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The Lancet; Nov 4-Nov 10, 2006; 368, 9547; ProQuest
pg. 1587

Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda

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Summary

Background Poverty and limited health services in rural Africa present barriers to adherence to antiretroviral therapy that necessitate innovative options other than facility-based methods for delivery and monitoring of such therapy. We assessed adherence to antiretroviral therapy in a cohort of HIV-infected people in a home-based AIDS care programme that provides the therapy and other AIDS care, prevention, and support services in rural Uganda.

Methods HIV-infected individuals with advanced HIV disease or a CD4-cell count of less than 250 cells per µL were eligible for antiretroviral therapy. Adherence interventions included group education, personal adherence plans developed with trained counsellors, a medicine companion, and weekly home delivery of antiretroviral therapy by trained lay field officers. We analysed factors associated with pill count adherence (PCA) of less than 95%, medication possession ratio (MPR) of less than 95%, and HIV viral load of 1000 copies per mL or more at 6 months (second quarter) and 12 months (fourth quarter) of follow-up.

Findings 987 adults who had received no previous antiretroviral therapy (median CD4-cell count 124 cells per µL, median viral load 217 000 copies per mL) were enrolled between July, 2003, and May, 2004. PCA of less than 95% was calculated for 0·7–2·6% of participants in any quarter and MPR of less than 95% for 3·3–11·1%. Viral load was below 1000 copies per mL for 894 (98%) of 913 participants in the second quarter and for 860 (96%) of 894 of participants in the fourth quarter. In separate multivariate models, viral load of at least 1000 copies per mL was associated with both PCA below 95% (second quarter odds ratio 10·6 [95% CI 2·45–45·7]; fourth quarter 14·5 [2·51–83·6]) and MPR less than 95% (second quarter 9·44 [3·40–26·2]; fourth quarter 10·5 [4·22–25·9]).

Interpretation Good adherence and response to antiretroviral therapy can be achieved in a home-based AIDS care programme in a resource-limited rural African setting. Health-care systems must continue to implement, evaluate, and modify interventions to overcome barriers to comprehensive AIDS care programmes, especially the barriers to adherence with antiretroviral therapy.

Lancet 2006; 368: 1587–94
Published **Online** August 4, 2006
DOI:10.1016/S0140-6736(06)69118-6
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Introduction

With the rapid expansion of access to combination antiretroviral therapy in resource-limited countries in Africa, Asia, South America, Central America, and the Caribbean, more people worldwide will have started therapy between 2004 and 2006 than in all the preceding years of the HIV/AIDS epidemic.[1–3] In response to this rapid increase, WHO has promoted a public-health approach to therapy that is standard and simple.[4] Among the many benefits of this approach are streamlined education and training about administration, tolerability, and adherence to antiretroviral therapy, which mean that learning about a few drugs is all that is needed. Good adherence to antiretroviral therapy is necessary to achieve the best virological response, lower the risk that drug resistance will develop, and reduce morbidity and mortality.[5] However, adherence barriers vary in different settings, and lessons from more developed countries[6] need to be adapted to resource-limited settings.[7] Good adherence to antiretroviral therapy has been shown in Africa,[8–14] though caution is needed about generalisation based on selective reporting of positive results, which are almost exclusively from urban areas.[15]

We describe adherence and virological response to antiretroviral therapy within the context of a novel home-based AIDS care programme in rural Uganda. The programme uses trained lay people who regularly visit participants at home to deliver medication and to collect information about adherence to antiretroviral therapy and possible toxic effects. The programme builds on studies of safe drinking water and prophylaxis with co-trimoxazole (trimethoprim and sulfamethoxazole) that lowered morbidity and mortality in the same community.[16,17]

Methods

Participants

In May, 2003, we began enrolling people in the home-based AIDS care programme in the Tororo and Busia districts of Uganda, a rural area where most people live in thatched houses in small villages. They are mostly subsistence farmers and are without access to municipal water supplies. Individuals eligible to be screened for participation in the project were clients of the AIDS Support Organization (TASO) and lived within a 100 km² area served by the organisation's regional branch.[18] This

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non-governmental organisation has provided HIV/AIDS care and support in Uganda since 1987. Medical criteria for antiretroviral therapy were that an HIV-infected person had a CD4-cell count of less than 250 cells per μL, or severe HIV disease defined as WHO stage 3 or 4, or a history of recurrent herpes zoster. Isolated pulmonary tuberculosis alone was not an inclusion criterion. The participants in the home-based AIDS care programme included in this analysis are part of a nested randomised trial on the efficacy of antiretroviral therapy, which is assessing three approaches: clinical monitoring only, clinical monitoring with quarterly CD4-cell counts, and clinical monitoring with quarterly CD4-cell counts and measurements of HIV viral load. Results from that trial will be presented elsewhere after 3 years of follow-up. A cost-effectiveness assessment of the home-based AIDS care programme will also be published elsewhere.

