# Methodology of intervention trials to reduce mother to child transmission of HIV with special reference to developing countries

François Dabis*, Philippe Msellati*†, Marie-Louise Newell‡, Neal Halsey§, Philippe Van de Perre**, Catherine Peckham‡, Philippe Lepage†† and the International Working Group on Mother To Child Transmission of HIV

AIDS 1995, 9 (suppl A):S67–S74

**Keywords: HIV, children, mother to child transmission, intervention, clinical trial, methodology.**

## Introduction

Many researchers have worked on observational studies on mother to child transmission of HIV infection throughout the world since the mid-1980s [1]. Among the practical problems faced in these studies were difficulties with the definitions used to calculate the rate of transmission of HIV from mother to child [2]. In 1992, a workshop was held in Ghent, Belgium, to address methodological issues in estimating these rates and a standardized methodology was proposed [3].

There is increasing pressure to start trials to evaluate methods aimed at reducing mother to child transmission of HIV infection in developing countries, particularly since the recent publication of the results of the first zidovudine trial carried out in the United States and France [4,5]. In order to avoid methodological problems

From *Unité INSERM 330, Université de Bordeaux II, Bordeaux, France, †ORSTOM Petit Bassam, Abidjan, Côte d'Ivoire, ‡Institute of Child Health, London, UK, §Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland, USA, **Ministry of Cooperation in Development, Brussels, Belgium, and ††Hôpital Ambroise Paré, Mons, Belgium.

In 1993 and 1994, the International Working Group on Mother To Child Transmission of HIV consisted of the following. Scientific Secretariat: François Dabis (France), Lieve Fransen (Commission of European Communities), Neal Halsey (USA), Joep Lange (WHO Global Programme on AIDS), Philippe Lepage (Belgium), Philippe Msellati (Côte d'Ivoire), Marie-Louise Newell (UK), Benjamin Nkowane (WHO Global Programme on AIDS), Catherine Peckham (UK) and Philippe Van de Perre (Rwanda); Investigators: Jim Balsley (USA), Anatolie Bazubagira (Rwanda) [deceased], Gunnel Biberfeld (Sweden), Stéphane Blanche (France), Marc Bulterys (USA), John Chiphangwi (Malawi), Tawee Chotpitayasunondh (Thailand), Homer Davis (Haiti), Kevin De Cock (UK), Jean-François Delfraissy (France), Abel Dushimimana (Rwanda), Ehounou Ekpini (Côte d'Ivoire), Joanne Embree (Canada), Antoine Fadoul (Haiti), Carlo Giaquinto (Italy), Glenda Gray (South Africa), Laura Guay (Uganda), Etienne Karita (Rwanda), Christian Kind (Switzerland), Marc Lallemant (Congo), Sophie Lallemant-Le Coeur (Congo), Valériane Leroy (France), James McIntyre (South Africa), Laurent Mandelbrot (France), Marie-Jeanne Mayaux (France), Nicolas Meda (Burkina Faso), Paolo Miotti (Malawi), Francis Mmiro (Uganda), Clemensia Nakabiito (Uganda), Ruth Nduati (Kenya), Anuvat Roongpisuthipong (Thailand), Paolo Rossi (Italy), Christine Rouzioux (France), Andrea Ruff (USA), Michael Saint-Louis (Zaïre), Roger Salamon (France), Nathan Shaffer (Thailand), Mauro Schechter (Brazil), Robert J. Simonds (USA), Marleen Temmerman (Kenya), Christiane Welffens-Ekra (Côte d'Ivoire) and Stephan Wiktor (Côte d'Ivoire); Statisticians: Daniel Commenges and Rachid Salmi (INSERM U 330, Bordeaux, France), David Dunn (Institute of Child Health, London, UK).

The following persons also participated in the 1993 or 1994 meetings in Ghent, Belgium: Joan Casanova (European Community AIDS Task Force), Eric Chevallier (France), Claude Desgranges (France), Katrien Fransen (Belgium), Catherine Hankins (Canada), Paul Jansegers (European Community AIDS Task Force), Normand Lapointe (Canada), Steve Lwanga (WHO), Anne-Marie Moulin (France), Daan Mulder (Uganda), Phil Nieburg (USA), Jorge Nieto (European Community AIDS Task Force), Michel Pletschette (Commission of European Communities), Joseph Saba (WHO), Abdourahmane Sow (WHO), Anna-Maria Stevens (Belgium), Cladd Stevens (USA) and Paul Stoffels (Belgium).

Sponsorship: This work was sponsored by the European Community AIDS Task Force and the Global Programme on AIDS of the World Health Organization.

