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REVIEW

Alternative switching strategies based on regimens with a low genetic barrier: do clinicians have a choice nowadays?

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Abstract

Clinicians sometimes use switching strategies based on regimens such as RAL + ABC/3TC or RPV + ABC/3TC in order to resolve tolerability or safety issues associated with conventional recommended first-line strategies. Despite the low genetic barrier of these regimens, high safety and efficacy rates have been reported in retrospective studies.

Keywords Switching · Raltegravir · Rilpivirine · Abacavir/lamivudine · Safety · Efficacy

The new combination antiretroviral treatment (cART) recommended by the main guidelines [1, 2] for the management of HIV-infected patients has led to high rates of virological suppression (over 90%) in naïve patients. However, in specific cases, treatment must be switched owing to tolerability/toxicity issues, interactions with other drugs, and the preexistence or exacerbation of comorbidities associated with some antiretroviral drugs. Consequently, clinicians seek alternative antiretroviral regimens, many of which have not been tested in large-scale clinical trials, to address these limitations while maintaining virologic suppression.

Alternative regimens include drugs such as raltegravir (RAL) [3] and rilpivirine (RPV) [4], both of which have good safety profiles and very few drug interactions when combined with abacavir/lamivudine (ABC/3TC). RAL is an integrase strand transfer inhibitor (INSTI) that was approved on July 8, 2009, and RPV is a second-generation non-nucleoside reverse-transcriptase inhibitor (NNRTI) approved on May 20, 2011. Both drugs were approved by the US Food and Drug Administration and are suitable for the treatment of naïve HIV-1-infected patients in combination with two nucleos(t)ide reverse-transcriptase inhibitors (NRTI) [3, 4]. ABC/3TC, a fixed-dose combination of two NRTI, is widely used in both clinical trials and real-world practice, especially when clinicians wish to avoid the toxicity of tenofovir disoproxil fumarate (TDF) [5, 6].

These regimens have been reported to be effective in naive patients [7, 8]; however, in recent years, they have been evaluated as switching strategies in virologically suppressed patients in real-world practice, mainly through retrospective studies. More than 1000 patients were analyzed in four studies on RPV + ABC/3TC (512 patients) [9–12] and five studies on RAL + ABC/3TC (619 patients) [13–17].

Given the availability of these retrospective studies, the main objective of this short review is to compile the data in order to analyze the efficacy and safety of these alternative regimens with a low genetic barrier. Data were obtained using a systematic review of all available published data in PubMed. Efficacy was evaluated by intention-to-treat analysis (including all treatment failures) and on treatment analysis (including only virological failures). All failures reported in each study were included to assess treatment failure. We also reviewed the resistance mutation ratio in all virological failures. Safety was evaluated by reviewing the frequency of adverse events (AEs) and changes in renal, lipid, and hepatic profiles.

The main characteristics of the nine studies are shown in Table 1. Patients shared baseline characteristics such as age, gender, baseline CD4, and reasons for switching. Problems associated with toxicity/tolerability were responsible for most

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Table 1 Main characteristics in switching studies with RAL or RPV plus ABC/3TC

