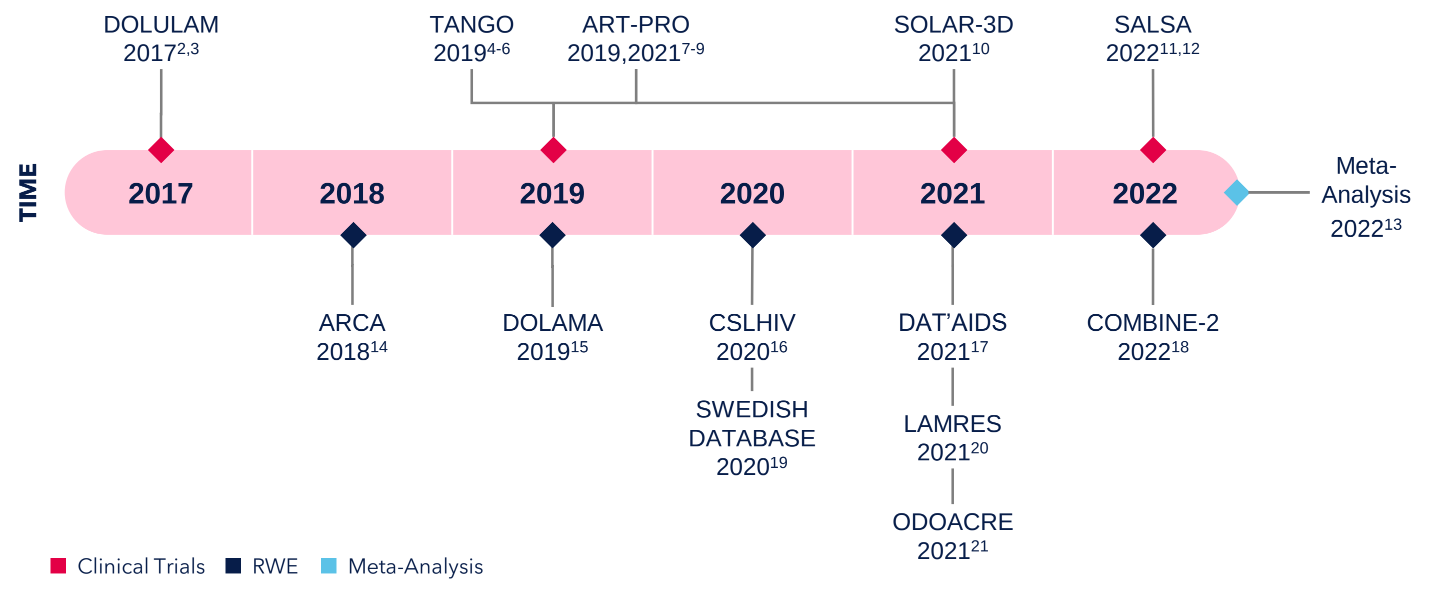
Use of *Dovato* in Patients With the M184V/I Resistance Mutation

Dovato (dolutegravir/lamivudine [DTG/3TC]) is not recommended for use in patients with current or past history of resistance to any components of DTG or 3TC.[1] Data specific to the use of *Dovato* in patients with the M184V/I resistance mutation are limited.

Summary of Data From Treatment Experienced Patients With M184V/I Receiving DTG + 3TC



In the TANGO and SALSA trials, 9 treatment-experienced participants with the M184V/I mutation (based on proviral DNA analysis) received DTG/3TC. All 9 patients maintained virological suppression (HIV-1 RNA < 50 copies/mL) at Week 48 (including Weeks 96 and 144 for TANGO).[4-6,11,12]

Prospective Study: TANGO[4-6]

TANGO is a phase 3, non-inferiority trial evaluating the efficacy and safety of a switch to DTG/3TC in HIV-1-infected adults with virologic suppression (HIV-1 RNA < 50 copies/mL) on a 3-drug TAF-based regimen.

Patients, n (%)	DTG/3TC (N = 318)[a]	TAF-based regimen (N = 308)[a]
Archived M184V/I at Baseline	4 (1)	3 (1)
HIV-1 RNA < 50 copies/mL at Week 48[b]	*4 (100)*	*3 (100)*
HIV-1 RNA ≥ 50 copies/mL at Week 48[b]	*0*	*0*

SALSA[11,12]

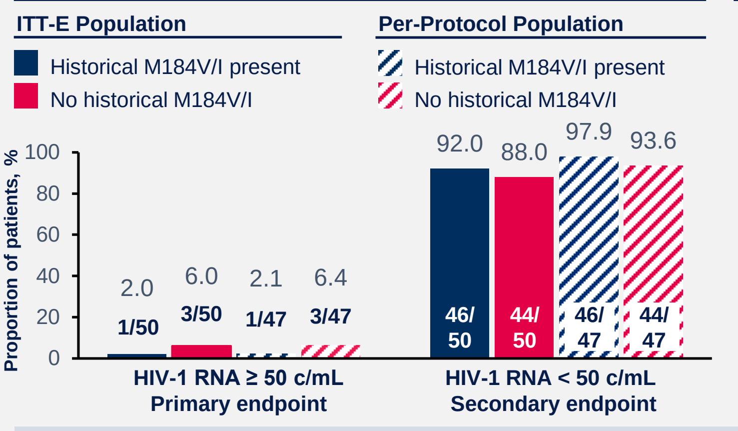
SALSA is a phase 3, non-inferiority trial evaluating the efficacy and safety of switching to the 2-drug regimen of DTG/3TC FDC compared with continuing any current 3- or 4-drug ART regimen in adults with HIV-1 over 48 weeks.

