P042

Viral Blips in the Doravirine Phase 3 Clinical Trials DRIVE-FORWARD and DRIVE-AHEAD

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Background

- Transient viremia, also known as viral blips, occurs frequently during antiretroviral therapy, with incidence rates up to 50% being reported[1,2]
  - Blips may represent random biologic variation, release of virus from latent reservoirs, ongoing replication due to suboptimal medication adherence, and/or random assay variability[3,4]
  - The clinical significance of viral blips is unclear, as there is conflicting evidence regarding an association between blip occurrence and virologic failure or the development of drug resistance[3-5]
  - Blips may lead to increased spending for repeat viral load measurements, drug level testing, and/or additional visits for adherence counseling[4]
- Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) designed to address limitations associated with earlier NNRTIs, such as resistance from common NNRTI resistance-associated mutations, the neuropsychiatric events observed with efavirenz, and the food requirement and high baseline viral load exclusion associated with rilpivirine[6]
- The efficacy and safety of DOR were demonstrated in 2 randomized, double-blind, phase 3 studies of first-line therapy in adults living with HIV-1
  - DOR 100 mg was non-inferior to ritonavir-boosted darunavir (DRV/r), each given with 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs), at week 48 and week 96 of the DRIVE-FORWARD study[7,8]
  - DOR 100 mg in fixed combination with lamivudine and tenofovir disoproxil fumarate (DOR/3TC/TDF) was non-inferior to efavirenz with emtricitabine and TDF (EFV/FTC/TDF) at week 48 and week 96 of the DRIVE-AHEAD study[9,10]
  - In both studies, the DOR regimen maintained high rates of virologic suppression and was generally well tolerated through week 192[11]

Objective

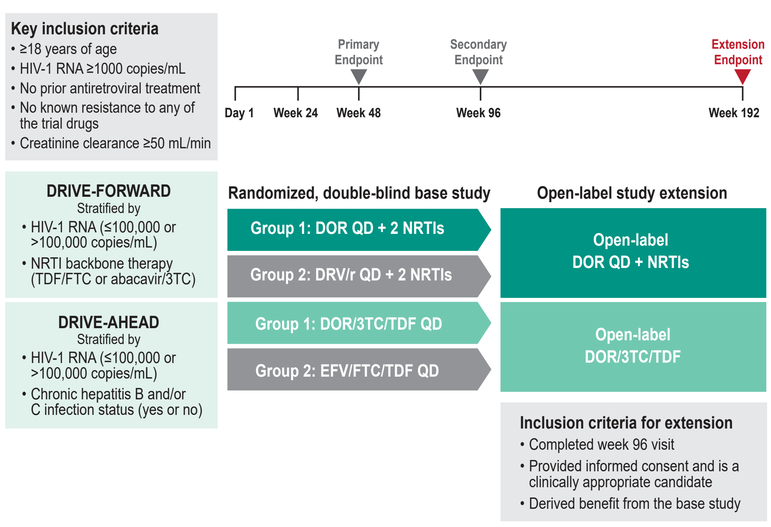
This was a post hoc analysis of the occurrence of viral blips, defined as HIV-1 RNA ≥50 copies/mL immediately preceded and followed by <50 copies/mL, possible predictors of viral blips, and the impact of viral blips on subsequent virologic rebound in the DRIVE-FORWARD and DRIVE-AHEAD studies.

Methods

Study design

- DRIVE-FORWARD (1439-018; NCT02275780) and DRIVE-AHEAD (1439A-021; NCT02403674) were randomized, double-blind, active-controlled, non-inferiority studies in adults with previously untreated HIV-1 (**Figure 1**)
  - Participants were randomly assigned to receive a DOR regimen (DOR + 2 NRTIs in DRIVE-FORWARD; DOR/3TC/TDF in DRIVE-AHEAD) or the comparator regimen (DRV/r + 2 NRTIs or EFV/FTC/TDF, respectively) for 96 weeks of double-blind treatment.
  - Upon completing the double-blind phase, eligible participants could enter an open-label study extension and either continue their DOR-based regimen (if originally randomized to the DOR group) or switch to the DOR-based regimen (if originally randomized to the comparator group) for 96 weeks

