

Change in US Research Policies and Directives Are Needed to Remove Barriers on HIV-1 Operational Research Programs in Developing Countries: A case report of two NIH clinical trials in South Africa

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National Institutes of Health (NIH) stated, or “acting,” policies have created a number of barriers to developing research studies targeted at specific needs within resource-poor settings. These include an unofficial policy preventing the purchase of antiretroviral drugs needed during clinical studies otherwise supported by NIH funds; regulations against using approved generic formulations of antiretroviral drugs in NIH-funded studies; and stipulations requiring the provision of continual access to

antiretroviral therapy (ART) for study subjects, irrespective of time-limits after study completion. Furthermore, restrictions against supporting research objectives under existing non-NIH programs for ART provision in developing countries, such as the Presidential Emergency Plan for AIDS Relief (PEPFAR) further limit research activity in areas where the US is providing ARTs.

Investigators interested in developing NIH-funded operational research proposals of potential benefit to resource-poor

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settings have addressed these barriers by approaching pharmaceutical companies for antiretroviral drug donations. Alternatively, they have relied on national treatment programs already implemented by the host country. Thus, the lack of funds to support drug procurement for research has largely limited ART-related operational research projects to countries with established population-wide ART access programs (e.g., Brazil, Botswana, Uganda, South Africa). The assumption that NIH endorsement and approval for funding after peer review will attract donation of antiretroviral drugs from the pharmaceutical industry has repeatedly proven inaccurate. In the experience of the authors, the pharmaceutical industry supports studies that further their marketing or drug development agenda, thereby increasing their commercial gain. As a result, investigators of studies to test implementation approaches that may not meet pharmaceutical industry's objectives are either required to raise private funds to cover the study's ART costs or to abandon the project. In the absence of private funds or the supply of FDA-approved antiretroviral drugs through government programs (note that most resource poor governments support generic rather than trademark ARTs), current operational NIH-funded research in need of study ART is subject to approval by pharmaceutical companies before it can be implemented.

A re-evaluation of current directives is needed in order to foster, rather than restrict, operational research in resource-poor settings. This is particularly urgent in light of the rapid expansion of treatment required by the increasing worldwide infection burden. To demonstrate

the potential risks to research progress of doing nothing, we present the experience of our US-South African teams following awards of an investigator-initiated R01 research and the Comprehensive International Program on Research in AIDS.¹ For example, we emphasize that despite peer review culminating in the award of NIH funds over the course of five years along with the endorsement of the Department of Health of the Republic of South Africa (SA), and approval for implementation by both US and South African ethics review boards, the lack of resources to pay for the ART needed to implement the NIH research (totaling \$250,000, or <10% of the total NIH award) raised the potential that the study would collapse once it was clear our research goals were not a priority for support by pharmaceutical companies.

There are currently several NIH-funded studies that remain inactive because investigators were unable to finalize ART support and/or agreements with the pharmaceutical industry. It is common for such agreements, when reached, to include additional "suggestions" or requirements that may go as far as to place restrictions on the data collected and to request protocol changes per industry needs independent of peer-review. In general, most investigators are amenable to altering their study designs with NIH approval, as the alternative is loss of ART support, which would diminish the likelihood that the study could be implemented. Most significantly, the usefulness of the research may be undermined by a shift to drugs not routinely used in resource-poor settings. If no change is made from the current approach to supporting ART-dependent studies in resource-poor settings or alternative venues for support

are not made available to investigators, pharmaceutical companies will continue to have a disproportionate influence on determining which and how NIH-funded studies in resource-poor settings will be implemented.

The Need for Antiretroviral Therapy in South Africa

The impact of AIDS on the economic, social and political stability of resource constrained nations threatens global security. Sub-Saharan Africa is at the epicenter of the AIDS epidemic, with about 10% of the world's population and 60% of the world's infected individuals.² More than 100,000 South Africans died from HIV/AIDS in 2003, with the annual death rate expected to rise to 500,000 by 2010, assuming the absence of treatment and an expected rise in the prevalence of infection in the general population from 13% to 27%.³ The Gauteng province, including Johannesburg, where our study teams are focused, has had the highest increase in HIV prevalence in South Africa (1999=22.4% vs. 2000=29.3%) as noted in the annual antenatal clinic sentinel surveys.^{4,6} By the year 2007, the average life expectancy will have declined by more than 20 years, to 30 years for women and 34 years for men.⁵ The characteristics of the African epidemic (virus genotypes, transmission routes, etc.) and the limitations of healthcare delivery reduce the applicability of knowledge acquired in clinical and laboratory studies based in the US and Western Europe.

