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Priorities for Antiretroviral Therapy Research in Sub-Saharan Africa: A 2002 Consensus Conference in Zambia

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Abstract

Background—A consensus conference was held to discuss priorities for antiretroviral therapy (ART) research in Zambia, one of the world's most heavily HIV-afflicted nations. Zambia, like other resource-limited settings, has increasing access to highly active antiretroviral therapy (HAART) because of declining drug costs, use of government-purchased generic medications, and increased global donations. For sustained delivery of care with HAART in a resource-constrained medical and public health context, operational research is required and clinical trials are desirable. The priority areas for research are most relevant today given the increasing availability of HAART.

Methods—A conference was held in Lusaka, Zambia, in January 2002 to discuss priority areas for ART research in Zambia, with participants drawn from a broad cross section of Zambian society. State-of-the-art reviews and 6 intensive small group discussions helped to formulate a suggested research agenda.

Results—Conference participants believed that the most urgent research priorities were to assess how therapeutic resources could be applied for the greatest overall benefit and to minimize the impact of nonadherence and viral resistance. Identified research priorities were as follows:

1. To determine when to initiate HAART in relation to CD4⁺ cell count
2. To assess whether HIV/AIDS can be managed well without the use of costly frequent viral load measurements and CD4⁺ cell count monitoring

3. To assess whether HIV/AIDS can be managed in the same fashion in patients coinfecting with opportunistic infections such as tuberculosis and HIV-related chronic diarrhea, taking into consideration complications that may occur in tuberculosis such as immune reconstitution syndrome and medication malabsorption in the presence of diarrhea
4. To carefully assess and characterize toxicities, adverse effects, and viral resistance patterns in Zambia, including studies of mothers exposed to prepartum single-dose nevirapine
5. To conduct operational research to assess clinical and field-based strategies to maximize adherence for better outcomes of ART in Zambia
6. To assess ART approaches most valuable for pediatric and adolescent patients in Zambia

Conference participants recommended that HIV-related clinical care and research be integrated within home-based care services and operated within the existing health delivery structures to ensure sustainability, reduce costs, and strengthen the structures.

Conclusion—Our consensus was that antiretroviral clinical trials and operational research are essential for Zambia to address the new challenges arising from increasing ART availability. There is global consensus that antiretroviral clinical trials in resource-constrained countries are possible, and the capacity for such trials should be developed further in Africa.

Keywords

HIV; AIDS; HAART; adherence; developing countries; Zambia

Zambia is a landlocked southern African country with one of the world's worst HIV epidemics. This democratic nation, about the size of Texas, had a population estimated at 10.2 million persons in 2002. The HIV prevalence rate in the general population is an estimated 16%, with rates among young women in urban centers of up to 31.9%.^{1,2} Since the 1980s, measures to control the HIV epidemic have been mainly preventive—through education, behavioral change campaigns, and condom use promotion. These measures have not achieved much success in adults, although declining trends of HIV prevalence among the youth may indicate an incipient salutary trend.^{3,4} Since 1999, prevention of mother-to-child HIV transmission through short-course zidovudine or nevirapine administration at the onset of labor has introduced antiretroviral therapy (ART) as a preventive tool, primarily in the capital city of Lusaka.⁵

In 2002, the Zambian government provided lower cost generic antiretroviral drugs purchased from an Indian pharmaceutical firm (Cipla, Mumbai, India), permitting initiation of a care program including highly active antiretroviral therapy (HAART) for more than 80 HIV-infected persons in a model care program at the University Teaching Hospital (the main teaching hospital in the country) located in Lusaka. Other government initiatives in 2003 have led to increased accessibility of HAART. It is hoped that the World Health Organization initiative to have 3 million people on treatment by the year 2005 as well as new resources from the United States; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; Europe; and Japan will add impetus to increase accessibility and availability of HAART in Africa.⁶

With increasing availability of HAART, new challenges are arising in care and research for the Zambian health care community as well as for consumers. This has given rise to fears that challenges encountered in developing countries such as Zambia could lead to unregulated use of therapy giving rise to antiretroviral anarchy.⁷ In 2001, the US National Institute of Allergy and Infectious Diseases launched the Comprehensive International Program for Research on AIDS (CIPRA) to promote and develop AIDS research led by local investigators in resource-limited countries. A 2-year planning grant was awarded to Zambia in 2001 (I. Zulu, Principal Investigator) for preparation of the infrastructure and capacity for ART clinical trials and operational research. As part of the research planning process, we held a consultative

conference with a broad cross section of medical, nursing, academic, government, and community leaders in Lusaka on January 4, 2002. The goal of the conference was to discuss and suggest a national therapeutic research agenda and to seek other ideas and improvements that could ensure strong support for future ART research from medical, nursing, and community leaders in Zambia. The increasing availability of HAART in the country has made the challenges and research priorities identified in 2002 even more urgent and relevant today.

