HIV and global health

Monitoring HIV treatment in developing countries

Serena P Koenig, Daniel R Kuritzkes, Martin S Hirsch, Fernet Léandre, Joia S Mukherjee, Paul E Farmer, Carlos del Rio

Laboratory monitoring of antiretroviral therapy helps limit resistance but is currently not feasible in developing countries. Alternative short term approaches are needed

Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA 02120, USA
Serena P Koenig *physician*

Section of Retroviral Therapeutics, Brigham and Women's Hospital
Daniel R Kuritzkes *director*

Division of Infectious Disease, Massachusetts General Hospital, Boston
Martin S Hirsch *professor of medicine*

Partners In Health, Boston
Joia S Mukherjee *medical director*

Program in Infectious Disease and Social Change, Department of Social Medicine, Harvard Medical School, Boston
Paul E Farmer *Presley professor of medical anthropology*

HIV and Tuberculosis Programmes, Zanmi Lasante, Cange, Haiti
Fernet Léandre *director*

Clinical Sciences and International Research, Center for AIDS Research, Emory University, Atlanta, GA, USA
Carlos del Rio *director*

Correspondence to:
S P Koenig
skoenig@partners.org

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HIV and AIDS remain the world's leading infectious cause of adult death despite the development of antiretroviral therapy. Although antiretroviral drugs have decreased HIV related mortality by about 80% in the industrialised nations,[1 2] most people (92%) who need the drugs in non-industrialised nations do not have access to them.[3] This is not surprising, as the international response to the epidemic has been inadequate in terms of both prevention and care. Yet there is some cause for optimism. Unprecedented multilateral and bilateral initiatives are poised to make comprehensive HIV care the world's best funded public health initiative. To maximise the effect of these resources, however, it is critical that HIV programmes adopt a comprehensive approach.

Need for simplified short term strategies

Human resources and healthcare infrastructures are severely limited in many of the countries that bear the greatest burden of HIV disease. We need to strike a balance between building systems for delivering antiretroviral drugs and investing in laboratory infrastructures to monitor treatment outcomes. In the short term, widespread implementation of antiretroviral drug programmes will be threatened if governments and providers in resource poor settings are required to follow the monitoring protocols currently used in middle and high income countries, which are costly and require vast human resources. After years of inadequate funding, the health systems in most developing countries have poorly functioning medical facilities, unreliable drug procurement systems, and a limited supply of essential medicines. In addition, most countries face a crisis in human resources, with insufficient numbers of healthcare providers, a problem that has been exacerbated by the high rate of HIV infection among doctors and nurses.

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Waiting for HIV drugs in Port-au-Prince

Even relatively simple procedures widely used to monitor drug safety (such as routine tests of hepatic function) are not yet widely available in resource poor settings. Acknowledging this state of affairs in its current guidelines for HIV treatment in resource poor settings, the World Health Organization indicates that it "recognizes the importance of laboratory monitoring for efficacy and safety but does not want restricted infrastructure for these tests to place undue limitations on the scale-up effort."[4]

Although advocating for different standards of care in industrialised and developing countries seems to perpetuate the inequalities that we are attempting to redress, the focus of our argument is the feasibility and public health benefits of immediately implementing widespread access to antiretroviral drugs, even in the absence of extensive laboratory capacity. Furthermore, clinical monitoring and close supervision of care—with community health workers making daily home visits, for example—can produce outcomes similar to those achieved in many US cities.[5–7] Scarce human and financial resources must be augmented and, in the short term, deployed to focus on urgent and coordinated provision of basic health services, prevention and treatment of opportunistic infections, and expansion of access to antiretroviral drugs. Effective strategies must be developed to procure and distribute medications, train technical staff in the diagnosis and clinical management of HIV and AIDS, build systems to ensure patient adherence, and monitor and evaluate programmes.

