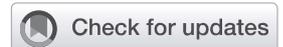


# Retrospective analysis of CD4 trends at district levels in South Africa between 2013 and 2023

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**Background:** South Africa has the largest HIV epidemic globally. Despite the scale-up of antiretroviral therapy, people living with HIV still present with CD4  $\leq$  200 cells/ $\mu$ L because of possible treatment interruptions and/or late presentation.

**Objectives:** This study assessed the proportion of CD4 specimens with counts  $\leq$  200 cells/ $\mu$ L by health district, comparing 2013 to 2023.

**Method:** This cross-sectional study analysed laboratory data. Annual test volumes, median CD4 and the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L were reported. The difference in the median CD4 between 2013 and 2023 was calculated. No de-duplication was possible because of the absence of unique identifiers.

**Results:** Data are reported for 5 821 932 specimens, with a significant decline in absolute numbers, while the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L declined by 0.4%. The median CD4 increased from 396 cells/ $\mu$ L in 2013 to 465 cells/ $\mu$ L by 2023. Between 2013 and 2023, eight districts showed a decrease in the median CD4, while 44 reported an increase ranging from 2 cells/ $\mu$ L (Sedibeng) to 192 cells/ $\mu$ L (uThukela). A percentage point reduction for counts  $\leq$  200 cells/ $\mu$ L between 2013 and 2023 was reported for 23 districts (44.2%), while 29 (55.8%) showed a percentage point increase.

**Conclusion:** Despite an upward trend in the national specimen-level CD4 count median over time, unacceptable levels of CD4 counts  $\leq$  200 cells/ $\mu$ L persisted. The analysis provides important insight into district burden of advanced HIV disease which warrants national attention and further investigation.

**Keywords:** HIV; CD4; advanced HIV disease; laboratory data; district.

**What this study adds:** This study provides important insights into the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L at district level, masked by overall national and provincial proportions. Specific districts in four provinces were identified that warrant further investigation and intervention.

## Introduction

South Africa has the world's largest HIV epidemic globally, with 7.7 million people living with HIV (PLHIV) in 2023.<sup>1,2</sup> An HIV prevalence of 12.7% was reported in 2023.<sup>3</sup> Several challenges remain, such as gaps in antiretroviral treatment (ART) coverage and sub-optimal virological suppression.<sup>1,3,4,5</sup> Provinces such as KwaZulu-Natal and Mpumalanga experience hyper-epidemics, with prevalence exceeding 15%.<sup>3</sup> Antiretroviral treatment coverage has increased substantially, reaching 77% of PLHIV by 2023.<sup>1</sup> Data from the Thembisa model showed that between 2013 and 2023, ART coverage increased by 35.6% at the national level, while the number of new HIV infections decreased fivefold.<sup>6</sup> In 2022, among PLHIV aged 15 years and older, 90% were aware of their status, 91% were on ART, and 94% were virally suppressed.<sup>3</sup>

Despite improvements in ART coverage and viral suppression, levels of advanced HIV disease (AHD) remain a concern.<sup>7,8,9</sup> Advanced HIV disease is defined as a CD4 cell count  $<$  200 cells/ $\mu$ L or WHO clinical stage 3 or 4.<sup>10</sup> Reports suggest that almost 30% of people that initiate ART are either ART-naïve patients or re-entering after a period of disengagement.<sup>9</sup> Carmona et al. reported that, between 2005 and 2011, the proportion of PLHIV aged  $\geq$  15 years entering care with a first CD4 count  $<$  200 cells/ $\mu$ L declined from 46.8% to 35.6%.<sup>7</sup>

However, between 2011 and 2016, the proportion of patients entering care with CD4 counts < 200 cells/ $\mu$ L remained relatively unchanged, at 32.9%.<sup>7</sup> A subsequent study reported that between 2017 and 2023, the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L ranged from 19.5% and 20.8%, despite a consistent increase in the median CD4.<sup>8</sup> Between 2013 and 2023, the percentage of specimens with a CD4 count  $\leq$  200 cells/ $\mu$ L decreased minimally, by 0.3%.<sup>8</sup> Of more notable concern is the increase in the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L between 2013 and 2023 in the Western Cape province.<sup>8</sup>

Re-entry into care by patients, after being on ART, at an advanced stage of HIV disease is also an important consideration.<sup>9</sup> It has been reported that many PLHIV start and stop ART multiple times in a cascade through which they can re-enter HIV care.<sup>11,12</sup> A Western Cape observational cohort study reported that 10% of PLHIV linked to HIV care disengaged after early ART initiation, and a further 12% disengaged after long-term ART.<sup>2,13</sup> Similarly, Osler et al. reported that in 2016, across 10 sites, 51.8% of the PLHIV with first CD4 < 50 cells/ $\mu$ L were ART-experienced.<sup>14</sup> Furthermore, 76% could be confirmed to either be off ART or to have had viraemia at the time of the index CD4 test.<sup>14</sup> This highlights the dual challenges of re-entry into care as well as ART-experienced PLHIV presenting with AHD.<sup>9,14</sup>

Substantial local data have been generated and reported on the burden of PLHIV who have a CD4 count  $\leq$  200 cells/ $\mu$ L at the national and provincial levels, with limited data for districts.<sup>1,8,15,16,17,18</sup>

## Objective

The objective of this study was to conduct an evaluation of the proportion of CD4 specimens with counts  $\leq$  200 cells/ $\mu$ L across 52 metropolitan and municipal health districts in South Africa, comparing data from 2013 and 2023.

## Research methods and design

### Context

The public-sector National Health Laboratory Service (NHLS) serves over 80% of the South African (largely indigent) population.<sup>19</sup> For the study period, CD4 testing was provided for using the following cytometry platforms supplied by Beckman Coulter (Miami, Florida, United States): (1) XL-MCL, (2) FC500 MPL/CellMek, and (3) Aquios CL. All CD4 data are collected via the laboratory information system (LIS) and collated into the NHLS Corporate Data Warehouse (CDW).<sup>19,20</sup> Relevant demographic data, provided on paper-based hand-written sample request forms and captured onto the LIS, are used to identify individual specimen-level data points. A hub-and-spoke laboratory network offers both decentralised and centralised CD4 testing using a tiered delivery approach that ensures nationwide coverage of laboratory services across all levels of care, from busy metropolitan centres to hard-to-reach rural

districts.<sup>21</sup> Strict electronic gate keeping (EGK), which is implemented using a rule-based system in the LIS, prevents the unnecessary retesting of specimens within a specific time frame.<sup>22</sup> In addition, local guidelines advise CD4 testing at specific timepoints and, based on this, there should not be more than one test performed on a single patient in a specified time. Therefore, EGK aims to limit retesting within the specified time interval in line with local guidelines.<sup>23,24</sup>

