Adherence to Antiretroviral Therapy Assessed by Drug Level Monitoring and Self-Report in Cameroon

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Objectives: To compare adherence to antiretroviral therapy using drug level monitoring and self-report and to explore the relation between these 2 methods and viral load measurements.

Methods: Sixty patients received a fixed-dose combination of nevirapine, stavudine, and lamivudine in a clinical study in Cameroon. Adherence was assessed every 6 months until month 36 by nevirapine minimal plasma concentration and self-report. Plasma HIV-1 viral load was determined at the same time. Analyses included 159 complete observations.

Results: The proportion of patients labeled as "adherent" was significantly lower using nevirapine monitoring (88.7%, 95% confidence interval [CI]: 82.7 to 93.2) than self-report (97.5%, CI: 93.7 to 99.3; $P = 0.002$). Virologic failure was associated with the nevirapine concentration (adjusted odds ratio [aOR] = 4.43; $P = 0.018$) but not with the self-reported adherence (aOR = 0.84; $P = 0.9$). As compared with the virologic outcome, the sensitivity of nevirapine level monitoring for predicting inadequate adherence was 20.5%, the specificity was 91.7%, the positive predictive value was 44.4%, and the negative predictive value was 78.0%. For self-report, the respective values were 2.6%, 97.5%, 25.0%, and 75.5%.

Conclusions: Drug level monitoring provided a more reliable estimate of adherence than self-report. This method could be used in research settings. Operational research is required to define how to improve the accuracy of the self-report method because it is the most feasible method in clinical practice.

Key Words: adherence, antiretroviral therapy, drug level monitoring, HIV, self-report, sub-Saharan Africa, viral load

(*J Acquir Immune Defic Syndr* 2008;48:216–219)

Received for publication November 19, 2007; accepted March 14, 2008.

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Supported by a grant from the French National Agency for Research on AIDS (ANRS 1274).

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Inadequate adherence to antiretroviral treatment leads to therapeutic inefficacy for patients and programs (virologic, immunologic, and clinical failure as well as emergence and transmission of resistant viruses).[1–3] Treatment adherence must therefore be evaluated in clinical care, in programmatic monitoring, and in trials assessing the effectiveness of antiretroviral regimens or adherence-improving interventions.[4,5] Several methods allow adherence assessment to medication, but none can be considered as the "gold standard", with each having advantages and disadvantages.[4,6] Self-report, pharmacy refill records, pill counts, visual analog scales, and electronic drug monitors have all been assessed in sub-Saharan Africa.[7–11] Self-report, which is simple and inexpensive, is the most frequently used method but is notably susceptible to memory and social desirability biases leading to usual overestimation of adherence.[12] In contrast, adherence measured by objective drug level monitoring has been poorly documented in this setting.[13] We compared adherence to a generic fixed-dose combination (FDC) of nevirapine, stavudine, and lamivudine (Cipla Ltd, Mumbai Central, Mumbai, India) using the nevirapine plasma level monitoring and the patient's self-report and explored the relation between these 2 methods and viral load measurements in patients followed for 36 months in a clinical study in Cameroon.

METHODS

Study Design

This study was performed among patients enrolled between November 2002 and April 2003 in a clinical trial designed to assess the effectiveness, safety, and quality of a FDC of nevirapine, stavudine, and lamivudine in Yaoundé, the capital of Cameroon.[14,15] All the patients were eligible for the present study if they were receiving the FDC of nevirapine, stavudine, and lamivudine at the time of adherence and viral load measurements. Antiretroviral therapy and care were provided free of charge. Patients attended clinical visits every month during the first year and then every 2 to 3 months, which included a physical examination and an interview. At each visit, the patients were questioned by the treating physicians on the number of antiretroviral doses that they did not take during the previous 7 days and, if necessary, on the reasons. Self-reported adherence was then calculated as the ratio of the number of effective intakes to the number of

prescribed intakes. A self-reported adherence rate of 95% was judged adequate.[16] The nevirapine minimal plasma concentration (C_{min}) was measured 12 hours after the last intake every 6 months in patients receiving the FDC of nevirapine, stavudine, and lamivudine using validated reverse-phase high-performance liquid chromatography coupled with ultraviolet detection assays.[17] Blood samples were drawn early in the morning (between 8:00 and 10:00 AM). Patients were questioned on the time of last intake to extrapolate to 12 hours the nevirapine concentration if the interval was different, as previously described.[18] Adherence was judged adequate if the nevirapine concentration reached 4000 ng/mL, corresponding to the threshold of nevirapine efficacy.[19] The plasma HIV-1 viral load was determined using the Bayer branched DNA (bDNA) HIV-1 Quantiplex assay (Bayer Diagnostics, Emeryville, CA) version 3.0 (limit of quantification of 50 copies/mL) every 6 months.

