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ELIMINATION OF MOTHER-TO-CHILD TRANSMISSION OF HIV: THE FINAL FRONTIER?

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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 her members in the diagnosis, management, and prevention of HIV disease as well as infections and complications. We hope this recording of Karen Beckerman's presentation, 'Elimination of Mother to Child Transmission of HIV: The Final Frontier' will be helpful to 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 education for physicians, nurse practitioners, and physician assistants. Membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Karen Beckerman, Director of the Outpatient High-Risk Obstetric Clinic and Antepartum Services at Bronx Hospital Center and Associate Professor of Clinical Obstetrics, Gynecology and Women's Health at the Icahn School of Medicine at Mount Sinai in New York City.

[00:01:05] Welcome everybody. So I thought I'd start with the front cover of Science magazine from August 1995 which is just before I went into the lab actually at UC San Francisco at the Gladstone Institute. And I kept this cover, believe it or not, on my bulletin board on my little carole in the lab and every morning I looked at it and I have to say it's what kept me going for many days, months, and years. And what I wanted to start with was an inspiring statement that I found in the last few months as I was reading and trying to gather data for tonight's talk. I always admired the New York State Department of Health, but man now they are my absolute number 1 heroes because what they said in the recent HIV Epidemiology Profile that was actually issued a year and a half ago, "despite having the heaviest HIV burden in the country, New York State has made Ending the Epidemic a goal that is at once aspirational." So that means now it's OK for us to hope for that but it's not only can we hope for it, we can expect to achieve it. And for anybody who worked in this area in the 80s, that really is unimaginable and even in the 90s or first decade of the 2000s. Man I really never had the courage to say that out loud. And now we have a State Department of Health with the largest number of HIV infected people in the United States saying this and they not only said it, they said it a year and a half ago. And I'll just remind you that what elimination means, the CDC has defined that for our purposes as transmission rate of less than 1 percent of HIV exposed infants and less than one case of mother to child transmission per 100000 live births. And we'll think about that as we see different data pop across that screen.

[00:03:24] This evening we'll be looking at the global view and talk about the phenomenon of pandemic ignition of HIV transmission. We'll talk about social and health comorbidities in New York City and we'll try to think about where have we arrived, where we are going. And we'll go through a number of case reviews and I'll propose a new paradigm of elimination, as it's defined care. And that is through couples testing, treatment as prevention, and PEP and PrEP for women. And then finally we're going to ask 'is pregnancy different?' when all of these things are concerned.

[00:04:03] So let's just look at the global view and spend one slide thinking about what has been going on. The pandemic obviously began many, many decades ago. It started to be detectable in the 1980s. We have data that we will go over from the 1970s from other cohorts where data was being collected, in particular the San Francisco Hepatitis B cohort. And we see this rapid uptick in transmission and of the number of new cases every year right up until about the year 1998 or so when it begins to level off. And interestingly it started to level off before antiretroviral treatment, and really there was not measurable antiretroviral treatment globally available until about the early 2000s. I took 2005. Globally there was a leveling off, just like in other cohorts there also was a leveling off. And this was something that was observed in the 80s by my colleague Steve Bacchetti and others in San Francisco, where they saw in this Hepatitis B cohort in a collection of specimens that remained available well into the HIV pandemic that the early spread of HIV at first had a very sort of flatline rapidly accelerated and then leveled off around 1983/84 in San Francisco. And that the Chicago MACS cohort, which was an HIV identified cohort, followed the men prospectively also showed that epidemic in Chicago had leveled off about a year and a half or two later. So what does this tell us? Well what we're going to be talking about and coming back to through the hour is that there is a certain aspect about primary infection, infectivity, and contagiousness that really gets the pandemic going. And I'm going to propose to you that that may be what got the got everything started and what allows for very rapid spread among naive populations. But it's also affecting us today here in New York City and most especially in the Bronx.

