BMJ Open

Chronic comorbidities and the use of co-medications in HIV-positive adults in Japan between 2010 and 2015: A cross-sectional study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019985
Article Type:	Research
Date Submitted by the Author:	11-Oct-2017
Complete List of Authors:	Ruzicka, Daniel; MSD K.K., Medical Affairs Imai, Kentaro; MSD K.K., Oncology Clinical Development Takahashi, Kenichi; MSD K.K., Japan Development Naito, Toshio; Juntendo University, Department of General Medicine
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases
Keywords:	INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

[Title Page]

Title:

Chronic comorbidities and the use of co-medications in HIV-positive adults in Japan between 2010 and 2015: A cross-sectional study

Authors and affiliations:

Daniel J. Ruzicka[1]; Kentaro Imai[2]; Kenichi Takahashi[3]; Toshio Naito[4]

[1] Medical Affairs, MSD K.K., Tokyo, Japan

[2] Oncology Clinical Development, MSD K.K., Tokyo, Japan

[3] Japan Development, MSD K.K., Tokyo, Japan

[4]Department of General Medicine, Juntendo University, Tokyo, Japan

Corresponding author:

Daniel J. Ruzicka

Medical Affairs, MSD K.K.

Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan

Tel.: +81-3-6272-1681, E-mail: daniel.ruzicka@merck.com

Word count: 3442 words

ABSTRACT (242/300 words)

Objectives: To investigate the prevalence of chronic comorbidities and the use of co-medications in Japanese HIV-positive patients aged ≥18 years.

Design: An observational, retrospective, cross-sectional study.

Setting: A medical claims database of Japanese hospitals.

Participants: A total of 1445 HIV-positive patients aged ≥18 years with a prescription record of antiretrovirals between January 2010 and December 2015 were identified from the database.

Outcome measures: The number and types of chronic comorbidities as well as the number and types of co-medications in different age groups of HIV-positive patients.

Results: The median (range) age of the patients was 45 (18–90) years, and 90.4% of patients were male. Of 1445 patients, 981 (67.9%) patients had at least one chronic comorbidity. Common chronic comorbidities included lipid disorders (31.6%), diabetes (26.8%), hypertension (18.2%), and hepatitis B/C co-infection (18.2%). Patients in the older age groups had greater numbers of chronic comorbidities. The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. The majority of patients used at least one co-medication, and patients in the older age groups used greater numbers of co-medications. The most common

therapeutic category of co-medications included antacids, antiflatulents, and antiulcerants (31.7%). Of 148 malignancies reported in 116 patients, 81 were AIDS-defining cancers, and 67 were non-ADIS-defining cancers.

Conclusions: Chronic comorbidities and co-medications were more common in older Japanese HIV-positive patients, suggesting the need for special attention to the appropriate management of HIV and comorbidities in this patient population.

Strengths and limitations of this study

- This is the first study to examine the chronic comorbidities and co-medications in HIV-positive adults in Japan, using a large-scale medical claims database.
- Patients were stratified into small age groups, which provided a clear picture of patients' comorbidity and co-medication profiles by age.
- The cross-sectional study design did not allow inference of causality between HIV infection and chronic comorbidities or co-medications.
- This study has limitations inherent in the use of a medical claims database, such as poorly recorded or absent information, which may result in misclassification.
- The generalizability of the study results may be limited because data contained in the database were collected from the hospitals that can provide acute-care.

[Text]

INTRODUCTION

Improvements in antiretroviral therapy (ART) over the last 15–20 years have prolonged the life expectancy of HIV-positive patients. It has been reported that the life expectancy of HIV-positive patients is now similar to that of HIV-negative individuals.[1] However, in addition to HIV-related conditions, age-associated chronic comorbidities negatively affect the mortality rates of HIV-positive patients, as shown in various international studies.[2-6] The increased number of chronic comorbidities in older HIV-positive patients is partly attributed to age-related changes in the physiological function and pharmacokinetics and/or pharmacodynamics of drugs.[7, 8] Other studies have suggested that a longer duration of ART, which leads to increased toxicity, and HIV-induced persistent immunodeficiency and inflammation might also contribute to the increased number of comorbidities or the higher prevalence of certain comorbidities in older HIV-positive patients.[9-12] It was also reported that chronic inflammation and immune system changes by HIV infection may be involved in the mechanisms for possible premature ageing in HIV-positive patients.[13]

Previous studies have shown that over 50% of HIV deaths are caused either by coinfection or age-associated non-infectious chronic comorbidities, including vascular

diseases, hypertension, lipid disorders, diabetes mellitus, kidney diseases, malignancies, and bone disorders.[14, 15] Such age-associated chronic comorbidities in HIV-positive patients have presented a new challenge for HIV treatment, especially in an ageing society such as Japan, which has the longest life expectancy worldwide.[16] In Japan, more than 10% of newly diagnosed HIV-positive patients in 2015 were aged ≥50 years,[17] indicating that a number of HIV-positive patients are relatively older. Although the majority of newly diagnosed HIV-positive patients were aged 20–49 years (88.2%),[17] these patients are also able to live to old age by appropriate management with antiretrovirals; thus, in line with the trends in other counties, in which the proportions of HIV-positive patients aged ≥50 years have increased,[18] the number of older HIV-positive patients may also be increasing in Japan. Because of the potentially long lifespans of HIV-positive patients in Japan, it is important to obtain real-world data regarding the comorbidity profiles of the Japanese HIV-positive population.

Despite the importance of the association of chronic comorbidities with mortality rates in HIV-positive patients, only a few small studies on chronic comorbidities in Japanese HIV-positive patients have been published to date,[19, 20] and there have been no large multi-centre epidemiological studies of chronic comorbidities in HIV-positive patients in Japan. Therefore, we initiated a retrospective,

cross-sectional study using a medical claims database to investigate 1) the frequency and type of chronic comorbidities of interest and 2) the use of co-medications among HIV-positive patients aged ≥18 years in Japan. The patient profiles of chronic comorbidities and co-medications in different age groups should provide a better understanding of the characteristics of the Japanese HIV-positive population.

METHODS

Study design

This was an observational, retrospective, cross-sectional database study. Study data were extracted from a medical claims database of acute care hospitals in Japan, constructed by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). This electronic record-based medical claims database contained information from approximately 17 million patients in 288 hospitals (as of January 2017) in Japan (https://www.mdv.co.jp/press/2017/detail_743.html). The data include approximately 17% of all acute care hospitals in Japan that use the diagnosis procedure combination/per-diem payment system. The majority of patients in the database are aged 15–64 years (51.5%), followed by ≥65 years (34.2%) and 0–14 years (14.3%).

Data included in the database were age, sex, department visited, date of medical service, diagnosis codes, hospitalization, medical procedures, and prescriptions.

Study population

HIV-positive patients aged ≥18 years with a diagnosis record of HIV and with a prescription record of antiretrovirals between January 2010 and December 2015 (study period) were enrolled in the study. All data of the HIV-positive patients during the study period, including data prior to the diagnosis of HIV infection, were considered as data pertaining to the HIV-positive patients and included in the analysis.

HIV-positive patients in the database were identified by the presence of at least one record of the International Classification of Diseases 10th Revision (ICD-10) codes B20–24: HIV disease resulting in infectious and parasitic diseases (B20), malignant neoplasms (B21), other specified diseases (B22), other conditions (B23), and unspecified HIV disease (B24). To examine polypharmacy in HIV-positive patients that could induce a potential drug-drug interaction (DDI) between antiretrovirals and co-medications as well as to exclude doubtful HIV-positive patients, such as those poorly recorded or intentionally recorded for the purpose of a claim, the patients were required to have at least one prescription record of an antiretroviral. An antiretroviral

was defined as a prescription for any of the following antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors.

The data of patients who met these criteria (n=1445) during the study period were extracted from the database. The patients were grouped based on their age at the time of their last hospital visit as follows: 18–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years old.

Definitions of measures

The following patient data during the study period were extracted from the database: demographic characteristics (age, sex), diagnoses of AIDS-defining illnesses, diagnoses of chronic comorbidities, prescriptions of antiretrovirals, and prescriptions of co-medications. The AIDS-defining illnesses were identified using the ICD-10 codes and disease names, which included the following: AIDS (B24); AIDS-related complex (B24); HIV disease resulting in cytomegaloviral disease (B20.2), candidiasis (B20.4), *Pneumocystis jirovecii* pneumonia (B20.6), Burkitt lymphoma (B21.1), and encephalopathy (B22.0); Kaposi sarcoma (B21.0/C46.9); and non-Hodgkin lymphoma

(B21.2/C82–85/C91.5).

The chronic comorbidities were defined based on the ICD-10 codes, and if the code was recorded at least once during the study period, the patients were considered to have that chronic comorbidity. All data of chronic comorbidities and co-medications during the study period were included regardless of whether they were recorded before or after the HIV infection, because it was considered from a clinical point of view that the comorbidities developed before the HIV infection were persistent over the whole study period. The chronic comorbidities in this study included type II diabetes (E11–14), hypertension (I10–15, except for I11/I13), lipid disorders (hypercholesterolaemia/hyperlipidaemia [E78.0–78.5]), vascular diseases (hypertensive heart and renal diseases [I11/I13], angina pectoris [I20], myocardial infarction [I21–22], stroke [I64]), kidney diseases (chronic renal failures [N18–19], urolithiasis [N20–21]), malignancies (B21.0/B21.2/C00–97), psychiatric disorders (dementia [F01/F03], psychosis [F20–29], mania and depression [F30–32], anxiety [F40–41], insomnia [F51]), bone disorders (osteoporosis [M80–81]), and hepatitis B/C co-infection (B18). Among malignancies, Kaposi sarcoma (B21.0/C46.9), non-Hodgkin lymphoma (B21.2/C82–85/C91.5) and cervix uteri (C53.9) were defined as AIDS-defining cancers according to the Shiels et al.'s study,[21] and all other malignancies were defined as

non-AIDS-defining cancers.

The co-medication was defined as a non-antiretroviral medication prescribed for use for ≥30 days in total during the study period based on the therapeutic subgroups (2nd level) of the Anatomical Therapeutic Chemical (ATC) codes.

Ethical statement

Because this was an observational study using de-identified claims data and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to a study exclusively using de-identified data, the requirement for informed consent was waived.

Statistical Analysis

Demographic data were summarized descriptively using the median and range for continuous variables or the number and percentage (%) of patients for categorical variables. Chronic comorbidities and co-medications were summarized descriptively by age group. The 95% confidence intervals (CIs) were calculated using the exact binomial method proposed by Clopper and Pearson.[22] All statistical analyses were performed using SAS release 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. Overall, 1445 HIV-positive patients enrolled from 47 hospitals were included in this study, with a median (range) age of 45 (18–90) years, and 90.4% were male. Of these patients, 703 (48.7%) had AIDS. The age and sex distribution of patients is shown in Figure 1. The majority of patients were aged 40–49 years, followed by 30–39, 50–59, 60–69, 18–29 and ≥70 years.

Table 1. Demographic characteristics of HIV-positive patients (n=1445)

	Total (n=1445)
	n (%)
Age (years), median (range)	45 (18–90)
Male	1306 (90.4)
AIDS	703 (48.7)
Chronic comorbidity	
Diabetes	387 (26.8)
Hypertension	263 (18.2)
Lipid disorders	456 (31.6)
Vascular diseases	62 (4.3)
Kidney diseases	110 (7.6)
Malignancies	116 (8.0)
Psychiatric disorders	219 (15.2)

Bone disorders	85 (5.9)
Hepatitis B/C co-infection	263 (18.2)
Use of a non-antiretroviral medication*	1086 (75.2)
Type of key drug among antiretrovirals	
INSTI	789 (54.8)
NNRTI	359 (24.9)
PI	617 (42.8)

*A non-antiretroviral medication prescribed for use for ≥30 days in total during the study period was taken into consideration.
INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Chronic comorbidities

Overall, 1961 chronic comorbidities were reported in 981 (67.9%) HIV-positive patients, and 274 (19.0%) patients had three or more chronic comorbidities. The most common chronic comorbidities were lipid disorders (31.6%; 95% CI, 29.2–34.0%), followed by diabetes (26.8%; 95% CI, 24.5–29.1%), hypertension (18.2%; 95% CI, 16.2–20.3%), and hepatitis B/C co-infection (18.2%; 95% CI, 16.2–20.3%) (Table 1).

Figure 2A shows the number of chronic comorbidities by age. Although 57.0% (57/100) of patients aged 18–29 years had no chronic comorbidity, the proportions of patients with no chronic comorbidity decreased in the older age groups. More patients in the older age groups had greater numbers of chronic comorbidities: 21.0% (65/309)

of patients aged 30–39 years, 44.5% (114/256) of patients aged 50–59 years, and 70.7% (58/82) of patients aged ≥70 years had two or more chronic comorbidities. No patients aged 18–29 years had four or more chronic comorbidities, while 25.6% (21/82) of patients aged ≥70 years had four or more chronic comorbidities.

Figure 2B shows the prevalence of different types of chronic comorbidities by age group. The prevalence of most chronic comorbidities tended to be higher in the older age groups, although the prevalence of psychiatric disorders and hepatitis B/C co-infection was similar across all age groups (12.0–17.8% and 17.1–20.4%, respectively). The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. Hypertension was the most common chronic comorbidity in the ≥70-year group (52.4%; 95% CI, 41.1–63.6%), diabetes in the 60–69-year group (46.3%; 95% CI, 39.0–53.7%), and lipid disorders in the 50–59-year group (35.9%; 95% CI, 30.1–42.1%). The prevalence of vascular diseases, kidney diseases, malignancies, or bone disorders in the ≥70-year group was 13.4–18.3%, which was approximately 10–15% higher than its counterpart in the 18–29-year group (1.0–4.0%).

Co-medications

Of 1445 HIV-positive patients, 1086 (75.2%) patients used at least one co-medication and 342 (23.7%) patients used five or more co-medications, besides antiretrovirals. Figure 3A shows the number of co-medications (excluding antiretrovirals) by age group. The proportions of patients who used at least one co-medication were 53.0% (53/100) in the 18–29-year group, 76.1% (388/510) in the 40–49-year group, and 86.6% (71/82) in the ≥70-year group. More patients in the older age groups used greater numbers of co-medications: 11.0% (34/309) of patients in the 30–39-year group, 29.3% (75/256) of patients in the 50–59-year group, and 47.6% (39/82) in the ≥70-year group used five or more co-medications.

The ten most common therapeutic categories were antacids, antiflatulents, and antiulcerants (31.7%); systemic antibacterials (22.2%); psycholeptics (22.0%); systemic antihistamines (18.5%); lipid-regulating/anti-atheroma preparations (17.2%); anti-inflammatory and anti-rheumatic products (15.5%); antidiarrhoeals, oral electrolyte replacers and intestinal anti-inflammatories (12.1%); agents acting on the renin-angiotensin system (11.1%); vitamins (10.2%); and cough and cold preparations (9.6%). For the top 5 common co-medications, the proportions of patients who took respective co-medications by age group are shown in Figure 3B. Antacids, antiflatulents, and antiulcerants were the most common in most of the age groups, especially in the

≥70-year group (52.4%). The proportions of patients taking systemic antibacterials, psycholeptics, or systemic antihistamines were similar across all age groups. Lipid-regulating agents were used more commonly in the older age groups, being used in 25–30% of patients aged ≥50 years.

Malignancies

In this study, 148 malignancies were reported in 116 HIV-positive patients, including 81 AIDS-defining cancers and 67 non-AIDS-defining cancers. More than two-thirds of non-AIDS-defining cancers (46 of 67) were observed in patients aged ≥50 years. Table 2 shows the proportions of patients who had cancers among these 116 patients with malignancies. For non-AIDS-defining cancers, the types of cancers that were present in more than one patient are listed. Non-Hodgkin lymphoma was the most common type of AIDS-defining cancer (54.3%), and bronchus or lung cancers were the most common type of non-AIDS-defining cancers (6.9%).

Table 2. Proportions of patients with different types of AIDS-defining cancers and non-AIDS-defining cancers in HIV-positive patients with malignancies (n=116)

	Patients with malignancy (n=116)
	n (%)

AIDS-defining cancer	
Non-Hodgkin lymphoma	63 (54.3)
Kaposi sarcoma	16 (13.8)
Cervix uteri	2 (1.7)
Non-AIDS-defining cancer*	
Bronchus or lung	8 (6.9)
Secondary malignant neoplasm of bone and bone marrow	6 (5.2)
Colon	3 (2.6)
Breast	3 (2.6)
Malignant neoplasm, without specification of site	3 (2.6)
Secondary malignant neoplasm of brain and cerebral meninges	3 (2.6)
Acute myeloblastic leukaemia (AML)	3 (2.6)
Multiple myeloma	3 (2.6)
Stomach	2 (1.7)
Secondary malignant neoplasm of lung	2 (1.7)
Liver cell carcinoma	2 (1.7)
Sigmoid colon	2 (1.7)
Thoracic part of oesophagus	2 (1.7)
Skin of trunk	2 (1.7)

*Non-AIDS-defining cancers that were present in more than one patient are listed.

DISCUSSION

This study quantified the prevalence of chronic comorbidities in different age groups of HIV-positive patients aged ≥18 years in Japan to understand the characteristics of an HIV-positive adult population in Japan. To date, no large-scale studies have described chronic comorbidities in HIV-positive patients in Japan. This

study found that chronic comorbidities were common in the Japanese HIV-positive population and that older patients had greater numbers of chronic comorbidities compared with younger patients.