Requests for reprints to: Prof. François Dabis, Unité INSERM 330, Université de Bordeaux II, 146 rue Léo-Saignat, 33076 Bordeaux Cedex, France.

such as those faced when comparing transmission rates from different observational studies, it is important to consider the comparability of the design, implementation, analysis and reporting of results of intervention trials.

Two workshops on these methodological issues were held in Ghent in September 3–5 1993 and December 2–4 1994 under the auspices of the European Community AIDS Task Force, in collaboration with the Global Programme on AIDS of the World Health Organization (WHO). The objectives were (1) to compare the rates and factors associated with transmission drawn from available cohort studies using the Ghent 1992 methodology; (2) to discuss various interventions that aim to reduce mother to child transmission of HIV infection; (3) to discuss methodological issues in the design and conduct of intervention trials; and (4) to provide guidelines for groups that might consider conducting these trials, particularly in developing countries.

## Methods

Twenty-two teams of investigators were asked to estimate rates of mother to child transmission of HIV infection using the Ghent 1992 methodology. In brief, this methodology consisted of a system of classifying children born to HIV-1-infected mothers according to the child's probable HIV infection status during the first 15 months of life [3]. The transmission rate can be calculated directly by applying this classification to cohorts of children born to HIV-seropositive mothers when sufficient follow-up data have been obtained to determine the child's infection status. The HIV transmission rate can also be calculated indirectly according to the persistence of antibodies in a cohort of 15-month-old children born to HIV-seropositive mothers, together with an estimate of HIV-associated mortality [3].

The International Working Group compared estimates of mother to child rates of transmission of HIV infection calculated using the Ghent 1992 methodology, and reviewed the factors associated with transmission. Consensus definitions of paediatric HIV infection for use as endpoints in future intervention trials were developed. Potential interventions for reducing mother to child HIV transmission in the context of developing countries were discussed. Recommendations were made for the design and conduct of trials, in particular for the formulation of hypotheses and objectives, sample size calculation, multicentre design, definition of target population, inclusion and exclusion criteria, use of placebo, follow-up, definition of endpoints, statistical analysis, data and safety monitoring board, ethical issues and the possible impact of trial results on public health policy.

## Comparison of estimates of mother to child transmission rates of HIV-1 and assessment of factors associated with transmission

### Rates of vertical transmission

Data from 13 observational studies have been presented elsewhere [6]. Overall, most studies from Africa and Haiti have reported vertical HIV transmission rates of 25–30%, regardless of the method of calculation. Preliminary results from Thailand are in accord with these figures [7].

Late seroconversion due to postnatal transmission of HIV has been reported, probably related to breast-feeding [8–11]. This phenomenon needs further investigation, possibly through an international registry, but is a potential problem for the interpretation of results of vertical transmission studies. The following definition was proposed. A child born to an HIV-positive woman is a late seroconverter if he/she has been antibody-negative at any time between nine and 15 months of age only to become antibody-positive again at 15 months of age or older. If these cases are frequent and such children are classified as infected, estimates of vertical transmission rates become unusually high with the direct method.

### Factors associated with transmission

Advanced maternal HIV disease and its markers, including a low CD4+ lymphocyte count, are the most consistent factors so far identified in mother to child HIV transmission [1,12,13]. Transmission through breast-feeding is now beyond doubt [14] but standardization between studies is needed.

Factors to be considered in the design of intervention trials include maternal age, syphilis, p24 antigenaemia, viral load, CD4+ lymphocyte count, clinical AIDS, gestational age, mode of delivery [15], length and complications of labour, therapy before, during pregnancy and around the time of delivery and mode of breast-feeding. Factors useful for a better understanding of mother to child transmission of HIV include chorioamnionitis [16], viral characteristics, pregnancy complications, sexual partners during pregnancy and primary HIV infection during pregnancy. For these latter factors, further research is needed.

## Timing of transmission: early diagnosis and definition of paediatric HIV infection

### Early diagnosis of HIV infection in infants

The early diagnosis of HIV infection in infants is usually based on viral culture, polymerase chain reaction, detection of anti-HIV immunoglobulin (Ig)A (after elimination of specific IgG), detection of p24 antigen (after dissociation of immune complexes) and *in vitro* production

of anti-HIV antibodies [17]. After anti-HIV IgG, polymerase chain reaction DNA is by far the most widely used diagnostic test in studies carried out in developing countries [7,18,19].

The sensitivity of the polymerase chain reaction technique has been estimated at 30–50% during the first week of life, 70–90% at 1–2 months of age and >95% after 3 months of age; it may be even higher than this in non-breast-feeding populations [17]. However, the techniques used are not standardized, there is no common quality control programme, few results are available from prospective cohort studies in developing countries and the detection rates in the neonatal period are low, either because the sensitivity of the method is low or because of intrapartum and/or early postnatal transmission. The value of cord blood specimens remains questionable at the present time. Capillary blood samples collected and stored on filter paper may be particularly useful in studies in developing countries.

