Working Group (WG) Updates

Adolescent Behaviors WG

Purpose
The purpose of our working group is to ask questions about the different behaviors of adolescents and young adults in PHACS. We are interested in the ways these behaviors affect their physical and mental health outcomes. Finally, we are also interested in their readiness to be young adults.

Areas of Focus
Behaviors

- Starting sexual activity
- Disclosure
- Use of alcohol, cigarettes, marijuana and other substances
- Adherence to HIV medicines
- Transition to adult HIV care
- Transition to adult functioning including jobs, advanced education and independent living

Health Outcomes

- Sexually transmitted infections
- Pregnancy
- Psychiatric outcomes

Accomplishments
Members of our working group have published several papers over the past two years. These papers have studied different behaviors among the youth participating in PHACS. These papers include:

- A study of how answers to questions about children's adherence to HIV medicines matched with their viral load. The study looked at how well children's answers to these questions matched caregivers' answers;
- A study of cigarette smoking, alcohol use and marijuana use by youth in AMP. The study looked at how rates of use by youth with HIV or exposed to HIV compared to youth in nationwide surveys;
- A study of how many youth with HIV were having sex and how old they were when they started. The study also looks at how they compared with youth from national surveys.

The Adolescent Behaviors working group has also been busy over the past two years helping with the development of the AMP Up study. AMP Up is enrolling young adults 18 years and older who were born with HIV or exposed to HIV during pregnancy. Our group was responsible for putting together the questions on sexual activity, substance use, and reproductive health. We were also responsible for questions about medication adherence and quality of life. We looked at a lot of measures used in other studies with similar groups of young people and adapted them for AMP Up. We also came up with some new questions.

Significance for the Community
The research of the Adolescent Risk Behaviors WG means a hope for the future. As we look for patterns of risk for youth and young adults affected by HIV, our findings that are published can influence the work of HIV providers in their communities. These providers can come up with and provide services that will then reduce risk behaviors. They can also promote healthy behaviors of young people who have grown up with or who are affected by HIV. This means that the risk of health complications due to poor adherence or substance use is reduced. The risk of transmission to partners or their own babies is reduced. This also means these youth have a greater chance to receive the care they need. It can also help youth receive interventions, services and screenings they may need to help them grow up to be healthy functioning adults.

Why the Adolescent WG?
The Adolescent Risk Behaviors WG focuses on what adolescents experience as they transition to adulthood. This time in any teenager's life is complex and unique. Combining the challenges of growing up with a chronic disease can make the transition even more difficult. It can affect their physical health and their mental health.

We see on a daily basis the struggles teens have with identity and sexuality. We also see their difficulties with responsibility for medication management and the threat of and loss of medical insurance once they hit 18 years of age. This WG gives its members the outlet to provide feedback in the areas we see teens struggling with growing up with HIV. We feel the information that will come out of this working group will support a healthy transition into adulthood.

Works in Progress
The Adolescent Behaviors working group has several concepts that are currently underway, including:

- A study of changes in medication adherence over time and how this may be affected by a child's age, social support, mental health and other factors;
- A paper that describes the steps involved in developing the AMP Up protocol;
- A study of how many HIV-infected and exposed children and youth had one or more doses of HPV vaccine. The study looks at the amount of antibody that develops after vaccination and how long it lasts depending on whether a child is HIV-infected and on other factors;
- A study of whether cognitive functioning and behavioral problems are associated with substance use;
- A paper describing the development of the new Amp This Up website;
- A paper about the barriers and facilitators of retaining young adults in long-term studies and the role technology plays in the transition to young adulthood; and
- A study of the factors that lead to sexually transmitted infections or that protects youth from becoming infected.

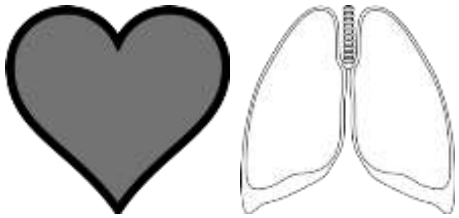
CAB Contribution
In the medical research community, we see things from a medical research point of view with everything. Our educational blinders sometimes prevent us from understanding the whole picture. That's where you come in, the CAB. The CAB helps us to see the whole picture. For example, we may study the rates of pregnancy in young HIV-infected women and be concerned about potential HIV transmission. However, CAB members can redirect our focus. They can remind us that these young people are growing into the age where they are beginning to want to start families, and that this is an occurrence that may be welcomed and considered a positive, hopeful one.

Another example is that we may be focused on the high incidence of sexually transmitted diseases in males 18 years of age. We may attribute this to the lack of circumcision. However, we may miss information about the lack of available services provided to males versus females by Medicaid. It may take you, a CAB member, to point out that there are programs in Medicaid for female reproductive health but none for males. A program is on the way for males. Someone in the community took notice. You, a CAB member, can help us get it right.

Future Goals/Plans

We plan to continue to study adolescent behaviors and how they affect our study participants' health. We are interested in the risky behaviors that some young people might participate in. But we are also interested in healthy behaviors that young people choose to practice. We also plan to spend time studying the transition of young people affected by HIV into young adulthood, and their success in finding work, continuing school, and forming relationships.

Cardiopulmonary WG



Purpose
The purpose of the Cardiopulmonary Working Group (CPWG) is to give scientific direction and support to studies of the heart and lung within PHACS. The CPWG has 10-20 experts in heart and lung medicine. Many experts also study the immune system. Some are also experts in pediatrics, biostatistics, and epidemiology.

