Coverage of Nevirapine-Based Services to Prevent Mother-to-Child HIV Transmission in 4 African Countries

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Context Few studies have objectively evaluated the coverage of services to prevent transmission of human immunodeficiency virus (HIV) from mother to child.

Objective To measure the coverage of services to prevent mother-to-child HIV transmission in 4 African countries.

Design, Setting, and Patients Cross-sectional surveillance study of mother-infant pairs using umbilical cord blood samples collected between June 10, 2007, and October 30, 2008, from 43 randomly selected facilities (grouped as 25 service clusters) providing delivery services in Cameroon, Côte d’Ivoire, South Africa, and Zambia. All sites used at least single-dose nevirapine to prevent mother-to-child HIV transmission and some sites used additional prophylaxis drugs.

Main Outcome Measure Population nevirapine coverage, defined as the proportion of HIV-exposed infants in the sample with both maternal nevirapine ingestion (confirmed by cord blood chromatography) and infant nevirapine ingestion (confirmed by direct observation).

Results A total of 27,893 cord blood specimens were tested, of which 3324 were HIV seropositive (12%). Complete data for cord blood nevirapine results were available on 3196 HIV-seropositive mother-infant pairs. Nevirapine coverage varied significantly by site (range: 0%-82%). Adjusted for country, the overall coverage estimate was 51% (95% confidence interval [CI], 49%-53%). In multivariable analysis, failed coverage of nevirapine-based services was significantly associated with maternal age younger than 20 years (adjusted odds ratio [AOR], 1.44; 95% CI, 1.18-1.76) and maternal age between 20 and 25 years (AOR, 1.28; 95% CI, 1.07-1.54) vs maternal age of older than 30 years; 1 or fewer antenatal care visits (AOR, 2.91; 95% CI, 2.40-3.54), 2 or 3 antenatal care visits (AOR, 1.93; 95% CI, 1.60-2.33), and 4 or 5 antenatal care visits (AOR, 1.56; 95% CI, 1.34-1.80) vs 6 or more antenatal care visits; vaginal delivery (AOR, 1.22; 95% CI, 1.03-1.44) vs cesarean delivery; and infant birth weight of less than 2500 g (AOR, 1.34; 95% CI, 1.11-1.62) vs birth weight of 3500 g or greater.

Conclusion In this random sampling of sites with services to prevent mother-to-child HIV transmission, only 51% of HIV-exposed infants received the minimal regimen of single-dose nevirapine.

JAMA. 2010;304(3):293-302 www.jama.com

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Global Fund to Fight AIDS, Tuberculosis, and Malaria\textsuperscript{8} and the US President's Emergency Plan for AIDS Relief.\textsuperscript{9}

Despite these advances, however, the worldwide implementation of services to prevent mother-to-child HIV transmission is floundering.\textsuperscript{7} What many believed at the outset would be a relatively simple matter of incorporating antenatal HIV diagnosis and maternal-infant antiretroviral prophylaxis into routine pregnancy and newborn care has in practice been frustratingly difficult to bring to scale. An intervention as basic as intrapartum and neonatal single-dose nevirapine\textsuperscript{8} seems to have fallen short,\textsuperscript{7} despite initial optimism that its simplicity would lead to near-universal coverage.

One critical obstacle to realizing the United Nations' goal has been the lack of consensus tools to evaluate program coverage and to enable improvements in existing services.\textsuperscript{9,10} Many programs rely on simple process tallies (eg, counting the numbers of women tested or prophylactic antiretroviral dispensed) to estimate service coverage and identify specific programmatic gaps, but the quality and timeliness of these data are generally poor.\textsuperscript{9,10} Furthermore, such data often do not contain the details needed to identify key programmatic bottlenecks. For instance, are all women being offered HIV testing as part of antenatal care? Are the women prescribed single-dose nevirapine for self-administration at labor onset actually ingesting the tablet? We sought to estimate the coverage of existing services to prevent mother-to-child HIV transmission by developing a strategy and field testing it in 4 African countries.

