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Incidence of diabetes mellitus among people living with and without HIV in British Columbia, Canada between 2001 and 2013: a longitudinal population-based cohort study

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ABSTRACT

Introduction People living with HIV (PLHIV) are increasingly at risk of age-related comorbidities such as diabetes mellitus (DM). While DM is associated with elevated mortality and morbidity, understanding of DM among PLHIV is limited. We assessed the incidence of DM among people living with and without HIV in British Columbia (BC), Canada, during 2001–2013.

Methods We used longitudinal data from a population-based cohort study linking clinical data and administrative health data. We included PLHIV who were antiretroviral therapy (ART) naïve at baseline, and 1:5 age-sex-matched persons without HIV. All participants had ≥5 years of historic data pre-baseline and ≥1 year(s) of follow-up. DM was identified using the BC Ministry of Health's definitions applied to hospitalisation, physician billing and drug dispensation datasets. Incident DM was identified using a 5-year run-in period. In addition to unadjusted incidence rates (IRs), we estimated adjusted incidence rate ratios (IRR) using Poisson regression and assessed annual trends in DM IRs per 1000 person years (PYs) between 2001 and 2013.

Results A total of 129 PLHIV and 636 individuals without HIV developed DM over 17 529 PYs and 88,672 PYs, respectively. The unadjusted IRs of DM per 1000 PYs were 7.4 (95% CI 6.2 to 8.8) among PLHIV and 7.2 (95% CI 6.6 to 7.8) for individuals without HIV. After adjustment for confounding, HIV serostatus was not associated with DM incidence (adjusted IRR: 1.03, 95% CI 0.83 to 1.27). DM incidence did not increase over time among PLHIV (Kendall trend test: p=0.9369), but it increased among persons without HIV between 2001 and 2013 (p=0.0136).

Conclusions After adjustment, HIV serostatus was not associated with incidence of DM, between 2001 and 2013. Future studies should investigate the impact of ART on mitigating the potential risk of DM among PLHIV.

Strengths and limitations of this study

- This is the first population-based cohort study to examine the association between HIV serostatus and incidence of diabetes among adults (≥19 years of age) in British Columbia.
- The study included all known people living with HIV in British Columbia, and an age-sex matched HIV-negative sample, which offers valuable insights into potential differences in diabetes outcomes between these two groups.
- The study was conducted using a large, longitudinal, population-based linked dataset comprised of administrative health data, clinical data, and census data, which facilitates large scale, complex research.
- The administrative data used may have included inaccurate billing and prescription data, and therefore may increase the risk for information bias.
- There was a lack of access to information on important traditional diabetes risk factors, which may have increased confounding bias.

INTRODUCTION

Substantial progress has been made in the treatment and control of HIV, narrowing the gap in life expectancy of people living with HIV (PLHIV) compared with the general population.[1–3] In particular, access to modern antiretroviral therapy (ART) for many PLHIV has greatly reduced the risk of AIDS-related morbidity and mortality,[4] leading to HIV being largely treated as a chronic condition. These trends have contributed to a demographic shift among PLHIV, with over 50% of PLHIV being 50 years of age or older in some high-income countries.[5 6] Nonetheless, mortality rates remain consistently higher among PLHIV compared with the general population.[7–9] PLHIV also continue to face an increased burden of comorbidity.[10 11] which impacts PLHIV's quality of life,[12] thus raising compelling health equity concerns.

The top causes of death and disability among PLHIV have been related to age-related non-communicable diseases (NCDs),[13] which cause 71% of all deaths worldwide.[14] Beyond their notable impact on global mortality and disability.[15] NCDs pose socioeconomic risks at the individual and healthcare system levels.[16] Importantly, NCDs disproportionally affect underserved populations such as PLHIV.[17] One of the NCDs that has become increasingly common among PLHIV in both Canada,[18] and around the world is diabetes mellitus (DM).[17 19] In 2019, 9.3% of the global population was estimated to experience DM, and an estimated 4.2 million deaths were directly attributable to DM.[20] In Canada, approximately 3.6 million individuals (9%) were living with DM in 2019,[21] and DM consistently ranks in the top 10 causes of death annually among the general population.[22] Among Canadian PLHIV, however, evidence related to DM at a provincial and national level is currently limited. Similarly, the association between HIV serostatus and incidence of DM is unclear. While some studies have found an increased burden of DM among PLHIV compared with the general population,[22–27] others have identified a similar risk of developing DM between the two populations.[28–30] Some studies have also highlighted a lower risk of DM among PLHIV when compared with individuals without HIV.[31 32]

This study aimed to contribute to this conflicting evidence base by calculating and comparing the incidence of DM in a large population-based cohort study of PLHIV and an age-sex-matched HIV-negative sample in British Columbia (BC), Canada. Additionally, this study also assessed the annual trends in DM incidence rates (IRs) in both samples between 2001 and 2013 in BC. We hypothesised that PLHIV in BC have an increased risk of developing DM compared with people living without HIV.

METHODS

Study design and data sources

This is a population-based longitudinal cohort study using data from the Comparative Outcomes And Service Utilization Trends (COAST) Study. COAST, which has been previously described in detail,[33] includes longitudinal data on all known PLHIV (≥19 years of age) in BC, and a comparison sample consisting of a random 10% sample of the general BC population (≥19 years of age) between 1 April 1996 and 31 March 2013.[33] COAST was developed through data linkages between the BC Centre for Excellence in HIV/AIDS's Drug Treatment Programme (DTP),[34] and several of Population Data BC (PopData)'s data holdings.[35–39] The DTP centrally manages ART dispensation across BC and contains clinical data and immunologic information for all treated PLHIV in BC. PopData is a provincial data repository that houses administrative health data for all 4.6 million BC residents.[40] PopData provided deidentified, individual level data from the following BC Ministry of Health (BC-MoH) datasets: the Medical Services Plan (MSP)[36] for physician billing records, the Consolidation File[37] for MSP registration and demographic data, the Discharge Abstract Database[35] for hospitalisation records, and PharmaNet[38] for eligible prescription drug data. The linked datasets used for the purpose of this study are described in more detail in online supplemental table 1 and the linkage process is described in more detail in the COAST cohort profile.[33]

The study complies with the BC Freedom of Information and Protection of Privacy Act and did not require informed consent as it is conducted retrospectively for research and statistical purposes only using anonymised data.

