RESEARCH ARTICLE

The prevalence of hyperglycemia and its impact on mortality among people living with HIV in Georgia

Tea Borkowska[1]*, Nikoloz Chkhartishvili[1], Ekaterine Karkashadze[1], Otar Chokoshvili[1], Pati Gabunia[1], Lali Sharvadze[1,2], Tengiz Tsertsvadze[1,2]

1 Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi, Georgia, 2 Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

* Theanozadze@yahoo.com

Abstract

Background

Life expectancy and quality of life of people living with HIV have been dramatically improved after introducing antiretroviral therapy, and the prevalence of non-communicable diseases has increased. Several studies have found that hyperglycemia with or without type 2 diabetes was associated with poor outcomes in people living with HIV.

The study's objective was to determine the prevalence of hyperglycemia and assess its impact on mortality.

Materials and methods

A retrospective cohort study was conducted among people living with HIV diagnosed in 2012–2018 and followed through 2020 at the Infectious Diseases, AIDS and Clinical Immunology Research Center in Tbilisi, Georgia. Primary outcomes of interest included the prevalence of hyperglycemia and mortality. Causes of death were classified according to the Coding of Death in HIV (CoDe) protocol.

Results

Our study included 2914 people living with HIV. Two hundred and forty-two (8.3%) patients had hyperglycemia, with an increasing prevalence by age. Three hundred one (9.7%) participants died over the median 3.71 (IQR: 2.14–5.37) years of follow-up. Among these, 139 (46.2%) were due to AIDS- related causes, 123 (40.9%)—were due to non-AIDS causes, and in 39 (12.9%) cases, the cause of death could not be determined. Overall, the cohort contributed to 11,148 person-years of follow-up (PYFU), translating into a mortality rate of 2.70 deaths per 100 PYFU. The mortality rate was significantly higher among individuals with hyperglycemia—11.17 deaths per 100 PYFU vs 2.07 deaths per 100 PYFU among normoglycemic patients($p < 0.0001$).

Conclusions

Hyperglycemia was associated with increased odds of mortality. Screening and management of hyperglycemia should be integrated into routine HIV clinical services as part of a comprehensive care package.

Introduction

Life expectancy and quality of life of people living with HIV (PLWH) have been dramatically improved after introducing antiretroviral therapy (ART) [1]. The longer people living with HIV are on ART, the more likely they are to develop non-communicable diseases, especially metabolic disorders [2–6].

It has been shown that HIV infection and ART increase the risk of metabolic disorders, abnormal glucose metabolism, and type 2 diabetes (T2D). The development of hyperglycemia and T2D during HIV depends on many factors, such as HIV infection's duration, degree of immunosuppression, and exposure to ARV medicaments [7]. Specific ARV medicaments, mainly protease Inhibitors (PI), nucleoside Reverse Transcriptase Inhibitors (NRTI), and some non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI-s), like efavirenz, are associated with T2D [8,9], dysglycemia, dyslipidemia, lipodystrophy, arterial hypertension, and myocardial infarction [7,8]. Longer ART exposure is linked to a higher prevalence of hyperglycemia and diabetes [2–4]. The prevalence of T2D in people living with HIV is two-fold higher [4,7] and ranges from 2% to 14% [2]. With or without T2D, hyperglycemia increases morbidity and mortality among people with infectious diseases, including tuberculosis and HIV [5,7,10–14]. Diabetes increases mortality risk due to circulatory system and kidney complications, which are significant causes of excess mortality in people living with HIV. After considering this dramatic effect, current guidelines recommend routine screening for glucose with appropriate management, including early detection and treatment of pre-diabetes and diabetes [15]. However, few programs offer integrated HIV/non-communicable disease management in resource-limited countries. There is a gap in data on the burden of non-communicable diseases among people living with HIV [16].

Georgia lacks knowledge regarding the relationship between hyperglycemia and mortality in people living with HIV. The study's objective was to determine the prevalence of hyperglycemia and assess its impact on mortality.

Materials and methods

A retrospective cohort study was conducted among people living with HIV receiving care at the Infectious Diseases, AIDS and Clinical Immunology Research Center in Tbilisi, Georgia, the country's referral institution for HIV providing care to 64% of people living with HIV. The study included adults (age ≥18 years) living with HIV diagnosed in 2012–2018 and followed through 2020. Patients who died or were lost to follow-up within six months of diagnosis (3.7%) were excluded from the analysis.

