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Raltegravir Pharmacokinetics in Treatment-Naive Patients Is Not Influenced by Race: Results from the Raltegravir Early Therapy in African-Americans Living with HIV (REAL) Study

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Racial differences in antiretroviral treatment responses remain incompletely explained and may be a consequence of differential pharmacokinetics (PK) associated with race. Raltegravir, an inhibitor of HIV-1 integrase, is commonly used in the treatment of HIV-infected patients, many of whom are African-American. However, there are few data regarding the PK of raltegravir in African-Americans. HIV-infected men and women, self-described as African-American and naive to antiretroviral therapy were treated with raltegravir (RAL) at 400 mg twice a day, plus a fixed dose of tenofovir-emtricitabine (TDF/FTC) at 300 mg/200 mg once daily. Intensive PK sampling was conducted over 24 h at week 4. Drug concentrations at two trough values of 12 and 24 h after dosing (C_{12} and C_{24}), area under the concentration-curve values (AUC), maximum drug concentration (C_{max}), and the time at which this concentration occurred (T_{max}) in plasma were estimated with noncompartmental pharmacokinetic methods and compared to data from a subset of white subjects randomized to the RAL twice a day (plus TDF/FTC) arm of the QDMRK study, a phase III study of the safety and efficacy of once daily versus twice daily RAL in treatment naive patients. A total of 38 African-American participants were enrolled (90% male) into the REAL cohort with the following median baseline characteristics: age of 36 years, body mass index (BMI) of 23 kg/m^2, and a CD4 cell count of 339/ml. Plasma HIV RNA levels were below 200 copies/ml in 95% of participants at week 4. The characteristics of the 16 white QDMRK study participants were similar, although fewer (69%) were male, the median age was higher (45 years), and BMI was lower (19 kg/m^2). There was considerable interindividual variability in RAL concentrations in both cohorts. Median C_{12} in REAL was 91 ng/ml (range, 10 to 1,386) and in QDMRK participants was 128 ng/ml (range, 15 to 1,074). The C_{max} median concentration was 1,042 ng/ml (range, 196 to 10,092) for REAL and 1,360 ng/ml (range, 218 to 9,701) for QDMRK. There were no significant differences in any RAL PK parameter between these cohorts of African-American and white individuals. Based on plasma PK, and with similar adherence rates, the performance of RAL among HIV-infected African-Americans should be no different than that of infected patients who are white.

Racial differences in clinical responses to HIV therapy have been a consistent finding of both clinical trials and cohort studies, with African-Americans having a greater risk for virologic failure compared to other races (1–6). For example, in AIDS Clinical Trials Group (ACTG) study A5202, a comparative trial of efavirenz- and atazanavir/ritonavir-based initial treatment regimens, African-American participants had a significantly shorter time to virologic failure compared to white participants (7). Similarly, the U.S. Department of Defense HIV Natural History Study found that for HIV-infected African-Americans there was a 40% lower odds of achieving undetectable HIV RNA levels compared to whites, even after adjustment for multiple demographic, and HIV disease- and treatment-related factors (2).

The relatively lower treatment response rates for African-American HIV-infected patients remain poorly explained. Suboptimal adherence to HIV therapy has been observed to be more common among African-American study participants, but treatment adherence alone does not fully account for racial differences in treatment failure (8–12). There is limited information on whether differential pharmacokinetics of antiretrovirals contributes to racial differences in treatment efficacy. A greater risk of intolerance to efavirenz among African-Americans compared to Hispanics and whites has been observed and an association between drug levels and polymorphisms of genes coding for drug metabolism demonstrated (7, 12–15).