HIV-infected individuals not eligible for antiretroviral therapy were referred to TASO for co-trimoxazole prophylaxis and invited to return to our home-based AIDS care programme for rescreening after 6 months. Eligible clients were given antiretroviral therapy, co-trimoxazole prophylaxis, and treatment for tuberculosis and other illnesses when indicated. After enrolment, no routine clinic visits were scheduled, but medical officers saw patients at the programme's facility-based clinic when needed as determined by patients' self-referrals or protocol-driven referrals for illness or suspected drug toxicity from the field.

The Uganda National Council of Science and Technology and the institutional review boards of the Uganda Virus Research Institute, the University of California San Francisco, and the US Centers for Disease Control and Prevention approved the study. Informed consent to participate in the programme was obtained from each participant in English or one of six local languages.

Procedures

Counselling in the home-based AIDS care programme includes structured individual and group sessions on HIV prevention, care, and treatment. All counsellors employed for the programme were proficient in one or more of the six local languages and had previous experience in HIV/AIDS counselling, but none had experience with clients taking antiretroviral therapy. Counsellors were trained in rapport-building techniques and how to elicit information from participants on sensitive topics in a neutral, non-judgmental way. They were also instructed on the benefits, risks, and limitations of antiretroviral therapy, the delivery of consistent and accurate messages to achieve sustained long-term adherence, the proper administration of the regimens to be used in the programme, and the expected side-effects. Counsellors visited clients at enrolment, 1 month after enrolment, and then quarterly for the first year of the programme for routine data collection; they also provided extra adherence support as needed.

During screening for eligibility for antiretroviral therapy, counsellors educated clients on benefits and limitations of antiretroviral drugs. For those found to be eligible, counsellors made a home visit before treatment started for further education of the client, his or her family, and a medicine companion (eg, household member, neighbour) who committed to help the client with adherence for 6 months by observing him or her taking at least one dose of antiretroviral therapy daily. An individual adherence plan was developed to identify daily event reminders for adherence, supporting individuals in the household, and expected barriers to adherence that formed the basis for further counselling and support. A satisfactory adherence plan was the final basis for clearance to start antiretroviral therapy and was reviewed by the counsellor a month after initiation and annually thereafter.

Each week a team of 25–30 field officers delivered medications to the homes of about 1000 clients by motorcycle. They administered a questionnaire designed to elicit symptoms of potential illness, symptoms of drug toxicity, and self-reported adherence to antiretroviral therapy. Field officers, with training similar to that of community health workers in Africa, were trained to elicit adherence information from clients in a structured, non-judgmental way, and addressed adherence problems either by solving issues on the spot or by referring the participant to counsellors or clinicians for assistance with more complex issues.

The first-line treatment regimen was stavudine, lamivudine, and nevirapine (or efavirenz for individuals also taking rifampicin) as individual pills from innovator (brand name) companies. A 7-day supply of drugs was prepared in the pharmacy of the AIDS care programme and placed in a waterproof pill box with 14 slots (one each for morning and evening). All clients were also prescribed co-trimoxazole once daily, which was included in the pill box. During the preparedness phase, clients and medicine companions were taught how to use the pill box and were instructed to leave any missed doses in the box. Medicine companions were also trained to complete a simple pictorial form, adapted for a low-literacy population, to record doses taken by the client. Each week, the field officer delivered a new pill box, collected the previous week's box, noted any missed doses in the box, asked the client about the reasons for missing any doses, and coded the responses on a structured form. Pill boxes with missed doses, the corresponding field officers' forms, and medicine companions' forms were reviewed by the programme pharmacist for accuracy and completeness; discrepancies were resolved before data entry.

As part of the randomised monitoring trial, all clients had baseline and quarterly measurements of viral load and counting of CD4-positive cells. These quarterly results were made available to the medical officers dependent on the participants' group assignment in the masked randomised trial. Blood samples were drawn in participants' homes by phlebotomists and transported to the Centers

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for Disease Control and Prevention laboratory in Entebbe for processing. We measured HIV viral loads with a Cobas Amplicor HIV-1 Monitor version 1.5 (Roche, Branchburg, NJ, USA) and counted CD4-positive cells by use of TriTEST reagents, according to an in-house dual-platform protocol, and MultiSET and Attractors software with a FACScan flow cytometer (Becton-Dickinson, Franklin Lakes, NJ, USA).

