PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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	Ruzicka, Daniel; Imai, Kentaro; Takahashi, Kenichi; Naito, Toshio

VERSION 1 – REVIEW

REVIEWER	David Vance University of Alabama at Birmingham Birmingham, Alabama United States of America
REVIEW RETURNED	25-Oct-2017

GENERAL COMMENTS	I read this article with a great deal of interest as much of my own research focuses on this topic as well. I really have no substantive comments to make. The article was clearly written, easy to understand, and presents the data in a logical manner.

REVIEWER	Claire Kendall University of Ottawa
REVIEW RETURNED	01-Nov-2017

GENERAL COMMENTS	General comments: In this study, the authors use hospital claims data to describe comorbidity and comorbidity related medication use among people living with HIV in Japan. I suspect Japan is an interesting population in which to study comorbidity related to people living with HIV, especially given the aging population described by the authors, and appreciate the opportunity to review their work. I believe it would be preferred to use the terms people living with (or just with) HIV versus controls (or people without HIV). Given data used in the study are administrative, I suggest the editor request that the authors use the RECORD guidelines and checklist to report this study, and provide a checklist for publication. http://www.record-statement.org/checklist.php. I have two major concerns: first that the HIV ascertainment method applied to 288 hospitals only identified people with HIV in 47 of these hospitals, and that the acute care nature of the data can not be extrapolated to a current population of people living with HIV who may receive most of their care in the community. I see several typos thus the paper would benefit from copyediting. Specific comments: Introduction: The study rationale and objectives are relatively clear. Methods:

	The authors clearly state the study design. It would be helpful for the authors to provide a little more data on the nature of the claims used. Do these data capture only inpatient admissions, or any emergency department our outpatient visits at these hospitals? Was HIV ascertained using a major diagnosis, any diagnosis, discharge diagnoses…etc. Has this approach been validated in Japan (not critical, but important to note)? By their current description of ART, it seems that patients not taking ART (for adherence or other issues) would be excluded? Did the authors look only at "triple" therapy - What about people with HBV or HCV who are on antivirals? It seems the authors captured a large number of data variables from their data sources. For chronic disease ascertainment, is it anticipated that the records used would identify only diagnoses recorded within the time frame, or would for example someone diagnosed with diabetes in 2008 be ascertained as having diabetes from the data pulled. I question the value of lumping chronic renal failure (which could be HIV or ART related) and nephrolithiasis together. If bone disorders only includes osteoporosis, the authors should just state "osteoporosis". It's unclear how malignancies were ascertained – as I read down, it sounds like all malignancies were considered but only some highlighted? In the abstract the authors speak to many AIDS-defining cancers, but in the methods they identify only a handful they are looking for (what about HIV-related cancers, like HPV?) I'm a bit confused by the prescription medication time period – if these are acute care visits, how are 30+ days of prescription identified? Results: Patients were enrolled – they were identified. Also, is it really possible that of 288 hospitals from which data was drawn, only 47 hospitals had any patients with HIV attending? I worry this is a fatal flaw. How many patients were identified with HIV but then excluded due to no ART prescriptions? Would it be more accurate to say 703 had an AIDS-defining condition at some point during the study period? The authors define multimorbidity as 3+ and 2+ chronic conditions. They should pick one and define in the methods section (do malignancies count? Psychosis?) With respect to the medications listed, it is my interpretation that many of these are related to acute care admissions, such as antibiotics and oral electrolyte replacers. The authors may want to focus on categories of medications related to chronic disease, or at least medications people are likely taking over the long term. Discussion I recommend that the discussion follow a tighter format: para 1 summarize what you found, para 2-3 discuss how this relates to the literature in this area, para 4 discuss limitations, para 5 discuss

	implications and conclusions. A definite limitation should be that this data only captures people living with HIV who receive care in acute care settings AND who are currently taking ART, thus likely missing those on ART well enough not to require acute care, as well as those with advanced HIV who are not receiving therapy.

REVIEWER	Pablo Perez-Guzman Imperial College London, United Kingdom Department of Infectious Disease Epidemiology Research Assistant
REVIEW RETURNED	04-Jan-2018

