Treatment of Hepatitis (and HIV) in Pregnancy 2010

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Zidovudine Chemoprophylaxis for HIV

• 1994, the 076: antepartum, intrapartum and newborn zidovudine (ZDV) reduced the risk of mother-to-child HIV-1 transmission from 25.5% to 8.3%

• 1994, a USPHS task force issued recommendations for ZDV use for the reduction of perinatal HIV-1 transmission

• Since then, studies have confirmed dramatic decreases in perinatal HIV-1 transmission with ZDV
Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985 – 2000, United States

Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases reported without a risk; data reported through December 2001

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Zidovudine Use for HIV-infected Pregnant Women or for Perinatally Exposed or Infected Children Born 1993-2000, 39 States

Note: Includes prenatal, intrapartum, or neonatal receipt of zidovudine to reduce perinatal HIV transmission. 39 areas conduct name-based HIV Surveillance; data reported through December 2001.
What has been learned since “076”? 

Factors associated with higher rates of HIV-1 transmission include

- Breast feeding
- Ruptured membranes for >4 hours
- Advanced maternal disease
- High maternal viral load, and possibly
- Concomitant infections, including hepatitis C
Current Recommendations – Prevention of Mother-to-Child HIV-1 Transmission

• Maternal viral load, greatest risk factor for transmission
  – Goal - control maternal viral load (low levels < 1000 copies/mL or undetectable)
• Standard of care in US – combination therapy
• For most women, zidovudine incorporated in treatment regimens
• Choice of the therapies need to be individualized based on maternal HIV disease, maternal co-morbid conditions, antiretroviral history, viral resistance, maternal toxicities, fetal toxicities
• If viral load is not controlled, c-section indicated
HIV Treatment in Pregnancy

- Generally favor boosted PI regimen
- Lopinavir/ritonavir
  - GI intolerance
  - Large increases in cholesterol and triglycerides
- Atazanavir/ritonavir (Boosted Reyataz)
  - Fewer lipid abnormalities
  - Proton-pump inhibitors decrease absorption
Labor Management

• With ART, risk of transmission 1.2% – 1.5%
• If viral load >1,000 RNA copies/ml, may be some benefit to elective C-section
• Benefit of non-elective c-section never demonstrated
• Maternal IV ZDV and newborn ZDV remains the standard of care
• For those without antepartum antiretroviral therapy, oral NVP (and probably 3TC) should be given in labor
WHICH ONE
DESERVES
TO DIE?

1 in 10 Asian Americans is infected with hepatitis B, the leading cause of liver cancer. But hepatitis B can be treated, even prevented. Get the simple blood test. Stop liver cancer by stopping hepatitis B.

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Identified and Expected Births to HBsAg-Positive Mothers, US, 1993-2003

Source: National Immunization Program, CDC

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
**SCREENING FOR HEPATITIS B VIRUS (HBV) INFECTION IN PREGNANCY**

**CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

<table>
<thead>
<tr>
<th>Population</th>
<th>All Pregnant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>Screen at the first prenatal visit</td>
</tr>
<tr>
<td><strong>Grade:</strong></td>
<td>A</td>
</tr>
</tbody>
</table>

**Screening Tests**
- Serologic identification of hepatitis B surface antigen (HBsAg).
- Reported sensitivity and specificity are greater than 98%.

**Timing of Screening**
- Order HBsAg testing at the first prenatal visit.
- Rescreen women with unknown HBsAg status or new or continuing risk factors at admission to hospital, birth center, or other delivery setting.

**Interventions**
- Administer hepatitis B vaccine and hepatitis B immune globulin to HBV-exposed infants within 12 hours of birth.
- Refer women who test positive for counseling and medical management.
- Counseling should include information about how to prevent transmission to sexual partners and household contacts.
- Reassure patients that breastfeeding is safe for infants who receive appropriate prophylaxis.

**Implementation**
- Establish systems for timely transfer of maternal HBsAg test results to the labor and delivery and newborn medical records.

