Clinical Infectious Diseases

BRIEF REPORT

Non-AIDS Comorbid Conditions in Persons Living With Human Immunodeficiency Virus (HIV) Compared With Uninfected Individuals 10 Years Before HIV Diagnosis

Andreas Ronit,[1] Jan Gerstoft,[1] Lars Nielsen,[2] Rajesh Mohey,[3] Lothar Wiese,[4] Birgit Kvinesdal,[5] Niels Obel,[1] and Magnus G. Ahlström[1]

[1]Department of Infectious Diseases 8632, Rigshospitalet and [2]Department of Infectious Diseases, Hvidovre Hospital, Copenhagen University Hospital, [3]Department of Infectious Diseases, Skejby University Hospital, Aarhus, [4]Department of Internal Medicine, Division of Infectious Diseases, Zealand University Hospital, Roskilde, and [5]Department of Internal Medicine, Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark

We evaluated the impact of non–human immunodeficiency virus (HIV) risk factors by assessing the prevalence of non-AIDS comorbidity up to 10 years before HIV diagnosis in a population-based cohort of persons living with HIV and the background population. These data demonstrates a trend toward increased non-AIDS comorbidity before HIV diagnosis.

Keywords. HIV; non-AIDS comorbidity; non-communicable disease; lifestyle; smoking.

Access to combination antiretroviral therapy (cART) has significantly decreased AIDS-related morbidity and mortality rates. As a consequence, the median survival for a 50-year-old individual living with human immunodeficiency virus (HIV) in Denmark, increased >10 years from 1996–1999 to 2006–2014, but the mortality rate remains higher than in the background population [1]. Similar trends have been reported in North America [2]. In addition, persons living with HIV (PLWH) seem to have an excess rate of most age-related comorbid conditions compared with the background population [3]. Besides lifestyle and environmental factors, risk factors directly associated with HIV infection, such as adverse effects of cART, immunodeficiency, and chronic immune activation, may be causative factors [4–6]. Owing to the inability of observational studies to eliminate residual confounding, it is often difficult to separate the impact of HIV-related and HIV-unrelated risk factors.

In an effort to temporally isolate the aggregated effect of non-HIV risk factors, we assessed the prevalence of non-AIDS comorbid conditions from 10 years before HIV diagnosis, using a nationwide population-based cohort of PLWH without injection drug use (IDU) and a matched cohort from the background population.

Received 21 February 2018; editorial decision 30 March 2018; accepted 12 April 2018; published online April 17, 2018.

Correspondence: A. Ronit, Department of Infectious Diseases 8632, University Hospital Rigshospitalet, Blegdamsvej 9B, DK-2100 Copenhagen Ø, Denmark (andreas.ronit@regionh.dk).

Clinical Infectious Diseases® 2018;67(8):1291–3

DOI: 10.1093/cid/ciy325

METHODS

Three data sources were used. The Danish HIV Cohort Study is a population-based, nationwide cohort study including all PLWH treated at Danish HIV centers since 1 January 1995. Individuals are consecutively enrolled at first contact with an HIV center, and data are updated annually [7]. The Danish Civil Registration System stores information on all Danish citizens, including data on migration, birth, and death, and it was used to identify uninfected controls. Finally, we used the Danish National Hospital Registry (DNHR) to identify comorbid conditions for both PLWH and the uninfected controls. The DNHR was established in 1977 and stores information on all inpatient and outpatient admission to nonpsychiatric hospitals. Diseases are categorized according to the *International Classification of Diseases* (*Eighth Revision* or *Tenth Revision*), for all admissions (*Ninth Revision* coding was never adopted in Denmark). Approval from a health research ethics committee system is not required by Danish legislation governing this type of research. The study was approved by the Danish Data Protection Agency (reference No. 2008-41-1781).

We used a composite measure of comorbidity [8]—Charlson comorbidity index (CCI) ≥1—to define the presence of any non-AIDS comorbid condition. The CCI includes 19 conditions: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, gastrointestinal disease, and mild and serious liver disease, uncomplicated and complicated diabetes mellitus, hemiplegia, moderate and severe renal disease, cancer, leukemia, lymphoma, and secondary metastasis. The CCI was not age adjusted, and HIV/AIDS and associated cancers (eg, non-Hodgkin lymphoma) were omitted from the CCI in the current study.

We also evaluated 5 additional comorbid conditions separately (*International Classification of Diseases* coding is supplied in online Supplement 1): (1) cardiovascular disease (myocardial infarction and congestive heart failure), (2) liver diseases not including infectious hepatitis, (3) renal disease, (4) non–AIDS-defining cancers, and (5) chronic pulmonary disease. The positive predictive value of the coding in DNHR for these conditions is high (98%) [9].

