among children <15 years of age increased by 72.9% between 1997 and 2004 (table 1) [7]. Much of the increase in mortality is attributable to HIV/AIDS, although registration of deaths has improved during this period.

PMTCT

It is impossible to discuss care for HIV-infected children in South Africa without focusing on PMTCT, because pediatric HIV infection is a preventable condition [8, 9]. In 2002, South Africa set a goal to reduce the proportion of infants infected with HIV by 20% by 2005 [10]. There is no reliable information to assess whether this has been achieved.

The uptake of voluntary counseling and testing (VCT) at antenatal services is reportedly low, with <50% of women attending PMTCT sites being tested nationally (PMTCT Task Team, Concerned Child Health Workers, unpublished report). Current approaches to VCT adhere to “opt-in” principles, although opt-out strategies appear to dramatically increase uptake of testing [11].

Pregnant women have a higher risk of acquiring HIV infection than do nonpregnant women [12]. The risk of transmission to infants is increased in women with high viral loads, particularly in those with acute primary HIV infection [13]. There is concern that women who experience seroconversion during pregnancy may miss the opportunity for PMTCT if they are not retested late in pregnancy.

HIV transmission to infants occurs through breastfeeding, although exclusive breastfeeding for the first few months of life is associated with lower transmission rates than is mixed feeding [14, 15]. Replacement feeding is available as an option for infants up to 6 months of age through the national PMTCT program. As a result of inadequate counseling, support, and education of women, late transmission of HIV to children through mixed feeding is reversing some of the effects of antiretroviral intervention [16].

Single-dose nevirapine given to mothers and babies has been the standard of PMTCT care in South Africa since 2003. Although simple and cost-effective, its efficacy is, at best, 50% [17]. Reports indicate that nevirapine coverage for HIV-infected pregnant women is no more than 30% (PMTCT Task Team, Concerned Child Health Workers, unpublished report).

In some urban facilities, where more women choose to formula feed, perinatal HIV transmission rates with single-dose nevirapine have been reported to be ~9% [18, 19]. The addition of zidovudine to single-dose nevirapine reduces the transmission rate to <2% for formula-fed infants [20–22]. The World Health Organization, in updated guidelines, recommends and advocates that countries consider implementing combination therapy when feasible [23]. The Western Cape has implemented this approach.

DIAGNOSIS OF HIV INFECTION IN INFANTS AND CHILDREN

Early identification of HIV-infected children is vital for their entry into comprehensive care and for evaluation of the efficacy of PMTCT programs. HIV DNA polymerase chain reaction (PCR) testing was introduced in 2004 for early diagnosis of HIV infection in infants from 6 weeks of age [24, 25]. Thirty percent of the ~1 million infants born in South Africa annually are estimated to be HIV exposed, requiring a laboratory capacity to perform 300,000 PCR tests per annum. In June 2006, ~6750 PCR tests were performed nationally at 6 sites, equalling 27% of the total capacity required for that month. The National Health Laboratory Service is scaling up the number of HIV DNA PCR laboratories nationally, to improve equity and accessibility.

Table 1. Increase in nos. of reported deaths of children <15 years of age in South Africa, 1997–2004.

| Year | 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 from 1997 to 2004 | 72.9% |

NOTE. Data are no. of reported deaths, unless otherwise indicated, and are from Statistics South Africa [7].
Table 2. Breakdown of nos. of children <14 years of age receiving antiretroviral therapy (ART), by province, in mid-2006 (public sector).

| Province            | Total patients receiving ART, no. | Children receiving ART, no. (% of total patients receiving ART) | Date   |
|---------------------|----------------------------------|------------------------------------------------------------------|--------|
| Eastern Cape        | 24,920                           | 1896 (7.6)                                                      | Aug 2006 |
| Free State          | 6950                             | 806 (11.6)                                                      | Jun 2006 |
| Gauteng             | 55,580                           | 6301 (11.3)                                                    | Sep 2006 |
| KwaZulu-Natal       | 59,404                           | 6378 (10.7)                                                    | Sep 2006 |
| Limpopo             | 11,660                           | 879 (7.5)                                                       | Sep 2006 |
| Mpumalanga          | 7989                             | 684 (8.6)                                                       | Aug 2006 |
| Northern Cape       | 4476                             | 695 (15.5)                                                     | Sep 2006 |
| North West          | 21,579                           | 1454 (6.7)                                                     | Sep 2006 |
| Western Cape        | 21,270                           | 2455 (11.5)                                                    | Sep 2006 |
| South Africa        | 218,828                          | 21,548 (10.1)                                                 | Aug/Sep 2006 |

NOTE. Data are from the Department of Health, South Africa [36].

