

# Improving on success: what treating the urban poor in America can teach us about improving antiretroviral programmes in Africa

Anthony Amoroso, Derek E. Spencer and Robert R. Redfield

Current treatment approaches cannot predict, ensure, or sustain the needed adherence required to achieve long-term successful therapy in many of our urban poor patients. The current treatment paradigm in the United States thus relies heavily on sequential therapy to maintain patient health. This approach is often unsuccessful in achieving viral durable suppression, increases the complexities of care, increases the costs of care, and can fail to improve patients' health. As the HIV epidemic shifts into the urban poor in the USA, the success of the current antiretroviral therapy approach to achieve durable viral suppression in this population remains under question. New treatment delivery programmes designed to address these concerns for the urban poor in the USA may represent models that can achieve high levels of treatment success in resource-limited countries.

© 2004 Lippincott Williams & Wilkins

*AIDS* 2004, **18** (suppl 3):S39–S43

**Keywords:** Treatment support, antiretroviral therapy, adherence, HIV, Directly observed Therapy

## Introduction

As the HIV/AIDS epidemic threatens the social fabric of countries struggling with HIV prevalence rates as high as 20–30% there is a clear and urgent need to begin comprehensive global antiretroviral therapy (ART) programmes. No longer should the debate be whether to start global ART programmes, but rather how to deliver efficacious, durable and sustainable ART. Providers of HIV care in the United States are faced with increased complexities of care as they encounter growing numbers of patients with drug resistance [1,2]. Reliance on the frequent use of viral load monitoring and genotypic analysis has become the recommended norm [3,4]. As the US epidemic shifts to the urban poor [5] and the world prepares for antiretroviral scale-up programmes in resource-limited nations, the need to achieve durable ART success across many different patient populations and to decrease the reliance on frequent viral loads and geno-

types to gauge treatment outcomes has become more apparent.

## Background

Current standards of treatment delivery do not ensure that durable viral suppression is achieved in a significant number if not the majority of patients treated. Diverse urban clinical cohorts in the USA and Europe have shown that between 40 and 60% of treated patients were unable to achieve viral suppression over the first 18 months of ART [6–10]. Although these cohorts represent many patients who received suboptimal therapy before the advent of highly active antiretroviral therapy (HAART), recent data showed similar success rates among treatment-naïve urban poor patients treated with HAART [11]. Recent clinical trials have demonstrated increased efficacy and durability with

---

From the Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA.

Correspondence and requests for reprints to Anthony Amoroso, MD, Institute of Human Virology, RM N555, 725 West Lombard Street, Baltimore, MD 21201, USA.

E-mail: amoroso@umbi.umd.edu

DOI: 10.1097/01.aids.0000131321.13515.39

newer agents. Unfortunately, this success has not been translated into all clinical practices. The first US study on the duration of initial HAART regimens for treatment-naïve patients [12] reported that the average initial HAART regimen is taken for only 1.6 years, and was switched mainly because of drug toxicities and treatment failure. Despite federal and state-funded HIV treatment programmes within the USA, a recent study found that only 10% of predominantly African-American inner-city patients who were initially diagnosed with HIV and referred for outpatient treatment had achieved an undetectable viral load at the end of one year [13].

Real clinical concerns regarding the clinical implications of inadequate viral suppression while on ART force providers to rely on the frequent use of viral load and genotypic monitoring: a practice, which if required, will severely limit the scalability of ART programmes in resource-limited settings. Although limited studies with short-term follow-ups of 3 years or less have failed to show increased mortality in the absence of viral suppression while on ART [6,10,14], these results may not be applicable in populations outside of the USA and Europe, in which initial ART is started late in disease after advanced immunosuppression has occurred, and where the same access to second and third-line ART regimens or adequate treatments for opportunistic infections are not available. Even with access to salvage regimens, a more recent study of a US urban poor cohort with 5 years of follow-up has confirmed significant increased mortality in patients failing to achieve viral suppression when treated with HAART [11].

