



HAL
open science

Intermittent two-drug antiretroviral therapies maintain long-term viral suppression in real life in highly experienced HIV-infected patients

Romain Palich, Basma Abdi, Marc Wirden, Giota Lourida, Roland Tubiana, Antoine Faycal, Marc-Antoine Valantin, Luminita Schneider, Sophie Seang, Rachid Agher, et al.

► To cite this version:

Romain Palich, Basma Abdi, Marc Wirden, Giota Lourida, Roland Tubiana, et al.. Intermittent two-drug antiretroviral therapies maintain long-term viral suppression in real life in highly experienced HIV-infected patients. *Journal of Antimicrobial Chemotherapy*, 2021, 10.1093/jac/dkab108 . hal-03201654

HAL Id: hal-03201654

<https://hal.sorbonne-universite.fr/hal-03201654v1>

Submitted on 19 Apr 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Title**

2 Intermittent two-drug antiretroviral therapies maintain long-term viral suppression in real life
3 in highly experienced HIV-infected patients

4

5 **Running title**

6 Virological efficacy of intermittent two-drug therapies

7

8 **Authors**

9 Romain PALICH^{1*}, Basma ABDI², Marc WIRDEN², Giota LOURIDA¹, Roland TUBIANA¹,
10 Antoine FAYCAL¹, Marc-Antoine VALANTIN¹, Luminita SCHNEIDER¹, Sophie SEANG¹,
11 Rachid AGHER¹, Anne SIMON¹, Cathia SOULIE², Minh-Patrick LE³, Gilles PEYTAVIN⁴,
12 Vincent CALVEZ², Anne-Geneviève MARCELIN², and Christine KATLAMA¹

13

14 **Affiliations**

15 1. Sorbonne University, Infectious Diseases Department, Pitié-Salpêtrière Hospital, AP-
16 HP, Pierre Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136,
17 Paris, France

18 2. Sorbonne University, Virology Department, Pitié-Salpêtrière Hospital, AP-HP, Pierre
19 Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136, Paris,
20 France

21 3. Bichat Claude Bernard Hospital, Pharmacology-Toxicology Department, AP-HP,
22 INSERM, UMRS 1144, Université de Paris, Paris, France

23 4. Bichat Claude Bernard Hospital, Pharmacology-Toxicology Department, AP-HP,
24 IAME, INSERM, UMRS 1137, Université de Paris, Paris, France

25

26

27 **Corresponding author**

28 Romain Palich, MD

29 Service des Maladies Infectieuses, hôpital Pitié-Salpêtrière, 47-83 boulevard de l'hôpital,

30 75013 Paris, France

31 Tel: +33.1.42.16.01.71, fax: +33.1.42.16.04.45

32 Email: romain.palich@aphp.fr

33

34 **Word count**

35 Abstract: 259

36 Text: 2100

37 **ABSTRACT**

38 **Objective:** To assess in real life whether two-drug regimens (2-DR) given 4 to 5 days a week
39 in virally suppressed patients can maintain viral suppression over 48 and 96 weeks.

40 **Method:** This observational single-center study enrolled all patients who initiated intermittent
41 2-DR between 01/01/2016 and 06/30/2019. Primary outcome was the virological failure rate
42 (VF) defined as confirmed plasma viral load [pVL] ≥ 50 copies/mL or single pVL ≥ 50
43 copies/mL followed by ART change at W48 and W96. Secondary outcomes were the 2-DR
44 intermittent strategy success rate (pVL < 50 copies/mL with no ART change), change in CD4
45 count, CD4/CD8 ratio and rate of residual viremia.

