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Infrequent Detection of HIV-1-Specific, But Not Cytomegalovirus-Specific, CD8+ T Cell Responses in Young HIV-1-Infected Infants

Zachary A. Scott,† Ellen G. Chadwick,‡ Laura L. Gibson,§ Michelle D. Catalina,¶ Margaret M. McManus,§ Ram Yoge,§ Paula Palumbo,§ John L. Sullivan,† Paula Britto,¶ Hannah Gay,§ Katherine Luzuriaga,§,† and PACTG 345 Investigators

Early potent combination antiretroviral therapies (ART) for HIV-1 infection can preserve or restore immune function, but control of viral replication early in infection may interfere with the development of HIV-1-specific immune responses. Using an IFN-γ ELISPOT assay, we evaluated the breadth and intensity of HIV-1-specific CD8+ T cell responses in 17 vertically infected infants who began ART at 1–23 mo of age. CMV-specific responses were also characterized in three infants coinfected with HIV-1 and CMV. Before ART, HIV-1-specific CD8+ T cell responses were detected in two of 13 (15%) infants <6 mo of age. HIV-1-specific CD8+ T cells became undetectable in these two infants after the control of viral replication. Intermittent HIV-1-specific responses were noted in six infants who did not experience durable control of viral replication. In contrast, HIV-1-specific responses were detected before ART in four of four infants >6 mo of age and became persistently undetectable in only one child. CMV-specific CD8+ T cell responses were persistently detected in all HIV-1 and CMV coinfected infants. In conclusion, HIV-1-specific CD8+ T cell responses were less commonly detected before therapy in young infants than in older infants. Suppression of viral replication appeared to interfere with the development and maintenance of HIV-1-specific CD8+ T cell responses. The detection of CMV-specific responses in HIV-1 and CMV coinfected infants suggests a selective defect in the generation or maintenance of HIV-1-specific CD8+ T cell responses. Therapeutic HIV-1 vaccine strategies in young infants may prolong the clinical benefit of ART by expanding the HIV-1-specific CD8+ T cell pool.
that boost the quantity and quality of HIV-1-specific CD8$^+$ T cells while still allowing for the continued clinical benefit of ART.

We serially evaluated HIV-1-specific CD8$^+$ T cell responses in 17 vertically infected infants who initiated ART between 1 and 23 mo of age. CMV-specific responses were also followed in three of these young infants coinfected with HIV-1 and CMV. Our data show that CD8$^+$ T cell responses are less commonly detected in young infants (<6 mo of age) than in older infants before treatment. Interestingly, CMV-specific responses were detected in several young infants, despite low-frequency or undetectable HIV-1-specific responses. These findings suggest a specific deficit in the generation of HIV-1-specific CD8$^+$ T cell responses in young HIV-1-infected infants. Novel vaccine strategies to boost HIV-1-specific cellular response during the course of ART may allow for better long-term control of HIV-1 in infected infants.

Materials and Methods

Study population

Seventeen infants with vertical HIV-1 infection were studied before and after combination ART. All but one infant were treated with zidovudine, lamivudine, and ritonavir and were participants in the Pediatric AIDS Clinical Trials Group Protocol 345, a clinical trial designed to evaluate the pharmacokinetics of ritonavir in young infants and the virologic and immunologic consequences of early therapy. Infant A13 received stavudine, lamivudine, nevirapine, and nelfinavir through the Pediatric AIDS Clinical Trials Group Protocol 356. Inclusion in the present study was based solely on PBMC sample availability. Clinical and immune status, viral loads, and response to therapy in our study population did not differ from the trial group as a whole.

Characteristics of the study population are presented in Table I. Age at study entry ranged from 1 to 23 mo. Subjects were divided between two groups based on age at therapy initiation: <6 mo of age (group A, n = 13; mean age, 2.9 mo) and >6 mo of age (group B, n = 4; mean age, 17.6 mo). PBMC samples from study wk 0 (baseline), 8 or 12, 24 or 28, and 48 were used in the analysis. Baseline CD4$^+$ T cell counts were <25% in only two infants. Six uninfected infants born to HIV-1-infected women, in the same age range as the 17 study infants, were used as control subjects (group C, mean age, 17.6 mo at baseline) and group B (>6 mo of age at baseline) are HIV-1-infected infants who underwent subsequent ART. Virologic responses to ART (R: virologic responder; IR: incomplete responder; NR: non-responder) are listed in column 3. Six uninfected infants, group C, were experimental negative controls. Group D consists of four older children with established HIV-1 infection. N/A, sample not available.

