

Adherence Profiles and Therapeutic Responses of Treatment-Naive HIV-Infected Patients Starting Boosted Atazanavir-Based Therapy in the ANRS 134-COPHAR 3 Trial

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The adherence profile of HIV-infected patients predicts the therapeutic outcome, in particular during the early phase of antiretroviral therapy (ART). We conducted a prospective observational multicenter trial monitoring adherence and virological and immunological parameters over the initial 6 months of treatment. Thirty-five subjects were starting a treatment regimen including atazanavir, ritonavir, and emtricitabine-tenofovir. Adherence was assessed using self-completed questionnaires, announced pill counts, and the medication event monitoring system (MEMS) for each drug. Three MEMS measures were defined: the percentages of doses taken, days with the correct dosing, and doses taken on time (± 3 h). Dynamic virological suppression (DVS) was defined as a reduction in the plasma HIV-RNA level of $> 1 \log_{10}$ per month or < 40 copies/ml. The cumulative treatment time was 5,526 days. A high level of adherence was observed. The MEMS-defined adherence for correct dosing (-0.68% per 4-week period, $P < 0.03$) and timing compliance (-1.60% per 4-week period, $P < 0.003$) decreased significantly over time. The MEMS-defined adherence data were concordant with the pill counts during the trial but not with the data from the questionnaires. The median [range] percentages of doses taken (100% [50 to 102]), days with the correct dosing (95% [41 to 100]), and doses taken on time (86% [32 to 100]) were significantly associated with DVS in separate models. Among these three measures, the percentage of doses taken on time had the greatest ability to predict DVS. Timing compliance should be supported to optimize DVS during the early phase of treatment by once-daily boosted protease inhibitor-based ART. (This study has been registered at ClinicalTrials.gov under registration no. NCT00528060.)

Adherence is a strong predictor of the virological response (1–3) and the survival (4, 5) of HIV-infected patients. Therefore, improving adherence has been an area of intense research among patients receiving antiretroviral therapy (ART). Efforts have focused on interventions aimed at changing patient behavior (6) and on improving treatment characteristics, leading to the simplification of treatment (7). Adherence to ART has generally been reported as the average number of doses taken divided by the prescribed doses during a defined period of observation (8). The two major limits of this analytical approach are (i) that it does not account for the dynamics of adherence (9) and (ii) that it does not account for the drug intake pattern (10). Depending on the ART class in terms of the pharmacokinetic profile, antiviral potency (11–13), and phase of treatment (14), different patterns of adherence have been associated with different virological outcomes. For example, the average adherence to boosted protease inhibitors (PIs) was found to be closely associated with the virological outcome (12, 15). Whether strict interdose timing is required for virological suppression is not known. Moreover, the ability to consider measurements of adherence to one drug as a surrogate for adherence to all drugs is speculative. The simultaneous intake of several individual components of combination ART is also required for optimal efficacy. Selective drug intake can lead to periods of single or dual agent exposure. There have been inconsistent data regarding the frequency of differential adher-

ence (16, 17), which has been shown to be associated with virological failure and drug resistance (18).

Another challenge is the method used to assess adherence to prescribed ART (19, 20). Although there is no gold standard, electronic monitoring appears to be the most reliable method to record dose timing in the research setting (19, 20).

The objectives of this work were to assess the concordance between different adherence measurement methods and to describe the dynamics of adherence to a newly initiated ART regimen. Medication Event Monitoring System (MEMS) caps were used to assess the simultaneity of drug taking. We identified adherence factors that correlated with virological suppression during the first 6 months of an antiretroviral regimen consisting of ritonavir-boosted atazanavir (ATV-RTV) combined with tenofovir-emtricitabine (Truvada [TVD]) in antiretroviral-naïve participants enrolled in the ANRS 134-COPHAR 3 trial.

