DTG Versus LPV/r in Second Line (DAWNING): Outcomes by WHO-Recommended NRTI Backbone

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Michael Aboud,[1] Carlos Brites,[2] Hongzhou Lu,[3] Khuanchai Supparatpinyo,[4] Luis Hercilla,[5] Jörg Sievers,[1] Maria Claudia Nascimento,[1] Judy Hopking,[6] Mark Underwood,[7] Dannae Brown,[8] Martin Gartland,[7] Kimberly Smith[7]

[1]ViiV Healthcare, Brentford, UK; [2]Federal University of Bahia, Salvador, Brazil; [3]Fudan University, Shanghai, China; [4]Chiang Mai University, Chiang Mai, Thailand; [5]Hospital Nacional Alberto Sabogal Sologuren, Callao, Peru; [6]GlaxoSmithKline, Uxbridge, UK; [7]ViiV Healthcare, Research Triangle Park, NC, USA; [8]ViiV Healthcare, Abbotsford, Australia

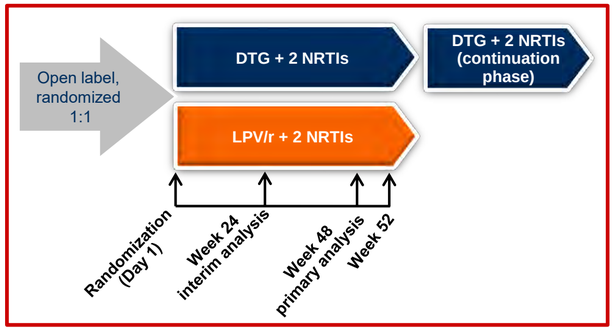
Introduction

- There remains a need to optimize second-line antiretroviral therapy (ART) in resource-limited settings
- DAWNING is a noninferiority study comparing dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) with a current World Health Organization (WHO)–recommended regimen of lopinavir/ritonavir (LPV/r) + 2 NRTIs in HIV-1–infected adults failing first-line therapy (HIV-1 RNA ≥400 c/mL) with a non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 NRTIs (ClinicalTrials.gov identifier, NCT02227238)
- Week 24 secondary endpoint (% HIV-1 RNA <50 c/mL; snapshot) data were presented at the International AIDS Society Conference on HIV Science in 2017[1]
- Prior to a 24-week interim analysis, the study's Independent Data Monitoring Committee recommended discontinuation of the LPV/r arm due to superior efficacy of DTG + 2 NRTIs based on available data; the study protocol was amended to allow participants receiving ongoing LPV/r to switch to the DTG arm

Methods

- Patients were randomized (1:1) to 52 weeks of open-label treatment with DTG or LPV/r combined with 2 investigator-selected NRTIs (Figure 1)
  - Key eligibility criteria: taking first-line 2 NRTIs + NNRTI regimen for ≥6 months; virologic failure (HIV-1 RNA ≥400 c/mL on 2 occasions); and no primary viral resistance to protease inhibitors or integrase strand transfer inhibitors (INSTIs)
  - Investigator-selected NRTIs included ≥1 fully active NRTI based on viral genotypic resistance testing at screening
  - Stratification: by HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)

Figure 1. DAWNING Study Design



- Post-hoc efficacy analyses were performed based on whether WHO-recommended second-line NRTIs were chosen per participants' first-line NRTIs; 59 participants not taking WHO-recommended first-line NRTIs were excluded
  - WHO-recommended second-line NRTIs were defined as tenofovir disoproxil fumarate (TDF) + (emtricitabine [FTC] or lamivudine [3TC]) and zidovudine (AZT) + 3TC when (AZT or stavudine [d4T]) + 3TC and TDF + (FTC or 3TC), respectively, were used as first-line NRTIs[2]

Results

- Of the 968 patients screened for the study, 627 (DTG group, n=312; LPV/r group, n=315) were randomly assigned to receive study medication, and 624 received ≥1 dose (DTG group, n=312; LPV/r group, n=312)
- 58 investigational centers in Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, the Russian Federation, South Africa, Thailand, and Ukraine randomized ≥1 study participant
- The most common reason for screening failure was not meeting inclusion criteria
  - Most common reason was HIV-1 RNA <400 c/mL in 134 patients (14%)
  - Only 78 (8%) were screen failures due to not having 1 fully active NRTI available
- Similar proportions of participants received either AZT + 3TC or TDF + (FTC or 3TC) as part of the second-line regimen within and across groups (Table)

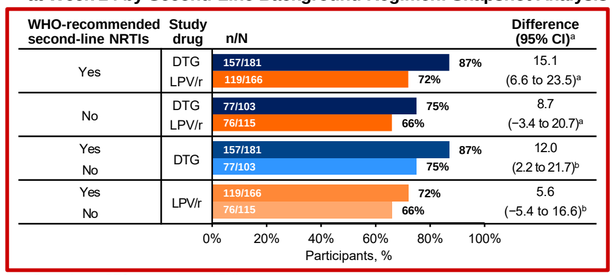
Table. Prior ART and Background NRTIs Received at Day 1

