Developing a Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Therapeutic Research Agenda for Resource-Limited Countries: A Consensus Statement

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To develop a research agenda for use of antiretroviral therapy (ART) in countries with highly limited resources for health, research questions focused on 3 areas: when therapy should be initiated, what therapies should be used, and the most appropriate methods for patient monitoring. Participants from 23 countries and 6 continents were clinical and academic researchers, health care practitioners, policy authorities, pharmaceutical experts, and health care advocates. The conference attendees reviewed background materials and participated in 13 state-of-the-art presentations on ART provision in resource-limited countries, treatment access, ethics, community issues, and sustainability. Conferees separated into smaller groups to identify priorities for specific research agendas. Existing multinational human immunodeficiency virus (HIV) clinical trials networks, such as the HIVNAT (The Netherlands, Australia, and Thailand) Network, were studied as infrastructure models for research into affordable, sustainable treatment and monitoring strategies suitable for resource-limited settings. The delivery of ART in resource-limited countries is a vital priority for health care providers and the millions of people living with HIV disease. To achieve sustainable approaches to HIV/acquired immunodeficiency syndrome care, research relevant to resource-limited settings must involve local researchers and community representatives to promote development of local capacity.

HIV infection/AIDS is spreading steadily through the resource-limited countries in Africa, Asia, Latin America, and eastern Europe. In several sub-Saharan African nations, prevalence of HIV infection has reached >20% in the adult population. Rates of infection are escalating in parts of the Caribbean, Russia and the other “newly independent states,” key regions of Asia, such as China and India, and parts of Africa, including Nigeria. The impact is staggering and unprecedented; the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates the lifetime risk of death from HIV disease for 15-year-old boys to be >30% in Cambodia, >60% in South Africa, and nearly 90% in Botswana [1].

Even if highly successful prevention efforts were implemented immediately in resource-limited settings around the world, tens of millions of people living with HIV disease face early death unless they receive antiretroviral therapy (ART) [2–4]. Occurring dispropor-
tionately among young economically productive adults, these deaths will exacerbate economic problems and result in millions of orphans [5, 6]. Despite the global crisis, the vast majority of HIV-positive persons in Africa, Asia, and even Latin America do not have access to ART or standard monitoring tests used for modern HIV care [7–15]. Hope for expanded access to AIDS therapy has increased enormously in recent years as health care advocates have pressed for greater access to care [16–18], ART prices have plummeted [19, 20], and an aware international community has begun to dedicate additional resources to improving AIDS-related care across the globe [21–24]. Projects sponsored by Doctors without Borders (Médecins san Frontières), the HIVNAT (The Netherlands, Australia, and Thailand) Network, Partners in Health, Harvard AIDS Institute, employers in Botswana and South Africa, the Brazilian Ministry of Health, and the Ugandan-based Joint Clinical Research Center/Academic Alliance for AIDS Care and Prevention promise to help guide needed clinical guidelines in resource-limited settings [25–31].

Yet the research base on which to build these guidelines is exceedingly limited at present [32, 33]. Research is needed on approaches to HIV therapy that can be applied and sustained globally [34, 35]. The Conference to Develop an HIV/AIDS Therapeutic Research Agenda for Resource-Limited Countries sought to outline a research agenda that can guide providers, patients, and policymakers. Conference attendees from 23 nations (figure 1) were charged with developing research proposals focusing on the delivery of ART in the most resource-constrained countries burdened with a preponderance of the world’s AIDS cases.

Because of time limitations, crafting a research agenda on treatment of HIV-related opportunistic infections (OIs), detailed review of health care infrastructure and economic development needs, drug pricing policies, policy strategies to increase ART availability, and details of ethical debates on research in resource-limited settings was not attempted. However, attendees did hear presentations on each of these issues to provide context to the research agenda discussions. The ethical concerns of international research and the cooperation of governments in both industrialized and developing nations, the pharmaceutical industry, and key international agencies were recognized as important issues in global access to ART research and implementation [36–40].

**CONFERENCE FINDINGS**

Research agendas were developed to address 3 interrelated areas of HIV therapy in resource-limited countries: (1) When should therapy be started? (2) What ART regimens are most suitable? (3) What monitoring approaches are best to track disease progression and the effects of therapy when means of determining CD4+ cell counts and virus loads are not available and/or affordable?

