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SUPPRESSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 VIRAL LOAD DURING ACUTE MEASLES

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Abstract

Acute measles virus infection can result in a transient decrease in plasma human immunodeficiency virus type 1 (HIV-1) RNA loads. We report the kinetics of plasma HIV-1 RNA loads in 2 Zambian children with confirmed and probable measles, and show that the decline in viral load is of similar magnitude to the first-phase decay rate after initiation of antiretroviral therapy.

Acute measles virus (MV) infection can result in a transient but profound decrease in plasma human immunodeficiency virus type 1 (HIV-1) RNA loads. Despite immune activation, plasma HIV-1 RNA loads were markedly reduced in Zambian children hospitalized with measles, returning to expected levels approximately 1 month after hospital discharge.[1] These observations were limited, however, by the fact that plasma HIV-1 RNA loads before hospitalization were not available. We report the kinetics of plasma HIV-1 RNA loads in 2 Zambian children with measles and show that the decline in viral load is of similar magnitude to the first phase decay rate observed after initiation of highly active antiretroviral therapy.

MATERIALS AND METHODS

The children participated in an observational study of the immunogenicity of measles vaccine among HIV-1-infected and uninfected Zambian children.[2] Children attending a public clinic for routine diphtheria-pertussis-tetanus and polio vaccinations from May 2000 to November 2002, who had not been vaccinated against measles and who resided in Chawama Township, Lusaka, Zambia, were invited to participate. At the time of the study, antiretroviral therapy was not available for treatment of HIV-1-infected children in Zambia outside the private sector. HIV testing was conducted anonymously and caretakers were offered the opportunity to take their child for voluntary counseling and testing at the clinic. Caregivers from whom written informed consent was obtained were interviewed using a standard questionnaire and were

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asked to return when the children were approximately 9 months of age for measles vaccination with standard-titer Edmonston-Zagreb measles vaccine strain (genotype A, Berna Biotec, formerly Swiss Serum and Vaccine Institute, Berne, Switzerland; lot 015.163.01) Vaccine potency was 1995 median tissue culture infective doses ($TCID_{50}$).[2] Children were asked to return for follow-up at 1 or 3 months after measles vaccination, and at 2 and 3 years of age.

At each study visit, blood was obtained by venipuncture and placed in ethylenediaminetetraacetic acid tubes. Blood samples were tested for antibodies to HIV by rapid immunoassay (Determine HIV-1/2, Abbott Laboratories, Abbott Park, IL). HIV-1 infection was determined in each HIV-seropositive child by detection of HIV-1 RNA by reverse transcription-polymerase chain reaction (RT-PCR; Amplicor HIV-1 Monitor v. 1.5, Roche Molecular Systems, Branchburg, NJ).

MV-specific immunoglobulin M (IgM) antibodies were detected by enzyme immunoassay (Wampole Laboratories, Cranbury, NJ) in plasma from children with suspected measles. To distinguish infection with wild-type and vaccine MV strains, we sought to detect MV RNA by RT-PCR in nasopharyngeal swab specimens obtained from children with suspected measles. RNA was extracted using TRIzol Reagent (Invitrogen, Carlsbad, CA) and resuspended in RNase-free water. Extracted RNA was amplified by RT-PCR, using Superscript One-Step RT-PCR for long templates with platinum Taq DNA polymerase (Invitrogen). MV-specific primers were directed to the C-terminus of the nucleocapsid (N) gene. Thermocycling was performed on a GeneAmp PCR system 2700 (Applied Biosystems, Foster City, CA). Amplicons of the expected size (631 base pairs) were visualized by 1% agarose gel electrophoresis. Final products were purified using a QIAquick PCR Purification kit (Qiagen, Valencia, CA) and sequenced directly using an ABI BigDye Terminator Cycle Sequence Ready Reaction kit (v 3.1) and the ABI 3730xl DNA analyzer (Applied Biosystems).

CASE REPORTS

A 5-month-old girl attending the clinic for routine childhood vaccination was enrolled. Her plasma HIV-1 viral load was 1,020,000 copies/mL. She returned to the clinic at age 10.5 months and was vaccinated against measles, at which time her plasma HIV-1 viral load was 86,856 copies/mL and her percentage of $CD4^+$ T-lymphocytes was 25.3%. Eight days later, she was hospitalized with fever, conjunctivitis, coryza, cough, and a morbilliform rash of 4 days duration. IgM antibodies to MV were detected in plasma and wild-type MV RNA (genotype D2) was detected by RT-PCR from a nasopharyngeal swab specimen. On the fourth day of hospitalization, her plasma HIV-1 viral load was undetectable (<400 copies/mL), representing a 2.3 $\log_{10}$ decrease at a rate of −0.19 $\log_{10}$ plasma HIV-1 RNA copies/mL/d. She was treated with vitamin A and discharged home after 10 days. She returned for follow-up at 2 and 3 years of age, at which time her plasma HIV-1 viral load was 1,171,741 and 605,767 copies/mL, respectively.

