

Antiretroviral (ARV) Therapy in Resource Poor Countries: What do we Need in Real Life?

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Abstract: Significant progresses have been made in the last 5 years towards the ultimate goal to provide universal access to care for all HIV/AIDS patients needing antiretroviral treatment in resource-poor countries. However, many barriers are still to be overcome, including (●) cost of care for the individual, (●) stigma, (●) lack of qualified human resources and infrastructure, especially in the rural setting, (●) rescue drugs for failing patients and (●) pediatric formulations. Priority actions to be promoted if the fight against HIV/AIDS is to be successful include: (i) promoting access to care in the rural areas, (ii) strengthening of basic health infrastructures, (iii) waiving of users' fee to get ARV, (iv) a larger variety of drugs, with particular regard to fixed dose combination third line drugs and pediatric formulations, (v) local quality training and (vi) high quality basic and translational research. While the universal access to HIV care is crucial in developing countries, a strong emphasis on prevention should be maintained along.

BACKGROUND

Despite the remarkable successes achieved in the North of the world in the last decade, mainly due to the increasing availability of new classes of drugs, the HIV/AIDS epidemic is still spreading in the poor world in the South. According to UNAIDS, 33 million persons were living with HIV/AIDS at the end of 2007, 94% of whom in resource-poor countries [1]. The HIV prevalence rate in the adult population is higher in the African continent. However, the absolute number of persons living with HIV/AIDS is higher in the Asian continent, more densely populated.

As a general rule, the fight against any diseases is multifactorial and may not be restricted to only one component. HIV/AIDS probably represents the paradigm of disease requiring a wide spectrum of interventions (medical, social, cultural, economic, etc.) to be finally controlled and defeated.

Among these interventions, improving access to adequate medical care for those in need is crucial, as demonstrated in those countries where the open access to antiretroviral drugs has caused an unprecedented decrease in suffering and deaths. However, it is to be strongly reaffirmed that access to pharmacological care needs to go along with renewed preventive efforts in the population.

This brief article will focus on the problems and constraints that represent the main barriers to the effective daily implementation of any project to fight HIV/AIDS in resource-limited settings. These problems need to be comprehensively taken into account if the fight against HIV/AIDS is to be successful.

While recognizing that any geographical setting may offer specific epidemiological and socio-cultural problems, this article is mainly based on our African experience, with particular regard to Burkina Faso (ranking 176/177 in the 2007 list of Human Development Index – HDI), where the University Hospital of Brescia and the NGO Medicus Mundi Italy cooperates with our African counterparts (the Camillian religious Order Vice-Province in Burkina Faso) to fight HIV/AIDS in the country. This article is based on the 6-year collaborative experience in the frame of the ESTHER (*Ensemble pour une Solidarité Thérapeutique Hospitalière en Réseau*) project involving 4 different health facilities in the suburbs of capital city Ouagadougou (St Camille Medical Center, *Centre d'Accueil Notre Dame de Fatima - CANDAF*, Bio-Molecular Research Center "Pietro Annigoni" - CERBA) and in the rural District of Nanoro (St Camille District Hospital). As to 31st December 2008, our team is following an active cohort consisting of over 1.000 adult patients and over 100 children under HAART.

THE PROBLEMS ENCOUNTERED

As well as in the industrialized world, the problems that are to be addressed in the fight against HIV/AIDS are multifaceted and will be briefly analyzed.

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a. Cost of Care

The complex system that has made the antiretroviral drugs cost reduction possible in the last decade even in the poor world will be the subject of other articles in this special issue and will not be reviewed by us. Cost reduction of drugs has been the corner-stone of a renewed interest in the fight against HIV/AIDS in resource-poor countries and has served as a locomotive for a more comprehensive approach. The international funding, offered until now by different agencies (Global Fund, World Bank, UNITAID/Clinton Foundation, PEPFAR, etc.), is assuring an increasingly more adequate coverage (at least for standard first line drugs) for those in need in resource-limited settings.

Since the early nineties, apart from leprosy and tuberculosis, patients in Burkina Faso are expected to pay a contribution to receive care as suggested by the Bamako Initiative strategy. Adult (but not pediatric) HIV/AIDS patients are also today expected to pay a 1.500 CFA/month fee (roughly 2,5 euros) to receive antiretroviral drugs by the Government. This contribution is intended to make sustainability of the drug procurement possible should the international aid be reduced in the future. However, two interlinked problems are arising at the peripheral level:

1. for how long the free procurement of antiretroviral drugs may be assured by the international community? This concern has forced a number of resource-poor countries to charge an out-of-pocket contribution to the HIV-infected persons receiving the drugs, as it is the case for Burkina Faso;
2. as a consequence, this phenomenon has already been described as a major factor of therapy interruptions in many poor settings [2]. Also in our experience, charging user fees to deliver antiretroviral drugs has resulted in loss to follow-up. Unpublished data from our cohort have shown that out-of-pocket contribution is a major barrier for as many as 20% of patients in the urban setting and for as many as 90% of patients in the rural areas! (data non published).