**Relevant USPSTF Recommendations**
- USPSTF recommendations on the screening of pregnant women for other infections, including asymptomatic bacteriuria, bacterial vaginosis, chlamydia, HIV, and syphilis, can be found at www.preventiveservices.ahrq.gov.

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to www.preventiveservices.ahrq.gov.

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Ann Intern Med 2009;150:869-873
Perinatal Transmission Without Prophylaxis

Mother: HBsAg +, HBeAg +

→ 70-90% risk of chronic HBV infection by age 6 months

38% not infected perinatally (~90% are not infected at birth) are positive by age 4

Serology Status and VT Rate

<table>
<thead>
<tr>
<th>Infection Rate</th>
<th>No immunoprophylaxis</th>
<th>HBI G+Vaccine (VT rate &gt; 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transient Infection</td>
<td>Persistent (&gt;6 months)</td>
</tr>
<tr>
<td>HBeAg +</td>
<td>10.1 %</td>
<td>78.8 %</td>
</tr>
<tr>
<td>HBeAg- eAb-</td>
<td>9.1 %</td>
<td>6.8 %</td>
</tr>
<tr>
<td>HBeAg- eAb+</td>
<td>9.3 %</td>
<td>1.5 %</td>
</tr>
<tr>
<td>HBcAb+ only**</td>
<td>6.6 %**</td>
<td>N/A</td>
</tr>
</tbody>
</table>

** Walz A, et al, J Inf Dis 2009;200:1227–1231 (Transient infection based on detectable DNA)

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Viral Load and HBeAg Are Significant Risk Factors for Perinatal Transmission

Transmission rate:
7% in HBeAg + mother
9% in DNA> 8Log10 c/mL

313 HBsAg + Mothers

65 lost to follow-up

110 DNA<5 log10 c/mL

27 DNA5-8 log10 c/mL

65 DNA>8 log10 c/mL

5 did not reach term

All infants received HBIG and Vaccine, HBsAg Status at 9 months after birth

All 91 infants born to low DNA mother were HBsAg(-) at 9 months of age

47 infants born

4 infected infants, all from HBeAg +Mother

1 infant with S mutant escape: (SD114E ) but the infant did not receive HBIG


Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Perinatal Transmission with Threatened Abortion

• In utero risk
  – Threatened abortion
    5 cases threatened abortion
    3/5 gave birth 6 weeks later, all infants infected
    2/5 delivered within 1 week, given HBIG, negative

Lin HH et al, J Pediatr 1987
Very Low Risk of Transmission of HBV to the Fetus after Amniocentesis in HBV Carriers

121 Mothers
HBsAg +
( DNA / HBeAg ?)

72 infants no Amnio
Cord blood
18% + HBsAg
4%+ DNA

47 Amnio Fluid
32% + HBsAg
0%+ DNA

30 had Amnio
Cord Blood
27% + HBsAg
0% + DNA

• In utero transmission of the virus is rare prior to the onset of labor
• Very low risk of transmission of HBV after amniocentesis


Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Intrauterine Hepatitis B virus (HBV) Infection by Transplacental Transmission (Case-Control Study)

Intrauterine infection rate of 3.7% in HBsAg+, with HBeAg +: 9.8%

TABLE I. Comparison of Maternal or Newborn’s Characteristics Between Cases and Controls (With and Without Intrauterine HBV Infection, Respectively)*

