

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

Jean-Jacques Parienti, Aurélie Barrail-Tran, Xavier Duval, Georges Nembot, Diane Descamps, Marie Vigan, Bernard Vrijens, Xavière Panhard, Anne-Marie Taburet, France Mentré, et al.

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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

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5 Jean-Jacques Parienti^{a,b#}, Aurélie Barrail-Tran^{c,d}, Xavier Duval^a, Georges Nembot^a, Diane
6 Descamps^e, Marie Vigan^a, Bernard Vrijens^f, Xavière Panhard^a, Anne-Marie Taburet^c, France
7 Mentré^a, Cécile Goujard^{g,h}

8
9 ^a Univ Paris Diderot, Sorbonne Paris Cité, UMR 738, F-75018 Paris, France; INSERM, UMR
10 738, F-75018 Paris

11 ^b Department of Biostatistics and Clinical Research, Faculté de Médecine de Caen, Centre
12 Hospitalier Universitaire de Caen Côte de Nacre, Caen

13 ^c Department of Clinical Pharmacy, Bicêtre Hospital, Assistance Publique Hôpitaux de Paris
14 (AP-HP), Le Kremlin-Bicêtre

15 ^d Department of Clinical Pharmacy, EA 4123, Faculté de Pharmacie, Univ Paris-Sud 11,
16 Chatenay Malabry

17 ^e Department of Virology, Bichat-Claude Bernard Hospital, AP-HP, Paris

18 ^f AARDEX Group, Sion, Switzerland

19 ^g Department of Internal Medicine, Bicêtre Hospital, AP-HP, Le Kremlin-Bicêtre

20 ^h INSERM U1018, CESP, and Univ Paris-Sud 11, Le Kremlin Bicêtre, France

21

22 Running Title : Adherence profile to atazanavir

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24 [#]Corresponding footnote: Dr. Jean-Jacques Parienti, INSERM U738, Université Paris Diderot,
25 Sorbonne Paris Cité, Site Bichat, 16, Avenue Henri Huchard, Paris, France

26 E-mail: parienti-jj@chu-caen.fr

27

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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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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-naïve 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) 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/ μ L [111 to 461], and the median HIV-RNA level was 4.4 log₁₀ 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/ μ 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 μ M/L [range: 2 to 19] at W0 to 39 μ M/L [range: 4
195 to 181] at W4 and 42 μ 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 μ 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-naive 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.

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The ANRS 134–COPHAR 3 study group:

Scientific Committee: A. Barrail-Tran, A. Brunet, M.-J. Commo, S. Couffin-Cadiergues, D. Descamps, X. Duval, C. Goujard, C. Le Guellec, F. Mentré, G. Nembot, A.-M. Taburet, B. Vrijens.

Clinical centers: Dr Ajana, Dr Aissi, Dr Baclet, Pr Besnier, Dr Bollens, Dr Boulanger, Mme Brochier, Dr Brunet, Dr Chaix, Dr Ciuchete, Dr Ghosn, Pr Duval, Dr Ferret, Mr Ferret, Mme Gaubin, Pr Goujard, Pr Girard, Dr Kouadio, Mme Lupin, Dr Parienti, Mme Parrinello, Dr Poinçon de la Blanchardière, Pr May, Mme Marien, Mme Medintzeff, Mme Metivier, Mme Mole, Pr Molina, Mme Nau, Dr Ouazene, Dr Pintado, Dr Quertainmont, Mme Ramani, Dr Rami, Dr Sellier, Dr Simon, Dr Talbi, Mme Thoirain, Pr Verdon, Pr Trépo, Dr Wassoumbou, Pr Yazdanpanah

Pharmacological centers: Dr Barrail-Tran, Dr Gagneux, Dr Delhotal, Dr Hoizey, Dr Houdret, Dr Leguellec, Dr Peytavin, Dr Poirier, Dr Sauvageon, Dr Taburet

