Longitudinal Dynamics of Viremic Events: A Multi-State Modeling Analysis of Dolutegravir/Lamivudine Versus 3-Drug Regimens

P052

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Key Takeaways

- Dolutegravir/Lamivudine was associated with a 23% lower hazard of transitioning from virologic suppression to viremia vs 3-drug regimens, with consistent findings through both Week 48 and Week 144
- Following a viremic event, the rate of re-suppression was comparable between dolutegravir/lamivudine and 3-drug regimens through Week 48
- Participants receiving dolutegravir/lamivudine spent numerically less time in viremia, and findings remained consistent over up to 3 years of follow-up, supporting durable virologic control

Plain Language Summary

- Across clinical studies, most people with HIV receiving dolutegravir/lamivudine or a 3-drug regimen were able to keep their virus under control through follow-up
- When the virus became detectable after being under control, people in both treatment groups returned to undetectable levels at similar rates
- People receiving dolutegravir/lamivudine transitioned less often from having the virus under control to having detectable virus and spent less time overall with detectable virus
- Findings remained consistent over up to 3 years of follow-up, supporting long-term control of HIV with dolutegravir/lamivudine

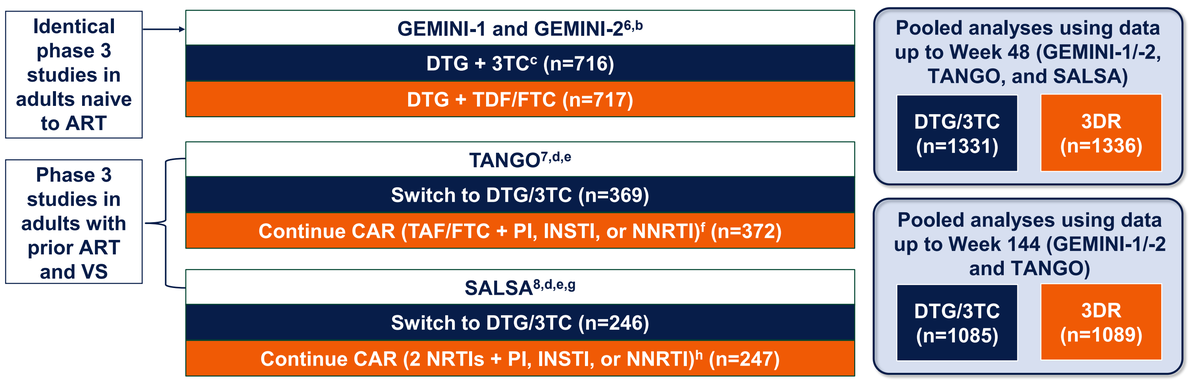
Introduction

- Detectable viral load after virologic suppression may occur in people receiving antiretroviral therapy (ART)[1-4]
- Dolutegravir/Lamivudine (DTG/3TC) has demonstrated non-inferiority to 3-drug regimens (3DRs) in populations naive to ART and with prior ART experience and suppression at switch,[5-8] but data on outcomes following viremic events (VEs) with continued treatment are limited
- Prior pooled analyses demonstrated similar VE incidences and outcomes with DTG/3TC and 3DRs[9]
- Here, multi-state modeling was used to evaluate longitudinal virologic state transitions in a pooled analysis of 4 randomized trials (GEMINI-1/-2 [ART naive]; TANGO and SALSA [ART experienced])

Methods

- This analysis included adults with HIV-1 from 4 randomized clinical trials among populations naive to ART (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) and with prior ART experience and suppression at switch (TANGO [NCT03446573] and SALSA [NCT04021290]; Figure 1)

