NIH Public Access
Author Manuscript
Pediatr Infect Dis J. Author manuscript; available in PMC 2015 August 01.

Published in final edited form as:
Pediatr Infect Dis J. 2014 August ; 33(8): 843–845. doi:10.1097/INF.0000000000000332.

Measles Seropositivity in HIV-Infected Kenyan Children on Antiretroviral Therapy

Laura P. Newman, MHS[a], **Anne Njoroge, MBChB**[b], **Leila Ben-Youssef, MD, MA**[c], **Michele Merkel, MS**[c,d], **Ann Gatuguta, MBChB, MPH**[b], **Quy Ton, MD, MPH**[c], **Elizabeth Maleche Obimbo, MBChB, MMed, MPH**[b], **Dalton Wamalwa, MBChB, MMed, MPH**[b], **Barbara Lohman-Payne, PhD, MSc**[c,d,g], **Barbra A. Richardson, PhD, MS**[e,f,g], **Ruth Nduati, MBChB, MMed, MPH**[d], and **Carey Farquhar, MD, MPH**[a,c,g]

[a]Department of Epidemiology, University of Washington, Seattle, WA, USA

[b]Department of Public Health, University of Nairobi, Nairobi, Kenya

[c]Department of Medicine, University of Washington, Seattle, WA, USA

[d]Department of Paediatrics and Child Health, University of Nairobi, Nairobi, Kenya

[e]Department of Biostatistics, University of Washington, Seattle, WA, USA

[f]Division of Vaccine and Infectious Disease, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

[g]Department of Global Health, University of Washington, Seattle, WA, USA

Abstract

This paper describes results from a cross-sectional study among HIV-infected children 15 months to 12 years of age who were receiving antiretroviral therapy. We found a low prevalence of measles IgG seropositivity (45.7%) and identified CD4% ≥ 25 as a predictor. Most HIV-infected children on ART were not measles seropositive and might benefit from revaccination.

Keywords

Measles; HIV; children; antiretrovirals; Kenya

INTRODUCTION

Despite recent advances in reducing overall measles incidence in Africa, measles outbreaks have occurred in countries with high HIV prevalence (1). Poor responses to measles vaccination in HIV-infected individuals not on treatment might pose a threat to herd immunity in countries with a large HIV burden. There is evidence that antiretroviral therapy (ART) initiation alone is not sufficient for restoring measles antibody titers. A study in

Correspondence: Laura Newman, Department of Epidemiology, University of Washington, Box 357236, Seattle, WA, 98195, USA. lpnewman@u.washington.edu.

The authors have no conflicts of interest to disclose.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

ART-naïve Kenyan children found that 33% had positive measles IgG antibody at baseline; after six months of ART only 42% had positive measles IgG antibody in the absence of measles revaccination (2). These data about ART-naïve children may not be generalizable to children on ART for longer durations or to those initiating ART before receiving measles vaccine. Data are lacking for these two populations and predictors are unknown for measles IgG seropositivity in immune reconstituted HIV-infected children.

In this report we describe the prevalence and correlates of measles IgG seropositivity in treated, immune reconstituted HIV-infected children as part of a study assessing the rationale and benefits of revaccinating children in HIV treatment programs.

METHODS

Study participants and procedures

HIV-infected children ≥15 months to 12 years old and their caretakers were recruited from the Comprehensive Care Centre at Kenyatta National Hospital (KNH) in Nairobi, Kenya from May 2011 until January 2013. Eligibility criteria included current treatment with ART and CD4% ≥15. Written informed consent was obtained from study participants and/or their caretakers and the study was approved by the KNH/University of Nairobi (UON) Ethics Review Committee and the University of Washington Human Subjects Division.

At enrollment, a questionnaire was administered to caregivers to obtain social and demographic data. Each child was examined, and HIV diagnosis, treatment, and past medical history were obtained from medical charts. Caregivers were asked to present the child's immunization card documenting all prior vaccinations, or report immunization history verbally if the card was unavailable. Blood was obtained to determine measles IgG antibody titers, CD4%, and complete blood count. Measles vaccine, provided by the Kenya Ministry of Health, was administered to each child at the enrollment visit.

Laboratory Assays

Laboratory assays were performed in the UON Department of Paediatrics Laboratory. Qualitative detection and quantitative determination of measles IgG antibodies were performed using an enzyme-linked immunosorbent assay (ELISA) (Enzygnost, Germany), with internal quality controls performed for each run. Optical density (OD) values were interpreted as negative if <0.1, equivocal if 0.1 – 0.2, and positive if >0.2. Equivocal samples were re-run in duplicate to confirm the result. Positive OD results were converted into measles-specific IgG mIU/mL using manufacturer's calculations based on the First International World Health Organization (WHO) Reference Preparation Standards. Measles seropositivity was defined as an IgG titer ≥ 350 mIU/mL (3).

Statistical Analysis

The sample size for this study was based on CD4 percent as a correlate of antibody titer. For a 2-sided test with α=0.05, a sample size of 230 provided >80% power to observe a minimum 2.3-fold difference in positive antibody responses between children with a CD4 percent above and below 25%. Log-binomial regression was used to compare characteristics

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of children who were measles IgG seropositive compared to those who were not. Stata version 11.1 was used for all analyses (StatCorp, College Station, TX).

