Effectiveness of Dolutegravir + Lamivudine in Real-world Studies in People With HIV-1 With M184V/I Mutations: A Systematic Review and Meta-analysis

P015

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Key Takeaways

- **Using real-world data from people with HIV-1 (PWH), a systematic literature review and a meta-analysis were performed to investigate the impact of historical or archived M184V/I on the effectiveness of dolutegravir + lamivudine (DTG + 3TC) in real-world switch populations; a sensitivity analysis was performed using data from interventional trials identified via a targeted literature review**
- **Virologic failure (VF) incidence was low, and no treatment-emergent INSTI resistance mutations were reported in populations with M184V/I that switched to DTG + 3TC, providing reassurance that M184V/I may have a limited impact on the efficacy of DTG + 3TC in PWH considering treatment change when drug resistance-associated mutations (RAMs) are unknown or inadvertently missed**

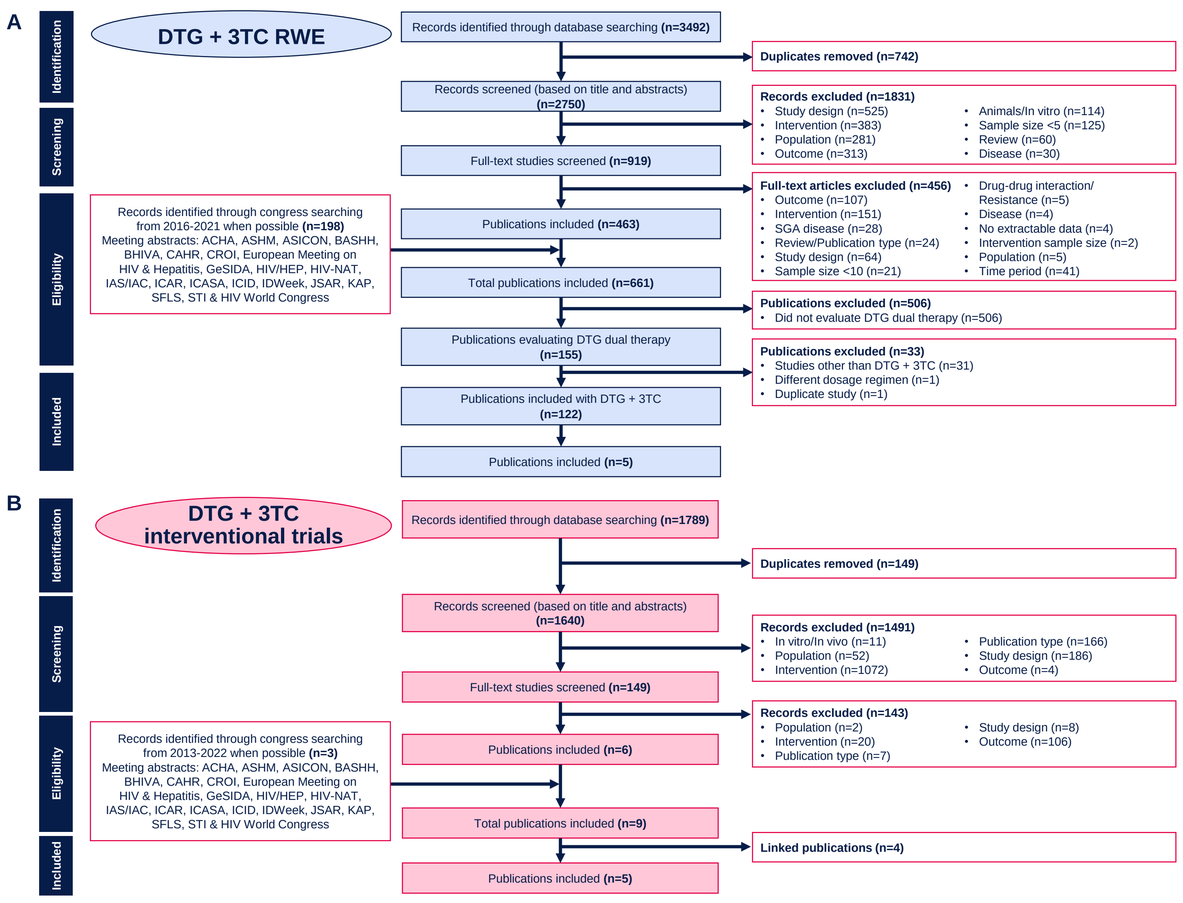
Introduction

- M184V/I is the most common RAM selected by 3TC[1]
- Clinical development phase 3 interventional trials excluded participants with known or suspected RAMs
  - The presence of archived M184V/I mutations in phase 3 trials evaluating switch to DTG/3TC (TANGO, n=4; SALSA, n=5)[2,3] did not impact virologic efficacy
  - Absence of historical resistance results or availability of prior genotype (pooled TANGO/SALSA analysis, n=294) also had no impact on results[4]
- In clinical practice, prior history of resistance is not always available when considering treatment options
- Real-world evidence (RWE) can help address the knowledge gap of whether switching to DTG + 3TC is safe in real-world clinical practice when full treatment history or historical genotype results are not available
- This meta-analysis describes VF at Weeks 24, 48, and 96 using real-world data from PWH receiving DTG + 3TC in a suppressed-switch setting, with historical RNA- or archived proviral DNA-detected M184V/I mutation
  - A sensitivity analysis was performed using interventional trial data

Methods

- A systematic literature review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1A)