Areas of Focus
The primary aims of the CPWG are:

- To evaluate the safety of antiretroviral (ARV) treatment given to pregnant mothers with HIV on the heart and lung health of their children; and
- To evaluate the effects of HIV and ARV treatment on heart and lung function in children born to mothers with HIV.

Accomplishments
Some of the past projects include;

- Evaluation of chemicals in the blood of children born to mothers with HIV to find out if there were signs that HIV and ARVs had affected the hearts of children born to mothers with HIV;
- Using an echocardiogram (ultrasound) test to check the heart health of youth born to mothers with HIV who took HAART and youth with HIV from the P2C2 study (most of whom did not take HAART); and
- Performing lung function tests on youth born to mothers with HIV.

To study heart health, we have completed studies that evaluated predictors of chemical markers in the blood (such as the C-reactive protein). We found associations of these markers with echocardiographic (ultrasound) measures in uninfected youth born to mothers with HIV in SMARTT. We have also shown that youth with HIV have improvement in heart functioning based on echocardiographic (ultrasound) measures. This is as compared to other studies of youth with HIV that were done when HIV was first being studied. However, there have been some differences from uninfected youth born to mothers with HIV of similar ages in AMP.

The CPWG also studied lung health. Members of the CPWG discovered an increased risk of asthma in youth with HIV born to mothers with HIV in AMP. This was compared to the uninfected youth born to mothers with HIV. This finding showed the need for more research. It also helped create a PHACS substudy, the Ancillary Pulmonary Complication of HIV Infection study. In this substudy, we did lung function testing on some AMP participants. This testing was done in order to better understand the role of HIV in asthma and other lung diseases.

The CPWG has also worked with other WGs. For example, the CPWG collaborated with the Metabolic, Nutrition, and Growth WG on a study of heart risk factors in youth aged 15 or older. This work was based on prediction models. The creation of a DNA library on PHACS participants also was endorsed by the CPWG.

Publications from the work of the Cardiopulmonary WG:

Wilkinson J, Williams P, Leister E, Zeldow B, Shearer W, Colan S, Siberry G, Dooley L, Scott G, Rich K & Lipshultz S, for the Pediatric HIV/AIDS Cohort Study. **Cardiac biomarkers in HIV-exposed uninfected children: The Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring**

for Antiretroviral Therapy Toxicities (SMARTT) Protocol. AIDS **2013**; 27(7):1099-108; PMCID:4142694.

Lipshultz SE, Williams PL, Wilkinson JD, Leister E, Van Dyke R, Shearer WT, Rich KC, Hazra R, Kaltman J, Jacobson D, Dooley LB, Scott GW, Rabideau N, and Colan SD for the Pediatric HIV/AIDS Cohort Study. **Cardiac status of HIV-infected children treated with long-term combination antiretroviral therapy: results from the Adolescent Master Protocol of the NIH multicentre Pediatric HIV/AIDS Cohort Study.** JAMA Pediatrics **2013**; 167(6):520-*7*.

Siberry G, Leister E, Jacobson D, Foster S, Seage GR III, Lipshultz S, Paul M, Purswani M, Colin A, Scott G, and Shearer W for the Pediatric HIV/AIDS Cohort Study. **Increased risk of asthma and atopic dermatitis in perinatally HIV-infected children and adolescents.** Clin Immunol **2012**; 142:201-8. PMCID: 3273595.

Patel K, Wang J, Jacobson DL, Lipshultz SE, Landy DC, Geffner ME, DiMeglio LA, Seage GR III, Williams PL,Van Dyke RB, Siberry GK, Shearer WT, Young L, Scott GB, Wilkinson JD, Fisher SD, Starc TJ, and Miller TL for the Pediatric HIV/AIDS Cohort Study. **Aggregate risk of cardiovascular disease among adolescents perinatally infected with the Human Immunodeficiency Virus**. Circulation **2013**; 129(11):1204-12; PMCID: 3991841.

Significance for the Community

In the earlier days of the HIV epidemic, a high percentage of youth who died had problems with their heart. Their deaths were often due to HIV-related cardiomyopathy (weakening of the heart muscle). So the parents of children in the PHACS study might still have concerns about whether HIV or antiretroviral (ARV) treatments could have any adverse effects on their children's hearts. Our research has shown that in the current era of treatment with combination ARV regimens, heart problems like cardiomyopathy are very rare. However, we have also shown that there are still small differences between youth born with HIV and those who are HIV-exposed but uninfected. So the PHACS community and participants may be interested in looking at whether there are any long-term associations of these small differences.

The PHACS community and participants might also be concerned about the high rates of asthma in their children. Children with asthma often miss school or other activities. They may have to take medications which add to those already taken for their HIV. So a better understanding of what the risk factors are for developing asthma and other lung conditions may help the community to change factors to lower their risk

Why the Cardiopulmonary WG?

All of the PHACS WGs have a co-leader. The Co-leader is a senior statistician or epidemiologist from the Data and Operations Center (DOC) at the Harvard School of Public Health. When PHACS was first developing the structure of the WGs, we had a small group at the DOC. Paige Williams, senior lecturer on biostatistics, became the co-leader of 4 of the 8 WGs (CPWG, Maternal Exposures, Heating/Language, and SMARTT Review Panel). Over time, we have hired new senior level research scientists. This helped Paige choose other researchers to be co-leaders of certain WGs. However, Paige is particularly passionate about heart and lung health. This is why the CPWG is one of the two working groups she continues to serve on as the co-leader.