Figure 1. Study design of DRIVE-FORWARD and DRIVE-AHEAD



Statistical methods

- This analysis included participants who had achieved an initial response of <50 copies/mL and had HIV-1 RNA measures between the date of initial response and the date of the last available visit
- The endpoints of interest were defined as follows:
  - Viral blip: HIV-1 RNA ≥50 copies/mL that was preceded by <50 copies/mL at the previous visit and followed by <50 copies/mL at the next visit
  - Virologic rebound: confirmed HIV-1 RNA ≥50 copies/mL (2 consecutive measures at least 1 week apart) after initial response of HIV-1 RNA <50 copies/mL at any time during the study
- Two time periods were analyzed:
  - Base study (double-blind): Day 1 to week 96, where participants received the DOR regimen or the comparator regimen (see **Figure 1**)
  - Study extension (open-label): Week 96 to week 192, where all participants received a DOR regimen, either DOR + 2 NRTIs in P018 or DOR/3TC/TDF in P021.
- A Cox proportional hazards model was used to analyze the relationship between blips and baseline characteristic factors, and a Cox model with time-varying blip status was used to analyze the relationship between blips and virologic rebound
- The following covariates were used in the models: age group (<50 or ≥50 years of age), history of AIDS (yes or no), baseline CD4 T-cell count (≥200 or <200 cells/mm^3), baseline HIV-1 RNA (≤100,000 or >100,000 copies/mL), race (Black, White, or Other), sex (male or female), study ID (P018 or P021), treatment group, and the interaction of study ID and treatment group

Results

Base studies (day 1 to week 96)

- Of 1,494 treated participants, 1,338 met the inclusion criteria for the analysis, 678 in the DOR groups and 660 in the comparator groups
- Blips occurred in 12.6% of participants overall (169/1338): 11.1 to 11.9% of participants in the DOR groups, and 12.1 to 15.4% of participants in the comparator groups (**Table 1**).
  - Most participants with blips had only one episode, and the median viral load at first blip was low, ranging from 61.5 to 73 copies/mL

Table 1. Summary of viral blips in DRIVE-FORWARD and DRIVE-AHEAD base studies, day 1 to week 96, by study and treatment group

	DRIVE-FORWARD (P018)		DRIVE-AHEAD (P021)	
	DOR + 2NRTIs n (%)[a]	DRV/r + 2NRTIs n (%)[a]	DOR/3TC/TDF n (%)[a]	EFV/FTC/TDF n (%)[a]
Participants	342	338	336	322
Total # of blips	42	56	54	46
Participants with blips	38/342 (11.1)	52/338 (15.4)	40/336 (11.9)	39/322 (12.1)
with 1 blip	35 (92.1)	48 (92.3)	28 (70.0)	35 (89.7)
with 2 blips	2 (5.3)	4 (7.7)	10 (25.0)	3 (7.7)
with 3 blips	1 (2.6)	0 (0.0)	2 (5.0)	0 (0.0)
with ≥4 blips	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
VL at first blip, median (IQR)	72.5 (56, 120)	70.5 (58, 92)	61.5 (55, 196.5)	73.0 (56, 98)
Participants with virologic rebound after blip	8 (21.1)	7 (13.5)	5 (12.5)	3 (7.7)
VL <200 copies/mL	3 (7.9)	3 (5.8)	3 (7.5)	2 (5.1)
VL ≥200 copies/mL	5 (13.2)	4 (7.7)	2 (5.0)	1 (2.6)

[a]Denominator for percentages is the number of participants with blips, unless otherwise specified.
IQR, interquartile range. VL, viral load (copies/mL).