\textbf{METHODS}

The PMTCT [prevention of mother-to-child HIV transmission] Effectiveness in Africa: Research and Linkages to Care (PEARL) Study is a 2-part, multicountry evaluation of the effectiveness of services to prevent mother-to-child HIV transmission at both the community and facility level. In this first report, we provide results from umbilical cord blood surveillance to determine coverage of minimum services to prevent mother-to-child HIV transmission among HIV-exposed infants delivered at health centers in Cameroon, Côte d'Ivoire, South Africa, and Zambia. The study was coordinated by the Lusaka-based Centre for Infectious Disease Research in Zambia and was conducted at 43 randomly selected facilities (grouped analytically as 25 service clusters) providing delivery services in the 4 countries. Many selected facilities provided delivery services both to women who had received their antenatal care onsite and to women whose care had been provided at smaller outlying feeder clinics. Each index facility had an established program to prevent mother-to-child HIV transmission. Prescribed antiretroviral prophylaxis to prevent mother-to-child HIV transmission varied somewhat among the sites; however, maternal and newborn administration of nevirapine was a component of all of the standard regimens.

Specimens were collected between June 10, 2007, and October 30, 2008. At each facility, existing trained maternity staff were instructed to obtain an umbilical cord blood specimen from every live-born delivery occurring during the study period. If a sample was missed, the reason was recorded. After delivery, approximately 5 mL of whole blood was drawn from the discarded umbilical cord and placed in a serum-separating tube affixed with a unique and anonymous identification number. Certain nonidentifying information was extracted from the mother's antenatal record onto a study form and anonymously linked to the cord blood sample by the unique number. Data collected on each mother included the place of her first antenatal visit, her age and gravidity, the mode of delivery, and whether she had received HIV pretest counseling, had been tested for HIV, had received her test result, and had received prophylaxis (and if so, which regimen) to prevent mother-to-child HIV transmission. In the event of twin or triplet births, a single sample was taken. In an effort to maintain patient anonymity, we recorded the month but not the day of delivery. A carbonless copy of the form, marked with the same unique number, was placed in the patient's record at delivery. At the time of discharge, clinical personnel recorded whether the infant received prophylaxis (and if so, which regimen was given) to prevent mother-to-child HIV transmission.

In Cameroon, we used a modified, nonanonymous design in which women presenting in labor were approached for consent to participate in the study after they delivered. Cord blood specimens were collected and set aside for each delivery (irrespective of whether the mother was of known or unknown HIV serostatus). The specimens of those women who chose not to participate (approximately 1%) were discarded. For the remainder, written informed consent was obtained and the cord blood was tested for HIV antibodies. Women were provided their test results and posttest counseling prior to discharge from the facility. Infants who were born to HIV-infected women were provided nevirapine syrup. Because the testing was performed postpartum, this modified approach would not be expected to alter the primary outcome of nevirapine coverage.

Our unit of evaluation was HIV-exposed, live-born infants. We defined coverage as the proportion of HIV-exposed newborns in the delivery population that received at least a minimum prophylactic regimen of both maternal and newborn single-dose nevirapine. Because maternal anti-HIV IgG antibodies cross the placenta freely throughout pregnancy, HIV antibody testing of the cord blood allowed a measure of each newborn's HIV-exposure status. Among those infants whose cord blood was HIV seropositive (ie, those who were exposed to HIV), we tested cord blood specimens for nevirapine.

Because administration of maternal
nevirapine was a common component of all regimens to prevent mother-to-child HIV transmission at the sampled sites, and because the drug can be detected in the fetal circulation (and thus cord blood) within minutes of its rapid oral absorption,\textsuperscript{11} the presence of nevirapine in the umbilical cord blood confirms the mother’s ingestion of the drug prior to delivery. We then extracted basic process data from each woman’s antenatal record, which included whether the infant received nevirapine prior to discharge from the health care facility. When these data points were combined for each mother-infant pair, we were able to define coverage as the proportion of HIV-antibody-positive cord blood specimens in which both nevirapine could be detected and infant nevirapine administration was documented in the medical record.

In most mother-infant pairs, sufficient documentation was available in the medical record to recreate the critical path that each seropositive mother-infant pair had to negotiate to achieve (or fail) prophylaxis. The elements of this cascade to prevent mother-to-child HIV transmission were (1) maternal HIV testing offered, (2) maternal HIV testing accepted, (3) positive maternal HIV test result received, (4) maternal nevirapine dispensed, (5) mother adherent to nevirapine (detection of nevirapine in cord blood), and (6) infant administered nevirapine prior to discharge. The final step, administration of nevirapine to the infant, is not contingent on steps 3 through 5.

