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Incomplete Immune Reconstitution Despite Virologic Suppression in HIV-1 Infected Children and Adolescents

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Abstract

Objectives—Some perinatally infected children do not regain normal CD4 T cell counts despite suppression of HIV-1 plasma viremia by antiretroviral therapy (ART), The frequency, severity, and significance of these discordant treatment responses remain unclear.

Design—We examined the persistence of CD4 lymphocytopenia despite virologic suppression (VS) in 933 children (>5 years of age) in the US, Latin America, and the Caribbean.

Methods—CD4 T-cell trajectories were examined and Kaplan Meier methods used to estimate median time to CD4 T cell count ≥ 500 cells/μL.

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Results—After 1 year of VS, most (99%) children achieved a CD4 T cell count of ≥200 cells/μl, but CD4 T cell counts remained below 500 cells/μL after 1 and 2 years of VS in 14% and 8%. Median times to first CD4 T cell count ≥ 500 cells/μl were 1.29, 0.78, and 0.46 years for children with <200, 200–349, and 350–499 cells/μL at the start of VS. New AIDS-defining events occurred in 9 children, including 4 in the first 6 months of VS. Other infectious and HIV-related diagnoses occurred more frequently and across a wide range of CD4 counts.

Conclusions—ART improved CD4 counts in most children, but the time to CD4 count of ≥ 500 cells was highly dependent upon baseline immunological status. Some children did not reach a CD4 T cell count of 500 cells/μl despite 2 years of VS. AIDS defining events occurred in 1% of the population, including children in whom VS and improved CD4 T cell counts were achieved.

Keywords

immune reconstitution; pediatrics; HIV; antiretroviral therapy; opportunistic infections; AIDS

INTRODUCTION

In most HIV-infected infants, children, and adults, combination antiretroviral therapy (cART) results in suppression of plasma viral load and an increase in peripheral CD4 T lymphocyte cell counts [1–2]. In the United States (US) and Western Europe, the availability of cART has been associated with a marked reduction in HIV-related mortality attributable to perinatal HIV infection [3–5]. These successes are being recapitulated in resource limited settings [3, 6–9].

Unfortunately, a discordant treatment response is seen in some pediatric patients in whom immunologic reconstitution does not occur despite virologic suppression (VS)[10–18]. This immunological failure (IF) phenotype has not been rigidly defined, but in a child age 5 years of age or older at baseline, it may be defined as a failure to achieve or maintain a CD4 T cell count above the level associated with severe immune suppression (CD4 <200 cells/mm^3) [2].

A variety of explanations could account for this discordant IF-VS phenotype, including the antiretroviral agents being used, depletion of bone marrow precursor cells that must undergo thymic differentiation into T cells, presence of active co-infections, malnutrition, failure of HIV RNA assays to detect the genetic subtype of HIV-1 with which the child is infected, or laboratory error [2]. Previous reports suggest that IF despite VS is more common in children with a lower nadir CD4+ T cell count and older age, but conflicting data have been reported [6, 19]. In all of these reports, the number of children with the IF-VS phenotype appears to be small, and, consequently, the frequency and clinical significance of IF among children with prolonged VS has remained unclear. In one recent study of adults with persistently low CD4 T cell counts during virologically successful therapy [20], the incidence rate of new AIDS events was higher in the first six months after VS was achieved than in later periods of follow-up. After 2 years of successful suppression, no new AIDS-defining illnesses were seen, despite persistent severe CD4+ lymphocytopenia (<200 cells/μL^3). No comparable data are available to inform the management of children and adolescents whose CD4 T cells

remain abnormal despite successful suppression of HIV plasma viremia by antiretroviral therapy.

We examined the frequency and clinical significance of the IF-VS phenotype in perinatally HIV-infected patients to enhance our understanding of immune reconstitution in HIV-infected children and the risks of continuing a cART regimen that has failed to achieve substantial improvement in CD4 T cell counts. We hypothesized that children and adolescents with incomplete immune reconstitution in the setting of sustained virologic suppression are at greater risk of new HIV/AIDS related clinical events than individuals whose CD4 T cell counts improve or remain above levels indicative of immune suppression.

