Paediatric ART: eligibility criteria and first line regimens (revised)

Dave le Roux

13 August 2016
Outline

• Eligibility criteria for starting ART
  Evolving evidence for earlier ART
• W Cape, National, WHO guidelines
• Challenges of paediatric ART
• Before starting ART
• First line regimens
  Neonatal: >2.5kg
  < Preterm / low birth weight
  Infant / child < 3 years
  Child >3 years
  Adolescent
Evolution of paediatric ART

- Roll out of ARV’s
- Accumulation of evidence
- Understanding of natural history
- Evolution of therapeutic options
Net survival of perinatally and postnatally HIV-infected children: a pooled analysis of individual data from sub-Saharan Africa

Milly Marston,1* Renaud Becquet,2,3 Basia Zaba,1 Lawrence H Moulton,4 Glenda Gray,5 Hoosen Coovadia,6 Max Essex,7 Didier K Ekouevi,2,3,8 Debra Jackson,9 Anna Coutsoudis,10 Charles Kilewo,11 Valériane Leroy,12 Stefan Wiktor,13 Ruth Nduati,14 Philippe Msellati,15 François Dabis,2,3 Marie-Louise Newell16,17 and Peter D Ghys18
Natural history untreated HIV

- Marston 2011: Child survival by timing of infection
Improved survival on ART

• Violari 2008:
  – CHER study of early vs deferred ART:

The New England Journal of Medicine

Original Article

Early Antiretroviral Therapy and Mortality among HIV-Infected Infants

Avy Violari, F.C.Paed., Mark F. Cotton, M.Med., Ph.D., Diana M. Gibb, M.D.,
Abdel G. Babiker, Ph.D., Jan Steyn, M.Sc., Shabir A. Madhi, F.C.Paed., Ph.D.,
Patrick Jean-Philippe, M.D., and James A. McIntyre, F.R.C.O.G.,
for the CHER Study Team*
Improved survival on ART

• Violari 2008:
  – CHER study of early vs deferred ART:
  – Early ART prevents early deaths (before 13 weeks)
Decreased morbidity and cost on ART
Decreased morbidity and cost on ART

- Lajoie 2016: systematic review and meta-analysis of incidence of opportunistic infections in children in low and middle income countries
- 88 studies, 55 679 HIV-infected children
- ART initiation based on 2010 WHO criteria averted 161 000 opportunistic infections and saved US$17 million per year
Decreased morbidity on ART

Table 2. Estimated Summary Incident Risk for Opportunistic Infections and Other Infections, by Antiretroviral Status

