PREZISTA® (darunavir)
Pharmacokinetics of PREZISTA

SUMMARY

- In the ARTEMIS study, plasma concentrations of darunavir (DRV) in patients receiving PREZISTA/ritonavir (PREZISTA/r) 800/100 mg once daily (QD) were consistently above the in-vitro protein-binding corrected median effective concentration (EC_{50}) for wild-type virus (55 ng/mL).[1]
- The median DRV minimum concentration (C_{0h}) exceeded the EC_{50} for protease inhibitor (PI)-resistant virus (550 ng/mL) for each treatment group in the pooled POWER 1 and 2 studies and in both arms of the ODIN study.[2,3]
- The EC_{50} for PI-resistant virus (550 ng/mL) was exceeded in all patients in the POWER 3, TITAN, and GRACE studies, all of whom received PREZISTA/r 600/100 mg twice daily (BID).[4-6]
- No direct relationship between DRV pharmacokinetics (PK) and safety or efficacy was observed in the ARTEMIS, ODIN, TITAN, GRACE, and POWER 1, 2, and 3 studies.[1-6]
- **Lloret-Linares et al (2018)**[7] conducted a prospective, single-center study to compare the steady state plasma concentrations of DRV in normal and overweight human immunodeficiency virus (HIV) infected adult patients treated with PREZISTA/r 800/100 mg QD. DRV concentrations tended to be higher in patients with body mass index (BMI) ≥25 kg/m^2 than in patients with BMI <25 kg/m^2 (2896.7±1689 vs 2091.9±1038, respectively, *P*=0.09) and was positively correlated with fat mass (*r*=0.32, *P*=0.02).
- **Calza et al (2017)**[8] conducted an observational, open-label study in HIV-1 infected patients treated with PREZISTA/r 800/100 mg QD plus emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) 200/300 mg QD. The geometric mean (GM) plasma trough concentration (C_{trough}) of DRV was significantly higher among patients aged ≥60 years (older patients) than among patients aged ≤40 years (younger patients) (2209 ng/mL [139%] vs 1876 ng/mL [162%], respectively; geometric mean ratio [GMR], 1.56; 95% confidence interval [CI], 1.22-1.88; *P*=0.004).
- **Tyrberg et al (2021)**[9] conducted a cross-sectional study to evaluate the differences in steady state concentrations of DRV, atazanavir (ATV), or efavirenz (EFV) following the administration of DRV/r 800/100 mg, ATV/r 300/100 mg, or EFV 600 mg QD in HIV-1 infected patients aged ≥65 years (study group, n=100) and ≤49 years (control group, n=99). Compared with the control group (n=30), DRV steady-state concentrations were significantly higher in the study group (n=25; *P*=0.047).
- **Tsirizani et al (2024)**[10] presented a PK substudy within the CHAPAS-4 trial, comparing DRV exposure in children with HIV to adults after once-daily PREZISTA/r treatment. Children had slightly higher area under the concentration-time curve from 0 to 24 hours (AUC_{0-24h}) and maximum plasma concentration (C_{max}) values than adults, but their C_{trough} levels were similar to adult reference values.

CLINICAL DATA

Treatment-Naïve Patients

ARTEMIS Study

The ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naïve HIV-1 infected Subjects) study was a randomized, controlled, open-label, 192-week phase 3 study comparing PREZISTA/r 800/100 mg QD versus either lopinavir/r (LPV/r) 800/200 mg QD or LPV/r 400/100 mg BID in treatment-naïve patients. All patients received a fixed-dose background regimen of FTC/TDF 200/300 mg QD (N=689).[11]

Study Design/Methods

- Sparse blood sampling for PK/pharmacodynamic (PD) analysis was carried out at weeks 4, 8, 24, and 48 in DRV/r patients.[1]

PK/PD Results

- PK data were available for 335 patients (Figure: Exposure Estimates for DRV 800 mg QD).
- Median (range) DRV population PK parameters:
  - Area under the concentration-time curve from t=0-24h (AUC_{0-24h}) (ng·h/mL)=87,854 (45,000-219,240)
  - Trough concentration (C_{0h}) (ng/mL)=2041 (368-7242)

