JECH Online First, published on November 4, 2014 as 10.1136/jech-2014-204535

OPEN ACCESS

First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa

Ameena E Goga,[1,2] Thu-Ha Dinh,[3] Debra J Jackson,[4,5] Carl Lombard,[6,7] Kevin P Delaney,[8] Adrian Puren,[9] Gayle Sherman,[9,10] Selamawit Woldesenbet,[1] Vundli Ramokolo,[1] Siobhan Crowley,[11] Tanya Doherty,[1,4,12] Mickey Chopra,[5] Nathan Shaffer,[13] Yogan Pillay,[14] for the South Africa PMTCT Evaluation (SAPMCTE) Team

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jech-2014-204535).

For numbered affiliations see end of article.

Correspondence to
Prof Ameena Ebrahim Goga, Francie van Zyl Drive, Parrowvallei, Cape Town 7505, South Africa;
Ameena.Goga@mrc.ac.za

Received 15 June 2014
Revised 4 September 2014
Accepted 13 October 2014

ABSTRACT

Background There is a paucity of data on the national population-level effectiveness of preventing mother-to-child transmission (PMTCT) programmes in high-HIV-prevalence, resource-limited settings. We assessed national PMTCT impact in South Africa (SA), 2010.

Methods A facility-based survey was conducted using a stratified multistage, cluster sampling design. A nationally representative sample of 10 178 infants aged 4–8 weeks was recruited from 565 clinics. Data collection included caregiver interviews, record reviews and infant dried blood spots to identify HIV-exposed infants (HEI) and HIV-infected infants. During analysis, self-reported antiretroviral (ARV) use was categorised: 1a: triple ARV treatment; 1b: azidothymidine >10 weeks; 2a: azidothymidine ≤10 weeks; 2b: incomplete ARV prophylaxis; 3a: no antenatal ARV and 3b: missing ARV information. Findings were adjusted for non-response, survey design and weighted for live-birth distributions.

Results Nationally, 32% of live infants were HEI; early mother-to-child transmission (MTCT) was 3.5% (95% CI 2.9% to 4.1%). In total 29.4% HEI were born to mothers on triple ARV treatment (category 1a) 55.6% on prophylaxis (1b, 2a, 2b), 9.5% received no antenatal ARV (3a) and 5.5% had missing ARV information (3b). Controlling for other factors groups, 1b and 2a had similar MTCT to 1a (Ref; adjusted OR (AOR) for 1b, 0.98, 0.52 to 1.83; and 2a, 1.31, 0.69 to 2.48). MTCT was higher in group 2b (AOR 3.68, 1.69 to 7.97). Within group 3a, early MTCT was highest among breastfeeding mothers 11.50% (4.67% to 18.33%) for exclusive breast feeding, 11.90% (7.45% to 16.35%) for mixed breast feeding, and 3.45% (0.53% to 6.35%) for no breast feeding). Antiretroviral therapy or >10 weeks prophylaxis negated this difference (MTCT 3.94%, 1.98% to 5.90%; 2.07%, 0.55% to 3.60% and 2.11%, 1.28% to 2.95%, respectively).

Conclusions SA, a high-HIV-prevalence middle income country achieved <5% MTCT by 4–8 weeks post partum. The long-term impact on PMTCT on HIV-free survival needs urgent assessment.

To cite: Goga AE, Dinh T-H, Jackson DJ, *et al*. *J Epidemiol Community Health* Published Online First: [*please include* Day Month Year] doi:10.1136/jech-2014-204535

INTRODUCTION

Eliminating mother-to-child transmission (MTCT) of HIV is a global public health priority.[1] Randomised clinical trials in the USA, Europe and Asia show that antenatal antiretroviral (ARV) interventions reduce the risk of MTCT from 15% to 30% during pregnancy and labour to <2% in non-breastfeeding populations and <5% in breastfeeding populations.[2 3] There is a paucity of data on the national (countrywide) population-level effectiveness of recent programmes to prevent MTCT (PMTCT) in high-HIV-prevalence countries such as South Africa (SA), and no consensus methodology for such evaluations.[4] Previous research evaluating PMTCT impact in routine settings have been mainly conducted in the era of single-dose nevirapine[5–10] (NVP) in confined settings[5–13]—except for the Zambian component of the PEARL study[13]—or in well-resourced settings.[14] As far as we know, the Zambian PEARL results have not yet been reported. Thus country-level PMTCT impact in resource-limited, high-HIV-prevalence settings cannot be extrapolated or assumed from previous studies.

We conducted a survey to assess the early population-level effectiveness of SA's PMTCT programme, using vertical HIV transmission between 4 and 8 weeks post partum as the main outcome of interest. The survey started 1 month after SA adopted WHO PMTCT Option A (see web appendix figure 1).

METHODS

Study design

A national facility-based evaluation using a stratified multistage probability proportional to size (PPS) sampling design was conducted from June to December 2010. A desired sample size of 12 200 infant dried blood spot (iDBS) specimens was calculated to measure a projected early MTCT risk of 6.6% with a precision of 1% and a design effect of 2 (see web appendix 2). The 12 200 specimens were partitioned between the nine South African provinces as follows: Eastern Cape 1400, Free State 1300, Gauteng 1800, Kwa-Zulu Natal 1400, Limpopo 1400, Mpumalanga 1600, Northern Cape 700, North West 1200 and Western Cape 1400. The facility sampling frame only included public primary healthcare clinics/community health centres (PHCs/CHCs) offering 6-week immunisation services and assumed population representativeness thereof for two reasons: (1) 6-weeks immunisation coverage has been documented as

99% (95% CI 98% to 99%)[15] and (2) at least 85% of 6-week immunisations are performed in public health facilities.[16] We stratified all PHC/CHC facilities into three strata per province based on their 6-week immunisation patient load and their 2008 annual antenatal HIV prevalence. The 6-week immunisation load was obtained from the 2007 District Health Information System (DHIS; see web appendix 3) and facilities were categorised based on their mean annual 6-week immunisations: ≥300 annual immunisations (busy facilities) with district HIV prevalence at or more than the national average (≥29%), busy facilities with district HIV prevalence <29%, and 130–300 annual immunisations (medium-sized facilities).[17] Facilities with a <130 annual immunisation load were excluded from the sampling frame. On the basis of the DHIS data, we calculated an estimated number of immunisations per facility over a feasible 3-week recruitment period (4 weeks in Northern Cape province) for each province. The number of facilities needed per stratum and thus per province to achieve the sample size of 12 200 was thus calculated as 580. These 580 facilities (34–79 facilities per province) were randomly selected within each stratum in each of the nine provinces with probability proportional to size (PPS).[18] A fixed number of caregiver/infant pairs were consecutively or systematically (in facilities with queues of mothers waiting for immunisation) selected from facilities over a planned recruitment window. Systematic sampling was conducted after determining the recruitment interval based on the sample size needed for that day and starting the selection with a randomly selected patient folder or mother. Data collectors (study nurses) were trained on sampling methods using standardised operating procedures. Infants aged 4–8 completed weeks, receiving their 6-week immunisation, whose caregivers provided informed consent were eligible to participate.

