Reduction of EARly mortality in HIV-infected adults and children starting antiretroviral therapy

Mags Thomason on behalf of the REALITY team

International Clinical Trials Day 19th May 2017
Background

- Data from South Africa showed that people starting ART with CD4<50 cells/mm$^3$ were six times more likely to die in the first year on treatment compared to those starting ART with CD4>200 cells/mm$^3$.

- In African adults aged 18 to 73 years (DART trial) and in children aged 4 months to 15 years (ARROW trial) in Uganda and Zimbabwe, early mortality was high in those with low CD4. (CID 2012: 55(12): 1707-18)

- Around 1 in 4 adults continue to present late (CD4 <100) in many African countries.

Risk of death in DART trial
18+ years (n=3316)

Hazard of death

Years from ART initiation

Pre-ART CD4
- 0-49
- 50-99
- 100-149
- 150-199

peak 30-43d

heterogeneity p<0.0001
Risk of death in ARROW 0.4-15 years (n=1206)

- Pre-ART CD4/CD4% & age
  - 0-49,4+
  - 50-99,4+
  - 100-149,4+
  - 150+,4+
  - <5%,<4
  - 5-<10%,<4
  - 10-<15%,<4
  - 15%+,<4

- Hazard of death
  - peak 41-51d
  - heterogeneity p=0.0007
    - 4-15 years: p=0.0001
    - 0.5-3 years: p=0.36
Rationale

Reasons for high early mortality are likely to be multi-factorial, including:

- advanced HIV infection
- high rates of co-infections (TB, bacterial infections, fungal/protozoal infections, parasites)
- malnutrition
Interventions to reduce early mortality after starting ART

- Is early mortality related to HIV?
  - More potent ART

- Is early mortality related to co-infections?
  - Prophylaxis
    - Antibiotics
    - TB prophylaxis: Isoniazid
    - Antifungal prophylaxis
    - De-worming at starting ART

- Is early mortality related to malnutrition?
  - Extra nutrition
Study Design

• A 2x2x2 open-label factorial multi-centre trial, conducted in 8 centres in 4 countries (Kenya, Malawi, Uganda, Zimbabwe)

• 1800 participants 5+ years randomised over maximum of 2 years

• Each intervention to be administered in addition to standard of care for 12 weeks ONLY

• Each participant to be followed for 48 weeks

• Primary outcome: mortality over 24 weeks after starting ART
REALITY Trial Sites

- Uganda
  - Fort Portal
  - Gulu
  - Mbale
  - Mbarara
- Kenya
  - Kilifi
  - Eldoret
- Zimbabwe
- Malawi
Challenges

• Recruitment of children
  - Only 4% 5-17 year olds

• Drug supply management
  - 14 drugs and RUSF from 5 companies

• Ready to use Supplementary Food
  - Acceptability, adherence, sharing

• Endpoint review process
  - 923 events

• Local monitoring
Challenges

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Despite being a very busy trial (e.g. recruiting and exiting at the same), STILL:
- Recruited ahead of 2 year planned recruitment
- Only 3% loss to follow-up
HIV-infected adult, adolescent or child aged 5 years or older; Naïve to ART including for drugs given to prevent mother-to-child transmission; CD4 T-cell count <100 cells/mm³ on screening blood test; Patient/carer providing consent (and children <18 years assent, as appropriate); No major contraindications to any study drugs; Not pregnant or intending to become pregnant during the next 12 weeks

All patients enter the three randomisations A, B, C simultaneously

**RANDOMISE (A)**
- Standard 2 NRTI+NNRTI plus integrase inhibitor for 12 weeks
- Standard 2 NRTI+NNRTI

**RANDOMISE (B)**
- Enhanced prophylaxis with cotrimoxazole, isoniazid, fluconazole plus 5 days azithromycin and single dose albendazole
- Standard cotrimoxazole prophylaxis (all patients) plus isoniazid from 12 weeks (not Malawi as not in guidelines)

**RANDOMISE (C)**
- 12 weeks Ready-to-Use Supplementary Food (RUSF)*
- Standard nutritional support*

* all patients meeting criteria for Ready to Use Therapeutic Food will receive this, regardless of randomisation
Interventions to reduce early mortality after starting ART

- Is early mortality related to HIV?
  - More potent ART

- Is early mortality related to early infections?
  - Prophylaxis
    - Antibiotics
    - TB prophylaxis: INH
    - Antifungal prophylaxis
    - De-worming at starting ART?

