Psychiatric Adverse Events in Clinical Study Participants Receiving *Dovato*

Summary

- Reported rates of psychiatric adverse events (AEs) within the GEMINI-1 and GEMINI-2 studies through 144 weeks were similar overall between the treatment groups of dolutegravir plus lamivudine (DTG + 3TC), the components of *Dovato* (DTG/3TC) and DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC).[1,2]
- Reported rates of psychiatric AEs within the TANGO study through 144 weeks were greater in the DTG/3TC group compared with tenofovir alafenamide (TAF) based regimen group.[3]
- Reported rates of psychiatric AEs within the SALSA study through 48 weeks were greater in the DTG/3TC group compared with current antiretroviral regimen (CAR) group.[4]
- Psychiatric AEs leading to withdrawal from the GEMINI, TANGO, and SALSA studies commonly occurred in participants with a documented history of psychiatric disorder.[1-4]
- Reported rates of psychiatric AEs within the single-arm STAT study through 48 weeks were comparable to 48-week data in the comparative clinical trials.[5]
- 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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GEMINI-1 AND GEMINI-2

Background

GEMINI-1 (NCT02831673) and GEMINI-2 (NCT02831764) were duplicate, double-blind, randomized Phase 3 studies designed to evaluate the efficacy and safety of DTG + 3TC as a 2-drug regimen in HIV-1 infected, treatment-naïve adult (≥18 years) participants with viral load ≤ 500,000 copies/mL. Safety data is from the Week 144 analyses.[6]

Rates of Psychiatric AEs

Overall, psychiatric AEs occurred at a similar rate between treatment groups in GEMINI-1 (25% for DTG + 3TC, 25% for DTG + TDF/FTC) and GEMINI-2 (16% for DTG + 3TC, 20% for DTG + TDF/FTC) (Table 1).[1,2] Insomnia, anxiety, depression, and suicidal ideation were the most common psychiatric AEs. All other events were reported in <2% of participants in the total study population. Most psychiatric AEs were grade 1 or 2 in severity.

Table 1. Summary of Psychiatric Adverse Events, Pooled Analysis from GEMINI-1 and GEMINI-2[1,2]

	DTG + 3TC (n = 716) n (%)[a]	DTG + TDF/FTC (n = 717) n (%)[a]
Any Psychiatric Adverse Event (AE)	148 (21)	161 (22)
Psychiatric AEs occurring in ≥ 2% of participants in either group		
Insomnia	46 (6)	59 (8)
Anxiety	36 (5)	33 (5)
Depression	30 (4)	30 (4)
Suicidal Ideation	10 (2)	15 (2)
Depressed Mood	5 (<1)	11 (2)
Drug-Related Psychiatric AEs		
Overall	42 (6)[b]	44 (6)[c]
Grade 1 or 2	35 (5)	42 (6)
Grade 3 or 4	7 (<1)	2 (<1)
SAEs	15 (2)	10 (1)
Psychiatric AEs leading to Study Withdrawal	11 (2)	8 (1)
Drug-Related Psychiatric AEs leading to Study Withdrawal	9 (1)	5 (<1)

[a] Frequencies <1% not rounded up; [b] Anxiety and insomnia occurred in 2% of patients; [c] Insomnia occurred in 3%

DTG = dolutegravir; 3TC = lamivudine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; SAE = serious adverse event.

Suicidal Ideation and Behaviors

AEs related to suicidal ideation and behavior occurred in 22 participants with 26 events reported in the DTG + 3TC group: suicidal ideation (14 events), suicide attempt (8 events), and suicidal behavior (4 events) and 19 participants reported 26 events in the DTG + TDF/FTC group: suicidal ideation (21 events), suicide attempt (2 events), depression suicidal (1 event), intentional overdose (1 event), and suicidal behavior (1 event).[1,2] Of the 41 participants, 22 reported a history of psychiatric disorder(s) and/or suicidal ideation, behavior, or self-harm.

Psychiatric AEs Leading to Withdrawal

Overall, 9 participants in the DTG + 3TC group and 5 participants in the DTG + TDF/FTC group withdrew from the study due to a drug-related psychiatric AE, as summarized in Table 2 below.[1,2]

Table 2. Psychiatric Adverse Events Leading to Discontinuation from GEMINI-1 and GEMINI-2[1,2]

Participant	Psychiatric AE(s) Leading to Withdrawal	Treatment Arm	Onset (Study Day)	Maximum Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
1	Substance-induced psychotic disorder	DTG + 3TC	1	3	Yes	Yes
2	Sleep disorder	DTG + 3TC	1	2	No	Yes
3	Insomnia	DTG + 3TC	353	2	No	No
	Psychotic disorder		353	3	Yes	Yes
4	Suicide attempt	DTG + 3TC	427	4	Yes	No
5	Suicidal ideation	DTG + 3TC	679	3	Yes	Yes
6	Anxiety	DTG + 3TC	458	2	No	Yes
7	Depressed mood	DTG + 3TC	475	2	No	Yes
8	Fatigue	DTG + 3TC	505	2	No	Yes

