

Analysis of Big Data for Improving Antiretroviral Treatment Programmes

Determinants of CD4 Immune Recovery among Individuals on ART in South Africa

A National Analysis | February 2016



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Evaluation of programmes to support adherence
during all stages of the HIV care cascade
in South Africa

**Determinants of CD4
immune recovery among
individuals on antiretroviral
therapy in South Africa:
a national analysis**

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LIST OF ACRONYMS

ART	Antiretroviral therapy
CCMT	Comprehensive care, management and treatment programme
CD4	Cluster of differentiation type 4 cells
CDC	Centres for Disease Control
CDW	Corporate Data Warehouse
EC	Eastern Cape Province
FS	Free State Province
GP	Gauteng Province
IQR	Interquartile range
HIV	Human immunodeficiency virus
KZN	KwaZulu Natal Province
LP	Limpopo Province
MDR/XDR	Multi drug resistant/ Extensive drug resistant
MP	Mpumalanga Province
NC	Northern Cape Province
NGOs	Non-governmental organisations
NICD	National Institute for Communicable Diseases
NHLS	National Health Laboratory Service
NW	North West Province
STI	Sexually Transmitted Infections
TB	Tuberculosis
VL	Viral load
WC	Western Cape Province
WHO	World Health Organisation

EXECUTIVE SUMMARY

Background

South Africa has the largest HIV epidemic in the world. About three million people were receiving antiretroviral therapy (ART) as of March 2015. ART is expected to suppress viral replication and allow immunological recovery. However, a significant proportion of adults who initiate ART fail to achieve immunological recovery. Sub-optimal immune recovery is associated with increased morbidity and mortality from HIV-associated opportunistic infections and illness. Linking patient-level CD4 and viral load test result data from the South African national health laboratory system and data from the health information system enabled a new analysis of immune recovery. This report describes the proportions of individuals 15 years or older who initiated ART between 2010 and 2014 and achieved CD4 count recovery to 200, 350 and 500 cells/ μ l, their time to CD4 count recovery, and extent of recovery in the first 12 months of follow up.

Methods

Routinely collected CD4 count and viral load laboratory data were linked to unique individuals using a probabilistic matching algorithm; a cohort of individuals who met eligibility criteria was identified and included in the analysis. In order to be eligible for inclusion individuals had to: i) be 15 years or older, ii) have two or more CD4 count results and at least one viral load in the corporate data warehouse database, iii) have an estimated date of ART initiation between 1st January 2010 and 31st December 2014. Individuals entered the cohort at ART initiation and exited on the date of CD4 count recovery or on the date of the latest viral load or CD4 count test if there was no CD4 count recovery. The proportions of individuals who achieved CD4 count recovery to different thresholds were determined, and modified Poisson regression used to identify factors independently associated with CD4 count recovery. Survival analysis was used to determine the time to CD4 count recovery. The Kaplan-Meier log-rank test was used to assess the association between time to recovery and factors including age, gender, year of starting ART, and CD4 count at the start of ART. Random effects panel regression was used to estimate the extent of recovery during the first 12 months of ART.

Linking patient-level CD4 and viral load test result data from the South African national health laboratory system and data from the health information system enabled a new analysis of immune recovery.

Findings

A total of 1,070,900 individuals were included in the analysis. Of these 30.3% were male. The median CD4 count at ART initiation was 213 cells/ μ l (interquartile range (IQR) 117–324 cells/ μ l), median of duration of follow up was 24 months (IQR 12.2–36.9 months) ; and 85.9% achieved viral suppression by the end of follow up. Of the 46.6% of individuals who initiated ART with a CD4 count less than 200 cells/ μ l, 79.7% achieved CD4 count recovery to 200 cells/ μ l in a median of 9.5 months. Among those who were virally suppressed by the end of follow up, the

proportions who recovered to CD4 count thresholds of 200, 350 and 500 cells/ μ l were 85.3%, 68.3% and 44.4% in a median time to recovery of 9.4, 12.4 and 17.3 months respectively. The proportion who achieved CD4 count recovery beyond the specified thresholds was lower among older individuals, males, those with low CD4 counts, and those with a shorter duration of follow up. The extent of CD4 count recovery during the first 12 months of follow up was greatest among those who were virally suppressed by the end of follow up and those with the lowest CD4 counts at ART initiation.

Discussion and conclusion

Close to half of ART patients included in the cohort had CD4 counts < 200 cells/ μ l at treatment initiation despite increases in the CD4 count eligibility thresholds for ART to 350 cells/ μ l in 2009 and 500 cells/ μ l in 2015. Among the factors assessed, virological suppression during follow up and the CD4 count at ART initiation were the strongest predictors of the likelihood and extent of CD4 count recovery. There is need to strengthen interventions to improve early HIV testing and linkage to HIV care and treatment at higher CD4 counts. Despite trends towards reduced frequency of CD4 count monitoring, continued monitoring may be warranted for individuals with sub-optimal CD4 count recovery and population groups with lower capacity for immune reconstitution such as older ART patients in order to guide care including prophylactic treatments. Analysis of large sets of routine data and novel approaches in record linkage (sometimes referred to as big data) can contribute to better targeting and more efficient implementation of the South African ART programme.

BACKGROUND

South Africa has the largest HIV epidemic in the world. In 2013, an estimated 6.3 million people were living with HIV and 2.5 million had initiated ART.⁽¹⁾ Routine programme monitoring data highlight rapid programme expansion with 3.09 million people on ART in March 2015.⁽²⁾ Initiation of ART by people living with HIV is usually followed by decreases in HIV viral load (VL), increases in CD4 count and reduced morbidity and mortality from HIV-associated opportunistic infections and illnesses. Over the years the country has increased the CD4 count threshold for ART initiation from <200 cells/ μ l in 2009 to <500 cells/ μ l in 2015.⁽³⁾ After landmark studies showed that ART initiation at CD4 counts >500 cells/ μ l was associated with lower morbidity, the World Health Organization (WHO) issued new guidance recommending that all HIV positive individuals be initiated on ART regardless of CD4 count.⁽⁴⁾ South Africa will likely amend its ART initiation guidelines to incorporate this “test and treat” strategy in line with the WHO recommendation.⁽⁴⁾

Despite the increases in the CD4 count threshold for ART eligibility over the years and the gradual increase in the median CD4 count among those starting ART, a significant proportion of individuals diagnosed with HIV continue to initiate ART late with CD4 counts <200 cells/ μ l.^(5–9) Optimal adherence to ART is required in order to achieve virological suppression and immune recovery.⁽¹⁰⁾ Currently there is no universally agreed definition of immunological recovery or lack thereof. Some definitions of failure to achieve immune recovery have included: failure to attain an increase in CD4 cell count of >30% above the baseline during the first six to 12 months after ART initiation, failure to attain an absolute CD4 cell count >200 cells/ μ l during the first six to 12 months on ART, a CD4 count increase <50 cells/ μ l after 12 months on ART, and failure to increase CD4 count to above 500 cells/ μ l (considered normal immunological function) after four to seven years of ART.^(11–13) About 20–30% of individuals living with HIV and initiated on ART fail to restore CD4 counts despite achieving virological suppression.^(13, 14) Late presentation to care associated with low nadir and baseline CD4 counts^(15, 16) has been associated with sub-optimal immunological recovery despite achieving virological suppression.^(17, 18) Studies from sub-Saharan Africa and elsewhere have shown that sub-optimal immune recovery is also associated with older age (>50 years) at ART initiation,^(19–22) being male,⁽²³⁾ having a longer duration of HIV infection before initiating ART, sub-optimal adherence to ART,⁽¹⁰⁾ co-infection with tuberculosis (TB) and other infections, and on-going immune activation.⁽¹¹⁾ The late presenters, the immunological non-responders, and the delayed immunological responders continue to be at risk of increased morbidity and mortality from HIV-related illnesses including TB as well as non-AIDS-defining illnesses.^(9, 13, 14, 24–27) In addition, the burden of illness in these groups continues to be a significant cost to the health care system largely due to costs of hospitalisations, additional investigations, and treatments.⁽²⁸⁾

South Africa has the largest HIV epidemic in the world. In 2013, an estimated 6.3 million people were living with HIV and 2.5 million had initiated ART.

As part of a broader evaluation of adherence and retention in HIV care within the South African National ART programme, this report describes the determinants of CD4 immune recovery among individuals on antiretroviral therapy in South Africa. Specifically we report on the proportion of people achieving CD4 recovery, the average time to recovery, and the extent of CD4 count recovery in the first 12 months of follow up among individuals initiated on ART in the South African National ART

programme between 1st January 2010 and 31st December 2014. We analyse these outcomes by age, sex, CD4 count at ART initiation, and VL suppression. We also analyse outcomes by province and district. We define CD4 immune recovery as an increase in CD4 cell count beyond a specific threshold: i) achieving a CD4 count >200 cells/μl if initiating at a CD4 count <200 cells/μl; ii) achieving a CD4 count >350 cells/μl if initiating at a CD4 count <350 cells/μl; iii) achieving a CD4 count >500 cells/μl if initiating at a CD4 count <500 cells/μl.

Objectives

The objectives of the study were:

- To estimate the proportion of individuals 15 years or older who initiated ART during the period 2010 to 2014 and achieved CD4 recovery to different CD4 count thresholds, by province, district, age, gender, and year of starting ART;
- To estimate the time to CD4 recovery beyond the specified CD4 count thresholds among eligible individuals by province, district, age, gender, and year of starting ART;
- To estimate the extent of immune recovery in the first 12 months of ART by age, gender, and CD4 count at initiation.

Methods

Setting

The South African government has been providing ART at public health facilities through the comprehensive care, management and treatment (CCMT) programme since 2004. The programme adopted a public health approach to scaling up ART. This approach uses simplified and standardised treatment regimens and treatment monitoring strategies. Over the years, the country has changed both the CD4 count thresholds at which ART is initiated and treatment monitoring strategies, in line with global recommendations and evidence. Table 1 below shows the evolution of the guidelines on ART initiation and treatment monitoring approaches since the programme began in 2004.

In addition to changes in the treatment initiation and monitoring guidelines, the South African CCMT programme expanded rapidly from a few facilities mostly managed by non-governmental organisations (NGOs) to over 3,775 facilities including primary health care centres providing ART in 2015. The National Health Laboratory Services (NHLS) provides CD4 count and viral load testing services for these facilities through a network of 60 CD4 count and 17 viral load testing laboratories. Specimen data from the laboratory management information system are archived in the corporate data warehouse (CDW) and were made available for this analysis. This analysis of routinely collected laboratory data was conducted in the context of a broader evaluation of adherence to ART and retention in HIV care within the CCMT programme

Table 1 Evolution of the ART initiation and treatment monitoring guidelines in adults

Year	ART initiation criteria	Treatment monitoring approach	Comments
2004 ⁽²⁹⁾	CD4 count <200 cells/μl irrespective of WHO stage WHO Stage IV disease irrespective of CD4 count Willingness to adhere to ART	CD4 count at baseline and six-monthly thereafter VL at baseline and six – monthly thereafter	

Table 1 Evolution of the ART initiation and treatment monitoring guidelines in adults *(Continued)*

Year	ART initiation criteria	Treatment monitoring approach	Comments
2010 ⁽³⁰⁾	CD4 count <200cells/μl irrespective of clinical stage CD4 count <350cells/μl for pregnant women and those with TB WHO stage IV irrespective of CD4 count MDR/XDR irrespective of CD4 count	CD4 count at baseline , at six months, 12 months and annually thereafter VL at six months, 12 months and annually thereafter	New guidelines also expedited initiation to (within two weeks for pregnant women eligible for lifelong ART, patients with very low CD4 (<100 cells/μl), Stage 4 disease , CD4 count not yet available, or with MDR/XDR TB
2012 ⁽³¹⁾	Any form of TB irrespective of CD4 count	CD4 count at baseline , then at 12 months with no further measurement unless clinically indicated VL at six months, 12 months and then every 12 months thereafter	New guidelines also further expedited initiation to same day for those with CD4 counts <200cells/μl and for HIV+ pregnant women
2013 ⁽³²⁾	CD4 count <350 cells/μl irrespective of WHO clinical stage Any form of TB irrespective of CD4 count HIV positive and pregnant or breast feeding irrespective of CD4 count Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4–6 weeks) irrespective of CD4 count WHO stage 3 or 4 irrespective of CD4 count	CD4 at baseline, then at 12 months with no further measurement unless clinically indicated VL at 6 months, 12 months on ART and then every 12 months thereafter	Guidelines introduced fixed dose combinations of ARVs
2015 ⁽³⁾	CD4 count <500 cells/μl irrespective of WHO clinical stage Immediate initiation of lifelong ART for all HIV-positive women who are pregnant, breastfeeding or within 1 year post-partum, regardless of CD4 cell count Provision of ART for all children under 5 years, regardless of their CD4 cell count or clinical staging ART initiation for children ≥5 years to start at CD4 count ≤500 cells/μl regardless of clinical staging Provision of ART for those with Hepatitis B (HBV) or TB/HIV co-infection, regardless of CD4 count or clinical staging	CD4 at baseline CD4 at 12 months, then annually if clinically indicated VL at month 6, month 12 on ART and then every 12 months	Expedited treatment start (within seven days) for children who meet the following criteria: <1 year of age and CD4 count ≤200 cells/μl or CD4 count % <15, WHO clinical stage 4 , MDR-TB or XDR-TB For adults—prioritise those with CD4 counts < 350 cells/μl.

The purpose of the broad evaluation was to (a) categorise facilities providing ART by the proportion of ART clients that are virally suppressed; (b) understand whether there is spatial clustering of facilities where lower proportions of ART clients are virally suppressed; (c) help classify ART clients for the purpose of targeted adherence interventions, by determining broad demographic characteristics of ART clients (location, age and gender) who are most likely not to

be virally suppressed (indicative of low drug adherence); and (d) better understand patterns of CD4 recovery rates and the overall HIV care cascade. The analysis presented in this report focused on absolute CD4 count recovery rates, the time to CD4 recovery, and the extent of CD4 count recovery in the first 12 months of follow up.

Study design and procedures

This was an analysis of routinely collected laboratory data. Because the CCMT programme lacks a unique identifier for individuals enrolled, and laboratory tests can be from the same individual having multiple tests over time and across sites, data were linked using a probabilistic matching algorithm, in order to determine the records that relate to each individual. In the probabilistic record linkage, personal identifiers were used together to determine how likely it was that a pair of records referred to the same individual. Variables incorporated into the algorithm included name, surname, initials, date of birth, and sex. The performance of the algorithm was tested against a gold standard dataset and found to have a type 2 error (over-matching) rate of 15% and a type 1 error (under matching) rate of 11%. The details of this linking algorithm are described in a separate report. ⁽³³⁾

Population, inclusion and exclusion criteria

From an initial dataset containing unique individuals with at least one viral load and one CD4 count test result, individuals who met the following criteria were identified and included in the analysis of CD4 recovery:

- Had at least one viral load test result in the CDW database.
- Had at least two CD4 count results in the database
- Had a CD4 count in the database that was done three to 12 months prior to the first viral load test. This criterion was used to determine the estimated ART start date for individuals who were likely to have started ART during this time (2010–14). Prior to 2010, national ART guidelines recommended a baseline VL. The 2010 ART guidelines formally adopted the recommendation in the 2009 update to the earlier guidelines to stop baseline VL testing.
- Aged 15 years or older

Data on eligible individuals were used to set up a cohort. Person-time was counted from ART initiation until the earliest of: (1) the date of CD4 recovery if there was CD4 recovery according to the specified threshold; or (2) the date of the last CD4 count or viral load test (whichever came last) if there was no CD4 recovery. Figure 1 illustrates how the cohort was set up for analysis of the proportion of eligible individuals with CD4 count recovery and time to CD4 count recovery.

Variables and definitions

Key variables in the analysis were defined as follows:

- Date of ART start—this was the date of the baseline CD4 count. The date of the baseline CD4 count was taken to be the date of the CD4 count done three to 12 months before the first viral load date. Where multiple CD4 count test dates and results were available for this time period, the earliest date was used.
- CD4 count at ART start—the result of the baseline CD4 count
- Follow up CD4 counts—results from the CD4 count tests done at any point after the ART start date
- Duration of follow up—the time interval between the date of ART initiation and the date of the latest CD4 count or viral load test result in the database
- Virally suppressed—having a viral load result of <400 copies/ml at any point during follow up
- Age—the individual's age recorded at the date of ART initiation
- Sex—the sex recorded at the date of ART start

- Year—the year of ART initiation
- Evidence of prior HIV care—having had CD4 count tests done prior to the date of ART start

Outcomes

Three outcome variables were measured:

1. The proportion of the cohort who achieved CD4 immune recovery to: i) 200 cells/ μ l, ii) 350 cells/ μ l, and iii) 500 cells/ μ l. This was calculated as the number of individuals whose CD4 count at ART initiation was below the specified threshold and who in subsequent follow up had one or more CD4 count results greater than the specified threshold, as a proportion of all individuals whose CD4 count at initiation was below the specified threshold.
2. The time to CD4 count recovery in months. This was calculated using Kaplan-Meier survival analysis techniques. Individuals exited on achieving recovery. Those who did not achieve recovery were right censored (the last follow-up date was either the date of the last CD4 count test or of the last viral load test result, whichever came later).
3. The extent of CD4 count recovery in the first 12 months of ART. This was measured by estimating the slope (coefficient) of CD4 count recovery using random effects panel regression and was restricted to the first 12 months of follow up. This was because the extent of CD4 count recovery typically is greater in the first 12 months on ART than in subsequent periods.

Data Analysis

Once the data were linked to unique individuals, it was exported to Stata version 12 (Stata Corp., College Station, Texas, USA) for analysis. The characteristics of individuals at cohort entry were described using medians and interquartile ranges for continuous variables and as proportions for categorical data.

■ Estimating the proportion of individuals who ever achieved CD4 recovery to different thresholds

The number of individuals who had CD4 recovery to a specific threshold was divided by the total number of individuals who initiated ART below that threshold. The chi-squared test was used to test the significance of any differences in the proportions achieving immune recovery across provinces, age categories, gender, year of ART initiation, and CD4 count categories at ART initiation. Modified-Poisson regression models with robust error variance were used to estimate the relative risk (RR) and 95% confidence intervals (CI) of the association between the different factors and the probability of CD4 count recovery to the different thresholds. Likelihood ratio tests were used to determine which factors were independently associated with CD4 recovery to the given thresholds. We carried out sensitivity analyses of the proportions who achieved CD4 count recovery to 200 cells/ μ l for those who were virally suppressed and for a group of participants whose names, gender and dates of births were exact matches for all CD4 count and viral load tests (in order to test the sensitivity of the results to the possibility of over-linking by the probabilistic linking algorithm).

