Susceptibility to Measles Among Perinatally HIV-Infected Adolescents and Young Adults

Lee E. Morris,[1] Roberto Posada,[1] Carole J. Hickman,[2] Donald R. Latner,[2] Tricia A. Singh,[3] Alyssa Rautenberg,[3] Jennifer Jao,[3,4] William J. Bellini,[2] and Rhoda Sperling[3]

[1]Division of Pediatric Infectious Disease, Mount Sinai School of Medicine, New York, New York; [2]Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Department of OB/Gyn, and [4]Division of Infectious Disease, Mount Sinai School of Medicine, New York, New York

Corresponding Author: Lee Morris, MD, MSPH, Pediatric Infectious Disease Group, Division of Fairfax Neonatal Associates, 2720-D Prosperity Ave, Fairfax, VA 22031. E-mail: leemorr@gmail.com.

Received January 4, 2013; accepted June 13, 2013; electronically published September 24, 2013.

Among our cohort of adolescents and young adults with perinatally acquired human immunodeficiency virus, few (17.6%) had measles protective antibodies by plaque reduction neutralization (PRN). Agreement was demonstrated between the commercial enzyme immunoassay and the PRN assay (K = 0.59 [95% confidence interval: 0.23–0.95]). Further studies are needed to understand the determinants of immunity in this population.

Key words. adolescents; HIV; measles immunity; perinatally acquired HIV infection.

Combination antiretroviral therapy (cART) has dramatically improved survival among children with perinatally acquired human immunodeficiency virus (PAH). As these survivors age into adolescence and adulthood, unanticipated health problems have emerged including inadequate seroprotection to vaccine-preventable illnesses such as measles [1–9]. In addition to the direct health risks for those with PAH, PAH individuals with poor or short-lived immunologic responses to measles, mumps, and rubella (MMR) vaccination may hinder global efforts to eradicate measles [9]. The possibility of reintroduction of measles into the United States remains an ongoing public health concern [10]. However, the greatest global health risk may be in low resource countries where the prevalence of human immunodeficiency virus (HIV) and measles are high [9, 10].

After MMR vaccination, low rates of initial seroconversion and waning immunity have been reported among children with PAH [1–5, 7–9]. In general, levels of immunoglobulin (Ig)G and antigen-specific memory B cells have strongly correlated with adherence to cART as well as the degree of immunosuppression [2–4, 7, 9]. Given the improved survival of children with PAH, it is important to determine the prevalence of measles immunity among adolescents and young adults with PAH and whether the commercially available measles enzyme immunoassay (EIA) is adequate to assess immunity. We designed our study to determine the prevalence of measles immunity among our population and to compare the performance of the commercially available measles EIA with the research gold standard, plaque reduction neutralization (PRN) assay used to identify seroprotection and the need for revaccination [11].

METHODS

Study Population

Individuals were recruited from the Jack Martin Clinic at Mount Sinai Hospital (MSH), New York, an urban clinic providing HIV care to pediatric and adult patients infected with HIV. All individuals with PAH who met inclusion criteria were offered enrollment in the study. Inclusion criteria were individuals with PAH aged 13 to 26 years, who were receiving care at MSH Jack Martin Clinic, and had previously documented MMR vaccination. Participants or their caregivers, as appropriate, provided verbal assent or consent before enrollment. This study was approved by the Mount Sinai School of Medicine Institutional Review Board.

Measurements

As part of their routine care, HIV-infected adolescents and young adults are screened for the presence of measles, mumps, and rubella IgG-neutralizing antibodies by the EIA used at MSH (using the Vidas automated immunoanalyzer

Journal of the Pediatric Infectious Diseases Society, Vol. 4, No. 1, pp. 63–6, 2015. DOI:10.1093/jpids/pit054

instrument by bioMerieux). Results are usually obtained within 5–7 days. After testing at MSH, remaining samples were sent to collaborators at the Centers for Disease Control and Prevention (CDC) for measles IgG testing by PRN assay. Measles immunity was defined as IgG titers >120 mIU by PRN assay and >0.70 IU by EIA. Participants found to be measles nonimmune will be offered revaccination, if they meet clinical criteria as defined by the Advisory Committee for Immunization Practices. Information regarding prior MMR vaccination, measles serology, CD4 cell count, nadir CD4 cell count, HIV RNA levels, opportunistic infections, comorbid conditions, and antiretroviral regimens was obtained via medical record review for each participant.

