Virological response and resistance among HIV-infected children on first-line antiretroviral therapy without routine virological monitoring

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Background

- UNAIDS target of 90-90-90

- 51% of HIV-infected children are currently on ART and numbers will increase with universal treatment guidelines

- WHO guidelines recommend regular viral load monitoring
  - 6 and 12 months after starting ART
  - Every 12 months thereafter

- Virological failure defined as VL >1000 copies/mL

- However, VL availability remains limited in sub-Saharan Africa (estimated at 25% in 2014)

- Question: What are the long-term virological outcomes and resistance of children managed without regular VL?
ARROW trial

1206 ART-naive children and adolescents (4 months - 17 years) in Uganda and Zimbabwe, meeting WHO 2006 criteria for ART initiation

**Laboratory and Clinical Monitoring (LCM)**
- 12 weekly biochemistry, FBC & CD4 (no VL)
- Other investigations & concomitant medications if clinically indicated
- Switch to second-line for
  - new/recurrent WHO 4 (or multiple WHO 3)
  - WHO CD4 criteria

**Clinically Driven Monitoring (CDM)**
- 12 weekly biochemistry, FBC & CD4 (no VL);
  - FBC & biochemistry only returned if clinically requested (or grade 4 toxicity);
  - CD4 never returned
- Other investigations & concomitant medications if clinically indicated
- Switch to second-line for
  - new/recurrent WHO 4 or recurrent/persistent WHO 3

As per WHO guidelines, switching before 48 weeks discouraged in both groups
**ARROW trial**

1206 ART-naive children and adolescents (4 months -17 years) in Uganda and Zimbabwe, meeting WHO 2006 criteria for ART initiation

**Laboratory and Clinical Monitoring (LCM)**
- 12 weekly biochemistry, FBC & CD4 (no VL)

**Clinically Driven Monitoring (CDM)**
- 12 weekly biochemistry, FBC & CD4 (no VL);

**Randomised**

**Viral loads were not measured in either group in real time or used for clinical management**

- Clinically indicated
  - Switch to second-line for
    - new/recurrent WHO 4 (or multiple WHO 3)
    - WHO CD4 criteria

- Clinically indicated
  - Switch to second-line for
    - new/recurrent WHO 4 or recurrent/persistent WHO 3

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ARROW trial

As well as monitoring randomization, factorial design with randomization to first-line ART strategies:

- Arm A: standard 3-drug ART throughout
- Arms B and C: Induction-maintenance (4 drugs for first 36 weeks)

Thus long-term in ARROW, 2/3 children on standard 2NRTI + NNRTI and 1/3 were on 3NRTI
Retrospective viral load testing after 4 years ART and longitudinally in a subgroup

Enrolled in ARROW and initiated ART containing ABC+3TC+NNRTI
Managed with or without CD4 tests
Followed for median 4 years (N=1206)

Cross-sectional
N=890

Longitudinal
N=316

VL assayed at weeks 4, 24, 36 and 48 post-ART, then 24-weekly

VL assayed in the 6 months before trial closure/death
N=1127 with available viral load data
Viral load and resistance testing

- Viral loads tested with lower limit of <80 copies/ml
- Samples with VL >1000 copies/ml genotyped
  - Reverse transcriptase only
  - In-house assay at JCRC, Uganda
- Major NRTI and NNRTI mutations defined according to IAS 2013
- Drug susceptibility predicted using Stanford algorithm v7
Virological definitions in longitudinal substudy

• Viral load response
  - VL <10,000 copies/ml (or >1 log drop) at week 4
  - VL <5000 copies/ml at week 24
  - <80 copies/ml at all measurements thereafter [except slow responders, VL declining but >80 at week 36]

• Blips
  - Single or dual measurement >80 copies/ml, provided prior and subsequent VL <80 copies/ml

• Persistent low-level viral load
  - VL persistently detectable but <5000 copies/ml

• Rebound
  - Confirmed VL >5000 copies/ml
Analysis

- **Cross-sectional study (n=1127)**
  - VL suppression and resistance compared between randomized monitoring and treatment arms, in the 6 months prior to trial closure/death, using chi-squared tests (ITT)

- **Longitudinal study (n=316)**
  - Predictors of children with VL blips, persistent low-level viral load (pLLVL), rebound, and pLLVL/rebound identified using logistic regression
  - Resistance summarized at the first VL in rebound, then at last subsequent genotype.
Results

• 1206 children initiated ART
  - Median age 6.0 years (IQR 2.4, 9.3)
  - Median CD4 at initiation 12% (7, 17)

• Median follow-up 4.0 years (range 3.3-5.0)
  - 5% with CD4 monitoring died vs 4% with clinical monitoring

• Only 63 (6%) switched to second-line ART

• At trial closure, 1132 (94%) alive and in follow-up
  - Viral loads available for 1127 (99.6%)
VL outcomes at 4 years by randomized first-line ART

