Forgiveness of dolutegravir-based triple therapy compared to older antiretroviral regimens: a prospective multicenter cohort of adherence patterns and HIV-RNA replication

Jean-Jacques Parienti¹,²,³*, Anna L. Fournier¹,², Laurent Cotte⁴, Marie-Paule Schneider⁵,⁶, Manuel Etienne⁷,⁸, Guillemette Unal²,⁷, Philippe Perre⁸, Jean-Jacques Dutheil³, Elodie Morilland-Lecoq³, Fabien Chaillot³, David R. Bangsberg⁹, Amandine Gagneux-Brunon¹⁰, Thierry Prazuck¹¹, Matthias Cavassini¹², Renaud Verdon¹,², Laurent Hocqueloux¹¹

*Corresponding author

¹Department of Infectious Diseases, University Hospital, Caen, France
²EA2656 Groupe de Recherche sur l’Adaptation Microbienne (GRAM 2.0), Université Caen Normandie, Caen, France
³Clinical Research Unit, University Hospital, Caen, France
⁴Department of Infectious Diseases, University Hospital, Lyon, France
⁵Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland
⁶School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland
⁷Department of Infectious Diseases, University Hospital, Rouen, France
⁸Department of Infectious Diseases, General Hospital, La Roche sur Yon, France
⁹School of Public Health, Oregon Health and Science University/Portland State University, Portland, OR, USA
¹⁰Department of Infectious Diseases, University Hospital, Saint-Etienne, France
¹¹Department of Infectious Diseases, Regional Hospital, Orléans, France
¹²Infectious Diseases Service, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

© The Author(s) 2021. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.
CORRESPONDING AUTHOR

Pr Jean-Jacques PARIENTI, MD, PhD
Service des Maladies Infectieuses,
Avenue de la Côte de Nacre,
CHU Côte de Nacre, 14000 Caen, France
Tel. : +33 231 06 4320 ;
e-mail: parienti-jj@chu-caen.fr
ABSTRACT

Background: For many people living with HIV (PLWH), taking antiretroviral therapy (ARV) every day is difficult.

Methods: Average adherence (Av-Adh) and log-transformed treatment interruption (TI) to ARV were prospectively measured over 6 months using electronic drug monitoring (EDM) in several cohorts of PLWH. Multivariate linear regression models including baseline confounders explored the influence of EDM-defined adherence ($R^2$) on 6-month Log10 HIV-RNA. Multivariate logistic regression models were used to compare the risk of HIV-RNA detection within subgroups stratified by lower ($\leq 95\%$) and higher ($>95\%$) Av-Adh.

Results: Three hundred ninety nine PLWH were analyzed with different ARV: dolutegravir (n=102), raltegravir (n=90), boosted PI (bPI; n=107), and NNRTI (n=100). In the dolutegravir group, the influence of adherence pattern measures on $R^2$ for HIV-RNA levels was marginal (+2%). Av-Adh, TI and Av-Adh x TI increased the $R^2$ for HIV-RNA levels by 54% and 40% in the raltegravir and bPI treatment groups, respectively. TI increased the $R^2$ for HIV-RNA levels by 36% in the NNRTI treatment group. Compared to dolutegravir-based regimen, the risk of VR was significantly increased for: raltegravir (adjusted OR (aOR), 45.6; 95% confidence interval (CI) [4.5 - 462.1], p=0.001); NNRTIs (aOR, 24.8; 95% CI [2.7 - 228.4], p=0.005) and bPIS (aOR, 28.3; 95%CI [3.4 - 239.4], p=0.002) in PLWH with Av-Adh $\leq 95\%$. Among PLWH with $>95\%$ Av-Adh, there were no significant differences on the risk of VR among the different ARV.

Conclusion

These findings support the concept that dolutegravir in combination with two other active ARVs achieves a greater virological suppression than older ARV, including raltegravir, NNRTI and bPI among PLWH with lower adherence.
INTRODUCTION

Suboptimal adherence to antiretroviral therapy can result in insufficient viral suppression\cite{1,2} and promotes the emergence of drug-resistant viral strains\cite{3}. A landmark study with unboosted protease inhibitors antiretrovirals (ARVs) proposed that more than 95\% adherence was required to achieve and maintain virological suppression, which led to the concept that an undetectable HIV viral load (VL) was equivalent to full adherence\cite{1}. Modern antiretroviral therapies with once-daily dosing and low pill burden improved the level of adherence compared to more complex regimens\cite{4,5}. Simpler regimens have improved adherence \cite{4,6} and potent regimens with more favourable pharmacokinetic profiles have allowed more forgiveness to missed doses. Studies investigating non-nucleosides reverse transcriptase inhibitors (NNRTI), boosted protease inhibitors (bPI) and integrase strand-transfer inhibitors (INSTI) as a part of ARV drug combination demonstrated that the minimal level of ARV adherence required to sustain virological suppression may range around 80\%.\cite{7,8} However, the methods used to measure adherence, such a self-report or pharmacy refill did not capture treatment interruptions, another independent driver of virological failure\cite{9} and resistance\cite{10}. In addition, these studies did not specifically investigate second-generation INSTI-based ARV combination, although widely recommended.

