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The Association of Ethnicity with Antibody Responses to Pneumococcal Vaccination among Adults with HIV Infection

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Abstract

Ethnicity may be associated with the incidence of pneumococcal infections and the frequency of protective vaccine responses. Earlier studies have suggested that HIV-infected persons of black ethnicity develop less robust immune responses to pneumococcal vaccination that may relate to their higher incidence of invasive disease. We evaluated the association of ethnicity with capsule-specific antibody responses to pneumococcal revaccination, with either the pneumococcal conjugate (PCV) or polysaccharide (PPV) vaccines among 188 HIV-infected adults. The proportion of the 77 African Americans (AA) and 111 Caucasians with comparable virologic and immunologic parameters who achieved a positive immune response (≥ 2 -fold rise in capsule-specific IgG from baseline with post-vaccination value ≥ 1 $\mu\text{g/mL}$ for ≥ 2 of 4 serotypes) at day 60 after revaccination was similar (43% vs. 49%, respectively, $p=0.65$). Results were also similar when vaccine types (PPV and PCV) were examined separately. Mean changes in $\log_{10}$ transformed IgG levels from baseline to days 60 and 180 post-vaccination were also not significantly different between AA and Caucasians. In summary, in this ethnically diverse cohort with equal access to care, we did not observe differential antibody responses between AA and Caucasian HIV-infected adults after pneumococcal revaccination.

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1. Introduction

Streptococcus pneumoniae infections are a common cause of morbidity among persons infected with the human immunodeficiency virus (HIV) [1–7]. Several studies have demonstrated an ethnic disparity among rates of pneumococcal disease with an increased risk among blacks compared with whites in both the general population and persons infected with HIV [3,8–12].

The efficacy of pneumococcal vaccinations in preventing invasive pneumococcal disease among HIV-infected adults is suboptimal in all ethnic groups [6]. A limited IgG antibody response to pneumococcal capsular polysaccharides, an important determinant of disease and protection, among black Americans and Africans has been proposed to contribute to the higher risk of disease in this ethnic group [12,13]. However, the exact nature of this proposed poor vaccine efficacy is unclear as little data are available that directly compare antibody levels generated post-vaccination among HIV-infected persons of differing ethnicities. Therefore, we utilized data from a prospective, randomized study to compare capsule-specific IgG levels prior to and following pneumococcal revaccination in African American (AA) and Caucasian HIV-infected adults.

2. Methods

2.1. Study Population

We performed subgroup analyses of capsule-specific IgG responses among AA and Caucasians from a randomized study comparing the immunogenicity of revaccination with pneumococcal conjugate vaccine (PCV) to pneumococcal polysaccharide vaccine (PPV) among HIV-infected adults previously vaccinated with PPV. The main study evaluated 204 HIV-infected adults who were randomized (2:1) to PCV (Pneumovax; Wyeth Pharmaceuticals, n=131) or PPV (Pneumovax, Merck & Co., Inc., n=73) between February 2006 and September 2008 [14].

Of all study participants, 77 were AA and 111 Caucasians, and these subjects are the focus of this sub-analysis. Data on ethnicity was based on self report. Study participants were infected with HIV (documented by a positive ELISA with Western Blot confirmation), between ages 18–60 years, had received a prior PPV vaccination 3–8 years earlier, and without significant concurrent medical conditions except for HIV infection. All participants were military beneficiaries who have open and free access to healthcare, and low rates of illicit drug use [15]. Study subjects provided written informed consent, and the study was approved by the governing institutional review boards and registered with the Clinical Trials network (registration NCT00622843).

2.2. Study Design and Procedures

The primary study outcome was achieving a positive immune response, defined as a ≥ 2 -fold rise in capsule-specific IgG with post-vaccination value ≥ 1 $\mu\text{g/mL}$, at day 60 post-vaccination for at least 2 of 4 serotypes. The endpoint was chosen in concordance with prior reports, and a threshold value of 1 $\mu\text{g/mL}$ was used to assure that fold rises represented meaningful post-vaccination antibody levels [16,17]. Secondary outcomes included positive IgG responses and changes in capsule-specific IgG concentrations for each serotype at each time point.

Pneumococcal vaccines were administered intramuscularly (0.5 ml) in the deltoid muscle using a 23-gauge, 1-inch needle in accordance with manufacturers' guidelines. Serum samples were collected at baseline (1–21 days prior to revaccination) and days 14, 60, and 180 after revaccination. We determined the capsule specific IgG levels to four

pneumococcal serotypes (4, 9V, 14, and 19F), which represented a range of important serotypes among HIV-associated pneumococcal infections.