METHODS

Conference participants were drawn from various sectors of society, including researchers from medical institutions in Zambia, members of the Ministry of Health, National AIDS Council staff, nongovernmental organization representatives, members of the public media, representatives from the Zambia Network of People Living with HIV/AIDS, and a few international HIV clinicians and facilitators. After morning state-of-the-art presentations on perceived challenges for HAART in Zambia, 6 afternoon intensive small group discussions helped to formulate the research agenda.

RESULTS

Conference participants believed that the most urgent research priority was to assess how therapeutic resources could be applied for the greatest overall benefit and to minimize the impact of nonadherence and viral resistance. Six major research priority areas were highlighted and are discussed in the following sections.

Determination of When to Initiate HAART in Relation to CD4⁺ Cell Count

HIV-infected Zambians typically seek treatment only when they are symptomatic; many have a low CD4⁺ cell count at this time. Observational studies have shown that benefits from HAART at this stage are reduced compared with somewhat earlier initiation.⁸ Whether the preferred approach should be that of industrialized countries, where earlier use (eg, at 350 CD4⁺ cells/ μ L) is the norm, cannot be assessed with current evidence. Whereas recent data have shown that adherence in African patients is comparable and sometimes superior to that in developed countries,^{9–11} there is still a concern that nonadherence may be more common in asymptomatic patients in Africa, where daily medication use among asymptomatic persons is uncommon. The cost of chronic use of antiretroviral medications and immunologic and virologic monitoring as well as the likelihood of adverse effects are key considerations, particularly when starting earlier therapy in an African setting. The conferees agreed that it is not known exactly at what level of CD4⁺ cell count HAART might be most appropriate in the African context. This question is being pursued in the United States and Australia in the “SMART” trial conducted by the Terry Bein Community Program for Clinical Research on AIDS.¹² Because the setting of the US sites is different, the conclusions of the trial may not be generalizable to the African situation; therefore, similar studies in the African environment are indicated.

Conference participants further advocated the formal study of whether commencement of HAART only when the patient develops symptoms is justified to avoid cost, nonadherence, drug resistance, and poorer long-term patient outcome in the social and economic context of severe resource constraints. Although there was a concern that a lack of data on CD4⁺ cell range and CD4⁺ cell stage at which opportunistic infections (OIs) occur in Zambia was a limiting factor to design such trials, CD4⁺ cell ranges in Zambians are probably comparable to those in industrialized countries, although OIs may occur at a relatively higher CD4⁺ cell range in the Zambian setting.¹³ It is also a priority to assess the drug combinations available in inexpensive formulations as a vital component of the scaling up of ART and how the generic combinations compare with the established brand names. Researchers should assess salvage

therapy strategies when treatment failure occurs, given the limited range of generic medications. With the increasing availability of ART, it would be important as a preventive activity to assess whether the use of ART is associated with any significant changes in risk behavior.

A key ethical issue to be considered is the current acceptable standard that HAART be continued lifelong once initiated. Provision of HAART during and after clinical trials has been recognized as a major stumbling block for clinical trials and requires attention in developing countries. It was believed that treatment should not be terminated just because a clinical trial has been completed; yet, guarantees of lifelong therapy from research or pharmaceutical funding sources are unlikely. Another concern was whether investigators would be willing to terminate the study if new and more beneficial therapies are developed and became available. It was agreed that if such knowledge arose, the procedures for Data Safety and Monitoring Board (DSMB) review of data and early study closure or study design modification would prevail. The conferees also agreed that “stopping rules” should be considered if mortality is especially high in 1 study arm so as to permit the study to be stopped early per the judgment of the DSMB. This would permit patients in the inferior arm or protocol to be administered the superior treatment strategy when indicated. It would also be ethically appropriate to provide HIV care, including ART when indicated, to other family members whenever someone from a family is recruited into an ART study.

