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Effect of adherence on virological response to once-daily versus twice-daily darunavir/ritonavir in treatment-experienced, HIV-1-infected patients with no darunavir resistance-associated mutations: ODIN 48-week data

Cassy Workman,[1] Paul Benson,[2] José Valdez Madruga,[3] Armin Rieger,[4] Tom Van de Casteele,[5] Ludo Lavreys,[5] Sabrina Spinosa-Guzman[5]

[1]AIDS Research Initiative, Darlinghurst, Australia; [2]Be Well Medical Center, Berkley, Michigan, USA; [3]Centro de Referência e Treinamento DST/AIDS, São Paulo, Brazil; [4]Medical University of Vienna, Vienna, Austria; [5]Tibotec BVBA, Beerse, Belgium

Address correspondence to: Cassy Workman, AIDS Research Initiative, Darlinghurst, Australia; Fax: +61 2 9331 1833; E-mail: cworkman@aids-research.COM.AU

Introduction

- The efficacy and safety of the protease inhibitor (PI) darunavir (DRV) with low-dose ritonavir (DRV/r) at a dose of 800/100mg qd in treatment-naïve patients, has been demonstrated in the ARTEMIS trial.[1]
- DRV/r 800/100mg qd is approved in combination with other antiretrovirals (ARVs) for the treatment of HIV-1 infection in treatment-naïve adults in the USA,[2] Europe[3] and other countries.
- ODIN (TMC114-C229; **O**nce-daily **D**arunavir **I**n treatment-experie**N**ced patients), a 48-week, Phase IIIb, randomised, open label trial, compared the efficacy, safety and tolerability of DRV/r 800/100mg qd versus DRV/r 600/100mg bid in treatment-experienced, HIV-1-infected patients with no DRV resistance-associated mutations (RAMs) at screening.
- The primary objective of the ODIN trial was to demonstrate non-inferiority in virological response of once-daily versus twice-daily DRV/r at 48 weeks.
- At Week 48, 72.1% of once-daily DRV/r and 70.9% of twice-daily DRV/r patients achieved HIV-1 RNA <50 copies/mL; the difference in response was 1.2% (95% confidence interval [CI]: –6.1 to 8.5%; p<0.001), establishing non-inferiority of once-daily DRV/r.[4]
- DRV/r once and twice daily was generally well tolerated, with the majority of adverse events (AEs) being grade 1 or 2 in severity
  - discontinuation due to AEs was low; 10 patients (3.4%) in the once-daily arm and 14 patients (4.7%) in the twice-daily arm discontinued.
- ARV adherence is known to be a strong predictor of long-term treatment response.[5]
- In the previous ARTEMIS 96-week study,[6] higher virological response rates were observed in adherent patients than suboptimally adherent patients.
- This analysis from the ODIN trial examined patient-reported adherence and its association with virological response to Week 48.

Methods

Study design

- Treatment-experienced, HIV-1-infected patients on a stable highly active ARV therapy regimen for >12 weeks with no DRV RAMs at screening and with HIV-1 RNA >1,000 copies/mL at baseline, were randomised to receive either DRV/r 800/100mg qd or DRV/r 600/100mg bid.
- Based on ARV history and resistance testing, patients also received an investigator-selected optimised background regimen consisting of ≥2 NRTIs.

Efficacy and safety assessments

- The intent-to-treat (ITT) population was used for the safety analysis.
- Patients fasted for at least 8 hours prior to each blood sample being taken for biochemistry testing.
- Laboratory abnormalities and incidence and severity of AEs (determined by the investigator) were assessed during each visit.

Adherence assessments

- Mean adherence (Weeks 4–48) was assessed during the last 30 days prior to study visits over 48 weeks using
  - the Modified-Medication Adherence Self-Report Inventory (M-MASRI) questionnaire. Rates were transformed into binary variables of >95% (adherent) and ≤95% (suboptimal adherent)[7]
  - DRV plasma concentrations being above (adherent) or below (suboptimal adherent) the detection limit of 10ng/mL
  - pill count (actual amount taken/amount to be taken) x 100%, and transformed into binary variables using a 95% cut-off to define adherent (>95%) and suboptimally adherent (≤95%) patients.
- Pharmacokinetic assessments were performed at Weeks 4, 8, 24 and 48.
- Safety data were collected at screening, baseline, Weeks 4, 12, 24, 36 and 48.
- Confirmed virological responses and AEs were tabulated over time by adherence.
- Between-group comparisons of adherence rates were performed using the Fisher's exact test.
- The study protocol and amendments were reviewed and approved by the appropriate institutional review board health authorities, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

Patient disposition and baseline characteristics

- In the ODIN trial, a total of 590 treatment-experienced, HIV-1-infected patients were randomised to receive either DRV/r 800/100mg qd (n=294) or DRV/r 600/100mg bid (n=296) plus ≥2 NRTIs.
- At baseline, demographical data and disease characteristics were generally well balanced between treatment arms (Table 1).