### Study design

A cross-sectional study design was used to analyse specimen-level CD4 laboratory data for calendar years 2013 and 2023 at the health district level. Because of the absence of unique identifiers on individual patient data records, it was not possible to de-duplicate data.<sup>25,26</sup>

### Data preparation

The data extract was provided by the NHLS CDW data repository, and included the following variables: (1) episode number, (2) result review date, (3) province, (4) health district, and (5) absolute CD4 count. The year and month were extracted from the result review date. The absolute CD4 count was categorised as  $\leq$  200 cells/ $\mu$ L and > 200 cells/ $\mu$ L. Data were limited to the nine provinces and 52 health districts reported in the District Health Information System organisational hierarchy.<sup>27</sup> The datasets were prepared and analysed using SAS 9.4 (SAS Institute, Cary, North Carolina, United States) and Stata SE (Stata Corporation, College Station, Texas, United States). Province and district naming conventions conformed to the descriptions used by the South African Municipal Demarcation Board (MDB) shapefile.<sup>28</sup> Choropleth maps were created using ArcGIS (Environmental Systems Research Institute, Redlands, California, United States). A choropleth is a form of statistical thematic mapping that employs pseudocolour to visually represent aggregated geographic data.<sup>29</sup> The choropleth colouration corresponds to a specific metric of a spatially defined unit.<sup>29</sup> Spatial files for health districts were obtained from the MDB.<sup>28</sup> Health district population estimates for 2013 and 2023 were obtained from Statistics South Africa to report the rate per 100 000 population,<sup>30</sup> as shown in Equation 1:

$$\begin{aligned} &\text{Rate per 100 000 population with a count } \leq 200 \text{ cells / } \mu\text{L} \\ &= \left( \frac{\text{Number of specimens with a CD4 } \leq 200}{\text{Health District Population}} \times 100\,000 \right) \quad [\text{Eqn 1}] \end{aligned}$$

The changes between 2013 and 2023 were also reported.

### Statistical analysis

The percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L was reported by health district. The difference in the median CD4 between 2013 and 2023 was analysed by district, and the number of districts where the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L exceeded the national value was reported by province. Choropleth maps reported the percentage of specimens with a count  $\leq$  200 cells/ $\mu$ L, using

the following buckets/categories with colours as indicated in brackets: (1) 6.6% – 11.9% (dark green), (2) 11.7% – 16.7% (light green), (3) 16.8% – 21.8% (yellow), (4) 21.9% – 26.9% (orange), and (5) 27.0% – 31.7% (red). The percentage change for specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023 was reported as a bar chart, with findings reported for each province. The data were analysed for districts with a percentage point increase between 2013 and 2023, reporting the number of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  in 2023 to identify districts with a higher burden. For this analysis, data were sorted in descending order by the number of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$ , while the percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  was reported as a line chart. The change in the rate per 100 000 population for a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023 was also reported.

### Ethical considerations

Ethical clearance for this study was obtained from the University of the Witwatersrand Human Research Ethics Committee (reference number: M220163). Anonymised secondary laboratory data were used.

## Results

Data are reported for 5 821 932 CD4 specimens (Table 1). The test volumes declined from 3 685 032 in 2013 to 2 136 900 by 2023. There was a decline in both absolute numbers of specimens with a CD4 count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 ( $n = 762\,868$ ) and 2023 ( $n = 435\,753$ ), as well as the percentage (20.7% in 2013 to 20.3% by 2023). The national median CD4 was 396 cells/ $\mu\text{L}$  (interquartile range [IQR]: 233–581) in 2013, compared to 465 cells/ $\mu\text{L}$  (IQR: 243–706) by 2023, showing an increase of the median CD4 count by 69 cells/ $\mu\text{L}$  over 10 years.

### Health district median CD4 analysis

In 2013, the health district median CD4 ranged from 364 cells/ $\mu\text{L}$  (IQR: 203–552) in Vhembe, to 504 cells/ $\mu\text{L}$  (IQR: 329–716) for uMkhanyakude (Table 1). For 2023, the median CD4 ranged from 344 cells/ $\mu\text{L}$  (IQR: 162–599) in Overberg to 617 cells/ $\mu\text{L}$  (IQR: 425–825) in uThukela. A wide variation in the median CD4 was noted in 2013 by district, ranging from 364 cells/ $\mu\text{L}$  (Vhembe) to 503 cells/ $\mu\text{L}$  (uMkhanyakude). A range of 344 cells/ $\mu\text{L}$  (Cape Winelands) to 617 cells/ $\mu\text{L}$  (uThukela) was reported for 2023. The change in the median CD4 between 2013 and 2023 ranged from –81 cells/ $\mu\text{L}$  (Cape Winelands) to 192 cells/ $\mu\text{L}$  (uThukela).

### Health district analysis: 2013

Only three districts (5.8%) reported a percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$   $\leq 16.7\%$  in 2013 (Umkhanyakude [11.9%], iLembe [16.5%], and Overberg [16.7%]) (Figure 1). There were 23/52 (44.2%) districts that reported a percentage of specimens with a count  $\leq 200$

cells/ $\mu\text{L}$  in the 21.9% – 26.9% category, distributed as follows: (1) Free State ( $n = 5/5$ ), (2) Gauteng ( $n = 5/5$ ), (3) Limpopo ( $n = 5/5$ ), (4) Eastern Cape ( $n = 4/8$ ), (5) North West ( $n = 2/4$ ), (6) Western Cape ( $n = 1/6$ ), and (7) Mpumalanga ( $n = 1/3$ ). There were no districts in the 21.9% – 24.9% category in the KwaZulu-Natal and Northern Cape provinces. The remaining districts reported a percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  in the 16.8% – 21.8% category. No districts were allocated to the 27.0% – 31.7% category.

### Health district analysis: 2023

There were eight districts (15.4%) where the percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  was classified in the 27.0% – 31.7% bucket, namely: (1) Western Cape: Cape Winelands, Garden Route, and Overberg, (2) Eastern Cape: Nelson Mandela Bay, and Sarah Baartman, (3) Gauteng: Ekurhuleni, and Sedibeng, and (4) Limpopo: Sekhukhune (Figure 1). On the opposite spectrum, there were 12 districts (23.0%) with a percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  classified in the 6% – 11.9% and 11.7% – 16.7% buckets.