Finally, cost of care has also to take into account other direct and indirect costs such as transportation and loss of working days respectively, that may also contribute to loss to follow-up of HIV/AIDS patients.

b. Qualified Human Resources

According to the World Health Organization (WHO), the number of physicians, and to a lesser extent of other health personnel, working in resource limited countries is dramatically poor. As a striking comparison, the number of medical doctors working in Burkina Faso (14 million people) is estimated to be 789 [3] a number that is roughly one eight of the over six thousands medical doctors registered in the Italian Province of Brescia (1,1 million inhabitants) where one of us (FC) is currently practicing. Furthermore, if HIV/AIDS is probably the most important public health challenge in such countries, many other causes of morbidity and mortality are to be considered (infant mortality, maternal mortality, malaria, diarrheal diseases, vaccine preventable diseases, etc.). Among the many problems arising from such

lack of qualified health personnel, we would like to highlight the following:

1. most qualified health personnel in resource-limited settings are concentrated in urban areas, where opportunities for profit are higher, leaving rural areas, where the need for health care is more urgent, understaffed. In rural areas of Burkina Faso, monitoring of HIV-infected patients under HAART is then the responsibility of nurses, who often have to rely exclusively on clinical criteria for efficacy and toxicity monitoring. As a consequence, the most tolerable drugs are to be used in first line regimens in these settings;
2. the drainage of health personnel from resource-limited settings to satisfy the health needs of industrialized world may be understood from an individual standpoint, but it is unacceptable and unbearable from the community standpoint in the long running;
3. training and qualification of health personnel in the fight against HIV/AIDS in resource-limited setting is often not adequate. Long overseas training may result in loss of human resources for the need of their countries and should be avoided by promoting local training opportunities;
4. vertical projects to fight HIV/AIDS are usually more easily funded than those projects addressing other diseases, leading to the paradoxical situation of attracting more local medical doctors or otherwise health personnel who are diverted from their duties in other equally crucial sectors.

We strongly believe that any technical or humanitarian partnership must include a strong training component. In our ESTHER (*Ensemble pour une Solidarité Thérapeutique Hospitalière en Réseau*) project in Burkina Faso, the University of Brescia and the University of Ouagadougou has signed an agreement where training is a crucial component.

c. Infrastructure

Luckily, the scaling-up of antiretroviral drugs in the developing world was not prevented by the scarcity of laboratory to monitor safety and efficacy of antiretroviral therapy. Millions of individuals would have died before the goal of settling an efficient laboratory network had been achieved. However, the necessity of a basic infrastructure performing at least safety monitoring and CD4 cell count is dramatically needed, especially in underprivileged rural areas. As a consequence, CD4+-based switching to second-line treatment in rural areas is often very late, with severe clinical consequences. In rural areas of Burkina Faso, access to health establishment with CD4+ count facilities is limited, especially for women and during the rainy season. The spreading of viral resistance to available drugs also require the immediate research effort to identify simplified methods to assess viremia and the installation of regional resistance monitoring institutions. In our opinion, the strengthening of the health system in resource-limited settings, even if crucial

to improve the fight against HIV/AIDS, should be viewed as a broader perspective aim to contribute to the greater long term objective to improve health.

d. Socio-Cultural Aspects

The strong impact that socio-cultural factors may play in both HIV detection and treatment may not be overemphasized in resource-limited (and even in industrialized) countries. We would like to highlight the most important socio-cultural barriers that substantially limit the effectiveness of any HIV control program in real life.

