CALL FOR EXPRESSION OF INTEREST

Invitation to submit an Expression of Interest (EOI) to provide interventions to grow capacity and increase sustainable access to CD4 testing and Opportunistic Infection (OI) screening.

Issue Date: June 20, 2024

Closing Date: August 2, 2024

List of abbreviations

AHD	Advanced HIV disease
ART	Antiretroviral Therapy
BD	Becton Dickinson
BMGF	Bill and Melinda Gates Foundation
CHAI	Clinton Health Access Initiative
CrAg	Cryptococcal Antigenemia
CSF	Cerebrospinal fluid
EDL	Essential Diagnostics List
EOI	Expression of Interest
ERP	Expert Review Panel
GMP	Good Manufacturing Practice
LMIC	Low- and Middle-Income Countries
MOH	Ministry of Health
OI	Opportunistic Infection
POC	Point-of-Care
PLHIV	People Living with HIV
SRA	Target Product Profile
TPP	Stringent Regulatory Authority
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WHO	World Health Organization Pre-Qualification

Disclaimer Notice and Confidentiality

This call for Expression of Interest (EOI) is issued by the Clinton Health Access Initiative and the Aurum Institute for planning and design purposes, with funding and technical support from Unitaid and in consultation with the Bill & Melinda Gates Foundation (BMGF). It should not be regarded as a Call for Proposals or a Request for Tender. Any information submitted in response to this EOI is provided to Aurum, CHAI, and Unitaid voluntarily and may be discussed in consultation with BMGF. CHAI, Aurum, Unitaid, or BMGF shall not be under any obligation to procure any of the services or products described herein, and the issuance of this EOI shall not be construed as a commitment to enter commercial or other business relations. CHAI, Aurum, Unitaid, or BMGF may use the information provided by respondents to the EOI to support strategic decisions and planning within its project portfolio or for internal purposes, including but not limited to the design of future Calls for Proposal or other solicitations which CHAI, Aurum, Unitaid or BMGF may issue.

Any information submitted in response to this EOI that needs to be treated as "confidential" should be marked as such on the completed form by the respondent. When information is marked confidential, CHAI, Aurum, Unitaid, and BMGF will take all reasonable measures to keep it confidential and will not share it with other entities or individuals outside of these organizations without the respondent's written authorization. However, this confidentiality commitment shall not apply if the information concerned, or any part of it (a) was known to the organizations before any disclosure by the respondent or (b) was in the public domain at the time of disclosure by the respondent, or (c) becomes part of the public domain

through no fault of the organizations, or (d) becomes available to the organizations from a third party who is not in breach of any legal obligation of confidentiality to the respondent. Information not marked as confidential will nevertheless not be shared with other entities or individuals outside the organizations without the respondent's written authorization unless that information has been anonymized or aggregated to deter identification of individual manufacturers (e.g., used without specifying individual Company or Organization names, product names, geographical location).

Overview

This call for expression of interest (EOI) solicits interest from manufacturers of CD4, cryptococcal antigen (CrAg), and histoplasmosis (Histo) tests. The scope of tests being solicited includes tests currently available on the market or in late-stage development (at least the design-lock stage). The tests should meet or have plans to meet minimal characteristics as defined in the World Health Organization (WHO) Target Product Profiles (TPP) requirements. TPPs already exist for Point-of-Care CD4 tests to support the identification of individuals with Advanced HIV Disease and CrAg rapid diagnostic tests. None currently exists for Histoplasmosis. Manufacturers seeking technical, regulatory, and/or financial support to scale access to existing tests or accelerate the commercialization of a quality-assured new test are encouraged to apply. The test does not need to be commercially available or owned by the Company during the EOI. This EOI process will help contribute to efforts by governments and global health stakeholders to improve access to CD4 testing, as well as Cryptococcal and Histoplasmosis infection screening in low- and middle-income countries (LMICs).

This call for EOI is issued by the Clinton Health Access Initiative (CHAI) and the Aurum Institute, funded partners of Unitaid, a hosted partnership of the WHO and in consultation with the Bill & Melinda Gates Foundation. The collaboration of CHAI, Aurum Institute, Unitaid, and BMGF aims to leverage collective capabilities and partnerships with other relevant not-for-profit organizations to accelerate access to Advanced HIV Disease (AHD) testing in LMICs.