**When to Start Therapy**

**Overview.** A review of the data from retrospective cohort studies in industrialized countries indicates that it is beneficial to initiate ART for HIV-infected persons who are symptomatic for OIs or malignancies and at CD4+ T cell levels of <200 cells/mm³ in asymptomatic patients [41–45]. The available data do not, however, give clear guidance as to whether initiation of ART at CD4+ cell counts of 350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities. Although current US clinical guidelines are flexible and generally recommend initiation of therapy at CD4+ cell levels of <350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities. Although current US clinical guidelines are flexible and generally recommend initiation of therapy at CD4+ cell levels of <350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities. Although current US clinical guidelines are flexible and generally recommend initiation of therapy at CD4+ cell levels of <350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities. Although current US clinical guidelines are flexible and generally recommend initiation of therapy at CD4+ cell levels of <350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities. Although current US clinical guidelines are flexible and generally recommend initiation of therapy at CD4+ cell levels of <350 cells/mm³ provides additional clinical or economic benefits, with its attendant long-term costs, challenges in promoting adherence, selection of resistant strains of HIV, and toxicities.
from clinical trials and in the face of competing health care needs. Although benefits from therapy for some asymptomatic persons with CD4+ cell counts of >200 cells/mm^3 are acknowledged, insufficient data are available on which to base a recommendation that would apply to all circumstances in developing countries, where drug shortages may necessitate treating only those who need therapy the most rather than everyone who would qualify under clinical guidelines crafted for industrialized countries, where drugs are available widely and with support from the public sector.

In the absence of relevant data, health practitioners in resource-limited countries should consider initiation of ART on the basis of local circumstances, including financial resources, health care infrastructures, monitoring costs associated with treatment, and adherence. A critical factor in deciding when to start therapy is the sustained availability of effective, affordable ART, something quite elusive at present in most developing nations. The question of when to start was looked at from 2 perspectives—that of the world’s poorest nations (per capital incomes of <$800 per year) and that of nations with more resources, termed “middle-income, resource-limited nations” ($800–$5000 per year) (all values are given in US dollars).

Even in countries that are not among the poorest, the need for ART exceeds the capacity to provide it. In the most resource-limited countries, widespread treatment of most patients for whom therapy is indicated is not feasible currently [48–52]. In these settings, health care researchers and providers may wish to consider starting ART in the context of a newly presenting patient with a serious OI, because the need for screening asymptomatic persons and providing suitable treatment will present huge logistic challenges [53]. Therefore, the question of when to treat may be of less relevance in the poorest nations; dire need and/or societal impact may dictate treatment, with influence from sociopolitical considerations rather than use of medical indications alone.

**Study design options.** There are several potential approaches to researching the question of when to treat in resource-limited settings: prospective randomized trials, observational database studies, and pathogenesis studies. Prospective randomized trials would enable researchers to compare outcomes of initiation of ART at different stages of disease but are costly and long in duration and require large sample sizes. However, these may be appropriate in countries that have existing infrastructures for clinical trials and an established health care system that could implement findings expeditiously.

Observational studies have the advantage of allowing examination of a variety of patient groups and treatment regimens, but comparisons of the effectiveness of initiation of care may be difficult, given the likelihood that nonrandomized intervention groups may differ from each other in important ways. When the question is not whether a given ART regimen is effective but rather how successful administration of ART is in a real-world setting, observational studies could be invaluable. Countries such as Brazil that make ART widely available are ideal venues for observational databases [54, 55]. Observational studies are also potentially suited to those lower-income nations in which program evaluation is included as a component of research. The need for observational and operations research into the use and community implications of the lower cost and broader availability of ART and HAART in developing countries is evident. ART will be increasingly available at pharmacies, or even from nonpharmacy sources, without the need for a prescription, in many countries. Poor patients seeking HIV care may seek affordable ART (perhaps monotherapy and for short periods of time) before they can access expert medical guidance. The study of policy implications for such “real world” use, especially its importance for extension of HIV drug resistance and implications for compromising success of initial ART regimens and of nevirapine- or zidovudine-based mother-to-child transmission programs, is vitally important. Also important for observational studies are selected pathogenesis studies that would likely be smaller in scope but could help identify lower-cost virological and immunological parameters of clinical significance.