  - Embase®, Ovid MEDLINE®, MEDLINE® In-Process, and Cochrane library (January 2013-March 2022) and relevant conference archives (2016-2021) were searched for real-world studies reporting virologic outcomes for PWH receiving DTG + 3TC
- A targeted literature review was performed to identify interventional trials assessing M184V/I impact on DTG + 3TC efficacy (Figure 1B)
- Studies were screened for suppressed-switch populations reporting M184V/I mutations before DTG + 3TC initiation
- For the primary objective, common- and random-effects model analyses were conducted using RWE studies
  - Random-effects models provide estimates that are more generalizable to the overall population of interest
  - Common-effects (or fixed-effects) models assume that the included studies are the population of interest and are more informative when zero VF events are observed
- For the secondary objective, sensitivity analyses were performed using interventional trial data
- In both RWE and interventional trial data sets, base analyses were performed using studies with identical VF definitions; sensitivity analyses were performed using all studies regardless of VF definition to maximize sample size

Figure 1. PRISMA Flow Charts for (A) RWE Studies and (B) Interventional Trials



Results

VF Outcomes in RWE Studies and Interventional Trials

- Of 3492 publications and 198 conference abstracts identified via systematic literature review, 5 real-world studies met all search criteria and were analyzed (Table)
  - The targeted literature review also identified 5 relevant interventional trials
- Proportions of PWH with historical M184V/I estimated to have VF at Weeks 24, 48, and 96 were low in real-world and interventional trial analyses based on reported VF outcomes at each time point
  - Real-world: 3/186 (1.61%), 7/237 (2.95%), and 7/186 (3.76%), respectively
  - Interventional trial: 0/42 (0%), 0/97 (0%), and 0/38 (0%), respectively
- No treatment-emergent resistance mutations were reported
- Including all studies regardless of VF definition increased sample sizes without significantly impacting estimates

Table. Summary of VF Definitions and Outcomes for PWH With M184V/I RAMs Receiving DTG + 3TC in Real-world Studies and Interventional Trials

