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ORIGINAL RESEARCH

Health care provider communication training in rural Tanzania empowers HIV-infected patients on antiretroviral therapy to discuss adherence problems

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Objectives

Self-reported adherence assessment in HIV-infected patients on antiretroviral therapy (ART) is challenging and may overestimate adherence. The aim of this study was to improve the ability of health care providers to elicit patients' reports of nonadherence using a "patient-centred" approach in a rural sub-Saharan African setting.

Methods

A prospective interventional cohort study of HIV-infected patients on ART for ≥ 6 months attending an HIV clinic in rural Tanzania was carried out. The intervention consisted of a 2-day workshop for health care providers on patient-centred communication and the provision of an adherence assessment checklist for use in the consultations. Patients' self-reports of nonadherence (≥ 1 missed ART dose/4 weeks), subtherapeutic plasma ART concentrations (< 2.5th percentile of published population-based pharmacokinetic models), and virological and immunological failure according to the World Health Organization definition were assessed before and after (1–3 and 6–9 months after) the intervention.

Results

Before the intervention, only 3.3% of 299 patients included in the study reported nonadherence. Subtherapeutic plasma ART drug concentrations and virological and immunological failure were recorded in 6.5%, 7.7% and 14.5% of the patients, respectively. Two months after the intervention, health care providers detected significantly more patients reporting nonadherence compared with baseline (10.7 *vs*. 3.3%, respectively; $P < 0.001$), decreasing to 5.7% after 6–9 months. A time trend towards higher drug concentrations was observed for efavirenz but not for other drugs. The virological failure rate remained unchanged whereas the immunological failure rate decreased from 14.4 to 8.7% at the last visit ($P = 0.002$).

Conclusions

Patient-centred communication can successfully be implemented with a simple intervention in rural Africa. It increases the likelihood of HIV-infected patients reporting problems with adherence to ART; however, sustainability remains a challenge.

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Introduction

Antiretroviral treatment (ART) has dramatically decreased rates of HIV-related morbidity and mortality, but these effects critically depend on successful lifelong treatment. Adherence to ART is essential for the success of HIV treatment. Without sufficient adherence, treatment failure is much more likely to occur, leading to avoidable HIV-related morbidity and mortality, emergence of resistant HIV strains and ongoing HIV transmission [1–4]. Maintaining good adherence to ART is challenging for many HIV-infected patients, making nonadherence a frequent and important problem globally [5–9]. A meta-analysis of 84 observational studies from high- and low-income countries in 2011 found that only an average of 62% of HIV-infected patients reported a sufficient intake of ≥ 90% of the prescribed ART drugs [7].

Interventions to improve, support and sustain adherence to ART are clearly needed. Adherence is crucial for the individual but also from a public health perspective, particularly in light of the new World Health Organization (WHO) recommendations to treat all patients living with HIV regardless of CD4 count and to implement treatment as prevention [10].

Different approaches to improve adherence exist [11–15]. They are all based upon the reliable detection of nonadherence. Self-reported adherence is most commonly used for adherence assessment because it is inexpensive and easy to apply in almost all settings [16–18]. However, self-reports tend to overestimate adherence because of recall or social desirability bias [3,19–23].

In order to improve patients' adherence, health care providers must encourage patients to talk about adherence problems [24–26]. Patients must feel invited to talk about their personal views, including their perspective on medication adherence. Eliciting the patient's perspective is a central element of patient-centred communication [27]. This approach, advocated as a central element of high-quality medical care mainly in western settings [28–30], has received little attention in many low-income countries including sub-Saharan Africa where a "doctor-centred" approach is still more commonly applied [31,32].

The aim of this study was to examine whether a 2-day workshop focussing on "patient-centred" communication improves the ability of health care providers to elicit patients' reports of problems with adherence in the rural setting of sub-Saharan Africa [33–35].

Methods

Study setting

Our 1-year prospective interventional cohort study was conducted at the Chronic Diseases Clinic of Ifakara (CDCI) at the St Francis Referral Hospital in rural Tanzania from October 2013 until September 2014.

The CDCI is a governmental accredited HIV clinic that provides free medical care and antiretroviral drugs for HIV-infected patients in the framework of the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO). At the time of the study, approximately 3000 patients at the CDCI were taking ART. Thirteen Tanzanian health care providers, that is, six physicians, four nurses, two adherence counsellors and one pharmacist, cared for an average of 73 HIV-infected patients daily (range 36–133).

Study population

All consecutive HIV-infected patients presenting at the CDCI between October and November 2013 fulfilling the inclusion criteria were enrolled in the study. Inclusion criteria were HIV-infected adult ≥ 16 years, therapy with an efavirenz-, nevirapine-, lopinavir/ritonavir- or atazanavir/ritonavir-based ART regime for at least 6 months, and provision of written informed consent. Patients on treatment with rifampicin or other drugs potentially inducing ART drug metabolism and patients from other HIV clinics were excluded.

