Identifying HIV Treatment and Research Priorities in Resource-Poor Settings

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Not 20 years since it was identified as the cause of AIDS, the human immunodeficiency virus (HIV) has become the world's leading infectious cause of death. In the United States and other industrialized nations, the success of highly active antiretroviral therapy (HAART) has provided a partial reprieve from the epidemic. Yet in developing nations—home to 90% of those living with HIV in the world—antiretroviral treatment is beyond the reach of most.

According to recent estimates from UNAIDS, 25 million people have died of HIV/AIDS to date, and 42 million people are currently living with the disease. Of these, approximately 800,000 are in North America, compared to 28.4 million in sub-Saharan Africa, 6 million in South and Southeast Asia, and 2 million in the Caribbean and South America. Providing a snapshot of one of the hardest hit countries as an example, Dr. Miriam Rabkin discussed the experience in Zambia, a country in Southern Africa, where HIV prevalence among people of reproductive age is in excess of 30%. Among men between the ages of 15 and 60 in Zambia, mortality has increased 68% since the beginning of the AIDS epidemic. There has also been a 50% increase in mortality among children under five years of age. And life expectancy at birth has dropped to 36 years, a statistic linked to the fact that 650,000 people have died of AIDS in a country of 11 million.

In recent years, some headway has been made in addressing the epidemic. First, there has been an increase in international financial support. Annual global resources for HIV/AIDS have grown from approximately $300 million in 1999 to $3 billion in 2002, with additional substantial funding increases from the United States now promised by the current White House administration. Second, there has been a decrease in the cost of treatment. Pharmaceutical companies producing brand-name and generic versions of various antiretroviral drugs have radically reduced the costs of HAART in resource-poor settings, which can now be purchased for as little as $350 a year (still higher than either the average per-capita income in many resource-poor countries or the annual government per-capita health expenditure). Others are working to decrease the cost of monitoring tests, and to develop cost-effective and simpler treatment algorithms. These changes have permitted nongovernmental organizations, such as the Nobel Peace prize-winning Médecins Sans Frontières (MSF) to initiate small pilot treatment programs in a number of resource-poor settings, and have encouraged the development of MTCT-Plus, a $50-million treatment initiative aimed at providing care to 10,000 HIV-infected individuals in Africa and Asia over the next three years.

Thus far, antiretroviral coverage in resource-poor countries remains tragically low. As Dr. Rabkin explained, an estimated 50,000 HIV-positive people in sub-Saharan Africa are currently receiving antiretroviral treatment—less than two percent of the 4.1 million people thought to require HAART today. In Asia, the coverage rate is 4%; in North Africa and the Middle East, the rate is 29%; in Latin America and the Caribbean, a slightly more optimistic coverage rate of 53% has been documented; and in Eastern Europe and Central Asia, the rate is 9%. Bringing all the numbers together, it is estimated that of the 5.5 million people worldwide who are believed to be in immediate need of antiretroviral medications, only 300,000 (5%) are currently receiving therapy.

While the availability of HAART is critical, fundamental questions about HIV/AIDS care in resource-poor settings remain. Provision of longitudinal care, patient education, and psychosocial support may demand different approaches in different places and will require strengthening of weak and often overburdened health-care systems. Strategies for optimal antiretroviral sequencing, patient monitoring, and adherence support in resource-limited environments also remain undefined. Can HAART be given safely if laboratory testing is unavailable? Can HIV care be provided by nonphysicians? According to Dr. Rabkin, not all of these questions can be answered expeditiously. "Some of these questions may take a long time to answer," she commented, "and some may not be answerable. This does not mean that we should put treatment programs on hold, but that we should identify the most important questions and coordinate our efforts to find solutions."

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Sign for St. Francis Hospital, Kampala, Uganda. St. Francis Nsambya is a mission hospital in Kampala, Uganda. Urban hospitals are the exception in sub-Saharan Africa, where the majority of health care is provided at health stations, often rural, and usually staffed by non-physicians.