Works in Progress

We have several concepts which are looking at heart structure and function using results from echocardiograms (ultrasounds). These tests were done in both SMARTT and AMP. One paper was just accepted by the Journal of AIDS. This paper summarizes findings of heart structure and function in uninfected youth born to mothers with HIV who took ARVs during pregnancy, aged 3-5. A second related paper has been drafted addressing the same question. However, in this paper we looked at older uninfected youth (over 6 years old) who were born to mothers with HIV. In the older youth, we

compared youth whose mothers took ARVs during pregnancy to mothers who did not. Only a few differences were found.

Another set of concepts related to heart functioning have been approved. Analyses have not yet started. One concept will look at the association of vitamin D with echocardiogram (ultrasound) measures. The other concept will look at chemical markers in the blood of AMP participants who were born to mothers with HIV. Both of these concepts required that participants' samples be analyzed to find out the level of these markers before statistical analysis can begin. We expect to begin these analyses in the Fall. Finally, we have just started analysis for a recently-approved concept. This concept is trying to come up with better measures for standardizing echocardiogram (ultrasound) parameters. This means coming up with better measures for making the process regular, and the same. The current approach is to base standardization for some parameters like heart mass on the body-surface area of each child. However, some researchers think we could improve this by using measures of lean body mass estimated from DXA scans.

One of our most exciting current projects is the PHACS Pulmonary Substudy. All of the lung function testing has been completed. We are just beginning to compare the percentage of children with asthma and other lung disease by HIV status. We are also beginning to find other risk factors for these lung conditions. This will be an active area of analysis this fall.

CAB Contribution

Several of the new proposed studies will require extra tests to be done in AMP or SMARTT. The CAB can make very helpful contributions to the design of these studies. CAB members can give input on how their children will handle the procedure and how likely they would be to participate in certain studies.

Future Goals/Plans

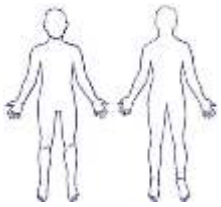
New studies will include proposals to look at children in the AMP study. We want to study heart biomarkers and vitamin D. In addition, we want to study the genetic makeup of youth born to mothers with HIV in the PHACS AMP studies. This will help us to better understand some youth are more likely to have heart or lung complications. These proposed genetic studies will take the PHACS program well into the next era of HIV medicine. It will help us look at the role of genetics in diagnosis and management of HIV infection in youth of all ages.

The CPWG will also be looking at Natural Killer (NK) cells. Certain molecules in the body bind to receptors on NK cells. People living with HIV who have certain types of one type of molecules (HLA-A) have increased chances of developing asthma. Those who have certain types of molecules (HLA-C) have a decreased chance of developing asthma. These findings suggest that NK cell immunity may have a role in HIV infection and HIV complications. The new role of the NK cells in lung complications in youth with HIV will be carefully studied in-depth.

Complications WG

Purpose

The primary aim of the Complications working group is to identify complications of HIV disease and evaluate their associations with antiretroviral (ARV) therapy. Our working group focuses mainly on the AMP participants in PHACS. We study youth born with HIV and uninfected youth born to mothers with HIV.



Areas of Focus

- Looking at trends in HIV-medication use. Looking at CD4 counts, HIV viral loads, and clinical events. Clinical events may include complications of HIV and HIV treatment;
- Evaluating long-term treatment management strategies having to do with ARV treatment failure, drug resistance and HIV tropism. HIV tropism is the cell type that HIV targets;
- Comparing the effectiveness of vaccines. Vaccines include measles, mumps, rubella, varicella, and human papillomavirus. We are looking at the effectiveness among youth born to mothers with HIV. We are focusing on finding correlates of good immune responses. This means finding immune responses that may be complementary to each other or related;
- Looking at the relationship between Tenofovir use and kidney disease;
- Estimating the commonness of liver disease;
- Looking oral health. This may include looking at the commonness of cavities and gum disease;
- Measuring the proviral load of youth who start ARV treatment early in life. This helps us to research future cure and vaccine strategies;
- Making a DNA repository for studies that use DNA;
- Collaborating with international pediatric studies to answer research questions that are relevant to babies exposed to HIV around the world.

Accomplishments

1) Immunity to Measles, Mumps, and Rubella in Youth with HIV

This abstract was presented at the 4th International Workshop On HIV Pediatrics in Washington, DC on July 20-21, 2012:

In this study, we looked at infected and uninfected youth born to mothers with HIV. We looked at blood samples to see whether youth with HIV who had received the measles, mumps, and rubella (MMR) vaccine when they were young, before they started antiretroviral therapy (ART), were still protected against these infections. We found that youth with HIV were much less likely than uninfected youth to have protection against measles, mumps or rubella. 46% of youth with HIV and 98% of uninfected youth were protected against measles. 59% of youth with HIV and 97% of uninfected youth had antibody against mumps. 65% of youth with HIV and 98% of uninfected youth were protected against rubella. We found that many school-aged youth with HIV in the US do not have protection against measles, mumps and rubella.

What does this mean?: Youth with HIV who got the MMR vaccine before starting HAART should be get the vaccines again once they are receiving HAART. Based partially on this study, these have become the official recommendations in the US.

2) Number of HIV-infected cells in the blood after controlling HIV at a young age and for a long time.

This paper has been published in JAMA Pediatrics.

In this study, we looked at how many HIV-infected cells were still present in the blood after up to 10 years of good virus control and whether if controlling the virus at a young age made a difference. We also looked to see if we can find a good marker of having only a small number of HIV-infected cells present after such long treatment.

