

## EDITORIAL

# Antiretroviral therapy in resource-poor settings: scaling up inequalities?

Matthias Egger,<sup>1\*</sup> Andrew Boulle,<sup>2</sup> Mauro Schechter<sup>3</sup> and Paolo Miotti<sup>4</sup>

Since 1996, the increasingly widespread use of potent antiretroviral therapy (ART), a combination of at least three drugs from different classes, has transformed a fatal infection into a chronic disease that is manageable in most patients.<sup>1–3</sup> However, in resource-poor settings in Africa, Asia, and Latin America, where 90% of people with HIV/AIDS live, access to ART has so far been limited to a minority of patients, owing to the high cost of drugs and the lack of an infrastructure capable of delivering ART on a large scale. In recent years, costs of proprietary drugs have fallen and low-cost generic preparations have increasingly become available. Many African countries have qualified for grants from the 'Global Fund to fight AIDS, Tuberculosis, and Malaria'. Worldwide, the Fund has approved over 1 billion US dollars for programmes against HIV/AIDS.<sup>4</sup> On December 1, 2003 (World AIDS Day) WHO launched the '3 by 5' initiative (3 million patients treated by 2005), whose strategy involves simplified, standardized tools for delivering and monitoring antiretroviral therapy.<sup>5</sup> The American 'President's Emergency Plan for AIDS Relief' (PEPFAR) intends to give 2 million people access to ART.<sup>6</sup> The government of South Africa, one of the countries hardest hit by the AIDS epidemic, has recently set up an 'Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment' to make antiretroviral drugs widely available in the public health system.<sup>7</sup>

Access to antiretroviral treatment has been steadily improving; however, a large majority of people who need treatment in developing and transitional countries still have no access to it. Table 1 shows the ART coverage in HIV-infected people aged 15–49 years at the end of 2004 in the 20 developing or transitional countries with the highest number of people in need of ART. About 80% of the total number of 5.8 million patients urgently needing ART live in these countries, but in most of them <10% of these patients received ART in December 2004.<sup>8</sup> Important exceptions with higher treatment coverage include Uganda (40%), Thailand (44%), Botswana (50%), and Brazil (86%).<sup>8</sup> Clearly, the global health emergency

that was declared by the United Nations General Assembly in 2001<sup>9</sup> continues.

## Act now and act well

There is increasing evidence that antiretroviral treatment in resource-limited settings can be very effective. In Brazil, for example, the national health system (Sistema Único de Saúde) introduced free ART as soon as drugs became available, including, from 1996 onwards, protease inhibitors; it also provided for monitoring of the HIV disease using CD4 cell counts and viral load.<sup>10</sup> As a result, a national study of survival among adult Brazilian AIDS patients diagnosed in 1995 and 1996 showed a substantial improvement of survival compared with AIDS patients diagnosed in the 1980s.<sup>11</sup> In the South African township of Khayelitsha, which includes formal and informal housing, three HIV/AIDS clinics started an ART programme in 2001. A recent analysis of patients with advanced immunodeficiency showed that the programme, which involves trained lay counsellors and peer support, achieved excellent adherence to treatment and good clinical outcomes.<sup>12,13</sup>

The debate on ART in developing countries has irrevocably moved from the question of whether the introduction of ART is feasible in the light of competing priorities and fragile health systems<sup>14,15</sup> to questions of how effective ART and care can best be delivered.<sup>16,17</sup> Indeed, as Veronica Miller observes in her commentary<sup>18</sup> on the study of survival—without ART—of Thai patients infected with HIV-1 subtype E<sup>19</sup> published in this issue, we should now put more emphasis on our research efforts with regard to patients starting HAART in resource-poor settings and support an evidence-based approach to the equitable provision of potent ART in those settings. An important concern is addressed by Antunes *et al.*<sup>20</sup> in this issue of the journal: is it possible to reduce AIDS deaths without reinforcing socioeconomic inequalities in health?

## Equitable access?

Antunes and colleagues examined trends in AIDS mortality in districts of São Paulo, Brazil, during the period in which potent ART was introduced in the Sistema Único de Saúde and found that district level indicators of socioeconomic development (for example average levels of income or education) were not associated with declines in AIDS deaths, and that trends of mortality were not poorer in deprived areas.<sup>20</sup> These results

<sup>1</sup> Institute for Social and Preventive Medicine, University of Berne, Berne, Switzerland.

<sup>2</sup> School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

<sup>3</sup> Hospital Universitario Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

<sup>4</sup> Office of AIDS Research, National Institutes of Health (NIH), Bethesda, USA.