Study population

Participants in COAST were registered in MSP (and ≥19 years of age) during the follow-up period from 1 April 2001 to 31 March 2013. PLHIV were enrolled in the DTP and were ART-naïve at baseline. We matched individuals without HIV on a 1:5 ratio to PLHIV by sex and birth year. Individuals without HIV fulfilled the matching criteria if: (1) sex was an exact match, (2) birth year was an exact match, (3) their earliest contact date (ie, earliest of hospital admission date, MSP service date, PharmaNet service date or MSP registration date) was ≥5 years earlier than the baseline date of the PLHIV they were matched to and (4) their end of follow-up date was ≥1 year later than the matched PLHIV's baseline date.

The baseline date for PLHIV was defined as the latest date of either 1 April 2001 or individuals' entry into COAST (the earliest date of either their first viral load test or the first ART prescription dispensation in the DTP, or their 19th birthday if either event occurred when they were younger than 19). Individuals without HIV were allocated the same baseline date as their matched PLHIV. Individuals were eligible for inclusion if they had at least 5 years of historic data prior to baseline, and a minimum of 1 year of follow-up post baseline. The end of the observation period in both samples was the earliest of the date of the first DM diagnosis, the last contact date for those lost to follow-up (defined as no record of contact with the healthcare system for at least 18 months), or the administrative end of COAST follow-up (31 March 2013). We excluded individuals who were diagnosed with DM during the 5-year run-in period prior to baseline (ie, prevalent DM cases), and women diagnosed with gestational diabetes 120 days prior or 180 days post childbirth.

Variables of interest

The outcome of interest was incident DM, while the exposure variable was HIV serostatus (positive vs negative). Cases of DM were identified using a case definition published by the BC-MoH.[41] The case definition, which involved using a combination of International Classification of Disease Ninth and Tenth-Canada revisions (ICD-9 and ICD-10-CA) diagnostic codes for type 1 and type 2 diabetes from physician billing and hospitalisation administrative data, and diabetes medications identifiers, is described in online supplemental table 2.

We selected potential confounders comprising demographic and clinical variables associated with HIV serostatus and DM in the literature. These included: sex (male vs female), age at baseline, health authority via census tract (Vancouver Coastal versus Interior, Fraser, Vancouver Island and Northern), neighbourhood income quintile (highest vs lowest, second lowest, middle and second highest), history of injection drug use (IDU) prior to baseline (no vs yes), period of cohort entry (2001–2004 vs 2005–2009 and 2010–2012) and history of hypertension prior to baseline (ie, proxy measure for cardiovascular risks; no vs yes). History of IDU was identified using the case definition developed and validated by Janjua *et al*.[42] The case definitions for IDU and hypertension are described in online supplemental table 2. Health authority and income are neighborhood-level variables derived from three-digit postal code information linked to Canadian census data. Neighbourhood income quintiles, measured in Canadian dollars, refer to the median household income in an area sharing the same three-digit postal code. Health authority identifies the health authority of individuals' residential addresses by converting BC postal codes to healthcare-related geographic areas.

Statistical analysis

Characteristics of the samples were compared using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. We calculated crude and age-and-sex stratified IRs per 1000 PYs for people living with and without HIV. We used two-sided Mann-Kendall trend tests to analyse the annual trends in DM IRs per 1000 PYs for PLHIV and HIV-negative samples between 2001 and 2013. We used univariable and multivariable Poisson regression models to calculate unadjusted and adjusted incidence rate ratios (IRRs), quantifying the magnitude of the association between HIV serostatus and incidence of DM. Key confounders were selected using backward elimination procedure, where, starting with the full model, potential confounders were dropped one at a time based on the relative change in the coefficient for HIV serostatus variable (ie, our main variable of interest). The process was done reiteratively until the minimum absolute change in the coefficient for HIV serostatus from the full model exceeded 5%.[43] Missing data were categorised under an 'Unknown' category and included in the regression models. All analyses were conducted using SAS 9.4 (SAS, Cary, North Carolina, USA).

Patient and public involvement

There was no direct patient involvement in this study, seeing that the datasets used mainly included linked administrative health data.

RESULTS

Included in our study were 2792 PLHIV and 13 869 matched individuals without HIV. Of these individuals, 129 PLHIV (4.6%) and 636 (4.6%) individuals without HIV developed DM over 17 529 person-years (PYs) and 88 672 PYs, respectively. The application of the exclusion and inclusion criteria is presented in more detail in figure 1. Demographic characteristics of the PLHIV and individuals without HIV included in the incidence analysis are presented in table 1.

After age-sex-matching, participants had a median age of 40.3 years (25th–75th percentiles (Q1–Q3): 32.5–47.5) and were predominantly men (79.5%). PLWH and participants without HIV included in the incidence analysis were followed for a median of 6.2 years (Q1–Q3: 3.6–8.9) and 6.4 years (Q1–Q3: 3.7–9.1), respectively (table 1). At baseline, more PLHIV lived in the two lowest neighbourhood income quintiles (58.7% vs 39.5%, p<0.001), more PLHIV had a history of IDU (33.4% vs 3.7%, p<0.001) when compared with individuals without HIV. Contrastingly, fewer PLHIV had a history of hypertension (6.6% vs 8.6%, p<0.001). There was no significant difference in the age at DM diagnosis between PLHIV and individuals without HIV (median age in years 46.9 (Q1–Q3: 39-53.9) vs 47 (Q1–Q3: 38.9-54), respectively).

