GROWING UP WITH HIV

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[video transcript]

[00:00:01] Welcome to Physicians Research Network. I'm Jim Braun the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease as well as its coinfections and complications. We hope this recording of Elaine Abram's presentation Growing Up With HIV will be helpful to you and your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, practitioners, and physician assistants. Membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Elaine Abrams, Senior Research Director at ICAP and Professor of Pediatrics and Epidemiology at the College of Physicians and Surgeons at Columbia University in New York City.

[00:01:00] Well good evening everyone. I'll be talking about growing up with HIV. I'll talk a little bit about the U.S. perinatal epidemic, HIV and ART complications and conditions. I'll speak some about the brain and behavior, and then growing up and growing older with perinatal HIV infection, and sort of the state of things now. So everybody's familiar with the first cases of HIV in the early 1980s, and by 1982 we had the first cases of HIV in children attributed to perinatal HIV infection. These cases were identified in New York, New Jersey, and California, and were described as these babies were born to women who were described as promiscuous and drug addicted mothers. Yes we were very PC at that point.

[00:02:03] I met my first patient with HIV as a medical student at Harlem Hospital. He was a little boy with pneumonia who we couldn't figure out what was wrong with him. He ended up in the Bronx with a lung biopsy and was included in one of these reports. I saw him just three weeks ago at a memorial for another patient. He's 36 years old, has two kids and a wife.

[00:02:32] So by 1994, more than 16000 cases of perinatal transmission were reported and without treatment the estimated mortality rate was 35 to 50 percent within the first two years of life. Bimodal distribution of disease manifestations was described with some children having very severe early infection characterized by opportunistic infections, HIV encephalopathy, and early mortality versus a more slowly progressive form of the disease. Probably what most of those who have lived into their 30s had from the very beginning.

[00:03:16] We also, particularly in New York City, had emerging serious social issues and characterized as a boarder baby crisis and this is one of the first legacies of the pediatric HIV epidemic. Many of the
children diagnosed with HIV who were born to promiscuous and drug using women were often unable to be cared for by their parents, either due to parental death to HIV or the parents were just too ill to care for the children. And many of the families particularly early in the epidemic had substance use problems, initially heroin, IVDU, and then we have the crack cocaine epidemic. And alcohol was a chronic theme in the background. The foster care system was wholly unprepared to meet the needs of these medically fragile children and children lived for months to years on hospital wards. At Harlem where I spent many years, three to five percent of pregnant women tested HIV positive and one in ten babies born at the hospital overall had positive urine toxicology for cocaine and went immediately into foster care.

This boarder baby crisis really culminated with the very sick children with HIV, some of them living for 7 to 12 months in the hospital wards. And one little boy who spent his whole five years of life in the hospital. And ultimately, this crisis did mobilize the foster care system which slowly started to prepare families to take in high needs medically fragile children. And also the establishment of Incarnation Children's Center which was a residential facility in Washington Heights for children with HIV. But many of the young adults with perinatal HIV touched the foster care system and sort of carried this history of parental loss and social disorder.

Well the turning point in the epidemic is attributed to 1994 ACTG 076, though Karen did point out there were some suggestion of a decline before the results of the study were released. And as you all know, women who didn't qualify for treatment were randomized to placebo or zidovudine during pregnancy, at delivery, and for six weeks to their babies. The DSMB halted the study because of a 67 percent reduction in perinatal HIV transmission.

And then over the 1990s as antiretroviral treatment became more complex in nonpregnant adults moving from mono to dual to multiple drug therapy, we saw the same thing happening during pregnancy where women on treatment became pregnant and where obstetricians and HIV specialists treated pregnant women with complex combination regimens. And along with that we saw a drop in the rate of MTCT all the way down to somewhere around 5 percent by the end of the 90s.

