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Selection of antiretroviral resistance in treatment-experienced PWH with virological failure while on B/F/TAF, DTG/3TC or CAB/RPV LA: Virostar 2.0 study

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BACKGROUND

Comtemporary integrase strand transfer inhibitors (INSTIs) have potent antiretroviral activity and a high barrier to resistance. They are recommended as components of both 2- and 3-drug regimens as initial or switch options. In phase 3 studies of B/F/TAF, DTG/3TC, or CAB+RPV LA IM the rate of virological failure (VF) is very low, with various rates of resistance emergence. Real word evidence regarding the development of resistance with those contemporary regimens remains poorly described.

OBJECTIVE

We evaluated the incident resistance mutation rates over 3 years in an observational study including treatment-experienced (TE) PWH who experienced a virological failure (VF) on B/F/TAF, DTG/3TC, or CAB+RPV LA IM after receiving at least one prior regimen.

METHODS

Retrospective analysis using a national French multicenter database of genotypic resistance assays and electronic medical records of demographics, therapeutic and immune-virological data of PWH between 01/01/2022 and 31/12/2024.

- Inclusion criteria: adult PWH with history of ≥1 prior regimen and receiving B/F/TAF, DTG/3TC, or CAB+RPV LA IM with evidence of VF (i.e. 2 consecutive HIV-1 plasma VL>50 c/ml).
- Exclusion criteria: HIV-2 infection, heavily TE PWH*.
- Sanger genotypic resistance assays performed as part of standard clinical care at the time of VF.

*(≥1 prior regimen and received either ibalizumab, enfuvirtide, fostemsavir, or lenacapavir; or ≥1 prior regimen with evidence of viremia [viral load >200 copies/mL] and received either maraviroc, etravirine, doravirine, dolutegravir twice daily, or darunavir twice daily).

CONCLUSIONS

- **While the overall prevalence of VF was low in this observational study, the prevalence of treatment-emergent RAMs at VF differed across regimens:**
  - **findings suggest that B/F/TAF has a low prevalence of treatment-emergent RAMs at VF compared with DTG/3TC and CAB + RPV among PWH with a history of ≥1 prior regimen.**
- **These findings underscore the importance of monitoring resistance patterns in real-world settings to optimize treatment outcomes for PWH.**

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CONTACT INFORMATION

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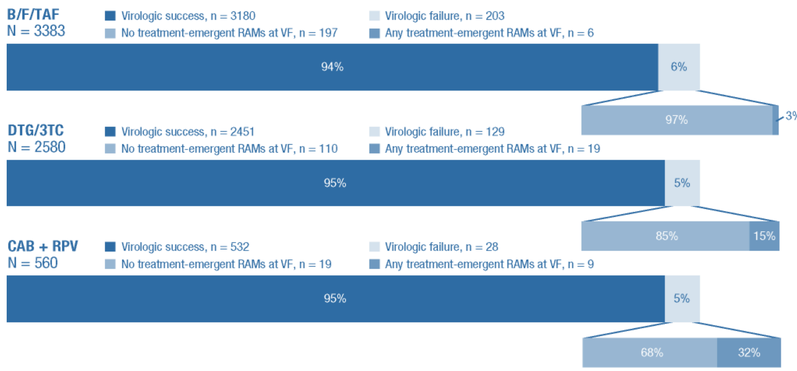
RESULTS

A total of 6523 PWH were followed over the 3-year study period as part of standard HIV clinical care, among which 3383 (52%) were receiving B/F/TAF, 2580 (40%) were receiving DTG/3TC, and 560 (9%) receiving CAB+RPV as a second or greater line of therapy. The proportion of PWH with VF was 6% (203/3383) for B/F/TAF and 5% for both DTG/3TC (129/2580) and CAB+RPV (28/560).

The observed incident resistance mutation rates at confirmed VF was 3% (6/203) with B/F/TAF, 15% (19/129) with DTG/3TC, and 32% (9/28) with CAB+RPV (Fig. 1).

