BMC Global and Public Health

RESEARCH

Open Access

Monitoring for advanced disease in the universal test and treat era: trends in CD4 count testing in South Africa

Cornelius Nattey[1*], Dorina Onoya[1], Khumbo Shumba[1], Dickman Gareta[2], William Macleod[1,3], Matthew P. Fox[1,3,4], Adrian Puren[5], Koleka Mlisana[5,6] and Jacob Bor[1,3,4]

Abstract

Background Under South Africa's Universal Test and Treat (UTT) policy, CD4 counts are no longer required to determine HIV treatment eligibility. However, CD4 count at presentation remains an important marker of disease progression. We assessed whether CD4 testing declined in the UTT era and, if so, by how much.

Methods We analysed CD4 count data from the National Health Laboratory Service (NHLS) National HIV Cohort and TIER.Net database for individuals in HIV care across five South African provinces. "First CD4 count" was defined as the first CD4 test recorded for each patient. In TIER.Net, "date of presentation" was the earliest date of HIV testing, CD4 measurement, or clinic visit. Trends in first CD4 testing volumes (2004–2018) were analyzed, with interrupted time-series analyses assessing the impact of UTT (September 2016).

Results Data included 5,274,218 (NHLS) and 2,265,557 (TIER.Net) individuals with a first CD4 count. In NHLS, first CD4 counts increased from 47,604 in 2004 to 383,705 in 2010 and then declined. Lower volumes were recorded in TIER.Net. Adjusting for prior trends, first CD4 counts increased slightly after UTT, by 32 individuals/day in NHLS (95% *CI*: − 6 to 61) and 88 individuals/day in TIER.Net (95% *CI*: 30 to 148). Among TIER.Net patients, the percentage with a CD4 count decreased by 4.3% (95% *CI*: − 5.2 to − 3.0%).

Conclusions We found no major decline in CD4 testing at presentation following UTT, contrasting findings from resource-constrained settings with greater reliance on external donors.

Keywords Universal Test and Treat (UTT), CD4 count testing, Advanced HIV disease, Trends in HIV care, Interrupted time-series analysis

*Correspondence:
Cornelius Nattey
phoyocon@gmail.com
[1] Health Economics and Epidemiology Research Office, Department of Internal Medicine, Faculty of Health Sciences, School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa
[2] Data Science Unit, Africa Health Research Institute, Durban, South Africa
[3] Department of Global Health, Boston University School of Public Health, Boston, MA, USA
[4] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[5] Centre for HIV & STIs, National Health Laboratory Service, National Institute for Communicable Diseases, Johannesburg, South Africa
[6] School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa

Background

In 2015, the World Health Organization (WHO) recommended immediate initiation of antiretroviral therapy (ART) for all people living with HIV, regardless of CD4 cell count or clinical stage [1], but these guidelines still recommend CD4 cell count testing at HIV diagnosis. South Africa eliminated the CD4 criteria for ART eligibility in 2016 under its Universal Test and Treat (UTT) policy [2] in response to evidence of the potential impact of immediate ART initiation on both patient health and onward transmission. However, CD4 cell count at entry into care remains an important marker of immunological status and a strong predictor of HIV-related morbidity and mortality [3–5]. South African treatment guidelines also use CD4 count to guide several prophylactic and diagnostic interventions, including reflex testing for opportunistic infections such as cryptococcus or tuberculosis [6, 7]. In September 2017, the UTT policy was updated to initiate ART on the day of HIV diagnosis (same-day ART initiation—SDI) maintaining the lack of requirement for CD4 testing [8].

Before September 2016, ART eligibility was determined in part by whether a patient's CD4 count was below a threshold value: < 200 cells/mm^3 up to August 2011 [9], < 350 up to January 2015 [10], and < 500 up to September 2016. Under UTT, all persons diagnosed with HIV are eligible for treatment regardless of CD4 count. As viral loads are now generally accepted as the preferred tool for monitoring treatment success, some countries are moving away from CD4 counts altogether. This is evident in a recent multi-country study in Southern Africa which reported that the proportion of people living with HIV having a CD4 cell count before starting treatment has declined substantially in recent years [11] [12]. Some argue that CD4 monitoring is no longer necessary in the era of UTT, as all individuals are eligible for ART regardless of their CD4 count [13].

While critical for monitoring, viral load alone may not capture all aspects of individual health and treatment success [14] [15]. Moreover, viral load monitoring after starting HIV therapy is inconsistent in resource-limited health settings [16] due to factors such as limited access to testing equipment, logistical challenges in sample processing, cost constraints, and irregular patient follow-up. Therefore, while viral load monitoring may be preferred for monitoring treatment success, CD4 monitoring still play a crucial role in the management of HIV in South Africa. In many resource-limited settings, the lower cost of CD4 testing makes it a more viable option for regular monitoring of individuals with HIV, although viral load testing is recommended for the most accurate management of the disease, especially for monitoring treatment efficacy and adherence [17].

Despite the shift towards immediate ART initiation, baseline CD4 testing remains recommended by WHO to assess immunological status and baseline risk, particularly for opportunistic infections. It is however unclear whether CD4 testing practice has changed over time. We therefore set out to use two novel databases to analyse trends in baseline CD4 at clinical presentation in South Africa and to assess whether baseline CD4 count testing has declined in the UTT era and, if so, by how much.

Methods

Study population and data sources

The study population consisted of individuals of all ages seeking care within the public sector HIV programme in five provinces where data were available for this study: Gauteng (excluding the city of Johannesburg), Limpopo, Mpumalanga, Northern Cape and KwaZulu-Natal, from January 1, 2004, through March 31, 2018 (with the exception of KwaZulu-Natal province which was integrated into the NHLS database in 2010).

