ACTHIV18

Evaluation of Cardiovascular Disease (CVD) Risk in HIV-1–infected Patients Treated With Darunavir/Ritonavir (DRV/r)

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Introduction

- Cardiovascular disease (CVD) is a leading cause of death in adults worldwide, and people living with human immunodeficiency virus (HIV)-1 infection may have an increased risk of CVD[1,2]
- Darunavir (DRV) is the only protease inhibitor (PI) that is recommended in guidelines from the US Department of Health and Human Services (DHHS) and the European AIDS Clinical Society (EACS). Once-daily DRV 800 mg, in combination with 2 nucleos(t)ide reverse transcriptase inhibitors, is recommended as follows:
  - US DHHS: as an initial antiretroviral (ARV) treatment option for HIV-1 infection when boosted with ritonavir (r), and considered an alternative regimen when boosted with cobicistat (c)[3]
  - EACS: as an initial regimen with either boosting agent (DRV/r or DRV/c)[4]
- DRV is approved as twice-daily and once-daily dosing regimens:
  - In 2006 (US; 2008 in Europe): twice-daily DRV 600 mg (boosted with ritonavir 100 mg) for treatment-experienced, HIV-1–infected patients with advanced disease
  - In 2009 (Europe; 2010 in the US): once-daily DRV 800 mg (boosted with ritonavir 100 mg) for treatment-naive and treatment-experienced patients without DRV resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V)[5]
- A recent observational study examined the association between CVD risk and use of 2 contemporary PIs, DRV/r and atazanavir (ATV)/r[6]

Objective

- To evaluate the CVD risk associated with DRV use and/or assess baseline demographic and clinical characteristics of DRV users by analyzing data from Janssen-sponsored clinical trials, post-marketing pharmacovigilance databases, and US administrative claims databases

Methods

CVD Events in Janssen-sponsored Clinical Trials

- This analysis was based on pooled data from 19 Janssen-sponsored; international; phase 2, 3, and 4 studies of DRV/r, with durations of up to 6 years
- Patient baseline demographic and clinical characteristics were determined for the pooled population
- *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms corresponding to the medical concepts of CVD events (myocardial infarction, stroke, sudden death, and invasive cardiovascular procedures such as coronary artery angioplasty or bypass or carotid endarterectomy) were retrieved. Incidence rates and incidence rates over time in the pooled clinical trial population were calculated for these CVD events
  - Results were also calculated by dosing regimen (once-daily DRV/r 800/100 mg and twice-daily DRV/r 600/100 mg), as this is an indicator of a specific target population in terms of HIV-1 and general disease characteristics
  - 95% confidence intervals (CIs) were derived from Poisson distribution

CVD Events in Post-marketing Pharmacovigilance Databases

- Spontaneously reported, post-marketing cases of CVD events in patients treated with DRV/r were identified in the Janssen Global Safety Database during the period from June 23, 2006 (international birth date [IBD]) to December 23, 2016. A trend evaluation was conducted using the following MedDRA terms:
  - Standardized MedDRA Queries (SMQs): central nervous system hemorrhages and cerebrovascular conditions (broad) and ischemic heart disease (broad)
  - Preferred terms: carotid angioplasty, carotid artery bypass, carotid artery stent insertion, carotid artery stent removal, carotid endarterectomy, carotid revascularization, coronary angioplasty, coronary arterial stent insertion, coronary artery bypass, coronary artery stent removal, coronary brachytherapy, and coronary endarterectomy
- Empirical Bayesian Geometric Mean (EBGM) scores were derived using Multi-Item Gamma Poisson Shrinker disproportionality methodology, which was used to evaluate disproportionality reporting of CVD events for DRV and other ARV agents in the US Food and Drug Administration Adverse Event Reporting System (FAERS) and World Health Organization VigiBase databases. The threshold for disproportional reporting was ≥3, EBGM ≥2, and lower bound of the 2-sided 90% CI around EBGM (EB05) >1

Demographic and Clinical Characteristics of DRV Users in US Administrative Claims Databases

- Baseline demographic and clinical characteristics of HIV-1–infected patients and new users of DRV and ATV were explored using 3 US administrative claims databases (Truven Medicaid [Truven MDCD], Truven Commercial Claims and Encounters [Truven CCAE], and Optum Extended Socio-Economic Status [Optum]; all data collected through September 2016)
- Additional analyses were conducted using data from Truven CCAE and Optum (January 2007 to September 2016) to evaluate the comparability of populations, with respect to comorbidities prior to initiating DRV and ATV, using propensity score matching and cohort characterization methods

