Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of interventions for the prevention of mother-to-child transmission

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Objective To report the rates of mother-to-child transmission (MTCT) of the human immunodeficiency virus (HIV), and the coverage of interventions designed to prevent such transmission, in KwaZulu-Natal.

Methods Mothers with infants aged ≤ 16 weeks and fathers or legal guardians with infants aged 4–8 weeks who, between May 2008 and April 2009, attended immunization clinics in six districts of KwaZulu-Natal were included. The mothers’ uptake of interventions for the prevention of MTCT was explored. Blood samples from infants aged 4–8 weeks were tested for anti-HIV antibodies and, if antibody-positive, for HIV desoxyribonucleic acid (DNA).

Findings Of the 19 494 mothers investigated, 89.9% reported having had an HIV test in their recent pregnancy. Of the 19 138 mothers who reported ever having had an HIV test, 34.4% reported that they had been found HIV-positive and, of these, 13.7% had started lifelong antiretroviral treatment and 67.2% had received zidovudine and nevirapine. Overall, 40.4% of the 7 981 infants tested were found positive for anti-HIV antibodies, indicating HIV exposure. Just 7.1% of the infants checked for HIV DNA (equating to 2.8% of the infants tested for anti-HIV antibodies) were found positive.

Conclusion The low levels of MTCT observed among the infants indicate the rapid, successful implementation of interventions for the prevention of such transmission. Sampling at immunization clinics appears to offer a robust method of estimating the impact of interventions designed to reduce such transmission. Large-scale elimination of paediatric HIV infections appears feasible, although this goal has not yet been fully achieved in KwaZulu-Natal.

Introduction

For the public health systems of countries with high prevalences of infection with the human immunodeficiency virus (HIV), the identification of HIV-infected pregnant women and their treatment with antiretroviral drugs are among the greatest opportunities and challenges. Reliable and robust methodologies for measuring and demonstrating the success of such identification and treatment, especially when applied on a large scale, are needed. 1

When combinations of antiretroviral drugs are given to HIV-positive women, either as lifelong treatment or as prophylaxis to prevent mother-to-child transmission of HIV, the rate of HIV transmission from mothers to non-breastfed infants can be reduced to < 1%. 2, 3 In breastfeeding communities, the additional postnatal transmission can similarly be reduced to < 1% when viral load is effectively suppressed. 4 The possibility of reducing the prevalences of HIV infection among HIV-exposed infants to such exceptionally low levels has inspired the belief that the elimination of HIV infection in infants is attainable. Current goals are to reduce the rate of mother-to-child transmission of HIV to < 5% by 2015. 5

Measurement of the effectiveness of interventions for the prevention of mother-to-child transmission (PMTCT) has several benefits: it encourages health workers to believe that they can change, at least for children, the course of the HIV epidemic; it helps fundraising, by providing donors with evidence that their investments are worthwhile; and it provides feedback to health managers about whether challenges to implementation have been effectively resolved.

HIV prevalence in the South African province of KwaZulu-Natal is among the highest in the world. In 2008, for example, HIV prevalence among women attending government-run antenatal clinics in the province was 38.7%. 6 In April of the same year, KwaZulu-Natal’s Department of Health bolstered its PMTCT programme to provide antenatal zidovudine from 28 weeks’ gestation to HIV-infected pregnant women, in addition to the single-dose nevirapine it was already providing to such women and their babies at the time of delivery. At this time, the province’s Department of Health also commissioned an impact assessment to determine to what extent the programme’s goal, to reduce HIV infection in infants, was being achieved. We report the findings of a study, designed to determine the rates of mother-to-child transmission of HIV in KwaZulu-Natal, in which all infants attending immunization clinics for their first immunizations served as a population proxy. Since > 95% of infants in KwaZulu-Natal attend such clinics for their first immunization, the sample included infants whose mothers might not have participated in the province’s PMTCT programme.