Previous international studies reported greater numbers of comorbidities in older HIV-positive patients,[23-25] similar to the findings of the current study. For types of comorbidities, older HIV-positive patients in Switzerland and the US were more likely to have diabetes mellitus, cardiovascular diseases, non-AIDS-defining malignancies, osteoporosis, or liver diseases than younger patients.[23, 24] Similar to these studies, diabetes mellitus, vascular diseases, and bone disorders were more common in older HIV-positive patients in this study. In addition, kidney diseases were more common in older patients, as suggested by a previous study reporting that both HIV infection and increased age are associated with an increased risk of kidney diseases in HIV-positive patients.[26]

In North America, AIDS-defining cancers remain a great concern in HIV-positive patients, and the cumulative incidence by age 75 years was reported to be 4.1% for Kaposi sarcoma and 4.0% for non-Hodgkin lymphoma in 2005–2009,[27] although previous studies have reported that the incidence of non-Hodgkin lymphoma and Kaposi sarcoma in HIV-positive patients has decreased by antiretrovirals.[21, 28] In

the current study, these cancers were not commonly observed (non-Hodgkin lymphoma, 4.4% [63/1445]; Kaposi sarcoma, 1.1% [16/1445]), and the prevalence was much lower than that reported in a previous Japanese study in which non-Hodgkin lymphoma and Kaposi sarcoma were present in 37.9% and 15.2%, respectively, of autopsied HIV-positive patients with an experience of antiretrovirals from 1985–2012.[29] This difference may be attributed to the different study populations. Autopsied patients are likely examined in more detail because they might be sicker than this study population, considering that an autopsy is conducted in many cases when the cause of death is unknown. Another reason for the difference in findings may be that this study population represents HIV-positive patients in the current antiretroviral era, when the improvement of HIV management by antiretrovirals has improved their immune function.

In this study, non-AIDS-defining cancers accounted for 45% of all malignancies, and more than two-thirds of non-AIDS-defining cancers were observed in patients aged ≥50 years. A previous study showed that age-related cancers, such as lung, prostate, colorectal, and breast cancers, were common in older HIV-positive patients.[30] Another study also reported an increase in non-AIDS-defining cancers among the HIV-positive population as a consequence of the ageing of the AIDS

population.[21] In light of these previous findings, our results highlight the importance of non-AIDS-defining cancers among HIV-positive patients because of their extended lifespans. The risks for several types of non-AIDS-defining cancers (e.g., Hodgkin lymphoma, and anal, vaginal, liver, and lung cancers) were even higher in HIV-positive patients than in the general population,[28] which may further increase the importance of these cancers in older HIV-positive patients. However, because of the small number of patients with malignancies in the current study, it was difficult to illuminate any trends in the prevalence of malignancies by age group. Thus, the prevalence of malignancies by age and cancer type should be interpreted carefully and further examined in future studies.

Several international studies reported an increased risk of age-associated comorbidities in HIV-positive patients compared with the general population or the HIV-negative population.[25, 31, 32] These studies showed that HIV-positive patients had a greater number of age-associated comorbidities at earlier ages than the HIV-negative population, suggesting premature ageing in HIV-positive patients.[25, 32] Future research is being planned to determine whether our study population has more chronic comorbidities at earlier ages compared to HIV-negative populations.

Our findings that older HIV-positive patients had greater numbers of chronic comorbidities indicate an increased need for co-medications to treat these comorbidities. This indication was confirmed by results showing that more co-medications were used among older HIV-positive patients. Similar trends were observed in a previous study showing that 32% of patients aged <50 years and 54% of patients aged ≥50 years used five or more co-medications,[33] although the corresponding proportions were smaller in the current study (18.0% in patients aged <50 years and 33.7% in patients aged ≥50 years). The results suggest that the management of HIV and comorbidities in older HIV-positive patients may be complicated because of DDIs. Indeed, several international studies reported an increased potential for DDIs in older HIV-positive patients because of increased use of co-medications.[34-37] Moreover, our study showed that the use of co-medications was common even in younger HIV-positive patients and that over half of patients aged 18–29 years used at least one co-medication. In light of this finding, our results suggest the importance of potential DDIs not only in the older HIV-positive patients but also in the younger HIV-positive patients in Japan.

It was reported that expected DDIs in HIV-positive patients were mostly between PIs or NNRTIs and co-medications, such as cardiovascular agents, anti-platelet agents, psychotropics, antidepressants, analgesics, and methadone.[34, 35] In the

current study, lipid-regulating agents and agents acting on the renin-angiotensin system were commonly used in HIV-positive patients, probably reflecting the high prevalence of lipid disorders and hypertension, especially in older patients. Although the mechanisms underlying lipid disorders in HIV-positive patients are complex, ART might be partly responsible for the occurrences of lipid disorders because certain types of antiretrovirals (e.g., NNRTIs and PIs) can be associated with changes in lipid metabolism.[38, 39] Psycholeptics were also commonly used in HIV-positive patients, regardless of age, which was consistent with previous studies.[34, 35] It was reported that psychiatric disorders are common in HIV-positive patients and that HIV disease progression and treatment with antiretrovirals are associated with psychiatric disorders.[40, 41] Antacids, antiflatulents, and antiulcerants were the most common co-medications in this study (31.7%). The proportion was much higher compared to a Swiss study reporting that gastrointestinal drugs were used in 11% of patients treated with antiretrovirals.[42] The common use of antacids in the current study may be related to the high prevalence of gastric ulcers in the Japanese population: it was reported that gastric ulcers were present in 27% of hospitalized Japanese patients aged ≥65 years and that peptic ulcer remedies were the second most common therapeutic category (11.2%) of all drugs prescribed.[43] Because antacids can reduce serum concentrations of

several antiretrovirals by altering the acid environment necessary for the optimal absorption of certain drugs,[44, 45] Japanese physicians may need to pay careful attention when prescribing antiretrovirals to patients using these drugs.

Limitation

This study has some limitations. Because this was a cross-sectional study, chronic comorbidities/co-medications were not examined against the timing of a diagnosis of HIV infection. It should be noted that chronic comorbidities/co-medications in this study included those coded before a diagnosis of HIV infection. This study is limited in its ability to draw valid conclusions about possible causality between HIV infection and chronic comorbidities/co-medications, so causality should always be confirmed by more rigorous studies. Other limitations include those that are inherent to observational studies using a medical claims database, such as poorly recorded or absent information, which may result in misclassification. For example, because the database is hospital-based, medical/treatment history recorded at different hospitals could not be obtained, meaning that patients may have received co-medications for other diseases at different hospitals. Additionally, the study results may not be generalizable to the overall HIV-positive patient population in Japan,

because patients in this database of acute-care hospitals might be more ill than other HIV-positive patients treated at non-acute care hospitals; HIV treatment choices in the acute care hospitals may not be representative of those made in non-acute care hospitals; and this study excluded patients without a record of antiretrovirals who represent HIV-positive patients not taking antiretrovirals. Finally, because detailed data regarding HIV infection status were not available, we could not analyse the potential relationships between chronic comorbidities and CD4 count, HIV-RNA, or ART duration.

Conclusions

In conclusion, the results of this study demonstrated that chronic comorbidities and co-medications were more common in older HIV-positive patients in Japan, suggesting the need for special treatment and attention by physicians. The application of our results can support the development of optimal healthcare strategies for this growing population.

Acknowledgments

Medical writing and statistical supports were provided by Clinical Study Support, Inc.

Author contributions

DJR contributed to the study design. DJR, KI, and KT contributed to the data analysis and interpretation. DJR, KI, KT, and TN revised the manuscript draft critically and approved the final version of the manuscript to be published.

Funding statement

This study was supported by MSD K.K., Tokyo, Japan.

Competing interests statement

DJR, KI, and KT are employees of MSD K.K., Tokyo, Japan. TN has received no funding for this study but received lecture fees from MSD K.K., Tokyo, Japan.

Data sharing statement

No additional data are available.

REFERENCES

1. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. *Curr Opin Infect Dis* 2013;26:17–25.

2. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.

3. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011;53:1130–9.

4. Wu PY, Chen MY, Hsieh SM, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PLOS ONE* 2014;9:e104945.

5. Vance DE, Mugavero M, Willig J, et al. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care* 2011;22:17–25.

6. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014;59:1787–97.

7. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6–14.

8. Sotaniemi EA, Arranto AJ, Pelkonen O, et al. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997;61:331–9.

9. Edelman EJ, Gordon KS, Glover J, et al. The next therapeutic challenge in HIV: polypharmacy. *Drugs Aging* 2013;30:613–28.

10. Seaberg EC, Muñoz A, Lu M, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS* 2005;19:953–60.

11. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009;338:a3172.

12. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141–55.

13. Wing EJ. HIV and aging. *Int J Infect Dis* 2016;53:61–8.

14. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006;166:1632–41.

15. Sackoff JE, Hanna DB, Pfeiffer MR, et al. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145:397–406.

16. Global Health Observatory (GHO) Data. World Health Organization (2016). http://www.who.int/gho/publications/world_health_statistics/2016/en/ (accessed 19 Mar 2017).

17. Trends in AIDS occurrence report (2015). In Japanese. http://api-net.jfap.or.jp/status/2015/15nenpo/15nenpo_menu.html (Accessed 19 Mar 2017).

18. Costagliola D. Demographics of HIV and aging. *Curr Opin HIV AIDS* 2014;9:294–301.

19. Yanagimoto S, Yotsuyanagi H, Kikuchi Y, et al. Chronic hepatitis B in patients coinfected with human immunodeficiency virus in Japan: a retrospective multicenter analysis. *J Infect Chemother* 2012;18:883–90.

20. Yanagisawa N, Ando M, Ajisawa A, et al. Clinical characteristics of kidney disease in Japanese HIV-infected patients. *Nephron Clin Pract* 2011;118:c285–91.

21. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–62.

22. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13.

23. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011;53:1130–9.

24. Goulet JL, Fultz SL, Rimland D, et al. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clin Infect Dis* 2007;45:1593–601.

25. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.

26. Hirschhorn LR, Kaaya SF, Garrity PS, et al. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS* 2012;26(Suppl 1):S65–S75.

27. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. *Ann Intern Med* 2015;163:507–18.

28. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008;148:728–36.

29. Katano H, Hishima T, Mochizuki M, et al. The prevalence of opportunistic infections and malignancies in autopsied patients with human immunodeficiency virus infection in Japan. *BMC Infect Dis* 2014;14:229.

30. Yanik EL, Katki HA, Engels EA. Cancer risk among the HIV-infected elderly in the United States. *AIDS* 2016;30:1663–8.

31. Hernandez-Romieu AC, Garg S, Rosenberg ES, et al. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009-2010. *BMJ Open Diabetes Res Care* 2017;5:e000304.

32. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and

uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014;59:1787–97.

33. Holtzman C, Armon C, Tedaldi E, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med* 2013;28:1302–10.
34. Tseng A, Szadkowski L, Walmsley S, et al. Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. *Ann Pharmacother* 2013;47:1429–39.
35. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011;66:2107–11.
36. Greene M, Steinman MA, McNicholl IR, et al. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. *J Am Geriatr Soc* 2014;62:447–53.
37. Rasmussen LD, Kronborg G, Larsen CS, et al. Use of non-antiretroviral drugs among individuals with and without HIV-infection: a Danish nationwide study. *Infect Dis (Lond)* 2017;49:42–54.

38. da Cunha J, Maselli LM, Stern AC, et al. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. *World J Virol* 2015;4:56–77.

39. Lake JE, Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis* 2013;13:964–75.

40. Brogan K, Lux J. Management of common psychiatric conditions in the HIV-positive population. *Curr HIV/AIDS Rep* 2009;6:108–15.

41. Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. *J Neurovirol* 2012;18:277–90.

42. Marzolini C, Elzi L, Gibbons S, et al. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010;15:413–23.

43. Mizokami F, Koide Y, Noro T, et al. Polypharmacy with common diseases in hospitalized elderly patients. *Am J Geriatr Pharmacother* 2012;10:123–8.

44. de Maat MM, Ekhart GC, Huitema AD, et al. Drug interactions between antiretroviral drugs and comedicated agents. *Clin Pharmacokinet* 2003;42:223–82.

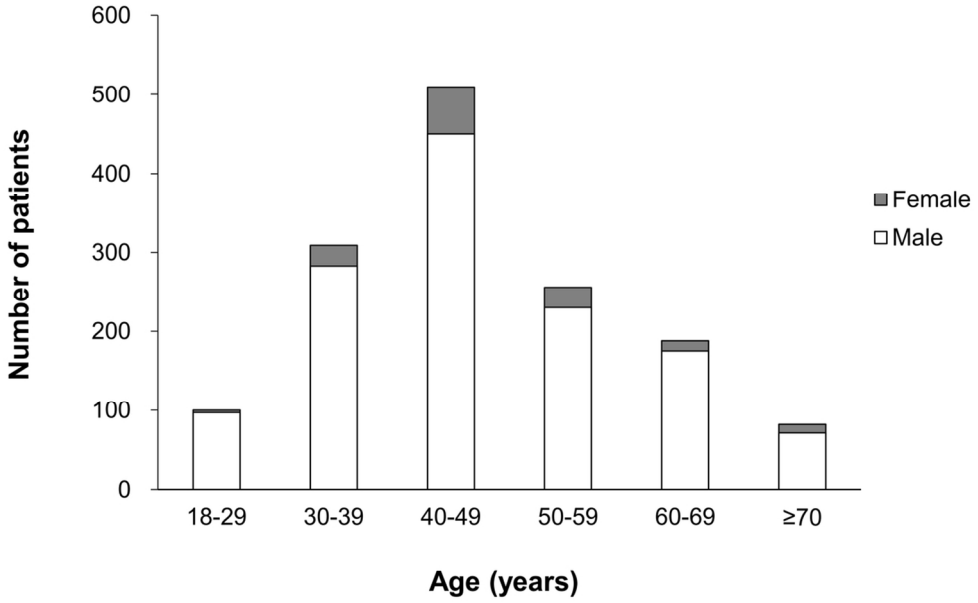
45. Nachega JB, Hsu AJ, Uthman OA, et al. Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS* 2012;26(Suppl 1):S39–S53.

[Figure legends]

Figure 1. Age and sex distribution of HIV-positive patients (n=1445)

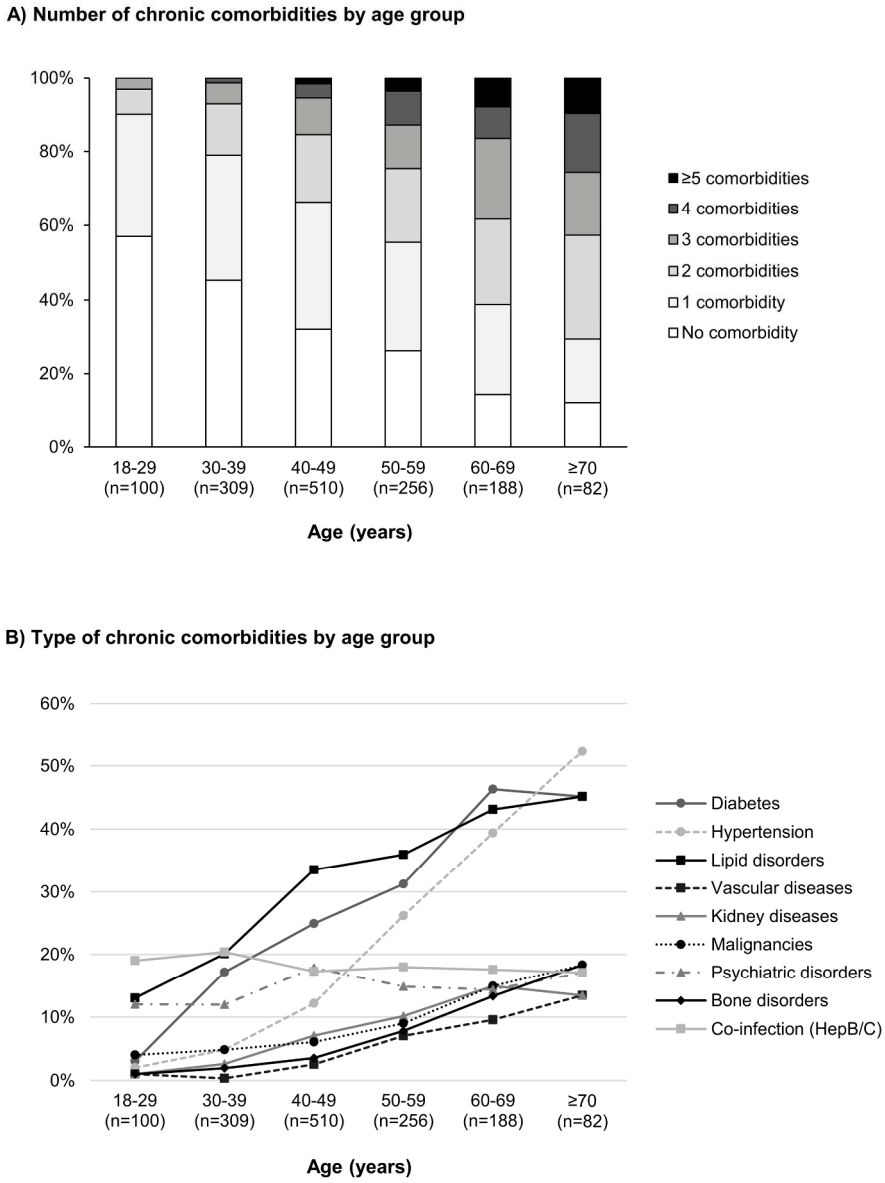
Figure 2. Number and type of chronic comorbidities by age group

Figure 3. Number and type of co-medications prescribed by age group. Figure 3B shows the top 5 common co-medications in this study.