RESULTS

Of the 272 children screened, 232 were enrolled. The most common reason for not enrolling was CD4% < 15, accounting for 11 (28%) of 40 screened but not enrolled. Children not enrolled did not differ from enrolled children by age, caregiver monthly rent, or caretaker occupation (data not shown).

Of 232 enrolled children, 228 (98%) had received one measles vaccine before one year of age, per Kenya immunization guidelines for the general population which recommend a single routine vaccination at 9 months. Measles vaccination was confirmed by presentation of a vaccination card for 106 (46%) caretakers, or by verbal report. Two caretakers (1%) reported no measles vaccination, and two reported that they were unsure whether their child was vaccinated. Male participants constituted 123 (53%) of the cohort, median CD4% was 32 (interquartile range [IQR] 27 – 38), and median age was 7.5 years (IQR 5.5 – 9.5 years). Of the 216 (93%) of children with recorded date of ART initiation, median time on ART was 3.4 years (IQR 1.8 – 4.9 years). Only 10 (10%) of 103 children with a vaccination card and recorded date of ART initiation were on treatment before the date of measles vaccination (Table 1). The majority, 190 (82%), of primary caregivers at the enrollment visit were the childrens' mothers. Primary caretakers' median age was 33 (IQR 30 – 38 years), and median years of completed school was 11 years (IQR 8 – 12). More than half of caregivers, 149 (64%), were married. Of the 199 (86%) renting their home, median monthly rent was 41 USD (IQR 24 – 59). Caretakers reported a median of 2 rooms (IQR 1 – 3) and 4 people (IQR 4 – 5) per household (data not shown).

At enrollment, 106 (45.7%) of 232 children were measles IgG seropositive. Median titer among those who were seropositive was 793 mIU/mL (IQR 466 – 3,245).

Children with CD4% ≥ 25 were 2.11 times as likely to be measles seropositive than children with a lower CD4% (OR 2.11, 95% CI 1.04 – 2.70). Children who were on ART prior to measles vaccination were 1.44 times as likely to be measles seropositive (OR 1.44, 95% CI 0.88 – 2.37), though this association was not statistically significant. There was no statistically significant association between age, gender, or time on ART and measles seropositivity (Table 1). No difference in measles seropositivity was observed between those whose caretaker presented a vaccination card compared to those whose caretaker verbally reported vaccination history.

DISCUSSION

In this Nairobi-based study, fewer than half of HIV-infected children on ART had seropositive measles-specific IgG antibody titers, and a CD4% ≥ 25 was identified as a predictor for measles seropositivity. Although the power to detect an association was limited, children who initiated ART prior to vaccination may have been more likely to be seropositive. The duration of immunity following measles vaccination in healthy, non-HIV-infected children can persist for decades, especially in countries where measles remains

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

endemic and immune responses may be boosted by exposure to wild-type measles virus (4). For example, a recent study in The Gambia found that 96% of HIV-uninfected children 8–9 years of age who were vaccinated once at 9 months of age had a seropositive measles antibody response (5). However, similar results among HIV-uninfected children who received one measles vaccine dose have been reported in areas where measles is not endemic (6), suggesting re-exposure alone is not the sole determinant for persistent measles seroprotection.

The low level of measles seropositivity in this HIV-infected Kenyan cohort could be due to poor initial or unsustained immune response after primary measles vaccination. Our findings are comparable to two recent studies in HIV-infected children on treatment where 52% of HIV-infected American children and 42% of HIV-infected Thai children had were seropositive for measles antibody (7, 8). These numbers are remarkably similar to our Kenyan cohort despite differences in treatment adherence, nutrition, type of measles vaccine, prevalence of measles disease, and living conditions, all variables that could affect the measles seropositivity in these three cohorts of HIV-infected children on treatment.

We also observed children with a CD4% ≥ 25 were more likely to have seropositive measles antibody titers. Interestingly, a CD4% ≥ 25 was also a predictor for measles seropositivity in the treated HIV-infected American children cohort referenced above (7). However, this finding differs from what was found in a study of HIV-infected, treatment-naïve Kenyan children who had been previously vaccinated. In that study CD4% was not a predictor of measles seropositivity (2), and median levels of CD4% were 6.3% (IQR 3.0, 10.6), much lower than in our cohort of children on ART. It is possible that not only immune reconstitution, but the degree of reconstitution plays a role in the initial and sustained response to measles vaccination. A lower CD4% can be indicative of a low nadir CD4% or a poor response to ART, both of which could potentially inhibit measles antibody seropositivity. Thus, by initiating ART early, per WHO recommendation, better responses to measles vaccination may be promoted by limiting HIV progression and preventing children from reaching a low nadir CD4%.

