The case for integrated multi-disease interventions & a package of care for advanced HIV disease

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20-tool checklist for diagnosing, treating and preventing AIDS
Diagnostic and treatment checklist for the management of HIV and advanced HIV disease in outpatient settings
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Coinfection is common in many diseases of global health importance

- 38 million people with HIV: 7 million untested; 26 million on ART requiring VL testing
- 10 million estimated new TB cases, 2.9 million cases missed and 1.2 million deaths
  - 820 000 new TB in PLHIV
  - 206 000 diagnosed with MDR TB out of 465 000 estimated
- TB, cryptococcal meningitis and severe bacterial infections major causes of death of PLHIV
- Malaria and HIV combined cause 2 million deaths annually; co-infection frequent
- 256 million people with chronic hepatitis B; only 9% know their status
- 71 million people with chronic hepatitis C; only 20% know their status;
  - 2.3 million HIV/HCV co-infected.
- AMR: 700,000 deaths per year; estimated 10 million deaths annually by 2050.
- Limited access to diagnostics remains a bottleneck.
Why we need more than test & treat to decrease HIV-related deaths

- 690,000 PLHIV died in 2019
- UNAIDS target of <500,000 deaths in 2020 has not been met
- Slowing gains against HIV mortality
- TB, severe bacterial and fungal infections are the main causes of death
  - Responsible for 80% of hospital admissions and deaths (Ford, 2015)
  - Very limited microbiological and antimicrobial resistance data
  - Estimated 1/3 deaths due to TB and 1/5 to cryptococcosis
- 1/3 PLHIV starting ART have Advanced HIV Disease (WHO, 2017)
- Increasing role of ART interruption and failure.
- Rise of deaths due to non-communicable diseases: cardiovascular diseases, diabetes, malignancies, hepatitis B and C
- Test & Treat is necessary but not sufficient.
Advanced HIV Disease basic screening package

We need a mix of CD4 testing tools to keep favorable costs.

- **PIMA**
  - 25 mins to result
  - 2-3 samples per hour
  - $6-10 per test (excl. device)

- **BD FACSpeRisto**
  - 25 mins to result
  - 8-10 samples per hour
  - $7.50 per test (excl. device)

- **Omega Visitect CD4 LFA**
  - 40 mins to result
  - $3.90 per test

- **GeneXpert**
  - HIV VL, MTB/Rif.
  - (for bigger Health Centers)

- **IMMY CrAg LFA**
  - 10 mins to result
  - $2 per test

- **Alere Urine TB Lam**
  - 25 mins to results
  - $3.5 per test

Storage requirements, training requirements & ease of use, time to results, additional materials, cost etc...

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We need a mix of CD4 testing tools to keep favorable costs.

**Where to test?**

- **Primary Health Care**
  - (including peripheral clinics, health posts, mobile outreach)
  - (Health care professionals, trained lay cadres but no trained lab personnel)

- **Secondary Level Hospital**
  - (Lab technicians and assistants)

- **Tertiary Level Hospital**
  - (Specialists/senior lab techs)
# 20-tool checklist for diagnosing, treating and preventing AIDS

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<td>19. Amphotericin B deoxycholate or liposomal</td>
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<td>20. Other opportunistic infection and cancer treatments (e.g. KS, CMV)</td>
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1. HIV Rapid Diagnostic Tests (RDT)

- Recommendation: entry point for treatment
- Forecasting: consider historic demand and coverage of PLHIV who know their status
- Price for LMIC: RDT 1 US$; Oraquick self-test (OraSure) 2 US$
- Indicator: % of PLHIV who know their status
2. Point-of-Care Nucleic Acid Test (POC NAT) for Infant Diagnosis

- **New WHO Recommendation:** POC NAT should be used to diagnose HIV among infants and children younger than 18 months of age.

