Scaling up antiretroviral treatment in resource-poor settings

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We are contemplating the future. For the past few months we have been working with our colleagues to prepare Malawi's antiretroviral treatment (ART) scale-up plan for 2006–10. This poor landlocked country is gripped by a serious HIV epidemic. With a population of almost 12 million, Malawi has an HIV/AIDS burden the same size as that of the USA; nearly 1 million people are infected with HIV. There are about 100 000 new HIV infections and 90 000 AIDS-related deaths per year, and an estimated 170 000 HIV-infected patients need ART.[1] Every year an additional 90 000 HIV-infected patients become eligible for ART as their immune systems become further compromised by the virus.

Recognition of the scale of the epidemic led Malawi, in early 2004, to develop its first ambitious national scale-up plan for ART (2004–05). Since then, the country has not done too badly. In January, 2004, about 4000 patients were on ART from nine facilities in the public sector and by the end of September, 2005, 30 055 patients had started free ART from 60 facilities. The number increased to 37 840 by the end of 2005. The table shows primary treatment outcomes for all patients who started free ART before the end of September, 2005. For the 23 168 who were alive and receiving ART, 97% were able to walk at home unaided, 93% were fit to work, 6% had major side-effects (mainly peripheral neuropathy), and 92% showed good adherence with therapy on the basis of pill counts (unpublished). These national figures compare favourably with those from Chiradzulu district in Malawi, which has received several years of support for HIV and ART services from Médecins Sans Frontières.[2] They also compared well with those from other similarly poor countries such as Haiti.[3]

However, although almost 25 000 patients first started ART in 2005, the unmet need is still massive. Most of the 140 000 patients who needed ART in 2005 but did not receive it either will have died in that year or will die in 2006,[4] while the programme to provide ART to communities is gradually being rolled out, aiming to provide 30 000 new patients with ART in 2006 and, by 2008, to start ART in 45 000 new patients every year. If the plan goes perfectly, by the end of 2010 there will be 245 000 patients ever started on treatment. This number is huge, but even if it is achieved only half the target of 90 000 patients who become eligible for ART every year will be reached.

The plan for new patients is not based on some fanciful idea; it is based on a realistic assessment of the 60 sites in the public sector now delivering ART, a further 40 sites being prepared for starting ART in the first half of 2006, an unknown number to be prepared in 2007, and the involvement of the small but important private sector. However, the assessment is made on the basis that these sites will work to full capacity, and therein lies the main difficulty. Malawi is very short of skilled health-care staff. Of the 21 337 health-care posts in the country, 33% are vacant, 64% of the nursing posts are unfilled, and the number of doctors practising is only a sixth of the recommended total.[5]

In Malawi, the approach to ART has always been public-health oriented.[6,7] It is based on the tuberculosis DOTS model,[8,9] and is dependent on a standard system of case finding, free standard treatment, and quarterly monitoring with standard treatment outcomes. What is done in one hospital or clinic is done in every other facility in the country. To be eligible for ART, a person must be HIV seropositive, understand the implications of ART, and be assessed as WHO clinical stage 3 or 4.[10] A CD4-lymphocyte count is not mandatory, and less than 10% of patients start therapy only because of having a CD4-cell count of less than 200 per µL. Treatment scale-up has focused on one first-line regimen, a generic fixed-dose combination of stavudine, lamivudine, and nevirapine (Triomune, Cipla, Mumbai, India), with nearly 95% of patients taking this regimen. Alternative first-line regimens (substituting zidovudine for stavudine in case of peripheral neuropathy and efavirenz for nevirapine in case of hepatitis and severe cutaneous reactions) are available in four central and two district hospitals and a system to make these drugs available for patients in other facilities has been developed and is now being implemented. At present, there is a small supply held at two central hospitals, of second-line treatment (a combination of zidovudine, lamivudine, tenofovir, lopinavir, and ritonavir) for 90 patients for whom the first-line regimen was not successful. Patients start ART on a first-come, first-served basis, although priority groups such as pregnant women and health-care workers are targeted through health-promotion campaigns. Patients are encouraged to select a guardian, in most cases a family member, to support them with adherence to long-term therapy. Other measures that might augment the benefits of ART, such as prophylaxis with co-trimoxazole (trimethoprim and sulfa-

	Number
Total patients ever started ART	30 055
Alive and receiving treatment at the facility where first registered	23 168 (77%)
Dead	2804 (9%)
Lost to follow-up	2005 (7%)
Stopped treatment	260 (1%)
Transferred to another facility	1818 (6%)

Data from HIV Unit, Malawi Ministry of Health.

Table: **Treatment outcomes in patients who started free ART in Malawi to Sept 30, 2005**

methoxazole), nutritional support, and bednets to protect against malaria, are being discussed but are not yet widely used. Hospitals are classified as low-burden sites (starting 25 new patients on ART per month), medium-burden sites (50 new patients per month), or high-burden sites (150 new patients per month). This classification system has enabled the development of a simplified method for procurement and distribution of ART with use of starter packs and continuation packs of drugs.[7]

So far, according to national figures, this approach has been associated with successful outcomes. In Chiradzulu, where the same methods of giving ART are used, but where monitoring through Médecins Sans Frontières is more intense, outcomes are also good.[2] 74% of patients were still on ART a median of 8 months after starting treatment, and the median gain in CD4-cell count was 165 cells per µL. Moreover, of a sample of 397 patients tested, 84% had a viral load of less than 400 copies per mL.[2]

However, use of our straightforward public-health approach has two main risks. First, use of clinical eligibility criteria only, means that patients in WHO stage 1 or 2 who might have severe immune dysfunction are not given treatment and some patients (eg, those with tuberculosis) in stage 3 or stage 4 might have high CD4-cell counts and not warrant treatment. Second, use of clinical outcome measures means that viral resistance and subsequent immune dysfunction are identified at a late stage, thus potentially compromising the benefit of second-line ART.

