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SHORT COMMUNICATION

A matched cohort study investigating premature, accentuated, and accelerated aging in people living with HIV

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Abstract

Introduction: The impact of HIV infection on the aging process is disputed and largely unknown. We aimed to identify whether people living with HIV experience premature, accelerated, and/or accentuated aging by investigating the development of four age-related non-communicable diseases in people living with versus without HIV.

Methods: This population-based matched cohort study design used UK-based primary care electronic health records from the IQVIA Medical Research Database. Between January 2000 and January 2020, all people living with and without HIV aged ≥18 years were eligible. Outcomes included cardiovascular disease (CVD), hypertension, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD), which were identified by Read codes. We used age at diagnosis to investigate premature aging and age at exit date to investigate accentuation and acceleration. For each outcome, people with and without HIV were excluded if they had the outcome of interest at baseline. Participants were matched based on propensity scores (1:1 ratio). Linear regression was used to report any difference in age at diagnosis between the two groups and to report the prevalence trends for age at exit date.

Results: In total, 8880 people living with HIV were matched with 8880 people without HIV and were found to have an earlier onset of CVD (54.5 vs. 56.8; $p = 0.002$). Similarly, people living with HIV had an earlier onset of hypertension (49.7 vs. 51.4; $p = 0.002$). No difference was found for T2DM or CKD (53.4 vs. 52.6; $p = 0.368$ and 57.6 vs. 58.1; $p = 0.483$, respectively). The burden of CKD increased over time, whereas no difference in the burden was found for the other conditions.

Conclusion: The earlier development of CVD and hypertension in people living with HIV than in those without HIV indicates premature aging, whereas the increased burden of CKD indicates accelerated aging.

KEYWORDS
cardiovascular disease, chronic kidney disease, diabetes mellitus, HIV, hypertension

INTRODUCTION

The increased availability of antiretroviral therapy (ART) has significantly improved the life expectancy of people living with HIV [1]. However, some studies suggest that biological age is dissimilar between people with and without HIV, with the former experiencing premature aging [2]. This concept has been driven by an exponential amount of evidence that, irrespective of age, people living with HIV have an elevated risk for age-associated conditions such as cardiovascular disease (CVD), hypertension, type 2 diabetes mellitus (T2DM), dementia, and bone, liver, and kidney diseases, among others [3, 4]. However, whether people living with HIV experience pathophysiological damage at an earlier age (i.e. premature age), at an increasing rate (i.e. accelerated age), or at the same rate (i.e. accentuated age) compared with people without HIV has been much disputed [5]. Determining this distinction is imperative for developing therapeutic tailored interventions to ensure healthy aging and further improvements in the life expectancy of people living with HIV.

Aging is distinguished by various biological deficits, including changes to the immune system, proteins, cells, lipids, and tissues [6, 7]. Similar damaging effects have been identified in young people living with HIV, indicating that the biological impact of HIV infection and/or exposure to ART may emulate the aging process [8]. To date, studies that have attempted to investigate the aging process in people living with HIV have often had major design limitations, including small samples, short follow-up time, restricted range of participant demographics, and the inability to match people living with HIV with those without HIV and to control for known confounders [2]. Thus, the degree of certainty in existing evidence is low, as is the feasibility of ascertaining whether the impact on age is due to HIV-related mechanisms or external factors related to people living with HIV (i.e. smoking, deprivation, ethnicity, and mental illness, among others [9]). Additionally, many studies have focused on epigenetic [10] or neurocognitive aging [2]; however, recognizing that the impact of HIV infection on immune aging is vital to understand the increased risk of cardiometabolic conditions in people living with HIV [3]. Given the extreme complexities of both the aging process and the biological impacts of HIV infection, a perfectly designed study is implausible. However, longitudinal studies with large well-matched and controlled samples will strengthen the evidence base available to deduce whether HIV accelerates or accentuates aging.

To enhance the existing yet limited evidence, we carried out a population-based matched cohort study to identify whether people living with HIV are at risk of premature, accelerated, and/or accentuated aging by investigating any differences in age at diagnosis for CVD, hypertension, T2DM, and chronic kidney disease (CKD) between people with and without HIV.

MATERIALS & METHODS

Study design and population

Data were extracted from the IQVIA Medical Research Database (IMRD)-UK, a UK population-representative database of primary care electronic records [11]. Further details on the data source are described elsewhere [3]. The Scientific Review Committee provided ethical approval (SRC reference number: 20SRC067).

