Comparison of Treatment-emergent Resistance-associated Mutations Among Single-tablet Regimens and Cabotegravir + Rilpivirine for the Treatment of Virologically Suppressed People With HIV: A Systematic Literature Review and Network Meta-analysis

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Conclusions

- In virologically suppressed people with HIV, bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) had the highest probability of preventing treatment-emergent resistance-associated mutations (TE-RAMs) and tended to have the lowest risk of TE-RAMs
- There was a trend in which cabotegravir + rilpivirine (CAB + RPV) dosed every 8 weeks (Q8W) had a higher risk of resistance compared to all integrase strand transfer inhibitor (INSTI)–based single-tablet regimens (STRs) and was not as protective as other 2-drug regimens, performing similarly to STRs with lower barriers to resistance
- The risk of discontinuation due to an adverse event was significantly higher for CAB + RPV than for the second-generation INSTI–based 3-drug STRs B/F/TAF and dolutegravir/abacavir/lamivudine
  - Compared to staying on B/F/TAF, switching to CAB + RPV was associated with a significantly higher risk of discontinuation due to adverse events in addition to a likely increased risk of TE-RAMs, particularly for CAB + RPV Q8W
- Until there is a cure, well-tolerated and durable antiretroviral regimens are needed for long-term success; moreover, clinicians should include the differential risk of TE-RAMs in shared decision-making discussions when switching antiretroviral therapy in stable, suppressed individuals since resistance impacts current and future treatment options

Plain Language Summary

- Oral single-tablet regimens (medicines that have more than 1 drug in them) are effective for people with HIV who take their medicine every day. These medicines help keep the virus from being found in the blood and help to stop resistance (which can cause the medicine to no longer work)
- Cabotegravir + rilpivirine is another treatment choice, which is given by injection and does not have to be taken every day. However, some people may still develop resistance to the medicine, even when they get their injections regularly
- If a medicine no longer works due to resistance, it becomes harder to find other medicines to treat HIV
- This study compared differences between oral single-tablet regimens and injectable cabotegravir + rilpivirine, including the chance of people becoming resistant to or having to stop taking the medicine due to side effects
- Bictegravir/emtricitabine/tenofovir alafenamide (a single-tablet regimen) was predicted to be the best at preventing resistance in people with HIV. Cabotegravir + rilpivirine had similar results to those of other single-tablet regimens that tend to lead to resistance development and stop working
- More people with HIV stopped taking cabotegravir + rilpivirine because of side effects compared to those taking bictegravir/emtricitabine/tenofovir alafenamide or dolutegravir/abacavir/lamivudine
- Switching to cabotegravir + rilpivirine was linked to a higher chance of stopping the medicine because of side effects. People who switched to cabotegravir + rilpivirine also had a higher chance of developing resistance

Introduction

- For people with fully susceptible HIV, current guideline-preferred single-tablet regimens (STRs) with a high barrier to resistance achieve and maintain durable virologic suppression without the emergence of resistance in those who are adherent to their oral antiretroviral therapy (ART)[1-3]
- Injectable cabotegravir + rilpivirine (CAB + RPV) provides an alternative method of administration for people with HIV (PWH), removing the need for daily oral therapy[1]
- Treatment-emergent resistance-associated mutations (TE-RAMs), including dual-class resistance, have been described in PWH who are adherent to the injection schedule for CAB + RPV; in 1 study, among 14 PWH who received CAB + RPV and had confirmed virologic failure, 7 developed dual-class TE-RAMs through 152 weeks despite receiving injections on time[4]
  - TE-RAMs complicate HIV control and management, limiting both current and future therapeutic options[5]
- This study compared the risk of TE-RAMs and discontinuation due to adverse events (AEs) among STRs and CAB + RPV in virologically suppressed PWH

