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ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (K CLAEYS AND A VEGA, SECTION EDITORS)

Simplifying ARV Therapy in the Setting of Resistance

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Abstract

Purpose of Review HIV treatment simplification is typically indicated for virologically suppressed patients with no baseline resistance-associated mutations (RAMs) or prior virologic failure (VF) to the simplification regimen. Simplification can occur to minimize pill burden, toxicities, drug-drug interactions, or costs. As most studies for treatment simplification excluded patients with baseline RAMs or prior VF, this review is aimed to critically analyze data regarding treatment simplification in treatment-experienced patients.

Recent Findings Antiretroviral (ARV) regimens containing three-, two-, and one-drug(s) have been scarcely studied to assess virologic efficacy in treatment-experienced patients. Three-drug regimens with the most data and highest efficacy are with integrase strand transfer inhibitors (INSTIs). Regimens including dolutegravir (DTG) and bictegravir have been shown to maintain efficacy in patients with certain baseline RAMs. Dual therapy regimens include the use of DTG plus either lamivudine (3TC), rilpivirine (RPV), or other ARVs. None of these studies evaluated patients with baseline DTG resistance. Baseline RAMs to 3TC were not a predictor of VF in patients on DTG/3TC. Efficacy was seen with DTG/RPV; however, studies showed high rates of discontinuation. DTG plus boosted-protease inhibitors were studied in smaller but promising studies. Two small studies assessed the use of monotherapy with boosted darunavir or DTG, both showing virologic efficacy.

Summary Currently, three- and two-drug ARV regimens may be considered in this population with most studies evaluating the use of DTG and bictegravir without baseline INSTI RAMs. Future studies should include heavily treatment-experienced patients with a variety of baseline RAMs and a larger sample size.

Keywords HIV · Simplification · Antiretroviral

Introduction

The optimization of antiretroviral therapy (ART) in the setting of viral suppression has become more commonplace as many people living with HIV (PLWH) are living longer and healthier lives. ART optimization, also known as treatment simplification, may be considered to minimize pill burden, toxicities, drug-drug interactions (DDIs), and potentially costs. Though many antiretroviral (ARV) regimens have been approved by the FDA to replace current ART in PLWH who

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have achieved virologic suppression (HIV RNA < 50 copies/mL) for at least 3–6 months, indications and studies often exclude patients with prior treatment failure or known resistance-associated mutations (RAMs) to the components of the treatment simplification regimen [1•]. Current FDA-approved ART for treatment simplification includes three- and two-drug regimens. With the incidence of RAMs in patients with prior treatment failure ranging from 40 to 60%, this review provides a critical analysis of the role of treatment simplification in the setting of baseline RAMs [2].

Three-Drug Simplification Regimens

Bictegravir-Based Regimen

Bictegravir is an unboosted integrase strand transfer inhibitor (INSTI) co-formulated with two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) in a single-tablet regimen (STR) with a high genetic barrier to resistance [3]. Coupled with high tolerability and low pill burden, bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) is an FDA-approved, simplification option in select treatment-experienced patients.

Two studies evaluated the continuation of a boosted-protease inhibitor (PI), atazanavir (ATV), or darunavir (DRV), plus two NRTIs or dolutegravir (DTG) plus abacavir (ABC) and lamivudine (3TC) versus switching to BIC/FTC/TAF in patients virologically suppressed for 6 months with no known baseline NRTI mutations [4, 5]. Switch to BIC/FTC/TAF maintained virologic suppression in > 98% of patients at week 48 without the emergence of RAMs [4, 5]. Two years after study completion, a pooled-analysis of BIC/FTC/TAF patients ($n = 570$) from both studies were evaluated for pre-existing resistance which identified 159 (27%) patients with at least one mutation including M184V/I ($n = 44$), thymidine analogue mutation (TAM; $n = 35$), and INSTI mutations including T97A ($n = 4$), E92G ($n = 1$), and S147G ($n = 1$) [6•, 7]. Maintenance of virologic suppression at median of 116 weeks after switch remained high despite resistance (M184V/I = 95%, TAM = 95%, INSTI mutations = 100%). Two patients with archived M184V/I experienced virologic failure (VF) (HIV RNA > 50 copies/mL). One patient had low bictegravir concentrations at week 12, an HIV RNA = 2860 copies/mL, and discontinued BIC/FTC/TAF at week 16 with no RAMs detected. The second patient had an HIV RNA = 61 copies/mL and decided to discontinue BIC/FTC/TAF. None of the baseline INSTI mutations seen in this study conferred bictegravir resistance.