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Summary of Incident Risk, % (95% CI) (No. of Studies)</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans meningitis</td>
<td>ART Naive: 0.55 (.10–1.36) (3) ART Exposed: 0.25 (.04–.66) (4)</td>
<td>0.42 (11–1.83)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>ART Naive: 3.48 (1.23–6.82) (7) ART Exposed: 2.49 (1.34–6.54) (7)</td>
<td>0.71 (50–1.01)</td>
</tr>
<tr>
<td>Oral anulitis</td>
<td>ART Naive: 0.05 (.01–2.01) (4) ART Exposed: 0.01 (.00–1.01) (4)</td>
<td>0.23 (14–11)</td>
</tr>
<tr>
<td>CMV reactivation</td>
<td>ART Naive: 0.17 (0.04–0.67) (3) ART Exposed: 0.17 (0.04–0.67) (3)</td>
<td>0.05 (42–89)</td>
</tr>
<tr>
<td>Varicell</td>
<td>ART Naive: 0.02 (0.00–0.03) (7) ART Exposed: 0.02 (0.00–0.03) (7)</td>
<td>0.28 (2.8–21)</td>
</tr>
<tr>
<td>Herpes</td>
<td>ART Naive: 0.02 (0.00–0.09) (1) ART Exposed: 0.02 (0.00–0.09) (1)</td>
<td>0.50 (32–66)</td>
</tr>
<tr>
<td>Kaposi</td>
<td>ART Naive: 0.03 (0.00–0.09) (7) ART Exposed: 0.03 (0.00–0.09) (7)</td>
<td>0.50 (32–66)</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>ART Naive: 0.02 (0.00–0.07) (3) ART Exposed: 0.02 (0.00–0.07) (3)</td>
<td>0.50 (32–66)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>ART Naive: 0.01 (0.00–0.03) (5) ART Exposed: 0.01 (0.00–0.03) (5)</td>
<td>0.50 (32–66)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis (unspecified types)</td>
<td>ART Naive: 12.36 (7.96–17.59) (15) ART Exposed: 8.84 (5.21–13.31) (18)</td>
<td>0.69 (63–75)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>ART Naive: 9.78 (5.37–15.34) (10) ART Exposed: 3.99 (2.66–5.66) (9)</td>
<td>0.38 (32–46)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis</td>
<td>ART Naive: 7.26 (3.00–13.18) (4) ART Exposed: 1.12 (0.40–2.18) (6)</td>
<td>0.15 (10–21)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>ART Naive: 25.01 (14.50–37.91) (9) ART Exposed: 22.11 (11.58–34.89) (7)</td>
<td>0.85 (78–92)</td>
</tr>
<tr>
<td>Isolated bacteremia</td>
<td>ART Naive: NA ART Exposed: 7.50 (.25–1.50) (1)</td>
<td>NA</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>ART Naive: 0.95 (.48–1.56) (3) ART Exposed: 0.80 (.36–1.42) (3)</td>
<td>0.85 (33–2.12)</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>ART Naive: 3.95 (1.46–7.58) (4) ART Exposed: 2.39 (.00–9.19) (4)</td>
<td>0.59 (47–75)</td>
</tr>
</tbody>
</table>

*Cryptosporium* diarrhoea: 90% decreased incidence

Extrapulmonary TB: 85% decreased incidence

CNS toxoplasmosis: 77% decreased incidence
Improved neurodevelopmental outcomes on ART

Early antiretroviral therapy improves neurodevelopmental outcomes in infants

Barbara LAUGHTON¹, Morna CORNELL², Debbie GROVE³, Martin KIDD⁴, Priscilla E SPRINGER⁵, Els DOBBELS¹, Anita JANSE VAN Rensburg¹, Avy VIOLARI⁶, Abdel G BABIKER⁷, Shabir A MADHI⁸, Patrick JEAN-PHILIPPE⁹, Diana M GIBB⁷, and Mark F COTTON¹
Improved neurodevelopmental outcomes on ART

• Laughton 2012: data from CHER study of early vs deferred ART
  Griffiths Mental Development Scales at 11 months
  All scores lower in the deferred arm (especially in locomotor sub-scale)
Improved survival on ART

• Evidence from adults: START study
  – Strategic Timing of Antiretroviral Treatment
  – 4685 adults at 215 sites in 35 countries with CD4 counts >500
  – Immediate vs deferred ART (CD4<350)
Improved survival on ART

• Evidence from adults: START study
  – 57% decrease in death / adverse events in immediate treatment group
  – Most events occurred when CD4 was >400
Guideline recommendations: WHO

• WHO 2016
Guideline recommendations: WHO

• WHO 2016
  – ART should be initiated in all **adults** living with HIV, regardless of WHO clinical stage and at any CD4 count (moderate quality evidence; strong recommendation)
  – ART should be initiated in all **adolescents** living with HIV, regardless of WHO clinical stage and at any CD4 count (low quality evidence; conditional recommendation)
  – ART should be initiated in all **children** living with HIV, regardless of WHO clinical stage and at any CD4 count
    • Children <1 year: (moderate quality evidence; strong recommendation)
    • Children 1-10 years: (low quality evidence; conditional recommendation)
Guideline recommendations: WHO

• WHO 2016:
  Acknowledge different priority groups
  Universal ART treatment for all
Guideline recommendations: SA