Though our findings are similar to recent studies, our estimate of measles seropositivity may be conservative. The gold standard for measles antibody detection is a plaque reduction neutralization (PRN) technique; a PRN titer ≥ 200 is considered the minimum protective correlate of immunity (3), which is equivalent to 200 mIU/mL. ELISA results are closely associated with PRN, though they lack sensitivity to detect measles antibody at low levels (9). The smallest antibody concentration detected in our cohort among those with a positive OD was 353mIU/mL, which is a higher titer than what is considered minimally protective against clinical measles.

In summary, we observed a low prevalence of seropositive measles-specific IgG antibody titers despite previous measles vaccination in HIV-infected children on treatment. A number of measles outbreaks have occurred recently in Kenya where, in 2012, there were nearly 2500 confirmed cases of measles (10). Considering these outbreaks and the low prevalence of measles seropositivity, a new vaccination strategy is needed for this population. HIV-infected children with a CD4% below 25 were observed to have particularly low prevalence

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

of measles seropositivity, and may constitute a target group for re-immunization if resources are limited. Since all HIV-infected children on treatment may benefit by measles revaccination, the effectiveness and sustainability of vaccine response after re-immunization should also be explored.

Acknowledgments

Support Acknowledgement: Research reported in this publication was supported by the Institute of Allergy and Infectious Disease of the National Institutes of Health under award number K24AI087399. LPN and QT were scholars in the University of Washington International AIDS Research and Training Program (D43TW000007) supported by the NIH Fogarty International Center. LPN also received support from the UW Thomas Francis Jr. Global Health Fellowship. LBY was supported by Grant Number 5 R24 TW007988 from National Institutes of Health, Fogarty International Center through Vanderbilt University. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health, Fogarty International Center, and Vanderbilt University.

References

1. Nilsson A, Chiodi F. Measles outbreak in Africa--is there a link to the HIV-1 epidemic? PLoS pathogens. 2011; 7(2):e1001241. Epub 2011/02/25. [PubMed: 21347342]
2. 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. The Pediatric infectious disease journal. 2009; 28(4): 295–9. Epub 2009/03/05. [PubMed: 19258919]
3. Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reevaluation of protective titers. The Journal of infectious diseases. 1990; 162(5):1036–42. Epub 1990/11/01. [PubMed: 2230231]
4. WHO. Measles Vaccines: World Health Organization Position Paper. World Health Organization; 2009. p. 349-60.[cited 84]Available from: http://www.who.int/wer/2009/wer8435/en/index.html
5. Viviani S, Mendy M, Jack AD, et al. EPI vaccines-induced antibody prevalence in 8–9 year-olds in The Gambia. Tropical medicine & international health: TM & IH. 2004; 9(10):1044–9. Epub 2004/10/16. [PubMed: 15482396]
6. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. The Cochrane database of systematic reviews. 2012; 2:CD004407. Epub 2012/02/18. [PubMed: 22336803]
7. Abzug MJ, Qin M, Levin MJ, et al. Immunogenicity, immunologic memory, and safety following measles revaccination in HIV-infected children receiving highly active antiretroviral therapy. The Journal of infectious diseases. 2012; 206(4):512–22. Epub 2012/06/14. [PubMed: 22693229]
8. Aurpibul L, Puthanakit T, Siriaksorn S, Sirisanthana T, Sirisanthana V. Prevalence of protective antibody against measles in HIV-infected children with immune recovery after highly active antiretroviral therapy. HIV medicine. 2006; 7(7):467–70. Epub 2006/08/24. [PubMed: 16925733]
9. 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. Journal of clinical microbiology. 1995; 33(4):811–5. Epub 1995/04/01. [PubMed: 7790442]
10. WHO. Reported measles cases and incidence rates by WHO Member States 2013. 2013. [05Mar2013]; Available from: http://www.who.int/immunization_monitoring/diseases/measlesreportedcasesbycountry.pdf

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Predictors of a seropositive measles antibody titer among HIV-infected children on treatment.

	Total N[1]	Measles seropositive[2] n (%)	OR[3]	95% CI[4]	p-value
Age (years)					
<2	7	2 (29)	1.0	Ref.	
2 – 4.9	40	20 (50)	1.75	0.52 – 5.89	0.365
5+	185	84 (45)	1.59	0.49 – 5.18	0.442
CD4%					
< 25	44	13 (30)	1.0	Ref.	
≥ 25	188	93 (49)	2.11	1.04 – 2.70	**0.035**
Time on ART (years)					
<1	26	10 (38)	1.0	Ref.	
1 – 4.9	142	67 (47)	1.22	0.73 – 2.06	0.438
5+	48	25 (52)	1.35	0.78 – 2.36	0.289
Sex					
Female	109	52 (48)	1.0	Ref.	
Male	123	54 (44)	0.92	0.70 – 1.22	0.561
On ART before date of measles vaccination					
No	93	38 (41)	1.0	Ref.	
Yes	10	6 (60)	1.44	0.88 – 2.37	0.149

[1] N indicates total number of children in the category for whom data are available

[2] Measles seropositive refers to number of children who had a measles IgG antibody titer ≥ 200 mIU/mL

[3] OR indicates odds ratio;

[4] CI confidence interval:

[5] ART antiretroviral therapy