Scaling up antiretroviral therapy in developing countries: what are the benefits and challenges?

A Boulle and N Ford

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Antiretroviral therapy

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A Boulle, N Ford

There is a critical need for appropriate technical innovation and development, as well as dramatically improved health sector financing

In recent years the case for antiretroviral therapy (ART) in those countries hardest hit by the HIV pandemic is seldom contested. Prior to the widespread availability of antiretroviral therapy in many developing countries, there were however frequent concerns expressed about the safety and feasibility of promoting widespread access to ART in countries such as those in Southern Africa. These concerns were premised on the potential ''anarchy'' that might be the result of weak health systems leading to widespread virological resistance,[1 2] on the grounds that there were more cost-effective interventions available given the limited funding baskets at the time,[3] and on the potential to do more harm than good if introducing large and complex new interventions into already weak and fragmented health systems, further increasing inequities.[4 5]

The first public-sector ART treatment programmes in developing countries (with the exception of Brazil) date back to 2000,[6] and data are now emerging on the effectiveness of the interventions.

SURVIVAL IN TREATMENT PROGRAMMES IN DEVELOPING COUNTRIES

Three clear messages are emerging from the accumulating outcomes reporting from public-sector adult ART treatment programmes in poor countries. First, treatment is effective for those accessing ART. Hogan summarised eight programmes from resource-limited settings,[7] demonstrating a range of survival outcomes at 1 and 2 years on ART, but all showing marked improvements over the anticipated natural history without ART. The comparative median survival in those eligible but not receiving ART is variously reported as 24 months, and less than a year for CD4 counts of less than 200 and less than 50 cells/μl, respectively.[8]

More recently the ART-LINC collaboration demonstrated cumulative mortality at 1 year of 6.4% in 2725 patients across 12 cohorts with active follow-up procedures in place.[9] The city-wide treatment programme in Lusaka reported a mortality of 16.1/100 person years of ART while rapidly scaling up care to over 16 000 patients.[10] In Malawi, cross-sectionally across 7000 adult patients who ever started ART, 74% remained alive and in care, while cumulatively 10% were estimated to have died by 1 year.[11] Mortality estimates at longer durations on ART include 16.9% of patients having died by 5 years in a cohort in South Africa,[12] and 24.6% by 5 years in a cohort in Senegal.[13]

Second, in spite of this massive health gain from the intervention, compared with the richest countries, there is still a higher mortality in the first 6 months of treatment in developing countries. The ART-LINC study referred to above demonstrated that compared with the ART-CC cohort collaboration from Europe and North America, patients starting ART in developing countries were at up to 4 times greater risk of dying in the first few months on ART after controlling for available measures of disease advancement at baseline. This corroborates the experience of many individual developing country cohorts who describe around two-thirds of all deaths on ART occurring in the first few months of treatment.[14 15] It is probable that the burden of co-morbidities could contribute to the early mortality as evidenced by autopsy studies which show frequent undiagnosed tuberculosis and other bacterial infections.[16] Due to the extreme differences in access to healthcare, it may also be that clinically there are residual differences across regions between patients in the same CD4 count and clinical stage strata.

Third, the evaluation of programme effectiveness is hindered by the patients who are lost to programmes—given the limited resources available, there is a fine balance between enrolling as many patients as possible, and retaining those already in care. The proportion of patients lost to care at various durations of follow-up often approaches or exceeds the proportion known to have died. Even programmes who attempt to actively trace patients who are lost to follow-up, may end up under-reporting the number of deaths. One study of patients lost to follow-up in Malawi demonstrated that half the patients who had been lost had died, and of those, 58% had died in the 3 months following their last clinic visit.[17] After 5 years of follow-up in Khayelitsha, the proportion lost to care increased from the 16.9% known to have died to 20.3% or 28.2% depending on whether 365 or 90 days were used as the definition of loss to follow-up.[12]

POPULATION-LEVEL IMPACT

Although on-programme ART effectiveness, even in some of the most challenging settings, has been shown to be good, it is important to reflect on whether or not treatment is being provided at sufficient scale to impact on the greatly reduced life expectancy in heavily affected countries. While global agencies have set a goal of reaching universal access to ART by 2010 (80% of those in need of ART accessing it), it is well documented that the majority of countries are falling well short of this target.[12 18] Where systems enable pre-ART mortality to be measured, a disconcerting pattern is emerging whereby the majority of on-programme deaths are occurring prior to patients accessing ART.[15 19] Reported ART programme outcomes mask continued high HIV-related mortality among patients receiving some care but not yet on ART. Even less visible are the deaths among those unable to access care at all: in many settings, issues such as stigma, user fees, distance from services and the non-availability of services still contrive to prevent people from accessing care in the first place.

