Incomplete Immune Reconstitution in HIV-1 Infected Children with Virological Suppression

Abstract # 913

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ABSTRACT

Background: Suppression of plasma viremia by antiretroviral therapy (ART) is generally associated with improvements in immunological status, but some individuals fail to achieve normalization of CD4 T cell counts. In adults, AIDS defining events rapidly decrease once virological suppression is achieved, even when CD4 T cell lymphocytopenia persists. Similar data are not available for children to determine the frequency of and risks associated with persistence of CD4 lymphocytopenia despite effective ART.

Methods: Data were pooled from 3,784 children enrolled in the 219C, NISDI and AMP cohorts, and 933 perinatally HIV-1 infected youth were identified with virologic suppression (VS) lasting at least 1 year at an age of >5 years, with available CD4 counts. For each child's first period of virologic suppression (VS) (plasma HIV RNA < 400 copies/ml), piecewise linear regression models were used to examine CD4 T cell trajectories during VS by CD4 at start of VS and Kaplan-Meier estimates for time to CD4≥500 cells/μL were generated for CD4 categories < 500 copies/μL.

Results: Of the 933 children in the study population, 50% were black, 36% Hispanic/Latino, and 14% white/Asian with a median age of 8.8 years at the start of ART that resulted in VS.

108 (12%) were from NISDI sites in Argentina, Brazil, Mexico, and Peru; 88% were from sites in the United States and Puerto Rico.

At the start of the regimen leading to VS, 92 (10%), 118 (13%), and 138 (15%) had CD4 T cell counts of <200, 200-350, and 350-499 cells/μL, respectively. Most (99%) children had a CD4 count of ≥200 cells/μL at 1 year into VS, but 14% failed to exceed 500 cells/μL at this time*. The rate of initial increase in CD4 T cells counts was inversely proportional to baseline CD4 T cell strata. The median time to first CD4 T cell counts > 500 was 15 months, 9 months, and 6 months for children <200, 200-350, and 350-499 cells/μL.
CDC C events occurred in 9 children after VS was achieved, including 1 report of encephalopathy*. Four CDC C events occurred in the first 6 months following VS; the others occurred between 6.6 and 20 months after VS was achieved.

Conclusions: Most children who maintain virological suppression improve their CD4 T cell counts. The time to achieving a CD4 count of > 500 T cells/μL is highly variable and depends upon CD4 counts at the start of VS. Although rare, AIDS defining events continued to occur in 1% of the population studied, despite VS and improved T cell counts. ** Corrected from initial submission of abstract.*

OBJECTIVES

1. Determine the frequency of failure to achieve immunologic reconstitution among children and adolescents who achieve virologic suppression (IF/VS).
2. Determine length of time until maximal immune reconstitution is observed in children and adolescents with durable suppression of HIV plasma viral load.
3. Evaluate the clinical significance of the IF/VS phenotype by comparing the rates of new clinical events among children with IF/VS and those with successful immune reconstitution.

METHODS

Study population

• The study population was derived from prospective cohorts of HIV-infected children enrolled from clinical sites in the U.S. and Puerto Rico (PHACS-AMP and IMPAACT P219C), and Latin America (NISDI: NICHD International Side Development Initiative).

• Periods of virologic suppression lasting at least 1 year were identified for all study participants and the first period of virologic suppression beginning on or after the age of 5 years was chosen for analysis.

Source Populations

Perinatally HIV+ (AMP, 219C, & NISDI):	N=3,784
AMP* and 219C**	N=2,752 (73% of 3,784)
NISDI	N=1,032 (27% of 3,784)
Period(s) of virologic suppression lasting ≥ 1 year	N=2,050 (54% of 3,784)
AMP and 219C	N=1,554 (76% of 2,050)
NISDI	N= 496 (24% of 2,050)
Virologic suppression after/on 5th birthday	N=1,490 (73% of 2,050)
AMP* and 219C**	N=1,247 (84% of 1,490)
NISDI	N= 243 (16% of 1,490)
CD4 data available†	N= 933 (63% of 1,490)
AMP* and 219C**	N= 825 (88% of 933)
NISDI	N= 108 (12% of 933)

* Restricted to subjects with baseline visit.
** Restricted to subjects characterized as definitely or probably perinatally infected.

