24-Month Outcomes on Second-Line Antiretroviral Therapy in South Africa: a Target Trial Emulation

669

Jennifer A. Brown[1,2,*], Lara Lewis[1], Yukteshwar Sookrajh[3], Lungile Hobe[4], Thulani Ngwenya[5], Johan van der Molen[1], Kwabena Asare[1,6], Kwena Tlhaku[1,7], Mlungisi Khanyile[1], Thokozani Khubone[3], Christian Bottomley[6], Nigel Garrett[1,7,8], Jienchi Dorward[1,2]

[1] Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa; [2] University of Oxford, Oxford, United Kingdom; [3] eThekwini Municipality Health Unit, Durban, South Africa; [4] Mseleni Hospital, uMkhanyakude District, KwaZulu-Natal, South Africa; [5] Bethesda Hospital, uMkhanyakude District, KwaZulu-Natal, South Africa; [6] London School of Hygiene and Tropical Medicine, London, United Kingdom; [7] University of KwaZulu-Natal, Durban, South Africa; [8] Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; * presenting

BACKGROUND

- Aligning with the WHO, South Africa has replaced LPV/r with DTG in second-line ART after treatment failure with TDF/XTC/EFV
- Initial guidance had special considerations for DTG use in women
- **Evidence gap: large-scale routine care data reporting long-term outcomes are scarce**

METHODS

- **Design:**
  - Uptake cohort to assess switches by gender over time
  - Outcome cohort and target trial emulation to assess treatment outcomes by regimen
- **Data:** routine de-identified data from 108 public healthcare facilities in KwaZulu-Natal, South Africa
- **Inclusion criteria:**
  - Adults with 2 consecutive viral loads (VLs) ≥1000 c/mL with TDF/XTC/EFV
  - Switched to AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG
  - Switch between Dec 2019 and Dec 2023 (uptake cohort) or Jul 2021 (outcome cohort)
- **Target trial emulation:**
  - Co-primary endpoint: 24-month death or LTFU:
    - Intention-to-treat (ITT): censoring at transfer-out or 24 months; pooled logistic regression with inverse probability of treatment weighting (IPTW)
    - Per-protocol (PP): censoring at transfer-out or regimen change; pooled logistic regression with IPTW and inverse probability of censoring weighting (IPCW)
  - Co-primary endpoint: 24-month VL >50 c/mL:
    - ITT: logistic regression with IPTW among people retained in care with a 24-month VL
    - PP: logistic regression with IPTW, IPCW (including censoring for death or LTFU), and weights for inverse probability of not having a 24-month VL
  - Confidence intervals obtained through bootstrapping

DTG-based second-line ART led to similar retention and less viraemia at 24 months than LPV/r-based ART in South Africa

RESULTS (I)

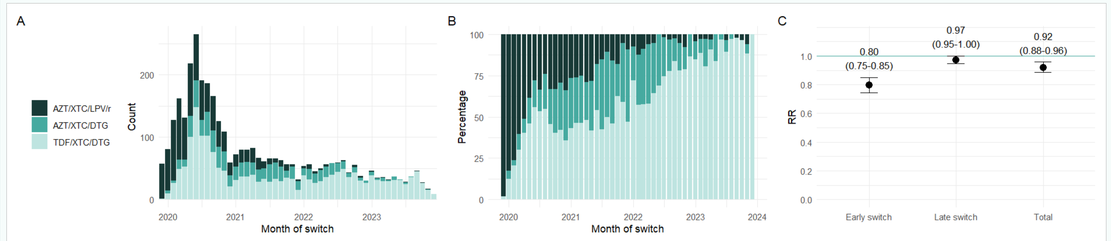


Figure: Switches to second-line ART over time. A, B. Switches to each second-line regimen by month as frequency (**A**) and percent (**B**). **C.** RR for women (vs men) to switch to DTG-based ART (early: Dec 2019 – May 2021; late: Jun 2021 – Dec 2023), with 95% CIs.

Table 1: Baseline characteristics in the outcome cohort and in the outcome cohort pseudo-population after IPTW. Results are shown as n (%) or median (IQR).

