Highlights & What’s New in the Recommendations to Reduce Perinatal HIV Transmission in the United States

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Objectives

By end of presentation:

- Participants will be aware of the HIV perinatal rates in Broward county
- Participants will understand the clinical management necessary to reduce perinatal transmission
- Participants will know the testing required of infants to determine infectious status
- Participants will know resources available for HIV positive pregnant women and exposed infants
STATE OF HIV IN BROWARD
Broward County by HIV Cases
Highest rates in State

- Women living well with HIV
- Youth becoming infected at alarming rates
- Perinatally HIV infected youth becoming adults
- With 1 in 78 Broward residents being HIV positive, more couples are discordant
Advances in HIV Medicine

- Survival rates nearly equal to general population
- More than 30 drugs available
- Single tablet regimens- 6 and soon 7
- PrEP
- Rapid tests
- Long-acting medications
# Drug Abbreviations

<table>
<thead>
<tr>
<th><strong>NRTI</strong></th>
<th><strong>PI</strong></th>
<th><strong>Entry Inhibitor</strong></th>
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<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Atazanavir (ATV)</td>
<td>Enfuvirtide (ENF, T-20)</td>
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<tr>
<td>Didanosine (ddI)</td>
<td>Darunavir (DRV)</td>
<td>Maraviroc (MVC)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Fosamprenavir (FPV)</td>
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</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Indinavir (IDV)</td>
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</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Lopinavir (LPV)</td>
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</tr>
<tr>
<td>Tenofovir DF (TDF)</td>
<td>Nelfinavir (NFV)</td>
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<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>Saquinavir (SQV)</td>
<td>Raltegravir (RAL)</td>
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<tr>
<td></td>
<td>Tipranavir (TPV)</td>
<td>Elvitegravir (EVG)</td>
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## NNRTI
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

## Pharmacokinetic Enhancers
- Ritonavir (RTV, /r)
- Cobicistat (COBI)

## INSTI
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)
Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2010 — United States and Dependent Areas

Note: Data have been adjusted for reporting delays and missing risk-factor information.
- Intervention led to a 66% reduction in risk for transmission ($P<0.001$)
- Efficacy was observed in all study subgroups

Results of Pediatric AIDS Clinical Trials Group 076
Infants Exposed to OR Infected w/ HIV/AIDS

TOTAL Perinatal HIV Exposures → 325
Perinatal HIV Infected → 7
Total= 332

Pediatric HIV (not AIDS) → 7
• 1 Hillsborough
• 1 Lee
• 1 Leon
• 1 Marion
• 1 Okaloosa
• 1 Orange
• 1 St. Lucie

Pediatric AIDS→ 0

Data as of 10/28/2016
Data as of 4/5/2017

Infants Exposed to OR Infected w/ HIV/AIDS

TOTAL Perinatal HIV Exposures ➔
Perinatal HIV Infected ➔

• 1 Broward

Pediatric HIV (not AIDS) ➔

Pediatric AIDS ➔
Your Federally funded Expert Resource for any HIV exposed or infected infant, child, youth, woman or family in Broward County.

Comprehensive Family AIDS Program (CFAP) at CDTC
## CFAP’s Perinatal Transmission

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</thead>
<tbody>
<tr>
<td>Total # of positive women served</td>
<td>962</td>
<td>907</td>
<td>978</td>
<td>1021</td>
<td>1017</td>
</tr>
<tr>
<td># of pregnancies</td>
<td>101</td>
<td>89</td>
<td>131</td>
<td>108</td>
<td>100</td>
</tr>
<tr>
<td># of babies</td>
<td>82</td>
<td>72</td>
<td>90</td>
<td>98</td>
<td>62</td>
</tr>
<tr>
<td># of positive babies</td>
<td>2*/**</td>
<td>1*</td>
<td>0</td>
<td>1**</td>
<td>0</td>
</tr>
<tr>
<td>Transmission rate per year(CFAP %)</td>
<td>2.4 (1.2)</td>
<td>1.4 (0)</td>
<td>0</td>
<td>1.0 (0)</td>
<td>0</td>
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</tbody>
</table>

