

Trends in Bacteremia in the Pre- and Post-HAART Eras among HIV-Infected Children in the U.S. Perinatal AIDS Collaborative Transmission Study (1986-2004)

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POSTER # R-108

Revised Abstract

Background: HIV-infected children are at high risk for bacteremia, particularly with encapsulated bacteria. Since its introduction in 1996, HAART has reduced rates of opportunistic infections; however, less is known about its effect on bacteremia rates. Even fewer are the data about the effect of HAART on these parameters in Children. We determined the effect of HAART on the incidence of bacteremia in HIV-infected children in the pre and post HAART eras.

Methods: The Perinatal AIDS Collaborative Transmission Study (PACTS) is a CDC-sponsored multi-center, prospective cohort study of HIV-exposed infants, enrolled during 1986 - 1999 to monitor mother-to-child transmission and natural history of pediatric HIV disease. HIV-infected children were followed through April 2004. In this analysis all pathogens were included except *Bacillus* species in patients without indwelling catheters and all non-*aureus Staphylococci* and viridans *Streptococci*. The incidence of bacteremia events was calculated (per 100 pt-years) for the pre- and post-HAART eras, i.e. before and after 1/1/97, respectively. Also, time to occurrence of 1st bacteremia among patients born in the pre- and post-HAART eras was analyzed using survival analysis.

Results: Among 364 HIV-infected children, 68 had 118 bacteremias, 97 before 1/1/97 and 21 after 1/1/97. *S. pneumoniae* constituted the majority of cases in the pre- and post-HAART eras, 56 (58%) and 13 (62%) cases, respectively.

Among children aged 0-24, 25-48 and 49-72 months, the incidence rate of bacteremia (95% CI) in the Pre-HAART era was 9.6 (7.2-12.7), 10.2 (7-14) and 9.2 (4.9-15.3) events per 100 person-years and in the post-HAART era was 1.8 (0.2-6.6), 2.3 (0.6-5.9) and 3.8 (1.8-7.1) events per 100 person-years, respectively. The overall incidence rate of bacteremia (95% CI) in the pre-HAART and post HAART eras was 9.8 (7.9-11.9) and 2.9 (1.7-4.8) events per 100 person-years, respectively. Patients aged 0-24, 25-48 and 49-72 months in the post-HAART era had 20% (5-80%), 20% (10-60%) and 40% (20-90%) of the pre-HAART risk for developing a bacteremia, respectively. Overall the risk of a post-HAART era patient developing a bacteremia was 30% (20-50%) of their pre-HAART counterpart.

Kaplan-Meier analysis for time to 1st bacteremia in children born during the pre-HAART compared to post-HAART eras revealed that 69% and 94% remained without bacteremia at a median follow up of 6 years (P=0.02, log rank test). The Cox proportional hazards model also showed a significant reduction of bacteremia in the post-HAART era, even after controlling for gender and race (HR=0.2; 95%CI 0.05-0.87).

Conclusions: A significant decrease in the cumulative incidence of bacteremia and a prolongation in the time to 1st bacteremia were seen in the post-HAART era among this U.S. perinatal cohort of HIV-infected children.

Methods

Subjects and Study Design: The Perinatal AIDS Collaborative Transmission Study (PACTS) is a CDC-sponsored multi-center, prospective cohort study of HIV-exposed infants, enrolled during 1986 - 1999 to monitor MTCT and natural history of pediatric HIV disease. HIV+ children were followed through 4/04.

Clinical and Laboratory Data Collection: Clinical charts were reviewed at each study visit and all interim blood stream infections (BSI) were identified by organism name in the majority of bacteremia events. Only pathogenic organisms causing bacteraemia were abstracted for use in the analysis. Microbiologic outcomes were compared between the pre- & the post-HAART era for pts w/ BSI.

Medications and Definition of "HAART era": Data were collected at each study visit regarding the use of any ARV medications used since the previous visit. Events that occurred during the pre- and post-HAART eras were defined as those that occurred prior to and after 1/1/97, respectively.

Outcome Measures: Our primary endpoint was BSI events that occurred in the pre- and post-HAART eras. These events were used to calculate the incidence rate of BSI during both time periods. Additional endpoints that were evaluated included the time to occurrence of 1st BSI in those patients born in the pre-HAART era and those born in the post-HAART era.