GENERAL COMMENTS	1. Although the authors comment on the fact that the data for the study comes from a medical claims database of hospitals that provide acute care, it is not explicitly mentioned what percentage of the study population corresponds to hospitalised, outpatient-acute-care or ambulatory-stable patients. This has major implications on: a) the adequacy of the title of the paper (i.e. the general population, as the current title suggests, or a population presenting for acute-care; b) the presentation of the abstract, as the characteristics of the population should be spelled out succinctly; c) whether the data is adequate to answer the research questions, as these allude to the general, HIV-positive population of Japan and not that of an acute-care setting; d) the types and percentages of co-medications expected (e.g. large number of acid-lowering agents for the prevention of peptic ulcers, prolonged courses with systemic antibacterials for hospital-acquired infections and/or AIDS defining conditions like PCP, toxoplasmosis, etc.); and, overall, e) the breadth and depth of the conclusions that can be drawn. A clearer description of the study setting and its population is necessary. This should include hospitalised vs non-hospitalised and, in the case of the former, whether the hospitalisation was related to the diseases of interest (especially vascular diseases, like stroke or myocardial infarction, and/or AIDS-defining conditions, among others) and duration of hospital stay (mean/SD or media/range, depending on the n). 2. In page 14, it's mentioned that the prevalence psychiatric disorders and hep B/C co-infection was similar across age groups. However, only a percentage range is given, which cannot support a conclusion of no-diference across the groups. This should be clarified with a Chi-squared test, since figure 2B does show an increase in prevalence from the 30-39 age group to 40-49, which subsequently declines gradually. Moreover, a cross-sectional, population-based survey by Omiya et al. (AIDS Care, 2014) described a prevalence of anxiety of 8.2% in employed HIV-positive Japanese patients, vs 10.2% in unemployed, and a prevalence of depression of 9.4% vs 11.4%, respectively. The numbers graphed in figure 2B are higher than this precedent, which warrants discussion. 3. Similarly, in the same page, it's argued that there is a 10-15% higher prevalence of vascular disease, kidney disease, malignancies and bone disorders in the older age groups, compared to 18-29 year-olds. Although the increase in prevalence in these conditions is evident from figure 2B, there was no statistical test performed to support this conclusion nor clear and disaggregated figures are given for the reader to conduct an analysis. 4. The results conveyed for co-medications found are largely

	unrelated to the diseases of interest (acute-care nature of the population?). This does not support the discussion led in pages 21-23 and, moreover, for readers with no medical background this could be misleading. Thus, the reason for this finding should be clearly discussed. Of special note, three of the top-five co-medications found (i.e. GI drugs, systemic antibacterials and systemic antihistamines) could contribute to a major overestimation of the co-medication profile of HIV-positive adults in Japan, if these in fact relate to patients in acute-care. 5. In table 2, the total count of cancers adds up to 125, which does not correspond to the total number of cancers cited in the text (n=148). If the authors decided to exclude single cancer-type cases from the table, it should included as "others n=23(19.8%)". Additionally, more information on the burden of cancer in the study population is necessary to back up the related discussion in page 20. Since there were 116 patients with cancer (81 AIDS-related and 35 non-AIDS related), a representation similar to figures 2A and 3A comparing AIDS vs non-AIDS cancers by age-groups is largely desirable. 6. For a researcher/researchers with access to the same medical database, the description of the patient search methods are not clear enough to allow reproducibility of the study. Moreover, the codes employed could be leading to misrepresentation of the diseases of interest. On the one hand, grouping ICD-10 codes for vascular disease presents a problem of lumping together patients with an acute presentation (e.g. acute MI or stroke) and with the history of having had one in the past. Additionally, the grouping of chronic renal failure, urolitiasis and kidney cancer as kidney diseases is inaccurate. Urolithiasis might not necessarily be related to chronic kidney disease and, in fact, warrants acute-care, most of the times, with urological procedures rather than co-medication. Kidney cancers should have been classified under malignancies. Lastly, there is no description of which ATC level 2 codes were selected. Overall, it would be desirable to resolve possible miss-classification issues, as there could be an overestimation of chronic vascular diseases and chronic kidney disease, and have the ICD-10 and ATC codes listed in a technical appendix with the number of patients that were retrieved with each.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: David Vance

Institution and Country: University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below

I read this article with a great deal of interest as much of my own research focuses on this topic as well. I really have no substantive comments to make. The article was clearly written, easy to understand, and presents the data in a logical manner.

Response:

Thank you very much for reviewing our manuscript. We hope our revisions have made the manuscript even more suitable for publication.

Reviewer: 2

Reviewer Name: Claire Kendall

Institution and Country: University of Ottawa

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

General comments: In this study, the authors use hospital claims data to describe comorbidity and comorbidity related medication use among people living with HIV in Japan. I suspect Japan is an interesting population in which to study comorbidity related to people living with HIV, especially given the aging population described by the authors, and appreciate the opportunity to review their work.