- *Not in CFAP until delivery
- **In CFAP less than 20 days prior to delivery
CFAP PERINATAL TRANSMISSION SUMMARY

987 babies delivered in past decade

13 babies infected in past decade = 1.3 % Transmission

6 babies infected while pregnant mother in CFAP care = 0.61 % Transmission
FL 2016 HIV Perinatal Transmissions

- Substance abuse- 2 (Miami)
- Prolonged ROM (Hillsborough)
- No PNC and no Rapid test (Okaloosa)
- Substance abuse/Mental illness (Miami)
- Late diagnosis, no ART in pregnancy/ Infant ZDV only (Leon)
- Non- adherent and PROM (Orange)
- Non- adherent/substance abuse (WPB)
Missed Opportunities
CFAP follows 9 positive children born since 2007

- Substance abuse (3)
- Mental Health (4)
- Lack of Prenatal Care (3)
- Stigma (1)
- Lack of HIV testing or follow up of results (2)
- Lack of adherence (3)
ANTEPARTUM CARE
Management of HIV positive woman

- Preconception Counseling
- If pregnant, HIV TEST and other routine pregnancy labs.
- If pregnant and HIV +:
  - CBC, RNA PCR, CD4, CMP, Genotype, other routine pregnancy labs. Monitor every trimester.
  - Start ARVs if not already on them; leave ARVs if on them unless Efavirenz and less than 6 weeks pregnant.
### Preferred 2-NRTI Backbone Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>ABC/3TC</strong></td>
<td>• Available as FDC, can be given once daily</td>
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<tr>
<td></td>
<td>• Potential HSR: ABC should not be used in patients who test positive for HLA-B*5701 because of risk of hypersensitivity reaction</td>
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<tr>
<td></td>
<td>• Not recommended with ATV/r or with EFV if pretreatment HIV RNA &gt;100,000 copies/mL</td>
</tr>
<tr>
<td><strong>TDF/FTC or TDF + 3TC</strong></td>
<td>• Available as FDC, can be given once daily</td>
</tr>
<tr>
<td></td>
<td>• TDF has potential renal toxicity, use with caution in patients with renal insufficiency</td>
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</table>
## Preferred PI Regimens

<table>
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<tr>
<th>Regimen</th>
<th>Comments</th>
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</thead>
</table>
| ATV/r + preferred 2-NRTI backbone | • Once daily administration  
• Extensive experience in pregnancy  
• Maternal hyperbilirubinemia     |
| DRV/r + preferred 2-NRTI backbone | • Better tolerated than LPV/r.  
• PK data available. Increasing experience in pregnancy  
• Must be used twice-daily in pregnancy. |
### Preferred Integrase Inhibitor Regimen

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<th>Comments</th>
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</table>
| RAL + preferred 2-NRTI backbone | - PK data available and increasing experience in pregnancy.  
- Rapid viral load reduction.  
- Useful when drug interactions with PI regimens are a concern.  
- Twice-daily dosing required. |
Moved off Preferred List

- Alternative Regimens
  - ZDV/3TC
  - Lopinavir/r
  - Efavirenz
Alternative Regimens:
Clinical trial data demonstrate efficacy in adults but experience in pregnancy is limited, data are lacking or incomplete on teratogenicity, or the drug or regimen is associated with dosing, tolerability, formulation, toxicity, or interaction issues.
# Initial ART for ARV-Naive Pregnant Women

## Alternative NRTI/NNRTI Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Advantages</th>
<th>Additional Notes</th>
</tr>
</thead>
</table>
| ZDV/3TC | • Most experience for use during pregnancy  
          • Available as FDC. Twice-daily administration  
          • Higher risk of hematologic toxicity | |
| EFV + preferred 2-NRTI backbone | • Birth defects in primates; risk in humans is unclear.  
                                    • Postpartum contraception must be ensured.  
                                    • Preferred regimen in women requiring coadministration of drugs with significant interactions with PIs or the convenience of co-formulated, single-tablet, once-daily regimen. | |