Intervention

All the Tanzanian health care providers (n = 13) with direct patient contact, including all six HIV physicians, received 2 days of training in the basic elements of patient-centred communication. Goals were defined as follows: to identify patients with nonadherenence, to identify their reasons for nonadherence, and to establish means to improve adherence. During the workshop, participants provided descriptions of difficult patient encounters and they identified their communication strategies when they had detected a patient with adherence problems, usually provision of information (see Fig. S1). Then, alternatives were offered and trained in role-plays among participants. Seminars were held in December 2013 and were delivered by an experienced communication teacher working in the HIV field (author W. Langewitz) [33–36]. In addition, all physicians received a written two-page adherence assessment

checklist, adapted from the published European AIDS Clinical Society 2011 guidelines [37], to facilitate future consultations and adherence assessment (see Fig. S2).

Study evaluations

All study patients were assessed by their physicians during their routine visits at the CDCI at three different time-points over 1 year (Fig. 1). No additional visits were scheduled for the study. The baseline visit (visit 1) took place at entry into the study. The communication training was performed shortly after completion of the baseline visits of all included patients. Follow-up visits were 1–3 months (visit 2) and 6–9 months (visit 3) after the intervention. Adherence, clinical parameters, comedications and laboratory HIV surrogate markers were evaluated at each study visit.

Self-reported adherence was assessed by the treating physicians using a validated short questionnaire that consisted of the following two questions as per the standard procedure in the CDCI [4,38,39]: (1) "How often have you missed a dose of your HIV medication in the past 4 weeks: daily, more than once a week, once a week, once every second week, once a month, never?" and (2) "Did you miss ART $\geq$ 2 days in a row in the last 4 weeks: yes or no?"

At each study visit, we carried out therapeutic drug monitoring (TDM) by measuring the plasma ART drug concentrations of efavirenz, nevirapine, lopinavir and atazanavir to assess short-term adherence. Plasma samples were analysed with a validated liquid chromatography tandem mass spectrometry method (LC-MS/MS; API 4000 QTrap; AB Sciex, Massachusetts, USA) at the analytical laboratory of the Division of Clinical Pharmacology at the University Hospital Basel (Basel, Switzerland).

CD4 cell count and HIV RNA were measured at every study visit. CD4 cell counts were analysed using a flow cytometry system (FACS Calibur; BD Company, Franklin Lakes, NJ). HIV RNA was prepared using the semi-automated extractor platform Prepito (PerkinElmer chemagen, Baesweiler, Germany) and quantified using a validated protocol [40] at the CDCI laboratory and a reference laboratory at the University of Basel (Basel, Switzerland).

All plasma sample aliquots for HIV RNA and ART TDM were stored at −80°C and shipped on dry ice to the reference laboratory in Switzerland for analysis.

HIV RNA and TDM results were not available to the health care providers before visit 3 for logistical reasons.

Definitions

Self-reported nonadherence in the questionnaire was defined as having missed at least one dose of ART medication in the last 4 weeks. We considered other less strict definitions of nonadherence: having missed at least two ART doses and having missed at least two consecutive ART doses (drug holidays) in the last 4 weeks. For TDM, an inadequate subtherapeutic drug concentration as a marker for nonadherence was defined as any concentration below the 2.5th percentile of published population-based pharmacokinetic models for efavirenz 600 mg once daily [41], nevirapine 200 mg twice daily [42], lopinavir/ritonavir 400/100 mg twice daily [43] and atazanavir/ritonavir 300/100 mg once daily [44]. Clinical failure was

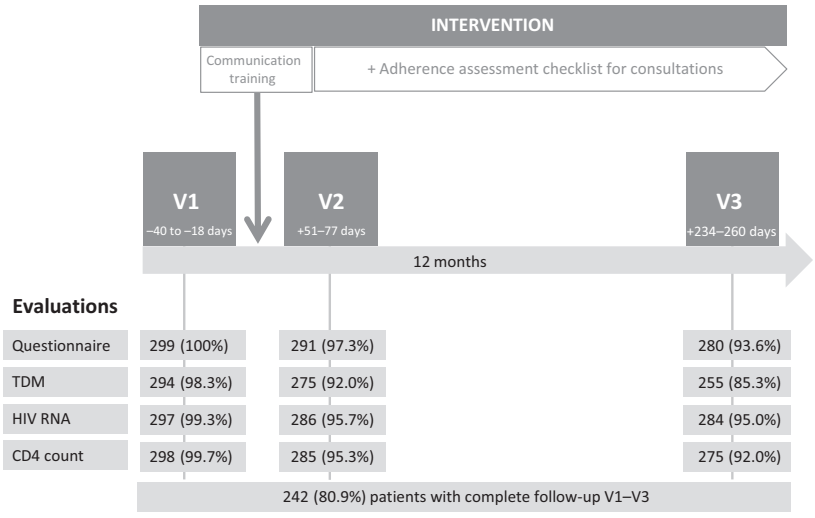

Fig. 1 The study algorithm. V1, visit 1 (baseline visit); V2, visit 2; V3, visit 3; Questionnaire, self-reported adherence questionnaire; TDM, therapeutic drug monitoring; days, days between the evaluation and the communication training (interquartile range); numbers represent numbers of patients.

defined as the occurence of any new WHO AIDS-defining disease, death, or loss to follow-up at visits 2 and 3. Virological failure was defined according to the WHO 2014 guidelines as a detectable HIV RNA of ≥ 1000 copies/ml. Immunological failure was defined as a decrease in CD4 count to below the baseline value at HIV diagnosis, a fall of > 50% from the value at the baseline study visit (visit 1), or persistent CD4 cell count < 100 cells/μl [45].

