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

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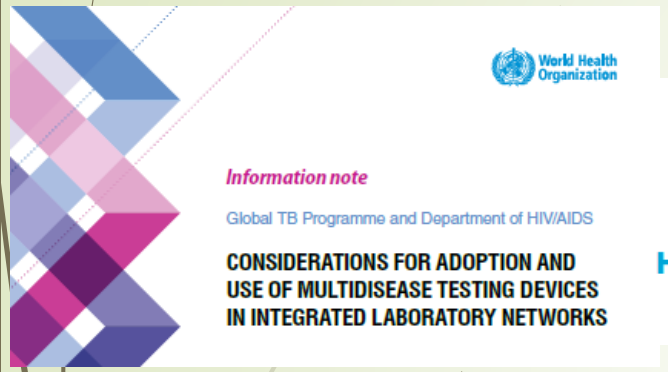
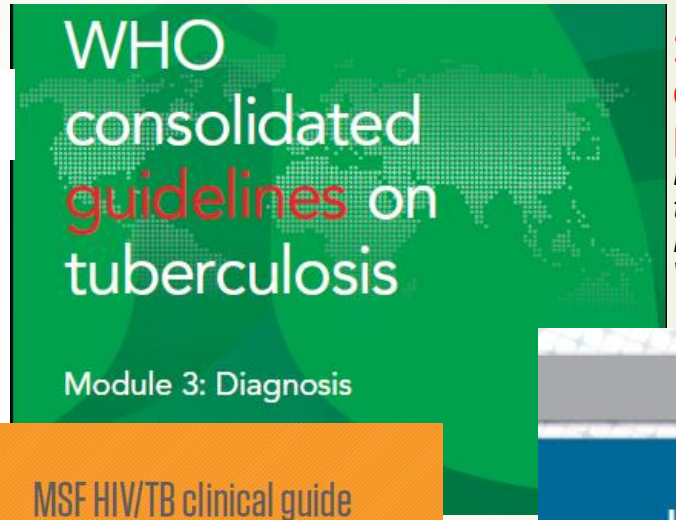
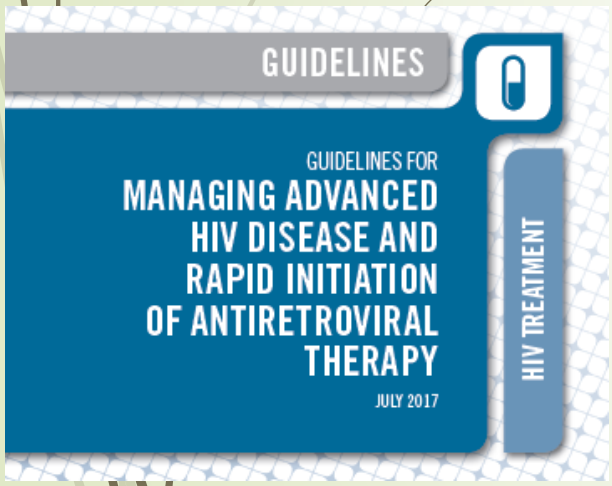
20-tool checklist for diagnosing, treating and preventing AIDS

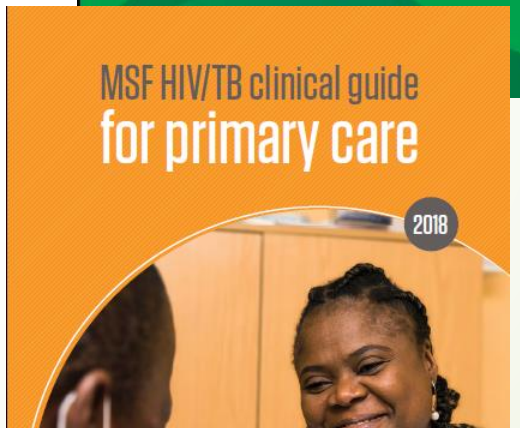
Diagnostic and treatment checklist for the management of HIV and advanced HIV disease in outpatient settings

