NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

The Impact of COVID-19 Public Health Measures on Diagnosis of Advanced HIV Disease, Cryptococcal Antigenaemia and Cryptococcal Meningitis in South Africa

15 June 2020

BACKGROUND

Cryptococcal meningitis continues to be one of the top causes for HIV-related deaths each year, across the African continent and in South Africa specifically, and is most common in persons with advanced HIV disease (CD4 count less than 200 cells/µL).1–3 Cryptococcal antigen (CrAg), a highly-specific biomarker for cryptococcal disease, can be detected in blood weeks to months prior to the onset of cryptococcal meningitis symptoms.[4] Routine screening for CrAg is operational nationwide at all public-sector CD4 laboratories, where blood samples with a CD4 count of less than 100 cells/µL, a marker of *very advanced HIV disease*, are automatically screened for CrAg so patients can be subsequently assessed for meningitis and treated with appropriate antifungal therapy.[5,6]

Advanced HIV disease and cryptococcal disease most often occurs in individuals who are newly diagnosed and have not yet initiated antiretroviral therapy (ART) or those who have previously been on ART but have interrupted treatment.[7,8] Access to HIV care is key to identifying patients with advanced HIV disease and appropriately screening for CrAg so that patients can be either pre-emptively treated to prevent development of cryptococcal meningitis or can be safely and rapidly initiated on ART.[9]

The spread of coronavirus disease (COVID-19) to South Africa in early 2020 has impacted on South Africa's health system and also led to public health measures to reduce the spread of the virus.[10] The South African government initially recommended social distancing in mid-March, banned all large gatherings and restricted international travel. This transitioned to a full-scale lockdown starting on the 27 March, after which the movement of people and use of public transit was strictly controlled and limited to essential workers or the procurement of essential goods. This lockdown, later known as Level 5 lockdown, was relaxed on 1 March 2020 as the country moved to Level 4 lockdown. During this period, people in selected jobs were able to return to work, and public transit resumed, though at a limited capacity. Additionally, public exercise hours and a night-time curfew were instated.

Using routine laboratory and clinical surveillance data, we analyse the impact of these COVID-related public health restrictions on public health sector a) advanced HIV disease diagnosis, b) routine CrAg screening, and c) cryptococcal meningitis diagnoses in South Africa from February through to May 2020.

METHODS

CrAg test results are captured along with CD4 results in the National Health Laboratory Service (NHLS) laboratory information system, TrakCare. The NICD Surveillance Data Warehouse (SDW) routinely extracts and processes data stored in the NHLS TrakCare system for use in NICD surveillance. To obtain surveillance results in this report, epidemiologists from the NICD's Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM) worked with SDW to compile an extract of all CD4 tests and accompanying CrAg results for all NHLS laboratories from 3 February 2017 through to 24 May 2020. All data were de-duplicated using laboratory episode numbers for test-level data and SDW-assigned unique ID numbers for patient-level data.11 Cryptococcal meningitis case data were obtained from the NICD GERMS-SA national surveillance database and we included CSF-positive cases confirmed in the laboratory by culture, India ink, or CSF cryptococcal antigen testing.

RESULTS

Over the 16-week period from 3 February 2020 through 24 May 2020, a total of 72 144 blood CrAg tests were performed on samples with CD4 <100 cells/µL received from public health sector facilities, of which 5 664 (7.9%) returned a positive result. In the 6 weeks prior to the implementation of COVID-related social distancing and lockdown, an average of 5 613 CrAg tests were performed weekly. A decrease in weekly testing volumes was then observed following the implementation of COVID-19 lockdown measures on 27 March - the most notable drop occurring the week of 27 April, with only 2 224 screening tests performed as the country transitioned from lockdown level 5 to level 4 (Figure 1).