**Note:** May be initiated after the first 8 weeks of pregnancy.
## Alternative PI Regimens

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<th>Comments</th>
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</table>
| LPV/r + preferred 2-NRTI backbone | • Abundant experience and established PK in pregnancy.  
• More nausea than preferred agents.  
• Twice-daily administration. Once-daily LPV/r is not recommended for use in pregnant women. |
### Alternative NNRTI Regimen

<table>
<thead>
<tr>
<th><strong>RPV + preferred 2-NRTI backbone</strong></th>
<th><strong>Comments</strong></th>
</tr>
</thead>
</table>
| • RPV not recommended with pretreatment HIV RNA >100,000 copies/mL or CD4 cell count <200 cells/mm³.  
• Do not use with PPIs.  
• PK data available in pregnancy but relatively little experience with use in pregnancy.  
• Available in co-formulated single-pill once daily regimen. |
Maternal and Fetal Monitoring during Pregnancy

- Monitor HIV RNA:
  - At the initial visit (AI)
  - 2-4 weeks after initiating or changing ARV drug regimens (BI)
  - Monthly until HIV RNA is undetectable (BIII)
  - At least every 3 months during pregnancy (BIII)
  - HIV RNA should also be assessed at approximately 34-36 weeks’ gestation to inform decisions about mode of delivery and about infant ARV prophylaxis (AIII).
Maternal and Fetal Monitoring during Pregnancy (3)

- **Monitor CD4 count:**
  - At initial antenatal visit (AI).
  - At least every 3 months during pregnancy (BIII).
  - Can monitor CD4 count every 6 months in patients on cART with consistently suppressed viral load who have CD4 counts well above the threshold for opportunistic infection risk (CIII).
Genotypic resistance testing should be performed at baseline in all HIV-infected pregnant women with HIV RNA levels >1,000 copies/mL (A1).

In individuals with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).

Tests should be performed whether the women are antiretroviral-naive or currently on therapy (AIII).
1 in 78 Broward Residents are HIV infected

SERODISCORDANT COUPLES
Reproductive Options for HIV-Concordant and Serodiscordant Couples (1)

For concordant (both partners are HIV infected) and discordant couples:

- Expert consultation is recommended so that approaches can be tailored to specific needs (AIII).

- Partners should be screened and treated for genital tract infections before attempting to conceive (AII).

- The HIV-infected partner should attain maximum viral suppression before attempting conception (AIII).
Reproductive Options for HIV-Concordant and Serodiscordant Couples

For discordant couples:

- The HIV-infected partner should be receiving combination antiretroviral therapy and demonstrate sustained suppression of plasma viral load below the limits of detection (AI).
  - cART for the infected partner may not be fully protective against sexual transmission of HIV.
- Periconception administration of antiretroviral preexposure prophylaxis (PrEP) for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission. (CIII)

The utility of PrEP for the uninfected partner when the infected partner is receiving cART and has a suppressed viral load has not been studied.
Repertive Options for HIV-Concordant and Serodiscordant Couples (3)

Discordant couples with HIV-infected women:

- The safest conception option is artificial insemination, including the option of self-insemination with a partner’s sperm during the periovulatory period (AIII).
Reproductive Options for HIV-Concordant and Serodiscordant Couples (4)

Discordant couples with HIV-infected men:

- The use of donor sperm from an HIV-uninfected male with artificial insemination is the safest option (AIII).

- When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or in vitro fertilization should be considered (AII).