There were some infants (n=621) who received nevirapine prior to discharge but whose cord blood was not positive for nevirapine. These infants did not meet our definition of coverage and are not reported in the primary outcome. Although not a stated outcome in the original protocol, we do provide unadjusted estimates for the separate maternal and infant components of coverage. As a planned secondary outcome, we defined maternal nevirapine adherence as the proportion of HIV-infected women who received nevirapine (per documentation in the antenatal record) and who also had nevirapine present in the cord blood.

The cord blood samples were tested for HIV antibodies using a rapid test algorithm. All sites performed screenings with the Determine test (Abbott Laboratories, Chicago, Illinois). In Cameroon, we confirmed seropositive samples using Bioline (Standard Diagnostics, Kyonggi-do, Korea); in Côte d’Ivoire, we confirmed seropositive samples using the Genie II HIV 1/HIV 2 (Biorad, Marnes-La-Coquette, France). Zambia and South Africa did not perform confirmatory testing, which is consistent with prior surveillance practice.\textsuperscript{12-14}

After determining the HIV status of cord blood specimens, we transferred the seropositive samples by pipette to filter paper. The resulting dried blood spots were then shipped to the University of Cape Town (Cape Town, South Africa) for nevirapine testing. Detection of nevirapine in the dried blood spots was performed using minor modifications of the method described by Koal et al\textsuperscript{13} in which nevirapine was extracted from the blood spots with 80% methanol and 0.2 M of zinc sulfate, which contained neostigmine as an internal standard. High-performance liquid chromatography was performed using a Phenomenex Fusion RP (Torrance, California) column (3×2×4 μm) with a gradient-to-effect elution of methanol to 10 mM of ammonium acetate.

We used an Applied Biosystems API 3200 tandem mass spectrometer (Foster City, California) in the multiple reaction monitoring mode to detect nevirapine. For qualitative assessment, blank and quality-control cut-off samples were included with each run. The limit of detection for nevirapine was set at 100 ng/mL.\textsuperscript{16} Values detected above this limit were reflected as positive and those below as negative. Interday and intraday coefficients of variation were less than 10% for all controls. We previously reported\textsuperscript{12} that of 179 women in whom nevirapine ingestion was directly observed by study personnel, 178 had detectable levels in their cord blood (99.4%); this validates cord blood high-performance liquid chromatography as an objective and sensitive measure of adherence.

We assumed that country coverage would be 55% (based on unpublished data from Zambia, J.S.A.S., January 2007) and that a 95% confidence interval (CI) between 0.52 and 0.58 around this estimate would offer acceptable precision. We then used Exact methods\textsuperscript{17} to calculate that a total sample of 800 HIV-seropositive specimens would be needed for each country. Because the total number of specimens required to obtain 800 seropositives is a function of prevalence, we divided the target sample size of 800 by an approximate recent maternal HIV seroprevalence figure for each country to determine the total number of samples to be collected. We then rounded to arrive at 8000 samples each for Cameroon and Côte d'Ivoire and 6000 specimens each for South Africa and Zambia.

We used random sampling to determine which sites to include in the surveillance. We began by obtaining lists of all delivery facilities known to be providing services to prevent mother-to-child HIV transmission from the local authorities in each country, and these lists were corrected and supplemented with information obtained by local field staff. From the resultant master list, we randomly selected sites for the survey. If a selected facility did not have sufficient delivery volume to provide our target sample of HIV-exposed neonates over a 1-year period, we added additional facilities to the sample by searching for the geographically closest next qualifying site. Service clusters selected in this way were accounted for in this analysis. If a selected site was estimated to refer more than 10% of its patients for delivery, we extended sample collection to the delivery centers to which the site referred its patients. In such a
NEVIRAPINE-BASED SERVICES TO PREVENT MOTHER-TO-CHILD HIV TRANSMISSION

