Published in final edited form as:
Pediatr Infect Dis J. 2013 October ; 32(10): 1089–1095. doi:10.1097/INF.0b013e31829ee893.

Incidence of opportunistic illness before and after initiation of highly active antiretroviral therapy in children in LEGACY

Steven R. Nesheim, MD[1,2], **Felicia Hardnett, MS**[2], **John T. Wheeling, MPH**[3], **George K. Siberry, MD, MPH**[4], **Mary E. Paul, MD**[5], **Patricia Emmanuel, MD**[6], **Beverly Bohannon, MS, RN**[2], **Kenneth Dominguez, MD, MPH**[2], and **the LEGACY Consortium**[2]

[1]Emory University School of Medicine

[2]Epidemiology Branch, Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB, Centers for Disease Control and Prevention

[3]Northrop Grumman Inc

[4]Pediatric Adolescent Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health

[5]Baylor College of Medicine

[6]University of South Florida School of Medicine

Abstract

Background—Little is known about immune-reconstitution inflammatory syndrome (IRIS) in children in the United States.

Methods—LEGACY is a longitudinal cohort study of HIV-infected participants age 0-24 years at enrollment during 2005-2007 from 22 US clinics. For this analysis, we included participants with complete medical record abstraction from birth or time of HIV diagnosis through 2006. Opportunistic illness (OI) included AIDS-defining conditions and selected HIV-related diagnoses. We calculated the incidence (#/100 patient-years) of OI diagnosed in the six months pre- and post-initiation of the first HAART regimen with a virologic response. We defined OI as IRIS if an OI's incidence increased after HAART initiation. "Responders" were defined as experiencing ≥1 log decline in viral load within six months following HAART initiation.

Results—Among 575 patients with complete chart abstraction, 524 received HAART. Of these 524 patients, 343 were responders, 181 were non-responders, and 86 experienced OI. Responders accounted for 98/124 (79%) of OI. Pre-HAART and post-HAART OI incidences were 43.7 and 24.4 (P = 0.003), respectively, among responders, and 15.9 and 9.1 (P =0.2), respectively, among non-responders. Overall, OI incidences among responders and non-responders were 33.8 and 12.3, respectively (P = 0.002). Responders were more likely to experience herpes simplex, herpes zoster, and CMV, before HAART initiation (all, P<0.05).

Corresponding author: Steven Nesheim, M.D. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, Phone: 404-639-8273, FAX: 404-639-6127, sxn9@cdc.gov. Alternate Corresponding author: Kenneth Dominguez, M.D., M.P.H. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, Phone: 404-639-6129, FAX: 404-639-6127, kld0@cdc.gov.

Financial disclosure: No competing financial interests exist.

Disclaimer: The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conclusions—We detected few OIs and no IRIS among participants initiating HAART. The unexpectedly higher OI prevalence among responders, mostly occurring before HAART initiation, may have motivated higher adherence by responders and subsequent categorization as a responder.

Keywords

HIV infection; pediatric; immune reconstitution inflammatory syndrome (IRIS); opportunistic infection; highly active antiretroviral therapy

Background

Immune reconstitution inflammatory syndrome (IRIS), also known as immune reconstitution syndrome or immune reconstitution disease, is the emergence of a present but previously unapparent opportunistic illness sometimes termed “unmasking,” or the exacerbation of a previous opportunistic illness, often characterized as “paradoxical worsening”. Both unmasking and paradoxical worsening result from recovery of dysregulated immune function after the initiation of highly active antiretroviral therapy (HAART) for human immunodeficiency virus type 1 (HIV) infection. It can be difficult to distinguish whether the emergence of an opportunistic illness represents a new incident illness resulting from persistent immunodeficiency or a manifestation of IRIS related to an existing illness. Illnesses documented in the syndrome are most frequently mycobacterial infections (tuberculous or non-tuberculous), cryptococcosis, and viral infections with hepatitis B virus or herpes viruses (e.g., varicella-zoster virus, herpes simplex virus [HSV], cytomegalovirus). IRIS has also been associated with infections with JC virus (manifested as progressive multifocal leukoencephalopathy), *Pneumocystis jirovecii* (PCP manifested as pneumonia), *Histoplasma capsulatum*, and parvovirus B19. Autommune disorders have also been attributed to IRIS. Reported incidence of the syndrome has varied widely among HIV-infected adults (3–39%), with generally higher rates among HAART recipients with severe immunosuppression and a previously diagnosed opportunistic illness [1, 2].