When comparing PLHIV with and without incident DM (table 2), those with incident DM were more likely to be older at baseline (median age in years 45 vs 40, p<0.001) and at ART initiation (median age 46.6 vs 42.3 years, p<0.001). Incident DM cases were also more likely to be exposed to ART for a shorter time (median exposure time 2.2 vs 4.3 years, p<0.001), start ART in an earlier treatment era (2001–2004) (36.4% vs 17%, p<0.001), have a lower CD4 cell count at baseline (median CD4 (cells/mm^3) 170 vs 230, p<0.001), have a higher proportion of follow-up time with a viral load ≥500 copies/mL (50% vs 34.8%, p<0.001), and have a prebaseline history of hypertension (14% vs 6.2%, p<0.001).

Among PLHIV and individuals without HIV, the unadjusted IRs of DM were 7.4 cases (95% CI 6.2 to 8.8), and 7.2 (95% CI 6.6 to 7.8) per 1000 PYs, respectively; the unadjusted IRR was 1.03 (95% CI 0.9 to 1.2). When stratified by age and sex, IRs for each age-sex stratum did not significantly differ between PLHIV and HIV-negative sample (table 3).

The incidence of DM was higher for older individuals; the IRs for DM among female and male PLHIV over 50 years of age were 13.4 and 12.2 per 1000 PYs, respectively. Kendall trend tests showed that the incidence of DM did not increase over time among PLHIV (p=0.9369), but that it significantly increased among individuals without HIV between 2001 and 2013 (p=0.0136) (figure 2).

After adjusting for key confounders in the multivariable model (ie, sex, age at baseline, health authority, neighbourhood income quintile, history of IDU prior to baseline, history of hypertension prior to baseline), the IRR of DM between 2001 and 2013 remained similar between the PLHIV and HIV-negative study groups (adjusted IRR: 1.03, 95% CI 0.83 to 1.27).

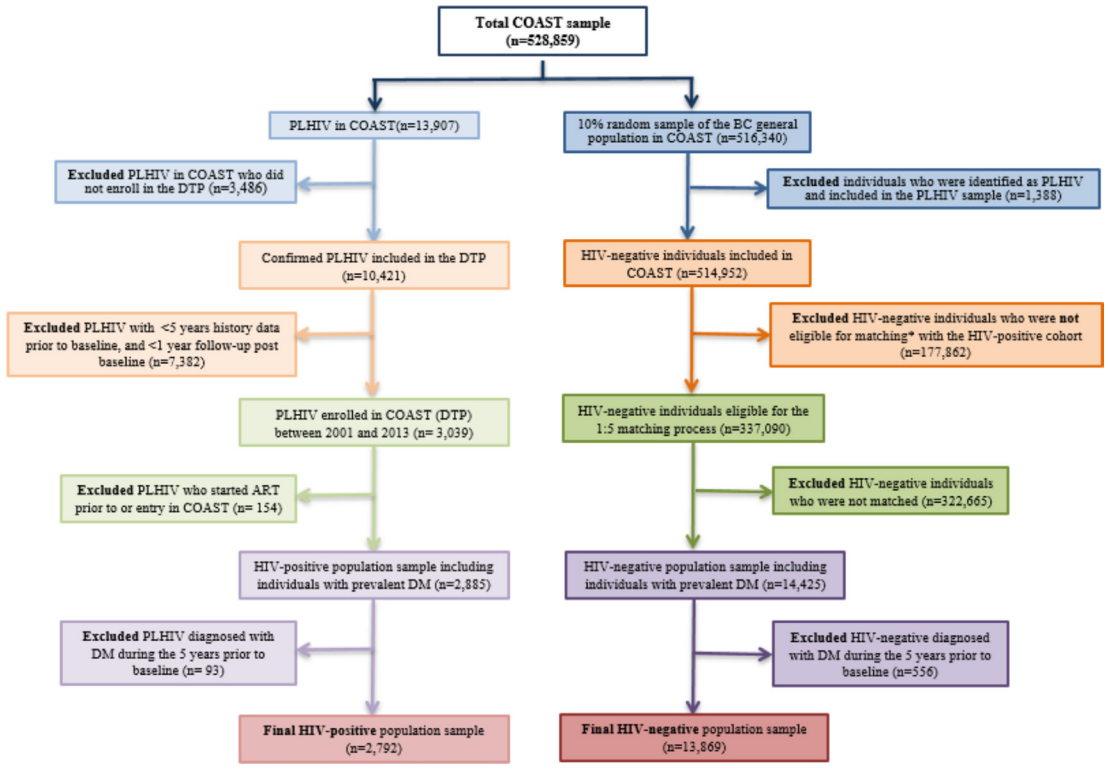

Figure 1 Flowchart outlining derivation of the two final comparison analytical samples of 2972 people living with HIV (PLHIV) and an age-sex-matched 13 869 HIV-negative individuals in British Columba, Canada between 2001 and 2013. *HIV-negative individuals were eligible for matching if matched at least one individuals from the final HIV-positive sample, where (1) sex was an exact match; (2) birth year was an exact match; (3) baseline date was older than or equal to PLHIV baseline date; (4) earliest contact date (ie, earliest of hospital admission date, Medical Services Plan (MSP) service date, PharmaNet service date or MSP registration date) was ≥5 years earlier than PLHIV baseline date and (5) end of follow-up date was ≥1 year later than the PLHIV baseline date.

Abbreviations: ART, antiretroviral therapy; BC, British Columbia; COAST: the Comparative Outcomes and Service Utilization Trends Study; DTP: Drug Treatment Programme; DM: diabetes mellitus.