Data Analysis and Statistical Methods: A BSI event was defined as only those blood stream infections documented by at least one blood culture growing pathogenic bacteria. Bacteria defined as non-pathogens were all non-*aureus Staphylococci*, viridans *Streptococci* and *Bacillus* species in patients without indwelling catheters and were excluded from analysis. The overall incidence rate of BSI was first calculated for the pre- and post-HAART periods utilizing a person-time approach and then further stratified by age, gender, race and study site to yield stratum-specific incidence rates with rate ratios and Mantel-Haenszel adjusted incidence rate ratios with 95% CIs. To further confirm the effects of HAART on bacteraemia incidence, survival analysis was used to compare the time until the development of the first bacteraemia among bacteremic HIV-infected children born before January 1, 1997 to that of those born after that date. After assumptions of the Cox Proportional hazard model were tested, the models were applied to determine the effect of the post-HAART era on the time to development of a first bacteraemia by testing interaction terms and assessing confounding by other covariates. While constructing the models, multi-collinearity and regression diagnostics were checked for the model fit. Assumptions for using January 1, 1997 as the date that defined the pre- and post-HAART eras were also checked by Kaplan-Meier methods and by evaluation of the frequency distribution of HAART initiation by calendar year among children born before and those born after January 1, 1997.

Characteristics of Study Population

Characteristics	Frequency (%)	Characteristics	Frequency (%)
Study site (n=364)		Baseline CD4% (n=354)	
Atlanta	46 (12.6%)	0-14.99%	9 (2.5%)
Maryland	48 (13.2%)	15-24.99%	31 (8.8%)
New Jersey	52 (14.3%)	>25%	314 (88.7%)
New York	218 (60%)	Median CD4% (interquartile range)	48 (36 to 57)
Gender (n=364)		Median CD4 count/mm ³ (interquartile range)	2409 (1566 to 3479)
Female	202 (55.5%)	# of events per person (n=364)	
Male	162 (44.5%)	0	296 (81.3%)
Race (n=364)		1	39 (10.7%)
White, non-hispanic or non-specified	17 (4.7%)	2	18 (5%)
Black, non-hispanic or non-specified	252 (69%)	3	7 (2%)
White, hispanic	20 (5.5%)	4	2 (0.5%)
Black, hispanic	13 (3.6%)	≥5	2 (0.5%)
Hispanic, non-specified	51 (14%)	Calendar yr of events (n=118)	
Other	3 (0.8%)	1986-88	3 (2.5%)
Unknown	8 (2.2%)	1989-91	14 (11.9%)
Calendar year of birth (n=364)		1989-91	14 (11.9%)
1986-88	39 (10.7%)	1992-94	54 (45.8%)
1989-91	94 (25.8%)	1995-96	26 (22%)
1992-94	141 (38.7%)	1997-98	11 (9.3%)
1995-96	52 (14.3%)	1999-2001	10 (8.5%)
1997-99	38 (10.4%)	Median CD4% at event (interquartile range) (n=65) ¹	20 (9 to 31)
Median follow-up years (interquartile range)	5.9 (2.2 to 9.5) (n=61) ¹	Median CD4 # / mm ³ at event (interquartile range) (n=61) ¹	686 (241 to 1353)

¹CD4+ level closest to the time of bacteremic event either within 6 months prior to the event or between 3-6 months after the event if CD4+ was unavailable in the former period. Note that CD4+ levels are not available within specified period in approximately half of events.

Characteristics of Bacteremia Events Pre & Post HAART

Study site	Pre-HAART cases (%)	Post-HAART cases (%)	X ² p-value	Year of birth	Pre-HAART cases (%)	Post-HAART cases (%)	X ² p-value
	n=97	n=21			n=97	n=21	
Atlanta	19 (20%)	4 (19%)	<0.001	1986-88	11 (11%)	0 (0%)	<0.001
Maryland	36 (37%)	1 (5%)		1989-91	52 (54%)	4 (19%)	
New Jersey	9 (10%)	14 (67%)		1992-94	33 (34%)	13 (62%)	
New York	33 (34%)	2 (10%)		1995-98	1 (1%)	4 (19%)	
Gender				Age(yrs) at diagnosis			
Female	48 (49%)	16 (76%)	0.027	0-3	74 (76%)	2 (10%)	<0.001
Male	49 (51%)	5 (24%)		3-6	23 (24%)	14 (67%)	
Race				6-9	0 (0%)	1 (5%)	
B, NH	81 (84%)	20 (95%)	0.88	9-13	0 (0%)	4 (19%)	
others	16 (16%)	1 (5%)					