We used two cohorts for this analysis, the NHLS National HIV Cohort and the TIER.Net cohort, as each has unique strengths and weaknesses to answer our primary questions. The NHLS National HIV Cohort includes the laboratory data of nearly all individuals receiving HIV care in the public sector since 2004 [18]. Using an anonymized unique patient identifier previously developed and validated, all individuals can be followed longitudinally through their laboratory results as they progress through the HIV care and treatment cascade [18]. Data from the NHLS has recently been deduplicated to create a National HIV Cohort database allowing the identification of the first CD4 entry for individuals appearing in the NHLS data. Using this NHLS Cohort, it is possible to identify individuals' first CD4 count. A strength of this cohort for our purposes is that it has complete laboratory data. A limitation is that it only includes laboratory data and does not include patient visit data.

TIER.Net is national HIV care and treatment monitoring database, utilized in direct patient management by all facilities nationally. TIER.Net contains all HIV-TB associated patient visit information, including ART initiation, prescriptions, and medicine collections [19]. While TIER.Net provides a rich source of cross-sectional and longitudinal routine ART data, there is currently no integrated national TIER.Net database. TIER.Net has collected data prospectively since 2011, and paper records were back-captured into TIER.Net from the start of the national HIV programme in 2004 through 2015. A strength of this cohort is that we can easily identify when ART initiation occurs. A limitation of TIER.Net is that it has only recently (since 2015) started capturing clinical data for

individuals on ART [20] [19]. Because first CD4 counts were historically obtained prior to ART initiation (now on the same day of entry into care), TIER.Net has gaps in first CD4 counts. TIER.Net data back-capture, which occurred after 2015, introduces distortions in the estimates of patient numbers and CD4 testing. These gaps in the TIER.Net database mean that it may underreport the true number of individuals entering care and those receiving CD4 tests, particularly in earlier periods.

Outcomes measures

Our primary outcome measure was "first CD4 count", defined as the first CD4 test for each patient within each database. As national guidelines specify CD4 testing at clinical presentation, we interpret the date of a individuals' "first CD4 count" as the date of entry into care. In the UTT era, this is typically at ART initiation, whereas prior to the UTT era, this could be substantially before ART initiation. However, not all individuals entering care have a CD4 count. Although we do not observe these individuals in the NHLS data, we may observe them in TIER.Net. We defined "date of clinical presentation" as the first of the following dates in TIER.Net: HIV diagnosis date, first visit date or first CD4 count date.

Statistical analysis

We assessed the number of individuals with a first CD4 count of the NHLS and TIER.Net databases. We used descriptive statistics to summarize baseline characteristics of individuals, categorizing the initial CD4 count values into four groups (0–199, 200–349, 350–500, > 500) and calculated median age across three distinct time periods (2004–2010, 2011–2014, 2015–2018). The 2004–2010 period is grouped together due to the stability in HIV treatment guidelines during these years, with the CD4 eligibility threshold set at 200 cells/mm^3. This phase reflects the early ART programme expansion, and further splitting would offer limited value while reducing statistical power. Later periods (2011–2014, 2015–2018) reflect significant policy changes, such as adjustments to CD4 thresholds and the introduction of UTT, justifying separate analysis. We compared data on first CD4 counts between the NHLS and TIER.Net databases, as well as total numbers of individuals entering HIV care within TIER.Net (with or without a CD4 count) in the same period. We then assessed changes in first CD4 count volumes with the implementation of UTT in September 2016. For each database, we calculated and plotted the monthly average of daily counts of individuals with a first CD4 test over the period from March 2015 to March 2018. Comparing estimates from NHLS and TIER.Net offers valuable insights into the consistency of data across different health information systems. Discrepancies may highlight areas for improving data collection and integration, while similarities reinforce the reliability of these systems. This comparison can also shed light on the coverage and quality of HIV-related services, indicating whether laboratory diagnostics align with treatment and management. To account for the incomplete data in TIER.Net, we calculated the proportion of individuals receiving a first CD4 count relative to the total number of individuals entering care. To address potential underreporting, we adjusted these proportions by multiplying with ratio NHLS-TIER.Net first CD4 ratio.

To measure the impact of the UTT policy on first CD4 count volumes, we performed a linear regression interrupted time-series (ITS) analysis by analysing changes in the first CD4 count before and after UTT for each database (NHLS and TIER.Net) [21]. By fitting the model independently to each dataset, we aimed to avoid confounding from structural differences between the databases and to ensure that trends in CD4 testing volumes were appropriately analysed within the context of each dataset's unique characteristics. This also allowed us to assess the impact of the Universal Test and Treat (UTT) policy on CD4 testing trends in each database independently, providing a more robust understanding of how CD4 testing has changed over time in both the NHLS laboratory and TIER.Net clinical settings. This approach leverages a continuous time variable, a binary indicator for the policy change (UTT) and interaction terms that account for the dynamic shifts over time due to the UTT policy.

The form of our interrupted time series is based on a linear model:

$$Y_t = \beta_0 + \beta_1 \cdot Time + \beta_2 \cdot Treatment + \epsilon_t$$

where Y_t is first CD4 count at time t, *Time* is a continuous variable coded in months starting from 18 months pre UTT (denoted -18 months) and increasing until 18 months post UTT, and *Treatment* is a binary indicator variable that is 0 before UTT and 1 after UTT and represents the effect of UTT on first CD4 counts.

