Use of *Dovato* in Real-world Settings

Summary

- A growing body of real-world evidence have been presented/published with data in >10,000 patients treated with *Dovato* (dolutegravir/lamivudine [DTG/3TC]) or the individual components as a 2-drug regimen.[1-48]
- A systematic literature review identified over 7000 patients worldwide who received *Dovato* or the individual components as a 2-drug regimen in real-world cohorts. The majority of the patients were virologically suppressed at baseline.[49]
    - High rates of virologic effectiveness were observed across real-world cohorts consistent with the Phase 3 GEMINI-1, GEMINI-2, TANGO, and SALSA trials.[50-56]
    - Discontinuation due to adverse events (AEs) with *Dovato*, or the individual components, in virologically suppressed patients ranged from 1.7%-7.9% in real-world studies and were consistent with the rates seen in the TANGO and SALSA trials.[49,53,55]
- A meta-analysis of 11 DTG + 3TC studies in virologically suppressed patients (n = 3021) and 3 studies in treatment-naïve patients (total n = 152) also confirmed high viral suppression (< 50 copies/mL) and low virological failure rates at Week 48 and Week 96.[56]
- Important safety information and boxed warning(s) can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

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PHASE 3 CLINICAL DEVELOPMENT PROGRAM

The DTG/3TC clinical development program Phase 3 studies have demonstrated non-inferiority of DTG + 3TC vs DTG + TDF/FTC in ART-naïve PLHIV to Week 144 (GEMINI-1 and GEMINI-2).[50-52] For additional information on the GEMINI-1 and GEMINI-2 studies, click here.

Switching to DTG/3TC was also non-inferior to remaining on a TAF-based 3-drug regimen through 144 weeks in the TANGO study or continuing antiretroviral regimen (CAR) through 48 weeks in the SALSA study. [43,45] For additional information on the TANGO and SALSA studies, click here.

REAL-WORLD COHORT DATA

A growing body of real-world data have been presented/published with data in >10,000 patients treated with DTG + 3TC show results consistent with the DTG/3TC clinical development program.[1-48] Over 40 real world cohorts have been identified, mainly located in Europe, and provide data for treatment-naïve patients, treatment experienced patients, patients with various comorbidities, and patients with a history of virologic failure. Potential overlap between patient cohorts cannot be ruled out.

Ten unique cohorts have reported various effectiveness outcomes (HIV-1 RNA <50 copies/mL was the effectiveness outcome in 7/10 cohorts), which ranged from 71.4%-100% with data up to 2 years, in treatment-naïve patients who received DTG + 3TC.[5,7,11,12,24,32,37,42,43,45,57] Virologic failure ranged from 0%-6.7% with no resistance mutations reported (resistance data not reported in TANDEM).

Several unique cohorts have reported various effectiveness outcomes (HIV-1 RNA <50 copies/mL, remained free of virologic failure, or probability of remaining free of virologic failure was the effectiveness outcome in the majority of cohorts), which ranged from 83.0%-99.5% with data up to Week 240, in treatment-experienced patients (N >100) who switched to DTG + 3TC in real world studies.[4,9,10,14,20,21,25,32,39,42,45,58-60] Virologic failure when reported ranged from 0%-4.8% (and 0.9-3.34 per

100 PYFU). Treatment-emergent resistance has been reported in 2 patients: 1 patient at baseline had T215Y, M184V and at virologic failure had T215CNSY, M184MV, M41ML and a single case study reported plasma HIV-1 genotypic deep sequencing showed R263K and S230N (no baseline genotype was reported because the patient had no previous history of virologic failure).[14,61]