	Outcome cohort				Outcome cohort pseudo-population after IPTW			
	Overall	AZT/XTC/LPVr	AZT/XTC/DTG	TDF/XTC/DTG	Overall	AZT/XTC/LPVr	AZT/XTC/DTG	TDF/XTC/DTG
	N = 2,321	N = 915	N = 415	N = 991	N = 2,307	N = 911	N = 406	N = 991
Women	1,364 (59%)	614 (67%)	219 (53%)	531 (54%)	1,353 (59%)	536 (59%)	239 (59%)	579 (58%)
Age in years	36 (30, 43)	36 (30, 42)	36 (30, 43)	36 (30, 43)	36 (30, 43)	36 (30, 43)	35 (30, 42)	36 (30, 43)
Years on ART	3.2 (1.7, 6.0)	3.2 (1.6, 6.0)	3.4 (1.6, 6.7)	3.2 (1.8, 5.9)	3.3 (1.7, 6.0)	3.4 (1.7, 6.0)	3.5 (1.7, 6.5)	3.1 (1.7, 5.7)
Days ≥1000 c/mL	371 (236, 581)	363 (230, 579)	342 (224, 563)	391 (254, 595)	377 (238, 594)	378 (235, 604)	351 (225, 563)	380 (251, 597)

Table 2: Co-primary endpoints. Results are shown in % (95% CI).

	Standardised risk			Adjusted risk difference		
Outcome	AZT/XTC/LPV/r	AZT/XTC/DTG	TDF/XTC/DTG	AZT/XTC/DTG - AZT/XTC/LPV/r	TDF/XTC/DTG - AZT/XTC/LPV/r	TDF/XTC/DTG - AZT/XTC/DTG
ITT						
Death or LTFU	31% (27, 34)	30% (24, 35)	34% (31, 37)	-1% (-8, 5)	3% (-2, 8)	4% (-2, 11)
VL >50 c/mL	49% (45, 54)	39% (31, 46)	38% (33, 43)	-11% (-17, -4)	-11% (-17, -4)	0% (-10, 8)
PP						
Death or LTFU	31% (27, 34)	27% (21, 32)	34% (31, 37)	-4% (-11, 2)	3% (-2, 8)	7% (1, 13)
VL >50 c/mL	52% (46, 58)	38% (29, 46)	38% (32, 42)	-13% (-25, -4)	-14% (-23, -4)	-1% (-9, 9)

RESULTS (II)

Table 3: Crude outcomes. Results are shown as n (%).

Outcome	Overall	AZT/XTC/LPV/r	AZT/XTC/DTG	TDF/XTC/DTG
	N=2,321	N=915	N=415	N=991
24-month retention				
Death or LTFU	720 (31%)	283 (31%)	117 (28%)	320 (32%)
Death	29 (1%)	3 (0%)	9 (2%)	17 (2%)
LTFU	691 (30%)	280 (31%)	108 (26%)	303 (31%)
Transfer-out	126 (5%)	52 (6%)	22 (5%)	52 (5%)
In care, no VL	205 (9%)	59 (6%)	36 (9%)	110 (11%)
In care with VL	1,270 (55%)	521 (57%)	240 (58%)	509 (51%)
Regimen change	442 (19%)	200 (22%)	95 (23%)	147 (15%)
24-month VL	N=1,270	N=521	N=240	N=509
≤50 (c/mL)	739 (58%)	272 (52%)	146 (61%)	321 (63%)
51-999 (c/mL)	273 (21%)	107 (21%)	56 (23%)	110 (22%)
≥1000 (c/mL)	258 (20%)	142 (27%)	38 (16%)	78 (15%)

Limitations

- The concurrent transition from TDF/XTC/EFV to TDF/XTC/DTG in **first-line** ART may have disadvantaged the TDF/XTC/DTG group in this analysis, as people may have changed to TDF/XTC/DTG without adequate adherence support
- While target trial emulation aims to minimize bias, we cannot rule out residual unmeasured confounding

CONCLUSIONS

- Women were less likely than men to get DTG before June 2021
- 24-month death or LTFU was similar and viraemia was lower with DTG compared with LPV/r-based second-line ART
- Treatment outcomes were poor regardless of regimen
- **Implications: these findings support current recommendations for DTG-based second-line ART and highlight the need for better adherence support**

Further INFORMATION

Correspondence: jennifer.brown@caprisa.org

Preprint: https://doi.org/10.12688/verixiv.686.1

Abbreviations: AZT: zidovudine; CI: confidence interval; c/mL: copies per millilitre; DTG: dolutegravir; EFV: efavirenz; IPCW: inverse probability of censoring weighting; IPTW: inverse probability of treatment weighting; ITT: intention-to-treat; IQR: interquartile range; PP: per-protocol; RR: relative risk; TDF: tenofovir disoproxil fumarate; VL: viral load; XTC: lamivudine or emtricitabine.

Funding: This work was supported by funding from the **Gates Foundation** (INV-051067). The conclusions and opinions expressed in this work are those of the authors alone and shall not be attributed to the Foundation. JAB is funded by the **Swiss National Science Foundation** (221966, to JAB). JD is funded by the **National Institute for Health and Care Research** (NIHR, grant number CL-2022–13–005, to JD) for this research project. The views expressed in this publication are those of the authors and not necessarily those of the NIHR, the National Health Service, or the UK Department of Health and Social Care.