Much thought has been given to defining clinical research priorities. As Dr. Rabkin noted, "one way to start is to ask ourselves: what are the questions whose answers may expand access to care for the millions of HIV-infected people in resource-poor settings?" These questions have been explored by a working group supported by the Health Equity Division of The Rockefeller Foundation and were recently published—along with potential research suggestions to help answer these questions—in the November 9, 2002 issue of *The Lancet* (Rabkin, 2002). What follows is a review of the more basic questions, along with the efforts that are now under way to address them.

Table 1. **Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection**

If CD4 testing is available:
• WHO stage IV irrespective of CD4 cell count[a]
• WHO stage I, II or III[a] with CD4 cell counts less than 200/mm³ [b]
If CD4 testing is not available:
• WHO stage IV irrespective of total lymphocyte count (TLC)
• WHO stage II or III[c] with TLC less than 1200/mm³ [c]

a. Treatment is also recommended for patients with advanced WHO stage III disease, including recurrent or persistent oral thrush and recurrent invasive bacterial infections, irrespective of the CD4 cell count or the total lymphocyte count.

b. The precise CD4 level above 200/mm³ at which to start ARV treatment has not been established, but the presence of symptoms and the rate of CD4+ cell decline (if measurement is available) should be factored into decision-making. A CD4+ count of 200 cells/mm³ corresponds to a CD4+ percentage of approximately 15%.

c. A total lymphocyte count below 1200 cells/mm³ can be substituted for the CD4+ cell count when the latter is unavailable and HIV-related symptoms exist. It is less useful in the asymptomatic patient. Thus, in the absence of CD4+ cell count testing, asymptomatic HIV-infected patients (WHO stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.

Source: World Health Organization, 2002. *Scaling Up Antiretroviral Therapy in Resource-Poor Settings: Guidelines for a Public Health Approach* (http://www.who.int.docstore/HIV/scaling/).

When to Start?

IN THE UNITED STATES AND OTHER NATIONS where HAART is widely available, there are lingering questions about the optimal time to initiate antiretroviral therapy. While treatment of patients with symptomatic disease and/or CD4 counts below 200 cells/mm³ clearly provides a mortality benefit, whether to start HAART in asymptomatic patients with more than 200 to 350 CD4+ cells/mm³ remains controversial. "This is not a question that keeps most of us up at night," Dr. Rabkin said. "In settings where we have the luxury of treating whomever we like, the decision whether to start at 200, 350, or higher is usually made on an individual patient level."

In developing nations, however, the question of when to start represents a critically important policy decision. The expense of medications, laboratory testing—even the costs associated with clinic visits—dominates discussions about when to initiate therapy. Starting too soon means using resources that could be programmed elsewhere. Starting too late risks unnecessary deaths. Some programs, Dr. Rabkin explained, use a CD4+ cutoff of 50 cells/mm³, others have used a CD4+ cutoff of 200 cells/mm³, and some are even more liberal. But some programs provide HAART without CD4 enumeration. "CD4+ cell testing is available in most capital cities in sub-Saharan Africa," Dr. Rabkin said. "But this can be prohibitively expensive. And for those who do not live in or near these capital cities, CD4+ count testing is simply not an option. A health station upcountry may not have access to more than the most basic tests. Does this mean that these people can never be treated? We don't think so."

According to treatment guidelines published in 2001 by the World Health Organization—entitled *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: a Public Health Approach*—clinical HIV staging, either alone, in combination with CD4+ cell testing, or cheaper, more widely available laboratory parameters may suffice to make decisions about when to start antiretroviral therapy (see Table 1) (WHO, 2001). For example, it is recommended that patients who meet WHO stage IV criteria—clinical AIDS—should receive antiretroviral therapy, regardless of CD4+ cell count. While the total lymphocyte count (TLC) correlates relatively poorly with the CD4+ cell count, it is a useful marker of prognosis and survival when used in combination with clinical staging. Where total lymphocyte counts are feasible, antiretroviral therapy should be offered to all patients who meet WHO stages II or III of HIV disease and have a total lymphocyte count below 1200 cells/mm³. An assessment of viral load is not considered an essential preliminary to therapy. In contexts where access to laboratory testing is severely limited, WHO guidelines recommend the use of HAART as long as a patient has had an HIV test and assessment of his/her hemoglobin level.