• SA National Dept Health
  April 2015
### Guideline recommendations: SA

- **SA National Dept Health**
  - April 2015

#### CLINICAL CRITERIA

<table>
<thead>
<tr>
<th>Age</th>
<th>Eligibility for Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child less than 5 years</td>
<td>All children should be started on ART</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>Symptomatic (stage 3 or 4) irrespective of CD4 count OR CD4 $\leq$ 500 cells/μl irrespective of WHO stage</td>
</tr>
<tr>
<td>Criteria for fast-tracking (i.e. start ART within 7 days of being eligible)</td>
<td></td>
</tr>
<tr>
<td>» Children less than 1 year of age</td>
<td></td>
</tr>
<tr>
<td>» CD4 count $\leq$ 200 cells/μl or $&lt;15%$</td>
<td></td>
</tr>
<tr>
<td>» WHO clinical stage 4</td>
<td></td>
</tr>
<tr>
<td>» MDR or XDR-TB</td>
<td></td>
</tr>
</tbody>
</table>

#### SOCIAL CRITERIA

- Social criteria are extremely important for the success of the programme and need to be adhered to. The principle is that adherence to treatment must be at least probable.
- At least one identifiable caregiver who is able to supervise the child for administering medication (all efforts should be made to ensure that the social circumstances of vulnerable children, e.g. orphans, are addressed so that they too can receive treatment).
- Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child’s ART.
- Treatment of mother/caregiver/other family member is to be actively promoted by ensuring same-site treatment or referral to the nearest treatment centre.
Guideline recommendations: W Cape

• W Cape
  May 2015
Guideline recommendations: W Cape

- W Cape
  May 2015

Box 3: Eligibility criteria for ART and fast-tracking of ART

<table>
<thead>
<tr>
<th>Eligibility for starting ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>- All children less than 5 years of age: irrespective of CD4 or clinical staging</td>
</tr>
<tr>
<td>- Children 5 years to 15 years: WHO clinical stage 3 or 4 OR CD4 ≤ 500 cells/mm³</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients requiring fast tracking (i.e. start ART within 7 days of being eligible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Children less than 1 year of age</td>
</tr>
<tr>
<td>- WHO clinical Stage 4</td>
</tr>
<tr>
<td>- MDR or XDR-TB</td>
</tr>
<tr>
<td>- CD4 count ≤ 200 cells/mm³ or ≤ 15%</td>
</tr>
</tbody>
</table>
Guideline recommendations: SA and W Cape 2015

• Children < 5 years: irrespective of CD4 or clinical staging
• Children > 5 years: if CD\(_{\leq} 500\), or WHO stage 3,4
• Fast track:
  – < 1 year
  – WHO stage 4
  – MDR / XDR TB
  – CD4 \(_{\leq} 200\)
Challenges of paediatric ART

- Eligibility criteria
- Complex regimens
- Palatability of meds
- Regular dose adjustments with growth
- Diagnosing / excluding TB
- Nutrition and growth
- Development
- Caregiver issues: denial, disclosure, adherence
Challenges of paediatric ART

• “Guideline stability”
Before starting ART

- Confirm HIV status
- Actively trace and link to care
- Assess clinical condition and other co-morbidities
- Screen for TB symptoms
- Ensure mother is on ART
- Document weight, length, head circumference
- Developmental assessment
- Advise on breastfeeding
- Counselling: disclosure, feeding choices
- Baseline investigations
- Get expert opinion for complicated cases
First line ARV regimens

- Neonates
- Infant / child <3 years
- Child > 3 years
- Adolescent
Neonates: transition from prophylaxis to treatment

- Get positive PCR result: most neonates still will be receiving PMTCT

- Concerns:
  - Variable absorption / excretion by age and gestation
  - Dosing / safety data lacking
  - Toxicity: lopinavir/ritonavir
Western Cape Gov
Amendments to Consolidated Guidelines, Nov 2015
Transition from prophylaxis to treatment

• Baseline assessment:
  
  Clinical review
  
  Bloods: confirmatory PCR, CD4 count/%; FBC / diff, ALT
  
  Genotype if mother failing 2\textsuperscript{nd} / 3\textsuperscript{rd} line

• Start ART on same day
  
  Commence zidovudine, lamivudine, nevirapine
  
  Doses as per neonatal dosing chart, to nearest 0.1 ml twice daily
## Transition from prophylaxis to treatment

