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PROPOSAL FOR THE PREVENTION OF MATERNAL – FETAL TRANSMISSION OF HIV IN SOUTH AFRICA

There is an urgent need to halt the spread of HIV/AIDS worldwide, particularly in parts of Africa that have already been hard hit by the epidemic. Given its capabilities and capacity to conduct biomedical research as well as the high incidence of HIV infection, South Africa is in a unique position to play a leadership role in HIV prevention research in Africa.

A recent study conducted in Uganda in collaboration with U.S. scientists and the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) demonstrated that a two dose regimen of nevirapine (NVP) – one dose to the mother at the time of labor and one dose to the newborn – reduced transmission of HIV from infected mothers to newborns by approximately 50%. There is now an urgent need to extend and implement these results in populations where the more lengthy zidovudine (ZDV) regimen is not practical or affordable.

PHASE 1. It is proposed that South Africa, through collaboration and assistance from the U.S. government and private foundations, devise and implement a two stage program that will lead to the wide-spread use of NVP to block the spread of HIV from infected mothers to their newborns in South Africa. Rapid assessment methodology will be employed throughout.

[This would not preclude the use of ZDV in South Africa in pregnant HIV-infected women who have access to pre- and post-natal care and who can afford the longer ZDV regimen. However, at this point in time, the two dose NVP regimen presents an affordable, safe and partially effective alternative for wide-spread use in populations where initiating anti-retroviral therapy prior to labor to the mother and/or after birth to the newborn is simply not practical]

This first phase could begin immediately and be comprised of two parallel paths:

- A demonstration project that will examine the safety and efficacy of using the 2 dose NVP regimen to stop the spread of HIV from infected mothers to newborns in South Africa.
- A planning project that will lay all the ground work necessary to rapidly implement a country-wide distribution of the 2 dose NVP regimen to HIV-infected mothers and their newborns.

Details of the demonstration project will be worked out in the coming 2-4 months by a joint team of South African and NIAID/NIH-supported researchers through development of a protocol that includes:

size of the trial; specific trial site(s) and investigators; milestones and timeframe for completion; exact cost; source and mechanism of funding; how the trial will be monitored to ensure it is ethically conducted and with the necessary scientific rigor, etc.

When the protocol is completed, it will be submitted for scientific and ethical reviews both in the U.S. and South Africa. UNAIDS will also be asked to comment on the

protocol. It is estimated that the project will be conducted in several South African clinical trial sites at a cost of approximately \$3.5-4.0 M over the next 12-18 months.

There will be many scientists, both within and outside of South Africa, who may criticize a demonstration project as a waste of time, citing the already available safety and efficacy information generated by the Uganda trial. However, this criticism can be addressed by:

- thoroughly examining the similarities and differences between the Ugandan and South African population; and
- immediately initiating a planning process for the wide-spread use of NVP, to be implemented as soon as safety and efficacy are confirmed in the demonstration project.

Specifically, a planning project will set in place all the ground work necessary to *implement a country-wide program* to reduce HIV transmission from infected mothers to their newborns. In South Africa, Approximately 25-30% of HIV-Infected pregnant women will pass the infection to their new-born infants in the peri-natal period (prior to or during delivery). The goal is to prepare to screen the approximately 1,000,000 pregnant women/year for HIV infection, and to ensure that the approximately 250,000 who are HIV-infected are afforded access to the two dose NVP regimen. This will involve training health care providers, putting screening tools in place and training clinic personnel on their use and interpretation, piloting counseling programs for the women, and other tasks as necessary.

This phase is anticipated to cost approximately \$10 -12 M in the first year and \$8-10M per year to implement in subsequent years.

[ROUGH ESTIMATE: 1,000,000 women x \$3/screen + 250,000 x \$4/for drug per pair + \$2.0 M counseling of women + \$2.0 M training/education of health care providers + \$2M other planning/other labor/overhead. The cost may vary considerably according to the existing health care delivery infrastructure in South Africa that would be needed to implement this project]

ADDITIONAL RESEARCH

BREASTFEEDING. While many women in South Africa have access to alternatives to breastfeeding, it is important to find approaches that will protect newborns from acquiring HIV through breast milk. South Africa, along with Zimbabwe, is currently conducting a clinical trial to determine how frequently newborns would have to be given NVP so that they maintain protective levels of the drug during the breastfeeding period. Results will be available early next year. Then, by the middle of 2001, a larger trial to examine the safety and efficacy of providing additional doses of NVP to newborns will be launched in populations where there are no breastfeeding alternatives (Uganda, Zimbabwe probably). When results from the larger trial become available in late 2002-3, South Africa will be in a better position to decide how best to help women with no alternatives to breast feeding.

OTHER PREVENTION RESEARCH. Protection of newborns from HIV is an immediate and practical goal that South Africa can accomplish in the coming few years. The larger

problem of sexual transmission among adults must also be tackled. Identification of a safe, effective HIV vaccine is the best hope to halt the spread of HIV among adults.

However, to accomplish this, several issues need to be addressed.

- Infrastructure and training to conduct trials must be strengthened. The U.S. NIH remains committed to continuing support of these activities in South Africa and in supporting the conduct of vaccine and other prevention trials in adults in South Africa.
- The factors that impact progression of HIV infection to AIDS need to be better characterized, so that the impact of candidate vaccines can be better assessed in South Africa and similar settings.

To ensure that these activities can be accomplished will require that the South Africa government be supportive of continued U.S. sponsored vaccine and prevention research in South Africa, including the study of how HIV infection leads to AIDS in South Africa.

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Date/Time: May 22, 2000
No. of pages to follow: 3

FYI – draft proposal for “Prevention of Mother-to-Child Transmission of HIV in South Africa”

DRAFT!

May 22, 2000

PROPOSAL FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV IN SOUTH AFRICA

There is an urgent need to halt the spread of HIV/AIDS worldwide, particularly in parts of Africa that have already been hard hit by the epidemic. Given its capabilities and capacity to conduct biomedical research as well as the high incidence of HIV infection, South Africa is in a unique position to play a leadership role in HIV prevention research in Africa.

A recent study conducted in Uganda, in collaboration with U.S. scientists and the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH), demonstrated that a two dose regimen of nevirapine (NVP) - one dose to the mother at the time of labor and one dose to the newborn - reduced transmission of HIV from infected mothers to newborns by approximately 50%. There is now an urgent need to extend and implement these results in populations where the more lengthy AZT regimen is not practical or affordable. Scaling up mother-to-child services must be linked to other prevention and care efforts.

PHASE 1. It is proposed that South Africa, through collaboration and assistance from the U.S. government and private foundations, devise and implement a two stage program that will lead to the wide-spread use of NVP to block the spread of HIV from infected mothers to their newborns in South Africa. Rapid assessment methodology will be employed throughout.

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This first phase could begin immediately and be comprised of two parallel paths:

- A demonstration project that will examine the safety and efficacy of using the 2 dose NVP regimen to stop the spread of HIV from infected mothers to newborns in South Africa. Particular attention will be paid to the issue of drug resistance.
- A planning project that will lay all the groundwork necessary to rapidly implement a country-wide distribution of the 2 dose NVP regiment to HIV-infected mothers and their newborns.

Details of the demonstration project will be worked out in the coming 2-4 months by a joint team of South African and USG-supported researchers through development of a protocol that includes:

size of the trial; specific trial site(s) and investigators; milestones and timeframe for completion; exact cost; source and mechanism of funding; how the trial will be monitored to ensure it is ethically conducted and with the necessary scientific rigor, etc.

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This phase is anticipated to cost approximately \$10 -12 M in the first year and \$8-10M per year to implement in subsequent years.

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A Call to Action to Prevent HIV Infection in Newborns

Background

We believe that no HIV prevention agenda is complete without programs to enable a mother to prevent perinatal infection of her child. The most effective means of doing so today is anti-HIV drugs for pregnant women and newborns.

The original AZT regimen tested in the U.S. and the shorter-course variants later tested in Thailand and southern Africa are, unfortunately, well beyond the means of most developing countries to implement. Trade and other legal issues cloud the picture further as poor countries consider how they may reduce cost and increase the distribution of anti-HIV drugs in this global economy. It has been four years since the original data were announced, and nothing has been happening very easily.

But now, everything is beginning to change.

Results from a joint Uganda/U.S. study recently demonstrated that the drug Nevirapine can reduce perinatal transmission of HIV by 47 percent. It is administered in a single dose to the mother at the onset of labor and in a single dose to the baby in its first three days of life. The entire course costs less than \$4 at Western list prices, without taking into account the reductions that may be possible with bulk purchase and negotiated pricing.

These research findings raise new questions, but the need for additional answers cannot be an excuse to delay a response now. These findings—and better ones as they emerge—must be turned into clinical practice.

Call to Action to Prevent Perinatal HIV Infection

We call for immediate action worldwide to prevent babies from becoming infected with HIV.

This action must include:

- The creation of information programs to raise public awareness of the issue of perinatal transmission and the possibility of reducing it;
- The establishment and enhancement of programs to deliver perinatal care and medications to pregnant women and babies;
- The purchase or acquisition of drugs to prevent perinatal transmission for countries that cannot afford them;
- The delivery of drugs to pregnant women and babies to prevent perinatal transmission; and
- Continuing research for additional interventions that might further reduce transmission and expanded efforts to prevent infection of all people.

We explicitly call for this action to be in addition to—not in lieu of—prevention programs for adolescents and adults.

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This call is directed at the governments of all industrial nations. We call on them for immediate support and assistance. We also call on them to negotiate for donations and dramatic discounts from pharmaceutical companies who make the needed drugs and diagnostics and for contributions from all pharmaceutical companies.

This call is directed at governments of developing nations. We call on them to create public information and education campaigns to make all potential parents aware of this step toward a healthy baby. We also call on them to strengthen their systems of perinatal care and programs for families.

This call is directed at pharmaceutical companies. We call on them to assist directly and indirectly with the cost of implementing programs to reduce infection of babies. We also call on them to donate, discount, and negotiate. Noting that several drug companies have received worldwide acclaim for donations of drugs to cure other diseases in poor nations, we call on all companies to respond to the human need in the HIV epidemic.

This call is directed at multinational corporations. We call on them to assist in setting up public information and education programs and in the delivery of drugs. Having proven themselves able to promote and distribute such discretionary products as soft drinks, music recordings, and athletic shoes, they can help spread both the knowledge and the simple means to save babies' lives. We also call on them to contribute, both for the good of their future markets and for the good of the world.

We call on religious groups, charities, foundations, and nongovernmental organizations. We call on them to take the lead in all areas. Partnerships between public and private sectors can expedite all actions.

We call on ourselves as well. We must set up a structure, we must plan, we must call out for funding in all venues, we must work on delivery systems, and we must continue research. We must work with all people affected by HIV to create and mobilize a comprehensive response to the epidemic.

Our call for action is immediate. A new baby is infected every minute of every day. Half of those infections can be prevented. All delays should be measured in those terms. With an investment of \$12 million now, we can begin to prevent the estimated 600,000 HIV infections in children each year. We will seek to raise at least that much as soon as possible.

- "I'll get back to you in a couple of days" means 2,400 babies infected who need not have been.
- "When the review committee meets in a month" means 35,000 babies infected who need not have been.
- "When the U.S. Congress returns in January" means 112,000 babies infected who need not have been.
- "Not until the patent expires," means millions of babies infected who need not have been.

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Conclusion

We call for the world to recognize its obligation to prevent needless HIV infection of babies and to do so today.

We will continue to work on research, on prevention programs for adults and adolescents, and on treatment for those people who are already infected. These are all part of the obligation of the world.

Attachment to Call for Action

The global HIV epidemic has reached staggering proportions and, at current rates, threatens to transcend all other health problems in the world. It is estimated that

- More than 33 million people are HIV-infected,
- 95% of these people live in developing nations;
- 6 million people are infected each year (or about 16,000 per day);
- Half of these newly infected people are young (age 15-24) and 40% are women;
- 600,000 of these newly infected people are newborns; and
- Over half a million children die annually from HIV.

In some countries, the HIV epidemic is erasing the gains in overall life expectancy that have been achieved in the last 25 years. In many countries, the HIV epidemic is erasing all progress in reducing infant mortality and child mortality.

Prevention of HIV infection among adolescents and adults is clearly necessary. Programs to prevent HIV infection associated with sexual relations or drug use should be undertaken and redoubled by all governments, nongovernmental organizations, and the private sector. Some such programs are underway and have shown early success. However, we believe that much more must be done in primary prevention. Such prevention programs will also reduce the number of infected babies, since uninfected parents will have uninfected babies.

However, while working to prevent infection among adolescents and adults, it is necessary to recognize that there are many women of childbearing age who are already infected. With no intervention, many of these women will transmit the infection to their babies.



The second conference on

Global Strategies

for the Prevention

of HIV Transmission

from Mothers to Infants

September 1-5, 1999

Hotel du Parc, Montréal, Canada

Conference Chair

Arthur J. Ammann, MD, USA

About the Conference

The second international conference on "Global Strategies for the Prevention of HIV Transmission from Mothers to Infants" that is being held September 1-5, 1999 in Montreal Canada, is sponsored by The International AIDS Society and the American Foundation for AIDS Research in collaboration with the Office of AIDS Research, NIH. Co-sponsors include Global Strategies for HIV Prevention, the Elizabeth Glaser Pediatric AIDS Foundation and the Harvard AIDS Institute (additional sponsors and planning committee attached). The conference chair, Arthur J. Ammann, MD, president of Global Strategies for HIV Prevention and co-chair, Mark Wainberg, PhD, McGill University, worked closely with an international planning committee to assemble over 140 speakers from developing and developed countries to address issues of immediate relevance to perinatal HIV prevention.

This conference is designed to facilitate the implementation of HIV prevention strategies which have been shown, through research in developed countries, to dramatically reduce perinatal HIV transmission. Recent clinical studies demonstrated a 47% reduction in perinatal HIV transmission using an inexpensive and simple treatment regimen. As a result, conference participants will urgently seek implementation strategies to prevent the estimated 1,600 infants infected each day with HIV. The daily program will begin with two keynote speakers, providing a scientific perspective on perinatal HIV transmission and relevant community issues such as, rapid HIV testing, women's rights, and the HIV orphan crisis. The plenary sessions are devoted to the most recent clinical and basic research information on topics related to HIV transmission including, HIV transmission via breast milk, results of clinical prevention trials, evaluation of HIV testing technologies, antiretroviral drug safety during pregnancy, and long term follow up of AZT exposed infants. The afternoon programs are divided into workshop sessions covering nine topics: Breast Feeding, Formula Feeding and Nutrition; Identification Resources for Prevention of Perinatal HIV Transmission; Implementation of Prevention Strategies for Prevention of Perinatal HIV Transmission in Developing Countries; Counseling and Testing: Technical, Social, Ethical and Policy Issues in Midwifery; Economics of HIV Prevention; Responding to the HIV/AIDS Orphan Crisis; Non Antiretroviral Interventions to Slow HIV Disease Progress and Benefit Non-HIV Infected Persons.

The conference acknowledges the importance of HIV prevention. Advances in therapy to prevent HIV transmission from mothers to infants has brought hope to thousands, but transmission of HIV continues to increase in developing countries. To reduce the worldwide incidence of mother-to-infant transmission, effective intervention strategies, usable by all nations, must be identified.

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Specific goals of the conference are:

- To provide basic and clinical updates on current issues concerning prevention of mother-to-infant HIV transmission.
- To allow opportunities for scientists and public health care workers from developed and developing countries to define questions.
- To identify effective and economical solutions to prevent primary infection in women.
- To identify effective and economical solutions for bringing an end to perinatal HIV transmission worldwide.
- To provide a forum for discussion of new and emerging issues related to HIV prevention.

Background

When the clinical trial, now referred to as ACTG 076, was first designed, the primary concerns were maximizing efficacy and minimizing toxicity of AZT during pregnancy and in the newborn period. Therefore, AZT therapy was not initiated until the second trimester and infants were treated for only the first six weeks after birth. In order to maximize the potential for determining efficacy, while minimizing the number of pregnant women and fetuses exposed to AZT, the clinical trial utilized a placebo control design. The wisdom of these decisions were validated when the study was terminated early because a preliminary analysis demonstrated a 68 percent reduction in HIV infection of infants (8 percent HIV transmission in the AZT group and 26 percent HIV transmission in the placebo group). The application of AZT therapy to the prevention of perinatal HIV transmission has had a profound impact in developed countries resulting in fewer than an estimated 300 newly infected infants per year in the entire United States. Aggressive perinatal HIV testing coupled with combination antiretroviral therapy and Cesarean section has further reduced HIV transmission to less than 3 percent in several clinical trials in the United States and Europe.

In 1997, when the first conference on Global Strategies for the Prevention of HIV Transmission From Mothers to Infants was held in Washington, DC, the goals were to define the obstacles to prevention strategies and develop solutions. One of the major obstacles was the cost and duration of treatment of the mother and infant necessary to prevent HIV transmission. Beginning in February of 1998, the results of a series of new perinatal HIV prevention trials demonstrated significant reductions in HIV transmission. A CDC/Thailand study which treated mothers for only the last four weeks of pregnancy only with AZT, showed 50 percent reduction in HIV transmission to infants who were not breast-fed. However, breast-feeding is considered by many to be absolutely necessary in developing countries. In February 1999, UNAIDS reported that a clinical study in Africa providing AZT plus 3TC during the last four weeks of gestation, and one week after delivery to both mothers and infants while breast feeding, also reduced perinatal HIV transmission by 50 percent.

Just prior to this meeting a new study from NIH and Uganda was reported demonstrating a 47 percent reduction in perinatal HIV transmission using a single dose of Nevirapine during labor and delivery for the mother and a single dose for the infant while breast feeding was continued.



This was good news – a single dose of a drug at an estimated total cost of \$4 US is an exciting way to start the second international conference.

Remaining Issues

Questions remain in spite of the good news, many of which are fundamental to health care for poor countries. Who is responsible for it to implement strategies to prevent HIV infection and death of 600,000 infants each year? As scientists and health care workers labor together to get answers – convenient and inexpensive methods for HIV prevention – will governments and public agencies respond? Will women be tested for HIV during pregnancy? Will women be tested prior to becoming pregnant? Are women's rights protected as they learn their HIV status? How do we overcome the discrimination that continues to impact more severely on women and children? How will we deal with the rapidly increasing numbers of children orphaned by HIV/AIDS, the majority of whom are HIV infected.

These and other issues, such as the community and national responses to HIV/AIDS prevention, will be the focus of the plenary scientific sessions and the individual workshops. Participants from over 60 developing countries will gather to learn and to share their experiences to help slow the epidemic. 1,600 newly infected infants each day is unacceptable. The conferences will seek to identify strategies to slow the epidemic in those continents such as Africa where a generation of children has been lost, and to prevent India and China, where HIV is now firmly established, from overtaking Africa in the number of HIV/AIDS people.

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Global Strategies for the Prevention of HIV Transmission from Mothers to Infants

September 1-5, 1999

Montreal, Canada

Press Conference Agenda September 1, 1999, 2:00 PM

PART I -- PRESENTATIONS

1. Opening Remarks

- *Arthur Ammann, MD*, President, Global Strategies for HIV Prevention and Conference Chair

2. Ugandan/NIH Perinatal Prevention Study Results – Worldwide significance

- *Brooks Jackson, MD*, Professor and Vice-Chairman of Pathology for Clinical Affairs, Johns Hopkins
- *Francis Mmiro, MD*, Professor of Obstetrics and Gynecology, Makerere Medical School, Kampala, Uganda

3. Women and HIV in Developing Countries

- *Geeta Gupta, PhD*, President, International Center for Research on Women

4. AIDS Orphans

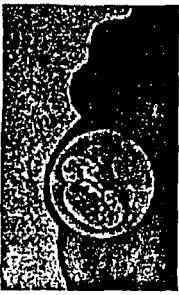
- *Ruth Nduati, MD*, Department of Pediatrics Consultant Pediatrician, University of Nairobi, Kenyatta National Hospital

5. Epidemics in India and China

- *Suniti Solomon, MD*, Founder, YRG Care, India

6. Closing Comments

- *Mark Wainberg, MD*, President, International AIDS Society



PART II – QUESTIONS AND ANSWERS

Additional participants include:

- ***Yuzhen Cao, MD***, Professor and Director, Clinical Virology Laboratory, Chinese Academy of Preventive Medicine, Beijing, China
- ***Laura Guay, MD***, Assistant Professor, Department of Pathology, Johns Hopkins School of Medicine
- ***Rod Hoff, MD***, National Institutes of Health
- ***Quarrisha Abdool Karim, MD***, Medical Research Council of South Africa
- ***Crispus Kiyonga, MP, MD***, Health Minister of Uganda
- ***Nkandu Luo***, Health Minister of Zambia
- ***Paulo Miotti, MD***, National Institutes of Health
- ***Philippa Mudido-Musoke, MBChB***, Professor, Makerere University Medical School, Kampala, Uganda
- ***Joseph Saba, MD***, Physician, Department of Policy, Strategy and Research, World Health Organization

Emerging recombinant human immunodeficiency viruses: uneven representation of the envelope V3 region

Boris Renjifo^a, Peter Gilbert^b, Beth Chaplin^a, Fredrik Vannberg^a,
Davis Mwakagile^c, Gernard Msamanga^d, David Hunter^e,
Wafaie Fawzi^f and Max Essex^a

Objective: To determine whether the envelope V3 region from HIV-1 subtypes A, C or D had the same probability of being present in intersubtype recombinant genomes.

Materials and methods: The envelope C2-C5 and the gag p24-p7 regions from one hundred infants infected perinatally in Tanzania were compared using phylogenetic and recombination analysis. Exact binomial and Fisher's exact tests were used to assess if various genomic regions were more likely to be overrepresented in intersubtype recombinants.

Results: Of one hundred HIV-1 positive infants analyzed, twenty-two (22%) showed exclusively subtype A sequence in gag and env. Subtype C accounted for twenty-two infants (22%) whereas nineteen infants (19%) were infected by HIV-1 subtype D. Intersubtype recombinant genomes accounted for thirty-seven infections (37%). The V3 region from subtype A was found in all fifteen A-D recombinants ($P = 0.00003$) and the V3 region from subtype C was found in all twelve C-D recombinants ($P = 0.0002$). Conversely, subtype D gag sequences were preferentially represented in the gag of A-D recombinants ($P = 0.0003$) as well as C-D recombinants ($P = 0.002$). In A-D recombinants, the V3 region of subtype A was generally surrounded by subtype A C3-C5 sequences. In contrast, the V3 region from subtype C was surrounded by subtype D C3-C5 sequences in C-D recombinants. Significant differences were not found in the number of subtype A or subtype C sequences in A-C recombinants.

Conclusion: We have shown that several recombinant HIV-1 viruses have been generated and efficiently transmitted to infants in Tanzania. The recombination patterns showed that the V3 region of subtypes A or C was always selected in A-D and C-D recombinants. This selection suggests that the fitness of subtype D-V3 in perinatal transmission may be reduced with respect to V3 from subtype A and/or subtype C. The elevated number of recombinants transmitted perinatally suggests that co-infection or super-infection by two HIV-1 subtypes is not uncommon in this population.