Virological centers: Pr André, Dr Soulié, Pr Calvez, Dr Morand-Joubert, Dr Harchi, Dr Bocket, Dr Mourez, Dr Palmer, Dr Pallier, Dr Deschamps, Dr Mazon, Mme Bolmann, Mr Storto, Mme Thanh Thuy

Monitoring: G. Nembot, G. Unal, F. Mentré

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Table and Figure Legends:

Table 1. Baseline characteristics of the 35 patients included in the ANRS 134 COPHAR-3 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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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, μ mol/L	
median [range]	9 [3-21]
HIV-RNA level, cp/mL	
median [range], log10	4.4 [2.0 - 5.7]
>100,000, n (%)	10 (29)
CD4 cells/mm ³	
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)
W0-W4			
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
W12-W16			
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
W20-W24			
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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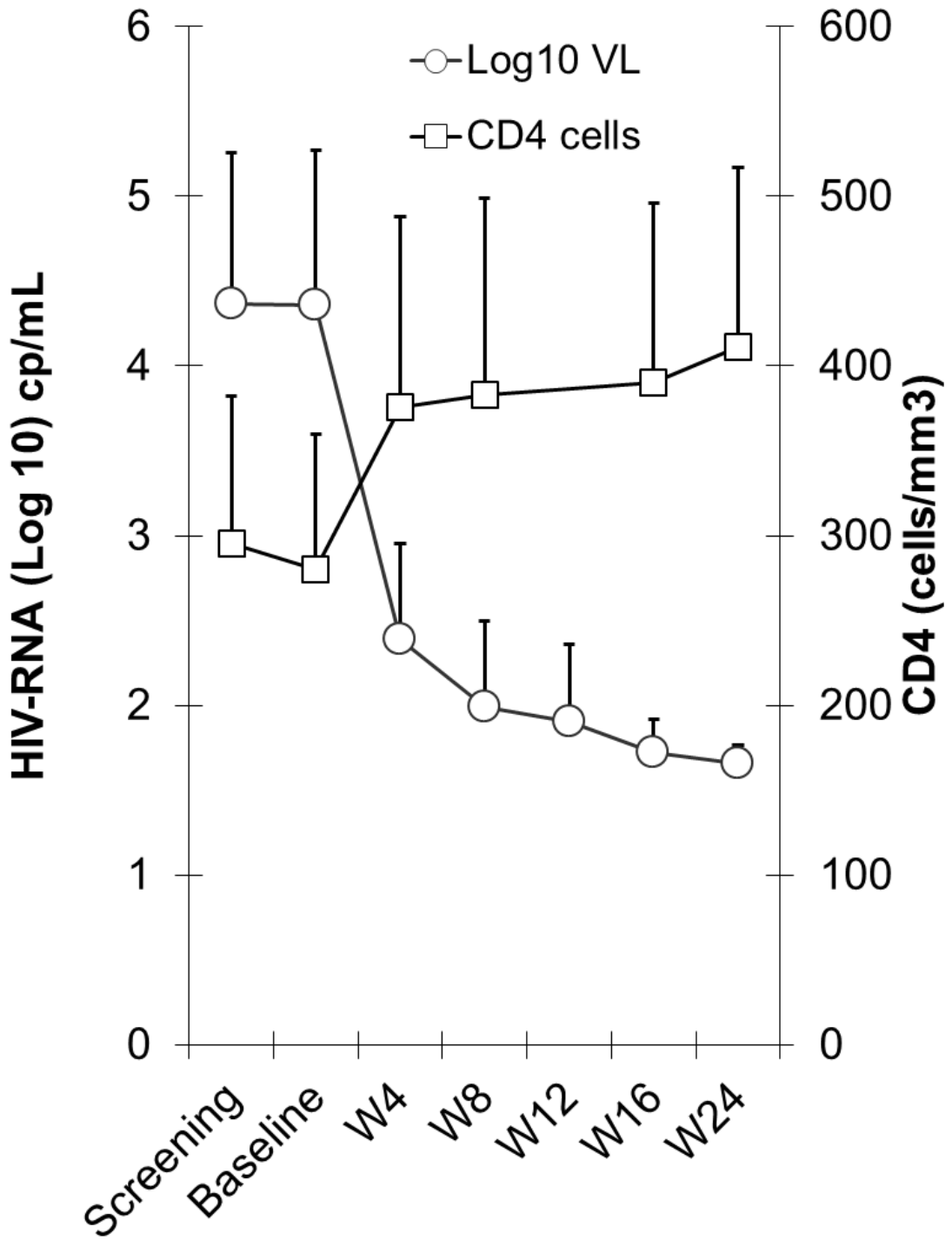
- 410 1. **Descamps D, Flandre P, Calvez V, Peytavin G, Meiffredy V, Collin G, Delaugerre**
411 **C, Robert-Delmas S, Bazin B, Aboulker JP, Pialoux G, Raffi F, Brun-Vezinet F.**
412 2000. Mechanisms of virologic failure in previously untreated HIV-infected patients
413 from a trial of induction-maintenance therapy. Trilege (Agence Nationale de
414 Recherches sur le SIDA 072) Study Team). *JAMA* **283**:205-211.
- 415 2. **Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener**
416 **MM, Singh N.** 2000. Adherence to protease inhibitor therapy and outcomes in
417 patients with HIV infection. *Ann Intern Med* **133**:21-30.
- 418 3. **Gross R, Bilker WB, Friedman HM, Strom BL.** 2001. Effect of adherence to newly
419 initiated antiretroviral therapy on plasma viral load. *AIDS* **15**:2109-2117.
- 420 4. **Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR,**
421 **Moss A.** 2001. Non-adherence to highly active antiretroviral therapy predicts
422 progression to AIDS. *AIDS* **15**:1181-1183.
- 423 5. **Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L,**
424 **Bamberger JD, Chesney MA, Moss A.** 2000. Adherence to protease inhibitors, HIV-
425 1 viral load, and development of drug resistance in an indigent population. *AIDS*