<table>
<thead>
<tr>
<th>Target dose</th>
<th>Lamivudine (3TC)</th>
<th>Zidovudine (AZT)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWICE daily (BD)</td>
<td>2mg/kg/dose</td>
<td>4mg/kg/dose</td>
<td>6mg/kg/dose</td>
</tr>
</tbody>
</table>

| Available formulation | 10mg/ml | 10mg/ml | 10mg/ml |

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
<th>Dose in ml</th>
<th>Dose in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2.5–&lt;3.0</td>
<td>0.6 ml BD</td>
<td>6 mg BD</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
</tr>
<tr>
<td>≥3.0–&lt;3.5</td>
<td>0.7 ml BD</td>
<td>7 mg BD</td>
<td>1.4 ml BD</td>
<td>14 mg BD</td>
<td>2.1 ml BD</td>
<td>21 mg BD</td>
</tr>
<tr>
<td>≥3.5–&lt;4.0</td>
<td>0.8 ml BD</td>
<td>8 mg BD</td>
<td>1.6 ml BD</td>
<td>16 mg BD</td>
<td>2.4 ml BD</td>
<td>24 mg BD</td>
</tr>
<tr>
<td>≥4.0–&lt;4.5</td>
<td>0.9 ml BD</td>
<td>9 mg BD</td>
<td>1.8 ml BD</td>
<td>18 mg BD</td>
<td>2.7 ml BD</td>
<td>27 mg BD</td>
</tr>
<tr>
<td>≥4.5–&lt;5.5</td>
<td>1.0 ml BD</td>
<td>10 mg BD</td>
<td>2.0 ml BD</td>
<td>20 mg BD</td>
<td>3.0 ml BD</td>
<td>30 mg BD</td>
</tr>
<tr>
<td>≥5.5–&lt;6.5</td>
<td>1.2 ml BD</td>
<td>12 mg BD</td>
<td>2.4 ml BD</td>
<td>24 mg BD</td>
<td>3.6 ml BD</td>
<td>36 mg BD</td>
</tr>
</tbody>
</table>
Follow up: weeks 1 and 2

• Weight bands at 2.5, 3.0 and 3.5kg:
  – Use weight bands for birth weight only to decide on starting doses
  – Do not adjust doses in the first 4 weeks of life

• Review at 1 week: clinical review and counselling, check blood results

• Review at 2 weeks: clinical review and counselling
Follow up week 4:

• Review at 1 month: Clinical review and counselling
  Bloods FBC/diff, chol + TG
  Start bactrim prophylaxis
  Adjust medication

• If >3 kg:
  Switch nevirapine to lopinavir/ritonavir: as per paed dosing chart
  Switch zidovudine to abacavir: as per paed dosing chart

• If still < 3 kg:
  Assess for failure to thrive
  Switch nevirapine to lopinavir/ritonavir: 1 ml twice daily
  zidovudine: 12mg/kg twice daily
  lamivudine: 4mg/kg twice daily
<table>
<thead>
<tr>
<th>Wt. (kg)</th>
<th>Current available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed</th>
<th>Available Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>Consult with a clinician experienced in paediatric ARV prescribing for neonates (&lt;28 days of age) and infants weighing &lt;3kg</td>
<td>Available Formulations</td>
</tr>
<tr>
<td>3.5-5.9</td>
<td>2ml bid</td>
<td>2ml bid</td>
</tr>
<tr>
<td>4.0</td>
<td>2ml bid</td>
<td>2ml bid</td>
</tr>
<tr>
<td>5.5-5.9</td>
<td>3ml bid</td>
<td>3ml bid</td>
</tr>
<tr>
<td>6-6.9</td>
<td>4ml bid</td>
<td>4ml bid</td>
</tr>
<tr>
<td>7-7.9</td>
<td>4ml bid</td>
<td>4ml bid</td>
</tr>
<tr>
<td>8-8.9</td>
<td>9-9.9</td>
<td></td>
</tr>
<tr>
<td>9.9-10.9</td>
<td>10-10.9</td>
<td>12ml od</td>
</tr>
<tr>
<td>11-13.9</td>
<td>14-16.9</td>
<td>15 ml od</td>
</tr>
<tr>
<td>16-19.9</td>
<td>17-19.9</td>
<td>16 ml od</td>
</tr>
<tr>
<td>20-22.9</td>
<td>23-24.9</td>
<td>24 ml od</td>
</tr>
<tr>
<td>25-29.9</td>
<td>25-29.9</td>
<td>28 ml od</td>
</tr>
</tbody>
</table>
Neonatal ART scenario 1

