Adherence is not a barrier to successful antiretroviral therapy in South Africa

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Objective: to determine adherence of an indigent African HIV-infected cohort initiating antiretroviral therapy (ART); to identify predictors of incomplete adherence (< 95%) and virologic failure (> 400 HIV RNA copies/ml).

Design: Prospective monitoring of adherence in a poor HIV-positive cohort, attending a public sector hospital and receiving ART through phase III studies.

Methods: Adherence to ART was determined over 48 weeks by counting tablet-returns. Logistic regression models including age, WHO HIV stage, home language, socio-economic status, complexity and type of regimen were fitted to determine predictors of incomplete adherence and virologic failure at 48 weeks.

Results: 289 patients were recruited between January 1996 and May 2001. Median (mean) adherence of the cohort was 93.5% (87.2%). Three times daily dosing [risk ratio (RR), 3.07; 95% confidence interval (CI), 1.40–6.74], speaking English (RR, 0.41; 95% CI, 0.21–0.80) and age (RR, 0.97; 95% CI, 0.94–0.99) were independent predictors of incomplete adherence. Socio-economic status, sex and HIV stage did not predict adherence. Independent predictors of virologic failure included baseline viral load (RR, 2.57; 95% CI, 1.57–4.22) and three times daily dosing (RR, 2.64; 95% CI, 1.23–5.66), incomplete adherence (RR, 1.92; 95% CI, 1.10–3.57), age (RR, 0.96; 95% CI, 0.92–0.99) and dual nucleoside therapy (RR, 2.69; 95% CI, 1.17–6.15).

Conclusion: The proportion of individuals achieving viral suppression matched results from the developing world. Speaking the same language as site staff and simplified dosing frequency were beneficial. Socio-economic status had no impact on adherence and should not be used as a limitation to ART access.

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Introduction

The majority of HIV infected individuals live in sub-Saharan Africa. Over 4.7 million people are infected in South Africa alone, approximately one in every five adults [1,2]. South Africa is a middle-income, developing country and until recently, treatment with antiretroviral therapy (ART) on a large scale was considered financially impossible. In 2001, however, the local pricing of triple ART decreased by approximately 75%, and it is now available for less than $1000 per year. A recent out of court settlement between the government and pharmaceutical industry has further encouraged reduced antiretroviral pricing, which will expand access to South Africans receiving health care in the public sector.

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Expectation of poor adherence is a major concern in expanding therapy to South Africans, many of whom live in severe poverty [3,4]. A spokesman for USAID encapsulated these assumptions with his statement: 'Ask Africans to take their drugs at a certain time of day, and they do not know what you are talking about' [5]. This is concerning because adherence to therapy is a strong predictor of viral load suppression, immune recovery, disease progression, and death [6–13]. There is also the widely held belief that non-adherence to therapy among sub-Saharan Africans will lead to rapid development and spread of HIV drug resistance [3]. In contrast to current expectations of non-adherence, Laurent *et al.* reported high levels of adherence in Senegal [14.] As yet there are no published studies of objectively measured adherence in resource-limited settings comprising the majority of HIV infected patients.

We set out to measure pill count adherence and virologic suppression in a cohort of semi-urban South Africans living in extreme poverty.

Methods

Eligibility and recruitment

Participants were recruited from the Cape Town AIDS Cohort (CTAC), a group of HIV-positive individuals presenting to University of Cape Town HIV clinics which serve largely indigent populations. Patients were referred to the clinic study site between January 1996 and May 2001 by a broad spectrum of health care workers in the public sector of the wider Cape Town area. All participants were antiretroviral naive and provided written consent to participate in multi-centre phase III clinical trials of combination ART. These studies were approved by the University of Cape Town Research Ethics Committee. Inclusion and exclusion criterion were trial determined. All antiretroviral naive patients who commenced ART on any established study by December 2000 were eligible for adherence monitoring.

ART, routine medical care from the site doctors and nursing staff, and trial-related laboratory monitoring were free. The routine public service hospital system, which requires payment from the patients proportional to their income, was accessed for treatment of inter-current problems, opportunistic infections or non-trial medication.

A single group education session (usually in English) is held prior to the consenting process and inclusion onto a study. There is no dedicated adherence counseling service, structured adherence support or formal adherence intervention as part of treatment. Patients access the site for 1–2 h every 2 or 3 months. There are no off-site visits by health care staff.