Statistical Analysis

Analyses were performed on complete observations, defined as observations with simultaneous available results of nevirapine C_{min}, self-reported adherence, and HIV-1 viral load, after at least 12 months of treatment (except month 18). Nevirapine C_{min}s in women and men were compared using the nonparametric Mann-Whitney 2-sample test. Adherence measured by the nevirapine C_{min} and self-report was compared using the McNemar χ^2 test. Multivariate random-effects logistic regression models were used to assess the association between nevirapine C_{min} (<4000 ng/mL vs. ≥4000 ng/mL) or self-reported adherence (<95% vs. ≥95%) and virologic failure (HIV-1 viral load >50 copies/mL) after adjustment on baseline covariates: age, gender, CD4 cell count, HIV-1 viral load, clinical stage, and body mass index. A backward elimination procedure was used to determine the final model containing only the main variable of interest (nevirapine concentration or self-reported adherence), together with significant covariates and potential confounders. The sensitivity, specificity, and positive and negative predictive values of nevirapine level monitoring or self-report as compared with virologic outcome were calculated. The 95% confidence intervals (CIs) of percentages were estimated by the binomial exact method. Data were analyzed using STATA 7.0 software (Stata Corporation, College Station, TX).

RESULTS

Of 60 patients included in the initial trial, 48 (80%) contributed to the present analysis. The other 12 patients did not have complete observations between 12 and 36 months after treatment initiation because of early death (6 patients), loss to follow-up (2 patients), antiretroviral drug substitution (1 patient with drug-related toxicity), antiretroviral drug substitution at month 12 and then loss to follow-up (1 patient with tuberculosis), or unavailable nevirapine C_{min} at month 12 (time between last drug intake and venipuncture not recorded) and then antiretroviral drug switch (1 patient with viral resistance) or death (1 patient).

The 48 patients provided 159 complete observations between months 12 and 36. The median number of observations per patient was 4 (interquartile range [IQR]: 3 to 4 observations). These patients were predominantly women (n = 36, 75%). At baseline, the median age was 35 years (IQR: 29 to 42 years); most patients were symptomatic (Centers for Disease Control and Prevention [CDC] stage A [19%], stage B [44%], and stage C [37%]); the median CD4 count was 130 cells/mm^3 (IQR: 94 to 167 cells/mm^3), and the median plasma HIV-1 RNA level was 80,418 copies/mL (IQR: 36,720 to 202,047 copies/mL). Two women had taken nevirapine for the prevention of HIV mother-to-child transmission at delivery (once each). During follow-up, the HIV-1 viral load was <50 copies/mL in 120 observations (75.5%).

The overall median nevirapine C_{min} was 6453 ng/mL (range: <50 to 21,096 ng/mL, IQR: 5128 to 8265 ng/mL), without significant difference between women (6605 ng/mL [range: <50 to 17,331 ng/mL, IQR: 5198 to 8765 ng/mL]) and men (6129 ng/mL [range: <50 to 21,096 ng/mL, IQR: 5012 to 7889 ng/mL]; $P = 0.5$). The concentration was at least 4000 ng/mL in 141 observations (88.7%, 95% CI: 82.7 to 93.2). In the other 18 observations (11.3%), the median concentration was 2905 ng/mL (IQR: 52 to 3730 ng/mL). A concentration <4000 ng/mL was significantly associated with virologic failure after adjustment on baseline covariates (odds ratio [OR] = 4.43; $P = 0.018$; Table 1). As compared with the virologic outcome, the sensitivity of the nevirapine level monitoring for predicting inadequate adherence was 20.5%; the specificity was 91.7%, the positive predictive value was 44.4%, and the negative predictive value was 78.0% (Table 2).

The self-reported adherence was at least 95% in 155 observations (97.5%, 95% CI: 93.7 to 99.3). In contrast, the self-reported adherence was 92.9% in 2 observations (drug intakes forgotten), 85.7% in 1 observation (visit postponed), or 0% in 1 observation (travel). The self-reported adherence was significantly higher than adherence measured by the nevirapine level monitoring ($P = 0.002$). The self-reported adherence was not associated with virologic failure (adjusted OR = 0.84; $P = 0.9$; see Table 1). As compared with the virologic outcome, the self-report had a low sensitivity for predicting inadequate adherence (2.6%); the specificity and the positive and negative predictive values were, respectively, 97.5%, 25.0%, and 75.5% (see Table 2).