Results

CVD Events in Janssen-sponsored Clinical Trials

- A total of 5,721 patients were enrolled across 19 Janssen clinical trials; baseline characteristics are summarized in **Table 1**

Table 1. Baseline Characteristics of Patients Enrolled in Clinical Trials

	Once-daily DRV/r 800/100 mg (N = 1,326)	Twice-daily DRV/r 600/100 mg (N = 3,058)	Any DRV/r dose* (N = 4,838)
Demographic characteristics			
Age, years, median (range)	40 (18-82)	43 (18-78)	43 (18-82)
Gender, n (%)			
Female	370 (28)	709 (23)	1,129 (23)
Male	956 (72)	2,349 (77)	3,709 (77)
Race, n (%)†			
Black	286 (22)	653 (21)	1,003 (21)
Caucasian	769 (58)	1,685 (55)	2,774 (57)
Hispanic	146 (11)	399 (13)	592 (12)
Asian	100 (8)	95 (3)	201 (4)
Other	25 (2)	226 (7)	268 (6)
BMI, kg/m², n (%)†,‡			
<18	20 (2)	157 (5)	198 (4)
18-26	877 (67)	2,086 (69)	3,286 (68)
26.1-30	275 (21)	508 (17)	869 (18)
>30	137 (10)	286 (9)	446 (9)
Smoking status, n (%)†			
Smoking	217 (16)	388 (13)	605 (13)
Nonsmoking	447 (34)	697 (23)	1,144 (24)
Missing	662 (50)	1,973 (65)	3,089 (64)
HIV-1 disease characteristics			
HIV-1 transmitted by IV drug use, n (%)	54 (4)	209 (7)	289 (6)
HIV-1 RNA viral load, $\log_{10}$ copies/mL, median (range)§	3.76 (1.6-6.7)	4.7 (1.7-7.1)	4.54 (1.6-7.5)
CD4+ cell count, cells/mm³, median (range)¶	347.5 (4-1,888)	140 (1-1,193)	191 (0-1,888)
Other disease characteristics			
Lipid parameters, mg/dL, mean (SE)#			
Total cholesterol	175.78 (1.428)	174.18 (0.855)	175.05 (0.705)
HDL-C	42.05 (0.509)	38.4 (0.259)	38.54 (0.217)
LDL-C	97.79 (1.203)	95.99 (0.729)	96.21 (0.596)
Triglycerides	153.13 (3.785)	248.89 (4.268)	232.92 (3.368)
Blood pressure, mmHg, mean (SE)**			
Systolic	122.17 (0.423)	120.31 (0.288)	120.88 (0.226)
Diastolic	76.64 (0.288)	76.05 (0.201)	76.3 (0.157)
$eGFR_{CG}$, mL/min, n (%)‡,††			
Normal (≥90)	839 (83)	2,055 (69)	3,224 (72)
Mild (≥60 to <90)	161 (16)	769 (26)	1,036 (23)
Moderate (≥30 to <60)	14 (1)	162 (5)	193 (4)
Severe (≥15 to <30)	0	5 (<1)	5 (<1)
Renal failure (<15)	0	1 (<1)	1 (<1)
Intake of lipid-lowering drugs, n (%)	12 (1)	240 (8)	289 (6)
Intake of antidiabetes drugs, n (%)	7 (1)	114 (4)	133 (3)
Intake of antihypertensive drugs, n (%)	29 (2)	254 (8)	318 (7)
Dyslipidemia, n (%)	874 (66)	2,082 (68)	3,315 (69)
Diabetes, n (%)	28 (2)	229 (7)	290 (6)
Hypertension, n (%)	259 (20)	712 (23)	1,084 (22)