426 **14**:357-366.
- 427 6. **Goujard C, Bernard N, Sohier N, Peyramond D, Lancon F, Chwalow J, Arnould**
428 **B, Delfraissy JF.** 2003. Impact of a patient education program on adherence to HIV
429 medication: a randomized clinical trial. *J Acquir Immune Defic Syndr* **34**:191-194.
- 430 7. **Parienti JJ, Bangsberg DR, Verdon R, Gardner EM.** 2009. Better adherence with
431 once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis* **48**:484-488.
- 432 8. **Bae JW, Guyer W, Grimm K, Altice FL.** 2011. Medication persistence in the
433 treatment of HIV infection: a review of the literature and implications for future
434 clinical care and research. *AIDS* **25**:279-290.
- 435 9. **Carrieri P, Cailleton V, Le Moing V, Spire B, Dellamonica P, Bouvet E, Raffi F,**
436 **Journot V, Moatti JP.** 2001. The dynamic of adherence to highly active antiretroviral
437 therapy: results from the French National APROCO cohort. *J Acquir Immune Defic*
438 *Syndr* **28**:232-239.
- 439 10. **Glass TR, Battegay M, Cavassini M, De Geest S, Furrer H, Vernazza PL,**
440 **Hirschel B, Bernasconi E, Rickenbach M, Gunthard HF, Bucher HC.** 2010.
441 Longitudinal analysis of patterns and predictors of changes in self-reported adherence
442 to antiretroviral therapy: Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr*
443 **54**:197-203.
- 444 11. **Parienti JJ, Das-Douglas M, Massari V, Guzman D, Deeks SG, Verdon R,**
445 **Bangsberg DR.** 2008. Not all missed doses are the same: sustained NNRTI treatment
446 interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS One*
447 **3**:e2783.
- 448 12. **Parienti JJ, Ragland K, Lucht F, de la Blanchardiere A, Dargere S,**
449 **Yazdanpanah Y, Dutheil JJ, Perre P, Verdon R, Bangsberg DR.** 2010. Average
450 adherence to boosted protease inhibitor therapy, rather than the pattern of missed
451 doses, as a predictor of HIV RNA replication. *Clin Infect Dis* **50**:1192-1197.
- 452 13. **Gras G, Schneider MP, Cavassini M, Lucht F, Loilier M, Verdon R, Bernard L,**
453 **Parienti JJ.** 2012. Patterns of adherence to raltegravir-based regimens and the risk of
454 virological failure among HIV-infected patients: the RALTECAPS cohort study. *J*
455 *Acquir Immune Defic Syndr* **61**:265-269.

