Dual and triple therapy to prevent mother-to-child transmission of HIV in a resource-limited setting – lessons from a South African programme

Rosemary Geddes, Janet Giddy, Lisa M Butler, Erika van Wyk, Tamaryn Crankshaw, Tonya M Esterhuizen, Stephen Knight

Objective. To determine outcomes of pregnant women and their infants at McCord Hospital in Durban, South Africa, where dual and triple therapy to reduce HIV vertical transmission have been used since 2004 despite national guidelines recommending simpler regimens.

Method. We retrospectively examined records of all pregnant women attending McCord Hospital for their first antenatal visit between 1 March 2004 and 28 February 2007. Uptake of HIV testing and HIV prevalence were determined, and clinical, immunological and virological outcomes of HIV-positive women and their infants, followed through to 6 months after delivery, were described.

Results. The antenatal clinic was attended by 5 303 women: 4 891 (92%) had an HIV test, and 703 (14%) were HIV positive. The HIV-positive women were subsequently followed up: 653 (93%) received antiretroviral therapy or prophylaxis, including 424 (60%) who received triple therapy. Of the 699 live babies delivered, 661 (94%) received prophylaxis. At 6 weeks 571 babies (82%) were brought back for HIV testing; 16 (2.8%) were HIV positive. After 6 months, only 150 women (21%) were receiving follow-up care at the adult HIV clinic.

Conclusion. Where a tailored approach to prevention of mother-to-child transmission (PMTCT) is used, which attempts to maximise available technology and resources, good short-term transmission outcomes can be achieved. However, longer-term follow-up of mothers’ and babies’ health presents a challenge. Successful strategies to link women to ongoing care are crucial to sustain the gains of PMTCT programmes.
The PMTCT treatment options at McCord were influenced by international best practice and evidence and did not follow the public sector guidelines, which at the time recommended single-dose nevirapine at birth for women with CD4 counts >200 cells/μl. Over the study period, McCord PMTCT programme clinical guidelines evolved as evidence emerged, drugs became more available, and funding for dual and triple therapy was secured. The choice of regimen for individual women was determined by CD4 count, viral load, prior use of antiretroviral therapy, cost factors and the gestational age at which women presented for antenatal care (Table I). Initially a caesarean section was offered to all women to reduce intrapartum HIV transmission. By mid-2005, a routine viral load test at 36 weeks enabled a policy of recommending vaginal delivery (if there was no obstetric indication for caesarean section) in women with a viral load <1000 copies/ml. All infants were to be given a single dose of nevirapine within 72 hours of birth and zidovudine for 1 week.

Records of all pregnant women attending McCord Hospital for their first antenatal visit between 1 March 2004 and 28 February 2007 were examined to determine uptake of HIV testing and HIV positive, and 266 (38%) of their partners were tested at McCord Hospital antenatal clinic; all received counselling, and 92% (N=4891) accepted HIV testing (Fig. 1). Of the tested women 703 (14%) were HIV positive, and 122 (84%) were commenced on HAART for life.

### Results

During the 3-year period, 5303 women attended the McCord Hospital antenatal clinic; all received counselling, and 92% (N=4891) accepted HIV testing (Fig. 1). Of the tested women 703 (14%) were HIV positive, and 266 (38%) of their partners were tested at McCord Hospital of whom 182 (68%) were HIV positive.

Of the 703 HIV-positive women, 653 (93%) received antiretroviral therapy; of these, 424 (60%) received triple therapy (Tables II and III). From programme year 1 to year 3 the use of triple therapy increased from 32% to 11% (χ²trend=34.9, p<0.001), while single-dose nevirapine prophylaxis decreased from 32% to 11% (χ²trend=34.9, p<0.001) (Table I). Dual therapy declined from 23% in year 1 to 8% in year 2 and 10% in year 3. Baseline CD4 counts were performed before antiretroviral initiation in 642 (91%) of the HIV-positive cohort, of whom 146 (23%) had CD4 counts >200 cells/μl. Over the study period, McCord PMTCT programme clinical guidelines were considered statistically significant. The study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the McCord Hospital Research Ethics Committee.

### Table I. Changing PMTCT treatment guidelines for HIV-positive pregnant women attending the McCord antenatal clinic, Durban, March 2004 - February 2007

<table>
<thead>
<tr>
<th>Time period</th>
<th>CD4 &lt;200 cells/μl</th>
<th>CD4 ≥200 cells/μl</th>
<th>Late presenters*</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2004 - May 2005</td>
<td>HAART* for life</td>
<td>Single-dose nevirapine, dual or triple therapy depending on woman’s ability to pay</td>
<td>Single-dose nevirapine</td>
</tr>
<tr>
<td>June 2005 - February 2007</td>
<td>HAART for life</td>
<td>Viral load (first visit) &lt;1500 copies/ml: dual therapy and lamivudine and lamivudine tail for 7 days</td>
<td>Viral load ≥1500 copies/ml: triple therapy from 28 weeks until birth and lamivudine and lamivudine tail for 7 days</td>
</tr>
</tbody>
</table>

*After 38 weeks’ gestation.
†Highly active antiretroviral therapy (actual regimens presented in Table III).
‡Dual therapy, zidovudine during pregnancy and nevirapine at delivery.