Analysis

Baseline characteristics were compared between measles immune and nonimmune groups using unpaired *t*, Wilcoxon rank sum, χ^2, or Fisher's exact tests as appropriate. Kappa statistic was calculated for MSH's commercially available measles EIA with 95% confidence intervals (CIs). Statistical analyses were performed using SAS 9.2 (Cary, NC).

RESULTS

Thirty-four subjects were enrolled between June and October 2011. Both MSH EIA and CDC PRN assays were conducted on all but 1 subject in whom the quantity of serum available was insufficient. The kappa statistic between the PRN and EIA assays was 0.59 (95% CI, .23–.95). There were 4 discrepant results between the MSH EIA and the CDC PRN assay. Two of these subjects were determined measles nonimmune by PRN assay but immune by EIA assay. Based on PRN assay, only 6 of 34 (17.6%) participants were measles immune.

Baseline characteristics of the cohort are shown in Table 1. Measles immune participants were younger than nonimmune subjects (median age 14.5 vs 19 years [$P = .01$]) and had fewer elapsed years since their last MMR vaccination than nonimmune subjects (7.5 vs 13 years [$P < .01$]). One (17%) measles immune participant had a history of opportunistic infections compared with 18 (62%) nonimmune participants ($P = .07$). The opportunistic infections reported included pneumocystis pneumonia (PCP), herpes simplex, cytomegalovirus, recurrent candida infections, *Mycobacterium tuberculosis, Mycobacterium avium intracellulare, Mycobacterium xenopi*, acquired immune deficiency syndrome wasting syndrome, viral warts, lymphoid interstitial pneumonitis, and herpes zoster. The majority of the subjects with opportunistic infections had more than 1 opportunistic infection in their past medical history. Median CD4 cell count at enrollment and nadir CD4 cell count were 682 cells/mm^3 and 299 cells/mm^3 in measles immune participants versus 263 cells/mm^3 ($P = .05$) and 143 cells/mm^3 ($P = .18$) in nonimmune participants, respectively. In addition, 83% of immune participants were receiving antiretroviral therapy (ART) (16.7% on monotherapy and 66.7% on cART) at the time of initial vaccination compared with 30% nonimmune participants ($P = .03$). Finally, there was no statistical difference in median number of MMR vaccinations between nonimmune and immune participants ($P = .62$).

Table 1. Baseline Characteristics of Adolescents With Perinatally Acquired HIV by Measles Immunity

	Measles Nonimmune by PRN Assay n = 28	Measles Immune by PRN Assay n = 6	*P* Value[a]
Age, years (median) (IQR)	19 (17–20)	14.5 (13–18)	*P* = .01
Female, No. (%)	19 (65%)	3 (50%)	*P* = .648
Race, No. (%)			*P* = .802
White	1 (4%)	0 (0%)	
African American	7 (24%)	1 (17%)	
Hispanic	16 (55%)	3 (50%)	
Other	5 (17%)	2 (33%)	
History of opportunistic infections, No. (%)	18 (62%)	1 (17%)	*P* = .07
CD4+ cells/mm^3 at enrollment (median) (IQR)	263 (161–378)	682 (255–1166)	*P* = .054
Nadir CD4+ cells/mm^3 (median) (IQR)	143 (23–231)	299 (34–442)	*P* = .175
Nadir CD4+ cells $\leq$ 200 cells/mm^3, No. (%)	20 (69%)	2 (33%)	*P* = .166
Nadir CD4% (median, IQR)	14 (3–25)	25 (7–41)	*P* = .227
Nadir CD4% <15, No. (%)	14 (48%)	2 (33%)	*P* = .666
HIV RNA $\log_{10}$ (copies/mL) at CD4 nadir (mean) (95% CI)	3.97 (3.42–4.53)	3.64 (2.24–5.03)	*P* = .65
HIV RNA $\log_{10}$ (copies/mL) at enrollment (mean) (95% CI)	3.74 (3.18–4.3)	2.79 (1.22–4.36)	*P* = .159
On cART at enrollment, No. (%)	21 (75%)	4 (67%)	*P* = .645
MMR vaccinations (median) (range)	2 (1–4)	2 (2–3)	*P* = .618
Age at first MMR, months (median) (IQR)	12 (11–18)	13.5 (11–15)	*P* = .873
On ART at time of first MMR, No. (%)	8 (30%)	5 (83%)	*P* = .025
On ART at time of second MMR, No. (%)	19 (79%)	6 (100%)	*P* = .553
Time since last MMR vaccination, years (median) (IQR)	13.5 (10.8–15)	7.5 (6–9)	*P* = .003

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; MMR, measles, mumps, rubella; PRN, plaque reduction neutralization.