Which Antiretrovirals to Use?

"IN WEALTHY COUNTRIES, THE SELECTION OF ANTIRETROVIRALS IS BASED on academic questions and individual circumstances," Dr. Rabkin said. "In many resource-poor settings, we need to use simple standardized regimens that will work for large numbers of people. We're not going to be seeing many doctors prescribing these drugs, simply because there are not enough doctors available. It's going to be nurses and community health workers who are providing HIV care. In turn, treatment decisions will be based on standardized algorithms, as they are in TB control programs. We may not be able to find a 'one-size-fits-all' regimen, but a 'one-size-fits-most' combination would be almost as helpful."

The WHO first- and second-line regimen recommendations for HIV-positive adults and adolescents in resource-poor settings are reviewed in Table 2. The recommended first- and second-line regimens for HIV-infected children are reviewed in Table 3.

ZDV/3TC is listed as initial recommendation for dual NRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. Other dual NRTI components can be substituted, including d4T/3TC, d4T/ddI and ZDV/ddI, depending on country-specific preferences (see text). ZDV and d4T should never be used together because of proven antagonism. Fixed-dose formulations are preferred whenever possible as they promote enhanced treatment adherence.

Choosing standardized "one-size-fits-most" regimens is a complicated task. One concern raised by Dr. Rabkin involves the use of efavirenz (Sustiva). "The MTCT-Plus program is designed for pregnant women and their families," Dr. Rabkin commented. "In this context, it's going to be difficult to use efavirenz, given its teratogenicity, at least that seen in animal studies. There's concern regarding widespread use of this drug in women of childbearing age, particularly where birth control is not widely available and where some women may not have complete con-

Table 2a. **Recommended first-line regimens in adults and adolescents**

Regimen[a]	Pregnancy considerations
ZDV/3TC/EFZ or ZDV/3TC/NVP	Substitute NVP for EFZ in pregnant women or women for whom effective contraception cannot be assured
ZDV/3TC/ABC[a]	ABC safety data limited
ZDV/3TC/RTV-PI[b] or	LPV/r safety data limited
ZDV/3TC/NFV	NFV: most supportive safety data

a. ZDV/3TC is listed as initial recommendation for dual NRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. Other dual NRTI components can be substituted, including d4T/3TC, d4T/ddI and ZDV/ddI, depending on country-specific preferences. ZDV and d4T should never be used together because of proven antagonism. Fixed-dose formulations are preferred whenever possible as they promote enhanced drug adherence.

b. RTV-PI includes IDV/r, LPV/r or SQV/r.

Table 2b. **Recommended second-line regimens in adults and adolescents**

First-line regimens	Second-line regimens for treatment failure	Alternative second-line regimens for treatment failure
ZDV/3TC/EFZ or ZDV/3TC/NVP	d4T/ddI/RTV-PI[a,b,c]	RTV-PI[a]/ABC/ddI[c,d] NFV + ABC/ddI[c,d] or d4T/ddI[b,c]/NFV
ZDV/3TC/ABC	d4T/ddI[b,c]/NNRTI[e]	d4T/ddI[b,c]/RTV-PI[a]
ZDV/3TC/RTV-PI or ZDV/3TC/NFV	d4T/ddI[b,c]/NNRTI[e]	ABC/ddI[c,d] /NNRTI[e]

a. RTV-enhanced PI = IDV/r, LPV/r, SQV/r. An RTV-enhanced PI regimen is preferred because of the potency of these regimens. NFV can be considered as an alternative for the PI component of second-line therapy if RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

b. Nucleoside cross-resistance may compromise the potency of d4T/ddI at the time of switching for treatment failure, as it is assumed that virological failure will have been prolonged at that point and several nucleoside analogue mutations (NAMs) are likely to be present. However, choices are limited in the setting of treatment failure. See also footnote c.

c. Tenofovir is a once-daily nucleotide analogue with activity against some nucleoside-resistant strains. If available, TDF can either be added to d4T/ddI or ABC/ddI or substituted for either d4T or ABC in these combinations. Its currently restricted availability in resource-limited settings is recognized.

d. High-level ZDV/3TC coresistance confers diminished susceptibility to ABC. If d4T/3TC is used as the first-line dual nucleoside backbone, AZT/ddI can be used as the second-line nucleoside component and vice versa.

e. NNRTI can be either EFZ or NVP.

