HIV Drug Resistance in infants, children and adolescents: Impact on treatment and outcomes

Dr Lee Fairlie

7 November 2017

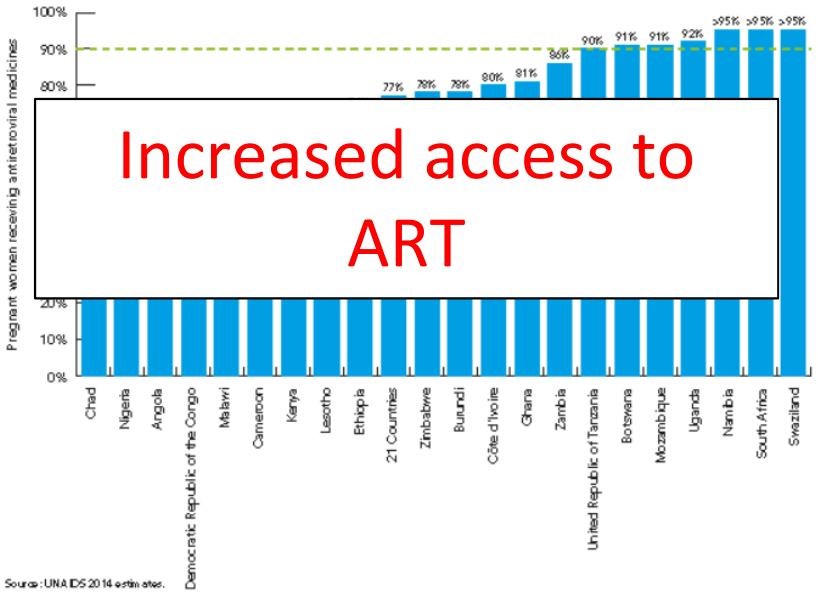
USAID
FROM THE AMERICAN PEOPLE

Overview

- PMTCT and resistance
- How does PMTCT affect current ART choices?
- Current ART regimens in children and adolescents
- Acquired resistance
- Full circle…..Pregnant PHIV


Prevention of mother-to-child transmission

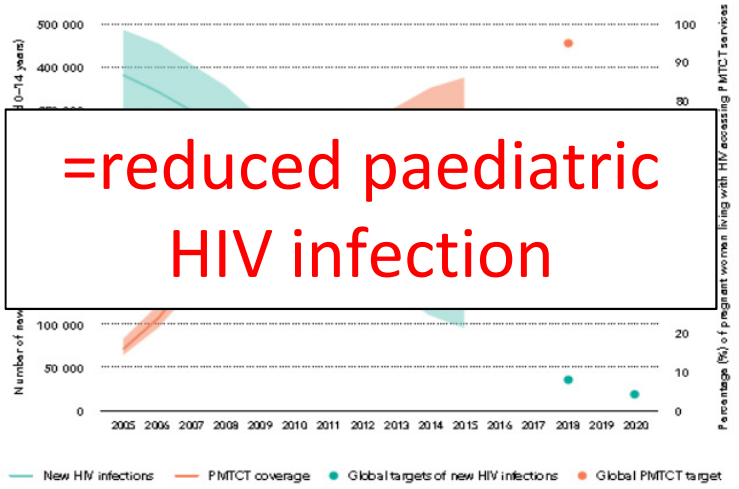
Figure 4
Percentage of pregnant women living with HIV receiving antiretroviral medicines to prevent mother-to-child transmission in 21 Global Plan priority countries, 2014



Source: UNAIDS 2014 estimates.

Increased access to ART

New HIV infections among children (aged 0-14 years) and percentage of pregnant women living with HIV receiving antiretroviral medicine (either prophylaxis or lifelong therapy) to prevent mother-to-child transmission, global, 2005-2015

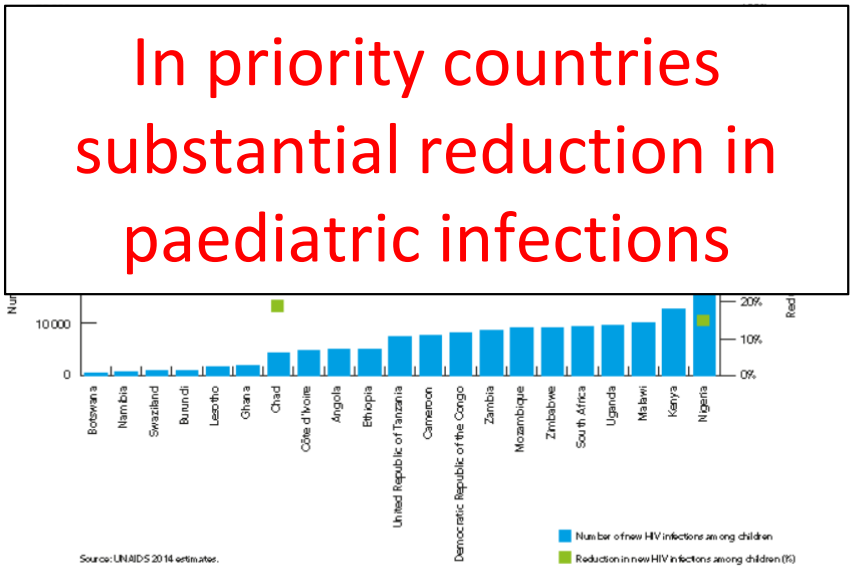


Source: UNAIDS 2016 estimates.

Note: In 2010, single-dose nevirapine was no longer included in ARV coverage as an effective regimen for the prevention of mother-to-child transmission.

=reduced paediatric HIV infection

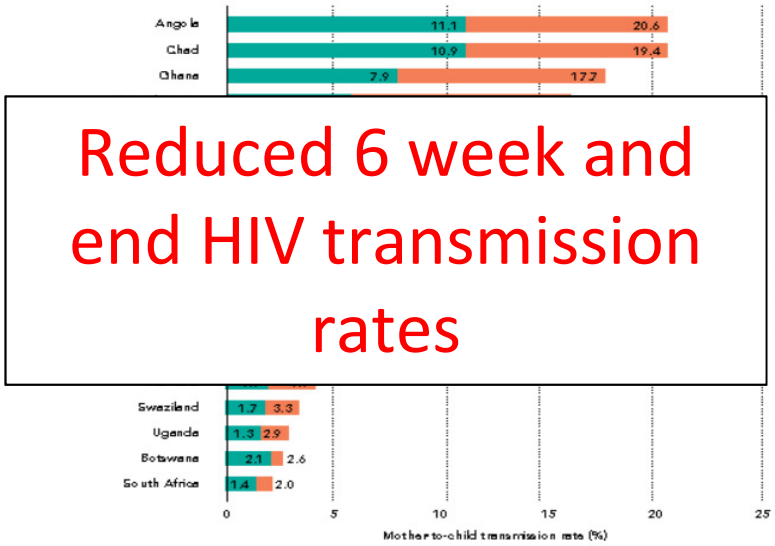
Figure 3
Number of new HIV infections among children in 2014 and percentage reduction in new HIV infections since 2009 in 21 Global Plan priority countries



Source: UNAIDS 2014 estimates.

In priority countries substantial reduction in paediatric infections

Six-week and final mother-to-child transmission rates, by country, 2015



Source: UNAIDS 2016 estimates.