Although the ART scale-up is managed in a straightforward way, the clinics are starting to feel the strain, since the numbers of eligible patients rise every month. A medium-burden site (of which there are already 26) working at 100% capacity starts ART in 50 new patients per month and therefore could have 600 patients on treatment by the end of the first year, with the number growing to 1200 by the end of the second year. Patients are monitored monthly according to standard primary outcomes (alive, dead, lost to follow up, stopped treatment, and transferred out) and secondary outcomes (ability to walk at home unaided, at work, side-effects, and drug adherence measured by pill counts).[7] The information is manually entered into master cards and ART registers and is used in quarterly cohort analyses. Very few patients have follow up biochemical or immunological measurements.

We are convinced that the only way to provide high-quality ART delivery is to make the process even simpler than it is already. The essential ingredients for ART success are a regular secure supply of drugs to the facilities, good adherence with therapy by patients,[11] and compliance with follow up, so that the virus is given the lowest chance possible to develop resistance. Many people from more developed countries who visit Malawi say that eventually all facilities will need to have machines for CD4-lymphocyte counting and that the country needs to start to monitor viral load. This opinion is shared by sections of the Malawi Ministry of Health. The belief is that Malawi's first-line regimen will eventually stop working and that increasing numbers of patients will have to be given various other first-line regimens when side-effects occur and second-line regimens when drugs fail. They think that the public-health approach should be replaced by a more technical and more medical approach.

Paradoxically, we believe that adoption of this type of approach will lead to the demise of the country's ART programme. Malawi's laboratory capacity is struggling to handle the biochemical, immunological, and viral-load measurements. Patients who already have long waits at ART clinics will be forced to wait even longer for blood tests that might not be reliable. The difficulties associated with poor laboratory services are not only faced in Malawi, but are also felt throughout Africa.[12,13] If the nurses who mostly give the ART drugs during clinic visits have to juggle with several different regimens, there is room for errors. National procurement and distribution of various regimens would be complicated and could increase the risk of mistakes. There is a well established inverse relation between the number of drugs a patient takes and adherence with the medication. Malawi's second-line therapy now has five different drugs, and requires patients to take nine tablets per day: this regimen is not conducive to good adherence.

Although well supported by the Global Fund against AIDS, Tuberculosis and Malaria, Malawi's finances are not limitless. Other first-line drugs cost on average three times more per patient per month than the combination of stavudine, lamivudine, and nevirapine, and second-line therapy costs eight times more (UNICEF cost estimates of antiretroviral drugs for Malawi, October, 2005). The old adage that the best is the enemy of the good rings loudly in our ears.

We strongly believe that Malawi should continue scaling up use of the first-line stavudine, lamivudine, and nevirapine regimen only, and should provide other first-line and second-line drugs in only a few centres. There is an important public-health consideration to support this view. Because there are many eligible HIV-infected people who are not yet receiving any treatment and because over 80% of patients do well on the first-line regimen[7] (table) priority should be given to provision of first-line treatment to those not yet receiving ART rather than offering better care to the minority already on ART. This approach is based on principles of equity and should result in an improved overall health gain. At present we are working with WHO and the US Centers for Disease Control and Prevention to develop a system in five busy ART sites for yearly monitoring of viral load and viral resistance in patients on the first-line ART regimen. These measurements will give us a national perspective of the effect of treatment and the standard outcomes will provide valuable information about longitudinal survival.

There will be continuous pressure from both within and outside Malawi to use advanced laboratory technology. We cannot support this position unless the technology for measurement of viral load and CD4-lymphocyte counts becomes cheaper, more straightforward, and more user friendly. In most health-care facilities in Malawi, essential laboratory services cannot be provided reliably and we think that the introduction of present laboratory technology that supports ART will weaken rather than strengthen general laboratory service delivery. Health-care staff will have to learn to trust their patients and aim to review them every 2–3 months instead of every month. Malawi will have to teach less qualified health-care workers to manage patients and to consider decentralisation to health centres to reduce the load on the hospital clinics and improve access for patients living in rural areas. For national monitoring, there might be a need to simplify the outcome analysis to standard primary outcomes only, because the task of wading through thousands of patients' master cards to report on side-effects and pill counts will become impossible. Some of Malawi's busy clinics use both a manual register and a computer system for monitoring of patients starting ART. Computerisation of all the ART facilities might be possible and we are exploring this option, but Africa is littered with broken computers that have been destroyed by power surges, lightning storms, or electronic viruses and we are not convinced that this is the answer.

Countries similar to Malawi have never before faced the challenge that will confront them in the next few years—to provide structured, indefinite, chronic care for 100 000–200 000 patients with HIV infection. Linked to treatment scale-up is the need to improve HIV-prevention services, counselling, HIV testing, and prevention of opportunistic infections, otherwise numbers of patients becoming infected and ultimately needing ART will continue to escalate. The 5-year plans for counselling and HIV testing, prevention of mother-to-child transmission of HIV, and use of co-trimoxazole preventive therapy are all well advanced. In view of the limited human resources, due attention should be given to ensuring that other health services do not suffer in the quest for improved HIV prevention and care; however, little is known about how best to do this. So far, with respect to our ART programme our little ship in Malawi is sailing well, but there are likely to be difficulties in the future. If we complicate the plan with technological accessories, it will be in great danger of failing. By keeping the ship trim, there is a good chance it will stay afloat.

Conflict of interest statement

We declare that we have no conflict of interest.

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