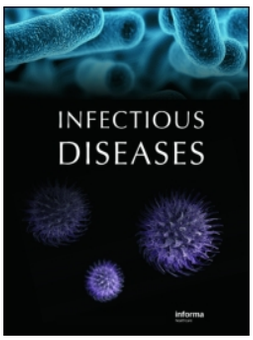

Infectious Diseases

ISSN: 2374-4235 (Print) 2374-4243 (Online) Journal homepage: http://www.tandfonline.com/loi/infd20

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To cite this article: Line D. Rasmussen, Gitte Kronborg, Carsten S. Larsen, Court Pedersen, Jan Gerstoft, Niels Obel & Anton Pottegård (2017) Use of non-antiretroviral drugs among individuals with and without HIV-infection: a Danish nationwide study, Infectious Diseases, 49:1, 42-54, DOI: 10.1080/23744235.2016.1212168

To link to this article: http://dx.doi.org/10.1080/23744235.2016.1212168

Published online: 11 Aug 2016.

INFECTIOUS DISEASES, 2017
VOL. 49, NO. 1, 42–54
http://dx.doi.org/10.1080/23744235.2016.1212168

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ORIGINAL ARTICLE

Use of non-antiretroviral drugs among individuals with and without HIV-infection: a Danish nationwide study

Line D. Rasmussen[a], Gitte Kronborg[b], Carsten S. Larsen[c], Court Pedersen[a], Jan Gerstoft[d], Niels Obel[d] and Anton Pottegård[e]

[a]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark; [b]Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark; [c]Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark; [d]Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [e]Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark

ABSTRACT

Aim: We investigated the use of non-antiretroviral drugs in the HIV-infected compared to the general population.

Methods: From the Danish HIV Cohort Study, we identified all HIV-infected individuals older than 18 years at HIV diagnosis who received care in Denmark through 1995–2013 and reported no injection drug abuse or hepatitis C infection. Population controls were identified from The Danish Civil Registration System and matched on age and gender (5:1). We analyzed the proportion of individuals who redeemed 0–1, 2–4, 5–9, or 10 or more non-antiretroviral drugs. Data were analyzed according to calendar time, age, time from initiation of combination antiretroviral therapy (cART) and stratified by gender, geographical origin and route of HIV transmission. We further analyzed the use of the 25 most used non-antiretroviral drug classes.

Results: We identified 4,928 HIV-infected individuals (median age: 37; 76.4% males). Overall, the HIV-infected population had a higher use of non-antiretroviral drugs compared to the background population. Whereas, the use of non-antiretroviral drugs in the HIV-infected population only changed marginally with time, the use in the background population increased considerably. Thus, use in the HIV-infected population only differed marginally from that of the background population in recent years. This difference was most pronounced in men who have sex with men (MSM).

Conclusion: Compared to the background population, HIV infected individuals have increased use of non-antiretroviral drugs. The excess use is mainly observed in MSM and has decreased with calendar time, why it in recent years only differs marginally from that observed in the background population.

ARTICLE HISTORY
Received 14 April 2016
Revised 8 June 2016
Accepted 28 June 2016
Published online 9 August 2016

KEYWORDS
HIV; HAART; polypharmacy; age-related diseases; multi-morbidity

Introduction

As a consequence of the introduction of combination antiretroviral therapy (cART) the mortality of HIV-infected patients has decreased markedly, thus increasing the prevalence of older HIV-infected individuals.[1–3] Although, the HIV-associated morbidity has been markedly reduced, HIV-infected individuals still have a higher risk of a number of age-related diseases compared to the general population,[3] and a higher risk of multi-morbidity has furthermore been suggested.[2,4–6] Accordingly, the prevalence of age-related conditions will increase over the coming years and clinicians will face new challenges and problems including complex drug management and risks associated with polypharmacy.[7]

Polypharmacy has been associated with risk of adverse drug reactions, medication errors and poor compliance independent of HIV status.[8–11] Clearly, the complexity and the pill burden associated with antiretroviral therapy has been reduced over the last 15 years;[12] still, the majority of the HIV-infected population is on cART regimens including at least three drugs. The need for additional therapy for age related co-morbidity has led to increased use of non-antiretroviral drugs.[12] Whereas 95% of the total pill burden consisted of antiretroviral drugs in 1990, a recent study showed that this proportion has declined to 51% in 2010.[12] As a result, it was stated that 'the benefit from simplifying cART may be overstated by addition of these concurrent therapies' thus enhancing the potential for drug interactions and loss of adherence.[12]

Clearly the need for cART does increase the total number of drugs; however, it is unclear whether the concurrent use of non-antiretroviral drugs is significantly more prevalent than that of the general population.

We performed a nationwide cohort study to investigate the use of non-antiretroviral drugs in the HIV infected population compared to that of the general population.

CONTACT Line Dahlerup Rasmussen, MD, PhD linedahlerup@hotmail.com Department of Infectious Diseases, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark

Methods

Setting

As of 1 January 2014, Denmark had a population of 5.5 million, with an estimated HIV prevalence of 0.1% among adults.[13,14] Treatment of HIV infection is restricted to eight specialized centres where patients are seen on an outpatient basis at intervals of 12–24 weeks. Danish health care is universal and tax funded, and antiretroviral treatment is provided free of charge. cART is prescribed according to national guidelines.[15]

Data sources

We used data from three nationwide data sources: The Danish HIV Cohort Study (DHCS),[16] The Danish National Prescription Registry [17] and The Danish Civil Registration System.[18]

DHCS, which has been described in detail elsewhere,[16] is a nationwide, prospective, population-based cohort study of all Danish HIV-infected individuals treated at Danish hospitals since 1 January 1995. DHCS consecutively enrols patients newly diagnosed with HIV and immigrants with HIV infection diagnosed prior to immigration.

The Prescription registry records individual-level data on all prescriptions dispensed at Danish community pharmacies since 1 January 1995.[17] The registry includes variables related to the drug, user, prescriber and pharmacy. The Anatomical Therapeutic Chemical Classification (ATC) code are established through a linkage to the World Health Organization's (WHO) Collaboration Centre for Drug Statistics Methodology.[19]

Data were linked using the unique 10-digit personal identification number [18] assigned to all individuals in Denmark at birth or upon immigration.

Study population

HIV cohort

From DHCS, we identified all HIV-infected individuals older than 18 years at HIV diagnosis. Individuals reporting injection drug abuse (IDU) and/or hepatitis C infection (HCV) were excluded. We included individuals at 1 January in the calendar year following date of HIV diagnosis or 1 January 1995, whichever was more recent. Individuals observed less than one calendar year were excluded.

General population comparison cohort

The comparison cohort consisted of five age and gender-matched population controls for each HIV-infected individual identified from DCRS. The population controls were matched 1 January at every calendar year in order to ensure complete matching throughout the calendar years. Criteria for inclusion and exclusion were the same as for the HIV-infected population. The date of inclusion of the comparison cohort members was the same as for the corresponding matched HIV-infected individual.

Outcome

We analyzed all prescriptions of non-antiretroviral drugs redeemed in Danish pharmacies. As some systemic anti-infectious drugs (~ATC group J and P) are provided free of charge from the HIV-clinics and are often only used for shorter periods, prescriptions for these drugs were disregarded in the analyses. Non-antiretroviral drugs were defined according to the fifth ATC level, i.e. single drug substances (Appendix A). Use of a drug was defined as having filled at least two prescriptions of a certain drug within a calendar year.

Statistical analysis

Use of non-antiretroviral drugs with increasing calendar time, age and time on cART

We analysed the proportion of individuals (HIV and controls) who had redeemed 0–1, 2–4, 5–9, or 10 or more non-antiretroviral drugs according to (a) calendar time, (b) age and (c) time after initiation of cART, and the difference in proportions (HIV vs controls) and 95% confidence interval (CI).

For all analyses, only individuals alive and living in Denmark by the end of the year (1995–2013) were included in the analysis.

We further stratified the analyses according to Danish/non-Danish origin, females, men who have sex with men (MSM) and heterosexual men. Additionally, we performed sensitivity analyses in which we (1) defined use of a drug as filling at least one prescription and (2) excluded psychotropic drugs (ATC: N05-6).