Exposure Estimates for DRV 800 mg QD

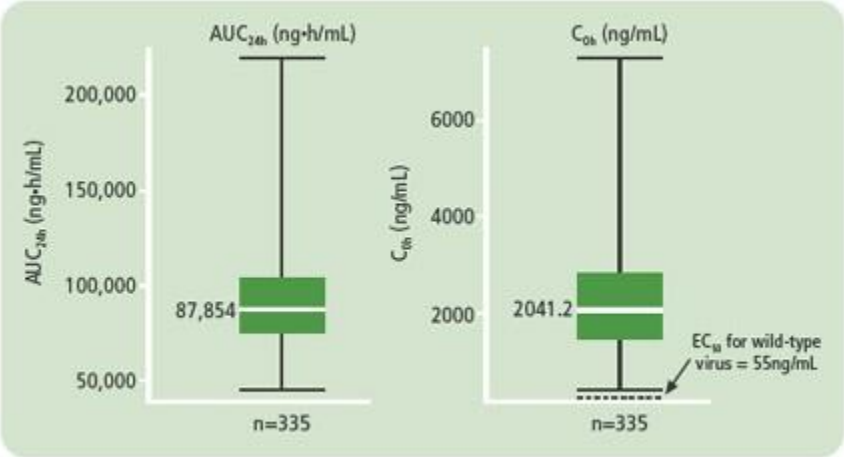

Figure 1. Median, 25% and 75% percentiles, minimum and maximum DRV AUC_{24h} and C_{0h}.

Abbreviations: AUC_{24h}, area under the concentration-time curve from t=0-24h; C_{0h}, trough concentration; DRV, darunavir; EC_{50}, median effective concentration; QD, once daily.

- C_{trough} was consistently above the EC_{50} for wild-type virus (55 ng/mL) in all patients.
  - Median C_{0h} was 37-fold greater than the EC_{50}.
- No relationship was observed between DRV exposure (AUC_{24h} and C_{0h}) and virologic response (VR) at week 48.
  - Mean reductions in viral load (VL) and the proportion of patients achieving VL <50 copies/mL were consistently similar across the range of AUC_{24h} and C_{0h} values measured through week 48.
- No relationship was observed between DRV exposure (AUC_{24h} and C_{0h}) and the occurrence of rash, nervous system, psychiatric, cardiac, gastrointestinal (GI), liver, lipid, and glucose-related adverse events (AEs).

Effect of Different Covariates on DRV/r PK Exposure

- Female patients had higher DRV exposures compared to male patients.[12]
  - Mean AUC_{24h} was 96,364 ng·h/mL and 84,754 ng·h/mL in female and male patients, respectively.
  - Mean C_{0h} was 2288 ng/mL and 1918 ng/mL in female and male patients, respectively.
- Mean DRV exposure and C_{trough} was lowest in Asian patients compared to other ethnic subgroups.[12]
  - Mean AUC_{24h} and C_{0h} were 79,824 ng·h/mL and 1763 ng/mL, respectively.
- The differences observed in DRV exposure with respect to gender and race were not considered clinically relevant.[12]
- Age, body weight, and hepatitis B and/or C coinfection had no effect on DRV exposure.[12]

Treatment-Experienced Patients

ODIN Study

The ODIN (**O**nce-daily **D**arunavir **I**n treatment-experie**N**ced patients) study was a randomized, open-label, parallel assignment, 48-week phase 3 study comparing PREZISTA/r 800/100 mg QD or PREZISTA/r 600/100 mg BID, each in combination with an optimized background regimen (OBR) consisting of ≥2 investigator-selected nucleoside reverse transcriptase inhibitors (NRTIs), in 590 treatment-experienced patients with no DRV resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V).[13]

Study Design/Methods

- Sparse blood sampling for PK/PD analysis was carried out at weeks 4, 8, 24, and 48.[3]

PK/PD Results

- Data were available for 280 patients in the QD arm and 278 patients in the BID arm (Table: DRV PK at Week 48 in the ODIN Study).

DRV PK at Week 48 in the ODIN Study[3]

PK Parameter, Median (Range)	PREZISTA/r 800/100 mg QD (n=280)	PREZISTA/r 600/100 mg BID (n=278)
AUC_{24h}, ng·h/mL[a]	87,788 (45,456-236,920)	109,401 (48,934-323,820)
C_{0h}, ng/mL	1896 (184-7881)	3197 (250-11,865)

Abbreviations: AUC_{12h}, 12-hour area under the plasma concentration-time curve; AUC24h, 24-hour area under the plasma concentration-time curve; BID, twice daily; C_{0h}, trough concentration; DRV, darunavir; PK, pharmacokinetic; QD, once daily; r, ritonavir.
[a]Calculated as AUC_{12h} x 2 in the BID group.