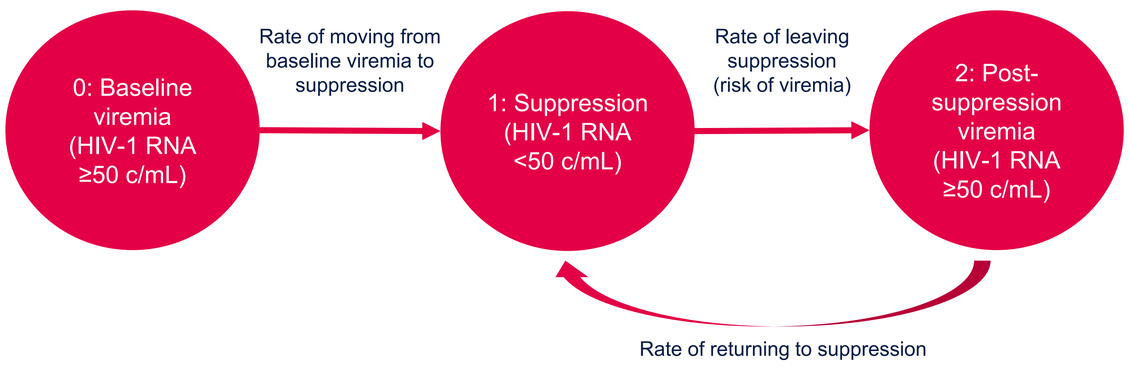
Figure 1. Pooled Analysis of 4 Randomized Trials: Study Design Overview[a]



CAR, current antiretroviral regimen; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VS, virologic suppression. [a]Pooled intention-to-treat–exposed population. [b]Randomization (1:1) was stratified by screening plasma HIV-1 RNA (≤100,000 or >100,000 c/mL) and screening CD4+ cell count (≤200 or >200 cells/mm^3). [c]Administered as multi-tablet formulation. [d]Participants who continued a 4-drug CAR were also included in the analysis. [e]Randomization (1:1) was stratified by baseline third-agent class (PI, INSTI, or NNRTI). [f]Participants were on uninterrupted TAF-based regimen for ≥6 months; participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [g]SALSA was included in the Week 48 pooled analysis only, as only Week 48 data were available. [h]Participants were on uninterrupted ART for ≥3 months.

- HIV-1 RNA was assessed at scheduled visits every 4-12 weeks through Week 48 (and every 12 weeks thereafter through Week 144 in GEMINI-1/-2 and TANGO); across the studies, re-testing was performed approximately 2-4 weeks after any HIV-1 RNA ≥50 c/mL[6-8]
- Multi-state models analyzed transitions between virologic states through Week 48 and Week 144, accounting for recurrent VEs
  - Separate multi-state models were fitted for analyses up to Week 48 and up to Week 144
- A 3-state continuous-time Markov model was specified (Figure 2), comprising baseline viremia (HIV-1 RNA ≥50 c/mL before initial suppression), transitioning to suppression (HIV-1 RNA <50 c/mL), and allowing transitions to/from post-suppression viremia (HIV-1 RNA ≥50 c/mL after prior suppression)
- Transition intensities between states were estimated using an Andersen-Gill proportional hazards model based on the framework in Figure 2, adjusted and stratified by baseline covariates
- Marginal state occupation probabilities were estimated using G-computation to quantify the proportion of individuals in each state under each treatment over time
- Confidence intervals were derived from stratified bootstrap resampling

Figure 2. Three-State Framework for Virologic Transitions



Results

Participant-Level VEs Through Week 48

- The proportion of participants who experienced ≥1 VE through Week 48 was low and similar between treatment groups (DTG/3TC, 10% [138/1331]; 3DR, 12% [161/1336])
- VEs were observed more frequently in the population naive to ART than the population with prior ART experience and suppression at switch, but proportions were comparable between treatment groups
- Most participants with VEs experienced a single event; multiple events were uncommon (median [range] number of VEs experienced: DTG/3TC, 1 [1-2]; 3DR, 1 [1-3])

State Transitions Through Week 48

- The multi-state modeling analysis up to Week 48 included a total of 2648 individuals (DTG/3TC, n=1320; 3DR, n=1328)
  - 19 individuals (DTG/3TC, n=11; 3DR, n=8) were excluded from the analysis due to incomplete data
- Through Week 48, the hazard of transitioning from suppression to post-suppression viremia was 23% lower with DTG/3TC compared with 3DRs (hazard ratio, 0.77 [95% CI, 0.61, 0.96]), while rates of suppression following either baseline viremia or post-suppression viremia were similar between groups (Table)