46 **Results:** Eighty-five patients were included: men: 67/85 (79%), median age: 57 years (IQR 50-
47 63), CD4 nadir: 233/mm³ (110-327), ART duration: 21 years (13-24), duration of virological
48 suppression: 6.5 years (3.7-10.8), CD4 count: 658/mm³ (519-867). Intermittent 2-DRs
49 consisted of: INSTI/NNRTI (58%), INSTI/NRTI (13%), 2 NRTIs (11%), PI/NRTI (7%), and
50 other combinations (11%). Median follow-up was 90 weeks (IQR 64-111). Overall, 4 VFs
51 occurred leading to a virological success rate of 98.8% (95%CI 93.6-100) at W48 and 95.3%
52 (95%CI 88.4-98.7) at W96. Resuming the same 2-DR 7 days a week led to viral resuppression
53 in 3 patients, whereas the M184V mutation emerged in one, leading to ART modification. There
54 was no significant change in the CD4 count or residual viremia rate, but a small increase in the
55 CD4/CD8 ratio (p=0,009) occurred over the study period.

56 **Conclusion.** This observational study shows the potential for intermittent 2-DRs to maintain a
57 high virologic success rate, which should be assessed in larger prospective randomized studies.

58

59 **INTRODUCTION**

60 Reducing cumulative exposure to antiretroviral drugs is one of the key challenges of lifelong-
61 ART, without departing from the dogma of undetectable plasma viral load (pVL), the only
62 condition currently able to insure optimal survival and quality of life with no risk of viral
63 transmission.¹

64 Two-drug regimens (2-DR) such as dolutegravir/lamivudine (DTG/3TC)² or
65 dolutegravir/rilpivirine (DTG/RPV)³ at standard daily doses are effective in maintaining
66 virological success after switching from three-drug regimens (3-DRs)⁴, and have entered
67 international guidelines. Reducing the number of drugs to induce viral suppression lowers the
68 risk of cumulative toxicities, especially for NRTIs, a class of drugs which has been used for
69 decades in some patients, as well as PIs. The BREATHER study, the single arm ANRS-162 4D
70 study, followed by the randomized ANRS-170 QUATUOR trial, demonstrated that intermittent
71 antiretroviral strategies with 2 to 3 days off per week were non inferior to a daily 3-DR in
72 maintaining control of HIV replication in virally suppressed patients on a 3-DR including
73 NNRTI-, boosted PI- and INSTI-based ART.⁵⁻⁷ These strategies resulted in a 30-40% decrease
74 in the amount of drugs administered, improving quality of life with a weekend off ART.

75 Drug-reduced strategies, including two-drug therapies as well as intermittent strategies, are
76 routinely prescribed in our department with over 35-40% patients on reduced ART. As some
77 patients had therefore been taking intermittent 2-DRs, on their own initiative or that of their
78 HIV clinician, we aimed in this study to assess in real life whether 2-DRs given 4 to 5 days a
79 week could maintain viral suppression over 48 and 96 weeks.

80

81 **METHODS**

82 *Study participants*

83 All HIV-1-infected adults ≥ 18 years old, having switched to a 2-DR taken 4 to 5 days a week,
84 from 01/01/2016 to 06/30/2019, were eligible in this observational study conducted in the
85 Infectious Diseases Department of Pitié-Salpêtrière Hospital, Paris, France.

86

87 *Study endpoints*

88 The primary endpoint was the proportion of participants in ITT population with virological
89 failure (VF) (confirmed pVL > 50 copies/mL, single pVL > 400 copies/mL or single pVL > 50
90 copies/mL with ART change) at week 48, using the Kaplan-Meier estimates. The ITT
91 population consisted of all participants who had started an intermittent 2-DR at least once.
92 Intermittent regimen was defined as ART taken 4 to 5 days a week. ART intensification was
93 defined as a switch to a 3-DR or same 2-DR taken 7 days a week. Secondary efficacy endpoints
94 included the proportion of participants with virological success at W96, with therapeutic
95 success (pVL ≤ 50 copies/mL without ART change) at weeks 48 and 96, using the Kaplan-Meier
96 estimates; the emergence of genotypic resistance and the plasma antiretroviral drug
97 concentration in the event of VF; change in CD4 count and CD4/CD8 ratio over the study
98 period, using the Wilcoxon paired test; and change in the proportion of participants with
99 residual viremia using the McNemar test (ultra-sensitive pVL in the range of 1-20 copies/mL
100 was indicated qualitatively – presence or absence of a detectable signal – using the Cobas
101 AmpliPrep/CobasTaqMan HIV-1 assay, Roche Diagnostics, Switzerland).