Real world studies of the 'forgiveness' to missed doses of ARV regimen are important, as they may help to predict regimen durability and risk of resistance in a context where suboptimal adherence is probably common\cite{11}. We hypothesised that the pharmacokinetic profile and genetic barrier provided by second-generation INSTI, namely dolutegravir-based ARV combination would allow high rate of virological suppression at low-to-moderate adherence levels. Therefore, we aimed to investigate the patterns of adherence to dolutegravir associated with virological replication in comparison to older third agents.
METHODS

Study design and participants

We conducted an international multicenter prospective cohort study of people living with HIV (PLWH) treated with a dolutegravir-based regimen. The DOLUTECAPS study took place in France and Switzerland, between May 2015 and December 2018. Details of the inclusion criteria are described at the clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT02878642. Briefly, adults living with HIV starting once or twice-a-day dolutegravir-based regimens were included at the physician’s discretion. Because we were interested to cover a large range of different pill taking behaviours, the participation of PLWH perceived by their treating physician at risk of suboptimal adherence was encouraged. Subjects had a genotypic sensitivity score of 3 or more, including dolutegravir. The genotypic sensitivity score represents the total number of ARV drugs in the regimen to which a patient’s HIV was susceptible (score, 1), possibly susceptible (score, 0.5), or resistant (score, 0), according to version 30 of the ANRS AC-43 resistance group algorithm (http://www.hivfrenchresistance.org/2019/tab6.html). We did not include people using pillbox organizers and those who were not responsible for taking their antiretroviral pills. Three groups of participants were defined: antiretroviral naïve who initiated dolutegravir (STARTING group); antiretroviral experienced who switched to dolutegravir for virological failure (FAILING group); antiretroviral experienced who switched to dolutegravir while HIV-RNA was suppressed (SWITCHING group). Dolutegravir combined with abacavir/lamivudine as a single tablet regimen and multi tablet regimens containing dolutegravir plus at least 2 other active ARVs were allowed.

Several centers from our group have incorporated the use of EDM devices in routine practice. In addition, we previously investigated adherence-virological outcome relationships for older ARV such as NNRTI [12], bPI [13,14] and raltegravir [15]. We contrasted the DOLUTECAPS cohort findings with other antiretroviral therapies from our EDM database (Supplemental Figure 1). All participants were followed prospectively with electronic adherence monitoring and an HIV-RNA determination at 6 months as the primary outcome.
**Data collection and adherence pattern measures**

Baseline characteristics including sociodemographic factors and clinical characteristics were collected at baseline for the 4 groups: dolutegravir, raltegravir, bPI and NNRTI. Patients were asked to use electronic drug monitoring (EDM, Aardex, Switzerland) devices to prospectively characterize their pattern of adherence to the third agent for 6 months. The same monitoring strategy and devices were used for the 4 groups. Other ARV pills (for example, "backbone nucleos/tide reverse transcriptase inhibitors), if any, were not monitored. Two measures were extracted from electronic dosing history for each participant: 1) the average percent dose adherence corresponding to the number of observed electronic pill cap opening events divided by the expected events; (2) the log_{10} transformed duration of the longest treatment interruption (in hours). EDM records were read and reviewed at all study visits, and allowed participants to add any doses taken when they knew they did not use the device. Seventeen participants with no EDM event during the 2 weeks prior month 6 were excluded. This is because non-persistence to any short-acting antiretroviral drug is known to be associated with virological replication in most situations.

**Patient Consent Statement.**

The Institutional Review Board of the University of Caen, France (which covers all French sites) and the Committee on Human Subjects Research of the University of Lausanne, Switzerland approved all study procedures and the participants provided written informed consent.

**Outcomes**

The primary outcome was HIV-1 RNA in plasma measured using the test available in each center with a limit of detection ≤50 HIV-1 RNA copies/mL plasma. We defined virological replication as a failure to suppress or sustain HIV-RNA to less than 50 copies/mL at 6-month., A value of ≤50 was imputed to PLWH who had a lower limit of detection above 50 copies/mL for 34 participants in the NNRTI and 56 participants in the bPI treatment groups. Emergence of resistance to dolutegravir and
to raltegravir was investigated by genotyping the integrase coding sequence of the virus after the development of virological replication.