[00:06:32] So just to review the concept of high contagiousness during primary infection, if we look at this log scale over here. And don't forget that for every increase in log, we're talking about a tenfold increase. During primary infection there were estimates in the 1980s and 90s that perhaps 10 to 30 percent of encounters could result in a transmission event. At the same time during the asymptomatic period this number was much much lower, maybe one in a thousand to one in 10000 encounters. And it again gets higher in the pre AIDS or AIDS phase of the infection.

[00:07:14] So what does this mean internationally? Well it means a lot of things. And one of the things that it means is that prevalence is not the same as incidence. In other words, the number of people living with HIV is not necessarily exactly the same or exactly reflected in the number of people who are getting infected every year. And we just see very different situations in different countries. And this is just taken from, again a very interesting set of articles and reviews in Science magazine from 2018, about two weeks ago. And this illustrates a couple of things. First if you look at the orange sort of polygon here and try to see through this spider web of data, you'll see that orange is the United States. And what the United States has going for it is that among industrialized countries it may be higher than most industrialized countries, but basically it's about the same as Russia in terms of the number of people living with HIV infection. However in Russia the number of people newly infected is far greater. So that infection is growing rapidly. Also in the United States, we have a higher number than those in Russia receiving treatment. And we have a comparatively vanishingly low number of transmissions to children or mother to child transmission, also low in Russia but not quite as low. And then all of this is dwarfed by the epidemic in some parts of sub-Saharan Africa, South Africa most notably has the most

people in the world living with HIV and yet their new infections is lower than Nigeria, and most especially their newly infected child rate is far, far lower than Nigeria. And one of the interesting points made in this collection of reviews is that the epidemic is absolutely exploding in Nigeria, a country in Western Africa where it was not thought to be a particular hotspot until recent years.

[00:09:33] So then if we move on, I'd just like to welcome you to the Bronx and show you that the Bronx is not today what I grew up thinking of it and seeing. And if any of you toured the Bronx in the 70s and 80s, you might have seen a picture like this indulging in air flying sports and water sports. And it was still a place though where you could dress up and go to see your grandma on a Sunday and things have changed very much now. It's a much safer place, it's bustling, and what we know is that the life expectancy in the Bronx has increased by 12 years overall. But what is still going on in the Bronx? Well Bronx is still the center of New York City for the lowest income, the highest poverty prevalence. And if you take this map and use the same colors, the same shades in the same location you can have an overlay of HIV prevalence in the Bronx, HIV death rate in the Bronx, and HIV acquisition rate. And this is an interesting slide that came out in the wrong orientation, but you can also overlay this onto food availability and a so-called supermarket need index. And it's highest in the Bronx of all of New York City where 25 percent of those surveyed report no fresh fruit or vegetables in the last 24 hours. And all of that is just reflected in the leadership that the Bronx takes in obesity and overweight and the prevalence of diabetes in the community. And I'll just tell you that the prevalence of diabetes in the women that we care for in our clinics, and especially in my high risk obstetric clinic, is far higher than 10 percent.

[00:11:25] But what's going on in New York State and New York City? We see that new diagnoses are falling, death among persons with HIV/AIDS is falling. And still however the number of persons living with AIDS and HIV continues to rise, and we see that people both without AIDS and with AIDS contribute to the overall figure. And there is still a considerable number of people with significant immunodeficiency who are still living with the disease. And here is our HIV prevalence slide and you just see the focus particularly among families and women in the Bronx even higher than Brooklyn, which is the other hot spot in the city, and Upper Manhattan of course I have to add.

[00:12:10] Okay this is the very famous slide of what happened over the last 30 years in terms of pediatric infection. Many of you have seen this already. And I'll just note that it's remarkable, it's always been remarkable to me, that the number of children being born with the virus peaked in 1992 which is a little bit before the introduction of the 076 results in 1994. And that it was on a slope downward well before the peak of the deaths in New York City, which occurred in about 1996 or so, and started following that curve almost as if the revolution that occurred in maternal to child transmission anticipated the revolution in HIV deaths and a decline in deaths due to antiretroviral therapy that became available in 1996. I will tell you that my prejudice has always been that while the 076, zidovudine alone prophylaxis, initially broke that curve and started reducing mother to child transmission. It was the appearance of protease inhibitors and the concept of combination antiretroviral

therapy that has driven it even lower to levels that we now know are considerably less than 1 percent of exposed infants being infected with the virus.