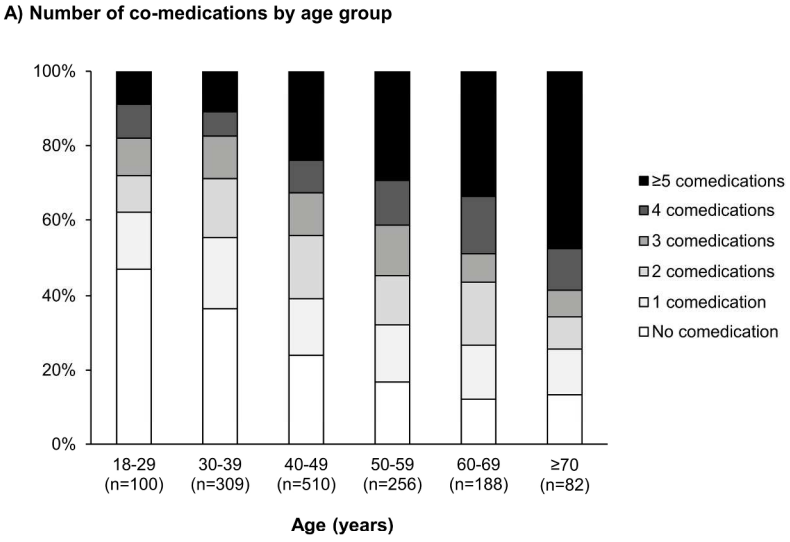
Age and sex distribution of studied patients living with HIV (n=1445)

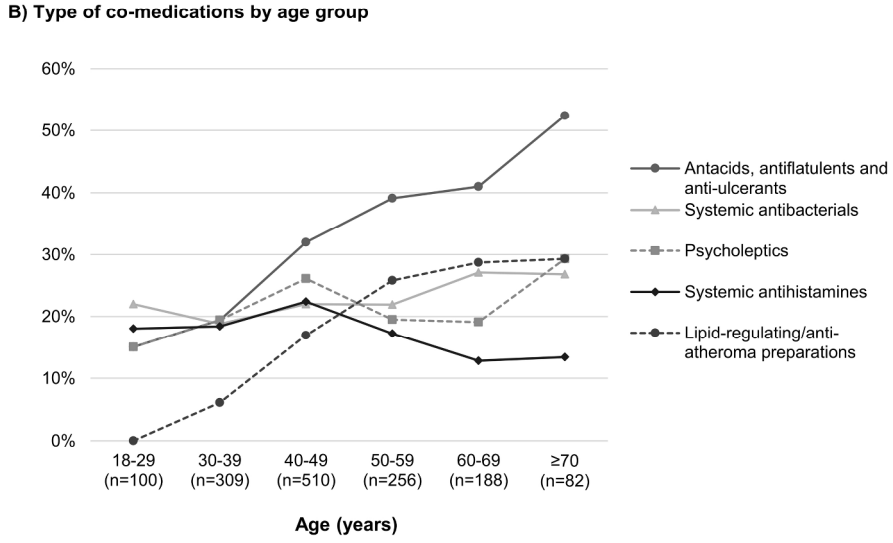
111x69mm (300 x 300 DPI)



Number and type of chronic comorbidities by age group

218x285mm (300 x 300 DPI)





Number and type of co-medications prescribed by age group. Figure 3B shows the top five common co-medications in this study.

223x288mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2–3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6–8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8–9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	12, 14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12–15
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15–16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22–23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23
Generalisability	21	Discuss the generalisability (external validity) of the study results	22–23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Chronic comorbidities and the use of co-medications in people living with HIV on antiretroviral therapy in Japan: a cross-sectional study using a hospital claims database

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019985.R1
Article Type:	Research
Date Submitted by the Author:	14-Feb-2018
Complete List of Authors:	Ruzicka, Daniel; MSD K.K., Medical Affairs Imai, Kentaro; MSD K.K., Oncology Clinical Development Takahashi, Kenichi; MSD K.K., Japan Development Naito, Toshio; Juntendo University, Department of General Medicine
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases
Keywords:	INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

[Title Page]

Title:

Chronic comorbidities and the use of co-medications in people living with HIV on antiretroviral therapy in Japan: a cross-sectional study using a hospital claims database

Authors and affiliations:

Daniel J. Ruzicka[1]; Kentaro Imai[2]; Kenichi Takahashi[3]; Toshio Naito[4]

[1] Medical Affairs, MSD K.K., Tokyo, Japan

[2] Oncology Clinical Development, MSD K.K., Tokyo, Japan

[3] Japan Development, MSD K.K., Tokyo, Japan

[4]Department of General Medicine, Juntendo University, Tokyo, Japan

Corresponding author:

Daniel J. Ruzicka

Medical Affairs, MSD K.K.

Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan

Tel.: +81-3-6272-1681, E-mail: daniel.ruzicka@merck.com

Word count: 3464 words

ABSTRACT (276/300 words)

Objectives: To investigate the prevalence of chronic comorbidities and the use of co-medications in people living with HIV (PLWH) and on antiretrovirals in Japan, by using a hospital claims database.

Design: Observational, retrospective, cross-sectional study.

Setting: A hospital claims database of Japanese hospitals that have advanced medical treatment capabilities (i.e., advanced treatment hospitals, general hospitals, acute care hospitals), which include those providing acute and chronic care (excluding nursing homes or hospices).

Participants: A total of 1445 PLWH aged ≥18 years and with a prescription record of antiretrovirals between January 2010 and December 2015 were identified from the database.

Outcome measures: The number and types of chronic comorbidities, as well as the number and types of co-medications, in different age groups of the PLWH.

Results: The median (range) age of patients was 45 (18–90) years, and 90.4% were men. Of the 1445 patients, 981 (67.9%) had at least one chronic comorbidity. Common chronic comorbidities included lipid disorders (31.6%), diabetes (26.8%), hypertension (18.2%), and hepatitis B/C co-infection (18.2%). Patients in the older age groups had

greater numbers of chronic comorbidities. The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. The majority of patients used at least one co-medication, and those in the older age groups used greater numbers of co-medications. The most common therapeutic category of co-medication included antacids, antiflatulents, and antiulcerants (31.7%). Of 148 malignancies reported in 116 patients, 81 were AIDS-defining cancers, and 67 were non-AIDS-defining cancers.

Conclusions: Chronic comorbidities and co-medications were more common in older PLWH taking antiretrovirals in Japan. This suggests the need for giving special attention to the appropriate management of this patient population.

Strengths and limitations of this study

- This is the first study to examine chronic comorbidities and co-medications in PLWH taking antiretrovirals in Japan, using a large-scale hospital claims database.
- Patients were stratified into small age groups, which provided a clear picture of patients' comorbidity and co-medication profiles by age.
- The cross-sectional study design prevented inference of causality between HIV infection and chronic comorbidities or co-medications.

- This study has limitations inherent in the use of a hospital claims database, such as poorly recorded or missing information, which may result in misclassification.
- The generalizability of the study results may be limited because data contained in the database were collected from Japanese hospitals that can provide advanced medical treatment to patients, not from all the hospitals providing HIV treatment in Japan.

[Text]

INTRODUCTION

Improvements in antiretroviral therapy (ART) over the last 15–20 years have prolonged the life expectancy of people living with HIV (PLWH). Life expectancy of PLWH is now reportedly similar to that of people without HIV.[1] However, in addition to HIV-related conditions, age-associated chronic comorbidities negatively affect the mortality rates of PLWH, as shown in various studies.[2-6] The increased number of chronic comorbidities among older PLWH is partly attributed to age-related changes in the physiological function and pharmacokinetics and/or pharmacodynamics of drugs.[7, 8] Other studies have suggested a longer duration of ART, which leads to increased toxicity, and HIV-induced persistent immunodeficiency and inflammation may also contribute to the increased number of comorbidities or higher prevalence of certain comorbidities among older PLWH.[9-12] Chronic inflammation and immune system changes by HIV infection were also found potentially involved in the mechanisms for possible premature ageing in PLWH.[13]

Studies have shown that over half of all HIV deaths are caused either by co-infection or age-associated non-infectious chronic comorbidities, including vascular diseases, hypertension, lipid disorders, diabetes mellitus, kidney diseases, malignancies,

and bone disorders.[14, 15] Such age-associated chronic comorbidities in PLWH have presented a new challenge for HIV treatment, especially in an ageing society such as Japan, which is among the countries with the longest life expectancy, for both sexes.[16] In Japan, more than 10% of newly diagnosed people with HIV in 2015 were aged ≥50 years,[17] indicating a number of PLWH are relatively older. Although the majority of newly diagnosed people with HIV were aged 20–49 years (88.2%),[17] these people are also able to live to old age through appropriate management with antiretrovirals. Thus, in line with the trends in other countries, in which the proportions of PLWH aged ≥50 years have increased,[18] the number of older PLWH may also be increasing in Japan. Because of the potentially long lifespans of PLWH in Japan, it is important to obtain real-world data regarding the comorbidity profiles of these people.

Despite the importance of the association of chronic comorbidities with mortality rates among PLWH, only a few small studies on chronic comorbidities among PLWH in Japan have been published to date,[19, 20] and there have been no large multi-centre epidemiological studies of chronic comorbidities in this population. Therefore in this study, to better understand a patient population, we examined the frequency and type of chronic comorbidities of interest and the use of co-medications in

different age groups of PLWH in Japan taking antiretrovirals and who were aged ≥18 years, using a Japanese hospital claims database.

METHODS

Study design

This was an observational, retrospective, cross-sectional database study. Study data were extracted from a hospital claims database of acute care hospitals in Japan, compiled by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). This electronic-record-based hospital claims database contained information from approximately 17 million patients in 288 acute care hospitals (as of January 2017) in Japan (https://www.mdv.co.jp/press/2017/detail_743.html); accounting for approximately 17% of all acute care hospitals in Japan that use the diagnosis procedure combination/per-diem payment system. It should be noted, however, that "acute care hospitals" included in this database are not merely acute care-only or emergency hospitals. It describes hospitals with advanced medical treatment capabilities (i.e., advanced treatment hospitals, general hospitals, acute care hospitals), so that hospitals providing both acute and chronic care (excluding nursing homes or hospices) are also included in the database. Because this terminology is highly specific to Japan, it may be

confusing for readers outside Japan or not familiar with the MDV database. Therefore, we refer to these hospitals included simply as "hospitals" hereinafter. We used this database because in Japan PLWH usually receive treatment at regional hospitals for HIV/AIDS treatment, and such designated hospitals are generally large and provide advanced medical treatment for patients with acute and chronic diseases. The majority of patients in the database are aged 15–64 years (51.5%), followed by ≥65 years (34.2%) and 0–14 years (14.3%). The database contains both inpatient and outpatient data from any department; these data include age, sex, department visited, date of medical service, diagnosis codes, hospitalization (if any), medical procedures, and prescriptions.

Study population

People living with HIV, aged ≥18 years, with a diagnosis record of HIV, and with a prescription record of antiretrovirals between January 2010 and December 2015 (study period) were included in the study. A person with any diagnosis record of HIV was identified by the presence of at least one record of the International Classification of Diseases 10th Revision (ICD-10) codes B20–24: HIV disease resulting in infectious and parasitic diseases (B20), malignant neoplasms (B21), other specified diseases (B22),

other conditions (B23), and unspecified HIV disease (B24). The patients were required to have at least one prescription record of any of the following antiretrovirals anytime during the study period: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors. This was for the purpose of examining polypharmacy in PLWH that could induce a potential drug–drug interaction (DDI) between antiretrovirals and co-medications, as well as to exclude people with uncertain HIV status, such as those poorly recorded or intentionally recorded for the purpose of a claim.

The data on patients who met these criteria (n=1445) during the study period were extracted from the database. The patients were grouped based on their age at the time of their last hospital visit, as follows: 18–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years old.

Definitions of measures

The following patient data during the study period were extracted from the database: demographic characteristics (age, sex), diagnoses of AIDS-defining conditions, diagnoses of chronic comorbidities, prescriptions of antiretrovirals, and prescriptions of

co-medications.

The AIDS-defining conditions were identified using the ICD-10 codes and disease names, and included the following: AIDS (B24); AIDS-related complex (B24); HIV disease resulting in cytomegaloviral disease (B20.2), candidiasis (B20.4), *Pneumocystis jirovecii* pneumonia (B20.6), Burkitt lymphoma (B21.1), and encephalopathy (B22.0); Kaposi sarcoma (B21.0/C46.9); and non-Hodgkin lymphoma (B21.2/C82–85/C91.5).

The chronic comorbidities were identified by the presence of relevant ICD-10 codes for particular diseases defined below. If the code was recorded at least once during the study period, the patients were considered to have that corresponding chronic comorbidity. These codes are recorded as disease records when patients receive not only diagnoses but also any medical procedures, treatment, or prescriptions for the disease. The chronic comorbidities in this study included type II diabetes (E11–14), hypertension (I10–15, except for I11/I13), lipid disorders (hypercholesterolaemia/hyperlipidaemia [E78.0–78.5]), vascular diseases (hypertensive heart and renal diseases [I11/I13], angina pectoris [I20], myocardial infarction [I22], stroke [I64]), kidney failure (N18–19), malignancies (B21.0/B21.2/C00–97), psychiatric disorders (dementia [F01/F03], psychosis [F20–29], mania and depression [F30–32],

anxiety [F40–41], insomnia [F51]), osteoporosis (M80–81), and hepatitis B/C co-infection (B18). Presence of two or more chronic comorbidities in a patient was defined as multimorbidity.

Although all malignancies were considered as one category of chronic comorbidity, we classified malignancies into two groups to further analyse them in terms of their types: (1) AIDS-defining cancers, defined as Kaposi sarcoma (B21.0/C46.9), non-Hodgkin lymphoma (B21.2/C82–85/C91.5) and cervix uteri (C53.9) in accordance with Shiels et al.,[21] and (2) non-AIDS-defining cancers, defined as all other malignancies.

Co-medication was defined as a non-antiretroviral medication prescribed for use for ≥30 days total during the study period. All medications other than antiretrovirals were considered in accordance with classification based on the therapeutic subgroups (second level) of the Anatomical Therapeutic Chemical (ATC) codes. To focus on the medications probably used for chronic treatment, or at least used for many days, instead of those used for only a short time, we set the minimum prescription days (i.e., total number of days for which the particular medication was supplied irrespective of whether it was prescribed continuously or intermittently during the study period) as 30.

All data on diseases and medications during the study period were considered

as data pertaining to the PLWH and thus were counted regardless of whether they were recorded before or after the diagnosis record of HIV. This was because it was considered from a clinical perspective that the comorbidities developed before the HIV infection were persistent over the whole study period.

Ethical statement

The requirement for informed consent was waived because this was an observational study using de-identified claims data and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to a study exclusively using de-identified data.

Statistical Analysis

Demographic data were descriptively summarized using the median and range for continuous variables or the number and percentage (%) of patients for categorical variables. Chronic comorbidities and co-medications were descriptively summarized by age group. The 95% confidence intervals (CIs) were calculated using the exact binomial method proposed by Clopper and Pearson.[22] All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) software.

RESULTS

Patient characteristics

Of 3155 PLWH, 1710 were excluded because of no prescription records of antiretrovirals. Overall, 1445 PLWH and with antiretroviral prescriptions, identified from 47 hospitals, were included in this study. They had a median (range) age of 45 (18–90) years, and 90.4% were men (Table 1). Of these patients, 703 (48.7%) had an AIDS-defining condition at some point during the study period. Figure 1 shows the age and sex distribution of patients. The majority were aged 40–49 years, followed by 30–39, 50–59, 60–69, 18–29 and ≥70 years.

Table 1. Demographic characteristics of studied people living with HIV (n=1445)

	Total (n=1445)
	n (%)
Age (years), median (range)	45 (18–90)
Male	1306 (90.4)
AIDS-defining conditions	703 (48.7)
Chronic comorbidity	
Diabetes	387 (26.8)
Hypertension	263 (18.2)
Lipid disorders	456 (31.6)
Vascular diseases	62 (4.3)
Kidney failure	110 (7.6)

Malignancies	116 (8.0)
Psychiatric disorders	219 (15.2)
Osteoporosis	85 (5.9)
Hepatitis B/C co-infection	263 (18.2)
Use of a non-antiretroviral medication*	1086 (75.2)
Type of key drug among antiretrovirals	
INSTI	789 (54.8)
NNRTI	359 (24.9)
PI	617 (42.8)

*Non-antiretroviral medication prescribed for use for ≥30 days total during the study period was taken into consideration.

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Chronic comorbidities

Overall, 1961 chronic comorbidities were reported in 981 (67.9%) PLWH, and 534 (37.0%) patients had multimorbidity (two or more chronic comorbidities). The most common chronic comorbidities were lipid disorders (31.6%; 95% CI, 29.2%–34.0%), followed by diabetes (26.8%; 95% CI, 24.5%–29.1%), hypertension (18.2%; 95% CI, 16.2%–20.3%), and hepatitis B/C co-infection (18.2%; 95% CI, 16.2%–20.3%) (Table 1).

Figure 2A shows the number of chronic comorbidities by age. Although 57.0% (57/100) of patients aged 18–29 years had no chronic comorbidity, the proportions with no chronic comorbidity decreased in the older age groups. More patients in the older

age groups had multimorbidity: 21.0% (65/309) of those aged 30–39 years, 44.5% (114/256) of those aged 50–59 years, and 70.7% (58/82) of those aged ≥70 years. No patients aged 18–29 years had four or more chronic comorbidities, while 25.6% (21/82) of those aged ≥70 years did.

Figure 2B shows the prevalence of different types of chronic comorbidities by age group. The prevalence of most chronic comorbidities tended to be higher in the older age groups, but such trends were not observed for psychiatric disorders (prevalence range: 12.0%–17.8%; p=0.3271, Cochran–Armitage trend test) and hepatitis B/C co-infection (17.1%–20.4%, p=0.4501, Cochran–Armitage trend test). The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. Hypertension was the most common chronic comorbidity in the ≥70-year group (52.4%; 95% CI, 41.1%–63.6%), diabetes in the 60–69-year group (46.3%; 95% CI, 39.0%–53.7%), and lipid disorders in the 50–59-year group (35.9%; 95% CI, 30.1%–42.1%). The prevalence of vascular diseases, kidney failure, malignancies, or osteoporosis in the ≥70-year group was 13.4%–18.3%, which was approximately 10%–15% higher than its counterpart in the 18–29-year group (1.0%–4.0%) ($p<0.0001$ for all four comorbidity types, Cochran–Armitage trend test).

