Role of Clinical Pharmacology in Developing Countries

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Sub-Saharan Africa: 22.4 million

Global estimation: 33.4 million
(31.1 – 35.8 million)
“Concentrate on Uganda”

.....It is vital, and in my view, in spite of its insects and its diseases, it ought in the course of time to become the most prosperous of all our East and Central African possessions....

Nowhere else in Africa will a little money go so far. Nowhere else will the results be more brilliant, more substantial or more rapidly realized

1908
Uganda

1985: HIV identified in “Slim” samples
1990: Adult HIV prevalence 25%
2001: 1 million deaths (cumulative)

2001: AU declares state of emergency

2003 – First ART guidelines released
Public health approach

2013: 1,600,000 People living with HIV
2013: Adult prevalence 7.4%
2014: 50% receiving ART
2013: 60,000 deaths
2014: 5,000 vertical transmissions
<table>
<thead>
<tr>
<th>Initial Regimen</th>
<th>N(t)RTI</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF + 3TC (FTC), or AZT + 3TC</td>
<td>EFV or NVP</td>
</tr>
</tbody>
</table>

2013: TDF + 3TC (or FTC) + EFV *
*Preferred for adults (women, pregnancy, BF, TB co-infection)*

<table>
<thead>
<tr>
<th>Second-line Regimen</th>
<th>N(t)RTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF + 3TC, or AZT + 3TC</td>
<td>ATV/r or LPV/r</td>
</tr>
</tbody>
</table>

2013: If TDF + 3TC used in first line, switch to AZT+3TC, and vice versa

2015 Recommendations: All HIV positive patients should be started on antiretroviral therapy regardless of CD4 Count
Ethnic Factors and Impact on Drug Therapy

Intrinsic factors
- Gender
- Age
- Race
- Polymorphism
- Height
- Body weight
- Diseases
- Food habits

Extrinsic factors
- Culture
- Socioeconomic factors
- Medical practice
- Drug compliance

ICH E5
Ethnic Factors and Impact on Drug Therapy

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Extrinsic factors
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- Socioeconomic factors
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- Drug compliance

ICH E5
Women and HIV

Non-pregnant
• Contraception plus ART?

Pregnancy/PMTCT
• Are my ARVs safe in pregnancy?
• Dose adjustments in pregnancy?

Post-partum/Breastfeeding
• Should I stop ART?
Contraception plus ART?

Levonorgestrel Implant (Jadelle)
K Scarsi et al.
Clin Infect Dis
Jan 2016

Etonogestrel Implant (Implanon)
Vieira C, et al.
JAIDS 2014

Etonogestrel AUC increased 52% with lopinavir/r ART

Etonogestrel AUC reduced 63% with efavirenz ART

Efavirenz versus no ART

<table>
<thead>
<tr>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMR : 0.53</td>
<td>0.43</td>
</tr>
</tbody>
</table>
### Efavirenz and Teratogenicity

**Fig. 1.** Relative risk of birth defects on efavirenz vs. nonefavirenz regimens. CI, confidence interval; EFV, efavirenz.
Intrapartum

Are dose adjustments necessary?

<table>
<thead>
<tr>
<th>Antiretroviral drug</th>
<th>T3 reduction</th>
<th>Dose adjustment?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>NA</td>
<td>No</td>
<td>Hill et al. AIDS 2014</td>
</tr>
<tr>
<td>NVP</td>
<td>20% (AUC)</td>
<td>No</td>
<td>Lamorde et al. JAIDS 2012</td>
</tr>
<tr>
<td>LPV</td>
<td>NA</td>
<td>No*</td>
<td>Cressey et al. JAC 2015</td>
</tr>
<tr>
<td>ATZ</td>
<td>34% (AUC)</td>
<td>No+</td>
<td>Colbers et al. Antivir Ther 2014</td>
</tr>
</tbody>
</table>

* Increased doses may be needed for >100kg, adherence problems, prior use of LPV/r
+ Some subjects may require increase of ATZ/r 400/100 mg.
Intrapartum

Can we use lower doses of EFV in pregnancy?

ENCORE-1 RCT (pregnancy was exclusion criterion)

• Proportion VL < 200 copies/mL (W96)
  – EFV 400mg 90%
  – EFV 600mg 90.6%

Should we use integrase inhibitors for late presenting women?

*Increased risk of transmission and adverse outcomes when PMTCT started at T3 versus earlier*

• Intensification with INSTI?
• Use Dolutegravir instead of EFV?

