Insights and Lessons Learned on Retention, Adherence, and Achieving and Maintaining Viral Suppression: The Third 90

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INTEREST WORKSHOP
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Disclosures:

- No disclosures to declare
Outline:

The Overview

The Context

Adherence to treatment

Retention

The Third 90

Conclusion
Overview

- HIV remains a major public health problem with Sub-Saharan Africa bearing the greatest burden.
- Remarkable progress has been made in reaching the **15 million target** of PLHIV on treatment.
- Recent scientific advances have proven that starting ART early has better clinical outcomes for PLHIV.
- Unfortunately, loss to follow up along all stages of the HIV cascade remains a key challenge for HIV programmes particularly in Sub-Saharan Africa.
The Context:

- Many countries particularly, in Resource-Limited Settings (RLS) are experiencing many constraints within their health systems:
  - have the least number of skilled health workforce to provide HIV services amidst having the highest disease burden
  - inadequate and under-maintained public health infrastructure (Bekker L., 2014)
  - long waiting times for patients (Govindasamy D, 2012)
- Urgent adaptations to existing service delivery models are therefore needed for effective delivery of programmes
Global Estimates (2014-15) vs the Gap to reach 90-90-90 Targets

HIV Positive People | Diagnosed | On ART | Viral Suppression
36.9 million | 19.8 million | 15.0 million | 15.3 million
13.4 million Undiagnosed | 53% | 41% | 32%*
14.9 million not treated

Adherence to life-long Therapy:
Barriers and Strategies
Adherence:

ART regimens require 70-90% adherence to be effective (Nachega JB., 2010)

Adherence to life-long treatment is an important factor for successful treatment response as it

• improves the patient’s own prognosis
• minimizes drug resistance and
• reduces the risk of HIV transmission to HIV-negative sexual partners (Cohen MS, 2011)

Previous studies reported adequate adherence by sub-Saharan African patients of 77% (95% CI, 68-85%, compared to 55% (95% CI 49-62%) in North America (Mills EJ., et al, 2006)
Adherence to ART

Near perfect adherence rates (>95%) are required to prevent:

- Treatment failure
- Higher mortality rates
- Lower rate of increasing CD4 cell count
- Disease progression
- Emergence of drug resistance
- Increase in hospital stays

Measuring adherence:

- **Direct** methods using biological markers
- **Indirect** methods
  - Self-report
  - Interview
  - Pill count
  - Pharmacy records
  - Computerized medication caps
  - Viral load monitoring

ART has changed AIDS from a life threatening disease to a chronic illness with proper use and adherence levels.
Identified Factors for the Challenges to ART Adherence

Treatment related adverse events contribute to poor adherence & treatment outcomes

- One-daily tablet FDC shown to support adherence (Ramjan R, et al. 2014)
- Need for simple, safe and well tolerated ARV regimens
- Need for innovation towards optimizing doses & use of medicines with better safety profiles

<table>
<thead>
<tr>
<th>ART Optimization Strategy</th>
<th>Tolerability</th>
<th>Resistance</th>
<th>Convenience</th>
<th>PW, TB, children</th>
<th>Cost Reduction</th>
<th>What actions are needed?</th>
<th>Considered for 2015 WHO guidelines review?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose EFV</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>• pK studies (PW &amp; TB)</td>
<td>✓</td>
</tr>
<tr>
<td>Low dose DRV/r (as FDC)</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>• pK studies (titration of best DRV:RTV ratio)</td>
<td>✓</td>
</tr>
<tr>
<td>DTG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>• Studies in PW, TB &amp; children</td>
<td>✓</td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<td>• Comparative trials (TDF /TAF in 1st line)</td>
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<td></td>
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<td></td>
<td></td>
<td>• RCT (DRV/r + DTG in 2nd line)</td>
<td></td>
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<tr>
<td>TAF</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>• Comparative trials using DTG</td>
<td>❌</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>• Studies in PW, TB &amp; children</td>
<td></td>
</tr>
<tr>
<td>Long-acting formulations</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>• Phase II/III studies (treatment &amp; preventive trials)</td>
<td>❌</td>
</tr>
</tbody>
</table>
Depression and ART adherence