Co-medications

Of the 1445 PLWH, 1086 (75.2%) used at least one co-medication and 342 (23.7%) used five or more, apart from antiretrovirals. Figure 3A shows the number of co-medications (excluding antiretrovirals) by age group. The proportions of patients who used at least one co-medication were 53.0% (53/100) in the 18–29-year group, 76.1% (388/510) in the 40–49-year group, and 86.6% (71/82) in the ≥70-year group. More patients in the older age groups used greater numbers of co-medications: 11.0% (34/309) of patients in the 30–39-year group, 29.3% (75/256) in the 50–59-year group, and 47.6% (39/82) in the ≥70-year group used five or more co-medications.

The 10 most common therapeutic categories were antacids, antiflatulents, and antiulcerants (31.7%); systemic antibacterials (22.2%); psycholeptics (22.0%); systemic antihistamines (18.5%); lipid-regulating/anti-atheroma preparations (17.2%); anti-inflammatory and anti-rheumatic products (15.5%); antidiarrhoeals, oral electrolyte replacers, and intestinal anti-inflammatories (12.1%); agents acting on the renin-angiotensin system (11.1%); vitamins (10.2%); and cough and cold preparations (9.6%). Regarding the top five most common co-medications, the proportions of patients who took respective co-medications by age group are shown in Figure 3B. Antacids, antiflatulents, and antiulcerants were the most common in most of the age

groups, notably in the ≥70-year group (52.4%). The proportions of patients taking systemic antibacterials, psycholeptics, or systemic antihistamines were similar across all age groups. Lipid-regulating agents were used more commonly in the older age groups: notably in 25%–30% of patients aged ≥50 years.

Malignancies

In this study, 148 malignancies were reported in 116 PLWH, including 81 AIDS-defining cancers and 67 non-AIDS-defining cancers. Figure 4 shows the proportions of patients with AIDS-defining cancers and those of patients with non-AIDS-defining cancers among patients with any malignancies within each age group. The figure illustrates that AIDS-defining cancers were more common in people <60 years old, whereas non-AIDS-defining cancers were more frequent in people aged ≥60 years. Table 2 shows the proportions of patients who had respective cancer types in these 116 PLWH with any malignancies. Non-Hodgkin lymphoma was the most common type of AIDS-defining cancer (54.3%), and bronchus or lung cancers were the most common types of non-AIDS-defining cancers (6.9%).

Table 2. Proportions of studied patients with respective cancer types among people living with HIV who had any malignancies (n=116)

	Patients with malignancy (n=116)
	n (%)
AIDS-defining cancer	
Non-Hodgkin lymphoma	63 (54.3)
Kaposi sarcoma	16 (13.8)
Cervix uteri	2 (1.7)
Non-AIDS-defining cancer	
Bronchus or lung	8 (6.9)
Secondary malignant neoplasm of bone and bone marrow	6 (5.2)
Colon	3 (2.6)
Breast	3 (2.6)
Malignant neoplasm, without specification of site	3 (2.6)
Secondary malignant neoplasm of brain and cerebral meninges	3 (2.6)
Acute myeloblastic leukaemia (AML)	3 (2.6)
Multiple myeloma	3 (2.6)
Stomach	2 (1.7)
Secondary malignant neoplasm of lung	2 (1.7)
Liver cell carcinoma	2 (1.7)
Sigmoid colon	2 (1.7)
Thoracic part of oesophagus	2 (1.7)
Skin of trunk	2 (1.7)
Others*	23 (19.8)

*Non-AIDS-defining cancer types present only in one patient were grouped and presented as "others."

DISCUSSION

This is the first study to investigate the prevalence of chronic comorbidities and the use of co-medications in PLWH taking antiretrovirals in Japan, using a large hospital claims database. The study found that chronic comorbidities were common in PLWH in Japan, particularly hypertension, diabetes, and lipid disorders among older patients. In terms of burden by age group, this study revealed that older patients had greater numbers of chronic comorbidities and also used greater numbers of co-medications than younger patients did.

Greater numbers of comorbidities in older people with HIV were also reported in previous international studies.[23-25] Additionally, older people with HIV in Switzerland and the United States were more likely to have diabetes mellitus, cardiovascular diseases, non-AIDS-defining malignancies, osteoporosis, or liver diseases than younger patients.[23, 24] Similar to those studies, in the present study, diabetes mellitus, vascular diseases, and osteoporosis were more common in older PLWH. Kidney failure was also more common in older patients, as suggested by a previous study reporting that both HIV infection and increased age were associated with an increased risk of kidney diseases in PLWH.[26] Previous studies also showed PLWH had a greater number of age-associated comorbidities at earlier ages than those living

without HIV, suggesting premature ageing in PLWH.[25, 27] This is a topic we plan to examine in our future research using a control group of people without HIV.

Despite the decreased incidence of non-Hodgkin lymphoma and Kaposi sarcoma, owing to antiretrovirals,[21, 28] AIDS-defining cancers remain a great concern in PLWH in North America.[29] However, in the present study, these cancers were not commonly observed (non-Hodgkin lymphoma, 4.4% [63/1445]; Kaposi sarcoma, 1.1% [16/1445]). Although direct comparison is not appropriate because of different study methods (i.e., different study populations, different antiretroviral eras), the prevalence was much lower than that reported in a previous Japanese study in which non-Hodgkin lymphoma and Kaposi sarcoma were present in 37.9% and 15.2%, respectively, of autopsied people with HIV and having received antiretrovirals from 1985–2012.[30] Another interesting finding of the present study was that non-AIDS-defining cancers, which accounted for 45% of all malignancies, seemed more frequent in patients in older age groups, being observed in >60% of PLWH aged ≥60 years who had any malignancies. A previous study showed that age-related cancers, such as lung, prostate, colorectal, and breast cancers, were common among older PLWH.[31] Another study also reported an increase in non-AIDS-defining cancers among the HIV population as a consequence of ageing of the AIDS population.[21] In

light of these previous findings, our results highlight the importance of non-AIDS-defining cancers among PLWH because of their extended lifespans. However, in the present study it was difficult to illuminate any trends in the prevalence of malignancies by age group because of the small number of patients with malignancies. Thus, the prevalence of malignancies by age and cancer type should be interpreted carefully, and examined further in future studies.

Our results indicated that use of co-medications was common among older PLWH, although the proportions of patients with five or more co-medications in those aged ≥50 years were smaller (33.7%) compared with a previous study (54%),[32] suggesting the management of older PLWH may be complicated because of DDIs attributed to increased use of co-medications.[33, 34] Moreover, in our study the use of co-medications was common even in younger PLWH, and over half of patients aged 18–29 years used at least one co-medication. These results suggest the importance of potential DDIs not only among the older PLWH but also the younger ones. For instance, DDIs between PIs or NNRTIs and co-medications (e.g., cardiovascular agents, anti-platelet agents, psychotropics, antidepressants, analgesics, and methadone) can be common in PLWH.[33, 34] The common use of lipid-regulating agents and agents acting on the renin-angiotensin system in the present study probably reflected the high

prevalence of lipid disorders and hypertension, especially in older patients, for some of whom antiretrovirals may be partly responsible for changes in lipid metabolism,[35, 36] although its underlying mechanisms in PLWH are complex. Psycholeptics were also commonly used irrespective of age, which was consistent with previous studies,[33, 34] and probably due to HIV disease progression and treatment with antiretrovirals associated with psychiatric disorders.[37, 38] The most common use, of antacids, antiflatulents, and antiulcerants (31.7%), may partly reflect the common presence of gastric ulcers in hospitalized older Japanese patients,[39] although not all of our study population had hospitalization. Because antacids can reduce serum concentrations of several antiretrovirals by altering the acid environment,[40, 41] Japanese physicians need to pay careful attention when prescribing antiretrovirals to patients using them.

The present study has some limitations. Because it was a cross-sectional study, chronic comorbidities/co-medications were not examined against the timing of a diagnosis of HIV infection. It should be noted that chronic comorbidities/co-medications in this study included those coded before a diagnosis record of HIV infection. This study is limited in its ability to draw valid conclusions about possible causality between HIV infection and chronic comorbidities/co-medications; therefore, causality should be confirmed through more

rigorous studies. Other limitations include those inherent to observational studies using a hospital claims database, such as poorly recorded or missing information, which may result in misclassification. For example, because the database is hospital-based, medical/treatment history recorded at different hospitals could not be obtained, meaning that patients may have received co-medications for other diseases at different hospitals. Additionally, the study results may not be generalizable to the overall population living with HIV with or without taking antiretrovirals in Japan, because some patients in this database who required acute care at these hospitals may be more ill than other PLWH who did not require acute care or those treated at hospitals not providing advanced medical treatment; in addition, co-medication results may over-represent drugs used by PLWH who sought hospital care, which may differ from those of PLWH who do not seek hospital care; HIV treatment choices in these included hospitals may not be representative of those made in other hospitals (i.e., hospitals not providing advanced medical treatment); and this study excluded patients without a record of antiretrovirals, who represent PLWH not taking antiretrovirals. Finally, because detailed data regarding HIV infection status were not available, we could not analyse the potential relationships between chronic comorbidities and CD4 count, HIV-RNA, or ART duration.

In conclusion, chronic comorbidities and co-medications were more common among older PLWH and taking antiretrovirals in Japan, suggesting the need for special treatment and attention by physicians. Although our results, particularly the types of co-medications, may not necessarily be extrapolated to a different patient population, they will help remind Japanese physicians of the importance of being aware of such complicated medical profiles of PLWH, especially patients who seek treatment at a hospital, so as to treat these people while mindful of potential DDIs. Application of our results can support the development of optimal healthcare strategies for this growing population.

Acknowledgments

Medical writing and statistical supports were provided by Clinical Study Support, Inc.

We are particularly grateful for the assistance given by Noriyo Ihara of MSD, K.K.

Author contributions

DJR contributed to the study design. DJR, KI, and KT contributed to the data analysis and interpretation. DJR, KI, KT, and TN revised the manuscript draft critically and approved the final version of the manuscript to be published.

Funding statement

This study was supported by MSD K.K., Tokyo, Japan.

Competing interests statement

DJR, KI, and KT are employees of MSD K.K., Tokyo, Japan. TN has received no funding for this study but received lecture fees from MSD K.K., Tokyo, Japan.

Data sharing statement

No additional data are available.

REFERENCES

1. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. *Curr Opin Infect Dis* 2013;26:17–25.

2. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.

3. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011;53:1130–9.

4. Wu PY, Chen MY, Hsieh SM, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PLOS ONE* 2014;9:e104945.

5. Vance DE, Mugavero M, Willig J, et al. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care* 2011;22:17–25.

6. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014;59:1787–97.

7. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6–14.

8. Sotaniemi EA, Arranto AJ, Pelkonen O, et al. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin Pharmacol Ther* 1997;61:331–9.

9. Edelman EJ, Gordon KS, Glover J, et al. The next therapeutic challenge in HIV: polypharmacy. *Drugs Aging* 2013;30:613–28.

10. Seaberg EC, Muñoz A, Lu M, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS* 2005;19:953–60.

11. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009;338:a3172.

12. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141–55.

13. Wing EJ. HIV and aging. *Int J Infect Dis* 2016;53:61–8.

14. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006;166:1632–41.

15. Sackoff JE, Hanna DB, Pfeiffer MR, et al. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145:397–406.

16. Global Health Observatory (GHO) Data. World Health Organization (2016). http://www.who.int/gho/publications/world_health_statistics/2016/en/ (accessed 19 Mar 2017).

17. Trends in AIDS occurrence report (2015). In Japanese. http://api-net.jfap.or.jp/status/2015/15nenpo/15nenpo_menu.html (Accessed 19 Mar 2017).

18. Costagliola D. Demographics of HIV and aging. *Curr Opin HIV AIDS* 2014;9:294–301.

19. Yanagimoto S, Yotsuyanagi H, Kikuchi Y, et al. Chronic hepatitis B in patients coinfected with human immunodeficiency virus in Japan: a retrospective multicenter analysis. *J Infect Chemother* 2012;18:883–90.

20. Yanagisawa N, Ando M, Ajisawa A, et al. Clinical characteristics of kidney disease in Japanese HIV-infected patients. *Nephron Clin Pract* 2011;118:c285–91.

21. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–62.

22. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13.

23. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011;53:1130–9.

24. Goulet JL, Fultz SL, Rimland D, et al. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clin Infect Dis* 2007;45:1593–601.

25. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.

26. Hirschhorn LR, Kaaya SF, Garrity PS, et al. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS* 2012;26(Suppl 1):S65–S75.

27. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014;59:1787–97.

28. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008;148:728–36.

29. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. *Ann Intern Med* 2015;163:507–18.

30. Katano H, Hishima T, Mochizuki M, et al. The prevalence of opportunistic infections and malignancies in autopsied patients with human immunodeficiency virus infection in Japan. *BMC Infect Dis* 2014;14:229.

31. Yanik EL, Katki HA, Engels EA. Cancer risk among the HIV-infected elderly in the United States. *AIDS* 2016;30:1663–8.

32. Holtzman C, Armon C, Tedaldi E, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med* 2013;28:1302–10.

33. Tseng A, Szadkowski L, Walmsley S, et al. Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. *Ann Pharmacother* 2013;47:1429–39.

34. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011;66:2107–11.

35. da Cunha J, Maselli LM, Stern AC, et al. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. *World J Virol* 2015;4:56–77.

36. Lake JE, Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis* 2013;13:964–75.

37. Brogan K, Lux J. Management of common psychiatric conditions in the HIV-positive population. *Curr HIV/AIDS Rep* 2009;6:108–15.

38. Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. *J Neurovirol* 2012;18:277–90.

39. Mizokami F, Koide Y, Noro T, et al. Polypharmacy with common diseases in hospitalized elderly patients. *Am J Geriatr Pharmacother* 2012;10:123–8.

40. de Maat MM, Ekhart GC, Huitema AD, et al. Drug interactions between antiretroviral drugs and comedicated agents. *Clin Pharmacokinet* 2003;42:223–82.

41. Nachega JB, Hsu AJ, Uthman OA, et al. Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS* 2012;26(Suppl 1):S39–S53.

[Figure legends]

Figure 1. Age and sex distribution of studied patients living with HIV (n=1445)

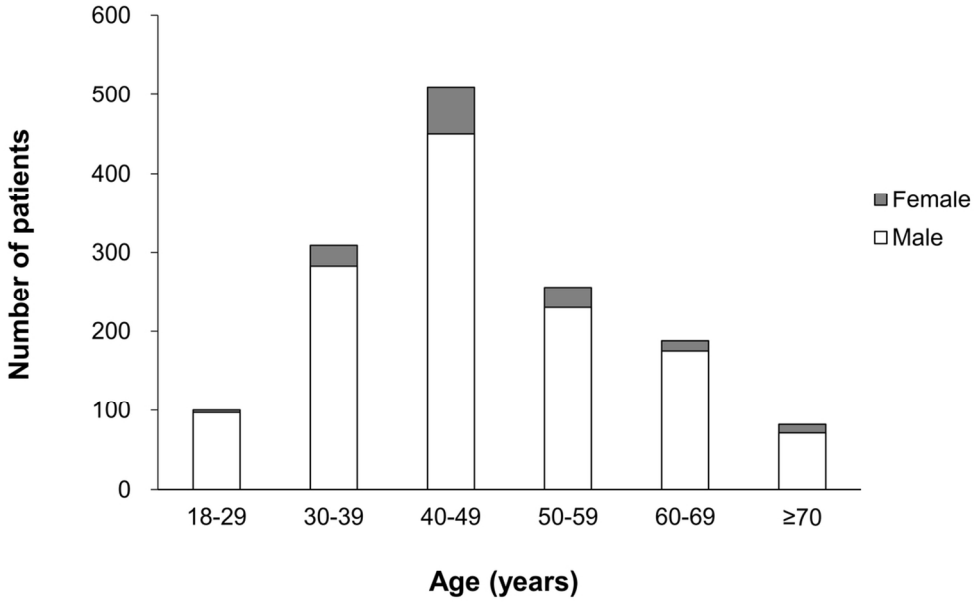
Figure 2. Number and type of chronic comorbidities by age group

Note: * indicates p <0.0001 under the Cochran–Armitage trend test.

Figure 3. Number and type of co-medications prescribed by age group

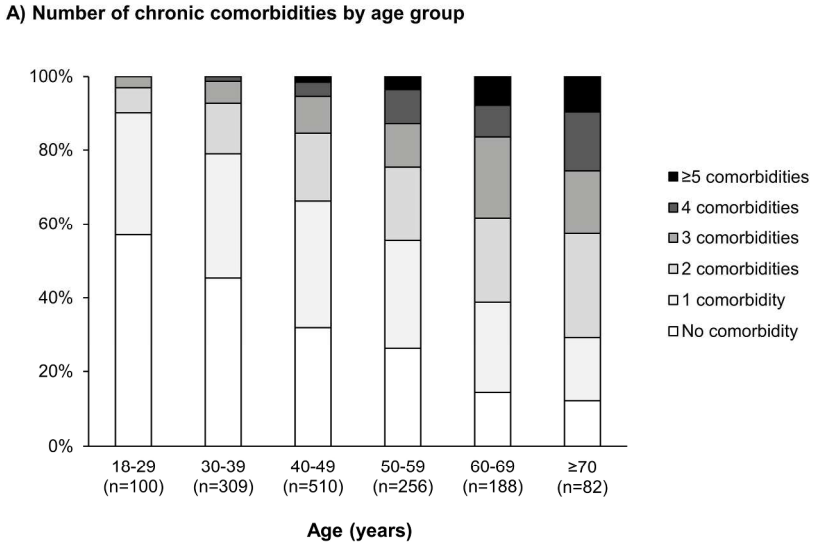
Figure 3B shows the top five common co-medications in this study.