I believe it would be preferred to use the terms people living with (or just with) HIV versus controls (or people without HIV). Given data used in the study are administrative, I suggest the editor request that the authors use the RECORD guidelines and checklist to report this study, and provide a checklist for publication. http://www.record-statement.org/checklist.php. I have two major concerns: first that the HIV ascertainment method applied to 288 hospitals only identified people with HIV in 47 of these hospitals, and that the acute care nature of the data can not be extrapolated to a current population of people living with HIV who may receive most of their care in the community. I see several typos thus the paper would benefit from copyediting.

Response:

Thank you very much for reviewing the manuscript and giving us valuable suggestions. Our replies to each comment are as follows.

1. In accordance with your advice, we have applied the terms, "people living with HIV (PLWH)" and "people without HIV".

2. We have submitted the STROBE checklist in accordance with the journal guidelines. However, based on your suggestion, we also used the RECORD guidelines and uploaded the checklist.

3. Regarding the above concerns about the nature of hospitals included, first, we wish to clarify that

the hospitals referred to in the manuscript as “acute-care hospitals” are not limited to just acute-care-only or emergency hospitals. MDV, the database provider, uses this terminology here in Japan to describe hospitals that can provide advanced medical treatment (i.e., advanced treatment hospitals, general hospitals, acute-care hospitals), including hospitals providing both acute and chronic care (excluding nursing homes and hospices). Now that we understand this terminology may lead to confusion and is potentially difficult to understand for readers outside Japan, or those unfamiliar with the MDV database, we have explained the terminology in more detail in the Methods section. Thereafter, we simply called them “hospitals.” We hope this adequately clarifies the term.

Regarding the relatively small number of hospitals with data on people living with HIV (47 of 288), one reason may be that people living with HIV in Japan usually receive treatment at regional hospitals specializing in HIV/AIDS treatment, and not usually at clinics in the community, and some among the 288 hospitals in the database are not such facilities. Considering that designated hospitals for HIV/AIDS treatment are generally large hospitals providing advanced medical treatment, we believe the MDV database is currently the most appropriate database in Japan for a study of people living with HIV, despite its not including all hospitals providing HIV care in Japan.

However, as you pointed out, this is definitely a major limitation of this study. Therefore, in the manuscript, we have mentioned the limited generalizability of our results due to the limited types of hospitals included.

4. We regret the typos and have used an English scientific copy editing service to resolve the issue. Thank you for your advice.

Specific comments:

Introduction: The study rationale and objectives are relatively clear.

Methods:

The authors clearly state the study design.

It would be helpful for the authors to provide a little more data on the nature of the claims used. Do these data capture only inpatient admissions, or any emergency department our outpatient visits at these hospitals? Was HIV ascertained using a major diagnosis, any diagnosis, discharge diagnoses…etc. Has this approach been validated in Japan (not critical, but important to note)? By their current description of ART, it seems that patients not taking ART (for adherence or other issues) would be excluded? Did the authors look only at “triple” therapy - What about people with HBV or HCV who are on antivirals?

Response:

In accordance with your comments, we have added more detailed explanations of the data included in the database, as well as the methodology of patient selection, in the Methods section.

1. The database includes both inpatient and outpatient data, incurred in any department, including emergency departments if they are present within the hospitals (as explained above, included hospitals are not limited to emergency hospitals). For instance, it also includes data on patients who only visited a hospital to receive outpatient care and without any hospitalization.

2. We used an "any diagnosis" record of HIV to identify patients diagnosed with HIV. In this database, "major diagnosis" records are available only for patients with hospital admission data (i.e., hospitalized patients), and no other specific diagnosis records (e.g., discharge diagnosis) are available. In this study, to include patients irrespective of the presence or absence of hospitalization, we used "any diagnosis" records.

3. We defined HIV patients as those with a diagnosis record of HIV and with prescription records of antiretrovirals. Although this means of patient selection has not been validated, we used this definition because relying on the presence of only one diagnosis record may result in inclusion of patients of uncertain status. In other studies using the same MDV database, similar methods (i.e., based on both diagnosis records and relevant prescription records) were used for identifying target patients[1),2)]. Under the limited availability of data (e.g., laboratory test results) and non-linkage to patients' medical records in this database, this means of patient identification is probably the most practical and appropriate.

   1) Tanaka K, et al. Risk for cardiovascular disease in Japanese patients with rheumatoid arthritis: a large-scale epidemiological study using a healthcare database. SpringerPlus. 2016;5(1):1111.
   2) Sato M, et al. Fracture risk and healthcare resource utilization and costs among osteoporosis patients with type 2 diabetes mellitus and without diabetes mellitus in Japan: retrospective analysis of a hospital claims database. BMC Musculoskelet Disord. 2016 Nov 25;17(1):489.

4. According to the definitions of target patients described above, people living with HIV, but who had no prescription records of antiretrovirals, during the study period were excluded. We have stated this as a limitation of the study.