The clinical capacity needed to perform HIV DNA PCR testing on infants at health care services, particularly outside of the major cities, is limited. Facilities are poorly staffed, and individuals with the skills required for pediatric venipuncture are scarce. Dried blood spots from heel pricks are easier to obtain than liquid blood, and health care workers are already trained to do this for other indications. HIV DNA PCR tests performed on dried blood spots and liquid blood samples have comparable accuracy, although it is more labor intensive to process dried blood spots in the laboratory [26–28]. Efforts are under way to massively scale up the use of dried blood spots nationally to improve the accessibility of diagnosis in the field.

Many older HIV-infected children have yet to be identified. The clinical features of HIV infection in children are too nonspecific to enable health care workers to reliably diagnose HIV infection on clinical grounds alone [29]. Opportunities for testing for and diagnosing HIV infection in children attending immunization programs, TB services, or in- and outpatient pediatric services, as well as in 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 infection [30]. In a nationwide report on in-hospital pediatric mortality, there was no confirmatory HIV infection diagnosis in 22% of deaths reported as being HIV/AIDS related [31].

**PROPHYLAXIS AGAINST OPPORTUNISTIC INFECTIONS**

Cotrimoxazole (CTZ) prophylaxis for preventing *Pneumocystis jirovecii* pneumonia and other commonly acquired infections reduces mortality among HIV-infected children by as much as 43% [32]. *P. jirovecii* pneumonia has a peak incidence in early infancy with a very high associated mortality [33]. South Africa follows World Health Organization guidelines in recommending CTZ prophylaxis from 4 to 6 weeks of age for all HIV-exposed infants, continuing in those with a definitive diagnosis of HIV infection until such time as a favorable CD4 cell response to ART is demonstrated [24].

In 2001, only a third of clinics in South Africa reported routine administration of CTZ to HIV-exposed children, and the majority of those providing CTZ were administering inappropriate doses [34]. Although good CTZ coverage has been reported in the Cape Town area, there are few data from elsewhere. Anecdotal reports indicate that CTZ coverage is still inadequate in other places.

**ART**

Highly active ART (HAART) has become increasingly available since the implementation of the South African Comprehensive HIV and AIDS Care, Management and Treatment Plan in 2004. During the first year, very few children were accessing ART. The number of children receiving ART has, however, increased from <3000 in February 2005 [35] to >21,000 by September 2006 [36]. The total number of children receiving treatment through private projects outside of the public health system is unknown, although it is anticipated to be low.

Despite the scaling up of ART access for children, marked inequities persist. The National Department of Health has called on provincial HIV/AIDS, sexually transmitted infection, and tuberculosis (HAST) directorates to ensure that at least 15% of all patients receiving ART are children. Most provinces have not yet achieved this target (table 2). Furthermore, there is considerable variability in access to pediatric ART between districts within the same province. For example, although KwaZulu-Natal has successfully increased the proportion of patients receiving ART who are children from <5% in November 2004 [37] to >10% in early 2006, the absolute numbers and percentages of children receiving ART across health districts vary considerably (table 3).
Table 3. Children <14 years of age receiving antiretroviral therapy (ART), by district in KwaZulu-Natal, March 2006.

| District     | Accredited ART facilities, no. | Adults receiving ART, no. | Children receiving ART, no. (% of total patients receiving ART) |
|--------------|--------------------------------|---------------------------|-----------------------------------------------------------------|
| Amajuba      | 3                              | 1530                      | 148 (9.8)                                                       |
| Ethekwini    | 9                              | 4769                      | 542 (10.2)                                                     |
| Ilembe       | 4                              | 1745                      | 234 (11.8)                                                     |
| Sisonke      | 4                              | 1932                      | 139 (7.7)                                                      |
| Ugu          | 4                              | 2107                      | 127 (6.0)                                                      |
| Umgungundlovu| 5                              | 3272                      | 816 (20.0)                                                     |
| Umkhnyagude  | 5                              | 3701                      | 548 (12.9)                                                     |
| Umzinyathi   | 4                              | 2784                      | 247 (8.1)                                                      |
| Uthukela     | 3                              | 2613                      | 265 (9.2)                                                      |
| Uthungulu    | 8                              | 3074                      | 329 (9.7)                                                      |
| Zululand     | 6                              | 1896                      | 127 (6.3)                                                      |
| KwaZulu-Natal| 55                             | 29,423                    | 3522 (10.7)                                                    |

NOTE. Data are from the KwaZulu-Natal Department of Health.

The provinces with the lowest estimated numbers of HIV-infected children, particularly the Western Cape and Northern Cape, are faring much better in meeting the demand for pediatric ART. Figure 2 depicts the differences in proportions of children accessing ART by province, under the assumption that at least 40% of children require ART. Although the percentage of coverage for each province is roughly calculated, it is clear that there are very large inequities among provinces. For example, a child with advanced disease in the Western Cape has an ~14-fold higher chance of receiving ART than does a child in Mpumalanga.

