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

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Background and Objectives

- In phase 3 trials TANGO and SALSA evaluating a switch to dolutegravir and lamivudine in virologically-suppressed PLWH without prior VF and no 3TC or INSTI mutations, neither the availability of a historical genotype nor the presence of the lamivudine-selected M184V/I mutation in proviral DNA did impact treatment efficacy
- Real-world evidence can help address the knowledge gap of whether switching to dolutegravir plus lamivudine is safe when treatment history or historical genotype results are not available
- **Objectives:**
  - To investigate the impact of historical RNA- or archived proviral DNA-detected M184V/I on the effectiveness of DTG + 3TC in real-world suppressed-switch populations via systematic literature review and meta-analysis
  - To conduct a sensitivity analysis using data from intervention studies identified via targeted literature review

Methodology

- A systematic literature review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines
  - 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 people with HIV (PWH) receiving DTG + 3TC
- A targeted literature review was performed to identify intervention studies assessing the M184V/I impact on DTG + 3TC efficacy
- Studies were screened for suppressed-switch populations reporting M184V/I mutations before DTG + 3TC initiation
- For the primary and secondary objectives, common- and random-effects model analyses were conducted using real-world evidence (RWE) and intervention studies respectively
  - 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
- In both RWE and intervention studies data sets, base analyses were performed using studies with identical virologic failure (VF) definitions; sensitivity analyses were performed using all studies regardless of VF definition to maximize sample size

Virologic Failure Definitions and Outcomes for PWH With M184V/I Receiving DTG + 3TC 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**
  - The targeted literature review also identified **5 relevant intervention studies**
- Reported **VF outcomes** were low in PWH with historical or archived M184V/I at Weeks 24, 48, and 96
  - **Real-world:** 3/186 (1.61%), 7/237 (2.95%), and 7/186 (3.76%), respectively
  - **Intervention studies:** 0/38 (0%), 2/93 (2.15%), and 0/34 (0%), respectively
- No treatment-emergent resistance mutations were reported

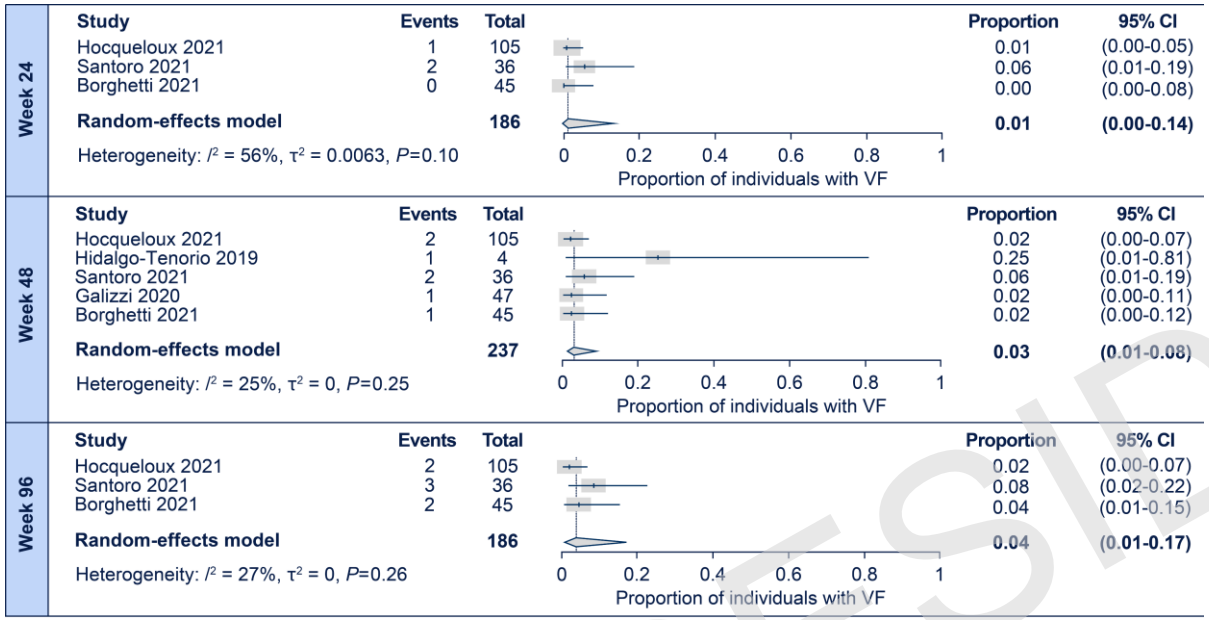
	Study (cohort)	Proportion with pre-switch M184V/I	M184V/I identification method	VF time point, week	VF outcomes, n/N (%)	VF definition
RWE studies	Hocqueloux 2021 (Dat'AIDS)[1]	105/695 (15.11%)	RNA and proviral DNA genotypes (pooling both)	24 48 96	1/105 (0.95) 2/105 (1.90) 2/105 (1.90)	2 consecutive confirmed VL >50 c/mL or 1 VL >200 c/mL
	Santoro 2021 (LAMRES)[2]	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)[3,4]	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)	1 VL ≥1000 c/mL or 2 consecutive VL ≥50 c/mL
	Galizzi 2020 (NR)[5]	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)[6]	4/178 (2.25%)	Baseline RNA genotype	24 48 96	— 1/4 (25.00) —	2 consecutive VL >50 c/mL
Intervention studies	ART PRO[7]	21/41 (51.21%) 17/41 (41.46%)	Historical RNA for 3TC resistance, M184V/I and K65R (baseline proviral DNA NGS M184V/I >5%)	24 48 96	0/21 (0/17) 0/21 (0/17) 0/21 (0/17)	VL ≥50 c/mL
	SOLAR 3D[8]	50/100 (50.00%)	Historical genotypes; does not specify RNA or proviral DNA	24 48 96	— 1/50 (2.00) —	VL ≥50 c/mL
	TANGO[9]	4/322 (1.24%)	Proviral DNA genotype	24 48 96	0/4[c] 0/4 —	VL ≥50 c/mL
	DOLULAM[10]	17/27 (62.96%)	RNA and proviral DNA genotypes	24 48 96	0/17 0/17 0/17	VL >50 c/mL
	SALSA[11]	5/192 (2.60%)	Proviral DNA genotype	24 48 96	— 1/5 (20.00)[d] —	VL ≥40 c/mL

