

Round Table Discussion

Antiretroviral therapy is only part of it

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There is as yet no cure for AIDS, but therapeutic strategies must play a part in any comprehensive approach to the epidemic — even in resource-poor countries. Farmer et al. (1) provide a starting point, but many more clinical trials are needed to investigate the efficacy of antiretrovirals (ARVs) in prolonging life and improving the quality of life lived with AIDS in developing countries (2).

This is because AIDS treatment in developing countries involves more than simply using western therapies in tropical settings (3). ARVs neither eradicate the virus from the body nor cure the disease. Also, potentially more effective new treatments are being developed in countries of the South or in collaboration with the North, including immunomodulatory agents isolated from traditional medicines, holistic approaches to AIDS care, and fusion inhibitors. Lastly, intersectoral approaches are vital to improve access to drugs, such as the recent successful court action of the South African government against the pharmaceutical industry.

Lack of monitoring facilities forced Farmer et al. to adopt treatment algorithms that may actually be the most appropriate — i.e. treatment late rather than early in the course of the disease, as recently recommended by the expert committee convened by the US National Institutes of Health. This could cut costs by reducing the numbers for whom treatment is indicated. Nevertheless initial diagnosis should include a CD4 count, as accurate diagnosis and appropriate selection of patients for treatment is crucial. Treatment of newly infected patients requires more research.

Piggybacking highly active antiretroviral therapy (HAART) on the standard directly observed treatment short course for tuberculosis (DOTS) seems logical because both conditions require a multidrug regimen; direct observation may be necessary for the effective use of HAART, for which default from treatment can be as high as 60%; and pulmonary TB is the commonest severe AIDS-related condition in African countries. However, this approach loses credibility when one considers that DOTS is curative whereas HAART is not; compliance is much higher for DOTS than for HAART; DOTS is a six-month regimen, whereas HAART is lifelong; mortality during DOTS is low whereas annual mortality of patients on HAART can be 5–10%; and even with the drastic reductions in price of ARVs, to US\$ 350 per annum, they remain un-

affordable for most developing countries. Even in an “upper middle” income country such as South Africa, per capita health care expenditure in the public sector is only US\$ 88 per annum.

Further pilot studies of ARV therapy in the public sector in developing countries (such as the ‘Protest initiative’ of WHO) are needed and, as Farmer et al. show, must be comprehensive, incorporating counselling, fixed dose combinations, structured treatment interruption protocols, prevention strategies, behavioural research, multivitamins, nutrition, treatment for opportunistic infections, therapy for sexually transmitted diseases, sexual health education, psychological support, poverty alleviation, social welfare support, and provision of clean water and sanitation as well as housing. ■

1. **Farmer P et al.** Community-based treatment of advanced HIV disease: introducing DOT-HAART. *Bulletin of the World Health Organization*, 2001, **79**: 1145–1151.
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3. **Harries AD et al.** Preventing antiretroviral anarchy in sub-Saharan Africa. *Lancet*, 2001, **358**: 410–413.

HAART — the need for strategically focused investments

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Farmer and his colleagues stress the importance of both prevention and treatment of HIV, in the light of an unparalleled global catastrophe (1). I fully agree. Their paper also describes some of the good progress made in Haiti through the work of their team. I am impressed by this work. The paper calls for antiretroviral drugs to be made available at a greatly reduced cost (as indeed is occurring). Again, I am in full agreement.

My dilemma is that the world is still a long way from being able to make antiretroviral drugs, even if they were free, effectively available to the majority of the people who are infected with HIV. I wish that the world was different. I wish that poor countries were not so poor. I wish that the health systems of poor countries were not so dysfunctional. I wish that rich countries were far more generous in their support for health sector activities in poor countries. Regrettably, none of this is the case in the real world in which we live. Farmer and his colleagues do not give us a clear idea of how to overcome these major constraints.

Let me caricature the debate on highly active antiretroviral therapy (HAART). On one side is the opinion: “HAART is too difficult, too expensive, and

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too prone to divert resources from other priority health investments, fuel drug resistance, and undermine progress in behavioural change. We should not launch into this on a large scale.” On the other side is the position: “HAART is a human right. Therapy that is available to gay men in San Francisco and Sydney should also be available to all infected people everywhere. We have no choice and no alternative. We must act on a huge scale and we must do so immediately.”

The first position, it seems to me, is clearly wrong, from both a public health and an ethical perspective. The second position may be right in a moral sense, but it is not practical. To advocate the impossible is to put at risk the achievement of more limited objectives.

The key to the achievement of more limited objectives is geographical focus. The experience of health development work is full of examples in which international agencies, with the best intentions, have tried to do too many things in too many places and have, as a result, achieved little. Being spread too thin is as undesirable in health investment as in any other form of human endeavour. What is needed is selected areas (these could be districts, or small countries, or towns and their rural hinterlands) in which the appropriate drugs and delivery systems are put in place on a serious scale and with adequate levels of investment. This investment should include the funding of the necessary research and evaluation efforts, so that epidemiological and clinical data can be collected and the programmes can be modified and improved over time.