The study period comprised the 20 years from 1 January 2000 to 1 January 2020. Adults aged ≥18 years with an HIV diagnosis on or after the study start date were eligible for inclusion. For each outcome assessed, people living with HIV and the control group (people without HIV) were excluded if they had the outcome of interest at baseline. HIV diagnosis and all outcomes were identified using Read codes and defined by the first coded diagnosis. Read codes represent a hierarchical clinical coding system that was introduced in the UK in 1985.

Outcome definitions

A previous study conducted by the authors [3] found that people living with HIV were at higher risk for composite CVD (comprising peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease, and heart failure), hypertension, T2DM, and CKD. These conditions were chosen as the primary outcomes in the current study. Conditions were clinically diagnosed in primary or secondary care settings of the UK national health service. The first of any event was used, and all subsequent events were not considered. The age at diagnosis was determined based on the date the Read code was given.

Statistical methods

All analyses were conducted in Stata 14.0 (College Station, Texas, USA). Propensity scores were calculated for each of the four outcome groups using a multivariate logistic regression with the following covariates entered, chosen based on data availability and existing evidence of risk factors for age-related conditions in the general population and in people living with HIV [9, 12, 13]: age at study entry, sex, ethnicity, deprivation (i.e. Townsend quintiles [14]), smoking status, substance use (i.e. alcohol, cocaine, or other drug misuse), body mass index, lipid-lowering drug use, and depression, anxiety, and severe mental illness (i.e. schizophrenia, bipolar disorder, or psychosis). Hypertension, T2DM, and CKD at baseline were also entered as covariates for the CVD outcome group; CVD, T2DM, and CKD at baseline were entered as covariates for the hypertension outcome group; CVD, hypertension, and CKD at baseline were entered as covariates for the T2DM outcome group; and CVD, hypertension, and T2DM at baseline were entered as covariates for the CKD outcome group. People living with HIV were then matched using a 1:1 ratio with people without HIV based on propensity scores. The accuracy of matching was assessed by comparing the propensity score density before and after matching and the standardized mean difference between the two groups.

Unadjusted and adjusted linear regressions with robust standard errors were used to determine any statistically significant difference between age at diagnosis between people with and without HIV for each outcome. Adjusted models included all variables used for propensity score matching aside from age at study entry. A univariable linear regression was conducted for each outcome using an interaction term for age group (<30, 31–39, 40–49, 51–59, 61–69, ≥70 years) at the time of the exit date and HIV status. Exit date for each participant was the earliest date of the following: death, date of the outcome event, study end date, date they transferred practices, or date of last medical record available. Margins from the interaction term were plotted with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant.

RESULTS

Over the 20-year study period, 8880 CVD-free people living with HIV were identified and matched with 8880 CVD-free individuals without HIV, 8520 hypertension-free people living with HIV were matched with 8520 hypertension-free controls, 8926 T2DM-free people living with HIV were matched with 8926 T2DM-free controls, and 9135 CKD-free people living with HIV were matched with 9135 CKD-free controls. No differences were seen between the density curves or standardized mean differences after matching for any outcome, indicating that both groups were similar in age, sex, ethnicity, deprivation, smoking status, substance use, body mass index, lipid-lowering drug use, depression, anxiety, severe mental illness, CVD, hypertension, T2DM, and CKD where these baseline events were included. For the CVD outcome group, 35% of people living with HIV were female; mean age at study entry was 41 years (± standard deviation 11); 37% were white, 23% were Black, 36% were missing ethnicity data, less than 5% was considered Asian, mixed ethnicity, or other; 23% were considered most deprived; 30% were current smokers; 9% experienced substance abuse; and 39% were of normal weight. Demographics were similar across all outcome groups (Table 1).

People living with HIV were diagnosed with CVD at a younger age than people without HIV (54.5 vs. 56.8 years, adjusted $p = 0.002$; 95% CI −5.477 to −1.263), and the same was observed for hypertension (49.7 vs. 51.4 years, adjusted $p = 0.002$; 95% CI −3.042 to −0.658) (Table 2). There was no difference in age at diagnosis for T2DM (53.4 and 52.6 years, adjusted $p = 0.368$; 95% CI −1.100–2.963) or CKD (57.6 and 58.1 years, adjusted $p = 0.483$; 95% CI −4.245–2.012). No evidence was found for accentuated aging in people living with HIV for any of the outcomes (Figure 1); however, there was evidence of accelerated aging in people living with HIV based on CKD starting from age 40 years.