To adjust for prior trends in first CD4 counts in the pre-UTT era, we fit linear regression models to the pre-UTT-period data (from 18 months before UTT adoption until September 2016). Adjusting for prior trends means accounting for the CD4 testing patterns that were occurring before UTT, which are critical for an interrupted time-series (ITS) analysis. This adjustment allows us to compare pre- and post-UTT trends accurately and isolate the specific impact of UTT. All statistical analyses, including the interrupted time-series (ITS) analysis, were conducted using STATA 18 (StataCorp, College Station, TX, USA). The analytic codes used for statistical analyses

in this study are publicly available at https://github.com/cnattey/CD4-trends-analysis/tree/main[22].

Results

We analyzed data from 5,274,218 individuals in the NHLS cohort and 2,265,557 individuals in the TIER.Net cohort with a first CD4 count from 1724 facilities in 5 South African provinces between January 2004 and March 2018 (Table 1).

Primary healthcare facilities constituted the majority of facilities (58.5% in NHLS and 66.6% in TIER.Net). The demographics of individuals with a first CD4 count were similar in the two databases: median age was 33 (*IQR*: 26, 44) years in NHLS and 33 (*IQR*: 27, 41) years in TIER.Net. The proportion of females was 65% in NHLS and 66% in TIER.Net. However, the first distribution of first CD4 counts in the NHLS database had many more individuals earlier in disease progression than in TIER.Net: 34% of individuals in NHLS and 48% in TIER.Net presented with a CD4 count < 200 cells/μl, and 23% of individuals presented with a CD4 count > 500 cells/μl in NHLS, while this proportion was 12.4% in TIER.Net.

Trends in the number of individuals with a first CD4 count

Within the NHLS, the number of individuals with a first CD4 count increased from 47,604 in 2004 to 383,705 in 2010. After 2010, decreasing trends were observed and persisted into the UTT era (Fig. 1) until 2018. TIER.Net data, which were back-captured in the early years of the treatment program, lagged behind the NHLS throughout the entire period. However, numbers in TIER.Net approximately tracked those in NHLS starting in 2015. Back-capturing can compromise the accuracy and reliability of the data especially if recording is incomplete or patient files are lost. This can result in inconsistencies, errors and gaps in TIER.Net data. In both databases, first CD4 testing volumes fell by about 26% from August 2016, a month before UTT, to March 2018 within the five provinces (Fig. 1).

Changes in CD4 monitoring with "Universal Test and Treat" in five South African provinces: regression estimates

We examined CD4 monitoring changes 18-month post-UTT adoption and the proportion of individuals entering care with a first CD4 count, and the results are presented in Table 2. Overall, first CD4 volumes

Table 1 Characteristics of the individual with first CD4 count in TIER.Net and NHLS 2004–2018

	2004–2010		2011–2014		2015–2018	
	NHLS	TIER.Net	NHLS	TIER.Net	NHLS	TIER.Net
Total entering care		558,106		1,138,518		1,342,226
Total number of individual with a first CD4 count	2,018,475	414,553	2,079,594	915,360	1,176,149	935,644
Gender						
Female	1,384,525 (68.6%)	275,185 (67.4%)	1,348,929 (64.9%)	603,231 (65.9%)	713,797 (60.7%)	616,375 (65.9%)
Male	603,734 (29.9%)	139,368 (33.6%)	693,424 (33.3%)	312,129 (34.1%)	439,696 (37.4%)	319,269 (34.1%)
Missing	30,216 (1.5%)		37,241 (1.8%)		22,656 (1.9%)	
Age						
Mean, (SD)	33.0 (11.6)	34.9 (11.9)	33.7 (11.8)	34.2 (11.2)	34.3 (11.7)	34.0 (10.7)
Median, (IQR)	32 (26 to 40)	34 (28 to 41)	33 (27 to 41)	33 (28 to 41)	33 (27 to 41)	33 (27 to 40)
Total number of facilities	1724	1724	1724	1724	1724	1724
First CD4 by facility type						
Community health care centre (CHC)	238,932 (11.8%)	56,694 (13.7%)	263,227 (12.7%)	121,052 (13.2%)	151,816 (12.9%)	133,935 (14.3%)
Primary health care (PHC)	1,060,301 (52.5%)	155,150 (37.4%)	1,274,472 (61.3%)	639,673 (69.9%)	748,932 (63.7%)	714,798 (76.4%)
Hospitals	719,242 (35.6%)	202,709 (48.9%)	541,895 (26.1%)	154,639 (16.9%)	275,401 (23.4%)	86,911 (9.3%)
First CD4 count categories						
< 200	796,655 (39.5%)	301,349 (77.2%)	679,242 (32.7%)	447,524 (50.5%)	365,972 (31.1%)	304,999 (33.3%)
200–350	481,406 (23.9%)	56,454 (14.5%)	503,974 (24.2%)	300,224 (33.9%)	268,612 (22.8%)	230,143 (25.1%)
> 350–500	323,218 (16.0%)	15,314 (3.9%)	387,324 (18.6%)	69,414 (7.8%)	218,413 (18.6%)	195,469 (21.3%)
> 500	417,196 (20.7%)	16,997 (4.4%)	509,054 (24.5%)	69,135 (7.8%)	323,152 (27.5%)	186,121 (20.3%)

Note and definitions: The table shows characteristics of individuals with first CD4 count captured in two databases "TIER.Net" and the "NHLS' across three distinct time period periods (2004–2010, 2011–2014, 2015–2018). Back-capturing of TIER.Net data which started in 2015 accounts for the distortion in our estimates of TIER.Net compared to NHLS. The total number of individuals with a first CD4 count represents 74.5% of the total number of individuals with a record (enter care). Total entering care is the total number of patient records only available in TIER.Net. Total number of individuals with a first CD4 count is the total number of individuals with a first CD4 count in TIER.Net out of the total number of individuals records (entering care). *SD* is the standard deviation. Median (IQR) is the median and interquartile range

