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HIV RNA Suppression Among HIV-Infected Ugandan Children With Measles

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To the Editor

In the course of HIV disease, coincident infections by several agents have been associated with transient increases in plasma HIV RNA levels,¹ but only a few, such as scrub typhus (*Orientia tsutsugamushi*),² have been associated with transient decreases. Low plasma HIV RNA levels during measles virus infection were first noted by Moss et al³ in a cross-sectional study of hospitalized Zambian children. When a recent measles outbreak occurred among HIV-infected children participating in a longitudinal observational cohort, we evaluated HIV RNA levels before, during, and after the measles episode. Because measles virus can elicit an immune response without manifesting the classic clinical syndrome,⁴ we also sought to determine whether such “subclinical” measles infection caused changes in plasma HIV RNA levels in this cohort. Finally, we evaluated HIV RNA levels among children without measles who received live-attenuated measles vaccine.

From October 2005 through September 2006, 300 HIV-infected children aged 1 to 10 years were enrolled into the Children with HIV and Malaria Project (CHAMP) from a dedicated pediatric HIV clinic at Mulago Hospital, Kampala, Uganda.⁵ The guardians of all children provided informed consent. The research was approved by the Uganda National Council of Science and Technology, the Makerere University Research and Ethics Committee, and the University of California, San Francisco Committee on Human Research and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Children with clinical measles were identified from the study clinic from June through December 2006. The World Health Organization (WHO) criteria of fever $\geq 38.0^{\circ}\text{C}$ and maculopapular rash with cough, coryza, and/or conjunctivitis were used as our case definition of measles.⁶ To identify cases of subclinical measles infection, dried blood spots (DBSs) that had been routinely collected from a convenience sample of 94 participants were screened for measles immunoglobulin M (IgM). To determine if vaccination affected HIV RNA level, the children who had routine laboratory tests coincidentally obtained in the 14-day period following measles vaccination (Sanofi Pasteur, Lyon, France) were retrospectively identified.

Plasma HIV RNA (Roche Amplicor Version 1.5 [level of detection of 400 copies/mL] Pleasanton, CA), absolute CD4 cell count, CD4 percent (CD4%), and total lymphocyte count were determined routinely at 12-week intervals and additionally obtained at the time

of clinical presentation. DBSs were tested for measles antibodies using Measles Enzygnost ELISA IgM Kits (Dade Behring, Marburg, Germany); the kit protocols were modified for use with DBSs, as per Riddell et al,^{7,8} yielding qualitative results of negative, equivocal, and positive for the presence of antibodies.

For all statistical analyses, the log transformation of plasma HIV RNA ($\log_{10}$ [copies/mL]) was used. To determine the acute change in plasma viral load, the HIV RNA level during measles was subtracted from the HIV RNA level obtained at the most recent preceding visit; these acute changes in HIV RNA level were then tested against the null hypothesis of no change, using the non-parametric Wilcoxon signed rank test. To determine if this acute change with measles differed from normal variation in HIV RNA level, a list of the changes in HIV RNA level between sequential visits on which participants reported no illness was generated from all available CHAMP data, randomly selecting 1 value per participant. The median changes with measles were then compared with the median changes between these routine visits, using the nonparametric Wilcoxon 2-sample test. To determine if the HIV RNA set point changed as a result of measles illness, the most recent HIV RNA level from before measles illness was subtracted from the first level available after the resolution of illness.

Among the 300 children in the CHAMP cohort, 14 developed clinical measles in the period from June to December 2006. Participants who had measles were similar to other study participants in median age (6.8 vs. 5.7 years), CD4 count (631 vs. 762 cells/ μ L), and CD4% (23% vs. 23%). The date of presentation and diagnosis ranged from 1 to 7 days after the onset of fever. Every HIV-infected child with detectable HIV RNA experienced a decrease in HIV RNA level during measles illness (Table 1). Among the antiretroviral therapy (ART)-naïve children, the median decrease was 1.4 $\log_{10}$ copies/mL (interquartile range [IQR]: 1.2 to 1.6; $P = 0.008$). A total of 114 sequential routine visits without concurrent illness were identified to measure normal variation in HIV RNA level; the median change of $-0.05 \log_{10}$ copies/mL was significantly different ($P < 0.0001$) from the changes during acute measles. Of the 6 children receiving ART, 3 had decreases in HIV RNA level during measles but they also had recent ART initiation; the remaining 3 children had undetectable HIV RNA before, during, and after clinical measles.

After resolution of measles, HIV RNA returned to preillness levels in all ART-naïve cases. At least 3 HIV RNA levels were available after illness for each participant; in all cases, at least 1 laboratory value was from more than 172 days after diagnosis. The earliest follow-up HIV RNA level was obtained in case 2: 9 days after measles diagnosis, 15 days after the onset of fever, and 8 days after its resolution. There was no significant difference between the first HIV RNA level available from after and the most recent level from before measles illness ($P > 0.38$). Total lymphocyte counts declined significantly by a median of 1.6×10^3 cells/mL (IQR: 1.9 to 0.5; $P = 0.009$). The absolute CD4 count likewise declined significantly by a median of 247 cells/mL (IQR: 371 to 42; $P = 0.013$); however, CD4% remained stable, with a median change of 0% (IQR: -1 to 1; $P = 0.67$).

