High Rates of HIVDR Complicate ART Choices for Children and Adolescents

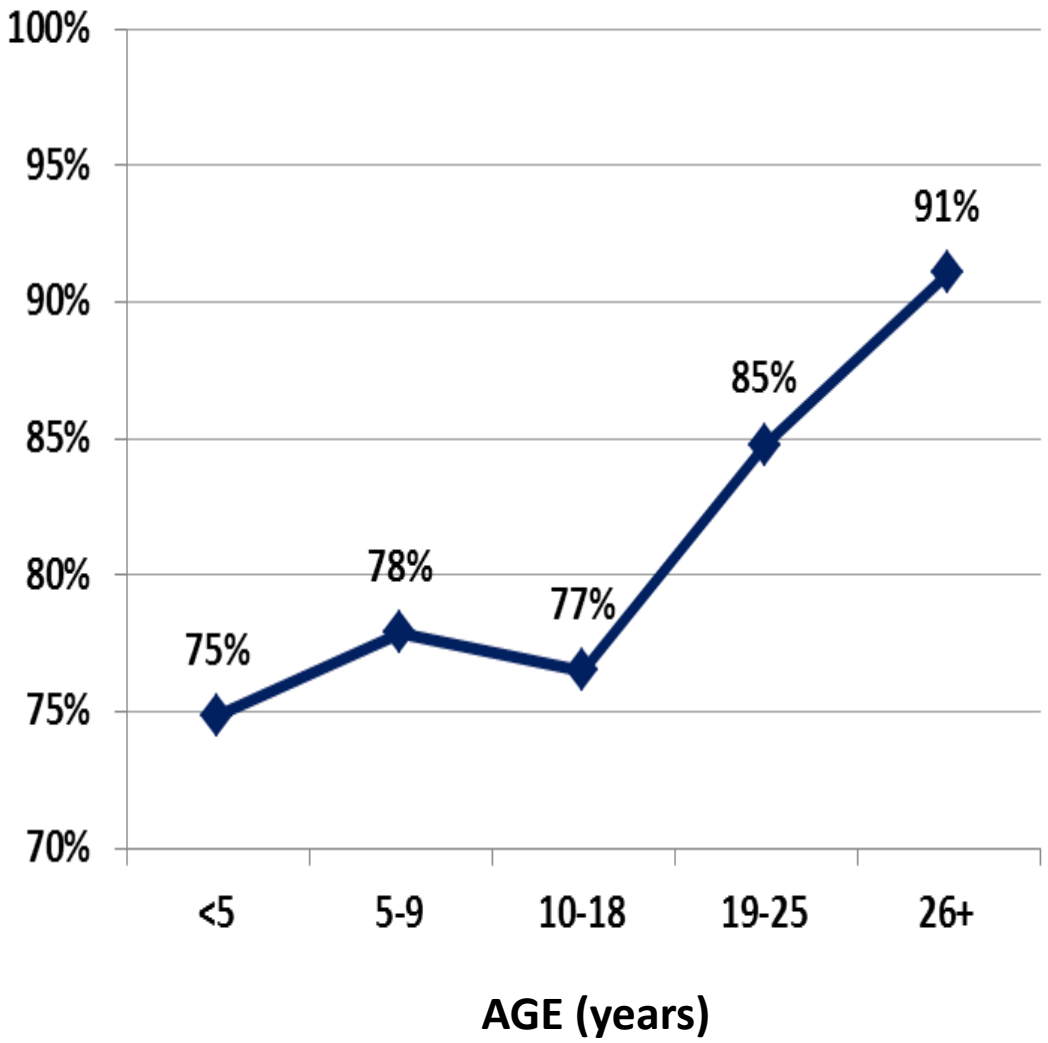
George K Siberry, MD, MPH
Senior Pediatric Technical Advisor
Office of the U.S. Global AIDS Coordinator
April 2016