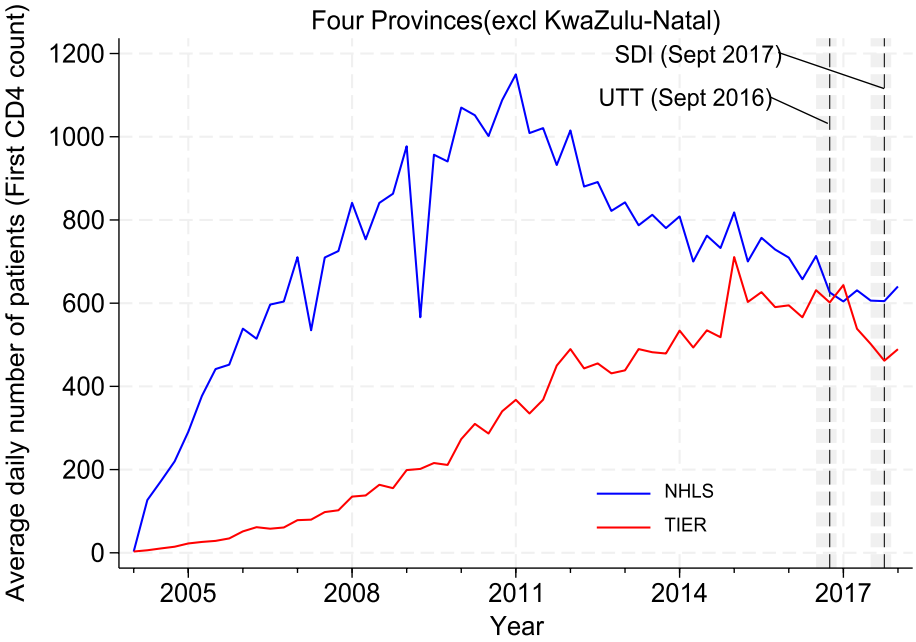

Fig. 1 Trends in number of individuals diagnosed with HIV in the public sector with first CD4 count by quarterly calendar period from January 2004 to March 2018 in NHLS and TIER.Net in four provinces of South Africa

Table 2 Changes in CD4 monitoring with "Universal TestandTreat" in five South African provinces: regression estimates from March 2015 to March 2018

Dependent variable	Total no. of individuals	Mean, 18-month pre-UTT (A)	Mean, 18-month post-UTT (B)	Mean change from pre- to post-UTT (B)-(A)	Mean change post-UTT, adjusted for pre-trend		
					0–18 months	0–6 months	7–18 months
Daily no. of first CD4s (NHLS)	1,100,064	1049	910	−139 (−201 to −78)	32 (−6 to 61)	−13 (−97 to 90)	58 (−0 to 117)
Daily no. of first CD4 (TIER.Net)	877,565	803	758	−45 (−123 to 33)	88 (30 to 148)	181 (51 to 310)	35 (−18 to 87)
% of individuals presenting for care (TIER.Net)	80.0%	73.2%	59.7%	−13.4% (−14.5 to −12.4%)	−4.3% (−5.2 to −3.0)	−0.6% (−1.9 to 0.5%)	−6.4% (−7.3 to −5.5)

Note and definitions: The table shows linear regression models' coefficients for indicator variable of 18-month pre-UTT and 18-month post-UTT per day. Main outcome was the number of "first CD4" count in a day. Adjusted post-UTT regression coefficient stratified by different post-UTT periods (0–18 months, 0–6 months and 7–18months) is also shown. *UTT*, Universal test and treat, 18-month pre-UTT and 18-month post-UTT, 18-month pre- and post-UTT, daily linear regression coefficient of indicator variable of pre-UTT and post-UTT. Daily no. presenting (NHLS) is the total number of individuals who presented in care within NHLS. Daily no. first CD4 count (TIER.Net) is the total number of individuals with a first CD4 count in .Net, % of individuals presenting for care (TIER.Net) is the percent of patient records in TIER.Net that had a CD4 count recorded

after UTT adoption decreased within the NHLS by an average 139 individuals per day [95% confidence interval (CI): −78 to −201]. After adjusting for the pre-UTT trend, we saw a modest increase of an average 32 individuals per day (95% *CI*: 32 (−6 to 61)) after UTT (Table 2). The average of 32 individuals per day refers to the increase in the number of individuals receiving a first CD4 count per day across all facilities within the NHLS database, following the implementation of UTT. This figure represents the estimated daily increase in CD4 testing volumes, averaged across the entire dataset, rather than being specific to individual facilities.

In TIER.Net we saw an increase in first CD4 testing volumes after UTT adoption by an average 88 individuals (95% *CI*: −16 to 210) per day after adjusting for the pre-UTT trend (Table 2).

The proportion of people entering care post-UTT who had a CD4 count test done decreased by an average 13.4% on a monthly basis (95% *CI*: −14.5 to −12.4%) (Table 2). After adjusting for pre-UTT trends, there was a marginal decrease of an average 4.3% (95% *CI*: −5.2

to − 3.0) in the share of people entering care who had a CD4 count done. A decline in number of first CD4 counts done post-UTT is visible in the TIER.Net data, but numbers were relatively stable in NHLS (Fig. 2). Thus, the decline in the proportion of TIER.Net individuals with a CD4 count could reflect increased underreporting of laboratory data in TIER.Net in the UTT era (Fig. 3). If we adjust for the ratio of first CD4 counts in NHLS to TIER.Net, the share of people entering care who had a CD4 count declines by only 21.1% with UTT (Fig. 4). This adjustment highlights discrepancies between the two datasets, particularly underreporting of CD4 counts in TIER.Net. Therefore, the 21.1% decline reflects the proportion of individuals

