Research and Long-term Follow-Up as part of the strategy to eliminate perinatal HIV transmission in the US

Why include research?

We know how to interrupt perinatal transmission:

1. give HAART to women to reduce viral loads
2. do a C. Section for those women who still have a viral load over 1,000
3. Give AZT or other prophylaxis to the infant

Why include research?

- We believe that most perinatal transmission is the result of pregnant women not receiving the interventions that would interrupt transmission

- Do we really need to invest in further research?

Why include research?

- Residual transmission still occurs – 200-300 cases per year – not all are because women did not receive the needed intervention
- Interventions to interrupt perinatal transmission must be as safe as possible; we have not succeeded if we interrupt transmission at the cost of injury to the mother or child
  - Unanswered questions related to women's health
  - Unanswered questions related to child's health

Research questions

- Women's health questions
- Child's health questions
- Questions about transmission despite interventions to interrupt it – residual transmission

Women's health questions

- Incident infection (discussed later)
- New antiretroviral medications
- Interactions with other medications
- Stopping or continuing HAART after pregnancy

New antiretrovirals during pregnancy

- As the epidemic continues, new medications are developed in response to the need for them
- Resistance to old medications drives a need for new classes of medications (integrase inhibitors, for example) and new generations of medicines of old classes
- Safety, side effect and tolerability issues drive new medicines so they be once-a-day or less

New antiretrovirals during pregnancy

- Women will enter pregnancy on these new antiretrovirals
- Each new drug will need to be assessed for safety to make sure there are no adverse effects and for pharmacokinetic levels to make sure the women are receiving adequate levels
- The IMPAACT p1026s study provides a framework to do this

Medication Interactions

- Although providers can often be quite hesitant to prescribe medicine during pregnancy, some medications (antihypertensives, for example) are frequently prescribed
- Studies of interactions between these and antiretroviral drugs are essential
- In addition, interactions between antiretroviral drugs and medications commonly prescribed primarily for women must be studied

To be or not to be (on HAART)

- A major question that persists is whether women who start HAART as prophylaxis during pregnancy should stay on it or not
- The current standard of care is that all people who start HAART **treatment** stay on it forever, but does this apply to women who are taking it as prophylaxis to benefit their babies?
- The **PROMISE** (PROmoting Maternal Infant Survival Everywhere) study will answer this.

Child Health concerns

- Adverse effects of in utero ARV Exposure
- Long-term follow-up
- The C word (last but not least)

Child Health Questions

- Over the past 25+ years, many cohort studies have looked at questions of infant health.
- Most studies have not found significant negative effects of antiretroviral drugs on children who were exposed to them
- Even with some currently licensed drugs, however, there are concerns.

Concerns about *in utero* ARV Exposure

- Efavirenz has been associated with congenital nervous system defects in fetal animals and in reported cases in humans (unknown causality)
- AZT has been associated with mild anemia
- Combination AZT/3TC was associated with nervous system problems in a French study
- Tenofovir has been associated with bone and growth problems in animals

The DES story

- Diethylstilbestrol was a drug approved by the FDA in 1947 for prevention of miscarriages
- In 1971, a link between *in utero* DES exposure and vaginal cancers in girls was noted Subsequently, other genital tract changes were also found to be related to DES

- Because the adverse effect did not occur until the exposed daughter reached puberty, it could not be identified until she was followed long-term

Long-term follow-up studies

- WITS, PACTS, PACTG 219c all closed
- Ongoing studies include PHACS (US) and NISDI (South and Central America).

- Other studies and registries do not provide long-term follow-up – especially lacking are studies looking at follow-up of children exposed to the newer antiretrovirals

Residual Transmission

About 200-300 cases of perinatal HIV transmission occur in the United States each year

It is suspected that the vast majority of the cases occur because of a failure to implement the interventions that we know to be successful

Colleagues at the CDC and HRSA are leading the efforts to improve case-finding and access to services to minimize these

Residual Transmission despite Care

- Incident infection during pregnancy and postpartum
  - Breastfeeding
- Genital Tract Viremia
- Resistance
- Other reasons for transmission

Incident Infection

- Incident infection in this case refers to women who become HIV-infected during pregnancy or postpartum
- This is a very substantial concern, as it impacts the health of the mother (who became HIV-infected) and the health of the infant (who is at high risk of transmission)

Risk of Incident Infection

- Pregnant women are known to have had unprotected sex – obviously

- Changes in the epithelia of the female genital tract appear to make pregnant women more susceptible to HIV infection

So how can we protect women and their babies?