102

103 *Data collection*

104 Clinical data and pVL were routinely collected at baseline through the *Nadis* database⁸, and
105 were collected, prior to switching to an intermittent 2-DR and at each routine visit. CD4 and
106 CD8 counts were collected at baseline and W48. Past HIV-RNA and HIV-DNA resistance
107 genotypes were collected and the cumulative genotype combined all past genotypic tests with

108 an updated interpretation using the latest version of the ANRS algorithm
109 (www.hivfrenchresistance.org). The genotypic sensitivity score (GSS) was calculated for each
110 patient from cumulative HIV-RNA and HIV-DNA resistance genotypes, when integrase
111 sequences were available. In the event of VF, genotypic data and antiretroviral plasma
112 concentrations (performed by UPLC-MS/MS) were collected when blood samples were
113 available, as part of our routine procedures.

114

115 *Ethics*

116 Patients at Pitié-Salpêtrière Hospital are routinely followed using the *Nadis* database.⁸ Data
117 from *Nadis* are collected prospectively, for which all patients provided signed consent
118 (registration number with the “Commission Nationale de l’Informatique et des Libertés,
119 CNIL”: 770134). All data were anonymized before analysis. There were no additional
120 biological samples or questionnaires used for this study.

121

122 **RESULTS**

123 *Study population*

124 Overall, 85 patients who switched to an intermittent 2-DR between 01/01/2016 and 06/30/2019
125 were analyzed. At time of analysis, 82 patients had at least one available pVL after W48, and
126 36 after W96.

127 Baseline patients characteristics are shown in Table 1. Median age was 57 years (IQR 50-63).
128 They were on ART for a median of 21 years (IQR 13-24) and were virologically suppressed for
129 a median of 6.5 years (IQR 3.7-10.8). Prior to switching to the intermittent 2-DR, 80/85 (92%)
130 were already on a daily 2-DR given 7 days a week for a median of 33 months (IQR 18-49).

131 From past HIV-RNA genotypes, acquired resistance to NRTIs, NNRTIs, PIs and INSTIs in the
132 history was observed in 63%, 53%, 29% and 7% of patients, respectively (Table 1). The M184V
133 mutation was present in 53% of patients.

134 Intermittent 2-DRs consisted of INSTI+NNRTI in 49/85 patients (58%), INSTI+NRTI in 11
135 patients (13%) and 2 NRTIs in 9 patients (11%) (Table 2). Thirty-one patients were on
136 DTG/RPV once daily, 12 on raltegravir/etravirine (RAL/ETR) twice daily, 8 on DTG/3TC once
137 daily and 8 on tenofovir/emtricitabine (TDF/FTC) once daily, at respective standard doses. The
138 GSS was 2 in 80% of patients in whom the score could be calculated (past available HIV-RNA
139 and/or -DNA genotype(s) with integrase sequence) and 1.0-1.5 in 20% of patients.

140 At inclusion, 80% of patients were on a 5-day weekly 2-DR, and 20% 4-daysweekly 2-DR. It
141 is worth noting that the 3 patients coinfecting with HBV were on a combination including
142 tenofovir.

143

144 *Virological and strategy success rates at W48 and W96*

145 Median follow-up was 90 weeks (IQR 64-111). Overall, 81/82 patients had a pVL \leq 50
146 copies/mL at W48, and 32/36 at W96, with one VF occurring during the first 48 weeks of
147 follow-up, and three additional VFs occurring during the subsequent 48 weeks. Virological
148 success rate was 98.8% (95%CI 93.6-100) at W48 and 95.3% (95%CI 88.4-98.7) at W96
149 (Figure 1A).