<table>
<thead>
<tr>
<th>Maternal or newborn’s characteristics</th>
<th>Cases (N = 15)</th>
<th>Controls (N = 387)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-positive</td>
<td>13</td>
<td>2</td>
<td>120</td>
<td>267</td>
<td>14.46</td>
</tr>
<tr>
<td>History of induced abortion</td>
<td>7</td>
<td>8</td>
<td>155</td>
<td>232</td>
<td>1.31</td>
</tr>
<tr>
<td>Multiparous</td>
<td>3</td>
<td>12</td>
<td>26</td>
<td>361</td>
<td>3.47</td>
</tr>
<tr>
<td>Caesarian section</td>
<td>1</td>
<td>14</td>
<td>78</td>
<td>309</td>
<td>0.29</td>
</tr>
<tr>
<td>Threatened abortion</td>
<td>1</td>
<td>14</td>
<td>70</td>
<td>317</td>
<td>0.32</td>
</tr>
<tr>
<td>Threatened preterm labour</td>
<td>3</td>
<td>12</td>
<td>14</td>
<td>373</td>
<td>6.66</td>
</tr>
<tr>
<td>Gestosis</td>
<td>2</td>
<td>13</td>
<td>39</td>
<td>348</td>
<td>1.37</td>
</tr>
<tr>
<td>Low Apgar score</td>
<td>1</td>
<td>14</td>
<td>14</td>
<td>373</td>
<td>1.84</td>
</tr>
</tbody>
</table>

*N.S. = non-significant, P > 0.05.

1. Maternal HBeAg Positive is a significant risk factor

2. Threatened preterm labor: partial placental leakage, leading to mixed circulation of fetal with maternal and is a significant risk factor

The Role of Close Family Contact in Early Childhood HBV (Horizontal) Transmission

Table 1. Serological evidence of hepatitis B virus transmission from hepatitis B surface antigen (HBsAg)-positive parents to their children

<table>
<thead>
<tr>
<th>HBsAg status</th>
<th>No. of couples</th>
<th>No. of HBsAg-positive children/ no. of children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg-positive mother, HBsAg-negative father</td>
<td>8</td>
<td>11/12 (91.7) 7/9 (77.8) 18/21 (85.7)</td>
</tr>
<tr>
<td>HBsAg-negative mother, HBsAg-positive father</td>
<td>7</td>
<td>7/11 (63.6) 10/15 (66.6) 17/26 (65.4)</td>
</tr>
<tr>
<td>Mother and father both HBsAg positive</td>
<td>5</td>
<td>9/9 (100) 5/7 (71.4) 14/16 (87.5)</td>
</tr>
</tbody>
</table>


*a P = .16, by χ² test.

Vertical Transmission
Mechanism of Transmission

- **Antenatal transmission (intrauterine infection)**
  - Transplacental
  - Placental leakage/threatened abortion
  - Amniocentesis

- **Intra- and Peripartum Infection**
  - Uterine contractions --> tear in the placenta: micro-transfusion of maternal blood
  - Vaginal infection during birth: ingestion of maternal blood, amniotic fluid or vaginal secretions
  - Contamination of abrasions can occur during instrumental vaginal delivery

- **Post-partum intimate contact**
  - Breastfeeding
  - Horizontal from household contacts
Effect of Delivery Mode on Transmission of HBV

HBsAg+ mothers in third trimester and infants received passive-active vaccination (100 IU and vaccine x 3)

<table>
<thead>
<tr>
<th>Newborn N = 301</th>
<th>Spontaneous vaginal N = 144</th>
<th>Forceps/ vacuum extraction N = 40</th>
<th>Cesarean section N = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBs (12 mo)</td>
<td>78.9%</td>
<td>84.6%</td>
<td>86.4%</td>
</tr>
<tr>
<td>HBsAg + (12 mo)</td>
<td>8.1%</td>
<td>7.7%</td>
<td>9.7%</td>
</tr>
<tr>
<td>HBV DNA + (12 mo)</td>
<td>7.3%</td>
<td>7.7%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

Caesarean section does not reduce the incidence of immunoprophylaxis failure


Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel
Post-partum Transmission of HBV

Breastfeeding and Risk of HBV Transmission

- HBV can be detected in breast milk
  - Wong et al (1980) 72% had HBsAg detected

- Breastfed infants are not at higher risk than formula-fed prior to vaccination
  - Beasley (1975): 92 breastfed vs. 55 formula-fed
    HBsAg + at 6 mo: 53% vs. 60%

- Neonates that are correctly immunized may be breastfed
  - Hill et al (2002): 101 breastfed vs. 269 formula-fed
    HBsAg+ at 6 mo: 0% vs. 3%

Immunoprophylaxis 1977 Taiwan

HBIG given to the infant in first 12 hours after birth
Delay HBIG or 1st dose of vaccine >48h → Higher VT rate
Completed HBV vaccination within the first year

Great variability in vaccine delivery, common use regimen for vaccine is 0, 1, 6 months or 0, 1, 2, 12 months.

