Advanced HIV disease and engagement in care among patients on antiretroviral therapy in South Africa: results from a multi-state model

Gabriela E. Patten[a], Jonathan Euvrard[a], Nanina Anderegg[b], Andrew Boulle[a], Kirsten D. Arendse[c], Erin von der Heyden[d], Nathan Ford[a] and Mary-Ann Davies[a]

Objective: Despite improved access to antiretroviral therapy (ART) for people with HIV (PWH), HIV continues to contribute considerably to morbidity and mortality. Increasingly, advanced HIV disease (AHD) is found among PWH who are ART-experienced.

Design: Using a multi-state model we examined associations between engagement with care and AHD on ART in South Africa.

Methods: Using data from IeDEA Southern Africa, we included PWH from South Africa, initiating ART from 2004 to 2017 aged more than 5 years with a $CD4^+$ cell count at ART start and at least one subsequent measure. We defined a gap as no visit for at least 18 months. Five states were defined: 'AHD on ART' ($CD4^+$ cell count <200 cells/μl), 'Clinically Stable on ART' ($CD4^+$ cell count ≥200 or if no $CD4^+$ cell count, viral load <1000 copies/ml), 'Early Gap' (commencing ≤18 months from ART start), 'Late Gap' (commencing >18 months from ART start) and 'Death'.

Results: Among 32 452 PWH, men and those aged 15–25 years were more likely to progress to unfavourable states. Later years of ART start were associated with a lower probability of transitioning from AHD to clinically stable, increasing the risk of death following AHD. In stratified analyses, those starting ART with AHD in later years were more likely to re-engage in care with AHD following a gap and to die following AHD on ART.

Conclusion: In more recent years, those with AHD on ART were more likely to die, and AHD at re-engagement in care increased. To further reduce HIV-related mortality, efforts to address the challenges facing these more vulnerable patients are needed.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

AIDS 2023, **37**:513–522

Introduction

Despite the successful scale-up in antiretroviral therapy (ART) programmes in the last decade, many patients continue to experience advanced HIV disease (AHD). A large proportion of people with HIV (PWH) continue to present to care with low $CD4^+$ cell counts, despite the implementation of the treat-all policy [1−3]. Reductions in HIV-related mortality have plateaued in more recent years [4], and HIV continues to contribute considerably to hospital admissions and mortality in high–burden settings [5].

[a]Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa, [b]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, [c]Médecins Sans Frontières, and [d]Western Cape Department of Health, Cape Town, South Africa.

Correspondence to Gabriela E. Patten, 4th Floor, Fairland House, 364B Victoria Road, Salt River, Cape Town 7925, South Africa.

E-mail: gem.patten@uct.ac.za

In South Africa, a growing proportion of adult HIV-related mortality is among ART-experienced PWH [6], and recent studies found that AHD is increasingly diagnosed among ART-experienced patients who are returning to care after treatment interruption, or are poorly adherent, or infected with a virus that is resistant to ART [5,7].

Few studies have examined longitudinal trends in patient engagement in care and AHD on ART as treatment programmes have expanded and matured in southern Africa. We aimed to estimate the transition probabilities to and from an AHD on ART state using a multi-state model and to describe associations with transitions.

Methods

Study population

We used routinely collected data contributed to the International epidemiology Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration from the Khayelitsha ART programme [8]. Khayelitsha is a peri-urban township in Cape Town, South Africa, with an estimated population of 500 000, and one of the highest HIV burdens with a prevalence among pregnant women of 34%. By 2017, approximately 40 000 patients were receiving ART from public sector clinics [9,10]. During the study period ART initiation guidelines were revised several times to expand from ART eligibility based on $CD4^+$ cell count and other co-morbidities, to all PWH becoming eligible for ART irrespective of $CD4^+$ cell count by 2016 [9,11−14]. Ethical approval to contribute anonymized, individual data to IeDEA-SA was obtained from the University of Cape Town.

Eligibility criteria

We included all patients initiating ART from 2004 to 2017 aged more than 5 years at ART initiation, with a $CD4^+$ cell count at ART initiation and at least one subsequent measure, ensuring at least 18 months between ART initiation and database closure (October 2018).

States of care/measures

We defined states of ART care from the time of each patient's first $CD4^+$ cell count after ART initiation. We defined a gap in care as having no recorded visit for at least 18 months, ensuring patients were truly out of care and without ART during that time. Early and late gaps were defined according to when they occurred during each patient's follow-up. We defined five states: 'AHD on ART' ($CD4^+$ cell count <200 cells/μl), 'Stable on ART' [$CD4^+$ cell count ≥200 cells/μl or if no $CD4^+$ cell count available in 12 month period, having a suppressed viral load (viral load <1000 copies/ml)], 'Early Gap' (gap commencing ≤18 months from ART initiation), 'Late Gap' (gap commencing >18 months from ART

initiation) and 'Death'. For periods with ongoing visits but no recorded $CD4^+$ cell count and no viral load for more than 12 months, time on ART was assigned to a censored state. Time on ART was also assigned to the censored state for periods with a recorded viral load of more than 1000 copies/ml, and no recorded $CD4^+$ cell count for more than 12 months. The model assumed periods spent in this censored state were in either of the two 'on ART' states.

