Consensus statement

Science, ethics, and the future of research into maternal infant transmission of HIV-1

*Perinatal HIV Intervention Research in Developing Countries Workshop Participants**

Effective, feasible interventions to prevent perinatal transmission of HIV-1 in developing nations are an urgent necessity. Scientific issues of concern include a need to identify other effective antiretroviral agents; to define the shortest effective course of therapy; to assess interventions other than antiretroviral agents; and to investigate interventions that may reduce HIV-1 transmission via breastfeeding. Sound scientific design is fundamental to all research studies. Ethical standards must guide such studies and include the necessity that the problem studied be a health priority in the host country; that the highest standard of care attainable in the country be assured to participants; that the health-care resources of the country not be harmed; that the informed consent of participants be obtained; and that a process of discussion ensure that a successful intervention will be considered for implementation. There are circumstances in which a no-antiretroviral comparison may be ethically justified.

Introduction

The Elizabeth Glaser Pediatric AIDS Foundation and the Emory/Atlanta Center for AIDS Research convened a workshop entitled *Perinatal HIV Intervention Research in Developing Countries: Public Health, Science, and Ethics* on June 9–10, 1998, at the Rollins School of Public Health at Emory University, USA, in response to controversy over perinatal interventions. We, the workshop participants, committed ourselves individually to encouraging ethical research on reducing perinatal HIV-1 transmission that is tailored to the specific needs of specific communities, and that is fully responsive to the economic, medical, and social context of those communities. Effective and affordable interventions to prevent perinatal transmission in developing nations are an urgent necessity because these nations sustain the vast majority of all paediatric HIV-1 infections. In the USA, there have been more than 8000 reported cases of paediatric AIDS[1] and more than 15 000 estimated paediatric HIV-1 infections.[2] However, WHO estimates that there are roughly 1600 children infected with HIV-1 every day or about 600 000 new infections annually in children throughout the world, 90% of which occur in developing countries.[3]

There was a 43% decrease in reported paediatric AIDS cases in the USA from 1992 to 1996,[4] probably owing to the establishment of a standard of care in the USA that stresses HIV-1 counselling and testing for all pregnant women, the provision of a regimen of zidovudine (ZDV) for HIV-1-infected pregnant women,[5] and careful obstetrical management. In addition, fewer HIV-1-positive women are giving birth in some areas. The three-part ZDV prophylaxis regimen (named for the Pediatric AIDS Clinical Trials Group [PACTG] 076 study, which established its efficacy) includes oral ZDV started after 14 weeks' gestation, intravenous ZDV during labour and delivery, and ZDV syrup for the infant for 6 weeks after delivery.[6] ZDV decreased HIV-1 RNA concentrations by only 0·2 log in the PACTG 076 study. Nevertheless, the 076 ZDV regimen diminished transmission by 68% in the PACTG 076 study, and decreased rates to less than 5–8% among women and infants in multiple observational studies[7–9] and in a secondary randomised trial.[10] Furthermore, the results of a trial[11] in Thailand announced in February, 1998, showed that a short course of ZDV, administered orally for the last 4 weeks of gestation and orally during labour and delivery, diminished HIV-1 transmission by 51% to infants who were not breastfeeding. The cost of ZDV is far less than the three-part PACTG 076 regiman, and the two-part regimen is simpler to administer. The costs of counselling and testing are still incurred, since the drug is only given to pregnant women known to be infected with HIV-1. Neither of these regimens seems to have any serious short-term side-effects on the women or their infants in follow-up for as long as 6 years.[12] The long-term effects are unknown and under study.

Need for research

The success that the 076 and Thai ZDV regimens have shown in limiting perinatal HIV-1 transmission means that all countries are encouraged to review these available proven interventions and to make every effort to implement them. Although the Thai regimen provides an affordable, feasible intervention for some developing countries, participants at this workshop were concerned that numerous factors inhibit the adoption of this regimen in other developing nations. First, although the cost of the Thai regimen is only a fraction of the cost of the 076 regimen, it is still five to 20 times more than the total annual health-care expenditure per capita in many developing countries.[13] Second, both regimens presuppose that a pregnant woman's HIV-1 status is known during pregnancy. The logistics and social ramifications of counselling and testing women for HIV-1 are formidable, and the costs are frequently prohibitive in developing nations. Prenatal HIV-1 counselling and testing programmes are currently limited in scope and availability, and are not likely to be implemented in the near future in many settings. Third, both regimens involve the assumption that a woman is in prenatal care

