Lessons Learned from Implementation of Cryptococcal Meningitis (CM) Care Package among People with Advanced HIV Disease (AHD) in Delhi, India

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Background
Introduction: Advanced HIV Disease (AHD)

Definition of AHD

- People living with HIV (PLHIV) aged >5 years with:
  - CD4 cell count <200 cells/mm³ or
  - WHO Clinical Stage 3/4
- CLHIV aged <5 years not on ART for up to a year & not clinically stable

Causes for 50% higher Mortality Rate

- Suboptimal OI Management: High turnaround time (TAT) of diagnosis; costly treatment
- Delay Initiation: Late registration and treatment centre, delayed ART initiation
- Poor Adherence: Lesser adherence to treatment leading to higher susceptibility

Progress of AHD Care in India

AHD Cascade for New Initiations

Guidance on AHD Management

- Zero AIDS-related deaths by 2030 (mandate to reduce mortality)
- Incorporation of AHD care packages in National AIDS Control Program’s (NACP’s) 2021 National Treatment Guidelines

Components of AHD Care Package

- Rapid management of Opportunistic Infections (OIs), such as Tuberculosis (TB) and Cryptococcal Meningitis (CM)
- CPT initiation, enhanced adherence counselling etc.

Recommend AHD packages are yet to be adopted at treatment centres due to lack of commodities and scaled implementation

Objective: Implementation of CM-AHD Care in Delhi

Following guidelines release on AHD management, Maulana Azad Medical College (Delhi, India) spearheaded implementation of the CM care package to facilitate on-ground availability of differentiated care for PLHIV with AHD

Objectives of Implementation

- **Initiate phased Implementation** of recently released NACO guidelines on AHD management, build capacity and sensitize facilities towards AHD and CM care
- **Rapidly identify and treat CM in AHD patients** to improve their health outcomes and decrease mortality in service of the “Zero new infections, Zero AIDS related deaths” goal
- **Document experiences & learnings** from implementation to create operational SOPs for roll-out in other ARTCs, and then across country

Details of Implementation

- **Implementing Site**: Loy Nayak Hospital ART Centre, under guidance from HIV CoE Maulana Azad Medical College (MAMC), Delhi (India)
- **Time period**: September 2022 – Ongoing
- **Target Population**: PLHIV presenting with AHD (i.e. CD4 cell count <200 cells/mm³ or WHO Clinical Stage 3/4)
Methodology: Cascade of Care and Interventions

In 2022, Cryptococcal Antigen Lateral Flow Assay (CrAg LFA) screening and CM care was implemented for PLHIV with AHD at Maulana Azad Medical College (Delhi, India) as recommended by NACP guidelines.

Cascade of Care and Interventions

- Adults with AHD identified basis CD4 tests and WHO Staging
  - PLHIV with CD4 cell count <200 cells/mm³ reflexively screened via Plasma CrAg LFA during CD4 testing
  - PLHIV with WHO clinical stage 3/4 screened via Serum CrAg LFA at the ART centre

- PLHIV found positive linked to confirmatory testing via cerebrospinal fluid (CSF) CrAg LFA
  - PLHIV found symptomatic / CSF CrAg positive given CM treatment
  - PLHIV found asymptomatic / CSF negative PLHIV given pre-emptive treatment

Capacity Building Measures

- Strategized operational protocols
- Trained healthcare workers
- Developed data and reporting tools
- Documented and monitored prevalence, uptake, challenges etc.

1 The implementation was undertaken via a donation of rapid CrAg LFA kits and optimal antifungal treatment commodities (Liposomal Amphotericin B (LAmB), Flucytosine, and Fluconazole) with support from Unitaid’s AHD initiative, Clinton Health Access Initiatives (CHAI) and the William J. Clinton Foundation (WJCF)
Results: Cohort Characteristics
Overview of Implementation Coverage

**Cascade of Coverage and Care**

- **91.4% screening coverage (57 re-screening tests conducted)**
- **0.7% positivity for cryptococcal infection**
- **6% based on WHO clinical staging / discretion**
- **94% based on CD4 cell count <200 cells/mm³**
- **0% positivity for meningeal infection**

*3 PLHIV screening positive were linked to CSF CrAg testing for confirmation and CM treatment / prophylaxis as per their results and symptoms*
AHD: Distribution by CD4 Cell Count

**Routes of AHD Occurrence**

**Immunological**

- 4,226 CD4 tests conducted (baseline and monitoring*)
- 7.5% results with CD4 cell count <200 cells/mm³

**Clinical**

- WHO clinical stage assessment during visit
- 29 instances of WHO clinical stage 3/4 or symptoms

**AHD Occurrence based on ART initiation**

- CD4<100 cells/mm³: 14%
- CD4 100-200 cells/mm³: 13%
- CD4>200 cells/mm³: 73%

- PLHIV newly initiating on ART
  - 1% CD4<100 cells/mm³
  - 5% CD4 100-200 cells/mm³
  - 94% CD4>200 cells/mm³