It is important to include viral culture assessments at various follow-up points in intervention trials whenever possible. Data on IgA have also been published [20], but this technique is likely to be helpful only at 6 months of age or over because of its low sensitivity before this age. Detection of p24 antigenaemia is helped by acid dissociation or heat denaturation. With the latter modification, the sensitivity of this technique may equal that of polymerase chain reaction [21], but its use for samples collected during the neonatal period needs to be assessed on a large scale in developing countries. More generally, a quality control programme of early diagnostic techniques should be implemented in the context of cohort studies and intervention trials on mother to child HIV transmission in developing countries.

## Definitions of paediatric HIV infection

Early case definitions need to be developed for both uninfected and infected children born to HIV-seropositive mothers, in relation to the timing of transmission. It is not clear at present exactly when vertical HIV transmission occurs between conception and delivery or through breast-feeding [1]. Transmission at a given point of time is not necessarily related to a single mechanism.

The relative importance of the different times of transmission is difficult to address, but increasing indirect evidence suggests the predominance of late transmission. The French Collaborative Study Group estimated that in a non-breast-fed population, 35% of the infants are infected late *in utero* and the remaining 65% during delivery [22]. In an exclusively breast-fed cohort in Kigali, Rwanda, the polymerase chain reaction positive rate was 30% on cord blood and 81% at 3 months. Thus, in these African children born to HIV-1-infected mothers, the estimated transmission rate in the late postnatal period is 5%, and in the intrapartum plus postnatal periods, 18% [18]. Understanding the timing of transmission is particularly important for the design of intervention trials and deserves further investigation.

While the Ghent 1992 classification of HIV infection used to calculate the rate of transmission by the direct method is not suitable for studying the timing of transmission, it does provide a reliable estimate of the overall rate of transmission up to the age of 15–18 months and it should be used for comparisons between groups and studies. Detailed reporting of losses to follow-up and death is necessary for a valid estimate. A working hypothesis of the relative importance of each period of transmission has been proposed by the Pediatric Virology Committee of the AIDS Clinical Trials Group for non-breast-fed populations [23]. However, it is difficult to measure intra-uterine transmission in breast-fed children. *In utero* and intrapartum transmission are also difficult to differentiate with current methods.

According to the general definition of vertically acquired HIV infection proposed by the International Working Group in 1993, a child born to a mother known to be HIV-infected is considered to be infected if (1) HIV IgG antibodies persist beyond 15 months of age; (2) at any age, AIDS is diagnosed or the child dies of HIV-related death; or (3) at any age, a positive viral culture or polymerase chain reaction is obtained for the first time and at least one subsequent sample is also positive.

Polymerase chain reaction and viral culture are considered to be the standard techniques for early case definitions. These methods should be applied to three consecutive samples collected between birth and 6 months of age, yielding 27 possible combinations of results. Table 1 shows the consensus reached by the Working Group on the HIV infection status of the child for each of these combinations.

Two levels of definition of early paediatric HIV infection, confirmed and probable, are generally considered. In practice, in developing countries, the second and third samples for polymerase chain reaction testing are usually collected at the time diptheria–tetanus–pertussis vaccine is given: 45 days for the first dose and 105 days for the third one. Additional samples should also be collected for polymerase chain reaction testing during any hospitalization in the first 6 months of life. This schedule allows the following Ghent 1993 early case definitions applied on three consecutive blood samples: (1) *in utero* transmission if the first positive result is obtained within 1 or 2 days of life (a cord blood sample provides no interpretable information); (2) *in utero* plus intrapartum transmission if the first positive result is obtained between 30 and 60 days of life; (3) intrapartum plus early postnatal transmission if the first positive result is obtained between 90 and 180 days of life. The Ghent 1993 early case definitions are not an alternative to the Ghent 1992 definitions for children aged 15 or 18 months but are complementary methods for measuring endpoints in intervention trials.

