Treatment-Emergent Integrase Strand Transfer Inhibitor (INSTI) Resistance-Associated Mutations Among People With HIV-1 Treated With Dolutegravir (DTG) + Lamivudine (3TC) With Pre-existing M184V/I From Real-world and Interventional Studies

Dainielle Fox,[1] Gary Blick,[2] Thibault Mesplède,[3] Gustavo Verdier,[4] Mónica Calderón,[1] Chris M. Parry,[5] Richard Grove,[6] Emilio Letang,[7] Julie Priest,[1] Bryn Jones,[5] Leigh Lehane[8]*

[1]ViiV Healthcare, Durham, NC, USA; [2]Health Care Advocates International, Stratford, CT, USA; [3]Erasmus University Medical Center, Rotterdam, Netherlands; [4]ViiV Healthcare, Montréal, Québec, Canada; [5]ViiV Healthcare, London, UK; [6]GSK, London, UK; [7]ViiV Healthcare, Tres Cantos, Madrid, Spain; [8]GSK, Dublin, Ireland

**Presenting on behalf of the authors.*

Key Takeaways

- **A systematic literature review (SLR) identified 300 publications representing 47,350 unique people using dolutegravir (DTG) + lamivudine (3TC) in both real-world and interventional settings**
- **Treatment-emergent integrase strand transfer inhibitor (INSTI) resistance rarely (<0.05%) developed in people initiating or switching to DTG + 3TC**
- **No people with HIV-1 with known pre-existing M184V/I experienced treatment-emergent INSTI resistance development at virologic failure (VF)**
- **These data support the in vitro findings that indicate that M184V/I antagonizes the development of resistance against DTG**

Introduction

- DTG + 3TC has a high barrier to resistance and is recommended as first-line and maintenance antiretroviral therapy (ART) for people with HIV-1[1-3]
- In vitro, tissue cultures exposed to DTG monotherapy selected INSTI resistance (R263K) with wild-type virus but not with M184V/I-containing virus[4]
- Though the M184V/I resistance mutation confers high-level resistance to 3TC, data suggest that M184V/I presence does not increase the risk of developing INSTI resistance VF in people with HIV-1 using DTG + 3TC
  - Archived M184V/I detected in proviral DNA did not impact efficacy in people with virologic suppression switching to DTG/3TC in randomized phase 3 trials (TANGO, n=4; SALSA, n=5)[5,6]
  - People who switched to DTG + 3TC while virologically suppressed had low rates of VF and no cases of treatment-emergent INSTI resistance, regardless of historical or current M184V/I, in the VOLVER study at Week 48,[7] the SOLAR-3D study through Week 144,[8] and in a meta-analysis of 12 real-world and interventional studies[9]
- Outcomes data, especially real-world evidence (RWE), continue to emerge for people with M184V/I using DTG + 3TC
- To assess the latest evidence on the impact of M184V/I on treatment-emergent INSTI resistance, we present an updated SLR with studies reporting DTG + 3TC use through March 2024 and include populations naive to ART

Methods

Systematic Literature Review

- An SLR was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
  - Ovid MEDLINE®, Embase®, PubMed, Cochrane library databases, and relevant congresses were searched for RWE studies reporting DTG + 3TC use in people with HIV-1 published between January 2013 and March 2024, as described previously[9]
  - Phase 3/3b DTG + 3TC randomized controlled trials from ViiV Healthcare were added to the interventional study pool post hoc
- Any records excluded from RWE study screening for having an interventional study design were screened separately for analysis inclusion