Adherence

- Across the three methods used, the percentage of patients who were adherent over the whole treatment period ranged from 57.5% to 83% (once-daily DRV/r) and 54% to 88% (twice-daily DRV/r)
- Based on the M-MASRI, the percentage of adherent patients was numerically greater in the once-daily DRV/r group (ranging between 66.8% and 70.7%) than in the twice-daily DRV/r group (ranging between 59.2% and 65.2%) at all measured timepoints (Figure 1), but not significantly so (all p≥0.10).

Table 1. Demographics and disease characteristics at baseline.

	DRV/r 800/100mg qd (n=294)	DRV/r 600/100mg bid (n=296)
Demographics		
Male, n (%)	179 (60.9)	198 (66.9)
Median age, years (range)	40 (18–70)	40 (18–77)
Race, n (%)		
Black	83 (28.2)	72 (24.3)
Caucasian/White	102 (34.7)	110 (37.2)
Hispanic	47 (16.0)	59 (19.9)
Asian	48 (16.3)	41 (13.9)
Other	14 (4.8)	14 (4.7)
Disease characteristics		
Mean HIV RNA, log_{10} copies/mL (SE)	4.19 (0.05)	4.13 (0.05)
Median CD4 cell count, cells/mm³ (range)	219 (24–1,306)	236 (44–864)
Mean known duration of infection, years (SE)	8.4 (0.29)	8.5 (0.30)
Previous ARV experience, n (%)		
PIs: 0	135 (45.9)	137 (46.3)
PIs: 1	74 (25.2)	77 (26.0)
PIs: ≥2	85 (28.9)	82 (27.7)
NRTIs: ≥3	174 (59.1)	164 (55.4)
NNRTIs: ≥1	258 (87.8)	258 (87.2)

SE = standard error

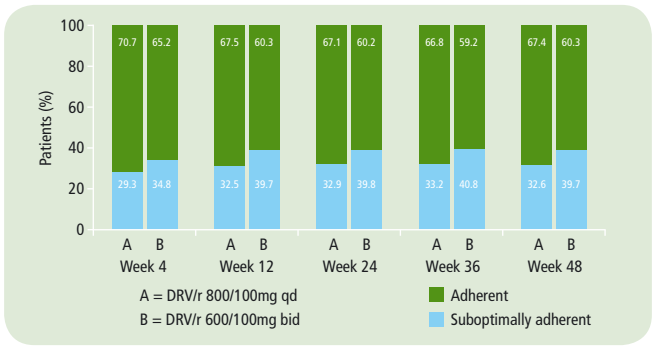

Figure 1. Proportion of adherent and suboptimally adherent patients, as assessed by the M-MASRI over time.

- Adherence rates were generally lower when calculated by pill count than by the M-MASRI
  - at all timepoints, the percentage of adherent patients was numerically higher in the once-daily DRV/r arm (ranging from 57.8% to 63.2%) than the twice-daily DRV/r arm (ranging from 42.4% to 59.3%) (Figure 2), but this was only significant at Week 4 (p<0.0001, all other timepoints: p≥0.06).

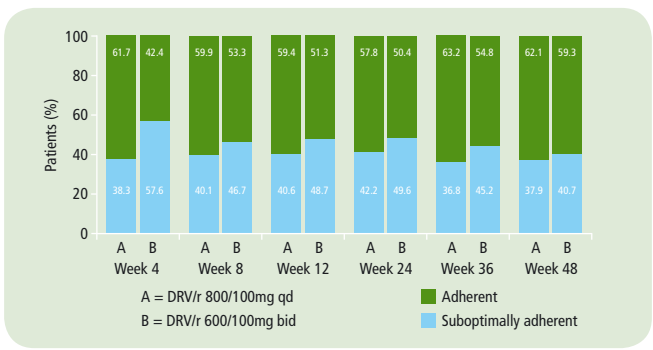

Figure 2. Proportion of adherent and suboptimally adherent patients, as calculated by pill count over time.

- Using plasma DRV concentrations as a measure of adherence, the percentage of adherent patients between the two treatment groups was comparable at all timepoints (once-daily DRV/r ranging from 86.2% to 94.2% vs twice-daily DRV/r ranging from 90.2% to 95.9%) (Figure 3), but not significantly so (all p≥0.19).

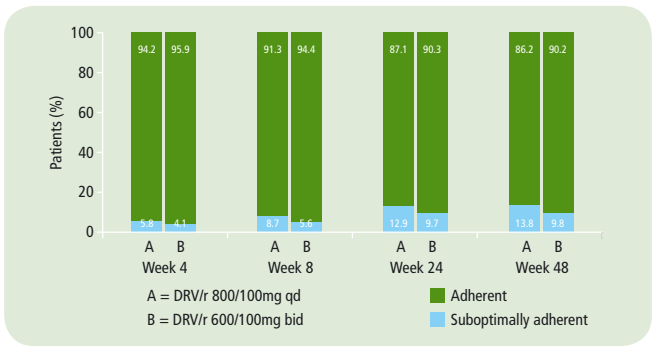

Figure 3. Proportion of adherent and suboptimally adherent patients assessed by DRV plasma concentrations over time.

