

Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa

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Objective The aim of this study was to estimate the field efficacy of the first routine programme for the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) initiated in South Africa, in the subdistrict of Khayelitsha.

Methods A consecutive sample of 658 mother–infant pairs, identified from the PMTCT register from 1 March to 30 November 2003, were identified for enrolment in this study. Details of the regimen received were established and HIV status of the infants at between 6 and 10 weeks of age was determined by qualitative DNA polymerase chain reaction. Zidovudine (AZT) was provided antenatally from week 34 of gestation and during labour. Infant formula milk was offered to mothers who chose not to breastfeed. The protocol was amended in July 2003 such that women who had received < 2 weeks of treatment with AZT were given a single dose of nevirapine (NVP) at the onset of labour, and the infant received a weight-adjusted dose of NVP within 72 h of delivery.

Results Of the 535 mother–infant pairs (81%) eventually included in the study, 410 (77%) received an effective PMTCT intervention according to the protocol. The rate of transmission of HIV from mother to child was 8.8% (95% confidence interval (CI), 6.2–10.9). A maternal age of > 25 years was the only significant independent risk factor for transmission (odds ratio, 2.12; 95% CI, 1.14–4.07).

Conclusion The results of this study demonstrate the feasibility and effectiveness of a large-scale PMTCT programme in an urban public-sector setting.

Keywords HIV infections/transmission/prevention and control/drug therapy; Disease transmission, Vertical/prevention and control; Zidovudine/therapeutic use; Nevirapine/therapeutic use; Breast feeding/adverse effects; Bottle feeding; Pregnancy; Outcome and process assessment (Health care); National health programs; Cross-sectional studies; South Africa (*source: MeSH, NLM*).

Mots clés Infection à VIH/transmission/prévention et contrôle/chimiothérapie; Transmission verticale maladie/prévention et contrôle; Zidovudine/usage thérapeutique; Névirapine/usage thérapeutique; Allaitement au sein/effets indésirables; Alimentation biberon; Grossesse; Evaluation résultats et méthodes (Soins); Programme national santé; Etude section efficace; Afrique du Sud (*source: MeSH, INSERM*).

Palabras clave Infecciones por VIH/transmisión/prevenición y control/quimioterapia; Transmisión vertical de enfermedad/prevenición y control; Zidovudina/uso terapéutico; Nevirapina/uso terapéutico; Lactancia materna/efectos adversos; Alimentación artificial; Embarazo; Evaluación de procesos y resultados (Atención de salud); Programas nacionales de salud; Estudios transversales; Sudáfrica (*fuente: DeCS, BIREME*).

Arabic

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Introduction

Mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV) is the most significant route of HIV infection in children. In South Africa, the risk of vertical transmission from HIV-infected mothers to their infants is estimated to be

between 19% and 36%, depending on whether or not the child is breastfed (1). The prevalence of infection with HIV among expectant mothers attending public-sector clinics was 27.9% in 2003 (2), and an estimated 75 000 infants would be born infected with HIV-1 in South Africa each year in the absence of

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programmes to reduce the risk of vertical transmission of HIV. International and local experience has shown that the provision of antiretroviral chemoprophylaxis and replacement feeding can cause a dramatic reduction in the risk of transmission from mother to infant in resource-constrained settings (3–8).

In 1999, the Department of Health of the Western Cape initiated the first pilot programme for the prevention of mother-to-child transmission (PMTCT) in South Africa (9), based on evidence from similar programmes elsewhere in the world that showed a reduction in MTCT of 50% (3). Antenatally, this included voluntary counselling and testing, and the provision of zidovudine (AZT) at a dose of 300 mg given twice per day from week 36 of gestation until labour. In labour, mothers received 300 mg of AZT every 3 h until delivery. Infant formula (replacement feeding) was offered for 9 months to mothers who chose not to breastfeed, after which the HIV status of the child was determined. Those children with a positive HIV test at age 9 months were re-tested at age 18 months. After delivery, women attended one of the eight local authority clinics weekly, or every 2 weeks, for 9 months. Support groups were an integral part of the services offered, both antenatally and postnatally.

The initial evolution of the programme has been described previously (9), including the move to earlier antenatal initiation of AZT therapy at week 34 of gestation in order to ensure that enrolled mothers received > 2 weeks of AZT therapy before delivery. Recent guidelines from WHO recommend that AZT should be provided from week 28 of gestation, where resources permit (10).