Primary and secondary endpoints

The primary endpoint was the rate of patients' self-reported nonadherence, defined as at least one missed ART dose in the last 4 weeks, detected by the physician after the teaching intervention (visits 2 and 3) compared with that detected at visit 1. Secondary endpoints were the rate of patients with subtherapeutic ART drug concentrations and the rate of patients with virological and immunological failure at the end of the study (visit 3) compared with those at visit 1.

Statistical analysis

A paired *t*-test was performed for continuous normally distributed data and a sign test or Wilcoxon signed-rank test was performed for nonparametric data to test the null hypothesis. For categorial variables, McNemar's test was used. A *P*-value < 0.05 was considered significant. A kappa test was used to analyse the agreement between different adherence measurements.

In accordance with the published literature [6–9], and assuming an adherence rate of 60%, a sample size of approximately 300 patients was calculated to be required to detect an increase to 70% (determined by TDM) with 90% power, $\alpha = 0.05$ and an estimated drop-out rate of 20%.

All analyses were performed using STATA™ software version 11 for Windows (Stata Corp, College Station, TX, USA).

Patient data were extracted from electronic and paper-based patient charts and anonymized before analysis.

Ethics

Research and ethical clearance was obtained from the Ifakara Health Institute Institutional Review Board (IHI/IRB/No.28-2013), the Medical Research Coordination Board of the Tanzanian National Institute for Medical Research (NIMR/HQIR.8a/V01.IXlI762), and the Tanzanian Commission for Science & Technology (No.2014-276-NA-2014-195). Written informed consent was obtained from all participants enrolled in the study.

Results

Baseline participant characteristics and clinical outcome

Three hundred and four patients were evaluated for study enrolment. Five patients were excluded because they were on current tuberculosis treatment ($n = 2$) or had medical care provided at another HIV clinic ($n = 3$). Data for a total of 299 HIV-infected patients on ART were finally analysed. Two hundred and 42 patients (80.9%) completed study evaluations at all three visits, including clinical and self-reported adherence assessment, CD4 cell count, viral load measurement and TDM (Fig. 1). Baseline characteristics are summarized in Table 1. The median age was 41 years [interquartile range (IQR) 35–48 years] and 28.8% were male. Most patients lived < 5 km from the CDCI (72.9%) and worked as farmers (85.9%). Two-thirds of the patients started ART because they had WHO stage IV disease or a CD4 cell count < 200 cells/μl. The median CD4 count nadir was 138 cells/μl (IQR: 59–220 cells/μl) and 59.2% had WHO stage III/IV disease. Median ART duration at baseline was 43 months (IQR: 22–64 months). Sixty-seven per cent were taking an efavirenz-based and 36.8% a one-pill fixed-dose combination ART regimen (efavirenz, tenofovir and emtricitabine or lamivudine). Nine per cent were on a second-line protease inhibitor-based ART regimen with lopinavir/ritonavir. One quarter of the patients had experienced at least one episode of nonadherence prior to the study. Only three patients reported signs of ART toxicity and one patient was newly diagnosed with Kaposi sarcoma at the baseline visit. Fifteen patients (5.4%) had an unfavourable outcome over the entire study period: six patients were diagnosed with a new AIDS-defining disease (four with tuberculosis and two with Kaposi sarcoma), six patients died (one from tuberculosis and five for unknown reasons), and three were lost to follow-up at visits 2 and 3 (Table 2).

Self-reported adherence assessed using the questionnaire

Only 3.3% of the patients reported nonadherence (missed at least one ART dose in the last 4 weeks) via the questionnaire at the baseline visit (visit 1) (Table 2). The median time from the intervention to visit 2 and visit 3 was 63 (IQR: 51–77) and 246 (IQR: 234–260) days, respectively. At visit 2, significantly more patients reported problems with adherence (10.7%) compared with baseline ($P < 0.001$). At visit 3, the detection rate decreased to 5.7%, which was not statistically different from that at baseline ($P = 0.201$). Similar results were obtained when

