ORIGINAL ARTICLE

A WINDOW INTO A PUBLIC PROGRAMME FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV: EVIDENCE FROM A PROSPECTIVE CLINICAL TRIAL

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Objectives. To evaluate efficacy of the antenatal, intrapartum and postnatal antiretroviral components of a public service prevention of mother-to-child (PMTCT) programme in infants.

Design. Analysis of prospectively collected screening data of demographic and MTCT-related interventions and HIV infection status of infants identified through HIV-specific DNA polymerase chain reaction.

Setting. Tygerberg Children's Hospital, Western Cape, South Africa.

Subjects. HIV-infected women and their infants identified through participation in a public service PMTCT programme were referred for possible participation in a prospective study of isoniazid prophylaxis.

Interventions. Key components of the programme include voluntary counselling and testing, administration of zidovudine to the mother from between 28 and 34 weeks' gestation and to the newborn infant for the first week, single-dose nevirapine to the mother in labour and to the newborn shortly after birth, and free formula for 6 months.

Main outcome measures. Number and percentage of HIV-infected infants and extent of exposure to antenatal, intrapartum and postnatal antiretrovirals.

Results. Of 656 infants with a median age of 12.6 weeks, screened between 1 April 2005 through May 2006, 39 were HIV-infected, giving a transmission rate of 5.9% (95% confidence interval (CI) 4.4 - 8.0%). Antenatal prophylaxis was significantly associated with reduced transmission (odds ratio (OR) 0.43 (95% CI 0.21 - 0.94)) as opposed to intrapartum and postpartum components (p=0.85 and p=0.84, respectively). In multivariable analysis the antenatal component remained significant (OR=0.40 (95% CI 0.19 - 0.90)).

Conclusions. The antenatal phase is the most important antiretroviral component of the PMTCT programme, allowing most opportunity for intervention.

HIV infection has a high prevalence in antenatal attendees in South Africa. In the annual seroprevalence survey conducted through the National Department of Health from 2005, the prevalence in the Western Cape province was 15.7%.[1] Here, a pilot zidovudine (ZDV)-based prevention of mother-to-child transmission (PMTCT) programme began in 1999,[2] and has gradually been expanded since January 2001. Since April 2003 the PMTCT interventions have been available at all public sector antenatal service facilities in the province (300 antenatal clinics and 53 delivery centres and hospitals) and 350 primary health care clinics where infant follow-up occurs. Attendees are offered voluntary, confidential counselling and testing (VCT) and if HIV positive, antiretrovirals (ARVs) for the mother and infant. Uptake was reported as 97% in 2006 (Status Report – Prevention of Mother-to-Child Transmission Programme, 14 July 2006, HIV/AIDS/STI Directorate,

Western Cape). Follow-up of mother and infant, co-trimoxazole from 6 weeks of age and modified infant feeding practices are also important components. The majority of women (95%) choose formula feeding, which is provided free for the first 6 months.

The initial ARV intervention was single-dose nevirapine (sd-NVP) to mother and infant, introduced after the success of the HIVNET 012 study.[3] Since mid-2003, ZDV was added from 34 weeks' gestation for the mother and for a week for the neonate.[4] In early 2006, antenatal ZDV from 28 weeks was gradually introduced. With the advent of the national antiretroviral rollout in 2004, all pregnant women with a CD4 count below 200 cells/µl were offered highly active antiretroviral therapy (HAART).

PACTG 1041 is a prospective phase III clinical trial evaluating the efficacy of isoniazid (INH) primary prophylaxis in HIV-exposed infected and uninfected infants. Through screening for this trial at Tygerberg Children's Hospital (TCH), we had the opportunity to evaluate the PMTCT programme in referred infants.

