Characterizing Resistance-Associated Mutations and Virological Status Among People Living With HIV Receiving Regimens Containing Bictegravir, Cabotegravir, or Dolutegravir

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Conclusions

- In a real-world study of > 150,000 people with HIV in the United States (US), resistance-associated mutations (RAMs) were detected among 388 (< 0.3%) receiving integrase strand-transfer inhibitor (INSTI)–based regimens in 2018-2025
  - Regimens included bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), dolutegravir/lamivudine (DTG/3TC), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), a dolutegravir multi-tablet regimen (DTG MTR), or cabotegravir plus rilpivirine (CAB + RPV)
- RAMs may have varying clinical impacts depending on the individual mutations present, levels of resistance conferred to antiretrovirals (ARVs), and drug classes impacted
  - Among people with RAMs, resistance interpretation scores predicted greater remaining antiretroviral activity among those receiving B/F/TAF compared with DTG/3TC, DTG/ABC/3TC, or CAB + RPV
    - One potential explanation is that nearly half of detected RAMs on B/F/TAF were M184V/I alone, with which virologic suppression can be maintained[1,2]
  - In this cohort, dual-class resistance was lower for people with RAMs on B/F/TAF compared with DTG-based regimens and CAB + RPV

Plain Language Summary

- This study looked at human immunodeficiency virus (HIV) drug resistance, which happens when the virus changes and HIV medicines become less effective
- We found that HIV drug resistance was rare in people taking treatments that include the newer medicines bictegravir, dolutegravir, and cabotegravir
- The effect of drug resistance depends on the specific changes that happen in the virus
- Some changes found in this study were predicted to decrease the activity of medicines in the treatment
- However, other changes were not predicted to reduce how well the medicines work, especially for treatment with bictegravir

Limitations

- Observational studies are limited by the frequency of resistance testing in routine clinical care
- RAM comparisons were descriptive due to small sample sizes (particularly for CAB + RPV) and do not establish differences by regimen in subsequent clinical outcomes

Introduction

- INSTI-based regimens (B/F/TAF, DTG-based, or CAB + RPV) recommended by current US ARV therapy guidelines have a high barrier to the emergence of resistance, and emergent RAMS are rare with these therapies[3,4]
- The clinical relevance of RAMs depends on the specific mutations present, levels of resistance conferred, and drug classes impacted in the regimen
- RAMs may be more common for people with virologic failure on CAB + RPV compared with oral INSTI regimens[5]
- Because resistance emerges so rarely on modern INSTI-based regimens, there have been limited opportunities to observe patterns of RAMs and their clinical impacts at the population level
- By leveraging real-world data on people with HIV in the US, this study aimed to conduct a larger assessment of RAMs than possible in prior work, and characterize potential clinical impacts for both oral and injectable INSTI-based regimens

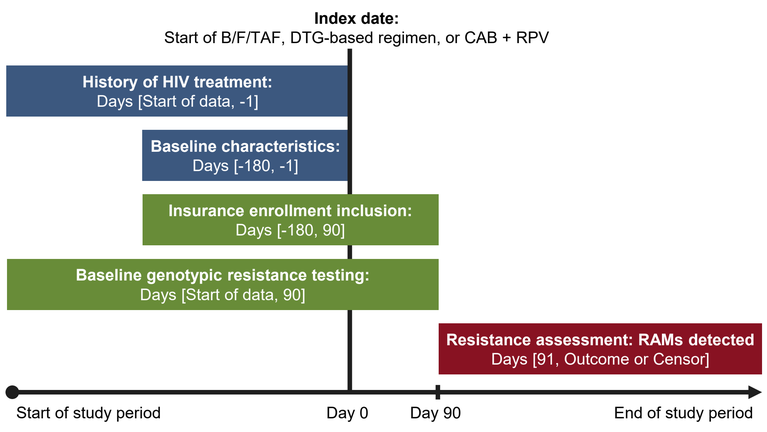
Objective

- Characterize resistance levels, drug classes impacted, and virologic status among people with RAMs detected after initiating B/F/TAF, DTG-based regimens, or CAB + RPV