MATERIALS AND METHODS

Study Population

The source populations for this study were the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Protocol 219C (219C), and the NICHD International Site Development Initiative (NISDI) [3, 21–22]. These prospective cohort studies were designed to evaluate the impact of HIV-infection and antiretroviral therapy (ART) on HIV-infected children and adolescents with perinatal infection and enrolled over 3700 perinatally HIV-1 infected children and adolescents in the US, Latin America, and the Caribbean. The protocols were approved by human subjects review boards at each participating institution and written informed consent was obtained from each child's parent or legal guardian. The final study population for our analysis was restricted to perinatally HIV-1 infected children only and included those with a documented period of VS lasting at least 1 year in duration beginning at or after age 5 years with available CD4 T cell counts at: 1) the start of the ART that led to VS, 2) the start of VS, and 3) at 1 year into the period of VS. Periods of VS were restricted to those starting after age 5 years to discount the variability in CD4 T cell count prior to 5 years of age [23]. For children with multiple periods of VS meeting the above eligibility criteria, their first period of VS was chosen for analyses.

Study definitions

Periods of VS were defined as beginning with two consecutive HIV viral load measures <400 copies/ml of plasma and maintaining subsequent measurements below 400 copies/ml, but allowing for isolated (single) measurements of ≥400 copies/ml (i.e. intermittent viremia). The period of VS was said to have ended at either the final <400 reading that preceded two consecutive ≥400 readings or the final viral load <400 copies/mL during follow-up if virologic rebound did not occur. If the last measurement during follow-up was ≥400 copies/mL and was preceded by a qualifying suppression period, the suppression period was defined to have ended at the time of the preceding viral load measurement of <400 copies/mL. A cART regimen was defined as at least three antiretroviral drugs from at least two different drug classes. Diagnoses with onset during the first three years of VS were reviewed and classified as meeting the definition of an AIDS-defining condition based on the age-appropriate Centers for Disease Control and Prevention (CDC) classification system

(i.e. meeting the definition of a CDC class C event) [24–25]. Other clinical outcomes of interest during the first three years of VS included bacterial meningitis, sepsis, cardiomyopathy, cervical dysplasia, mucocutaneous herpes simplex virus (HSV) infections, herpes zoster, lymphoid interstitial pneumonia, nephropathy, nocardiosis, oropharyngeal candidiasis, pneumonia, and disseminated varicella.

Statistical Methods

CD4 T cell count trajectories during VS were examined by plotting mean CD4 T cell counts during the study period of VS by CD4 count at the start of VS and fitting piece-wise linear regression models to estimate the observed slopes. CD4 T cell counts at 6 months, 1 year, and 2 years after VS were also compared relative to counts at the start of VS. Kaplan-Meier survival curves were used to estimate the median time to achieve CD4 T cell counts ≥500 cells/μl, relative to CD4 T cell count categories at the beginning of VS. Kaplan-Meier survival curves were also used to estimate time to first sustained measures of CD4 <200, <350, and <500 cells/μl among those with CD4 ≥500 cells/μl at baseline to inform CD4 monitoring strategies. To evaluate the clinical significance of incomplete immune reconstitution during VS, incidence rates for first AIDS-defining event during the first three years of follow-up were calculated by CD4 T cell count at the time of the event and CD4 T cell count at baseline. Events were also plotted by time since VS and CD4 count at the time of the event. Similar analyses were conducted for the other clinical outcomes of interest. Sensitivity analyses excluding those with intermittent (single) viral loads ≥10,000 copies/ml were also conducted for the evaluation of incidence of all clinical events. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Study population

