

Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited

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Objectives: To determine rates and causes of switching from first- to second-line antiretroviral treatment (ART) regimens in a large treatment-naïve cohort (a South African community-based ART service) where a targeted adherence intervention was used to manage initial virological breakthrough.

Methods: ART-naïve adults ($n=929$) commencing first-line non-nucleoside-based ART [according to WHO (2002) guidelines] between September 2002 and August 2005 were studied prospectively. Viral load (VL) and CD4⁺ T-cell counts were monitored every 4 months. All drug switches were recorded. Counsellor-driven adherence interventions were targeted to patients with a VL >1,000 copies/ml at any visit (virological breakthrough) and the VL measurement was repeated within 8 weeks. Two consecutive VL measurements >1,000 copies/ml was considered virological failure, triggering change to a second-line regimen.

Results: During 760 person-years of observation [median (IQR) 189 (85–441) days], 823 (89%) patients were retained on ART, 2% transferred elsewhere, 7% died and 3% were lost to follow-up. A total of 893 (96%) patients remained on first-line therapy and 16 (1.7%) switched to second-line due to hypersensitivity reactions ($n=9$) or lactic acidosis ($n=7$). A Kaplan–Meier estimate for switching to second-line due to toxicity was 3.0% at 32 months. Virological breakthrough occurred in 67 (7.2%) patients, but, following use of a targeted adherence intervention, virological failure was confirmed in just 20 (2.2%). Kaplan–Meier estimates at 32 months were 20% for virological breakthrough but only 5.6% for confirmed virological failure.

Conclusion: Regimen switches were due to virological failure or toxicity. Although follow-up time was limited, over 95% of individuals remained on first-line ART using a combination of viral monitoring and a targeted adherence intervention.

Introduction

The major impact of antiretroviral therapy (ART) on HIV-associated morbidity and mortality in high-income countries has been well documented [1,2]. Early data from resource-limited countries have shown similar clinical and virological successes [3–11]. However, in many resource-limited settings, ART options are limited to a single non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen, followed by a single protease inhibitor (PI)-based second-line regimen [12,13]. In South Africa, the national ART programme supplies first- and second-line regimens free of charge, but thereafter offers no further treatment options [12]. Only four NRTIs are available as backbone therapy within the two available regimens. Treatment options following development of either drug toxicity or virological failure are often limited due

to the high costs of alternative medications. Even within the limited options available, second-line therapy is on average three times more costly than first line.

For long-term health to be maintained within a framework of very limited ART options, it is important to maximise the clinical benefits derived from each regimen. Reports from high-income countries have raised concerns about rapid exhaustion of treatment options, leading to high rates of virological failure [14,15]. In the UK the reported median duration of the first-line ART regimen was 17 months and 38% of patients experienced all three classes of antiretrovirals within 2 to 5 years of commencing therapy [14,15]. There are no similar studies from resource-limited countries, where such high rates of therapy switching would result in a large proportion of the ART-treated population quickly exhausting

their limited treatment options. A balance must be maintained between switching early with resultant loss of regimens and continuing a failing regimen, which may encourage development of viral resistance.

The utility of viral load (VL) monitoring in resource-limited settings has not been well established. However, our experiences in a community-based public sector ART service in Cape Town suggest that use of regular follow-up VL measurements coupled with an intensive peer counsellor adherence intervention to promptly manage initial virological breakthrough is associated with a low rate of confirmed failure, thereby retaining individuals on first-line therapy and conserving more expensive second-line therapy for future use. Here we report the rates of initial virological breakthrough and confirmed virological failure in this service and the rate of switching to second-line therapy for reasons of both virological failure and toxicity.

Methods

Site description

The Hannan Crusaid Treatment Centre is the ART roll-out clinic for the Nyanga district, a township near Cape Town, South Africa where people live in conditions of low socioeconomic status [11,16,17]. An estimated 300,000 people live in this district, which had an antenatal HIV-1 seroprevalence rate of 28% in 2003. The site began recruiting in September 2002 and by September 2005 cared for more than 1,500 adults and children needing ART. Drugs and laboratory investigations are supplied free of charge.