The complexities of ART, which prevent durable viral suppression, should not be underestimated, and include the need for absolute adherence, the rapid development of resistance, and the impact of cross resistance, unequal potency of antiretroviral agents, pharmacokinetic limitations, and drug toxicities. Treatment programmes in clinics that serve the urban poor in the USA are addressing these complexities to improve long-term treatment success.

## Objective

The JACQUES (Joint AIDS Community-wide Quest for Unique and Effective Treatment Strategies) initiative is an example of an innovative care delivery model for the treatment of HIV. This model provides intensive treatment preparation and longitudinal treatment support based on the evidence that the long-term benefits of ART require extremely tight adherence to ensure durable viral suppression. Viral failure occurs in up to 55% of patients whose adherence is as good as

90–95% [15]. Directly observed therapy (DOT) studies showed that 95% of patients achieve viral suppression at 80 weeks compared with 75% of patients who self-administered therapy [16]. The programme's primary treatment objective is to achieve durable viral suppression with initial antiretroviral regimens in 95% or more of the patients started on ART measured over a 2-year period.

## Design

HIV care providers within the Institute of Human Virology/University of Maryland associated clinics were asked to refer all patients they identified to be ready to start ART for the first time or who have failed their first ART regimen and are ready to start their second ART regimen to a 4-h treatment preparation workshop along with their identified support system of family members, partners, and friends. At completion of the workshop, patients were asked to consider enrolling in a longitudinal treatment support programme. Attending the treatment preparation workshop and subsequent participation in the treatment support programme, although highly encouraged, is completely voluntary. Interested patients are allowed to self-select one of six treatment support modalities described below. Once a patient had completed the treatment preparation workshops and self-selected a treatment support modality, an antiretroviral regimen is selected and initiated after consultation with the referring physician. Treatment support does not replace scheduled clinic visits with the patient's medical provider. Patients with active untreated substance abuse or mental health disease are referred to appropriate treatment before the initiation of ART. Patients with underlying medical conditions that would interfere in the completion of the 2-year study period were excluded from the longitudinal treatment support programme. Also, patients with multiple class drug-resistant virus were excluded from the study.

## Intervention

The intervention includes the integration of intensive treatment preparation with extensive treatment support to manage patients starting ART. All participants engage in an interactive treatment preparation curriculum centered on the HIV disease process, the importance of adherence, concepts of resistance, the impact of behavioral factors such as life stressors, drug use, and depression on successful treatment. The need for secondary prevention is also stressed. Patients are taught how to manage medication and tackle problems such as forgetting, delays, side-effects, and changes in daily

routine. The curriculum is organized by nurses, psychologists, physicians, peer advocates, social workers and various community leaders in the field of HIV. The curriculum was developed to incorporate feedback from many community-based organizations, medical providers, community leaders and HIV-infected individuals. After treatment preparation, patients are requested to volunteer for a range of self-selected longitudinal support options. The options include and range from highly supportive treatment support modalities such as daily DOT to self-administered therapy. The six observed therapy tracts include:

### **Directly observed therapy tract**

Patients are required to come to the clinical center daily (7 days a week) for the administration of ART. A nurse or pharmacist observes the ingestion of medication. Patients who take medications twice a day may do a modified DOT when their evening dose is self-administered. A review of systems is performed and recorded weekly to evaluate any medical problems or medication side-effects. Patients are counseled through symptom management as needed during these visits, and are scheduled to see a medical provider if necessary.

### **Treatment coaches tract**

Treatment coaches are hired employees of the initiative. The goal is to hire HIV-positive individuals who are doing very well in care. Each treatment coach has a 'case load' of 20–25 patients depending on the frequency of ART dosing. They are responsible for ensuring adherence to medications and medication side-effect recognition. They provide the needed support, encouragement, and education either in the patient's home or at a mutually designated location. Treatment coaches serve as a liaison to the patient and needed services such as mental health appointment and substance abuse treatment programmes.