**Statistical analysis**

Continuous variables were summarized as the mean values, median values, SDs, and interquartile ranges [IQRs] depending on their distributions. Dichotomous data were summarized as numbers and proportions. Regarding baseline and follow-up characteristics, quantitative variables were compared between ARV classes using an analysis of variance or a Kruskal-Wallis test, as appropriate and qualitative variables were compared using Fisher exact test. In order to characterize the adherence pattern associated with HIV-RNA replication, we displayed a three-dimensional scatter plot reporting the level of log HIV-RNA (vertical Z-axis) according to the average adherence (horizontal X-axis) and log longest treatment interruption (horizontal Y-axis). Because the original data did not contain enough combinations of x, y, and z values to generate an empirically derived surface plot with <64% average adherence, we censored these observations for data visualization. In addition, we used a smoothing spline interpolation method with λ=0.1 as a trade-off between closeness to the original data and smoothness. For each antiretroviral group, we computed three different linear regression models: (i) with average adherence (Model 1); (ii) with treatment interruption (Model 2); (iii) with average adherence, treatment interruption and the product (interaction) of average adherence x treatment interruption (Model 3), as independent covariables with the log HIV-RNA at 6-month as the dependent variable. These models were also adjusted for potential confounders (age, sex, baseline treatment scenarios, i.e naïve, switch or treatment failure, baseline HIV-RNA and CD4-cell count).

The influence of the EDM-defined adherence pattern on 6-month HIV-RNA was assessed in two ways: (i) by testing the slope of each adherence pattern parameter coefficient to zero; (ii) by assessing the incremental R-squared value (or variance explained) for each model, compared to a model without EDM adherence measurement (i.e. including only baseline factors).

The effect size of factors associated with the probability of virological detection (HIV-RNA>50 copies/mL) was estimated by calculating odds ratios (ORs) and adjusted OR using univariate and
multivariate logistic regression models, respectively. This analysis was performed in the overall cohort and in subgroups with higher (>95%) and lower (≤95%) average adherence[1]. Analyses were performed using PowerView, version 2.3.3 (Aardex Group, Sion, Switzerland) and SAS, version 9.4 (SAS Institute, Cary, NC). All reported P values are 2-sided, and a P value of 0.05 or less denoted statistical significance.

RESULTS

Baseline characteristics

The baseline characteristics of the participants are shown in Table 1. Seventy-two percent of the participants treated by dolutegravir-based regimen were men and the mean age was 47.7 years. Approximately, one-quarter of the participants treated by dolutegravir-based regimen were treatment-naive at baseline. Forty-seven (46%) PLWH had a plasma HIV RNA <50 copies/mL at study entry. The median baseline CD4 cell count was 494 (IQR, 290–705), and the median baseline plasma HIV RNA level was 2.1 log10 (IQR, 1.6–4.1). The baseline characteristics from PLWH treated with other third agents are presented in Table 1. In the NNRTI-based group, the third agent was nevirapine for 70 PLWH, efavirenz for 12 PLWH and rilpivirine for 18 PLWH. In the boosted PI group, the third agent was lopinavir for 54 PLWH, atazanavir for 48 PLWH and other boosted PI for 3 PLWH.

HIV-RNA at month-6

In the dolutegravir treatment group (Table 2), eight PLWH had low levels of HIV-RNA replication: 5/24 (17%) in the failing group (median HIV-RNA 132 cp/mL, range [88-168]); 2/26 (8%) in the starting group (HIV-RNA 80 and 161 cp/mL) and 1/46 (2%) in the switching group (HIV-RNA 73 cp/mL). Among those, 3/8 were amplified and none demonstrated resistance mutation to the INSTI class. In the raltegravir treatment group (Table 2), 18 PLWH had HIV-RNA replication (median HIV-RNA 362 copies/mL, range [57-51300]) and 14/18 were subjected to nucleic acid amplification and sequencing: 4 samples harboured INSTI conferring resistance to raltegravir (Q148H, N155H, Q148R and Y143A). In the NNRTI treatment group (Table 2), 12 PLWH had HIV-RNA replication (median
HIV-RNA 854 copies/mL, range [66-15000]). In the bPI group (Table 2), 26 PLWH had HIV-RNA replication (median HIV-RNA 11000 copies/mL, range [59-801400]). No data were available for resistance testing in the bPI and NNRTI groups.

