Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa

David Coetzee[a], Andrew Boulle[a], Katherine Hildebrand[a], Valerie Asselman[b], Gilles Van Cutsem[b] and Eric Goemaere[b]

Objective: To describe the approach used to promote adherence to antiretroviral therapy (ART) and to present the outcomes in the first primary care public sector ART project in South Africa.

Design: The study is a prospective open cohort, including all adult patients naive to previous ART who received antiretroviral treatment in Khayelitsha, from May 2001 to the end of 2002. Patients were followed until their most recent visit before 31 July 2003.

Methods: Plasma viral load was determined at 3, 6, 12, 18 and 24 months after ART was initiated, and CD4 cell counts 6-monthly. Kaplan–Meier estimates were determined for the cumulative proportions of patients surviving, and patients with viral load suppression and viral rebound.

Results: A total of 287 patients were initiated on triple therapy. The probability of survival was 86.3% at 24 months. The median CD4 cell count gain was 288 cells/μl at 24 months. Viral load was less than 400 copies/ml in 89.2, 84.2 and 69.7% of patients at 6, 12 and 24 months, respectively. The cumulative probability of viral rebound (two consecutive HIV-RNA measurements above 400 copies/ml) after achieving an HIV-RNA measurement below 400 copies/ml was 13.2% at 18 months.

Conclusion: The study shows that, with a standard approach to patient preparation and strategies to enhance adherence, a cohort of patients on ART can be retained in a resource-limited setting in a developing country. A high proportion of patients achieved suppression of viral replication. The subsequent probability of viral rebound was low. © 2004 Lippincott Williams & Wilkins

Introduction

In rich countries the use of antiretroviral therapy (ART) has significantly reduced the morbidity and mortality of patients who are infected with HIV [1]. Although many have claimed that the use of ART in resource–limited settings such as in sub-Saharan Africa is not feasible because of the complexity of ART and the alleged inability of poor individuals to adhere to lifelong therapy, projects in these countries have demonstrated that treatment programmes can achieve adherence rates comparable to those described in wealthier, developed countries with smaller epidemics [2,3].

From the [a]Infectious Disease Epidemiology Unit, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa; and [b]Médecins Sans Frontières, South Africa.

Correspondence to David Coetzee, 1.38 Falmouth Building, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925, South Africa.

Fax: +27 21 4066764; e-mail: dcoetzee@phfm.uct.ac.za

Approaches that optimize adherence to therapy are essential, and remain a key challenge, especially when considering the target of reaching the large numbers of individuals who are in need of ART. Methods used to enhance adherence in the primary care setting have not been well described. The objectives of this paper are to describe the approach used to promote adherence and to present the outcomes in the first primary care public sector ART project in South Africa.

Setting

Khayelitsha is a township in Cape Town, with a population of 400 000. The HIV-1 seroprevalence in public-sector antenatal clinics in this health district in 2002 was 24.9% [4]. There is widespread poverty, and unemployment levels are extremely high. Most residents rely on health services delivered by the state. In April 2000, the provincial health department concluded an agreement with Médecins Sans Frontières (MSF), to open services for patients with HIV-related illnesses within three community health centres in Khayelitsha. MSF started providing ART in May 2001. MSF pays for the antiretroviral medication, the viral load measurements and half of the staff, whereas the provincial department of health pays for other expenses.

Clinical services are provided by a doctor–nurse–counsellor team in each of the three clinics. The teams currently consist of one doctor, two nurses and two counsellors. At the end of 2002, the clinics were managing 250 adults and 50 children on ART, and had accumulated a combined client base of 4500 patients. An additional 25 patients were being placed on ART each month.

Only patients who attended the HIV clinic regularly and who lived in Khayelitsha were considered for ART. Clinical, biological, adherence and social criteria had to be fulfilled in order for patients to be eligible for ART. Only patients in stages III or IV according to the World Health Organization classification and who had also a CD4 cell count of less than 200 cells/μl were eligible on clinical grounds. Regular clinic attendance and previous adherence to co-trimoxazole prophylaxis and tuberculosis treatment were used to assess the ability to adhere to ART. All patients were visited at home before starting ART to verify their residence, disclosure to at least one individual and to assess support structures. A community selection committee reviewed clinical and non-clinical eligibility criteria. Patient preparation after selection involved three structured individual counselling sessions.

A patient-centred preparation programme supported adherence to ART. Patients were enrolled into com-prehensive HIV care, and developed relationships with the care team well before starting ART. The adherence promotion programme consisted of three components.

