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A qualitative evaluation of an implementation study for cryptococcal antigen screening and treatment in Uganda

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Abstract

Cryptococcal meningiti s causes 15% of AIDS-related deaths globally. Screening and preemptive treatment for cryptococcal antigen (CrAg) in the blood of persons with advanced HIV/AIDS reduces mortality. National and international HIV guidelines recommend CrAg screening; however, implementation studies and evaluations of how to integrate CrAg screening programs into existing HIV care infrastructure are lacking.

During a CrAg screening program in Kampala, Uganda, we interviewed 15 health care workers (2 coordinating research nurses and 13 clinic personnel) from 6 HIV clinics between March and April 2017, to identify barriers to implementation as well as facilitating factors for program success. The interviews were coded and themes compiled.

We found key factors for successful implementation of a CrAg screening program were: adequate supplies of fluconazole and CrAg lateral flow assay (LFA) point-of-care tests, timely patient follow-up, and quick turnaround time of laboratory results. Although both CrAg LFA kits and fluconazole are on the national formulary, stockouts are common, affecting patient care. The CrAg screening recommendation by national HIV guidelines remains integral to the success of the program, as overburdened clinics are otherwise reluctant to adopt additional screening. Collaboration with Ministries of Health for support with enforcing national guidelines, and procuring supplies is paramount to a successful CrAg screening program.

Development of a CrAg screening and treatment program within the HIV clinic infrastructure has a number of barriers. Education and training of clinic staff, along with partnership with the Ministry of Health to ensure adequate supplies, facilitated the program.

Abbreviations: AIDS = Acquired Immune Deficiency Syndrome, ART = antiretroviral therapy, CD4 = CD4+ T helper cells, CrAg = cryptococcal antigen, HIV = Human Immunodeficiency Virus, LFA = CrAg Lateral Flow Assay.

Keywords: cryptococcal screening, cryptococcus, field study, implementation science, qualitative research

1. Introduction

Cryptococcal meningitis has been estimated to cause 15% of AIDS-related deaths globally.[1] Mortality in sub-Saharan Africa is estimated at 50% to 70%, given delayed presentation to care, poor access to optimal antifungal medications, and complex medical therapy including serial lumbar punctures.[2,3] Cryptococcal antigen (CrAg) is detectable in the blood weeks before onset of meningitis.[4] Screening for CrAg in the blood of asymptomatic persons with advanced HIV infection, and preemptively treating those CrAg-positive persons with fluconazole reduces mortality.[5] Indeed, in a randomized controlled trial in Tanzania and Zambia, screening HIV-infected persons with a CD4 cell count <200 cells/μL for cryptococcal antigenemia and pre-emptively treating those CrAg-positive persons with fluconazole plus adherence support reduced mortality by 28%.[6] Thus, CrAg screening is recommended by the World Health Organization and multiple national HIV guidelines.[7]

However, HIV outpatient care in sub-Saharan Africa is already under-resourced and overburdened; an additional screening recommendation is not trivial. Implementation research regarding how to best integrate CrAg screening is limited.[8] Studies with high rates of loss to follow-up or delayed initiation of antiretroviral therapy (ART) have not replicated the survival benefit seen in clinical trials.[8,9] The role of healthcare workers in the screening program, perceived barriers, and facilitating factors as described in this qualitative evaluation of a successful CrAg screening program have not previously been described.

To better understand how best to perform CrAg screening outside of a clinical trial setting, an implementation study was undertaken in outpatient HIV clinics in Kampala, Uganda.[10] As part of this evaluation, qualitative interviews of healthcare workers were performed to better understand barriers as well as facilitating factors associated with success.

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2. Methods

A CrAg screening and treatment program was implemented at 11 Kampala Capital City Authority (KCCA) clinics beginning in December 2015.[10] CrAg screening was reflexively performed in the laboratory for all CD4 cell count results $\leq$100 cells/μL. Main features of this program were: clinic-wide medical education sessions on cryptococcal meningitis and screening recommendations, laboratory staff training in performing CrAg screening and reporting results using CrAg lateral flow assay (LFA) point-of-care kits, a research nurse to identify a clinic point-person responsible for screening, training this point-person in operational aspects of screening and troubleshooting clinic-specific difficulties, and a system for ongoing clinic review and feedback. Success for the implementation study was defined as having >90% of asymptomatic CrAg+ persons treated, who were eligible for treatment, initiating fluconazole within 2 weeks of CrAg+ result, and initiating ART within 4 weeks of CrAg+ result. To evaluate the above implementation study, qualitative interviews were performed with several of the research staff and clinic staff participating in the screening program, to evaluate barriers and facilitating factors for future implementation.