Table 1 Baseline characteristics of the 299 study patients

Baseline characteristics	
Age (years) [median (IQR)]	41 (35–48)
Sex, male [*n* (%)]	86 (28.8)
Pregnant [*n* (%)]	7 (2.3)
Distance from clinic [*n* (%)]*	
< 5 km	218 (72.9)
5–50 km	56 (18.7)
> 50 km	24 (8.0)
Marital status [*n* (%)]	
Married	137 (45.8)
Not married	162 (54.2)
Education [*n* (%)]*	
None	27 (9.1)
Primary school	252 (84.6)
Secondary school or higher	19 (6.3)
Occupation [*n* (%)]	
Employed	32 (10.7)
Farmer	256 (85.6)
Other (e.g. unemployed)	11 (3.7)
AIDS-defining diseases (WHO stage III/IV) in the past [*n* (%)]	
Tuberculosis	91 (30.4)
Cryptoccocus	4 (1.3)
Kaposi sarcoma	8 (2.7)
Reason for starting ART*	
CD4 < 200 cells/μl and/or WHO stage IV [*n* (%)]	194 (65.1)
CD4 < 350 cells/μl and/or WHO stage III [*n* (%)]	95 (31.9)
Time from ART initiation to start of study (months) [median (IQR)]	43 (22–64)
ART regimen [*n* (%)]**	
Efavirenz-based	200 (66.9)
Nevirapine-based	73 (24.4)
Lopinavir/ritonavir-based	26 (8.7)
Atazanavir/ritonavir-based	0 (0.0)
Backbone tenofovir + emtricitabine	135 (45.2)
Backbone zidvoduine + lamivudine	164 (54.8)
One-pill regimen (EFV + TDF + FTC or 3TC)	110 (36.8)
ART toxicity at baseline visit [*n* (%)]	3 (1.0)
Comedication [*n* (%)]	
Cotrimoxazole prophylaxis	125 (41.8)
Other drugs	66 (22.1)
WHO stage at baseline visit [*n* (%)]	
Stage I/II	122 (40.8)
Stage III/IV	177 (59.2)
Clinical/laboratory data [mean (SD)]	
BMI (kg/m^2)	23.2 (4.5)
Blood pressure systolic/diastolic (mmHg)	122/76 (20.2/12.6)
White blood cells ($\times 10^9$/l)	5.4 (1.6)
Haemoglobin (g/dl)	12.1 (1.8)
Alanin aminotransferase (ALAT) (IU/l)	21.9 (15.2)
Serum creatinine (μmol/l)	58.5 (22.0)
History of self-reported nonadherence prior to study	
Patients with ≥ 1 previous episode of ≥ 1 missed ART dose [*n* (%)]	73 (24.4)
Absolute CD4 count (cells/μl) [median (IQR)]	
At HIV diagnosis	174 (75–319)
Nadir	138 (59–220)

ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; WHO, World Health Organization. *One patient had missing data. **Prescribed ART dosages were as follows: efavirenz (EVF) 600 mg once daily, nevirapine 200 mg twice daily, lopinavir/ritonavir 400 mg/100 mg twice daily, atazanavir/ritonavir 300 mg/100 mg once daily, tenofovir disoproxil fumarate (TDF) 300 mg once daily, emtricitabine (FTC) 200 mg once daily, lamivudine (3TC) 300 mg once daily or 150 mg twice daily, and zidovudine 300 mg twice daily.

stratifying for protease inhibitor and nonnucleoside reverse transcriptase inhibitor therapy as well as for one-pill- and poly-pill-based ART regimens.

When alternative cut-offs were used to define nonadherence (at least two missed ART doses and drug holidays in the last 4 weeks), the reported nonadherence rate was significantly higher at visit 2 (5.5 and 2.7%, respectively) and remained significantly higher at visit 3 (3.9 and 3.2%, respectively) compared with baseline (0.7% and 0.3%, respectively) (Table 2 and Fig. 2).

Reasons for missed ART doses were available in 28 of the 59 patients (47%) who reported nonadherence during the study period. The most common reasons for missed ART doses were running out of pills (64.3%), forgetting to take the pills (10.7%), travel problems (7.1%) and feeling depressed (3.6%).

Adherence assessment by plasma ART therapeutic drug monitoring

Plasma drug concentrations were measured for efavirenz (n = 543), nevirapine (n = 199), lopinavir (n = 70) and atazanavir (n = 12). Concentration–time plots for efavirenz, nevirapine and lopinavir are shown in Fig. 3. The mean time interval between last ART intake and drug concentration measurement was 14:40 h for efavirenz [standard deviation (SD) ± 2:50 h], 13:32 h for nevirapine (SD ± 3:46 h) and 12:48 h for lopinavir (SD ± 3:13 h) and was similar at each of the three visits. At visit 1, 6.5% of patients had a subtherapeutic drug concentration (< 2.5th percentile) for any of the ART compounds (Table 2). In univariate models, the only factors associated with a decreased likelihood of subtherapeutic drug concentrations at baseline were female gender (P = 0.03) and nevirapine-based regimen (compared with efavirenz-based regimen; P = 0.06). For all ART compounds, the rate of subtherapeutic drug concentrations did not change significantly over the study period despite the intervention (P = 0.80). For efavirenz only, there was a time trend towards fewer patients with subtherapeutic drug concentrations after the intervention (P = 0.08) (Table 2).

Three patients (two on efavirenz and one on lopinavir) had comedication with rifampicin at visit 3 because of newly diagnosed tuberculosis during the study. One of them had an undetectable efavirenz drug concentration.

