

# Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach

*Erik J Schouten, Andreas Jahn, Dalitso Midiani, Simon D Makombe, Austin Mnthambala, Zengani Chirwa, Anthony D Harries, Joep J van Oosterhout, Tarek Meguid, Anne Ben-Smith, Rony Zachariah, Lutgarde Lynen, Maria Zolfo, Wim Van Damme, Charles F Gilks, Rifat Atun, Mary Shawa, Frank Chimbandira*

*Lancet* 2011; 378: 282–84

See *World Report* page 215

**Department of HIV and AIDS, Ministry of Health, Lilongwe, Malawi** (E J Schouten MD, A Jahn PhD, D Midiani BSc, S D Makombe Dipl Clin Med, A Mnthambala MPH, Z Chirwa MBCh, F Chimbandira MBBS); **Management Sciences for Health, Lilongwe, Malawi** (E J Schouten); **ITECH Malawi and University of Washington, Seattle, WA, USA** (A Jahn, Z Chirwa); **International Union Against Tuberculosis and Lung Disease, Paris, France** (Prof A D Harries MD); **London School of Hygiene and Tropical Medicine, London, UK** (Prof A D Harries); **College of Medicine, Blantyre, Malawi** (Prof J J van Oosterhout PhD); **Kamuzu Central Hospital, Lilongwe, Malawi** (T Meguid MD); **Maame Akua, Lilongwe, Malawi** (A Ben-Smith PhD); **Médecins Sans Frontières (Operational Research Unit), Luxembourg** (R Zachariah PhD); **Institute of Tropical Medicine, Antwerp, Belgium** (L Lynen PhD, M Zolfo MD, Prof W Van Damme PhD); **UNAIDS, New Delhi, India** (Prof C F Gilks FRCP); **Department of Medicine (Prof C F Gilks) and Business School (Prof R Atun FFPH) Imperial College, London, UK; The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland** (Prof R Atun); **and Office of the President and Cabinet, Lilongwe, Malawi** (M Shawa PhD)

Correspondence to: Dr Erik J Schouten, Department of HIV and AIDS, Ministry of Health, PO Box 30377, Lilongwe, Malawi [eschouten@msh.org](mailto:eschouten@msh.org)

Like many other countries in Africa, Malawi is preparing to revise its policies for prevention of mother-to-child transmission (PMTCT) of HIV and for antiretroviral therapy (ART) in response to WHO's 2010 guidelines.<sup>1,2</sup> This guidance is timely in view of the limited efficacy of single-dose nevirapine used in many PMTCT programmes<sup>3</sup> and the challenges facing the effective expansion of health service delivery.<sup>4</sup> The drive from the Global Fund to Fight AIDS, Tuberculosis and Malaria to increase coverage of PMTCT services is increasing, particularly in countries with high burdens of HIV infection; high coverage is essential to reduce transmission to infants, to provide treatment for HIV-infected women, and to meet the relevant 2015 Millennium Development Goals of reducing child mortality, improving maternal health, and combating HIV infection and AIDS, malaria, and other diseases.

The WHO guidelines specify that a CD4 cell count is crucial to decisions on the eligibility of HIV-infected pregnant women for lifelong ART. In Malawi, however, access to CD4 cell count analysis is minimal (panel)<sup>5</sup> and is unlikely to improve anytime soon. Thus, to make this test a prerequisite for increasing the coverage of PMTCT services and early access to ART would hinder rapid expansion in countries with heavily constrained health systems. Malawi, therefore, proposes a strategy that does not rely solely on CD4 cell counts but is based on the WHO guidelines and the public health approach outlined in the current Ministry of Health ART guidelines.<sup>6</sup> This strategy takes into account the weaknesses in the Malawi health system<sup>7</sup> yet should increase the coverage notably from the current 35%. It should also narrow the gap among the estimated 950 000 people living with HIV infection between the 225 000 currently receiving ART and the 440 000 who are eligible.<sup>5,8</sup>