And nowhere were the results more stunning than in New York State where we very rapidly moved scientific discovery into guidelines, into implementation, and clinical practice. So in the 1990s they were about 500 perinatal cases of HIV with a transmission rate of about 25 percent and you could follow the curve down, so by the 2000s the transmission rate was less than 5 percent. And as Karen noted in 2013, there were two cases and then about 18 to 24 month hiatus until another case in 2016. And we continue to have one or two cases in the state each year.
[00:07:47] If we look at the U.S. overall, the estimates are somewhat weak. There is no routine state surveillance and actually efforts to do any surveillance have decreased over the last decade. But the estimate, the most recent estimate, was that there were 69 new cases of perinatally acquired HIV infection in persons born in the U.S. in 2013. I also recently heard the estimate is that there are about 5000 HIV positive pregnant women annually now in the U.S.

[00:08:28] And of interest, foreign born children now account for the majority of pediatric HIV infections in the U.S. During 2008 to 2014, there were about 1500 children less than 13 years of age living in the U.S., about half U.S. born and half foreign born, and the proportion US born was 70 percent in 2008 decreasing to 40 percent in 2014. Foreign born children exceed U.S. born children in number, have exceeded number since 2011, and about two thirds are born in subsaharan Africa and then a sizable portion from Eastern Europe.

[00:09:16] Now the introduction of ART not only reduced the number of new pediatric infections, but had a fairly dramatic impact on morbidity and mortality among children living with HIV infection. Now in this first, I don't know how well you can see this, these across here are years or birth cohort bands. Children born prior to 1996, 97 to 99, 2000 to 2002, and 2003 to 2006, and this is from a collaborative cohort in the U.K. And here in pink you see AIDS, in blue death, and hospital admissions in black. And you can see fairly dramatic drops with the introduction of combination ART in all of the parameters through the mid 2000s. In this U.S. cohort, the PACTS cohort, we see a similar experience. And here we're looking at monotherapy, dual therapy, and combination therapy with a mortality rate of 20 fold difference in mortality rate as you introduce more complex antiretrovirals. This PACTS cohort with a collaborative cohort of children followed in five or six centers in New York City, New Jersey, and Atlanta. It's also noteworthy that while mortality rate has declined it's still higher, three to twentyfold higher depending on where, among children living with perinatal HIV infection compared with population norms.

[00:11:14] So most adolescents and young adults living with perinatal HIV infection in high income countries have had multiple ARV exposures. And these are data from the U.S. PHACS cohort which is another multicenter cohort of perinatally infected individuals, mostly adolescents and young adults now across the U.S. And what you can see here, these are ART at their first regimen again by birth cohorts when the children were born. And you could see overall that only about 35 percent of the youth in the PHACS cohort received combination triple drug therapy as their first regimen. The median number of ARVs received in this cohort was seven, the median number of regimens was 5. And as you could see the kids born in later years were much more likely to start their first regimen with a triple drug therapy. These young people also often have multiple drug resistance mutations, 35 to 50 percent have dual class resistance and somewhere around 15 percent have triple class resistance.
So these birth cohorts or year of birth is a marker for the availability of effective HIV therapy, as well as the age of initiation of effective therapy. And individuals with perinatal HIV often bear the legacy of late ART initiation. More recent birth cohorts have reduced rates of AIDS and death and are more likely to have viral suppression and better immune control over time than earlier cohorts. So basically the earlier you start, the better you do. You want one of those upfront kind of corrals when you're starting your race.

Now let's look at what's going on in New York City. In New York, the majority of people living with perinatally acquired HIV are in their 20s. These are data from New York City Department of Health, they estimate there are about 1600 individuals living with perinatally acquired HIV in New York City. Half male, half female. Predominantly Black and Hispanic. The median age is 22 years. And as you can see here, 62 percent of these individuals are in their 20s. And actually there are about 100 who are in their 30s. And this is the face of the pediatric perinatal epidemic in New York City. And New York is usually a little ahead of the rest of the country in the epidemic here with a little bit older, but most of the U.S. is following close behind.

