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Weak HIV Antibody Responses in Perinatally-Infected Young Adults

Allison R. Kirkpatrick, BS*, Aylin B. Unsal, BS*, Joel N. Blankson, MD, PhD[†], Richard D. Moore, MD[†], Thomas C. Quinn, MD, MSc^{*,†}, Colleen Hadigan, MD, MPH[†], and Oliver Laeyendecker, PhD, MBA^{*,†}

*Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH, Baltimore, Maryland [†]Dept. of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Abstract

We compared the antibody response to HIV using two serologic cross-sectional incidence assays in adults with perinatally-acquired HIV, to elite controllers and individuals exposed to antiretroviral therapy who were all infected as adults. Low antibody responses were seen more frequently in adults with perinatally-acquired HIV, both overall and when stratified by viral suppression status.

Keywords

HIV; Incidence; United States

Background

Young adults who acquired HIV infection perinatally comprise a significant proportion of HIV-infected individuals in some populations, particularly in sub-Saharan Africa, where the burden of HIV is highest. For example, among the young women enrolled in the HPTN 068 trial (Pettifor et al., 2016), 1.5% of non-sexually active 13–14 year old girls were HIV positive. In this trial, 38/81 young women who were HIV positive denied any sexual activity. These individuals would be classified as recently infected by age-based HIV prevalence models (Hallett et al., 2008) which may lead to over estimates of incidence. Besides age-based prevalence models, HIV cross-sectional incidence testing, which identifies individuals based on antibody profiles, can be used to estimate population level incidence (Busch et al., 2010). However, there is currently little information on the antibody responses in perinatally-infected young adults.

Weak antibody responses could impact the interpretation of serologic assays used for cross-sectional HIV incidence estimation, which use antibody avidity, or binding strength, as a

biomarker to differentiate between recent (often less than two years) and long-term HIV infection. Other factors previously shown to be associated with low antibody responses include having subtype D infection, being an elite controller and low viral load (Kassanjee et al., 2014; Longosz, Mehta, et al., 2014; Longosz, Serwadda, et al., 2014). We compared serologic characteristics in young adults with perinatally-acquired HIV infection (PN) to two groups who were infected as adults and who are frequently misclassified as recently infected using cross-sectional HIV incidence assays: elite controllers (EC) and adults exposed to antiretroviral therapy (ART).

Methods

Sample Set Characteristics

Samples were collected from participants of HIV cohort studies conducted in the Baltimore-Washington area. (1) PN group: 229 samples dating from 2007 to 2015 from 23 adolescents and adults perinatally-infected between 1984 and 1996; mean age: 20 years, age range: 12–30; 70% (160/229) of samples had viral loads (VL) <400 copies/ml, including many who received sequential monotherapy early in treatment (Abd-Elmoniem et al., 2014). None of these individuals received suppressive treatment at birth, though all samples tested come from individuals who have been exposed to ARVs for years. (2) ART group: 478 samples from 379 adults exposed to ART; 61% (290/478) samples had VL <400 copies/ml, mean minimum duration of infection: 13 years, range: 8 to 25 years (Moore, 1998). None of the subjects were virally suppressed within the first year of infection. (3) EC group: 40 samples from 21 adults with natural control of HIV infection; all samples had VL <400 copies/ml (Bailey et al., 2006).

Laboratory Methods

Samples were tested with the Limiting Antigen Avidity Assay (LAg-Avidity; Sedia, Portland, OR) and an avidity-modified version of the Genetic Systems 1/2 + O EIA (BioRad-Avidity; Bio-Rad, Redmond, WA). The LAg-Avidity assay was run according to the manufacturer's protocol (Wei et al., 2010). For the LAg-Avidity assay, a normalized optical density (OD-n) < 1.5 is the cut off value used to designate recent infection. As all samples tested in the present study were from individuals infected more than two years, any sample below this cut off is considered misclassified. The modification of the BioRad assay has been described previously (Longosz, Serwadda, et al., 2014). Briefly, each sample is run in duplicate. A chaotropic agent, 0.1M diethylamine (DEA) diluted in deionized water, is added to the first well; assay wash buffer is added to the second. The avidity index (AI) is the ratio of optical density of the DEA-treated well to that of the wash buffer-treated well, multiplied by 100%. For our present study, samples with an AI value <80% were considered to have low avidity.