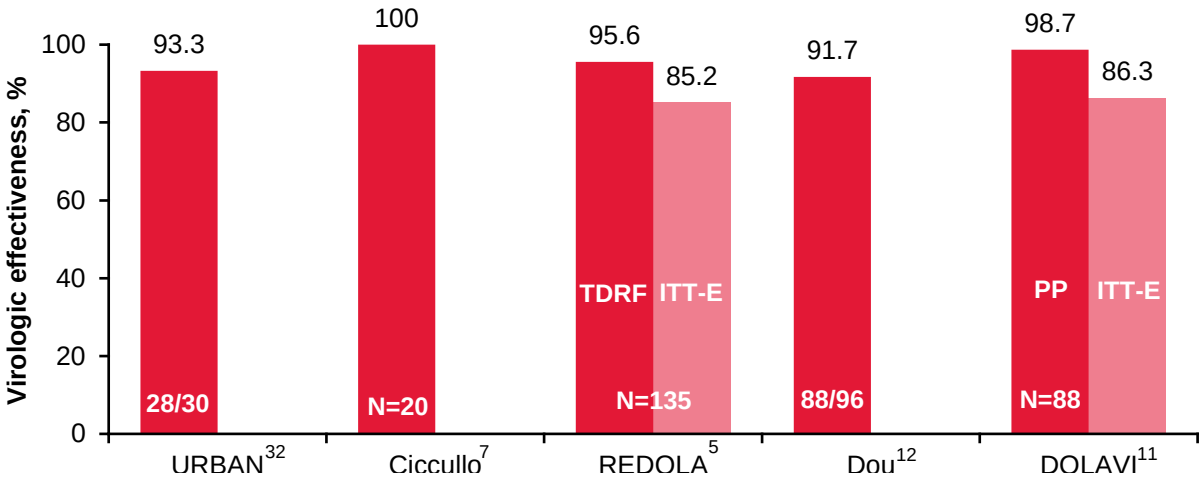
Systematic Literature Review (Letang, et al)

A systematic literature review of databases and international conferences was conducted between January 2013 and October 2021 to identify real-world observational studies of DTG + 3TC (either dosed separately or as a fixed-dose combination) in treatment-naïve and treatment experienced patients.[49] Over 7000 patients have received DTG + 3TC in real-world cohorts with the majority of people being virologically suppressed at Baseline. Click here to view the full poster from BHIVA 2022.

Treatment-Naïve Patients

Real-world studies have identified > 400 treatment-naïve patients treated with DTG + 3TC and reported effectiveness data.[49] While most of the cohorts were small, 5 studies reported effectiveness outcomes for ≥20 treatment-naïve patients receiving DTG + 3TC.[5,7,11,12,32] These studies showed similar efficacy and safety results as in the randomized clinical trials.[50-52] See Figure 1 for a summary. These multicenter cohort studies had various study designs and definitions of effectiveness summarized in Table 1. Among 3 of the cohorts, treatment discontinuation ranged from 0-4.4% with the most common discontinuation reason reported due to adverse drug reaction(s).[5,7,32] Among 4 of the cohorts, 2/273 (0.7%) virologic failures were reported, with no resistance-associated mutations (RAMs) emerged among those with virological failure (one patient did not have INI resistance testing performed).[5,7,11,32]

Figure 1. Proportion of Patients in Real-world Treatment-Naïve Studies Treated with DTG + 3TC Reporting Effectiveness



ITT-E = intention to treat exposed; PP = per protocol; TDRF = treatment related discontinuations equals failure