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AIDS 1999, 13:1613-1621

Keywords: HIV-1, genetic subtypes, env, gag, V3 region, perinatal, transmission, recombination

Introduction

The human immunodeficiency virus type 1 (HIV-1) pandemic is caused by at least 10 subtypes designated A

to J within the M group [1-3]. The global HIV-1 pandemic is made up of distinct regional epidemics with unique subtypes and risk factors. Countries in sub-Saharan Africa account for more than half the HIV-1

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infections in the world. In Africa, heterosexual and perinatal transmissions are the most common routes of infection [4]. HIV-1 subtypes A and D predominate in the epidemic of East Africa, and HIV-1 subtype C has dominated the expanding epidemic in Southern Africa and Ethiopia [5].

Perinatal transmission of HIV-1 is the only major source of infection in children. Perinatal transmission rates of 15 to 43% have been described in different geographical locations [6]. HIV-1 transmission may occur during pregnancy, at delivery, or later through infected milk. Several maternal factors, including seroconversion during pregnancy, high viral load, low CD4 cell counts, and progression to AIDS have been associated with higher rates of perinatal transmission [7–14]. Virological determinants and their role in perinatal transmission have not been well established. HIV-1 in the infant may represent a minor viral quasispecies from the mother, and macrophage-tropic non-syncytium-inducing viruses are the most frequently transmitted viral phenotype [15–22]. It is still unknown which and how many genetic determinants drive this selection. In addition, it is still unknown if HIV-1 subtypes differ in their perinatal transmission rates.

Due to the ability of HIV-1 to recombine and the presence of multiple subtypes in the population, several recombinant genomes have been described, some of which showed different HIV-1 subtypes between the *gag* and *env* genes [23–25]. The biological relevance of recombinant genomes in the HIV-1 epidemic has been well recognized in Thailand with the spread of HIV-1 subtype E in the heterosexual population [26]. We recently reported that HIV-1 subtype C is expanding in Tanzania where HIV-1 subtype A and D once dominated the epidemic [27]. By studying recombinant genomes in a population such as this, where multiple subtypes are represented at significant levels, it may be possible to map viral determinants associated with the preferential expansion of the new viruses. Since variation in the envelope gene, particularly the V3 region, has been shown to correlate with co-receptor affinity and cell tropism as well as immune evasion, we evaluated characteristics of HIV-1 *env* from 100 infants neonatally exposed to different subtypes of HIV-1.

Methods

Patient population

The samples analyzed were from infants participating in a randomized double-blind trial to determine whether vitamin supplements could reduce the rate of perinatal transmission of HIV-1 in Dar es Salaam, Tanzania. Information regarding the treatment received by the infant-mother pairs is still under code and not available

at this time [28]. The samples in this report represented the first 100 HIV-1-positive infants for which the *gag* and *env* genes were examined. Whole blood was collected from infants ranging from 3 to 50 weeks of age.

PCR amplification, cloning and DNA sequencing

Peripheral blood mononuclear cell separation, lysate preparation, and determination of HIV-1 infection by polymerase chain reaction (PCR) have been previously described [27]. A nested PCR amplification protocol was performed to amplify the C2-C5 envelope regions and the 3'-p24/5'-p7 region of *gag*. For envelope amplification, twenty microliters of crude cell extract were used for the first PCR amplification with primers vpu157 (position 6209–6228 according to HxB2 numbering [3]), vpu232 (6283–6303), p130 (7945–7924) and p131 (7970–7948). Four microliters of the first PCR amplification was subjected to nested PCR with primers Bstq2+ (6858–6880) and env1556 (7815–7783). Cycles for both envelope amplifications consisted of 39 cycles of 1 min at 94°C, 1 min at 52°C, 3 min at 72°C and a final extension cycle for 10 min at 72°C. Two individual reactions with HIV-1-negative cell extracts and a reaction without DNA were included in every set of PCR reactions. To amplify *gag* sequences, 20 µl of cell extract was used for the first PCR amplification with primers p108 (764–782) and p109 (2281–2264). The nested *gag* PCR amplification was done with primers p91 (1550–1572) and p92 (2043–2024). PCR conditions were similar to those for envelope amplification but annealing was done for 1 min. Amplicons were gel-purified using a Gel DNA purification kit (Boehringer Mannheim, Indianapolis, IN, USA) and cloned into a TopoVector (Invitrogen, Carlsbad, CA, USA). Individual bacterial colonies were screened for the presence of the insert with restriction enzyme analysis of plasmid DNA. *Env* and *gag* clones were sequenced in both directions by cycle sequencing with dye terminators using an ABI 373 system (Applied Biosystems, Foster City, CA, USA). In some samples, a new sequence was obtained directly from PCR products to corroborate the sequences obtained from cloned fragments. Nucleotide sequences have been submitted to GenBank under accession numbers AF038052–AF038064, AF038067–AF038075, AF038077–AF038080, AF038082–AF038091, AF038093–AF038094, AF038098, AF038100–AF038106, AF038108–AF038110, AF038112–AF038121, AF106332–AF106472.

Phylogenetic classification

Individual *gag* and *env* sequences were classified into HIV-1 subtypes by comparison with control HIV-1 subtype sequences from the Los Alamos HIV-1 Sequence Database [3]. Nucleotide sequences from samples and controls were aligned using the Clustal W software package [29]. Alignments were subjected to phylogenetic analysis using the neighbor-joining method and the

Kimura two-parameter model for calculation of distances [30]. Bootstrap resampling (1000 replicas) was used to assess the robustness of the phylogenetic trees. In all cases, clones from one infant clustered together and separately from any clones from other infants.

Identification of intragenic recombinants

The Recombination Identification Program (RIP) and neighbor-joining trees were used to identify *gag* and *env* intragenic recombinants [31]. Nucleotide sequences from one representative clone of each infant was compared to a master *gag* and *env* nucleotide consensus alignment of HIV-1 subtypes [31]. A four-sequence alignment including the consensus sequence of the two putative subtype parents and an outgroup sequence (SIVcpz GAB) was used to localize breakpoints [23]. To further establish the presence of two subtypes, nucleotide sequences on both sides of the breakpoint were analyzed separately by constructing phylogenetic trees. The nomenclature of recombinants was based on the subtypes involved and the location in the genome (5' end to 3' end) of each subtype. To determine whether the samples with similar recombinant patterns originated independently, the Viral Epidemiology Signature Program Analysis (VESPA) and Monte Carlo randomization were used to assess the statistical significance of differences in amino acids frequencies [32]. Background genome sequences of HIV-1 subtypes A, C, or D corresponded to all the samples in this study classified as non-recombinant subtype A (22), subtype C (22), or subtype D (19).

Subtype contribution in recombinants

For sequences identified as a recombinant of two subtypes, an exact binomial test was used to assess if various genomic regions were more likely to consist of one subtype than the other. The null hypothesis for this test consisted of the V3 region being equally likely to belong to either subtype involved in the recombinant. Fisher's exact tests (two-sided) were used to assess whether the proportional representation of subtypes in V3 differed from that in the C3-C5 region of *env*. A similar analysis was carried out to compare V3 to *gag*.

Results

Classification of HIV-1 subtypes transmitted perinatally

A summary of the results of phylogenetic analysis and RIP analysis of *env* and *gag* sequences is shown in Fig. 1. Of 100 HIV-1 positive infants analyzed, 22 samples (22%) showed exclusively HIV-1 subtype A sequences in both *gag* and *env*. HIV-1 subtype C accounted for 22 infections (22%) whereas 19 samples (19%) showed HIV-1 subtype D sequences in *gag* and *env*. Thirty-six infants (36%) showed intersubtype recombinant genomes from two HIV-1 subtypes and one sample

(1%) showed evidence for recombination between three HIV-1 subtypes.

Recombination patterns

Not all possible HIV-1 *gag* and *env* combinations were found in infants infected with recombinant viruses. Based on the localization of the breakpoints and the subtypes involved in the recombinant, 11 recombination patterns were found in 37 infants infected with recombinant viruses (Fig. 1). In 18 of 37 (49%) recombinants, the breakpoint could not be located inside the regions sequenced in *gag* or *env*. In the remaining 19 recombinants (51%), it was possible to detect a breakpoint between two subtypes in *gag* and/or *env*. Seven recombinants showed breakpoints in *gag* (three C/A, three D/A, and one C/D) whereas 12 recombinants showed breakpoints in *env* (nine D/C/D and three D/A/D) (Fig. 1). We did not detect subtype A envelopes with V3 regions from subtypes C or D, nor did we find subtype C envelopes with V3 regions from subtypes A or D. Strikingly, none of the 13 recombinant subtype D envelopes had a subtype D-V3 region.

Recombinants composed of subtype D(*gag*)-A(*env*) and D(*gag*)-D/C/D(*env*) accounted for 18 of 36 (50%) intersubtype recombinants involving two HIV-1 subtypes. To determine if these two recombination patterns originated from independent recombination events or if they originated from a single recombination event, which expanded into the population, we analyzed them by phylogenetic trees and VESPA. We hypothesized that if recombinants with the same subtype conformation originated from a single recombination event, they would form a distinct cluster under phylogenetic analysis and signature sequences would be found throughout the entire length of recombinant sequences. We compared each region of the recombinants against the corresponding region from non-recombinant genomes belonging to the same subtype. These controls were used to avoid a bias due to geographical origin of the controls. Phylogenetic trees of *gag* (Fig. 2a), *env* V3 (Fig. 2b) or *env* C3-C5 (Fig. 2c) from D(*gag*)-A(*env*) recombinants showed that recombinant samples do not cluster when we compared them against 19 non-recombinant subtype D *gag* sequences or 22 non-recombinant V3 or C3-C5 subtype A *env* sequences. A total of eight samples were D(*gag*)-D/C/D(*env*) and the envelope V3 and C3-C5 regions were analyzed separately since they belong to two different subtypes. Figures 2d, e, and f show that the *gag* or C3-C5 sequences from the D(*gag*)-D/C/D(*env*) recombinants did not cluster together when we compared them to the background subtype D sequences. Although there was a tendency for the V3 region from recombinant samples to cluster together, the bootstrap value for this sub-cluster was too low to support an epidemiological linkage between these samples (Fig. 2). Amino acid analysis of D(*gag*)-D/C/D(*env*) sequences using VESPA and

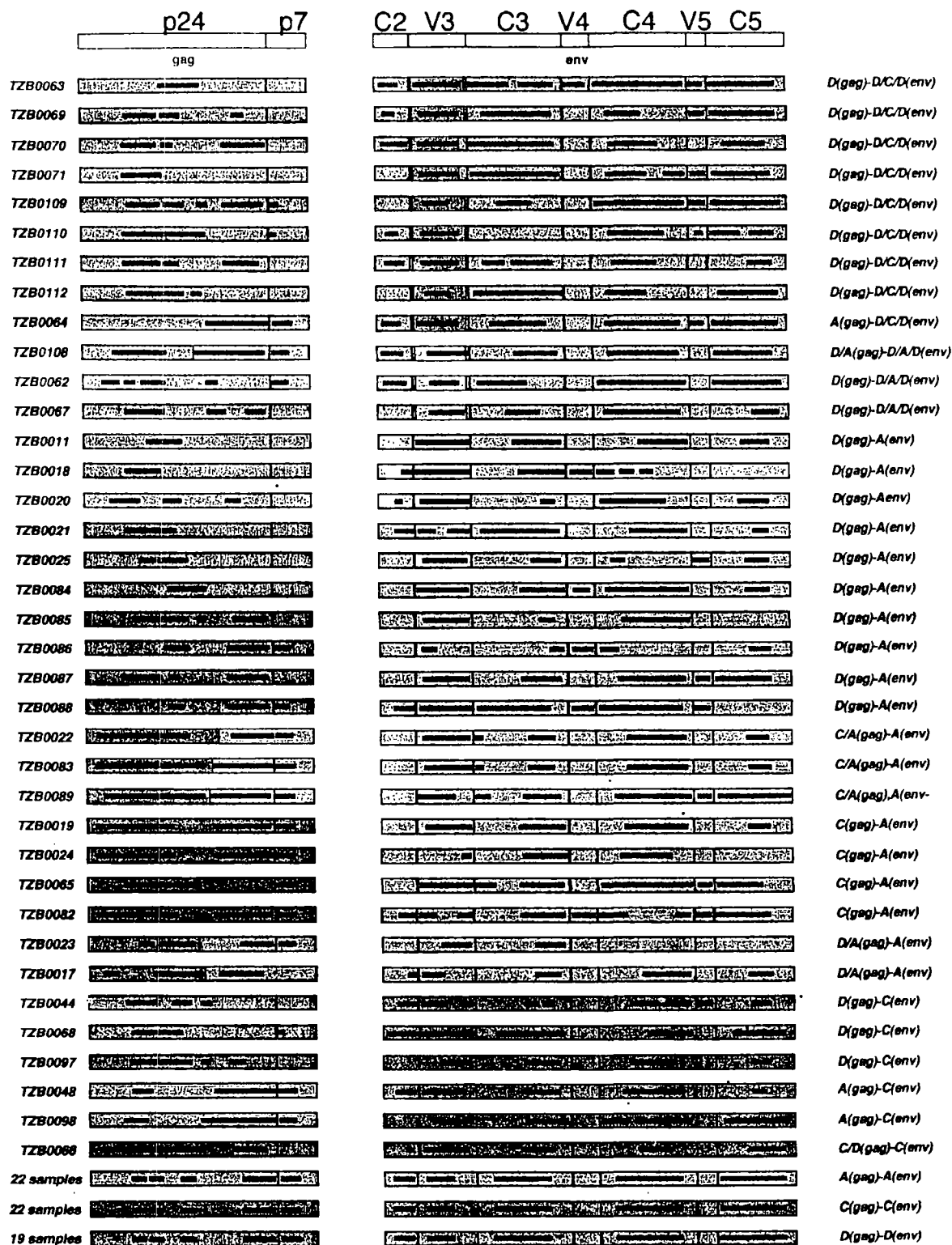


Fig. 1. Schematic representation of RIP outputs belonging to HIV-1 subtype A, C or D in gag and envelope from recombinant and non-recombinant samples. Gag and env sequences were classified into HIV-1 subtypes by comparing them with control sequences from the Los Alamos HIV-1 sequence database [3]. Localization of crossover breakpoints between HIV-1 subtypes was done by a four-sequence alignment. Green, blue, and red colored boxes represent sequences from HIV-1 subtype A, C, or D respectively. Black bars indicate a scale-size series of RIP windows showing ≥ 0.9 similarity and $\geq 90\%$ certainty with a particular HIV-1 subtype. Confirmation of recombination was conducted by constructing phylogenetic trees of the putative recombinant region against representative control sequences. Recombinants nomenclature was based on the subtypes involved (gag or env) and the location of each subtype (5' end to 3' end) in the recombinant. Non-recombinant HIV-1 subtype A, C, and D are listed at the bottom.

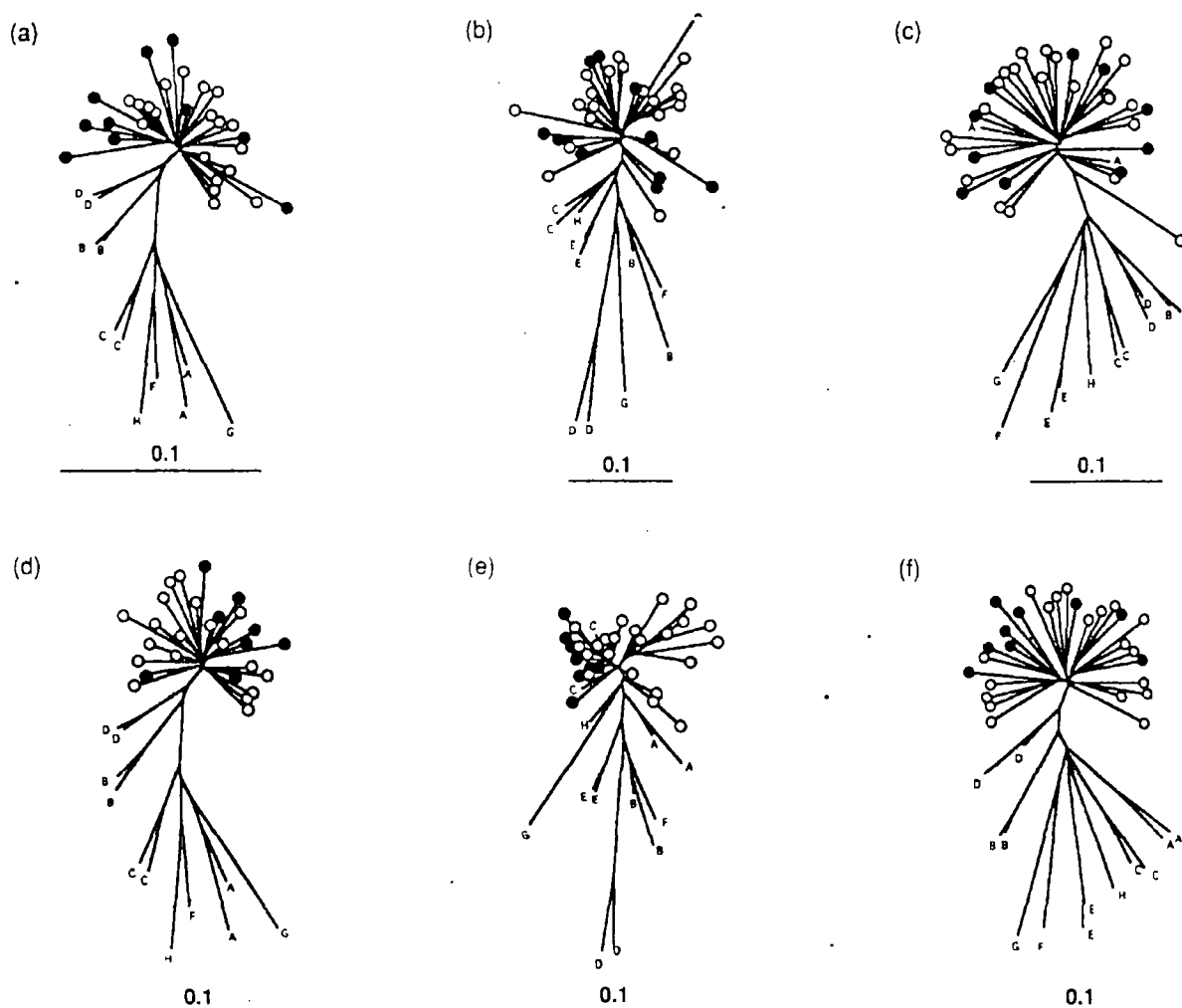


Fig. 2. Schematic representation of neighbor-joining trees of samples with *D(gag)-A(env)* and *D(gag)-D/C/D(env)* and lack of phylogenetic clustering. Samples with *D(gag)-A(env)* (filled circles) were compared against 19 non-recombinant HIV-1 subtype D gag sequences (a), 22 non-recombinant HIV-1 subtype A V3 region sequences (b), or to the C3-C5 region from 22 non-recombinant HIV-1 subtype A envelopes (c). Samples with *D(gag)-D/C/D(env)* (filled circles) were compared against 19 non-recombinant HIV-1 subtype D gag sequences (d), 22 non-recombinant HIV-1 subtype C-V3 region sequences (e), or to the C3-C5 region from 22 non-recombinant HIV-1 subtype D envelopes (f).

Monte Carlo showed that amino acid position 375 (T instead of S) in C3 was preferentially found in the recombinant set (adjusted P value < 0.005) (Table 1).

Significant differences in the V3 region were not found between recombinants and background sequences.

Together, these analyses suggest that either the recombinants originated from independent recombination events or they had been present in the population for a prolonged period. This is supported by the lack of phylogenetic clustering and by the variability of the RIP patterns showing > 90% certainty in sequences of the same subtype or recombinant structure (Figs 1 and 2).

To further address whether a founder effect may have been involved in the distribution of transmitted recombinants, we also amplified and sequenced the long

terminal repeat (LTR) from several samples with *D(gag)-A(env)*, *D(gag)-D/C/D(env)*, *C(gag)-A(env)* or *D(gag)-D/A/D(env)* [33]. The lack of identity between LTR, *gag*, and *env* in with *D(gag)-A(env)*, *C(gag)-A(env)* and *D(gag)-D/A/D(env)* supports our previous findings that many of these recombinants could have originated via independent events.

Genetic contribution of subtype A, C and D to the recombinants

If HIV-1 subtypes A, C, and D have the same intrinsic ability to be transmitted perinatally as well as to be represented in a recombinant virus, the genetic composition of a recombinant should not have any preferential representation of any particular HIV-1 subtype. We compared three groups of recombinants to determine whether different subtypes had the same representation

Table 1. Comparison of amino acid frequencies in D(gag)-D/C/D(env) against background genomes. The most common amino acid at each position in the D(gag)-D/C/D(env) sequences were compared to the most common amino acid positions in the background sequences. Fisher's exact test was conducted for every position that differed between both groups excluding regions of insertion or deletions. A *P*-value adjusted for the multiple tests was calculated via Monte Carlo computer simulations. Two hundred sequence datasets were generated by randomly permuting sequence group status (recombinant or background).

C3-C5 region (subtype D)					
Amino acid (frequency) in nine recombinant sequences	E(4), G(1)	R(5), G(4)	T(6), S(3)	I(6), M(3)	A(7), E(1)
Amino acid (frequency) in nineteen background sequences	E(3), G(5)	R(6), G(11)	T(0) ^a , S(19)	I(8), M(11)	A(5), E(12)
Amino acid position in gp160 ^b	337	351	375	433	439
V3 region (subtype C)					
Amino acid (frequency) in nine recombinant sequences	K(6), R(1)	Y(5), H(4)			
Amino acid (frequency) in twenty-two background sequences	K(7), R(8)	Y(7), H(15)			
Amino acid position in gp160 ^b	305	330			
Gag region (subtype D)					
Amino acid (frequency) in nine recombinant sequences	R(4), K(4)				
Amino acid (frequency) in nineteen background sequences	R(2), K(15)				
Amino acid position in P7 gag ^b	26				

^aAdjusted *P*-value < 0.005; ^bamino acids positions are according to HxB2 numbering (3).

in recombinants between subtypes A and D, A and C, or C and D. Despite the amplified envelope including C2 to C5 regions, we did not include in the comparison the C2, V4, or V5 regions. Their small size (C2) and frequent insertion/deletions (V4, V5) made it difficult to assign a particular subtype when subjected to phylogenetic analysis as individual nucleotide segments. The contribution of each subtype in V3, C3, C4, C5, and gag for A-D, A-C, and C-D recombinants are shown in Table 2. Subtype A was preferentially represented in the V3 region from A-D recombinants, with all 15 samples possessing a V3 from subtype A (exact binomial test $P = 0.00003$). Conversely, subtype D was preferentially represented in gag in A-D recombinants (exact binomial test $P = 0.0003$). A Fisher's exact test comparing the proportion A V3 to the proportion of A gag was highly significant ($P = 0.00001$). Similar results was obtained when we compared the proportion of subtype A C3-C5 to subtype D gag. This suggests that A-D recombinants with A V3, C3-C5 and D gag may hold an advantage for perinatal transmission. On the other hand, comparison the proportion of subtype A in V3 to the proportion of subtype A in C3-C5 was not significant ($P = 0.22$). Based on this result, it did not appear that a V3 region of subtype A was a determinant separate from the C3-C5 region of env. All (12 of 12) C-D recombinants had a V3 region from subtype C ($P = 0.0002$) whereas 0.5 had a gag from subtype C ($P = 0.002$). The Fisher's exact test comparing proportions was highly significant ($P = 0.0001$). Unlike A-D recombinants, the proportion of C-D recombinants with V3 region of subtype C was larger than the proportion of C-D samples with C3-C5 region of subtype C ($P = 0.0013$), suggesting that the presence of subtype C in the V3 region could be a determinant separate from C3-C5. The proportion of subtype A or subtype C sequences in A-C recombinants did not reach statistical significance even though the number of subtype A sequences was higher than the number of subtype C sequences.