Reduced 6 week and end HIV transmission rates

HIV resistance in pregnant women

Transmitted resistance:

- 3% (India) NRTI> NNRTI>PI;
- SA >5%;
- 6% Republic of Congo;
- 16-17% (Rio de Janiero) PR>NRTI=NNRTI (Brazil)

2°PMTCT (Pre-option B/B+)

- sdNVP: High percentage of women have RM after sdNVP→ Treatment failure on NNRTI (6-18 months)
- Zidovudine monotherapy 14%
- ? Impact of zidovudine and TDF/FTC on NVP resistance

De Lourdes Teixeira; Delatorre; Mani; Steegan; Samuel; Bruzzone; Olson, Lockman, Stringer

Option B/B+

- Postpartum period particularly challenging for adherence, VL suppression and resistance
- Most commonly first line EFV/FTC/TDF
- Low genetic barrier to resistance
- May result in transmitted resistance to infants/sexual partners
- Malawi PURE study: 55% of full cohort suppressed at 6 months (84% in retained and VL tested); 35% resistance, mainly NNRTI
- Uganda: small cohort-low drug resistance (6%)
- Tanzania: Ngarina et al 12 months PP 61% VL >400cps/ml and resistance 34%
- Increasing use of dolutegravir (Botswana) and some countries recommend Raltegravir or PI first line

Hosseinipour, Machnowska, Ngarina

May frequently need Infant prophylaxis

World Health Organization

4.4.7 Infant prophylaxis	NEW Infants born to mothers with HIV who are at high risk of acquiring HIV[2] should receive dual prophylaxis with AZT (twice daily) and NVP (once daily) for the first 6 weeks of life, whether they are breastfed or formula fed (strong recommendation, moderate-quality evidence).
	NEW Breastfed infants who are at high risk of acquiring HIV, including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional 6 weeks (total of 12 weeks of infant prophylaxis) using either AZT (twice daily) and NVP (once daily) or NVP alone (conditional recommendation, low-quality evidence).
	Infants of mothers who are receiving ART and are breastfeeding should receive 6 weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given 4–6 weeks of infant prophylaxis with daily NVP (or twice-daily AZT) (strong recommendation, moderate-quality evidence for breastfeeding infants; strong recommendation, low-quality evidence for infants receiving only replacement feeding). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2013 (http://www.who.int/hiv/pub/guidelines/arv2013/download/en).

AIDSinfo

- A 4-week neonatal zidovudine prophylaxis regimen can be used for full-term infants when the mother has received a standard antiretroviral therapy regimen (ART) during pregnancy with sustained viral suppression and there are no concerns related to maternal ...rence **(BII)**. Otherwise, a 6-week course as part of a combination infant prophylaxis regimen is recommended **(AI)**.
- ...mbination infant prophylaxis regimen is recommended in infants at higher risk of HIV acquisition, including those born to HIV-...ed women who:
  - ...ave not received antepartum or intrapartum ARV drugs **(AI)**, *or*
  - Have received only intrapartum ARV drugs **(AI)**, *or*
  - Have received antepartum ARV drugs but do not have viral suppression near delivery **(BIII)**.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Mother on ART but viral load not suppressed:			
1st line treatment failure in ...rence ...nd review: ...her as treatment	NVP + AZT daily for 12 weeks	Do birth HIV PCR Birth PCR positive : Start neonatal ART Birth PCR negative: Continue NVP + AZT until mother is suppressed on 2nd line ART Encourage breast feeding	It is assumed that with failed 1st line there likely is NVP resistance and exposure to increased likelihood of MTCT
2nd or 3rd line treatment and VL not suppressed	NVP + AZT daily Seek expert advice	Do birth HIV PCR Birth PCR positive : Start neonatal ART Birth PCR negative: Seek expert advice Advise not to breast feed and prescribe replacement feeding	Assume that with failed 1st + 2nd +/- 3rd-line ART there likely is current and archived resistance and increased likelihood of MTCT

Questions remaining…..

- Should we base PMTCT prophylaxis on VL monitoring?
- What is the impact of maternal resistance on HIV transmission to infants?
- Limited data to support triple therapy in infants….is more better?
- What should we do for breastfeeding infants where maternal VL is ↑?

Extended pre-exposure prophylaxis with lopinavir–ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial

Nicolas Nagot*, Chipepo Kankasa*, James K Tumwine, Nicolas Meda, G Justus Hofmeyr, Roselyne Vallo, Mwiya Mwiya, Mary Kwagala, Hugues Traore, Amwe Sunday, Mandisa Singata, Chafye Siuluta, Eric Some, David Rutagwera, Desire Nebova, Grace Ndeezi, Debra Jackson, Valérie Maréchal, Dorine Neveu, Ingunn M S Engebretsen, Carl Lombard, Stéphane Blanche, Halvor Sommerfelt, Claire Rekacewicz, Thorkild Tylleskärt, Philippe Van de Perre†, for the ANRS 12174 Trial Group‡

Findings Between Nov 16, 2009, and May 7, 2012, we enrolled and randomised 1273 infants and analysed 1236; 615 assigned to lopinavir–ritonavir or 621 assigned to lamivudine. 17 HIV-1 infections were diagnosed in the study period (eight in the lopinavir–ritonavir group and nine in the lamivudine group), resulting in cumulative HIV-1 infection of 1·4% (95% CI 0·4–2·5) and 1·5% (0·7–2·5), respectively. Infection rates did not differ between the two drug regimens (hazard ratio [HR] of lopinavir–ritonavir versus lamivudine of 0·90, 95% CI 0·35–2·34; p=0·83). Clinical and biological severe adverse events did not differ between groups; 251 (51%) infants had a grade 3–4 event in the lopinavir–ritonavir group compared with 246 (50%) in the lamivudine group.

Interpretation Infant HIV-1 prophylaxis with lopinavir–ritonavir was not superior to lamivudine and both drugs led to very low rates of HIV-1 postnatal transmission for up to 50 weeks of breastfeeding. Infant pre-exposure prophylaxis should be extended until the end of HIV-1 exposure and mothers should be informed about the persistent risk of transmission throughout breastfeeding.