NR, not reported; 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).[4] [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]Assumption: Week 24 was not reported, but reports described no VF to Week 48. [d]VFs and discontinuations were not directly reported; study reported n (%) with VL <40 c/mL and target not detected (TND), and here the participant had VL <40 c/mL with qualitative target detected (TD) outcome.

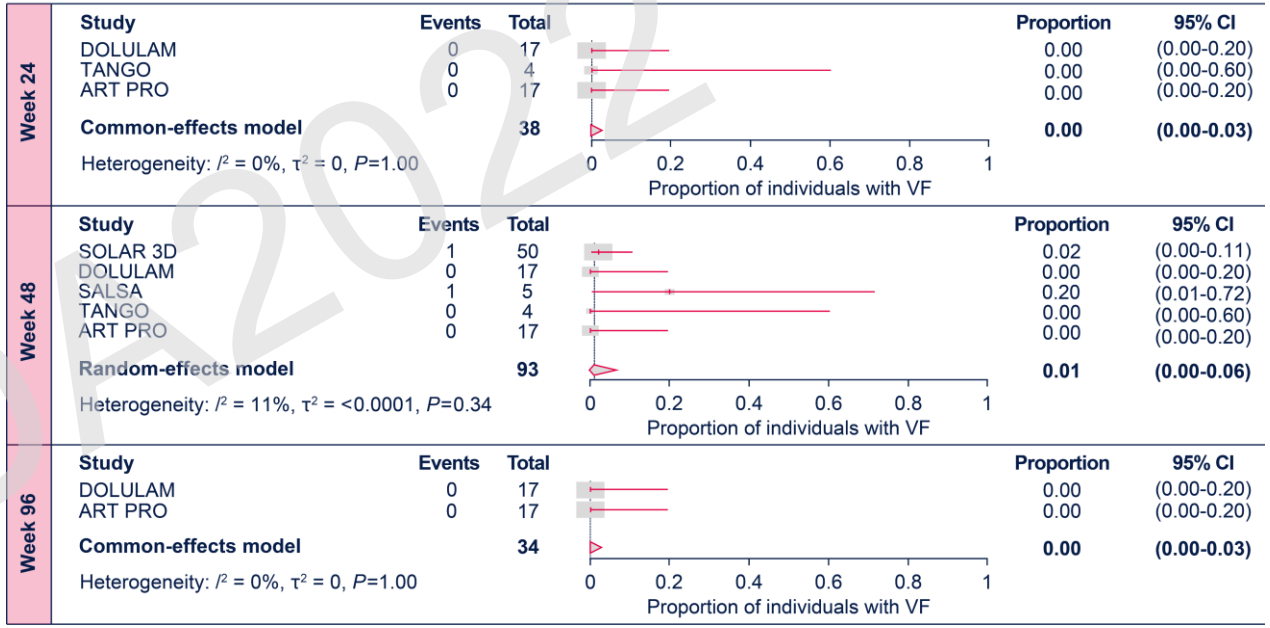
1. Hocqueloux et al. EACS 2021; Virtual and London, UK. Slides OS1/2. **2.** Santoro et al. CROI 2021; Virtual. Poster 429. **3.** Borghetti et al. *Open Forum Infect Dis*. 2021;8:ofab103. **4.** Baldin et al. *Int J Antimicrob Agents*. 2019;54:728-734. **5.** Galizzi et al. *Int J Antimicrob Agents*. 2020;55:105893. **6.** Hidalgo-Tenorio et al. *Medicine (Baltimore)*. 2019;98:e16813. **7.** Rial-Crestelo et al. *J Antimicrob Chemother*. 2021;76:738-742. **8.** Blick et al. EACS 2021; Virtual and London, UK. Poster PE2/65. **9.** van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929. **10.** Reynes et al. IAS 2017; Paris, France. Poster MOPEB0322. **11.** Underwood et al. CROI 2022; Virtual. Poster 481.

Meta-analysis Estimates of Proportions of VF in PWH With Reported M184V/I Receiving DTG + 3TC, Inclusive of All VF Definitions

Systematic Literature Review–Identified RWE Studies



Targeted Literature Review–Identified Intervention Studies



- Including all studies regardless of VF definition increased sample sizes without significantly impacting estimates
- **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
- **Intervention studies common-effects models** estimated the proportions (95% CI) of individuals with VF were 0.01 (0.00-0.05) at Week 48
  - Common-effects models better represented Week 24 and Week 96 data consisting of zero observed events each; random-effects models estimated Week 24 and Week 96 proportions (95% CI) were 0.00 (0.00-0.00)

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 RWE findings were consistent with results from available intervention studies assessing the impact of M184V/I on efficacy
- DTG/3TC should not be prescribed in the presence of a known M184V/I mutation, but this meta-analysis provides reassuring data on outcomes in PWH with incomplete history or in cases where M184V/I was inadvertently missed

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