\* Corresponding author. Institute for Social and Preventive Medicine, University of Berne, Finkenhubelweg 11, CH-3012 Bern, Switzerland. E-mail: egger@ispm.unibe.ch

**Table 1** Estimated antiretroviral therapy (ART) coverage in HIV-infected people aged 15–49 years in 2004 in developing and transitional countries, December 2004

| WHO region/country               | Number of people needing ART | Number of people receiving ART | ART therapy coverage (%) <sup>a</sup> |
|----------------------------------|------------------------------|--------------------------------|---------------------------------------|
| <b>African region</b>            |                              |                                |                                       |
| South Africa                     | 837 000                      | 37 000–62 000                  | 7                                     |
| Nigeria                          | 558 000                      | 12 000–150 00                  | 2                                     |
| Zimbabwe                         | 295 000                      | 75 000–9000                    | 3                                     |
| United Republic of Tanzania      | 263 000                      | 2000–3500                      | 1                                     |
| Kenya                            | 220 000                      | 24 000–330 00                  | 13                                    |
| Ethiopia                         | 211 000                      | 10 000–130 00                  | 5                                     |
| Mozambique                       | 199 000                      | 6500–8000                      | 4                                     |
| Democratic Republic of the Congo | 167 000                      | 3500–4500                      | 2                                     |
| Zambia                           | 149 000                      | 18 000–22 000                  | 13                                    |
| Malawi                           | 140 000                      | 10 000–12 000                  | 8                                     |
| Uganda                           | 114 000                      | 40 000–50 000                  | 40                                    |
| Cameroon                         | 95 000                       | 12 000–15 000                  | 14                                    |
| Côte d'Ivoire                    | 84 000                       | 4000–5000                      | 5                                     |
| Botswana                         | 75 000                       | 36 000–39 000                  | 50                                    |
| Lesotho                          | 56 000                       | 2500–3000                      | 5                                     |
| <b>South-east Asia region</b>    |                              |                                |                                       |
| India                            | 770 000                      | 20 000–36 000                  | 4                                     |
| Thailand                         | 114 000                      | 45 000–55 000                  | 44                                    |
| <b>Region of the Americas</b>    |                              |                                |                                       |
| Brazil                           | 179 000                      | 151 000–157 000                | 86                                    |
| <b>Western Pacific region</b>    |                              |                                |                                       |
| China                            | 122 000                      | 7500–9500                      | 7                                     |
| <b>European region</b>           |                              |                                |                                       |
| Russian Federation               | 92 000                       | 3000–3500                      | 3                                     |

The 20 countries with the highest number of people needing therapy are shown.

<sup>a</sup> Best coverage estimate based on the midpoints of the number of people receiving antiretrovirals. Adapted from WHO's '3 by 5' Progress Report, December 2004.<sup>8</sup>

refute, at least in the case of ART in São Paulo, the 'inverse equity hypothesis', which stipulates that health inequities will get worse as effective new public health interventions initially reach those of higher socioeconomic status and only later the poor.<sup>21</sup> The study was ecological in nature and does not allow inferences at the individual level. Also, in contrast to the era before therapy became available, when the large majority of deaths were associated with recent AIDS-defining events, AIDS is only an incomplete measure of HIV-related deaths in the era of potent ART.<sup>22</sup> Nevertheless, it seems likely that in São Paulo the large scale and free provision of ART meant that access to therapies and quality of care was equitable, and patients of different socioeconomic background were reached at around the same time. This is a truly remarkable achievement but it does not mean that the provision of ART is equitable in Brazil at large, for example, between genders, urban and rural populations, and between more affluent and poor or marginalized populations in other regions of the country. In Southern Africa, there is much concern that outside of cities, there may be severe geographical inequalities in access to care, and possibly an increasingly inequitable distribution of already

scarce health resources as a consequence of vertical, donor-driven interventions for HIV.<sup>23</sup> These concerns should never be used to argue against an intervention of proven benefit but rather be seen as a challenge to build a minimum health service infrastructure in areas that currently are unable to deliver the new intervention.