DISCUSSION

In a well-controlled, matched sample of people with and without HIV, CVD and hypertension occurred on average around 2 years earlier in people living with HIV, indicating premature aging. The prevalence trends for CKD indicated accelerated aging in people living with HIV. Few studies have used the same age-related conditions as a proxy for biological age, making comparability a challenge. However, one study conducted in the USA reported differences in prevalence for CVD, hypertension, and T2DM across various age groups for people with and without HIV [15]. The authors found that people living with HIV had a higher prevalence of T2DM for all age groups; however, the difference for CVD and hypertension was only seen in the younger age groups, supporting our findings. Differences could be due to the age groups defined, sample sizes, and selection biases reported in the US study [15]. Our study included more

TABLE 1 Demographics of people with and without HIV for each outcome investigated

	CVD outcome group		Hypertension outcome group		T2DM outcome group		CKD outcome group	
	People with HIV (n = 8880)	People without HIV (n = 8880)	People with HIV (n = 8520)	People without HIV (n = 8520)	People with HIV (n = 8926)	People without HIV (n = 8926)	People with HIV (n = 9135)	People without HIV (n = 9135)
Age at study entry	40.5 ± 10.6	40.2 ± 10.5	40.1 ± 10.5	39.8 ± 10.4	40.7 ± 10.8	40.7 ± 10.9	40.9 ± 10.9	40.6 ± 10.8
Age at exit date	44.9 ± 11.4	45.3 ± 1.4	44.3 ± 11.2	44.7 ± 11.3	45.1 ± 11.6	45.7 ± 11.8	45.3 ± 11.6	45.7 ± 11.8
Sex								
Female	3088 (34.8)	3304 (37.2)	2905 (34.1)	3026 (35.5)	3077 (34.5)	3146 (35.3)	3138 (34.4)	3217 (35.2)
Ethnicity								
White	3256 (36.7)	3066 (34.5)	3189 (37.4)	3052 (35.8)	3319 (37.2)	3206 (35.9)	3397 (37.2)	3388 (37.1)
Black	2032 (22.9)	2227 (25.1)	1867 (21.9)	1965 (23.1)	1982 (22.2)	2115 (23.7)	2045 (22.4)	2169 (23.7)
Asian	88 (1.0)	79 (0.9)	82 (1.0)	89 (1.0)	83 (0.9)	80 (0.9)	88 (1.0)	69 (0.8)
Mixed	151 (1.7)	161 (1.8)	143 (1.7)	168 (2.0)	151 (1.7)	151 (1.7)	153 (1.7)	164 (1.8)
Other	170 (1.9)	143 (1.6)	157 (1.8)	147 (1.7)	164 (1.8)	152 (1.7)	173 (1.9)	170 (1.9)
Missing	3183 (35.8)	3204 (36.1)	3082 (36.2)	3099 (36.4)	3227 (36.2)	3222 (36.1)	3279 (35.9)	3175 (34.8)
Townsend/deprivation quintile								
1st quintile (least deprived)	673 (7.6)	639 (7.2)	643 (7.6)	626 (7.4)	678 (7.6)	661 (7.4)	688 (7.5)	684 (7.5)
2nd quintile	837 (9.4)	837 (9.4)	813 (9.5)	801 (9.4)	852 (9.6)	830 (9.3)	872 (9.6)	865 (9.5)
3rd quintile	1255 (14.1)	1251 (14.1)	1218 (14.3)	1237 (14.5)	1278 (14.3)	1262 (14.1)	1298 (14.2)	1297 (14.2)
4th quintile	1686 (19.0)	1747 (19.7)	1613 (18.9)	1680 (19.7)	1691 (18.9)	1708 (19.1)	1716 (18.8)	1768 (19.4)
5th quintile (most deprived)	2076 (23.4)	2116 (23.8)	1996 (23.4)	2031 (23.8)	2073 (23.2)	2135 (23.9)	2141 (23.4)	2191 (24.0)
Missing	2353 (26.5)	2290 (25.8)	2237 (26.3)	2145 (25.2)	2354 (26.4)	2330 (26.1)	2420 (26.5)	2330 (25.5)
Body mass index								
Underweight (<18.5 kg/m^2)	292 (3.3)	260 (2.9)	300 (3.5)	273 (3.2)	301 (3.4)	243 (2.7)	301 (3.3)	279 (3.1)
Normal weight (18.5 kg/m^2 to <25 kg/m^2)	3430 (38.6)	3498 (39.4)	3396 (39.9)	3465 (40.7)	3480 (39.0)	3614 (40.5)	3532 (38.7)	3557 (38.9)
Overweight (25 kg/m^2 to <30 kg/m^2)	2052 (23.1)	2014 (22.7)	1928 (22.6)	1911 (22.4)	2061 (23.1)	2048 (22.9)	2119 (23.2)	2121 (23.2)
Obese (≥30 kg/m^2)	1098 (12.4)	1102 (12.4)	927 (10.9)	933 (11.0)	1045 (11.7)	1054 (11.8)	1131 (12.4)	1123 (12.3)
Missing	2008 (22.6)	2006 (22.6)	1969 (23.1)	1938 (22.8)	2039 (22.8)	1967 (22.0)	2052 (22.5)	2055 (22.5)
Smoking status								
Current smoker	2625 (29.6)	2639 (29.7)	2620 (30.8)	2653 (31.1)	2681 (30.0)	2664 (29.9)	2737 (30.0)	2761 (30.2)
Ex-smoker	1202 (13.5)	1100 (12.4)	1149 (13.5)	1088 (12.8)	1229 (13.8)	1170 (13.1)	1270 (13.9)	1186 (13.0)