The WHO defines AHD among adults and children more than 5 years as having a $CD4^+$ cell count less than 200 cells/μl or WHO Stage 3 or 4 disease [15]. Clinical staging data were not available throughout patient follow-up, so we used $CD4^+$ cell count only to indicate AHD. We defined the stable state using both $CD4^+$ cell count and viral load measures, since from 2013 $CD4^+$ monitoring on ART was recommended only at 1 year after ART initiation, with viral load monitoring recommended at months 6, 12 and annually thereafter [13].

Vital status was ascertained through linkage to the national population registry for patients with a recorded South African national identity number. Follow-up time was measured until death, transfer or database closure.

Model description

A parametric, continuous-time multi-state Markov model was used to identify associations with transitioning between states. We modelled 12 transitions among five states, with reverse transitions allowed except to early gap and from death (Fig. 1), with transitions to and from AHD on ART being the primary interest. The early gap state was the initial state for any patient with a gap commencing 18 months or less on ART. This ensured that transitions to a gap state from either of the 'on ART' states were to the late gap state, removing any potential time dependence. We estimated the 5-year probability of transition between states. We included the following fixed covariates to adjust for differences in transition by sex (male or female), year of ART initiation (2004−2006, 2007−2009, 2010−2012, 2013−2017), $CD4^+$ cell count at ART initiation (0−50, 51−200, 201−500 and >500 cells/μl) and age at ART initiation (5−≤15, >15−≤25, >25−≤40 and >40 years). We also included the time-updated covariates of any recorded prior tuberculosis (TB) diagnosis and any recorded pregnancy. For the pregnancy covariate, to adjust for any potential increase in the risk of a gap postpartum [16], we defined the postpartum period as between 9 months and 2 years after the first antenatal date.

Multi-state models assume time spent in each state follows an exponential distribution and transition probabilities are independent of previous states. Covariate effects are assumed constant over time and multiplicative, similar to Cox proportional hazard models. The model allowed for unobserved transitions between the AHD and Stable on
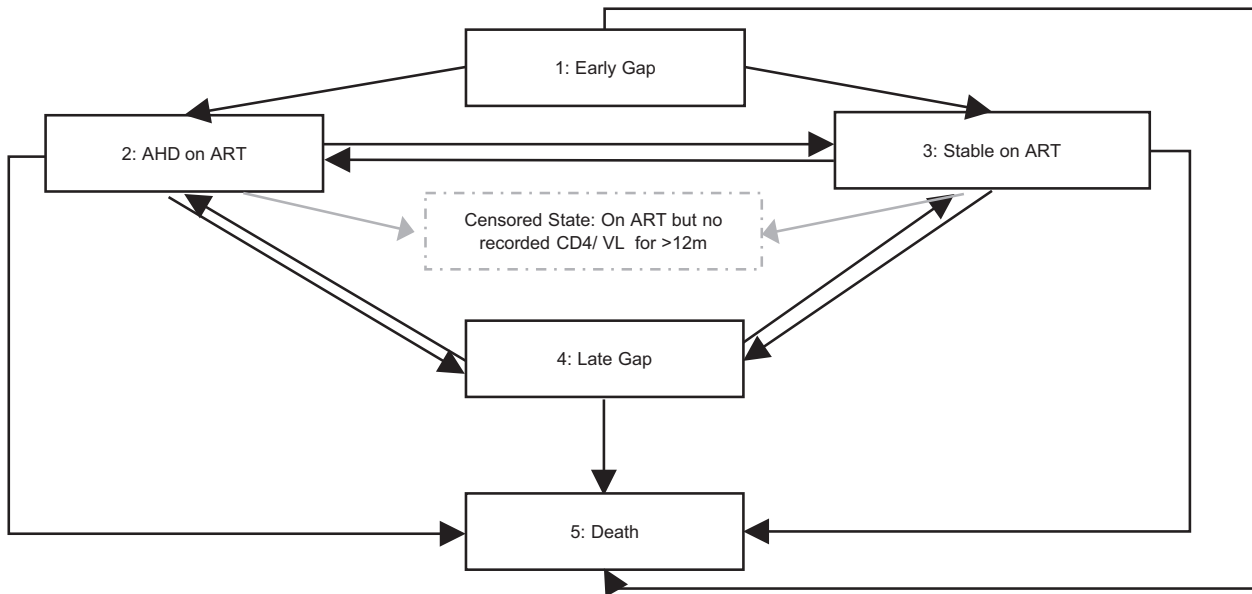
Fig. 1. Diagram of states and transitions of the multi-state model. Advanced HIV disease on antiretroviral therapy, Advanced HIV disease on antiretroviral therapy; ART, antiretroviral therapy; Censored state, In care with no recorded CD4+ cell count or viral load for more than 12 months, or no CD4+ cell count and viral load at least 1000 copies/ml; Early Gap, gap commencing 18 months or less from antiretroviral therapy start; Gap in care, no recorded visit for at least 18 months; Late Gap, gap commencing more than 18 months from antiretroviral therapy start; Stable on antiretroviral therapy, CD4+ cell count at least 200 cells/μl or if no CD4+ cell count available in 12 month period, having viral load (viral load <1000 copies/ml).

ART states, while the exact time of transitions to and from gap states and to death were specified.

Sensitivity analyses were performed to address potential biases. Since ART eligibility changed during the study period and was also based on clinical criteria, which we were unable to assess, we performed a stratified analysis by CD4+ cell count at ART initiation to explore potential differences in the effect of year of ART initiation on transition probabilities. Those who started ART in the most recent years have shorter follow-up, with late gaps occurring at a shorter duration on ART. We repeated our analysis using a restricted dataset which included each patient's first 5 years on ART only. To explore the effect of missing CD4+ cell count data during follow-up we modelled a best and worst-case scenario where all time in the censored state was assigned to stable or to AHD on ART, respectively. To understand the potential effects of differences in mortality ascertainment, we repeated our analysis using a restricted dataset, including only those with South African identity numbers.