2.3 Assays

Serotype-specific pneumococcal IgG concentrations were measured by ELISA, as previously described [14,18]. In brief, sera were preadsorbed with 4 µg/mL of cell wall polysaccharide and 2 µg/mL of type 22F capsular polysaccharide overnight to eliminate non-capsule-specific antibodies [19,20]. Capsular polysaccharides were adhered to 96-well microtiter plates, and capsule-specific IgG was detected with affinity-purified horseradish peroxidase-conjugated goat anti-human IgG label and appropriate substrates. Samples were tested in triplicate. Antibody concentrations on each plate were based on extrapolation from standard values on each plate (Standard Reference Serum 89-SF; provided by the Food and Drug Administration).

2.4. Data Analysis

Descriptive statistics are presented as means with standard deviations (SD) and medians with interquartile ranges (IQR). Proportions were compared between ethnic groups using Chi-square tests, and medians compared using Kruskal-Wallis tests. Odds ratios (OR) for achieving a positive immune response (AA vs. Caucasian) were generated with adjusted logistic regression models. Sensitivity analyses for the primary outcome included evaluating the effect of different post-vaccination threshold values. Secondary analyses evaluated changes from baseline in IgG concentrations, calculated after log₁₀ transformation for AA and Caucasians for each serotype at each study time point, and were compared using adjusted generalized linear fixed-effects regression models. OR and change from baseline data are presented with 95% confidence intervals (CI). All logistic and linear regression models were adjusted for vaccine group (PCV vs. PPV), baseline type-specific IgG concentrations after log₁₀ transformation, age (≤40 years vs. >40 years), prior pneumonia, CD4+ T cell number (<500 cells/mm³ vs. ≥500 cells/mm³), plasma HIV RNA level (≤50 copies vs. >50 copies/mL), and antiretroviral use at time of vaccination. All p-values are two sided and analyses were conducted using SAS (version 9.2, SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Study Population Characteristics

The median age of participants was 42 (IQR 36–47) years and 95% were males (Table 1). The median number of prior PPV immunizations were one, which was administered a median of 4.5 years prior to study enrollment. Eighteen percent of participants had a history of prior pneumonia. Regarding HIV history, the median duration of HIV infection was 9.5 (IQR 5–16) years, median CD4+ T cell count was 540 (IQR 391–701) cells/mm³, and 81% were receiving HAART. Of the 188 participants, 121 were randomized to be revaccinated with PCV and 67 were randomized to be revaccinated with PPV. There were no differences in baseline characteristics between AA and Caucasian participants, except that Caucasians were more likely to have a history of pneumonia (23% vs. 10%, p=0.03).

3.2. Immune Responses to Pneumococcal Vaccination

Pre-vaccination antibody levels did not vary by ethnicity for any of the four serotypes (Table 2). The proportion of AA and Caucasians who achieved a positive immune response at day 60 after revaccination was similar (43% vs. 49%, respectively, p=0.65) (Figure 1). For IgG responses for individual serotypes, a lower proportion of AA generated responses for serotypes 9V and 14 compared with responses in Caucasians after revaccination at day 14.

However, by days 60 and 180, there were no differences between the ethnic groups for any serotype (Figure 1). Results were similar for the primary endpoint when modifying the criterion from achieving a post-vaccination level of ≥ 1 $\mu\text{g/mL}$ to achieving a level of ≥ 0 $\mu\text{g/mL}$, ≥ 0.35 $\mu\text{g/mL}$, or ≥ 5 $\mu\text{g/mL}$ (data not shown).

There were no significant differences in median unadjusted IgG levels ($\mu\text{g/mL}$) between Caucasians and AA for any serotype at any timepoint (Table 2). The adjusted mean changes in IgG concentration (expressed as $\log_{10}$ $\mu\text{g/mL}$) from baseline to day 60 or day 180 were also similar among Caucasians and AA for all serotypes (Figure 2). In addition, when the two pneumococcal vaccines (PCV and PPV) were examined separately for positive immune responses and changes in GMC at day 60, results showed no significant ethnic differences. Finally, we examined if a history of prior pneumonia was associated with antibody responses and found no significant associations (data not shown).