We found that age at when you control the virus did make a difference for youth with HIV. The viral reservoirs were much smaller in those who controlled the virus from multiplying by one year of age. This was compared to those in which control happened later.

We also found that if you have a small reservoir, you were likely to also test negative for HIV antibody. The negative HIV antibody test doesn't mean the child is not infected. It means that the child has a small amount of virus infected cells present. This means that some older youth with HIV will test negative for HIV. We learned that there are long term effects on the amount of HIV hanging around after years of treatment in children.

What does this mean?: Treating youth as babies limits the number of HIV infected cells in their blood for a long time. These findings are important for knowing when to start treatment. It also helps us know how well our current treatment is doing in keeping HIV in check in youth.

3) Factors Associated with Retention of Subjects in the Pediatric HIV/AIDS Cohort Studies

This abstract was presented at the 16th *International Workshop on HIV Observational Databases in Athens, Greece on March 29-31.* 2012

It is important to prevent children from dropping out of studies like AMP and SMARTT. Children who drop out may be different from those who remain. This can make the results of the study less valid. We wanted to identify reasons that children drop out so it can be prevented. In this study, we looked at youth in PHACS to see how many left the study early. We looked at the age and reasons that youth left the study to help us understand why they left.

We studied all of the children enrolled in AMP and SMARTT. We looked at the age that children dropped out and what factors were related to dropping out.

In AMP, 451 youth born with HIV and 227 uninfected youth born to mothers with HIV were enrolled. As of October 2011, 14.9% of youth with HIV and 8.4% of uninfected youth had dropped out. Risk factors for dropping out (in addition to death, being in jail, or the site closing) were: living with HIV, an older age when starting the study, a higher caregiver education, and the region of the study site. The drop-out rate was not higher for youth with HIV when age and site region were considered. For youth with HIV, the drop-out rate was higher for those with a lower viral load at entry. For the uninfected youth, drop-out rate was higher for those with a lower household income.

In SMARTT:

2476 uninfected youth born to mothers with HIV enrolled in SMARTT, including 1240 Static and 1236 Dynamic participants. 11.8% of Static and 12.9% of Dynamic youth dropped out. Risk factors for dropping out (in addition to death, being in jail, or the site closing) were: a younger age when starting the study and site region. Youth aged 1-2 years when starting the study had a drop-out rate more than twice that of youth 5-12 years of age. The drop-out rate is highest for uninfected youth enrolled before 2 years of age. The drop-out rate for youth with HIV increases as they age through adolescence. This will make it difficult to continue to study them as they become adults.

What does this mean?: The drop-out rate is very different at different study sites. It will be important to find the reasons for these differences so that we can prevent children from dropping out. Because of the increasing drop-out rate in the second decade, we developed the AMP-Up protocol. We hope that its simpler visit schedule will decrease the drop-out rate as the youth age into adulthood.

Significance for the Community
CAB members and youth can be leaders in encouraging people to get immunizations and getting immunizations according to the most recent recommendations. Families should also be aware of local outbreaks. Families should know their own/their child's immunization history and protection against vaccine preventable diseases.

Identifying youth with HIV at an early age is important. Maintaining adherence to ARV medications is hard but it helps in reducing the number of HIV-infected cells in the blood. We need your help in finding ways in which to help with adherence to medications.

We need your continued input and support in helping to find ways to come up with strategies that would support continued participation in this and other studies.

Why the Complications WG?

- I joined the Complications group because we can learn so much, and can share with our youth, about how HIV really can become a chronic infection that when suppressed can result in healthy lives without side effects.
- I joined the Complications group because I wanted to be part of the research group that not only identifies complications of HIV infection and its treatments, but is active in pursing approaches that are designed to minimize/prevent potential complications, and increases the potential for long term health of those affected.
- I joined the working group to participate in studies of HIV and chronic kidney disease.

Works in Progress

- Genetic markers of ancestral origins (AIMS);
- Youth with virologic suppression who continue to have low CD4 counts;
- A genetic marker of chronic kidney disease (APOL-1 genotype);
- Looking at the oral health of participants;
- Looking at the frequency of viral resistance;
- ARV strategies after HAART failure;
- Immunity to varicella after immunization; and
- Markers of inflammation and immune activation and pulse wave velocity.

CAB Contribution
The CAB has a critical role in all aspects of research. From the moment of capsule development CAB input is needed to help us understand how we can improve feasibility of studies that may require clinical input. The CAB can also help us understand how we can better communicate with the CAB about the status of ongoing projects and results. This can be accomplished by:

- Active participation on conference calls;
- Asking questions about specific areas of research;

- Sharing personal experiences that may contribute to future research;
- Bringing information from this group back to the CAB; and
- Inviting Complications Group leaders to participate in CAB conference calls when there are issues/questions that need clarification.

A question back to the CAB- how do you think the CAB may contribute to the Complications WG?

Future Goals/Plans

The AMP-up protocol will allow us to learn about the course of HIV as our youth born with HIV age into adulthood. We want to know how both the infection and the youth's immune system change over time. We want to know what happens to the abnormalities we have found as the youth age. We also want to know whether any new problems develop. Specific questions include whether we will see the development of immune problems, heart problems, liver disease, or kidney disease.

Hearing/Language WG

Purpose
The purpose of the Hearing and Language Working Group (WG) is to provide scientific leadership to the PHACS project for studies of hearing, speech impairments and language impairments in PHACS.