The centre accepts referrals from nine local HIV clinics and the local midwife obstetric unit. The majority of those referred to the centre are ART-naïve. Patients are referred to the clinic based on eligibility for ART under the WHO 2002 guidelines, which include those with a CD4⁺ T-cell count of <200 cells/ μ l or a prior AIDS-defining illness as defined by the WHO classification system [13].

Employment of local peer counselling staff is enabled by donor funding. One counsellor is assigned up to 50 patients entering the clinic. Counsellors are responsible for preparing the patients for ART at three small group education sessions ('treatment readiness' sessions), and for on-treatment adherence support. This care includes scheduled visits to patients at home every 2 weeks pre-treatment and monthly after starting treatment until viral suppression is achieved. Thereafter the counsellors make a routine home visit to each patient once every 3 to 4 months and also whenever the need arises. Active follow-up of patients by counsellors was used when patients failed to attend appointments.

Patients are medically reviewed every 2 weeks prior to ART, and then at 4, 8 and 16 weeks of ART and

16-weekly thereafter. HIV RNA load and CD4⁺ T-cell count assessments are made pre-treatment and every 16 weeks during ART. Viral load assays were done using the branch DNA hybridization technique [Bayer HIV-1 RNA 3.0 assay (branch DNA); Bayer Healthcare, Leverkusen, Germany]. Additional safety tests are performed according to the provincial ART protocol and vary according to the treatment regimen [18].

Drug regimen

First-line ART is comprised of stavudine (d4T) and lamivudine (3TC) plus an NNRTI [efavirenz (EFV) or nevirapine (NVP)]. Pregnant women are started on zidovudine (AZT), 3TC and NVP and the AZT is switched to d4T after delivery. The second-line regimen for those failing first-line treatment comprises lopinavir/ritonavir (LPV/r), AZT and didanosine.

Switches to a regimen containing LPV/r was considered to be second-line therapy, whatever the reason for the switch. For example, patients with symptomatic hyperlactataemia (lactate >5–10 mmol/l with clinical symptoms of hyperlactataemia) were switched to an NRTI-sparing regimen of EFV and LPV/r.

Details of all switches in ART were recorded, but the primary focus of this study was switches to a second-line regimen.

Adherence intervention

Patients with a VL >1,000 copies/ml at any follow-up visit during ART (defined as initial virological breakthrough) were reviewed and received a targeted adherence intervention. This included being issued with a pill box and a dosing diary. The frequency of counsellor home visits was increased to weekly and the patient was required to re-attend the three education sessions. The VL measurement was repeated after 6 to 8 weeks of this intensive counselling. Virological failure was defined by a second VL >1,000 copies/ml and triggered a switch to second-line therapy. A VL between 50 and 1,000 copies/ml prompted continuation on first-line therapy, with high frequency home visits continuing. Only once the patient's VL had fallen below 50 copies/ml was the alert status removed and routine visits recommenced.

Analysis

Patients commencing ART at the clinic between 2 September 2002 and 11 August 2005 were considered for this analysis. Those <15 years of age and those who were non-naïve to ART were excluded. Data were accessed from structured clinical and laboratory records that were maintained on all patients screened on entry to the ART programme and which were transferred on a weekly basis to a database. Outcomes were assigned to all patients, including dates of leaving the programme.

Patients were right-censored on 11 August 2005 if they remained in care. Patients who were more than 4 weeks late for a scheduled visit were considered lost to follow-up, and were considered lost to the programme 28 days after their last visit to the clinic, at which point they would have run out of drugs. Patients who were transferred out were considered lost to the programme (censored) on the date they agreed with the clinic to leave the programme.

