PMTCT from research to reality — results from a routine service

G G Sherman, S A Jones, A H Coovadia, M F Urban, K D Bolton

Objectives. Assessment of the efficacy of a prevention of mother-to-child transmission (PMTCT) programme in a routine service setting in comparison to a research environment.

Design. Descriptive study over a 13-month period utilising retrospective data obtained from hospital records complemented by prospective data on a sample of patients enrolled in a study to determine an affordable HIV diagnostic protocol for infants.

Setting. Routine PMTCT service at Coronation Women and Children's Hospital (CWCH) situated in Johannesburg and affiliated to the University of the Witwatersrand.

Subjects. Pregnant women known to be HIV infected who delivered at CWCH from 1 October 2001 to 31 October 2002.

Outcome measures. The HIV transmission rate to infants, which reflects nevirapine (NVP) delivery and infant feeding practices, and follow-up rates of perinatally exposed children.

Results. Of the 8 221 deliveries, 1 234 (15%) occurred in women known to be HIV infected. HIV transmission rates of 8.7% at 6 weeks and 8.9% at 3 months of age in the study population verifies the high rate of NVP administration and the ability of women to formula-feed their babies and abstain from breast-feeding. More than one-third of infants never return for follow-up and more than 70% are lost to follow-up by 4 months of age.

Conclusions. The low HIV transmission rate confirms the efficacy of this routine service PMTCT programme. HIV-infected children are not being identified for medical management as part of PMTCT follow-up. It is imperative that record keeping is improved to facilitate ongoing monitoring.

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Prevention of mother-to-child transmission (PMTCT) programmes have been implemented in South Africa at government-designated pilot sites and nationally, by order of a July 2002 Constitutional Court judgement ordering the government to make nevirapine (NVP) universally available to HIV-infected pregnant women. The efficacy of local routine services in comparison to research-based PMTCT programmes, remains to be evaluated. The national PMTCT programme offers voluntary counselling and testing, administration of NVP to mother and baby,[1] provision of free milk formula for the first 6 months of life, and follow-up for infants on co-trimoxazole prophylaxis from 6 weeks of age to 12 months of age when their HIV infection status is determined using an HIV enzyme-linked immunosorbent assay (ELISA) test. Earlier HIV testing using HIV DNA PCR tests is considered too expensive. Prolonged follow-up of large numbers of predominantly HIV-uninfected children has resulted in poor follow-up rates at government pilot sites. The outcome is a lack of data on HIV transmission rates, undermining the government's ability to assess the efficacy of local PMTCT programmes. The supply of free milk formula is contentious and presently under review, but in the absence of HIV transmission rate data the prevalence and effect of breast-feeding on the programme cannot be accurately assessed. Coronation Women and Children's Hospital (CWCH) has had a formal PMTCT programme in place since October 2001 operating as a routine clinical service. Ongoing evaluation of the PMTCT programme is essential to evaluate successes, identify deficiencies and put systems in place to improve the service. HIV-infected women and their children born at CWCH from January to September 2002 had the opportunity to participate in an infant HIV diagnostic study that would determine the HIV infection status of the children at 4 months of age. The study, approved by the Ethics Committee of the University of the Witwatersrand, aimed to establish an accurate, locally affordable infant HIV diagnostic protocol to determine the HIV infection status of perinatally exposed infants as early on in life as possible. This study provided an opportunity to assess components of the routine PMTCT service in a research setting.

Department of Molecular Medicine and Haematology, National Health Laboratory Service and University of the Witwatersrand, Johannesburg, South Africa.

G G Sherman, MB BCh, DCH (SA), MMed (Haem), DTM&H

Department of Paediatrics, Coronation Hospital and University of the Witwatersrand, Johannesburg

S A Jones, MB BCh, DCH (SA)
A H Coovadia, BSc, MB ChB, DCH (SA), FCP (Paed) (SA)
M F Urban, MB BCh, FCP (Paed) (SA)
K D Bolton, MB BCh, DCH (SA), FCP (Paed) (SA)

