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-03201654>

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.

Title

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

Running title

Virological efficacy of intermittent two-drug therapies

Authors

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

Affiliations

1. Sorbonne University, Infectious Diseases Department, Pitié-Salpêtrière Hospital, AP-HP, Pierre Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136, Paris, France
2. Sorbonne University, Virology Department, Pitié-Salpêtrière Hospital, AP-HP, Pierre Louis Epidemiology and Public Health Institute (iPLESP), INSERM 1136, Paris, France
3. Bichat Claude Bernard Hospital, Pharmacology-Toxicology Department, AP-HP, INSERM, UMRS 1144, Université de Paris, Paris, France
4. Bichat Claude Bernard Hospital, Pharmacology-Toxicology Department, AP-HP, IAME, INSERM, UMRS 1137, Université de Paris, Paris, France

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

ABSTRACT

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

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

Results: Eighty-five patients were included: men: 67/85 (79%), median age: 57 years (IQR 50-63), CD4 nadir: 233/mm³ (110-327), ART duration: 21 years (13-24), duration of virological suppression: 6.5 years (3.7-10.8), CD4 count: 658/mm³ (519-867). Intermittent 2-DRs consisted of: INSTI/NNRTI (58%), INSTI/NRTI (13%), 2 NRTIs (11%), PI/NRTI (7%), and other combinations (11%). Median follow-up was 90 weeks (IQR 64-111). Overall, 4 VFs occurred leading to a virological success rate of 98.8% (95%CI 93.6-100) at W48 and 95.3% (95%CI 88.4-98.7) at W96. Resuming the same 2-DR 7 days a week led to viral resuppression in 3 patients, whereas the M184V mutation emerged in one, leading to ART modification. There was no significant change in the CD4 count or residual viremia rate, but a small increase in the CD4/CD8 ratio ($p=0.009$) occurred over the study period.

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

INTRODUCTION

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

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

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

METHODS

Study participants

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

Study endpoints

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

Data collection

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

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

Ethics

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

RESULTS

Study population

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

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

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

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

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

Virological and strategy success rates at W48 and W96

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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.

REFERENCES

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

284 9. Aboud M, Orkin C, Podzamczar 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)

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

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

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

Figure 2. Change in CD4 count, CD4/CD8 ratio and proportion of residual viremia during follow-up (median time: 90 weeks, IQR 64-111).

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