So let's talk about HIV ART complications and conditions. So not unlike adults, we see complications of HIV and ART It is a multi-system impact, and we see all sorts of complications on the heart. There are metabolic complications, bone, renal, malignancies and increasingly obesity. And in many ways these are quite the same that's been described in adult populations. However they are not entirely like adults, and perhaps somewhat more complicated, because the disease and the therapy impact during critical periods of growth and development. So for example and I'll dig a little deeper in a couple of these, the effect of decreased bone mineral density in growing bones rather than shrinking or fading bones as in adult populations. Lipodystrophy disfigurement is often worse during puberty and seems to have poor recovery. And cardiovascular abnormalities detected in an earlier age suggest increasing risk for early cardiovascular disease, and this is often compounded by genetic, demographic, and behavioral risk factors associated with poor cardiovascular disease health.

So if we look at bone mineral density from a meta analysis on bone health in children with HIV infection. Can't tell what you can and can't see, but this is prevalence of low bone mineral density and these are across various countries where studies have been done. And as you can see, depending on the particular study and country, rates of low bone mineral density could be as high as 30 percent and as low as 4 percent.

Skeletal bone mass doubles during puberty and in HIV infected children, bone development is affected by both HIV and treatment. There's accelerated bone resorption, and increased bone formation resulting in low bone mass, osteopenia, and osteoporosis. And there is a hypothetical but potential increased risk of fractures. And this is a graph that just tries to point out the theoretical possibility of
what happens with perinatal infection, because you can see bone mineral density increases in
uninfected individuals all up through the 20s. And in prenatally infected individuals, you have a much
lower rate so that they start off this sort of period going into the time when they lose bone mineral
density at a much lower starting point.

Yin and colleagues did some very interesting studies looking at bone mass in individuals who
had HIV infection and looked at young men, 15 who had perinatal exposure and 15 who had acquired
HIV during adolescence. And they were all in their 20s, on ART, and they found that they all had lower
bone mineral density, abnormal trabecular plate and cortical microarchitecture, and decreased whole
bone stiffness when compared with the HIV controls. So it may not just be the HIV or the ART, but also
the having HIV during puberty and later development. And just to note that the pediatric community has
stayed away from tenofovir up through puberty because of concerns about bone effect.

We've also seen some cardiac findings. Early evidence of cardiovascular disease in another
analysis from the PHACS study, they measured the carotid intimal media thickness in 150 HIV positive
adolescents and compared them to age and sex matched controls. They were predominantly perinatally
exposed and on ART and three quarters were suppressed. And they found that intimal media thickness
was higher in the HIV positive individuals compared to the controls overall, and that it was highest in
those who were suppressed at less than 50. There was no association with activation markers.

And in another very interesting analysis from the same cohort, they looked at aggregate risk
of cardiovascular disease among adolescents with perinatal HIV using pathological determinants of
atherosclerosis in youth or PDAY. And among 165 HIV infected adolescents, about half had a coronary
artery score of greater than or equal to one and a quarter with an aorta score greater than equal to one.
Suggesting potentially an increased risk of atherosclerotic cardiovascular disease burden. There were
several predictors of this increased scores including use of PIs and history and duration of ART use.

So there are other complications which are unique to children and adolescents with perinatal
HIV and this is because the disease and therapy impact during critical periods of growth and
development, particularly infancy and early childhood as well as puberty. And these complications
include growth failure, delayed puberty, a spectrum of neurologic and developmental abnormalities
including encephalopathy which thankfully we don't see much of, and chronic pulmonary disease.

A look particularly a growth failure. Growth failure in children and adolescents with HIV. It's a
common manifestation of untreated HIV infection. It's related to the infection and opportunistic
infections, rather than the treatment. The severity of growth failure is related to the severity of HIV
disease. And effective therapy results in improvements in both weight and height. And once again,
earlier ART is associated with better growth. The age of ART initiation predicts age for height Z scores as well as age of puberty. Once again the earlier you start, the better you do.