Methods

Descriptive data on the PMTCT service were collected retrospectively from labour ward, postnatal ward and paediatric PMTCT follow-up clinic records over a 13-month period from 1 October 2001 to 31 October 2002. The Ethics Committee of the University of the Witwatersrand approved collection of the retrospective data from hospital records. At the time of discharge post delivery, all HIV-infected women on the PMTCT programme were given a 2-week follow-up appointment as a lead into the PMTCT follow-up service for their infants. HIV-infected women delivering at CWCH were eligible to participate in the infant diagnostic study if they gave informed consent and could be contacted telephonically. Enrolment of 300 infants was commenced in January 2002 and all 6-week visits had been completed by October 2002. The 300 infants included 3 sets of twins, therefore 297 mothers were enrolled. Infants failing to attend the 6-week visit by 8 weeks of age were removed from the study. The minimum HIV testing performed included a Roche Amplicor version 1.5 HIV DNA PCR (Roche Molecular Systems, Basel, Switzerland) at 6 weeks and 3 months of age and an HIV ELISA at 12 months of age. A child was considered HIV-infected if the HIV DNA PCR results at 6 weeks and 3 months of age were positive and there were clinical stigmata of HIV infection. If these conditions did not apply, a further clinical examination and HIV DNA PCR test were performed at 4 months of age.[2] Infants were deemed HIV-uninfected if they had negative HIV DNA PCR results at both the 6-week and 3-month visits with no overt clinical stigmata of HIV infection. Infant feeding histories were noted at each visit. In order to ensure good follow-up, mothers were reminded of their appointments a week before their study visit. If they failed to keep their appointments they were given another. If they could not be contacted telephonically, community workers visited them at home. Mothers' travel costs were reimbursed at each visit. Patients not enrolled in the study at 2 weeks were given appointments for a 6-week follow-up visit and seen at the same outpatient clinic as the study patients. They received no reminders and if they defaulted, no further appointment was scheduled.

Results

Data extraction from current PMTCT records proved laborious because they are not stringently kept and are in a fragmented format with no central co-ordination. The poor accessibility of the data made it difficult to measure all aspects of the PMTCT programme. There were 8 221 deliveries documented at CWCH over the 13-month period averaging 632 deliveries per month, which included a median of 38 deliveries (6%) to women who had not attended an antenatal clinic. HIV-infected women accounted for a total of 1 234 of the deliveries, averaging 95 per month, with 15 twin pregnancies. The HIV prevalence rate in women attending the hospital's antenatal clinic who consent to HIV testing is 15%, with a range of 14 -18% per month. The official antenatal prevalence rate for the Johannesburg area in 2001 was 29.8%.[3] The discrepancy in HIV prevalence rates may be due to reduced uptake of HIV testing. Delivery before reaching the hospital was the commonest reason for study mothers not receiving NVP (Table I). The retrospective record review and the study data concur in showing a high rate (≥ 95%) of NVP administration to the baby and very few documented cases of a lack of NVP administration to mother (2%) and baby (< 1%). Poor documentation of NVP administration to mothers compared with babies in the routine setting may be a consequence of the environment in which these records are maintained, viz. labour ward versus the more stable and controlled environment of the postnatal wards. A total of 794 (64%) of the babies born to HIV- infected women were seen at some stage for medical evaluation within the PMTCT programme after delivery. Fifty- six per cent of babies (N = 705) returned for their 2-week visits. The follow-up rate for children at the PMTCT outpatient clinic in the routine service programme versus the research setting is illustrated in Fig. 1. Follow-up rates are biased in favour of the study patients by the study protocol, ensuring 100% follow-up at 6 weeks of age. By 31 October 2002 approximately the same number of children had attended their 6-week visits in the routine and research settings. By the 4-month visit, with approximately the same number of study (19%) and routine (25%) patients still due to attend, substantially more routine patients (79%) than study patients (8%) had missed their appointments (Fig. 1). The 7 - 9-month visit had similar numbers of children due for their appointments in the study (57%) and routine (62%) settings; however, the number of children lost to follow-up continued to be strikingly disproportionate at 14% and 75% respectively. In the routine setting, 67 children were ≥ 12 months of age and therefore eligible for HIV ELISA testing. No deaths were recorded in this group of children and the lost to follow-up rate in this small number of patients was 85%.

Of the 1 234 women recorded to have participated in the PMTCT programme 16 women (1.3%) reported breast-feeding

Table I. NVP administration in a routine versus a research environment

	Routine records		Study records	
NVP status	Mother (%)	Baby (%)	Mother (%)	Baby (%)
NVP received	896 (73)	1198 (96)	288 (97)	297 (99)
NVP not received	30 (2)	7 (0.5)	7 (2)	2 (0.7)
No record of NVP administration	308 (25)	44 (3.5)	2 (1)	1 (0.3)
Total	1 234	1 249	297	300