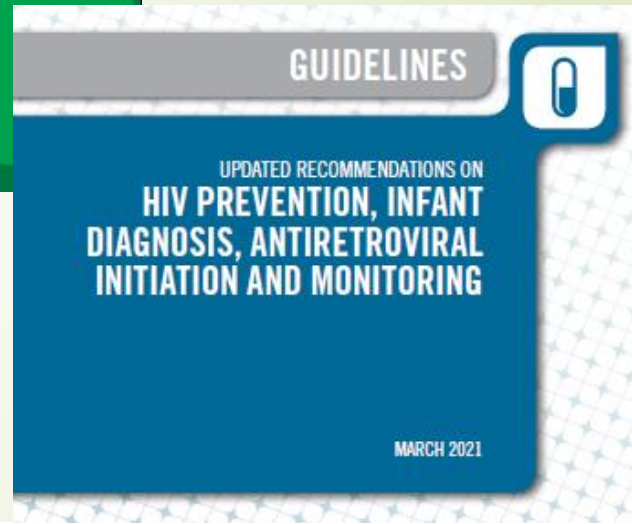
Version 2, January 2021











Framework for the implementation of advanced HIV disease diagnostics in sub-Saharan Africa: programmatic perspectives

Zibusiso Ndlovu, Rosie Burton, Rosanna Stewart, Helen Bygrave, Teri Roberts, Emmanuel Fajardo, Anafi Mataka, Elisabeth Szumilin, Bernhard Kerschberger, Gilles Van Cutsem, Tom Ellman

Lancet HIV 2020; 7: e514–20

Patients with advanced HIV disease have a high risk of mortality, mainly from tuberculosis and cryptococcal

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 10million 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

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

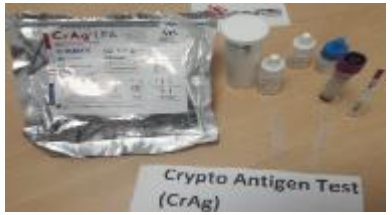
PIMA
25mins to result
2-3 samples per hour
$6-10 per test (excl device)

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

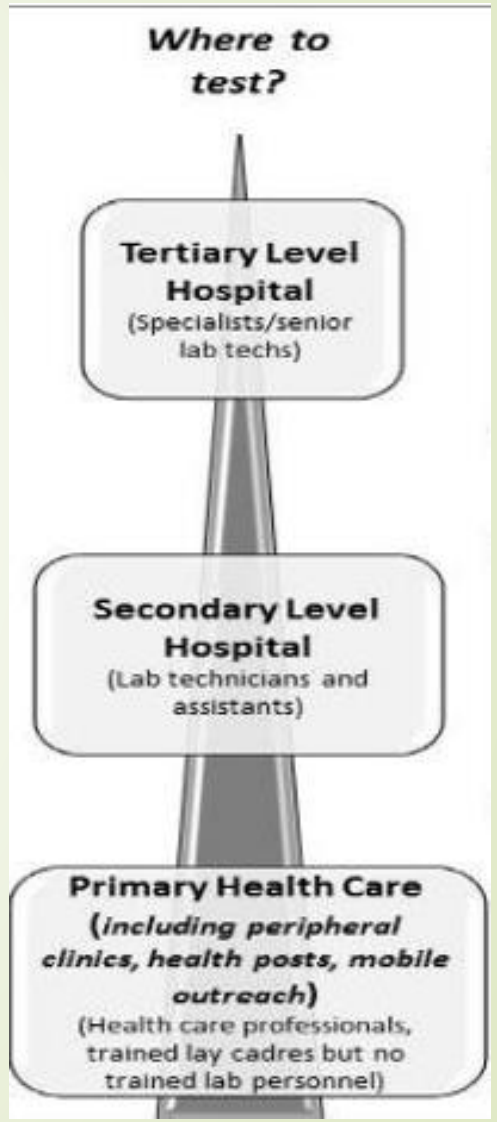
Omega Visitect CD4 LFA
***40mins* to result**
$3.90 per test

Alere Urine TB Lam (*25mins to results; $3.5 per test*)

IMMY CrAg LFA (*10mins to result; $2 per test*)



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



PLOS ONE

RESEARCH ARTICLE

Diagnostic performance and usability of the VISITECT CD4 semi-quantitative test for advanced HIV disease screening

Zibusiso Ndlovu[1]*, Lamin Massaquoi[2], Ndim Eugene Bangwen[2], John N. Batumba[2],