For PLWH, we defined the index date as the date of HIV diagnosis. We included all PLHW who (1) had a Danish personal identification number, (2) were living in Denmark

from 10 years before the index date until the index date, (3) had HIV diagnosed between January 1995 and July 2015, (4) were aged ≥16 years at the index date, and (5) did not report IDU as route of infection (to eliminate confounding from this risk factor). From the Danish Civil Registration System, we identified 5 uninfected controls for each individual in the PLWH cohort; controls were matched for age and sex and assigned the same index date. Uninfected controls were eligible for inclusion if they were present in Denmark 10 years before index date until the index date. All individuals were followed up from 10 years before index date until 10 years after the index date, loss to follow-up, emigration, death, or 1 July 2015, whichever came first. We depicted annual unadjusted odds ratios (ORs) for non-AIDS comorbid conditions. If an individual was registered with one of the events of interest, this individual would continue to be counted as diseased throughout follow-up. Fisher exact test was used to compare the prevalence of outcomes at different time points. Statistical analyses were performed using R software, version 3.3.2.

RESULTS

We identified 2322 eligible study participants from the Danish HIV Cohort Study. A matched cohort of 11 706 uninfected controls was included. The median age at diagnosis was 40.3 years (interquartile range, 32.6–50.0 years), and 87.2% were male in both cohorts. PLWH were mostly white (92.1%) and men having sex with men (57.8%) or heterosexual (35.8%). The mean CD4 cell count at time of HIV diagnosis was 623/μL (standard deviation, 324/μL), and 1917 (82.6%) were receiving cART 5 years after HIV diagnosis.

The point prevalence of any non-AIDS comorbid condition increased in both groups over time and was higher in PLWH than in the control cohort throughout the 10-year period before HIV diagnosis, although reaching statistical significance only 1 and 2 years before diagnosis (Figure 1). Thus, 10 years before HIV diagnosis, the prevalence of any non-AIDS comorbid condition was 5.5% (95% confidence interval [CI], 4.7%–6.5%) in PLWH and 4.8% (4.4%–5.2%) in uninfected controls, and the ORs of any non-AIDS comorbid condition were 1.15 (95% CI, .94–1.40) and 1.16 (1.00–1.34), respectively, at 10 and 2 years before diagnosis. The odds of liver disease was higher in PLWH 10 years before HIV diagnosis (OR, 1.94; 95% CI, 1.13–3.23). The 3 most common liver conditions included unspecified hepatitis (46%), alcoholic liver cirrhosis (22%), and alcoholic fatty liver disease (12%) (Figure 1).

The prevalence of any non-AIDS comorbid condition, cardiovascular disease, liver disease, non–AIDS-defining cancers, chronic pulmonary disease, and renal disease increased around the time of HIV diagnosis and was thereafter consistently higher than for uninfected controls (Figure 1). For example, the prevalence of cardiovascular disease 5 years after HIV diagnosis was 7.3% (95% CI, 6.2%–8.7%) for PLWH versus 4.5% (4.1%–5.0%) in the control cohort (OR, 1.68; 95% CI, 1.35–2.06). The ORs for non-AIDS comorbid condition stratified by age (≤45 or >45 years) are shown in online Supplement 2.