DISCUSSION

We aimed to estimate and compare the incidence of DM in a population of PLHIV and an age-sex-matched HIV-negative sample in BC between 2001 and 2013. PLHIV did not experience a higher incidence of DM compared with age-sex matched individuals without HIV in BC between 2001 and 2013. While the incidence of DM remained stable over the 13 years of follow-up among PLHIV, there was a significant increase in the annual trends of DM incidence in the HIV-negative sample during the same period. There was no difference between the age-sex stratified IRs of DM between PLHIV and the HIV-negative sample. It should be noted that the PLHIV in COAST are predominantly male (80%), and relatively older, with a median age at baseline of 38 years,[33] which is consistent with the demographic characteristics of the HIV-positive population in BC.[44]

Our main finding of no association between HIV serostatus and DM incidence is contrary to our hypothesis that HIV serostatus is associated with incidence of DM. While this finding is also contrary to some of the current evidence,[22–25] it is consistent with the findings of other studies.[28–30 32] The conflicting evidence could be explained by variations in the methodologies used for analysis, such as using different case definitions to select variables of interest, or differences in the types of datasets used (eg, primary or secondary (administrative) health data). Additionally, differences in our findings compared with other studies could be explained by variations in healthcare access; our study was set in Canada, which has a universal healthcare system, and therefore the available data could be significantly different when compared with studies set in the USA, which comprised of jurisdictions without universal health insurance. Moreover, the lower-than-expected DM incidence among PLHIV may in part be explained by the potential increased engagement of treated PLHIV with the BC publicly funded healthcare system. Given their chronic viral illness, regular clinical monitoring of PLHIV may be helping to identify and address DM-related risk factors early on.[45] Importantly, our cohort study follow-up covers a period during which modern ART regimens have been widely prescribed in BC. Historically, first-generation ART regimens, developed prior to 2000, were found to be associated with DM,[23 28 46 47] while newer ARTs present have fewer metabolic complications.[47 48] Furthermore, exposure to ART has been associated with higher body mass index (BMI),[49] which is a key risk factor for DM.[50] Given that our study

Table 1 Baseline characteristics of people living with and without HIV in British Columbia between 2001 and 2013 included in the analysis

Characteristics	PLHIV (n=2792)	People without HIV (n=13 869)	P values
Incident DM during follow-up (n, %)	129 (4.6)	636 (4.6)	0.937
Median age in years at baseline (Q1, Q3)	40.3 (32.5, 47.5)	40.3 (32.5, 47.5)	0.790
Median age in years at DM diagnosis (Q1, Q3)*	46.9 (39.0, 53.9)	47 (38.9, 54.0)	0.829
Median follow-up time in years (Q1, Q3)	6.2 (3.6, 8.9)	6.4 (3.7, 9.1)	0.085
Period of cohort entry (n, %)			
2001–2004	1084 (38.8)	5369 (38.7)	1.000
2005–2009	1246 (44.6)	6192 (44.7)	
2010–2012	462 (16.6)	2308 (16.6)	
Sex (n, %)			
Male	2220 (79.5)	10 967 (79.1)	0.604
Female	572 (20.5)	2902 (20.9)	
Health authority† (n, %)			
Interior	175 (6.3)	2225 (16)	**<0.001**
Fraser	601 (21.5)	4617 (33.3)	
Vancouver Coastal	1466 (52.5)	3453 (24.9)	
Vancouver Island	348 (12.5)	2254 (16.3)	
Northern	193 (6.9)	990 (7.1)	
Unknown	9 (0.3)	330 (2.4)	
Neighbourhood income (SES) quintile† (n, %)			
Lowest	1092 (39.1)	2732 (19.7)	**<0.001**
Second lowest	547 (19.6)	2751 (19.8)	
Middle	500 (17.9)	2839 (20.5)	
Second highest	360 (12.9)	2695 (19.4)	
Highest	269 (9.6)	2559 (18.5)	
Unknown	24 (0.9)	293 (2.1)	
History of IDU‡ (n, %)	931 (33.4)	511 (3.7)	**<0.001**
History of hypertension‡ (n, %)	183 (6.6)	1193 (8.6)	**<0.001**
History of heart failure‡ (n, %)	18 (0.6)	43 (0.3)	**0.008**
History of stroke‡ (n, %)	6 (0.2)	21 (0.2)	0.447

P values calculated with 'Unknown' group excluded; p values significant at 0.05.
*Only applicable to people living with HIV (PLHIV) and individuals without HIV with incident diabetes mellitus (DM).
†Via census tract data.
‡Prior to baseline.
DM, Diabetes Mellitus; IDU, injection drug use; PLHIV, people living with HIV; (Q1, Q3), 25th–75th percentiles; SES, socioeconomic status.

only included PLHIV who started ART in or after 2001, the PLHIV in our study were less likely to have been exposed to high-DM-risk ART medications, and they may have had a lower BMI; both of these factors may have contributed to their lower DM incidence.

In both samples, the IR of DM was approximately 7 per 1000 PYs during the follow-up period. Overall, the DM IR in our HIV-negative sample is higher than the national DM incidence among the general Canadian population during 2008–2009 (9.0 vs 6.3/1000 PYs).[18] While this comparison provides some general context for our results, it is important to highlight that the general population average may not be entirely comparable to our sample. Studies investigating DM incidence among PLHIV also report widely varying estimates, with the observation that estimates for DM incidence in North America are generally higher than international or European estimates. For example, a nation-wide Danish study reported an incidence of 3.7 per 1000 PYs among PLHIV,[51] whereas an international study among 33 389 PLHIV on ART at 212 clinics across Europe, the USA, Argentina and Australia, reported an incidence of 5.7 per 1000 PYs.[52] On the

Table 2 Baseline characteristics of people living with HIV with and without incident diabetes mellitus between 2001 and 2013 in British Columbia