There are a limited number of reports of IRIS in children, mostly from non-industrialized countries. Mycobacterial etiologies have predominated, including Bacille Calmette-Guerin (BCG) [3–8], focal *Mycobacterium avium* complex disease [9], disseminated non-tuberculous mycobacterial disease [10], and tuberculosis [11]. Cohorts from Thailand [12], Peru [13], Uganda [14], and South Africa [15] have reported IRIS incidence rates of 19–38% among children beginning HAART, with mycobacterial etiologies (BCG or tuberculosis) accounting for 29–44% of IRIS events in three cohorts [12–14] and 88% in South Africa [15]. In industrialized countries, there are case reports of HIV-infected children for whom IRIS manifested as BCG-IRIS [16, 17], sarcoidosis [18], progressive multifocal leukoencephalopathy [19], and delirium [20]; however few reports describe population or cohort level incidence of IRIS in children. There have been several reports of herpes zoster (zoster) as IRIS in adults and children [1, 2, 21, 22]. The only cohort study of IRIS among children from an industrialized country (USA) identified IRIS in 11.5% of 61 participants initiating HAART; all IRIS events were attributed to zoster [21]. It has been observed in a separate report from a cohort of 536 perinatally HIV-infected children with documented prior varicella that the incidence of zoster in the 90 days before and after the initiation of HAART were similar [22]. This observation brings into question the biological plausibility of zoster disease as an IRIS-related condition because it implies that zoster occurs in persons with suppressed immune systems, who have started HAART but have yet to reconstitute. Most adult and pediatric case series have defined IRIS as the unmasking or paradoxical worsening of selected Acquired Immunodeficiency Syndrome (AIDS)-defining or HIV-related illnesses (e.g., zoster) in the time period immediately after HAART initiation without considering the incidence of the illness prior to HAART initiation. The objective of this

study was to characterize the frequency and spectrum of pediatric IRIS in a United States (U.S.) setting, and compare the incidence of opportunistic illness before and after initiation of a HAART regimen in a cohort of HIV-infected US children and youth who had had a virologic response to HAART.

Methods

The Longitudinal Epidemiologic Study to Gain Insight into HIV/AIDS in Children and Youth (LEGACY) study is a Centers for Disease Control and Prevention (CDC)-funded, observational, prospective cohort study of HIV-infected children and adolescents enrolled between birth and 24 years of age from 22 HIV specialty clinics across the United States (U.S.). We used a 3-stage cluster probability-proportional-to-size sampling method to select a population of HIV-infected infants, children and adolescents receiving care in geographically diverse small, intermediate, and large-sized facilities. This study was approved by the Institutional Review Boards of CDC and each local study site. A consolidated 301 (d) Certificate of Confidentiality was obtained for LEGACY to provide an added level of strict privacy protection for participants. Between November 2005 and June 2007, at least 80% of eligible HIV-infected youth presenting for care at LEGACY clinic sites were offered enrollment. Participation was voluntary. Written informed assent and consent was obtained from minors and parents, as appropriate. The medical records of participants were reviewed and abstracted by trained data abstractors, from birth or from the date of diagnosis. Data collected included demographics (age, race, ethnicity, gender, educational level); mode of HIV infection (perinatal [includes breastfeeding], behavioral [includes heterosexual or homosexual activity, and injection drug use], and other [includes sexual abuse, blood transfusion]); clinical diagnoses; antiretroviral (ARV) and non-ARV medications; vaccines; laboratory test results, including CD4+ T-lymphocyte (CD4) cell counts, plasma HIV-RNA determinations, HIV genotype and phenotype drug resistance test results, chemistries, hepatitis testing, and urinalysis; reproductive history (age of menarche, sexual activity, contraceptive use, history of previous pregnancies and diagnosed sexually transmitted infections); psychosocial data (HIV disclosure status, substance abuse, sexual history, caregiver data); and mortality data. Data were obtained from review of medical records from birth or the time of the earliest record available to time of enrollment, on all HIV-clinic visits and hospitalizations. Of 2,039 LEGACY enrollees, complete data from birth through 2006 was abstracted for 575 study participants, known as the longitudinal cohort. Patient lists at each site were sorted in a random fashion and abstractors were asked to abstract patient charts for the longitudinal component of the LEGACY study in the order they appeared on their lists to avoid selection bias. Only data from the longitudinal cohort were used for the present analysis.