Methods

- **Data source:** Medical and pharmacy claims and laboratory records from HealthVerity™ Marketplace, representing nearly 900,000 people with HIV in the US insured under commercial, Medicare, or Medicaid plans
- **Inclusion criteria:** Aged ≥ 18 years, diagnosed with HIV-1, and starting an index regimen in 2018-2024 with or without prior antiretroviral therapy (ART) experience
  - Index date was the first claim for B/F/TAF, DTG/3TC, DTG/ABC/3TC, DTG MTR, or CAB + RPV in 2018-2024; DTG MTR included DTG + F/TAF or DTG + F/TDF
  - Continuous enrollment required for ≥ 180 days pre- and ≥ 90 days post-index
- **Follow-up period:** From index until the earliest of the RAM outcome or censoring (regimen switch, insurance disenrollment, or end of study)
- **Resistance assessment:** Extracted genotyping results from laboratory records and applied interpretation system from the Stanford HIV Drug Resistance Database (HIVdb) to identify RAMs conferring any level of resistance (high, intermediate, low, potential-low)[6]

Figure 1. Study Design Schematic



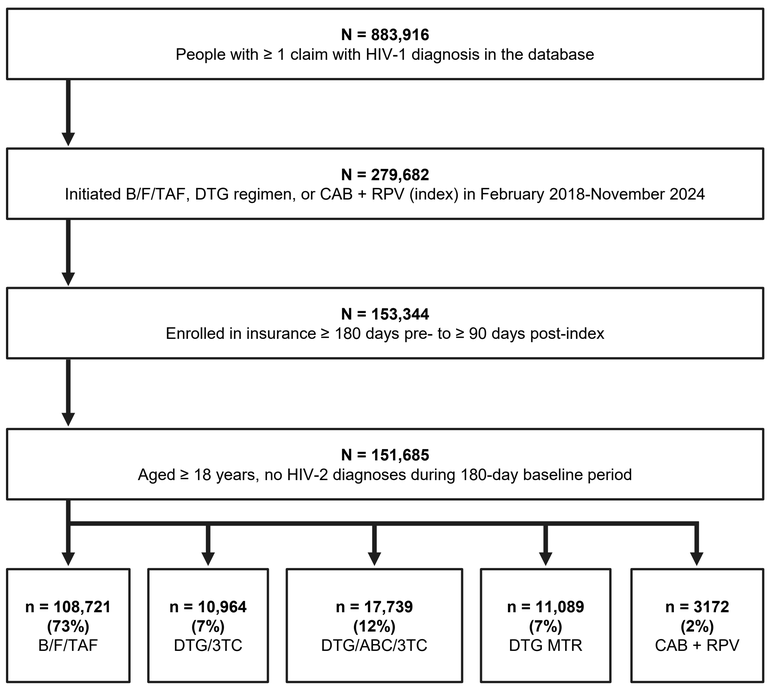
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV, cabotegravir plus rilpivirine; DTG, dolutegravir; RAM, resistance-associated mutation.

Outcome Assessment and Statistical Analysis

- **The RAM outcome was defined as follows:**
  - **Newly detected:** The first RAM(s) detected after ≥ 90 days on regimen and not at baseline
  - **Specific to regimen:** RAM associated with resistance to ≥ 1 index regimen component
  - **Linked to viremia:** Genotypic test performed for plasma RNA (not proviral DNA) or HIV RNA ≥ 200 copies/mL was documented within 90 days of RAM detection
    - Either one or both conditions met
- **Statistical analyses** were descriptive, as sample sizes with RAMs were insufficient for formal hypothesis testing comparing regimens
  - **Overall study population:** Frequencies of demographics, treatment experience, baseline genotyping, and the RAM outcome
  - **People with RAMs:** Frequencies of individual mutations, resistance levels to each ARV, drug classes impacted, and documented viremia
    - Genotypic susceptibility scores for the full regimen were calculated as the sum of the HIVdb resistance levels for the individual ARVs, rescaled between 0 and 1: 0 (high-level resistance), 0.25 (intermediate resistance), 0.5 (low-level resistance), 0.75 (potential-low resistance), and 1 (susceptible), as in prior work[1,7]

Results

Figure 2. Inclusion Criteria for the Study Population



Percentages may not sum to 100% due to rounding.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB+RPV, cabotegravir plus rilpivirine; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen.

