Pharmacokinetics/Pharmacodynamics and Safety of ARVs During Breastfeeding

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IMPAACT
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Adolescent AIDS Clinical Trials Network

Pharmacologic Issues with BF in HIV Exposed and Infected Infants

- BF has general health benefits for mother and infant
- ARV concentrations in BM may have antiviral effects – enhance PMTCT
- Low ARV concentrations in BM may promote resistance in infants with established or acute HIV infection
- Infant exposure to ARVs via Breast Feeding may lead to infant toxicity
  - ARV exposure exclusively through BF
  - ARV dosing in conjunction with BF

Benefits of Breastfeeding for the Infant

Condition	Reduced Risk
Otitis media	23-77%
Respiratory tract infections	63-77%
Gastroenteritis	64%
SIDS	36%
Atopic dermatitis	27-42%
Inflammatory bowel disease	31%
Diabetes mellitus, 1 and 2	30-40%
Leukemia	15-20%
Obesity	13%
Asthma (?)*	26-40%

AAP. Pediatrics 2012;129:e827-41.
*Colen CG, Ramey DM. Soc Sci Med 2014;109:55-65.
Horta BL et al. Acta Pediatrica 2015;104:30-37.

Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

Parvaz Madadi Gideon Koren, MD, FRCPC James Cairns, MD David Chitayat, MD Andrea Gaedigk, PHD
J. Steven Leeder, PHARMD, PHD Ronni Teitelbaum, MSC Tatyana Karaskov, MD Katarina Aleksa, PHD

Canadian Family Physician 2007

Maternal CYP2D6 UM associated with excessive conversion of codeine to morphine

Published Case Reports on Drug Adverse Reactions to Various Drugs through BF

141 publications worldwide
153 infants reported
- 2 probable deaths
  - codeine
  - oxycodone
- 5 possible deaths
  - bromazepam
  - 3 methadone (1 with cocaine)
  - phenytoin + phenobarbital

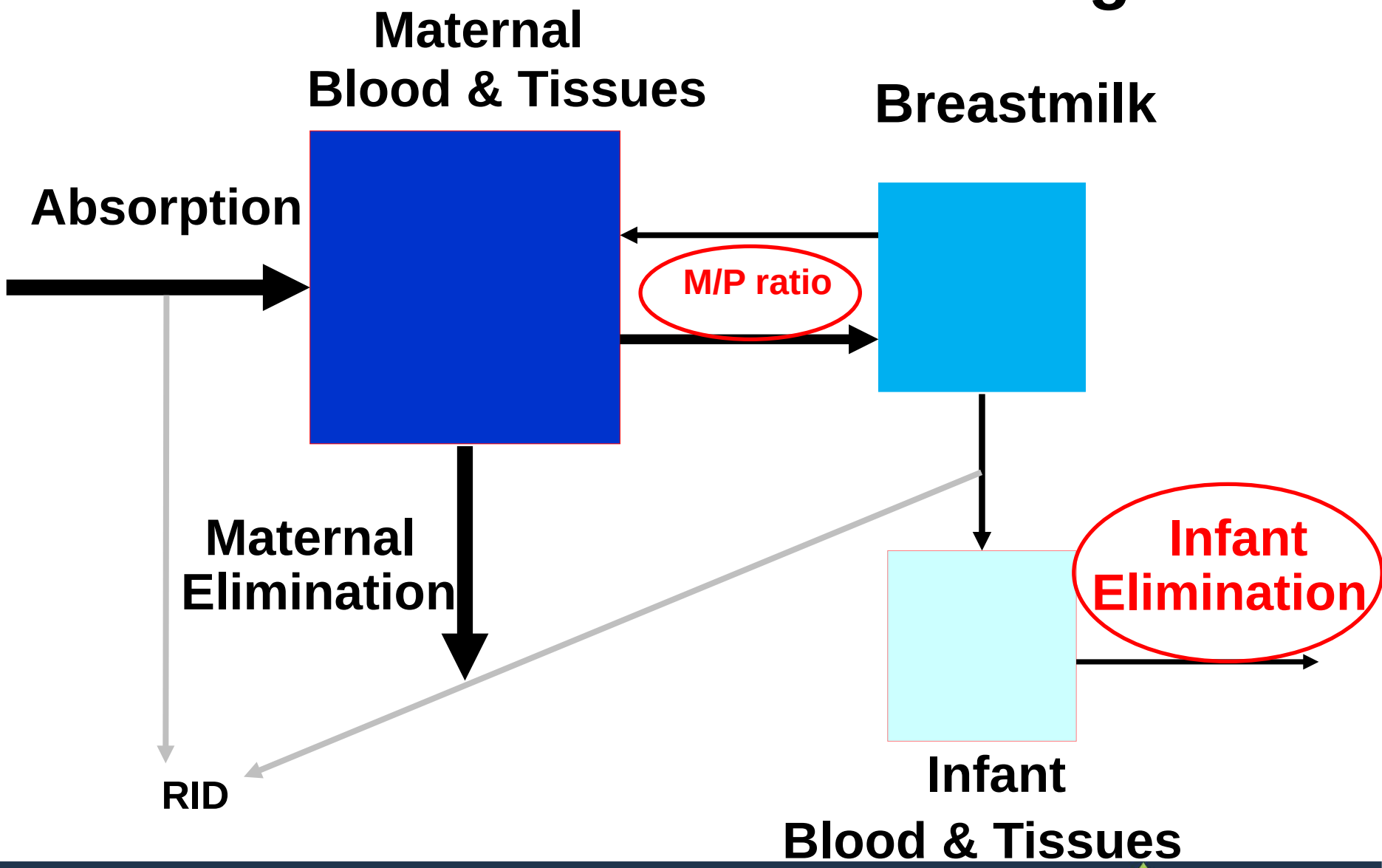
Clin Pediatr 2003;42:325-40,Clin Pediatr 2016;55:236-44, J Forensic Sci 2016;61:576-80.