METHODS

HIV-exposed infants between 3 and 4 months of age were referred for study participation from health care facilities in the urban and semi-rural areas close to TCH. Referring clinics were requested not to refer infants exposed to TB. Infants were pre-screened by lay counsellors and nurses for eligibility to enrol in PACTG 1041. Exclusion criteria included exposure to tuberculosis and not receiving bacille Calmette-Guérin (BCG) immunisation within the first week of life. Eligible subjects were entered onto a screening log, comprising the dataset for the present report.

A medical doctor undertook formal screening. Note was taken of the extent of participation in the PMTCT programme and whether the mother received HAART in pregnancy.

Those receiving either antenatal HAART or ZDV were categorised as having received antenatal prophylaxis. Intrapartum prophylaxis was either ZDV or NVP or both. Postnatal intervention to the neonate was either ZDV or NVP or both.

HIV DNA polymerase chain reaction (PCR) was performed on all exposed infants eligible for the trial. All samples were tested in duplicate. For discordant results, the test was repeated in duplicate.

Simple percentages were used to estimate rates of transmission and 95% confidence intervals (CIs) were based on the score method. Medians and interquartile ranges (IQR) were used to summarise continuous data. Logistic regression was used to evaluate the effectiveness of PMTCT components. Odds ratios (ORs) were calculated through the logistic regression model and 95% CIs are based on the profile likelihood. For antenatal HAART, Fisher's exact test was used because of the small cell size. In multivariable logistic regression analysis, we evaluated all two-way and three-way interactions between the three PMTCT programme components and found no statistically significant interactions, and therefore present a multivariable model that includes main effects for the three components. All tests are two-sided at the 5% significance level and are not adjusted for multiple comparisons. Analyses were done using SAS 9.1 (Cary, NC, USA).

Permission to conduct P1041 and to report on antenatal interventions was obtained from the Committee for Pharmaceutical Trials, Stellenbosch University, and the Medicines Control Council of South Africa. The trial was approved by the National Institute of Allergy and Infectious Diseases (NIAID) according to the Office of Human Rights Protection, National Institutes of Health guidelines.

RESULTS

Between 1 April 2005 and 31 May 2006, 773 infants were referred for pre-screening. Seven infants were excluded because their mothers were HIV-negative and had been referred in error. One hundred and ten HIV-exposed infants were excluded at pre-screening, of whom 52 (47.3%) had known exposure to tuberculosis.[5] Other common reasons included the infant being too old for participation in the INH trial (15), BCG given after 7 days of life (15) and family relocating (7).

Six hundred and fifty-six infants were entered onto the screening log and are reported on here. The median age (IQR) of infants was 12.6 (11.0 - 13.6) weeks and that of mothers 26 (23 - 30) years. Thirty-nine of 656 infants had a positive HIV DNA PCR, giving a transmission rate of 5.9% (95% CI 4.4 - 8.0%). Two hundred and seventy-eight (85.8%) of 324 mothers who were asked decided on exclusive formula feeding.

Data on transmission and extent of participation in the PMTCT programme are shown in Table I. We evaluated the antenatal, intrapartum and postnatal components of the programme separately, using logistic regression (Table II). We found that antenatal prophylaxis was significantly associated with a reduction in rate of transmission (OR 0.43 (95% CI 0.21 - 0.94), p=0.035) as opposed to intrapartum and postnatal components (p=0.85 and p=0.84, respectively).

The results of fitting a multivariable logistic regression model to the data, which included the three components of the PMTCT programme, are shown in Table III.

TABLE I. EXTENT OF PARTICIPATION OF MOTHERS AND THEIR INFANTS IN THE PMTCT PROGRAMME AND HIV TRANSMISSION RATES

PMTCT	Screened (*N* (%))* 656	Infants HIV-infected (*N* (% of screened)) 39 (5.9)
Full participation	348 (53.0)	21 (6.0)
Antenatal only	105 (16.0)	4 (3.8)
Antenatal + postnatal (no intrapartum)	42 (6.4)	1 (2.4)
Antenatal + intrapartum	15 (2.3)	1 (6.7)
Postnatal only	39 (5.9)	4 (10.3)
Intrapartum only	18 (2.7)	1 (5.6)
Intrapartum + postnatal	25 (3.8)	3 (12.0)
None	13 (2.0)	3 (23.1)
No data	51 (7.8)	1 (2.0)

*Percentages do not add to 100.0 due to rounding.
Antenatal = either ZDV or HAART; intrapartum and postnatal = sd-NVP, ZDV.