Analysis

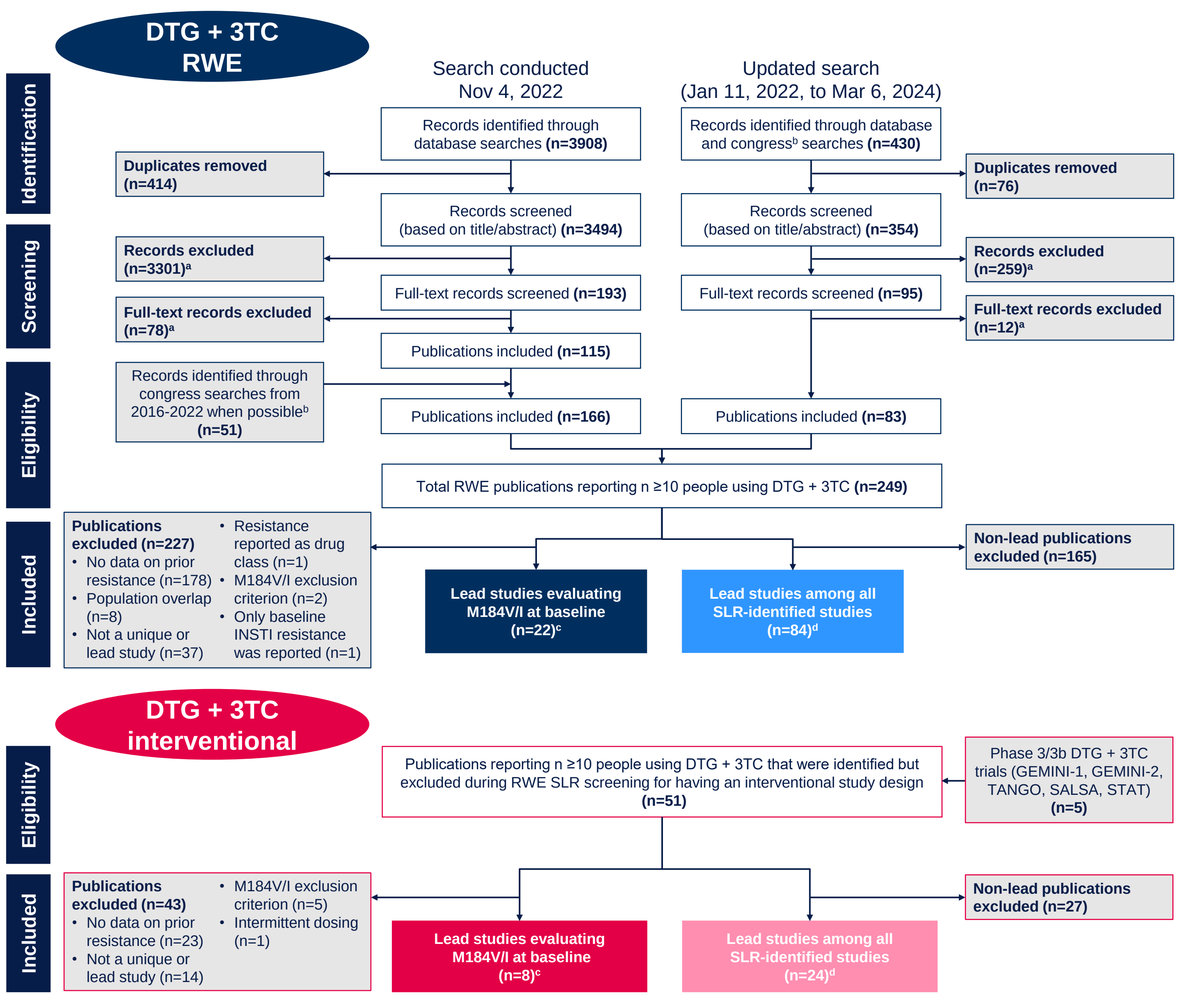
- Descriptive analyses were independently performed for 2 groups of SLR-identified studies with different screening criteria:
  - Studies evaluating M184V/I at baseline: included all publications with ≥10 people using DTG + 3TC that evaluated baseline M184V/I (even if 0 people with baseline M184V/I are reported)
    - Studies in which M184V/I was an exclusion criterion were excluded, apart from 2 interventional studies that reported archived resistance data[6,7]
    - For people naive to ART, baseline is the time of DTG + 3TC initiation; for people with prior ART use, baseline is the time of switch to DTG + 3TC
  - All studies: included all publications with ≥10 people using DTG + 3TC
- After screening, "lead" studies with the most data and/or highest n per cohort were identified and used to represent unique populations within each group and avoid double-counting people across multiple and/or overlapping publications or overlapping with another cohort
  - Lead studies among studies evaluating M184V/I at baseline may include non-lead studies from the group of all studies
- Analysis denominators use the total n of people using DTG + 3TC, not the total n of people with resistance tests performed