BMI, body mass index; IV, intravenous; SE, standard error; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; $eGFR_{CG}$, estimated glomerular filtration rate calculated using the Cockcroft-Gault method.
*Includes doses other than twice-daily DRV/r 600/100 mg and once-daily DRV/r 800/100 mg; baseline characteristics data were not available for subjects in 1 study.
†Percentages may not total 100% due to rounding.
‡Once-daily DRV/r 800/100 mg, n = 1,309; twice-daily DRV/r 600/100 mg, n = 3,037; any DRV/r dose, n = 4,799.
§Once-daily DRV/r 800/100 mg, n = 1,326; twice-daily DRV/r 600/100 mg, n = 3,056; any DRV/r dose, n = 4,836.
¶Once-daily DRV/r 800/100 mg, n = 1,326; twice-daily DRV/r 600/100 mg, n = 3,040; any DRV/r dose, n = 4,817.
#Once-daily DRV/r 800/100 mg, n = 1,039 (total cholesterol), n = 796 (HDL-C), n = 792 (LDL-C), n = 1,052 (triglycerides); twice-daily DRV/r 600/100 mg, n = 3,005 (total cholesterol), n = 2,727 (HDL-C), n = 2,524 (LDL-C), n = 3,005 (triglycerides); any DRV/r dose, n = 4,498 (total cholesterol), n = 3,972 (HDL-C), n = 3,720 (LDL-C), n = 4,511 (triglycerides).
**Once-daily DRV/r 800/100 mg, n = 1,326; twice-daily DRV/r 600/100 mg, n = 3,001; any DRV/r dose: n = 4,781.
††Once-daily DRV/r 800/100 mg, n = 1,014; twice-daily DRV/r 600/100 mg, n = 2,992; any DRV/r dose: n = 4,459.

- Among all studies, the treatment duration was up to 6 years (median: 1.8 years; interquartile range [IQR]: 0.94-2.75 years; range: 0-6.13 years; **Table 2**)
- The incidence rate (95% CI) per 1,000 person-years of CVD events in the overall pooled database (any DRV dose; N = 5,721) was 6.15 (2.91-11.88), and was lower for the study population treated with once-daily DRV/r 800/100 mg (0.71 [0.16-3.05]) than for the study population treated with twice-daily DRV/r 600/100 mg (9.21 [4.94-16.04]; **Table 2**)
- CVD event rates did not increase with continued exposure to DRV/r over time in clinical trials; a caveat is that the number of patients with exposures of 5 or 6 years was limited (**Table 3**)

Table 2. Summary of CVD Events With DRV/r Use (Pooled Data) From 19 Clinical Trials With Durations of Up to 6 Years

	Once-daily DRV/r 800/100 mg (N = 1,326)	Twice-daily DRV/r 600/100 mg (N = 3,058)	Any DRV/r dose* (N = 5,721)
Total CVD events, n	2	47	66
Treatment duration, years, median (IQR) [range]	1.9 (0.93-2.78) [0-6.13]	1.7 (0.93-2.30) [0.003-5.66]	1.8 (0.94-2.75) [0-6.13]
Total exposure, person-years	2,812	5,105	10,725
Incidence rate (95% CI), per 1,000 person-years	0.71 (0.16-3.05)	9.21 (4.94-16.04)	6.15 (2.91-11.88)

*Includes doses other than twice-daily DRV/r 600/100 mg and once-daily DRV/r 800/100 mg.

Table 3. Summary of CVD Events With DRV/r Use (Pooled Data) From 19 Clinical Trials by Interval of Exposure