Patients, n	DTG/3TC (N = 246)[c]	CAR (N = 247)[c]
Archived M184V/I at Baseline	5	5
VL < 40 copies/mL and TND at Week 48	*4*	*3*
VF	*0*	*0*

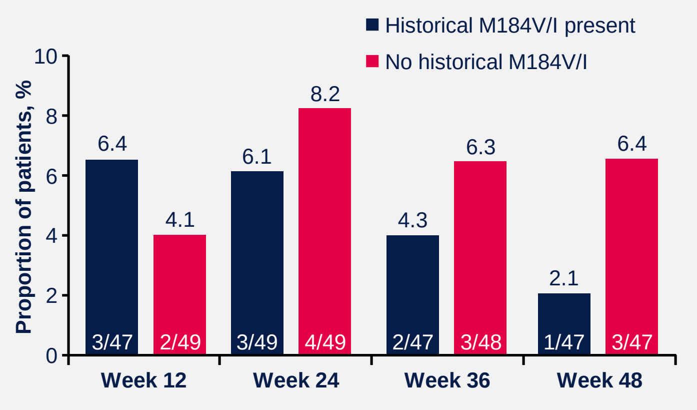
- Limited prospective and observational cohort data are available specific to the use of DTG + 3TC in patients with varying levels of treatment experience and with a history of M184V/I.[2,3,7-10,14-21]
- LAMRES, Dat'AIDS, and SOLAR-3D are the largest studies in virologically suppressed patients switching to DTG + 3TC in the presence or absence of archived resistance.

SOLAR 3D: Virologic control in the presence and absence of M184V/I through Week 48[10]

Virologic Suppression at Week 48 (FDA Snapshot Analysis)



Frequency of VL Blips Through Week 48

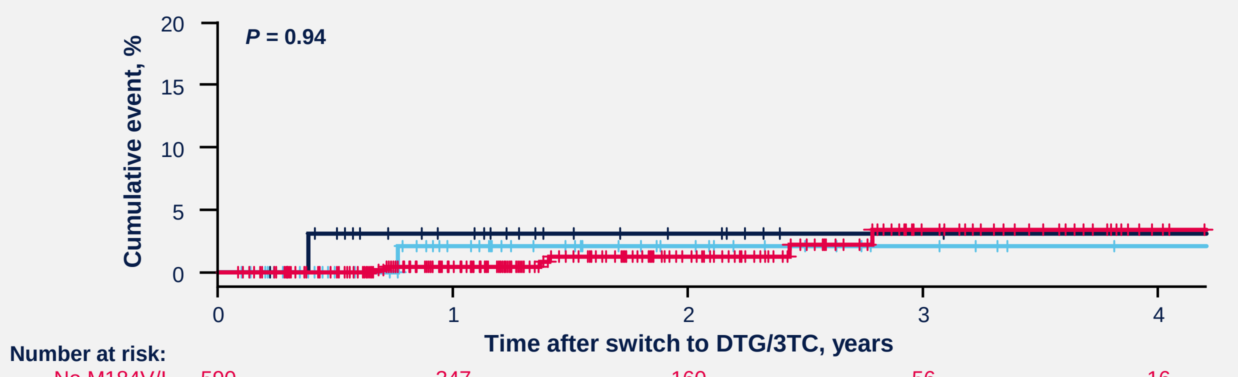


Key findings:

- In this prospective study of 100 virologically suppressed patients switching to DTG/3TC, historic M184V/I was detected in 50 patients, 15 of whom had proviral M184V/I at baseline.[d]
- At Week 48, the proportion of participants with HIV-1 RNA < 50 c/mL was similar between groups.
- The VL TND[e] at Week 48 was 84% and 80% in participants with and without M184V/I, respectively.
- Drug-related AEs and AEs leading to withdrawal were similar across treatment arms.
- There were no cases of CVF, and thus, no cases of treatment-emergent resistance

Dat'AIDS: Incidence of VF and probability of survival without VF in the presence and absence of M184V[17]