On the basis of the results of trials on the efficacy of PMTCT programmes based on peripartum therapy with nevirapine (NVP), the Province of the Western Cape and the National Department of Health subsequently developed NVP-based protocols for the expansion of PMTCT services. The Khayelitsha district continued, however, to provide a PMTCT intervention based on a short course of treatment with AZT.

Between January 1999 and December 2003, 37 223 pregnant women registered with antenatal health-care services in Khayelitsha; 31 528 (84%) of these women were tested for HIV and 7043 (22.3%) were identified as being infected. The proportion of women testing positive for HIV increased from 15.4% in 1999 to 25.9% in 2003, consistent with estimates from district antenatal surveys (11). In 2003, the rate of acceptance for voluntary counselling and testing had further improved to attain 97% of the 7314 women presenting for first antenatal visits.

The determination of HIV status in children born to mothers participating in the PMTCT programme previously relied on testing for anti-HIV antibodies, performed between ages 9 and 18 months, by which time a high proportion (30–40%) of children were lost to follow-up. Of the 1732 babies tested by the end of 2002, 12.5% tested positive for HIV.

Although the efficacy of PMTCT regimens based on a short course of treatment with AZT has been established in clinical trials (3, 5, 12), the effectiveness of such regimens in a large-scale programme integrated into routine antenatal and obstetric health-care services has not been accurately demonstrated in the South African setting. A recent local study reported on the operational effectiveness of a NVP-based regimen (13).

By 2003, the PMTCT programme in the Western Cape covered all districts in the province, as a result of the expansion of the NVP-based protocol. The protocol in Khayelitsha was

amended in July 2003, midway through the study, to allow women who had received < 2 weeks of antenatal treatment with AZT to follow the NVP-based protocol, i.e. a single dose of 200 mg of NVP to the mother at the onset of labour, and a weight-adjusted dose to the infant within 72 h of delivery.

This study aimed to estimate the field efficacy of the PMTCT programme in Khayelitsha, and to provide details on the antiretroviral regimens received by mothers and infants.

Methods

This was a cross-sectional study in which the primary outcome was the HIV-status of infants aged 6–10 weeks. The study population was all mothers and infants enrolled in the Khayelitsha PMTCT programme and followed in the three largest local authority clinics, which account for > 75% of all postnatal follow-up related to the PMTCT programme in the district. A sample size of 500 mother–infant pairs was selected in order to provide a point estimate of transmission, with a 95% confidence interval (CI) of 6%, premised on an anticipated risk of transmission of 9%.

Using the clinic registers, all infants enrolled in the PMTCT programme in the three clinics were identified. At age 6 weeks, after pre-test counselling by the facility-based counsellors and obtaining written consent from the mother for the HIV test, 50 µl of blood was drawn from the heel of each infant and divided among three capillary tubes containing ethylenediaminetetraacetic acid (EDTA). Specimens were transported daily to the Department of Virology at the University of Cape Town, where tests for HIV-1 were performed based on qualitative DNA polymerase chain reaction (PCR) (AMPLICOR®HIV-1 DNA test, version 1.5; Roche). All mothers were interviewed to determine the feeding status of their infant from birth until the date of the interview, the respective number of doses of antiretroviral therapy received by the mother and infant, and the place and mode of delivery. Primary clinical records were not reviewed and there was no record of the extent of advancement of disease attributable to HIV in the mother during pregnancy. Mothers were given the option of receiving the test result with post-test counselling. The majority of mothers received the result within 2 weeks of testing.

Statistical analyses were done using STATA™ (*Stata Statistical Software: Release 8*, College Station, TX: Stata Corporation LP). Transmission proportions were described with exact binomial 95% CI. Risk factors for transmission were assessed by multivariate logistic regression.

Table 1. Profile of mothers and infants enrolled in the study

Parameter	Value
Number of children tested	535
Median age of mother (years) (IQR)	26 (23–29)
Median age of child when tested (weeks) (IQR ^a)	6.57 (6.14–10.14)
Proportion of deliveries by Caesarian (95% CI) ^{b,c}	0.23 (0.20–0.27)
Proportion of deliveries in hospital (95% CI)	0.52 (0.48–0.56)
Number of patients reporting mixed feeding ^c	4

^a IQR = intraquartile range.

^b CI = confidence interval.

^c n = 533 owing to unavailability of data.