Areas of Focus
We focus on looking at possible increased risk for hearing loss, speech or language impairments, and related impairments. We look for these problems in our participants. We also look at predictors of risk. This includes studying the safety of treatment methods. This also includes studying aspects of youth and their families that may be related to risk for hearing, speech, and/or language impairments.

Our focus areas fall under the general term "communication disorders." These are disorders that have lifelong consequences for people who have them. As noted by Robert Ruben, *"The economic basis of American society—the way in which people make their livelihoods—has undergone fundamental change during the last half of the 20th century. In the past we depended largely on manual labor. Today we depend on communication skills—hearing, voice, speech, and language. This shift, in turn, has had a profound effect on definitions of illness, and on society's expectations of and demands on the medical profession…"*
[Ruben, R.J. Redefining the survival of the fittest: Communication disorders in the 21st century. *The Laryngoscope*, 110, 241-245.]

Accomplishments
Rice, M.L., et al, 2012, Language impairment in children perinatally infected with HIV compared to children who were HIV-exposed and uninfected. *Journal of Developmental & Behavioral Pediatrics*, 33, 112-123.

Rice, M.L., et al, 2013, Evaluation of risk for late language emergence after in utero antiretroviral drug exposure in HIV-exposed uninfected infants, *Pediatric Infectious Disease Journal*, 32, 10, e406-e413
Torre, P. et al, 2012, Hearing loss in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents, *Pediatric Infectious Disease Journal*, 31, 8, 835-841

Torre, P., 2014, Submission of R01 proposal titled, Hearing Sensitivity Characteristics, in Adolescent Master Protocol (AMP) Up Young Adults

Significance for the Community
The outcomes of the research led by the WG will add to our understanding of the effects of HIV and HIV treatment on youth's hearing, speech, and language development. It will also help us understand possible risks for impairments and possible directions for treatments to reduce impairments. It will help us find information about the ways in which hearing, speech and language contribute to youth's cognitive (in the mind) and social outcomes. This will help us as youth transition into adulthood

Why the Hearing/Language WG?
The topic area is interesting and is relevant to all youth**.** Hearing, speech and language abilities closely line up with youth's social development, cognitive abilities, and ability to function well in the world. The research also lines up with their interactions with families, other youth and at school. What we talk about on our monthly calls is informative about challenges in coming up with and carrying out studies relevant to our WG. All comments and input are welcome!

Works in Progress
Rice, M.L., Frederick, A., Yao, T.J., Russell, J., Purswani, M., Siberry, G., Redmond, S. Hoffman, H., Williams, P. Risk for Speech and Language Impairments in HIV-exposed Uninfected Children at 3 and

5 Years with in utero combination Antiretroviral (cARV) Exposure. Approved February, 2014. Final data analyses underway.

Redmond, S., et al., Persistence of Primary and Concomitant Language Impairment in Perinatally HIV-infected (PHIV) Adolescents Compared to PHEU Adolescents. Concept document in progress for submission for approval.

Papers submitted and under review:
Torre, P., Yao, T.J., Zeldow, B., Williams, P.L., Hoffman, H.J., and Siberry, G.K. (Submitted). Distortion product otoacoustic emission data in perinatally HIV-infected and HIV-exposed but uninfected children and adolescents in the Pediatric HIV/AIDS Cohort Study. Pediatric Infectious Disease Journal.

Torre, P., Zeldow, B., Hoffman, H.J., Siberry, G.K., Purswani, M., Frederick, T., Spector, S.A., Williams, P.L. (Submitted) Newborn hearing screenings on human immunodeficiency virus-exposed, but uninfected infants. International Journal of Pediatric Otorhinolaryngology.

CAB Contribution
We recently requested input from CAB for questions to include in the upcoming PHACS October retreat for discussion at the WG session on the agenda. This would help us to talk about hearing, speech and language impairments of relevance to the larger PHACS group and to the community representatives. We welcome suggestions for how to better share our research findings with the PHACS community

Future Goals/Plans
Our goals include further studies of growth of children with hearing, speech, and language impairments. We also want to continue to look at how HIV treatment or exposure can affect risks for impairments and possible effects on social outcomes or school achievement.

Maternal Exposures WG

Purpose

The purpose of the Maternal Exposures Working Group is to look for factors that occur during pregnancy for mothers with HIV, which can affect the health of their children. Although transmitting HIV from mother to baby is uncommon currently in the US, we are looking at whether women's use of antiretroviral (ARV) drugs during pregnancy affect their children. To study this we focus on many factors in pregnancy. Factors include the severity of the mother's HIV disease, the ARVs they take, and pregnancy complications. We also focus on substance use, and psychological and social factors including mental health, timing of pregnancy care and income. The pregnancy outcomes we focus on include the length of pregnancy, whether the woman had a cesarean section or vaginal delivery, and growth outcomes at birth and young ages (including birthweight, length).

Areas of Focus

A major focus of our work is to see whether specific ARVs that moms take during pregnancy are associated with birth outcomes. We also want to see if they affect the children's health as they grow. We are doing studies to examine the growth of babies who were exposed to the ARVs during pregnancy. We want to examine whether the medications have any genetic effects, and to see if there are changes in how the cells utilize energy (mitochondrial function). A number of studies are going on that focus on measuring the amount of ARVs a baby was exposed to before they were born by testing the presence of these medicines in the baby's meconium (first stool) and hair. This will help us learn if babies with higher ARV levels have different outcomes than babies with lower ARV levels.