2.1. Qualitative interviews

2.1.1. Research team and reflexivity. Interviews were conducted at the participant's clinic by the first author S.M.L. S.M.L. participated in the parent study for approximately 9 months before the interviews and collected data for the parent study.

The interviewer knew the study nurses for the duration of her involvement with the parent study. The study nurses had worked in each clinic for 2 months and then acted as a resource to that clinic for multiple subsequent months. Thus, the clinic participants knew the study nurses well but not the interviewer, SML.

2.1.2. Study design. The study was completed using grounded theory as methodologic orientation and theory. The study nurses contacted the clinic participants by phone or in person to assess willingness to participate in an interview. The sample was a convenience sample. Clinic staff from 6 of the clinics where CrAg testing was implemented were interviewed as were as the 2 coordinating research nurses. Clinic staff participants included doctors, clinical officers, nurses, pharmacists, and laboratory technologists. The study nurses were interviewed alone. The clinic staff members were either interviewed with just the first author or with the first author and the study nurse who had worked at the same clinic as the clinic staff member. The selection and numbers of informants in this program evaluation was selected to gain a breadth of perspectives.

2.1.3. Ethics approval. The CrAg screening program was considered to be routine care, per HIV treatment guidelines in Uganda. Ethical approval was obtained for the parent study carrying out the programme, and measuring outcomes. We simply interviewed the staff who were working in this program. No patients were interviewed for the study.

2.1.4. Data collection. Data were collected through semi-structured one-time interviews. The interviews were recorded and then transcribed. The interviewer took notes in addition to the recording. Both recordings and notes were used for analysis. The first author conducted all interviews from March to April 2017. There were two interview guides. One interview guide was directed towards clinic staff, regarding their experience with the CrAg program, challenges, benefits, and recommended changes to help others implement CrAg testing. The second interview guide was for coordinating research nurses, regarding clinic sites they worked with, barriers to rollout, difficulties during the program, and department specific questions related to the laboratory, pharmacy, and clinicians. The interview guides were piloted with staff from the Infectious Disease Institute.

The interviews of the study nurses took 90 minutes ,whereas the interviews of the clinic staff took 15 to 20 minutes. The transcripts were not returned to the participants, although findings were discussed with study nurses who concurred that the interviewer's findings were consistent with their experience.

2.1.5. Analysis. Given this is a program evaluation, the design uses descriptive qualitative methods. The results were categorized by site and role, specifically as clinicians (physicians, clinical officers, and nurses), laboratory technicians, or pharmacy personnel. The data were analyzed for themes of drug availability, testing supply availability, turnaround time, and overall impressions of the CrAg screening program. The first author coded the data. A fishbone diagram was created but no coding tree was generated. Recommendations for future CrAg screening and treatment programs were also obtained and compared. Data analysis was done using Microsoft Word. Quotations were made from the data, and they were identified by participant role.

The data presented and themes found were compared for consistency. The major themes were presented clearly in the findings. Minor themes were also explored. All data reporting was done according to the Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist.[11]

3. Results

In March and April 2017, 13 clinic staff and 2 research nurses were interviewed. Seven clinicians were interviewed, 4 laboratory technicians, and 2 pharmacists. Given the relationships between the study nurses and the clinic staff as well as the first author and the study nurses, interviews were readily accepted.

One initial barrier the research nurses tasked with overall education and implementation noted was resistance from staff to participate in CrAg screening without additional compensation. However, over time, clinic staff became willing to participate given that CrAg screening was recommended by Ugandan national HIV guidelines. When educated about how CrAg screening improves patient health, there was more acceptance of the program.

> "Some of the staff in the health facilities expected to have a <salary> top-up, in terms of money . . . ." "But finally they came to realize it was beneficial to the client, and they have been doing it . . . They have been doing it routinely." [Research nurse]

We found that although resistance to adding a screening program to a busy HIV clinic without additional staff incentives was difficult, once the staff could see the benefits for the patient, the program ran smoothly.

Facilitating factors are noted in Table 1. A critical facilitating factor was selecting a point-person for CrAg testing at each site. This point of contact for study staff was responsible for following up CrAg-positive patients, and ensuring that they got timely evaluation and treatment. These facilitators helped to clearly define who was to manage patients and ensure that follow-up occurred.

There were a number of barriers to the program (Table 2), including an inadequate supply of fluconazole. One medical

Table 1

Factors facilitating success in CrAg screening and treatment programs.