The absolute and relative use of non-antiretroviral drugs during 1995–2013

To identify the most used non-antiretroviral drugs for the HIV-infected population and the matched comparison cohort, we estimated the absolute use of non-antiretroviral drugs (defined by the annual prevalence) for the years 1995, 2004 and 2013. Further, the relative drug use was estimated by standardized prevalence ratios (SPR), i.e. the ratio between the prevalence proportion in the HIV-infected population and the controls, standardized by age, gender, and calendar year. In these analyses, the estimated drugs were aggregated at the third ATC-level (i.e. pharmacological subgroup, Appendix A). We performed additional subanalyses for drugs affecting the nervous system (ATC-level N) and the cardiovascular system (ATC-level C). Furthermore, the abovementioned analyses were stratified according to the age above or below 50 years.

Data were analyzed by means of descriptive statistical measures. STATA software, version 13 (StataCorp, College Station, TX) was used for data analysis.

Ethical approval

Data from DNHR, DNRCD and DCRS were obtained with approval from The Danish National Board of Health. The study was approved by the Danish Data Protection Agency

(journal no 2008-41-1781). Ethics approval and individual consent are not required by Danish legislation governing this type of research.

Results

The 6308 HIV-infected individuals older than 18 years and living in Denmark were identified from DHCS, of whom 1017 (16.1%) were excluded due to IDU+/-HCV and 363 (6.9%) were excluded due to follow-up less than a full calendar year. In total, 4928 HIV-infected individuals with a median age of 37 (interquartile range (IQR): 30–45) and 76.4% males were included in the analyses (Table 1). The control cohort consisted of an age and gender matched (1:5) population control cohort. As controls were matched for each calendar year, the number of individuals (HIV vs controls), the proportion of men and the median age for each calendar year are provided along with additional characteristics of the population in Table 1 and Appendix B Table B1. During 1995–2013 the proportion of men changed from 81.8% to 74.0% and the median age changed from 37 years (IQR: 31–45) to 48 years (IQR: 40–56) (Appendix B Table B1).

In the early calendar years, the proportion of HIV-infected individuals who used non-antiretroviral drugs was substantially higher than in the background population, but this effect was reduced considerably with calendar time (Figure 1). In 1995, 28.5% of the HIV-population compared to 12.3% of the background population used two or more non-antiretroviral drugs (absolute difference 16.2%; 95% CI 13.8–18.6). In 2013, these numbers were 32.7% and 28.2%, respectively (absolute difference 4.5%; 95% CI: 2.8–6.1)]. Similar calendar effects were observed for the proportion of individuals using five or more non-antiretroviral drugs. The increased use of non-antiretroviral drugs with calendar time and time since initiation of cART was mainly observed in MSM (Figure 1(b)–(f)).

Use of non-antiretroviral drugs during 1995–2013 is shown in age strata in Figure 2. With calendar time, the use of non-antiretroviral drugs in the HIV-infected population approached that observed in the population controls (Figure 2). This effect was mainly due to an increased drug-use with calendar time in the population controls while the use in the HIV-infected population only varied marginally.

The proportion of HIV infected individuals who used two or more non-antiretroviral drugs increased slightly with time after initiation of cART, but the difference in proportions (HIV vs controls) remained stable (Figure 3(a)). The increased use of non-antiretroviral drugs with calendar time and time since initiation of cART was mainly observed in MSM (Figure 3(b)–(f)).

We still observed a considerable difference in the use of non-antiretroviral drugs, when we excluded psychotropic drugs from the analyses (Appendix C, Figures C1,C2). In sensitivity analyses, in which we defined the use of a drug as one or more redemption, no large difference in the overall results was observed (results not shown).

In Table 2, the use of the 25 most commonly used non-antiretroviral drugs in 2013 are reported for the calendar years 1995, 2004 and 2013. During this period, the use of many drug groups increased considerably, but compared to the comparison cohorts the relative use of most of the drug groups reached levels similar to that of the general population (Table 2 and Appendix D, Tables D1,D2). Concerning drugs affecting the nervous system, the absolute use of opioids has been stable over the years, but the relative prevalence has decreased from a fivefold increased use (SPR: 5.22; 95% CI: 4.22–6.40) to a level almost similar to that of the general population (SPR: 1.13; 95% CI: 0.97–1.30). A similar trend was found for other analgesics (paracetamol) (Table 2 and Appendix D, Table D3). Although the relative use of anxiolytics, hypnotics and sedatives, antidepressants and antiepileptics decreased in the same period, HIV-infected individuals still had a higher use of many of these drugs in year 2013 compared to the general population (Table 2 and Appendix D, Table D3).

Although, the absolute use of drugs affecting the cardiovascular system has increased over the years, the relative use of most of these drugs (not beta blockers) did not increase with time (Appendix D, Table D4).

Table 1. Baseline characteristics of the HIV-infected population.

	HIV-infected individuals ($N = 4,928$)
Male, *N* (%)	3767 (76.4)
Age, median (IQR)	37 (30–45)
Danish born, *N* (%)	3326 (67.6)
Mode of transmission	
Heterosexuals, *N* (%)	2050 (41.7)
MSM, *N* (%)	2524 (51.3)
IDU, *N* (%)	0
Other, *N* (%)	354 (7.2)
HCV, *N* (%)	0
HIV before 1995, *N* (%)	1344 (27.3)
AIDS before inclusion, *N* (%)	182 (3.7)
CD4 cell count, median (IQR)*	308 (130–500)
VL >400 copies/mL, *N* (%)*	581 (12.2)
On HAART before inclusion, *N* (%)	52 (1.1)
PYR, *N* (%)	52,118

IQR: interquartile range; MSM: men who have sex with men; IDU: injection drug abuse; HCV: Hepatitis C virus; PYR: person-years of follow-up.
*Baseline CD4 cell count: Missing in 159, Baseline VL missing in 28.

Discussion

We found that the use of non-antiretroviral drugs was only slightly higher among HIV-infected individuals with no IDU or HCV compared to the general population. The differences were mainly carried by a higher use of drugs among HIV-infected individuals reporting MSM as route of infection and could not exclusively be ascribed to a higher use of psychotropic drugs. Whereas the mid-nineties was marked by a larger use of non-antiretroviral drugs by the young HIV-infected population compared to the young controls, the relative excess use of non-antiretroviral drugs among the HIV-infected individuals has declined over the calendar years for all age groups.

In a recent study by Greene et al,[20] 74% of HIV-infected individuals were taking five or more non-antiretroviral drugs