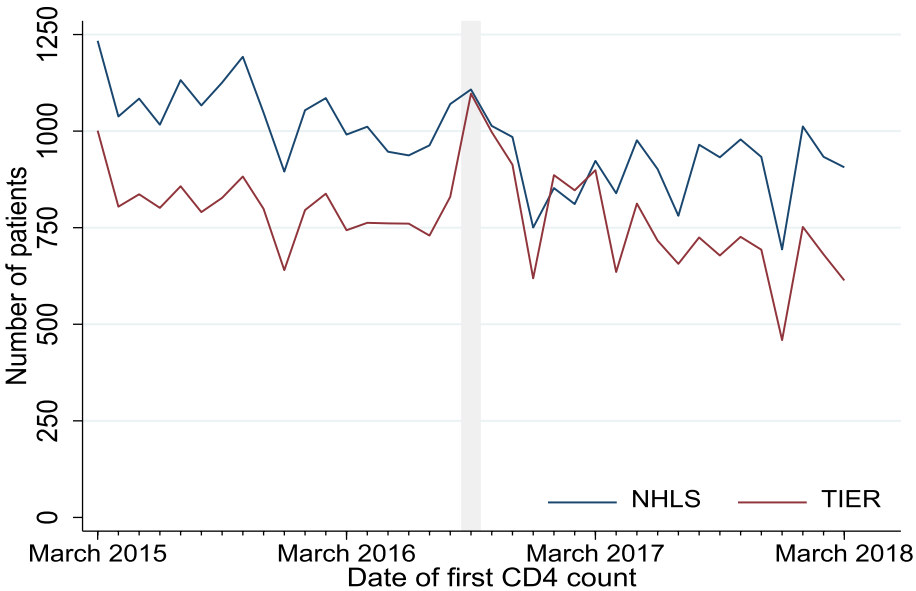

Fig. 2 Average number of new individuals (per day) with a first CD4 count in NHLS and TIER.Net databases from March 2015 to March 2018. The grey bar indicates the implementation of the Universal Test and Treat (UTT) policy in September 2016

Fig. 3 Percent of patient records in TIER.Net that had a CD4 count recorded from March 2015 to March 2018. The grey bar indicates the implementation of the Universal Test and Treat (UTT) policy in September 2016

Fig. 4 Adjusted percent of patient records in TIER.Net that had a CD4 count recorded from March 2015 to March 2018. The grey bar indicates the implementation of the Universal Test and Treat (UTT) policy in September 2016

whose CD4 count was documented in TIER.Net rather than an actual clinical reduction in CD4 testing.

Comparison of distribution of CD4 counts (2015–2017) in NHLS and TIER.Net

We compared distribution of first CD4 distribution within NHLS and Tier.Net using kernel plots (Additional file 1: Fig. S3). The NHLS data shows that the CD4 count distributions for 2015, 2016, and 2017 are similar, with minimal variation across the years. The peak density occurs around 50–100 cells/μL, indicating that a large proportion of individuals are presenting with very low CD4 counts (severe immunosuppression) during this period. The distribution has a long tail, extending to higher CD4 counts, but there is little indication of a significant shift in distribution between the 3 years. This suggests that NHLS data shows consistent patterns in terms of CD4 count distribution at presentation, with no substantial improvement or worsening over time.

The TIER.Net data displays a more pronounced variation between the years, particularly between 2015 and 2016. The peak density for 2015 is higher than for 2016 and 2017, especially in the low CD4 count range (0–200 cells/μL), indicating that more patients had severe immunosuppression in 2015 compared to subsequent years. There is a noticeable shift in the distribution in 2016 and 2017, suggesting a slight improvement, as the curve flattens for higher CD4 counts (200–600 cells/μL). This might indicate that after UTT introduction, more individuals are being diagnosed earlier, thus presenting with higher CD4 counts.

The data shows a consistent pattern across 2015–2017 within the NHLS, with a large proportion of individuals having low CD4 counts at presentation. There is little variation between the years. TIER.Net: There is a more noticeable shift over time, particularly with fewer individuals having very low CD4 counts after 2015. This suggests some positive impact of UTT in identifying patients earlier, as reflected by the increase in CD4 counts.

Discussion

In this study, we assessed trends in first CD4 count testing from five provinces in South Africa between January 2004 and March 2018. We also compared the number of first CD4 counts in the 18 months after UTT to 18-month pre-UTT per day after adjusting for pre-trends. The decline in number of CD4 counts done post-UTT is visible in the TIER.Net data, whereas numbers were stable in NHLS, with any decline fully consistent with pre-trends going back years. There was no evidence of substantial decline in CD4 count monitoring after adjusting pre-trends in the UTT era.

A recent study at 17 public sector primary care clinics in rural South Africa between July 2014 and March 2019 [23] found that the proportion of individuals without baseline CD4 counts increased over time, particularly after the policy change to UTT. A large proportion of individuals had advanced HIV at ART initiation despite the eligibility expansion in the same study. Similarly, in