### Health district percentage point change for counts $\leq 200$ cells/ $\mu\text{L}$ between 2013 and 2023

Of 52 districts, 23 (44.2%) showed a reduction, while 29 (55.8%) reported an increase. All 11 KwaZulu-Natal districts saw declines (up to –10.4% in uThukela). In the Eastern Cape, Alfred Nzo and Joe Gqabi reported percentage point reductions over two points; others increased by up to 7.3%. The Free State had two declining districts, while others rose to 3.2%. Only Johannesburg declined in Gauteng (–0.7%); other districts increased up to 3.8% (Figure 2). In Limpopo, three districts declined (lowest: –2.5% in Waterberg), while Mopani rose by 3.5% and Sekhukhune by 6.7%. Mpumalanga's Gert Sibanda declined (–8.0%), while two others increased. In the North West, only Dr Ruth Segomotsi Mompati declined (–2.5%). Northern Cape's John Taolo Gaetsewe dropped (–3.6%), with others rising to 6.6%. In the Western Cape, only Central Karoo declined (–2.5%); others rose sharply, up to 14.8% in Overberg.

### Health district analysis: Rate per 100 000 population

In 2013, the district rate per 100 000 population for specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  ranged from 87 (Cape Winelands) to 2441 (Ugu), compared to a national value of 1414 (Figure 3). By 2023, the national rate per 100 000 population had decreased to 701 (a reduction of 713 from 2013). The district rate per 100 000 population for a count  $\leq 200$  cells/ $\mu\text{L}$  in 2023 ranged from 414 (Sekhukhune) to 1096 (Buffalo City). The change in the district rate per 100 000 population for a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023 ranged from –1797 (Ugu) to 584 (Cape Winelands). The districts where the biggest change in the rate per 100 000 population for a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and

**TABLE 1:** Health district analysis of the median CD4 and percentage of specimens with a count of  $\leq 200$  cells/ $\mu$ L by health district in 2013 and 2023.