Fig. 1. Flow diagram of follow-up of women attending McCord antenatal clinic, Durban, March 2004 - February 2007.
At 6 weeks, 571 (82%) of the babies returned for HIV testing by PCR, and 16 (2.8%, 95% confidence interval (CI) 1.7 - 4.6%) were found to be HIV positive. Bivariate analysis found no statistically significant association between potential maternal risk factors (including age, marital status, gestation at first visit, CD4 counts and delivery method) and loss to follow-up at 6 weeks. Of the 694 HIV-positive women with live births, 524 (76%) were lost to follow-up 3 months after delivery. After 6 months, of 700 women who delivered only 150 (21%) were receiving ongoing care at the McCord Hospital general HIV clinic, including only 54 (37%) of the 146 women who were initially eligible for HAART for life (Fig. 1).

**Discussion**

We examined a PMTCT programme in a high HIV prevalence setting in sub-Saharan Africa, which used dual and triple therapy and opt-out testing. Of the women presenting for antenatal care, 92% were tested for HIV and overall HIV transmission occurred in less than 3% of babies tested 6 weeks after delivery. This is in sharp contrast to transmission rates in KZN public sector clinics at the time, where an estimated 20.8% (95% CI 18.2 - 23.6) of 6-week-old infants born to HIV-positive pregnant women, where only single-dose nevirapine was utilised, were found to be infected.13 Of HAART-eligible women, 84% were commenced on HAART, compared with only 51% in a 2010 study from Cape Town.14 However, of those women identified as HIV positive, only 21% were attending the general HIV clinic 6 months later. At McCord Hospital, access (financial and geographical) and the stigma of follow-up at the 'HIV clinic' may in part have been responsible for this drop-off. Longer-term follow-up is important to encourage mothers to engage with services and stay healthy and adherent to medication, thereby improving their own and their infants' chances of survival. This is recognised as a challenge to PMTCT providers.15

<table>
<thead>
<tr>
<th>Maternal regimen</th>
<th>No drug given (N (%))</th>
<th>Single-dose nevirapine (N (%))</th>
<th>Dual therapy† (N (%))</th>
<th>Triple therapy‡ (N (%))</th>
<th>No record (N (%))</th>
<th>Total (N (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All HIV-positive women</strong></td>
<td>19 (2.7)</td>
<td>135 (19.2)</td>
<td>94 (13.4)</td>
<td>424 (60.3)</td>
<td>31 (4.4)</td>
<td>703 (100)</td>
</tr>
<tr>
<td><strong>Year treated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>8 (3.9)</td>
<td>67 (32.2)</td>
<td>48 (23.1)</td>
<td>82 (39.4)</td>
<td>3 (1.4)</td>
<td>208</td>
</tr>
<tr>
<td>Year 2</td>
<td>5 (2.3)</td>
<td>39 (17.7)</td>
<td>18 (8.2)</td>
<td>145 (65.9)</td>
<td>13 (5.9)</td>
<td>220</td>
</tr>
<tr>
<td>Year 3</td>
<td>6 (2.2)</td>
<td>29 (10.5)</td>
<td>28 (10.2)</td>
<td>197 (71.6)</td>
<td>15 (5.5)</td>
<td>275</td>
</tr>
<tr>
<td><strong>CD4 count (cells/μl)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>5 (3.4)</td>
<td>11 (7.5)</td>
<td>1 (0.7)</td>
<td>122 (83.6)</td>
<td>7 (4.8)</td>
<td>146</td>
</tr>
<tr>
<td>≥200</td>
<td>6 (1.2)</td>
<td>80 (16.1)</td>
<td>90 (18.2)</td>
<td>297 (59.9)</td>
<td>23 (4.6)</td>
<td>496</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (13.1)</td>
<td>44 (72.1)</td>
<td>3 (4.9)</td>
<td>5 (8.2)</td>
<td>1 (1.6)</td>
<td>61</td>
</tr>
</tbody>
</table>

**Pregnancy outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Vaginal delivery</th>
<th>Caesarean section</th>
<th>Intra-uterine death</th>
<th>Miscarriage</th>
<th>Mother/fetus died</th>
<th>Delivery method unknown</th>
<th><strong>All live babies</strong>*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No record (N (%))</td>
<td>11 (4.5)</td>
<td>30 (12.1)</td>
<td>33 (13.4)</td>
<td>168 (68.0)</td>
<td>5 (2.0)</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>8 (1.9)</td>
<td>104 (24.3)</td>
<td>61 (14.3)</td>
<td>251 (58.8)</td>
<td>3 (0.7)</td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td>6 (1.2)</td>
<td>80 (16.1)</td>
<td>90 (18.2)</td>
<td>297 (59.9)</td>
<td>23 (4.6)</td>
<td>496</td>
<td></td>
</tr>
<tr>
<td>Year 3</td>
<td>6 (1)</td>
<td>44 (72.1)</td>
<td>3 (4.9)</td>
<td>5 (8.2)</td>
<td>1 (1.6)</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