5. As explained in the manuscript, we included people with HIV and with at least one prescription record of antiretrovirals. Thus, the ART that patients received is not necessarily "triple therapy." Because patients were required to have both HIV diagnosis records and ART prescription records, people without HIV (e.g., with HBV or HCV) and who take antivirals were not included in this study. We revised the text to clarify the data extraction methods, including the definitions of ART (more precisely, antiretrovirals).

It seems the authors captured a large number of data variables from their data sources. For chronic disease ascertainment, is it anticipated that the records used would identify only diagnoses recorded within the time frame, or would for example someone diagnosed with diabetes in 2008 be ascertained as having diabetes from the data pulled. I question the value of lumping chronic renal failure (which could be HIV or ART related) and nephrolithiasis together. If bone disorders only includes osteoporosis, the authors should just state "osteoporosis".

Response:

1. We identified a chronic comorbidity if someone had a relevant ICD-10 code ("disease record"), which is recorded when the patient received not only diagnosis but also any medical procedures/treatment/prescriptions for the disease, anytime between 2010 and 2015. Data

recorded outside the study period were not considered. In regard to your example, someone diagnosed with diabetes in 2008 was not considered as having diabetes unless the person had any "disease record" of diabetes—not necessarily a diagnosis record—during the study period, which would most likely exist if the person continued to visit the hospital for treatment of diabetes. We revised the relevant parts in the Methods section to make the descriptions of this methodology clearer.

2. Originally, we grouped chronic renal failure (N18–19) and urolithiasis (N20–21) together under "kidney diseases," in accordance with the grouping used in other studies. However, upon considering your comments, we decided to exclude urolithiasis from this comorbidity category and renamed the category "kidney failure."

   We conducted reanalysis using the revised definition, but this did not result in changes in the prevalence of "kidney failure" and the number of comorbidities among people living with HIV. Among the 1445 people living with HIV, 35 had urolithiasis, and all 35 also had renal failure.

3. We changed the term from "bone disorders" to "osteoporosis."

It's unclear how malignancies were ascertained – as I read down, it sounds like all malignancies were considered but only some highlighted? In the abstract the authors speak to many AIDS-defining cancers, but in the methods they identify only a handful they are looking for (what about HIV-related cancers, like HPV?)

Response:

We considered all malignancies as indicated by the ICD-10 code block C00-97 (malignant neoplasms) under the definition of "malignancies." Then, to further examine the results by type of malignancy, we classified them as either AIDS-defining cancers or non-AIDS-defining cancers, in accordance with the classification described in the cited literature. Incidentally, cervix cancer (which is related to HPV) was classified under AIDS-defining cancers. To avoid confusing the readers, we made a slight revision to the descriptions in the manuscript.

I'm a bit confused by the prescription medication time period – if these are acute care visits, how are 30+ days of prescription identified?

Response:

We calculated the total number of "prescription days" during the study period; i.e., the total number of days for which the particular medication was supplied regardless of whether the medication was prescribed continuously for 30+ days or prescribed on and off for a total of 30+ days.

As explained above, "hospitals" in this study were not necessarily those providing acute care only, and there were hospitals that also provided chronic care. This means the database includes data of patients who regularly visit these hospitals, or those hospitalized for a long period. These patients may have been prescribed a particular medication for a long period. Additionally, in Japan, physicians can prescribe most medications (especially those for chronic treatment) at one time for use for a

considerable number of days (e.g., 14, 30, or even longer). Therefore, there are cases where patients visit these hospitals only a couple of times but receive medication for use for a total of 30+ days.

Results:

Patients were enrolled – they were identified. Also, is it really possible that of 288 hospitals from which data was drawn, only 47 hospitals had any patients with HIV attending? I worry this is a fatal flaw.

Response:

1. Thank you for your comment. Accordingly, we changed “enrolled” to “identified.”

2. As explained above, one reason for the relatively small number of hospitals that had data on people with HIV (47 of 288) may be that not all 288 hospitals were regional hospitals specializing in HIV/AIDS treatment, at which people with HIV in Japan usually receive HIV care. We consider that certain proportions of people with HIV in Japan and receiving HIV care are included in this database because such designated facilities are generally large hospitals providing advanced medical treatment.

How many patients were identified with HIV but then excluded due to no ART prescriptions?

Response:

Of 3155 people living with HIV, 1710 people did not have ART records during the study period, and therefore were excluded. For readers interested in that fact, we added this information in the manuscript.

The number of people with HIV without ART was higher than expected. One reason may be that some patients without ART records received ART at different hospitals that are not included in the database.