Methods

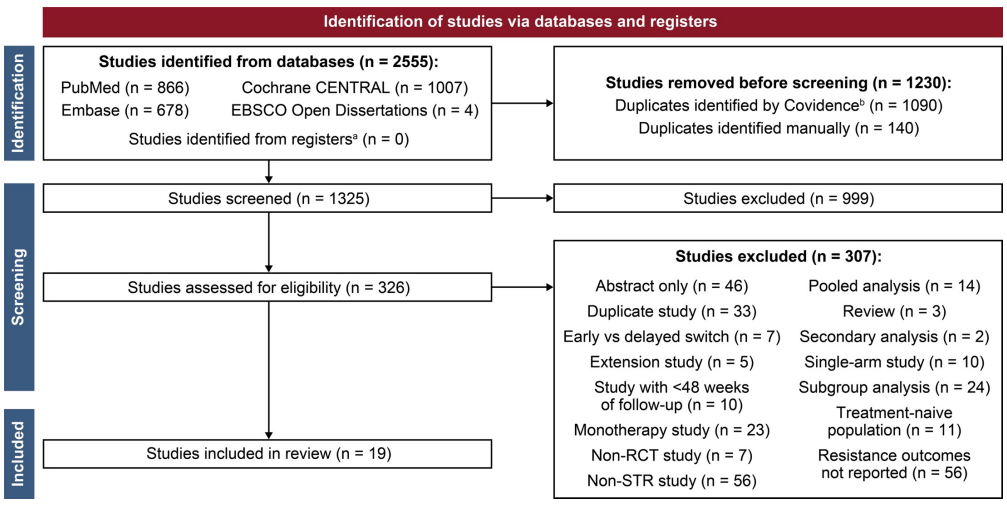
- A systematic literature review was conducted for Phase 2, 3, and 4 randomised controlled trials (RCTs) that investigated switching to any STR or CAB + RPV with ≥48 weeks of follow-up in both arms and with results published from January 2003 to March 2024; studies were retrieved from PubMed, Embase, Cochrane CENTRAL, and EBSCO Open Dissertations
  - Participants in the trials were virologically suppressed PWH aged ≥12 years
  - Arms composed of multi-tablet regimens were included only if the intervention arm in the study was an STR
  - For studies with multiple regimens in the comparison arm, the regimen with the most participants was used
  - Outcomes of interest were rates of TE-RAMs and discontinuation due to AEs
- Risk of bias (RoB) in the RCTs was evaluated using the Cochrane RoB 2 tool to assess internal validity
- Risk ratios (RRs) with 95% CIs were estimated using a random-effects model
- Surface under the cumulative ranking curve (SUCRA) was used to rank interventions to prevent TE-RAMs and discontinuation due to AEs
  - SUCRA scores signal the probability a treatment has of being among the best options in the network; higher scores represent better ranking

Results

- Overall, 19 RCTs encompassing 10,760 participants were included in the analysis (**Figure 1**)[6-24]

For RoB assessments of the included RCTs, please scan the QR code

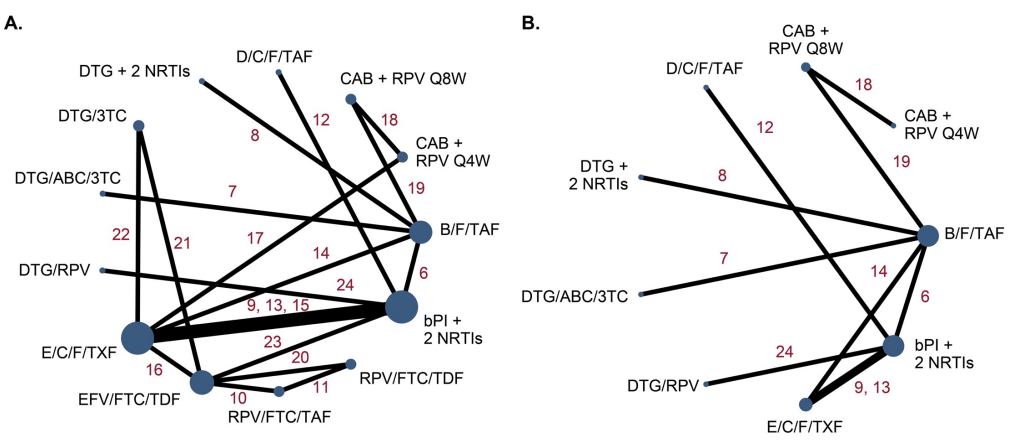
Figure 1. PRISMA Flow Chart



[a]Registers refers to clinical trial registries (eg, ClinicalTrials.gov).
[b]Covidence automation tool.
PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised controlled trial; STR, single-tablet regimen.