- Is early mortality related to profound catabolic state?
  - Extra nutrition
Enhanced Prophylaxis (B)

ART-naïve HIV-infected adults & children >5 years with CD4<100 cells/mm³

Initiated ART and randomised 1:1

Enhanced prophylaxis: CTX* +
- 12 weeks INH/B6* 300/25mg/d (anti-TB)
- 12 weeks fluconazole 100mg/d (anti-fungal)
- 5 days azithromycin 500mg/d (anti-bacterial & anti/protozoal)
- single-dose albendazole 400mg (anti-helminth)

Standard prophylaxis: CTX
(most received additional INH/B6* from 12 weeks depending on national guidelines)

*INH/B6/CTX scored FDC
Half doses if <12 years

Follow-up to week 48
Safety bloods at screening, weeks 4 and 48;
FBC & CD4 at weeks 0, 12, 24, 36, 48;
Viral loads retrospectively at weeks 0, 4, 12, 24, 48

Produced by Cipla Pharmaceuticals Ltd
After day 5, only one extra pill (fluconazole 100mg) taken each day in enhanced prophylaxis group.

Enhanced Prophylaxis

One dose: Albendazole
5 Days: Azithromycin
12 weeks: INH/B6/Cotox FDC
Fluconazole 100mg

Standard of Care (Cotox)

After 12 weeks, INH started in countries as per national guidelines (e.g. not in Malawi)
Patients changed from cotox to the FDC
Results: All-cause mortality

- Mortality at 24 weeks: **8.9% enhanced Px vs 12.2% standard Px**

\[
\text{w24: HR=0.73} \\
(95\% \text{ CI 0.54-0.97}) \\
\text{p=0.03}
\]

\[
\text{w48: HR=0.75} \\
(95\% \text{ CI 0.58-0.98}) \\
\text{p=0.04}
\]

- 56 (3.1%) lost to follow-up at 48 weeks
- 0-12w: **93% vs 14%** on isoniazid and **95% vs 3%** on fluconazole (Px or Rx)
- No interactions with other randomisations (p>0.8)
Results: All-cause mortality

- Mortality at 24 weeks: **8.9% enhanced Px vs 12.2% standard Px**

  - [Graph showing mortality over time]

  - **w24:** $HR=0.73$ (95% CI 0.54-0.97) $p=0.03$
  - **w48:** $HR=0.75$ (95% CI 0.58-0.98) $p=0.04$

  - **3.3 lives saved for every 100 treated**
  - **NNT=30**

- 56 (3.1%) lost to follow-up at 48 weeks
- 0-12w: 93% vs 14% on isoniazid and 95% vs 3% on fluconazole (Px or Rx)
- No interactions with other randomisations (p>0.8)
Primary cause of death
adjudicated by an independent ERC blind to randomisation

• COD were multifactorial - very sick patients
  - Most had several secondary causes
  - Many patients died at home/had unclear COD

<table>
<thead>
<tr>
<th>Main cause of death</th>
<th>Enhanced Px</th>
<th>Standard Px</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>2.3%</td>
<td>2.5%</td>
<td>0.81</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>0.4%</td>
<td>1.5%</td>
<td>0.03</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>2.0%</td>
<td>1.7%</td>
<td>0.68</td>
</tr>
<tr>
<td>Other</td>
<td>2.3%</td>
<td>2.6%</td>
<td>0.68</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.8%</td>
<td>6.0%</td>
<td>0.02</td>
</tr>
</tbody>
</table>
• No evidence of difference in Viral Load suppression

Taking enhanced prophylaxis did not affect viral load suppression, suggesting adherence was just as good

• No evidence of difference in CD4 reconstitution (p=0.55)
Enhanced Prophylaxis (B) Conclusions

- In HIV-infected adults/children with CD4<100 cells/mm$^3$
  - **Enhanced prophylaxis** at ART initiation
    - Reduced early mortality from 12.2% to 8.9% (27% relative reduction, 3.3% absolute reduction)
    - Reduced adverse events and hospitalisations

- The additional pill burden did not adversely affect VL suppression and was decreased by a well-accepted FDC of CTX/INH/B6 (WHO pre-qualified in December 2016; EDL 2017)

- Policy-makers should consider adopting and implementing this low-cost broad infection prevention package which could **save 3.3 lives for every 100 individuals treated**
The REALITY trial tested whether a bundle of drugs, used to prevent infections during the first 12 weeks of ART, could prevent these deaths.