One reason we only included people with ART was that we wanted to avoid including patients of uncertain status (e.g., overdiagnosis, incorrect records), as explained in the manuscript. Another reason was that unknown status regarding those with or without ART in the study population made interpretation of our co-medication results difficult. As mentioned above, patients’ lacking ART records does not necessarily mean they do not receive ART anywhere. With such limitations of the database in mind, to examine medication profiles of people with HIV, we considered it best to include only those who indeed received ART, rather than including all patients who may or may not have received ART.

Would it be more accurate to say 703 had an AIDS-defining condition at some point during the study period?

Response:

We have revised the sentence accordingly.

The authors define multimorbidity as 3+ and 2+ chronic conditions. They should pick one and define in the methods section (do malignancies count? Psychosis?)

Response:

In the Methods section, we defined multimorbidity as two or more chronic comorbidities, and revised the relevant parts of the results. For counting the number of chronic comorbidities, as provided in the Methods section, we considered nine categories of chronic comorbidities, including malignancies and psychiatric disorders.

With respect to the medications listed, it is my interpretation that many of these are related to acute care admissions, such as antibiotics and oral electrolyte replacers. The authors may want to focus on categories of medications related to chronic disease, or at least medications people are likely taking over the long term.

Response:

Our aim was to examine co-medication use in people with HIV—i.e., examine all medications other than ART that are frequently used by these people—rather than the medications for specific diseases. Whatever the purpose of a medication is (for acute or chronic care), if the medication is used for a long period it could interfere with ART. Therefore, we defined a co-medication as a non-ART drug prescribed for use for 30+ days, so as not to count drugs prescribed for only a short period. With this definition, we could focus on medications likely for chronic use or at least used for many days. Ultimately, some of the most common co-medications in this study were those probably related to acute care; however, owing to the reasons provided above, we believe these results are still important to physicians who should treat people with HIV with the potential DDIs in mind.

Discussion

I recommend that the discussion follow a tighter format: para 1 summarize what you found, para 2-3 discuss how this relates to the literature in this area, para 4 discuss limitations, para 5 discuss implications and conclusions.

Response:

Accordingly, we revised the Discussion to tighten the format, and made it a shorter. Thank you for your advice.

A definite limitation should be that this data only captures people living with HIV who receive care in acute care settings AND who are currently taking ART, thus likely missing those on ART well enough not to require acute care, as well as those with advanced HIV who are not receiving therapy.

Response:

As explained above, because hospitals providing chronic care as well as acute care are also included, patients examined in this study are not necessarily those with HIV diseases requiring acute care. We excluded people without ART in this study; reasons were provided in our responses to your comments above. This is certainly one of several limitations of the study. Nonetheless, because this was the first study to use a large data set to examine the comorbidity/co-medication profiles of people living with HIV, and taking ART, in Japan, we still believe it provides important information for Japanese physicians who treat these people.

Reviewer: 3

Reviewer Name: Pablo Perez-Guzman

Institution and Country: Imperial College London, United Kingdom, Department of Infectious Disease Epidemiology, Research Assistant

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

1. Although the authors comment on the fact that the data for the study comes from a medical claims database of hospitals that provide acute care, it is not explicitly mentioned what percentage of the study population corresponds to hospitalised, outpatient-acute-care or ambulatory-stable patients. This has major implications on: a) the adequacy of the title of the paper (i.e. the general population, as the current title suggests, or a population presenting for acute-care; b) the presentation of the abstract, as the characteristics of the population should be spelled out succinctly; c) whether the data is adequate to answer the research questions, as these allude to the general, HIV-positive population of Japan and not that of an acute-care setting; d) the types and percentages of co-medications expected (e.g. large number of acid-lowering agents for the prevention of peptic ulcers, prolonged courses with systemic antibacterials for hospital-acquired infections and/or AIDS defining conditions like PCP, toxoplasmosis, etc.); and, overall, e) the breadth and depth of the conclusions that can be drawn. A clearer description of the study setting and its population is necessary. This should include hospitalised vs non-hospitalised and, in the case of the former, whether the hospitalisation was related to the diseases of interest (especially vascular diseases, like stroke or myocardial infarction, and/or AIDS-defining conditions, among others) and duration of hospital stay (mean/SD or media/range, depending on the n).

Response:

Thank you very much for giving us valuable suggestions and an opportunity to revise our manuscript.