[00:13:41] So this is also from the article in Science magazine that I mentioned. And just to review what the latest trends in the United States are, that for newly infected children we have a problem actually in Florida. Which in some ways is very surprising because my experience at least with the Florida Department of Health is that they were always right on top of reporting to the antiretroviral pregnancy registry, that it's a state that has a great mechanism for tracking infection, tracking infection in pregnant women, and transmission to children. So I don't really understand what's happening in Florida except that in 2016 they had 20 infected kids as opposed to New York State's I think two infected children. And we also see here that New York State, if you look at it these colors have changed a little bit, but New York State is gray right here. Our seroprevalence rate is higher than Florida's, and yet if you go here you'll see our transmission rate to children is significantly lower. So lots of things to think about within the United States, it's not just Africa where women are transmitting to babies and it's also not just Florida. We still have two cases from 2016.

[00:15:09] So just to get us thinking and wake up a little bit after those spider web curves. True or false? Pregnancy is a good time to give as few antiretrovirals as possible because of potential maternal and especially fetal toxicity? You all can raise your hands or you can just make a little note on your notepad or in your brains. But who would go for true, anybody? OK. Either you're too scared or too shy or you know the truth, because the answer to this is absolutely false. All right. The greatest risk to an exposed fetus is, and this may be my opinion but I think it's widely held, the virus itself poses the greatest risk to an exposed fetus. Transmission risk is directly proportional to maternal viral load. The antiretroviral pregnancy registry now has greater than 20000 prospective reports, that means pregnancies that are registered before the outcome is known and followed prospectively and the outcome for the baby, birth defects in the baby, are reported back to the registry. And no birth defects signal has been detected in the registry to date. We'll talk about a potential birth defects signal reported recently with the drug dolutegravir, and we'll talk about that in a few minutes. And in addition, pregnancy pharmacokinetic studies consistently suggest that, when necessary for certain medications, doses need to increase not decrease. In other words pregnancy is not a time to stop and it's not a time to reduce dosages because of fears of exposure to mom or to fetus.

[00:16:56] The other important point about organogenesis is that most women do not know they're pregnant until the most important period of organogenesis is over. So that if you are really worried about birth defects in the women of reproductive age that you care for, you want to have them on a regimen that you would feel comfortable with them continuing right through the early part of pregnancy, if they should become pregnant. The other thing you want them to have is a plan to institute if they should get pregnant, what to do.

[00:17:31] So let's just review our experience with antiretrovirals historically. And I'm presenting here data from San Francisco where at the Bay Area Perinatal AIDS Center, as it was known in those years, we found our patients had a very rapid uptake, as most other places in the United States, of the 076 regimen which was zidovudine monophylaxis both anti-partum, intra-partum, and during the neonatal period. Our clients adapted this readily but they maxed out in 1996, and by 1997 they actually were more interested in taking two drugs than one drug. Even then, women who became informed and educated about the possibilities of resistance were more eager to be on two drugs than one drug. And then by 1998 we knew that the zidovudine lamivudine combination could also be associated with induction of resistance. We had patients opting away from that and either going on zero or one or two or three medications, and in 1998 that was either a protease inhibitor or the non-nuc nevirapine. And by 1999, we had very few women electing to take zidovudine alone, and we even had some women on for drugs as we became very, very passionate about getting maternal viral load as absolutely low as possible before delivery.

[00:19:07] And what did we find? Well, no one was as surprised as us when by 1999 we saw that we had, among women who had zero drugs, 25 percent transmission. For one drug we had about a five percent transmission. And I'm not making these numbers up, they really were this tight. And for two drugs we had one transmission of a baby treated only intra-partum via mom. And then for three drugs we had absolutely no transmissions at all. And it was quite amazing to see how over the next 20 years these data folded out or came out and so that finally by 15 years later we knew that this absolutely did represent the truth. It wasn't just a coincidence that three drugs or more was best for baby and was best for mom.