• (>2.5 at birth, >3 at 4 weeks)
• 37 weeks, 2900g. PCR taken at birth, obtain positive result on day 3. Clinically well, no other co-morbidity. Current prophylaxis NVP 1.5ml daily and ZDV 1ml twice daily

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>ZDV dose (twice daily)</th>
<th>3TC dose (twice daily)</th>
<th>NVP dose (twice daily)</th>
<th>ABC dose (twice daily)</th>
<th>LPV/r dose (twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>2900</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>2920</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>3120</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>3370</td>
<td>STOP</td>
<td>2ml</td>
<td>STOP</td>
<td>2ml</td>
<td>1ml</td>
</tr>
</tbody>
</table>
Neonatal ART scenario 2

- (>2.5 at birth, <3 at 4 weeks)
- 37 weeks, 2680g. Current prophylaxis NVP 1.5ml daily and ZDV 1ml twice daily

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>ZDV dose (twice daily)</th>
<th>3TC dose (twice daily)</th>
<th>NVP dose (twice daily)</th>
<th>LPV/r (twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>2680</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>2670</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>2740</td>
<td>1.2ml</td>
<td>0.6ml</td>
<td>1.8ml</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>2920</td>
<td>3.5ml</td>
<td>1.2ml</td>
<td>STOP</td>
<td>1ml</td>
</tr>
</tbody>
</table>
Neonatal ART scenario 3

- Preterm, <2.5 at birth
- 34 weeks, 2260g
- Confirm PCR result; stop prophylaxis
- Discuss with paediatric specialist re:
  - Risk / benefits of early treatment
  - Dosages and adjustments
    - 3TC: same dose (2mg/twice daily)
    - NVP lower dose (4mg/kg twice daily)
    - ZDV: lower dose (2mg/kg for 2 weeks then 3mg/kg twice daily)

Must be on full oral feeds
Shouldn’t use LPV/r till 42 weeks corrected gestational age
Infant / child < 3

- More than 4 weeks / 3kg but less than 3 years / 10 kg
- Commence abacavir, lamivudine, lopinavir/ritonavir as per ART dosage chart
Child >3 years, >10kg

- 2015 SA National Guideline
  ABC, 3TC, EFV

- 2015 W Cape Guideline
  No perinatal NVP exposure:
    ABC, 3TC, EFV
  Had perinatal NVP for at least 6 weeks:
    ABC, 3TC, LPV/r

- Children started on ABC, 3TC, LPV/r when less than 3 years to stay on their regimen
Adolescents

- NB disclosure
- Pre-ART counselling re stigma and adherence
- Check creatinine clearance if considering TDF
- Weight <40kg:
  - ABC, 3TC, EFV (as per children’s dose chart)
- Weight >40kg and CrCl >80:
  - TDF, FTC, EFV (as odimmune fixed dose combination)
- Renal disease:
  - ABC, 3TC, EFV
Adolescents (cont)

- Other combinations based on specific contra-indications as per adult guidelines
- Psychiatric co-morbidity:
  - Avoid EFV, use NVP if CD4 low
  - Use LPV/r if CD4 >250 (female) or >400 (male)
- Hypersensitivity to ABC: use ZDV
- Severe anaemia: avoid ZDV, use d4T
- Monitoring depends on regimen
Conclusion

• “Eligibility criteria” evolved; need to await local implementation of new WHO advisory

• NB to identify urgent / priority / fast track cases

• NB follow the correct version of the guidelines