Demographic and socio-economic data collection

The socio-economic status of participants was assessed using the Cape Metropolitan Council per-suburb composite index which is based on household income (percentage of households earning less than US $1500 per annum), education level (percentage of adults with less than 8 years of schooling), unemployment status (unemployed adults who are actively seeking work as a percentage of all adults), welfare status (percentage of household heads who are single women with three or more children) and overcrowding status (percentage of households with more than 1.5 people per habitable room). The composite index is the sum of these five percentages (maximum 500%) and tends to range from 4 to >70. A score of >28.5 correlates well (r, 0.7) with extremely poor conditions of living (shack or informal dwellings with outside tap or public sector housing blocks). An index of 10–28.5 indicates a moderate standard of living (low-cost housing, basic amenities), and an index of <10 indicates a high standard of living (brick house, full amenities) [15]. For analysis purposes a cut-off of 28.5 was used as the break between poor and reasonable socio-economic circumstances.

Other demographic variables recorded include: age at commencement of therapy, language spoken at home (to question the impact of English-based education processes on adherence), sex, World Health Organisation (WHO) HIV stage, as well as viral load and CD4 cell count at baseline.

Antiretroviral treatment

Patients were assigned to one of six multi-center phase III studies. Patients in two studies in 1996 were given dual therapy with an additional third concurrent, placebo-controlled and double-blinded drug (placebo versus a non-nuceoside reverse transcriptase inhibitor regimen). In the other four studies patients were given triple therapy regimens.

Adherence monitoring

Adherence to therapy was assessed using clinic-based pill counts and pharmacy refill data over a period of 48 weeks. All ART was dispensed from the single study site. Patients were provided with more medication than required, i.e. tablets were usually dispensed in multiples of 30, whereas visits were booked in multiples of 28 days. Patients were instructed to return all medication bottles and unused pills at each study visit, but were not told that the returns were to be counted. All tablets of each antiretroviral medication were counted prior to dispensing and upon return. Adherence to therapy was calculated using the formula: (sum of tablets dis-

pensed – sum of tablets returned) / (total tablets prescribed over the 48-week study interval).

Patients who did not complete at least 30 days of ART were excluded from the analysis. Patients who completed at least 30 days of therapy, but who failed to bring any tablet returns over the study period have been included in the analysis and assigned a 0% adherence value. For those who withdrew from the study before 48 weeks, the last data available has been brought forward to be included in the 48-week data analysis.

Statistical analysis

Chi-squared test was used to compare categorical data and the student's t test was used for continuous variables. Associations were examined at the $P < 0.05$ level of significance. Logistic regression models were fitted to determine variables predictive of adherence and virologic failure. Only variables which were predictive on univariate analysis ($P < 0.05$) were included in the multivariate modeling.

Factors used in the univariate model for predicting adherence less than 95% included age (modeled as a continuous variable), language spoken at home (English), three times daily medication dosing, socio-economic status (low), WHO HIV clinical stage (stage 3 or 4), sex (female), and baseline CD4 cell count and viral load.

The univariate models for virologic failure (> 400 HIV RNA copies/ml at 48 weeks) included the baseline viral load, age, daily dosing schedule, adherence and antiretroviral regimen type. Viral load at baseline, age, three times a day regimens, medication-related food restrictions, taking more than 10 tablets a day, adherence < 95% and dual nucleoside therapy were modeled as baseline risk factors.

Results

Recruitment and retention

A total of 289 patients was eligible for adherence monitoring. Eleven patients (3.8%) were excluded from the analysis because they withdrew consent (six patients) or discontinued therapy due to toxicity (five patients) within 4 weeks of treatment initiation. An additional 36 patients (12.4%) withdrew from the study after the first 4 weeks and were included in the analysis.

Patient and regimen characteristics

The mean age of the cohort at commencement of ART was 33.4 years (SD, 8.7) and 43% of the cohort was female. Forty-two per cent of the cohort was drawn from poor socio-economic conditions areas (approximately US $1500 per annum per household). A further 20% came from moderate income areas (approximately US $5500 per annum per household). Only 20% of the cohort spoke English as their home language. The majority of the cohort spoke Xhosa, the local African language (48%), or Afrikaans (28%). Demographic and clinical characteristics of the cohort are presented in Table 1.