<table>
<thead>
<tr>
<th></th>
<th>No Vaccine</th>
<th>HBIG only</th>
<th>HBIG + Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants infected HBV</td>
<td>95%</td>
<td>28%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Steven CE et al. NEJM 1975;292:771-4
HBV Transmission among Infants of Chinese-American Mothers with CHB New York City 2009

- Newborns at risk for HBV were retrospectively identified at 2 New York hospitals (N=641)
- Contact was attempted to test infants for HBV
  - Loss to FU ~50% in this population
- 76 mothers + 81 infant pairs tested
  - 9.2% HBV transmission rate despite standard HBIG and vaccine
  - Risk factors include HBeAg(+)
- Perinatal transmission occurs in the US
  - Infants of HBsAg(+) mothers should be followed closely

<table>
<thead>
<tr>
<th></th>
<th>69 mother with babies HBsAg-</th>
<th>7 mothers with babies HBsAg +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age +/- SD</td>
<td>29.0 +/-4.7 (20.6-40.9)</td>
<td>29.4 +/-5.9 (22.5-38.0)</td>
</tr>
<tr>
<td>HBeAg Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16 (30.8%)</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td>Negative</td>
<td>36 (69.2%)</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>HBV DNA (copies/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 160</td>
<td>8 (30.8%)</td>
<td>0</td>
</tr>
<tr>
<td>160-10⁸</td>
<td>13 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 10⁸</td>
<td>5 (19.2%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>Mean Prenatal ALT (U/L) +/- SD (range)</td>
<td>26.8 +/-12.9 (8-73)</td>
<td>26.6 +/-11.4 (15-45)</td>
</tr>
</tbody>
</table>

Presented at the 6th International Workshop on HIV & Hepatitis Co-infection, 31 May – 2 June 2010, Tel Aviv, Israel

Mi L, et al. 60th AASLD; Boston, MA; October 30-November 3, 2009; Abst 1438.
## Immunoprophylaxis of VT: HBIG 400 IU Monthly at Third Trimester
### HBV Markers at Birth and at 1 Year After Birth

<table>
<thead>
<tr>
<th>HBV Markers</th>
<th>At Birth</th>
<th>At One year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBIG n=118</td>
<td>Control (Standard of Care) n=133</td>
</tr>
<tr>
<td>Maternal DNA at birth</td>
<td>7.54±1.72 log_{10} cp/ml</td>
<td>7.22±1.72 log_{10} cp/ml</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>27 (23%)</td>
<td>32 (20%)</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>9 (9%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Anti-HBc+</td>
<td>2 (1.7%)</td>
<td>2 (1.5%)</td>
</tr>
</tbody>
</table>

250 HBsAg+ HBeAg+ pregnant mothers randomly assigned to HBIG x 3 antepartum vs. no treatment along with passive-active vaccination in all infants


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Lamivudine Therapy during High Viremic HBV Pregnancy – Historical Control Study

- Pregnant women with HBV mono-infection
  - DNA $\geq 1.1 \times 10^7$ IU/mL
  - Lamivudine 150 mg given daily wk 34 until partum (n=8)

- Newborn received 300 IU of HBIG and HBV vaccine 20 ug at 2, 3, 4 and 11 months

- Historical controls selected from HBsAg+ mothers with HBV-DNA $1.1 \times 10^7$ IU/mL