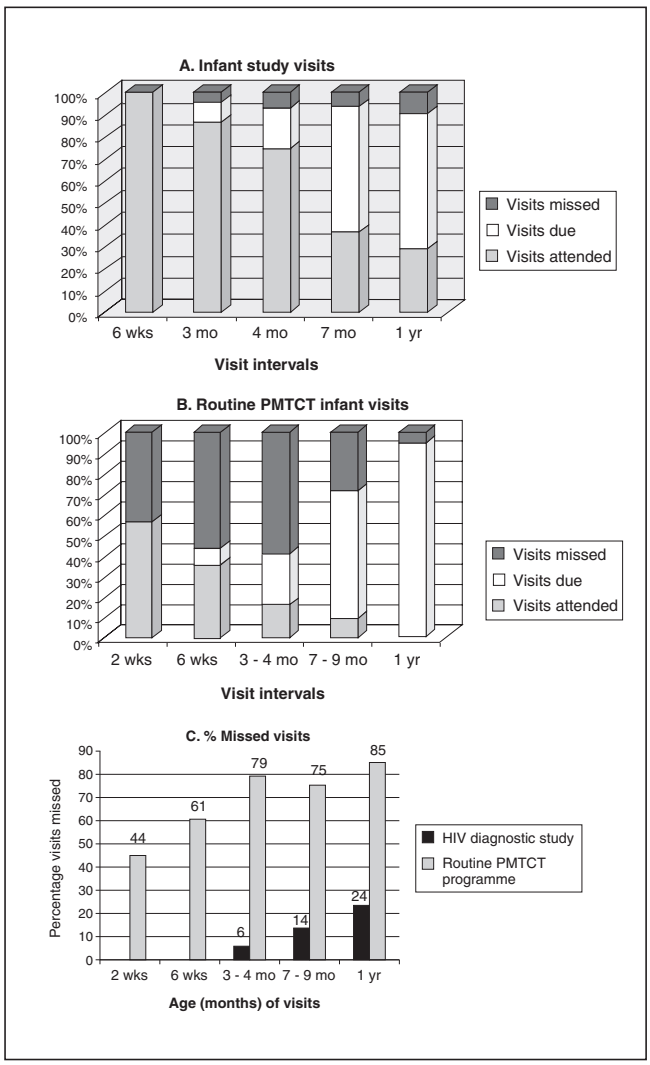

Fig. 1. A and B. Visit attendance figures for routine patients exclude study patients as additional resources were expended to ensure good follow-up rates among the latter. 'Visits due' refers to visits during the study period that infants could still be expected to attend when they reached that specific age. C. The percentage of visits missed increased with time in both settings but was strikingly higher in the routine setting where almost 80% of children were lost 3 - 4 months into the 12-month programme. Despite a research environment, the loss to follow-up at 1 year approached 25%.

their babies, 743 (60%) reported formula-feeding, and not breast-feeding, and the feeding practices of 475 women (38%) were unrecorded. In the study sample, 6 women (2%) reported having breast-fed their infants and all had discontinued by 3 months of age. The 6-week HIV DNA PCR test results for the 300 study infants revealed 26 HIV-positive and 274 HIV-negative results, an HIV transmission rate of 8.7%. At 3 months of age, the HIV DNA PCR results concurred with the 6-week PCR results in every case, however 7 patients who had tested PCR-negative had been lost to follow-up. The 3-month HIV transmission rate was 8.9%. The follow-up study visits conducted to date have confirmed the final HIV status determined at 4 months of age in all cases.

Discussion

Evaluation of the first 13 months of the formal routine PMTCT service at CWCH was considerably enhanced by the availability of data collected in a research environment over the same time period. The study enrolled 297 (24%) of the total 1 234 HIV-positive women registered with the PMTCT service, therefore despite any bias introduced by the inclusion criteria and study design the sample represents a significant proportion of patient outcomes in the routine service.

A single dose of NVP administered to the mother at the onset of labour and to the baby within 72 hours of birth significantly reduces MTCT of HIV (Table II).[2] The low HIV transmission rates achieved in a routine PMTCT programme at CWCH surpass the best results achieved in research PMTCT settings using NVP. If most women in the CWCH PMTCT programme were breast-feeding, then according to the current literature the expected transmission rate at 6 weeks and 3 months of age would be in the region of 11.9% and 13.1% respectively.[2] The MTCT rate documented in a predominantly non-breast-feeding population at CWCH (~9%) at 6 weeks of age versus the predominantly breast-feeding population in HIVNET 012 (~12%) at 6 - 8 weeks, confirms previous estimates that breast-feeding contributes an additional ~3% of cases of HIV infection in the first 6 weeks of life (Table II).[1,4,5] The reduction in MTCT of HIV achieved by the CWCH

Table II. Comparison of MTCT rates achieved using NVP in populations with variable rates of breast-feeding

Study	% Women breast-feeding	MTCT rate (age in weeks)	MTCT rate (age in weeks)	Increase in MTCT rate attributed to breast-feeding (age in weeks)
HIVNET 012[1]	> 95	11.9% (6 - 8)	13.1% (14 - 16)	3.6% (6 - 8)
SAINT[4]	42	12.3% (8)		5.6% (8)
PEP[5]	17	13.4% (6)		3.1% (6)
CWCH PMTCT	2	8.7% (6)	8.9% (14)	

SAINT = South African Intrapartum Nevirapine Trial; PEP = Post-Exposure Prophylaxis Trial.