4. Discussion

Vaccination is a central strategy for pneumococcal disease prevention and is advocated for high-risk groups, including persons with HIV infection [21]. As such, it is important to determine if ethnic disparities in pneumococcal disease incidence rates may be associated with differences in the immunogenicity and efficacy of vaccinations among ethnic groups. Two studies have shown that the administration of PPV among HIV-infected black Americans [12] and Africans [13] result in disproportionately limited efficacy, and may even be associated with detrimental effects [13]. The mechanisms underlying the poor vaccine efficacy among blacks in these studies is unclear. Immunogenicity studies among HIV-infected Africans have found suboptimal responses to PPV [22] and have correlated low post-vaccination capsule-specific IgG levels with clinical events [23]. Whether poor responses were due to advanced HIV disease, nutritional/environmental factors, or other ethnicity-associated factors remains unclear since those studies did not have a racially-diverse comparator group.

We investigated whether HIV-infected AA compared with Caucasians generated differential immune responses to pneumococcal vaccination. In our ethnically diverse HIV cohort with equal access to care, we did not observe differential post-vaccination immune responses at days 60 or 180 between AA and Caucasians to either vaccine preparation. Hence, our data suggest that previously described ethnic disparities in pneumococcal disease frequencies may not be associated with differences in vaccine immunogenicity, particularly when controlled for clinical and immune status as well as access to care. Indeed, a recent trial showed protection against invasive pneumococcal disease among black HIV-infected African adults with prior disease who received PCV [24]. Thus, African ethnicity alone may not be associated with poorer vaccine responses. Of note, our study had the advantage of directly comparing responses among AA and Caucasians in a comparable controlled setting, a strength compared with prior studies [13,24].

The reasons for the higher rates of pneumococcal disease reported among blacks require further investigation [3,8–12]. That one epidemiologic study found that blacks had a 5-fold higher rate of pneumococcal disease compared to whites, independent of socioeconomic status or population density [9,10], suggests that population genetics may play a role. However, differences in socioeconomic status or crowding leading to varying healthcare access or other environmental factors may also contribute to these differential rates of disease. Understanding of the basis for previously described ethnic differences in pneumococcal disease incidences and responses to vaccination are especially important among HIV-infected persons, among whom the incidence of invasive pneumococcal disease

is substantially increased [1,4,7]. Furthermore, the majority of the 33 million HIV-infected persons worldwide are of African descent [25,26].

Our study had potential limitations. Our study did not determine IgM anti-pneumococcal responses which may be suboptimal among HIV-infected persons [27]. However IgM responses are typically transient and we focused on IgG responses which represent more durable responses that likely best correlate with pneumococcal protection over time. Furthermore, data on the functionality of the IgG antibodies as determined by opsonophagocytic assays or avidity are not currently available for our study cohort. Finally, although our randomized study comparing the immunogenicity of PCV vs. PPV revaccination was adequately powered [14], as a substudy, these analyses were not powered to detect differences by ethnicity. Nonetheless, we did not find any patterns for differences of durable antibody responses (at days 60 or 180) among the two ethnic groups.

Our U.S.-based study provides important clinical data by demonstrating that AA and Caucasians infected with HIV respond equally to pneumococcal revaccination. Since our population consisted of an early-diagnosed and treated U.S. HIV cohort, we recommend further studies examining pneumococcal capsule-specific IgG responses among various ethnic groups in other settings, including Africa. We recognize that AA participants in our study cohort likely come from diverse ethnic backgrounds in Africa, and that our study did not include genetic analyses. Hence we advocate further studies examining the role of host genetics and environmental variables on disease rates and vaccine responses among persons of various ethnicities.

In summary, our study showed that pneumococcal IgG responses both prior to and following revaccination with both the 23-valent polysaccharide and the 7-valent conjugate vaccine were similar among AA and Caucasian HIV-infected adults. These data suggest that environmental or other host factors, rather than differing antibody responses to vaccination, may underlie differential rates of pneumococcal disease reported among persons of different ethnic backgrounds.