Everyone got daily cotrimoxazole, and antiretroviral therapy.

Half of people taking part in REALITY also got:

- 12 weeks of daily isoniazid and pyridoxine to prevent TB
- 12 weeks of daily fluconazole to prevent cryptococcal disease and candida
- 5 days of azithromycin to prevent infections
- A single dose of albendazole to get rid of worms
The bundle of drugs worked:

- Deaths in the first 6 months on treatment: 27%
- TB incidence: 28%
- Cryptococcal disease: 62%
- Candidiasis: 58%
- Presumed severe bacterial infections: No change (but hard to diagnose)
- Hospitalisations: 17%
The impact of enhanced prophylaxis:

Enhanced prophylaxis saves 3 lives for every 100 people treated.

About reality

1805 people with CD4 counts <100 cells/mm3 took part from:

- Kenya
- Malawi
- Uganda
- Zimbabwe
Interventions to reduce early mortality after starting ART

• Is early mortality related to HIV?
  ➢ More potent ART

• Is early mortality related to early infections?
  ➢ Prophylaxis
    • Antibiotics
    • TB prophylaxis: INH
    • Antifungal prophylaxis
    • De-worming at starting ART?

• Is early mortality related to profound catabolic state?
  ➢ Extra nutrition
Results: HIV VL<50 copies/ml

- >99% compliance with randomised strategy
- 98% and 99% of time to 48 weeks spent on allocated ART as at randomisation or having made within class substitutions only

![Graph showing percentage of patients with VL<50 copies/ml over time for Additional RAL and Standard-of-care groups.](image-url)
Results: change in CD4

- No evidence of difference in CD4 reconstitution overall (GEE p=0.30)
Results: all cause mortality

- Mortality at 24 weeks: **10.9% RAL** vs **10.2% standard-of-care**

\[
\begin{align*}
\text{w24: } & HR=1.09 \\
& (95\% \text{ CI } 0.82-1.46) \\
& p=0.54
\end{align*}
\]

\[
\begin{align*}
\text{w48: } & HR=0.98 \\
& (95\% \text{ CI } 0.75-1.27) \\
& p=0.86
\end{align*}
\]

- 56 (3.1%) lost to follow-up at 48 weeks
- No interactions with other randomisations (p>0.7)
Enhanced ART (A)
Conclusions

- Standard triple ART intensified with raltegravir for 12 weeks
  - was well tolerated
  - resulted in faster VL reduction through 24 weeks
  - increased CD4 at 48 weeks
- But did not reduce mortality or WHO 3/4 events through either week 24 or 48
Interventions to reduce early mortality after starting ART

• Is early mortality related to HIV?
  ➢ More potent ART

• Is early mortality related to early infections?
  ➢ Prophylaxis
    • Antibiotics
    • TB prophylaxis: INH
    • Antifungal prophylaxis
    • De-worming at starting ART?

• Is early mortality related to profound catabolic state?
  ➢ Extra nutrition
Ready-to-use Supplementary Food (RUSF) Randomisation C

- ART-naïve HIV-infected adults, adolescents and children >5 years with CD4<100 cells/mm³

1:1 randomisation

12 weeks Ready-to-use Supplementary Food

Standard of care nutritional support
Results: all-cause mortality

- Mortality at 24 weeks: 10.9% RUSF vs 10.3% no-RUSF

\[ \text{w24: HR}=1.05 \]
\[ (95\% \text{ CI } 0.79-1.40) \]
\[ p=0.75 \]

\[ \text{w48: HR}=0.98 \]
\[ (95\% \text{ CI } 0.75-1.27) \]
\[ p=0.87 \]

- 32 (1.8%) lost to follow-up at 48 weeks
- No interactions with other randomisations (p>0.7)
• There was no difference in VL suppression (GEE p=0.62)

⇒ RUSF did not affect ART adherence
• Nor was there any difference in CD4 (p=0.62)

<table>
<thead>
<tr>
<th>Change from randomisation (cells/mm³)</th>
<th>RUSF</th>
<th>No-RUSF</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUSF</td>
<td>+66</td>
<td>+98</td>
<td>+113</td>
</tr>
<tr>
<td>No-RUSF</td>
<td>+62</td>
<td>+94</td>
<td>+111</td>
</tr>
<tr>
<td>Overall GEE p=0.34</td>
<td>0.20</td>
<td>0.22</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Change in CD4 count