There are few opportunities to truly explore the impact of ART at a population level. In Brazil where universal access to ART has been available for longer, researchers were able to demonstrate temporal improvements in the survival of patients with AIDS in representative samples from different time periods.[20] This has been accompanied by a documented decrease in hospital admissions.[21]

Earlier this year, researchers in South Africa were able to demonstrate for the first time that the previously inexorable year-on-year increase in recorded death rates through the vital registration system had in some provinces slowed down, with the age, gender and geographical profiles of the gains being aligned with those of the patient population accessing ART.[22]

Even at moderate coverage, it appears the survival benefits at a population level are starting to be discernible.

A characteristic of treatment programmes in Southern Africa is the predominance of women among adults accessing care whereby two-thirds of new patients are women.[23] This disproportion could not be predicted by the epidemiology of the epidemic alone, suggesting differential healthcare access between men and women in this region. While children are not discussed in detail here, the results of ART in children in developing countries are similarly encouraging.

ADHERENCE, VIROLOGICAL SUPPRESSION AND RESISTANCE

Given that the majority of scaling up of ART has occurred in the past few years, differences in adherence between rich and poor countries may not yet have translated into medium or long-term mortality differences. Ivers conducted a meta-analysis of virological suppression in the first year on ART, and found that in 10 predominantly African programmes, proportions of patients suppressing their viral load were similar to those from richer countries, with a combined estimate of virological suppression of 70% at 6 months and 57% at 1 year. Individual programmes have however demonstrated much higher proportions of patients with virological suppression.[24 25] Egger presented a comparison between these programmes and the Swiss HIV cohort,[26] and demonstrated that the time to virological suppression and time to rebound were comparable after adjusting for the frequency of viral load measurements.

Given that the treatment populations in these settings are largely ART-naïve, and are not necessarily marginalised communities, it is anticipated that virological outcomes should be good in the early years of scaling up, while access to the structured treatment programmes and adherence counselling remains good. The early concerns about resistance resulted in programme designs that were very structured, and that placed a premium on counselling and support. Adherence studies based largely on self-reports also demonstrate that where access to care is good (as in most research settings), patients in sub-Saharan Africa take their medications as reliably if not more reliably than patients in North America.[27]

The poor availability of treatment in developing countries prior to the scaling-up initiatives has resulted in low levels of transmitted resistance in patients starting ART in these countries, obviating the need for routine resistance testing in patients starting ART.[28 29] Genotypic studies of patients failing their first-line regimens demonstrate however high-level resistance to two out of three classes of drug in most instances.[30]

Linked to the fear of emerging drug resistance is the concern that the availability of treatment would lead to an increase in unsafe sexual practices. A review was unable to demonstrate any evidence as yet of behavioural disinhibition as a result of ART availability in developing countries,[31] albeit that there are as yet very few studies addressing this question. Conventionally most commentators have assumed that the availability of treatment would rather strengthen prevention interventions.[32]

CHALLENGES

Each year, the demand on the health systems in the countries with the largest HIV disease burden is greater than the year before, and yet the systems themselves are buckling under the already increased load of ART, with little capacity for the impending burden of care that must follow the further scaling up of ART. In spite of all the innovation associated with delivering ART through primary care services, the intervention is exposing inherent systemic weaknesses in the health systems of many poor countries. Earlier this year, Médecins Sans Frontières drew attention to the health worker crisis in the face of the HIV/AIDS challenges, focussing on Malawi, Mozambique, Lesotho and South Africa.[33] In addition to trying to cope with the immediate staff shortages through retention interventions and task-shifting, the report called for donors to support recurrent human resource costs, as well as for countries to spend more on health overall and human resource development in particular. In 2001, African governments undertook to commit 15% of annual budgets to healthcare in the Abudja declaration. Countries are falling well short of this stated goal.

It is an unfair expectation of health services in many countries to expect that they alone can enrol and retain huge numbers of patients in care on such an unprecedented scale. In addition to improved financing of health services, national responses at a political and civil society level are key to ensuring that maximal benefit is derived from the health sector investments, as demonstrated by contrasting HIV/AIDS policies between Uganda and South Africa.[34]

BALANCING PROGRAMME SOPHISTICATION AGAINST COVERAGE

Senior health officials from Malawi wrote an impassioned plea in the Lancet requesting that the global treatment community do not add complexity to treatment guidelines, given the challenges that country was facing in meeting their target of 50% coverage of ART.[35] This target could be threatened if pressure for more complex monitoring and pervasive access to second-line drugs was prioritised. This highlights the tension between optimal clinical design and health service factors that facilitate scaling up care. For example, data are gradually becoming more compelling in support of earlier initiation of ART than the traditional threshold of a CD4 count of 200 cells/μl contained in many developing country guidelines, while the health service consequence of raising this threshold is an even bigger treatment backlog.