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Methods

Participants were enrolled in a cross-sectional study conducted between May 2008 and April 2009. The study, which was designed to assess the impact of the provincial PMTCT programme in KwaZulu-Natal, South Africa, included all primary-health care facilities in six of the 11 districts of KwaZulu-Natal. All fixed clinics providing immunizations in the six study districts were included in the sample; mobile clinics were excluded. The study districts were primarily urban (three) or primarily rural (three) and were purposively selected in collaboration with KwaZulu-Natal’s Department of Health. At the time of the study, the six study districts had a combined population of 7.1 million, representing about 69.5% of the population of KwaZulu-Natal. All mothers with children aged <6 years and all fathers and legal guardians with infants aged 4–8 weeks who attended the study immunization clinics were invited to participate in the parent study. Children attending with other caregivers were excluded because the other caregivers would be unable to provide consent for blood sampling or, if it was felt, provide reliable information about the HIV status of the mother and child. Mothers were asked about their histories of HIV testing and uptake of other PMTCT services in their most recent pregnancy. Consent was requested from a parent or legal guardian of each infant aged between 4 and 8 weeks (i.e. 28–62 days) to collect a heel-prick blood sample from the infant for anonymous HIV testing, regardless of the reported HIV status of the infant’s mother or the participation of the infant’s mother in the provincial PMTCT programme. The samples were stored as dried blood spots before being tested.

Sampling

To permit detection of a point estimate for a vertical transmission frequency of 15–20% (± 3% at a 95% confidence level), or a 6% HIV prevalence among all infants, it was estimated that at least 1200 dried blood spot samples should be collected in each study district. The number of weeks required to collect this number of samples in each district was estimated from the mean number of infants who received first immunizations in the same district during each week from April to December 2007 (N. Moodley, unpublished data, 2008), allowing for up to 20% non-participation. Although the total number of weeks of data collection varied between districts, data were collected for the same number of weeks in each study clinic in a given district. In each study district, therefore, each clinic contributed dried blood spot samples in proportion to the total number of children presenting for immunization in that clinic, thereby producing a self-weighted sample. 9

HIV testing

Heel-prick blood samples were collected from infants aged 4–8 weeks, using a spring-loaded launching device (ACCU-CHEK Softclix, Roche Diagnostics, Burgess Hill, United Kingdom), onto filter paper and dried. Each resultant dried blood spot sample was then tested for anti-HIV antibodies using a commercial kit (Vironostika HIV Uni-Form II plus O, bioMérieux Boxtel, Netherlands). If HIV-specific antibodies were detected, the same dried blood spot sample was then tested for HIV DNA using a commercial PCR-based assay (HIV-1 DNA Amplicor version 1.5, Roche Diagnostics, Pleasanton, United States of America). 10

HIV testing was anonymous: enrolled infants were each assigned a unique study number at enrolment, no identifying information was collected, and HIV results were added to the database after completion of the study. Linked non-anonymous HIV counseling and testing were, however, provided for the child of any caregiver who wished to receive the results of his or her child’s HIV test.

Statistical analysis

The present analyses were restricted to mothers with children aged ≤16 weeks, and all fathers and legal guardians with infants aged 4–8 weeks. Uptake of drugs for PMTCT in the last pregnancy was assessed for mothers whose infants were ≤16 weeks of age at the time of interview; this age was chosen to reduce recall bias and reflect the most current status of PMTCT coverage. HIV exposure and transmission rates were estimated from the results of the HIV testing of all infants aged 4–8 weeks, irrespective of caregiver type. The rates of mother-to-child transmission were assessed according to complete or incomplete PMTCT intervention as self-reported by mothers. A PMTCT intervention was considered complete if: (i) the mother had been on lifelong antiretroviral treatment before delivery; (ii) the mother had been on zidovudine for at least 4 weeks and the baby, for at least 7 days; or (iii) the mother had been on zidovudine for <4 weeks and the baby, for at least 28 days. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between maternal age and PMTCT regimen in pregnancy and HIV transmission to infants were calculated using generalized estimation equations (GEE) and the proc genmod procedure in SAS version 9.2 (SAS Institute, Cary, USA). This analysis allowed consideration of the potential correlation of outcomes measured in the same clinic. 11

Research ethics

The University of KwaZulu-Natal’s Biomedical Ethics Review Committee granted ethical approval for the study.

Results

Fig. 1 shows the study profile. Data were collected from 348 (99%) of the 349 fixed immunization clinics in the six study districts between May 2008 and April 2009; one fixed clinic was excluded because of poor road access. In total, 38 866 eligible caregivers (i.e. mothers, fathers or legal guardians) were invited to participate in the parent study, of who 766 (2.0%) refused consent. Of the 38 100 caregivers who agreed to participate in the parent study, 19 494 were mothers attending the study clinics with infants aged ≤16 weeks, six were fathers attending with infants aged 4–8 weeks, and 24 were legal guardians attending with infants aged 4–8 weeks. Characteristics of the infants who participated in the study are shown in Table 1.

