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ORIGINAL RESEARCH

Shorter Time to Discontinuation Due to Treatment Failure in People Living with HIV Switched to Dolutegravir Plus Either Rilpivirine or Lamivudine Compared with Integrase Inhibitor-Based Triple Therapy in a Large Spanish Cohort

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ABSTRACT

Introduction: Standard therapy for HIV treatment has consisted of two nucleoside analogue reverse transcriptase inhibitors (NRTI) paired with a third agent. Use of two-drug regimens (2DR) has been considered for selected patients in part to avoid toxicities associated with the use of NRTIs. This study aimed to compare the real-world outcomes of integrase inhibitor (INSTI)-based three-drug regimens (3DR) versus 2DR of dolutegravir (DTG) + rilpivirine (RPV) or DTG + lamivudine (3TC).

Methods: All patients in the Spanish VACH cohort switching to INSTI-based 3DR or a 2DR consisting of DTG + RPV or DTG + 3TC between May 2, 2016 and May 15, 2019 were included. Kaplan–Meier curves and Cox proportional hazard models were used to assess time to/risk of discontinuation due to treatment failure (TF) (defined as virologic failure [VF], immunologic failure, or disease progression) and adverse events (AEs). Three secondary analyses were performed: (1) in restricting the

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analysis to patients who were virologically suppressed (HIV RNA < 50 copies/mL) at switch; (2) matched analysis (2:1, matched by age, sex, number of previous VFs, and line of regimen), and (3) using VF as the primary endpoint in all patients.

Results: Overall, 5047 3DR and 617 2DR patients were analyzed. Baseline characteristics differed between groups; 2DR patients were older, more treatment experienced, and more likely to be virologically suppressed at switch. Time to discontinuation due to TF was significantly shorter for 2DR ($P = 0.002$). The hazard ratio (HR) for discontinuation due to TF on 2DR vs 3DR was 2.33 ($P = 0.003$). No difference was observed for time to discontinuation ($P = 0.908$) or risk of discontinuation due to AEs (HR = 0.80; $P = 0.488$). Results were qualitatively similar in virologically suppressed patients, matched analysis, and for VF.

Conclusion: In the real world, the risks of discontinuation due to TF and VF were more than two times higher in patients switching to DTG-based 2DR than INSTI-based 3DR, with no difference in discontinuation due to AEs.

PLAIN LANGUAGE SUMMARY

People living with HIV (PLHIV) need lifelong treatment to prevent progression to AIDS. Standard HIV treatments use three different drugs in combination, but these can potentially cause unwanted side effects. Treatments using just two drugs have been developed. These aim to reduce side effects and treat HIV effectively. This study included 5664 participants in Spain who were split into two groups: 5047 participants switched from their old treatment to a three-drug regimen (3DR), and 617 participants switched to a two-drug regimen (2DR). The researchers measured how long it took for the participants to stop taking their treatment because it was not working, or it caused too many side effects. At the end of the study, more than 70% of participants in either group were still taking the same treatment. Of the 30% of participants who stopped treatment because it stopped working, those taking a 2DR stopped sooner than those taking a 3DR. This difference started to appear at about 18 months and got bigger until the study ended, which was 3 years

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after starting treatment. Participants taking a 2DR were twice as likely to stop treatment because it was not working than those taking a 3DR. There was no difference between the groups for how long it took for participants to stop their treatment because of side effects. These results show that for some PLHIV, the 2DR stopped working sooner than 3DR, without the benefit of fewer side effects.

Keywords: Adverse events; Effectiveness; HIV; Time to discontinuation; Triple therapy; Two-drug combinations; Virologic failure

Key Summary Points

Why carry out this study?

Three-drug antiretroviral regimens (3DR) have been the standard of care since 1996, but two-drug regimens (2DR) have been developed to avoid short- and long-term toxicities and reduce costs

This study compared outcomes in a large cohort of People living with HIV (PLHIV) who switched to integrase inhibitor-based 3DR or 2DR of dolutegravir + rilpivirine or dolutegravir + lamivudine

What was learned from the study?

Patients who switched to the dolutegravir-based 2DR were at greater risk of discontinuing treatment because of treatment failure and virologic failure than those who switched to integrase inhibitor-based 3DR

There was no difference between the two groups in the risk of discontinuing treatment because of adverse events

INTRODUCTION

HIV infection remains a major cause of morbidity and mortality worldwide; in its latest update, the World Health Organization reported 1.7 million new cases and 690,000 deaths during 2019 [1]. Without antiretroviral therapy (ART) most patients with HIV will show evidence of disease progression within 8–10 years, and nearly half will die within 2 years of the onset of AIDS [2, 3]. ART completely inhibits HIV replication, which is the absolute driver of HIV-disease pathogenesis, thereby transforming HIV to a chronic and manageable condition with which affected individuals may live in good health.

Regimens for ART evolved in the mid-years of the past century from single-drug regimens to three-drug regimens (3DR) since trials conducted in the early 1990s showed little benefit of two-drug regimens (2DR) compared with single-drug regimens [4, 5]. Since 1996, the standard of care for ART has been 3DR consisting of a backbone of two nucleoside analogue reverse-transcriptase inhibitors (NRTI) combined with a third drug [6–9]. However, long-term toxicities associated with the NRTIs tenofovir disoproxil fumarate (TDF) [10, 11] and abacavir (ABC) [12], as well as cost-related factors, have led to the development and evaluation of treatment options that can help people living with HIV (PLHIV) achieve optimal long-term health. One such option includes a variety of 2DR.