In middle-income, resource-limited nations, a need exists for multidisciplinary research involving health and community groups, leading to a variety of culturally based observational and randomized studies of local relevance. Operations research into different implementation strategies for ART delivery can make particularly important contributions in lowest-income countries, where ART will be administered in advance of any major research infrastructure or research funding opportunities. Some of the primary operational questions for study on initiating therapy include the utility of directly observed therapy for ART, types of social support services needed, role of community facilitators, and strategies to reduce community stigma and increase adherence to ART [36, 56–59].

**Specific research concepts.** Primary care, including therapy and prophylaxis for common OIs, should be provided to all patients as per World Health Organization guidelines, regardless of clinical trial status or research group assignment [60]. Researchers can consider several specific trial designs that emerged from the conference discussions.

**Concept 1.** One sample trial would test whether it is practical to start therapy on the basis of syndromic management (i.e., when patients become ill), an approach that could save monitoring and drug costs compared with beginning therapy when a patient reached a given asymptomatic CD4+ cell count (e.g., 200 cells/mm^3) [61]. The open-label study would have a principal end point of survival at 2 years.

**Concept 2.** Randomization on the community or clinic level of asymptomatic versus symptomatic therapy rather than
individually would allow researchers to test the community impact of different approaches to ART. The study population would be HIV-infected persons with CD4+ cell counts of <350 cells/mm³; persons in some randomized clinical settings would begin therapy at that threshold regardless of clinical status, whereas persons at comparable, randomized sites would receive later therapy when they became symptomatic or reached the 200 cells/mm³ threshold. Primary end points would be rates of illness or hospitalization, and secondary end points would be ART adherence and death rates.

**Concept 3.** A third trial would test when ART should be started during the course of an OI. It is unknown whether ART should be started simultaneously or after the patient is stabilized with OI therapy. OIs can be treated first because of the potential risk of restoring the immune system too quickly, causing death from the sometimes overwhelming immunologic response to the OIs themselves (e.g., tuberculosis) [62, 63]. However, the opposite approach (that is, prompt initiation of ART) might be a superior option. HIV-infected persons presenting with defined OIs would be randomized between receiving simultaneous administration of ART and initial therapy for OIs versus receiving OI therapy followed by ART a short time later. The primary end point would be survival with a secondary end point assessing morbidity.

Other potentially valuable studies on the subject of when to treat include assessing when to start ART among children in clinical trials [64], considering circumstances when virus loads are unavailable to guide clinical decisions; testing whether ART increases survival for breast-feeding mothers, regardless of CD4+ cell count, and reduces transmission of HIV to their infants via breast milk [65, 66]; and studying whether therapeutic vaccination (when a candidate vaccine becomes available) results in continued suppression of virus load after initiation of ART, particularly if ART is stopped.

**Which Drugs to Use**

**Overview.** In resource-limited settings, therapeutic efficacy must be weighed not only against side effects and adherence issues but also against extremely limited financial resources and patient monitoring tools [67–69]. Patients may have to travel significant distances to access health care and drugs, adding an additional potential barrier to adherence. The availability of properly trained health care providers experienced with ART is limited and is worsening in many areas because of economic out-migration (e.g., from Zambia to South Africa, or from South Africa to Australia) and the decimation of health professionals themselves by HIV disease [70, 71].

The specific characteristics of the HIV epidemic, the general health of the population in communities, and the diseases endemic to the region (e.g., malaria, tuberculosis, and enteric parasites) influence ART decisions [72–74]. Drug interactions have been studied largely in the context of copathogens in temperate climates. Differences in drug metabolism, pharmacodynamics, and pharmacokinetics across population groups, as well as the relative shelf life and temperature sensitivity of drugs, may lead to alternative ART approaches. Initial choices of ART protocols should be informed by the impact that drug choices may have on future treatment options, particularly potential resistance patterns that make future regimens less effective [75, 76].

Determination of appropriate ART in resource-limited settings would benefit from research in several areas. Comparative studies of various drug regimens, as well as studies of drug resistance patterns and toxicities, are needed. Because pharmacokinetics can vary by population, they should be studied widely, to assess the impact of this variation on treatment efficacy. Structured treatment interruption should be studied as well, because its use could potentially improve treatment efficacy, save financial resources, reduce toxicity, and improve patient adherence and quality of life [77, 78].

Research is also needed to determine the effective doses of various drugs and how dosages should be adjusted for weight and nutritional status [79, 80]. Adherence research is essential, although there is evidence in both the industrialized and developing worlds that populations in resource-limited communities may be just as adherent to ART regimens as are patients in more economically advantaged settings [79–81].