The study used routinely available data collected as part of the standard of care. All data, including demographic, clinical, and laboratory information, was extracted from the national AIDS health information system (AIDS HIS), a secure web-based database collecting data on all confirmed HIV cases.

During the study period, national HIV guidelines recommended checking for glycemia at the entry into HIV care and then annually. Given that care for endocrinologic disorders was

not integrated into HIV care, patients with hyperglycemia were referred to relevant specialists for further management. Therefore, AIDS HIS contained information only on glycemia. Glucose levels used for the statistical analysis were checked before ART initiation.

American Diabetes Association criteria defined hyperglycemia as a fasting glucose level> 5.6 mmol/l. or postprandial glucose level >7.8 mmol/l [17]. According to International Diabetes Federation (IDF), postprandial and postmeal plasma glucose levels should not rise above 7.8 mmol/l in healthy people [18]. Glucose measurements were considered postprandial if it was unknown whether it was measured during fasting or not.

Statistical analysis

Primary outcomes of interest included the prevalence of hyperglycemia and mortality (including all-cause mortality and cause-specific mortality). Causes of death were classified according to the Coding of Death in HIV (CoDe) protocol [19]. Based on CoDe protocol, deaths were classified into the following categories: AIDS-related deaths, non-AIDS and unknown.

The descriptive analysis was performed using the median and interquartile range for continuous variables and frequency/percentage for categorical data. Bivariate comparisons were tested using Pearson's chi-square test. Time-to-event approach was used for deriving mortality rates calculated as the number of deaths divided by the number of total person-years of follow-up (PYFU) contributed to the observation period. Kaplan-Meier method was used to estimate the probability of survival by hyperglycemic status. The association between hyperglycemia and mortality was assessed in Cox proportional hazards regression analysis with a competing risk model used for estimating the cause-specific adjusted hazard ratios [20]. In the sensitivity analysis, we evaluated the influence of hyperglycemia on all-cause and cause-specific mortality by CD4 cell strata (people with CD4 count <200 and ≥200 cells/mm^3). A p-value <0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The study was approved by the Institutional Review Board of the Infectious Diseases, AIDS and Clinical Immunology Research Center (OHRP #: IRB00006106). All patients initiating HIV care provide informed consent on the use of information collected as part of routine clinical care for research. The study used secondary data extracted from the national HIV database as an anonymous dataset with no personal identities. Therefore, informed consent was waived by IRB.

Results

Our study included 2914 people living with HIV. The median age was 36 (IQR: 28–45) years, and 2205 (75.7%) were men. Overall, 619 (21.2%) participants had a CD4 count of ≤200 cells/mm^3 at HIV diagnosis. AIDS was documented in 1189 (40.8%) patients. Every single patient has begun ART. Comorbidities, including cardiovascular diseases, kidney disease, and cancer, were present in 183 (6.3%) cases (Table 1).

The information about fasting glucose was unknown in 18.6% of cases. Two hundred and forty-two (8.3%) patients had hyperglycemia, increasing prevalence by age. People with baseline CD4 count <200 cells/mm^3 and a history of AIDS diagnosis had a statistically significantly higher prevalence of hyperglycemia (Table 1). The distribution of hyperglycemia in people living with HIV did not differ significantly by gender.

A total of 301 (9.7%) people living with HIV died over the median 3.71 (IQR: 2.14–5.37) years of follow-up. Among these 301 death events, 139 (46.2%) were due to AIDS-related

Table 1. Study population characteristics and prevalence of hyperglycemia by baseline characteristics (n = 2914).

Characteristic	Total N	Hyperglycemia, n (%)	p-value
Total cohort	2914	242 (8.3)	
Age at HIV diagnosis			
18<30	868	28 (3.2)	<0.0001
30-<40	947	65 (6.9)	
40-<50	716	82 (11.5)	
50-<65	357	62 (17.4)	
65+	26	5 (19.2)	
Gender			
Men	2205	193 (8.7)	0.12
Women	709	49 (6.9)	
Baseline CD4 cell count			
<200	619	98 (15.8)	<0.0001
200–500	1085	82 (7.6)	
>500	1210	62 (5.1)	
AIDS diagnosis			
Yes	1189	169 (14.2)	<0.0001
No	1725	73 (4.2)	
Non-communicable comorbidities			
With comorbidities	183	50 (27.3)	<0.0001
Without comorbidities	2712	192 (7.0)	

https://doi.org/10.1371/journal.pone.0276749.t001

causes, 123 (40.9%)—were due to non-AIDS causes, and in 39 (12.9%) cases, the cause of death could not be determined.