SSAT063 Trial

DolPHIN-1 Trial
Post-partum

- Interruption of ART for PMTCT
  - Programmatic (Option B)
  - Non-adherence/loss to follow-up in Option B+

Stopping strategy to minimise risk of resistance:

AZT/3TC/EFV – NRTI tail for 2 weeks

TDF/3TC/EFV – No data to inform recommendation

Lamorde et al. AIDS 2014; 28
Post-partum/Breastfeeding

WHO and Uganda recommend exclusive breastfeeding for 6 months

Food habits & Culture

Food

Traditional medicine
Food drug interactions

- Culture of taking drugs with food
- Reality of lack of food
- Study design issues
  - Single dose versus steady state
  - Simulation of a missed meal (for drugs requiring food)

Lamorde et al. JAC 2015 (in press)
Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda

Mohammed Lamorde a,b,*, John R.S. Tabuti c, Celestino Obua d, Collins Kukunda-Byobona e, Hindam Lanyero d, Pauline Byakika-Kibwika a,b,f, Godfrey S. Bbosa d, Aloysius Lubega d, Jasper Ogwal-Okeng d, Mairin Ryan b, Paul J. Waako d, Concepta Merry a,b,f,g

103 plant species were reported by 25 traditional medicine practitioners
Treatments were oral decoctions containing several plants
1 in 5 traditional medicine practitioners treated children
Diseases

- Tuberculosis
- Malaria
- Neglected Tropical Disease
- Emerging Infectious Diseases
Tuberculosis

First-line ART
- Recommends efavirenz-based ART + rifampicin
- Avoid nevirapine + rifampicin

Second-line ART
- Consider rifabutin + PI-based ART
- Avoid rifampicin + PIs
First-line ART

- Recommends efavirenz-based ART + rifampicin
- Avoid nevirapine + rifampicin

CARINEMO RCT for TB/HIV Co-infection
Week 48 VL <50 copies/ml
- NVP (no-lead in) 60%
- EFV 68.4%

Bonnet et al. Lancet ID 2013

2013 CDC Guidelines: efavirenz is preferred but if nevirapine must be used, avoid lead-in dosing
**Tuberculosis**

**First-line ART**
- Recommends efavirenz-based ART + rifampicin
- Avoid nevirapine + rifampicin

**Second-line ART**
- Consider rifabutin + PI- ART

**Rifabutin 150 mg X 3 weekly or 150 mg daily?**

*Low rifabutin levels reported with 150 mg X 3 weekly*

Boulanger et al, CID, 2009; Ramachandran IJTLD, 2013

**CDC suggests 150 mg once daily**
## Malaria

<table>
<thead>
<tr>
<th>Co-administered drug</th>
<th>Effect on artemether-lumefantrine exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>artemether</td>
</tr>
<tr>
<td>rifampicin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>89% ↓</td>
</tr>
<tr>
<td>nevirapine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>72% ↓</td>
</tr>
<tr>
<td>efavirenz&lt;sup&gt;2&lt;/sup&gt;</td>
<td>77% ↓</td>
</tr>
<tr>
<td>LPV/r&lt;sup&gt;3&lt;/sup&gt;</td>
<td>43% ↓</td>
</tr>
</tbody>
</table>

Simulations suggest **artemether-lumefantrine** dose increases required<sup>4</sup>:
- **250% dose increase** with efavirenz
- **75% dose increase** with nevirapine

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<sup>1</sup>Lamorde et al AIDS 2013  
<sup>2</sup>Byakika-Kibwika et al JAC 2012  
<sup>3</sup>Byakika-Kibwika JAC 2012  
<sup>4</sup>Hoglund BJCP 2014

Interactions between ART and NTD drugs

Evidence for all recommendations: low quality or very low quality

Seden et al. AIDS 2013
Viral Hemorrhagic Fevers

2014 – 2015: Most severe Ebola Virus Disease outbreak in West Africa
- Paradigm shift from isolation to aggressive supportive treatment
- Not over: Male survivors can transmit up to 6 months after recovery.


EVD, Marburg, Congo-Crimea Hemorrhagic Fever have all occurred in Uganda
- Potential impact on HIV programming: HIV service delivery disruptions
- Emergency drugs versus ART

Medical countermeasures needed...

Other Diseases emerging e.g. Zika
Local capacity for Phase I/II drug development trials
Study participants

Investigators and study teams
Ceppie Merry
David Back
Elly Katabira
Harriet Mayanja-Kizza
Harriet Tikakabikoba
John Tabuti
Jonathan Mayito
Jonson Magoola
Jamila Nakku
Lillian Nabukeera
Mairin Ryan
Marta Boffito
Mohammed Lamorde
Moses Kamya
Nadine Pakker,
Niklas Lindegardh
Paul Waako
Pauline Byakika-Kibwika
Peter J de Vries
Richard Hoglund
Saye Khoo
Violet Okaba-Kayom
Joel Tarning

Collaborating Institutions
Haughton Institute; Dublin and Trinity College Dublin
University of Liverpool
Northwestern University, Chicago
University of Nebraska
Mahidol University Thailand
University of Amsterdam
University of Turin
University of Nijmegen

Capacity building
Infectious Diseases Network for Treatment and Research in Africa (INTERACT)

Funding
European and Developing Countries Clinical Trials Partnership
Health Research Board, Ireland
INTERACT
Janssen Pharmaceutica
Gilead Foundation
University of Liverpool
HIV Research Trust

Infectious Diseases Institute, Makerere University
College of Health Sciences
Alex Coutinho
Yuka Manabe
AIDS Treatment Information Centre
IDI Research Department and Clinic staff

MU-JHU Core Lab staff
Thank you