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MATERIALS AND METHODS

Study design and population. The ANRS 134-COPHAR 3 trial was a multicenter prospective study conducted on HIV-1-infected treatment-naïve patients starting a PI-containing ART regimen consisting of 300 mg of atazanavir (2 capsules of 150 mg) boosted with 100 mg ritonavir (1 soft capsule) and a fixed-dose combination of two coformulated nucleoside analogs: tenofovir disoproxil fumarate (300 mg) and emtricitabine (200 mg). Thirty-five patients were included and were followed for 24 weeks. The trial enrolled HIV-1-infected subjects from the outpatient clinics of 14 French university and general hospitals and was completed between February and November 2008. All patients' viruses were demonstrated to be sensitive to each component of the therapy using a genotypic resistance assay prior to inclusion of the patients in the study. The study was performed according to the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Ile de France VII (Le Kremlin-Bicêtre, France), which applies for all centers according to the French law. All subjects provided written informed consent. The EUDRA CT number is 2007-003203-12, and the protocol has been registered under the identifier NCT00528060 (ClinicalTrials.gov). The patients were evaluated at baseline and during five subsequent visits at week 4 (W4), W8, W12, W16, and W24. The laboratory data were collected as part of routine clinical care and included the plasma HIV-RNA level (lower limit of quantification, <40 copies/ml), the CD4 cell count, and safety parameters (creatinine clearance, bilirubinemia, and liver enzyme levels, assessed according to the Agence Nationale de Recherche contre le Sida [ANRS] scale to grade the severity of adverse events [<http://www.anrs.fr/index.php/content/download/2242/12805/file/ANRS-GradeEI-V1-En-2008.pdf>]).

Measurements of patient adherence to the ART regimen. We used three methods to assess adherence. First, a pharmacist performed a monthly announced pill count for each ART component. Second, self-reported adherence was measured using the ANRS adherence questionnaire (9) at W4, W16, and W24. Briefly, the questionnaire asked subjects to report the number of missed doses during a 4-day period, the last weekend, and a 4-week period to detect subjects with <95% adherence. Third, the adherence was prospectively monitored using three Medication Event Monitoring System caps (MEMS; AARDEX Group, Switzerland), one for each bottle containing atazanavir capsules, ritonavir soft capsules, or tenofovir-emtricitabine fixed-dose regimen tablets. The patients and physicians were not aware of the dosing history data compiled using the MEMS caps during the study. Each bottle containing antiretroviral drugs was filled by the pharmacist who delivered the drugs monthly to the pharmacy hospital during refill. The MEMS caps monitored the exact time and date of the opening of each pill bottle. We summarized the adherence as (i) the taking compliance (corresponding to the number of openings divided by the number of prescribed doses), (ii) correct dosing (corresponding to the number of days with openings performed as prescribed divided by the number of monitored days) and (iii) the timing compliance (corresponding to the number of openings \pm 3 h from the dosing prescription divided by the number of prescribed doses). The simultaneity of the drug intake was evaluated based on the delays between MEMS cap openings. Because we found high levels of simultaneity, we averaged the adherence of the 3 MEMS caps for the subsequent analyses. Finally, we assessed the self-reported impact of MEMS use on convenience and adherence at the end of the trial.

Virological outcomes. The cross-sectional virological success was defined at three different time points according to the French guidelines (http://www.sante.gouv.fr/IMG/pdf/Rapport_2010_sur_la_prise_en_charge_medicale_des_personnes_infectees_par_le_VIH_sous_la_direction_du_Pr_Patrick_Yeni.pdf) as follows: an HIV-RNA reduction of $>2 \log_{10}$ at W4, a viral load of <400 copies/ml at W12, and a viral load of <40 copies/ml at W24.

TABLE 1 Baseline characteristics of the 35 patients included in the ANRS 134-COPHAR 3 trial

Characteristic	Value
Age in yr, median (range)	36 (24–66)
Male, <i>n</i> (%)	29 (83)
Completion of high school, <i>n</i> (%)	30 (86)
Smoker, <i>n</i> (%)	12 (35)
Alcohol >4 times/wk, <i>n</i> (%)	4 (12)
Cannabis during the last year, <i>n</i> (%)	7 (21)
Infection via sexual intercourse, <i>n</i> (%)	34 (97)
AIDS, <i>n</i> (%)	3 (9)
Creatinine clearance, ml/min, median (range)	104.8 (52.4–177.6)
Total bilirubinemia, μ mol/liter, median (range)	9 (3–21)
HIV-RNA level, copies/ml	
Median (range), \log_{10}	4.4 (2.0–5.7)
>100,000, <i>n</i> (%)	10 (29)
CD4 cells/mm ³	
Median (range)	280 (111–461)
<200, <i>n</i> (%)	5 (14)