- C_{0h} and AUC_{24h} of DRV were lower with QD dosing than with BID dosing.
- The entire range of plasma concentrations for DRV QD and BID were above the EC_{50} (55 ng/mL) for wild-type HIV (adjusted for protein binding).
- No clinically relevant relationships between DRV PK and efficacy were found.
- No relationships between DRV PK and laboratory lipid abnormalities or rash, cardiac, GI, liver, lipid, or glucose-related AEs were found.

Effect of Different Covariates on DRV PK Exposure

- Age, body weight, and hepatitis coinfection status did not affect DRV exposure.
- Differences in DRV exposure with respect to gender and race were not considered to be clinically relevant.
  - Mean DRV AUC_{24h} was higher in females (QD regimen: 94,780 ng·h/mL; BID regimen: 111,744 ng·h/mL) than in males (QD regimen: 84,031 ng·h/mL; BID regimen: 107,810 ng·h/mL).
  - DRV exposure was highest in blacks, followed by Caucasians and Hispanics, and lowest in Asians.

TITAN Study

The TITAN (**T**MC114/r **I**n **T**reatment-experienced p**A**tients **N**aive to lopinavir) study was a randomized, controlled, open-label, 96-week phase 3 study comparing PREZISTA/r 600/100 mg BID or LPV/r 400/100 mg BID, each in combination with an investigator-selected OBR that consisted of ≥2 antiretrovirals (NRTIs ± non-nucleoside

reverse transcriptase inhibitors [NNRTIs]), in treatment-experienced, LPV-naïve patients (N=595).[14]

Study Design/Methods

- Sparse blood sampling for PK analysis was carried out at weeks 4, 8, 24, and 48 in PREZISTA/r patients (n=285).[5]

PK/PD Results

- Median (range) C_{0h} was 3306 (1517-13,198) ng/mL, which consistently exceeded the EC_{50} value for PI-resistant HIV-1 strains (550 ng/mL).
- Median (range) 12-hour area under the plasma concentration-time curve (AUC_{12h}): 55,816 (32,437-177,680) ng·h/mL.
- No relationship was observed between DRV exposure (AUC_{12h}, C_{0h}) and VR (VL <400 copies/mL).
- No relationship was observed between the incidence of AEs of interest experienced by patients and DRV exposure.

Effect of Different Covariates on DRV PK Exposure

- DRV AUC_{12h} was not affected by coadministration of nevirapine or EFV, age, body weight, or hepatitis B or C coinfection.[15]
- The differences observed in DRV exposure (AUC_{12h}) with respect to gender and race were not considered to be clinically relevant.[15]
  - DRV AUC_{12h} was 8% higher in females (59,072 ng·h/mL) compared to males (54,547 ng·h/mL).
  - DRV exposure was highest in blacks (62,280 ng·h/mL) and lowest in Asian/Orientals (45,749 ng·h/mL).
- Patients with higher baseline alpha 1-acid glycoprotein (AAG) levels experienced higher exposure to DRV compared to those with lower baseline AAG levels.[15]
  - Differences in exposure may be related to the high binding affinity of DRV to AAG protein.

GRACE Study

The GRACE (Gender, Race And Clinical Experience) study was an open-label, multicenter, 48-week phase 3b study which evaluated gender and race differences in the efficacy, safety, PK, and tolerability of PREZISTA/r 600/100 mg BID plus an OBR in treatment-experienced men (n=142) and women (n=287).[16]

Study Design/Methods

- PK analysis was conducted using the following 2 sampling methods:
  - Sparse PK sampling was performed for DRV in all patients at weeks 4, 8, 24, and 48.
  - Intensive PK sampling was performed for DRV/r in a subset of patients at weeks 4, 24, and 48.
    - At each of the timepoints, a sample was collected 15 minutes predose and 1, 2, 3, 4, 6, 9, and 12 hours postdose.
- Relationship of DRV PK with efficacy and safety was assessed at week 48.