- 456 14. **Meresse M, Carrieri MP, Laurent C, Kouanfack C, Protopopescu C, Blanche J,**
457 **Cohen J, Laborde-Balen G, Aghokeng AF, Spire B, Moatti JP, Delaporte E,**
458 **Boyer S.** 2013. Time patterns of adherence and long-term virological response to non-
459 nucleoside reverse transcriptase inhibitor regimens in the Stratall ANRS
460 12110/ESTHER trial in Cameroon. *Antivir Ther.* In press
- 461 15. **Gandhi M, Ameli N, Bacchetti P, Anastos K, Gange SJ, Minkoff H, Young M,**
462 **Milam J, Cohen MH, Sharp GB, Huang Y, Greenblatt RM.** 2011. Atazanavir
463 concentration in hair is the strongest predictor of outcomes on antiretroviral therapy.
464 *Clin Infect Dis* **52**:1267-1275.
- 465 16. **Wilson IB, Tchetgen E, Spiegelman D.** 2001. Patterns of adherence with
466 antiretroviral medications: an examination of between-medication differences. *J*
467 *Acquir Immune Defic Syndr* **28**:259-263.
- 468 17. **Shuter J, Sarlo JA, Kanmaz TJ, Rode RA, Zingman BS.** 2007. HIV-infected
469 patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of
470 virologic suppression despite adherence rates less than 95%. *J Acquir Immune Defic*
471 *Syndr* **45**:4-8.
- 472 18. **Gardner EM, Sharma S, Peng G, Hullsiek KH, Burman WJ, Macarthur RD,**
473 **Chesney M, Telzak EE, Friedland G, Mannheimer SB.** 2008. Differential
474 adherence to combination antiretroviral therapy is associated with virological failure
475 with resistance. *AIDS* **22**:75-82.
- 476 19. **Paterson DL, Potoski B, Capitano B.** 2002. Measurement of adherence to
477 antiretroviral medications. *J Acquir Immune Defic Syndr* **31 Suppl 3**:S103-106.
- 478 20. **Vrijens B, Urquhart J.** 2005. Patient adherence to prescribed antimicrobial drug
479 dosing regimens. *J Antimicrob Chemother* **55**:616-627.
- 480 21. **Savic RM, Barrail-Tran A, Duval X, Nembot G, Panhard X, Descamps D,**
481 **Verstuyft C, Vrijens B, Taburet AM, Goujard C, Mentre F.** 2012. Effect of
482 Adherence as Measured by MEMS, Ritonavir Boosting, and CYP3A5 Genotype on
483 Atazanavir Pharmacokinetics in Treatment-Naive HIV-Infected Patients. *Clin*
484 *Pharmacol Ther.*; **92**:575-83
- 485 22. **Vrijens B, Goetghebeur E, de Klerk E, Rode R, Mayer S, Urquhart J.** 2005.
486 Modelling the association between adherence and viral load in HIV-infected patients.
487 *Stat Med* **24**:2719-2731.
- 488 23. **Ferguson NM, Donnelly CA, Hooper J, Ghani AC, Fraser C, Bartley LM, Rode**
489 **RA, Vernazza P, Lapins D, Mayer SL, Anderson RM.** 2005. Adherence to
490 antiretroviral therapy and its impact on clinical outcome in HIV-infected patients. *J R*
491 *Soc Interface* **2**:349-363.
- 492 24. **Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, Christian J,**
493 **Maldonado T, Duran D, Kaplan AH, Wenger NS.** 2001. A comparison study of
494 multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* **134**:968-
495 977.
- 496 25. **Petersen K, Riddle MS, Jones LE, Furtek KJ, Christensen AR, Tasker SA, Hale**
497 **BR.** 2005. Use of bilirubin as a marker of adherence to atazanavir-based antiretroviral
498 therapy. *AIDS* **19**:1700-1702.
- 499 26. **Rekic D, Clewe O, Roshammar D, Flamholz L, Sonnerborg A, Ormaasen V,**
500 **Gisslen M, Abelo A, Ashton M.** 2011. Bilirubin-a potential marker of drug exposure
501 in atazanavir-based antiretroviral therapy. *AAPS J* **13**:598-605.
- 502 27. **Rekic D, Roshammar D, Bergstrand M, Tarning J, Calcagno A, D'Avolio A,**
503 **Ormaasen V, Vigan M, Barrail-Tran A, Ashton M, Gisslen M, Abelo A.** 2012.
504 External Validation of the Bilirubin-Atazanavir Nomogram for Assessment of
505 Atazanavir Plasma Exposure in HIV-1-Infected Patients. *AAPS J*.