150 The four VFs occurred at W8, W49, W79 and W88: all 4 patients had one single pVL $>$ 50
151 copies/mL (74, 479, 236 and 133 copies/mL, respectively), on dolutegravir/rilpivirine,
152 abacavir/lamivudine, raltegravir + darunavir/ritonavir and tenofovir disoproxil fumarate +
153 darunavir/ritonavir, respectively. All had a GSS of 2 before enrolling in the study. Poor
154 adherence was declared by the patient with a rebound of pVL=479 copies/mL, confirmed by
155 low plasma concentrations (C_{12h} for abacavir: 39 ng/mL, C_{12h} for lamivudine: 108 ng/mL), and

156 the emergence of the M184V mutation. After starting dolutegravir/lamivudine 7 days a week,
157 pVL dropped to ≤ 50 copies/mL. No blood samples were available for the patient with a
158 pVL=236 copies/mL; therefore, no plasma drug measurement or resistance genotype test could
159 be performed. In the two remaining patients, reported medication adherence was good; plasma
160 concentrations reached expected levels for dolutegravir and rilpivirine (C_{24h} : 3256 and 199
161 ng/mL, respectively) and were low for darunavir and tenofovir (C_{24h} : 214 and 20 ng/mL,
162 respectively, attributable to the 4-days-a-week regimen); a resistance genotype test was
163 performed but HIV-RNA was not amplifiable. These 3 patients recovered pVL ≤ 50 copies/mL
164 after resuming the same 7-days-a-week treatment. No protocol-defined VF occurred after W96
165 in patients with sustained follow-up at time of analysis.

166 Overall, intermittent 2-DR was discontinued for reasons other than VF at W8, W14, W46, W58
167 and W145: weight gain on DTG/3TC (n=2), clinician decision (n=2) and death due to pancreatic
168 cancer (n=1), leading to a final strategy success rate of 95.3% (95%CI 88.4-98.7) at W48, and
169 90.6% (95%CI 82.3-95.8) at W96 (Figure 1B). During follow-up, efavirenz, rilpivirine and
170 etravirine were substituted for doravirine in 5 patients, and raltegravir for dolutegravir in 2 of
171 these patients, for prevention of toxicity, drug-drug interactions or simplification reasons.

172 Furthermore, 9/68 patients (13%) switched from a 5-days-a-week to a 4-days-a-week regimen.
173 After switching to an intermittent 2-DR, the median duration before pVL was tested was 11
174 weeks (IQR 8-20), and the mean number of pVL tests carried out per year until the end of
175 follow-up was 2.6 (+/- 0.7).

176 Overall, the intermittent 2-DR strategy led to an average of 149 days off ART per patient during
177 the study period.

178 There was no significant change in CD4 count over the study period: -8 cells/mm³ (95% CI -
179 40 to +28, p=0.69) (Figure 2A) but a slight increase in CD4/CD8 ratio was observed: +0.06
180 (0.01-0.08, p=0.009) (Figure 2B).

181 There was no significant change in the proportion of patients with residual viremia from
182 inclusion to the end of follow-up: 24.7% versus 32.9%, respectively (p=0.15) (Figure 2C).

183

184 **DISCUSSION**

185 This observational study on 85 patients suggests that two-drug therapies given 4 to 5 days a
186 week (intermittent 2-DRs) could maintain the control of HIV replication, with a virological
187 success rate >95% at 48 and 96 weeks, in previously virally suppressed patients on a 7-days-a-
188 week 2-DR or intermittent 3-DR. This is the level of efficacy required to maintain treatment in
189 the current context of HIV care. As no class of drugs is free of side effects and the cumulative
190 long-term impact of ART over decades is unknown, drug-reduced ART is now a key issue.
191 Intermittent two-drug therapies offer an opportunity to combine two drug reduction methods.
192 In this study, we chose to define VF strictly, including one single rebound of pVL \geq 50
193 copies/mL with change of treatment. Among the four VF observed, one was related to
194 adherence difficulties on a 2-DR with a low genetic barrier (abacavir/lamivudine), with the
195 emergence of the M184V mutation, while there was no clear explanatory factor for the three
196 other viral rebounds with a low pVL, except suboptimal therapeutic pressure. As these 3
197 patients with good adherence were resuppressed after resuming the same 2-DR 7 days a week,
198 emergence of resistance is unlikely.

