

Prevention of mother-to-child transmission of HIV in developing countries: recommendations for practice

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Objectives: Different approaches to prevent mother-to-child transmission of HIV are being evaluated in developing countries. The first trials using a short regimen of zidovudine have been successful in Thailand, Côte d'Ivoire and Burkina Faso. International and local strategies are now being considered. The Ghent International Working Group on Mother-to-Child Transmission of HIV developed public health policy options to integrate these interventions into basic and maternal and child health (MCH) services.

Methods: The following tasks were undertaken: a critical review of randomized trials; an international pooled analysis of late postnatal transmission of HIV through breastfeeding; a review of the cost-effectiveness and cost-benefit of antiretroviral prophylaxis; a feasibility assessment of preventive strategies, including a postal survey on HIV voluntary counselling and testing (VCT) of pregnant women; the identification of requirements and research priorities for prenatal, obstetric and paediatric care. These projects provided the background for a three-day workshop in Ghent, Belgium, in November 1997. Conclusions were further refined, based on 1998 research findings.

Results: A summary of relevant evidence and ten public health recommendations are reported. VCT for pregnant women, a short regimen of zidovudine together with alternatives to breastfeeding currently represent the best option to reduce vertical transmission in most developing countries. The primary goal of the integrated package supporting these interventions is to alleviate overall maternal and infant morbidity and mortality.

Conclusion: Prevention of mother-to-child transmission of HIV should now be considered for integration into basic health and MCH services of selected countries, with the involvement of governments and donor agencies.

Introduction

The magnitude of the pandemic of human immunodeficiency virus type 1 (HIV) infection in developing countries¹ is such that multiple approaches are required to slow its spread and alleviate the burden on the health sector and society in general. Primary prevention of heterosexual transmission of HIV remains a key component of HIV/AIDS programmes, and should be led by governments and donor agencies.²

Women of childbearing age constitute nearly half of the 30 million adults currently living with HIV/AIDS worldwide.³ Mother-to-child transmission, restricted here to vertical transmission of HIV during pregnancy, delivery and the

breastfeeding period, is the major mode of acquisition of infection for young children, with an estimated 1600 of the 16 000 new infections each day, most in developing countries. The increasing number of infected women and children has implications for both the organization of equitable and sustainable health care and the prevention of vertical transmission.

There is now clear evidence that in non-breastfeeding populations mother-to-child transmission can be greatly reduced by the administration of zidovudine (ZDV) orally to the woman initiated between 14 and 34 weeks of gestation, intravenously during labour and orally to the neonate in the first six weeks of life according to the ACTG 076 – ANRS 024 validated protocol.⁴ In 1998, the efficacy of a short ZDV regimen

administered orally during the last month of pregnancy and labour to non-breastfeeding HIV-infected women in Thailand was demonstrated.⁵ The short-term efficacy of a similar regimen of ZDV⁶ and of a slightly longer one, with the addition of one week of postpartum maternal treatment,⁷ was recently demonstrated in breastfeeding HIV-infected women in Côte d'Ivoire and Burkina Faso. Preliminary results of a trial in East and Southern Africa indicate that short regimens of ZDV and lamivudine (3TC) combined may be at least as efficacious as ZDV alone in reducing mother-to-child transmission in breastfeeding populations.⁸ These findings provide a strong rationale for the world-wide policy of use of ZDV prophylaxis adopted by UNAIDS, WHO and UNICEF in March 1998,⁹ with a proposed phased approach considering the diversity of national and local capacities and of HIV prevalence in pregnant women.

Availability of drugs and the infrastructure required to provide ZDV and other antiretroviral drugs (ARV) to pregnant women are not yet established in most developing countries.¹⁰ To facilitate the implementation of programmes based on these research findings, appropriate public health strategies for the prevention of mother-to-child transmission of HIV in resource-poor countries are required. The International Working Group on Mother-to-Child Transmission of HIV, or Ghent Group, was created in 1992 with the support of the European Commission (DG VIII/8). Within this initiative, in collaboration with WHO and then UNAIDS, and involving experts in the field of mother-to-child transmission and in public health, the Ghent Group has addressed issues including the methodology for estimating the rate of mother-to-child transmission,¹¹ the international comparison of transmission rates¹² and the methodology of intervention trials.¹³ The Ghent Group worked in 1997–1998 to review current information on mother-to-child transmission of HIV and its prevention, and to propose policy options for developing countries. We report here a summary of the key findings and propose essential public health strategies.