Characteristics	PLHIV with incident DM (n=129)	PLHIV without incident DM (n=2663)	P values
Median age in years at baseline (Q1, Q3)	45 (39.9, 52.2)	40 (32.3, 47.3)	**<0.001**
Sex (n, %)			
Male	107 (83.0)	2113 (79.4)	0.323
Female	22 (17.1)	550 (20.7)	
Ethnicity (n, %)			
Indigenous	11 (8.5)	348 (13.1)	0.382
White	38 (29.5)	683 (25.7)	
Asian	6 (4.7)	85 (3.2)	
Hispanic	≤5	23 (0.9)	
Black	≤5	18 (0.7)	
Unknown	70 (54.2)	1506 (56.6)	
Health authority* (n, %)			
Interior	8 (6.2)	167 (6.3)	0.061
Fraser	32 (24.8)	569 (21.4)	
Vancouver Coastal	68 (52.7)	1398 (52.5)	
Vancouver Island	20 (15.5)	328 (12.3)	
Northern	≤5	192 (7.2)	
Unknown	≤5	9 (0.3)	
Neighbourhood income (SES) quintile* (n, %)			
Lowest	36 (27.9)	1056 (39.7)	0.141
Second lowest	30 (23.3)	517 (19.4)	
Middle	27 (20.9)	473 (17.8)	
Second highest	19 (14.7)	341 (12.8)	
Highest	15 (11.6)	254 (9.5)	
Unknown	≤5	22 (0.8)	
On ART during study period† (n, %)			
No	30 (23.3)	83 (3.1)	**<0.001**
Yes	99 (76.7)	2580 (96.9)	
Median age at ART initiation in years (Q1, Q3)	46.6 (41.7, 53.9)	42.32 (34.7, 49.2)	**<0.001**
Period of ART initiation† (n, %)			
2001–2004	36 (36.4)	439 (17.0)	**<0.001**
2005–2009	52 (52.5)	1280 (49.6)	
2010–2013	11 (11.1)	861 (33.4)	
Total duration of ART exposure† (years, (Q1, Q3))	2.2 (0.8, 4.2)	3.4 (1.7, 5.6)	**<0.001**
Main class of first ART regimen (n, %)			
NRTI+INSTI	≤5	37 (1.4)	**0.034**
NRTI+NNRTI	30 (30.3)	1108 (43)	
NRTI+PI	68 (68.7)	1401 (54.3)	
Other	≤5	34 (1.3)	
Treatment Interruption ≥3 months† (n, %)			
No	88 (88.9)	1936 (75)	0.002
Yes	11 (11.1)	644 (25)	
Median CD4 at baseline (cells/mm^3 (Q1, Q3))	170 (55, 295)	230 (120, 360)	**<0.001**

Continued

Table 2 Continued

Characteristics	PLHIV with incident DM (n=129)	PLHIV without incident DM (n=2663)	P values
Median VL at baseline (log 10 copies/mL (Q1, Q3))	5 (4.6, 5.0)	4.9 (4.3, 5.0)	**<0.001**
Proportion of follow-up time with VL ≥500 copies/mL (% (Q1, Q3))	50 (20, 100)	34.8 (16.7, 56.5)	**<0.001**
History of hypertension‡ (n, %)	18 (14.0)	165 (6.2)	**<0.001**
History of heart failure‡ (n, %)	≤5	24 (0.5)	**<0.001**
History of IDU‡ (n, %)	37 (28.7)	894 (33.6)	0.250

P values calculated with 'Unknown' group excluded.
*Via census tract data.
†Only applies to people living with HIV (PLHIV) who are on antiretroviral therapy (ART) during the study period (n=2679).
‡Prior to baseline.
ART, antiretroviral therapy; DM, diabetes mellitus; IDU, injection drug use; INSTI, integrase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitors; PI, protease inhibitor; PLHIV, people living with HIV; (Q1, Q3), 25th–75th percentiles; SES, socioeconomic status; VL, viral load.

other hand, the DM incidence in a study among PLHIV who were treated through the South Carolina Medicaid programme (1994–2011) was 11.35 per 1000 PYs,[32] and a prior study among PLHIV in BC, aged 50 and over, reported a DM IR of 16.1 per 1000 PYs.[24] Importantly, our descriptive analyses show that PLHIV with incident DM in this study had a shorter duration of exposure to ART than PLHIV without incident DM when compared with other studies. As the risk for DM is strongly affected by a variety of interconnected factors such as age, sex, ART and polypharmacy-related toxicity, behavioural risk factors (eg, alcohol consumption, tobacco smoking), BMI, or severity of HIV infection,[53–55] differences in IRs between our and other studies may be explained by a different distribution of these factors across samples, and whether they were or were not adjusted for, in the analyses. Additionally, comparisons should be interpreted cautiously due to differences in the way in which diabetes diagnoses are recorded across different geographic settings and data collection systems, as well as variations in the manner by which diabetes is measured across various studies.

Contrary to prior literature suggesting that PLHIV develop DM at a younger age than the general population,[51 56] the median age at incident DM diagnosis among PLHIV and people without HIV in our study were similar. Our descriptive analyses further found that a significant difference in the socioeconomic situations between people living with and without HIV in our study; this reflects Canadian statistics showing that many PLHIV are disproportionally affected by poverty.[57] Socioeconomic factors, including income, are well-known predictors of better health among PLHIV.[58–61] Our descriptive findings draw attention to the potential vulnerability of PLHIV to health inequity and the need for consistent monitoring of DM behavioural risk factors among PLHIV.

A key strength of our longitudinal study is that it was conducted in a large population-based linked dataset comprised of a variety of administrative health data, clinical data, and census data; this centralization of data facilitates large scale and complex research while minimising resource requirements. In addition, we included an age-sex matched HIV-negative sample. Moreover, we used a relatively long run-in period to identify incident cases of DM (ie, 5 years), which likely minimised the risk of misclassifying prevalent DM cases as incident. While a potential limitation of this approach was that it likely

Table 3 Age-sex stratified incidence rates and incidence rate ratios for diabetes mellitus in the two comparison samples

		PLHIV			HIV negative			Rate ratio
	Age group	Frequency	PYs	IR per 1000 PYs (95% CI)	Frequency	PY	IR per 1000 PYs (95% CI)	IRR (95% CI)
Female	19–40	6	1942.5	3.09 (1.4 to 6.9)	18	9877.3	1.8 (1.15 to 2.9)	1.7 (0.7 to 4.3)
	41–50	8	1064.8	7.5 (3.8 to 15.0)	34	5563.0	6.1 (4.4 to 8.6)	1.3 (0.6 to 2.7)
	51+	8	596.0	13.4 (6.7 to 26.8)	34	3443.3	9.9 (7.1 to 13.8)	1.4 (0.7 to 3.0)
Male	19–40	12	4410.1	2.7 (1.6 to 4.8)	55	21 472.7	2.6 (2.0 to 3.3)	1.1 (0.67 to 2.0)
	41–50	44	5322.7	8.3 (6.3 to 11.1)	192	26 543.8	7.2 (6.3 to 8.3)	1.1 (0.8 to 1.6)
	51+	51	4192.5	12.2 (9.3 to 16.0)	303	21 771.7	13.9 (12.4 to 15.6)	0.0 (0.7 to 1.2)

CI, confidence intervals; IR, incidence rate; IRR, incidence rate ratio; PLHIV, people living with HIV; PY, person-years.