Analysis was carried out using Stata version 9 (StataCorp, College Station, TX, USA). Patient characteristics were described using median values and interquartile ranges (IQR) for continuous variables, and counts and percentages for categorical data. Differences of proportion were tested using a χ^2 test. Product-limit (Kaplan–Meier) estimates of survival were calculated using all eligible patients. Where appropriate, confidence intervals were also calculated from the product-limit estimator.

Results

The analysis included 929 people who commenced treatment between 2 September 2002 and 11 August 2005 (Table 1). The median age at entry was 33 years (IQR 28–38). The analysis cohort was predominantly female ($n=671$, 72%) of whom 111 (12%) were pregnant at enrolment. The majority of individuals had advanced symptomatic disease, with 488 (54%) having WHO stage 3 disease and 255 (28%) having stage 4 disease. The median CD4⁺ T-cell count was 95 cells/ μ l (IQR 47–151) and the median HIV RNA level was 4.83 log₁₀ copies/ml (IQR 4.48–5.23). Following initiation of ART, 760 person-years of observation accrued, with a median duration of follow-up of 189 days per person (IQR 85–441).

Table 1. Baseline characteristics of treated cohort

Population, <i>n</i>	929
Female, <i>n</i> (%)	671 (72.2)
Age, years	33 (28–38)
WHO stage 3, <i>n</i> (%)	488 (53.7)
WHO stage 4 (AIDS), <i>n</i> (%)	255 (27.5)
CD4 ⁺ T-cell count, cells/ μ l	95 (47–151)
CD4 ⁺ T-cell count <50 cells/ μ l, <i>n</i> (%)	244 (26.3)
HIV RNA level, log ₁₀ copies/ml	4.83 (4.48–5.23)
Starting regimen, <i>n</i> (%)	
d4T/3TC/EFV	784 (84.4)
AZT/3TC/NVP	99 (10.6)
d4T/3TC/NVP	34 (3.7)
AZT/3TC/EFV	12 (1.3)

Unless stated all figures are medians and interquartile ranges. 3TC, lamiduvine; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine.

Programme outcomes

Of those who started ART, 89% ($n=823$) remained in care at this clinic, 2% ($n=18$) were transferred to another ART programme and 6.7% ($n=62$) of patients died, with the majority of these deaths occurring during the first 4 months of treatment, with no deaths after 16 months of ART. Death rates and causes of early and late mortality have been published elsewhere [16,17]. Losses to follow-up were few ($n=26$, 2.8%). Kaplan–Meier estimate of survival at 3 years was 90% and of overall retention within this service was 84%.

Regimen changes due to toxicity

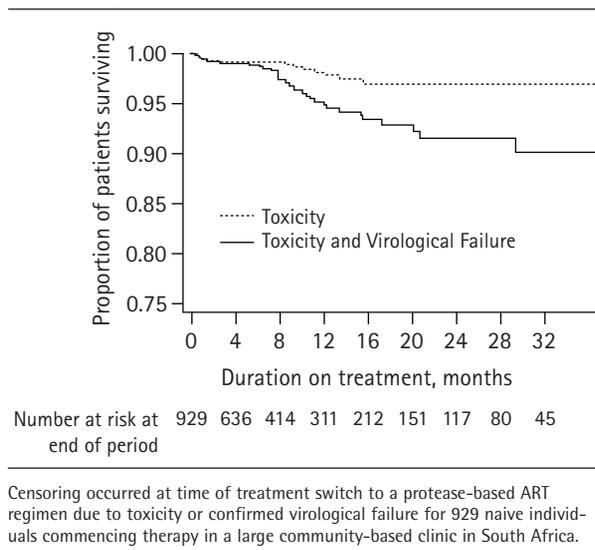
At the time of reporting, changes to treatment regimens were infrequent in this cohort. Changes within first-line therapy that did not necessitate a change to a PI regimen ($n=45$, 4.8%) were more common than regimen switches. These included switches from d4T to AZT among 25 people (2.7%) and were largely due to ACTG grade 3 or 4 peripheral neuropathy or subjectively significant lipodystrophy. AZT was switched to d4T in six (0.6%) patients due to either ACTG grade 3 or 4 anaemia or a protocol-specified change at the end of pregnancy. EFV was switched to NVP in nine (1.0%) patients due to EFV-related central nervous system toxicity ($n=1$) or intended or confirmed pregnancy ($n=8$). NVP was switched to EFV in the remaining five (0.5%) patients for reasons that included commencement of concurrent anti-tuberculous therapy, NVP hypersensitivity and end of a pregnancy.

