

**Adherence profiles and therapeutic responses of treatment-naïve HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial.**

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1 Adherence profiles and therapeutic responses of treatment-naive HIV-  
2 infected patients starting boosted atazanavir-based therapy: the ANRS  
3 134-COPHAR 3 trial

4  
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21

22 Running Title : Adherence profile to atazanavir

23

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32

33 BACKGROUND:

34 The adherence profile of HIV-infected patients predicts the therapeutic outcome, in particular  
35 during the early phase of antiretroviral therapy (ART).

36

37 METHODS:

38 We conducted a prospective observational multicenter trial monitoring adherence, virological  
39 and immunological parameters over the initial 6 months of treatment. Thirty-five subjects  
40 were starting a treatment regimen including atazanavir, ritonavir and emtricitabine-tenofovir.  
41 Adherence was assessed using self-completed questionnaires, announced pill counts and the  
42 medication event monitoring system (MEMS®) for each drug. Three MEMS measures were  
43 defined: the percentages of doses taken, days with the correct dosing and doses taken on time  
44 (+/-3 hours). Dynamic virological suppression (DVS) was defined as a reduction in the  
45 plasma HIV-RNA level of  $>1 \log_{10}$  per month or  $< 40$  copies/mL.

46

47 RESULTS:

48 The cumulative treatment time was 5,526 days. A high level of adherence was observed. The  
49 MEMS-defined adherence for correct dosing (-0.68% per 4-week,  $p < 0.03$ ) and timing  
50 compliance (-1.60% per 4-week,  $p < 0.003$ ) decreased significantly over time. The MEMS-  
51 defined adherence data were concordant with the pill counts along the trial, but not with the  
52 data from the questionnaires. The median [range] percentages of doses taken (100% [50-  
53 102]), days with the correct dosing (95% [41-100]) and doses taken on time (86% [32-100])  
54 were significantly associated with DVS in separate models. Among these three measures, the  
55 percentage of doses taken on time had the greatest ability to predict DVS.

56

57 CONCLUSION: Timing compliance should be supported to optimize DVS during the early  
58 phase of treatment by once-daily boosted protease inhibitor-based ART.

59

60 TRIAL REGISTRATION: Clinical trial NCT00528060

61

62 **Introduction**

63 Adherence is a strong predictor of the virological response (1-3) and the survival (4, 5)  
64 of HIV-infected patients. Therefore, improving adherence has been an area of intense research  
65 among patients receiving antiretroviral therapy (ART). Efforts have focused on interventions  
66 aimed at changing patient behavior (6) and on improving treatment characteristics, leading to  
67 the simplification of treatment (7). Adherence to ART has generally been reported as the  
68 average number of doses taken divided by the prescribed doses during a defined period of  
69 observation (8). The two major limits of this analytical approach are (i) that it does not  
70 account for the dynamics of adherence (9) and (ii) that it does not account for the drug intake  
71 pattern (10). Depending on the ART class in terms of the pharmacokinetic profile, antiviral  
72 potency (11-13) and phase of treatment (14), different patterns of adherence have been  
73 associated with different virological outcomes. For example, the average adherence to boosted  
74 protease inhibitors (PI) was found to be closely associated with the virological outcome (12,  
75 15). Whether strict inter-dose timing is required for virological suppression is not known.  
76 Moreover, the ability to consider measurements of adherence to one drug as a surrogate for  
77 adherence to all drugs is speculative. The simultaneous intake of several individual  
78 components of combination ART is also required for optimal efficacy. Selective drug intake  
79 can lead to periods of single or dual agent exposure. There has been inconsistent data  
80 regarding the frequency of differential adherence (16, 17), which has been shown to be  
81 associated with virological failure and drug resistance (18).