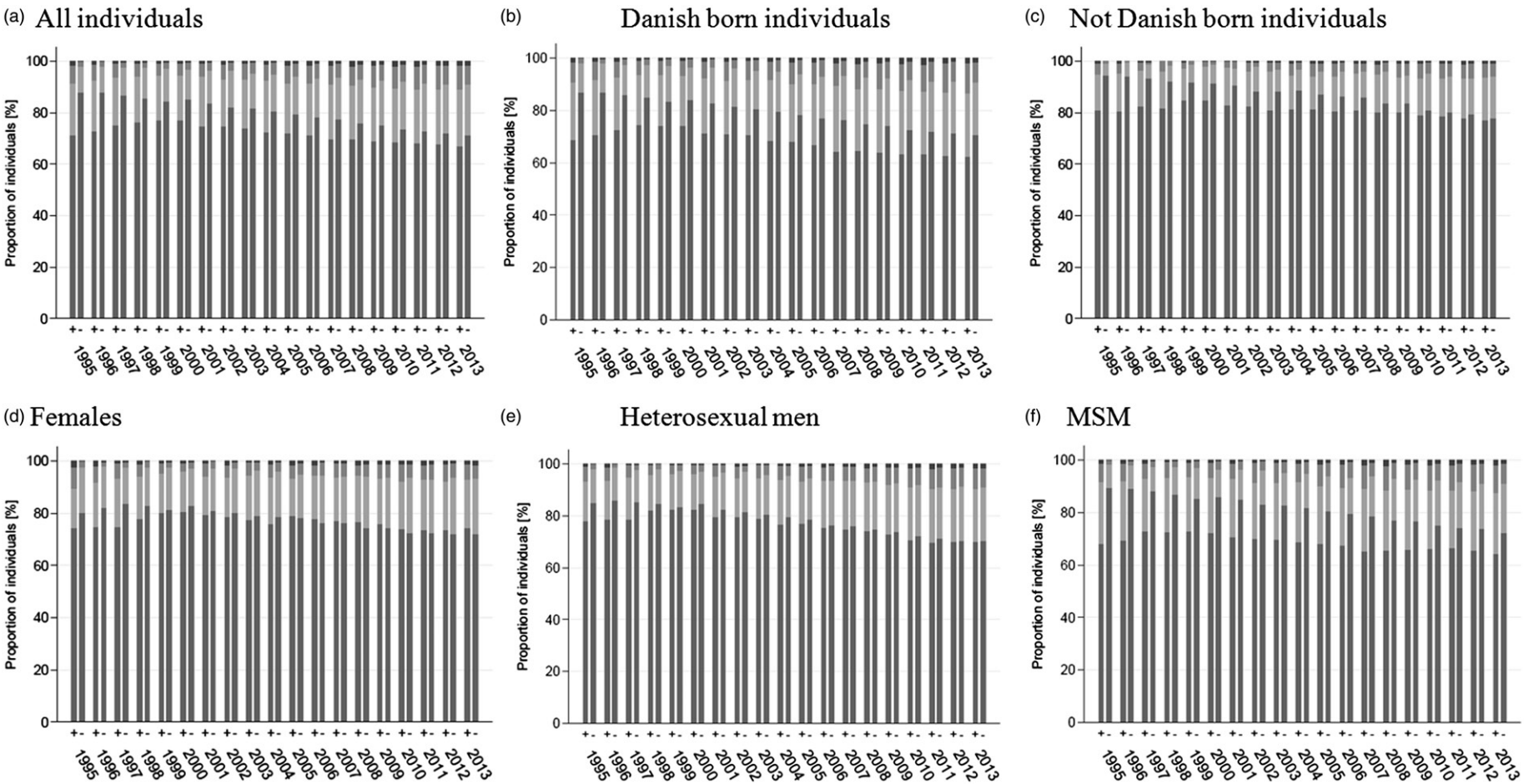

Figure 1. Use of non-antiretroviral drugs in HIV-infected individuals and controls from the background population (1995–2013). (a) The proportion of HIV-infected individuals (+) and age and gender-matched controls from the background population (−) who have redeemed 0–1 (very dark grey), 2–4 (light grey), 5–9 (darker grey), or 10 or more (black) non-antiretroviral drugs according to calendar years. (b–f) illustrate subanalyses: only for Danish-born individuals, not Danish-born individuals, females, heterosexual men and MSM.

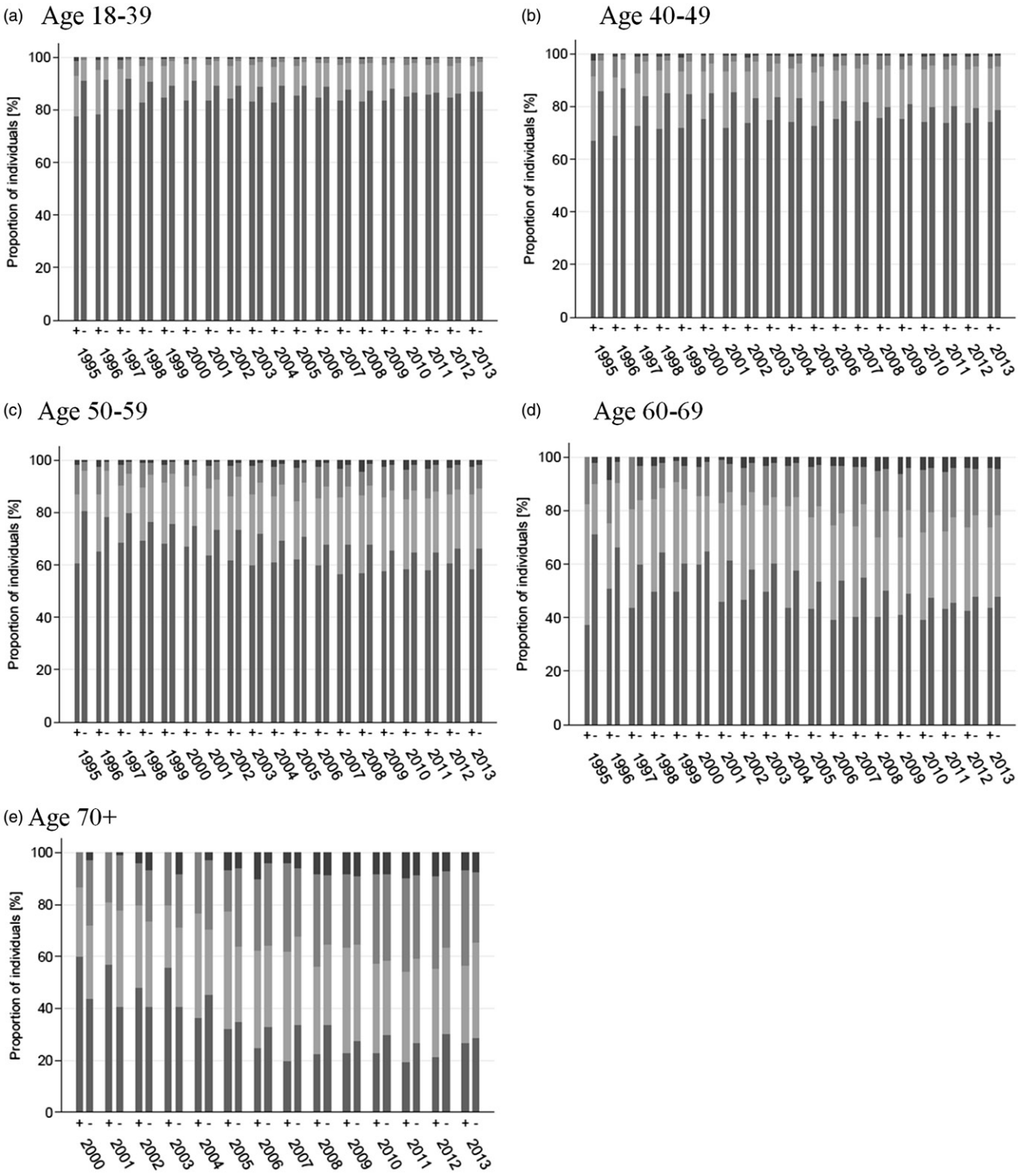

Figure 2. Use of non-antiretroviral drugs with age in individuals with and without HIV infection (1995–2013). The proportion of HIV-infected individuals (+) and age and gender matched controls (−) who have redeemed 0–1 (very dark grey), 2–4 (light grey), 5–9 (darker grey), or 10 or more (black) non-antiretroviral drugs according to calendar years by age groups [(a)18–39, (b) 40–49, (c) 50–59, (d) 60–69, (e) 70+ years]. Due to low numbers of individuals with an age above 70 years in year 1995–1999, proportions could not be accounted for in these years.

and 48% where taking nine or more non-antiretroviral drugs. In contrast, the annual prevalence of non-antiretroviral drug-use detected in our study was much lower. This difference may to some extent rely on differences in the population under observation (e.g. age, gender and socio-economic status). Furthermore, only drugs registered in the prescription database were included in our study. Nevertheless, our study was a large longitudinal study, based on data from a highly valid national prescription database and furthermore included a control population with no HIV infection, whereas the study by Greene et al. [20] was a small cross-sectional study, based on retrospective chart review.

