Incidence rate, predictors and outcomes of interruption of HIV care: nationwide results from the Belgian HIV cohort.

Shortened title: Interruption of HIV care in a national cohort.

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Abstract

Objectives: We aimed to study HIV care interruption (HCI) incidence rate, predictors and outcomes in Belgium.

Methods: We analyzed data of adult patients with at least 2 HIV care records in the Belgian HIV cohort between 01/01/2007 and 31/12/2016. HCI episode was defined as one year without HIV care record. HCI incidence rate was analyzed using Poisson regression, return to HIV care with a cumulative incidence function with death as competing risk, and VL status upon return to HIV care using logistic regression.

Results: We included 16066 patients accounting for 78625 person-years of follow-up. The incidence rate of HCI was 5.3/100 person-years (95% CI: 5.1-5.4/100). The incidence of return to HIV care after HCI was estimated at 77.5 % (95%CI: 75.7-79.2%). Of those returned, 43.7% had a VL <200 copies/mL suggesting care abroad or suboptimal care (without HIV-related care record) in Belgium during HCI. And 56.3% returned without controlled VL and were therefore considered as having experienced a real gap in HIV care, they represented 2.3/100 person-years in follow-up. Factors individually associated with HCI were no ART uptake, lower age, IDU, non-Belgian nationalities, male gender, not being a man having sex with men, shorter time since HIV diagnosis, no high blood pressure and CD4 < 350.

Conclusions: This study highlights the need to investigate return to care and viral status at return, to better understand HCI. Identified predictors can help healthcare workers to target patients at higher risk of HCI for awareness and support.

Introduction

Since the introduction of antiretroviral therapy (ART) and the resulting increase of life expectancy among HIV-infected people (1), HIV has evolved to a chronic disease requiring decades of engagement in dedicated care for more and more patients. Sustained maintenance of the patients in HIV care and on ART is crucial to ensure the best outcomes in mortality and morbidity, and reduce onward transmission (2). Nevertheless, this is a challenge for a number of patients (3).

Retention in care is one of the key stages of the continuum of HIV care (4;5). In Belgium, this step is amongst those with highest attrition (6). Improving retention in care would therefore further support our national progress towards the UNAIDS targets (7).

In Belgium, HIV care is well structured and mainly centralized in 12 multidisciplinary specialized care centers, the HIV reference centers (HRCs). Patients might also consult in other hospitals or in primary care. High ART uptake (>97% in 2017) and viral load (VL) control (>95% of those on ART) are reported for those in regular care (8). HIV care is guided by the EACS guidelines which recommend a medical visit with VL measure every 3 to 6 months (9).

Studies on HIV care interruption (HCI) and loss to follow-up in European countries have reported incidence rates around 2.5-3.5/100 person-years (10-12). In a large multi-country European cohort study, 50% of the patients had, between 1995 and 2005, a period of more than 1 year without a follow-up visit (13). In one Belgian HRC, an incidence rate of loss to follow-up of 5.5/100 persons each year was observed between 1999 and 2009 (14). Comparison between studies is hampered by differing approaches for selection of the population studied and the lack of standardized definitions for ‘loss to follow-up’ and ‘HCI’. This is partly due to the diversity of situations leading to HCI, as illustrated in Figure 1. Patients might permanently leave the national HIV care system due to out-migration. Or, patients might receive care abroad before returning to care in Belgium. Alternatively, patients might have ART renewal in Belgium without HIV medical follow-up hence without VL records, which would be considered as suboptimal care. Finally, patients might experience a real gap in HIV care before return to care. Disentangling the diverse pathways behind HCI will inform actions to improve long-term maintenance in HIV care.

This study aims to study HCI in Belgium and better understand the drivers of the different pathways, particularly for those experiencing a real gap during their HCI in Belgium.

Methods

Study setting and population

The Belgian HIV cohort was set up in 2007. It includes data on all HIV-infected patients in care in Belgium collected from the AIDS reference laboratories (ARLs) and the HRCs. All VL measures in the country are performed and reported by the ARLs. This provides a national coverage of the patients in HIV care. HRCs follow more than 80% of the HIV-infected patients in care in the country. Those not attending HRCs are mainly followed up in other hospitals and, less frequently, in primary care. A description of the Belgian HIV cohort was previously published (15).

The cohort data includes a reliable unique patient identifier based on a combination of the encrypted civil registry number and a code using gender and date of birth. Nevertheless, missing or erroneous records may occur. This is more frequent for patients with HIV follow-up outside of HRCs. We therefore focused our analysis on those in care in HRC to ensure the most reliable patient identifier.

In this study, we analyzed data of patients aged 18 years or more, with at least 2 records of HIV care in HRCs between 01/01/2007 and 31/12/2016.