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

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

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95

96 **Methods**

97 *Study design and population*

98 The ANRS 134-COPHAR 3 trial was a multicenter prospective study conducted on HIV-1-  
99 infected treatment-naive patients starting a PI-containing ART regimen consisting of 300 mg  
100 of atazanavir (2 capsules of 150 mg) boosted with 100 mg ritonavir (1 soft capsule) and a  
101 fixed dose combination of two co-formulated nucleoside analogs: tenofovir disoproxil  
102 fumarate (300 mg) and emtricitabine (200 mg). Thirty-five patients were included and were  
103 followed for 24 weeks. The trial enrolled HIV-1-infected subjects from the outpatient clinics  
104 of 14 French university and general hospitals and was completed between February and  
105 November 2008. All patients' viruses were demonstrated to be sensitive to each component of  
106 the therapy using a genotypic resistance assay prior to inclusion of the patients in the study.  
107 The study was performed according to the Declaration of Helsinki and its amendments and  
108 was approved by the Ethics Committee of Ile de France VII (Le Kremlin-Bicêtre, France),  
109 which applies for all centers according to the French law. All subjects provided written  
110 informed consent. The EUDRA CT number is 2007-003203-12, and the protocol has been  
111 registered under the identifier NCT00528060 (Clinicaltrials.gov). The patients were evaluated  
112 at baseline and during five subsequent visits at weeks (W) 4, W8, W12, W16 and W24. The  
113 laboratory data were collected as part of routine clinical care and included the plasma HIV-  
114 RNA level (lower limit of quantification, <40 cp/mL), the CD4 cell count and safety  
115 parameters (creatinine clearance, bilirubinemia and liver enzyme levels, assessed according to  
116 the ANRS scale to grade the severity of adverse events:  
117 [http://www.anrs.fr/index.php/content/download/2242/12805/file/ANRS-GradeEI-V1-En-](http://www.anrs.fr/index.php/content/download/2242/12805/file/ANRS-GradeEI-V1-En-2008.pdf)  
118 [2008.pdf](http://www.anrs.fr/index.php/content/download/2242/12805/file/ANRS-GradeEI-V1-En-2008.pdf) ).

119

120 *Measurements of patient adherence to the ART regimen*

121 We used three methods to assess adherence. First, a pharmacist performed a monthly  
122 announced pill count for each ART component. Second, self-reported adherence was  
123 measured using the ANRS adherence questionnaire (9) at W4, W16 and W24. Briefly, the  
124 questionnaire asked subjects to report the number of missed doses during a 4-day period, the  
125 last week end and a 4-week period to detect subjects with < 95% adherence. Third, the  
126 adherence was prospectively monitored using three Medication Event Monitoring System  
127 caps (MEMS®; AARDEX Group, Switzerland), one for each bottle containing atazanavir  
128 capsules, ritonavir soft-capsules or tenofovir/emtricitabine fixed dose regimen tablets. The  
129 patients and physicians were not aware of the dosing history data compiled using the MEMS

130 caps during the study. Each bottle containing antiretroviral drugs was filled by the pharmacist  
131 who delivered the drugs monthly to the pharmacy hospital during refill. The MEMS caps  
132 monitored the exact time and date of the opening of each pill bottle. We summarized the  
133 adherence as (1) the taking compliance (corresponding to the number of openings divided by  
134 the number of prescribed doses), (2) correct dosing (corresponding to the number of days with  
135 openings performed as prescribed divided by the number of monitored days) and (3) the  
136 timing compliance (corresponding to the number of openings +/- 3 hours from the dosing  
137 prescription divided by the number of prescribed doses). The simultaneity of the drug intake  
138 was evaluated based on the delays between MEMS cap openings. Because we found high  
139 levels of simultaneity, we averaged the adherence of the 3 MEMS caps for the subsequent  
140 analyses. Finally, we assessed the self-reported impact of MEMS use on convenience and  
141 adherence at the end of the trial.

142

#### 143 *Virological outcomes*

144 The cross-sectional virological success was defined at three different time points according to  
145 the French guidelines

146 ([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](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  
147 HIV-RNA reduction of  $> 2 \log_{10}$  at W4, a viral load  $< 400$  cp/mL at W12 and a viral load  $<$   
148  $40$  cp/mL at W24.