**Baby 6-week PCR**

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Unknown</th>
<th><strong>All live babies</strong>*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No record (N (%))</td>
<td>0</td>
<td>7</td>
<td>95</td>
<td>427 (23)</td>
</tr>
</tbody>
</table>

**HIV transmission**

<table>
<thead>
<tr>
<th>No record (N (%))</th>
<th>0/7</th>
<th>7/101</th>
<th>1/85</th>
<th>8/373</th>
<th>0/5</th>
<th>16/571</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0%)</td>
<td>(6.9%)</td>
<td>(1.2%)</td>
<td>(2.1%)</td>
<td>(0%)</td>
<td>(2.8%)</td>
<td></td>
</tr>
</tbody>
</table>

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*6 sets of twins, so 709 fetuses but 10 died or miscarried (including 1 pair twins), resulting in 699 live births.
†Dual therapy, zidovudine during pregnancy and nevirapine at delivery.
‡Triple-therapy regimens in Table III.
The retrospective nature of the study may have led to information and selection bias. Specifically, the 18% loss to follow-up of babies 6 weeks after delivery may have led us to underestimate transmission. Although unlikely, if all 128 infants who did not return at 6 weeks were infected, transmission may have been as high as 20.6% (95% CI 17.6 - 23.6). Poor retention following delivery also compromised our ability to accurately determine the HIV transmission to infants by 6 months of age and to assess other maternal and child health outcomes.

Because of the user fee, patients attending McCord Hospital are likely to be socio-economically and educationally better off than those attending public facilities. This may influence general health and adherence to medication and results may therefore not be generalisable to the broad antenatal population of South Africa, limiting the external validity of the study.

Triple therapy for PMTCT is feasible in the sub-Saharan setting, but implementation requires sufficient resources for staff, their training, and the availability of basic laboratory technology and drugs. A goal of the South African National Strategic Plan for HIV/AIDS and Sexually Transmitted Infections 2007 - 2011 is to reduce MTCT of HIV to less than 5%. Results of operational research at sites using dual therapy suggest that it is unlikely that vertical transmission of less than 5 - 9% will be achieved.17,18 This study demonstrates that the appropriate use of available resources can achieve good outcomes; in particular, the use of CD4 counts and viral loads in this programme allowed tailored prophylactic regimens and a reduced caesarean section rate. Focusing solely on short-term MTCT of HIV, however, is insufficient and results in lost opportunities. Outcomes such as 6-month and 1-year HIV-free infant survival should become standard indicators. The importance of longer-term follow-up must be emphasised, and successful strategies to link women to ongoing care are crucial to sustain the gains of PMTCT programmes.

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References

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| Table III. Triple therapy prescribed to 424 HIV-positive women attending the McCord antenatal clinic, Durban, 1 March 2004 - 28 February 2007 |
|-----------------|------|-----------------|
| Triple therapy regimen | N   | %    |
| AZT, 3TC & NVP     | 89  | 21.0 |
| AZT, 3TC & efavirenz| 34  | 8.0  |
| d4T, 3TC & NVP     | 83  | 19.6 |
| AZT, 3TC & lopinavir/ritonavir | 187 | 44.1 |
| d4T, 3TC & efavirenz| 18  | 4.3  |
| AZT, 3TC & nelfinavir| 2  | 0.5  |
| AZT, ddI, lopinavir/ritonavir | 1 | 0.2  |
| 3TC, d4T & lopinavir/ritonavir | 10 | 2.3  |
| Total             | 424 | 100  |

Notes:
- 424 pregnant women, 204 antenatally HIV positive.
- 424 women started ART in antenatal care.
- 94% of ART was started in first trimester.
- 125 women were given only 1 dose of zidovudine.
- 87 women were given zidovudine, 3TC.
- 10 women were given HAART for life (CD4 <200) but where NNRTIs contraindicated.
- 40 women were given non-nucleoside RT inhibitors (NNRTI).
- 36 women were given ritonavir/lopinavir.
- 4 women were given zidovudine and ritonavir/lopinavir.
- 2 women were given stavudine, 3TC, lopinavir/ritonavir.
- 1 woman was given stavudine, 3TC, nelfinavir.

VL = viral load; AZT = zidovudine; 3TC = lamivudine; d4T = stavudine; NVP = nevirapine; ddI = didanosine; NNRTI = non-nucleoside reverse transcriptase inhibitor; DOH = KwaZulu-Natal Department of Health; TB = tuberculosis.

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