Data collection procedures

Trained study nurses conducted face-to-face interviews. Mode of delivery, gestational age at delivery, and infant birth weight were documented from each infant's patient-held health chart.[19] Self-reported data on maternal HIV testing, maternal CD4 test uptake/results, maternal ARV regimens, maternal antenatal care (ANC) and infant feeding practices (recall of previous 8 days) were gathered. Data on maternal ARV regimens were documented after showing mothers pictures of ARVs, and samples where available. No data were collected on exact drug regimens in women on antiretroviral therapy (ART), drug dosages, duration of ART and compliance. Data were collected using hand-held devices (cellphones) and interview data were uploaded real-time into a web-based database.[20]

Pretest counselling was conducted and iDBS were obtained from heel prick blood draw onto Munktell-TFN 5-spot paper. Infant HIV testing, using iDBS at 6 weeks post partum has been the standard of care in South Africa since 2005. As study nurses were drawing blood from all consented infants regardless of PMTCT or HIV exposure, iDBS were processed for HIV exposure and infection (see section below). Study nurses or routine national systems returned test results to facilities. Study nurses trained Department of Health nurses on the interpretation of study results and the latter returned test results to participants. Anonymised results were captured in the study database. Mothers and infants were referred into routine HIV-related care and treatment services as needed. No maternal blood was drawn.

Laboratory testing and definitions

All iDBS samples were tested in one accredited laboratory at the National Institute for Communicable Diseases, National Health Laboratory Services, Johannesburg, using standardised accredited procedures. iDBS underwent serology testing for HIV antibody using an enzyme immunoassay (EIA; Genscreen HIV1/2 Ab EIA V.2, Bio-Rad Laboratories, France). All antibody-positive and 10% of negative iDBS specimens were retested using a second EIA (Vironostika HIV Uni-form II plus O, bioMèrieux Clinical Diagnostics, Marcy-L'Etoile, France). Discordant results (discordance between mother's reported HIV status and infant EIA result or discordance between the first and second EIA results) were checked using Western blot (GS HIV-1, Bio-Rad France). iDBS with concordant positive or discordant EIA results or from self-reporting HIV-positive mothers were tested using a qualitative DNA PCR to determine the infant's HIV infection (COBAS AmpliPrep/COBAS TaqMan—CAP/CTM—Qualitative assay V.1.0 assay, Roche Diagnostics, Branchburg, New Jersey, USA). Confirmed antibody-positive iDBS specimens indicated infant HIV exposure (HIV-exposed infant (HEI)). EIA and PCR positive iDBS were defined as confirmed early HIV infection.

Statistical methods

Using information from the sampling design and SA's 2010 live-birth distribution across provinces, the survey sample was weighted to account for sample ascertainment due to non-response (refusal), undersampling (related to clinic immunisation uptake), lost and poor quality iDBS specimens within each facility, as well as the disproportionate sampling of provinces. Analysis procedures thus accounted for the stratified cluster survey design and were weighted for non-response.[21–23] All statistical analyses were carried out using SAS (V.9.2, SAS Institute, Cary, North Carolina, USA). Weighted point estimates of transmission risks were estimated at national and provincial levels, and for six treatment subgroups (created during analysis and defined below) with 95% CIs using standard bivariate analyses appropriate for the sample design. All multivariate analyses used sample survey procedures to conduct logistic regression with both the complete case data and a full-imputed data set.[21 24] This multivariate logistic regression analysis was used to assess the association between key interventions and behaviours and MTCT.

We categorised maternal self-reported ARV uptake into three main groups, with two subcategories in each group (figure 1): We also considered two other MTCT interventions: vaginal versus caesarean delivery and infant feeding practice, which was categorised into no breast feeding (NBF), exclusive breast feeding (EBF) or mixed breast feeding (MBF), as a measure of breast milk exposure. Several factors including sociodemographic (education, socioeconomic status) and pregnancy-related factors (gestational age at first antenatal visit, pregnancy planned or not, reported maternal CD4 cell count, infant birth weight and parity) were considered potential confounders of the measured effect of these interventions. The socioeconomic status variable was constructed using a clustering algorithm that considered 10 interview items (see web appendix 4).[25 26] Self-reported gestational age at first ANC and CD4 cell count was missing for approximately 16.5% and 44% of the population, respectively, as a result of poor documentation or mothers not being told or not remembering their CD4 cell count. Multiple imputations were used to calculate gestational age for participants with missing values and were also considered for

We categorized maternal self-reported antiretroviral uptake into three main groups with two sub-categories in each group:

(1) **Advanced regimen group** including those mothers on
  (1a) antiretroviral treatment/triple therapy antenatally (ART) or
  (1b) mother received Azidothymidine (AZT) for >10 weeks and infant received Nevirapine (NVP) and/or AZT at birth (ARVP>10wks)

(2) **Other ARV regimen group** including those
  (2a) mother received AZT for ≤10 weeks and infant received NVP and/or AZT at birth (ARVP≤10 weeks) or
  (2b) mothers or infants (but not both) received any ARVs (incomplete ARVP)

(3) **No known ARV group** including those
  (3a) mothers and infants reported receiving no ARV (no ARV) or
  (3b) no information on ARV uptake available (missing ARV information).

Figure 1 Categorisation of self-reported antiretroviral uptake (ARV, antiretroviral; ARVP, ARV prophylaxis; wks, weeks).