Methodology

Members of the Ghent Group initiated four projects in 1997 to provide background information for policy formulation.

Postnatal transmission of HIV through breastfeeding is an essential component of the overall risk of mother-to-child transmission and must be taken into account when designing prevention strategies in developing countries. To increase understanding of this issue, an international pooled analysis of available observational data was carried out to quantify the risk of transmission through breastfeeding after 2.5 months of age, when diagnosis of postnatal transmission of HIV becomes possible.

Prevention of vertical transmission of HIV in developing countries raises financial and economic concerns. During a two-day workshop in London (June 1997), both completed and on-going cost-effectiveness analyses (CEAs) and cost-benefit analyses (CBAs) of the use of ARV to prevent mother-to-child transmission of HIV in developing countries

were reviewed. Methodological issues central to the comparison of existing study results and to the conduct of future analyses were discussed.

To present a background against which the CEAs and CBAs of the use of ARV could be assessed, a review was undertaken of commonly used indicators of demographic and economic status and utilization of health care services, for countries in which ARV trials are being carried out, or in which policy strategies are already being developed. This was complemented by a review of current experience in antenatal care services, including voluntary counselling and HIV testing (VCT) of pregnant women, in countries with ongoing research. For this purpose, an international postal survey was conducted to document the acceptability of VCT among pregnant women. We defined acceptability of VCT as the product of the initial rate of HIV test acceptance and the rate of women returning for their test result.

Even if the rate of vertical transmission is reduced, eradication of paediatric HIV infection cannot be targeted and the needs for appropriate care of HIV-infected children will remain. A postal survey was conducted among clinical investigators and HIV paediatric centres in developing countries to document the natural history of paediatric HIV infection and the current care practices for infected children, necessary variables for cost-effectiveness analyses. Paediatricians participating in a workshop in Paris in September 1997 reviewed the available natural history data on paediatric HIV infection, discussed experience in case management and identified key areas for clinical research to improve paediatric care in developing countries.

During the 3-day workshop in Ghent (November 13–15, 1997), public health recommendations were formulated by 36 experts, based on the available and reviewed evidence from the preparatory projects. Subsequent revisions were prepared by the Scientific Secretariat taking into account the results of the Thailand and African ARV trials^{5–8} and the conclusions of two meetings convened by UNAIDS, WHO and UNICEF in March and April 1998 on, respectively, planning the implementation of programmes to prevent vertical transmission¹⁴ and infant feeding and HIV.¹⁵

Summary of findings

HIV vertical transmission and health burden on women and children in developing countries

Estimates of the vertical transmission rate of HIV-1 previously published by the Ghent International Working Group¹² were confirmed with current data, giving a range of plausible values of 25–35% in breastfed populations. The variation in vertical transmission rates between populations and over time within a given population¹⁶ should be taken into account when designing future intervention trials and selecting comparison groups, and in choosing baseline assumptions for developing indicators of programme success.

Late postnatal transmission through breastfeeding is significant and needs to be considered when evaluating interventions

in breastfeeding populations.^{17,18} The Ghent Group conducted an analysis on pooled data from eight individual cohorts in seven different settings. A detailed report is published elsewhere.¹⁹ The estimated risk of late postnatal transmission of HIV-1 after 2.5 months of age is 3.2 cases each year per 100 breastfed children born to HIV-positive women and uninfected at that age (95% confidence interval: 3.1 – 3.8), but information about the exact timing remains scarce. Evaluation of the effect of interventions which target the peripartum period needs to allow for the possibility that cases thus averted may become infected later through breastfeeding. Ongoing trials may partly address this latter question.

Background levels of maternal and child morbidity and mortality, as well as the availability of maternal and child health (MCH) services vary from place to place, as does the prevalence of HIV.²⁰ Table 1 shows demographic and HIV burden indicators for 13 selected developing countries (12 African plus Thailand). To estimate the magnitude of the paediatric HIV epidemic in a given country, key parameters are: HIV prevalence among pregnant women, population and birth rate. Each needs to be disaggregated for the urban and rural populations, though it is possible to use only the urban figures

in settings where the urban prevalence is much higher than the rural or where the degree of urbanization is very high. Because prenatal care, availability of drugs and the proportion of births that occur in hospital are all typically higher in urban areas, the estimated number of births to HIV-infected women in urban areas highlights potential for prevention of vertical transmission. Among the 13 countries examined, this ranges from 5000 children born to HIV-infected mothers per year in Botswana to 96 000 in South Africa, and should be compared with more general morbidity and mortality indicators in the same populations.²¹