Outline

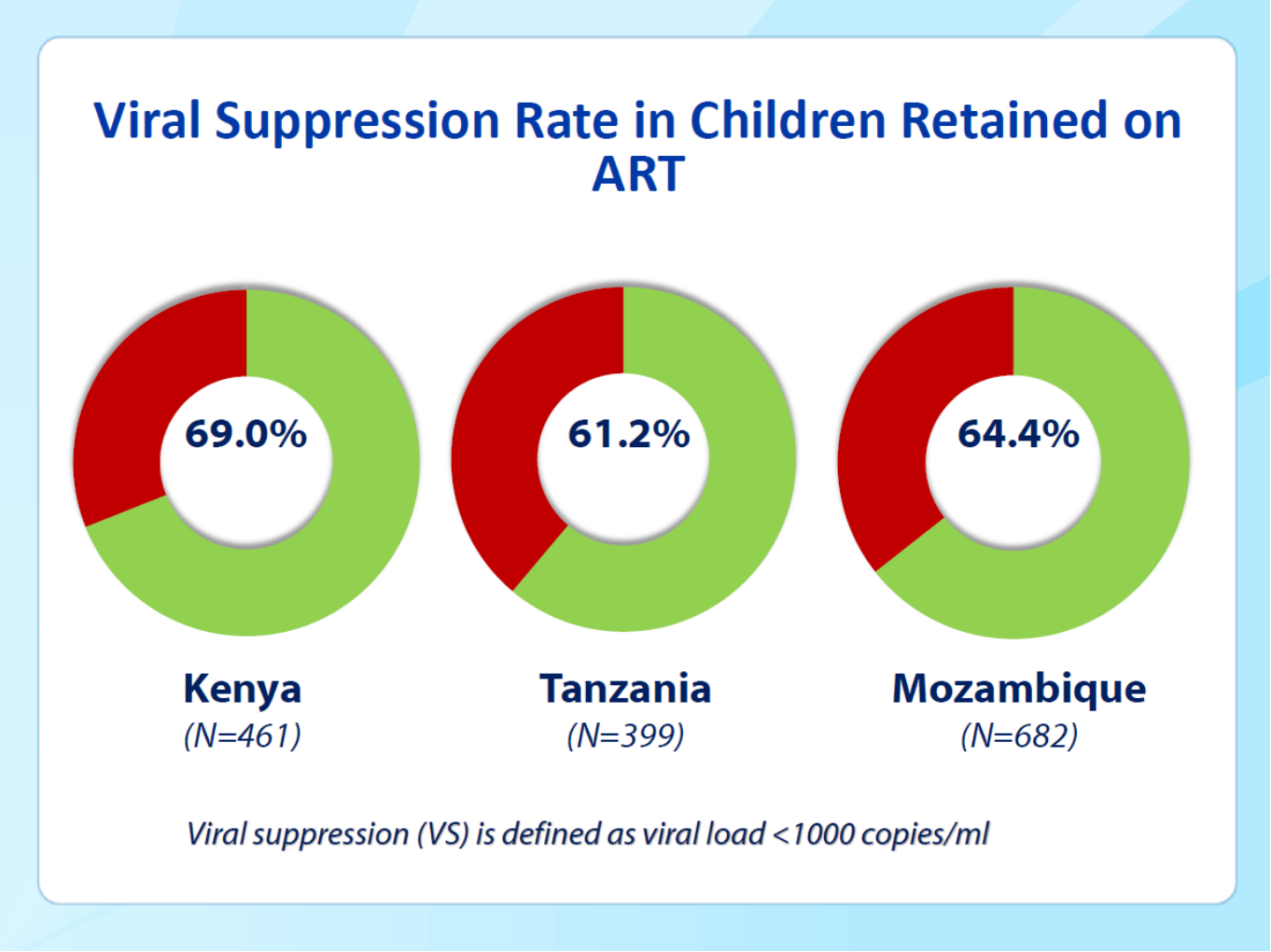
- Epidemiology of virologic failure with drug resistance in children
- Unique factors in children that contribute to drug resistance
- Available and upcoming treatment options for children
  - Reduce drug resistance
  - Active in the face of drug resistance

Uganda VL Suppression Rates by Age

(data from Uganda MOH, Dec 2015)



Virologic Suppression Among Children (<15 yrs old) on ART ≥6 months – Viral Load Scale-up in 3 Countries



Failure rates of 31-39%

RED: VL≥1000 copies/mL

Suzanne Beard, CDC – ACT Workshop 2015

Drug Resistance (HIVDR) in Children with Virologic Failure

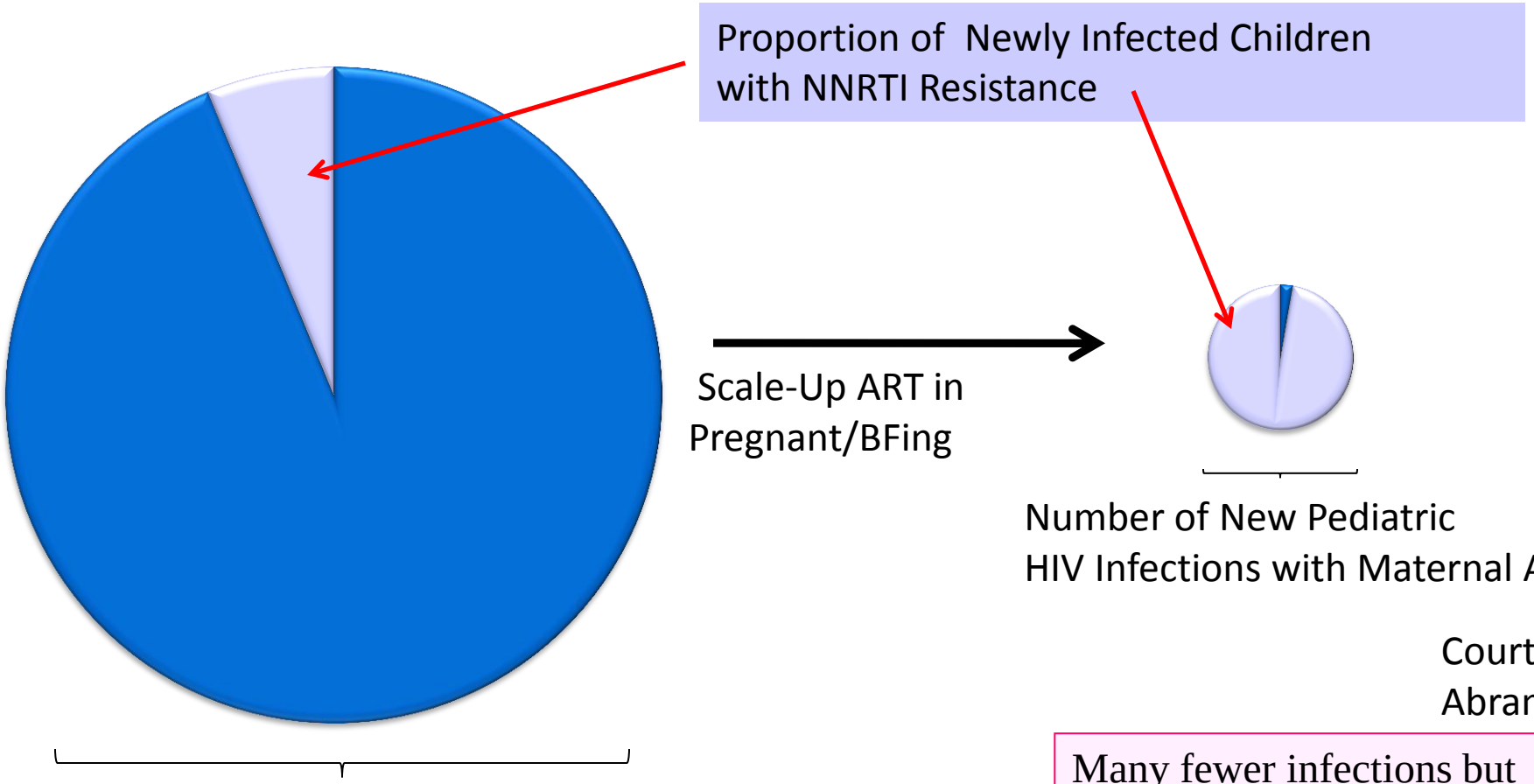
HIVDR Prevalence Among Children Failing Treatment