Study population

For this analysis, we included antiretroviral-therapy-naive adults (aged 18 years or older) who started antiretroviral therapy between July, 2003, and May, 2004. Follow-up data up to June 30, 2005, were analysed. At enrolment and every 3 months thereafter, counsellors carried out private structured interviews with participants at their homes. At enrolment, the counsellor collected sociodemographic and clinical data and administered a modified Center for Epidemiologic Study depression scale. A questionnaire on adherence and antiretroviral therapy knowledge was administered quarterly to assess self-reported adherence, sharing of antiretroviral therapy or co-trimoxazole, reasons for missing doses, daily event reminders that were helpful to improve adherence, and support provided by the medicine companion. We linked each of these questionnaires to the viral-load measurement closest to it by date, using the viral-load value measured nearest to days 182 and 365 after the start of antiretroviral therapy (second and fourth quarters, respectively), but not more than 45 days before or after those dates.

We calculated pill count adherence (PCA) from data stored in the computerised pharmacy database as: (number of pills delivered minus number of pills returned) divided by number of pills delivered.

We also calculated a medication possession ratio (MPR) for each client that incorporated his or her pill-count data and any lapses in pill delivery that occurred when clients were on a drug holiday or were away from home on the delivery day.[19] We were thus able to estimate the proportion of time during an interval that each client had antiretroviral therapy available. MPR was calculated as (days' supply of drug delivered minus days' supply of drug returned) divided by number of days in the interval.

We used lamivudine tablets as the source for calculations of PCA and MPR since there were no changes of this drug as part of the first-line regimen, whereas single-drug substitutions for toxic effects were permitted for stavudine (to zidovudine) and nevirapine (to efavirenz). PCA and MPR results were very similar for patients who were taking lamivudine and either stavudine/zidovudine or nevirapine/efavirenz (data not shown).

Statistical analysis

We examined PCA and MPR for all four calendar quarters by summarising the mean, median, and range for these variables. We analysed sociodemographic, clinical, and programmatic factors associated with three outcomes in both the second and fourth quarters: PCA of less than 95%; MPR of less than 95%; and HIV viral load of at least 1000 copies per mL. We chose thresholds of 95% for defining low PCA and low MPR a priori because

	Number (% of total)
M/F	258 (26%)/729 (74%)
Age, years	
18–25	22 (2%)
26–35	364 (37%)
36–45	424 (43%)
46–55	142 (14%)
≥56	35 (4%)
Highest level of education completed	
None	220 (23%)
Primary	515 (54%)
Post primary	227 (24%)
Missing	25
Current marital status	
Single	40 (4%)
Married/cohabiting	359 (37%)
Separated/divorced	111 (12%)
Widowed	451 (47%)
Missing	26
Main source of income	
Farming	319 (33%)
Wage or salary	144 (15%)
Remittances	223 (23%)
Trade	274 (29%)
Missing	27
Depression scale*	
Depressed	433 (45%)
Not depressed	521 (55%)
Missing	33
Drinks alcohol†	
Yes	155 (16%)
No	831 (84%)
Missing	1
Received antiretroviral therapy in past (women only)‡	7 (1%)
Median (range) weight, kg	53 (32–96·5)
Body-mass index, kg/m²	
<18·5	299 (31%)
18·5–24·9	631 (64%)
25·0–29·9	39 (4%)
>30·0	10 (1%)
Missing	8
Baseline CD4-cell count, cells per μL	
Median (IQR)	124 (64–190)
<50	199 (20%)
50–99	195 (20%)
100–199	386 (39%)
200–250	177 (18%)
>250	30 (3%)

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Baseline viral load, copies per mL	
Median (IQR)	217 000 (76 500–533 000)
Mean	307 658
<1000	9 (1%)
1000–9999	33 (3%)
10 000–99 999	265 (27%)
≥100 000	680 (69%)
Negative expectations from antiretroviral therapy: more likely to§	
Feel weak	41 (4%)
Feel nauseous	153 (16%)
Lose appetite	29 (3%)
Get skin rash	144 (15%)
Feel more isolated	52 (5%)
Positive expectations from antiretroviral therapy: better able to§	
Eat more	942 (95%)
Dig/work more	946 (96%)
Do daily housework	953 (97%)
Pay school fees for children	817 (83%)
Contribute to family expenses	924 (94%)
Earn more money	923 (94%)
Associate more closely with family and friends	960 (97%)
Care for children	941 (95%)

*Modified Center for Epidemiologic Studies depression scale; 0–22 is deemed not to be depressed and 23–60 depressed. †From global question at baseline about medical history. ‡For prevention of mother to child transmission; single-dose nevirapine for six, unknown for one. §Knowledge/expectations at baseline. Responses missing for 18–23 instances and added to the denominator for this analysis.