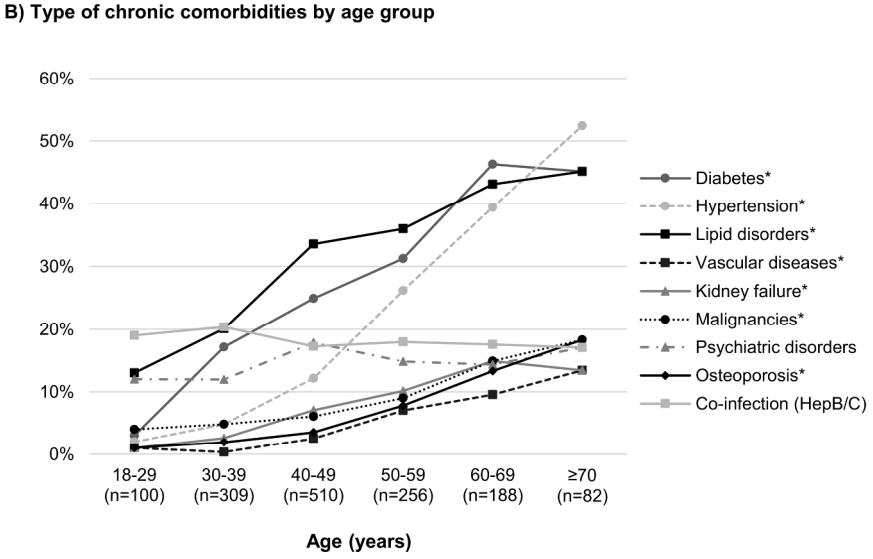
Figure 4. Proportions of studied patients with AIDS-defining cancers and non-AIDS-defining cancers among patients with any malignancies within each age group



Age and sex distribution of studied patients living with HIV (n=1445)

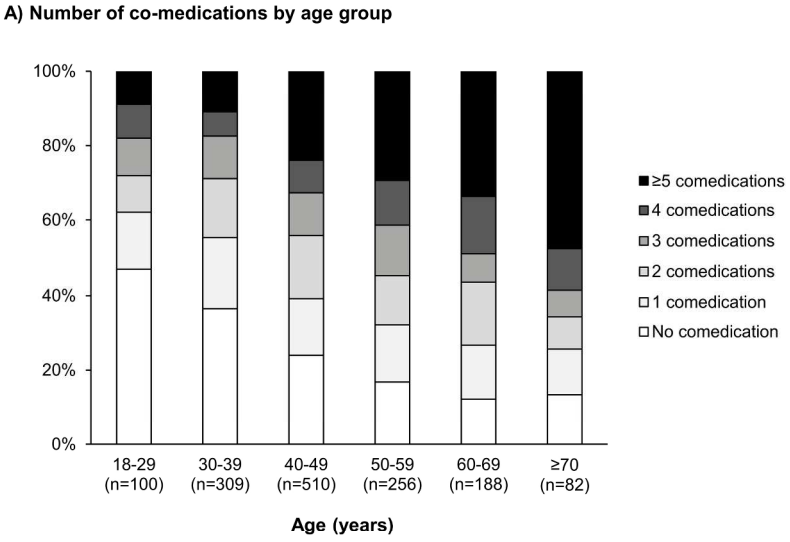
111x69mm (300 x 300 DPI)

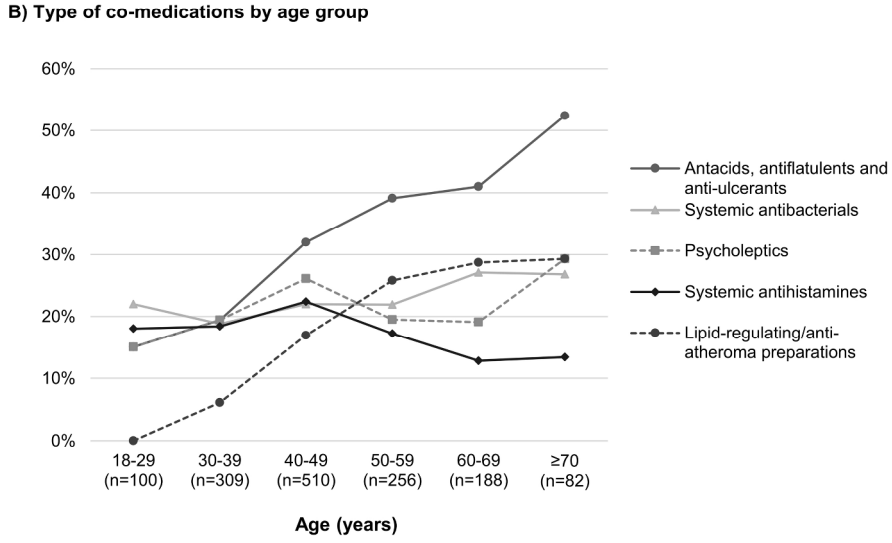




Number and type of chronic comorbidities by age group. Note: * indicates p <0.0001 under the Cochran–Armitage trend test.

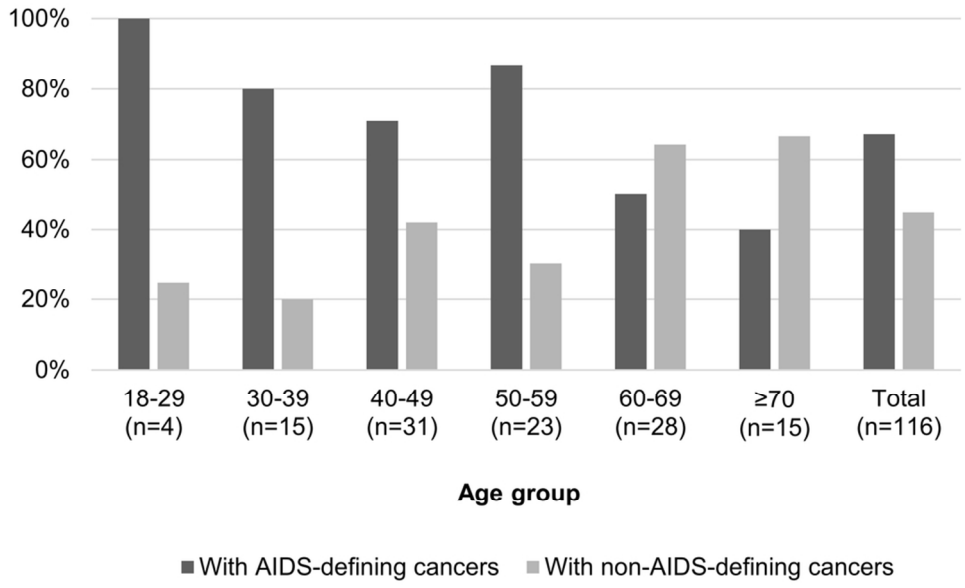
218x294mm (300 x 300 DPI)





Number and type of co-medications prescribed by age group. Figure 3B shows the top five common co-medications in this study.

223x288mm (300 x 300 DPI)



Proportions of studied patients with AIDS-defining cancers and non-AIDS-defining cancers among patients with any malignancies within each age group

90x57mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3–4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 3 Page 3 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 8		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 9–10		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	Page 9–10	RECORD 6.1: The methods of study population selection (such as codes or	Page 9–10

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	N/A	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 11–12	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 11–12
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 10		
Bias	9	Describe any efforts to address potential sources of bias	Page 10		
Study size	10	Explain how the study size was	Page 9–10		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 13		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 13 N/A N/A N/A N/A		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Not reported. Not reported.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	N/A

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 14 Page 14 N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 14
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 14–15 N/A N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page 15, 17		
Main results	16	(a) Give unadjusted estimates	Page 15–18		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 20		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 23–24	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 23–24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 25		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 23–24		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 26		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 26

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Comorbidities and the use of co-medications in people living with HIV on antiretroviral therapy in Japan: a cross-sectional study using a hospital claims database

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019985.R2
Article Type:	Research
Date Submitted by the Author:	26-Apr-2018
Complete List of Authors:	Ruzicka, Daniel; MSD K.K., Medical Affairs Imai, Kentaro; Merck & Co., Inc., Oncology Clinical Development Takahashi, Kenichi; MSD K.K., Japan Development Naito, Toshio; Juntendo University, Department of General Medicine
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Infectious diseases
Keywords:	INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

[Title Page]

Title:

Comorbidities and the use of co-medications in people living with HIV on antiretroviral therapy in Japan: a cross-sectional study using a hospital claims database

Authors and affiliations:

Daniel J. Ruzicka[1]; Kentaro Imai[2]; Kenichi Takahashi[3]; Toshio Naito[4]

[1] Medical Affairs, MSD K.K., Tokyo, Japan

[2] Oncology Clinical Development, Merck & Co., Inc., Kenilworth, New Jersey, USA

[3] Japan Development, MSD K.K., Tokyo, Japan

[4] Department of General Medicine, Juntendo University, Tokyo, Japan

Corresponding author:

Daniel J. Ruzicka

Medical Affairs, MSD K.K.

Kitanomaru Square, 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo 102-8667, Japan

Tel.: +81-3-6272-1681, E-mail: daniel.ruzicka@merck.com

Word count: 3777 words

ABSTRACT (283/300 words)

Objectives: To investigate the prevalence of chronic comorbidities and the use of co-medications in people living with HIV (PLWH) and on antiretrovirals in Japan, by using a hospital claims database.

Design: Observational, retrospective, cross-sectional study.

Setting: A hospital claims database of Japanese hospitals that have advanced medical treatment capabilities (i.e., advanced treatment hospitals, general hospitals, acute care hospitals), which include those providing acute and chronic care (excluding nursing homes or hospices).

Participants: A total of 1445 PLWH aged ≥18 years and with a prescription record of antiretrovirals between January 2010 and December 2015 were identified from the database.

Outcome measures: The number and types of chronic comorbidities, as well as the number and types of co-medications, in different age groups of the PLWH.

Results: The median (range) age of patients was 45 (18–90) years, and 90.4% were men. Of the 1445 patients, 972 (67.3%) had at least one chronic comorbidity. Common chronic comorbidities included lipid disorders (31.6%), diabetes (26.8%), hypertension (18.2%), and hepatitis B/C co-infection (18.2%). Patients in the older age groups had

greater numbers of chronic comorbidities. The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. The majority of patients used at least one co-medication, and those in the older age groups used greater numbers of co-medications. The most common therapeutic category of co-medication included antacids, antiflatulents, and antiulcerants (31.7%). Of 151 malignancies reported in 117 patients, 84 were AIDS-defining cancers, and 67 were non-AIDS-defining cancers.

Conclusions: Chronic comorbidities and co-medications were common among PLWH in Japan taking antiretrovirals; Particularly among older patients, who more frequently used co-medications. This suggests the need for giving special attention to the appropriate management of this patient population.

Strengths and limitations of this study

- This is the first study to examine chronic comorbidities and co-medications in PLWH in Japan taking antiretrovirals, using a large-scale hospital claims database.
- Patients were stratified into small age groups, which provided a clear picture of patients' comorbidity and co-medication profiles by age.

- The cross-sectional study design prevented inference of causality between HIV infection and chronic comorbidities or co-medications.
- This study has limitations inherent in the use of a hospital claims database, such as poorly recorded or missing information, which may result in misclassification.
- The generalizability of the study results may be limited because data contained in the database were collected from Japanese hospitals that can provide advanced medical treatment to patients, not from all the hospitals providing HIV treatment in Japan.

[Text]

INTRODUCTION

Improvements in antiretroviral therapy (ART) over the last 15–20 years have prolonged the life expectancy of people living with HIV (PLWH). Life expectancy of PLWH is now reportedly similar to that of people without HIV.[1] However, in addition to HIV-related conditions, age-associated chronic comorbidities negatively affect the mortality rates of PLWH, as shown in various studies.[2-6] Considering their extended lifespans, some chronic comorbidities among older PLWH may be partly attributed to normal age-related changes in physiological functioning,[7] as with older people in general. Moreover, a longer duration of ART, which leads to increased toxicity, and HIV-induced persistent immunodeficiency and inflammation may also contribute to the increased number of comorbidities or higher prevalence of certain comorbidities among older PLWH.[8-11] Chronic inflammation and immune system changes by HIV infection were also found potentially involved in the mechanisms for possible premature ageing in PLWH.[12]

Studies have shown that over half of all HIV deaths are caused either by co-infection or age-associated non-infectious chronic comorbidities, including vascular diseases, hypertension, lipid disorders, diabetes mellitus, kidney diseases, malignancies,

and bone disorders.[13, 14] Such age-associated chronic comorbidities in PLWH have presented a new challenge for HIV treatment, especially in an ageing society such as Japan, which is among the countries with the longest life expectancy, for both sexes.[15] In Japan, more than 10% of newly diagnosed people with HIV in 2015 were aged ≥50 years,[16] indicating a number of PLWH are relatively older. Although the majority of newly diagnosed people with HIV were aged 20–49 years (88.2%),[16] these people are also able to live to old age through appropriate management with antiretrovirals. Thus, in line with the trends in other countries, in which the proportions of PLWH aged ≥50 years have increased,[17] the number of older PLWH may also be increasing in Japan. Because of the potentially long lifespans of PLWH in Japan, it is important to obtain real-world data regarding the comorbidity profiles of these people.

Despite the importance of the association of chronic comorbidities with mortality rates among PLWH, only a few small studies on chronic comorbidities among PLWH in Japan have been published to date,[18, 19] and there have been no large multi-centre epidemiological studies of chronic comorbidities in this population. Therefore in this study, to better understand a patient population, we examined the frequency and type of chronic comorbidities of interest and the use of co-medications in

different age groups of PLWH in Japan taking antiretrovirals and who were aged ≥18 years, using a Japanese hospital claims database.

METHODS

Study design

This was an observational, retrospective, cross-sectional database study. Study data were extracted from a hospital claims database of acute care hospitals in Japan, compiled by Medical Data Vision Co., Ltd. (MDV, Tokyo, Japan). This electronic-record-based hospital claims database contained information from approximately 17 million patients in 288 acute care hospitals (as of January 2017) in Japan (https://www.mdv.co.jp/press/2017/detail_743.html); accounting for approximately 17% of all acute care hospitals in Japan that use the diagnosis procedure combination/per-diem payment system. It should be noted, however, that "acute care hospitals" included in this database are not merely acute care-only or emergency hospitals. It describes hospitals with advanced medical treatment capabilities (i.e., advanced treatment hospitals, general hospitals, acute care hospitals), so that hospitals providing both acute and chronic care (excluding nursing homes or hospices) are also included in the database. Because this terminology is highly specific to Japan, it may be

confusing for readers outside Japan or not familiar with the MDV database. Therefore, we refer to these hospitals included simply as "hospitals" hereinafter. We used this database because in Japan PLWH usually receive treatment at regional hospitals for HIV/AIDS treatment, and such designated hospitals are generally large and provide advanced medical treatment for patients with acute and chronic diseases. The majority of patients in the database are aged 15–64 years (51.5%), followed by ≥65 years (34.2%) and 0–14 years (14.3%). The database contains both inpatient and outpatient data from any department; these data include age, sex, department visited, date of medical service, diagnosis codes, hospitalization (if any), medical procedures, and prescriptions.

Study population

People living with HIV, aged ≥18 years, with a diagnosis record of HIV, and with a prescription record of antiretrovirals between January 2010 and December 2015 (study period) were included in the study. A person with any diagnosis record of HIV was identified by the presence of at least one record of the International Classification of Diseases 10th Revision (ICD-10) codes B20–24: HIV disease resulting in infectious and parasitic diseases (B20), malignant neoplasms (B21), other specified diseases (B22),

other conditions (B23), and unspecified HIV disease (B24). The patients were required to have at least one prescription record of any of the following antiretrovirals anytime during the study period: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and entry inhibitors. This was for the purpose of examining polypharmacy in PLWH that could induce a potential drug–drug interaction (DDI) between antiretrovirals and co-medications, as well as to exclude people with uncertain HIV status, such as those poorly recorded or intentionally recorded for the purpose of a claim.

The data on patients who met these criteria (n=1445) during the study period were extracted from the database. The patients were grouped based on their age at the time of their last hospital visit, as follows: 18–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years old.

Definitions of measures

The following patient data during the study period were extracted from the database: demographic characteristics (age, sex), diagnoses of AIDS-defining conditions, hospital admission, diagnoses of chronic comorbidities, prescriptions of antiretrovirals,

and prescriptions of co-medications.

The AIDS-defining conditions were identified using the ICD-10 codes, which included the following: AIDS (B24); AIDS-related complex (B24); cytomegaloviral disease (B20.2/B25 except for B25.1); candidiasis (B20.4/B37.1); encephalopathy (B22.0); wasting syndrome (B22.2); coccidioidomycosis (B38.3–38.9); cryptococcosis (B45.1–45.9); cryptosporidiosis (A07.2); herpes simplex infections (B00); histoplasmosis (B39.3–39.9); isosporiasis (A07.3); pulmonary mycobacterial infection (A31.0); tuberculosis (A15–19/B20.0); mycobacterial infections (A31.8); pneumocystosis (B59, B20.6); recurrent pneumonia (J12–18/B01.2); progressive multifocal leukoencephalopathy (A81.2); salmonella septicaemia (A02.1); toxoplasma meningoencephalitis (B58.2); Burkitt lymphoma (B21.1/C83.7); Kaposi sarcoma (B21.0/C46); non-Hodgkin lymphoma (B21.2/C82–85 except for C83.7/C91.5); and cancer of the cervix uteri (C53).

The chronic comorbidities were identified by the presence of relevant ICD-10 codes for particular diseases defined below. If the code was recorded at least once during the study period, the patients were considered to have that corresponding chronic comorbidity. These codes are recorded as disease records when patients receive not only diagnoses but also any medical procedures, treatment, or prescriptions for the disease.

The chronic comorbidities in this study included type II diabetes (E11–14), hypertension (I10–15, except for I11/I13), lipid disorders (hypercholesterolaemia/hyperlipidaemia [E78.0–78.5]), vascular diseases (hypertensive heart and renal diseases [I11/I13], angina pectoris [I20], myocardial infarction [I22], stroke [I64]), kidney failure (N18–19), malignancies (B21.0–21.2/C00–97), psychiatric disorders (dementia [F01/F03], psychosis [F20–29], mania and depression [F30–32], anxiety [F40–41], insomnia [F51]), osteoporosis (M80–81), and hepatitis B/C co-infection (B18). Presence of two or more chronic comorbidities in a patient was defined as multimorbidity.