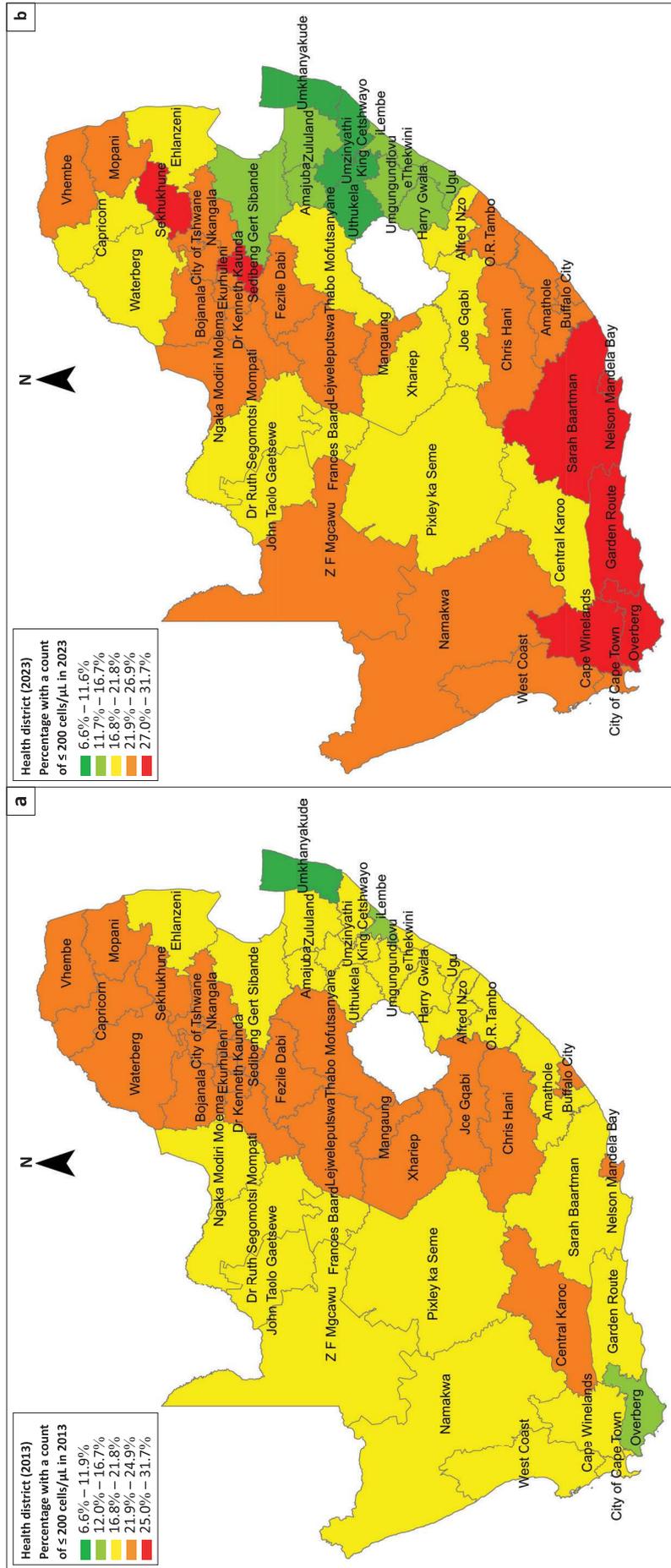
| Province district       | Year   |         |        |         |                 |        |         |      |         |      | $\Delta$ (%) |
|-------------------------|--------|---------|--------|---------|-----------------|--------|---------|------|---------|------|--------------|
|                         | 2013   |         | 2023   |         | Median $\Delta$ |        | 2013    |      | 2023    |      |              |
|                         | Median | IQR     | Median | IQR     | Volume          | %      | Volume  | %    | Volume  | %    |              |
| EC Alfred Nzo           | 396    | 234-586 | 492    | 274-719 | 96              | 10 004 | 48 571  | 20,6 | 26 535  | 17,9 | -2,7         |
| EC Amathole             | 412    | 247-597 | 419    | 207-664 | 7               | 10 720 | 56 349  | 19,0 | 25 246  | 24,3 | 5,3          |
| EC Buffalo City         | 389    | 216-585 | 400    | 196-650 | 11              | 9 815  | 42 848  | 22,9 | 37 565  | 25,6 | 2,7          |
| EC Chris Hani           | 381    | 221-560 | 392    | 196-628 | 11              | 13 006 | 58 975  | 22,1 | 26 588  | 20,8 | 3,5          |
| EC Joe Gqabi            | 376    | 215-563 | 452    | 236-686 | 76              | 5 975  | 25 946  | 23,0 | 16 860  | 20,8 | -2,3         |
| EC Nelson Mandela Bay   | 371    | 205-560 | 382    | 179-636 | 11              | 14 410 | 59 053  | 24,4 | 47 358  | 27,7 | 3,3          |
| EC O R Tambo            | 398    | 236-584 | 421    | 217-659 | 23              | 19 884 | 97 472  | 20,4 | 42 228  | 23,2 | 2,8          |
| EC Sarah Baartman       | 403    | 239-596 | 390    | 185-642 | -13             | 4 273  | 21 594  | 19,8 | 20 379  | 27,1 | 7,3          |
| FS Fezile Dabi          | 370    | 211-544 | 400    | 194-634 | 30              | 8 533  | 36 257  | 23,5 | 16 941  | 25,7 | 2,2          |
| FS Lejweleputswa        | 371    | 221-547 | 390    | 199-619 | 19              | 11 756 | 53 377  | 22,0 | 18 246  | 25,2 | 3,2          |
| FS Mangaung             | 386    | 222-572 | 415    | 202-668 | 29              | 12 958 | 58 601  | 22,1 | 34 051  | 24,8 | 2,7          |
| FS Thabo Mofutsanyana   | 370    | 220-540 | 460    | 238-692 | 90              | 13 948 | 62 993  | 22,1 | 28 295  | 20,9 | -1,3         |
| FS Xhariep              | 382    | 220-570 | 467    | 242-712 | 85              | 16 388 | 73 933  | 22,2 | 53 445  | 20,4 | -1,7         |
| GP City of Johannesburg | 370    | 206-551 | 409    | 212-639 | 39              | 71 349 | 293 812 | 24,3 | 190 815 | 23,6 | -0,7         |
| GP City of Tshwane      | 396    | 223-591 | 452    | 217-708 | 56              | 37 372 | 167 876 | 22,3 | 89 066  | 23,3 | 1,0          |
| GP Ekurhuleni           | 369    | 210-547 | 373    | 182-609 | 4               | 53 013 | 223 713 | 23,7 | 102 301 | 27,5 | 3,8          |
| GP Sedibeng             | 382    | 213-567 | 384    | 186-627 | 2               | 15 689 | 67 090  | 23,4 | 29 636  | 27,1 | 3,7          |
| GP West Rand            | 366    | 206-543 | 399    | 199-633 | 33              | 16 654 | 68 508  | 24,3 | 34 035  | 25,2 | 0,8          |
| KZN Amajuba             | 378    | 224-549 | 515    | 295-746 | 137             | 11 011 | 50 781  | 21,7 | 31 940  | 15,9 | -5,8         |
| KZN eThekweni           | 407    | 254-584 | 504    | 284-738 | 97              | 61 427 | 346 417 | 17,7 | 178 559 | 16,6 | -1,1         |
| KZN Harry Gwala         | 401    | 247-581 | 547    | 293-823 | 146             | 6 333  | 33 287  | 19,0 | 14 336  | 16,6 | -2,4         |
| KZN iLembe              | 422    | 268-595 | 523    | 292-761 | 101             | 10 140 | 61 565  | 16,5 | 34 275  | 16,1 | -0,4         |
| KZN King Cetshwayo      | 428    | 262-621 | 583    | 367-804 | 155             | 13 350 | 76 916  | 17,4 | 74 874  | 11,0 | -6,3         |
| KZN Ugu                 | 408    | 249-589 | 567    | 326-824 | 159             | 17 424 | 93 129  | 18,7 | 37 391  | 14,2 | -4,5         |
| KZN uMgungundlovu       | 418    | 260-600 | 568    | 346-797 | 150             | 20 923 | 119 769 | 17,5 | 71 128  | 12,4 | -5,0         |
| KZN uMkhanyakude        | 504    | 329-716 | 576    | 381-776 | 72              | 8 590  | 71 954  | 11,9 | 53 721  | 9,5  | -2,4         |
| KZN Umzinyathi          | 407    | 247-588 | 575    | 374-784 | 168             | 9 394  | 49 696  | 18,9 | 41 696  | 10,1 | -8,8         |
| KZN uThukela            | 425    | 263-618 | 617    | 425-825 | 192             | 12 336 | 72 169  | 17,1 | 81 685  | 6,6  | -10,4        |
| KZN Zululand            | 396    | 240-573 | 539    | 334-756 | 143             | 18 402 | 93 607  | 19,7 | 43 160  | 12,9 | -6,8         |
| LP Capricorn            | 374    | 201-570 | 479    | 253-730 | 105             | 15 773 | 63 418  | 24,9 | 41 440  | 19,6 | -5,3         |
| LP Mopani               | 370    | 214-548 | 391    | 187-635 | 21              | 16 171 | 70 100  | 23,1 | 23 369  | 26,6 | 3,5          |
| LP Sekhukhune           | 376    | 202-571 | 349    | 152-615 | -27             | 10 543 | 42 475  | 24,8 | 17 121  | 31,5 | 6,7          |
| LP Vhembe               | 364    | 203-552 | 435    | 210-681 | 71              | 13 624 | 55 159  | 24,7 | 29 684  | 24,0 | -0,7         |
| LP Waterberg            | 383    | 213-578 | 474    | 240-735 | 91              | 10 264 | 43 936  | 23,4 | 30 973  | 20,9 | -2,5         |
| MP Ehlanzeni            | 420    | 248-614 | 447    | 235-692 | 28              | 34 166 | 178 774 | 19,1 | 66 723  | 21,0 | 1,9          |
| MP Gert Sibande         | 397    | 233-582 | 548    | 338-770 | 151             | 19 892 | 95 763  | 20,8 | 73 112  | 12,8 | -8,0         |

Table 1 continues on the next page →

**TABLE 1 (Continues...):** Health district analysis of the median CD4 and percentage of specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  by health district in 2013 and 2023.