ART has dramatically improved morbidity and reduced mortality for patients with HIV/AIDS in the developed world.

All of the treatment algorithms and programs in the developed world that led to this treatment benefit were developed from NIH-funded research study results. In all of these cases, the medications were donated by the pharmaceutical industry as part of a joint effort towards new drug development. In resource-constrained countries, such as South Africa, the use of ARTs is limited to specific research sites, such as ours. Recent studies conducted in South Africa have established the cost-effectiveness of drug-based strategies aimed at reducing vertical transmission related to childbirth.^{7,8}

The implementation of a national treatment program by the South African Department of Health to treat adult populations at advanced disease, while considered beneficial, is limited by cost, lack of appropriate cost-effective treatment strategies and infrastructural needs. The initiation of the Department of Health National ART Roll-Out Plan has led to the development of over 50 sites in major centers targeting the treatment of 50,000 individuals by May 2005. This target is only 10% of the estimated 500,000 individuals that require treatment in 2005, based on national treatment guidelines targeting the sickest patients with CD4+ count less than 200 cells/mm³. Many rural and marginalized communities are also accessing treatment through the PEPFAR programs or small NGO-funded programs.

Given the scarcity of available resources, studies of alternative treatment delivery models are needed to simplify and enhance the geographic distribution of ART services. US treatment guidelines are not necessarily applicable to these settings, and research questions about the implementa-

tion of ART strategies that may best apply to resource-poor settings with limited drug supplies can also be different. For example, proposed study aims such as determining if sequential short-term structured interruptions of ART can retain the immune reconstitution benefits of continuous treatment while potentially lessening rates of toxicity and cost associated with continuous therapy strategies are likely to be of greater significance in settings where drug options are limited.⁸

Case Study 1: NIH R01 Clinical Study Application and Approval

ART has been a milestone in the treatment of HIV infection; it allows for viral suppression and the restoration of immune response and lymphoid architecture, among other effects.¹⁰ However, the feasibility of life-long ART-mediated viral suppression has been challenged by the discovery of a long-lived latent viral reservoir (preventing eradication), as well as by problems with ART, such as treatment-associated costs, sub-optimal adherence, drug-related toxicity, adverse effects and the emergence of viral resistance. As a result, alternative therapeutic approaches that could allow for a limited exposure to ART while retaining the benefits of continuous therapy have become an active area of investigation.

Since 1998, we have studied the outcomes of brief interruptions of ART in chronically infected persons in Philadelphia. With NIH support, we conducted a randomized clinical trial to evaluate safety, viral and immune outcomes of sequential treatment interruptions in HIV-1-infected

subjects stably suppressed under ART.

Our results, published in December 2004, confirmed that short cycles of ART interruption were not associated with adverse events or a loss of therapy benefits with regard to immune function.¹¹ These results provided the rationale for proposing a subsequent R01-funded clinical study in South Africa with the long-term goal of determining if providing intermittent ART to virally suppressed patients could allow for the maintenance of immune parameters (e.g., CD4 counts, immune responses, etc.) at a level comparable to those observed under continuous ART. While such a strategy may also lead to reduced long-term toxicity and lower overall costs for ART, the maintenance of immune function in the presence of intermittent therapy would be expected to delay disease progression. Specifically, we proposed to test the hypothesis that repeated cycles of 2-8 weeks off ART followed by 16 weeks on ART (leading to a maintenance strategy decreasing drug exposure by 33%) are not inferior to continuous therapy over the same period, with non-inferiority defined by the sustained levels of immune parameters associated with disease progression. This hypothesis-driven proposal represents an international multidisciplinary research effort by the Wistar Institute (Philadelphia, PA), the Clinical HIV Research Unit and Departments of Haematology, Chemical Pathology and Medicine (Endocrinology Division) at the University of the Witwatersrand (Johannesburg, South Africa), the AIDS Virus Research Unit at the National Institute for Communicable Diseases (Johannesburg, South Africa) and the University of Pennsylvania's Center for Clinical Epidemiology and Biostatistics

(Philadelphia, PA).