***Table 1:* Characteristics of 987 participants**

	Quarter 1	Quarter 2	Quarter 3	Quarter 4
Number with antiretroviral therapy dispensed at least once	981	942	927	912*
Number with viral load available†	934	913	908	894
Questionnaire matched to viral load value‡	888	873	864	846
Number still using a medicine companion§	749	608	504	378
PCA, %				
Mean	99	>99	>99	>99
Median	100	100	100	100
Range	49–100	69–100	69–100	50–100
Number with PCA <95%	25 (2·6%)	14 (1·5%)	6 (0·7%)	7 (0·8%)
MPR, %				
Mean	98	99	99	99
Median	100	100	100	100
Range	15–100	20–100	15–100	15–100
Number with MPR <95%	109 (11·1%)	58 (6·2%)	31 (3·3%)	36 (4·0%)

*Excludes two patients who switched to second-line therapy during the fourth quarter. †Within 45 days of day 91, 182, 273, and 365 for quarters 1–4, respectively. ‡Questionnaire about adherence and antiretroviral treatment knowledge within 45 days of viral load. §Medicine companions were asked to commit to support the participant for only 6 months.

***Table 2:* PCA and MPR by quarter for 987 patients who started antiretroviral treatment**

non-adherence at this threshold has been linked to suboptimum virological and immunological responses in previous studies. We chose HIV viral load of 1000 copies per mL as the minimum threshold indicative of virological failure relevant to resource-limited settings below which clinicians would be unlikely to change therapy since there is in many such settings only one second-line regimen. Univariate associations were examined by Mantel-Haenszel relative risk with 95% CI and the χ^2 test or Fisher's exact test. Separate multiple logistic regression models were constructed to assess whether PCA or MPR of less than 95% was associated with HIV viral load of at least 1000 copies per mL during the second and fourth quarters. These models adjusted for two key predictors of virological response identified in univariate analyses: baseline CD4-cell count and baseline HIV viral load. The analysis team was unaware of participants' assignment in the efficacy-monitoring trial. Analyses were done with SAS (version 8.02).

Role of the funding source

Funding was provided by the US Centers for Disease Control and Prevention and the US Agency for International Development, through the US President's Emergency Plan for AIDS Relief. Staff at the Centers for Disease Control and Prevention participated in the design; collection, analysis, and interpretation of the data; writing of the report; and the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May, 2003, and December, 2004, 1139 people started antiretroviral therapy in the home-based AIDS care programme. This analysis includes 987 antiretroviral-naïve adults enrolled during their first screening for antiretroviral-therapy eligibility between July 1, 2003, and May 31, 2004 (table 1).

Before learning about the home-based AIDS care programme, 581 (59%) of 987 participants had heard of antiretroviral drugs. At baseline and after initial counselling, 967 (98%) participants believed they would be able to take antiretroviral drugs daily, 48 (5%) participants believed they would need to stop taking antiretroviral therapy owing to side-effects, and seven of 883 (missing data for 104) expected to be pressured to share the drugs. Before enrolling in the programme, 939 (97%) of 969 clients (missing data for 18) were taking daily co-trimoxazole prophylaxis and 287 (31%) of 932 (missing data for 55) had used a medicine companion for this treatment. In the 30 days before the interview, 332 (36%) of 926 participants reported missing at least one dose of co-trimoxazole and 57 (6%) of 931 participants reported sharing it with another person.