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for at least a few weeks before delivery, whereas, in may instances, pregnant women in developing countries may not present for care until late in pregnancy or during labour. Fourth, both regimens presuppose that labour and delivery are occurring in a medical setting where the proper ZDV regimen can be administered and monitored. In many developing nations, deliveries in the absence of trained health-care professionals are frequent. Finally, the effect of the Thai or similar regimens in a breastfeeding population is unknown at present. Data on the efficacy of the short-course regimen in a breastfeeding population will be available in the near future from studies on the Ivory Coast. The acknowledged importance of breastfeeding for the health of children has led WHO/UNAIDS United Nations Children's Fund to recommend that women continue to breastfeed in situations where they lack ensured, uninterrupted access to nutritionally adequate breastmilk substitutes that are safely prepared, despite the risk of HIV-1 transmission from an infected mother.[14]

In acknowledgment of these current realities, an optimally implementable intervention for the prevention of HIV-1 infection from mother to infant in developing nations would need to be extremely inexpensive to administer; would need to be applicable to all pregnant women, or just to their infants; would not require the presence of trained medical staff or advanced medical technology to administer; and would be implemented during or after labour and delivery, and then only in a single or a limited number of doses. Once available, these promising and more practical interventions should be rapidly assessed in developing nations. Whatever interventions are developed or chosen, the need will remain to decrease or eliminate transmission by breastfeeding.

Scientific questions

We agreed that eliminating the substantial gap between the practical requirements for implementation of the only two regimens proven to diminish HIV-1 perinatal transmission and the economic, medical, and social realities of developing nations must occur if perinatal HIV-1 infection is to be controlled worldwide. This agreement led us to a consensus that the findings from the CDC/Thailand study—while encouraging and implementable in some settings—do not eliminate the need to identify new, affordable, and perhaps more effective interventions to prevent perinatal HIV-1 transmission, including that which occurs during breastfeeding. Antiretroviral agents with properties such as longer intracellular half-life or more rapid antiviral effects are available.

We developed a consensus that there were four defined scientific issues of immediate concern in perinatal-HIV-1-transmission research in resource-poor settings. First, to identify other effective antiretroviral agents that provide an even more feasible approach than the CDC/Thailand short-course ZDV regimen to prevent perinatal transmission. Second, to define the shortest course (eg, intrapartum only or newborn only) of antiretroviral therapy that would be feasible and effective in reducing perinatal transmission. Third, to assess simple and feasible interventions other than antiretroviral agents for their efficacy in diminishing maternal/infant transmission of HIV-1, especially those that can be administered to all pregnant women without the knowledge of the women's HIV-1 status. Fourth, to assess a range of currently available interventions and new interventions that may reduce HIV-1 transmission occurring via breastfeeding.

Ethical principles

Following the CIOMS/WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects, we also agreed that sound scientific design is a fundamental ethical principle of all research studies, and that appropriate ethical standards must guide such studies.[15-20] Based on these international guidelines, we endorsed the following five ethical principles. First, the problem under study should be a health priority established by the public-health officials in the host country, and should be relevant to study participants as well as to the host country. Second, study participants should be assured the highest standard of care practically attainable in the country in which the trial is being carried out. Third, the study should not harm the health-care resources or infrastructure of the locality. Fourth, informed consent, including the knowledge that a decision not to participate in a study will not prevent access to the highest standard of care practically attainable in the host country, must be obtained from all study participants. Fifth, there must be a process of discussion and mutual understanding involving all relevant parties that should the intervention being studied prove effective and safe, it will be considered for implementation in the country in which the trial is carried out within a reasonable time-frame. Whenever possible, a written plan should be formulated. Studies are only appropriate if there is a reasonable likelihood that the populations in which they are carried out stand to benefit from successful results. The expected role of the local and international investigators in this effort should be discussed and understood before the study starts. These measures are intended to avoid exploitation of vulnerable populations as well as undue restrictions on research, the benefits of which can neither be predicted nor guaranteed.

Ethical standards in designing research trials should always be applied so as to reflect the economic, public-health, medical, and social realities of the host country.[21,22] We recognise that there is substantial heterogeneity among developing nations, which must be individually considered in the design of each research study.[23] We also acknowledge that to define the highest standard of care practically attainable in the host country is difficult and may be different from the existing standard of care. A majority of us agreed that, at the very least, the highest standard of care practically attainable in the host country should be provided to all study participants. There is no obligation to provide study participants with the highest standard of care attainable elsewhere in the world.

We also acknowledged that when the health care provided to all study participants—irrespective of whether or not they receive an experimental intervention—conforms to the highest standard of care practically attainable in the host country, the clinical study may be perceived as advantageous to potential participants when this standard of care is not universally available to them. Although this may serve as a powerful inducement to some potential participants, the alternative of not providing the highest standard of care practically attainable in the host country may be ethically worse.