Figure 1. Profile of the PEARL Study Cord Blood Surveillance

<table>
<thead>
<tr>
<th>Event</th>
<th>Count</th>
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<tbody>
<tr>
<td>28,955 Women gave birth to live infants in public-sector facilities</td>
<td></td>
</tr>
<tr>
<td>996 Cord blood specimens not obtained</td>
<td></td>
</tr>
<tr>
<td>27,957 Cord blood specimens obtained</td>
<td></td>
</tr>
<tr>
<td>64 Specimens not tested</td>
<td></td>
</tr>
<tr>
<td>27,863 Specimens tested for HIV antibodies</td>
<td></td>
</tr>
<tr>
<td>24,569 Specimens had seronegative HIV test results</td>
<td></td>
</tr>
<tr>
<td>3324 Cord blood specimens had seropositive HIV test results</td>
<td></td>
</tr>
<tr>
<td>128 Specimens did not have nevirapine results available</td>
<td></td>
</tr>
<tr>
<td>3196 Cord blood specimens had nevirapine results available</td>
<td></td>
</tr>
</tbody>
</table>

HIV indicates human immunodeficiency virus; PEARL, PMTCT (prevention of mother-to-child HIV transmission) Effectiveness in Africa: Research and Linkages to Care.

dened with ongoing research and the surveillance might not be conducted successfully there. Finally, in Zambia, where the entire country was included in the sampling frame, we formed 8 service clusters by selecting 11 sites from the 192 that were eligible. The differences in numbers of service clusters and sites among countries are the result of the sampling process and the anticipated delivery volume of randomly selected sites. In all countries except Cameroon, selected facilities were operated by their respective governments. In Cameroon, 4 were government facilities, 3 were faith-based facilities, and 1 was a facility that provides free health care to plantation workers.

To achieve the target sample sizes for individual clinics in each country, we monitored the HIV prevalence and the expected number of HIV-seropositive deliveries by clinic. Specimen collection proceeded at each service cluster until the target sample size was reached or until 1 year had transpired, whichever came first.

Statistical analyses were performed between November 1, 2008, and February 26, 2010, using SAS statistical software version 9.1.4 (SAS Institute Inc, Cary, North Carolina) and R software version 2.4.1 (http://www.r-project.org). To describe the baseline characteristics of participants within each country, we computed medians and interquartile ranges (IQRs) for continuous variables and percentages for categorical variables and used the Wilcoxon rank sum test, respectively.

We used both crude and adjusted methods to estimate the coverage of services to prevent mother-to-child HIV transmission and maternal nevirapine adherence for each country. For crude estimates, we used simple proportions; to avoid asymptotic assumptions, we calculated corresponding binomial CIs using Exact methods. For adjusted estimates, we used generalized estimating equations to account for potential correlation among patients within the same service cluster and a Huber-White sandwich estimator to allow for robust standard errors. We estimated predictors of both population nevirapine coverage and maternal nevirapine adherence using generalized estimating equations. Predictors were classified as statistically significant if the corresponding 95% CI did not contain 1. Mother-infant pairs in which any covariate information was missing were removed from the multivariable models. Finally, an overall weighted estimate for population coverage was calculated as the mean of the estimated proportions from all 4 countries and a corresponding 95% CI was generated using a bootstrapping method.

The PEARL study and its unlinked anonymous design received continuing ethical approval from the institutional review boards at the US Centers for Disease Control and Prevention, the University of Alabama at Birmingham, and the local research ethics review bodies in each of the participating countries. With the exception of Cameroon, where informed consent was obtained for all participants, each institutional review board approved an informed consent form waiver.

RESULTS

We conducted the cord blood surveillance across 25 service clusters (43 delivery sites) in the 4 countries of Cameroon, Côte d’Ivoire, South Africa, and Zambia. The median service cluster took 275 days (IQR, 152-335 days) to complete the surveillance. Across all sites, a total of 28,955 women gave birth to live infants, of whom 27,957 had cord blood samples collected (96.6%). Of these, 27,893 were tested for HIV (99.8%; Figure 1). The median age of seropositive mothers was 27 years (IQR, 23-31 years). These women had a median of 2 (IQR, 2-4) total pregnancies and had attended a median of 4 (IQR, 2-5) antenatal care visits. Data were available for 3005 women and of these, 1394 received antenatal care (46.4%) at the delivery center. The median time between HIV test-
ing and delivery was 3 months (IQR, 2-5 months) and 2960 were vaginal deliveries (92.9%). The median birth weight was 3050 g (IQR, 2700-3400 g). Descriptive statistics by country are provided in Table 1.