Table 2. Number of mother–infant pairs receiving each PMTCT regimen

Antenatal AZT therapy received ^a	NVP therapy received ^a				Total
	Mother and infant	Mother only	Infant only	None	
Antenatal and in labour	18	10	13	240	281 ^b
Antenatal only	27	16	4	30	77 ^c
Labour only	9	2	4	8	23
< 14 days of antenatal AZT therapy	16	5	4	6	31 ^d
None	77	20	9	17	123
Total	147	53	34	301	535

^a Figures in bold type reflect treatment exactly in accordance with the protocol. Figures in italic type reflect treatment that at minimum comprised a complete regimen according to the protocol.

^b Median, four weekly packs of AZT were received by the mother (IQR, 3–6).

^c Median, three weekly packs of AZT were received by the mother (IQR, 2–5).

^d A single weekly pack of AZT was received by the mother.

Results

A total of 658 mothers were registered on the PMTCT programme from 1 April to 30 November 2003, and 535 mother–infant pairs were enrolled into the study (Table 1). This gives an overall response rate of 81%. An attempt was made to locate the 123 remaining children: 2 out of the 36 infants who could be traced had died, 25 had been transferred to other clinics in Cape Town or to the Eastern Cape and 9 subsequently returned to the clinics after absences of various lengths of time. The remaining non-responders (87) could not be traced due to insufficient contact information in the facility records.

Half the infants (278) in the study were delivered in hospital, and 23% (124) of all infants were delivered by Caesarean section. Four women (< 1%) reported giving mixed feeding for between 1 and 18 days after delivery, with the rest reporting exclusive formula feeding.

Fifty-three percent of mothers (281) reported receiving at least 2 weeks of antenatal treatment with AZT in addition to AZT therapy during labour (Table 2). An additional 24% (129) of mothers and infants received the appropriate NVP-based back-up regimen for mothers who had received insufficient AZT therapy before delivery. Thus 77% of women (410) received the correct regimen according to the policy at the time. The remaining 23% of mothers and infants (125)

received non-standard combinations of the two regimens, including 3% (17) who reported not receiving any antiretrovirals. The median number of weeks of antenatal therapy with AZT received by those mothers who received AZT antenatally was 4 (intraquartile range (IQR), 3–6). The median number of doses of AZT given during labour was 3 (IQR, 2–5) in those mothers who received AZT during labour. Of the infants tested, 181 received neonatal prophylaxis with NVP.

Of the infants tested for HIV (535), 8.8% (47) tested positive (95% CI, 6.2–10.9%). The median age of children when the PCR test was done was 6.6 weeks (IQR, 6.1–10.1). The majority of women (513; 96%) elected to receive the PCR test result.

Although the study was not powered to detect differences in transmission based on risk factors or the regimen received, a multivariate analysis of the impact of a number of factors on transmission (Table 3) revealed that women aged > 25 years were more likely to transmit HIV to their infants.

Discussion

The majority of pregnant women in Khayelitsha accept HIV testing during pregnancy and are prepared to join the PMTCT programme. The high rates of acceptance for testing and subsequent enrolment are key to the effectiveness of the programme.

Table 3. Risk of transmission (by regimen) and odds of transmission (by risk factor)

Category of antiretroviral treatment	<i>n</i>	% positive for HIV ^a	95% CI ^b
Overall rate of transmission	535	8.8	6.2–10.9
Short course of AZT ^c therapy as per protocol, no NVP ^d therapy	240	8.8	5.5–13.1
Short course of NVP therapy as per protocol, no AZT therapy	93	7.5	3.1–14.9
Either regimen as per protocol	333	8.4	5.7–11.9
Multivariate odds ratio of transmission (<i>n</i> = 535)	Odds ratio	<i>P</i>	95% CI
Either regimen as per protocol	0.85	0.917	0.46–1.58
Caesarian section	0.85	0.663	0.41–1.77
Maternal age > 25 years	2.15	0.019	1.14–4.08

^a HIV = human immunodeficiency virus.

^b Confidence interval.

^c AZT = zidovudine.

^d NVP = nevirapine.

A number of studies in Africa have demonstrated the feasibility of PMTCT programmes in routine settings, but generally report a high rate of attrition between being offered testing and subsequent enrolment in the programme (14–16).

More than 50% of women were referred to higher levels of care, either antenatally or during labour, reflecting an increase over previous years, and 23% (123) of all infants were delivered by Caesarian section. This could be due in part to the fact that more pregnant women are being referred for specialized care as a consequence of HIV infection, as good referral services exist.