■ Estimating time to CD4 recovery

The time to CD4 count recovery was determined using survival analysis techniques, as the time in months between the date of ART initiation and the date of exit from the cohort. Individuals exited the cohort at the date of the first CD4 count higher than the specified threshold or at the date of the latest CD4 count or viral load if there was no CD4 count recovery to the specified threshold. Kaplan-Meier survival curves were plotted and the log-rank test used to compare differences in the time to CD4 count recovery across different sub-groups by age, gender, year of ART initiation, CD4 count category at ART initiation, and

province. Cox proportional hazards regression was used to determine factors associated with time to recovery.

■ **Estimating the extent of immune recovery during follow up**

Random effects panel data regression was used to estimate the coefficients (slope) associated with CD4 count changes in the first 12 months (+/- three months) of ART. These coefficients estimated the extent of CD4 recovery per day of follow up using a random effects model. The extent of CD4 count recovery in the first 12 months was determined by sex, age, CD4 count at ART initiation, and the presence of viral suppression by the end of follow up.

FINDINGS

Description of the Population

From 3,977,761 unique individuals who had at least one viral load test and one CD4 count test captured in the CDW database between January 2000 and March 2015, 1,070,900 (26.9%) individuals met the criteria for inclusion in the cohort. Figure 2 shows the numbers of individuals who were excluded from the analysis and the reasons for the exclusions. Compared to individuals included in the cohort, the individuals excluded from the cohort were more likely to be male (33.3% vs. 30.1%), older (median 46 years [IQR 38–55 years] vs. 44 years [IQR 37–52 years]), have a higher median nadir (lowest ever) CD4 count (200 cells/μl vs. 167 cells/μl) and less likely to be from KwaZulu-Natal Province (22% vs. 31.9%).

The individuals included in the cohort were from all nine provinces in the country. The 1871 (0.17%) individuals for whom a province could not be assigned were included in the national analysis and excluded from provincial comparisons. The number of individuals by province ranged from 17,451 (1.6%) for the Northern Cape (NC) to 341,180 (31.9%) for KwaZulu-Natal (KZN). The median duration of follow up was 24 months (IQR 12.2–36.9 months) for the full cohort and ranged from 20.9 months in Limpopo (LP) to 25.3 months in the Western Cape (WC). Almost a quarter of the population (24.7%) had duration of follow up of less than 12 months. The median number of CD4 count measurements post ART initiation (including the one at ART initiation) was 3 (IQR 2–4). Table 2 shows the distribution of demographic and clinical characteristics of individuals included in the analysis by province.

Of the individuals included in the analysis, 919,649 (85.9%) were virally suppressed by the end of follow up.

The estimated median CD4 count at ART initiation was 213 cells/μl (IQR 117–324 cells/μl), and ranged from a median of 187 cells/μl in Gauteng (GP) to 234 cells/μl in KZN (Table 3). Overall, the proportion of individuals who started ART with CD4 counts <200 cells/μl was highest in GP at 53.8% and lowest in KZN at 41.9%; and decreased over time from 58% in 2010 to 36% in 2014. The estimated median CD4 count at ART start was higher among females than males (231 cells/μl vs. 175 cells/μl), and among those who had one or more CD4 counts done prior to the estimated date of ART start—suggesting pre-ART monitoring or prior ART use—than among those without prior CD4 counts (243 cells/μl vs. 185 cells/μl). Consistent with the increased coverage of HIV counselling and testing from HIV Counselling and Testing (HCT) campaigns, the median CD4 count at initiation increased with calendar year—from 177 cells/μl in 2010 to 271 cells/μl in 2014. Table 3 also shows that CD4 count at ART initiation decreased with increasing age of the patient from a median of 249 cells/μl among youth aged 15–24 years to 199 cells/μl among individuals 50 years or older.

Of the individuals included in the analysis, 919,649 (85.9%) were virally suppressed by the end of follow up. Individuals who were virally suppressed by the end of follow up were less likely to be male (29.6 % vs. 32.8%), more likely to be older than 40 years (68% vs. 60%), more likely to have initiated ART in 2012 or earlier (70.4% vs. 56.5%) and more likely to have initiated ART

with CD4 counts less than 200 cells/ μ l (46.9% vs. 44.9%). Virally suppressed individuals were also less likely to have evidence of prior HIV care (49.2% vs. 54.7%) when compared to those who were not virally suppressed by the end of follow up.

Among the individuals included in the cohort, 740 468 (69%) were eligible for inclusion in the exact match dataset (the dataset of individuals whose names, dates of birth and gender were exact matches across CD4 count and viral load results). The individuals in the exact match dataset were similar to those not included in the complete dataset with respect to demographic characteristics and CD4 count at ART initiation. However, the individuals in the exact match dataset differed from those included in the complete dataset as a result of the linking algorithm by being more likely to be from KZN (45.6% vs. 1.1%); to be virally suppressed (88.5% vs. 80%) and to have longer duration of follow up (median 25.5 months vs. 19.8 months). However, they were less likely to have evidence of prior HIV care (47.1% vs. 56.2%).

CD4 Count Recovery to 200 cells/ μ l

Absolute CD4 count recovery to 200 cells/ μ l

From the 1,070,900 individuals included in the cohort, 498,785 (46.6%) had a CD4 <200 cells/ μ l at ART initiation and were therefore eligible for inclusion in the analysis of CD4 count recovery to 200 cells/ μ l. The median CD4 count at ART initiation in this group was 110 cells/ μ l (IQR 57–157 cells/ μ l). Of the 498,785 individuals, 397,475 (79.7%) achieved CD4 count recovery to 200 cells/ μ l at some time during follow-up. The proportion of the eligible population who achieved CD4 recovery to 200 cells/ μ l varied across the provinces, ranging from 76.3% in LP to 83.1% in KZN (X^2 p-value <0.001). The proportion also varied with age, gender, year of ART initiation, and CD4 count at ART initiation. Table 4 shows the distribution of proportions of individuals who achieved CD4 recovery to 200 cells / μ l by province across different age categories, gender, CD4 count at ART initiation, and year of ART initiation. Generally the proportion with CD4 count recovery to 200 cells/ μ l was lowest in LP, among males, among those \geq 50 years, among those who started ART in the latter years—2013 and 2014 (due to shorter duration of follow up), and among those with CD4 counts <50 cells/ μ l at ART initiation. The proportion of males \geq 50 years with CD4 counts <50 cells/ μ l at ART initiation from LP (n=1503, 0.3 %) who had CD4 count recovery beyond 200 cells/ μ l was 50.3 % compared to the national average of 79.7%. In a multivariable Poisson model adjusting for the effect of age, sex, CD4 count category at ART initiation, year of ART initiation, duration of follow up, viral suppression by the end of follow up, and province, all variables were independently associated with CD4 recovery to 200 cells/ μ l (Table 5). Compared to those aged 25–34 years, the relative risk of CD4 recovery to 200 cells/ μ l was 3–7% lower among older age groups (p<0.001) but 5% higher among those aged 15–24 years. The risk of CD4 recovery to 200 cells/ μ l was 7% lower among males than females, 0–3 % lower in other provinces compared to KZN, 7–30% lower among those who had CD4 counts <150 cells/ μ l at ART initiation compared to those with \geq 150 cells/ μ l. Risk of recovery to 200 cells/ μ l was 1% higher among those initiating ART in the years 2011–2013 than in 2010, 29–53% higher among those with more than 12 months of follow up than those with 12 months or less and 69% higher among those who achieved viral suppression at any point during follow up.

In the district level analysis, the proportion of individuals with CD4 count recovery to 200 cells/ μ l ranged from 65.7% in Central Karoo District, WC to 86.5% in Umkhanyakude DM, KZN

Overall, 80% of those who initiated with a CD4 count <200 cells/ μ l achieved CD4 count recovery to 200 cells/ μ l. Women, younger people and those who were virally suppressed were more likely to achieve immune recovery.

(Table 6). Of the 52 districts, 33 (63.4%) had CD4 recovery rates which were lower than the national average of 79.7%.

In an analysis restricted to individuals who were virally suppressed by the end of follow up (430,837/498,785), the overall proportion of participants who recovered to 200 cells/ μ l was 85.3% (367,575/ 430,837). Table 7 shows the distribution of CD4 count recovery beyond 200 cells/ μ l among those who had viral suppression by the end of follow-up. The proportion of individuals who recovered to 200 cells/ μ l was higher among females than males, decreased with increasing age and year of starting ART (because of reduced duration of follow up), and increased with increasing CD4 count at ART initiation. In a multivariable Poisson regression model adjusting for the effects of sex, age, CD4 count at ART initiation, year of starting ART, and duration of follow up (Table 8), the relative risk of CD4 count recovery was 6% lower among males than females, 2–6% lower among those aged 35 years or older compared to those aged 25–34 years, 5–25% lower among those with CD4 counts less than 150 cells/ μ l at ART initiation compared to those with CD4 counts of 150–199 cells/ μ l at ART initiation (which may be due partly to the fact they are closer to the ‘threshold of recovery’), 1–7% lower among those who initiated ART in the years 2011–2014 compared to 2015, and 1–4% lower among those from other provinces compared to KZN. The relative risk for CD4 recovery to 200 cells/ μ l increased with increasing duration on ART. In the district level analysis (see Table 6) of CD4 recovery among those who were virally suppressed, the proportions who had CD4 count recovery to 200 cells/ μ l ranged from 74.6% in Central Karoo District, WC to 90.4% in Umkhanyakude DM, KZN; 24 districts had recovery rates below the national average of 85.3%.

The proportion of eligible individuals in the exact match dataset (350,808/ 498,785, 70.3%) who had CD4 count recovery to 200 cells/ μ l was 81.4% compared to 75.5% of individuals who did not have exact matches and 79.7% for the full dataset. The absolute immune recovery patterns by sex, age, CD4 count at ART initiation and year were similar to the pattern for the full cohort.

Time to CD4 count recovery to 200 cells/ μ l

The median time to CD4 count recovery beyond 200 cells/ μ l among all eligible individuals was 9.5 months (IQR 6.9– 14.8 months) (Table 9). The univariable analysis of time to event showed the median times varying across the provinces from 9.0 months in North West (NW) to 10.8 months in WC ($p < 0.001$). Time to recovery was generally longer in males ($p < 0.001$), increased with age ($p < 0.001$), and increased by calendar year ($p < 0.001$) with the exception of 2014, likely reflecting the limited duration of follow up among those who initiated ART in 2014. The time to recovery decreased with increasing CD4 count at ART initiation from a median of 12.6 months among those with CD4 counts < 50 cells/ μ l to 8.2 months among those with CD4 counts of 150–199 cells/ μ l. Time to recovery was longer among those who were not virally suppressed by the end of follow up compared to those who were (10.3 months [IQR 7.0–17.2 months] vs. 9.4 months [IQR 6.4–14.5 months], $p < 0.001$). Figures 3 and 4 show the Kaplan-Meier curves of time to recovery by sex, age, year of ART initiation, and CD4 count at ART initiation for all individuals eligible for CD4 count recovery to 200 cells/ μ l and among those who were virally suppressed by the end of follow up. The curves show that the time to recovery varied more with CD4 count at ART initiation and virological suppression, than the other variables. Table 9 also shows the times to CD4 recovery beyond 200 cells/ μ l by province, sex, age category, year of ART initiation, and CD4 count at ART initiation for all those eligible. Table 10 shows the hazard ratios associated with the risk of recovery to CD4 count of 200 cells among all those eligible. The analyses highlight the lower likelihood of CD4 count recovery to 200 cells/ μ l with decreasing CD4 count at ART initiation, increasing age, and among

The median time to CD4 count recovery to 200 cells/ μ l was 9.5 months. Time to recovery was generally longer in males, increased with age and decreased with viral suppression.

males; and the higher likelihood with viral suppression and ART initiation in the more recent calendar years, even after adjusting for length of follow up. Tables 11 and 12 present the corresponding data for the sub-group who were virally suppressed. Across all the sub-groups (age, sex, CD4 count at ART initiation, and year of ART initiation), time to recovery was generally shorter among those virally suppressed. Among the virally suppressed, the likelihood of CD4 count recovery to 200 cells/ μ l was lower with decreasing CD4 count at ART initiation, with increasing age, and among males, but increased across calendar years after 2010.

At the district level, the median time to CD4 count recovery beyond 200 cells/ μ l among all eligible individuals ranged from a median of 8.4 months in Zululand District, KZN to 11.5 months in Sedibeng District, GP. Twenty-five of the 52 districts (48%) had median times to recovery longer than the national average. Among those who were virally suppressed, the median time to recovery ranged from 8.2 months in Uthukela District, KZN to 11.5 months in Sedibeng District, GP (see Table 6).

CD4 Count Recovery to 350 Cells/ μ l

Absolute CD4 count recovery to 350 cells/ μ l

Because virological suppression was so strongly correlated with likelihood of CD4 count recovery to 200 cells/ μ l, the analysis of CD4 count recovery to 350 cells/ μ l was restricted to individuals with evidence of virological suppression during follow up. There were 752,742 individuals (81.9 %) who had a CD4 count <350 cells/ μ l at ART initiation and achieved viral suppression by the end of follow up. Their median CD4 count at ART initiation was 179 cells/ μ l (IQR 100– 258 cells/ μ l). Of this group, 514,333 (68.3 %) had absolute CD4 recovery to 350 cells/ μ l (Table 13). The proportion with CD4 count recovery to 350 cells/ μ l was highest in KZN (71.7%) and lowest in GP (64.9%), (X^2 p-value <0.001). The overall proportion with recovery to 350 cells/ μ l was lower among males than females (56.4% vs. 74.0%, X^2 p-value <0.001), increased with increasing CD4 count at ART initiation (from 39.1% among those with CD4 counts <50 cells/ μ l to 85.2% among those with CD4 counts 200–349 cells/ μ l (p <0.001), and decreased with increasing age (79.6% and 80.3% in the 15–24 and 25–35 years groups compared to 69% and 61.2% among the 35–49 year olds and 50 years or older group, X^2 p-value <0.001), and decreased with year of ART initiation after 2010 (from 76.5% for 2010 to 47.1% in 2014). The proportion of males older than 50 years from GP who had CD4 counts <50 cells/ μ l at ART initiation (n =4525, 0.6%) whose CD4 count recovered to 350 cells/ μ l was 23.7% (compared to the national average of 68.3%). Table 14 shows the relative risks associated with sex, age category, CD4 count at ART initiation category, calendar year of ART initiation, duration of follow up, and province. The adjusted relative risks of CD4 recovery to 350 cells/ μ l were: 14% lower in males than females, 1–7% lower in other provinces compared to KZN, 1–4% lower among those who initiated ART in 2011, 2013 or 2014 compared to 2010, 7–15% lower among those aged 35 years or older compared to those aged 25–34 years, 26–54% lower among those with CD4 counts less than 200 cells/ μ l at initiation compared to CD4 counts 200–349 cells/ μ l at ART initiation, and 37–97% higher among those with durations of follow up greater than 12 months compared to 12 months or less. The proportion of individuals with CD4 recovery to 350 cells/ μ l at district level ranged from 61.5% in the City of Johannesburg district to 78.2% in Umkhanyakude DM in KZN (see Table 6). Of the 52 districts, 25 (48%) had recovery rates lower than the national average of 68.3%.

68% of those who initiated ART with a CD4 count <350 cells/ μ l and who were virally suppressed achieved recovery to 350 cells/ μ l in a median of 12.4 months.

Time to CD4 count recovery to 350 cells/ μ l

The median time to CD4 count recovery beyond 350 cells/ μ l was 12.4 months (IQR 7.9–22.9 months) nationally (Table 15). The median time to recovery beyond 350 cells/ μ l in the provinces ranged from 11.6 months in NW to 13.5 months in WC. Time to recovery beyond 350 cells/ μ l was longer in males than females (13.7 months vs. 11.9 months, $p < 0.001$), increased with age (from 10.3 months among those aged <25–34 years to 13.4 months among those ≥ 50 years, $p < 0.001$) and decreased over calendar year of ART initiation (from 16.9 months for 2010 to 7.4 months for 2014, $p < 0.001$) and with CD4 count at ART initiation (from a median of 19.8 months among those with CD4 count <50 cells/ μ l to 10.0 months among those with CD4 count 200–349 cells/ μ l) (see Figure 5). The median time of recovery to CD4 count >350 cells/ μ l varied from 10.9 months in Vhembe District, LP to 14.7 months in Central Karoo District, WC, with 23 (44.2%) districts having median recovery times longer than the national average of 12.4 months (Table 6). Table 16 shows the hazard ratios associated with different factors. The risk of CD4 count recovery was lower with decreasing CD4 counts at ART initiation, with increasing age, among males, and better for more recent calendar years of initiation compared to 2010 (likely reflecting the increased CD4 count at ART initiation).

CD4 Count Recovery to 500 Cells/ μ l

Absolute CD4 count recovery to 500 cells/ μ l

As was the case with the analysis of CD4 count recovery to 350 cells/ μ l, the analysis of absolute CD4 count recovery to 500 cells/ μ l was also restricted to individuals who had viral suppression by the end of follow up. Of 844,699 individuals (78.9%) who had a CD4 count <500 cells/ μ l at ART initiation and were virally suppressed by the end of follow up (median CD4 count 196 cells/ μ l [IQR 111–290 cells/ μ l]), 374,874 (44.4%) achieved a CD4 count >500 cells/ μ l in follow up. The proportion with CD4 count recovery to 500 cells/ μ l was highest in KZN (48.8%) and lowest in GP (40.1 %) (X^2 p -value <0.001). As seen with absolute recovery to 200 cells/ μ l and 350 cells/ μ l, the overall proportions with recovery to 500 cells/ μ l were lower among males than females (31.1% compared 50.4%), decreased with increasing age (59.1% in 25–34 year olds to 37.1% in those 50 years or older) and more recent year of initiation (from 53.5% in 2010 to 27.6% in 2014), and increased with higher CD4 count at ART initiation (from 19.6% among those with CD4 counts <50 cells/ μ l to 69.9% among those with CD4 counts 350–499 cells/ μ l (Table 17). The proportion whose CD4 count recovered to 500 cells/ μ l was 9.4% among males ≥ 50 years with CD4 count <50 cells/ μ l from GP ($n=4525$ [0.5%]) compared to 44.4% nationally. Table 18 shows the relative risks of CD4 count recovery to 500 cells/ μ l associated with age, sex, year of ART initiation, CD4 count at ART initiation, duration of follow up, and province. The adjusted relative risk of recovery was 26% lower among males than females, 15–26% lower among those aged ≥ 35 years compared to those aged 25–34 years, 19–71% lower among those with CD4 counts <350 cells/ μ l at initiation compared to 350–499 cells/ μ l at initiation, and 2–10% lower among those from other provinces compared to KZN. The relative risks of recovery were 4–7% higher among those who initiated ART in the years 2012–14 compared to 2010, 6% higher among individuals aged 15–24 years compared to those aged 25–34 years, and 55–300% higher among those with a duration of follow up greater than 12 months compared to 12 months or less. At the district level the proportion of individuals who had CD4 recovery to 500 cells/ μ l varied from 36.6% in the City of Johannesburg, GP to 59.2% in Umkhanyakude DM, KZN. Of the 52 districts, 28 (53.8%) had recovery rates below the national average of 44.4% (Table 6).

