Bacteraemia in HIV-1 infected children on antiretroviral therapy in Uganda and Zimbabwe in the ARROW clinical trial

Victor Musiime, Adrian Cook, Sabrina Bakeera-Kitaka, Tichaona Vhembo, Joseph Lutaakome, Rosette Keishanyu, Andy Prendergast, Sam Lubwama, Val Robertson, Peter Hughes, Kusum Nathoo, Paula Munderi, Philippa Musoke, Diana M Gibb

on behalf of the ARROW trial team

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
Background

• Bacteraemia is a common cause of morbidity and mortality in HIV infected children [1, 2]

• Bacteria that have been commonly isolated include: *Streptococcus pneumoniae, Staphylococcus aureus* and *Enterobacteriaceae* [2, 3, 4]

• Most isolates are susceptible to cephalosporins but high rates of resistance to cotrimoxazole and penicillin have been observed [2, 4]

• Data on patterns of the bacteraemia pathogens and their antimicrobial sensitivity patterns, particularly in Africa, is limited


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Methods
The ARROW Trial

- An open randomised controlled trial of monitoring practice and first line ART strategies in HIV infected children
  - 4 clinical sites: 3 in Uganda, 1 in Zimbabwe

- 1206 children enrolled; their baseline characteristics:
  - Age distribution: Median (IQR) 6yrs (2,9)
  - 610 (51%) female
  - 1199 (99.4%) vertical transmission

- Median time of follow up: 156 weeks (3yrs) [Maximum – 210 weeks (4yrs)]

- Trial ongoing; follow-up 5 years by trial end in March 2012

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www.arrowtrial.org
Methods

• Children who developed febrile illnesses in follow up were investigated for infections including blood culture and sensitivity

• Most children had received *Haemophilus influenzae* type *B* vaccination as part of the EPI schedule
  - None had received pneumococcal vaccination

• Most were on cotrimoxazole prophylaxis
Methods

• Blood cultures were done in 3 labs (2 in Uganda, 1 in Zimbabwe) using Bactec blood culture systems, with the positive cultures being sub-cultured on various culture media
   Identification of pathogens and antimicrobial susceptibility testing was done using the BD Phoenix™ Automated Microbiology System in one of the labs
   In the other labs pathogens were identified using serological tests and antimicrobial susceptibility was done using the Kirby-Bauer disc diffusion method

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Results

- 848 blood cultures obtained from 461 children
  - 123 (14.5%) from 105 children were positive
    - 4 samples had 2 isolates each, hence 127 isolates in total

- Among children with positive isolates:
  - 54/105 (51%) were girls
  - Median age was 4 (range: 0.5 - 15) years

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Results

Culture positive rate

Event rate for positive cultures per 100 person years of follow up

- < 3 months: 18.8
- 3 to 11 months: 4.2
- ≥ 12 months: 1.6

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Results

Proportions of pathogens isolated from HIV-1 infected children with bacteraemia in the ARROW trial (N=127)

- 28%; S. pneumoniae
- 23%; Other bacteria
- 9%; S. aureus
- 9%; Other staph spp
- 8%; Other strep spp
- 5%; K. pneumoniae
- 5%; Salmonella spp
- 5%; P. aeruginosa
- 4%; E. coli
- 3%; Fungal spp
- 1%; H. influenzae
- 1%; Other bacteria

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Other significant bacteria isolated

- *Enterococcus* species – 3%
- *Corynebacteria* species - 2%
- *Moraxella* species – 2%
- *Proteus mirabilis* – 1%
- *Shingomonas* species – 1%

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Antibiotic susceptibility pattern of *Streptococcus pneumoniae* isolates

<table>
<thead>
<tr>
<th>Name of Antibiotic</th>
<th>Number of susceptible isolates (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>26/26 (100%)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>22/22 (100%)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>22/22 (100%)</td>
</tr>
<tr>
<td>Amoxicillin/ clavulanic acid</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>17/19 (89%)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>11/13 (85%)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>5/7 (71%)</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>14/22 (64%)</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>11/19 (58%)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>1/22 (5%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0/5 (0%)</td>
</tr>
</tbody>
</table>

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# Antibiotic susceptibility patterns of other bacteraemia isolates

<table>
<thead>
<tr>
<th>Name of antibiotic</th>
<th>S. aureus</th>
<th>Salmonella spp</th>
<th>E.coli</th>
<th>P.aeruginosa</th>
<th>K.pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>4/5 (80%)</td>
<td>5/5 (100)</td>
<td>2/2 (100)</td>
<td>1/2 (50)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>3/4 (75%)</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>-</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Meropenem/Imipenem</td>
<td>-</td>
<td>2/2 (100)</td>
<td>3/3 (100)</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3/3 (100%)</td>
<td>3/3 (100)</td>
<td>-</td>
<td>2/2 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>-</td>
<td>-</td>
<td>2/2 (100)</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3/5 (60%)</td>
<td>3/4 (75)</td>
<td>1/2 (50)</td>
<td>2/3 (67)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>5/8 (63%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
<td>-</td>
<td>0/1 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1/4 (25)</td>
<td>1/4 (25)</td>
<td>0/2 (0)</td>
<td>0/1 (0)</td>
<td>0/3 (0)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>0/8 (0)</td>
<td>1/3 (33)</td>
<td>0/2 (0)</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
</tbody>
</table>

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Conclusions

• High rates of proven bacteraemia were observed during the first year and especially in the first 3 months on ART in African HIV-infected children.

• *Streptococcus pneumoniae* was most commonly isolated, suggesting a need for effective prophylactic antibiotics and/or pneumococcal vaccination.

• High rates of resistance to commonly used antibiotics suggest that newer agents like ceftriaxone may be more effective for treatment of HIV-infected children with possible bacteraemia.
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  Data Monitoring Committee: A Breckenridge (Chair), C Giaquinto, C Hill, J Matenga, J Tumwine
  
  Endpoint Review Committee: G Tudor-Williams (Chair), H Barigye, HA Mujuru, G Ndeezi, MF Bwakura-Dangarembizi, V Musilme, P Musoke, P Nahyira-Ntege, JM Crawley, DM Gibb
  
  
  
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