Highly active antiretroviral therapy (HAART) was defined as any regimen of at least three antiretroviral (ARV) drugs. Based on review of diagnoses that occurred after HAART initiation, opportunistic illnesses were our outcomes of interest and included any AIDS-defining condition (ADC) [23, 24] or other selected HIV-related diagnosis (SHRD). Specific ADCs and SHRDs used in this analysis are listed in Table 4. For purposes of characterizing the immunologic response to HAART, children were assigned a baseline and follow-up immunologic classification during the periods before HAART initiation (pre-HAART) and after HAART initiation (post-HAART), respectively, based on the CDC immunologic classification (Table 1) [23].

We defined the pre-HAART and post-HAART periods as the 6 months preceding and following, respectively, the initiation of or change in a HAART regimen. Virologic response was defined as a decline of ≥ 1 $\log_{10}$ in quantitative plasma HIV RNA (viral load, VL) from the pre-HAART baseline. Study participants who had virologic response were categorized

as “responders” and those without virologic response as “non-responders”. Among responders prescribed at least one HAART regimen that resulted in a virologic response, we determined the incidence of opportunistic illness in the pre-HAART and post-HAART periods for the first such regimen. Among non-responders, we determined the incidence of opportunistic illness in the six-month pre-HAART and post-HAART periods for the participants’ first-ever HAART regimen. We categorized potential IRIS events by the type of opportunistic illness, and defined a category as IRIS if the incidence of the respective opportunistic illness in the cohort during the post-HAART period exceeded the rate in the pre-HAART period. The pre-HAART baseline viral load and CD4 were defined as the last values determined prior to the start of the HAART regimen and did not have to be obtained on the same date. Participants’ nadir absolute CD4 cell count and percentage were the lowest values recorded in their medical record, irrespective of their relation in time to pre- and post-HAART period analyzed. The follow-up CD4 cell measurement was defined as the highest value measured during the post-HAART period. Determination of a change in CDC Immunologic Classification among responders and non-responders (Table 1) was based solely on change in absolute CD4 cell count or percentage; that is, only the immunologic component of the classification was used.

We computed the incidence of each opportunistic illness as well as the combined incidence of all reported opportunistic illnesses in the two periods of observation. We calculated pre-HAART person-time as the time window 180 days prior to and 14 days after HAART initiation, and post-HAART person-time as the time window 15 to 180 days after HAART initiation. We imposed the two-week delay to allow time for initial virologic and immunologic responses to HAART. Person-time for patients who initiated HAART at fewer than 180 days of life was left-censored at the date of birth. For patients with an opportunistic illness diagnosed during either the pre-HAART or post-HAART period, person-time was computed as the number of days from the start of observation until the first diagnosis of each opportunistic illness. Subsequent diagnoses of the same opportunistic illness in the respective time period of observation were not counted. Total person-time was calculated as the number of days from the start of observation until the diagnosis date of any opportunistic illness of interest or until they were censored.

We used Poisson regression analysis with a log link function to assess differences in the pre- and post-HAART incidence of each type of opportunistic illness in responders and non-responders. We used PROC GENMOD in SAS version 9.1.2 with the natural log of the person-years (PY) as the offset.

Results

Among the 575 study participants with complete medical record abstraction from birth through 2006, 524 were prescribed at least one HAART regimen, of whom 343 (65%) were responders and 181 (35%) were non-responders. Of the 524 study participants, 294 (56%) were female, 416 (79 %) acquired HIV infection through perinatal routes of transmission and 78 (15%) through behavioral mediated routes, 318 (61%) were black, non-Hispanic and 168 (32%) were Hispanic. The mean age was 9.2 years (range: 0.05 to 24.8 years). Selected baseline characteristics of responders and non-responders are described in Table 2. Compared with non-responders, responders were older (9.7 years vs. 8.0 years; P = 0.0001) and had higher median pre-HAART VLs (P <0.0001). The mean number of non-HAART regimens taken prior to the first HAART regimen for responders and non-responders were 1.3 and 1. 5 (P = 0.8), respectively; the corresponding median values were 0 and 1 (P = 0.96). At baseline, responders and non-responders did not differ by gender, mode of HIV transmission, race/ethnicity, CD4 cell percentage, absolute CD4 cell count, or CD4 cell

count nadir. For responders, the mean and median numbers of HAART regimens up to and including the responsive regimen were 2 and 1, respectively (data not shown).