CD4 Screening

The most recent UNAIDS 2023 report suggests that 30-40% of people newly initiating antiretroviral therapy (ART) in LMICs have AHD.[1] Several studies have shown that a high proportion of people with AHD have no signs or symptoms of illness – for example, the REALITY trial found that 47.3% of people with AHD were asymptomatic or mildly symptomatic at the time of diagnosis. These studies demonstrate that detecting up to half of AHD cases can be difficult based solely on WHO clinical staging.[2]

Thus, CD4 testing remains a critical gateway for the timely diagnosis and management of advanced disease. However, demand for CD4 tests is far lower than the actual need (based on eligibility according to WHO guidelines), and the market faces a huge problem of excess and access – thousands of analyzers lay unused while people who need a CD4 do not have access to one. At a recent CD4 roundtable discussion convened by CHAI, the Ministries of Health (MOH) and implementing partners reported challenges with

[1] UNAIDS. The Path That Ends AIDS 2023 UNAIDS Global AIDS Update. Link

[2] Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced prophylaxis plus antiretroviral therapy for advanced HIV infection in Africa. N Engl J Med [Internet]. 2017;377(3):233–45. Available from: http://dx.doi.org/10.1056/nejmoa1615822

suboptimal CD4 coverage for their eligible patient populations due to limited supply, procurement delays, and a substantial number of devices that require costly and time-intensive servicing.

The CD4 market is at a critical juncture. The two device-based point-of-care (POC) manufacturers, Abbott and Becton Dickinson (BD), are ceasing to manufacture new devices and, in the case of BD, completely withdrawing from the POC CD4 market in March 2024. Abbott has committed to supporting reagents for the foreseeable future for facilities with functional platforms. The price of the Abbott Pima CD4 cartridge has recently increased to $7.70 per cartridge.

CrAg Testing

Cryptococcal disease is one of the most common opportunistic infections among people living with AHD and is a major contributor to illness, disability, and mortality.[3] Clinically significant invasive disease is primarily caused by the reactivation of latent infection among immunocompromised individuals, such as people living with HIV (PLHIV), months to years after initial exposure.[4] By far the most common presentation of cryptococcal disease is cryptococcal meningitis, which accounts for an estimated 15% of all HIV-related deaths globally.[5]

Mortality from cryptococcal meningitis remains highest in low-income countries. The estimated one-year mortality of people living with HIV who receive care for cryptococcal meningitis is 70% in low-income countries versus 20–30% for high-income countries.[6] A major reason for this high mortality is delay in diagnosis, largely due to limited access to lumbar puncture and rapid diagnostic assays at the point of need.

Early diagnosis and treatment of cryptococcal meningitis are vital to reduce mortality from cryptococcal disease. Healthcare professionals should have a low threshold for suspecting cryptococcal meningitis among people with AHD. Additionally, the WHO recommends that national programs prioritize reliable access to rapid diagnostic CrAg assays, preferably lateral flow assays, for use in cerebrospinal fluid (CSF), serum, plasma, or whole blood.

Histoplasmosis Screening

Histoplasmosis is a fungal infection linked to manipulating soil and exploring caves in regions where bats and birds reside. The disease is amenable to treatment but has the potential to kill sufferers of AHD if left undiagnosed. Its strong association with AHD in the Americas has led WHO/PAHO to provide guidelines for managing this fungal infection within the context of AHD. Data from South and Central America has shown that disseminated histoplasmosis contributes significantly to the morbidity and mortality of HIV-

[3] Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 Available from: https://apps.who.int/iris/handle/10665/255884.
[4] Garcia-Hermoso D, Janbon G, Dromer F. Epidemiological evidence for dormant Cryptococcus neoformans infection. J Clin Microbiol. 1999;37:3204–9.
[5] Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17:873–81.
[6] Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17:873–81.

infected patients. [7] Disseminated histoplasmosis was classified as an acquired immunodeficiency syndrome (AIDS)-defining infection in 1987.[8] Histoplasmosis is still widely misdiagnosed as tuberculosis and even as multidrug-resistant tuberculosis, leading to numerous preventable deaths[9,10] This recent data from some African countries demonstrates that disseminated histoplasmosis is an issue in the advanced HIV diseases population, with documentation of cases of co-infection of TB and histoplasmosis.

A recent publication reviewed existing diagnostic methods for Histoplasmosis, including culture, pathological evaluation, antigen and/or antibody testing, and polymerase chain reaction, and recognized the contribution of the following factors to test performance, namely suspected syndrome, specimen type, resource availability, and the immune status of the source patient. The WHO/PAHO guidelines for managing Histoplasmosis among People Living with HIV recommended diagnosing disseminated histoplasmosis among people living with HIV by detecting circulating Histoplasma antigens, while the 2023 edition of the WHO Essential Diagnostics List recommended an immunoassay test format on urine samples for the detection of Histoplasma capsulatum antigen.