† CD4 count (cells/μL) readings within preceding 6 months of initiation of suppressing ART, on or up to 3 months after the start of virologic suppression, and ±3 months of one year from the start of virologic suppression.

Definitions and statistical methods

Definitions

Virologic suppression: a consecutive series of viral load readings <400 copies/mL, allowing for interleaving readings of 400+ copies/mL after the first two <400 copies/mL readings.

Significant New Clinical Events: Onset of bacterial meningitis, sepsis, cardiomyopathy, cervical dysplasia, herpes simplex virus stomatitis, herpes zoster, lymphoid interstitial pneumonia, nephropathy, nocardiosis, pneumonia, and disseminated varicella.

Statistical Approaches

Objective 1: We evaluated how CD4 count changed at 6 months, 1 year, and 2 years into the period of virologic suppression with respect to the CD4 count at the start of suppression. We also evaluated mean CD4 counts during the first 3 years of virologic suppression relative to CD4 count at the start of virologic suppression.

Objective 2: We compared time to CD4 count ≥500 cells/ μL by CD4 count at start of suppression using Kaplan-Meier survival curves.

Objective 3: We identified significant new clinical events of interest during virologic suppression, including AIDS-defining conditions, and plotted them by CD4 count at the time of diagnosis and time of diagnosis relative to the start of suppression. Incidence rates of new clinical events were also calculated by CD4 count at time of diagnosis.

RESULTS

Table 1: Frequencies of subjects by CD4 count at initiation of ART resulting in virologic suppression and start of suppression period

CD4 count (cells/μL) at start of virologic suppression **	Total (N=933)	CD4 count (cells/μL) at start of suppressing ART* <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 back from ART start date allowed).
** Nearest CD4 reading to the start of virologic suppression (readings up to 3 months after start allowed).

Table 2: Characteristics of subjects by study cohort

Characteristics	Total (N=933)	AMP/219C (N=825)	NISDI (N=108)
Male	441 (47%)	389 (47%)	52 (48%)
Female	492 (53%)	436 (53%)	56 (52%)
Race/ethnicity			
White/Asian/Other (Non-Hispanic)	132 (14%)	118 (14%)	14 (13%)
Black/Mulato (Non-Hispanic)	464 (50%)	458 (56%)	6 (6%)
Hispanic or Native American	334 (36%)	246 (30%)	88 (81%)
Missing	3 (0%)	3 (0%)	0 (0%)
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%)
CD4 count at start of suppressing ART			
<200 CD4 cells/μL	92 (10%)	82 (10%)	10 (9%)
200 to <350 CD4 cells/μL	118 (13%)	101 (12%)	17 (16%)
350 to <500 CD4 cells/μL	138 (15%)	123 (15%)	15 (14%)
500+ CD4 cells/μL	585 (63%)	519 (63%)	66 (61%)
Nadir CD4 absolute count (cells/μL) Prior to start of suppression*	368 (196, 583)	353 (187, 576)	458 (276, 664)
Highest known HIV-1 viral load (log_{10} copies/mL) prior to start of suppression*	4.8 (4.0, 5.4)	4.7 (3.9, 5.4)	5.2 (4.7, 5.8)
Type of ART Regimen producing Virological Suppression			
cART using Protease Inhibitor+NRTI	483 (52%)	421 (51%)	62 (57%)
cART using NNRTI +NRTI	115 (12%)	84 (10%)	31 (29%)
cART using NNRTI and PI+ NRTI	200 (21%)	195 (24%)	5 (5%)
Other combinations	36 (4%)	31 (4%)	5 (5%)
Non-cART regimen	95 (10%)	90 (11%)	5 (5%)
ARV information incomplete/missing	4 (0%)	4 (0%)	0 (0%)