- Semen analysis is recommended for HIV-infected males before conception is attempted to prevent unnecessary exposure to infectious genital fluid when the likelihood of getting pregnant is low because of semen abnormalities (AIII).
Reproductive Options for HIV-Concordant and Serodiscordant Couples (5)

- Periconception PrEP
  - Very few data to date on periconception PrEP; studies under way.
  - Infected partner should be on ART with fully suppressed HIV viral load.
  - Once daily tenofovir/emtricitabine is currently FDA approved for PrEP; CDC recommends 1 month before and 1 month after conception attempted.
  - Couples should use condoms at all times except during periovulatory intercourse.
  - No reported increase in congenital anomalies for children whose mothers were exposed to tenofovir or emtricitabine during first trimester.
Reproductive Options for HIV-Concordant and Serodiscordant Couples (6)

- Baseline laboratory testing for HIV infection, renal function, pregnancy, and chronic HBV infection should be done before initiating PrEP.
  - HBV-uninfected individuals should be vaccinated.
  - Monitor for potential side effects such as renal dysfunction and clinical toxicities.
  - Conduct pregnancy test every 3 months.
  - Test HIV-uninfected partner for HIV every 3 months; if result is HIV positive, discontinue PrEP to minimize drug resistance and refer for treatment.
INTRAPARTUM CARE
Intrapartum ARV Therapy/Prophylaxis

- Scheduled cesarean delivery at 38 weeks’ gestation (compared to 39 weeks for most indications) is recommended for women who have HIV RNA >1,000 copies/mL near delivery (AI).

- Women who present in labor with unknown HIV status should undergo expedited HIV testing (AII). If positive result:
  - Do a confirmatory HIV test ASAP and initiate maternal (IV ZDV) and infant (combination ARV prophylaxis) ARV drugs pending results of the confirmatory test (AII).
  - If the maternal confirmatory HIV test result is positive, infant ARV drugs should be managed as discussed under Infant ARV Prophylaxis (AI); if the maternal confirmatory result is negative, maternal and infant ARV drugs should be stopped.
Transmission and Mode of Delivery

For pregnant women receiving cART with HIV RNA levels <1,000 copies/mL:

- Scheduled cesarean delivery is not routinely recommended due to the low rate of perinatal transmission in this group and the potential for increased complications following cesarean delivery in HIV-infected women (AII).

- C-sections performed for standard obstetrical indications should be scheduled for 39 weeks’ gestation (AII).
Other Intrapartum Management Considerations (1)

- The following should generally be avoided because of a potential increased risk of transmission, unless there are clear obstetric indications:
  - Artificial rupture of membranes (BIII).
  - Routine use of fetal scalp electrodes (BIII).
  - Operative delivery with forceps or vacuum extractor and/or episiotomy (BIII).
Other Intrapartum Management Considerations (2)

- Consider the ARVs a woman is receiving when treating excessive postpartum bleeding resulting from uterine atony:
  - If receiving a cytochrome (CYP) 3A4 enzyme inhibitor (e.g., a PI), use methergine only if no alternative treatments are available and the need for pharmacologic treatment outweighs the risks. If methergine is used, it should be administered in the lowest effective dose for the shortest possible duration (BIII).
  
- If receiving a CYP3A4 enzyme inducer such as NVP, EFV, or etravirine, additional uterotonic agents may be needed because of the potential for decreased methergine levels and inadequate treatment effect (BIII).
Postpartum Care (5)

- Breast-feeding is not recommended for HIV-infected women in the United States (AII).
  - cART dramatically reduces but does not eliminate breast milk transmission.
  - Safer infant feeding options are available.
  - Other potential risks include toxicity to the neonate or ARV resistance should transmission occur due to variable passage of ARV drugs into breast milk.

- Health care providers should routinely inquire about premastication, instruct HIV-infected caregivers against this feeding practice, and advise on safer feeding options.
CARE OF THE NEONATE
Infant Antiretroviral Prophylaxis (2)

- ZDV, at gestational age-appropriate doses, should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery (AII).