Overview of completed, ongoing and planned randomized trials

There is no ongoing evaluation of the effect of a combination of interventions on vertical transmission, although this may be an essential approach in most developing countries. Several individual interventions are evaluated in 18 different randomized trials in developing countries (Table 2) and 10 of them have been completed so far. One trial in Malawi failed to provide evidence that vaginal disinfection with chlorhexidine is efficacious in reducing vertical transmission

Table 1. Demographic and HIV burden indicators for 12 selected African countries and Thailand

Country	Total no. of births per year (1995)	% population urban (1995)	HIV prevalence (%) in urban pregnant women ^a	Estimated annual no. of births to urban HIV-infected women
Botswana	54 000	28	33	5000
Burkina Faso	471 000	27	9–10	13 000
Côte d'Ivoire	697 000	44	12–14	43 000
Ethiopia	2 597 000	13	10	34 000
Kenya	1 231 000	28	13	45 000
Malawi	540 000	14	29	22 000
Rwanda	346 000	6	28–34	7 000
South Africa	1 260 000	51	15	96 000
Tanzania	1 252 000	24	12	36 000
Uganda	1 071 000	13	20	28 000
Zambia	409 000	43	30	53 000
Zimbabwe	423 000	32	30	41 000
Thailand	1 124 000	20	2	4 500

^a Latest figure available.

Table 2. Randomized trials for the prevention of vertical transmission of HIV in developing countries (May 1999)

Type of intervention	Number of trials ^a		
	completed	ongoing	planned
Antiretrovirals	4	2	2
Vaginal disinfection	2	1	–
Vitamin A and other micronutrients	3	2	–
HIV intravenous immune globulins	–	1	–
Artificial feeding	1	–	–
Total	10	6	2

^a All trials conducted in Africa except 2 antiretroviral trials in Thailand (1 completed and 1 ongoing), where breastfeeding was discouraged.

of HIV, except in the case of rupture of membranes >4 hours.²² The trial conducted in Thailand concluded in February 1998 that a short regimen of ZDV reduced vertical transmission by 50% in the absence of breastfeeding.⁵ All the trials with a placebo arm abandoned it right after the announcement of the results of the Thailand trial.²³ Vaginal disinfection with antiseptic or virucidal agents, supplementation with vitamin A and other micronutrients, intravenous HIV-specific immune globulins, and formula feeding are still under study in Africa.

Table 3 describes in greater detail the eight trials evaluating ARV. All the African trials are conducted in breastfeeding populations, although national policies and practices regarding breastfeeding in HIV-infected women vary. The drug regimens evaluated are complementary and shorter (a few weeks at the most) than the ZDV regimen used in the ACTG 076 – ANRS 024 trial,⁴ one of them⁶ being identical to the Thailand regimen.⁵ Some of the trials include a short post-partum treatment component for the mother⁷ and the newborn,⁸ of about 1 week. Three of the African trials have provided results on the short-term efficacy of these interventions, with reduction of HIV transmission estimated between 37 and 50%, based on the proportion of infants diagnosed with infection between six weeks and six months of age.^{6–8} However, the overall reduction in vertical transmission will not be fully evaluated until the end of the breastfeeding period of the last child enrolled.

Financial and economic considerations

Few studies have addressed the issue of CEA and CBA of prevention of vertical transmission of HIV in developing countries, and those that have, have concentrated on the use of ARV.^{24,25} These economic evaluations have been shown to be

extremely sensitive to certain parameters, such as the cost of drugs, the cost of providing counselling and testing, and the prevalence of HIV. The review by the Ghent Group of CEAs and CBAs concluded that widespread implementation of ARV interventions cannot currently be recommended in all developing countries.²⁶ Further CEAs and CBAs are required within ARV trials and future programmes as policy decisions regarding their implementation are now taken in several developing countries, following a 1998 UNAIDS meeting.¹⁴

The cost-effectiveness of ARV in low-income countries is considerably more sensitive to the drug price than in middle- or high-income economies. US\$40 per disability-adjusted life-years would compare favourably to the portfolio of existing health services in many low-income developing countries.^{2,27,28} Within the current range of ARV interventions, already being discussed in developing countries,²⁹ it is likely that prevention of mother-to-child transmission will prove both more cost-effective and affordable than child and adult ARV treatment.

