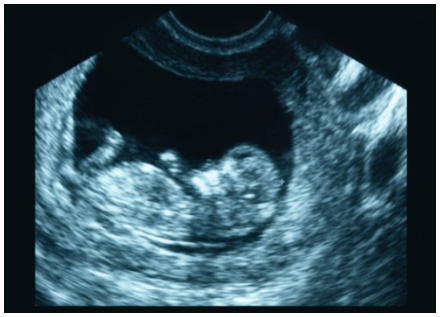
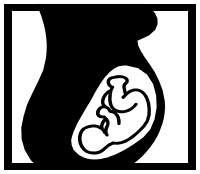


Antiretroviral Drugs and Pregnancy

Lynne M. Mofenson, M.D.
Pediatric, Adolescent and Maternal AIDS Branch
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
National Institutes of Health
Department of Health and Human Services

AIDS 2008
XVII INTERNATIONAL AIDS CONFERENCE
Mexico City, 3-8 August

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development



Drug Therapy Often Needed in Pregnancy, But Dosing/Safety Data Often Lacking

Treatment may be needed for:

- **Maternal conditions, such as asthma, hypertension, diabetes, seizures, HIV infection**
- **Pregnancy-related conditions such as gestational diabetes, pre-eclampsia**
- **Fetal conditions, such as preterm delivery**

Drug Therapy in Pregnancy

Balancing act

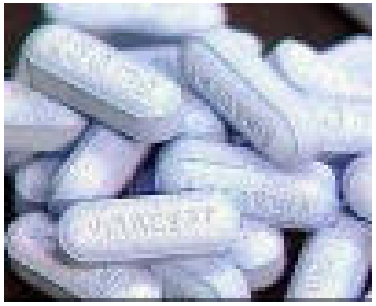
Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Unfortunately, Often Little Scientific Data to Make Recommendations

Special Considerations in Pregnancy Regarding Antiretroviral Drug Use and Choice

- Prevention of HIV Transmission
- Drug pharmacokinetics
- Safety for mother and infant
- Teratogenicity



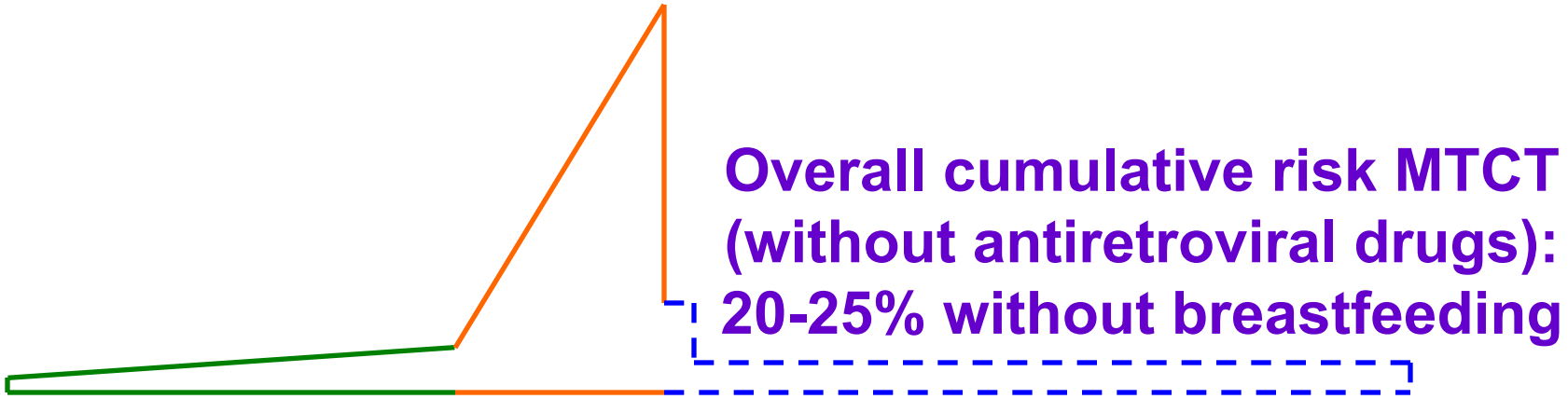
Prevention of Mother to Child HIV Transmission

