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Optimizing Antiretroviral Therapy in Treatment-Experienced Patients Living with HIV: A Critical Review of Switch and Simplification Strategies. An Opinion of the HIV Practice and Research Network of the American College of Clinical Pharmacy

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Abstract

Simplifying or switching antiretroviral therapy (ART) in treatment-experienced people living with HIV (PLWH) may improve adherence, tolerability, toxicities, and/or drug–drug interactions. The purpose of this review is to critically evaluate the literature for efficacy and safety associated with switching or simplifying ART in treatment-experienced PLWH. A systematic literature search using MEDLINE was performed from January 1, 2010 to April 30, 2018. References within articles of interest, the Department of Health and Human Services guidelines, and conference abstracts were also reviewed. Switch/simplification strategies were categorized as those supported by high-level clinical evidence and those with emerging data. Rates of virologic suppression were noninferior for several switch/simplification strategies when compared to baseline ART. Potential for reducing adverse events was also seen. Additional evidence for some strategies, including most 2-drug regimens, is needed before they can be recommended.

Keywords

HIV, antiretroviral therapy, switch therapy, simplification therapy

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Introduction

Switching or simplifying antiretroviral therapy (ART) in the setting of HIV suppression may improve pill burden, dosing frequency, safety, tolerability, and/or food requirements.[1] At times, ART switch or simplification is elective, such as consolidating a multiple-tablet to a single-tablet regimen (STR). Other times, it is necessary to eliminate drug–drug interactions (DDIs) and/or minimize active or potential treatment-associated adverse events (AEs), as well as due to costs of therapy, barriers to access, and/or financial constraints.

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What Do We Already Know about This Topic?

The increase in available antiretroviral agents has prompted many providers and patients living with HIV to switch or simplify current antiretroviral therapy (ART) due to improving pill burden, dosing frequency, safety, tolerability, food requirements, and/or financial constraints.

How Does Your Research Contribute to the Field?

This review critically evaluates the literature for efficacy and safety associated with switching or simplifying ART in treatment-experienced patients living with HIV.

What Are Your Research's Implications toward Theory, Practice, or Policy?

With the growing number of clinical trials evaluating switch and simplification strategies, it is critical to keep providers abreast of treatment updates.

The fundamental principle of switching or simplifying ART is to preserve virologic suppression without jeopardizing future ART options.[1] Prior to ART modification, a full review of the patient's ART and resistance history should be conducted, as evidenced by the SWITCHMRK study,[2] including virologic responses, toxicities, and intolerances. Additionally, insurance restrictions, readiness to switch, DDIs, and supporting evidence should be assessed. The purpose of this review is to critically evaluate the literature for efficacy and safety associated with switching or simplifying ART in treatment-experienced people living with HIV (PLWH).

Methods

Search Strategy and Selection Criteria

A systematic literature search using MEDLINE was performed from January 1, 2010 to April 30, 2018, to ensure all data evaluating switch and simplification strategies were identified. The following search terms were used: HIV, reverse transcriptase inhibitor, tenofovir alafenamide, tenofovir disoproxil fumarate, rilpivirine, integrase inhibitor, elvitegravir, dolutegravir, bictegravir, cabotegravir, protease inhibitor, atazanavir, darunavir, and switch*, simplify*, or spare*. References within articles of interest, the Department of Health and Human Services (DHHS) guidelines,[1] and conference abstracts were reviewed to capture additional citations. Articles in English identified from the search evaluating the efficacy and safety of switch or simplification strategies were included. Studies were excluded if the focus was antiretroviral (ARV) monotherapy, pharmacokinetics, infants, children, adolescents, or hepatitis B virus (HBV) or hepatitis C virus coinfection. Data extracted from each study included methodology, patient demographics, treatment arm(s) or group(s), follow-up, virologic and immunologic outcomes, development of resistance-associated mutations (RAMs), and safety. Studies were then organized into 2 main categories: strategies supported by high-level clinical evidence and emerging strategies.

Results

Strategies Supported by High-Level Clinical Data

Most often, "within-class switches" are performed to decrease drug- or comorbidity-related toxicities, while minimizing the risk of virologic failure.[1,3] Data are increasing to support "between-class switches," aimed at simplifying ART by improving dosing frequency, pill burden, tolerability, and DDIs.[4,5] For some regimens, supporting evidence led to a Food and Drug Administration (FDA)-approved indication for ART switch. Typically, regimens with low barriers to resistance are switched to those with a higher barrier to increase the probability of maintaining virologic suppression.

Tenofovir formulation switches. Data generated from various clinical trials consistently demonstrate switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) is associated with a reduction in renal and bone AEs (Table 1),[6–12] likely due to reduced systemic exposure of circulating tenofovir when administered as TAF.

Switch criteria were relatively consistent between studies where virologically suppressed individuals with a creatinine clearance (CrCl) $\geq$50 mL/min were randomized to remain on TDF or switched to TAF with emtricitabine (FTC) plus a third agent.[6–12] Although most studies had the end point of 48 weeks, 1 study evaluated TAF- to TDF-containing regimens in the presence of a boosted protease inhibitor (PI) compared to an unboosted third agent at 96 weeks, which demonstrated FTC/TAF, regardless of third agent, was effective and well tolerated with minimal rates of RAMs. In addition, the study was able to demonstrate improved renal and bone outcomes.[13] Interestingly, another study demonstrated a higher decline in CrCl at 48 weeks in the TAF arm compared to TDF when evaluating rilpivirine (RPV)/FTC/TAF (−4.1 mL/min; 95% confidence interval [95% CI]: −12.7 to 4.6) to efavirenz (EFV)/FTC/TDF (−0.6 mL/min; 95% CI: −7.8 to 6.7; $P <$ .0001).[11] This decrease in CrCl is likely the result of RPV inhibiting tubular secretion of creatinine by interacting with renal transporters.[14] However, safety end points were not significantly different between unboosted regimens containing TAF and TDF in a meta-analysis.[15] It should be noted that while fasting lipid and total cholesterol levels increased in TAF-containing regimens, the total cholesterol to high-density lipoprotein (HDL) ratio did not differ between groups in the clinical trials.[6–9,11–13] Although all of these studies occurred in the clinical trial setting and demonstrated

Table 1. Summary of Trials Comparing Tenofovir Formulations in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Study Agents	Study Design and Patient Population	Virologic Suppression 48 weeks	CrCl (mL/min)[a]	Bone Density (%)[a]		Lipids (TC:HDL ratio)[a]	Treatment-Emergent RAMs
				Hip	Lumbar Spine		
EVG/c/FTC/TAF versus ATV + RTV + FTC/TDF[10]	Open label, switch, women, noninferiority	EVG/c/FTC/TAF: 94% (150/159)	4.2	2.1	2.8	0.1	None
		ATV + RTV + FTC/TDF: 87% (46/53)	−1.8; $P = .06$[b]	1.3; $P = .29$[b]	0; $P < .001$[b]	0.0; $P = .075$[b]	None
GS-US-366-1160; RPV/FTC/TAF versus EFV/FTC/TDF[11]	Multicenter, randomized double blind, placebo controlled, noninferiority	RPV/FTC/TAF: 90% (394/438)	−4.1 (95% CI: −12.7 to 4.6)	1.28	1.65	0.1	None
		EFV/FTC/TDF: 92% (402/437)	−0.6 (95% CI: −7.8 to 6.7); $P < .0001$[b]	−0.13; $P < .0001$[b]	−0.05; $P < .0001$[b]	0; $P = .20$[b]	M184V, V106I/L (n = 1)
GS-US-311-1089 (subgroup analysis); boosted PI[c] + FTC/TAF or FTC/TDF versus unboosted-third agent[d] + FTC/TAF or FTC/TDF[a,6]	Multicenter, controlled, double blind, switch	Boosted PI[c] + FTC/TAF: 92%	7.7 (95% CI: 0.1 to 15.1)	1.233	1.544	0.1 (95% CI: −0.2 to 0.7)	M184V (n = 1)
		Boosted PI[c] + FTC/TDF: 93%	3.3 (95% CI: −6.0 to 12.3); $P < .05$[b]	−0.089; $P < .001$[b]	−0.354; $P < .001$[b]	0.1 (95% CI: -0.3 to 0.4)	None
		Unboosted third agent[d] + FTC/TAF: 97%	9.3 (95% CI 0.6-15.8)	1.051	1.511	0.1 (95% CI: −0.3 to 0.5)	None
		Unboosted third agent[d] + FTC/TDF: 93%	2.8 (95% CI 3.7 to 10.1); $P < .05$[b]	−0.205; $P < .001$[b]	−0.081; $P < .001$[b]	0.0 (95% CI: −0.4 to=0.4)	None
GS-US-366-1216; RPV/FTC/TAF versus RPV/FTC/TDF[7]	Multicenter, randomized double blind, switch, noninferiority	RPV/FTC/TAF: 94% (296/316)	4.5 (95% CI: −4.1 to 12.3)	1.04	1.61	0.1	None
		RPV/FTC/TDF: 94% (294/313)	0.7 (95% CI: −6.6 to 8.1); $P = .0024$[b]	−0.25; $P < .0001$[b]	0.08; $P < .0001$[b]	0.1; $P = .18$[b]	None
GS-US-311-1089; TAF versus TDF[8]	Multicenter, controlled, double blind, switch	TAF: 94% (314/333)	8.4 (95% CI 0.2 to 15.6)	1.135	1.527	0.1	M184V (n = 1)
		TDF: 93% (307/330)	2.8 (95% CI: −5.1 to 10.9); $P < .0001$[b]	−0.152; $P < .001$[b]	−0.206; $P < .001$[b]	0; $P = .073$[b]	None