199 Two-drug suppressive therapies are increasingly important in a context of lifelong required
200 ART. The benefit of several 2-DRs has been demonstrated through improved metabolic, renal
201 and bone markers. The switch from a tenofovir alafenamide (TAF)-based 3-DR to DTG/3TC
202 has been associated with a decrease in total cholesterol, LDL-cholesterol and triglycerides, as
203 well as insulin resistance biomarkers.² In the SWORD studies, switching to DTG/RPV has been
204 associated with a significant improvement in renal biomarkers and bone formation and
205 resorption markers in patients who took TDF at baseline.⁹ In the ANRS ETRAL study,

206 participants improved their lipid profile and bone mineral density after stopping PIs and TDF.¹⁰
207 Prevention of cardiovascular and renal function impairment as well as bone fracture risk
208 attributable to ART is a key concern for people living with HIV who are all aging. In a
209 substantial number of cases, two-drug therapies are good options for optimizing therapeutic
210 strategies.⁴

211 Recently, the ANRS-170 QUATUOR study demonstrated the non-inferiority of various 3-DRs
212 4 days a week, including INSTIs as a third agent, compared to maintaining a 7-days-a-week
213 regimen.⁶ In 2016, the BREATHER study showed that ART-related adverse events were
214 significantly less frequent in the “short cycle therapy” group; at the end of follow-up, 90% of
215 participants in the “short cycle therapy” group reported that weekend breaks made life easier
216 than daily ART.⁵ These intermittent strategies appear to be appreciated, associated with a
217 decrease in the mental burden of HIV infection, and lead to a 30-40% reduction in cumulative
218 antiretroviral quantity and cost, as illustrated in our cohort.

219 By controlling viral replication, ART leads to immune restoration and persistent decrease in
220 HIV reservoirs, CD8 T-cell activation and systemic inflammation. The use of “drug-reduced”
221 strategies to control these parameters is often challenged. Several trials have demonstrated the
222 stability of CD4 counts, CD4/CD8 ratios, total HIV-DNA, residual plasma HIV-RNA and
223 inflammation markers after switching to a 2-DR or intermittent regimens.¹¹ In this study, we
224 showed there was no change in CD4 count or residual pVL, suggesting no additional risk of
225 morbidity in included patients. We even observed a slight increase in the CD4/CD8 ratio.

226 There was a heterogeneous distribution of ART in our population because of the observational
227 nature of the study, the study’s long period, with changes in prescription attitudes, and the
228 patients’ long virological history. A vast majority of them had acquired resistance mutations in
229 the past, limiting therapeutic options and leading sometimes to unconventional combinations.

230 Our study has some limitations: it was an observational retrospective single-center cohort, and
231 the two-drug therapies in our analysis were not those most commonly prescribed currently.
232 Reasons for switch were not systematically specified. Some cases were discussed by a
233 multidisciplinary board, including clinicians, virologists and pharmacologists, in order to
234 optimize ART with regard to virological history and possible drug-drug interactions. The results
235 obtained are encouraging but they need to be confirmed as only a small number of patients
236 reached W96.

237 **In conclusion**, there is a clear need to investigate drug-reduced antiretroviral strategies
238 targeting lifelong viral suppression. Our findings suggest that in patients with long-term viral
239 suppression, several two-drug therapies have the potential for intermittent administration. Used
240 as a proof of concept, our study argues in favor of a randomized clinical trial to assess the
241 capacity of intermittent 2-DRs, such as DTG/3TC and DTG/RPV, to maintain virological
242 success, in comparison with a 7-days-a-week 2-DR.