The HIV-1 integrase inhibitor raltegravir (RAL) is approved in the United States for the treatment of HIV infection and, in combination with tenofovir-emtricitabine (TDF/FTC), is listed as preferred for initial therapy of HIV-infected adults and adolescents by the U.S. Department of Health and Human Services (DHHS) (16). The pharmacological characteristics of RAL have been the focus of study following observations of considerable intra- and interindividual variability in the pharmacokinetic (PK) profile of the drug and a nonlinear relationship between RAL plasma concentrations and antiretroviral effect (17–19). Although the high variability in plasma concentrations of RAL relative to other antiretrovirals has complicated the modeling of RAL PK and therapeutic drug monitoring, the greater risk of treatment failure observed with once daily compared to twice daily RAL regimens suggests that drug exposure remains a critical determinant of the efficacy of this agent (20).

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Whether there are racial differences in RAL PK among HIV-infected persons is not known. Early-phase studies of RAL in HIV-uninfected study volunteers found no effect of sex or race on RAL PK (18), and the drug has been studied in infected populations that are racially diverse (21, 22). However, there are limited data regarding the PK, efficacy, and tolerability of RAL in African-American HIV-infected individuals, despite the fact that a significant proportion of patients prescribed RAL in the United States is African-American. We conducted a PK study to describe RAL PK properties in antiretroviral naive, African-American, HIV-infected patients.

(Preliminary data from were presented in part in July 2010 at the XVIII International AIDS Conference, Vienna, Austria [WEPE0103].)

MATERIALS AND METHODS

Study design and population. In this single-arm, open-label PK study, HIV-infected individuals who self-identified as being African-American were recruited and prescribed the antiretroviral combination of RAL at 400 mg twice daily orally plus a fixed dose of TDF/FTC at 300 mg/200 mg once daily. In addition to being African-American, participants were required to have less than seven cumulative days of prior exposure to antiretroviral therapy, a plasma HIV RNA level of >1,000 copies/ml, an estimated glomerular filtration rate by a modification of diet in renal disease (MDRD) of at least 60 ml/min/1.73 m^2, and hepatic transaminase levels no more than three times the upper limit of normal to be eligible for study entry. A genotypic resistance assay was performed as part of routine clinical care and those with detected resistance to tenofovir or emtricitabine were not enrolled.

Subjects were recruited at four HIV care clinics in North Carolina, including the University of North Carolina Infectious Diseases Clinic in Chapel Hill, the Wake Forest University Health Sciences Infectious Diseases Clinic in Winston-Salem, the Durham County Early Intervention Clinic in Durham, and the Wake County Early Intervention Clinic in Raleigh. All subjects had to be able to provide informed consent. The institutional review boards at UNC and Wake Forest Health Sciences approved the study protocol.

Sample collection and processing. At 4 weeks after study treatment was initiated, a PK visit was conducted, and blood samples were obtained immediately prior to the next dose (time = 0), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after an observed dose of RAL/TDF/FTC, as well as 4 and 12 h after receiving a second dose at 12 h (16 and 24 h after the first dose). Whole blood was obtained using EDTA-containing collection tubes (BD Diagnostics, Franklin Lakes, NJ) and was centrifuged for 15 min at 4°C. The resultant blood plasma (BP) was aliquoted into labeled cryovials and stored at −80°C until analysis of RAL concentrations.

Routine chemistry and hematology laboratories, including serum creatinine, hepatic transaminases, hemoglobin, and hematocrit, were also drawn and processed at the UNC clinical laboratories.

On the day of the PK visit, a standardized breakfast (500 to 682 kcal, 23 to 25% calories from fat) was provided 30 min prior to the PK sampling, and lunch was given after the 4-h blood draw. Participants were asked to eat their meals within ~30 min and to eat all of the food provided, if possible. Grapefruit and grapefruit juice were not permitted in the meals provided.

Analytical methods. RAL concentrations in BP were measured using a validated and previously published HPLC/UV method (23). The dynamic range was 20 to 10,000 ng/ml, with a minimum of 90% accuracy, and interday and intraday variabilities of 2.4 to 7.9% and 1.4 to 3.8%, respectively.