(continued)

Table 1. (continued)

Study Agents	Study Design and Patient Population	Virologic Suppression 48 weeks	CrCl (mL/min)[a]	Bone Density (%)[a]		Lipids (TC:HDL ratio)[a]	Treatment-Emergent RAMs
				Hip	Lumbar Spine		
GS-US-292-0109; EVG/c/FTC/TAF versus TDF-based therapy[9]	Open label, switch	EVG/c/FTC/TAF: 97% (932/959)	1.2 (95% CI: −6.6 to 9.1)	1.47	1.56	NR	M184I/M (n = 1)
		TDF-based therapy: 93% (444/477)	−3.7 (95% CI: −10.5 to 3.5); $P < .0001$[b]	−0.34; $P < .0001$[b]	−0.44; $P < .0001$[b]		None
EMERALD; Boosted PI + FTC/TDF versus DRV/c/FTC/TAF STR[12]	Multicenter, randomized, open label, switch Primary boosted PIs at enrollment: DRV: 70% versus 70%; ATV: 22% versus 22%; LPV: 8% versus 8%; c: 17% versus 14%	Boosted PI[e] + FTC/TDF: 94% (354/378)	−1.9; $P = .0007$	−0.26; $P = .78$	−0.63; $P = .98$	0.1	None
		DRV/c/FTC/TAF STR: 95% (724/764)	−0.4; $P = .24$	1.43; $P < .001$	1.49; $P < .001$	0.2	None

Abbreviations: ART, antiretroviral therapy; ATV, atazanavir; c, cobicistat; CI, confidence interval; CrCl, creatinine clearance; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; HDL, high-density lipoprotein; LPV, lopinavir; NR, not reported; PI, protease inhibitor; PLWH, people living with HIV; RAM, resistance-associated mutation; RPV, rilpivirine; RTV, ritonavir; STR, single-tablet regimen; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate.

[a]Change from baseline.

[b]*P* values for all between-group differences (FTC/TAF versus FTC/TDF).

[c]Boosted PI = ATV + RTV, DRV + RTV, or lopinavir/RTV (LPV/r).

[d]Unboosted third agent = unboosted third agents (EFV, RPV, nevirapine, raltegravir, dolutegravir, or maraviroc).

[e]Boosted PI = DRV/c, DRV/r, ATV/r, ATV/c, LPV/r.

noninferiority in terms of efficacy, "real-world" evaluations would be beneficial to better assess safety and efficacy.

Based on these clinical trial data, we recommend switching patients from TDF- to TAF-based regimens. If resources are limited, it is reasonable to target patients at the highest risk for TDF-related AEs (i.e., those with existing renal or bone density issues). For patients stable on a TDF-based regimen who are unwilling to switch to TAF, continuing TDF with monitoring and continued discussion regarding switching is reasonable. Switches in which the third agent is kept the same or within the same class may increase patient acceptability and allow for less frequent postswitch monitoring. However, TDF to TAF switches provide an opportunity to modernize third agents as well.

Integrase strand transfer inhibitor switches

Elvitegravir. Elvitegravir (EVG) requires coadministration with cobicistat (c) leading to DDIs similar to PIs, administration with food for maximal absorption, and a low genetic resistance barrier resulting in cross-resistance to the first approved integrase strand transfer inhibitor (INSTI), raltegravir (RAL).[16]

Seven studies investigated switching to an EVG-based regimen (EVG/c/FTC/TAF or EVG/c/FTC/TDF; Table 2).[10,17–22] These studies evaluated both within- and between-class switches in virologically suppressed patients. One study included 15 patients with baseline nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAMs (M184V/I, n = 14; thymidine analog mutations [TAMs], n = 8; other mutations, n = 1).[19] Four studies required 6 months of suppression prior to the switch,[17,18,20–22] while 1 study required suppression at the end of an initial 48-week blinded phase[10] and another was an observational cohort without a specific time requirement.[19] One study evaluated EVG/c/FTC/TAF as a switch strategy for patients with end-stage renal disease (ESRD) on hemodialysis (HD).[22]

Most patients switched to an EVG-based regimen maintained virologic suppression as virologic failure (2 consecutive HIV-RNA >50 copies/mL) was low across all studies and study arms.[10,17–22] Among those with baseline RAMs, 2 discontinued therapy, 1 experienced virologic failure, and 2 experienced virologic blips, while the others achieved virologic suppression.[19] In clinical trials, resistance testing was conducted in participants with HIV-RNA >50 to 400 copies/mL,[10,17,18,20–22] while the observational trial did not have a specific threshold.[19] Treatment-emergent RAMs were not detected in participants switched to EVG-based regimens in most clinical trials[10,17,18,20,21] but were detected in 2 patients in an observational study, although none with baseline RAMs[19] and 1 patient in an open label trial.[22]

EVG-based regimens were overall well tolerated.[10,17–21] For patients switched to EVG-based regimens, AE-related discontinuations were more common in the observational trial (27%)[19] than in the clinical trials (0%-5%).[10,17,18,20–22] This is due to the wider definition of AEs used in the observational trial, which may be more representative of true use in practice. In clinical trials, treatment-related AE discontinuations were seen in 7 patients: 1 for generalized edema[22]; 1 for allergic pruritis[22]; 1 for worsening renal function[20]; 1 for renal transplant[22]; 1 for suicidal ideation, depression, and paranoia[20]; and 2 for dysgeusia.[21]

In STRATEGY-NNRTI, participants switched from nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens to EVG/c/FTC/TDF reported statistically significant improvements in neuropsychiatric symptoms ($P < .05$ versus baseline, $P < .05$ versus no-switch).[21] In STRATEGY-PI, participants switched from PI-based regimens to EVG/c/FTC/TDF reported significant improvements in diarrhea ($P < .001$ versus baseline, $P = .01$ versus no-switch) and bloating ($P = .017$ versus baseline, $P < .01$ versus no-switch).[18] Symptomatic improvement in both studies was seen as early as 4 weeks and maintained through 96 weeks.[18,21]

EVG-based regimens, however, are not completely without AEs. In other clinical trials, patients switched to EVG-based regimens commonly reported insomnia (13%), fatigue (6%-10%), anxiety (10%), dizziness (5%-6%), diarrhea (10%-11%) and/or nausea (5%-22%); however, there was no significant difference compared to baseline.[10,17,18,20–22] In the aforementioned observational study, 4 patients discontinued EVG/c/FTC/TAF due to neuropsychiatric AEs and 4 more due to gastrointestinal (GI) AEs.[19]

Overall, switching/simplifying to an EVG-containing STR was well tolerated and maintained virologic suppression in patients, including women, those with renal impairment, and even those with ESRD on HD, on a variety of baseline regimens or with baseline NRTI RAMs. Switching to EVG provides an opportunity to modernize ART and switch to an STR; EVG/c/FTC/TAF is preferred over EVG/c/FTC/TDF for reasons discussed in the tenofovir section. Clinicians should carefully review for DDIs before switching due to the cobicistat component. In most situations, new switches to an EVG-based STR have fallen out of favor since the approval of the bictegravir (BIC)-containing STR due to the potential for decreased DDIs and increased barrier to resistance.

Dolutegravir-based 3-drug regimens. Dolutegravir (DTG) provides most patients a once-daily (QD) option with high potency, minimal toxicities, high barrier to resistance, and minimal DDIs.[30] DTG is available in an STR including DTG/lamivudine (3TC)/abacavir (ABC).[1]

Virologic suppression was evaluated in 4 studies that switched patients to a DTG-based regimen from baseline ART (Table 2).[23–25,31] Each study showed high level of virologic suppression after the switch, ranging from 92% to 97%.

Serious AEs and treatment discontinuations were low in both groups of an open label randomized study of participants switched to DTG/3TC/ABC from various baseline regimens at study entry (early-switch group) or at week 24 (late-switch group).[23] The most common AEs in the early-switch group were nausea (10%), fatigue (7%), diarrhea (6%), and headache (5%), which occurred in 1% of the late-switch participants during weeks 1 to 24. Psychiatric AEs were more common in the early-switch group compared to the late-switch group

Table 2. INSTI-Based Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/L.