Our data illustrated that, in spite of a higher prevalence of age-related diseases among HIV-infected individuals

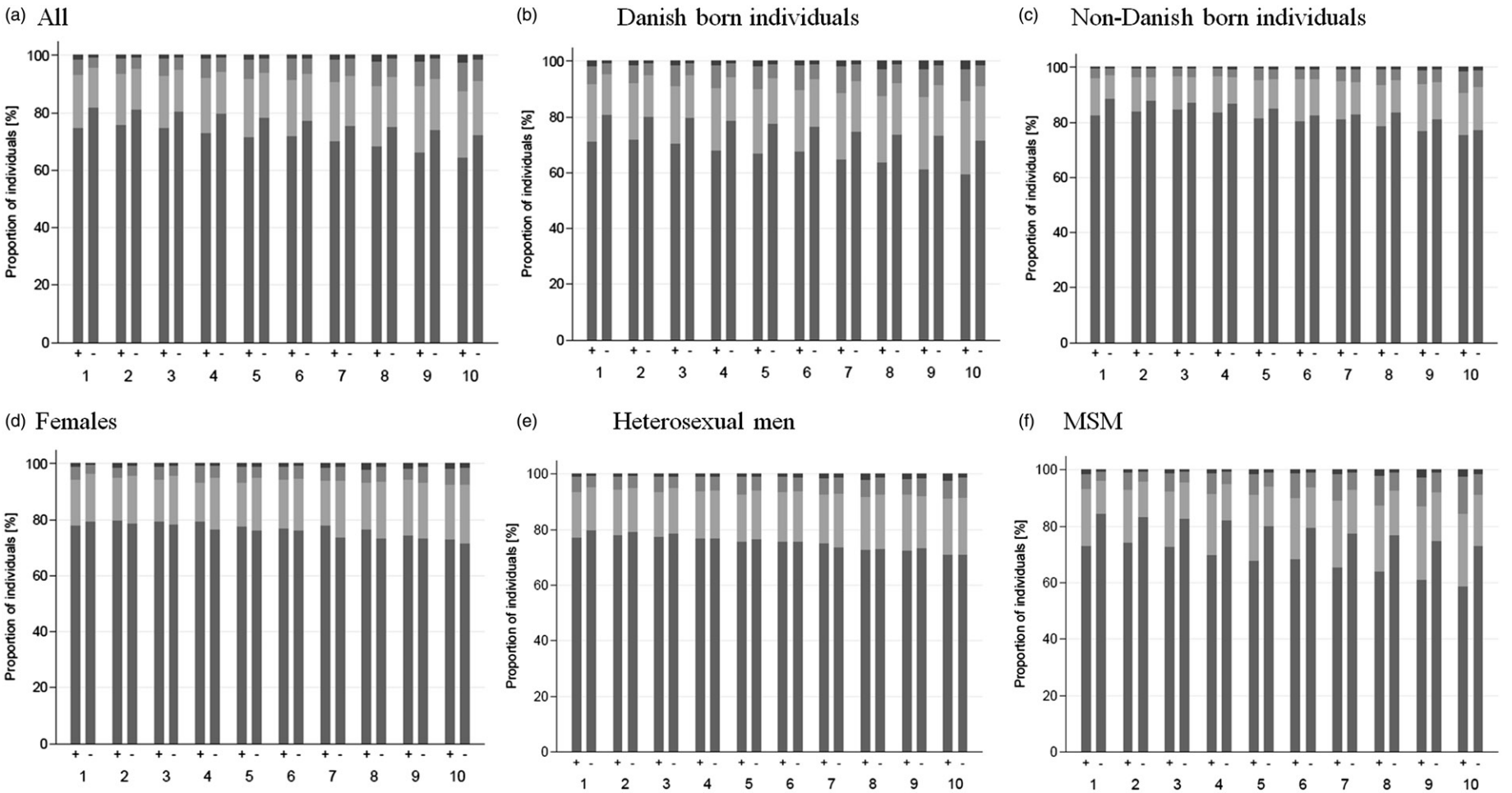

Figure 3. Use of non-antiretroviral drugs with time on cART in individuals with and without HIV infection in the same time period (year 1–10 after initiation of cART). (a) The proportion of HIV-infected individuals (+) and age and gender matched controls from the background population (−) who have redeemed 0–1 (very dark grey), 2–4 (light grey), 5–9 (darker grey), or 10 or more (black) non-antiretroviral drugs to time on cART (1–10 years). (b–f) illustrate subanalyses: only Danish-born individuals, not Danish-born individuals, females, heterosexual men and MSM.

Table 2. The absolute and relative use of non-antiretroviral drugs for HIV-infected individual (1995–2013).

		1995		2004		2013	
ATC codes	Common drug name	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)
A02B	Anti-ulcer drugs	3.9% ($n = 60$)	1.99 (1.52––2.56)	5.1% ($n = 140$)	1.67 (1.41–1.97)	6.6% ($n = 253$)	1.11 (0.98–1.26)
A10B	Blood glucose-lowering drugs, excl. insulins	$n < 10$	NA	1.2% ($n = 34$)	0.87 (0.60–1.21)	2.8% ($n = 108$)	0.78 (0.64–0.94)
B01A	Antithrombotic agents	$n < 10$	NA	4.7% ($n = 128$)	1.25 (1.04–1.48)	8.8% ($n = 337$)	1.28 (1.15–1.42)
C03A	Thiazides	$n < 10$	NA	2.1% ($n = 58$)	0.97 (0.74–1.25)	2.4% ($n = 91$)	0.81 (0.65–1.00)
C03C	High-ceiling diuretics	$n < 10$	NA	0.9% ($n = 24$)	1.17 (0.75–1.73)	1.7% ($n = 65$)	1.25 (0.96–1.59)
C07A	Beta blockers	1.2% ($n = 19$)	1.20 (0.72––1.88)	3.6% ($n = 100$)	1.11 (0.90–1.35)	5.5% ($n = 210$)	1.03 (0.89–1.18)
C08C	Calcium-channel blockers	$n < 10$	NA	1.5% ($n = 42$)	0.74 (0.53–1.00)	4.9% ($n = 190$)	0.84 (0.72–0.97)
C09A	ACE inhibitors	$n < 10$	NA	3.2% ($n = 88$)	1.19 (0.96–1.47)	7.0% ($n = 270$)	1.33 (1.17–1.50)
C09C	Angiotensin II antagonists, plain	$n < 10$	NA	0.9% ($n = 26$)	0.71 (0.46–1.04)	2.0% ($n = 78$)	0.72 (0.57–0.90)
C09D	Angiotensin II antagonists, combinations	$n < 10$	NA	$n < 10$	NA	1.7% ($n = 65$)	0.75 (0.58–0.96)
C10A	Cholesterol-lowering drugs	$n < 10$	NA	4.5% ($n = 123$)	1.21(1.01–1.44)	12.1% ($n = 464$)	1.26 (1.15–1.38)
D01A	Topical antifungals	9.2% ($n = 141$)	8.92 (7.51–10.52)	2.9% ($n = 80$)	2.82 (2.23–3.51)	2.1% ($n = 81$)	2.17 (1.72–2.69)
D07A	Topical steroids	6.3% ($n = 97$)	3.46 (2.81–4.23)	2.8% ($n = 77$)	2.10 (1.66–2.63)	2.1% ($n = 79$)	1.34 (1.06–1.67)
G04B	Urologicals	$n < 10$	NA	4.5% ($n = 124$)	4.11 (3.42–4.90)	5.9% ($n = 226$)	2.79 (2.44–3.18)
M01A	NSAIDs	5.6% ($n = 85$)	1.59 (1.27–1.96)	5.9% ($n = 163$)	0.91 (0.77–1.06)	4.7% ($n = 179$)	0.78 (0.67–0.90)
N02A	Opioids	6.1% ($n = 93$)	5.22 (4.22–6.40)	4.1% ($n = 112$)	1.56 (1.28–1.87)	5.0% ($n = 193$)	1.13 (0.97–1.30)
N02B	Other analgesics (= Paracetamol)	3.7% ($n = 56$)	2.98 (2.25–3.87)	2.9% ($n = 80$)	1.65 (1.31–2.06)	3.7% ($n = 142$)	0.99 (0.84–1.17)
N03A	Antiepileptics	2.4% ($n = 37$)	2.31 (1.63–3.19)	2.5% ($n = 70$)	1.79 (1.40–2.27)	3.2% ($n = 124$)	1.24 (1.03–1.48)
N05A	Antipsychotics	2.2% ($n = 33$)	1.77 (1.22–2.49)	2.3% ($n = 63$)	1.49 (1.14–1.90)	3.2% ($n = 122$)	1.60 (1.33–1.91)
N05B	Anxiolytics	8.8% ($n = 135$)	3.25 (2.72–3.84)	4.7% ($n = 129$)	1.91 (1.60–2.27)	3.0% ($n = 114$)	1.94 (1.60–2.33)
N05C	Hypnotics	10.1% ($n = 154$)	5.66 (4.80–6.63)	7.8% ($n = 214$)	3.64 (3.17–4.16)	5.1% ($n = 198$)	2.41 (2.09–2.78)
N06A	Antidepressants	4.4% ($n = 67$)	2.77 (2.15–3.52)	8.4% ($n = 232$)	1.84 (1.61–2.09)	9.4% ($n = 363$)	1.39 (1.25–1.54)
R01A	Nasal decongestants	1.9% ($n = 29$)	1.37 (0.92–1.96)	1.7% ($n = 48$)	1.12 (0.82–1.48)	1.7% ($n = 66$)	0.78 (0.61–1.00)
R03A	Inhaled beta-agonists	2.2% ($n = 33$)	1.20 (0.82–1.68)	3.1% ($n = 85$)	1.37 (1.09–1.69)	3.5% ($n = 134$)	1.03 (0.86–1.22)
R03B	Inhaled anticholinergics and steroids	1.0% ($n = 16$)	0.75 (0.43–1.23)	1.2% ($n = 34$)	0.80 (0.55–1.12)	1.7% ($n = 65$)	0.93 (0.72–1.18)

ATC: anatomical therapeutic chemical classification (The drugs are aggregated at the third ATC-level); SPR: standardized prevalence ratio; 95% CI: 95% confidence interval; NA: not applicable.
The absolute (∼annual prevalence) and relative use (∼relative prevalence = SPR) for the 25 most commonly used non-HAART drugs in 2013.

compared to the background population,[2–6] the use of non-antiretroviral drugs, which to some extent could also act as a mean of multi-morbidity (including diseases only registered at a general practitioner), was only slightly higher for the HIV-infected population compared to background population.