Most earlier clinical trials with older 2DR showed a higher incidence of virologic failure (VF) compared with 3DR [13–17]. However, since 2018 several randomized controlled clinical trials have demonstrated non-inferiority of 2DR consisting of dolutegravir (DTG) plus either rilpivirine (RPV) or lamivudine (3TC) compared with 3DR in patients without prior virological failure. The SWORD 1 and 2 trials showed that DTG + RPV was non-inferior to a 3DR for maintenance of virologic suppression [18]; the GEMINI 1 and 2 trials showed that DTG + 3TC was non-inferior to 3DR of DTG + TDF/emtricitabine (FTC) in ART-naïve adults [19]; and the TANGO trial showed that switching to DTG/3TC was non-inferior to remaining on a three- or four-drug tenofovir alafenamide (TAF)-based regimen [20]. Based on the aforementioned trials, some guidelines recommend a 2DR of DTG + 3TC as an initial treatment

option for PLHIV meeting specific criteria and both DTG + 3TC and DTG + RPV as recommended options for PLHIV who switch regimens [7, 8]. Currently, 2DR are not recommended for rapid start, which is increasingly becoming the standard of care globally.

Selection of patients for HIV clinical trials can be stringent. The SWORD, TANGO, and GEMINI trials excluded patients with HBV co-infection and mutations associated with known drug resistance to any of the major drug classes. For example, 12% of potential enrolees in the GEMINI trial were excluded because of evidence of a pre-existing resistance mutation [19]. Previously treated patients in SWORD and TANGO were stably suppressed and had no history of VF [18, 20]. In the real-world, PLHIV may have comorbidities, co-infections, resistance mutations, and a range of viral loads and CD4 counts, which makes applying conclusions from clinical trials to real-world settings problematic [21]. Furthermore, adherence in the real world is often below 80% [22–24], whereas adherence in clinical trials is often at least 95% [25, 26]. Adherence has a direct impact on VF [27, 28], although evidence suggests that adherence of at least 80% to contemporary 3DR may be sufficient to maintain viral suppression [29, 30]. It is unknown whether this applies to DTG-containing 2DR.

In a previous study in the Spanish VACH cohort, we found that the risk of VF as reported in the database by the clinician (with or without a reason) was at least two times higher with protease inhibitor- or DTG-based 2DR vs integrase strand transfer inhibitor (INSTI)-based 3DR [31]. Furthermore, there was no difference in discontinuations due to adverse events (AEs) between the 2DR and 3DR groups. The current study updates the previous VACH 2DR versus 3DR analysis to include a more recent period of data after the availability of elvitegravir (EVG)/cobicistat (c)/TAF/FTC in Spain, a larger number of patients, and by focusing on the 2DR of most clinical relevance in the current landscape (DTG + RPV and DTG + 3TC) [7, 8]. It should be noted that at the time of the analysis, the single-tablet coformulations of those 2DR were not available. Therefore, all patients in the analysis on 2DR were on two-tablet regimens and not on the single-tablet 2DR that were subsequently approved.

METHODS

A retrospective analysis was performed using data from the VACH cohort, a prospective Spanish cohort of 14,833 adult PLHIV from 23 investigational centers which has been enrolling patients since 1997 [32]. Patient data were prospectively collected in a standardized electronic case record form and electronically stored in the Aplicación de Control Hospitalario (AC&H^{TM}). All data were transformed into a standardized format and collected into a central data set. Patient data were deidentified and each patient assigned a unique code. The study was reviewed and approved by Ethics Review Board of Cantabria IDIVAL. The study was performed in accordance with the Helsinki Declaration. Consent to the registration of their data in the AC&H^{TM} clinical management program and the use of anonymous data for epidemiologic studies was given by patients who were included in the analysis.

Patient Selection Criteria

All patients switching to INSTI-based 3DR or to DTG + RPV or DTG + 3TC at any point between May 2, 2016 and May 15, 2019 were included. 2016 was chosen as the starting date for the analysis because that was the year of the last approval for all the regimens being considered in the analysis. Patients were excluded if the reason for treatment switch in either the previous regimen or the study regimen was for a programmed interruption or intermittent treatment, re-initiation after being lost to follow-up, or for the intention of restoring wild-type virus. Patients were also required to have a minimum follow-up of 2 days.

Endpoints

Two primary analysis endpoints were defined: time to discontinuation due to treatment failure (TF; defined as clinician-assessed VF,

immunologic failure, or disease progression) and time to discontinuation due to AEs. Additional endpoints were the risk of discontinuation due to TF or AEs. Reasons for switch or discontinuation were captured in the AC&H database via selections from a drop-down menu when the clinician reported a treatment switch or discontinuation. There was no definition for each reason (e.g., VF, immunologic failure, disease progression, AEs, intolerance) in the database. As such, VF, immunologic failure, disease progression, and AEs were per the clinician's definition.

Statistical Analysis

Patients were censored at loss to follow-up, death, or end of observation period (June 20, 2019). Baseline continuous variables were compared by Student's *t* test and categorical variables were compared by the χ^2 test if all cells had expected counts more than 5, otherwise Fisher's exact test was used.

To evaluate consistency of results, three secondary analyses were performed. First, patients included were restricted to those virologically suppressed (HIV RNA < 50 copies/mL) at the time of regimen switch; second, patients included were restricted to a subsample of matched patients who were virologically suppressed at switch in the two groups. Matching was performed as two 3DR patients for each 2DR patient by means of age, sex, number of previous VFs, and line of regimen as matching variables. Third, analysis of the TF endpoint was restricted to VF only.

In both primary and secondary analyses, times to discontinuation due to TF or AEs were estimated by Kaplan–Meier curves. Hazard ratios (HR) for risk of discontinuations due to TF or AEs were estimated using Cox proportional hazard models. Cox proportional hazard models were controlled for age, sex, viral load, CD4 counts, injection drug user (ever), HCV coinfection, HBV coinfection (as identified by HBsAg in patient sera), prior AIDS diagnosis, number of previous regimens, number of previous VFs, and years on ART.

All analyses were performed using STATA SE Version 15 (StataCorp LLC, College Station, TX).