Design of scientific studies

We agreed that scientific questions are the primary determinants of study design. Equivalency design (a comparison of two interventions) and superiority design (a comparison of an intervention to an untreated group receiving the highest standard of care practically attainable in the host country) answer different questions. The selection of study design (equivalency or superiority design) was discussed, and we decided that this choice must take into account the circumstances and population of the host country, and the time required to obtain an answer. An equivalency study including an intervention that cannot be implemented in the host country will probably not produce information that is useful to policy makers if the non-implementable intervention proves to be more efficacious. This is because such a trial design will not reveal if the less efficacious intervention is an improvement over the current level of care. In addition, an intervention not previously proven to be effective in the study setting may not serve as an appropriate control comparison. Selection of a design requiring a longer study period should take into account the net impact on individuals who might not receive the benefits of an effective regimen during the additional time necessary to carry out the study. However, the timeliness of obtaining an answer may be used as an ethical justification for trial design only if there is a commitment to immediate translation of findings into public-health programmes. Finally, reliable efficacy date and subsequent cost-benefit analyses are necessary to convince decision-makers of the level of priority to be accorded a new intervention.

We agreed that there is no single, universal, "best" trial design to address the scientific issues already identified. The majority of us agreed that trials must be designed to provide at least the highest standard of care practically attainable in the host country in which the trial is being done. In addition, there must be an understanding involving all relevant parties that if the intervention under study proves effective and safe, it will be considered for implementation in the country within a reasonable time frame.

First, in the host country, where either the three-part 076 ZDV regimen or the two-part Thai ZDV regimen (or another regimen proven to be efficacious) can feasibly be implemented, and where it can reasonably be concluded that the regimen will reduce transmission, subsequent antepartum antiretroviral studies should use one of those regimens as the appropriate comparison. This includes countries where the regimen is currently being provided in government-run facilities; where funds have been committed to provide it within a year; where the cost is affordable for a substantial proportion of pregnant women to purchase it themselves; or where ZDV is provided for a substantial proportion of women through in-country health-insurance plans, government-sponsored programmes, or donor programmes.

Second, where there is no antiretroviral therapy currently available in the host country, and no reasonable expectation of its availability during the time frame of the planned trial, it is imperative to test and identify rapidly a regimen that is more effective than no anti-HIV-1 intervention and more affordable and implementable than the proven ZDV regimens. Most of us at the workshop believe that a no-antiretroviral comparison may be ethically justified in such settings. In the specific instance of the study of non-antiretroviral interventions (eg, vaginal lavage or antibiotic treatment), most of us also believe that a no-drug intervention control design may be ethically justified.

Third, when an intrapartum or newborn (only) intervention, or both, has been found to be effective in diminishing mother-to-infant transmission in the context of a scientifically valid clinical trial, and is affordable and implementable by the public-health sector in the country in which a planned trial is to be done, that intervention should be used as the control arm in all subsequent clinical trials until such time as an even better intervention is developed.

Fourth, until an intrapartum or newborn (only) intervention, or both, has been found to be effective in diminishing mother-to-infant transmission, a no intervention controlled design may be ethically justified in host countries where there is no antiretroviral therapy currently available and no reasonable expectation of its availability during the time frame of the planned trial.

Fifth, at the current time, the only proven means of diminishing HIV-1 transmission via breastfeeding is the cessation of breastfeeding. There is a need to define further the risk associated with so-called replacement feeding (alternative to breastfeeding). In particular, there is a need to ascertain whether any negative health and social consequences of replacement feeding occur, and to assess the potential of these negative consequences to offset any gains resulting from reduction of HIV-1 transmission. Sixth, because no data exist on the efficacy of postpartum interventions (such as antiretrovirals), either in the presence or absence of breastfeeding, experimental postpartum interventions using a no-antiretroviral intervention controlled design may be ethically justified.

We stress that there is a global obligation to diminish the worldwide disparities in health care. We acknowledge, however, that to expect this profound global injustice to be rectified soon is unrealistic. In the meantime, it is critical to indentify effective interventions that can reduce perinatal HIV-1.

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This report reflects the general consensus of the participants of the workshop, and has been reviewed and agreed to by all who attended. Some participants might not agree with some aspects of the report.