CD4 cell count (see web appendix 5).[24] Imputed CD4 cell count was not used in the final multivariate analysis due to the large number of missing values. With the exception of mother's age, all potential confounding factors were included in multivariate analyses as categorical variables. Interactions between the ARV regimen and breast feeding were considered a priori as these were two main exposures of interest. Confounding assessment was conducted on the full model which included all potential confounders and this interaction effect. Variables that changed the effect of either exposure variable by more than 10% were considered as likely confounders in these data.[27] The model including all potential confounders did not change estimates of the relative odds of MTCT by >10% (compared with Model 1, table 3), but the

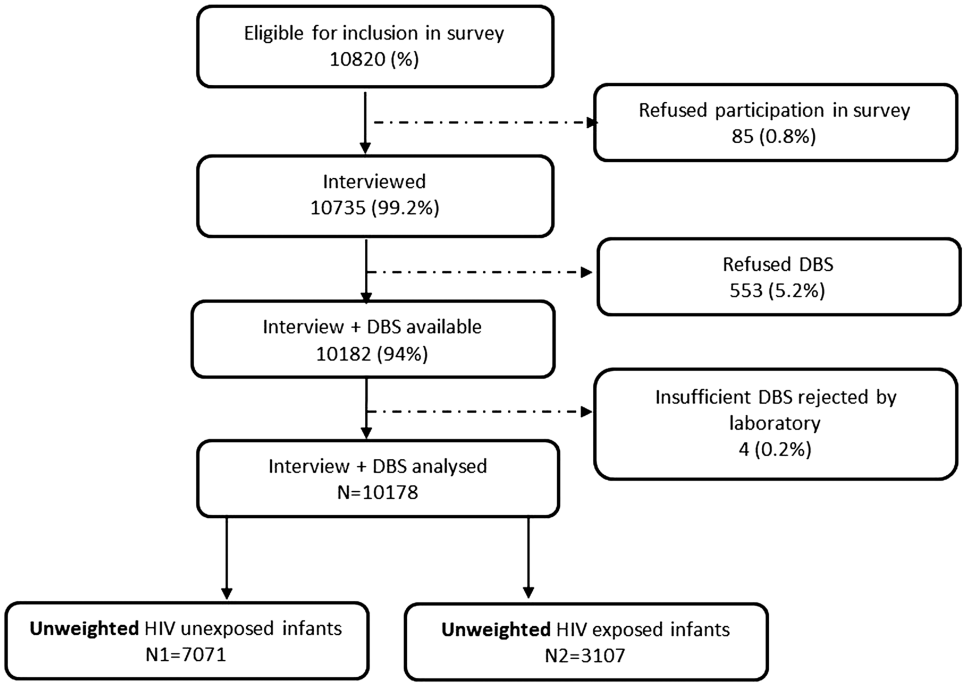

Figure 2 Eligibility and participation in the 2010 South African PMTCT survey: unweighted numbers (DBS, dried blood spot; PMTCT, preventing mother-to-child transmission).

Table 1 Characteristics of the study population by infant HIV exposure status, South Africa, 2010

	HIV-unexposed infant n=7071 N_w=875 220 (weighted)		HIV-exposed infant n=3107 N_w=412 634 (weighted)	
Maternal characteristics	**Weighted%**	**95% CI**	**Weighted%**	**95% CI**
Mother	96.8	96.2 to 97.2	96.9	96.3 to 97.5
Other caregiver	3.2	2.8 to 3.8	3.1	2.5 to 3.7
Maternal age mean (range)	25.9 (13 to 49)		27.7 (15 to 46)	
Married status*				
Single	72.6	70.8 to 74.4	78.4	76.4 to 80.5
Married/cohabiting	27.1	25.3 to 28.8	20.2	18.2 to 22.2
Widow/divorced	0.2	0.1 to 0.3	0.8	0.5 to 12
No information	0.1	0.03 to 0.2	0.6	0.3 to 0.8
Education level*				
None	2.0	1.3 to 2.0	2.6	2.0 to 3.2
Grade 1–7	13.4	12.4 to 14.4	18.2	16.7 to 19.8
Grade 8–12	77.8	76.7 to 79.3	75.6	73.8 to 77.5
Grade 12+	6.5	5.7 to 7.3	2.7	2.1 to 3.4
Missing	0.4	0.3 to 0.6	0.8	0.5 to 1.1
SES*				
Average†	70.5	68.5 to 72.6	64.3	61.6 to 67.0
Lower	14.5	12.7 to 16.2	23.1	20.5 to 25.7
Lowest	15.0	13.7 to 16.4	12.6	11.1 to 14.1
Parity*				
1	41.9	40.6 to 43.2	21.5	19.8 to 23.2
2	28.6	27.5 to 29.8	36.6	34.7 to 38.5
≥3	26.8	25.6 to 28.0	39.5	37.7 to 41.3
Missing	2.6	2.2 to 3.0	2.4	1.9 to 2.8
Number of live children*				
1	45.1	43.7 to 46.4	27.2	25.4 to 28.9
2	28.4	27.9 to 29.4	37.5	35.7 to 39.3
≥3	23.9	22.8 to 25.1	33.0	31.2 to 34.7
Missing	2.6	2.2 to 3.0	2.4	1.9 to 2.8
Planned pregnancy*				
Yes	39.7	38.1 to 41.3	35.5	33.3 to 37.8
No	57.2	55.6 to 56.9	61.4	59.1 to 63.6
Missing	3.1	2.6 to 3.5	3.1	2.5 to 3.7
Number of ANC visits				
Had 1 ANC	96.5	96.0 to 97.0	96.4	95.8 to 96.9
Had <1 ANC	3.5	3.2 to 4.0	3.6	3.1 to 4.2
Gestational age of first ANC visit (weeks)				
≤12	23.2	22.0 to 24.4	20.0	18.3 to 21.7
13–16	13.5	12.5 to 14.6	13.6	12.3 to 14.9
17–20	19.1	18.0 to 20.2	18.9	17.1 to 20.7
21–24	14.9	13.8 to 15.9	17.6	16.0 to 19.4
25–28	9.3	8.3 to 10.2	9.3	8.1 to 10.5
29–32	2.2	1.8 to 2.5	2.0	1.5 to 2.4
33–36	0.6	0.4 to 0.8	0.7	0.4 to 1.0
37+	0.7	0.5 to 0.9	0.9	0.5 to 1.2
Missing	16.5	14.7 to 18.4	17.0	14.7 to 19.3
Infant characteristics				
Infant sex (male)	51.2	50.0 to 52.4	49.1	47.1 to 51.1
Infant's birth weight*				
<2.5 kg	11.4	10.4 to 12.4	13.4	12.1 to 14.7
≥2.5 kg	88.6	87.6 to 89.6	86.6	85.3 to 87.9

*p<0.05 (Rao-Scott χ^2 test) N_w=weighted population number.
†'Average' SES in this population would be low compared with SES of groups using private healthcare or living in 'developed' countries.
ANC, antenatal care; SES, socioeconomic status.

interaction between the ARV and breast feeding exposure variables was significant in the logistic regression models. Therefore, to simplify interpretation, we report an interaction between our exposures by creating variables representing the possible two-way combinations of our exposures and then estimating the proportion of exposed infants with evidence of transmission in each strata without adjustment for other factors.[28–30]

RESULTS

Description of study population

A total of 10 178 caregiver–infant pairs (83.4% of the desired sample size) with eligible iDBS samples from 565 facilities were analysed (figure 2).