PK/PD of Codeine During BF

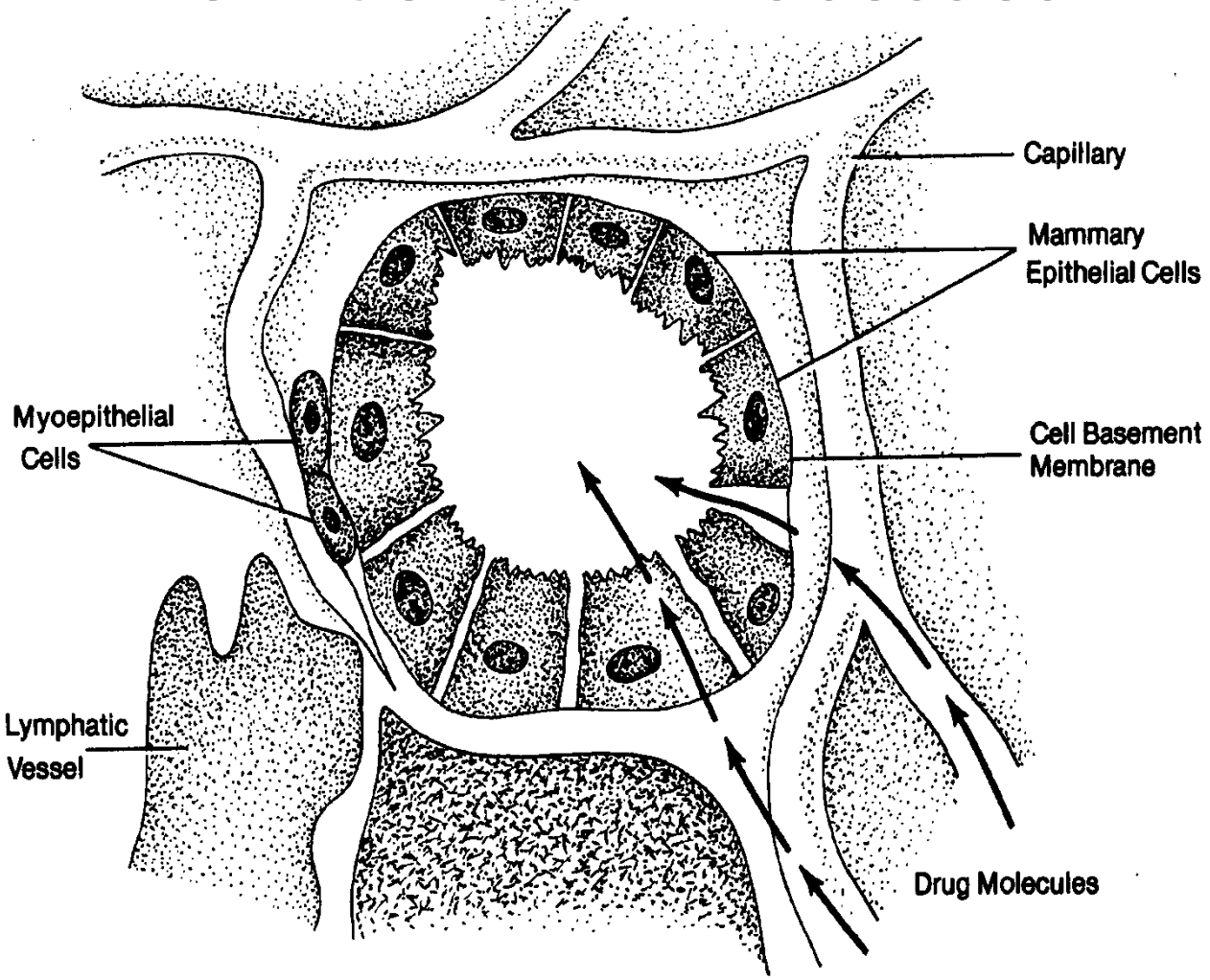
- Previous reports of CNS depression in up to 24 percent of BF infants where mothers report codeine use
- Five out 238 (2.1 %) met criteria for CNS depression
- Duration of maternal use a risk factor
- Pharmacogenomics not predictive in infants
  - CYP2D6
  - UGT 2B7
  - MDR1
  - OPRM1
  - COMT
- MDR1 polymorphism associated with maternal sedation

Kelly et al 2013 PLoS ONE 8(7): e70073.