First, we should clarify what we meant in the manuscript. The hospitals referred to as “acute-care hospitals” are not limited to “acute-care-only” or emergency hospitals. In Japan, the term “acute-care hospital” refers to hospitals with advanced medical treatment capabilities (i.e., advanced treatment hospitals, general hospitals, acute-care hospitals), which include those providing both acute and chronic care (excluding nursing homes or hospices). Thus, patients included in this study were not necessarily those who were hospitalized or who required acute care. Moreover, it should be noted that patients with HIV in Japan usually receive treatment at regional hospitals specializing in HIV/AIDS treatment, rather than at clinics in the community, and such designated facilities are probably included in the database because they are usually large hospitals that provide advanced medical treatment. Therefore, although the generalizability is limited, we consider that our study population still represents certain proportions of patients with HIV and on ART in Japan.

As you pointed out, this is critically important information for interpreting the results of this study. We therefore added these explanations in the manuscript.

With this in mind, please also see our responses to each point you raised.

a) To provide more information in the title, we revised it as follows: “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.” The title now indicates this is a hospital claims database study. We felt it best to describe in the text the characteristics of hospitals included because it is difficult to properly describe them in only a few words.

b) In the abstract, we added descriptions of the hospitals included in the database, so readers can correctly understand the study settings.

c) We revised the sentences so readers would not misunderstand the study population.

d) As explained above, the hospitals included were not limited to emergency hospitals, and those providing chronic care besides acute care were also included. However, our results would definitely reflect acute-phase treatment that some patients received in these hospitals. Thus, the co-medication profiles of patients in this study would probably differ from those treated at different hospitals. We stated this as a limitation of the study.

e) We revised the text to make it clear that our results are of patients from the included hospitals; thus, the results, particularly the types of co-medications, need to be interpreted with care. Nevertheless, we still believe it is important to suggest that physicians who treat HIV patients should be aware of such increases in the number of chronic comorbidities and co-medications with age.

Incidentally, of the 1445 people with HIV, 324 (22.4%) had a record of hospitalization (for any reason) at any time during the study period. The comorbidity/co-medication profiles may differ between hospitalized and non-hospitalized patients, but examining such differences was not our aim. Apart

from that, the number of patients who were hospitalized because of HIV diseases seems much smaller. Therefore, in this study, we only examined these 1445 patients.

2. In page 14, it's mentioned that the prevalence psychiatric disorders and hep B/C co-infection was similar across age groups. However, only a percentage range is given, which cannot support a conclusion of no-difference across the groups. This should be clarified with a Chi-squared test, since figure 2B does show an increase in prevalence from the 30-39 age group to 40-49, which subsequently declines gradually. Moreover, a cross-sectional, population-based survey by Omiya et al. (AIDS Care, 2014) described a prevalence of anxiety of 8.2% in employed HIV-positive Japanese patients, vs 10.2% in unemployed, and a prevalence of depression of 9.4% vs 11.4%, respectively. The numbers graphed in figure 2B are higher than this precedent, which warrants discussion.

Response:

We additionally conducted the trend test to examine the differences in prevalence of each comorbidity between age groups. These results supported our interpretation that, unlike the other seven comorbidities, the prevalence of psychiatric disorders and HepB/C co-infection did not increase with age. Although we did not intend to discuss our results based on the statistical test results, for readers' interest, we have now provided these test results in the manuscript as supporting data.

Chronic comorbidity	**p-value** (Cochran–Armitage test)
Diabetes	<.0001
Hypertension	<.0001
Lipid disorders	<.0001
Vascular diseases	<.0001
Kidney failure	<.0001
Malignancies	<.0001
Psychiatric disorders	0.3271
Osteoporosis	<.0001
HepB/C co-infection	0.4501

For psychiatric disorders, Omiya et al. (AIDS Care, 2014) reported the mean scores of HADS anxiety and depression subscales among employed and non-employed HIV patients, not prevalence. Those results were interesting, but as we have only data on presence or absence of a diagnosis of relevant diseases, we consider it difficult to discuss our results by comparing the two studies.

3. Similarly, in the same page, it's argued that there is a 10-15% higher prevalence of vascular disease, kidney disease, malignancies and bone disorders in the older age groups, compared to 18-29 year-olds. Although the increase in prevalence in these conditions is evident from figure 2B, there was no statistical test performed to support this conclusion nor clear and disaggregated figures are given for the reader to conduct an analysis.

Response:

As provided above, the results of the trend test supported our interpretation of Figure 2B. Again, we have now provided these test results in the manuscript as supporting data.

4. The results conveyed for co-medications found are largely unrelated to the diseases of interest (acute-care nature of the population?). This does not support the discussion led in pages 21-23 and, moreover, for readers with no medical background this could be misleading. Thus, the reason for this finding should be clearly discussed. Of special note, three of the top-five co-medications found (i.e. GI drugs, systemic antibacterials and systemic antihistamines) could contribute to a major overestimation of the co-medication profile of HIV-positive adults in Japan, if these in fact relate to patients in acute-care.