our study, we found that 34.9% of individuals presented with advanced HIV disease (CD4 count < 200 cells/μl) at ART initiation. This aligns with observations from other studies in the region, suggesting that the removal of CD4 criteria for ART eligibility has not fully addressed the challenge of late presentation for care [24]. The persistence of late-stage disease at initiation, despite expanded ART eligibility, points to the need for continued efforts in improving early diagnosis, linkage to care, and engagement with HIV services. Two other studies in Southern Africa using regression discontinuity design found first CD4 testing slightly increased in Zambia but decreased substantially with UTT in Malawi and moderately in Mozambique, with no effect in Lesotho or Zimbabwe [11] [25]. Several factors may explain these trends in decrease in first CD4 count after the adoption of the UTT policy. First, in the pre-UTT era, ART eligibility was determined by CD4 thresholds [< 200 cells/mm^3 up to 2010 [26], ≤ 350 up to 2013 [10] [27]], requiring repeat CD4 tests to monitor patients who were not yet eligible for ART. However, with the introduction of UTT, repeat testing for ART eligibility became unnecessary, leading to a decrease in overall CD4 testing volumes, as observed in our study and others from the region [13]. Second, following UTT implementation, health workers may have selectively conducted CD4 tests for patients perceived to be at higher risk of advanced disease, focusing on those with signs of severe immunosuppression. This selective approach likely reduced the overall increase in CD4 testing volumes under UTT, as CD4 tests were concentrated on those with clinical indications rather than performed universally. This pattern of reduced CD4 testing volumes post-UTT is consistent with findings from other studies in Southern Africa [12], which also observed declines in CD4 testing following the policy shift, particularly as viral load monitoring gained prominence and repeat CD4 testing for ART eligibility was no longer necessary. Third, lack of staffing and other resource shortages may have limited timely implementation of the UTT policy due to limited training or competing clinical priorities [28] [29]. Additionally, variations in healthcare infrastructure and resource allocation across facilities could have influenced the consistency of CD4 testing. South Africa's relatively strong investment in domestic funding for HIV services may have mitigated the sharp declines in CD4 testing seen in other countries reliant on external donors [17]. Furthermore, broader shifts in HIV management, particularly the increased emphasis on viral load monitoring, could have reduced reliance on CD4 testing, though it remains essential in resource-limited settings to monitor immunological status and guide interventions for opportunistic infections. Competing health priorities, such as tuberculosis control or economic constraints, may have further impacted CD4 testing availability during this period [30]. The expected impact of UTT was an increase in baseline CD4 testing due to the demand for immediate ART initiation for all HIV-positive individuals [23]. A notable trend in this study is the decline in CD4 testing that began before the introduction of UTT, which several factors could have contributed to this earlier decline, including a shift towards prioritizing viral load monitoring, healthcare worker shortages, and evolving clinical priorities in HIV care [31]. These factors may have influenced testing volumes prior to UTT and could have persisted or evolved during the UTT era. Understanding the role of these pre-existing trends is critical for interpreting our results. By adjusting for pre-UTT trends in our statistical model, we aimed to isolate the specific impact of UTT on CD4 testing, ensuring that the observed changes were not simply a continuation of broader, ongoing shifts in HIV care practices.

We found that TIER.Net first CD4 testing data showed fewer individuals with a first CD4 count than the NHLS data until 2015, after which volumes were similar, although some gaps still do persist between the two data sources. A recent study, highlighting challenges with tracing individuals on antiretroviral therapy who are late for clinic appointments in rural South Africa [20], reported that what appears in TIER.Net does not always reflect what is captured in patient files suggesting data documentation and record-keeping challenges.

Finally, a number of important limitations need to be considered when interpreting our results. Firstly, data analysed are until 2018, and we were unable to extend the analysis beyond this period. Since then, there may have been significant changes in HIV care, including updates to ART protocols and CD4 testing practices, which could impact the trends observed in this study. These changes may have introduced new dynamics in CD4 testing patterns, which we were unable to capture. Future research should aim to incorporate more recent data to reflect these developments and provide a more up-to-date understanding of CD4 testing trends in the context of evolving HIV care. Secondly, first CD4 count recorded may not reflect the true baseline CD4 count, particularly if there are delays between diagnosis and entry into care. This could lead to misclassification of individuals' baseline immunological status and an underestimation of the proportion of individuals with advanced HIV disease. Consequently, our interpretation of trends in CD4 testing and advanced disease may be affected, potentially masking the full extent of late presentation for care. Thirdly, this study uses observational design, which does not account for other concurrent changes in the healthcare system that may have coincided with the implementation of UTT and influenced CD4 testing. Without

controlling for these external factors, the findings may be affected by broader shifts in HIV care or other policy changes during the study period. Fourthly, our study did not account for differences in the level of care or access to laboratory testing that may vary across and within provinces as a result of different facility types and locations. Fifthly, we observed substantial differences between the NHLS and TIER.Net databases. While we attempted to account for these discrepancies by adjusting the TIER.Net data using the NHLS ratio, this simple adjustment only partially addresses the challenges. TIER.Net relies on manual data entry, which often results in missing or incomplete records, and its coverage may not be as comprehensive as the NHLS laboratory data. Consequently, the differences in data structure and reporting between the two databases limit the effectiveness of this adjustment, and it does not fully correct for the inadequacies of TIER.Net. This underscores the need for more robust data integration to ensure accurate comparisons of CD4 testing trends between the two sources. Lastly, while interrupted time series (ITS) is a robust method for assessing the effects of interventions over time, it has several limitations. First, ITS cannot account for all potential confounders that may influence the outcome during the study period, such as concurrent policy changes or shifts in healthcare infrastructure that could have affected CD4 testing independently of UTT implementation. Second, ITS assumes that trends before the intervention would have continued unchanged without the intervention, which may not always hold true. External factors such as changes in resource allocation, staffing, or diagnostic capacities may also have contributed to the observed trends. Finally, although ITS adjusts for pre-existing trends, it cannot fully address unmeasured variables that might influence outcomes, limiting the ability to definitively attribute changes solely to the introduction of UTT.

CD4 count test remains an important marker of the immunological status for newly diagnosed HIV individuals and at the same time an important tool in predicting future HIV-related morbidity [3] [4]. While the observed first CD4 count decreasing trends in the both the NHLS and TIER.Net databases may be due to decreasing number of individuals entering into care [32] [33] and not changes in clinical practice, the need to re-emphasize the upscaling of first CD4 count uptake must be considered.