PK Model for Breast Feeding



Drug Transfer into BM By Trans- and Peri-Cellular Processes

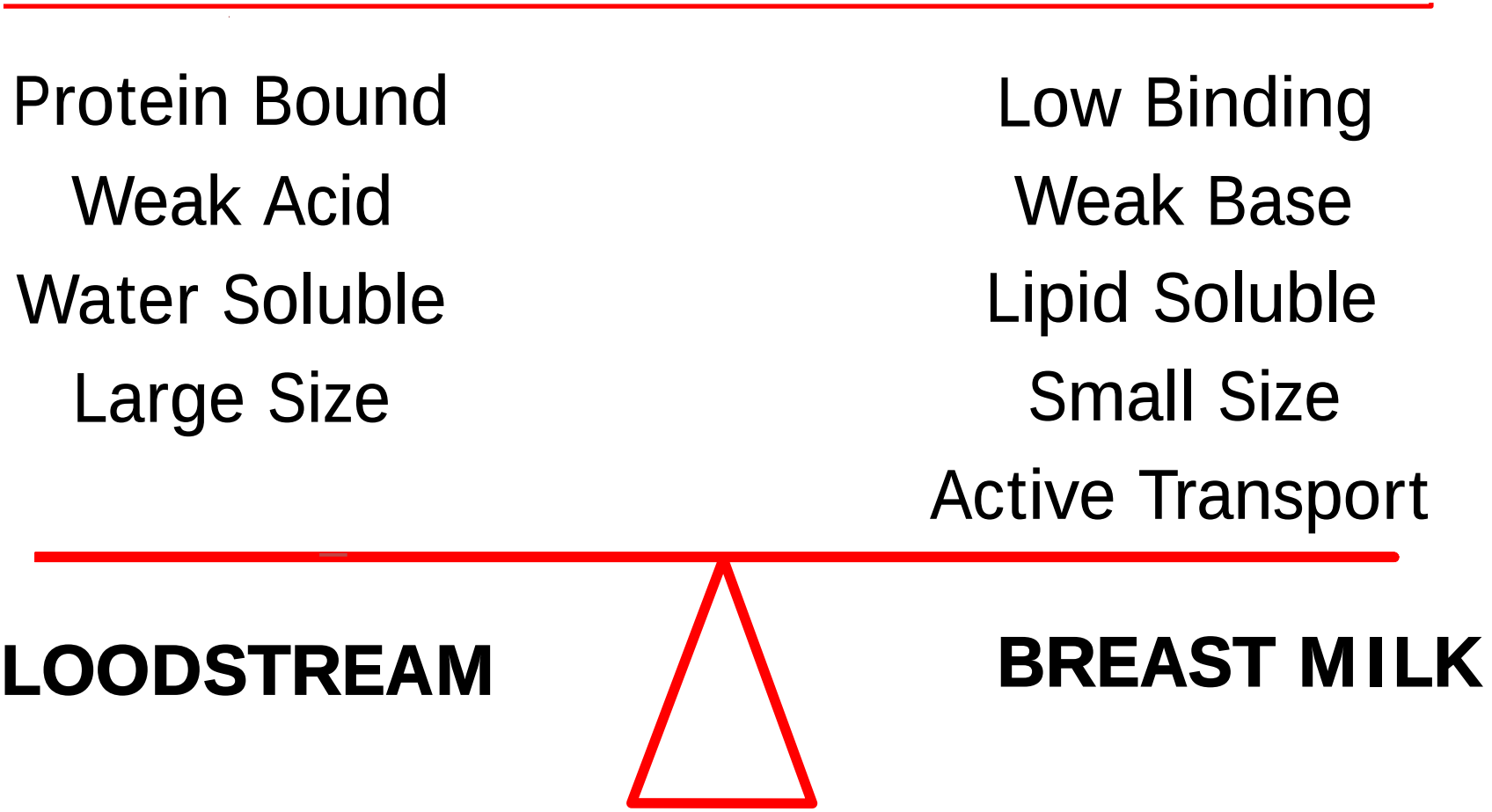


Unique Issues with BM Distribution of Drugs

- **Ion Trapping** – BM "traps" bases with pH of 6.5
- **Lipid Trapping** – Although only ~3-5% of BM is fat, lipid fraction can account for up 50-75% of BM drug (e.g. diazepam)
- **Reduced Protein Binding** – Albumin in BM 1% of plasma. Mostly BM protein whey and casein. Even drugs highly bound in plasma are often <50% bound in BM
- **Maternal Dose Time** vs BF time may be important for short half-life drugs.
- **Active Transport** into BM– BCRP (e.g. acyclovir)

Factors in BM/Plasma Ratio

Small, Unbound, Water Soluble => BM/Plasma Ratio ~1



Infant ARV Dosage Through BF

Infant Dosage = Milk Drug Concentration x Milk Volume

Average Milk Volume = 150 mL/kg/day

Example:

If Maternal ARV $Conc_{(ave)}$ = 1 mg/L & BM/PL ratio = 1

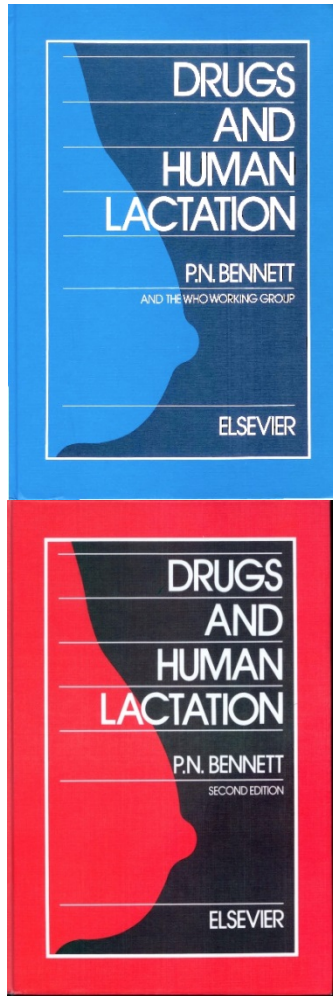
Then Infant Dose = 0.15 mg/kg/d

Infant dose higher than 0.15 mcg/kg/d, if active secretion into BM

BF Classification System (RID) –

BM/Plasma Ratio has Ambiguous Clinical Implications

- **Acceptable**
  - < 10% of maternal dosage
- **Caution**
  - 10% to 25% of maternal dosage
- **Unacceptable**
  - >25% of maternal dosage
  - inherent toxicity (eg, cytotoxics)
  - credible reported toxicity
- **Does not account for altered F from BM**



Bennett PN ed. Drugs and human lactation. Elsevier 1988 & 1996.