Data collection

Routine individual patient data are collected annually from HRCs and ARLs. Demographic information and VL results are collected from both HRCs and ARLs. Clinical and additional laboratory information are collected from HRCs.

Death data was extracted from medical records and reported by the HRCs. In addition, some HRCs and ARLs databases are linked to Belgium's civil registry, allowing to identify additional deaths declared among their patients.

HIV data collection is performed by Sciensano, the Belgian Scientific Institute of Public Health, legally entitled for HIV surveillance in Belgium (Royal Decree of 08/10/1996). The HIV

surveillance was authorized by an independent administrative authority protecting privacy and personal data (https://www.autoriteprotectiondonnees.be/sites/privacycommission/files/documents/d%C3%A9lib%C3%A9ration_SS_017_2014.pdf), and approved by the ethical committee of Ghent University Hospital (RN B670201420495).

Definition of outcomes and variables

The first outcome studied was the incidence rate of HCI. A HIV care record was defined as a measure of CD4, VL or a medical visit in a HRC. Study start date was defined as 01/01/2007 for those previously in care in HRC or as the date of first HIV care record for those entering care later. An episode of HIV care interruption (HCI) was defined as the occurrence of one year without HIV care record in HRCs if the patient did not die or have a VL record outside of HRCs (by ARL) during this period. In case of HCI, data were censored at date of last record preceding HCI. In case of VL reported outside HRCs during the one-year period, patients were considered as shifted to care outside HRC and censored at date of VL measure reported by ARL. Patients who died were censored at date of death. If none of these events occurred, data were censored at 31/12/2016. Care records were analyzed up to 31/12/2017 to ensure a one-year period of hindsight required to define HCI.

The second outcome studied was the cumulative incidence of return to HIV care, analyzed among those presenting a HCI. The analysis period initiated after the first year of HCI. It was censored at the date of return to HIV care, the date of death or 31/12/2017, whichever occurred first. Return to HIV care was defined as a care record in a HRC or a VL record out of HRC (reported by an ARL).

The third outcome studied was the VL status upon return to HIV care. Patients presenting a VL below or equal to 200 copies/mL upon return to care were considered as having accessed ART during their period of HCI, either through HIV care abroad or through suboptimal care in Belgium (ART renewal without VL follow-up). Those having a VL above 200 copies/mL were classified as having experienced a gap in care.

The following patients' characteristics were studied for their association with each outcome: gender, age, mode of HIV acquisition, nationality, time since diagnosis of HIV, CD4, ART uptake,

HRC of care and year of care. Urbanization of place of residence was categorized in 3 levels of population density based on a European method applied on the Belgian census data (16-18). Income data of municipality of residence was retrieved from the Belgian statistical office as the average net taxable income per capita per municipality (19). Income was divided into 3 terciles. High systolic blood pressure was defined as at least one measure above 140 mm Hg during follow-up, it was used as an indicator of higher risk of comorbidity. Smoking (at least one record of smoking during follow-up) and obesity (at least one measure of BMI>30 kg/m^2 during follow-up) were used to identify those with unhealthy lifestyle. Regularity of care was defined as at least one HIV care record in each semester during the year preceding censoring.

Statistical analyses

To deal with missing values among risk factors (proportion of missing values per variable reported in table 1), multiple imputation was applied to the data prior to statistical analyses. The SAS MI procedure was used to generate 10 imputed data sets. The imputation process included all the studied factors and the postal code as auxiliary variable. Models for analyses of HCI, return to HIV care and VL status at return were applied on each imputed data set and parameter estimates were subsequently combined into a single set of results for each model using the SAS proc mianalyze statement.

Incidence rate of first HCI and associated factors were analyzed with Poisson regression. Return to HIV care of those presenting a HCI was assessed using the cumulative incidence function (CIF) with death as competing risk and associated factors were identified using cause-specific hazard models. VL status upon return to HIV care and associated factors were analyzed using logistic regression.

The following variables - age, time since HIV diagnosis, year of care, ART and CD4 - were considered time-varying for the HCI analysis and stratified by Lexis expansion. For the analyses of return to HIV care and VL status upon return, their values at time of HCI were used.

All analyses were performed in SAS EG version 7.13.

Results

Population description

Over the 10-year study period, 18891 patients were followed for HIV in Belgium. Of these, 16066 (85%) patients in care in the HRC were included in the analysis, accounting for 78625 person-years of follow-up. Most patients were male, median age at inclusion was 39 years. Reported mode of HIV acquisition was 52% heterosexual, 42% men having sex with men (MSM), 3% injecting drug use (IDU), 1% mother-to-child transmission (MTCT) and 2% other (namely contaminated blood-products for transfusion or haemophilia treatment). Half (53%) of the patients were Belgians, 29% Sub-Saharan Africans, 11% non-Belgian Europeans and 7% of other nationalities. Table 1 presents characteristics of the patients.