Pathogenic Bacteria Distribution in Pre & Post-HAART Cases

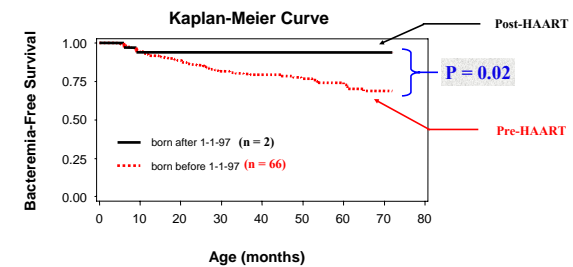
Pathogenic bacteria (n=122) ¹	Pre-HAART cases (%)	Post-HAART cases (%)	X ² p-value
<i>Streptococcus pneumoniae</i>	56 (58%)	13 (62%)	0.79
<i>Staphylococcus aureus</i>	14 (14%)	2 (10%)	
<i>Enterococcus spp.</i>	13 (13%)	1 (5%)	
<i>Pseudomonas aeruginosa</i>	5 (5%)	2 (10%)	
<i>Escherichia coli</i>	5 (5%)	1 (5%)	
<i>Klebsiella pneumoniae</i>	4 (4%)	2 (10%)	
<i>Salmonella spp.</i>	3 (3%)	0 (0%)	
<i>Haemophilus influenzae</i>	1 (1%)	0 (0%)	

BSI Incidence among HIV+ Children in the First 6 Years of Life

Age at diagnosis	Pre-HAART		Post-HAART		Incidence rate ratio (95% CI)
	Events (N)	Incidence rate per 100 person-years (95% CI)	Events (N)	Incidence rate per 100 person-years (95% CI)	
0-24 mos	50	9.6 (7.2-12.7)	2	1.8 (0.2-6.6)	0.2 (0.05-0.8)
25-48 mos	33	10.2 (7-14)	4	2.3 (0.6-5.9)	0.2 (0.1-0.6)
49-72 mos	14	9.2 (4.9-15.3)	10	3.8 (1.8-7.1)	0.4 (0.2-0.9)
Cumulative	97	9.8 (7.9-11.9)	16	2.9 (1.7-4.8)	0.3 (0.2-0.5)

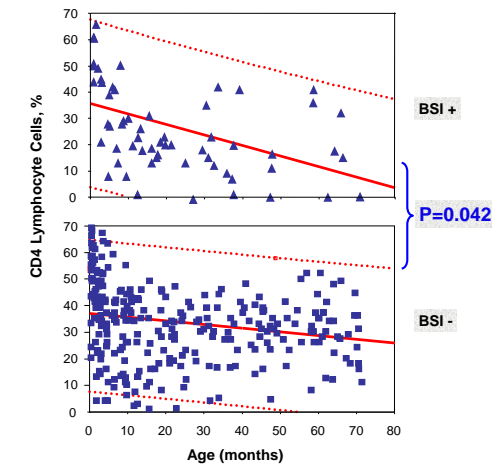
- Each study site except New Jersey experienced at least an 80% reduction
- Both males and females experienced a 70% reduction
- African American patients experienced a 70% reduction
- Non-African American patients experienced a 90% reduction

Time to 1st BSI Between Children Born Pre- & Post-HAART



- Cox PH model also showed a significant reduction of BSI in post-HAART era, even after controlling for gender & race (HR=0.2; 95%CI 0.05-0.87).

Decline of CD4% Slower in Children without BSI



- Analysis of all available viral load data did not yield significant trends.

Conclusions

- In this US cohort of perinatally infected children
- Significant decrease in the cumulative incidence of BSI from pre- to post-HAART
- Prolongation in time to development of 1st BSI in the post-HAART era
- Slower decline of temporal CD4% in children without BSI
- Associations with co-morbid conditions need further investigation

Acknowledgements

We are indebted to Mrs. Vickie Grimes for her tireless devotion to data entry and management for this study. We also thank Mr. David Maggio for his helpful participation in gathering background information and for his initial descriptive analysis of the Atlanta cohort. We also thank the Grady Health System pediatric IDP clinic staff for their excellent technical help.

We are also indebted to the CDC support staff who assisted with the PACTS and PACTS-HOPE projects: Barb Freedman, April Bell, Margaret Lampe for their roles as project coordinators and Doc Yang, Jeff Wiener, Shawn Wei, and Joanne Ethier-Ives for their work on data management.

PACTS and PACTS-HOPE were supported through cooperative agreements between the CDC and the University of Medicine and Dentistry of New Jersey (U67/CCU202219), the University of Maryland School of Medicine (U67/CCU306825), Emory University School of Medicine (U67/CCU404456) and Medical & Health Research Associates (U67/CCU207228).

Finally, we would like to thank the study patients and their families whose selfless participation in this research project made the current analysis possible.