Muula recently illustrated the difficulties of making access to ART equitable in Malawi.<sup>24</sup> Problems start with the diagnosis of HIV infection: the guidelines postulate that eligible patients must produce written evidence of a positive HIV-test result, which, according to Muula, cannot generally be obtained from a public counselling and testing site but is easily purchased from a private laboratory. This confirmation and a documented CD4 cell count of <200 cells per µl can rapidly establish eligibility for ART. However, in Malawi, CD4 testing both in the public and private sector is limited to large cities, which makes it likely that relatively well-off urban dwellers will benefit from public sector ART programmes more than the rural poor. In addition, the WHO eligibility criteria are problematic in children: they stipulate that an adult care giver must consent to HIV testing of the child and then to the child's treatment. As Muula points

out,<sup>24</sup> adults may not always act in the best interest of the child, and laws to protect children are either lacking or not enforced. AIDS orphans may be excluded simply because they do not have access to an adult care giver. Finally, for children aged <18 months the criteria state that, 'in the absence of virological testing and CD4 cell assay availability, HIV-exposed infants <18 months of age should generally not be considered for ART regardless of symptoms'. The virological testing required in this situation is not available outside research laboratories in Malawi, meaning that sick, HIV-infected children in this age group may not receive ART.

## Multilevel, multisite action research

WHO and other organizations stress that there are almost no models for implementing ART programmes in resource-poor settings, but that incomplete evidence should not constrain efforts to scale up ART programmes. There is widespread agreement that research and evaluation efforts are urgently needed and must be synchronized, so that epidemiological and clinical data can be collected and treatment programmes can be modified and improved over time.<sup>5,6</sup> For this to occur, questions have to be asked at different levels, including the individual and household, the treatment programme and health service, the community, and the country and international level. Examples of relevant clinical, operational, and policy questions are shown in Table 2. While answering some of these questions will require dedicated studies and surveys, other questions can be addressed by the creative use of clinical databases and patient information systems. A requisite for this type of multisite, multilevel research is the collection across sites, using standardized methods and definitions, of an agreed upon core set of clinical variables on patients starting ART. For most resource-poor settings the number of variables must be kept to a minimum so that data collection can be integrated in routine care, while allowing the option of collecting more data in tertiary care or research-based centres. Ultimately, this approach should allow for meaningful comparisons between several treatment programmes that differ in terms of operational procedures and serve different communities in different countries.

How can such research be funded? The Institute of Medicine recommends that a fixed percentage of ART programme funding be dedicated to monitoring, evaluation, and operational research and that all stakeholders and donors agree on a standard set of requirements.<sup>25</sup> The Request for Applications (RFA) for International Epidemiologic Databases to Evaluate AIDS (IEDEA),<sup>26</sup> which was recently issued by the US National Institutes of Health is another approach that may provide opportunities in this context. The aim is to establish regional data centres in all continents, each being further divided into several regions, to address HIV-related research questions. Such data centres will compile datasets on diverse populations and use the data to address research questions that cannot be answered by one site alone. This endeavour is expected to allow regions to more accurately characterize their HIV epidemic, monitor critical outcomes of interventions, and generate future research and programmatic hypotheses. In the years to come, IEDEA and future complementary initiatives may provide a much needed platform for global health services research and represent a timely attempt to assess in a rigorous fashion the

**Table 2** Scaling up antiretroviral treatment: examples of research questions at different levels

| Level                           | Research question   |
|---------------------------------|---|
| <b>Individual and household</b> | When should treatment be started?   |
|                                 | How can treatment be monitored if laboratory facilities are limited?  |
|                                 | When should treatment be changed?   |
|                                 | What is the quality of life of treated patients and what toxicities and adverse events do they experience?                            |
|                                 | How does treatment affect patients' preventive behaviours?  |
|                                 | What is the impact of treatment on the household economy?   |
| <b>Treatment programme</b>      | Is access to treatment and care equitable?  |
|                                 | How should patients be prepared for treatment to maximize adherence and reduce adverse events?  |
|                                 | What is the place of family-based approaches to treatment?  |
|                                 | What is the role of other interventions, including nutritional interventions and supplements?   |
|                                 | What is the role of the private sector and of traditional medicine?   |
|                                 | What are the main points of entry into the treatment programme?   |
| <b>Community</b>                | What is the role of community-based treatment support, for example, community health workers?   |
|                                 | What are the levels of stigma and how does stigma and discrimination affect treatment programmes and outcomes?                        |
| <b>Health systems</b>           | How can treatment programmes best be integrated with other programmes, including tuberculosis and mother and child health programmes? |
|                                 | What is the appropriate level of staffing of treatment programmes and what is the role of medical assistants?                         |
|                                 | How can the supply of medicines be secured and made sustainable?  |
| <b>Country</b>                  | How will treatment scale-up influence the course of the epidemic?   |
|                                 | What is the impact on macro-economic indicators?  |
| <b>International</b>            | How can the agenda of trade organizations, governments, donor agencies, and the pharmaceutical industry be influenced?                |

real-world impact of ART, including its impact on inequalities in health.