Every child in the cohort who did not develop clinical measles received measles vaccination; in 11 cases, laboratory studies were routinely collected in the 14 days after vaccination. No significant change in HIV RNA level was observed (median of $-0.13 \log_{10}$ [copies/mL], IQR: -0.26 to 0.14). For 2 children, this was their first vaccination; for 7, it was their second; and for 2, it was their third; no differences were noted between those subgroups. Among the 94 children who were screened for subclinical infection, no IgM-positive samples were identified.

Although measles infection was associated with low plasma HIV RNA level in a prior report,³ this is the first study to document a decline in HIV RNA level prospectively in individual children during clinical measles. This enabled us to demonstrate universal suppression of plasma HIV RNA in a small group of children and to quantify the dramatic change, with a median decrease of 1.4 log₁₀ (copies/mL) among the ART-naïve children. The decreases in HIV RNA level were transient and without effect on the HIV RNA set point. Similar changes were not observed after measles vaccination.

The underlying mechanism by which measles infection affects plasma HIV RNA is unknown. Measles virus is known to cause multiple immunomodulatory changes in infected hosts, including a profound lymphopenia affecting circulating T-cell populations⁹ that could result in a loss of host cells for HIV replication. Studies using HIV-infected peripheral blood mononuclear cell (PBMC) cultures have shown that measles virus lowers p24 antigen production independent of cell death, however.¹⁰ Our study provides clinical correlation for this finding; a profound drop in HIV RNA level was seen despite a rise in total lymphocyte count in 3 cases, and a rise in absolute CD4 count was seen in 1 case. Thus, although a loss of host cells may contribute, it seems to not be the sole mechanism for the decline in HIV RNA level.

It is interesting that vaccination with live-attenuated measles was not associated with decreases in HIV RNA level in our study. The attenuated Edmonston B strain of measles, used for vaccination in the 1960s and 1970s, is able to generate significant HIV suppressive effects in PBMCs and ex vivo lymphoid tissue.^{10,11} It may be that the same HIV suppressive factors follow vaccination and wild-type infection but that their magnitude is simply too low after vaccination to affect HIV replication. Modern measles vaccines use more attenuated strains of measles that produce fewer side effects, do not elevate interferon (IFN)- γ levels, and have been shown to generate lower titers of anti-measles IgM and IgG than wild-type infection.¹² It would have been interesting to evaluate changes in HIV RNA levels after subclinical infection by wild-type virus, but we did not identify any cases.

Despite dramatic suppression of HIV replication by measles virus in vivo and in laboratory assays, the precise mechanism remains unclear. Further investigation of this powerful interaction between measles virus, the host immune response, and HIV may yield insight into the control of HIV replication and directions for new means of ART.

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TABLE 1

Plasma Viral Load and CD4 Cell Count Before, During, and After Measles Illness

Patient No.	Plasma HIV RNA Load (log ₁₀ [Copies/mL])			CD4 Count (Cells/μL)			CD4%		TLC (× 10 ³ Cells/μL)		
	Before	During	After	Δ	Before	During	After	Before	During	After	After
ART-naïve											
1	5.9	3.9	3.5*	-2.0	173	85	309	5	4	7	4.9
2	5.6	3.7	5.9	-1.9	411	369	437	34	23	33	1.4
3	5.1	3.7	5.5	-1.4	835	935	631	35	34	30	2.1
4	5.0	3.5	5.7	-1.5	n/a	527	591	n/a	16	27	2.5
5	4.7	3.4	4.5	-1.3	1295	749	1513	32	33	28	4.8
6	4.6	3.6	4.7	-1.0	633	262	565	27	28	26	2.1
7	4.5	3.1	4.7	-1.4	622	353	467	21	21	20	2.5
8	4.0	3.6	4.1	-0.5	568	408	445	24	21	29	1.7
Receiving ART											
9	5.3	3.7 [†]	2.8	-1.7	621	753	1010	11	21	27	2.8
10	4.6	2.8 [‡]	2.6	-1.8	646	300	814	10	11	31	3.4
11	3.0	2.8 [§]	n/a	-0.3	1634	334	n/a	20	19	n/a	n/a
12	und	und	und	-	628	111	548	27	16	33	1.8
13	und	und	und	-	347	100	347	8	7	17	2.1
14	und	und	und	-	900	874	1435	31	32	35	4.0

* Began ART after measles diagnosis and 2 weeks before the follow-up measles laboratory tests.

[†] Began ART 7 days before measles diagnosis.

[‡] Began ART 1 year before measles diagnosis with variable plasma HIV RNA level since then.

[§] Began ART 3.5 months before measles diagnosis; died as a result of measles illness.

Before indicates 9 to 73 days before measles diagnosis; During, day of measles diagnosis; After, 9 to 76 days after measles diagnosis; Δ, During – Before. n/a indicates not available; TLC, total lymphocyte count; und, undetectable (<400 copies/mL).