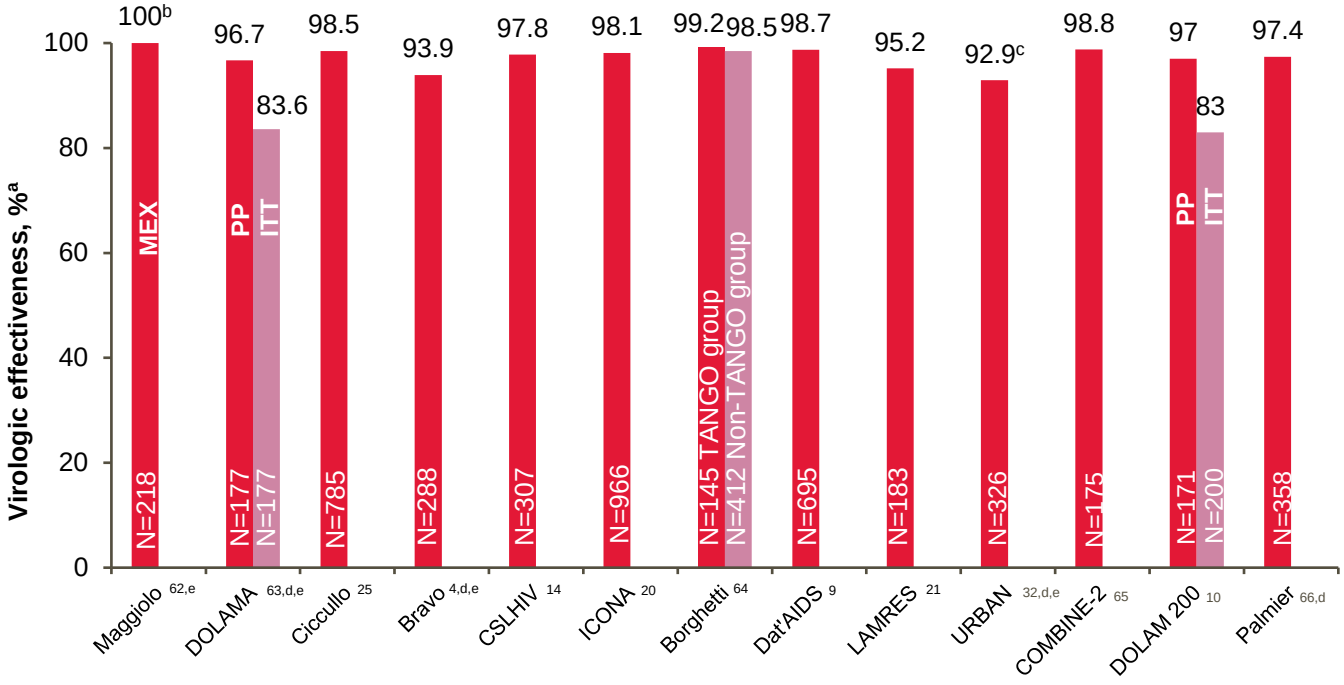
Table 1. Real-world Evidence in Treatment-Naïve Patients who Initiated DTG + 3TC

	URBAN[32]	Ciccullo[7]	REDOLA[5]	Dou[12]	DOLAVI[11]
Study Design	Prospective, non-interventional 3-year German cohort	Retrospective, observational	Multicenter, cohort	Prospective, multicenter, observational cohort	Single-arm, multicenter
Endpoint	Month 12	Week 48	Week 48	Week 24	Week 48
Effectiveness	HIV-1 RNA <50 c/mL or 50-200 c/mL with subsequent HIV-RNA <50 c/mL in the effectiveness set (missing = excluded)	Proportion of patients achieving HIV-1 RNA <50 c/mL	Proportion of patients achieving virologic suppression (HIV-1 RNA < 50 c/mL)	HIV-RNA <50 c/mL or 50-200 c/mL with subsequent HIV-RNA <50 in the effectiveness set (missing = excluded)	Proportion of patients achieving HIV-1 RNA <50 c/mL

Treatment Experienced Patients

High rates of virologic effectiveness were observed across real-world cohorts at Week 48, consistent with the Phase 3 TANGO and SALSA studies. Figure 2 represents RWE studies of treatment experienced patients who were virologically suppressed. Figure 2 is not all-inclusive of all cohort data that has been published and/or presented; criteria for inclusion were cohorts with ≥ 100 patients treated with DTG + 3TC (potential overlap between groups cannot be ruled out). Additional study details are summarized in Table 2.

Figure 2. Effectiveness Outcomes in Real-world Treatment Experienced Studies Treated with



[a] Treatment effectiveness includes all patients who finished the study and were below the pre-established viral threshold, except where indicated; [b] Excludes 50 patients who discontinued treatment; [c] Treatment effectiveness reported at Month 12; [d] Viremic at baseline: Palmier, n=15, URBAN, n=14, DOLOMA, n=8, BRAVO, n=16; [e] Patients excluded from original analysis: URBAN, missing data, n=7; DOLAMA, not treated per protocol, n=29;Bravo, did not complete Week 48 assessment, n=222; Maggiolo, discontinued treatment, n=50.

ITT = intention to treat; MEX = missing equals excluded; PP = per protocol.