Timing of Mother to Child HIV Transmission

Majority Transmission is Intrapartum

No Breastfeeding

In Utero **Peripartum** *Postpartum*



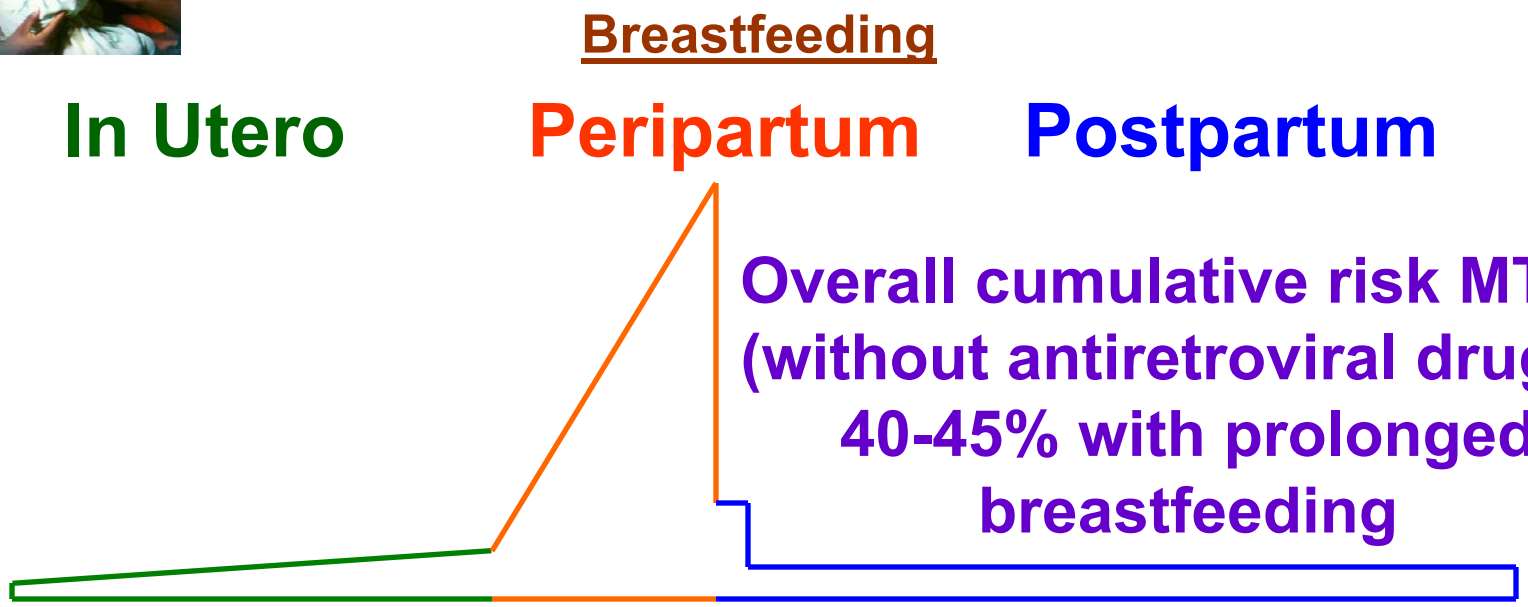
25-35% in utero

(majority late)

65-75% peripartum

Timing of Mother to Child HIV Transmission:

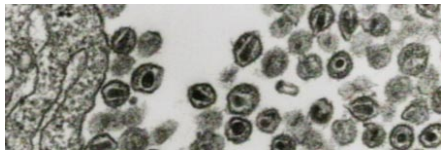
~Doubling of Risk with Breastfeeding



20-25% in utero
(majority late)

35-50% peripartum

40-45% postpartum



Key Biological Factors in MTCT

- Maternal viral load
- Low CD4 count
- New (primary) HIV infection in mother
- Prolonged membrane rupture (>4 hrs)
- Vaginal delivery
- Preterm birth / low birth weight
- Breastfeeding