Comedications other than rifampicin (e.g. antihypertensives, antibiotics, iron tablets, anti-histaminics, antimalarials and vitamins) were more frequent in patients with lower drug concentrations (34.6%) compared with those with adequate drug concentrations (22.4%;

Table 2 Adherence assessment and outcome measures over the study period

	Visit 1	Visit 2	Visit 3	*P* values
Self-reported adherence assessed using questionnaire	*n* = 299	*n* = 291	*n* = 280	
≥ 1 ART dose missed in last 4 weeks [*n* (%)]	10 (3.3)	31 (10.7)	16 (5.7)	V1 *vs.* V2: $P < 0.001$*
				V1 *vs.* V3: $P = 0.200$*
				V2 *vs.* V3: $P = 0.016$*
≥ 2 ART doses missed in last 4 weeks [*n* (%)]	2 (0.7)	16 (5.5)	11 (3.9)	V1 *vs.* V2: $P = 0.001$*
				V1 *vs.* V3: $P = 0.013$*
				V2 *vs.* V3: $P = 0.300$*
≥ 2 consecutive ART doses missed in last 4 weeks (*n* (%)]	1 (0.3)	8 (2.7)	9 (3.2)	V1 *vs.* V2: $P = 0.020$*
				V1 *vs.* V3: $P = 0.011$*
				V2 *vs.* V3: $P = 0.808$*
Adherence assessment by TDM of ART: subtherapeutic drug concentrations[†]	*n* = 294	*n* = 275	*n* = 255	
All ART compounds [*n* (%)]	19 (6.5)	20 (7.3)	12 (4.7)	V1 *vs.* V3: $P = 0.800$*
Efavirenz[‡] [*n* (%)]	17 (8.7)	12 (6.7)	7 (4.2)	V1 *vs.* V3: $P = 0.080$[§]
Nevirapine[¶] [*n* (%)]	1 (1.4)	4 (5.9)	1 (1.7)	
Lopinavir** [*n* (%)]	1 (4.0)	3 (12.0)	3 (15.0)	
Atazanvir[††] [*n* (%)]	NA	1 (33.3)	1 (11.1)	
HIV viral load	*n* = 297	*n* = 286	*n* = 284	
HIV RNA ≥ 1000 copies/ml [*n* (%)]	23 (7.7)	26 (9.1)	26 (9.2)	V1 *vs.* V3: $P = 0.500$[‡‡]
CD4 cell count	*n* = 298	*n* = 285	*n* = 275	
Absolute CD4 count (cells/μl) [median (IQR)]	413 (268–610)	464 (313–630)	504 (329–647)	V1 *vs.* V3: $P < 0.001$[§§]
CD4 percentage [median (IQR)]	21 (14–21)	22 (16–29)	22 (17–29)	
Immunological failure [*n* (%)]	43 (14.4)	31 (10.9)	24 (8.7)	V1 *vs.* V3: $P = 0.002$[‡‡]
Clinical outcome for all visits		*n* = 299		
Unfavourable outcome, cumulative [*n* (%)]		15 (5.0)		NA
AIDS-defining disease[¶¶] [*n* (%)]		6 (2.0)		NA
Death*** [*n* (%)]		6 (2.0)		NA
Loss to follow-up[†††] [*n* (%)]		3 (1.0)		NA

NA, not applicable; V1, visit 1; V2, visit 2; V3, visit 3; IQR, interquartile range; TDM, therapeutic drug monitoring; ART, antiretroviral therapy. *McNemar test. [†]Subtherapeutic drug concentration was defined as any concentration below the 2.5th percentile of published population-based pharmacokinetic models for efavirenz [41], nevirapine [42], lopinavir/ritonavir [43] and atazanavir/ritonavir [44]. [‡]Efavirenz: *n* = 196, 179 and 168 at visits 1, 2 and 3, respectively. [§]Chi-squared trend analysis. [¶]Nevirapine: *n* = 73, 68 and 58 at visits 1, 2 and 3 respectively. **Lopinavir: *n* = 25, 25 and 20 at visits 1, 2 and 3, respectively. [††]Atazanavir: *n* = 0, 3 and 9 at visits 1, 2 and 3, respectively. [‡‡]Repeated measures logistic regression.[§§]Paired Wilcoxon rank test., [¶¶]Four patients with tuberculosis and two with Kaposi sarcoma. ***One patient died because of tuberculosis (not counted in AIDS-defining diseases).[†††]Did not return to clinic for visits 2 and 3.

$P = 0.04$); however, no significant drug–drug interactions with ART could be identified.

CD4 cell count and HIV viral load

The median CD4 cell count was 413 (IQR: 268–610) cells/μl at baseline, and increased significantly over time by 91 cells/μl to 504 cells/μl at visit 3 ($P < 0.001$ for the comparison of visit 1 with visit 3). Immunological failure was observed in 43 patients (14.4%) at baseline. The odds of immunological failure decreased over time (odds ratio 0.75; $P = 0.002$) (Table 2). Of the 53 patients with immunological failure at visit 1 and/or visit 2, only eight patients were switched to a second-line treament with lopinavir or atazanavir.

Twenty-three patients (7.7%) demonstrated virological failure, with HIV RNA ≥ 1000 copies/ml, at baseline (Table 2). Independent of the ART regimen, there was no significant change in the virological failure rate observed over time despite the intervention (odds ratio 1.09; $P = 0.50$). Of the 39 patients with virological failure at visit 1 and/or visit 2, five patients were switched to a second-line ART regimen with lopinavir or atazanavir because of concurrent immunological failure.

