Resistance Data for Dolutegravir + Lamivudine in Treatment-naïve Clinical Trials

Summary

- Protocol-defined virologic failure (PDVF) was identified in 3 patients who received dolutegravir plus lamivudine (DTG + 3TC) in the ACTG 5353 study.[1]
  - One of the PDVF patients with non-adherence developed M184V plus the mixture R263R/K at week 14.
- Confirmed virologic withdrawal (CVW) was identified in 12 patients who received DTG + 3TC in the pooled analysis of the GEMINI-1 and GEMINI-2 studies.[2] None of these patients had virus with treatment-emergent integrase strand transfer inhibitor (INSTI) or nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations through Week 144.[3]
  - One non-CVW patient with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 and R263R/K at Week 144.[3]
- Important safety information and boxed warning(s) can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

RESISTANCE DATA

AIDS CLINICAL TRIALS GROUP (ACTG) 5353

ACTG 5353 was a 48-week, single arm, phase 2 study designed to evaluate the safety and efficacy of DTG 50 mg once-daily plus 3TC 300 mg once-daily in ART-naïve patients (n = 120) infected with HIV-1.[1] The primary efficacy endpoint was the proportion of patients with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot definition.[1] PDVF was defined as a confirmed HIV-1 RNA > 400 copies/mL at Weeks 16 or 20, or, confirmed HIV-1 RNA > 200 copies/mL at/after Week 24.

Overall, there were three PDVFs through Week 24.[1] See Table 1 below for details about each patient. Each patient had more than one time point associated with HIV-1 RNA >50 copies/mL where their DTG plasma concentration was at or below the limit of detection.

Table 1. PDVF in ACTG 5353 Through Week 24[1]

Patient	Baseline HIV-1 RNA (copies/mL)	HIV-1 RNA < 50 copies/mL by Week:	Time Point of first HIV-1 RNA ≥ 50 copies/mL (Week)	Time Points of Low/ Undetectable DTG Concentrations (Week)	Mutations Detected[a]
A	> 100,000	12	20	20, before Week 32	None
B	≤ 100,000	4	8	4, 8, 24, before Week 32[b]	M184V[c] R263RK[d]
C	≤ 100,000	4	20	20, 24[e]	V106I (at Week 24)

[a]M184V reduces 3TC susceptibility by >100-fold; R263K reduces DTG susceptibility by ~2–fold; V106I is a polymorphic, accessory non-nucleoside reverse transcriptase inhibitor mutation.[4] [b]Off DTG + 3TC after Week 16.[c]Between Weeks 16 and 20, at Week 24. [d]Between Weeks 16 and 20 only. [e]Off DTG + 3TC after Week 24. ART=antiretroviral therapy; DTG=dolutegravir

Patient B experienced viral rebound and prolonged viremia, discontinuing study treatment due to noncompliance at week 18. This patient had confirmed virologic failure at week 24 (off ART) with the M184V mutation in RT detected (no mutation found pre-treatment). Population-based genotyping of samples obtained prior to PDVF showed no mutations at week 8 (HIV-1 RNA 6579 copies/mL) and M184V plus the mixture R263R/K in integrase at week 14 (HIV-1 RNA 446 copies/mL).

GEMINI-1 and GEMINI-2

GEMINI-1 and GEMINI-2 are ongoing, 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) patients with viral load ≤ 500,000 copies/mL.[2]

CVW was defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound and was measured between 2 and 4 weeks after a Suspected Virologic Withdrawal (SVW).[2] A total of 12 patients in the DTG + 3TC group and 9 patients in the DTG plus tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) group met CVW criteria by Week 144.[3] All patients meeting CVW criteria were classified as Virologic Rebound, defined as confirmed rebound in plasma HIV-1 RNA levels to ≥ 200 copies/mL after prior confirmed suppression to <200 copies/mL. Patients who met any CVW criterion were discontinued from the study and virologic resistance testing was triggered. There was no treatment emergent INSTI or NRTI resistance observed for any patients meeting CVW criteria through Week 144.[3]