Most HIV-infected children in Gauteng are receiving care at tertiary care facilities (figure 3). The scale up of ART at primary care and secondary care facilities in Gauteng has been hampered by limited human resources and inadequate pediatric clinical skills. Many facilities lack physicians, and primary health care nurses have not been trained to manage patients receiving ART. At Chris Hani Baragwanath Hospital in Soweto, primary health care nurses have been adequately trained and are successfully initiating ART in children and managing children receiving ART under the supervision of physicians.

The Western Cape has made progress with the decentralization of pediatric ART. As evidence of this, the proportion of children receiving ART at the 3 academic hospitals has declined from 78.4% to 38% between March 2004 and September 2006 (B. Eley, University of Cape Town, personal communication, October 2006).

No national data on the outcomes of children receiving ART in South Africa are available. In countries with adequate resources, ART has allowed children to have healthy and productive lives well into adolescence and early adulthood [38, 39]. Programs in countries with fewer resources have also documented good outcomes for children receiving ART—for instance, in the Ivory Coast, a 2-year survival rate of 98% was reported among children with a CD4 cell percentage of ≥5% [40]. Although some South African ART facilities have published data demonstrating the early benefits of ART in children enrolled in the program [41–44], routine data on adherence, retention, viral load suppression, clinical status, mortality, and adverse effects are required to assess the impact of the program.

CHALLENGES OF SCALING UP PEDIATRIC ART

The integration of ART with primary health care services has been very limited, with vertical programs independently managing PMTCT, immunization, integrated management of child-

Figure 2. Estimated percentages of children in South Africa who urgently need antiretroviral therapy (ART) and are receiving it, by province, 2006. Data are compiled from mid-2006 estimates extracted from Actuarial Society of South Africa AIDS and Demographic Model (ASSA2003) [2] and table 3, under the assumption that 40% of HIV-infected children require ART.
The lack of capacity in the health system to provide treatment to all those who need it could be contributing to the indirect rationing of treatment to certain groups, such as those who are better informed, live closer to treatment sites, have time to wait in queues every month, or have a higher socioeconomic status. Furthermore, ART services for adults and children are frequently separated by clinic day or even location, with few family-based clinic services.

Human-resource challenges include (1) shortages of staff comfortable managing general medical problems in children [45]; (2) the isolation of medical staff, frequently with only 1 physician appointed to each site, which results in poor staff morale and logistical difficulties, because training staff off-site leads to service interruptions; (3) the lack of a nationally standardized training program in pediatric ART; and (4) the fact that there is little on-site mentorship of physicians and nurses.

The lack of capacity in the health system to provide treatment to all those who need it could be contributing to the indirect rationing of treatment to certain groups, such as those who are better informed, live closer to treatment sites, have time to wait in queues every month, or have a higher socioeconomic status [46, 47]. The concentration of children receiving ART in tertiary/regional facilities results in inappropriate utilization of highly skilled staff to manage well children. These experienced staff will increasingly be needed to attend to more complicated cases related to adverse reactions and treatment failure as the provision of ART matures.

In addition, provision of ART to HIV-infected children is more complex than provision to adults, because

- **CD4 cell percentage**, rather than the absolute CD4 cell count, is used in children, and the cutoff for initiating therapy differs according to the age of the child;
- **drug doses** need to be regularly reviewed to keep up with growth;
- **no guidance** is provided in the South African guidelines for infants <6 months of age, because few formulations have been studied in this age group, and, because 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 in dispensing medication—for example, drawing up solutions requires good vision and basic arithmetic skills.

### RECOMMENDATIONS

**Recommendations to improve PMTCT.** The following measures are recommended to improve PMTCT ([48] and PMTCT Task Team, Concerned Child Health Workers, unpublished report):

- Incorporation of VCT into family-planning activities and incorporation of family planning into VCT services
- Implementation of an opt-out approach to VCT at antenatal clinics
- Implementation of repeated testing for HIV-negative pregnant women in the third trimester
- Implementation of routine testing for infants presenting to immunization clinics at 6 weeks of age (the potential for negative impact on routine immunization uptake exists and should be evaluated)
- Training of all nursing staff who interact with pregnant women or mothers of young infants to provide information on PMTCT, infant feeding choices, CTZ prophylaxis, and infant diagnosis and treatment
- Improvement of counselor training, with regular review and monitoring of messages provided by counselors
- Immediate CD4 cell count determination for all pregnant women testing HIV positive, to assess whether ART is indicated (point-of-service CD4 cell count machines should be introduced at PMTCT sites)
- Provision of ART to pregnant women with CD4 cell counts <200 cells/mm³, as a matter of urgency, with systems put in place to expedite this intervention
- Inclusion of zidovudine with nevirapine for PMTCT, in accordance with World Health Organization recommendations [49]
- Provision of nutritional support for women who decide to breastfeed for the first 6 months

Sentinel surveillance at health care facilities and population-based prevalence surveys that include children <2 years of age are required from all provinces to monitor and evaluate the coverage and impact of the PMTCT program and the rollout of ART, because routinely collected 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 program.