A prospective study evaluated patients switching to DTG plus FTC/TAF or BIC/FTC/TAF with baseline NRTI, non-nucleoside reverse transcriptase inhibitor (NNRTI), or PI resistance [7]. Pooled outcomes at week 12 showed HIV RNA < 50 copies/mL in 97% (29/30) of patients with high NRTI resistance (K65R/E/W/N or ≥ 3 TAMs), 95% (20/21) patients with isolated M184V/I, and 98% (59/60) patients with M184V/I plus at least another RAM.

An in vitro analysis of bictegravir susceptibility in 22 clinical samples derived from patients with VF on raltegravir (RAL) or DTG 50 mg twice daily showed that 63.6% of isolates had primary INSTI mutations including G140S (50%), Q148H (50%), E138K (18%), and Y143R (14%). Bictegravir susceptibility was reduced with the presence of G140S plus Q148H with or without at least one other mutation including L74M, T97A, S119P/T, E138A/K, or Y143C/R/H and G163R [8]. This study demonstrates the opportunity to evaluate bictegravir use with baseline INSTI RAMs.

Albeit, each of these studies included a sample size fewer than 50 patients, the extent of NRTI resistance is higher than many other studies assessing treatment outcomes in treatment-experienced patients. All studies had a short follow-up period of 12–24 weeks which may not be long enough to assess virologic outcomes and sustainability. Lastly, none of the aforementioned studied evaluated patients with baseline RAMs specific to DTG or BIC which are known to have the highest barrier to resistance compared to other INSTIs. As a convenient STR that has no food restrictions, minimal DDIs, high barrier to resistance, and favorable tolerability profile, BIC/FTC/TAF is an efficacious option for treatment simplification in patients with baseline NRTI RAMs, specifically M184 V/I but potentially for other NRTI RAMs, in addition to those previously exposed to earlier generation INSTIs including raltegravir and elvitegravir.

Dolutegravir-Based Regimen

DTG is currently formulated in a three-drug STR including ABC/3TC. It was approved by the FDA in 2014, but not for treatment simplification [1•]. Three observational studies have been conducted to assess its feasibility for treatment simplification in treatment-experienced patients. One study compared patients who remained on a PI-containing regimen ($n = 313$) versus those who switched to a DTG-containing regimen ($n = 189$) for 48 weeks. Patients were excluded if prior VF was to an INSTI or if baseline DTG RAMs were identified. In each group > 90% of patients were on FTC or 3TC, with > 50% also being on tenofovir disoproxil fumarate (TDF). Resistance testing was available in 87 (46%) and 56 (18%) patients in the DTG- and PI-containing groups, respectively. In the DTG group, 97.1% of patients with an archived M184 V/I mutation achieved viral suppression compared to 98.1% of those without that mutation. Patients on DTG with a genotypic susceptibility scores of 2, 1–1.75, or 0–0.75 had no statistically different virologic outcome. In the PI-containing group, 76.7% achieved viral suppression with the M184V/I mutation compared to 96.2% viral suppression in the group without M184V/I. Lastly, in the PI group with a GSS = 2, only

74.1% of patients were able to achieve viral suppression which is significantly lower than a GSS = 1–1.75 and GSS = 0–0.75 (96.2% and 100%, respectively). The lower rate of viral suppression seen with PI-based ART was thought to be due to lack of adherence [9].

Another observational study evaluated virologically suppressed patients on any baseline ART who switched to a DTG-containing regimen ($n = 239$). Patients were allowed to be on regimens containing ≥ 2 drugs plus DTG. Patients were placed into three groups based on genotypic susceptibility score (GSS); group 1:GSS = 1–1.5 (resistant), group 2:GSS = 2–2.5 (possibly resistant), and group 3:GSS = 3 (susceptible). At week 48 after the switch, 90% viral suppression was seen in all groups. Four patients had VF. In addition to DTG, each patient was also on ABC/3TC (patient #1: GSS = 3), ABC/3TC plus boosted DRV (patient #2: GSS = 2.5), FTC/TDF (patient #3: GSS = 3), and boosted DRV (patient #4: GSS = 2). Patients 1 and 4 had no baseline RAMs. Patient #2 had an archived M184V mutation and patient #3 had a TAM. Patient #2 and #4 had suboptimal DTG concentrations at the time of VF [10].