During the process of peer review of this proposal, we acquired endorsements from the South African Department of Health and the South African national research agency, the Medical Research Council; independent reviewers stated that the proposal came from a “highly experienced group of investigators who are capable of conducting the proposed investigations” with an experimental approach that “will be critical to increase our understanding of how to improve the long-term management of HIV-infected persons.” Furthermore, reviewers stated “The extension of structured therapy interruptions to South Africa where the need for cost effective use of antiretroviral therapies is critical, and the clade C strain of HIV [endemic HIV-1 subtype in South Africa] may respond differently from clade B [endemic HIV-1 subtype in USA and Western Europe], is important and innovative.”

Final peer review was completed in April of 2003. The National Institutes of Allergy and Infectious Diseases (NIAID) approved a funding allocation of \$2.9 million for this study in May 2003 and declared the grant award active in July 2003. ART provision for this study was included as a study cost in the requested NIH budget as part of the first submission in September 2001 but had to be subsequently removed at the request of reviewers and NIAID staff, who expected that, once the study was approved, the drug supply would likely follow from pharmaceutical industry partners. As investigators, we similarly assumed relations between the pharmaceutical industry and NIH would facilitate this process. We and NIAID program staff later learned both assumptions

were incorrect.

Case Study 1: NIH R01 Implementation Barriers

The award of funds by NIAID for a clinical study proposed through the investigator-initiated R0-1 format requires that a more detailed version of the study be prepared in the format of a full protocol for subsequent review and critique by the internal NIAID Clinical Study Review Board. It was clear at the time we underwent this additional review in October 2003 that the uncertainty regarding the source of support for the ART needed for the study would prevent us from completing the necessary additional steps required to open the study until the drugs were received. Note that NIAID directives state that on-study drugs may not be purchased as a consumable expense with grant funds even if required for the implementation of the approved study. Therefore, NIAID asked us to identify and secure a sponsor for ART costs for our study in the absence of any direct intervention or request by NIH on our behalf to the pharmaceutical industry or other funders. The NIAID program staff members were understanding of our predicament and supported our efforts throughout, even though there was little they could do. In effect, the study would be halted until we could secure a supply for ART supply for the duration of the study, even if relying on the South African Rollout plan for post-study drug.¹² Current requirements also stipulate that ART supplies be trademark brands (not generics) and be registered for use in South Africa, which further increased the cost

burden and restricted the number of pharmaceutical companies we could approach. In parallel, the Department of Health in South Africa has encouraged and supported the development of an in-country generic manufacturing process, using voluntary licensing patent and rights transfer, bioequivalence data and in-country good manufacturing processes. A recent award has directed over 80% of the total South African drug supply to these generic manufacturers. For US researchers with an interest to work in this area, the increased use of generics means that the conundrum of drug supplies for research cannot be solved by support from the Department of Health.

Our applications to multiple pharmaceutical companies, even with the utilization of a paid industry lobbyist, were met with rejections, as we were proposing to test approaches to limit drug use rather than following the standard of care with continuous drug administration. Concurrently, we approached all major private foundations that welcome applications for support of biomedical HIV research (including the Bill and Melinda Gates Foundation, Doris Duke Foundation, Rockefeller Foundation and the Clinton Foundation). None of these foundations accepted applications for drug support, with the exception of for the Doris Duke Foundation, which eventually declined to support the study. Interestingly, most of the foundation staff with whom we discussed our need for support reacted with surprise to our predicament, as most assumed that NIH would provide funds to cover ART costs for their approved studies.

The inability to secure drug funds by April 2004 for an award initiated in July

2003 (with a termination date of December 2007 and a 3.5 year research plan) indicated that, irrespective of our team readiness and NIH support of the study, time would run out in the near future. What prevented us from having to terminate the study was a last-minute plan by our academic research institutions to pay for the ART costs needed to cover the study period from their own operational or research funds. Once we provided a drug procurement plan to NIH in April 2004, we have completed further evaluations of our study by the Data Safety Monitoring Board and completed additional site and study monitoring evaluations (contracted by NIH). We are currently awaiting NIH clearance for initiating recruitment in May 2005.

Study Case 2: NIH Application and Approval to Comprehensive International Program on Research in AIDS in South Africa (CIPRA-SA).

Two applications from South Africa were successfully submitted in 2002 to the NIH CIPRA program. Together, the program project grants exceeded \$40 million over a five-year period.¹³ These awards included both prevention and treatment research. For the period of the grant award the investigators were obliged to identify the ART sources for the studies.