Discussion

Mother-to-child-transmission of HIV-1 is a multifaceted phenomenon involving host resistance factors as well as the properties of the transmitted virus. It has been shown that viral samples taken from young infants are substantially homogeneous, suggesting that one or few infectious units infected the infant [15-19]. Phenotypic studies of transmitted viruses suggested that most early viral isolates from perinatally infected children are tropic for monocyte-derived macrophages (MDM) [34]. These results raised the possibility that sequences in the V3 region could be responsible for escaping maternal immune responses while preserving determinants specific for tropism of cells exposed around or during birth.

At the present time, the viral genetic determinants responsible for perinatal infection as well as whether genetic differences detected between HIV-1 subtypes have biological consequences are largely unknown. As such, intersubtype recombinants could represent useful molecular tools to map viral determinants associated with perinatal transmission in the context of HIV-1 subtypes. In this study, we found 22% of infants infected with HIV-1 subtype A, 22% infected with HIV-1 subtype C, 19% infected with HIV-1 subtype D, and 37% percent infected with recombinant viruses. These estimates do not indicate the subtype-specific transmission rates. It is necessary to identify the prevalence of HIV-1 subtypes in the mothers to determine whether HIV-1 subtypes A, C, D, and recombinants have different rates of transmission.

Analysis of genomic patterns showed that viruses with similar recombination patterns infected several infants. Despite the fact that these recombinant patterns clearly originated from independent events involving different subtypes, they all supported a selection bias for the V3 region. These recombinants could be grouped into two

population, and the V3 region might represent an important region for this selective expansion.

In summary, we have shown that a variety of recombinant HIV-1 viruses have been generated and efficiently transmitted to infants in Tanzania. The recombination patterns in these samples suggest that the V3 region could be a key determinant for transmission. The elevated number of recombinants transmitted perinatally suggests that co-infection or super-infection by two HIV-1 subtypes is not uncommon in this population.

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Sequence Note

Epidemic Expansion of HIV Type 1 Subtype C and Recombinant Genotypes in Tanzania

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HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) subtypes are distributed unevenly across African nations.¹ In East and Central African countries such as Uganda, Rwanda, Kenya, and Tanzania, the HIV-1 epidemic has involved two HIV-1 subtypes, A and D. In contrast, HIV-1 subtype C has dominated the rapidly expanding epidemic in Malawi and South Africa.¹⁻³ The relative roles played by virological, behavioral, and host determinants in the epidemic expansion of any particular HIV-1 subtype are unclear. Characterization of the transmissibility and pathogenic potential of distinct HIV-1 genetic subtypes is currently under investigation in many regions of the world. Careful surveillance of genetic subtypes prevalent in a given population is one particularly important approach to better understand the biological properties of different HIV-1 subtypes.

The presence of HIV-1 subtypes A and D in asymptomatic carriers and AIDS patients from several geographical locales in Tanzania has been previously described.⁴⁻⁷ An analysis of samples collected in 1988 showed that 10 of 15 (67%) envelope V3 sequences from Tanzanian samples were found to belong to subtype D. The remaining five samples (33%) belonged to HIV-1 subtype A.⁴ In Dar es Salaam, *vpu* and *env* sequences from 8 of 10 AIDS patients (80%) clustered with subtype D viruses and the remaining 2 (20%) with subtype A.⁵ A study in northern Tanzania reported that the *env*-encoded gp41 regions from 12 samples also clustered with HIV-1 subtypes A and D.⁶ In another report from northern Tanzania, four of eight (50%) envelope sequences sampled encompassing the C2V3 region belonged to subtype A and the other half to subtype D.⁷ Envelope sequences from HIV-1-infected individuals of Tanzanian origin, but living in Sweden, showed that three of four samples were HIV-1 subtype C and the remaining sample was HIV-1 subtype A.⁸ Even though this study suggested that HIV-1 subtype C was now present in Tanzania, it could not establish definitively that these infections were acquired in Tanzania, nor

were the cases documented as thoroughly as the samples described in this sequence note. In the present study, we describe HIV-1 subtypes A, D, C, and recombinants (C/A, C/D, A/D) in infants from Dar es Salaam, Tanzania.

Whole blood was collected from 387 infants, ranging from 6 to 62 weeks of age, attending the Muhimbili Medical Center neonatal clinic in Dar es Salaam. The infants were participating in a randomized trial to determine whether vitamin supplements could reduce the rate of mother-to-child transmission of HIV-1. Samples analyzed corresponded to the latest blood sample available from each infant. Peripheral blood mononuclear cells (PBMCs) were separated by centrifugation on Ficoll density gradients in Dar es Salaam and frozen cells were transferred to the laboratory in Boston. PBMCs were thawed, washed, and counted. HIV infection in the infants was determined by polymerase chain reaction (PCR) using the Amplicor HIV-1 detection kit (Roche Diagnostic Systems, Nutley, NJ) with modifications that increased primer sensitivity to non-B HIV-1 genotypes.⁹ All samples that gave a PCR signal according to the manufacturer standards were then used for envelope PCR amplification and sequence analysis. Two HIV-1-negative samples were included with each cell lysate preparation. Twenty microliters of crude cell extract was used for heminested PCR amplification with primers located in the envelope region of HIV-1. The first PCR amplification was done with primer *vpu*157 (nucleotides 5754-5774 according to HxB2 numbering¹⁰) and *env*1556 (nucleotides 7361-7328). Four microliters of the first PCR amplification was subjected to heminested PCR with primers *env*768 (nucleotides 6535-6559) and *env*1556. The amplification cycles for both reactions lasted for 3 min at 94°C, followed by 39 cycles of 1 min at 94°C, 1 min at 52°C, 3 min at 72°C, and a final extension cycle for 10 min at 72°C. Two separate reactions of an HIV-1-negative cell extract and a reaction without DNA were

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included with every PCR reaction. Amplified products were confirmed by Southern blot hybridization using internal ^{32}P -labeled probes. Amplicons were gel purified and cloned into a TopoVector (Invitrogen, San Diego, CA). Four *env* clones from each sample were sequenced in both directions by automated cycle sequencing with dye terminators using an ABI 373 system (Applied Biosystems, Foster City, CA). Six hundred and fifty nucleotides of each individual clone were subjected to phylogenetic analysis and recombination analysis through comparisons with the C2–C4 regions of previously classified HIV-1 subtypes A, B, C, D, E, F, G, and H¹⁰ (Table 1).

Eighty-six of 387 infants tested (22.2%) were found to be HIV-1 positive by the Amplicor test and confirmed by in-house PCR. Envelope sequences were obtained from 71 infants. Genotype classification by phylogenetic trees revealed that all 71 samples clustered inside or next to control sequences belonging to HIV-1 subtype A, D, or C. Samples that clustered next to a specific subtype group did not subcluster within that group were further analyzed using the recombination identification program (RIP) (Table 1).¹⁰ This analysis revealed the presence of recombinant genotypes between A, D, and C parent genomes. Consequently, all samples in this sequence note were subjected to subtype classification by both phylogenetic trees and RIP analysis. In addition, analyses of previously described sequences from Tanzania^{4–7} using similar algorithms were con-

ducted to confirm the presence of HIV-1 subtypes A, D, and C as well as to rule out the presence of recombinant genomes.

We found that phylogenetic analysis alone was not able to detect recombinant genomes since they were located as outliers of HIV-1 subtype A, D, or C clusters. Identification of recombinant genomes was possible only when RIP analysis was performed on these samples (Table 1). Twenty-five samples (35.2%) were classified as subtype A by phylogenetic and RIP analysis. The range of age for these infants was 6 to 62 weeks (mean of 17 weeks). Twelve samples (16.9%) were classified as HIV-1 subtype D with an age range of 10 to 50 weeks (mean of 21 weeks). Twenty-three samples (32.4%) with ages ranging from 6 to 51 weeks (mean of 18 weeks) were classified as HIV-1 subtype C by the same analysis. Although this study analyzed a fragment of one locus of the HIV-1 genome (650 base pairs), recombinant genotypes accounted for 11 samples (15.5%) in this study. The ages of these infants ranged from 6 to 26 weeks (mean of 13 weeks). Nine of these recombinant envelope fragments (82%) contained HIV-1 subtype C sequences (two C/A and seven C/D recombinant) and the other two were of the A/D genotype variety. Similar results were obtained independent of the clone used for the analysis. Without exception, clones belonging to one sample always clustered together and away from any other clone or control sequence used in the analysis. None of the sequences from the infants sam-

TABLE 1. HIV-1 SUBTYPES BASED ON PHYLOGENETIC AND RECOMBINANT IDENTIFICATION PROGRAM ANALYSIS OF SEQUENCES FROM TANZANIAN SAMPLES

Report ^a	Year of sampling ^b	Location ^c	HIV-1 loci ^d	HIV-1 subtypes by RIP analysis ^e			
				A	D	C	Rec.
4	1988	Turiani, Iringa, Dar es Salaam, Kilimanjaro	102–111 bp <i>env</i> V3	5 (33.3%)	9 (60.0%)	1 ^f (6.7%)	0 (0.0%)
5	1988	Dar es Salaam	231 bp <i>env</i> V3	2 (20.0%)	8 (80.0%)	0 (0.0%)	0 (0.0%)
6	1995 ^g	Moshi	50 aa <i>env</i> gp41	4 (33.3%)	8 (66.7%)	0 (0.0%)	0 (0.0%)
7	1987/1994	Mara region	336 bp <i>env</i> C2–V3	4 (50.0%)	3 (37.5%)	0 (0.0%)	1 (12.5%)
Present study	1996/1997	Dar es Salaam	650 bp <i>env</i> C2–C4	25 (35.2%)	12 (16.9%)	23 (32.4%)	11 (15.5%)

^aNumbers correspond to the reference number.

^bYear of sampling according to report.

^cGeographical location where the samples were obtained.

^dHIV-1 loci used in the study. bp, Base pairs; aa, amino acids.

^eFrequency of HIV-1 subtypes among samples subjected to RIP analysis. Percentages are shown in parentheses. Detection of intersubtype recombinants was performed using the recombinant identification program (RIP) from the Los Alamos HIV sequence database.¹⁰ RIP parameters included a 50-base window, 90% threshold for statistical significance, and stripped gaps between sequences. Each sample was compared with a master alignment (comprising consensus sequences from HIV-1 subtypes A, B, C, D, E, F, G, and H) obtained from the Los Alamos HIV sequence database. In addition, each sample was compared with consensus sequences from two putative subtype parent sequences (A–D, A–C, or C–D, respectively) and an outgroup sequence (SIVcpzGAB or HIV-1 MN).

^fThis sample, TZ10, clustered with HIV-1 subtype C controls by phylogenetic and RIP analysis.

^gJ. Shao, personal communication, 1997.

Nucleotide sequences were deposited in GenBank under accession numbers AF038051–AF038121.

ples clustered together with any sequence present in our sequence database and none of the clones from samples with recombinant genomes showed evidence of nonrecombinant sequences.

The results described here allow us to conclude that subtypes A, C, D, and their recombinants are currently present in the general population of Dar es Salaam, Tanzania. Since our findings of HIV-1 subtype C contrasted with the relative absence of subtype C in previous studies, we performed similar phylogenetic and RIP analyses to confirm the absence of subtype C and recombinants in earlier samples from Tanzania (Table 1). We were able to identify 1 HIV-1 subtype C and 1 HIV-1 C/D recombinant in 42 previously reported sequences. Sample TZ10 was not identified as subtype C since only controls of HIV-1 subtypes A, B, and D were used in their analysis.⁴ The other sample, TZ1585, was classified as HIV-1 subtype D by phylogenetic analysis,⁷ but the RIP analysis showed that this sample corresponded to a C/D recombinant.

The fact that subtype C genotypes, including recombinants containing a portion of subtype C, were found in about 45% of the infected newborns, as opposed to only 2 of the 45 samples (4.4%) described earlier, supports the hypothesis that different HIV-1 genotypes might be spreading at different rates in this area. A 1994 report of *vpu* and *env* sequences from 10 AIDS patients in the same geographical location as the present study classified 8 samples as HIV-1 subtype D and 2 samples as HIV-1 subtype A.⁵ Phylogenetic and RIP analyses of these 10 samples did not show evidence of HIV-1 subtype C or HIV-1 recombinant genomes.

The rate of perinatal transmission from HIV-1-positive mothers infected with distinct subtypes or recombinant viruses is not known at the present time. However, it is likely that the virus subtype detected in the infants indicates the presence of at least that subtype in the mother. We were able to detect recombinant sequences in infants as young as 6 weeks, which suggests that these recombinant viruses were probably transmitted from their mothers. If we assume that all HIV-1 subtypes are equally transmitted from mother to infants, HIV-1 subtype C appears to have been introduced after HIV-1 subtypes A and D were already established in Dar es Salaam and has quickly become one of the major subtypes present in that city. This assumption is supported by the elevated numbers of infants infected by HIV-1 subtype C and the apparent decrease in the proportion of those infected by subtype D. The rate of HIV-1 subtype D in all four previous studies range from 37.5 to 80.0% of all samples analyzed,⁴⁻⁷ as opposed to 16.9% in the current study. Conversely, if we assume that subtype C accounts for a minority of infections in pregnant women and the general population of Dar es Salaam, our results would suggest that HIV-1 subtype C (alone or its recombinants) showed higher rates of transmission from mother to infants than HIV-1 subtype A, D, or A/D recombinants. This assumption is supported by the fact that HIV-1 subtype C and its recombinants (C/A and C/D) account for 45% (23 individuals infected with HIV-1 subtype C and 9 with subtype C recombinants) of infant infections in a geographical locale where only HIV-1 subtypes A and D once predominated.^{4,5} We cannot rule out that the differences between our results and those of four previous reports on the subtypes prevalent in Tanzania may be due to geographic heterogeneity of the population sampled, or to an artifact of sensitivity related to the different primers used for PCR amplifica-

tion. However, the overwhelming number of infections by HIV-1 subtype C makes this possibility unlikely. Based on 650 bp of *env*, we cannot rule out that the number of recombinant genomes is higher than the 15.5% reported. It has been described that about 10% of the HIV-1 isolates sequenced over large regions including several genes are intersubtype recombinants.^{11,12} It is plausible that additional samples would be classified as recombinant if other HIV-1 genes were analyzed. Since our analysis was done directly from the infant peripheral blood mononuclear cells (PBMCs) to avoid tissue culture artifacts, these findings suggest that recombinant viruses are efficiently transmitted from infected mothers to infants.

To determine accurately the prevalence of HIV-1 subtype C and its recombinants in Tanzania and their ability to be transmitted from mother to infant, further studies are needed of the HIV-1 subtypes present in transmitting and nontransmitting mothers. These estimates can be subsequently compared with the HIV-1 subtypes present in infected newborns.

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RAPID COMMUNICATION

Transmission of Human Immunodeficiency Type 1 Viruses with Intersubtype Recombinant Long Terminal Repeat Sequences

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Retroviruses such as human immunodeficiency virus type 1 (HIV-1) contain two RNA strands per virion, and recombination can occur frequently during reverse transcription. Recombination may occur between HIV-1 genomes of the same subtype or among genomes of two or more distinct subtypes present in an individual. In the current study, we found that recombinatorial events were not limited to viral structural genes such as *gag* and *env*, but rather, recombination could likewise occur within the 5' long terminal repeat (LTR). Intersubtype recombinant LTRs among HIV-1 subtypes A, C, and D were found in Tanzanian infants. By introducing novel LTR sequences, these recombinant LTR viruses may further increase the adaptive potential and fitness of HIV-1. © 1999 Academic Press

Human immunodeficiency virus type 1 (HIV-1) sequences from around the world are extremely diverse. Distinct subtypes have been categorized based on phylogenetic analyses of *gag* and *env* genes (1, 2). To date, 10 HIV-1 subtypes have been documented (3). The high rate of mutation leading to greater genetic diversity within HIV-1 may be due to the error-prone nature of the viral reverse transcriptase enzyme. However, the recombination of RNA genome strands during proviral synthesis has been demonstrated between different HIV genomes of the same subtype or multiple distinct subtypes simultaneously infecting a single individual (4). This may provide another mechanism through which HIV-1 genetic diversity is increased. It has been reported that recombinant viruses account for approximately 10% of all HIV-1 isolates globally (5). Notably, the relevance of recombinant viruses has been demonstrated in Southeast Asia, where an A/E recombinant virus is the most prevalent genotype of HIV (6, 7). The HIV-1 epidemic in Tanzania, once attributed mainly to HIV-1 subtypes A and D, now appears to have a substantial presence of HIV-1 subtype C as well as recombinant viruses (8). The relevance of intersubtype recombination may be effectively studied in HIV-1-infected infants for multiple reasons. First, the virus almost certainly came from a single source of infection—the mother. Second, HIV-1 diversity is restricted

shortly after perinatal infection (9) such that a virus from the mother should represent the majority sequence in infected newborns. Third, the recombinant virus has to be infectious to be transmitted to the infant.

The long terminal repeat region (LTR) of HIV-1 is essential for proviral synthesis, integration of the proviral DNA into the host cell's genome, and regulation of HIV-1 transcription. Previously, we have shown that LTRs from HIV-1 subtypes B, C, and E contain distinct sequence patterns within critical regulatory elements (10). For instance, HIV-1 subtype C isolates typically contain three functional NF- κ B enhancer sites while subtype B contains only two. These sites serve to upregulate viral replication in response to the Rel family of DNA-binding proteins in multiple cell types (11). Theoretically, this may lead to increased fitness of viruses containing 3 NF- κ B enhancers by directly affecting viral growth and/or disease progression. As no data describing recombination within the 5' LTR have been published to date, we were interested in determining if field isolates of HIV-1 also exhibit intersubtype recombination in nonstructural regulatory regions of the genome.

Twenty-four LTR sequences (from 18 recombinant-infected and 6 non-recombinant-infected Tanzanian infants) were found to cluster with subtype A, C, or D references (Fig. 1), confirming previous subtype classification by analysis of the envelope gene (8). Samples TZB0065, TZB0023, TZB0024, TZB0001, TZB0003, TZB0020, TZB0022, TZB0067, and TZB0017 clustered with HIV-1 subtype A. Samples TZB0070, TZB0069, TZB0063,

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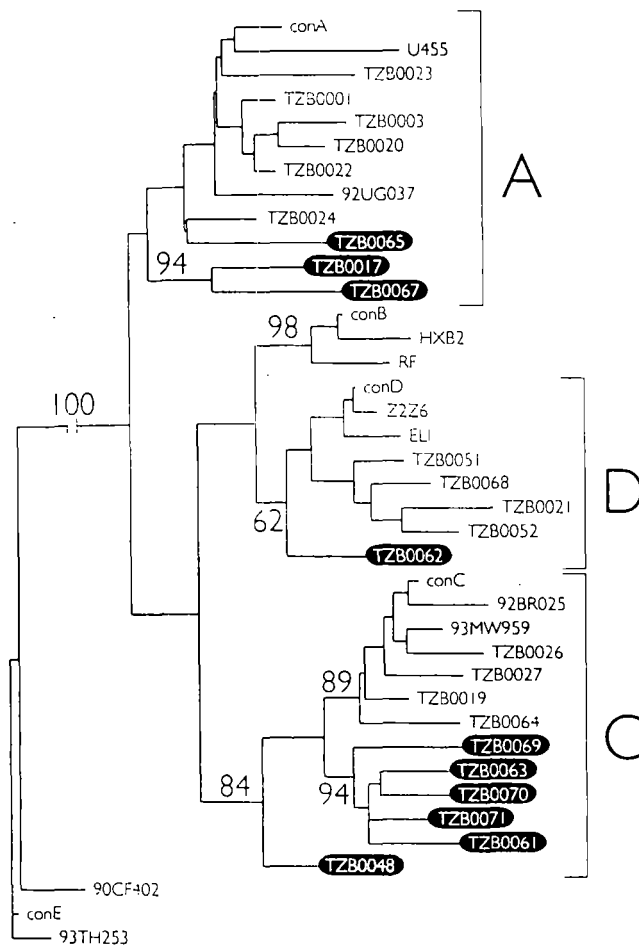


FIG. 1. Tanzania 5' LTR sequences (–392 to +310) were aligned in Clustal-W and compared with sequences from HIV-1 subtypes A–E. The phylogenetic tree was generated using PAUP under the assumption of minimum evolution with a neighbor-joining criterion ($\gamma = 0.5$, distance measure HKY85). Subtype C references were 30 nucleotides shorter at the 5' end of the LTR than other database references. All Tanzania isolates (indicated by the letters TZB, followed by a four-digit identifier) belong to subtype A, C, or D. Circled names indicate intersubtype LTR recombinants. Only relevant bootstrap values greater than 70 (out of 100) are given.

TZB0071, TZB0061, TZB0048, TZB0064, TZB0019, TZB0027, and TZB0026 clustered with subtype C. Samples TZB0021, TZB0068, TZB0051, TZB0062, and TZB0052 clustered with subtype D. However, samples TZB0070, TZB0061, TZB0071, TZB0063, and TZB0069 formed a distinct subcluster (94 of 100 bootstraps) within the subtype C branch, while samples TZB0067 and TZB0017 formed a distinct subcluster (94 of 100 bootstraps) within the A subtype. Samples TZB0048, TZB0062, and TZB0065 also appeared to be outliers within respective subtypes. The Recombinant Identification Program (RIP) was used to determine if these outliers represented intersubtype LTR recombinants. Because some of the recombinants identified by RIP were not outliers within particular subtypes, all 24 LTR isolates were analyzed using RIP. Twelve of eighteen *env/gag* recombinant-infected infants were identified as putative LTR recombinants (Table 1). Of the

six non-recombinant-infected infants, only TZB0001 was identified as a potential LTR recombinant using RIP.