Sample ascertainment was affected by the availability of immunisation services at PHC facilities, poor weather and funding constraints. Sociodemographic data from the screening questionnaire showed that there were no statistically significant differences between 662 pairs who either refused participation in the study or refused iDBS and those included. Considering the sampling design and weighting, these 10 178 infants (median age 39 days, Q1-3 37–41 days) represented the estimated 1 287 854 live births in SA during 2010.

Overall, most infants were born to mothers who described themselves as single (unmarried and non-cohabiting; 74.5%), completed 8 years of schooling (77.2%), and had their first antenatal visit ≤28 weeks of pregnancy (79.8%); 98.8% (98.5–99.0%) had been tested for HIV and 98.6% (98.4–98.9%) had received their result. Most (68.5%) infants lived in households with an average socioeconomic status, were born at ≥2.5 kg (88%), had ≥1 sibling (60.7%), and almost all (96.8%) were accompanied by their mothers. Of these, 29.4% self-reported being HIV-infected; 78% of HIV-infected mothers reported CD4 cell count testing and 43% knew their result; of these, 62% reported a CD4 cell count ≤350 cells/μL.

Almost one-third (32.0% (95% CI 30.4% to 33.3%)) of sampled infants were HEI. This varied by province (see web appendix 6, table 15). HEI were significantly more likely to be born with low birth weight, from an unplanned pregnancy to a single mother with less education, lower socioeconomic status and higher parity, compared with HIV-unexposed infants (table 1).

Among HEI (n=3107), at least 85% were born to mothers who reported receiving some ARVs antenatally, including 29.4% on ART (group 1a, figure 1) and 55.6% on ARV prophylaxis (ARVP). The latter included 27.8% on ARVP >10 weeks (group 1b), 22.8% on ARVP ≤10 weeks (group 2a) and 5% on incomplete ARVP (group 2b); 9.5% of mothers with HEI reported not receiving ARVs (group 3a) and 5.5% had missing ARV information. With regard to postnatal prophylaxis, 80% of all HEI received either NVP or azidothymidine (AZT) at birth, including 96% of infants born to women on ART. In total, 34% HEI were on NVP when interviewed. Among HEI, 61.5% (95% CI 59.2% to 63.8%) reportedly received formula feeding (no breast milk), 20.4% (95% CI 18.5% to 22.3%) EBF, and 18.1% (95% CI 16.5% to 19.7%) MBF.

Weighted population-level risk of early (4–8 weeks) MTCT

The national cumulative risk of early MTCT measured at 4–8 weeks post partum was 3.5% (95% CI 2.9% to 4.1%), based on 125 HIV transmissions. This varied by province (see web appendix 6, table 15). The determinants of these provincial variations will be presented and discussed in another manuscript.

The unadjusted risk of early MTCT was similar whether mothers received ART (group 1a, figure 3—2.1%, 95% CI 1.2% to 3.0%), ARVP >10 weeks (group 1b—2.2%, 95% CI 1.2% to 3.0%), or ARVP ≤10 weeks (group 2a—3.0%, 95% CI 1.9% to 4.0%). Mothers who reportedly received incomplete ARVP (group 2b—8.4%, 95% CI 4.0% to 12.7%) or no ARVs (group 3a—9.0%, 95% CI 6.4% to 11.5%) were significantly more likely to transmit HIV to their infants than mothers in the other three ARV categories (figure 3).

Models adjusted for sociodemographic and pregnancy-related factors did not result in meaningful differences (>10% change) in the relative odds of early MTCT (table 2). There was no statistically significant difference in the odds of MTCT between mothers receiving ART (group 1a, figure 1, reference—adjusted OR (AOR)=1) and those receiving either ARVP >10 weeks (group 1b—AOR 0.98, 95% CI 0.52 to 1.83)) or ARVP ≤10 weeks (group 2a—AOR 1.31, 95% CI 0.69 to 2.48)). However, early MTCT was almost four times (AOR 3.68, 95% CI 1.69 to 7.97) as high when ARVP was incomplete (group 2b), compared with ART. Controlling for other factors including ARV, early transmission was almost twice as high among mothers practising EBF (AOR 1.79, 95% CI 1.09 to 2.92) or MBF (AOR 1.70, 95% CI 1.09 to 2.67), compared with NBF (table 2). Mode of delivery did not significantly vary the adjusted odds of early MTCT.

Table 3 shows how the proportion of children who were HIV infected by 4–8 weeks post partum varied by ARV regimen and breast feeding practice. MTCT was significantly high among breastfeeding mothers with no ARV exposure (11.50%, 95% CI 4.67% to 18.33% for EBF and 11.90%, 95% CI 7.45% to 16.35% for MBF, compared with NBF 3.45%, 95% CI 0.53% to 6.37%). However, maternal ART or ARVP >10 weeks (advanced regimens) significantly reduced early MTCT among breastfeeding mothers (3.94%, 95% CI 1.98% to 5.90% for EBF, 2.07%, 95% CI 0.55% to 3.60% for MBF) whose early MTCT was similar to non-breastfeeding mothers on advanced regimens (2.11%, 95% CI 1.28% to 2.95%). Early MTCT rates were similar across levels of ARV exposure for both birth weight and mode of delivery, suggesting no interaction between ARV use and these factors.

DISCUSSION

Our data show that in SA, a high-HIV-prevalence setting with the largest population of HIV-infected pregnant women,[31] PMTCT programming was able to reduce early MTCT nationally to 3.5% (95% CI 2.9% to 4.1%). Assuming 1.2 million live births/year in SA and previously estimated 25% transmission in the absence of ARV interventions, these results estimate an 86% reduction in early MTCT with an estimated 82 560 early infant HIV infections averted annually. These results were achieved with maternal self-reported 29.4% ART coverage, 55.6% ARVP coverage, 34% infant NVP coverage until interview, and 38.5% prevalence of breast feeding. In exclusively or mixed breastfed infants, maternal ART or ARVP >10 weeks or ARVP ≤10 weeks or incomplete ARVP significantly reduced MTCT compared with no known ARV (group 3, figure 1).