[a] *P* values from *t* test or Wilcoxon test for continuous variables and χ^2 test or Fisher's exact test for categorical variables.

DISCUSSION

In this study of adolescents and young adults with PAH, we found very low rates of measles immunity despite appropriate prior vaccination. In addition, consistent with prior studies evaluating the sensitivity and specificity of commercially available measles EIA assays compared with PRN [12], our findings demonstrate some agreement between the EIA used at MSH (Vidas) and the gold standard PRN assay available through the CDC.

As measured by PRN assay, 82% of previously vaccinated adolescents and young adults enrolled in our study were not immune to measles. Worldwide, significant variability in rates of seroprotection amongst children with PAH have been reported in the literature (5.5%–88%). However, the majority of these studies have demonstrated low rates of immunity among this population [2–9]. Studies of youth with PAH from the United States reported a wide range (31%–94%) of children lacking immunity to measles, despite prior vaccination [2–6, 9]. These studies followed children from 1 month to several years after vaccination, but, overall, the longitudinal follow-up between vaccination and final visit was significantly less time than in our study [2–6, 9]. Most recently, 1 study reported a 52% rate of seroprotection among children with PAH enrolled through the International Maternal Pediatric Adolescent AIDS Clinical Trials Group [9]. In addition, children on cART with viral load suppression had higher rates of seroprotection after measles revaccination. Overall, studies have demonstrated short-lived initial immune responses; the lack of a durable immune response could explain our observations of low rates of measles immunity in an older population. This lack of durable immune response also may account for the very low rates (5.5%) of measles immunity in older patients with advanced HIV disease reported by Melvin and Mohan [2].

In our study, measles seroprotection was associated with higher median CD4 cell count at study enrollment, which reached borderline significance. However, higher median nadir CD4 cell count was weakly associated with seroprotection, but this data did not reach significance. In the literature, measles seroprotection has been associated with better viral control and improved immune status both at the time of vaccination and over time [2–5, 7–9]. However, inconsistencies are reported among studies regarding the role viral load and CD4 cell count play in sustained measles immunity and primary vaccine response after revaccination [2–5, 7, 9].

Finally, in our study, measles immunity was associated with ART at the time of first MMR vaccination. This is consistent with many reports demonstrating a generally positive association between cART and adequacy of vaccine response [1–5, 7–9]. However, waning immunity after cART initiation has been observed among some children who were measles immune [3–5, 7, 8]. A study of children with PAH in Kenya demonstrated that 53% of children who were initially measles immune became nonimmune after 6 months of cART and immune reconstitution [7]. Likewise, a study in the Netherlands demonstrated that 40% of children with PAH who were initially immune to measles lost their measles antibodies while on cART with immune reconstitution [8]. Future research will need to investigate the effect of cART on immune responses to live virus vaccines and the ideal timing of vaccination in relation to the initiation of cART [1–9].

Our study is subject to a number of limitations. Small numbers make interpretation of results with wide CIs challenging and preclude meaningful assessment of a number of variables of interest. Evaluation of viral load and rates of viral suppression at the time of first and subsequent MMR vaccinations as well as ART status at the time of third MMR vaccination by measles immune status could have provided valuable information. At the time of diagnosis for many of our subjects, routine viral load testing had not yet become available. In addition, whether the majority of our patients were on ART at the time of their first MMR vaccination was determined by ART availability. In the early to mid-1990s there were few antiretroviral medications available, particularly in pediatric formulations. Most of the patients in this study who were started on ART early in life were started on single or dual therapy with cART being initiated years later, often after the first MMR vaccination was administered. Because the median age of the measles immune group was significantly younger than the nonimmune group in this study, many in the measles immune group may have had access to cART at the time of their initial MMR vaccination as opposed to others in the older measles nonimmune group who may not have had access to cART at that time. A previous study indicated that a PRN titer of >120 mIU correlates with protection from measles [13]. Although it is possible that the seronegative individuals described here may have residual measles-specific B and T cell memory, it is not known what level of protection the cellular components might provide especially given numerous reports of B and T cell dysfunction as a result of HIV infection. However, the possibility that cellular immunity in these individuals could provide protection should be the subject of further investigation because it may circumvent multiple revaccinations, which do not seem to provide long-lasting serum antibody in this population.