Opportunistic illness occurred in 86 children, of whom 59 had one opportunistic illness, 17 had two, nine had three, and one had four diagnosed OI's (data not shown). Of the 124 opportunistic illnesses occurring in the study population, 98 (79%) occurred in responders and 26 (21%) in non-responders (Table 3). The pre-HAART and post-HAART incidences of opportunistic illness were 43.7/100 PY and 24.4/100 PY (P = 0.003), respectively, among responders, and 15.9/100 PY and 9.1/100 PY (P =0.2), respectively, among non-responders. Overall, opportunistic illness incidence among responders and non-responders were 33.8/100 PY and 12.3/100 PY, respectively (P = 0.002). In addition, the pre-HAART incidence rates among responders compared to non-responders were significantly higher for herpes simplex (8.5/100 PY vs. 0.0/100PY, respectively; P=0.002,) and zoster (7.1/100PY vs. 0.0/100PY, respectively; P=0.002). Because herpes simplex is often a clinical diagnosis which may lack specificity and constituted a high percentage of the opportunistic illnesses in our cohort, we recalculated the incidence of opportunistic illness among responders and non-responders after removing herpes simplex. Despite removing herpes simplex from our calculations, there remained a significant discrepancy in the incidence of opportunistic illness among responders and non-responders (28.0 vs. 11.9, respectively [p=0.02]). There also continued to be a decline in the pre-HAART to post-HAART incidence of opportunistic illness among responders. The pre-HAART and post-HAART overall incidences of opportunistic illness were 35.3/100 PY and 21.0/100 PY (P = 0.02), respectively, among responders, and 15.9/100 PY and 8.2/100 PY (P =0.12), respectively, among non-responders.

The absolute numbers and incidence of opportunistic illness among responders and non-responders are described in Table 4. Despite the predominance and higher rate of opportunistic illness among responders in general, no significant differences were detected in the pre- and post-HAART incidences of any opportunistic illness among either responders or non-responders, with the exception of the rate of PCP which declined (Table 4). A sensitivity analysis was performed, reassigning as "post-HAART" those OIs which occurred in the first 14 days after HAART initiation; neither the overall OI incidence, nor the incidence of any single OI, changed as a result of this change (data not shown). Thus, within the definition of this study, no disease qualified as IRIS and we were unable to analyze the immunologic or virologic changes accompanying IRIS. Instead, we compared immunologic and virologic changes between responders and non-responders (Table 5). Responders had a higher median increase in CD4 cell percentage (5.3 percentage points vs. 2.0 percentage points, P = 0.008), a more frequent improvement in CDC Immunologic Classification (30% vs. 5.5%, P <0.0001), a much larger absolute decline in VL (209,458 vs. 44,210 copies/mL, P <0.0001), and a larger decline in the $\log_{10}$ VL (2.3 vs. 0.2, P <0.0001).

Discussion

In this multi-site study of 524 North American children beginning HAART, the overall occurrence of opportunistic illness (Table 4) was low. The overall incidences of opportunistic illness in the pre- and post-HAART periods did not differ statistically for participants with or without a virologic response to HAART. However, there were differences in the pre- and post-HAART incidences of PCP. It is curious that responders had a higher opportunistic illness incidence than non-responders in both the pre-HAART and post-HAART periods and that a higher percentage of responders than non-responders had at least one opportunistic illness. This difference in incidence rates was not the result of differences in their immunological baseline. We observed no difference in the pre-HAART degree of immune suppression — by absolute CD4 cell count or CD4 cell percentage —

between responders and non-responders. As previously described, the difference in incidence of opportunistic infections remained despite removing herpes simplex from our calculations. Another possible explanation of the discrepancy in incidence of opportunistic illnesses between responder and non-responders is that children who had more frequent opportunistic illnesses were more motivated to adhere to their HAART regimen and thus were more likely to categorized in the “responder” category. We also found that during the pre-HAART period, responders compared to non-responders had higher incidence rates of herpes simplex and zoster. It is possible that the pain associated with these OIs encouraged a higher degree of adherence to HAART. However, there may have been other differences between responders and non-responders that this study did not identify and that also affected risk of having opportunistic illness.

This study’s design was based on the premise that an increase between pre- and post-HAART periods in the incidence of opportunistic illness would be attributable to immune reconstitution. To our knowledge, this study is the first to compare opportunistic illnesses between responders and non-responders before and after HAART initiation. We were unable to compare the virologic and immunologic parameters of study participants with and without IRIS. Instead, when comparing participants with and without a virologic response, responders were older and had a higher baseline VL but had comparable CD4 cell percentages and absolute CD4 cell counts. Responders may have been older than non-responders only because we calculated age among non-responders at time of initiation of first HAART regimen compared to first responsive HAART regimen among responders. The same can be said about the higher baseline VL among the responders. There was a significant increase in CD4 cell percentage and improvement in CDC immunologic category among responders, as might be expected.