PK parameters, including maximum concentration (C_{max}), time to maximal concentration (T_{max}), the area under the time-concentration curve over the 12-h dosing interval (AUC; measured in ng·h/ml), and the trough concentrations (C_{12} and C_{24}) were estimated using WinNonlin Professional (version 5.2; Pharsight, Inc., Cary, NC). For PK analyses, concentration measurements below the lower limit of detection were imputed as zero and those below the lower limit of quantitation (LLQ) were imputed as 10 ng/ml (50% the LLQ).

Statistical methods. PK data from the 38 African American subjects from the UNC study were compared to data generated in 16 white subjects from the QDMRK study (Merck & Co.). Parameters included C_{12} and C_{24}, AUC, C_{max}, and T_{max} (20). Since only C_{12} data were available from the QDMRK subjects, these values were used for comparisons to both the C_{12} and the C_{24} data from the UNC participants. To statistically assess whether or not one study tended to have larger (or smaller) values for each of these variables, a Wilcoxon rank-sum test was conducted for each of the variables described.

TABLE 1 Descriptive characteristics of participants in the REAL cohort (African-American) and a subset of white QDMRK participants

Characteristic	REAL (n = 38)	QDMRK (n = 16)	P^a
Male (%)	89	69	0.11*
Median age (yr)	31.5	45	0.10
Median wt (kg)	81.2	72.8	0.06
Median BMI (kg/m^2)	26	19	<0.001
Median CD4 cell count at study entry (cells/mm^3)	338.5	342	0.48
Median HIV RNA at study entry (copies/ml)	27,258	45,100	0.02
Median HIV RNA at PK study week (copies/ml)[b]	39	39	0.86
HIV RNA level <200 copies per ml at PK study week (%)	95	75	0.06†

[a] P values were obtained using Wilcoxon rank-sum tests unless otherwise noted. *, P value obtained using the Fisher exact test.
[b] Values below lower limit of assay detection (40 copies/ml) are calculated as 39 copies/ml.

RESULTS

Raltegravir PK in African-American patients with HIV infection. A total of 38 African-American participants underwent intensive week 4 PK sampling. Most were middle-aged males (82% male, median age of 36 years). The major characteristics of the cohort participants are detailed in Table 1. Almost all (95%) had suppressed HIV viremia (HIV RNA level < 200 copies/ml) at week 4, suggesting high levels of adherence.

The concentration-time profiles for each subject over 24 h, with median/interquartile ranges, shown in Fig. 1 demonstrate considerable interindividual variability in RAL levels. Summary statistics of the PK parameters are listed in Table 2 and presented graphically in Fig. 2.

Comparison to established raltegravir pharmacokinetic data. To provide a context in which to interpret the PK data obtained from the African-American patient cohort, these results were compared to the data published in the RAL package insert (18), as well as a subset of white participants of the QDMRK Trial with available PK data (characteristics included in Table 1). The mean RAL C_{max}, T_{max}, $t_{1/2}$, and $AUC_{0\text{-}12}$ reported in the RAL package insert were within the range seen in the African-American subjects (Table 2). When comparing the data from the African-American cohort participants and the white QDMRK participants, there were no statistically significant differences between any of the PK variables (Fig. 2).