- Infants at higher risk of HIV acquisition should receive prophylaxis with ZDV and NVP. This includes infants born to women who:
  - received only intrapartum ARV drugs (AI), or
  - have not received antepartum or intrapartum antiretroviral drugs (AI), or
  - have received antepartum ARV drugs but have had suboptimal viral suppression (>1000 copies/mL) near delivery (BIII).
Infant Antiretroviral Prophylaxis (3)

- The prophylaxis regimen for infants at higher risk of HIV acquisition:
  - ZDV (4mg/kg given twice daily) for 6 weeks combined with
  - 3 doses of NVP 8mg or 12mg in the first week of life
    - 1st dose at birth
    - 2nd dose 48 hours later
    - 3rd dose 96 hours after the second dose.
- Begin regimen as soon as possible after birth.
- Some experts use 3TC 2mg/kg orally twice daily for high risk infants.
Initial Postnatal Management of the HIV-Exposed Neonate (1)

- Obtain a CBC with differential as a baseline evaluation before initiation of ARV prophylaxis (BIII).

- Birth HIV RNA or DNA PCR- for determination of intrapartum infection and opportunity for enhanced prophylaxis through available trials
Diagnosing HIV Infection in Infants (2)

- Virologic tests should be performed at (All):
  - 14-21 days,
  - 1-2 months, and
  - 4-6 months.

- Virologic test may be performed at birth:
  - If mother did not have good virologic control during pregnancy, or
  - If adequate follow-up cannot be assured.

- Confirm a positive HIV virologic test with a second virologic test on a different specimen.
Diagnosing HIV Infection in Infants (3)

- HIV infection in an infant is diagnosed by 2 positive virologic tests on separate specimens.
  - Some experts prefer to use HIV DNA assays (rather than HIV RNA) for infant HIV diagnosis, although the effects of maternal or infant ARV exposure on the sensitivity of virologic testing—particularly HIV RNA assays—are unknown.
Diagnosing HIV Infection in Infants (4)

- HIV infection is excluded:
  - **Presumptively** by 2 negative virologic tests, 1 at age ≥14 days and 1 at age ≥1 month.
  - **Definitively** (in non-breast-fed infants) by 2 negative virologic tests, 1 at age ≥1 month or older and 1 at age ≥4 months.
  - Many experts confirm negative status by antibody testing at 12-18 months (HIV antibodies can sometimes occur at or beyond 18 months).
Postnatal Management of the HIV-Exposed Neonate: Prophylaxis and Immunizations

- To prevent *Pneumocystis jirovecii* pneumonia (PCP), prophylaxis should begin at age 4-6 weeks, after completion of ARV prophylaxis (AII).
  - Unless HIV infection can be presumptively excluded

- Evaluate and treat infants as indicated for transmittable maternal coinfections identified through history or physical evaluation.

- HIV-exposed infants should follow the routine immunization schedule.
Infant Feeding Practices and Risk of HIV Transmission

- To prevent HIV transmission, HIV-infected women in the U.S. should not breast-feed.
  - Safe infant feeding alternatives are available.
  - ART may decrease free HIV virus in breast milk, but cell-associated virus remains and may pose transmission risk.

- Feeding with premasticated foods may transmit HIV. Health care providers should routinely inquire about premastication and
  - Instruct HIV-infected caregivers to avoid this practice, and
  - Advise on safer feeding options (AII).
• All positive babies should **start cART** as soon as possible.
• ART prophylactic doses should be stopped and treatment doses with triple ARVs started.
• Limited choices of ARVs available in this age group so consult an HIV specialist for drug options and dosing.

**ART of HIV Infected Infants**
Close follow up of HIV –RNA PCR until undetectable, initially in 2 weeks then monthly until suppressed and then every 3 months is recommended.

- Monitor T cells every 3 months.
- Monitor CBC and chemistries including liver and renal function 2-4 weeks after initiating ART medications and every 3 months thereafter.