HIV care interruption and return to HIV care

During the study period, 4151 (25.8%) patients interrupted HIV care, 2160 (13.4%) went to care out of HRCs, 417 (2.6%) died and 9338 (58.1%) were retained in care without experiencing any of those events. The incidence rate of HCI was 5.3/100 person-years (95% CI: 5.1-5.4/100 person-years).

Of those having interrupted care for at least one year, 2364 (57.0%) subsequently returned to HIV care in a HRC and 421 (10.1%) out of HRCs, 8 (0.2%) died and 1358 (32.5%) remained out of Belgian HIV care by 31/12/2017. After the initial one-year period of HCI, the cumulative incidence of return to HIV care was estimated at 77.5 % (95% CI: 75.7-79.2%) within a maximum period of 8 years of which 51.4 % (95% CI: 49.8%-53.0%) and 72.4 % (95% CI: 70.8%-73.9%) within respectively one year and 5 years (Figure 2). Median time to return to HIV care was 179 days (IQR: 50-496).

A VL measure was available upon return into HIV care for 2695 patients (97%). Of these, 1178 (43.7%) had a controlled VL suggesting alternative access to medical care and ART during the HCI period. And 1517 (56.3%) had uncontrolled VL and were considered as having experienced a gap in HIV care.

By combining the results of the cumulative incidence model with the assessment of VL status upon return, incidence rates by type of HCI were estimated. The incidence rate of HCI related to

outmigration was 1.2/100 person-years in care (22.3%*5.3/110 py). The incidence rate of HCI with care abroad or with ART renewal without VL follow-up was 1.8/100 person-years in care (77.5%*43.7%*5.3/100 py). HCI with gap in HIV care had an incidence rate of 2.3/100 person-years in care (77.5%*56.3%*5.3/100 py) and HCI followed by death had an incidence rate of 0.01/100 person-years in care (0.2%*5.3/100 py).

Associated factors

After adjustment, higher incidence rate of HCI was strongly associated with no ART uptake and moderately with younger age, IDU, non-Belgian nationality, more recent HIV diagnosis and low CD4 (Table 2). Lower incidence rate of HCI was associated moderately with female gender, being MSM and high blood pressure. Smoking, obesity, urbanisation level and income of place of residence were not associated with the incidence rate of HCI. Those having regular care during the last year of observation had a higher incidence rate of HCI than others. The HCI incidence rates were lower in the period 2007-2011 compared to the following years..

For those presenting a HCI, return to HIV care was associated, after adjustment, with younger age and female gender. HIV diagnosis in more recent years, non-Belgian nationalities, being MSM, other mode of HIV acquisition and low CD4 at HCI were associated with less return to care. For those who returned to HIV care, factors associated with experiencing a gap during HCI in the multivariable analysis were female gender, younger age, a more recent HIV diagnosis, no ART uptake at HCI and a low CD4 at HCI. Europeans had lower risk of gap compared to other nationalities.

Immune status and evolution after a gap in HIV care

Among the patients who returned to care after a gap and with an available CD4 count at time of return (N=1246), 31.4% had a CD4 below 200 CD4/mm³, 23.0% between 200-350 CD4/mm³ and 45.6% ≥350 CD4/mm³. The mean decrease in CD4 during the gap in care was 75 CD4/mm³/year (95% CI: 68.9—81.2).

The incidence rate of death amongst all patients who remained in HIV care was 0.5/100 person-years (95% CI: 0.5-0.6/100 py). In comparison, the incidence rate of death in the year following return to care after a gap was 1.0/100 person-years (95% CI: 0.6-1.7/100 py; p=0.02), and

2.7/100 person-year (95% CI: 1.4-5.0/100 py; p<0.0001) for those with a CD4 below 200 CD4/mm^3 upon return.

Discussion

Each year, one in 20 HIV-infected patients in care presents a HCI in Belgium. This study on a 10-years period allowed the assessment of longstanding care relationships for 85% of the patients in care in Belgium even if they changed center of HIV care, thanks to multicentric data collection.

Analysis of return to care and health status upon return are necessary to disentangle the various situations behind HCI. The estimated incidence rate of gap in HIV care was 2.3/100 HIV persons in care in Belgium per year. This seems in line with studies in other Western European countries (10;11) although comparison should be made with caution given the varying definitions and approaches to handle out-migration in these analyses.