Economic evaluations should conform to commonly agreed methodologies of economic evaluation in health care. It is desirable that trials and, more importantly, pilot or demonstration programmes include economic evaluation as a core element of the protocol. Such evaluations should encompass not only CEA and/or CBA, but also address the issues of affordability and willingness to pay for a given intervention package, considering both direct costs to individuals and societal costs.

Prenatal and obstetric care

Although an increasing number of pregnant women in developing countries are offered VCT for HIV infection,

Table 3. Anti-retroviral randomized trials for the prevention of vertical transmission of HIV in developing countries (December 1999)

Primary sponsor (trial name)	Country(s)	Phase	Overall sample size (arms), BF	Drug	Placebo ^a	Status [reference]
CDC	Thailand	III	397 (2), no BF	ZDV	Yes	Trial ended [5]
ANRS (049a)	Burkina Faso, Côte d'Ivoire	II/III	421 (2), BF	ZDV ^b	Yes	Trial ended [7]
CDC	Côte d'Ivoire	III	280 (2), BF	ZDV	Yes	Trial ended [6]
NIH	Thailand	III	1500 (4), no BF	ZDV ^b	No	ongoing ^c
NIH HIVNet (006/012)	Uganda	II/III	1500 (3), BF	ZDV ^b or Nevirapine ^b	No	Trial ended [46]
UNAIDS (Petra)	South Africa, Tanzania, Uganda	III	1792 (4), BF	ZDV ^b and 3TC ^b	Yes	Trial ended [8]
NIH	Ethiopia	III	900 (2), BF	ZDV ^b	No	planned
– (SAINT)	South Africa	III	1170 (2), BF	Nevirapine ^b or ZDV ^b and 3TC ^b	No	ongoing

ZDV: zidovudine; 3TC: lamivudine; BF: breast-feeding allowed.

^a Placebo arm abandoned in February 1998; ^b treatment includes a postnatal component of mother and/or child; ^c 1000 women included.

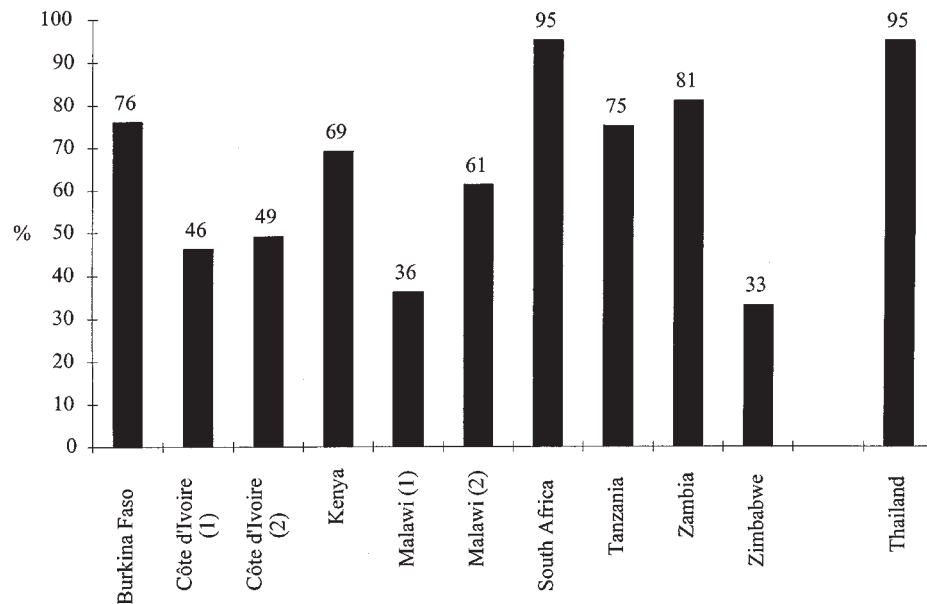


Figure 1. Acceptability* of HIV testing (%) by pregnant women in 11 selected centres in developing countries

Source: International survey of the Ghent International Working Group on Mother-to-Child Transmission of HIV, August–October 1997

*Acceptability rate = acceptance rate of the test after pre-test × return rate to post-test

usually in research projects until 1998, uptake is still low. In the 10 selected African urban sites surveyed, 92% of pregnant women accepted to be tested (range: 77–99%), but only 70% (range: 33–100%) returned for their test result, and the overall median acceptability rate was 65% (range: 33–95%). The acceptability rate reached 95% in Thailand (Figure 1). A full report of this survey is published elsewhere.³⁰