RESULTS

Patient Population

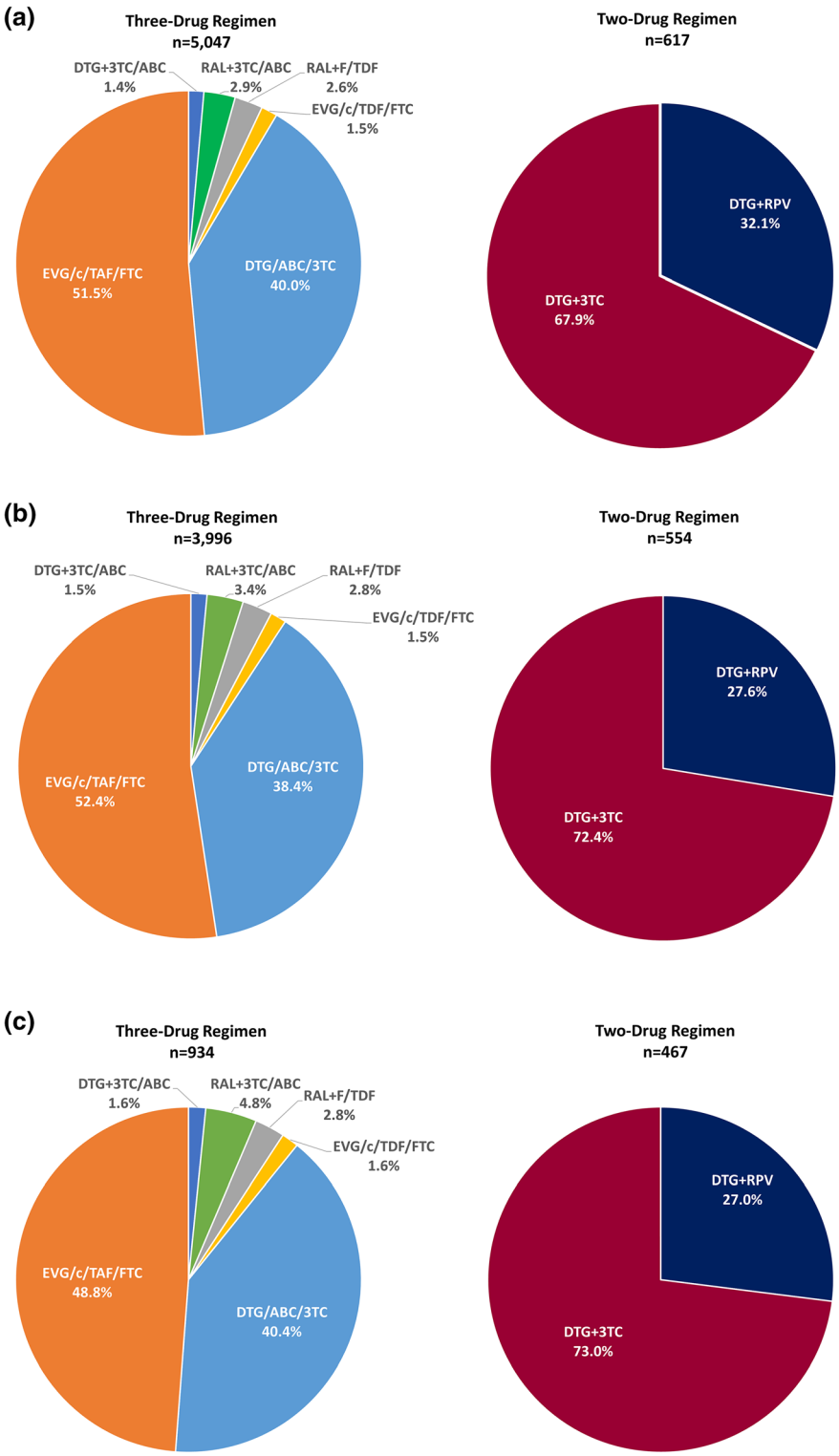
In all, 5047 3DR (8617 person-years) patients and 617 (756 person-years) 2DR patients were included in the analysis. Most patients in the 3DR group were on either EVG/c/TAF/FTC or DTG/ABC/3TC (Fig. 1a). The majority (67.9%) of the patients in the 2DR group were on DTG + 3TC (Fig. 1a). Baseline characteristics differed between groups (Table 1); patients on 2DR were older, had a longer duration of ART, had a higher number of previous regimens and of prior VF, and were more likely to be virologically suppressed at switch.

In the population of virologically suppressed patients at regimen switch, 3996 3DR (7059 person-years) and 554 (681 person-years) 2DR patients were analyzed. The regimen distribution in the virologically suppressed population was similar to the full analysis population (Fig. 1b). Similar differences in baseline characteristics between the 3DR and 2DR patients were observed in the virologically suppressed.

In the matched population, 934 (1638 person-years) 3DR and 467 (575 person-years) 2DR virologically suppressed patients were included in the analysis. The regimen distribution was similar to the full analysis population and the unmatched virologically suppressed population (Fig. 1c). Patients on 2DR had a shorter duration on ART, and a lower proportion were HBV infected (Table 1).

Outcomes in the Full Analysis Population (Primary Analysis)

The majority of patients in both the 2DR (77.5%) and 3DR (72.3%) groups were still on treatment at the end of the study period. The main reason for discontinuation was treatment switch in both the 2DR (16.0%) and 3DR (19.5%) groups (Supplementary Material


(a)
Three-Drug Regimen
n=5,047
DTG+3TC/ABC
1.4%
RAL+3TC/ABC
2.9%
RAL+F/TDF
2.6%
EVG/c/TDF/FTC
1.5%
EVG/c/TAF/FTC
51.5%
DTG/ABC/3TC
40.0%
Two-Drug Regimen
n=617
DTG+RPV
32.1%
DTG+3TC
67.9%
(b)
Three-Drug Regimen
n=3,996
DTG+3TC/ABC
1.5%
RAL+3TC/ABC
3.4%
RAL+F/TDF
2.8%
EVG/c/TDF/FTC
1.5%
EVG/c/TAF/FTC
52.4%
DTG/ABC/3TC
38.4%
Two-Drug Regimen
n=554
DTG+RPV
27.6%
DTG+3TC
72.4%
(c)
Three-Drug Regimen
n=934
DTG+3TC/ABC
1.6%
RAL+3TC/ABC
4.8%
RAL+F/TDF
2.8%
EVG/c/TDF/FTC
1.6%
EVG/c/TAF/FTC
48.8%
DTG/ABC/3TC
40.4%
Two-Drug Regimen
n=467
DTG+RPV
27.0%
DTG+3TC
73.0%