Lamivudine group 12.5 %
Historical Control 28 % HBsAg+ at year 1

Antiviral Therapy for the Prevention of Vertical Transmission During Pregnancy

- All infants received vaccine (10 g/0.5mL) + HBIG (200 IU, single dose)
- Primary endpoint: HBsAg- positive infant at 1 year
- Secondary endpoint: HBsAb+, HBV DNA+

Improved outcomes for the infants receiving LAM

<table>
<thead>
<tr>
<th>Infant Status at 52 Wks, %</th>
<th>LAM (n = 56)</th>
<th>Placebo (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg positive</td>
<td>18</td>
<td>39</td>
<td>.014</td>
</tr>
<tr>
<td>HBV DNA positive</td>
<td>20</td>
<td>46</td>
<td>.003</td>
</tr>
<tr>
<td>HBsAb positive</td>
<td>84</td>
<td>61</td>
<td>.008</td>
</tr>
</tbody>
</table>

# Safety Consideration on Antiviral Therapy

- Data from the Antiretroviral Pregnancy Registry

**Primary Registry Analysis**


## Population for Analysis - Prospective Registry Cases

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies Enrolled</td>
<td>11209</td>
</tr>
<tr>
<td>Pending Cases(^1)</td>
<td>431 (3.8%)</td>
</tr>
<tr>
<td>Cases lost to follow-up(^2)</td>
<td>889 (7.9%)</td>
</tr>
<tr>
<td>Reports used in analysis</td>
<td>9889 (88.2%)</td>
</tr>
</tbody>
</table>

1. Cases where the outcome of pregnancy is not yet known.
2. Cases where the outcome of pregnancy has never been received despite requests or if the reporter did not know whether there was a birth defect.

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The Antiretroviral Pregnancy Registry
First Trimester Exposure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Defects/Live Births</th>
<th>Prevalence % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (LAM)</td>
<td>85/2784</td>
<td>3.1 (2.4, 3.8)</td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>11/491</td>
<td>2.2 (1.1, 4.0)</td>
</tr>
<tr>
<td>Adefovir (ADV)</td>
<td>0/23</td>
<td>-</td>
</tr>
<tr>
<td>Entecavir (ETV)</td>
<td>0/2</td>
<td>-</td>
</tr>
<tr>
<td>Telbivudine (LdT)</td>
<td>0/1</td>
<td>-</td>
</tr>
<tr>
<td>Zidovudine (ZDV)</td>
<td>87/2808</td>
<td>3.1 (2.5, 3.8)</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>33/972</td>
<td>3.4 (2.3, 4.7)</td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>18/737</td>
<td>2.4 (1.5, 3.8)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>19/651</td>
<td>2.9 (1.8, 4.5)</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>16/628</td>
<td>2.5 (1.5, 4.1)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>17/512</td>
<td>3.3 (1.9, 5.3)</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>10/364</td>
<td>2.7 (1.3, 5.0)</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>16/353</td>
<td>4.5 (2.6, 7.3)</td>
</tr>
<tr>
<td>Lopinavir (LPV)</td>
<td>6/328</td>
<td>1.8 (0.7, 3.9)</td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>6/272</td>
<td>2.2 (0.8, 4.7)</td>
</tr>
</tbody>
</table>

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Antiviral Exposure in Different Trimester in Registry Analysis

Tenofovir: 800 births (491 in 1st trimester and 309 in 2nd/3rd trimester)

<table>
<thead>
<tr>
<th></th>
<th>1st Trimester Exposure</th>
<th></th>
<th>2nd/3rd Trimester Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Defects /Live Births</td>
<td>Prevalence % (95% CI)</td>
<td>Defects /Live Births</td>
</tr>
<tr>
<td>Any TDF</td>
<td>11/491</td>
<td>2.2 (1.1, 4.0)</td>
<td>4/309</td>
</tr>
</tbody>
</table>

- CDC population-based birth defects surveillance system
- Total prevalence of birth defects identified among births from 1989 through 2003 was 2.72 per 100 live births (95% CI: 2.68, 2.76)
- Advisory Committee Consensus: For tenofovir, sufficient numbers of first trimester exposures have been monitored to detect at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date

