



Disparate Virologic Response to HAART between Ethnicities

Amy Weintrob^{1,2}, Greg Grandits^{2,3}, Brian Agan^{2,4}, Anuradha Ganesan^{2,5}, Nancy Crum-Cianflone^{2,6}, Susan Fraser^{2,7}, Sugat Patel^{2,8}, Glenn Wortmann^{1,2}, Scott Wegner², Vincent Marconi^{2,4}

¹Walter Reed Army Medical Center, Washington, DC; ²Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, MD; ³University of Minnesota, Minneapolis, MN; ⁴San Antonio Military Medical Center, San Antonio, TX; ⁵National Naval Medical Center, Bethesda, MD; ⁶Naval Medical Center San Diego, San Diego, CA; ⁷Tripler Army Medical Center, Honolulu, HI; ⁸Naval Medical Center Portsmouth, Portsmouth, VA

Amy Weintrob, MD
WRAMC Bldg 2, Ward 63, Rm 6312
6900 Georgia Ave NW
Washington, DC 20307
Amy.Weintrob@na.amedd.army.mil
(202) 782-8710 phone
(202) 782-0551 fax

ABSTRACT

Background: Current DHHS guidelines note that viral suppression should be achieved within 24 weeks of HAART initiation. Several cohorts have shown that African Americans (AA) have different virologic outcomes post HAART than European Americans (EA). This disparity has been attributed, in part, to social and economic barriers to care. We evaluated the impact of a health care system with equal access to free healthcare on these differences.

Methods: 1031 HIV-infected subjects from a large longitudinal US military cohort who initiated HAART between 1996-2006 were analyzed to identify factors related to achieving an undetectable VL (<400 c/ml) after 6 months of HAART. Factors investigated were age, gender, race, baseline VL, nadir CD4 count, prior AIDS event, prior antiretroviral use, HAART regimen, era, and co-morbidities. Logistic regression modeling was used for univariate and multivariate analyses.

Results: Of the 1031 subjects (mean age 34.7 years, 93% male, 43% EA, 45% AA, median VL at HAART start 33,100 c/ml, mean CD4 nadir 305), 684 (66% overall, 73% of EA, 59% of AA) achieved viral suppression 6 months after starting HAART. In the multivariate model, the following were associated with increased odds of viral suppression after 6 months: increasing age (OR 1.3 per 10 years, 95%CI 1.1 - 1.5), EA versus AA race (OR 2.0, 1.4 - 2.7), lower baseline VL (OR 1.6 per 1 log₁₀, 1.3 - 2.0), higher nadir CD4 count (OR 1.7 of CD4<350 compared to <200, 1.1 - 2.6), no prior AIDS event (OR 1.5, 1.0 - 2.4), no prior antiretroviral use (OR 3.8, 2.6 - 5.4), NNRTI versus PI regimen (OR 1.9, 1.3 - 2.7), and not having Hepatitis B (OR 2.0, 1.1 - 3.8). Gender, hemoglobin, HAART era (before year 2000 or on/after year 2000), and Hepatitis C were not associated with the odds of viral suppression at 6 months. There were no differences between the ethnicities in initial HAART regimens and at 6 months post HAART, equal percentages of EA and AA had changed or stopped their initial HAART regimens. The difference between ethnicities persisted at 12 months post HAART, where EA had an OR of 1.7 (95%CI 1.3 - 2.0) of achieving viral suppression compared to AA.

Conclusions: Despite access to free healthcare and starting similar HAART regimens, AA had only half the odds as EA of achieving viral suppression 6 months after starting HAART. This difference persisted at 12 months and was not explained by discontinuations or changes in initial therapy.

BACKGROUND

*In the U.S., African Americans (AA) are disproportionately infected with HIV.

*Studies of HAART efficacy have predominantly involved men of European descent.

*Biologic or behavioral differences between races may impact response to HAART¹⁻³.