Lastly, another observational study evaluated patients who switched to DTG plus FTC/TDF for 48 weeks ($n = 123$). A history of VF was seen in 56% of patients with the DTG-containing regimen having an estimated probability of maintaining virologic suppression of 96.1%. Baseline genotypic results were not available for this study [11].

Treatment simplification with DTG-containing regimens in patients with baseline NRTI mutations have shown high virologic efficacy. The M184V/I mutation can cause low-level resistance to ABC which is co-formulated with DTG; however, 40–60% of patients in both observational studies were on an ABC-containing regimen. Neither of those studies indicated any worsened outcomes in patients also taking ABC.

Elvitegravir-Based Regimen

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) and EVG/c/FTC/TAF are FDA approved for treatment simplification in patients stable on ART for at least 6 months with no history of VF and no baseline RAMs [1•].

An open-label study evaluated 37 patients virologically suppressed for at least 6 months on two NRTIs plus a PI, NNRTI, or INSTI, with a known M184V/I mutation, who were switched to EVG/c/FTC/TAF. Patients were excluded if prior VF on PI or INSTI had occurred or if patients presented with baseline TAMs, INSTI, or PI mutations. All patients maintained virologic suppression at weeks 12 and 24 with no treatment-emergent mutations. This study is currently conducting part 2 which is enrolling patients with M184V/I plus ≤ 2 TAMs [12].

An observational study evaluated 186 patients switching to EVG/c/FTC/TDF from any ART. Prior VF was seen in 39% of patients with approximately 50% receiving a PI plus 2 NRTIs at baseline. The estimated probability of maintaining virologic suppression with EVG/c/FTC/TDF at week 48 was 95.4% [11]. Another case series evaluated the efficacy of switching to EVG/c/FTC/TDF in 15 patients with baseline NRTI mutations including M184V/I only ($n = 6$), M184 V plus TAMs ($n = 8$), and other mutations ($n = 1$). Five patients with TAMs had possible resistance to tenofovir. One patient (baseline NRTI mutations: M184V, T215F, K219Q) experienced VF at week 12 with HIV RNA = 9717 copies/mL, suboptimal drug concentrations, but did not develop additional NRTI or INSTI mutations. Viral blips with HIV RNA as high as 72 copies/mL was seen in 2 patients. Eight of nine patients remaining on therapy at week 48 had HIV RNA < 20 copies/mL [13]. Lastly, a switch to EVG/c/FTC/TAF plus DRV or continuation of a DRV-containing ART was studied in 135 virologically suppressed patients with a history of VF to at least 2 prior ARV regimens and confirmed resistance to at least 2 ARV classes. Patients were excluded if they had any DRV- or INSTI-specific mutations or required DTG twice daily dosing. Patients in the EVG/c/FTC/TAF plus DRV group ($n = 89$) had up to three TAMs (44%), K65R (20%), and/or M184V/I (95%). Virologic suppression at week 24 was similar between the switch and baseline regimen groups (96.6% vs. 91.3%; 95% CI − 3.4 to 17.4%, respectively). No patients developed VF [14].

Switching to EVG/c/FTC/TAF or EVG/c/FTC/TDF in virologically suppressed patients with minor NRTI mutations poses a simple option to maintain efficacy. EVG/c/FTC/TAF plus DRV can be optimal for treatment-experienced patients with a high pill burden and multiple NRTI mutations especially those conferring tenofovir resistance. Patients switching to this STR should lack a history INSTI VF or INSTI RAMs. Despite the positive results, most of the studies had a small sample size and were observational. Lastly, as EVG requires boosting with cobicistat, resulting in DDIs, this STR may be less attractive compared to other INSTI-containing regimens for treatment simplification.

Raltegravir-Based Regimen

RAL was the first INSTI FDA approved and is currently not co-formulated into a STR, resulting in a higher pill burden compared to other STRs. The largest studies evaluating the use of RAL in virologically suppressed patients were SWITCHMRK 1 and 2. Combined, these studies assessed the virologic outcome of patients switched to RAL plus 2 NRTIs ($n = 350$) versus those who continued on a boosted lopinavir-containing ART ($n = 352$). A sub-analysis of patients with prior VF showed that patients on RAL versus lopinavir-containing regimens had a lower rate of virologic

suppression at 24 weeks (76.7% vs. 91.9%; 95% CI −24.9 to 6.2, respectively) [15]. Due to the availability of STRs with better virologic outcomes in patients with a history of VF, RAL is not currently recommended for treatment simplification.