Records were available for 3,784 children with perinatal HIV enrolled in the AMP and 219C cohorts in the US and Puerto Rico and NISDI sites in Central and South America (Brazil, Mexico, Argentina, Puerto Rico, and Peru). Among these, CD4 T cell counts and plasma HIV viral load data needed for analysis were available for 933 children who experienced at least 1 year of VS at 5 years of age or more after starting a cART regimen (Supplemental Table 1). Most were seen at centers in the US (87%) (Table 1), with the majority of the AMP/219C cohort born prior to 1996 (83%). By contrast, the majority of the NISDI cohort (72%) was born after 1996. Prior to the initiation of a suppressive cART regimen, many had only been previously treated with a non-cART regimen (32% of children from the United States and Puerto Rico, 15% from NISDI sites). At the time of first suppressive cART, participants had a median age of 8.8 years. VS was achieved in most cases with cART that employed an HIV protease inhibitor plus nucleoside/nucleotide reverse transcriptase inhibitors (nRTIs) (52%), a non-nucleoside reverse transcriptase inhibitor plus nRTIs (12%), or both protease inhibitor and non-nucleoside reverse transcriptase inhibitor in combination with nRTIs (21%) (Table 1).

Immunological Changes in Response to cART

At the time of initiation of cART that resulted in VS, 92 children (10%) had CD4 T cell counts below 200 cells/μL, while 118 (13%) had 200 to 349 CD4 T cells/μL and 138 (15%) had 350 to 499 CD4 T cells/μL (Table 2). Early improvements in CD4 T cell counts were commonly seen, and by the time VS was achieved, the number of children with CD4 T cell counts under 500/μL had decreased from 348 to 206 (37% to 22% of the total cohort) and only 29 (3%) children still had a CD4 T cell count of <200 cells/μL (Table 2). In children whose CD4 T cell counts were initially <500 /μL, a biphasic response was seen with CD4 T cell numbers rising more rapidly during the first six months after cART initiation than in subsequent months (Figure 1, panel A). The rate of initial rise was twice as great in children with baseline CD4 T cell counts <200 /μL than in children with 350 to 499 CD4 T cells (556 versus 258 cells/year). (Supplemental Table 2). The time until the first CD4 T cell count exceeded 500/μL was strongly and inversely related to the baseline CD4 values (Figure 1, Panel B): the median time to reach this value was 1.29, 0.78 and 0.46 years for children with CD4 T cells at baseline of <200, 200–<350, and 350 to 499 cells/μL, respectively. The proportion of children with CD4 T cell counts <500 cells/μL progressively declined during VS, but CD4 counts below this threshold were observed in 14% after one year and 8% at two years (Supplemental Table 3).

CD4 T cell counts were very stable among the 727 children (78% of the total study population) whose counts were 500 cells/μL or higher at the time that VS was confirmed: fewer than 10% experienced sustained periods in which CD4 T counts dropped below thresholds of either 350 or 200 cells/μL (Figure 2, Panel A). This was also true for the NISDI cohort when examined separately from children in the United States in Puerto Rico (Supplemental Figure 1).

These data indicate that durable increases in CD4 T cell counts occur in children with perinatal HIV infection, although maximal improvement in the T cell count may not occur for years after VS has occurred. However, prolonged CD4 lymphocytopenia is seen in some individuals even after prolonged virologic suppression. (Supplemental Table 3).

Clinical events occurring during virologic suppression

To assess the clinical impact of low CD4 T cell counts at the beginning of and during virologic suppression, we examined the incidence of new clinical events indicative of immune suppression. As outlined in Table 3, 9 children experienced one or more new CDC C events during the first three years following VS, including 4 in the first 6 months following VS and 5 at a time when CD4 T cell counts were 500 cells/μl or more. Incidence rates for the first CDC C event during this follow-up period did not statistically differ by person-time spent with CD4 T cell counts <500 cells/μL or by CD4 T cell counts at start of virologic suppression (data not shown).