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

157

#### 158 *Statistical analysis*

159 The sample size was defined for the pharmacokinetic analysis of atazanavir with ritonavir  
160 (21). The categorical variables were summarized using percentages, and continuous variables,  
161 such as adherence, were summarized using medians and ranges. The agreement between the  
162 methods for discriminating adherence  $> 95\%$  during similar periods was calculated using  
163 Cohen's Kappa coefficient. The longitudinal data with repeated measurements were analyzed

164 using generalized linear mixed models (22, 23). For the continuous outcomes, such as  
165 adherence, we used the MIXED procedure in SAS with the same 5 periods defined for DVS.  
166 To analyze DVS, which is a discrete binary variable, we used the GLIMMIX procedure in  
167 SAS. The abilities of several separate models to predict DVS using the MEMS-defined  
168 adherence measurements (percentages of doses taken, days with correct dosing and doses  
169 taken on time) were assessed by the area under the Receiver Operating Characteristic (ROC)  
170 curve. In addition, a cut-off for adherence that can predict DVS was explored by computing  
171 the sensitivity, specificity and Youden J index in R (package ‘pROC’: [http://cran.r-](http://cran.r-project.org/web/packages/pROC/pROC.pdf)  
172 [project.org/web/packages/pROC/pROC.pdf](http://cran.r-project.org/web/packages/pROC/pROC.pdf)). The analyses were conducted with SAS  
173 software V 9.2 (SAS institute, Cary, NC), and a p-value < 0.05 was considered statistically  
174 significant.

175

176

## 177 **Results**

### 178 *Baseline characteristics, efficacy and tolerance*

179 Thirty-five subjects were included in the study. Their baseline characteristics are shown in  
180 [Table 1](#). The median age was 36 years [range: 24 to 66], and 83% of the patients were male.  
181 At enrollment, 9% of the patients had a clinical AIDS-defining event. The median CD4 count  
182 was 280 cells/ $\mu$ L [111 to 461], and the median HIV-RNA level was 4.4 log<sub>10</sub> cp/mL [2.0 to  
183 5.6].

184 The therapeutic outcomes are shown in [Figure 1](#). Twenty-three patients (66%) had decreases  
185 in the HIV-RNA level of > 2 log at W4, 32 patients (94%) had an HIV-RNA level < 400  
186 cp/mL at W12 and 30 patients (86%) had HIV-RNA level < 40 cp/mL at W24 (the remaining  
187 patients had levels of 45, 47, 59, 72 and 154 cp/mL). The median CD4 cell count increased  
188 from 280 at W0 to 369 at W4 and 436 cells/ $\mu$ L at W24. One out of the 25 patients with a  
189 baseline HIV-RNA level < 100,000 cp/mL had a W24 HIV-RNA level > 40 cp/mL, and 4/10  
190 patients with a baseline HIV-RNA level > 100,000 cp/mL had a W24 HIV-RNA level > 40  
191 cp/mL (p < 0.02 by Fisher’s exact test). None of the adherence measures was significantly  
192 associated with virological success in the cross-sectional analyses (35 patients) at W4, W12  
193 and W24.

194 The median bilirubinemia increased from 9  $\mu$ M/L [range: 2 to 19] at W0 to 39  $\mu$ M/L [range: 4  
195 to 181] at W4 and 42  $\mu$ M/L [range: 8 to 101] at W24. Creatinine clearance was stable over  
196 time. Two severe adverse events occurred. One patient had a grade 4 hyperbilirubinemia at  
197 W8 (195  $\mu$ mol/L; 11 times the normal value). The treatment regimen was discontinued, and

198 RTV was stopped. At W16, this patient's bilirubinemia decreased to 75  $\mu\text{mol/L}$ . Another  
199 patient had transient hepatitis with an elevated ALAT level (421 IU/L; 9 times the normal  
200 value, corresponding to Grade 3) at W8 without recurrence after the same treatment was  
201 resumed at W10.

202

### 203 *Adherence measures and agreement between methods*

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

210 The MEMS-defined adherence levels for percentages of doses taken, days with correct dosing  
211 and doses taken on time over time are presented in Figure 2A. The percentage adherence  
212 decreased significantly over time for days with correct dosing (-0.68% per 4-week,  $p < 0.03$ )  
213 and doses taken on time (-1.60% per 4-week,  $p < 0.003$ ) but did not significantly decrease for  
214 percentages of doses taken (-0.44% per 4-week,  $p=0.10$ ). For 70 days (1.3%), only 1 or 2  
215 MEMS openings were recorded per day, and for 204 days (3.7%), there were no recorded  
216 openings. Among the 5,252 remaining days with 3 MEMS openings, 5,225 (99.5%) days had  
217 the 3 openings performed within 30 minutes.