TABLE II. UNIVARIATE ANALYSES

Programme component	Received component/total (%) Infant not HIV infected	Infant HIV infected	OR (95% CI)	*p*-value†
Antenatal PMTCT	483/568 (85.0)	27/38 (71.1)	0.43 (0.21 - 0.94)	0.035
Intrapartum PMTCT	380/568 (66.9)	26/38 (68.4)	1.07 (0.54 - 2.25)	0.85
Postnatal PMTCT	425/568 (74.8)	29/38 (76.3)	1.08 (0.52 - 2.48)	0.84
Antenatal HAART*	56/564 (9.9)	1/38 (2.6)	0.25 (0.01 - 1.52)	0.24

*Exact CI and Fisher's exact test *p*-value provided for antenatal HAART due to the small number of infections among those who received antenatal HAART.
†Likelihood ratio test from logistic regression model, except for antenatal HAART which is a Fisher's exact test.

TABLE III. MULTIVARIABLE ANALYSIS

PMTCT component	Adjusted OR (95% CI)	*p*-value*
Antenatal	0.40 (0.19 - 0.90)	0.027
Intrapartum	1.26 (0.57 - 2.89)	0.57
Postnatal	1.05 (0.46 - 2.60)	0.91

*Likelihood ratio test.

The antenatal component of the PMTCT regimen remained significant in the multivariable model, indicating that it is an independent predictor of decreased transmission (OR 0.40 (95% CI 0.19 - 0.90), *p*=0.027).

Of 57 mothers with CD4 cell counts below 200/µl receiving HAART, only 1 (1.8% (95% CI 0.3 - 9.3%)) transmitted HIV to her infant versus 26 of 453 with CD4 counts >200/µl not receiving HAART (5.7% (95% CI 3.9 - 8.3%), *p*=0.34).

Fifty-one (7.8%) mother/infant pairs with missing PMTCT information were excluded from the above analyses. Of these, only 1 woman (2.0% (95% CI 3.5 - 10.3%)) transmitted HIV to her infant.

DISCUSSION

There is little information on vertical transmission in the absence of intervention in South Africa. Transmission rates vary between 15% and 34%.[6,7] In the ZDV-based pilot programme in Khayelitsha, Western Cape, the transmission rate was 11%.[2] In a study evaluating sd-NVP in different South African settings, the transmission rate in Paarl, a recruitment site for P1041, was 8.3% at 3 weeks of age.[8] The combination of antenatal ZDV from 28 weeks and sd-NVP under optimal circumstances is associated with a transmission rate as low as 1.1%.[4]

Our data confirm a relatively effective PMTCT programme despite only 53% actually participating in all components of the programme. Importantly, an additional 25% received antenatal ARVs. A multi-faceted intervention programme means that there are many opportunities for intervention, as opposed to one relying on only a single intervention such as sd-NVP, which, if missed, severely compromises efficacy. The World Health Organization has endorsed the programme as practised in the Western Cape.[9] Our data confirm the relative importance of antenatal as opposed to perinatal or postnatal intervention. The transmission rate of 5.9% was achieved due to concerted efforts to facilitate success of the programme despite widespread perceived obstacles to initial implementation.[10] Although we did not record duration of antenatal ARVs in each case, 75% of mothers were reported to have received ≥2 weeks of therapy, defined as adequate by the programme (personal communication – Pauline Pieters, PMTCT Co-ordinator, 20 September 2006).