As expected, we observed an age-associated increase in use of non-antiretroviral drugs; however, of importance the largest difference in proportion of individuals using two or more non-antiretroviral drugs was found in the mid-nineties, whereas these proportions has approached that of the background population during later years. This is in line with recent results from the DAD study [21] and from the Danish HIV Cohort Study [3] illustrating stable or decreasing trends in absolute and relative risk in many of the major age-related diseases and associated death over recent calendar years.

Naturally, and in line with other studies,[2,7,22] the use of co-medications increased among the HIV-infected individuals with older age. However, despite a large difference in non-antiretroviral drug-use between HIV-infected individuals and population controls in the early calendar years, this difference was almost negligible in recent time independent of age. As illustrated in Figure 2, this was a result of opposing trends in the two populations: a slightly reduced use in the HIV-infected population and an increased use in the background population over time.

The higher use of non-antiretroviral drugs observed in our study was mainly seen in MSM. In accordance with these results, a Canadian cohort study analyzed HIV-infected individuals in the Southern Alberta Cohort during 1990–2010 (population sizing from 365–1419 in the study period) and found a higher pill burden among MSM than heterosexuals. [12] Also the high utilization of antidepressants among HIV-infected individuals compared to the general population has previously been confined to MSM;[23] however, as in the present study, controls were not matched on sexuality. Whereas the association with antidepressants seems independent of HIV status,[24–26] there is to our knowledge no evidence of such association with polypharmacy. Generally, many factors associated with patient characteristics and the patient–physician relationship may affect the allocation of a patient to a certain therapy including ethnicity, abuse, compliance and health-seeking behaviour. We cannot distinguish whether the higher use in MSM was a surrogate marker for a higher medical attention, a higher compliance, or a more frail population.

We have previously shown that the use of psychotropic drugs is high among HIV-infected individuals, even in a population with no IDU, and that the utilization of anxiolytics, hypnotics and sedatives increases with older age.[23] However, the excess use of non-antiretroviral drugs in the present study could not be explained by the high utilization of psychotropic drugs.

Concerning the type of drugs used, we observed some changes over the years that to some extent illustrate the aging of the HIV-infected population. Furthermore, in addition to the reduced risk of HIV-associated morbidity, risk of several of the major age-related diseases (HIV vs controls) has recently been found to decrease over later years independent of age.[3]

The prescription strategy for paracetamol has changed from previously being sold over-the-counter and only prescribed for individuals with a large use (i.e. need of reimbursement) to prescriptions being needed for all packages containing more than 20 tablets (500 mg) during later years. Despite this change, a substantial reduction in the relative use of both paracetamol and opioids was observed, which indicate that the HIV-infected population suffers less from pain-associated conditions. Moreover, in line with the results from other studies,[20] we observed that the most common drugs used in later years were drugs affecting the nervous and cardiovascular system. This is of particular interest as most drug–drug interactions described are between these drug groups and antiretroviral drugs.[7,22,27]

For individuals with or without HIV-infection, increasing age is associated with reduced drug metabolism due to decreased renal and hepatic function with age.[28,29] Moreover, liver and kidney dysfunction is more prevalent in the HIV-population [3,30,31] and may lead to increased risk of intolerance and toxicities. Furthermore, protease inhibitors (especially ritonavir), cobicistat and non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, and nevirapine) are active inducers or inhibitors of the hepatic cytochrome P450 3A4 pathway, which may affect the drug metabolism of some non-antiretroviral drugs.[32] Shared metabolism through several other mechanisms may also lead to drug–drug interactions.[27,32,33] In a previous study from Marzolini et al,[27] use of two or more non-antiretroviral drugs (co-medications along with combination antiretroviral therapy) was associated with an almost twofold odds ratio (Odds ratio: 1.89; 95% CI: 1.32–2.70) of theoretical drug–drug interactions. In addition, several studies [7,22] have indicated that the risk of drug–drug interactions increase with age and polypharmacy. As drug pauses or cessation of the antiretroviral therapy have been proven to increase mortality,[34] use of antiretroviral therapy is indispensable. Therefore, the use of a rational conservative drug prescription strategy seems of utmost importance in the aging of HIV-infected population in order to reduce drug–drug interactions and increase adherence.[10]

The strengths of our study include the use of a population-based, nationwide HIV cohort along with well-matched general population controls. We used Danish registries [16–18] of a high quality to obtain data on vital status, migration and drug redemption thus eliminating risk of recall bias. Due to the high coverage and long follow-up of the Danish HIV-infected population we were able to assess longitudinal trends in drug utilization. We are not aware of other studies with a similar design.

The study has some limitations. Although, the completeness and quality of data from pharmacy databases is high and potentially superior to other measures of drug intake, the prescription registry only captures prescriptions filled at community pharmacies and thereby does not cover drugs provided by the hospital, e.g. during admissions as well as biologic drugs, chemotherapeutics and antiretroviral therapy. Additionally, over-the-counter drugs are not captured by the

database. Nevertheless, as Denmark is very restrictive concerning over-the-counter drugs, the latter problem seems of less magnitude. Furthermore, as individuals with IDU as route of HIV infection may have a substantial intake of recreational drugs and also differ in prevalence of comorbidities and other characteristics, we restricted the population to individuals with no IDU. As HIV-infected individuals co-infected with HCV in Denmark are often transmitted through drug abuse, these individuals were also excluded. From this, and due to the exclusion of anti-infectious drugs from our analyses, our results pertain to drugs used for chronic conditions. Finally, as all individuals had to live throughout the calendar year to be included in the analysis of that year, we cannot exclude that our results may illustrate a slightly healthier population. Nevertheless, this method excluded competing risk by death.

Acknowledgements

We are grateful to the staff of our clinical departments for their continuous support and enthusiasm.

Centers in the Danish HIV Cohort Study

Departments of Infectious Diseases at Copenhagen University Hospitals, Rigshospitalet (J Gerstoft, N Obel) and Hvidovre (G Kronborg), Odense University Hospital (C Pedersen), Aarhus University Hospitals, Skejby (CS Larsen) and Aalborg (G Pedersen), Herning Hospital (AL Laursen), Hillerød Hospital (L Nielsen) and Kolding Hospital (J Jensen).

Disclosure statement

Larsen CS and Kronborg G report no conflicts of interest.

The study was investigator-driven and thus independent of any pharmaceutical company. The funding sources were not involved in study design, data collection, analyses, report writing, or decision to submit the paper. The authors had full access to all data in the study and the responsibility for the decision to submit for publication was shared between all authors.

Funding

This work was supported by Preben og Anna Simonsens Fond, NOVO Nordisk Foundation, The Danish AIDS Foundation, The Augustinus Foundation and Odense University Hospitals Frie fonds midler. Obel N has received funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abott, Boehringer Ingelheim, Janssen-Cilag and Swedish Orphan Drugs. Pedersen C has received funding from Abott, Gilead and Merck Sharp & Dohme. Gerstoft J has received payment from Gilead, ViiV, Abbvie Merck, Bristol-Myers Squibb, Medivir and Janssen. Pottegård A has received funding from Servier, Boehringer-Ingelheim, Astellas, Astra-Zeneca, Almirall and Alcon – all paid to the institution where he was employed. Rasmussen LD has received speaker payment from Bristol-Myers Squibb, attended courses held by ViiV, Gilead, Janssen and Bristol-Myers Squibb and received payment for boarding, transport and course fees.