The changes in the CD4 market described above, as well as the growing awareness for the need and availability of screening for opportunistic infections, including Histoplasmosis, come while PEPFAR highlights their commitment to support regional manufacturing for critical HIV commodities, including rapid HIV diagnostics, as part of its five-year strategy. Identification of potential regional manufacturers for these AHD diagnostics solutions could contribute to increased access to low-cost testing, prevent shortages in facilities due to shipping delays, and ultimately speed up the transition to newer innovations, altogether saving more lives while supporting regional capacitation.

1. Summary of Target Product

This EOI is open to manufacturers who can provide a viable, affordable, quality-assured solution for the LMIC market to accelerate widespread access to CD4 testing, cryptococcus, and histoplasmosis infection screening. Interested manufacturers should provide evidence and plans to scale up access to currently available POC CD4 testing options, and/or CrAg or Histoplasmosis screening before the end of 2025, while manufacturers with tests in the pipeline should provide evidence and plans to bring these tests to market within 2.5 years (by the end of 2026).

2. Intent of the EOI

This EOI is designed to identify opportunities to increase access to CD4 testing and/or CrAg or Histoplasmosis screening for PLHIV in LMICs, especially in high-burden countries where major gaps in AHD screening persist, and there is a particular interest or need for POC testing. The goal is to gather information on potential opportunities that support sustainable access to POC testing either with a

7 Pasqualotto AC, Quieroz-Telles F. (2018). Histoplasmosis dethrones tuberculosis in Latin America. Lancet Infect Dis 2018; 18: 1058-60.

8 Adenis AA, Valdes A, Cropet C, et al. (2018). Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: a modelling study. Lancet Infect Dis 2018; 8: 1150-9

9 Oladele RO, Osaigbovo II, Akanmu AS, Adekanmbi OA, Ekeng BE, Mohammed Y, Alex-Wele MA, Okolo MO, Ayanbeku ST, Unigwe US, Akase IE. (2022) Prevalence of histoplasmosis among persons with advanced HIV disease, Nigeria. Emerging Infectious Diseases. 2022 Nov;28(11):2261.

10 Mandengue CE, Ekeng BE, Oladele RO. (2021). Disseminated Histoplasmosis; A threat in advanced HIV Disease population in sub-Saharan Africa? J. adv. Med. Med. Res. 2021; 33(3): 115-44

product that is already approved by a Stringent Regulatory Authority (SRA) or the WHO Prequalification Programme (PQ) and commercially available or for a product dossier to be filed by selected manufacturers with an SRA or the WHO PQ and for the product to be registered in selected high-burden LMICs at an affordable price. Manufacturers based in Africa or with some element of the final distribution already in place or planned for development in Africa are strongly encouraged to apply.

In this context, Aurum, CHAI, the Bill & Melinda Gates Foundation, and Unitaid also seek to understand the extent to which manufacturers may be interested in potentially receiving support towards achieving set target access requirements. The available support could be one or a combination of the following: regulatory assistance for registration and/or WHO PQ; support associated with technology transfer for regional manufacturing of a new POC CD4, CrAg or Histoplasmosis test; support with transitioning some manufacturing capacities to Africa; support for WHO expert review panel quality assurance review; acquiring a POC CD4, CrAg or Histoplasmosis test from another Company and bringing it to market; advance market commitment for partner-funded procurement volumes. Manufacturers are encouraged to collaborate with civil society and/or implementing partners for engagement at the country level, to seek their input on the feasibility and sustainability of approaches, to identify critical gaps, and to develop implementation plans.

Manufacturers are required to indicate willingness to collaborate on a wide range of activities, which may include some or all of the following:

- Provision of a report that includes information on the status of test development, analytical method development and validation, and stability studies.
- Preparation and submission of a regulatory dossier for an SRA or the WHO PQ and the Expert Review Panel (ERP)[10] as well as other acceptable regulatory mechanisms.
- Preparation and submission of a plan for regulatory filings and product commercialization in LMICs.
- Production and supply planning/commitment to cover at least five years (through 2030) that ensures the capacity to supply the target market within a mutually agreed manufacturing lead time and
- Agreement to supply product at an affordable price (which may be at or below a ceiling price) to be finalized in the award contract on a continuous basis for qualified orders within a validity period. Depending on the conditions, other access commitments, such as supply security, minimum production volumes, etc., may also be necessary.