These sites would achieve three things. First, they would bring HAART to tens of thousands of infected people in an effective way. Second, they would be islands of good practice where new drugs and new delivery techniques are continually being applied and evaluated and a major learning experience is going on. Third, they would provide powerful demonstration sites where the cost, impact and feasibility of using HAART in resource-poor settings could be clearly seen.

This is not to argue that HAART should be unavailable in other places in other ways. But it is to argue that an international effort focused on establishing and sustaining a number of islands of learning and good practice is likely to make a greater contribution to the reduction of suffering and unnecessary death than spreading limited resources thinly across the low-income countries.

The approach that I recommend is very difficult for international agencies to adopt, for obvious political reasons. It is, however, an approach that the major foundations can take. The investment by the Bill and Melinda Gates Foundation in HIV/AIDS therapy in Botswana is a case in point. Let us make sure that the best is not seen as the enemy of the good and that we do not, by calling for unachievable objectives, undermine the prospects of making good progress and bringing substantial rewards in the longer term. ■

1. **Farmer P et al.** Community-based treatment of advanced HIV disease: introducing DOT-HAART. *Bulletin of the World Health Organization*, 2001, **79**: 1145–1151.

AIDS care is learnt by doing it

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There is consensus that prevention is the most important strategy to halt the AIDS pandemic (1), and introducing an HIV vaccine is our ultimate tool for doing this. However, the inconsistent success of prevention programmes, and the absence of effective vaccines now and in any near future, provide ample grounds for looking more seriously at care for AIDS patients in resource-poor countries. We have reached a point of no return, moving from the *if* and the *when* of effective care to the *how*.

Reasons for taking up the challenge of care now include the following. First, the sheer magnitude of the global AIDS crisis. Silently infected before, millions of people living with HIV/AIDS are now falling sick and dying. Second, there is moral outrage over this tragedy when therapy exists for those who can afford it. Public opinion now demands a shift from unmitigated suffering to hope. Third, indifference to such suffering reduces the credibility of prevention efforts. Treatment is thus an essential component of the AIDS control continuum. Fourth, a 97% reduction in antiretroviral (ARV) prices (2) and hospital cost savings in Brazil have made previous arguments over affordability obsolete, and given rise to confidence that AIDS care in poor countries is not only feasible but inevitable. Fifth, mounting pressure — politically and even legally — on multinational pharmaceutical companies, local governments, and the international community is opening the door to new resources.

Universal access to highly active antiretroviral therapy (HAART) for millions of people is not feasible today, but doing nothing is unacceptable. One parallel with tuberculosis (TB) is that a much simpler and curative regimen reaches only 25% of patients despite a decade-long campaign (3). AIDS care is daunting by comparison. Talking of billions of dollars is easy compared with the demands of setting priorities (e.g. what regimen, where to start) and raising and allocating vast resources. But if the risks are high, so too are the opportunities.

Moving forward, there are at least two steps we need to take before going full speed ahead: demonstration projects, and targeted research. Small pilot projects by dedicated physicians, such as the Partners in Health work in Haiti (4), bring hope and suggest the feasibility of AIDS care in poor countries. Newer models designed to target a specific subset of

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the population (e.g. HIV-infected pregnant women) are another way to advance public health without overburdening fragile health care systems. Their experience will show the way forward to the scale-up of AIDS care in the coming years.

Farmer et al. draw on the lessons and infrastructure of the directly observed treatment short course for TB (DOTS) to plan for AIDS care (4). TB programmes, however, cannot be taken for granted, nor did they evolve overnight (5–7). The DOTS strategy, for example, calls for passive case finding, targeting smear-positive cases, and supervised outpatient treatment. These controversial parameters were set through clinical epidemiology and operational research, enlightened leadership and management, and unrelenting advocacy and training. We are not there yet in AIDS care, though we are not short of ideas to test.

Until recently, AIDS care research in Africa and its rationale had been neglected (8). Most non-experts had assumed that we knew how to treat AIDS from what had been done in the OECD countries (9). In fact, we are today with AIDS treatment where we were in 1970 with anti-tuberculosis treatment: there were many drugs developed a decade earlier, which were life-saving in the hands of experts. It took over two decades of sound research to develop a standardized TB programme (DOTS) that could be implemented in developing countries (later it was adopted in OECD countries too (10)). Africa cannot afford to wait two decades to tackle AIDS. Yet, the required research has been scant, owing to reservations about the feasibility of HAART, clinical overconfidence and ethical paralysis.