Having detectable viral loads, patients with a gap in HIV care may contribute to HIV transmission in the community. Moreover, those patients were more vulnerable to poor clinical evolution, with a higher mortality incidence rate in the year following their return to care ,compared with mortality incidence rates of patients maintained in HIV care. Significantly higher mortality rates were found in those who had CD4 counts < 200 cell/mm^3 upon return. Given that patients with low CD4 had twice the rate of HCI and also a higher risk of gap during HCI, this calls for specifically prompt and intensive intervention for retention in care in case of missed appointment among patients with low CD4.

ART uptake is the strongest predictor of better retention in HIV care identified by our analysis. In Belgium, reimbursement of ART was contingent upon a CD4 value below 500 CD4/mm^3 or presence of clinical symptoms up to the 1st of December 2016. From then on, reimbursement for all HIV patients was implemented. Observed ART coverage in the HRCs increased from 75% in 2007 to 97% in 2017 (8). Given the strong association of ART with retention in care, we might expect the high ART coverage to reinforce regular care in recent years and in the future.

Younger patients were more vulnerable to HCI and to a gap in HIV care in line with findings of other studies (3;20-23), but were less prone to permanent outmigration. It might be particularly challenging for young people to cope at once with the stigmatizing dimension of the disease, its impact on their sexual and emotional well-being and the necessary commitment to a life-long medical care (20;24). Also, increased mobility of young people related to relationships, jobs and study might impact on their capacity to remain in HIV care. Other demographic predictors of HCI identified in this analysis were male gender and foreign nationality, those were less likely to return to HIV care in Belgium due to higher permanent out-migration during HCI. MSM were less likely to experience HCI compared to heterosexuals, as reported in the literature (10;11;25-27).

Injecting drug users had higher incidence rates of HCI. Assessment of drug use, including "chemsex" which has been increasingly reported among PLHIV (28), should be performed regularly among patients in HIV care to provide targeted advice, support and possibly referral to drug treatment services for collaborative care. Other substance use like alcohol was identified as predictor of HCI in other studies (3;20;23), although no data on these exposures were available in this study.

Difficulties to face a recent diagnosis of HIV might contribute to the higher incidence rates of HCI for those recently diagnosed. For those in HCI, a recent diagnosis was associated with higher hazard of no return to care due to out-migration, and higher risk of gap for those returning to care in Belgium. The period following diagnosis is crucial as poor engagement in HIV care during the first year following diagnosis is associated with a higher mortality (29). A greater frequency of medical contacts when initiating treatment increases opportunities for providing targeted support for engagement in HIV care to newly diagnosed patients facing social or administrative barriers. In contrast with our findings, both in a Spanish and an English study, recently diagnosed patients had less missed medical appointments (25;30), but these studies were not following retention in HIV care on a long period.

Irregular care did not predict subsequent HCI in our study. Many of the patients with irregular care according to our definition had in fact a very stable HIV disease requiring less frequent medical visits. Those in regular care that experienced more HCI might include patients identified as more vulnerable to HCI for whom clinicians plan more frequent visits.

Patients with a higher risk of comorbidity were less prone to HCI, in line with a previous study showing a dose-response relationship between number of comorbidities and optimal retention (21). We found no association between HCI and indicators of unhealthy lifestyle, nor with urbanization or income levels of place of residence. A recent Swiss study also found no association between neighborhood socio-economic position and loss to follow-up (31).

Our analysis of determinants of HCI or gap in HIV care was restricted to factors available in the cohort data. Other individual factors such as mental health illness and perceived stigma (32;33) or aspects related to health care services and external environment (23;32) may also play a key role in retention in HIV care in Belgium. For example, a confident relationship with the HIV care provider and a facilitating health care structure such as ease of reach by phone, ease of appointment taking, extended hours of consultation, automatic text messages or pre-consultation reminder phone calls and positive waiting room experience have been frequently reported as facilitators (12;33-36).

Guidelines for HIV care recommend a routine assessment at entry in HIV care of new patients (9). Based on the factors identified in this study and in others, the gathered information might be used to identify patients at increased risk of HCI and provide them targeted support. Peers could play a role here, as shown in UK and US programs reporting enhanced patient empowerment, retention in care and adherence to treatment following peer interventions (27;37).

Guidelines (9) advise an HIV care visit every 3 to 6 months. We used a definition of one year without HIV care record to allow some flexibility for stable patients spacing their appointments while remaining properly followed-up. Various metrics have been used to study regularity of HIV care, each with its own strengths and weaknesses (30;38). Our definition is relevant for an epidemiological approach of HCI and its predictors. In clinical practice, with the aim of early intervention for patients deviating from regular care to prevent long-term attrition, monitoring of missed appointments is more suitable and easier to implement routinely.