1. *gender* may play an important role in favoring or hampering access to antiretroviral drugs and compliance. In our experience, PMTCT (Prevention of Mother-to-Child Transmission) activities were crucial to identify HIV infected pregnant women. Even if VCT (Voluntary Counseling and Testing) uptake rate was far than optimal using an opt-in strategy [4], women were nonetheless favored since their access to care resulted to be earlier than that of their male partners. Females might also be more prone to screening wherever gender context permits [5];
2. *poor education* was earlier considered an argument to advise against the scaling-up of antiretroviral therapy in resource-poor countries for fear of inadequate comprehension of the complex therapeutic regimens by patients. In our experience illiteracy was indeed a relative obstacle. However, careful counseling and appropriate communication techniques (anthropomorphic drawings, etc.) were able to compensate more than adequately a lack of education. In a recent multicenter study in various sub-Saharan African countries, poor education has also been reported to be correlated to exclusive breastfeeding (negative correlation) and prolonged breastfeeding (positive correlation) [6]. Registered compliance to scheduled out-patient departments visits with the caring teams in Burkina Faso were in the same range of those registered in the industrialized world [7];
3. *stigma* is also a powerful obstacle to care and prevention of HIV/AIDS. The success rate of contact tracing and caring of family members of HIV-infected pregnant women (PMTCT-plus) has been variable in different settings [8] mainly due to reticence of family members to undergo HIV testing. Rejection of the infected partner (particularly if female) may have a deleterious effect on access to care for her and her offspring. Again, stigma has been reported to have dramatic negative impact on infant feeding modalities, preventing the adoption of safe practices such as formula feeding [9].

While addressing the interested readers to read more comprehensive treatises on the socio-cultural aspects of health, we only would like to advise against any HIV control program that does not take into preliminary consideration those aspects that may later result to be an insuperable barrier to its effective implementation.

e. Drug-Specific Constraints

When considering the impressive scaling-up of antiretroviral drugs in developing countries in the last 5 years, the balance is certainly positive. However, treating an HIV-infected patient in the south of the world is even today much more difficult than in western industrialized countries:

1. *treatment guidelines*: criteria to start and change HAART in resource-limited settings are mainly clinical and/or immunological: (i) CD4 cell count below 200/ μ l irrespective of clinical stage, (ii) WHO stage IV irrespective of CD4 cell count, (iii) WHO clinical stage III and CD4 cell count below 350/ μ l [10]. WHO guidelines are being revised and an earlier initiation of HAART is being advocated to avoid the mortality excess observed during the first 6 month of therapy. Furthermore, recent data suggest that an earlier initiation of HAART is associated with longer AIDS-free period and improved survival [11]. The emerging and long-anticipated problem of viral resistance limits in real life the effectiveness therapeutic decisions based only on clinical (or immunological) grounds, even if recent reports are somehow reassuring [12]. Second-line drugs are scarce and will probably experience a short effective period due to the above-mentioned problem of resistance. Virtually no third-line regimens are available at the present time in resource-limited settings;
2. *toxicity*: (i) stavudine is still considered a suitable drug for first-line regimens [10], despite its well recognized toxicity (peripheral neuropathy), because of its low cost and its poor potential for mielotoxicity in areas or malaria endemicity; (ii) NNRTI are recommended for first-line regimens. However, in areas with high fertility rate, both nevirapine (hypersensitive reactions) and efavirenz (teratogenic potential) have disadvantages.
3. *drug storage* conditions are far from optimal in developing countries, requiring all effort to enhance their stable shelf-life conditions;
4. *pediatric HIV infection* has dramatic epidemiological dimensions in the south of the world. However, only 4% of all persons under HAART in Burkina Faso are children [13], probably due to family reticence to children testing and to the exclusive urban location of most pediatric centers delivering antiretroviral drugs. Furthermore, pediatric formulations are not given adequate priorities in pharmaceutical research activities.

f. Specific Issues

1. *Pregnancy and lactation*: (i) the use of first-line regimens containing NNRTI in countries with high fertility rates may expose to the risk of teratogenicity (efavirenz) or hypersensitivity reactions (nevirapine); (ii) the advocated earlier criteria for HAART in pregnancy [14] will have a favorable impact on vertical HIV transmission [15], but will probably

- enhance the risk of viral resistance; (iii) the risk of perinatal transmission *via* lactation requires innovative strategies, including HAART during the lactation period irrespective of maternal criteria to start HAART [16].
2. *HIV-HBV co-infection*: in resource-poor countries, co-infection with hepatotropic viruses is highly prevalent. In Burkina Faso, as many as 10% of our HIV-infected patients are also infected with HBV [17], requiring that drugs that exert activity against both viruses (lamivudine, emtricitabine, tenofovir) are largely available and used [18].
 3. *HIV-TB co-infection*: 9.3 million new cases of tuberculosis (TB) were estimated to occur in 2007, 1.4 million of whom in HIV-infected persons, resulting in 1.7 million deaths worldwide [19]. In sub-Saharan Africa, TB is probably the first cause of death among HIV-infected patients [20]. HAART decreases the risk of tuberculosis and other opportunistic diseases in HIV-infected patients [21]. Furthermore, early HAART may increase survival in HIV-TB co-infected patients. However, severe constraints to the provision of HIV treatment in the context of poor TB control exist: (i) the great burden on undiagnosed TB at programme entry, (ii) complex drug-drug interactions between rifampicin and antiretrovirals of the NNRTI (Non Nucleosidic Reverse Transcriptase Inhibitor) and PI (Protease Inhibitor) classes and finally (iii) the risk of TB transmission in HIV care settings, especially at the light of the emergence of multi-drug and extensively-drug resistance in *M. tuberculosis*.