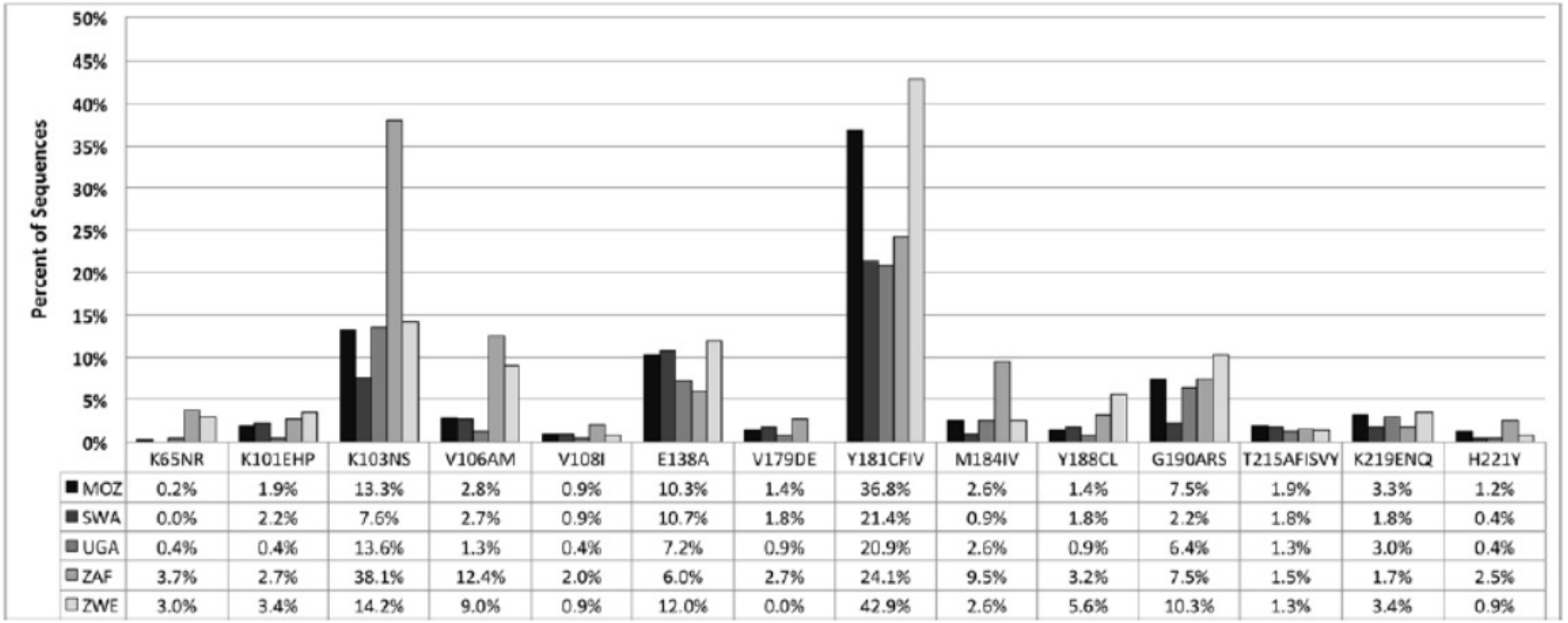
EuroCoord-CHAINEPPICC Mananas, Amazonas

Pre-treatment drug resistance (Boerma et al):

Overall:

- Pre-treatment drug resistance (PDR) 42.7% (95%CI 26.2%–59.1%) PMTCT-exposed children; 12.7% among PMTCT-unexposed children (P=0.004)
- Increased RM in PMTCT-unexposed 2004-2013-0-26.8%-
- NNRTI most common (32.4% exposed and 9.7% unexposed)
- NNRTI 25%; NRTI 5.4%; PI 1.3%
- NNRTI RM more common in children < 3 years
- In children <3 years, 46.1% PMTCT-exposed children and 19.2% PMTCT-unexposed children had PDR
- > 3 years, 36.2% of PMTCT-exposed children and 9.3% of PMTCT-unexposed children had PDR

Boerma, *JAC*, 2017



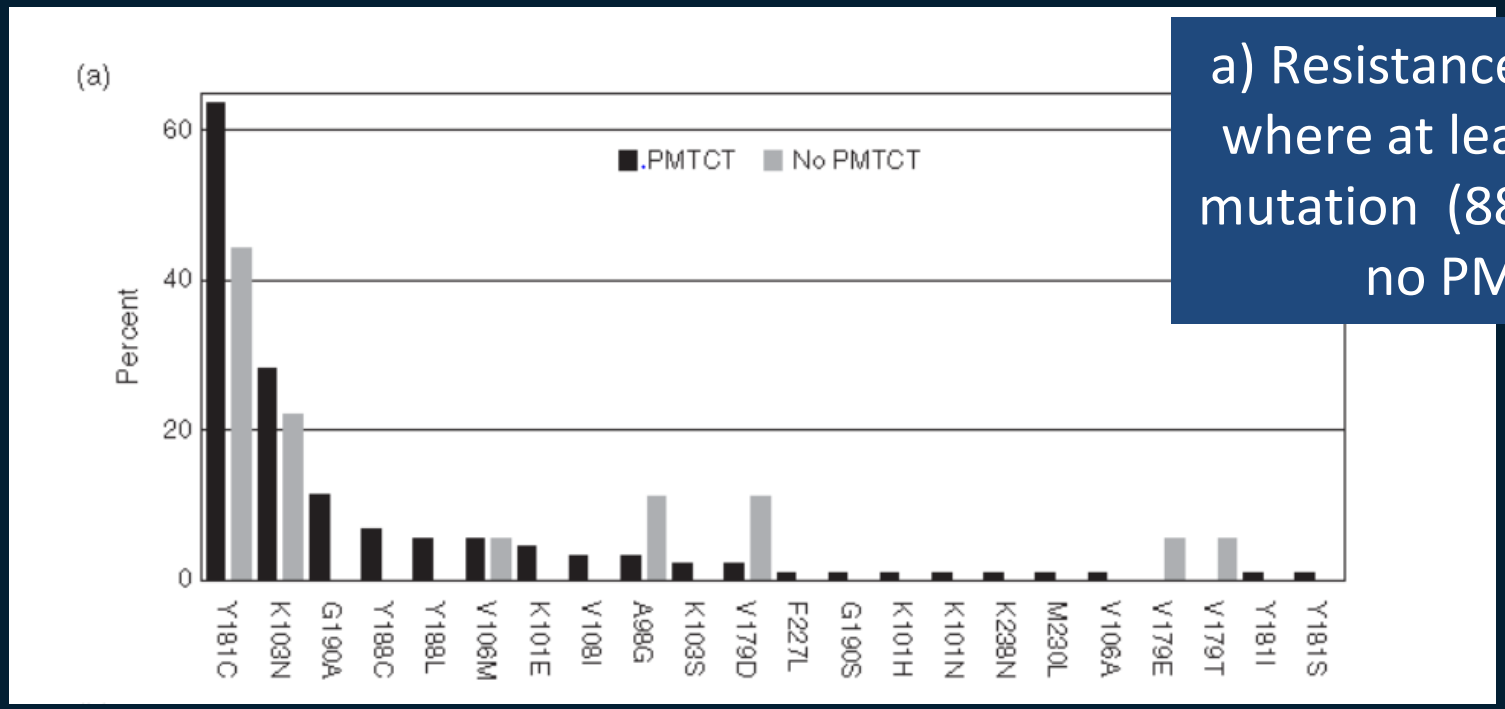
	K65NR	K101EHP	K103NS	V106AM	V108I	E138A	V179DE	Y181CFIV	M184IV	Y188CL	G190ARS	T215AFISVY	K219ENQ	H221Y
MOZ	0.2%	1.9%	13.3%	2.8%	0.9%	10.3%	1.4%	36.8%	2.6%	1.4%	7.5%	1.9%	3.3%	1.2%
SWA	0.0%	2.2%	7.6%	2.7%	0.9%	10.7%	1.8%	21.4%	0.9%	1.8%	2.2%	1.8%	1.8%	0.4%
UGA	0.4%	0.4%	13.6%	1.3%	0.4%	7.2%	0.9%	20.9%	2.6%	0.9%	6.4%	1.3%	3.0%	0.4%
ZAF	3.7%	2.7%	38.1%	12.4%	2.0%	6.0%	2.7%	24.1%	9.5%	3.2%	7.5%	1.5%	1.7%	2.5%
ZWE	3.0%	3.4%	14.2%	9.0%	0.9%	12.0%	0.0%	42.9%	2.6%	5.6%	10.3%	1.3%	3.4%	0.9%

Figure 3. Frequency of nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor drug resistance mutations observed in children aged <18 months and diagnosed with human immunodeficiency virus through early infant diagnosis (n = 1450, children aged <18 months). Mutations are defined per the Stanford HIVdb algorithm and only those ones that are present in ≥1% of all sequences analyzed are shown. Abbreviations: MOZ, Mozambique; SWA, Swaziland; UGA, Uganda; ZAF, South Africa; ZWE, Zimbabwe.