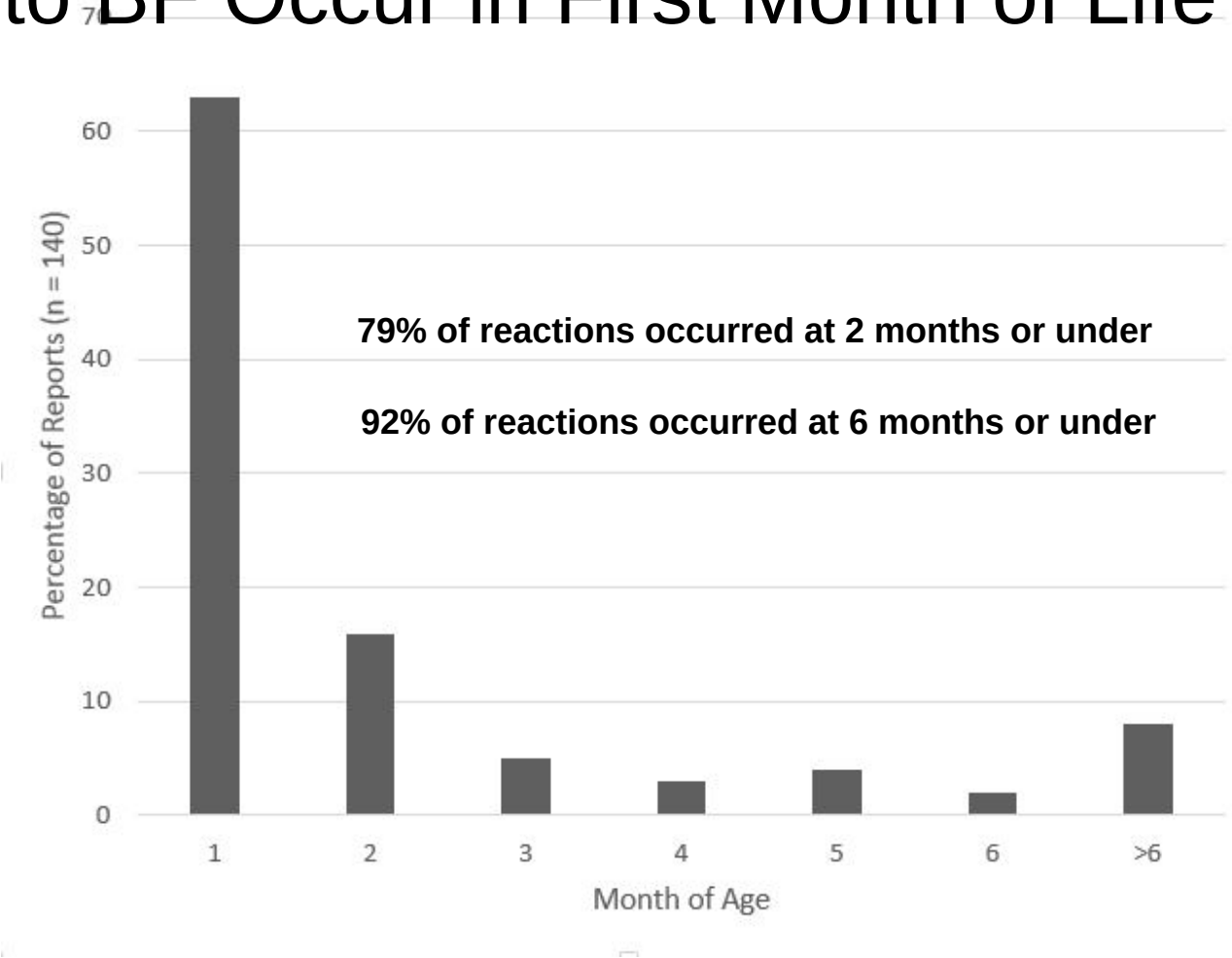
Relative Infant Dosage (RID) Compared to Mother's Dosage for 205 Drugs

Relative Dosage*	Percentage of Drugs		Adverse Reactions (%)
< 1%	47%		0%
1-4.9%	28%	87%	2%
5-9.9%	12%		8%
10-24.9%	10%		19%
> 25%	3%		100%

*Wt. adjusted

Bennett PN, Notarianni LJ. Br J Clin Pharmacol 1996;42: P673-4. Abstract.

Most Drug Related Adverse Reactions Due to BF Occur in First Month of Life



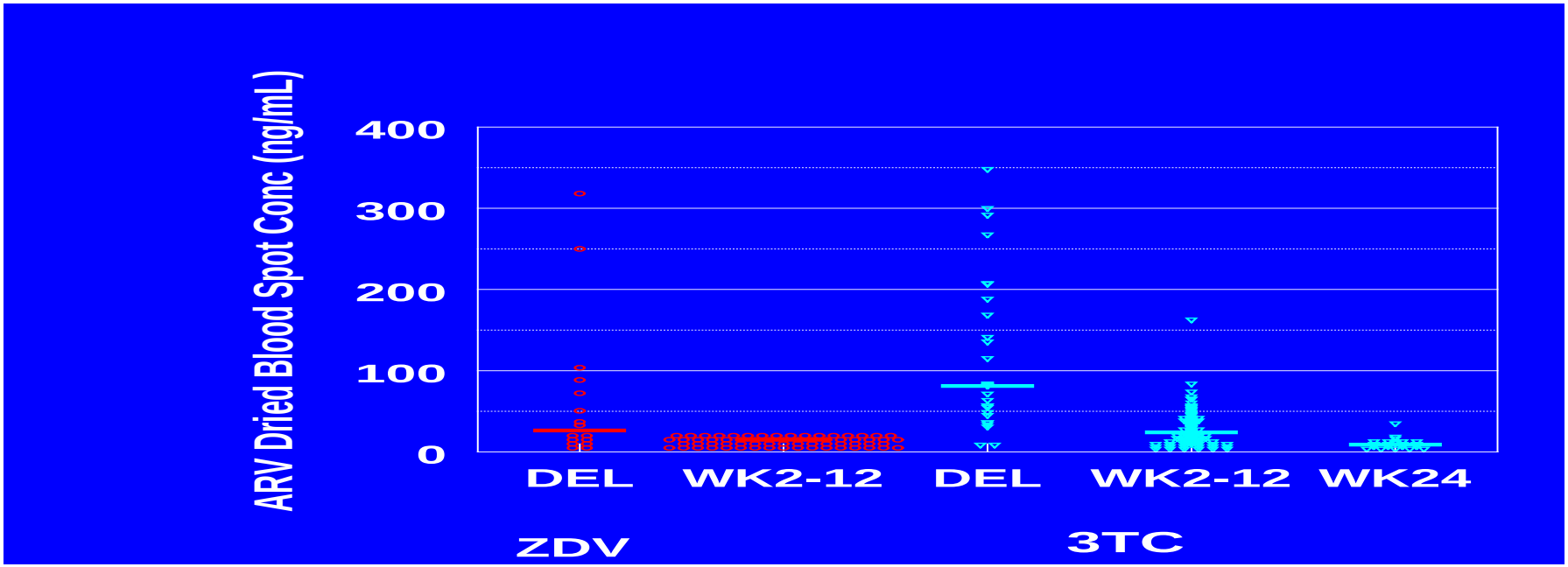
Anderson PO et al. Clin Pediatr 2016;55:236-44.