Trained counsellors were available during clinic hours to assist and support individual patients having difficulties with any aspect of ART. All patients were requested to identify a 'treatment assistant', usually someone living in their household, who could assist them with adherence issues. The treatment assistant signed the consent to start treatment together with the patient. Homes were visited as required for a more thorough follow-up of those patients with specific problems.

Peer support groups exclusively for patients on ART facilitated discussions on factors that enhanced or were barriers to adherence, adverse events, disclosure and other psychosocial issues, and also served as forums for health promotion and education.

Material support such as pillboxes, drug identification charts, daily schedules, diaries and educational materials were provided and explained the schedules, risks and benefits of ART. A treatment access non-governmental organization (Treatment Action Campaign) was active in the area, and contributed to the treatment literacy of patients and an understanding of the mode of action of ART.

Standard triple therapy regimens were used. First-line therapy included zidovudine, lamivudine and nevirapine or efavirenz.

All patients on ART were assessed biologically according to a standard schedule. Plasma viral load measurements were conducted before initiating ART and repeated at 3 and 6 months' duration on ART and then 6-monthly thereafter. CD4 cell counts were conducted 6-monthly after the initiation of ART.

A standard approach has been developed for dealing with viral rebound. When the first level above 400 copies/ml is noted, the patient is asked to bring the treatment assistant to the next consultation, and begins a cycle of adherence visits in which the pillbox is filled at the clinic with the counsellor or clinician in attendance. This is done weekly for 4 weeks. For the subsequent 8 weeks, the patient attends every 2 weeks and fills the pillbox and receives an additional week's treatment at each visit. Any problems with adherence are explored and individual support is provided. At the end of this 12-week period, the viral load test is repeated.

Methods

The study of clinical outcomes is a prospective open

cohort, including all adult patients naive to previous ART who initiated antiretroviral treatment at any of the three health centres referred to above, between May 2001 and the end of 2002. The cohort is ordered and analysed by duration on treatment. Patients were followed until their most recent visit before 31 July 2003.

Viral load suppression was defined in this analysis as an HIV-RNA measurement below 400 copies/ml. It was calculated in an as-tested analysis at the durations after starting ART when these tests are scheduled according to the protocol, namely at 3, 6, 12, 18 and 24 months. The Kaplan–Meier method was used to calculate the cumulative proportion of patients who had achieved undetectable viral loads. In a separate analysis, entry was changed to the point of the first undetectable viral load, and the Kaplan–Meier method was used to determine the cumulative proportion of patients with viral rebound. Viral rebound was defined as two consecutive viral load levels above 400 copies/ml. The median CD4 cell count on the initiation of ART was calculated for the above cohort as well as for adults beginning ART between the end of 2002 and 30 September 2003.

Loss to follow-up was defined as exit from the cohort with no information available on current status for a duration of 3 months or longer in patients who had not negotiated a transfer out of the programme.

Patients who underwent the structured adherence-enhancing programme in response to a detectable viral load were identified. The virological response to this input is described as the proportion of patients with repeat viral load measurements that were below 400 copies/ml.

Plasma HIV-RNA levels were measured using the nucleic acid sequence-based amplification procedure Nuclisens HIV-1 QT assay (BioMerieux, Boxtel, the Netherlands). Analyses were performed using STATA software (version 8.0; Stata Corp., College Station, TX, USA).

The Research Ethics Committee of the South African Medical Association approved the protocol for this project.
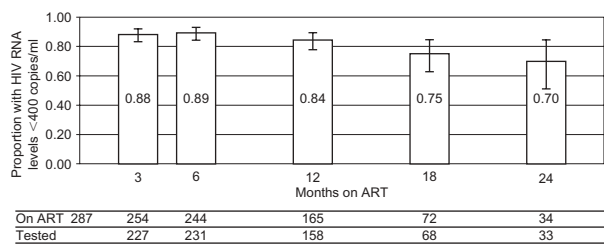
Results

Between May 2001 and December 2002 a total of 287 treatment-naive patients began ART. Table 1 summarizes the characteristics of patients initiated on ART, including baseline CD4 cell counts, viral load measurements and the initial regimens on which they were started. The median CD4 cell count on initiating ART for the cohort was 43 cells/μl. The cumulative probability of survival was 86.3% at 24 months, at which duration on treatment the median CD4 cell count gain was 288 cells/μl. The viral load was suppressed in 89.2% of patients at 6 months on ART, but this decreased to 84.2% at 12 months and 69.7% at 24 months (Fig. 1). Detailed outcomes from this cohort have been reported elsewhere [5]. At the end of July 2003, one patient from the cohort was lost to follow-up, three patients had moved to a different province, six patients were still attending the service but had stopped ART, whereas three patients had stopped attending the services altogether but were known to be in good health.