These results are noteworthy as they closely reflect a countrywide African context: although the survey was conducted in only 17% of primary healthcare facilities, we targeted immunisation services where >85% infants nationally received care, included all eligible infants aged 4–8 weeks regardless of their HIV and PMTCT programme exposure and selected facilities randomly after a multistage PPS sampling methodology. Sampling included stratification by antenatal HIV prevalence and results were weighted for sample ascertainment and population live births. This made it possible for us to provide results that closely approximate provincial and national countrywide HIV prevalence and MTCT. The data show coherence between self-reported maternal HIV seropositivity and 2009 antenatal seroprevalence (29.4% and 29.3%, respectively), further illustrating the validity of our estimates.[32] Our limitations could have biased the results towards underestimating early MTCT: we excluded small facilities from the sampling frame (7% total

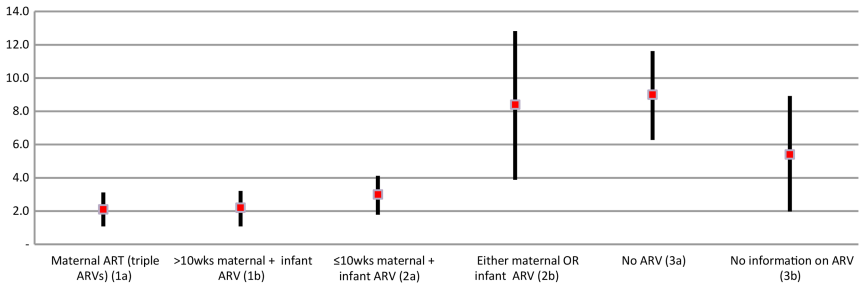

Figure 3 Weighted perinatal mother-to-child transmission rate measured at 4–8 weeks post partum by ARV regimen, South Africa, 2010* (ART, antiretroviral therapy; ARV, antiretroviral; wks, weeks).

facilities), but have no evidence to believe that MTCT is higher in these facilities; we excluded early infant deaths before 4–8 weeks post partum (150–290 infants die annually by 4 weeks of age in SA[33]) and there is currently no information about their HIV exposure or infection status; and we also excluded infants with poor access to care who receive their 6 weeks immunisation after 8 weeks post partum (who represent 15–20% of the population eligible for 6 week immunisations).[15 16] The latter two limitations could have underestimated MTCT risk and overestimated the absolute number of HIV infections averted and ARV coverage. Furthermore, the use of a single PCR test for infant diagnosis in populations with 4 weeks or more of ART/ARVP use could have reduced test sensitivity to 86.2–99%, resulting in biases in diagnosis,[34 35] and underestimating the MTCT point estimate. However, it is quite likely that the adjusted MTCT is still within the current 95% CI. It is possible that mothers who reported no ARV exposure received ARVs during labour (information bias) or were a healthy population with good access to care and high CD4 cell counts (selection bias) underestimating MTCT in the 'no ARV' group. Accurate information on the exact PMTCT regimens, duration of these regimens and adherence was not available, as our data are self-reported and did not cover adherence. Thus, data on MTCT by regimen or duration of ART or ARVP should be interpreted cautiously as the direction of the biases (underestimating or overestimating MTCT) cannot be predicted. In this manuscript, we do not report on other factors that determine PMTCT outcome, including the uptake of maternal HIV testing and duration of ARV exposure. The former will be reported on in another manuscript and the data on the latter are not available. Furthermore, we do not present data on facility-level/health system factors that could affect MTCT, for example, PMTCT quality, quality of facility infrastructure, patient satisfaction and patients' understanding of medication. These factors were significantly associated with infant NVP coverage in the PEARL study and may have helped us understand our data from a health system perspective.[36] Finally, our data are limited by the lack of data on MTCT beyond 8 weeks post partum.

Table 2 Associations between key PMTCT interventions and weighted perinatal infant HIV infection status in HIV-exposed infants, South Africa, 2010

Indicators	Frequency of HIV-exposed infants with PCR results* n=3088 N_w=410 046	Frequency of HIV-infected infant n=125 of 3088 N_w=14 192	Unadjusted OR (95% CI)	Adjusted OR† Model 1	Adjusted OR† Model 2	Adjusted OR† Model 3	Adjusted OR‡ Final model
Mothers self-reported last CD4 cell count							
≤350	839	19	1.67 (0.89 to 3.13)	–	–	–	–
>350	837	20	Ref.	–	–	–	–
Missing	1412	86	NA	–	–	–	–
ARV coverage during pregnancy§							
Maternal ART (1a)	873	15	Ref.	Ref.			Ref.
ARVP >10 weeks (1b)	822	23	1.03 (0.56 to 1.90)	1.03 (0.54 to 1.99)			0.98 (0.52 to 1.83)
ARVP ≤10 weeks (2a)	710	28	1.42 (0.78 to 2.57)	1.45 (0.76 to 2.75)			1.31 (0.69 to 2.48)
Incomplete ARVP (2b)	163	13	4.24 (2.06 to 8.73)	3.95 (1.82 to 8.57)			3.68 (1.69 to 7.97)
No ARV (3a)	328	36	4.57 (2.63 to 7.95)	4.04 (2.14 to 7.62)			3.59 (1.94 to 6.66)
Missing ARV information (3b)	192	10	2.68 (1.21 to 5.90)	1.94 (0.66 to 5.75)			2.26 (0.89 to 5.73)
Feeding (8 days recall)							
No breast milk	1870	50	Ref.		Ref.		Ref.
Exclusive breast feeding	618	32	1.82 (1.13 to 2.93)		1.86 (1.11 to 3.10)		1.79 (1.09 to 2.92)
Mixed breast milk	600	43	2.32 (1.54 to 3.51)		2.35 (1.49 to 3.71)		1.70 (1.09 to 2.67)
Delivery type							
Caesarean	677	26	Ref.				
Vaginal	2411	99	0.88 (0.57 to 1.38)			0.90 (0.56 to 1.47)	0.87 (0.53 to 1.42)

*19 (unweighted) exposed infants with missing HIV DNA test results were excluded from this analysis; thus, the total number of HIV-exposed infants differs between tables 1 and 2.
†Adjusted for maternal age, SES, marital status, education, gestational age at first ANC visit (4 week intervals), total number of lifetime pregnancies, whether or not the current pregnancy was planned and whether or not the infant weighed <2.5 kg at birth.
‡Adjusted for maternal age, SES, marital status, education, gestational age at first ANC visit (4 week intervals), total number of lifetime pregnancies, whether or not the pregnancy was planned and whether or not the infant weighed <2.5 kg at birth. In this model, missing gestational age was imputed using a Markov chain Monte Carlo multiple imputation algorithm (see methods).
§See figure 1 for definitions 1a, 1b, 2a, 2b, 3a, 3b.
ANC, antenatal care; ART, antiretroviral therapy; ARV, antiretroviral; ARVP, ARV prophylaxis; PMTCT, preventing mother-to-child transmission; SES, socioeconomic status.