In HIV-infected pregnant women ART use is recommended when CD4 cell counts are 350 cells per  $\mu\text{L}$  or less, irrespective of WHO clinical stage, or in women with disease in clinical stage 3 or 4. For pregnant women with CD4 cell counts higher than 350 cells per  $\mu\text{L}$  or with disease at clinical stage 1 or 2 who do not yet need ART for their own health, WHO proposes two time-limited options for antiretroviral prophylaxis (table). The Ministry of Health in Malawi chose to use a regimen of tenofovir, lamivudine, and efavirenz in these women. This regimen is simple, it avoids zidovudine-induced side-effects, particularly anaemia, which is a common feature of

pregnancy in Malawi, and it will be used as the first-line regimen in adolescents and adults. The logistics of delivery will be improved, the risks of running out of stocks lessened, the need for multiple guidelines and training eliminated, and the likelihood of successful implementation increased. Moreover, the proposed regimen is available in a fixed-dose combination of one tablet per day, can be safely used with antituberculosis drugs, is effective against hepatitis B virus, and can be used without routine laboratory monitoring of toxic effects.<sup>9</sup>

We propose to offer all HIV-infected pregnant women lifelong ART. This approach is not completely new, but rather is a more feasible alternative to WHO's proposed option B, which we call option B+. The proposed change is akin to the test and treat mathematical model elucidated by Granich and colleagues.<sup>10</sup> In view of the regimen's good safety profile, the difficulties involved in expansion of CD4 cell count testing, and the urgent need to increase the coverage of the PMTCT programme, we argue that waiting 2–3 years for the results of a pilot study would not be ethical. We therefore propose immediate implementation of this approach. If CD4 counts did become more accessible in Malawi, the guidelines could be adapted.

The expansion of the PMTCT programme in Malawi through implementation of option B+ would have various other benefits. The total fertility rate in Malawi is high, around 5·6 births per woman,<sup>11</sup> which is unlikely to be much lower in HIV-infected women.<sup>12</sup> Soon after the breastfeeding period (median duration 23 months<sup>13</sup>) many women become pregnant again. Thus, a stop-start approach to ART administration is almost redundant. Many women present for antenatal care late in pregnancy—an estimated 50% are thought to attend after 28 weeks of gestation—and continuing prophylaxis with antiretroviral drugs would mean that the next pregnancy could be protected from conception. The stopping of ART after cessation of breastfeeding might lead to viral rebound, with the risk of transmission to a sexual partner or fetus being notably raised. Scheduled stopping is also difficult to implement, as it requires tapering of doses to prevent drug resistance, owing to the different half-lives of the antiretroviral drugs. Additionally, the risks of opportunistic disease or death might be raised.<sup>14</sup> Tenofovir and lamivudine are active against hepatitis B virus; 10–15% of people living with HIV infection in Malawi are also infected with

hepatitis B virus,<sup>15</sup> and reactivation of this virus is a risk if ART is stopped.

Universal, lifelong ART for HIV-infected pregnant women will achieve maximum coverage and could potentially lead to elimination of paediatric HIV/AIDS.

In women in Zimbabwe even those with CD4 cell counts higher than 350 cells per  $\mu\text{L}$  had a risk of death around six times higher than that in non-infected women within 24 months post partum, and early ART could reduce mortality by 50–90%.<sup>16</sup> Prevention of maternal deaths has a striking effect on child survival, independent of any effect gained from the prevention of HIV transmission.

The risk of developing tuberculosis increases with declining CD4 cell counts, from 500 cells per  $\mu\text{L}$ ;<sup>17</sup> the majority of pregnant women have CD4 cells counts in this range. Early initiation of ART, therefore, reduces the risk of tuberculosis.<sup>18</sup> Observational cohort studies in the USA and Europe also suggest that the early starting of ART significantly lowers mortality related to HIV infection and AIDS.<sup>19</sup>

In Malawi, most HIV-infected women starting prophylaxis with zidovudine do so without the CD4 cell count being known. As about 50% of these women will have counts of 350 cells per  $\mu\text{L}$  or lower, all receive zidovudine monotherapy de facto. Although there is no evidence that exposure to zidovudine prophylaxis in women with advanced HIV disease increases the risk of drug resistance, this possibility is of concern.

HIV-transmission in couples is an important contributor to overall transmission rates, and the use of ART greatly reduces the risk of HIV-transmission to non-HIV-infected partners.<sup>20</sup>

HIV status and pregnancy can be confirmed in virtually all health centres in Malawi that provide maternal health services. The message that triple therapy must be taken for life and on a daily basis from the start is simple. Both these features mean the option B+ policy could be rapidly rolled out to and implemented by all centres.