*Several studies⁴⁻⁷ have shown that compared to European Americans (EA), AA:

- obtain undetectable viral loads less often
- experience viral rebound more often

*The objective of this study is to determine if there is a difference in virologic response to HAART between AA and EA subjects enrolled in the TriService AIDS Clinical Consortium (TACC) HIV National History Study (NHS) where there is equal access to free healthcare and medications.

METHODS

*The TACC HIV NHS is an ongoing, prospective multicenter observational study which began in 1987 and has followed approximately 5000 HIV-infected persons, half of whom have documented negative HIV tests prior to their first positive test allowing for estimation of their seroconversion date. In the TACC HIV NHS, race is self-reported.

*900 AA and 894 EA who initiated HAART between 1996-2004 were compared for virologic response to HAART and for selected factors at the time of HAART initiation which may affect virologic response.

*Logistic regression modeling was used for univariate and multivariate analyses of factors related to achieving an undetectable viral load (<400 c/ml) at 6 months and 12 months post HAART initiation.

RESULTS

Table 1. Comparison of Selected Factors Between African and European Americans Initiating HAART

	Total	African Americans	European Americans	P-Value (AA v EA)
Number in cohort starting HAART	1794	900	894	
Demographics				
Mean Age at HAART (y)	34.7 ± 8.4	33.8 ± 8.3	35.8 ± 8.3	<.001
Female (%)	9.2	12.1	6.1	<.001
Rank of Officer/Warrant (%)	18.1	4.9	18.2	<.001
HIV Disease Factors (mean ± SD)				
Viral Load at HIV diagnosis (log ₁₀)	4.4 ± 0.9	4.3 ± 0.9	4.4 ± 0.9	0.285
Viral Load at HAART start (log ₁₀)	4.3 ± 1.0	4.3 ± 0.9	4.3 ± 1.0	0.819
CD4 at HIV diagnosis (cells/mm ³)	516 ± 247	478 ± 233	552 ± 255	<.001
CD4 at HAART initiation (cells/mm ³)	285 ± 179	275 ± 168	284 ± 190	0.628
CD4 at HAART initiation (cells/mm ³)	389 ± 222	333 ± 209	367 ± 233	0.004
Time AIDS defining illness (y)	18.7	18.0	11.4	0.011
Time ARV Use (y)	57.2	64.4	60.0	0.018
Initial HAART Regimen (%)				
PI without zidovudine	61.9	62.4	61.3	
PI with zidovudine	7.6	6.2	9.1	
NNRTI	22.4	23.0	21.7	
Efficiency (% of total regimens)	19.8	21.3	18.2	0.099
PI plus NNRTI	3.0	2.7	4.4	
3 NRTIs	4.2	4.7	3.8	
Coinfections at HAART Start (%)				
Hepatitis B	6.7	8.4	5.1	0.007
Hepatitis C	6.7	7.6	5.8	0.153
Serum Levels at HAART Start				
Hemoglobin (g/dl)	14.0 ± 1.6	13.6 ± 1.5	14.4 ± 1.6	<.001
ALT (U/l)	45.9 ± 58.3	47.1 ± 50.8	44.8 ± 60.9	0.660
Creatinine (mg/dl)	1.0 ± 0.2	1.1 ± 0.3	1.0 ± 0.2	<.001
Duration Factors				
% with estimated seroconversion (SC) date	72.3	71.6	73.0	0.482
Estimated SC to HIV diagnosis (months)	10.8 ± 9.0	10.2 ± 8.2	11.2 ± 9.6	0.087
Estimated SC to HAART start (months)	83.2 ± 90.7	52.0 ± 40.4	84.8 ± 90.9	0.233
Viral load to HAART (months)	57.8 ± 49.1	58.8 ± 56.2	57.2 ± 48.0	0.890
Nadir CD4 to HAART start (months)	14 ± 22	14 ± 24	13 ± 21	0.244
Year Starting HAART	1998 ± 2.4	1998 ± 2.3	1998 ± 2.5	0.332

*No significant difference in time from seroconversion to HAART start or from HIV diagnosis to HAART start between AA and EA. Also no difference in time from nadir CD4 count to HAART start between the two races.