Of the collected and tested cord blood specimens, 3324 were HIV seropositive (11.9%; 95% CI, 11.5%-12.3%). The seroprevalences by country were 21.3% (95% CI, 20.1%-22.5%) for South Africa, 5.9% (95% CI, 5.4%-6.4%) for Côte d’Ivoire, 10.6% (95% CI, 10.0%-11.3%) for Cameroon, and 16.9% (95% CI, 15.8%-17.9%) for Zambia. Cord blood results for nevirapine were not available for 128 of the seropositive samples (4%; 65 from Cameroon, 2 from Zambia, and 61 from South Africa). Complete data are reported on 3196 HIV seropositive mother-infant pairs.

Of the 3196 HIV-exposed infants in the surveillance population, 1845 had nevirapine detected in the umbilical cord blood (unadjusted maternal coverage rate: 58%; 95% CI, 56.5%-59%) and 2346 were administered nevirapine prior to hospital discharge (unadjusted infant coverage rate: 73%; 95% CI, 72.7%-75%). The primary outcome of total coverage (both maternal and infant dosing) was achieved in 1725 HIV-exposed infants (unadjusted total coverage rate: 54%; 95% CI, 52.5%-56%). Total coverage rates varied by country. In adjusted analyses, in which we accounted for potential correlation among individuals delivering within the same service cluster and country, the overall estimate for the 4 countries was 51% (95% CI, 49.2%-53%); Table 2).

By linking these coverage data to medical record extraction, we were able to recreate the cascade of events that occurred prior to hospital discharge and therefore, these infants were administered nevirapine prior to hospital discharge. Of the 2956 women whose mothers ingested nevirapine prior to delivery, 2157 received the infant dose prior to discharge from the delivery center. An additional 621 HIV-exposed infants were administered nevirapine prior to discharge who had cord blood that was negative for nevirapine at delivery. Therefore, these infants were not included in the primary outcome measure.

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(Reprinted) JAMA, July 21, 2010—Vol 304, No. 3 297
Total coverage and the components of failed coverage varied greatly by country and service cluster (FIGURE 3 and eTables 1 and 2 at http://www.jama.com). Elements of failed coverage in the remaining 49% (adjusted for country) included HIV testing not offered (8.8%; 95% CI, 7.7%-9.9%); testing not accepted (3.9%; 95% CI, 3.0%-4.7%); positive test result not received (5.6%; 95% CI, 4.6%-6.6%); maternal nevirapine not dispensed (4.5%; 95% CI, 3.6%-5.4%); maternal nonadherence to nevirapine (13.3%; 95% CI, 12.1%-14.5%); and infant nevirapine dose not administered (3.9%; 95% CI, 3.2%-4.7%). The cause could not be determined in 9.0% (95% CI, 7.8%-10.2%).

In multivariable analysis, failed coverage was significantly associated with (1) maternal age younger than 20 years (adjusted odds ratio [AOR], 1.44; 95% CI, 1.18-1.76) and maternal age between 20 and 25 years (AOR, 1.28; 95% CI, 1.07-1.54) vs maternal age older than 30 years; (2) 1 or fewer antenatal care visits (AOR, 2.91; 95% CI, 2.40-3.54), 2 or 3 antenatal care visits (AOR, 1.93; 95% CI, 1.60-2.33), and 4 or 5 antenatal care visits (AOR, 1.56; 95% CI, 1.34-1.80) vs 6 or more antenatal care visits; (3) vaginal delivery (AOR, 1.22; 95% CI, 1.03-1.44) vs cesarean delivery; and (4) infant birth weight of less than 2500 g (AOR, 1.34; 95% CI, 1.11-1.62) vs birth weight of 3500 g or greater (TABLE 3).

Maternal nonadherence (ie, absence of nevirapine in the cord blood among women with documented dispensation of antenatal nevirapine) was common and varied by country: 115 of 749 women in Cameroon (15.4%; 95% CI, 12.8%-18.1%); 61 of 196 women in Côte d’Ivoire (31.1%; 95% CI, 12.8%-18.1%); 117 of 663 women in South Africa (17.6%; 95% CI, 14.8%-20.8%); and 140 of 670 women in Zam-

Figure 2. Cascade of Events Negotiated by Mothers Infected With Human Immunodeficiency Virus (HIV) and Their HIV-Exposed Infants to Prevent Mother-to-Child HIV Transmission