Regimens containing protease inhibitors were used by 120 (41.5%) patients. Ninety-four (32.5%) patients received non-nucleoside based regimens, 30 (10.4%) took triple nucleoside regimens and 45 (15.6%) of the patients, who commenced treatment in 1996, received dual nucleoside reverse transcriptase inhibitor therapy. Fifty-five percent of the cohort took more than 10 tablets a day and 41% had dietary restrictions related to antiretroviral medication.

Treatment discontinuation

Forty-seven patients (16.2%) discontinued therapy within 48 weeks. Those who discontinued were significantly younger, and had increased viral loads at baseline, with lower CD4 cell counts. Socio-economic status, sex, language spoken at home and WHO stage of HIV illness were not associated with discontinuation.

Treatment adherence and viral suppression

The median adherence of the cohort up to 48 weeks was 93.5% (mean, 87.2%; n, 278). This includes eight patients who did not return any tablets after continuing therapy beyond 4 weeks and who were assigned 0% adherence. Sixty-three percent of the patients main-

Table 1. Baseline characteristics of the cohort (n, 289): patients who completed 48 weeks of therapy were compared with those who withdrew before 48 weeks. Chi-squared analysis for categorical data and t tests for continuous data show that there was no significant difference in the groups with regards to sex, socio-economic status, HIV stage and home language. The group withdrew were significantly younger, and had increased viral loads with decreased CD4 cell counts at baseline.

Characteristic	Completed [n (%)]	Discontinued [n (%)]	*P*
Total number of patients	242	47	
Mean age [years (SD)]	34.1 (8.4)	31 (8.6)	$P < 0.05$[a]
Female	105 (43.4)	19 (40.4)	$P = 0.7$
Home language (English)	47 (19.4)	10 (21.2)	$P = 0.8$
WHO stage (3 or 4)	119 (49.2)	18 (38.3)	$P = 0.2$
Low socio-economic status	103 (43.6)	17 (36.2)	$P = 0.4$
Mean CD4 cell count (SD)	268 (165.2)	197 (147.8)	$P < 0.01$[a]
Mean $\log_{10}$ viral load (SD)	5.49 (0.67)	5.71 (0.75)	$P < 0.05$*

[a]t test for age, viral load, CD4 cell count), χ^2 test for the remaining variables.

tained adherence of ⩾ 90% to the prescribed tablets. There was no significant difference in adherence to protease regimens compared to non-nucleoside based regimens. The proportion of subjects in each adherence category is illustrated in Fig. 1.

Dosing interval, age and speaking English at home were independently associated with incomplete adherence (Table 2). Medication-related food restrictions (RR, 1.01; 95% CI, 0.63–1.63), taking 10 or more tablets a day (RR, 1.23; 95% CI, 0.77–1.98), low socio-economic status (RR, 1.42; 95% CI, 0.88–2.29) and HIV stage 3 or 4 (RR, 0.90; 95% CI, 0.56–1.45) were not significantly associated with adherence in univariate models and therefore were not included in the multivariate model.

Adherence, modeled as a continuous variable, was significantly associated with reduction in viral load at 48 weeks (r, −0.2923; $P = 0.001$). Of those who reached 48 weeks of therapy (n, 242), 66.1% had a viral load of < 400 HIV RNA copies/ml. This included 70.9% of those on triple therapy and 41.0% of those on dual therapy. For those who were ⩾ 95% adherent at 48 weeks, 73.4% had a viral load of < 400 copies/ml compared with only 61.0% of those whose adherence was < 95% ($P = 0.018$).

Independent predictors of virologic failure included baseline viral load, three times daily dosing, adherence < 95%, age and dual nucleoside therapy. Taking 10 or more tablets a day (RR, 1.11; 95% CI, 0.57–2.17) and medication-related food restrictions (RR, 1.95; 95% CI, 0.95–4.03) were not independently associated with virologic failure at 48 weeks (Table 3).

Discussion

We found that indigent patients recruited from the greater Cape Town area, receiving free therapy on clinical trials, took 93.5% of their medication as measured by clinic-based pill count and, of those on triple therapy, 70.9% maintained a viral load of < 400 copies at 1 year in the absence of formal adherence intervention. This data is consistent with the high levels of self-reported adherence and viral suppression in poor patients receiving ART in Senegal [14]. This level of adherence and viral suppression is similar to or better than that reported in most observational and clinical trial cohorts in developed countries where objective measures of adherence indicate that patients take 70% of their HIV antiretroviral medications (range 53–93%) and rate of viral load suppression is 50% (range 37–72%) on similar regimens [6–10,16–18].