ARV Characteristics and BM PK

Drug	BM Conc (mcg/mL)	BM/PL Ratio	Maternal PL Conc (Ave) mcg/mL	Infant PL Conc mcg/mL	IC50 mcg/mL	RID (%)	Lipophilicity - Log(P)	Plasma Protein Binding
ZDV	<0.05	0.2-0.9	0.001-2.0 (0.15-0.3)	**BQL**	0.0053	<5	-0.3	30-38%
3TC	0.3-1.8	**0.9-3.7**	0.1-2 (0.3-0.5)	**0.005-0.050 (0.18)**	0.55	<5-10	-1.1	<36%
FTC	0.18-0.68	NR	0.1-2 (0.4-0.6)	**NR**	0.5	2	-0.9	<5%
ABC	0.057	0.6-1	0.2-3 (0.2-0.4)	**BQL - <0.005**	0.46	<5	0.39	50%
TDF	0.002-0.014	**<0.1**	0.05-1.5 (0.1)	**BQL - <0.025**	0.20	0.02	-3.7	<7%
NVP	1.8-6.8	0.6-0.9	4-6	**0.5-1**	0.024	**12**	2.49	60%
EFV	1.1-8.9	1-1.2	1-3	**0.09-1.7**	0.51	4	4.46	>99%
LPV	<0.25-1.8	0.02-0.40	4-10	**<0.01-0.5 (0.1)**	**0.0019**	**<1 / ?RTV**	4.69	98-99%
DTG (n=1)	0.1	**~0.02-0.1**	1-4	**0.01**	1.13	<1	1.1	**>98.9%**

NRTIs in Breast Feeding

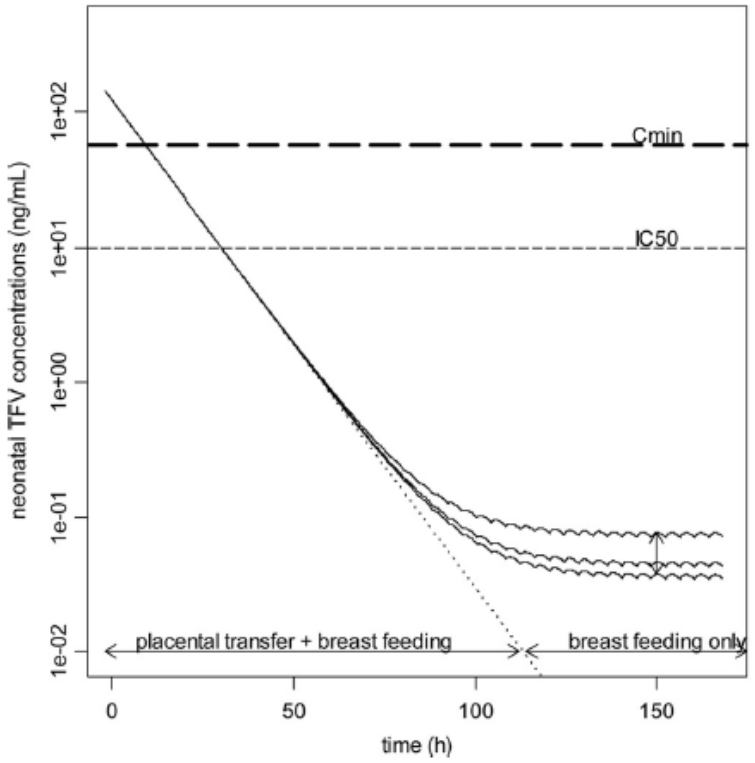
	Maternal Plasma (ng/ml) ZDV/3TC n=45/201	Breast Milk (ng/ml) n=37/192	Breast Milk/Plasma Ratio n=35/168	Infant Dried Blood Spot (ng/ml) n=82/190
ZDV	23 (median) 12-59 (IQR)	9 (bql-26)	.46 (.25-.86)	bql (bql-bql)
3TC	403 (230-758)	1158 (735-1622)	2.51 (1.79-3.69)	25 (10-41)



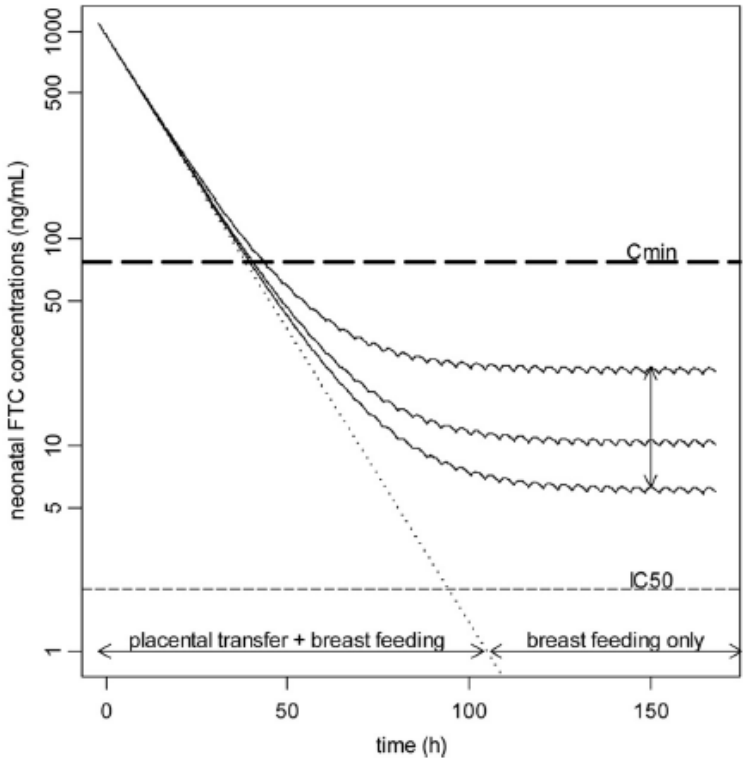
Mirochnick AAC 2009

Predicted TFV and FTC Exposure in Infants-
Maternal Transfer In Utero and Through BF