Overall, the cohort contributed to 11,153 person-years of follow-up (PYFU), translating into a mortality rate of 2.70 deaths per 100 PYFU. The mortality rate was significantly higher among individuals with hyperglycemia—11.17 deaths per 100 PYFU vs. 2.07 deaths per 100 PYFU among normoglycemic patients (p<0.0001). Kaplan-Meier survival estimates showed statistically significant differences between hyperglycemic and normoglycemic groups for all-cause and cause-specific mortality (Fig 1).

Hyperglycemia remained significantly associated with increased hazards of death for all-cause mortality (HR: 2.32, 95% CI: 1.76–3.04. p<0.0001), for AIDS-related mortality (HR: 2.24, 95% CI: 1.50–3.35, p<0.0001) and non-AIDS mortality (HR: 1.93, 95% CI: 1.18–3.14, p = 0.008) in multivariate regression analysis (Table 2). In sensitivity analysis, hyperglycemia was associated with increased hazards of all-cause mortality in both people with CD4 count <200 cells/mm^3 (HR: 2.02, 95% CI: 1.47–2.78, p<0.0001) and CD4 count ≥200 cells/mm^3 (HR: 3.26, 95% CI: 1.96–5.42, p<0.0001). Regarding cause-specific mortality, among people with CD4 count <200 cells/mm^3, hyperglycemia was associated with AIDS-related mortality but not with non-AIDS deaths, and vice versa among persons with CD4 count >200 cells/mm^3 hyperglycemia was associated with non-AIDS mortality and not with AIDS-related mortality (Table 3). Hyperglycemia did not show a significant association with mortality from unknown causes in any multivariate regression model.

Discussion

Hyperglycemia is common among people living with HIV, which has a detrimental effect on survival. In our study, hyperglycemia was associated with a more than 2-fold increase in mortality risk. Association between diabetes mellitus and death has been well documented [21],
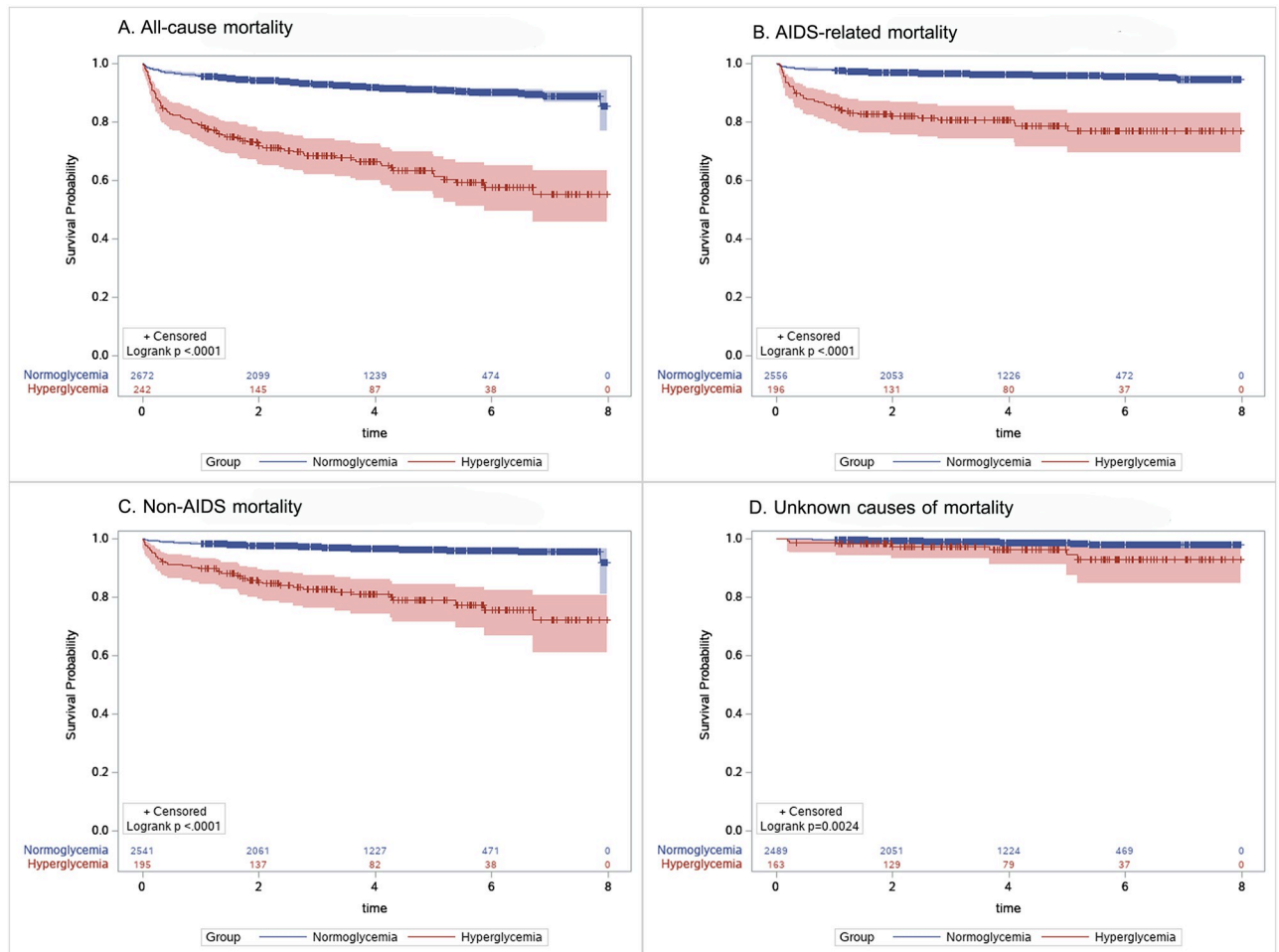
Fig 1. Kaplan-Meier survival estimates for all-cause and cause-specific mortality with number of participants at risk and 95% confidence intervals.