Table 2. Real-world Evidence in Virologically Suppressed Patients Who Switched to DTG + 3TC[a]

Study	Study Type (duration of study)	Effectiveness Outcome	Virologic Failure[b]
Maggiolo et al. (2021)[62]	Prospective, multicenter, cohort (5 years)	Remained free of VF	0
DOLAMA (2019)[63]	Retrospective cohort (48 weeks)	VL < 50 c/mL	5 (2/5 underwent resistance testing)
Ciccullo, et al. (2021)[25]	Retrospective cohort (1992.6 patient-years of follow-up)	Estimated probability of maintaining VL < 50 c/mL	18 (no evidence of new mutations in patients experiencing VF)
Bravo (2019)[4]	Retrospective, multicenter, cohort (48 weeks)	VL < 50 c/mL	0
CSLHIV (2019)[14]	Retrospective, single-center cohort (48 weeks)	Estimated probability of maintaining VL < 50 c/mL	17 (14 patients had resistance testing available)
ICONA (2020)[20]	Retrospective, multicenter cohort (1505 person-years of follow-up)	Remained free of VF	0.7-1.2 x 100 person-years of follow-up

Study	Study Type (duration of study)	Effectiveness Outcome	Virologic Failure[b]
Borghetti et al. (2020)[64]	Observational cohort (ongoing until 144 weeks)	Estimated probability of maintaining VL < 50 c/mL	TANGO group: 1 Non-TANGO group: 11 (no resistance-associated mutations emerged after VF)
Dat'AIDS (2021)[9]	Retrospective, multicenter cohort (1.2 years, median)	Remained free of VF	6
LAMRES (2021)[21]	Retrospective, multicenter cohort (2 years)	Probability of remaining free of VF	4.8%
URBAN[32] (2021)	Prospective, non-interventional cohort (3 years)	VL < 50 c/mL	3 (no treatment-emergent resistance)
COMBINE-2[65] (2021)	Prospective, observational cohort (96 weeks)	VL < 50 c/mL	0
DOLAM 200[10]	Retrospective, observational, multicenter cohort (48 weeks)	VL < 50 c/mL	5
Palmier, et al.[66] (2021)	Retrospective, descriptive, observational, single-center cohort (96 weeks)	VL < 50 c/mL	2

[a] These studies did not compare DTG + 3TC with a 3-drug cART; [b] Virologic failure defined as patients who are above the pre-established viral threshold at the time of follow-up

No on-treatment resistance was reported in treatment-naïve patients.[49] Among 9 studies in treatment-experienced patients switched to DTG + 3TC documenting on-treatment resistance (n=3527), 8/9 reported no cases of treatment-emergent resistance, and 1/9 studies reported 1 case (<1%) of treatment-emergent resistance. The 1 case of VF and treatment-emergent resistance had NRTI RAMs at baseline (T215Y, M184V) and after VF (M41M/L, M184M/V, T215C/N/S/Y).[14]

Discontinuations due to AEs ranged from 1.7%-7.9% in virologically-suppressed real-world studies and AEs were consistent with those reported in the Phase 3 clinical studies.[49,53-55] Reasons for discontinuation may have been classified as intolerance, toxicity, or other (GI and/or hepatic toxicity, n = 19; hypersensitivity, n = 2; neuropsychological, n = 37; renal toxicity, n = 6; weight gain, n = 3; myalgia/asthenia or headache, n = 3; other, n = 16).[62,63,67-69] Reasons for discontinuation or safety data were not reported in every study. In the treatment-naïve RWE the most common ADR reported was depression (n=3) in the URBAN cohort and 3 patients discontinued treatment due to CNS side effects in the REDOLA cohort.[5]

Systematic Literature Reviews in Subgroups

Participants who did not Meet Inclusion Criteria for the Phase 3 Clinical Development Program

A separate systematic literature review was conducted to review effectiveness outcomes for patients with baseline characteristics that were not consistent with inclusion criteria for the Phase 3 clinical development program for DTG/3TC in treatment naïve or virologically suppressed patients.[70] Twenty-seven unique publications comprised of 2015 patients were identified from databases and international conference proceedings from January 2013 to February 2022. Of the 27 unique publications only 7 reported effectiveness outcomes. See Table 3 for a summary of findings.