243

244

245 **ACKNOWLEDGMENTS**

246 We thank Fiona McBrearty for proofreading this article prior to submission.

247 This work was presented as a poster at the 17th European AIDS Conference (EACS), 2019,

248 Basel, Switzerland (Abs. PE2/66).

249

250 **FUNDING**

251 This work was partially funded by the ANRS (French National Agency for Research on AIDS
252 and Viral Hepatitis).

253

254 **TRANSPARENCY DECLARATION**

255 RP, MW, GL, RT, MAV, LS, SS, AS, CS, GP, VC, AGM and CK have received travel grants
256 and advisory fees from Gilead, ViiV Healthcare and Merck. BA, AF, RA and MPL have no
257 conflicts of interest to declare. VC is a founder and board member of SkinDermic. AGM
258 declares a conflict of interest with Theratec.

259 **REFERENCES**

- 260 1. Ghosn J, Taiwo B, Seedat S, *et al.* HIV. *Lancet Lond Engl* 2018; **392**: 685–97.
- 261 2. van Wyk J, Ajana F, Bisshop F, *et al.* Efficacy and Safety of Switching to
- 262 Dolutegravir/Lamivudine Fixed-Dose Two-Drug Regimen Versus Continuing a Tenofovir
- 263 Alafenamide-Based Three- or Four-Drug Regimen for Maintenance of Virologic Suppression
- 264 in Adults With HIV-1: Phase 3, Randomized, Non-inferiority TANGO Study. *Clin Infect Dis*
- 265 *Off Publ Infect Dis Soc Am* 2020; **71**: 1920–9.
- 266 3. Llibre JM, Hung C-C, Brinson C, *et al.* Efficacy, safety, and tolerability of dolutegravir-
- 267 rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3,
- 268 randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet Lond Engl* 2018; **391**:
- 269 839–49.
- 270 4. Katlama C, Ghosn J, Murphy RL. Individualized antiretroviral therapeutic approaches: less
- 271 can be more. *AIDS Lond Engl* 2017; **31**: 1065–71.
- 272 5. The BREATHER (PENTA 16) Trial Group. Weekends-off efavirenz-based antiretroviral
- 273 therapy in HIV-infected children, adolescents, and young adults (BREATHER): a
- 274 randomised, open-label, non-inferiority, phase 2/3 trial. *Lancet HIV* 2016; **3**: e421–30.
- 275 6. Landman R, De Truchis P, Assoumou L, *et al.* ANRS 170 QUATUOR 4/7 days
- 276 maintenance strategy in antiretroviral treated adults with HIV-1 infection: an open
- 277 randomised parallel non-inferiority phase III trial. IAS Conference on HIV Science, Mexico,
- 278 21-24 July 2019; Abs. WEAB0406LB.
- 279 7. de Truchis P, Assoumou L, Landman R, *et al.* Four-days-a-week antiretroviral maintenance
- 280 therapy in virologically controlled HIV-1-infected adults: the ANRS 162-4D trial. *J*
- 281 *Antimicrob Chemother* 2018; **73**: 738–47.
- 282 8. Pugliese P, Cuzin L, Cabié A, *et al.* A large French prospective cohort of HIV-infected
- 283 patients: the Nadis Cohort. *HIV Med* 2009; **10**: 504–11.

- 284 9. Aboud M, Orkin C, Podzameczer D, *et al.* Efficacy and safety of dolutegravir–rilpivirine for
285 maintenance of virological suppression in adults with HIV-1: 100-week data from the
286 randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV* 2019; **6**:
287 e576–87.
- 288 10. Katlama C, Assoumou L, Valantin M-A, *et al.* Dual therapy combining raltegravir with
289 etravirine maintains a high level of viral suppression over 96 weeks in long-term experienced
290 HIV-infected individuals over 45 years on a PI-based regimen: results from the Phase II
291 ANRS 163 ETRAL study. *J Antimicrob Chemother* 2019; **74**: 2742–51.
- 292 11. Cento V, Perno CF. Two-drug regimens with dolutegravir plus rilpivirine or lamivudine in
293 HIV-1 treatment-naïve, virologically-suppressed patients: Latest evidence from the literature
294 on their efficacy and safety. *J Glob Antimicrob Resist* 2020; **20**: 228–37.
- 295
- 296

