

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

Madhusudan Kabra,¹ Tristan J. Barber,^{2,3} Clotilde Allavena,⁴ Anne-Geneviève Marcelin,⁵ Simona Di Giambenedetto,⁶ Juan Pasquau,⁷ Nicola Gianotti,⁸ Matthew Turner,⁹ Cale Harrison,⁹ Tammy Wynne,⁹ Gustavo Verdier,¹⁰ Chris Parry,¹ Bryn Jones,¹ Chinyere Okoli,¹ Julie Priest,¹¹ Emilio Letang¹²

¹ViiV Healthcare, Brentford, UK; ²Ian Charleson Day Centre, Royal Free London NHS Foundation Trust, London, UK; ³Institute for Global Health, University College London, London, UK; ⁴CHU Hôtel-Dieu, Nantes, France; ⁵Hôpital Pitié-Salpêtrière, Paris, France; ⁶Fondazione Policlinico Universitario Agostino Gemelli IRCCS and Università Cattolica del Sacro Cuore, Rome, Italy; ⁷Virgen de las Nieves University Hospital, Granada, Spain; ⁸IRCCS Ospedale San Raffaele, Milan, Italy; ⁹HEOR Ltd, Cardiff, UK; ¹⁰ViiV Healthcare, Montréal, QC, Canada; ¹¹ViiV Healthcare, Durham, NC, USA; ¹²ViiV Healthcare, Madrid, Spain



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 randomized controlled trials (RCTs) 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 3TC¹
- Clinical development phase 3 RCTs 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 results⁴
- 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 RCT 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 RCTs 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 RCT data
- In both RWE and RCT 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

Results

VF Outcomes in RWE Studies and RCTs

- 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 RCTs
- Proportions of PWH with historical M184V/I estimated to have VF at Weeks 24, 48, and 96 were low in real-world and RCT 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
 - RCT: 0/38 (0%), 2/93 (2.15%), and 0/34 (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 RWE Studies and RCTs

Study (cohort)	Proportion with pre-switch M184V/I	M184V/I identification method	VF time point, week	VF outcomes, n/N (%)	VF definition
RWE studies					
Hocqueloux 2021 (Dat'AIDS) ⁵	105/695 (15.11%)	RNA and proviral DNA genotypes (pooling both)	24	1/105 (0.95)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
			48	2/105 (1.90)	
			96	2/105 (1.90)	
Santoro 2021 (LAMRES) ⁶	36/533 (6.75%)	RNA and proviral DNA genotypes	24	2/36 (5.56)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
			48	2/36 (5.56)	
			96	3/36 (8.33)	
Borghetti 2021 (ODOACRE) ^{7,8}	48/669 (7.17%) ^a	Historical genotypes; does not specify RNA or proviral DNA	24	0/45	1 VL ≥1000 c/mL or 2 consecutive VL ≥50 c/mL
			48	1/45 (2.22)	
			96	2/45 (4.44)	
Galizzi 2020 (NR) ⁹	47/174 (27.01%) ^b	Either RNA or proviral DNA genotypes at baseline (before switch)	24	—	2 consecutive confirmed VL >50 c/mL or 1 VL >50 c/mL followed by ART modification or 1 VL >1000 c/mL
			48	1/47 (2.13)	
			96	—	
Hidalgo-Tenorio 2019 (DOLAMA) ¹⁰	4/178 (2.25%)	Baseline RNA genotype	24	—	2 consecutive VL >50 c/mL
			48	1/4 (25.00)	
			96	—	
RCTs					
ART PRO ¹¹	17/41 (41.46%)	Proviral DNA genotype	24	0/17	VL ≥50 c/mL
			48	0/17	
			96	0/17	
SOLAR 3D ¹²	50/100 (50.00%)	Historical genotypes; does not specify RNA or proviral DNA	24	—	VL ≥50 c/mL
			48	1/50 (2.00)	
			96	—	
TANGO ²	4/322 (1.24%)	Proviral DNA genotype	24	0/4 ^c	VL ≥50 c/mL
			48	0/4	
			96	—	
DOLULAM ¹³	17/27 (62.96%)	RNA and proviral DNA genotypes	24	0/17	VL >50 c/mL
			48	0/17	
			96	0/17	
SALSA ³	5/192 (2.60%)	Proviral DNA genotype	24	—	VL ≥40 c/mL
			48	1/5 (20.00) ^d	
			96	—	

NR, not reported. ^aCohort reference reporting the proportion with VF for individuals with M184V/I was used for analysis (n=45 individuals with M184V/I). ^bAssumption: 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). ^cAssumption: Week 24 was not reported, but reports described no VF to Week 48. ^dAssumption: VFs and discontinuations were not directly reported; study reported n (%) with VL <40 c/mL and TND, and here VF is assumed to be VL ≥40 c/mL.