Adherence pattern and HIV-RNA relationships

Figure 1 displays the 6 months Log10 HIV-RNA according to the EDM-defined adherence pattern by antiretroviral regimen among 399 PLWH. As shown in Figure 2A, the surface plot for dolutegravir-based triple therapy is flat, indicating a low level of HIV-RNA replication regardless of the adherence pattern. None of the models including adherence pattern parameters was significantly associated with 6-month HIV—RNA level (Figure 2A) and the incremental HIV-RNA variance explained by the inclusion of adherence pattern variables was minimal (2%). In contrast, the adherence patterns were significantly associated with the level of virological replication above the detection threshold for all older ARV, with an incremental variance explained ($R^2$) ranging from 14% (Figure 2D, model 2) to 54% (Figure 2B, model 3). The model 3 had the highest HIV-RNA level variance explained for the raltegravir group (Figure 2B) and the bPI group (Figure 2D), suggesting that the influence of one adherence measure depends on the value of the other. Regarding the NNRTI group (Figure 2C), the longer treatment interruption (model 2) had the highest variance explained to predict HIV-RNA level.

Predictors of HIV-RNA > 50 copies/mL

In the overall cohort, factors associated with virological detection (i.e. probability of 6-month HIV-RNA ≥ 50 copies/mL) in the univariate and multivariate analyses are shown in Table 2. In the subgroup analyses based on average adherence, the risk of virological detection was similar between all ARVs among PLWH with >95% adherence levels (Table 3) in multivariate analysis. Among PLWH with ≤95% adherence levels (Table 3) and compared to those receiving dolutegravir-based regimen, the risk of virological detection was significantly and independently increased for raltegravir-based regimen, NNRTIs and bPIs in multivariate analysis.
DISCUSSION

In this cohort of PLWH followed by EDM, the adherence pattern to dolutegravir-based triple therapy was not a predictor of suppressed HIV-RNA. This picture contrasts with the strong association between adherence pattern and HIV-RNA level found for older regimens, including raltegravir, NNRTI and bPI-based ARV therapies. In addition, the use of dolutegravir therapy outperformed all other ARV strategies in term of virological suppression below the limit of detection among PLWH in the lower adherence subgroup, in multivariate analysis adjusting for age, sex, CD4 cell count and group (starting, switching and failing) and baseline HIV-RNA. No emerging mutation conferring resistance to INSTI was detected in the dolutegravir group with detectable HIV RNA, in contrast with the raltegravir group. Taken together, these results suggest that dolutegravir-based ARV therapies are more forgiving to missed doses (either by average adherence or treatment interruptions) than the other investigated ARV regarding the risk of HIV-RNA replication. In addition, dolutegravir-based triple therapy is more forgiving to missed doses than raltegravir-based triple therapy regarding the risk resistance.

Most of the previous studies in this area of research attempted to identify an adherence threshold required for virological suppression with the aim to challenge the >95% historical threshold. For example, Byrd et al[8] reported that 75% average adherence defined by pharmacy refill to INSTI-based ARV therapy was required to suppress 90% of the treated patients. In this large cohort, first- and second-generations INSTI were pooled although we found the level of forgiveness between dolutegravir and raltegravir strongly differed (as suggested in Figure 2A and 2B, respectively). Overall, the multivariate analysis of the risk of virological replication (Table 1, n=399) is consistent with the >80% level of average adherence found in other studies[2,7,8] but reaffirms the importance of treatment interruption length (aOR, 4.6; 95% CI [1.3 - 16.9], p=0.02), as an independent risk factor[9,10,16].

Importantly, the use of dolutegravir was significantly and independently associated with a lower risk of virological replication compared to other ARVs in the subgroup with lower adherence. Although
the 95% confidence intervals were large due to smaller sample size in this subgroup, this superiority is consistent with a network meta-analysis of 20 randomized trials in which a significantly higher proportion of naïve PLWH starting dolutegravir achieved virological suppression at week 96 compared to protease inhibitors, efavirenz and cobicistat-boosted elvitegravir[17]. The pharmacokinetic forgiveness of dolutegravir-based regimen is supported by the 14 hours dolutegravir terminal elimination half-life and its duration of inhibitory effect (>2-fold higher than the IC90 for 72 h after the last dose)[18]. In contrast, raltegravir, boosted atazanavir and boosted lopinavir have shorter terminal elimination half-life, respectively 10-12[19], 8.3 and 2.4 hours[20]. NNRTIs do have a long plasma half-life but a relatively low genetic barrier to HIV-1 resistance. While a prolonged plasma exposure improves pharmacokinetic forgiveness[21], a period of functional monotherapy following NNRTI-based treatment interruption may select for low-frequency resistant strains. Despite a high genetic barrier, dolutegravir monotherapy does promote INSTI-resistant strains[22] but only after a long period of exposure. This scenario is unlikely to occur when combined with other nucleosides in a fixed dose combination or when combined with nucleotides dosed once-daily whose anabolites have long intracellular half-lives.