Group	N	VF (n)	Genotyped (n)	HIVDR (n)	HIVDR %	95% C.I.
Kenya	461	143	136	121	89.0%	76.7%-95.2%
Tanzania	399	155	141	122	86.5%	78.4%-91.9%
Mozambique	682	243	232	222	95.7%	92.3%-97.6%

Conclusion: Most children failed treatment due to HIVDR

Suzanne Beard, CDC – ACT Workshop 2015

Increasing Use of ART for Pregnant & Breastfeeding Women: Impact on New Infant Infection Incidence and Drug Resistance



Courtesy: Abrams

Many fewer infections but proportionally more of those who become infected despite ARV may have ARV resistance

Drug resistance in newly diagnosed children (<2 yrs old), **2011** South Africa Kuhn AIDS2014

- Of 230 children tested, 155 (**67%**) ARV-exposed via PMTCT (Maternal and/or Infant)

DR Class	ARV Exposed (155; 67%)	ARV Unexposed (75; 33%)	Most common DRM
NNRTI	57%	24%	181C >> 103N>190A
NRTI	15%	11%	184V, 69N, 74V
PI	<2%	<2%	46I/L/T

- 181C with NVP exposure more common in children (103N in adults) – less deleterious impact on EFV activity
  - High-level NVP DR in 54% PMTCT exposed; 17%PMTCT unexposed
  - **High-level EFV DR in 22% PMTCT exposed; 7% unexposed**
- Delayed diagnosis compromises DR testing utility
  - NNRTI DRM detected in 86% tested <=8 wks old, 57% tested <= 17-26 wks old. <25% tested beyond 1 yr old

Virological outcome and DR prevalence stratified by regimen type for children (<15 yrs old)

CDC, Program Data – Viral Load Scale-up

Country	Regimens	N	Virologic outcome		HIVDR	
			VS	VF	no DR	DR
Kenya	NVP-containing	287 (62%)	59.6%	40.4%[1]	65.5%	34.5%[2]
	EFV-containing	**133 (29%)**	**86.5%**	**13.5%**	**87.9%**	**12.1%**
	Other	41 (9%)	78.0%	22.0%	80.5%	19.5%
Tanzania	NVP-containing	269 (67%)	58.0%	42.0%[3]	65.1%	34.9%[4]
	EFV-containing	**122 (31%)**	**70.5%**	**29.5%**	**77.3%**	**22.7%**
	Other	8 (2%)	25.0%	75.0%	37.5%	62.5%
Mozambique	NVP-containing	615 (90%)	64.9%	35.1%	67.5%	32.5%
	Other/missing	67 (10%)	59.7%	40.3%	61.5%	38.5%

[1]Compared to EFV-containing regimens, $P<0.001$, ***OR=4.33*** (95% C.I. 2.50-7.51);
[2]Compared to EFV-containing regimens, $P<0.001$, ***OR=3.82*** (95% C.I. 2.14-6.81);
[3]Compared to EFV-containing regimens, $P = 0.02$, ***OR=1.73*** (95% C.I. 1.09-2.74);
[4]Compared to EFV-containing regimens, $P = 0.02$, ***OR=1.83*** (95% C.I. 1.11-3.01).

Emergence of Drug Resistance During Breastfeeding

Inzaule JAC 2016; Fogel CID 2011; Zeh PlosMed 2011

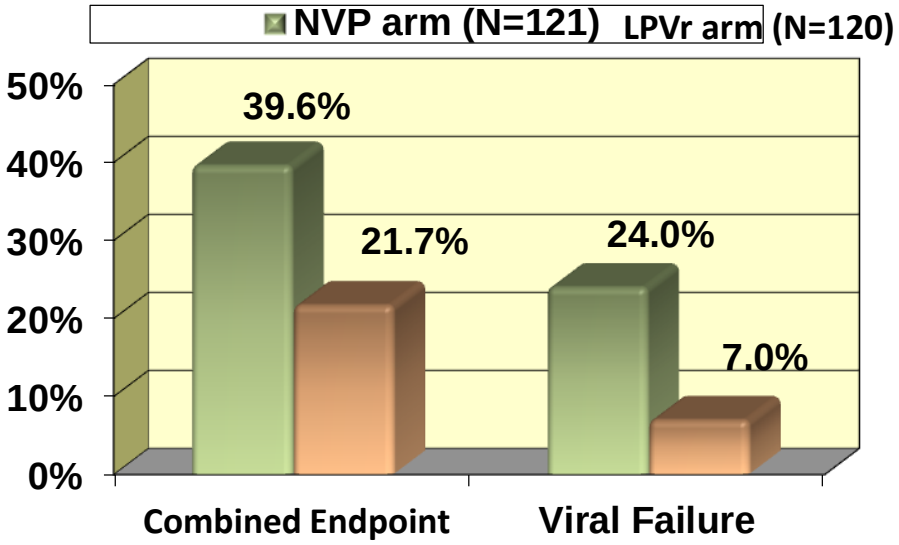
- KiBS (Kisumu BFing Study): maternal NVP or NFV with ZDV-3TC from 34 wks through 6-mos* breastfeeding
  - Only **6.4%** infected but **16/24 (67%)** with DRM detected by age 6 mos
  - **Only 4/18 (22%)** DRM detected at time point of **first** positive PCR
  - Mutations detected at first emergence of DRM
    - 184V (12 – 8 only); **65R** (4); 181C (4); 190A (2); 103N (2)
- PEPI-Malawi subset: women started d4T-3TC-NVP** postpartum
  - Of 37 infants infected during BFing (with post maternal ART GT available), 81% with NNRTI DRM and (11) **30% with multi-class DRM** with most common NRTI mutations being 184V (7) & **65R** (6).