- Median age 4 months
- Overall resistance 54% (mainly NNRTI-53%)
- Neonatal ART exposure risk factor
- Decreased resistance with increasing age

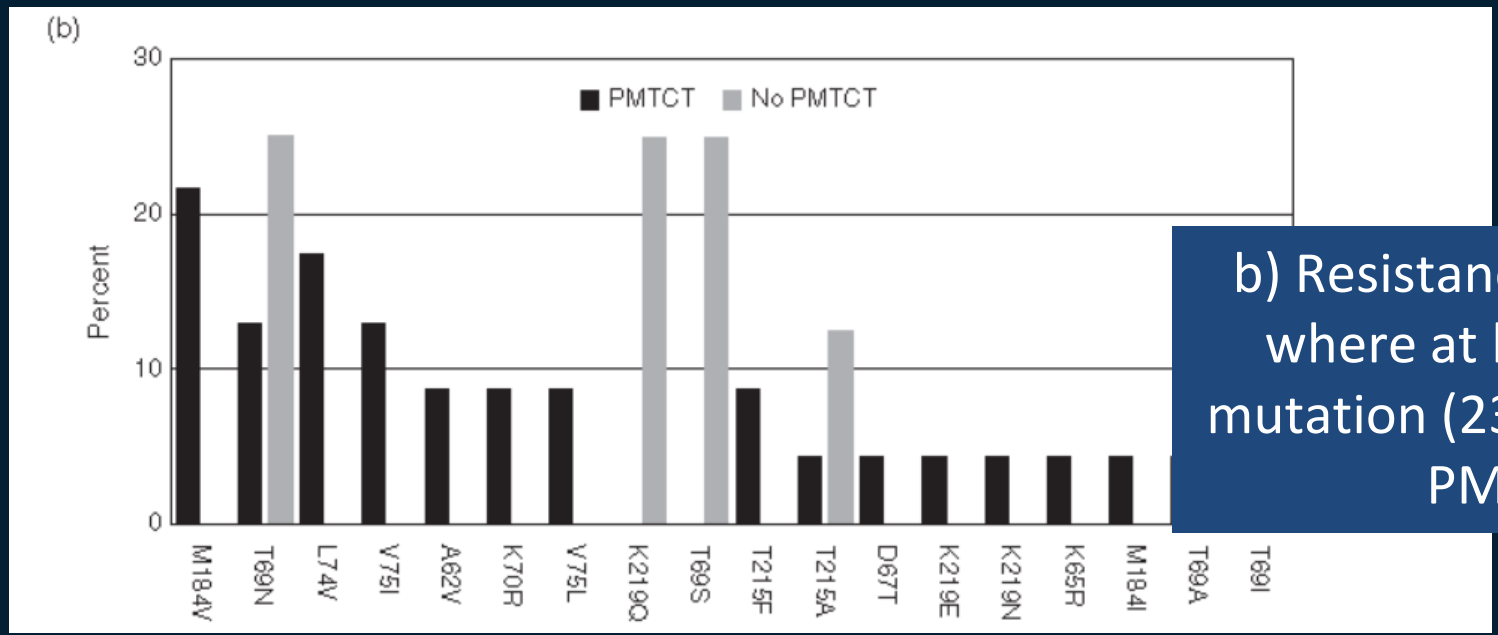
Hudson, *CID*, 2017

Resistance mutations in HIV+ infants



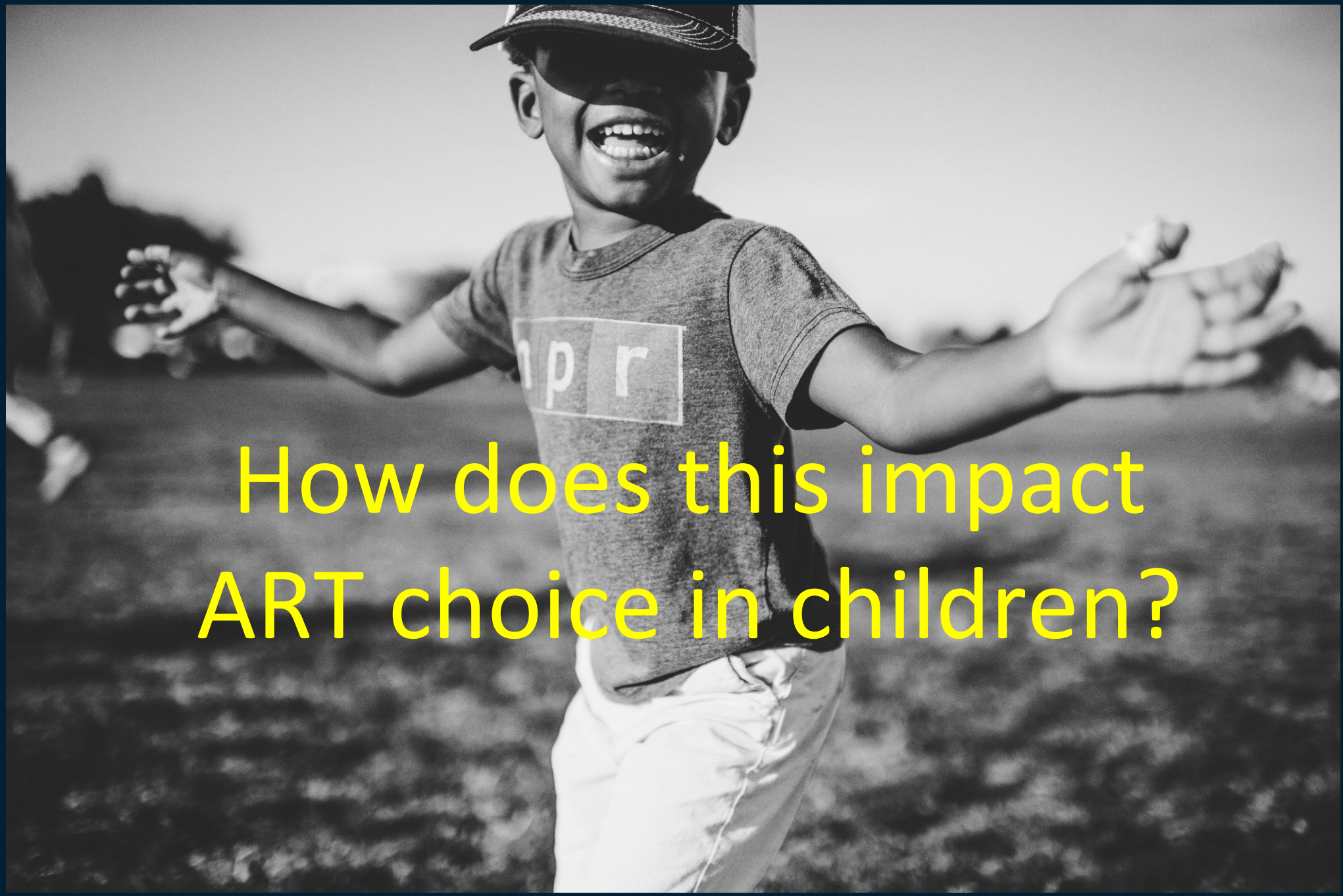
a) Resistance mutations where at least 1 NNRTI mutation (88 PMTCT, 18 no PMTCT)

78% PMTCT exposed with NRTI resistance also had NNRTI resistance



b) Resistance mutations where at least 1 NRTI mutation (23 PMTCT, 8 no PMTCT)

Kuhn, *AIDS,* 2014


How does this impact
ART choice in children?

