Patients with Advanced HIV Disease

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Disclosures

• No disclosures
Guidance Documents

• Consolidated guidelines on when to start ART-WHO 2016.
• Managing Advanced HIV Disease and Rapid Initiation of ART, July 2017.
• Differentiated Service Delivery for Adults at High Risk of HIV Disease Progression. A Call to Action. ICAP, 2017.
• ICAP Approach to Differentiated Care, 2017.
Outline-Advanced HIV Disease

- Background/Rationale
- Patients with Advanced HIV Disease
- Major causes of Mortality and Morbidity
- Management of Patients with Advanced HIV Disease
- Treatment of Co-Morbid conditions
- Antiretroviral therapy
- The How of care of Patients with Advanced HIV Disease
- Conclusions
Background/Rationale

- The scale up of ART is one of the world’s greatest public health success stories
- PLH on ART in 2003-400,000; by 2017 the number went up to 22.9 million
- Number of deaths averted by ART scale up-7.8 million
- HIV infection has dropped by 35% since 2000 through prevention and treatment services

Challenges in HIV/AIDS Service Delivery

• Changing guidelines
• Ambitious global targets
• Rapid expansion of people eligible for ART
• To meet 90-90-90 targets the number will need to be doubled by 2020
• Global funding has plateaued
• Overcrowded health facilities
• Sub-optimal retention rates
Differentiated Service Delivery (DSD)

- DSD is a patient-centred model of care that aims to enhance quality, efficiency and patient satisfaction while maintaining the principles of the public health approach.

- Examples include:
  - Fast-track appointments
  - Multi-month ART prescribing
  - Decreased visit frequency
  - Community based-ART groups
  - Etc.

Duncombe C. Trop Med Int Health 2015; El-Sadr. AIDS 2016
Advanced HIV Disease-Definition

- WHO (2016 Consolidated ARV Guidelines)
  - Adults & adolescents & Children above 5 years
    - CD4 count <200 cells/mm$^3$ or WHO stage 3 or 4 event
  - All HIV infected children below 5 years

ICAP overview of Patient classification
For Differentiated Care. (ICAP Approach to Differentiated Care 2017)

Table 1: Defining High-Risk Patients

<table>
<thead>
<tr>
<th>New to ART / Advanced Disease</th>
<th>On ART for &gt; 1 year / Unstable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly initiating ART or on ART for &lt;1 year and CD4 &lt;200/mm³ and/or WHO stage III/IV</td>
<td>On ART for &gt;1 year and any of the following: Not virally suppressed*</td>
</tr>
<tr>
<td>CD4 &lt;200/mm³ and/or WHO stage III/IV</td>
<td>CD4 &lt;200/mm³</td>
</tr>
<tr>
<td>Adverse drug reaction requiring ongoing monitoring</td>
<td>Active opportunistic infection, including TB</td>
</tr>
<tr>
<td>Subsistence use</td>
<td>Non-adherent with ART**</td>
</tr>
<tr>
<td>Comorbid condition(s) requiring frequent follow up</td>
<td></td>
</tr>
</tbody>
</table>

*Not virally suppressed = most recent VL >1,000 and/or no VL in the past 6 months
**Non-adherent = 2+ missed doses a month for patients on once-daily regimens, 4+ missed doses a month for patients on twice-daily regimens; and/or misses drug pickups
Advanced HIV Disease

• High risk of mortality and morbidity
  • Worse with CD4 <50 cell/mm³
• Less robust CD4 recovery on initiating ART
• High risk of OIs
### 1 Year Mortality

50 published cohort studies by region

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mortality proportion, median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-saharan Africa (n=35)</td>
<td>17% (11-24%)</td>
</tr>
<tr>
<td>Asia (n=5; China, Cambodia, Thailand)</td>
<td>11% (10-13%)</td>
</tr>
<tr>
<td>Americas (n=2; Haiti, Peru)</td>
<td>7% (1%-20%)</td>
</tr>
<tr>
<td>Multiregional (n=5; Asia including India, Africa, South America, Caribbean)</td>
<td>8% (6-10%)</td>
</tr>
</tbody>
</table>

Gupta et al PLOS One 2011
Mortality by baseline CD4 cell count
(ART-LINC and ART-CC)

Sub-Saharan Africa

Europe & North America

Cumulative mortality (%)

Months after starting ART

< 25 cells/µL
25-49 cells/µL
50-99 cells/µL
100-199 cells/µL
≥ 200 cells/µL
Causes of early mortality after initiating ART

• Tuberculosis
  • Main cause of mortality among patients initiating ART
• Bacterial sepsis
  • Septicaemia, pneumonia, GI infection, CNS infection, other
• Cryptococcal meningitis
  • Cryptocococaemia leads to meningitis
  • Less common in children < 5 years
• Pneumocystis jirovecii pneumonia
• Malnutrition
• Wasting syndrome

Causes of early mortality after initiating ART

• Other
  • Toxoplasmosis
  • Cytomegalovirus infection
  • Histoplasmosis
  • Talaromycosis (penicilliosis)
  • Kaposi’s sarcoma
  • Gastrointestinal infections
  • Renal failure