Conclusions

The decline in number of CD4 counts done post-UTT is visible in TIER.Net data, but numbers were stable in the NHLS, with any decline fully consistent with pre-trends going back years. However, many of these results are not making it into TIER.Net, which may be driving the misperception that CD4 testing stopped. Falling test volumes since 2011 may reflect falling numbers of people entering HIV care over time, rather than changes in clinical practice. Integrating NHLS and TIER.Net data electronically may help reduce observed gaps in the two data sources. Nonetheless, the finding of these study is primarily applicable to South Africa and should be interpreted with caution, and further research using more recent data is necessary to fully understand the long-term trends in CD4 testing post-UTT.

Abbreviations

UTT	Universal Test and Treat
ART	Antiretroviral therapy
NHLS	National Health Laboratory Service
TIER.Net	Three Interlinked Electronic Registers Network
SDI	Same-day ART initiation
ITS	Interrupted time series

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s44263-024-00118-6.

Additional file 1. Supplementary figures: Figure S1. Trends in number of individuals diagnosed with HIV in the public sector with first CD4 count by quarterly calendar period from January 2004-March 2018 in NHLS and TIER.Net in five provinces of South Africa. Figure S2: Number of new individuals (per day) with a first CD4 count in NHLS and TIER.Net databases from March 2015 to March 2018 in five provinces in South Africa. Figure S3. Kernel density plot of CD4 count distributions for 2015, 2016, and 2017 (NHLS vs TIER.NET). The plot shows the distribution of CD4 counts for individuals presenting for HIV care in the NHLS database.

Acknowledgements

We gratefully acknowledge the use of data from the TIER.Net system, which is managed by the South African National Department of Health. We thank all the healthcare providers and data capturers for their dedicated work in collecting and maintaining these data. This research would not have been possible without their contributions. We also wish to acknowledge the South African National Health Laboratory Services for access to laboratory data.

Authors' contributions

JB, DO and CN conceptualized this analysis. JB and DO designed the analytic strategy and CN analyzed the data. CN, JB and DO drafted the manuscript and all authors helped to interpret the finding and provided critical review and editing the manuscript text and figures. All authors read and approved final manuscript.

Funding

This research was funded by National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number R01AI152149. The NHLS cohort was also supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development/National Institute of Allergy and Infectious Disease and National Institutes of Health under grant U01HD080441. The views expressed are solely those of the authors and do not necessarily represent the views of the NIH. The funding source had no role in. the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit the results.

Data availability

Datasets from NHLS and TIER.Net used in this study are not publicly accessible. These databases are maintained by the South African National Health Laboratory Service and the South African provincial departments of Health, and access to these data is governed by strict confidentiality agreements and ethical approvals, which prevent public sharing. The analytic codes used for statistical analyses in this study are publicly available at https://github.com/cnattey/CD4-trends-analysis/tree/main.

Declarations

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee (HREC) of the University of Witwatersrand (ref. no. M200447) in South Africa and Boston University in the USA (IRB no. H-31968). No study participant recruitment took place since all data were collected as part of routine care in both databases. Data access for anonymized patient laboratory records in TIER.Net and NHLS were obtained from provincial departments of health as well as the NHLS.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 24 June 2024 Accepted: 6 December 2024
Published online: 02 January 2025

