P-360

Real-world Effectiveness and Safety Outcomes in People With HIV-1 Switching to Dolutegravir + Lamivudine (DTG + 3TC) With Unknown Prior Genotype: A Systematic Literature Review and Meta-analysis

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Key Takeaways

- **Using a systematic literature review, we identified 14 publications representing 3535 unique people switching to dolutegravir + lamivudine with unknown prior genotype in real-world settings**
- **Across 5 real-world studies (n=637), no individuals developed virologic failure at Week 48 (random-effects model, 0.0000; 95% CI, 0.0000-0.0057)**
- **Among studies reporting resistance outcomes, on-treatment integrase strand transfer inhibitor resistance-associated mutations were rare; low-level resistance mutations were detected in only 1 individual (0.03%; 1/3468) at virologic failure**
- **With only 1 individual with unknown prior genotype developing low-level resistance at virologic failure, these findings provide reassurance that switching to dolutegravir + lamivudine can be an effective option in real-world settings in the absence of a prior genotype**

Introduction

- Dolutegravir/Lamivudine (DTG/3TC) is a guidelines-recommended antiretroviral therapy (ART) regimen[1,2] that has demonstrated robust efficacy and a high barrier to resistance as a switch option in phase 3 trials[3,4] and real-world studies[5]
  - In the US, DTG/3TC is indicated as a switch option for people with virologic suppression (VS) on stable ART with no history of treatment failure and no known DTG or 3TC resistance-associated mutations (RAMs)[6]
  - In the EU, DTG/3TC is indicated for HIV-1 treatment in those with no known or suspected DTG or 3TC RAMs[7]
- In clinical practice, people with HIV-1 do not always have historical genotype tests, and healthcare providers may not always have access to existing prior genotype results or full treatment history at ART switch
- The prevalence of major integrase strand transfer inhibitor (INSTI) RAMs is very low,[8] and the presence of minor INSTI RAMs has not been associated with VF on INSTI-based regimens[9]
  - Among individuals with stable VS and a prior M184V mutation, switching to DTG/3TC has led to very low VF rates and rare emergence of new resistance across clinical trials and real-world cohorts[10-13]
- In a pooled post hoc analysis of the phase 3 TANGO and SALSA randomized clinical studies,[14] high proportions of participants with and without prior genotype maintained VS at Week 48: no prior genotype, 93% (272/294); prior genotype, 95% (304/321)
- The impact of unknown prior genotype on regimen effectiveness after switch to DTG/3TC in clinical practice remains a real-world data gap
- Previously, a systematic literature review (SLR) of real-world studies found that switching to DTG/3TC (including both fixed-dose single-tablet DTG/3TC and multi-tablet DTG + 3TC) with an unknown prior genotype resulted in high rates of VS, low rates of VF, and rare development of INSTI resistance[15]
- Here, we expand on this SLR and report a meta-analysis from the subset of studies in populations switching to DTG + 3TC with unknown prior genotype to determine point estimates of VF at Week 48

Methods

Systematic Literature Review

- We systematically searched Ovid MEDLINE®, Embase, and Cochrane databases and relevant congresses for observational studies reporting on DTG + 3TC use published between January 2013 and November 2024, per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
- Publications reporting effectiveness, safety, and/or tolerability outcomes for people switching to DTG + 3TC with unknown prior genotype (ie, no historical or baseline genotype results or no available prior results) were included
- Lead studies were identified after screening based on the highest number with unknown prior genotype per cohort
  - Lead studies were used to represent unique populations and to avoid double-counting individuals across potentially overlapping studies
- Rates of VS and VF, INSTI RAMs at VF, safety, and tolerability were summarized using descriptive statistics across lead studies

Meta-analysis

- The SLR-included studies were screened to identify all studies reporting VF at Week 48 for inclusion in the meta-analysis (5 studies; n=637 individuals)
- A single-arm meta-analysis produced point estimates from common- and random-effects models for proportions of individuals with VF at Week 48
  - Denominators used the number of people switching to DTG + 3TC with unknown prior genotype
- Data sets were transformed using double-arcsine transformations
  - Sensitivity analyses used Freeman-Tukey transformations
- Publication bias was evaluated with funnel plots and Egger's test

Results

Overview of SLR-Identified Studies

- We identified 310 publications representing 61,334 people with HIV-1 using DTG + 3TC through the SLR after accounting for population overlap
- 14 publications reported outcomes for 3535 unique individuals with ART experience who switched to DTG + 3TC with unknown prior genotype[16-29]
  - Cohorts were represented across Europe (n=8), Asia (n=4), and South America (n=2)
  - Not all individuals had VS at switch, but HIV-1 genotype was not specified for those with baseline viremia

