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 and more than 15 000 estimated paediatric HIV-1 infections. 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.

There was a 43% decrease in reported paediatric AIDS cases in the USA from 1992 to 1996, 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, 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. 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 and in a secondary randomised trial. Furthermore, the results of a trial 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 regimen, 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. 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. 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
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 short-course regimen 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 expressed, 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.19-20 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.3 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) answered 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 any 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
could 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 Gianzi 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 possible if there is a reasonable likelihood that the populations in which they are carried out stand to benefit from successful results." It is Leonard Gianzi’s opinion that this determination needs to be made before carrying out research among impoverished populations for such research to be ethical. Leonard Gianzi 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 that it would be irresponsible to carry out 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