- A (upper bar) represents all the women in the surveillance population who were seropositive at delivery. Steps C through G represent a critical path, each of which is contingent on the previous one being successfully negotiated. Coverage, defined as the proportion of infected or exposed mother-infant pairs who received both the maternal and infant nevirapine doses, was 1725/3196 or 54% (this estimate is not weighted for country [see “Methods” section]). There were 240 cases for whom we know coverage failed (because there was no nevirapine in the cord blood) but due to inadequate documentation in the antenatal record, we could not ascertain the reason for the failure. Step H is not contingent on steps E, F, or G; an additional 621 HIV-exposed infants were administered nevirapine prior to discharge who had cord blood that was not positive for nevirapine at delivery. Thus, these infants were not included in the primary outcome measure.
bia (20.9%; 95% CI, 17.9%-24.2%). In multivariable analysis, failed coverage of nevirapine-based services was significantly associated with maternal age younger than 20 years (adjusted odds ratio [AOR], 1.44; 95% CI, 1.18-1.76) and maternal age between 20 and 25 years (AOR, 1.28; 95% CI, 1.07-1.54) vs maternal age of older than 30 years; 1 or fewer antenatal care visits (AOR, 1.56; 95% CI, 1.34-1.80) vs 6 or more antenatal care visits; vaginal delivery (AOR, 1.22; 95% CI, 1.03-1.44) vs cesarean delivery; and infant birth weight of less than 2500 g (AOR, 1.34; 95% CI, 1.11-1.62) vs birth weight of 3500 g or greater. We also found less maternal nonadherence (ie, better adherence) in women prescribed highly active antiretroviral therapy during pregnancy than in those prescribed single-dose nevirapine (AOR, 0.53 [95% CI, 0.36-0.78]; Table 3).

**COMMENT**

In this multicountry evaluation, only half of the infants born to HIV-infected mothers received at least a minimum prophylactic course of maternal-infant single-dose nevirapine. Although the anonymous nature of our study limited the information we were able to collect from individual mothers, we did identify 2 important predictors of failed coverage. In adjusted analysis, fewer antenatal visits and younger maternal age were both strongly associated with failure to receive prophylaxis. This has immediate implications regarding counseling of younger mothers and confirms the general importance of repeat antenatal visits as part of good obstetrical care.

A common way to monitor services to prevent mother-to-child HIV transmission is to count the numbers of new antenatal attendees, women testing positive for HIV, and doses of prophylaxis dispensed. This allows an estimate of the number of HIV-exposed infants in the population and the proportion of them that receives an intervention to prevent mother-to-child HIV transmission. However, such a reliance on process indicators collected from clinic log books and tally sheets can result in erroneous estimates of program impact. Because the HIV seroprevalence among women who are not tested during antenatal care may differ substantially from those who are...
tested, and because it is common for women who are HIV negative at an early antenatal visit to seroconvert during pregnancy, traditional monitoring methods may substantially underesti-
mate the proportion of infants in the population who are exposed to HIV. Mat-
ternal nonadherence, an unfortunate but frequent occurrence, is not reliably cap-
tured by process indicators. In some cases, routine data collected at remote or underresourced sites can simply be in-
complete or incorrect. A recent World Health Organization report estimated that 41% of pregnant women in Côte d’Ivoire received an intervention to pre-
vent mother-to-child HIV transmission in 2008, but our study, which was con-
ducted concurrently, puts this estimate at 16% (95% CI, 8%-23%).

Outside the commonly cited agency estimates, few assessments of popula-
tion effectiveness to prevent mother-
to-child HIV transmission are pub-
licly available. Fewer still can be found in the peer-reviewed literature. A 2007 article with data from 6 provinces in Thailand reported on 2200 HIV-
exposed infants registered at delivery and followed up as they returned for im-
munization visits. The HIV infection status was directly available for 76% of infants and the investigators were able to estimate transmission rates of the re-
mainder based on known characteristics of the mothers (overall rate, 10.2%).