Although all malignancies were considered as one category of chronic comorbidity, we classified malignancies into two groups to further analyse them in terms of their types: (1) AIDS-defining cancers, defined as Burkitt lymphoma (B21.1/C83.7), Kaposi sarcoma (B21.0/C46), non-Hodgkin lymphoma (B21.2/C82–85 except for C83.7/C91.5) and cancer of the cervix uteri (C53); and (2) non-AIDS-defining cancers, defined as all other malignancies.

Co-medication was defined as a non-antiretroviral medication prescribed for use for ≥30 days total during the study period. All medications other than antiretrovirals were considered in accordance with classification based on the therapeutic subgroups

(second level) of the Anatomical Therapeutic Chemical (ATC) codes.[20] To focus on the medications probably used for chronic treatment, or at least used for many days, instead of those used for only a short time, we set the minimum prescription days (i.e., total number of days for which the particular medication was supplied irrespective of whether it was prescribed continuously or intermittently during the study period) as 30.

All data on diseases and medications during the study period were considered as data pertaining to the PLWH and thus were counted regardless of whether they were recorded before or after the diagnosis record of HIV. This was because it was considered from a clinical perspective that the comorbidities developed before the HIV infection were persistent over the whole study period.

Ethical statement

The requirement for informed consent was waived because this was an observational study using de-identified claims data and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to a study exclusively using de-identified data.

Patient and public involvement

This was a hospital claims database study exclusively using pre-existing, de-identified claims data, and patient recruitment was not carried out specifically for this study. Thus, no patient involvement existed in this study.

Statistical analysis

Demographic data were descriptively summarized using the median and range for continuous variables or the number and percentage (%) of patients for categorical variables. Chronic comorbidities and co-medications were descriptively summarized by age group. The 95% confidence intervals (CIs) were calculated using the exact binomial method proposed by Clopper and Pearson.[21] All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) software.

RESULTS

Patient characteristics

Of 3155 patients with a diagnosis record of HIV, 1445 (45.8%) also had a prescription record of antiretrovirals, and were therefore included in this study. They had a median (range) age of 45 (18–90) years, and 90.4% were men (Table 1). Of these patients, 915 (63.3%) had an AIDS-defining condition at some point during the study

period. The majority of patients (77.6%) had only outpatient data, and 22.4% had at least one record of hospital admission for any reason during the study period (see Supplementary Table 1 for a full list of non-AIDS-defining illnesses that led to hospital admission in patients who had hospital admission only for non-AIDS-defining conditions). Figure 1 shows the age and sex distribution of patients. The majority were aged 40–49 years, followed by 30–39, 50–59, 60–69, 18–29 and ≥70 years.

Table 1. Demographic characteristics of studied people living with HIV (n=1445)

	Total (n=1445)
	n (%)
Age (years), median (range)	45 (18–90)
Male	1306 (90.4)
AIDS-defining conditions[a]	915 (63.3)
Hospital admission[b]	
No	1121 (77.6)
Yes	324 (22.4)
For an AIDS-defining condition[c]	120 (8.3)
For non-AIDS-defining conditions only[d]	196 (13.6)
For unknown reason[e]	8 (0.6)
Chronic comorbidity	
Diabetes	387 (26.8)
Hypertension	263 (18.2)
Lipid disorders	456 (31.6)
Vascular diseases	55 (3.8)
Kidney failure	78 (5.4)
Malignancies	117 (8.1)
Psychiatric disorders	219 (15.2)

Osteoporosis	85 (5.9)
Hepatitis B/C co-infection	263 (18.2)
Use of a non-antiretroviral medication[f]	1086 (75.2)
Type of key drug among antiretrovirals	
INSTI	789 (54.8)
NNRTI	359 (24.9)
PI	617 (42.8)

[a]Patients were considered to have an AIDS-defining condition if they had at least one disease record of AIDS-definig conditions during the study period. The only exception is for recurrent pneumonia; patients were considered to have recurrent pneumonia only when they had two or more codes of pneumonia (J12–18/B01.2) recorded within 18 months.

[b]Hospital admissions for any cause during the study period.

[c]Patients with at least one record of hospital admission and whose reason for admission included an AIDS-defining condition.

[d]Patients with at least one record of hospital admission and whose reason for admission was only non-AIDS-defining conditions.

[e]Patients with at least one record of hospital admission and whose reason for admission was unknown (i.e., no data available).

[f]Non-antiretroviral medication prescribed for use for ≥30 days total during the study period was taken into consideration.

INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Chronic comorbidities

Overall, 1923 chronic comorbidities were reported in 972 (67.3%) PLWH, and 523 (36.2%) patients had multimorbidity (two or more chronic comorbidities). The most common chronic comorbidities were lipid disorders (31.6%; 95% CI, 29.2%–34.0%), followed by diabetes (26.8%; 95% CI, 24.5%–29.1%), hypertension (18.2%; 95% CI,

16.2%–20.3%), and hepatitis B/C co-infection (18.2%; 95% CI, 16.2%–20.3%) (Table 1) (see Supplementary Table 2 for the breakdown of prevalence of each disease, classified under vascular diseases and psychiatric disorders).

Figure 2A shows the number of chronic comorbidities by age. Although 58.0% (58/100) of patients aged 18–29 years had no chronic comorbidity, the proportions with no chronic comorbidity decreased in the older age groups. More patients in the older age groups had multimorbidity: 21.0% (65/309) of those aged 30–39 years, 44.1% (113/256) of those aged 50–59 years, and 70.7% (58/82) of those aged ≥70 years. No patients aged 18–29 years had four or more chronic comorbidities, while 24.4% (20/82) of those aged ≥70 years did.

Figure 2B shows the prevalence of different types of chronic comorbidities by age group. The prevalence of most chronic comorbidities tended to be higher in the older age groups, but such trends were not observed for psychiatric disorders (prevalence range: 12.0%–17.8%; p=0.3271, Cochran–Armitage trend test) and hepatitis B/C co-infection (17.1%–20.4%, p=0.4501, Cochran–Armitage trend test). The most common chronic comorbidities in the older age groups were hypertension, diabetes, and lipid disorders. Hypertension was the most common chronic comorbidity in the ≥70-year group (52.4%; 95% CI, 41.1%–63.6%), diabetes in the 60–69-year

group (46.3%; 95% CI, 39.0%–53.7%), and lipid disorders in the 50–59-year group (35.9%; 95% CI, 30.1%–42.1%). The prevalence of vascular diseases, kidney failure, malignancies, or osteoporosis in the ≥70-year group was 11.0%–18.3%, which was approximately 10%–15% higher than its counterpart in the 18–29-year group (0%–4.0%) ($p<0.0001$ for all four comorbidity types, Cochran–Armitage trend test).

Co-medications

Of the 1445 PLWH, 1086 (75.2%) used at least one co-medication and 342 (23.7%) used five or more, apart from antiretrovirals. Figure 3A shows the number of co-medications (excluding antiretrovirals) by age group. The proportions of patients who used at least one co-medication were 53.0% (53/100) in the 18–29-year group, 76.1% (388/510) in the 40–49-year group, and 86.6% (71/82) in the ≥70-year group. More patients in the older age groups used greater numbers of co-medications: 11.0% (34/309) of patients in the 30–39-year group, 29.3% (75/256) in the 50–59-year group, and 47.6% (39/82) in the ≥70-year group used five or more co-medications.

The 10 most common therapeutic categories were antacids, antiflatulents, and antiulcerants (A02) (31.7%); systemic antibacterials (J01) (22.2%); psycholeptics (N05) (22.0%); systemic antihistamines (R06) (18.5%); lipid-regulating/anti-atheroma

preparations (C10) (17.2%); anti-inflammatory and anti-rheumatic products (M01) (15.5%); antidiarrhoeals, oral electrolyte replacers, and intestinal anti-inflammatories (A07) (12.1%); agents acting on the renin-angiotensin system (C09) (11.1%); vitamins (A11) (10.2%); and cough and cold preparations (R05) (9.6%). Regarding the top five most common co-medications, the proportions of patients who took respective co-medications by age group are shown in Figure 3B. Antacids, antiflatulents, and antiulcerants were the most common in most of the age groups, notably in the ≥70-year group (52.4%). The proportions of patients taking systemic antibacterials, psycholeptics, or systemic antihistamines were similar across all age groups. Lipid-regulating agents were used more commonly in the older age groups: notably in 25%–30% of patients aged ≥50 years.

Malignancies

In this study, 151 malignancies were reported in 117 PLWH, including 84 AIDS-defining cancers and 67 non-AIDS-defining cancers. Figure 4 shows the proportions of patients with AIDS-defining cancers and those of patients with non-AIDS-defining cancers among patients with any malignancies within each age group. The figure illustrates that AIDS-defining cancers were more common in people

<60 years old, whereas non-AIDS-defining cancers were more frequent in people aged ≥60 years. Table 2 shows the proportions of patients who had respective cancer types in these 117 PLWH with any malignancies. Non-Hodgkin lymphoma was the most common type of AIDS-defining cancer (52.1%), and bronchus or lung cancers were the most common types of non-AIDS-defining cancers (6.8%).

Table 2. Proportions of studied patients with respective cancer types among people living with HIV who had any malignancies (n=117)

	Patients with malignancy (n=117)	
	n	(%)
AIDS-defining cancer		
Non-Hodgkin lymphoma	61	(52.1)
Kaposi sarcoma	16	(13.7)
Burkitt lymphoma	5	(4.3)
Cervix uteri	2	(1.7)
Non-AIDS-defining cancer		
Bronchus or lung	8	(6.8)
Secondary malignant neoplasm of bone and bone marrow	6	(5.1)
Colon	3	(2.6)
Breast	3	(2.6)
Malignant neoplasm, without specification of site	3	(2.6)
Secondary malignant neoplasm of brain and cerebral meninges	3	(2.6)
Acute myeloblastic leukaemia (AML)	3	(2.6)
Multiple myeloma	3	(2.6)
Stomach	2	(1.7)
Secondary malignant neoplasm of lung	2	(1.7)

Liver cell carcinoma	2 (1.7)
Sigmoid colon	2 (1.7)
Thoracic part of oesophagus	2 (1.7)
Skin of trunk	2 (1.7)
Others[a]	23 (19.7)

[a]Non-AIDS-defining cancer types present only in one patient were grouped and presented as "others."

DISCUSSION

This is the first study to investigate the prevalence of chronic comorbidities and the use of co-medications in PLWH in Japan taking antiretrovirals, using a large hospital claims database. The study found that chronic comorbidities were common in PLWH in Japan, particularly hypertension, diabetes, and lipid disorders among older patients. In terms of burden by age group, this study revealed that older patients had greater numbers of chronic comorbidities and also used greater numbers of co-medications than younger patients did.

Greater numbers of comorbidities in older people with HIV were also reported in previous international studies.[2, 3, 22] Additionally, older people with HIV in Switzerland and the United States were more likely to have diabetes mellitus, cardiovascular diseases, non-AIDS-defining malignancies, osteoporosis, or liver diseases than younger patients.[3, 22] Similar to those studies, in the present study,

diabetes mellitus, vascular diseases, and osteoporosis were more common in older PLWH. Kidney failure was also more common in older patients, as suggested by a previous study reporting that both HIV infection and increased age were associated with an increased risk of kidney diseases in PLWH.[23] Previous studies also showed PLWH had a greater number of age-associated comorbidities at earlier ages than those living without HIV, suggesting premature ageing in PLWH.[2, 6] This is a topic we plan to examine in our future research using a control group of people without HIV.

Despite the decreased incidence of non-Hodgkin lymphoma and Kaposi sarcoma, owing to antiretrovirals,[24, 25] AIDS-defining cancers remain a great concern in PLWH in North America.[26] However, in the present study, these cancers were not commonly observed (non-Hodgkin lymphoma, 4.2% [61/1445]; Kaposi sarcoma, 1.1% [16/1445]). Although direct comparison is not appropriate because of different study methods (i.e., different study populations, different antiretroviral eras), the prevalence was much lower than that reported in a previous Japanese study in which non-Hodgkin lymphoma and Kaposi sarcoma were present in 37.9% and 15.2%, respectively, of autopsied people with HIV and having received antiretrovirals from 1985–2012.[27] Another interesting finding of the present study was that non-AIDS-defining cancers, which accounted for 44.4% of all malignancies, seemed

more frequent in patients in older age groups, being observed in >60% of PLWH aged ≥60 years who had any malignancies. A previous study showed that age-related cancers, such as lung, prostate, colorectal, and breast cancers, were common among older PLWH.[28] Another study also reported an increase in non-AIDS-defining cancers among the HIV population as a consequence of ageing of the AIDS population.[24] In light of these previous findings, our results highlight the importance of non-AIDS-defining cancers among PLWH because of their extended lifespans. However, in the present study it was difficult to illuminate any trends in the prevalence of malignancies by age group because of the small number of patients with malignancies. Thus, the prevalence of malignancies by age and cancer type should be interpreted carefully, and examined further in future studies.

Our results indicated that use of co-medications was common among older PLWH, although the proportions of patients with five or more co-medications in those aged ≥50 years were smaller (33.7%) compared with a previous study (54%),[29] suggesting the management of older PLWH may be complicated because of DDIs attributed to increased use of co-medications.[30, 31] Moreover, in our study the use of co-medications was common even in younger PLWH, and over half of patients aged 18–29 years used at least one co-medication. These results suggest the importance of

potential DDIs not only among the older PLWH but also the younger ones. For instance, DDIs between PIs or NNRTIs and co-medications (e.g., cardiovascular agents, anti-platelet agents, psychotropics, antidepressants, analgesics, and methadone) can be common in PLWH.[30, 31] The common use of lipid-regulating agents and agents acting on the renin-angiotensin system in the present study probably reflected the high prevalence of lipid disorders and hypertension, especially in older patients, for some of whom antiretrovirals may be partly responsible for changes in lipid metabolism,[32, 33] although its underlying mechanisms in PLWH are complex. Psycholeptics were also commonly used irrespective of age, which was consistent with previous studies,[30, 31] and probably due to HIV disease progression and treatment with antiretrovirals associated with psychiatric disorders.[34, 35] The most common use, of antacids, antiflatulents, and antiulcerants (31.7%), may partly reflect the common presence of gastric ulcers in hospitalized older Japanese patients,[36] although not all of our study population had hospitalization. Because antacids can reduce serum concentrations of several antiretrovirals by altering the acid environment,[37, 38] Japanese physicians need to pay careful attention when prescribing antiretrovirals to patients using them.

The present study has some limitations. Because it was a cross-sectional study, chronic comorbidities/co-medications were not examined against the timing of a

diagnosis of HIV infection. It should be noted that chronic comorbidities/co-medications in this study included those coded before a diagnosis record of HIV infection. This study is limited in its ability to draw valid conclusions about possible causality between HIV infection and chronic comorbidities/co-medications; therefore, causality should be confirmed through more rigorous studies. Other limitations include those inherent to observational studies using a hospital claims database, such as poorly recorded or missing information, which may result in misclassification. For example, because the database is hospital-based, medical/treatment history recorded at different hospitals could not be obtained, meaning that patients may have received co-medications for other diseases at different hospitals. Acute conditions may be missclassified into chronic comorbidities, as these were defined only by the presence of one relevant ICD-10 code. Co-medications only for treating acute condition may contaminate co-medications prescribed only for chronic medical conditions, although medications prescribed for <30 days were excluded from co-medications in this study. Additionally, the study results may not be generalizable to the overall population living with HIV and taking antiretrovirals in Japan. This is because PLWH in this database who require acute care at hospitals covered in the database may be more ill than other PLWH who do not require acute care, or those who

receive HIV treatment at non-acute care hospitals not covered in the database. In addition, the study results, particulary results on co-medications, may not accurately represent comorbidity and co-medication profiles in the general population living with HIV. This is because this study did not investigate these profiles for inpatients separately from those for outpatients. Supplementary Table 3 shows co-medication lists by patients with or without a hospital admission record during the study period. Co-medication results may also over-represent drugs used by PLWH who sought hospital care, which may differ from those of PLWH who do not seek hospital care. HIV treatment choices in these included hospitals may not be representative of those made in other hospitals (i.e., hospitals not providing advanced medical treatment). This study excluded patients without a record of antiretrovirals, who represent PLWH not taking antiretrovirals. However, we might have excluded some PLWH with antiretroviral therapy because PLWH in this database may have received antiretrovirals at hospitals not covered in the database. Finally, because detailed data regarding HIV infection status were not available, we could not analyse the potential relationships between chronic comorbidities and CD4 count, HIV-RNA, or ART duration.

In conclusion, chronic comorbidities and co-medications were common among PLWH in Japan taking antiretrovirals, especially among older patients, who more

frequently used co-medications. This suggests the need for special treatment and attention by physicians. Although our results, particularly the types of co-medications, may not necessarily be extrapolated to a different patient population, they will help remind Japanese physicians of the importance of being aware of such complicated medical profiles of PLWH, especially patients who seek treatment at a hospital, so as to treat these people while mindful of potential DDIs. Application of our results can support the development of optimal healthcare strategies for this growing population.

Acknowledgments

Medical writing and statistical supports were provided by Tetsumi Toyoda and Yuri Haga of Clinical Study Support, Inc. We are particularly grateful for the assistance given by Noriyo Ihara of MSD, K.K.

Author contributions

DJR contributed to the study design. DJR, KI, and KT contributed to the data analysis and interpretation. DJR, KI, KT, and TN revised the manuscript draft critically and approved the final version of the manuscript to be published.

Funding statement

This study was supported by MSD K.K., Tokyo, Japan.

Competing interests statement

DJR, KI, and KT are employees of MSD K.K., Tokyo, Japan. TN has received no funding for this study but received lecture fees from MSD K.K., Tokyo, Japan.

Data sharing statement

No additional data are available.

REFERENCES

1. Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. *Curr Opin Infect Dis* 2013;26:17–25.

2. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53:1120–6.

3. Hasse B, Ledergerber B, Furrer H, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011;53:1130–9.

4. Wu PY, Chen MY, Hsieh SM, et al. Comorbidities among the HIV-infected patients aged 40 years or older in Taiwan. *PLOS ONE* 2014;9:e104945.