297 **Table 1. Patient characteristics at baseline (n=85).**

Age, years, median (IQR)	57 (50-63)
Gender, n/N (%)	
- Male	67/85 (79)
- Female	18/85 (21)
Birth Country, n/N (%)	
- France	68/85 (80)
- Other	17/85 (20)
Transmission group, n/N (%)	
- MSM	42/85 (50)
- Heterosexual	24/85 (28)
- Other	19/85 (22)
CDC stage C, n/N (%)	22/85 (26)
CD4 nadir, cells/mm³ (IQR)	233 (110-327)
Pretherapeutic HIV-RNA, log₁₀ cp/mL (IQR)	5.02 (4.52-5.47)
Time from HIV diagnosis, years, median (IQR)	24 (17-28)
Time from ART initiation, years, median (IQR)	21 (13-24)
HIV subtype, n/N (%)	
- B	32/42 (76)
- Other than B	10/42 (24)
Past resistance to ART (analysis of cumulative HIV-RNA genotype),	
n/N (%)*	
- At least one NRTI	37/59 (63)
- At least one NNRTI	31/59 (53)
- At least one PI	17/58 (29)

- At least one INSTI 2/27 (7)

Genotypic sensitivity score, n/N (%)*

- 2.0 28/35 (80)

- 1.5 2/35 (6)

- 1.0 5/35 (14)

Duration of viral suppression, years, median (IQR) 6.5 (3.7-10.8)

CD4 count, cells/mm³ (IQR) 658 (519-867)

CD4/CD8 ratio, median (IQR) 0.88 (0.57-1.10)

Previous antiretroviral strategy, n/N (%)

- 3-DR 4 to 5 days a week 4/85 (5)

- 2-DR 7 days a week 80/85 (92)

- Monotherapy 7 days a week 1/85 (1)

Time from 7/7 days a week 2-DR initiation to intermittent 2-DR for the 80 patients concerned, months, median (IQR) 33 (18-49)

Type of intermittent strategy at inclusion, n/N (%)

- 5 days a week 68/85 (80)

- 4 days a week 17/85 (20)

298 **NOTES.** *Calculated from cumulative historical HIV-RNA and HIV-DNA genotypes with
299 reverse transcriptase, protease and/or integrase available sequences.