There are several important limitations to this study. Adherence was monitored by EDM so we cannot prove that the ARVs were ingested. The duration of the study, 6 month was short and any virologic breakthrough before 6 month remained unnoticed. We compared non-randomized groups of PLWH with different baseline characteristics. In particular, the distribution of PLWH who started treatment as a switch, treatment failure and first therapy was different among treatment groups (Table 1). The use of multivariate analysis adjusting for important predictors of virological replication may have contributed to attenuate this risk of bias, although residual confounding may remain. The cohorts comparing different treatment groups were not contemporaneously studied. We investigated dolutegravir-based triple therapy. Therefore, our results regarding dolutegravir should not be generalized to dual-therapies (with either rilpivirine or lamivudine) or to bictegravir-based triple therapy. Further reseach in this area is warranted.
The study has also strengths. Our large sample size of 399 PLWH representing 73,017 EDM events with various ARV including dolutegravir makes this cohort unique. The diversity of ARV and adherence pattern behaviors allowed us to identify significant interactions between average adherence and treatment interruption. While prior work have demonstrated that short-term treatment interruptions can be reliably predicted by average adherence[23], our results suggest that: (i) they are not interchangeable measures[24]; (ii) their influence differs by ARV[21]. In addition, the use of historical controls allowed contrasting virological outcomes with dolutegravir to older regimens at similar adherence patterns (Figure 2A to D) or different adherence strata (Table 3).

Consistently high adherence should remain the goal of treatment, despite the high rates of suppression across a wide range of adherence level and patterns suggest a high degree of short-term forgiveness on dolutegravir-based regimens. Low levels of tenofovir by dried blood spots predicted future virological replication among PLWH receiving INSTI-based regimens (adjusted Odds Ratio, 1.9, 95% confidence interval [1.0 – 3.4], p=0.036)[25]. Moreover, suboptimal adherence[26] to ARVs and ARVs treatment interruptions[27] were both associated with higher levels of inflammation amongst people with full suppression and is associated with clinically significant morbidity in treated PLWH.[28]

As the WHO recommends, the transition from NNRTIs- to dolutegravir-based HIV treatment regimens in resource-limited settings should limit the risk or resistance following unstructured drug interruption due to toxicities, poor retention in care and drugs being out of stock locally. Our results are in line with the current International Antiviral Society-USA Panel guideline[29] in which second-generation INSTIs are preferred ARV treatment for most PLWH. However, our results do not support the European AIDS Clinical Society 2020 guideline[30]. Starting a raltegravir-based regimen as preferred initial antiretroviral therapy may expose PLWH with suboptimal adherence to the risks of incomplete viral replication and potential emergence of resistance to INSTI.
CONCLUSION

Our findings suggest that PLWH treated with dolutegravir-based combination may be at lower risk of detectable virological replication than those treated with older regimens at similar low-to-moderate adherence levels. While many factors not evaluated in this work should influence the choice of ARV therapy, including tolerance, pill burden, PLWH preference, the risk of drug-drug interaction and costs, we recommend using dolutegravir-based regimens for PLWH who struggle to achieve high levels of adherence or at risk of treatment interruptions.
Acknowledgments

The authors wish to thank all participants, the staff from all participating centers, in particular Pascale Goubin, Arnaud de la Blanchardière, Sylvie Dargère, Aurélie Baldolli, Jocelyn Michon, and Anne Martin. This work has been previously presented in part at the 12th International Conference on HIV Treatment and Prevention Adherence held in Miami, FL, June 4-6, 2017 (Abstract 389)

Financial support. Funded by ViiV healthcare

Disclaimer. All operational aspects of the study, including monitoring, data collection, and statistical analyses, were managed by Caen University Hospital. The funder had no role in the study design, data collection, data analysis, data interpretation, and manuscript writing. All authors had final responsibility for the decision to submit for publication.

Potential Conflicts of Interest. J-J. P. reports personal fees and non-financial support from Gilead Sciences, MSD, and ViiV Healthcare, outside the submitted work. L.C. reports personal fees and non-financial support from Abbvie, Janssen Cilag, Gilead Sciences, MSD, and ViiV Healthcare, outside the submitted work. L.H. reports personal fees from Abbvie, Gilead, Janssen, Merck, and ViiV Healthcare, outside the submitted work. All other no reported conflicts.