Participant	Psychiatric AE(s) Leading to Withdrawal	Treatment Arm	Onset (Study Day)	Maximum Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
	Anxiety		566	2	No	Yes
	Irritability		566	2	No	Yes
9	Suicidal ideation	DTG + 3TC	137	3	Yes	Yes
10	Anxiety	DTG + 3TC	312	3	No	Yes
	Depression		312	3	No	Yes
11	Suicide attempt	DTG + 3TC	805	4	Yes	No
1	Psychotic disorder	DTG + TDF/FTC	574	2	No	No
2	Sleep disorder	DTG + TDF/FTC	669	2	No	No
3	Insomnia	DTG + TDF/FTC	1	1	No	Yes
4	Alcoholic psychosis	DTG + TDF/FTC	101	2	Yes	No
5	Suicidal ideation	DTG + TDF/FTC	111	3	Yes	Yes
6	Suicidal ideation	DTG + TDF/FTC	1013	2	Yes	Yes
7	Anxiety	DTG + TDF/FTC	135	2	No	Yes
8	Depression	DTG + TDF/FTC	490	3	No	Yes
	Suicide attempt		512	4	Yes	Yes

AE = adverse event; DTG = dolutegravir; 3TC = lamivudine; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine.

TANGO

Background

TANGO (NCT03446573) was a randomized, open-label, phase 3 non-inferiority trial evaluating the efficacy and safety of a switch to DTG/3TC FDC in HIV-1–infected adults with virologic suppression on a 3- or 4-drug tenofovir alafenamide (TAF)-based regimen.[7] Safety data is from the Week 144 analyses.

Rates of Psychiatric AEs

Overall, psychiatric AEs were greater in the DTG/3TC group (30%) compared with the TBR group (23%) in the TANGO study (Table 3)[3] Anxiety, depression, and insomnia were the most common psychiatric AEs. All other events were reported in ≤2% of participants in the total study population. There were more drug-related psychiatric AEs in the DTG/3TC group. Most psychiatric AEs were grade 1 or 2 in severity.

Table 3. Summary of Psychiatric Adverse Events from TANGO through Week 144[3]

	DTG + 3TC (n = 369) n (%)[a]	TBR (n = 371) n (%)[a]
Any Psychiatric Adverse Event (AE)	110 (30)	87 (23)
Psychiatric AEs occurring in ≥ 2% of patients in either group		
Anxiety	35 (9)	29 (8)
Depression	26 (7)	22 (6)
Insomnia	25 (7)	18 (5)
Suicidal ideation	6 (2)	7 (2)
Depressed mood	6 (2)	5 (1)
Drug-Related Psychiatric AEs		
Overall	21 (6)[b]	2 (<1)
Grade 1 or 2	20 (5)	2 (<1)
Grade 3 or 4	1 (<1)	0 (0)

	DTG + 3TC (n = 369) n (%)[a]	TBR (n = 371) n (%)[a]
Psychiatric AEs leading to Study Withdrawal	12 (3)	3 (<1)
Drug-Related Psychiatric AEs leading to Study Withdrawal	9 (2)	2 (<1)

[a] Frequencies <1% not rounded up; [b] Insomnia occurred in 2%

DTG = dolutegravir; 3TC = lamivudine; TBR = TAF based regimen

Suicidal Ideation and Behaviors

Emergent AEs relating to suicidality and self-injury were reported in 7 (2%) participants (reporting 1 event each) in the DTG/3TC group and 8 (2%) participants (reporting 1 event each) in the TBR group.[3] All 15 participants had a history of psychiatric disorders, particularly depression, and/or psychosocial stressors reported at the time of the event.

Psychiatric AEs Leading to Withdrawal

Twelve participants in the DTG + 3TC group and 3 participants in the TBR group withdrew from the study due to a drug-related psychiatric AE, as summarized in Table 4 below.[3]

Table 4. Psychiatric Adverse Events Leading to Discontinuation from TANGO[3]

Participant	Psychiatric AE(s) Leading to Withdrawal	Treatment Arm	Onset (Study Day)	Maximum Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
1	Depression	DTG + 3TC	589	2	No	Yes
2	Substance abuse	DTG + 3TC	782	5	Yes	No
3	Suicidal ideation	DTG + 3TC	396	3	No	Yes
4	Depression	DTG + 3TC	716	3	No	No
5	Depression	DTG + 3TC	217	2	No	Yes
6	Suicidal ideation	DTG + 3TC	156	3	Yes	No
7	Anxiety	DTG + 3TC	1	1	No	Yes
8	Irritability	DTG + 3TC	94	1	No	Yes
9	Anxiety	DTG + 3TC	43	2	No	Yes
	Insomnia		43	2	No	Yes
10	Anxiety	DTG + 3TC	3	1	No	Yes
11	Insomnia	DTG + 3TC	15	1	No	Yes
12	Fatigue	DTG + 3TC	21	1	No	Yes
	Insomnia		265	2	No	Yes
1	Suicide attempt	TBR	241	4	Yes	No
2	Anxiety	TBR	700	2	No	Yes
3	Depression	TBR	9	2	No	Yes