Table 3. Reported Efficacy of DTG + 3TC From Real-world Studies in Patients with Characteristics Inconsistent with RCT Inclusion Criteria[70]

Characteristic	Number of Publications (Total/Reported Outcomes)	Number of patients (Total/Reported Outcomes)	Effectiveness outcomes
Previous VF	7/1	1134/194	• Over ~1500 PYFU, probability of VF at 1 year was 0.4% or 1.2%, depending on VF criteria[20]

Characteristic	Number of Publications (Total/Reported Outcomes)	Number of patients (Total/Reported Outcomes)	Effectiveness outcomes
Evidence of BL drug resistance	10/4	253/211	• VF ranged from 0-5.4% at ~1 year[9,21,71,72] • Difference in VF between those with or without M184V/I was not significant in 3 of 4 cohorts • A treatment-emergent resistance mutation (M41L, not selected by DTG or 3TC) was observed in 1 patient with evidence of baseline resistance
Evidence of HBV	6/1	166/35	• No patient with HBV experienced VF[67]
Evidence of HCV	13/0	431/0	• No studies reported effectiveness outcomes in this subgroup
Treatment-naïve with BL VL >500,000	1/1	18/18	• 89% (16/18) of patients with BL VL >500,000 copies/mL achieved VL < 50 copies/mL or 50-200 copies/mL with subsequent VL <50 copies/mL at Week 24[12]
Treatment-experienced with VL <50 copies/mL for <6 months before switch	1/0	13/0	• No studies reported effectiveness outcomes in this subgroup

[a] 1 patient reported for VF outcome had chronic HCV[21]

BL = baseline; DTG = dolutegravir; 3TC = lamivudine; PYFU = patient year follow-up; VF = virologic failure; VL = viral load

Women

Overall, 122 publications were identified in a systematic literature review of real-world studies which reported on DTG + 3TC use.[73] Thirty-one studies reported the number of women at baseline: 1658/6948 (24%); of these 4 studies reported efficacy outcomes stratified by sex (N=254). Virologic effectiveness ranged from 96%-100% when defined as free from virologic failure over time or HIV-1 RNA <30 copies/mL. One study assessed odds of virologic suppression among treatment-naïve patients by sex at birth and found no significant difference between sexes (OR: 1 [95% CI 1-23]). Two studies reported safety outcomes, and both found higher rates of discontinuation in women vs men: 10% (5/50) vs 5% (7/153) and 15% (4/26) vs 3% (2/74), respectively.

Meta-Analysis

A systematic literature review of PubMed and Embase along with 24 regional and international conferences was conducted between January 2013 and August 2021 to identify RWE studies of DTG + 3TC in PLHIV.[56] A total of 89 RWE studies comprised of > 5000 PLHIV using DGT + 3TC were identified. A total of 11 DTG + 3TC studies (n = 3021) reported data on therapy experienced virologically suppressed PLHIV with at least one outcome of interest (proportion of patients with virological suppression [< 50 c/mL], virological failure and discontinuations) at a timepoint of interest (Week 48 and Week 96). Adverse events were not evaluated within this meta-analysis. Studies included within this meta-analysis may be included in the real-world cohorts presented above.

Treatment-Experienced Patients

- In the snapshot analysis, the viral suppression rate was 86.4% (95% CI: 81.7, 90.5) and 87.6% (95% CI: 74.2, 96.7) at Week 48 and Week 96, respectively.
- For the on-treatment analysis, the viral suppression rate was 98.7% (95% CI: 97.3, 99.6) and 98.1% (95% CI: 96.0, 99.5) at Week 48 and Week 96, respectively.

- The virological failure rate was 1.2% (95% CI: 0.4, 2.2) and 1.7% (95% CI: 0.5, 3.4) at Week 48 and Week 96, respectively.

Therapy-Naïve Patients

- In the snapshot analysis, viral suppression rate was 85.4% (95% CI: 78.6, 91.3) at Week 48.
- For the on-treatment analysis, viral suppression rate was 100% (95% CI:100.0, 100.0) at Week 48.
- The virological failure rate was 0% (95% CI: 0.0, 0.0) at Week 48.

No studies reported therapy-emergent resistance and discontinuation rates ranged from 11.9%-13.6%. Limitations to this analysis include the inherent clinical heterogeneity between included studies (given the single-arm, non-comparative methodology) and the small sample size (n ≤ 50) of several studies included in this analysis. Click here to view the full poster from IDWeek 2021.