Within this study’s design, no disease met criteria for a manifestation of IRIS. On the other hand, of the 98 opportunistic illness diagnoses in responders, there were 62 pre-HAART diagnoses and 36 post-HAART diagnoses (data not shown). An analysis based only on post-HAART diagnoses would have determined that these 36 diagnoses — or at least some subset of them — were IRIS. Examined in this way, IRIS occurred in 36 (10%) of 343 responders or 36 (6.9%) of all 524 children who began HAART. These rates are similar to the 11.5% reported by the other cohort study of IRIS in North American children [21]. In that 1996–2002 Florida cohort study, all case patients with opportunistic illness occurring after the initiation of HAART (all of which were zoster) were classified as IRIS. In our cohort study, although the incidences of zoster pre- and post-HAART did not differ statistically, there were seven cases of zoster among responders in the post-HAART period, constituting 7 (2 %) of 343 responders. In our study, the pre- and post-HAART rates of zoster among HAART responders were 7.1 and 4.8 per 100 person-years, respectively. These rates are slightly higher than the rate identified by Levin (1.4–3.1 per 100 person-years) during 2001–2006 in a study of US children with documented histories of prior varicella [22]. That study used 90-day observation periods before and after HAART initiation, but, as in the present study, found that zoster incidence rates were not significantly different in the two periods.

IRIS has been reported among HIV-infected children outside the United States. In Thailand [12], 19% of children beginning HAART for the first time developed IRIS based only on post-HAART incidence. The same group also reported that 29% of hospitalizations in the first six months after initiating HAART were a result of IRIS [25]. In Peru, the incidence of IRIS during the first year after HAART initiation was 19.8 per 100 person-years [13], and among children in a Ugandan study who had received HAART for up to six months, the overall cross-sectional prevalence of IRIS was 38% [14]. In all of these studies, IRIS cases

were defined as diagnoses occurring during a pre-defined period after the initiation of HAART without consideration of comparison to the pre-HAART period.

Overall, it appears that IRIS events were uncommon in the LEGACY cohort. There are several possible reasons for this finding, including low rates of tuberculosis in the U.S. and increasing varicella vaccine use among children in the general population and declining varicella rates among HIV-infected children in the U.S. since 1999. Also, the LEGACY study took place in 2004–2006, an era during which survivors who were eligible for enrollment were likely more immunocompetent and less likely to experience IRIS compared with those who had died prior to enrollment. It is possible that principal investigators may have been less likely to enroll children who were severely immune suppressed; however, we attempted to minimize such a bias by requiring a minimum of 80% of HIV-infected children in a study site: the mean enrollment for LEGACY was 83% of all HIV-infected patients receiving care at LEGACY sites at study initiation [26][28]. Furthermore, a high percent of LEGACY's HAART recipients (74% of responders, 69% of non-responders) were receiving antimicrobial prophylaxis for *Pneumocystis* pneumonia. Such prophylactic regimens are likely to also prevent toxoplasmosis.

In reports from countries other than the United States, mycobacterial disease — both tuberculosis and systemic infection with BCG — account for a high proportion of IRIS cases. In many of these countries, the greater prevalence of tuberculosis and the more widespread use of BCG vaccination for infants is in obvious contrast to the rarity of tuberculosis and BCG vaccination in the U.S. There were no cases of tuberculous or non-tuberculous mycobacterial disease in our study population, consistent with the other reported series of IRIS in HIV-infected American children [21] but in contrast to every study of IRIS among children from non-industrialized countries. Mycobacterial disease accounted for 44% of IRIS cases among children in Thailand and 33% of IRIS cases in children in Peru (including BCGosis) [13]. In Uganda, 29% of IRIS cases in children were attributable to tuberculosis [14]. Finally, a pediatric cohort in South Africa [15] reported a mycobacterial etiology (BCG or tuberculosis) in 30 (88%) of 34 IRIS cases.