44% of those who initiated ART with a CD4 count <500 cells/ μ l and who were virally suppressed achieved recovery to 500 cells/ μ l in a median of 17.3 months.

In an analysis restricted to 53 485 women aged 15–49 years who initiated ART with CD4 counts ≥ 350 cells/ μL —likely to be PMTCT candidates who would have started ART at higher CD4 counts (6.3% of the full sample), 73.7% recovered their CD4 counts to more than 500 cells/ μL compared to 42.4% for the rest of the study population.

Time to CD4 count recovery to 500 cells/ μL

The median time to CD4 count recovery beyond 500 cells/ μL was 17.3 months (IQR 10.0–29.6 months). This varied from 15.6 months in Limpopo Province to 19.3 months in the Western Cape Province (Table 19). Time to recovery was longer in males (19.0 months vs. 16.6 months, $p < 0.001$), increased with age (from 13.5 months in 15–24 years to 19.2 months in those aged ≥ 50 years, $p < 0.001$) and decreased with more recent year of ART initiation from 31.3 months among those who started in 2010 to 7.7 months among those who started in 2014 ($p < 0.001$), likely reflecting the increase in the CD4 count at ART initiation by calendar year (from 178 cells/ μL in 2010 to 260 cells/ μL in 2014) and despite the limited duration of follow up among the individuals who started in the latter years (Figure 6). Table 20 shows the hazard ratios for CD4 count recovery to 500 cells/ μL associated with age, sex, year of ART initiation, CD4 count at ART initiation, and province. The risk of CD4 count recovery to 500 cells/ μL was also lower among males, decreased with increasing age above 35 years and with decreasing CD4 count at ART initiation and increased with more recent calendar year reflecting increased CD4 counts at ART initiation. The median time to CD4 count recovery beyond 500 cells/ μL ranged from 13.4 months in Harry Gwala District to 22.6 months in West Coast District in WC (Table 6). Twenty eight (53.8%) districts had median recovery times longer than the national average of 17.3 months.

The extent of CD4 recovery in the first 12 months of ART

The extent of recovery in the first 12 months of ART is presented in Table 21. The average extent of recovery in the first 12 months after ART initiation was 154 cells/ μL . Generally the extent of recovery during this period was greater among females than males and decreased with increasing age. The extent of recovery in the first 12 months following ART initiation was also greater among those who were virally suppressed compared to those who were not and among those with lower CD4 counts at ART initiation.

The average CD4 count gain in the first 12 months following ART initiation was 154 cells/ μL and greater among the virally suppressed, younger people and among females.

DISCUSSION

General discussion

This report describes the proportions of eligible individuals in a study cohort using laboratory test data who attained absolute CD4 count recovery to 200 cells/ μ l, 350 cells/ μ l and 500 cells/ μ l, the median time to reach these thresholds of CD4 recovery across the provinces, age categories, sex, and calendar year of ART initiation, as well as the extent of CD4 recovery in the first twelve months following ART initiation. Of the 498 785 individuals with CD4 counts less than to 200 cells/ μ l at ART initiation, 79.7% attained CD4 recovery to 200 cells/ μ l in a median time of 9.5 months. The proportions of eligible individuals with CD4 count recovery to 200, 350 and 500 cells/ μ l were higher among those who had viral suppression during follow up, with 85.3%, 68.3% and 44.4% achieving recovery in a median of 9.4, 12.4 and 17.3 months respectively. The proportions with CD4 count recovery varied with CD4 count at ART initiation, age, sex, and year of ART initiation. Across all CD4 count thresholds, CD4 recovery was lower among males and decreased with increasing age. The time to recovery was longer among males and increased with increasing age. The extent of recovery in the first year on treatment was less among older people and males and greater among those with lower CD4 counts at ART initiation.

Our findings on the factors associated with immune recovery among those who have attained virological suppression were consistent with results reported in other studies from sub-Saharan Africa and elsewhere. Studies have shown that lack of virological suppression is associated with poor immunological recovery, while poor immune recovery in the presence of virological suppression is associated with low nadir CD4 counts and low CD4 counts at ART initiation, ^(15, 16) with older age, and with being male. (19–22) Almost 50% of our study cohort had a CD4 count < 200 cells/ μ l at ART initiation, in an era when the threshold for initiating ART was higher. The data show that despite the increase in CD4 count thresholds for eligibility, a significant proportion of people living with HIV still initiate ART late. More needs to be done to ensure that more people living with HIV, especially men, are tested for HIV early in the course of infection and are successfully linked and maintained in care.

A few studies from South Africa have looked at the extent of immune recovery during the first year on treatment. Greater extent of CD4 count recovery has been found among those with lower CD4 counts at ART initiation, in adolescents compared to older adults, and among adult females compared to adult males. (21–23) Lawn et al. reported a CD4 recovery of 25 cells/ μ l/month (equivalent to 300 cells/ μ l during the first 12 months) among adults with a median CD4 count of 97 cells/ μ l at ART initiation ⁽²⁵⁾, while Hoffmann et al. found a rate of 1.4 cells/ μ l/week in the first 4–48 weeks of treatment (equivalent to 73 cells/ μ l over 12 months) in a cohort with a median CD4 count of 112 cells/ μ l. ⁽³⁴⁾ Our estimated extent of CD4 count recovery of 15 cells/ μ l/month or 3.5 cells/ μ l/week (183 cells/ μ l over 12 months for CD4 counts 50–200 cells/ μ l at ART initiation) were somewhat comparable to those reported in these studies. Estimating the extent of CD4 recovery is important as slow CD4 recovery early in the course of ART has been shown to predict later delayed immunological response or non-response ⁽³⁵⁾, which are in turn associated with increased morbidity and mortality on ART.

A better understanding of the factors associated with sub-optimal immune recovery in the context of the South African National ART programme will assist with identifying patients who need additional interventions to support and improve immune recovery. Older males and those with low CD4 counts (< 200 cells/ μ l) could be prioritised for screening for co-infections and initiation of appropriate prophylactic treatment, initiation of ART, and continued CD4 count monitoring. In addition, interventions to ensure that individuals initiated on ART adhere to treatment need to be strengthened and targeted to those most at risk of sub-optimal recovery—older males and those with low CD4 counts at ART initiation. As a low CD4 count at ART initiation was a strong predictor of immunological recovery during the first year among those virally suppressed, interventions could also be targeted to districts whose unique socio-economic circumstances may be associated with sub-optimal linkage to care (as measured by higher proportions of individuals initiating ART at CD4 counts <200 cells/ μ l) and retention in care.

Recently, there have been suggestions that continued CD4 count monitoring among virologically suppressed individuals may not be necessary in an era of increasing availability of viral load monitoring, and that reducing the frequency of or doing away with CD4 count monitoring for stable ART patients may free up resources to put more people on ART.^(36, 37) However, a CD4 count measurement at ART initiation may need to continue in order to identify individuals with low CD4 counts who require prophylactic treatments and also to monitor the effectiveness of HIV testing and linkage to care interventions. The significant proportion of individuals who had sub-optimal immune recovery in our cohort (for instance, 14.7% of those with CD4 counts <200 cells/ μ l and who were virally suppressed

did not achieve CD4 count recovery beyond 200 cells/ μ l), means there is a group of individuals who will continue to require prophylaxis for opportunistic infections until immunological recovery occurs as they are at greater risk for AIDS-related morbidity. Continued CD4 count monitoring allows these individuals to be identified and managed accordingly and may reduce excess morbidity and mortality, making CD4 count monitoring more cost effective than viral load monitoring alone.⁽³⁸⁾ Also, persistently low median CD4 counts at ART initiation may suggest lack of timely testing and linkage to care and can be used to identify areas and groups where efforts to increase timely linkage to care are needed.

A significant proportion of individuals did not achieve CD4 count recovery during follow up. Such persons may require continued CD4 count monitoring to guide decisions on prophylaxis.

Limitations

This analysis used laboratory data linked to unique individuals through the use of a probabilistic matching algorithm to create a cohort and determine CD4 recovery outcomes. There are some limitations to this kind of analysis. First, the accuracy of the cohort data depends on the performance of the algorithm used to link CD4 count and viral load data to unique individuals, and on the completeness of data in the database. The algorithm used to construct the cohort had a sensitivity of 89% and a positive predictive value of 85%, which means it matched correctly for the majority of individuals in the cohort. The proportion of individuals with CD4 count recovery to 200 cells/ μ l in a group of individuals whose CD4 count and viral load data were exact matches was similar to that obtained in the analysis of the full cohort (81% compared to 79.7%). It is unlikely that the performance of the matching algorithm affected our findings, although there may be residual bias from under-matching in the exact match dataset. Second, strict eligibility criteria were applied. The resultant cohort included only 27% of all unique individuals in the initial database. This may have resulted in selection bias and may limit the extent to which these findings can be generalised to all individuals enrolled in the CCMT programme in South Africa. The comparison of demographic and clinical characteristics of those excluded to those included

suggests that those excluded would likely have lower and slower recovery rates as they were more likely to be male and older, although they had higher nadir CD4 counts. Third, guidance on the frequency of CD4 count monitoring changed between 2010 and 2014. From 2010–2011, CD4 count measurements were taken at ART initiation, at 6 months, 12 months, and annually thereafter; whereas from 2012 onwards, CD4 count measurements were taken at ART initiation then at 12 months and annually or as indicated thereafter. This meant that fewer individuals in the later years had a baseline CD4 count and at least one other CD4 count. Also, individuals who initiated ART in the latter years were less likely to be included as they had limited follow up time. In addition, the assumptions in the analysis are sensitive to guideline adherence by clinicians. Differences in the extent to which facilities adhered to the guidelines on CD4 count and viral load monitoring could cause variability across provinces and districts with respect to eligibility to enter the cohort and in the number of CD4 counts in follow up. It is known that the proportions of individuals on ART who have viral loads done at 6 months or 12 months varies substantially across districts, sub-districts and facilities. ⁽³³⁾ Fourth, the actual ART start dates for the cohort were not known but were inferred from the dates of the baseline CD4 counts which were in turn estimated from the date of the first viral load test. We may have overestimated the values of the CD4 count at the start of ART by including people who were already on ART as newly initiated on ART. Fifth, because the data used all came from laboratories, there were no data on deaths or retention in care. The individuals included in this cohort were therefore those who survived and were retained in care long enough to have CD4 count tests done. The absence of data on people who died or had no test results during the study period limits the extent to which the data on CD4 recovery can be used to assess performance across districts or provinces. Longer time to recovery may be a positive sign in some cases as it means patients are surviving and included in laboratory monitoring (especially relevant for very late ART initiations). Last, there was wide variation in the numbers of eligible individuals included at provinces, district and sub-districts, with very small numbers from some provinces and districts. This may in part account for the wide variations in rates of recovery and time to recovery.

Despite these limitations, the construction and use of a laboratory data-based cohort is a novel approach which allows HIV programmes with limited use of electronic medical records but good laboratory information systems to use existing data to monitor and evaluate the effectiveness of their programmes. This analysis, which to our knowledge is the first to look at immunological recovery at the national level, provides insight into the extent of CD4 count recovery within the CCMT programme in South Africa and may be useful in informing proposed changes to ART treatment monitoring guidelines. The findings from this laboratory data cohort analysis could be validated through sentinel surveillance for HIV care and treatment or through the analysis of programme data once the set up and introduction of an electronic medical record with a unique identifier is completed. Further analyses of these data will be conducted in order to: i) improve the performance of the algorithm; ii) incorporate other laboratory tests done around ART initiation in order to better determine ART start dates; and iii) incorporate other laboratory tests to determine morbidity during follow up. The feasibility and interpretation of any future analyses of CD4 count recovery using the CDW database will depend largely on guidance on CD4 count monitoring. Currently, the guideline recommends CD4 count measurement to determine ART eligibility, at 12 months, and as clinically indicated thereafter.

Interventions to increase CD4 count at ART initiation and improve adherence and retention in HIV care need to be strengthened to ensure CD4 count recovery on ART.

Conclusions

This report describes the proportions of eligible individuals who achieved CD4 count recovery to 200 cells/μl and of virally suppressed individuals who achieved absolute CD4 count recovery

beyond 200, 350 and 500 cells/ μ l, the median times to recovery beyond these thresholds, and the extent of recovery during the first twelve months of treatment. Over the five year period included in the study, almost half of the cohort initiated ART at CD4 counts <200 cells/ μ l. The proportions that had absolute CD4 recovery were lower among older males, those with lower CD4 count at ART initiation, and those with no virological suppression by the end of follow up. There is a need to identify HIV-positive individuals earlier, initiate ART earlier, improve adherence to ART and retention in care in order to improve CD4 recovery on ART. Secondary analysis of large sets of routine data and novel approaches in record linkage (sometimes referred to as big data) can contribute to better targeting and more efficient implementation of the South African ART programme.

APPENDICES

Appendix A Tables

Table 2 Demographic characteristics of cohort by province

Province*	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
Number included in the main cohort (n, %)	109,615 (10.2)	62,785 (5.9)	223,080 (20.8)	341,180 (31.9)	66,567 (6.2)	92,660 (8.7)	17,451 (1.6)	65,585 (6.1)	90,105 (8.4)	1,070,900 (100)
Gender** Male (n, %)	29,275 (26.7)	18,681 (29.8)	72,806 (32.6)	102,316 (30.0)	16,184 (24.3)	26,887 (29.0)	5,801 (33.2)	19,654 (30.0)	29,764 (33.0)	321,945 (30.1)
Age distribution (n, %)										
15–24	1 184 (1.1)	743 (1.2)	1,498 (0.7)	49,698 (1.5)	634 (1.0)	1,166 (1.3)	158 (0.9)	681 (1.0)	479 (0.5)	11,521 (1.1)
25–34	20,220 (18.4)	9,172 (14.6)	27,904 (12.5)	62,481 (18.3)	8,657 (13.0)	15,654 (16.9)	2,623 (15.0)	9,576 (14.6)	15,518 (17.2)	172,009 (16.1)
35–49	55,817 (50.9)	31,174 (49.6)	122,694 (55.0)	178,576 (52.3)	33,244 (49.9)	46,529 (50.2)	9,020 (51.7)	32,375 (49.4)	52,246 (58.0)	562,693 (52.5)
50+	32,394 (29.6)	21,695 (34.6)	70,984 (31.8)	95,155 (27.9)	24,032 (36.1)	29,311 (31.6)	5,650 (32.4)	22,953 (35.0)	21,862 (24.3)	324,677 (30.3)
Year of starting of ART (n, %)										
2010	19 627 (17.9)	11 736 (18.7)	43 825 (19.6)	74,032 (21.7)	13,166 (19.8)	15,426 (16.7)	3,233 (18.5)	13,502 (20.6)	18,007 (19.9)	212,906 (19.9)
2011	27 146 (24.8)	17 098 (27.2)	57 249 (25.7)	77,690 (22.8)	17,505 (26.3)	24,128 (26.0)	4,156 (23.8)	16,369 (25.0)	21,421 (23.8)	263,824 (24.6)
2012	26 448 (24.1)	15 211 (24.2)	54 334 (24.4)	79,782 (23.4)	15,140 (22.7)	22,829 (24.6)	4,307 (24.7)	15,420 (23.5)	22,401 (24.9)	255,998 (23.9)
2013	24 801 (22.6)	13 718 (21.9)	46 834 (21.0)	71,316 (20.9)	14,054 (21.1)	19,834 (21.4)	3,880 (22.2)	13,471 (20.5)	20,436 (22.7)	228,555 (21.4)
2014	11 593 (10.6)	5 022 (8.0)	20 838 (9.3)	38,360 (11.2)	6,702 (10.1)	10,443 (11.3)	1,875 (10.8)	6,822 (10.4)	7 840 (8.7)	109,617 (10.2)
Evidence of prior HIV care (n, %)	62 684 (57.2)	31 552 (50.3)	111 345 (49.9)	142 005 (41.6)	33 993 (51.1)	51 745 (55.8)	10 418 (59.7)	39,953 (56.3)	52 859 (58.7)	534,747 (49.9)
Duration of follow up,										
Months		22.6	23.2	25.0	20.9	23.1	22.7	22.6	25.3	24
Median (IQR)	22.8 (12–35.9)	(11.9–35.1)	(12.3–35.9)	(12.7–39.0)	(11.2–34.7)	(11.7–35.1)	(11.6–35.6)	(11.2–36.0)	(13.7–37.8)	(12.2– 36.9)
Virally suppressed in follow up (n, %)	89 412 (81.6)	55,531 (88.4)	194,962 (87.4)	307,249 (90.1)	54,263 (81.5)	78,065 (84.3)	13,626 (78.1)	51,626 (78.7)	73,261 (81.3)	919,649 (85.9)
Duration of follow up (n, %)										
<12	27,569 (25.2)	15,947 (25.4)	53,498 (24.0)	77,919(22.8)	19,537 (29.4)	24,663 (27.1)	4,726 (27.1)	18,912 (28.8)	15,848 (17.6)	258,964 (24.7)
12–23	29,767 (27.2)	17,247 (27.5)	61,275 (27.5)	81,142 (23.8)	17,224 (25.9)	23,290 (25.1)	4,410 (25.3)	15,711 (24.0)	25,688 (28.5)	276,028 (25.8)
24–35	25,047 (22.9)	14,748 (23.5)	52,674 (23.6)	77,197 (22.6)	14,426 (21.7)	21,242 (22.9)	4,073 (23.3)	14,520 (22.1)	22,267 (24.7)	246,600 (23.0)
36–47	18,668 (17.0)	10,424 (16.6)	37,657 (15.9)	64,100 (18.8)	10,658 (16.0)	16,295 (17.6)	2,841 (16.3)	11,054 (16.9)	16,867 (18.7)	189,271 (17.7)
>=48	8,564 (7.8)	4,419 (7.0)	17,976 (8.1)	40,822 (12.0)	7,222 (7.1)	7,170 (7.7)	1,401 (7.6)	5,388 (8.2)	9,435 (10.5)	100,037 (9.3)

Note: * = province missing for 1871 individuals (0.17% of total); ** = gender missing for 16587 (1.6% of total)

Table 3 Distribution of CD4 counts at ART start by age, gender, year of ART start and province

