The Future of Antiretroviral Therapy in Africa: Perspectives from Uganda

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Discussion Outline

A. Characteristics of Current ART Responses in Africa
   I. Late Presentation and its Complications
   II. Experiences with ART Adherence

B. Earlier/Wider Access to ART- Implications
   I. ART Initiation at Higher CD4 counts
   II. ART Programmes for High Patient Loads

C. HIV as a Chronic Diseases in a RLS
   I. HIV, Aging and Non-Communicable Diseases
   II. Post-1\textsuperscript{st} Line ART (2\textsuperscript{nd} and 3\textsuperscript{rd} ART for Africa)

D. Summary
ART IN RLS Mostly Leads Improved Survival

World Bank Report 2008
Patients Starting ART at Higher CD4+ Cell Counts Overall, but Disparities Remain

- CD4+ cell count at start of ART (cells/mm³), 2009[1]

- In San Francisco study, overall trends of starting ART at higher CD4+ counts, but pts initiating ART at CD4+ counts > 350 cells/mm³ significantly more likely to be white, older, MSM, nonpoor, and diagnosed by private provider[2]

ART in RLS Associated with Higher Early Mortality

Figure 1

Incidence of deaths (95% Confidence Intervals) in the first 24 months of antiretroviral treatment

Figure 2

Cumulative probability of death during the first 2 years of antiretroviral treatment according to baseline CD4+ count

Castelnuovo B et al CID 2009; 49: 965-72

Log rank test p<0.001
The Evolution of KS lesion Post ART

Randomization 8 weeks 12 weeks
16 weeks 20 weeks 24 weeks
CLINICAL CONSEQUENCES OF IRIS-Resolution
Implications: The Immune Reconstitution Inflammatory Syndrome (IRIS)

- Inflammatory presentation within 12 weeks of ART initiation
- Driven by co-existing antigens (TB, Crypto)
- Associated with low CD4 count nadir
- Usually self-limiting
- In some instances life-threatening (CNS)
Immune Reconstitution Inflammatory Syndrome
Two Common Scenarios

• “Unmasking IRIS”
  – Occult, subclinical opportunistic infection
  – Unmasked by ART
  – Infectious pathogens present

• “Paradoxical IRIS”
  – Clinical recrudescence of a treated infection
  – Symptomatic relapse despite treatment success.
  – Antigen driven immune activation
  – Sterile cultures
ART Initiation Dilemma with Co-infections

Early ART Start

Delayed ART Start

PILL BURDEN
DRUG–DRUG INTERACTIONS
IRIS EVENTS

LOSS TO FOLLOW-UP
OI RISK
Implications: When to Start ART?

- TB Versus Crypto Story...
When to Start ART in TB – Building on previous studies

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<td>CD4 (IQR)</td>
<td>77 (36,145)</td>
<td>25 (11,56)</td>
<td>150 (77, 254)</td>
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\(^1\) Blanc, IAC, 2010 \(^2\) Abdool Karim, NEJM, 2010
Significant Reduction in Death/AIDS Among Those with TB and CD4 < 50 Cells/μL

ART Initiation within the first 2 weeks of Cryptococcal Meningitis is associated with Higher Mortality: A Multisite Randomized Trial

David R Boulware, David B Meya, Conrad Muzoora, Melissa A Rolfes, Kathy Huppler Hullsiek, Abdu Musubire, Kabanda Taseera, Henry W Nabeta, Charlotte Schutz, Darlisha Williams, Radha Rajasingham, Joshua Rhein, Melanie W Lo, Friedrich Thienemann, Andrew Kambugu, Yukari Manabe, Edward N. Janoff, Paul R Bohjanen, Graeme Meintjes, and the COAT Team

Cryptococcal Optimal ART Timing (COAT) Trial

Clinicaltrials.gov NCT01075152
Randomized Strategy Trial
Cryptococcal Optimal ART Timing (COAT) Trial

HIV-infected, ART-naive persons with Cryptococcal Meningitis
Study Entry at 7-11 days of anti-fungal therapy

Early ART Group
Start ART at <48 hours after study entry
n=250

Standard ART Group
Start ART at ≥4 weeks after study entry
n=250

Randomization Stratified by Site and by Altered Mental Status
Enrollment Criteria