Author contributions. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: J-J.P., L.C., M.C., D.R.B. and L.H. All authors were involved in acquisition of data. J-J.P., A.L.F., J-J.D., E.M.L. and F.C. analysed data. J-J.P., M.C. and L.H. contributed to clinical oversight of the study. J-J.P. provided statistical expertise. J-J.P., A.L.F., L.C., M-P.S., D.R.B., M.C., R.V. and L.H. participated in data interpretation and drafted the report. All authors provided input to the report and approved the final version.
Table 1. Baseline and follow-up characteristics by antiretroviral class

| Variables                      | Dolutegravir-based (n=102) | Raltegravir-based (n=90) | NNRTI-based (n=100) | bPI-based (n=107) | p-value |
|--------------------------------|-----------------------------|--------------------------|---------------------|-------------------|---------|
| Baseline characteristics       |                             |                          |                     |                   |         |
| Age, mean (SD), years          | 47.7 (13.2)                 | 46.2 (11.2)              | 46.8 (10.6)         | 41.3 (7.6)        | <0.001  |
| Male, sex, n(%)                | 73 (72)                     | 65 (72)                  | 86 (86)             | 88 (82)           | 0.028   |
| CD4+ cells, median (IQR)       | 494 (290 - 705)             | 490 (309 - 709)          | 510 (383 - 723)     | 311 (229 - 450)   | <0.001  |
| Treatment groups, n (%) /      |                             |                          |                     |                   |         |
| Log HIV-1 RNA, median [IQR]    |                             |                          |                     |                   |         |
| Switched treatment             | 47 (46) / 1.7               | 69 (77) / 1.7            | 100 (100) / 1.7     | 31 (29) / 1.7     | <0.001  |
| Treatment-naive                | 26 (26) / 4.6 [4.0-5.0]     | 10 (11) / 5.4 [3.6-5.5]  | 0 (0) / -           | 43 (40) / 4.4 [3.8-5.1] | <0.001  |
| Failed treatment               | 29 (28) / 3.2 [2.6-4.1]     | 11 (12) / 4.6 [4.0-5.0]  | 0 (0) / -           | 33 (31) / 2.8 [2.3-3.6] |         |
| Backbone                       |                             |                          |                     |                   |         |
| TDF/FTC or TAF/FTC             | 22 (22)                     | 49 (54)                  | 22 (22)             | 56 (52)           |         |
| ABC/3TC                        | 47 (46)                     | 6 (7)                    | 38 (38)             | 10 (9)            |         |
| Other NRTIs combination        | 8 (8)                       | 12 (13)                  | 40 (40)             | 13 (12)           |         |
| Other class combination        | 25 (25)                     | 23 (26)                  | 0 (0)               | 28 (26)           | <0.001  |
| Adherence follow-up            |                             |                          |                     |                   |         |
|                           | Average adherence, median (IQR) | Longest TI in days, median (IQR) |
|---------------------------|----------------------------------|----------------------------------|
|                           | 96.0 (87.0 - 99.0)               | 2.1 (1.3 - 2.8)                  |
|                           | 97.0 (91.0 - 100.0)              | 1.5 (1.0 - 2.7)                  |
|                           | 96.0 (84.5 - 99.0)               | 1.3 (1.1 - 1.9)                  |
|                           | 95.3 (82.0 - 100.0)              | 2.0 (1.0 - 7.0)                  |
|                           | 0.32                             | <0.001                           |

Abbreviations: bPI, boosted protease inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; TDF, tenofovir; FTC, emtricitabine; TAF, tenofovir alafenamine; ABC, abacavir; 3TC, lamivudine; NRTI, Nucleoside Reverse Transcriptase Inhibitor; TI, treatment interruption.
Table 2. Factors associated with virological replication (>50 copies/mL) at month-6 in the overall cohort (n=399)

