Prevalence and Predictors of HIV Drug Resistance Among US Children and Youth with Perinatal HIV

Russell B Van Dyke[1], Kunjal Patel[2], Ron M Kagan[3], Shirley Traite[4], William A Meyer III[5], Katherine Tassiopoulos[2], George R Seage III[2], Lorna M Seybolt[6], Sandra Burchett[7], and Rohan Hazra[8] for the Pediatric HIV/AIDS Cohort Study (PHACS)

[1] Tulane University School of Medicine, New Orleans, LA; [2] Harvard School of Public Health, Department of Epidemiology, Boston, MA; [3] Quest Diagnostics, Nichols Institute, San Juan Capistrano, CA; [4] Harvard School of Public Health, Center for Biostatistics in AIDS Research, Boston, MA; [5] Quest Diagnostics, Baltimore, MD; [6] Louisiana State University Health Sciences Center, Department of Pediatrics, New Orleans, LA; [7] Harvard Medical School, Department of Pediatrics, Boston, MA; [8] Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

Abstract # 897

Russell Van Dyke, M.D.
Pediatrics, TB-8
Tulane University School of Medicine
1440 Canal Street
New Orleans, LA 70112
vandyke@tulane.edu

ABSTRACT

Background: With extensive antiretroviral (ARV) exposure and the challenge of maintaining adherence, children and youth with perinatal HIV are at high risk for acquired drug resistance.

Methods: The Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study is a prospective study being conducted at 14 U.S. sites. From 2007 to 2009, we enrolled 451 subjects with perinatal HIV who were 7-16 years of age at entry. We abstracted results from genotypic resistance testing performed for clinical care. For subjects without these results and with a viral load (VL) ≥400 copies/mL, their most recent plasma sample was sent for genotypic resistance testing at a reference laboratory (Quest Diagnostics). Results were compared to the overall results from the reference laboratory for 2006 and 2012. Correlates of resistance were assessed using the Wilcoxon Test for continuous and Chi-square Test for categorical variables.

Results: Of the 446 subjects with at least one VL performed on study, 284 (64%) had at least one VL ≥400 copies/mL and 230 had resistance testing results from 2007-2013 (median 2010). Their median age at testing was 14.8 years; 57% were female, 70% black and 25% Hispanic. 74% had any ARV resistance; 61%, 40%, and 34%, respectively, had resistance to any NRTI, any NNRTI, or any PI, substantially higher than that of the reference laboratory population. The prevalence of resistance was highest for: zidovudine, nevirapine, and efavirenz (40%); stavudine (39%); lamivudine (37%); and didanosine and nelfinavir (32%). The prevalence of resistance was lowest for lopinavir (18%), etravirine (15%), tipranavir (10%), and darunavir (4%). Resistance to all ARVs in a class was uncommon. Univariable correlates of any resistance included more cumulative years of HAART (p=0.03), more HAART regimens (p=0.005), a lower pre-HAART nadir CD4% (p=0.001), a higher pre-HAART peak VL (p<0.001), and a lower current VL (p=0.02). Factors not significantly associated with resistance included use of ART prior to HAART, current CD4 count, current CDC class, and current ARV adherence. At their most recent visit, 67% of AMP subjects had a VL < 400 copies/mL.

Conclusions: Viral resistance is common among U.S. youth with perinatal HIV, including resistance to multiple ARV classes, with a prevalence of resistance substantially higher than that of the general U.S. HIV-infected population. Resistance to newer ARVs is less common and effective regimens are available for most youth with viral resistance.

BACKGROUND

With extensive ARV exposure and the challenge of maintaining adherence, children and youth with perinatal HIV are at high risk for acquired viral drug resistance.

OBJECTIVES

- To determine the prevalence of ARV-resistant virus among perinatally HIV-infected children and youth in AMP and to compare the prevalence of resistance by ARV class to that of national data from a commercial laboratory.
- To describe the pattern of drug resistance among these subjects
- To identify predictors and correlates of ARV resistance

METHODS

Study Population

The Adolescent Master Protocol of the Pediatric HIV/AIDS Cohort Study is a prospective study being conducted at 14 U.S. sites. From 2007 to 2009, we enrolled 451 subjects with perinatal HIV who were 7-16 years of age at entry. We abstracted results from genotypic resistance testing performed for clinical care. For subjects without resistance testing and with a viral load (VL) ≥400 copies/mL, their most recent plasma sample was sent for genotypic resistance testing at a reference laboratory (Quest Diagnostics). Results were compared to the overall results from the reference laboratory for 2006 and 2012. Self-reported adherence is the proportion of ARV doses missed in the prior 7 days.

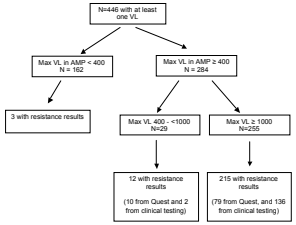
Statistical Methods

Correlates of resistance were assessed using the Wilcoxon Test for continuous and Chi-square Test for categorical variables.