Treatment Experience in the US

TANDEM Study

The TANDEM study was a retrospective chart review of 24 sites throughout the US designed to describe real-world prescribing behaviors and treatment outcomes of DTG 2 drug-based regimens (2DR).[45] Out of a total population of 469 patients, 318 received DTG/3TC, of whom 126 were treatment-naïve and 192 were virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ART regimen for ≥3 months upon DTG-based 2DR initiation (SS). Patients had to have at least 6 months of clinical follow-up after initiation of DTG/3TC. Treatment-naïve patients who started DTG/3TC had a median time of 1.3 years on DTG/3TC and SS patients had a median time of 1.6 years on DTG/3TC.

The most common reason for initiation of DTG/3TC was avoidance of long-term toxicities in both treatment-naïve (32.5%) and SS (27.1%).[45] 95.8% (184/192) of SS patients maintained suppression. Four patients who became detectable remained on DTG/3TC and resuppressed, 2 patients remained on DTG/3TC and did not resuppress, and 2 patients were lost to follow-up. 93.7% (118/126) of treatment-naïve patients achieved virologic suppression and 83.3% (105/126) remained suppressed. One treatment naïve patient and 3 SS patients discontinued DTG/3TC by the data cut-off. Click here to view the full poster from AIDS 2022.

A descriptive analysis was performed of treatment naïve patients with high baseline viral loads (≥100,00 copies/mL) within the TANDEM cohort.[74] Sixteen patients had high baseline viral loads: 9 had values of 100,000-250,000 copies/mL and 7 were >250,000 copies/mL. Out of the 16 patients with high baseline viral loads, 13 experienced sustained virological suppression with no treatment discontinuations.

Approximately half (61/126) of the treatment naïve patients received DTG/3TC within a test and treat approach.[75] Relevant treatment considerations differed between the test and treat group and non-test and treat with the main consideration in the test and treat group identified as limited access to healthcare; whereas comorbidities were the main consideration for the non-test and treat group.

At data cut-off, 57 (93.4%) of the test and treat group achieved virologic suppression, 3 (4.9%) did not, and 1 (1.6%) was still unknown; in the non-test and treat group, 59 (95.2%) achieved virologic suppression.[75] Of the 3 individuals in the test and treat group who did not achieve viral suppression, 2 remained on DTG/3TC and 1 was switched to BIC/FTC/TAF. Virologic rebound occurred in 6 patients in the treatment naïve cohort, with 1 of these occurring in the test and treat group. See Table 4 for additional virologic outcomes.

Table 4. Virologic Outcomes in the TANDEM Study[75]

	Test & Treat (n = 61)	Non-Test & Treat (n = 62)
Time to virologic suppression following DTG/3TC initiation (weeks) Median (IQR)	9.7 (5.8, 17.7)	10.7 (5.4, 19.3)
Time since virological suppression observed (weeks)		
Median (IQR)	59.9 (33.3, 79.3)	48.5 (29.8, 77.6)
% sustaining viral suppression to 24 weeks[a]	48 (78.7)	45 (72.6)
Discontinuation Status, n (%)		
Discontinued DTG/3TC[b]	1 (1.6)	0 (0.0)
Ongoing DTG/3TC	60 (98.4)	60 (96.8)
Unknown/lost to follow-up	0 (0.0)	2 (3.2)

3TC = lamivudine; DTG = dolutegravir; IQR = interquartile range.

[a] All had at least 24 weeks of clinical follow-up post-initiation of DTG/3TC; n=3 test and treat and n=7 non test and treat patients had remained virologically suppressed to data abstraction but had not yet reached 24 weeks suppressed; [b] Primary reason for the n=1 discontinuation was due to 'persistent low-level viremia or viral blips'.

A separate descriptive analysis by age group was performed for SS patients in the TANDEM cohort.[76] Out of a total of 192 DTG/3TC SS patients, the number in each age group was 86 (<50 years), 106 (≥50 years), and 20 (≥65 years; [≥50 years and ≥65 years were not mutually exclusive groups]). More patients in older age groups reported comorbidities (12.8% <50 years; 34.9% ≥50 years; 45.0% ≥65 years) and polypharmacy (5.8% <50 years; 17.9% ≥50 years; 30.0% ≥65 years). Patients aged ≥50 years were more likely to have had >1 previous ART regimen (81.1%) compared to those aged <50 years (47.7%). Within the oldest subgroup of ≥65 years, the majority (55.0%) had received 3 or more regimens, and 30.0% received more than 5 ART regimens in the past before switching to DTG/3TC. The primary reason for switching to DTG/3TC was avoidance of long-term toxicities in patients ≥50 years (reported by 32.1% of HCPs), while simplification/streamlining of treatment was most common in the <50 years cohort (27.9%).

