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Short Communication

Preparing for the next pandemic: Lessons from rapid scale-up of SARS-CoV-2 testing in a South African high-throughput automated HIV molecular laboratory

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ABSTRACT

Africa's readiness to respond to the SARS-COV-2 pandemic was tested due to reliance on rapid turn-around-time of polymerase chain reaction results for clinical management, isolation and quarantine decisions. The NHLS HIV Molecular Laboratory in Johannesburg, South Africa, is one of the largest automated HIV molecular laboratories worldwide. Despite its extensive molecular capacity and experience in managing high volumes acquired from a large HIV program, significant challenges were encountered during its rapid transition to large scale SARS-CoV-2 testing. We describe the strategies employed to manage these challenges that resulted in a 30% improvement in SARS-CoV-2 test turn-around-time during the first wave peak during which approximately 25000 samples were tested per month, and further improvement during the second wave peak, with 81% within targeted turn-around-time.

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Africa's initial readiness to respond to the SARS-CoV-2 pandemic was questioned due to reliance on rapid turnaround-time (TAT) of polymerase chain reaction (PCR) results for clinical management, isolation and quarantine decisions. The National Health Laboratory Service (NHLS) HIV Molecular Laboratory in Johannesburg, South Africa, is one of the largest automated HIV laboratories worldwide, performing 1.2 million HIV viral load (HIVVL) tests annually. Despite extensive experience in managing high volumes, significant challenges were encountered during the rapid transition to large-scale SARS-CoV-2 testing. Here, we describe mitigating strategies put in place, particularly related to human resources, biosafety measures, introduction of new assays, and changes in workflow, to avoid moving resources from HIV testing.

The initial testing strategy introduced at government level was based on the World Health Organization's 'test-test-test' recommendation, aiming to couple molecular testing with quarantine and isolation policies (Winning, 2020). However, this approach was quickly confronted by multiple challenges, including the sudden arrival of large volumes of SARS-CoV-2 samples that overwhelmed laboratories' testing capacity.

Perhaps the most challenging component to manage was human resources: staff shortages, staff hesitancy due to fear, infection and high workloads. Managing this required constant intervention. As community transmission increased, staff infections rose, and severe staff shortages were experienced due to self-isolation and quarantine. As a result, all levels of staff, including managers, were temporarily reassigned to SARS-CoV-2 bench duties. Staff from non-molecular laboratories were recruited and utilised according to their skill sets. Rosters subsequently needed rapid revision but staff, now familiar with testing, adapted at short notice. The employment of temporary staff two months into the peak coincided with a matured workflow and reduction in staff anxiety, permitting a seamless move to a 24-h SARS-CoV-2 service.

The provision of a safe work environment was a priority. Immediate SARS-CoV-2 safety training was provided, and protocols introduced, including designated testing areas. Refresher safety training occurred whenever needed, particularly when

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inconsistent use of non-pharmaceutical interventions within and outside the testing space became apparent.

Introducing new assays into the laboratory was facilitated by using existing equipment. However, early in the pandemic, verification of new tests under time constraints was problematic. The laboratory had only the Food and Drug Administration Emergency Use Authorization (FDA-EUA) (FDA, 2017), no standardised protocols as routinely used in molecular evaluations nor local authority guidelines for testing, and was without suitable testing material. The laboratory validated the cobas SARS-CoV-2 Qualitative assay (cobas assay) (Roche, 2020) and the Abbott RealTime SARS-CoV-2 (*m*2000 assay) (Abbott, 2020) shortly after receiving the FDA-EUA. The lack of detailed manufacturer-led validations and the abbreviated performance review by the FDA left laboratories to resolve problems that would ordinarily have been resolved prior to market entry, e.g., determination of lower limit of detection (LoD) using copies/mL for the cobas assay. The cobas assay evaluation was hindered by a lack of testing material, in particular, clinical samples with low level detectable viral RNA, and locally produced reference material that contained the DNA sequence to which the Target 2 probe (E gene) of assay bound but not Target 1 (ORF 1a/b gene) and for which the viral load had not been quantified.

Internationally peer-reviewed HIV (WHO, 2017) and local respiratory validation protocols were adapted for the cobas assay. Clinical performance had to be evaluated comparing new assays due to the lack of a SARS-CoV-2 molecular reference assay. Positive clinical specimens were diluted to verify clinical accuracy and sensitivity at lower levels of detectable viral RNA. While precision was verified for Target 2 only and LoD was partially verified for the cobas assay using the local reference material, these results were adequate for conditional approval by the NHLS Virology Expert Committee, pending further evaluation when material became available. Subsequently, well characterised commercial material was used to complete the LoD and precision analyses, which proved to be significant when determining whether variants, including the "South African" B.1.351 variant, could be detected. The *m*2000 validation included more clinical and analytical data at the outset. However, complex analyses were required when comparing results of the two assays, particularly when determining clinical sensitivity at lower levels of viral RNA because of differing combinations of PCR targets and cycle threshold (Ct) calculation algorithms. The *m*2000 assay combined E and N gene target was found to be, on average, 10 Cts lower than the cobas assay Target 2. Later, acceptable external quality assessment results confirmed the reliability of both assays.