We used Stata version 15 for descriptive statistics and the *msm* package in R for the multi-state model [17].

Results

Table S1, http://links.lww.com/QAD/C732 [Supplemental Digital Content (SDC) 1] summarizes characteristics of patients included and excluded from our study.

Our analysis included 32 452 patients, of whom 63% were linked to the national population registry. Among those excluded, 6718 (81%) initiated ART after 2013 and had no CD4+ cell count after ART initiation. At ART initiation median age was 32.9 years [interquartile range (IQR): 27.9−39.2], the median CD4+ cell count was 175 (IQR: 94−267), 70% were female of whom 26% experienced pregnancy during follow-up, and 33% had evidence of TB prior to or during follow-up (Table 1).

Over a median follow-up of 6.1 years (IQR 3.4−8.9), 2859 (9%) died, 28 226 (87%) experienced a stable state, 11 222 (35%) had AHD on ART, 4518 (14%) had an early gap and 6814 (21%) a late gap in care. Of those with AHD on ART, 3239 (29%) had two or more episodes of AHD on ART, separated by either a gap or a stable state. Most patients with AHD on ART had AHD as their starting state (6510, 58%), almost a third (3416, 30%) had AHD directly after being stable, 9% (997) after an early gap and 9% (1053) after a late gap.

Although the prevalence of AHD on ART declined between 2004 and 2017 (40−8%), the number of PWH with AHD on ART has remained stable since 2009 (Fig. 2). Prevalence of late gap has steadily increased, while the prevalence of stable state has remained steady since 2013.

Figure 3 summarizes the key results of our multi-state model by sex, age and year of ART start. We found men were more likely to transition to unfavourable states

Table 1. Characteristics of patients more than 5 years initiating antiretroviral therapy between 2004 and 2017 in Khayelitsha, South Africa (n = 32 452).

Characteristic		Total		AHD on ART		AHD after ART start		After early gap		After late gap		After stable	
Total		32 452		11 222		6510		997		1053		3416	
Sex	Males	9877	30%	4314	38%	2682	41%	611	61%	358	34%	1203	35%
	Females	22 575	70%	6908	62%	3828	59%	386	39%	695	66%	2213	65%
Age at ART start (years)	Median (IQR)	32.9 (27.9–39.2)		33.3 (28.3–39.4)		34.4 (29.4–40.4)		31.1 (26.5–37.1)		30.5 (26.6–35.5)		33.0 (27.9–39.3)	
	5–≤15	404	1%	97	1%	35	1%	8	1%	15	1%	41	1%
	>15–≤25	3618	11%	1133	10%	492	8%	155	16%	172	16%	391	11%
	>25–≤40	21 048	65%	7383	66%	4269	66%	679	68%	733	70%	2192	64%
	>40	7382	23%	2609	23%	1714	26%	155	16%	133	13%	792	23%
CD4+ cell count at ART start	Median (IQR)	175 (94–267)		97 (46–163)		69 (31–125)		147 (89–217)		129 (69–188)		112 (60–176)	
	0–50	4192	13%	3028	27%	2438	37%	125	13%	179	17%	685	20%
	51–200	14 793	46%	6561	58%	3621	56%	577	58%	652	62%	2171	64%
	201–500	12 035	37%	1576	14%	434	7%	288	29%	213	20%	538	16%
	>500	1432	4%	57	1%	17	0%	7	1%	9	1%	22	1%
Year of ART start	2004–2006	4513	14%	2296	20%	1339	21%	90	9%	240	23%	1103	32%
	2007–2009	6956	21%	3160	28%	1862	29%	201	20%	357	34%	1140	33%
	2010–2012	9949	31%	3248	29%	1745	27%	398	40%	365	35%	837	25%
	2013–2017	11 034	34%	2518	22%	1564	24%	308	31%	91	9%	336	10%
Postpartum[a] during follow-up		5804	18%	1683	15%	795	12%	190	19%	233	22%	612	18%
TB at ART start or after		10 657	33%	5434	48%	3315	51%	387	39%	491	47%	1761	52%
TB at ART start		7251	22%	3563	32%	2233	34%	268	27%	317	30%	1087	32%

AHD, advanced HIV disease; Early Gap: gap in care (no recorded visit for ≥18 months) starting 18 months or less of ART start; IQR, interquartile range; Late Gap, gap in care (no recorded visit for ≥18 months) starting more than 18 months since ART start; Stable, CD4+ cell count at least 200 cells/μl or if no CD4+ cell count available in 12 month period, having viral load (VL) (VL < 1000 copies/ml); TB, tuberculosis.