Incidence of VF



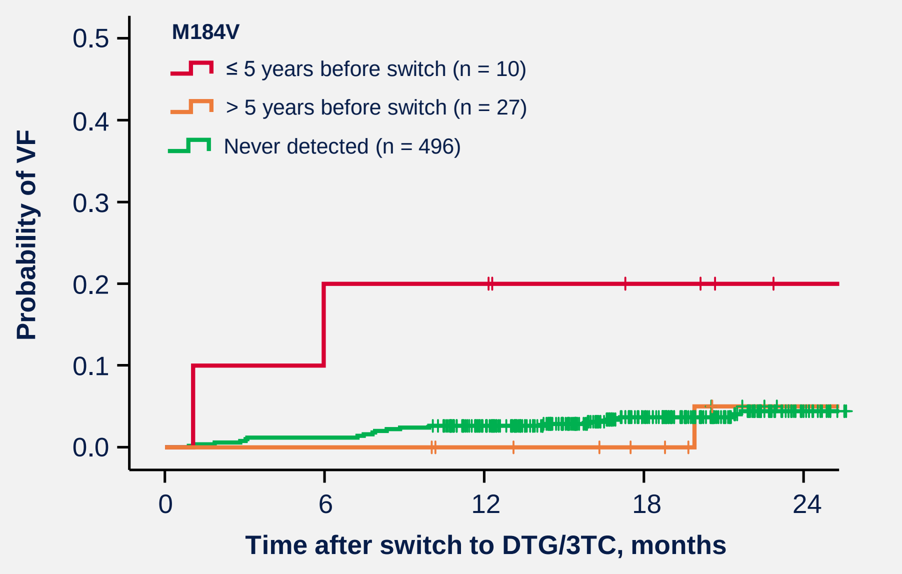
Number at risk:	0	1	2	3	4
No M184V/I	590	347	160	56	16
M184V/I < 5 years pre-switch	34	23	13	7	6
M184V/I ≥ 5 years pre-switch	71	40	20	11	5

Key findings:

- This was a retrospective study nested in the French Dat'AIDS cohort. Virologically suppressed patients with ≥ 1 previous HIV-1 RNA and/or HIV-1 DNA genotype who switched to DTG/3TC were included in the analysis (N = 695)
- VF occurred in 2/105 (1.9%) participants with M184V/I and 7/590 (1.2%) of those without M184V/I; no treatment-emergent M184V/I was detected in available genotypes at VF (4 participants without previous M184V)
- After a median of 1.2 years of follow-up, there was no significant difference in the probability of VF between those with or without previously detected M184V/I (log-rank, $P = 0.81$); rate of VF was not affected by the time of detection of M184V/I prior to switch ($P = 0.94$)

LAMRES: Probability of VF in virologically suppressed patients in the presence and absence of M184V[20]

Kaplan-Meier estimates of VF by presence or absence of M184V and by time of last M184V detection



Key findings:

- LAMRES was a retrospective study of a cohort of virologically suppressed participants switching to DTG/3TC (N = 533). VF occurred in 3/37 of participants with M184V.
- Probability of VF with presence vs absence of M184V was 5.4% vs 2.6% at 1 year; 9.2% vs 4.4% at 2 years ($P = 0.345$)
- Higher probability of VF if M184V detected ≤ 5 years vs > 5 years before switching to DTG + 3TC

Systematic Literature Review[13]

A systematic literature review and meta-analysis evaluated the impact of historical or archived M184V/I on the effectiveness of DTG + 3TC. Virologic failure rates ranged from 0.0%–3.76% up to Week 96, and no treatment-emergent mutations were reported.[13]

Data describing the use of DTG + 3TC in treatment naive patients who have the M184V/I is very limited.

STAT Study[22,23]

The STAT study (ClinicalTrials.gov, NCT03945981) is a phase 3b, multicenter, open-label, single-arm, pilot study assessing the feasibility, efficacy, and safety of using DTG/3TC as a first-line regimen in a "test-and-treat" model of care in the United States.

Of 131 participants, one had baseline resistance (M184V) identified at Week 4.

- **Baseline:** HIV-1 RNA, 18,752 copies/mL
- **Day 47:** HIV-1 RNA, undetectable[f]
- **Day 49:** Genotypic resistance to 3TC was identified and the patient was switched to DTG/RPV
- **Day 57:** HIV-1 RNA, 54 copies/mL
- **Day 106:** Participant withdrew consent (due to relocation)

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FOOTNOTES:

[a] ITT-E Population with baseline proviral DNA resistance result, with ≥ 1 post-Baseline on-treatment HIV-1 RNA viral load result and excluding participants who have withdrawn from the study because of protocol deviation (n = 5); [b] Last available on-treatment HIV-1 RNA viral load through Week 48 analysis using last on-treatment HIV-1 RNA viral load before discontinuation (percentages based on baseline mutation status, n); [c] Overall proportions of participants with HIV-1 RNA < 50 c/mL at last available on-treatment VL were DTG/3TC, 191/192 (> 99%); CAR, 182/185 (98%); no participants in either arm met CVW criteria; [d] Assessed by NGS using a 10% detection threshold; [e] VL < 20 copies/mL; [f] VL < 40 copies/mL.

ABBREVIATIONS:

3TC = lamivudine; AE = adverse event; ARCA = Antiretroviral Resistance Cohort Analysis; ART = antiretroviral therapy; CAR = current antiretroviral regimen; CVF = confirmed virologic failure; CVW = confirmed virologic withdrawal; DNA = deoxyribonucleic acid; DTG = dolutegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; ITT-E = Intention to Treat-Exposed; RPV = rilpivirine; RWE = real world evidence; RNA = ribonucleic acid; TAF = tenofovir alafenamide; TND = target not detected; VF = virologic failure; VL = viral load.

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