- **Rationale:** POC reduces TAT, increases % of infants initiated on ART with 60 days and is cost-effective (Frank, 2019)

- **Forecasting:** consider historic demand and add additional need according to new WHO guidelines

- **Price for LMIC:** Cartridge: US$20 (Abbott Alere q (/m-PIMA) HIV-1/2 Detect) or US$14.90 (Cepheid Xpert HIV Qual)

- **Indicator:** % of HIV+ children receiving an EID; Of those, % who have a POC EID (POC EID/total EID)
3. Routine Viral Load (VL)

- **New WHO recommendation**: POC VL may be used to monitor ART; new algorithm
- What’s needed: Routine VL monitoring and in people with symptoms of clinical failure or adherence difficulties.
- POC VL has certain advantages with respect to fast TAT and linkage to care, especially for higher-risk groups.
- Forecasting: Number of PLHIV on ART (annual VL); Number of new enrollments; 10-15% repeats for number of people >6 months on ART
- Price for LMIC: Lab-based: US$10 (e.g., Roche, Abbott, Hologic); POC cartridge: US$20 (Abbott m-PIMA HIV-1/2 VL) or US$14.90 (Cepheid Xpert HIV VL)
- Indicators: % PLHIV started on ART >6 months ago with a VL result within the last year; % PLHIV started on ART >6 months ago with a VL <1000 copies/mL; % PLHIV with repeat VL >1000 copies/mL switched to second-line therapy
4. CD4 cell count

- What’s needed: Baseline for all new initiations or PLHIV returning to care; targeted CD4 for people who are clinically sick or have a detectable VL (>1000 copies/mL). CD4 results should be available within 7 days of testing.
- Rationale: CD4 is essential for diagnosing (especially asymptomatic) advanced HIV disease (AHD) as clinical staging/symptom screening misses half of people with AHD at entry and re-entry into care, according to the REALITY study.
- Forecasting: Annual CD4 need is based on cumulative number of newly enrolled PLHIV, number of people on ART monitored with 6-month CD4 in lieu of VL, number of people on ART with unsuppressed VL/clinically unstable/with new opportunistic conditions (10-15% of annual VL)
- Price for LMIC: POC RDT for CD4 cell cutoff at 200 cells/mm3: US$3.98 (Omega VISITECT test; price under CHAI’s Early Market Access Vehicle); Lab-based CD4 counting: US$6.50 (Abbott PIMA) or US$7.60 (BD FACS Presto; includes leasing and maintenance of equipment)
- % of PLHIV initiating ART with baseline CD4; % of PLHIV monitored with CD4 6 monthly where there is no access to VL; % of PLHIV with unsuppressed VL or clinically unstable who get CD4 test
5. TB Rapid Molecular Diagnostic

- **What’s needed:** Initial TB test for all symptomatic patients
- **Rationale:** WHO considers undiagnosed TB as a main killer of PLHIV
- **Forecasting:** See MSF adaptation of WHO Global Laboratory Initiative (GLI) tool for testing sputum and extrapulmonary TB clinical samples (see [MSF TB tool](#))
- **Price for LMIC:** Cartridge-based MTB/RIF tests: US$9.98 (Cepheid GeneXpert MTB/RIF and Ultra) or US$9-12 (Molbio Truenat MTB or Truenat MTB Plus; Truenat RIF tests are free)
- **Indicator:** Number of PLHIV with TB symptoms at presentation screened with MTB/RIF; Number of PLHIV with TB symptoms
6. TB lipoarabinomannan (LAM) test

- WHO recommends TB-LAM at all levels of care, including at hospital level for all HIV+ inpatients with TB symptoms or seriously ill irrespective of their CD4 count. If CD4 <200 cells/mm$^3$, TB-LAM is recommended even in the absence of TB symptoms. For outpatients this is less than 100 cells/mm$^3$.

- Rationale: POC urinary TB-LAM testing increases the diagnosis of TB, particularly at lower CD4 cell counts, and shortens the time to TB treatment with a subsequent reduction of deaths.