We also examined reports of non-AIDS defining clinical events of interest. Ninety individuals experienced a CDC C event and/or a non-AIDS defining clinical event of interest throughout the first three years of virologic suppression; these events largely occurred at a time when CD4 counts were ≥ 500 cells/μl. (Figure 2, Panel B and

Supplemental Table 4). Similar to the CDC C events, incidence rates for these events did not statistically differ by person-time spent with CD4 T cell counts <500 cells/μL or by CD4 T cell counts at start of virologic suppression. We performed a similar analysis with data related to the CDC-C and the other clinical events combined, with similar findings: the incidence rates of these events were not influenced by these CD4 T cell parameters. Twenty-three subjects experienced recurrent events (CDC C and/or non-AIDS defining) during the first three years of follow-up; 14 of these individuals experienced one or more episodes of pneumonia after an earlier significant clinical event. (Supplemental Table 5).

DISCUSSION

In adults, discordant virologic and immunological responses to antiretroviral therapy have been associated with a higher risk of death from both AIDS-defining and non-AIDS-defining causes among those with persistently low CD4+ lymphocyte counts. [20, 26–28]. A failure of cART to increase CD4 T cell counts, despite suppression of HIV-1 plasma viremia, also occurs in infants, children and adolescents, but the frequency and clinical significance of this phenomenon have been unclear. In this multinational, large pediatric observational study, we found that a failure to achieve or maintain a CD4 T cell count above 200 cells/μL in the setting of VS appears to be rare: at 2 years into VS, only 4 children had CD4 counts recorded below this threshold. Subsequent sustained periods of severe CD4 lymphocytopenia (<200 cells/μL) also appeared to be very uncommon during prolonged follow-up, occurring in only 3 of 727 (0.4%) individuals with data extending to 15 years of follow up (Figure 2, Panel A). These data contrast with studies of adults, in whom failure to achieve full CD4+ T cell count reconstitution appears to be more common; this likely reflects residual thymic function generally seen in children and adolescents, including those with histories of AIDS defining conditions [27, 29].

However, immune reconstitution was protracted in some children. In agreement with smaller pediatric studies [15, 30–35], the time to achieve a maximal CD4 T cell count was highly dependent on the CD4 count at the beginning of the cART regimen that resulted in VS. We found this to be true when data from the smaller NISDI and the larger AMP/219c cohorts were examined separately, or when the data were examined together. Children with the lowest CD4 T cell counts showed the greatest relative and absolute initial improvements in CD4 T cell concentration, but took the longest to achieve a normal CD4 count threshold. These data are consistent with adult cohort studies [26–27]. Data from this study also suggest that clinicians should anticipate that the maximal improvement in CD4 T cell count may not occur for several years after VS has occurred.

The clinical significance of having low CD4 T cell counts during VS has been evaluated in a limited number of studies of adults. Zoufaly et al examined clinical outcomes of HIV-infected adults with discordant virologic and immunological responses to antiretroviral therapy [20]. New AIDS-defining events occurred most frequently during the initial 6 months of complete VS and decreased significantly thereafter. We attempted to replicate this analysis but found that AIDS defining illnesses were uncommon in the pediatric cohorts studied: only 9 study subjects experienced one or more new CDC C events during the first 2 years of VS. This likely reflects the fact that only 10% of subjects' studied had CD4 T cell

counts below 200 cells/μL at the beginning of cART. It may also reflect the fact that majority of children were receiving some form of antiretroviral therapy when the regimens resulting in VS were begun, as immunologic improvements may occur even if HIV viremia is not fully suppressed. However, we also noted a high frequency of serious, albeit non-AIDS defining, illnesses among children in this cohort (Supplemental Table 5). The occurrence of these events throughout the follow-up period was independent of CD4 T cell count and is indicative of ongoing immunologic deficits. Nonetheless, incidence rates for CDC C defining and non-AIDS defining clinical events did not statistically differ by person-time spent with CD4 T cell counts <500 cells/μL (compared to time above this threshold) or by CD4 T cell counts at start of virologic suppression, serving as a reminder that CD4 T cell counts are an imperfect indicator of immune function [36].