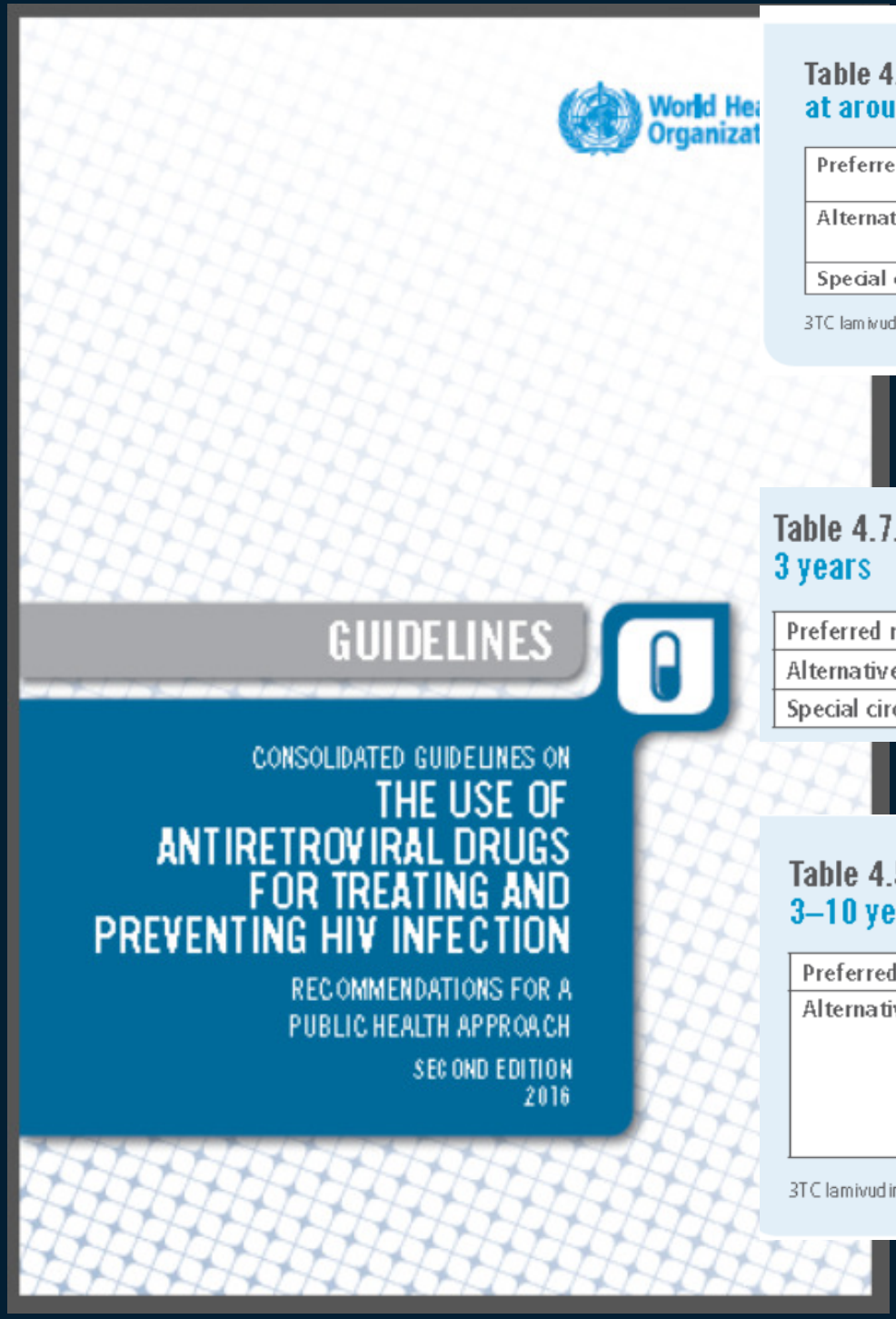


Table 4.8. Sequencing of ARV formulations for newborns starting treatment at around birth

	0–2 weeks →	2 weeks–3 months →	3–36 months
Preferred	AZT + 3TC + NVP	ABC or AZT + 3TC + LPV/r syrup	ABC or AZT + 3TC + LPV/r pellets
Alternative	AZT + 3TC + NVP		ABC or AZT + 3TC + LPV/r pellets
Special circumstances	AZT + 3TC + NVP	ABC or AZT + 3TC + RAL	

3TC lamivudine, ABC abacavir, AZT zidovudine, LPV lopinavir, NVP nevirapine, r ritonavir, RAL raltegravir.

Table 4.7. Summary of first-line ART regimens for children younger than 3 years

Preferred regimens	ABC[a] or AZT + 3TC + LPV/r[b]
Alternative regimens[c]	ABC[a] or AZT + 3TC + NVP
Special circumstances[d]	ABC[a] or AZT + 3TC + RAL[e]

Table 4.5. Summary of recommended first-line ART regimens for children 3–10 years of age

Preferred	ABC + 3TC + EFV
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir

ORIGINAL RES

Paediatric European Network for (PENTA) guidelines for treatmen infection 2015: optimizing healt for adult life

A Bamford,[1*] A Turkova,[2*] H Lyall,[3] C Foster,[3] N Klein,[4] D Basti
P Clayden,[9] M Della Negra,[10] V Giacomet,[11] C Giaquinto,[12] D Gib
E Nastouli,[18] T Niehues,[19] A Noguera-Julian,[20] P Rojo,[21] C Rudin
SB Welch[25] (PENTA Steering Committee)

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[2]Medical Research Counc
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University College London Hospitals, London, UK, [19]Centre for Pe
Krefeld, Krefeld, Germany, [20]Infectious Diseases Unit, Pediatrics
Barcelona, Barcelona, Spain, [21]12th of October Hospital, Madrid,
Switzerland, [23]Department of Paediatric Immunology and Infectio
Medical Centre, Amsterdam, The Netherlands, [29]Imperial College,
UK

Similar recommendations

National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults

24 December 2014

health
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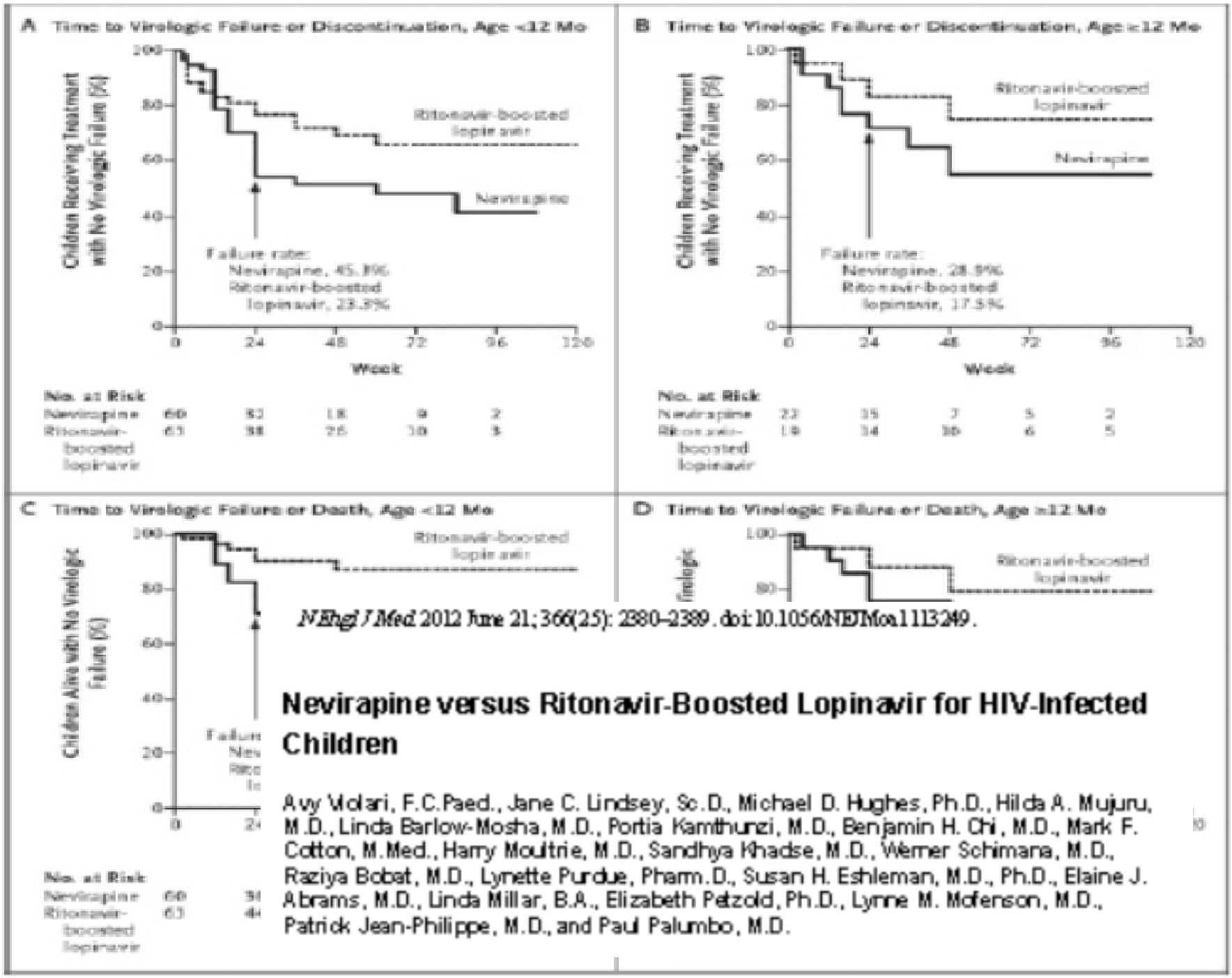