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Appendix A

ATC: anatomical chemical classification.

Drugs are classified in groups at five different levels according to the main therapeutic use of their main active ingredient, on the basic principle of assigning only one ATC code for each pharmaceutical formulation{, Oslo 2013 #1043}:

First level: Anatomical main group (e.g. A ∼ alimentary tract and metabolism)

Second level: Therapeutic subgroup (e.g. A10 ∼ Drugs used in diabetes)

Third level: Pharmacological subgroup (e.g. A10B ∼ Blood glucose lowering drugs, excl. insulins)

Fourth level: Chemical subgroup (e.g. A10BA ∼ Biguanides)

Fifth level: Chemical substances (e.g. A10BA02 ∼metformin)

First level:
A: Alimentary tract and metabolism
B: Blood and blood forming organs
C: Cardiovascular system
D: Dermatologicals
G: Genito-urinary system and sex hormones
H: Systemic hormonal preparations, excl sex hormones and insulin
J: Antiinfectives for systemic use
L: Antineoplastic and immunomodulating agents
M: Musculo-skeletal system
N: Nervous system
P: Antiparasitic products, insecticides and repellents
R: Respiratorysystem
S: Sensory organs
V: Various

Appendix B

Table B1. Characteristics of the HIV-infected population and the controls per calendar year.

Calendar years	Controls	Male *N* (%)	Danish born *N* (%)	Age (IQR)	HIV	Male *N* (%)	Danish born *N* (%)	Age (IQR)	≥50 years *N* (%)	Starts HAART *N* (%)	On HAART *N* (%)
1995	7655	6265 (81.8)	6706 (87.6)	37 (31–45)	1531	1253 (81.8)	1202 (78.5)	37 (31–45)	237 (15.5)	29 (1.9)	4 (0.3)
1996	7950	6415 (80.7)	6968 (87.6)	37 (31–46)	1590	1,283 (80.7)	1218 (76.6)	38 (31–46)	265 (16.7)	397 (25.0)	36 (2.3)
1997	8615	6905 (80.2)	7533 (87.4)	38 (32–47)	1723	1381 (80.2)	1302 (75.6)	38 (32–47)	333 (19.3)	571 (33.1)	418 (24.3)
1998	9270	7355 (79.3)	8126 (87.7)	39 (33–48)	1854	1471 (79.3)	1382 (74.5)	39 (33–48)	400 (21.6)	255 (13.8)	962 (51.9)
1999	10,060	7825 (77.8)	8821 (87.7)	39 (33–48)	2012	1565 (77.8)	1460 (72.6)	39 (33–48)	453 (22.5)	235 (11.7)	1178 (58.5)
2000	10,800	8260 (76.5)	9472 (87.7)	40 (34–49)	2160	1652 (76.5)	1545 (71.5)	40 (34–49)	521 (24.1)	214 (9.9)	1,387 (64.2)
2001	11,590	8765 (75.6)	10,155 (87.6)	40 (34–49)	2318	1753 (75.6)	1630 (70.3)	40 (34–49)	565 (24.4)	233 (10.1)	1561 (67.3)
2002	12,340	9215 (74.7)	10,818 (87.7)	41 (35–50)	2468	1843 (74.7)	1708 (69.2)	41 (35–50)	649 (26.3)	187 (7.6)	1767 (71.6)
2003	12,935	9660 (74.7)	11,385 (88.0)	42 (36–51)	2587	1932 (74.7)	1780 (68.8)	42 (36–51)	708 (27.4)	169 (6.5)	1910 (73.8)
2004	13,755	10,295 (74.8)	12,030 (87.5)	42 (36–51)	2751	2059 (74.8)	1894 (68.8)	42 (36–51)	774 (28.1)	193 (7.0)	2036 (74.0)
2005	14,450	10,820 (74.9)	12,609 (87.3)	42 (37–51)	2890	2164 (74.9)	1980 (68.5)	42 (37–51)	865 (29.9)	160 (5.5)	2185 (75.6)
2006	15,200	11,335 (74.6)	13,302 (87.5)	43 (37–52)	3040	2267 (74.6)	2070 (68.1)	43 (37–52)	938 (30.9)	202 (6.6)	2311 (76.0)
2007	16,060	11,975 (74.6)	14,087 (87.7)	44 (37–52)	3212	2395 (74.6)	2180 (67.9)	44 (37–52)	1015 (31.6)	200 (6.2)	2465 (76.7)
2008	16,960	12,605 (74.3)	14,870 (87.7)	44 (38–53)	3392	2521 (74.3)	2286 (67.4)	44 (38–53)	1103 (32.5)	256 (7.5)	2634 (77.7)
2009	17,515	12,985 (74.1)	15,339 (87.6)	45 (38–53)	3503	2597 (74.1)	2359 (67.3)	45 (38–53)	1194 (34.1)	229 (6.5)	2830 (80.8)
2010	18,190	13,470 (74.1)	15,941 (87.6)	46 (38–54)	3638	2694 (74.1)	2449 (67.3)	46 (38–54)	1303 (35.8)	253 (7.0)	3013 (82.8)
2011	18,844	13,959 (74.1)	16,549 (87.8)	46 (39–54)	3769	2792 (74.1)	2538 (67.3)	46 (39–55)	1408 (37.4)	227 (6.0)	3219 (85.4)
2012	19,153	14,193 (74.1)	16,872 (88.1)	47 (40–55)	3831	2839 (74.1)	2581 (67.4)	47 (40–55)	1530 (39.9)	157 (4.1)	3398 (88.7)
2013	19,243	14,233 (74.0)	16,981 (88.2)	48 (40–56)	3849	2847 (74.0)	2577 (67.0)	48 (40–56)	1647 (42.8)	104 (2.7)	3484 (90.5)

In year 2011, 2012 and 2013, 1, 2 and 2 controls are missing, respectively.

Appendix C

Appendix C1. Use of non-antiretroviral drugs in HIV-infected individuals and controls from the background population (1995–2013).
Psychotropic drugs excluded.

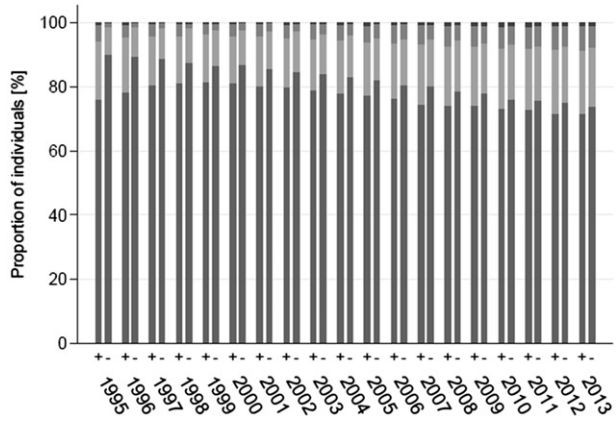

Figure C1. The proportion of HIV-infected individuals (+) and age and gender matched controls from the background population (-) who have redeemed 0–1 (very dark greyblack), 2–4 (light grey), 5–9 (darker grey), or 10 or more (dark greyblack) non-antiretroviral drugs according to calendar years.

Appendix C2. Use of non-antiretroviral drugs with time on combination antiretroviral therapy (cART) in individuals with and without HIV infection in the same time period (year 1-10 after initiation of cART)
Psychotropic drugs excluded

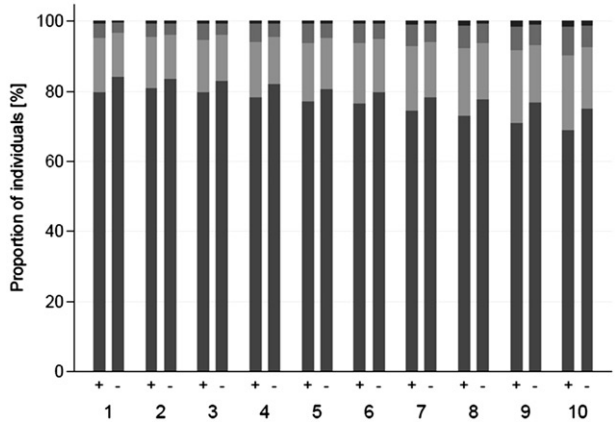

Figure C2. The proportion of HIV-infected individuals (+) and age and gender matched controls from the background population (-) who have redeemed 0–1 (very dark greyblack), 2–4 (light grey), 5–9 (darker grey), or 10 or more (dark greyblack) non-antiretroviral drugs according to time on combination Antiretroviral Therapy (cART).