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
 - RCT common-effects models estimated the proportions (95% CI) of individuals with VF were 0.01 (0.00-0.05) at Week 48 and 0.00 (0.00-0.03) at Week 96; random-effects estimates for these time points are in Figure 2B
 - Common-effects models better represented Week 24 data consisting of zero observed events (Figure 2B); random-effects models estimated Week 24 proportions (95% CI) were 0.00 (0.00-0.00)

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

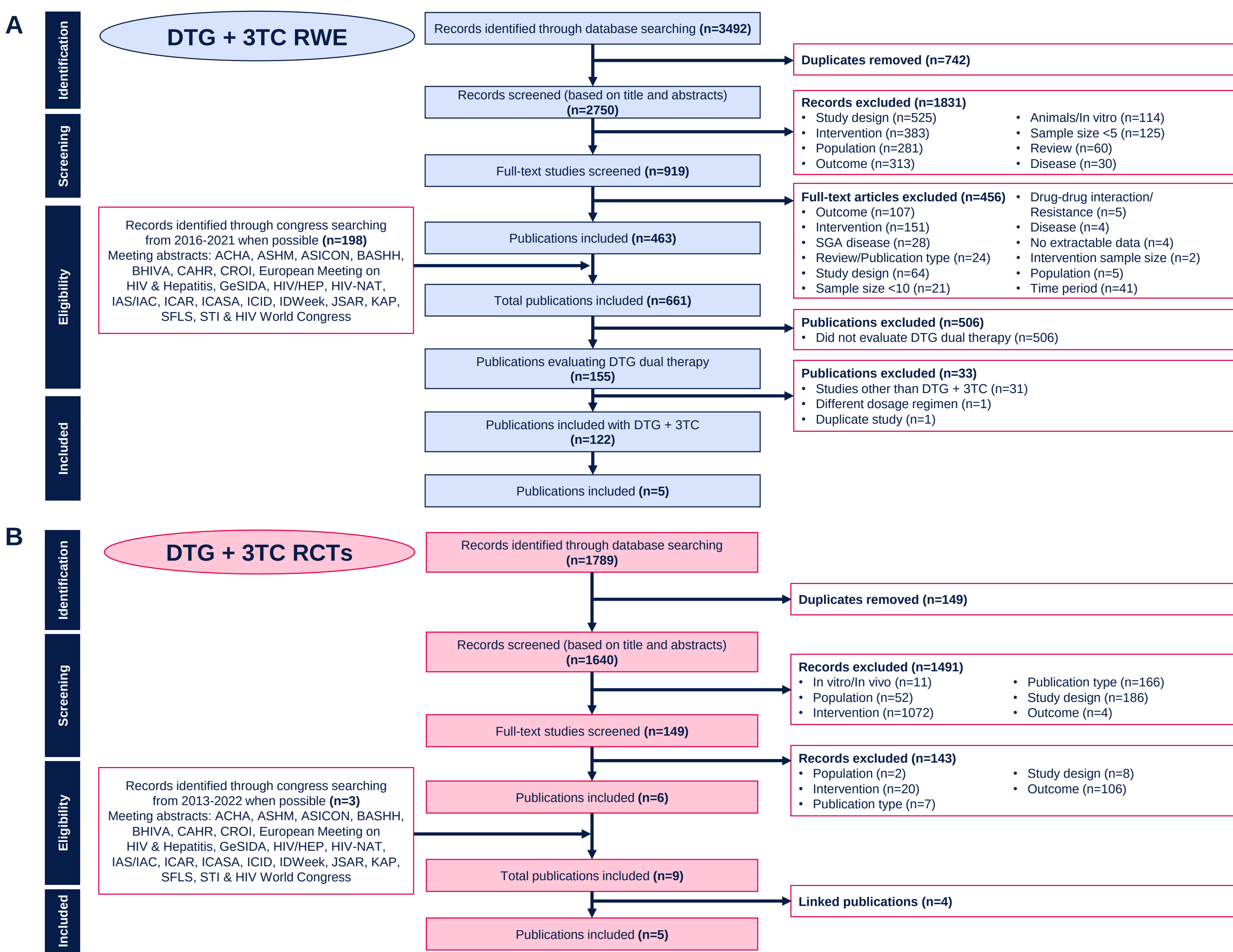
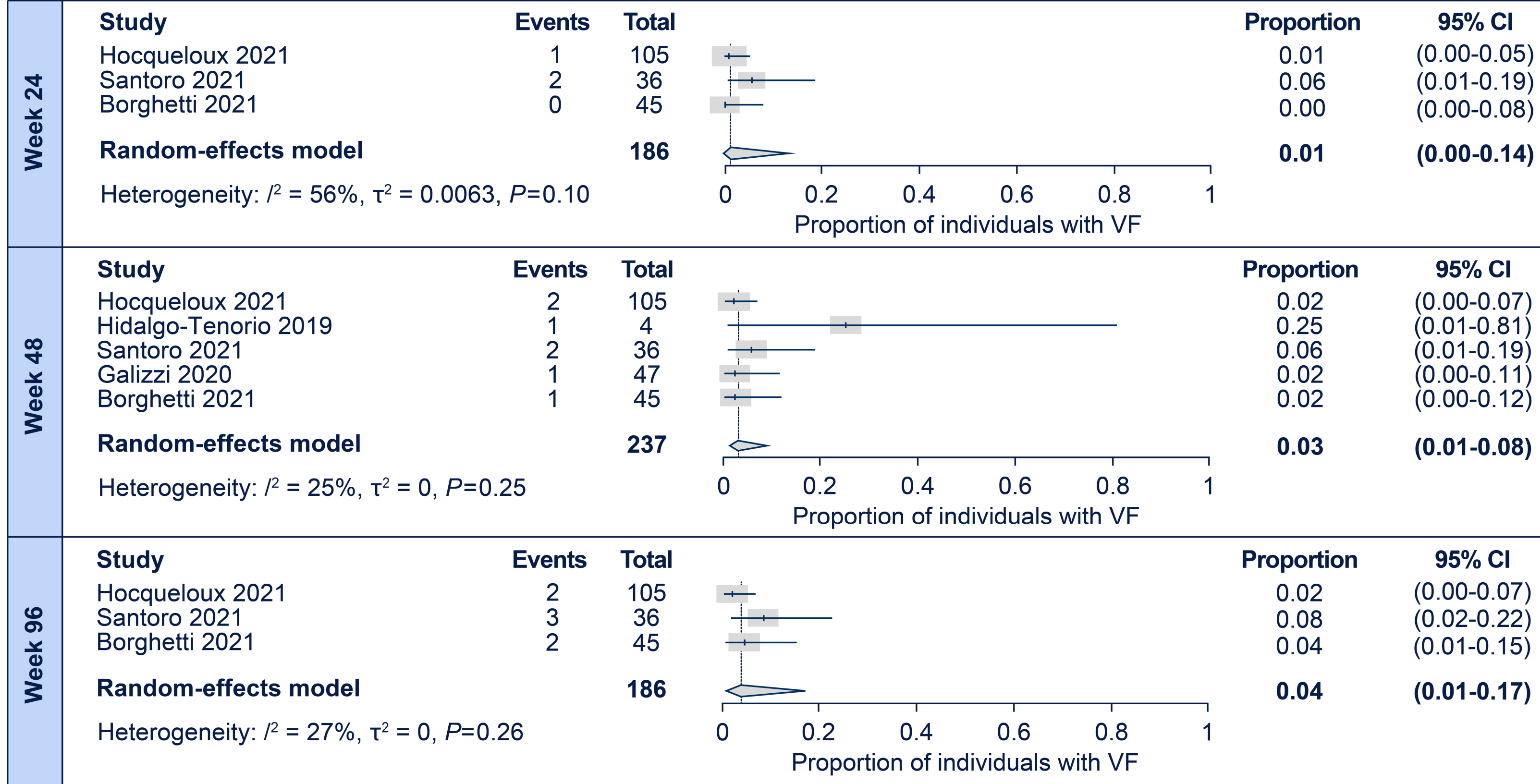
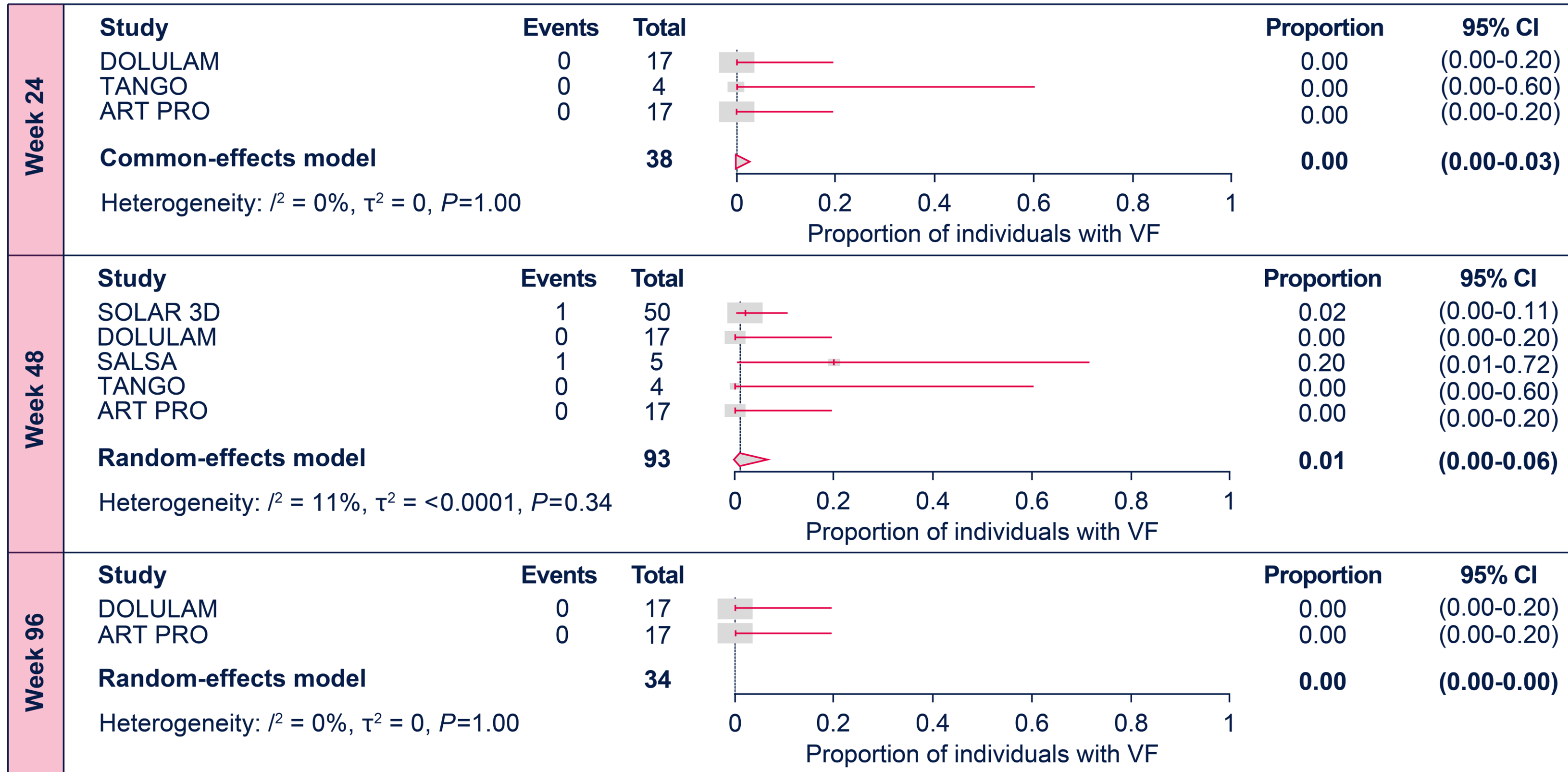


Figure 2. Meta-analysis Estimates of Proportions of VF at Weeks 24, 48, and 96 in PWH With Reported M184V/I Receiving DTG + 3TC From (A) Systematic Literature Review-Identified RWE Studies and (B) Targeted Literature Review-Identified RCTs, Inclusive of All VF Definitions

A. RWE studies



B. RCTs



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 RCTs
 - Genotypic data at the time of VF were unavailable and the occurrence of resistance mutations to 3TC or DTG at failure could not be 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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