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AETC
AIDS EDUCATION AND TRAINING CENTER

19th Annual HIV CONFERENCE
May 14-15, 2010 • Orlando, FL

Pediatric HIV Research An Overview

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Have you ever participated in a Research Study?

- A. Yes
- B. No



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Principles of Research

- Usually done to advance knowledge in a field and answer an important question
- Must be ethical and done with the proper protections for human subjects. (IRB)
- Participants must have the research described in their own language and sign an informed consent or assent.
- Participants may discontinue the research at any time without affecting their medical care.



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Goals of Pediatric HIV Research

- Prevention of perinatal transmission
- Understand the pathophysiology of HIV in children and adolescents
- Improve quality of life
- Develop and determine the appropriate use of ARV
- Minimize side effects of these drugs
- Maximize survival
- Develop an effective vaccine



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Mother to Child HIV Transmission

- **Successes**
- Perinatal Transmission of HIV has been reduced to approximately 1% in most large obstetrical services in the US.
- Antiretroviral therapy for reduction of perinatal transmission in US, 3-part regimen



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Mother to Child HIV Transmission

- In developing countries, short course of ZDV, NVP with or without other drugs
- Rapid HIV testing protocols for pregnant women at delivery have further decreased perinatal transmission of HIV.
- Elective C-section
- Identification of pre-mastication as a factor in transmission of HIV
- Tests for early diagnosis of HIV in infants



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Premastication of Food: A Risk Factor for HIV Transmission

- 3 cases described of children diagnosed with HIV at ages 9, 15 and 39 months
- In one case mother was not HIV-infected
- Two cases had had screening for HIV and were previously negative
- All 3 children were fed food that had been premasticated by an HIV infected caregiver
- Phylogenetic analysis of the viruses supported that these children were infected through premastication practices
- A. Gauer, K. Dominguez, M. Kalish et al. Pediatrics 124:658-666, 2009



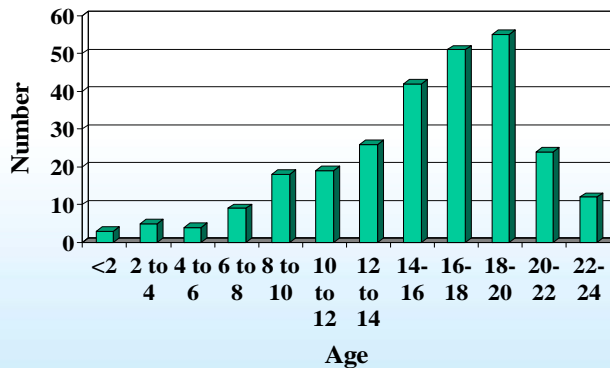
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Florida Statistics

- There were 598 HIV exposed newborns born in Florida in 2008. Of these, 9 infants were infected with HIV. This is an 84% decrease from the 107 perinatally infected babies born in Florida in 1993 (the peak year).

Children Living With HIV Infection - Miami, Florida June 2009



Mother to Child Transmission of HIV

- **Challenges**
 - Prevention of post-natal transmission through breast milk
 - Some success in prevention by:
 - Exclusive Breast feeding during the first 6 mos.
 - Maternal HAART therapy
 - Infant prophylaxis



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Antiretroviral Therapy

- **Successes**
 - Pharmacokinetics, dosing and formulations of antiretroviral therapies available for many ARV.
 - Safety and tolerance of most ARV during pregnancy
 - Prevention of MTCT
 - Long term survival with fewer deaths



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Antiretroviral Therapy

- **Challenges**
- Newer ARV's not tested or available for use in children. No combination products.
 - NRTI: Tenofovir, Emtricitibine
 - NNRTI: Etravirine
 - Protease Inhibitors: Darunavir, Atazanavir, Tipranavir
 - Integrase Inhibitors: Raltegravir,
 - Entry inhibitors: CCR5, Fusion inhibitors



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Antiretroviral Therapy

- **Challenges**
- Adherence
- Short and long term adverse effects/complications
 - Lipodystrophy, fat redistribution
 - Cardiac effects, Lipid abnormalities
 - Bone density, osteopenia
 - Growth and development, puberty



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Antiretroviral Therapy

- **Short and long term adverse effects/complications (cont.)**
- Neurodevelopment
 - Hearing and language
 - Learning disabilities
 - ADHD
 - IQ
 - Executive functioning



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Antiretroviral Therapy

- **Challenges**
- *Mitochondrial Toxicity – associated with ZDV, 3TC*
 - *Effect on uninfected infants born to HIV infected women*
- *Metabolic syndrome*
- *Decrease burden of multiple pills daily*



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International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)

- Phase I, II, III, IV Clinical Drug trials for infants, children, youth and pregnant women (pk, safety, tolerance, effectiveness)
- Observational Studies of Pregnant women and their infants; Infected children
- Studies of antibody response to vaccines – H1N1, meningococcus, HPV, *Pneumococcus*
- Complications of HIV; Opportunistic Infection.