programme provides unequivocal confirmation that a routine service programme is capable of delivering NVP to mothers and babies and of supporting women to formula-feed instead of breast-feeding. It is well documented that in communities in developing countries formula-feeding and abstaining from breast-feeding can be extremely difficult for women to achieve,[6,7] however the data suggest that women attending the CWCH PMTCT service are highly motivated not to breast-feed and are able to exercise this choice in the community. Factors that are important in determining infant feeding practices in this community of women (e.g. the PMTCT counselling regarding infant feeding choices, the social environment, disclosure of HIV status and provision of free milk formula as part of the PMTCT programme) are currently under investigation. Despite the difficulties surrounding infant feeding practices, the MTCT data provide evidence that women enrolled on the CWCH PMTCT programme managed to use the free supply of milk formula to protect their babies from contracting HIV infection. The national PMTCT protocol makes provision for follow-up care of mothers and infants beyond the time of birth; however the guidelines on the care of children in South Africa have been described as 'largely unrealistic'.[8] The increased attrition rates over time were anticipated, but the scale of the problem and the finding that over 40% of children are lost as early as 2 - 6 weeks of age was not. If no provision is made for follow-up care for children in the PMTCT programmes then HIV-infected children will first present for medical care when they develop symptoms of HIV disease or die undiagnosed in their communities. The opportunity to counsel, educate, medically manage and support HIV-affected families will be lost, as will the ability to monitor PMTCT programmes. Discontinuation of the follow-up phase of the PMTCT programme is therefore an unacceptable option. At CWCH the number of children requiring follow-up per clinic has increased 3.5 fold from October 2001 to January 2003. Additional resources in the form of infrastructure and trained health care workers are necessary to improve follow-up, particularly if current government guidelines are pursued. Local clinics will need to be equipped to assume responsibility for follow-up of children as part of the routine well baby and immunisation services which would have the advantage of strengthening the country's general health care service.[8] The infant HIV diagnostic protocols developed in the First World require a minimum of two HIV DNA PCR tests. Preliminary results of the infant diagnostic study described here suggest that permutations of HIV testing other than the extremes of two early HIV PCR tests versus a late HIV ELISA test (advocated by the current national policy) can be used with excellent results. Adapting infant HIV diagnostic algorithms to suit specific local settings may prove an alternative, cost-effective strategy for providing follow-up care of infants in routine PMTCT programmes. Early diagnosis of HIV infection status would dramatically reduce the number of follow-up visits required for HIV-exposed children. The cost effectiveness of this approach over providing the additional resources needed to implement national guidelines is being assessed.

Conclusion

This routine service PMTCT programme is highly effective in reducing the MTCT rate of HIV but fails in follow-up of children. The failure can be attributed predominantly to the hospital's lack of capacity to implement the national programme guidelines for follow-up of perinatally exposed children. Women from the communities attending this PMTCT programme are able to abstain from breast-feeding to reduce MTCT. Record keeping systems that document all facets of the PMTCT service need to be designed to facilitate regular audit and intervention. Cost-effective, early HIV diagnostic algorithms will improve identification of HIV-infected children and enable HIV-affected children to access appropriate health care.

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References

1. 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.
2. Centers for Disease Control. *Revised Guidelines for Prophylaxis Against* Pneumocystis carinii *Pneumonia for Children Infected with or Perinatally Exposed to Human Immunodeficiency Virus*. Atlanta: CDC, 1995: 44(RR-4), 1-11.
3. Department of Health. *National HIV and Syphilis Sero-prevalence Survey of Women Attending Public Antenatal Clinics in South Africa, 2001*. Pretoria: DOH, 2002.
4. Moodley D, Moodley J, Coovadia H, *et al*. A multicenter randomized controlled trial of Nevirapine versus a combination of Zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003; **187:** 725-735.
5. Gray GE, Urban M, Violari A, *et al*. Preliminary analysis of a randomized controlled study to assess the role of post-exposure prophylaxis in reducing mother to child transmission of HIV-1. In: Program supplement of the XIV International AIDS Conference, Barcelona, Spain, 7-12 July 2002, abstract LBbOr13.
6. Varga C A. *Social and Community Perspectives on PMTCT in Limpopo Province*. Final Project Report to UNICEF South Africa. Durban: HSRC, 2002.
7. Chopra M, Piwoz E, Sengwana J, *et al*. Effect of a mother-to-child HIV prevention programme on infant feeding and caring practices in South Africa. *S Afr Med J* 2002; **92:** 298-302.
8. McCoy D. Updated 07/03/2002. Interim findings on the national PMTCT pilot sites: Lessons and recommendations. **http://www.hst.org.za/pubs/pmtct/pmtctinterim.htm** or **http://www.hst.org.za** (last accessed 15 Feb 2004).

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