Identification of a point-person for the program
Recommendations for CrAg screening per national guidelines
Education about the impact of the program
Adequate fluconazole supply
Adequate supply of CrAg testing kits
Good relationships between trainers and clinic staff
Education about cryptococcal disease
Supervision and feedback, especially at the beginning of the program

CrAg = cryptococcal antigen.

officer noted his clinic always had fluconazole if a study was in place. If a research study was not running, however, the clinic had occasional stockouts. At a smaller clinic pharmacy, it was noted:

> "We dispense fluconazole if we have it." [Dispensing Nurse] "Do you usually have <fluconazole>?" [Interviewer] "No, sometimes it is out of stock." "How often is it out of stock?" "It is usually out of stock . . . . We tell them to go and look for it elsewhere." "Do you think they usually get it elsewhere?" "I don't think that they get it." "How often would you give them a partial amount?" "Most of the time."

> "Previously the challenge had been the availability of the fluconazole. Currently we have a steady supply" (in the setting of a donation of Diflucan (fluconazole) to Uganda). [Medical Officer]

Overall supply of fluconazole varied by location and size of clinic. Patients could generally not afford fluconazole if it was not provided and a patient's ability to go to a different public clinic where the drug might be available was limited by transportation costs.

Another barrier to the CrAg screening program was turnaround time for CD4 cell count and CrAg testing. Reflex CrAg testing could be done either in the laboratory at the clinic site, or at a central lab. The clinics that did on-site CD4 testing used the Pima CD4 platform Alere. The CD4 counts using the Pima would be done the day of the patient's visit or the next day. Subsequently, CrAg testing would be performed on-site either on the day of the visit or the next day. Other sites sent blood samples for CD4 testing to a central laboratory where CrAg testing would also be done reflexively. Clinic staff would be called within 1 week when a sample was CrAg-positive, but paper printouts were not received for up to 2 weeks. Most clinicians noted the turnaround time had decreased under the CrAg testing program; however, 2 clinicians still felt the 1 to 2 week turnaround time for laboratories sent to CD4 testing hubs was acceptable. On-site testing with fast turnaround time was preferred if the capability was there, but send-out centralized testing was acceptable.

Table 2

Barriers to CrAg screening and treatment.

Fluconazole shortages
CrAg testing shortages
Staff wanting extra payment for program
Contacting patients –wrong phone numbers, lack of mobile phone airtime, poor charting
Patients not having funds for transport back to clinic
Performing CrAg titers—timing and training
Understaffing of clinics
Lack of education about cryptococcal infection, screening, and preemptive therapy
Poor adherence to fluconazole

CrAg = cryptococcal antigen.

A third barrier to the CrAg program was with performing CrAg titers. Two laboratory personnel cited this as a problem. Performing titers required serial dilutions of the samples to identify the correct titer. This was feasible eventually for all staff but was unfamiliar and required additional training and time, presenting challenges initially.

> "How did you overcome challenges?" [Interviewer] "Re-training whenever there is a gap-like the CrAg titer. Some labs had a problem catching up with the CrAg titer. But we did re-training." [Research Nurse]

> "Is it a burden <to do titers>?" [Interviewer] "It takes some time." [Clinic Lab Manager] "Is it hard or just time?" "It is just time. If you know what you are doing it is not hard because we were trained. They trained us . . . what I find the challenge people get is the titration. So as you train you have to put much emphasis on it."

At all clinic laboratories, the technicians were able to eventually do the CrAg titers. Some technicians required more training than the initial standard training but all were competent by the completion of the study.

A final CrAg program barrier was patient retention-in-care, although this was in a minority of patients as only 7% of patients were lost to follow-up. There were a number of difficulties with patient follow-up, as the patients did not always return to clinic, clinics did not always have correct contact information documented, and staff did not always have mobile phone airtime to call patients on their personal phones.

> "When they contact the client, sometimes they don't have the contacts. In the case of someone turns positive. Calling them back may not be easy. That's a general problem." [Research Nurse] "Do patients change their phones a lot or what is the problem?" [Interviewer] "They don't change. Sometimes they don't have. We call and they are not available. Or sometimes it is a network problem. You can't tell." [Research Nurse] "We get wrong numbers. Promise I'm coming. Phone off." [Medical Officer] "The challenge was . . . the results would come in. The CrAg+. You call them in and someone says I am coming in today. Someone does not come in. Yet you really want to attend to this person so fast." [Clinical Officer]

Overall, none of the staff felt the CrAg screening program was a burden. Many expressed pride about being able to understand the CrAg screening program and help patients. When asked what was best about the program, they noted seeing "patients improving."

The results from this field analysis were compiled into a fish bone diagram as seen in Figure 1. This diagram highlights the steps required for an HIV clinic to implement CrAg screening, along with possible barriers.