Province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
CD4 count at baseline Median (IQR)	216 (122–324)	202 (112–308)	187 (96–291)	234 (132–347)	203 (103–328)	213 (116–324)	224 (127–337)	220 (120–337)	218 (124–316)	213 (117–324)
Distribution of CD4 counts baseline, (n, %)										
<200	50,360 (45.9)	31,053 (49.5)	120,084 (53.8)	142,786 (41.9)	32,771 (49.2)	43,413 (46.9)	7,701 (44.1)	29,681(45.3)	40,373 (44.8)	
200–350	37,535 (34.2)	21,374 (34.0)	72,247 (32.4)	115,005 (33.7)	19,682 (29.6)	30,836 (33.3)	5,875 (33.7)	21,174 (32.3)	34,023 (37.8)	785,258 (33.5)
351– 500	11,934 (10.9)	5,879 (9.4)	17,600 (7.9)	42,885 (12.6)	7,267 (10.9)	9,555 (10.3)	2,049 (11.7)	7,709 (11.7)	9,681 (10.7)	114,885 (10.7)
>500	9,786 (8.9)	4,479 (7.1)	13,149 (5.9)	40,504 (11.9)	6,847 (10.3)	8,856 (9.6)	1,826 (10.5)	7,021 (10.7)	60,278 (6.7)	98,972 (9.2)
Gender, Median (IQR)										
Male	175 (88–283)	170 (82–274)	154 (70–253)	192 (96–307)	158 (70–272)	173 (84–282)	190 (98–300)	175 (87–289)	182 (93–281)	175 (85–284)
Female	232 (138–336)	218 (127–320)	202 (113–306)	253 (150–366)	220 (117–341)	230 (132–338)	242 (142–352)	241 (140–353)	236 (143–330)	231 (134–338)
Age categories Median (IQR)										
15–24	257 (147.5–384)	226 (120–331)	214 (92–341)	273 (144–427)	217 (83–352)	222 (98–341)	284 (160–396)	250 (131–383)	278 (182–375)	249 (129–382)
25–34	258 (157–364)	256 (157–350)	240 (143–336)	274 (169–394)	274 (165–413)	263 (157–378)	277.5 (174–419)	281 (175–415.5)	256 (165–347)	263 (161–371)
35–49	207 (115–316)	197 (107–303)	185 (95–287)	221 (122–333)	199 (100–323)	206 (110–316)	221 (124–333)	216 (117–331)	212 (119–309)	206 (111–316)
50+	203 (115–311)	189 (104–293)	171 (86–272)	228 (129–347)	185 (94–306)	197 (108–309)	204 (112–314)	199 (109–318)	204 (112–304)	199 (108–312)
Year of starting of ART Median (IQR)										
2010	168 (93–255)	157 (85–232)	152 (79–226)	224 (129–386)	153 (76–245)	165 (91–258)	160 (89–243)	167 (92–259)	171 (100–238)	177 (98–284)
2011	198 (117–295)	193 (112–284)	179 (96–268)	206 (118–313)	192 (104–302)	193 (109–291)	203 (119–296)	204 (118–305)	212 (125–294)	196 (112–295)
2012	228 (131–318)	228 (125–317)	200 (102–295)	230 (130–321)	221 (112–328)	227 (125–321)	250 (144–344)	243 (138–341)	235 (134–320)	224 (123–317)
2013	255 (141–368)	237 (125–346)	217 (107–329)	258 (143–365)	249 (123–382)	252 (134–374)	275 (152–409)	271 (144–411)	260 (141–366)	249 (132–359)
2014	276 (150–420)	261 (130–404)	239 (114–369)	286 (160–432)	272 (130–447)	269 (141–408)	283 (156–429)	277 (142–434)	268 (135–405)	271 (141–414)
Evidence of prior HIV care Median (IQR)										
Yes	238 (144–341)	233 (142–330)	216 (125–316)	271 (167–381)	235 (130–356)	242 (142–347)	247 (147–350)	251 (149–364)	240 (147–334)	243 (145–346)
No	186 (96–295)	173 (89–279)	159 (76–258)	206 (112–324)	174 (82–292)	178 (90–286)	189 (98–306)	183 (93–299)	187 (97–284)	185 (95–296)

Table 4 CD4 recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
Overall CD4 count recovery to 200cells/μl (n/N, %)										
	39,042/50,360 (77.6)	24,466/31,055 (78.8)	94,110/120,084 (78.4)	118,615/142,786 (83.1)	24,998/32,771 (76.3)	34,458/43,413 (79.6)	5,971/7,701 (77.5)	23,015/29,681 (77.5)	32,256/40,373 (79.9)	397,475/498,785 (79.7)
By Gender										
Females	26,757/32,726 (81.2)	16,330/19,680 (83.0)	60,171/72,906 (82.5)	74,939/86,284 (86.9)	18,054/22,656 (79.7)	22,990/27,458 (83.7)	3,688/4,508 (81.8)	14,919/18,246 (81.8)	19,767/23,515 (84.1)	257,865/308,310 (83.6)
Males	11,563/16,644 (69.5)	7,849/11,005 (71.3)	33,013/45,928 (71.9)	41,093/53,333 (77.1)	6,765/9,879 (68.5)	11,087/15,359 (72.2)	2,178/3,050 (71.4)	7,884/11,556 (70.7)	12,031/16,295 (73.9)	133,623/182,873 (73.1)
By age										
Age 15–24	346/431 (80.3)	250/329 (75.9)	554/703 (78.8)	1,452/1,774 (81.9)	230/304 (75.7)	424/530 (80.0)	43/51 (84.3)	202/259 (77.9)	116/137 (84.7)	3,618/4,520 (80.0)
Age 25–34	5,698/7,200 (79.1)	2,700/3,290 (82.1)	9,124/11,061 (82.5)	17,371/20,133 (86.3)	2,298/2,865 (80.2)	4,645/5,4921 (84.6)	650/824 (78.9)	2,375/2,957 (80.3)	4,340/5,278 (82.2)	49,241/59,153 (83.2)
Age 35–49	20,893/26,830 (77.9)	12,692/15,873 (80)	52,972/66,709 (79.4)	66,335/79,820 (83.1)	12,909/16,654 (77.5)	17,971/22,526 (79.8)	3,173/4,070 (77.9)	11,701/14,953 (78.3)	19,544/24,296 (80.4)	218,447/272,064 (80.3)
Age ≥50	12,125/15,899 (76.3)	8,823/11,561 (76.3)	31,460/41,611 (75.6)	33,457/41,059 (81.5)	9,561 /12,948 (73.8)	11,508/14,866 (77.4)	2,105/2,756 (76.4)	8,737/11,512 (75.9)	8,256/10,662 (77.4)	126,169/163,048 (77.4)
By Year of baseline CD4 count										
2010	10,521/12,208 (86.2)	6,830/7,958 (85.8)	26,069/30,017 (86.9)	29,986/33,069 (90.7)	7,342/8,678 (84.6)	8,555/9,658 (88.6)	1,810/2,093 (86.5)	7,282/8,455 (86.1)	9,905/11,088 (89.3)	108,450/123,404 (87.9)
2011	11,320/13,730 (82.5)	7,434/8,946 (83.1)	27,285/32,611 (83.7)	32,795/37,466 (87.5)	7,498/9,153 (81.9)	10,755/12,604 (85.3)	1,667/2,039 (8.2)	6,653/8,013 (83.0)	8,430/9,856 (85.5)	114,013/134,644 (84.7)
2012	8,570/11,104 (77.2)	5,043/6,532 (77.2)	21,334/27,132 (78.6)	23,310/33,459 (84.6)	5,101/6,833 (74.7)	7,842/9,808 (79.9)	1,238/1,600 (87.4)	4,630/6,034 (76.7)	7,265/9,063 (80.2)	89,367/111,607 (80.1)
2013	6,384/9,315 (68.5)	4,036/5,687 (70.9)	14,664/21,536 (68.1)	19,767/26,258 (75.3)	3,772/5,665 (66.6)	5,168/7,572 (68.3)	906/1,330 (68.1)	3,085/4,769 (64.7)	5,236/7,501 (69.8)	63,066/89,706 (70.3)
2014	2,267/4,003 (56.7)	1,122/1,930 (58.1)	4,759/8,788 (54.1)	7,757/12,534 (61.9)	1,285/2,442 (52.6)	2,228/3,771 (59.1)	350/639 (54.8)	1,365/2,410 (56.6)	1,420/2,865 (49.6)	22,579/39,424 (57.3)

Table 4 CD4 recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation by province (Continued)

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
By Estimated CD4 count at ART start										
<50 cells/μl	5,513/9,714 (56.8)	3,802/6,483 (58.6)	17,432/29,314 (59.5)	19,028/28,670 (66.4)	4,756/8,134 (58.5)	6,000/9,672 (62.0)	828/1,465 (56.5)	3,538/6,109 (57.9)	4,779/8,045 (59.4)	65,731/107,706 (61.0)
50-99 cells/μl	8,590/12,013 (71.5)	5,236/7,314 (71.6)	20,713/28,334 (73.1)	25,621/32,867 (77.9)	5,707/7,918 (72.1)	7,502/10,081 (74.4)	1,298/1,824 (71.2)	5,085/7,125 (71.4)	6,928/9,439 (73.3)	86,785/117,063 (74.1)
100-149 cells/ μl	11,063/3,383 (82.7)	6,888/8,091 (85.1)	25,640/29,947 (85.6)	33,202/37,940 (87.5)	6,709/8,122 (82.6)	9,516/11,196 (85.0)	1,742/2,120 (82.1)	6,437/7,712 (83.5)	9,081/10,662 (85.2)	110,377/129,299 (85.4)
≥150 cells/μl	13,896/15,250 (91.1)	8,539/9,165 (93.2)	30,325/32,489 (93.4)	40,764/43,309 (94.1)	7,826/8,597 (91.0)	11,530/12,464 (92.5)	2,103/2,292 (91.8)	7,955/8,735 (91.1)	11,475/12,227 (93.9)	134,582/144,717 (93.0)

Table 5 Risk ratios associated with absolute CD4 count recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation

Variable	Category	Multivariable RR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.05 (1.02–1.09)	
	35–49	0.97 (0.96–0.97)	
	50+	0.93 (0.92–0.94)	
Gender	Females	1	<0.001
	Males	0.93 (0.93–0.94)	
	Unknown	0.97 (0.94–0.99)	
Year	2010	1	<0.001
	2011	1.00 (0.99–1.01)	
	2012	1.01 (1.01–1.02)	
	2013	1.01 (0.99–1.02)	
	2014	0.97 (0.96–0.99)	
CD4 category at ART initiation (cells/μl)	150–199	1	<0.001
	100–149	0.94 (0.93–0.94)	
	50–99	0.83 (0.82–0.84)	
	<50	0.70 (0.70–0.71)	
Duration in follow up	<12	1	<0.001
	12–23	1.30 (1.28–1.31)	
	24–35	1.44 (1.42–1.45)	
	36–47	1.50 (1.48–1.52)	
	≥48	1.53 (1.51–1.55)	
Virally suppressed	No	1	<0.001
	Yes	1.69 (1.67–1.71)	
Province	KwaZulu-Natal	1	<0.001
	Eastern Cape	0.97 (0.95–0.98)	
	Free State	0.97 (0.96–0.99)	
	Gauteng	0.98 (0.97–0.99)	
	Limpopo	0.98 (0.97–1.00)	
	Mpumalanga	1.00 (0.98–1.01)	
	Northern Cape	0.98 (0.96–1.01)	
	North West	0.99 (0.97–1.00)	
	Western Cape	0.97 (0.96–0.98)	

Table 6 Proportion of individuals with CD4 count recovery to 200, 350 and 500 cells/ μ l and the time to recovery to these threshold by district

Province	District name	% recovery 200	Time to recovery 200 (median, IQR)	% recovery 350	Time to recovery 350 (median, IQR)	% recovery 500	Time to recovery 500 (median,IQR)
EC	A Nzo DM	86.6	9.9 (7.5–14.5)	67.7	13.1 (8.7–22.9)	41.9	14.9 (8.8–28.9)
EC	Buffalo City MM	84.6	10.3 (7.3–15.2)	67.5	13.3 (8.6–23.3)	41.8	13.4 (8.3–25.2)
EC	Sarah Baartman DM	84.3	9.8 (7.2–14.8)	68.4	12.9 (8.3–23.7)	44.5	14.0 (8.4–27.4)
EC	Amathole DM	84.6	9.5 (7.1–13.9)	68.9	12.6 (8.2–22.4)	44.9	15.1 (9.2–27.5)
EC	C Hani DM	85.2	9.8 (7.2–14.3)	67.6	12.9 (8.4–23.4)	42.4	15.5 (9.2–27.4)
EC	Joe Gqabi DM	85.7	9.2 (6.9–13.7)	67.8	11.9 (7.3–23.1)	44.7	15.9 (10.2–27.9)
EC	N Mandela Bay MM	80.9	10.1 (7.2–15.4)	62.4	13.0 (8.4–24.1)	37.5	16.0 (9.4–28.1)
EC	O Tambo DM	86.8	9.6 (7.0–13.7)	69	11.9 (8.1–22.7)	43.8	15.9 (9.2–27.8)
FS	Fezile Dabi DM	82.4	9.4 (6.8–14.9)	63.4	12.5 (7.8–23.9)	38.6	16.4 (9.4–28.7)
FS	Lejweleputswa DM	83.8	9.3 (6.9–14.0)	64.2	12.2 (7.8–22.8)	38.6	16.2 (9.9–28.7)
FS	Mangaung MM	85.5	9.0 (6.9–13.7)	67.8	12.4 (7.9–22.4)	42.7	16.6 (9.8–28.7)
FS	T Mofutsanyane DM	85.2	9.5 (6.9–14.7)	67.7	12.0 (7.8–22.6)	44.3	16.3 (9.9–28.5)
FS	Xhariep DM	81.5	9.2 (6.6–14.0)	64.4	12.1 (7.8–22.7)	41.8	16.1 (10.6–27.8)
GP	Ekurhuleni MM	84.5	9.4 (7.1–14.8)	66.7	12.7 (8.0–24.0)	42.2	16.9 (9.4–27.7)
GP	Johannesburg MM	82.6	9.8 (7.2–15.5)	62.1	13.3 (8.4–23.4)	36.6	16.9 (9.6–28.1)
GP	Sedibeng DM	86.1	11.6 (7.5–15.7)	69.2	13.8 (9.4–24.6)	45.1	16.7 (10.7–28.7)
GP	Tshwane MM	84.3	9.5 (7.2–14.9)	65.6	13.0 (8.2–23.6)	40.9	16.9 (9.8–30.1)
GP	West Rand DM	83.5	9.2 (7.1–15.8)	64.9	12.7 (8.1–24.2)	39.7	16.8 (9.6–28.8)
KZN	Amajuba DM	85.3	8.8 (6.8–13.6)	67.7	10.9 (7.4–22.9)	43.7	17.3 (10.1–29.5)
KZN	eThekwinini MM	87.3	9.4 (6.8–14.9)	71.2	12.3 (7.7–22.7)	47.1	17.5 (9.7–30.0)
KZN	Harry Gwala DM	85.8	9.6 (6.9–15.1)	68.7	12.4 (7.9–23.0)	44.3	17.5 (10.1–29.6)
KZN	iLembe DM	86.8	9.0 (6.6–14.1)	71.5	11.5 (7.5–22.4)	48.2	17.4 (9.4–29.6)
KZN	Ugu DM	87.8	9.1 (6.8–13.7)	71.8	11.0 (7.6–28.8)	49.6	16.9 (9.9–28.8)
KZN	uMgungundlovu DM	88.3	9.4 (6.9–14.4)	72.7	12.6 (7.9–22.6)	48.8	17.0 (8.6–30.7)
KZN	Umkhanyakude DM	90.4	8.7 (6.6–14.2)	78.2	11.3 (7.4–22.3)	59.2	17.4 (10.0–29.6)
KZN	Umkhanyathi DM	85.7	9.0 (6.7–14.0)	70.2	11.5 (7.6–22.9)	47.8	17.2 (8.7–31.2)
KZN	Uthukela DM	87.6	8.2 (6.3–12.5)	73.9	11.1 (7.1–20.5)	53.6	17.1 (9.2–30.1)
KZN	Uthungulu DM	86.7	9.0 (6.6–13.7)	72	11.4 (7.4–20.2)	49.5	17.4 (10.4–29.9)

Table 6 Proportion of individuals with CD4 count recovery to 200, 350 and 500 cells/ μ l and the time to recovery to these threshold by district *(Continued)*

Province	District name	% recovery 200	Time to recovery 200 (median, IQR)	% recovery 350	Time to recovery 350 (median, IQR)	% recovery 500	Time to recovery 500 (median,IQR)
KZN	Zululand DM	86.8	8.3 (6.1–13.9)	70.3	11.2 (6.9–22.5)	48.1	17.3 (10.9–29.6)
LP	Capricorn DM	83.3	9.3 (6.9–14.9)	66	12.4 (7.8–23.6)	42.3	17.7 (11.3–29.4)
LP	Mopani DM	82.2	9.2 (6.9–13.6)	64.4	11.6 (7.7–21.8)	40.5	17.6 (10.9–29.3)
LP	Sekhukhune DM	84.8	10.3 (7.1–15.2)	66.6	12.8 (8.1–22.9)	42.8	17.7 (9.9–30.7)
LP	Vhembe DM	83	8.3 (6.6–12.5)	65.3	10.9 (7.2–18.8)	42.7	17.6 (9.2–30.9)
LP	Waterberg DM	85.9	9.5 (7.0–15.1)	67.5	12.4 (7.9–24.3)	45.4	17.7 (9.1–30.1)
MP	Ehlanzeni DM	85.8	9.0 (6.9–13.6)	70.1	11.7 (7.6–20.8)	46.9	17.9 (9.8–30.3)
MP	G Sibande DM	85.5	9.4 (6.9–14.4)	68.2	11.8 (7.6–23.1)	44.8	17.9 (10.2–29.6)
MP	Nkangala DM	83.5	9.4 (6.9–14.4)	66.7	12.2 (7.9–22.9)	42.7	17.9 (10.7–29.5)
NC	Frances Baard DM	85.2	8.9 (7.0–13.8)	67.3	11.9 (8.0–23.4)	40.8	18.3 (10.1–30.4)
NC	J T Gaetsewe DM	86.8	8.5 (6.7–12.2)	65.8	11.0 (7.3–21.3)	42.3	18.1 (10.4–30.1)
NC	Namakwa DM	89.1	10.1 (7.6–15.6)	68.9	13.2 (8.7–26.0)	46.2	18.1 (10.9–29.9)
NC	Pixley ka Seme DM	85.8	9.4 (6.9–14.3)	69	12.6 (8.0–23.2)	45.5	18.1 (10.9–30.3)
NC	ZF Mgcau DM	86.7	9.7 (7.3–14.6)	69.8	13.4 (8.7–23.9)	46.8	18.1 (9.5–30.9)
NW	Bojanala Platinum DM	83.9	9.1 (7.0–13.9)	64.9	11.6 (7.8–22.1)	40.9	18.3 (12.1–30.0)
NW	Dr K Kaunda DM	87.3	8.6 (6.4–13.0)	70.9	11.5 (7.5–22.6)	46.9	19.0 (10.1–30.8)
NW	Ngaka Modiri Molema DM	84.9	8.7 (6.8–13.2)	68.5	11.4 (7.6–22.3)	43.6	18.7 (9.4–31.2)
NW	Ruth Segomotsi Mompati DM	85.4	8.8 (6.7–13.5)	70.6	12.2 (7.6–23.0)	48	18.8 (10.8–31.2)
WC	Cape Town MM	85.1	10.7 (6.6–14.9)	69.5	13.5 (8.5–24.2)	44.2	19.2 (12.2–31.7)
WC	Cape Winelands DM	86.2	10.1 (6.5–14.9)	69.2	13.2 (8.3–24.2)	44.4	19.3 (12.3–31.7)
WC	Central Karoo DM	74.6	10.9 (7.8–17.4)	61.5	14.7 (8.7–24.2)	38.6	22.6 (12.2–33.7)
WC	Eden DM	82.9	10.8 (6.9–16.2)	67.2	13.9 (8.5–24.4)	42.3	21.8 (12.9–35.6)
WC	Overberg DM	86.3	10.3 (6.8–15.4)	71.1	14.4 (9.3–24.8)	46.2	19.4 (12.0–32.8)
WC	West Coast DM	88.2	10.3 (7.2–14.5)	73.3	13.6 (8.9–24.4)	47.4	19.2 (12.2–31.7)