Living in poor socio-economic circumstances, as defined by the Cape Metropolitan Council index, did not impact on adherence to therapy [15]. In contrast to our study, most patients receiving ART in sub-Saharan Africa directly purchase their medications and pay for

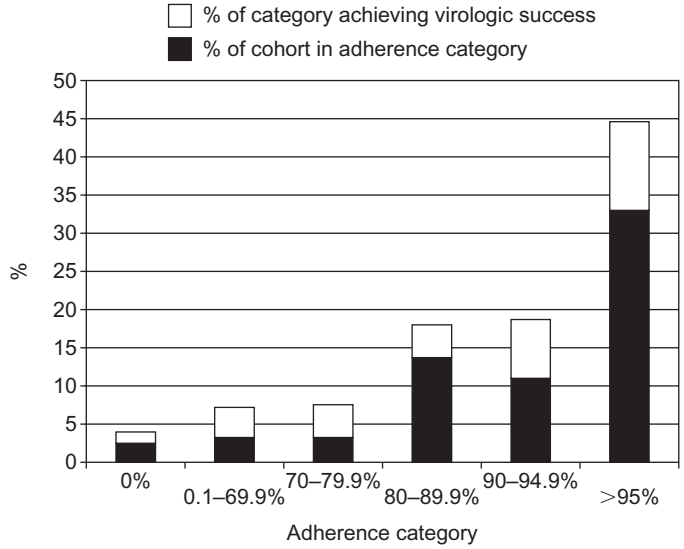

Fig. 1. Proportion of patients in each adherence category at 48 weeks (n, 242). Each full column represents the percentage of the cohort (n, 278) in each adherence category. The actual numbers per category are given below the graph. The 11 people with no tablet returns are recorded as 0% adherence. The dark shaded area within each column reflects the proportion of patients in that adherence category who achieved an undetectable viral load at 48 weeks. The actual percentage that achieved virologic success is recorded below the graph.

Table 2. Three times daily dosing predicted adherence < 95% in both the univariate and multivariate analyses. Increasing age and speaking English as a home language were protective against poor adherence in both analyses. Socio-economic index, sex, number of tablets per day, medication-related food restrictions and stage of HIV disease did not impact on adherence.

	Univariate analysis		Multivariate analysis	
Variables	RR	95% CI	RR	95% CI
Age	0.97	0.94–0.99	0.97	0.94–0.99
Home language (English)	0.45	0.25–0.84	0.41	0.21–0.80
Dosing (three times a day)	2.07	1.11–3.84	3.07	1.40–6.74

RR, Risk ratio; CI, confidence interval.

Table 3. In the univariate analysis baseline viral load, three times daily dosing, dual nucleoside regimens, taking more than 10 tablets a day and medication-related food restrictions predicted virological failure (> 400 HIV RNA copies/ml) at 48 weeks. Increasing age and adherence > 95% were protective against failure. In the multivariate model baseline viral load, three times daily dosing and adherence < 95% predicted virological failure. Increasing age remained protective.

	Univariate analysis		Multivariate analysis	
Variables	RR	95% CI	RR	95% CI
Age	0.98	0.97–0.99	0.96	0.92–0.99
Baseline viral load (log_{10})	2.71	1.74–4.25	2.57	1.57–4.22
Dosing (three times a day)	5.58	2.96–10.52	2.64	1.23–5.66
Adherence (< 95%)	2.13	1.22–3.57	1.92	1.10–3.57
Antiretroviral therapy (two NRTI)	3.94	1.96–7.89	2.69	1.17–6.15
Tablets (> 10 a day)	1.85	1.08–3.16	1.11	0.57–2.17
Food restrictions	3.57	1.97–6.49	1.95	0.95–4.03

RR, Risk ratio; CI, confidence interval. NRTI, Nucleoside reverse transcriptase inhibitor.

the cost of monitoring which can be a significant barrier to sustained treatment adherence [19]. Our results suggest that poor patients in sub-Saharan Africa can have successful treatment outcomes when the financial barriers to treatment are removed.