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
EVG					
EVG/c/FTC/TDF, n = 48 (switched from RAL + FTC/TDF)[17]	Single arm, open label, switch	Median duration RAL therapy prior to switch: 2.9 years	Week 48: 100%	None	Not evaluated[a]
STRATEGY-NNRTI EVG/c/FTC/TDF, (n = 290) versus continue NNRTI + FTC/TDF (n = 143)[21]	Randomized (2:1 switch: no-switch), open label	Primary NNRTI at enrollment: EFV = 78%	Week 96: 87% versus 80% (95% CI: −1.3 to 14.2)	Week 96: 3% versus 1% (NR[b])	Switch: 1 evaluated; NA[c] No-switch: 2 evaluated; 1 developed K101K/E, Y181Y/C, 1 NA[c]
STRATEGY-PI EVG/c/FTC/TDF (n = 290) versus continue boosted PI + FTC/TDF (n = 139)[18]	Randomized (2:1 switch: no-switch), open label	Primary PIs at enrollment: ATV/r: 40% and DRV/r: 40%	Week 96: 87% versus 70% (95% CI: 8.7 to 26.0)	Week 96: 1% versus 6% (NR[b])	Switch and no-switch: not detected[d]
EVG/c/FTC/TAF (n = 159) versus continue ATV/r + FTC/TDF (n = 53)[10]	Randomized (3:1 switch: no-switch), open label	Women only Randomized after initial randomized blinded phase	Week 48: 94% versus 87% (95% CI: −1.2 to 19.4)	Week 48: 3% versus 6% (NR[b])	Switch: 5 evaluated; not detected No-switch: 2 evaluated; not detected
EVG/c/FTC/TDF, n = 166 (switched from baseline ART)[19]	Prospective, observational, open label, switch	Group 1: no baseline RAMs (n = 151) Group 2: baseline TFV and/or F/3TC RAMs (n = 15) Median time of virologic suppression prior to switch: group 1: 24 months Group 2: 26 months Baseline ART (both groups): PI based: 48% NNRTI based: 38% RAL based: 8% Other: 6%	Week 48: group 1: 97% (63/65); group 2: 89% (8/9)	Week 48: group 1: 3.3% (95% CI: 0.4-6.2); group 2: 7% (NR[b])	Group 1: 3 evaluated; 1 developed M184V, 1 developed D67N, M184V, N155H, 1 not detected Group 2: 1 evaluated; not detected
GS-US-292-0112; EVG/c/FTC/TAF, n = 242 (switched from baseline ART)[20]	Single-arm, open label, switch	Renal impairment (CrCl: 30-69 mL/min) Baseline ART: PI based: 44% NNRTI based: 42% INSTI based: 24%	Week 48: 92%	Week 48: 1%	1 evaluated; not detected

(continued)

Table 2. (continued)

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
		ESRD on chronic HD for ≥6 months Baseline NRTIs: 3TC: 73% FTC: 7% ABC: 56% TDF: 29% Baseline ART third agent: PI based: 44% NNRTI based: 27% INSTI based: 51% CCR5 antagonist based: 2%	Week 48: 82%	Week 48: 4%	K65R (n = 1)[e]
EVG/c/FTC/TAF, n = 55 (switched from baseline ART)[22]	Prospective, observational, open label, switch				
DTG 3-drug regimens					
STRIIVING; DTG/3TC/ABC (early switch), n = 275, versus continue baseline ART and switch at week 24 (late switch), n = 278[23]	Randomized (1:1 early: late switch)	Median duration ART prior to study entry: 51 to 54 months Baseline ART: PI: 43% NNRTI: 32% INSTI: 25%	Week 24: 85% versus 88% (95% CI: −9.1 to 2.4)	Week 24: none	Not evaluated[a]
NEAT022; DTG + 2 NRTIs (n = 205) versus continue boosted PI + 2 NRTIs (n = 210)[32]	Randomized (1:1 switch: no-switch), open label	High cardiovascular risk (>50 years of age or >18 years of age with a Framingham score >10%) HIV-RNA <50 copies/mL on ART ≥6 months Baseline ART: TDF/FTC: 65.4% versus 64.3% ABC/3TC: 30.7% versus 31.9% LPV/r: 6.4% versus 11% ATV/r: 37.7% versus 35.2% DRV/r: 51.5% versus 51%	Week 48: 93.1% versus 95.2% (95% CI: −6.6 to 0.8)	Week 48: 2% versus <1%	None
DTG + 3TC/ABC (n = 37) versus continue boosted PI + 3TC/ABC (n = 36)[24]	Randomized (1:1 switch: no-switch), open label	Osteopenia or osteoporosis Baseline PI: LPV/r: 16% versus 14% ATV/r: 27% versus 25% DRV/r: 54% versus 58% FPV/r: 19% versus 22%	Week 48: Switch: 97% (95% CI: 84.19 to 99.86); no-switch: 91.7% (95% CI: 76.41 to 97.82)	Week 48: None	Switch: 1 evaluated; developed D67N No-switch: 3 evaluated; 1 developed E138G[f]

(continued)

Table 2. (continued)

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
DTG-based regimens (n = 157)[25]	Retrospective review	Treatment-naive: 32% Switch: 68% Detectable HIV-RNA at switch: 26% (24/92) Regimens prior to switch[g]: PI based: 48% NNRTI based: 32% INSTI based: 25% (23% RAL, 3% EVG/c) DTG-based regimens in switch patients: DTG/3TC/ABC: 65% DTG + FTC/TDF: 35%	Week 12 (switch only): 96% (88/92)	Week 12 (switch only): 4% (4/92)	M184V (n = 1) N155H and V1511I/L (n = 2)[h]
DTG/RPV					
DTG/RPV (n = 516) versus continue current ART (n = 512)[26]	Randomized, multicenter, open label, parallel group, noninferiority	HIV-RNA <50 copies/mL on ART ≥6 months Baseline ART third agent: NNRTI: 54% versus 54% PI: 26% versus 27% INSTI: 20% versus 19%	Week 48: 95% versus 95% (95% CI:−3 to 2.5)	Week 48: <1% versus 1%	None
BIC					
BIC/FTC/TAF (n = 290) versus continue DRV/r or ATV/r + 2 NNRTIs (n = 287)[27]	Randomized (1:1 switch: no-switch), open label	Virologically suppressed at study entry[i] NNRTIs: FTC/TDF or 3TC/ABC Most common ART at screening: Boosted PI + FTC/TDF: 85%	Week 48: 92 versus 89% (NR[b])	Week 48: 1.7% versus 1.7% (95% CI: −2.5 to 2.5)	Switch: none detected[d] No-switch (DRV/r + ABC/3TC): 1 developed L74V[d]
BIC/FTC/TAF (n = 282) versus continue DTG/3TC/ABC (n = 281)[28]	Randomized (1:1 switch: no-switch), double blind	HIV-RNA <50 copies/mL × ≥3 months at study entry	94% versus 95% ($P = .59$)	Week 48: 1.1% versus 0.4% (95% CI: −1.0 to 2.8)	Switch and no-switch: not detected[d]

(continued)

Table 2. (continued)

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
BIC/FTC/TAF (n = 234) versus continue baseline ART (n = 236)[29]	Randomized (1:1 switch: no-switch), open label	Women only HIV-RNA <50 copies/mL × ≥6 months at study entry Continued baseline ART: EVG/c/FTC/TAF: 53% EVG/c/FTC/TDF: 42% ATV/r + FTC/TDF: 6%	Week 48: 96% versus 95% (NR[b])	Week 48: 1.7% versus 1.7% (95% CI: −2.9 to 2.9)	Switch: 1 evaluated; none detected No-switch: 2 evaluated; 1 developed M184M/I/V, 1 not detected

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ATV, atazanavir; ATV/r, atazanavir/ritonavir; BIC, bictegravir c, cobicistat; CCR5, C-C chemokine receptor type 5; CI, confidence interval; CKD, chronic kidney disease; DRV, darunavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FPV/r, fosamprenavir, ritonavir; FTC, emtricitabine; HD, hemodialysis; INSTI, integrase strand transfer inhibitor; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; RAL, raltegravir; RAM, resistance-associated mutation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

[a]HIV-RNA <400 copies/mL throughout the study.

[b]CI or *P* value not reported.

[c]HIV-RNA returned to <50 copies/mL.

[d]Number evaluated not reported.

[e]Preexisting M184V, G140S, and Q148H.

[f]Believed to be present at baseline as not related to study drugs.

[g]>100% because 5 patients previously on multiple third agent.

[h]Suppressed with twice-daily DTG.