In case of HCI or missed appointment, prompt contact with the patient for return to care is facilitated if all contact information of the patient are available, for instance through a systematic assessment at initiation of care of patient's agreement to be contacted back and how. This topic could be added in the initial assessment section of HIV care guidelines. Tracing of patients might

be facilitated if they have a regular general practitioner (GP), it has also been shown that those with a regular GP have less missed appointments (27). The potential use of the Belgian eHealth (39) system - electronic exchange of health-related data between healthcare providers - for supporting retention and return to care should be further explored.

This study helped to disentangle the heterogeneity of situations behind HCI by looking at the 3 main pathways defined for our analysis. Nevertheless, medical care during HCI was not fully captured. For instance, patients returning to care with a controlled VL after HCI were grouped as a single entity although their individual care use during HCI may have been diverse, including care abroad, incarceration and various patterns of access to ART. Also the group of patients classified as having experienced a gap in care based on uncontrolled VL upon return might present heterogeneity in terms of partial or complete gap in care throughout HCI. Further research using alternative sources of medical data will help refine our understanding of individual HIV care trajectories.

This study has limitations. First, our analysis did not include patients receiving care exclusively out of HRCs, who represented 15% of all patients in HIV care in Belgium during the study period. They differed from those followed in the HRCs, with slightly more PWID, less MSM, more women and less Belgians (6). As these characteristics are associated with HCI incidence rate, our results might slightly underestimate the national levels of HCI. Secondly, the cohort includes both patients who entered care after the study start date and patients already in care beforehand. In case of HCI and return before the study start date, a subsequent episode of HCI during the study period will be misclassified as first HCI for those patients. Whether incidence rates of repeated and first HCI differ was not captured by the design of our study. Finally, our HIV surveillance is linked to Belgium's civil registry to ascertain death status in some HRCs but not at central level. Nevertheless, deaths of patients due to chronic conditions will most probably be captured in the medical records of the HRC where the patients were in care. Few sudden deaths might remain unrecorded, and possibly lead to a slight underestimation of the number of deaths in our results. As only few death would be missed, complete absence of care or death records for the whole follow-up period following HCI was interpreted as outmigration.

In Belgium, the incidence rate of HIV care interruption is low, and less than half of the patients experience a real gap in care during interruption. High access to HIV care in Belgium through fully

reimbursed ART and multidisciplinary HIV care centers contributes to limit HCI and facilitate return to HIV care. Young patients, heterosexual men, foreigners, IDU, those recently diagnosed, those with low CD4 and those with lower risk of comorbidities were found at higher risk for HCI and should be targeted for prevention. This could be supported by the addition of a section in HIV care guidelines on investigation of HCI risk and means of contact. Despite a decreasing pace of HIV infection in Belgium in recent years, the HIV-infected population continues to grow and live longer (8). To allow them the full benefit of therapy and a good health-related quality of life, awareness and support for long-term maintenance in HIV care will be increasingly necessary.