TFV

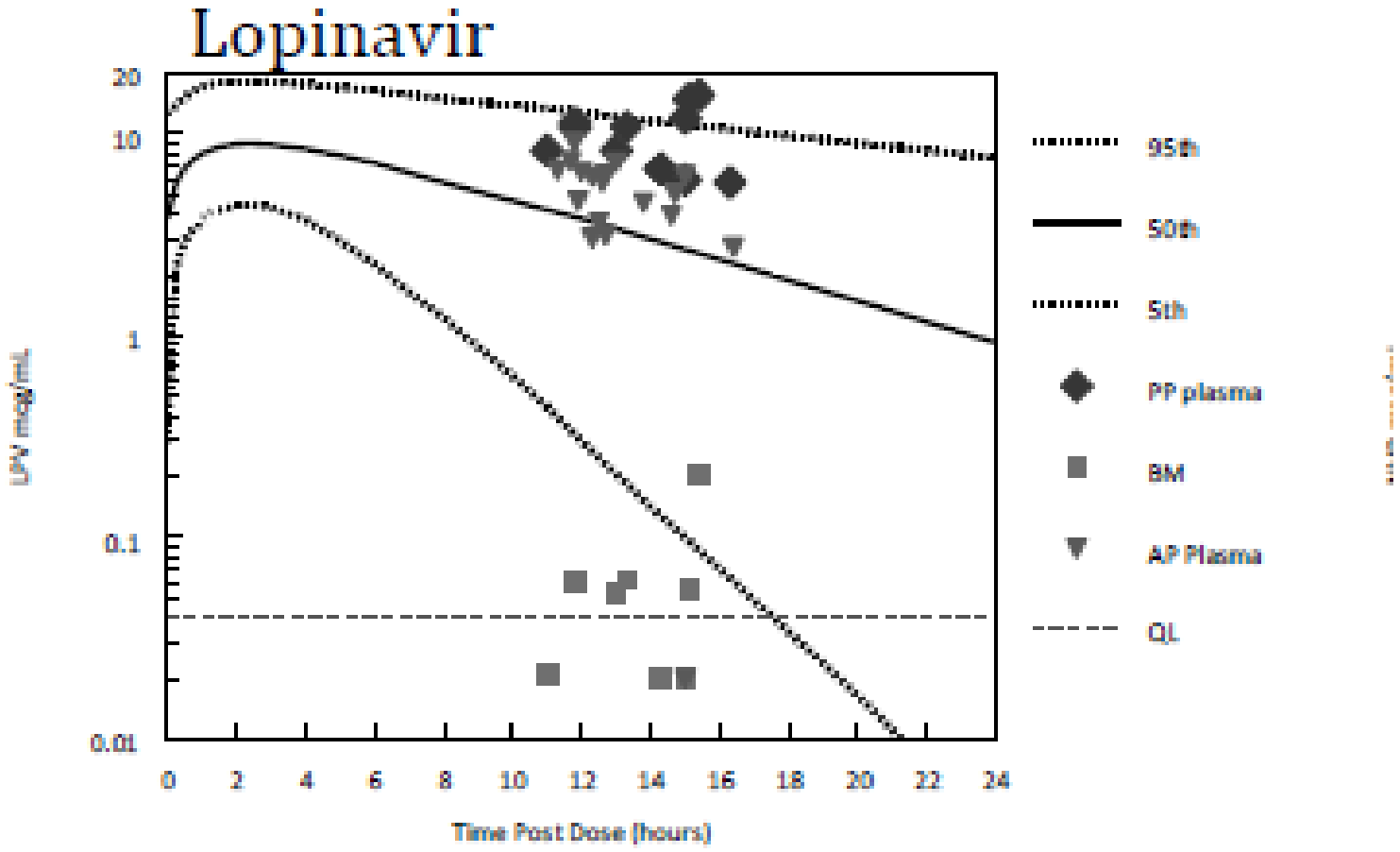


FTC



S Benaboud et al. AAC 2011

Limited LPV found in Human BM of Women Receiving LPV/r containing cART

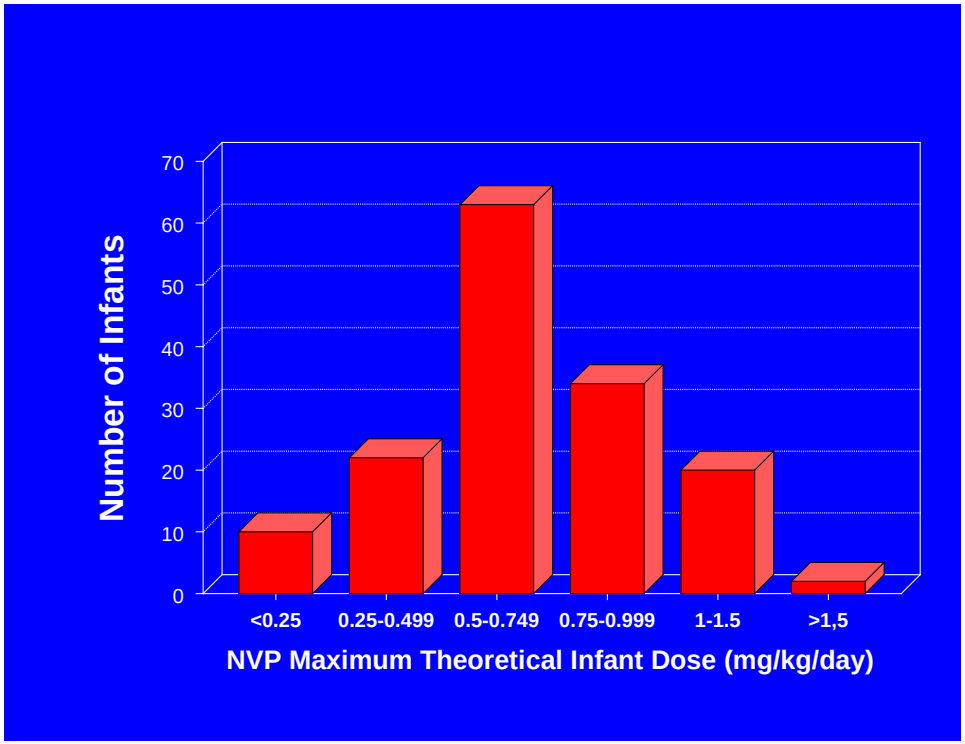


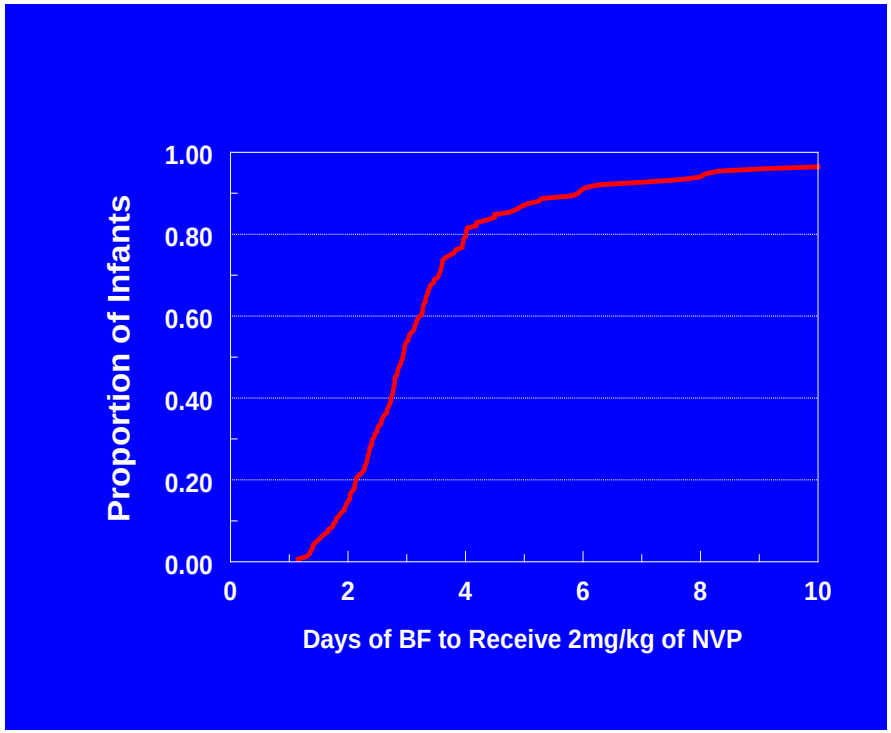
R Shapiro et al. 2012 Antiviral Ther

Nevirapine (NVP) Results

Maternal Plasma (ng/ml) n=194	Breast Milk (ng/ml) n=184	Breast Milk/Plasma Ratio n=175	Infant Dried Blood Spot (ng/ml) n=192
5802 (median) 4490-7377 (IQR)	4386 (3177-5565)	0.73 (0.60-0.88)	911 (526-1356)

