PREZISTA® (darunavir)
Safety Information of PREZISTA: Effect on Lipids in Treatment-Naive Adults

SUMMARY

- The METABOLIK study compared changes in triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in treatment-naïve patients receiving PREZISTA/ritonavir (r) or atazanavir/r (ATV/r). At week 48, patients had a mean increase from baseline in TG of 26.1 mg/dL in the PREZISTA/r arm and 9.6 mg/dL in the ATV/r arm.[1]
- The ACTG A5257 study evaluated the metabolic profiles of PREZISTA/r, ATV/r, and raltegravir (RAL) in treatment naïve patients. Both boosted protease inhibitors (bPI) had greater increases in all lipid values, excluding HDL, relative to RAL at week 96 ($P \leq 0.001$).[2]
- In the ATADAR study, patients in the ATV/r arm had increased TG relative to the PREZISTA/r arm, however TC and HDL increases were comparable in the two arms.[3]
- In the ARTEMIS study, patients in the lopinavir (LPV)/r group compared with the PREZISTA/r 800/100 mg QD group had a higher incidence of grade 2-4 increases in TC (32.7% vs. 24.3%; $P=0.018$) and TG (16% vs. 5.9%; $P<0.001$) at week 192.[4]
- In the DRIVE-FORWARD study, patients in the PREZISTA/r group compared to the doravirine (DOR) group had higher increases in TC (21.9 mg/dL vs 4.1 mg/dL), LDL (14.0 mg/dL vs. -0.4 mg/dL), and TG (22.5 mg/dL vs. -1.1 mg/dL), and similar increases in HDL (4.2 mg/dL vs. 4.5 mg/dL) at week 96.[5]

STUDIES EVALUATING THE EFFECT OF PREZISTA/R ON LIPID PARAMETERS

METABOLIK Study

The METABOLIK (**M**etabolic **E**valuation in **T**reatment-naïves **A**ssessing the impact of two **BO**osted protease inhibitors on **LI**pids and other mar**K**ers) study evaluated the metabolic effects of PREZISTA/r compared to ATV/r in treatment-naïve, HIV-1–infected patients.[1]

Study Design/Methods

- Phase 4, randomized, open-label, multicenter, 48-week study (N=65).
- Patients were randomized (1:1) to either PREZISTA/r 800/100 mg QD (n=34) or ATV/r 300/100 mg QD (n=31). All patients received a fixed-dose background regimen of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200/300 mg QD.
- Select inclusion criteria: treatment-naïve HIV-1 infected adults (≥18 years), VL ≥1,000 copies/mL, HIV-1 sensitive to ATV, DRV, FTC, and tenofovir (TFV) upon baseline resistance testing.
- Select exclusion criteria: LDL >130 mg/dL, TG >200 mg/dL, fasting glucose >110 mg/dL, body mass index (BMI) >30 kg/m^2, acute/chronic hepatitis A, B, or C.
- Lipid-lowering agents were not allowed from 28 days prior to baseline through week 12, and then allowed after week 12.
- Primary endpoint: change in TG levels from baseline to week 12
- Secondary endpoints to week 48 included changes in:
  - TG, TC, HDL, measured LDL, and apolipoproteins (apo) A1 and B
  - Glucose levels, insulin levels, and insulin sensitivity (measured by homeostasis model assessment of insulin resistance [HOMA-IR] method)
  - Inflammatory biomarkers: interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-RII), and high sensitivity C-reactive protein (hs-CRP)
  - Coagulation biomarkers: fibrinogen and d-dimer
  - Bacterial translocation marker: lipopolysaccharide (LPS)
  - VL and CD4+ cell count
  - Fat redistribution, which was evaluated using computed tomography (CT) scans performed at L4-L5 and mid-thigh at baseline and week 48 and centrally analyzed

for total (TAT), subcutaneous (SAT), visceral (VAT), and peripheral (PAT) adipose tissue.
  - In addition, the self-reported Assessment of Body Change and Distress (ABCD) questionnaire was administered at baseline and at weeks 12 and 48.

