Poster #900

Discontinuation of Antiretroviral Therapy among Children with Perinatally-Acquired HIV Infection

George Siberry[1], Kunjal Patel[2], Sandra Burchett[3], Melanie Bacon[4], Rohan Hazra[1], Jennifer Read[1], George Seage[2], Lynne Mofenson[1], Miriam Chernoff[2], Russell Van Dyke[5], for the Pediatric HIV/AIDS Cohort Study (PHACS)

NICHD-PAMA Branch, NIH, Bethesda, MD[1], Harvard Sch. of Pub. Health, Boston, MA[2], Children's Hosp., Boston, MA[3],NIAID-Epidemiology Branch, NIH, Bethesda, MD[4], and Tulane Univ. Health Sciences Center, New Orleans, LA[5]

Name: George Siberry
Mailing Address:
6100 Exec Blvd,
4B11H. Bethesda, MD
20852
Tel: 301.496.7350
Fax: 301.496.8678
Email: siberryg@mail.nih.gov

ORIGINAL ABSTRACT* #S115

Background: In the U.S., it is routine to treat all infants and children with perinatally-acquired HIV infection because of the high risk of rapid disease progression in this population and the inability to identify those destined to be non-progressors. Some older children who discontinue ART do not experience HIV disease progression, but there is no systematic approach to identifying such children for a trial off therapy. We assessed the frequency and characteristics of children who appeared to safely discontinue ART in the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS), a prospective cohort study designed to determine outcomes of children with perinatally-acquired HIV.

Methods: PHACS AMP enrolled 7-16 year old children with perinatally acquired HIV infection at 12 sites, beginning in March 2007. Within this study we identified children who were not receiving ART, had not received ART for ≥ 6 months, maintained CD4 ≥20% and >350 cells/mm3, and had not progressed to AIDS (CDC clinical stage C) over their lifetime. Demographics and clinical characteristics of these children, defined as non-progressors, were summarized.

Results: Of the 240 children with complete ART history enrolled in PHACS AMP as of August, 2008, 12 (5%) were not receiving ART for ≥6 months, eight (3%) of whom met the CD4 and clinical criteria for non-progressors (Table 1). The median age for these eight children was 14.5 years, 5 (63%) were female, 5 (63%) were black, and six (75%) were CDC category N/A. All had previously received ART but subjects 1-5 (63%) had never received HAART. Median age at ART initiation was 2.2 years and median duration on ART was 8.8 years. The current duration since discontinuation of all ART ranged from 0.6-5.2 years (median: 4.0).

Conclusions: This report identifies a small proportion of non-progressors despite ART discontinuation among children who survived many years with perinatal HIV infection. The vast majority of children with perinatally-acquired HIV infection are receiving ART, but there were children who have never experienced severe disease or immunosuppression despite periods of six months to five years without ART. It is not known if early or intermittent ART modified their disease progression. Research is needed to develop a systematic approach to identify perinatally HIV-infected children who may be candidates to discontinue ART.

* Data presented in abstract based on data available by August 16th, 2008; additional (9th) subject off ARV identified after abstract submission.

BACKGROUND

- Routine to treat all infants and children with perinatally-acquired HIV infection[1,2]
  - Higher overall risk of rapid disease progression
  - Difficult to identify only those at high risk
- Non-progressors (~2% of perinatally infected children[3]) or elite controllers likely included but indistinguishable from progressors, if all treated
- Most treatment interruption associated with immunologic decline, morbidity and mortality in children and adults[4,5]
- Some older children discontinue anti-retroviral therapy (ART) and do not experience HIV disease progression
- Currently, there is no systematic approach to identifying which children might be able to safely interrupt ART treatment when needed to help manage drug toxicities or adherence problems.

OBJECTIVE

Assess proportion and characteristics of children who appeared to safely discontinue ART in PHACS AMP

METHODS*

Overall Study Description

The Adolescent Master Protocol (AMP), which is part of Pediatric HIV/AIDS Cohort Study (PHACS), is a prospective cohort study conducted at 12 US sites designed to define the impact of HIV infection and antiretroviral therapy on pre-adolescents and adolescents with perinatal HIV infection. A group of HIV-uninfected but perinatally HIV-exposed children from similar sociodemographic backgrounds and age distribution has been enrolled for comparison. Domains to be investigated include growth and sexual maturation, metabolic risk factors for cardiovascular disease, cardiac function, bone health, neurologic, neurodevelopment, language, hearing and behavioral function, and human papillomavirus (HPV) infection. Children from 7 years of age until their 16th birthday born to HIV-infected mothers are eligible for enrollment into AMP. Enrollment began in March 2007. As of December 16, 2008, there were 319 HIV-infected children and 101 HIV-uninfected enrolled in AMP.

* Data presented in poster based on data available by December 16th, 2008

ARV Stoppers: Inclusion Criteria & Study Plan

- 7-16 year old children with perinatally acquired HIV infection at 12 sites (March 2007)
- No ART for ≥ 6 months (including at Entry)
- CD4 ≥20% and >350 cells/mm3
- No progression to CDC clinical stage C (AIDS) ever
- Sites were queried to confirm that identified subjects were not receiving ART, to report reason(s) that subject was not receiving ART, and to report if ART was reinitiated and reason(s) for re-initiaiton.
- Demographics and clinical characteristics of these children, defined as non-progressors, were summarized

Flow Diagram: Identifying ART Stoppers

319 perinatally infected children enrolled in PHACS-AMP as of December 16, 2008

↓

306 children with baseline visit

↓

297 children with historical data from previous protocols

↓

247 children enrolled into PHACS-AMP from IMPAACT 219/219C (historical data for ARV, CD4, Viral Load)