In the first 3 years of the implementation of the option B+ policy we estimate that ART would be started in 25 000 more pregnant women per year than at present; of note, these women would have required ART at some point, and are merely starting treatment earlier. To hit this target, the number of health facilities providing ART would have to increase from 377 to all 650 with mother and child health services. Current constraints on health systems and human resources will need to be addressed to accommodate additional burdens, such as extended intervals between appointments, task-shifting, and expansion of the health staff.

The chosen ART regimen is more expensive than a regimen of stavudine, lamivudine, and nevirapine (US\$176 per person per year<sup>21</sup> vs \$65), but we believe that the advantages justify the initial added cost. In addition, drug prices are expected to lower over time, and

#### Panel: Factors hampering universal coverage for CD4 cell count testing in Malawi

##### Technology

- No easy-to-use, rapid, and reliable test (eg, dipstick technology) is currently available for use by health-care workers at the point of care in all health facilities
- Reliable stocks of reagents and regular maintenance and supervision of existing CD4 cell count equipment are difficult to provide
- Most equipment is currently based in tertiary and district hospitals
- Most machines available at peripheral health facilities are still bench-top machines that require skilled laboratory staff to operate them
- Various quality assurance issues remain unresolved

##### Health facilities

- The numbers of health-care workers able to do CD4 cell counts within facilities or to do the related administration for remote testing are limited
- Transport of blood samples in a timely manner from all 650 health facilities in Malawi is cumbersome and impracticable, and samples may become unusable
- Blood collection in tubes for transport is associated with the risk of mixing up labelling and results
- Stocks of reagents frequently run out

##### Patients

- The need for repeat visits to the health centre to collect results implies additional indirect journey costs
- Referral of patients to different clinics where CD4 cell counts can be done leads to loss to follow up, low uptake of referrals, or both, especially among pregnant women

	WHO option A	WHO option B	Malawi Ministry of Health option B+
Mother	Antepartum zidovudine from 14 weeks' gestation, single-dose nevirapine at onset of labour, and zidovudine plus lamivudine during labour and delivery and for 7 days' postpartum	Triple ART regimen from 14 weeks' gestation until 1 week after all exposure to breastmilk has ended	Triple ART regimen started from 14 weeks' gestation and taken for life
Breastfeeding baby	Daily nevirapine from birth to 1 week after all exposure to breastmilk has ended	Daily nevirapine syrup from birth to 6 weeks	Daily nevirapine from birth to 6 weeks

ART=antiretroviral therapy.

**Table: Antiretroviral prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health**

reductions in the number of infections, morbidity, and mortality in children and adults will contribute to a decline in overall treatment cost. Moreover, the management costs of option B+ are likely to be similar to those for option A or B, since the frequency of follow-up for mothers and infants is similar in all three. A full economic analysis, however, is needed.

Efavirenz is potentially teratogenic in the first trimester, but the risk seems to be lower than previously thought.<sup>22</sup> In the absence of conclusive evidence, women who desire pregnancy could be offered an alternative ART regimen in which nevirapine replaces efavirenz, until the second trimester of the pregnancy. Other women receiving ART should be offered contraceptives

in line with a comprehensive PMTCT strategy. We recognise that exposure to efavirenz cannot be completely avoided in the first trimester, but this risk seems outweighed by increased coverage and much-reduced overall mortality.

Our approach offers a real opportunity to integrate HIV treatment into mother and child health services and make tangible progress towards achieving the relevant Millennium Development Goals. Option B+ favours women rather than men in terms of ART accessibility, although we feel this inequality is acceptable in view of the policy's potential contribution to the elimination of paediatric HIV infection.

The public health model outlined in this Viewpoint is so far untried and untested, but we are confident that it can work. Concerns about the acceptability to the general population of HIV testing and ART when that programme was scaled up in 2004 proved unfounded. Community acceptability for this approach would, however, have to be assessed from the start and human rights would have to be protected at all times. In the meantime, community leaders and health-care workers would have to be careful not to coerce people into being tested. National guidelines clearly state that everyone has the right to decline HIV testing without any consequences. We would expect community members and people living with HIV and AIDS to play important parts in the delivery strategy. We propose that sentinel sites are set up to improve human resources, infrastructure, and monitoring and reporting of drug tolerability. The people who would be responsible for administration of ART should be specified before implementation.