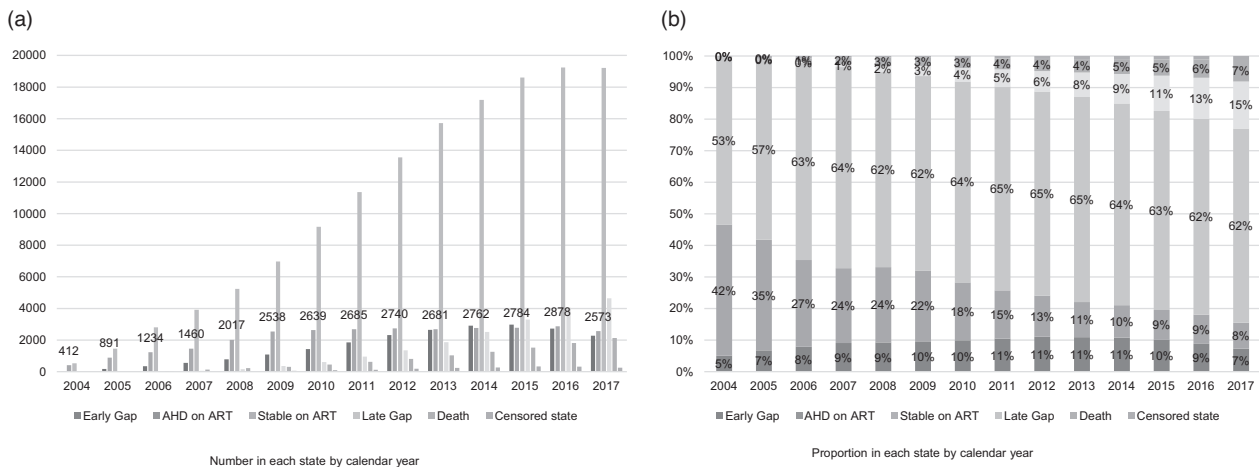[a]Postpartum period defined as between 9 months and 2 years after the first antenatal date.

Fig. 2. Number (a) and proportion (b) in each state by calendar year.

(AHD on ART, late gap and death), and less likely to transition to the stable state compared with women (Fig. 3a). Those aged 15−25 years were more likely to transition from stable to AHD on ART and late gap, and from AHD on ART to late gap. Those aged 15−25 had a similar risk of death to those aged more than 40 years (Fig. 3b). Later year of ART initiation was associated with reduced transition from stable to AHD on ART, increased transition from stable to late gap and increased re-engagement in care in either the AHD on ART or stable states. Later year was also associated with reduced transition from AHD on ART to stable and increased transition from AHD on ART to death (Fig. 3c).

Lower $CD4^+$ cell count at ART initiation was associated with worse progression, with increased transition to AHD on ART, and reduced transition to stable. Those with higher $CD4^+$ cell count at ART initiation were more likely to transition to late gap. Having TB and being postpartum was associated with increased risk of progression to AHD on ART from stable (Table S2, http://links.lww.com/QAD/C733 SDC 2).

Sensitivity analyses
In stratified analysis by $CD4^+$ cell count at ART initiation, there were too few transitions to model associations for those with $CD4^+$ cell count of more than 500 cells/μl. For the other strata, adjusted hazard ratios (aHRs) differed by year of ART initiation (Table S3, http://links.lww.com/QAD/C734 SDC 3). For those starting ART with low $CD4^+$ cell count ($CD4^+$ 0−50 and 50−200), later year of ART initiation was associated with an increased risk of re-engaging in care with AHD. Transitioning from AHD to stable was less likely, while mortality increased with later years. For those starting ART with higher $CD4^+$ cell count ($CD4^+$ of 200−500), transitions from stable to AHD on ART were less likely, while transitions from stable to late gap increased with later years.

When restricting the dataset to include each patient's first 5 years on ART, results were similar, although for transitions from late gap many of the confidence intervals were no longer significant when compared with the full dataset (Table S4, http://links.lww.com/QAD/C735 SDC 4).

We did not see significant differences when exploring the effects of missing $CD4^+$ cell count data (Tables S5, http://links.lww.com/QAD/C736 and S6, http://links.lww.com/QAD/C737 SDC 5 and 6), except for transitions from stable to AHD on ART in the worst case scenario. This suggests that we may be overestimating the association between initiating ART with AHD and experiencing AHD on ART following a stable state. However, the worst-case scenario is somewhat unrealistic since stable patients may be more likely to have longer periods without $CD4^+$ monitoring.

When we restricted our analysis to only those linked to the national population registry (Table S7, http://links.lww.com/QAD/C738 SDC 7), we found associations with transitions from AHD on ART did not change substantially, although some were removed by widening of confidence intervals due to smaller study size. Similarly, there was little change in the results for transitions to AHD on ART, but notably, there was no longer an association between the year of ART start and the transition from late gap to AHD on ART.

Re-engaging in care
Figure 4 and Fig. S1, http://links.lww.com/QAD/C730 (SDC 8) show the five-year probabilities of resuming ART after either gap state, and the proportions re-engaging with AHD.

Across all covariates, the probability of re-engaging after a gap was higher after an early compared with a late gap. Women, those with higher $CD4^+$ cell count at ART initiation and younger PWH had the highest probability of re-engaging in care.