Inclusion:
• HIV-infection
• ART naïve
• Age >14 years
• Cryptococcal meningitis by:
  – CSF culture
  – CSF cryptococcal antigen
• Receiving amphotericin-based therapy
• Informed consent

Exclusion:
• Prior cryptococcal meningitis
• Pregnancy or breastfeeding
• Cannot attend regular visits
• Chemotherapy
• Inability to take enteral meds
• Serious co-morbidities, co-infections, or laboratory values who should not receive ART immediately or have ART delayed
• Females must use >2 methods of contraception.
  (fluconazole is teratogenic in 1st Trimester)
Overall Survival

Cumulative Probability of Survival

- 1: Early ART
- 2: Deferred ART

Number at Risk:
1: 88 54 51 47 47 45 44
2: 89 71 65 60 60 58 57

P = 0.03

Months From Randomization

70% at 1 month
55% at 2 months
Prevention Strategies for Early Mortality/ IRIS

- Earlier ART Initiation

- Screening for common OIs in severely immuno-suppressed (CD 4<100 cells/ul)
  - TB
  - Cryptococcal disease

- Prophylaxis for common OIs in severely immuno-suppressed (CD 4<100 cells/ul)
  - TB
  - Cryptococcal disease

- Accelerated ART initiation for OIs
  - TB
  - Cryptococcal disease (COAT Trial Results CROI 2013)
The Retention Challenge

Retention & the Leaky PMTCT & Peds Cascade

Among infants testing HIV positive via EID, an estimated 38% will initiate treatment, and an estimated 28% will be retained and alive on treatment after 12 months.

Cascade based on Data from Lesotho, Malawi, South Africa, Uganda, Zambia, & Zimbabwe
Sources: Chatterjee et al, BMC Public Health 2011; 11:553;
Adherence Better than Expected!

• Many Africans may not have watches to enable them to adhere to medications as prescribed............but they have Radios!
Move to Earlier ART Initiation
The number of patients on treatment is expected to grow to 15.2M by 2016 in all low- and middle-income countries.

Historical and estimated scale-up in low & middle income countries

Source: CHAI ARV forecasting model; WHO Towards Universal Access Report for historical numbers; CHAI Market Sizing Analysis
Task-Shifting/Sharing
Effectiveness of Task Shifting/Sharing

Task shifting of antiretroviral treatment from doctors to primary-care nurses in S parallel, cluster-random

Lara Fairall, Max O Bachmann, Carl Lombard, Venessa Tir Christopher J Colvin, Simon Levin, Gill Fors, Ruth Corrick Ronald Chapman, Eric Bateman
Implications of Higher CD4 counts at ART initiation

• Lessons from:
  • HIV Serodiscordant Couples

• Option B+
Potential Strategies to Support Adherence

• Single pill per day / good toxicity profile regimen

• Future regimens: Depo preparations
The target product profile for optimal ARV candidates was defined at CADO in June 2010

**Tolerability**
- Low incidence of side effects and toxicities
- Relationship to adherence

**Resistance**
- High barrier to resistance
- Forgiveness
- Context of regimen

**Convenience**
- Once-daily dosing (or less)
- Low pill burden
- No cumbersome testing reqs, Other (no lead-in dosing)
- For regimen eval: same dosing schedule for all drugs

**Special Popns**
- Pregnant women
- HIV/TB co-infected patients
- Children
- Hepatitis B and C

**Cost**
- Cost w/o dose reduction
- Potential cost w/ dose reduction
- Impact of programmatic cost
The ARV pipeline for adults and children contains several important products at late stages of development.
GSK1265744 LAP Single Injection Provides Detectable Drug in Plasma for 48 Weeks

Mean Plasma GSK1265744 Concentration-Time Profiles following Single Dose LAP Injections in Healthy Subjects (Cohorts 1-7)

Spreen et al. 19th IAC Jul 2012. Abstract TUPE040
Patient-Led Efforts

• Self-Monitoring

• Adherence Support/Drug Pick-up Groups
Summary

• Initial ART roll-out in Africa characterized by late presentation and sub-optimal retention, but better than anticipated outcomes observed generally

• The expanded access effort presents challenges with high patients loads with HR and adherence concerns

• Opportunities driven by technology and sharing of the clinical burden by low cadre health care workers and patients will be critical
Acknowledgements

• IDI Research Cohort

• The IDI-UMN Collaboration

• The CADO Community