4. Discussion

In this study, we found that adequate supplies of fluconazole and CrAg testing kits, timely patient follow-up, and turnaround time of results were key factors in implementing a successful CrAg

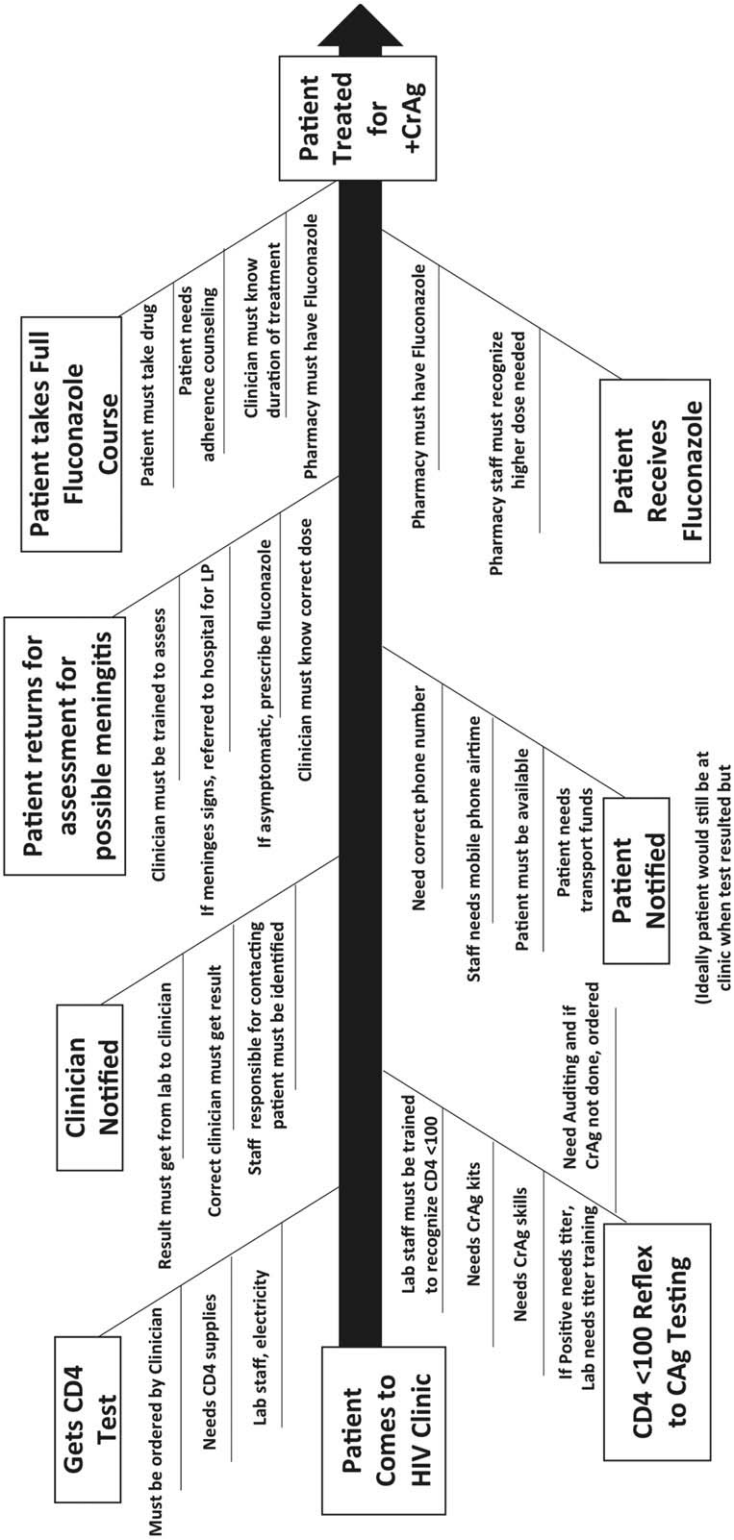

Figure 1. Fishbone diagram of cryptococcal antigen screening program cascade of care and possible programmatic barriers.

screening program. Although both CrAg LFA kits and fluconazole are on the National HIV formulary, stockouts are common and directly affect patient care. The CrAg screening recommendation by Ugandan National HIV guidelines remains integral to the success of the program, as overburdened and understaffed clinics are otherwise reluctant to adopt additional screening. Collaboration with Ministries of Health for support with enforcing national guidelines, and procuring supplies is paramount to the success of the program.