Table 1. Study population characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Baseline (months)</th>
<th>Virologic Responder Status</th>
<th>%CD4$^+$ T Cells at Baseline</th>
<th>Plasma Viral Load at Baseline</th>
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<td>5.0</td>
<td>R</td>
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<tr>
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<td>IR</td>
<td>35</td>
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<td>1.5</td>
<td>R</td>
<td>51</td>
<td>610,000</td>
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<td>36</td>
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</tbody>
</table>

Peripheral blood and cell lines

PBMCs were isolated from whole blood using the Ficoll-Paque (Amer- sham Pharmacia Biotech, Piscataway, NJ) density centrifugation method and were viably cryopreserved in RPMI 1640 containing 10% DMSO (13). For use in the ELISPOT assay, cells were thawed and washed twice in RPMI 1640 medium supplemented with 10% FCS, 25 mM HEPES, and 10 ng/ml gentamicin (R10 medium) before counting. Autologous B-LCLs were generated for each study participant by EBV/cyclospir A transfor- mation. B-LCLs were maintained in R10 medium. For each recombinant vaccinia vector used in the ELISPOT assays, 5 × 10$^5$–1 × 10$^6$ B-LCL cells were infected at a multiplicity of infection of 10 and allowed to incubate for 16–20 h (overnight) at 37°C in 5% CO$_2$. Before addition to the ELIS- POT plate, infected B-LCLs were washed twice in R10 medium and counted.

ELISPOT assay

A modified IFN-γ ELISPOT assay was developed based on a previously published method (14). Our assay used autologous B-LCLs as APCs to assay for HIV-1-specific release of IFN-γ by Ag-specific CD8$^+$ T cells. Before the addition of cells, a 96-well flat-bottom plate (MAIPN1450; Millipore, Bedford, MA) was coated with 1 mg/ml anti-IFN-γ mAb (D1K; Mabtech, Nacka, Sweden) and allowed to sit overnight at 4°C. After washing the plate with cold PBS, each plate was blocked for nonspecific Ab binding by addition of 200 μl/well R10 medium for 2 h at 37°C. Fifty thousand PBMCs from each time point were added, in duplicate, for each HIV-1 recombinant vector tested. Ten thousand vaccinia recombinant-infected B-LCLs were added to appropriate wells to bring the total volume in each well to 100 μl. This constituted an E:T ratio (PBMC:B-LCL) of 5:1. To ensure biologic consistency, all study time points (per study subject) and vaccinia recombinant targets were assayed on the same ELISPOT plate. Each plate was incubated for 16–20 h overnight at 37°C in 5% CO$_2$. After overnight incubation, the plate was washed with cold PBS, and 0.5
CD8+ T cell depletion

Cryopreserved baseline PMBC samples on patients A10 and B2 were depleted of CD8+ T cells using magnetic bead separation according to the manufacturer’s specifications (Dynal Biotech, Oslo, Norway). FACS analysis (using anti-CD4 and anti-CD8 Abs) was used to confirm that the small lymphocyte population consisted of <4% CD8+ T cells after depletion (FACScan; BD Biosciences, Mountain View, CA). CD8+ T cell-depleted and -nondepleted PBMC aliquots were then used in the ELISPOT assay as previously outlined.

Results

Autologous B-LCLs can be used as APCs in an ELISPOT assay

Previous studies using limiting dilution assays or nonspecific in vitro stimulation have shown that cytotoxic T cell responses are uncommonly detected in the PBMCs of young vertically infected infants (9,15). The IFN-γ ELISPOT assay has been widely used to detect functional Ag-specific CD8+ T cell responses after minimal in vitro stimulation in several viral systems. To increase the chances of detecting HIV-1-specific responses in the present study using the ELISPOT assay, a panel of four recombinant vaccinia vectors carrying HIV-1 gag, pol, env, and nef were used. This strategy avoids limiting the breadth of detected responses to previously defined class I HLA-restricted HIV-1 epitopes.