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | No VR (n=335) | VR (n=64) | p-value | aOR [95%CI] | p-value |
| Age, mean (SD)                   | 44.5 (11.8) | 41.6 (11.3) | 0.07 | 0.88 [0.63 - 1.22] | 0.44 |
| Male                             | 259 (77.3) | 53 (82.8) | 0.41 | 1.36 [0.6 - 3.2] | 0.48 |
| CD4 cells, mean (SD)             | 494 (256) | 402 (250) | 0.009 | 0.97 [0.86 - 1.14] | 0.92 |
| Log HIV-RNA, cp/mL, mean (SD)    | 2.44 (1.23) | 2.90 (1.37) | 0.008 | 1.61 [0.97 - 2.68] | 0.07 |
| Third antiretroviral agent        | 0.005 | | | | |
| Dolutegravir-based               | 94 (28.1) | 8 (12.5) | Ref. | | |
| Raltegravir-based                | 72 (21.5) | 18 (28.1) | 7.7 [2.4 - 25.2] | 0.0007 |
| bPI-based                        | 81 (24.2) | 26 (40.6) | 1.9 [0.6 - 6.0] | 0.29 |
| NNRTI-based                      | 88 (26.3) | 12 (18.8) | 3.4 [0.9 - 12.7] | 0.07 |
| Treatment Group                  | <0.0001 | | | | |
| Switched treatment               | 221 (66.0) | 26 (40.6) | Ref. | | |
| Treatment-naïve                  | 70 (20.9) | 9 (14.1) | 0.6 [0.1 - 4.2] | 0.63 |
| Failed treatment                 | 44 (13.1) | 29 (41.3) | 4.4 [1.4 - 14.0] | 0.012 |
| Adherence class | n (%)     | n (%)     | Ref. | p-value |
|-----------------|-----------|-----------|------|---------|
| >95%            | 211 (63.0)| 20 (31.2) |      | <0.001  |
| [90%-95%]       | 39 (11.6) | 3 (4.7)   | 0.5  | [0.1 - 2.1] | 0.35 |
| [80%-90%]       | 47 (14.0) | 5 (7.8)   | 0.8  | [0.2 - 2.6] | 0.69 |
| [60%-80%]       | 29 (8.7)  | 13 (20.3) | 3.2  | [1.0 - 10.0] | 0.043 |
| <60%            | 9 (2.7)   | 23 (35.9) | 5.9  | [1.5 - 23.7] | 0.012 |

Longest treatment interruption in hours, Log mean (SD)

|                | 1.63 (0.28) | 2.06 (0.48) | <0.0001 | 4.6 [1.3 - 16.9] | 0.02 |

Abbreviations: VR, virological replication with HIV-RNA>50 cp/mL; aOR, adjusted odds ratio; CI, confidence interval;
bPI, boosted protease inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor
Table 3. Predictors of virological replication by average adherence subgroups in multivariate analysis*

| Third antiretroviral agent | Higher adherence (>95%) | Lower adherence (≤95%) |
|---------------------------|-------------------------|-----------------------|
|                           | n=211                   | n=188                 |
| Dolutegravir-based         | Ref.                    | Ref.                  |
| Raltegravir-based          | 3.7 [0.9 - 16.1]        | 45.6 [4.5 - 462.1]    | 0.001     |
| bPI-based                  | 0.6 [0.1 - 3.1]         | 28.3 [3.4 - 239.4]    | 0.002     |
| NNRTI-based                | 3.4 [0.3 - 36.2]        | 24.8 [2.7 - 228.4]    | 0.005     |

*Adjusting for age, sex, baseline CD4 cells, baseline HIV-RNA and treatment group (failing, switching or starting) Abbreviation: NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; bPI, Boosted Protease Inhibitor;
Figure 1. Virological replication levels (Log HIV-RNA) at 6-month by electronic drug monitoring (EDM) adherence pattern according to antiretroviral regimen class (n=399).

Each circle symbol represents a people living with HIV (PLWH) connected to the plane by a vertical needle. The length of the needle represents the HIV-RNA level of replication at 6 month in log cp/mL (Z-axis). The horizontal plane coordinates correspond to the EDM defined adherence pattern during the 6 months period with the average adherence on the X-axis and the longest treatment interruption in log10 hours on the Y-axis. PLWH with higher adherence are those on the bottom corner.

Abbreviation: DTG, Dolutegravir; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor, NVP, nevirapine; EFV, Efavirenz; RPV, Rilpivirine; bPI, Boosted Protease Inhibitor; LPV/r, Lopinavir/Ritonavir; ATV/r, Atazanavir/Ritonavir

Figure 2. Surface forgiveness plot and linear regression models of adherence patterns explaining HIV-RNA by antiretroviral regimen.
REFERENCES

1. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; 133:21–30.

2. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure. Medicine (Baltimore) 2016; 95. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839839/. Accessed 29 October 2020.

3. Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. AIDS 2009; 23:1035–1046.

4. Nachega JB, Parienti J-J, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. Clin Infect Dis 2014; 58:1297–1307.

5. Hemmige V, Flash CA, Carter J, Giordano TP, Zerai T. Single tablet HIV regimens facilitate virologic suppression and retention in care among treatment naïve patients. AIDS Care 2018; 30:1017–1024.

6. Parienti J-J, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once-daily antiretroviral regimens: a meta-analysis. Clin Infect Dis 2009; 48:484–488.