Service coverage

Of the 19 494 mothers participating in the study, 15 164 (77.8%) reported having attended antenatal care at least four times during their recent pregnancy and 19 138 (98.2%) reported ever having had an HIV test. Although 17 521 (89.9%) of the mothers reported having been tested for HIV during their recent pregnancy, 12 386 (70.7%) reported that they had only been tested during the last trimester. Among those mothers who had been tested, 6586 (34.4%) said that they had known or learned that they were HIV-infected during their recent pregnancy, and, of these, 6337 (96.2%) had
received either antiretroviral drugs for PMTCT or lifelong antiretroviral treatment for their own health. Among the 6594 women who reported themselves to be HIV-infected, 584 (8.9%) said that they had known they were HIV-infected before their recent pregnancy. The self-reported distribution of the various antiretroviral regimens taken is presented in Table 2.

Prevalence and transmission

Of the 8999 infants aged 4–8 weeks who were brought to the study clinics during data collection, 8969 presented with their mothers, six with their fathers, and 24 with their legal guardians. Although dried blood spot samples were collected from 7998 (88.2%) of these infants, 17 samples were excluded because they were considered inadequate. Anti-HIV antibodies, indicating HIV exposure, were detected in 3225 (40.4%) of the 7981 infants with evaluable dried blood spot samples. Overall, 17.3%, 38.2%, 54.2%, 38.3% and 44.7% of the tested infants of mothers aged <20, 20–24, 25–29, 30–34 and >34 years were found seropositive for HIV antibodies, respectively; infant seropositivity was positively correlated with maternal age ($P < 0.0001$). Complete data regarding feeding practices were available for 3143 (97.7%) of the 3217 infants who attended the study clinics with their mothers and tested positive for anti-HIV antibodies. Of these 3143, 1172 (37.3%) were exclusively breastfeeding, 1850 (58.9%) were receiving formula milk only, and 121 (3.8%) were receiving mixed feeds.

Of the 3225 dried blood spot samples found to be positive for HIV antibodies, 3192 (99%) were tested in a PCR-based assay for HIV desoxyribonucleic acid (DNA) and 225 were found positive for viral DNA. The frequency of peripartum HIV transmission, from the HIV-positive mothers to their infants, was 7.1% overall (95% CI: 6.2–8.0%), although it varied according to the reported PMTCT regimen taken by the mother (Table 3).

The association between the frequency of vertical transmission and the duration of drug treatment/prophylaxis for PMTCT taken by the mothers and infants was assessed. (Infant nevirapine was not included in this assessment because most mothers reported not knowing whether their infants had received nevirapine.) The rate of mother-to-child transmission was significantly reduced in infants who, with their mothers, received the full, recommended PMTCT regimen. It was 7.7% among the 480 mothers who reported taking an incomplete regimen but 4.9% among the 1912 mothers who reported taking a full regimen. Among the 527 mothers for whom duration of zidovudine or lifelong antiretroviral treatment could not be reliably assessed, the frequency of mother-to-child transmission was 9.9%.

Anti-HIV antibodies were detected in the infants of 209 mothers who reported themselves to be HIV-negative. Twenty-four of these mothers reported taking an antiretroviral regimen. Although three dried blood spot samples from infants of the remaining 185 mothers were unsuitable for testing for HIV DNA, such DNA was detected in the dried blood spot samples from 30 infants of the other 182 mothers, indicating a rate of mother-to-child transmission of 16.5% (95% CI: 11.4–22.7%).

Discussion

Our findings show that, in the province with the highest HIV prevalences in South Africa, low rates of mother-to-child transmission at population level were achieved within a short period of
the most recent pregnancy began. Ensuring their most recent pregnancy, and 9% had been tested for HIV during their pregnancy. Almost 90% reported that they had been tested for HIV and knew their HIV status; almost all of the mothers investigated for the present study began, most of the women who reported themselves to be HIV-infected said that they had received prophylaxis, are consistent with the widespread uptake of dual antiretroviral prophylaxis.2 The rate of mother-to-child transmission in the province is likely to decrease further as delivery of these interventions continues to improve. Lastly, almost 14% of the HIV-positive mothers detected had started lifelong antiretroviral treatment. HIV-infected mothers with a low CD4+ T lymphocyte (CD4+ cell) count and their infants incur the greatest risk of illness and HIV transmission.13 Initiating lifelong antiretroviral treatment in such women will make the greatest contribution to reducing HIV infections in children and mortality in mothers. In a study conducted in KwaZulu-Natal in 2005 (at a time when only nevirapine was offered and lifelong antiretroviral treatment was only just starting to become available) in which similar methods were used, 20.2% of infants of HIV-positive women were HIV-infected by 6 weeks of age.14 Compared with these earlier data, the current results indicate a 66% reduction in mother-to-child transmission. While this is not quite the 90% reduction defined by the elimination agenda,3 it is an important step in that direction.