Principles Related to Antiretroviral Drug Use by HIV-Infected Pregnant Women

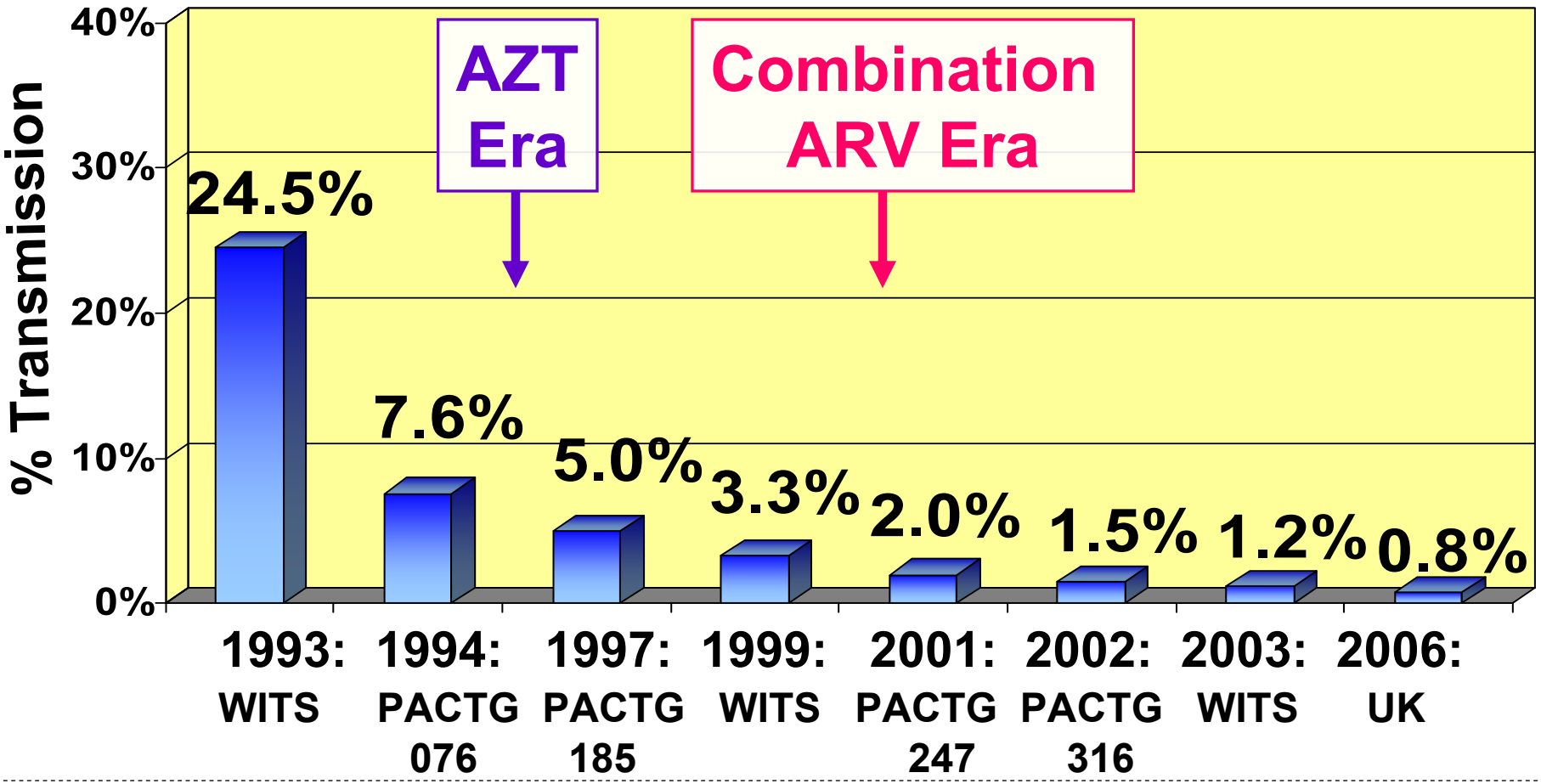
- **Therapies of known/potential benefit should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus or infant and these side effects outweigh potential benefit to the woman.**
- **ARV therapy or prophylaxis during the antepartum period should be recommended to all HIV-infected pregnant women regardless of plasma HIV RNA level or CD4.**
- **Criteria for starting ARV therapy in pregnant women are same as in non-pregnant.**

U.S. Guidelines for Starting Antiretroviral Treatment in Adults, including Pregnant Women

Clinical Category	$CD4^+$ T Cell Count	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Treat
Asymptomatic	<200 cells/μL	Treat
Asymptomatic	200-350 cells/μL	Treat, *especially* if pregnant
Asymptomatic	>350 cells/μL	Can defer, individual considerations* ARV prophylaxis if pregnant

*Such as pregnancy; HIV nephropathy; HBV coinfection

Mother to Child HIV Transmission in Resource-Rich Countries Over Time



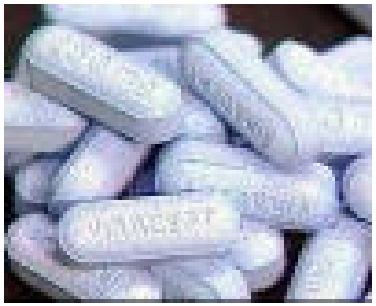
Decline due to:

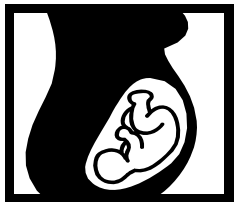
- Enhanced prenatal HIV testing
- Increase in use of HAART by HIV+ women
- Increase in elective C/S by HIV+ women
- Avoidance of breastfeeding

How Do Antiretroviral Drugs Reduce Mother to Child HIV Transmission?