N Engl J Med 2012 June 21; 366(25): 2380–2389. doi: 10.1056/NEJMoa1113249.

Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children

Avy Violari, F.C.Paed., Jane C. Lindsey, Sc.D., Michael D. Hughes, Ph.D., Hilda A. Mujuru, M.D., Linda Barlow-Mosha, M.D., Portia Kamthunzi, M.D., Benjamin H. Chi, M.D., Mark F. Cotton, M.Med., Harry Moultrie, M.D., Sandhya Khadse, M.D., Werner Schimana, M.D., Raziya Bobat, M.D., Lynette Purdue, Pharm.D., Susan H. Eshleman, M.D., Ph.D., Elaine J. Abrams, M.D., Linda Millar, B.A., Elizabeth Petzold, Ph.D., Lynne M. Mofenson, M.D., Patrick Jean-Philippe, M.D., and Paul Palumbo, M.D.

BUT.....

- In many LMIC LPV/r (and RTV) is not available:
  - Expensive
  - Storage difficult
  - Newer formulations such as pellets-limited access
- FDA Black box warning- neonates < 2 weeks post conception age……problem ↑ birth testing
- NNRTIs still backbone of ART regimens in under 3 years in most SSA
- And advantages to NNRTI (especially in older children)
  - More FDC options
  - Better tolerability than kaletra
  - Once daily regimen- adherence advantage
  - Lower long term metabolic toxicity

What is the impact of using NNRTIs clinically?

ARROW Trial:

- VL response in children exposed vs not exposed to NVP→NVP-based regimen
- Similar VL suppression rates (<80 cps/ml) at week 144
- No difference in NNRTI or NRTI resistance mutations
- Option in LMIC especially those > 1 year even if NVP-exposed

Kay et al: Uganda: NVP-exposed infants initiated on NVP at median 8.3 months

- Probability of VL suppression at 18 months 56%
- Factors associated with VL suppression: increasing age, lower baseline VL and increased CD4%

Musoke, *AIDS*, 2015; Kay, *J Trop Ped*, 2012

NEVEREST(SDNVP exposure)

NEVEREST NVP

- Using primary endpoint of VL< 50 cps/ml switch group
- BUT those in switch group had a higher probability of VL> 1000 copies/ml (20%)
- Switch group 87% with VF had NNRTI resistance (67% Y181C)
- Pre-treatment NNRTI RM strongly associated with VL > 1000 copies/ml
- 31/143: 25 Y181C; 4 K103N
- At 156 weeks risks
  cps/ml similar in bo
- All children in switc
  weeks

NEVEREST EFV

- Switch to EFV from 3 years with VL suppressed on LPV/r
- Lower probability of VL > 50 cps/ml and VF in the switch group (48 weeks)
- 3/4 with VF K103N mutation
- PMTCT exposure → Y181C predominates →may explain more success with EFV compared to NVP

VL monitoring is key-↑ frequency

Coovadia, *JAMA*, 2010; Kuhn, *Lancet*, 2012; Coovadia, *JAMA,* 2015

MONOD ANRS 12206 (Burkina Faso & Cote De Ivoire)

- Similar design to NEVEREST EFV
- 40% no PMTCT exposure
- 12 months similar rates viral suppression (< 500 cpls/ml) between arms
- Similar rates VF (> 1000 copies/ml)
- VF: 77% DRT
  - NNRTI 69% (K103N; Y181C)
  - 4 cross resistance to 2nd generation rilpivirine &etravirine
  - NRTI 46% (M184V)
  - 43% in each arm had NNRTI resistance mutations

EFV non-inferior to LPV/r

IeDEA:

- VL suppression rates in children initiating EFV-based ART through different ART eras
- PMTCT exposure not associated with VF

IeDEA Southern Africa
International epidemiologic Databases to Evaluate AIDS

Dahourou, *BMC Med*, 2017; Fairlie, unpublished


Acquired resistance in
children and adolescents

Children are more likely to develop VF +- resistance

- Poor adherence
  - Palatability of ART
  - Pill burden
  - Formulations eg no dispersible ABC/3TC & FDCs uncommonly available
- Treatment of co-disease especially TB
- Dependency on adult
- PMTCT
- Socio-economic factors

Adolescents:
- psychological and structural barriers
- peer acceptance
- disclosure
- emotional challenges of puberty

Treatment-Emergent Mutations and Resistance in HIV-Infected Children Treated with Fosamprenavir-Containing Antiretroviral Regimens

Lisa L. Ross[*,1], Mark F. Cotton[2], Haseena Cassim[3], Eugeny Voronin[4], Naomi Givens[5], Jorg Sievers[5], and Katharine Y. Cheng[5] For the APV29005 & APV20002 Pediatric Study Groups

Tackling virological failure in HIV-infected children living in Africa

Mohammad-Ali Jenabian, Cecilia T Costiniuk, Ralph-Sydney Mboumba Bouassa, Linda Chapdeleine Mekue Mouafo, Thomas V Brogan & Laurent Bélec

Expert Review of
Anti-infective Therapy

Treatment Failure in HIV-Infected Children on Second-line Protease Inhibitor–Based Antiretroviral Therapy

Rapeepan Suaysod,[1,2] Nicole Ngo-Giang-Huong,[1,3,4] Nicolas Salvadori,[1,3] Tim R. Cressey,[1,3,4] Suparat Kanjanavanit,[5] Pornchai Techakunakorn,[6] Sawitree Krikajornkitti,[7] Sakulrat Srirojana,[8] Laddawan Laomanit,[1,3] Suwalai Chalermpantmetagul,[1,3] Marc Lallemant,[1,3,4] Sophie Le Coeur,[1,4,9] Kenneth McIntosh,[10] Patrinee Traisathit[1,11,12]

IDSA Infectious Diseases Society of America
hivma hiv medicine association

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

Linda Harrison, MSc[1], Ann Melvin, MD[2], Susan Fiscus, PhD[3], Yacine Saidi, PhD[4], Eleni Nastouli, MD[5], Lynda Harper, MSc[6], Alexandra Compagnucci, MD[4], Abdel Babiker, PhD[6], Ross McKinney, MD[7], Diana Gibb, MD MRCP MSc[6], Gareth Tudor-Williams, MD[8], and the PENPACT-1 (PENTA 9/PACTG 390) Study Team

JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES

Factors Associated with the Development of Drug Resistance Mutations in HIV-1 Infected Children Failing Protease Inhibitor-Based Antiretroviral Therapy in South Africa

Theresa M. Rossouw[1,2]*, Ute D. Feucht[2,3], George Melikian[3], Gisela van Dyk[1], Winifred Thomas[3], Nicolette M. du Plessis[3], Theunis Avenant[2]

PLOS

Antiretroviral Drug Resistance Among Children and Youth in the United States With Perinatal HIV

Russell B. Van Dyke,[1] Kunjal Patel,[2] Ron M. Kagan,[2] Brad Karalius,[2] Shirley Traite,[4] Meyer III,[5] Katherine K. Tassiopoulos,[2] George R. Seage III,[2] ybolt,[6] Sandra Burchett,[7] and Rohan Hazra[2], for the Pediatric HIV/AIDS y (PHACS)

IDSA Infectious Diseases Society of America
hivma hiv medicine association

Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe

A Judd,[1] R Lodwick,[2] A Noguera-Julian,[3,4,5] DM Gibb,[1] K Butler,[6] D Costagliola,[7] C Sabin,[2] A van Sighem,[8] B Ledergerber,[9] C Torti,[10] A Mocroft,[2] D Podzamczer,[11] M Dorrucci,[12] S De Wit,[13] N Obel,[14] F Dabis,[15,16] A Cozzi-Lepri,[2] F Garcia,[17] NH Brockmeyer,[18] J Warszawski,[19] MI Gonzalez-Tome,[20] C Mussini,[21] G Touloumi,[22] R Zangerle,[23] J Ghosn,[24,25] A Castagna,[26] G Fätkenheuer,[27] C Stephan,[28] L Meyer,[29,30] MA Campbell,[31] G Chene[15,16,32] and A Phillips[2] The Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord

HIV MEDICINE

Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa

T. Sonia Boender[1,2]*, Cissy M. Kityo[3], Ragna S. Boerma[1,2], Raph L. Hamers[1,4], Pascale Ondoa[1], Maureen Wellington[5], Margaret Siwale[6], Immaculate Nankya[7], Elizabeth Kaudha[8], Alani Sulaimon Akanmu[9], Mariette E. Botes[6], [1] and Kim C. E. Sigaloff[1,4]

Journal of Antimicrobial Chemotherapy
JAC

Virologic Failure Among Children Taking Lopinavir/Ritonavir-containing First-line Antiretroviral Therapy in South Africa

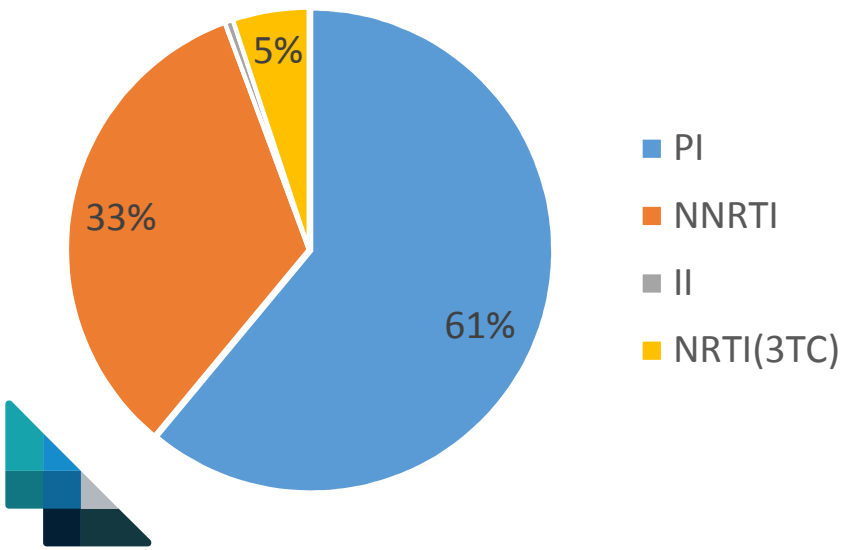
Tammy Meyers, PhD,* Shobna Sawry, MPH,† Jessica Y. Wong, MPH,‡ Harry Moultrie, MPH,† Francoise Pasllos, MD,‖ Lee Fairlie, MD,† and Gert van Zyl, PhD‖

The Pediatric Infectious Disease Journal
An official publication of the European Society for Paediatric Infectious Diseases

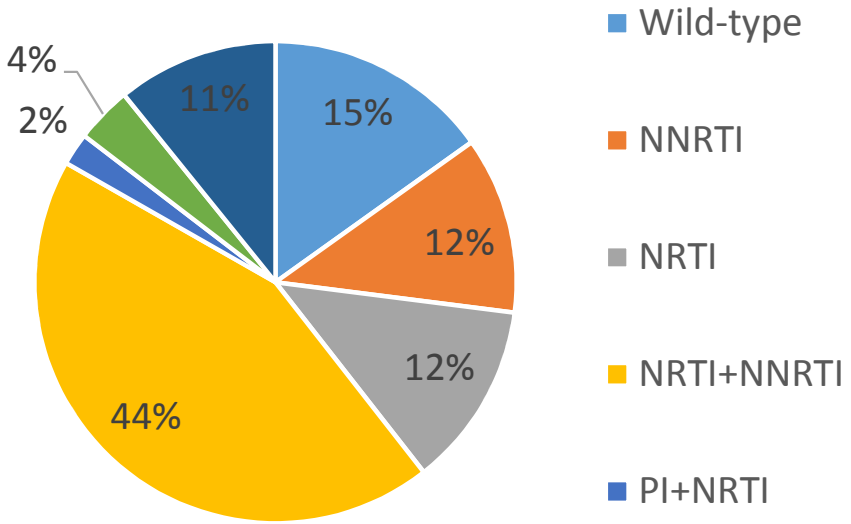
HIVDR in Paediatric Patients failing ART

- A national cross sectional facility based study of HIVDR among children on ART who are experiencing VF was implemented in 2017
  - 45 sentinel ART sites in 9 provinces
  - Sample size: 1475 specimens spanning 1-5, 5-10, 10-15 and 15 – 19 years age groups

Regimen



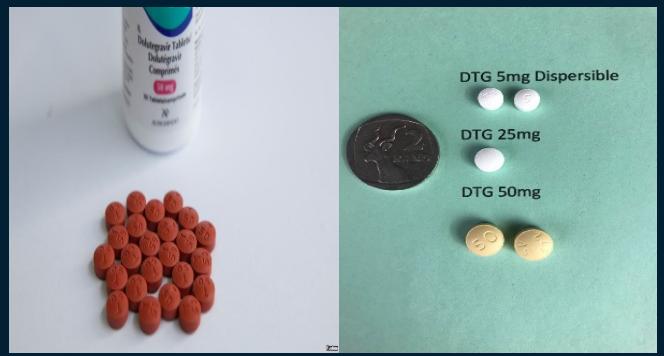
Resistance patterns



Hunt et al

What does this mean for future regimens

- Will need DRT
  - Prolonged NNRTI-based ART
  - Failing PI-based ART (early if previous TB)
- Access to 2nd and 3rd line regimens
- Dolutegravir…..
- Still need dosing and registration down to youngest ages



Clinical associations of white matter damage in cART-treated HIV-positive children in South Africa