Table 7 CD4 recovery to 200 cells/μl among those with CD4 counts <200 cells/μl and were virally suppressed by the end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
Overall CD4 count recovery to 200cells/μl (n/N, %)	35,308/41,685 (84.7)	23 073/27 376 (84.3)	87,659/104,484 (83.9)	111,975/128,242 (87.3)	22,783/27,221 (83.7)	31,396/36,831 (85.2)	5,337/6,208 (86.0)	20,710/24,324 (85.1)	28,940/33,990 (85.1)	367,575/430,837 (85.3)
By Gender										
Females	24,303/27,501 (88.4)	15,459/17,629 (87.7)	56,151/64,096 (87.6)	70,871/78,217 (90.6)	16,469/19,023 (86.6)	20,980/23,649 (88.7)	3,315/3,702 (89.6)	13,493/15,250 (88.5)	17,729/19,895 (89.1)	239,010/269,230 (88.8)
Males	10,333/13,370 (77.3)	7,351/9,429 (78.0)	30,637/39,305 (78.0)	38,668/47,187 (82.0)	6,154/8,002 (76.9)	9,996/12,692 (78.8)	1,928/2,394 (80.5)	7,027/8,850 (79.4)	10,805/13,624 (79.3)	123,050/155,054 (79.4)
By age										
Age 15–24	288/310 (92.9)	208/243 (85.6)	455/509 (89.4)	1,247/1,365 (91.4)	185/199 (92.9)	338/371 (91.1)	35/37 (95.4)	147/162 (90.7)	89/102 (87.3)	2,993/3,300 (90.7)
Age 25–34	4,794/5,413 (88.6)	2,419/2,697 (89.7)	8,153/9,061 (89.9)	15,741/17,172 (91.7)	1,955/2,164 (90.4)	4,059/4,438 (91.5)	526/583 (90.2)	1,959/2,159 (90.7)	3,807/4,291 (88.7)	43,441/48,014 (90.5)
Age 35–49	18,969/22,216 (85.4)	11,988/13,975 (85.8)	49,424/57,983 (85.2)	62,879/71,859 (87.5)	11,732/13,773 (85.2)	16 331/19 062 (85.7)	2 848/3 275 (86.9)	10 585/12 248 (86.4)	17 619/20 559 (85.7)	202,609/235,232 (86.1)
Age ≥50	11,257/13,746 (81.9)	8,458/10,461 (80.9)	29 627/36 931 (80.2)	32,108/37,846 (84.8)	8,911/11,085 (80.4)	10,668/12,960 (82.3)	1,928/2,313 (83.4)	8,019/9,755 (82.2)	7,425/9,038 (82.2)	118,532/144,291 (82.2)
By Year of baseline CD4 count										
2010	9,648/10,492 (92.0)	6,483/7,180 (90.2)	24,727/27,129 (91.2)	28,474/30,172 (94.4)	6,850/7,559 (90.6)	7,954/8,593 (92.6)	1,685/1,820 (92.6)	6,700/7,315 (91.6)	9,525/10,268 (92.8)	102,188/110,699 (92.3)
2011	10,333/11,584 (89.2)	7,046/7,956 (88.6)	25,828/29,129 (88.7)	31,074/33,847 (91.8)	6,920/7,824 (88.5)	9,987/11,067 (90.2)	1,526/1,707 (89.5)	6,065/6,758 (89.8)	7,932/8,862 (89.5)	106,872/118,931 (89.9)
2012	7,657/9,052 (84.6)	4,730/5,668 (83.5)	19,734/23,459 (84.1)	26,859/30,263 (88.8)	4,607/5,585 (82.5)	7,185/8,399 (85.6)	1,070/1,237 (86.5)	4,162/4,867 (85.5)	6,152/7,233 (85.1)	82,181/95,793 (85.8)
2013	5,716/7,510 (76.1)	3,783/4,968 (76.1)	13,340/18,085 (73.8)	18,542/23,365 (79.4)	3,333/4,483 (74.3)	4,474/6,019 (74.3)	777/998 (77.9)	2,680/3,669 (73.0)	4,240/5,678 (74.7)	56,928/74,832 (76.1)
2014	1,954/3,047 (64.1)	1,031/1,594 (64.7)	4,030/6,682 (60.3)	7,026/10,595 (66.3)	1,073/1,770 (60.6)	1,796/2,753 (65.2)	278/447 (62.2)	1,103/1,715 (64.3)	1,091/1,949 (56.0)	19,406/30,582 (63.5)

Table 7 CD4 recovery to 200 cells/μl among those with CD4 counts <200 cells/μl and were virally suppressed by the end of follow up by province *(Continued)*

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
By Estimated CD4 count at ART start										
≤50 cells/μl	5,070/7,494 (67.7)	3,616/5,367 (67.4)	16,368/23,983 (68.2)	17,851/24,145 (73.9)	4,343/6,260 (69.4)	5,436/7,635 (71.2)	769/1,106 (69.5)	3,219/4,635 (69.5)	4,336/6,363 (68.2)	61,058/87,066 (70.1)
50-99 cells/μl	7,853/9,818 (80.0)	4,963/6,375 (77.9)	19,275/24,385 (79.0)	24,145/29,235 (82.6)	5,217/6,514 (80.1)	6,783/8,418 (80.6)	1,175/1,443 (81.5)	4,595/5,777 (79.5)	6,261/7,894 (79.3)	80,365/99,985 (80.4)
100-149 cells/ μl	9,923/11,230 (88.4)	6,497/7,266 (89.4)	23,833/26,609 (89.6)	31,340/34,568 (90.7)	6,093/6,904 (88.2)	8,678/9,742 (89.1)	1,559/1,751 (89.0)	5,738/6,387 (89.8)	8,104/9,072 (89.3)	101,857/113,635 (89.6)
≥150 cells/μl	12,462/13,143 (94.8)	7,997/8,368 (95.7)	28,183/29,507 (95.5)	38,639/40,294 (95.9)	7,130/7,543 (94.5)	10,499/11,036 (95.1)	1,834/1,908 (96.1)	7,158/7,525 (95.1)	10,239/10,661 (96.0)	124,295/130,151 (95.5)

Table 8 Risk ratios associated with absolute CD4 count recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation and were virally suppressed by the end of follow up

Variable	Category	Multivariable RR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.05 (1.01–1.09)	
	35–49	0.98 (0.97–0.99)	
	50+	0.94 (0.93–0.95)	
Gender	Females	1	<0.001
	Males	0.94 (0.93–0.94)	
	Unknown	0.97 (0.94–0.99)	
Year	2010	1	<0.001
	2011	1.00 (0.99–1.01)	
	2012	1.00 (0.99–1.01)	
	2013	0.98 (0.97–1.00)	
	2014	0.93 (0.92–0.95)	
CD4 category at ART initiation (cells/μl)	150–199	1	<0.001
	100–149	0.95 (0.94–0.95)	
	50–99	0.86 (0.85–0.86)	
	<50	0.75 (0.74–0.76)	
Duration in follow up	<12	1	<0.001
	12–23	1.27 (1.25–1.28)	
	24–35	1.38 (1.37–1.40)	
	36–47	1.43 (1.41–1.45)	
	>=48	1.46 (1.43–1.48)	
Province	KwaZulu-Natal	1	<0.001
	Eastern Cape	0.97 (0.96–0.98)	
	Free State	0.98 (0.97–1.00)	
	Gauteng	0.98 (0.97–0.99)	
	Limpopo	0.99 (0.97–1.00)	
	Mpumalanga	0.99 (0.96–1.00)	
	Northern Cape	0.99 (0.97–1.00)	
	North West	0.99 (0.97–1.00)	
	Western Cape	0.96 (0.94–0.97)	

Table 9 Time to CD4 recovery to 200 cells/μl among those who had CD4 counts <200 cells/μl at ART initiation.

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu- Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	All
Overall time to CD4 count recovery in months (median, IQR)										
	9.9 (7.2–15.0)	9.4 (6.9–14.5)	9.7 (7.1–15.4)	9.2 (6.7–14.5)	9.4 (6.9–14.6)	9.2 (6.9–14.2)	9.2 (7.0–14.5)	9.0 (6.8–14.0)	10.8 (6.7–15.3)	9.5 (6.9–14.8)
By gender										
Females	9.7 (7.1–14.2)	9.1 (6.9–13.8)	9.4 (7.1–14.5)	8.9 (6.6–13.6)	9.2 (6.9–14.0)	9.0 (6.8–13.5)	9.0 (6.9–13.5)	8.8 (6.7–13.1)	10.1 (6.6–14.5)	9.1 (6.9–14.0)
Males	10.6 (7.4–16.9)	10.0 (7.1–16.1)	10.4 (7.3–17.3)	9.8 (6.8–16.5)	10.0 (7.1–16.4)	9.8 (7.1–15.8)	9.8 (7.2–15.7)	9.4 (6.9–15.8)	11.6 (6.8–16.8)	10.1 (7.1–16.6)
By age										
Age 15–24	9.9 (7.4–14.9)	9.2 (6.7–12.9)	9.6 (6.9–14.5)	9.0 (6.7–14.0)	9.5 (7.0–13.8)	9.1 (7.0–14.5)	8.3 (6.7–14.9)	9.1 (6.7–13.9)	8.5 (6.4–14.5)	9.2 (6.8–14.2)
Age 25–34	9.5 (6.9–13.9)	8.7 (6.7–12.8)	8.9 (6.9–13.4)	8.5 (6.3–12.6)	8.6 (6.5–12.9)	8.6 (6.5–12.6)	9.0 (7.1–13.6)	8.5 (6.5–11.8)	9.5 (6.4–14.2)	8.8 (6.6–13.1)
Age 35–49	9.9 (7.2–15.0)	9.3 (6.9–14.3)	9.6 (7.1–15.1)	9.2 (6.7–14.7)	9.4 (6.9–14.4)	9.2 (6.9–12.2)	9.3 (7.0–14.5)	9.0 (6.8–13.9)	11.0 (6.7–15.3)	9.5 (6.8–14.8)
Age ≥50	10.2 (7.3–15.4)	9.8 (7.0–15.6)	10.2 (7.3–16.5)	9.4 (6.8–15.4)	9.7 (7.0–15.4)	9.5 (7.0–14.7)	9.3 (7.1–14.7)	9.2 (6.9–15.0)	11.2 (6.7–15.9)	9.8 (7.1–15.6)
By year of ART start										
2010	9.8 (7.2–16.2)	9.4 (7.1–16.1)	9.4 (7.2–17.9)	9.4 (6.9–16.5)	9.3 (7.1–16.9)	9.3 (7.2–15.2)	9.6 (7.4–17.1)	9.2 (7.7–16.3)	8.9 (6.9–14.9)	9.4 (7.1–16.5)
2011	9.5 (7.2–17.1)	9.0 (6.9–16.8)	9.6 (7.2–18.4)	9.3 (6.9–17.9)	9.3 (7.0–17.2)	9.1 (7.0–16.1)	9.5 (7.2–17.1)	8.9 (6.8–15.4)	8.7 (6.2–17.1)	9.3 (7.0–17.4)
2012	11.5 (7.5–18.1)	10.8 (7.1–17.7)	11.0 (7.5–17.7)	9.9 (6.9–17.1)	11.2 (7.3–17.7)	11.0 (7.2–17.1)	10.1 (7.1–16.5)	9.9 (7.0–16.2)	13.0 (7.3–18.5)	10.9 (7.1–17.5)
2013	11.3 (7.5–13.9)	10.5 (6.9–13.3)	11.1 (7.3–13.9)	9.7 (6.9–13.3)	10.1 (6.9–13.0)	9.9 (6.9–13.3)	9.2 (6.9–12.7)	9.5 (6.7–13.1)	12.6 (9.2–14.7)	10.7 (7.0–13.6)
2014	7.4 (5.9–10.0)	7.1 (5.7–9.6)	7.3 (5.9–9.4)	7.0 (5.7–8.9)	6.9 (5.8–9.0)	7.1 (5.8–8.9)	7.1 (5.9–8.9)	6.9 (5.6–9.0)	6.9 (5.0–10.9)	7.1 (5.7–9.3)
By Estimated CD4 count at ART start										
<50 cells/μl	12.7 (8.1–22.5)	12.4 (7.8–21.7)	13.1 (8.1–22.7)	12.2 (7.5–21.3)	11.9 (7.6–20.6)	11.8 (7.6–21.1)	12.7 (7.8–23.1)	11.5 (7.4–20.9)	13.5 (9.1–23.8)	12.6 (7.8–21.9)
50–99 cells/μl	11.0 (7.5–17.5)	10.5 (7.1–18.1)	10.9 (7.4–18.1)	10.3 (7.0–17.6)	10.1 (7.1–16.3)	10.0 (7.1–16.1)	10.2 (7.2–17.5)	9.7 (7.0–16.5)	12.3 (7.2–18.5)	10.6 (7.2–17.6)
100–149 cells/μl	9.6 (7.1–13.8)	8.9 (6.8–13.1)	9.0 (7.0–13.5)	8.7 (6.6–12.9)	9.0 (6.8–13.1)	8.9 (6.8–12.9)	8.8 (6.9–12.5)	8.7 (6.7–12.4)	9.7 (6.5–14.2)	9.0 (6.8–13.3)
100–199 cells/μl	8.8 (6.8–11.8)	8.2 (6.6–11.3)	8.3 (6.9–11.3)	8.0 (6.2–11.2)	8.2 (6.5–11.5)	8.2 (6.5–11.3)	8.4 (6.7–11.2)	8.1 (6.4–11.0)	8.2 (6.0–12.4)	8.2 (6.5–11.5)

Table 10 Hazard ratios associated with CD4 count recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation

Variable	Category	Multivariable HR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.05 (1.02–1.09)	
	35–49	0.89 (0.89–0.90)	
	50+	0.80 (0.79–0.81)	
Gender	Females	1	<0.001
	Males	0.83 (0.83–0.84)	
	Unknown	0.93 (0.90–0.95)	
Year	2010	1	<0.001
	2011	1.00 (1.00–1.02)	
	2012	0.96 (0.95–0.97)	
	2013	1.05 (1.04–1.06)	
	2014	1.70 (1.68–1.73)	
CD4 category at ART initiation (cells/μl)	150–199	1	<0.001
	100–149	0.75 (0.74–0.75)	
	50–99	0.52 (0.51–0.52)	
	<50	0.36 (0.36–0.37)	
Virally suppressed	No	1	<0.001
	Yes	2.16 (2.14–2.19)	
Province	KwaZulu-Natal	1	<0.001
	Eastern Cape	0.88 (0.87–0.89)	
	Free State	0.95 (0.93–0.96)	
	Gauteng	0.93 (0.93–0.94)	
	Limpopo	0.96 (0.95–0.97)	
	Mpumalanga	0.98 (0.97–0.99)	
	Northern Cape	0.97 (0.95–1.00)	
	North West	1.00 (0.99–1.02)	
	Western Cape	0.92 (0.91–0.93)	

Table 11 Time to CD4 recovery to 200 cells/μl among those with CD4 counts <200 cells/μl and were virally suppressed by the end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	All
Overall time to CD4 count recovery in months (median, IQR)										
	9.8 (7.2–14.5)	9.3 (6.9–14.2)	9.7 (7.1–15.2)	9.0 (6.7–14.2)	9.2 (6.9–14.2)	9.2 (6.9–13.9)	9.0 (7.0–13.8)	8.9 (6.8–13.5)	10.6 (6.6–15.0)	9.4 (6.9–14.5)
By gender										
Females	9.5 (7.1–13.8)	9.0 (6.9–13.4)	9.3 (7.1–13.3)	8.7 (6.6–13.3)	9.0 (6.9–13.5)	8.9 (6.8–13.3)	8.8 (6.9–12.9)	8.7 (6.7–12.7)	9.8 (6.5–14.2)	9.0 (6.9–13.7)
Males	10.6 (7.4–16.5)	9.9 (7.0–15.8)	10.6 (7.3–17.5)	9.7 (6.9–16.2)	9.9 (7.0–16.2)	9.7 (7.1–15.6)	9.6 (7.2–15.1)	9.2 (6.9–15.4)	11.6 (6.8–16.7)	10.1 (7.1–16.5)
By age										
Age 15–24	9.5 (7.4–13.6)	8.9 (6.7–12.2)	8.9 (6.9–13.6)	8.5 (6.5–12.6)	8.9 (6.9–12.8)	8.9 (6.9–13.1)	7.7 (6.6–11.0)	8.9 (6.6–12.6)	8.9 (6.7–14.4)	8.9 (6.7–13.0)
Age 25–34	9.2 (6.9–13.1)	8.4 (6.6–12.4)	8.7 (6.7–12.1)	8.4 (6.3–12.2)	8.3 (6.4–11.9)	8.4 (6.5–11.9)	8.7 (6.9–12.4)	8.3 (6.5–11.5)	9.0 (6.3–13.8)	8.6 (6.5–12.6)
Age 35–49	9.8 (7.1–14.5)	9.2 (6.9–13.9)	9.6 (7.1–14.9)	9.1 (6.7–14.3)	9.2 (6.9–13.9)	9.2 (6.9–14.0)	8.9 (6.9–13.5)	8.8 (6.0–13.3)	10.9 (6.7–15.1)	9.4 (6.9–14.5)
Age ≥50	10.2 (7.4–15.2)	9.7 (7.7–15.4)	10.3 (7.3–16.6)	9.4 (6.9–15.2)	9.6 (6.9–15.1)	9.5 (7.0–14.6)	9.1 (7.1–14.4)	9.2 (6.9–14.7)	11.0 (6.7–15.9)	9.8 (7.1–15.6)
By year of ART start										
2010	9.6 (7.5–15.4)	9.3 (7.1–15.6)	9.3 (7.2–17.5)	9.2 (6.9–15.6)	9.1 (7.1–15.6)	9.2 (7.2–14.4)	9.4 (7.3–15.3)	9.1 (7.1–15.4)	8.8 (6.8–14.2)	9.2 (7.1–15.8)
2011	9.2 (7.1–15.5)	8.9 (6.9–15.4)	9.5 (7.1–17.9)	9.1 (6.8–17.2)	9.0 (6.9–15.6)	8.9 (6.9–15.1)	9.1 (7.1–15.6)	8.7 (6.7–14.2)	8.5 (6.2–16.3)	9.1 (6.9–16.5)
2012	11.5 (7.4–17.2)	10.6 (7.0–17.0)	10.9 (7.4–17.1)	9.8 (6.8–16.5)	11.0 (7.2–16.9)	10.8 (7.1–16.3)	9.6 (6.9–15.5)	9.5 (6.9–15.1)	12.9 (7.1–17.9)	10.7 (7.1–16.8)
2013	11.5 (7.5–13.8)	10.5 (6.9–13.3)	11.4 (7.4–13.9)	9.6 (6.7–13.2)	10.1 (6.8–12.9)	9.9 (6.8–13.3)	8.9 (6.9–12.5)	9.3 (6.7–13.0)	12.6 (9.3–14.6)	10.7 (7.0–13.6)
2014	7.3 (5.9–10.1)	7.0 (5.8–9.6)	7.3 (5.9–9.6)	6.9 (5.7–8.9)	6.9 (5.8–8.9)	7.0 (5.8–8.9)	7.0 (5.9–8.7)	6.9 (5.8–9.1)	6.9 (5.0–11.3)	7.1 (5.8–9.3)
By Estimated CD4 count at ART start										
<50 cells/μl	12.9 (8.1–22.7)	12.7 (7.8–22.1)	13.5 (8.2–23.1)	12.4 (7.5–21.3)	12.0 (7.6–20.7)	12.1 (7.6–21.4)	12.9 (7.8–23.9)	11.6 (7.4–20.9)	13.8 (9.7–24.4)	12.9 (7.8–22.3)
50–99 cells/μl	10.8 (7.4–16.5)	10.4 (7.1–17.7)	11.0 (7.4–18.1)	10.2 (6.9–17.3)	9.8 (7.0–15.6)	9.9 (7.1–15.8)	10.2 (7.2–17.3)	9.6 (7.0–16.3)	12.3 (7.1–18.2)	10.6 (7.2–17.3)
100–149 cells/μl	9.4 (7.1–13.5)	8.8 (6.8–12.9)	8.9 (7.0–13.4)	8.7 (6.7–12.8)	8.8 (6.8–12.9)	8.8 (6.8–12.8)	8.5 (6.8–11.8)	8.5 (6.7–11.9)	9.4 (6.5–14.0)	8.9 (6.8–13.1)
100–199 cells/μl	8.7 (6.9–11.8)	8.1 (6.6–11.2)	8.3 (6.7–11.3)	7.9 (6.2–11.0)	8.1 (6.5–11.4)	8.2 (6.5–11.2)	8.3 (6.7–10.8)	8.1 (6.4–10.8)	8.0 (6.0–12.1)	8.2 (6.5–11.3)