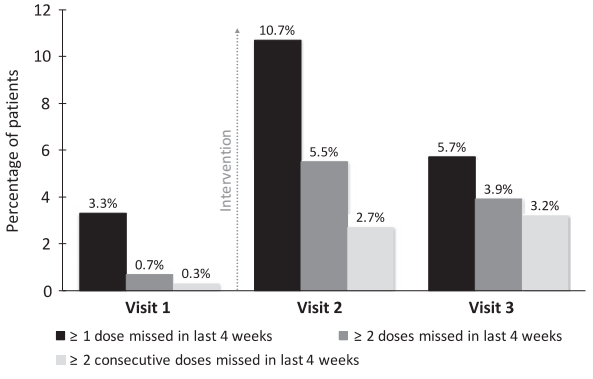

Fig. 2 Percentage of patients with self-reported nonadherence to antiretroviral therapy (ART) assessed using the questionnaire at each study visit. The *y*-axis shows the percentage of patients with self-reported nonadherence.

In a sensitivity analysis including only the 242 patients with complete evaluations at all three visits (excluding all patients who missed visit 2 or 3; Fig. 1), very similar results were obtained (data not shown).

Test agreement between self-reported adherence assessed using the questionnaire, plasma ART therapeutic drug monitoring and virological failure

Test agreement between adherence assessed using the questionnaire and subtherapeutic ART drug concentration measurements was moderate to weak and differed over the three visits and depending on the definition of self-reported nonadherence (Table 3). The highest agreement was found at visit 2 when nonadherence was defined as at least two missed ART doses or at least two missed consecutive ART doses in the last 4 weeks (κ 0.11 and 0.18; both $P < 0.05$). Virological failure (HIV RNA $\geq$ 1000 copies/ml) was significantly correlated with subtherapeutic ART drug concentration across all three visits (κ 0.329; $P < 0.0001$) but not with self-reported nonadherence assessed using the questionnaire (κ −0.0614 to 0.0099) (Table 3).

Discussion

Interventional studies with the goal to specifically improve adherence in HIV-infected patients in low-income countries are rare [11,12]. Our intervention aimed to enhance health care providers' ability to encourage HIV-infected patients to talk about adherence problems, which is a unique approach for sub-Saharan Africa. We demonstrated that "patient-centred" communication can be taught within a limited period of time without the need for a month-long run-in phase as proposed by other authors [27,31,32,46,47], and substantially contributed to improving adherence assessment in a rural HIV clinic in Tanzania. Remarkably, the adherence and virological response rate, which was greater than 90% in our selected study population on ART at the beginning of the study, was excellent.

As an objective method to measure adherence, we used TDM of ART compounds, because self-reported adherence assessment is frequently inaccurate when not properly performed, with the consequence of missing patients with nonadherence. The value of TDM in assessing mainly short-term adherence has been shown in various studies [48–52]. The high adherence rate in our study using this measurement contrasts with other studies from sub-Saharan Africa [6–9], in which the adherence rate, mainly assessed using patients' self-reported adherence, was found to be on average only 70%. Possible explanations for the high adherence rate in our study include a survivor treatment bias in our selected study population and the well-organized and well-staffed CDCI.

The low virological failure rate of only 7.7% at baseline using the HIV RNA cut-off of $\geq$ 1000 copies/ml proposed by WHO is in line with multiple studies indicating that HIV infection can be very effectively treated in resource-limited countries [53–55]. With a lower cut-off of $\geq$ 500 copies/ml, the failure rate was similar (9.1%; data not shown).

Assessment of self-reported adherence revealed that only a small minority of the patients (3.3%) disclosed any adherence problems to the physicians at baseline, compared with a nonadherence rate of 6.9% as measured by TDM. The results of our study indicate that a patient-centred communication approach has a significant impact on the ability of the health care provider to elicit patients' reports of nonadherence (3-fold increase in self-reports of nonadherence at visit 2). However, the effect of the communication training seemed to decline over time, as measured after 6–9 months, although the significance depended on the cut-off used to define nonadherence.

Adherence assessment, which is the first, fundamental step towards improving adherence, is challenging and may be inaccurate [56–58]. Studies mainly from high-income countries have shown that patient-centred communication improves adherence and outcome by establishing a trusting and respectful patient−health care provider relationship [28–30,59]. In sub-Saharan Africa, doctor-centred concepts are still more commonly used. However, interpersonal interactions with health care providers are of central importance across different cultural settings, including African countries [31,60,61], suggesting that a patient-centred approach is also likely to improve the quality of health care in resource-limited countries.

No clear impact of our intervention on patients' adherence assessed using TDM and virological response rate over time was shown. This may be explained by our sample size, which was too small in the setting of unexpectedly high baseline adherence and virological suppression rate. The target population of our study was patients on ART for $\geq$ 6 months (median 3.5 years), and therefore a survivor treatment bias could have led to selection of the most adherent patients. We tried to minimize the selection bias by enrolling all consecutive HIV-infected patients presenting at the HIV-clinic fulfilling the inclusion criteria. In addition, viral load results were not available during the study in a timely fashion for logistical reasons, impeding the ability of physicians to adapt ART appropriately in the case of virological failure.