	DTG (n=312)	LPV/r (n=312)
First-line agent, n (%)		
Efavirenz	242 (78)	242 (78)
TDF	181 (58)	186 (60)
AZT	89 (29)	89 (29)
Second-line NRTI, n (%)		
AZT + 3TC	131 (42)	121 (39)
TDF + (FTC or 3TC)	128 (41)	134 (43)
TDF + AZT	36 (12)	40 (13)
ABC + 3TC	7 (2)	7 (2)
Other[a]	10 (3)	10 (3)

ABC, abacavir. [a]Includes AZT + ABC, AZT + TDF + 3TC, and TDF + ABC.

- At Week 24, DTG + 2 NRTIs was superior to LPV/r + 2 NRTIs, with 82% (257/312) and 69% (215/312) of participants, respectively, achieving HIV-1 RNA <50 c/mL (adjusted difference, 13.8%; 95% confidence interval [CI], 7.3-20.3; *P*<0.001).[1] The difference was mainly driven by lower rates of snapshot virologic nonresponse in the DTG group
- Overall, 90% of participants in the DTG group and 84% in the LPV/r group achieved the secondary efficacy endpoint of plasma HIV-1 RNA <400 c/mL at Week 24
- 56% (347/624) of participants received second-line NRTIs in accordance with the WHO algorithm, and their snapshot response rates within each arm were higher than those for participants who did not. Regardless of WHO-recommended NRTI use, response rates were higher with DTG- versus LPV/r-based regimens (Figure 2)

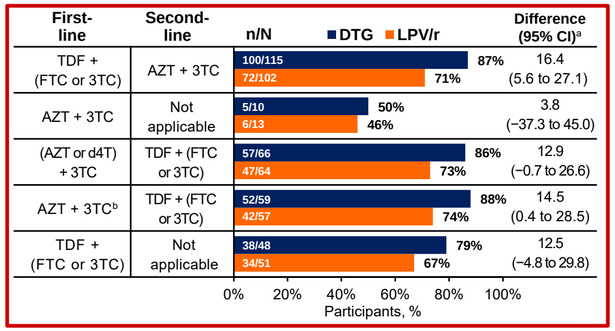
Figure 2. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by Second-Line Background Regimen: Snapshot Analysis



[a]Proportion on DTG – proportion on LPV/r.
[b]Proportion with WHO-recommended NRTIs – proportion without WHO-recommended NRTIs.

- Snapshot response rates were higher with DTG- versus LPV/r-based regimens regardless of the first-line to second-line NRTI change (Figure 3)

Figure 3. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by First- and Second-Line NRTI Choice: Snapshot Analysis



[a]Proportion on DTG – proportion on LPV/r (unadjusted).
[b]Excludes participants who received d4T + 3TC in their first-line regimen (7 per treatment arm).

- The overall safety profile of DTG + 2 NRTIs was favorable compared with LPV/r + 2 NRTIs, with more drug-related adverse events reported in the LPV/r group[1]
- In this 24-week interim analysis, there were no treatment-emergent primary INSTI or NRTI resistance mutations in the DTG group through the randomization phase[1]

Discussion

- 24-week interim data from the DAWNING study showed that DTG + 2 NRTIs is superior to LPV/r + 2 NRTIs in second-line therapy
- Subgroup analyses of virologic efficacy based on stratification of whether or not a WHO-recommended second-line NRTI background regimen was taken not only favor DTG versus LPV/r but also the regimen with WHO-recommended NRTIs within each treatment group
- One limitation of these analyses is that genotyping was used to select ≥1 fully active NRTI, and the resulting NRTI background regimen conforming to WHO guidance or not was incidental
- Outcomes from the SECOND-LINE and EARNEST studies suggest resistance testing may not be required in lieu of an appropriate algorithm for selection of second-line NRTIs[3,4]

Conclusions

- In the DAWNING study, response rates were highest in participants receiving DTG + WHO-recommended second-line NRTIs
- Within each arm, study participants had higher response rates when receiving WHO-recommended versus other second-line NRTIs, reinforcing the WHO algorithm for NRTI selection in second-line treatment
- The DAWNING study provides important information to help guide second-line treatment decisions in resource-limited settings

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References: 1. Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. Abstract TUAB0105LB. Published at: 9th IAS Conference on HIV Science (IAS); July 23-26, 2017; Paris, France. **2.** World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. 2016. **3.** SECOND-LINE Study Group. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study. *Lancet.* 2013;381:2091-2099. **4.** Paton NI, Kityo C, Thompson J, et al. Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. *Lancet HIV.* 2017;4:e341-e348.