- 506 28. **Farley J, Hines S, Musk A, Ferrus S, Tepper V.** 2003. Assessment of adherence to
507 antiviral therapy in HIV-infected children using the Medication Event Monitoring
508 System, pharmacy refill, provider assessment, caregiver self-report, and appointment
509 keeping. *J Acquir Immune Defic Syndr* **33**:211-218.
- 510 29. **Krummenacher I, Cavassini M, Bugnon O, Spirig R, Schneider MP.** 2010.
511 Antiretroviral adherence program in HIV patients: a feasibility study in the Swiss HIV
512 Cohort Study. *Pharm World Sci* **32**:776-786.
- 513 30. **Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J,
514 David N, Moyle G, Mancini M, Percival L, Yang R, Thiry A, McGrath D.** 2008.
515 Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in
516 combination with tenofovir and emtricitabine, for management of antiretroviral-naïve
517 HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study.
518 *Lancet* **372**:646-655.
- 519 31. **Bangsberg DR.** 2006. Less than 95% adherence to nonnucleoside reverse-
520 transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis* **43**:939-
521 941.
- 522 32. **Nelson M, Girard PM, Demasi R, Chen L, Smets E, Sekar V, Lavreys L.** 2010.
523 Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared
524 with lopinavir/ritonavir in treatment-naïve, HIV-infected patients: 96 week ARTEMIS
525 data. *J Antimicrob Chemother* **65**:1505-1509.
- 526 33. **Liu H, Miller LG, Hays RD, Golin CE, Wu T, Wenger NS, Kaplan AH.** 2006.
527 Repeated measures longitudinal analyses of HIV virologic response as a function of
528 percent adherence, dose timing, genotypic sensitivity, and other factors. *J Acquir
529 Immune Defic Syndr* **41**:315-322.
- 530 34. **Gill CJ, Sabin LL, Hamer DH, Keyi X, Jianbo Z, Li T, Wu WJ, Wilson IB,
531 Desilva MB.** 2010. Importance of dose timing to achieving undetectable viral loads.
532 *AIDS Behav* **14**:785-793.
- 533 35. **Le Tiec C, Barrail A, Goujard C, Taburet AM.** 2005. Clinical pharmacokinetics
534 and summary of efficacy and tolerability of atazanavir. *Clin Pharmacokinet* **44**:1035-
535 1050.
- 536 36. **Shuter J, Sarlo JA, Rode RA, Zingman BS.** 2009. Occurrence of selective ritonavir
537 nonadherence and dose-staggering in recipients of boosted HIV-1 protease inhibitor
538 therapy. *HIV Clin Trials* **10**:135-142.
- 539 37. **Gebremeskel B, Liu H, Arnsten J, Bangsberg D, Goggin K, Golin C, Reynolds N,
540 Rosen M, Simoni J, Wilson I, Gross R.** Is Percentage Adherence Enough?
541 Correlation of the Various Adherence Metrics from the MACH14 Study. 7th
542 International Conference on HIV Treatment and Prevention Adherence, Florida,
543 Miami California, 3-5 June 2012.
- 544 38. **Pasternak AO, de Bruin M, Jurriaans S, Bakker M, Berkhout B, Prins JM,
545 Lukashov VV.** 2012. Modest Nonadherence to Antiretroviral Therapy Promotes
546 Residual HIV-1 Replication in the Absence of Virological Rebound in Plasma. *J Infect
547 Dis* **206**:1443-1452.
- 548 39. **Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy
549 N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S,
550 Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-
551 Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J,
552 Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE,
553 Nielsen-Saines K, Celentano D, Essex M, Fleming TR.** 2011. Prevention of HIV-1
554 infection with early antiretroviral therapy. *N Engl J Med* **365**:493-505.