These are data from a global collaborative cohort which includes hundreds of thousands of children and adolescents with HIV, and it looks at the age of ART initiation and height for age Z scores. And think of height for age Z scores as where the group falls on the growth curve. And it looks by different region. We are particularly interested in the red, which is the high income region. And as you can see ART start, and this is age and time point, ART start was at a young age of about two years in this cohort of kids from the high income countries and at the last visit they were somewhere around 15 years of age. If we look at where they were on their height growth curve, most of them were below the norm at ART start, and even years later at their last visit they still, while they had an improvement overall in height, they still for the most part remain below the norm. Weight gain is generally seen first followed by height, but normal height is often not attained and this can be extremely stigmatizing and is often a way you can differentiate young people who've acquired HIV infection horizontally versus those who were born with the infection.

So let's turn to brain and behaviour. From birth to 5 years of age 90 percent of brain growth occurs. The prefrontal cortex development continues well into adolescents and young adulthood and that includes complex cognitive function, personality expression, decision making skills, moderates social behavior, and enables goal directed behavior. And well into young adulthood there's also a maturation, further maturation, of the amygdala which is responsible more or less for your emotions and the corpus callosum which has the ability to help with processing information. But most of brain development occurs early on, during those first five years of life.

A large number of connections are built resulting in plasticity of the child brain through a blooming and pruning process. Normal development demonstrates reductions in grey matter throughout adolescence into young adulthood. And adolescents with perinatal HIV infection demonstrated to have reduced grey matter compared to unexposed and uninfected youth, and white matter abnormalities are also present and can be progressive despite ART.

We know that early ART improves neurodevelopmental outcomes in infants, but the impact of ART in older children is much less certain. The CHER study was a study in pediatrics that was as monumental as 076. Infants were randomized to ART versus CD4 directed A.R.T, and this is in the days before we were treating everyone. The days before START and Temprano trials. And the study demonstrated the importance of early ART before symptoms develop in infants to avert morbidity and mortality. In this sub study, 90 children who were randomized at less than 12 weeks of age were evaluated for their neurodevelopment at a year of age, and those who started ART early perform much
better or those who started later performed worse. And repeatedly, other studies have demonstrated the earlier you start for brain development and general development the better you do.

[00:26:36] When it comes to nerve developmental outcomes in older children and adolescents, the findings are much less certain. The majority of studies suggest poor performance in children and adolescents with perinatal infection, a history of more severe disease especially encephalopathy is associated with greater impairment. But many demographic and social factors likely impact the neurodevelopmental and intellectual outcomes of these young people. Across the board many studies done in many different ways, they have seen a consistent finding of deficiency in executive function. This executive function is responsible for processing speed, emotional control, working memory, attention, concentration, the ability to plan and organize. And these deficiencies in executive function may be contributing to or associated with some risk taking behaviours, including sexual risk taking, substance use, and the chronic theme of inadequate adherence to ARTs.

[00:27:54] And then onto that we add this thing called adolescence or teenagehood where aliens seem to take over the brain, no matter where your starting point. And at some point a human emerges. But there's a whole thing that goes on here that seems to be unrelated to HIV, ART, or anything that we can yet explain. And as the mother of four almost adult children, I am very confident with this anatomy.

[00:28:29] So what I am going to do now is going to give you a snapshot of some behavioral health outcomes among young adults living with perinatal HIV in New York, and share with you the results of that CASAH cohort study. It's a longitudinal behavioral health study of perinatally HIV infected and HIV exposed young people who were enrolled in prospective follow up at five New York City hospitals between 2003 and 2008. And some of you may actually have taken care of CASAH participants. And they have done comprehensive behavioral assessments every 18 to 24 months, medical record reviews, and psychiatric neurocognitive functioning assessments, and sexual and substance use behaviors, health and reproductive health outcomes, and young adult milestones. And Claude Anne Mellins is the PI that studies the Child and Adolescent Self Awareness and Health study.