### **Weekly direct observed therapy tract**

Patients come to the clinical center on a weekly basis for the distribution of ART. The pharmacist or treatment coach pre-fills pillboxes with a week's supply of medication, and undertakes pill counts of the returned pillbox. Opportunity exists for the direct review of systems by the nurse in order to monitor for medical or medication complications.

### **Treatment partners tract**

Two HIV-infected patients are paired together, ideally with an acquaintance or family member. They sign contract agreements with the initiative and each other to support each other through therapy. Daily direct observation of their partner's ingestion of medication is encouraged, but if this is not possible daily phone calls or e-mails are encouraged.

### **Care partners tract**

Patients are paired with a care partner of their choice. This tract is very similar to the treatment partner arm except the care partner is a close family member, friend or significant other who is HIV negative. This care partner agrees to attend all scheduled appointments and workshops. The care partner signs a contract of agreement to observe directly the ingestion of ART or make daily phone calls etc. in support of daily adherence with therapy.

### **Standard of care tract (self-administration)**

Patients may elect to stay within a self-administration mechanism of delivery. Patients are able to transition to different levels of supportive therapy depending on their needs and success within the previous modality. Barriers to adherence evaluations, provider advice and patient willingness to adhere to the demands of each supportive therapy option guide transitions from one supportive therapy to another. For example, patients doing well on DOT may choose to de-intensify to any of the less supportive treatment options, whereas a patient in the care partner option who needs additional support may choose DOT if their schedule allows. The staff work intimately with each patient to achieve durable viral suppression.

## **Outcomes**

The programme supports three urban clinics consisting of approximately 3000 patients and several community outreach programmes in downtown Baltimore. Of the patients cared for, 87% are African American and 34% are women of child-bearing age. As of December 2003, 70 patients have been enrolled (Table 1); 288 patients were referred for treatment preparation; 142 treatment naive or first failures completed treatment preparation workshops; 106 of these patients volunteered for longitudinal treatment support and 36 were referred back to their providers for not meeting the criteria for enrolment into the study because of multi-drug resistance, untreated active substance abuse or mental illness. Over half of the patients in the programme were deemed by their providers to have a high likelihood of treatment failure and were likely not to have been prescribed ART without patient participation in some type of adherence programme.

Response from the community has been favourable, as evidenced by enrolment in treatment preparation workshops. Over 30% of the attendance at these sessions has been from family, friends and interested community members (Table 2). Ninety-Five per cent of patients after at least 3 months on therapy have a non-detectable viral load (< 400 copies/ml) (Table 3). The majority of patients have chosen very highly

supportive therapy, DOT in 46%, and weekly pillbox in 40%. No patients selected the self-administration of therapy. Data on 2-year treatment durability are being collected. Data on transitioning patients to less supportive therapy are currently being gathered and are too

early to report because patients are given 3 months to stay in DOT before transitioning to less supportive therapy. The development of resistance was rare and probably reflects the impact that frequent medication refill requirements (weekly pillbox or DOT) has on the length of time suboptimal adherence can occur.

**Table 1. Demographics of first 70 patients enrolled into programme.**

Race	
White (%)	7 (10)
Black (%)	63 (90)
Sex	
Men (%)	37 (53)
Women (%)	33 (47)
Age	
Range	31–53
Mean years	42
HIV risk factors (%) by self-report	
Homosexual	15 (21)
Intravenous drug use	35 (50)
Heterosexual	20 (29)
Substance abuse (self-report)	
In the past year	80%
In the past 6 months	56%
History of mental illness	40%
Mean HIV-1-RNA level	84 689
Mean CD4 cell count (cells/mm <sup>3</sup> )	137
Percentage below 200 cells/mm <sup>3</sup>	61%

**Table 2. Treatment preparation is made available to patients starting treatment, their families, and friends.**

Total registered	692
Total actual attendees	360
Total HIV + attendees	288
Number of naive patients or first failure	142
Number who enrolled in treatment support	70