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HBV Conclusion

• Vertical transmission occurs despite perinatal immunoprophylaxis, especially in mothers with (+) HBeAg and high viral load (>8 log10 c/mL)

• Limited data suggests that antiviral therapy for high viral load mothers may significantly reduce vertical transmission

• Antepartum use of HBIG, c-section or formula-fed for infants failed to show any impact on VT rate

• Vertical transmission rates in U.S will likely increase due to influx of immigrants from Asia
## DHHS Recommendations For Treatment of HBV/HIV Coinfected Patients

<table>
<thead>
<tr>
<th>Need to Treat</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV and HBV</strong></td>
<td><strong>TDF/FTC or TDF + 3TC considered first-choice NRTI backbones</strong>&lt;br&gt;<strong>OR</strong>&lt;br&gt;<strong>ETV + 1 NRTI above (&amp; two other preferred ARVs)</strong>&lt;br&gt;<strong>Avoid use of 3TC, FTC, or TDF as the only active anti-HBV agent because of the risk of HBV resistance</strong></td>
</tr>
<tr>
<td><strong>HIV but not HBV</strong></td>
<td><strong>TDF/FTC or TDF + 3TC considered first-choice NRTI backbones</strong>&lt;br&gt;<strong>Avoid use of 3TC, FTC, or TDF as the only active anti-HBV agent should be avoided because of the risk of HBV resistance</strong></td>
</tr>
<tr>
<td><strong>HBV but not HIV</strong></td>
<td><strong>Peg-IFN-α or ADV (theoretical risk of HIV resistance)</strong>&lt;br&gt;<strong>Avoid FTC, 3TC, TDF, ETV w/o full HAART regimen because of HIV resistance. Combination (Telbivudine and ADV seems ideal) DTD</strong></td>
</tr>
</tbody>
</table>

FTC and TDF are not FDA approved for treatment of HBV (TDF approval expected 2008)
Pregnancy Outcomes

• 749 pregnant women in Israel with hepatitis B or C
• Significantly higher rates:
  – preterm delivery
  – membrane rupture
  – abruption
  – C-section
  – mortality
  – malformations
  – low birth weight
• HCV infection increased risk of developing glucose abnormalities

Safir A, Levy A, Sikuler E, Sheiner E
Prospective Cohort Study of Mother-to-Infant Infection and Clearance of Hepatitis C in Rural Egyptian Villages

- 15.7% and 10.9% of pregnant women had anti-HCV and HCV-RNA, respectively
- 329 infants: 10.0% tested positive for both anti-HCV and HCV-RNA 2 months after birth
- Viremia was 155-fold greater in mothers of infants with persistent than mothers of infants with transient infections
- Maternal-infant transmission of HCV is more frequent than generally reported
- Both early and late clearance of infection frequently occurs:
  - 4.6% HCV RNA + at 1 year
  - 2.4% HCV RNA + at 2-3 years

HCV Transmission

- Genetic factors in mother-to-child transmission of HCV infection
  - HCV infection transmission rate is about 5%
    - HIV and high maternal HCV RNA have higher rates
  - 384 Italian subjects, including 38 HCV-positive mother/child pairs; 104 infected, non-transmitting mothers with their 114 children; 21 vertically infected children and 69 HCV-exposed, uninfected children
  - Maternal HLA-DRB104 correlated with protection from vertical transmission (p=0.023)
  - HLA-DRB110 in children was a risk factor (p=0.036)
  - HLA mismatch between mother and child was a protective factor (p=0.017) indicating that alloreactive immune responses are involved in preventing HCV vertical transmission

Risk Factors for Perinatal Transmission of Hepatitis C Virus (HCV) and the Natural History of HCV Infection Acquired in Infancy