(a)

Male sex vs female

(b)

Age vs >15-≤25
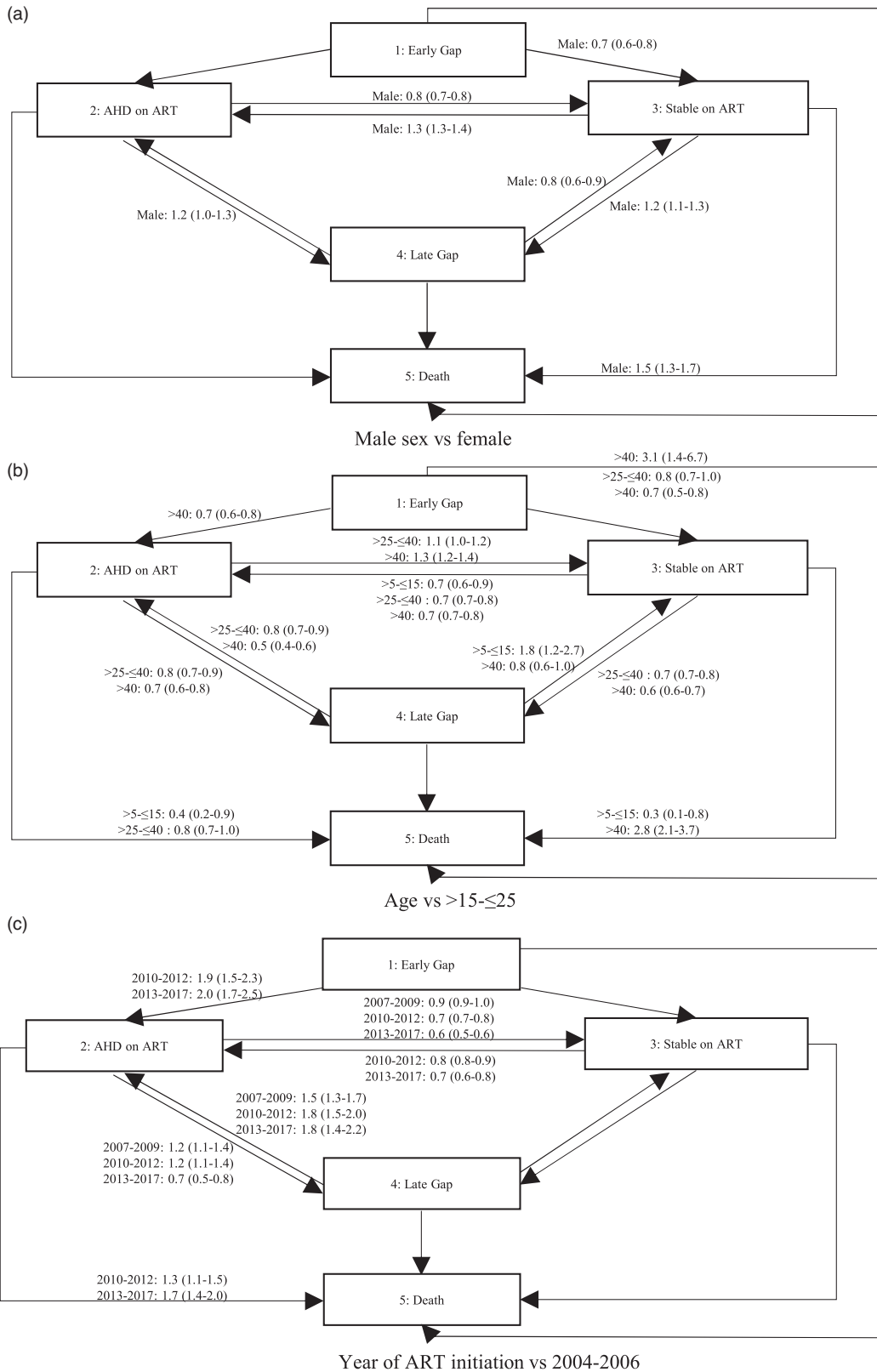
(c)

Year of ART initiation vs 2004-2006

Fig. 3. Estimated hazard ratios from a multi-state model, adjusted hazard ratios (95% confidence interval).
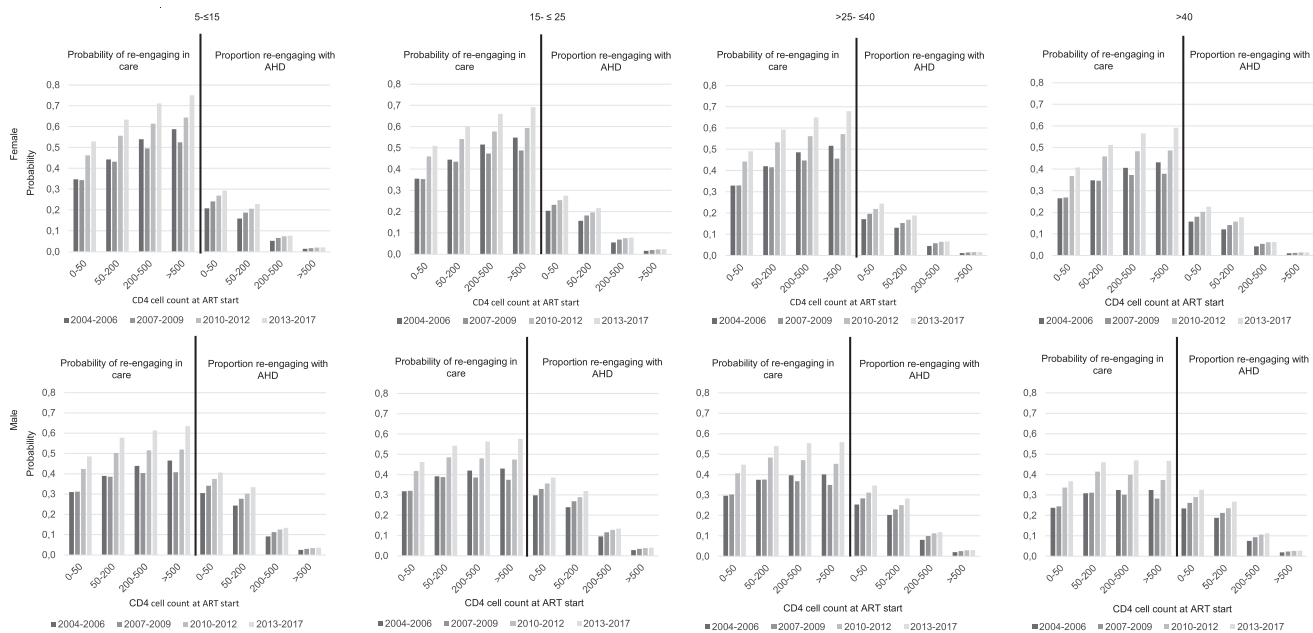
Fig. 4. Five-year probability of re-engaging in care following an early gap, and proportion re-engaging with advanced HIV disease.