The numbers of participants to whom antiretroviral therapy was dispensed at least once, available viral loads,

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and numbers with matching questionnaires on adherence and antiretroviral-therapy knowledge and of participants still using a medicine companion for each quarter are given in table 2. During the first four quarters, 72 (7%) of 987 participants were known to have died and one was lost to follow-up. By the end of the fourth quarter, two participants had been switched to a second-line regimen: tenofovir, didanosine, and lopinavir or ritonavir. At each quarterly interview, self-reported adherence to antiretroviral drugs was "excellent" for 74–81%, "good" for 19–24%, and "fair/poor" for less than 2% of participants. The proportion of participants who reported missing any doses of antiretroviral drugs in the previous 3 months ranged from 10% to 21%; the commonest reasons for missing were being away from home (3·2–5·9%) and forgetting (3·5–5·7%). No other single reasons for missing doses were reported by more than 2% of participants in more than one quarter. 0·5–1·4% of participants reported they were under pressure to share antiretroviral drugs in any quarter; however, actual sharing of the drugs was reported only once. In the week before the quarterly interviews, medicine companions were present to observe participants take pills seven or more times for 73–83% of participants, five to six times for 4–6% of participants, two to four times for 9–15% of participants, and once or no times for 4–6% of participants. The most important aids to taking drugs on schedule were daily events as reminders (45–52%), support from the medicine companion (13–19%), the weekly visit of the field officer (10–14%), and support from the counsellor at the home-based AIDS care programme (1–3%); other reasons were given by 18–25%. 106 participants had 125 extra adherence sessions with a counsellor: in the first quarter for nine, second quarter for 42, third quarter for 36, and fourth quarter for 38.

Up to June, 2005, the pharmacy at the home-based AIDS care programme dispensed 3 291 577 antiretroviral pills in 83 205 weekly pill boxes delivered by field officers. For all individual drug products, more than 99% of pills delivered were not returned. 8769 (<1%) pills were returned to the pharmacy untaken owing to non-adherence in 1382 (2·1%) pill boxes. Participants provided 1416 reasons for non-adherence: forgetfulness for 533 (38%), pills not available (because the participant was away from home at the dose time or another reason) for 471 (33%), concurrent condition for 243 (17%), instructions from the health-care provider for 41 (3%), toxicity for 37 (3%), medication fatigue for 13 (1%), pills not working for six, and other reasons for 72 (5%).

Quarterly mean PCA was at least 99% (table 2), and PCA of less than 95% was calculated for 0·7–2·6% of participants in any quarter. Quarterly mean MPR was 98–99% and MPR of less than 95% was calculated for 3·3–11·1% of participants in any quarter. Univariate analyses for the second and fourth quarters showed that PCA and MPR below 95% were associated with few sociodemographic or clinical characteristics of participants (table 3).

	Second quarter			Fourth quarter		
	PCA<95%	MPR <95%	Viral load ≥1000 copies per mL*	PCA<95%	MPR <95%	Viral load ≥1000 copies per mL*
Sex						
Women	1·00	1·00	1·00	1·00	1·00	1·00
Men	1·16 (0·37–3·66)	0·92 (0·51–1·65)	1·32 (0·51–3·44)	0·48 (0·06–4·00)	1·85 (0·96–3·56)	1·26 (0·61–2·60)
Age, years						
>35	1·00	1·00	1·00	1·00	1·00	1·00
≤35	1·56 (0·55–4·42)	0·89 (0·53–1·49)	1·39 (0·57–3·38)	2·10 (0·47–9·27)	0·88 (0·45–1·72)	1·10 (0·56–2·14)
Education						
None	0·29 (0·04–2·32)	0·91 (0·45–1·87)	0·56 (0·12–2·68)	NE (p=0·96)	0·20 (0·05–0·85)	0·79 (0·31–2·04)
Primary	1·00	1·00	1·00	1·00	1·00	1·00
Post-primary	1·13 (0·34–3·80)	1·49 (0·81–2·76)	2·53 (0·96–6·64)	3·07 (0·68–13·83)	1·26 (0·61–2·60)	1·51 (0·70–3·29)
Marital status						
Single	1·92 (0·22–16·86)	1·54 (0·43–5·46)	1·32 (0·16–11·05)	NE (p=0·98)	1·71 (0·48–6·15)	1·55 (0·34–7·26)
Married/ cohabitating	1·00	1·00	1·00	1·00	1·00	1·00
Separated/ divorced	2·01 (0·47–8·55)	1·23 (0·50–3·02)	1·44 (0·37–5·68)	1·12 (0·12–10·85)	0·58 (0·17–2·01)	0·55 (0·12–2·54)
Widowed	0·65 (0·17–2·42)	1·21 (0·66–2·20)	0·93 (0·33–2·59)	0·80 (0·16–3·98)	0·60 (0·29–1·25)	1·19 (0·57–2·53)
Main source of income						
Farming	1·00	1·00	1·00	1·00	1·00	1·00
Wage or salary	4·46 (0·40–49·59)	1·64 (0·65–4·17)	3·17 (0·99–10·18)	1·52 (0·25–9·24)	1·16 (0·42–3·15)	1·71 (0·64–4·60)
Remittances	7·59 (0·88–65·49)	3·37 (1·61–7·08)	1·23 (0·33–4·67)	1·08 (0·18–6·54)	0·95 (0·37–2·44)	0·82 (0·28–2·43)
Trade	6·00 (0·70–51·73)	1·65 (0·74–3·66)	0·71 (0·17–3·00)	NE (p=0·95)	1·10 (0·48–2·54)	1·48 (0·62–3·48)
Depression scale						
0–22	1·00	1·00	1·00	1·00	1·00	1·00
23–60	1·79 (0·56–5·68)	1·32 (0·79–2·20)	1·15 (0·46–2·87)	1·74 (0·39–7·80)	1·29 (0·68–2·45)	2·09 (1·06–4·11)
Drinks alcohol						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	0·41 (0·05–3·01)	0·61 (0·27–1·39)	0·29 (0·04–2·17)	0·86 (0·10–7·04)	1·47 (0·68–3·17)	1·14 (0·48–2·71)
Any previous co-trimoxazole treatment						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	0·99 (0·06–16·4)	1·83 (0·26–12·8)	NE (p=0·55)	0·20 (0·03–1·60)	1·16 (0·17–8·21)	NE (p=0·62)
Pre-existing client of TASO						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	0·52 (0·07–3·84)	1·11 (0·28–4·38)	NE (p=0·46)	0·24 (0·03–1·93)	0·68 (0·17–2·71)	1·23 (0·17–8·68)
Baseline CD4-cell count, per µL						
>100	1·00	1·00	1·00	1·00	1·00	1·00
0–99	2·09 (0·73–6·00)	1·69 (1·02–2·77)	8·54 (2·51–29·1)	0·27 (0·03–2·23)	0·81 (0·41–1·61)	1·95 (1·02–3·74)

