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National coverage of reflex cryptococcal antigen screening: A milestone achievement in the care of persons with advanced HIV disease

HIV/AIDS-related mortality accounts for almost one-third of deaths in South Africa (SA), and globally ~15% of AIDS-related mortality is associated with cryptococcal disease.[1,2] The burden of cryptococcal meningitis has remained high in SA among severely immunosuppressed HIV-positive patients, despite substantial improvements in antiretroviral treatment (ART) coverage over the past decade.[3] Approximately one-third of patients entering HIV care in the SA public sector in 2016 had advanced HIV disease (defined as a CD4+ T-lymphocyte count <200 cells/μL), and 17% had a CD4+ count <100 cells/μL.[4] In 2011, the World Health Organization (WHO) recommended that countries consider integrating cryptococcal antigen (CrAg) screening into HIV programmes to detect cryptococcal disease at an earlier point in its trajectory, followed by pre-emptive antifungal treatment to reduce AIDS deaths.[5] The CrAg screen-and-treat intervention therefore aligns with the Joint United Nations Programme on HIV/AIDS (UNAIDS) over-arching goal to reduce global AIDS deaths to >500 000 by 2020, and has been included in a new WHO-recommended package of care for managing advanced HIV disease.[6] Since it was first included in SA's national strategic plan for HIV/AIDS, tuberculosis and STIs in 2012, evidence has mounted in favour of the CrAg screen-and-treat intervention. A randomised controlled trial from Zambia and Tanzania revealed that pre-ART CrAg screening with pre-emptive antifungal treatment for patients with a CD4+ count <200 cells/μL, coupled with 4 weeks of community-based ART adherence support, resulted in a 28% reduction in all-cause mortality at 12 months.[7]

In the light of these data, on 1 October 2016 the National Health Laboratory Service (NHLS) implemented a ground-breaking service to provide the world's first and largest national laboratory-based CrAg screening programme aimed at detecting early cryptococcal disease before progression to meningitis in all HIV-seropositive patients with a CD4+ count <100 cells/μL across SA. The launch of the programme was the culmination of a long, successful, nationally co-ordinated effort by the National Institute for Communicable Diseases (NICD), the National Department of Health (NDoH), the NHLS and other local and international partners.

Several activities preceded this important milestone. Following a circular (circular no. H116/2012) from the Western Cape provincial government to screen all patients whose CD4+ count was <100 cells/μL, a provider-initiated CrAg screening initiative was implemented in the Western Cape in mid-2012. No clinical training was offered, and no feedback was provided to clinicians in terms of the proportion of eligible patients screened at their clinics. A retrospective evaluation showed that just over a quarter of eligible patients were screened under this initiative; compared with those who were screened, those who were not screened were almost twice as likely to develop disseminated cryptococcal disease.[8] In contrast, a simpler laboratory-based approach using remnant CD4+ samples reflexively tested for CrAg if the CD4+ count was <100 cells/μL was simultaneously piloted in four districts in Gauteng and Free State provinces from 2012 through to 2015.[9,10] This initiative was paired with intensive clinician training on how to appropriately manage CrAg-positive patients identified through reflexed testing. In this scenario, almost 100% of eligible patients were screened for cryptococcal antigenaemia.

Implementation of these two contrasting approaches offered a valuable opportunity for parallel evaluation. A detailed cost-effectiveness model demonstrated that laboratory-based reflex CrAg screening was simpler and more cost-effective than a clinician-initiated approach, allowed for almost universal screening coverage, and potentially saved more lives.[11] In 2014, the NDoH adopted a detailed screen-and-treat clinical algorithm for seamless integration into the HIV care cascade. This algorithm has subsequently been included in the Standard Treatment Guidelines/Essential Medicines List at all healthcare levels.[12,13] Several skills-based training workshops for management of cryptococcal disease were developed and cascaded downwards to healthcare workers at facility level. On the NHLS side, the initiative facilitated the evaluation of several CrAg assays and workflow analyses for scaling up state laboratory services.[14-17] The NHLS also undertook intensive training of laboratory personnel based on standard operating procedures and on-site assessment of laboratory work flow, enabling integration into existing CD4+ services. The development of a national laboratory proficiency testing scheme (PTS) by the NICD/NHLS completed the final phase of service delivery implementation; the first batch of PTS samples was distributed to NHLS CD4+ laboratories in November 2016. On the NDoH side, a public health planning and resource allocation exercise was conducted, specifically to ensure that fluconazole was procured and made available at all healthcare levels.

A laboratory dashboard for CrAg has been integrated into a broader SA HIV programme dashboard, with two key indicators: CrAg screening coverage and prevalence of cryptococcal antigenaemia. Good linkage to laboratory CrAg results is the cornerstone of this programme. Several methods are being implemented to ensure that CrAg-positive patients return for clinical evaluation and begin appropriate antifungal treatment. Weekly CrAg results for action (RFA) reports are emailed to registered end-users (currently including district/facility managers or registered healthcare workers at 220 facilities in 32 districts). RFA reports are formatted as line-lists of patients with a positive CrAg result who need urgent follow-up.

Looking ahead, the impact of the CrAg screen-and-treat programme on patient outcomes will be evaluated by clinic-based field surveys over the next 5 years through the NICD's CAST-NET project. Several interventions will also be explored to optimise implementation of CrAg screen-and-treat, including intensive refresher healthcare worker training with novel methods of delivery, patient education, enhanced delivery of laboratory results to clinicians, and risk stratification of patients by piloting semi-quantitative CrAg testing on reflexively tested blood specimens.[18]

Through this national CrAg screening initiative, 276 125 patients were screened during the first year (October 2016 through to September 2017) with 95% coverage, and 15 757 (5.7%) were identified with cryptococcal antigenaemia,[19-21] highlighting both the large burden of advanced HIV disease and opportunistic infections in SA and the urgent need to recruit these very ill patients into care.

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