The mainstay of treatment in Southern Africa is based on a generic first-line fixed-dose combination of stavudine, lamivudine and nevirapine taken as a single tablet twice daily. The appeal of an affordable and standardised combination such as this is obvious as stated by the Malawi officials, and yet there are clinical concerns. The regimen is poorly tolerated by some individuals with an unfavourable short- and long-term toxicity profile of stavudine,[36 37] and there are concerns about concomitant use of nevirapine with rifampicin-containing tuberculosis treatment in a setting where up to a third of patients starting ART have prevalent tuberculosis. Better fixed-dose combinations are available, but less affordable, and some countries are in a position to provide second-line regimens but are limited by the high cost of alternative regimens. The international trade environment continues to fail patients with respect to ensuring the availability of newer treatment to poor countries.[38 39]

The monitoring of treatment response varies between immunological and virological in poor countries. The added value of virological measures at a programme level are debated, and guidelines for resource-limited setting do not make virological monitoring obligatory. On the other hand, viral load measures are potentially an invaluable tool for assessing adherence, and innovations that would allow point-of-care immunological and virological monitoring are urgently needed.[40]

More than ever there is a critical need for technical innovation and development, but with a view to treatment simplification and ease of service delivery, as opposed to adding complexity to existing treatment guidelines. This means adapting the research and development agenda to the reality of resource-poor settings where skilled staff are in short supply, health services are spread all too thin, treatment

must be provided at the most basic primary care level, and need continues to far outstrip the availability of services.

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Authors' affiliations
A Boulle, University of Cape Town, South Africa
N Ford, Médicins Sans Frontières, South Africa

Correspondence to: A Boulle, University of Cape Town, PO Box 13203 Mowbray, South Africa; andrew.boulle@uct.ac.za