Table 3 Effect modification of ARV by feeding practice, birth weight, and mode of delivery on the weighted national perinatal MTCT rates, South Africa, 2010

ARV	Other variable	Unweighted frequency	Weighted MTCT risk estimate%	95% CI
Advanced ARV regimens	No breast milk at all	22	2.11	1.28 to 2.95
	Exclusive BF	14	3.94	1.98 to 5.90
	Mixed BF	7	2.07	0.55 to 3.60
Other ARV regimens	No breast milk at all	16	2.57	1.31 to 3.84
	Exclusive BF	9	3.42	1.19 to 5.66
	Mixed BF	11	4.87	2.01 to 7.74
No ARV	No breast milk at all	5	3.45	0.53 to 6.37
	Exclusive BF	9	11.50	4.67 to 18.33
	Mixed BF	22	11.90	7.45 to 16.35
Advanced ARV regimens	Low birth weight	8	2.39	0.54 to 3.54
	Normal birth weight	35	2.49	1.78 to 3.33
Other ARV regimens	Low birth weight	10	9.28	3.81 to 14.80
	Normal birth weight	26	2.32	1.40 to 3.23
No ARV	Low birth weight	8	8.37	2.68 to 17.04
	Normal birth weight	28	9.15	5.69 to 12.01
Advanced ARV regimens	No C-section	34	2.41	1.63 to 3.19
	C-section	9	2.72	1.05 to 4.38
Other ARV regimens	No C-section	32	3.52	2.31 to 4.72
	C-section	4	1.77	0.01 to 3.53
No ARV	No C-section	27	7.46	5.00 to 9.93
	C-section	9	15.18	6.36 to 23.99

Refer to figure 1 for ARV categories: advance ARV regimens=groups 1a and 1b; other ARV regimens=groups 2a and 2b; no ARV group=group 3a. Note: the missing ARV information group 3b is excluded from this analysis; Feeding=previous 8 days recall.
ARV, antiretroviral; BF, breast feeding; C-section, caesarean section; MTCT, mother-to-child transmission.

Building on previous research that used hospital[10 37] or laboratory data[38] of known HEI and research that used district-wide facility-based surveillance among all infants receiving 6-week immunisation,[8 12] this study assessed population-level PMTCT effectiveness at country and provincial levels. Our low early MTCT of 3.5% is likely to be driven by the high proportion of women receiving ART or ARVP with low levels of breast feeding. A previous South African study conducted in 6 (of 12) districts in one province measured 7.1% (6.2–8.0%) early MTCT when 13.8% mothers reported being on ART, and 73.8% reported dual therapy.[12] The overall early MTCT risk measured (3.5%) is similar to early MTCT in the long-long arm reported in Lallemant's clinical trial (4.1%, 95% CI 1.4 to 6.7%) from Thailand[39] where all women received AZT from 28 weeks (10 weeks of maternal AZT), and infants received 6 weeks of ARVs.

Similar to the findings by Stringer *et al*,[13] we show a population-level MTCT dose–response to the ARV regimen. In our study, we show that transmission was low and similar in pregnant women receiving ART (2.1%, 95% CI 1.2% to 3.0%), ARVP >10 weeks (2.2%, 95% CI 1.2% to 3.1%) or ARVP ≤10 weeks (3.0%, 95% CI 1.9% to 4.0%), and highest among those receiving incomplete ARVP (8.4%, 95% CI 4.0% to 12.7%) or no ARVs (9.0%, 6.4% to 11.5%). For women receiving ART, we found higher early MTCT (2.1%) compared with that measured using routine perinatal surveillance in Canada (1% overall and 0.4% with >4 weeks ART) where breast feeding was not recommended.[14] Since our study recruited infants aged 4–8 weeks in June–December 2010, maternal ART eligibility was confined to CD4 count ≤250 cells/μL or AIDS stage 4 disease. Limiting our crude analysis to mothers with reported CD4 results, we observed marginal MTCT differences if the CD4 result was ≤350 cells/μL or >350 cells/μL (table 2). As most (>60%) of our pregnant women attended the first ANC visit after 13 weeks gestation, we postulate a delay in ART initiation, which may have reduced the population-level impact of ART. Forbes *et al*[14] show that MTCT among HIV-positive mothers who receive <4 weeks ART was 9%. We postulate that if appropriate, timely PMTCT interventions were provided, MTCT in the ART group could have been further reduced, despite breast feeding (table 3).

To the best of our knowledge, this is the first population-level countrywide estimate of the effectiveness of a national PMTCT

What is already known on this subject

Only six studies on preventing mother-to-child transmission (MTCT) effectiveness have been conducted in settings larger than two or three sites. These were surveys in Thailand, the PEARL study in Zambia, Cote d'Ivoire, Cameroon, South Africa (two provinces), South Africa (one province—seven sites) and Canada. The South African study conducted in all primary healthcare facilities in 6 of 11 health districts of KwaZulu-Natal province (May 2008–April 2009), South Africa reported a 7.1% (95% CI 6.2 to 8.0%) risk of HIV transmission at 4–8 weeks, which was stratified into 7.7% among the 480 mothers who reported taking an incomplete regimen and 4.9% among the 1912 mothers who reported taking a full regimen. Among the 527 mothers with unreliable antenatal antiretroviral duration, the frequency of MTCT was 9.9%. The PEARL study reported 10.9% early MTCT. The Canadian study, using routine surveillance data, reported 5.2% overall MTCT between 1990 and 2010, reducing to 2.9% after 1997. MTCT in mothers on highly active antiretroviral therapy (HAART) was 1%, and in mothers who received HAART for more than 4 weeks it was 0.4%. No confidence limits are reported.

What this study adds

- The South Africa preventing mother-to-child transmission (PMTCT) Evaluation was a national population-level evaluation of PMTCT effectiveness conducted at immunisation services using a probability proportional to size sampling methodology and weighted analysis to adjust for sample realisation and population live births. It shows an 86% reduction in vertical transmission of HIV (from 25% pre-PMTCT interventions to 3.5% in 2010) with approximately 82 560 early infant HIV infections averted annually among mothers on predominantly single or dual therapy antenatal antiretroviral (ARV) prophylaxis or antiretroviral therapy from CD4 cell count ≤250. The >10 week-long course of azidothymidine regimen and triple ARV regimen achieved the same level of perinatal effectiveness (just exceeding 2%). Incomplete ARV prophylaxis or not receiving ARV drugs with exclusive or mixed breast feeding was associated with increased perinatal mother-to-child transmission (MTCT).
- The survey provides population-level evidence to demonstrate the impact of recent investments in PMTCT (to increase coverage and improve regimens). The survey also illustrates the utility of national surveys in corroborating antenatal survey data, tracking MTCT and measuring the PMTCT cascade, especially the uptake of interventions.
- Despite the early population-level PMTCT effectiveness in a high-HIV-prevalence setting, more data are needed to track progress, measuring long-term PMTCT effectiveness and infant HIV-free survival by 24 months postpartum.