*AA had lower CD4 counts at HIV diagnosis and at HAART start although the decline in CD4 counts from HIV diagnosis to HAART initiation was not faster in AA compared to EA.

*No significant difference in VL at HIV diagnosis or at HAART initiation between AA and EA.

*No difference in initial HAART regimens between AA and EA.

Table 2a. Comparison of Factors 6-Months After HAART Between African and European Americans

	Total	African Americans	European Americans	P-Value (AA v EA)
Viral Load				
VL < 400 c/ml (%)	65.6	58.3	73.3	<.001
VL change from start - 6 mos post HAART (log ₁₀)	-1.6 ± 1.3	-1.5 ± 1.3	-1.8 ± 1.3	<.001
HAART Regimen at 6 months (%)				
No Change from Start	49.0	70.4	67.6	0.041
Change - Different HAART	26.7	19.4	22.1	
Change - Not on HAART	10.2	10.1	10.4	

RESULTS (continued)

Table 2B. Comparison of Factors 12-Months After HAART Between African and European Americans

	Total	African Americans	European Americans	P-Value (AA v EA)
Viral Load				
VL < 400 c/ml (%)	61.6	55.7	67.9	<.001
VL change from start - 12 mos post HAART (log ₁₀)	-1.6 ± 1.3	-1.4 ± 1.3	-1.7 ± 1.4	<.001
HAART Regimen at 12 months (%)				
No Change from Start	54.0	54.3	53.8	
Change - Different HAART	34.4	34.2	34.6	0.980
Change - Not on HAART	11.6	11.5	11.6	

Table 3. Comparison of Viral Suppression Between AA and EA by Initial HAART Regimen

HAART Regimen	VL < 400 at 6 months after HAART (%)			On original HAART regimen after 6 months (%)		
	African American	European American	Difference* (AA v EA)	African American	European American	Difference (AA v EA)
PI w/o RTV	50	69	-19	71	70	+1
PI w RTV	38	68	-38	45	57	-12
NNRTI	78	81	-3	74	68	+6
PI + NNRTI	47	83	-36	80	54	+26
3 NRTIs	83	78	+5	71	68	+3

RTV = zidovudine, *p-value = 0.07 for overall interaction

Table 4. Odds ratio of having a viral load <400 c/ml at 6 months post HAART from multivariate logistic regression model (N=1082)^{a,b,c,d}

Factor	OR Comparison	Multivariate Odds Ratio (95% CI)	P-value
Race	AA v EA	0.5 (0.4 - 0.7)	<.001
Age at HAART	10 years	1.3 (1.1 - 1.6)	0.004
Gender	Women v Men	0.8 (0.5 - 1.4)	0.467
VL at HAART	1 log ₁₀ VL	1.1 (0.4 - 1.7)	<.001
CD4 at HAART	100 cells	1.1 (1.0 - 1.2)	0.099
AIDS prior to HAART	Yes v No	0.8 (0.5 - 1.5)	0.564
ARV prior to HAART	Yes v No	0.3 (0.2 - 0.4)	<.001
PI with RTV regimen	PI w/o RTV	0.8 (0.5 - 1.3)	0.405
NNRTI regimen	PI w/o RTV	1.4 (0.9 - 2.2)	0.124
PI + NNRTI regimen	PI w/o RTV	2.5 (1.1 - 5.6)	0.029
Triple NRTI regimen	PI w/o RTV	1.6 (0.7 - 3.6)	0.244
Hemoglobin at HAART	2 mg/dl	1.0 (0.8 - 1.3)	0.865
Hepatitis B co-infection	Yes v No	0.5 (0.3 - 1.0)	0.055
Year of HAART Start	1 year	1.1 (1.0 - 1.2)	0.066

^aSubjects in multivariate model above had to have values for all factors considered and a viral load result available 6 months after starting HAART

^bALT was not included in above model due to a limited number of subjects who had ALT measured at the time of HAART initiation.