[00:20:06] We also were really surprised that when we were able to control maternal viremia or actually when we paid attention to maternal viremia and treated as needed to control it, that we also were able to prevent or there was no transmission even associated with prolonged ruptured membranes. Even when ruptured membranes in labor were for more than 24 hours, which we know without prophylaxis or without maternal treatment that 24 hours is associated with significantly elevated risk of transmission. In our small group it was 40 percent.

[00:20:41] So what challenges then if we had gotten that far by 1999 and 2000, what challenges have slowed our progress in the actual elimination of maternal to child transmission? Well stigma was there then, it's there today, and it'll be there tomorrow. We have a lot of erroneous assumptions about ourselves, about our country, and about our clients. And we have missing fail-safe safety mechanisms. And I would propose to you that near misses for transmission both to women and to their children go undetected and are likely too many to count, particularly in high endemic areas such as the Bronx. And we have not, at least in the United States, fully recognized the risks and dangers of testing out. And what I mean by that is getting a negative HIV test and then assuming by both caregivers and clients that there is no more problem. 'I'm HIV negative I don't have to worry about my baby getting HIV, I don't have to

worry about any of that with my pregnancy.' So that we have a long way to go with that and especially if we expect to get to true final frontier elimination of maternal to child transmission, we're going to have to be addressing the risks that women who have tested out face.

[00:22:07] We also have yet to shift our focus from a newborn to the risk that a family might have, for a family at risk. And we have to use our imagination in many different areas. So where are the misses or the not so near misses? In other words, where are the direct hits that we've experienced in the last 20 years? The first two cases that I'd like to just share with you come from San Francisco. We had no transmissions actually in our cohort at Bay Pack after 1994, but there was transmission among women who were not registered in Bay Pack. 1996 an 18 year old did not receive HIV testing because she was married and considered to be low risk by her midwife. She had a normal vaginal delivery at term and her baby was healthy until about three months of age, with increasing irritability and a persistent cough. In 1998 another woman was a health care professional herself receiving care at the University Medical Center, she had early care. Her health was excellent, she was offered and declined HIV testing because she stated she had no risk factors and her obstetrician didn't offer it again because she was a colleague and said she had no risk factors. She had a normal delivery of a normal weight baby who presented with failure to thrive at six months of age. What did both of these babies have and how their mothers were diagnosed with HIV? Both of these babies had pneumocystis carinii, now known as jirovecii pneumonia. And as you all may know, mortality rates from PCP in the first year of life were about 50 percent in those days.

[00:24:07] So we've taken care of a lot of those problems. And these data show that women living with HIV aware of their status prior to delivery as of 2015 was up to 96 percent. So 96 percent is great. It's a lot better than it was in San Francisco in 1996 to 1998, but it's not 100 percent. And we'll just be studying this slide again later in the evening, but we'll just see that we've had not only a decrease in the number of exposed births overall but the the number of HIV infected births. So that with this red line here in this particular chart, you can't even find the red marks down here. And that even though this chart goes to 2014, by 2015 actually in New York state it seems to be true that there were no infected babies born. So are we out of the woods forever? Well hardly. We were back up to 0.5 percent transmission and 0.8 percent transmission in subsequent years. So the question that I think we ask ourselves tonight, are we facing a final frontier of elimination of transmission or not? Is this just going to linger on and keep going and is there anything we can do about it?

[00:25:34] So for case number three, in 2007 we had a woman present in active term labor from an outside hospital at our very, very busy unit in the Bronx. Not the hospital I'm at currently. And she was a 28 year old multip with prenatal care at another facility, she was brought in by ambulance complaining of active labor, leaking fluid, and she openly stated she had been HIV infected for five years was taking combination therapy and told us that her last viral load was about two weeks before and had been undetectable. Admission labs were sent and an expedited HIV test confirmed that she was indeed HIV

positive and she was allowed to deliver rapidly, and she got a little bit of intravenous zidovudine for one hour and she delivered after three pushes. Her baby was a healthy girl and received the zidovudine elixir for a month, and sadly at one month was found to be HIV-1 PCR positive and a viral load, it turned out that had been drawn when mom delivered, was 40000.