AE = adverse event; DTG = dolutegravir; 3TC = lamivudine; TBR = TAF based regimen

Week 196 Data

After Week 144, TANGO entered a continuation (non-comparative) phase assessing a 4-year follow-up for participants who switched to DTG/3TC at Day 1 (referred to as the early-switch (ES) group) and a 1-year follow-up for participants who continued TAF-based regimens and maintained virologic suppression at Week 144 and then switched to DTG/3TC at Week 148 (referred to as the late-switch (LS) group).[8]

In total to Week 196, 130 (35%) participants in the ES group (N=369) experienced any psychiatric AE.[3] In the ES group, 21 (6%) participants experienced a drug-related psychiatric AE, 20 of which were Grade 1 or 2 severity. All psychiatric AEs leading to study withdrawal, including those considered by study investigators to be drug-related, occurred by Week 144. See Table 3 and Table 4 above.

Between Week 148 and Week 196, 31 (10%) participants in the LS group (N=298) experienced any psychiatric AE.[3] In this group, 8 participants experienced drug-related psychiatric AEs, 7 of which were Grade 1 or 2 severity. Three participants experienced psychiatric AEs leading to study withdrawal, all considered by study investigators to be drug related.

Over 48 weeks of treatment (Day 1 to Week 48 for ES group and Week 148 to Week 196 for LS group), rates of psychiatric AEs, drug-related psychiatric AEs, and psychiatric AEs leading to study withdrawal were numerically greater in the ES group (14% vs 10%, 5% vs 3%, and 2% vs 1%, respectively).[3]

SALSA

SALSA (NCT04021290) was a phase 3, randomized, open-label, noninferiority study evaluating the efficacy and safety of switching to DTG/3TC compared with continuing the current antiretroviral regimen (CAR) in virologically suppressed adults with HIV.[9] Safety data is from the Week 48 analyses.

Rates of Psychiatric AEs

Overall, psychiatric AEs were greater in the DTG/3TC group (11%) compared to the CAR group (8%), as summarized in Table 5.[4]

Three participants in the DTG/3TC group and 1 in the CAR group withdrew from the study due to psychiatric AEs, and all were considered by the study investigators to be related to study drug.[4] Psychiatric AEs leading to withdrawal were insomnia (reported in 2 participants) and anxiety in the DTG/3TC group, and suicidal ideation in the CAR group.

Table 5. Summary of Psychiatric Adverse Events from SALSA[4]

	DTG/3TC (N = 246) n (%)	CAR (N = 247) n (%)[a]
Any Psychiatric Adverse Event (AE)	28 (11)	19 (8)
Psychiatric AEs occurring in ≥ 1% of patients in either group		
Insomnia	14 (6)	4 (2)
Anxiety	5 (2)	6 (2)
Sleep disorder	3 (1)	3 (1)
Drug-Related Psychiatric AEs		
Overall	12 (5)[b]	3 (1)
Grade 1	8 (3)	1 (<1)
Grade 2	4 (2)	2 (<1)
Grade 3 to 5	0	0
Psychiatric AEs leading to Study Withdrawal	3 (1)	1 (<1)
Drug-Related Psychiatric AEs leading to Study Withdrawal	3 (1)	1 (<1)

[a] Frequencies <1% not rounded up; [b] Insomnia occurred in 3%

DTG = dolutegravir; 3TC = lamivudine; CAR = current antiretroviral regimen

STAT

STAT (NCT03945981) was a phase 3b, open label, 52-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of using DTG/3TC fixed-dose combination as a first-line regimen in a US test-and-treat setting.[10] The study enrolled 131 antiretroviral treatment (ART) naïve adults (aged ≥18 years) with a

confirmed HIV-1 diagnosis within 14 days of study entry, no prior history of hepatic or renal impairment, and no known or suspected hepatitis B (HBV) coinfection.

Rates of Psychiatric AEs

Psychiatric AEs were reported by 24 participants (18%), 14 of whom had psychiatric disorders before or at the time of study enrollment.[10] The most common psychiatric AEs were depression (7%), insomnia (6%), and anxiety (5%), all of which were grade 1 or 2. No psychiatric AEs were considered as SAEs by the study investigators.[5] One psychiatric AE was considered drug-related, an event of insomnia starting on Day 1, which resolved on Day 57.

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Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

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