Other pieces of information may also be useful for an early diagnosis (Table 1). These techniques include p24 antigenaemia (at ≥3 months of age), anti-HIV IgA (at ≥6 months of age) or polymerase chain reaction RNA. If the only two positive results are obtained from the same

**Table 1.** HIV infection status according to virology results from polymerase chain reaction (PCR), viral culture and p24 antigen measured in blood specimens at birth and after 6 weeks and 3 months of life in children born to HIV-seropositive mothers. At any age, clinical AIDS or HIV-related death is taken as an indication that a child is infected. From the International Working Group on Mother to Child Transmission of HIV, Ghent, Belgium, 1993–1994.

| Birth sample (1–2 days), no cord blood sample | 6-week sample, PCR (30–60 days) | 3-month sample, PCR (90–180 days) | HIV status at 3 months by PCR | 3-month sample, p24 antigen | HIV status at 3 months by PCR and p24 antigen |
|---|---|---|---|---|---|
| + | + | + | Infected, confirmed | | |
| + | + | – | Infected, probable | Positive | Infected, confirmed |
| | | | | Negative | Infected, probable |
| + | + | NA | Infected, confirmed | | |
| + | – | + | Infected, confirmed | | |
| + | – | – | Uninfected, probable | Positive | Wait |
| | | | | Negative | Uninfected, confirmed |
| + | – | NA | Indeterminate | | Wait |
| + | NA | + | Infected, confirmed | | |
| + | NA | – | Indeterminate | | Wait |
| + | NA | NA | Indeterminate | | Wait |
| – | + | + | Infected, confirmed | | |
| – | + | – | Indeterminate | | Wait |
| – | + | NA | Indeterminate | | Wait |
| – | – | + | Infected, probable | Positive | Infected, confirmed* |
| | | | | Negative | Wait |
| – | – | – | Uninfected, confirmed | | |
| – | – | NA | Indeterminate | | Wait |
| – | NA | + | Infected, probable | Positive | Infected, confirmed* |
| | | | | Negative | Wait |
| – | NA | – | Uninfected, confirmed | | |
| – | NA | NA | Indeterminate | | Wait |
| NA | + | + | Infected, confirmed | | |
| NA | + | – | Indeterminate | | Wait |
| NA | + | NA | Indeterminate | | Wait |
| NA | – | + | Infected, probable | Positive | Infected, confirmed* |
| | | | | Negative | Wait |
| NA | – | – | Uninfected, confirmed | | |
| NA | – | NA | Indeterminate | | Wait |
| NA | NA | + | Infected, probable | Positive | Infected, confirmed* |
| | | | | Negative | Wait |
| NA | NA | – | Uninfected, probable | Positive | Wait |
| | | | | Negative | Uninfected, confirmed* |
| NA | NA | NA | Indeterminate | | Wait |

NA, not available. Cutoff point for p24 antigen not yet defined. Wait refers to PCR and/or p24 antigen and/or immunoglobulin A results at 6 months. *Another sample from the same child needed to exclude the possibility of labelling errors.

sample with two different techniques, another sample from the same child might be needed to exclude the possibility of labelling errors (Table 1). Clinical criteria such as clinical AIDS and HIV-related deaths can also be used as additional criteria at any point in time, using the Ghent 1992 methodology [3].

Early case definitions should be developed *a priori* in intervention trials. They should be intervention-specific in order to take account of the mechanism(s) of transmission amenable to a given intervention and the possible effect of the intervention itself on the timing of the acquisition of paediatric HIV infection. The timing of the transmission can be modified by an intervention, for example, antiretroviral drugs or passive immunization can delay the transmission. Thus, the sensitivity of the tests used can also be modified, and late samples collected between 6 and 15 months of age are necessary; these should be tested with the same laboratory techniques as those used in the early case definitions.

## Potential interventions to reduce mother to child transmission of HIV in developing countries

In 1992–1994, interventions to reduce mother to child HIV transmission were specifically discussed at several international meetings and reviews were published [24–26]. These interventions must take the timing of transmission into account, i.e. *in utero*, intrapartum or postnatal, but other considerations such as availability, cost, public health relevance, advantages and disadvantages of each method may be important too. Limiting factors in the assessment of the effectiveness of interven-

tions to reduce vertical HIV transmission include (1) the results of the first zidovudine trial [4], a reference for future trials, (2) the limited numbers of HIV-infected women in industrialized countries and (3) the worldwide scarcity of funds and facilities. There is therefore a need to set priorities and a great need for coordination of trials in this field.

The following interventions to reduce mother to child HIV transmission have been proposed: alternatives to breast-feeding, caesarean section delivery, vaginal disinfection, antiretroviral drugs including zidovudine and non-nucleoside reverse transcriptase inhibitors such as nevirapine, immunological interventions, either passive immunoprophylaxis or active immunization, and combinations of interventions. Table 2 summarizes the trials to be carried out in developing countries and discussed during the 1993 and 1994 Ghent workshops.