Rilpivirine-Based Regimen

Rilpivirine (RPV) is a second-generation NNRTI that maintains efficacy in patients harboring the K103N mutation conferring first-generation NNRTIs resistance. It was FDA approved in a STR with FTC/TDF and FTC/TAF in 2013 and 2016, respectively. Both STRs are approved for patients who are virologically suppressed for at least 6 months with no history of VF and no RAMs. Five studies were found that evaluated the use of RPV-containing STRs in patients with baseline RAMs and/or prior VF.

A prospective, randomized study evaluated an immediate (study day 1; $n = 317$) versus delayed (study week 24; $n = 159$) switch to RPV/FTC/TDF in patients virologically suppressed for at least 6 months on a boosted PI plus 2 NRTIs. At 48 weeks, virologic efficacy was seen in 89.3% and 92.1% in the immediate and delayed groups, respectively. Four patients developed virologic failure at 48 weeks. One patient was found to have Y181C/Y and M184I at baseline. The second patient had no known baseline RAMs but had treatment-emergent V90I, L100I, K103N, and M184I. The third patient also had no known baseline RAMS but had treatment-emergent E138E/K and M184V/I/M. The last patient was found to have K103N and V179V/I as baseline and subsequently developed M184V, E138K, and V108V/I [16].

A cohort study evaluated ART-experienced, virologically suppressed (HIV RNA < 400 copies/mL) patients who switched to RPV/FTC/TDF ($n = 131$) from an INSTI-, PI-, or NNRTI-based regimen plus 2 NRTIs. In the RPV/FTC/TDF group, 100 patients had baseline resistance testing available which revealed one patient with E138A and another with K65R plus M184V mutations. Both patients achieved virologic suppression (HIV RNA < 40 copies/mL) at week 24; however, were switched to fully active agents at this time. Three patients in this study developed VF but none had baseline RAMs. Pre-existing K103N mutation was present in 8 patients, all of whom achieved virologic suppression by week 24. Although a high rate of virologic suppression was observed (92%), this study had numerous limitations, such as including patients with HIV RNA up to 400 copies/mL which may include patients harboring RAMs, the lack of historic genotypic data for ~ 25% of participants, and only a 24 weeks follow-up period. A longer duration may have provided additional data on the maintenance of virologic efficacy [17]. A similar cohort study evaluated the efficacy of switching patients ($n = 304$) virologically suppressed for 3 months on a three-drug regimen to RPV/FTC/TDF. Baseline resistance data was available for 196 patients, with resistance seen to FTC ($n = 14$), RPV ($n = 8$), or FTC plus RPV ($n = 3$). Virologic suppression at 12 months was seen in 93.4% of patients. Five patients developed VF; one with a baseline M184V, three TAMs, and K103N and another with a baseline L210M and K103N both of which had treatment discontinued. Overall, 12 patients in this study had a baseline K103N mutation, 10 of which achieved virologic suppression [18].

Another observational, cohort study evaluated 281 virologically suppressed patients who switched to a RPV-containing regimen. Virologic suppression was achieved in 59% of patients at 12 months and 72% using data beyond 12 months. Sixteen (6%) patients developed VF at 12 months with 10 having baseline genotype results available. VF was significantly associated with patients who had a baseline M184V/I mutation ($p = 0.02$) and use of a non-NNRTI as a third agent prior to the switch ($p = 0.03$) [19].

Lastly, a retrospective study evaluated the impact of baseline NRTI and NNRTI resistance on virologic suppression after switching to RPV/FTC/TDF ($n = 309$). Dual resistance to NRTI plus NNRTIs was identified in 5.8%, while single class resistance occurred in 12.6% at baseline. By week 72, virologic rebound was identified in 11.3% of patients. Risks for virologic rebound included dual resistance and pre-ART viremia > 500,000 copies/mL. Probability of virologic rebound was identified as 36.45, 9.7%, and 17.8% in patients with intermediate to full resistance to FTC/TDF and RPV, full susceptibility to FTC/TDF and RPV, and intermediate to full resistance to FTC/TDF or RPV, respectively ($p = 0.011$) [20].