**Table 3. Available treatment outcomes in first 40 patients reaching at least 24 weeks in programme.**

Total number of patients reaching 6 months on therapy	40
Patients with viral suppression < 400 copies/ml at 3 months	40/42 (95%)
Patients with viral suppression < 50 copies/ml at 6 months	31/40 (78%)
Number of virological failures (two consecutive viral loads > 400 copies/mm <sup>3</sup> )	4
Number of patients with genotypic resistance	1/4
Number of patients not on therapy or had medications stopped	5 (4/5 stopped therapy with viral loads < 50 copies/mm <sup>3</sup> )
Number of patients stopping or failing therapy because of active substance abuse or mental illness	9

**Table 4. Desired components of adherence programme.**

1. Ensure adherence to therapy at time of treatment initiation and at least until viral suppression and immune reconstitution has occurred.
2. Provide a closer link and easy access to medical care for early side-effect recognition.
3. Improve education about HIV.
4. Enhance outlook and attitude towards HIV treatment.
5. Improve access to general healthcare.
6. Improve ability to self-administer medications.
7. Allow patients to be active in their care.
8. Involve family members, friends, and community in care to decrease stigma.
9. Provide patient testimonials from treatment failures and successes.
10. Supply patients with simple strategies for adherence.
11. Provide longitudinal interactions.

## Discussion

The JACQUES initiative creates a model treatment support structure applicable to an urban US population, but this model is now being adopted in treatment projects in rural Malawi and urban Nigeria. The characteristics of this programme that can be adapted to any population or environment are listed in Table 4.

Despite some obvious major social and economic differences and immense differences in access to care, some similar barriers to successful therapy exist between the HIV-infected population in resource-limited countries and the US urban poor. Young age at the time of infection, a high degree of negative stigma, and advanced immune suppression at the time of diagnosis are shared significant hurdles. Delaying therapy until CD4 cell counts are below 200 cells/mm<sup>3</sup> or symptomatic AIDS occurs will also mirror the US urban poor, in which the time of diagnosis for most patients occurs at CD4 cell counts less than 200 cells/mm<sup>3</sup> and undoubtedly impacts treatment success [17]. Both populations also have significant co-morbidities that can hamper successful ART, such as hepatitis C,

depression, and substance abuse in the USA, and tuberculosis, hepatitis B, and nutritional deficiencies in resource-limited countries. In addition, with the expansion of nevirapine-based mother-to-child transmission programmes and wider access to unregulated ART, patients in some resource-limited countries may develop drug resistance from exposure to suboptimal ART that closely approximates the rate of drug-resistant HIV acquisitions seen in newly infected patients in the USA.

When one considers the combination of such barriers to successful therapy as advanced disease, serious comorbidities, and intense stigma the successful expansion of new treatment delivery models into resource-limited settings may be required to ensure long-term treatment success. Supportive care such as the JACQUES initiative provides can be provided with minimal training and can be applicable to village-based programmes. Good adherence support programmes such as this can expand the reach of medical providers and can minimize the reliance on viral load monitoring, genotypic analysis, and expensive second-line therapies, thus making them fundamental to 'scalable' ART programmes in resource-limited settings.

Currently under evaluation is determining the adherence 'required' once viral suppression has occurred and immune reconstitution is restored. The dynamics of viral rebound suggest that the maintenance of viral suppression may be achievable without absolute adherence, thus patients could be transitioned to less supportive therapy over time [18].

ART strategies and outcomes can be improved on and are being improved on as ours and other models have demonstrated. 'Successful' ART should be viewed not only in terms of widescale accessibility to HAART, but also in terms of sustainable treatment outcomes. Delivering ART in a way that is both durable and scalable is the challenge that must be confronted to build sustainable ART programmes, not only in resource-limited settings but also in the USA. Historically, we may be at a crucial moment. International commitments have been made to provide ART to countries who cannot afford them. Whereas widescale access to ART will give immediate relief, continued long-term funding will be needed. Only by developing programmes with sustainable treatment outcomes can long-term commitments to fund these programmes be ensured.