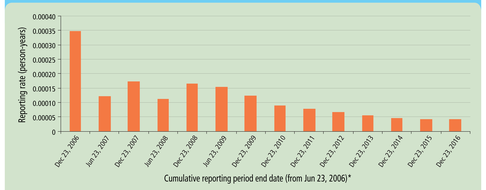
	Exposure to DRV/r, years					
Once-daily DRV/r 800/100 mg	**0-1 (N = 492)**	**1-2 (N = 315)**	**2-3 (N = 252)**	**3-4 (N = 125)**	**4-5 (N = 41)**	**5-6 (N = 96)**
Total CVD events, n	0	0	1	1	0	0
Treatment duration, years, median (range)	0.9 (0.003-1.00)	1.9 (1.01-2.00)	2.8 (2.00-3.00)	3.7 (3.10-3.98)	4.4 (4.08-4.96)	5.5 (5.06-5.99)
Total exposure, person-years	373	566	679	463	182	525
Incidence rate (95% CI), per 1,000 person-years	0	0	1.47 (0.41-4.62)	2.16 (0.67-5.85)	0	0
Twice-daily DRV/r 600/100 mg	**0-1 (N = 1,083)**	**1-2 (N = 1,075)**	**2-3 (N = 493)**	**3-4 (N = 364)**	**4-5 (N = 34)**	**5-6 (N = 9)**
Total CVD events, n	12	17	9	9	0	0
Treatment duration, years, median (range)	0.8 (0.003-1.00)	1.8 (1.00-2.00)	2.6 (2.00-3.00)	3.2 (3.01-3.99)	4.1 (4.01-4.84)	5.4 (5.03-5.66)
Total exposure, person-years	695	1,764	1,248	1,206	144	49
Incidence rate (95% CI), per 1,000 person-years	17.3 (10.87-26.31)	9.64 (5.24-16.61)	7.21 (3.59-13.35)	7.46 (3.76-13.69)	0	0
Any DRV/r dose*	**0-1 (N = 1,636)**	**1-2 (N = 1,910)**	**2-3 (N = 1,343)**	**3-4 (N = 625)**	**4-5 (N = 96)**	**5-6 (N = 105)**
Total CVD events, n	15	22	17	12	0	0
Treatment duration, years, median (range)	0.8 (0-1.00)	1.7 (1.00-2.00)	2.7 (2.00-3.00)	3.3 (3.01-4.00)	4.2 (4.00-4.96)	5.5 (5.03-5.99)
Total exposure, person-years	1,035	3,124	3,429	2,126	412	574
Incidence rate (95% CI), per 1,000 person-years	14.5 (8.76-22.85)	7.04 (3.48-13.12)	4.96 (2.18-10.18)	5.64 (2.59-11.16)	0	0

*Includes doses other than twice-daily DRV/r 600/100 mg and once-daily DRV/r 800/100 mg.

CVD Events in Post-marketing Pharmacovigilance Databases

- Trend analysis of post-marketing pharmacovigilance data showed that cumulative reporting rates of CVD events generally declined over time (**Figure 1**)
  - A higher reporting rate was observed during the period from 2006 to 2009 (when only twice-daily DRV/r 600/100 mg was registered)
- Spontaneously reported CVD events were not disproportionately reported with DRV in FAERS/VigiBase
  - First-generation PIs (indinavir, nelfinavir, ritonavir, saquinavir) displayed a higher number of drug-event pairs that met the threshold for disproportionate reporting compared with second-generation PIs (ATV, DRV, fosamprenavir, tipranavir)

Figure 1. Cumulative reporting rate for spontaneous cases reporting CVD events identified with DRV treatment by time interval (June 23, 2006 to December 23, 2016).



*Cumulative Periodic Benefit-Risk Evaluation Report (PBRER)-Periodic Safety Update Report (PSUR) reporting period.

Demographic and Clinical Characteristics of DRV Users in US Administrative Claims Databases

- Compared with the general HIV-1–infected population and ATV users, higher proportions of DRV users were male, older, and had CVD risk factors (**Table 4**)
- Clinical variables that are known or are likely risk factors for CVD events were more prevalent among patients initiating DRV versus those initiating ATV (**Table 5**)

Table 4. Baseline Characteristics of DRV and ATV Users and the General HIV-1–infected Population in the US

	Truven MDCD			Truven CCAE			Optum		
Parameter	**HIV-1–infected (N = 80,522)**	**DRV users (N = 4,637)**	**ATV users (N = 4,664)**	**HIV-1–infected (N = 220,589)**	**DRV users (N = 8,360)**	**ATV users (N = 8,977)**	**HIV-1–infected (N = 149,145)**	**DRV users (N = 4,771)**	**ATV users (N = 6,413)**
Gender, n (%)									
Female	36,024 (45)	2,057 (44)	2,376 (51)	53,985 (24)	1,536 (18)	1,955 (22)	40,717 (27)	795 (17)	1,187 (19)
Male	44,498 (55)	2,580 (56)	2,288 (49)	166,604 (76)	6,824 (82)	7,022 (78)	108,428 (73)	3,976 (83)	5,226 (81)
Age, years									
Mean (SD)	41.0 (14)	42.6 (12)	40.8 (12)	41.3 (12)	44.7 (10)	42.9 (10)	42.3 (13)	47.2 (11)	43.6 (10)
<50, n (%)	57,548 (71)	3,211 (69)	3,491 (75)	163,479 (74)	5,424 (65)	6,608 (74)	107,958 (72)	2,757 (58)	4,757 (74)
≥50, n (%)	22,973 (29)	1,426 (31)	1,173 (25)	57,110 (26)	2,936 (35)	2,369 (26)	41,187 (28)	2,014 (42)	1,656 (26)
Comorbidities, %									
CV disorder	30	64	52	23	50	38	29	61	44
Metabolic disorder	26	57	44	25	51	38	33	65	49
Hypertension	21	45	35	15	31	22	19	41	26
Hyperlipidemia	10	27	18	17	37	26	25	50	37
Diabetes	9	17	12	7	10	8	10	15	9

SD, standard deviation.

