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

Dr Lee Fairlie
7 November 2017
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
Increased access to ART

In priority countries, substantial reduction in paediatric infections

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

Hosseini, Machnowska, Ngarina
May frequently need Infant prophylaxis
### 4.4.7 Infant prophylaxis

| New | Infants born to mothers with HIV who are at high risk of acquiring HIV 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). |
| New | 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). |


- 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 adherence (BII). **Otherwise, a 6-week course as part of a combination infant prophylaxis regimen is recommended (A1).**

- **Combination infant prophylaxis regimen is recommended** in infants at higher risk of HIV acquisition, including those born to HIV-infected women who:
  - Have not received antepartum or intrapartum ARV drugs (A1), or
  - Have received only intrapartum ARV drugs (A1), or
  - Have received antepartum ARV drugs but do not have viral suppression near delivery (BIII).

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**Mother on ART but viral load not suppressed:**

<table>
<thead>
<tr>
<th>1st line treatment failure in</th>
<th>NVP + AZT daily for 12 weeks</th>
<th>Do birth HIV PCR</th>
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<tbody>
<tr>
<td>Infants born to mothers who</td>
<td>NVP + AZT daily for 12 weeks</td>
<td>Birth PCR positive: Start neonatal ART</td>
</tr>
<tr>
<td>are at high risk of acquiring</td>
<td></td>
<td>Birth PCR negative: Continue NVP + AZT</td>
</tr>
<tr>
<td>HIV who are receiving ART and</td>
<td></td>
<td>until mother is suppressed on 2nd line ART</td>
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<tr>
<td>are breastfeeding should</td>
<td></td>
<td>Encourage breastfeeding</td>
</tr>
<tr>
<td>receive 6 weeks of infant</td>
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<tr>
<td>prophylaxis with daily NVP.</td>
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</table>

**2nd or 3rd line treatment and VL not suppressed:**

| Assume that with failed 1st + |
| 2nd +/- 3rd-line ART there |
| is likely current and archived resistance and increased likelihood of MTCT |
| NVP resistance and exposure to |
| increased likelihood of MTCT |
| NVP resistance and exposure to |
| 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


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.
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
- 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)

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

Kuhn, *AIDS*, 2014

78% PMTCT exposed with NRTI resistance also had NNRTI resistance
How does this impact ART choice in children?
### Table 4.8. Sequencing of ARV formulations for newborns starting treatment at around birth

<table>
<thead>
<tr>
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<th>0–2 weeks</th>
<th>2 weeks–3 months</th>
<th>3–36 months</th>
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<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>AZT + 3TC + NVP</td>
<td>ABC or AZT + 3TC + LPV/r syrup</td>
<td>ABC or AZT + 3TC + LPV/r pellets</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>AZT + 3TC + NVP</td>
<td></td>
<td>ABC or AZT + 3TC + LPV/r pellets</td>
</tr>
<tr>
<td><strong>Special circumstances</strong></td>
<td>AZT + 3TC + NVP</td>
<td>ABC or AZT + 3TC + RAL</td>
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</tbody>
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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

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td><strong>Preferred regimens</strong></td>
<td>ABC* or AZT + 3TC + LPV/r*</td>
</tr>
<tr>
<td><strong>Alternative regimens</strong></td>
<td>ABC* or AZT + 3TC + NVP</td>
</tr>
<tr>
<td><strong>Special circumstances</strong></td>
<td>ABC* or AZT + 3TC + RAL*</td>
</tr>
</tbody>
</table>

*Use of NVP and LPV/r is recommended in children with HIV-1 RNA > 100,000 copies/mL or when resistance to these drugs is likely.

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

<p>| | |</p>
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<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>ABC + 3TC + EFV</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>ABC + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + EFV</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + NVP</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + EFV</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC (or FTC) + NVP</td>
</tr>
</tbody>
</table>

3TC lamivudine, ABC abacavir, AZT zidovudine, EFV efavirenz, FTC emtricitabine, NVP nevirapine, TDF tenofovir.
Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of HIV infection 2015: optimizing health outcomes for adult life

A Bamford,1* A Turkova,2* H Lyall,3 C Porter,9 N Klein,4 D Basta,4 P Clayden,9 M Della Negra,10 V Giacomet,11 C Giaquinto,12 D Gibb,12 E Nastouli,13 T Niêues,19 A Nogueira-Julian,20 P Rojo,21 C Rudin,21 SB Welch25 (PENTA Steering Committee)

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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
Nevirapine versus Ritonavir-Boosted Lopinavir for HIV-Infected Children

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%

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 were similar in both groups
- All children in switch group had VL suppressed

**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

MONOD ANRS 12206 (Burkina Faso & Cote De Ivoire)
- Similar design to NEVEREST EFV
- 40% no PMTCT exposure
- 12 months similar rates viral suppression (< 500 cpl/s/ml) between arms
- Similar rates VF (> 1000 copies/ml)
- VF: 77% DRT
  - NNRTI 69% (K103N; Y181C)
  - 4 cross resistance to 2\textsuperscript{nd} generation rilpivirine & etravirine
  - NRTI 46% (M184V)
  - 43% in each arm had NNRTI resistance mutations

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

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

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

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

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

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

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

Accumulation of HIV-3 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa

The Pediatric Infectious Disease Journal

An official publication of the European Society for Pediatric 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:
- 61% PI
- 33% NNRTI
- 5% NRTI (3TC)
- 2% others

Resistance patterns:
- Wild-type: 44%
- NNRTI: 15%
- NRTI: 12%
- NRTI+NNRTI: 11%
- PI+NRTI: 12%
- others: 4%

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 2\textsuperscript{nd} and 3\textsuperscript{rd} 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

Jacqueline Hoare • Jean-Paul Fouche • Nicole Phillips • John A. Joska • Kirsten A. Donald • Kevin Thomas • Dan J. Stein

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.
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