◀**Fig. 1** Regimen distribution of three-drug regimens and two-drug regimens in **a** the total analysis population, **b** the virologically suppressed at switch subgroup population, and **c** the matched virologically suppressed at switch subgroup population. *3TC* lamivudine, *ABC* abacavir, *c* cobicistat, *DTG* dolutegravir, *EVG* elvitegravir, *FTC* emtricitabine, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil fumarate, *RAL* raltegravir, *RPV* rilpivirine

Fig. S1). The most common reason for switching was TF (18.2%) in the 2DR group and simplification (22.5%) in the 3DR group (Supplementary Material Table S1). Of those who switched, the proportion of patients who switched treatments due to VF was numerically higher in the 2DR (11.1%) versus the 3DR (5.8%) group (Supplementary Material Table S1). Treatment switch due to VF was 1.8% in the entire 2DR cohort and 1.1% in the entire 3DR cohort (Supplementary Material Table S1).

Time to discontinuation due to TF was significantly shorter for 2DR versus 3DR ($P = 0.002$; Fig. 2a), whereas there was no significant difference for time to discontinuation due to AEs ($P = 0.908$; Fig. 2b). After we controlled for demographic and clinical characteristics, the risk of discontinuation due to TF was 2.3 times higher on 2DR versus 3DR (HR = 2.33; $P = 0.003$; Table 2), and no difference was observed for discontinuations due to AEs (HR = 0.80; $P = 0.488$).

Outcomes in the Virologically Suppressed at Switch Population

In the secondary analysis of virologically suppressed patients at regimen switch, time to discontinuation due to TF was significantly shorter for 2DR versus 3DR ($P = 0.001$; Fig. 3a), whereas there was no significant difference for time to discontinuation due to AEs ($P = 0.961$; Fig. 3b). As in the full analysis population, after we controlled for demographic and clinical characteristics, the risk of discontinuation due to TF was 2.3 times higher on 2DR versus 3DR (HR = 2.28; $P = 0.011$; Table 2). No difference between 2DR and 3DR was observed for risk of discontinuations due to AEs (HR = 0.82; $P = 0.575$).

Outcomes in the Matched Virologically Suppressed at Switch Population

In the secondary analysis of matched virologically suppressed patients, time to discontinuation due to TF was significantly shorter for 2DR versus 3DR ($P = 0.003$; Fig. 4a). There was no significant difference for time to discontinuation due to AEs ($P = 0.699$; Fig. 4b). The risk of discontinuation due to TF was 3.0 times higher on 2DR versus 3DR (HR = 3.00; $P = 0.017$; Table 2). No difference between 2DR and 3DR was observed for risk of discontinuations due to AEs (HR = 0.85; $P = 0.736$).

Secondary Analysis of VF as Endpoint

In the full analysis population, time to discontinuation due to VF was significantly shorter for 2DR versus 3DR ($P = 0.037$; Fig. 5a) and risk of discontinuations due to VF was 2.2 times higher on 2DR versus 3DR (HR = 2.24; $P = 0.024$; Table 2). The times to discontinuation due to VF in the virologically suppressed and matched populations were similar to those in the full analysis population (Figs. 5b, c). The risks of discontinuations due to VF in the virologically suppressed and matched populations were approximately two times higher on 2DR versus 3DR, but the differences were not statistically significant (Table 2).

DISCUSSION

In this retrospective analysis of a large Spanish cohort of PLHIV, the time to discontinuation due to TF, and more specifically due to VF, was significantly shorter in patients switching to DTG + RPV and DTG + 3TC versus INSTI-based 3DR. The risk of discontinuation due to TF or VF with 2DR was approximately twofold higher compared with 3DR. There was no significant difference between time to or risk of discontinuation due to AEs between the 2DR and 3DR groups. The same general results were

Table 1 Patient demographics and clinical characteristics at baseline

Characteristics	Total analysis population			Suppressed at switch subgroup population			Matched suppressed at switch subgroup population		
	3DR (*N* = 5047)	2DR (*N* = 617)	*P* value	3DR (*N* = 3996)	2DR (*N* = 554)	*P* value	3DR (*N* = 934)	2DR (*N* = 467)	*P* value
Age, years, mean (SD)	48.1 (10.7)	52.0 (10.3)	< 0.001	48.1 (10.5)	52.1 (10.5)	< 0.0001	50.5 (10.0)	51.0 (9.7)	0.520
Female, %	23.4	28.4	0.002	22.4	28.0	0.004	26.3	26.3	1.00
Prior AIDS Diagnosis, % Yes	23.2	26.7	0.026	22.1	25.8	0.047	25.6	24.6	0.696
$CD4^+$ T cell count < 350 cells/μL, %	81.8	82.9	0.453	86.1	84.8	0.417	86.5	86.3	0.912
HIV RNA < 50 copies/mL, %	81.0	90.2	< 0.001	100	100	N/A	100	100	N/A
Illicit drug use, % yes	26.6	30.3	0.029	30.0	29.4	0.108	31.3	29.6	0.512
HCV coinfection, % yes	32.6	35.3	0.132	31.6	34.3	0.226	36.4	34.7	0.560
HBV coinfection, % yes	4.1	1.8	0.004	4.4	1.6	0.004	4.3	1.5	0.010
Duration on ART, years, mean (SD)	12.0 (8.4)	14.9 (8.1)	< 0.001	12.1 (8.2)	14.7 (8.1)	< 0.0001	14.7 (7.9)	13.7 (7.9)	0.030
Number of previous ART regimens, mean (SD)	5.3 (3.6)	7.4 (4.6)	< 0.001	5.1 (3.3)	7.3 (4.5)	< 0.0001	6.3 (3.6)	6.4 (3.8)	0.454
Number of previous virologic failures, mean (SD)	1.1 (2.4)	1.5 (2.9)	< 0.001	1.1 (2.3)	1.5 (3.0)	< 0.0001	1.4 (3.1)	1.4 (3.1)	0.971