Factors contributing to this variation may be population-specific and the woman's choice is often influenced by partner and family.^{31–33} There is no evidence that the acceptance rate differs when pre-test counselling is carried out in a group (with individual consent) or individually. Factors related to the risk of discrimination and stigmatization and difficulties in transportation need to be considered when assessing the return rate. VCT services in MCH clinics and basic health facilities require well-trained and experienced personnel, able to address all aspects of VCT, including the reduction of the risks of sexual and postnatal transmission of HIV. Rapid test procedures require proper evaluation as experience has been limited in the context of prenatal services. The benefits of VCT of pregnant women on reduction of primary and secondary sexual transmission of HIV are unknown. Family planning services offer an additional opportunity to address VCT, contraception options and prevention of HIV sexual transmission appropriate to HIV infection status.³⁴

Availability of VCT for pregnant women is an important factor limiting the success of programmes for the prevention of HIV vertical transmission. Furthermore, many women present too late for antenatal care to benefit from a complete short course of ARV after proper VCT procedures. Interventions which do not require VCT and could be applied to all women are important alternatives to consider. Although initial results on the use of vaginal disinfection to reduce mother-to-child trans-

mission were inconclusive in Malawi,²² results of this trial and of other similar trials show a reduction in overall maternal and infant morbidity and mortality regardless of HIV infection.^{35,36} There is some evidence that antenatal screening for and treatment of other sexually transmitted diseases, such as syphilis, would have benefits beyond HIV.^{37,38} In addition, correcting vitamin deficits such as vitamin A also has benefits beyond the reduction of mother-to-child transmission.³⁹ An improvement in adverse pregnancy outcomes has been demonstrated very recently in Tanzania for HIV-infected women with multi-vitamin supplementation.⁴⁰ The effect on vertical transmission is still unknown.

Apart from VCT, requirements for antenatal and obstetrical management of HIV-infected women change little as a result of HIV infection. Given the unpredictable nature of many life-threatening complications, the priority remains to ensure access to high quality essential obstetrical services for all pregnant and recently delivered women.⁴¹ Because many women require blood transfusions around the time of delivery and obstetrical procedures are often invasive, safe blood supply and universal precautions are part of basic obstetrical care and should reduce the risk of nosocomial and occupational transmission of HIV.

Paediatric care

Although the overall progression to serious morbidity and mortality in HIV-infected children varies between studies in developing countries,⁴² rapid progression to AIDS and death in the first two years of life is common in observational cohort studies. At least one-third of HIV-infected African children followed prospectively from birth are diagnosed with AIDS before their second birthday and up to half of these die before they are 2 years old. However, interpretation of these findings

is hampered by the use of different clinical case definitions of AIDS and information is still lacking on the natural history in older children due to the limited length of follow up in large prospective studies.

The postal survey conducted in 1997 by the Ghent Group collected data on paediatric HIV infection from 14 studies in 11 developing countries, and demonstrated a wide variation in the course of the disease and also in the management of HIV-infected children. A more detailed report is published elsewhere.⁴³ Specific treatment protocols are not generally available for HIV-infected children, even in clinical referral centres.

Based on this review of available natural history data and current clinical experience in the management of HIV-infected children, clinical research priorities for developing countries were identified.⁴³ Primary prophylaxis of opportunistic and bacterial infections of children born to HIV-infected mothers and/or HIV-infected children is a key issue to address, as current recommendations do not apply to most developing country settings.⁴⁴ Options for the management of persistent diarrhoea in HIV-infected children should be explored. Information is required on the aetiology of pulmonary infections in HIV-infected children, clinical manifestations of AIDS and the main causes of mortality. Early diagnosis of paediatric HIV infection remains difficult and costly,¹³ but such tools are required if programmes of reduction of vertical transmission aim to counsel women on their infants' health; low-cost HIV-detection tests usable with minimal technical capabilities under variable field conditions have to be developed for this purpose. Finally, as a child is frequently the first in a family to be identified with HIV infection, VCT of children and families requires innovative approaches.

Public health recommendations – conclusion

Box 1 summarizes the ten priority recommendations formulated by the Ghent Group for the development, design and implementation of programmes targeting the prevention of HIV vertical transmission in developing countries. Several of

them are based on limited evidence and require further research.