- **Meta-analyses:**
  - 1 review of 95 independent studies from high income countries:
    - Association between depression and ART non-adherence (p=0.0001; 95% CI: 0.14–0.25)
  - 2 systematic reviews from low and middle income countries:
    - aOR= 1.13–3.13 and aOR = 1.75–3.36 for association of depression & non-adherence to ART
- **Poor ART adherence may partly explain the association between depression and increased risk of HIV disease progression.**
- Corollary effects of suicidal ideation, negative thinking, forgetfulness, poor concentration, or deficits in problem solving associated with depressed mood can lead to poor adherence.

Comparison of six adherence methodologies in an ART-naïve cohort - which best predicts virological and resistance outcome?

**Methods:**
- Collected multiple adherence measures in a prospective ART-naïve cohort over 48 weeks.
- Electronic adherence monitoring device (Wisepill)
- Clinic-based pill counts (60 day),
- Self-recall (3-day),
- Pharmacy refill (cumulative or gaps),
- Mid-dose EFV level.

**Viral load at week 48:** >40 copies/ml = failure.

**Logistic regression model for prediction; generated area under receiver operator characteristic curve (AUC ROC) for each measure.**

(Catherine Orrell CROI, Feb. 2016)
Adherence measures vs virological failure (>40 c/ml) or resistance: week 48

**Results:** Adherence data from Electronic adherence monitoring device and pharmacy refill measures predicted resistance and virological failure similarly. Pharmacy refill data is a reasonable option for monitoring adherence in resource-limited settings where electronic monitoring is unavailable.

(Catherine Orrell CROI, Feb. 2016)
Service delivery interventions to improve adolescents’ linkage, retention and adherence to ART and HIV Care (MacPherson P., et al, 2015)

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>INTERVENTIONS</th>
<th>STUDIES IN THIS REVIEW INFORMING RECOMMENDATION</th>
<th>ADOLESCENT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLICY/HEALTH SYSTEM-LEVEL</td>
<td>Decentralisation</td>
<td>Davila&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Pre-ART clinic attenders ART clinic attenders ART failure/poor adherence</td>
</tr>
<tr>
<td>PROVIDER/HEALTH FACILITY-LEVEL</td>
<td>Adolescent/youth-friendly opening hours</td>
<td>Lamb&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Pre-ART clinic attenders ART clinic attenders</td>
</tr>
<tr>
<td></td>
<td>Adolescent-specific services</td>
<td>Davila&lt;sup&gt;16&lt;/sup&gt;, Lamb&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Pre-ART clinic attenders ART clinic attenders</td>
</tr>
<tr>
<td>COMMUNITY-LEVEL</td>
<td>Peer-support</td>
<td>Funck-Brentano&lt;sup&gt;20&lt;/sup&gt;</td>
<td>ART clinic attenders ART failure/poor adherence</td>
</tr>
<tr>
<td>INDIVIDUAL-LEVEL</td>
<td>Education and counselling (Including education sessions, individual and group counselling, motivational interviewing and case management)</td>
<td>Lyon&lt;sup&gt;25&lt;/sup&gt;, Berrian&lt;sup&gt;16&lt;/sup&gt;, Letourneau&lt;sup&gt;24&lt;/sup&gt;, Kaihin&lt;sup&gt;22&lt;/sup&gt;, Bhana&lt;sup&gt;17&lt;/sup&gt;, Lamb&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Pre-ART clinic attenders ART clinic attenders ART failure/poor adherence</td>
</tr>
<tr>
<td></td>
<td>Directly observed therapy</td>
<td>Glickman&lt;sup&gt;31&lt;/sup&gt;, Parsons&lt;sup&gt;26&lt;/sup&gt;</td>
<td>ART failure/poor adherence</td>
</tr>
<tr>
<td></td>
<td>Adherence support devices</td>
<td>Berrian&lt;sup&gt;16&lt;/sup&gt;, Foster&lt;sup&gt;19&lt;/sup&gt;</td>
<td>ART clinic attenders ART failure/poor adherence</td>
</tr>
<tr>
<td></td>
<td>Financial incentives</td>
<td>Foster&lt;sup&gt;19&lt;/sup&gt;</td>
<td>ART failure/poor adherence</td>
</tr>
</tbody>
</table>
Interventions to Support Treatment adherence