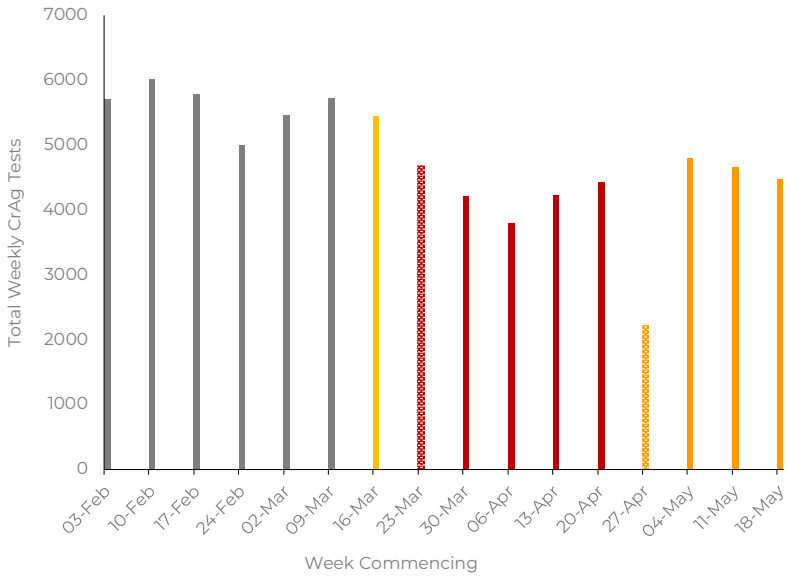

Figure 1. Total CrAg Tests by Week in Public Health Sector Starting 3 February to 25 May 2020, South Africa, n = 72 144

During the period of declining test volumes following lockdown, an initial spike in the proportion of positive CrAg tests was simultaneously observed between the weeks of 23 March and 13 April (Table 1). This indicates that, although fewer individuals received CrAg screening during the initial phase of lockdown, those who were screened had a higher likelihood of testing positive for disseminated cryptococcal disease. .

Table 1. Total CrAg Tests, Positive CrAg Tests and Positivity Rate in the Public Health Sector by Week Starting 3 February to 25 May 2020, South Africa, n= 5 664 / 72 144 (7.9%)

Week commencing	COVID-19 national intervention	Positive Tests	Total Tests	Percent Positive
03-Feb-20	None	394	5 698	6.9%
10-Feb-20	None	412	6 020	6.8%
17-Feb-20	None	447	5 779	7.7%
24-Feb-20	None	336	5 009	6.7%
02-Mar-20	None	384	5 458	7.0%
09-Mar-20	None	392	5 719	6.9%
16-Mar-20	Social distancing	394	5 441	7.2%
23-Mar-20	Social distancing/Lockdown	374	4 679	8.0%
30-Mar-20	Lockdown – Level 5	388	4 214	9.2%
06-Apr-20	Lockdown – Level 5	295	3 799	7.8%
13-Apr-20	Lockdown – Level 5	333	4 225	7.9%
20-Apr-20	Lockdown – Level 5	328	4 434	7.4%
27-Apr-20	Lockdown – Level 4/5	160	2 224	7.2%
04-Mar-20	Lockdown – Level 4	355	4 785	7.4%
11-Mar-20	Lockdown – Level 4	316	4 660	6.8%
18-Mar-20	Lockdown – Level 4	356	4 472	8.0%