Le T. CID 2011; Hu Y. Myopathologia 2013
Management of Advanced HIV Disease

- Identification of Advanced HIV Disease
- Screening for major diseases causing morbidity and mortality
- Prophylaxis and pre-emptive therapy
- Antiretroviral therapy initiation
Package of Care-Advanced Disease

• Achieving immune system recovery with ART is the primary way to reduce morbidity and mortality in HIV disease
• Prompt initiation of OI prophylaxis
• Screening and treatment of co-morbidities
• Swift initiation of ART (if no Crypto)
• Follow-up & monitoring
  – Adherence
  – Adverse drug reactions
  – IRIS
Table 1  Components of the package of care for people with advanced HIV disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LF-LAM for TB diagnosis among people with symptoms and signs of TB</td>
<td>≤100 cells/mm³ Or at any CD4 count if seriously ill</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Sputum microscopy</td>
<td>≥200 cells/mm³</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 1 Components of the package of care for people with advanced HIV disease

<table>
<thead>
<tr>
<th>Prophylaxis and pre-emptive treatment</th>
<th>CD4 cell count</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole prophylaxis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≤350 cells/mm&lt;sup&gt;3&lt;/sup&gt; or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes For criteria, see Annex 1</td>
</tr>
<tr>
<td>TB preventive treatment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluconazole pre-emptive therapy for cryptococcal antigen-positive people without evidence of meningitis</td>
<td>&lt;100 cells/mm&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Not applicable (screening not advised)</td>
</tr>
</tbody>
</table>
**Table 1** Components of the package of care for people with advanced HIV disease

<table>
<thead>
<tr>
<th>Intervention</th>
<th>CD4 cell count</th>
<th>Adults</th>
<th>Adolescents</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid ART initiation (as recommended in Chapter 3)</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)</td>
<td>Any</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible</td>
<td>&lt;200 cells/mm³</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Antiretroviral therapy initiation

• ART Treat All
• Need to start early
• Rapid initiation of ART
  • Issues of patient readiness-psychological and logistical
  • Screening for OIs
  • Need to start ART early
• Rapid ART initiation
  • Within 1 week of HIV diagnosis or eligibility determination
  • Same-day start of ART
• Who will provide ART-NIMART
• Adherence/adherence support
• Loss to follow-up
REALITY Trial

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

- Two other factorial randomisations investigated
  - 12 weeks adjunctive raltegravir (FRAB0102LB)
  - 12 weeks supplementary food

- Primary endpoint: 24-week mortality

Hakim J. NEJM 2017
## Baseline characteristics (N=1805)

*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/mm³)</td>
<td>38 (16-64)</td>
<td>36 (16-60)</td>
</tr>
<tr>
<td>0-24 cells/mm³</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>&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>
Results: All-cause mortality

- Mortality at 24 weeks: 8.9% enhanced Px vs 12.2% standard Px
  \[
  \begin{align*}
  \text{w24: } & HR=0.73 \\
  & (95\% \text{ CI } 0.54-0.97) \\
  & p=0.03
  \end{align*}
  \]
  \[
  \begin{align*}
  \text{w48: } & HR=0.75 \\
  & (95\% \text{ CI } 0.58-0.98) \\
  & p=0.04
  \end{align*}
  \]

- 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)

3.3 lives saved for every 100 treated
NNT=30
• No evidence of difference in VL suppression (GEE p=0.75)

• No evidence of difference in CD4 reconstitution (GEE p=0.55)
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%
      (25% 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-qualification in progress)
  
  - 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 “How” of care for patients with Advanced HIV Disease

• How should these packages of care be delivered?
• In an ICAP review key challenges and barriers were identified for high risk patients
<table>
<thead>
<tr>
<th>Challenge</th>
<th>Illustrative Barriers/Challenges</th>
</tr>
</thead>
</table>
| Identification of high-risk patients | Delayed ART eligibility assessment  
               Delayed identification of failing regimens  
               Delayed linkage from testing to treatment |
| ART initiation and management | Delayed switch to 2nd/3rd line regimens  
               Lack of standard operating protocols (SOPs) for high risk patients |
| Prevention and management of acute co-morbid condition(s) | Insufficient or absent OI screening/prophylaxis  
               Weak linkages for up-referral to more specialized site/providers  
               Discontinuity between inpatient, outpatient, and community-based services  
               Siloed HIV and NCD services |
| Management of chronic co-morbid condition(s) | Lack of strong home care systems  
               Need for specialized adherence support |
Innovations of DSD services for high risk patients

• Severely immunosuppressed package of care (SIPCO)-Kenya
• Advanced, Late and Unstable patients (ALUP)-Malawi
  • Also delivers the REALITY package
• Models in the SEARCH study in Uganda
Conclusions

• Patients with advanced HIV disease
• Package of care should be implemented
• Early identification
• Screening for common causes of morbidity and mortality
• Pre-emptive treatment and specific treatment for opportunistic conditions
• Rapid ART initiation
• Several research gaps exist both in the “what” and “how” to manage these patients
Thank you