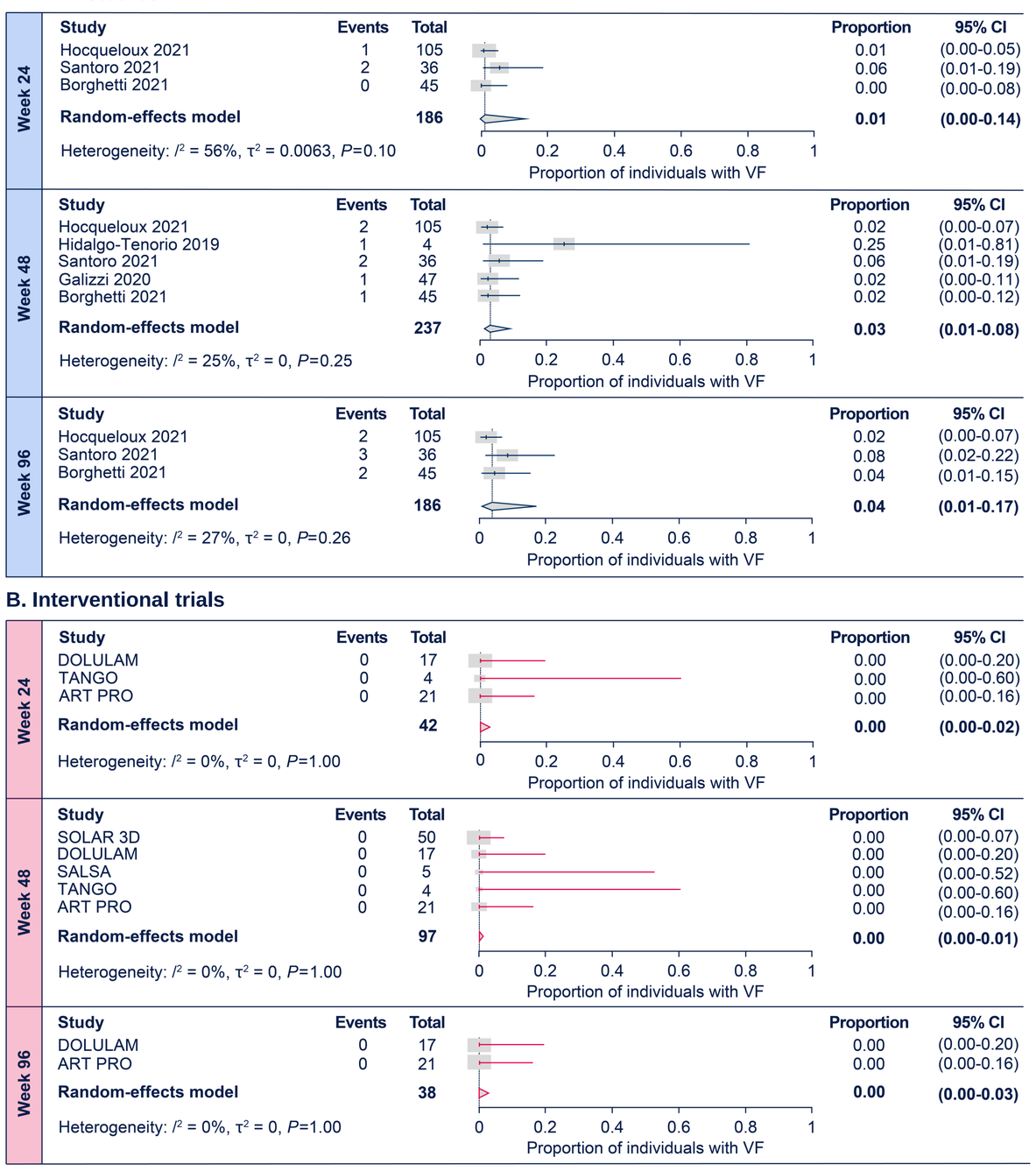
Study (cohort)	PWH with pre-switch M184V/I, n/N (%)	M184V/I identification method	VF time point, week	VF outcomes, n/N (%)	VF definition
Real-world studies					
Hocqueloux 2021 (Dat'AIDS)[5]	105/695 (15.11)	RNA and proviral DNA genotypes (pooling both)	24 48 96	1/105 (0.95) 2/105 (1.90) 2/105 (1.90)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
Santoro 2021 (LAMRES)[6]	36/533 (6.75)	RNA and proviral DNA genotypes	24 48 96	2/36 (5.56) 2/36 (5.56) 3/36 (8.33)	2 consecutive confirmed VL >50 c/mL or 1 VL ≥200 c/mL
Borghetti 2021 (ODOACRE)[7,8]	48/669 (7.17)[a]	Historical genotypes; does not specify RNA or proviral DNA	24 48 96	0/45 1/45 (2.22) 2/45 (4.44)	2 consecutive VL ≥50 c/mL or 1 VL ≥200 c/mL
Galizzi 2020 (NR)[9]	47/174 (27.01)[b]	Either RNA or proviral DNA genotypes at baseline (before switch)	24 48 96	— 1/47 (2.13) —	2 consecutive confirmed VL >50 c/mL or 1 VL >50 c/mL followed by ART modification or 1 VL >1000 c/mL
Hidalgo-Tenorio 2019 (DOLAMA)[10]	4/178 (2.25)	Baseline RNA genotype	24 48 96	— 1/4 (25.00) —	2 consecutive VL >50 c/mL
Interventional trials					
ART PRO[11]	21/41 (51.22)[c]	Historical DNA genotype	24 48 96	0/21[d] 0/21 0/21	VL ≥50 c/mL
SOLAR 3D[12]	50/100 (50.00)	Historical genotypes; does not specify RNA or proviral DNA	24 48 96	— 0/50 —	VL ≥50 c/mL followed by consecutive VL >200 c/mL
TANGO[2]	4/322 (1.24)	Proviral DNA genotype	24 48 96	0/4[e] 0/4[e] —	VL ≥50 c/mL followed by consecutive VL ≥200 c/mL
DOLULAM[13]	17/27 (62.96)	RNA and proviral DNA genotypes	24 48 96	0/17 0/17 0/17	VL >50 c/mL
SALSA[3]	5/192 (2.60)	Proviral DNA genotype	24 48 96	— 0/5 —	VL ≥40 c/mL