Results

Patient Characteristics

- At baseline, patients in the PREZISTA/r arm had higher viral loads, lower median CD4+ counts, and lower TC and LDL levels than patients in the ATV/r arm.

Select Baseline Characteristics[1]

Parameter	PREZISTA/r (n=34)	ATV/r (n=31)
Male, n (%)	29 (85.3)	27 (87.1)
Age, median years (range)	36.5 (19.0-58.0)	35.0 (20.0-65.0)
Race, n (%)		
White	21 (61.8)	12 (38.7)
Black	13 (38.2)	17 (54.8)
VL, log_{10} copies/mL, mean (SD)	5.0 (0.8)	4.6 (0.7)
CD4+ cell count, cells/mm^3, median (range)	267 (10–532)	316 (39–813)
BMI, mean (SD)	23.8 (3.1)	24.5 (3.6)
Abbreviations: ATV, atazanavir; BMI, body mass index; r, ritonavir; SD, standard deviation; VL, viral load.		

Lipid Evaluations

- Lipid parameters were evaluated in 28 patients in the PREZISTA/r group and 27 patients in the ATV/r group.
- There were no lipid-lowering agents started after week 12.
- Primary endpoint: from baseline to week 12, patients receiving PREZISTA/r had a mean increase in TG of 22.0 mg/dL and patients receiving ATV/r had a mean increase of 8.1 mg/dL (difference 13.8, 95% CI: -25.8 to 53.4).
- By week 48, the mean increase in TG from baseline was 26.1 mg/dL in the PREZISTA/r arm and 9.6 mg/dL in the ATV/r arm (difference 16.5, 95% CI: -25.0 to 58.0) (Table: Lipid Parameters at Baseline, Week 12, and Week 48, Mean [SD]).
- Differences between arms in other fasting lipid parameters were small and similar at week 48.

Lipid Parameters at Baseline, Week 12, and Week 48, Mean (SD)[1]

Parameter, mg/dL	PREZISTA/r (n=28)			ATV/r (n=27)			Difference (BL to Week 48); 95% CI
	BL	Change from BL at 12 weeks	Change from BL at 48 weeks	BL	Change from BL at 12 weeks	Change from BL at 48 weeks	
TG	113.7 (57.4)	22.0 (62.7)	26.1 (69.0)	114.2 (84.1)	8.1 (81.2)	9.6 (73.7)	16.5 (-25.0 to 58.0)
TC	141.8 (28.3)	20.3 (30.5)	22.3 (30.7)	165.1 (30.0)	4.6 (26.7)	11.8 (31.9)	10.5 (-7.7 to 28.8)
LDL	84.6 (21.9)	13.6 (25.1)	14.7 (25.9)	100.2 (23.9)	9.6 (20.8)	13.9 (27.1)	0.8 (-14.6 to 16.3)

HDL	37.9 (13.4)	6.6 (11.6)	6.0 (7.4)	45.0 (13.6)	2.2 (8.7)	3.7 (9.9)	2.3 (-2.8 to 7.3)
Abbreviations: ATV, atazanavir; BL, baseline; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein, r, ritonavir, SD, standard deviation; TC, total cholesterol; TG, triglycerides.							

ACTG A5257 Study

The ACTG A5257 study aimed to evaluate the metabolic profiles of PREZISTA/r, ATV/r, and RAL in randomized treatment naïve patients with a VL >1000 copies/mL.[2]

Study Design/Methods

- Phase 3, randomized, open label, 96-week study.
- Patients were randomized 1:1:1 to receive PREZISTA/r 800mg/100mg once daily (n=601), ATV/r 300mg/100mg once daily (n=605), or RAL 400mg twice daily (n=603), each in combination with FTC/TDF 200mg/300mg once daily and were stratified by baseline VL (< or ≥100,000 copies/mL), cardiovascular risk, and metabolic for substudy participation.[6]
- Metabolic endpoints: change from baseline in fasting TC, HDL-C, TG, non-HDL-C, calculated LDL-C, plasma glucose, waist:height ratio, and prevalence of metabolic syndrome
- An association between plasma ritonavir C_{24} at steady state and fasting plasma lipid levels were also evaluated from baseline to 48 weeks between the bPI groups.