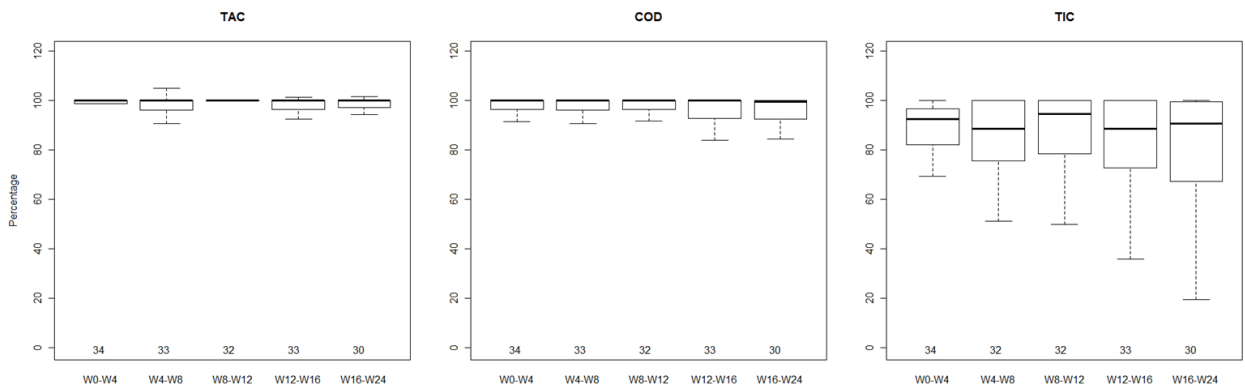
- 555 40. **Geretti AM, Smith C, Haberl A, Garcia-Diaz A, Nebbia G, Johnson M, Phillips**
556 **A, Staszewski S.** 2008. Determinants of virological failure after successful viral load
557 suppression in first-line highly active antiretroviral therapy. *Antivir Ther* **13**:927-936.
- 558 41. **Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC,**
559 **Gelman BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I,**
560 **Ellis RJ.** 2008. Validation of the CNS Penetration-Effectiveness rank for quantifying
561 antiretroviral penetration into the central nervous system. *Arch Neurol* **65**:65-70.
- 562 42. **Graham SM, Masese L, Gitau R, Jalalian-Lechak Z, Richardson BA, Peshu N,**
563 **Mandaliya K, Kiarie JN, Jaoko W, Ndinya-Achola J, Overbaugh J, McClelland**
564 **RS.** 2010. Antiretroviral adherence and development of drug resistance are the
565 strongest predictors of genital HIV-1 shedding among women initiating treatment. *J*
566 *Infect Dis* **202**:1538-1542.
- 567 43. **Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R,**
568 **Orrell C, Altice FL, Bangsberg DR, Bartlett JG, Beckwith CG, Dowshen N,**
569 **Gordon CM, Horn T, Kumar P, Scott JD, Stirratt MJ, Remien RH, Simoni JM,**
570 **Nachega JB.** 2012. Guidelines for Improving Entry Into and Retention in Care and
571 Antiretroviral Adherence for Persons With HIV: Evidence-Based Recommendations
572 From an International Association of Physicians in AIDS Care Panel. *Ann Intern Med*
573 **156**:817-833.
- 574
- 575
- 576