- Risk for blips was significantly lower in participants with baseline HIV-1 RNA ≤100,000 copies/mL:
  - Incidence 10.5% (114/1081) vs 21.1% (54/256) for >100,000 copies/mL (P<0.001)
  - Hazard ratio (HR) 0.41, 95% CI 0.29, 0.58 (**Table 2**).
- Virologic rebound occurred in 7.0% of all participants in the base studies (94/1338), and risk for virologic rebound was significantly higher in participants with blips:
  - Incidence 13.6% (23/169) vs 6.1% (71/1169) in those without blips (P=0.001)
  - HR 3.79, 95% CI 2.32, 6.18 (**Table 3**)
- Treatment regimen did not appear to impact the risk for blips (**Table 2**) or the risk for virologic rebound after blip (**Table 3**)

Table 2. Hazard ratio for blips in DRIVE-FORWARD and DRIVE-AHEAD base studies, day 1 to week 96, pooled data (all treatment groups)

Description	Hazard Ratio	
	(95% CI)	P-value
Age group (<50 vs ≥50)	0.80 (0.51, 1.26)	0.344
History of AIDS (Yes vs No)	1.01 (0.59, 1.74)	0.957
Baseline CD4 count (≤200 vs >200 cells/mm^3)	1.08 (0.65, 1.80)	0.754
Baseline HIV RNA (≤100,000 vs >100,000 copies/mL)	**0.41 (0.29, 0.58)**	**<.001**
Race group: Black vs White	1.55 (1.05, 2.27)	0.027
Race group: Other vs White	1.10 (0.70, 1.71)	0.678
Female vs Male	0.73 (0.46, 1.17)	0.192
P018: DOR+2NRTIs vs DRV/r+2NRTIs	0.66 (0.44, 1.01)	0.057
P021: DOR/3TC/TDF vs EFV/FTC/TDF	0.96 (0.62, 1.50)	0.865
DOR+2NRTIs (P018) vs DOR/3TC/TDF (P021)	0.92 (0.58, 1.46)	0.730
DRV/r+2NRTIs (P018) vs EFV/FTC/TDF (P021)	1.34 (0.86, 2.08)	0.201

Table 3. Hazard ratio for virologic rebound in DRIVE-FORWARD and DRIVE-AHEAD base studies, day 1 to week 96, pooled data (all treatment groups)

Description	Hazard Ratio	
	(95% CI)	P-value
Blip status (Yes vs No)	**3.79 (2.32, 6.18)**	**<.001**
Age group (<50 vs ≥50 years)	4.02 (1.27, 12.76)	0.018
History of AIDS (Yes vs No)	1.03 (0.50, 2.12)	0.927
Baseline CD4 count (≤200 vs >200 cells/mm^3)	1.45 (0.75, 2.81)	0.265
Baseline HIV RNA (≤100,000 vs >100,000 copies/mL)	0.67 (0.41, 1.10)	0.115
Race group: Black vs White	1.24 (0.74, 2.11)	0.416
Race group: Other vs White	1.37 (0.77, 2.46)	0.287
Female vs Male	1.57 (0.93, 2.67)	0.094
P018: DOR+2NRTIs vs DRV/r+2NRTIs	0.74 (0.42, 1.30)	0.296
P021: DOR/3TC/TDF vs EFV/FTC/TDF	1.06 (0.58, 1.94)	0.840
DOR+2NRTIs (P018) vs DOR/3TC/TDF (P021)	1.38 (0.72, 2.67)	0.332
DRV/r+2NRTIs (P018) vs EFV/FTC/TDF (P021)	2.00 (1.05, 3.80)	0.035

Study extensions (week 96 to week 192)

- Of 1,052 subjects who entered the study extensions, 1,029 met the inclusion criteria for the analysis, 539 who continued their DOR regimen and 490 who switched from comparator to a DOR regimen.
- Blips were less common during the study extensions than during the base studies, occurring in 6.9% of participants overall (71/1,029): 5.5 to 6.6% of participants who continued their DOR regimen, and 7.6 to 7.9% of those who switched to a DOR regimen (**Table 4**)
  - Most participants with blips had only one episode, and the median viral load at first blip was low, ranging from 66 to 85 copies/mL

Table 4. Summary of viral blips in DRIVE-FORWARD and DRIVE-AHEAD study extensions, week 96 to week 192, by study and treatment group