**Table 2.** Intervention trials to reduce mother to child transmission of HIV in developing countries as at December 1994.

| Type of intervention | Country |
|---|---|
| Alternative to breast-feeding | Kenya (trial under way)<br>South Africa (trial under way) |
| Caesarean section | No plan (European trials may include some selected centres in developing countries) |
| Vaginal disinfection | Burkina Faso and Côte d'Ivoire (tolerance study of benzalkonium chloride under way)<br>Kenya (trial of chlorhexidine planned)<br>Malawi (trial of chlorhexidine under way)<br>South Africa (tolerance study of chlorhexidine and povidone iodine planned) |
| Antiretroviral drug (zidovudine) | Burkina Faso and Côte d'Ivoire (tolerance study under way)<br>Côte d'Ivoire (trial planned)<br>Haiti (trial planned)<br>South Africa, Tanzania and Uganda (multicentre trial planned*)<br>Thailand (trials planned)<br>Brazil (considered*) |
| Passive immunoprophylaxis | Haiti (trial planned)<br>Uganda (trial under way) |
| Active immunization | No plan |
| Vitamin A supplements | Malawi, South Africa and Tanzania (considered) |
| Combination of interventions | No plan |

*Other antiretrovirals apart from zidovudine are also considered but none are yet available for inclusion in trials of this kind.

The first phase III, randomized, placebo-controlled trial of zidovudine with a three-step intervention in previously untreated women has shown an important reduction in the rate of transmission, from 25.5 to 8.3% [4] and recommendations have been issued for the use of zidovudine in pregnant women in some industrialized countries [27,28]. The usefulness of this drug in developing countries is not yet clear [5,29,30] but several trials are already planned (Table 2), generally with simplified, shorter and standardized regimens of administration, as recommended by WHO [31]. There is also a need for more information on the effect of zidovudine on the maternal viral load.

A strategy of combination of interventions, such as vaginal disinfection and non-nucleoside reverse transcriptase inhibitors or passive and active immunization, based on the hepatitis B model [32], can be justified, since the accessible populations are limited and the interventions could have additive or synergistic actions. However, trials to evaluate these combinations will be statistically complex and none have so far been proposed. Other interventions such as vitamin A supplementation may also be evaluated for developing countries [33], based on recent results from observational studies [34].

## Guidelines for intervention trials to reduce mother to child transmission of HIV infection

When attempting to evaluate an intervention to reduce mother to child transmission of HIV infection in a given population, the following criteria should be discussed [24]: the rationale of the intervention (putative mechanism of action), the potential advantages and disadvantages, particularly in terms of safety, availability, the cost of the trial and the public health strategy of implementation if the intervention proves effective. Several problems are expected in the choice of intervention and in the design, conduct and interpretation of trial results in developing countries. In particular, (1) many interventions will be evaluated in breast-fed populations; (2) interventions that have to be applied early in pregnancy are unlikely to be realistic in most populations; and (3) collaboration is needed to make the best use of limited cohorts.

Before implementing a preventive intervention in a population, the following questions should be answered: What is its efficacy? What is its toxicity? What are the optimal conditions for use? What does it cost? Phase III studies in the classical comparative trial design [35] allow measurements of efficacy. Indeed, to generate substantial valid evidence, with adequate and well controlled investigation, a comparative study is needed. The fundamental principle involved in a comparison of treatment groups in a clinical trial is that groups must be alike in all important aspects and only differ in the treatment that each group receives. This is the main reason for random allocation to groups, which is the most statistically powerful way of achieving comparability.

## Explanatory and pragmatic approaches in clinical trials

Many trials lead either to no conclusion or to conclusions which are not followed by action. There are

several reasons for this, but the main one is usually an inadequately formulated primary problem with confusion between two types of objective: either to increase knowledge or to promote action, i.e. evaluating either the activity of a treatment or the efficacy of a policy. Thus, the sentence 'comparison of two treatments A and B' is ambiguous and can be taken to indicate either a scientific inquiry, the explanatory approach, or to a decision-making process, the pragmatic approach (Table 3) [36]. Evaluating the efficacy of a new antiretroviral drug to reduce mother to child transmission of HIV infection is clearly a scientific question that requires a design close to a laboratory experiment in a selected population. In contrast, answering the question of whether vaginal disinfection should be recommended in developing countries requires a different approach, in which the representativeness of the study groups is of paramount importance, and judgement criteria other than the transmission rate, such as the clinical and biological tolerance, are also important in order to evaluate the cost: benefit ratio of this intervention. Intention-to-treat analysis, a method that ignores treatment modifications, is generally recommended from a methodological standpoint and is the natural approach for a pragmatic trial. For an explanatory trial, it is essential to minimize loss to follow-up and improve compliance [37].