Table 5. Pre-exposure Conditions and Cardiac Risk Factors*

Condition	DRV users (N)	DRV user prevalence	ATV users (N)	ATV user prevalence	Absolute difference	Relative risk (DRV vs ATV)
Diabetes without complication	56	0.011	4	0.001	0.140	18.550
Type 2 diabetes without complication	55	0.011	4	0.001	0.138	18.219
Hyperglycemia	34	0.007	3	0.000	0.106	15.017
Chronic heart failure	63	0.013	11	0.002	0.131	7.589
Chronic systolic heart failure	49	0.010	9	0.001	0.114	7.214
Acute systolic heart failure	41	0.008	8	0.001	0.103	6.791
Acute heart failure	58	0.012	12	0.002	0.121	6.404
Venous hypertension	51	0.010	11	0.002	0.112	6.143
Dilation of aorta	53	0.011	13	0.002	0.110	5.402
Peripheral circulatory disorder associated with type 2 diabetes	48	0.010	12	0.002	0.104	5.300
Chronic kidney disease stage 2	111	0.022	28	0.004	0.159	5.253
Deep venous thrombosis of lower extremity	84	0.017	22	0.003	0.136	5.059
Chronic kidney disease stage 1	57	0.012	15	0.002	0.112	5.035

*Conditions with a relative risk of ≥5 are reported.

Limitations

- The durations of the Janssen-sponsored clinical trials of DRV/r were limited (up to 6 years)
- Post-marketing pharmacovigilance data mining results cannot be used to confirm or refute a causal association between drug and event; rather, these results are a measure of statistical association and need to be placed in a medical context
- Results of the epidemiological analysis were based on 3 US claims databases and, thus, may not be generalizable; moreover, the analysis focused only on baseline characteristics

Conclusions

- **Analysis of pooled data from 19 Janssen-sponsored clinical trials did not indicate an increased risk of CVD events with DRV/r use over treatment durations of up to 6 years**
  - **The CVD event incidence rate was lower for the study population treated with once-daily DRV/r 800/100 mg compared with the study population treated with twice-daily DRV/r 600/100 mg. The relatively higher CVD event rate for patients receiving twice-daily DRV/r 600/100 mg may reflect differences in the patient population, as this dosing regimen was approved for treatment-experienced, HIV-1–infected patients with advanced disease who may be at high risk of experiencing a CVD event**
- **The trend of CVD post-marketing cases over time showed a decline in the cumulative reporting rate of cases with CVD events from June 23, 2006 to December 23, 2016. A higher reporting rate was observed during the period from 2006 to 2009 when only twice-daily DRV/r 600/100 mg was registered**
- **The data mining analysis of post-marketing pharmacovigilance databases (FAERS and VigiBase) exhibited disproportionality of CVD events mainly for first-generation PIs (eg, indinavir, nelfinavir, ritonavir, saquinavir)**
- **Examination of baseline characteristics from 3 US claims databases indicated that HIV-1–infected patients who use DRV tend to be sicker than those who use ATV, with a much higher proportion of factors that could increase the risk of having a CVD event. This suggests the possibility that patients with higher rates of comorbidities, and specifically CV conditions, may be channeled into DRV treatment rather than ATV treatment**
- **Taken together, this review of clinical, post-marketing, and epidemiological data does not suggest that CVD should be considered an important risk for users of DRV**

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- If you have any additional questions or would like to request a copy of this poster, call +1-800-JANSSEN (+1-800-526-7736) or go to www.janssenMD.com.
- For more information about darunavir at this conference, please see Poster ACTHIV15 entitled "Demographic and Clinical Characteristics of Patients Living With HIV Treated With Darunavir- and Atazanavir-based Regimens in the Real-world Setting."

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