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REFERENCES

1 **Gilks C**, AbouZhar C, Turmen T. HAART in Haiti—evidence needed. *Bull World Health Organ* 2001;**79**:1154–5.
2 **Harries AD**, Nyangulu DS, Hargreaves NJ, *et al.* Preventing antiretroviral anarchy in sub-Saharan Africa. *Lancet* 2001;**358**:410–4.
3 **Marseille E**, Hofmann PB, Kahn JG. HIV prevention before HAART in sub-Saharan Africa. *Lancet* 2002;**359**:1851–6.
4 **Loewenson R**, McCoy D. Access to antiretroviral treatment in Africa. *BMJ* 2004;**328**:241–2.
5 **McCoy D**, Chopra M, Loewenson R, *et al.* Expanding access to antiretroviral therapy in sub-saharan Africa: avoiding the pitfalls and dangers, capitalizing on the opportunities. *Am J Public Health* 2005;**95**:18–22.
6 **Farmer P**, Leandre F, Mukherjee J, *et al.* Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bull World Health Organ* 2001;**79**:1145–51.
7 **Hogan DR**, Salomon JA. Prevention and treatment of human immunodeficiency virus/acquired immunodeficiency syndrome in resource-limited settings. *Bull World Health Organ* 2005;**83**:135–43.
8 **Cleary SM**, McIntyre D, Boulle AM. The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa—a primary data analysis. *Cost Eff Resour Alloc* 2006;**4**:20.
9 **Braitstein P**, Brinkhof MW, Dabis F, *et al.* Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;**367**:817–24.
10 **Stringer JS**, Zulu I, Levy J, *et al.* Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA* 2006;**296**:782–93.
11 **Libamba E**, Makombe SD, Harries AD, *et al.* Malawi's contribution to "3 by 5": achievements and challenges. *Bull World Health Organ* 2007;**85**:156–60.
12 **Van Cutsem G**, Hilderbrand H, Coetzee D, *et al.* Clinical outcomes and emerging challenges after 5 years of ART in Khayelitsha, South Africa. *14th Conference on Retroviruses and Opportunistic Infections* 2007.
13 **Etard JF**, Ndiaye I, Thierry-Mieg M, *et al.* Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS* 2006;**20**:1181–9.
14 **Coetzee D**, Hildebrand K, Boulle A, *et al.* Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* 2004;**18**:887–95.
15 **Lawn SD**, Myer L, Harling G, *et al.* Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clin Infect Dis* 2006;**43**:770–6.
16 **Martinson NA**, Karstaedt A, Venter WF, *et al.* Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. *AIDS* 2007;**21**:2043–50.
17 **Yu JK**, Chen SC, Wang KY, *et al.* True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. *Bull World Health Organ* 2007;**85**:550–4.
18 **Egger M**, Boulle A, Schechter M, *et al.* Antiretroviral therapy in resource-poor settings: scaling up inequalities? *Int J Epidemiol* 2005;**34**:509–12.
19 **Fairall L**, Bachmann M, Louwagie G, *et al.* Effectiveness of antiretroviral treatment in a South African program: cohort study. *Arch Intern Med.* In press.
20 **Marins JR**, Jamal LF, Chen SY, *et al.* Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;**17**:1675–82.
21 **Teixeira PR**, Vitoria MA, Barcarolo J. Antiretroviral treatment in resource-poor settings: the Brazilian experience. *AIDS*, 2004;**18**(Suppl 3), S5–S7.
22 **Laubsher R**, Bradshaw D, Bourne D, *et al.* Rapid surveillance of AIDS mortality in South Africa (437). *3rd South African AIDS Conference* 2007.
23 **Braitstein P**, Boulle A, Nash D, *et al.* Gender and the use of potent antiretroviral treatment in resource-constrained settings: Findings from a multi-centre collaboration. *J Women's Health*. In press.
24 **Orrell C**, Harling G, Lawn S, *et al.* Conservation of first line antiretroviral treatment regimen where therapeutic options are limited. *Antivir Ther*. In press.
25 **Coetzee D**, Boulle A, Hildebrand K, *et al.* Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. *AIDS*, 2004;**18**(Suppl 3), S27–S31.
26 **Egger M**. Outcomes of ART in resource-limited and industrialized countries. *14th Conference on Retroviruses and Opportunistic Infections* 2007.
27 **Mills EJ**, Nachega JB, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA* 2006;**296**:679–90.
28 **Bussmann H**, Novitsky V, Wester W, *et al.* HIV-1 subtype C drug-resistance background among ARV-naive adults in Botswana. *Antivir Chem Chemother* 2005;**16**:103–15.
29 **Bessong PO**, Mphahlele J, Choge IA, *et al.* Resistance mutational analysis of HIV type 1 subtype C among rural South African drug-naive patients prior to large-scale availability of antiretrovirals. *AIDS Res Hum Retrovir* 2006;**22**:1306–12.
30 **Kamya MR**, Mayanja-Kizza H, Kambugu A, *et al.* Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;**46**:187–93.
31 **Kennedy C**, O'Reilly K, Medley A, *et al.* The impact of HIV treatment on risk behaviour in developing countries: a systematic review. *AIDS Care* 2007;**19**:707–20.
32 **Berkman A**. Confronting global AIDS: prevention and treatment. *Am J Public Health* 2001;**91**:1348–9.
33 **Médecins Sans Frontières**. *Help wanted. Confronting the health care worker crisis to expand access to HIV/AIDS treatment: MSF experience in southern Africa*. Johannesburg: Médecins Sans Frontières, 2007.
34 **Parkhurst JO**, Lush L. The political environment of HIV: lessons from a comparison of Uganda and South Africa. *Soc Sci Med* 2004;**59**:1913–24.
35 **Harries AD**, Schouten EJ, Libamba E. Scaling up antiretroviral treatment in resource-poor settings. *Lancet* 2006;**367**:1870–2.
36 **Boulle A**, Orrel C, Kaplan R, *et al.* Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. *Antivir Ther* 2007;**12**:753–60.
37 **Calmy A**, Hirschel B, Cooper DA, *et al.* Clinical update: adverse effects of antiretroviral therapy. *Lancet* 2007;**370**:12–4.
38 **Ford N**, Wilson D, Costa CG, *et al.* Sustaining access to antiretroviral therapy in the less-developed world: lessons from Brazil and Thailand. *AIDS*, 2007;**21**(Suppl 4), S21–S29.
39 **Havlir DV**, Hammer SM. Patents versus patients? Antiretroviral therapy in India. *N Engl J Med* 2005;**353**:749–51.
40 **Calmy A**, Ford N, Hirschel B, *et al.* HIV viral load monitoring in resource-limited regions: optional or necessary? *Clin Infect Dis* 2007;**44**:128–34.

Vaginal practices

Vaginal practices, microbicides and HIV: what do we need to know?

A Martin Hilber, M F Chersich, J H H M van de Wijgert, H Rees, M Temmerman

The goal of a safer vaginal environment could be reached by identifying harmful vaginal practices and an effective microbicide, thereby increasing options for HIV prevention

The global burden of HIV, its increasing feminisation, and chronic difficulties with development of options for HIV prevention all argue for an intensified re-examination of factors influencing the efficiency of heterosexual HIV transmission. This includes vaginal practices and products used by large numbers of women worldwide to tighten, dry, warm and clean their vagina. Women's efforts to change their genital environment can undermine each component of innate defences against pathogens.[1] In particular, vaginal practices have been linked with loss of lactobacilli and disruption of the vaginal epithelium.[2–4] These practices may therefore be an important mediator in acquisition of STI, including HIV, or worsen pre-existing infections. Despite this, surprisingly little is known about the effects of specific vaginal practices on HIV transmission dynamics.

In past decades, both cross-sectional and longitudinal studies have found an association between intravaginal cleans-