

Incidence of Resistance-Associated Mutations Among People With HIV Receiving B/F/TAF Versus DTG-Based Regimens

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Conclusions

- Resistance-associated mutations (RAMs) were rare across all integrase strand-transfer inhibitor (INSTI)-based regimens in this large real-world study of nearly 150,000 people with HIV in the US
- Following adjustment for baseline characteristics, RAM rates were similar between people receiving bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), dolutegravir/lamivudine (DTG/3TC), dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), or a DTG multi-tablet regimen (MTR)
- The percentage of days covered (PDC) by prescription fills (a claims-based proxy for adherence) varied in the 90 days preceding RAM detection for people with RAMs
 - Some RAMs occurred in people with higher PDC (85-100%) on DTG/3TC, while this appeared less common on B/F/TAF or a three-drug DTG regimen
- Findings should be interpreted in the context of limitations of observational analyses, including incomplete resistance ascertainment and potential residual confounding
 - Resistance testing was not systematically performed in the study population
 - Newly detected RAMs may not represent treatment-emergent resistance
 - PDC does not confirm medication ingestion and may misclassify adherence

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 drug resistance was rare in people taking commonly prescribed HIV treatments, including the newer medicines bictegravir and dolutegravir
- For people with resistance, we used prescription fill records to estimate how consistently they had their medicines available before resistance was found, and this measure differed across HIV treatments

Introduction

- RAMs have been rarely observed in clinical trials of INSTI-based regimens containing bictegravir or dolutegravir¹
- Previous observational studies of RAMs have not accounted for individual differences, especially in adherence^{2,3}
- The relationship between adherence and resistance has not been well characterized for modern INSTI-based regimens
 - The relationship is not the same for all antiretrovirals,⁴ and it is not the same as the adherence-virologic suppression relationship⁵
 - Rare cases of RAMs have been detected with these regimens, including in individuals with apparently high adherence^{1,6}
- Leveraging real-world data enables greater characterization of RAMs, including regimen comparison and assessment of adherence, in a large population living with HIV