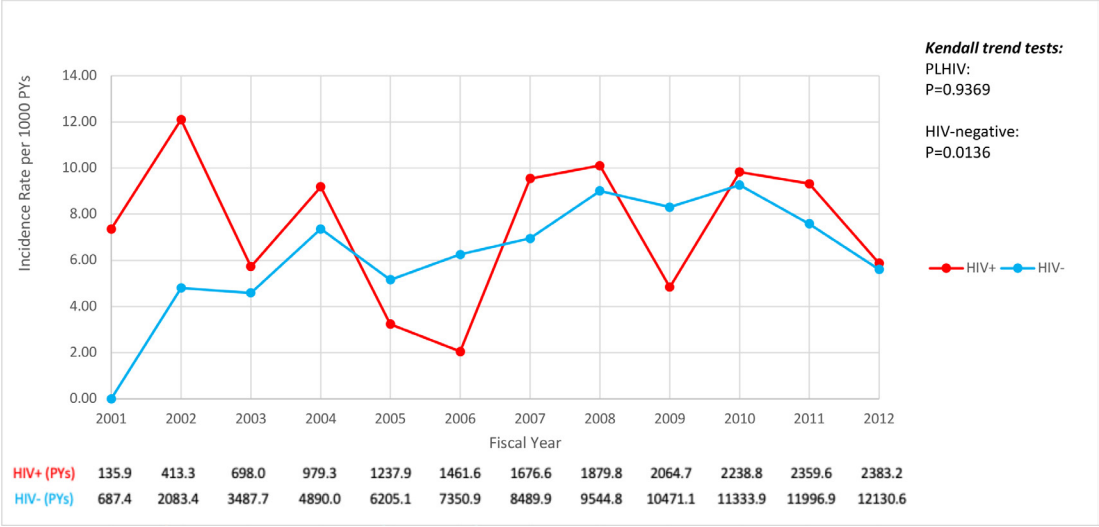

Figure 2 Annual trends in unadjusted incidence rates of diabetes mellitus in British Columbia, Canada, during 2001–2012 (by fiscal year). Note: fiscal years in this study start from 1 April to 31 March. For example, the year 2001 in the figure refers to the year between 1 April 2001 and 31 March 2002; and year 2012 refers to 1 April 2012–31 March 2013.
Abbreviations: PYs, person years; PLHIV, people living with HIV.

increased the number of excluded participants with DM in our study, we considered a longer run-in period to be a strength given the fact that our sample size was relatively large. There are also other limitations that need to be considered. First, our analyses use administrative data, which were not originally collected for research purposes. We were, therefore, reliant on the accuracy of billing and prescription data, which can include coding errors, and may increase the risk for information bias. Nonetheless, we selected case definitions published by the BC-MoH, which was specifically designed for research use in BC to identify DM cases. However, the inability of a BC-MoH-published case definition to distinguish type 1 and type 2 DM rendered us unable to focus type 2 DM; type 2 DM is typically of greatest interest. Given that 90%–95% of all diabetes cases in BC are type 2,[62] and that the incidence of type 1 DM after the age of 19 is very low,[63] we are confident that, overall, the trade-off between using a valid but unspecific DM case definition is acceptable. Another limitation of our study is that the COAST datasets have a limited repertoire of variables that may be relevant to DM research. For example, we did not have access to information on important traditional DM risk factors such as BMI, blood lipid profile, family history of DM, or behavioural risk factors for DM (eg, smoking, alcohol consumption, lack of exercise). Additionally, while hepatitis C infection is a known risk factor for DM,[64] we only had information on this variable among PLHIV. Therefore, we could not include it in our regression models. We tried to mitigate this by including history of IDU as a confounder, which is highly associated with hepatitis C infection, which is why history of IDU was included as a confounder in our models, even though there is little evidence that history of IDU itself is a risk factor for incident DM. An additional limitation regarding the variables included in the main model is relevant to the data available for time of ART initiation. Seeing that the observation period was only up to 2013, we were unable to include data relevant to more recent ART regimes such as integrase strand transfer inhibitors, which were associated with the development of DM,[65] or DM-related risk factors such as increases in body mass index.[66]

CONCLUSIONS

Our study described and compared the incidence of DM among PLHIV and age-sex-matched HIV-negative samples from a large population-based cohort in BC between 2001 and 2013. While we hypothesised was that PLHIV would experience a higher incidence of DM when compared with individuals without HIV, in a setting where HIV care is widely accessible, we found no differences in incidence of DM between the two groups. This result supports the growing evidence that HIV seropositivity is not significantly associated with incidence of DM. While the annual incidence of DM between 2001 and 2013 significantly increased among the individuals without HIV, it did not increase among PLHIV. A variety of factors could explain these findings, including the fact that the PLHIV in our sample were likely exposed to ART regimens with relatively low DM risks,[47 48] as well as other biochemical and pathophysiological mechanisms that warrant further exploration.[53–55] Our findings highlight the importance of early and consistent monitoring and management of individual DM risk factors among PLHIV. Further studies should investigate the impact of ART on the risk of developing DM among PLHIV when compared with individuals without HIV.

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Contributors AB designed the study, guided the research process, and developed the draft of the manuscript, under the supervision of RH. TM, KK, KS and NGAN provided epidemiological expertise, and contributed towards strengthening the study design and manuscript development. SG provided clinical expertise and contributed towards the research design. JL and JT were responsible for the data extraction and management, and MY conducted all the statistical analyses. PS and VL provided further support and supervision regarding the data selection, management, and analysis. All authors reviewed and contributed towards the development of the final manuscript.