Estimated Infant NVP BM "Dose"



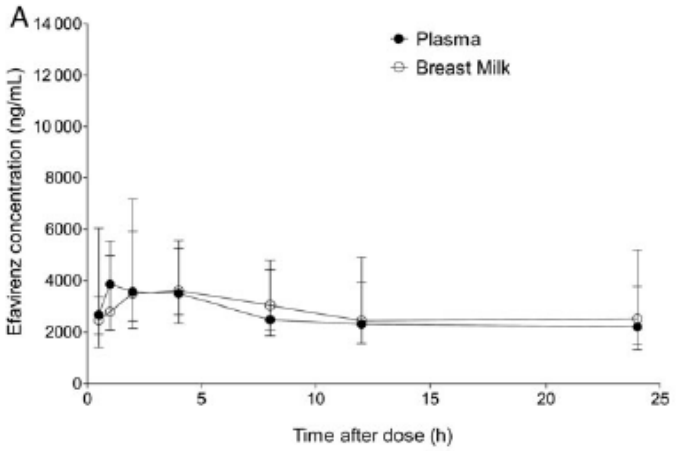


Mirochnick AAC 2009

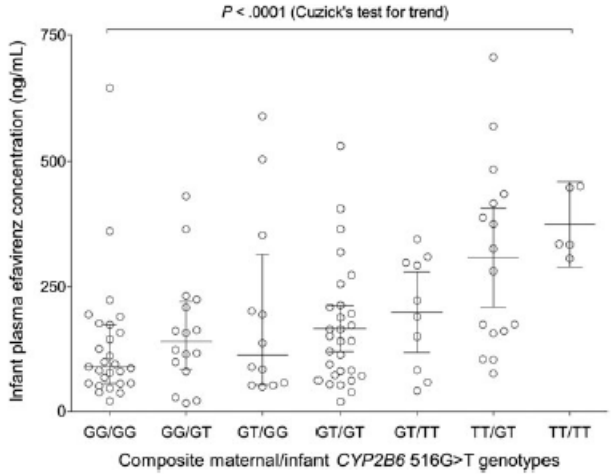
Breast Milk PK of Efavirenz

- Maternal EFV cART and BF infants 134 pairs
- BM/plasma ratio 1.1; RID 4%
- Infant levels in ~10xs higher in first week of life:
  - 1590 vs 157 ng/mL
  - Immature metabolism + in utero transfer
  - Other studies suggest some persistence substantial EFV in infants beyond the firs week of life
- CYP 2B6 genotype impacted BM conc but not BM/plasma ratio