To assess the relationship between MEMS-defined adherence and virological suppression, we defined dynamic virological suppression (DVS), which takes into account the dynamics of both adherence and viral decline following ART initiation. DVS was evaluated at the end of each of five time periods (W0 to W4, W4 to W8, W8 to W12, W12 to W16, and W16 to W24) and was defined as an HIV-RNA level reduction of $>1 \log_{10}$ per 4-week period (3) or a level of <40 copies/ml. The ends of the periods corresponded to the times at which HIV-RNA measurements were performed as part of the ANRS 134-COPHAR 3 trial.

Statistical analysis. The sample size was defined for the pharmacokinetic analysis of atazanavir with ritonavir (21). The categorical variables were summarized using percentages, and continuous variables, such as adherence, were summarized using medians and ranges. The agreement between the methods for discriminating adherence of >95% during similar periods was calculated using Cohen's kappa coefficient. The longitudinal data with repeated measurements were analyzed using generalized linear mixed models (22, 23). For the continuous outcomes, such as adherence, we used the MIXED procedure in SAS with the same 5 periods defined for DVS. To analyze DVS, which is a discrete binary variable, we used the GLIMMIX procedure in SAS. The abilities of several separate models to predict DVS using the MEMS-defined adherence measurements (percentages of doses taken, days with correct dosing, and doses taken on time) were assessed by the area under the receiver operating characteristic (ROC) curve. In addition, a cutoff for adherence that can predict DVS was explored by computing the sensitivity, specificity, and Youden J index in R (pROC package [<http://cran.r-project.org/web/packages/pROC/pROC.pdf>]). The analyses were conducted with SAS software V 9.2 (SAS Institute, Cary, NC), and a *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics, efficacy, and tolerance. Thirty-five subjects were included in the study. Their baseline characteristics are shown in Table 1. The median age was 36 years (range, 24 to 66 years), and 83% of the patients were male. At enrollment, 9% of the patients had a clinical AIDS-defining event. The median CD4 count was 280 cells/ μ l (range, 111 to 461), and the median HIV-RNA level was 4.4 \log_{10} copies/ml (range, 2.0 to 5.6).

The therapeutic outcomes are shown in Fig. 1. Twenty-three patients (66%) had decreases in the HIV-RNA level of $>2 \log$ at W4, 32 patients (94%) had HIV-RNA levels of <400 copies/ml at

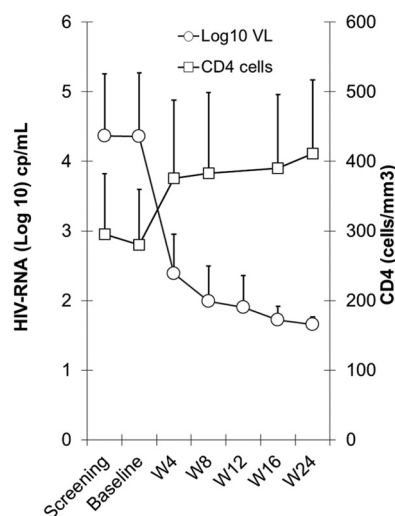


FIG 1 Changes in the HIV-RNA level and CD4 cell count during the ANRS 134-COPHAR 3 trial ($n = 35$). The error bars represent the standard deviations.

W12, and 30 patients (86%) had HIV-RNA levels of <40 copies/ml at W24 (the remaining patients had levels of 45, 47, 59, 72, and 154 copies/ml). The median CD4 cell count increased from 280 at W0 to 369 at W4 and 436 cells/ μ l at W24. One out of the 25 patients with a baseline HIV-RNA level of $<100,000$ copies/ml had a W24 HIV-RNA level of >40 copies/ml, and 4/10 patients with a baseline HIV-RNA level of $>100,000$ copies/ml had a W24 HIV-RNA level of >40 copies/ml ($P < 0.02$ by Fisher's exact test). None of the adherence measures was significantly associated with virological success in the cross-sectional analyses (35 patients) at W4, W12, and W24.