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Tables and figures

Figure 1: Diagram of HIV care interruptions pathways

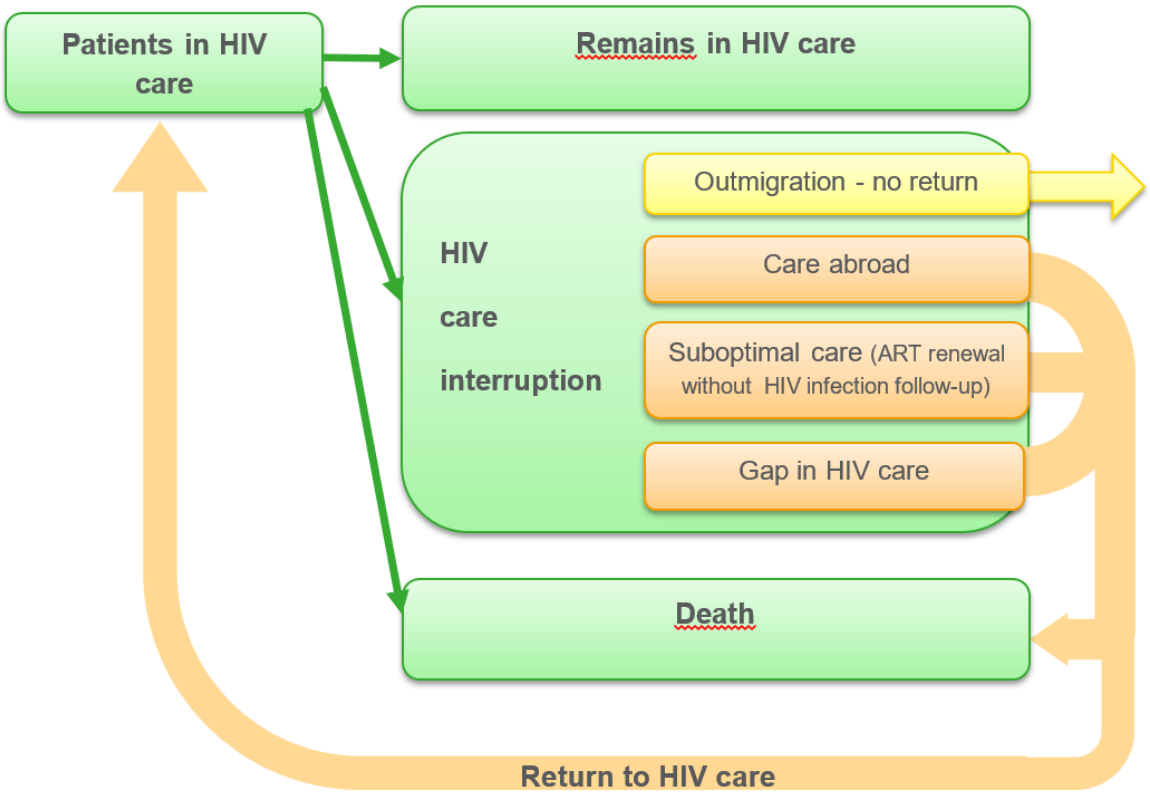

Table 1. Socio-demographic and selected behavioural and clinical characteristics of patients in care for HIV, Belgium, 2007-2016.

Characteristic	**N (%)**
Sex (N=16026; No. missing: 40 (0.2%))	
Male	10560 (65.9%)
Female	5448 (34.0%)
Other	18 (0.1%)
Age at baseline (N=16066; No. missing: 0)	
Mean age (SD), yrs	40 (11)
Mode of HIV acquisition (N=14493; No. missing: 1573 (9.8%))	
Heterosexual	7571 (52.2%)
MSM	6091 (42.0%)
IDU	365 (2.5%)
MTCT	174 (1.2%)
Other	292 (2.0%)
Nationality (N=15353; No. missing: 713 (4.4%))	
Belgian	8209 (53.5%)
SSA	4488 (29.2%)
European	1608 (10.5%)
Other	1048 (6.8%)
Time period of HIV diagnosis (N=15349; No. missing: 717 (4.5%))	
1980-89	678 (4.4%)
1990-99	3010 (19.6%)
2000-09	6655 (43.4%)
2010-16	5006 (32.6%)
Nadir CD4 (N=15938; No. missing: 128 (0.8%))	

0 - < 350	8396 (52.7%)
≥ 350	7542 (47.3%)
ART status (N=15237; No. missing: 829 (5.2%))	
Ever on ART	14117 (92.6%)
No ART	1120 (7.4%)
Systolic blood pressure (N=9430; No. missing: 6636 (41.3%))	
High	2909 (30.8%)
Normal	6521 (69.2%)
Smoking (N=8887; No. missing: 7179 (44.7%))	
Yes	3472(39.1%)
No	5415 (60.9%)
BMI (N=7565; No. missing: 8501 (52.9%))	
≥ 30 (Obesity)	1151 (15.2%)
< 30	6414 (84.8%)

Figure 2. Cumulative incidence for return to HIV care and death after the initial one-year period of HCI, Belgium.