Our healthcare workers preferred point-of-care CD4 and CrAg testing performed at the individual clinic lab due to faster turnaround time of results as compared to blood samples being

sent to a centralized laboratory. Most of our clinic laboratories have Pima CD4 instruments, which could be point-of-care, but results generally return to the clinician the next day. Reflexive laboratory-based CrAg testing is clearly superior to physician ordered CrAg testing[8,12]; however, this reflex testing is performed depends on the resources and system capacity of each individual setting.

One additional concern of our laboratory workers was that the process of performing serial dilutions to obtain titers was time consuming. A 2-band CrAg LFA categorizing a high (≥1:160) or low titer would be advantageous, as no additional dilutions would be necessary. This may assist with laboratory technician training, and eliminate the time needed to perform titers.

One barrier to the CrAg screening program was loss-to-follow-up of patients. Of those lost to follow-up (7%), the majority were lost before returning to clinic for CrAg results. Efficient clinic-wide systems such as a comprehensive chart filing system, obtaining correct patient contact information, and sustainable mechanisms for contacting patients are needed. These are needed not just for CrAg screening programs, but also for successful HIV care in general. Efficient turnaround time of CD4 and CrAg results is essential to reduce mortality before first follow-up clinic visit. Although the use of point-of-care CD4 testing decreased turnaround time, the ideal of having the patient wait for their CD4 and CrAg result before leaving the clinic visit was not achieved.

Finally, for successful implementation outside of the context of a study, there is a need for ongoing training for clinicians, laboratory, and pharmacy staff, a steady supply of fluconazole, and enthusiasm for an additional program in the setting of very busy clinics.

4.1. Limitations

This study was performed in a subset of sites in Kampala, Uganda, and thus may not be generalizable to rural areas or other countries where barriers and facilitating factors may be different. We worked with sites that have participated in clinical trials in the past. As the leadership of these clinics was highly receptive to our evaluation, this may not be generalizable to other settings.

4.2. Recommendations for future implementation

Success for our implementation study was judged by having a functional, integrated screening system in each clinic thus demonstrating feasibility and acceptability. The success of our cryptococcal screening program relied on clinic-wide education and provider-specific training in tasks associated with the program. Identification of a clinic staff member to be a point-person for the program was central to the success of this program. We used reflexive lab-based testing successfully, as has been recommended by other groups. Finally, feedback regarding weaknesses within the system is important for an efficient program. Adequate supplies of CrAg tests and fluconazole are paramount, and coordination through the Ministry of Health to ensure adequate supplies, targeted health care worker educational programs, and measurement of outcomes would result in a stronger national screening program. Implementation efforts must continue to translate this life-saving intervention into routine HIV care.

Author contributions

Conceptualization: Sarah M. Lofgren, Elizabeth Nalintya, David Meya, David R. Boulware, Radha Rajasingham.
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References

[1] Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 2017;17:873–81. Epub 2017/05/10. doi: 10.1016/S1473-3099(17)30243-8. PubMed PMID: 28483415.
[2] Williamson PR. The relentless march of cryptococcal meningitis. Lancet Infect Dis 2017;17:790–1. Epub 2017/05/10. doi: 10.1016/S1473-3099(17)30245-1. PubMed PMID: 28483416.
[3] Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. Clin Infect Dis 2014;59:1607–14.
[4] French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 2002;16:1031–8.
[5] Ramachandran A, Manabe Y, Rajasingham R, et al. Cost-effectiveness of CRAG-LFA screening for cryptococcal meningitis among people living with HIV in Uganda. BMC Infect Dis 2017;17:225.
[6] Mfinanga S, Chanda D, Kivuyo SL, et al. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial. Lancet 2015;385:2173–82.
[7] World Health Organization. Guideline for managing advanced HIV disease and the timing for initiating antiretroviral therapy 2017 [31 July 2017]. Available at: http://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/.
[8] Vallabhaneni S, Longley N, Smith M, et al. Implementation and operational research: evaluation of a public-sector, provider-initiated cryptococcal antigen screening and treatment program, Western Cape, South Africa. J Acquir Immune Defic Syndr 2016;72:e37–42.
[9] Govender NP, Roy M, Mendes JF, et al. Evaluation of screening and treatment of cryptococcal antigenaemia among HIV-infected persons in Soweto, South Africa. HIV Med 2015;16:468–76.
[10] Nalintya E, Meya DB, Lofgren S, et al. A prospective evaluation of a multisite cryptococcal screening and treatment program in HIV Clinics in Uganda. J Acquir Immune Defic Syndr 2018;78:231–8.
[11] Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349–57.
[12] Greene G, Sriruttan C, Le T, et al. Looking for fungi in all the right places: screening for cryptococcal disease and other AIDS-related mycoses among patients with advanced HIV disease. Curr Opin HIV AIDS 2017;12:139–47.