Accomplishments

Several papers have been published in the past two years:

One study (Siberry, 2012) looked to see if tenofovir use in pregnancy was associated with early growth outcomes in children. Tenofovir use was not associated with increased risk for low birthweight or being small for gestational age. However, babes whose mothers took tenofovir in pregnancy were slightly smaller on some measures of growth at age 1 year. This should be studied further. This is because it is not clear whether the differences are big enough to be of clinical significance.

Another study (Watts, 2013) examined combination ARV use and preterm birth. It found that protease inhibitor use (type of ARV) in the first trimester may be associated with increased risk for prematurity. However, this was not found for other types of ARVs, or for use of combination antiretroviral therapy use later in pregnancy.

A group of investigators (Himes, 2014) has created a new test to measure newborn baby's exposure to different ARVs detected in meconium (the baby's first stool).

Most recently, a study to see if specific ARVs were associated with birth defects is currently in press (Williams, in Press).

Significance for the Community

We feel that this research will be useful to participants because results of our studies of drug safety could help improve our knowledge of how frequently adverse outcomes occur and why. This information can be used to help prevent adverse outcomes in the future. For example, the information could shape medical guidelines for doctors to determine which ARVs women with HIV should take during pregnancy that will be safe in the long term for their children. Results from our studies can be used on how best to support women as well as their children.

Why the Maternal Exposures WG?
I joined the WG because I am very interested in doing work that supports the health and lives of women with HIV during and after pregnancy, as well as the outcomes for their children.

Works in Progress
Current concepts include the following:
-Study of epigenetic consequence of antiretroviral exposure during pregnancy.
-A study to look at birth outcomes of mothers who were born with HIV compared to mothers who got HIV in other ways. Some of the outcomes being studied include being born small for gestational age or having low birthweight and length.
-A study to determine the concentration of ARVs in the hair of mothers and their newborns.
-Examination of the effect of ARV exposure on later growth by the baby.

CAB Contribution
We would be very interested in CAB members' ideas on how to expand our research agenda. We would like to know from CAB members what their most pressing questions and concerns are about pregnancy and outcomes for mothers, their infants and children that they think would be important for us to study. We also have appreciated input from the CAB on the best way to approach mothers on obtaining small samples of hair from the mother and baby to look for evidence of ARV use during the pregnancy.

Future Goals/Plans
We would like to continue our study of the safety of ARVs and other exposures during pregnancy and early childhood. Now that we have data gathered at multiple time points in children's lives we are interested in changes over time in some of the outcomes we examine. We are also interested in a wide range of genetic and biological factors as well as factors in the children's environment. We will also be expanding our collection of data about the mother's health during pregnancy which will help improve our studies in the future.

Nutrition, Growth, and Metabolism WG

Purpose

The purpose of our working group is to try to understand how youth with HIV, or who were exposed to HIV, grow. We want to try to understand what factors might cause these youth to have problems with under or over nutrition. We are also interested in understanding why youth with HIV or who were exposed to HIV sometimes have problems with high lipid levels (cholesterol, triglycerides), have diabetes or show signs that they will develop diabetes. We are looking at why these youth might have risk factors for heart attacks or strokes at an earlier age than expected. In addition, we are evaluating how strong the bones are in these youth and if they have greater number of fractures than the average youth and if so, why that would be.

Areas of Focus

- Growth;
- Nutrition (diet); physical activity;
- Lipid levels;
- Cardiovascular disease risk;
- Diabetes;
- Bone health; and
- Maternal nutrition health

Accomplishments

1: Patel K, Wang J, Jacobson DL, Lipshultz SE, Landy DC, Geffner ME, Dimeglio LA, Seage GR 3rd, Williams PL, Van Dyke RB, Siberry GK, Shearer WT, Young L, Scott GB, Wilkinson JD, Fisher SD, Starc TJ, Miller TL; Pediatric HIV/AIDS Cohort Study (PHACS). **Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus**. Circulation. 2014 Mar 18;129(11):1204-12. doi: 10.1161/CIRCULATIONAHA.113.001978. Epub 2013 Dec 23. PubMed PMID: 24366631; PubMed Central PMCID: PMC3991841.

2: Williams PL, Abzug MJ, Jacobson DL, Wang J, Van Dyke RB, Hazra R, Patel K, Dimeglio LA, McFarland EJ, Silio M, Borkowsky W, Seage GR 3rd, Oleske JM, Geffner ME; International Maternal Pediatric and Adolescent AIDS Clinical Trials P219219C Study and the Pediatric HIVAIDS Cohort Study. **Pubertal onset in children with perinatal HIV infection in the era of combination antiretroviral treatment**. AIDS.
2013 Jul 31;27(12):1959-70. doi: 10.1097/QAD.0b013e328361195b. PubMed PMID:
24145244; PubMed Central PMCID: PMC4143250.

3: Sharma TS, Jacobson DL, Anderson L, Gerschenson M, Van Dyke RB, McFarland EJ, Miller TL; Pediatric HIV/AIDS Cohort Study (PHACS). Short communication: **The relationship between mitochondrial dysfunction and insulin resistance in HIV-infected children receiving antiretroviral therapy.** AIDS Res Hum Retroviruses. 2013 Sep;29(9):1211-7. PubMed PMID: 23742635; PubMed Central PMCID:
PMC3749716.