3. Instructions to interested parties

a. Expression of Interest (EOI):

[10] Expert Review Panel (ERP) is an independent technical body composed of external technical experts, hosted by WHO Department of Essential Medicines and Pharmaceutical Policies, to review the potential risks/benefits associated with the use of FPPs that are not yet WHO-prequalified or SRA-authorized and to advise the Global Fund in its decision on whether to allow grant funds to be used to procure FPP

i. All EOIs should be submitted in English and be signed by an authorized representative of the Responder on both the cover letter and the "General Information" tab of the Excel form.

ii. The following documents shall be completed and submitted with the EOI response. EOI responses will not be considered if either of these components is missing. Only applicants who respond to the EOI will be invited to respond to any potential future Request for Proposal:

- The cover letter should include a summary of the supplier's proposed solution, an overview of the support needed to bring the solution to market, and a statement of commitment to engage further on a solicitation to achieve the desired objectives of this call.
- The Excel form detailing company information, prior experience, and details about the proposed product.

iii. EOIs should be submitted via e-mail with the subject line **Expression of Interest – AHD** to AHDDx@clintonhealthaccess.org

b. Timelines

The timeline for the EOI process is described below. EOIs received after the deadline will not be considered.

EOI Released	June 20, 2024
EOIs Due	August 2, 2024

**Late submissions will not be accepted.*

c. Questions and answers

i. A formal period during which questions regarding this EOI are answered will follow the posting of the EOI on the Unitaid and partner websites. (Please reference above for timeline).

Questions should be sent via email to AHDDx@clintonhealthaccess.org

ii. All enquiries must be received via email by the stipulated deadline for questions.

iii. It will not be possible to engage in telephone enquiries.

d. Eligibility

The EOI is open to all Manufacturers who meet the following criteria:

- Company has previously submitted dossiers to WHO PQ, United States Food and Drug Administration (US FDA), or other SRA for any product and received Prequalification and/or SRA approval **OR** Company will make a commitment to submit a dossier to US

FDA (or other SRA to be mutually agreed) and/or WHO PQ with this product.

- Company's production facility operates under current Good Manufacturing Practice (GMP), has obtained or is in the process to obtain ISO 13485 certification, and/or the manufacturing site/unit has been successfully audited for GMP by WHO PQ or US FDA/SRA; Company must be able to provide evidence of certifications and/or completion of prior audits if they are engaged for further consideration for an award;
- Company has the proven ability to manufacture rapid diagnostic tests at a commercial scale **OR** is working on a downstream solution that will support cost-effective and sustainable access to an existing POC test for CD4, CrAg, or Histo;
- Company must agree to host and must pass a quality assurance/GMP audit if they are engaged for further consideration for an award;
- The company may be required to establish a project team structure that includes representatives from one or more of the collaborating institutions (Aurum, CHAI, Unitaid, and BMGF) and host regular meetings (in person and/or via teleconference) as/when required.

Manufacturers with established regional manufacturing capacity and/or presence in Africa are strongly encouraged to apply.

e. Costs of preparing documents

All costs associated with preparing and submitting an EOI will be borne by the Company.

f. Disclosure

Information relating to the examination, clarification, and evaluation of responses shall not be disclosed to Manufacturers or any other persons not officially concerned with such process.

4. The Clinton Health Access Initiative, Inc. Company Information

The Clinton Health Access Initiative, Inc. (CHAI) is a global health organization committed to saving lives and reducing the burden of disease in low- and middle-income countries while strengthening. the capabilities of governments and the private sector in those countries to create and sustain high-quality health systems that can succeed without our assistance. For more information, please visit: http://www.clintonhealthaccess.org.

5. Aurum Institute Company Information

The Aurum Institute is a proudly African organisation working to advance health, science and innovation to create a healthier world for future generations. We partner with governments, the private sector, and civil society to design and deliver high-quality care and treatment to people in developing communities. https://www.auruminstitute.org/

6. Unitaid Information

Unitaid is an international organization that invests in innovations to prevent, diagnose, and treat HIV/AIDS, tuberculosis, and malaria more quickly, affordably, and effectively. Unitaid works to improve access to diagnostics and treatment for HIV co-infections such as hepatitis C and human papillomavirus (HPV). For more information, please visit http://www.unitaid.org.

7. Bill and Melinda Gates Foundation Company Information

Guided by the belief that every life has equal value, the Bill & Melinda Gates Foundation works to help all people lead healthy, productive lives. In developing countries, it focuses on improving people's health and giving them the chance to lift themselves out of hunger and extreme poverty.
https://www.gatesfoundation.org/