2DR two-drug regimens, *3DR* three-drug regimens, *ABC/3TC/ + DTG* abacavir, lamivudine, and dolutegravir combination, *ART* antiretroviral therapy

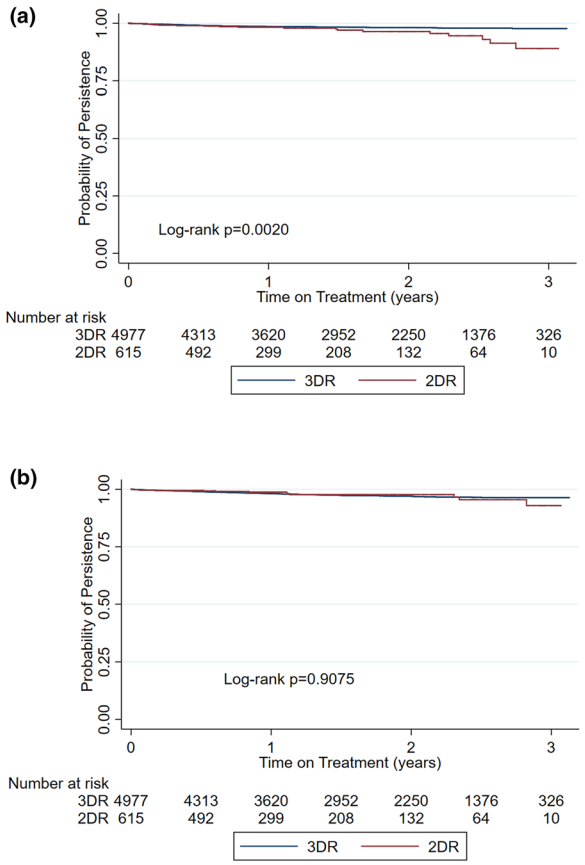


Fig. 2 Time to discontinuation due to **a** treatment failure and **b** adverse events in the total analysis population

Table 2 Risk of discontinuation due to treatment failure (TF), adverse events (AEs), or virologic failure (VF) in patients switched to two-drug regimens (2DR) or three-drug regimens (3DR)

Analysis population	aHR[a]	(95% CI)	*P* value
Total analysis population: 2DR vs 3DR			
Discontinuation due to TF	2.33	1.3, 4.1	0.003
Discontinuation due to AEs	0.80	0.4, 1.5	0.488
Discontinuation due to VF	2.24	1.1, 4.5	0.024
Virologically suppressed at switch subgroup population: 2DR vs 3DR			
Discontinuation due to TF	2.28	1.2, 4.3	0.011
Discontinuation due to AEs	0.82	0.4, 1.7	0.575
Discontinuation due to VF	2.01	0.9, 4.4	0.078
Matched virologically suppressed at switch subgroup population: 2DR vs 3DR			
Discontinuation due to TF	3.00	1.2, 7.4	0.017
Discontinuation due to AEs	0.85	0.3, 2.2	0.736
Discontinuation due to VF	2.83	0.9, 8.6	0.066

aHR adjusted hazard ratio, *CI* confidence interval
[a]Adjusted for demographics, viral load, CD4, number of previous regimens/VFs, and years on antiretroviral therapy

maintained when restricting the analysis to an unmatched and matched population of patients who were virologically suppressed at the time of switch. These data confirm the results from the initial analysis that demonstrated a shorter time to discontinuation and higher risk of discontinuation due to VF with 2DR than 3DR without a difference in discontinuation due to AEs [31]. Thus, there is a higher risk of TF with 2DR than 3DR, with no benefit from a safety or tolerability standpoint in the context of the limited study period. Long-term safety and tolerability benefits of a NRTI-sparing 2DR may be possible.

Evidence regarding differences in VF between 2DR and 3DR in a real-world setting is mixed. Consistent with the results in this analysis, one real-world observational study of over 250 French and Italian PLHIV found that among those with VF, the time to VF was almost 2 years shorter for 2DR versus 3DR [33]. A retrospective analysis of PLHIV in the OPERA observational database in the USA found that the difference in the incidence of VF between 2DR (7.9 per 100 person-years) and 3DR (6.0 per 100 person-years) was not statistically significant, although the difference in time to VF between 2DR and 3DR neared statistical significance ($p = 0.06$) [34]. Analysis of PLHIV in the European EuroSIDA database found that real-world virologic and immunologic outcomes of 2DR were similar to 3DR [35]. In contrast to the

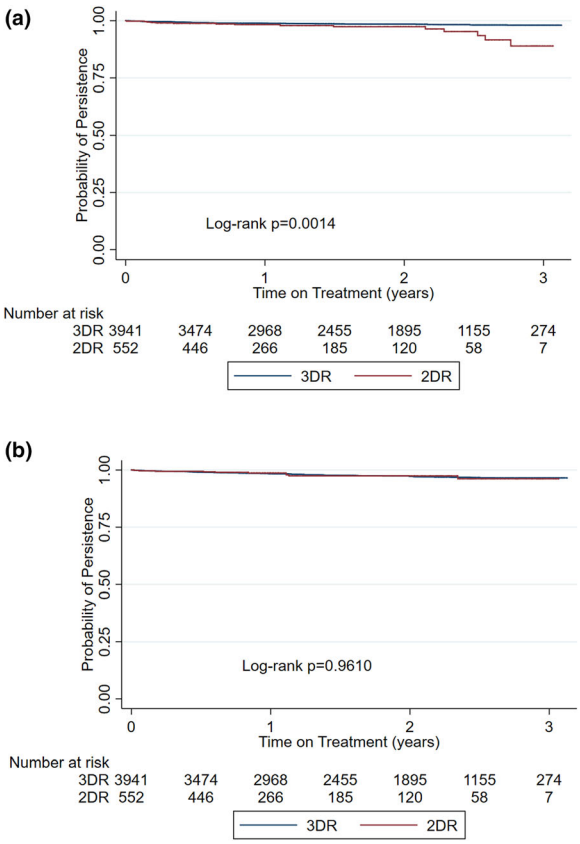


Fig. 3 Time to discontinuation due to **a** treatment failure and **b** adverse events in the virologically suppressed at switch subgroup population