Statistical Methods

The Fischer exact test and Wilcoxon rank-sum test were used where appropriate. Additionally, regression analysis was performed using generalized estimating equations to control for potential correlation of LAg-Avidity and BioRad values within a subject. The

analysis was also adjusted for viral suppression, as this is a known effect modifier of the antibody response.

Results

The PN group had higher frequency of samples with low avidity assay results than the ART and the EC groups (see Figure 1). For LAg-Avidity, 43% (10/23) of individuals in the PN group had at least one sample with OD-n result <1.5 and 32% (74/229) of all samples tested had <1.5 OD-n. In comparison, 7% (27/379) of individuals and 6% (27/478) of samples in the ART group ($P<0.001$) and 20% (4/21) of individuals and 23% (9/40) of samples in the EC group ($P=0.01$) had OD-n <1.5. For BioRad-Avidity, 39% (9/23) of individuals and 23% (57/229) of samples in the PN group had <80% AI. In comparison, 0.8% (3/379) of individuals and 0.6% (3/478) of samples in the ART group ($P<0.001$) had <80% AI. There were no samples in the EC group with an AI <80% (compared to PN group, $P<0.001$).

Comparing the PN to ART group stratified by viral suppression status, PN samples were more likely to have low LAg-Avidity and BioRad values. For VL<400 copies/mL and LAg-Avidity <1.5 OD-n: PN 71/160 vs. ART 25/290 ($P<0.001$). For VL<400 copies/mL and BioRad AI <80%: PN 52/160 vs. ART 3/290 ($P<0.001$). Among VL>400 copies/mL, LAg-Avidity <1.5 OD-n: PN 3/69 vs. ART 2/188 ($P<0.01$) and BioRad AI <80%: PN 5/69 vs. ART 1/188 ($P<0.01$).

In the regression analysis, LAg-Avidity values were 1.12 OD-n higher (95% CI 0.47, 1.58; $P<0.001$) in the ART group than the PN group which was not attenuated when adjusting for viral suppression. Virally suppressed PN subjects had average 1.02 lower LAg-Avidity OD-n (95% CI 0.18, 1.98; $p=0.019$) than ES subjects. For the BioRad results, PN subjects had AI values that were on average 11.7% (95% CI 3.9, 20.3; $P=0.004$) than ART subjects, with near identical results when controlled for viral suppression. Additionally, among virally suppressed PN subjects had average 12.6% lower AI (95% CI 4.0, 21.3; $P=0.004$) than ES subjects.

Conclusions

Young adults infected perinatally had lower HIV specific antibody responses as measured by HIV incidence assays than their counterparts who were infected as adults. These lower antibody responses were seen for both virally suppressed and viremic perinatally-infected individuals compared to individuals who were infected as adults. This lowered marker of the anti HIV antibody response would result in a higher frequency of long term infected individuals being misclassified as recently infected resulting in increased estimates of HIV incidence in populations where significant proportion of these individuals occur.

It is known that adults and children who are aggressively treated during the acute stage infection fail to develop mature antibody responses to the virus (Zanchetta et al., 2008). For individuals who do develop an HIV-specific immune response, the alteration of the natural course of infection through ART treatment, combined with a developing immune system, could be one explanation for the weak antibody responses observed in these individuals (De Rossi, 2002). Adults taken off the antiviral medication generate a vigorous antibody

response to their infection. In our sample population, the perinatally-infected individuals were infected prior to the advent of highly active antiviral therapy, and therefore many had long episodes of sustained viral infection to which their humoral response would have been given adequate antigen to mount highly avid antibodies. The decreased antibody avidity in these individuals may have been either through the destruction of helper T-cells to the HIV specific response or other mechanism.

Whatever the mechanism, these young adults have low antibody responses as measured by HIV cross-sectional incidence assays. Even though these individuals have been infected for approximately two decades, they misclassify as recently infected. Many time points tested are virologically positive but have low LAg-Avidity or BioRad Avidity results. These results could impact the precision of HIV incidence estimates in studies using these assays to analyze populations that include perinatally-infected adults. Further studies are needed to determine reason for the reduced antibody responses in these individuals.

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Figure 1.

Avidity values for each sample group by viral load (VL) status (open circles: VL < 400 copies/mL; solid circles: VL > 400 copies/mL). The median values are indicated with horizontal lines. 1A. LAg-Avidity normalized optical density (OD-n); 1B. BioRad-Avidity Avidity Index (AI). P values were calculated using a Wilcoxon rank-sum test. Arrows designate the groups being compared.