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IMPAACT Trials in Children and Adolescents

- Safety and PK study of MK 0518 in HIV+ children
- Intensive PK studies of ARV Combinations
- PK, safety and tolerance of vicriviroc
- Safety of Atorvastatin for PI associated high LDL cholesterol
- Impact of oral alendronate on bone mineral density in HIV+ children and adol.
- H1N1Vaccine in HIV+ children (completed)



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IMPAACT Trials

- Studies in Pregnant women and their infants
- PK study of ARV therapy during pregnancy
- Perinatal Core Protocol
- Promise study: Ongoing treatment of pregnant women postpartum versus stopping the ARV.
- H1N1 vaccine in pregnant women (Complete)
- Planned trial of pneumococcal vaccine in pregnant women



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Vaccine Research

- ***Meningococcal Vaccine MCV 4 (Groups A, C, Y and W-135)- P1065***
 - Enrolled 319 subjects, median age 17yo
 - 50% Black, 38% Latino, 59% male
 - Baseline protective immunity: A-41%, C-11%, W-135-15%, Y-35%
 - Stratified by CD₄



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Vaccine Research MCV 4

- Immunogenic response A -68%, C -52%, W-135 -73%, Y -63% (Lower than in HIV neg. peers - 80-97%)
- Safe, immunogenic with lower response rates in youth with lower CD₄ and higher viral loads.

Silberry, G., Williams, P., Lujan-Zilberman, J. et al. PIDJ 29:391-396, 2010



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Question

- **A clinical research study involves giving a new vaccine to children with HIV. The child will have to return for six visits with two vaccinations and blood drawing. Transportation to the visits will be provided.**
- **An eight year old child is attending his routine clinic visit. What are the appropriate measures to be taken to enroll this patient into the study?**

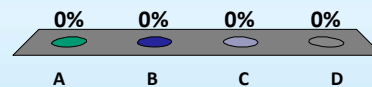


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Responses

- A. The research nurse explains the study and makes sure the child meets the eligibility criteria. Informed consent and assent is obtained.
- B. The research nurse explains the study and offers the parent a \$25 coupon to the local food store for participating in the study
- C. The mother has agreed to the study, but the child does not want to do the study because of the "shots". Mother signs him up anyway.
- D. The mother usually asks too many questions and the study is not offered to her child by the research team.



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Pediatric HIV AIDS Cohort (PHACS)

- Create a body of data to understand more fully the effect of HIV and ARV medications on sexual maturation, pubertal development and socialization of perinatally infected children
- Acquire more information regarding long term safety of antiretroviral agents when used during pregnancy and in newborns
- Ensure follow up of these populations



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**Surveillance Monitoring for Antiretroviral
Therapy Toxicities in HIV-uninfected
Children Born to HIV- infected Women
(SMARTT study)**

- 22 sites
- *Dynamic cohort* – enrollment of newborn infants (Birth to 72 hrs. of age) born to HIV infected women and their caregivers (800/year)
- *Static cohort* – enrollment of uninfected infants ages <12 y.o. and born to HIV infected women/caregivers (1625)



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**Surveillance Monitoring for Antiretroviral
Therapy Toxicities in HIV-uninfected
Children Born to HIV- infected Women
(SMARTT study)**

- *Reference Cohort* – enrollment of children age 1, 3, 5, 9 as controls for the other two cohorts (200)
- *Maternal Cohort* – enrollment of HIV infected pregnant women during pregnancy for nutritional evaluation



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Surveillance Monitoring for Antiretroviral Therapy Toxicities in HIV-uninfected Children Born to HIV- infected Women (SMARTT study)

- Goals of study are to estimate the occurrence of potential ART toxicities through an ongoing surveillance system among HIV uninfected children born to women with HIV infection with exposure to ART in utero and/or for six weeks after birth



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Surveillance Monitoring for Antiretroviral Therapy Toxicities in HIV-uninfected Children Born to HIV- infected Women (SMARTT study)

- Study domains
 - Neurologic, Neurodevelopmental, Behavior, Language and Hearing
 - Metabolic Function and Growth
 - Cardiac Function
 - Other (Birth defects, laboratory abnormalities, etc.)



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Adolescent Master Protocol (AMP)

- **15 sites**
 - HIV infected cohort between 7 and 16 yo
n=600
 - HIV uninfected cohort between 7 and 16 yo
n=200
- Prospective study to define the impact of HIV infection and ARV on pre-adolescents and adolescents with perinatal HIV infection.



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Adolescent Master Protocol (AMP)

Domains:

- Growth and development, sexual maturation, bone health,
- Metabolic risk factors for cardiovascular disease, cardiac function,
- Neurodevelopmental testing, language, hearing and behavioral function.
- Adolescent gynecology and HPV



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Conclusions

- Presently there is a broad spectrum of studies being conducted in the HIV infected pregnant women and perinatally infected children and youth.
- Many questions remain unanswered
- Population of perinatally infected children is decreasing as youth are aging out into adult care and we continue to implement measures to prevent perinatal transmission in the US



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Conclusions

- There are many studies ongoing internationally and in developing countries that will provide information about HIV pathogenesis in children.
- We need to all work together, through care and research to foster better understanding of HIV in children and prevent new cases. Our goal is to provide long term survival with as few side effects as possible.

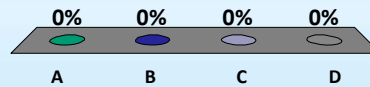


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What are some of the most significant findings resulting from Pediatric HIV Research?

- A. Prevention of HIV perinatal transmission
- B. Early diagnosis of HIV in infants
- C. Safety and dosing of antiretroviral agents in infants and children
- D. All of the above



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