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Baseline viral load, copies per mL						
<100 000	1·00	1·00	1·00	1·00	1·00	1·00
≥100 000	6·10 (0·80–46·5)	1·80 (0·97–3·35)	8·55 (1·15–63·7)	0·63 (0·14–2·81)	0·75 (0·39–1·44)	2·76 (1·08–7·04)
Missed taking antiretroviral therapy in previous 3 months†						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	11·0 (2·79–43·5)	5·02 (2·86–8·81)	2·29 (0·82–6·40)	4·92 (0·83–29·1)	5·73 (2·94–11·2)	3·88 (1·86–8·10)
Self-reported adherence to antiretroviral therapy†‡						
Good/fair/poor	1·00	1·00	1·00	1·00	1·00	1·00
Excellent	0·08 (0·02–0·36)	0·35 (0·20–0·62)	0·49 (0·18–1·30)	0·39 (0·07–2·32)	0·44 (0·22–0·87)	0·37 (0·18–0·76)
Still using medicine companion†						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	1·52 (0·32–7·27)	0·76 (0·41–1·38)	1·04 (0·37–2·93)	NE (p=0·07)	0·74 (0·37–1·50)	0·76 (0·36–1·59)
Extra counselling visit for adherence§						
No	1·00	1·00	1·00	1·00	1·00	1·00
Yes	0·72 (0·04–11·9)	1·59 (0·60–4·18)	0·55 (0·03–8·68)	NE (p=1·00)	2·96 (1·10–7·92)	1·45 (0·36–5·81)
PCA						
≥95%			1·00			1·00
<95%			14·1 (4·7–42·0)			7·92 (2·34–26·8)
MPR						
≥95%			1·00			1·00
<95%			10·3 (4·24–25·0)			7·33 (3·57–15·0)

NE=not evaluable because at least one cell's value was zero. *Value closest to 182 days (+/–45 days) for second quarter and 365 days (+/–45 days) for fourth quarter. †Answer to question from quarterly questionnaire on adherence and antiretroviral therapy knowledge; answered yes to missing medicines for any of 14 a-priori defined potential responses as well as other open-ended self-reported responses. "People may miss taking their medicines for various reasons. Here is a list of possible reasons why you may miss taking your medicines. In the last 3 months, have you ever missed taking your medicines...?" ‡Participants were asked the following: "Which of the following words best describes how well you have done to stay on the schedule your doctor gave you for taking your antiretroviral medicines? Excellent, Good, Fair, Poor". §Unscheduled visits to client's home to address adherence problems.