↓

244 children with entry ARV information

↓

13 children not on ARV in PHACS-AMP

↓

12 children recently off of ARV for at least 6 months

↓

9 children with lifetime CD4≥20%, CD4 count>350, and CDC≠C

RESULTS

TABLE 1: Characteristics of ART Stoppers

Subject	Age at Entry (yrs)	Sex	Race/ Ethnicity	Nadir* CD4%	Nadir* CD4 (cells/ mm3)	Max.* Viral Load (copies/ mL)	CDC Clinical Category	Most Recent Duration Off ART (yrs)	Duration on ART (yrs)	Age (yrs) at ART initiation	# of HAART regimens	# of non-HAART regimens	Last CD4% off ART	Last CD4 off ART (cells/mm3)	Last Viral Load Off ART (copies/ mL)	Closest CD4% before off ART date	Closest CD4 before off ART date (cells/mm3)	Closest Viral Load before off ART date (copies/ mL)
1	14.5	F	Unknown	22	568	1700	A	5.5	8.0	2.5	0	2	33	568	680	30	958	400
2^	14.6	M	Black	20	462	260000	A	5.2	7.7	2.6	0	1	21*	524*	27,000	33	1107	2200
3	11.3	M	Black	28	654	30,300	A	3.8	8.1	0.6	0	1	34	573	24,000	36	765	1720
4	14.6	F	>1 race	31	392	206,000	A	4.9	9.6	1.9	0	1	38	608	41690	---	---	---
5	14.7	F	Black	32	590	250,260	---	3.1	11.1	1.0	0	2	42	550	1110	44	790	2400
6	14.4	M	Black	22	430	205,000	A	14.8	0	n/a	0	0	35	730	9600	n/a	n/a	n/a
7	14.5	F	Latino	24	564	570,000	B	5.5	10.6	0.1	2	3	36	679	16000	46	1242	400
8^	15.7	F	Black	25	737	3,160	A	0.9	9.4	5.8	3	0	35	534	750	46	1103	400
9	11.3	M	Black	20	537	63,300	N	2.1	3.3	7.4	3	0	28	542	11600	36	537	15986

Footnotes: ^ = subjects who restarted ART. *Nadir CD4 and Max VL prior to ART interruption.

Descriptive Summary of ART Stoppers

- Of 244 children with complete ART history enrolled in PHACS AMP, 12 (5%) not receiving ART for ≥6 months
  - 9 (4%) met CD4 and clinical criteria
- Characteristics of 9 ARV Stoppers
  - Median age: 14.5 years
  - 5 (56%) female
  - 5 (56%) black
  - 6 (67%) CDC category N/A
  - All but one had previously received ART but 5 (56%) had never received HAART
  - Median age at ART initiation: 2.2 years
  - Median ART duration: 8.8 years
  - Duration of ART discontinuation: Median 4.9 yrs, Max 5.5 yrs

Trends in Viral Load (VL)

- Subject #1, likely a Viremic Controller[6]
  - VL<2000 copies/mL Off ART for ≥1 year
- ALL Subjects: Viral Load (VL) after stopping ART < Peak VL
- 5 Subjects: VL Off ART << Peak VL, despite no ART for ≥2.7 years
  - Subjects #2, 4, 5, 6, 7

TABLE 2: Reasons Reported for ART Discontinuation

#(%) Subjects	Reason (adapted from Saitoh[4])
7 (78%)	1. **ARV not clinically indicated** at this time in the judgment of treating physician
2 (22%)	2. **Medication fatigue** (subjects who were unable to take ART because of pill burden and/or non-adherence)
2 (22%)	3. **Behavior issues** (developmental issues such as refusal to swallow pills or resistance to instructions by parents or caregivers)
1 (11%)	4. **Social issues** (family interactions that made it difficult for subjects to continue to take their medications)
1 (11%)	5. **Adverse effects** (subject-driven complaints such as diarrhea, vomiting, nausea, abdominal pain, body characteristic changes, or other symptoms associated with the use of antiretroviral medications)
Multiple responses allowed: Reasons 2,3,4 for Subject #9; Reasons 1,2 for Subject #1; Reasons 1,5 for Subject #7	

Additional Subject Details

- Subject #7:Had a buffalo hump which resolved approximately 1.5- 2 years after stopping ARV meds.
- Subject #2 initiated HAART after 5.2 year ART interruption
  - Hospitalized for scalp kerion requiring surgical I & D
  - VL =27,000 copies/mL before initiation
  - No HIV clinical events or CD4 decline
- Subject #8 reinitiated HAART after 11 month interruption
  - Interrupted by subject for medication fatigue
  - No HIV clinical events, VL rise or CD4 decline

CONCLUSIONS

- In this observation cohort study, 4% of long-term survivors of perinatal HIV infection remained off ART at least 6 months without apparent immunologic or clinical progression
- The commonest reason for lack of ART was physician judgment that ART was not indicated
- Though 2 subjects restarted ART, neither had developed clinical, virologic or immunologic indications for ART
- Pre-ART history of high VL was not associated with high VL, CD4 decline or clinical progression at ART discontinuation in these subjects
- Perinatally HIV-infected children who have never experienced CDC class C disease or low CD4 (CD4<20% or CD4<350cells/mm3), regardless of peak VL, may be able to discontinue ART safely for at least 6 months, but such a strategy requires systematic, prospective evaluation.
- Developing strategies for safe interruption of ART, even for a limited time, in perinatally HIV-infected children may be useful for those children experiencing periods of increased adherence difficulty or drug intolerance.

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