Effectiveness and Safety Outcomes Across All SLR-Included Studies

- Of the 14 SLR-included publications,[16-29] 12 reported on effectiveness, representing 3513 unique individuals, 3499 of whom had follow-up data ranging from 6 to 33 months[16-27]
  - Among these studies, VS rates were reported for 410 individuals, and VFs and discontinuations for virologic reasons were reported for 3499 individuals
- VS rates were high (98%; 401/410), and VFs and discontinuations for virologic reasons were rare (0.29%; 10/3499)
- Among the 9 studies that reported resistance outcomes,[16,17,19-22,25-27] 1 individual (0.03%; 1/3468) had substitutions conferring low-level resistance to DTG at treatment discontinuation (Table 1)
  - INSTI RAMs T97A, E138K, and N155H were detected at Month 24 (HIV-1 RNA 540 c/mL) after switch to DTG + 3TC
  - The individual subsequently resuppressed on DTG + 3TC (<40 c/mL) by the time of treatment discontinuation at Month 25
  - ART history was limited to immediate prior use of DTG + TAF/FTC
  - The individual switched to DRV/c/FTC/TAF + DTG after DTG + 3TC discontinuation[21]
- Resistance tests at VF were available for 5/10 individuals who experienced VF[16,17,19-22,25-27]

Table 1. INSTI RAMs at VF Among SLR-Included Studies Reporting Resistance Outcomes (n=9 Studies; n=3468 Individuals; Follow-up, 6-33 Months)

Study	People using DTG + 3TC, n	People with unknown prior genotype using DTG + 3TC, n	INSTI RAMs detected at VF
Noe et al 2023[21]	335	1[a]	Low-level resistance: T97A, E138K, N155H

[a]Effectiveness was reported for 1 individual with unknown prior genotype, but overall number with unknown prior genotype was not reported.

- Of the 14 SLR-included publications, 5 (n=356 unique individuals) reported on safety and/or tolerability[15]
- <1% of individuals discontinued DTG + 3TC due to adverse events (3/356), and no drug-related discontinuations were reported[15]

Meta-analysis Effectiveness Estimates

- Of the 14 SLR-included studies, 5 reported VF outcomes data for 637 individuals at Week 48 and were included in meta-analysis estimates[16,20,22,24,27]
- While no 2 studies used identical definitions of VF, definitions were similar and broadly aligned with HIV treatment guidelines[1,2,30] (Table 2)

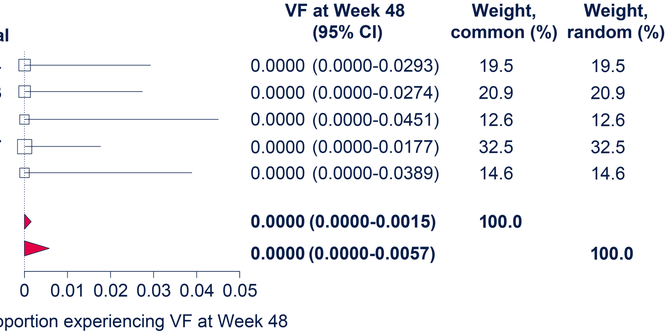
Table 2. Meta-analysis–Included Studies Reporting VF Outcomes at Week 48

Study	VF definition	VF n/N (%)
Mussini et al 2022[27]	2 consecutive VL ≥200 c/mL or 1 VL ≥200 c/mL followed by regimen discontinuation	0/124 (0)
Lagi et al 2023[16]	2 consecutive VL >50 c/mL or 1 VL >50 c/mL followed by ART modification	0/133 (0)
Lee et al 2022[20]	Persistent VL >1000 c/mL after ≥6 months of ART	0/80 (0)
Piñeiro et al 2025[22]	2 consecutive VL >200 c/mL	0/207 (0)
Stagnaro et al 2024[24]	NR[a]	0/93 (0)[b]

NR, not reported; VL, viral load. [a]n=3 individuals had detectable VL (43, 51, and 373 c/mL). [b]Assumption; study stated both n=92 and n=93 people had follow-up data.

- No people with HIV and unknown prior genotype who switched to DTG + 3TC experienced VF at Week 48 (Figure 1)
  - Estimated proportions were 0.0000 (95% CI, 0.0000-0.0057) using a random-effects model and 0.0000 (95% CI, 0.0000-0.0015) using a common-effects model
  - Sensitivity analysis–estimated proportions were similar and robust
  - Funnel plots provided no evidence of publication bias; Egger's test was not applicable as studies reported 0 events

Figure 1. Meta-analysis–Estimated Proportions of People Switching to DTG + 3TC With VF at Week 48



Note: each study used distinct definitions of VF, which were broadly aligned with HIV treatment guidelines.[1,2,30]

Conclusions

- Real-world effectiveness and/or safety outcomes were reported in 3535 unique people with ART experience who switched to DTG + 3TC with unknown prior genotype
- Across all SLR-included studies that reported effectiveness data at any time point, this population showed high rates of VS (98%; 401/410) and low rates of VF (0.29%; 10/3499)
  - On-treatment INSTI RAMs were rare and detected in only 1 individual (0.03%; 1/3468) at Month 24 among SLR-identified studies that reported resistance outcomes
- Treatment with DTG + 3TC was well tolerated across studies, with no drug-related discontinuations reported
- Among 637 individuals across 5 real-world studies, none developed VF at Week 48 (random-effects model, 0.0000; 95% CI, 0.0000-0.0057)
- These findings are consistent with those from randomized clinical studies[3,4,14] and provide reassurance for using DTG + 3TC as a switch option if genotype is unknown

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