[i]HIV-RNA and duration not specified.

during weeks 1 to 24 and weeks 24 to 48 (13% versus 3% and 9%, respectively) and included mainly grade 1 and grade 2 effects. Treatment-limiting AEs included GI, psychiatric, and skin disorders.

In a study investigating switching from PI- to DTG-based regimens in patients with osteoporosis or osteopenia, no discontinuations were determined to be drug related.[24] However, 2 patients in the DTG/3TC/ABC group reported drug-related AEs (anxiety and nausea), which resolved without treatment interruption. No significant changes in bone mineral density (BMD) or bone turnover markers from baseline were found.

In contrast, AEs and treatment discontinuations were more common in a retrospective, real-world analysis of patients switched to DTG-based regimens, with 35% of patients experiencing AEs. These included central nervous system (CNS; 25%), GI (20%), rash (3%), sweating (2%), and musculoskeletal (1%) AEs.[25] Thirteen (8%) patients discontinued DTG-based therapy due to AEs (insomnia, mood, anxiety).

Based on the available data, DTG in combination with 2 NRTIs is an efficacious simplification strategy for patients on a variety of baseline regimens. However, patients should be counseled regarding common CNS and GI AEs. Due to growing cardiovascular concerns with ABC therapy,[32] pairing DTG with an FTC/TAF backbone over a 3TC/ABC backbone in patients with history of, or at high risk for, cardiovascular events may be preferred.

Dolutegravir/RPV. SWORD-1 and SWORD-2 were the largest studies leading to FDA approval of the 2-drug regimen (2DR) DTG/RPV for ART simplification.[26] In these identical studies, DTG/RPV was noninferior to 3-drug regimens (Table 2). Dolutegravir/RPV was also noninferior to 3-drug regimens in the proportion of patients with virologic failure. The most common AEs were nasopharyngitis (DTG/RPV: 10% versus conventional treatment group: 10%) and headache (8% versus 5%, respectively).

A substudy of SWORD-1 and SWORD-2 assessed changes in BMD and bone turnover markers in subjects with HIV RNA <50 copies/mL who received TDF-containing regimens for at least 6 months.[33] Patients switched to DTG/RPV had a significantly greater increase in total hip BMD compared to participants who continued current ART and significantly greater reductions in bone formation and resorption markers. It is currently unknown whether this simplification strategy improves or stabilizes BMD to the same degree as a TAF-containing regimen.

Based on the available data, a switch to DTG/RPV is recommended in virologically suppressed patients without resistance to either agent or a history of virologic failure. Additional studies are needed before DTG/RPV can be recommended in other clinical situations. Studies of DTG/RPV in combination with other ARV medications to simplify highly resistant patients on complex regimens will be helpful. A notable limitation of DTG/RPV is the food requirement for optimal RPV absorption and the potential DDI with acid-suppressive agents. Counseling on appropriate administration and potential of DDIs with over-the-counter products is recommended.

Bictegravir. Bictegravir is the newest INSTI approved which is administered QD and does not require boosting. Bictegravir is more potent and maintains efficacy in isolates resistant to EVG and RAL.[34] In addition, no studies have shown BIC resistance in clinical trials.[35]

Three trials evaluated switching to BIC/FTC/TAF (Table 2).[27–29] All trials randomized virologically suppressed participants to switch to BIC/FTC/TAF or continue baseline ART. Two trials included a small sample of women (11%-17%), while the third only enrolled females.[29] BIC/FTC/TAF was noninferior to the comparator arm in each trial, and no patients developed RAMs.[27–29] Adverse events across all studies were similar between BIC and the comparator arms with no treatment-related discontinuations. Common AEs included upper respiratory tract infections, diarrhea, headache, and vulvovaginal candidiasis.

In clinical trials, switching to BIC/FTC/TAF was well tolerated and virologically noninferior compared to continuing baseline ART, even in a small number of patients with M184V/I.[36] BIC/FTC/TAF is an optimal INSTI-based STR option because it avoids the DDIs associated with EVG/c-containing STRs and the ABC component of the DTG-containing STR associated with cardiotoxicity and a lower barriers to resistance. However, as the newest INSTI, only limited data and clinical experience are available thus far. Additional studies conducted in real-world populations may be helpful to confirm findings of randomized trials. Further, larger studies in PLWH with baseline RAMs will help guide BIC/FTC/TAF use in this population.

Non-nucleoside reverse transcriptase inhibitor switches. Rilpivirine/FTC/TDF offered a convenient STR with less AEs and DDIs and greater activity in the presence of EFV-induced K103N compared to EFV/FTC/TDF.[1] Studies, ECHO and THRIVE, found RPV/FTC/TDF noninferior to EFV/FTC/TDF in treatment-naive patients, which provided the framework to investigate RPV/FTC/TDF,[37,38] and more recently, RPV/FTC/TAF[7,11] for switch or simplification.

Rilpivirine-based regimens. Six studies evaluated switch or simplification to RPV/FTC/TDF (Table 3)[39–43] or RPV/FTC/TAF (Table 1) in virologically suppressed patients, some of which had baseline NRTI in combination with NNRTI RAMs.[40,42,43] Virologic suppression was maintained in 59% to 99% of the patient population evaluated. Pretreatment HIV-RNA viral load or CD4 was not predictive of virologic suppression in patients switching to RPV/FTC/TDF[42]; however, baseline M184V/I was significantly associated with developing virologic failure.[43] The wide range of virologic suppression was due to low attrition rates and variable study end points. The RAM development after virologic failure with RPV/FTC/TDF was more common in patients switched from PI-based regimens and those with baseline NNRTI or NRTI RAMs.[40–43]

Table 3. RPV-Based Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Treatment Regimens/ Dosing	Design	Study Population	Virologic Suppression (HIV-RNA < 50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
RPV/FTC/ TDF (n = 49)[39]	Phase 2b, prospective, multicenter, single arm, open label	ART-experienced EFV/FTC/TDF × ≥3 months duration with baseline HIV-RNA <50 copies/mL	Week 48: 93.9% (46/49) (95% CI: 83.1-98.7)	Week 48: 4.1% (2/49)	None
RPV/FTC/ TDF (n = 281)[43]	Retrospective, single arm, open label, single center	ART-experienced with baseline HIV-RNA <50 copies/mL 51%: PI based 39%: NNRTI based 7%: INSTI based 3%: triple NRTI	12 months: 59% (167/281)	12 months: 6% (16/281)	NRTI/NNRTI RAMs (n = 5) E138A/K K103N + V106I + H221Y + M230L V179I + Y181C M184V + K103N + E138A/K + V179I + P225H M184V + D67N + K70R + T215F + K219Q + K101E + Y181I
RPV/FTC/ TDF (n = 131)[40]	Retrospective, single arm, open label, single center	ART-experienced with baseline HIV-RNA <400 copies/mL 56%: PI based 36%: NNRTI based 3%: INSTI based 3%: triple NRTI	Week 24: 92% (128/131)	Week 24: 2% (3/131)	NRTI/NNRTI RAMs (n = 1) K65R + M184V + L74I + L100I + K103N + E138E/K
RPV/FTC/ TDF (n = 307)[41]	Retrospective, single arm, open label, single center	ART-experienced with baseline HIV-RNA <50 copies/mL 59%: PI based 27%: NNRTI based 11%: INSTI based	PI-based switch (median 6.7 months): 87% (156/180) Non-PI-based switch (median 8.6 months): 91% (117/127)	PI-based switch: 2% (3/180) Non-PI-based switch: 0% (0/127)	None
SPIRIT: continue PI-based ART versus RPV/ FTC/ TDF[42]	Phase 3b, randomized, open label, international	ART-experienced with baseline HIV-RNA <50 copies/mL for ≥6 months	PI-based ART (n = 159); IS (n = 317); DS (n = 152) Week 24: 89.9% (143/159); 93.7% (297/317); – 95% CI (−1.6 to 9.1) Week 48: –; 89.3% (283/317); 92.1% (140/152)	Week 48 all groups: 2.1% (10/469)	NRTI/NNRTI RAMs (n = 4) K103N + L100I + M184V/I M184V/I E138E/K + M184V/I E138K + V108V/I + M184V/I

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; DS, delayed switch at 48 weeks; EFV, efavirenz; FTC, emtricitabine; IS, immediate switch at 24 weeks; IQR, interquartile range; NR, not reported; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; RAM, resistance-associated mutation; TDF, tenofovir disoproxil fumarate.