Across all covariates re-engaging in care with AHD was higher following a late gap compared with an early gap. Among those re-engaging with AHD, a higher proportion were men. There were smaller differences between age groups, with those aged 15−25 years being more likely to re-engage with AHD. Higher $CD4^+$ cell count at ART initiation dramatically reduced the proportion of re-engaging with AHD. In later years a higher proportion re-engaged with AHD, especially among those with low $CD4^+$ cell count at ART initiation.

Validation

Comparing model projections with the observed prevalence of different states, our model overpredicted AHD on ART and underpredicted the stable state (Fig. S2, http://links.lww.com/QAD/C731 SDC 9). However, the observed prevalence assumed that where no $CD4^+$ cell count is recorded, the patient remained in their previous state, unlike our model which allowed for unobserved transitions. With stable patients less likely to have their $CD4^+$ cell count measured and longer times between measures, the observed data may overestimate the prevalence of the stable state and underestimate AHD on ART.

Discussion

Although the prevalence of AHD has substantially decreased, the number of PWH experiencing AHD on ART remained stable since 2009. We found that in more recent years those with AHD on ART were increasingly more likely to die, and less likely to become stable. Over time, progression to AHD from stable became less likely,

but re-engaging in care with AHD following a gap became increasingly more likely. The proportion of patients in a stable state has not improved since 2013, and an increasing proportion are in the late gap state. We found that male sex, age 15−25 and lower $CD4^+$ cell count at ART initiation were associated with progression to unfavourable states. Those aged 15−25 at ART initiation were as likely to die following AHD compared with older age groups, and more likely to transition to AHD from any state than any other age group.

Those initiating ART with low $CD4^+$ cell counts in more recent years appear to be a particularly vulnerable group. In our stratified analysis we found that among those with low $CD4^+$ cell count at ART initiation, those initiating ART in later years were less likely to transition from AHD to stable, more likely to die following AHD, and more likely to have AHD when re-engaging in care. Re-engaging in care with AHD was far more likely among those who initiate ART with low compared with higher $CD4^+$ cell counts. Although those with higher $CD4^+$ cell count at ART initiation were less likely to progress to AHD, and more likely to transition to the late gap, higher $CD4^+$ cell count dramatically reduced the proportion with AHD among those re-engaging. Even so, for adults and adolescents initiating ART more recently with $CD4^+$ cell count of 200−500 cells/μl, among those re-engaging in care more than 9% of women and more than 15% of men were estimated to do so with AHD, suggesting that AHD will continue to be a significant burden to the health system.

According to recent hospital-based studies among PWH in Southern Africa, relatively few admitted patients are ART naive [18−20]. This marks a change from earlier

years where most AHD was seen among ART-naïve patients, to an emerging challenge of patients with AHD, aware of their HIV status and ART-exposed, but with very high mortality. Several studies have employed multi-state models to examine engagement in care and HIV disease progression [21−23]. A Zambian study exploring patient stability found transitions to an unstable state and gaps in care were common. They found similar results to our study, with lower rates of transition from a stable state to instability, and higher rates of gaps among those enrolling more recently. Men had lower rates of transition from an unstable to a clinically stable state. They did not report transitions to death or include an adolescent age group [23].

Other Southern African studies simultaneously examining engagement in care and mortality among PWH include a Zambian group-based multi-trajectory analysis [24]. In broad agreement with our findings, they found a higher risk of mortality with a worse engagement trajectory. They identified trajectory groups that distinguished between early and late loss to follow-up, supporting the two gap states employed in our model. The Trajectory group strongly predicted mortality, independent of baseline characteristics. They did not explore trends over time. Our findings are consistent with a number of studies that show that those with lower $CD4^+$ cell count at ART initiation, men and adolescents have poorer outcomes [25,26]. Our finding that higher $CD4^+$ cell count was associated with an increased probability of late gap is also consistent with other studies [27,28].

Although several studies have demonstrated declining AHD at ART initiation, few have examined the outcomes of patients with AHD once on treatment. To our knowledge, this is the only study examining engagement in care and AHD on ART in Southern Africa. With many PWH already ART-exposed, and an increasing number experiencing gaps in care, our study used methods allowing for repeated disengagement and re-engagement in care, instead of the more traditional linear 'HIV cascade of care' approach. Our study follows a large public sector cohort over many years, providing insights into the outcomes of patients experiencing AHD on ART and how these have changed as ART programmes have grown and policies shifted to more inclusive ART eligibility criteria. Our findings are likely generalizable to other urban cohorts in the region where similar expansion in ART programmes occurred.

Our study has several limitations. Our results regarding trends over time are subject to some bias since those initiating ART more recently had a shorter follow-up, and their 'late gaps' thus occurred at shorter duration on ART. Our multi-state model assumes transition probabilities are independent of time, whereas, adherence and engagement in care may vary with the duration on ART.