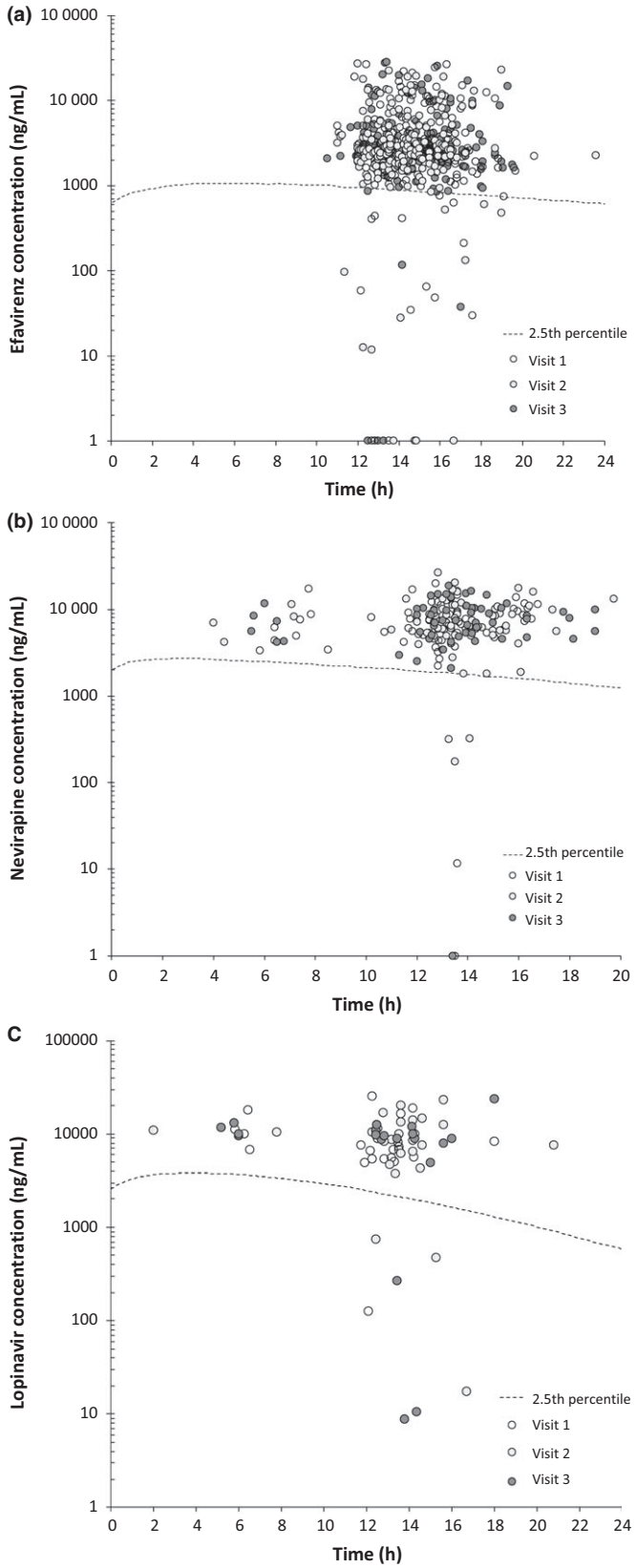

Fig. 3 Plasma concentration—time plots for different antiretroviral therapy (ART) drugs. (a) Plasma concentration—time plots for patients receiving 600 mg efavirenz once daily for all three study visits. (b) Plasma concentration—time plots for patients receiving 200 mg nevirapine twice daily for all three study visits. (c) Plasma concentration—time plots for patients receiving 400/100 mg lopinavir/ritonavir twice daily for all three study visits. The *y*-axis has a logarithmic scale. Circles represent patient samples. The dashed line represents the 2.5th percentile concentration curve derived from published population-based pharmacokinetic models (efavirenz [41], nevirapine [42] and lopinavir [43]). Concentrations of ART drugs below the 2.5th percentile are considered subtherapeutic. Circles on the *x*-axis represent patient samples with drug concentrations below the lower limit of quantification or undetectable.

Interestingly, we noted a significant decrease in the number of patients with immunological failure and an increase in the median CD4 cell count over time. Furthermore, although it was not significant, there was a trend towards higher drug concentrations in the subgroup of patients treated with efavirenz, the most commonly prescribed ART drug.

Further limitations include the following. (1) Our study was designed without a control group, that is, patients treated by health care providers not trained in basic communication skills. A control group was not included in view of ethical considerations and the risk of a contamination bias in a clinic where all health care providers work closely together. To minimize a potential Hawthorne effect, we compared self-reported adherence at post-intervention visits with that at the baseline visit before the intervention. (2) ART drug concentration measurements were compared with published mixed-population based pharmacokinetic models (mainly for Caucasians), which could have influenced the interpretation of drug concentrations in an exclusively African population. However, our cut-off (< 2.5th percentile) was set at a very low level which probably allowed discrimination between patients with good and those with insufficient ART intake. (3) Test agreement between adherence assessed using the questionnaire and subtherapeutic ART drug concentration measurements was rather low, which suggests that self-reports of adherence might frequently be inaccurate. This is in line with the recent FEM-PrEP study [62], in which rates of reports of nonadherence were very low compared with drug concentration measurements in an African setting. It is noteworthy that the inter-test agreement in our study was best after the communication training at visit 2, supporting the conclusion that the effect of the communication training increased the validity of self-reports.