4: DiMeglio LA, Wang J, Siberry GK, Miller TL, Geffner ME, Hazra R, Borkowsky W, Chen JS, Dooley L, Patel K, van Dyke RB, Fielding RA, Gurmu Y, Jacobson DL; Pediatric HIVAIDS Cohort Study (PHACS). **Bone mineral density in children and adolescents with perinatal HIV infection**. AIDS. 2013 Jan 14;27(2):211-20. doi: 10.1097/QAD.0b013e32835a9b80. PubMed PMID: 23032412; PubMed Central PMCID: PMC4157938.

Significance for the Community

Our research shows that youth who were born with HIV and/or uninfected youth who were born to mothers with HIV do have some problems in their growth. We find that youth with HIV to be shorter and lighter than national norms. Uninfected youth born to mothers with HIV have higher than expected rates of obesity. We find that youth with HIV have higher rates of bone breaks earlier in life. This is as compared to uninfected youth. We find that youth with HIV have higher heart attack and stroke risk compared to uninfected youth. Overall, our findings suggest that youth with HIV or who were exposed to HIV should be followed carefully for growth and nutritional problems. They should also be followed for bone breaks and heart attack risk in the future.

Why the Nutrition, Growth, and Metabolism WG?

We have had many years interest in nutrition and growth of youth with chronic illness and how nutrition affects the child's health (in both good and bad ways). Studying HIV and nutrition in youth has shown us that if we can optimize nutrition, along with good medical care in youth born to mothers with HIV, we can help keep them healthy.

Works in Progress

We will be looking at how and why youth develop diabetes or sugar intolerance over time. We will be evaluating if a low vitamin D level contributes to low bone density in youth with HIV. We are determining how common it is for youth to have bone breaks. We will be looking at how cholesterol and other lipids change over time in youth with HIV and if any antiretroviral medications cause high lipid levels. We will be look at whether youth born to mothers with HIV have problems with obesity and high cholesterol or other lipids. We are looking at the diet of pregnant mothers with HIV and seeing if anything in their diet in pregnancy affects their baby's growth and development. We are looking at the mitochondria, also known as the "powerhouse" of the cell, to see if problems with the mitochondria can cause youth with HIV to develop diabetes.

CAB Contribution

As we follow the youth into young adulthood, it is extremely important to try to keep the youth and young adults engaged. This is because some of the problems that we are finding now may only get worse in later adulthood. Therefore, making sure the youth come in for regular check-ups will help us monitor them. The CAB can certainly help get the word out on why it is important for them to keep coming in to the clinic.

Future Goals/Plans

We will continue the work we are doing. The PHACS study is very important because it is tracking youth into the future. Because the study is doing that, we have the ability to see what might be causing the youth to lose or gain weight, have high lipid levels, be more prone to bone breaks, or develop diabetes.

Brain Development and Mental Health WG

Purpose

The Neurodevelopmental and Neurology Working Group is a team of people who are interested in the health and development of children, teenagers and young adults affected by HIV. This includes youth who were born with HIV or who are uninfected but born to mothers with HIV.

We are interested in learning how HIV and HIV medications affect brain development, learning, and the emotional-well-being of youth and young adults. We try to figure out how health and development change if HIV disease becomes more severe over time. We also realize that HIV is only one of many aspects of life that affect how well each person grows, learns, solves problems, and functions by themselves. Therefore, we try to take into account the impact of children's family and home environment. We also take into account their school life and social support, and their neighborhood and community. We try to understand how stressful life events and protective factors affect youth and how some of them cope better even though they face many challenges in their lives.

Areas of Focus

- To examine the mental health and brain development effects of HIV and/or ARVs on youth who were born to mothers with HIV;
- To study potential short- and long-term consequences of exposure to or infection with HIV and its treatment on cognition, academic achievement, and on the neurological, emotional, and behavioral development of youth over time; and
- To look at how environment and other possible factors contribute to all of these developmental outcomes.

Accomplishments

1. Kapetanovic S, Leister E, Nichols S, Miller T, Tassiopoulos K, Hazra R, Gelbard H, Malee K, Kammerer B, Mendez A, and Williams P for the Pediatric HIV/AIDS Cohort Study. **Relationships between markers of vascular dysfunction and neurodevelopmental outcomes in perinatally HIV-infected youth.** AIDS **2010**; 24:1481-91. PMCID: 2885052. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2885052/?tool=pmcentrez

2. Malee K, Tassiopoulos K, Huo Y, Siberry G, Williams P, Hazra R, Smith R, Allison S, Garvie P, Kammerer B, Kapetanovic S, Nichols S, Van Dyke R, Seage G, and Mellins C for the Pediatric HIV/AIDS Cohort Study. **Mental health functioning among children and adolescents with perinatal HIV infection and perinatal HIV exposure.** AIDS Care **2011**; 23:1533-44. PMCID: 3062576. http://www.ncbi.nlm.nih.gov/pubmed/21702707

3. Smith R, Chernoff M, Williams P, Malee K, Sirois P, Mellins C, Wilkins M, Nichols S, and Rutstein R for the Pediatric HIV/AIDS Cohort Study. **Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence.** Pediatr Infect Dis J **2012**; 31:592-598. PMC Journal – In Process. http://www.ncbi.nlm.nih.gov/pubmed/22592486

4. Sirois PA, Huo Y, Williams PL, Malee K, Garvie PA, Kammerer B, Rich K, Van Dyke RB, Nozyce M. **Safety of Perinatal Exposure to Antiretroviral Medications: Developmental Outcomes in Infants.** Pediatr Infect Dis J 2013;32:648-655.