^cSerum creatinine at HAART initiation and hepatitis C status were not significant in the univariate analysis and therefore were not included in the multivariate model

^dResults of the above analysis are not significantly different when rank is included in the model

*The odds ratio for obtaining a viral load <400 c/ml at 12 months post HAART for AA compared to EA (N=1017) is 0.6 (0.4 - 0.8) in the multivariate model adjusting for the same factors as above.

CONCLUSIONS

*In a military healthcare system with equal access to free healthcare and free medications:

-African Americans (AA) had significantly lower odds of obtaining a viral load < 400 c/ml at 6 months and 12 months post HAART initiation compared to European Americans (EA).

-The differences in viral suppression rates between AA and EA remained significant after adjusting for age, sex, rank, viral load and CD4 count at HAART initiation, prior AIDS events, prior antiretroviral use, specific HAART regimen, hepatitis B co-infection, hemoglobin level, and year of HAART initiation.

-A subgroup analysis of the interaction between race and specific HAART regimens demonstrated the difference in viral suppression between AA and EA at 6 months was greater for protease inhibitor based regimens than either NNRTI based or triple NRTI regimens.

-There were no significant differences in time from seroconversion, HIV diagnosis, or CD4 nadir to HAART initiation between AA and EA. AA did not progress faster in terms of CD4 decline or VL increase between diagnosis and HAART start.

-Rates of HAART discontinuation or change were similar between AA and EA.

*Potential reasons for the differences in viral suppression between AA and EA include:

-Differences in adherence.

*This study is limited by lack of data on adherence.

*Other studies have shown mixed results as to whether there are adherence differences between individuals of different ethnicities^{1,4-6}.

-Differences in co-morbidities (including mental health illnesses)^{2,5}.

-Differences in drug absorption, metabolism, and distribution.

*Genetic polymorphisms which may be more common in certain ethnicities may lead to lower drug concentrations (thereby decreasing efficacy) or higher drug concentrations (leading to increased rates of side effects or toxicities).

*Polymorphisms in the gene that codes for CYP2B6 and the gene that codes for MDR1 (which lead to higher concentrations of Efavirenz and protease inhibitors, respectively) are more common in AA but have not been shown to directly affect viral response to HAART^{7,8,9}.

*Given the large number of AA infected with HIV, it is imperative that we learn why AA do not obtain the same rate of viral suppression as EA and intervene appropriately in order to maximize HAART response and clinical outcome.

REFERENCES

- Anastou K, Schneider MF, Gange SJ, et al. The association of race, socioeconomic, and behavioral characteristics with response to highly active antiretroviral therapy in women. J Acquir Immune Defic Syndr 2005;39:537-44.
- Pence JW, Ostrin E, Gama V, et al. The influence of psychosocial characteristics and race/ethnicity on the use, duration, and success of antiretroviral therapy. J Acquir Immune Defic Syndr 2008;47:194-201.
- Moore R, Kernan J, Gebo K, Lucas GM. Racial differences in Efavirenz discontinuation in clinical practice. 12th CROI 2006; poster 619.
- Gebo RM, Rinaldo HJ, Shikuma CM, et al. Three vs four drug antiretroviral regimens for the initial treatment of HIV-1 infection. JAMA 2006;296:769-81.
- McGinnis KA, Fine MJ, Sharma RK, et al. Understanding racial disparities in HIV using data from the Veterans Aging Cohort-3 site study and VA administrative data. Am J Public Health 2005;95:1728-33.
- Gifford AL, Bornman JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multiple antiretroviral regimens. J Acquir Immune Defic Syndr 2003;23:386-95.
- Felley J, Maffioletti R, Echebaum M, Brinkmann U, et al. Frequency of C3435T polymorphism of MDR1 gene in African people. Lancet 2001;358:83-4.
- Schellier C, Meaden ER, et al. Response to antiretroviral treatment in HIV-1 infected individuals with allelic variants of the multidrug resistance transporter-1: a pharmacogenetics study. Lancet 2002;359:30-6.
- Hao DW, Wu H, Huihong L, et al. MDR1 gene polymorphisms and plasma viral decay during HIV-1 infection. J Acquir Immune Defic Syndr 2003;34:295-8.