	DRIVE-FORWARD (P018)		DRIVE-AHEAD (P021)	
	Continued DOR + 2NRTIs n (%)[a]	Switched to DOR + 2NRTIs n (%)[a]	Continued DOR/3TC/TDF n (%)[a]	Switched to DOR/3TC/TDF n (%)[a]
Participants	253	225	286	265
Total # of blips	14	22	20	24
Participants with blips	14/253 (5.5)	17/225 (7.6)	19/286 (6.6)	21/265 (7.9)
with 1 blip	14 (100.0)	13 (76.5)	18 (94.7)	18 (85.7)
with 2 blips	0 (0.0)	3 (17.6)	1 (5.3)	3 (14.3)
with 3 blips	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)
VL at first blip, median (IQR)	66 (63, 76)	85 (57, 126)	74 (56, 154)	76 (61, 89)
Participants with virologic rebound after blip	1 (7.1)	1 (5.9)	1 (5.3)	3 (14.3)
VL <200 copies/mL	1 (7.1)	1 (5.9)	1 (5.3)	2 (9.5)
VL ≥200 copies/mL	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)

[a]Denominator for percentages is the number of participants with blips, unless otherwise specified.
IQR, interquartile range. VL, viral load (copies/mL).

- Baseline HIV-1 RNA ≤100,000 copies/mL was associated with lower risk for blips in participants who continued DOR: HR 0.41 (0.19, 0.87) (**Table 5**)
- Baseline CD4 T-cell count ≤200 cells/mm^3 was associated with increased risk for blips in participants who switched to DOR: HR 3.47 (1.43, 8.43) (**Table 6**)
- Virologic rebound occurred in 3.8% of all participants in the study extensions (39/1,029) and was more common among participants with blips (8.5%, 6/71) vs those without blips (3.4%, 33/958); however, the impact of blips on virologic rebound in the study extensions was unclear due to the low number of events

Table 5. Hazard Ratio for blips in DRIVE-FORWARD and DRIVE-AHEAD study extensions, week 96 to week 192, DOR continued groups

Description	Hazard Ratio	
	(95% CI)	P-value
Age group (<50 vs ≥50)	1.14 (0.39, 3.35)	0.806
History of AIDS (Yes vs No)	1.61 (0.54, 4.81)	0.396
Baseline CD4 count (≤200 vs >200 cells/mm3)	1.10 (0.34, 3.59)	0.873
Baseline HIV RNA (≤100,000 vs >100,000 copies/mL)	**0.41 (0.19, 0.87)**	**0.021**
Race group: Black vs White	0.98 (0.36, 2.70)	0.968
Race group: Other vs White	0.60 (0.23, 1.61)	0.314
Female vs Male	0.29 (0.07, 1.29)	0.105

Table 6. Hazard Ratio for blips in DRIVE-FORWARD and DRIVE-AHEAD study extensions, week 96 to week 192, DOR switch groups

Description	Hazard Ratio	
	(95% CI)	P-value
Age group (<50 vs ≥50)	1.13 (0.39, 3.31)	0.818
History of AIDS (Yes vs No)	1.82 (0.68, 4.89)	0.234
Baseline CD4 count (≤200 vs >200 cells/mm3)	**3.47 (1.43, 8.43)**	**0.006**
Baseline HIV RNA (≤100,000 vs >100,000 copies/mL)	1.42 (0.61, 3.29)	0.414
Race group: Black vs White	0.70 (0.25, 1.96)	0.495
Race group: Other vs White	2.27 (0.98, 5.29)	0.057
Female vs Male	1.13 (0.45, 2.83)	0.791

Conclusions

- In the DRIVE-FORWARD and DRIVE-AHEAD base studies, the incidence of viral blips was similar in participants who received a DOR regimen and those who received a comparator regimen
- In the study extensions, the incidence of viral blips was lower than in the base studies and was similar in participants continuing or switching to a DOR regimen
- Most participants with viral blips had only one episode, irrespective of the treatment regimen
- Baseline HIV-1 RNA ≤100,000 copies/mL was associated with lower risk for viral blips in all treatment groups during the base studies and in the DOR continued groups during the study extensions
- Baseline CD4 T-cell count ≤200 cells/mm^3 was associated with higher risk for viral blips in the DOR switch groups during the study extensions
- The incidence of virologic rebound was low overall: 7.0% during the base studies and 3.8% during the study extensions
  - In the base studies, viral blips were associated with increased risk for virologic rebound
  - In the study extensions, 5 of the 6 participants with virologic rebound after blip had low-level viremia (rebound viral load <200 copies/mL)

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