References

1. World Health Organization. Consolidated guidelines on the use of antiretro_viral drugs for treating and preventing HIV infection: recommendations for a public health approach.le. Vol. 2nd ed. Geneva; 2016. Available from: https://www.who.int/hiv/pub/arv/arv-2016/en/
2. South African National Department of Health (South Africa). Implementation of Universal Test and Treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria; 2016.
3. Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med. 2013;10(4):e1001418. https://doi.org/10.1371/journal.pmed.1001418.
4. Boulle A, Schomaker M, May MT, Hogg RS, Shepherd BE, Monge S, et al. Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: a collaborative analysis of prospective studies. PLoS Med. 2014;11(9)e1001718. https://doi.org/10.1371/journal.pmed.1001718.
5. May M, Boulle A, Phiri S, Messou E, Wood PR, Keiser O, et al. Up programmes. 2011;376(9739):449–57.
6. Ford N, Meintjes G, Vitoria M, Greene G, Chiller T. The evolving role of CD4 cell counts in HIV care. Curr Opin HIV AIDS. 2017;12(2). Available from: https://journals.lww.com/co-hivandaids/Fulltext/2017/03000/The_evolving_role_of_CD4_cell_counts_in_HIV_care.5.aspx
7. World Health Organization. Managing advanced HIV disease and rapid initiation of antiretroviral therapy. Genenva; 2017. Available from: https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/
8. South African National Department of Health. Tracking implementation of the 90–90–90 strategy for HIV, through the implementation of test and treat (TT) policy and same-day anti-retroviral therapy (art) initiation for HIV positive patients. Pretoria; 2017.
9. World Health Organization. Scaling up antiretroviral therapy in resource limited settings: guidelines for a public health approach. Geneva; 2002. Available from: https://www.who.int/hiv/pub/guidelines/pub18/en/
10. Granich R, Gupta S, Hall I, Aberle-Grasse J, Hader S, Mermin J. Status and methodology of publicly available national HIV care continua and 90–90-90 targets: a systematic review. PLoS Med. 2017Apr;14(4): e1002253.
11. Zaniewski E, Dao Ostinelli CH, Chammartin F, Maxwell N, Davies M-A, Euvrard J, Trends in CD4 and viral load testing 2005 to 2018: multi-cohort study of people living with HIV in Southern Africa. J Int AIDS Soc., et al. 1;23(7):e25546. Available from: 2020. https://doi.org/10.1002/jia2.25546.
12. Brazier E, Tymejczyk O, Zaniewski E, Egger M, Wools-Kaloustian K, Yiannoutsos CT, et al. Effects of national adoption of Treat-All guidelines on pre-antiretroviral therapy (ART) CD4 testing and viral load monitoring after ART initiation: a regression discontinuity analysis. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2021;73(6):e1273–81.
13. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva; 2015. Available from: https://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/
14. Lamp K, McGovern S, Fong Y, Atem CD, Nfetam JBE, Nzuobontane D. Proportions of CD4 test results indicating advanced HIV disease remain consistently high at primary health care facilities across four high HIV burden countries. PLoS One. 7;15(1):e0226987. Available from: 2020. https://doi.org/10.1371/journal.pone.0226987.
15. Carmona S, Bor J, Nattey C, Maughan-Brown B, Maskew M, Fox MP, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa's National HIV Program: data from a nationwide laboratory cohort. Clin Infect Dis. 2018;66(S2):S111–S117. https://doi.org/10.1093/cid/ciy045.
16. Lecher S, Williams J, Fonjungo PN et al. Progress with scale-up of HIV viral load monitoring – seven sub-Saharan African countries, January 2015-June 2016. 2016. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6547a2.htm
17. Jamieson L, Meyer-Rath G, Kubjane M, Johnson L. South African HIV Investment Case Full Report 2023 Update. 2023;(December).
18. Bor J, Macleod W, Oleinik K, Potter J, Brennan AT, Candy S, Building a National HIV Cohort from routine laboratory data: probabilistic record-linkage with graphs., et al. cited 2019 Aug 20. Available from: 2018. https://doi.org/10.1101/450304.
19. Osler M, Hilderbrand K, Hennessey C, Arendse J, Goemaere E, Ford N, et al. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. J Int AIDS Soc. 2014;17(1):18908.
20. Etoori D, Wringe A, Renju J, Kabudula CW, Gomez-Olive FX, Reniers G. Challenges with tracing patients on antiretroviral therapy who are late for clinic appointments in rural South Africa and recommendations for future practice. Glob Health Action. 2020Dec;13(1):1755115.
21. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017Feb;46(1):348–55.
22. Nattey, Cornelius, Onoya, Dorina, Shumba, Khumbo, Gareta, Dickman, Macleod, William, Fox, Matthew P., Puren, Adrian, Mlisana, Koleka, Bor, Jacob. CD4 trends analysis. GitHub Repository. https://github.com/cnattey/CD4-trends-analysis/tree/main (2024).
23. Yapa HM, Kim H-Y, Petoumenos K, Post FA, Jiamsakul A, De Neve J-W, et al. CD4+ T-cell count at antiretroviral therapy initiation in the "Treat-All" era in rural South Africa: an interrupted time series analysis. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2022Apr;74(8):1350–9.
24. Asare K, Lewis L, van der Molen J, Sookrajh Y, Khubone T, Ngwenya T, et al. Impact of increasing CD4 count threshold eligibility for antiretroviral therapy initiation on advanced HIV disease and tuberculosis prevalence and incidence in South Africa: an interrupted time series analysis. medRxiv. 2024 Jan 1;2024.06.21.24309333. Available from: http://medrxiv.org/content/early/2024/06/23/2024.06.21.24309333.abstract
25. Zaniewski E, Brazier E, Ostinelli CHD, Wood R, Osler M, Technau K-G, et al. Regression discontinuity analysis demonstrated varied effect of Treat-All on CD4 testing among Southern African countries. J Clin Epidemiol. 2021;140:101–10. Available from: https://www.sciencedirect.com/science/article/pii/S089543562100281X
26. Organization WH. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach. World Health Organization; 2004.
27. Organization WH. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach-2010 revision. World Health Organization; 2010.
28. Yapa HM, Dhlomo-Mphatswe W, Moshabela M, De Neve J-W, Herbst C, Jiamsakul A, et al. A continuous quality improvement intervention to improve antenatal HIV care testing in rural South Africa: evaluation of implementation in a real-world setting. Int J Heal policy Manag. 2022May;11(5):610–28.
29. Michel J, Chimbindi N, Mohlakoana N, Orgill M, Bärnighausen T, Obrist B, et al. How and why policy-practice gaps come about: a South African universal health coverage context. J Glob Heal reports. 2019;3: e2019069.
30. Barnabas RV, Revill P, Tan N, Phillips A. Cost-effectiveness of routine viral load monitoring in low- and middle-income countries: a systematic review. J Int AIDS Soc. 2017;20Suppl 7(Suppl 7):e25006. https://doi.org/10.1002/jia2.25006.
31. Roberts T, Cohn J, Bonner K, Hargreaves S. Scale-up of routine viral load testing in resource-poor settings: current and future implementation challenges. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2016;62(8):1043–8.
32. Lauren E, Shumba K, Fox MP, MacLeod W, Stevens W, Mlisana K, The fall—and rise—in hospital-based care for people with HIV in South Africa:

2004–2017. PLOS Glob Public Heal., et al. 5;4(9):e0002127. Available from: 2024. https://doi.org/10.1371/journal.pgph.0002127.
33. Kitenge MK, Fatti G, Eshun-Wilson I, Aluko O, Nyasulu P. Prevalence and trends of advanced HIV disease among antiretroviral therapy-naïve and antiretroviral therapy-experienced patients in South Africa between 2010–2021: a systematic review and meta-analysis. BMC Infect Dis. 2023;23(1):549.

Publisher's Note