Severe AEs with RPV were uncommon, with most studies noting grade 1 or grade 2 GI or neuropsychiatric AEs, with low rates of discontinuation (0%-8%).[11,39–43] Switching to RPV-based regimens has shown a lower incidence of neuropsychiatric AEs (0%-11%) compared to EFV, with resolution noted in 74% to 86% of patients switched to RPV.[39–45] Lastly,

decreases in total cholesterol, HDL, low-density lipoprotein (LDL), and/or triglycerides were observed after switching to RPV-based regimens.[11,39,41,42]

Switching virologically suppressed patients from an EFV- to RPV-based regimen offers an efficacious, well-tolerated STR with less neuropsychiatric AEs. Switching from EFV to RPV is a preferred option for PLWH who may want a within-class switch. Switching from PIs or INSTIs to RPV may be suboptimal due to availability of ART with improved resistance, tolerability, and DDI profiles. Additionally, switching to an RPV-based regimen should be avoided in patients with baseline NRTI RAMs. Counseling on RPV food requirements and DDIs with acid-suppressive agents is essential. Prior ART, archived genotypes, and historical virologic failures are vital to successful RPV-based simplification regimens due to its lower barrier to resistance compared to other ART classes.

Protease inhibitor switches

Darunavir/c/FTC/TAF. Although PIs offer a desirable efficacy profile as a potential switch strategy, it must be coupled with an increased risk of potential toxicities and until recently, a higher pill burden. The EMERALD trial randomized virologically suppressed patients to continue their baseline PI-based regimen or switch to DRV/c/FTC/TAF as an STR (Table 1).[12] While patients with a history of virologic failure on DRV or DRV RAMs were excluded, 14% and 15% of patients with a history virologic failure were included in each group, respectively. Rates of virologic suppression were similar between groups, including those with a history of virologic failure, but a higher percentage of patients who switched to DRV/c/FTC/TAF experienced virologic rebound (2.1% versus 2.5%, respectively; $P < .0001$) at week 48. No treatment-emergent RAMs to study drugs were detected in patients who underwent genotypic testing. A significantly higher incidence of treatment-related AEs occurred in patients who switched to DRV/c/FTC/TAF, which included nasopharyngitis, diarrhea, and headache (11% versus 10%, 8% versus 3%, and 8% versus 4%, respectively), although only 1% of patients in each group experienced AEs prompting study drug discontinuation.

Switching to DRV/c/FTC/TAF was virologically noninferior to continuing baseline PI-based ART. In addition, virologic suppression was maintained at a similar rate among patients with a history of virologic failure. The higher rate of treatment-related AEs may prove to outweigh the appealing characteristics of a PI-based STR as a potential switch strategy. Additional studies are warranted in virologically suppressed patients with a history of virologic failure and baseline RAMs.

Emerging Switch/Simplification Strategies

Use of some switch strategies, most notably those that aim to avoid NRTIs, is limited due to small sample size and/or lack of long-term safety and efficacy data. Nucleoside/nucleotide reverse transcriptase inhibitor-sparing regimens have the potential to decrease cardiovascular, renal, and bone toxicities.[46–48] Emerging data suggest additional 2DRs, particularly boosted PI + 3TC or DTG + 3TC, maintain virologic suppression, but longer follow-up is needed to confirm regimen durability. However, some 2DRs, such as boosted PI + RAL,[49] boosted PI + maraviroc (MVC),[50] and RAL + MVC,[51] have been associated with unacceptably high rates of virologic failure and treatment discontinuations and therefore should not be used.

Elvitegravir/c/FTC/TAF ± DRV. An open label, multicenter, noninferiority study of virologically suppressed treatment-experienced patients on a DRV-based regimen were randomized 2:1 to continue their current ART (n = 46) or switch to EVG/c/FTC/TAF + DRV 800 mg QD (n = 89).[52] Patients had a history of 2 or more failed regimens and RAMs to 2 or more ART classes (M184V/I: 95%; K103N/S: 88%). K65R was present in 20% and 40% in the EVG/c/FTC/TAF + DRV and baseline ART groups, respectively, but no patients had DRV or INSTI RAMs.

At week 48, virologic suppression was maintained in 94.4% and 76.1% (95% CI: 3.5-33.0, $P = .004$) of the EVG/c/FTC/TAF + DRV group and the baseline ART group, respectively, which met both noninferiority and superiority criteria. Rates of self-reported AEs were higher in the EVG/c/FTC/TAF + DRV group but were likely the result of initiating new ART. Additionally, EVG/c/FTC/TAF + DRV was associated with an improved renal safety profile compared to baseline regimens and higher treatment satisfaction ($P < .001$) coupled with fewer missed doses.

An open label pilot study also evaluated switching virologically suppressed patients with an M184V/I mutation to EVG/c/FTC/TAF.[53] This study included 37 patients who were suppressed at least 6 months prior to the switch. At 12 and 24 weeks after the switch, 100% of patients maintained virologic suppression.

Switching to EVG/c/FTC/TAF ± DRV, QD, may be efficacious in virologically suppressed patients with a history of multiclass resistance and prior treatment failure. Currently, EVG/c/FTC/TAF + DRV should not be pursued in patients with DRV RAMs or more than 3 TAMs.[52] Simplification to EVG-based regimens in patients with RAMs has the potential to decrease pill burden from approximately 5 to 1 or 2 tablets daily. Larger studies are necessary to ensure safety and efficacy of this strategy. Additional data on switch strategies with other ART in the setting of RAMs are also needed to solidify appropriate management of this complicated patient population.

Dolutegravir + 3TC. Three studies evaluated QD DTG + 3TC in virologically suppressed patients (Table 4).[54–56] The studies varied in their inclusion criteria by enrolling patients who were virologically suppressed for at least 6 months to over 2 years on their baseline regimen without a history of NRTI or INSTI RAMs. Virologic suppression was high (93-100%) at study end points for the DTG + 3TC group.

In the prospective cohort study, 3 patients did not complete the study; however, no discontinuations were due to treatment failure or treatment-associated AEs.[54] CD4 increased +66 cells/mm^3 from baseline ($P = .006$) in addition to an increase

Table 4. DTG + 3TC Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Treatment Regimens/ Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
DTG 50 mg + 3TC 300 mg QD (n = 94)[54]	Prospective, clinical, observational, trial	ART-experienced × ≥6 months duration with baseline HIV-RNA <50 copies/mL PI based: 28.8% NNRTI based: 57.4% INSTI based: 17%	Week 24: 100%	None	None
ASPIRE: DTG 50 mg + 3TC 300 mg QD (n = 44) versus continue ART (n = 45)[56]	Open label, randomized, multicenter, clinical trial	ART-experienced × ≥ 48 weeks duration with baseline HIV-RNA <50 copies/mL PI based: 33% versus 32% NNRTI based: 33% versus 27% INSTI based: 33 versus 41%	Week 24: 93.2% versus 91.1% (95% CI: 11.2 to 15.3%, *P* = .71) Week 48: 90.9% versus 88.9% (95% CI: −12.6 to 16.5%, *P* = .76)	Week 48: 0% versus 3%	None
ANRS 167: DTG 50 mg + 3TC 300 mg QD[55]	Noncomparative, open label, single arm, multicenter study with 2 phases Phase 1: Third agent replaced with DTG 50 mg QD plus current NRTI backbone (n = 110) Phase 2: DTG 50 mg + 3TC 300 mg QD for 48 weeks (n = 104)	ART-experienced × ≥2 years duration with baseline HIV-RNA <50 copies/mL	Week 48: 97%	3%	None

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CI, confidence interval; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; RAM, resistance-associated mutation; QD, once daily.

in serum creatinine (SCr) after 8 weeks of treatment (0.87 to 0.95 mg/dL, $P < .0001$). The SCr plateaued through the remainder of the study period.

The ASPIRE study defined treatment failure as HIV-RNA >50 copies/mL, lost to follow-up, or modification/discontinuation of treatment regimen, which occurred in 6.8% and 6.7% (90% CI: −9.8 to 10.2) in the DTG + 3TC group and the ART-continuation group, respectively.[56] Of these participants, virologic failure occurred in 1 patient in the DTG/3TC group, without evidence of NRTI or INSTI RAMs.

ANRS 167 Lamidol trial is an ongoing study that included an 8-week phase 1 period, where participants were changed to DTG plus their current dual NRTI backbone.[55] Patients with an HIV-RNA ≤50 copies/mL at the end of phase 1 were transitioned to DTG/3TC (phase 2). Virologic failure occurred in 3 patients on DTG + 3TC (lost to follow-up, ART modification, HIV-RNA of 77 copies/mL; n = 1 each). No patients developed INSTI RAMs; however, one developed an NRTI RAM. Serious AEs occurred in 5 patients, including suicidal ideation (n = 1) during phase 1 and depression (n = 1) during phase 2.

Most data evaluating the efficacy of DTG + 3TC for treatment simplification are from open label trials. Although virologic suppression has been observed in >90% of participants in these trials, sample sizes remain small with strict exclusion criteria limiting data to only those without baseline RAMs, which limits generalizability. For now, DTG + 3TC seems best suited for virologically suppressed patients with no history of virologic failure or NRTI or INSTI RAMs.