An optimal and country-specific strategy of HIV-specific interventions and strengthening of MCH care needs to be defined. Any specific intervention package to reduce mother-to-child transmission of HIV should be fully integrated in the overall antenatal, obstetrical, and paediatric care, the prime goal of which is to reduce overall maternal and infant morbidity and mortality. Such a package should include maternal tetanus toxoid immunization, STD screening and treatment (at least syphilis), iron and folate supplementation, malaria prophylaxis where appropriate, basic obstetric care and information on HIV prevention, VCT, infant feeding and family planning options. In addition, serious consideration should be given to routine provision of vitamin A supplementation and vaginal disinfection with a generally available antiseptic such as chlorhexidine, considering their potential benefit for maternal and infant morbidity and mortality. As the results of four randomized trials show that a short regimen of ARV can be effective in preventing transmission,⁵⁻⁸ consideration has to be given to its inclusion in antenatal care, beginning in pilot programmes in areas of high HIV prevalence. This has been clearly stated in a statement issued by the UN agencies after a meeting held in Geneva in March 1998.¹⁴ ARV prophylaxis for pregnant women will require the setting up of appropriate VCT services. The introduction of such an integrated strategy for the care of women and children, with specific interventions to prevent HIV transmission, will have to be stepwise in pilot programmes and closely monitored through operational research in wide-scale demonstration projects, including economic evaluations.²⁶

International policies addressing infant feeding options for HIV-infected women have been adapted by WHO, UNICEF and UNAIDS to evolving knowledge, and now support the possibility that an HIV-infected woman informed of her HIV-positive status will choose the safest feeding option.¹⁵ In particular, the policy states 'those HIV-infected women who decide not to breastfeed their children must be ensured access to sufficient quantities of nutritionally adequate breast-milk substitutes they can prepare safely'.¹⁵ It is likely that ARV

Box 1. Public health recommendations formulated by the Ghent International Working Group on Mother-to-Child Transmission of HIV for the development of HIV vertical-transmission intervention programmes in developing countries

1. Define optimal and country-specific strategy of HIV-specific interventions and strengthening of maternal and child health care.
2. The prime goal of this integrated strategy should be to reduce overall maternal and infant morbidity and mortality.
3. A short regimen of antiretroviral therapy (ARVT) and other means of prevention of vertical transmission should be considered now, especially in areas of high HIV prevalence.^a
4. Voluntary HIV counselling and testing of women must be widely available.
5. Implement pilot programmes through a stepwise approach and conduct operational research in demonstration projects.
6. Use and evaluate appropriate policies regarding infant feeding options.^b
7. Further research is needed on postnatal transmission of HIV through breastfeeding^b and other unresolved issues (long-term side effects of ARVT, orphans . . .).
8. No discrimination in the care of HIV-infected pregnant women.
9. Improve standards of care for children born to HIV-infected women and promote their utilization.
10. Preventing vertical transmission implies long-term commitment of donors, governments and health care professionals appropriate to setting and individual family circumstances.

^a UNAIDS, ref. 14

^b UNAIDS, ref. 15

and alternatives to breastfeeding will constitute two key components of the intervention package to reduce vertical transmission in many settings. Further research will thus be needed to assess the possible risk associated with such alternatives to breastfeeding, against current infant morbidity and mortality patterns, the general risk associated with prolonged and inappropriate breastfeeding⁴⁵ and the risk of late postnatal transmission of HIV.¹⁹

The basic MCH needs of HIV-infected pregnant women are similar to those who are uninfected and discrimination should be discouraged. Diagnosis of HIV infection in pregnant women implies a long-term public commitment to a basic package of care adapted to the setting but also to the individual woman, children and family. Standards of care for HIV-infected children need to be improved, especially for primary prophylaxis of opportunistic and bacterial infections, after appropriate research has been performed.⁴³

Although not specifically addressed by the Ghent Group, at least two issues also need research: the follow-up for long-term side effects in children exposed to ARV to prevent vertical transmission but who are proven to be uninfected, at least those included in the ongoing trials; the social and medical needs of orphaned children, both HIV-infected and uninfected.

In conclusion, the prevention of vertical transmission of HIV infection is becoming part of the international and national public health response to the HIV/AIDS pandemic in developing countries. Programme implementation could ultimately result in a slowing down of the HIV paediatric pandemic, especially in African countries with the highest HIV prevalence figures. A comprehensive approach to reduce vertically acquired HIV infection offers an opportunity to boost basic health and MCH services and to reduce maternal and child morbidity and mortality in many developing countries.

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Appendix

The 1997 Ghent International Working Group on Mother-to-Child Transmission of HIV included (*indicates participation in the meeting where recommendations were formulated):

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