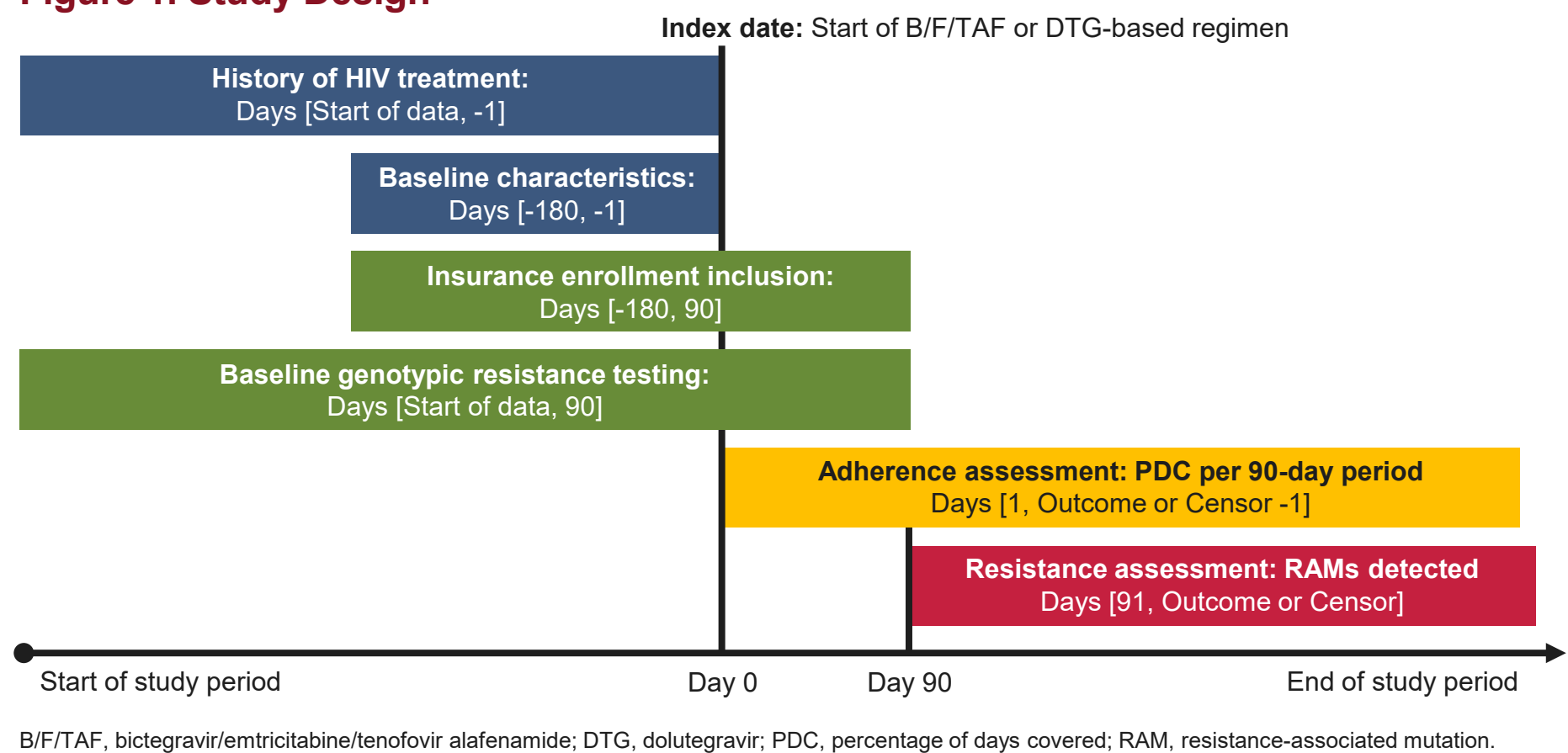
Objectives

- Primary objective:** To examine the incidence of RAMs in a real-world population of people with HIV in the US initiating the daily oral regimens B/F/TAF, DTG/3TC, DTG/ABC/3TC, or DTG MTR in 2018-2024
- Secondary objective:** To describe claims-based PDC leading up to RAMs, by regimen

Methods

- Data source:** Medical and pharmacy claims and laboratory records from HealthVerity™ Marketplace, representing people in the US insured under commercial, Medicare, or Medicaid plans, including nearly 900,000 people with HIV
- Inclusion criteria:** Aged ≥ 18 years, diagnosed with HIV-1, and initiated B/F/TAF, DTG/3TC, DTG/ABC/3TC, or DTG MTR in 2018-2024
- Follow-up period:** From regimen initiation (index) until the earliest of the RAM outcome or censoring (regimen switch, insurance disenrollment, end of study) (**Figure 1**)
- Adherence assessment:** PDC for 90-day periods post-index and classified as < 65%, 65-85%, or 85-100%, reflecting thresholds associated with virologic response^{1,7,8}
- Resistance assessment:** Extracted genotyping results from laboratory records and applied interpretation system from Stanford HIV Drug Resistance Database to identify RAMs conferring any level of resistance (high, intermediate, low, potential-low)⁹