It is also essential that HIV prevention activities such as community education and condom promotion are strengthened to avoid a possible increase in HIV transmission as patients' lives are extended, potentially without complete suppression of the virus. Other ongoing critical health needs (tuberculosis control, clean water supply, vaccination and women's health programmes, nutritional support, etc) must also be tackled.[7] Investing in AIDS prevention and care in this manner strengthens primary health care, as has been shown in Haiti.[8]

Preserving first line regimens

Health systems in the world's poorest nations are unlikely to rapidly develop the capacity to measure CD4 cell counts, viral loads, or resistance mutations until these tests become technically less demanding and less expensive. A regular supply of electricity is lacking in many areas in which AIDS is endemic and laboratory staff are scarce. In addition, the costs of most second line drugs remain prohibitively high for widespread use and, as a result, many countries have elected to have a restrictive drug formulary that limits the options for

those in whom first line regimens fail. Thus, the development of cheaper drugs and diagnostic strategies remain urgent priorities for long term success in treating HIV and AIDS in resource poor settings.[9 10]

In the meantime, many countries and programmes are launching and scaling-up AIDS treatment with standard first line drugs and clinical monitoring algorithms. Most patients will thrive with this approach. However, since viral load is not routinely measured, early treatment failure (inability to suppress viral replication before clinical worsening) may not be detected. Patients with persistent viraemia during drug treatment will be at risk of accumulating an increasing number of HIV resistance mutations that may limit future therapeutic options. Once clinical failure ensues, the ability to select an optimal treatment regimen will be further limited by the inability to test for resistance.

For these reasons, prolonging the clinical efficacy of first line antiretroviral drugs regimens in resource limited settings is critical. Meticulous adherence to treatment, which has been shown in multiple studies to be the most important factor in delaying the development of drug resistance, must be emphasised.[11–14] In the United States, the emergence of resistant strains, which now account for up to 15% of all new infections in certain cities, has little to do with the lack of sophisticated laboratory capacity but rather the lack of social support needed for vulnerable patients to adhere to demanding regimens (C del Rio et al, 8th annual conference on retroviruses and opportunistic infections, Chicago, IL, 2001).[15]

The global epidemic of multidrug resistant tuberculosis, fuelled by underfunded and poorly functioning systems of care, provides another sobering example of this phenomenon. Labelled a ticking time bomb,[16] multidrug resistant tuberculosis has now been reported in more than 100 countries worldwide, accounting for over 20% of all cases in the mostly highly burdened areas.[17] The consequences of erratic adherence to HIV therapy may be even greater because antiretroviral drugs are required for life and the risk of poor adherence is therefore much higher. Adherence to treatment for tuberculosis is highest with community based, supervised patient care.[18 19] It seems reasonable to assume that treatment support will also be a cornerstone of HIV therapy.[6 7]

Haiti's model

Haiti is the western hemisphere's most impoverished nation and, not coincidentally, also has the hemisphere's largest HIV epidemic. In 2003, the Global Fund to Fight AIDS, Tuberculosis and Malaria began providing funding for HIV treatment, and the United States' President's Emergency Plan for AIDS Relief provided additional funds starting in 2004. Although Haiti is in the midst of a political crisis and has a United Nations stabilisation force in place, the scale-up of antiretroviral treatment has proceeded apace in both urban and rural areas.

In Port-au-Prince, the Groupe Haïtien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) provides comprehensive prevention and treatment programmes for HIV and AIDS (including antiretroviral drugs) free of charge, targeting care to the surrounding population of about two million people. Adherence is encouraged through visits from community health and social workers, telephone cards, peer educators, support groups, and counselling by pharmacists and healthcare providers. Clinical signs are closely followed at clinic visits, and laboratory evaluations (including safety monitoring and CD4 cell counts) are done biannually. The one year survival rate for the first 1004 patients receiving antiretroviral drugs was 87% for adults and 98% for children.[20] In adults, the median increase in CD4 cell count from baseline after 12 months was 163×10^6/l. In a subset of 100 patients, 76% had an undetectable viral load after 48-56 weeks of treatment.