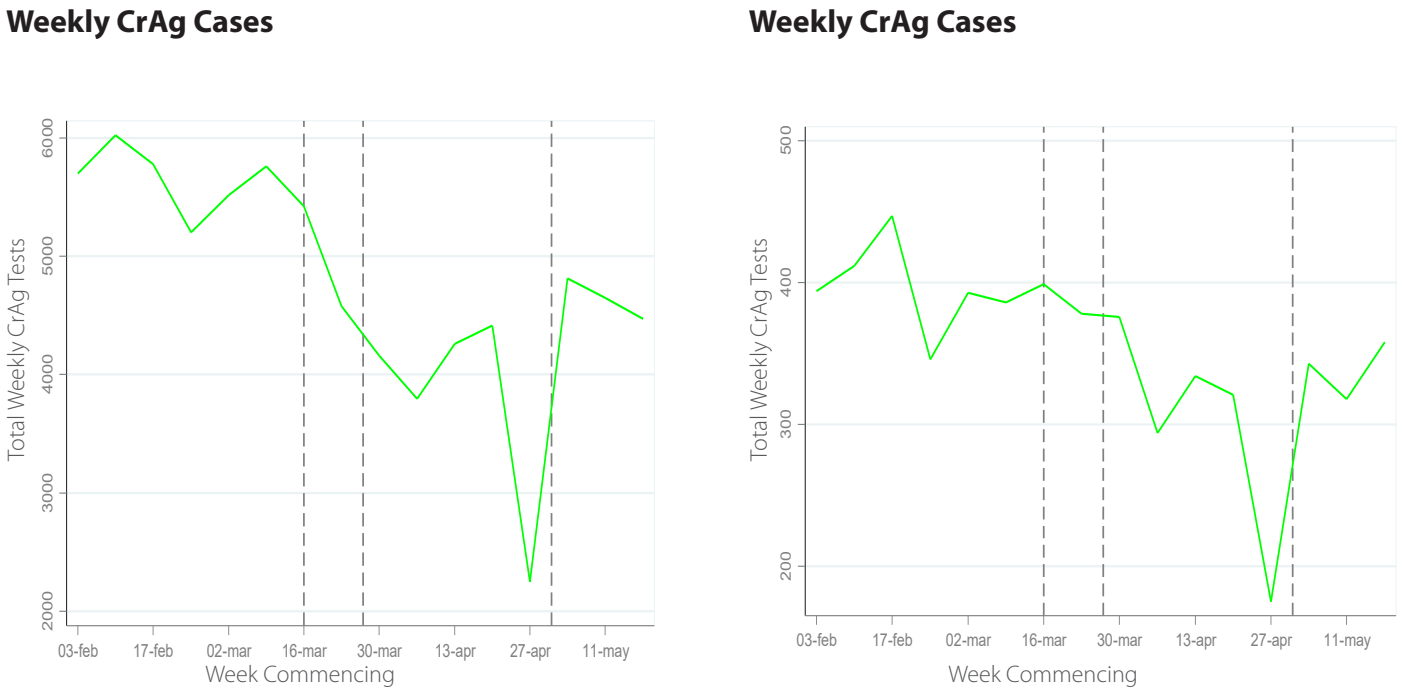

Figure 2. Weekly CrAg Tests and Cases in the Public Health Sector during COVID Restrictions, 3 Feb 2020 – 24 May 2020, South Africa (dashed vertical lines represent lockdown events)

Although the percentage of positive CrAg tests did increase during the initial weeks of lockdown, total weekly numbers of CrAg-positive tests still decreased sharply, mirroring the trend observed in weekly testing numbers (Figure 2). This indicates that, although individuals who were screened for CrAg during the initial weeks of lockdown were more likely to be CrAg-positive, overall fewer CrAg-positive individuals were screened over the period, suggesting the possibility that cryptococcal disease cases went undetected during the period.

Figure 3. Historical Comparison of Weekly CrAg Tests in the Public Health Sector for the Period 3 February to 24 May, n = 72 144 (dashed vertical lines represent lockdown events)

Comparing the trends in weekly CrAg testing volumes during lockdown to those of 2017, 2018, and 2019 during the same time of year, CrAg testing in 2020 followed a similar trend leading up to lockdown as in previous years (Figure 3). However, the decline in testing that began near the time of social distancing was sustained at the onset of lockdown where a recovery was observed in previous years. A similarly pronounced dip in testing numbers was observed across years, with exception of 2019, over the last 2 weeks of April, possibly related to several public holidays occurring at this time. However, although 2020 trends resembled that of previous years, overall testing numbers were considerably lower than those over the same period in the past. .