The primary objectives of the CIPRA-SA "Safeguard the Household" Project 1 are to address the limitations of expanded access to ART in resource-poor settings,

including 1) limited numbers of health care workers, in particular doctors; 2) cost of treatment and monitoring; 3) enhanced geographic distribution to remote rural areas, often served only by primary health care facilities. The chief hypothesis of this project is that ART can be implemented in a resource-poor setting at a primary care facility, with ART monitoring provided by trained primary healthcare “sisters.” Primary healthcare sisters are nurses with training in diagnosis and treatment prescription according to the Essential Drug List for South Africa. In this primary healthcare model, it is hypothesized that any subject who fails first line therapy will benefit from the addition of community-based directly observed therapy (DOT), administered by a member of the community trained and monitored by the research staff. To test these hypotheses, the implementation of ART at a primary health care level monitored by a sister (investigative arm) will be compared with the standard or doctor-based monitoring model (control arm).

In addition the CIPRA-SA “Safeguard the Household” projects are testing effective ways to reach multiple HIV-positive members of a household while also supporting efforts to develop low cost laboratory monitoring techniques for CD4+ and viral load testing, and procedures for the shipping of samples from remote rural areas.

The CIPRA-SA program project grant was awarded in September 2002.

Case Study 2: CIPRA-SA Implementation Barriers

After an initial period in which the investigators and the NIAIDS’s Division of AIDS (DAIDS) came to an agreement on the terms of the grant award, protocol development was initiated in October 2002. Even at this point, it was clear that the provision of study drugs for the proposed ART was the responsibility of the investigator and should a guarantee of post-trial treatment access. To test the study hypotheses according to treatment guidelines, two sequential treatment triple therapy regimens were required, including a non-nucleoside based regimen and protease inhibitor based regimen.

The investigator team spent almost a year negotiating for the provision of antiretroviral drugs with pharmaceutical companies. During the negotiations, it became clear that the pharmaceutical companies’ focus was on providing drugs which had recently been registered in the US and Europe but were still unregistered in South Africa and were not supported by the World Health Organization’s treatment guidelines. In turn, the use of new drugs in development meant that companies providing the balance of required triple therapy regimens were not interested in supporting the study due to the conflict in commercial interest of the next generation of drug being tested. The circular debate that resulted led to a final outcome in which it was impossible for investigators to construct a first and second line treatment regimen.

At this stage the program approached a number of philanthropic foundations requesting treatment support. None of these foundations were able to support the research program. The breakthrough for the program came in November 2003

with the announcement by the South African Department of Health that a national treatment program for ART would be undertaken. This program, initiated in April 2004, created the possibility of support of the research program, provided that the treatment regimens used in the research were the same as the national roll-out regimens. A new conundrum arose: NIH policy required that research be conducted using FDA-registered drugs. The South African Department of Health in turn issued a procurement tender for antiretroviral drugs that was eventually awarded in 2005, almost exclusively to generic manufacturers. Application has been made to DAIDS to authorize the use of in-country registered generic medicines, and we are awaiting the decision.

Recommendations for Change

Our experiences indicate that the rules regulating NIH efforts with regards to funding antiretroviral drug-based studies are not only creating long delays in trial implementation and accrual but may also prevent current NIH-funded clinical trials from being implemented, restrict the impact of studies that are prevented from incorporating the therapy approaches in use by government programs and halt future development of studies that can address critical needs in operational research within the developing world. Based on these conclusions, we propose the following policy changes:

1. Enact legislation to amend PEPFAR to specifically allow interaction between

active PEPFAR programs and NIH-sponsored research projects. This would, in effect, allow investigators not to be solely dependent on pharmaceutical industry donations for the implementation of operational research goals. This will also benefit the PEPFAR program by providing answers to implementation questions that will enable more rapid and successful scale-up.

2. Request that the NIH Office of AIDS Research appoint a task force or "blue ribbon" panel to evaluate current international research programs supported by NIH to determine: a) how many approved protocols are currently kept from implementation due to a lack of confirmed ART support; b) the anticipated research needs with regard to on-study antiretroviral drugs for the planned expansion of CIPRA, which currently funds multi-project programs in South Africa (\$31.3 million award, 2002), China (\$14.8 million award, 2002), Peru (\$3.1 million award, 2004) and Thailand (\$4.6 million award, 2004) and which has an additional 28 awardees currently fostering infrastructural capacity towards full CIPRA status; and c) the research implications of relying on non-NIH support for the implementation of all NIH-funded studies that require antiretroviral drugs. The current disconnect between stated research objectives for resource-poor countries and support options (e.g., lack of support for ART) will become an increasing problem for research development in the expanding CIPRA program as each awardee becomes increasingly dependent on NIH funds to implement operational research goals that are responsive to in-country needs.

