CrAg LFA IMPLEMENTATION OVERVIEW & LESSONS LEARNT

CONTEXT:

- IMMY's CrAg LFA, approved by the FDA in 2011, is an immunochromatographic dipstick assay that detects the presence of the CrAg antigen without requiring laboratory infrastructure.
- IMMY's CrAg LFA test is fast and accurate with a turnaround time of 10 minutes and a 100% sensitivity and specificity in serum and CSF samples, both of which are samples approved by the FDA for the test. Despite its performance, it is still recommended to confirm a positive diagnosis with a lumbar puncture.

Advantages of CrAg LFA

Quick results: the test can provide an accurate result in 10 minutes, enabling rapid linkage to care

Suitable for decentralized settings: When a lumbar puncture is not available, this test's performance with blood samples allows for same day screening in any facility

Improved cost-effectiveness: More years of life saved per dollar

Updated WHO 2018 guidelines:

- ✓ WHO strongly recommends screening for cryptococcal antigen followed by pre-emptive antifungal therapy before initiating or reinitiating ART for AHD adults and adolescents. Screening is not recommended for children due to due low prevalence of CM in younger patients.
- ✓ *Where lumbar puncture is immediately available,* WHO recommends a lumbar puncture and a CrAg LFA test using cerebral spinal fluid for the sample.
- ✓ *Where lumbar puncture is not immediately available,* WHO recommends a CrAg LFA test with a serum, plasma, or whole blood sample.

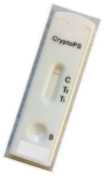
CURRENT GLOBAL CHALLENGES AND RECOMMENDATIONS:

CHALLENGE:	LESSONS LEARNT / RECOMMENDATIONS:
1. Gaps in inter-intra facility linkage • In some countries, CM management and care may not be directly managed by ART clinicians at some facilities. For example, if a patient in a spoke site needed to be referred to a hub for additional screening, this patient may be LTFU or their data may not be adequately captured. A referral isn't complete until the client is there and receives care.	***1. Capturing transfers in reporting systems*** • A clear plan should be developed to address intra/interfacility referral for LP. CM trainings should be extended to clinicians outside of the ART clinic.
2. Lack of ancillary materials • One anticipated challenge in some facilities was a lack of spinal needles needed to collect samples for the CrAg LFA among facilities. Further, there remained a need to budget and fund these needles, and to ensure that all patients, CM and otherwise, would be able to access them. • Patients receiving Liposomal-amphotericin B as part of their treatment require a supplement of electrolytes to rehydrate the body after care.	***2. Quantifying ancillary products alongside diagnostics*** • After CHAI raised these challenges, PEPFAR agreed to ensure provision of spinal needles across the sites. • Supply of spinal needles should be assessed before and during implementation. Furthermore, governments must be responsible for strengthening these health systems nationally to ensure supply is not limited to certain disease areas or programs. • While the availability of electrolytes is limited for 'emergency' patients in some countries, CHAI has been quantifying for and procuring this product until sustainable funding is secured.

3. Additional barriers to LP • Across multiple countries, there was and remains low uptake of lumbar puncture (LP). A survey in one country found that 11% of patients refused LP when offered, likely because the procedure is painful. Also, because very sick patients needing LP sometimes die shortly after diagnosis, there is a misconception that LPs themselves are dangerous. • Of those surveyed, 3% of patients who did not receive a lumbar puncture died or were LTFU before their follow up.	***3. Advocating for LPs*** • Prompt identification and treatment of clients with CM is needed to reduce mortality. • CHAI strongly encourages clarifying the misconception that LPs are dangerous. CHAI is currently working with the Community Advisory Board to develop resources and advocacy materials for patients to get educated on the benefit of LPs.
4. Cost barriers to lumbar puncture • A larger 54% of those surveyed in one country cited the cost of an LP as being prohibitive. Prior to the procedure, a patient is required to receive an IV and stay in the hospital for up to a week, thereby adding the cost of admission as an additional barrier.	***4. Reducing out of pocket costs*** • Some countries offer free LPs, though the stay of the hospital remains an out-of-pocket cost. • CHAI secured commitments for some facilities to not charge patients for LP. Hopefully, this practice will spread to others, allowing better access to the test.
5. Over-quantification of CM • Prior to implementation in one country, it was estimated that 50% of patients receiving a CSF CrAg would be positive, according to a study. From phase 1 implementation data, 30% of those receiving a serum test were positive and 31% of CSF patients were positive.	***5. Understanding lower numbers*** • It is possible that the figures that the study referenced for number of CM clients might not have been an accurate estimate of CM cases, which are unevenly distributed across geographical regions. • It is likely that the discrepancy in CM prevalence is partly due to low screening volumes. Some patients died from CM before being screened at all. By increasing the number of patients who come in for confirmatory lumbar puncture, it is likely that these numbers would better align.
6. Supply chain challenges • Supply chain disruption of CM therapeutics affected treatment provision. Stockouts of L-AmB, fluconazole, CrAg LFA kits, TB LAM, and CD4 reagents occurred, and HCWs were not certain on the process of quantifying and reporting low supply in multiple countries.	***6. Procuring from multiple suppliers where possible*** • Alternative CM therapeutic commodities should be made available to ensure access in case of supply chain disruptions. With Strides now manufacturing QA 5-FC, programs and procurement partners should consider them as an alternative supplier to Viatris. Viatris is expected to resume production in H2 2022. In the event of supply gaps, countries should consider inter/intra country transfers of product to fill gaps until new product comes in. Additionally, orders should be placed as soon as possible to anticipate delays.
7. Staff turnover • In several countries, there were reports of high staff turnover, which led to loss of confidence in administering CM treatment.	***7. Filling and understanding knowledge gaps*** • Trainings and retrainings are recommended to ensure that staff are confident administering all components of the package of care, regardless of staff turnover. • There may need to be an assessment of a workflow and burden on the existing staff and consideration for task shifting.

LOOKING AHEAD:

While CrAg LFA offers an opportunity for fast diagnosis of CM without laboratory infrastructure, there remain opportunities to simplify the algorithm for timely diagnosis for CM patients. CHAI continues to monitor the landscape for future CM diagnostic products.

Comparing leading diagnostic devices for cryptococcal meningitis			
Product name	 **IMMY CrAg LFA**	 **Biosynex Crypto PS**	 **IMMY CrAg SQ**
Test type	• Qualitative • Whole blood, serum, plasma, or CSF	• Semi-quantitative • Whole blood, serum, plasma, or CSF	• Semi-Quantitative • Whole blood, serum, plasma, or CSF
Time to process	• 10 min/test • *Up to ~48 tests/day*	• 10 min/test • *Up to ~48 tests/day*	• 10 min/test • *Up to ~48 tests/day*
Performance	• Sensitivity 93% • Specificity 100%	• Sensitivity: 95% • Specificity: 100%	• Sensitivity: 98.1% • Specificity: 95.8%
Upfront investment	• $0	• $0	• $0
Price per test	**$2.34**	**$2.42- $3.02**[16]	**~$2.34-$3.50**[17]

16 *USD equivalent of €2.00- 2.50/test at a rate of 1 EUR = 1.16 USD as of 1 Nov 2020*

17 *Preliminary information from IMMY team*