Fig. 1. Proportions of PWH with VF and treatment-emergent HIV resistance with B/F/TAF, DTG/3TC, and CAB + RPV



Among PWH with treatment-emergent RAMs at VF, the NRTI RAM M184V, which confers resistance to 3TC and FTC, was detected in 67% (4/6) of PWH receiving B/F/TAF and 47% (9/19) of PWH receiving DTG/3TC. The single treatment-emergent InSTI RAM E138K was detected in 22% (2/9) of PWH with treatment-emergent RAMs at VF with CAB + RPV. No single treatment-emergent InSTI RAMs were detected at VF for PWH receiving B/F/TAF or DTG/3TC. Dual treatment-emergent InSTI and M184V RAMs were detected in 33% (2/6) and 53% (10/19) of PWH with treatment-emergent RAMs at VF with B/F/TAF and DTG/3TC, respectively. Dual treatment-emergent NNRTI and InSTI RAMs were detected in 78% (7/9) of PWH with treatment-emergent RAMs at VF with CAB+RPV **(Table 1)**.

Overall, 34 cases of treatment-emergent RAMs at VF were observed. The median (IQR) age of PWH with treatment-emergent RAMs at VF was 47 (42-57) years and 50% were male. Prior to VF, PWH received a median (IQR) of 4 (3-5) treatment lines, 71% were previously exposed to InSTIs, and 47% experienced a prior VF. At the time of the VF, the median (IQR) HIV-1 viral load was 443 (218-1147) c/mL and the median (IQR) CD4 cell count was 492 (302-610) cells/mm3.
The most common previous regimens were DRV+RTV+FTC/TDF amongst those receiving B/F/TAF at VF (50%, 3/6), B/F/TAF amongst those receiving DTG/3TC at VF (37%, 7/19), and DTG + RPV amongst those receiving CAB + RPV at VF (44%, 4/9). HIV-1 VL at VF were generally higher among PWH receiving DTG/3TC (median [IQR]: 1145 [752-1284] c/mL) compared with those receiving B/F/TAF (median [IQR]: 213 [159-239] c/mL) or CAB + RPV (median [IQR]: 216 [164-226] c/mL; **Table 2**).

Table 1. Details of treatment-emergent RAMs at VF for each regimen

	B/F/TAF (N = 3383)	DTG/3TC (N = 2580)	CAB + RPV (N = 560)
PWH with confirmed VF, n/N (%)	203/3383 (6)	129/2580 (5)	28/560 (5)
PWH with any treatment-emergent RAM at confirmed VF, n/N (%)	6/203 (3)	19/129 (15)	9/28 (32)
Treatment-emergent InSTI RAMs alone	N = 0	N = 0	N = 2 2 E138K
Treatment-emergent InSTI + M184V RAMs	N = 2 1 M184V + E138K 1 M184V + N155H	N = 10 4 M184V + R263K 3 M184V + N155H 3 M184V + G140S/Q148R	N/A
Treatment-emergent NRTI RAMs alone	N = 4 4 M184V	N = 9 9 M184V	N/A
Treatment-emergent NNRTI + InSTI RAMs	N/A	N/A	N = 7 1 E138K[a] + Q148R[b] 1 E138K[a] + N155H[b] 1 E138A[a] + R263K[b] 2 Y181C[a] + Q148R[b] 1 K101E[a] + E138K[b] 1 K101E[a] + E138K/Q148R[b]

Table 2. Characteristics of PWH with treatment-emergent RAMs at VF for each regimen