programme using a facility-based approach previously validated in a high-immunisation coverage and a high-HIV-prevalence setting.[8 12]

This survey found large gaps in current systems to eliminate MTCT—viz. 61%, unplanned pregnancy amongst HEI (table 1), 50% first antenatal clinical attendance >20 weeks gestation (web appendix table 12) and 85% ARV coverage. Despite these gaps population level early MTCT of <5% was achieved. This compares with 4–6 week MTCT results modelled on 100% uptake of WHO Option A in a breastfeeding population.[40] Although the study was conducted 1–8 months after the South African PMTCT policy changed to WHO Option A, our data show delayed translation of the new PMTCT policy into practice: 29.4% mothers reported being on ART, although 62% reported CD4 cell counts <350 cell/mm^3; additionally, only 34%, rather than 100%, of mothers reported current (6 weeks postdelivery) infant NVP use. Thus, these results were achieved mainly with the dual therapy policy adopted in February 2008 (see web appendix 1): we assume that most mothers would have started ART at CD4 cell count ≤250 cells/mm^3 with a recommended regimen of stavudine, lamivudine and NVP (switching to efavirenz after the first trimester).[41] While this triggers concerns for the time lag between policy adoption and translation into practice, it does convey optimism for population-level impact of PMTCT programming.

CONCLUSIONS

Country-level success in reducing early MTCT to <5% has been demonstrated in a high-HIV-prevalence African setting. Although this is a significant achievement, we postulate that more early infant HIV infections could have been averted if pregnancies were planned and adequate antenatal and PMTCT-related care were accessed earlier. The impact of PMTCT interventions on long-term infant HIV-free survival, as well as the population-level impact of various PMTCT regimens and of WHO PMTCT Option A, needs urgent assessment.

Author affiliations
[1]Health Systems Research Unit, Medical Research Council, Cape Town, South Africa
[2]Department of Paediatrics and Child Health, Kalafong Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
[3]Division of Global HIV/AIDS, Centers for Disease Control and Prevention, Center for Global Health, Atlanta, Georgia, USA
[4]School of Public Health, University of the Western Cape, Bellville, South Africa
[5]UNICEF New York, New York, USA
[6]Biostatistics Unit, Medical Research Council, Cape Town, South Africa
[7]School of Public Health and Family Medicine, Cape Town, South Africa
[8]Division of HIV/AID Prevention, Centers for Disease Control and Prevention, National Center for HIV, Hepatitis, STD, and Tuberculosis Prevention, Atlanta, Georgia, USA
[9]Division of National Health Laboratory Services, National institute of Communicable Diseases, Sandringham, Johannesburg, South Africa
[10]Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Witwatersrand, Parktown, Johannesburg, South Africa
[11]Affiliated with UNICEF South Africa at the time of the study. Currently affiliated to Elma Philanthropies, New York USA, Pretoria, South Africa
[12]School of Public Health, University of the Witwatersrand, Johannesburg South Africa
[13]World Health Organization, Geneva, Switzerland
[14]National Department of Health, Pretoria, South Africa

Acknowledgements The authors thank all the women and children who participated in this study, all data collectors and supervisors, all provincial maternal and child health/PMTCT managers and all laboratory staff. In particular, they thank Nonhlanhla Dlamini and Thabang Mosala at the National Department of Health for their support and contributions to the survey questionnaire; Wondwossen Lerebo at the University of the Western Cape for his assistance with sampling and data cleaning; Wesley Solomon, Nobuntu Noveve, Lucille Heyns, Jazelle Kiewitz, Pumza Mbenenge, Madoda Xokwe, Eva Mboweni, Similo Mzolo, Ria Molewa, Rose Hlabangani, Tshawe Ncedana, Nomalipheze Sitawutawu, Faith Nyati and Christalien Husselman at the Medical Research Council for their assistance with survey implementation; Katherine Robinson at CDC for her assistance with protocol development and CDC approval; Mobenzi—a division of Clyral—for the development of cellphone technology, provincial supervisors; Tsakani Mhlongo for conducting the training on infant dried blood spots; Beverley Singh, Ushmita Patel and Ewaldé Cutler at the National Institute for Communicable Diseases for direct oversight of all laboratory procedures and posting of all results; the NICD/NHLS for providing consumables for the survey and the South African National Research Foundation for supporting DJJ and TD.

Contributors AEG was responsible for protocol development, submission to Ethics, study implementation and monitoring, data analysis and manuscript writing. DJJ and T-HD were responsible for protocol development, submission to CDC Ethics (T-HD), study monitoring, data analysis and manuscript writing. GS and AP contributed to laboratory technical procedures and training. SW and VR oversaw the fieldwork and did initial cleaning of the data. T-HD, KPD, CL, AEG and DJJ guided the data analysis; and KPD, CL and T-HD conducted the data analysis. YP contributed to the study design, interpretation of data and manuscript writing. All authors contributed towards the manuscript and the decision to submit it for publication.

Funding This evaluation was primarily supported by the President's Emergency Plan for AIDS Relief under the Cooperative Agreement between CDC and MRC (1U2GPS001137-02 and 1U2GPS001137-03). UNICEF, a cosponsor, provided technical support to protocol development, development and implementation of mobile technology for data collection and manuscript writing. The National Department of Health funded all the 6-week PCR tests. TD and DJJ were supported by the National Research Foundation, South Africa.

Competing interests None.

Patient consent Obtained.

Ethics approval The evaluation protocol was approved by the institutional review board of the SA Medical Research Council (MRC), study number EC09-002 and the Office of Associate Director of Science at the USA Centers for Disease Control and Prevention (CDC).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Unpublished data from this study will be used by MRC and CDC staff to write further peer-reviewed manuscripts. After 5 years, the data sets will be shared on a public website for public review and use.