Zoster accounted for 22% and 33% of pediatric IRIS cases in series from Peru [13] and Thailand [25], respectively, and all of the cases in Florida [21], in contrast to the number of cases of zoster observed in the present study. Interestingly, despite the high prevalence of dermatologic conditions in the Ugandan series [14], no cases of IRIS were attributed to zoster. The use of varicella vaccine to prevent varicella in mildly symptomatic HIV-infected children with CD4 cell percentages ≥25% was first recommended in 1999 [27]. The baseline mean and median CD4 cell percentages in LEGACY, 22.3% and 22.0%, respectively among responders, and 23.1% and 21.2% respectively among non-responders, indicate that substantial numbers of children in this cohort would have been eligible for varicella vaccine prior to the 2005 recommendation for its use in HIV-infected children with CD4 cell percentages ≥15% [28]. In fact, of the 524 children in this study, 60 (11.5%) had received varicella vaccine prior to the pre-HAART observation period. On the other hand, since follow-up of the LEGACY cohort went only through 2006, it is possible that vaccine practice minimally affected the acquisition of zoster in this population. The incidence of primary varicella declined nationwide in the years after the 1996 recommendation to use the vaccine [28], and among HIV-infected children there has been a decline between the "pre-vaccine era" and the "vaccine era" in the incidence of primary varicella (103.3 per 1,000 PY, and 36.8 per 1,000 PY, respectively), and of zoster (40.4 per 1,000 PY, and 0 among those vaccinated, respectively) [29].

The baseline CD4 cell percentages in LEGACY (see above) indicate a low risk for opportunistic illness in general, and for zoster in particular, in this population. On the other

hand, it is unlikely that the LEGACY selection strategy inadvertently sampled a population with exceptionally good immune status for the enrollment period 2005–2006, given the strategy by which sites were selected and the requirement that ≥80% of a site's population be approached for enrollment. The mean CD4 cell count and cell percentage among LEGACY participants were comparable to those described for the Pediatric HIV/AIDS Cohort Study (PHACS) [30]. However, LEGACY selected among children who were perinatally infected and who were alive in 2005. Perhaps these children were less likely to have experienced opportunistic illness compared with children who had died by 2005.

Strengths of this study include its large sample size from several geographic sites with varying prevalence of disease, lifetime antiretroviral medication histories, and few exclusion criteria. Due to the randomized approach for selecting patients at each site, the socio-demographic and clinical characteristics of patients in the longitudinal sub-cohort were similar to those of the overall cohort (data not shown). Limitations of this study include the retrospective nature of the LEGACY study and increased likelihood that sicker children experiencing opportunistic illness earlier in the epidemic may not have survived to participate in LEGACY. We were unable to control for differences in recording of diagnoses by providers at various LEGACY sites. For example, providers who were especially concerned about the possibility of IRIS may have been more likely to seek and record IRIS-related diagnoses in the months preceding and following the initiation of HAART. We defined the pre-HAART period as extending 14 days after initiation of HAART in order to account for possible delay in the effect of treatment. It is unlikely that this slight inequality in the pre- and post-HAART observation periods significantly biased ascertainment of diagnoses in favor of the longer pre-HAART period. LEGACY enrolled living participants during 2005–2007. Thus, HIV-infected children with severe disease born during the years of peak perinatal transmission (i.e., 1991–1994) were likely underrepresented in this cohort because many may have already died.

In conclusion, IRIS appeared to be uncommon in the LEGACY cohort, when defined as opportunistic illness with greater incidence after HAART initiation compared with prior to HAART initiation. If only those diagnoses that occurred after initiating HAART were included, as is the case in most IRIS series, the rate we observed would have been similar to rates reported from the other series from an industrialized country, but still much lower than rates observed in non-industrialized settings. As an increasing proportion of HIV-infected infants begin ARV therapy at a very young age, which is, by implication, at an early point of immunosuppression, in settings where HAART is readily available, one might project that the rate of IRIS will remain low, and perhaps may further decline.

Acknowledgments

Funding: This project was funded through CDC Solicitation No. 2004-N-01211.

We thank investigators and abstractors at the LEGACY study sites: Edward Handelsman, Hermann Mendez, Jeffrey Birnbaum, Betsy Eastwood, Diana Mason, Ava Dennie, Gail Joseph (SUNY Downstate, Brooklyn NY*), Ninad Desai, Liberato Lao (Kings County Hospital Center, Brooklyn NY*) Andrew Wiznia, Joanna Dobroszycki, Tina Alford (Jacobi Medical Center, Bronx NY**), Lisa-Gaye Robinson, Tina Alford (Harlem Hospital, New York City NY**), Arry Dieudonne, Peggy Latortue (University of Medicine and Dentistry of New Jersey, Newark NJ*), Tamara Rakusan, Sarah McLeod, Deborah Rone (Children's National Medical Center, Washington DC**), Richard Rutstein, Ariane Adams, Rebecca Thomas, Olivia Prebus (The Children's Hospital of Philadelphia, Philadelphia PA**), Allison Agwu, Rosanna Setse, Jenny Chang (The Johns Hopkins Medical Institutes, Baltimore MD**), Sheryl Henderson, Vickie Grimes, Julianne Gaston (Emory University, Atlanta GA**), Clemente Diaz,