Cabotegravir + RPV. Cabotegravir (CAB) is an analogue of DTG currently in development.[57] Given its long half-life (~40 hours), ease of administration, and minimal potential for DDIs, it has been studied as both an oral and intramuscular (IM) formulation with RPV for the maintenance of virologic suppression. Notably, the oral formulation is being developed as a safety lead-in and bridge between injections, if needed.

The LATTE trial evaluated the safety and efficacy of oral CAB + RPV versus a 3-drug EFV-based regimen maintaining virologic suppression.[57] In this study, CAB doses of 10 to 60 mg daily were noninferior to EFV-based regimens with viral suppression rates ranging from 85% to 87%. The results of

Table 5. CAB Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Study	Design	Treatment Regimens/Dosing	Study Population	Virologic Suppression (HIV-RNA <50 copies/mL)	Virologic Failure	Treatment Emergent RAMs
LATTE[57]	Phase2b, randomized, multicenter, parallel group	Phase 1: Oral CAB 10, 30, or 60 mg or EFV 600 mg + 2 NRTIs × 24 weeks (n = 60, 60, 61, 62, respectively)	Phase 1: ART-naive, baseline HIV-RNA ≥1000 copies/mL, CD4 ≥200 cells/mm^3, no RAMs	Week 24: 82% (all CAB groups) versus 71%	CAB 10 mg: 1 CAB 30 mg: 1 CAB 60 mg: 1 EFV: 4	None
		Phase 2: CAB + RPV (n = 156) versus EFV + 2NRTIs (n = 46) × 72 weeks	Phase 2: HIV-RNA <50 copies/mL at end of phase 1	Week 48: 82% (95% CI: 77-88) versus 71% (95% CI: 60-82) Week 96: 76% (95% CI: 69-82) versus 63% (95% CI: 51-75)	CAB 10 mg: 2 CAB 30 mg: 1 CAB 60 mg: 0 EFV: 2	CAB 10 mg: 1 patient (E138Q, Q148R) and 1 patient (K101K/E, E138E/A) CAB 30 mg: 0 CAB 60 mg: 0 EFV: 0
LATTE-2[58]	Randomized, multicenter, phase 2b, open label	Phase 1: oral CAB + ABC/3TC × 20 weeks	Phase 1: ART-naive, baseline HIV-RNA ≥1000 copies/mL, CD4 ≥200 cells/mm^3, no RAMs	–	–	–
		Phase 2: IM CAB 400 mg + RPV 600 mg q 4 weeks or IM CAB 600 mg + RPV 900 mg q 8 weeks or oral CAB + ABC/3TC × 96 week (n = 115, 115, 56, respectively)	Phase 2: HIV-RNA <50 copies/mL at end of phase 1	Snapshot week 32: 94% (difference 2·8% [95% CI: −5·8 to 11·5] versus oral treatment) versus 95% (difference 3·7% [−4·8 to 12·2] versus oral treatment) versus 91%, respectively Week 96: 87% versus 94% versus 84%	IM CAB q 4 weeks: 0 IM CAB q 8 weeks: 2 Oral CAB: 1	IM CAB q 4 weeks: 0 IM CAB q8 weeks: 1 patient (R269R/G) and 1 patient (K103N, E138G, K238T, Q148R) Oral CAB: 0

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ABC, abacavir; CAB, cabotegravir; CI, confidence interval; EFV, efavirenz; IM, intramuscular; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PLWH, people living with HIV; RPV, rilpivirine; RAM, resistance-associated mutation.

this study led to LATTE-2, which evaluated the safety and efficacy of long-acting IM CAB + RPV to oral CAB + ABC/3TC.[58] Both studies found CAB + RPV, regardless formulation and dose, to be as efficacious versus the comparator groups (Table 5).[57,58]

In LATTE, treatment-related AEs were reported by 51% and 68% of patients in the CAB + RPV and EFV groups, respectively.[57] The most common AEs were headache, nausea, and diarrhea in the CAB group and dizziness, abnormal dreams, nausea, fatigue, and insomnia in the EFV group. Most of the headaches in the CAB group were grade 1 (16%) and transient with similar incidence between groups. In LATTE-2, injection site pain was the most commonly reported AE in the IM treatment groups (97% and 96% in the 4-week and 8-week groups, respectively).[58] Most of the injection site reactions were mild or moderate and resulted in discontinuation in 2 patients. Diarrhea, headache, and nasopharyngitis were other commonly reported AEs.

Given the efficacy and acceptable safety profile of the long-acting injectable, this regimen may prove to be appealing for patients with virologic suppression who have barriers to daily oral ART. Further switch studies are warranted in virologically suppressed patients on a non-EFV-based regimen as well as those with a history of virologic failure or RAMs.

Boosted PI + NRTI. Prior to the advent of INSTIs, PIs were the mainstay of HIV treatment, especially for those requiring a high barrier to resistance. However, PI-based regimens can increase

Table 6. Boosted PI + NRTI or NNRTI Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤50 copies/mL)	Virologic Failure	Treatment-Emergent RAMs
OLE/RIS-EST13: LPV/r 400/100 mg BID + 3TC 300 mg QD (n = 127) versus LPV/r 400/100 mg BID + 2 NRTIs (n = 123)[59]	Randomized, open label, noninferiority trial	ART-experienced receiving 2 NRTIs plus LPV/r × ≥6 months duration with baseline HIV-RNA <50 copies/mL	Week 48: 87.8% versus 86.6% (95% CI: −9.6 to 7.3, *P* = .92)	Week 48: 2.4% versus 2.4%	NRTI/NNRTI RAMs (n = 1 in LPV/r + 3TC) K103N + M184V
SALT: ATV/r 300/100 mg + 3TC 300 mg QD (n = 133) versus ATV/r 300/100 mg QD + 2 NRTIs (n = 134)[64]	Randomized, open label, noninferiority trial	ART-experienced × ≥6 months duration with baseline HIV-RNA <50 copies/mL[62] PI/r: 64% (ATV/r: 44%) versus 66% (ATV/r: 34%) NNRTI: 33% (EFV: 28%) versus 32% (EFV: 28%) TDF/FTC: 83% versus 81% ABC/3TC: 15% versus 15%	Week 96: 74.4% versus 73.9% (95% CI: −9.9 to 11)	Week 96: 7% versus 4%	NRTI/NNRTI RAMs (n = 1 in ATV/r + 2 NRTIs) M184V
ATLAS-M: ATV/r 300/100 mg + 3TC 300 mg QD (n = 133) versus ATV/r 300/100 mg QD + 2 NRTIs (n = 133)[61]	Phase IV, multicenter, randomized, open label study	ART-experienced receiving 2 NRTIs plus ATV/r × ≥3 months duration with baseline HIV-RNA <50 copies/mL and CD4 >200 cells/mm^3 × ≥6 months TDF/FTC or 3TC: 89% versus 84% ABC/3TC: 19% versus 14%	Week 48: 89.5% versus 79.7% (95% CI: 1.2 to 14.8)	Week 48: 1.5% versus 4.5%	None
DUAL-GESIDA 8014-RIS-EST45: DRV/r 800/100 mg + 3TC 300 mg QD (n = 126) versus DRV/r 800/100 mg QD + 2 NRTIs (n = 123)[63]	Multicenter, open label, noninferiority trial	ART-experienced receiving 2 NRTIs plus DRV/r × ≥6 months duration with baseline HIV-RNA <50 copies/mL TDF: 76% versus 75% ABC: 26% versus 24%	Week 48: 88.9% versus 92.7% (95% CI: −11 to 3.4)	Week 48: 3% versus 2%	PI RAMs (n = 1 in DRV/r + 2 NRTIs) L10I + A71T + L76W
ATV/r 300/100 mg + 3TC 300 mg QD (n = 70) versus DRV/r 800/100 mg + 3TC 300 mg QD (n = 52)[60]	Observational, retrospective study	ART-experienced receiving 2 NRTIs plus DRV/r × ≥12 months duration with baseline HIV-RNA <50 copies/mL DRV/r: 17.3% versus 41.4% ATV/r: 42.3% versus 15.7% LPV/r: 34.6% versus 32.8% FPV/r: 3.8% versus 7.1%	12 months: 88.4% versus 92.8% (*P* = .109)	12 months: 3.8% versus 1.4%	None
PROBE: DRV/r + RPV (n = 30) versus boosted PI + 2 NRTIs (n = 30)[65]	Randomized, open label, proof of concept, noninferiority	ART experienced × ≥6 months duration with baseline HIV-RNA <50 copies/mL	Week 24: 100% versus 90.1% (95% CI: −0.7 to 20.7) Week 48: 96.7% versus 93.4% (95% CI: −7.5 to 13.5)	None	N/A

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; BID, twice daily; CI, confidence interval; DRV/r, darunavir/ritonavir; FPV/r, fosamprenavir/ritonavir; LPV/r, lopinavir/ritonavir; RAM, resistance-associated mutation; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; RAM, resistance-associated mutation; QD, once daily.

regimen complexity with a high pill burden in addition to numerous DDIs and toxicities. Treatment simplification studies have been completed to address these issues (Table 6).[59–64]

The OLE/RIS-EST13 study compared switching to ritonavir-boosted lopinavir (LPV/r) + 3TC twice daily to continuing previous ART of LPV/r + 2 NRTIs.[59] Virologic

suppression was noninferior between groups at 48 weeks. Virologic failure was noted in 3 patients in each group, of which 1 patient in the LPV/r + 3TC group developed a K103N and M184V but had a history of nonadherence prior to study enrollment. Adverse events were similar in both groups, LPV/r + 3TC: 53% versus LPV/r + 2 NRTIs: 58%, while serious AEs were noted in 4% and 7%, respectively. Significantly higher total cholesterol and LDL were noted in the LPV/r + 3TC group.