TABLE 1 (Continued)

	CVD outcome group		Hypertension outcome group		T2DM outcome group		CKD outcome group	
	People with HIV (n = 8880)	People without HIV (n = 8880)	People with HIV (n = 8520)	People without HIV (n = 8520)	People with HIV (n = 8926)	People without HIV (n = 8926)	People with HIV (n = 9135)	People without HIV (n = 9135)
Never smoker	4372 (49.2)	4435 (49.9)	4076 (47.8)	4101 (48.1)	4329 (48.5)	4413 (49.4)	4438 (48.6)	4510 (49.4)
Missing	681 (7.7)	706 (8.0)	675 (7.9)	678 (8.0)	687 (7.7)	679 (7.6)	690 (7.6)	678 (7.4)
Substance use status								
Substance abuse	766 (8.6)	682 (7.7)	765 (9.0)	711 (8.4)	806 (9.0)	790 (8.9)	825 (9.0)	776 (8.5)
Non-substance abuse	8114 (91.4)	8198 (92.3)	7755 (91.0)	7809 (91.7)	8120 (91.0)	8136 (91.2)	8310 (91.0)	8359 (91.5)

Data are presented as mean ± standard deviation or n (%).

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

age groups to better identify trends, although this resulted in smaller sample sizes for each group. For instance, the prevalence of T2DM in people living with HIV aged ≥60 years was two percentage points higher than in people without HIV, but the 95% CIs were wide and overlapped.

Given the similarities between people living with HIV and their matched controls in terms of key demographics, socioeconomic status, lifestyle behaviours, and comorbidities, premature aging identified by CVD and hypertension diagnoses implies that either underlying mechanisms of HIV infection and/or exposure to ART are important drivers. However, compared with other risk factors such as smoking, the aging effect of HIV/ART is not as large; for instance, smoking has been found to result in coronary atherosclerosis 10 years earlier than never smoking [16]. It is difficult to ascertain what aspects of living with HIV have the most impact on our results, i.e. CD4 count, viral load, exposure to ART, or just the presence and duration of HIV. ART data were not available within our dataset, although ART coverage was 86% in 2011 (earliest reported data), with 94% of those on ART experiencing viral suppression. This increased to 99% on ART and 97% virally suppressed by 2020 [17]. ART coverage and viral suppression may have been lower prior to 2011, so the diverse and numerous biological impacts of a high viral load may contribute to our results [10]. Although ART partially restores biological defects in people living with HIV [10], disturbances to the immune system are moderately sustained, including T-cell changes, an imbalance of T-helper cells, and cell alterations of the innate immune system [18]. While the impact of ART on aging and the development of comorbidities is complex and unclear [9, 10, 19], evidence suggests that certain ART, particularly older ART, can increase the risk and potentially the early onset of cardiometabolic conditions [20]. The presence of HIV in the body leads people living with HIV on or off treatment to also experience microbial translocation, epithelial dysfunction, an imbalance in pro- and anti-inflammatory cytokines, and cell senescence, which can result in chronic inflammation and immune deregulation [8]. In aging people without HIV, the same physiological changes occur as a natural phenomenon [6] and are associated with atherosclerotic burden and development of hypertension. Such changes occurring earlier in people living with HIV are likely a key contributor to premature aging in people living with HIV [8, 21].