PK Substudy Results

- Sparse PK sampling was undertaken in 376 patients:
  - Women 66% (n=248); black 60% (n=226); Hispanic 22% (n=84).
- Intensive PK sampling was undertaken in 37 patients:
  - Women (n=25); black (n=25); Hispanic (n=10); Caucasian (n=2).

PK — Sparse Sampling

- Based on the PK data available, the median (range) DRV AUC_{12h} and C_{0h} were 60,642 (26,117-128,790) ng·h/mL and 3624 (931-9570) ng/mL, respectively.
  - DRV C_{trough} exceeded the EC_{50} for resistant virus (550 ng/mL) for all patients (median C_{0h}= 6.5×EC_{50}).

PK — Intensive Sampling

- The plasma concentrations of DRV/r did not show a time-dependent relationship over 48 weeks.
- DRV/r exposures were comparable to population PK data.

Effect of Different Covariates on DRV PK Exposure

- Based on univariate analysis, DRV PK did not differ between women and men or by ethnic subgroups.
- Based on multivariate analysis, higher DRV exposure was statistically correlated with female gender and age; however, these were not considered clinically relevant (as seen in the univariate analysis).
- No relationship was observed between DRV AUC_{12h} or C_{0h} and change in VL from baseline to week 48, the proportion of patients that achieved VL <50 copies/mL, or incidence of AEs such as rash, cardiac, GI, liver, glucose, nervous system, or psychiatric-related disorders.

POWER 1, 2, and 3 Studies

The POWER 1, POWER 2, and POWER 3 studies were 144-week phase 2b studies that evaluated the efficacy and safety of PREZISTA/r in highly treatment-experienced HIV-1 infected patients.[17-19]

Study Design/Methods

- The POWER 1 and 2 studies were randomized, controlled, partially blinded studies evaluating the safety and efficacy of various dosing regimens of PREZISTA/r (400/100 mg QD, 800/100 mg QD, 400/100 mg BID, or 600/100 mg BID) in comparison with other PIs, each in combination with an OBR.[17,18]
- POWER 3 was an analysis of 2 open-label, single-arm trials evaluating the efficacy and safety of PREZISTA/r 600/100mg bid plus an OBR.[20,21]
- PK data for the POWER 1, 2, and 3 studies were based on population PK modeling on sparse samples.

PK Results

DRV PK Through Week 24[2,4]

PK Parameter, Median (Range)	Pooled POWER 1 and 2				POWER 3
	PREZISTA/r 400/100 mg QD (n=118)	PREZISTA/r 800/100 mg QD (n=118)	PREZISTA/r 400/100 mg BID (n=113)	PREZISTA/r 600/100 mg BID (n=119)	PREZISTA/r 600/100 mg BID (n=292)
AUC_{24h}, ng·h/mL[a]	56,576 (13,035-163,950)	89,845 (25,828-214,040)	95,592 (37,030-197,186)	123,336 (67,714-212,980)	119,858 (56,128-295,000)
C_{0h}, ng/mL	1258 (140-5380)	1840 (256-5868)	2806 (646-6391)	3539 (1255-7368)	3806 (1233-10,761)

Abbreviations: AUC_{12h}, 12-hour area under the plasma concentration-time curve; AUC24h, 24-hour area under the plasma concentration-time curve; BID, twice daily; C_{0h}, predose concentration; DRV, darunavir; PK,

PK Parameter, Median (Range)	Pooled POWER 1 and 2				POWER 3
	PREZISTA/r 400/100 mg QD (n=118)	PREZISTA/r 800/100 mg QD (n=118)	PREZISTA/r 400/100 mg BID (n=113)	PREZISTA/r 600/100 mg BID (n=119)	PREZISTA/r 600/100 mg BID (n=292)
pharmacokinetic; QD, once daily; r, ritonavir. [a]AUC_{24h} for the BID regimens were calculated by AUC_{12h} multiplied by 2.					

- No direct relationship was observed between DRV PK and VR or AEs.

Effect of Body Weight and Composition

Lloret-Linares et al (2018)[7] conducted a prospective, single-center study in France to compare the steady-state PK of DRV in normal and overweight HIV infected adult patients receiving PREZISTA/r 800/100 mg QD combined with at least 2 NRTIs and determined the relationship between concentrations and fat mass.

Study Design/Methods

- Patients received the PREZISTA/r QD regimen for at least 6 months prior to study enrollment.
- Blood samples were collected 24 hours (±1 hour) after the last PREZISTA/r dose.