Following RIP analysis, breakpoints for each putative LTR intersubtype recombinant were estimated. Phylogenetic analysis of LTR fragments upstream and downstream of each putative breakpoint confirmed the presence of 10 intersubtype LTR recombinant sequences. Five samples were identified as LTR recombinants between subtypes C and D (C/D): one as C/A, two as A/D, one as A/C, and one as D/A/D. The 5' LTR from sample TZB0062 actually contained two distinct breakpoints, making it a D/A/D recombinant. Figure 2 shows the approximate breakpoint for each intersubtype recombinant LTR. Only two breakpoints (samples TZB0062 and TZB0017) were identified in the modulatory/core region (–392 to –1) of the LTR, while two breakpoints (samples TZB0065 and TZB0067) were identified within the Tar region (+1 to +60). However, seven breakpoints (samples TZB0062, TZB0048, TZB0069, TZB0063, TZB0070,

TABLE 1

Sample	Age at draw (weeks)	LTR subtype	<i>env</i> subtype (8)
Recombinant infants			
TZB0017	39	A/D*	A
TZB0019	14	C	A
TZB0020	14	A	A
TZB0021	8	D	A
TZB0022	26	A*	A
TZB0023	10	A	A
TZB0024	10	A	A
TZB0048	51	C/A*	C
TZB0061	18	C/D*	D/C
TZB0062	11	D/A/D*	D/A
TZB0063	9	C/D*	D/C
TZB0064	14	C*	D/C
TZB0065	14	A/C*	A
TZB0067	14	A/D*	D/A
TZB0068	14	D	C
TZB0069	18	C/D*	D/C
TZB0070	6	C/D*	D/C
TZB0071	6	C/D*	D/C
Nonrecombinant infants			
TZB0001	25	A*	A
TZB0003	6	A	A
TZB0026	50	C	C
TZB0027	26	C	C
TZB0051	26	D	D
TZB0052	14	D	D

Note. "Recombinant" describes samples with evidence of intersubtype recombination within *env* or *gag* genes or discordant *gag-env* subtypes. Envelope data have been previously published (11). "Age at draw" indicates the age in weeks of the infant when the sample was drawn for sequence analysis. Asterisks indicate putative LTR recombinant sequences identified using the Recombination Identification Program (17). Only when results with both RIP and breakpoint analysis occurred were sequences considered to be intersubtype LTR recombinants of HIV-1; such intersubtype LTR recombinants are shown in boldface.

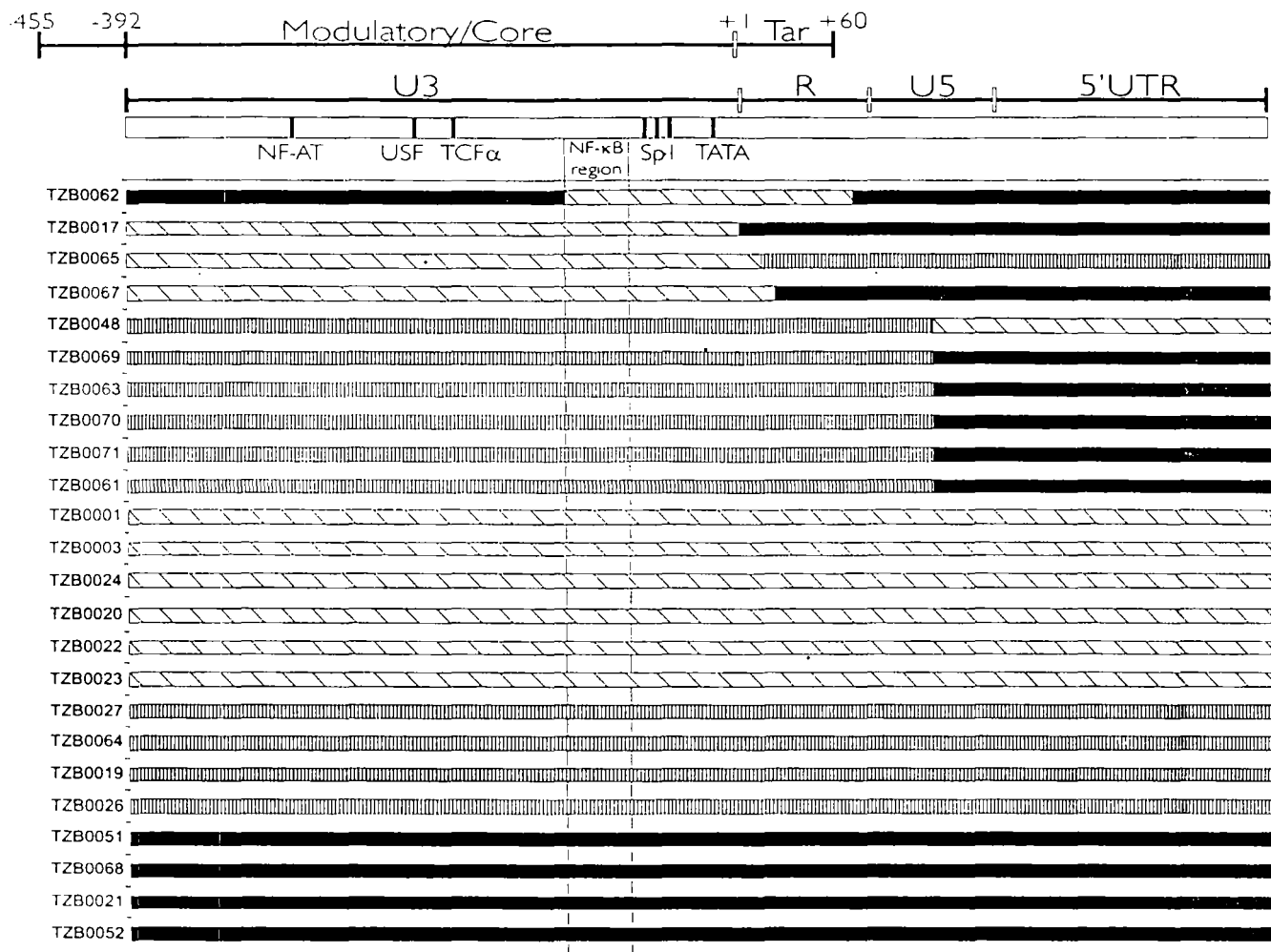


FIG. 2. Schematic representation of the 5' LTR is shown with important enhancer elements and regulatory regions of the LTR. All 5' LTR sequences sequenced in this study are drawn to scale showing their relative breakpoints. Nonrecombinant LTR sequences are indicated by a single shade corresponding to the appropriate HIV-1 subtype (A—light diagonal, C—strong vertical, D—solid black) while intersubtype recombinant LTRs are indicated by two shades.

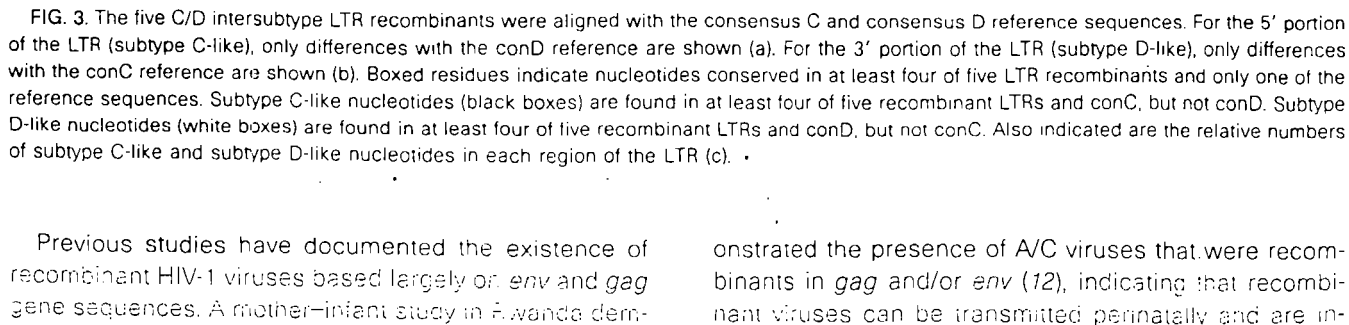
TZB0071, and TZB0061) were identified downstream of Tar, with five breakpoints occurring at approximately +100 relative to the transcription start site.

Although RIP initially suggested that samples TZB0022, TZB0064, and TZB0001 may have been intersubtype LTR recombinants, no breakpoints could be identified for these samples; therefore, they were not considered intersubtype LTR recombinants. Thus, within the *env/gag* recombinant-infected infant group, intersubtype LTR recombinants were identified within the 5' LTR of 10 of 18 infants; however, no intersubtype breakpoints were identified in the 6 infants constituting the HIV-1-infected, nonrecombinant group.

All five of the C/D recombinant LTRs had approximately the same breakpoint: four had breakpoints within 5 nucleotides of each other (as estimated by the RIP alignment), while the breakpoint of sample TZB0069 was approximately 25 nucleotides upstream of the other four. The highly conserved nature of these recombinant C/D LTRs was demonstrated by alignment with the consen-

sus C and consensus D reference sequences (Fig. 3). Upstream of the breakpoint for these five sequences were 53 subtype C-like nucleotides and only 6 subtype D-like nucleotides. However, downstream of the breakpoint, there were only 3 subtype C-like nucleotides and 16 subtype D-like nucleotides.

In an infant cohort infected with HIV-1 subtypes A, C, and D, as well as recombinant viruses, we identified the existence of multiple intersubtype recombinants within nonstructural regions of the HIV-1 genome, i.e., the 5' LTR. In this population with evidence of recombination within structural genes, 8 of 18 envelope sequences analyzed were intragenic recombinants (8) while 10 of 18 LTR sequences were intersubtype recombinants. C/D, A/D, C/A, A/C, and D/A/D intersubtype LTR recombinants have been identified. When present, recombinant LTR sequences are the only readily detectable sequences within the infants studied; therefore, these LTR recombinant viruses described presumably represent infectious viruses



fectious. Infants thus represent an ideal population in which to study the biological consequences of recombination within the HIV-1 genome. The functional relevance of intersubtype LTR recombinants has not been addressed here; however, different arrangements of enhancer elements and/or changes in the copy number of important protein binding motifs may represent adaptations of the viral LTR to particular host pressures. In other retroviruses, LTR sequences have also been shown to contain determinants important to cell tropism, transforming potential, and disease phenotype (13). By creating novel enhancer configurations, recombination within the HIV-1 LTR may increase its adaptive and/or evolutionary potential in multiple biologically relevant manners.

Although recombination within the LTR may be a random process, selective pressures acting on recombinant regulatory regions may generate viruses with increased fitness. For example, HIV-1 subtype C now accounts for approximately half of all infections in the world (14), suggesting that genomic sequences within subtype C may represent an important component contributing to its epidemic spread (15). There may also be a propensity for certain regions of subtype C genomes to survive following recombination. For example, we have previously shown that LTR sequences from HIV-1 subtype C contain three functional NF- κ B enhancers, whereas other HIV-1 subtypes have only one or two (10). Changes in the copy number of NF- κ B enhancers were also observed to correlate with divergent LTR activation in response to Rel-p65 protein. Since this enhancer is known to upregulate viral replication in several cell types, a virus containing three NF- κ B enhancers may have a fitness advantage over other viruses. Recombinant events that occur between non-C subtypes—A and D in this instance—and subtype C viruses may act to preserve the three NF- κ B enhancers of subtype C isolates while leaving other cellular and viral protein binding motifs elsewhere within the genome unmodified. This acquisition of an additional NF- κ B enhancer may partially explain the presence of a large number of C/D recombinant LTRs in Tanzania (as well as the C/A LTR recombinant that preserves three NF- κ B enhancers). By acquiring an additional NF- κ B enhancer through recombination with expanding subtype C viruses, subtype A and D viruses in Tanzania may have gained increased ability to replicate in activated cell types with high endogenous levels of Rel-family proteins. Conservation of subtype-specific nucleotides in both the subtype C and subtype D regions of these C/D recombinants supports the idea that these sequences are related. Because these five C/D LTRs also appear to contain the same recombinant C/D envelope with the same breakpoint (Renjifo, unpublished), the possibility that they represent a single recombination event that occurred previously and was independently transmitted to multiple persons,

including the Tanzanian infants in the current study, must be considered. This supports the idea that these recombinant viruses are just as able to survive in the studied population as their nonrecombinant counterparts. The two A/D recombinant LTRs also appear to have very similar breakpoints—within 11 nucleotides of one another—suggestive that they too may also have arisen from a single recombinatorial event. As the other three intersubtype LTR recombinants do not share common breakpoints, they most likely represent independent recombination events.

In conclusion, we find that recombination can occur within the 5' LTR of HIV-1. Such LTR recombinant viruses can be transmitted in a population of HIV-1-infected individuals, have occurred multiple times, and may expand the adaptive potential of HIV-1 recombinant genomes.

Whole blood was collected from infants ranging from 6 to 51 weeks of age whose mothers are participating in a randomized trial of vitamin supplements in the prevention of perinatal transmission in Dar es Salaam, Tanzania (Table 1). Peripheral blood mononuclear cells (PBMCs) were separated by centrifugation on Ficoll density gradients. For polymerase chain reaction (PCR) amplifications, DNA from PBMC crude cell lysates was used. In a previous study by our laboratory, the envelope sequences (650 nucleotides) from 71 infants were analyzed, indicating a high prevalence of HIV-1 subtypes A, C, and D as well as recombinant envelope viruses (8). Eighteen infants shown to be infected with recombinant viruses in the previous study or others subsequently shown to be infected with recombinant *gag* viruses and/or having discordant *gag-env* subtypes were selected for further analysis. An additional six HIV-1-positive infants (two each of subtypes A, C, and D) showing no evidence of infection with recombinant viruses were also selected for inclusion as reference local genotypes.

A 720-nucleotide fragment including the 5' LTR and the 5' untranslated region (UTR) was amplified using a heminested PCR. Primers used for the first-round amplification were LTR-A (5'-CAAGGATCCTTCCC TGATTG-GCAGAACTAC-3') (nucleotides 9147-9177 according to number of HxB2) and PBS-B (5'-CTTAATACTGACGCTCTCGCACCCAT-3') (nucleotides 816-790). Primers for the second-round amplification were LTR-A and PBS-D (5'-CTCTCCTTCTAGCCTCCGCTAGTC-3') (nucleotides 788-764). The LTR was purified and ligated into the PCR2.1-TOPO vector for sequencing using an ABI373 automated sequencer. Three to six clones per sample were analyzed and used to obtain a consensus sequence for each LTR isolate. Consensus LTR sequences were aligned in Clustal-W (16) and compared with reference sequences (A: conA, U455, 92UG037; B: conB, HXB2, RF; C: conC, 92BR025, 93MW959; D: conD, Z2Z6, EL1; E: conE, 93TH253, 90CR402) to assign an HIV-1 subtype. All sequences were analyzed using the RIP (17) with a 100-bp window and gap striding. Using the RIP

alignment, breakpoints for putative intersubtype LTR recombinant sequences were estimated. Further phylogenetic analyses with HIV-1 subtype A, C, and D references were performed to confirm that sequences upstream (5') of the recombinant breakpoint belonged to one subtype while sequences downstream (3') of the breakpoint belonged to a different subtype. Only when agreement occurred between both RIP and the breakpoint analysis were sequences considered to be intersubtype LTR recombinants. Sequences were submitted to Genbank under Accession Nos. AF096633-AF096657.

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Research Forum: Ethics and Studies of HIV

Human Rights and Maternal-Fetal HIV Transmission Prevention Trials in Africa

George J. Annas, JD, MPH, and Michael A. Grodin, MD

ABSTRACT

The human rights issues raised by the conduct of maternal-fetal human immunodeficiency virus transmission trials in Africa are not unique to either acquired immunodeficiency syndrome or Africa, but public discussion of these trials presents an opportunity for the United States and other wealthy nations to take the rights and welfare of impoverished populations seriously. The central issue at stake when developed countries perform research on subjects in developing countries is exploitation. The only way to prevent exploitation of a research population is to insist not only that informed consent be obtained but also that should an intervention be proven beneficial the intervention will be delivered to the impoverished population. Human rights are universal and can not be compromised solely on the basis of beliefs or practices of any one country or group. The challenge to the developed countries is to implement programs to improve the health of the people in developing countries both by improving public health infrastructure and by delivering effective drugs and vaccines to the people. (*Am J Public Health* 1998;88:560-563).

Introduction

Since the adoption of the Universal Declaration of Human Rights by the United Nations General Assembly in 1948, the countries of the world have agreed that all humans have dignity and rights. In 1998, the 50th anniversary of the Universal Declaration of Human Rights, the Declaration's aspirations have yet to be realized, and poverty, racism, and sexism continue to conspire to frustrate the worldwide human rights movement. The human rights and public health issues of maternal-fetal human immunodeficiency virus (HIV) transmission prevention trials in Africa, Asia, and the Caribbean are not unique to acquired immunodeficiency syndrome (AIDS) or to those countries. Open discussion of these issues provides an opportunity to move the real human rights agenda forward.¹ This is why Global Lawyers and Physicians (GLP), a transnational organization dedicated to promoting and protecting the health-related provisions of the Universal Declaration of Human Rights, joined with Ralph Nader's Public Citizen organization to challenge the conduct of a series of AIDS clinical trials in these developing countries² (S. M. Wolfe et al., written communication to Secretary of Health and Human Services Donna Shalala, April 22, 1997).

The Clinical Trials

In 1994, the first effective intervention to reduce the perinatal transmission of HIV was developed in the United States in AIDS Clinical Trials Group (ACTG) Study 076. In that trial, use of zidovudine administered orally to HIV-positive pregnant women as early as the second trimester of pregnancy, intravenously during labor, and orally to

their newborns for 6 weeks reduced the incidence of HIV infection by two thirds (from about 25% to about 8%).³ Six months after stopping the study, the US Public Health Service recommended the ACTG 076 regimen as the standard of care in the United States.⁴ In June 1994, the World Health Organization (WHO) convened a meeting in Geneva at which it was concluded (in an unpublished report) that the 076 regime was not feasible in the developing world. At least 16 randomized clinical trials (15 using placebos as controls) were subsequently approved for conduct in developing countries, primarily in Africa. These trials involve more than 17 000 pregnant women. Nine of the studies, most of them comparing shorter courses of zidovudine, vitamin A, or HIV immunoglobulin with placebo, are funded by the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH).²

Most of the public discussion about these trials has centered on the use of placebos.^{2,5,6} The question of placebo use is a central one in determining how a study should be conducted. But we believe the more important issue these trials raise is the question of whether they should be done at all. Specifically, when is medical research ethically justified in developing countries that do not have adequate health services (or on US populations that have no access to basic health care)? This question is espe-

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cially pertinent since February 1998 when, on the basis of a Thailand study that demonstrated that a short course of zidovudine reduced HIV transmission by 50%, CDC, NIH, and the United Nations Program on AIDS (UNAIDS) officials announced that they would recommend that the use of placebo be halted in all mother-to-fetus transmission studies.⁷

Research on Impoverished Populations

The central issue involved in doing research with impoverished populations is exploitation. Harold Varmus, speaking for NIH, and David Satcher, speaking for CDC, both seem to realize this. They wrote in the *New England Journal of Medicine* last year that "trials that make use of impoverished populations to test drugs for use solely in developed countries violate our most basic understanding of ethical behavior."⁸ However, instead of trying to demonstrate how the study interventions, such as a shorter course of zidovudine (AZT), could actually be delivered to the populations of the countries in the studies, they assert that the studies can be justified because they will provide information that the host country can use to "make a sound judgment about the appropriateness and financial feasibility of providing the intervention."⁹ However, what these countries require is not good intentions, but a real plan to deliver the intervention, should it be proven beneficial.

Unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gained from the clinical trials for the developed countries' own benefit. If the research reveals regimens of equal efficacy at less cost, these regimens will surely be implemented in the developed world. If the research reveals the regimens to be less efficacious, these results will be added to the scientific literature, and the developed world will not conduct those studies. Ethics and basic human rights principles require not a thin promise, but a real plan as to how the intervention will actually be delivered. Actual delivery is also, of course, required to support even the utilitarian justification for the trials, which is to find a simple, inexpensive, and feasible intervention in as short a time frame as possible because so many people are dying of AIDS. No justification is supportable unless the intervention is actually made widely available to the relevant populations.

TABLE 1—Health Care Expenditures of African Countries Involved in Mother-to-Child HIV Transmission Prevention Trials

Country (Year)	Per Capita (US dollars)	As % of GDP*
Burkina Faso (1992)	22	5.5
Cote d'Ivoire (1995)	22	3.4
Ethiopia (1990)	5	3.9
Kenya (1992)	13	2.5
Malawi (1990)	11	5.0
Tanzania (1990)	5	5.0
Uganda (1994)	10	3.9
Zimbabwe (1991)	86	6.5

Data from World Bank Sector Strategy, Health Nutrition, and Population, 1997.

*GDP = gross domestic product.

Neither NIH nor CDC (nor the host countries) has a plan that would make the interventions they are studying available in Africa, where more than two thirds of the people in the world reside who are infected with HIV.⁷ As an example, Varmus and Satcher point out that the wholesale cost of zidovudine in the 076 protocol is estimated to be in excess of \$800 per mother and infant and that this amount is far greater than what most developing countries can pay for standard care.⁶ The CDC estimates the cost of the "short course" zidovudine regimens being investigated to be roughly \$50 per person. The cost of merely screening for HIV disease, a precondition for any course of therapy, is approximately \$10, and all pregnant women must be screened to find the cases to treat. These costs must be compared with the total per capita health care expenditures of the countries where this research is being conducted (Table 1). Given this fact, African countries involved in the clinical trials (or some other funder) must make realistic assurances that if a research regimen proves effective in reducing mother-to-fetus transmission of HIV, resources will be made available so that the HIV-positive pregnant women in their countries will receive this regimen.

However, the mere assertion that the interventions will be feasible for use in the developing countries is simply not good enough, given our experience and knowledge of what happens in Africa now. For example, we already know that effectively treating sexually transmitted diseases such as syphilis, gonorrhea, and chancroid with the simple and effective treatments that are now available can drastically lower the incidence of HIV infection. Yet, these inexpensive and effective treatments are not delivered to poor Africans. For example, a recent study showed that improving the treatment of sexually transmitted diseases in rural Tanzania could reduce HIV infections by 40%.⁸ Nonetheless, this relatively inexpen-

sive and effective intervention is not delivered. Vaccines against devastating diseases have also been developed with sub-Saharan African populations as test subjects.⁹ Nonetheless, even though vaccines such as the group A meningococcal meningitis vaccine are inexpensive and effective, they are not adequately delivered to the relevant sub-Saharan African populations.⁹

Cultural Relativism or Universal Human Rights?

In their article in the *New England Journal of Medicine*, Varmus and Satcher sought to bolster their ethical position by quoting the chair of the AIDS Research Committee of the Uganda Cancer Institute, who wrote in a letter to Dr. Varmus:

These are Ugandan studies conducted by Ugandan investigators on Ugandans. . . . It is not NIH conducting the studies in Uganda, but Ugandans conducting their study on their people for the good of their people.⁶

Two points are especially striking about Varmus' and Satcher's using this justification. First, their justification is simply not accurate. If NIH and CDC were not involved in these studies, these agencies would not have to justify them; indeed, the studies would not have been undertaken. These US agencies *are* involved—these trials are not just Ugandans doing research on other Ugandans. Second, and more importantly, the use of this quotation implies support for an outdated and dangerous view of cultural relativism.