Some potential bias was removed by including early and late gap states and our sensitivity analysis found little bias when restricting data to each patient's first 5 years on ART. There may be some bias in our estimates due to differences in mortality ascertainment with the calendar year of ART initiation, and further research is needed to quantify re-engagement in care with AHD. In the earliest years, those with clinical disease were eligible to start treatment regardless of $CD4^+$ cell count. Although we included prior TB diagnosis as a covariate, we were unable to include other clinical data. Those initiating ART with higher $CD4^+$ cell counts during the earlier years of ART were likely to have clinical illness, which would worsen their prognosis compared with patients initiating ART with higher $CD4^+$ cell counts in later years. Our stratified analysis attempted to remove this bias, but without knowing how the prevalence of clinical illness at ART initiation has changed over time, we remain cautious in interpreting the hazard ratios, especially for those with higher $CD4^+$ count at ART initiation. It is possible that AHD is underestimated in more recent years due to reduced $CD4^+$ monitoring. We made use of viral load data, to include periods without $CD4^+$ cell count measurement but with suppressed viral load in the stable state. We may, therefore, underestimate AHD since low $CD4^+$ cell count can persist even with viral suppression [29]. With limited $CD4^+$ cell count data in later years, we did not model $CD4^+$ cell count trajectory which may more accurately predict transitions to and from AHD. Our model could not account for trajectory through previous states, potentially an important predictor of outcomes.

Our finding that death following AHD is increasingly more likely suggests a change in the patient profile. Those initiating ART with a low $CD4^+$ cell count in more recent years did not access treatment earlier in their disease progression despite it being available. Their low $CD4^+$ cell count not only makes them more vulnerable to morbidity and mortality, but they are also likely a population facing extra barriers in accessing care and may have more complicated clinical and psychosocial needs as a result. Although $CD4^+$ cell count at ART initiation has increased, there are concerns that starting ART without disease may increase disengagement from care, ultimately leading to increased AHD after ART initiation. Our study found that low $CD4^+$ cell count at ART initiation is strongly predictive of AHD on ART, and while those with higher $CD4^+$ cell count were indeed more likely to experience gaps care, higher $CD4^+$ cell count was also protective against having AHD when re-engaging. This strongly supports universal ART combined with measures that reduce barriers to re-engaging in care and normalize interruptions, as a means of reducing AHD. Although only a small proportion of those with high $CD4^+$ cell count at ART initiation re-engage with AHD, with the increasing proportion of patients who experience gaps in care, AHD is likely to grow, and models of

care such as welcome-back services [30–32] will be important in identifying those who require more urgent care. As ART programmes shift to a differentiated care approach, viral load monitoring has been emphasized as an important tool in identifying stable patients [33]. Our study emphasizes the importance of CD4$^+$ cell count measurement, at least at ART initiation, in identifying more vulnerable patients. More data from the treat-all era is needed to understand how AHD trends are likely to change.

In conclusion, while AHD is declining in the modern ART era, those with AHD are more likely to die, and AHD at re-engagement in care is increasing. To further reduce HIV-related mortality, efforts to address the challenges facing these more vulnerable patients are needed, along with programmes to ensure long-term retention in care.

Acknowledgements

Conflicts of interest
The authors declare no conflicts of interest.