The median bilirubinemia increased from 9 μ M/liter (range, 2 to 19) at W0 to 39 μ M/liter (range, 4 to 181) at W4 and 42 μ M/liter (range, 8 to 101) at W24. Creatinine clearance was stable over time. Two severe adverse events occurred. One patient had a grade 4 hyperbilirubinemia at W8 (195 μ mol/liter; 11 times the normal value). The treatment regimen was discontinued, and RTV was stopped. At W16, this patient's bilirubinemia decreased to 75 μ mol/liter. Another patient had transient hepatitis with an elevated alanine aminotransferase (ALAT) level (421 IU/liter; 9 times the normal value, corresponding to grade 3) at W8 without recurrence after the same treatment was resumed at W10.

Adherence measures and agreement between methods. Overall, 5,526 days were monitored. The results of the three methods used to assess adherence are shown in Table 2. At W4, the results for MEMS-defined adherence of $>95\%$ exhibited an excellent agreement with the results for pill count-defined adherence of $>95\%$ (kappa = 0.8; 95% confidence interval, 0.5 to 1.0) but poor agreement with the self-reported results from the questionnaires (kappa = 0.0; 95% confidence interval, -0.1 to 0.2). The concordance results between the adherence measures were lower at W16 or W24.

The MEMS-defined adherence levels for percentages of doses taken, days with correct dosing, and doses taken on time over time are presented in Fig. 2A. The percentage adherence decreased significantly over time for days with correct dosing (-0.68% per 4-week period, $P < 0.03$) and doses taken on time (-1.60% per

4-week period, $P < 0.003$) but did not significantly decrease for percentages of doses taken (-0.44% per 4-week period, $P = 0.10$). For 70 days (1.3%), only 1 or 2 MEMS openings were recorded per day, and for 204 days (3.7%), there were no recorded openings. Among the 5,252 remaining days with 3 MEMS openings, 5,225 (99.5%) days had the 3 openings performed within 30 min.

Relationship between adherence and dynamic virological suppression. The numbers of patients achieving dynamic virologic suppression (DVS) per period were 35/35 for W0 to W4, 18/35 for W4 to W8, 20/35 for W8 to W12, 27/35 for W12 to W16, and 30/35 for W16 to W24. The numbers of patients for whom MEMS data were available for each period were 34/35 for W0 to W4, 33/35 for W4 to W8, 32/35 for W8 to W12, 33/35 for W12 to W16, and 30/35 for W16 to W24. In the longitudinal analysis (162 observations in 35 patients), the percentages of doses taken (odds ratio, 1.7; 95% confidence interval, 1.1 to 2.9; $P = 0.04$), days with correct dosing (odds ratio, 1.6; 95% confidence interval, 1.1 to 2.5; $P = 0.03$), and doses taken on time (odds ratio, 1.4; 95% confidence interval, 1.1 to 1.8; $P = 0.02$) were significantly associated with DVS in separate models. Figure 2B depicts the ROC curves corresponding to the 3 MEMS adherence measures. The timing compliance had a greater discriminatory value for DVS than did percentages of doses taken and days with correct dosing, with an area under the curve of 0.68. The timing compliance cutoff that maximized the sensitivity and specificity to predict a >1 -log₁₀ reduction in the HIV-RNA level over 4 weeks or an HIV-RNA level of <40 copies/ml at any time was 78%.

Self-reported questionnaires on the use of MEMS. Twenty-nine out of the 30 patients who responded to the questionnaire reported that the use of MEMS was easy. Nine reported that they felt they were being spied on. None reported that MEMS use affected the patient-physician relationship. No modification of drug-taking behavior was reported by 16 of the 30 patients (53%), whereas the remaining patients reported that MEMS helped them to maintain better adherence to their regimens (4/30, sometimes, and 10/30, frequently).

