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CD4 count at ART initiation in the UTT era: an interrupted time series analysis

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1. Introduction

- Higher CD4+ T-cell counts at antiretroviral therapy (ART) initiation are associated with lower morbidity and mortality [1,2]
- South Africa has the largest HIV programme in the world, with ~7.7 million people living with HIV (PLHIV)
- In January 2015, South Africa expanded CD4 eligibility criteria to include lifelong ART for pregnant or breastfeeding women (Option B+) and <500 cells/μL for all other adults
- In September 2016, South Africa removed all CD4 eligibility criteria for ART (Universal Test and Treat [UTT])
- Population-level CD4 at ART initiation can collectively estimate HIV testing, linkage to care and ART coverage in HIV programmes, but data are lacking in the UTT era from sub-Saharan Africa
- ***We hypothesised that mean CD4 at ART initiation would increase due to UTT, among men and women attending public sector primary care clinics in rural South Africa***

2. Methods

This longitudinal study was conducted in the Hlabisa sub-district of northern KwaZulu-Natal, at 17 nurse-led primary care facilities from July 2014 to March 2019. CD4 and HIV viral load monitoring are routinely available at facilities. Ethical approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee and the University of New South Wales Human Research Ethics Committee.

- We included women and men aged ≥16 years initiating ART between 01 July 2014 and 31 March 2019
- Data were sourced from the national routine ART monitoring and evaluation database, TIER.Net
- **CD4 at ART initiation** was defined as the nearest CD4 count to the ART initiation date, within a window of 6 months prior to ART initiation and up to 3 months after ART initiation
- **The main exposure of interest was** calendar time, categorized by CD4 eligibility expansions:
  - (i) Prior to 01 January 2015 (pre-Option B+ era); (ii) 01 January 2015 to 31 August 2016 (Option B+ era); (iii) 01 September 2016 to 31 March 2019 (UTT)
- **Statistical analyses**
- Time trends in:
  - proportion of individuals without a pretherapy CD4, as those without a pretherapy CD4 may have undiagnosed severe immunosuppression
  - CD4 at ART initiation using smoothed polynomial regression by sex
- *Interrupted time series analysis (segmented linear regression)* to measure the impact of UTT on mean CD4 at ART initiation with the following covariates:
  - Continuous time variable
  - Binary variable for each policy change ("level" change)
  - Time-by-policy interaction term (trend change) immediately following each policy and 12 months after each policy change
  - Adjustments for sex, age, and clinic

3. Participant characteristics

A total of 20,599 individuals aged ≥16 years were analysed, 15,265 of whom had a CD4 available within the specified window (**Table 1**).

Table 1. *Number of women and men initiating ART by study period.*

	Women			Men		
	Pre-Option B+ *n*=1565	Option B+ *n*=5300	UTT *n*=7433	Pre-Option B+ *n*=560	Option B+ *n*=2181	UTT *n*=3560
Age, median (IQR)	28 (23-34)	29 (24-36)	28 (23-36)	35 (29-42)	34 (29-41)	34 (29-41)
CD4 category, n (%)						
≤100 cells/μL	134 (8.6%)	407 (7.7%)	362 (4.9%)	139 (24.8%)	437 (20.0%)	456 (12.8%)
101-200 cells/μL	178 (11.4%)	544 (10.3%)	481 (6.5%)	133 (23.8%)	414 (19.0%)	461 (13.0%)
201-350 cells/μL	496 (31.7%)	1148 (21.7%)	1053 (14.2%)	203 (36.2%)	605 (27.7%)	628 (17.6%)
351-500 cells/μL	200 (12.8%)	1482 (28.0%)	1042 (14.0%)	42 (7.5%)	480 (22.0%)	447 (12.6%)
>500 cells/μL	214 (13.7%)	664 (12.5%)	1819 (24.5%)	15 (2.7%)	95 (4.4%)	486 (13.6%)
No CD4 within window	343 (21.9%)	1055 (19.9%)	2676 (36.0%)	28 (5.0%)	150 (6.9%)	1082 (30.4%)

- **UTT led to an immediate and significant boost in mean CD4 at ART initiation among women and men.**
- The initial rise may be due to clearing a backlog of recently eligible patients presenting for care before declining to the population 'steady state'
- Persistent late presentations to care (particularly among men) limit the long-term impact of UTT