Just 16 patients (1.7%) changed from first to second-line therapy due to drug toxicity: nine (1.0%) had a hypersensitivity reaction to EFV necessitating use of LPV/r. A further seven patients (0.7%) changed to an NRTI-sparing regimen of LPV/r and EFV due to development of symptomatic hyperlactataemia (serum lactate >5 mmol/l with clinical symptoms). Kaplan–Meyer survival analysis estimates that toxicity would result in 3.0% of individuals switching to second-line therapy at 32 months and would contribute less to regimen switching than would virological failure (Figure 1).

Virological and immunological outcomes

Viral load and CD4⁺ T-cell counts were measured every 4 months and these data were available for 92.9% of HIV RNA tests and 93.0% of CD4⁺ T-cell counts. Each patient had a median of 3.37 (IQR 2.99–3.92) VL measurements per year. The proportions of patients at each timepoint with viral suppression to <1,000, <400 and <50 copies/ml were 94–100%, 93–98% and 77–88%, respectively (Figure 2A). The median CD4⁺ T-cell count increased steadily throughout follow-up, rising from 95 cells/ μ l at baseline to 404 cells/ μ l at 32 months.

Figure 1. Kaplan–Meier survival estimate for time on first-line therapy



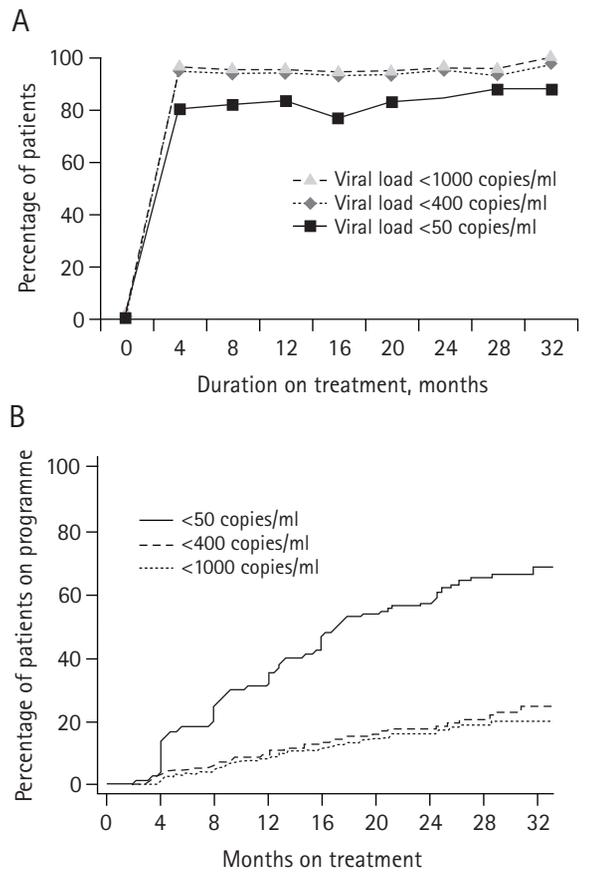
Virological failure and change to second-line therapy

Rapid expansion of the programme in the latter part of the study period resulted in a majority of the cohort having a short duration of follow-up relative to the total duration of the study (median 189 days, IQR 85–441). A total of 67 people (7.2%) had ≥ 1 follow-up VL measurements of $>1,000$ copies/ml. Of these, 43 had a second VL test prior to data censorship and 24 people were awaiting this test. At censor date, 20 people (2.2%) were confirmed as virological treatment failures and had commenced or were shortly to commence the second-line treatment regimen. The demographic characteristics of patients with ≥ 1 VL measurement $>1,000$ copies/ml did not significantly differ from those of the rest of the cohort.