- **Lowering maternal blood/genital viral load**
  - **In women with high viral load, this mechanism likely most important.**
  - **However, drugs reduce transmission with low viral load and are effective even when antenatal drugs are not given.**
- **Two other important mechanisms through which antiretrovirals reduce transmission:**
  - **Pre-exposure prophylaxis of infant (through transplacental drug passage).**
  - **Post-exposure prophylaxis of infant (through continued drug after birth).**

Modification of Drug Pharmacokinetics by Pregnancy





Physiologic Changes During Pregnancy Can Affect Therapeutic Drug Administration

- Cardiovascular changes
- Gastrointestinal changes
- Renal changes
- Hepatic enzyme activity changes

Cardiovascular Changes in Pregnancy

- **Gestational age dependent**
- **Plasma volume expansion**
  - **Start 6-8 weeks, peaks at 32 weeks; additional 1.5 liters**
  - **Decrease in serum albumin concentration**
- **Increase in cardiac output**
  - **Increase 30-50% (stroke volume early, heart rate late)**
- **Alterations in regional blood flow**
  - **Increased flow uterus, kidney, breast, skin**

Changes in Other Organ Systems in Pregnancy

Gastrointestinal Changes

- Gastric emptying delayed
- Transit time increased (progesterone)
- Gastric acidity decreased

Renal Changes

- Increase in glomerular filtration rate 20-60% beginning 1st trimester

Hepatic Enzymatic Changes

- Related to pregnancy hormonal changes

Hepatic Enzyme Changes in Pregnancy

Increased

- CYP3A4
  - Most common drug metabolizing enzyme
  - Time course increase not defined
- CYP2D6
  - 2nd most common
  - Increase late pregnancy
- CYP2C9
- CYP2A6
- UGT1A4
- UGT2B7

Decreased

- CYP1A2
  - Induced in smokers
- CYP2C19

Consequences of Physiologic Changes During Pregnancy

- **Volume expansion = dilution effect**
- **Increase in free fraction of drug**
  - **Due to decreased albumin**
- **Clearance changes (increase or decrease)**
  - **Renal and enzymatic**
- **Gastrointestinal changes that can affect oral drug absorption**

Result: Dosing changes may be needed

Pregnancy & Antiretroviral Pharmacokinetics

NRTIs

Abacavir	No Δ
Didanosine	No Δ
Emtricitabine	No Δ
Lamivudine	No Δ
Stavudine	No Δ
Zidovudine	No Δ

NNRTIs

Efavirenz	No data
Etravirine	No data
Nevirapine	No Δ

PIs

Atazanavir	No Δ?
Darunavir	No data
Fosamprenavir	AUC ↓?
Indinavir	AUC ↓
Lopinavir/rit	AUC ↓
Nelfinavir	AUC ↓
Ritonavir	AUC ↓
Saquinavir	AUC ↓
Tipranavir	No data

NUCLEOTIDES

Tenofovir AUC↓

FUSION INHIBITORS

Enfuvirtide No data

INTEGRASE INHIBITORS

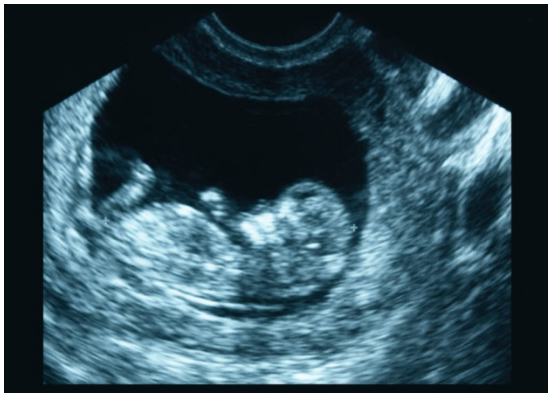
Raltegravir No data

CCR5 CO-RECEPTOR ANTAGONISTS

Maraviroc No data

IMPAACT P1026s: Study of Antiretroviral Pharmacokinetics in Pregnant HIV+ Women

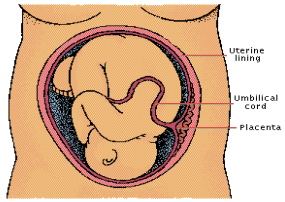
- Opportunistic study of pharmacokinetics of antiretroviral drugs that pregnant women are prescribed for their own health.
- Several arms open at once for to evaluate new drugs not studied previously.
- Evaluates pharmacokinetics at three time points: 2nd trimester (if present early enough), 3rd trimester and postpartum.
- Allows comparison with target based on non-pregnant adults in general, and comparison of drug levels antepartum and postpartum.