RESULTS

- Of the 451 AMP subjects, 446 had at least one viral load performed while on study and 230 of these had resistance testing results. (Fig. 1)
- Of the 230 subjects with resistance testing results, 170 (74%) had at least one resistance mutation (Table 2, Figure 2)

Figure 1: Derivation of AMP Subjects with Resistance Testing Results



RESULTS

Table 1: Characteristics of 230 AMP Subjects with Resistance Testing Results

	Any Resistance	No Resistance	P-value
N	170	60	
Age at resistance testing (median)	14.7 yrs.	15.6 yrs.	0.15
Male	45%	38%	0.39
Race/Ethnicity			0.61
White/other	4%	7%	
Black	72%	65%	
Hispanic	24%	27%	
Ever use of ART	100%	95%	0.003
Age at ART initiation (median)	0.8 yrs.	1.1 yrs.	0.31
Ever use of HAART	97%	83%	<0.001
Age at HAART initiation (median)	2.7 yrs.	4.4 yrs.	0.10
ART prior to HAART	68%	58%	0.97
Cumulative duration HAART (mean)	9.1 yrs.	7.6 yrs.	0.03
Number of HAART regimens (median)	4.0	2.5	0.005
Nadir CD4 <15% prior to HAART	24%	13%	0.001
Peak VL > 500,000 copies/ mL prior to HAART	38%	17%	<0.001
VL at testing < 5,000 copies/ mL	55%	43%	0.02
100% adherence at resistance testing	42%	27%	0.12

Figure 2: Prevalence of Any ART Resistance Overall by Drug Class and by Multiple Drug Classes – AMP Subjects

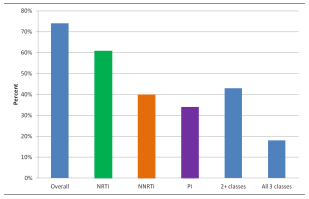


Table 2: Prevalence of HIV Resistance by Drug Class and Combination of Classes

Resistance	PHACS AMP Subjects (N=230)			Reference Lab (N >=10,000)	
	2007-2013			2006	2012
	N	Prevalence	95% CI	Prevalence	
Any ARV	170	74%	68-79%	44%	36%
At least 1 class					
NRTI					
Any	140	61%	54-67%	33%	21%
All	19	8%	5-13%	6%	2%
NNRTI					
Any	93	40%	34-47%	28%	26%
All	35	15%	11-21%	0.9%	1%
PI					
Any	78	34%	28-40%	17%	7%
All	7	3%	1-6%	1%	0.4%
At least 2 classes					
NRTI + NNRTI					
Any	68	30%	24-36%	18%	12%
All	5	2%	1-5%	0.4%	0.2%
NRTI + PI					
Any	70	30%	25-37%	15%	5%
All	3	1%	0.3-4%	0.6%	0.2%
All 3 classes					
Any	41	18%	13-23%	8%	3%
All	1	0.4%	0-2%	0%	0.1%

Any: any drug in class or any in each class
All: all drugs in class or all in each class
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor

Figure 3: Distribution of the 170 AMP Subjects With Any Resistance Mutations by ARV Class/Classes of Resistance

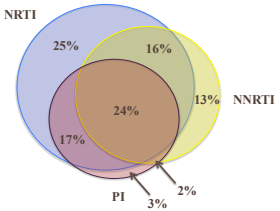


Table 3: Prevalence of Resistance to NRTIs – AMP Subjects

Any NRTI	61%
zidovudine	40%
stavudine	39%
lamivudine/ emtricitabine	37%
didanosine	32%
abacavir	28%
tenofovir	22%
All NRTIs	8%

Table 4: Prevalence of Resistance to NNRTIs – AMP Subjects

Any NNRTI	40%
nevirapine	40%
efavirenz	40%
rilpivirine	20%
etravirine	15%
All NNRTIs	15%

Table 5: Prevalence of Resistance to PIs – AMP Subjects

Any PI	34%
nelfinavir	32%
saquinavir	21%
atazanavir	20%
fosamprenavir	20%
indinavir	20%
lopinavir	18%
tipranavir	10%
darunavir	4%
ALL PIs	3%

SUMMARY

- Resistance testing was performed between 2007 & 2013 (median 2010)
- Median age at testing was 14.9 years
- 74% of subjects had any ARV resistance (Table 2)
  - 61% to at least one NRTI
  - 40% to at least one NNRTI
  - 34% to at least one PI
- Resistance to all ARVs in a class was uncommon (Table 2)
- Univariable correlates of resistance:
  - More cumulative years of HAART
  - Greater number of HAART regimens
  - A lower pre-HAART nadir CD4%
  - A higher pre-HAART peak VL
  - A lower VL at the time of resistance testing
- Not associated with resistance:
  - Use of ART prior to HAART
  - CD4 count at the time of resistance testing
  - CDC category at the time of resistance testing
  - ART adherence at the time of resistance testing
- At their most recent visit, 67% of AMP subjects had a VL < 400 copies/ mL

CONCLUSIONS

- ARV resistance is common among U.S. children and youth with perinatal HIV, including resistance to multiple ARV classes
- The prevalence of resistance is substantially higher than that of the general U.S. HIV-infected population
- Resistance to newer ARVs is less common
- Most children and youth with resistant HIV remain sensitive to newer agents from all classes, allowing salvage therapy.
- Resistance is associated with more advanced disease prior to starting HAART, a longer duration of HAART, and a greater number of HAART regimens.

REFERENCE

Van Dyke RB, Patel K, Siberry GK, et al for the Pediatric HIV/AIDS Cohort Study. Antiretroviral Treatment of U.S. Children with Perinatally-Acquired HIV Infection: Temporal Changes in Therapy between 1991 and 2009 and Predictors of Immunologic and Virologic Outcomes. *J Acquired Immune Defic Syndr* 2011; 57: 165-173.

ACKNOWLEDGMENTS

National Institutes of Health
Turning Discovery Into Health

Funded by the National Institutes of Health, under cooperative agreements HD052104 (PHACS Coordinating Center, Tulane University School of Medicine) and HD052102 (PHACS Data and Operations Center, Harvard School of Public Health). We thank the study participants, clinical sites, PHACS CAB, Frontier Science & Technology Research Foundation, and Westat.