Based on the aforementioned studies, patients with underlying NRTI RAMs should avoid this STR as VF may occur, resulting in resistance and limiting future ART options. Patients with K103N may benefit from the use of RPV-containing STRs; however, a thorough review of other NNRTI and NRTI mutations should be done. RPV regimens are less efficacious in patients with HIV RNA ≥ 100,000 copies/mL and poor immunologic function. That coupled with food restrictions, DDIs, and lower barrier to resistance compared to INSTIs, RPV may not be the best option unless patients are switching from earlier generation NNRTI therapies.

Boosted-Protease Inhibitor-Based Regimen

Protease inhibitors have been used in patients requiring ART with a higher barrier to resistance, having a low CD4 nadir, and a high baseline HIV RNA. Despite the high efficacy seen with PIs, the toxicities, DDIs, and high pill burden, make PI-containing regimens difficult to comply with. In 2018, the FDA-approved STR containing darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF) which can help decrease pill burden and is indicated for

treatment simplification in patients on stable ART for at least 6 months without DRV and/or tenofovir resistance [1•].

A retrospective study evaluated 32 patients with a baseline M184V who were on boosted DRV and FTC/TDF. Baseline PI mutations were seen in 19 (59%) patients; however, all were DRV susceptible. Some degree of TDF resistance was seen in 10 (31%) patients, with 90% of them achieving virologic suppression. Six patients developed VF but no DRV RAMs were identified in that population. Virologic failure was attributed to potential medication nonadherence [21].

The EMERALD study evaluated the efficacy of switching to DRV/c/FTC/TAF ($n = 763$) in patients virologically suppressed on a boosted PI-containing regimen for at least 2 months compared to those remaining on baseline PI-based ART ($n = 378$). In this study, 15% of patients had a history of VF. At 48 weeks, 2.5% and 2.1% virologic rebound was seen in the switch versus PI-containing group, respectively ($p < 0.0001$). In each group 2% (total $n = 27$) of patients experienced VF. Only 24 of those patients had baseline genotypic results and all showed no RAMs [22].

With the approval of the first PI-based STR, simplification with this regimen may be feasible. Though limited in the studies available for treatment simplification, efficacy has been seen in patient with baseline NRTI RAMs, specifically in patients with decreased tenofovir susceptibilities. Although no patients were identified as having baseline RAMs in the EMERALD study, VF occurred in few patients but was not associated with treatment-emergent RAMs. Further prospective studies would need to be done to assess the role of PIs in treatment simplification for patients with baseline RAMs.

Two-Drug Simplification Regimens

Dolutegravir and Lamivudine

In 2019, the FDA approved a STR of DTG/3TC for treatment-naïve adults with no known/suspected RAMs to DTG or 3TC [1•]. Although studies have been done in treatment-experienced patients, most excluded patients with baseline resistance to DTG or 3TC [23]. One prospective and seven retrospective studies evaluated switches to DTG/3TC in treatment-experienced patients with baseline RAMs and/or prior VF.

The DOLULAM study evaluated the efficacy of switching to DTG/3TC in treatment-experienced patients virologically suppressed for at least 12 months with no baseline INSTI mutations ($n = 27$). Of those, 17 (63%) patients had an M184V/I mutation of which none experienced VF at 96 weeks. Two patients experienced one viral blip at weeks 12 and 36. Three patients elected to discontinue DTG/3TC; two for fatigue and one after the blip [24, 25]. Although this study was small, many patients had M184V/I, it was prospective, and it had a long follow-up period. No correlation between the presence of M184V/I and virologic outcome could be made during this study period due to lack of VFs.

Results of retrospective studies that had virologic outcomes of treatment-experienced patients with history of VF and/or baseline RAMs who switched to DTG/3TC are presented in Table 1 [26–30, 31•]. The most common baseline RAM across the studies was M184V/I; however, none of the studies found that M184V/I alone was a predictor of VF; however, it was associated with VF in one study if the time of virologic suppression prior to the switch was < 96 months [26–30]. It was also found to be a predictor of viral blips in another study that compared patients with and without M184V. Patients in this study were switched to a variety of two-drug regimens, not limited to DTG/3TC [26]. In other studies, the cumulative duration of prior ART or peak HIV RNA > 500,000 copies/mL were associated with VFs [26, 30]. VFs were low across all studies and no treatment-emergent resistance was discovered, although genotypes were not available in some cases.