[00:26:49] The next case at another institution was in 2009 where a patient in prenatal care, never missed a visit, presented with a fever of unknown origin late in pregnancy. She had flu like symptoms and was admitted actually. We were very worried about her. She was taken care of, she was cared for by infectious disease and maternal fetal medicine services. Everything was negative. Tuberculosis, TORCH titers, legionella, HIV antibody was negative and she was discharged home on hospital day 8 after being afebrile for two days, feeling much better. And the maternal fetal medicine service sent an HIV viral load on the day of discharge. She came in a couple of weeks later, at 37 weeks, and had her baby. And she had been feeling much better at that time. She had a normal delivery. Again this was a healthy boy and the boy went home with his mom on day of life number two per routine. She did not receive expedited testing at the time of her delivery because she had just had a negative test two weeks before and the admitting physician did not review her labs with the fine tooth comb, but apparently did just look for abnormal labs. The infant PCR sent to the Department of Health in Albany returned at 600000 copies per mil on day of life 16. So here is a true hit, it's not a near miss and a perhaps preventable case of vertical transmission.

[00:28:30] So how could we have missed this at our high volume, experienced hospital? Why? And what other tests could we have done? So another multiple choice question, what did we miss? 'A. The patient was promiscuous, unreliable, and could not be trusted' and I think more people than we might like to acknowledge would say this. Or 'B. The providers never asked about her partner's status.' Or 'C. There is there is no way to detect a new HIV infection during the six week window period.' Or 'D. The providers never checked lab results.' And so different combinations of that and we'll just cut to the chase. She wasn't promiscuous, she had no missed visits, she was very reliable. She came to the hospital and stayed in that miserable place for eight days while we couldn't figure out what was going on. And so the B, we never asked about her partner's status and never asked if her partner might come in for testing. And it would have been possible to detect an early infection perhaps with her, either at the time she was in the hospital or at the time that she presented to labor and delivery, and indeed her viral load was detectable during the admission but nobody ever checked it. So providers never checked the viral load they sent and we missed preventing that transmission and helping this mother.

[00:29:58] So case number 5 in 2013, a little more recent. Client of ours had a negative third trimester HIV antibody test, which is the test that we use routinely in our prenatal clinic and we employed since 2013. She was a 31 year old gravida 5 para 2 at 34 weeks gestation, she had eight prenatal visits and her antibody test had been a negative when she registered for care and at 32 weeks. She presented in strong labor, again with a preterm baby and she was in labor for three hours. She was five centimeters

dilated and she was allowed to deliver. Her son was healthy with Apgar's typical of a preemie at 1740 grams and he was admitted to the neonatal intensive care unit for mild respiratory distress, ruled out sepsis, and CPAP which is a form of respiratory support very commonly used in neonatal care in this day and age, was continued till day of life 5. His septic work up was negative meaning that most preemies receive septic work ups to make sure they don't have a bacterial infection, and he was then admitted to the stepdown preemie nursery as a so-called 'grower.' And on day of life 18, we received the call from the New York State Department of Health with a positive HIV antibody from newborn screening. And the HIV-1 quantitative PCR returned seven days later for the baby at a 120000 copies per mil.

[00:31:47] So since then what have we changed? So since 2015 at our hospital women are asked at their first prenatal visit if they know the HIV status of their partner. And pregnant women presenting in the third trimester identified as at risk are tested with expedited HIV antibody tests, HIV antibody screen, and viral load. I would add that we might also do this earlier in pregnancy if the situation warranted and we'll talk about a situation where that was warranted. And we strongly recommend PrEP and post exposure prophylaxis during pregnancy. So the question that I'd like to ask, and I don't think we have a clear answer is, 'is this enough? And what more can we do?'