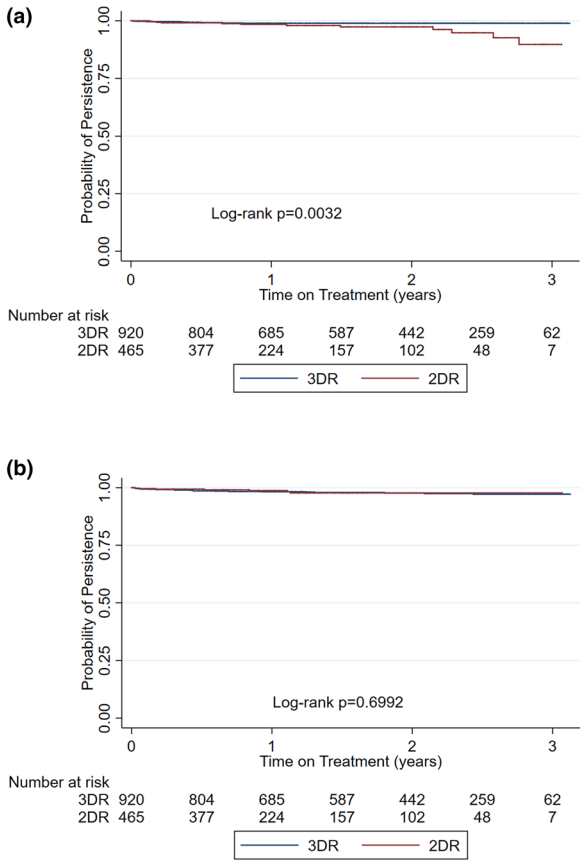


Fig. 4 Time to discontinuation due to **a** treatment failure and **b** adverse events in the matched virologically suppressed at switch subgroup population

current study, these other real-world studies included a variety of 2DR, with a small proportion being DTG-based 2DR, and a wide range of 3DR rather than only INSTI-containing 3DR.

As in the real-world studies, there are mixed clinical trial data regarding the risk of VF between 2DR and 3DR. A meta-analysis published in 2016 found that the risk of VF in clinical trials of either treatment-naïve or virologically suppressed patients significantly increased with 2DR compared with 3DR in patients with baseline viral load greater than 100,000 copies/mL [36]. Furthermore, there was a twofold risk of selecting resistance mutations with 2DR versus 3DR [36]. In contrast, the SWORD clinical trials found that DTG + RPV was non-inferior to 3DR in the proportion of participants classified as experiencing VF, and in the TANGO trial no participants treated with DTG/3TC met the criteria for confirmed virologic withdrawal [18, 20]. The European AIDS Clinical Society in their treatment guidelines concluded that the DTG + RPV and DTG + 3TC regimens were not associated with more virologic rebounds than 3DR, although they noted that there have been a few cases of one- and two-class resistance emergence with DTG + RPV and two-class resistance with DTG + 3TC [8, 37, 38].

The discrepancy between the results for VF in the current study versus the SWORD and TANGO trials likely lies in the characteristics of the study population. The SWORD and TANGO trials selected participants who were virologically suppressed (viral load less than 50 copies/mL) and with no history of previous VF or resistance mutations [18, 20], while patients in the current real-world analysis were unselected

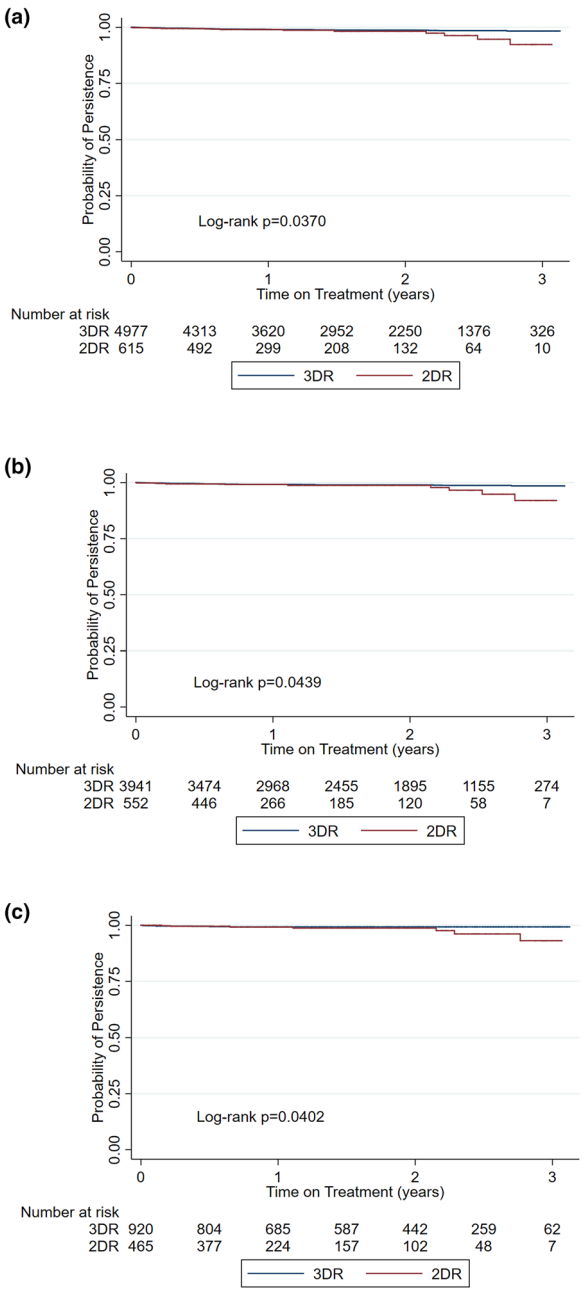


Fig. 5 Time to discontinuation due to virologic failure in the **a** total analysis population, **b** virologically suppressed at switch subgroup population, and **c** matched virologically suppressed at switch subgroup population

for virologic characteristics. The proportion of patients who switched treatment due to TF or VF in the 2DR cohort was more than twice that of the 3DR cohort. Together these data suggest that carefully selected patients may have a comparable benefit with DTG + RPV as with 3DR. No historic genotypic data were available for the VACH cohort, and more research is needed on the risk of VF with 3DR and 2DR in PLHIV who have previous VF or resistance mutations.