*Contributed patient data to: 2006 cohort only
**Contributed patient data to: All LEGACY cohorts

Francisca Cartagena (University of Puerto Rico, San Juan PR**), Delia Rivera, Dianne Demeritte (University of Miami, Miami FL**), Jose Carro, William Blouin, Vivian Hernandez-Trujillo, Marcelo Laufer, Dianne Demeritte (Miami Children's Hospital, Miami FL**), Ana Puga, Yanio Martinez (Children's Diagnostic and Treatment Center, Fort Lauderdale FL*), Janet Sullivan, AJ Sikes, (University of South Florida, Tampa FL*), Mobeen Rathore, Kristy Champion, Ellen Trainer (University of Florida, Jacksonville FL**), Samuel B. Foster, Amy Leonard (Baylor College of Medicine/Texas Children's Hospital, Houston TX**), Gloria Heresi, Gabriela del Bianco (University of Texas-Houston, Houston TX**), Theresa Barton, Janeen Graper (University of Texas-Southwestern/Children's Medical Center, Dallas TX**), Toni Frederick, Andrea Kovacs, Suad Kapetanovic, Michael Neely, LaShonda Spencer, Mariam Davtyan, Uhma Ganesan (University of Southern California, Los Angeles CA**), Marvin Belzer, Molly Flaherty (Children's Hospital of Los Angeles, Los Angeles CA*), Jane Bork, Mariam Davtyan (Loma Linda University Medical Center, Loma Linda CA*), Dean Blumberg, Lisa Ashley, Molly Flaherty (University of California – Davis, Sacramento CA**).

In addition, we thank Kathy Joyce, Julie Davidson, Sharon Swanigan, Patrick Tschumper, Amanda Fournier and Kathleen Paul at Westat Inc. (Rockville MD) for contractual support, site monitoring and data management support. We also thank Vicki Peters (New York City Department of Health and Mental Hygiene) who has served as a consultant to the LEGACY project.

We are also grateful to the patients and caregivers who consented to participate in LEGACY, as well as the administrative personnel at each study site, Westat and CDC. We thank Jenine Milum who provided data management assistance for this analysis.

We mourn the deaths of Dr. Jose Carro and Dr. Edward Handelsman, fellow LEGACY co-investigators, who dedicated their professional lives to HIV-prevention and improving the health and lives of HIV-infected children, adolescents, and their mothers.

The LEGACY project was funded by the Centers for Disease Control and Prevention, Atlanta GA, contract number 200-2004-09976

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Table 1

Immunologic categories based on age-specific CD4+ T-lymphocyte counts and percent of total lymphocytes [23], LEGACY, 1988–2006

Immunologic category	Age of child					
	<12 months		1–5 years		6–12 years	
	cells/μL	(%)	cells/μL	(%)	cells/μL	(%)
1: No evidence of suppression	≥1,500	(≥25)	≥1,000	(≥25)	≥500	(≥25)
2: Evidence of moderate suppression	750–1,499	(15–24)	500–999	(15–24)	200–499	(15–24)
3: Severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

From Table 2 in Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No.RR-12) [available at http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf]

Table 2

Baseline characteristics according to virologic response or non-response to HAART, LEGACY, 2005–2006

Characteristic	Responders n = 343		Non-responders n = 181		P value
Gender (%)					
Male	155	(67.4)	75	(32.6)	
Female	188	(63.95)	106	(36.1)	0.4
Age					
Years, mean (range)	9.7	(0.9–24.8)	8.0	(0.05–22.8)	<0.0001
Mode of transmission, n (%)					
Perinatal	266	63.9	150	36.1	0.3
Behavioral	55	(70.5)	23	(29.5)	
Other/unknown	22	(73.3)	8	(26.7)	
Race/ethnicity					
Black, non-Hispanic	216	(67.9)	102	32.1	0.08
Hispanic	99	(58.9)	69	(41.1)	
White non-Hispanic/other/unknown	28	(73.7)	10	(26.3)	
Non-HAART regimens prior to HAART, n (range)					
Mean	1.3	(0–8)	1.5	(0–11)	0.8
Median	0	(0–8)	1	(0–11)	0.96
Prophylaxis for PCP					
Percentage who received prophylaxis	74.3		69.1		0.2
Baseline CD4					
Percent, mean	22.3		23.1		0.7*
Percent, median	22.0		21.2		0.7†
Count (cells/mm^3), mean	699		771		0.5*
Count (cells/mm^3), median	456		516		0.3†
Nadir CD4 cells					
Percent, mean‡	19.3		20.3		0.5*
Percent, median‡	19		19		0.4†
Count (cells/mm^3), mean‡	601.2		564		0.6*