Table 12 Hazard ratios associated with CD4 count recovery to 200 cells/μl among those with CD4 counts <200 cells/μl at ART initiation and were virally suppressed by end of follow up

Variable	Category	Multivariable HR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.08 (1.04–1.12)	
	35–49	0.89 (0.89–0.90)	
	50+	0.79 (0.78–0.80)	
Gender	Females	1	<0.001
	Males	0.83 (0.82–0.83)	
	Unknown	0.93 (0.90–0.95)	
Year	2010	1	<0.001
	2011	1.01 (1.00–1.02)	
	2012	0.96 (0.95–0.97)	
	2013	1.03 (1.02–1.04)	
	2014	1.65 (1.63–1.68)	
CD4 category at ART initiation (cells/μl)	150– 199	1	<0.001
	100– 149	0.75 (0.74–0.75)	
	50– 99	0.53 (0.52–0.53)	
	<50	0.38 (0.37–0.38)	
Province	KwaZulu–Natal	1	<0.001
	Eastern Cape	0.88 (0.87–0.89)	
	Free State	0.95 (0.94–0.97)	
	Gauteng	0.93 (0.92–0.93)	
	Limpopo	0.97 (0.95–0.98)	
	Mpumalanga	0.97 (0.96–0.98)	
	Northern Cape	0.99 (0.96–1.01)	
	North West	1.00 (0.99–1.02)	
	Western Cape	0.90 (0.89–0.92)	

Table 13 CD4 recovery to 350 cells/ μ l among those with CD4 counts <350 cells/ μ l and who were virally suppressed by the end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu- Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
Overall CD4 count recovery to 350cells/μl (n/N, %)										
	49,859/74,139 (67.3)	31,023/47,041 (65.9)	110,925/170,710 (65.0)	169,135/235,874 (71.7)	29,118/44,217 (65.9)	44,256/64,216 (68.9)	7,502/11,078 (67.7)	28,625/42,183 (67.9)	43,279/62,359 (69.4)	514,333/752,742 (68.3)
By Gender										
Females	37,999/52,175 (72.8)	22,993/32,209 (71.4)	79,265/111,536 (71.1)	119,781/154,987 (77.3)	22,913/32,506 (70.5)	32,645/43,810 (74.5)	5,139/7,008 (73.3)	20,925/28,455 (73.5)	30,116/39,721 (75.8)	372,199/502,983 (74.0)
Males	10,905/20,547 (53.1)	7,696/14,302 (53.8)	30,625/57,447 (53.3)	45,821/75,749 (60.5)	5,983/11,382 (52.6)	11,026/19,547 (56.4)	2,229/3,868 (57.6)	7,445/13,349 (55.8)	12,595/ 21,814 (57.7)	134,504/238,341 (56.4)
By age										
Age 15–24	496/614 (80.8)	338/447 (75.6)	637/839 (75.9)	2,112/2,615 (80.8)	253/317 (79.8)	517/648 (79.8)	52/69 (75.4)	256/317 (80.8)	218/262 (83.2)	4,833/6,133 (79.6)
Age 25–34	8,986/11,578 (77.6)	4,590/5,835 (78.7)	14,672/18,636 (78.7)	31,405/38,205 (82.2)	3,700/4,580 (80.8)	7,591/9,338 (81.3)	1,027/1,316 (78.0)	3,953/4,898 (80.7)	7,529/9,584 (78.6)	83,522/104,061 (80.3)
Age 35–49	26,072/38,467 (67.8)	15,939/23,675 (67.3)	62,975/94,685 (66.5)	91,471/128,104 (71.4)	15,108/22,219 (68.0)	22,719/32,809 (69.3)	4,013/5,815 (69.0)	14,664/21,167 (69.3)	25,697/36,892 (69.7)	278,997/404,344 (69.0)
Age \geq 50	14,305/23,480 (60.9)	10,156/17,084 (59.5)	32,641/56,550 (57.7)	44,147/66,950 (65.9)	10,057/17,101 (58.8)	13,429/21,421 (62.7)	2,410/3,878 (62.2)	9,752/15,803 (61.7)	9,835/15,621 (63.0)	146,931/238,204 (61.6)
By Year of baseline CD4 count										
2010	11,010/14,711 (74.8)	6,916/9,692 (71.4)	26,711/36,667 (72.9)	39,264/48,247 (81.4)	7,394/10,070 (73.3)	9,145/11,928 (76.7)	1,820/2,467 (73.7)	7,498/10,111 (74.2)	12,290/15,701 (78.3)	122,230/159,839 (76.5)
2011	14,393/19,929 (72.2)	9,719/13,799 (70.4)	33,326/47,209 (70.6)	44,966/58,298 (77.1)	9,088/12,676 (71.7)	14,048/18,654 (75.3)	2,180/3,035 (71.8)	8,670/11,717 (74.0)	12,979/17,189 (75.5)	149,675/202,965 (73.7)
2012	13,025/18,679 (69.7)	7,728/11,401 (67.8)	28,577/42,815 (66.8)	45,359/60,814 (74.6)	6,695/10,181 (65.8)	11,689/16,547 (70.6)	1,862/2,654 (70.2)	6,899/9,958 (69.3)	10,375/14,882 (69.7)	132,242/187,989 (70.4)
2013	8,578/14,906 (57.6)	5,351/9,278 (57.7)	17,141/32,154 (53.3)	28,909/47,162 (61.3)	4,544/8,126 (55.9)	6,696/ 11,732 (57.1)	1,207/2,026 (59.6)	4,037/7,194 (56.1)	6,264/11,094 (56.5)	82,789/143,780 (57.6)
2014	2,853/5,914 (48.2)	1,309/2,871 (45.6)	5,170/11,865 (43.6)	10,637/21,353 (49.8)	1,397/3,164 (44.2)	2,678/5,355 (50.0)	433/869 (48.3)	1,521/3,203 (47.5)	1,371/3,493 (39.3)	27,397/58,169 (47.1)

Table 13 CD4 recovery to 350 cells/μl among those with CD4 counts <350 cells/μl and who were virally suppressed by the end of follow up by province (Continued)

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
By Estimated CD4 count at ART start										
<50 cells/μl	2,726/7,494 (36.4)	1,845/5,367 (34.4)	8,642/23,983 (36.0)	10,676/24,145 (44.2)	2,497/6,260 (39.9)	3,242/7,635 (42.5)	397/1,106 (35.9)	1,760/4,635 (37.9)	2,220/6,363 (34.9)	34,032/87,066 (39.1)
50- 99 cells/μl	4,290/9,818 (43.7)	2,644/6,375 (41.5)	10,280/24,385 (42.2)	14,496/29,235 (49.6)	3,117/6,514 (47.9)	4,012/8,418 (47.7)	620/1,443 (42.9)	2,650/5,777 (45.9)	3,442/7,894 (43.6)	45,608/99,985 (45.6)
100- 199 cells/μl	15,379/24,373 (63.1)	9,788/15,634 (62.6)	35,483/56,116 (63.2)	50,512/74,862 (67.5)	9,292/14,447 (64.3)	13,630/20,778 (65.6)	2,335/3,359 (63.8)	8,987/13,912 (64.6)	12,857/19,733 (65.2)	158,425/243,786 (65.0)
200-349 cells/μl	27,464/32,454 (84.6)	16,746/19,665 (85.2)	56,520/66,226 (85.3)	93,451/107,632 (86.8)	14,212/16,996 (83.6)	23,372/27,385 (85.4)	4,150/4,870 (85.2)	15,228/17,859 (85.3)	24,760/28,369 (87.3)	276,268/321,905 (85.2)

Table 14 Risk ratios associated with absolute CD4 count recovery to 350 cells/ μ l among those with CD4 counts <350 cells/ μ l and were virally suppressed by the end of follow up

Variable	Category	Multivariable RR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.07 (1.04–1.10)	
	35–49	0.93 (0.92–0.94)	
	50+	0.85 (0.84–0.86)	
Gender	Females	1	<0.001
	Males	0.86 (0.85–0.86)	
	Unknown	0.94 (0.92–0.97)	
Year	2010	1	<0.001
	2011	0.99 (0.98–1.00)	
	2012	1.01 (1.00–1.02)	
	2013	0.99 (0.97–1.00)	
	2014	0.96 (0.95–0.98)	
CD4 category at ART initiation (cells/ μ l)	200–349	1	<0.001
	100–199	0.74 (0.74–0.95)	
	50–99	0.54 (0.53–0.54)	
	<50	0.46 (0.46–0.47)	
Duration in follow up	<12	1	<0.001
	12–23	1.37 (1.36–1.38)	
	24–35	1.63 (1.61–1.65)	
	36–47	1.81 (1.79–1.84)	
	\geq 48	1.95 (1.92–1.98)	
Province	KwaZulu–Natal	1	<0.001
	Eastern Cape	0.95 (0.94–0.96)	
	Free State	0.96 (0.95–0.98)	
	Gauteng	0.96 (0.96–0.97)	
	Limpopo	0.99 (0.98–1.00)	
	Mpumalanga	0.99 (0.98–1.00)	
	Northern Cape	0.97 (0.95–0.99)	
	North West	0.98 (0.97–1.00)	
	Western Cape	0.93 (0.93–0.94)	

Table 15 Time to CD4 recovery to 350 cells/µl among those with CD4 counts <350 cells/µl and were virally suppressed by the end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu- Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	All
Overall time to CD4 count recovery in months (median, IQR)										
	12.8 (8.3–23.3)	12.3 (7.8–22.8)	13.1 (8.2–23.8)	11.8 (7.6–22.2)	11.9 (7.7–22.2)	11.8 (7.7–22.0)	12.1 (7.9–23.2)	11.6 (7.6–22.4)	13.5 (8.5–24.3)	12.4 (7.9–22.9)
By gender										
Females	12.4 (8.1–21.6)	11.9 (7.7–21.6)	12.5 (8.0–22.1)	11.3 (7.4–20.6)	11.7 (7.6–21.0)	11.4 (7.6–20.3)	11.7 (7.6–21.6)	11.3 (7.6–20.9)	13.1 (8.1–22.4)	11.9 (7.7–21.2)
Males	13.9 (8.9–25.6)	13.2 (8.3–24.8)	14.3 (8.8–25.8)	13.2 (8.1–24.9)	13.0 (8.1–24.8)	13.0 (8.2–24.8)	13.2 (8.3–25.4)	12.6 (7.9–24.9)	14.6 (9.6–26.4)	13.7 (8.4–25.3)
By age										
Age 15– 24	11.1 (7.7–18.6)	10.2 (7.0–16.7)	11.3 (7.6–19.3)	10.6 (7.2–18.7)	10.2 (7.2–15.4)	10.4 (7.6–17.6)	9.8 (6.9–15.5)	9.4 (6.9–14.7)	12.1 (7.4–16.7)	10.7 (7.3–18.0)
Age 25– 34	11.2 (7.6–17.8)	10.1 (7.1–15.9)	10.4 (7.4–17.0)	9.8 (6.9–16.2)	9.9 (7.0–15.7)	9.9 (7.1–15.9)	10.2 (7.3–16.9)	9.7 (7.1–15.8)	12.3 (7.4–18.5)	10.3 (7.1–16.7)
Age 35– 49	12.9 (8.3–23.5)	12.2 (7.8–22.7)	13.0 (8.2–23.5)	11.9 (7.6–22.4)	11.9 (7.7–21.8)	11.8 (7.7–21.8)	12.3 (7.9–23.2)	11.5 (7.6–21.8)	13.7 (8.7–24.5)	12.5 (7.9–22.9)
Age ≥50	13.6 (8.9–24.9)	13.2 (8.3–24.8)	14.2 (8.9–25.5)	12.9 (8.0–24.7)	12.8 (7.9–24.3)	12.9 (8.2–24.6)	12.9 (8.3–25.2)	12.8 (8.1–24.9)	14.2 (9.2–25.6)	13.4 (8.4–25.0)
By year of ART start										
2010	17.9 (9.3–35.5)	17.6 (9.0–35.1)	19.5 (9.0–35.6)	15.7 (8.5–33.7)	15.7 (8.5–32.4)	15.6 (8.7–33.0)	17.0 (9.0–34.2)	16.8 (8.7–33.8)	15.2 (8.5–34.0)	16.9 (8.7–34.3)
2011	15.3 (8.7–28.7)	13.8 (8.0–27.4)	15.3 (8.7–28.3)	15.7 (8.4–29.4)	13.5 (8.0–26.6)	13.4 (8.2–27.1)	14.9 (8.7–29.1)	13.3 (8.2–26.9)	14.0 (7.8–28.2)	14.7 (8.3–28.3)
2012	13.7 (8.8–23.1)	12.9 (8.0–22.3)	13.6 (8.4–23.1)	12.8 (7.8–22.7)	13.0 (8.1–21.9)	12.9 (8.1–22.5)	13.1 (8.1–23.0)	11.7 (7.7–21.8)	15.0 (11.0–24.2)	13.3 (8.2–22.9)
2013	12.1 (8.3–14.7)	11.7 (7.6–14.2)	12.4 (8.3–14.9)	11.3 (7.4–14.6)	11.5 (7.5–14.0)	11.5 (7.5–14.4)	11.2 (7.6–14.1)	10.8 (7.3–14.4)	13.1 (11.4–15.6)	11.8 (7.8–14.7)
2014	7.7 (6.3–10.7)	7.2 (5.9–10.0)	7.6 (6.2–10.2)	7.2 (5.9–9.4)	7.2 (6.0–9.5)	7.3 (6.0–9.4)	7.4 (6.1–9.2)	7.3 (6.0–9.6)	7.7 (5.1–11.7)	7.4 (6.0–9.9)
By Estimated CD4 count at ART start										
<50 cells/µl	20.4 (11.8–31.1)	19.3 (11.4–30.7)	20.4 (11.9–31.0)	19.2 (10.6–30.3)	17.7 (10.2–29.0)	19.0 (10.3–30.1)	21.5 (11.8–34.7)	18.6 (9.7–30.8)	23.6 (13.0–34.7)	19.8 (11.3–30.9)
50– 99 cells/µl	17.9 (11.0–29.3)	18.1 (10.0–29.2)	18.9 (11.2–29.6)	18.3 (9.9–29.6)	15.6 (9.2–27.5)	16.4 (9.5–27.9)	18.9 (10.6–31.5)	17.1 (9.2–29.2)	22.2 (12.6–32.7)	18.2 (10.4–29.5)
100–199 cells/µl	13.9 (9.0–26.1)	13.4 (8.3–24.9)	14.0 (8.6–25.1)	13.4 (8.1–24.5)	12.5 (7.8–23.4)	13.0 (8.1–24.3)	13.6 (8.4–25.5)	13.1 (8.1–24.9)	14.8 (9.7–26.2)	13.6 (8.4–24.9)
200– 349 cells/µl	10.7 (7.4–15.5)	9.9 (7.1–14.6)	10.1 (7.4–14.9)	9.6 (6.9–14.9)	9.8 (7.0–14.9)	9.6 (7.1–14.4)	9.9 (7.2–14.7)	9.6 (7.0–14.6)	11.5 (7.2–15.7)	10.0 (7.1–15.0)

Table 16 Hazard ratios associated with CD4 count recovery to 350 cells/ μ l among those with CD4 counts <350 cells/ μ l at ART initiation and were virally suppressed by the end of follow up

Variable	Category	Multivariable HR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.07 (1.04–1.10)	
	35–49	0.80 (0.79–0.80)	
	50+	0.67 (0.66–0.67)	
Gender	Females	1	<0.001
	Males	0.75 (0.74–0.75)	
	Unknown	0.89 (0.87–0.91)	
Year	2010	1	<0.001
	2011	1.11 (1.10–1.11)	
	2012	1.25 (1.24–1.26)	
	2013	1.40 (1.39–1.42)	
	2014	2.33 (2.30–2.37)	
CD4 category at ART initiation (cells/ μ l)	200–349	1	<0.001
	100–199	0.51 (0.51–0.52)	
	50–99	0.29 (0.29–0.30)	
	<50	0.24 (0.24–0.24)	
Province	KwaZulu–Natal	1	<0.001
	Eastern Cape	0.88 (0.87–0.89)	
	Free State	0.95 (0.94–0.96)	
	Gauteng	0.94 (0.93–0.95)	
	Limpopo	1.00 (0.99–1.02)	
	Mpumalanga	1.01 (1.00–1.02)	
	Northern Cape	0.96 (0.94–0.98)	
	North West	1.00 (0.98–1.01)	
	Western Cape	0.89 (0.88–0.90)	