The duration of the study periods may also explain the differences in VF between this real-world analysis and clinical trials. In the current analysis, time to discontinuation due to TF did not begin to diverge between the 2DR and 3DR until approximately 1 year, with sharper drop-offs appearing at approximately 2 years. However, the 2DR cohort in the second year of follow-up was small, which could have impacted the results. The SWORD, GEMINI, and TANGO trials were only 48 weeks in duration [18–20]. It is possible that more than 1 year of treatment is needed to see differences in VF between 2DR and 3DR. At the 148-week follow-up of the SWORD trials, participants who switched from 3DR to DTG + RPV generally maintained virologic suppression; 11 (1%) met the confirmed virologic withdraw criteria, but there was no corresponding 3DR group for comparison [39]. Real-world settings also present more challenges compared with randomized controlled trials, such as poorer adherence and less viral load monitoring, which can impact TF and VF [40, 41].

A strength of this updated analysis is that the time period of the study allows for the inclusion of more recent 3DR that were developed to reduce the toxicity (e.g., EVG/c/TAF/FTC) associated with some of the older TDF-and TAF-based 3DR, as well as single-tablet 3DR that improve ease of use. Since the completion of this study, additional TAF 3DR have become available that warrant further study. Also, the assessed 2DR are those that will likely increase in use based on the support of large randomized controlled trials [18–20] and revised guideline recommendations [7, 8]. The results of this study need to be considered within the context of a few limitations. At the time of analysis, the 2DR available were multi-tablet regimens, which may affect adherence. Baseline characteristics were different in the 2DR and the 3DR groups, with more treatment-experienced patients and more virologically suppressed

patients at the time of switch in the 2DR group. This indicates potential confounding by indication. However, the results were maintained in the population of patients virologically suppressed at switch. There is also the possibility of residual confounding because of prescriber bias in the selection of patients for 2DR and because of reduced confidence in the robustness of 2DR. We recognize that factors such as previous regimens and number of previous VFs can impact VF [42–44]. Thus, an additional analysis of virologically suppressed patients at switch matched by age, sex, number of previous VFs, and treatment line was conducted, and the results from the full analysis population were maintained. An additional limitation is that the VACH database does not define VF, immunologic failure, or disease progression. They are merely drop-down choices that can be selected by investigators as a reason for treatment switches or discontinuation. Thus, the subjectivity of determining VF, immunologic failure, or disease progression could have impacted the results.

CONCLUSIONS

Three-drug therapy plays an important role in effectively managing HIV. In addition to clinical trial data, real-world data need to be considered when weighing the evidence for new ART regimens.

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Compliance with Ethics Guidelines. The study was reviewed and approved by Ethics Review Board of Cantabria IDIVAL. The study was performed in accordance with the Helsinki Declaration. Consent to the registration of their data in the AC&H^{TM} clinical management program and the use of anonymous data for epidemiologic studies was given by patients who were included in the analysis.

Data Availability. The data that support the findings of this study are available on request from the corresponding author, RT. The data are not publicly available due to restrictions (e.g., their containing information that could compromise the privacy of research participants).

REFERENCES

1. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. World Health Organization, Geneva. 2021. https://www.who.int/publications/i/item/9789240027077. Accessed December 10, 2021.

2. Poorolajal J, Hooshmand E, Mahjub H, Esmailnasab N, Jenabi E. Survival rate of AIDS disease and

mortality in HIV-infected patients: a meta-analysis. Public Health. 2016;139:3–12.

3. Sabin CA, Lundgren JD. The natural history of HIV infection. Curr Opin HIV AIDS. 2013;8(4):311–7.

4. Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Lancet. 1996;348(9023):283–91.

5. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. N Engl J Med. 1996;335(15):1081–90.

6. AIDS Study Group (GeSIDA) of the Spanish Society of Infectious Diseases and Clinical Microbiology and the National AIDS Plan. Executive summary of the GeSIDA/National AIDS Plan consensus document on antiretroviral therapy in adults infected by the human immunodeficiency virus (updated January 2018). Enferm Infecc Microbiol Clin. 2019;37(3):195–202.

7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. 2019. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed December 10, 2021.

8. EACS Guidelines 2020 Version 10.1. European AIDS Clinical Society. 2020. https://www.eacsociety.org/files/guidelines-10.1_30032021_1.pdf. Accessed December 10, 2021.

9. Antinori A, Di Biagio A, Marcotullio S, et al. Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update 2016. New Microbiol. 2017;40(2):86–98.

10. Casado JL, Santiuste C, Vazquez M, et al. Bone mineral density decline according to renal tubular dysfunction and phosphaturia in tenofovir-exposed HIV-infected patients. AIDS. 2016;30(9):1423–31.

11. Jotwani V, Scherzer R, Estrella MM, et al. Brief report: cumulative tenofovir disoproxil fumarate exposure is associated with biomarkers of tubular injury and fibrosis in HIV-infected men. J Acquir Immune Defic Syndr. 2016;73(2):177–81.

12. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med. 2010;11(2):130–6.

13. Bedimo RJ, Drechsler H, Jain M, et al. The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health. PLoS One. 2014;9(8):e106221.