Antiretroviral Safety and Pregnancy

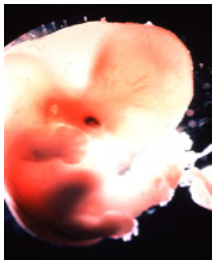
What are Potential Risks of Antiretroviral Exposure for the Woman and her Infant?

- **Short-term**
  - **Maternal - pregnancy-related changes in drug dose requirements(could lead to toxicity or resistance); immediate and postpartum toxicity**
  - **Fetus - pregnancy outcome, congenital abnormalities**
  - **Infant - neonatal and infant toxicity**
- **Long-term**
  - **Maternal - resistance, disease progression**
  - **Child - mitochondrial dysfunction, malignancy?**



Issues Related to Toxicity of Antiretroviral Prophylaxis of MTCT

- **The extent of fetal risk may vary by:**
  - **Timing of exposure**
  - **Dose**
  - **Route of exposure**
  - **Duration of exposure**
- **The longest (and most complex) regimens have the greatest efficacy but also the greatest exposure (and hence greater risk).**



Timing (Gestational Age) of Drug Exposure Affects Fetal Risk

Embryogenesis
potential for
major organ defects
(eg, cardiac, CNS)

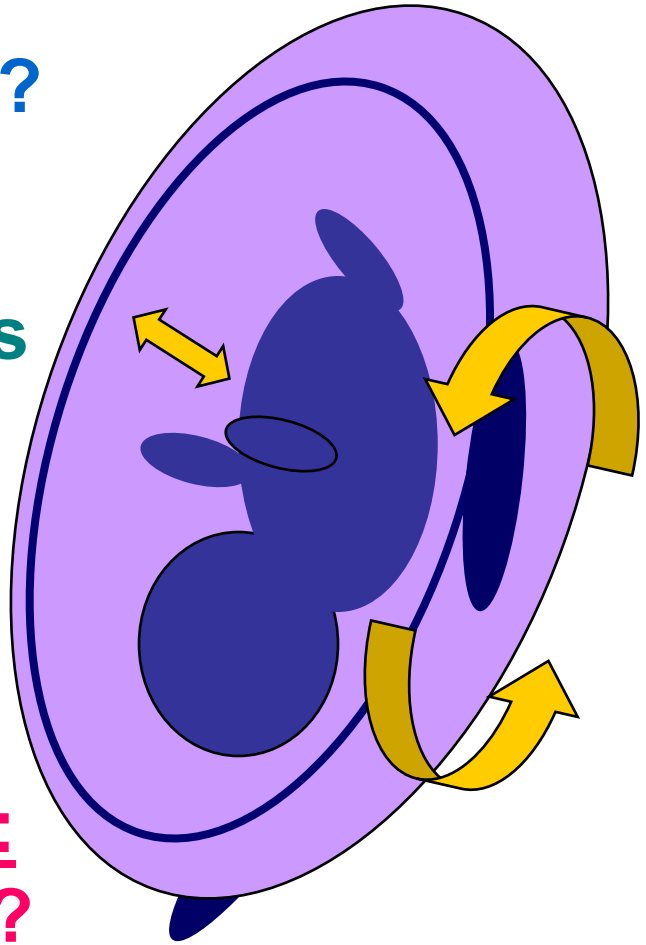
Ex: Neural tube closure by day 28
Oral structures form by day 36

Fetal development
potential for
developmental defects
(eg, brain development,
fetal growth)

Ex: Alcohol exposure after 24 wks
Smoking after 20 wks

Determinants of Fetal and Infant Drug Exposure and Risk

- **Placental transfer:**
  - Does drug cross placenta?
- **Placental/fetal metabolism:**
  - Potential toxic metabolites
- **Fetal GI absorption:**
  - Is drug concentrated in amniotic fluid?
- **Drug transfer via breastmilk:**
  - Is drug secreted into milk?