• 4.7% of infants born to mothers who were HCV RNA positive at delivery became infected
• Transmission was 3.8% in HIV negative, 25.0% in HIV positive (P<.05)
• Three infected infants resolved their infection
• In multivariate analysis, factors associated with transmission
  – membrane rupture ≥6 h (OR: 9.3)
  – internal fetal monitoring (OR: 6.7)
• CONCLUSION: If duration of membrane rupture and internal fetal monitoring are confirmed, interventions may be possible to decrease the risk of transmission. **elective C section**

Conclusions

• Treatment of HIV in pregnancy sets the bar very high
• Both pregnancy and HBV are indications for treatment of HIV
• Prophylaxis of HBV is not 100% effective
• Treatment of HBV in pregnancy will likely lower risk
  – Several drugs are Category B: tenofovir is the most effective
• HCV transmission remains about 5% in HIV negative and 25% HIV+
• There is clearance of HCV in infected infants
• Peripartum issues increase HCV transmission and may trigger elective C section
Assessment of TDF-Containing Regimens in Pregnancy Using the ART Pregnancy Registry

- APR is an international, prospective exposure registration cohort to monitor teratogenic effects of ART
  - Established 1989
  - TDF data collected since 2001
- 1301 cases (1045 live births) receiving TDF regimens
  - Majority HIV infected women exposed to combination ART
    - 9 women HBV mono-infected

| TDF Regimens Maternal Demographics at Registration (Pregnancies Enrolled=1,186) |
|------------------|------------------|
| Median Age (years) | 30               |
| Race             |                  |
| Black            | 63.2%            |
| Hispanic         | 16.3%            |
| White            | 11.8%            |
| Asian            | 2.2%             |
| Other            | 2.6%             |
| CD4+ T-Cell Count at Start of Pregnancy |                  |
| ≥ 500 cells/µL   | 23.3%            |
| 200-499 cells/µL | 48.9%            |
| <200 cells/µL    | 21.4%            |
| HIV Infected     |                  |
| A. Asymptomatic, acute (primary) HIV or PGL | 56.7% |
| B. Symptomatic, not (A) or (C) | 5.7% |
| C. AIDS – indicator conditions | 31.4% |
| HIV Uninfected   |                  |
| HIV post-exposure prophylaxis | 0 |
| Hepatitis B mono-infected | 0.7% |
TDF-Containing Regimens in Pregnancy: Findings from the Antiretroviral Pregnancy Registry

- Congenital anomaly rate with TDF containing ART:
  - 2.4% (95% CI: 1.4-3.8) for 1st trimester
  - 1.6% (95% CI: 0.6-3.4) for 2nd/3rd trimester
- Similar to CDC’s population-based birth defects surveillance system and other ART regimens
- Data on other HBV agents (except LAM) are limited

### Birth Defect Rates By Trimester of Earliest Exposure to TDF Regimens and All ARV Regimens in APR

<table>
<thead>
<tr>
<th>Earliest Exposure to ARVs</th>
<th>Number of Defects / Live Births</th>
<th>TDF Regimens</th>
<th>All ARV Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Trimester</td>
<td></td>
<td>16/678</td>
<td>130/4530</td>
</tr>
<tr>
<td>Prevalence (95% CI)</td>
<td></td>
<td>2.4% (1.4 – 3.8)</td>
<td>2.9% (2.4 – 3.4)</td>
</tr>
<tr>
<td>2nd or 3rd Trimester</td>
<td></td>
<td>6/385</td>
<td>147/5874</td>
</tr>
<tr>
<td>Number of Defects / Live Births</td>
<td></td>
<td>1.6% (0.6 – 3.4)</td>
<td>2.5% (2.1 – 2.9)</td>
</tr>
</tbody>
</table>

### Birth Defect Prevalence for First Trimester Exposure to Anti-HBV Drugs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Defects / Live Births</th>
<th>Prevalence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>93/3226</td>
<td>2.9 (2.3, 3.5)</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>16/678</td>
<td>2.4 (1.4, 3.8)</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>0/37</td>
<td>0</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0/8</td>
<td>0</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>0/3</td>
<td>0</td>
</tr>
</tbody>
</table>