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Figure 1.
Adjusted Odds Ratios for Achieving a Positive Immune Response* to Pneumococcal Revaccination for African Americans versus Caucasians
*Achieving a ≥ 2 -fold rise in capsule-specific IgG with post-vaccination value $\geq 1 \mu\text{g/mL}$

Figure 2.
Adjusted Means (SE) of change in IgG Concentration (expressed as $\log_{10} \mu\text{g/mL}$) from Baseline to Days 14, 60, and 180 by Serotype among African Americans versus Caucasians

Table 1

Baseline Characteristics of Study Population by Ethnicity

Characteristic	Total Cohort N=188	African Americans N=77	Caucasians N=111	p-value *
Demographics				
Age, years (median, IQR)	42 (36 – 47)	42 (35 – 48)	42 (37 – 46)	0.92
Gender, male (%)	178 (94.7%)	71 (92.2%)	107 (96.4%)	0.21
History of Prior Pneumococcal Vaccination and Pneumonia				
No. of Previous PPVs (median, IQR)	1 (1 – 2)	1 (1 – 2)	1 (1 – 2)	0.70
Time since last PPV, years (median, IQR)	4.5 (3.6 – 6.0)	4.5 (3.7 – 5.9)	4.7 (3.5 – 6.1)	0.95
History of Pneumonia ** (%)	33 (17.6%)	8 (10.4%)	25 (22.5%)	0.03
HIV-Related History				
Duration of HIV infection, years (median, IQR)	9.5 (4.7 – 16.0)	9.3 (4.4 – 16.3)	9.5 (5.1 – 15.4)	0.92
CD4+ T Cell Count, cells/mm ³ (median, IQR)	540 (391 – 701)	550 (390 – 711)	532 (392 – 692)	0.76
CD4+ percentage, % (median, IQR)	30 (23 – 36)	30 (23 – 35)	30 (24 – 37)	0.45
Plasma HIV RNA, % undetectable ($\leq$ 400 copies/mL)	143 (76.5%)	58 (75.3%)	85 (77.3%)	0.76
Plasma HIV RNA, log ₁₀ copies/mL (median, IQR)	1.70 (1.7 – 2.4)	1.70 (1.7 – 2.5)	1.70 (1.7 – 2.3)	0.88
Receipt of HAART *** , %	153 (81.4%)	60 (77.9%)	93 (83.8%)	0.31
Treatment Allocation During Original Study				
Received PCV during study, %	121 (64.4%)	50 (64.9%)	71 (64%)	0.89

* p-values comparing proportions were calculated using Chi-square tests, and p-values comparing medians were calculated using a Kruskal-Wallis.

** Type of pneumonia not specified.

*** HAART refers to highly active antiretroviral therapy as defined by treatment guidelines.

Table 2

Absolute IgG levels ($\mu\text{g/mL}$) at Baseline and at Days 14, 60, and 180 Post-Vaccination among African Americans and Caucasians

	African Americans		Caucasians		p-value*
	No.	Median (IQR)	No.	Median (IQR)	
Serotype 4					
Day 0	75	0.28 (0.11, 0.73)	108	0.29 (0.10, 0.70)	0.83
Day 14	72	0.83 (0.29, 1.73)	107	0.89 (0.32, 4.33)	0.12
Day 60	68	0.79 (0.25, 2.39)	105	0.72 (0.30, 3.35)	0.84
Day 180	66	0.73 (0.31, 1.78)	102	0.79 (0.28, 2.03)	0.89
Serotype 9V					
Day 0	75	0.59 (0.28, 1.74)	108	0.46 (0.20, 1.19)	0.16
Day 14	72	1.52 (0.60, 3.97)	107	2.24 (0.68, 5.67)	0.19
Day 60	68	1.72 (0.58, 3.88)	105	2.04 (0.69, 6.14)	0.37
Day 180	66	1.30 (0.40, 3.33)	102	1.38 (0.44, 4.10)	0.55
Serotype 14					
Day 0	75	0.97 (0.42, 5.00)	108	0.60 (0.24, 3.59)	0.21
Day 14	72	2.82 (0.80, 10.41)	107	2.56 (0.80, 9.32)	0.81
Day 60	68	2.52 (0.75, 9.91)	105	2.88 (0.67, 12.87)	0.98
Day 180	66	2.76 (0.67, 7.14)	102	3.28 (0.65, 7.62)	0.67
Serotype 19F					
Day 0	75	0.83 (0.33, 1.82)	108	0.53 (0.26, 1.71)	0.14
Day 14	72	0.97 (0.41, 3.30)	107	0.95 (0.38, 3.16)	0.91
Day 60	68	1.19 (0.44, 3.26)	105	0.85 (0.34, 2.42)	0.28
Day 180	66	0.94 (0.41, 2.36)	102	1.02 (0.37, 2.33)	0.89

* p-value if from Kruskal-Wallis Test comparing African Americans to Caucasians. IQR, interquartile range; N, number.