The strengths of this study include its multinational composition, prolonged data collection period, and study population that reflects the racial and ethnic diversity of communities most affected by pediatric HIV in the western hemisphere. However, this analysis has several limitations. First, it focused on children 5 years of age or more. In contrast to this older population, disease progression is more rapid among infants and younger children, in whom AIDS defining illnesses often occur at CD4 T cell counts that are well above normal range for adolescents and adults. In addition, the spacing of viral load measurements from some individual children may have been broad enough to miss periods of HIV viremia that had deleterious effects on immune reconstitution. We used <400 copies/ml as the threshold for defining VS, as most data in the cohorts studied were accumulated prior to widespread use of HIV-1 RNA monitoring with greater levels of sensitivity. It is possible that lower level viremia, or transient increases in HIV viral load, may have interfered with or disrupted immune reconstitution in some children. In an effort to determine if subjects with high transient increases in viral load might have significantly influenced our results, we performed an additional analysis restricted to subjects who did not experience a viral load at or above 10,000 copies/mL during the first three years of follow-up. Removing these 34 subjects from the original set of 933 did not alter our estimates of the rates of CDC C or other clinical events or the impact of baseline CD4 T cell counts on CD4 cell reconstitution (data not shown).

Although not the primary focus of this study, we also examined the stability of CD4 T cell counts in children who had counts of 500 cells/μL or more at the time that virologic suppression was confirmed. It was very uncommon for these children to have subsequent reductions in CD4 T cell counts to below 500 cells/μL, lending support to the recent suggestion that infrequent CD4 count monitoring may be reasonable during long periods of VS. [2]

Overall, the vast majority of children with perinatal HIV infection in this study who began a cART regimen associated with VS experienced significant improvements in CD4 T cell counts. This immunological improvement was not maximized in some individuals for several years. Additionally, a small, but significant proportion of children (8%) did not reach a CD4 T cell count of 500 cells/μl or more during VS during the periods of observation. The continued occurrence of clinically important diagnoses despite CD4 cell reconstitution in most subjects highlights the need for improved measures of immune function in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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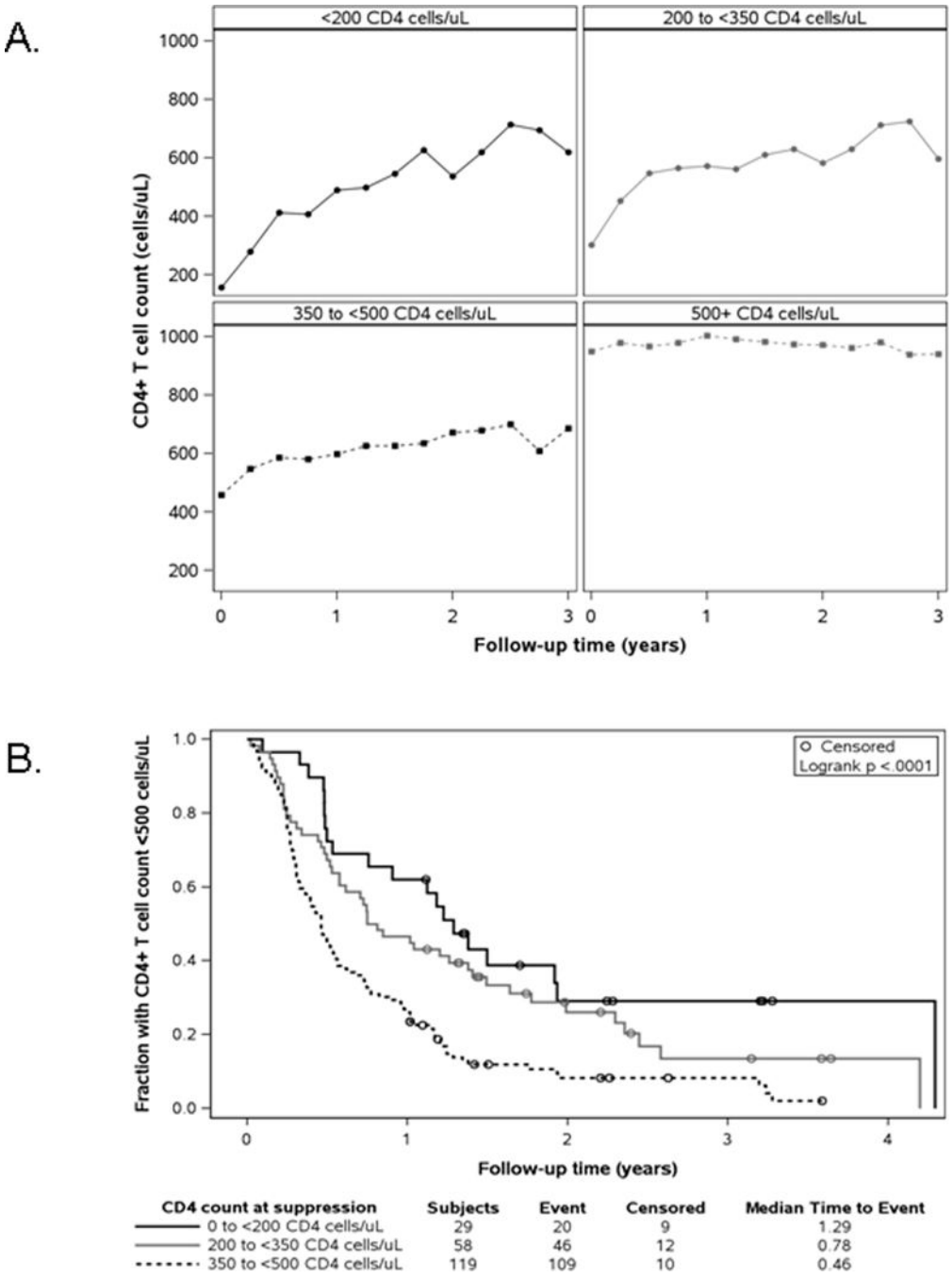