Source: World Health Organization, 2002. *Scaling Up Antiretroviral Therapy in Resource-Poor Settings: Guidelines for a Public Health Approach* (http://www.who.int.docstore/HIV/scaling/).

trol over their own fertility. We don't plan to exclude its use in nonpregnant women, but we will have to be very careful." In their *Scaling Up* guidelines, the WHO authors state: "Efavirenz is not recommended for use in women who could become pregnant because of its potential teratogenic effect on fetuses in the first trimester."

Other obstacles include interactions between antiretroviral agents and tuberculosis medications. "The prevalence of tuberculosis among HIV-infected persons in sub-Saharan Africa is very, very high," Dr. Rabkin said. "So it's going to be difficult to use nevirapine (Viramune) or the protease inhibitors in the setting of simultaneous TB treatment."

Other issues raised by Dr. Rabkin include the ineffectiveness of some anti-HIV medications, most notably the non-nucleoside reverse transcriptase inhibitors, in countries where HIV-2 is the primary concern, not HIV-1. Another factor to consider is that medications like ritonavir (Norvir, Kaletra) and liquid stavudine (Zerit) need to be refrigerated, which is not an option in many settings, particularly outside of the clinic. There are also issues surrounding the use of medications in the face of other medical conditions. Anemia, for example, is prevalent in many areas and could be problematic in the event that zidovudine (Retrovir, Trizivir, and Combivir) is selected for first-line regimens. Hydration issues with indinavir (Crixivan) can also be a deal-breaker, explained Dr. Rabkin, "in places where the average temperature is 100 degrees and people simply don't have access to eight glasses of clean water a day." The use of abacavir (Ziagen and Trizivir) may also prove to be troublesome. Many of the symptoms of abacavir-associated hypersensitivity are similar to those of malaria and other common endemic illnesses, and excluding the syndrome in the absence of laboratory testing may be nearly impossible.

The cost of antiretroviral medications will be a significant factor in decisions regarding standardized regimens, and has already resulted in some countries endorsing one drug over another. Organizations working in developing countries are eager to procure and distribute generic versions of antiretrovirals that are significantly cheaper than discounted brand-name antiretrovirals. In fact, the WHO has included some generic antiretrovirals in its March 2002 prequalification list of agents suitable for use in resource-poor settings, although significant questions remain regarding quality control, quality insurance, and international trade law infringement. "The prequalification list reflects antiretrovirals that are endorsed by WHO," Dr. Rabkin said. "With WHO support, many countries are planning to use these generic drugs."

Questions regarding the most appropriate antiretrovirals to use, at least when it comes to putting together an initial regimen, have also surfaced in programs designed to prevent mother-to-child-transmission of HIV (PMTCT programs). "These programs are widespread," Dr. Rabkin commented. "In many ways, they are beacons of hope in terms of decreasing vertical transmission of HIV. But they also mean that there is a growing number of women and infants who have received single-dose nevirapine, which may lead to high-level nevirapine resistance." Should NNRTIs be reserved exclusively for PMTCT programs? Should women and infants who receive single-dose nevirapine to prevent transmission subsequently receive nevirapine-containing triple-drug regimens? These are just two of the important questions that remain.

How to Monitor?