and our findings add to the body of knowledge showing that hyperglycemia is an independent risk factor for mortality [11,13,22,23]. Hyperglycemia can indicate missed diagnosis of diabetes mellitus, especially in resource-limited settings where care for non-communicable diseases is rarely integrated into HIV service delivery [24]. HIV treatment programs in resource-limited countries, including Eastern Europe, are primarily focused on acute care of HIV, mainly because of high rates of late diagnosis resulting in excess morbidity and mortality [25]. Comprehensive screening and treatment for diabetes and pre-diabetes are required to improve disease outcomes [26].

The overall prevalence of hyperglycemia was 8.3%, which is lower than studies conducted in China [2] and Africa [27], where the prevalence of hyperglycemia was 19.99% and 12.4%, respectively. The prevalence of hyperglycemia was significantly higher in older people, which is not surprising because hyperglycemia and diabetes mellitus are more common in the older population, and the prevalence increases with age [17]. Many other studies have found a similar relationship between increasing age and the prevalence of T2D among people living with HIV [5,28,29]. It should be taken into account that our cohort was relatively young, with a median age of 36 years, which might have influenced the overall prevalence. Furthermore, weight gain, obesity and insulin resistance can increase blood glucose levels [30]. The high

Table 2. Multivariate analysis of the association of hyperglycemia with all-cause and cause-specific mortality (n = 2914).

	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
All-cause mortality				
Hyperglycemia	5.14 (4.00–6.60)	<0.0001	2.32 (1.76–3.04)	<0.0001
Normoglycemia	1		1	
AIDS-related mortality				
Hyperglycemia	4.71 (3.26–6.81)	<0.0001	2.24 (1.50–3.35)	<0.0001
Normoglycemia	1		1	
Non-AIDS mortality				
Hyperglycemia	5.40 (3.69–7.88)	<0.0001	1.93 (1.18–3.14)	0.008
Normoglycemia	1		1	
Mortality from unknown cause				
Hyperglycemia	2.34 (1.04–5.28)	0.04	1.72 (0.69–4.26)	0.24
Normoglycemia	1		1	

The multivariate regression model was adjusted for age, gender, HIV transmission mode, baseline CD4 cell count, history of AIDS diagnosis, and non-communicable comorbidities.

https://doi.org/10.1371/journal.pone.0276749.t002

prevalence of hyperglycemia among people with comorbidities is not surprising, given the well-known association between diabetes and the risk of other non-communicable diseases [30,31].