**Specific research concepts.** Several specific trial designs should be considered.

**Concept 4.** One trial would compare a variety of ART options in treating ART-naive, HIV-infected persons with CD4+ cell counts of either <200 cells/mm³ or <350 cells/mm³. This would be a large, randomized, multicenter trial of 3 or 4 regimens, potentially comparing different classes of drugs and different schedules. Is the simplicity of a zidovudine-lamivudine-abacavir regimen outweighed by its potential toxicity? Will a triple-therapy regimen with a protease inhibitor be feasible economically and practical in consideration of the need to monitor for side effects? Is efavirenz useful even if the risk of pregnancy is high? Can a triple-therapy regimen of nonnucleoside reverse-transcriptase inhibitors be used without serious compromise of the community utility of nevirapine-based programs to prevent mother-to-child transmission of HIV? These and other key questions might be addressed in large trials unencumbered by unnecessary laboratory tests and questionnaires that would complicate the studies but would not contribute much to the primary research question. Primary end points would be surrogate markers, such as CD4+ cell count and virus load, with adherence rates and clinical status at 2 years as secondary end points.

**Concept 5.** An open-label phase I trial of HIV-infected persons without other infections would assess sex, age, and
Concept 6. What to use is related to how to use it. A key trial would test whether structured treatment interruption is a reasonable approach in resource-limited settings [77, 78]. Treatment-naive HIV-infected persons would be randomized to receive continual ART versus intermittent ART, such as the “1 week on and 1 week off” design that has shown promise. The primary end point would be success in suppression of virus load, with secondary end points of CD4+ cell count, virus resistance, drug toxicity, adherence, and clinical events. One structured treatment interruption trial is scheduled to begin in Uganda and Zimbabwe, but studies of several structured treatment interruption approaches will be needed given the diversity and complexity of the options. The inadvertent practice of treatment interruption is common when money is scarce or when drugs are available only intermittently, but this is not at all structured, highlighting the urgency of research in this area. Careful studies of virus resistance patterns and treatment results with resistant organisms will be needed.

Concept 7. An observational study would examine whether provision of ART changes community-wide uptake of voluntary counseling and testing or alters frequency of unsafe sexual behavior [56, 57]. The trial would enroll drug-naive, HIV-infected persons from communities that have started to make treatment widely available compared with communities not yet in a position to do so. Uptake rates of voluntary counseling and testing in the communities and serial cross-sectional prevalence of sexually transmitted infections among HIV-infected persons would be primary end points. Although difficult in urban settings, this kind of community-wide study might be well suited to rural areas with stable, nonmigratory populations. Because ART cannot be provided immediately everywhere, this study might be suitable for study of behavior in circumstances of incremental introduction of ART, with those receiving the drug earliest being compared with those receiving it later.

Concept 8. A study of patient knowledge, attitudes, practices, and behavior would assess the acceptability of various ART regimens in resource-limited settings, with the hope that patient satisfaction and adherence may improve with the use of more popular, and therefore sustainable, regimens. The study population would be composed of HIV-infected persons being treated with a variety of ART regimens, and researchers would use surveys and in-depth interviews to understand patient perceptions of barriers to adherence. The primary end points would be qualitative behavioral assessment of acceptability and epidemiological assessments of adherence.

Other potentially valuable studies on the subject of which drugs to use include testing whether ART has significant interactions with drugs used to treat endemic infections or with traditional medicines; whether single-dose nevirapine induces clinically significant virus resistance in women; which regimen sequences are best; and whether increased access to ART decreases the incidence of HIV infection (because of lower transmissibility) or increases it (because of higher-risk behavior and/or survival of infectious persons) at a community level [82].

Suitable Monitoring Approaches

Overview. Two principal research areas related to monitoring of disease and treatment were identified. First, research on clinical monitoring is necessary, including disease diagnosis and staging, monitoring of treatment effects and failures, drug toxicity, adherence and emergence of HIV resistance to drugs, and cost effectiveness. Second, research on simplified diagnostics and field performance of available technologies is needed. Further study of quality-control methods should be an aspect of all monitoring research for resource-limited settings.