218

### 219 *Relationship between adherence and dynamic virological suppression*

220 The numbers of patients achieving dynamic virologic suppression (DVS) per period were  
221 35/35 for W0-W4, 18/35 for W4-W8, 20/35 for W8-W12, 27/35 for W12-W16 and 30/35 for  
222 W16-W24. The numbers of patients for whom MEMS data were available for each period  
223 were 34/35 for W0-W4, 33/35 for W4-W8, 32/35 for W8-W12, 33/35 for W12-W16 and  
224 30/35 for W16-W24. In the longitudinal analysis (162 observations in 35 patients), the  
225 percentages of doses taken (Odds Ratio, 1.7; 95% confidence interval [1.1 to 2.9];  $p=0.04$ ),  
226 days with correct dosing (Odds Ratio, 1.6; 95% confidence interval [1.1 to 2.5];  $p=0.03$ ) and  
227 doses taken on time (Odds Ratio, 1.4; 95% confidence interval [1.1 to 1.8];  $p=0.02$ ) were  
228 significantly associated with DVS in separate models. Figure 2B depicts the ROC curves  
229 corresponding to the 3 MEMS adherence measures. The timing compliance had a greater  
230 discriminatory value for DVS than percentages of doses taken and days with correct dosing,  
231 with an area under the curve of 0.68. The timing compliance cut-off that maximized the



232 sensitivity and specificity to predict a  $> 1 \log_{10}$  reduction in the HIV-RNA level over 4 weeks  
233 or an HIV-RNA level  $< 40$  cp/mL at any time was 78%.

234

#### 235 *Self-reported questionnaires on the use of MEMS*

236 Twenty-nine out of the 30 patients who responded to the questionnaire reported that the use of  
237 MEMS was easy. Nine reported that they felt they were being spied on. None reported that  
238 MEMS use affected the patient-physician relationship. No modification of drug-taking  
239 behavior was reported by 16 of the 30 patients (53%), whereas the remaining patients reported  
240 that MEMS helped them to maintain better adherence to their regimens (4/30, sometimes, and  
241 10/30, frequently).

242

243

#### 244 **Discussion**

245 Our data show that a once-daily multiple-tablet regimen consisting of ritonavir-boosted  
246 atazanavir in combination with tenofovir/emtricitabine for the initial treatment of  
247 antiretroviral-naïve HIV-1-infected patients was associated with a high adherence level, a  
248 high simultaneous drug intake and an excellent rate of virological response over the first 24  
249 weeks of treatment. This observation should be interpreted in the context of a clinical trial  
250 together with intensive monitoring. Despite this high overall level of adherence, we were able  
251 to demonstrate significant associations between virological response and the average  
252 adherence (particularly timing compliance) during the 4-week period preceding the  
253 virological evaluation.

254 Self-reported adherence questionnaires generally tend to overestimate adherence (24). In our  
255 study, more patients were classified as  $<95\%$  adherent with questionnaires compared with  
256 MEMS or pill count. This might be due to the stringent algorithm we used to classify self-  
257 reported adherence in the questionnaire and the difference between perceived adherence and  
258 objective adherence. Bilirubin level, which is more objective, has been linked to adherence to  
259 atazanavir (25, 26). Of note, our dataset served for external validation of the use of bilirubin  
260 level to detect sub-optimal atazanavir exposure, as reported elsewhere (27). Nevertheless, the  
261 bilirubin normogram and therapeutic drug monitoring of atazanavir concentrations had lower  
262 predictive power to detect past non-adherence episodes. In addition, only MEMS can provide  
263 a reliable history of timing compliance. Consistent with previous studies, the MEMS data  
264 exhibited strong agreement with the pharmacy adherence data (28). Gross et al. reported a  
265 lower overall MEMS-defined taking compliance of 84% during the first 4-month period of