SALT[62,64] and ATLAS-M[61] were similar studies that evaluated ritonavir-boosted atazanavir (ATV/r) + 3TC in patients virologically suppressed on a 3-drug regimen. SALT showed ATV/r + 3TC simplification was noninferior compared to ATV/r + 2 NRTIs at weeks 48[62] and 96.[64] Nine and 5 patients in the ATV/r + 3TC and ATV/r + 2 NRTIs groups, respectively, experienced virologic failure, of which M184V was identified in only 1 patient receiving a 3-drug regimen. ATLAS-M showed ATV/r + 3TC simplification was noninferior, and then superior in a post hoc analysis, to continuing an ATV/r-based 3-drug regimen.[61] Virologic failure occurred in 2 and 6 patients in the ATV/r + 3TC and ATV/r + 2 NRTI groups (95% CI: −7.1 to 1.1, $P = .282$), respectively. No RAMs were detected among the 7 patients who underwent genotypic testing. However, serum ATV concentrations were undetectable in 50% and 60% of patients experiencing virologic failure in the 2DR and 3-drug regimens, respectively.

In the SALT study, grade 3 and 4 AEs occurred at similar rates in each group (ATV/r + 3TC: 55% versus ATV/r + 2 NRTIs: 55%).[62] Grades 3 and 4 hyperbilirubinemia occurred in 51% of patients in both groups. Fewer treatment-related discontinuations occurred among patients receiving ATV/r + 3TC versus ATV/r + 2 NRTIs (5% versus 7.1%, $P = .46$). Significant improvements in total cholesterol, triglycerides, and total cholesterol to HDL index were noted in the ATV/r + 2 NRTI group, likely affected by prior receipt of tenofovir or PI/r in the switch group. In ATLAS-M, grade 3 and 4 hyperbilirubinemia occurred more frequently in the ATV/r + 3TC arm (44.4% versus 28.3%, $P = .027$).[61] Higher mean changes in total cholesterol (+14 mg/dL versus −3 mg/dL, $P < .001$), LDL (+6 mg/dL versus −1 mg/dL, $P = .047$), HDL (+4 mg/dL versus 0 mg/dL, $P = .001$), and triglycerides (+11 mg/dL versus −3 mg/dL, $P = .147$) occurred in patients receiving ATV/r + 3TC compared to ATV/r + 2 NRTIs.

In a similarly designed study, DUAL-GESIDA-8014-RIS-EST45, maintenance of virologic suppression with DRV/r + 3TC was noninferior to a DRV/r + 2 NRTIs at 48 weeks.[63] Virologic failure occurred in 2 patients receiving DRV/r + 3TC compared to 4 in the 3-drug regimen, of which 1 developed PI RAMs (L10I, A71T, and L76W). Adverse events occurred in 69.8% of patients in the DRV/r + 3TC group and 75.6% of patients in the 3-drug regimen group. Adverse event-related treatment discontinuations occurred in 1 and 2 patients in the 2-drug and 3-drug regimens, respectively ($P = .55$). Darunavir (DRV/r)/r + 3TC was associated with significant increases in total cholesterol ($P < .001$), LDL ($P = .01$), and HDL ($P < .001$), but not total cholesterol to HDL index ($P = .45$) or triglycerides ($P = .71$).

Lastly, a retrospective study evaluated DRV/r + 3TC compared to ATV/r + 3TC for maintenance of virologic suppression.[60] After 12 months, virologic suppression was observed in >88% of patients in both groups. Virologic failure occurred in 2 and 1 patients in the ATV/r and DRV/r 2DR groups, respectively. Discontinuations due to AEs occurred in 7.7% and 5.7% of patients in the ATV/r and DRV/r groups, respectively. No grade 3 and 4 or serious AEs were noted. Comparable mean increases in total cholesterol (ATV/r: +16.5 mg/dL versus DRV/r: +18.6 mg/dL), LDL (ATV/r: +7.1 mg/dL versus DRV/r: +8.4 mg/dL), and HDL (ATV/r: +1.1 mg/dL versus DRV/r: +1.4 mg/dL) and decreases in triglycerides (ATV/r: −22.7 mg/dL versus DRV/r: −20.1 mg/dL) from baseline were observed in both groups.

Currently, the DHHS treatment guidelines recommend the use of boosted PI + FTC or 3TC to maintain virologic suppression in patients who received TDF, TAF, or ABC are contraindicated and/or suboptimal.[1] Additional studies are needed to evaluate safety and efficacy beyond 12 months. Furthermore, switching to a boosted PI + NRTI regimen may not improve pill burden or DDIs. Studies investigating 2DRs with cobicistat-boosted PI combination tablets are needed to address pill burden.

Boosted PI + NNRTI. Combining a boosted PI + an NNRTI represents yet another emerging switch strategy to avoid NRTIs; however, limited data exist evaluating this approach. PROBE evaluated switching patients to DRV/r + RPV or continuing their current 3-drug boosted PI-based regimen.[65] Of the patients continuing their current regimen, 43% continued DRV/r while 57% continued ATV/r and 90% were maintained on a TDF/FTC backbone. High virologic suppression was maintained throughout the study in both groups, meeting noninferiority criteria (Table 6). While no patient met criteria for virologic failure, DRV/r + RPV and current ART groups failed to achieve 100% virologic suppression due to viral blips at week 24 (0 versus 2, respectively) and week 48 (0 versus 1, respectively) in addition to missing data at weeks 24 (0 versus 1, respectively) and 48 (1 versus 1, respectively). No grade 3 and 4 severe AEs or treatment-related discontinuations occurred throughout the study period.

Although DRV/r + RPV was noninferior compared to standard PI/r-based ART, the promising results of this study are limited by its small sample size. Until more data are available, switching virologically suppressed patients to DRV/r + RPV cannot be recommended.

Boosted PI + RAL. Switching to a boosted PI + RAL was evaluated in virologically suppressed patients in 2 studies (Table 7).[49,66] HARNESS randomized virologically suppressed patients treated with 2 NRTIs + a third ARV medication to switch to ATV/r + either RAL or TDF/FTC.[49] Virologic suppression was maintained in fewer patients treated with ATV/r + RAL compared to ATV/r + TDF/FTC at 24 and 48 weeks.

Virologic rebound at week 48 occurred in 9 patients in the ATV/r + RAL group compared to 1 patient in the ATV/r + TDF/FTC group. Of the 5 patients in the ATV/r + RAL group who underwent genotypic testing, one developed both PI and INSTI RAMs, while another developed INSTI RAMs only. Fewer patients completed treatment in the ATV/r + RAL group compared to the ATV/r + TDF/FTC group, 77.8% versus 86.5%, respectively. Treatment discontinuations were due to AEs (4 versus 1), lack of efficacy (3 versus 1), consent withdrawal (4 versus 1), nonadherence (1 versus 1), and other reasons (4 versus 1) in the ATV/r + RAL and ATV/r + TDF/FTC groups, respectively. Similar rates of hyperbilirubinemia occurred in the ATV/r + RAL and ATV/r + TDF/FTC groups (49.3% versus 40.5%, respectively), but higher rates of renal and urinary disorders occurred in patients receiving TDF/FTC (1.4% versus 16.2%, respectively). At week 48, rates of dyslipidemia decreased from baseline in both groups (ATV/r + RAL: −5.2% versus ATV/r + TDF/FTC: −2.2%).