Scientific research must be marshalled to “fast track” the scaling-up of AIDS care beyond pilot projects. Research can bridge the gap between increasingly cheaper ARVs and the limited infrastructure to deliver them in Africa. Research need not hold back care. We should learn by doing. Better action can be informed by research, just as research priorities should be driven by the imperatives of action. Competing needs in the fight against AIDS and poverty demand that we go into comprehensive care armed with the right weapons. The seeds are sown. ■

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3. **Dye C et al. for the WHO Global Surveillance and Monitoring Project.** Global Burden of Tuberculosis. Estimated incidence, prevalence, and mortality by country. *JAMA*, 1999, **282**: 677–686.
4. **Farmer P et al.** Community-based treatment of advanced HIV disease: introducing DOT-HAART. *Bulletin of the World Health Organization*, 2001, **79**: 1145–1151.

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HAART in Haiti — evidence needed

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Farmer et al. present a remarkable achievement: the establishment of a care service for people with HIV/AIDS in a community of poor displaced people living in a remote rural area of Haiti (1). The conditions under which this has been accomplished are particularly difficult, yet the service has included the provision of antiretroviral therapy (ART) to 60–100 people. This has been possible, they argue, by learning from the history of tuberculosis control and using a model they have called DOT-HAART (directly observed therapy with highly active antiretroviral therapy), implemented through a team of community-health workers called “accompagna-teurs” to supervise therapy.

If the claims of the authors are substantiated, such a model would have enormous potential for replication in other resource-poor settings. If, on the other hand, the authors’ claims are exaggerated, the potential for doing more harm than good would be great (and the authors’ dismissal of the “spectre of

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acquired drug resistance” is alarming). In the end, the scientific soundness of the evidence must be the decisive factor. It is unfortunate, therefore, that the paper reads more like a statement of positive self-evaluation than a careful presentation and analysis of the facts. The paper is instructive not so much for what it presents as for what it does not reveal. It makes no serious attempt to consider what really are the lessons for Haiti, and other countries, if they want to scale up efforts to provide care to those infected with HIV/AIDS.

The authors’ main contention is that the concerns voiced about treating HIV-positive people with HAART — namely high cost of drugs, lack of health system capacity to deliver them effectively, possibility of non-compliance, and risk of drug resistance — are ill-founded. If we are to be convinced that this is so, we need better evidence than that provided in this paper. Let us look briefly at some important issues the authors did not mention.

First, logistics: what clinical input and staff time was required to set up and then run this intervention? Apart from the “accompagnateurs”, how many physician hours were involved? In the real world, any broadly accessible initiative will have to be clinical-officer or nurse-practitioner led — there just are not enough physicians to go around. With rapidly falling prices, capacity, not cost, will be the big issue. The human resources and capacities needed to implement the model intervention need to be very carefully listed for a real evaluation of their programme to be made.

Second, entry criteria: ad hoc criteria are used to start individuals on treatment. What are “recurrent opportunistic infections difficult to manage with antibacterials or antifungals”? What is “otherwise unexplained and significant weight loss” compared to “chronic enteropathy with wasting”? The severe neurological complications include peripheral neuropathy which may be more present in the earlier stages of disease than other problems. The reliance on haematological indices including low platelet counts and “severe leukopenia” (not defined) suggests access to automated haematology analysers, which are not available outside research projects or capital cities. Also, why have patients with active TB been excluded?

Third, unforeseen benefits: what is the evidence that the intervention has improved staff morale? What observations have been made for the group to form an “impression” that AIDS-related stigma has been reduced? And how do they relate the increase in voluntary counselling and testing to this intervention rather than other changes (there is no control group and many things have changed over the three years)? We would all want these benefits to be forthcoming, but public health physicians need evidence rather than impressions.

Fourth, costs: how much did it cost to deliver the drugs? Reference is made to 75–80% of the costs being for medication — but this is for drugs purchased in which market and at what price? Eighty per cent of current US prices for triple drug (perhaps US\$ 8000–10 000) is a lot more than 80% of the current best (cheapest) prices quoted by Médecins Sans Frontières and other nongovernmental organizations — around US\$ 350 per patient per year. This incomplete presentation of the facts the group may well have at hand suggests that the costs are high, which would then put the intervention in a very different light. Of course any research initiative will have additional costs which will be shed if other nongovernmental organizations start to deliver the model. But if very costly, how can this intervention ever be scaled up and replicated, and sustained?

By any evaluation criteria — whether cost-effectiveness, sustainability, feasibility, or absence of unintended negative consequences — this success story must be classified as non-proven. Yes, we know with exceptional circumstances, motivation, resources and generous research funding positive outcomes can be achieved, but replication is something else entirely. Yes, it is true that with huge inputs the miracle of ART will produce stunning successes. And certainly, acting when others have failed to do so is noble. However, for lack of appropriate design and scientific evaluation, important lessons that might have been applied in other settings simply cannot be drawn from this study. ■

1. **Farmer P et al.** Community-based treatment of advanced HIV disease: introducing DOT-HAART. *Bulletin of the World Health Organization*, 2001, **79**: 1145–1151.