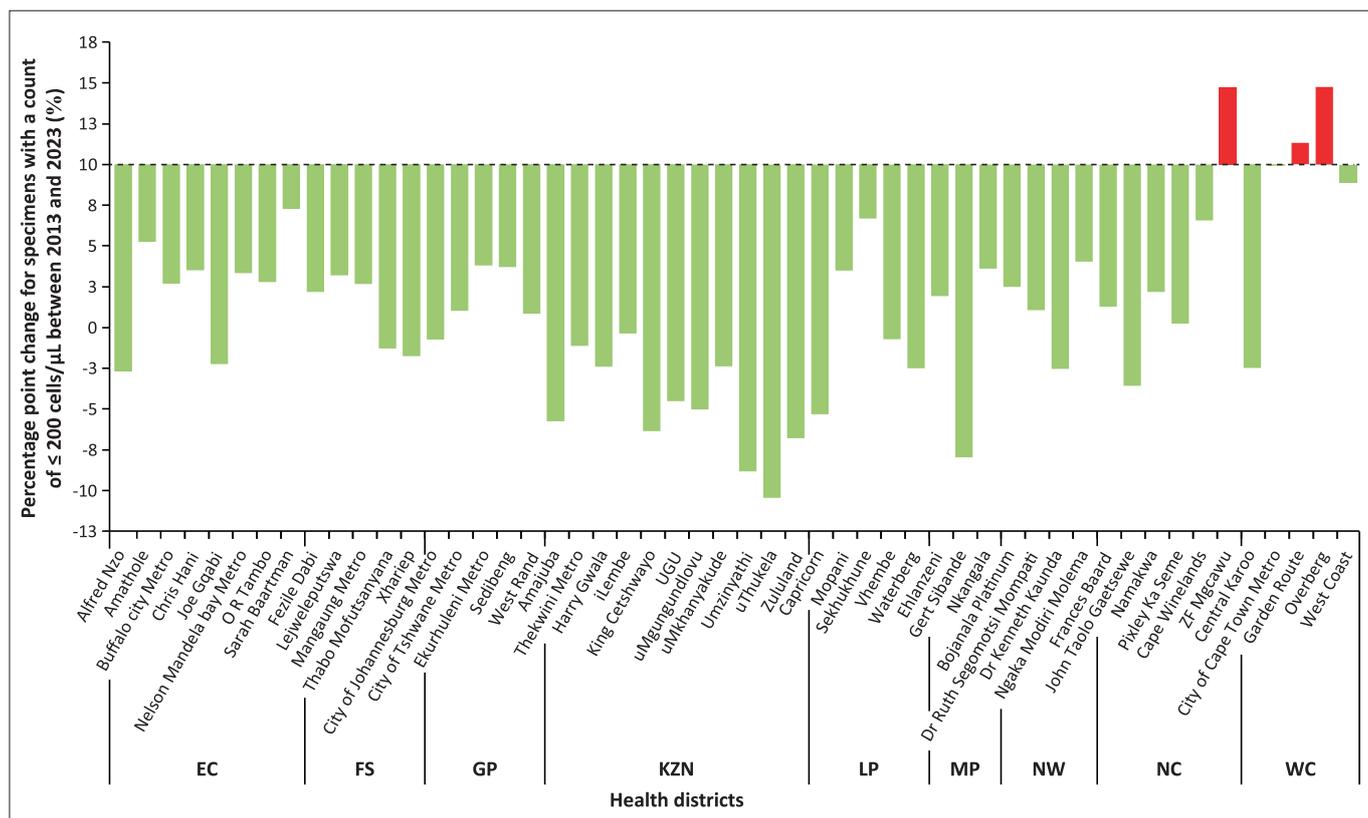
| Province district    | Year       |                |            |                |                 |                  |                                      |             |                  |                                      | $\leq 200$ cells/ $\mu\text{L}$<br>$\Delta$ (%) |             |
|----------------------|------------|----------------|------------|----------------|-----------------|------------------|--------------------------------------|-------------|------------------|--------------------------------------|---|-------------|
|                      | 2013       |                |            |                |                 | 2023             |                                      |             |                  |                                      |   |             |
|                      | Median     | IQR            | Median     | IQR            | Median $\Delta$ | Volume           | $\leq 200$ cells/ $\mu\text{L}$<br>N | %           | Volume           | $\leq 200$ cells/ $\mu\text{L}$<br>N |   | %           |
| MP Nkangala          | 378        | 218–556        | 390        | 191–635        | 12              | 76 664           | 17 311                               | 22.6        | 36 804           | 9650                                 | 26.2  | 3.6         |
| NC Frances Baard     | 424        | 252–630        | 477        | 247–730        | 53              | 29 236           | 5525                                 | 18.9        | 22 896           | 4624                                 | 20.2  | 1.3         |
| NC JT Gaetsewe       | 396        | 232–581        | 477        | 269–702        | 81              | 13 459           | 2843                                 | 21.1        | 14 964           | 2625                                 | 17.5  | -3.6        |
| NC Namakwa           | 404        | 235–597        | 466        | 227–727        | 62              | 2566             | 516                                  | 20.1        | 2783             | 621                                  | 22.3  | 2.2         |
| NC Pixley Ka Seme    | 403        | 245–592        | 470        | 249–715        | 67              | 12 571           | 2398                                 | 19.1        | 9002             | 1739                                 | 19.3  | 0.2         |
| NC ZF Mgcawu         | 414        | 248–615        | 393        | 197–644        | -22             | 9716             | 1829                                 | 18.8        | 9078             | 2306                                 | 25.4  | 6.6         |
| NW Bojanala Platinum | 386        | 221–574        | 402        | 201–650        | 16              | 92 853           | 20 783                               | 22.4        | 43 782           | 10 900                               | 24.9  | 2.5         |
| NW Dr Kenneth Kaunda | 396        | 222–596        | 417        | 213–664        | 21              | 65 673           | 14 631                               | 22.3        | 36 911           | 8622                                 | 23.4  | 1.1         |
| NW Dr RS Mompoti     | 406        | 242–592        | 497        | 276–735        | 91              | 32 747           | 6433                                 | 19.6        | 27 786           | 4757                                 | 17.1  | -2.5        |
| NW NMi Molema        | 389        | 228–570        | 408        | 198–665        | 19              | 55 819           | 11 823                               | 21.2        | 23 283           | 5877                                 | 25.2  | 4.1         |
| WC Cape Winelands    | 425        | 263–619        | 344        | 162–599        | -81             | 4263             | 724                                  | 17.0        | 21 100           | 6 690                                | 31.7  | 14.7        |
| WC Central Karoo     | 371        | 210–565        | 451        | 239–684        | 80              | 2085             | 486                                  | 23.3        | 2546             | 531                                  | 20.9  | -2.5        |
| WC City of Cape Town | 424        | 266–598        | 391        | 189–632        | -33             | 184 258          | 30 944                               | 16.8        | 113 167          | 30 244                               | 26.7  | 9.9         |
| WC Garden Route      | 409        | 258–580        | 362        | 176–611        | -47             | 20 241           | 3554                                 | 17.6        | 18 532           | 5350                                 | 28.9  | 11.3        |
| WC Overberg          | 417        | 263–595        | 344        | 163–602        | -73             | 7920             | 1324                                 | 16.7        | 7014             | 2209                                 | 31.5  | 14.8        |
| WC West Coast        | 417        | 261–599        | 392        | 189–645        | -25             | 5618             | 984                                  | 17.5        | 10 575           | 2795                                 | 26.4  | 8.9         |
| <b>National</b>      | <b>396</b> | <b>233–581</b> | <b>465</b> | <b>243–706</b> | <b>69</b>       | <b>3 685 032</b> | <b>762 868</b>                       | <b>20.7</b> | <b>2 136 900</b> | <b>435 753</b>                       | <b>20.4</b>                                     | <b>-0.3</b> |