*ART continued/restarted if extant ART indications met.
**Infants also rec'd NVP prophylaxis

P1060 : Comparing NVP to LPVr in Infants/Young Children

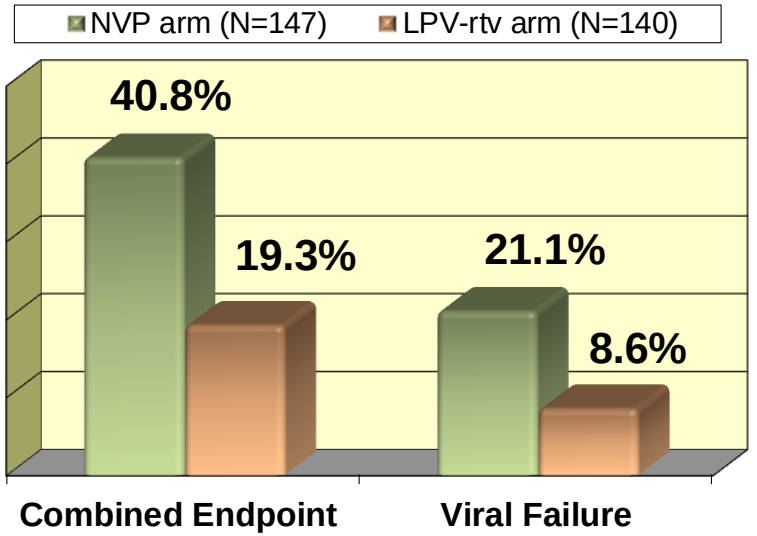
Cohort 1: NVP-exposed

Palumbo NEJM2010



Cohort 2: No NVP Exposure

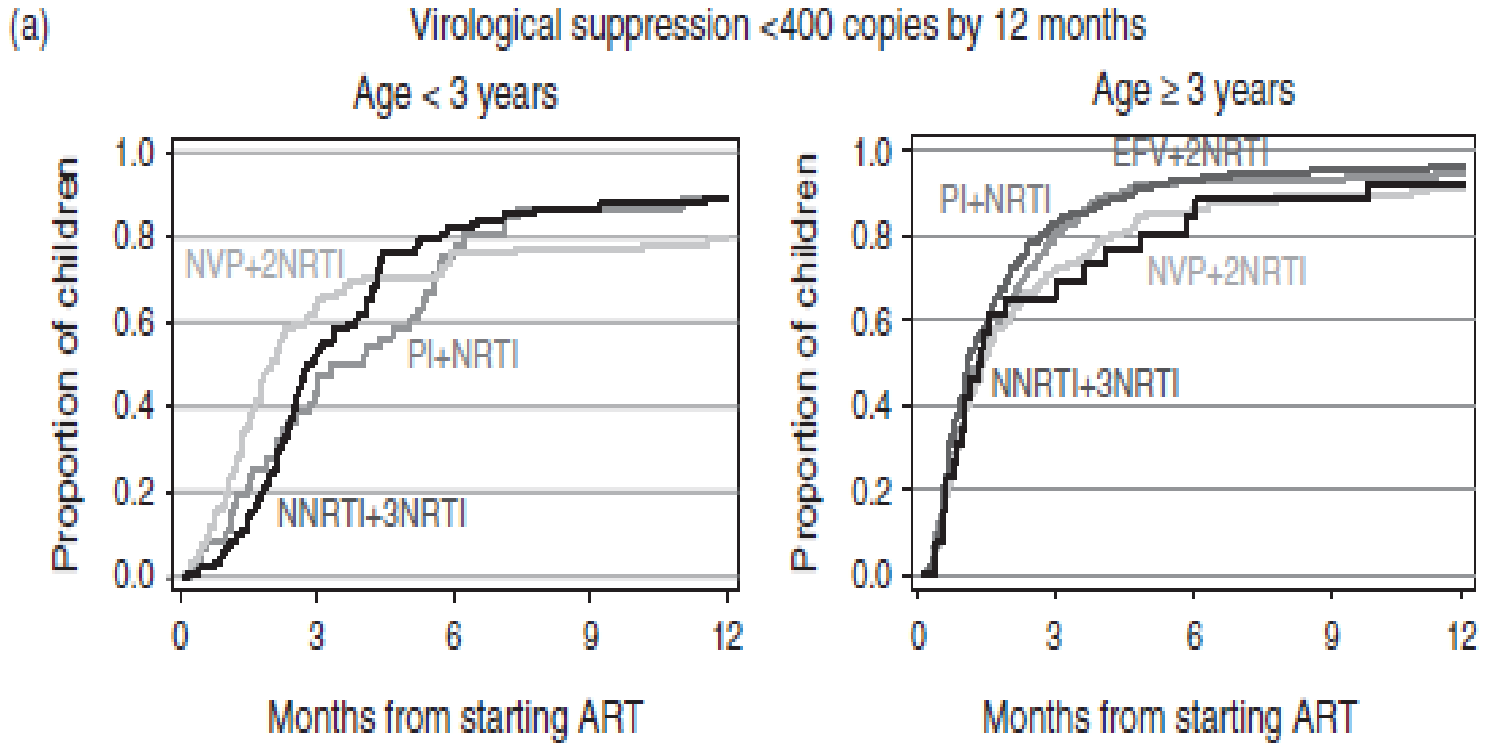
Violari NEJM 2012



Combined endpoint= Viral Failure, Off Study Drug, or Death

- Similar rates of overall failure (combined endpoint) & viral failure in NVP-exposed AND NVP-unexposed cohorts.
- Past (known) NNRTI exposure does not fully explain risk of NVP failure in children <3 years old

Longer time to virologic suppression in younger children



Duong et al, AIDS 2014, 28:2395-2405.