Case #	Sex and age (male or female, years)[c]	Regimen at VF[b]	HIV-1 plasma viral load at VF (c/mL)[d]	HIV-1 subtype[c]	CD4 count at VF (cell/mm³)[d]	Previous InSTI use[c]	Previous regimen[c]	Number of prior treatment lines[c]	Treatment-emergent NRTI mutations[d]	Treatment-emergent NNRTI mutations[d]	Treatment-emergent InSTI mutations[d]
1	F, 29	B/F/TAF	241	B	527	Yes	DRV/r + FTC/TDF	3	M184V	N/A	–
2	M, 48	B/F/TAF	231	B	662	No	RPV/FTC/TAF	4	M184V	N/A	–
3	F, 59	B/F/TAF	196	CRF_02	296	Yes	EVG/c/FTC/TAF	5	M184V	N/A	–
4	M, 53	B/F/TAF	85	CRF_02	547	Yes	DRV/r + FTC/TDF	6	M184V	N/A	–
5	F, 65	B/F/TAF	246	B	369	Yes	DRV/r + FTC/TDF	6	M184V	N/A	E138K
6	F, 62	B/F/TAF	147	CRF_06	187	Yes	RAL + FTC/TDF	7	M184V	N/A	N155H
7	M, 53	DTG/3TC	1148	B	618	No	RPV/FTC/TAF	2	M184V	N/A	–
8	F, 34	DTG/3TC	1205	B	243	No	RPV/FTC/TAF	2	M184V	N/A	R263K
9	F, 32	DTG/3TC	1266	B	532	No	DRV/r + FTC/TAF	3	M184V	N/A	–
10	M, 61	DTG/3TC	798	B	251	No	ATV/r + FTC/TDF	3	M184V	N/A	R263K
11	F, 35	DTG/3TC	1195	CRF_06	586	Yes	DTG/ABC/3TC	3	M184V	N/A	N155H
12	F, 44	DTG/3TC	1091	CRF_06	829	No	RPV + ABC/3TC	3	M184V	N/A	–
13	M, 61	DTG/3TC	1320	B	353	Yes	DTG/ABC/3TC	4	M184V	N/A	G140S, Q148R
14	M, 32	DTG/3TC	1301	B	272	Yes	RAL + FTC/TDF	4	M184V	N/A	–
15	F, 38	DTG/3TC	1388	CRF_06	413	Yes	B/F/TAF	4	M184V	N/A	–
16	M, 55	DTG/3TC	1145	B	767	Yes	B/F/TAF	4	M184V	N/A	N155H
17	M, 43	DTG/3TC	982	CRF_01	737	No	RPV/FTC/TAF	5	M184V	N/A	–
18	F, 62	DTG/3TC	551	non B	690	Yes	B/F/TAF	5	M184V	N/A	–
19	M, 53	DTG/3TC	335	B	824	Yes	RAL + FTC/TDF	5	M184V	N/A	–
20	F, 50	DTG/3TC	711	B	639	Yes	B/F/TAF	5	M184V	N/A	R263K
21	M, 47	DTG/3TC	127	B	522	Yes	DTG/ABC/3TC	5	M184V	N/A	R263K
22	F, 44	DTG/3TC	1357	CRF_02	358	Yes	B/F/TAF	6	M184V	N/A	–
23	M, 32	DTG/3TC	794	CRF_02	454	Yes	DTG/ABC/3TC	6	M184V	N/A	N155H
24	F, 63	DTG/3TC	678	C	525	Yes	B/F/TAF	6	M184V	N/A	G140S, Q148R
25	F, 34	DTG/3TC	1426	B	319	Yes	B/F/TAF	6	M184V	N/A	G140S, Q148R
26	M, 43	CAB + RPV	216	CRF_02	461	No	RPV/FTC/TAF	3	N/A	E138K	Q148R
27	M, 44	CAB + RPV	141	B	733	Yes	DTG/RPV	3	N/A	E138A	R263K
28	F, 46	CAB + RPV	226	B	181	Yes	DTG/RPV	4	N/A	–	E138K
29	M, 58	CAB + RPV	241	B	536	No	RPV/FTC/TAF	4	N/A	Y181C	Q148R
30	M, 42	CAB + RPV	164	CRF_02	257	Yes	DTG/3TC	5	N/A	K101E	E138K, Q148R
31	F, 50	CAB + RPV	105	CRF_02	321	Yes	DTG/RPV	5	N/A	E138K	N155H
32	F, 46	CAB + RPV	226	CRF_06	181	Yes	RPV/FTC/TAF	4	N/A	–	E138K
33	M, 58	CAB + RPV	241	B	536	No	RPV/FTC/TAF	4	N/A	Y181C	Q148R
34	M, 42	CAB + RPV	164	CRF_01	257	Yes	DTG/RPV	5	N/A	K101E	E138K

REFERENCES

[a]NNRTI RAM, [b]InSTI RAM. [c]Measured prior to the 3-year follow-up. [d]Measured during the 3-year follow-up. ATV/r + FTC/TDF; atazanavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV, cabotegravir + rilpivirine; DRV/r + FTC/TAF; darunavir/ritonavir + emtricitabine/tenofovir alafenamide; DRV/r + FTC/TDF; darunavir/ritonavir + emtricitabine/tenofovir disoproxil fumarate; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC; dolutegravir/abacavir/lamivudine; DTG/RPV, dolutegravir/rilpivirine; EVG/c/FTC/TAF, elvitegravir/cobicistat + emtricitabine/tenofovir alafenamide; F, female; InSTI, integrase strand transfer inhibitor; M, male; N/A, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PWH, people with HIV; RAL + FTC/TDF; raltegravir + emtricitabine/tenofovir disoproxil fumarate; RAM, resistance-associated mutation; RPV + ABC/3TC; ripilvirine +abacavir/lamivudine; RPV/FTC/TAF, ripilvirine/emtricitabine/tenofovir alafenamide; VF, virologic failure; VL, viral load.