20-tool checklist for diagnosing, treating and preventing AIDS

Diagnostics

1. HIV rapid diagnostic test (RDT)
2. Early infant diagnosis (EID) nucleic acid amplification test (NAAT)
3. Routine viral load (VL)
4. CD4 cell count
5. TB Rapid Molecular Diagnostic
6. TB lipoarabinomannan (LAM) test
7. Cryptococcal antigen (CrAg) RDT

Treatment & Prevention

8. Pre-exposure prophylaxis: TDF/3TC or TDF/FTC
9. First-line adult antiretroviral (ARV) therapy
10. First-line paediatric ARVs
11. Second-line adult ARVs
12. Second-line paediatric ARVs
13. TB medicines
14. TB prophylaxis therapy (TPT) for adults
15. TB prophylaxis therapy (TPT) for children
16. Cotrimoxazole
17. Fluconazole
18. Flucytosine
19. Amphotericin B deoxycholate or liposomal
20. Other opportunistic infection and cancer treatments (e.g. KS, CMV)

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/mm^3.
- 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

Who to test?	Where to test?	What test to do?	Who does the testing?	When to test?
	Tertiary-level hospital • Specialists or senior laboratory technicians	• **CD4⁺ cell count using bench-top instruments and near POC CD4⁺ for inpatient and outpatient departments and emergency testing** • **Urine TB LAM** • **CrAg and or semiquantitative CrAg LFA** • **Rapid HIV test and HIV self-test** • Cerebrospinal fluid microscopy and culture • Molecular *Mycobacterium tuberculosis* and resistance to rifampicin testing • HIV viral load and early infant diagnosis (LFTs, creatine tests, and electrolyte tests) • Blood culture for severe bacterial sepsis • Gram, Ziehl-Neelsen, or Giemsa staining • Malaria, hepatitis B, and hepatitis C rapid diagnostic tests	• Laboratory technicians (for all laboratory-based tests) • Lay cadres, nurses or clinicians (in Rapid Assessment Units, ART clinics, inpatient departments, or emergency rooms)	
• All at ART initiation • All at re-engagement to care (welcome back service) • All suspected ART failures* • All pregnant women who are HIV positive • All seriously ill patients (suspected WHO stage 3 or 4) • All children <5 years	**Secondary-level hospital** • Laboratory technicians and assistants	• **CD4⁺ cell count using bench-top instruments and near POC CD4⁺** • **Urine TB LAM** • **CrAg and or semiquantitative CrAg LFA** • **Rapid HIV test and HIV self-test** • Cerebrospinal fluid microscopy and culture • Molecular *M tuberculosis* and resistance to rifampicin testing • HIV viral load and early infant diagnosis (LFTs, creatine tests, and electrolyte tests) • Blood culture for severe bacterial sepsis • Gram, Ziehl-Neelsen and Giemsa staining • Malaria, hepatitis B, and hepatitis C rapid diagnostic tests	• Laboratory technicians (for all laboratory-based tests) • Lay cadres, nurses or clinicians (in Rapid Assessment Units, ART clinics, inpatient departments, or emergency rooms)	• Laboratory and POC-initiated reflex testing including provider-initiated requests • Advanced HIV disease laboratory test results in less than 3 h • Advanced HIV disease POC test results in less than 2 h • 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
	Primary-level health care (including peripheral clinics, health posts, and mobile outreach) • Health-care professionals, trained lay cadres, but no trained laboratory personnel	• **POC CD4⁺ cell count instrument** • **Urine TB LAM** • **CrAg and or semiquantitative CrAg LFA** • **Rapid HIV test and HIV self-test** • Primary health care with mini-laboratory can have near-POC molecular multi-disease testing device (*M tuberculosis* and resistance to rifampicin, HIV viral load and early infant diagnosis) or Ziehl-Neelsen plus Gram staining and malaria rapid diagnostic tests	• Lay cadres, nurses, or clinicians • Select overall responsible person for advanced HIV disease diagnostics	
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
- MSF Guidelines
- Ndlovu et al. Framework for the implementation of advanced HIV disease diagnostics in sub-Saharan Africa: programmatic perspectives, Lancet HIV 2020,
- WHO HTM TB 2017
- https://unitaid.org/news-blog/multi-disease-testing-offers-new-ways-streamline-disease-management-report-says/#en
- https://www.clintonhealthaccess.org/improving-diagnosis-through-integrated-testing/