Dr, doctor; OR, Oliver Reginald; ZF Zwellentlanga Fatman; RS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; LP, Limpopo; MP, Mpumalanga; NW, North West; NC, Northern Cape; WC, Western Cape; IQR, interquartile range;  $\Delta$ , difference.



Dr, doctor; OR, Oliver Reginald; ZF, Zwellentlanga Fatman.

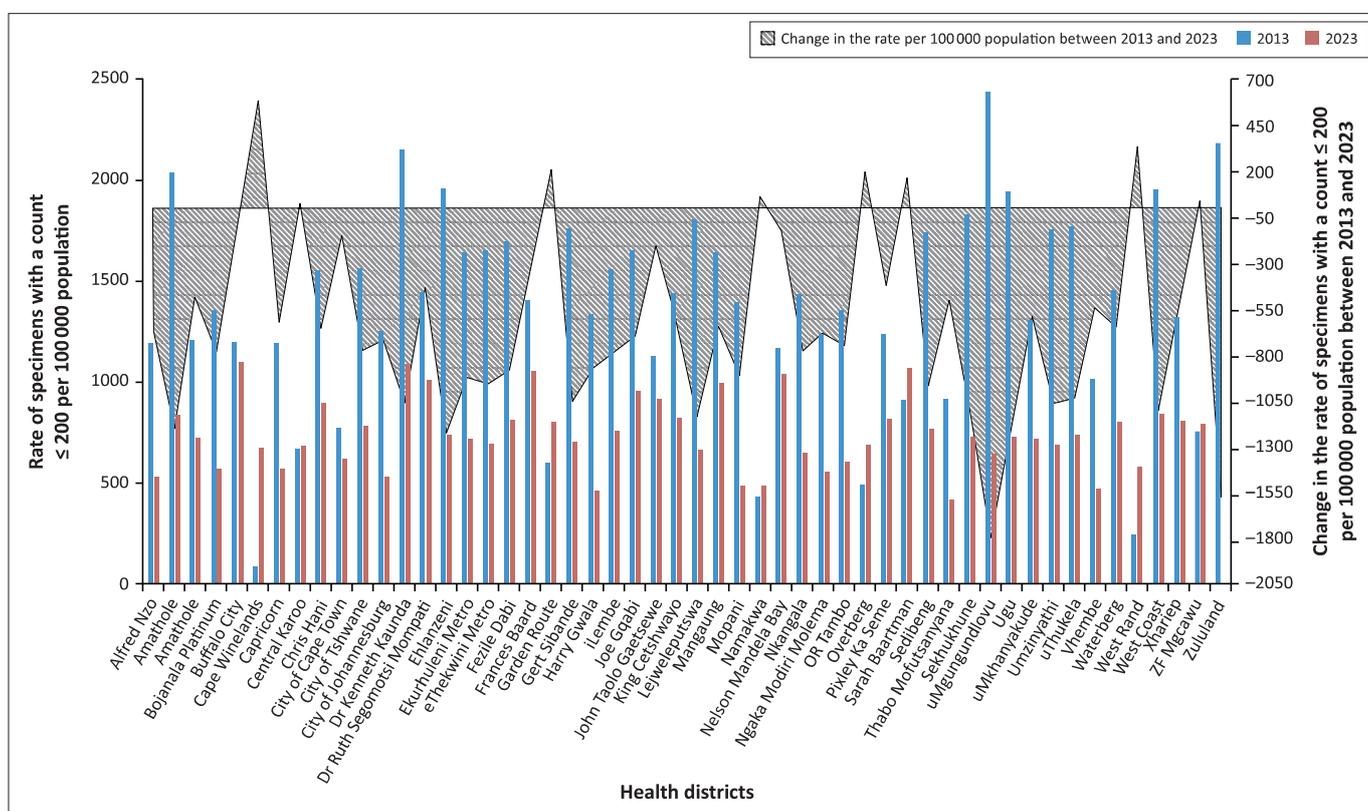
**FIGURE 1:** Choropleth maps reporting the percentage of CD4 specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  by health district in 2013 (a) and 2023 (b) in South Africa. The map is categorised into five buckets as follows: (1) 6.6% – 11.9%, (2) 11.7% – 16.7%, (3) 16.8% – 21.8%, (4) 21.9% – 26.9%, and (5) 27.0% – 31.7%.



Note: A percentage change ≥ 0% was reported using red bars.