Figure 1.

Tempo of immune reconstitution during periods of virological suppression.

A. CD4 count (cells/μL) means over follow-up, by CD4 count at the start of the virologic suppression periods.

B. Kaplan-Meier survival curves for time to first CD4 count ≥500 cells/μL, by CD4 count at the start of the virologic suppression period.

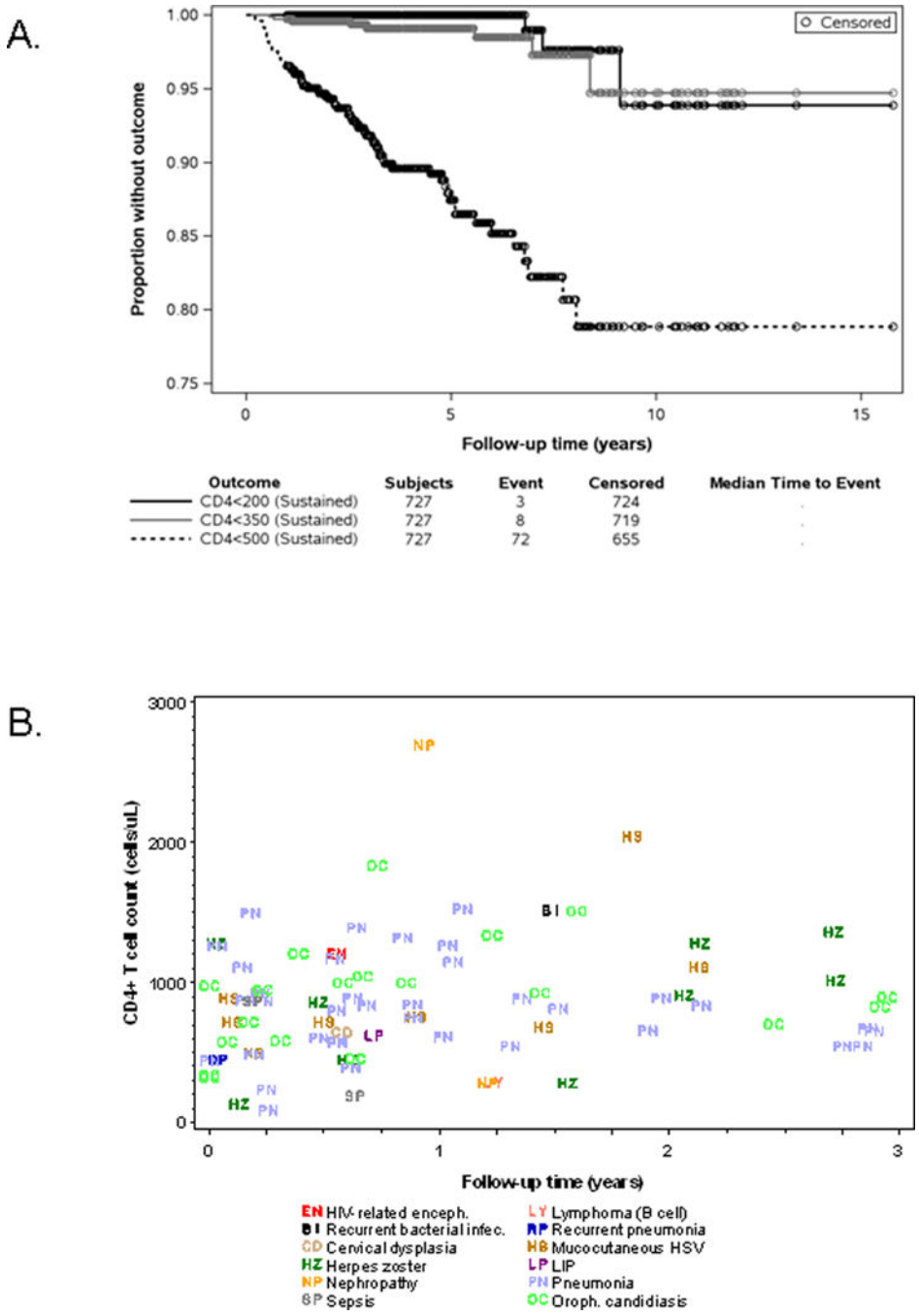

Figure 2.

Development of low CD4 counts and serious clinical events during virologic suppression.

A. Kaplan-Meier survival curves for time to first sustained low CD4 count outcome, among subjects with CD4 ≥ 500 at the start of the virologic suppression period.

B. New Clinical Events (CDC C and non-AIDS defining) during the first three years of study follow-up, by CD4 count at event. Only first clinical event for an individual is shown

Table 1

Characteristics of Study Population

Characteristics	Total (N=933)	Study cohort: AMP/219C* (N=825)	Study cohort: NISDI (N=108)
Female Gender	492 (53%)	436 (53%)	56 (52%)
Age (years) at start of ART resulting in VS**	8.8 (6.2, 11.6)	8.8 (6.2, 11.8)	8.5 (5.6, 10.6)
Birth cohort			
Born prior to 1996	718 (77%)	688 (83%)	30 (28%)
Country of origin			
Argentina	8 (1%)	0 (0%)	8 (7%)
Brazil	79 (8%)	0 (0%)	79 (73%)
Mexico	19 (2%)	0 (0%)	19 (18%)
Peru	2 (0%)	0 (0%)	2 (2%)