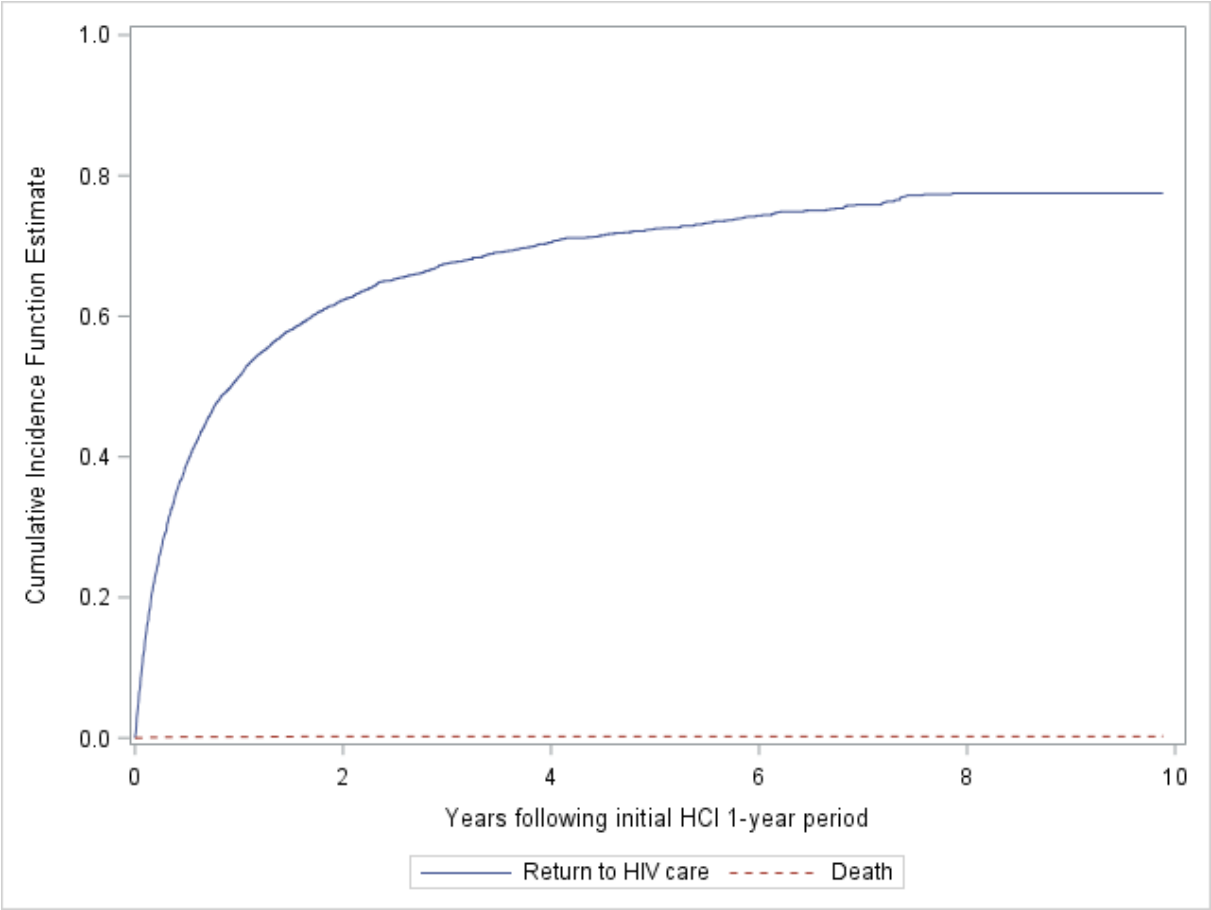

Table 2: Crude and adjusted relative risk for HCI, for return in HIV care and for experiencing a gap during HCI, Belgium, 2007-2016.