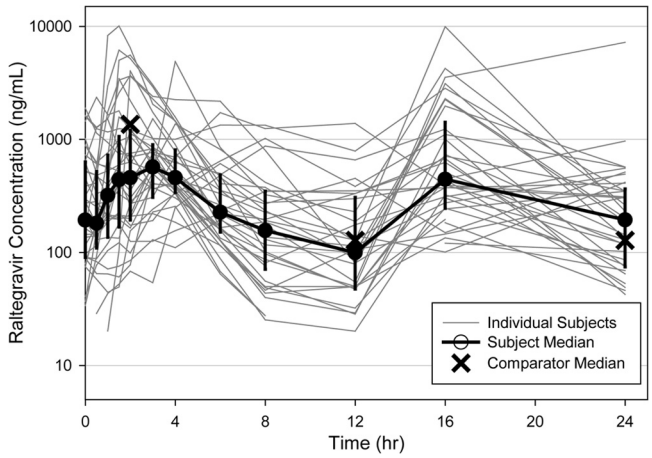

FIG 1 Individual subject concentration-time profiles over the 24-h study period for African-American REAL cohort participants ($n = 38$). RAL doses were administered at 0 and 12 h. Boldface line indicates median concentration value at each time point, with 25th and 75th percentile error bars. X indicates median concentration reported in white QDMRK participants ($n = 16$).

DISCUSSION

RAL is a component of one of the four regimens preferred by the U.S. DHHS antiretroviral guideline panel for initial therapy of HIV, and given that 44% of the ~48,000 individuals infected with HIV each year are black/African-American, a substantial number of African-Americans can be expected to be prescribed this antiretroviral (24). However, this is the first study, to our knowledge, to examine the PK profile of RAL exclusively among African-Americans.

As has been previously described in more racially heterogeneous cohorts, considerable variability in plasma concentrations of RAL was observed (17–19). There is incomplete understanding of the cause of the variability of RAL PK within and between individuals. The human UDP glucuronosyltransferase isozyme 1A1 converts RAL to its the glucuronide metabolite and serves as the major mechanism of clearance of the drug. However, RAL is also subjected to renal excretion and variability in absorption, metabolism, and excretion may all contribute to the variability of RAL PK.

To place our findings in perspective, we explored whether the PK profile derived from African-American participants differed markedly from the PK data obtained in earlier studies of RAL. Comparisons of the PK data from the present study to the summary PK data published in the RAL package insert (derived from HIV-uninfected and infected volunteers) and the more detailed data from 12-h intensive PK of white QDMRK participants revealed no evidence of a significant effect of race on any PK parameter.

There are limitations to our study. Foremost among them, comparisons were made to PK data from a cohort of white individuals who had been receiving therapy for 96 weeks, as opposed to 4 weeks for the African-American UNC subjects. There can be significant differences between individuals with short- and longer-term antiretroviral treatment in terms of viremia and inflammation. However, given that the half-life of raltegravir is ~9 h, steady-state antiretroviral conditions should have been achieved by 5 days of therapy and at both time points the vast majority of subjects had suppressed viremia. Regardless, caution should be exercised when interpreting this comparison, especially as the sample size in each group is relatively small and PK properties can be variable. In addition, the intracellular pharmacology of RAL was not assessed here. There are several papers describing the intracellular concentrations and activity of RAL, including those measuring residence time of the drug on the integrase-DNA integration complex (19, 25). The intracellular partitioning ratio relative to plasma has been reported as ~11%, with no time-related trends (26). The absence of any significant racial difference in plasma PK does not exclude the possibility of such a difference in intracellular pharmacology of RAL, but with no previous evidence of accumulation, excellent therapeutic responses in all populations, and no significant differences in tolerability, this is unlikely.

Overall, the present study is the first to describe RAL PK among a cohort of African-American HIV-infected individuals. Our findings suggest that based on plasma PK, with similar adherence rates, as evidenced by suppression of HIV replication, the perfor-

TABLE 2 Descriptive statistics overall for the REAL African-American cohort and white QDMRK participants

Study	Variable[a]	*n*	Minimum	25th%	Median	Mean	75th%	Maximum	SD
REAL	AUC	38	1,012	2,404	4,424	5,989	7,132	20,389	5,006
	C_{12}	38	10	47	91	190	219	1,386	268
	C_{24}	38	10	80	173	425	349	7,218	1,151
	C_{max}	38	196	532	1,042	1,799	1,686	10,092	2,075
	T_{max}	38	0.5	2.0	3.0	3.3	4.0	8.0	1.9
QDMRK[b]	AUC	16	878	4,573	6,248	7,656	6,864	27,780	7,181
	C_{12}	16	15.3	51	128	239	302	1,074	283
	C_{24}	16	15.3	51	128	239	302	1,074	283
	C_{max}	16	218	760	1,360	2,105	2,219	9,701	2,373
	T_{max}	16	0.5	1.0	2.0	3.1	4.0	8.0	2.5
Package insert	AUC					6,900			
	C_{12}					69			
	C_{max}					1,370			
	T_{max}					3.0			