Some of the aforementioned components of immune system dysfunction and chronic inflammation are also associated with the development of T2DM and CKD; however, we found that these conditions did not occur earlier in people living with HIV than in people without

TABLE 2 Unadjusted and adjusted differences in age at diagnosis for cardiovascular disease, hypertension, type 2 diabetes mellitus, and chronic kidney disease

	Sample size, N	Events, n (%)	Incidence rate per 1000 PYs	Age at diagnosis, mean ± SD	Unadjusted models			Adjusted models[a]		
					Coef.	*p*-value	95% CI	Coef.	*p*-value	95% CI
CVD[b]										
People without HIV	8880	167 (1.9)	3.73	56.8 ± 10.1	Ref.			Ref.		
People with HIV	8880	207 (2.3)	5.33	54.5 ± 11.3	−2.396	**0.032**	−4.580 to −0.213	−3.370	**0.002**	−5.477 to −1.263
Hypertension										
People without HIV	8520	417 (4.9)	10.13	51.4 ± 9.4	Ref.			Ref.		
People with HIV	8520	456 (5.4)	12.70	49.7 ± 9.3	−1.651	**0.009**	−2.894 to −0.408	−1.850	**0.002**	−3.042 to −0.658
T2DM										
People without HIV	8926	162 (1.8)	3.62	52.6 ± 10.2	Ref.			Ref.		
People with HIV	8926	197 (2.2)	5.06	53.4 ± 10.1	0.707	0.513	−1.415–2.829	0.932	0.368	−1.100–2.963
CKD										
People without HIV	9135	89 (1.0)	1.92	58.1 ± 11.9	Ref.			Ref.		
People with HIV	9135	160 (1.8)	3.99	57.6 ± 12.2	−0.550	0.730	−3.683–2.584	−1.117	0.483	−4.245–2.012

Abbreviation: CI, confidence interval; CKD, chronic kidney disease; Coef., coefficient; CVD, cardiovascular disease; PYs, person years; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a]Models are adjusted for the following baseline variables: sex, ethnicity, smoking status, body mass index, deprivation, study entry date, substance use, lipid-lowering drug use, and events for CVD, hypertension, T2DM, CKD, depression, anxiety, and severe mental illness (the event being investigated was removed from the model).

[b]CVD comprises peripheral vascular disease, stroke, myocardial infarction, ischaemic heart disease, and heart failure.