- The network map in **Figure 2A** shows which treatment regimens were compared in the 19 RCTs included in the analysis of rates of TE-RAMs
  - Tests for inconsistency (P = 0.999) and residual heterogeneity (I^2: 0.00; P = 0.996) were not significant
- The network map in **Figure 2B** shows which treatment regimens were compared in the 10 RCTs included in the analysis of rates of discontinuation due to AEs
  - Tests for inconsistency (P = 0.621) and residual heterogeneity (I^2: 0.00; P = 0.368) were not significant

Figure 2. Network Maps of (A) TE-RAMs and (B) Discontinuation Due to AEs at 48 Weeks[a,b]



[a]The reference(s) for each comparison is denoted in red on the network maps.
[b]Node size is proportional to the number of participants across all included studies for a treatment regimen, and line thickness is proportional to the number of studies that compared the 2 treatment regimens.
AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bPI, boosted protease inhibitor; CAB + RPV, cabotegravir + rilpivirine; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG/RPV, dolutegravir/rilpivirine; E/C/F/TXF, elvitegravir/cobicistat/emtricitabine/(tenofovir disoproxil fumarate or tenofovir alafenamide); EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV/FTC/TAF, rilpivirine/emtricitabine/tenofovir alafenamide; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; TE-RAM, treatment-emergent resistance-associated mutation.

- At 48 weeks, the risk of TE-RAMs with bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) and dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) was an estimated 78% lower than that of CAB + RPV every 8 weeks (Q8W; RR, 0.22 [95% CI, 0.02-2.02] and 0.22 [95% CI, 0.00-19.72], respectively) and tended to be lower than that of CAB + RPV every 4 weeks (Q4W) and all 2- and 3-drug STRs (**Table 1**)
- The risk of TE-RAMs with CAB + RPV Q4W was an estimated 60% lower than that of CAB + RPV Q8W (RR, 0.40 [95% CI, 0.15-1.09])
- There were no statistically significant differences between treatment regimens for TE-RAM RRs
- The risk of discontinuing therapy due to AEs at 48 weeks was significantly (85% and 84%) lower with B/F/TAF compared to CAB + RPV Q4W and CAB + RPV Q8W, respectively (**Table 1**)
- The risk of discontinuing therapy due to AEs was significantly (95%) lower with DTG/ABC/3TC compared to both CAB + RPV Q4W and CAB + RPV Q8W
- B/F/TAF ranked the highest for probability of preventing TE-RAMs (71.4%), and efavirenz/emtricitabine/tenofovir disoproxil fumarate ranked the lowest (23.1%; **Table 2**)
- CAB + RPV Q8W showed a lower probability of preventing TE-RAMs than all integrase strand transfer inhibitor– and protease inhibitor–based STRs (33.7%)
- Both CAB + RPV regimens ranked the lowest for probability of preventing discontinuation due to AEs (**Table 2**)

Table 1. Pooled Estimates for Risk of TE-RAMs and Discontinuation Due to AEs at 48 Weeks[a]