5. Vance DE, Mugavero M, Willig J, et al. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care* 2011;22:17–25.

6. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. *Clin Infect Dis* 2014;59:1787–97.

7. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6–14.

8. Edelman EJ, Gordon KS, Glover J, et al. The next therapeutic challenge in HIV: polypharmacy. *Drugs Aging* 2013;30:613–28.

9. Seaberg EC, Muñoz A, Lu M, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS* 2005;19:953–60.

10. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009;338:a3172.

11. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141–55.

12. Wing EJ. HIV and aging. *Int J Infect Dis* 2016;53:61–8.

13. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006;166:1632–41.

14. Sackoff JE, Hanna DB, Pfeiffer MR, et al. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145:397–406.

15. Global Health Observatory (GHO) Data. World Health Organization (2016). http://www.who.int/gho/publications/world_health_statistics/2016/en/ (accessed 19 Mar 2017).

16. Trends in AIDS occurrence report (2015). In Japanese. http://api-net.jfap.or.jp/status/2015/15nenpo/15nenpo_menu.html (Accessed 19 Mar 2017).

17. Costagliola D. Demographics of HIV and aging. *Curr Opin HIV AIDS* 2014;9:294–301.

18. Yanagimoto S, Yotsuyanagi H, Kikuchi Y, et al. Chronic hepatitis B in patients coinfected with human immunodeficiency virus in Japan: a retrospective multicenter analysis. *J Infect Chemother* 2012;18:883–90.

19. Yanagisawa N, Ando M, Ajisawa A, et al. Clinical characteristics of kidney disease in Japanese HIV-infected patients. *Nephron Clin Pract* 2011;118:c285–91.

20. EphMRA. EphMRA Anatomical Classification Guidelines. http://www.ephmra.org/user_uploads/atcguidelines2016final.pdf. (Accessed 24

May 2017).

21. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13.

22. Goulet JL, Fultz SL, Rimland D, et al. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clin Infect Dis* 2007;45:1593–601.

23. Hirschhorn LR, Kaaya SF, Garrity PS, et al. Cancer and the 'other' noncommunicable chronic diseases in older people living with HIV/AIDS in resource-limited settings: a challenge to success. *AIDS* 2012;26(Suppl 1):S65–S75.

24. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst* 2011;103:753–62.

25. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med* 2008;148:728–36.

26. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. *Ann Intern Med* 2015;163:507–18.

27. Katano H, Hishima T, Mochizuki M, et al. The prevalence of opportunistic infections and malignancies in autopsied patients with human immunodeficiency virus infection in Japan. *BMC Infect Dis* 2014;14:229.

28. Yanik EL, Katki HA, Engels EA. Cancer risk among the HIV-infected elderly in the United States. *AIDS* 2016;30:1663–8.

29. Holtzman C, Armon C, Tedaldi E, et al. Polypharmacy and risk of antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med* 2013;28:1302–10.

30. Tseng A, Szadkowski L, Walmsley S, et al. Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. *Ann Pharmacother* 2013;47:1429–39.

31. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011;66:2107–11.

32. da Cunha J, Maselli LM, Stern AC, et al. Impact of antiretroviral therapy on lipid metabolism of human immunodeficiency virus-infected patients: Old and new drugs. *World J Virol* 2015;4:56–77.

33. Lake JE, Currier JS. Metabolic disease in HIV infection. *Lancet Infect Dis* 2013;13:964–75.

34. Brogan K, Lux J. Management of common psychiatric conditions in the HIV-positive population. *Curr HIV/AIDS Rep* 2009;6:108–15.

35. Watkins CC, Treisman GJ. Neuropsychiatric complications of aging with HIV. *J Neurovirol* 2012;18:277–90.

36. Mizokami F, Koide Y, Noro T, et al. Polypharmacy with common diseases in hospitalized elderly patients. *Am J Geriatr Pharmacother* 2012;10:123–8.

37. de Maat MM, Ekhart GC, Huitema AD, et al. Drug interactions between antiretroviral drugs and comedicated agents. *Clin Pharmacokinet* 2003;42:223–82.

38. Nachega JB, Hsu AJ, Uthman OA, et al. Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS* 2012;26(Suppl 1):S39–S53.

[Figure legends]

Figure 1. Age and sex distribution of studied patients living with HIV (n=1445)

Figure 2. Number and type of chronic comorbidities by age group

Note: * indicates p <0.0001 under the Cochran–Armitage trend test.

Figure 3. Number and type of co-medications prescribed by age group

Figure 3B shows the top five common co-medications in this study.

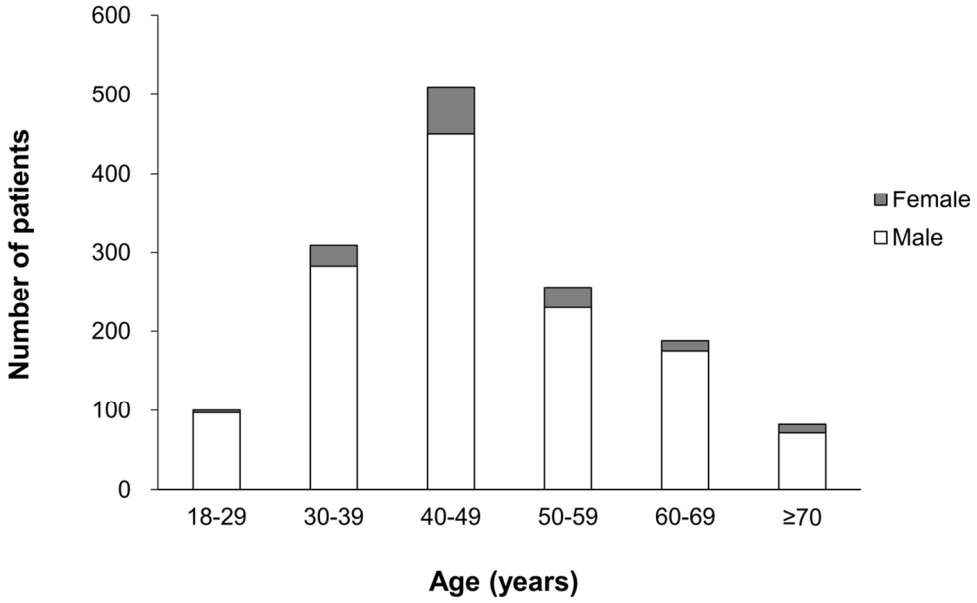
Figure 4. Proportions of studied patients with AIDS-defining cancers and non-AIDS-defining cancers among patients with any malignancies within each age group

Supplementary Material

Supplementary Table 1. Diseases that led to hospital admission among patients with a hospital admission record for non-AIDS-defining conditions only (n=196)

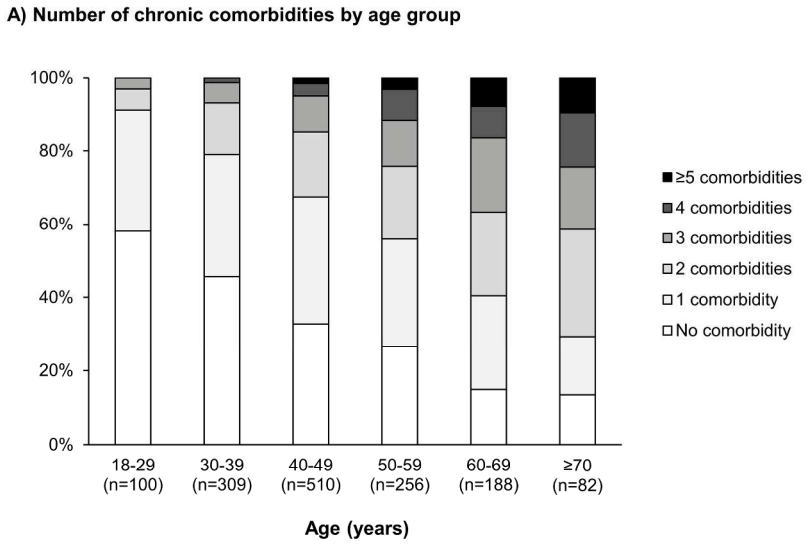
Supplementary Table 2. Number of patients with each disease classified under the same comorbidity category (vascular diseases and psychiatric disorders)

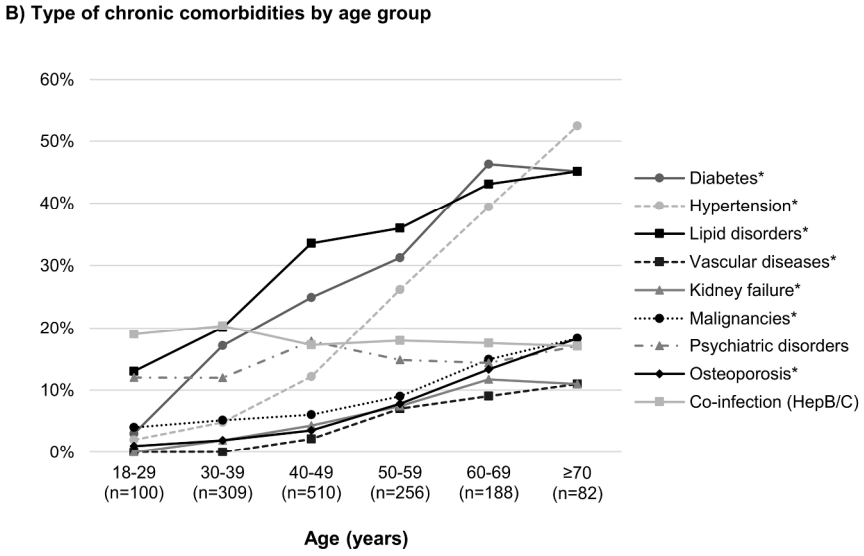
Supplementary Table 3. Co-medications frequenty used by patients with or without a hospital admission record during the study period



Age and sex distribution of studied patients living with HIV (n=1445)

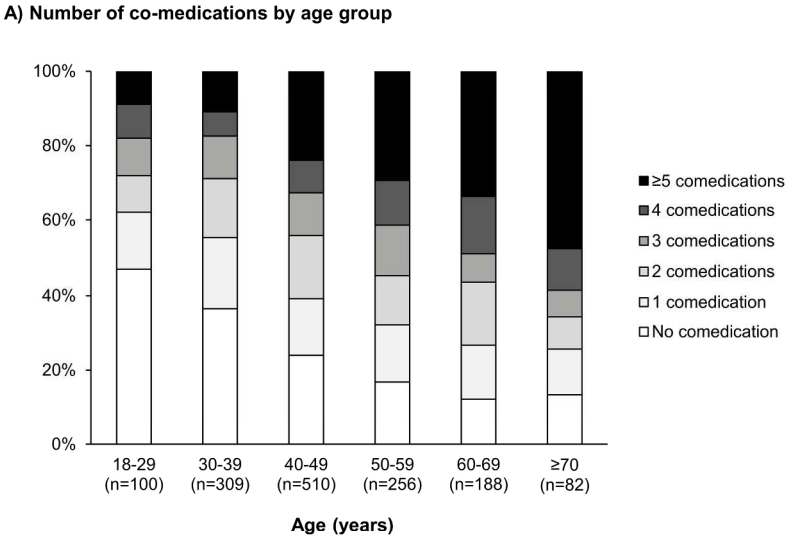
111x69mm (300 x 300 DPI)

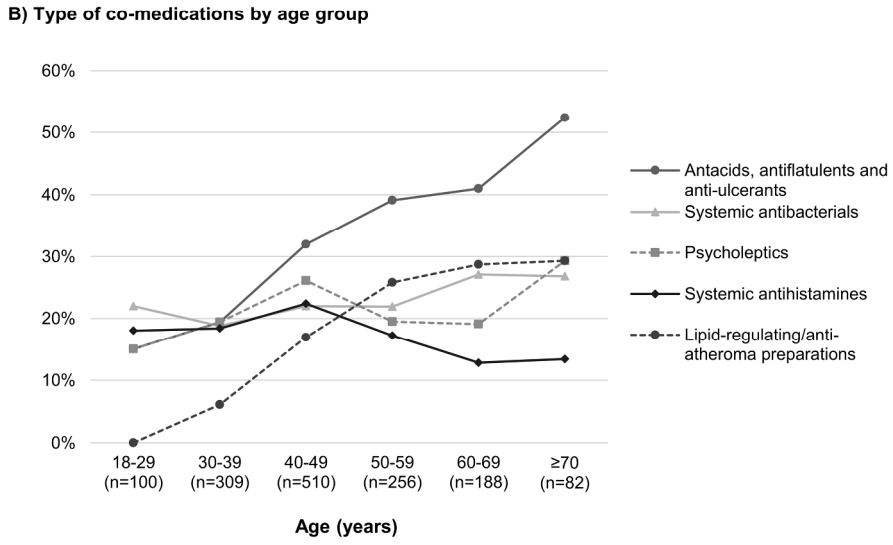




Number and type of chronic comorbidities by age group. Note: * indicates p <0.0001 under the Cochran–Armitage trend test.

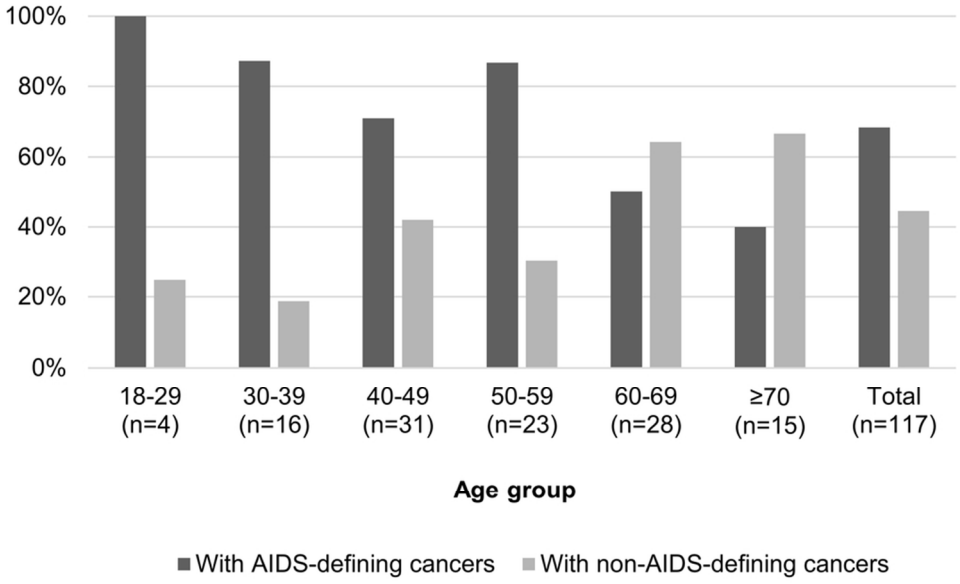
219x295mm (300 x 300 DPI)





Number and type of co-medications prescribed by age group. Figure 3B shows the top five common co-medications in this study.

223x288mm (300 x 300 DPI)



Proportions of studied patients with AIDS-defining cancers and non-AIDS-defining cancers among patients with any malignancies within each age group

89x56mm (300 x 300 DPI)

Supplementary Table 1.
Diseases that led to hospital admission among patients with a hospital admission record for non-AIDS-defining conditions only (n=196)

ICD-10 code	Disease	n	%
K35.9*	Acute appendicitis, unspecified	6	3.1%
A09	Other gastroenteritis and colitis of infectious and unspecified origin	5	2.6%
D66	Hereditary factor VIII deficiency	5	2.6%
E86	Volume depletion	5	2.6%
J15.9	Bacterial pneumonia, unspecified	5	2.6%
A41.9	Sepsis, unspecified	4	2.0%
B18.2	Chronic viral hepatitis C	4	2.0%
D70	Agranulocytosis	4	2.0%
I50.0	Congestive heart failure	4	2.0%
J69.0	Pneumonitis due to food and vomit	4	2.0%
K85	Acute pancreatitis	4	2.0%
A06.4	Amoebic liver abscess	3	1.5%
A52.3	Neurosyphilis, unspecified	3	1.5%
B02.7	Disseminated zoster	3	1.5%
B23.0	Acute HIV infection syndrome	3	1.5%
G40.8	Other epilepsy	3	1.5%
G51.0	Bell palsy	3	1.5%
H33.0	Retinal detachment with retinal break	3	1.5%
I20.8	Other forms of angina pectoris	3	1.5%
I61.0	Intracerebral haemorrhage in hemisphere, subcortical	3	1.5%
I70.2	Atherosclerosis of arteries of extremities	3	1.5%
J18.9	Pneumonia, unspecified	3	1.5%
N18.0*	End-stage renal disease	3	1.5%
N39.0	Urinary tract infection, site not specified	3	1.5%
B02.9	Zoster without complication	2	1.0%
C15.1	Malignant neoplasm: Thoracic part of oesophagus	2	1.0%
C34.1	Malignant neoplasm: Upper lobe, bronchus or lung	2	1.0%
I48	Atrial fibrillation and flutter	2	1.0%
I49.5	Sick sinus syndrome	2	1.0%
I50.9	Heart failure, unspecified	2	1.0%
I63.9	Cerebral infarction, unspecified	2	1.0%
J03.9	Acute tonsillitis, unspecified	2	1.0%
J84.1	Other interstitial pulmonary diseases with fibrosis	2	1.0%
J84.9	Interstitial pulmonary disease, unspecified	2	1.0%
N17.9	Acute renal failure, unspecified	2	1.0%
N18.9	Chronic kidney disease, unspecified	2	1.0%
N20.1	Calculus of ureter	2	1.0%
R50.9	Fever, unspecified	2	1.0%
S72.0	Fracture of neck of femur	2	1.0%
T78.2	Anaphylactic shock, unspecified	2	1.0%
T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	2	1.0%
A48.1	Legionnaires disease	1	0.5%
A49.9	Bacterial infection, unspecified	1	0.5%
A52.1	Symptomatic neurosyphilis	1	0.5%
A53.9	Syphilis, unspecified	1	0.5%
A63.0	Anogenital (venereal) warts	1	0.5%
B20.2	HIV disease resulting in cytomegaloviral disease	1	0.5%
B45.0	Pulmonary cryptococcosis	1	0.5%
C16.3	Malignant neoplasm: Pyloric antrum	1	0.5%
C22.0	Malignant neoplasm: Liver cell carcinoma	1	0.5%
C30.0	Malignant neoplasm: Nasal cavity	1	0.5%
C44.7	Malignant neoplasm: Skin of lower limb, including hip	1	0.5%
C92.0	Acute myeloblastic leukaemia [AML]	1	0.5%
D13.5	Benign neoplasm: Extrahepatic bile ducts	1	0.5%
D29.0	Benign neoplasm: Penis	1	0.5%
D37.0	Neoplasm of uncertain or unknown behaviour: Lip, oral cavity and pharynx	1	0.5%
D61.9	Aplastic anaemia, unspecified	1	0.5%
D64.8	Other specified anaemias	1	0.5%
D69.3	Idiopathic thrombocytopenic purpura	1	0.5%
D76.3	Other histiocytosis syndromes	1	0.5%
E10.3	Type 1 diabetes mellitus with ophthalmic complications	1	0.5%
E11	Type 2 diabetes mellitus	1	0.5%
E11.0	Type 2 diabetes mellitus with coma	1	0.5%
E11.4	Type 2 diabetes mellitus with neurological complications	1	0.5%