Puerto Rico	13 (1%)	13 (2%)	0 (0%)
US	812 (87%)	812 (98%)	0 (0%)
Race/ethnicity			
Black/Mulato (Non-Hispanic)	464 (50%)	458 (56%)	6 (6%)
Hispanic(Regardless of Race) & Native American	334 (36%)	246 (30%)	88 (81%)
White/Asian/Other (Non-Hispanic)	132 (14%)	118 (14%)	14 (13%)
Missing	3 (0%)	3 (0%)	0 (0%)
CDC C diagnosis prior to VS	300 (32%)	299 (36%)	1 (1%)
Ever on cART prior to suppressing regimen			
Yes	585 (63%)	508 (62%)	77 (71%)
No, previous non-cART	279 (30%)	263 (32%)	16 (15%)
No, no prior regimen	69 (7%)	54 (7%)	15 (14%)
Type of regimen immediately preceding suppressing regimen			
cART	411 (44%)	351 (43%)	60 (56%)
Non-cART regimen	310 (33%)	291 (35%)	19 (18%)
Off Antiretroviral therapy	143 (15%)	129 (16%)	14 (13%)
No prior regimen	69 (7%)	54 (7%)	15 (14%)
Type of regimen at start of VS†			
cART (PI + nRTIs)	483 (52%)	421 (51%)	62 (57%)
cART (PI + NNRTI ± nRTIs)	200 (21%)	195 (24%)	5 (5%)
cART (NNRTI + nRTIs)	115 (12%)	84 (10%)	31 (29%)
Other cART regimen#	36 (4%)	28 (3%)	5 (5%)
Non-cART regimen	95 (10%)	90 (11%)	5 (5%)
Antiretroviral therapy data incomplete/missing	4 (<1%)	4 (<1%)	0 (0%)
Highest known viral load (log_{10} copies/mL) at start of VS***	4.8 (4.0, 5.4)	4.7 (3.9, 5.4)	5.2 (4.7, 5.8)
Lowest known CD4 T cells at start of VS			
Absolute number***	368 (196, 583)	353 (187, 576)	458 (276, 664)