- **Risk factors for virologic failure included <u>NVP regimen, younger age, and higher VL</u>. NOTE: Young children – especially infants – have higher baseline VL than older children and adults**

Usual Lead-in NVP Dosing Produces Inadequate Exposure at Week 2

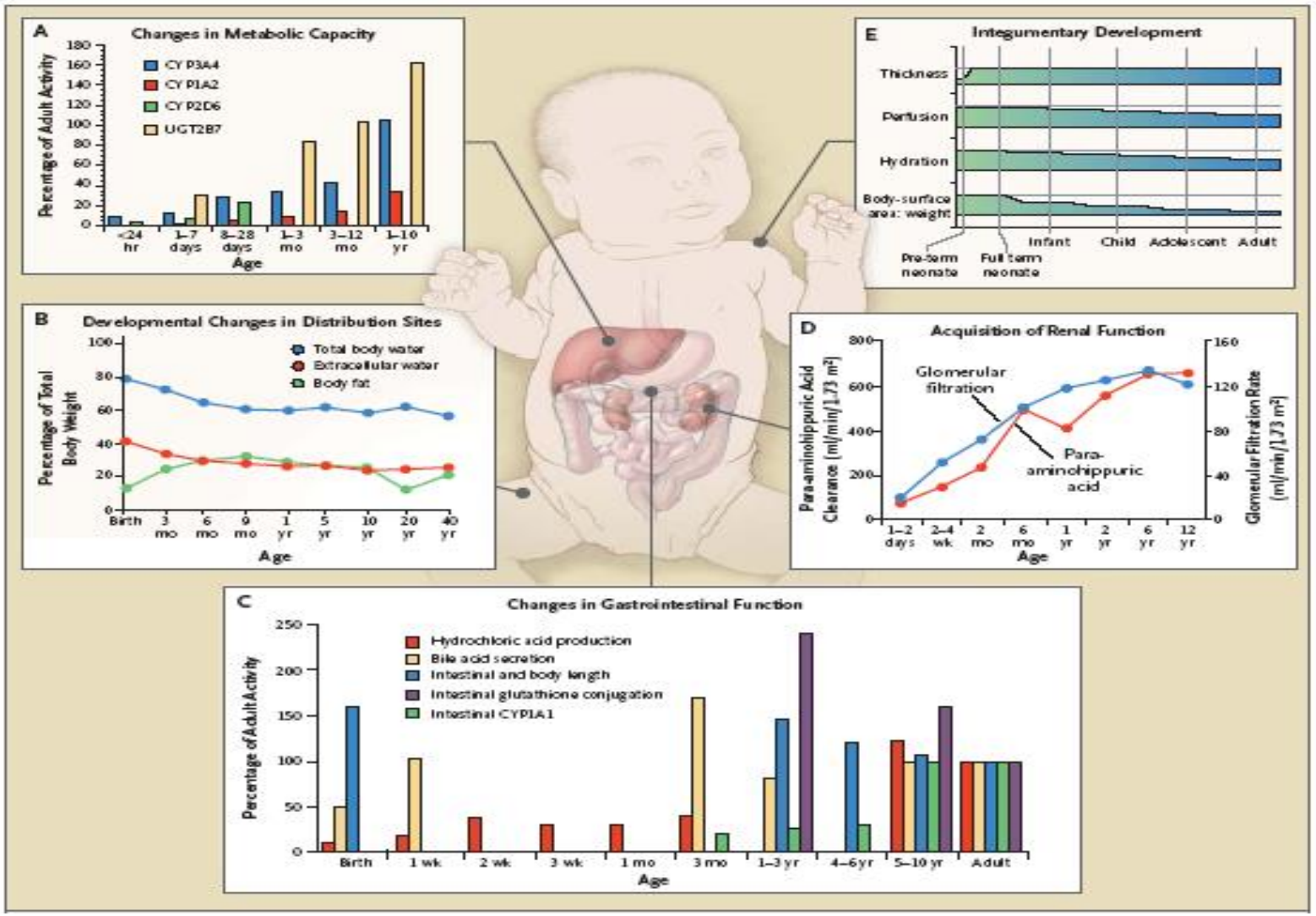
Fillekes CHAPAS AIDS 2013

	Children <2 years ($n=45$)	Children >2 years ($n=117$)	P
Nevirapine plasma concentration (mg/l)			
Full-dose group ($n=83$)	5.3 (4.2–9.0)	10.0 (7.9–12.2)	0.001
Dose-escalation group ($n=79$)	4.8 (2.9–6.4)	5.0 (3.9–6.6)	0.41
P value comparing full-dose versus dose-escalation	0.14	<0.001	*
Subtherapeutic nevirapine concentrations, n (%)			
Full-dose group ($n=83$)	3 out of 23 (13%)	4 out of 60 (7%)	0.39
Dose-escalation group ($n=79$)	7 out of 22 (32%)	7 out of 57 (12%)	0.05
P value comparing full-dose versus dose-escalation	0.16	0.35	**