The estimated proportions of individuals who had had one VL above each of three virological thresholds were plotted (Figure 2B). At 32 months, the cumulative risk of having one or more VL measurements >50 copies/ml was 70% with a rate of 38.8 per 100 person-years. In contrast, the risk of having a VL >400 copies/ml was just 23% or 9.6 per 100 person-years. The risks for a single VL of $>1,000$ (20% or 7.9 per 100 person-years) was similar to that of >400 copies/ml (Figure 2B). Further analyses used 1,000 copies/ml as specified by the ART programme guidelines used in this service.

To determine the likelihood of virological failure above $>1,000$ copies/ml, we plotted Kaplan–Meier proportion estimates (Figure 3). At 32 months, 20% (CI 14.7–25.1) of patients would be estimated to have a ≥ 1 VL measurement $>1,000$ copies/ml and receive the targeted adherence intervention. It was estimated that virological failure would subsequently be confirmed in 29% of these; comprising just 5.6%

Figure 2. Virological outcomes of the cohort over time



(A) Percentage of patients with a viral load (VL) of <50 , <400 or $<1,000$ copies/ml at each timepoint for the on-treatment cohort ($n=929$). (B) Cumulative percentage of patients with a first VL >50 , >400 or $>1,000$ copies/ml. Measurements are made 4-monthly, hence the step-wise increase in the curves.

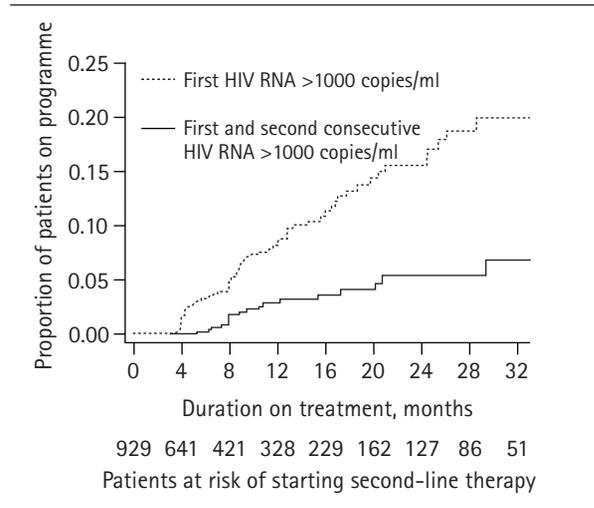
(CI 3.8–11.4) of the whole cohort. This corresponds to a rate of 2.2 per 100 person-years.

Discussion

There are few data concerning switching ART to second-line regimens in a resource-limited setting. We have demonstrated that in this setting ART can be provided to a large number of patients attending a public-sector clinic while retaining more than 95% of patients on a first-line treatment regimen over 3 years. At the time of reporting, with a median follow-up time of 189 days (IQR 85–144), switches to second-line therapy were infrequent (3.9%) and were attributable to either drug toxicity (1.7%) or virological failure (2.2%). Using a system of early detection of virological breakthrough leading to implementation of a targeted adherence strategy, 23 (53%) of 43 people with initial VL $>1,000$ copies/ml subsequently achieved full virological suppression.

Rates of regimen switch due to toxicity were low. Less than 5% of patients required a single drug switch

Figure 3. Kaplan–Meier failure estimate for time to first, then second consecutive HIV RNA level >1,000 copies/ml



within the first-line regimen and all changes were attributed to well-recognised adverse effects of the drugs used [19]. In particular, widespread use of d4T in a first-line treatment regimen is frequently associated with drug switching due to peripheral neuropathy, lipodystrophy and hyperlactataemia. Only 1.7% of patients changed to second-line therapy as a result of toxicity and the estimated cumulative proportion of patients requiring such a switch was just 3% at 32 months. Lack of drug choices may have served to significantly limit both the potential and the inclination of the health-care provider to switch drugs unless strongly indicated. In addition, the rate of switch due to drug-related toxicity, and possibly virological failure, may be expected to rise as the follow-up time of this cohort increases.