Adherence support interventions should be provided to all people on ART *(strong, moderate)*

Interventions that demonstrated effectiveness:

- Peer counsellors
- Mobile phone text messages
- Reminder devices
- Cognitive behavioural therapy
- Behavioural skills training /medication adherence training
- Fixed dose combinations and once daily regimens

WHO, 2015 ARV Guidelines Dissemination Meeting, Johannesburg, 25-29\textsuperscript{th} April, 2016
Retention on ART: Barriers and Strategies
Poor retention before and after ART initiation is one of the important factors in determining the overall impact of treatment.

Source: IeDEA-WHO 2015

Data from 6 regions; 41 countries and 304,000 patients

Retention worse for Men, Children & adolescents
Rates of ART Retention in Zimbabwe, 2013-2015

Source: Zimbabwe MOHCC, 2016
Gender-related differences in outcomes and attrition on antiretroviral treatment among an HIV-infected patient cohort in Zimbabwe: 2007-2010

<table>
<thead>
<tr>
<th>Comparison of clinical and immunological ART outcomes by gender¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Original</strong> Frequency (N=3,919)</td>
</tr>
<tr>
<td><strong>All patients</strong> Rate/100 PY</td>
</tr>
<tr>
<td><strong>ART outcomes</strong></td>
</tr>
<tr>
<td><strong>Attrition</strong></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
</tr>
<tr>
<td><strong>Loss to follow-up</strong></td>
</tr>
<tr>
<td><strong>Stopped ART</strong></td>
</tr>
<tr>
<td><strong>Immunological failure by different definitions</strong></td>
</tr>
<tr>
<td>CD4 count &lt; 100 cells/ml after at least 6 months of initiating therapy</td>
</tr>
<tr>
<td>CD4 count less than pre-therapy CD4 count at baseline after at least 6 months of initiating therapy</td>
</tr>
<tr>
<td>50% drop from peak CD4 count value</td>
</tr>
<tr>
<td>Immunological failure (any definition)</td>
</tr>
</tbody>
</table>

ART = antiretroviral therapy; PY = person years; HR = hazard ratio; AHR = adjusted hazard ratio; CI = confidence interval; TB = tuberculosis.

N= total number of patients with recorded data for each variable.

The bold font was meant to highlight all analysis which had significant p-values (i.e., p < 0.05).

¹ Females are the reference category when interpreting both the univariate and multivariate-adjusted hazard ratios.

² Take note that sex was missing for 12 patients.

³ Hazard ratios have been adjusted for potential confounding effect of age, baseline weight, baseline WHO clinical stage, prior/current TB, anemia, patient residence and size of OI/ART clinic.

⁴ Rate/100PY is defined as the number of new cases attaining each outcome in the patient population per 100 person-years at risk.

⁵ Attrition refers to patients who were documented as having died, stopped ART or were lost to follow-up (a patient absent from a healthcare facility for more than 90 days after his/her last scheduled appointment with the healthcare provider or pharmacy).