DECIDING WHEN AND HOW TO INITIATE ANTIRETROVIRAL TREATMENT are only two issues to consider. Another major issue to consider is how to monitor patients for efficacy, toxicity, and emerging drug resistance. In the United States and other countries where both HAART and

laboratory monitoring are widely available, CD4+ cell counts, viral load, and chemistries are typically checked every three to four months after antiretroviral therapy is initiated. Needless to say, the high costs of such tests place them beyond the reach of most people living in resource-poor areas. In fact, the cost of routine laboratory monitoring is now on a par with the cost of antiretroviral therapy itself. "Can ARVs be used without lab monitoring of asymptomatic patients?" asked Dr. Rabkin. "What about less frequent monitoring, or monitoring using less expensive tests? Are these strategies safe? Are they effective?" Systematic evaluation of this type of cost-conscious approach to care is an essential prerequisite to widespread antiretroviral use.

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Medical records at St. Francis Hospital, Kampala, Uganda. Maintenance of on-site medical records is unusual in most resource-poor settings, where the norm is for patients to keep their own health information cards.

How to Support Adherence?

"THERE IS NO EVIDENCE TO SUPPORT THE FEAR that adherence to antiretroviral therapy will be more problematic in resource-poor settings than it is in resource-rich settings," Dr. Rabkin emphasized. "But that may not be reassuring to those of us who realize what a problem it is in resource-rich contexts." As issues of poor adherence become better understood—both in industrialized and developing countries—it is likely that tools to promote adherence will continue to evolve. As explained by Dr. Rabkin, these tools can be divided into four broad categories: patient education, behavior modification, streamlined regimens, and interpersonal support (including directly observed therapy). Adherence programs in resource-poor areas will likely need to rely on a combination of these tools—once the specific issues associated with adherence in these settings are identified. Another issue we need to consider is the effect of traditional healers and parallel health-care systems on adherence to antiretroviral treatment, Dr. Rabkin noted. "Can these care providers be enlisted to help us support adherence?" she wondered.

Table 3a. **Recommended first-line antiretroviral regimens for children**[a]

Regimen	Comments
ZDV/3TC[b] plus ABC	Preferred if concomitant anti-tuberculosis therapy is being received
ZDV/3TC[b] plus NNRTI	NNRTI choice: if <3 years or <10 kg, NVP if ≥3 years or ≥10 kg, NVP or EFV

a. Country-specific considerations and preferences should determine which regimen or regimens to make available.

b. ZDV/3TC is the first choice dual NRTI regimen for children, as the largest amount of clinical experience has been gained with this one. Other dual NRTI components can be substituted for children, including ZDV/ddI, d4T/3TC, d4T/ddI and ddI/3TC. ZDV and d4T should never be used together because of proven antagonism.

Table 3b. **Recommended second-line antiretroviral regimens for children**

First-line regimen	Second-line regimen	Alternative second-line regimen
ZDV/3TC/ABC	d4T/ddI plus LPV/r[a] or NFV or an NNRTI[b]	d4T/ddI plus an NNRTI[b] plus either LPV/r[a] or NFV
ZDV/3TC/NNRTI	d4T/ddI plus LPV/r[a] or NFV	

a. For children who can swallow capsules and for whom the current capsule formulations allow appropriate dosing calculated on the basis of body weight or body surface area, additional options include SQV/r and IDV/r.

b. NNRTI choice: if <3 years or <10 kg, NVP; if >3 years or >10 kg, NVP or EFV.

Source: World Health Organization, 2002. *Scaling Up Antiretroviral Therapy in Resource-Poor Settings: Guidelines for a Public Health Approach* (http://www.who.int.docstore/HIV/scaling/).

Conclusion

CLEARLY, THERE ARE MANY QUESTIONS REGARDING how best to provide widespread HIV care in resource-poor settings. "What I've tried to outline are the vitally important questions that remain unanswered—questions that are going to make or break the success of expanded access to antiretroviral therapy and HIV care," Dr. Rabkin said. A real concern, Dr. Rabkin explained, is the fact that it's not clear who will go about answering these questions. "The countries themselves do not have the resources to fund the necessary large-scale clinical studies to answer these questions. Some of the organizations that do have the resources don't necessarily have the mandates to do research in sub-Saharan Africa and elsewhere. This is an area of advocacy that we all need to think about." prn

References

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