*Sponsorship: Support of this program is provided by grants from the Abel Foundation, Baltimore, MD, USA; and HRSA, through the Ryan White Program.*

## References

1. Richman DD, Bozzetti S, Morton S, Chien S, Wrin T, Dawson K, Hellmann N. **The prevalence of antiretroviral resistance in the US.** In: *41st Interscience Conference on Antimicrobial Agents and Chemotherapy*. Chicago, 18 December 2001 [Abstract LB17].
2. Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC. **Antiretroviral-drug resistance among patients recently infected with HIV.** *N Engl J Med* 2002, **347**:385–394.
3. Hughes MD, Johnson VA, Hirsch MS, Bremer JW, Elbeik T, Erice A. **Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response.** ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med* 1997, **126**:929–938.
4. Hirsch MS, Brun-Vézinet F, D'Aquila RT, Hammer SM, Johnson VA, Kuritzkes DR. **Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society–USA Panel.** *JAMA* 2000, **283**:2417–2426.
5. Karon JM, Fleming PL, Steketee RW, De Cock KM. **HIV in the United States at the turn of the century: an epidemic in transition.** *Am J Public Health* 2001, **91**:1060–1068.
6. Moore RD, Chaisson RE. **Natural history of HIV infection in the era of combination antiretroviral therapy.** *AIDS* 1999, **13**:1933–1942.
7. Lucas GM, Chaisson RE, Moore RD. **Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions.** *Ann Intern Med* 1999, **131**:81–87.
8. Deeks SG, Hecht FM, Swanson M, Elbeik T, Loftus R, Cohen PT, Grant RM. **HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy.** *AIDS* 1999, **13** (Suppl.):F35–F43.
9. Casado JL, Perez-Elias MJ, Marti-Belda P, Antela A, Suarez M, Ciancas E, *et al.* **Predictors of long-term response to protease inhibitor therapy in a cohort of HIV-infected patients.** *AIDS* 1998, **12** (Suppl.):F131–F135.
10. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M. **Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study.** *Swiss HIV Cohort Study.* *Lancet* 1999, **353**:863–868.
11. Lucas GM, Chaisson RE, Moore RD. **Survival in an urban HIV-1 clinic in the era of highly active antiretroviral therapy: a 5-year cohort study.** *J Acquired Immune Defic Syndr* 2003, **33**:321–328.
12. Chen RY, Westfall AO, Mugavero MJ, Cloud GA, Raper JL, Chatham AG. **Duration of highly active antiretroviral therapy regimens.** *Clin Infect Dis* 2003, **37**:714–722.
13. Del Rio C, Green S, Abrams C, Lennox J. **From diagnosis to undetectable: the reality of HIV/AIDS care in the inner city.** In: *Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections*. Chicago, IL, 4–8 February 2001 [Abstract S21].
14. Thiebaut R, Morlat P, Jacqmin-Gadda H, Neau D, Merci P, Dabis F, Chene G. **Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment.** *Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA).* *AIDS* 2000, **14**:971–978.
15. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, *et al.* **Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.** *Ann Intern Med* 2000, **133**:21–30.
16. Fischl M, Castro J, Monroig R, Scerpella E, Thompson L, Rechtme D, Thomas D. **Impact of directly observed therapy on long-term outcomes in HIV clinical trials.** In: *Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections*. Chicago, IL, 4–8 February 2001 [Abstract 528].
17. Dybul M, Bolan R, Condluci D, Cox-Iyamu R, Redfield R, Hallahan CW. **Evaluation of initial CD4+ T cell counts in individuals with newly diagnosed human immunodeficiency virus infection, by sex and race, in urban settings.** *J Infect Dis* 2002, **185**:1818–1821.
18. Dybul M, Chun TW, Yoder C, Hidalgo B, Belson M, Hertogs K. **Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters.** *Proc Natl Acad Sci USA* 2001, **98**:15161–15166.