DISCUSSION

Our data show that a once-daily (QD) multiple-tablet regimen consisting of ritonavir-boosted atazanavir in combination with

TABLE 2 Adherence of $>95\%$ according to different measures and for different periods and concordance with MEMS data

Period and measure	Total	Adherence of $<95\%$, n (%)	Kappa with MEMS (95% CI) ^a
W0 to W4			
Pharmacy pill count	34	4 (12)	0.8 (0.5–1.0)
Questionnaire	35	7 (20)	0.0 (-0.1 –0.2)
MEMS	34	6 (18)	NA
W12 to W16			
Pharmacy pill count	33	3 (9)	0.4 (0.1–0.7)
Questionnaire	33	12 (36)	-0.3 (-0.6 –0.0)
MEMS	33	9 (27)	NA
W20 to W24			
Pharmacy pill count	31	10 (32)	0.6 (0.3–0.9)
Questionnaire	35	14 (40)	-0.2 (-0.4 –0.1)
MEMS	33	8 (24)	NA

^a Abbreviations: CI, confidence interval; NA, not applicable.

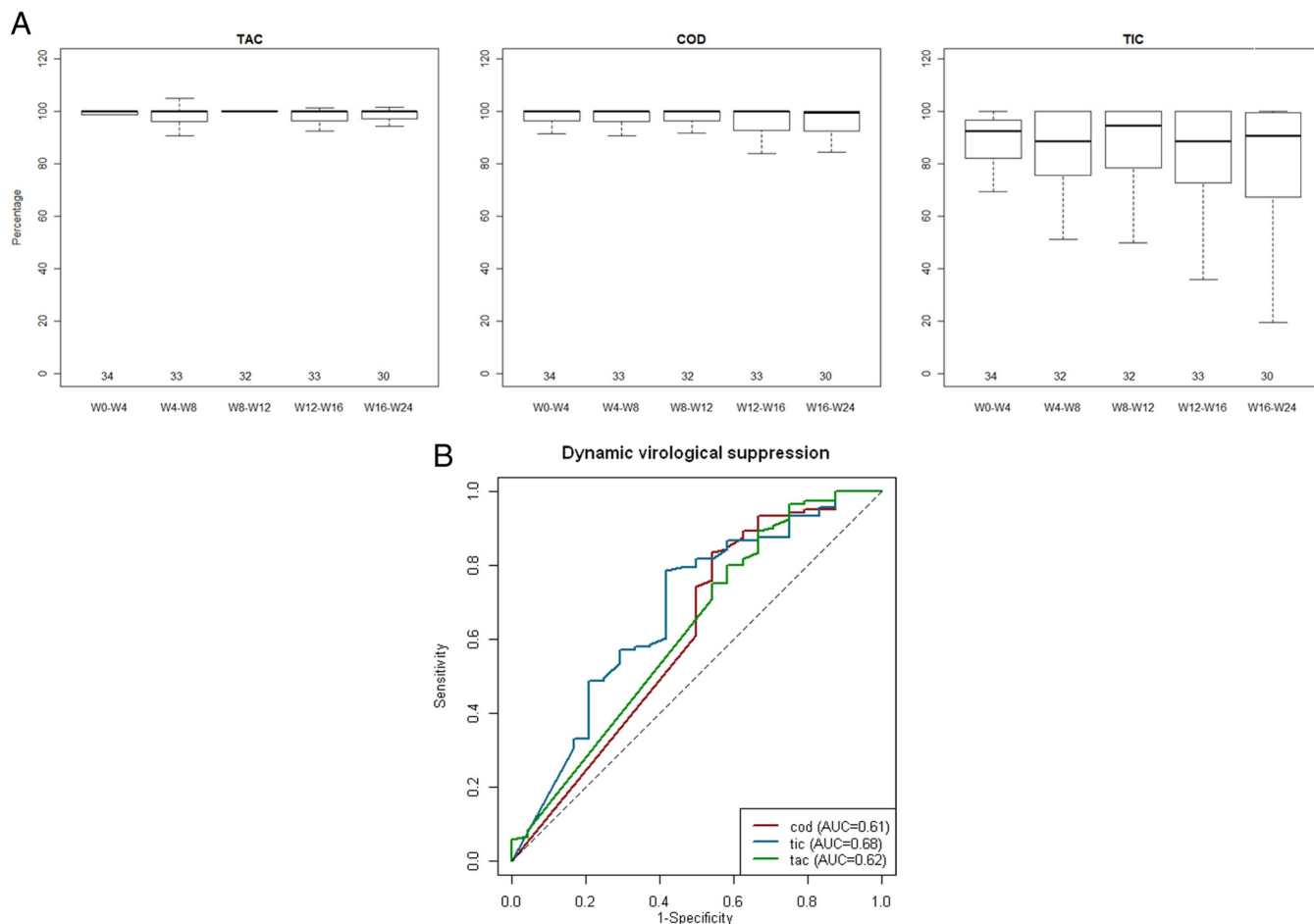


FIG 2 Box plots of the MEMS-defined percentages of doses taken, days with correct dosing, and doses taken on time (A) (error bars represent 1.5 times the interquartile range) and their abilities to predict dynamic virological suppression (B). Abbreviations: TAC, taking compliance; COD, correct dosing; TIC, timing compliance.

tenofovir-emtricitabine for the initial treatment of antiretroviral-naïve HIV-1-infected patients was associated with a high adherence level, a high simultaneous drug intake, and an excellent rate of virological response over the first 24 weeks of treatment. This observation should be interpreted in the context of a clinical trial together with intensive monitoring. Despite this high overall level of adherence, we were able to demonstrate significant associations between virological response and the average adherence (particularly timing compliance) during the 4-week period preceding the virological evaluation.

Self-reported adherence questionnaires generally tend to overestimate adherence (24). In our study, more patients were classified as <95% adherent with questionnaires than with MEMS or pill count. This might be due to the stringent algorithm that we used to classify self-reported adherence in the questionnaire and the difference between perceived adherence and objective adherence. Bilirubin level, which is more objective, has been linked to adherence to atazanavir (25, 26). Of note, our data set served for external validation of the use of bilirubin level to detect suboptimal atazanavir exposure, as reported elsewhere (27). Nevertheless, the bilirubin normogram and therapeutic drug monitoring of atazanavir concentrations had lower predictive power to detect past nonadherence episodes. In addition, only MEMS can provide