E11.6	Type 2 diabetes mellitus with other specified complications	1	0.5%
E11.7	Type 2 diabetes mellitus with multiple complications	1	0.5%
E11.9	Type 2 diabetes mellitus without complications	1	0.5%
E14	Unspecified diabetes mellitus	1	0.5%
E14.2	Unspecified diabetes mellitus with renal complications	1	0.5%
E23.0	Hypopituitarism	1	0.5%
E23.2	Diabetes insipidus	1	0.5%
E26.0	Primary hyperaldosteronism	1	0.5%
E87.5	Hyperkalaemia	1	0.5%
F32.9	Depressive episode, unspecified	1	0.5%
G00.9	Bacterial meningitis, unspecified	1	0.5%
G62.9	Polyneuropathy, unspecified	1	0.5%
G64	Other disorders of peripheral nervous system	1	0.5%
H26.2	Complicated cataract	1	0.5%
H40.5	Glaucoma secondary to other eye disorders	1	0.5%
H71	Cholesteatoma of middle ear	1	0.5%
H81.1	Benign paroxysmal vertigo	1	0.5%
H91.2	Sudden idiopathic hearing loss	1	0.5%
I20.0	Unstable angina	1	0.5%
I20.9	Angina pectoris, unspecified	1	0.5%
I21.1	Acute transmural myocardial infarction of inferior wall	1	0.5%
I25.2	Old myocardial infarction	1	0.5%
I25.6	Silent myocardial ischaemia	1	0.5%
I61.9	Intracerebral haemorrhage, unspecified	1	0.5%
I63.3	Cerebral infarction due to thrombosis of cerebral arteries	1	0.5%
I63.4	Cerebral infarction due to embolism of cerebral arteries	1	0.5%
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	1	0.5%
I63.8	Other cerebral infarction	1	0.5%
I65.0	Occlusion and stenosis of vertebral artery	1	0.5%
I65.2	Occlusion and stenosis of carotid artery	1	0.5%
I71.0	Dissection of aorta [any part]	1	0.5%
I74.8	Embolism and thrombosis of other arteries	1	0.5%
I84.2*	Internal haemorrhoids without complication	1	0.5%
J06.9	Acute upper respiratory infection, unspecified	1	0.5%
J15.0	Pneumonia due to Klebsiella pneumoniae	1	0.5%
J18.0	Bronchopneumonia, unspecified	1	0.5%
J20.9	Acute bronchitis, unspecified	1	0.5%
J30.4	Allergic rhinitis, unspecified	1	0.5%
J35.0	Chronic tonsillitis	1	0.5%
J36	Peritonsillar abscess	1	0.5%
J40	Bronchitis, not specified as acute or chronic	1	0.5%
J44.9	Chronic obstructive pulmonary disease, unspecified	1	0.5%
J46	Status asthmaticus	1	0.5%
J67.8	Hypersensitivity pneumonitis due to other organic dusts	1	0.5%
J86.9	Pyothorax without fistula	1	0.5%
J93.1	Other spontaneous pneumothorax	1	0.5%
J94.0	Chylous effusion	1	0.5%
J96.0	Acute respiratory failure	1	0.5%
J96.1	Chronic respiratory failure	1	0.5%
K22.1	Ulcer of oesophagus	1	0.5%
K25.0	Gastric ulcer : acute with haemorrhage	1	0.5%
K25.3	Gastric ulcer : acute without haemorrhage or perforation	1	0.5%
K26.1	Duodenal ulcer : acute with perforation	1	0.5%
K35.1*	Acute appendicitis with peritoneal abscess	1	0.5%
K36	Other appendicitis	1	0.5%
K42.9	Umbilical hernia without obstruction or gangrene	1	0.5%
K52.9	Noninfective gastroenteritis and colitis, unspecified	1	0.5%
K57.3	Diverticular disease of large intestine without perforation or abscess	1	0.5%
K60.3	Anal fistula	1	0.5%
K65.8	Other peritonitis	1	0.5%
K66.1	Haemoperitoneum	1	0.5%
K75.0	Abscess of liver	1	0.5%
K80.3	Calculus of bile duct with cholangitis	1	0.5%
K92.2	Gastrointestinal haemorrhage, unspecified	1	0.5%
L03.1	Cellulitis of other parts of limb	1	0.5%
L03.9	Cellulitis, unspecified	1	0.5%
L04.3	Acute lymphadenitis of lower limb	1	0.5%
L08.0	Pyoderma	1	0.5%
L20.8	Other atopic dermatitis	1	0.5%
L53.0	Toxic erythema	1	0.5%
L56.3	Solar urticaria	1	0.5%

L75.0	Bromhidrosis	1	0.5%
M16.9	Coxarthrosis, unspecified	1	0.5%
M46.5	Other infective spondylopathies	1	0.5%
M54.1	Radiculopathy	1	0.5%
M62.8	Other specified disorders of muscle	1	0.5%
M87.9	Osteonecrosis, unspecified	1	0.5%
M95.0	Acquired deformity of nose	1	0.5%
N04.0	Nephrotic syndrome : minor glomerular abnormality	1	0.5%
N10	Acute tubulo-interstitial nephritis	1	0.5%
N13.1	Hydronephrosis with ureteral stricture, not elsewhere classified	1	0.5%
N15.1	Renal and perinephric abscess	1	0.5%
N21.0	Calculus in bladder	1	0.5%
N25.8	Other disorders resulting from impaired renal tubular function	1	0.5%
N40	Hyperplasia of prostate	1	0.5%
N45.9	Orchitis, epididymitis and epididymo-orchitis without abscess	1	0.5%
N70.0	Acute salpingitis and oophoritis	1	0.5%
N87.2	Severe cervical dysplasia, not elsewhere classified	1	0.5%
O00.1	Tubal pregnancy	1	0.5%
O42.0	Premature rupture of membranes, onset of labour within 24 hours	1	0.5%
O42.9	Premature rupture of membranes, unspecified	1	0.5%
O75.7	Vaginal delivery following previous caesarean section	1	0.5%
O82.9	Delivery by caesarean section, unspecified	1	0.5%
Q27.3	Peripheral arteriovenous malformation	1	0.5%
R40.2	Coma, unspecified	1	0.5%
R56.8	Other and unspecified convulsions	1	0.5%
R63.0	Anorexia	1	0.5%
S00.8	Superficial injury of other parts of head	1	0.5%
S32.0	Fracture of lumbar vertebra	1	0.5%
S36.4	Injury of small intestine	1	0.5%
S72.1	Pertrochanteric fracture	1	0.5%
S82.0	Fracture of patella	1	0.5%
S83.2	Tear of meniscus, current	1	0.5%
T07	Unspecified multiple injuries	1	0.5%
T18.5	Foreign body in anus and rectum	1	0.5%
T84.0	Mechanical complication of internal joint prosthesis	1	0.5%
T84.5	Infection and inflammatory reaction due to internal joint prosthesis	1	0.5%
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status	1	0.5%
S83.2	Tear of meniscus, current	1	0.5%
T07	Unspecified multiple injuries	1	0.5%
T18.5	Foreign body in anus and rectum	1	0.5%
T84.0	Mechanical complication of internal joint prosthesis	1	0.5%
T84.5	Infection and inflammatory reaction due to internal joint prosthesis	1	0.5%
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status	1	0.5%

Patients can have multiple records of hospital admissions during the study period.
* indicates the code that does not exist in the ICD-10 (2016 version). For K35.9, N18.0, and K35.1, disease names are according to the ICD-10 (2008 version), and for I84.2 the disease name is according to the ICD-10 (2010 version).

Supplementary Table 2. Number of patients with each disease classified under the same comorbidity category (vascular diseases and psychiatric disorders)

Comorbidity	ICD-10 code	Total (n=1445)
		n (%)
Vascular diseases	-	55 (3.8)
Hypertensive heart and renal diseases	I11, I13	1 (0.1)
Angina pectoris	I20	55 (3.8)
Myocardial infarction	I22	0 (0.0)
Stroke	I64	0 (0.0)
Psychiatric disorders	-	219 (15.2)
Dementia	F01, F03	4 (0.3)
Psychosis	F20–29	62 (4.3)
Mania and depression	F30–32	121 (8.4)
Anxiety	F40–41	78 (5.4)
Insomnia	F51	17 (1.2)

Supplementary Table 3. Co-medications frequently used by patients with or without a hospital admission record during the study period

Patients with a record of hospital admission (n=324)					Patients with no record of hospital admission (n=1121)				
Rank	Drug subgroup name	ATC Code	n	%	Rank	Drug subgroup name	ATC Code	n	%
1	Antacids, antiflatulents and anti-ulcerants	A02	178	54.9%	1	Antacids, antiflatulents and anti-ulcerants	A02	280	25.0%
2	Systemic antibacterials	J01	137	42.3%	2	Psycholeptics	N05	223	19.9%
3	Psycholeptics	N05	95	29.3%	3	Systemic antihistamines	R06	203	18.1%
4	Anti-inflammatory and anti-rheumatic products	M01	69	21.3%	4	Lipid-regulating/anti-atheroma preparations	C10	185	16.5%
5	Systemic antihistamines	R06	65	20.1%	5	Systemic antibacterials	J01	184	16.4%
6	Lipid-regulating/anti-atheroma preparations	C10	64	19.8%	6	Anti-inflammatory and anti-rheumatic products	M01	155	13.8%
7	Antithrombotic agents	B01	58	17.9%	7	Antidiarrhoeals, oral electrolyte replacers and intestinal anti-inflammatories	A07	120	10.7%
8	Agents acting on the renin-angiotensin system	C09	56	17.3%	8	Agents acting on the renin-angiotensin system	C09	104	9.3%
9	Antidiarrhoeals, oral electrolyte replacers and intestinal anti-inflammatories	A07	55	17.0%	9	Vitamins	A11	93	8.3%
10	Vitamins	A11	55	17.0%	10	Cough and cold preparations	R05	91	8.1%
11	Analgesics	N02	54	16.7%	11	Calcium antagonists	C08	80	7.1%
12	Systemic agents for fungal infections	J02	53	16.4%	12	Anti-gout preparations	M04	74	6.6%
13	Cough and cold preparations	R05	47	14.5%	13	All other therapeutic products	V03	53	4.7%
14	Calcium antagonists	C08	45	13.9%	14	Functional gastro-intestinal disorder drugs	A03	53	4.7%
15	Systemic corticosteroids	H02	44	13.6%	15	Cholagogues and hepatic protectors	A05	53	4.7%
16	All other therapeutic products	V03	43	13.3%	16	Analgesics	N02	52	4.6%
17	Intravenous solutions	K01	39	12.0%	17	Drugs used in diabetes	A10	49	4.4%
18	Functional gastro-intestinal disorder drugs	A03	38	11.7%	18	Psychoanaleptics excluding anti-obesity preparations	N06	44	3.9%
19	Antivirals for systemic use	J05	38	11.7%	19	Antithrombotic agents	B01	40	3.6%
20	Anti-gout preparations	M04	38	11.7%	20	Anti-epileptics	N03	37	3.3%
21	Anti-epileptics	N03	38	11.7%	21	Anti-asthma and copd products	R03	35	3.1%
22	Drugs used in diabetes	A10	35	10.8%	22	Anti-anaemic preparations	B03	32	2.9%
23	Antiprotozoals and anthelmintics	P01	33	10.2%	23	Antiprotozoals and anthelmintics	P01	27	2.4%
24	Cholagogues and hepatic protectors	A05	30	9.3%	24	Systemic agents for fungal infections	J02	25	2.2%
25	Drugs for constipation and bowel cleansers	A06	29	9.0%	25	Drugs for constipation and bowel cleansers	A06	24	2.1%
26	Psychoanaleptics excluding anti-obesity preparations	N06	26	8.0%	26	Systemic corticosteroids	H02	22	2.0%
27	Diuretics	C03	24	7.4%	27	Antivirals for systemic use	J05	22	2.0%
28	Anti-asthma and copd products	R03	19	5.9%	28	Beta-blocking agents	C07	22	2.0%
29	Blood coagulation system, other products	B02	18	5.6%	29	Urologicals	G04	21	1.9%
30	Anti-anaemic preparations	B03	18	5.6%	30	Diuretics	C03	18	1.6%
31	Beta-blocking agents	C07	15	4.6%	31	Other cns drugs	N07	18	1.6%
32	Urologicals	G04	15	4.6%	32	Muscle relaxants	M03	17	1.5%
33	Antimycobacterials	J04	14	4.3%	33	Thyroid therapy	H03	14	1.2%
34	Dietetic agents	V06	14	4.3%	34	Cardiac therapy	C01	11	1.0%
35	Other cns drugs	N07	13	4.0%	35	Blood coagulation system, other products	B02	10	0.9%
36	Cardiac therapy	C01	12	3.7%	36	Antimycobacterials	J04	10	0.9%
37	All other non-therapeutic products	V07	12	3.7%	37	Other drugs for disorders of the musculo-skeletal system	M05	10	0.9%
38	Mineral supplements	A12	8	2.5%	38	Antihypertensives	C02	8	0.7%
39	Injection solutions/infusion additives (<100ml)	K04	7	2.2%	39	Dietetic agents	V06	6	0.5%
40	Muscle relaxants	M03	7	2.2%	40	Other dermatological preparations	D11	6	0.5%
41	Antihypertensives	C02	6	1.9%	41	Digestives, including digestive enzymes	A09	5	0.4%
42	Other drugs for disorders of the musculo-skeletal system	M05	6	1.9%	42	Mineral supplements	A12	4	0.4%
43	Immunostimulating agents	L03	5	1.5%	43	Other cardiovascular products	C06	3	0.3%
44	Other cardiovascular products	C06	4	1.2%	44	Antifungals, dermatological	D01	3	0.3%
45	Antifungals, dermatological	D01	4	1.2%	45	Anti-parkinson drugs	N04	3	0.3%
46	Thyroid therapy	H03	4	1.2%	46	Cerebral and peripheral vasotherapeutics	C04	3	0.3%
47	Other hormones	H04	4	1.2%	47	Intravenous solutions	K01	2	0.2%
48	Anaesthetics	N01	4	1.2%	48	Topical corticosteroids	D07	2	0.2%
49	Anti-parkinson drugs	N04	4	1.2%	49	Other alimentary tract and metabolism products	A16	2	0.2%
50	Digestives, including digestive enzymes	A09	3	0.9%	50	Cytostatic hormone therapy	L02	2	0.2%
51	Antiemetics and antinauseants	A04	2	0.6%	51	Topical anti-rheumatics	M02	1	0.1%
52	Cerebral and peripheral vasotherapeutics	C04	2	0.6%	52	Antivaricosis/anti-haemorrhoidal preparations	C05	1	0.1%
53	Topical corticosteroids	D07	2	0.6%	53	Immunosuppressants	L04	1	0.1%
54	Gynaecological anti-infectives	G01	2	0.6%	54	Cardiovascular multitherapy combination products	C11	1	0.1%
55	Topical anti-rheumatics	M02	2	0.6%	55	Emollients, protectives	D02	1	0.1%
56	Stomatologicals, mouth preparations, medicinal dentifrices etc	A01	1	0.3%	56	Nonsteroidal products for inflammatory skin disorders	D05	1	0.1%
57	Anabolics, systemic	A14	1	0.3%	57	Anti-acne preparations	D10	1	0.1%
58	Antivaricosis/anti-haemorrhoidal preparations	C05	1	0.3%	58	Sex hormones and products with similar desired effects, systemic action only	G03	1	0.1%
59	Antiseptics and disinfectants	D08	1	0.3%	59	Ophthalmologicals	S01	1	0.1%
60	Antineoplastics	L01	1	0.3%	-	-	-	-	-
61	Immunosuppressants	L04	1	0.3%	-	-	-	-	-

Co-medications prescribed for use for ≥30 days total during the study period, regardless of whether they are inpatient/outpatient prescriptions, are listed.
Co-medications were classified based on the therapeutic subgroups (2nd level) of ATC codes.
Gray-shaded cells indicate the class of hospital solutions (categorized under "K" in EphMRA ATC).

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 3–4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page 3 Page 3 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 7		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 8		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 9–10		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	Page 9–10	RECORD 6.1: The methods of study population selection (such as codes or	Page 9–10

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	 N/A	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	 N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 11–12	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 11–12
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 10		
Bias	9	Describe any efforts to address potential sources of bias	Page 10		
Study size	10	Explain how the study size was	Page 9–10		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 13		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 13 N/A N/A N/A N/A		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Not reported. Not reported.
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	N/A

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 14 Page 14 N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 14
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 14–15 N/A N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page 15, 17		
Main results	16	(a) Give unadjusted estimates	Page 15–18		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 20		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 23–24	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 23–24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 25		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 23–24		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 26		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 26

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.