The complexity of pre-and post-analytical workflow of large volumes of specimens is often overlooked; this was demonstrated more clearly during this epidemic. In contrast to the automated HIVVL workflow, which requires minimal hands-on time, SARS-CoV-2 tests required manual preparation. This encompassed physical inspection of samples, labelling of additional tubes and aliquoting of swabs received in medium, or cutting and immersing dry swabs into a fluid matrix, followed by mixing and aliquoting, then manual loading/unloading of the instruments. Following a comprehensive analysis of the new workflow, staff adapted to the unfamiliar process by introducing simple measures like standardising sample preparation procedures between different assays and using excel spreadsheets to streamline processes from sample receipt to storage. In addition, remote access to the laboratory information system and instrument software enabled rapid release of results, cataloguing of residual samples and rapid retrieval of invalid samples for repeat testing. These process changes successfully increased the percentage of samples reported within the acceptable TAT of 48 h from collection.

The laboratory started performing SARS-CoV-2 testing in April 2020, overlapping with the highly restrictive level 5 lockdown, during which approximately 97% of HIVVL and 50% of SARS-CoV-2 tests were reported within TAT. This outcome was probably due to a lockdown-related drop in expected HIVVL and relatively low SARS-CoV-2 test requests (Figure 1). After transitioning to the less restrictive level 4 lockdown in May 2020, TAT dropped to 14% and 67% for SARS-CoV-2 and HIVVL, respectively, as sample volumes for both tests increased and reagent supply was unstable. The introduction of the improvement strategies resulted in an increase to 50% within TAT for SARS-CoV-2 tests during the peak month of July 2020 when 28 613 samples were tested and reaching >90% as the first COVID-19 wave subsided. With the arrival of the second

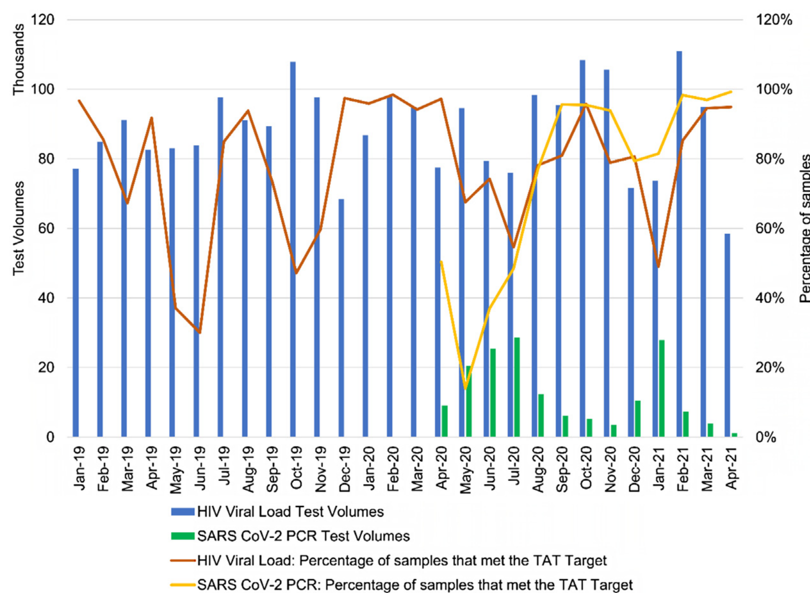

Figure 1. The comparative HIV Viral load (HIVVL) volumes for 2019, 2020 and 2021 and SARS-CoV-2 volumes for 2020 and 2021. Percentages within turnaround time (TAT) for SARS-CoV-2 and HIV viral load (HIVVL) displayed an upward trend from June 2021 and after July 2021, respectively. The drop in HIVVL percentage within TAT in November 2021 was due to instrument breakdowns. The second COVID-19 wave started during mid-December, with the January 2021 volumes comparable to the July 2021 peak. HIVVL was significantly impacted by supplier reagent and consumable shortages in January 2021.

wave coinciding with the Christmas vacation period, TAT dropped to 52% in December when there were planned staff absences, the relocation of some temporary staff and numerous out-of-province referrals. The rapid redeployment of staff, stable supply of reagents and continuous use of the improvement measures lead to a further improvement during the January 2021 peak of the second wave compared to the first wave, with 81% within TAT.

This experience has challenged our team, but we responded effectively with remarkable agility and resourcefulness. High-throughput labs are well-suited for pandemics and will serve us well in future events.

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