[a] Time (T_{max}) is measured in hours, and concentrations (C_{12}, C_{24}, and C_{max}) are measured in ng/ml.
[b] The values for C_{12} are used for C_{24} for the QDMRK data.

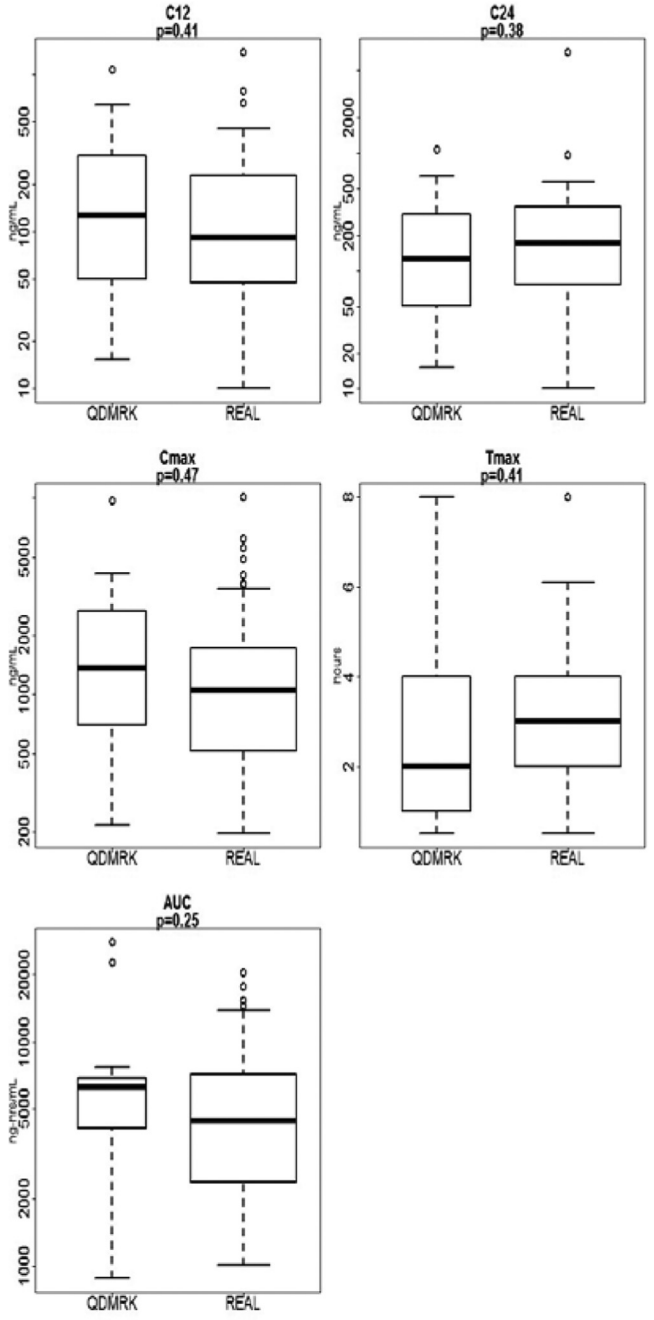

FIG 2 Box plots by study for AUC, C_{12}, C_{24}, T_{max}, and C_{max} for the REAL African-American cohort and white participants in QDMRK.

mance of RAL among HIV-infected African-Americans should be no different than that of infected patients who are white.

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