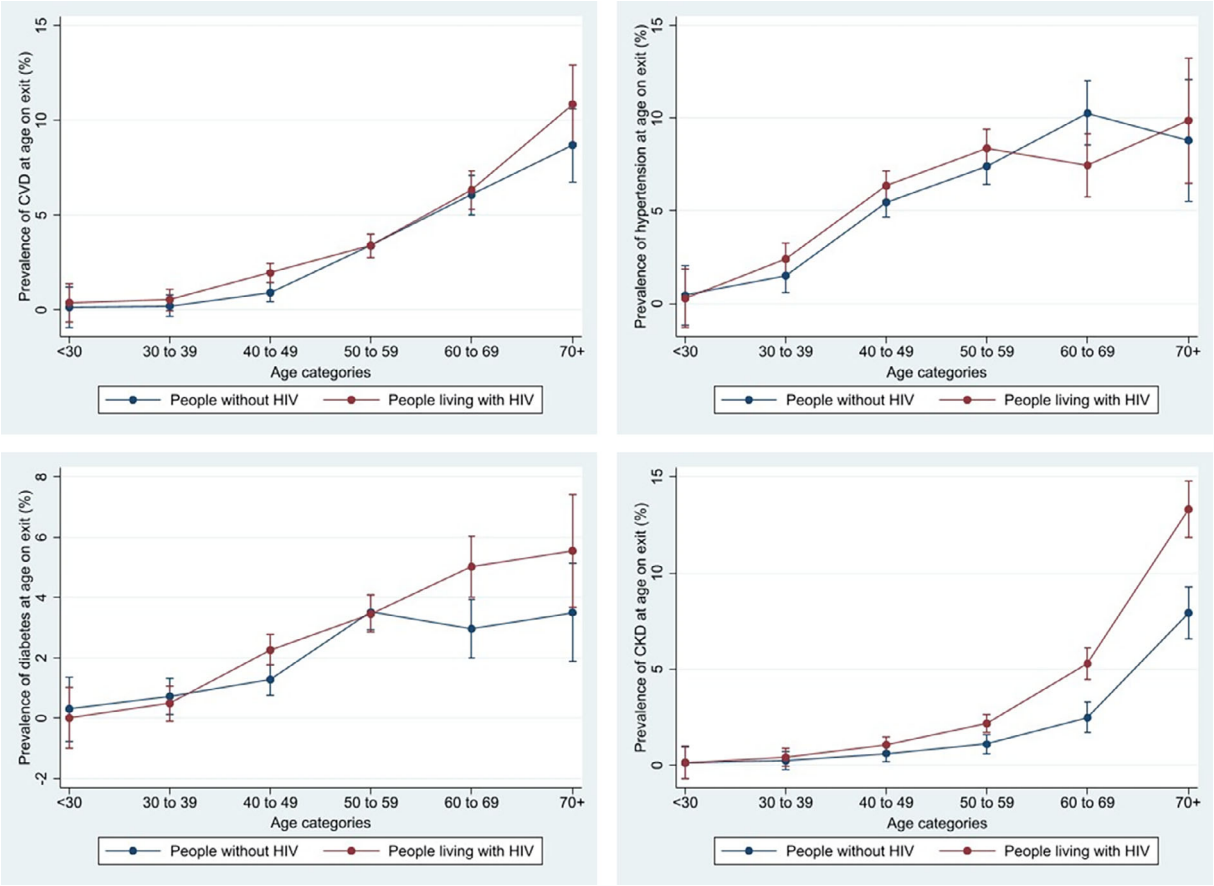

FIGURE 1 Prevalence of cardiovascular disease (CVD), hypertension, type 2 diabetes mellitus, and chronic kidney disease (CKD) by age at exit date for people with and without HIV

HIV. This indicates that the impact of living with HIV may not affect organ-specific deterioration earlier than in people without HIV. However, evidence of an increased burden of CKD was seen in people living with HIV. This could be due to increased exposure time to ART. However, the impact of ART on CKD is well known [22, 23] and could influence screening practices, potentially contributing to an inproved identificaiton of CKD as people living with HIV age. Further investigations are needed for improved understanding of this phenomenon.

A limitation of this study is the lack of data about ART, CD4, and viral load, which meant we were unable to further investigate which aspects of living with HIV impact on aging. Although the majority of people living with HIV within our sample were understood to be on ART and virally suppressed [17], certain ART may impact comorbidity risk differently, and nadir CD4 count may play a role in the earlier development of comorbidities [19]. Screening bias could be present for all outcomes investigated, as people with any chronic condition may be screened more often than the general population. Although we matched people with and without HIV on a number of confounders, unmeasured confounders may still have differed between the two groups.

Our study partially supports the model of premature and accelerated aging in people living with HIV. CVD and hypertension developed at a younger age in people living with than in those without HIV, and the burden of CKD increased over time. These findings are likely due to the persistent immune response, chronic inflammation, and/or exposure to various ART over time. Further investigations into these mechanisms will prove useful in adding to our global understanding of the aging process in people living with HIV. As the life expectancy of people living with HIV continues to increase, future research should prioritize ascertaining how to alleviate any increased aging in people living with HIV to ensure optimal wellbeing and quality of life as they age.

AUTHOR CONTRIBUTIONS

TEG, ST, KN, and GNT conceptualized the study. TEG and JW applied for ethical approval. TEG carried out all analyses, guided by JW and DZ. SG, SMH, KN, and GNT supervised the work. TEG wrote each draft of the

manuscript, and all authors reviewed and approved the final draft for publication.

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CONFLICT OF INTEREST

No conflict of interest declared.

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