**Table 3.** Possible approaches in clinical trials to evaluate interventions that aim to reduce mother to child transmission of HIV.

| Approach | Explanatory | Pragmatic |
|---|---|---|
| Treatments | Equal conditions | Optimum conditions |
| Criteria | One (or few) | Many (efficiency, cost, etc.) |
| Comparison | Statistical testing | Decision-making |
| Patients | Selected group | Representative sample |

## Sample size and its reduction

The efficacy of an intervention against mother to child HIV transmission is based on a reduction in the transmission rate in the study population. In order to establish a significant difference with confidence, in a trial comparing no intervention versus any intervention, several hundreds of mother/child pairs must be enrolled into a study (Table 4) [38]. Multicentre trials or joint studies in developed and developing countries are needed to achieve this and they are particularly suitable for explanatory trials. Several other advantages accrue from this organization, such as generalizability and credibility of the results. However, the organization of multicentre trials poses logistical problems.

**Table 4.** Power (probability of getting a statistically significant difference) for a two-arm trial comparing no intervention (assumed transmission rate of 30%) against an intervention of varying effectiveness.

| n (each group) | Reduction in mother to child HIV transmission to: 25% | 20% | 15% | 10% | 5% |
|---|---|---|---|---|---|
| 100 | 12 | 38 | 73 | 95 | 99 |
| 200 | 20 | 64 | 95 | 100 | 100 |
| 300 | 28 | 81 | 99 | 100 | 100 |
| 400 | 36 | 91 | 100 | 100 | 100 |
| 500 | 43 | 93 | 100 | 100 | 100 |
| 1000 | 71 | 100 | 100 | 100 | 100 |

*Power against two-tailed significance α type 1 error, 0.05.

## Factorial designs

Combining different types of interventions may be worthwhile, especially if their mode and timing of effect may be complementary. Statistically, the most satisfactory design to evaluate interventions, separately and overall, is the factorial design. However, factorial trials lead to statistical complexity and may require difficult negotiations if several manufacturers are involved.

## Judgement criteria

The main criterion in evaluating the efficacy of an intervention to reduce mother to child transmission of HIV infection remains the overall transmission rate measured when the child is ≥15 months of age, depending how long breast-feeding is continued. However, it is not currently possible to measure accurate and precise rates for each potential transmission period or mechanism of transmission with early case definitions. Thus, the reduction achieved by any intervention at one time may be hidden by increased transmission afterwards as the sample at risk will be increased. It is particularly important to publish any negative trial results, and also results from the long-term follow-up of women and children exposed to interventions to reduce mother to child HIV infection, especially with antiretroviral agents [39].

## Ethical issues

General guidelines, such as those of the Council for International Organizations of Medical Sciences (CIOMS) [40], answer the basic ethical questions that arise in evaluating interventions to reduce mother to child transmission of HIV. Any intervention trial should be relevant to the population where the study takes place. Trials in developing countries should try to strengthen the

national research capacity in shared responsibility with donor agencies. An ethical review within the country, different from a scientific peer review, is necessary to assess the suitability of the trial for a particular population. The cost of the study, the cost of the drug and the cost of the infrastructure needed to deliver the intervention once efficacy has been established are important parameters in the cost–benefit analysis. Results of the trials should be made available to the population.

The most important transcultural problems to be solved in the design and conduct of these trials occur in the following areas: counselling and support of the women enrolled, avoidance of stigmatization, informed consent, particularly for randomization and the use of placebo, confidentiality and incentives to improve compliance without coercion [37]. Double-blind placebo-controlled trials offer the best option for a rapid and scientifically valid assessment of antiretroviral drugs in reducing mother to child transmission of HIV [31].

In all trials, it is necessary to create an independent Data and Safety Monitoring Board. Investigators should hold regular meetings with the funding agencies and particular attention should be paid to avoiding individual conflicts of interest. The steering committee for each intervention trial should include national decision-makers from the country where the trial takes place and representatives of the funding agencies. In any case, a long-term follow-up of women and children should be planned, as for trials in industrialized countries [38].

## Conclusions and perspectives

The Ghent International Working Group formulated international standards for the development, implementation and analysis of intervention trials to reduce mother to child transmission of HIV in developing countries. The optimum intervention for use in developing countries should be simple to apply, require few antenatal visits and little active participation by the pregnant women, be of relatively low cost and, ideally, should not require HIV antibody testing.

The development of guidelines for intervention trials is a continuous process and should cover all aspects of protocols in this field in detail. In these trials, there is a need for a multicentre approach and complementary protocols between teams. International coordination is necessary in order to share the information from ongoing and planned trials. This has implications for organizations like the Global Programme on AIDS (WHO) or the European Communities AIDS Task Force which could make a major contribution to the success of intervention trials in supporting the coordination, the trials themselves and the exchange and distribution of information. Affordable, sustainable and appropriate interventions with proven efficacy are urgently needed to decrease the burden of mother to child HIV transmission in developing countries.