⁶ Immunologic failure is defined as either CD4 <100cells/ml 6 months after initiating therapy; CD4 count less than pre-therapy CD4 count, at least 6 months after initiating ART; a 50% drop from the peak CD4 cell count value; or any other definition of immunologic failure.
Some of the reasons cited for failure to retain in care include:

- feeling well and not needing ART (Krebs DW, 2008)
- use of alternative (traditional) medicines in rural Mozambique (Groh K., 2011)
- discordance in Ethiopia (Deribe K, 2008)
- financial challenges for transport to the clinic and fee for service (Maskew M, 2007)
- work/child care responsibilities (Geng E., 2010)
Results: 34,277 adults on ART were followed in East Africa. 5,780 patients (17%) were lost to follow-up, 991 (17%) were selected for tracing between June 10, 2011, and Aug 27, 2012, and vital status was ascertained for 860 (87%). With incorporation of outcomes from the patients lost to follow-up, estimated 3 year mortality increased from 3·9% to 12·5%.
TB the leading cause of in-hospital mortality worldwide in ART era.

### Causes of mortality in HIV-positive adults and children admitted to hospital worldwide

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>AIDS related</td>
<td>57% (46–69)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>27% (20–34)</td>
</tr>
<tr>
<td>Toxoplasmosic encephalitis</td>
<td>15% (10–20)</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>13% (9–16)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>13% (7–19)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>6% (4–7)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>23% (17–30)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>19% (12–25)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>17% (8–26)</td>
</tr>
<tr>
<td>Neurological</td>
<td>8% (5–12)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9% (2–16)</td>
</tr>
<tr>
<td>Liver</td>
<td>6% (4–8)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>AIDS related</td>
<td>56% (30–81)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>30% (11–49)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>29% (5–52)</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>36% (3–70)</td>
</tr>
<tr>
<td>Bacteraemia</td>
<td>9% (0–18)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>31% (6–56)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>23% (3–43)</td>
</tr>
<tr>
<td>Malnutrition/wasting*</td>
<td>15% (7–22)</td>
</tr>
</tbody>
</table>

- Dotted lines show specific conditions within categories.

### Explanations
- Increased risk of TB in PLHIV even on ART
- Late diagnosis of HIV & advanced immuno-suppression
- Suboptimal adherence
Framework for Differentiated approach to Care:

Different Care packages for different types of patients

- Stable on ART
- Unstable on ART
- Well Patients
- Late Presenters

Sub-populations:

- Children
- Adolescents
- Pregnant & Breast-feeding Women
- Men
- KPs
- SW, Prisoners, Migrant Workers

Fig. 3. Key factors in differentiated approaches to HIV care

- ART initiation
- Clinical monitoring
- Adherence support
- Laboratory tests
- PI treatment
- Psychosocial support
- Refills

- Monthly
- 3–6 months

- Physician
- Clinical officer
- Nurse
- Pharmacist
- Community Health worker
- Patient/poor/family

Manual provides guidance on the “how to” to implement the National ART Guidelines

Defines the minimum package of care per service delivery level, decentralisation scope of practice and capacity building strategies for health workers,

Emphasizes on integration of services

Identifies operational strategies that aim to address leakages in the cascade

Highlights special considerations for children, adolescents, pregnant and lactating women
Community ART refill groups (CARGs)

Model
- self-selecting patient groups
- one representative picks up ARVs for the group on quarterly basis
- group contribute money for transport/lunch/in kind support (eg work their fields)

Results: 9 month pilot evaluation (n=207)
- 100% retention
- 99% virally suppressed
- Time saving
- Secondary benefits in increased resilience, reduced stigma, increased peer support, more participation by community in health governance.

Zimbabwe, Buhera district: MSF Project
## Approaches to Differentiated Care:

<table>
<thead>
<tr>
<th>Context</th>
<th>Adherence Clubs</th>
<th>Community ART Distribution Points (PODI)</th>
<th>Community ART Groups (CAGs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appointment spacing and fast-track drug refill</strong></td>
<td>Urban &amp; rural</td>
<td>Urban</td>
<td>Rural</td>
</tr>
<tr>
<td><strong>ART refill</strong></td>
<td>1 to 3-monthly</td>
<td>2-monthly</td>
<td>1 to 3 Monthly</td>
</tr>
<tr>
<td><strong>Mode</strong></td>
<td>Individual</td>
<td>Group</td>
<td>Group</td>
</tr>
<tr>
<td><strong>Where</strong></td>
<td>Health facility</td>
<td>Health facility or community venues</td>
<td>Community distribution points</td>
</tr>
<tr>
<td><strong>Led by</strong></td>
<td>Lay worker</td>
<td>Lay worker</td>
<td>Lay worker of network of PLHIV</td>
</tr>
<tr>
<td><strong>Clinical consultation</strong></td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Blood drawing</strong></td>
<td>Yearly viral load</td>
<td>Yearly viral load</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

- ART refills follow the maximum duration allowed by MoH
- In absence of VL monitoring, consultation & blood drawing for CD4 is done 6-monthly

Source: MSF Publications
**Developing an evidence-base**

**Community Models Reduce Costs, Improve Retention, and Reduce Burden on Patient and Health System**

![Diagram showing ART Cost (US $ pppy), Retention at 48 Months, Time for drug pick up (min), and ART Refill visits (pppy)].

**ART Cost (US $ pppy)**
- Conventional care: $109
- Adherence club: $58

**Retention at 48 Months**
- Conventional care: 78%
- CAG: 91%

**Time for drug pick up (min)**
- Facility: 85
- Community point (PODI): 14

**ART Refill visits (pppy)**
- Conventional care: 6.5
- CAG: 2.6

*Based on data from Khayelithsa, RSA¹*
*Based on data from Tete, Mozambique*
*Based on data from Kinshasa, DRC*
*Based on data from Thyolo, Malawi*

Source: MSF Publications
Achieving and Maintaining Viral Suppression: Barriers and Strategies
Viral Suppression

- poor adherence to therapy
- low potency of the antiretroviral regimens
- viral resistance to antiretroviral therapy
- pharmacokinetic interactions

Inadequate viral suppression may result due to:

Inadequate drug delivery

Transmission of antiretroviral resistant viruses

Results: Among 9 cohorts where viral suppression was defined as <1,000 copies/ml; 83.5% (95% CI: 77.8-88.4; n=3,192) of the on-treatment populations were virally suppressed. The corresponding value for the intention-to-treat analyses for four cohorts; estimated viral suppression was 77.5% (95% CI 67.6-86.1, n=1,201).
Third 90: 73% achieving viral suppression for 31 full cascades

Percentage of Total HIV Positive People
Achieving Undetectable HIV RNA For 31 Countries with Full Cascades

UNAIDS 90-90-90 Target of
73% Viral Suppression
HIVDR can threaten achieving last "90"

Acquired HIVDR (ADR)

Pre-Treatment HIVDR (PDR)

Source: WHO 2015 Guidelines Dissemination Meeting, April, 2016
Pre-treatment HIVDR increases risk of virological failure of >3 times

TDR and partially-active ART
HR = 3.13 (p < 0.0001)

TDR and fully-active ART
HR = 1.47 (p = 0.12)

European Cohort Collaboration (N = 10,056)
Essential Elements of a Viral Load Scale Up Plan

- Laboratory Infrastructure, Equipment, Service and Maintenance;
- Sample Type and Transportation;
- Procurement and Supply Chain Management;
- Data Management and Results Transmission;
- PLHIV Education and Adherence Counselling and Support;
- Human Resources, Training and Mentorship;
- Quality Assurance;
- Program Management and Monitoring and Evaluation
Country challenges with viral load testing implementation

Update on UNAIDS Diagnostics Access Initiative work on viral load testing, March 2015
Conclusions:

- Remarkable progress has been made in reaching the **15 million target** of PLHIV on treatment; however more is needed to reach more and retain patients on treatment
- Unfortunately, **loss to follow up** along the stages of the HIV cascade remains a key challenge for HIV programmes particularly in Sub-Saharan Africa
- Ensuring adherence and retention to treatment requires an understanding of the multiple barriers that patients face and developing interventions that overcome these barriers
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