An important preliminary finding in our study is that among women with CD4 cell counts <200/µl, only 1 of 57 mothers on HAART (1.8%) transmitted HIV, as opposed to 26 (5.7%) of 453 mothers receiving ZDV. Although this was not statistically significant, we expect-

ed more transmission among these mothers because of their low CD4 counts before initiation of HAART.

There are a number of limitations to our study. We did not record the mothers' CD4 counts; rather, we assumed that they were appropriately managed according to the PMTCT guidelines. Also, we only screened infants whose mothers expressed interest in their infants participating in the INH study. Nevertheless, our data are similar to those of the Department of Health, Western Cape, which reports a transmission rate of 6.2% (personal communication – Pauline Pieters, PMTCT Coordinator, 20 September 2006).

There were missing PMTCT data on 7.8% of screened mother/infant pairs, and the transmission rate was low in this group (2.0%). If we assume that none of these women received any component of PMTCT or that these women received all components of PMTCT, the conclusions drawn here remain unchanged.

The antenatal ARV component is extremely important for reduction of MTCT and reduces intra-uterine infection, For example, Lallemant *et al.* showed that initiating ZDV at 28 weeks was far more effective than at 35 weeks and was not compensated for by extending postnatal ZDV for 6 weeks.[11] Nevertheless, the intrapartum and postnatal components also have an important role. For example, Wade *et al.* showed that in the absence of ZDV, perinatal transmission of HIV was 26.6% (95% CI 21.1 - 32.7%).[12] When ZDV was begun antenatally, the transmission rate was 6.1% (95% CI 4.1 - 8.9%). Administration of postnatal ZDV alone within 48 hours of life had a transmission rate of 9.3% (95% CI 4.1 - 17.5%), indicating the importance of the postnatal component.[12] Gray *et al.* found postnatal sdNVP to be slightly more effective than ZDV for 6 weeks when neither antenatal nor intrapartum ARVs could be given.[13]

CONCLUSIONS

The public service PMTCT programme in the Western Cape has successfully reduced the vertical transmission of HIV. The antenatal ARV component is critical for success.

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REFERENCES

1. National Department of Health. *National HIV and Syphilis Seroprevalence Survey South Africa 2005.* Pretoria: National Department of Health, 2005.
2. Abdullah MF, Young T, Bitalo L, Coetzee N, Myers JE. Public health lessons from a pilot programme to reduce mother-to-child transmission of HIV-1 in Khayalitsha. *S Afr Med J* 2001; 81: 579-583.
3. Guay LA, Musoke P, Fleming T, *et al.* Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999; 354: 795-802.
4. 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(3): 217-228.
5. Cotton MF, Schaaf HS, Lottering G, Weber HL, Coetzee J, Nachman S. Tuberculosis exposure in HIV-exposed infants in a high-prevalence setting. *Int J Tuberc Lung Dis* 2008; 12(2): 225-227.
6. Bobat R, Coovadia H, Coutsoudis A, Moodley D. Determinants of mother-to-child transmission of human immunodeficiency virus type 1 infection in a cohort from Durban, South Africa. *Pediatr Infect Dis J* 1996; 15(7): 604-610.
7. 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, placebo-controlled trial. *Lancet* 2002; 359: 1178-1186.
8. Good Start Study Team. The Good Start Study: Early Perinatal Transmission, Infant Feeding and HIV-Free Survival. Paper presented at the 25th Conference on Priorities in Perinatal Care, 7 - 10 March 2006, Drakensberg, KwaZulu-Natal.
9. World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-limited Settings: Towards Universal Access. Recommendations for a Public Health Approach.* Geneva: WHO, 2006.
10. Delva W, Draper B, Temmerman M. Implementation of single-dose nevirapine for prevention of MTCT of HIV – lessons from Cape Town. *S Afr Med J* 2006; 96: 706-709.
11. 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(14): 982-991.
12. Wade NA, Birkhead GS, Warren BL, *et al.* Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med* 1998; 339(20): 1409-1414.
13. Gray GE, Urban M, Chersich MF, *et al.* A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS* 2005; 19(12): 1289-1297.