Data for DTG/3TC in treatment-experienced patients with and without resistance is promising. However, larger sample size trials in this population are absent. Therefore, DTG/3TC should be reserved for carefully selected treatment-experienced patients. Most data in treatment-experienced patients with baseline resistance comes from patients with M184V/I and no INSTI mutations. DTG/3TC in patients with other RAMs cannot be recommended at this time.

Dolutegravir and Rilpivirine

The two-drug regimen of DTG/RPV was FDA approved in 2017 for treatment simplification in patients who were virologically suppressed for at least 6 months on ART with no history of VF and/or no known RAMs to DTG or RPV. Four retrospective studies were identified that evaluated the use of DTG/RPV for treatment simplification in patients with baseline resistance or prior VF (Table 2). Although none of the studies included patients with specific mutations to RPV or DTG, the patients included were heavily treatment-experienced. High rates of virologic suppression were seen among all studies with most treatment discontinuation attributed to DDIs and tolerability [26, 31•, 32, 33]. Due to food restrictions with RPV, DDIs, and low barrier to resistance, DTG/RPV should be initiated in carefully selected patients and counseling on appropriate administration would be imperative.

Dolutegravir and Boosted-Protease Inhibitors

Boosted DRV combined with DTG has been evaluated as a switch strategy in treatment-experienced patients in three studies, of which one included patients with virologic suppression

Table 1 Summary of retrospective studies evaluating switch to DTG/3TC in treatment-experienced patients with history of virologic failure and/or baseline resistance mutations

Study	Patients included (*n*)	VF definition[1]	Previous VF allowed Y/N (%)	Previous resistance allowed Y/N (*n*(%))	Median months with HIV VL < 50	Virologic outcome	VF outcomes
Baldin et al. [24] JAC 2019	221	HIV RNA ≥ 1000 × 1 or ≥ 50 × 2	Y (43.4)	Y M184V: 20 (9%)	96	Probability remaining free from VF, 144 weeks: 95.3% (93.4–97.2)	7 (3%) no correlation with baseline mutations
Borghetti et al. [25] BMC ID 2019	183	HIV RNA ≥ 1000 × 1 or ≥ 50 × 2	Y (51.4)	Y M184V: 16 (8.7%)	96	Probability remaining free from VF, 96 weeks: 94.5% (89.6–99.4)	5 (2.7%) no correlation with baseline mutations
Borghetti et al. [26] HIV MED 2018	206	HIV RNA ≥ 1000 × 1 or ≥ 50 × 2	Y (40.5)	Y M184V: 12(5.8%)	70	Probability maintaining VS, 96 weeks: 95.1%	4 (1.9%); 1 with baseline M184V/I no correlation with baseline mutations
Ciccullo et al. [27] AVT 2019	229	HIV RNA ≥ 1000 × 1 or ≥ 50 × 2 in 3 months	Y (38.6)	Y w/ BL GT: *n* = 141: NRTI: 30 (22%) NNRTI: 29 (20.6%) PI: 20 (14.2%) INSTI: 0 (0%)	77.8	Probability remaining on study drug, 96 weeks = 85.8% Probability of maintaining VS at 96 weeks = 95.3%	10 (4%)
Gagliardini et al. [28] OFID 2018	126	HIV RNA ≥ 200 × 1 or > 50 × 2	NR	Y M184V+: 21 (24%)	M184V−:45.6 M184V+:79.2	Probability remaining free from VF, 1 year: M184V+: 100% M184V−: 97.5%	2 (both M184V−) no correlation with baseline mutations
Allavena et al. [29] CROI 2019	677	HIV RNA > 50 × 2	Y (13.7%)	NR	79	Treatment discontinuation occurred: 127 (18.7%)	12 (1.7%)

VF = virologic failure; *VL* viral load; *BL GT* = baseline genotype; *VS* = virologic suppression; *NR* = not reported; *NRTI* nucleoside/nucleotide reverse transcriptase inhibitor; *NNRTI* non-nucleoside reverse transcriptase inhibitor; *PI* protease inhibitor; *INSTI* integrase strand transfer inhibitor

[1] All viral loads are reported in copies/mL

Table 2 Summary of retrospective studies evaluating switch to DTG/RPV in treatment-experienced patients with history of virologic failure and/or baseline resistance mutations