WHERE WE ARE AND WHAT DO WE NEED IN REAL LIFE?

In Burkina Faso and other resource-limited settings, many good news are to be recorded.

First of all, the availability of generic drugs, of international funding and transfer of technical assistance have made a quick scaling-up of HAART possible despite the many difficulties encountered. International and national guidelines have also contributed to assure quality. Secondly, the spectrum of available drugs has progressively widened, allowing the definition of standard second-line regimens. A few drugs are also available to treat HIV-HBV co-infection. The availability of thermo stable lopinavir/r and of fixed dose combinations have facilitated drug storage and patients' compliance. The main limit of such a process, i.e. the urban focus of scaling-up, was probably unavoidable. In cities, in fact, many favoring factors were present: (i) patients' concentration and patients' associations (ii) equipped and staffed hospitals, (iii) adequate technologies for laboratory workout.

Despite a number of excellent achievements, a lot still need to be done. Starting from our experience in fighting HIV/AIDS in developing countries, we estimate that the following actions may not be delayed further if the

Millennium Development Goal n. 6 (*Combat HIV/AIDS, malaria and other diseases*) is to be achieved.

1. Promoting access to HAART in rural areas is a priority. To do so efficiently, drugs with poor potential for toxicity are needed since clinical management is mainly relied upon nurses with limited access to laboratory tests. Poor tolerance may also cause low compliance, though increasing the spread of resistance. Such an extensive approach is financially demanding because a larger number of patients will require drugs and a large scale training of peripheral personnel will be needed.
2. To promote access to antiretroviral care in underprivileged areas, strengthening of basic health infrastructure to assure safety monitoring is a priority and may also benefit many other aspects of health promotion.
3. Users' fees to have access to antiretroviral treatment in countries where yearly *pro-capita* health budget is as low as 10-15 US dollars are to be abolished. The international community needs to look for and find alternative ways to insure sustainability of drug procurement in the future. The loss to follow-up of HIV-infected persons who deliberately choose to give-up treatment is a dreadful risk for the individual, his/her family and the community where he or she lives.
4. A larger variety of drugs is needed to better tailor first-line and second-line regimens should first line drugs fail. Operational research is crucial in developing countries to better transfer results from randomized clinical trial into real life [22, 23].
5. Time has come to consider third line drugs should failure occur in those patients with a long treatment history in resource-poor countries. Fixed dose combination drugs are eagerly awaited to save lives and to limit the spreading of resistant viral strains.
6. Pediatric HIV infection is an increasing large problem that may not wait further for specific solutions. Pediatric drug formulations are desperately needed to help hundreds of thousands mothers and tutors to treat their infants.
7. Viral resistance spreading is ongoing. Monitoring and surveillance of such phenomenon is crucial in order to prevent and anticipate large scale pharmacological failures. The introduction of new molecules in a specific region needs to take into account the results of resistance surveillance.
8. High quality research is to be designed and implemented in collaboration between researchers from the south and the north in order to assure that adequate technology platform is in line with priority research questions. Research activities need to be adequately funded and must address both basic questions and operational questions. Socio-cultural and anthropologic issues are to be addressed. Basic

and operational research activities that are able to provide clues to make antiretroviral care as widespread as possible are welcome.

9. Training in HIV/AIDS management is crucial. High quality training is to be performed in the field in order to optimize resources and to avoid purely academic training. Academic and research institutions of the south need to take responsibility for such training, with the constant help of the international community. The creation of regional training networks is of particular added value. Among other valuable initiatives, the network RAF-VIH (www.raf-vih.org) gather training Institutions in Benin, Burundi, Burkina Faso, Sénégal, Congo Democratic Republic and Niger with the support of many international Agencies and Universities.
10. Last, but not least, we strongly believe that effective care effort should never divert attention from preventive activities, as it has occurred too widely in the western society after the availability of HAART.

The last achievement that we would like to promote is Millennium Development Goal n. 8 (*Develop a global partnership for development*). The fight to provide free access to anti-HIV drugs and care is a component of the wider struggle for global development, including education, equity and freedom.

CONTRIBUTORSHIP

F. Castelli conceived and drafted the manuscript.

V. Pietra, I. Diallo, R.F. Schumacher and J. Simporé provided valuable conceptual inputs to the manuscript and critically revised the text.

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