A 9-month-old girl was vaccinated against measles, at which time her plasma HIV-1 viral load was 18,400 copies/mL ($CD4^+$ T-lymphocyte percentage was not available). Six days later, she was hospitalized with fever, conjunctivitis, coryza, cough, and a morbilliform rash of 3 days duration. IgM antibodies to MV were detected in plasma. MV RNA was not detected in a nasopharyngeal swab specimen by RT-PCR. Her plasma HIV-1 viral load at the time of hospitalization was 1040 copies/mL, representing a 1.3 $\log_{10}$ decrease at a rate of −0.21 $\log_{10}$ plasma HIV-1 RNA copies/mL/d. She was treated with vitamin A and antibiotics but died of clinically diagnosed pneumonia on the fourth hospital day.

DISCUSSION

We describe a dramatic decline in plasma HIV-1 RNA loads from baseline after vaccination with standard-titer measles vaccine and during acute MV infection. Our previous description of the suppression of HIV-1 replication during acute measles was in hospitalized children for whom baseline plasma HIV-1 RNA loads were not available.[1] A mean 1.4 $\log_{10}$ decline in plasma HIV-1 viral load was observed in 8 HIV-infected Ugandan children with acute measles, similar to the decrease we observed, but no decline was observed after measles vaccination of 11 children.[3]

Infection with wild-type MV was confirmed in 1 child through genetic characterization of MV RNA obtained from a nasopharyngeal swab specimen. In the second child, we cannot exclude the possibility that her illness, starting 3 days after vaccination, was a result of infection with measles vaccine virus, although adverse reactions typically occur 6-12 days after vaccination. These children developed suspected measles before the reduction in MV transmission in Zambia after the supplementary immunization activity in June 2003, at a time when the annual incidence of measles in Zambia was estimated to be approximately 8 in 1000 children younger than 5 years of age.[4] During the month of November 2000 (when the second child was hospitalized with suspected measles), 81 children were admitted to the University Teaching Hospital (the main public referral hospital in Lusaka, Zambia) with suspected measles, and 80% of 45 of these hospitalized children had detectable IgM antibodies to MV (unpublished observations).

The effect of measles vaccination on plasma HIV-1 RNA loads is not known, and part of the decline in HIV-1 RNA loads could result from replication of measles vaccine virus. We did not observe changes in HIV-1 RNA loads 1 month after measles vaccination (unpublished observations), although this interval is likely too long to observe an effect.

Both children were vaccinated against measles less than 1 week before the onset of symptoms, within the typical 10-14 day incubation period for wild-type MV infection. The plasma HIV-1 RNA level at the time of measles vaccination in the first child may have already been decreasing as a consequence of concurrent wild-type MV infection, with the actual drop attributed to MV infection greater than we were able to measure.

The rate of decline of plasma HIV-1 RNA was approximately −0.2 log copies/mL/d from the time of measles vaccination to hospitalization with measles. Although limited by a small number of study children and samples, this decay rate is similar in magnitude to the decline in plasma HIV-1 RNA loads after initiation of antiretroviral therapy, which follows a biphasic pattern.[5] Assuming that treatment completely suppresses new HIV-1 replication, the first phase decay represents the death of productively infected cells and the second-phase decay represents the death rate of long-lived or latently infected cells. First phase HIV-1 decay rates ranged from 0.26 to 2.02 $\log_{10}$ HIV RNA copies/mL/d, with a median decay rate of 1.03, in 1 study of 12 HIV-1 infected children in the United States.[6] In contrast, second-phase HIV-1 decay rates ranged from 0.02 to 0.15 $\log_{10}$ HIV RNA copies/mL/d, with a median decay rate of 0.06. In another study of 48 HIV-infected infants enrolled in a trial of ritonovir dosing schedules in the United States, first-phase decay ranged from 0.35 to 0.59 and second-phase decay rates ranged from 0.01 to 0.05 $\log_{10}$ copies/mL/d.[7] The similarities in decay rates among children initiating antiretroviral therapy and children with acute MV infection are consistent with the hypothesis that MV infection results in near complete suppression of the release of new HIV-1 virions from productively infected cells.

Multiple mechanisms could account for the suppression of HIV-1 replication by MV. In an ex vivo model using human lymphoid tissues, MV inhibited replication of both CXCR4-tropic and CCR5-tropic HIV-1, but the inhibitory effect was greater for CCR5-tropic HIV-1.[8] MV

upregulated RANTES in tissues coinfected with CCR5-tropic HIV-1, suggesting that increased levels of [beta]-chemokines may in part account for the suppression of CCR5-tropic HIV-1. In vitro, suppression of HIV-1 replication by MV was not associated with [beta]-chemokine production [9] but was associated with a block in the proliferation of $CD4^+$ T-lymphocytes, target cells for HIV-1 replication.[10] The decay rate in plasma HIV-1 RNA loads during acute measles is consistent with a block in target cell proliferation, transiently inhibiting HIV-1 replication.

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