Results

Included Studies and Populations

- The SLR identified 300 publications (n=249 RWE, n=51 interventional) that reported ≥10 people with HIV-1 using DTG + 3TC
  - These studies represented 108 discrete cohorts and trials and 47,350 unique people with HIV-1 after accounting for population overlap
- The number of lead studies included for each analysis group is summarized in the Table
  - 30 lead studies (N=10,383) were included in the analysis group of studies evaluating M184V/I at baseline (n=1049 naive to ART; n=9318 prior ART use; n=16 not specified)
- 108 lead studies (N=47,350) were included in the analysis group of all studies, regardless of whether M184V/I was evaluated at baseline (n=3404 naive to ART; n=21,912 prior ART use; n=22,034 not specified)

Figure 1. PRISMA Flowchart



[a]Publications excluded due to interventional study design were screened separately for inclusion in the analysis. [b]Searched congresses included the Asian Conference on Hepatitis and AIDS; Australasian HIV & AIDS Conference; British Association for Sexual Health and HIV; British HIV Association; Canadian Conference on HIV/AIDS Research; Conference on Retroviruses and Opportunistic Infections; European AIDS Clinical Society; Grupo de Estudio del SIDA-SEIMC; HIV & Hepatitis in the Americas; HIV Glasgow; IDWeek; International AIDS Society/International AIDS Conference; International Conference on AIDS and Sexually Transmitted Infections in Africa; International Conference on Antiviral Research; International Congress on Infectious Diseases; International Francophone Conference on HIV/Hepatitis/Sexual Health/Emerging Infections (AFRAVIH; searched May 24, 2022); Japanese Society for AIDS Research; Kenya Association of Physicians; National Conference of AIDS Society of India; Société Française de Lutte contre le Sida; and The HIV Netherlands Australia Thailand Research Collaboration. [c]Includes studies that report any number of individuals with M184V/I at baseline, even n=0, and excludes studies with M184V/I as an exclusion criterion. [d]Includes all studies regardless of whether M184V/I at baseline is evaluated (ie, includes studies with M184V/I presence as an exclusion criterion and where M184V/I may be present but not reported).

Prevalence of Baseline M184V/I

- Overall prevalence of M184V/I at baseline was 5% (512/10,383) among studies evaluating M184V/I at baseline and 0.9% (406/47,350) among all studies (Table)
  - 4 of the cohorts that were included in both analysis groups were each represented by a different lead study between analysis groups, due to differences in screening criteria
    - Thus, the analysis of all studies has a higher total n than the analysis of studies evaluating M184V/I at baseline, which provides a higher estimate of people with baseline M184V/I
- Prevalence of M184V/I reported by interventional studies was 20% (219/1096) and 8% (221/2914) among studies evaluating M184V/I at baseline and among all studies, respectively (Table)
  - Several of these interventional studies focus on M184V/I and thus overestimate its prevalence

Table. Summary of SLR-Identified Publications Reporting People Using DTG + 3TC by Study Type