REFERENCES

1 United Nations. The Millennium Development Goal Report. 2012. http://www.undp.org/content/dam/undp/library/MDG/english/The_MDG_Report_2012.pdf. (accessed 8 Jul 2013).
2 The Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother-to-child in Tanzania, South Africa and Uganda (Petra study): a randomised, double-blind plaebo-controlled trial. *Lancet* 1999;353:1178–86.
3 Lallemant M, Jourdain G, Le Coeur S, *et al*. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004;351:217–28.
4 Stringer E, Chi B, Chintu C, *et al*. Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower income countries. *Bull World Health Organ* 2008;86:57–62.
5 Ayouba A, Tene G, Cunin P, *et al*. Low rate of mother-to-child transmission of HIV-1 after nevirapine intervention in a public pilot health programme in Yaounde, Cameroon. *J Acquir Immune Defic Syndr* 2003;34:274–80.
6 Colvin M, Chopra M, Doherty T, *et al*. Operational effectiveness of single dose nevirapine in the South African programme to prevent mother-to-child transmission of HIV. *Bull World Health Organ* 2007;85:466–73.
7 Jackson D, Chopra M, Doherty T, *et al*. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1. *AIDS* 2007;21:509–16.
8 Rollins N, Little K, Mzoloa S, *et al*. Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening. *AIDS* 2007;21:1341–47.
9 Rollins N, Mzolo S, Moodley T, *et al*. Universal HIV testing of infants at immunisation clinics: an acceptable and feasible approach for early infant diagnosis in high HIV prevalence settings. *AIDS* 2009;23:1851–7.
10 Sherman GG, Jone S, Coovadia A, *et al*. PMTCT from research to reality—results from a routine service. *South African Med J* 2004;94:289–92.
11 Coetzee D, Hilderbrand K, Boulle A, *et al*. Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa. *BullWorld Health Organisation* 2005;83:489–94.
12 Horwood C, Vermaak K, Butler L, *et al*. Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of interventions for the prevention of mother-to-child transmission. *Bull World Health Organisation* 2012;90:168–75.
13 Stringer J, Stinson K, Tih P, *et al*. Measuring coverage in MNCH: population HIV-free survival among children under two years of age in four African countries. *PLoS Med* 2013;10:e1001424.
14 Forbes J, Alimentia A, Singer J, *et al*. A National review of vertical HIV transmission. *AIDS* 2012;26:757–63.
15 Fadnes L, Jackson D, Engebretsen I, *et al*. Vaccination coverage and timeliness in three South African areas: a prospective study. *BMC Public Health* 2011;11:404–14.
16 Fonn S, Sartorius B, Levin J, *et al*. Immunisation coverage estimates by cluster sampling survey of children (aged 12–23 months) in Gauteng Province, 2003. *South African J Epidemiol Infect* 2006;21:164–69.
17 National Department of Health. National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa. 2008. Published 2009. http://www.info.gov.za/view/DownloadFileAction?id=109007. (accessed 8 Jul 2013).
18 Lehtonen R, Pahkinen E. *Practical methods for design and analysis of complex surveys*. 2nd edn. West Sussex, UK: John Wiley & Sons; 2004.
19 National Department of Health. The Road to Health Chart: Guidelines for Health Workers. http://www.doh.gov.za/docs/factsheets/guidelines/health/healthchart.htm. (accessed 12 May 2013).
20 Tomlinson M, Solomon W, Singh Y, *et al*. The use of mobile phones as a data collection tool in a household survey: a feasibility study. *BMC Med Inform Decis Mak* 2009;9:51.
21 Heeringa SG, West B, Berglund PA. *Applied survey data analysis*. Boca Raton, FL: Chapman & Hall/CRC; 2010.
22 Vinnard C, Wileyto E, Bisson G, *et al*. First use of multiple imputation with the National Tuberculosis Surveillance System. *Epidemiol Res Int* 2013. doi:10.115/2013/875234
23 Zaidi J, Grapsa E, Tanser F, *et al*. Dramatic increases in HIV prevalence after scale-up of antiretroviral treatment: a longitudinal population-based HIV surveillance study in rural Kwa-Zulu-Natal. *AIDS* 2013;27:2301–5.
24 Schafer J. *Analysis of incomplete multivariate data*. New York: Chapman and Hall; 1997.
25 Spath H. *Cluster analysis algorithms*. Chichester: Ellis Horwood; 1980.
26 Horwoord E, Hartigan J. Statistical theory in clustering. *J Classif* 1985;2:63–76.
27 Kleinbaum D, Klein M. *Logistic regression: a self-learning text*. New York: Springer Science and Business Media; 2010.
28 Knol M, VanderWeele T. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* 2012;41:514–20.
29 VanderWeele T, Robins J. Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *Am J Epidemiol* 2007;166:1096–104.
30 VanderWeele T, Robins J. Erratum: Directed acyclic graphs, sufficient causes, and the properties of conditioning on a common effect. *Am J Epidemiol* 2008; 167:249.
31 UNAIDS. Together we will end AIDS 19 July 2012. http://globalhealth.kff.org/Daily-Reports/2012/July/19/GH-071912-UNAIDS-Report.aspx. (accessed 19 Jul 2012).
32 National Department of Health. National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2009. Published 2010 http://www.health-e.org.za/documents/85d3dad6136e8ca9d02cceb7f4a36145.pdf. (accessed 27 Aug 2011).
33 Lawn J, Cousens S, Zupan J, for the Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? where? why? *Lancet* 2005;365:891–900.
34 Shapiro D, Balasubramanian r, Fowler M, *et al*. Time to HIV DNA-PCR Positivity According to Maternal/Infant Antiretroviral Prophylactic Regimen in Non-Breastfed HIV-Infected Infants in Populations with Predominantly Non-B HIV Subtype: A Collaborative Analysis of Data from Cohorts in Thailand, South Africa, Botswana, and the United Kingdom. *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*. Rome, 2011.
35 Lilian R, Kalk E, Bhowan K, *et al*. Early diagnosis of in utero and intrapartum HIV infection in infants prior to 6 weeks of age. *J Clin Microbiol* 2012;50:2373–7.
36 Ekouevi D, Stringer E, Coetzee D, *et al*. Health facility characteristics and their relationship to coverage of PMTCT of HIV services across Four African Countries: the PEARL Study. *PLoS ONE* 2012;7:e29823.
37 Tchendjou P, Same-Ekobo C, Nga A, *et al*. Effectiveness of multidrug antiretroviral regimens to prevent mother-to-child transmission of HIV-1 in Routine Public Health Services in Cameroon. *PLoS ONE* 2010;5:e10411.
38 Creek T, Tanuri A, Smith M, *et al*. Early diagnosis of human immunodeficiency virus in infants using polymerase Chain reaction on dried blood spots in Botswana's National Program for Prevention of Mother-to-Child Transmission. *Pediatr Infect Dis J* 2008;27:22–6.
39 Lallemant M, Jourdain G, Le Coeur S, *et al*. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med* 2000;343:982–91.
40 Ciaranello A, Perez F, Keatinge J, *et al*. What will it take to eliminate paediatric HIV? Reaching WHO target rates of mother-to-child transmission in Zimbabwe: a model-based analysis. *PLoS Med* 2012;9:E1001156.
41 National Department of Health. Policy and Guidelines for the Implementation of the PMTCT programme. 2008. http://www.info.gov.za/view/DownloadFileAction?id=77877. (accessed 1 Oct 20).