Table. HRs for State Transitions Through Week 48: DTG/3TC Relative to 3DR

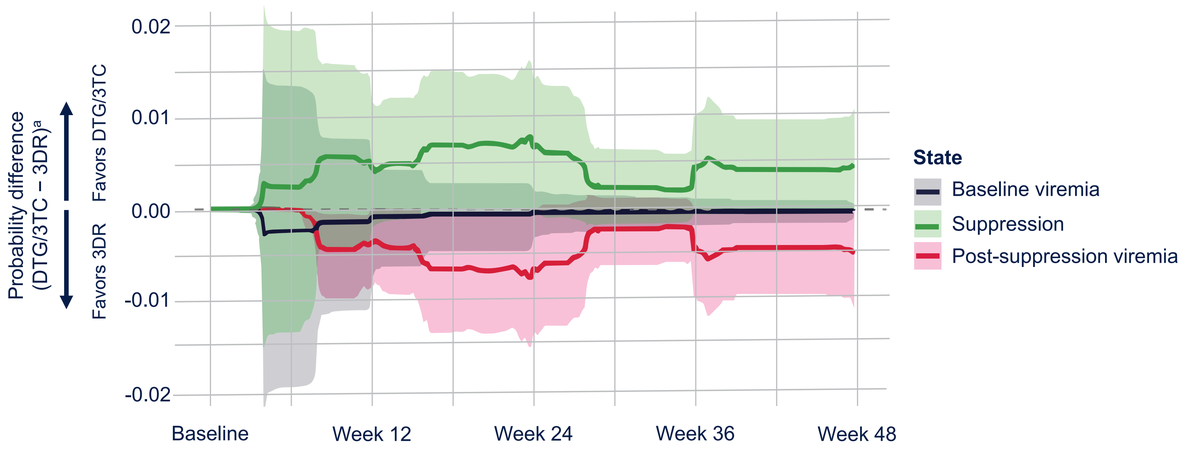
State transition	HR (95% CI)[a]
Baseline viremia → suppression	1.01 (0.93, 1.10)
Suppression → post-suppression viremia	0.77 (0.61, 0.96)
Post-suppression viremia → suppression	0.98 (0.84, 1.15)

HR, hazard ratio. [a]HRs estimated using the 3-state Andersen-Gill multi-state model (stratified by study and adjusted for covariates) and calculated as DTG/3TC divided by 3DR.

Occupation Probabilities Through Week 48

- Through Week 48, 98% of individuals in each group were estimated to be in the suppression state, while 2% were estimated to be in post-suppression viremia (Figure 3)
- Differences in state-occupation probabilities between treatment groups were small

Figure 3. Difference in Marginal State–Occupation Probability Between DTG/3TC and 3DRs Through Week 48



[a]Transition probabilities derived by applying the Aalen-Johansen estimator to cumulative hazards obtained from the Andersen-Gill multi-state model (stratified by study and adjusted for covariates).

Average Time Spent in Post-Suppression Viremia Through Week 48

- The estimated average time spent in the post-suppression viremia state was low and similar between groups (DTG/3TC, 0.60 [95% CI, 0.45, 0.77] weeks; 3DR, 0.78 [95% CI, 0.59, 0.99] weeks; treatment difference, -0.18 [95% CI, -0.37, 0.00] weeks)

State Transitions Through Week 144

- The Week 144 multi-state modeling analysis included 2174 individuals (DTG/3TC, n=1085; 3DR, n=1089) from GEMINI-1/-2 and TANGO; SALSA did not contribute beyond Week 48
- Results through Week 144 were consistent with those through Week 48
- Through Week 144, the estimated transition rate from suppression to post-suppression viremia remained lower with DTG/3TC than with 3DRs (hazard ratio, 0.77 [95% CI, 0.64, 0.93]), while rates of re-suppression following a VE were comparable between groups
- Through Week 144, 98% of individuals in both groups were estimated to be in the suppression state; however, the adjusted probability of being suppressed remained higher with DTG/3TC than with 3DRs (treatment difference, 0.005 [95% CI, 0.001, 0.011])

Conclusions

- DTG/3TC was associated with lower hazards of transitioning from virologic suppression to viremia compared with 3DRs through Weeks 48 and 144
- Rates of re-suppression following post-suppression viremia were comparable between groups, post-suppression viremia was uncommon, and DTG/3TC was associated with numerically less time spent in viremia than 3DRs, supporting virologic control through up to 3 years of follow-up
- By accounting for recurrent transitions, multi-state modeling characterized the longitudinal course of suppression and viremia beyond first-event or single–time point analyses
- These findings support durable virologic control with DTG/3TC in populations naive to ART and with prior ART experience

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