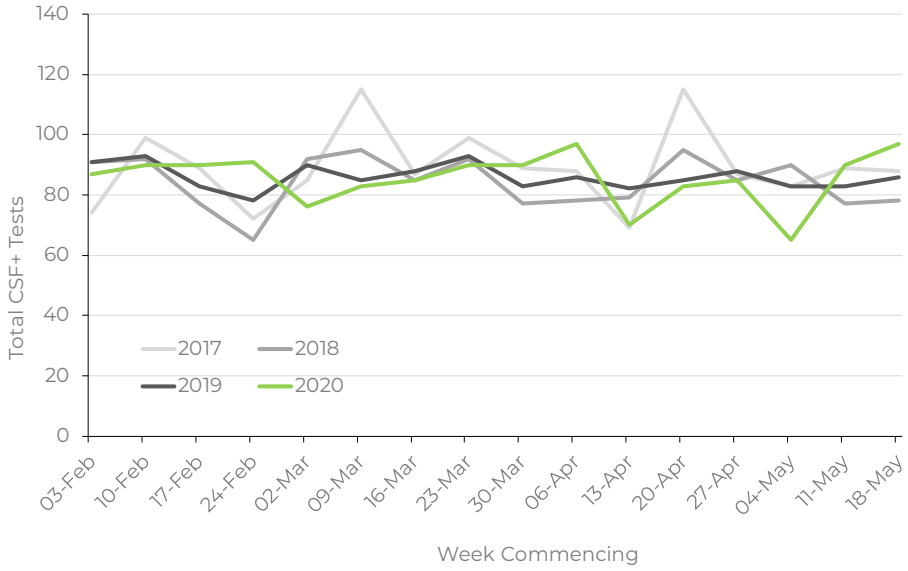

Figure 4. Historical Comparison of Weekly CSF-confirmed Cryptococcal Meningitis Cases in the Public Health Sector for the Period 3 February to 24 May, n = 1 369 (dashed vertical lines represent lockdown events)

The numbers of laboratory-confirmed cases of cryptococcal meningitis during the lockdown period, however, do not appear to have appreciably been affected when compared to previous years (Figure 4).

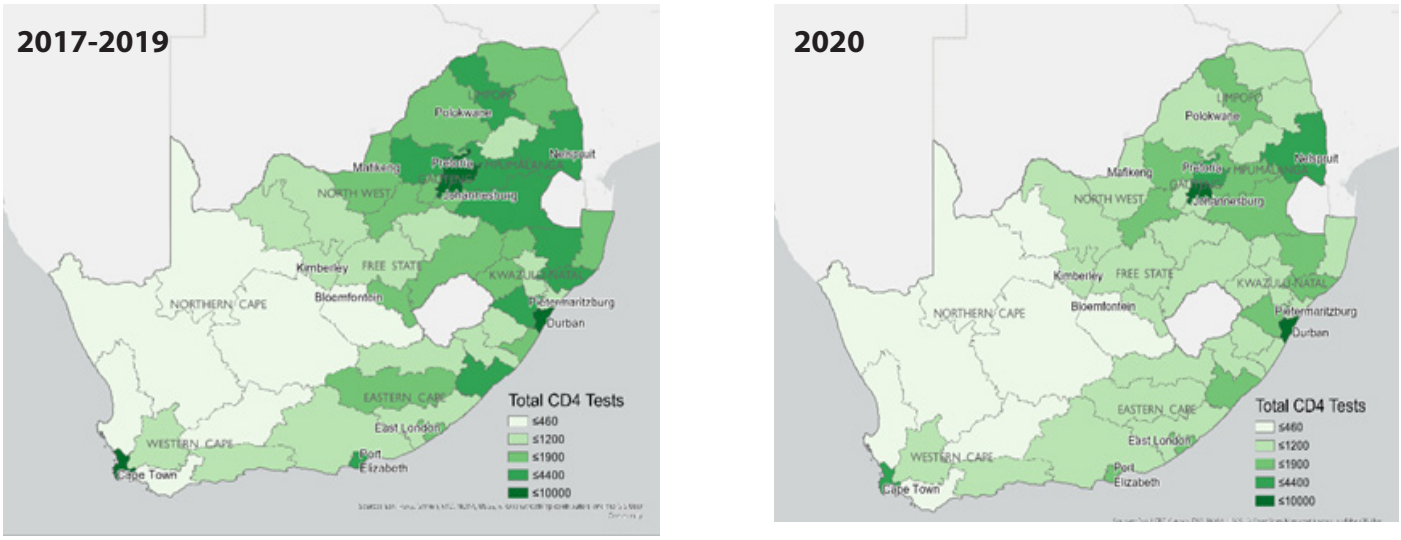

Figure 5. Comparison of the Average of Total CD4 Tests < 200 cells/µL across 2017-2019 to the Total CD4 Tests < 200 cells/µL in 2020 over the same period of 27 March – 24 May, by district

In terms of advanced HIV disease diagnosis, defined as CD4 < 200 cells/µL, a decline in total cases detected was observed across all districts (n=52) in South Africa when comparing the first 8.5 weeks of lockdown period (27 March – 24 May) to the average of the same period for 2017-2019.