Our study was not powered to explain the association found between hyperglycemia and advanced HIV disease (low CD4 cell count, AIDS diagnosis). Similar associations have been reported from China and Thailand, suggesting that hyperglycemia might be connected with ART and HIV itself, especially with uncontrolled HIV [2,32].

HIV can cause chronic inflammation [33,34]. As a result, the concentration of pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α, IL-6, IL-8 and IL-18 increases. Insulin resistance, metabolic syndrome and T2D are associated with elevated IL-18 levels [35]. During HIV, systemic inflammation and tryptophan catabolism alert the gut microbiota. As a

Table 3. Multivariate analysis of the association of hyperglycemia with all-cause and cause-specific mortality by baseline CD4 cell count (n = 2914).

	CD4 <200 (n = 558)		CD4 ≥200 (n = 2,356)	
	Adjusted Hazard ratio (95% CI)	p-value	Adjusted Hazard ratio (95% CI)	p-value
All-cause mortality				
Hyperglycemia	2.02 (1.47–2.78)	<0.0001	3.26 (1.96–5.42)	<0.0001
Normoglycemia	1		1	
AIDS-related mortality				
Hyperglycemia	2.47 (1.63–3.75)	<0.0001	0.84 (0.19–3.67)	0.82
Normoglycemia	1		1	
Non-AIDS mortality				
Hyperglycemia	1.16 (0.65–2.06)	0.62	4.60 (2.28–9.26)	<0.0001
Normoglycemia	1		1	
Mortality from unknown cause				
Hyperglycemia	1.30 (0.40–4.27)	0.66	2.36 (0.59–9.37)	0.22
Normoglycemia	1		1	

The multivariate regression model was adjusted for age, gender, HIV transmission mode, history of AIDS diagnosis, and non-communicable comorbidities.

https://doi.org/10.1371/journal.pone.0276749.t003

result, *Bifidobacterium*, *Bacteroides*, *Clostridium*, *Anaerovibri*, *Akkermansia*, *Finegoldia*, *Anaerococcus*, *Faecalibacterium*, and *Roseburia* concentrations are significantly lower among people living with HIV. *Anaerococcus* produce butyrate, which has an anti-inflammatory effect. Moreover, butyrate improves insulin sensitivity and reduces the risk of diabetes. Based on the aforesaid, low *Anaerococcus* concentration alerts metabolism and leads to metabolic syndrome and T2D [33,34,36,37]. The higher prevalence of hyperglycemia in people with advanced HIV should be interpreted in light of previous studies that showed an association between a low CD4 cell count and non-AIDS events [38,39].

Our findings align with previous reports indicating increased mortality among persons with hyperglycemia. While some of the reports suggest an increased risk of death among people living with HIV with serious opportunistic infections (e.g., tuberculosis, cryptococcal meningitis) [11,13,22], our data suggest the negative impact of hyperglycemia on survival irrespective of HIV disease status. After adjusting for CD4 cell count and history of AIDS diagnosis, hyperglycemia was significantly associated with all-cause and cause-specific mortality. Moreover, sensitivity analyses, stratified by CD4 cell count, further confirmed the negative effect of hyperglycemia on all cause-mortality. Increased risk of AIDS-specific mortality among people with low baseline CD4 cell count could suggest a reciprocal relationship between hyperglycemia and advanced HIV disease, which should be considered in light of high rates of late HIV diagnosis and serious AIDS-defining conditions in the country [40,41].

Our study has limitations. The major limitation is the potential underestimation of hyperglycemia because all glucose measurements with unknown fasting information were considered postprandial. We did not have information on diabetes diagnosis. Some patients might have been on anti-diabetic drugs and thus presented with normal glucose levels. Another potential source of misclassification is the use of single-point random glucose levels may cause misclassification of some patients as hyperglycaemic without further confirmation using OGTT or HbA1c. As a result of this study, these tests are being implemented as part of routine care. Also, this study did not assess other factors, such as obesity/high BMI and lifestyle, that may contribute to hyperglycemia/impaired fasting glucose.

Despite these limitations, the study provides essential information to address the growing problem of non-communicable diseases among people living with HIV. This was the first study to assess the prevalence and impact of hyperglycemia in a nationally representative sample of people living with HIV in Georgia and the entire Eastern European region. Our research showed that hyperglycemia is common among people living with HIV, resulting in increased mortality risk. Screening and management of hyperglycemia should be integrated into routine HIV clinical services as part of a comprehensive care package.