Results

Patient Characteristics

- Baseline characteristics were similar among groups.
- Overall population: median age 37 years; 76% male; 34% white/42% black/22% Hispanic; median VL 4.6 (log_{10}) copies/mL; VL ≥100,000: 30.6%; median CD4+ <200: 29.6%.

Lipid Specific Baseline Characteristics[2]

Characteristic	Treatment		
	PREZISTA/r (n=595)	ATV/r (n=602)	RAL (n=600)
Fasting TC, mg/dL			
Median (Q1, Q3)	154 (133, 179)	154 (134, 176)	155 (134, 181)
<200 mg/dL	529 (89)	537 (89)	523 (87)
Fasting HDL-C, mg/dL			
Median (Q1, Q3)	38 (31, 47)	37 (30, 45)	38 (31, 46)
≥40 mg/dL	259 (44)	249 (41)	272 (45)
Fasting TG, mg/dL			
Median (Q1, Q3)	99 (73, 148)	105 (74, 150)	103 (73, 146)
<150 mg/dL	447 (75)	449 (75)	456 (76)
Fasting non-HDL-C, mg/dL			
Median (Q1, Q3)	112 (93, 138)	115 (96, 137)	115 (96, 140)
<160 mg/dL	531 (89)	542 (90)	533 (89)
Fasting calculated LDL-C, mg/dL[a]			

Median (Q1, Q3)	89 (73, 111)	93 (75, 111)	93 (74, 115)
<130 mg/dL	536 (90)	542 (90)	528 (88)
Presence of metabolic syndrome	119 (20)	141 (23)	121 (20)
On lipid-lowering treatment	38 (6)	33 (5)	35 (6)

Abbreviations: ATV, atazanavir; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; Non-HDL-C, non-HDL cholesterol; Q, quarter; r, ritonavir; RAL, raltegravir; TC, total cholesterol; TG, triglycerides.
[a]Calculated as [fasting calculated LDL-C (mg/dL) = fasting TC – fasting HDL-C – (fasting TG/5)], only for subjects with fasting TG ≤400 mg/dL; subjects with fasting TG >400 mg/dL were excluded.

Lipid Evaluations

- 1797 patients with confirmed baseline fasting samples and clinical measures were included in the metabolic analyses: PREZISTA/r (n=595); ATV/r (n=602); RAL (n=600).

Summary of the Absolute Levels: Treatment Group Comparison of Lipids Over Time[2]