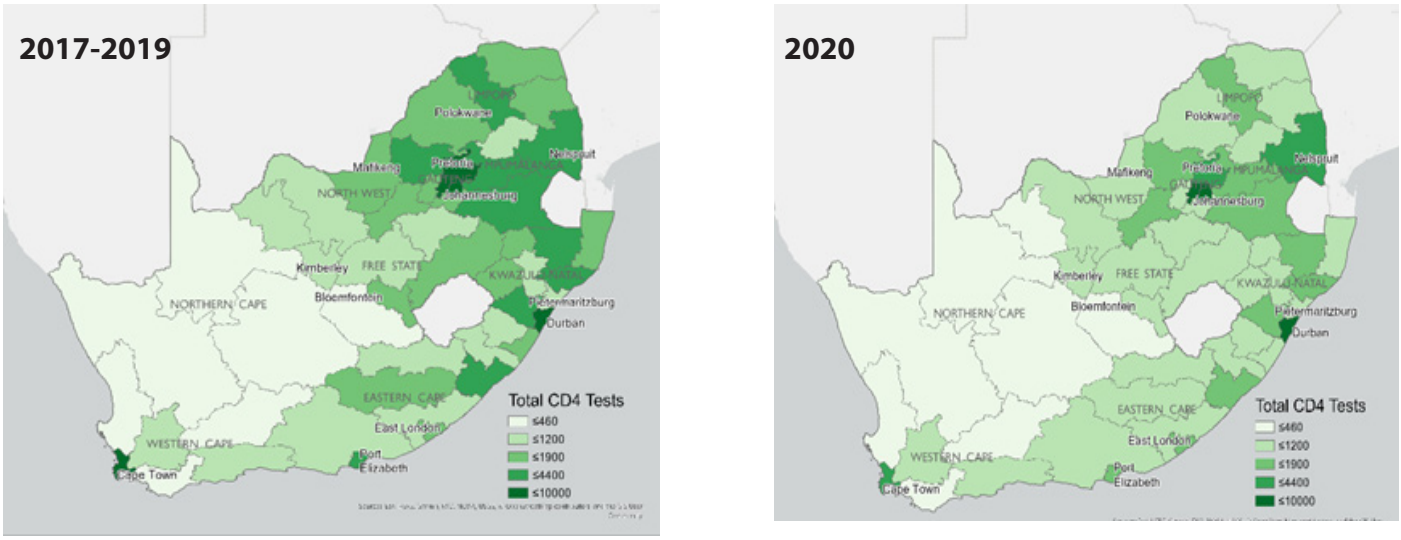

Figure 6. Comparison of Average of Total CrAg Tests across 2017-2019 to Total CrAg Tests in 2020 over the same period of 27 March – 24 May, by district

The 2020 weekly average of CrAg test volumes exhibited a similar decline across all 52 districts over 8.5 weeks of lockdown (27 March – 24 May) when compared to the average weekly average of tests for 2017-2019.