7. Viswanathan S, Detels R, Mehta SH, Macatangay BJC, Kirk GD, Jacobson LP. Level of adherence and HIV RNA suppression in the current era of highly active antiretroviral therapy (HAART). AIDS Behav 2015; 19:601–611.

8. Byrd KK, Hou JG, Hazen R, et al. Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-World Data. J Acquir Immune Defic Syndr 2019; 82:245–251.

9. Genberg BL, Wilson IB, Bangsberg DR, et al. Patterns of antiretroviral therapy adherence and impact on HIV RNA among patients in North America. AIDS 2012; 26:1415–1423.

10. Parienti J-J, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 2004; 38:1311–1316.

11. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 2006; 296:679–690.

12. Parienti J-J, Das-Douglas M, Massari V, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. PLoS ONE 2008; 3:e2783.

13. Parienti J-J, Ragland K, Lucht F, et al. Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. Clin Infect Dis 2010; 50:1192–1197.
14. Parienti J-J, Barrail-Tran A, Duval X, et al. Adherence profiles and therapeutic responses of treatment-naive HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial. Antimicrob Agents Chemother 2013; 57:2265–2271.

15. Gras G, Schneider M-P, Cavassini M, et al. Patterns of adherence to raltegravir-based regimens and the risk of virological failure among HIV-infected patients: the RALTECAPS cohort study. J Acquir Immune Defic Syndr 2012; 61:265–269.

16. Meresse M, March L, Kouanfack C, et al. Patterns of adherence to antiretroviral therapy and HIV drug resistance over time in the Stratall ANRS 12110/ESTHER trial in Cameroon. HIV Med 2014; 15:478–487.

17. Nickel K, Halfpenny NJA, Snedecor SJ, Punekar YS. Comparative efficacy, safety and durability of dolutegravir relative to common core agents in treatment-naive patients infected with HIV-1: an update on a systematic review and network meta-analysis. BMC Infect Dis 2021; 21:222.

18. Elliot E, Amara A, Jackson A, et al. Dolutegravir and elvitegravir plasma concentrations following cessation of drug intake. J Antimicrob Chemother 2016; 71:1031–1036.

19. Iwamoto M, Wenning LA, Petry AS, et al. Safety, tolerability, and pharmacokinetics of raltegravir after single and multiple doses in healthy subjects. Clin Pharmacol Ther 2008; 83:293–299.

20. Boffito M, Else L, Back D, et al. Pharmacokinetics of atazanavir/ritonavir once daily and lopinavir/ritonavir twice and once daily over 72 h following drug cessation. Antivir Ther 2008; 13:901–907.

21. Morrison A, Stauffer ME, Kaufman AS. Relationship Between Adherence Rate Threshold and Drug ‘Forgiveness’. Clin Pharmacokinet 2017; 56:1435–1440.

22. Hocqueloux L, Raffi F, Prazuck T, et al. Dolutegravir Monotherapy Versus Dolutegravir/Abacavir/Lamivudine for Virologically Suppressed People Living With Chronic Human Immunodeficiency Virus Infection: The Randomized Noninferiority MONotherapy of TiviCAY Trial. Clin Infect Dis 2019; 69:1498–1505.

23. Harris RA, Haberer JE, Musinguzi N, et al. Predicting short-term interruptions of antiretroviral therapy from summary adherence data: Development and test of a probability model. PLoS One 2018; 13:e0194713.

24. Parienti J-J, Paterson DL. Number of missed doses: why 1 × 7 does not make 7 × 1? AIDS 2012; 26:1437–1440.

25. Morrow M, MaWhinney S, Coyle RP, et al. Predictive Value of Tenofovir Diphosphate in Dried Blood Spots for Future Viremia in Persons Living With HIV. J Infect Dis 2019; 220:635–642.

26. Castillo-Mancilla JR, Brown TT, Erlandson KM, et al. Suboptimal Adherence to Combination Antiretroviral Therapy Is Associated With Higher Levels of Inflammation Despite HIV Suppression. Clin Infect Dis 2016; 63:1661–1667.
27. Musinguzi N, Castillo-Mancilla J, Morrow M, et al. Antiretroviral Therapy Adherence Interruptions Are Associated With Systemic Inflammation Among Ugandans Who Achieved Viral Suppression. J Acquir Immune Defic Syndr 2019; 82:386–391.

28. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Adv Immunol 2013; 119:51–83.

29. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society-USA Panel. JAMA 2020; 324:1651–1669.

30. Initial Regimens: ART-naïve Adult. Available at: https://eacs.sanfordguide.com/art/initial-regimens-arv-naive-adults. Accessed 30 November 2020.