266 antiretroviral therapy with nelfinavir (3). The differences between our study and the study of  
267 Gross et al. could be explained by differences in a better tolerance profile or simpler dosing  
268 for the ATV/RTV plus TVD QD regimen. Other alternative explanations for high adherence  
269 levels are selection bias and the Hawthorne effect. The volunteers, who agreed to use the  
270 MEMS caps and to undergo more frequent blood sampling to participate in the clinical trial,  
271 may be more likely to adhere. In turn, such intensive monitoring may also support and sustain  
272 high adherence levels, as shown in a prior intervention study using MEMS (29) and in the  
273 qualitative evaluation of the MEMS in our study. The virological success rate reported in this  
274 trial (91% of HIV-RNA levels <50 cp/mL at W24) outperformed the results of the CASTLE  
275 study (70% of HIV-RNA levels <50 cp/mL at W24), one of the largest trial to evaluate the  
276 use of ATV/RTV and TVD by treatment-naive HIV-infected patients (30). Of note, contrary  
277 to the CASTLE study, all our patients were assessed for treatment drug resistance, and we  
278 planned to exclude patients with resistance mutations to any drug in the combined regimen.  
279 Although it has been suggested that newer potent antiretroviral combinations are effective at  
280 moderate levels of adherence (17, 31, 32), we found herein a significant association between  
281 average adherence and dynamic virological suppression in the context of high levels of  
282 adherence. The dose timing has been previously reported as an important factor to achieve  
283 virological success with antiretroviral therapy (33, 34). The added value of incorporating dose  
284 timing errors has received less scrutiny. In a previous study (21), the use of MEMS-defined  
285 dosing data halved the unexplained variability in ATV clearance. Of note, the use of timing  
286 compliance improved our ability to predict insufficient DVS relative to the use of the  
287 percentages of doses taken and days with correct dosing (Figure 2B), with an optimized  
288 predictive value at the timing compliance cut-off of 78%. This result might be specific to the  
289 short half-life of ATV/RTV (mean, 7 to 10 hours), which requires regular inter-dose intervals  
290 for the drug concentration to remain within the therapeutic range. In addition, timing  
291 compliance may be more relevant for atazanavir and tenofovir due to the food effect, which  
292 enhances bioavailability and reduces pharmacokinetic variability (35). We hypothesized that  
293 the variability in the ATV pharmacokinetics related to timing compliance (21) also influenced  
294 DVS among treatment-naive HIV-infected subjects starting antiretroviral therapy,  
295 strengthening the link between pharmacokinetics and pharmacodynamics.  
296 The level of simultaneity in taking drugs was rather good, in accordance with the results of a  
297 previous study (16) but in contrast to the results of Shuter et al., who found 47% of the  
298 patients staggered at least once the doses of ritonavir (36).

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

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

311  
312 We are aware of the limitations in this study. First, the sample size was rather small as it was  
313 defined for the pharmacokinetics analysis of atazanavir with ritonavir (21). We took  
314 advantage of the dynamics of both virological suppression and adherence to study several  
315 periods per subject. We were able to increase the power of the longitudinal analysis of the  
316 DVS compared to the cross-sectional analysis of virological success. Nevertheless, we could  
317 not adjust for confounding variables when predicting the virological outcome. Second, the  
318 follow-up was limited to 6 months, even though the use of antiretroviral therapy is life long.  
319 However, the effect of non-adherence seems to wane over time, and the first 6 months are  
320 therefore critical. Third, our study population had a relatively good immuno-virological status  
321 at the start of the study, and both the potency and the pharmacological characteristics of  
322 recent antiretroviral drugs have improved in the last decade. These improvements have led to  
323 the development of simpler regimens that are easier to adhere to and have led to more robust  
324 virological effects. Patients are also being treated sooner than previously, and all these factors  
325 result in improved treatment efficacy. Fourth, because our study population had a high overall  
326 adherence level, gaps in medications were infrequent. In addition, treatment gaps and the  
327 coefficient of variation in dose timing are strongly correlated (37). Therefore, we were unable  
328 to incorporate such gaps as a factor. Finally, our results cannot be extrapolated to treatment-  
329 experienced subjects who initiate a new ART regimen or to the use of other antiretroviral  
330 combinations by treatment-naive patients. For example, ART drugs with longer half-lives,  
331 such as non-nucleoside reverse transcriptase inhibitors, may be less susceptible to irregular

332 dose timing (31), underscoring the importance of studying adherence patterns separately for  
333 each antiretroviral regimen.