After evaluation of this assay system using adult PBMCs (data not shown), PBMCs from four HIV-1-infected children (group D) were tested (Fig. 1A). IFN-γ ELISPOT responses were detected in all four children against HIV-1 gag (range, 240-1480 SFCs/106 PBMCs; mean, 750 SFCs/106 PBMCs). The env-specific responses (range, 230–770 SFCs/106 PBMCs; mean, 580 SFCs/106 PBMCs) were also detected at similar levels in three of three children studied. Although the response to vaccinia alone was 180 SFCs/106 PBMCs in one child (D2), all other background responses were low (60 SFCs/106 PBMCs or less, representing less than three SFCs per well at 5 × 103 PBMCs per well).

HIV-1 specificity of T cell responses

To confirm that IFN-γ ELISPOT responses detected against these HIV-1 recombinants were HIV-1 specific, six uninfected infants (group C) ranging in age from 2 to 24 mo were also studied. Responses to HIV-1 gene products were not detected in any of the uninfected infants (Fig. 1B).

HIV-1-specific T cell responses before ART

Before the initiation of ART, IFN-γ responses to HIV-1 gene products were detected in only two infants (15%) <6 mo of age (Fig. 2). Infant A5 generated a low-level response to nef (80 SFCs/106 PBMCs). Infant A10 generated responses to both the env and nef gene products (720 and 700 SFCs/106 PBMCs, respectively). Conversely, IFN-γ responses to at least a single HIV-1 gene product were detected at baseline in all four infants (100%) >6 mo of age (group B). Three of four older infants generated responses against single HIV-1 gene products (pol, 2; nef, 1), whereas responses to gag (920 SFC/106 PBMC), pol (100 SFC/106 PBMC), and env (100 SFC/106 PBMC) were detected in one infant (B2). Interestingly, infant B2 presented with the lowest baseline plasma viral load of the 17 study participants (1700 copies per milliliter of plasma). The difference in the detection of HIV-1-specific IFN-γ responses between the two age groups was highly significant (p < 0.005) by Fisher’s exact test. Overall baseline IFN-γ ELISPOT responses were directed against only one HIV-1 gene product in four of six infants (67%); infants A5, B1, B3, and B4) who generated detectable responses before therapy initiation. The hierarchy
FIGURE 2. HIV-1-specific IFN-γ ELISPOT responses in young infants before and during ART. IFN-γ ELISPOT responses are shown for all study infants against wild-type vaccinia virus (NYCBH) (A), HIV-1 gag (B), HIV-1 pol (C), HIV-1 env (D), and HIV-1 nef (E). Virologic responder status is indicated as outlined in Table I. Asterisks indicate significant responses as defined in Materials and Methods. Blank spaces indicate experiments not performed.
of responses among all infants was as follows: nef/pol (n = 3) > env (n = 2) > gag (n = 1). Background responses were low in all infants and ranged from 0 to 60 SFCs/10^6 PBMCs (mean, 9 SFCs/10^6 PBMCs).

**HIV-1-specific T cell responses after the initiation of ART**

To investigate the ability of vertically infected infants to generate and maintain responses during combination ART, the 17 infants were followed longitudinally through 48 wk. In both young infants (A5 and A10) with detectable IFN-γ ELISPOT responses before therapy, HIV-1-specific responses became undetectable after control of viral replication. It should be noted that both infants were classified as virologic responders and had undetectable plasma viral loads by 8 wk after therapy initiation.

Intermittent low-level IFN-γ ELISPOT responses were detected in six group A infants over the course of ART. Infants A2, A6, A7, A8, A9, and A13 generated responses against gag, pol, and nef, with a mean of 130 SFCs/10^6 PMBCs (range, 60–240 SFCs/10^6 PBMCs). Only one of these infants was classified as a virologic responder (A13) and four of six had detectable plasma viral RNA at the time of the positive IFN-γ ELISPOT response.

IFN-γ ELISPOT responses were again detected at subsequent time points in all four of the older infants (group B) after therapy. In three of four infants (B1, B2, and B3), these responses were directed at the same HIV-1 gene products as detected at baseline. Two of these three infants (B1 and B3) broadened the IFN-γ ELISPOT response to include a second HIV-1 gene product (in both cases, env). The gag-specific ELISPOT responses were detected through wk 8 in infant B2; however, pol and env responses were not maintained. The pol responses were not detected after therapy in infant B4; however, an intermittent response to gag was detected at wk 24 of therapy. In three of four infants, ELISPOT responses were detected after the initiation of ART, even after the control of viral replication (B1).