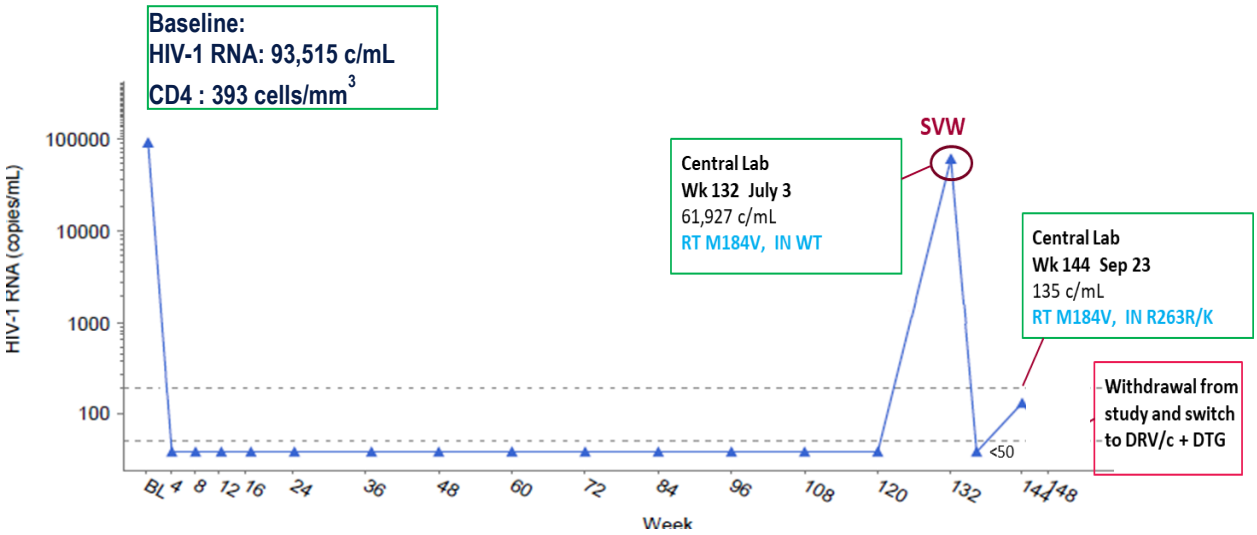
Table 2. Summary of Resistance Data through Week 96 for CVW Patients in DTG+3TC Arms[5,6]

Patient	CVW Visit	Integrase/NRTI Genotype[a]	DTG FC Baseline	DTG FC CVW	3TC FC Baseline	3TC FC CVW
1	W16	None	0.67	0.72	1.13	1.12
2	W24	None	0.76	0.7	0.98	0.69
3	W24	None	0.88	0.86	1.02	1.43
4	W48	None	0.8	0.79	0.9	1.74
5	W24	None	0.92	0.8	1.16	1.16
6	W24	None	0.81	0.87	1.17	1.09
7	W60	None	0.89	1.13	0.95	0.87
8	W60	None	0.7	0.71	0.86	0.86
9	W72	None	0.64	0.81	0.84	0.69
10	W96	None	0.72	0.83	1.09	1.04
11	W72	None	0.84	0.9	0.84	0.73

[a] Genotype at CVW, "none" indicates no IAS-USA major mutations or integrase pre-specified resistance mutations observed. Pre-specified mutations included H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E.
CVW = confirmed virologic withdrawal; NRTI = nucleoside reverse transcriptase inhibitor; FC = fold change compared to wild type HIV-1 virus.

One non-confirmed virologic withdrawal patient who received DTG + 3TC developed M184V (HIV-1 RNA 61,927 copies/mL) at Week 132 and R263R/K (HIV-1 RNA 135 copies/mL) at Week 144, conferring a 1.8-fold change in susceptibility to DTG.[3] The patient had a baseline HIV-1 RNA: 93,515 copies/mL and suppressed to HIV-1 RNA <50 copies/mL from Week 4 through Week 120; HIV-1 RNA 61,927 copies/mL detected at Week 132, with successive HIV-1 RNA of <50, 135, and 61 copies/mL after Week 132. The patient was withdrawn due to lack of efficacy at Week 144, switched to DTG once daily + darunavir/cobicistat, and regained virological suppression (Figure 1).

Figure 1. HIV-1 Viral Load and Genotype Details of Non-Confirmed Virologic Withdrawal Patient in GEMINI[3]



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