The overall rate of transmission in this study was < 10%. This estimate falls within a range consistent with data from trials in which the same regimens were applied (3, 7, 17). This reflects the effectiveness of the PMTCT programme delivered within routine health-care services. Owing to the high uptake of replacement feeding, it is unlikely that these estimates would differ if measured in older children. The estimates for mode of feeding are consistent with those previously reported from this programme in Khayelitsha (18).

The association between maternal age and MTCT could be a function of the advancement of the disease. It has been shown previously that the more advanced the disease, as measured by CD4+ lymphocyte count, the higher the rate of vertical transmission (19).

In addition to the protocol change midway through the study, there are a number of other limitations to this study. The non-response rate of 19% is a concern and (although lower than that reported previously) may still result in some selection bias, as those children whom it was not possible to locate may have died as a result of infection with HIV. It was not possible to review the primary obstetric records. There is therefore also the potential for information bias in ascertaining the interventions received, as this relied on patient recall rather than on primary clinical records.

The operational changes to the programme during the study provided a unique study opportunity. At short notice, staff were able to provide a back-up regimen for a large proportion of mothers who had not received the primary intervention for an adequate duration. If PMTCT interventions include antenatal antiretroviral therapy for 4–12 weeks, many women may present for delivery without having received adequate therapy. This study has demonstrated that a back-up strategy based on peripartum therapy with NVP can be effectively implemented to address missed opportunities. The administration by clinical staff of NVP to the mother on admission in labour (as was the practice at the time of this study), rather than self-administration of a take-home dose, should increase the pre-delivery uptake of antiretroviral therapy.

In this study, one-third of women presented for delivery having received AZT therapy for an inadequate duration, despite the earlier protocol adjustment to begin AZT therapy at week 34 of gestation. The current WHO guidelines on PMTCT protocols for resource-constrained settings stress the added benefit of beginning AZT at week 28 of gestation (10). It is clear from this study that this would not only further reduce the rate of transmission in those women receiving 10 or more weeks of AZT therapy, but would also ensure that a smaller proportion of women presented for delivery having received < 2 weeks of AZT therapy.

After this study was concluded, there was a further protocol change in Khayelitsha and elsewhere in the province such that in addition to antenatal treatment with AZT, mothers are now routinely given peripartum treatment with NVP and their

infants now receive 7 days of treatment with AZT and a single dose of NVP. With this protocol it is anticipated that rates of transmission will decrease to < 5%, in line with results of trials elsewhere (12). It is now routine practice in the Western Cape to test infants participating in the PMTCT programme for HIV by PCR at age 14 weeks, and the initial results from Khayelitsha indicate that the vertical transmission rate is indeed falling. At the time of writing, the province is considering increasing the duration of antenatal therapy with AZT by providing AZT from week 28 of gestation. Although it appears that there are no studies in Africa that have reported on this regimen, data from a trial in Thailand suggest a rate of transmission of close to 2% (5). Operational research in this province could yield valuable information for PMTCT programmes in Africa.

The same study in Thailand has provided the first data on outcomes of post-PMTCT maternal treatment with antiretrovirals that has raised serious concerns about resistance to NVP (20). There are two approaches to minimize these risks. Firstly, there is early evidence to suggest that providing additional antiretroviral therapy to post-partum mothers when their serum concentrations of NVP are falling may reduce the proportion of mothers who develop resistance to NVP (21). Secondly, mothers that are eligible for lifelong three-drug antiretroviral therapy programmes can be started on combined antiretroviral therapy (cART) while they are pregnant, in line with WHO guidelines (10). With this in mind, routine testing for CD4+ lymphocyte count in mothers infected with HIV has been introduced as part of the PMTCT programme, with a view to referring eligible women for cART. There are also strong advocates for the provision of cART to all pregnant women infected with HIV. All these approaches are premised on regimens that require that mothers receive treatment with antiretrovirals at least twice per day for some part of their pregnancy or of the postnatal period.

This study has demonstrated that complex regimens can be delivered effectively on a large scale within routine health-care services, in areas with a high prevalence of infection with HIV. With simple amendments to the PMTCT programme described here, further reductions in the vertical transmission of HIV should be realized. Routine testing for HIV by PCR of all infants at age 14 weeks will ensure that these improvements are documented, that HIV-infected infants are managed earlier and that the quality of family counselling is improved.