Comparison Regimen		Pooled Estimates (RR [95% CI])	
		TE-RAMs	Discontinuation Due to AEs
B/F/TAF vs	EFV/FTC/TDF	0.12 (0.01-2.22)	–
	RPV/FTC/TDF	0.12 (0.00-7.15)	–
	bPI + 2 NRTIs	0.21 (0.02-1.90)	1.46 (0.18-11.49)
	CAB + RPV Q8W	0.22 (0.02-2.02)	**0.16 (0.04-0.67)**
	E/C/F/TXF	0.34 (0.04-2.61)	2.16 (0.24-19.42)
	D/C/F/TAF	0.41 (0.00-37.45)	1.34 (0.13-13.56)
	DTG/3TC	0.44 (0.01-15.60)	–
	CAB + RPV Q4W	0.54 (0.06-5.27)	**0.15 (0.03-0.75)**
	DTG/RPV	0.68 (0.01-60.43)	0.69 (0.02-24.91)
	RPV/FTC/TAF	0.84 (0.02-40.27)	–
	DTG + 2 NRTIs	0.99 (0.02-49.69)	0.99 (0.32-3.03)
	DTG/ABC/3TC	1.00 (0.02-50.04)	2.99 (0.61-14.68)
CAB + RPV Q4W vs	EFV/FTC/TDF	0.22 (0.01-4.57)	–
	RPV/FTC/TDF	0.22 (0.00-14.23)	–
	bPI + 2 NRTIs	0.38 (0.03-4.58)	9.85 (0.71-136.53)
	CAB + RPV Q8W	0.40 (0.15-1.09)	1.08 (0.50-2.35)
	E/C/F/TXF	0.62 (0.08-4.72)	14.61 (0.95-224.66)
	D/C/F/TAF	0.76 (0.01-79.17)	9.03 (0.53-153.28)
	DTG/3TC	0.82 (0.02-29.88)	–
	DTG/RPV	1.25 (0.01-127.83)	4.66 (0.09-239.34)
	RPV/FTC/TAF	1.54 (0.03-80.53)	–
	DTG + 2 NRTIs	1.82 (0.02-168.37)	6.69 (0.93-48.22)
	DTG/ABC/3TC	1.83 (0.02-169.56)	**20.20 (2.07-196.86)**
	B/F/TAF	1.84 (0.19-17.83)	**6.76 (1.33-34.42)**
CAB + RPV Q8W vs	EFV/FTC/TDF	0.55 (0.02-12.15)	–
	RPV/FTC/TDF	0.55 (0.01-37.28)	–
	bPI + 2 NRTIs	0.95 (0.07-12.16)	9.11 (0.74-112.34)
	E/C/F/TXF	1.55 (0.18-13.16)	13.51 (0.98-185.72)
	D/C/F/TAF	1.91 (0.02-205.02)	8.35 (0.55-127.23)
	DTG/3TC	2.05 (0.05-79.26)	–
	CAB + RPV Q4W	2.51 (0.92-6.90)	0.92 (0.43-2.01)
	DTG/RPV	3.14 (0.03-331.05)	4.31 (0.09-204.95)
	RPV/FTC/TAF	3.87 (0.07-211.48)	–
	DTG + 2 NRTIs	4.57 (0.05-415.33)	6.18 (1.00-38.06)
	DTG/ABC/3TC	4.61 (0.05-418.26)	**18.68 (2.20-158.91)**
	B/F/TAF	4.62 (0.50-43.15)	**6.25 (1.49-26.15)**

[a]RRs are for first column:second column. Bolding signifies statistically significant RRs.
AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bPI, boosted protease inhibitor; CAB + RPV, cabotegravir + rilpivirine; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG/RPV, dolutegravir/rilpivirine; E/C/F/TXF, elvitegravir/cobicistat/emtricitabine/(tenofovir disoproxil fumarate or tenofovir alafenamide); EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV/FTC/TAF, rilpivirine/emtricitabine/tenofovir alafenamide; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; RR, risk ratio; TE-RAM, treatment-emergent resistance-associated mutation.

Table 2. SUCRA Rankings of TE-RAMs and Discontinuation Due to AEs at 48 Weeks

Treatment Regimen	SUCRA Score (%)	
	TE-RAMs	Discontinuation Due to AEs
B/F/TAF	71.4	51.8
RPV/FTC/TAF	65.2	–
DTG + 2 NRTIs	63.9	51.9
DTG/ABC/3TC	63.7	81.3
CAB + RPV Q4W	59.1	10.4
DTG/RPV	58.6	44.7
DTG/3TC	52.8	–
D/C/F/TAF	50.3	59.4
E/C/F/TXF	46.6	76.3
CAB + RPV Q8W	33.7	12.0
bPI + 2 NRTIs	33.6	62.3
RPV/FTC/TDF	27.9	–
EFV/FTC/TDF	23.1	–

AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bPI, boosted protease inhibitor; CAB + RPV, cabotegravir + rilpivirine; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG/RPV, dolutegravir/rilpivirine; E/C/F/TXF, elvitegravir/cobicistat/emtricitabine/(tenofovir disoproxil fumarate or tenofovir alafenamide); EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; NRTI, nucleoside reverse transcriptase inhibitor; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV/FTC/TAF, rilpivirine/emtricitabine/tenofovir alafenamide; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; RR, risk ratio; SUCRA, surface under the cumulative ranking curve; TE-RAM, treatment-emergent resistance-associated mutation.

Limitations

- In studies with multiple regimens in the comparison arm, only 1 regimen could be included in the network, limiting the overall dataset
- A low number of events was observed for both TE-RAMs and discontinuation due to AEs
- There were few direct head-to-head clinical trials in the analysis
- The majority of studies were open-label studies, which are susceptible to AE reporting bias
- The analysis of discontinuation due to AEs was restricted to 10 out of the 19 total studies due to the lack of details when comparator arms contained multiple regimens

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