[00:29:35] So just as an overview, these children were enrolled in 2003 to 2008. I'll be referring, PHIV are those with infection. PHEU are exposed uninfected. The median age at enrollment was about 12 to 13 years. The average annual household income was twenty eight thousand dollars. It's half boys and girls, primarily African-American and Latino. And overall the two groups were actually quite similar, with the exception of the caregiver type. Only 35 percent of the young kids living with HIV were living with the biological parent, compared with 70 percent of those who were exposed uninfected. We know that women with advanced HIV during pregnancy are much more likely to have babies with HIV and also at much higher risk for death, hence explaining why so few of these children actually were living with their
biological parents and speaking some to what we saw earlier in the epidemic in Harlem with many children having no families to go to.

So in 2014 to 2017 at the last visit, we had about 248 of these young people. 150 positive adults or young people, so about a hundred fewer than we started with. Mean age was 22 with a range of 18 to 28. And over the course of the study there were 11 reported deaths, 10 in the positive young people and 1 due to an accident in the exposed cohort. So the profile of the young people with HIV infection, CD4 of about 500. Half were suppressed to less than 50. Half were on integrase inhibitor containing regimen. Half on a boosted PI. 40 percent on a combination PI and integrase inhibitor. And 8 were reported they weren't taking any treatment. Interestingly 42 percent of the positives were accessing mental health services versus 20 of the exposed, and 16 percent reported being on psychotropic medications.

Okay so these are psychiatric disorders and the sides are more or less the same. Orange are the positive, yellow are the exposed. And the main thing that you can see here for any psychiatric disorder, mood disruptive or anxiety, there were no significant differences by HIV status but overall about a quarter of the cohort were diagnosed with a psychiatric disorder at their last visit. The rates of attention deficit disorder or disruptive behavior disorders were actually quite low which is very different from what we have reported in younger children living with HIV disease. If we look at substance use disorders primarily alcohol and marijuana, again we see no significant differences by color, by cohort. And about 20 to 30 percent got diagnosed with a substance use disorder. Close to 40 had reported being drunk within the last 30 days and about 20 percent were smoking marijuana daily.

Similar to what's been reported, we found lower scores of executive function in the positives compared with the exposed young people, in a series of tests that measured different measures of executive function. And many across the cohort appear to be achieving expected adult milestones across a range of domains. So 75 percent have a high school degree or a GED. About 60 percent are working or in school. 10 percent reported ever being homeless. And about half were currently in a relationship.

Outcomes overall are not dissimilar to other youth growing up in poor urban communities, and just across these more negative outcomes you can see that the psychiatric disorders, substance use disorders were same in both groups. We did begin to see incarceration being reported with about 12 to 15 percent of all of the youth reported having been incarcerated. And about 15 percent reporting homelessness. Most, if not all, had been in a relationship. Amongst the girls there were no differences again by group, about 40 percent were ever pregnant. Twenty percent were living with a child. And the males about 40 percent had gotten someone pregnant. So there are clearly well on their way to starting families.
So most behavioral health outcomes are indistinguishable by HIV status. We saw lower executive function among individuals living with perinatal HIV infection as has been previously described. We had high rates of psychiatric and behavioral disorders, but similar to others growing up under similar conditions. And for the HIV positives, they had good access and uptake to mental health services probably through their HIV programs. And these are something that it's important to keep in mind and continue. Many are achieving adult milestones suggesting resilience despite substantial challenges. But there are some troubling findings, high rates of incarceration, substance use disorders, and high rates of immunodeficiency and viremia for a substantial portion of this population. 20 percent of the participants in CASAH had CD4 less than 200 and about a third were viremic greater than a thousand copies.