a reliable history of timing compliance. Consistent with previous studies, the MEMS data exhibited strong agreement with the pharmacy adherence data (28). Gross et al. reported a lower overall MEMS-defined taking compliance of 84% during the first 4-month period of antiretroviral therapy with nelfinavir (3). The differences between our study and the study by Gross et al. could be explained by differences in a better tolerance profile or simpler dosing for the ATV-RTV-plus-TVD QD regimen. Other alternative explanations for high adherence levels are selection bias and the Hawthorne effect. The volunteers, who agreed to use the MEMS caps and to undergo more frequent blood sampling to participate in the clinical trial, may be more likely to adhere. In turn, such intensive monitoring may also support and sustain high adherence levels, as shown in a prior intervention study using MEMS (29) and in the qualitative evaluation of the MEMS in our study. The virological success rate reported in this trial (91% of HIV-RNA levels being <50 copies/ml at W24) outperformed the results of the CASTLE study (70% of HIV-RNA levels being <50 copies/ml at W24), one of the largest trials to evaluate the use of ATV-RTV and TVD by treatment-naïve HIV-infected patients (30). Of note, in contrast to the CASTLE study, all our patients were assessed for treatment drug resistance, and we planned to

exclude patients with resistance mutations to any drug in the combined regimen.

Although it has been suggested that newer potent antiretroviral combinations are effective at moderate levels of adherence (17, 31, 32), we found here a significant association between average adherence and dynamic virological suppression in the context of high levels of adherence. The dose timing has been previously reported as an important factor to achieve virological success with antiretroviral therapy (33, 34). The added value of incorporating dose timing errors has received less scrutiny. In a previous study (21), the use of MEMS-defined dosing data halved the unexplained variability in ATV clearance. Of note, the use of timing compliance improved our ability to predict insufficient DVS relative to the use of the percentages of doses taken and days with correct dosing (Fig. 2B), with an optimized predictive value at the timing compliance cutoff of 78%. This result might be specific to the short half-life of ATV-RTV (mean, 7 to 10 h), which requires regular interdose intervals for the drug concentration to remain within the therapeutic range. In addition, timing compliance may be more relevant for atazanavir and tenofovir due to the food effect, which enhances bioavailability and reduces pharmacokinetic variability (35). We hypothesized that the variability in the ATV pharmacokinetics related to timing compliance (21) also influenced DVS among treatment-naïve HIV-infected subjects starting antiretroviral therapy, strengthening the link between pharmacokinetics and pharmacodynamics.