Even if it were true that the studies in question were done by Ugandans on Ugandans, this would not mean that the United States or the international community could conclude that they should not be criticized. (This rationale did not inhibit criticism of apartheid in South Africa, genocide in Rwanda, or torture and murder in the Congo.) Human Rights Watch, referring to

repression in Central Africa, said in its December 1997 review of the year on the issue of human rights that the slogan "African solutions to African problems" is now used as a "thin cover" for abusing citizens.¹⁰ That observation can be applicable to experimentation on citizens as well.

The other major justification both NIH and CDC use for the trials is the consensus reached at the June 1994 meeting of researchers at WHO. Of the many analogies that have been drawn between the HIV transmission prevention trials and the US Public Health Service's Tuskegee syphilis study, perhaps most striking is their reliance on professional consensus instead of ethical principle to justify research on poor, black populations. As historian James Jones wrote in his book *Bad Blood*, which was written about the Tuskegee experiment: "The consensus was that the experiment was worth doing, and in a profession whose members did not have a well-developed system of normative ethics, consensus formed the functional equivalent of moral sanction."¹¹

Neither researcher consensus nor host country agreement is ethically sufficient justification for choosing a research population. As the National Research Council's Committee on Human Genome Diversity properly put it, in the context of international research on human subjects, "[s]ensitivity to the specific practices and beliefs of a community cannot be used as a justification for violating universal human rights."¹² Justice and equity questions are also important to the ability of individual research subjects to give informed consent.

Informed Consent

Research subjects should not be drawn from populations who are especially vulnerable (e.g., the poor, children, or mentally impaired persons) unless the population is the only group in which the research can be conducted and the group itself will derive benefits from the research. Even when these conditions are met, informed consent must also be obtained.^{13,14} In most settings in Africa, voluntary, informed consent will be problematic and difficult, and it may even preclude ethical research. This is because, in the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as "better than nothing" and research will almost inevitably be confused with treatment, making informed consent difficult.

Interviews with women subjects of the placebo-controlled trial in the Ivory Coast support this conclusion. For example, one subject, Cecile Guede, a 23-year-old HIV-infected mother participating in a US-financed trial, told the *New York Times*, "They gave me a bunch of pills to take, and told me how to take them. Some were for malaria, some were for fevers, and some were supposed to be for the virus. I knew that there were different kinds, but I figured that if one of them didn't work against AIDS, then one of the others would."¹⁵ The *Times* reporter who wrote the front-page story, Howard W. French, said, "For Ms Guede, the reason to enroll in the study last year was clear: it offered her and her infant free health care and a hope to shield her baby from deadly infection. . . . [T]he prospect of help as she brought her baby into the world made taking part in the experiment all but irresistible."¹⁵

Persons can make a gift of themselves by volunteering for research. However, it is extremely unlikely that poor African women would knowingly volunteer to participate in research that offered no benefit to their communities (because the intervention would not be made available) and that would only serve to enrich the multinational drug companies and the developed world.¹² Thus, a good ethical working rule is that researchers should presume that valid consent cannot be obtained from impoverished populations in the absence of a realistic plan to deliver the intervention to the population. Informed consent, by itself, can protect many subjects of research in developed countries, but its protective power is much more compromised in impoverished populations who are being offered what looks like medical care that is otherwise unavailable to them.

The International Community and the AIDS Pandemic

If the goal of the clinical trials is to reduce the spread of HIV infection in developing countries, what strategy should public health adopt to achieve this end? It is not obvious that the answer is to conduct clinical trials of short-term zidovudine treatment. In the developed world, for example, HIV-infected women are advised not to breast-feed their infants because 8% to 18% of them will be infected with HIV from breast milk.¹⁶ However, in much of the developing world, including in most African countries, WHO continues to rec-

ommend breast-feeding because the lack of clean water still makes formula-feeding more dangerous. As long as this recommendation stays in effect, and is followed, even universal use of the ACTG 076 regimen, which would lower the overall newborn infection rate by about 16%, would only likely serve to reduce the incidence of HIV infection in infants by about the same amount that it is increased by breast-feeding (8% to 18%). A more effective public health intervention to improve the health of women and their children may be to put more efforts into providing clean water and sanitation. This will help not only to deal with HIV, but also to alleviate many other problems, including diarrheal diseases.

President Jacques Chirac of France was on target in his December 1997 speech to the 10th International Conference on Sexually Transmitted Disease and AIDS in Africa, which was held in the Ivory Coast. President Chirac proposed creating an international "therapy support fund" that is primarily funded by European countries (the former colonial powers in Africa).¹⁷ Although he put emphasis on the new drugs available for AIDS treatments, it would be more useful to consider the public health priorities of the countries themselves, for example, prevention, especially in areas such as sanitation, water supply, nutrition, education, and the delivery of simple and effective vaccines and medical treatments for sexually transmitted diseases.

Conclusion

Actual delivery of health care requires more than just paying lip service to the principles of the Universal Declaration of Human Rights; it requires a real commitment to human rights and a willingness on the part of the developed countries to take economic, social, and cultural rights as seriously as political and civil rights. □

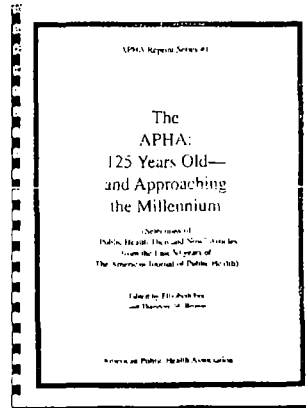
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Placebo Controls in HIV Perinatal Transmission Trials: A South African's Viewpoint

Salim S. Abdool Karim, MMed(CH), MS, FFCH(SA)

Introduction

The scale of the human immunodeficiency virus (HIV) epidemic in South Africa,¹ where 0.76% of pregnant women were HIV infected in 1990 and 14.07% in 1996,² highlights the importance of research to find practical and affordable interventions to curb HIV transmission. Lurie and Wolfe³ and Angell⁴ have raised the vexed issue under intensive discussion for some time now in South Africa of whether a placebo arm is ethical in studies of vertical transmission of HIV.

I agree with Lurie and Wolfe³ that researchers and research agencies from sponsoring countries should not conduct research in poor countries that would be unethical in their own countries, except under justifiable extenuating circumstances. Indeed, this is also advocated by the Council for International Organizations of Medical Sciences (CIOMS). However, the situation in South Africa is somewhat different; the funding sources for ongoing HIV vertical transmission trials, with placebo arms, are local agencies and the United Nations Program on Acquired Immunodeficiency Syndrome (UNAIDS).

One of the two large HIV perinatal transmission trials currently under way in South Africa is assessing the effect of vitamin A supplementation; the other trial is a 4-arm trial assessing a combination of zidovudine and 3TC given for a short period before, during, or after delivery. The vitamin A study has recruited almost 400 women and is funded by the South African Department of Health and the South African Medical Research Council. The short-course combination therapy trial, known as the Petra Study, is a multicenter trial funded by UNAIDS, and about 400 women will be recruited in each of the 2 sites in South Africa. Both trials are double-blinded, randomized control trials with placebo arms, and both have been scrutinized by institutional review boards, known in South Africa as ethics committees. The vitamin A study was approved by the University of Natal Ethics Committee, and the Petra study was approved by both the University of Natal and the University of the Witwatersrand.

These studies aim to find an intervention that will be affordable and implementable in a setting such as South Africa. They are critically important if the AIDS Clinical Trial Group (ACTG) 076 regimen of zidovudine,⁵ which has been shown to be effective, cannot be implemented.

Is the ACTG 076 Regimen Implementable in South Africa?

Although South Africa is a middle income country, cost is a constraint. Program planning with detailed costing reveals that the ACTG 076 regimen is not affordable without substantial redirection and reprioritization of health care resources. Currently, approximately 1.2 million births occur each year in South Africa. Substantial new resources will be required to test pregnant women with pre- and posttest counseling. Implementing the ACTG 076 regimen for those identified to be HIV infected will require further resources to increase the number of clinic visits several fold and to provide the close clinical management required for patients on antiretroviral drugs. Although the cost of zidovudine is substantial, important contributors to the costs of implementing the ACTG regimen in South Africa are the health service costs. Costs associated with HIV testing and medical care will be applicable regardless of the therapeutic regimen, but those costs will not be applicable to an intervention such as vitamin A supplementation, which can be given to all pregnant women without testing for HIV infection—hence the specific relevance of the vitamin A trial to the South African situation.

In South Africa, a second constraint to implementation of the ACTG 076 regimen is the high frequency of home deliveries, particularly in rural communities. A third constraint is the high frequency of booking for antenatal care appointments that are too late for the prenatal component of the ACTG 076 regimen, making its widespread use almost impossible. Additionally,

Editor's Note. See related article by Karim et al. (p 637) in this issue.

because breast-feeding is common in rural South Africa, HIV-positive women participating in the ACTG 076 regimen will have to be discouraged from breast-feeding. This could be possible only if breast-milk substitutes are provided either free or at heavily subsidized prices.⁶

If the ACTG 076 regimen is not being implemented in this country or cannot be implemented, should it be the standard of care in the control arm of HIV vertical transmission trials in South Africa? In this commentary, I will consider some of the scientific and ethical issues in this dilemma.

Other Treatment Options for the Control Group

Fundamentally, the research question at issue is whether shorter courses of combination antiretroviral therapy or micronutrient supplementation reduce vertical transmission of HIV sufficiently to warrant their wide-scale implementation in South Africa. If these interventions are hypothesized to be as good as or better than ACTG 076, then a control arm with the ACTG 076 regimen is entirely appropriate. What if the study interventions are not as good as ACTG 076? This possibility—in stark contrast to the “more optimistic view” taken by Lurie and Wolfe³—must be seriously considered in the design of the trials.

In considering each of the 3 options for the control group in these trials, the real possibility must be considered that shorter course drug regimens or micronutrient supplementation may not reduce the HIV vertical transmission rate to the same extent as the ACTG 076 regimen (e.g., they may be only be half as efficacious).

Option 1: No Concurrent Control Group; Historical Data Provide the Comparison Vertical Transmission Rate

The vertical transmission rate in South Africa has been changing over time. In a cohort of 111 subjects recruited in 1990 through 1991 at King Edward VIII Hospital, the HIV vertical transmission rate was 27%,⁷ while a cohort of 180 subjects recruited at the same hospital in 1993 through 1994 had a rate of 38% (Dr D. Moodley, personal communication). If a hypothetical non-randomized study was conducted in 1993 to 1994 with an intervention that was 33% effective, the outcome would have been an HIV vertical transmission rate of 26%. Without placebo data providing the concurrent rate of 38%, comparing the study rate of 26% with the rate in 1990 through 1991 of

27% would have led to the conclusion that the intervention had no effect.

The vertical transmission rate is influenced by many factors, including cesarean section rates, maternal viral load, and breast-feeding rates. As these factors change over time, the HIV vertical transmission rate will also change, either increasing or decreasing depending on which factors change and to what extent. Given the changing HIV vertical transmission rate, historical comparisons may lead to spurious conclusions and are therefore not acceptable.

Option 2: A Control Group Using the ACTG 076 Regimen

If a control group uses the ACTG 076 regimen, the clinical trial may be viewed as an equivalency study. An equivalency study is informative if the study interventions are found to be as good as, or better than, the control (equivalent) intervention and if the expected outcome of the control intervention is known. However, the effect of the ACTG 076 regimen in South Africa is not known, and extrapolation based on data from other settings is fraught with problems, given differences in breast-feeding rates, sexually transmitted disease rates, cesarean section rates, levels of viral load, and other variables.

The following is an extension of the example used to illustrate option 1:

A hypothetical randomized control trial with the ACTG 076 regimen in the control arm was conducted in 1993 through 1994. The study produced an HIV vertical transmission rate of 13% (66% effective on a baseline rate of 38%) in the control ACTG 076 arm and 26% (33% effective on the baseline rate of 38%) in the intervention arm. The conclusion would be that the intervention had doubled the vertical transmission rate of ACTG 076. In the absence of concurrent placebo data showing the baseline rate to be 38%, it would be impossible to interpret these results further and to make any conclusions about the efficacy of the new intervention, other than to say that it is not as good as the ACTG 076 regimen. Because the effect of the ACTG 076 regimen in South Africa is not known, it would be impossible to interpret a vertical transmission rate in the intervention arm if it were higher than the rate in the ACTG 076 arm. Hence, a control group with the ACTG 076 regimen is clearly inappropriate.

Option 3: A Placebo Control Group

A placebo control group is the only option that would enable the calculation of

the absolute reduction in the HIV vertical transmission rate, regardless of the extent to which it may differ from the effect of the ACTG 076 regimen. The essential concurrent comparison HIV vertical transmission rate is available. A meaningful result would be obtained even if the effect of the study interventions were lower than that of the ACTG 076 regimen. It would be possible to calculate whether the study interventions make any difference at all and, if so, to what extent they lower the HIV vertical transmission rate. Therefore, on scientific grounds, a placebo control group is essential.

Is a Placebo Control Group Ethically Justifiable?

The starting point for all clinical trials is the assurance that trial participants will be protected from exploitation. Persons who are being recruited into a research project must be allowed to exercise their own judgment freely (autonomy) in deciding whether or not to participate in the research. Ethics committees in South Africa have a strong tradition of vigorously upholding this principle. Legally, the South African Medical Research Council has an obligation to protect and uphold the ethical standards of research in South Africa.⁸ Guidelines from the Council for International Organizations of Medical Sciences are extensively applied and the Medical Research Council's guidelines⁹ have been widely adopted in South Africa. Although institutional review has been undertaken for all the HIV perinatal transmission trials in South Africa, further steps to monitor the ethical standards of informed consent¹⁰ have also been voluntarily pursued by some of the research groups.

Informed and voluntary participation requires an understanding of the risks and benefits inherent in the research. In this context, participants should not be exposed to harm or undue risk, but this can be judged only in relation to a standard. The reality is that standards—in this case, the standard of care—differ across the world and even within countries; they are seldom agreed upon internationally. Although the ACTG 076 regimen of therapy is the standard of care in some countries, it is not an international standard, such as is set by the World Health Organization. Providing high-quality routine care to the control arm without providing the ACTG 076 regimen of zidovudine cannot then be construed as causing undue risk or harm to the study participants. No therapy that they may otherwise receive is being withheld from study

participants. To extend this argument, if the control arm has to be afforded an external standard of care that can produce a substantial reduction in the HIV vertical transmission rate, it then cannot be justified for participants to be randomized in a study intervention arm if there is a reasonable chance that the interventions under study are not as good as the ACTG 076 regimen. It is, therefore, my opinion that the placebo control arm is ethically justifiable.

Standards of care evolve, and the acceptable standards of care will change over time. This does not mean that ethics are flexible; the consistent application of the basic principles of ethics in a world that varies markedly and changes rapidly is not inconsistent with differing standards of care being ethically acceptable in different settings or at different times.

Conclusion

Everyone agrees that there is an urgent need to reduce vertical transmission of HIV,

and this remains the central goal of the studies in South Africa. The local imperative is to develop and demonstrate further the efficacy of an affordable and implementable intervention to reduce HIV vertical transmission. While such an intervention need not be as good as the ACTG 076 regimen of therapy, its impact on HIV vertical transmission must be known, because this information will be the basis of policy that will aim to protect hundreds of thousands of infants from becoming infected with HIV. □

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Ethical Challenges in Efficacy Trials of Vaginal Microbicides for HIV Prevention

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ABSTRACT

This paper discusses some of the ethical challenges raised by advanced clinical trials designed to assess the safety and efficacy of vaginal microbicides in protecting women from HIV infection. The ethical principles that guide clinical research involving human subjects require that all participants in such trials be provided available measures known to reduce the risk of HIV infection. However, this will reduce the ability of the study to assess the protective effect of the test microbicide. In addition, providing extensive services to trial participants may be construed as an undue inducement if the study is being conducted among vulnerable groups such as sex workers or women from disadvantaged communities. Suggestions are provided to resolve this dilemma in the planning and implementation of HIV prevention services for trial participants. (*Am J Public Health*. 1998; 88:571-575)

Introduction

A critical need in stemming the spread of the HIV/AIDS pandemic is to expand the range of methods that women can use for the prevention of all sexually transmitted infections,^{1,2} including vaginal microbicides.^{3,4} A number of products have reached the stage of advanced clinical trials to assess their safety and efficacy in protecting women from HIV infection.⁵ A major challenge is to design microbicide trials that are "both scientifically rigorous and ethically defensible."³

This paper discusses an issue that looms large in the design of such trials: the provision of HIV prevention services to participants. Discussion first centers on why such services are required and why they should focus on the promotion of condom use. The ethical and practical dilemmas raised by this requirement are then described. Finally, implications for the design and planning of microbicide efficacy trials are explored.

The Ethical Imperatives

The most rigorous and reliable approach to measuring the efficacy of a new product, such as a microbicide, and obtaining approval for its widespread distribution is a randomized controlled trial (although for various reasons, including ethical difficulties, other designs may sometimes be more appropriate^{5,6}). Such trials should include sufficient participants to have adequate statistical power to measure the benefits and any adverse effects of the experimental product. Sample size depends on the expected incidence of HIV infection in the trial participants, on the predicted reduction in incidence related to microbicide use, and on other factors such as the retention and compliance of trial participants.⁴ Trials of this kind are often conducted in developing countries, among women who are at particularly high risk of heterosexually transmitted HIV infection (e.g., sex workers, clients of sexually transmitted disease clinics, and partners of HIV-infected men).

Biomedical research involving human subjects is guided by a number of basic ethical principles that are considered to be universally valid.⁷ According to the principles of beneficence and nonmaleficence, investigators have an obligation to maximize bene-

fits and to minimize risks for individuals who agree to participate in a study. This means that they have a duty to protect the health and well-being of study participants by providing them necessary health services. In clinical research, all study participants should be assured of the "most appropriate currently established" interventions to deal with the problem at hand.⁸ Investigators must also be vigilant to ensure that individuals avoid all possible harm that might arise from their participation in the research. In microbicide efficacy trials, there is therefore an ethical mandate to provide services known to reduce the risk of HIV infection and accepted as the standard of care.

At present, male latex condoms are widely available and generally considered to be the most effective method, apart from sexual abstinence, of preventing the heterosexual transmission of HIV.⁹ It is therefore generally recommended that, at the very least, all participants in a microbicide trial be given free supplies of condoms and be urged to use both the vaginal product and a condom during each act of intercourse.¹⁰ (The issue of female condoms has not yet been raised in the context of microbicide trials. Nonetheless, they would need to be offered along with the male condom in areas where they have been introduced and are available.) Statistical techniques are used to measure the protective effect of microbicides over and above the protection provided by the use of condoms alone.

The Investigator's Dilemma

These ethical imperatives place investigators in a bind. The problem is that the provision of HIV prevention services to both the control and the experimental groups should reduce the incidence of HIV infection. In addition, high levels of condom use will result in a small proportion of sex acts that are protected by the microbicide alone (only these sex acts can contribute to efficacy). This will blunt the ability of the study to assess the protective effect of the microbicide. Investigators thus have a disincentive to

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provide services that will significantly increase condom use and reduce HIV infections among trial participants.

A complicating factor is that participants are often sought among sex workers or women from disadvantaged communities, who are usually poor, are often exploited by employers or other community members, and have restricted access to health and social services, particularly in developing countries. Investigators are ethically bound to protect vulnerable subjects, and they need to pay particular attention to providing benefits in exchange for participation and to reducing heightened risks and burdens.¹¹ The difficulty is that, on the one hand, providing extensive services to such populations may be an undue inducement to participate in the trial.^{6,7} On the other hand, conducting research among them without attending to their basic health care and social needs would only increase their exploitation.

The dilemma, then, is that of striking the right balance between the need to protect the rights and health of women at risk of HIV and the need to meet demands of validity and efficiency⁶ in the testing of microbicides. The available evidence regarding the efficacy of existing candidate products is inconclusive,^{2,6,12,13} and there has been a call for further research. Basic rules must, of course, be observed to protect research participants. We must be careful, however, that efficacy trials do not become impractical, or else promising candidate microbicides will remain untested and unavailable, thus delaying for women access to these products that they so urgently need.

At this time, there is no argument with the ethical requirement to provide all trial participants prevention and health services, "within reasonable limits,"¹¹ to ensure that they derive benefits from their participation and are not exposed to undue coercion. The questions posed are as follows: What is a competent and acceptable package of services that should be offered to trial participants? and How should this package be developed? Some suggestions are offered for addressing these questions.

Implications for the Provision of Services to Trial Participants

What Condom Promotion Services Should Be Considered?

Studies of the impact of interventions to promote condom use among women at risk of HIV infection, although scant,¹⁴ indicate that condom use can be increased under specific circumstances. In particular, interven-

tions among women exposed to extreme risks of HIV infection, such as sex workers, have resulted in an increased proportion of commercial and casual sexual encounters in which condoms are used.¹⁵⁻¹⁹ Essential elements of condom promotion efforts include ready access to condoms and education and training in HIV risk reduction strategies.^{14,20,21} Training in social and sexual communication and assertiveness skills to deal with difficult situations and persist with condom use seems to be critical, particularly for disadvantaged women.^{14,20,21,23} In addition, it may be useful to include opportunities for collective problem solving and peer support, which can change peer norms about condom use, and to specify workable condom negotiation strategies.^{14,20-23}

All in all, studies indicate that interventions incorporating these elements can result in consistent condom use rates up to 60%. These rates, however, are often much lower despite intensive and sustained intervention efforts. Repeatedly, male resistance to condom use emerges as a major constraint that interventions targeted at women cannot break through. Furthermore, considerable heterogeneity in condom use is found among different types of sexual partnerships. In stable relationships, unprotected sex tends to be the norm.²⁴ Some interventions have successfully reached beyond individual women to their male partners, with high levels of consistent condom use recorded in couples in which both partners have been exposed to HIV counseling and testing^{25,26} (in particular, HIV-discordant couples²⁷⁻²⁹). These interventions, however, are not universally applicable.¹⁴ Ultimately, it is likely that widespread and sustained HIV risk reduction will be realized only if male involvement is ensured and if the environmental, political, and structural barriers to behavior change are addressed^{22,30,31} through community mobilization, legal action, and social change.³²⁻³⁴

Contextual interventions need further evaluation and may not be feasible or appropriate in the context of a randomized, controlled trial of a microbicide. On the other hand, an intervention that combines the promotion and distribution of condoms, the provision of tailored AIDS education, and training in social and sexual assertiveness skills, aimed at individual women or groups of women who participate in the trial, is eminently practical.

What Other HIV Prevention Services Should Be Provided?

Provision of clinical services for sexually transmitted infections has a powerful impact on HIV transmission, even in the

absence of any significant behavioral change,³⁵ and should therefore also be required in microbicide efficacy trials. In fact, many trials will include the incidence of sexually transmitted infections as a major outcome and will, as a result, involve regular monitoring of the presence of these infections. Because of their impact on HIV transmission, there is a strong case for offering treatments of sexually transmitted infections and attendant counseling services not just as part of monitoring activities but on demand as well, as an additional service to the trial participants.

Optimal management of sexually transmitted infections also includes partner management.³⁶ Thus, any woman who is found to have a sexually transmitted infection should be counseled about partner management, and the required drugs and counseling services should be provided to partners whom she refers for treatment. Other approaches to partner management, such as contact tracing, may be recommended at the study site and may have to be considered as well.