Three times daily therapy was the strongest predictor for both poor adherence and virologic failure in the multivariate analyses. Food restrictions on medication taking and absolute tablet count did not impact on adherence in this cohort and only predicted poor virologic outcomes at a univariate level. Several other studies have also shown that the best improvement in adherence comes with the reduction of dosing frequency from three to two times a day, but have also shown a negative effect of increasing tablet burden on adherence, which this study did not [20,21].

Increasing age was found to correlate with a higher likelihood of remaining on therapy for 48 weeks, as well as improved adherence and virological outcomes. This has been noted in recent literature and is particularly relevant given the rapid increase in HIV seroprevalence in young (19–25-year-old) South Africans [18,22,23].

The home language of each patient was collected as a demographic factor on the hypothesis that patients speaking the same language as the site staff would have an adherence advantage compared to those who were being educated in a second language. People who spoke English, did appear have an adherence benefit. This was unrelated to socio-economic status.

Adherence above 95% to treatment regimens predited virological success. Other factors which impacted on virologic outcome included baseline viral load and regimen type. We noted decreased virologic success with dual nucleoside therapy. Increased viral load at baseline reduced the likelihood of successful viral suppression after 1 year. These factors have been noted to impact similarly elsewhere [18,24].

In this study, clinical stage of HIV at commencement of therapy did not predict adherence, whereas this has been previously reported as a significant predictor [3,20]. Individuals with or without AIDS had the same adherence. Patients in this cohort, in view of their poor socio-economic circumstances and the lack of availability of ART in the South African public sector, may have similar adherence because of the global recognition of the lack of other options for therapy.

In this edition of *AIDS*, Liechty and Bangsberg [25]

argue that the anticipated need to deliver ART as directly observed therapy in developing countries may be premature [3,5,26]. Our results which indicate that poor patients in sub-Saharan Africa can achieve high rates of adherence and viral suppression in the absence of formal adherence intervention support this view.

We used clinic-based pill counts as the primary adherence measure. Whilst there are other measures of adherence that may more accurately reflect pill-taking behavior than clinic-based pill counts [7,8,27–30], this was the only practical and objective method that gave consistent, comparable data across different ART trials. Patients were generally not informed that returns were counted, although this information was not purposefully withheld. Tablet counts are widely used as a marker for adherence [8,11,22,28,29,31]. Pill consumption, however, is not directly measured and therefore the data may represent the upper boundary of actual patient adherence. Patients may not bring in all their medications or some may empty (pill dump) their bottles prior to a clinic visit [22,30]. While these possibilities cannot be excluded, the high rate of viral suppression combined with the significant association between adherence and viral load data suggest the tablet counts in this study correlated with actual adherence. Other investigators have also found a close association between similar clinic-based refill data, as a proxy for adherence, and HIV viral load as well as HIV clinical outcomes, including AIDS and death [12,13, 16,32,33].

The decision to enter patients onto therapy in this study was made on clinical and immunologic criteria; however it is possible that there may have been a selection bias towards patients likely to have better adherence than the general population. ART is not widely available in Cape Town, and, out of large numbers of people with HIV, this cohort was motivated enough to warrant referral from their primary care clinic to a secondary hospital. Subjects on trial also received information and encouragement on a regular basis from medical staff and counselors. This may have enhanced adherence and limit more general applicability.

Most subjects completed 48 weeks of therapy. Subjects who actively withdrew from therapy with in the 48 weeks of the study, tended to do so early in therapy. These patients were generally younger and, although they were not clinically more advanced in terms of disease staging, they tended to have more advanced immunologic and virologic disease. This may have resulted in increased adverse events leading to withdrawal through removal of consent, toxicity, or an HIV-related event. Other demographic factors, such as sex, language and socio-economic status, did not differ between those that withdrew and the rest of the cohort, confirming how difficult it is to predict patient behavior [8,9,34,35].

This study demonstrates that the high levels of adherence required to implement successful ART were achieved in an African cohort without formal adherence intervention. Factors impacting on adherence and virologic outcomes elsewhere were similarly reflected in this cohort. Clinical and virologic benefits were maintained after 1 year. Most importantly, low socioeconomic status was not a barrier to success. Individuals with HIV disease, who could potentially benefit from ART, should not be denied access based on otherwise unsubstantiated expectations of poor adherence.

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