In rural Haiti, the funding has been used to rapidly scale-up prevention and treatment of HIV and AIDS as well as to provide comprehensive primary health services throughout Haiti's central plateau. In the past three years, annual patient visits have increased from 200 000 to 1 million a year at seven Partner in Health clinics and hospital complexes, each run in collaboration with the ministry of health. HIV infected patients are seen at least once a month by doctors and nurses in the clinic. Adherence (and daily monitoring) is guaranteed by directly observed treatment, which is provided by community health workers *(accompagnateurs)* who visit the patients in their homes at least once a day and serve as a link between the rural villages and the central health facilities.[7]

Laboratory capacity in rural Haiti is limited to two clinics with flow cytometers to monitor CD4 cell count. Patients' CD4 cell counts are used primarily as a criterion for enrolment. All laboratories can do a range of microscope based procedures, but none has the capacity to perform mycobacterial cultures or measure viral load. Although laboratory capacity is limited, clinical outcomes have been excellent. Of 1860 patients taking antiretroviral drugs, fewer than 5% have switched to second line treatment because of treatment failure.[21]

Importance of further research

To maximise long term beneficial outcomes, further clinical trials must be conducted to produce evidence to guide treatment and laboratory monitoring in resource poor settings. WHO, the US National Institutes of Health, and other organisations are increasingly taking part in this research. The challenge is to determine which of the costly diagnostic and monitoring interventions used in industrialised countries are indispensable to provide antiretroviral drugs in less developed settings. We need trials comparing the health outcomes and treatment costs of patients monitored by clinical criteria, CD4 cell counts, and viral load testing. We also need to determine the optimal time to switch from first line to second line therapy in the absence of resistance testing and salvage regimens. Safety monitoring algorithms must also be evaluated for use in resource limited settings, to minimise the risk of toxicity related to antiretroviral drugs. These and many other issues must be addressed in order to develop evidence based treatment guidelines that maximise the impact of our limited resources.[22]

Conclusions

The first priority for the global public health community should be rapid expansion in the provision of antiretroviral drugs using simplified treatment algorithms. All programmes, especially those that lack

Summary points

- Developing countries do not have the infrastructure or human resources for laboratory monitoring of antiretroviral therapy
- Treatment cannot await the development of such facilities
- In the short term resources should be used for treatment and prevention not laboratories
- Support to achieve good adherence to treatment minimises problems of resistance
- Further work is needed to improve clinical algorithms for monitoring treatment

laboratory capacity, can improve outcomes by providing treatment support to encourage optimal adherence and thus minimise the development of drug resistance. Over time, laboratory capacity should be improved, and more laboratory dependent monitoring strategies implemented as feasible technologies become available. Operational and clinical research are essential to guide the formulation of evidence based algorithms for HIV treatment in resource limited settings. In the meantime, we must not allow the perfect to be the enemy of the good. Further delays in scale-up will mean more deaths and ongoing transmission; tuberculosis, the leading opportunistic infection, will also become more difficult to control. The opportunity to make long awaited treatment available to people infected with HIV cannot be missed.

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Contributors and sources: This article was prepared from the clinical expertise of the authors and review of the relevant literature. DRK has extensive experience in the design and conduct of AIDS clinical trials and is an expert on antiretroviral drug resistance. MSH has studied AIDS, particularly HIV pathogenesis and developing effective combination therapies. FL directs a programme that provides comprehensive HIV, TB, and primary care in rural Haiti and is also involved in implementing treatment programmes throughout the Caribbean and Africa. SPK, JSM, and PEF have extensive experience in implementing primary care and complex health interventions in resource poor settings. CDR was executive director of the National AIDS Council in Mexico and has studied barriers to HIV care among disadvantaged people in the US and elsewhere. SPK wrote the first draft of this manuscript, which was substantially edited by each of the other authors. All the authors are guarantors.