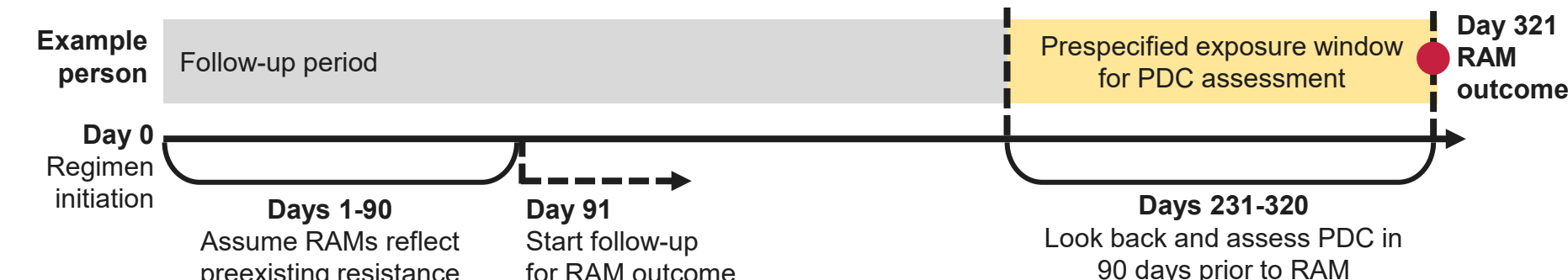
Figure 1. Study Design



Outcome Assessment

- The RAM outcome was defined as follows:**
 - Newly detected:** RAM first detected after 90 days on regimen and not present at baseline or earlier
 - Specific to regimen:** RAM associated with resistance to ≥ 1 regimen component
 - Linked to viremia:** Genotypic test performed for plasma RNA (not proviral DNA) or HIV RNA ≥ 200 copies/mL within 90 days of RAM detection
- Comparison with older INSTIs:** RAMs confirmed to be higher for regimens containing elvitegravir or raltegravir (older INSTIs) versus bictegravir or dolutegravir prior to proceeding with analysis (data not shown)
- Linked to adherence:** PDC assessed for the 90 days prior to RAM detection (**Figure 2**)

Figure 2. RAM Outcome Follow-Up and PDC Assessment in the 90 Days Before RAM



PDC, percentage of days covered; RAM, resistance-associated mutation.