On the date of censorship, 2.2% of this cohort had switched to second-line therapy due to virological failure; Kaplan–Meier estimates predicted failure rates of just 5.6% at 32 months. More than 50% of people who developed initial virological breakthrough (VL >1,000 copies/ml) did not progress to confirmed virological failure. Recent studies in the developed world have noted that initial or primary virological failure (one elevated VL) is more likely to be due to treatment interruption or poor adherence rather than viral resistance [20,21]. Thus, management of initial virological failure using targeted programmatic interventions to improve adherence has the potential to have a positive impact on maintaining low rates of transfer to second-line therapy.

The threshold of virological failure has not been clearly defined. The lower the virological failure threshold, the higher the cumulative incidence of failure that will be detected. In our cohort, the cumula-

tive incidence of having at least one VL of >50 copies/ml was 70% in 32 months, although the risk at any given timepoint was 13% or less. Viral loads between 50 and 400 copies/ml typically return to viral suppression without specific intervention and stochastic variation about the mean is a likely explanation for a majority of these VL increases [22].

A much smaller cumulative proportion of the cohort reached a VL of >400 or 1,000 copies/ml (23% or 20%, respectively) over 32 months. These proportions were not significantly different from each other and were similar to those of ART-naive patients in the EuroSIDA cohort [23]. Random variation about the mean is far less likely at a VL level of 400 or 1,000 copies/ml than at 50 copies/ml and any value >400 copies/ml is more likely to reflect significant viral breakthrough [22]. Our programme defined people with a VL >1,000 copies/ml as being potentially at risk of failure – a figure justified by these observations.

In the absence of a controlled trial it is not possible to definitively attribute the low rates of virological failure to the adherence strategy targeted at those with virological breakthrough. However, we believe that this intervention plays a very important role and would consider a randomized trial examining this to be unethical. Virological breakthrough is likely to represent a combination of poor adherence and emerging viral resistance. As reported previously, the demographics (age, gender and baseline WHO clinical stage) of patients within this cohort with virological breakthrough did not differ from those of the rest of the cohort [24]. Among individuals with an initial VL >1,000 copies/ml, 53% subsequently achieved VL suppression and therefore remained on first-line therapy. It is possible that our results may be affected by survival bias due to mortality or losses to follow-up. However, rates of these losses were low compared with other African cohorts [7,8,25,26]. Moreover, a majority of mortality occurred in the first 4 months prior to any follow-up VL measurements and we have previously shown that patients lost to follow-up did not have poor response to ART prior to leaving the service [17].

The completeness of the data is an important strength of this study. In addition to implementation of targeted adherence support, the peer counsellors played an important role in patient retention and data integrity. There is always concern about the generalisability of data such as those presented here. The clinical and socioeconomic characteristics of this cohort reflect those of many other African cohorts being treated on government programmes [3,4,7,26]. However, the national programmes in this and most other countries in sub-Saharan Africa do not provide the intensive counselling staff levels that may have contributed to our high levels

of success. The cost-effectiveness of such a system on a wide scale needs to be assessed. Use of VL monitoring in community-based settings has been debated and a system for detecting failure through clinical and immunological means has recently been suggested by Colebunders and colleagues [27]. However, the proposed algorithm had very low sensitivity for detecting virological failures in this cohort [28,29]. At present, all South African ART sites have access to VL monitoring; data from other programmes are needed to further evaluate different patient management strategies.

A public health approach to ART requires optimal use of limited treatment regimens. Use of VL measurement, coupled with a targeted adherence intervention, was associated with a low rate of virological failure and resulted in more than 95% of patients remaining on first-line therapy in this resource-limited setting. This study demonstrates that it is possible conserve future ART options by maintaining the majority of individuals on first-line regimens.

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