NR, not reported; RAM, resistance-associated mutation; VF, virologic failure; VL, viral load.
[a]Cohort reference reporting the proportion with VF for individuals with M184V/I was used for analysis (n=45 individuals with M184V/I).[8] [b]Assumption: n=60 PWH with M184V/I were reported out of N=220 total PWH with available pre-switch genotype resistance data across 2 groups but not reported for DTG + 3TC specifically. Table n with M184V/I was calculated according to the proportion of PWH in the DTG + 3TC (n=174) vs other group (n=46). [c]Of the 20 PWH without known M184V/I at baseline, next-generation sequencing identified n=7, n=3, and n=1 with M184I at 1%, 5%, and 20% thresholds, respectively. [d]Refers to the number of PWH with historical 3TC resistance (M184V/I and/or K65R/E/N); 3 PWH with historical 3TC resistance discontinued before Week 24 but had VL <50 c/mL at time of discontinuation (2 protocol violations and 1 adverse event–related discontinuation). [e]Assumption: Week 24 was not reported, but reports described no VF to Week 48.

VF Estimates

- Random-effects models are associated with greater uncertainty vs common-effects models but can be used to estimate results for the wider population of interest based on the sample of studies used in the analysis
- Common-effects (or fixed-effects) models assume that the included studies are the population of interest and can be more appropriate and informative when zero VF events are observed
  - RWE common-effects models estimated the proportions (95% CI) of individuals with VF were 0.01 (0.00-0.03) at Week 24, 0.03 (0.01-0.06) at Week 48, and 0.04 (0.02-0.08) at Week 96; random-effects estimates are in Figure 2A
  - Interventional trial common-effects models estimated the proportions (95% CI) of individuals with VF were 0.00 (0.00-0.02) at Week 24, 0.00 (0.00-0.01) at Week 48, and 0.00 (0.00-0.03) at Week 96; random-effects estimates are in Figure 2B

Figure 2. Meta-analysis Estimates of Proportions of VF at Weeks 24, 48, and 96 in PWH With Reported M184V/I Receiving DTG + 3TC From (A) Systematic Literature Review–Identified RWE Studies and (B) Targeted Literature Review–Identified Interventional Trials, Inclusive of All VF Definitions



Proportions were log-transformed, or arcsine-transformed if any studies reported zero events.

Conclusions

- Overall, pre-switch M184V/I prevalence was low in PWH in RWE studies
- Real-world studies of PWH with historical or archived M184V/I receiving DTG + 3TC identified low incidence of VF through 96 weeks and no reported cases of INSTI treatment-emergent mutations; these findings were consistent with results from interventional trials
  - Genotypic data at the time of VF were not always available, and although INSTI resistance was not documented in any of the studies, the occurrence of resistance mutations to 3TC or DTG at failure could not be fully described
- This meta-analysis provides reassuring data on outcomes with DTG + 3TC in PWH with incomplete history or in cases where M184V/I was inadvertently missed

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