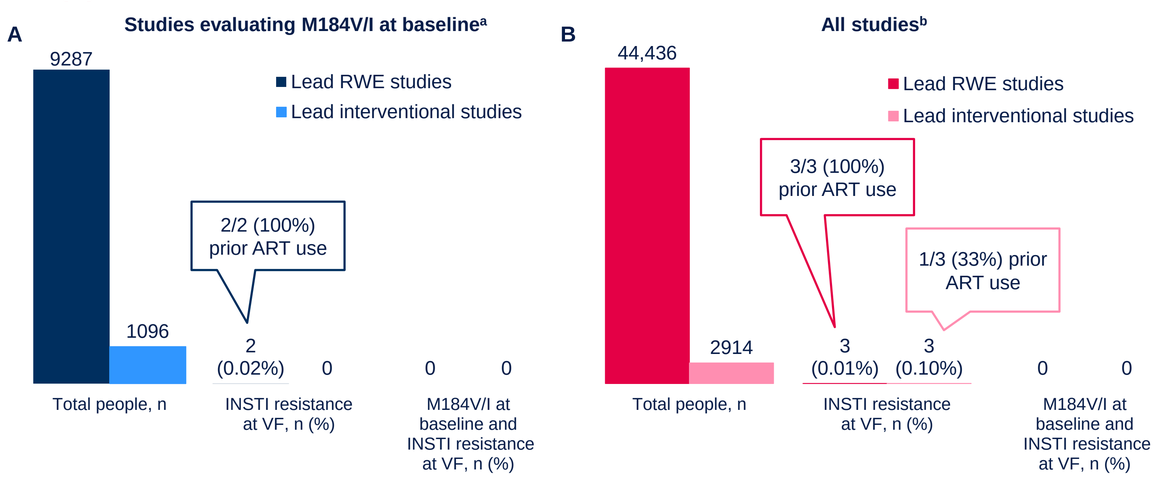
	Lead[a] RWE studies	Lead[a] interventional studies	Total
Studies evaluating M184V/I at baseline[b]			
Studies, n	22	8	30
People using DTG + 3TC, n	9287	1096	10,383
People with baseline M184V/I, n (%)	293 (3)[c]	219 (20)	512 (5)
RNA or unspecified	165 (2)[c]	201 (18)	366 (4)
Proviral DNA	128 (1)[d]	18 (2)	146 (1)
All studies[e]			
Studies, n	84	24	108
People using DTG + 3TC, n	44,436	2914	47,350
People with baseline M184V/I, n (%)	185 (0.4)[c]	221 (8)	406 (0.9)
RNA or unspecified	162 (0.4)[c]	202 (7)	364 (0.8)
Proviral DNA	23 (0.05)[d]	19 (0.7)	42 (0.1)

[a]The publication with the largest n for each RWE cohort or interventional trial was selected to represent that cohort/trial, to account for potentially overlapping populations. Lead studies for each analysis group were selected after all SLR-identified publications were screened for inclusion. [b]Includes studies that report any number of individuals with M184V/I at baseline, even n=0, and excludes studies with M184V/I as an exclusion criterion. [c]1 study[10] reported that n=60 people overall had historical M184V/I (DTG + 3TC, n=174; DTG + RPV, n=46) and at least n=1 person using DTG + RPV did not have historical M184V/I; therefore, at least n=15 people using DTG + 3TC had historical M184V/I. [d]n=2 confirmed through personal communications. [e]Includes all studies regardless of whether M184V/I at baseline is evaluated (ie, includes studies with M184V/I presence as an exclusion criterion and where M184V/I may be present but not reported).

Treatment-Emergent INSTI Resistance

- Figure 2 summarizes INSTI resistance detected at VF in each group of studies:
  - 2/10,383 (0.02%) people (n=512 with known pre-existing M184V/I) among studies evaluating M184V/I at baseline
  - 6/47,350 (0.01%) people (n=406 with known pre-existing M184V/I) among all studies
- None of the people who developed treatment-emergent INSTI resistance had known pre-existing M184V/I

Figure 2. Treatment-Emergent INSTI Resistance Reported at VF With DTG + 3TC Across Populations From Lead RWE or Lead Interventional Studies (A) Evaluating M184V/I at Baseline and (B) Overall



[a]Includes studies that report any number of individuals with M184V/I at baseline, even n=0, and excludes studies with M184V/I as an exclusion criterion. [b]Includes all studies regardless of whether M184V/I at baseline is evaluated (ie, includes studies with M184V/I presence as an exclusion criterion and where M184V/I may be present but not reported).

Conclusions

- No people with HIV-1 with known pre-existing M184V/I experienced treatment-emergent INSTI resistance development at VF
  - One potential explanation for these findings is that M184V/I may have a protective effect against the development of INSTI resistance with DTG + 3TC, as was previously reported for in vitro tissue culture studies[4]
  - Overall rates of VF were very low across all types of studies included in this analysis
- This SLR further supports the growing body of evidence showing that use of DTG + 3TC in the presence of M184V/I does not increase the risk of INSTI mutations developing at VF
  - This provides reassurance for considering DTG/3TC as a first-line or switch option if resistance test results or complete treatment histories are unavailable, or in cases where M184V/I is inadvertently missed

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Presenting author: Leigh Lehane; leigh.a.lehane@gsk.com