Although limited by a small sample size, the overwhelmingly low rates of measles immunity found in our cohort merits further investigation. Perinatally acquired HIV infection affects the development of B and T cells, impairing responses to infections and vaccination with attenuated live virus vaccines like MMR [2–4, 6, 8]. Initiating cART at an early stage of HIV infection, specifically within the first year of life, may preserve enough B and T cell function to form lasting and effective antibody against measles and other vaccine-preventable diseases [1–8]. Vaccine responses among individuals with immune reconstitution after cART warrants further study. In addition, our findings support the need to investigate early immune responses after MMR revaccination to determine predictors of vaccine success and identify strategies to improve vaccine responsiveness. In this study, those subjects found to be nonimmune to measles will be offered revaccination with MMR as part of a larger study currently under development to better understand the immune response to live viral vaccines in this vulnerable population.

Studies demonstrate a growing population of children with PAH who are reaching adolescence and adulthood with inadequate seroprotection to measles. Their increased presence in high transmission settings such as colleges, schools, and chronic care facilities may pose a larger public health risk. As more low-resource countries have access to cART for the management of pediatric HIV, the rising number of perinatally HIV-infected adolescents and young adults worldwide who do not maintain immunity to live virus vaccines could potentially undermine global eradication efforts of measles and other diseases.

Acknowledgments

We thank all of the patients, their families, and participating staff at MSH and the CDC.

Financial support. J. J. received salary support from the National Institute of Child Health and Human Development 1K23HD070760-01A1 during the preparation of this manuscript.

Potential conflict of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript has been disclosed.

References

1. Aurpibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Persistence of measles, mumps, and rubella protective antibodies 3 years after revaccination in HIV-infected children receiving antiretroviral therapy. Clin Infect Dis **2010**; 50: 1415–8.
2. Melvin A, Mohan K. Response to immunization with measles, tetanus, and *Haemophilus influenzae* type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with highly active antiretroviral therapy. Pediatrics **2003**; 111:e641–4.
3. Sutcliffe C, Moss W. Do children infected with HIV receiving HAART need to be revaccinated? Lancet Infect Dis **2010**; 10: 630–42.
4. Rainwater-Lovett K, Moss W. Immunologic basis for revaccination of HIV-infected children receiving HAART. Future Virol **2011**; 6:59–71.
5. Scott P, Moss W, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. J Infect Dis **2011**; 204:S164–78.
6. Chandwani S, Beeler J, Li H, et al. Safety and immunogenicity of early measles vaccination in children born to HIV-infected mothers in the United States: results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 225. J Infect Dis **2011**; 204: S179–89.
7. Farquhar C, Wamalwa D, Selig S, et al. Immune responses to measles and tetanus vaccines among Kenyan human immunodeficiency virus type 1 (HIV-1)-infected children pre- and post-highly active antiretroviral therapy and revaccination. Pediatr Infect Dis J **2009**; 28:295–9.
8. Bekker V, Scherpbier H, Pajkrt D, et al. Persistent humoral immune defect in highly active antiretroviral therapy-treated children with HIV-1 infection: loss of specific antibodies against attenuated vaccine strains and natural viral infection. Pediatrics **2006**; 118:e315–22.
9. Abzug M, Qin M, Levin M, et al. Immunogenicity, immunologic memory, and safety following measles revaccination in HIV-infected children receiving highly active antiretroviral therapy. J Infect Dis **2012**; 206:1–11.
10. Centers for Disease Control and Prevention (CDC). Measles - United States, 2011. MMWR Morb Mortal Wkly Rep **2012**; 61: 253–7.
11. Albrecht P, Herrmann K, Burns G. Role of virus strain in conventional and enhanced measles plaque reduction neutralization test. J Virol Methods **1981**; 3:251–60.
12. Ratnam S, Gadag V, West R, et al. Comparison of commercial enzyme immunoassay kits with plaque reduction neutralization test for detection of measles virus antibody. J Clin Microbiol **1995**; 33:811–5.
13. Chen R, Markowitz L, Albrecht P, et al. Measles antibody: reevaluation of protective titers. J Infect Dis **1990**; 162: 1036–42.