Metabolic Parameters	Study Week	Treatment		
		ATV/r Mean (95% CI)	RAL Mean (95% CI)	PREZISTA/r Mean (95% CI)
Fasting TC, mg/dL	0	156.7 (154.0–159.4)	158.3 (155.4–161.2)	157.0 (154.0–160.0)
	24	166.3 (163.1–169.4)	157.9 (154.9–160.9)	169.2 (166.1–172.3)
	48	169.8 (166.4–173.2)	159.5 (156.5–162.4)	172.3 (168.9–175.6)
	96	172.3 (169.0–175.6)	163.4 (160.3–166.4)	172.4 (169.0–175.8)
Fasting HDL-C, mg/dL	0	38.8 (37.8–39.8)	39.5 (38.3–40.6)	40.4 (39.2–41.5)
	24	43.4 (42.2–44.6)	43.9 (42.7–45.0)	44.4 (43.1–45.7)
	48	45.1 (43.8–46.5)	44.5 (43.3–45.7)	45.9 (44.6–47.1)
	96	45.2 (43.9–46.5)	45.4 (44.2–46.7)	45.6 (44.2–47.0)
Fasting TG, mg/dL	0	123.8 (117.2–130.4)	123.4 (116.9–129.9)	124.3 (117.1–131.5)
	24	140.3 (133.0–147.6)	109.3 (103.4–115.2)	137.3 (129.7–144.9)
	48	139.7 (132.1–147.4)	115.3 (108.8–121.9)	139.5 (131.3–147.6)
	96	140.9 (133.0–148.8)	116.3 (109.6–122.9)	141.1 (131.1–151.1)
Fasting non–HDL-C, mg/dL	0	117.9 (115.4–120.4)	118.8 (116.2–121.5)	116.6 (113.9–119.3)
	24	122.9 (119.9–126.0)	114.0 (111.1–116.9)	124.8 (121.8–127.9)
	48	124.6 (121.4–127.9)	115.0 (112.1–117.8)	126.5 (123.2–129.7)
	96	127.1 (123.9–130.3)	118.0 (114.9–121.0)	126.9 (123.6–130.1)
Fasting calculated LDL, mg/dL	0	93.7 (91.4–96.0)	94.9 (92.4–97.5)	93.0 (90.5–95.4)
	24	95.4 (92.8–98.1)	92.2 (89.7–94.7)	98.0 (95.3–100.6)
	48	97.4 (94.5–100.2)	92.0 (89.6–94.3)	99.1 (96.3–101.9)
	96	99.4 (96.5–102.3)	95.1 (92.5–97.7)	99.9 (97.1–102.7)

Abbreviations: ATV, atazanavir; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; r, ritonavir; RAL, raltegravir; TC, total cholesterol; TG, triglycerides.

- There were no differences between the ATV/r and PREZISTA/r arms (all $P > 0.05$) in all lipid measures from baseline to weeks 24, 48, and 96.
- There were greater increases in each of bPI arms compared to the RAL arm in TC, TG, non–HDL-C, and LDL-C (all $P \leq 0.001$).

- All treatment arms had an increase in HDL-C (an average increase of 6 mg/dL over 96 weeks), with no significant differences between the three arms (all *P* >0.06).
- Each arm had an increase in lipid-lowering agents from baseline to week 96: ATV/r: 5% to 11%, RAL: 6% to 9%, PREZISTA/r: 6% to 14%.
- There was no association between ritonavir troughs and lipid parameters for PREZISTA/r and ATV/r.

ATADAR Study

The ATADAR study compared the effects of PREZISTA/r and ATV/r on metabolism, body composition, overall tolerability, and efficacy in treatment-naïve, HIV-1 infected patients (N=178).[3]

Study Design/Methods

- Phase 4, randomized, open-label, multicenter, 96-week study.
- ARV-naïve adults with VL ≥1000 copies/mL were randomized (1:1) to receive either PREZISTA/r 800/100 mg QD (n=88) or ATV/r 300/100 mg QD (n=90). All patients received a fixed-dose background regimen of FTC/TDF QD.
- Primary endpoint: change in TC levels from baseline to week 24.
- Secondary endpoints included:
  - Proportion of patients free of treatment failure or virologic failure (VF; VL ≥50 copies/mL) at week 96.
  - Proportion of patients with study drug discontinuation due to AEs at week 96.
  - Changes in lipids, total bilirubin, and CD4+ counts at weeks 48 and 96.
  - Changes in dual-X absorptiometry (DXA)- and computed tomography (CT)-derived body composition parameters at weeks 48 and 96.

Results

Patient Characteristics

- baseline characteristics were similar between groups except for CD4+ count.
  - PREZISTA/r: mean age 37 years; 89% male; mean (SD) VL: 4.8 (0.8) $\log_{10}$ copies/mL; VL ≥100,000 copies/mL: 33%; CD4+ <200 cells/mm^3 14.1%.
  - ATV/r: mean age 35 years; 87% male; mean (SD) VL: 4.8 (0.7) $\log_{10}$ copies/mL; VL ≥100,000 copies/mL: 36%; CD4+ <200 cells/mm^3 27.8%.
- No patients received lipid-lowering therapy at baseline or during the study.