Table 1. Study Population Characteristics by Index Regimen

Baseline Characteristic	B/F/TAF n = 108,721	DTG/3TC n = 10,964	DTG/ABC/3TC n = 17,739	DTG MTR n = 11,089	CAB + RPV n = 3172
Age, years, median (IQR)	45 (33-55)	47 (35-57)	48 (36-57)	46 (36-57)	46 (36-56)
Female sex, n (%)	27,761 (26)	2790 (25)	4396 (25)	3697 (33)	786 (25)
US region, n (%)					
South	35,842 (33)	4263 (39)	6015 (34)	3498 (32)	856 (27)
Northeast	21,143 (19)	1859 (17)	3328 (19)	2432 (22)	619 (20)
West	19,999 (18)	1954 (18)	3367 (19)	2104 (19)	683 (22)
Midwest	14,176 (13)	1152 (11)	2039 (11)	1169 (11)	461 (15)
Multiple or missing	17,561 (16)	1736 (16)	2990 (17)	1886 (17)	553 (17)
Insurance type, n (%)					
Commercial	39,108 (36)	5069 (46)	6872 (39)	2977 (27)	1227 (39)
Medicaid	40,395 (37)	3012 (27)	5793 (33)	4746 (43)	1041 (33)
Medicare	5318 (5)	663 (6)	1042 (6)	663 (6)	167 (5)
Multiple or missing	23,900 (22)	2220 (20)	4032 (23)	2703 (24)	737 (23)
Year of initiation, n (%)					
2018-2019	36,349 (33)	925 (8)	11,407 (64)	7165 (65)	0
2020	16,574 (15)	1576 (14)	2512 (14)	1388 (13)	0
2021	14,120 (13)	2019 (18)	1203 (7)	788 (7)	202 (6)
2022	16,157 (15)	2458 (22)	1404 (8)	793 (7)	1062 (33)
2023-2024	25,521 (23)	3986 (36)	1213 (7)	955 (9)	1908 (60)
Prior claims for antiretroviral therapy, n (%)	56,631 (52)	6627 (60)	11,288 (64)	7275 (66)	2379 (75)
Prior genotypic resistance testing, n (%)	8139 (7)	893 (8)	887 (5)	601 (5)	261 (8)
Charlson Comorbidity Index score ≥ 2 (excluding HIV), n (%)	14,412 (13)	1440 (13)	2364 (13)	1923 (17)	373 (12)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV, cabotegravir plus rilpivirine; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen.

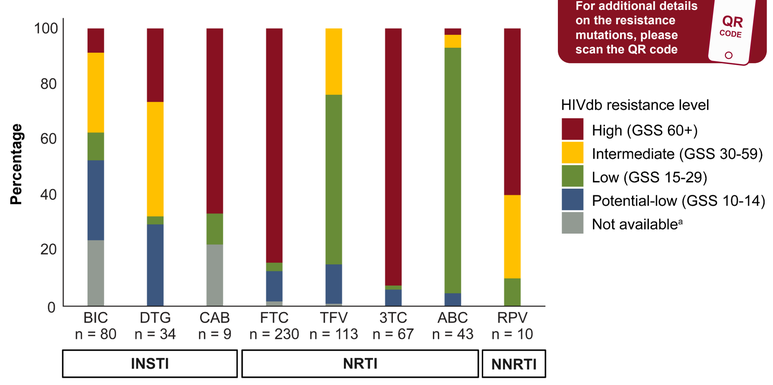
- During the study period, 151,685 people started a regimen of interest (**Figure 2**)
- Overall, most were male (74%) with median age 45 years and insured by commercial plans (36%) or Medicaid (36%); over half (56%) had claims for prior ART (**Table 1**)
- Of the 388 (0.3%) with the RAM outcome, dual-class resistance was lower for people with RAMs on B/F/TAF (14%) compared with those with RAMs on DTG-based regimens (29%) and CAB + RPV (73%) (**Table 2**)
  - For 3-drug regimens, most (76%) on DTG/ABC/3TC had ≥ 1 ARV predicted to be inactive compared with only 21% for both B/F/TAF and DTG MTR
  - For 2-drug regimens, half on DTG/3TC (50%) and CAB + RPV (55%) had ≥ 1 ARV predicted to be inactive
- Predicted genotypic susceptibility varied by ARV, with high-level resistance most common for 3TC, FTC, CAB, and RPV (**Figure 3**)