Conclusion

The Khayelitsha PMTCT programme has entered its sixth year and the proportion of women opting to join remains high. A back-up strategy, using peripartum treatment with NVP for mothers receiving AZT therapy for an inadequate duration before delivery, was successfully implemented. The rate of transmission is low, at < 10%. These results corroborate those reported in Johannesburg at Coronation Hospital (13), and demonstrate the feasibility and effectiveness of a PMTCT programme within busy routine obstetric services in an urban primary health-care setting. ■

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Competing interests: none declared.

Résumé

Effacité du premier programme de prévention de la transmission mère-enfant du VIH, mené en Afrique du Sud à l'échelle du district

Objectif La présente étude vise à évaluer l'efficacité sur le terrain du premier programme de prévention systématique de la transmission de la mère à l'enfant (PTME) du virus de l'immunodéficience humaine, lancé dans le sous-district de Khayelitsha, en Afrique du Sud.

Méthodes Un échantillon consécutif de 658 couples mère-nourrisson a été constitué à partir de l'analyse du registre de PTME du 1^{er} mars au 30 novembre 2003, pour servir de support à l'étude. Les enquêteurs ont déterminé de manière précise l'alimentation reçue par le nourrisson et le statut VIH de celui-ci entre 6 et 10 semaines par une recherche qualitative de l'ADN par PCR. Les mères ont reçu de la Zidovudine (AZT) pendant la période anténatale, à partir de la 34^e semaine de grossesse et pendant le travail. Des préparations pour nourrissons ont été proposées aux mères ayant choisi de ne pas allaiter. En juillet 2003, les enquêteurs ont apporté au protocole une modification prévoyant l'administration au début

du travail d'une dose unique de névirapine (NVP) aux femmes traitées pendant moins de 2 semaines à l'AZT et d'une dose de NVP déterminée en fonction du poids au nourrisson dans les 72 heures suivant l'accouchement.

Résultats Parmi les 535 couples mère-nourrisson (81 %) inclus en fin de compte dans l'étude, 410 (77 %) ont effectivement bénéficié d'une intervention de PTME conforme au protocole. Le taux de transmission du VIH de la mère à l'enfant était de 8,8 % [intervalle de confiance à 95 % (IC) : 6,2 - 10,9]. Le seul facteur de risque indépendant jouant un rôle important dans la transmission était un âge maternel supérieur à 25 ans (odds ratio : 2,12, intervalle de confiance à 95 % : 1,14 - 4,07).

Conclusion Les résultats de cette étude démontrent la faisabilité et l'efficacité d'un programme de PTME à grande échelle dans un centre de soins public et urbain.

Resumen

Eficacia del primer programa distrital de prevención de la transmisión del VIH de la madre al niño en Sudáfrica

Objetivo Estimar la eficacia sobre el terreno del primer programa sistemático de prevención de la transmisión de la madre al niño (PTMN) del virus de la inmunodeficiencia humana (VIH) iniciado en Sudáfrica, en el subdistrito de Khayelitsha.

Métodos Se reclutó para el estudio a una serie consecutiva de 658 pares de madre y lactante, identificados mediante el registro de PTMN entre el 1 de marzo y el 30 de noviembre de 2003. Se establecieron los detalles del tratamiento administrado y se utilizó la PCR (reacción en cadena de la ADN-polimerasa) cualitativa para determinar la serología VIH de los lactantes entre las 6 y las 10 semanas de edad. Se proporcionó zidovudina (AZT) prenatal a partir de la 34 semana de gestación y durante el parto. A las madres que decidieron no dar de mamar se les ofreció leche maternizada. El protocolo se modificó en julio de 2003 de manera que a las

mujeres tratadas con AZT durante menos de 2 semanas se les administró una dosis única de nevirapina (NVP) al comienzo del parto, y el lactante recibía una dosis de NVP ajustada a su peso dentro de las primeras 72 horas tras el parto.

Resultados De los 535 pares de madre y lactante (81%) finalmente incluidos en el estudio, 410 (77%) recibieron una intervención eficaz de PTMN según el protocolo. La tasa de transmisión del VIH de madre a hijo fue del 8,8% (intervalo de confianza (IC) del 95%: 6,2-10,9). Una edad materna superior a 25 años fue el único factor de riesgo de transmisión independiente y significativo (OR: 2,12; IC95%: 1,14-4,07).

Conclusión Los resultados de este estudio demuestran la viabilidad y la eficacia de un programa de PTMN a gran escala en un entorno urbano del sector público.

Arabic

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