The vertical transmission to the infants who were found to have anti-HIV antibodies, even though their mothers reported themselves to be HIV-negative, was 16.5%. These mothers may have chosen not to disclose their HIV-positive status, while others may have tested negative antenatally and then only recently been infected.15 Women with incident infections are likely to have much higher transmission rates16; if the infection occurs late in pregnancy, however, the increased transmission risk may only become evident when assessing postnatal infections.

The present data reveal several weak areas of the PMTCT programme where improvement is needed. Most of the women investigated had only been tested for HIV in the last trimester of their most recent pregnancy, possibly because of their late initial attendance at an antenatal clinic. Although antenatal clinic attendance is high in South Africa, few women attend before 20 weeks’ gestation17 and many attend only in the third trimester.18 Furthermore,
because they were tested for HIV late in their pregnancies, many of the HIV-infected women did not receive a CD4+ cell result during their pregnancies; one third of the women reporting CD4+ cell counts of < 200 cells per mm³ had not started lifelong antiretroviral treatment. KwaZulu-Natal’s Department of Health has already responded to these findings in an effort to improve service delivery. Maternal HIV prevalence remains extremely high, a fact that underlines the continued importance of primary prevention strategies.

Although the Global Fund to Fight AIDS, Tuberculosis and Malaria implements performance-based financing, there are, as yet, no simple approaches for directly counting the number of infant HIV infections and measuring the impact of investments in PMTCT. The method used to collect the present data is simple and replicable and can be used to monitor progress towards eliminat-

### Table 2. Self-reported coverage of interventions against mother-to-child transmission of HIV among HIV-positive mothers, KwaZulu-Natal, South Africa, 2008–2009 (n = 19 494)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral prophylaxis in pregnancy by women who self-report HIV positive (n = 6 586)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (0.05)</td>
</tr>
<tr>
<td>None</td>
<td>246 (3.7)</td>
</tr>
<tr>
<td>Nevirapine alone</td>
<td>868 (13.2)</td>
</tr>
<tr>
<td>Zidovudine alone</td>
<td>143 (2.2)</td>
</tr>
<tr>
<td>Nevirapine and zidovudine</td>
<td>4424 (67.2)</td>
</tr>
<tr>
<td>Lifelong antiretroviral treatmentb</td>
<td>902 (13.7)</td>
</tr>
<tr>
<td>CD4+ cell count monitoringc</td>
<td></td>
</tr>
<tr>
<td>Had CD4+ cell count taken during recent pregnancy (n = 6 562)</td>
<td>5242 (79.9)</td>
</tr>
<tr>
<td>Obtained CD4+ cell count result (n = 5 242)</td>
<td>4379 (83.5)</td>
</tr>
<tr>
<td>Reported CD4+ cell count of &lt; 200 cells per mm³ (n = 4 379)</td>
<td>967 (22.1)</td>
</tr>
<tr>
<td>Among women reporting CD4+ cell counts of &lt; 200 cells per mm³, on lifelong antiretroviral treatment at time of interview (n = 967)</td>
<td>670 (69.3)</td>
</tr>
</tbody>
</table>

CD4+ cell, CD4+ T lymphocyte; HIV, human immunodeficiency virus.

a The data refer to women who presented with an infant aged ≤ 16 weeks and reported that they were HIV-infected during their most recent pregnancy.

b May have been started before or during pregnancy.

c Reductions in denominators reflect either missing data or mothers who preferred not to provide a response or who did not know the relevant information.