What About the Care and Support of Persons Living with HIV/AIDS?

HIV testing will usually be provided prior to enrollment in the trial, since HIV-seronegative women must be identified and followed up to ascertain the incidence of HIV infection. It has been pointed out that inclusion of HIV-infected individuals may be necessary to preserve the confidentiality of HIV test results.¹⁰ It may also be helpful in that these women would contribute information about the safety of the product and its efficacy against sexually transmitted infections other than HIV.¹⁰ More women will seroconvert after entry into the trial. All trial participants with HIV infection should be referred to services for essential medical care and social and psychological support. This raises a problem when appropriate services of this kind are not available and the social environment discriminates against persons living with HIV/AIDS.

Who Should Have Access to These Services?

Elias and Heise³ have argued that essential services such as condoms, HIV education, and reproductive health care should also be made available to women who choose not to participate in the trial so that women will not feel under pressure to gain access to these scarce resources. One approach might be to make some services (such as condom distribution and clinical

achieved but that this is a challenge. For many reasons, including the fact that women do not control the use of condoms, it is apparent that correct and consistent condom use is observed only among a minority of individuals. Thus, women who are exposed to extreme risks (e.g., sex workers and partners of seropositive men) may continue to suffer high HIV incidence rates, even if they receive, on an individual basis, high-quality and intensive condom promotion services. For example, incidence rates of 3 to 5 per 100 person-years have been documented, after a focused and intensive intervention, among sex workers in India¹⁶ and Zaire¹⁸ and among women attending antenatal and child health clinics in Rwanda.²⁵ In completed microbicide efficacy trials in which trial participants received condoms and repeated HIV education, HIV incidence rates of up to 7 and 9 per 100 person-years have been found among sex workers in Cameroon¹³ and among individuals in serodiscordant couples in Zambia,⁴¹ respectively.

The assumption that microbicide use presents fewer constraints to women than condom use is borne out by intervention studies in which the use of microbicides (or other female-controlled methods) is higher than that of condoms when both products are promoted together.⁴¹⁻⁴⁴ Therefore, trials in populations with high HIV incidence rates in which the incidence rate is measurable after the introduction of additional interventions will still be able to determine the efficacy of microbicide use if the incremental protection afforded by the use of the product is large enough and a sufficient proportion of sex acts are protected by the microbicide alone. Clearly, however, the more successful the interventions are in increasing condom use rates and reducing baseline HIV incidence rates, the more difficult it becomes to measure the incremental reduction in HIV incidence that can be attributed to microbicide use and the larger the required sample size.³ Sample sizes remain large even in situations of high HIV incidence, and it is likely that the greatest chance for success lies in the conduct of multicenter, multisite studies.³

Conclusions

Efficacy trials of microbicides raise a number of ethical and practical issues, many of which are common to controlled trials of other HIV preventive interventions and are being raised with respect to ongoing drug trials among HIV-infected pregnant women⁴⁵⁻⁴⁷ and planned HIV vaccine trials.⁴⁸ This paper has discussed considera-

tions related to the selection and implementation of HIV prevention services for participants in microbicide efficacy trials. The conclusion is that it should be possible to meet the scientific standards of trials that can answer the urgent questions posed regarding the safety and efficacy of candidate microbicides and, at the same time, to fulfill the ethical obligations of such trials (although the basic conditions may be difficult to achieve in very vulnerable populations and/or in very disadvantaged settings). However, the path ahead is narrow and troublesome, and finding the way will require "building a new consensus"⁶ through the concerted dialogue and action of scientists, activists, and community members. □

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Erratum

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The postal code in the address given for reprints and correspondence was incorrect. The correct code is G12 8RZ.

The Debate over Maternal-Fetal HIV Transmission Prevention Trials in Africa, Asia, and the Caribbean: Racist Exploitation or Exploitation of Racism?

Ronald Bayer, PhD

Introduction

On September 18, 1997, an editorial appeared in the *New England Journal of Medicine*¹ denouncing the conduct of clinical trials in Africa, Asia, and the Caribbean that were designed to determine the efficacy of interventions to reduce maternal-fetal transmission of human immunodeficiency virus (HIV). The attack, signed by Marcia Angell, MD, the journal's executive editor, signaled an escalation in what had been a simmering battle over the conditions under which trials could occur involving alternatives to the standard of care in Western nations for interrupting vertical transmission of HIV. That encounter was, in turn, embedded in the far broader debate on the conditions under which research in poor Third World nations, burdened by extraordinary rates of HIV infection, should take place.

Almost 4 years earlier, in February 1994, the Data Safety and Monitoring Board of the US National Institute of Allergies and Infectious Diseases had interrupted AIDS Clinical Trial Group (ACTG) Study 076 because preliminary data revealed a statistically significant and dramatic difference in vertical HIV transmission rates in women receiving zidovudine vs those who had been given a placebo.² The rate for the former was 8.3%; for the latter, 25.5%. Coming at a moment of profound pessimism regarding both therapeutic prospects and vaccine development for HIV, this finding was all the more striking. The ACTG 076 regimen, which involved giving zidovudine to the pregnant woman during the last 2 trimesters, an intravenous bolus of zidovudine during delivery, and zidovudine to the newborn for 6 weeks, quickly became the standard of care.

There was, however, in all of this a bitter irony. The cost of per-patient prophylactic treatment—\$800 for zidovudine alone³—was affordable only in industrialized nations where vertical transmission, although tragic, represented a relatively limited problem. In developing countries, however, where maternal-fetal transmission represents an epidemiologically significant

disaster, the costs of prophylactic treatment (disregarding the absence of the infrastructure necessary for intravenous treatment during delivery) put treatment with zidovudine out of reach. Until recently, it was believed that 200 000 infants worldwide become infected with HIV annually. In November 1997, United Nations estimates more than doubled that figure to 580 000 newly infected infants each year. The greatest proportion of such infections occur in poor nations. In Uganda, among the poorest of Third World nations, for example, the cost of the zidovudine component of the ACTG 076 regimen represents 400 times the yearly per capita expenditure on health care.

It was, therefore, a matter of some urgency that trials begin to determine whether radically cheaper alternatives to the ACTG 076 regimen could achieve at least some measure of reduced maternal-fetal HIV transmission. In June 1994, a special consultation of the World Health Organization (WHO) considered the challenge and called for the launching of studies to achieve that goal. The consultation made clear its conclusion that placebo-controlled trials "offer the best option for obtaining rapid and scientifically valid results."⁴

In all, 16 placebo-controlled trials were launched in developing countries, including the Ivory Coast, Uganda, Tanzania, Malawi, Ethiopia, Burkina Faso, Zimbabwe, Kenya, Thailand, Dominican Republic, and South Africa. Nine of the studies were funded by the Centers for Disease Control and Prevention (CDC) or the National Institutes of Health (NIH); 5 were funded by other governments, including Denmark, France, and South Africa; and one was funded by the United Nations Program on Acquired Immune Deficiency Syndrome (UNAIDS). Fifteen of the studies involved the use of placebos.

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Critics Argue Placebo-Controlled Trials Unethical

There is no question that a placebo-controlled trial of efforts to reduce further vertical transmission in the wake of clinical trial 076 would be considered unethical in the United States or any other advanced industrial nation. No trial that denies access to the ACTG 076 regimen, or to an intervention thought to hold the promise of being at least as effective as, if not more effective than, the prevailing standard of care, would satisfy the requirements of ethical review. The question posed by the recent controversy is whether it is ethical to conduct such a trial in a poor country where the ACTG 076 regimen is out of reach as a potential therapy. (The issue is not whether the ACTG 076 would be affordable for the very limited number of research subjects. It is.) In short, can it be considered ethical to provide placebos to women in Uganda when doing so would constitute an outrage in Brooklyn? To that question, Marcia Angell responds with a thunderous no:

Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment.¹

Given this premise, Angell rejects as irrelevant the fact that health care available in most Third World countries provides nothing like health care available in industrialized countries. Citing the Declaration of Helsinki for authority, she notes that control groups have to be provided with the best current therapy, not simply that which is available locally.

The shift in wording between "best" and "local" may be slight, but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsor country.¹

Then, with the obvious suggestion that racism was involved, she compares the recent research studies with the infamous Tuskegee syphilis study in which poor, African-American men were studied for decades to learn the consequences of untreated venereal disease, even after effective, inexpensive therapy became available. Angell argues that the justifications used for the recent trials are reminiscent of the justifications used for the Tuskegee study.

Women in the Third World would not receive antiretroviral treatment anyway, so the investigators are simply observing what

would happen to the subjects' infants if there were no study. And a placebo-controlled study is the fastest, most efficient way to obtain unambiguous information that will be of greatest value in the Third World.¹

Finally, Angell suggests darkly that narrow financial interests might have decided the shape of the research she attacks—clinical trials have become big business, and as in any big business, work must be done efficiently. The ethics of research, however, has a different logic, one that is not driven by considerations of efficiency above all else. To the extent that the logic of business has displaced the logic of research ethics, she warns, we have "not come very far from Tuskegee after all."¹

Similarly Effective Interventions Proposed

However sharp the tone of Angell's editorial, it is constrained by the venue of the august *New England Journal of Medicine*. Angell was even harsher when she denounced her antagonists in an op-ed piece in the *Wall Street Journal*.

All the rationalizations boil down to asserting that the end justifies the means—which it no more does in Africa than it did in Alabama. It is easy to see the findings of the Tuskegee study from a safe distance of 25 years. But those so offended by the comparison of the African research with Tuskegee have yet to show how these studies differ in their fundamental failure to protect the welfare of human subjects.⁵

Angell does not make clear what research would pass muster. However, given the status of the ACTG 076 regimen as the standard of care, the logic of her argument would suggest that, to be acceptable, a randomization must include the ACTG 076 regimen as the control, as well as an experimental arm that researchers have some reason to believe will be as good as, if not better than, the ACTG 076 regimen. That the limited resources of the Third World might have justified an effort to find an affordable intervention that, while effective, is less effective than the ACTG 076 regimen, would appear to Angell beyond the ethical pale.

Angell's editorial was sparked by a companion Sounding Board piece in the *New England Journal of Medicine*,⁶ authored by Peter Lurie, MD, and Sid Wolfe, MD, both physicians at the Health Research Group, part of Ralph Nader's Public Citizen organization. That piece, in turn, had its origins 6 months earlier in an open letter to Secretary of the US Department of Health and Human Services Donna Shalala,

denouncing the placebo studies (P Lurie et al., written communication, April 22, 1997).

In addition to being signed by Lurie and Wolfe, the open letter bears the signatures of other individuals long concerned with the ethics of research and the interests of medically vulnerable populations: George Annas, JD, Professor at the Boston University School of Public Health and a regular contributor to the *New England Journal of Medicine* on issues involving ethics; Michael Grodin, MD, Annas' colleague; and George Silver, an emeritus professor at Yale University who serves as contributing editor for the Policy Forum of the *American Journal of Public Health*.

Unless you act now as many as 1002 newborn infants in Africa, Asia, and the Caribbean will die from unnecessary HIV infections they will contract from their HIV-infected mothers in nine unethical research experiments funded by your Department. (P. Lurie et al., written communication, April 22, 1997)

These deaths, the letter charges, could be averted if Secretary Shalala were to require that all women involved be given some regimen of zidovudine or a similarly effective intervention. Although not opposed to randomized trials, the letter's authors insist that the randomization cannot entail a denial of interventions already proven effective.

Lurie et al., like Angell, cite the Tuskegee study and see the ACTG 076 studies in Africa, Asia, and the Caribbean as racist—as involving the exploitation of people of color.

Many people will hear in these experiments echoes of the notorious Tuskegee syphilis study. . . . This time, the people of color affected are babies from Africa, Asia, and the Caribbean, many hundreds of whom will die unnecessarily in the course of this unethical, exploitative research. (P. Lurie et al., written communication, April 22, 1997)

A Charge of Institutional Failure of Ethical Review

In underscoring the extent to which the placebo-controlled research violates international protocols governing research, the open letter by Lurie et al. cites the guidelines of the Council of the International Organization of Medical Societies (CIOMS):

An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than they would be in the case of research carried out in the sponsoring

country [emphasis supplied in letter].
(P. Lurie et al., written communication,
April 22, 1997)

Given the thrust of the CIOMS principles as well as those of the WHO enunciated in the Declaration of Helsinki and the Nuremberg Code, it is remarkable, the letter's authors note, that the placebo-controlled studies passed ethical review. Although the proponents of placebo-controlled trials would point to such oversight to justify the challenged research, Lurie et al. see in the approval of the trials a sign of institutional failure, even corruption: Researchers in developing countries are from higher social classes than those who are research subjects, and, thus, those researchers are unlikely to safeguard their subjects' interests. The lure of collaboration might simply overcome ethical scruples, given the "obvious benefits in prestige and, perhaps, in salary" (P. Lurie et al., written communication, April 22, 1997).

Affordability of Similarly Effective Interventions

A second and very different charge in the letter to Secretary Shalala underscores the claim that the placebo-controlled trials are exploitative of poor people, who are being manipulated into serving the interests of those who live in wealthy nations. Although the new strategies being examined might be less costly than the ACTG 076 regimen, they may still be unaffordable in the nations being used for testing. In that case, the new knowledge only provides cheaper options for industrialized nations (P. Lurie et al., written communication, April 22, 1997).

Surprisingly, having made this charge, the authors of the letter to Secretary Shalala go on to make clear that the only research that would be acceptable would raise the very questions of affordability.

We are, therefore, not opposed to research that modifies the regimen provided in Protocol 076 in order to identify a simpler, less expensive, similarly effective or more cost-effective intervention. . . . For example, one study arm could receive AZT [zidovudine] and the other AZT [zidovudine] and the experimental prophylactic regimen. (P. Lurie et al., written communication, April 22, 1997)

Equivalency Trials Accepted by Some—New Interventions Proposed

When this letter at last made its way into the *New England Journal of Medicine*

as a Sounding Board piece⁶ published together with Marcia Angell's editorial, it took a significantly different form from the open letter sent to Secretary Shalala—the 1002 babies who would die because of unethical research now became, more vaguely, "hundreds of babies." Rather than focusing on the claim that it was by definition unethical to conduct a placebo-controlled trial in the post-clinical trial ACTG 076 era, Lurie and Wolfe now asserted that, given the evidence of ACTG 076 itself, it is appropriate to conduct equivalency trials. Thus, their moral outrage is muted in the service of a set of methodological claims.

An equivalency trial, they point out,⁶ is conducted when a regimen has already been proven effective and when there is interest in determining whether a second regimen is about as effective but less toxic or expensive. Given the results of the ACTG 076 clinical trial, it was clear, Lurie and Wolfe aver, that shorter regimens would be more effective than placebos. They write: "These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds. . . ." ⁶ More critically, they claim that there is good reason to be optimistic that "researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen." ⁶

This reading of the data available when the placebo-controlled trials were being launched has not gone unchallenged. Jeffrey Laurence, director of the Laboratory for AIDS Virus Research at the New York Hospital-Cornell University Medical College, notes, for example, that the less costly interventions are "certain to be less effective than the standard regimen." ⁷

By way of summary, then, those who have opposed the recent trials have done so for a number of not always compatible reasons. Some have argued that, in the aftermath of clinical trial ACTG 076, research subjects in randomized trials must have access to the prevalent standard of care in the West; that zidovudine should be affordable for the limited numbers enrolled in trials; and that a zidovudine-based control arm should be provided to research subjects regardless of local prevailing medical practice. Some have been simply offended by the use of placebos in the trials conducted after ACTG 076, and they have urged comparisons of new interventions against historical controls, i.e., local experience with untreated populations. Finally, some, like Lurie and Wolfe, have asserted that, because the time is ripe for equivalency trials, placebos are methodologically unwarranted.

Placebo-Controlled Trials Defended; Changes Proposed

A formal public response to the challenge in the *New England Journal of Medicine* appeared 2 weeks later on October 2, 1997,³ signed by David Satcher, director of the CDC, and Harold Varmus, director of the NIH (the timing was possible only because information about the planned publication of the Lurie-Wolfe editorial had been leaked). Locating the criticized trials in the context of the profound poverty of many nations where vertical transmission is so critical an issue, Satcher and Varmus make clear in their letter that placebo-controlled trials were dictated by the urgency of the situation.

Nevertheless, they reject as "too simple" the argument that, because most women in the countries where placebo-controlled trials have been conducted received no care before participating in the trials, placebos represented no additional risk above standard practice. Satcher and Varmus thus seek to distance themselves from the charge that the research under attack took advantage of the poverty of the women involved. They also reject the argument that such trials could produce faster results with fewer subjects. More aggressive recruitment, they note, might have expedited the trial results.

Satcher's and Varmus' willingness to forgo these justifications reflects their extraordinary effort to neutralize the charge that narrow, economic concerns provided the warrant for research designs that involved a misuse of poor subjects. Thus, Satcher and Varmus lose the opportunity to engage the question of whether prevailing conditions in many Third World countries could justify trials that would not require "very large numbers of women in order to see a statistically significant improvement." ⁷ They also lose the opportunity to examine the difficult ethical question of how one should balance the claims of research subjects and their offspring against the claims of those who might be placed at risk if the use of non-placebo designs were to require trials of more extended duration. Time is not an ethically neutral consideration, given that, in the period before definitive answers become available, untreated mothers and their offspring continue to suffer the risk of vertical transmission.

In the end, Satcher and Varmus, like Lurie and Wolfe, seek a methodological rationale for their claims. Only placebo-controlled trials, they argue, can provide "definitive," "clear," "firm" answers about which interventions have worked, thus allow-

ing governments to make "sound judgments about the appropriateness and financial feasibility of providing the intervention."³

On methodological grounds, Satcher and Varmus argue that testing 2 or more interventions of unknown benefit against each other would not make clear whether either intervention would prove more effective than no intervention. In addition, even if one intervention were superior, it might be difficult to determine the extent of the advantage because the interventions might differ in other ways, e.g., in terms of toxicity or cost. Further, they point out, comparing an intervention of unknown benefit against the ACTG 076 regimen, which is likely to be more effective, would be of little use if the ACTG 076 regimen were unaffordable and therefore unavailable. Finally, the failure to employ a placebo control would make it difficult to clearly determine whether the affordable but less effective intervention is better than no intervention at all. In short, they conclude, placebos are crucial to policymakers required to make relatively costly decisions under conditions marked by profound poverty and scarce public health resources.

To bolster their argument, Satcher and Varmus underscore the extent to which consultation with host country scientists, physicians, and others has produced agreement on research design. Indeed, they quote Ugandan physician Edward Mbidde, MD, chair of the AIDS Research Committee: "These are Ugandan studies, conducted by Ugandan investigators, on Ugandans, for the good of their people."³

However heartfelt Mbidde's observation may be, it would be easy to challenge as involving an overstatement of the provenance of the research on vertical transmission. Likewise, one can easily imagine how Lurie and Wolfe would characterize such support, since they so contemptuously decry the self-interest of craven host-nation researchers.⁶ Nevertheless, local groups' consent to and collaboration in the research under challenge creates a far more complex picture than is suggested by the image of Western scientific imperialism imposing its will on hapless neocolonial societies.

Conclusion

The invective that characterizes the controversy outlined above is striking, in part because, despite assertions to the con-

trary, this debate is not an instance of the ongoing clash between those—called ethical imperialists by some, universalists by others—who believe that a single Western-dominated ethical standard should apply to all research and others who believe that ethical standards for research should reflect local values. Rather than a clash over first principles, this is a dispute over the application of agreed-upon principles in radically different social conditions. The controversy is also striking because persons with well-known commitments to the protection of the rights of research subjects find themselves confronting each other across a bitter divide.

Among those who have publicly supported the use of placebo-controlled trials are Arthur Amman, MD, president of the American Foundation for AIDS Research; Robert Levine, MD, of Yale University, long-time editor of *IRB: A Review of Human Subjects Research* and author of the standard text *Ethics of Regulation of Clinical Research*⁸; and Norman Fost, MD, a pediatrician and director of the Medical Ethics program at the University of Wisconsin, Madison. Among the trials' opponents, in addition to Marcia Angell, are Jonathan Mann, MD, former director of the WHO Global Programme on AIDS and a well-known advocate for human rights in the context of public health practice; Arthur Caplan, PhD, director of the Medical Ethics Program at the University of Pennsylvania and perhaps the most widely cited bioethicist in America; George Annas; and, of course, Lurie and Wolfe. Many remain conflicted or agnostic, most notably Ruth Faden, PhD, director of the Bioethics Institute at the Johns Hopkins University and former chair of the presidential commission established to examine the abuse of subjects in the context of radiation experiments.

This deep divide among the deeply committed at once explains the debate's fury and provides a clear sign that the issues involved are complex and not easily reduced to posturing and sloganeering. It is, therefore, especially troubling that the scandal of Tuskegee has been invoked to denounce the recent trials. Tuskegee was both cruel and deceptive: there was not even the pretense of informed consent, and ultimately the poor African-American men involved in that study were willfully deprived of socially affordable therapy for the treatment of their syphilis. Indeed,

every effort was made, through dissimulation, to keep those men from gaining access to effective therapy. In the trials under attack, however, women have given their informed consent, however problematic,⁹ and the studies have been examined by local review committees and an ethics committee of UNAIDS. Perhaps most important, everyone acknowledges that the ACTG 076 regimen is not socially affordable in most nations, given the price of zidovudine and the infrastructure requirements for its administration.

The tragedy of the recent trials is that they bear a profound moral taint, not of a malevolent research design but, rather, of a world economic order that makes effective prophylaxis for the interruption of maternal-fetal HIV transmission available but unaffordable for many—this is true, as well, for a host of treatments for AIDS and other diseases. In a just world, this would not be the case and the very research under attack would be unnecessary. It is the social context of maldistribution of wealth and resources that both mandates these studies and, at the same time, renders them so troubling. □

Acknowledgments

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meaning but, in our view, misguided pressure?⁹⁻¹¹ Or has Congress perhaps turned this scientific and ethical issue into a political one? In view of the consequences of the new joint position taken by the 4 agencies, the international community surely incurs a moral obligation to act. The particular and pressing issue is how to make the new intervention, or other alternatives to the standard regimen, affordable in the poorest nations.

Radical reduction in transmission of HIV from mother to child—and, hence, in the number of babies born with HIV infection—is now within reach. In the international community, then, does the political will exist to make good on the obligations entailed by this decision? Will the financial resources and support for providing the requisite treatment and building service structures for delivery be mobilized? That is one way to rescue this judgment by major agencies from charges of ill-considered haste, at best, and much else, at worst.

This new development only enhances the relevance to the current research scene of the papers in this issue of the Journal. In the face of international collaboration on research between rich and poor nations, these papers raise matters that will have to be confronted again and again. It is in that light that the papers should be read. In this instance once more, the past is prologue. □

Mervyn Susser
Editor

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Editorial: HIV Research, Ethics, and the Developing World

Six articles in this issue of the Journal address the conduct of human immunodeficiency virus (HIV) research in the developing world. The issues they raise, however, are neither unique to HIV nor unique to developing countries. In this editorial, we discuss several of these issues, including the failure to provide interventions of known efficacy, ethical relevance of study design, informed consent, and exploitation.