Study name	Regimen	*n*	Age (IQR)	Male gender (%)	Baseline CD4 (cells/mm^3)	Co-infections (%)	Main reasons for switching No. (%)	Main previous cART (%)
SIMRIKI[9] (2016)	RPV + ABC/3TC	209	49 (41–54)	155 (75.6)	667 (471–870)	HbsAg+ 4 (2) HCV PCR+ 41 (20)	Toxicity 197 (42)	NNRTI (59.4) PI (24.3)
Palacios et al.[10] (2016)	RPV + ABC/3TC	85	47.4 (42.5–53.7)	63 (74.1)	718 (541–866)	ND	Toxicity 50 (68.9)	NNRTI (97.6)
Marshall et al.[11] (2016)	RPV + ABC/3TC	118	43	72 (85)	626 (107–1468)	HbsAg+ 9 (11) HCV Ab+ 2 (2)	Toxicity 76 (82)	NNRTI (78) PI (28)
Galizzi et al.[12] (2018)	RPV + ABC/3TC	100	48.7 (42.6–53.7)	80 (80)	691 (513–899)	HCV Ab+ 17 (17)	Toxicity 73 (73)	PI (41) NNRTI (40)
Martínez et al.[13] (2012)	RAL + ABC/3TC	27	47 (43–60)	24 (89.9)	565 (416–806)	ND	ND	PI (100)
RASTA[14] (2014)	RAL + ABC/3TC	20	43.4 (40.7–50.2)	12 (60)	505 (413–739)	HCV PCR+ 3 (15)	Toxicity 15 (75)	PI (55) NNRTI (45)
Suzuki et al.[15] (2016)	RAL + ABC/3TC	11	44 (31–68)	8 (72.7)	586 (414–1441)	ND	Toxicity 11 (100)	PI (55) NNRTI (45)
ORASWIRAL[16] (2017)	RAL + ABC/3TC	94	50.3 (46.1–53.2)	ND	534 (382–824)	ND	Toxicity 49 (51.5)	PI (50) INI (22)
KIRAL[17] (2018)	RAL + ABC/3TC	467	49 (45–53)	352 (75.4%)	580 (372–781)	HbsAg+ 14 (3%) HCV PCR+ 156 (33.4%)	Toxicity 197 (42)	PI (48.2) INI (25.9)

n, number; *HCV*, hepatitis c virus; *Hbs Ag*, hepatitis b surface antigen; *ND*, no data; *NNRTI*, non-nucleoside reverse-transcriptase inhibitor; *PI*, protease inhibitor; *INI*, integrase inhibitor

Table 2 Virological suppression rates and treatment failures in switching studies with RAL or RPV plus ABC/3TC

Study name	Type of study	Regimen	Weeks	*n*	Efficacy 48 weeks	VF	No. (%) of mutations	Mutations
SIMRIKI[9] (2016)	Retrospective	RPV + ABC/3TC	48	209	ITT 91.2% OT 97.4%	5 (2.4%)	2 (1%)	A98G, K103N, K238T, E138K, M41L, M184V, T215F, K219Q, A62V
Palacios et al.[10] (2016)	Retrospective	RPV + ABC/3TC	48	85	ITT 88% OT 96%	1 (1.2%)	1 (1.2%)	E138K
Marshall et al.[11] (2016)	Retrospective	RPV+ABC/3TC	48	118	ITT 83% OT 99%	1 (0.9%)	1 (0.9%)	E138K, M184I/V
Galizzi et al.[12] (2018)	Retrospective	RPV + ABC/3TC	144	100	ITT 88% OT 98.8%	1 (1%)	1 (1%)	L100IL, K103N, E138AE
Martínez et al.[13] (2012)	Randomized trial	RAL + ABC/3TC	48	27	ITT 89% OT 96%	1 (3.7%)	ND	
RASTA[14] (2014)	Randomized pilot study	RAL + ABC/3TC	48	20	ITT 90% OT 100%	0%		
Suzuki et al.[15] (2016)	Retrospective	RAL + ABC/3TC	48	11	OT 100%	0%		
ORASWIRAL[16] (2017)	Retrospective	RAL + ABC/3TC	96	94	OT 97%	5 (5.3%)	ND	
KIRAL[17] (2018)	Retrospective	RAL + ABC/3TC	48	467	ITT 78.5% OT 98%	9 (1.9%)	6 (1.3%)	N155H, L163E, G163H, K65R, K70T, L74V, M184V, T215F

n, number of patients; *ITT* intention to treat; *ND*, no data; *OT*, on treatment; *VF*, virological failure

changes in cART, followed by drug interactions, mainly due to NNRTI (efavirenz) or protease inhibitors, especially in the case of older protease inhibitors [18].