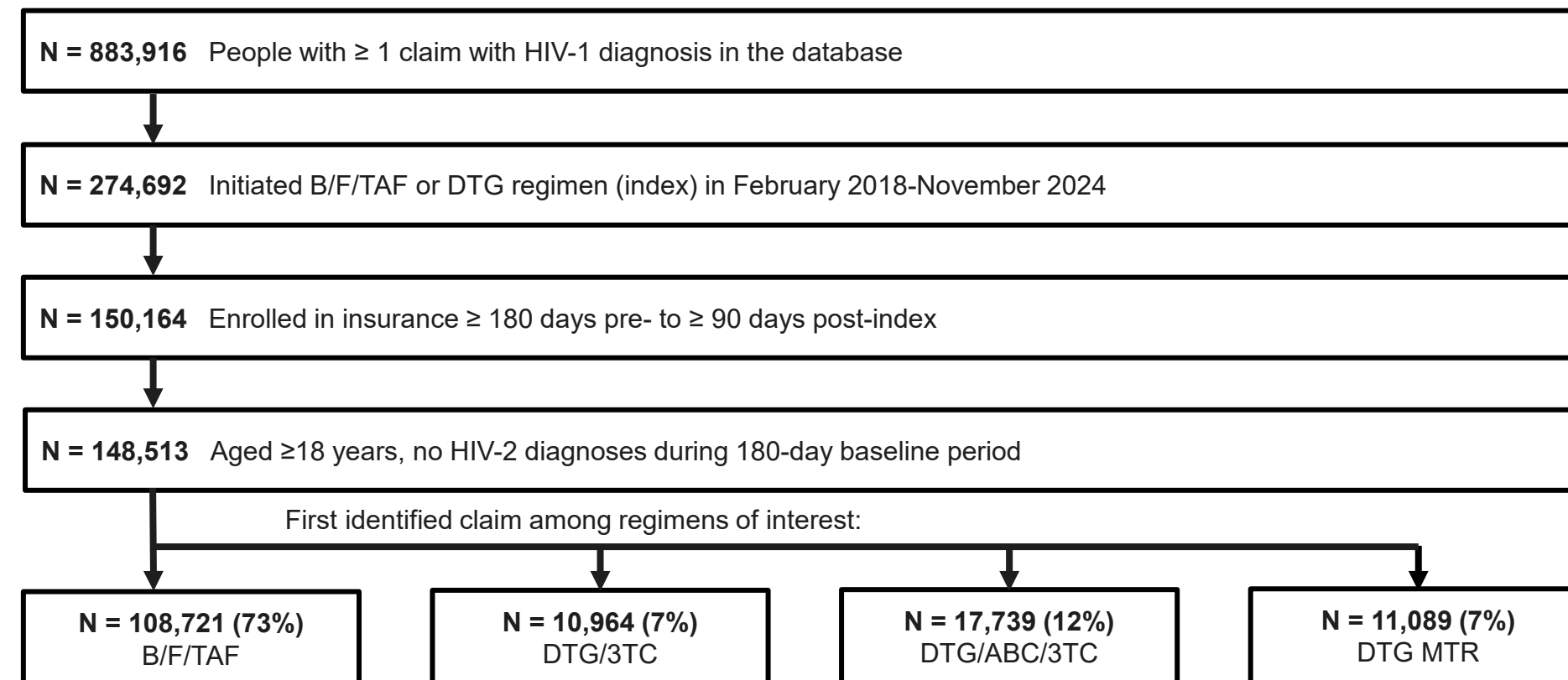
Statistical Analysis

- Poisson regression was used to estimate incidence rates and rate ratios (RRs) with 95% CIs:
 - Rates were the count of persons with ≥ 1 RAMs by total person-time under follow-up for each index regimen
 - RRs were the rate for each DTG regimen group divided by the rate for B/F/TAF (< 1 if rates were lower for DTG; > 1 if rates were higher for DTG)
- Weighted RRs (using inverse probability of treatment weights, IPTW) balanced baseline characteristics that may confound the relationship between index regimen and RAMs:
 - Demographics
 - History of HIV treatment and resistance testing
 - Charlson Comorbidity Index and individual comorbidities
 - Comedication use

Results

- During the study period, 148,513 people were eligible and started a regimen of interest. 108,721 (73%) of these started B/F/TAF, 10,964 (7%) started DTG/3TC, 17,739 (12%) started DTG/ABC/3TC, and 11,089 (7%) started a DTG MTR (**Figure 3**)
- Prior to adjusting for baseline characteristics (**Table 1**), the unweighted incidence rate of RAMs was lower for B/F/TAF compared with DTG/3TC, but similar compared with DTG/ABC/3TC and DTG MTR (**Figure 4**)
- After adjusting for baseline characteristics using IPTW, the weighted rate of RAMs was similar by regimen, although DTG/ABC/3TC trended higher than B/F/TAF (RR: 1.40; *P* = 0.08) (**Table 2**)
- Overall PDC across follow-up was similar by regimen, but PDC in the 90 days preceding RAMs differed by regimen of those with RAMs (**Figure 5**)
 - Among people with a detected RAM, 34% of the DTG/3TC group had PDC of 85-100% in the preceding 90 days, compared with 15% for B/F/TAF, 9% for DTG/ABC/3TC, and 5% for DTG MTR
 - These percentages describe PDC among RAM cases and do not estimate RAM risk within an overall adherence category

Figure 3. Inclusion Criteria for the Study Population



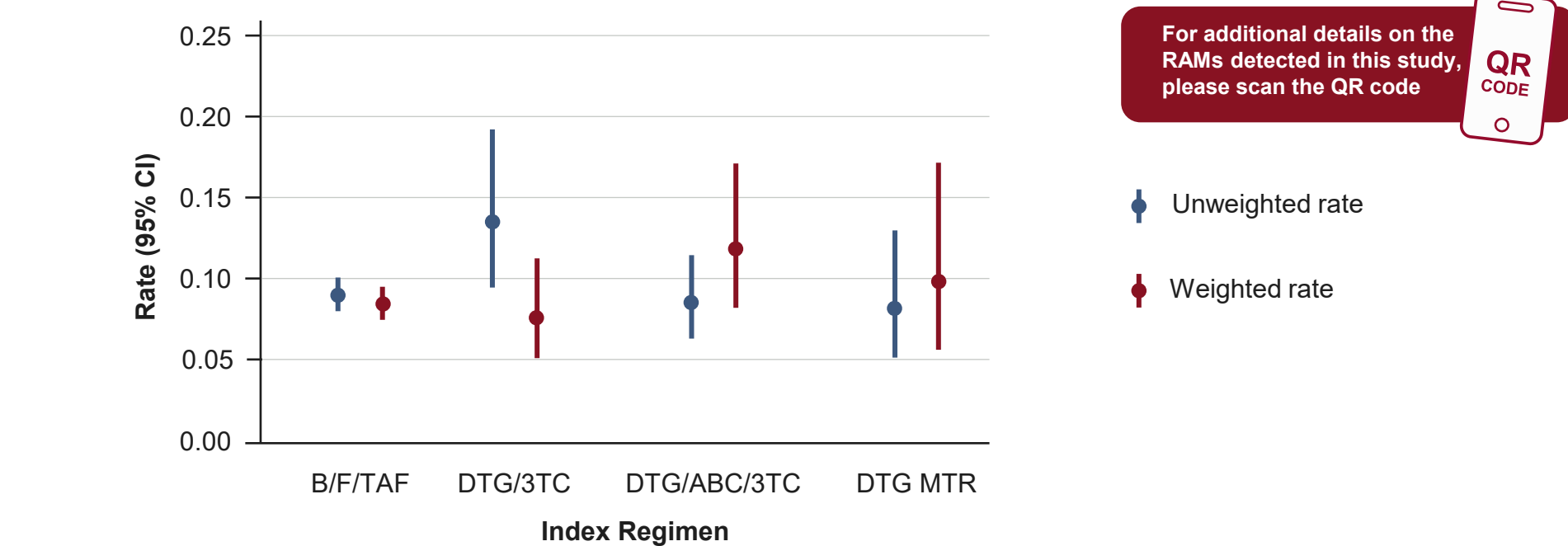
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; MTR, multi-tablet regimen.