References

1. Leeme TB, Mine M, Lechiile K, Mulenga F, Mosepele M, Mphoyakgosi T, et al. **Utility of CD4 count measurement in the era of universal antiretroviral therapy: an analysis of routine laboratory data in Botswana.** *HIV Med* 2021; **22**:1–10.
2. Brennan AT, Maskew M, Larson BA, Tsikhutsu I, Bii M, Vezi L, et al. **Who is seeking antiretroviral treatment for HIV now? Characteristics of patients presenting in Kenya and South Africa in 2017–2018.** *J Int AIDS Soc* 2019; **22**:e25358.
3. Lilian RR, Rees K, Mabitsi M, McIntyre JA, Struthers HE, Peters RPH. **Baseline CD4 and mortality trends in the South African human immunodeficiency virus programme: analysis of routine data.** *South Afr J HIV Med* 2019; **20**:963.
4. UNAIDS. *UNAIDS fact sheet – world AIDS day 2020.* Geneva, Switzerland: UNAIDS; 2020.
5. Meintjes G, Kerkhoff AD, Burton R, Schutz C, Boulle A, Van Wyk G, et al. **HIV-related medical admissions to a South African district hospital remain frequent despite effective antiretroviral therapy scale-up.** *Medicine (Baltimore)* 2015; **94**:e2269.
6. Johnson LF, May M, Dorrington RE, Cornell M, Boulle A, Egger M, et al. **Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study.** *PLoS Med* 2017; **14**:e1002468.
7. Osler M, Hilderbrand K, Goemare E, Ford N, Smith M, Meintjes G, et al. **The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa.** *Clin Infect Dis* 2018; **66 (Suppl 2)**:S118–S125.
8. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. **Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa.** *Int J Epidemiol* 2012; **41**:1256–1264.
9. Stinson K, Goemaere E, Coetzee D, van Cutsem G, Hilderbrand K, Osler M, et al. **Cohort profile: the Khayelitsha antiretroviral programme, Cape Town, South Africa.** *Int J Epidemiol* 2017; **46**:e21.
10. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. **Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa.** *AIDS* 2010; **24**:563–572.
11. National Department of Health SA. *Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients.* Pretoria, South Africa: National Department of Health SA; 2016.
12. National Department of Health SA. *National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults.* Pretoria, South Africa: National Department of Health SA; 2014.
13. National Department of Health SA. *The South African antiretroviral treatment guidelines.* Pretoria, South Africa: National Department of Health SA; 2013.
14. National Department of Health SA. *Clinical guidelines for the management of HIV and AIDS in adults and adolescents.* Pretoria, South Africa: National Department of Health SA; 2010.
15. World Health Organization. *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy.* Geneva: World Health Organization; 2017.
16. Phillips TK, Clouse K, Zerbe A, Orrell C, Abrams EJ, Myer L. **Linkage to care, mobility and retention of HIV-positive postpartum women in antiretroviral therapy services in South Africa.** *J Int AIDS Soc* 2018; **21 (Suppl 4)**:e25114.
17. Jackson C. **Multi-state models for panel data: The msm package for R 2011.** *J Stat Softw* 2011; **38**:28.
18. Quan V, Toro-Silva S, Sriruttan C, Chetty V, Chihota V, Candfield S, et al. **Pathways to care and outcomes among hospitalised HIV-seropositive persons with cryptococcal meningitis in South Africa.** *PLoS One* 2019; **14**:e0225742.
19. Barak T, Neo DT, Tapela N, Mophuthegi P, Zash R, Kalenga K, et al. **HIV-associated morbidity and mortality in a setting of high ART coverage: prospective surveillance results from a district hospital in Botswana.** *J Int AIDS Soc* 2019; **22**:e25428.
20. Laher AE, Venter WDF, Richards GA, Paruk F. **Profile of presentation of HIV-positive patients to an emergency department in Johannesburg, South Africa.** *South Afr J HIV Med* 2021; **22**:1177.
21. Wang L, Krebs E, Min JE, Mathews WC, Nijhawan A, Somboonwit C, et al. **Combined estimation of disease progression and retention on antiretroviral therapy among treated individuals with HIV in the USA: a modelling study.** *Lancet HIV* 2019; **6**:e531–e539.
22. Gillis J, Loutfy M, Bayoumi AM, Antoniou T, Burchell AN, Walmsley S, et al. **A multi-state model examining patterns of transitioning among states of engagement in care in HIV-positive individuals initiating combination antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2016; **73**:531–539.
23. Roy M, Holmes C, Sikazwe I, Savory T, Mwanza MW, Bolton Moore C, et al. **Application of a multistate model to evaluate visit burden and patient stability to improve sustainability of human immunodeficiency virus treatment in Zambia.** *Clin Infect Dis* 2018; **67**:1269–1277.
24. Mody A, Eshun-Wilson I, Sikombe K, Schwartz SR, Beres LK, Simbeza S, et al. **Longitudinal engagement trajectories and risk of death among new ART starters in Zambia: a group-based multitrajectory analysis.** *PLoS Med* 2019; **16**:e1002959.
25. Cornell M, Schomaker M, Garone DB, Giddy J, Hoffmann CJ, Lessells R, et al. **Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study.** *PLoS Med* 2012; **9**:e1001304.
26. Tsondai PR, Braithwaite K, Fatti G, Bolton Moore C, Chimbetete C, Rabie H, et al. **Characteristics and outcomes of adolescents living with perinatally acquired HIV within Southern Africa.** *AIDS* 2020; **34**:2275–2284.

27. Grimsrud A, Cornell M, Schomaker M, Fox MP, Orrell C, Prozesky H, *et al*. **CD4 count at antiretroviral therapy initiation and the risk of loss to follow-up: results from a multicentre cohort study.** *J Epidemiol Community Health* 2016; **70**:549–555.

28. Kaplan SR, Oosthuizen C, Stinson K, Little F, Euvrard J, Schomaker M, *et al*. **Contemporary disengagement from antiretroviral therapy in Khayelitsha, South Africa: a cohort study.** *PLoS Med* 2017; **14**:e1002407.

29. Balachandra S, Rogers JH, Ruangtragool L, Radin E, Musuka G, Oboho I, *et al*. **Concurrent advanced HIV disease and viral load suppression in a high-burden setting: findings from the 2015-6 ZIMPHIA survey.** *PLoS One* 2020; **15**:e0230205.

30. Ford N, Geng E, Ellman T, Orrell C, Ehrenkranz P, Sikazwe I, *et al*. **Emerging priorities for HIV service delivery.** *PLoS Med* 2020; **17**:e1003028.

31. Nabaggala MS, Parkes-Ratanshi R, Kasirye R, Kiragga A, Castlenuovo B, Ochaka I, *et al*. **Re-engagement in HIV care following a missed visit in rural Uganda.** *BMC Res Notes* 2018; **11**:762.

32. Layer EH, Brahmbhatt H, Beckham SW, Ntogwisangu J, Mwampashi A, Davis WW, *et al*. **I pray that they accept me without scolding: experiences with disengagement and re-engagement in HIV care and treatment services in Tanzania.** *AIDS Patient Care STDS* 2014; **28**:483–488.

33. Phillips A, Shroufi A, Vojnov L, Cohn J, Roberts T, Ellman T, *et al*., Working Group on Modelling of Antiretroviral Therapy Monitoring Strategies in Sub-Saharan Africa. **Sustainable HIV treatment in Africa through viral-load-informed differentiated care.** *Nature* 2015; **528**:S68–76.