- Children <2yrs old have lower exposure with full dose
- Almost 1/3 of children <2 yrs old have subtherapeutic NVP levels when lead-in dose used

Subtherapeutic nevirapine levels defined as <3.0 mg/L

Developmental Changes in Physiologic Factors Influencing Drug Disposition in Pediatrics



Kearns GL et.al. NEJM 2003;349:1157-67

Difficulties with ARV Administration to Children

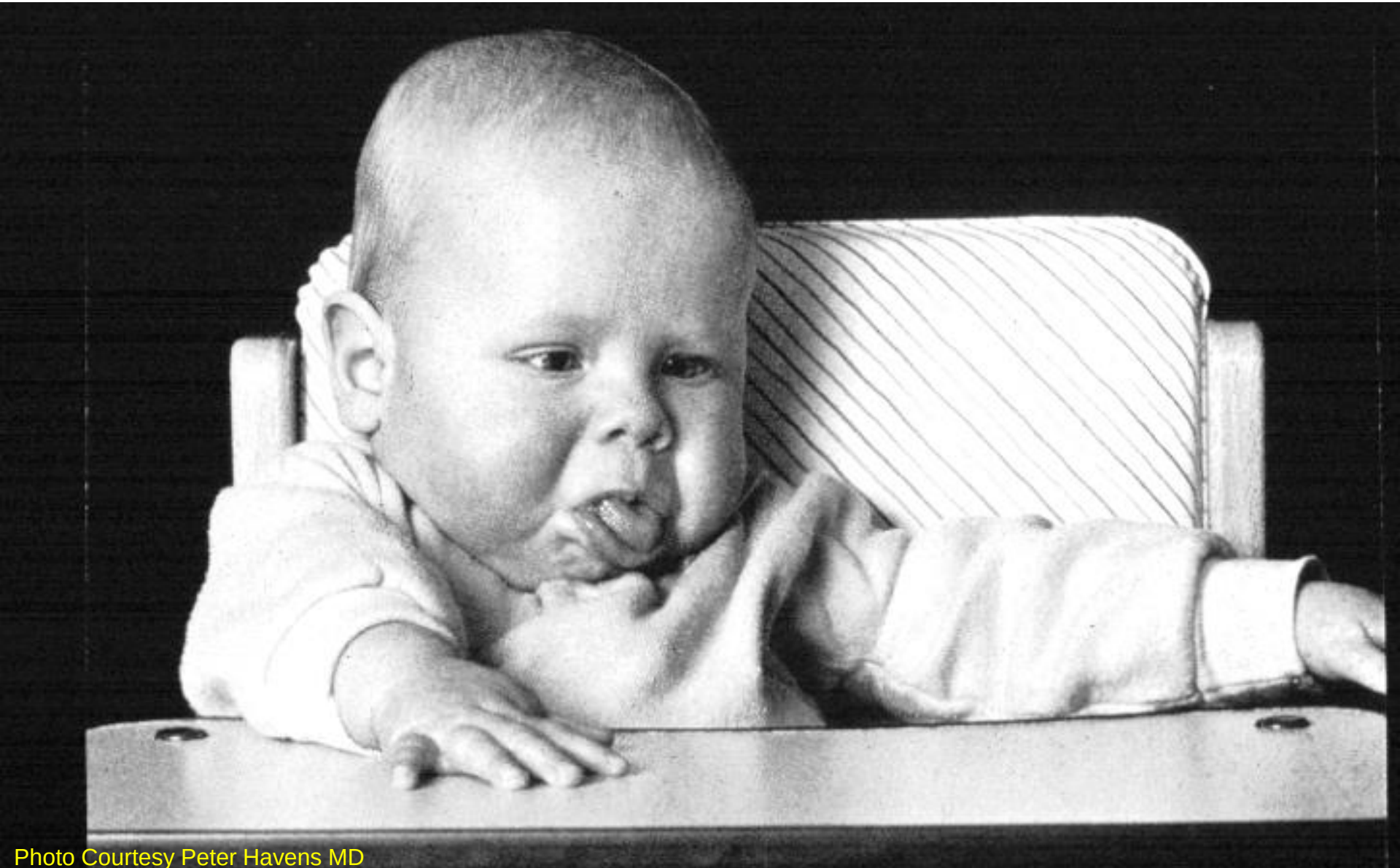


Photo Courtesy Peter Havens MD

Many Drugs Cannot Be Used in Children < 2-3 Years Old

NRTIs	**Abacavir (ABC)**	**≥ 3 months**
	Didanosine (ddI)	**≥ 2 weeks**
	Emtricitabine (FTC)	**Birth and up**
	Lamivudine (3TC)	**>3 months**
	Stavudine (d4T)	**Birth and up**
	Tenofovir (TDF)	≥ 2 years
	Tenofovir (TAF)	≥ 12 years
	Zidovudine (ZDV)	**Premature infants and up**
NNRTIs	*Efavirenz (EFV)*	*≥ 3 months/ ≥ 3.5 kg-* ***unreliable PK***
	Etravirine (ETR)	≥ 6 years, at least 16 kg
	Nevirapine (NVP)	**≥ 15 days**
	Rilpivirine (RPV)	≥ 12 years
PIs	**Atazanavir (ATV)**	**≥ 3 mos/5 kg**
	Darunavir (DRV)	≥ 3 years, ≥ 10 kg - warning against use <3 yrs old
	Fosamprenavir (FPV)	≥ 2 years
	Indinavir (IDV)	> 18 years
	Lopinavir/ritonavir (LPV/r)	**≥ 14 days**
	Nelfinavir (NFV)	≥ 2 years
	Ritonavir (RTV)	**≥ 14 days**
	Saquinavir (SQV)	> 16 years
	Tipranavir (TPV)	≥ 2 years (with ritonavir)
Entry/Fusion inhibitors	Enfuvirtide (T-20)	≥ 6 years
	Maraviroc (MVC)	≥ 16 years
Integrase inhibitors	**Raltegravir (RAL)**	**≥ 4 weeks**
	Dolutegravir (DTG)	≥ 12 years
	Elvitegravir (in some coforms)	≥ 12 years

WHO 2015 Guidelines

PREFERRED AND ALTERNATIVE FIRST-LINE ART REGIMENS		
First-line ART	**Preferred first-line regimen**	**Alternative first-line regimens[1,2]**
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG[3,4] TDF + 3TC (or FTC) + EFV_{400}[3,4,5] TDF + 3TC (or FTC) + NVP
Pregnant/breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG[3,4] TDF (or ABC) + 3TC (or FTC) + EFV_{400}[3,4,5] TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

- In many countries, NVP still first-line instead of EFV (3 - < 10 yo) or LPVr (<3yo)
- ZDV rather than ABC in children remains common(< 10 years old)

WHO 2015 3rd Line Recommendations

POPULATION	1ST LINE REGIMEN	2ND LINE REGIMENS	3RD LINE REGIMENS
Adults	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r[1] + DTG (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r	
	2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r + 2 NRTIs ± NNRTI