## Acknowledgements

On behalf of the scientific secretariat of the Ghent International Working Group, we thank Geneviève Chene (INSERM U330, Bordeaux), Anne-Marie Moulin (INSERM U158, Paris), Daan Mulder (Medical Research Council, Kampala), Christine Rouzioux (Hôpital Necker, Paris), Roger Salamon (INSERM U330, Bordeaux), Rachid Salmi (INSERM U330, Bordeaux) and Cladd Stevens (New York Blood Center, New York City) for help in the preparation of the manuscript. In addition, we thank Mrs D. Dellicour (Commission of European Communities, Brussels) and Dr David Heymann (WHO Global Programme on AIDS, Geneva) for encouragement and support. Finally, we thank Maryke Bontinck (EC AIDS Task Force, Brussels), Marna Baccarani and Marie-Pierre Martin (INSERM U330, Bordeaux), Evelyne Bloch-Mouillet (Université de Bordeaux II), Valérie Bottero and Dominique Nicolini (ARMA, Bordeaux) for secretarial help in the organization of the Ghent workshops.

## References

1. Mofenson L: **Epidemiology and determinants of vertical HIV transmission.** *Semin Pediatr Infect Dis* 1994, 5:252–265.
2. Ryder R, Behets F: **Reasons for the wide variation in reported rates of mother-to-child transmission of HIV-1 [editorial].** *AIDS* 1994, 8:1495–1497.
3. Dabis F, Msellati P, Dunn D, *et al.*: **Estimating the rate of mother-to-child transmission of HIV. Report of a workshop on methodological issues, Ghent (Belgium), 17–20 February 1992.** *AIDS* 1993, 7:1139–1148.
4. Connor E, Sperling R, Gelber R, *et al.*: **Reduction of maternal–infant transmission of human immunodeficiency virus type 1 with zidovudine therapy.** *N Engl J Med* 1994, 331:1173–1180.
5. Rogers M, Jaffe H: **Reducing the risk of maternal–infant transmission of HIV: a door is opened [editorial].** *N Engl J Med* 1994, 33:1222–1223.
6. The Working Group on Mother-To-Child Transmission of HIV: **Rates of mother-to-child transmission of HIV-1 in Africa, America and Europe: results from 13 perinatal studies.** *J Acquir Immune Defic Syndr* 1995, 8:506–510.
7. Chotpitayasunondh T, Chearskul S, Siriwasin W, Roongpisuthipong A, Young N, Shaffer N: **HIV-1 vertical transmission in Bangkok, Thailand.** *X International Conference on AIDS/V STD World Congress.* Yokohama, August 1994 [abstract 221C].
8. Lepage P, Van de Perre P, Simonon A, Msellati P, Hitimana D, Dabis F: **Transient seroreversion in children born to HIV-1 infected mothers.** *Pediatr Infect Dis J* 1992, 11:892–894.
9. Datta P, Embree J, Kreiss J: **Resumption of breast-feeding in later childhood: a risk factor for mother to child human immunodeficiency virus type 1 transmission.** *Pediatr Infect Dis J* 1992, 11:974–976.
10. Ekpini E, Wiktor SZ, Sibailly T, *et al.*: **Late postnatal mother-to-child HIV transmission in Abidjan, Côte d'Ivoire.** *X International Conference on AIDS/V STD World Congress.* Yokohama, August 1994 [abstract 218C].
11. Bulterys M, Chao A, Dushimimana A, Saah A: **HIV-1 seroconversion after 20 months of age in a cohort of breastfed children born to HIV-1 infected women in Rwanda.** *AIDS* 1995, 9:93–94.
12. Consensus Workshop: **Report of a Consensus Workshop, Siena, Italy, January 17–18, 1992: maternal factors involved in mother-to-child transmission of HIV-1.** *J Acquir Immune Defic Syndr* 1992, 5:1019–1029.