Lipid Evaluations

- At week 24, TC increased by 11.5 mg/dL and 7.2 mg/dL and HDL increased by 3.9 mg/dL and 5.5 mg/dL in the PREZISTA/r and ATV/r arms, respectively.
- Increases in TG were higher in the ATV/r arm than in the PREZISTA/r arm at week 96 (difference 21.5 mg/dL, 95% CI: -0.7 to 43.8; *P*=0.058).

Lipid Changes at Week 96, Mean (SD)[3]

Lipid change mg/dl	Week 96		
	PREZISTA/r (n=74)	**ATV/r (n=72)**	***P* value**
TC	+14.63 (29.18)	+11.31 (35.96)	0.7134
LDL	+8.22 (25.70)	+1.86 (29.44)	0.1711
HDL	+4.90 (10.91)	+4.80 (10.50)	0.8211
TG	+15.65 (69.53)	+38.89 (71.74)	0.0567

Abbreviations: ATV, atazanavir; HDL, high-density lipoprotein; LDL, low- density lipoprotein cholesterol; r, ritonavir; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

DATA FROM OTHER CLINICAL TRIALS

ARTEMIS Study

The ARTEMIS study is a randomized, controlled, open-label, 192-week phase 3 study comparing PREZISTA/r 800/100 mg QD versus either lopinavir/ritonavir (LPV/r) 800/200 mg QD or LPV/r 400/100 mg twice daily (BID) in treatment-naïve patients. All patients received a fixed-dose background regimen of FTC/TDF 200/300 mg QD (N=689).[7]

Lipid Results

Lipid Abnormalities Occurring in Either Treatment Arm[8]

Incidence, n (%)	PREZISTA/r (n=343)	LPV/r (n=346)	*P* value
Grade 2-4 Lipid-Related Abnormalities (incidence ≥2% patients)[a]			
TG increased[b]	20 (5.9)	55 (16)	<0.001
TC increased[b]	83 (24.3)	112 (32.7)	0.018
LDL (calculated) increased[b]	78 (22.9)	63 (18.4)	NS
Nongraded Laboratory Abnormalities			
HDL below normal limits	76 (22.3)	78 (22.7)	NS

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPV, lopinavir; NS, not significant; r, ritonavir; TC, total cholesterol; TG, triglycerides.
[a]Number of patients with data available varies per parameter.
[b]Based on the Division of AIDS table for grading the severity of adult and pediatric adverse events.

- Patients in the LPV/r group compared with PREZISTA/r group experienced greater median increases in TG and TC.
- Median TG, TC, and LDL-C levels were below the National Cholesterol Education Program (NCEP) cut-offs for patients that received PREZISTA/r.

DRIVE-FORWARD

Molina et al (2018)[5] conducted a phase 3, randomized, controlled, double-blind, parallel-group, multicenter, 96-week noninferiority study to compare PREZISTA/r 800/100 mg QD and DOR 100 mg QD, given with 2 investigator-selected NRTIs (FTC/TDF or abacavir [ABC]/lamivudine [3TC]) for previously untreated HIV-1 infection (N=769).

Lipid Results

- Mean change from baseline to week 96 in fasting lipids, PREZISTA/r vs DOR (95% CI):
  - LDL cholesterol: 14.0 (11.0 to 17.0) vs -0.4 (-2.8 to 1.9) mg/dL
  - Non-HDL cholesterol: 17.7 (14.3 to 21.0) vs -0.5 (-3.3 to 2.3) mg/dL
  - Total cholesterol: 21.9 (18.3 to 25.5) vs 4.1 (1.0 to 7.1) mg/dL
  - Triglycerides: 22.5 (13.6 to 31.4) vs -1.1 (-8.9 to 6.6) mg/dL
  - HDL cholesterol: 4.2 (2.3 to 5.5) vs 4.5 (3.3 to 5.8) mg/dL
- Few patients modified their lipid-lowering therapy during the study (PREZISTA/r, n=11; DOR, n=10).

LITERATURE SEARCH

A literature search of MEDLINE® EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 21 December 2023

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