Assessment of Whether HIV/AIDS Can Be Managed Well Without the Use of Costly Frequent Viral Load Measurements and CD4⁺ Cell Count Monitoring

Conference participants highlighted the need to assess alternative monitoring tools for patients on HAART other than the use of costly CD4⁺ cell counts and viral load measurements. Increasing priority should be given to assessing the value of surrogates such as erythrocyte sedimentation rate, hematocrit, and total lymphocyte count as well as how total lymphocyte count compares with CD4⁺ counts.¹⁴ The urgency of this question is evident, because CD4⁺ cell counts and viral load tests are not readily available or affordable in most Zambian centers and will not be practical for most rural hospitals or clinics for a long time to come.

Assessment of Whether HIV/AIDS Can Be Managed in the Same Fashion in Patients Coinfected With Opportunistic Infections Such as Tuberculosis and HIV-Related Chronic Diarrhea

Tuberculosis and HIV-related chronic diarrhea are among the most common OIs in Zambia. Paradoxical worsening of tuberculosis when HAART is introduced has been noted. Such a paradox would presumably be a result of exacerbated pathogenesis with partial immune reconstitution.¹⁵ This research agenda would have as its goal to assess immune reconstitution prospectively when HAART is commenced and to establish guidelines for the exact timing of commencement of HAART in tuberculosis-coinfected patients.

HIV-related chronic diarrhea is often caused by protozoal infections in Zambian patients. Malabsorption is a common complication arising from intestinal mucosal villous damage and increased intestinal motility. Malabsorption of medications is thus a concern, perhaps selectively depending on the specific drug involved. It would be important to assess the best time to initiate HAART in patients with diarrhea, whether immediately or after the diarrhea is under better control. Pharmacokinetic studies among patients with severe diarrhea may help to determine optimal strategies for ART use.

Assessment and Characterization of Toxicities, Adverse Effects, and Viral Resistance Patterns in Zambia, Including Studies of Mothers Exposed to Prepartum Single-Dose Nevirapine

Comprehensive but practical assessment strategies for HAART adverse effects in African patients are needed. Adverse effects and toxicities that are known to HIV treatment experts are those documented from patients in the wealthier nations. Because of influences of environment, nutrition, coinfections, host genetics, and other factors, the adverse effect profile in Africans may differ. From cohorts of treated HIV-infected patients in clinical care, it would be useful to assess tolerance and adverse effects of ART by tracking and reporting any adverse effects that may develop to a centralized data unit established for collecting and analyzing such information. It is also vital to assess the molecular epidemiology of the epidemic, including viral subtypes, recombinants, and viral drug resistance patterns. Apart from studies designed to assess viral resistance, programs for viral resistance surveillance in populations on treatment should be established. A special concern applies to women who have been exposed to single-dose nevirapine, given the high drug resistance frequencies noted in their subsequent viral assays. Resistance data suggest that response to subsequent nevirapine-containing HAART regimens is reduced in women who had earlier taken single-dose nevirapine to prevent mother-to-child HIV transmission [11th Conference on Retroviruses and Opportunistic Infections (CROI) meeting]. It is a priority to assess improvement and revision on nevirapine monotherapy before widespread resistance to nonnucleoside reverse transcriptase inhibitors develops.

Performance of Operational Research to Assess Clinical and Field-Based Strategies to Maximize Adherence for Better Outcomes of Antiretroviral Therapy in Zambia

Directly observed therapy (DOT) has been effective in tuberculosis programs in countries in which the strategy has been properly implemented. DOT has been used in treating patients with HIV in Haiti and the United States to maximize adherence and has been shown to be feasible in Botswana and South Africa.^{9–11,16} The meeting participants agreed that there is a need for operational research, especially at a community level, and for clinical trials to assess ways of enhancing adherence in Zambian patients. One such approach would be the use of community health workers and family members and friends for DOT implementation to maximize adherence to HAART. Because there is a potential stigma with DOT, it was recommended that there should be antistigma campaigns (ie, community organizing and education) to help make DOT more successful. One recent study suggests that enthusiasm for DOT in HAART delivery may be dampened because of a lack of evidence that observed dosing is superior to self-administered therapy based on a mistaken assumption that adherence is lower in resource-limited countries.¹⁷ Such doubts can only be resolved by further studies comparing outcomes in DOT versus self-administered therapy. Results may differ by region, by tribal group, by educational status, or in rural versus urban settings. One theoretic limitation of the DOT strategy is the added cost in implementing and sustaining such a program, whereas its theoretic advantage is the community support and improved adherence received.