Our study also has several strengths. (1) Our study was prospective with a unique intervention targeting the important issue of adherence in a rural sub-Saharan African clinic. (2) Our intervention was intentionally kept simple and consisted of a short course of communication training and an easy-to-apply adherence assessment reminder checklist, making such an intervention feasible and appealing for use in other resource-limited countries. (3) We used examiner-independent TDM, which allowed a more reliable estimation of adherence.

In conclusion, our study results indicate that a simple intervention with a short course of training in basic patient-centred communication for health care providers is successfully applicable in rural sub-Saharan Africa and has significant benefits in empowering HIV-infected patients to talk about their adherence problems. However, the findings suggest that health care providers need to be repeatedly trained in view of a loss of the training effect over time. This may be achieved, for example, by online teaching or repeated short training sessions delivered by dedicated local staff [47,63,64].

With the aim of achieving the goal of the "90-90-90" Joint United Nations Programme on HIV/AIDS (UNAIDS) to significantly reduce the HIV epidemic, ART coverage is to be scaled up rapidly in the near future [65], with more than 20 million HIV-infected patients to be started on ART until 2020, most of them living in sub-Saharan Africa. Efforts and interventions to improve and maintain

Table 3 Test agreement between adherence questionnaire, therapeutic drug monitoring and viral load measurements

		Visit	κ	*P*-value
Self-reported adherence and therapeutic drug monitoring				
Adherence questions and subtherapeutic drug concentrations*	Missed ≥ 1 ART dose in last 4 weeks	V1	−0.047	0.80
		V2	0.079	0.09
		V3	0.022	0.36
	Missed ≥ 2 ART doses in last 4 weeks	V1	−0.013	0.65
		V2	0.110	0.03
		V3	0.052	0.20
	Missed ≥ 2 consecutive ART doses in last 4 weeks	V1	−0.007	0.60
		V2	0.180	< 0.001
		V3	0.058	0.17
Self-reported adherence and viral load				
Adherence questions and HIV RNA ≥ 1000 copies/ml	Missed ≥ 1 ART dose in last 4 weeks	V1–3	0.002	0.48
	Missed ≥ 2 ART doses in last 4 weeks	V1–3	0.010	0.37
	Missed ≥ 2 consecutive ART doses in last 4 weeks	V1–3	−0.061	0.73
Viral load and therapeutic drug monitoring				
HIV RNA ≥ 1000 copies/ml and subtherapeutic drug concentrations*		V1	0.385	< 0.0001
		V2	0.251	< 0.0001
		V3	0.359	< 0.0001
		V1–V3	0.329	< 0.0001

ART, antiretroviral therapy; V1, visit 1; V2, visit 2; V3, visit 3. *< 2.5th percentile of published population-based pharmacokinetic models.

patients' adherence, which is critical for the success of scaling up ART, have to be reinforced. Implementing patient-centred communication, as shown in our study, may contribute to the achievement of better adherence in resource-limited countries.

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Authors' contributions

M.B. contributed to the conception and design of the study, analysed and interpreted the data and contributed to writing the manuscript. S.E. contributed to the conception and design of the study, conducted the project onsite, collected, analysed and interpreted the data, and wrote the first draft of the manuscript. W.L. was responsible for the communication training onsite. E.L. contributed to the conduct of the study onsite, the analysis and interpretation of the data, and writing of the manuscript. T.R.G. performed all statistical analyses and contributed to the interpretation of the data. J.N., D.M. and L.M. performed the laboratory analyses onsite, including viral load and CD4 cell count measurements. H.M. contributed to the conduct of the project onsite. M.H., U.D. and B.B. performed and analysed all drug concentration measurements. J.B. and T.K. performed and analysed viral load measurements in Switzerland. C.M. contributed to the analyisis and intepretation of the data. L.E. contributed to the conception and design of the study. All authors contributed to development of the manuscript and have reviewed the final manuscript.

Appendix: The Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) study group

Aschola Asantiel, Manuel Battegay, Adolphina Chale, Diana Faini, Ingrid Felger, Gideon Francis, Hansjakob Furrer, Anna Gamell, Tracy Glass, Christoph Hatz, Speciosa Hatz, Bryson Kasuga, Aneth V Kalinjuma, Namvua Kimera, Yassin Kisunga, Thomas Klimkait, Emilio Letang, Antonia Luhombero, Lameck B Luwanda Herry Mapesi, Leticia Mbwile, Mengi Mkulila, Julius Mkumbo, Margareth Mkusa, Dorcas K Mnzava, Germana Mossad, Dolores Mpundunga, Daimon Msami, Athumani Mtandanguo, Kim D Mwamelo, Selerine Myeya, Sanula Nahota, Regina Ndaki, Agatha Ngulukila, Alex John Ntamatungiro, Leila Samson, George Sikalengo, Marcel Tanner and Fiona Vanobberghen.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Use of a blackboard during the communication training. The image shows four examples of health care provider strategies to convince a patient to start antiretroviral therapy (ART), written on a blackboard.
Fig. S2. Adherence assessment checklist.