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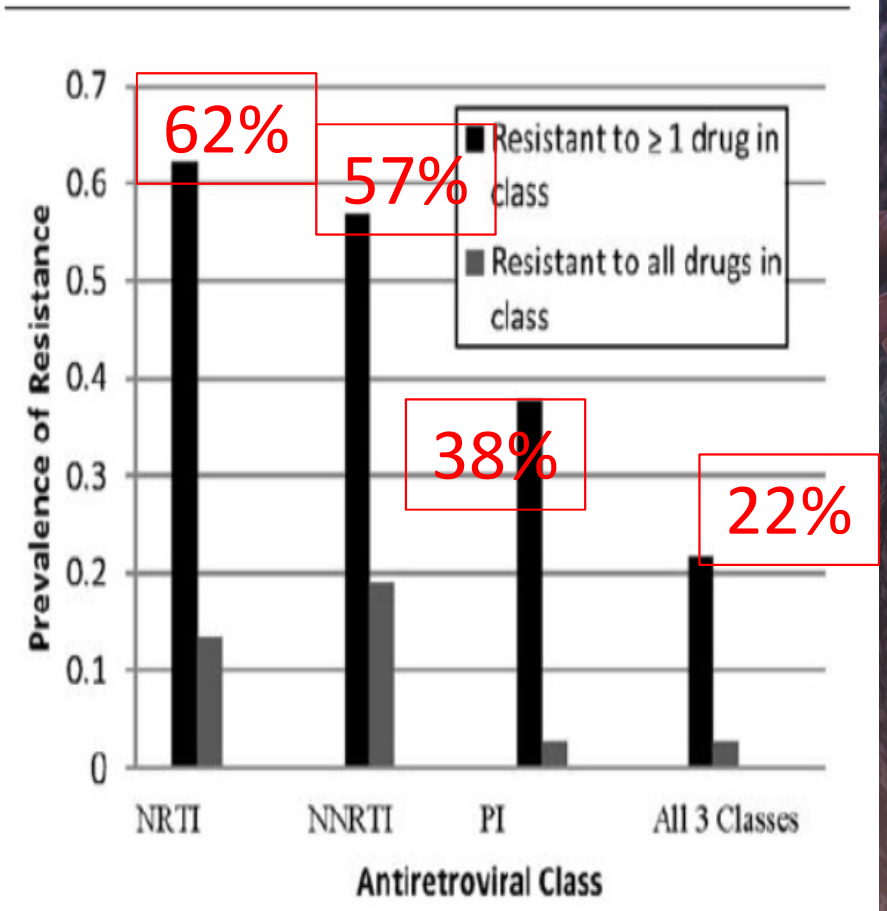
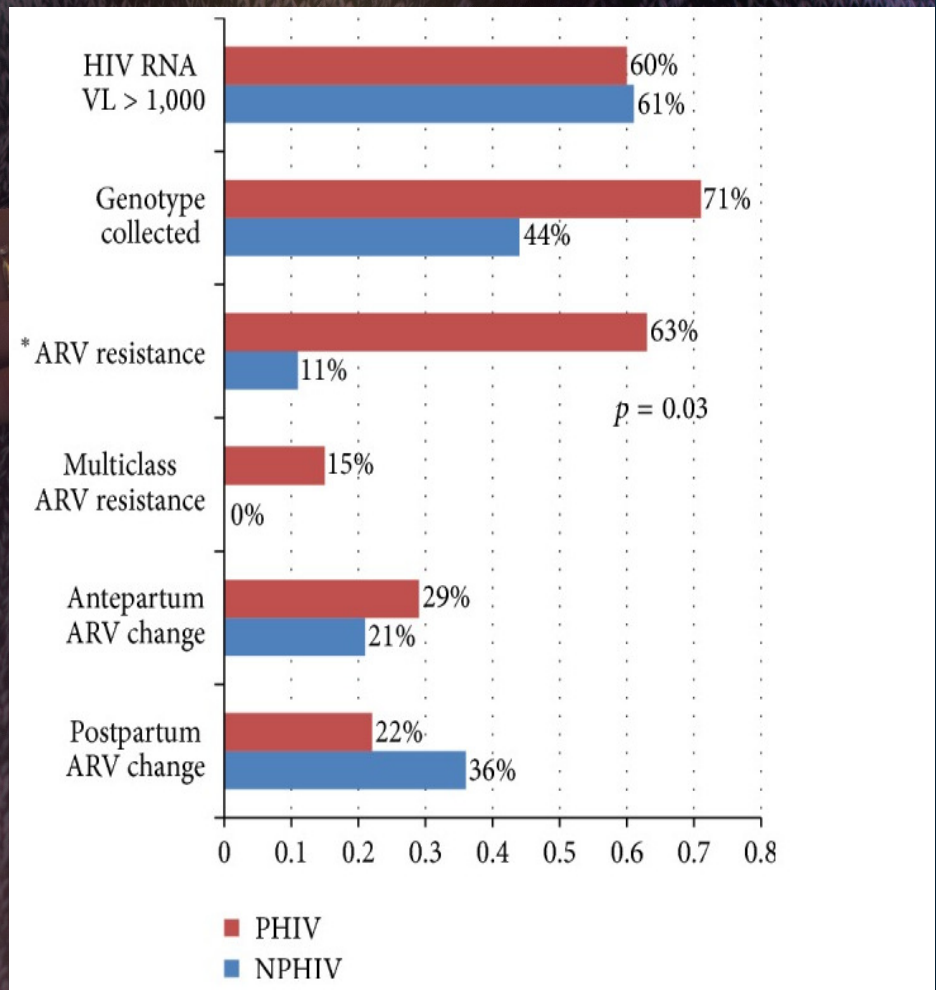
Abstract A range of factors contributes to white matter damage in vertically infected HIV-positive children. These may include combination antiretroviral treatment (cART) regimen, sociodemographic factors, nutritional hematological status, HIV-relevant clinical variables, and cognitive functioning. We explored associations between a number of these factors and diffusion tensor imaging (DTI) measures in 50 cART-treated children aged 6 to 15 years. Fractional anisotropy (FA), mean diffusion (MD), radial diffusion (RD), and axial diffusion (AD) were derived from 48 cerebral white matter regions. Significant associations between a number of the clinical variables and white matter integrity were found. Decreased FA, a measure of neuronal damage, was associated with being on second-line cART, low hemoglobin, and younger age. Children with increased MD, a measure of neuronal damage, were younger, had reduced albumin and hemoglobin, and increased viral load. Decreased AD, a measure of axonal damage, was associated with increased viral load and total protein, decreased albumin and hemoglobin, younger age, poorer fronto-striatal cognition, and being on second-line cART. Increased RD, a measure of myelin loss, was associated with younger age, low current CD4 count, low albumin and hemoglobin, and higher viral load and total protein. The current findings underline the possible association of first-line

The findings emphasize the need for early identification of adherence problems or resistance to first-line cART in HIV-infected children living in sub-Saharan Africa, improved access to support with issues relating to poor adherence, and the integration of antiretroviral treatment programs with other health-care services, such as nutritional support, and the importance of examining the effects of HIV disease in the context of treatable clinical variables such as anemia. A longitudinal study assessing HIV-relevant clinical variables and nutritional hematological predictors of white matter damage is needed to clarify the associations observed in this study.

Full circle……



Tassiopoulos, *CID*, 2015:
-Sexual Initiation associated with increased non-adherence
-62% unprotected SI
- 42% VL > 5000 cps/ml



Lazenby, *Inf Dis O&G*, 2016:
- More likely to have increased DR
- Increased likelihood of nonstandard ART regimens
- No increased AE

Conclusions

- Optimised maternal ART regimens and VL suppression key =no transmission
- Current infant prophylaxis drugs may not be effective if maternal resistance
- Paediatric ART is complex in face of resistance (Transmitted and acquired)
- Newer drugs (dolutegravir) hold promise but still need completed dosing, safety, efficacy and registration