Characteristics	Total (N=933)	Study cohort AMP/219C* (N=825)	Study cohort NISDI (N=108)
CD4%	17 (11, 25)	17 (10,25)	19 (13,25)
Time from start of suppressing ART to VS			
Median	5.6 (2.3, 20.4)	6.4 (2.3, 22.5)	3.1 (1.8, 6.1)
<9 months	541 (58%)	453 (55%)	88 (81%)
≥9 to ≤15 months	84 (9%)	76 (9%)	8 (7%)
>15 months	308 (33%)	296 (36%)	12 (11%)

Data are presented as number (%) or median (IQR).

* Includes subjects enrolled in AMP (n=76), 219C (n =592) or both (n=157).

** VS = virologic suppression

*** p <0.001 for comparison between AMP/219C and NISDI cohorts

† PI = HIV protease inhibitor, NNRTI = non-nucleoside analogue reverse transcriptase inhibitor, nRTI = nucleoside/nucleotide reverse transcriptase inhibitor

cART with fusion inhibitor or integrase inhibitor (with or without PI or NNRTI).

Table 2

Frequencies of subjects by CD4 count at time of initiation of virologic suppressing cART and at start of suppression period

		CD4 count (cells/μL) at start of suppressing ART*			
CD4 count (cells/μL) at start of virologic suppression**	**Total (N=933)**	**<200 (N=92)**	**200 to 349 (N=118)**	**350 to 499 (N=138)**	**≥500 (N=585)**
<200	29 (3%)	24 (26%)	3 (3%)	1 (1%)	1 (0%)
200 to 349	58 (6%)	20 (22%)	23 (19%)	11 (8%)	4 (1%)
350 to 499	119 (13%)	19 (21%)	45 (38%)	30 (22%)	25 (4%)
≥500	727 (78%)	29 (32%)	47 (40%)	96 (70%)	555 (95%)

* CD4 reading nearest to start of suppressing ART (up to 6 months prior to ART start date allowed).

** Nearest CD4 reading to the start of virologic suppression (readings up to 3 months after start allowed).

Table 3

Details of the first CDC C classification event by subjects during the first three years of study follow-up

Days from start of period of virologic suppression	Age at Time of Event	CD4 T cell count at time of event	Event
0	6	152	Esophageal candidiasis
13	15	454	Recurrent pneumonia*
60	15	889	Mucocutaneous HSV (chronic)
168	11	182	Mucocutaneous HSV (chronic)
201	12	1209	HIV-related encephalopathy
405	14	1409	Recurrent pneumonia*
450	7	286	Lymphoma (B cell)
544	11	1516	Recurrent bacterial infections
624	11	2070	Recurrent pneumonia*

* Culture-confirmed bacterial pneumonia occurring within two years of a previous episode.