		2 NRTIs + DRV/r	Optimize regimen using genotype profile
Pregnant/breastfeeding women	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	DRV/r + DTG (or RAL) ± 1–2 NRTIs
		2 NRTIs + DRV/r	
Children	2 NRTIs + LPV/r	If less than 3 years: 2 NRTIs + RAL[2]	DTG[4] + 2 NRTIs DRV/r[3] + 2 NRTIs DRV/r[3] + DTG[4] ± 1–2 NRTIs
Many still on NVP as 1st line		If older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTIs + EFV	2 NRTIs + ATV/r[5] or LPV/r	

- Second-line similar for older children who started on EFV
- If LPVr first-line failure , EFV or RAL as second line
- Typically, NRTI sequence in children is ZDV -> TDF (if old enough) . Where ABC used first line, ABC -> ZDV or TDF
- Third-line options very limited for young children, in whom DTG (<12yrs) or DRV (<3 yrs) cannot be used

WHO 2015 Guidelines

Antiretroviral Drug Resistance Profiles and Response to Second-Line Therapy Among HIV Type 1-Infected Ugandan Children

ARHR 2013;29(3):449

Victor Musiime,[1] Elizabeth Kaudha,[1] Joshua Kayiwa,[1] Grace Mirembe,[1] Matthew Odera,[1] Hilda Kizito,[1] Immaculate Nankya,[1] Francis Ssali,[1] Cissy Kityo,[1] Robert Colebunders,[2] and Peter Mugyenyi[1]

- 142 children failing first-line NNRTI-based ART (58% NVP; 36% EFV).
  - Mean age: 10.9 yrs. Mean 5.9yrs on ART.
- Resistance
  - NRTI: 184V, 91%. TAMs, **43%**. ≥3TAMs, 11%.
  - NNRTI: 103N, 51%. 109A/S, 32%. 181C, 23%. **≥1, 98%.**
- LPVr+2-3 NRTIs
  - VL<400: 80%, wk 24; 85%, wk 48.

DR in Children Failing PI-Based ART

Meyers PIDJ 2015

- Virologic failure (confirmed VL >1000) in 152/1203 **(12.6%)** South African children started on first-line LPVr-based ART at age < 3 years
- Of 75 with GT testing
  - 8 (10.7%) with sig. LPVr DRM*
  - Of 63 (84%) who remained on LPVr, 32 (51%)suppressed incl/ 2 with sig. LPVr mutations.
  - Of 12 who switched to EFV, 4 (33%) suppressed.

Sig. LPVr DRM: L10F, L24I, V32I, L33F, M46IL, I47A, I50V, I54MLV, L76V, V82ATSFMC, I84V, L89V and L90M

Pharmacokinetics, Safety, and 48-Week Efficacy of Oral Raltegravir in HIV-1–Infected Children Aged 2 Through 18 Years

CID 2014;58(3):413–22

Sharon Nachman,[1] Nan Zheng,[2] Edward P. Acosta,[3] Hedy Teppler,[4] Brenda Homony,[4] Bobbie Graham,[5] Terence Fenton,[2] Xia Xu,[4] Larissa Wenning,[4] Stephen A. Spector,[6] Lisa M. Frenkel,[7] Carmelita Alvero,[2] Carol Worrell,[8] Edward Handelsman,[9,a] and Andrew Wiznia[10]; for the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1066 Study Team