***Table 3*: Relative-risk estimates by univariate analyses of associations between participants' characteristics and PCA, MPR, and viral-load outcomes in second and fourth quarters**

	Odds ratio (95% CI) for viral load ≥1000 copies per mL	
	Second quarter	Fourth quarter
Model 1		
PCA <95%	10·6 (2·45–45·7)	14·5 (2·51–83·6)
Baseline CD4-cell count 0–99 cells per µL	6·74 (1·92–23·7)	1·75 (0·86–3·57)
Baseline viral load ≥100 000 copies per mL	5·02 (0·65–38·73)	2·64 (0·99–7·06)
Model 2		
MPR <95%	9·44 (3·40–26·2)	10·5 (4·22–25·9)
Baseline CD4-cell count 0–99 cells per µL	6·63 (1·89–23·4)	1·71 (0·83–3·51)
Baseline viral load ≥100 000 copies per mL	5·45 (0·71–42·1)	2·81 (1·04–7·62)

For multivariate analyses of virological response, we constructed separate models for PCA (model 1) and MPR (model 2) because the two measures were highly correlated. In addition, the models adjusted for CD4-cell count and viral load at baseline; no other covariates were consistently associated with virological outcome. PCA and MPR were both modelled as <95% *vs* ≥95%. Baseline CD4-cell count was modelled as 0–99 cells per µL *vs* ≥100 cells per µL. Baseline viral load was modelled as ≥100 000 copies per mL *vs* <100 000 copies per mL.

***Table 4*: Multivariate model for viral load ≥1000 copies per mL in second quarter and fourth quarters**

During follow-up, most participants achieved a viral load of less than 1000 copies per mL: 894 (98%) of 913 participants in the second quarter and 860 (96%) of 894 in the fourth quarter. Viral load above this threshold was significantly associated with PCA and MPR of less than 95% in separate univariate analyses. In the second quarter, three (25%) of 12 participants with PCA less than 95% compared with 16 (2%) of 901 participants with PCA over 95% had viral loads of at least 1000 copies per mL (p=0·0014); the corresponding proportions in the fourth quarter were two (29%) of seven participants with PCA less than 95% and 32 (4%) of 887 participants with higher PCA (p=0·025). For MPR, in the second quarter seven (14%) of 49 participants with a value less than 95% versus 12 (1%) of 864 participants with a value above 95% had a viral load of at least 1000 copies per mL (p<0·0001); in the fourth quarter the proportions were eight (22%) of 36 with values below 95% versus 26 (3%) of 858 with higher values (p<0·0001). Viral load of at least 100 000 copies per mL at baseline and CD4-cell count of less than 100 cells per µL at baseline were significantly associated with viral load of at least 1000 copies per mL in both the second and fourth quarters (table 3).

Because PCA and MPR were closely correlated, we examined virological response by constructing separate multivariate models that included viral load and CD4-cell count at baseline and either PCA or MPR of less than 95%. For the second and fourth quarters, both PCA less than 95% or MPR less than 95% were associated with viral load of at least 1000 copies per mL when adjusted for CD4-cell count and viral load at baseline (table 4).

Discussion

The comprehensive home-based model of AIDS care used in this rural African setting resulted in excellent retention in care and adherence to antiretroviral therapy in a population with limited access to transportation and health-care services. Good adherence to antiretroviral therapy was associated with suppressed viral load that was sustained in most surviving clients during their first year on antiretroviral therapy. The programme removed the external economic constraints to retention in care and adherence by providing free antiretroviral therapy with home delivery. Patients have extreme difficulty in accessing transportation to a health centre in rural Africa, and the requirement to pay for antiretroviral therapy has been associated with worse treatment outcomes in Uganda.[20] The comprehensive approach to supporting adherence in the home-based AIDS care programme, which included medicine companions, more extensive counselling, development of personal adherence plans, and weekly visits by field officers, successfully addressed barriers to adherence and achieved an excellent virological response. These interventions increased logistical needs and costs, but the lessons learned from this approach should spur evaluation of other models of home delivery of AIDS care that could achieve similar results with less investment.

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We measured adherence in two complementary ways—PCA and MPR. Values of less than 95% for either of these measures were associated with the failure to achieve virological suppression to below 1000 copies per mL. The MPR is analogous to pharmacy refill information, since it reflects the actual possession (dispensing) of medication over time.[21] The MPR differs from traditional adherence measures (pill count) by accounting for the gaps in time when a participant does not have medicine based on refill patterns. MPR could become an important measure in adherence assessments, particularly for Africa, where unreliable drug supplies and distribution networks can be major barriers to medication adherence that are beyond patients' control. Although PCA and MPR values might to some degree exaggerate adherence (eg, if participants discarded pills without the knowledge of the field officer), our findings suggest that values of less than 95% identify non-adherent patients well and are associated with HIV viral load of more than 1000 copies per mL.