577 Figure 1



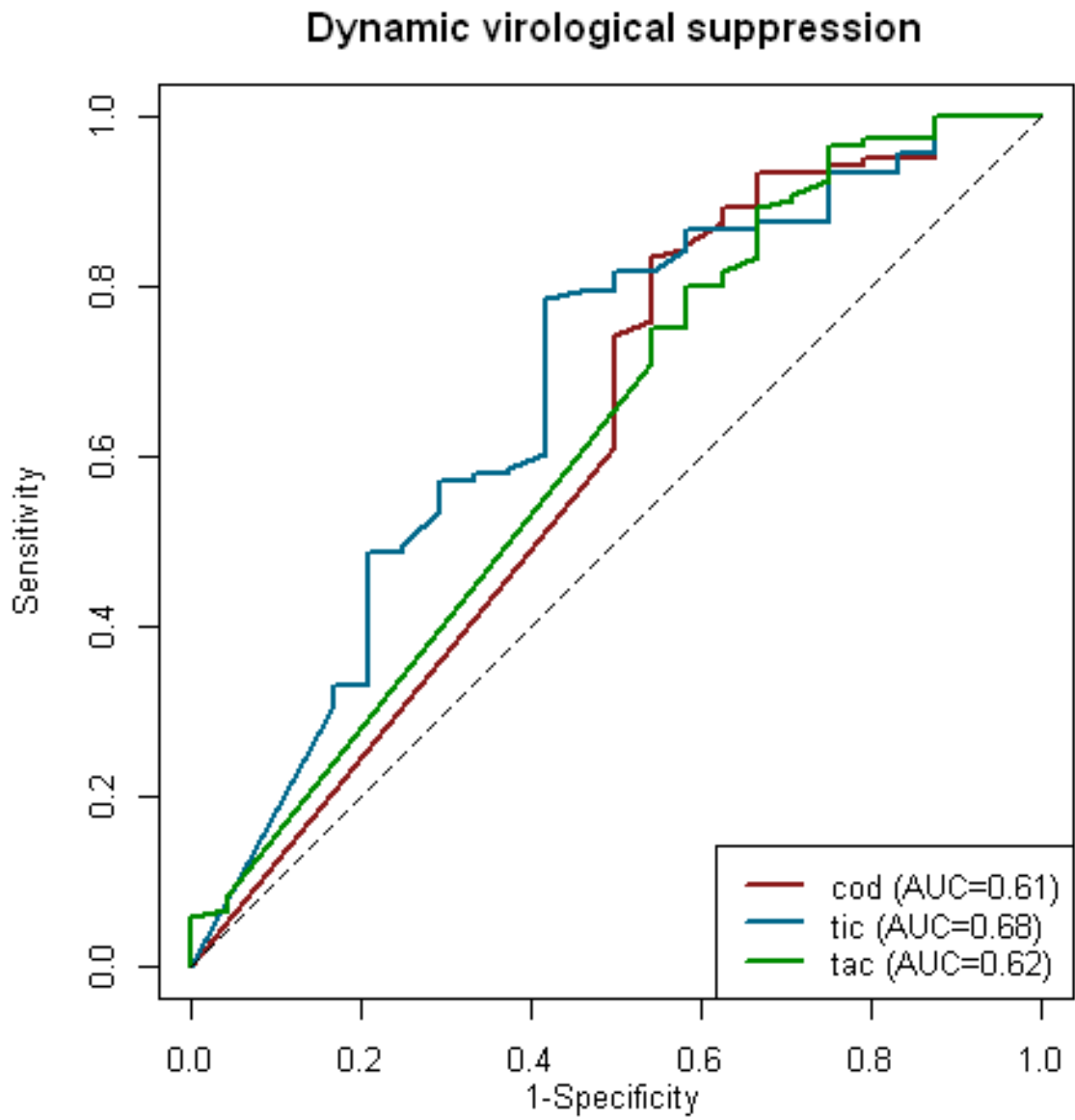
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583 Figure 2A



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585 Figure 2B



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