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

343  
344 Although current guidelines for improving adherence to antiretroviral treatment (43)  
345 acknowledge the importance of treatment simplification to once-a-day regimens and fixed  
346 dose regimens consisting of one pill per day, there is no explicit recommendation for taking  
347 doses at regular time intervals. Here, we found that a once-daily 4-pill-per-day regimen was  
348 associated with excellent adherence, excellent simultaneity of drug intake and high rates of  
349 viral suppression . In the context of treatment-naive HIV-infected subjects starting once-daily  
350 ATV/RTV and TVD combination, our findings suggest that timing compliance predicts the  
351 viral suppression outcome better than other average adherence measures.

352

353

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357 thank the study subjects for their participation.

358

359 **The ANRS 134–COPHAR 3 study group:**

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377 **Previous presentations:** Portions of this study were presented at the 7th International  
378 Conference on HIV Treatment and Prevention Adherence, Florida, Miami California, 3-5  
379 June 2012, and at the 15<sup>th</sup> ESPACOMP Annual Meeting Ghent, Belgium, 25-27 October  
380 2012.

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382

383 Table and Figure Legends:

384

385 Table 1. Baseline characteristics of the 35 patients included in the ANRS 134 COPHAR-3  
386 trial

387 Table 2. Adherence > 95% according to different measures and for different periods and the  
388 concordance with the MEMS data

389

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

392 Figure 2. Boxplots of the MEMS-defined percentages of doses taken, days with correct dosing  
393 and doses taken on time (Panel A, the error bars represent 1.5 time the interquartile range),  
394 and their abilities to predict dynamic virological suppression (Panel B).

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397

398 Table 1.

399

Characteristics

Age, median [range]	36 [24 - 66]
Male, n (%)	29 (83)
High school, n (%)	30 (86)
Smoker, n (%)	12 (35)
Alcohol >4 times/week, n (%)	4 (12)
Cannabis during the last year, n (%)	7 (21)
Infection via sexual intercourse, n (%)	34 (97)
AIDS, n (%)	3 (9)
Creatinine clearance, mL/min	
median [range]	104.8 [52.4 - 177.6]
Total bilirubinemia, $\mu$ mol/L	
median [range]	9 [3-21]
HIV-RNA level, cp/mL	
median [range], log <sub>10</sub>	4.4 [2.0 - 5.7]
>100,000, n (%)	10 (29)
CD4 cells/mm <sup>3</sup>	
median [range],	280 [111 - 461]
<200, n (%)	5 (14)

400 AIDS: Acquired Immunodeficiency Syndrome, which refers to Category C clinical condition of the CDC  
401 Classification System 1993