Increasing the uptake of PMTCT linked with access to CD4 cell count testing has been a major challenge. Progress towards the relevant Millennium Development Goals will, therefore, depend on additional strategies to substantially increase PMTCT coverage. We need to bridge the implementation gap with a bold PMTCT public health approach.<sup>6</sup>

#### Contributors

EJS, AJ, ABS, and ADH wrote the article. EJS, AJ, DM, SDM, AM, ZC, ADH, JjvO, TM, AB-S, RZ, LL, MZ, WVD, CFG, RA, MS, and FC contributed to the concept of the article. All co-authors were involved in revising drafts and writing and approving the final paper.

#### Conflicts of interest

WVD has received a grant from the European Commission (grant no. FP7). The other authors declare that they have no conflicts of interest.

#### Acknowledgments

We thank Kevin De Cock and Beth Barr for their valuable comments on an earlier draft of this paper. EJS is supported by Management Sciences for Health, Cambridge, MA, USA. AJ is supported by the International Training and Education Center for Health, Seattle, WA, USA. ADH is supported by the International Union Against Tuberculosis and Lung Diseases, Paris, France. The views expressed in this paper are personal and do not necessarily reflect the views of the institutions to which the authors are affiliated.

#### References

- 1 WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach (2010 version). Geneva: World Health Organization, 2010.
- 2 WHO. Antiretroviral therapy for HIV Infection in adults and adolescents: recommendations for a public health approach (2010 version). Geneva: World Health Organization, 2010.
- 3 UNAIDS. 09 AIDS epidemic update: November 2009. [http://data.unaids.org/pub/Report/2009/JC1700\\_Epi\\_Update\\_2009\\_en.pdf](http://data.unaids.org/pub/Report/2009/JC1700_Epi_Update_2009_en.pdf) (accessed Jan 24, 2010).
- 4 Mofenson LM. Prevention in neglected subpopulations: prevention of mother-to-child transmission of HIV infection. *Clin Infect Dis* 2010; **50** (suppl 3): S130–48.
- 5 HIV Unit, Ministry of Health, Malawi. Antiretroviral therapy. <http://www.hivunitmohmw.org/Main/AntiretroviralTherapy> (accessed March 16, 2011).
- 6 Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006; **368**: 505–10.
- 7 Harries AD, Schouten EJ, Libamba E. Scaling up antiretroviral treatment in resource-poor settings. *Lancet* 2006; **367**: 1870–72.
- 8 WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010. Geneva: World Health Organization, 2010.
- 9 DART Trial Team. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet* 2010; **375**: 123–31.
- 10 Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009; **373**: 48–57.
- 11 WHO. World health statistics 2009. Geneva: World Health Organization, 2009.
- 12 Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med* 2010; **7**: e1000229.
- 13 National Statistical Office, ORC MACRO. Malawi demographic and health survey 2004. Calverton, MD: National Statistics Office and ORC MACRO, 2005.
- 14 The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**: 2283–96.
- 15 Sutcliffe S, Taha TE, Kumwenda NI, Taylor E, Liomba GN. HIV-1 prevalence and herpes simplex virus 2, hepatitis C virus, and hepatitis B virus infections among male workers at a sugar estate in Malawi. *J Acquir Immune Defic Syndr* 2002; **31**: 90–97.
- 16 Hargrove JW, Humphrey JH. Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe. *AIDS* 2010; **24**: F11–14.
- 17 Lawn SD, Meyer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy. *AIDS* 2009; **23**: 1717–25.
- 18 Harries AD, Zachariah R, Corbett EL, et al. The HIV-associated tuberculosis epidemic—when will we act? *Lancet* 2010; **375**: 1906–19.
- 19 When To Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; **373**: 1352–63.
- 20 Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; **375**: 2092–98.
- 21 Campaign for access to essential medicines, Médicins sans Frontières. Untangling the web of antiretroviral price reductions: tenofovir disoproxil fumarate/lamivudine/efavirenz (TDF/3TC/EFV). <http://utw.msfaaccess.org/drugs/tdf-3tc-efv> (accessed Jan 24, 2010).
- 22 Ford N, Mofenson L, Kranzer K, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS* 2010; **24**: 1461–70.