Antiretroviral Medications and Fetal Risk: Current FDA Pregnancy Categories

A: No risk in adequate human studies

B: Animal studies do not demonstrate risk but no adequate human studies (or animal studies positive but human studies negative)

C: Animal studies positive for fetal risk or not done and safety in humans not determined

D: Positive evidence of human risk based on adverse event reporting, but potential benefits may outweigh risk

X: Positive evidence animal studies or human risk that indicate risk outweighs benefit

FDA Proposed Revisions to Pregnancy Drug Label

1. Pregnancy registry information and contact, if any.
2. Risk of adverse pregnancy outcome.
3. "Fetal Risk Summary": risks of malformations, miscarriage/stillbirth, neonatal death, functional and growth abnormalities.
4. Standardized risk statements differentiate animal and human data.
5. If contraindicated, the specific circumstances, such as timing, described.
6. Clinical considerations to address inadvertent vs. intentional exposure, risks of untreated disease, gestational use, and dose considerations in pregnancy.
7. A summary of the data underlying the fetal risk and clinical consideration statements.

Current Antiretroviral Medications and Fetal Risk: FDA Pregnancy Categories

NRTIs

Abacavir	C
Didanosine	B
Emtricitabine	B
Lamivudine	C
Stavudine	C
Zidovudine	C

NNRTIs

Efavirenz	D
Etravirine	B
Nevirapine	B

PIs

Atazanavir	B
Darunavir	B
Fosamprenavir	C
Indinavir	C
Lopinavir/rit	C
Nelfinavir	B
Ritonavir	B
Saquinavir	B
Tipranavir	C

NUCLEOTIDES

Tenofovir B

FUSION INHIBITORS

Enfuvirtide B

INTEGRASE INHIBITORS

Raltegravir C

CCR5 CO-RECEPTOR ANTAGONISTS

Maraviroc B

Safety and Toxicity of ARV in Pregnant Women:

Nucleoside/tide Reverse Transcriptase Inhibitors (NRTI/NtRTI)

- In general, there are no changes in pharmacokinetics of NRTI drugs in pregnancy, so standard dosing can be used.
- Recent data suggest tenofovir levels may be ↓in 3rd trimester; unclear if dose increase needed.
- Mitochondrial toxicity possible with all NRTIs.
  - Woman: ↑risk of lactic acidosis/hepatic steatosis with stavudine + didanosine.
  - Infant: *in utero* exposure and rare toxicity.

Safety and Toxicity of ARV in Pregnant Women:

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs)

- Clinical trial and pharmacokinetic (PK) data in human pregnancy available only for nevirapine; no dose adjustment needed.
- Concern related to hepatic toxicity of nevirapine in women with high CD4 count limits use of NVP for ARV prophylaxis in women who don't require therapy for own health (women with CD4 >250-350).
- Animal and human data suggesting potential central nervous system teratogenicity with efavirenz with 1st trimester exposure.

First Trimester Efavirenz Use and Central Nervous System Defects

- Antiretroviral Pregnancy Registry prospective data do not indicate an increase in overall birth defects (10/364, overall 2.7%, 95% CI 1.3-5.0%).
- However, with *in utero* exposure in primates at doses resulting in drug levels similar to human exposure, 3/20 infant monkeys had severe central nervous system (CNS) defects (e.g., anencephaly, anophthalmia).
- Five retrospective human cases of CNS defects (e.g., meningomyelocele) with first trimester efavirenz exposure.
- FDA Class D (+ animal & potential human risk).

Safety and Toxicity of ARV in Pregnant Women:

Protease Inhibitors (PIs)

- **More limited data available PIs in pregnancy.**
  - **Small studies on atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir.**
  - **In general, lower drug levels (area under the curve [AUC]) in 3rd trimester then postpartum.**
  - **Low dose ritonavir boosting recommended (except for nelfinavir).**
  - **Other PIs not yet studied.**
- **Data indicate hyperglycemia not different than non-PI regimens, *but* HIV+ women may have higher risk hyperglycemia in pregnancy.**
- **Conflicting data re: preterm delivery with PIs.**

Safety and Toxicity of ARV in Pregnant Women:


Entry Inhibitors and Integrase Inhibitors

- No pharmacokinetic or clinical data.