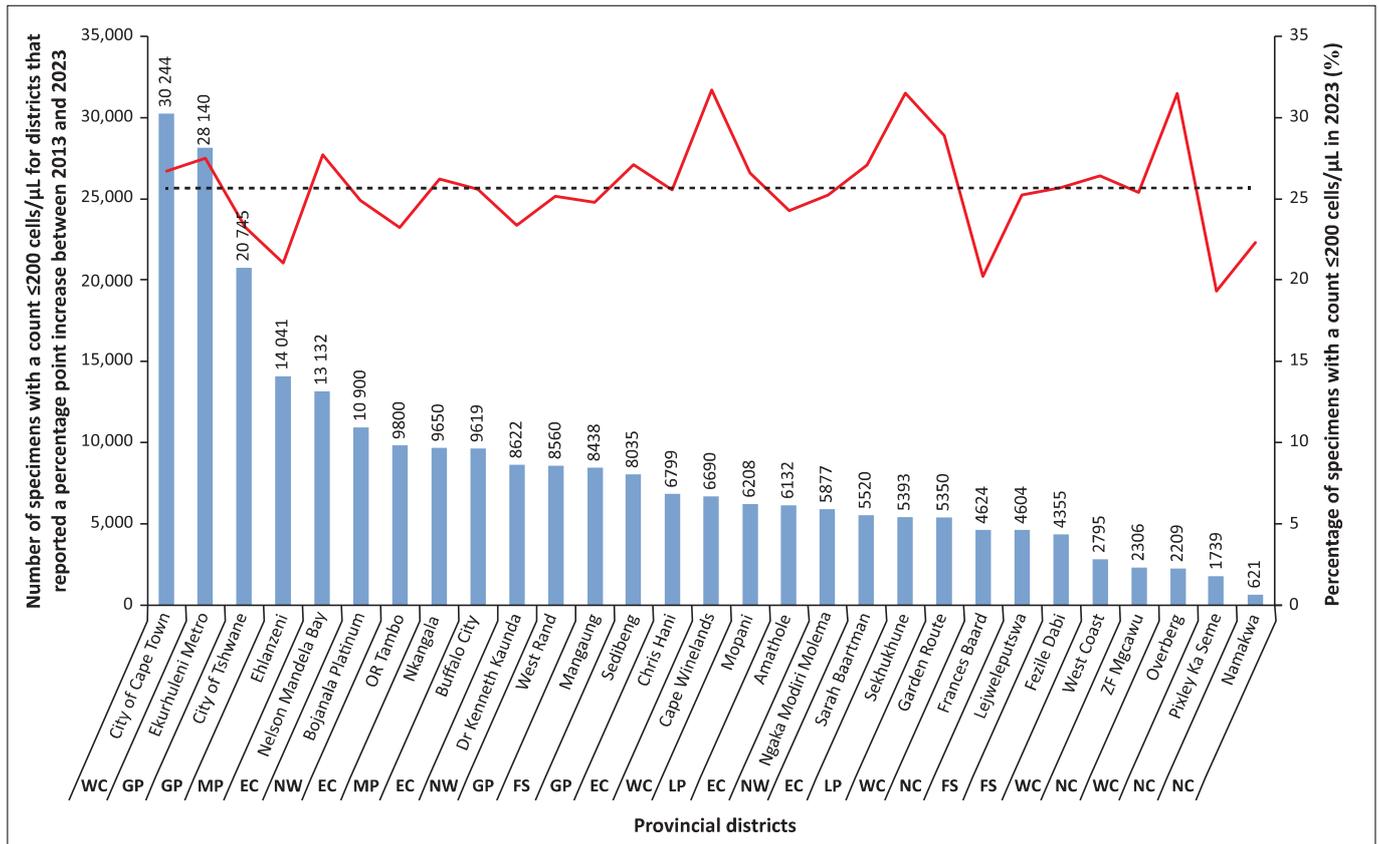
Dr, doctor; OR, Oliver Reginald; ZF, Zwelentlanga Fatman; EC, Eastern Cape; FS, Free State; GP, Gauteng; KZN, KwaZulu-Natal; LP, Limpopo; MP, Mpumalanga; NW, North West; NC, Northern Cape; WC, Western Cape.

FIGURE 2: Analysis of the percentage point change for specimens with a count of ≤ 200 cells/μL between 2013 and 2023 by health district, grouped by province.



Dr, doctor; OR, Oliver Reginald; ZF, Zwelentlanga Fatman.

FIGURE 3: Analysis of the rate of specimens with a count of ≤ 200 cells/μL per 100,000 population in 2013 and 2023, with the change reported on the secondary y-axis.



Note: The analysis reported the number of specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  in 2023 in descending order. The secondary y-axis reports the percentage of specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  in 2023. The overall percentage of specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  for these districts is reported as a black dotted line.

Dr, doctor; OR, Oliver Reginal; ZF, Zwelentlanga Fatman; EC, Eastern Cape; FS, Free State; GP, Gauteng; LP, Limpopo; MP, Mpumalanga; NW, North West; NC, Northern Cape; WC, Western Cape.

**FIGURE 4:** Analysis for districts where the percentage point change for specimens with a count of  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023 decreased.

2023 was noted were Cape Winelands, Garden Route, Overberg, Sarah Baartman, and West Coast.

### Health district analysis: Percentage point increase between 2013 and 2023

Among the 29 districts (55.8%) reporting a percentage point increase, 17 contributed the most specimens with CD4 counts  $\leq 200$  cells/ $\mu\text{L}$  (Figure 4). Thirteen of these districts (44.8%) exceeded this threshold, with the highest percentage point increases observed in Cape Winelands, City of Cape Town, and Ekurhuleni Metro. Other districts with elevated highest percentage point increases included Fezile Dabi, Garden Route, Mopani, Nelson Mandela Bay, Nkangala, Overberg, Sarah Baartman, Sedibeng, Sekhukhune, and West Coast.

## Discussion

This study aimed to evaluate the proportion of CD4 specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  across 52 health districts in South Africa, comparing data from 2013 and 2023. Our findings reveal a slight improvement in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$ . However, a substantial increase in the median CD4 count was noted. The improvement in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  as well as the median CD4 was predominantly noted in the KwaZulu-Natal province, followed by selected districts in the Eastern Cape, Limpopo,

Mpumalanga, North West, and the Northern Cape provinces. Districts in the Western Cape (Cape Winelands, Overberg, and Garden Route), Eastern Cape (Sarah Baartman, and Nelson Mandela Bay), Gauteng (Ekurhuleni, and Sedibeng) and Limpopo (Sekhukhune) provinces, reported proportions of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  exceeding 27% by 2023. This is high compared to national values of around 20% in both 2013 and 2023. This was supported by the decrease observed in the median CD4 noted between 2013 and 2023 in these eight districts.