4. Impact of UTT on CD4 at ART

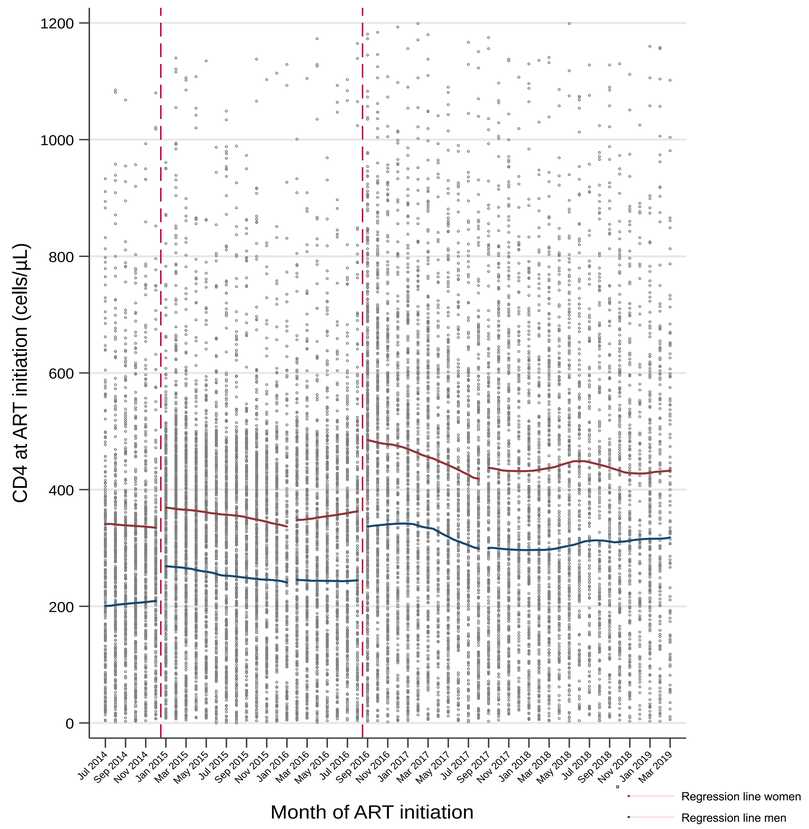


Figure 2. *CD4 at ART initiation among women and men. Dashed vertical lines depict policy change: January 2015, CD4 eligibility cut-off <500 cells/μL for adults or Option B+ for pregnant/breastfeeding women (Option B+ era); September 2016, Universal Test & Treat (UTT)*

4 contd. Impact of UTT on CD4 at ART

- **UTT led to an increase in mean CD4 at ART initiation of 123 cells** (95% CI 103 to 144 cells/μL, p<0.001).
- Compared with the pre-UTT trend, there was a downward monthly trend in mean CD4 after UTT of 9 cells/μL (95% CI -12 to -6 cells/μL, p<0.001). This stabilised after 12 months.
- **Mean CD4 at ART initiation among men was 116 cells/μL lower than women** (95% CI -124 to -108, p<0.001)

5. Proportion without pretherapy CD4

There was an increasing trend in the proportion of individuals without a pretherapy CD4 at ART initiation particularly after UTT (**Figure 3)**. However, this did not vary by clinic size or sex (data not shown).

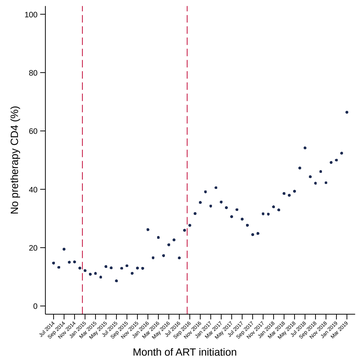


Figure 3. *Percentage individuals without a pretherapy CD4 recorded. Dashed vertical lines depict policy change.*

Acknowledgements

The authors wish to thank all study participants, South African National Department of Health partners, and the Africa Health Research Institute (AHRI) Research Data Management team. HMY is supported by an Australian Government Research Training Programme Scholarship, University of New South Wales, Sydney, Australia. The Kirby Institute is funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales. AHRI receives core funding from the UK Wellcome Trust and Howard Hughes Medical Institute.

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