Table 17 CD4 recovery to 500 cells/μl among those with CD4 counts <500 cells/μl and were virally suppressed by end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
Overall CD4 count recovery to 500cells/μl (n/N, %)	35,073/82,862 (42.3)	21,500/51,980 (41.4)	74,193/185,034 (40.1)	133,172/273 106 (48.8)	21,090/49,575 (42.5)	32,588/71,634 (45.5)	5,357/12,475 (42.9)	20,655/47,326 (43.6)	30,712/69,493 (44.2)	374,874/ 844,699 (44.4)
By Gender										
Females	28,200/59,064 (47.7)	16,879/36,000 (46.9)	56,725/122,418 (46.3)	100,597/182 974 (55.0)	17,430/36,947 (47.2)	25,635/49,614 (51.7)	3,938/8,059 (48.9)	16,123/32,479 (49.6)	22,960/45,004 (51.0)	288,880/ 573 337 (50.4)
Males	6,235/22,226 (28.0)	4,395/15,390 (28.6)	16,783/60,729 (27.6)	29,767/84,094 (35.4)	3,501/12,258 (28.6)	6,543/21,095 (31.0)	1,337/4,194 (31.9)	4,362/14,426 (30.2)	7,382/23,593 (31.3)	80,434/258,419 (31.1)
By age										
Age 15- 24	414/727 (56.9)	280/522 (53.6)	519/979 (53.0)	1,924/3,164 (60.8)	216/366 (59.0)	425/732 (58.1)	39/76 (51.3)	210/368 (57.1)	193/325 (59.4)	4,225/7,265 (58.2)
Age 25- 34	7,434/13,523 (55.0)	3,871/6,817 (56.8)	12,099/21,236 (57.0)	28,572/45,963 (62.2)	3,314/5,495 (60.3)	6,574/10,878 (60.4)	899/1 574 (57.1)	3,446/5,860 (58.8)	6,157/11,136 (55.3)	72,430/122,602 (59.1)
Age 35-49	18,155/42,802 (42.4)	10,973/26,066 (42.1)	41,852/102,363 (40.9)	69,955/146,628 (47.7)	11,022/24,898 (44.3)	16,574/36,451 (45.5)	2,868/6 551 (43.8)	10,603/23,694 (44.8)	17,937/40,752 (44.0)	200,227/ 450,859 (44.4)
Age ≥50	9,070/25,810 (35.1)	6,376/18,575 (34.3)	19,723/60,456 (32.6)	32,721/77,351 (42.3)	6,538/18,816 (34.5)	9,015/23, 573 (38.2)	1,551/4,274 (36.3)	6,396/17,404 (36.8)	6,425/17,280 (37.2)	97,992/263,973 (37.1)
By Year of baseline CD4 count										
2010	7,979/15,752 (50.7)	4,731/10,211 (46.3)	18,266/38,398 (47.6)	35,107/57,448 (61.1)	5,327/10,758 (49.5)	6,987/12,844 (54.4)	1,275/2,621 (48.7)	5,426/10,814 (50.2)	8,649/16,324 (53.0)	93,888/175,441 (53.5)
2011	10,003/21,737 (46.0)	6,545/14, 804 (44.2)	22,335/50,141 (44.5)	34,629/65,253 (53.1)	6,544/13,909 (47.0)	10,367/20,233 (51.2)	1,522/3,257 (46.7)	6,245/12,822 (48.7)	9,194/18,652 (49.3)	107,679/ 221,479 (48.6)
2012	9,021/20,664 (43.7)	5,449/12,707 (42.9)	18,852/46,085 (40.9)	34,237/68,264 (50.1)	4,806/11,458 (41.9)	8,572/18,378 (46.6)	1,358/3,066 (44.3)	4,983/11,247 (44.3)	7,477/16,814 (44.5)	94,787/208,759 (45.4)
2013	6,086/17,524 (14.7)	3,824/10,796 (35.4)	11,221/36,440 (30.8)	21,531/56,008 (38.4)	3,375/9,621 (35.8)	4,791/13,751 (34.8)	898/2,472 (36.3)	2,896/8,606 (33.7)	4,460/13,326 (33.5)	59,131/168,674 (35.1)
2014	1,984/7,185 (27.6)	951/3 462 (27.5)	3,519/13,970 (25.2)	7,668/26,133 (29.3)	1,038/3,829 (27.1)	1,871/6,428 (29.1)	304/1,059 (28.7)	1,105/3,837 (28.8)	932/4 377 (21.3)	19,389/70,346 (27.6)

Table 17 CD4 recovery to 500 cells/µl among those with CD4 counts <500 cells/µl and were virally suppressed by end of follow up by province *(Continued)*

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	South Africa
By Estimated CD4 count at ART start										
<50 cells/µl	1,315/7,494 (17.6)	878/5,367 (16.4)	4,119/23,983 (17.2)	5,693/24,145 (23.6)	1,262/6,260 (20.2)	1,722/7,635 (22.6)	161/1,106 (14.6)	889/4,635 (19.2)	1,022/6,363 (16.1)	17,074/87,066 (19.6)
51- 99 cells/µl	1 995/9,818 (20.3)	1,222/6,375 (19.2)	4,835/24,385 (19.8)	7,576/29,235 (25.9)	1,538/6,514 (23.6)	2,080/8,418 (24.7)	296/1 443 (20.5)	1,264/5,777 (21.9)	1,559/7,894 (19.8)	22,391/99,985 (22.4)
100- 199 cells/µl	8,003/24,373 (32.8)	4,923/15,634 (31.5)	18,517/56,116 (33.0)	28,666/74,862 (38.3)	5,197/14,447 (36.0)	7,794/20,778 (37.5)	1,198/3,659 (32.7)	4,858/13,912 (34.9)	6,596/19,733 (33.4)	85,829/243,786 (35.2)
200- 349 cells/µl	17,945/32,454 (55.3)	11,049/19,665 (56.2)	37,140/66,226 (56.1)	63,852/107,632 (59.3)	9,503/16,996 (55.9)	15,973/27,385 (58.3)	2,728/4,870 (56.0)	10,158/17,859 (56.9)	16,710/28,369 (58.9)	185,276/321,905 (57.7)
350- 499 cells/µl	5,815/8,723 (66.7)	3,428/4,939 (69.4)	9,582/14,324 (66.9)	27,385/37,232 (73.6)	3,590/5,358 (67.0)	5,019/7,418 (67.7)	974/1,397 (69.7)	3,486/5,143 (67.8)	4,825/7,134 (67.6)	64,304/91,957 (69.9)

Table 18 Risk ratios associated with absolute CD4 count recovery to 500 cells/ μ l among those with CD4 counts < 500 cells/ μ l and were virally suppressed by the end of follow up

Variable	Category	Multivariable RR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.06 (1.03–1.10)	
	35–49	0.85 (0.84–0.85)	
	50+	0.73 (0.73–0.74)	
Gender	Females	1	<0.001
	Males	0.74 (0.73–0.75)	
	Unknown	0.90 (0.88–0.93)	
Year	2010	1	<0.001
	2011	0.99 (0.98–1.00)	
	2012	1.05 (1.03–1.06)	
	2013	1.04 (1.02–1.05)	
	2014	1.03 (1.00–1.05)	
CD4 category at ART initiation (cells/ μ l)	350–499	1	<0.001
	200–349	0.81 (0.80–0.82)	
	100–199	0.48 (0.48–0.49)	
	50– 99	0.32 (0.32–0.33)	
	<50	0.29 (0.28 –0.29)	
Duration in follow up	<12	1	<0.001
	12–23	1.55 (1.53–1.58)	
	24–35	2.11 (2.08–2.14)	
	36–47	2.57 (2.52–2.61)	
	>=48	2.96 (2.91–3.02)	
Province	KwaZulu–Natal	1	<0.001
	Eastern Cape	0.92 (0.91–0.93)	
	Free State	0.95 (0.93–0.96)	
	Gauteng	0.94 (0.94–0.95)	
	Limpopo	0.99 (0.98–1.00)	
	Mpumalanga	1.00 (0.99–1.02)	
	Northern Cape	0.95 (0.92–0.97)	
	North West	0.97 (0.96–0.99)	
	Western Cape	0.90 (0.89–0.91)	

Table 19 Time to CD4 recovery to 500 cells/µl among those with CD4 counts <500 cells/µl and were virally suppression by end of follow up by province

Characteristic/ province	Eastern Cape	Free State	Gauteng	KwaZulu– Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	All
Overall time to CD4 recovery, (median, IQR)										
	17.1 (10.7–29.2)	16.9 (9.9–28.9)	17.8 (10.5–29.7)	17.2 (9.5–29.6)	15.6 (9.2–28.8)	16.1 (9.4–28.2)	17.2 (9.9–30.0)	17.2 (9.4–29.7)	19.3 (12.3–31.9)	17.3 (10.0–29.6)
By gender										
Females	16.6 (10.3–28.5)	16.4 (9.6–28.4)	17.0 (10.0–28.8)	16.5 (9.2–28.6)	15.1 (9.0–27.3)	15.5 (9.1–27.5)	16.4 (9.6–29.0)	16.8 (9.2–29.1)	18.5 (12.0–30.6)	16.6 (9.7–28.7)
Males	18.6 (11.4–31.2)	18.0 (10.4–30.2)	19.5 (11.5–31.4)	19.1 (10.5–31.9)	17.1 (9.8–29.7)	17.7 (10.2–30.1)	18.8 (10.4–31.9)	18.4 (9.8–31.3)	21.5 (12.8–34.4)	19.0 (10.9–31.6)
By age										
Age 15–24	13.8 (8.8–25.7)	13.5 (8.1–25.0)	14.5 (9.0–27.0)	13.8 (8.3–25.9)	12.7 (8.3–23.9)	13.8 (8.9–23.4)	13.6 (8.5–28.9)	12.0 (7.6–23.2)	14.7 (10.2–25.3)	13.8 (8.5–25.5)
Age 25–34	14.1 (8.9–25.7)	13.0 (8.3–24.2)	13.8 (8.5–25.3)	12.8 (8.0–24.0)	12.2 (7.9–23.6)	12.9 (8.0–24.5)	13.6 (8.6–24.9)	13.1 (8.0–25.0)	16.1 (10.9–25.6)	13.5 (8.4–24.9)
Age 35–49	17.4 (10.8–29.6)	17.0 (9.9–29.0)	17.8 (10.5–29.6)	17.8 (9.8–30.1)	15.6 (9.3–27.7)	16.4 (9.4–28.4)	17.4 (8.9–29.9)	17.1 (9.3–29.6)	20.0 (12.5–32.5)	17.6 (10.2–29.8)
Age ≥50	18.8 (11.5–30.7)	18.7 (10.8–30.7)	19.6 (11.5–31.4)	19.5 (10.6–32.3)	17.2 (9.9–29.7)	18.1 (10.3–30.1)	19.1 (10.6–32.2)	19.0 (10.3–31.7)	21.1 (12.6–33.5)	19.2 (11.0–31.5)
By year of ART start										
2010	32.7 (16.1–46.3)	31.1 (14.1–45.3)	32.6 (16.7–46.0)	30.5 (12.2–46.0)	27.9 (11.9–43.8)	29.7 (12.8–44.9)	31.8 (14.7–46.1)	30.6 (14.1–45.6)	34.1 (15.6–47.9)	31.3 (14.1–45.9)
2011	26.3 (13.8–36.8)	25.0 (12.4–35.4)	25.6 (13.5–36.2)	27.2 (13.5–36.9)	23.5 (11.0–34.7)	25.0 (11.8–36.3)	26.9 (13.6–37.1)	24.8 (11.8–35.8)	27.3 (14.0–37.3)	26.0 (13.1–36.5)
2012	19.5 (12.0–26.0)	18.2 (10.8–25.5)	19.3 (11.6–26.0)	20.2 (11.3–26.5)	17.7 (10.5–25.2)	18.5 (11.0–25.7)	19.3 (11.7–26.4)	18.8 (10.1–25.7)	21.5 (13.8–26.9)	19.5 (11.5–26.1)
2013	12.8 (9.6–15.8)	12.3 (8.6–15.3)	12.9 (9.4–15.9)	12.4 (8.7–16.5)	12.0 (8.5–15.1)	12.4 (8.5–15.7)	12.2 (8.4–15.5)	11.8 (8.1–15.9)	13.7 (11.8–16.8)	12.7 (9.1–16.0)
2014	8.0 (6.4–11.0)	7.5 (6.1–10.4)	7.9 (6.4–10.5)	7.5 (6.1–10.0)	7.4 (6.2–10.0)	7.6 (6.3–9.8)	7.7 (6.2–9.8)	7.6 (6.1–9.9)	8.5 (5.5–11.7)	7.7 (6.2–10.3)
By Estimated CD4 count at ART start										
<50 cells/µl	24.3 (12.7–36.5)	22.8 (12.3–35.3)	24.1 (12.9–35.8)	23.4 (12.2–35.6)	21.9 (11.7–35.2)	23.8 (12.0–35.9)	25.5 (12.7–38.4)	22.7 (11.2–36.2)	25.6 (13.9–38.0)	23.8 (12.5–36.0)
50–99 cells/µl	23.9 (12.7–36.4)	22.5 (12.1–34.9)	23.8 (13.0–35.6)	23.7 (12.3–35.8)	21.3 (11.6–34.7)	22.7 (11.7–35.3)	24.2 (12.7–36.6)	23.2 (11.7–36.4)	26.0 (14.1–38.5)	23.8 (12.5–36.0)
100–199 cells/µl	22.1 (12.3–34.1)	21.3 (11.7–33.3)	22.0 (12.4–33.5)	21.6 (11.6–33.9)	18.8 (10.6–30.9)	20.7 (11.3–32.6)	23.1 (11.8–35.6)	21.7 (11.3–34.4)	24.9 (13.6–37.1)	21.8 (11.9–33.9)
200–349 cells/µl	14.4 (9.5–25.3)	13.8 (8.7–24.7)	14.2 (9.0–24.8)	14.3 (8.7–25.6)	13.1 (8.4–24.1)	13.4 (8.5–24.4)	14.1 (8.9–25.6)	13.8 (8.5–25.2)	16.1 (11.5–27.3)	14.3 (8.9–25.3)
350–499 cells/µl	11.8 (8.0–19.8)	11.5 (8.0–18.7)	11.4 (7.6–19.0)	11.5 (7.6–21.1)	11.3 (7.5–19.9)	11.3 (7.5–19.2)	11.5 (7.6–18.7)	11.5 (7.8–20.7)	13.6 (9.4–19.4)	11.6 (7.8–20.0)

Table 20 Hazard ratios associated with CD4 count recovery to 500 cells/μl among individuals with CD4 counts < 500 cells/μl at ART initiation and were virally suppressed by the end of follow up

Variable	Category	Multivariable HR (95% CI)	LR p-value
Age (years)	25–34	1	<0.001
	15–24	1.08 (1.05–1.12)	
	35–49	0.74 (0.73–0.74)	
	50+	0.61 (0.60–0.61)	
Gender	Females	1	<0.001
	Males	0.67 (0.66–0.67)	
	Unknown	0.88 (0.85–0.90)	
Year	2010	1	<0.001
	2011	1.17 (1.16–1.18)	
	2012	1.51 (1.49–1.52)	
	2013	1.94 (1.92–1.97)	
	2014	3.25 (3.21–3.32)	
CD4 category at ART initiation (cells/μl)	350–499	1	<0.001
	200–349	0.70 (0.69–0.71)	
	100–199	0.33 (0.33–0.33)	
	50–99	0.20 (0.20–0.20)	
	<50	0.18 (0.17–0.18)	
Province	KwaZulu–Natal	1	<0.001
	Eastern Cape	0.87 (0.86–0.89)	
	Free State	0.95 (0.94–0.96)	
	Gauteng	0.95 (0.94–0.95)	
	Limpopo	1.04 (1.02–1.05)	
	Mpumalanga	1.04 (1.03–1.05)	
	Northern Cape	0.94 (0.92–0.97)	
	North West	0.98 (0.96–0.99)	
	Western Cape	0.84 (0.83–0.85)	

Table 21 The extent of CD4 count recovery by gender, age, viral suppression and CD4 count at ART initiation during the first 12 months of follow up

Variable	Category	Coefficient (cells/μl/day) (95% CI)	Estimated gain over 12 months (cells/μl)
Overall		0.422 (0.421–0.423)	154
Male	15–24	0.477 (0.452–0.501)	174
	25–34	0.427 (0.416–0.437)	156
	35–49	0.373 (0.370–0.376)	136
	>=50	0.364 (0.360–0.367)	133
	All males	0.374 (0.372–0.376)	137
Females	15– 24	0.492 (0.472–0.510)	180
	25– 34	0.490 (0.487–0.493)	179
	35– 49	0.445 (0.443–0.447)	163
	>=50	0.400 (0.397–0.404)	146
	All females	0.442 (0.441–0.444)	162
CD4 count at ART initiation	<50	0.489 (0.486–0.491)	179
	50–99	0.489 (0.489–0.492)	179
	100–99	0.504 (0.501–0.506)	184
	200–349	0.505 (0.503–0.507)	184
	350–499	0.235 (0.231–0.239)	86
	>=500	0.124 (0.132–0.116)	0
Viral suppression in follow up	Yes	0.456 (0.464–0.467)	167
	No	0.112 (0.109–0.116)	41