Table 2. RAM Outcome, Drug Classes Affected, Genotypic Susceptibility Score, and Documented Viremia

Overall Population	B/F/TAF n = 108,721	DTG/3TC n = 10,964	DTG/ABC/3TC n = 17,739	DTG MTR n = 11,089	CAB + RPV n = 3172
RAM outcome, n (%)[a]	280 (0.3)	32 (0.3)	46 (0.3)	19 (0.2)	11 (0.3)
Characteristics of People With RAMs					
Drug classes affected, n (%)					
INSTI and NRTI/NNRTI	38 (14)	16 (50)	11 (24)	1 (5)	8 (73)
INSTI only	42 (15)	3 (9)	3 (7)	0	1 (9)
NRTI only	200 (71)	13 (41)	32 (70)	18 (95)	—
NNRTI only	—	—	—	—	2 (18)
Regimen GSS, median (IQR)	2.0 (2.0-2.3)	0.9 (0.3-1.0)	1.5 (1.5-1.5)	2.0 (2.0-2.3)	0.3 (0.0-1.0)
Regimen GSS, n (%)					
0-0.75 (< 1 active ARV)	15 (5)	16 (50)	7 (15)	0	6 (55)
1-1.75 (1-< 2 active ARVs)	45 (16)	16 (50)	28 (61)	4 (21)	3 (27)
2-2.75 (≥ 2 active ARVs)	199 (71)	—	11 (24)	13 (68)	—
Not available[b]	21 (8)	0	0	2 (11)	2 (18)
Documented viremia ± 90 days of RAM, n (%)					
≥ 200 copies/mL	215 (77)	27 (84)	40 (87)	16 (84)	11 (100)
< 200 copies/mL	12 (4)	3 (9)	2 (4)	0	0
No HIV RNA; discontinued or switched regimen	31 (11)	1 (3)	4 (9)	2 (11)	0
No HIV RNA; stayed on regimen	22 (8)	1 (3)	0	1 (5)	0

[a]The percentages with RAMs do not reflect differing time under follow-up by regimen group.
[b]Regimen GSS was "Not available" when genotyping results reported resistance but did not specify mutation(s).
ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CAB + RPV, cabotegravir plus rilpivirine; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen; GSS, genotypic susceptibility score; INSTI, integrase strand-transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

Figure 3. Resistance Levels to Each ARV Predicted by HIVdb for People With RAMs



[a]Resistance level was "Not available" when genotyping results reported resistance to the ARV but did not specify mutation(s) in order to calculate the GSS.
3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; BIC, bictegravir; CAB, cabotegravir; DTG, dolutegravir; FTC, emtricitabine; GSS, genotypic susceptibility score; HIVdb, HIV Drug Resistance Database; INSTI, integrase strand-transfer inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation; RPV, rilpivirine; TFV, tenofovir.

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Disclosures: **SNL** is an employee of IQVIA and works exclusively on Gilead studies. **PM**, **WW**, **MLD'A**, and **TL** are employees of, and hold stock in, Gilead Sciences, Inc. **ZY** is an employee of The Lotus Group (Pine Brook, NJ, USA) and works exclusively on Gilead studies.

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