[00:32:39] So case number 6, 2017. This family is relatively new to the Bronx. This was a 36 year old gravida 6 para 4 who presented as planned in labor at term. She was referred from an outside clinic where she had been late to care. She was a recent arrival from West Africa with her four children, finally able to join her husband who had been living in the Bronx since 2010 and he had been visiting his family once every year back in West Africa. Her prenatal labs were unremarkable. She had hemoglobin AA, in other words no sickle trait, she was not terribly anemic and her HIV antigen antibody test was negative. Her initial exam in labor was 4 centimeters, she rapidly progressed into active labor. She was interviewed and her past medical history was thought to be unremarkable. Her prenatal records were available and reviewed, and per the 2015 protocol she was asked again by the admitting physicians if she knew her partner's HIV status and she stated her husband was HIV negative. Her labor and delivery admission labs, including HIV expedited antigen antibody, and I will say that our providers on Labor and Delivery are very liberal in ordering these labs and we get them on just about everybody who has not been recently tested or comes in from an outside facility. At any rate, she delivered a very healthy girl without complications four hours later and was successful yet again as she had been with all her other children with exclusive breast feeding and went home with her baby on postpartum day number two. She had an uneventful newborn and postpartum follow up, the baby was doing well and she missed no visits. The newborn screen was unremarkable and negative. And at three months postpartum, interestingly mom presented to the adult emergency department with the worst headache of her life with flu symptoms. The headache was so bad that the emergency room doctors actually got an MRI, which was negative. MRI of the head which was negative. And other parts of the evaluation all was negative. And she was sent home with presumptive influenza and Tamiflu, and she got better after about a week.

[00:35:17] Three days later her baby, about three months old at that time, presented to our pediatric emergency department with fever, irritability, and poor feeding. The evaluation was significant for persistent cough, the chest x ray was negative, and the baby was sent home on Pedialyte. The baby did not improve and the parents went to different clinics all over northern New York City as they remained concerned and could not get any answers anywhere, until they went actually to Harlem Hospital. And at Harlem Hospital they felt the baby was so ill it was time to go to University Hospital, and pediatric infectious diseases and pulmonary medicine were consulted in that emergency room. And after admission, the baby deteriorated rapidly. Began to desaturate and required intubation and the aspirate from the endotracheal tube was sent for analysis. And this is what was seen. Anybody know what those are? Yeah, but now it's called pneumocystis jirovecii. And I have to say, I thought I would never again see a mother diagnosed with HIV by the finding of pneumocystis in her baby. But here we are. And here is what our challenges are going to be now as we face what this really is, maybe a final frontier in maternal to child transmission.

[00:36:53] So the baby was intubated for three to four weeks. The mother was found to be HIV infected, the father was found to be HIV infected. And what did we miss at this high volume, experienced hospital yet again? Why did we miss it? And what other tests could we have done? These answers are much more difficult, but I would propose to you that our patient or her son could have received an HIV-1 quantitative PCR in the emergency department that might have been positive in either of them, although most clinicians that have reviewed this have said that they would have been very hard pressed to send that on either of them. One person I've heard say 'well a terrible headache and a negative MRI, you really should do an LP and as part of the LP you'd send HIV testing with that.' But most people I know, including myself, are not sure that we would have made a different call in the emergency department but maybe we have to start thinking differently. Particularly for patients or families from areas of other different seroprevalence than New York or the United States.

[00:38:08] Maybe something to think about as a universal couples testing protocol. This would be easy to implement. I can tell you in my clinic I see fathers all the time with my patients, they come in for genetic testing, they come in for blood typing, for Rh status. It's not a big deal right now to justify testing a father in a prenatal clinic. Maybe this is something that we need to think about. And so that really the answer to this multiple choice question is any of the above might have caught this baby before he was near death with a pneumocystis.

[00:38:47] And let's just review this thought of the high contagiousness during the primary infection and I'll just put to you right now that this risk of transmission doesn't just apply to naive populations in the early stages of the pandemic or a local spread, but that it's going to apply to our HIV uninfected women who are pregnant or anticipating pregnancy. And that if they have a partner who has a primary infection or if they develop a primary infection during pregnancy or breast feeding, that baby is highly, highly likely to become infected. And just for those of you who like to play with numbers, what this log scale

when translated to absolute numbers, you see that we have infectivity per one per 10000 contacts. Again we're looking at 30 percent possibly as high in the period of primary infection. We're looking at 1 to 10 per 10000 encounters in the asymptomatic period and a bit higher in the pre-AIDS period.