The probability of achieving viral load suppression increased rapidly in the first year on ART, with cumulatively 93.0% [95% confidence interval (CI) 88.9–95.9] of patients achieving this in the first year. All patients who had undetectable viral load measurements achieved these levels in the first year. If the

Table 1. Summary of characteristics of cohort.

Baseline	
Number starting ART	287
Women	201 (70%)
Median CD4 cell count (IQR)	43 (IQR 13–94) cells/μl
Viral load (mean $\log_{10}$ copies/ml)	5.18 (SD 0.68)
Initial regimens	Zidovudine/lamivudine/efavirenz (60%)
	Zidovudine/lamivudine/nevirapine (38%)
	Other (2%)
Follow-up	
Duration of follow-up (all)	13.9 (IQR 9.2–18.1) months
Survival at 24 months	86.3 (95% CI 81.7–89.8)%
Median CD4 cell count gain at 24 months	288 (IQR 181–470) cells/μl
Patient retention on 31 July 2003	
Patients lost to follow-up	1
Transferred out	3
In care but stopped ART	6
Alive but no longer in care	3

ART, Antiretroviral therapy; CI, confidence interval; IQR, interquartile range; SD, standard deviation.

Fig. 1. Prevalence of viral load results below 400 copies/ml by duration on antiretroviral therapy. ART, Antiretroviral therapy.

analysis was restricted to the 168 patients who were in the analysis for at least a year, 95.8% (92.8−98.5) had at least one viral load measurement below 400 copies/ml.

Eleven out of 18 patients (61%) with raised viral load measurements at 6 months' duration of ART had subsequent viral load suppression after the period of adherence promotion. At one clinic where the standardized approach to raised viral load measurements was particularly well applied, 10 out of 12 patients who had raised levels at 6 months' duration on ART had levels below 400 copies/ml at the next test. Only two out of eight patients with raised HIV-RNA measurements at 12 months achieved viral suppression below this level after the adherence intervention at the same clinic.

The cumulative probability of viral rebound (two consecutive viral load measurements above 400 copies/ml) after achieving viral load suppression was 13.2% (95% CI 8.1−21.2) at 18 months since the first level below 400 copies/ml (Fig. 2). As this analysis only includes the first 2 years of the programme, there are no data for this parameter beyond 18 months since the first undetectable viral load level. Twelve patients had started second-line treatment by the end of July 2003 [Kaplan−Meier estimate at 24 months of 8.7% (95% CI 4.0−18.1)].
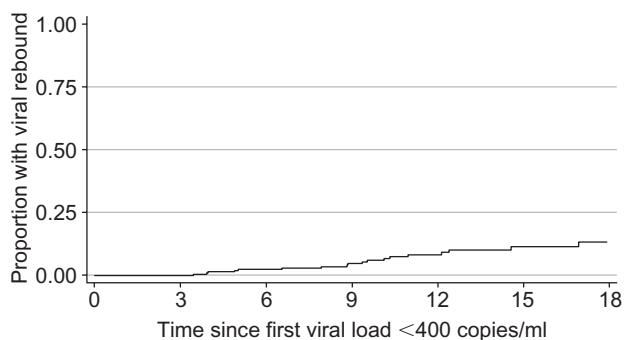
Fig. 2. Cumulative proportion of patients with confirmed viral rebound (two consecutive viral load results above 400 copies/ml).

Discussion

These results demonstrate that a cohort of patients initiated on ART in a resource-limited setting in a developing country can be retained. The fact that only one patient was lost to follow-up, and so few others left care, is remarkable. In addition, a substantial proportion of patients achieved suppression of viral replication. This compares very favourably with other data from developed and developing countries [2,3,6].

The excellent retention of patients could be related to services being situated within the primary care setting close to patients' homes and family environment as well as to the careful preparation of patients. As it is difficult to ascertain robust predictors of adherence [7,8], there has been a move to concentrate on patient preparation before the initiation of ART rather than the use of non-clinical predictors of adherence or selection criteria. A paradigm focused on preparation rather than selection is better suited to the aggressive targets for the scaling up of ART in countries with large epidemics (such as in South Africa) [9], where the view of ART as a very expensive rationed intervention is rapidly changing.