- 96 children, all but 1 (99%) with prior ARV use
  - Mean duration prior ART use 5 years (less in younger cohorts)
  - 95% with prior use of 2+ classes
  - 78% with prior NNRTI use; 83% with prior PI use
- 79% VL<400 at week 48 of RAL-based ART
  - Concomitant PI in 81% (LPVr, 41%; DRVr, 40%).
  - EFV, 14%. ETR, 22%.
- 87.5% VL<400 by week 48 for 4mo-2yo cohorts (Nachman JPIDS 2015)

Changing Regimens in Context of **Successful** Treatment

Original Investigation

Efavirenz-Based Antiretroviral Therapy Among Nevirapine-Exposed HIV-Infected Children in South Africa

A Randomized Clinical Trial

JAMA. 2015 Nov 3;314(17):1808-17

Ashraf Coovadia, MBChB; Elaine J. Abrams, MD; Renate Strehlau, MBChB; Stephanie Shiau, MPH; Francoise Pinillos, MBChB; Leigh Martens, MBChB; Faeezah Patel, MBChB; Gillian Hunt, PhD; Wei-Yann Tsai, PhD; Louise Kuhn, PhD

- HIV-infected children exposed to NVP for PMTCT who were ≥ 3 years old and had VL< 50 copies/mL on LPVr–based ART
- Randomly assigned to switch to EFV-based therapy (n = 150) or continue LPVr–based therapy (n = 148).
- Endpoint: Viral failure = confirmed VL >1000 copies/mL
- Result: Risk of viral failure was 2.7% in EFV group vs 2.0% in LPVr group (NS).
- Conclusion: Switching to EFV, compared with continuing LPVr, did not result in significantly higher rates of viral failure

Improving Treatment Outcomes for Children

- Promote use of recommended first-line
  - Active despite PMTCT ARV exposure
  - Favorable PK and virologic efficacy
- Prioritize children in virologic monitoring scale-up
  - Suppressed: new regimen options
  - Failing: adherence/new regimen before more DR
- Promote development, testing and availability of appropriately formulated drugs for children
  - IMPAACT P1093: DTG ≥ 4wks. Data under review for 6-12 yo. Approved ≥ 12 yo.

DRAFT 2016 IATT Paediatric ARV Optimal Formulary

10 Products

Drug Class	Drug	Formulation	Dose
NNRTI	EFV	Tablet (scored)	200 mg
NNRTI	NVP	Tablet (disp, scored)	50 mg
NNRTI	NVP	Oral liquid*	50 mg/5mL, 100ml
PI	LPV/r	Tablet (heat stable)	100 mg/25mg
PI	LPV/r	Oral liquid	80 mg/20 mg/mL
PI	LPV/r	Oral pellets	40mg/10mg
FDC	AZT/3TC	Tablet (disp, scored)	60 mg/30 mg
FDC	ABC/3TC	Tablet (disp, scored)	60 mg/30 mg, 120mg/60mg
INSTI	RAL	Chewable tab	100mg

<u>Changes</u>

- LPV/r oral pellets added
- RAL 100mg tab added
- AZT/3TC/NVP moved to limited use

Courtesy of N. Sugandhi

Lopinavir 40mg/ritonavir 10mg pellets

- Taste masked
- Does not require refrigeration
- Approved ≥ 14 days of age and ≥ 5 kg
- Not yet used for infants <3 months old

3rd Line/PI-failure Regimens

- Very limited options for young children (RAL)
  - DRV cannot be used <3 yrs old
  - DTG approved for 12+; promising result for 6- <12 (CROI 2016); under study for <6 yrs old (P1093)
  - ETR approved for 6+; under study for <6 (not on WHO list)
- Most 3rd line depend on innovator (name brand) rather than generic mfg
- Potential value of individual resistance testing
  - Adherence vs Resistance, especially for PI regimens
  - Extensive NRTI resistance more common with prolonged failure
  - Uncertainty about value of including NRTIs based on extrapolation from studies in adults

THANK YOU

Use of Dried-Blood-Spot Samples and In-House Assays To Identify Antiretroviral Drug Resistance in HIV-Infected Children in Resource-Constrained Settings[▽]

JCM 2011

Carrie Ziemniak,[1] Yohannes Mengistu,[2] Andrea Ruff,[3] Ya-Hui Chen,[1] Leila Khaki,[4] Abubaker Bedri,[2] Birgitte B. Simen,[5] Paul Palumbo,[6] Susan H. Eshleman,[4] and Deborah Persaud[1]*

HIV-1 Drug Resistance and Second-Line Treatment in Children Randomized to Switch at Low Versus Higher RNA Thresholds

JAIDS 2015;70:42–53

Linda Harrison, MSc, Ann Melvin, MD,† Susan Fiscus, PhD,‡ Yacine Saidi, PhD,§ Eleni Nastouli, MD,‖ Lynda Harper, MSc,¶ Alexandra Compagnucci, MD,§ Abdel Babiker, PhD,¶ Ross McKinney, MD,# Diana Gibb, MD, MRCP, MSc,¶ and Gareth Tudor-Williams, MD,** and the PENPACT-1 (PENTA 9/PACTG 390) Study Team*

- PI (50% LPVr; 49% NFV) vs NNRTI (38% NVP; 62% EFV) with switch (PI->NNRTI; NNRTI->PI) at 1K vs 30K copies/mL in children. Europe, N&S America.
- Greatest risk of new NRTI mutations in NNRTI-30K group. Risk of NRTI DRM low in PI, esp in LPVr (even at 30K).
- Emergence of NNRTI >> PI mutations
- Response to 2nd line (switch): VL < 400 by week 24….
  - **PI-> NNRTI**: 79% for PI-1K, 63% for PI-30K
  - NNRTI -> PI: 64% for NNRTI-1K, 100% for NNRTI-30K
  - 93% overall if no NRTI DRM