[00:40:00] So case number 7, our last case for the evening. 'I'm going to tell you the truth.' This was a routine new O.B. registration visit at nine weeks and the evaluation was notable for a confirmed pregnancy. And when her midwife asked her about a history of sexually transmitted diseases or if she knew the status of her partner, this young woman stated that she was going to tell the truth and with her partner present she disclosed that he was living with HIV since birth. He confirmed this and stated also that he had not taken antiretrovirals since released from Rikers three months previously. Their most previous encounter at that presentation was two nights before, so with her new O.B. labs an expedited fourth generation antigen antibody test was negative. Viral load was sent and was cooking, and the expedited test was negative. She was started on NPEP as per CDC guidelines, and a week later her viral load was back at 43 copies per milliliter. Two weeks later she returned saying she had only missed two doses and by that time interestingly her viral load on NPEP, 3 drugs Truvada plus raltegravir twice a day, her viral load was 30 and her antibody was positive but her antigen P24 was negative. And she continues in prenatal care at present on meds with lots of challenges ahead.

[00:41:44] So here are our five most recent cases in the last 10 years and this is what we're facing now and this is what I would say, this is our sort of final frontier. And we have to redefine risk and think of new ideas of what is risk as we're down to zero or two cases of transmission in New York state a year. We have a big risk among infection during pregnancy or breast feeding. We have a risk of infection and transmission among transmitted partners. And we know from Susan Allen's work in Africa that most new transmissions or most transmissions to women occur from their longstanding partners. And in those populations that Dr. Allen studied, those were married couples where the husband was infected. Women identified as HIV infected who are able to purchase participate in care and take combination therapy are at extraordinarily low risk of transmission to their infants. And women testing out are at significant risk of transmitting HIV to their babies, should their partners be infected and should the woman herself become infected. And sadly we've now learned in the Bronx that breastmilk transmission can occur anywhere in the world and primary maternal infection carries markedly increased risk.

[00:43:23] So what about pregnancy? Well pregnancy is a big risk. Unprotected sex is required for pregnancy, once pregnant women are at increased risk of infection. And women testing out are at significant risk because they rightly or wrongly believe that they've tested out and might be safe. And I'll just share with you Renee Heffron's data that was presented at CROI this year which is that in pregnancy, even though data has been conflicting in recent years about whether HIV infectivity increases with pregnancy, she did a meticulous study of HIV infectivity per sex act and found that yes indeed in her cohort of women who high adherence to condom use, in fact only 10 percent of acts were

without condoms, there was significantly increased risk of transmission per act. And that this risk of transmission was highest during the postpartum period.

[00:44:26] So how can uninfected pregnant women at risk of HIV infection protect themselves? Known partners can maximize their adherence, maximize their own adherence to early treatment. Uninfected women who know or learn they are in an ongoing discordant relationship can engage in safer sex practices and begin PrEP, nPEP, or when it's certain that they're not infected PrEP itself. And they can also adopt safer sex practices, undergo antibody and viral testing, and if negative at 28 days graduate from nPEP to PrEP. So in case you haven't heard and all of us in this room have heard many times, undetectable means untransmissible. And there is no reason to believe that doesn't apply to pregnancy also.

[00:45:18] So I'll just move forward. And just mention the CDC 2016 nPEP guidelines in the area of negligible risk. It's interesting to me that how many women want nPEP, even though they may have negligible risk of acquisition, and they'll go ahead and take the antiretroviral prophylaxis even though their transmission may be thought by caregivers to be very minimal risk or their exposure may be minimal risk. And I'll just say that in terms of the CDC guidelines, the case by case determination seems to be the rule rather than the exception for pregnancy or potential exposures during breast feeding. And these are cases where we just have to individualize, we have to work hard at educating our clients so that they can make the best informed decisions.