Response:

As you pointed out, ultimately, some of the most common co-medications in this study were probably those related to acute care. Our results may indeed be misleading without considering that these patients are all from hospitals that provide advanced medical treatment; therefore, we have now stated in the manuscript that these results need to be interepreted with care.

However, these common co-medications in this study were medications actually prescribed for people with HIV on ART at least for a certain period (30+ days). Whether it was for acute or chronic treatment, if a medication is used for a long period, it could interfere with ART. Therefore, despite several limitations of the study, we believe our results are still informative for physicians who should treat people with HIV with the potential DDIs in mind.

5. In table 2, the total count of cancers adds up to 125, which does not correspond to the total number of cancers cited in the text (n=148). If the authors decided to exclude single cancer-type cases from the table, it should included as "others n=23(19.8%)". Additionally, more information on the burden of cancer in the study population is necessary to back up the related discussion in page 20. Since there were 116 patients with cancer (81 AIDS-related and 35 non-AIDS related), a representation similar to figures 2A and 3A comparing AIDS vs non-AIDS cancers by age-groups is largely desirable.

Response:

First, based on your comments, we grouped the types of non-AIDS-defining cancers that were present only in one patient and displayed as “others n=23 (19.8%)” in Table 2: proportions of patients who had respective cancer types in patients with any malignancies.

Second, we created a figure showing the proportions of patients with AIDS-defining cancers and those with non-AIDS-defining cancers in patients with any malignancy within each age group, and included this in the manuscript as Figure 4. However, the figure may be difficult to interpret. For one, a patient can have both AIDS-defining and non-AIDS-defining cancers; thus, the total percentages in each age group could exceed 100% (this makes it difficult to create a figure similar to our Figures 2A and 3A). Additionally, because there are very few patients in each age group, we were concerned that discussions based on the exact percentages in each age group might be overestimated and misleading. We therefore presented this figure to help readers grasp the overall picture, rather than to discuss each result by age group.

6. For a researcher/researchers with access to the same medical database, the description of the patient search methods are not clear enough to allow reproducibility of the study. Moreover, the codes employed could be leading to misrepresentation of the diseases of interest. On the one hand, grouping ICD-10 codes for vascular disease presents a problem of lumping together patients with an acute presentation (e.g. acute MI or stroke) and with the history of having had one in the past. Additionally, the grouping of chronic renal failure, urolitiasis and kidney cancer as kidney diseases is inaccurate. Urolithiasis might not necessarily be related to chronic kidney disease and, in fact, warrants acute-care, most of the times, with urological procedures rather than co-medication. Kidney cancers should have been classified under malignancies. Lastly, there is no description of which ATC level 2 codes were selected. Overall, it would be desirable to resolve possible miss-classification issues, as there could be an overestimation of chronic vascular diseases and chronic kidney disease, and have the ICD-10 and ATC codes listed in a technical appendix with the number of patients that were retrieved with each.

Response:

For data extraction, all the relevant ICD-10 codes necessary for identifying patients and diseases of interest were included. However, the types of records (e.g., “any diagnosis record” or “major diagnosis record”) were not clearly stated; therefore, we added explanations to our methodology regarding patient selection/data extraction. With the information now provided in the manuscript, readers can reliably reproduce the study.

We originally defined each comorbidity category in accordance with the grouping used in other studies. However, based on your comments, we revised the definitions of “vascular diseases” and “kidney diseases.”

1. We excluded the ICD-10 code for acute MI (I21) from “vascular diseases.” However, the remaining codes were retained because we could not differentiate whether they indicate acute or chronic conditions from the ICD-10 codes themselves. Regarding the expressed concern about confusion with past history, we only considered the diseases recorded during

the study period. We therefore confirm that past history of the relevant disease before the study period was not counted.

2. Because urolithiasis (N20–21) should not be considered as a chronic condition, as you pointed out, we removed it from the disease category, which was renamed “kidney failure.” Kidney cancers were not included in the category, and were instead treated as malignancies.

We conducted reanalysis using these revised definitions, but it did not result in changes in the prevalence of “vascular diseases” and “kidney failure”: Among 1445 patients, 14 patients had acute MI (I21), but all 14 had other vascular diseases (I11, I13, I20, I22, I64) as well. Similarly, among the 1445 patients, 35 had urolithiasis, and all 35 also had renal failure.

For co-medications, we would like to make clear that we did not examine the use of some “selected” medications. In this study, all the medications were considered based on the classification using the second level of ATC codes. That is why no specific ATC codes are displayed in the Methods section. We revised the relevant parts in the Methods section to explain this more explicitly.