300

301 **Table 2. Composition of intermittent 2-DR at baseline.**

1 INSTI + 1 NNRTI, n(%) **49/85 (58)**

- DTG/RPV 29/49

- RAL/ETR 12/49

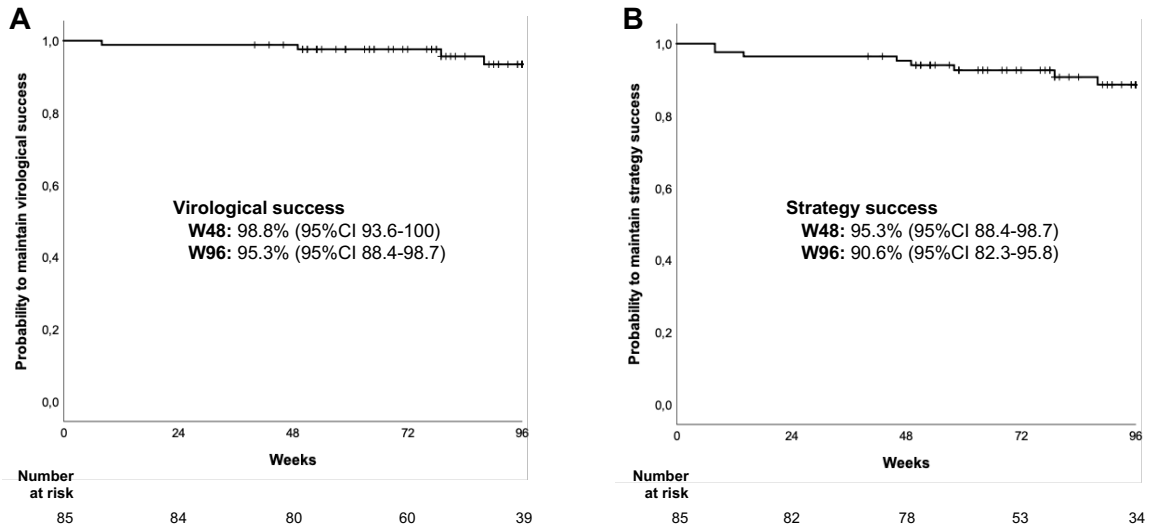
- RAL/NVP 3/49

- RAL/RPV	2/49
- RAL/EFV	2/49
- DTG/NVP	1/49
1 INSTI + 1 NRTI, n(%)	11/85 (13)
- DTG/3TC	10/11
- RAL/3TC	1/11
2 NRTIs, n(%)	9/85 (11)
- TDF/FTC	8/9
- ABC/3TC	1/9
1 PI + 1 NRTI, n(%)	6/85 (7)
- DRV/r/3TC	2/6
- ATV/r/3TC	2/6
- DRV/r/TDF	2/6
1 PI + 1 INSTI, n(%)	3/85 (3)
- ATV/r/DTG	2/3
- DRV/r/RAL	1/3
Other, n(%)	7/85 (8)
- EFV/3TC	1/7
- RPV/3TC	1/7
- RPV/TDF	1/7
- ETR/MCV	1/7
- DRV/r/NVP	1/7
- DRV/r/ETR	1/7
- DRV/r/MCV	1/7

302 **NOTES.** ABC, abacavir. TDF, tenofovir disoproxil fumarate. 3TC, lamivudine. FTC,
303 emtricitabine. NVP, nevirapine. EFV, efavirenz. RPV, rilpivirine. ETR, etravirine. DRV/r,
304 darunavir/ritonavir. ATV/r, atazanavir/ritonavir. RAL, raltegravir. DTG, dolutegravir.

305

306 **Figure 1. Virological success rate (A) and treatment success rate (B) at W48 and W96.**

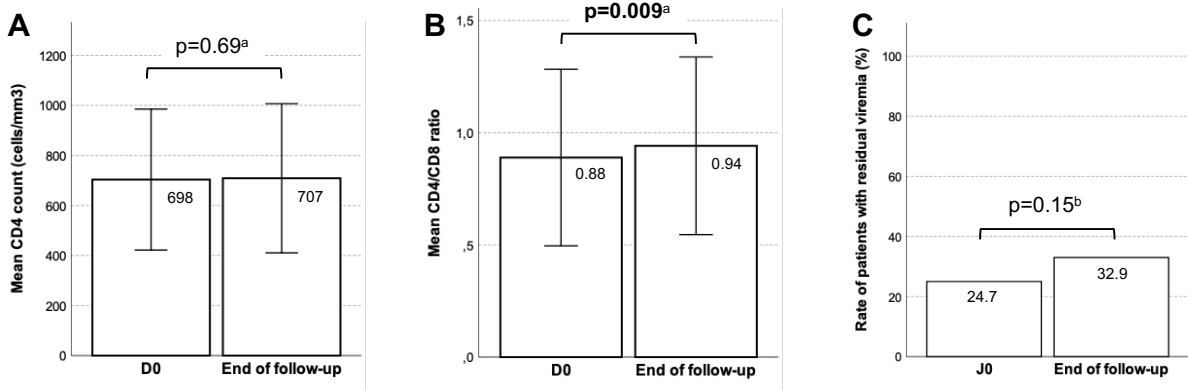


307

308

309 **Figure 2. Change in CD4 count, CD4/CD8 ratio and proportion of residual viremia**

310 **during follow-up (median time: 90 weeks, IQR 64-111).**



311

312 NOTES. a. Wilcoxon paired test. b. McNemar test.