Adherence and efficacy

- Overall, adherent patients in both the once- and twice-daily DRV/r treatment groups achieved greater virological responses (HIV-1 RNA <50 copies/mL; ITT/time-to-loss of virological response) than suboptimally adherent patients across all three adherence methods (Table 2).

Adherence and safety

- When measured by the M-MASRI, for the most frequent AEs (observed in >5% of all subjects), suboptimally adherent patients reported more AEs than adherent patients; 52.6% (51/97) vs 37.3% (62/166) in the once-daily DRV/r arm and 55.5% (66/119) vs 43.0% (64/149) in the twice-daily DRV/r arm.

Table 2. Virological response (HIV-1 RNA <50 copies/mL) at Week 48 by adherence measure.

Parameter	DRV/r 800/100mg qd N	DRV/r 800/100mg qd Number of responders, n (%)	DRV/r 600/100mg bid N	DRV/r 600/100mg bid Number of responders, n (%)	DRV/r qd–DRV/r bid Difference in response (%) (95% CI of difference in response)
Adherence measured by M-MASRI					
Adherent	166	141 (84.9)	149	127 (85.2)	–0.3 (–8.2; 7.6)
Suboptimally adherent	97	55 (56.7)	119	74 (62.2)	–5.5 (–18.7; 7.7)
Adherence measured by pill count					
Adherent	169	139 (82.2)	160	134 (83.8)	–1.5 (–9.7; 6.7)
Suboptimally adherent	125	73 (58.4)	136	76 (55.9)	2.5 (–9.6; 14.6)
Adherence based on DRV plasma concentrations					
Adherent	238	197 (82.8)	248	203 (81.9)	0.9 (–5.9; 7.7)
Suboptimally adherent	48	15 (31.3)	35	7 (20.0)	11.3 (–8.1; 30.6)

- Fewer AEs were reported in the once-daily versus twice-daily DRV/r group in both adherent and suboptimally adherent patients.
- Overall, the incidence of gastrointestinal (GI) disorders was higher in suboptimally adherent patients than adherent patients in both treatment groups (Figure 4)
  - incidence of GI disorders decreased over time in both treatment groups for both adherent and suboptimally adherent patients.

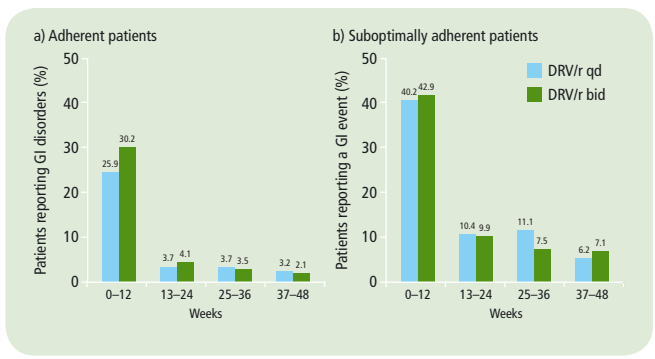

Figure 4. Incidence of GI disorders across all timepoints in a) adherent patients and b) suboptimally adherent patients.

Conclusions

- Adherence rates were numerically, but not significantly higher in the once-daily DRV/r group than in the twice-daily DRV/r group.
- In this treatment-experienced patient population, regardless of the adherence methodology used, virological response was greater in adherent than suboptimally adherent patients in both the once- and twice-daily DRV/r treatment groups.
- Based on the M-MASRI, suboptimal adherence had a greater effect on virological response in treatment-experienced patients (ODIN) than treatment-naïve patients (ARTEMIS[6])
  - suboptimal adherence decreased response by 6% in ARTEMIS (76% in suboptimally adherent patients vs 82% in adherent patients
  - suboptimal adherence decreased response by 23–28% in ODIN (57–62% in suboptimally adherent patients vs 85% in adherent patients)
  - this could be due to the NRTI background regimen not always being active in ODIN. However, in the treatment-naïve population in ARTEMIS, it would be likely that the background regimen would be fully active (unless there was transmitted resistance).
- In ODIN, suboptimally adherent patients reported more AEs than adherent patients in both treatment groups when measured by the M-MASRI
  - fewer AEs were reported in the once-daily DRV/r group compared with the twice-daily DRV/r group.
- GI disorders were generally higher in suboptimally adherent patients than in adherent patients in both treatment groups. In both the once-daily and twice-daily groups, the incidence of GI disorders decreased over time for both adherent and suboptimally adherent patients.

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