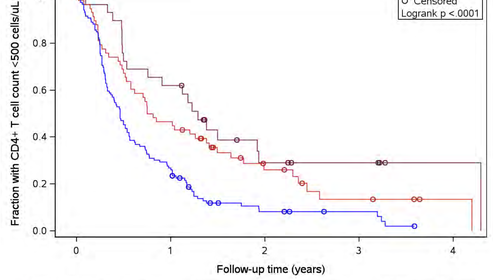
*Median (IQR)

Table 3: Characteristics by CD4 count at start of the virologic suppression (VS) period

Characteristics	Total (N=933)	CD4 count (cells/μL) at start of virologic suppression* <200 (N=29)	200 to 349 (N=58)	350 to 499 (N=119)	500+ (N=727)
CD4 count (cells/μL) 6 months into VS**					
<200	7 (1%)	4 (14%)	2 (3%)	0 (0%)	1 (0%)
200 to 349	22 (2%)	12 (41%)	6 (10%)	3 (3%)	1 (0%)
350 to 499	104 (11%)	4 (14%)	22 (38%)	44 (37%)	34 (5%)
500+	754 (81%)	7 (24%)	26 (45%)	64 (54%)	657 (90%)
Missing	46 (5%)	2 (7%)	2 (3%)	8 (7%)	34 (5%)
CD4 count (cells/μL) 1 year into VS**					
<200	7 (1%)	3 (10%)	2 (3%)	1 (1%)	1 (0%)
200 to 349	36 (4%)	9 (31%)	8 (14%)	12 (10%)	7 (1%)
350 to 499	89 (10%)	8 (28%)	22 (38%)	24 (20%)	35 (5%)
500+	801 (86%)	9 (31%)	26 (45%)	82 (69%)	684 (94%)
CD4 count (cells/μL) 2 years into VS**					
<200	4 (0%)	0 (0%)	1 (2%)	0 (0%)	3 (0%)
200 to 349	17 (2%)	6 (21%)	1 (2%)	5 (4%)	5 (1%)
350 to 499	53 (6%)	4 (14%)	13 (22%)	17 (14%)	19 (3%)
500+	577 (62%)	12 (41%)	26 (45%)	59 (50%)	480 (66%)
Missing	282 (30%)	7 (24%)	17 (29%)	38 (32%)	220 (30%)

* Nearest CD4 reading to the start of virologic suppression (readings up to 3 months after start allowed).
** Nearest CD4 reading to time point was used (readings up to ± 3 months were allowed).

Figure 1: Kaplan-Meier survival curves for time to first CD4 count ≥500 cells/μL by CD4 count at the start* of VS

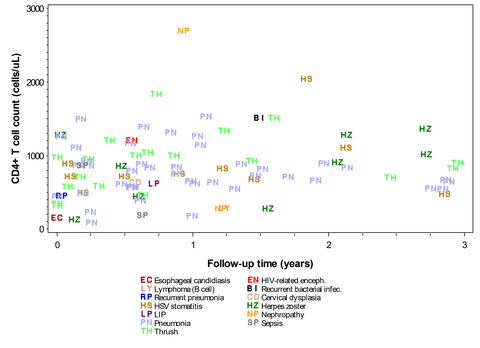


CD4 count at suppression	Subjects	Event	Censored	Median Time to Event
0 to <200 CD4 cells/uL	29	20	9	1.29
200 to <350 CD4 cells/uL	58	46	12	0.78
350 to <500 CD4 cells/uL	119	109	10	0.46

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

RESULTS

Figure 2: New CDC C and clinical events of interest during the first three years of study follow-up, by CD4 count at time of event



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CONCLUSIONS

1. Nearly all children who achieve virological suppression during combination ART will experience CD4 T cell count improvement.
2. CD4 T cell improvement is more rapid in those with most severe CD4 T cell lymphocytopenia prior to virologic suppression.
3. Time to achieving a "normal" CD4" T cell count is inversely correlated with the degree of initial lymphocytopenia
4. CDC-C and other clinical events are rare following prolonged virologic suppression but may occur despite CD4+ T cell count improvements.

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