14. Girard PM, Cabie A, Michelet C, et al. A randomized trial of two-drug versus three-drug tenofovir-containing maintenance regimens in virologically controlled HIV-1 patients. J Antimicrob Chemother. 2009;64(1):126–34.

15. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. Lancet. 2014;384(9958):1942–51.

16. Rossetti B, Gagliardini R, Meini G, et al. Switch to maraviroc with darunavir/r, both QD, in patients with suppressed HIV-1 was well tolerated but virologically inferior to standard antiretroviral therapy: 48-week results of a randomized trial. PLoS One. 2017;12(11):e0187393.

17. van Lunzen J, Pozniak A, Gatell JM, et al. Brief report: switch to ritonavir-boosted atazanavir plus raltegravir in virologically suppressed patients with HIV-1 infection: a randomized pilot study. J Acquir Immune Defic Syndr. 2016;71(5):538–43.

18. Llibre JM, Hung CC, 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. 2018;391(10123):839–49.

19. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019;393(10167):143–55.

20. van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. Clin Infect Dis. 2020;71(8):1920–9.

21. Williams AJ, Wallis E, Orkin C. HIV research trials versus standard clinics for antiretroviral-naive

patients: the outcomes differ but do the patients? Int J STD AIDS. 2016;27(7):537–42.

22. Akinwunmi B, Buchenberger D, Scherzer J, et al. Dose-related and contextual aspects of suboptimal adherence to antiretroviral therapy among persons living with HIV in Western Europe. Eur J Public Health. 2021;31(3):567–75.

23. de Los Rios P, Okoli C, Punekar Y, et al. Prevalence, determinants, and impact of suboptimal adherence to HIV medication in 25 countries. Prev Med. 2020;139:106182.

24. Sutton SS, Magagnoli J, Hardin JW. Odds of viral suppression by single-tablet regimens, multiple-tablet regimens, and adherence level in HIV/AIDS patients receiving antiretroviral therapy. Pharmacotherapy. 2017;37(2):204–13.

25. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390(10107):2063–72.

26. Parienti JJ, 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(5):2265–71.

27. Li JZ, Paredes R, Ribaudo HJ, et al. Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure. AIDS. 2012;26(2):185–92.

28. Santos JR, Blanco JL, Masia M, et al. Virological failure to raltegravir in Spain: incidence, prevalence and clinical consequences. J Antimicrob Chemother. 2015;70(11):3087–95.

29. Kobin AB, Sheth NU. Levels of adherence required for virologic suppression among newer antiretroviral medications. Ann Pharmacother. 2011;45(3):372–9.

30. Viswanathan S, Justice AC, Alexander GC, et al. Adherence and HIV RNA suppression in the current era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2015;69(4):493–8.

31. Teira R, Diaz-Cuervo H, Aragão F, et al. Real world effectiveness of standard of care triple therapy versus two-drug combinations for treatment of people living with HIV. PLoS One. 2021;16(4):e0249515.

32. Suarez-Lozano I, Fajardo JM, Garrido M, et al. Epidemiological trends of HIV infection in Spain: preventative plans have to be oriented to new target populations (Spanish VACH Cohort). AIDS. 2002;16(18):2496–9.

33. Calvez V, Armenia D, Charpentier C, et al. Clinical consequences of failing PI and DTG-based two drug combinations versus PI and INI based triple therapies in HIV patients without previous virological failures. HIV Glasgow; 2018; Glasgow, UK.

34. Pierone G, Henegar C, Fusco J, et al. Two-drug antiretroviral regimens: an assessment of virologic response and durability among treatment-experienced persons living with HIV in the OPERA(®) Observational Database. J Int AIDS Soc. 2019;22(12):e25418.

35. Neesgaard B, Pelchen-Matthews A, Ryom L, et al. Uptake and effectiveness of two-drug compared with three-drug antiretroviral regimens among HIV-positive individuals in Europe. AIDS. 2019;33(13):2013–24.

36. Achhra AC, Mwasakifwa G, Amin J, Boyd MA. Efficacy and safety of contemporary dual-drug antiretroviral regimens as first-line treatment or as a simplification strategy: a systematic review and meta-analysis. Lancet HIV. 2016;3(8):e351–60.

37. Cahn P, Sierra-Madero J, Arribas JR. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naive adults with HIV-1 infection: 3-year results from the GEMINI studies. HIV Glasgow; 2020 October 2020; Virtual.

38. Taiwo BO, Zheng L, Stefanescu A, et al. ACTG A5353: a pilot study of dolutegravir plus lamivudine for initial treatment of human immunodeficiency virus-1 (HIV-1)-infected participants with HIV-1 RNA <500000 copies/mL. Clin Infect Dis. 2018;66(11):1689–97.

39. van Wyk J, Orkin C, Rubio R, et al. Brief report: durable suppression and low rate of virologic failure 3 years after switch to dolutegravir + rilpivirine 2-drug regimen: 148-week results from the SWORD-1 and SWORD-2 randomized clinical trials. J Acquir Immune Defic Syndr. 2020;85(3):325–30.

40. Bachmann N, von Braun A, Labhardt ND, et al. Importance of routine viral load monitoring: higher levels of resistance at ART failure in Uganda and Lesotho compared with Switzerland. J Antimicrob Chemother. 2019;74(2):468–72.

41. Kiweewa F, Esber A, Musingye E, et al. HIV virologic failure and its predictors among HIV-infected adults on antiretroviral therapy in the African Cohort Study. PLoS One. 2019;14(2):e0211344.

42. Deeks SG. Determinants of virological response to antiretroviral therapy: implications for long-term strategies. Clin Infect Dis. 2000;30(Suppl 2): S177–84.

43. Reekie J, Mocroft A, Ledergerber B, et al. History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. HIV Med. 2010;11(7):469–78.

44. Rusconi S, Santoro MM, Gianotti N, et al. Is the rate of virological failure to cART continuing to decline in recent calendar years? J Clin Virol. 2019;116: 23–8.