Monitoring an HIV Infected Infant
• PCP prophylaxis with Folate antagonists (eg, TMP-SMX) continues until 12 months of age. Assess CD\textsubscript{4} count and if <15 % continue PCP prophylaxis
• Counsel on possible sulfa allergy symptoms
• Additional prophylaxis for Toxoplasma and Mycobacterium may be necessary based on CD\textsubscript{4} count.

PCP Prophylaxis
Vaccination of HIV Infected Newborn

- All routine Pediatric Vaccines can be used.
- No OPV
- Nasal Flu vaccine is controversial
  Inactive Flu vaccine is okay
- If HIV infected, then MMR and VZV based on CD4 count
  - >15% for MMR
  - >24% for VZV
Getting to ZERO Maternal to Child Transmissions
• P1115 <48HRS OF BIRTH (CURE Study)
• P1112 <72 HRS OF BIRTH (VRC01 vaccine)
• P1110 Raltegravir in infants of HIGH RISK pregnancy
• P1081 Various ART combos for Moms identified late in pregnancy: 28-36 weeks
• SMARTT study
• ZIKA study

Ongoing CDTC HIV Research
Getting to Zero

PREP
Why PrEP?:
Reduce HIV Transmission


PrEP Knowledge Base for HIV Prevention: Heterosexual Women

**Partners PrEP** (KEN, UGA)
- Daily tenofovir DF
- Daily emtricitabine/tenofovir DF

**iPrEx** (NA/SA, THA, ZAF)
- Daily emtricitabine/tenofovir DF

**PROUD** (GBR)
- Daily emtricitabine/tenofovir DF

**Ipergay** (FRA, CAN)
- Intermittent emtricitabine/tenofovir DF

**TDF2** (BWA)
- Daily emtricitabine/tenofovir DF

**Bangkok Tenofovir Study** (THA)
- Daily tenofovir DF

**CAPRISA 004** (ZAF)
- Vaginal tenofovir gel

**FACTS 001** (ZAF)
- Vaginal tenofovir gel

**FEMPrEP** (KEN, ZAF, ZWE)
- Daily emtricitabine/tenofovir DF

**MTN/VOICE 003** (ZAF, UGA, ZWE)
- Vaginal tenofovir gel
- Daily tenofovir DF
- Daily emtricitabine/tenofovir DF

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BWA: Botswana; CAN: Canada; FRA: France; GBR: Great Britain; KEN: Kenya; NA/SA: North/South America; THA: Thailand; UGA: Uganda; ZAF: South Africa; ZWE: Zimbabwe.

PrEP Safety: Sexual and Reproductive Health Outcomes

- No evidence indicated that PrEP led to risk compensation in sexual practices, such as decreased condom use or more sexual partners
- PrEP does not appear to affect the effectiveness of hormonal contraception
- Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy

HIV infections can be stopped with PrEP and with Treatment of Positives

HIV infection in infants in the US is preventable

Any positive case is a sentinel event and needs to be evaluated accordingly.

Broward County has a stellar network of care for prevention of mother to child transmission- use your resources!
ARV Pregnancy Registry (APR)

- Report cases of prenatal exposure to ARV drugs (either alone or in combination) to:

  ARV Pregnancy Registry
  Research Park
  1011 Ashes Drive
  Wilmington, NC 28405
  (T) 1-800-258-4263
  (F) 1-800-800-1052

  http://www.APRegistry.com
Broward County Resources

- Ryan White Part D Program (CFAP)-
  - Nadia Graham 954-728-1036
  - Dr. Puga 954 548-0859
- Multiple HIV knowledgeable Perinatologists and Obstetricians
- Pediatric HIV Providers in Broward County
- HIV Clinical Trials for Pregnant Women
  - IMPAACT Study Coordinators 954-728-1125
- Broward County Perinatal Network
  - Yvette Gonzalez (formerly Rivero)
References

- www.floridahealth.gov
- Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States Last Updated: October 26, 2016
- Ryan White CareWare database, accessed March 31, 2017
Websites to Access the Guidelines

- http://www.aidsetc.org