[00:46:21] Just a few obvious notes about nPEP, only for potentially exposed persons without HIV infection. Routine assessment with HIV antigen antibody test kits, should take less than 60 minutes. And if results are not available at an initial evaluation, a decision can be based on the assumption that the exposed person is not infected and in three days when more information is available we can regroup and re strategize to accommodate the information that we gain. So the guidelines for nPEP do say that it's for infrequent exposures and within 72 hours of evaluation. And that PrEP is more appropriate after completion of nPEP in 28 days. And these are the guidelines, they're available. It's important to stay up to date with them as they're reissued periodically. And I don't think I need to review them here.

[00:47:27] To move ahead to the safety of antiretrovirals in pregnancy, just to stress. No signal in the antiretroviral pregnancy registry which has an open web site easy to access, easy to get their data. And that there is a recent potential signal with dolutegravir from Botswana. Many of you have heard that already. And the risk of neural tube defects in that cohort, carefully assembled in Botswana with very large numbers, appears to have increased among women exposed to dolutegravir in the early first trimester from one in a thousand to one in 100. That's a tenfold increase. It also is important for patients or women who may present after a dolutegravir exposure that they understand that the likelihood that their newborn has a normal spine and a normal neural tube is still 99 percent, so that she

can gain even further reassurance with prenatal testing and ultrasounds. And the details regarding study methodology of the dolutegravir findings are not yet available and we'll know a lot more this summer after the AIDS Conference in Amsterdam. So it's also easy to keep up with the dolutegravir advisory at AIDSInfo.NIH.gov, and I'm sure that will be updated frequently.

[00:48:59] So couples testing has been successfully shown in demonstration products all over the world in the 1990s. In India it can be modeled in a low seroprevalence setting, or in Rwanda in Zambia in high seroprevalence with studies of discordant couples. And like I said, partners can be easily tested and I would just ask you that if this couple in sub-Saharan Africa are brave enough to be asked then to come in for testing for the health of their family, I think that couples in the Bronx are just as committed and just as courageous to come in for that testing. We have to create environments of blame-free disclosure, couples testing allows for mutual disclosure and can only be effective, I would put to you, if it's on site and a routine part of prenatal care. It should not be an exceptional part of prenatal care.

[00:49:59] And I'll just end with looking at this lovely cascade of care in New York State and suggests that it may not look as good as we think it does. If our numbers instead of estimated infected persons, if we start with estimated exposed persons. And as we see here many people in the gold bars are not tested recently and particularly our patient's partners are not tested recently. And if you look at the top bar here, estimated HIV exposed uninfected women could be quite high. If you look at the top bar. And we don't know how high it is and we don't know how high the number of these women exposed are, and that we have a long way to go to identify them and protect them from infection so that our near misses are missed. We don't know how much that is, and further investigation might help us understand that so we can deal with that.

[00:51:03] And I just like to celebrate the college graduation of two girls who are very dear to many of us in San Francisco. These girls were born in 1994. I don't know which one peed on me right away as she emerged from her mom's belly, but one of them sure did. And it took their mother great courage. She was a highly educated woman with great suspicion of AZT prophylaxis. She looked at the data. She decided that she didn't want to take AZT, but she would. The girls were uninfected and they both graduated from UCLA last week. So that's a big deal. And we have a lot to be thankful for, but we have a lot more to do because we want to make every baby in the Bronx and everywhere else have the same sort of outcome.

[00:52:04] So we know how to prevent transmission of HIV to newborns. We know how to prevent sexual transmission. We know how to prevent IVDU transmission, but we can't prevent what we don't see and don't try to find. And I'll just in contrast to the very positive mother baby picture that I started with in 1995, this is what Science magazine put on their cover last week. And this is of a 12 year old infected child with a devastating sequelae of HIV infection and that whole front part of that issue of

Science magazine is to where we aren't doing so well with that infection. And Nigeria is one country that they focus on, and it's not to point fingers at Nigeria. It's to point fingers at all of us and what we can do to work very hard of not letting what's happening in Nigeria happen anywhere else. So I'll stop there. Thanks.

[End]