Working in the KwaZulu Natal Prov-
ince of South Africa, Rollins et al collected blood spots from 2489 infants at-

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<tr>
<th>Maternal age, y</th>
<th>No./Total</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)</th>
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<th>AOR (95% CI)</th>
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<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Delivery method</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vaginal</td>
<td>1393/2960</td>
<td>1.41 (1.15-1.72)</td>
<td>1.22 (1.03-1.44)</td>
<td>412/2088</td>
<td>1.71 (1.19-2.45)</td>
<td>1.45 (1.01-2.08)</td>
</tr>
<tr>
<td>Missingc</td>
<td>9/11</td>
<td>NA</td>
<td>NA</td>
<td>1/9</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤&lt;2500</td>
<td>248/422</td>
<td>1.76 (1.39-2.21)</td>
<td>1.34 (1.11-1.62)</td>
<td>59/251</td>
<td>1.39 (0.96-2.01)</td>
<td>1.34 (0.93-1.92)</td>
</tr>
<tr>
<td>2500-3499</td>
<td>970/2107</td>
<td>1.07 (0.92-1.25)</td>
<td>0.96 (0.84-1.09)</td>
<td>287/1500</td>
<td>1.04 (0.79-1.38)</td>
<td>1.03 (0.82-1.30)</td>
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<tr>
<td>Missingc</td>
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<td>NA</td>
<td>NA</td>
<td>2/35</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Prophylaxis type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine only</td>
<td>NAd</td>
<td>NA</td>
<td>NA</td>
<td>168/908</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
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<td>Nevirapine and zidovudine</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>227/998</td>
<td>1.02 (0.73-1.43)</td>
<td>1.03 (0.73-1.46)</td>
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<td>Highly active antiretroviral therapy</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>38/231</td>
<td>0.56 (0.37-0.84)</td>
<td>0.53 (0.36-0.78)</td>
</tr>
<tr>
<td>Missingc</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0/241</td>
<td>NA</td>
<td>NA</td>
</tr>
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</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; NA, not available; OR, odds ratio.

aGeneralized estimating equations were used to calculate the ORs to account for correlation among patients within the same service cluster.

bThe numbers in the column headings refer to the number of mother-infant pairs who were included in the adjusted analysis. To be included, patients must have had complete data on all covariates in the model. It should be noted that the reason there were fewer women in the failed coverage analysis overall is that there were fewer at risk. Some women did not negotiate the proximal aspects of the cascade to prevent transmission of human immunodeficiency virus from mother to child that would lead them to be prescribed a prophylaxis regimen.

cThe denominator is the number of mother-infant pairs at risk for whom data were missing. The numerator is the number not covered or the number not adherent.

dData cannot be calculated because patients must negotiate the proximal steps in the cascade to prevent transmission of human immunodeficiency virus from mother to child to be assigned a prophylaxis type.
tending routine 6-week immunization visits and found 20.2% of HIV-exposed children to be infected.

The PEARL study is unique among studies published thus far in its use of random sampling to allow country-based estimates of service coverage. Our design also has allowed a precise accounting of the critical path that must be negotiated by mother-infant pairs for services to prevent mother-to-child HIV transmission to be effective. As displayed in Figure 3, failures along this prevention cascade differed greatly by site; overall, no particular step seems to be entirely responsible for failed coverage.

Maternal nonadherence, described previously by members of our team, remains prevalent and concerning. Overall, more than 1 in 4 women who were dispensed prophylactic nevirapine during antenatal care failed to swallow the tablet during labor. While our study design did not allow the precise reasons for this nonadherence to be determined, subjective experience suggests that stigma and fear of disclosure figure prominently among them.23,24 We also noted nonadherence among 38 of 231 women who had been prescribed highly active antiretroviral therapy during pregnancy. Given the long half-life of nevirapine, this suggests that a substantial proportion of women are not taking their prescribed antiretrovirals at all during the weeks prior to delivery. Adherence could likely be improved in a number of ways, including promotion of couples’ HIV testing during antenatal care, repeat counseling at each antenatal visit, and training of labor ward staff to redispense nevirapine to women who present in labor without having self-administered the drug at labor onset.

There are limitations to this study. While we believe the sites we randomly selected are representative of facilities providing services to prevent mother-to-child HIV transmission in the 4 targeted countries, our coverage estimates must be interpreted as a best-case scenario because we only conducted the surveillance in facilities that national authorities indicated were actually providing these services. In addition, we have only sampled institutional deliveries; infants who are delivered at home may be less likely to receive prophylaxis, but they would not be captured by our estimate. Finally, we have applied a strict definition of service coverage that requires evidence of both mother and infant dosing. A randomized controlled trial in Botswana demonstrated that the maternal nevirapine dose may not be necessary if zidovudine is provided during pregnancy. It is conceivable that partial efficacy may be obtained with only the maternal or infant dose, even in settings in which antenatal zidovudine is not provided.