A challenge raised by de Zoysa et al.¹, Karim,² Wittkowski et al.,³ and others,^{4,5} is whether, or under what conditions, it is ethical in research to fail to provide an intervention of known efficacy. Perhaps the easiest case is raised by de Zoysa et al., in which they argue that HIV spermicide trials cannot be conducted ethically without also providing all participants with condoms. When the efficacy of spermicides is unknown and a cheap, effective, and available alternative (condoms) exists, no one disagrees that condoms must be provided to all research participants, even though knowledge about spermicide efficacy would come more quickly and with greater certainty if a placebo-controlled spermicide trial or an equivalency trial were conducted.

The further we diverge from this situation, in which an effective, easy-to-implement intervention is available, to situations that resemble the international clinical trials to prevent perinatal transmission of HIV, as discussed by Bayer⁴, Karim², and Annas and Grodin⁵, the less clear the ethical mandate

becomes. Here, the debate has focused on whether the standard of care in the United States—an expensive and complex regimen of zidovudine—must be provided to all HIV-infected pregnant women who join a research study in the developing world. Different scientists and scholars in bioethics have drawn the line differently in terms of what interventions routinely available in the developed world must be provided to research participants in the developing world. At an extreme, no one suggests requiring that the most expensive and complex of Western tertiary care, for example, renal dialysis or coronary bypass, must be provided in research conducted in the developing world. Indeed, public debates about the HIV perinatal transmission trials have not even focused on whether the women in the trials should be provided HIV combination therapy as they would be in the West⁸ or whether they should even have the zidovudine continued postpartum.

In addition to discussing the recent debate concerning international HIV research, these articles also focus on whether or not randomized, controlled trials must be conducted for researchers to learn about an intervention's efficacy. The choice of a study design is not simply between ethically questionable perfect trials that produce complete knowledge versus imperfect designs that produce no knowledge at all. Moreover, less rigorous designs, such as observational studies, that resolve certain ethical quandaries—as de Zoysa et al. suggest in

the context of condom distribution in spermicide trials—are not necessarily free of other ethical problems. One such problem is that these studies may provide only limited guidance for public health policy. This is illustrated by Wittkowski et al., who report on a repeat analysis of an observational study that strongly suggests vaginal spermicides effectively prevent HIV transmission. The authors acknowledge, however, that an observational design cannot match a randomized trial in accounting for potential confounding and that their results should be interpreted with caution.

Clearly, basing public health policy on a single observational study would be premature; however, multiple observational studies with findings comparable to the analysis by Wittkowski et al. could provide ethical justification for designing randomized equivalency trials comparing the effectiveness of condoms with spermicide. The results of these trials, in turn, should be sufficient for developing public health policy. Under many circumstances, this research strategy may appropriately accommodate ethical considerations with public health needs. The lapse of time in establishing an acceptable treatment in such a series of studies, however, should

Editor's Note. See related articles by de Zoysa et al. (p 571), Karim (p 564), Wittkowski et al. (p 590), Bayer (p 567), Annas and Grodin (p 560), and Karim et al. (p 637) in this issue.

be weighed against the prospect of obtaining quicker results from one or two placebo-controlled trials.

Another issue raised in these articles is that of informed consent, one of the cornerstones of research ethics. Clearly, as Karim et al.⁹ suggest, the quality of informed consent is compromised when potential patient-participants believe, even wrongly, that their medical care is contingent on their agreeing to participate in research. In contexts such as the Karim et al. study, it is important to emphasize to potential participants that neither their access to medical care, nor the quality of the care they receive, will be affected in any respect by their decision. Although it is sometimes difficult to clarify this separation of research from medical care, potential participants can be made aware through effective communication that a decision about research has no implications for their medical best interests. A more challenging situation occurs when potential participants *rightly* believe that their medical care is contingent on their agreeing to enroll in research. This issue is raised by de Zoysa et al. and Annas and Grodin. All too often, a research project offers the best medical care or the only medical care available, and it may be impossible for potential subjects who are ill or at risk to refuse research participation.

When such circumstances prevail, informed consent is profoundly compromised. The burden of proof is on the proponents of the research. At minimum, they must provide good, morally relevant reasons why the research should be conducted in a population that ordinarily does not have access to the medical care in question, rather than in a population that does. Additionally, without question, all subjects must be better off for being in the research. The risks and burdens imposed must be no worse than would be permitted were the research conducted in an economically advantaged population.

This last condition is introduced to prevent exploitation. We agree with Annas and Grodin that the risk of exploitation is a central moral concern in research. Exploitation occurs when unfair advantage is taken of the negative circumstances of others. These include poverty, absence of medical care, homelessness, imprisonment, and serious illness. Under conditions horrific enough, people may be better off as research subjects, even if they are thereby exposed to significant risk or painful procedures that in the end have no medical benefit. Although conducting research with disadvantaged people can be morally appropriate, the ethical stakes are much higher.

Problems with exploitation and informed consent often coincide, but they are

separable concerns. Annas and Grodin maintain that it is extremely unlikely that poor Africans would knowingly volunteer for research that would accrue benefits solely for the multinational drug companies and the developed world and not for their own communities (because the intervention would not be made available). Thus, researchers should presume that "valid consent cannot be obtained from impoverished populations in the absence of a realistic plan to deliver the intervention to the population."

On the contrary, we believe some poor Africans might knowingly participate in research that offers sufficient personal benefit to them at minimal risk but no benefit to their communities. That some or even many Africans might so consent to participation, however, does not make the research ethically acceptable. We agree with Annas and Grodin that such research is exploitive. It is fundamentally wrong to use the bodies of the poor to advance the exclusive interests of the wealthy.

In the specific, recent controversy surrounding HIV vertical transmission trials, no one is claiming otherwise. A foundational premise of the argument by Karim² in defense of the trials is that the results are urgently needed in Africa to guide the delivery of affordable and implementable interventions. Annas and Grodin are challenging that premise. They see no real plan for delivering even a short course of zidovudine to pregnant women of African countries (should a short course prove effective), given the extreme resource constraints that those and other developing nations face.

Annas and Grodin's challenge is well taken. Ethics requires more than vague promises. But what would an acceptable plan for implementation look like? Who would have to make what kind of assurances to whom? For example, would it be necessary for drug companies and international organizations to guarantee that, from the end of the trial forward, all affected pregnant women in the country in which the trial is conducted will receive the short course if it is efficacious? What if the guarantee is only for 5 years, or for one? Or only for the women of the township, not the nation? Who is to judge the adequacy and assess the validity of whatever assurance of access is made? These are difficult questions that the international research community must address if we are to have an adequate structure for ensuring the ethics of research in developing countries.

Also central to these difficult questions are deep challenges about who has the standing or authority to resolve them, and by what standards. Procedurally, American regulations and practices require that research set in the

developing world and conducted or funded, even in part, by Americans must be approved by an American institutional review board (IRB) and a similar board in the local country, where the research will be conducted. In the current controversy over the placebo-controlled trials, much has been made about approval of the trials by local review boards and of the defense of the trials by investigators from the affected developing countries. Although such support is clearly relevant to the ethics debate, Annas and Grodin rightly point out that approval by local authorities and review groups does not in itself guarantee that research is ethical, nor does it remove the moral ground for criticism by outsiders.

It is less clear, however, whether cultural relativism in research ethics is the basis for the dispute between some African supporters of the clinical trials and some Western critics. If these countries had health care budgets similar to our own, little disagreement might arise between Africans and Americans about what constitutes an ethical trial design. The more relevant question is not whether different cultural values justify different research designs, but rather whether different economic situations do. Surely the ethics of research are affected by relevant background conditions, but in what ways? What are the ethical implications when research studies are designed to address public health crises under extreme resource constraints?

Finally, we concur with Bayer that the use of the Tuskegee analogy when discussing the recent controversy in international perinatal HIV research is wholly inappropriate. The relevant question is whether the trials are *ethical*, not whether the trials resemble Tuskegee (here, in fact, we agree with Bayer that the two cases are significantly different morally). The Tuskegee analogy, as does the Holocaust analogy, guarantees attention to an argument. At very least, however, these analogies distract from a critical and honest dialogue, offend many, and belittle grim history.

The ethics of American researchers or funders conducting research in resource-poor environments is challenging beyond words. In the examples at hand, we face an agonizing choice. On the one hand, by adhering to Western standards of medical care, we could produce great benefit to the persons who participate in trials but slower progress for medical science. On the other hand, by providing less benefit to research participants in developing countries than that which is provided in developed countries, we are more likely to yield quicker and more relevant answers for the larger community. Such a dilemma calls for extensive further public discussion, which must include the voices of all relevant communities, from American researchers, fun-

ders, and IRBs, to local country researchers, governments, review boards, and, most especially, potential research participants and their communities. We can be confident that the ethics of international research will benefit from so much public attention. □

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Public Health Policy Forum

Trade-Offs in Prenatal Detection of Down Syndrome

ABSTRACT

Objectives. This paper presents the results of different screening policies for prenatal detection of Down syndrome that would allow decision makers to make informed choices.

Methods. A decision analysis model was built to compare 8 screening policies with regard to a selected set of outcome measures. Probabilities used in the analysis were obtained from official administrative data reports in Spain and Catalonia and from data published in the medical literature. Sensitivity analyses were carried out to test the robustness of screening policies results to changes in uptake rates, diagnostic accuracy, and resources consumed.

Results. Selected screening policies posed major trade-offs regarding detection rates, false positive results, fetal loss, and costs of the programs. All outcome measures considered were found quite robust to changes in uptake rates. Sensitivity and specificity rates of screening tests were shown to be the most influential factors in the outcome measures considered.

Conclusions. The disclosed trade-offs emphasize the need to comprehensively inform decision makers about both positive and negative consequences of adopting one screening policy or another. (*Am J Public Health* 1998;88:551-557).

Mateu Serra-Prat, MD, MPH, Pedro Gallo, MA, MSc, Albert J. Jovell, MD, DPH, PhD, Marta Aymerich, MD, and M. Dolors Estrada, MD

Introduction

Several studies have shown that maternal age is clearly a risk factor for having a child with Down syndrome.¹ A prenatal screening policy for Down syndrome based exclusively on a priori risk according to maternal age has in itself a low detection rate.² Thus, in recent years, new noninvasive tests for prenatal screening with biochemical markers²⁻⁷ and ultrasonography⁸⁻¹⁰ have been developed. In any screening test for Down syndrome, a confirmatory diagnostic test for positive results has to be performed by means of a chromosomal study of amniotic liquid cells obtained by amniocentesis or chorionic villus sampling.

However, even with the best expertise and equipment, these invasive tests are not without procedure-related risks. There is evidence that amniocentesis and chorionic villus sampling have estimated attributed risks of fetal loss of 1% and 3%, respectively.^{11,12}

The aim of this study was to carry out a comparative analysis of different screening policies for prenatal detection of Down syndrome. Decision analysis has been used as a methodological tool and as a means to present and assess how the different options compare with regard to a selected set of outcomes. The criteria for choosing among the plausible screening policies for prenatal detection of Down syndrome should include not only effectiveness, equity, and efficiency measures but also the need to minimize both false-positive rates and the adverse effects of performing invasive tests. The objective of this analysis was to comprehensively present the results of different options for prenatal screening and diagnosis of Down syndrome. These results would allow decision makers, at both the provider

and the consumer level, to make informed choices on the basis of effectiveness, safety, and efficiency criteria.

Methods

Decision analysis is a structured, explicit, and quantitative methodological tool that makes possible the quantification of selected outcomes associated with different courses of action in conditions of uncertainty.^{13,14}

We built a decision analysis model that includes 8 screening policies or options (see Figure 1):

Option 1: Do nothing.

Option 2: Offer amniocentesis to all pregnant women but offer no previous screening (neither biochemical nor ultrasonographic).

Option 3: Offer amniocentesis to all pregnant women older than 35 and offer ultrasonographic screening (nuchal fold > 6 mm, second trimester) to all pregnant women younger than 35. If ultrasonographic screening is positive, then amniocentesis is offered.

Option 4: Offer biochemical screening to all pregnant women (triple test with alpha-

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Topics for Our Times

Editorial

Editor's Note: The Prevention of Perinatal HIV Transmission in the Less-Developed World

A set of papers in this issue bears on the controversy surrounding prophylactic trials in the less developed world to avert maternal-to-infant transmission of human immunodeficiency virus (HIV).¹⁻⁷ These papers were rapidly assembled with the help of Ronald Bayer as guest editor, a task I invited him to assume once his own commentary had been accepted. The trials at issue aimed to establish alternatives to the now-standard US regimen for reducing vertical HIV transmission.

The controversy, which erupted in 1997, was brought to a resolution of sorts on February 18, 1998. The Centers for Disease Control and Prevention (CDC) announced that a trial in Thailand had been halted because of encouraging results: the data indicated that abbreviated prenatal treatment, at an anticipated cost of 10% of the standard US regimen (\$80 rather than \$800), reduced the rate of maternal/fetal transmission by half. (In a randomized controlled trial, the US regimen had reduced the transmission by about two thirds.) At the same time, the CDC recommended, in a joint statement with the National Institutes of Health (NIH), the Joint United Nations Program on Acquired Immunodeficiency Syndrome (UNAIDS), and Agence Nationale de Recherche sur la SIDA, that placebo arms no longer be used in such trials.

Critical issues remain, and new ones arise. The embargo on placebo trials, although not spelled out in detail, seems misguided. First, this encouraging result could not have been achieved without a placebo arm, as the CDC press release itself observes. An "equivalency trial," the alternative that some advocate—in which a new treatment is used against the standard treatment with the object of showing equivalence or better—could only have resulted in rejection of the now-heralded shortened regimen. The same result would follow for any other modification of the standard regimen so far proposed.

Second, the success of the Thai study is but one result, and it is one with wide confidence limits. One would have thought the not-infrequent reversals and failed replications of trial results are, in the HIV field, sufficiently recent and bitter to have stayed judgment.

Third, a condition of the Thai study was that the women should not breast-feed. The epidemic rages hottest in areas where breast-feeding is often a virtual necessity for the survival of many infants. Yet, breast-feeding threatens their survival, because it is also a main mode of HIV transmission from mother to infant. The Thai result for a non-breast-feeding population cannot fairly be extrapolated to breast-feeding populations. Indeed, the CDC press release is careful to say so.

Fourth, we can anticipate that the new recommendation will injure the poorest countries—those most vulnerable to the epidemic—and, most of all, the poorest and most vulnerable people within those countries. These people, for whom the S80 Thai regime is out of reach, are in dire need of low-cost interventions, which, albeit they are less effective, improve upon nothing at all. The combined force of 4 major international research funding agencies is behind the recommendation. Thus, it is almost certain to serve as a diktat blocking the most direct path to establishing affordable prophylaxis and treatment for poor, vulnerable populations.

Why the joint recommendation should depart from the carefully reasoned position of Dr Varmus (director of NIH) and Dr Satcher (then director of CDC) in favor of placebo-controlled trials⁸ is a puzzle. Have the agencies involved capitulated to well-

Editor's Note. See related articles by Faden et al. (p 548), Annas and Grodin (p 560), Karim (p 564), Bayer (p 567), de Zoysa et al. (p 571), Wittkowski et al. (p 590), and Karim et al. (p 637) in this issue.

meaning but, in our view, misguided pressure?⁹⁻¹¹ Or has Congress perhaps turned this scientific and ethical issue into a political one? In view of the consequences of the new joint position taken by the 4 agencies, the international community surely incurs a moral obligation to act. The particular and pressing issue is how to make the new intervention, or other alternatives to the standard regimen, affordable in the poorest nations.

Radical reduction in transmission of HIV from mother to child—and, hence, in the number of babies born with HIV infection—is now within reach. In the international community, then, does the political will exist to make good on the obligations entailed by this decision? Will the financial resources and support for providing the requisite treatment and building service structures for delivery be mobilized? That is one way to rescue this judgment by major agencies from charges of ill-considered haste, at best, and much else, at worst.

This new development only enhances the relevance to the current research scene of the papers in this issue of the Journal. In the face of international collaboration on research between rich and poor nations, these papers raise matters that will have to be confronted again and again. It is in that light that the papers should be read. In this instance once more, the past is prologue. □

Mervyn Susser
Editor

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Editorial: HIV Research, Ethics, and the Developing World

Six articles in this issue of the Journal address the conduct of human immunodeficiency virus (HIV) research in the developing world. The issues they raise, however, are neither unique to HIV nor unique to developing countries. In this editorial, we discuss several of these issues, including the failure to provide interventions of known efficacy, ethical relevance of study design, informed consent, and exploitation.

A challenge raised by de Zoysa et al.¹, Karim,² Wittkowski et al.,³ and others,^{4,5} is whether, or under what conditions, it is ethical in research to fail to provide an intervention of known efficacy. Perhaps the easiest case is raised by de Zoysa et al., in which they argue that HIV spermicide trials cannot be conducted ethically without also providing all participants with condoms. When the efficacy of spermicides is unknown and a cheap, effective, and available alternative (condoms) exists, no one disagrees that condoms must be provided to all research participants, even though knowledge about spermicide efficacy would come more quickly and with greater certainty if a placebo-controlled spermicide trial or an equivalency trial were conducted.

The further we diverge from this situation, in which an effective, easy-to-implement intervention is available, to situations that resemble the international clinical trials to prevent perinatal transmission of HIV, as discussed by Bayer⁴, Karim², and Annas and Grodin⁵, the less clear the ethical mandate

becomes. Here, the debate has focused on whether the standard of care in the United States—an expensive and complex regimen of zidovudine—must be provided to all HIV-infected pregnant women who join a research study in the developing world. Different scientists and scholars in bioethics have drawn the line differently in terms of what interventions routinely available in the developed world must be provided to research participants in the developing world. At an extreme, no one suggests requiring that the most expensive and complex of Western tertiary care, for example, renal dialysis or coronary bypass, must be provided in research conducted in the developing world. Indeed, public debates about the HIV perinatal transmission trials have not even focused on whether the women in the trials should be provided HIV combination therapy as they would be in the West⁶ or whether they should even have the zidovudine continued postpartum.

In addition to discussing the recent debate concerning international HIV research, these articles also focus on whether or not randomized, controlled trials must be conducted for researchers to learn about an intervention's efficacy. The choice of a study design is not simply between ethically questionable perfect trials that produce complete knowledge versus imperfect designs that produce no knowledge at all. Moreover, less rigorous designs, such as observational studies, that resolve certain ethical quandaries—as de Zoysa et al. suggest in

the context of condom distribution in spermicide trials—are not necessarily free of other ethical problems. One such problem is that these studies may provide only limited guidance for public health policy. This is illustrated by Wittkowski et al., who report on a repeat analysis of an observational study that strongly suggests vaginal spermicides effectively prevent HIV transmission. The authors acknowledge, however, that an observational design cannot match a randomized trial in accounting for potential confounding and that their results should be interpreted with caution.

Clearly, basing public health policy on a single observational study would be premature; however, multiple observational studies with findings comparable to the analysis by Wittkowski et al. could provide ethical justification for designing randomized equivalency trials comparing the effectiveness of condoms with spermicide. The results of these trials, in turn, should be sufficient for developing public health policy. Under many circumstances, this research strategy may appropriately accommodate ethical considerations with public health needs. The lapse of time in establishing an acceptable treatment in such a series of studies, however, should

Editor's Note See related articles by de Zoysa et al. (p 571), Karim (p 564), Wittkowski et al. (p 590), Bayer (p 567), Annas and Grodin (p 560), and Karim et al. (p 637) in this issue.

Fertility and reproductive choice in women with HIV-1 infection

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Objective: To measure fertility and birth rates and to describe the reproductive histories of women diagnosed with HIV-1 infection in Australia.

Methods: The medical records of 294 women with HIV-1 infection in four states of Australia were reviewed. Expected fertility and birth rates were calculated using national statistics.

Results: In the study population, 152 (52%) women had at least one pregnancy prior or subsequent to HIV-1 diagnosis. At maternal HIV-1 diagnosis, 71 (24%) women had a total of 106 children aged under 15 years. During the study period, 246 women were aged 15–44 years and 58 (23%) of these became pregnant after HIV-1 diagnosis. Women whose exposure to HIV-1 was injecting drug use were twice as likely to become pregnant and more likely to have multiple pregnancies than women who did not report injecting drug use. The annual general fertility rate was 30 per 10 000 compared with 63 per 10 000 for the Australian female population (aged 15–44 years), and the birth rate in women with HIV-1 infection was one-half that of the general female population. Of pregnancies confirmed after HIV-1 diagnosis, 47% were voluntarily terminated, a rate more than double that of the general population. All multiple terminations were among women whose exposure to HIV-1 was injecting drug use.

Conclusions: Fertility and birth rates among women with HIV-1 infection are lower than the general population and the rate of termination higher. The results of this study provide a basis for the management of women with HIV-1 infection who are considering pregnancy.

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Keywords: HIV, women, reproductive histories, pregnancy, terminations, fertility rates

Introduction

The first cases of AIDS were reported in the United States in 1981 [1,2]; AIDS appeared in Australia 1 year later [3]. In 1992, the World Health Organization estimated that, globally, over 4.5 million women had been

infected with the HIV-1, representing 40% of all adult cases [4]. In Australia, to 31 December 1995, 19 453 people had been diagnosed with HIV-1 infection, 6567 diagnosed with AIDS, and 4723 had died [5]. HIV-1 infection in Australia has continued to be primarily transmitted among men who have sex with men, and

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women account for 5% of the cumulative reported cases of HIV-1 infection [5,6].

Most research into pregnancy in women with HIV-1 infection has focused upon vertical transmission or the impact of pregnancy on the progression of HIV-1 disease [7-9]. Although there have been reports of the incidence of spontaneous abortions, birth defects, and the characteristics of pregnant women, there have been few data published on the reproductive choices of women with HIV-1 infection [9-11]. In this study we report on fertility rates and the reproductive choice of women diagnosed with HIV-1 infection in Australia from 1984 to December 1994.

Methods

A national collaborative group was formed, consisting of clinicians from the major sites caring for women with HIV-1 infection in five of the six states of Australia. Community representatives were also involved in the development of the data extraction form. Information was gathered by reviewing the medical records of all women, aged over 13 years, diagnosed with HIV-1 infection who attended a collaborating centre for clinical care. The starting point for retrospective follow-up was the first visit after a diagnosis of HIV-1 and the endpoint was either death, loss to follow-up or 31 December 1994, whichever occurred first.

Demographic characteristics and reproductive histories were extracted from the medical records, and included details of all confirmed pregnancies, regardless of whether antecedent or subsequent to HIV-1 infection, and the reported pregnancy outcome, that is, whether the pregnancy continued to full-term, miscarried, or was voluntarily terminated.

To determine whether pregnancy outcomes in women with HIV-1 infection differed to those of the general population in Australia, a comparison was made between women in the study aged between 15 and 44 years and the available general population statistics of the same group. General fertility rates (the number of births in a year per 1000) were calculated for the study group and compared with the general population rates, published by the Australian Bureau of Statistics [12].