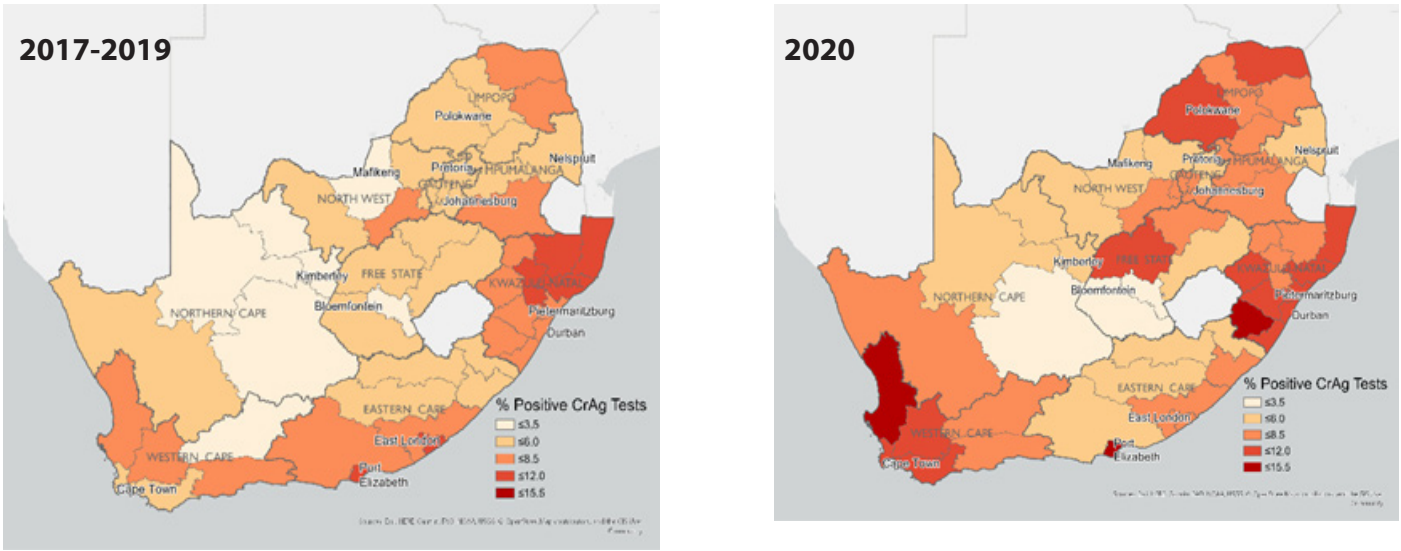

Figure 7. Comparison of the Percent Positive CrAg Tests from 2017-2019 to the Percent Positive CrAg Tests in 2020 over the same period of 27 March – 24 May, by district

The proportion of positive CrAg tests during the 8.5-week lockdown period in 2020 increased in 44 of 52 districts compared to the proportion of positive tests for 2017-2019. The proportion of positive tests was lower than that of previous years in the remaining 8 districts, all rural except one major metropolitan district – Buffalo City Metro containing the city of East London.

[1]Average of total CD4 tests < 200 cells/µL across 2017-2019 calculated by adding all CD4 tests less than 200 cells/µL from 27 March to 24 May for 2017, 2018, and 2019 and dividing by 3

[2] Average of total CrAg tests across 2017-2019 calculated by adding all CrAg tests from 27 March to 24 May for 2017, 2018, and 2019 and dividing by 3

DISCUSSION

During the COVID-related social distancing and lockdown period beginning on 16 March 2020, a general decline in CrAg screening as well as diagnoses of advanced HIV disease and cryptococcal antigenaemia was observed. Despite a higher percentage of those CrAg-tested being identified as CrAg-positive, overall cryptococcal antigenaemia case numbers were still lower than expected compared to previous years. This suggests that the COVID-related lockdown measures may have led to fewer individuals seeking HIV care in which they would receive a CD4 count (i.e. baseline testing or re-initiation of treatment) and subsequently be identified as having advanced HIV disease and screened for CrAg. On the other hand, CSF-confirmed diagnoses of cryptococcal meningitis do not appear to have been affected by lockdown measures. We speculate that these observations due to several factors, although these explanations are yet to be confirmed. First, lockdown measures severely impacted the availability of public transportation and the ability of individuals to move freely beyond their homes. Secondly, the treatment of COVID-19 cases at public health facilities may have influenced some to avoid healthcare settings and the perceived risk of COVID-19 exposure. These factors may have especially influenced individuals with mild or no symptoms of advanced disease and cryptococcal disease or other opportunistic infections to delay or entirely avoid care-seeking.[12,13] However, in the case of cryptococcal meningitis, the severity of symptoms and urgent need for medical care may have overridden the barriers encountered by lockdown restrictions. [14]

The decline in both advanced HIV disease and cryptococcal disease case detection across all South African districts during the lockdown period demonstrates that this effect of care-seeking delay or avoidance due to lockdown restrictions has occurred nationwide. An increase in the percentage of positive CrAg tests in most districts may indicate that very ill individuals continued to seek care, while asymptomatic cases may have delayed seeking care and are currently missed by routine screening, though further research will be required to confirm this. The 8 districts with a decrease in the percentage of positive CrAg tests were predominately rural, meaning that transportation may have presented an issue even prior to lockdown measures and may have been exacerbated by lockdown to the point that even individuals with symptoms of advanced HIV disease-related illness were unable to seek care.[15] One exception to this was Buffalo City Metro District, which contains the city of East London. It is unclear why both absolute numbers of cases and percentage of positive tests declined here, though East London did have several high-profile COVID outbreaks. This may have contributed to reduced HIV care-seeking behaviour by individuals in the area.