DISCUSSION

Our study showed a high proportion of patients labeled as "adherent" by nevirapine plasma level monitoring (88.7%)

TABLE 1. Association Between Nevirapine Plasma C_{min} or Self-Reported Adherence and Virologic Failure (HIV-1 Viral Load >50 Copies/mL) From Multivariate Random-Effects Logistic Regression Analyses

	Adjusted* OR	95% CI	P
Nevirapine C_{min} (<4000 vs. ≥4000 ng/mL)	4.43	1.29 to 15.23	0.018
Self-reported adherence (<95% vs. ≥95%)	0.84	0.06 to 11.53	0.9

*Adjusted on baseline CD4 cell count and body mass index.

TABLE 2. Performances of Nevirapine Level Monitoring and Self-Report as Compared With Viral Load Measurement for Predicting Inadequate Adherence

	Viral Load						
	>50 Copies/mL	<50 Copies/mL	Total	Se	Sp	PPV	NPV
Nevirapine concentration				20.5%	91.7%	44.4%	78.0%
<4000 ng/mL	8	10	18				
≥4000 ng/mL	31	110	141				
Self-report				2.6%	97.5%	25.0%	75.5%
<95%	1	3	4				
≥95%	38	117	155				
Total	39	120	159				

NPV indicates negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

and self-report (97.5%). Adherence-favoring measures included free provision of drugs and care, use of FDCs, and support through educational and counseling sessions.[20] Adherence measured by nevirapine plasma level monitoring was significantly lower than self-reported adherence, however ($P = 0.002$).

The nevirapine level monitoring seemed to provide a better estimate of adherence than the self-report. Indeed, a low nevirapine level was strongly associated with virologic failure (OR = 4.43, 95% CI: 1.29 to 15.23; $P = 0.018$), as in a cross-sectional study in Malawi (OR = 6.0, 95% CI: 2.4 to 15.3).[13] Because of the long plasma half-life of nevirapine, a concentration >4000 ng/mL suggested probable adherence for several days. This was a clear advantage over drugs having a short plasma half-life, whose drug level only provides information on adherence in the previous hours, and are therefore more vulnerable to the "white-coat adherence" phenomenon (improvement of patient's adherence before a medical visit). Nevertheless, it should be noted that plasma drug level is not predictive of adherence behavior in all patients, because nevirapine concentration may be altered (increased or decreased) for reasons other than adherence (eg, drug interactions, individual metabolism variation, poor quality of the drug). In our study, the quality of the FDC of nevirapine, stavudine, and lamivudine tablets was good[14,15] and no drugs potentially interacting with nevirapine were used. In particular, nevirapine was replaced by efavirenz in case of antituberculosis treatment (including rifampicin), and these patients were excluded from our analysis. The genetic polymorphism that may influence the metabolism was not investigated.

In contrast, self-reported adherence was not associated with virologic outcome ($P = 0.9$). Self-report also had poorer ability than the nevirapine level monitoring to detect nonadherent patients (sensitivity: 2.6% vs. 20.5%), for whom adherence-improving interventions are necessary before the development of resistance. Identification of nonadherent patients is also particularly important in contexts in which drug resistance testing is not routinely performed before switching to second-line treatment. Interviews by persons other than the treating physicians (eg, peer counselors, social workers, pharmacists) are recommended to improve the estimates. Training these persons to interview patients nonjudgmentally is also required.

Clearly, although drug level monitoring is a better predictor of virologic failure than self-report, it could not be used in routine clinical practice for many years because of its high cost and the need for laboratory testing capacity that is unavailable in most African countries. In contrast, this method would provide more reliable estimates of adherence than self-report in research settings. Interestingly, the collection of blood spots on filter paper reduces the cost of sample storage and forwarding. Operational research is required to (1) compare drug level monitoring and electronic drug monitoring, which are known to provide better estimates of adherence than self-report; (2) define how to improve the accuracy of the self-report method, because it is presently the most feasible method in clinical practice; and (3) define new performance methods adapted to resource-limited countries, where they are most needed.

ACKNOWLEDGMENTS

The authors thank all the patients and staff of the Military Hospital and the Central Hospital in Yaoundé who participated in the study and the National AIDS Program, Yaoundé, Cameroon.

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