SPARE investigated virologically suppressed patients receiving LPV/r + TDF/FTC who either continued on baseline ART or switched to DRV/r + RAL.[66] Virologic suppression was lower in the DRV/r + RAL group versus the LPV/r + TDF/FTC group. Three patients discontinued DRV/r + RAL by week 48 due to lower extremity weakness, acute HBV infection, and consent withdrawal (n = 1 each). The primary end point of this study was to assess a >10% improvement in estimated glomerular filtration rate which occurred in 25% and 11% (95% CI: 0.067-0.354, $P = .272$) of patients in the DRV/r + RAL and LPV/r + TDF/FTC groups, respectively. Grade 3 and 4 laboratory abnormalities included increased ALT (n = 1) and increased LDL (n = 3) in the DRV/r + RAL group and increased LDL (n = 1) and hypophosphatemia (n = 3) in the LPV/r + TDF/FTC group.

Although, switching to an NRTI-sparing regimen is an attractive option in virologically suppressed patients, maintenance of virologic suppression was lower in the PI/r + RAL groups; however, each of these studies was limited by their small sample size. Due to the lack of efficacy currently seen, switching to a PI/r + RAL regimen cannot be recommended.

Darunavir/r + DTG. While a boosted PI + RAL is an appealing 2DR, combining DRV/r + DTG presents an even more attractive option given the potency and high genetic barrier to resistance of each individual agent and has been evaluated in 2 studies.[67,68] TIVISTA, Tivicay plus Prezista Observational cohort, was a multicenter, observational study of Italian patients who were switched to DRV/r + DTG.[67,69] Of the 130 patients included at the time of switch, 89.2%, 75.4%, 70%, and 10.6% had NRTI, NNRTI, PI, and INSTI RAMs, respectively. At baseline, 60% had HIV-RNA <50 copies/mL, which increased to 90.7% at week 48. Among the 8 patients with HIV-RNA ≥ 50 copies/mL at week 48, 3 developed RAMs to at least 3 drug classes with high-level DRV resistance. Glucose, lipids, SCr, and liver function tests were comparable to baseline at week 48.

A retrospective study in Manitoba, Canada, evaluated the efficacy of switching virologically suppressed patients with TAM, originally included in the TRIO study,[70] treated with first-line NRTI-sparing regimens to DRV/r + DTG.[68] Among the 60% (13 of 22) who switched, none of which harbored PI or INSTI RAMs, and all patients maintained virologic suppression for over 12 patient years (median 9 [range 1-22] months). Only 1 patient reported AEs, which were attributed to an alternative diagnosis.

Although virologic suppression was maintained in patients switched to DRV/r + DTG, many of whom had baseline RAMs, these studies are limited by their loose inclusion criteria, small sample size, and heterogenous population. Until additional data are available, switching to DRV/r + DTG should be reserved for patients with NRTI and/or NNRTI RAMs.

Switching ART in Special Circumstances

ART switch in pregnancy. Patients of childbearing potential should undergo pregnancy testing prior to switching ART.[1] In most situations, pregnant PLWH who are trying to conceive and are on stable ART can remain on the same regimen. However, regimens should be assessed for safety and efficacy prior to switching as certain ARV medications are not preferred during pregnancy. While virologically suppressed pregnant patients on stable TAF-containing ART can be continued on these regimens, insufficient data exist to support switching these patients to TAF-containing ART.[1] Preliminary data from the Tsepamo observational study in Botswana found an increased rate of neural tube defects in infants born to pregnant females receiving DTG compared with other ART at the time of conception (0.67% versus 0.12%, respectively).[71] As a result of these findings, DHHS recommends avoiding DTG or DTG-containing regimens in pregnant women and those within 12 weeks postconception, in addition to women of childbearing potential.[1] Furthermore, due to structural similarities with DTG and lack of safety data, BIC should also be avoided. Cobicistat-containing ART should not be used in pregnant patients due to decreased drug exposure and resultant risk of virologic breakthrough.[72]

ART switches in patients with a history of virologic failure or baseline RAMs. Limited data are available evaluating switch strategies in PLWH with a history of prior virologic failure with or without RAMs. Virologic suppression was achieved in a higher percentage of patients receiving LPV/r than RAL-containing regimens among patients with a history of virologic failure in the SWITCHMRK study.[2] In addition, higher rates of virologic failure were observed in patients with baseline NRTI RAMs who switched to RPV-based regimens.[40,42,43] Rates of virologic rebound were similar between patients with and those without a history of virologic failure after switching to DRV/c/FTC/TAF.[12] Elvitegravir-based regimens with or without the addition of DRV maintained virologic suppression in patients with minimal baseline NRTI RAMs but should not be used in

Table 7. Boosted PI + RAL-Based Switches in ART-Experienced PLWH with Baseline HIV-RNA <50 copies/mL.

Treatment Regimens/Dosing	Design	Study Population	Virologic Suppression (HIV-RNA ≤ 50 copies/mL)	Virologic Failure	Treatment Emergent RAMs
HARNESS: ATV/r 300/100 mg plus TDF/FTC 300/200 mg QD (n = 37) versus ATV/r 300/100 mg QD plus RAL 400 mg BID (n = 72)[49]	Prospective, randomized, open label, parallel-group, multinational study	ART-experienced receiving 2 NRTIs plus third ARV medication (excluding ATV) × ≥3 months duration with baseline HIV-RNA <50 copies/mL	Week 24: 94.6% (35/37, 95% CI: 81.8-99.3) versus 80.6% (58/72, 95% CI: 69.5-88.9) Week 48: 86.5% (32/37, 95% CI: 71.2-95.9) versus 69.4% (50/72, 95% CI: 57.5-79.8)	Week 24: 2.7% versus 9.7% Week 48: 2.7% versus 12.5%	None versus NRTI/NNRTI RAMs (n = 1) L10V + G16Q + L33F + P39Q + M46L + G48V + Q58E + I62V + L63I/T + I64L + A71V + I72V + V77I + V82A + T91S + I93L INSTI RAMs (n = 2) F21Y Y143C + N155H
SPARE: LPV/r 800/200 mg plus TDF/FTC 300/200 mg QD (n = 30) versus DRV/r 800/100 mg QD plus RAL 400 mg BID (n = 28)[66]	Phase 3B, multicenter, randomized, open label, parallel-group study	ART-experienced receiving LPV/r 800/200 mg plus TDF/FTC 300/200 mg QD × ≥15 weeks duration with baseline HIV-RNA <50 copies/mL	Week 24: 96.7% versus 89.3% (95% CI: −21 to 6) Week 48: 96.7% versus 85.7% (95% CI: −24 to 4)	None	None

Abbreviations: ART, antiretroviral therapy; ATV, atazanavir; ATV/r, atazanavir/ritonavir; BID, twice daily; CI, confidence interval; DRV/r, darunavir/ritonavir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; LPV/r, lopinavir/ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; RAM, resistance-associated mutation; QD, once daily; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

patients with DRV RAMs or greater than 3 TAMs.[19,52] Although data are available for 2DR, such as DRV/r + DTG, it is limited by a small sample size.[68,70]

ART switches in geriatric patients. Due to the higher rate of non-AIDS-related comorbidities, chronic kidney disease, cardiovascular disease, and osteoporosis in older PLWH, ART switch may be necessary to mitigate potential ART-related toxicities and DDIs.[1] Furthermore, men aged 50 years or older, postmenopausal women, those with low BMD, or risk factors for osteoporosis should be switched from regimens associated with an increased risk of decreased BMD, including boosted PI- and TDF-containing regimens.[73] Additional considerations for switch in geriatric patients include age-related declines in renal and hepatic function. Switch strategies may not be generalizable to geriatric patients, as most studies include relatively few older PLWH. In addition, the primary objective of most switch strategies is maintenance of virologic efficacy through 48 to 96 weeks, which limits the assessment of comorbid conditions long term. Due to the paucity of available data, switch studies are critically needed in older PLWH.

Switching ART due to financial constraints. Although the cost-effectiveness of ART has been proven, patients may be required to switch therapies entirely or switch to generic ARV medications due to financial and/or insurance constraints.[1] Compared to brand name ARV medications, similar efficacy and toxicity rates have been observed in patients who switched to generic ARV medications.[74] However, switching to generic ARV medications may lead to increased pill burden and potential for nonadherence, as well as more health-care encounters per month.[75–77] While STR should be given preference, similar considerations should be taken by clinicians when switching patients to a new regimen, in addition to understanding available affordability resources.

Conclusion

Switch and simplification data demonstrate comparable virologic efficacy to previous standards of care with the promise of reduced side effects and improved tolerability. However, switch data are lacking in several key populations, including those with renal and hepatic impairment and geriatric patients. It is important that virologic efficacy and safety parameters continue to be monitored at regular intervals to assess for new AEs associated with ART modification along with DDIs. With reduced pill burden, frequency of administration, similar, if not improved virologic efficacy, safety, and tolerability, many of the newer agents studied for ART switches allow for patients to remain on these therapies for many years without the need to switch again. As PLWH are living longer and newer ARV medications continue to be developed, we hope for a growing

pool of data for ARV medication switches, inclusive of all patient subpopulations, to help guide clinician decisions.

Authors' Note

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