Antiretroviral Pregnancy Registry

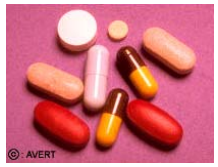
- International registry jointly sponsored by manufacturers of all ARV drugs.
- Voluntary registration of prenatal exposures by treating providers (international).
- Purpose: to estimate risk of major birth defects and compare to that of general population (CDC's population-based birth defects surveillance system).
- Contact information:
  - Telephone: (800) 258-4263
  - Fax: (800) 800-1052
  - Available at http://www.apregistry.com

Antiretroviral Pregnancy Registry 1/89- 1/08

Prospective Cases (http://www.APRegistry.com)

	% Birth Defect
CDC general birth defect surveillance	2.7% (2.7-2.8%)
1st trimester any ARV exposure	3.0% (2.5 - 3.5%)
ABC-containing (17/512)	3.3% (1.9 - 5.3%)
AZT-containing (87/2808)	3.1% (2.5 - 3.8%)
3TC-containing (85/2784)	3.1% (2.4 - 3.8%)
d4T-containing (19/651)	2.9% (1.8 - 4.5%)
Indinavir-containing (6/272)	2.2% (0.8 - 4.7%)
Nelfinavir-containing (33/972)	3.4% (2.3 – 4.7%)
Nevirapine-containing (18/737)	2.4% (1.5 – 3.8%)
Ritonavir-containing (16/628)	2.5% (1.5 – 4.1%)
Lopinavir-containing (6/328)	1.8% (0.7 – 3.9%)
Tenofovir-containing (11/491)	2.2% (1.1 – 4.0%)
ddI-containing (16/353)	4.5% (2.6 – 7.3%)

Antiretroviral Drugs and Breastfeeding



- **Differential secretion of drugs into breast milk:**
  - **If penetrate but in subtherapeutic levels?**
  - **If one penetrates but others do not?**
  - **May end up with resistant virus in milk (eg, NVP resistance higher in milk than plasma).**
- **Infant exposure: Breastfeeding infants with moms on HAART have detectable AZT, 3TC, NVP levels but below therapeutic levels.**
- **Infant exposure gives potential protection but also exposes to potential toxicity and drug resistance if becomes infected.**

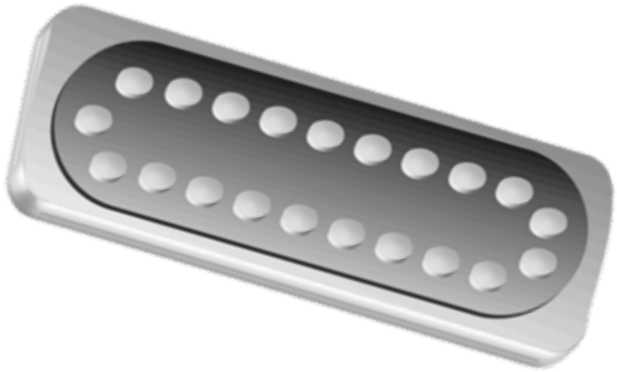
What do We Know About Antiretroviral Drugs in Breast Milk?

DRUG	ANIMAL DATA	COMMENTS
ABC	**YES (rats)**	
AZT	**YES (rats)**	
ddI	**YES (rats)**	
FTC	Not stated	
3TC	**YES (rats)**	
d4T	**YES (rat)**	
TFV	**YES (primate)**	**BM/Mat serum: 3% peak-20% AUC**
EFV	**YES (rats)**	
ETV	Not stated	
NVP	**YES (rats)**	
APV	**YES (rats)**	
ATV	**YES (rats)**	
DRV	**YES (rats)**	
IDV	**YES (rats)**	
LPV	**YES (rats)**	
NFV	**YES (rats)**	
SQV	Not stated	
TPV	Not stated	
RAL	**YES (rats)**	
MVC	**YES (rats)**	**“Extensive secretion in rat milk”**

DRUG	Animal	HUMAN DATA
ABC	YES (rats)	Unk
AZT	YES (rats)	**YES**
ddI	YES (rats)	Unk
FTC	Not stated	Unk
3TC	YES (rats)	**YES**
d4T	YES (rat)	Unk
TFV	YES (primate)	Unk
EFV	YES (rats)	**YES**
ETV	Not stated	Unk
NVP	YES (rats)	**YES**
APV	YES (rats)	Unk
ATV	YES (rats)	Unk
DRV	YES (rats)	Unk
IDV	YES (rats)	**YES**
LPV	YES (rats)	Unk
NFV	YES (rats)	**YES**
SQV	Not stated	Unk
TPV	Not stated	Unk
RAL	YES (rats)	Unk
MVC	YES (rats)	Unk