Given the decline in advanced HIV and cryptococcal disease testing during lockdown, it is likely that cases have been missed. Ongoing surveillance will be important to determine if these possible missed cases later lead to a spike in diagnosed cryptococcal meningitis. However, many AIDS-related deaths, including cryptococcal meningitis, occur outside the healthcare system and are thus beyond the scope of routine laboratory-based surveillance, meaning that even if a spike in cases or deaths does indeed occur, it may go undetected. [16]

CONCLUSIONS

COVID-related lockdown measures put in place by the South African government in mid-March have had the unintended consequence of reducing diagnosis of advanced HIV disease and cryptococcal antigenaemia. Increased vigilance in laboratory and healthcare surveillance systems will be necessary to detect and respond to any subsequent increase in the development of cryptococcal meningitis as well as other life-threatening opportunistic infections that may result from this.

REFERENCES

1. Radha Rajasinghma, Smith RM, Park B, Jarvis JN, Govender N, Chiller TM, et al. Update on the Global Burden of Disease of HIV-Associated Cryptococcal Meningitis. Unpublished. 2016;

2. Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):16.
3.
4. National Institute for Communicable Diseases. GERMS-SA annual report [Internet]. 2017 [cited 2020 Jun 12]. Available from: http://www.nicd.ac.za/publications/archives/

5. Kaplan JE, Vallabhaneni S, Smith RM, Chideya-Chihota S, Chehab J, Park B. Cryptococcal antigen screening and early antifungal treatment to prevent cryptococcal meningitis: a review of the literature. J Acquir Immune Defic Syndr 1999. 2015 Apr 15;68 Suppl 3:S331-339.
6.
7. Govender N. Phased implementation of a public health programme: cryptococcal antigen screening and treatment in South Africa [Internet]. 2017. Available from: http://www.nicd.ac.za/wp-content/uploads/2017/12/CAST_NET_4_Jan_2017_protocol_V1_Submit.pdf

8. Govender NP, Glencross DK. National coverage of reflex cryptococcal antigen screening: A milestone achievement in the care of persons with advanced HIV disease. S Afr Med J. 2018 Jun 26;108(7):534-535–535.

9. Calmy A, Ford N, Meintjes G. The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S103-SS105.

10. Chihana ML, Huerga H, Cutsem GV, Ellman T, Goemaere E, Wanjala S, et al. Distribution of advanced HIV disease from three high HIV prevalence settings in Sub-Saharan Africa: a secondary analysis data from three population-based cross-sectional surveys in Eshowe (South Africa), Ndhiwa (Kenya) and Chiradzulu (Malawi). Glob Health Action. 2019 Dec 13;12(1):1679472.

11. World Health Organization. Guidelines for the diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva; 2018 Mar.

12. South African Government. COVID-19 / Novel Coronavirus [Internet]. [cited 2020 Jun 12]. Available from: https://www.gov.za/Coronavirus

13. Bassett IV, Huang M, Cloete C, Candy S, Giddy J, Frank SC, et al. Assessing the completeness and accuracy of South African National Laboratory CD4 and viral load data: a cross-sectional study. BMJ Open [Internet]. 2018 Aug 1 [cited 2019 Dec 10];8(8). Available from: https://bmjopen.bmj.com/content/8/8/e021506

14. World Health Organization. Social Stigma associated with COVID-19: A guide to preventing and addressing social stigma [Internet]. 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/covid19-stigma-guide.pdf?sfvrsn=226180f4_2

15. Logie CH. Lessons learned from HIV can inform our approach to COVID-19 stigma. J Int AIDS Soc [Internet]. 2020 May 4 [cited 2020 Jun 12];23(5). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197953/

16. Mapuroma R, Cohen C, Kuonza L, Musekiwa A, Tempia S, Tshangela A, et al. Healthcare seeking behaviour for common infectious syndromes among people in three administrative regions of Johannesburg, South Africa, 2015: a cross-sectional study. Pan Afr Med J. 2019;33:159.

17. Harris B, Goudge J, Ataguba JE, McIntyre D, Nxumalo N, Jikwana S, et al. Inequities in access to health care in South Africa. J Public Health Policy. 2011;32:S102–23.

18. Karstaedt AS. Profile of cause of death assigned to adults on antiretroviral therapy in Soweto. S Afr Med J. 2012 Jun 28;102(8):680-682–682.

Data Source

National Institute for Communicable Diseases, Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses

Contact

Prof Nelesh Govender:
neleshg@nicd.ac.za

Greg Greene:
gregg@nicd.ac.za

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service