The retention in care of all but one participant in this programme shows that HIV-infected people in rural Africa can continue in a longitudinal care model that benefits their health and welfare. Programmes in which participants pay for part or all of their antiretroviral therapy have experienced high rates of drop-outs, presumably due mostly to financial constraints.[22–27] Retention in care will remain an important indicator for treatment programmes in resource-limited settings, and other reports of good retention in care are encouraging.[14,28,29]

As access to antiretroviral therapy expands in resource-limited settings, programmes need to address how to overcome transportation constraints. Purely facility-based approaches will probably be insufficient to achieve optimum adherence for many geographic regions. In Uganda, where the majority of HIV-infected people reside in rural areas and families live on less than US$1/day per person,[30] transportation costs can pose an important barrier to adherence success. Home delivery of antiretroviral therapy could reduce this barrier, although direct weekly delivery to clients' homes might not be achievable in all settings. Home delivery might be more feasible on a monthly or quarterly basis, which would reduce costs substantially and allow a single field officer to cover between 100 and 300 participants. Reduced frequency of delivery could be implemented after the first few weeks of antiretroviral therapy, once initial adherence issues and toxic effects have been addressed. TASO has implemented monthly home deliveries of antiretroviral therapy as its standard practice for about 8000 clients registered at its other centres in Uganda. Combination facility-based and community outreach models might also be worth exploring, such as medication delivery to peripheral health workers who in turn distribute the medications to clients in their catchment area and collect basic information on health status and adherence that they return to the facility.

Our findings should be interpreted in light of several caveats. This cohort was drawn from a pool of people who had already joined a community AIDS organisation in which participants were encouraged to disclose HIV status to others or had already done so. Many households had already participated in a home-based study. Thus, our findings may not reflect the degree of adherence to antiretroviral therapy in African populations with less community-based support. Because of the small number of individuals who had PCA or MPR of less than 95% or who had viral loads of 1000 copies per mL or higher, our relative-risk estimates for many covariates were imprecise. We may not have detected some weaker associations between characteristics of participants and these outcomes owing to insufficient statistical power. Conversely, owing to the large number of potential associations we explored in univariate analyses, some significant ($p<0·05$) associations could have occurred by chance alone. To address this possibility, in the multivariate analyses of predictors of virological non-response we included only the four factors that were clinically plausible predictors for viral load of at least 1000 copies per mL and were significantly associated with this outcome consistently in both the second and fourth calendar quarters. We implemented a comprehensive package of adherence support measures, but because all participants received the same care and there is no control group, we cannot assess the effects of specific components of the programme, including the effect of home-based weekly delivery, use of medicine companions, development of personal adherence plans, intensive counselling, or use of pill boxes that provided a convenient method for storing and protecting medications. We cannot assess the potential influence on PCA, MPR, or virological outcomes of participants' assignment in the current trial monitoring antiretroviral-therapy efficacy, but these analyses are planned on the completion of the trial.

We have found that good adherence to antiretroviral therapy and corresponding high rates of sustained virological suppression can be achieved in a resource-limited area in a rural African setting. We were also able to demonstrate retention in care at a proportion that would have been unthinkable a few years ago. Health-care systems must continue to implement, evaluate, and modify interventions to overcome barriers to comprehensive AIDS care programmes, including improvement in adherence to antiretroviral therapy and retention in care. These steps will be necessary to bring effective AIDS care to the millions of HIV-infected people in less developed countries who need it.

Contributors

Paul J Weidle, Nafuna Wamai, Cheryl Liechty, Peter Solberg, Willy Were, Jonathan Mermin, and Rebecca Bunnell conceived the study. Paul J Weidle, Rebecca Bunnell, Cheryl Liechty, Peter Solberg, Jonathan Mermin, Nafuna Wamai, Willy Were, Sam Sendagala, Prosper Behumbiize, and Ray L Ransom designed it. Paul J Weidle, Kate Buchacz, Rebecca Bunnell, Prosper Behumbiize, and

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Ray L Ransom did the analysis. Paul J Weidle, Nafuna Wamai, Cheryl Liechty, Kate Buchacz, and Rebecca Bunnell led the writing of the report. All the authors reviewed and contributed to the report. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

We thank the volunteers, staff, and clients of TASO; the staff of CDC-Uganda; and the Global AIDS Program Headquarters.

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