Supporting information

S1 File. Dataset.
(XLSX)

Acknowledgments

Author Contributions

Conceptualization: Tea Borkowska, Nikoloz Chkhartishvili.

Data curation: Tea Borkowska, Nikoloz Chkhartishvili, Ekaterine Karkashadze, Otar Chokoshvili.

Formal analysis: Nikoloz Chkhartishvili, Ekaterine Karkashadze, Otar Chokoshvili.

Investigation: Tea Borkowska, Nikoloz Chkhartishvili.

Methodology: Tea Borkowska.

Project administration: Tea Borkowska, Pati Gabunia, Lali Sharvadze, Tengiz Tsertsvadze.

Resources: Tea Borkowska.

Software: Nikoloz Chkhartishvili, Ekaterine Karkashadze, Otar Chokoshvili.

Supervision: Tea Borkowska, Nikoloz Chkhartishvili, Pati Gabunia, Lali Sharvadze, Tengiz Tsertsvadze.

Visualization: Tea Borkowska, Ekaterine Karkashadze.

Writing – original draft: Tea Borkowska, Nikoloz Chkhartishvili.

Writing – review & editing: Tea Borkowska, Nikoloz Chkhartishvili, Ekaterine Karkashadze, Otar Chokoshvili, Pati Gabunia, Lali Sharvadze, Tengiz Tsertsvadze.

References

1. Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Current opinion in HIV and AIDS. 2016; 11(5):492–500. https://doi.org/10.1097/COH.0000000000000298 PMID: 27254748

2. Shen Y, Wang Z, Liu L, Zhang R, Zheng Y, Lu H. Prevalence of hyperglycemia among adults with newly diagnosed HIV/AIDS in China. BMC Infectious Diseases. 2013; 13:79. https://doi.org/10.1186/1471-2334-13-79 PMID: 23394285

3. Brown TT, Tassiopoulos K, Bosch RJ, Shikuma C, McComsey GA. Association between systemic inflammation and incident diabetes in HIV-infected patients after initiation of antiretroviral therapy. Diabetes care. 2010; 33(10):2244–9. https://doi.org/10.2337/dc10-0633 PMID: 20664016

4. Coelho AR, Moreira FA, Santos AC, Silva-Pinto A, Sarmento A, Carvalho D, et al. Diabetes mellitus in HIV-infected patients: fasting glucose, A1c, or oral glucose tolerance test—which method to choose for the diagnosis? BMC Infectious Diseases. 2018; 18. https://doi.org/10.1186/s12879-018-3221-7 PMID: 29980190

5. Hernandez-Romieu AC, Garg S, Rosenberg ES, Thompson-Paul AM, Skarbinski J. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. BMJ Open Diabetes Research & Care. 2017; 5(1). https://doi.org/10.1136/bmjdrc-2016-000304 PMID: 28191320

6. Pelchen-Matthews A, Ryom L, Borges Á H, Edwards S, Duvivier C, Stephan C, et al. Aging and the evolution of comorbidities among HIV-positive individuals in a European cohort. AIDS (London, England). 2018; 32(16):2405–16.

7. Duncan AD, Goff LM, Peters BS. Type 2 diabetes prevalence and its risk factors in HIV: A cross-sectional study. PLoS ONE. 2018; 13(3). https://doi.org/10.1371/journal.pone.0194199 PMID: 29529066

8. Husain NE, Noor SK, Elmadhoun WM, Almobarak AO, Awadalla H, Woodward CL, et al. Diabetes, metabolic syndrome and dyslipidemia in people living with HIV in Africa: re-emerging challenges not to be forgotten. HIV/AIDS (Auckland, NZ). 2017; 9:193–202.

9. Karamchand S, Leisegang R, Schomaker M, Maartens G, Walters L, Hislop M, et al. Risk Factors for Incident Diabetes in a Cohort Taking First-Line Nonnucleoside Reverse Transcriptase Inhibitor-Based Antiretroviral Therapy. Medicine. 2016; 95(9).

10. Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, et al. Effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance. Journal of the Formosan Medical Association = Taiwan yi zhi. 2011; 110(6):372–81. https://doi.org/10.1016/S0929-6646(11)60055-7 PMID: 21741005

11. Kyaw NTT, Satyanarayana S, Oo HN, Kumar AMV, Harries AD, Aung ST, et al. Hyperglycemia and Risk of All-cause Mortality Among People Living With HIV With and Without Tuberculosis Disease in Myanmar (2011–2017). Open Forum Infectious Diseases. 2019; 6(1).