	Among all patients in HIV care		Among those in HCI		Among those returned	
	Crude RR for HCI	Adjusted RR for HCI	Crude HR for return	Adjusted* HR for return	Crude OR for gap	Adjusted* OR for gap
Gender						
Men	ref	ref	ref	ref	ref	ref
Women	**1.1 (1.1-1.2)**	**0.8 (0.8-0.9)**	**1.2 (1.1-1.3)**	**1.1 (1.0-1.3)**	**1.2 (1.0-1.4)**	**1.4 (1.1-1.6)**
Age						
18-24 years	**3.4 (3.0-3.9)**	**2.1 (1.8-2.5)**	1.1 (0.9-1.3)	**1.4 (1.1-1.6)**	**6.1 (4.2-9.1)**	**3.9 (2.5-6.2)**
25-39 years	**2.1 (1.9-2.3)**	**1.6 (1.4-1.7)**	1.0 (0.9-1.1)	**1.2 (1.1-1.4)**	**3.2 (2.6-4.0)**	**2.5 (1.9-3.2)**
40-49 years	**1.4 (1.3-1.5)**	**1.2 (1.1-1.3)**	1.1 (1.0-1.2)	**1.1 (1.0-1.3)**	**1.8 (1.4-2.3)**	**1.7 (1.3-2.1)**
≥ 50 years	ref	ref	ref	ref	ref	ref
Mode of HIV acquisition						
Hetero	ref	ref	ref	ref	ref	ref
MSM	**0.7 (0.7-0.8)**	**0.7 (0.6-0.8)**	**0.8 (0.8-0.9)**	**0.9 (0.8-1.0)**	1.2 (1.0-1.4)	1.1 (0.9-1.5)
IDU	**1.9 (1.6-2.2)**	**1.5 (1.2-1.8)**	1.0 (0.8-1.2)	1.1 (0.9-1.3)	0.9 (0.6-1.4)	0.8 (0.5-1.2)
MTCT	1.1 (0.8-1.5)	0.8 (0.6-1.1)	**1.5 (1.1-2.0)**	1.1 (0.8-1.6)	1.8 (0.9-3.6)	1.6 (0.7-3.7)
Other	0.9 (0.7-1.1)	0.9 (0.7-1.2)	**0.7 (0.5-1.0)**	**0.7 (0.5-1.0)**	0.9 (0.5-1.6)	0.9 (0.5-1.8)
Nationality						
Belgian	ref	ref	ref	ref	ref	ref
SSA	**1.7 (1.6-1.9)**	**1.4 (1.3-1.6)**	**0.8 (0.7-0.8)**	**0.7 (0.7-0.8)**	1.1 (0.9-1.3)	1.1 (0.9-1.3)
Europe	**2.1 (1.9-2.3)**	**1.8 (1.6-2.0)**	**0.4 (0.4-0.5)**	**0.5 (0.4-0.6)**	0.9 (0.7-1.2)	**0.7 (0.5-1.0)**
Other	**2.0 (1.7-2.2)**	**1.5 (1.3-1.7)**	**0.6 (0.5-0.6)**	**0.7 (0.5-0.8)**	1.0 (0.7-1.4)	0.8 (0.6-1.2)
Systolic BP						
Normal	ref	ref	ref	ref	ref	ref
High	**0.7 (0.7-0.8)**	**0.8 (0.8-0.9)**	1.1 (1.0-1.2)	1.0 (0.9-1.1)	**0.7 (0.6-0.9)**	0.9 (0.7-1.1)
Obesity						
BMI<30	ref	ref	ref	ref	ref	ref
BMI>=30	**1.2 (1.1-1.3)**	1.1 (1.0-1.3)	1.1 (0.9-1.2)	1.0 (0.9-1.1)	1.0 (0.8-1.4)	1.1 (0.8-1.5)
Smoking						
No	ref	ref	ref	ref	ref	ref
Yes	1.0 (0.9-1.0)	1.1 (1.0-1.2)	1.0 (0.9-1.1)	1.1 (0.9-1.2)	1.1 (0.9-1.4)	1.1 (0.8-1.4)
Time since HIV diagnosis						
< 1 yr.	**3.2 (2.9-3.5)**	**1.3 (1.1-1.4)**	**0.5 (0.4-0.5)**	**0.5 (0.5-0.6)**	**4.4 (3.3-5.9)**	1.4 (0.7-2.0)
1 to 3 yr.	**1.7 (1.6-1.9)**	1.0 (0.9-1.1)	**0.7 (0.6-0.7)**	**0.7 (0.7-0.8)**	**2.8 (2.2-3.6)**	1.1 (0.9-1.3)
>3 to 10 yr.	**1.3 (1.2-1.4)**	1.0 (0.9-1.1)	**0.8 (0.7-0.9)**	**0.8 (0.8-0.9)**	**1.7 (1.4-2.0)**	**2.2 (1.7-2.9)**
>10 yr.	ref	ref	ref	ref	ref	ref
CD4						
>=350	ref	ref	ref	ref	ref	ref
<350	**2.4 (2.2-2.6)**	**2.2 (2.0-2.4)**	**0.8 (0.7-0.9)**	**0.8 (0.7-0.9)**	**2.1 (1.7-2.6)**	**2.2 (1.7-2.9)**
ART						
Yes	ref	ref	ref	ref	ref	ref
No	**4.6 (4.3-4.9)**	**4.4 (4.1-4.7)**	0.9 (0.9-1.0)	1.1 (1.0-1.2)	**7.0 (5.6-8.8)**	**5.3 (4.1-6.9)**
Degree of urbanisation						
Low	0.9 (0.8-1.0)	0.9 (0.7-1.0)	1.0 (0.8-1.3)	1.1 (0.9-1.3)	1.0 (0.7-1.4)	1.0 (0.7-1.5)
Mid	ref	ref	ref	ref	ref	ref

High	**1.2 (1.1-1.3)**	1.0 (0.9-1.1)	0.9 (0.8-1.1)	1.0 (0.9-1.1)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Municipality income						
Low	**1.2 (1.1-1.3)**	1.0 (0.9-1.2)	0.9 (0.8-1.0)	0.9 (0.8-1.1)	1.0 (0.8-1.3)	1.1 (0.8-1.4)
Mid	1.1 (1.0-1.2)	0.9 (0.8-1.0)	1.0 (0.9-1.2)	1.0 (0.9-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.3)
High	ref	ref	ref	ref	ref	ref
Regularity of HIV care						
Regular	ref	ref	ref	ref	ref	ref
Not regular	0.9 (0.8-1.1)	**0.8 (0.7-0.9)**	**1.3 (1.1-1.5)**	1.2 (1.0-1.4)	1.1 (0.8-1.6)	1.0 (0.7-1.5)

** Relative risks are adjusted for all variables statistically significant at univariate analysis and HRC and year of HIV care (year of HCI for the analyses of return to care and gap in care)*

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Conflict of interest

The authors declare no conflict of interest.

Authors contributions

DVB and JM defined the research theme. DVB, HVO and JM designed the study. EF, SDW and CWT contributed to data collection. DVB and AS performed the data management. DVB performed the statistical analyses and drafted the manuscript. EF, SDW, AS, HVO and JM supervised the study. All authors contributed to interpretation, reviewed drafts of the manuscript, and approved the final manuscript.