Weeks since randomisation (ART initiation)
Enhanced nutrition (C)  
Conclusions

• RUSF for 12 weeks at ART initiation:
  - Improved anthropometric status during supplementation
  - Did not improve mortality, health outcomes, immunological recovery or viral load outcomes

• First conclusive randomised evidence of effect of supplementary food

• Focus on assessment, counselling and support for a balanced diet with adequate energy, and food supplementation for malnourished individuals or in food-insecure areas, rather than universally providing relatively high-cost lipid-based ready-to-use supplementary foods
Qualitative Substudy (unpublished)
Janet Seeley and Frances Cowan

- 48 patients from Uganda and Zimbabwe
- Purposeful sampling of those with high & low pill burden:
  - No differences in adherence or acceptability
    - ‘Not a single patient complained that pill burden was unacceptable or too high’
    - Patients commented on ‘dramatic improvement in health’
- Reasons for late presentation:
  - Did not feel sick or waiting until tried usual treatments
  - Did not see themselves at risk
  - Unaware of messages on benefits of earlier presentation
  - STIGMA
Milestones and Next Steps

- First Patient Enrolled: June 2013; Last Patient Enrolled: April 2015
- Last Patient Exit: March 2016
- Investigator Results Meeting: May 2016
- Late Breaker Presentation: IAS, Durban, S. Africa July 2016
- Database Lock: November 2016
- Submission OI prophylaxis paper to NEJM November 2016; response to reviewer comments Feb 2017
- MRC microbiology/immunology grant successful Feb 2017
- CRAG substudy ongoing with stored samples
- Qualitative study being written up
- Poster - causes/timing of deaths to IWHOD meeting March 2017
- Raltegravir and Food supplementation randomisations - presented at Durban IAS and CROI 2017; papers ongoing (note no effects and no interactions with OI Prophylaxis randomisation)
We thank all the patients and staff from all the centres participating in the REALITY trial.


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## Baseline characteristics

n (%) or median (IQR)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enhanced Px (N=906)</th>
<th>Standard Px (N=899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>477 (53%)</td>
<td>484 (54%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36 (29-42) [6-71]</td>
<td>36 (30-42) [5-78]</td>
</tr>
<tr>
<td>5-17 years</td>
<td>39 (4%)</td>
<td>33 (4%)</td>
</tr>
<tr>
<td>Current TB disease</td>
<td>122 (13%)</td>
<td>125 (14%)</td>
</tr>
<tr>
<td>WHO stage 1 or 2</td>
<td>436 (48%)</td>
<td>418 (46%)</td>
</tr>
<tr>
<td>CD4 (cells/mm$^3$)</td>
<td>38 (16-64)</td>
<td>36 (16-60)</td>
</tr>
<tr>
<td>0-24 cells/mm$^3$</td>
<td>323 (36%)</td>
<td>333 (37%)</td>
</tr>
<tr>
<td>VL (c/ml) (N=1568)</td>
<td>229,690</td>
<td>230,540</td>
</tr>
<tr>
<td>VL&gt;100,000 c/ml</td>
<td>574/782 (73%)</td>
<td>563/786 (72%)</td>
</tr>
<tr>
<td>EFV-based ART</td>
<td>820 (91%)</td>
<td>799 (89%)</td>
</tr>
<tr>
<td>TDF/FTC NRTI backbone</td>
<td>716 (79%)</td>
<td>706 (79%)</td>
</tr>
</tbody>
</table>
Similarly, cause-specific mortality reached its maximum at day 16-22.

Deaths occurred soon after taking ART.
Secondary/other outcomes

- WHO 4 or death: p=0.006
- WHO 3 or 4 or death: p=0.007
- New TB disease: p=0.01
- New cryptococcal disease: p=0.01
- New candida disease: p=0.02
- Presumptive severe bacterial infection: p=0.35
Secondary/other outcomes

- WHO 4 or death
- WHO 3 or 4 or death
- New TB disease
- New cryptococcal disease
- New candida disease
- Presumptive severe bacterial infection
- SAE
- Hospitalisations
- Grade 4 AE
- Grade 3 or 4 AE
- Grade 4 AE def/prob/poss related to Px
- Grade 4 AE def/prob related to Px
- AE leading to OI drug modification

**Enhanced better vs. Standard better**

- p=0.006
- p=0.007
- p=0.01
- p=0.01
- p=0.02
- p=0.35
- p=0.06
- p=0.04
- p=0.07
- p=0.21
- p=0.60
- p=0.21
- p=0.97