Characteristic	Responders n = 343	Non-responders n = 181	P value
Count (cells/mm^3), median‡	378	386	0.5†
Viral load			
Log_{10} mean (copies/ml)	4.8	4.0	<0.0001*
Log_{10} median (copies/ml)	4.9	4.1	<0.0001†

*Test of significance is based on t-distribution with a folded F-test for equality of variances.

†Test of significance is based on the Wilcoxon Rank Sum Test.

‡Nadir values available for 371 participants (324 responders, 47 non-responders)

Table 3

Number and incidence of opportunistic Illnesses in HIV-infected children pre- and post-HAART initiation, LEGACY, 2005 – 2006

	Responders n =343	Non-responders n = 181	Total n=524
Children by opportunistic illness status, n (%)			
Without opportunistic illness	274 (80)	164 (91)	438 (84)
With opportunistic illness	69 (20)	17 (9)	86 (16)
Number and incidence of opportunistic illnesses			
Total number of opportunistic illnesses	98	26	124
Pre-HAART opportunistic illness incidence per 100 PY	43.7	15.9	---
Post-HAART opportunistic illness incidence per 100 PY	24.4	9.1	---
Pvalue (pre- vs. post- HAART*)	0.003	0.2	---

Table 4

Number and incidence of opportunistic illnesses among responders and non-responders before and after HAART initiation, LEGACY, 2005–2006

Diagnoses	Responders n = 343				Non-Responders n = 181			
		Before HAART	After HAART			Before HAART	After HAART	
	Number	Rate*	Rate*	P-value	Number	Rate*	Rate*	P-value
AIDS-defining conditions								
Candidiasis	5	3.5	0.0	†	2	2.0	0.0	†
Cervical cancer	1	0.0	0.7	†	0	0.0	0.0	†
Cytomegalovirus	11	5.7	2.0	†	2	2.0	0.0	†
Encephalopathy (progressive)	0	0.0	0.0	†	1	0.0	0.9	†
Histoplasmosis	2	0.7	0.7	†	1	1.0	0.0	†
HSV (oral or genital)	17	8.5	3.4	0.07	1	0.0	0.9	†
LIP‡	4	2.1	0.7	0.3	2	2.0	0.0	†
PCP§	5	3.5	0.0	0.008	4	3.0	0.9	0.3
Selected HIV-related diagnoses								
Bell palsy	0	0	0.0	*	1	0.0	0.9	0.2
ITP‖	9	3.5	2.7	0.7	3	2.0	0.9	0.5
Molluscum contagiosum	8	2.1	3.4	0.1	2	2.0	0.0	
Warts(perianal/genital)	10	4.3	2.7	0.5	4	2.0	1.8	0.09
Warts(non-perianal/non-genital)	9	2.9	3.4	0.8	2	0.0	1.8	0.1
Zoster	17	7.1	4.8	0.3	1	0.0	0.9	0.2
Total	98				26			

*Incidence per 100 person-years

†Data were insufficient to produce stable results

‡Lymphocytic interstitial pneumonitis

§Pneumocystis jirovecii Pneumonia

‖Immune thrombocytopenic purpura

Table 5

Immunologic and virologic changes in participants according to response to HAART. LEGACY, 2005–2006

Indicator	Responders n = 343	Non-responders n = 181	P-value
CD4 %, mean absolute change *	3.1	5.7	0.61
CD4 %, median absolute change	5.3	2.0	0.008
No. (%) children with change in CDC immunologic category †,	103 (30%)	10(5.5%)	<0.0001
Mean Δ absolute HIV-1 viral load, copies/mL ‡	209,458	44,210	<0.0001
Mean of Δ $\log_{10}$ HIV-1 viral load §	2.3	0.2	<0.0001

* Change is for the difference in the value of the indicator between baseline and the viral load value which defines response (or the last viral load in the six month period following HAART initiation, in the case of non-responders)

† Change in CDC immunologic category from 3 to 2 or 1; 2 to 1) (See Table 4a below)[23]

‡ Mean of differences in absolute HIV-1 viral load before and after initiation of HAART regimen

§ Mean of differences in $\log_{10}$HIV-1 viral load before and after initiation of HAART regimen