Study	Patients included (*n*)	VF definition[1]	Previous VF allowed Y/N (%)	Previous resistance allowed Y/N (*n*(%))	Median months with VS	Virologic outcome	VF outcomes
Allavena et al. [29] CROI 2019	974	HIV RNA > 50 × 2	Y (26%)	NR	89	Treatment discontinuation occurred: 215 (22%)	18 (1.8%)
Ciccullo et al. [27] AVT 2019	187	HIV RNA ≥ 1000 × 1 or ≥ 50 × 2 in 3 months	Y (51.3%)	Y w/ BL GT: *n* = 166: NRTI: 65 (39.2%) NNRTI: 20 (12%) PI: 25 (15.1%) INST: 2 (1.2%)	85.1	Probability remaining on study drug, 96 weeks = 94.2% Probability of maintaining VS at 96 weeks = 96.9%	5 (2.7%) 1 due to non-compliance
Capetti et al. [30] Ann Pharm	145	HIV RNA ≥ 50 × 1	Y (81.4%)	Y* NNRTI: 100I: 2 101E: 1 181C:3 190S:1 INSTI: 140S:1 148H:1	NR	Week 96: 100% VS (*n* = 138)	None
Riccardi et al. [31•]	7	HIV RNA ≥ 50 × 1	Y (86%)	Y No RPV or INSTI mutations noted	≥ 6 months	Week 24: 100% VS (*n* = 7)	None

*Other NRTI, NNRTI, PI, and INSTI mutations seen. Only those relevant to DTG and RPV were listed here. *VF* = virologic failure; *VL* viral load; *BL GT* = baseline genotype; *VS* = virologic suppression; *NR* = not reported; *NRTI* = nucleoside/nucleotide reverse transcriptase inhibitor; *NNRTI* = non-nucleoside reverse transcriptase inhibitor; *PI* = protease inhibitor; *INSTI* = integrase strand transfer inhibitor

[1] All viral loads are reported in copies/mL

Table 3 Summary of retrospective studies evaluating switch to DTG plus boosted PIs in treatment-experienced patients with history of virologic failure and/or baseline resistance mutations

Study	Patients included (*n*)	VF definition[1]	Previous VF allowed Y/N (%)	Previous resistance allowed Y/N (*n*(%))	Months with HIV VL < 50	Virologic outcome[1]	VF outcomes *N* (%)
Capetti et al. [32] BMC ID 2017	130	HIV RNA ≥ 50	Y (82.3%)	Y NRTI: 116 (89.2%) NNRTI: 98 (75.4%) PI: 91 (70%) INSTI: 12 (10.6%)	NR	Week 48: HIV RNA <50 = 76.1%; detectable HIV RNA < 50 copies/mL = 14.6%	8 (6.2%)
Jablonowska et al. [33] PLOS 2019	76	HIV RNA > 50	Y (40%)	NR	NR	Week 48: HIV RNA < 50 = 85.5%; HIV RNA 50–200 = 6.6%	6 (8%)
Navarro et al. [34] PHARM 2019	50	HIV RNA ≥ 50 × 1	Y (100%)	Y NRTI:93.2% NNRTI:72.7% PI:27.3% INSTI:15.9%	52	Median 25 months: 98% virologic suppression	1 (20%) due to lack of follow-up

VF = virologic failure; *VL* = viral load; *BL GT* = baseline genotype; *VS* = virologic suppression; *NR* = not reported; *NRTI* = nucleoside/nucleotide reverse transcriptase inhibitor; *NNRTI* = non-nucleoside reverse transcriptase inhibitor; *PI* = protease inhibitor; *INSTI* = integrase strand transfer inhibitor

[1] All viral loads are reported in copies/mL

while the other two included viremic patients (Table 3) [34–36].

All studies included were retrospective and included patients with a history of VF ranging from 40 to 100% of the population studied. Overall, virologic suppression was seen in over 75% of patients included. Combined, 15 patients had VF. Three patients were lost to follow-up but later were able to suppress on DTG and boosted DRV; 8 patients were continued on therapy due to HIV RNA < 200 copies/mL, 1 patient had ART discontinued due to HIV RNA > 200 copies/mL; however, no treatment-emergent mutations were identified; and 3 patients had resistance to 3 ARV classes [35, 36].

At this time, boosted DRV and DTG are not co-formulated which may not decrease a patients' pill burden; in addition, boosting agents, such ritonavir and cobicistat, may lead to increased incidence of DDIs and further toxicities. This may be an efficacious two-drug regimen in treatment-experienced patients with baseline RAMs if other options are not ideal for specific patients.