In an effort to ensure comparability across sites, we chose to centralize the nevirapine testing in this study. However, there are at least 2 assays available for qualitative nevirapine testing that could be used locally. These include simple thin-layer chromatography and a dipstick immunochromatographic method, either of which could be easily and affordably incorporated into a program’s ongoing monitoring and quality-improvement plan.

In conclusion, successful prevention of mother-to-child HIV transmission requires each mother-infant pair to negotiate a critical path that begins with the offering of an HIV test and proceeds through posttest counseling to drug adherence and beyond. Our findings indicate that programmatic failures are common along this path, and that each clinic faces its own mix of challenges in maximizing service coverage. In November 2009, the World Health Organization published revisions to its international guidelines that made more efficacious (and complex) drug regimens to prevent mother-to-child HIV transmission standard. This is a critical move toward global pediatric AIDS control, yet it holds only half the key. The other half lies in service coverage. Even the most potent interventions will not protect those infants who do not receive them.

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**Acquisition of data**: E. Stringer, Ekouevi, Coetzee, Tih, Creek, Welty, Chintu, Wilfert, Shaffer, Dabis, J. Stringer.

**Analysis and interpretation of data**: E. Stringer, Coetzee, Tih, Creek, Giganti, Welty, Chi, Wilfert, Shaffer, Dabis, J. Stringer.

**Drafting of the manuscript**: E. Stringer, Coetzee, Giganti, Welty, Wilfert, Dabis, J. Stringer.

**Critical revision of the manuscript for important intellectual content**: E. Stringer, Ekouevi, Coetzee, Tih, Creek, Stinson, Welty, Chintu, Chi, Wilfert, Shaffer, Dabis, J. Stringer.

**Statistical analysis**: Giganti, J. Stringer.

**Obtained funding**: E. Stringer, Coetzee, Creek, Giganti, Welty, Chi, Wilfert, Shaffer, Dabis, J. Stringer.

**Administrative, technical, and material support**: E. Stringer, Ekouevi, Coetzee, Tih, Creek, Stinson, Giganti, Welty, Chintu, Chi, Wilfert, Shaffer.

**Study supervision**: E. Stringer, Ekouevi, Coetzee, Creek, Giganti, Welty, Dabis, J. Stringer.

**Financial Disclosures**: None reported.

**Funding/Support**: The Zambia, South Africa, and Côte d’Ivoire work was supported by contract T0906150021 from the US Centers for Disease Control and Prevention Global AIDS Program. The Cameroon work was supported by the Bill and Melinda Gates Foundation grant 351-07, which was awarded to the Elizabeth Glaser Pediatric AIDS Foundation.

**Role of the Sponsors**: The US Centers for Disease Control and Prevention (CDC) was not involved in data collection or management, but through coauthors and the CDC manuscript clearance process, the CDC was substantially involved in the preparation, review, and approval of the manuscript. The Bill and Melinda Gates Foundation was not involved in the design or conduct of the study, collection, management, analysis, or interpretation of the data, nor was it involved in preparation, review, or approval of the manuscript. The Elizabeth Glaser Pediatric AIDS Foundation was not involved in data collection, management, or analysis, but through a coauthor was involved in design of the study, data interpretation, and manuscript preparation, review, and approval.

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Disclaimer: The findings and conclusions of the article are solely the responsibility of the authors and do not necessarily represent the official views of the US Centers for Disease Control and Prevention.

Previous Presentation: These data were presented in part at the 5th International AIDS Conference on HIV Pathogenesis, Treatment, and Prevention; July 19-22, 2009; Cape Town, South Africa. Abstract WELB0101.

Online-Only Material: eTable 1 and eTable 2 are available at http://www.jama.com.

Additional Contributions: We thank all of the patients, physicians, nurses, community workers, and support staff who contributed to the completion of this study. We also acknowledge Andrew Bouelle, MD (University of Cape Town, Cape Town, South Africa), Marc Butlers, MD, PhD (US Centers for Disease Control and Prevention, China), Latsaha Teger (US Centers for Disease Control and Prevention, South Africa), and Wendy Mazimba (Centre for Infectious Disease Research in Zambia) for their contributions to this study. None received compensation.

REFERENCES