Appendix D

Table D1. Absolute and relative use of non-antiretroviral drugs (age below 50 years).

		1995		2004		2013	
ATC	Common name	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)	Annual Prevalence	SPR (95% CI)
A02B	Antiulcer drugs	3.5% ($n = 45$)	2.32 (1.69–3.10)	3.5% ($n = 69$)	1.59 (1.24–2.01)	3.4% ($n = 75$)	0.98 (0.77–1.23)
A10B	Blood glucose-lowering drugs, excl. insulins	$n < 10$	–	$n < 10$	–	1.2% ($n = 26$)	0.98 (0.64–1.44)
B01A	Antithrombotic agents	$n < 10$	–	1.6% ($n = 32$)	1.51 (1.03–2.13)	2.3% ($n = 50$)	1.49 (1.10–1.96)
C05A	Topical treatment of haemorrhoids and anal fissures	2.6% ($n = 34$)	5.31 (3.68–7.42)	1.6% ($n = 31$)	2.77 (1.88–3.93)	1.5% ($n = 34$)	1.72 (1.19–2.40)
C07A	Beta blockers	1.2% ($n = 16$)	2.35 (1.34–3.82)	1.8% ($n = 36$)	1.23 (0.86–1.71)	2.3% ($n = 50$)	1.33 (0.99–1.75)
C08C	Calcium-channel blockers	$n < 10$	–	0.8% ($n = 16$)	1.11 (0.64–1.80)	1.7% ($n = 37$)	0.90 (0.63–1.24)
C09A	ACE inhibitors	$n < 10$	–	1.8% ($n = 35$)	1.77 (1.23–2.46)	2.6% ($n = 57$)	1.33 (1.01–1.72)
C10A	Cholesterol-lowering drugs	$n < 10$	–	1.9% ($n = 38$)	1.52 (1.08–2.09)	4.0% ($n = 88$)	1.39 (1.11–1.71)
D01A	Topical antifungals	9.0% ($n = 116$)	8.78 (7.2610.54)	2.9% ($n = 58$)	2.99 (2.27–3.86)	1.8% ($n = 40$)	2.13 (1.52–2.90)
D07A	Topical steroids	5.6% ($n = 72$)	3.18 (2.49–4.01)	2.6% ($n = 52$)	2.36 (1.77–3.10)	1.5% ($n = 34$)	1.14 (0.79–1.59)
G03A	Hormonal contraceptives for systemic use	2.2% ($n = 28$)	0.43 (0.29–0.63)	1.7% ($n = 33$)	0.24 (0.17–0.34)	1.3% ($n = 28$)	0.22 (0.15–0.32)
G04B	Urologicals	$n < 10$	–	3.1% ($n = 61$)	5.98 (4.57–7.68)	3.9% ($n = 86$)	4.26 (3.40–5.26)
M01A	NSAIDs	4.9% ($n = 63$)	1.78 (1.37–2.28)	4.7% ($n = 92$)	0.93 (0.75–1.14)	3.5% ($n = 77$)	0.74 (0.58–0.92)
N02A	Opioids	5.6% ($n = 72$)	5.90 (4.62–7.43)	2.6% ($n = 52$)	1.26 (0.94–1.66)	3.3% ($n = 73$)	1.04 (0.82–1.31)
N02B	Other analgesics (= Paracetamol)	3.3% ($n = 43$)	3.98 (2.88–5.36)	1.7% ($n = 33$)	1.57 (1.08–2.21)	1.4% ($n = 30$)	0.65 (0.44–0.93)
N03A	Antiepileptics	2.2% ($n = 28$)	2.15 (1.43–3.11)	2.1% ($n = 41$)	1.68 (1.21–2.28)	2.5% ($n = 55$)	1.04 (0.78–1.35)
N05A	Antipsychotics	1.9% ($n = 25$)	1.67 (1.08–2.46)	2.1% ($n = 42$)	1.62 (1.16–2.18)	3.5% ($n = 77$)	1.85 (1.46–2.31)
N05B	Anxiolytics	8.1% ($n = 105$)	3.59 (2.94–4.35)	3.2% ($n = 63$)	1.69 (1.30–2.17)	2.2% ($n = 49$)	2.11 (1.56–2.79)
N05C	Hypnotics	8.5% ($n = 110$)	6.04 (4.97–7.28)	5.4% ($n = 107$)	3.79 (3.11–4.59)	3.4% ($n = 74$)	2.64 (2.07–3.32)
N06A	Antidepressants	3.9% ($n = 50$)	2.66 (1.97–3.50)	7.6% ($n = 150$)	1.86 (1.57–2.18)	8.6% (n = 190)	1.33 (1.15–1.53)
N07B	Drugs used in addictive disorders	1.1% ($n = 14$)	1.94 (1.06–3.26)	1.0% ($n = 20$)	2.13 (1.30–3.29)	0.9% ($n = 20$)	1.75 (1.07–2.71)
R01A	Nasal decongestants	2.0% ($n = 26$)	1.41 (0.92–2.07)	1.7% ($n = 33$)	1.30 (0.89–1.82)	1.4% ($n = 31$)	0.72 (0.49–1.03)
R03A	Inhaled beta-agonists	1.9% ($n = 24$)	1.12 (0.72–1.67)	2.4% ($n = 48$)	1.31 (0.97–1.74)	2.3% ($n = 51$)	1.03 (0.77–1.35)
R06A	Antihistamines for systemic use	4.1% ($n = 53$)	3.23 (2.42–4.23)	2.2% ($n = 43$)	1.60 (1.16–2.16)	1.1% ($n = 25$)	0.70 (0.45–1.03)
S01A	Ophthalmological anti-infectives	1.3% ($n = 17$)	1.08 (0.63–1.72)	1.0% ($n = 20$)	1.59 (0.97–2.45)	0.9% ($n = 20$)	2.04 (1.25–3.15)

ATC: anatomical therapeutic chemical classification (The drugs are aggregated at the third ATC-level); SPR: standardized prevalence ratio; 95% CI: 95% confidence interval. The absolute (∼annual prevalence) and relative use (∼relative prevalence = SPR) for the 25 most commonly used non-HAART drugs in 2013.

Table D2. Absolute and relative use of non-antiretroviral drugs (age 50 years or above).