5. Kapetanovic S, Griner R, Zeldow B, Nichols S, Gelbard HA, Leister E, Miller T, Mendez AJ, Hazra R, Malee K, Kammerer B, & Williams PL for the Pediatric HIV/AIDS Cohort Study. **Biomarkers and Neurodevelopment in Perinatally HIV-Infected or Exposed Youth: A Structural Equation Model Analysis.** AIDS **2014.** 28(3):355-64.

6. Malee KM, Mellins CA, Huo Y, Tassiopoulos K, Smith R, Sirois PA, Allison SM, Kacanek D, Kapetanovic S, Williams PL, Grant ML, Marullo D, Aidala AA for the Pediatric HIV/AIDS Cohort Study (PHACS). **Prevalence, Incidence and Persistence of Psychiatric and Substance Use Disorders Among Mothers Living with HIV.** J Acquir Immune Defic Syndro **2014**; 65:526-34.

7. Garvie P, Zeldow B, Malee K, Nichols S, Smith R, Wilkins M, & Williams P for the Pediatric HIV/AIDS Cohort Study. **Discordance of Cognitive and Academic Achievement Outcomes in Youth with Perinatal HIV Exposure.** Pediatr Infect Dis J, 2014; 33 (9): e232-e238.

8. Nozyce ML, Huo Y, Williams PL, Kapetanovic S, Hazra R, Nichols S, Hunter S, Smith R, Seage GR III, & Sirois P for the Pediatric HIV/AIDS Cohort Study. **Safety of in utero neonatal ARV exposure: cognitive and academic outcomes in HIV-exposed, uninfected children age 5-13 years.** Pediatr Infect Dis J, in press.

Significance for the Community

- These studies can help PHACS learn about children's health and development during different stages of life; and
- This research can help figure out how to best support youth and young adults so they can look forward to a healthy and happy future and avoid risky behaviors that may place their well-being in jeopardy.

Why the Brain Development and Mental Health WG?

The Neurodevelopmental and Neurology Working Group is a team of people who are interested in the health and development of children, teenagers and young adults affected by HIV. This includes youth who were born with HIV or who are uninfected but born to mothers with HIV.

Works in Progress

1. Memory substudy PH201: Participants have completed their second and final study visit as of 7-31-2014. Statistical analyses of initial evaluation have been completed; longitudinal analyses of all data are underway. Multiple papers are planned and at various stages of completion.

   Poster presented at the 18th International Workshop on HIV Observational Databases, Sitges, Spain March 27-29, 2014.

   Nichols S, Chernoff M, Hazra R, Malee K, Kammerer B, Garvie P, Harris L, Sirois P, Nozyce M, Wilkins M, & Williams P for the Pediatric HIV/AIDS Cohort Study (PHACS). Learning and Memory in Children and Adolescents with Perinatal HIV Exposure and/or Infection

2. Neuroimaging: 40 AMP participants participated in pilot Neuroimaging study in Chicago. Analyses are partially complete and two manuscripts are in final stages of preparation. Grant submission for study of large cohort expected in 2015.

3. Executive Function and Adherence: Manuscript in preparation.
   Oral presentation at the 9th Annual International Conference on HIV Treatment and Prevention Adherence, Miami, FL, Jun 8-10, 2014.

Garvie PA, Allison S, Brummel SS, Malee K, Wilkins ML, Harris LL, Chernoff M, Nichols SL for the Pediatric HIV/AIDS Cohort Study (PHACS). Roles of medication responsibility, executive and adaptive functioning in adherence for youth with perinatal HIV.

4. Viral suppression and impact on neurocognitive function during childhood. Manuscript submitted and reviewed by AIDS and is currently under revision.
   Oral presentation at the Conference on Retroviruses and Opportunistic Infections, Boston, March 3-6, 2014.

   Crowell C, Huo Y, Tassiopoulos K, Malee K, Yogev R, Hazra R, Rutstein R, Nichols S, Smith R, & Muller W for the IMPAACT 219C Study Team and the Pediatric HIV/AIDS Cohort Study. Early Viral Suppression Improves Neurocognitive Outcomes in HIV-infected Children.

5. Executive Function in Children and Adolescents with Perinatal HIV Infection: manuscript submitted and reviewed by PIDJ. Additional analyses complete and response to reviewers is in preparation.

6. Neurological diagnoses in SMARTT cohort: review of cases and data analyses are ongoing.

7. Lead exposure and ND outcomes in young children in PHACS: Plans for analysis are being finalized.

8. Relationships among HIV disease severity, caregiver and home environment, psychosocial factors and cognition upon mental health functioning of children exposed to HIV: analyses are underway.

9. Prevalence of mental health diagnoses and treatment services in youth in SMARTT and AMP – Concept sheet approved and analyses in preparation.

CAB Contribution

1. Participate in meetings/ discussions of proposed projects. Offer advice and feedback.

2. Suggest research questions of interest to CAB, family members and PHACS participants.

3. Attend working group meetings at PHACS meetings.

4. Communicate with leadership and members of the WG who will share your input with the entire WG.

5. Share what we all learn together with the members of your local CAB.

Future Goals/Plans

We hope to continue to work together to achieve the goals and aims of PHACS. More specifically, we hope to continue to study the results of past and ongoing evaluations of youth in PHACS. By doing this, we will understand the many strengths of youth and families affected by HIV. We will understand aspects of their development that may be affected by HIV and ongoing treatment. We will be able to come up with possible interventions and therapies that could support youth and their families when problems exist. We may also learn how to prevent difficulties by working together with youth and families before problems become very serious. Through our collaboration with PHACS participants and families, we hope that all youth and young adults will have better opportunities for good health and a productive adult life in the future.