- Forecasting: 60% of people with CD4 <100 who likely would be evaluated for TB based on signs or symptoms or danger signs, 30% people with CD4 <200

- Price for LMIC: Abbott Determine POC TB LAM RDT: US$3.76/test

- Indicator: % of HIV+ inpatients tested with TB-LAM; Number of PLHIV with CD4 <200 at presentation screened with POC TB-LAM
7. Cryptococcal Antigen Lateral Flow Assay (CrAg LFA)

- WHO recommends CrAg for diagnosis of cryptococcal meningitis in symptomatic patients and CrAg screening in all PLHIV with CD4 <200 cells/mm³.
- **Rationale:** CM remains the second-leading AIDS-related killer, second to TB. Prevention and early diagnosis and treatment are paramount to reducing CM-related mortality.
- **Forecasting:** Number of PLHIV with baseline CD4 <200 (30%)
- **Price for LMIC:** POC CrAg RDT (IMMY: US$2.00; Biosynex: US$2.40)
- **Indicator:** Number of PLHIV with baseline CD4 <200 with CrAg tested
Additional diagnostic tests depending on local epidemiology, population & resources

- Glucose
- Malaria Rapid Diagnostic Test
- Gram stain
- Blood cultures for invasive bacterial infections
- Hepatits B RDT
- Hepatitis C RDT
- Xpert HCV VL
- Xpert Ebola
- Xpert HPV
<table>
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<tr>
<th>Who to test?</th>
<th>Where to test?</th>
<th>What test to do?</th>
<th>Who does the testing?</th>
<th>When to test?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertiary-level hospital</td>
<td>Specialist or senior laboratory technician</td>
<td>CD4+ cell count using bench-top instruments and near POC CD4+ for inpatient and outpatient departments and emergency testing</td>
<td>Laboratory technicians (for all laboratory-based tests)</td>
<td>Laboratory and POC-initiated reflex testing including provider-initiated requests</td>
</tr>
<tr>
<td>Secondary-level hospital</td>
<td>Laboratory technicians and assistants</td>
<td>CD4+ cell count using bench-top instruments and near POC CD4+</td>
<td>Laboratory technicians (for all laboratory-based tests)</td>
<td>Advanced HIV disease laboratory test results in less than 3 h</td>
</tr>
<tr>
<td>Primary-level health care (including peripheral clinics, health posts, and mobile outreach)</td>
<td>Health-care professionals, trained lay cadres, but no trained laboratory personnel</td>
<td>POC CD4+ cell count instrument</td>
<td>Lay cadres, nurses, or clinicians</td>
<td>Where laboratory or mini-laboratory closes, minimum advanced HIV disease testing must remain available to be used 24/7 at POC for real-time results</td>
</tr>
</tbody>
</table>

Community level: HIV self testing (oral and blood based tests)
Conclusion

- Co-infections of major infectious diseases are common, especially in PLHIV.
- Basic package for HIV should include: HIV RDT, EID NAAT, HIV VL, CD4, TB-LAM, CrAg, and Rapid Molecular Diagnostic MTB/RIF.
- Additional tests to consider depending on local epidemiology, population and resources: malaria RDT, stool microscopy, Gram stain, blood cultures, HBV RDT, HCV RDT, histoplamosis RDT, HPV RDT, Ebola RDT.
- Point-of-care often preferable due to shorter TAT to results and treatment initiation.
- Most POC can be successfully task-shifted to lay cadres.
- R&D is needed for neglected causes of HIV mortality: PCP, toxoplasmosis, severe bacterial infections & ABR, MDR TB, CMV, herpes, resistance to DTG...
More information & references

- [https://www.who.int/publications](https://www.who.int/publications)
- [MSF Guidelines](https://www.who.int/publications)
- [Ndlovu et al. Framework for the implementation of advanced HIV disease diagnostics in sub-Saharan Africa: programmatic perspectives, Lancet HIV 2020](https://www.who.int/publications)
- [WHO HTM TB 2017](https://www.who.int/publications)
- [https://www.clintonhealthaccess.org/improving-diagnosis-through-integrated-testing/](https://www.clintonhealthaccess.org/improving-diagnosis-through-integrated-testing/)