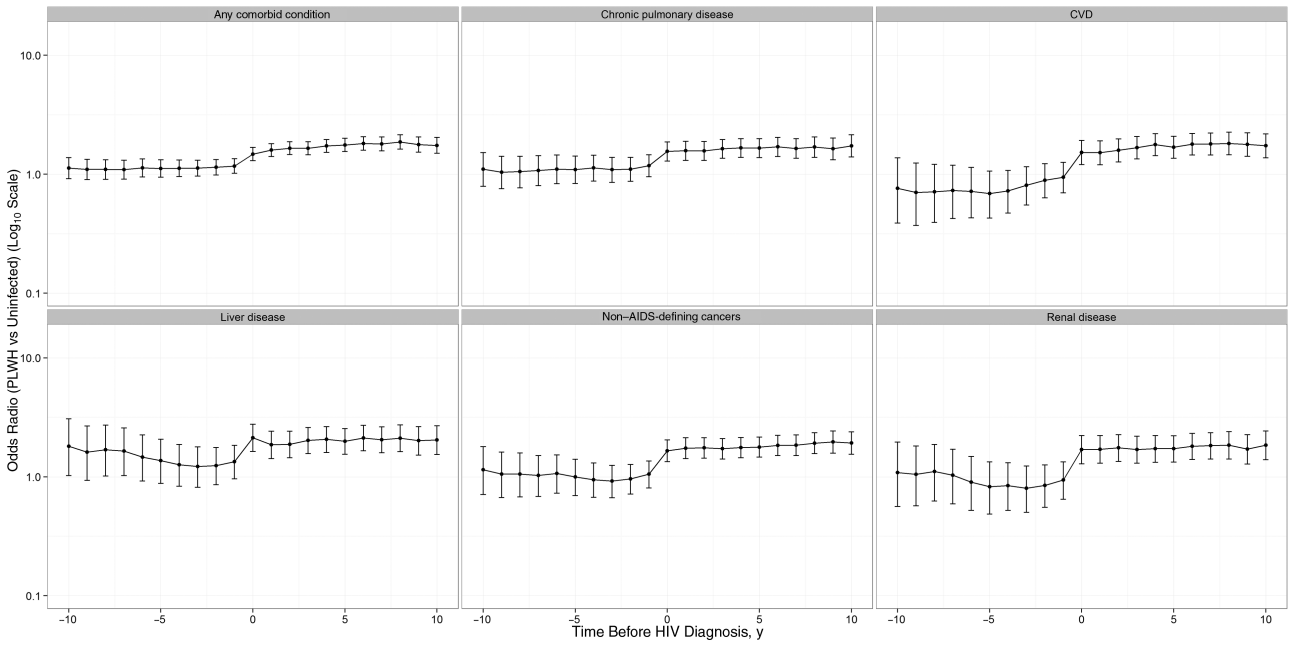

Figure 1. Odds ratios of non-AIDS comorbid conditions in persons living with human immunodeficiency virus (HIV) (PLWH) versus uninfected controls. Abbreviation: CVD, cardiovascular disease.

DISCUSSION

To the best of our knowledge this is the first study to assess non-AIDS comorbid conditions before HIV diagnosis. We show that the prevalence of non-AIDS comorbid condition may be higher in PLWH before HIV diagnosis, which is probably explained by higher rates of smoking, alcohol use, and other non–HIV-related risk factors. Liver diseases, primarily driven by unspecified hepatitis, seemed to be an important contributor to the excess risk of non-AIDS comorbid conditions before HIV diagnosis.

We observed a substantial increase in the prevalence and odds of all non-AIDS comorbid conditions around the time of HIV diagnosis. The biological consequences of HIV infection (eg, immunodeficiency and immune activation) or cART initiation may explain this phenomenon. The psychological consequences of an HIV diagnosis may also induce behavioral changes that place individuals at increased risk of non-AIDS comorbid conditions. However, because a long natural history often underlies these conditions, the upward shift in odds around the time of HIV diagnosis is more likely to reflect an epidemiological phenomenon in which a HIV diagnosis led to a subsequent diagnosis of another preexisting condition. Conversely, a diagnosis of non-AIDS comorbid condition may have led to a diagnosis of HIV infection. The actual prevalence of non-AIDS comorbid condition before acquisition of HIV infection may consequently have been even higher than what we observed. Interestingly, the increased risk of non-AIDS comorbid condition seemed to stabilize shortly after the date of HIV diagnosis and did not continue to accelerate during subsequent follow-up, which may suggest that the increased prevalence of non-AIDS comorbid condition may be an epidemiological phenomenon rather than due to a biological effect of HIV.

There were several important limitations to these analyses. Assessment of non-AIDS comorbid condition before HIV diagnosis was conditioned on being alive after 10 years, which may have introduced bias. Moreover, the designated index date (date of HIV diagnosis) is not the same as the date of HIV infection. In most infected individuals, HIV infection is diagnosed during chronic rather than acute infection, so they may have been HIV infected for several years before diagnosis, causing misclassification of exposure. We did not have access to data on smoking, alcohol use, and drug abuse in the control cohort. The prevalence of IDU in Denmark is low (approximately 0.2%), so inclusion of these individuals in the control population does not substantially affect our estimates of relative risk. Finally, we cannot rule out the possibility of undercoding in the control cohort or miscoding for some conditions (eg, unspecified hepatitis may include cases of infectious hepatitis). The strength of the study includes the nation-wide population-based design, a well-matched cohort of uninfected individuals with identical registry data, and a long follow-up time without loss to follow-up.

In conclusion, an increased prevalence of non-AIDS comorbid condition was observed before HIV diagnosis, which probably reflects a time before HIV-related factors contribute to disease development. The excess burden of non-AIDS comorbid conditions before HIV diagnosis complicates the effort to close the gap in life expectancies and traditional preventive lifestyle interventions should be commenced at the time of HIV diagnosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgment. This work was supported by the Preben and Anne Simonsens Foundation, the Novo Nordisk Foundation, Rigshospitalet, Copenhagen University, the Danish AIDS Foundation, the Augustinus Foundation, and the Danish Health Foundation.

Potential conflicts of interest. J. G. has received honoraria for consulting and presenting, paid to his institution from Gilead, AbbVie, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen, and Medivir. N. O. has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag, and Swedish Orphan. M. G. A. has received travel grants from GlaxoSmithKline and Janssen. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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