To compare birth rates, the indirect standardization technique was used to calculate the expected number of births in women with HIV-1 infection, based upon general population birth rates [12]. As the majority of births in this study occurred during the 1987-1992 period the analysis compared the general population birth rates with the subset of women who gave birth

during this period. The standardized birth ratio (observed births/expected births) was then used to assess whether women with HIV-1 infection had higher or lower age-specific birth rates than the Australian population. Pregnancy termination rates in women registered in the study were compared with published data [13-15].

Results

Demographic characteristics

A total of 346 medical records were reviewed at 14 sites in four states of Australia. As 52 women attended more than one site, the 346 records corresponded to 294 individuals, representing 43% of the 685 women reported with HIV-1 infection in Australia at the date of commencement of the study. The length of time each patient attended the sites for clinical care ranged from 1 month to 9.8 years, with a median of 3.5 years, representing a total of 1015 person-years of retrospective follow-up.

Age at HIV-1 diagnosis ranged between 15 and 78 years (median, 29 years). The predominant route for HIV-1 transmission was heterosexual contact (50%) followed by injecting drug use (32%) and medical procedures (15%): blood transfusions related to peripartum blood loss in 4% of women, other blood transfusions in 10% and artificial insemination in less than 1%, the exposure category was not reported for 3% of cases.

At the end of the follow-up period, AIDS had been diagnosed in 110 women (37%), of whom 66 (25%) had died after AIDS diagnosis and 62 (21%) had been lost to follow-up. During the follow-up period, 246 women were of reproductive age (15-44 years). The majority of women were born in Australia ($n = 197$, 72%), including four women (1.5%) who were of Aboriginal or Torres Strait Islander descent. Forty-three (15%) women were born in Europe, 10 (4%) in the South-east Asia or Pacific region, 10 (4%) in Africa and the Middle East, and the country of birth was not reported for 5% of cases.

Reproductive choices

In the study population, 152 (52%) women had had at least one pregnancy. Of these women, 58 (38%) became pregnant after HIV-1 diagnosis and 94 (62%) were pregnant before HIV-1 diagnosis; 71 of the 94 (76%) continued their pregnancies to term and had a total of 106 children aged younger than 15 years at maternal HIV-1 diagnosis. Further analyses were restricted to those 75 pregnancies in 58 women confirmed subsequent to the maternal diagnosis of HIV-1 infection.

Table 1. Number of pregnancies confirmed after HIV-1 diagnosis and pregnancy outcome by reported route of HIV-1 infection in women aged 15–44 years.

Reported HIV-1 exposure	n (%)				
	Women pregnant after HIV-1 diagnosis	Total pregnancies after HIV-1 diagnosis	Pregnancies continued to term	Pregnancies terminated	Pregnancies miscarried
Injecting drug use (n = 91)	29 (32)	39 (53)	13 (33)	23 (59)	3 (8)
Heterosexual contact (n = 128)	25 (20)	32 (43)	16 (50)	12 (38)	4 (12)
Medically acquired (n = 27)	3 (11)	3 (4)	3 (100)	0	0
Total (n = 246*)	58 (23)	75 (100)	33 (44)	35 (47)	7 (9)

*Total number of women in the study aged 15–44 years during the study period. Route of HIV-1 transmission unknown for one case.

Fifty-eight women, aged 15–44 years, had at least one pregnancy during the follow-up period of the study, representing 23% of all study participants within this age range (Table 1). No pregnancies were reported outside this age-group. Of these women, 46 (79%) became pregnant once, seven (12%) became pregnant twice, and five (9%) women had three pregnancies. Three of the 58 women became pregnant after a diagnosis of AIDS.

Of women whose HIV-1 infection was attributed to injecting drug use, 32% had pregnancy confirmed after their diagnosis of HIV-1. In comparison, 20% of women whose HIV-1 was reported as heterosexually acquired and 11% with medically acquired HIV-1 became pregnant after HIV-1 diagnosis. Despite only 32% of the study population being women who reported injecting drug use as their source of HIV-1 infection, these accounted for one-half of all women who had a single pregnancy confirmed after HIV-1 diagnosis and 80% of women with multiple pregnancies.

Of the 75 pregnancies recorded as having occurred subsequent to HIV-1 diagnosis, 33 (44%) were continued to full-term, seven (9%) resulted in miscarriage and 35 (47%) were terminated. Of the three pregnancies confirmed after an AIDS diagnosis, two were terminated and the third continued to term with the infant dying in the neonatal period.

Although no time trends were apparent in the proportion of pregnancies being terminated or continuing to full-term, the annual number of recorded pregnancies declined with time following an HIV-1 diagnosis. Almost one-half of all reported pregnancies occurred within 1 year of diagnosis of HIV-1 and 54% of these were terminated. Between 1 and 5 years after the

HIV-1 diagnosis, the annual number of pregnancies halved and the pattern of pregnancy outcome was reversed with over 50% of pregnancies continuing to full-term. The annual number of pregnancies confirmed 5 years after HIV-1 diagnosis declined to nine (12% of all pregnancies) of which six were terminated, and three continued to term.

Pregnancy outcome differed by reported HIV-1 exposure category. In women whose HIV-1 infection was attributed to injecting drug use, 59% of pregnancies were terminated, compared with 38% of pregnancies in women who reported heterosexually acquired HIV-1 infection. Half the pregnancies in this latter group of women continued to full-term, compared with 33% of pregnancies in women for whom injecting drug use was the reported route of HIV-1 infection.

The average general fertility rate for women in this study, aged 15–44 years, was 29.6 per 10 000, 53% lower than the average general fertility rate for women aged 15–44 years in the Australian population, which was 63.5 per 10 000 during the same period [12]. The highest age-specific fertility rate in women registered in the study was within the 20–24-year age-group followed by the 25–29-year age-group, whereas in the general population, the 25–29-year age-group had the highest fertility rate followed by women aged 30–34 years [12].

The observed number of births differed from the rate expected, on the basis of the Australian population data, in all age-groups (Table 2). The lowest birth ratio was in women aged 30–34 years, followed by the 25–29-year age-group. Overall, the adjusted birth rate in the study population was under one-half (45%) that of the overall birth rate in Australian women.

Table 2. Indirectly standardized age-specific birth rates between 1987–1992 for women diagnosed with HIV-1 infection in Australia*.

Age-group (years)	No. women	Person-years	Expected births	Observed births	Standardized birth ratios
15–19	12	47.7	0.1	1	10.48
20–24	51	155.6	12.0	8	0.67
25–29	54	180.2	24.1	10	0.41
30–34	33	99.3	9.9	1	0.10
35–39	24	86.0	3.0	2	0.66
40–44	13	37.2	0.2	0	0.00
Total	187	606	49.3	22	0.45

*As 67% of births occurred during the 1987–1992 period the birth rate data is based upon the subset of women who gave birth during this period. Calculated using birth rates obtained from the Australian Bureau of Statistics [12].

The rate of pregnancy terminations in the study population was 47%. In comparison, in South Australia [13] the rate of terminations was 19%, and has been estimated to be 29% in New South Wales [14,15]. Of women who had voluntary pregnancy terminations following HIV-1 diagnosis, 24 (82%) had a single termination and five women (18%), had multiple terminations. Over half the women with a single termination of pregnancy (53%) had a history of injecting drug use, and all cases of multiple terminations were within this group of women.

Of the 33 babies born after their mothers' HIV-1 diagnosis, three were confirmed to have acquired HIV-1 infection. A further eight babies born prior to the maternal HIV-1 diagnosis were confirmed as HIV-1 antibody-positive. Twenty-two of these babies were born during the period 1987–1992.

Three babies were not yet old enough to have their HIV-1 status confirmed at the time the study was terminated and the HIV-1 antibody status of nine babies was not recorded in the mother's medical record.

Discussion

This appears to be the first study to report on the reproductive choices of women with HIV-1 infection. We have found that these women have a birth rate about half that of Australian women, and that they also have higher rates of pregnancy termination. In women with HIV-1 infection, both the birth and termination rates were higher among those women for whom a history of injecting drug use was reported.

There are several limitations related to the retrospective nature of this study. Most notably, the source of information relating to pregnancies and their outcome was based on routine medical records. It is possible that information regarding reproductive events was under-reported by the HIV treatment centres participating in this study, particularly in cases where pregnancies were confirmed or terminated early in HIV-1 disease. It may be that women choose to visit a local general practitioner or family planning clinic in relation to reproductive issues rather than attend their usual HIV treating doctor; however, it is unlikely that any information on pregnancies would not be recorded at the centre the woman usually attended for her HIV-1 management. It is possible that the number of pregnancies may have been underestimated in this study, and although it is difficult to assess the extent of under-reporting, loss to follow-up was relatively low. It is also possible that the study population was not truly representative of women with HIV-1 infection in Australia, although, based on available demographic and other characteris-

tics, there was a high degree of similarity.

The higher rate of pregnancy terminations observed in injecting drug users than in women whose HIV infection was attributed to heterosexual contact could be related to issues associated with their history of injecting drug use rather than their HIV-1 infection. There is some indication [16] that decisions to terminate pregnancies in this population are related to variables such as previous terminations or a negative emotional reaction to the pregnancy rather than concerns about perinatal transmission of HIV.

The lower birth rate in women with HIV-1 infection in this study, compared with women in Australia as a whole, may have been due to a number of factors. First is the likelihood of increased condom use, either as a method of HIV risk reduction or contraception following an active decision to avoid pregnancy. It has been reported that up to 85% of women report condom use following a diagnosis of HIV-1 infection [17]. Secondly, some studies have found that sexual activity in women is reduced following HIV-1 diagnosis, in association with their stage of HIV-1 disease progression [17,18]. Notably, in our study only three women out of 110 became pregnant following a diagnosis of AIDS. Thirdly, the number of pregnancy terminations in this group would have had an impact on the fertility rate, which is calculated using the number of babies born alive. Compared with studies in other countries, Australian women with HIV-1 infection have a high rate of pregnancy terminations. In a multicentre study in the United States, the termination rate was 27% [19] and a study by the European Study Group found 37% of pregnancies were terminated [11] compared with 47% in the present study.

Women with HIV-1 infection were once advised against pregnancy [20]. There is now increasing recognition that decisions relating to conception and continuance of pregnancy are varied and complex, and maternal HIV status is only one of multiple factors that influence reproductive decisions [11].

Because avoidance of breastfeeding [21,22] and Cesarean delivery [23], and more recently, the use of zidovudine during pregnancy can reduce the likelihood of vertical transmission [24], women with HIV-1 infection can be made fully aware of their options and be provided with counselling to assist in making informed reproductive decisions. While decisions on the continuance, or not, of a pregnancy are often based upon the perceived risk of vertical transmission, they may well involve a range of other sociocultural issues, which must be taken into account when counselling pregnant women with HIV-1 infection [16].

Support services should also focus on those women who already have young dependent children at the

time of maternal HIV-1 diagnosis, because adverse family functioning, including financial strain and conflict [25], often arises in association with HIV-1 infection and disease progression.

In conclusion, the results of this study provide a better understanding of the reproductive choices and the maternal characteristics of women aware of their HIV-1 infection, and a basis for the management of women with HIV-1 infection who are considering pregnancy.

Acknowledgements

The authors acknowledge the support of M. Robertson and A. McNulty of Taylor Square Private Clinic, D. Chambers and L. Mann of the Leichhardt Family Medical Practice, in data collection, and H. Ree of the AIDS Unit, Queensland Health, Brisbane, A. Kesson of Royal Newcastle Hospital and V. Munro of Positive Women NSW.

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DRAFT!

May 22, 2000

PROPOSAL FOR THE PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HIV IN SOUTH AFRICA

There is an urgent need to halt the spread of HIV/AIDS worldwide, particularly in parts of Africa that have already been hard hit by the epidemic. Given its capabilities and capacity to conduct biomedical research as well as the high incidence of HIV infection, South Africa is in a unique position to play a leadership role in HIV prevention research in Africa.

A recent study conducted in Uganda, in collaboration with U.S. scientists and the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH), demonstrated that a two dose regimen of nevirapine (NVP) - one dose to the mother at the time of labor and one dose to the newborn - reduced transmission of HIV from infected mothers to newborns by approximately 50%. There is now an urgent need to extend and implement these results in populations where the more lengthy AZT regimen is not practical or affordable. Scaling up mother-to-child services must be linked to other prevention and care efforts.

PHASE 1. It is proposed that South Africa, through collaboration and assistance from the U.S. government and private foundations, devise and implement a two stage program that will lead to the wide-spread use of NVP to block the spread of HIV from infected mothers to their newborns in South Africa. Rapid assessment methodology will be employed throughout.

[This would not preclude the use of AZT in South Africa in pregnant HIV-infected women who have access to pre- and post-natal care and who can afford the longer AZT regimen. However, at this point in time, the two dose NVP regimen presents an affordable, safe and partially effective alternative for wide-spread use in populations where initiating anti-retroviral therapy prior to labor to the mother and/or after birth to the newborn is simply not practical.]

This first phase could begin immediately and be comprised of two parallel paths:

- A demonstration project that will examine the safety and efficacy of using the 2 dose NVP regimen to stop the spread of HIV from infected mothers to newborns in South Africa. Particular attention will be paid to the issue of drug resistance.
- A planning project that will lay all the groundwork necessary to rapidly implement a country-wide distribution of the 2 dose NVP regimen to HIV-infected mothers and their newborns.

Details of the demonstration project will be worked out in the coming 2-4 months by a joint team of South African and USG-supported researchers through development of a protocol that includes:

size of the trial; specific trial site(s) and investigators; milestones and timeframe for completion; exact cost; source and mechanism of funding; how the trial will be monitored to ensure it is ethically conducted and with the necessary scientific rigor, etc.

When the protocol is completed, it will be submitted for scientific and ethical reviews both in the U.S. and South Africa. UNAIDS will also be asked to comment on the protocol. It is estimated that the project will be conducted in several South African clinical trial sites at a cost of approximately \$3.5-4.0 M over the next 12-18 months.

There will be many scientists, both within and outside of South Africa, who may criticize a demonstration project as a waste of time, citing the already available safety and efficacy information generated by the Uganda trial. However, this criticism can be addressed by:

- thoroughly examining the similarities and differences between the Ugandan and South African population; and
- immediately initiating a planning process for the wide-spread use of NVP, to be implemented as soon as safety and efficacy are confirmed in the demonstration project.

PHASE 2. Specifically, a planning project will set in place all the groundwork necessary to *implement a country-wide program* to reduce HIV transmission from infected mothers to their newborns. In South Africa, approximately 25-30% of HIV-infected pregnant women will pass the infection to their new-born infants in the peri-natal period (prior to or during delivery). The goal is to prepare to screen the approximately 1,000,000 pregnant women/year for HIV infection, and to ensure that the approximately 250,000 who are HIV-infected are afforded access to the two dose NVP regimen. This will involve training health care providers, putting screening tools in place and training clinic personnel on their use and interpretation, piloting counseling programs for the women, and other tasks as necessary. This intervention will also afford the opportunity to provide basic care and support for the infected mother and those infants who become infected.

This phase is anticipated to cost approximately \$10 -12 M in the first year and \$8-10M per year to implement in subsequent years.

[ROUGH ESTIMATE: 1,000,000 women x \$3/screen + 250,000 x \$4/for drug per pair + \$2.0 M counseling of women + \$2.0 M training/education of health care providers + \$2M other planning/other labor/overhead. The cost may vary considerably according to the existing health care delivery infrastructure in South Africa that would be needed to implement this project]

ADDITIONAL RESEARCH

BREASTFEEDING. While many women in South Africa have access to alternatives to breastfeeding, it is important to find approaches that will protect newborns from acquiring HIV through breast milk. South Africa, along with Zimbabwe, is currently conducting a clinical trial to determine how frequently newborns would have to be given NVP so that they maintain protective levels of the drug during the breastfeeding period. Results will be available early next year. Then, by the middle of 2001, a larger trial to examine the safety and efficacy of providing additional doses of NVP to newborns will be launched in populations where there are no breastfeeding alternatives (Uganda, Zimbabwe probably). When results from the larger trial become available in late 2002-3, South Africa will be in a better position to decide how best to help women with no alternatives to breast feeding.

OTHER PREVENTION RESEARCH. Protection of newborns from HIV is an immediate and practical goal that South Africa can accomplish in the coming few years. The larger problem of sexual transmission among adults must also be tackled. Identification of a safe, effective HIV vaccine is the best hope to halt the spread of HIV among adults.

However, to accomplish this, several issues need to be addressed.

- Infrastructure and training to conduct trials must be strengthened. The U.S. NIH remains committed to continuing support of these activities in South Africa and in supporting the conduct of vaccine and other prevention trials in adults in South Africa.
- The factors that impact progression of HIV infection to AIDS need to be better characterized, so that the impact of candidate vaccines can be better assessed in South Africa and similar settings.

To ensure that these activities can be accomplished will require that the South African government be supportive of continued U.S. sponsored vaccine and prevention research in South Africa, including the study of how HIV infection leads to AIDS in South Africa.



OFFICE OF NATIONAL AIDS POLICY
EXECUTIVE OFFICE OF THE PRESIDENT
THE WHITE HOUSE

FACSIMILE TRANSMITTAL SHEET

TO: Deborah Van Zinken FROM: Cheryl Bauerle
COMPANY: DATE: February 21, 2000
FAX NUMBER: 690-7560 TOTAL NO. OF PAGES INCLUDING COVER:
PHONE NUMBER:

RE: Interagency Working Group on International AIDS

☐ URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Per the discussion last Friday, a follow-up meeting of the Legislation and Budget Subcommittee of the Interagency Working Group on International AIDS will take place at 4:30PM on Tuesday, February 22 in our office at 736 Jackson Place, NW.

Please feel free to call me if you have any questions at (202) 456-2959. We look forward to seeing you tomorrow.

Many thanks.

736 Jackson Place
Washington, DC 20503
(202) 456-2437
(202) 456-2438 (fax)

*** TX REPORT ***

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THE WHITE HOUSE
WASHINGTON

Memorandum for the Interagency Working Group on International AIDS

From: Sandra L. Thurman
Director
Office of National AIDS Policy

Date: February 10, 2000

Re: Follow-up to IWG Meeting, February 8

Thank you for attending the first meeting of the Interagency Working Group on International AIDS. Attached please find a list of those who attended.

As discussed, we have formed five sub-committees that will develop plans of action based on current resources, as well as plans for what would be possible if additional resources are identified. The action plans will need to be finalized before our next meeting scheduled for March 6th at 1:00PM (Announcement to follow).

The sub-committees are as follows:

- **Budget and Legislation** – Chair: Sandra Thurman, ONAP
- **Diplomacy and Awareness** – Chair: Jack Chow, State
- **Security** – Chair: Ken Bernard, NSC, and Co-Chair: Nancy Walker, DOD
- **Economics, Trade and Finance** – Chair: Alan Bowser, Commerce, and Co-Chair: Helen Walsh, Treasury
- **Prevention and Care** – Chair: Paul Delay, USAID

I encourage all of you to participate on one or more of the sub-committees. Please contact the Chairs directly. As you know, there is a tremendous amount to do in a very short time, and your input continues to be invaluable.

If I can assist you in any way, please feel free to call me at (202) 456-2437 or call Ken Bernard at NSC at (202) 456-9391. Thank you again for your continued efforts and I look forward to seeing you all at our next meeting.



Alex Ross <aross@afri-sd.org>
07/24/2000 03:53:55 PM

Record Type: Record

To: Cheryl S. Bauerle/OPD/EOP, Cheryl S. Bauerle/OPD/EOP

cc:

Subject: Calling a meeting for this Thursday

Cheryl,

After the meeting this past Friday with Fuerth, I canvassed Fauci, Gayle and others who indicated that this Thursday afternoon would be good for them. I am faxing to you a sheet with the names, telephone and fax numbers of the attendees at Friday's meeting. NOT on the list are Ken Bernard, Jim Babbis, and I forgot who else. Please add them too. Thanks

Alex

Nora Dempsey

Can you please send out a fax invitation to the folks Sandy wishes to come to a meeting to discuss the following (clear with Sandy on text):

As a follow up to the interagency meeting held last Friday, a meeting will be held this Thursday, July 27, from 1:00 pm-3:00 pm at the ONAP Office at 736 Jackson Place. We will discuss:

1. A US government strategic plan for expanding mother/parent-to-child transmission of HIV prevention in Africa
2. USG coordination efforts post-Durban.

Please let Cheryl Bauerle know of your ability to attend at 202-456-2959.

Thank you

Sandy Thurman

July 20, 2000

INFORMATION

MEMORANDUM FOR LEON FUERTH

FROM: JIM BABBITT

SUBJECT: Mother-to-Child Roundtable Discussion

As you requested, I have extended an invitation to a range of individuals to meet with you for a discussion on potential interventions to break the transmission of HIV from mother-to-child (MTCT). The meeting has been set for 1:15 – 2:45 PM tomorrow in the Vice President's Ceremonial Office. A list of invited participants is attached.

I believe we can make the best use of the available time by engaging in an informal discussion of MTCT and associated issues. You may wish to make use of the following questions to guide the discussion and ensure that the range of relevant issues are brought out.

- What is the scale of the challenge posed by MTCT in sub-Saharan Africa?
 - How many annual births?
 - What is the range of infection rates among mothers?
 - Without intervention, what percentage of children will be born HIV+ from mothers who themselves carry the virus?
- Where do we stand in establishing effective interventions to prevent MTCT (AZT, Nevirapine)?
 - In layman's terms what is the course of treatment?
 - What reduction in transmission rates could be expected?
 - Are these interventions ready to move beyond the clinical test/model trial stage?
 - What medical delivery infrastructure is required to allow for broad access to these interventions?
 - Demands for skilled medical staff
 - Associated voluntary testing and counseling (VTC)
 - Access to pharmaceuticals – Who produces
 - Physical facilities
 - Public education and promotion program
 - What are the associated costs?
- What do the clinical trials tell us about the risk of infection to the infant through breastfeeding?

- How do we protect a HIV- newborn from subsequent infection through mother's milk?
 - What obstacles must be overcome?
 - Access to clean water
 - Cultural bias
 - Cost of breastfeeding alternatives
- Do we confront a moral or ethical responsibility to extend care to the HIV+ parent(s) or to a child beyond immediate intervention at birth?
- Is there a rationale argument to be made that limited resources should be allocated to MTCT at the expense of less funding for other prevention, treatment, or research options?
- What would be the bold elements of a phased approach to rapidly expand the availability of this intervention in a single country, and then, throughout Africa?
 - Potential funding sources

Attachments

- Tab A Participants List
- B Reporting Cable – Impression of the XIII International AIDS Conference
- C Press – AIDS Drugs Protect babies a Year Later
- D Press – S.Africa Skeptical of German AIDS Drug Offer

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001. list	Participants, Mother-To-Child Transmission Discussion (partial) (3 pages)	07/21/2000	b(6)
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Clinton Presidential Records
National AIDS Policy Office

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FOLDER TITLE:

Perinatal Transmission [2]

2007-1550-F
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RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

Freedom of Information Act - [5 U.S.C. 552(b)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
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P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

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RR. Document will be reviewed upon request.

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
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b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

[001]

**List of Participants
Mother-to-Child Transmission Discussion
July 21, 2000**

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5

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