Preventing incident infection

- Topical Microbicides
- PrEP

We now have proof-of-concept trials that show that topical microbicides and oral PrEP agents can prevent HIV infection

It is essential, and the Microbicide Trials Network is doing this, that such products be tested for safety in pregnant and breastfeeding women

Reducing perinatal transmission in the setting of Incident Infection

- Infants whose mothers were infected while pregnant are at very high risk for becoming infected
- This is presumably because of the high viral load spike during acute infection and because the women are unaware of being infected and thus will not be offered prophylaxis
- In both Botswana (high prevalence area) and New York state (low prevalence area), studies have shown significant percentages of the HIV-infected infants were born to newly-infected mothers

Reducing perinatal transmission in the setting of Incident Infection

- What research questions can help us reduce incident infection transmission?

1. Which women need more than 1 HIV test during pregnancy? (Who to test?)
2. What are the best strategies to time HIV testing for pregnant women (When to test?)
3. Can tests be developed and implemented that will detect acutely infected women, or (How to test?)

Who to test?

- Should we re-test all women who report having had unprotected sex/high-risk activity since 6 weeks before her previous test?
- Should we retest all women who live in an area that exceeds a certain prevalence rate?

When to test?

- There is a lag time between when someone turns positive and when someone tests positive - the current easily-available tests will show someone's HIV status anywhere from a couple of weeks ago to 3 months ago
- The ideal is to reduce a newly-infected woman's viral load as quickly as possible during pregnancy, but the absolutely essential time-point is at delivery.
- Antiretrovirals will take several weeks to months to reduce viral load to undectectable

When to test?

- Given that the number of times we can test a woman is limited, when do we test and retest?

1. As early as possible during each trimester?
2. Once as early as possible, once at 28 weeks?
3. Once as early as possible, once at 34 weeks?

With early testing, our intervention has more time to take effect, but we will miss later infections

With later testing, we capture more infections but our intervention will be less complete

How to test?

- Currently available inexpensive tests look for antibodies, which means there is a delay in when a person turns positive and when she tests positive.

- Can we develop and test new available and affordable assays that will identify someone as positive right after she is infected?

How to Treat?

- For women identified as HIV-infected late during pregnancy, what is the regimen that will bring the viral load down the most rapidly (before delivery)?

- IMPAACT P1081 will address this question in the next 2-3 years.

Breastfeeding

- Why include breastfeeding when we advise all HIV-infected women in the US not to breastfeed?
- Because women who test HIV negative during pregnancy are advised to breastfeed, and if they get infected during breastfeeding, they are at a high risk for transmission.
- Should we offer HIV testing during breastfeeding?

Genital Tract Viremia

- While the presence of an “undetectable” viral load clearly reflects a very low risk of transmission, it doesn’t reflect no risk
- The viral load is the amount of virus in the blood. While this usually correlates with the viral load in the genital secretions, it doesn’t absolutely rule out having virus in the genital secretions

Resistance

- Many women have had multiple HAART regimens, and may have resistant virus.
- If a virus is resistant to all HAART regimens, what kind of prophylaxis should she get?
- Should she change her regimen a few weeks before delivery to try to decrease viral load?
- If so, when?

The C Word

CURE

Keys to a cure

The best chance of a cure would be in a person who:

1. has acute infection, with minimal or no development of reservoirs, and
2. has uniform virus leading to susceptibility to antiretroviral and immune-based therapies

Cure Research in Infants

- Reservoirs are cell lines that reproduce very infrequently – once every few decades. Since most of antiretroviral activity takes place during its reproduction, HIV that gets into these reservoirs is extremely hard to eradicate.
- These reservoirs develop very shortly after a person is infected.
- Since the timing of infant infection is usually known, infants may be the one group that can be treated BEFORE these reservoirs are established

Cure Research in Infants

- Since infants received all their virus from their mother and different subpopulations of virus may have different abilities to cross the placenta, an infant's viral population is likely to be very uniform.
- This uniformity may make it especially sensitive to antiretroviral and to immune therapies, and thus easier to cure.

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