Table 1. Study Population Characteristics With Baseline Differences by Index Regimen

Selected* Baseline Characteristics, n (%)	B/F/TAF N = 108,721	DTG/3TC N = 10,964	DTG/ABC/3TC N = 17,739	DTG MTR N = 11,089
Age 18-39 years	42,662 (39)	3799 (35)	5848 (33)	4078 (37)
Age ≥ 65 years	5620 (5)	890 (8)	1152 (6)	590 (5)
Female sex	27,761 (26)	2790 (25)	4396 (25)	3697 (33)
South region	35,842 (33)	4263 (39)	6015 (34)	3498 (32)
Midwest region	14,176 (13)	1152 (11)	2039 (11)	1169 (11)
Commercial insurance	39,108 (36)	5069 (46)	6872 (39)	2977 (27)
Medicaid insurance	40,395 (37)	3012 (27)	5793 (33)	4746 (43)
Initiated regimen in earliest study years (2018, 2019)	36,349 (33)	925 (8)	11,407 (64)	7165 (65)
Initiated regimen in latest study years (2023, 2024)	25,521 (23)	3986 (36)	1213 (7)	955 (6)
Prior claims for antiretroviral therapy regimens	56,631 (52)	6627 (60)	11,288 (64)	7275 (66)
Prior genotypic resistance testing	8139 (7)	893 (8)	887 (5)	601 (5)
Charlson Comorbidity Index score ≥ 2 (excluding HIV)	14,412 (13)	1440 (13)	2364 (13)	1923 (17)
Mental health disorders	28,581 (26)	2662 (24)	4265 (24)	3393 (31)
Severe mental health disorders	20,345 (19)	1715 (16)	3167 (18)	2583 (23)
Substance use disorder	12,860 (12)	759 (7)	1742 (10)	1597 (14)
Chronic kidney disease	4227 (4)	747 (7)	1199 (7)	517 (5)
Gastrointestinal symptoms	15,637 (14)	1191 (11)	1942 (11)	1814 (16)
Hyperlipidemia	18,217 (17)	2498 (23)	3071 (17)	1736 (16)
Cardiovascular medications (including lipid lowering)	29,714 (27)	3538 (32)	5143 (29)	3180 (29)
Antipsychotics	7430 (7)	672 (6)	1014 (6)	987 (9)

*Selected covariates differed by index regimen at baseline (absolute standardized mean difference > 0.1 for each DTG regimen vs B/F/TAF). B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG, dolutegravir; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; MTR, multi-tablet regimen.

Figure 4. Unweighted and Weighted RAM Rates per 100 Person-Years by Index Regimen



B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen; RAM, resistance-associated mutation.