PK Results

- A total of 48 patients were enrolled in the study.
- DRV concentrations tended to be higher in patients with BMI ≥25 kg/m^2 (P=0.09) and was positively correlated with fat mass (r=0.32, P=0.02). Clusters of differentiation (CD)4+ T cell count and the percentage of patients with a VL of <20 copies/mL did not differ according to the BMI group (Table: Antiretroviral Drug Concentration and Immune Status of Patients Treated With DRV With Respect to BMI).
- According to BMI quartiles, the DRV concentrations were:
  - BMI 17.4-18.3 (n=4): 2174.0±864.2 µg/L
  - BMI 18.5-24.8 (n=23): 2077.6±1082 µg/L
  - BMI 25.3-29.9 (n=14): 2701.1±1410.3 µg/L
  - BMI 30.3-35.4 (n=7): 3287.7±223.1 µg/L
- In a subgroup analysis, the effect of fat mass on serum concentrations was significant in the 52.1% of patients from Sub Sahara Africa (r=0.4, P=0.04).

Antiretroviral Drug Concentration and Immune Status of Patients Treated With DRV With Respect to BMI[7]

	BMI <25 kg/m^2 (n=27)	BMI ≥25 kg/m^2 (n=21)
Mean drug concentration±SD, µg/L	2091.9±1038	2896.7±1689
Mean CD4 cell count±SD, cells/mm^3	537±193	577±189
Viral load <20 cells/mm^3, %	74.1%	81%
Abbreviations: BMI, body mass index; CD, clusters of differentiation; DRV, darunavir; SD, standard deviation.		

Older vs Younger Patients

Calza et al (2017)[8] conducted a observational, open-label study to evaluate the plasma concentrations of DRV following administration of PREZISTA/r 800/100 mg QD in combination with FTC/TDF in HIV-1 infected patients ≥60 years old (older patients; n=21) in comparison with those ≤40 years old (younger patients; n=25).

Study Design/Methods

- The plasma C_{trough} of DRV/r were assessed at steady state (>4 weeks after the start of treatment).
- Blood samples were obtained before the morning dose and 23-25 hours after the previous morning dose of PREZISTA/r.

PK Results

- The GM plasma C_{trough} (coefficient of variation [CV%]) of DRV was 2017 ng/mL (145%), and was significantly higher in older patients than in younger patients (Table: DRV Plasma Concentrations in Younger and Older Patients).
- Overall, the mean DRV C_{trough} (CV%) was significantly higher in female patients (2144 ng/mL; 143%) than in male patients (1991 ng/mL; 128%; GMR 1.48; 95% CI: 1.21-1.89; *P*=0.041), in patients with BMI <24 kg/m^2 (2219 ng/mL; 119%) than in those with BMI ≥24 kg/m^2 (1887 ng/mL; 152%; GMR 1.57; 95% CI: 1.29-1.78; *P*=0.039), and in patients with albumin concentration <3.5 g/dL (2144 ng/mL; 167%) than in those with albumin concentration ≥3.5 g/dL (1914 ng/mL; 148%; GMR 1.66; 95% CI: 1.26-1.98; *P*=0.019).
- Similar results were observed with mean ritonavir C_{trough} levels (data not shown).

DRV Plasma Concentrations in Younger and Older Patients[8]

	DRV C_{trough} (ng/mL)		*P*-Value
	Age ≤40 Years (n=25)	Age ≥60 Years (n=21)	
Overall	1876 (162%)	2209 (139%)	0.004
Male patients	1855 (152%)	2158 (144%)	<0.001
Female patients	1921 (134%)	2246 (153%)	<0.001
BMI ≥24 kg/m^2	1709 (141%)	2156 (119%)	0.021
BMI <24 kg/m^2	1915 (133%)	2417 (135%)	0.019
Albumin ≥3.5 g/dL	1754 (147%)	2145 (102%)	<0.001
Albumin <3.5 g/dL	1922 (121%)	2327 (125%)	0.042

Abbreviations: BMI, body mass index; C_{trough}, plasma trough concentration; CV, coefficient of variation; DRV, darunavir.
Data are presented as geometric mean (CV; %).