DRUG	Animal	HUMAN	BREAST MILK/MATERNAL DRUG RATIO
ABC	YES (rats)	Unk	
AZT	YES (rats)	**YES**	**BM 2-3x higher than Mat serum**
ddI	YES (rats)	Unk	
FTC	Not stated	Unk	
3TC	YES (rats)	**YES**	**BM 2-3x higher than Mat serum**
d4T	YES (rat)	Unk	
TFV	YES (primate)	Unk	BM/Mat serum: 3% peak-20% AUC
EFV	YES (rats)	**YES**	
ETV	Not stated	Unk	
NVP	YES (rats)	**YES**	
APV	YES (rats)	Unk	
ATV	YES (rats)	Unk	
DRV	YES (rats)	Unk	
IDV	YES (rats)	**YES**	
LPV	YES (rats)	Unk	
NFV	YES (rats)	**YES**	
SQV	Not stated	Unk	
TPV	Not stated	Unk	
RAL	YES (rats)	Unk	
MVC	YES (rats)	Unk	“Extensive secretion in rat milk”

DRUG	Animal	HUMAN	BREAST MILK/MATERNAL DRUG RATIO
ABC	YES (rats)	Unk	
AZT	YES (rats)	**YES**	**BM 2-3x higher than Mat serum**
ddI	YES (rats)	Unk	
FTC	Not stated	Unk	
3TC	YES (rats)	**YES**	**BM 2-3x higher than Mat serum**
d4T	YES (rat)	Unk	
TFV	YES (primate)	Unk	BM/Mat serum: 3% peak-20% AUC
EFV	YES (rats)	**YES**	**BM/Mat plasma ratio 54%**
ETV	Not stated	Unk	
NVP	YES (rats)	**YES**	**BM/Mat plasma ratio 67-90%**
APV	YES (rats)	Unk	
ATV	YES (rats)	Unk	
DRV	YES (rats)	Unk	
IDV	YES (rats)	**YES**	**BM/Mat plasma ratio: 90-540%**
LPV	YES (rats)	Unk	
NFV	YES (rats)	**YES**	**BM/Mat plasma ratio: 6-24%**
SQV	Not stated	Unk	
TPV	Not stated	Unk	
RAL	YES (rats)	Unk	
MVC	YES (rats)	Unk	“Extensive secretion in rat milk”



Antiretroviral Drugs and Hormonal Contraceptives

Interactions Hormonal Contraceptives and Protease Inhibitors

ARV	Effect on EE/NE	Recommendation
Atazanavir	**↑ EE 48% ↑ NE 110%**	**Use lower dosage or Alternative methods**
Darunavir/ rtv	**↓ EE**	**Alternative methods**
Fos-amprenavir	**↑ EE/NE levels ↓ APV 20%**	**Do not coadminister Alternative methods**
Indinavir	**↑ EE 24% ↑ NE 26%**	**No change**
Lopinavir	**↓ EE 42%**	**Alternative methods**
Nelfinavir	**↓ EE 47% ↓ NE 18%**	**Alternative methods**
Ritonavir	**↓ EE 40%**	**Alternative methods**
Saquinavir	**No data**	**No data**
Tipranavir	**↓ EE 50%**	**Alternative methods**

EE= Ethinyl estradiol, NE= Norethindrone

DHHS Guidelines: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Interactions Hormonal Contraceptives and NNRTI

ARV	Effect on EE	Recommendation
Nevirapine	**↓ EE 20%**	**Alternative methods**
Efavirenz	**↑ EE 37%**	**Alternative methods**
Delavirdine	**EE may increase**	**Unknown significance** **Dose unchanged**
Etravirine	**↑ EE 22%** **No change NE**	**Dose unchanged**

EE= Ethinyl estradiol, NE= Norethindrone

DHHS Guidelines: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

Pregnancy and Antiretroviral Development and Prevention Research: Summary

- **Women get pregnant:**
  - **Half of pregnancies are unplanned.**
  - **Inadvertent exposure to drugs before the woman knows she is pregnant is common.**
  - **Therefore, essential to have data on safety in pregnancy because pregnancies will occur in real life.**
  - **Drug interaction with hormonal contraceptives may increase risk of pregnancy.**

Pregnancy and Antiretroviral Development and Prevention Research: Summary

- **Need pharmacokinetic studies in pregnancy:**
  - **Drug dosing may need modification.**
- **Placental passage of drug:**
  - **Important for prevention of MTCT and also for infant safety.**
- **Breast milk passage of drug:**
  - **Important for issues of development of drug resistance in milk virus, infant safety and possibly also prevention of MTCT.**

Pregnancy and Antiretroviral Development and Prevention Research: Summary

- **Maternal toxicity:**
  - Possible increase in toxicity in pregnancy (lactic acidosis, NVP hepatic toxicity).
- **Fetal toxicity:**
  - Need to support ARV Pregnancy Registry to better assess risk for birth defects.
- **Infant toxicity:**
  - Need for studies to follow-up of uninfected infants for late toxicity of *in utero* exposure.

Thank You For Your Attention