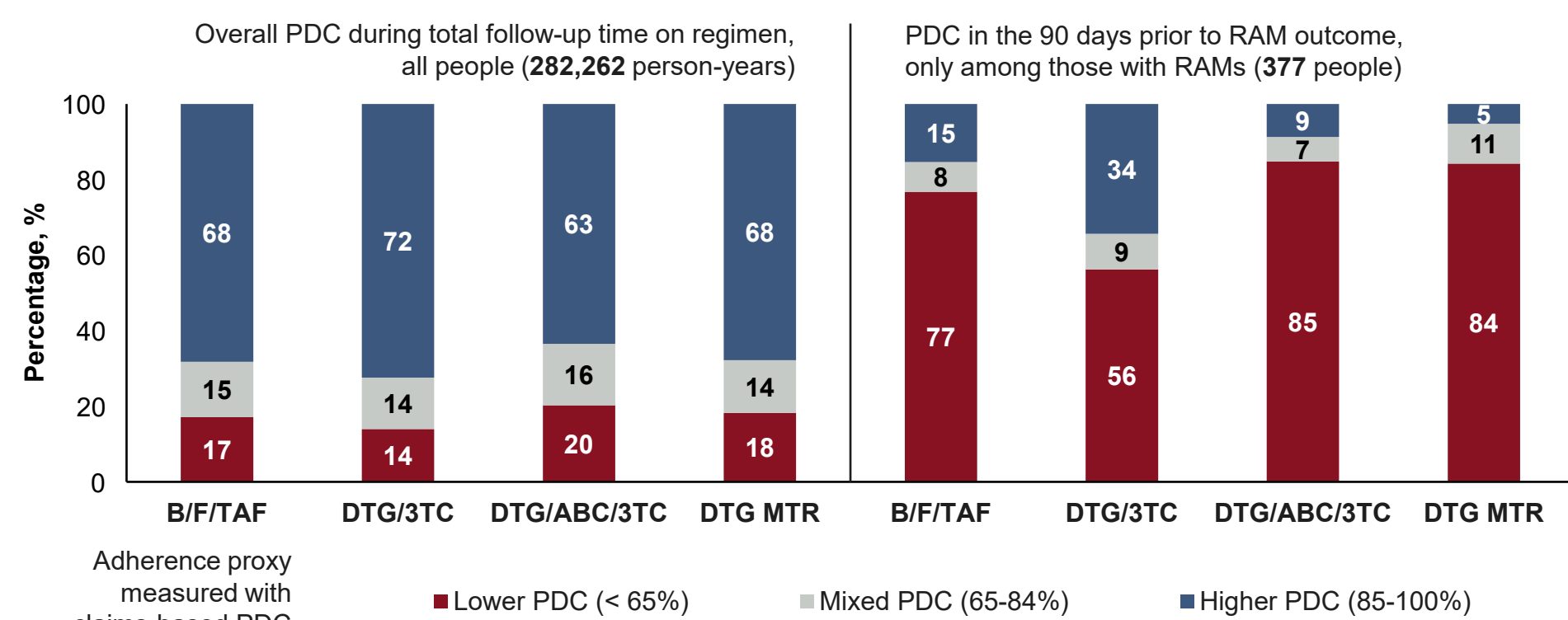
Table 2. RAM Rates and RRs Comparing Index Regimens

Index Regimen	Unweighted People With RAMs / Total N	Weighted RR (95% CI)
B/F/TAF	280 / 108,721	–
DTG/3TC	32 / 10,964	0.90 (0.60, 1.35)
DTG/ABC/3TC	46 / 17,739	1.40 (0.96, 2.04)
DTG MTR	19 / 11,089	1.16 (0.66, 2.04)

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen; RAM, resistance-associated mutation; RR, rate ratio.

Weighted RAM rates were similar after balancing pre-index characteristics, although DTG/ABC/3TC trended higher compared with B/F/TAF

Figure 5. PDC Across Follow-Up in Overall Population and PDC Preceding RAM Outcome



B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/3TC, dolutegravir/lamivudine; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG MTR, dolutegravir multi-tablet regimen; PDC, percentage of days covered; RAM, resistance-associated mutation.

Limitations

- PDC calculated from real-world pharmacy claims is an imperfect measure of adherence
- Consistently refilled prescriptions may not necessarily be taken as directed
- It is possible that gaps in medication supply could be filled by medication hoarding, medication sharing, or other means

Overall PDC was similar by regimen (Figure 5, left), but for people with RAMs, PDC in the 90 days preceding RAM detection differed by regimen (Figure 5, right)