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Ethics approval The COAST study has received approval from the University of British Columbia/Providence Health Care Research Ethics Board (#H09-02905) and Simon Fraser University Office of Research Ethics (#2013 s0566).The study complies with the BC Freedom of Information and Protection of Privacy Act (FIPPA) and did not require informed consent as it is conducted retrospectively for research and statistical purposes only using anonymized data.

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Data availability statement Data may be obtained from a third party and are not publicly available. The British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) is prohibited from making this dataset available publicly due to prohibitions in the information sharing agreement under which the data stewards provided the data to the BC-CfE. The underlying analytical codes are available from the authors on request.

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REFERENCES

1 Samji H, Cescon A, Hogg RS, *et al*. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013;8:e81355.
2 Gueler A, Moser A, Calmy A, *et al*. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. *AIDS* 2017;31:427–36.
3 Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. *Curr Opin HIV AIDS* 2016;11:492–500.
4 INSIGHT START Study Group, Lundgren JD, Babiker AG, *et al*. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373:795–807.
5 Wing EJ. Hiv and aging. *Int J Infect Dis* 2016;53:61–8.
6 Lima VD, Eyawo O, Ma H, *et al*. The impact of scaling-up combination antiretroviral therapy on patterns of mortality among HIV-positive persons in British Columbia, Canada. *J Int AIDS Soc* 2015;18:20261.
7 Eyawo O, Franco-Villalobos C, Hull MW, *et al*. Changes in mortality rates and causes of death in a population-based cohort of persons living with and without HIV from 1996 to 2012. *BMC Infect Dis* 2017;17:174.
8 Croxford S, Kitching A, Desai S, *et al*. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health* 2017;2:e35–46.
9 The Antiretroviral Therapy Cohort Collaboration. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. *Int J Epidemiol* 2009;38:1624–33.
10 Rodriguez-Penney AT, Iudicello JE, Riggs PK, *et al*. Co-Morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. *AIDS Patient Care STDS* 2013;27:5–16.
11 Vance DE, Mugavero M, Willig J, *et al*. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care* 2011;22:17–25.
12 Langebeek N, Kooij KW, Wit FW, *et al*. Impact of comorbidity and ageing on health-related quality of life in HIV-positive and HIV-negative individuals. *AIDS* 2017;31:1471–81.
13 Smith CJ, Ryom L, Weber R, *et al*. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet* 2014;384:241–8.
14 World Health Organization. Noncommunicable diseases: key facts, 2018. Available: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
15 Kruk ME, Nigenda G, Knaul FM. Redesigning primary care to tackle the global epidemic of noncommunicable disease. *Am J Public Health* 2015;105:431–7.
16 Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR. The global economic burden of noncommunicable diseases. Geneva World Economic Forum; 2011.
17 World Health Organization. Global status report on noncommunicable diseases 2010: description of the global burden of NCDs, their risk factors and determinants: Chapter 2: NCDs and development, 2018. Available: https://www.who.int/nmh/publications/ncd_report2010/en/
18 Public Health Agency of Canada. Diabetes in Canada: facts and figures from a public health perspective, 2012. Available: https://www.diabetes.ca/media-room/press-releases/one-in-three-canadians-is-living-with-diabetes-or-prediabetes,-yet-knowledge-of-risk-and-complicatio
19 Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4–14.
20 International Diabetes Federation. IDF diabetes atlas, 9th edn, 2019. Available: https://www.diabetesatlas.org/en/resources/
21 Diabetes Canada. Diabetes in Canada, 2019. Available: https://www.diabetes.ca/DiabetesCanadaWebsite/media/About-Diabetes/Diabetes%20Charter/2019-Backgrounder-Canada.pdf
22 Hernandez-Romieu AC, Garg S, Rosenberg ES, *et al*. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. *BMJ Open Diab Res Care* 2017;5:e000304.
23 Brown TT. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the Multicenter AIDS cohort study. *Arch Intern Med* 2005;165:1179.
24 Samad F, Harris M, Puskas CM, *et al*. Incidence of diabetes mellitus and factors associated with its development in HIV-positive patients over the age of 50. *BMJ Open Diabetes Res Care* 2017;5:e000457.
25 Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr* 2009;50:499–505.
26 Capeau J, Bouteloup V, Katlama C, *et al*. Ten-Year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment. *AIDS* 2012;26:303–14.
27 Galli L, Salpietro S, Pellicciotta G, *et al*. Risk of type 2 diabetes among HIV-infected and healthy subjects in Italy. *Eur J Epidemiol* 2012;27:657–65.
28 Ledergerber B, Furrer H, Rickenbach M, *et al*. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV cohort study. *Clin Infect Dis* 2007;45:111–9.
29 Brar I, Shuter J, Thomas A, *et al*. A comparison of factors associated with prevalent diabetes mellitus among HIV-infected antiretroviral-naive individuals versus individuals in the National health and