**CD8^+ T cells mediate detectable HIV-1-specific IFN-γ responses**

As described above, vigorous IFN-γ responses were detected in the baseline PBMC samples of patients A10 (env and nef) and B2 (gag). CD8^+ T cell depletions were performed to determine which T cell population mediated these responses. Baseline PBMC samples from both infants were divided into two fractions, one of which was depleted of CD8^+ T cells by magnetic separation. FACS analysis confirmed that CD8^+ T cells represented <4% of the total small lymphocyte pool after depletion. The ELISPOT assay was used to enumerate IFN-γ responses in both the CD8^+ and CD8^- PBMC fractions for both patients. Positive responses, against env and nef by infant A10 and against gag by infant B2, again were detected only in the CD8^+ fractions (data not shown). IFN-γ responses were not detected in the CD8^- fraction of either infant.

**Detection of CMV-specific CD8^+ T cell responses despite low or absent HIV-1-specific responses**

Three young infants (A9, A12, and A13) coinfected with HIV-1 and CMV were evaluated to determine whether CMV-specific CD8^+ T cell responses were generated before and during the course of ART (Fig. 3). Recombinant vaccinia viruses encoding the CMV late gene products pp65 and gB were used with autologous B-LCLs in an ELISPOT assay. CMV pp65-specific responses were detected in two infants, A9 and A13, before and during ART (Fig. 3B; range, 100–240 SFCs/10^6 PBMCs). Baseline CMV responses in infant A12 were not tested; however, at wk 8 and 48 on therapy, pp65-specific (Fig. 3B; 200 and 340 SFCs/10^6 PBMCs).
PBMCs, respectively) and gB-specific (Fig. 3C; 80 and 60 SFCs/10^6 PBMCs, respectively) responses were detected. Responses to either CMV gene product were not detected in the PBMCs of two CMV seronegative infants (data not shown).

**Discussion**

Data from adult human (1, 16, 17) and simian (2, 3) studies have demonstrated the importance of the HIV-1-specific CD8^+ T cell response in controlling primary HIV-1 viremia. The expansion of HIV-1-specific CD8^+ T cell populations during the acute phase of infection is thought to contribute to the establishment of an equilibrium between viral replication and the host immune system (viral setpoint) that is predictive of subsequent disease progression. HIV-1-specific CD8^+ T cells also appear to play a critical role in the control of viral replication during the course of chronic infection (18).

Although much effort has been made to characterize the breadth, intensity, and timing of HIV-1-specific CD8^+ T cell responses in infected adults, the generation and maintenance of HIV-1-specific CD8^+ T cells in vertically infected infants are less well understood. A general paucity of PBMC samples and infrequent detection of Ag-specific CD8^+ T cells has made study of HIV-1-specific CD8^+ T cell responses difficult in young infants. Responses to reported immunodominant epitopes commonly recognized by adults with established infection (19) are rarely detected in young infants (data not shown). This may indicate differential recognition of HIV-1 epitopes over the course of infection (20) or that different HIV-1 peptide epitopes are preferentially recognized by young infants. A modified IFN-γ ELISPOT, using autologous B-LCLs as APCs, has facilitated the detection and enumeration of low-frequency CD8^+ T cell-restricted responses to several HIV-1 gene products. This approach is well suited for studying CD8^+ T cell responses in infants and children because it requires only small numbers of PBMCs to evaluate CD8^+ T cell-restricted responses to HIV-1 gag, pol, env, and nef. By maintaining a consistent E:T ratio between PBMCs and B-LCLs (as well as the infecting multiplicity of infection), Ag presentation is better standardized when compared with direct infection of PBMC cultures. Finally, low background responses by infants to vaccinia and the EBV-transformed B-LCLs make this assay particularly well suited to the study of pediatric samples.

In the present report, HIV-1-specific CD8^+ T cell responses were studied in 17 HIV-1 vertically infected infants before and during the course of ART. Our data demonstrate that HIV-1 CD8^+ T cell responses were less commonly detected in younger infants (<6 mo) than in older infants (>6 mo) before ART. After the initiation of ART, HIV-1-specific CD8^+ T cell responses were uncommonly detected in infants with persistent control of viral replication.