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1 Detels RMA, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, Schrager LK, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA* 1998;280:1497-503.
2 CASCADE (Concerted Action on Seroconversion to AIDS and Death in Europe) Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. *Lancet* 2000;355:1158-9.
3 World Health Organization. *"3×5" progress report.* Geneva: WHO, 2004.
4 World Health Organization. *Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public heath approach.* Geneva: WHO, 2004. www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf (accessed 13 Feb 2005).
5 Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis* 2004;38(suppl 5):S429-36.
6 Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;18:887-95.
7 Farmer PE, Léandre F, Mukherjee JS, Claude M, Nevil P, Smith-Fawzi MC, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001;358:404-9.
8 Walton DA, Farmer PE, Lambert W, Léandre F, Koenig SP, Mukherjee JS. Integrated HIV prevention and care strengthens primary health care: lessons from rural Haiti. *J Public Health Policy* 2004;25:137-58.
9 Gupta RIA, Raviglione MC, Kim JY. Scaling-up treatment for HIV/AIDS: lessons learned from multidrug-resistant tuberculosis. *Lancet* 2004;363:320-4.
10 Calmy A, Klement E, Teck R, Berman D, Pecoul B, Ferradini L. Simplifying and adapting antiretroviral treatment in resource-poor settings: a necessary step to scaling-up. *AIDS* 2004;18:2353-60.
11 Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21-30.
12 De la Rosa R, Ruiz-Mateos E, Rubio A, Abad MA, Vallejo A, Rivero L, et al. Long-term virological outcome and resistance mutations at virological rebound in HIV-infected adults on protease inhibitor-sparing highly active antiretroviral therapy. *J Antimicrob Chemother* 2004;53:95-101.
13 Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clin Infect Dis* 2003;37:1112-8.
14 Harrigan PR, Hogg RS, Dong WW, Yip B, Wynhoven B, Woodward J, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. *J Infect Dis* 2005;191:339-47.
15 Weinstock HS, Zaidi I, Heneine W, Bennett D, Garcia-Lerman JG, Douglas JM, et al. The epidemiology of antiretroviral drug resistance among drug-naive HIV-1-infected persons in 10 US cities. *J Infect Dis* 2004; 189:2174-80.
16 Iseman MD. Tailoring a time-bomb. Inadvertent genetic engineering. *Am Rev Respir Dis* 1985;132:735-6.
17 Partners in Health, Harvard Medical School, Foundation BMG. *A DOTS-Plus handbook: guide to the community-based treatment of MDR-TB.* Boston, MA: Harvard Press, 2003.
18 Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med* 1994;330:1179-84.
19 Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am Rev Respir Dis* 1993;147:1311-20.
20 Severe P, Leger P, Charles M, Noel F, Bonhomme G, Bois G, et al. Antiretroviral therapy in 1000 patients with AIDS in Haiti. *N Engl J Med* 2005; 353:2392-4.
21 Partners in Health. *Annual report to the GFATM 2005.* Boston: PiH, 2005.
22 Rabkin M, El-Sadr W, Katzenstein DA, Mukherjee J, Masur H, Mugyenyi P, et al. Antiretroviral treatment in resource-poor settings: clinical research priorities. *Lancet* 2002;360:1503-5.

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Endpiece

The force of truth

Not long since the trite and frivolous question following was debated in a very polite and learned company, viz, Who was the greatest man, Caesar, Alexander, Tamerlane, Cromwell, &c?

Somebody answered that Sir Isaac Newton excelled them all. The gentleman's assertion was very just; for if true greatness consists in having received from heaven a mighty genius, and in having employed it to enlighten our own mind and that of others, a man like Sir Isaac Newton, whose equal is hardly found in a thousand years, is the truly great man. And those politicians and conquerors (and all ages produce some) were generally so many illustrious wicked men. That man claims our respect who commands over the minds of the rest of the world by the force of truth, not those who enslave their fellow-creatures: he who is acquainted with the universe, not they who deface it.

Voltaire. On Francis Bacon, Letter XII, from *Lettres Philosophiques*, 1778

A Váradi, senior lecturer in medicine, Semmelweis University, Budapest