nutritional examination survey cohort. *J Acquir Immune Defic Syndr* 2007;45:66–71.
30 Tien PC, Schneider MF, Cole SR, *et al*. Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study. *AIDS* 2007;21:1739–45.
31 Butt AA, McGinnis K, Rodriguez-Barradas MC, *et al*. HIV infection and the risk of diabetes mellitus. *AIDS* 2009;23:1227–34.
32 Tripathi A, Liese AD, Jerrell JM, *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. *Diabet Med* 2014;31:1185–93.
33 Eyawo O, Hull MW, Salters K, *et al*. Cohort profile: the comparative outcomes and service utilization trends (coast) study among people living with and without HIV in British Columbia, Canada. *BMJ Open* 2018;8:e019115.
34 Drug Treatment Program. BC centre for excellence, HIVAIDS, 2010. Available: http://bccfe.ca/drug-treatment-program
35 Canadian Institute for Health Information (2014). Discharge Abstract Database (Hospital Separations). Population Data BC. Data Extract. MOH (2014). Available: http://www.popdata.bc.ca/data
36 British Columbia Ministry of Health (2014a) British Columbia Ministry of Health (2014b). Medical Services Plan (MSP) Payment Information File: Population Data BC [publisher]. Data Extract. MOH (2011). Available: http://www.popdata.bc.ca/data
37 British Columbia Ministry of Health (2014). Consolidation File (MSP Registration & Premium Billing). Population Data BC. Data Extract. MOH (2014). Available: http://www.popdata.bc.ca/data
38 British Columbia Ministry of Health (2014). PharmaNet. Population Data BC. Data Extract. Data Stewardship Committee (2014). Available: http://www.popdata.bc.ca/data
39 British Columbia Vital Statistics Agency (2014). Vital Statistics Deaths. Population Data BC. Data Extract. Vital Statistics Agency (2014). Available: http://www.popdata.bc.ca
40 Population Data BC. About PopData [Internet]. Population Data BC. 2017 [cited 2019 Sep 27]. Available from. Available: https://www.popdata.bc.ca/aboutus
41 BC Ministry of Health Chronic Disease Information Working Group. Bc chronic disease and selected procedure case definitions, 2015. Available: https://www2.gov.bc.ca/assets/gov/health/conducting-health-research/data-access/chronic-disease-registries-case-definitions.pdf [Accessed 30 Jun 2020].
42 Janjua NZ, Islam N, Kuo M, *et al*. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy* 2018;55:31–9.
43 Lima VD, Geller J, Bangsberg DR, *et al*. The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 2007;21:1175–83.
44 Public Health Agency of Canada (PHAC). Hiv in Canada—Surveillance report, 2017, 2018. Available: https://www.canada.ca/content/dam/phac-aspc/documents/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-12-december-6-2018/ccdrv44i12a03-eng.pdf
45 Ley SH, Hamdy O, Mohan V, *et al*. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *The Lancet* 2014;383:1999–2007.
46 Kalra S, Agrawal N. Diabetes and HIV: current understanding and future perspectives. *Curr Diab Rep* 2013;13:419–27.
47 Gelpi M, Afzal S, Fuchs A, *et al*. Prior exposure to thymidine analogs and didanosine is associated with long-lasting alterations in adipose tissue distribution and cardiovascular risk factors. *AIDS* 2019;33:675–83.
48 Capel E, Auclair M, Caron-Debarle M, *et al*. Effects of ritonavir-boosted darunavir, atazanavir and lopinavir on adipose functions and insulin sensitivity in murine and human adipocytes. *Antivir Ther* 2011;17:549–56.
49 Nduka CU, Uthman OA, Kimani PK, *et al*. Body fat changes in people living with HIV on antiretroviral therapy. *AIDS Rev* 2016;18:198–211.
50 Ganz ML, Wintfeld N, Li Q, *et al*. The association of body mass index with the risk of type 2 diabetes: a case–control study nested in an electronic health records system in the United States. *Diabetol Metab Syndr* 2014;6:50.
51 Rasmussen LD, Mathiesen ER, Kronborg G, *et al*. Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study. *PLoS One* 2012;7:e44575.
52 De Wit S, Sabin CA, Weber R, *et al*. Incidence and Risk Factors for New-Onset Diabetes in HIV-Infected Patients: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. *Diabetes Care* 2008;31:1224–9.
53 Kendall CE, Wong J, Taljaard M, *et al*. A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. *BMC Public Health* 2014;14:161.
54 Petoumenos K, Huang R, Hoy J, *et al*. Prevalence of self-reported comorbidities in HIV positive and HIV negative men who have sex with men over 55 years-The Australian Positive & Peers Longevity Evaluation Study (APPLES). *PLoS One* 2017;12:e0184583.
55 Goulet JL, Fultz SL, Rimland D, *et al*. Do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clinical Infectious Diseases* 2007;45:1593–601.
56 Guaraldi G, Orlando G, Zona S, *et al*. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.
57 Public Health Agency of Canada. Population specific HIV/AIDS status report: people living with HIV/AIDS, 2013. Available: https://www.catie.ca/sites/default/files/SR-People-Living-with-HIV.pdf
58 Hogg RS, Strathdee SA, Craib KJP, *et al*. Lower socioeconomic status and shorter survival following HIV infection. *The Lancet* 1994;344:1120–4.
59 Razera F, Ferreira J, Bonamigo RR. Factors associated with health-related quality-of-life in HIV-infected Brazilians. *Int J STD AIDS* 2008;19:519–23.
60 Tran BX, Hwang J, Nguyen LH, *et al*. Impact of socioeconomic inequality on access, adherence, and outcomes of antiretroviral treatment services for people living with HIV/AIDS in Vietnam. *PLoS One* 2016;11:e0168687.
61 Walker RJ, Smalls BL, Campbell JA, *et al*. Impact of social determinants of health on outcomes for type 2 diabetes: a systematic review. *Endocrine* 2014;47:29–48.
62 Diabetes Canada. One in three Canadians is living with diabetes or prediabetes, yet knowledge of risk and complications of disease remains low, 2019. Available: https://www.diabetes.ca/media-room/press-releases/one-in-three-canadians-is-living-with-diabetes-or-prediabetes,-yet-knowledge-of-risk-and-complications
63 Diaz-Valencia PA, Bougnères P, Valleron A-J. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC Public Health* 2015;15:255.
64 Gastaldi G, Goossens N, Clément S, *et al*. Current level of evidence on causal association between hepatitis C virus and type 2 diabetes: a review. *J Adv Res* 2017;8:149–59.
65 AIDSmap. Do integrase inhibitors increase the risk of diabetes? 2019. Available: https://www.aidsmap.com/news/oct-2019/do-integrase-inhibitors-increase-risk-diabetes
66 Bedimo R, Adams-Huet B, Xilong L. Integrase Inhibitors-based HAART is associated with greater BMI gains in blacks and Hispanics, 2018. Available: https://idsa.confex.com/idsa/2018/webprogram/Paper71208.html