Both regimens demonstrated high rates (> 95%) of maintained virological suppression (HIV-1 RNA < 50 copies/mL) 48 weeks after switching cART (Table 2). This finding is similar to those for other conventional switching strategies [19, 20]. The frequency of virological failure was very low, even though the drugs had a low genetic barrier. Only 22 virological failures were registered in the studies analyzed, 9/512 patients (1.8%; range, 1–2.4%) in the RPV studies and 15/619 patients (2.4%; range, 1.9–5.3%) in the RAL studies. Several of the virological failures were described as low-level failures (< 200 copies/mL), and most patients who maintained the same treatment normalized viral load to undetectability within a few weeks. Emergent mutations were detected in around 1% of patients (only 10 patients developed genotypic resistance mutations).

This observation is very interesting if we consider that in many cases, the regimens were used in vulnerable populations with incomplete adherence to cART—injection drug users or HIV/HCV-coinfected patients—and in patients with high pre-ART viral loads or low nadir CD4+ cell counts. Clinicians prioritized these strategies owing to their good tolerability and safety profiles rather than other aspects, such as the low genetic barrier or the availability of other single-tablet regimens.

Treatment failures (155/619 in RAL + ABC/3TC and 52/512 in RPV + ABC/3TC) were mainly associated with simplification to a fixed-dose cART in the RAL studies (probably due to the previous twice-daily dosing, and the appearance of new single-tablet regimens with better dosing and tolerability profiles) or with the very low number of toxicity/tolerability problems in both RPV or RAL studies.

Patients maintained high CD4 T cell counts [15, 17] or even experienced a significant increase in absolute values in some of the RPV (32 to 137 cells/mm^3) [9, 10, 12] or RAL studies (48 to 54 cells/mm^3) [13, 14, 16].

No clinically significant differences were observed with respect to changes in blood profile. Contrary to expectations [21, 22], a slightly significant improvement was observed in plasma lipids, including total cholesterol, LDL-cholesterol, and triglycerides in some RPV [9, 10] and RAL studies [13, 15], although in most studies, no impact on the ratio of total cholesterol to HDL cholesterol was found, probably owing to the favorable lipid profile of RPV and RAL or the replacement of previous regimens containing ritonavir-boosted protease inhibitors [23]. Regardless of the improvement in resolution of renal toxicity associated with TDF after the switch to ABC/3TC [24], the estimated glomerular filtration rate did not change markedly in most studies, not even in those patients who had previously received treatments including TDF. An exception to this last observation can be seen in the results of the SIMRIKI study [9].

The safety profile of these regimens is consistent with that reported in other switching studies [19, 20], with high overall levels of tolerability, low rates of AEs, and very low rates of serious AEs (grade 4) (around 1%; 0.5% [9] to 3.1% [16]). Most of the AEs were grade 1 and resolved without clinical intervention. No clear relationship with HIV treatment was found or suspected in most cases. The frequency of discontinuation due to AEs was low, around 5%:4.1% in RPV studies (1.4% [9] to 8.4% [11]) and 5.6% in RAL studies (0% [13, 15] to 7.4% [16]). The most frequently registered AEs (< 5%) were gastrointestinal disorders or neurological disturbances. These data reflect the good tolerability profile of both regimens, which was mainly due to the third drug, RPV or RAL.

The availability of a generic co-formulation of ABC/3TC [25] with a more competitive price makes these regimens more attractive than some newer antiretroviral regimens. This could have a significant impact on hospital drug expenditure at a time when funding is a global concern [26].

Despite the retrospective nature of the studies evaluated, this integrated analysis provides real-world data on over 1000 patients and shows similar safety outcomes. Both these aspects add value to our findings, despite the fact that this is not a clinical trial and no control group is available. Therefore, it can be concluded that the high rates of maintained virological suppression and the excellent safety profiles could make these strategies a favorable, inexpensive option when attempting to avoid the toxicity or drug interactions associated with conventional regimens.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval Ethical approval has not been necessary as this article is based on a review of published data.

Informed consent Informed consent has not been necessary as this article is based on a review of published data.

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