The increase in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$ , specifically in the Western Cape, is consistent with a local analysis of CD4 data for the same period.<sup>8</sup> What is surprising is that the district analysis in this study reported a percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  27% also being seen in other provinces, such as the Eastern Cape, Gauteng, and Limpopo provinces. This finding was not expected and could in part be explained by lower ART coverage rates, compared to a national ART coverage of 76.6% identified by the Thembeisa model.<sup>31</sup> In 2023, ART coverage rates for Western Cape (73.2%), Eastern Cape (71.6%), Gauteng (72.1%), and Limpopo (71.1%) provinces were lower than other provinces.<sup>8</sup> The KwaZulu-Natal province, with the lowest percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$ , reported an ART coverage of 83.4%.<sup>6</sup> Despite the national increase in ART coverage by 35.6% between 2013 and 2023, selected districts reported a

high level of the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$ , that could in part be explained by lower ART coverage.<sup>6</sup>

There are multiple factors that could contribute to the differences noted in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  at the district level. One possible explanation may relate to some districts having a much higher HIV/tuberculosis co-infection rate, reported to exceed 50%.<sup>32</sup> An analysis of 2023 laboratory data for the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  and the *Mycobacterium tuberculosis* complex detection rates at the district level, reported a correlation coefficient of 0.62.<sup>33</sup> This indicates that HIV/tuberculosis coinfection might explain some of the differences in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$ .<sup>33</sup> This was repeated for reflexed cryptococcal antigenaemia detection rates offered for counts  $< 100$  cells/ $\mu\text{L}$ , surprisingly reporting a negative correlation coefficient of  $-0.209$ .<sup>33</sup> Cryptococcal antigenaemia is a common and clinically significant opportunistic infection in individuals with AHD, often serving as a precursor to cryptococcal meningitis, and associated with increased morbidity and mortality in the absence of timely screening and pre-emptive antifungal therapy.<sup>23,24</sup> However, factors such as other co-infections are outside the scope of this study, and may have played a contributing role.<sup>10,24</sup>

Additionally, socioeconomic factors, as well as access to healthcare services, may also play a role.<sup>34,35</sup> Delays in diagnosis and treatment may also contribute, including poor communication and long waiting times at public health facilities that could discourage patients from seeking timely care.<sup>36</sup> Integration of local clinical and laboratory data is urgently needed, specifically to understand the underlying reasons for the worrying trends documented here in the Cape Winelands, Overberg, Garden Route, Sarah Baartman, and Sekhukhune districts, where a median CD4 decrease is reported in this study between 2013 and 2023. Importantly, integration of this database would enable further work to identify what percentage of testing was done for ART-naïve patients versus patients re-entering care. Furthermore, the disaggregation of data by facility type would help to elucidate where these patients with a count  $\leq 200$  cells/ $\mu\text{L}$  are presenting for care (at hospitals or primary healthcare facilities). Finally, a geospatial analysis should be conducted using facility coordinates to identify hotspots in these districts. These findings could be used to focus programmatic interventions.

Despite advancements in the accessibility of HIV services as well as improved ART coverage, the wide gap in the median CD4 at the district level across South Africa is of great concern.<sup>6,37</sup> This work is the first known study to identify South Africa districts with higher than expected or, in some instances, rising proportions of patients with AHD that would have been otherwise masked by only examining provincial trends. In 2023, despite a national median exceeding 460 cells/ $\mu\text{L}$ , there were three districts where the

median CD4 was below 350 cells/ $\mu\text{L}$ . The decline in median CD4 values in these districts warrants special programmatic investigations. Of interest was that by 2023, the Sekhukhune district reported a percentage of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  above 30%, yet the rate per 100 000 population had declined substantially. There was a notable reduction in the absolute number of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023, with a corresponding increase of 13.3% in population estimates.<sup>30</sup> These findings confirm that, in addition to the percentage of specimens and the rate per population, the absolute number of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  is an important factor to consider in programmatic interventions. The increase in the median CD4 is also reflected as a continued increase in the percentage of specimens with a count  $\geq 500$  cells/ $\mu\text{L}$  (associated with HIV wellness).<sup>8,16</sup>

The analysis of the 29 districts that reported a percentage point increase in specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  between 2013 and 2023 indicates that over a third of specimens originate from three metropolitan districts. Furthermore, the data outcomes reported here could enable policymakers and programme stakeholders at provincial level to optimise allocation of public funds to target 95-95-95 interventions towards specifically identified populations at the district level with a higher burden of AHD.<sup>38</sup> However, focusing only on districts with high numbers of specimens with a count  $\leq 200$  cells/ $\mu\text{L}$  would be a challenge in terms of universal coverage.<sup>38</sup>

## Limitations

The laboratory data used in this study could not distinguish between first-ever and follow-up CD4 tests, and may account for differences in disease burden previously reported.<sup>7</sup> The absence of a unique patient identifier in the public healthcare system in South Africa makes it difficult to de-duplicate data, apart from data repositories built in one province that integrated clinical and laboratory data.<sup>39,40</sup> There is a need to move towards a person-centred electronic medical record system that supports longitudinal analysis using a unique patient identifier.<sup>40,41</sup> The absence of clinical data is a limitation. The value of combining laboratory and clinical data systems and socio-economic indicators (i.e. data reported by the Profile and Analysis District Development Model from the Department of Cooperative Governance and Traditional Affairs) to make these programmatic decisions cannot be overemphasised, given the value demonstrated by the Western Cape data centre.<sup>39,42</sup> There is a need to integrate health data to provide real-time monitoring of the interventions proposed.

## Conclusion

Despite a consistent increase in the national median CD4 count since 2013, persisting high levels of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  continue to be seen at specific health districts in 2023 that include the Western Cape (Cape Winelands, Overberg, and Garden Route), Eastern Cape

(Sarah Baartman, and Nelson Mandela Bay), Gauteng (Ekurhuleni, and Sedibeng) and Limpopo (Sekhukhune) provinces. This warrants urgent attention and further investigation. To our knowledge, this is the first South African study to document the variation in the percentage of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  at the district level, with an earlier study reporting variation at the provincial level.<sup>8</sup> Despite lack of de-duplication, this analysis provides important information about specific districts and highlights areas of concern with rising burden of specimens with counts  $\leq 200$  cells/ $\mu\text{L}$  that would otherwise be masked by provincial-level data.<sup>8</sup> This work provides the impetus for the development of better monitoring systems, including the integration of laboratory and clinical data for meaningful analysis and interpretation at the patient-level to provide a framework for patient-centric data approaches for interventions.

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## Competing interests

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## CRedit authorship contribution

Naseem Cassim: Conceptualisation, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualisation. Pedro da Silva: Project Administration, Writing – Review & Editing, Supervision. Deborah K. Glencross: Writing – Review & Editing, Supervision. Wendy S. Stevens: Project Administration, Writing – Review & Editing, Supervision. Lindi-Marie Coetzee: Conceptualisation, Methodology, Formal Analysis, Data Curation, Writing – Original Draft, Writing – Review & Editing, Supervision. All authors reviewed the article, contributed to the discussion of results, approved the final version for submission and publication, and take responsibility for the integrity of its findings.

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## Data availability

The authors do not have permission to share the laboratory data.

## Disclaimer

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