Appendix B Figures

Figure 1 Illustration of cohort set up

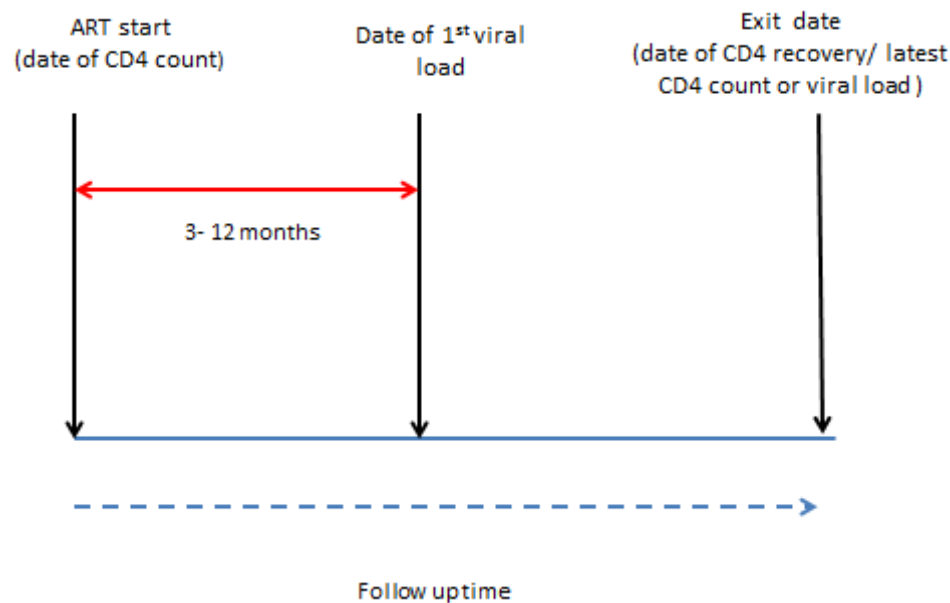


Figure 2 Study Flow

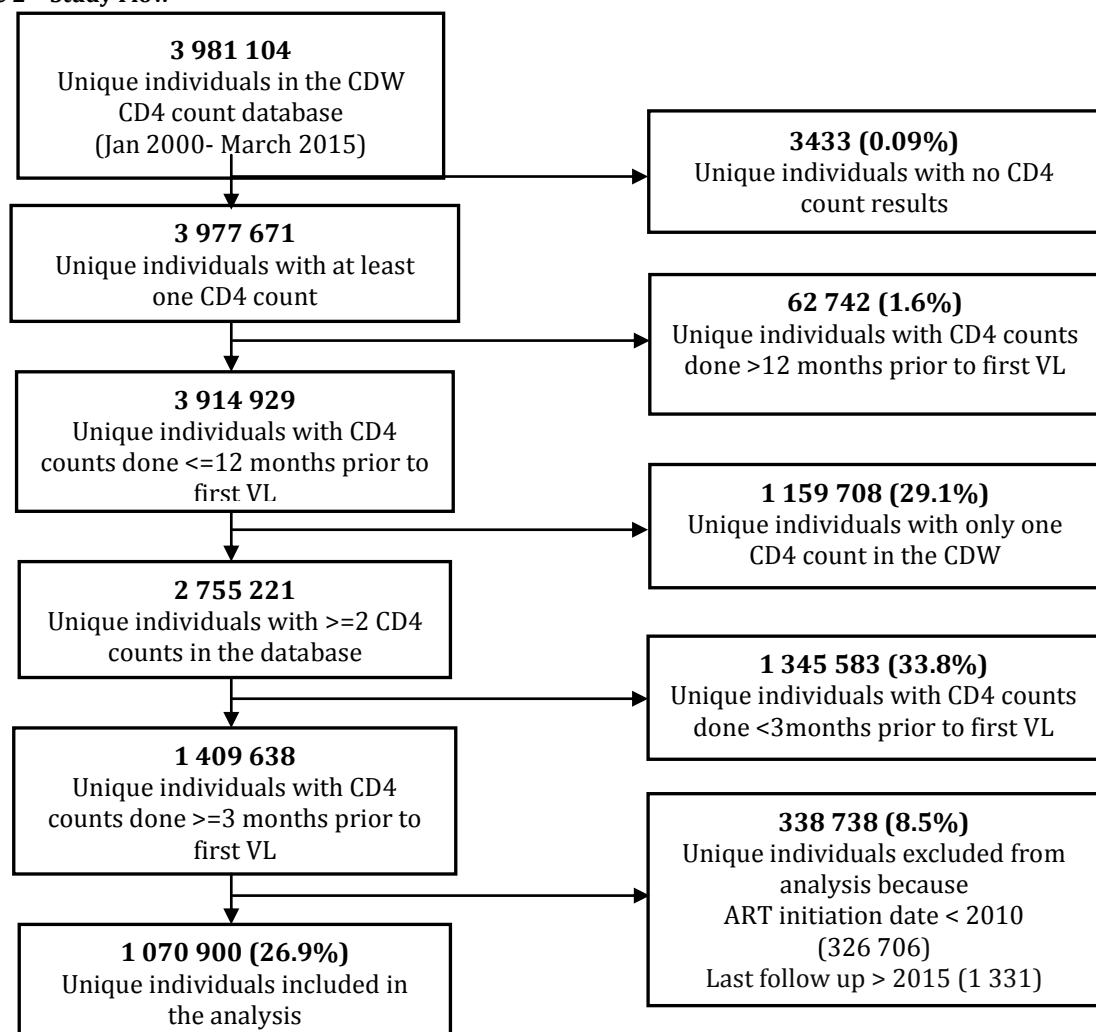
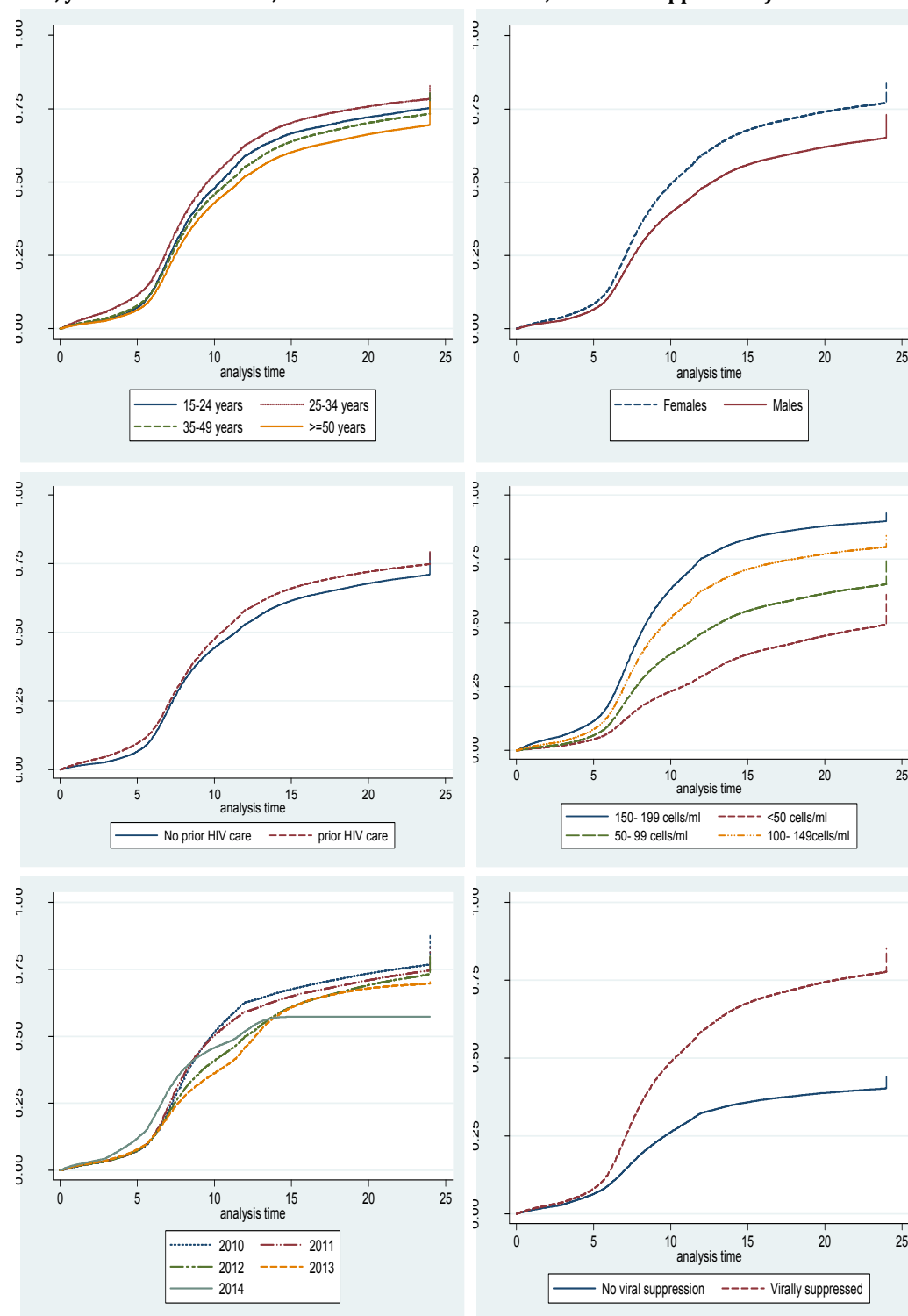
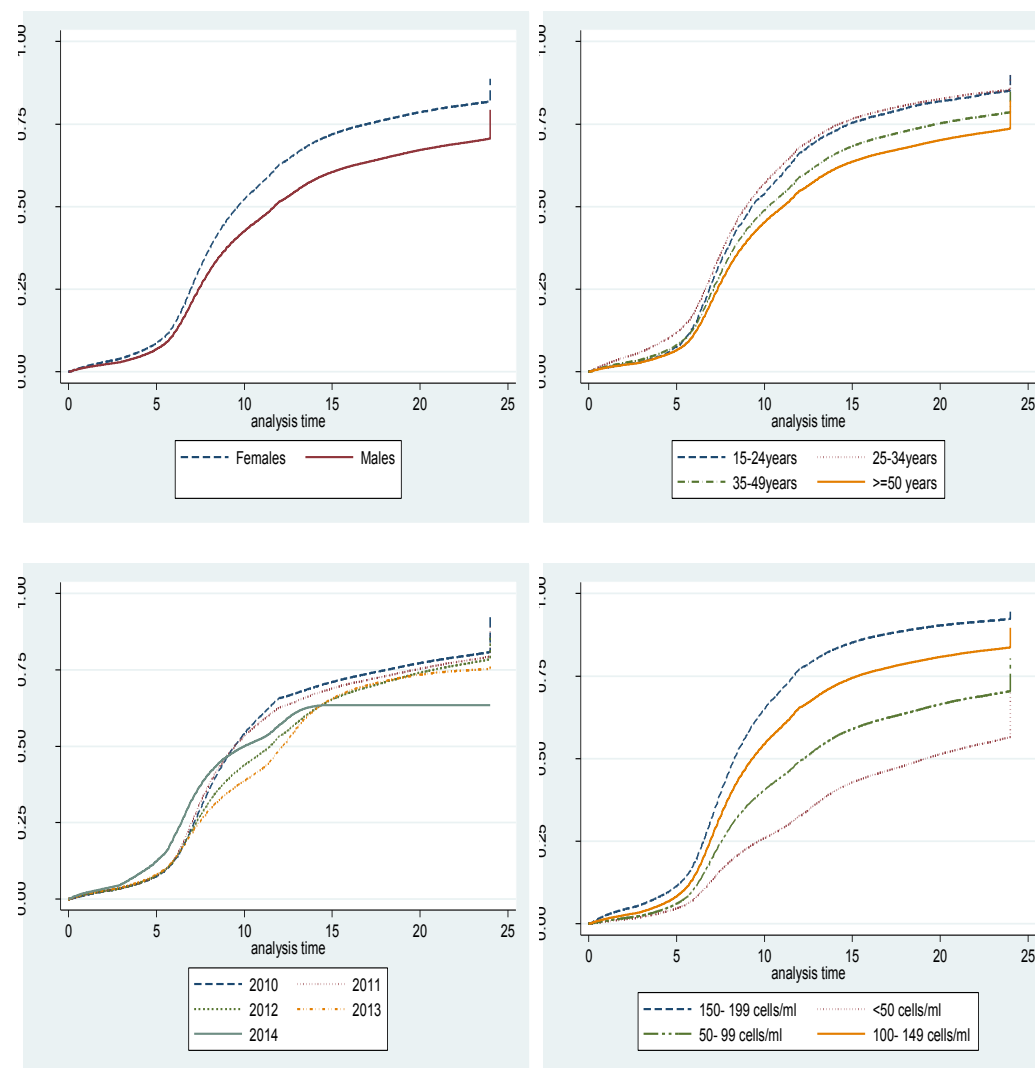


Figure 3 Recovery beyond 200 cells/ μ l in the first 24 months of follow up by gender, age, prior HIV care, year of ART initiation, CD4 count at ART initiation, and viral suppression)



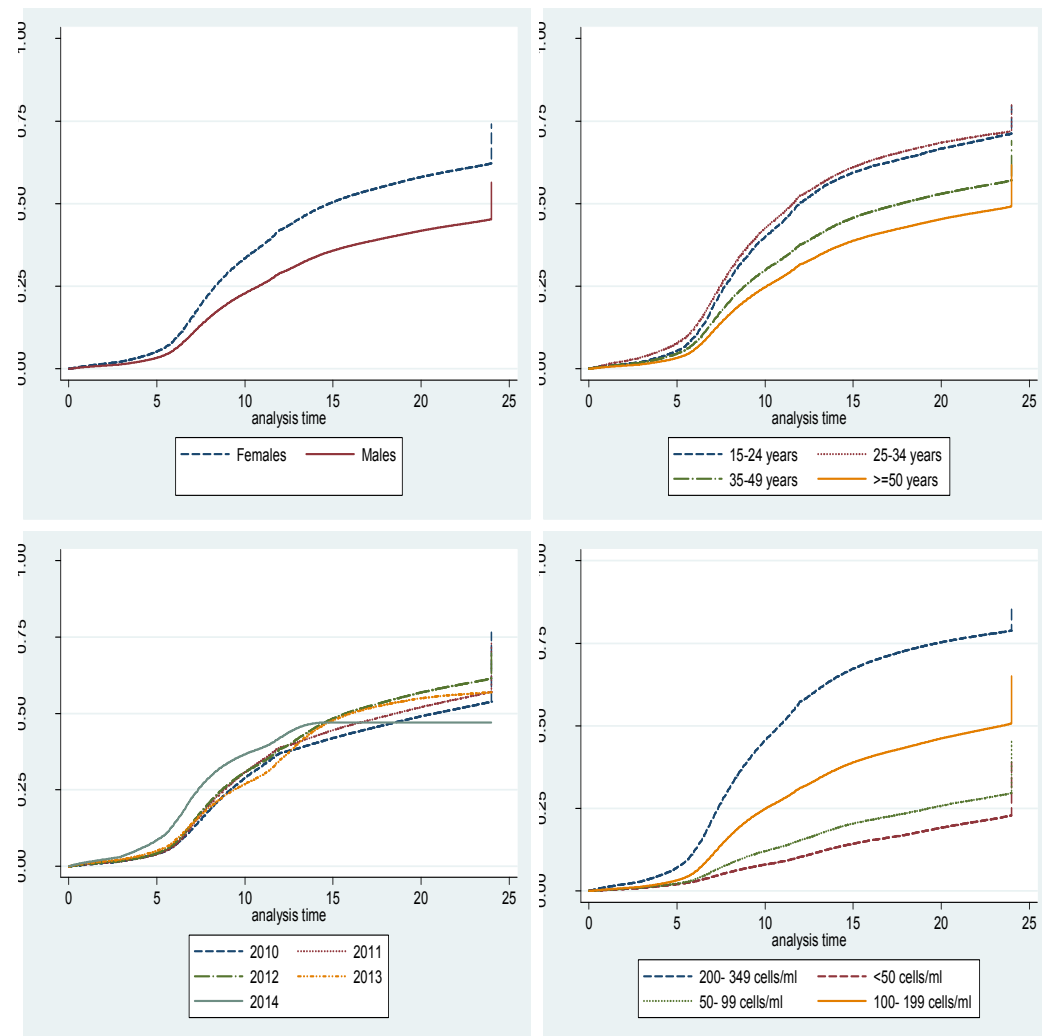
Note: Y-axis = the proportion with CD4 recovery.

Figure 4 Recovery beyond 200 cells/ μ l in the first 24 months of follow up among the virally suppressed by gender, age, year of ART initiation, and CD4 count at ART initiation



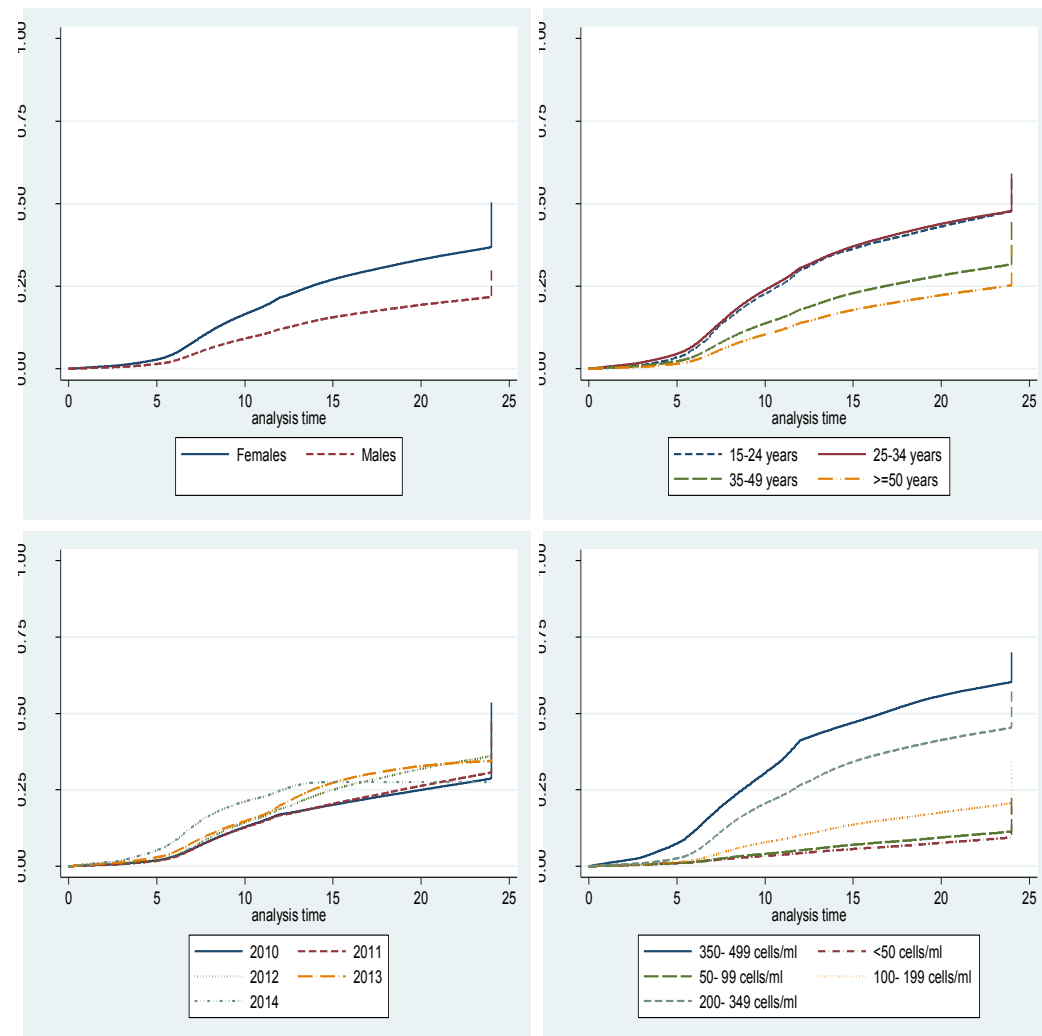
Note: Y-axis = the proportion with CD4 recovery.

Figure 5 Recovery beyond 350 cells/ μ l by gender, age, year of ART initiation, and CD4 count at ART initiation (showing first 24 months of follow up)



Note: Y-axis = the proportion with CD4 recovery.

Figure 6 Recovery beyond 500 cells/ μ l by gender, age, year of ART initiation, and CD4 count at ART initiation (showing first 24 months of follow up)



Note: Y-axis = the proportion with CD4 recovery

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