3. Request that the NIH Office of

AIDS Research report on the projected financial burden of covering ART costs during the study period. Projections for costs of on-study drugs during the time of NIH funding (usually up to 5 years) could take into account that ART provision following study completion is to be transferred to government or other drug-access programs (note no firm restriction on generic drugs have been placed on the source of drugs after study completion, just on those used during the study).

4. Request that the NIH Office of AIDS Research recognize foreign country ethics committees that have defined acceptable periods for post-study drug provision. For example, South African ethics boards have recently approved that periods of five years of drug supply are in compliance with local South African clinical research guidelines. Allowing input from foreign countries where the research is conducted to balance local research needs with study subjects' rights to benefit from participation may allow for greater access and research development across different country settings.¹⁴ At present, US-guided ethical definitions of life-long drug supplies for study subjects are based on resource-rich settings with non-limiting drug access.

5. Enact legislation to amend the PEP-FAR program (and hopefully adapted by NIH programs) to allow the use of in-country registered generic drugs. Standards for the use of generic medicines currently require FDA registration. The national treatment programs of many countries in resource-poor settings have already decided to use generic drugs for their treatment programs. Acceptable antiretroviral drugs for use in research should have undergone a regulatory review process in the country

where the research is being conducted. This process needs to include 1) good manufacturing practices to standardize the manufacture of medicines, 2) bioequivalence of the generic medicine to the original brand medicine and 3) registration for use in the country where research is being conducted and for the research population. 🏹

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References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS), "Sub-Saharan Africa", <http://www.unaids.org/EN/Geographical+Area/By+Region/sub-saharan+africa.asp>.
2. J. Stephenson, "AIDS in South Africa takes center stage". *JAMA* 284 (2000): 165-167.
3. Department of Health, South Africa, "National HIV and Syphilis Sero-Prevalence Survey of women attending Public Antenatal Clinics in South Africa 2000", <http://www.doh.gov.za/facts/index.html>.
4. E. Gouws, B.G. Williams, H.W. Sheppard, B. Enge, and S.A. Karim. "High incidence of HIV-1 in South Africa using a standardized algorithm for recent HIV seroconversion". *J Acquir Immune Defic Syndr*. 29(2002):531-535.
6. G.J. Churchyard, I. Kleinschmidt, E.L. Corbett, D. Mulder, and K.M. De Cock. "Mycobacterial disease in South African gold miners in the era of HIV infection". *Int J Tuberc Lung Dis*. 3(1999):791-798.
7. D. Wilkinson, K. Floyd, and C.F. Gilks. "Anti-retroviral drugs as a public health intervention for pregnant HIV-infected women in rural South Africa: an issue of cost-effectiveness and capacity". *AIDS* 12 (1998):1675-1682.
8. G. Mansergh, A.C. Haddix, R.W. Steketee, P.I. Nieburg, D.J. Hu, R.J. Simonds, and M. Rogers. "Cost-effectiveness of short-course zidovudine to prevent perinatal HIV type 1 infection in a sub-Saharan African developing country setting". *JAMA*, 276 (1996): 139-145.
9. L. Azzoni, E. Papisavvas, and L.J. Montaner. "Lessons learned from HIV treatment interruption: safety, correlates of immune control, and drug sparing". *Curr HIV Res*. 1(2003):329-42.

10. R. Detels, A. Munoz, G. McFarlane, L. A. Kingsley, J. B. Margolick, J. Giorgi, L. K. Schragar, and J. P. Phair. "Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators". *JAMA* 280 (1998):1497-503.
11. E. Papasavvas, J.R. Kostman, K. Mounzer, R.M. Grant, R. Gross, C. Gallo, L. Azzoni, A. Foulkes, B. Thiel, M. Pistilli, A. Mackiewicz, J. Shull, and L.J. Montaner. "Randomized, Controlled Trial of Therapy Interruption in Chronic HIV-1 Infection". *PLoS Med.* 1(2004):e64.
12. J. Cohen, "AIDS research. Drug trials without the drugs?" *Science* 300(2003):1212-1213.
13. National Institutes of Allergy and Infectious Diseases, "Comprehensive International Program on Research in AIDS (CIPRA)", <http://www.niaid.nih.gov/daids/cipra/award-r03.htm> (November 19, 2004)
14. A A Hyder, S A Wali, A N Khan, N B Teoh, N E Kass, and L Dawson. Ethical review of health research: a perspective from developing country researchers. *J. Med. Ethics*, 30(2004): 68-72.