BM and Plasma PK Profiles



PG and EFV in BF Infants



Olagunju et al. CID 2015

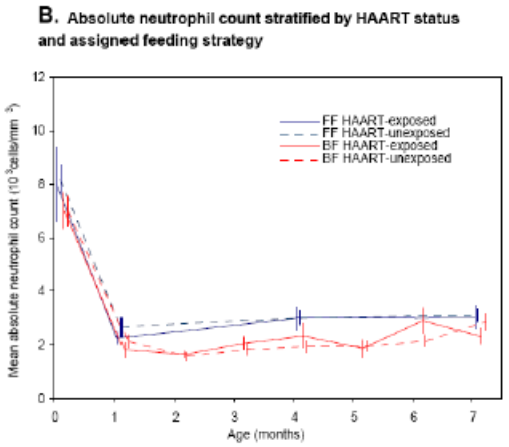
AEs in Infants Exposed to NVP cART through BF

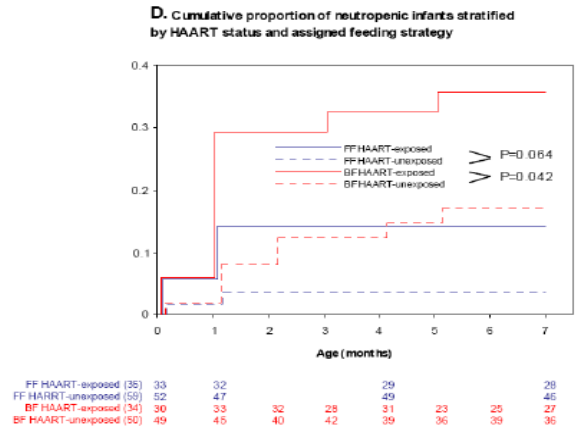
AE – in BF Infants of Mothers with cART (Minniear TD et al PIDJ 2012)

- NVP (n=258) vs NFV (n=206)
- Moderate rash 2.7% NVP vs. 0.5% NFV at 2 weeks PP
- Hepatoxicity 0% NVP vs 1.9% NFV
- Early high-risk hyperbilirubinia 4.5% overall (first 48h)

Maternal HAART, BF and Neutrapenia

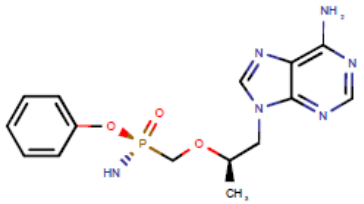
MASHI Sub-Study Bae et al AIDS 2008



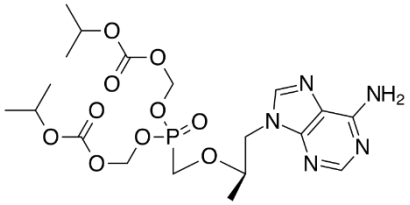


Neutropenia Risk
Maternal In utero HAART
15.9% vs 3.7%

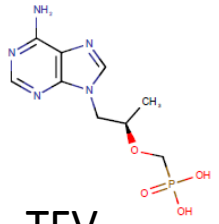
Expected BM Exposure with TAF



TAF



TD



TFV
(PMPA)

- TFV (PMPA): BM/PL ratio <0.1 and RID <1
  - Infant TFV Conc 23 and <3 ng/mL at 6m & 12m (L Palombi JAC 2016)
  - >90% Infant TFV Conc < 0.3 ng/mL at 1-24 wk (Mugwanya PLoSMed 2016)
  - Infant TFV Conc 2.4 ng/mL after 1% intravaginal gel x 6 d (Noguchi AAC 2016)

- TAF vs TDF – Key properties associated with BM disposition
  - TAF slight more lipophilic than TDF (**reduced** skim BM conc)
  - TAF ~2xs larger than TDF (**reduced** BM conc)
  - TAF > 10x plasma protein binding (**reduced** BM conc)
  - H_20 solubility 0.25 that of TDF (**reduced** BM conc)
  - Ave maternal conc 10% of TDF (**reduced** BM conc)
  - TAF transport, lipid & cell associated TFV in BM ?

Potential Infant Exposure Through Breastfeeding of **Unstudied** ARVs

Drug	Plasma Protein Binding	Food Effect on F	Maternal Plasma Conc (Ave) mcg/mL	Predicted Infant Dose (mg/k/d) If BM/PL Ratio=1*	Predicted RID If BM/PL Ratio=1*
TAF	80%	1.65	0.01	0.0015	<1
DRV	**95%**	1.30	4-7	0.75	4.4
RPV	**>99%**	1.67	0.05-0.15	0.015	4.2
MVC	76%	0.67	0.05-0.15	0.015	<1
RAL	83%	2.00	6-9	1.125	**9.8**
DTG	**≥99%**	1.66	1-4	0.375	**52 (vs <0.1[+])**

For RID predictions a high BM/PL ratio = 1 was used as "highest infant exposure" possible scenario. It is liberal estimate and is likely overestimates the true RID by several fold for drugs with high protein binding [+]Case Report estimated RID

Summary

- BF PK data overall limited, variable and results are study collection time and matrix (skim vs whole milk) dependent
- Highest drug exposure and risk for related AEs in first few weeks of life
  - Combination of in utero / BF sources
  - Immature newborn elimination
- PK/PD implications of ARV exposure via BF vary greatly among compounds.
  - ZDV, ABC, TDF – very low conc unlikely to have any clinical impact
  - 3TC, FTC, LPV –low conc limited antiviral or toxicity effect but may be in range to promote resistance
  - NNRTI – significant conc – but less than with systemic dosing
  - INI / TAF / mAB / Boosters – suspected limited conc but need studies

- Kisumu Study Investigators
  - Mark Mirochnick
  - Mary Glenn Fowler
  - Michael Thigpen
  - Paul Weidle
- Mna Bana Investigators
  - Roger Shapiro
  - Shahin Lockman
- Study Participants and Site Personnel
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