Lopinavir Concentrations Do Not Differ Between African-Americans and Caucasians Administered Once Daily HIV Therapy: The AAQD Study

David A. Wohl[1], Prema Menezes[1], Rafael Torres[2], Kelly Vollmer[3], Babafemi Taiwo[4], Carol Golin[1], Hsiao-Chuan Tien[1], Megan Avots[1], Danielle Haley[1], John Rublein[5], Cheri E Klein[5], Becky Stephenson[1], and Angela DM Kashuba[1]

[1] UNC- Chapel Hill, Center for Infectious Diseases, NC, US [2] Tricounty Community Health Center, NC, US [3] HealthServe Community Health Center, NC, US [4] Durham County Health Department, NC, US, [5] Abbott Laboratories, IL, NC

Abstract (Updated)

Background: African-Americans have worse HIV outcomes than Caucasians and AIDS continues to be a leading cause of death among African-Americans aged 25-44 years. The differences between racial groups are multiply-determined but may include differential metabolizing enzyme activity leading to altered drug exposure. We compared the pharmacokinetics (PK) of once daily lopinavir/ritonavir (LPV/r) in HIV+ African-Americans and Caucasians.

Methods: Prospective, single-arm study enrolling 35 HIV+ ART-naïve African-Americans administered once daily regimen of soft-gel lopinavir/ritonavir (LPV/r) 800mg/200mg, tenofovir (TDF) 300mg and lamivudine (3TC) 300mg x 48 weeks. At week 4, 24h LPV PK was conducted (data on 29 subjects reaching week 4) and compared to 24h PK data from 18 HIV+ Caucasians in the QD arm of Abbott 418, a clinical trial of the same agents administered at identical doses and frequency. LPV concentrations were analyzed with a validated LC/UV method and noncompartmental PK parameters were calculated (WinNonlin). Linear mixed model was used to compare LPV concentrations between studies. HIV RNA, CD4 count, fasting lipids, whole body DEXA and adherence monitoring with electronic caps were performed among African-Americans.

Results: Median entry data among African-Americans (34% women): age = 36 years, CD4 = 169/uL, HIV RNA = 269,367 c/mL and BMI = 24.6 kg/m2. For Caucasian subjects (11% women) median age = 38 years, CD4 = 144/uL, HIV RNA = 177,644 c/mL and BMI = 23.7 kg/m2.

LPV exposure (AUC24, Cmax and C24h) was not significantly different between African-Americans and Caucasians (p=0.55). Data are plotted as mean ± SE.

From baseline to week 4, median HIV RNA change was -5.0 log10 and median CD4 change was 59 cells/mL. There were no treatment limiting toxicities.

Conclusions: There was no significant difference in LPV exposure when administered once daily with TDF and 3TC among HIV+ African-Americans and Caucasians. Further, this regimen was found to be potent, well-accepted and well-tolerated among African-Americans.

Background

- African-Americans have worse HIV outcomes than Caucasians and AIDS continues to be a leading cause of death among African-Americans aged 25-44 years.
- The differences between racial groups are multiply-determined but may include differential metabolizing enzyme activity leading to altered drug exposure.
- Few studies have examined the influence of race/ethnicity on ARV pharmacokinetics (PK)
- We compared the PK of lopinavir/ritonavir (LPV/r) administered once daily in HIV+ African-Americans and Caucasians.

Methods

Design: Prospective, single-arm, cohort study.

Population:
- -Documented HIV infection
- -Self-identified as African-American
- -Age ≥ 18 years
- -Naïve to ARV
- -CD4+ cell count < 400/uL
- -HIV RNA PCR > 1000/mL

Regimen:
Soft-gel LPV/r 800mg/200mg + tenofovir (TDF) 300mg and lamivudine (3TC) 300mg all administered once daily for 48 weeks

Evaluations:
- -24 hour PK (hours 1, 2, 4, 6, 8, 10, 12, 18, 24) was performed at week 4
- -HIV RNA PCR and CD4+ cell count were measured at weeks 0, 4, 8, 16, 24, 32, 40 and 48)
- -Adherence was assessed using Medication Event Monitoring System (MEMS) caps placed on LPV/r bottles, self-report and pill count