**Leonard Glantz* disagrees with most of paragraph five on page 3, which attempts to address the issue of making successful interventions available to the population from which research participants are drawn. He agrees with the sentence in that paragraph that reads, "Studies are only appropriate if there is a reasonable likelihood that the populations in which they are carried out stand to benefit from successful results." It is Leonard Glantz's opinion that this determination needs to be made before carrying out research among impoverished populations for such research to be ethical. Leonard Glantz believes that nothing in the rest of the paragraph supports the important principle expressed in this sentence. He believes that the rest of the paragraph runs directly contrary to the implementation of this principle, and could permit research in developing countries in which there is no reason to believe that the resulting benefits will reach the population from which the research participants were drawn. He believes also that having discussions and an understanding that the introduction of successful interventions will be considered is not sufficient to decide that there is a "reasonable likelihood" that successful intervention will benefit the population.

References

1 1997 year-end edition, HIV/AIDS surveillance report. Centers for Disease Control and Prevention, US Department of Health and Human Services, Public Health Service, Atlanta, GA. 1998; **9:** 1–43.

2 Davis SF, Byers RH, Lindegren ML, et al. Prevalence and incidence of vertically acquired HIV infection in the United States. *JAMA* 1995; **247:** 952–55.

3 Prevention of HIV transmission from mother-to-child: planning for programme implementation. UNAIDS, World Health Organization, Geneva, Switzerland: March 23–24, 1998.

4 Centers for Disease Control. Update: perinatally acquired HIV/AIDS—United States, 1997. *MMWR* 1997; **46:** 1086–92.

5 Centers for Disease Control. Public health service task force recommendations for the use of antiretroviral drugs in pregnant women infected with human immunodeficiency virus-1 for maternal health and for reducing perinatal HIV-1 transmission in the US. *MMWR* 1998; 47 (suppl RR-2): 1–30.

6 Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of HIV type 1 with ZDV treatment. *N Engl J Med* 1994; **331:** 1173–80.

7 Fiscus SA, Adimora AA, Schoenbach VJ, et al. Importance of maternal ZDV therapy in the reduction of perinatal transmission of HIV: abstracts of the 4th Conference on Retroviruses and Opportunistic Infections. Washington DC: Jan 22–29, 1997: abstr 379.

8 Birkhead GS, Warren BL, Charbonneau TT, et al. Evidence for intermediate rates of perinatal HIV transmission with partial 076 regimens: results of an observational study. Abstracts of the 5th Conference on Retroviruses and Opportunistic Infections. Chicago, IL: Feb 1–5, 1998: abstr 244.

9 Mayaux M-J, Teglas J-P, Mandelbrot L, et al. Acceptability and impact of zidovudine for prevention of mother-to-child human immunodeficiency virus type 1 transmission in France. *J Pediatr* 1997; **131:** 857–62.

10 Mofenson L, Stiehm ER, Lambert J, et al. Efficacy of ZDV in reducing perinatal HIV-1 tranmission in HIV-1 infected women with advanced disease (abstr). In: Proceedings of 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada: September 1997; abstr I–117.

11 Centers for Disease Control. Administration of ZDV during late pregnancy and delivery to prevent perinatal HIV transmission—Thailand. *MMWR* 1998; **47:** 151–54.

12 Culnane M, Fowler MG, Lee S, et al. Evaluation for late effects of in utero (IU) ZDV exposure among uninfected infants born to HIV positive women enrolled in 076 and 219. *Clin Infect Dis* 1997; **25** (abstr).

13 World Bank Sector Strategy Health, Nutrition, and Population, 1997.

14 HIV and infant feeding. UN Children's Fund. UNAIDS. WHO: June, 1998.

15 Council of International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO): International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: CIOMS, 1993.

16 De Zoysa I, Elias CJ, Bently ME. Ethical challenges in efficacy trials of vaginal microbicides for HIV prevention. *Am J Public Health* 1998; **88:** 571–75.

17 Karim SSA. Placebo controls in HIV perinatal transmission trials: a South African's viewpoint. *Am J Public Health* 1998; **88:** 564–66.

18 Bayer R. Research to prevent maternal fetal transmission of HIV: racist exploitation or exploitation of racism? *Am J Public Health* 1998; **88:** 567–70.

19 Susser M. Editor's note: the prevention of perinatal HIV transmission in the less developed world. *Am J Public Health* 1998; **88:** 547–48.

20 Faden R, Kass N. Editorial: HIV research, ethics, and the developing world. *Am J Public Health* 1998; **88:** 548–50.

21 Bloom BR. The highest attainable standard: ethical issues in AIDS vaccines. *Science* 1998; **279:** 186–88.

22 Levine RJ. The "Best Proven Therapeutic Method" standard in clinical trials in technologically developing countries: IRB, 1998: a review of human subjects research: 20 (number 1): 5–9.

23 Pragmatism in codes of research ethics (editorial). *Lancet* 1998; **351:** 225.