Dolutegravir Plus Other Antiretroviral(s)

Gubavu et al. evaluated DTG monotherapy ($n = 21$) versus dual DTG (DD) given with either RPV ($n = 11$), ATV ($n = 8$), boosted ATV ($n = 4$), boosted DRV (n = 1), maraviroc ($n = 3$), 3TC (n = 3), or ABC ($n = 1$). Prior VF was seen in 65% and 24% in the DD and monotherapy groups, respectively, with 26% and 5% prior VF seen with an INSTI-containing regimen, respectively. Though baseline INSTI mutations were seen, DTG susceptibility was maintained in all patients. By week 24, all patients achieved virologic suppression except 1 due to non-compliance [37]. One of the goals of two-drug regimens is to minimize long-term toxicities with NRTIs, such as those observed with tenofovir and ABC. Many patients require NRTI sparing regimens due to various reasons including renal dysfunction and resistance. Though many of the above-stated regimens have shown to be efficacious in small, retrospective studies, larger, prospective studies, with longer durations of follow-up are needed to ensure durability of virologic suppression in patients with baseline resistance.

Monotherapy Regimens

Monotherapy for treatment simplification is not currently approved by the FDA; however, studies have assessed its efficacy and safety in patients with no baseline mutations or prior VF. Most of these studies evaluated the use of INSTIs, specifically DTG, or boosted PIs. Even in patients with no VF history or baseline RAMs, monotherapy has been associated with a higher risk of treatment failure compared to two- or three-drug regimens for treatment simplification [38]. A small, observational study, assessed switching to low dose boosted

DRV (600 mg) monotherapy in virologically suppressed patients ($n = 31$) previously on a PI-containing regimen. One patient in this study did have a baseline I84V mutation which can decrease DRV susceptibility; however, all patients maintained virologic suppression at week 48 [39].

As discussed earlier, Gubavu et al. evaluated DTG monotherapy ($n = 21$), where 24% had prior VF and 5% had failure on an INSTI-containing regimen. All patients in the monotherapy group were able to achieve virologic suppression at the last study visit (median 39 weeks) [37]. With the lack of larger studies evaluating baseline RAMs in patients using monotherapy for treatment simplification, the use of any monotherapy ARV in a resistant population should be avoided at this time.

Conclusions

Treatment simplification has been shown to minimize toxicities and DDIs, and improve patient satisfaction all while maintaining virologic suppression in PLWH. Though many HIV simplification regimens are FDA approved, few have been evaluated in patients with baseline RAMs and prior VF. With PLWH living longer and presenting with a long history of ARV exposure, it is imperative to find ART simplification options for this population. Three-drug regimens including INSTI plus 2 NRTIs have been shown to be effective in patients with underlying NRTI mutation, M184V. This would allow patients to maintain on a STR despite the presence of this common mutation. The use of NNRTI plus 2 NRTIs with underlying NRTI mutations has shown poorer outcomes and should not be recommended at this time. For PI plus 2 NRTI regimens, limited data is available in patients with underlying NRTI and/or PI mutations, and therefore cannot be recommended at this time.

Though DTG/3TC and DTG/RPV are FDA approved for treatment simplification in patients with no baseline RAMs or VF history, studies assessing their use were mostly retrospective. The most common underlying mutation evaluated was M184V which was found to have no correlation alone to VF unless suppression on previous ART was < 96 months. No studies with baseline DTG and RPV mutations were evaluated in patients receiving DTG/RPV; however, patients were heavily treatment-experienced and maintained virologic efficacy. DTG/RPV should be used in patients that can comply with the appropriate medication administration and with a thorough review of prior treatment failures to ensure no baseline DTG and RPV mutations. Lastly, dual therapies including PIs have been shown to be effective but may not be ideal given toxicities, DDIs, and the lack of a STR with DTG. Monotherapy is controversial even in patients with no baseline mutations. Limited data exists for patients with underlying mutations and/or a VF history and should not be recommended in this population. Future studies should look to include patients with a VF history and baseline mutations to INSTIs to evaluate the appropriate use for treatment simplification regimens in larger, randomized, controlled studies.

Compliance with Ethical Standards

Conflict of Interest Neha Sheth Pandit, Daniel B. Chastain, Andrea M. Pallotta, Melissa E. Badowski, Emily C. Huesgen, and Sarah M. Michienzi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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