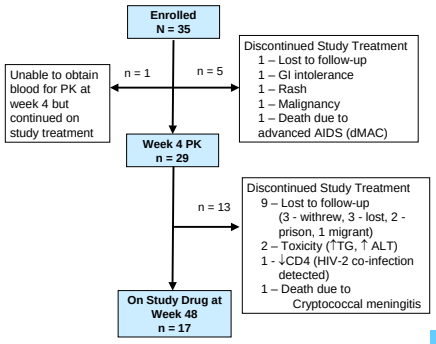
Analyses:
24 hour LPV PK was conducted and compared to 24 hour PK data from 18 HIV+ Caucasians in the once daily arm arm of Abbott Study 418, a clinical trial of the same agents administered at identical doses and frequency. LPV concentrations were analyzed with a validated LC/UV method and noncompartmental PK parameters were calculated (WinNonlin). Linear mixed model was used to compare LPV concentrations between studies.

Definition of virologic failure:
- -HIV RNA level does not decrease at least 1.0 $\log_{10}$ c/mL from baseline by Week 8
- -Plasma HIV RNA > 1.0 $\log_{10}$ increase from the nadir value and > 1000 c/mL in subjects whose plasma HIV-1 RNA never became undetectable
- -HIV RNA level is below 50 c/mL for two consecutive study visits but subsequently increases above 200 c/mL for two consecutive study visits.

Participant Baseline Characteristics

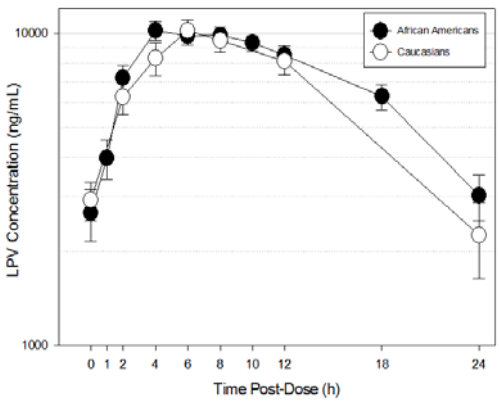
Variable	African-American Cohort AAQD (n=35)	Caucasian Cohort Abbott 418 (n=18)
Median Age	36 y	38 y
Women	30%	11%
Median CD4+ Count	169/uL	144/uL
Median HIV VL	260,367 c/mL	177,644 c/mL
BMI	24.6 kg/m^2	23.7 kg/m^2
Homeless/ Marginally Housed	43%	NA
Reporting Substance Abuse	66%	NA

Results



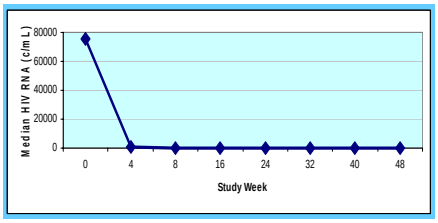
Pharmacokinetics

Comparison of LPV PK among African-American (n=29) and Caucasians (n=18) receiving LPV/r + TDF + 3TC once daily (Data are plotted as mean ± SE)

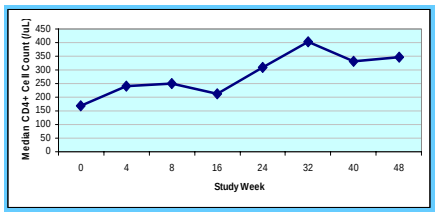


- **LPV exposure (AUC24, Cmax and C24h) was not significantly different between African-Americans and Caucasians (p=0.55).**

HIV Viral Load and CD4 Cell Responses among African-American Cohort (On Treatment Analysis)



N = 35 29 24 23 21 14 16 17



- **A total of 7 of the 30 (23%) subjects with at least one HIV RNA PCR level subsequent to week 0 experienced documented virologic failure and in each of these cases adherence was documented or suspected to be extremely sub-optimal.**
- **At week 48, 12 of the 17 (71%) subjects remaining on study assigned therapy had an HIV RNA level <50 c/mL**

Conclusions

- **There was no significant difference in LPV exposure among HIV+ African-Americans and Caucasians when administered once daily with TDF and 3TC.**
- **Extended therapy with the regimen in this cohort of patients with advanced HIV infection and high rates of substance abuse was found to be potent and few patients experienced virologic failure.**
- **The study regimen was generally well-tolerated with few treatment limiting adverse events.**

Acknowledgments

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