## References

- 1 Egger M, Hirschel B, Francioli P *et al.* Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. *BMJ* 1997;**315**:1194–99.
- 2 Hogg RS, Yip B, Kully C *et al.* Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *CMAJ* 1999;**160**:659–65.

- <sup>3</sup> Mocroft A, Vella S, Benfield TL *et al.* Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998;**352**:1725–30.
- <sup>4</sup> The Global Fund to fight AIDS, Tuberculosis and Malaria. Available on <http://www.theglobalfund.org/en/> (Accessed April 2005).
- <sup>5</sup> WHO '3 by 5' initiative. Available on <http://www.who.int/3by5/en/> (Accessed April 2005).
- <sup>6</sup> Feachem R. HAART—the need for strategically focused investments. *Bull World Health Organ* 2001;**79**:1152–53.
- <sup>7</sup> Task Team. *Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*. Pretoria: Department of Health, 2003.
- <sup>8</sup> World Health Organization. *"3 by 5" Progress Report. December 2004*. Geneva: World Health Organization, 2005.
- <sup>9</sup> United Nations General Assembly Special Session on HIV/AIDS, 25–27 June 2001. *Declaration of Commitment on HIV/AIDS*. New York: United Nations, 2001.
- <sup>10</sup> Galvao J. Access to antiretroviral drugs in Brazil. *Lancet* 2002;**360**:1862–65.
- <sup>11</sup> Marins JR, Jamal LF, Chen SY *et al.* Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;**17**:1675–82.
- <sup>12</sup> Coetzee D, Boulle A, Hildebrand K, Asselman V, Van Cutsem G, Goemaere E. Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. *AIDS* 2004;**18** (suppl. 3):S27–S31.
- <sup>13</sup> 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.
- <sup>14</sup> Marseille E, Hofmann PB, Kahn JG. HIV prevention before HAART in sub-Saharan Africa. *Lancet* 2002;**359**:1851–6.
- <sup>15</sup> Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* 2002;**359**:1635–43.
- <sup>16</sup> De Cock KM, Mbori-Ngacha D, Marum E. Shadow on the continent: public health and HIV/AIDS in Africa in the 21st century. *Lancet* 2002;**360**:67–72.
- <sup>17</sup> Farmer P, Leandre F, Mukherjee JS *et al.* Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001;**358**:404–09.
- <sup>18</sup> Miller V. Commentary: Sifting through the maze of viral and host diversity and HIV/AIDS clinical progression. *Int J Epidemiol* 2005;**34**:584–85.
- <sup>19</sup> Costello C, Nelson KE, Suriyanon V *et al.* HIV-1 subtype E progression among northern Thai couples: traditional and non-traditional predictors of survival. *Int J Epidemiol* 2005;**34**:577–84.
- <sup>20</sup> Antunes JL, Waldman EA, Borrell C. Is it possible to reduce AIDS deaths without reinforcing socioeconomic inequalities in health? *Int J Epidemiol* 2005;**34**:586–92.
- <sup>21</sup> Victora CG, Vaughan JP, Barros FC, Silva AC, Tomasi E. Explaining trends in inequities: evidence from Brazilian child health studies. *Lancet* 2000;**356**:1093–98.
- <sup>22</sup> Lewden C, Salmon D, Morlat P *et al.* Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* 2005;**34**:121–30.
- <sup>23</sup> Loewenson R, McCoy D. Access to antiretroviral treatment in Africa. *BMJ* 2004;**328**:241–42.
- <sup>24</sup> Muula AS. Ethical and programmatic challenges in antiretroviral scaling-up in Malawi: challenges in meeting the World Health Organization's "Treating 3 million by 2005" initiative goals. *Croat Med J* 2004;**45**:415–21.
- <sup>25</sup> Curran J, Debas H, Arya M, Kelley P, Knobler S, Pray L (eds). *Scaling Up Treatment for the Global AIDS Pandemic: Challenges and Opportunities*. Institute of Medicine. Washington, DC: The National Academies Press, 2004.
- <sup>26</sup> International Epidemiologic Databases to Evaluate AIDS (IEDEA). Request For Applications (RFA) Number: RFA-AI-05-014. Available on <http://grants2.nih.gov/grants/guide/rfa-files/RFA-AI-05-014.html> (Accessed April 2005).