The level of simultaneity in taking drugs was rather good, in accordance with the results of a previous study (16) but in contrast to the results of Shuter et al., who found that 47% of the patients staggered at least once the doses of ritonavir (36).

Adherence declined over time. Gross et al. (3) reported that there is a 1-month “honeymoon” period after treatment initiation before the adherence rate begins to decline. In our study, the dose timing and correct dosing were more affected by pill burden fatigue than the taking compliance was in the context of a QD 4-pill regimen. This result supports the recommendation that QD ATV-RTV and TVD be taken at a regular time every day during the early stage of treatment. Whether this statement remains valid for the maintenance phase, once virological suppression has been achieved, is unknown, however.

None of the adherence measures was significantly associated with the milestone of cross-sectional virological success at W4, W12, and W24 as defined in international guidelines. The statistical power for this analysis was limited, while our 35 patients showed a high adherence levels. Interestingly and counterintuitively, the percentage of virological success increased between W4 and W12, while MEMS-defined adherence decreased after the first month.

We are aware of the limitations in this study. First, the sample size was rather small, as it was defined for the pharmacokinetics analysis of atazanavir with ritonavir (21). We took advantage of the dynamics of both virological suppression and adherence to study several periods per subject. We were able to increase the power of the longitudinal analysis of the DVS compared to the cross-sectional analysis of virological success. Nevertheless, we could not adjust for confounding variables when predicting the virological outcome. Second, the follow-up was limited to 6 months, even though the use of antiretroviral therapy is lifelong. However, the effect of nonadherence seems to wane over time, and the first 6 months are therefore critical. Third, our study pop-

ulation had a relatively good immunovirological status at the start of the study, and both the potency and the pharmacological characteristics of recent antiretroviral drugs have improved in the last decade. These improvements have led to the development of simpler regimens that are easier to adhere to and have led to more robust virological effects. Patients are also being treated sooner than previously, and all these factors result in improved treatment efficacy. Fourth, because our study population had a high overall adherence level, gaps in medications were infrequent. In addition, treatment gaps and the coefficient of variation in dose timing are strongly correlated (37). Therefore, we were unable to incorporate such gaps as a factor. Finally, our results cannot be extrapolated to treatment-experienced subjects who initiate a new ART regimen or to the use of other antiretroviral combinations by treatment-naïve patients. For example, ART drugs with longer half-lives, such as nonnucleoside reverse transcriptase inhibitors, may be less susceptible to irregular dose timing (31), underscoring the importance of studying adherence patterns separately for each antiretroviral regimen.

Our results may have important implications for clinical practice and future research. In the modern antiretroviral era, the role of adherence goes beyond achieving an undetectable plasma viral load at a predetermined time point (38). New paradigms have emerged, such as treatment as prevention (39), maximal virological suppression to reduce immune activation (40), and the control of HIV replication in viral reservoirs, such as the central nervous system (41) and the genital tract (42). Our study assessed the use of electronic devices to monitor and support high sustained adherence levels because adherence is crucial for improving virological outcomes at the start of antiretroviral therapy. It showed that such devices are easy to use and are well accepted by patients.

Although current guidelines for improving adherence to antiretroviral treatment (43) acknowledge the importance of treatment simplification to once-a-day regimens and fixed-dose regimens consisting of one pill per day, there is no explicit recommendation for taking doses at regular time intervals. Here, we found that a once-daily 4-pill-per-day regimen was associated with excellent adherence, excellent simultaneity of drug intake, and high rates of viral suppression. In the context of treatment-naïve HIV-infected subjects starting a once-daily ATV-RTV and TVD combination, our findings suggest that timing compliance predicts the viral suppression outcome better than do other average adherence measures.

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