**Recommendations for the scaling up of pediatric diagnosis.** At the clinical level, a diagnostic service has to be commenced. This will require the following:

- Identification of facilities where pediatric diagnosis can be performed (e.g., PMTCT programs, immunization clinics, TB clinics, and inpatient facilities)
• Provision of appropriate staffing at these facilities (e.g., phlebotomists, counselors, and laboratory staff)
• Training of staff in blood sampling, laboratory logistics, record keeping, and tracking and interpretation of test results
• Procurement and distribution of consumables to enable dry blood spot testing
• Laboratory space for new instruments
• Research and development to increase laboratory capacity—for example, automation with careful quality control

Validation of algorithms that utilize rapid HIV tests is required to improve diagnosis. 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.

**Recommendations to scale up and improve pediatric ART services.** The differences in infrastructure, disease burden, and resources between provinces and districts require that local solutions tailored to local conditions be found. District-level health provider networks with community representation should be formed to coordinate services and test strategies to improve the functional integration of services. Appointing staff employed for the ART rollout program to a district-based cluster 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 district strategy needs to be tested.

In addition, the following is recommended:
• Clear targets for treating children with ART should be set at provincial and district levels. These targets should be calculated according to the number of children who need ART rather than as a percentage of the total number of adults and children receiving ART.
• Primary health care nurses should become the key personnel to manage and prescribe treatment for patients receiving ART whose conditions are stable. Pharmacist assistants should likewise be utilized.
• Family-oriented services should be established at all ART facilities, with at least 1 day/week being assigned for families.
• Theoretical training for nursing and medical students should be aligned with the South African treatment guidelines for children.
• Outreach from sites with experience in treating children to inexperienced sites should be encouraged, to provide patient-based mentoring.
• An expert advisory team should be appointed by the Department of Health to regularly update guidelines. A strategy for dissemination of updated guidelines needs to be developed.
• A standardized patient management tool to support both the care of patients and the reporting of indicators needs to be developed and piloted. Ideally, the system needs to support the tracking of patients across the vertical programs (VCT, PMTCT, infant diagnosis, and ART) and between provinces.
• Program managers need to be trained to use available data to improve the efficiency and effectiveness of their service.

The following has been recommended (Pharmacology Task Team, Concerned Child Health Workers, unpublished report) to address some of the concerns regarding pharmacological challenges with pediatric treatment:
• Stavudine 15 mg is not widely procured for the ART rollout program; although higher-strength capsules are available, the 15-mg strength of stavudine formulation is very helpful for pediatric use, and we recommend that it become readily available at all sites.
• The Medicines Control Council should fast-track the registration of pediatric (i.e., chewable or dispersible) fixed-dose drug combinations.
• Even distribution of the active ingredient within adult formulations and scoring tablets to facilitate use in older children should be ensured.
• The thermostability and palatability of pediatric solutions should be improved.
• The color coding of individual antiretroviral agents should be standardized country-wide.
• Attention needs to be paid to the care of infants <6 months of age; infants should be monitored at least monthly for clinical deterioration and should have ART commenced as soon as there is any indication to do so.
• District Child Care Forums, involving the health sector, social welfare, businesses, nongovernmental organizations, and community-based organizations, need to be strengthened; a registry of highly vulnerable children should be kept in each district to coordinate support.
• Adolescent-friendly clinic services should be made available in every district; adolescent-focused training materials, such as those developed by the National Adolescent-Friendly Clinic Initiative, need to be updated to include information on ART and disseminated.
• Psychosocial issues for children need to be considered, and, where possible, a multidisciplinary approach should be implemented to deal with these issues—for example, disclosure of HIV infection status.

**CONCLUSION**

The implementation of the PMTCT program and the Comprehensive HIV and AIDS Care, Management and Treatment Plan has made some progress toward alleviating the burden of
the pediatric HIV epidemic in South Africa. However, both the technical content and the implementation of these programs need to be strengthened if South Africa is to succeed in achieving the Millennium Development Goals. In the absence of good-quality monitoring and evaluation demonstrating the impact on the pediatric epidemic, there is little to guide the program. It is essential that a focus on the plight of children be maintained, so that their needs not be subsumed to the overwhelmingly large adult program. Equity of care must be addressed urgently, so that all children in the country may benefit equally from services that they deserve and to which they have a right.

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