The conferees further agreed that HIV-related clinical care and research should be integrated within home-based care services and operated within the existing health delivery structures. This has the best chance of ensuring sustainability, reducing costs, and strengthening national and local health care structures.¹⁸

Assessment of Antiretroviral Therapy Approaches That Are Most Valuable for Pediatric and Adolescent Patients in Zambia

The consensus from participants was that all the above research questions apply to children and adolescents as well. There is a need to design and conduct pediatric trials in this same vein.

It is a serious concern that children will not be attended to with the same vigor in treatment research as adults, although their needs and rights are just as valid and compelling.

DISCUSSION

The consensus from the meeting was that antiretroviral clinical trials and operational research are essential for Africa in general and for Zambia in particular. The new ARTs being introduced have created new challenges that must be addressed through research of specific relevance to Zambia and other resource-limited settings. There is now global consensus that antiretroviral clinical trials in resource-limited countries are possible, and the capacity for such studies must be developed further in Africa.^{9,10,19,20}

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References

1. Central Statistical Office (Zambia), Central Board of Health (Zambia), and ORC Macro. Zambia Demographic and Health Survey 2001–2003. Vol. 236. Calverton, MD: Central Statistical Office, Central Board of Health and ORC Macro; 2003.
2. Handema R, Terunuma H, Kasolo F, et al. Emergence of new HIV-1 subtypes other than subtype C among antenatal women in Lusaka, Zambia. *AIDS Res Hum Retrovir* 2001;17:759–763. [PubMed: 11429116]
3. Fylkenses K, Musonda RM, Sichone M, et al. Declining HIV prevalence and risk behaviors in Zambia: evidence from surveillance and population based surveys. *AIDS* 2001;15:907–916. [PubMed: 11399963]
4. Piot P, Coll Seck AM. International response to the HIV/AIDS epidemic: planning for success. *Bull World Health Organ* 2001;79:1106–1112. [PubMed: 11799442]
5. Stringer SA, Rouse DJ, Vermund SH, et al. Cost-effective use of nevirapine to prevent vertical HIV transmission in sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2000;24:369–377. [PubMed: 11015154]
6. [Accessed April 2, 2004]. <http://www.who.int/mediacentre/factsheets/2003>
7. Harries AD, Nyangulu DS, Hargreaves NJ, et al. Preventing antiretroviral anarchy in Sub-Saharan Africa. *Lancet* 2001;358:410–414. [PubMed: 11502341]
8. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001;15:983–990. [PubMed: 11399980]
9. Weiser S, Wolfe W, Bangsberg D, et al. Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana. *J Acquir Immune Defic Syndr* 2003;34:281–288. [PubMed: 14600572]
10. Orrell C, Bangsberg DR, Badri M, et al. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS* 2003;17:1369–1375. [PubMed: 12799558]
11. McNeil DG Jr. Africans outdo US patients in following AIDS therapy. *New York Times* September 3;2003 3:A1.
12. Deleted in proof.
13. Kelly P, Zulu I, Amadi B, et al. Morbidity and nutritional impairment in relation to CD4 count in a Zambian population with high HIV prevalence. *Acta Trop* 2002;83:151–158. [PubMed: 12088856]

14. Kumarasamy N, Mahajan AP, Flanigan TP, et al. Total lymphocyte count (TLC) is a useful tool for the timing of opportunistic infection prophylaxis in India and other resource-constrained countries. *J Acquir Immune Defic Syndr* 2002;31:378–383. [PubMed: 12447007]
15. Orlovic D, Smego RA Jr. Paradoxical tuberculous reactions in HIV-infected patients. *Int J Tuberc Lung Dis* 2001;5:370–375. [PubMed: 11334257]
16. Farmer P, Leandre F, Murkherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001;358:404–409. [PubMed: 11502340]
17. Liechty CA, Bangsberg DR. Doubts about DOT: antiretroviral therapy for resource-poor countries. *AIDS* 2003;17:1383–1387. [PubMed: 12799560]
18. Stringer EA, Sinkala M, Stringer JS, et al. Prevention of mother-to-child transmission of HIV in Africa: successes and challenges in scaling-up a nevirapine-based program in Lusaka, Zambia. *AIDS* 2003;17:1377–1382. [PubMed: 12799559]
19. Stringer JS, Sinkala M, Stout JP, et al. Comparisons of two strategies for administering nevirapine to prevent perinatal HIV transmission in high-prevalence, resource-poor-settings. *J Acquir Immune Defic Syndr* 2003;32:506–513. [PubMed: 12679702]
20. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002;359:2059–2064. [PubMed: 12086758]