- In-care PLHIV already on ART
  - 94% CD4<100 cells/mm³
  - 5% CD4 100-200 cells/mm³
  - 1% CD4>200 cells/mm³

**AHD Occurrence based on CD4 Cell Count**

- 92% PLHIV with CD4>200 cells/mm³
- 5% PLHIV with CD4 100-200 cells/mm³
- 2% PLHIV with CD4≤100 cells/mm³

**Non-AHD PLHIV that received a CD4 test**

- 21% higher proportion of PLHIV newly initiating on ART presented with CD4<200 cells/mm³ (27%) than in-care PLHIV already on ART (6%)

* CD4 testing recommended for all newly registering PLHIV and then every 6 months. It can be discontinued in PLHIV with CD4 count >350 cells/mm³ and viral load <1000 copies/ml (at the same time)
Characteristics of PLHIV with AHD

Demographic Characteristics

- 82% adults aged 20-49 years, 13% adults aged >50 year, 4% others
- 79% Males, 20% Females, 1% Transgenders
- 51% heterosexuals, 31% of unknown typology, 12% unsafe injection practices

Clinical Characteristics

- 41% of PLHIV with AHD screening positive for 4-symptom screening, of which 35% had a confirmed diagnosis of tuberculosis
- 34% of PLHIV’s HIV viral load was “Not Detected”

Current Status in Care

- 87% Alive on ART
- 4% Died
- 5% Loss to Follow-up
- 4% Transferred / Opted Out

Time Since ART Initiation

<table>
<thead>
<tr>
<th>Time Period</th>
<th>#PLHIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 4 weeks</td>
<td>13</td>
</tr>
<tr>
<td>1-3 months</td>
<td>38</td>
</tr>
<tr>
<td>3-6 months</td>
<td>55</td>
</tr>
<tr>
<td>6-12 months</td>
<td>71</td>
</tr>
<tr>
<td>1-2 years</td>
<td>65</td>
</tr>
<tr>
<td>2-5 years</td>
<td>101</td>
</tr>
<tr>
<td>5-10 years</td>
<td>62</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td></td>
</tr>
</tbody>
</table>

Note: This data is representative of 409 identified as presenting with AHD, of which 390 were screened via CrAg LFA
**CrAg Screening Coverage**

### CrAg Screening Coverage within AHD Care

- **Instances of AHD:** 489
- **CrAg screening tests conducted:** 447
- **CrAg tests conducted within a month:** 342

- **Coverage:**
  - 91%
  - 70%

### CrAg Screening Coverage based on ART initiation

- **PLHIV newly initiating on ART:** 28%
- **PLHIV already on ART:** 72%
- **PlHP identified for screening basis CD4:** 76%
- **In-care PLHIV already on ART:** 56%

- **Time period:** September 2022 – August 2023
Status of PLHIV Screened Positive

CrAg Positivity among PLHIV with AHD

- PLHIV screened Negative for Serum / Plasma CrAg
- PLHIV Positive for CSF CrAg
- PLHIV Negative for CSF CrAg
- PLHIV not tested with CSF CrAg

Health Outcomes of PLHIV Screening Positive for CrAg

<table>
<thead>
<tr>
<th>Category</th>
<th>PLHIV 1</th>
<th>PLHIV 2</th>
<th>PLHIV 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Prophylactic Phase</td>
<td>Maintenance</td>
<td>Maintenance</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Latest CD4 Count</td>
<td>348</td>
<td>373</td>
<td>229</td>
</tr>
<tr>
<td>Latest Viral Load</td>
<td>Not detected</td>
<td>Not detected</td>
<td>Viral load due (2 visit missed)</td>
</tr>
<tr>
<td>Adherence to Fluconazole</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
<td>Pills not brought during latest visit (previously &gt;95%)</td>
</tr>
</tbody>
</table>
Results: Implementational Learnings
**What Went Well: Ownership and Coordination**

- **Assigned staff roles** for patient-tracking (counsellor, data manager, care coordinator, pharmacist etc.)
- **Demarcated AHD records** via stickers that highlight their status, positivity and need for follow-up
- **Counselling effectively** (medical officer, counsellor, and care coordinator); only 2 PLHIV required counselling by all three healthcare workers
- **Consolidated record-keeping and coordination** of testing details (CrAg screening register, updates / pictures on WhatsApp etc.)
- **Rapid linkage to care** for PLHIV screening positive for CrAg LFA and comprehensive monitoring of health outcomes

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**Use of Stickers for Demarcation of AHD Records**

- All 3 PLHIV currently on maintenance phase
- Fluconazole prophylactic treatment – 2 with suppressed viral load and >95% adherence to Fluconazole
The Challenge: Linkage Loss from Identification to Rapid CrAg Screening

**Delay in AHD Diagnosis**
- One-day turnaround time (TAT) of CD4 results due to batching of samples, departmental approvals and high-load of samples