The percent of patients that remained virologically suppressed at data retrieval (minimum of 6 months after index date) were 95.3% (<50 years, n=82), 96.2% (≥50 years, n=102), and 95.0% (≥65 years, n=19).[76] Three SS patients, all in the ≥50 years cohort, discontinued DTG/3TC. Reasons for discontinuation were toxicity/intolerance (n=1), patient preference (n=1), and concerns about weight gain (n=1).

OPERA Cohort

Electronic health record data from the OPERA cohort (made up of 84 clinics throughout 18 US states/territories) was analyzed to assess incidence rates of discontinuation, loss of suppression and confirmed virologic failure in 787 virologically suppressed (HIV-1 RNA <50 copies/mL). patients.[46]

Of the 787 patients who switched to DTG/3TC, 54% switched from DTG/ABC/3TC, 31% from BIC/TAF/FTC and 16% from DTG + TAF/FTC.[46] The median follow-up was 13.6 months (IQR: 8.2-22.3). There were ≤5 (masking of data with 1 to 5 individuals is required by HIPAA) confirmed virologic failures (defined as 2 viral loads ≥200 copies/mL or discontinuation after 1 viral load ≥200 copies/mL) with an incidence rate of 0.43 per 100 person-years (95% CI: 0.16-1.00).

In this cohort 170 patients discontinued DTG/3TC (101 did not identify a reason for switch, 6 patients had a treatment-related reason and 66 had "other" reasons).[46] The incidence rate of DTG/3TC discontinuation was 17.47 per 100 person-years. Loss of suppression defined as 1 viral load ≥50 copies/mL occurred at a rate of 14.02 per 100 person-years, or 3.29 per 100 person-years when defined as 1 VL ≥200 copies/mL. Click here to view the full poster from AIDS 2022.

In a separate analysis from the OPERA cohort, confirmed virologic failure (defined as 2 consecutive viral loads ≥ 200 copies/mL) and regimen discontinuation were evaluated among patients switched DTG/3TC, BIC/TAF/FTC, or DTG + 2 NRTI's in patients suppressed to viral load < 200 copies/mL at switch.[77] The incidence rate of confirmed virologic failure was 0.66 (95% CI: -.35, 1.23) per 100 person-years for DTG/3TC (N=1450), 0.84 (95% CI: 0.66, 1.09) per 100 person-years for BIC/TAF/FTC, and 1.78 (95% CI: 1.11, 2.86) per 100 person-years for DTG + 2 NRTIs. There was no difference in risk of confirmed virologic failure observed between DTG/3TC and BIC/TAF/FTC (HR: 1.39; 95% CI: 0.61, 3.17). A difference was observed between DTG/3TC and DTG + 2 NRTIs (HR: 5.21; 95% CI: 1.85, 14.67).

See Table 5 for duration of follow-up and regimen discontinuation. Treatment-related discontinuations (included viral load ≥ 200, side effects, and/or lab abnormality) ranged from 7-11%.

Table 5. Duration of follow-up and regimen discontinuation[77]

	DTG/3TC N = 1450	BIC/TAF/TDF N = 5691	DTG + 2 NRTIs N = 896
Median months of follow-up (IQR)	13.6 (7.3, 18.3)	15.8 (11.6, 19.8)	13.4 (7.9, 18.2)
Regimen discontinuation			
IR per 100 person-years (95% CI)	17.7 (15.7, 19.9)	8.3 (7.7, 9.0)	24.9 (21.9, 28.3)
HR[a] (95% CI)	Ref	0.51 (0.42, 0.62)	1.69 (1.30, 2.19)

[a] Cox proportional hazards model with inverse probability of treatment weights (IPTW): baseline age (quadratic), # of ART classes (quadratic), female, Black race, Hispanic ethnicity, Southern US, core agent class of prior regimen, CD4 cell count (quadratic)

3TC = lamivudine; BIC = bictegravir; CI = confidence interval; DTG = dolutegravir; HR = hazard ratio; IQR = interquartile range; IR = incidence rate

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