12. Leonidou L, Mouzaki A, Michalaki M, DeLastic AL, Kyriazopoulou V, Bassaris HP, et al. Cytokine production and hospital mortality in patients with sepsis-induced stress hyperglycemia. The Journal of infection. 2007; 55(4):340–6. https://doi.org/10.1016/j.jinf.2007.05.177 PMID: 17631968

13. Moreira J, Castro R, Lamas C, Ribeiro S, Grinsztejn B, Veloso VG. Hyperglycemia during tuberculosis treatment increases morbidity and mortality in a contemporary cohort of HIV-infected patients in Rio de Janeiro, Brazil. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2018; 69:11–9.

14. Han JH, Crane HM, Bellamy SL, Frank I, Cardillo S, Bisson GP. HIV infection and glycemic response to newly initiated diabetic medical therapy. AIDS (London, England). 2012; 26(16):2087–95. https://doi.org/10.1097/QAD.0b013e328359a8e5 PMID: 22951636

15. Ryom L, Cotter A, De Miguel R, Béguelin C, Podlekareva D, Arribas JR, et al. 2021 update of the European AIDS Clinical Society Guidelines for treatment of people living with HIV version 11.0. 2021.

16. Patel P, Rose CE, Collins PY, Nuche-Berenguer B, Sahasrabuddhe VV, Peprah E, et al. Noncommunicable diseases among HIV-infected persons in low-income and middle-income countries: a systematic review and meta-analysis. AIDS (London, England). 2018; 32 Suppl 1(Suppl 1):S5–s20. https://doi.org/10.1097/QAD.0000000000001888 PMID: 29952786

17. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes care. 2021; 44(Suppl 1):S15–s33. https://doi.org/10.2337/dc21-S002 PMID: 33298413

18. Ceriello A, Colagiuri S. International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. Diabetic medicine: a journal of the British Diabetic Association. 2008; 25(10):1151–6. https://doi.org/10.1111/j.1464-5491.2008.02565.x PMID: 19046192

19. Kowalska JD, Friis-Moller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology. Epidemiology. 2011; 22 (4):516–23. https://doi.org/10.1097/EDE.0b013e31821b5332 PMID: 21522013

20. Bakoyannis G, Touloumi G. Practical methods for competing risks data: a review. Statistical methods in medical research. 2012; 21(3):257–72. https://doi.org/10.1177/0962280210394479 PMID: 21216803

21. Park J, Zuñiga JA, García AA. Diabetes negatively impacts the ten-year survival rates of people living with HIV. International journal of STD & AIDS. 2019; 30(10):991–8. https://doi.org/10.1177/0956462419857005 PMID: 31335273

22. Tsai ST, Lin FY, Chen PS, Chiang HY, Kuo CC. Three-year mortality in cryptococcal meningitis: Hyperglycemia predict unfavorable outcome. PLoS ONE. 2021; 16(5):e0251749. https://doi.org/10.1371/journal.pone.0251749 PMID: 34048463

23. Bijker R, Kiertiburanakul S, Kumarasamy N, Pujari S, Sun LP, Ng OT, et al. Survival after long-term ART exposure: findings from an Asian patient population retained in care beyond 5 years on ART. Antiviral therapy. 2020; 25(3):131–42. https://doi.org/10.3851/IMP3358 PMID: 32369040

24. Adeyemi O, Lyons M, Njim T, Okebe J, Birungi J, Nana K, et al. Integration of non-communicable disease and HIV/AIDS management: a review of healthcare policies and plans in East Africa. BMJ global health. 2021; 6(5). https://doi.org/10.1136/bmjgh-2020-004669 PMID: 33947706

25. The Late Presentation Working Groups in EuroSIDA and COHERE. Estimating the burden of HIV late presentation and its attributable morbidity and mortality across Europe 2010–2016. BMC Infectious Diseases. 2020; 20(1):728. https://doi.org/10.1186/s12879-020-05261-7 PMID: 33028235

26. El-Sadr WM, Goosby E. Building on the HIV platform: tackling the challenge of noncommunicable diseases among persons living with HIV. AIDS (London, England). 2018; 32 Suppl 1:S1–s3.