		1995		2004		2013	
ATC code	Common name	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)
A02B	Antiulcer drugs	6.3% ($n = 15$)	1.39 (0.78–2.30)	9.2% ($n = 71$)	1.76 (1.37–2.22)	10.8% ($n = 178$)	1.18 (1.01–1.37)
A10A	Insulins and analogues	$n < 10$	–	1.7% ($n = 13$)	1.27 (0.68–2.18)	2.9% ($n = 47$)	1.19 (0.88–1.59)
A10B	Blood glucose-lowering drugs, excl. insulins	$n < 10$	–	3.2% ($n = 25$)	0.91 (0.59–1.34)	5.0% ($n = 82$)	0.73 (0.58–0.91)
B01A	Antithrombotic agents	$n < 10$	–	12.4% ($n = 96$)	1.18 (0.96–1.44)	17.4% ($n = 287$)	1.25 (1.11–1.40)
C03A	Thiazides	$n < 10$	–	4.5% ($n = 35$)	0.81 (0.57–1.13)	4.6% ($n = 75$)	0.82 (0.64–1.03)
C03C	High-ceiling diuretics	$n < 10$	–	2.2% ($n = 17$)	1.10 (0.64–1.77)	3.0% ($n = 49$)	1.06 (0.78–1.40)
C07A	Beta blockers	$n < 10$	–	8.3% ($n = 64$)	1.05 (0.81–1.34)	9.7% ($n = 160$)	0.96 (0.82–1.12)
C08C	Calcium-channel blockers	$n < 10$	–	3.4% ($n = 26$)	0.61 (0.40–0.89)	9.3% ($n = 153$)	0.83 (0.70–0.97)
C09A	ACE inhibitors	$n < 10$	–	6.8% ($n = 53$)	0.98 (0.74–1.28)	12.9% ($n = 213$)	1.33 (1.16–1.52)
C09B	Ace inhibitors, combinations	$n < 10$	–	$n < 10$	–	2.7% ($n = 44$)	0.73 (0.53–0.97)
C09C	Angiotensin II antagonists, plain	$n < 10$	–	2.5% ($n = 19$)	0.71 (0.43–1.11)	3.8% ($n = 62$)	0.72 (0.55–0.92)
C09D	Angiotensin ii antagonists, combinations	$n < 10$	–	$n < 10$	–	3.0% ($n = 50$)	0.68 (0.50–0.90)
C10A	Cholesterol-lowering drugs	$n < 10$	–	11.0% ($n = 85$)	1.11 (0.89–1.37)	22.8% ($n = 376$)	1.23 (1.11–1.36)
D07A	Topical steroids	10.5% ($n = 25$)	4.64 (3.00–6.85)	3.2% ($n = 25$)	1.71 (1.11–2.53)	2.7% ($n = 45$)	1.55 (1.13 –2.08)
G04B	Urologicals	$n < 10$	–	8.1% ($n = 63$)	3.15 (2.42–4.03)	8.5% ($n = 140$)	2.30 (1.94–2.72)
M01A	NSAIDs	9.3% ($n = 22$)	1.21 (0.76–1.83)	9.2% ($n = 71$)	0.87 (0.68–1.10)	6.2% ($n = 102$)	0.81 (0.66–0.99)
N02A	Opioids	8.9% ($n = 21$)	3.76 (2.33–5.75)	7.8% ($n = 60$)	1.95 (1.49–2.51)	7.3% ($n = 120$)	1.19 (0.98–1.42)
N02B	Other analgesics (=Paracetamol)	5.5% ($n = 13$)	1.63 (0.87–2.79)	6.1% ($n = 47$)	1.72 (1.26–2.28)	6.8% ($n = 112$)	1.15 (0.95–1.39)
N03A	Antiepileptics	$n < 10$	–	3.7% ($n = 29$)	1.99 (1.33–2.85)	4.2% ($n = 69$)	1.47 (1.14–1.86)
N05A	Antipsychotics	$n < 10$	–	2.7% ($n = 21$)	1.28 (0.79–1.96)	2.7% ($n = 45$)	1.29 (0.94–1.73)
N05B	Anxiolytics	12.7% ($n = 30$)	2.43 (1.64–3.46)	8.5% ($n = 66$)	2.19 (1.69–2.78)	3.9% ($n = 65$)	1.83 (1.41–2.33)
N05C	Hypnotics	18.6% ($n = 44$)	4.90 (3.56–6.58)	13.8% ($n = 107$)	3.50 (2.87–4.23)	7.5% ($n = 124$)	2.30 (1.91–2.74)
N06A	Antidepressants	7.2% ($n = 17$)	3.16 (1.84–5.05)	10.6% ($n = 82$)	1.81 (1.44–2.25)	10.5% ($n = 173$)	1.45 (1.25–1.69)
R03A	Inhaled beta-agonists	$n < 10$	–	4.8% ($n = 37$)	1.45 (1.02–1.99)	5.0% ($n = 83$)	1.02 (0.82–1.27)
R03B	Inhaled anticholinergics and steroids	$n < 10$	–	2.1% ($n = 16$)	0.78 (0.45–1.27)	3.1% ($n = 51$)	1.05 (0.78–1.38)

ATC: anatomical therapeutic chemical classification (The drugs are aggregated at the third ATC-level); SPR: standardized prevalence ratio; 95% CI: 95% confidence interval. The absolute (∼annual prevalence) and relative use (∼relative prevalence = SPR) for the 25 most commonly used non-HAART drugs in 2013.

Table D3. Absolute and relative use of drugs affecting the nervous system used for the HIV-infected individuals.

		1995		2004		2013	
ATC	Common name	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)
N02A	Opioids	6.1% ($n = 93$)	5.22 (4.22–6.40)	4.1% ($n = 112$)	1.56 (1.28–1.87)	5.0% ($n = 193$)	1.13 (0.97–1.30)
N02B	Other analgesics (=Paracetamol)	3.7% ($n = 56$)	2.98 (2.25–3.87)	2.9% ($n = 80$)	1.65 (1.31–2.06)	3.7% ($n = 142$)	0.99 (0.84–1.17)
N02C	Antimigraine preparations	$n < 10$	–	0.5% ($n = 14$)	0.57 (0.31–0.95)	0.7% ($n = 26$)	0.62 (0.41–0.91)
N03A	Antiepileptics	2.4% ($n = 37$)	2.31 (1.63–3.19)	2.5% ($n = 70$)	1.79 (1.40–2.27)	3.2% ($n = 124$)	1.24 (1.03–1.48)
N05A	Antipsychotics	2.2% ($n = 33$)	1.77 (1.22–2.49)	2.3% ($n = 63$)	1.49 (1.14–1.90)	3.2% ($n = 122$)	1.60 (1.33–1.91)
N05B	Anxiolytics	8.8% ($n = 135$)	3.25 (2.72–3.84)	4.7% ($n = 129$)	1.91 (1.60–2.27)	3.0% ($n = 114$)	1.94 (1.60–2.33)
N05C	Hypnotics	10.1% ($n = 154$)	5.66 (4.80–6.63)	7.8% ($n = 214$)	3.64 (3.17–4.16)	5.1% ($n = 198$)	2.41 (2.09–2.78)
N06A	Antidepressants	4.4% ($n = 67$)	2.77 (2.15–3.52)	8.4% ($n = 232$)	1.84 (1.61–2.09)	9.4% ($n = 363$)	1.39 (1.25–1.54)
N06B	Psychostimulants	$n < 10$	–	$n < 10$	–	0.4% ($n = 17$)	1.12 (0.65–1.79)
N07B	Drugs used in addictive disorders	1.0% ($n = 15$)	1.83 (1.02–3.02)	1.1% ($n = 29$)	1.99 (1.33–2.85)	1.1% ($n = 44$)	1.98 (1.44–2.66)

ATC: anatomical therapeutic chemical classification (The drugs are aggregated at the third ATC-level); SPR: standardized prevalence ratio; 95% CI: 95% Confidence Interval. The absolute (∼annual prevalence) and relative use (∼relative prevalence = SPR) for the 25 most commonly used non-HAART drugs in 2013.

Table D4. Absolute and relative use of drugs affecting the cardiovascular system used for the HIV-infected individuals.

		1995		2004		2013	
ATC	Common name	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)	Annual prevalence	SPR (95% CI)
C03A	Thiazides	$n < 10$	–	2.1% ($n = 58$)	0.97 (0.74–1.25)	2.4% ($n = 91$)	0.81 (0.65–1.00)
C03C	High-ceiling diuretics	$n < 10$	–	0.9% ($n = 24$)	1.17 (0.75–1.73)	1.7% ($n = 65$)	1.25 (0.96–1.59)
C07A	Beta blockers	1.2% ($n = 19$)	1.20 (0.72–1.88)	3.6% ($n = 100$)	1.11 (0.90–1.35)	5.5% ($n = 210$)	1.03 (0.89–1.18)
C08C	Calcium-channel blockers	$n < 10$	–	1.5% ($n = 42$)	0.74 (0.53–1.00)	4.9% ($n = 190$)	0.84 (0.72–0.97)
C09A	ACE inhibitors	$n < 10$	–	3.2% ($n = 88$)	1.19 (0.96–1.47)	7.0% ($n = 270$)	1.33 (1.17–1.50)
C09B	Ace inhibitors, combinations	$n < 10$	–	$n < 10$	–	1.5% ($n = 57$)	0.76 (0.58–0.99)
C09C	Angiotensin II antagonists, plain	$n < 10$	–	0.9% ($n = 26$)	0.71 (0.46–1.04)	2.0% ($n = 78$)	0.72 (0.57–0.90)
C09D	Angiotensin II antagonists, combinations	$n < 10$	–	$n < 10$	–	1.7% ($n = 65$)	0.75 (0.58–0.96)
C10A	Cholesterol-lowering drugs	$n < 10$	–	4.5% ($n = 123$)	1.21 (1.01–1.44)	12.1% ($n = 464$)	1.26 (1.15–1.38)

ATC: anatomical therapeutic chemical classification (The drugs are aggregated at the third ATC-level); SPR: standardized prevalence ratio; 95% CI: 95% confidence interval. The absolute (∼annual prevalence) and relative use (∼relative prevalence = SPR) for the 25 most commonly used non-HAART drugs in 2013.