Viral load <1000 copies/ml

- 2 NRTI + NNRTI: 80%
- 3 NRTI: 65%

Viral load <80 copies/ml

- 2 NRTI + NNRTI: 74%
- 3 NRTI: 52%

P<0.001

Long-term 3NRTI first-line ART is virologically inferior to standard 2NRTI + NNRTI ART
VL outcomes at 4 years by randomized monitoring strategy

Viral load <1000 copies/ml

- CD4: 81%
- Clinical: 79%
- P=0.43

Viral load <80 copies/ml

- CD4: 75%
- Clinical: 73%
- P=0.57

No difference in virological outcomes by monitoring strategy (all on WHO-recommended 2NRTI + NNRTI)
Resistance data by monitoring strategy and first-line ART at 4 years (all with VL > 1000)

- No difference in intermediate/high-level resistance to NRTIs and NNRTIs by monitoring strategy
- On WHO-recommended 2NRTI + NNRTI, only 15% had intermediate/high-level resistance to TDF and 9% to ZDV at 4 years
- 7% had K65R
Longitudinal viral load responses over 4 years by first-line ART

N=311 children alive and achieving VL response by week 4

Week 4: Viral load response, Current or previous blip, Low level viral load, Rebound, Died, Non responder

Arms A/B
- Viral load response
- Current or previous blip
- Low level viral load
- Rebound
- Died
- Non responder

Arm-C
- Viral load response
- Current or previous blip
- Low level viral load
- Rebound
- Died
- Non responder

Weeks 24, 36, 48, 72, 96, 120, 144, 168, 192, 216
Longitudinal viral load responses over 4 years by monitoring strategy

- Similar virological classification regardless of monitoring strategy throughout follow-up

N=305 at week 144; P=0.94
Longitudinal viral load responses over 4 years by monitoring strategy

Predictors of low-level viral load / rebound:
• 3 NRTI regimen compared to 2NRTI+NNRTI; P<0.001
• ART initiated at older age; P=0.03
• ART initiated with higher viral load; P=0.048

Similar virological classification regardless of monitoring strategy throughout follow-up

N=305 at week 144; P=0.94
Development of resistance during 2 years of viral rebound (n=12 on 2NRTI + NNRTI)

(a) Stanford score at rebound:

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
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<tbody>
<tr>
<td>3TC</td>
<td>ABC</td>
</tr>
<tr>
<td>ZDV</td>
<td>DDI</td>
</tr>
<tr>
<td>D4T</td>
<td>FTC</td>
</tr>
<tr>
<td>TDF</td>
<td>EFV</td>
</tr>
<tr>
<td>ETR</td>
<td>RPV</td>
</tr>
</tbody>
</table>

(b) Change in Stanford score between rebound and 2 years subsequently:

<table>
<thead>
<tr>
<th>Change</th>
<th>Susceptible</th>
<th>Potential low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
<td>Same</td>
<td>+1</td>
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<tr>
<td>+2</td>
<td>+3</td>
<td>+4</td>
<td></td>
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</tbody>
</table>

(i) Arm A or Arm B (n=12)

• After median 2.3 years of rebound, median 1 additional NRTI major mutation accumulated; P=0.009
• Little impact on predicted drug susceptibility: only one child developed intermediate/high-level resistance to TDF and ZDV
Probability of resuppressing a detectable viral load

• 18% of single viral loads >1000 copies/ml (and 8% of confirmed VL >1000) were immediately followed by VL<1000

• Logistic regression to explore probability of single VL>1000 returning to <1000 copies/ml
Discussion

• Virological outcomes in children from Zimbabwe and Uganda in the ARROW trial were very good
  - Almost 3/4 fully suppressed (<80) after 4 years of ART
  - Only 6% switched to second-line ART

• No difference in virological failure or resistance between children managed with CD4 monitoring and clinical monitoring

• 3NRTI regimen was virologically inferior to standard 2NRTI + NNRTI first-line ART
Discussion

- Virological blips are common
- Persistent viraemia/rebound occurs in a minority
  - Only 20% of those on standard 2NRTI + NNRTI regimens
- Intermediate-high level drug resistance only found in a minority of children with virological failure
- Children with virological rebound (>5000 copies/ml) developed slight increase in NRTI resistance over 2 years, suggesting there should not be a substantial delay in switching at this level.
Programme implications

• Excellent virological outcomes are achievable even without routine VL monitoring
  - Reassuring in low-level health facilities where VL not available

• Single VL >1000 copies/ml should be interpreted with caution
  - Blips are common
  - Low-level viraemia may be followed by resuppression, even without adherence counselling

• Confirmed viral rebound >5000 copies/ml may lead to resistance mutations and should prompt consideration of switch to second-line.
We thank all the patients and staff from all the centres participating in the ARROW trial.