Studies on approaches to clinical monitoring should include evaluation of surrogate CD4+ cell testing methods, with a focus on affordable products that are adaptable to existing treatment settings in resource-limited environments. Head-to-head comparisons of various CD4+ cell testing methods are needed to determine the best approaches. Cheaper alternatives to more-definitive hematologic indices need further study, particularly the extent to which total lymphocyte count mimics CD4+ cell count, and under what circumstances they correlate well or poorly. DNA- and RNA-based diagnostic methods also need to be compared between infants and adults. Research should establish normal readings for WBC counts, total lymphocyte counts, and CD4+ cell counts in various geographic regions, in the presence of chronic endemic infections, and with attention to variations in nutritional status and habits of the population. In addition, studies should determine the viral subtypes prevalent in the populations being studied.

There is need for assessment of cheap and rapid diagnostic systems that can be used in a variety of settings. Rapid tests that have improved efficiency can avoid false-positive and false-negative results for HIV infection itself. Neither PCR nor flow cytometry are practical, affordable global field tools at present. Lack of an alternative to PCR is of particular concern in the case of HIV-exposed infants, because methods for the practical diagnosis of HIV infection are needed to expedite appropriate care for the infants who are infected.

Financial and staffing constraints often make the use of ideal monitoring technologies not feasible. In these settings, clinical...
markers should be tested against CD4⁺ cell counts, total lymphocyte counts, virus loads, and other tests for their appropriateness in informing treatment decisions. The World Health Organization (WHO) has developed a staging system for HIV infection that has proven useful in clinical assessment [55, 60]. The system incorporates clinical conditions of prognostic significance, from asymptomatic to advanced disease, as well as CD4⁺ cell count or, when that is unavailable, total lymphocyte count. Research is needed to determine whether this system can be improved to enable simplified diagnosis, prognosis, and decision-making in a resource-limited setting, both with and without treatment access.

Guidelines for testing and evaluation are needed in several areas. Laboratory monitoring protocols are not yet standardized for developing countries. Clinical and virological definitions for resistance must be developed, and population-level surveillance for toxicities and resistance should be incorporated with ART delivery, when possible. This surveillance will indicate the degree to which treatment and adherence programs are succeeding and will inform standardized population-based changes in ART therapy. Criteria for performing liver function, metabolic, hematological, and other tests need evaluation, and the ability of CD4⁺ cell counts, lymphocyte counts, and other measures to predict drug resistance needs to be determined.

Monitoring of patient adherence to ART regimens is critical, but we do not know what methods are most appropriate to use. Options include observational measures, such as pill counts, and laboratory tests of blood and other fluids—for example, RBC indices to assess adherence to zidovudine treatment. Adherence studies should include research on the efficacy of directly observed therapy compared with that of less-intensive approaches to regimen compliance [56, 81].

Study priorities for laboratory research include performance testing of various monitoring technologies, including cheaper CD4⁺ cell and virus load tests. Several operational issues related to monitoring technologies are also worthy of study, including methods for transportation of specimens, better understanding of appropriate fixatives and transport conditions, and the cost-benefit analysis of the use of central versus local laboratories.

Specific research concepts. Several specific trial or study concepts are suggested to test monitoring approaches.

Concept 9. A multicenter, large, randomized, controlled trial could compare different monitoring approaches and technologies, such as syndromic management (i.e., management based only on clinical examination of the patient), total lymphocyte count, p24 antigen testing, and hemoglobin level or other RBC indices versus CD4⁺ cell count and virus load monitoring. The trial would compare the clinical benefits of low- and high-technology monitoring approaches. In future studies of children, the study could include assays not typically used when CD4⁺ cell counts and virus loads are readily available, such as determination of IgA in tears and blood of newborns, if these are validated in earlier trials. Although IgA assays would not seem to hold much advantage in simplicity over determination of CD4⁺ cell count and virus load, such assays could be made into cheaper tools that are less reliant on high start-up investment (as with a flow cytometer or a thermocycler). Morbidity, disability, and mortality would be ideal but impractical end points; a surrogate marker for these might be the independent assessment of clinical status comparing the groups being monitored more or less intensively.

Concept 10. An observational study could be nested within other clinical trials to test the success of clinical signs and symptoms in mimicking well-validated surrogates to establish whether quality care is feasible without costly monitoring. The study population would include persons being treated with ART, with changes in therapy to be based on laboratory monitoring and current standards of care. At the end of the study, clinical symptoms would be assessed by clinical field staff who are not providing primary care for the patient and who are not aware of the patient’s laboratory status, on the basis of patient self-report and the clinician’s physical examinations; these clinical assessments would then be correlated with CD4⁺ cell count and virus load measurements. The trial end point would be a measurement of concordance between clinical assessment and CD4⁺ cell and virus load measurements.