### Table 3. Association between mother-to-child transmission of HIV and antiretroviral regimens taken in pregnancy, KwaZulu-Natal, South Africa, 2008–2009 (n = 2858)

<table>
<thead>
<tr>
<th>Regimena</th>
<th>Infants with anti-HIV antibodiesb No. tested by PCR</th>
<th>OR 95% CI P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antiretroviral prophylaxis</td>
<td>68</td>
<td>11</td>
</tr>
<tr>
<td>Nevirapine alone</td>
<td>242</td>
<td>32</td>
</tr>
<tr>
<td>Zidovudine alone</td>
<td>63</td>
<td>2</td>
</tr>
<tr>
<td>Nevirapine and zidovudine</td>
<td>2089</td>
<td>118</td>
</tr>
<tr>
<td>Lifelong ART</td>
<td>396</td>
<td>20</td>
</tr>
</tbody>
</table>

ART, antiretroviral treatment; CI, confidence interval; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; OR, odds ratio; PCR, polymerase chain reaction.

a Mothers were allocated to regimen groups irrespective of the reported duration of each antiretroviral intervention.

b The infants tested were aged 4–8 weeks.

c Reference category.

In conclusion, the number of HIV infections in young infants can be greatly reduced on a large scale, although major programmatic challenges must still be overcome to achieve the elimination of paediatric HIV infections. HIV testing early in pregnancy, and ensuring that > 95% of the women are to be HIV-positive themselves by the age of 6 weeks. Furthermore, if the overall rate of mother-to-child transmission is to be kept below the 2015 target of 5%, at least 90% of HIV-infected women will need to receive the antiretroviral interventions currently recommended by the World Health
Organization throughout breastfeeding; more effective family planning, HIV counselling and support, and primary prevention of HIV will also be required. We have shown that the number of HIV infections in infants can be directly measured in populations through a simple and robust approach. The current data, and the ability to measure such data, will become even more relevant as 2015 approaches and the need to track progress towards the Millennium Development Goals becomes even more critical.

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Resumen

Eliminación del VIH pediátrico en KwaZulu-Natal, Sudáfrica: valoración a gran escala de las intervenciones para prevenir la transmisión materno-infantil

Objetivo Notificar los índices de transmisión materno-infantil (TMI) del virus de la inmunodeficiencia humana (VIH) y la cobertura de las intervenciones diseñadas para prevenir dicha transmisión en KwaZulu-Natal.

Métodos Se incluyeron las madres con hijos con edad igual o inferior a 16 semanas y los padres o tutores legales con niños de edades comprendidas entre 4 y 8 semanas que hubieran asistido a los centros de vacunación de seis distritos de KwaZulu-Natal entre mayo de 2008 y abril de 2009. Se evaluó la aceptación de las madres respecto a las intervenciones para la prevención de la transmisión del VIH de la madre al niño. Se analizaron las muestras de sangre de niños de entre 4 y 8 semanas para comprobar la presencia de anticuerpos anti-VIH y, en el caso de obtener un resultado positivo para dichos anticuerpos, se comprobó la presencia del ácido desoxirribonucleico (ADN) del VIH.

Resultados El 89,9% de las 19 494 madres que participaron en el estudio afirmaron haberse realizado una prueba del VIH en su último embarazo. De las 19 138 madres que afirmaron haberse realizado una prueba del VIH, 34,4% aseguró que la prueba para el VIH resultó positiva en su caso y, de ese porcentaje, un 13,7% inició un tratamiento crónico con antirretrovirales y un 67,2% recibió zidovudina y nevirapina. En total, el 40,4% de los 7 981 niños estudiados obtuvo un resultado positivo de anticuerpos anti-VIH, lo que indica su exposición al VIH. Seis por ciento de los 7 981 niños mostró seropositividad (equivalente al 2,8% de los niños a quienes se les realizó pruebas de anticuerpos anti-VIH) en total, se confirmó la presencia del ADN del VIH en 13,7% de las 7 981 muestras de sangre de niños de 4 a 8 semanas que habían asistido a los centros de vacunación de seis distritos de KwaZulu-Natal.
Conclusión Los bajos niveles de TMT del VIH observados en los niños reflejan una puesta en práctica rápida y fructífera de las intervenciones para la prevención de dicha transmisión. Las tomas de muestras en los centros de vacunación parecen constituir un método sólido para calcular el impacto de las intervenciones diseñadas para reducir dicha transmisión. La eliminación de las infecciones pediátricas del VIH a gran escala parece viable, si bien este objetivo no está completamente conseguido en KwaZulu-Natal.