**Reluctance to Revisit**
- PLHIV unwilling to revisit for sample collection due to cost, time and inconvenience of travel
- ART drugs collected by care-givers instead of PLHIV (~5-10 cases/day)
- Inability of staff to contact for counselling due to incorrect or out of order phone numbers

**Low Visibility of PLHIV with AHD**
- Difficulty in demarcating PLHIV with a pending CrAg test at the centre due to high traffic
- Limited visibility of staff into all pending tests and need for targeted tracking and follow-up

**Challenges in Monitoring**
- Lack of AHD/CM indicators in current data systems
- Manual consolidation of multiple data sources for progress reports
- Re-screening over time not tracked (likely every 6 months)
### The Solutions: Reflex Testing, Strengthened Tracking and Data Monitoring (1/2)

#### Key Interventions

**Reflex Testing**
- Separated whole blood samples of results with CD4 cell count <200 cells/mm³, extract plasma and immediately screen via CrAg LFA (collaboration with microbiology department needed)

#### Impact

- **100% same-day CrAg coverage** for PLHIV with CD4 cell count <200 cells/mm³
- Median TAT reduced between CrAg and CD4 testing reduced from **26 days to 1 day**
- **Reduction in time and efforts** required by healthcare workers (monitor screening gap, call those with a pending test to revisit, physically track files etc.)

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#### Same-month CrAg LFA Screening Coverage

<table>
<thead>
<tr>
<th>Month</th>
<th>CrAg Screening Tests Conducted</th>
<th>Instances of AHD Recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep-22</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Oct-22</td>
<td>56%</td>
<td>0%</td>
</tr>
<tr>
<td>Nov-22</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Dec-22</td>
<td>35%</td>
<td>0%</td>
</tr>
<tr>
<td>Jan-23</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Feb-23</td>
<td>63%</td>
<td>92%</td>
</tr>
<tr>
<td>Mar-23</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Apr-23</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>May-23</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Jun-23</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Jul-23</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Aug-23</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Introduction of Reflex Testing**

**Introduction of AHD file stacking**
The Solutions: Reflex Testing, Strengthened Tracking and Data Monitoring (2/2)

Key Interventions

Targeted Tracking and Follow-up Operations
- Created a separate and visible stack for AHD records with a pending CrAg test to highlight arrival
- Guided staff to close screening gap among PLHIV with a pending test under effective leadership

Improvements in Monitoring Tools and Processes
- Capacitated data manager via on-the-job support
- Introduced AHD and targeted tracking line lists
- Develop an excel-based dashboard for program guidance and assessment of AHD characteristics

Impact

- ~95% backlog clearance of PLHIV with a pending CrAg test within a short period (2 months)
- Ease of healthcare workers in identifying PLHIV presenting with AHD during their ART visits

- Systemized follow-up via tracking lists for calls to PLHIV and record identification
- Ability to track repeat tests via cohort-tracking
- Ease of data manager in generating accurate reports

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**CrAg Screening Positivity**
- 99% Positive
- 1% Negative

**CM Positivity**
- 381 Total tests conducted
- 13
- PLHIV without AHD screened via CrAg LFA
  - 3
- PLHIV found positive via CrAg Screening
  - 0
- PLHIV initiated on CM Treatment
  - 346
- PLHIV screened via CrAg LFA
  - 0
- PLHIV found symptomatic for Cryptococcal Infection
  - 2
- PLHIV tested via CSF CrAg LFA
  - 3
- PLHIV initiated on CM Prophylaxis
  - 0

**Turnaround Time for CrAg Screening**
- Median Turnaround Time (TAT) of CrAg Screening:
  - 24.53%
  - 1.13%
  - 14.34%
  - 5.66%
  - 13.58%
  - 10.57%
  - 2.26%
  - 11.70%
  - 16.23%

**CD4 to CrAg Test TAT Ranges**
- 2-7 Days
- 1-2 Weeks
- 2-4 Weeks
- 1-2 Months
- 3-6 Months
- 6-12 Months
- #PLHIV Tested
  - 40
  - 38
  - 15
  - 31
Way Forward
Scope for Improvement and Way Forward

**Scope for Improvements**

**Feasibility of Reflex Testing**
- Requirement of a centrifuge machine to extract plasma for reflex testing (limited availability)

**Re-screening of the Cohort**
- ~57 PLHIV re-screened after 6 months
- Limited guidance on re-screening of PLHIV with more than two negative CrAg LFA results

**Improvements in Reporting Format**
- Overwriting of data after re-screening via 2 tests
- Manual data extraction from current data system

**Way Forward**

**Wider Implementation of AHD Care Package**
- Scale-up across treatment centres
- Defined modus operandi
- Evaluation of expansion of AHD care to further OIs / co-morbidities

**Further System Strengthening**
- TAT reduction of CD4 tests
- Incorporation and integration of AHD-related metrics in current reporting systems
- Capacity building and sensitization of healthcare workers
Thank you!