27. Agbeko DK, Toyi T, Lihanimpo D, Dzidzonu NK, Laconi K, Abago B, et al. [Patients living with human immunodeficiency virus on antiretroviral therapy diagnosed with lipid and carbohydrate disorders who are at risk of cardio-vascular disease: study conducted at the Medical Centre of the ONG Espoir Vie in Lomé]. The Pan African medical journal. 2019; 34:203.

28. Capeau J, Bouteloup V, Katlama C, Bastard JP, Guiyedi V, Salmon-Ceron D, et al. Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. AIDS (London, England). 2012; 26(3):303–14. https://doi.org/10.1097/QAD.0b013e32834e8776 PMID: 22089377

29. Tripathi A, Liese AD, Jerrell JM, Zhang J, Rizvi AA, Albrecht H, et al. Incidence of diabetes mellitus in a population-based cohort of HIV-infected and non-HIV-infected persons: the impact of clinical and therapeutic factors over time. Diabetic medicine: a journal of the British Diabetic Association. 2014; 31 (10):1185–93.

30. Kalra S, Kalra B, Agrawal N, Unnikrishnan A. Understanding diabetes in patients with HIV/AIDS. Diabetology & Metabolic Syndrome. 2011; 3:2. https://doi.org/10.1186/1758-5996-3-2 PMID: 21232158

31. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World journal of diabetes. 2015; 6(13):1246–58. https://doi.org/10.4239/wjd.v6.i13.1246 PMID: 26468341

32. Paengsai N, Jourdain G, Chaiwarith R, Tantraworasin A, Bowonwatanuwong C, Bhakeecheep S, et al. Incidence and clinical outcomes of diabetes mellitus in HIV-infected adults in Thailand: a retrospective cohort study. BMC Public Health. 2018; 18(1):1079. https://doi.org/10.1186/s12889-018-5967-7 PMID: 30165821

33. Hoel H, Hove-Skovsgaard M, Hov JR, Gaardbo JC, Holm K, Kummen M, et al. Impact of HIV and Type 2 diabetes on Gut Microbiota Diversity, Tryptophan Catabolism and Endothelial Dysfunction. Scientific Reports. 2018; 8. https://doi.org/10.1038/s41598-018-25168-3 PMID: 29712976

34. Moon JY, Zolnik CP, Wang Z, Qiu Y, Usyk M, Wang T, et al. Gut microbiota and plasma metabolites associated with diabetes in women with, or at high risk for, HIV infection. EBioMedicine. 2018; 37:392–400. https://doi.org/10.1016/j.ebiom.2018.10.037 PMID: 30366816

35. Hivert M, Sun Q, Shrader P, Mantzoros C, Meigs J, Hu F. Circulating IL-18 and the risk of type 2 diabetes in women. Diabetologia. 2009; 52(10):2101–8. https://doi.org/10.1007/s00125-009-1455-z PMID: 19669125

36. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. Diabetologia. 2017; 60(6):943–51. https://doi.org/10.1007/s00125-017-4278-3 PMID: 28434033

37. Ouyang J, Isnard S, Lin J, Fombuena B, Marette A, Routy B, et al. Metformin effect on gut microbiota: insights for HIV-related inflammation. AIDS Research and Therapy. 2020; 17. https://doi.org/10.1186/s12981-020-00267-2 PMID: 32156291

38. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. Journal of acquired immune deficiency syndromes (1999). 2010; 55(2):262–70. https://doi.org/10.1097/QAI.0b013e3181e9be6b PMID: 20700060

39. Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, et al. CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. AIDS (London, England). 2008; 22 (7):841–8. https://doi.org/10.1097/QAD.0b013e3282f7cb76 PMID: 18427202

40. Chkhartishvili N, Chokoshvili O, Bolokadze N, Tsintsadze M, Sharvadze L, Gabunia P, et al. Late presentation of HIV infection in the country of Georgia: 2012–2015. PLoS ONE. 2017; 12(10):e0186835. https://doi.org/10.1371/journal.pone.0186835 PMID: 29084276

41. Kempker RR, Chkhartishvili N, Kinkladze I, Schechter MC, Harrington K, Rukhadze N, et al. High Yield of Active Tuberculosis Case Finding Among HIV-Infected Patients Using Xpert MTB/RIF Testing. Open Forum Infectious Diseases. 2019; 6(6):ofz233. https://doi.org/10.1093/ofid/ofz233 PMID: 31211163