The difference in detectable HIV-1-specific CD8^+ T cell responses between infants of the two age groups before therapy was highly significant and may reflect age-related differences in the dynamics of activation and expansion of Ag-specific CD8^+ T cells in young infants. In this regard, it is interesting to note that the infrequent detection of HIV-1-specific CD8^+ T cell responses in young infants before ART contrasts with the frequent detection of HIV-1-specific CD8^+ T cell responses before therapy in adults with primary HIV-1 infection (4). HIV-1-specific CD8^+ T cell responses were lower in frequency and less broad in adults who initiated ART within 6 mo of infection compared with individuals who initiated ART >6 mo after infection, suggesting that a reduction in viral replication during primary infection decreases the frequency and breadth of HIV-1-specific CD8^+ T cell responses. However, HIV-1-specific CD8^+ T cell responses were persistently detected in the majority of adults at least 1 year after the initiation of potent combination ART.

Several unique characteristics of the neonatal cellular immune system and the dynamics of vertical HIV-1 infection may help to explain the infrequent detection of CD8^+ T cell responses to HIV-1. First, the cellular immune system in neonates and young infants may have different requirements for the activation and expansion of Ag-specific CD8^+ T cells. The Ag processing and presentation capability of infant APCs has been questioned, especially with regard to dendritic cell function (21). Inefficient presentation of HIV-1 Ags to naive CD8^+ T cells may hinder the generation of effector and memory CD8^+ T cell populations. Second, Selin et al. (22, 23) have demonstrated that sequential viral infections shape the memory T cell pool through the expansion or deletion of cross-reactive CD8^+ T cell populations. Limited exposure to heterologous viruses during the first months of life may impair the generation and expansion of CD8^+ T cell populations cross-reactive with HIV-1.

However, the detection of CMV-specific CD8^+ T cells in three young HIV-1/CMV coinfected infants suggests that young infants are capable of generating virus-specific CD8^+ T cell responses. CMV-specific responses were detected at all time points studied in three young coinfected infants, at frequencies similar to those detected in CMV seropositive, HIV-1-uninfected adults (data not shown). Initiation of ART did not appear to alter CMV-specific CD8^+ T cell frequencies over time. The detection of CMV-specific CD8^+ T cells in young HIV-1/CMV coinfected infants suggests that young infants are capable of generating virus-specific CD8^+ T cell responses and that the paucity of detectable HIV-1-specific CD8^+ T cell responses represents a selective defect in the generation or maintenance of HIV-1-specific CD8^+ T cells.

There are several potential explanations for the apparent selective defect in the generation or maintenance of HIV-1-specific CD8^+ T cells in these young infants. First, murine models suggest that the development of neonatal CD8^+ T cell responses is highly influenced by Ag load and the APC (24, 25). Therefore, differences in the kinetics and sites of HIV-1 and CMV replication may lead to differential generation or maintenance of cellular immune responses directed against these viruses in coinfected hosts. Second, the acquisition of HIV-1 infection in the presence of high titers of passively acquired maternal Abs may also affect the generation of HIV-1-specific CD8^+ T cell responses. Finally, the deletion of HIV-1-specific CD4^+ T cells by the cytopathic effects of HIV-1 may contribute to the low frequency of HIV-1-specific CD8^+ T cells. HIV-1-specific CD4^+ T cell responses appear to be important for the generation and maintenance of potent HIV-1-specific CD8^+ T cell responses (6, 26). Although 11 of 13 young infants in the present study had CD4^+ counts >25% at baseline, it is possible that a selective reduction in HIV-1-specific CD4^+ T cell frequency contributes to the lack of detectable HIV-1-specific CD8^+ T cell responses. We previously have shown that persistent HIV-1-specific CD4^+ responses were rarely detected in a similar cohort of HIV-1 vertically infected infants who received early combination ART (11). Further efforts to prospectively enumerate HIV-1- and CMV-specific CD4^+ T cell responses in young infants are underway.

In summary, HIV-1-specific CD8^+ T cell responses were less commonly detected in younger infants (<6 mo) than in older infants (>6 mo) before ART. After the initiation of ART, HIV-1-specific CD8^+ T cell responses were uncommonly detected in infants with persistent control of viral replication. The detection of
CD8^+ T cell responses in young HIV-1/CMV co-infected infants indicates that young infants are capable of generating and maintaining CD8^+ T cell response directed against a vertically acquired viral infection. Further efforts to clarify why young infants may not generate similar HIV-1-specific responses are underway. Therapeutic vaccine strategies to boost HIV-1-specific CD8^+ T cell responses may increase the durability and clinical benefit of ART in vertically infected infants.

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References