402

403 Table 2.

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

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408 Reference

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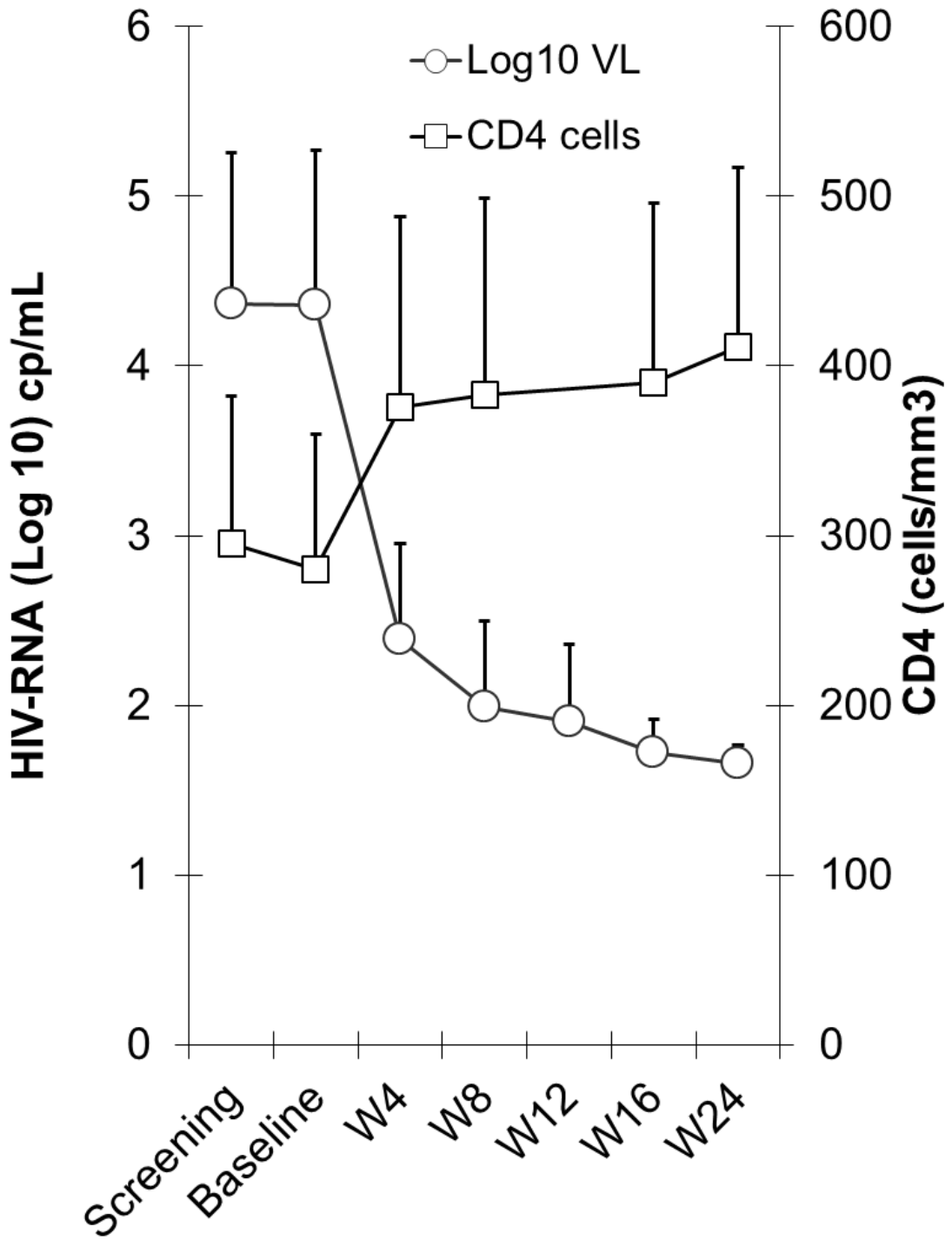
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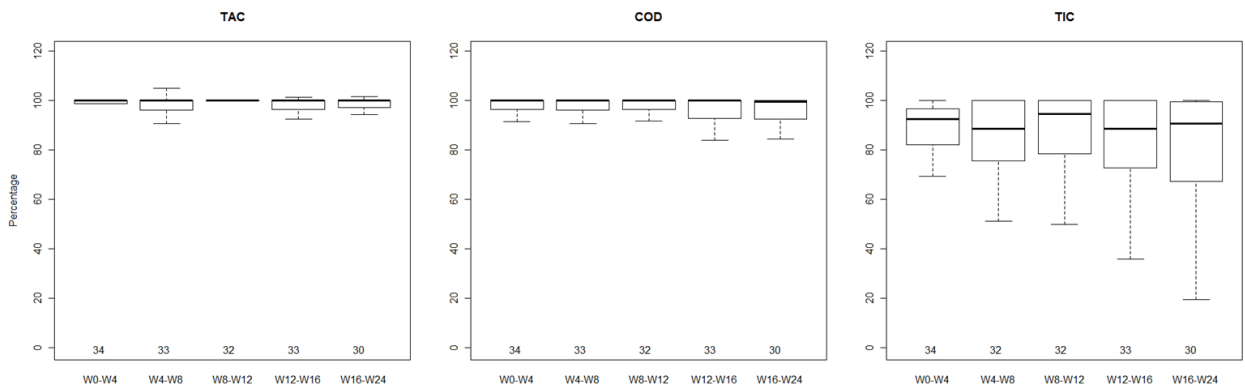
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577 Figure 1