With scaling up, the key challenge will be balancing programme quality (and in particular adherence promotion) against coverage. Already in Khayelitsha, we have seen the backlog of patients requiring ART diminish, reflected by the increasing median CD4 cell count on initiation of treatment, from 43 cells/μl in the cohort from 2001 to the end of 2003, to 61 cells/μl in the 2003 cohort. The length of time in care before starting ART has also decreased dramatically, as well as the extent of pre-ART morbidity. Many more patients than those currently on ART (670 anticipated at end of 2003) should be on ART in Khayelitsha, and the duration from testing to being on ART is likely to shorten even further. The extent to which pre-ART morbidity and duration in care have contributed to adherence is difficult to quantify, and the role of these factors will be difficult to discern from programmatic changes as the numbers of patients on ART increase.

Continuity of care and the fact that patients see the same team at each visit certainly promote adherence in our opinion. This has implications for the large-scale roll-out of antiretroviral agents in South Africa, as it appears that continuity of care and knowledge of each patient are important, and that it is better to have more facilities with manageable patient numbers than a few large referral facilities that struggle to keep track of their patients. A challenge that is emerging is maintaining a reasonably sized programme in which patient-centred care and continuity of care are possible while enrolment is ongoing and total patient numbers are constantly increasing.

Initially, all patients on ART attended the same support groups. As the programme developed, it was found that patients on ART for some time had different needs and problems to those who had recently been initiated on therapy. Separate support groups were therefore organized for these patients in an attempt to orientate the support infrastructure to the needs of patients who have been on ART for many months or years. Additional research is needed to identify the optimal strategies to promote long-term adherence and particularly to respond to those patients who do not adhere to therapy.

Although the Khayelitsha programme is rooted in the public sector primary care services, external resources have been required to achieve the described levels of adherence. Preliminary cost data from Khayelitsha suggest that, in spite of the falling prices of antiretroviral drugs [10], the costs of clinical care and programme support are relatively modest compared with drugs and laboratory tests. Given the huge threat to society posed by HIV/AIDS, we need to advocate for these extra resources to be invested in primary care services generally.

Viral load measurements can be used as a marker of adherence in the first year on ART. The high proportion of patients achieving viral load suppression after adherence support in response to a raised level at 6 months' duration on ART confirms that raised levels in this period are mostly caused by adherence-related problems in a treatment-naive context. In programmes in which viral load measurements are part of the clinical protocol, a standardized health service response to raised levels should be anticipated and planned for, both in terms of adherence promotion and regimen change. There is a trade-off between repeating the level after 4 weeks in which adherence had been tightly monitored, but the duration is sub-optimal to achieve full suppression, and repeating the level after 3 months when clinicians can be less certain that adherence issues have not resurfaced. International advice on ART for poor countries is unclear on the roll of viral load measurements in those countries that can afford them [11]. When only two regimens are available, there is a temptation to rely on immunological failure as a trigger for regimen switching, especially as regimens with less cross-resistance emerge. As the price of technologies to quantify viral load falls, it is important to recognize the role of this technology both in adherence promotion and in determining when to switch regimens.

The high proportion of patients with undetectable viral loads in the first year on treatment underpins the fact that adherence rates comparable to those in rich countries are achievable in resource-limited settings if interventions are appropriately implemented through public sector primary care services. Many issues are emerging related to adherence promotion, and current strategies will need to be re-evaluated in the context of much larger programmes.

Acknowledgements

References

1. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. **Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies.** *Lancet* 2002, **360**:119–129.
2. Laurent C, Diakhate N, Gueye NF, Toure MA, Sow PS, Faye MA, et al. **The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study.** *AIDS* 2002, **16**:1363–1370.
3. Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, Downing R, et al. **Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance.** *Lancet* 2002, **360**:34–40.
4. Department of Health, Western Cape. *Antenatal HIV and syphilis prevalence survey.* 2002.
5. Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, et al. **Outcomes at 24 months in a primary care antiretroviral treatment programme in South Africa.** *AIDS* 2004, **18**:1–9.
6. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al. **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.
7. Spire B, Duran S, Souville M, Leport C, Raffi F, Moatti JP. **Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach.** *Soc Sci Med* 2002, **54**:1481–1496.
8. Turner BJ, Hecht FM. **Improving on a coin toss to predict patient adherence to medications.** *Ann Intern Med* 2001, **134**:1004–1006.
9. World Health Organization. **2003–08: a programme of quiet thunder takes shape [Editorial].** *Lancet* 2003, **362**:179.
10. Cleary S, Boulle A. *Cost-effectiveness of antiretroviral treatment for HIV-positive adults in a South African township.* Health Economics Unit, Infectious Disease Epidemiology Unit, University of Cape Town; 2003.
11. World Health Organization. *Scaling up antiretroviral therapy in resource limited settings: guidelines for a public health approach.* Geneva: WHO; 2002.