So if we talk about viremia and we go back to that New York City cohort I started with, you can see rates of viral suppression by age among persons living with perinatal HIV here 0 to 15. And here we go up by year to 30 to 36. And for those of you in the back, we hover for the most part around 60 percent. So this is viral suppression to less than 200.

There are other studies that have been done that have looked at viral suppression among adolescents with perinatal HIV. This is a big multicenter cohort from the adolescent treatment networks and probably the most important columns here are children on ART. Of the 650, 80 percent were on ART and the overall rate of viral suppression was 35 percent. Nothing close to 90-90-90 or U=U.

When we looked at reported adherence across different cohorts. This was the PHACS cohort. These were different time points in the CASAH cohort. You find that about half, if not more, of participants report missed doses in the past month. When you compare that with adherence for other chronic illnesses, it's actually quite similar. So there's nothing extraordinary about not taking your ART.

And in a systematic review and meta analysis of ART adherence in adolescence, we find that viral load as a measure about 62 percent were considered adherent and using self report about 60 percent. Many factors have been associated with reduced ART adherence in young people living with perinatal HIV infection. I'm sure none of these are new to anybody in this room and there are not particular to adolescents. Very few interventions have been demonstrated to improve adherence among adolescents. There's been a suggested benefit of a number of tools or approaches including using devices, cell phone support, individual and group support and motivational interviewing, conditional cash transfers. But none of these have had large clinical trials that have demonstrated improved adherence that's maintained over time. Adolescents imply the importance of improving knowledge, better formulations, additional adherence support, earlier disclosure. But then again, they're the ones who often aren't taking the medications. And given the success of long acting contraceptives in many
adolescent populations, there's great interest in long acting ART formulations whether these could bend the curve or potentially impact treatment outcomes in this population.

[00:39:58] So finally let's just chat briefly about transition. Transition can be interpreted in two ways. One is moving from pediatric and adolescent health services to adult services, and the other is the whole concept of transitioning from childhood into adulthood. The health service transition requires greater self efficacy and independence, and it's also a critical point where kids are at risk for falling out of care. And the transition into adulthood means achieving adult milestones and leading life with greater independence. What we've seen is that there is a suggestion of an uptick in mortality with aging of this population and increasingly it seems to be attributed to untreated, not untreatable, HIV infection.

[00:40:57] In an analysis from the UK they evaluated mortality among about a thousand perinatally infected youth over 13, and some of these young people were cared for and had transitioned into adult clinics. The median age of transfer is 17. And they found that mortality, when they looked at age and where they were cared for, increased fairly dramatically amongst those who were older and cared for in the adult clinics. And amongst those who died, they had very complex medical and psychosocial issues. 82 percent of the deaths were associated with poor adherence and advanced HIV disease, mental health diagnoses, and two deaths to suicide. And while it is I think anecdotal, there's a rising whisper within the pediatric community about many young people who while can be treated, they're giving up on living with HIV disease and stopping their treatment and dying. So it's a sort of arc to the curve that we hope we can reverse in some way moving forward.

[00:42:14] So in conclusion, the introduction of potent combination ART transformed the pediatric HIV epidemic in the U.S. We have an aging population of adolescents and young adults with chronic multi-system disease. Years of birth or birth cohort and timing of ART initiation are major determinants of disease course and current health status. The social legacy of perinatal HIV infection, poverty, early neglect, family losses, HIV stigma likely impacts these long term outcomes as well. Psychosocial and behavioral health outcomes are not dissimilar to youth growing up in poor urban communities. We see strong evidence of resilience for many individuals, you've seen by their milestones and things they're able to accomplish as they move forward into adulthood. There's clearly an ongoing need for supportive social and mental health services. High rates of viremia, immunosuppression, drug resistance and inadequate adherence warrant concern and attention. And mortality rates remain comparatively high, possibly elevated, in early adulthood. And thanks!

[End]