13. Newell M, Peckham C: **Risk factors for vertical transmission of HIV-1 and early markers.** *AIDS* 1993, **7** (suppl 1):S91–S97.
14. Dunn D, Newell M, Ades A, Peckham C. **Risk of human immunodeficiency virus type 1 transmission through breastfeeding.** *Lancet* 1992, **340**:585–588.
15. Dunn D, Newell M, Mayaux M, *et al.*: **Mode of delivery and vertical transmission of HIV-1: a review of prospective studies.** *J Acquir Immune Defic Syndr* 1994, **7**:1064–1066.
16. Saint-Louis M, Kamenga M, Brown C, *et al.*: **Risk for perinatal HIV-1 transmission according to maternal immunologic, virologic, and placental factors.** *JAMA* 1993, **269**:2853–2859.
17. Consensus Workshop: **Report of a Consensus Workshop, Siena, Italy, January 17–18, 1992: early diagnosis of HIV infection in infants.** *J Acquir Immune Defic Syndr* 1992, **5**:1169–1178.
18. Simonon A, Lepage P, Karita E, *et al.*: **An assessment of the timing of mother-to-child transmission of human immunodeficiency virus type 1 by means of polymerase chain reaction.** *J Acquir Immune Defic Syndr* 1994, **7**:952–957.
19. Paterlini P, Lallemant-LeCoeur S, Lallemant M, *et al.*: **Polymerase chain reaction for studies of mother-to-child transmission of HIV-1 in Africa.** *J Med Virol* 1990; **30**:53–57.
20. Quinn T, Kline R, Halsey N, *et al.*: **Early diagnosis of perinatal HIV infection by detection of viral-specific IgA antibodies.** *JAMA* 1991, **266**:3439–3442.
21. Schüpbach J, Böni J, Tomasik Z, *et al.*: **Sensitive detection and early prognostic significance of p24 antigen in heat-denatured plasma of human immunodeficiency virus type 1 infected infants.** *J Infect Dis* 1994, **170**:318–324.
22. Rouzioux C, Costagliola D, Burgard M, *et al.*: **Timing of mother-to-child HIV-1 transmission depends on maternal status.** *AIDS* 1993, **7** (suppl 2):S49–S52.
23. Bryson Y, Luzuriaga K, Sullivan J, Wara D: **Proposed definitions for *in utero* versus intra-partum transmission of HIV-1 [letter].** *N Engl J Med* 1992, **327**:1246–1247.
24. Consensus Workshop: **Report of a Consensus Workshop, Siena, Italy, June 3-5, 1993: strategies for prevention of perinatal transmission of HIV infection.** *J Acquir Immune Defic Syndr* 1995, **8**:161–178.
25. Van de Perre P, Meda N: **Interventions to reduce perinatal transmission of HIV.** *AIDS* 1995, **9** (suppl A):S59–S66.
26. Minkoff H, Mofenson LM: **The role of obstetric interventions in the prevention of pediatric human immunodeficiency virus infection.** *Am J Obstet Gynecol* 1994, **171**:1167–1175.
27. Centers for Disease Control and Prevention: **Recommendations of the U.S. Public Health Service Task Force on the use of zidovudine to reduce perinatal transmission of human immunodeficiency virus.** *MMWR* 1994, **43** (RR-11):1–20.
28. Anonymous: **Zidovudine for mother, fetus and child: hope or poison [editorial]?** *Lancet* 1994, **344**:207–209.
29. Lallemant M, Le Coeur S, Tarantola D, Mann J, Essex M: **Antiretroviral prevention of HIV perinatal transmission [letter].** *Lancet* 1994, **343**:1429–1430.
30. Dabis F, Mandelbrot L, Msellati P, Van de Perre P: **Zidovudine to decrease mother-to-child transmission of HIV-1: is it good for developing countries [letter]?** *AIDS* 1995, **9**:204–206.
31. World Health Organization Global Programme on AIDS: *Recommendations from the meeting on prevention of mother-to-infant transmission of HIV by use of antiretrovirals.* Geneva: WHO; 1994.
32. Centers for Disease Control and Prevention: **Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP).** *MMWR* 1991, **40** (RR-13):1–25.
33. Bridford K, Willoughby A: **Vitamin A and mother-to-child HIV-1 transmission [editorial].** *Lancet* 1994, **343**:1585–1586.
34. Semba R, Miotti P, Chiphangwi J, Saah A, Canner J, Dallabetta G: **Maternal vitamin A deficiency and mother-to-child transmission of HIV-1.** *Lancet* 1994, **343**:1593–1597.
35. Pocock S: *Clinical Trials: A Practical Approach.* New York: John Wiley; 1983.
36. Schwartz D, Lellouch J: **Explanatory and pragmatic attitudes in therapeutic trials.** *J Chronic Dis* 1967, **20**:637–648.
37. Besch CL: **Compliance in clinical trials.** *AIDS* 1995, **9**:1–10.
38. Dunn D: **Statistical considerations in intervention studies.** In *International Seminar Series: Measures to Decrease the Risk of Mother-to-child Transmission of HIV Infection.* Edited by Peckham C. London: Colwood House Medical Publications; 1993:14–18.
39. Centers for Disease Control and Prevention: **Birth outcomes following zidovudine therapy in pregnant women.** *MMWR* 1994, **43**:409–416.
40. Council for International Organizations of Medical Sciences: *International Guidelines for Ethical Review of Epidemiological Studies.* Geneva: CIOMS; 1991.