Concept 11. Another observational study would merge features that are studied in concepts 9 and 10 to assess whether lower-technology laboratory monitoring is feasible in selected settings. The study would enroll persons being treated with ART and compare a family of plausible, lower-technology measures of immune activation and disease progression with CD4⁺ cell count and virus load as measures of response to ART. The study would not be a randomized clinical trial of a higher-technology versus lower-technology clinical monitoring strategy, as with concept 9, nor would it compare a purely clinical monitoring approach nested within other clinical trials, as with concept 10. Rather, it would assess the concordance of the higher technology (determination of CD4⁺ cell count and virus load) with lower technology (determination of total lymphocyte count, hemoglobin level, and perhaps erythrocyte sedimentation rate) within the context of routine patient care.

Another key issue that can help improve ART monitoring includes the extent to which reagent costs can be reduced for resource-limited settings, analogous to what is happening to antiretroviral drugs in the face of generic competition and flexible interpretations of patent rights versus national health emergencies. An ideal is a cheap and reliable dipstick approach to HIV diagnosis, CD4⁺ cell monitoring, and virus load. Such innovation may require public sector investment, because the
DISCUSSION

Research on delivery of ART could benefit greatly the millions of people living with HIV disease in resource-limited countries. This research must be designed to maximize the utility of ART and facilitate access in the communities in which these studies are based. The precipitous decrease in the cost of ART in developing nations has given a sense of urgency to the need for such research [82–84]. Research cannot be separated from the day-to-day survival issues of people living with HIV in these settings, most of whom face huge challenges in finding access to appropriate care. Hence, the global research agenda should focus on HIV care, not merely on ART, although the latter was the focus of our conference.

A variety of different research designs are relevant in resource-limited environments. Researchers should consider local differences in treatment options, specifics of the HIV epidemic, and other health care conditions affecting local populations when designing research studies. The concepts suggested here are broadly defined, and we recognize the work that will be needed to improve them, tailoring them to specific circumstances through precise protocols.

Sustainability of ART in study communities after research finishes is critical, yet this may be problematic in countries where health care services are generally unavailable. Researchers and funding institutions should work with governments, pharmaceutical companies, and community members to overcome the challenge of sustainability. The new Global Fund to Fight AIDS, Tuberculosis, and Malaria should be most helpful in building bridges between research and ongoing care.

To the extent possible, common research protocols should be developed to make research results more comparable. Research institutions and funding agencies should promote standardization of research outcomes and facilitate the exchange of information and results between researchers. Many of the studies proposed above are not central to the current research priorities of key funding agencies, so special programs should be developed to support these efforts. An example is the HIV-NAT Network, in which investigators from The Netherlands and Australia worked closely with Thai scientists to address treatment questions of special relevance to Thailand. A recent example of an effort to mimic this level of coordination is the International AIDS Clinical Trials Group initiative from the National Institutes of Health (NIH) in the United States, bridging clinical trials expertise to the earlier efforts towards the development of a global research infrastructure supported through the NIH-sponsored HIV Prevention Trials Network.

Research studies should be designed and managed by local investigators who understand the HIV epidemic in their home settings. Funding agencies have a critical role in assisting with the training, institutional strengthening, and transfer of technology to carry out these studies. UNAIDS and the WHO routinely take this approach [70, 71]. The recent NIH initiative, the Comprehensive International Program for Research on AIDS, requires that the principal investigators and recipient institutions be from developing countries. Awards made directly to foreign institutions that include indirect cost contributions are a new precedent for the NIH.

Research must be considered a partnership with study communities, involving them in all aspects of the research. Study protocols should be designed so that research contributes to development of local capacity and respects the culture, traditions, and social practices of affected communities. Antiretroviral research must be placed in the broader context of community-based health care and prevention education [85–87]. The results of the research must be shared with communities that have made this research possible. Just a few years ago, ART was thought to be unattainable in resource-limited settings; we now face plummeting drug prices and the hope that ART can be expanded worldwide. The international research community needs to embrace an ART and OI research agenda in resource-limited settings as an urgent global HIV priority.

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