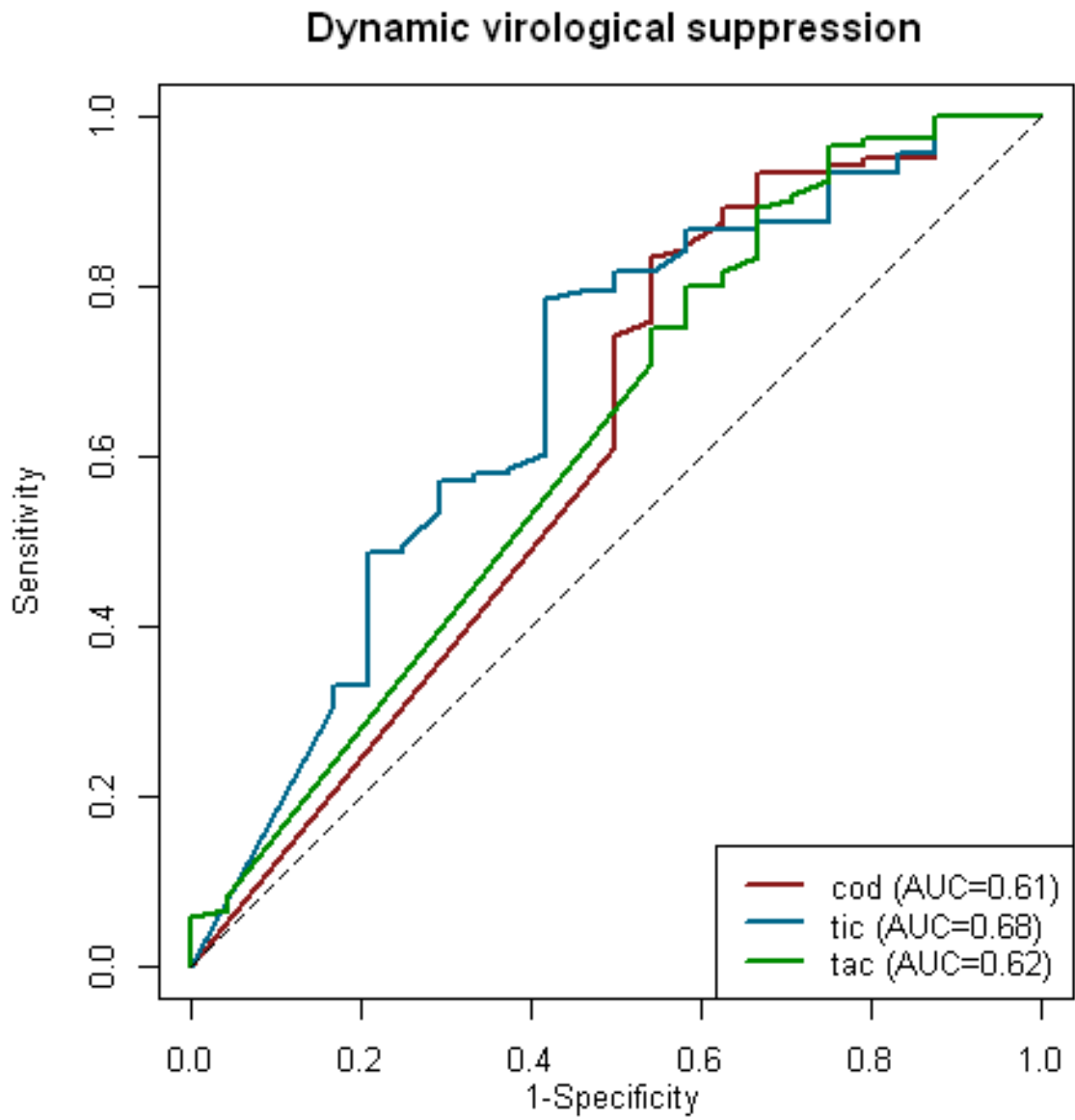
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583 Figure 2A



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585 Figure 2B



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