Effect of Different Covariates on DRV/r PK Exposure

- Female gender and BMI <24 kg/m^2 were significantly associated with increased plasma concentrations of DRV (C_{trough} >2200 ng/mL) by univariate and multivariate analysis.
- Albumin concentration <3.5 g/dL was significantly associated with increased plasma levels of DRV by both analyses (Table: Univariate and Multivariate Logistic Regression Analyses of Factors Associated With Increased Plasma Concentrations of DRV).

Univariate and Multivariate Logistic Regression Analyses of Factors Associated With Increased Plasma Concentrations of DRV[8]

Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Female gender	1.49	1.21-1.77	0.012	1.45	1.25-1.87	0.031
BMI <24 kg/m^2	1.76	1.39-1.98	<0.001	1.62	1.38-1.85	0.029
Albumin <3.5 g/dL	1.54	1.28-1.82	0.044	1.35	1.12-1.57	0.037

Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Abbreviations: BMI, body mass index; CI, confidence interval; C_{trough}, plasma trough concentration; DRV, darunavir; OR, odds ratio. Increased plasma concentrations defined as C_{trough} >2200 ng/mL.						

Tyrberg et al (2021)[9] conducted a cross-sectional study to evaluate the differences in steady state concentrations of DRV, ATV, or EFV following the administration of DRV/r 800/100 mg, ATV/r 300/100 mg, or EFV 600 mg QD in HIV-1 infected patients aged ≥65 years (study group, n=100) and ≤49 years (control group, n=99).

Study Design/Methods

- HIV-1 infected patients aged ≥65 years (study group) and ≤49 years (control group) who were on stable treatment with ATV, DRV, or EFV for more than 6 months were included from 4 HIV centers in Sweden.
- Blood samples were collected on the day of inclusion for the measurement of plasma drug levels.
- For the analysis of steady-state drug levels, blood samples were collected between 6 and 36 hours after the last dose of the drug.

PK Results

- Between November 2013 and August 2015, 100 (DRV, n=35; ATV, n=19; EFV, n=46) and 99 patients (DRV, n=37; ATV, n=18; EFV, n=44) were included in the study and control groups, respectively.
- Compared with the control group (n=30), the DRV steady-state concentrations were significantly higher in the study group (n=25; *P*=0.047).
- Compared with the control group, the GM steady-state concentration was 48% higher in the study group.

Tsirizani et al (2024)[10] presented results of a PK substudy of the PREZISTA/r arm within the CHAPAS-4 trial, which was an open-label, multicenter, randomized trial that evaluated the virological efficacy and PK of boosted protease inhibitors and dolutegravir, in combination with either tenofovir alafenamide fumarate (TAF) or non-TAF-based NRTI backbones. The present study compared exposures between children with HIV (age range, 3-15 years; weight, ≥14 kg) and adults with HIV infection and evaluated the impact of NRTI backbones and other covariates on the PK of DRV.

Study Design/Methods

- PREZISTA/r dosing was based on World Health Organization weight bands (14-19.9 kg, 20-24.9 kg, 25-34.9 kg, and ≥35 kg).
- Children with HIV were treated with once-daily PREZISTA/r at a dose of 600/100 mg (weight, 14-24.9 kg) and 800/100 mg (weight, ≥25 kg), in combination with either TAF/FTC, abacavir/lamivudine (ABC/3TC), or zidovudine/lamivudine (ZDV/3TC).
- They were monitored for a duration of 96 weeks, and blood samples for detailed PK analysis were collected at week 6 at predose and at intervals of 1, 2, 4, 6, 8, 12, and 24 hours after drug intake.

PK Results

- Between January 2019 and March 2021, 59 children were included in the study; the median age was 10.9 years, and the median weight was 26.0 kg.
- In children, the GM (CV%) AUC_{0-24h} was 94.3 (50%) mg·h/L, and the C_{max} was 9.1 (35%) mg/L. These were slightly higher than the median (range) adult AUC_{0-24h} of 69.4 (33.0-88.4) mg·h/L and mean (SD) adult C_{max} of 5.5 (1.3) mg/L, respectively.

- The GM (CV%) C_{trough} in children was 1.5 (111%) mg/L, which was similar to the mean (SD) adult C_{trough} of 1.4 (0.5) mg/L.
- An exponential relationship was found between alpha-1-acid glycoprotein and clearance, with a slope of -0.582 (95% CI, -0.236 to -0.667; *P*<0.001).
- No significant impact of NRTI backbones on the PK of DRV was observed.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 18 March 2025.

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