VERSION 2 – REVIEW

REVIEWER	Claire Kendall Bruyere Research Institute, Ottawa, Canada
REVIEW RETURNED	22-Feb-2018

GENERAL COMMENTS	Thanks for the opportunity to re-review this paper after response to editorial and peer review comments. I recognize and appreciate the effort the authors put into addressing these (both mine and reviewer C). This is likely a unique cohort with important location implications, but my remaining concerns will need to be assessed by the editor for final decision: 1. cohort selection - I appreciate that the authors now state that almost half of the original cohort with an HIV diagnosis code were excluded as not also on ART. This is a major limitation - we don't know whether in fact these people don't have HIV, are simply not on therapy, or are receiving treatment elsewhere as the authors postulate. This should be stated in the limitation. First sentence of the results should be more specific - Among those with a diagnostic code for HIV, only x% were found to also have an ART prescription and were included in the cohort. 2. There are many published validated algorithms for chronic disease ascertainment, but the authors only use one diagnosis code for all of those included in this manuscript. I worry about insomnia being a listed mental health comorbidity and in fact I imagine it gets listed as a concern in many inpatient admissions (see concern 3). This needs to be listed as a limitation. 3. I think there is an overlap of acute vs chronic which is a significant limitation of this paper. The title implies chronic comorbidity but many of the medications are acute, as I and one other reviewer have noted. I still really struggle with electrolyte replacement being a co-medication, as well as the fact that we do not really know whether some of these prescriptions are in patient for 30 days or outpatient

	30 day prescriptions. As such, this paper struggles to identify the chronic management of people living with HIV. This should be acknowledged. Perhaps the title should read simply comorbidity and comedication use among a cohort of people living with HIV and receiving care in hospital settings in Japan, or something. 4. It is unsurprising that comorbidities increase with increasing age among this cohort of people living with HIV or any other cohort for that matter, so I'm not sure too much should be made of this. Clearly DDI are important across age groups for people living with HIV in this cohort as all are on ART and the vast majority are on other medications.

REVIEWER	Pablo Perez Imperial College London, United Kingdom
REVIEW RETURNED	01-Mar-2018

GENERAL COMMENTS	I commend the considerable effort and time dedicated by the authors to address the issues and challenges raised in the previous round of reviews. It's encouraging to receive a much improved version of the manuscript. Minor comments for the present version are as follows: 1. Page 6 - ines 28/29: changes on PK/PD are not necessarily a cause of increased number or NCDs. Does this statement refer to the case of alterations in lipid and/or glucose profiles? If it does, such effect is not age-bound, but an adverse effect of specific ART drugs. 2. Page 8 - lines 40 to 46: the authors clearly defined the issue of acute care hospitals in the context of Japan. They also comment that demographic and clinical variables were extracted from the database. They should, thus, clearly express the proportion of patients that, during the study, required: 1) admission for an AIDS-defining illness; 2) admission for another acute-care reason; and 3) were stable, ambulatory patients. This will enrich the discussion and conclusions, as it would allow to flesh out the strength vs limitation of using the claims database to answer the research questions. 3. The dominion of academic written English by the authors is very good. Minor copy-edditing, however, could strengthen coherence and cohesion throughout. Particularly, shorter and more succinct paragraphs will increase the clarity and strength of messages conveyed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: Claire Kendall

Institution and Country: Bruyere Research Institute, Ottawa, Canada

Please state any competing interests or state ‘None declared’: None delcared

Thanks for the opportunity to re-review this paper after response to editorial and peer review comments. I recognize and appreciate the effort the authors put into addressing these (both mine and reviewer C). This is likely a unique cohort with important location implications, but my remaining concerns will need to be assessed by the editor for final decision:

1. cohort selection - I appreciate that the authors now state that almost half of the original cohort with an HIV diagnosis code were excluded as not also on ART. This is a major limitation - we don't know whether in fact these people don't have HIV, are simply not on therapy, or are receiving treatment elsewhere as the authors postulate. This should be stated in the limitation. First sentence of the results should be more specific - Among those with a diagnostic code for HIV, only x% were found to also have an ART prescription and were included in the cohort.

Response:

Thank you very much for re-reviewing the manuscript and giving us important suggestions.

First, we now state in the limitation that although patients without a record of antiretroviral prescription, who represent PLWH not taking antiretrovirals, were excluded, 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. (Page 26 of our revised manuscript word file without tracked-changes). Second, we have also revised the first sentence of the Results and provided the proportion of patients with a record of antiretroviral prescriptions in patients with a diagnosis record of HIV infection (Page 14).

2. There are many published validated algorithms for chronic disease ascertainment, but the authors only use one diagnosis code for all of those included in this manuscript. I worry about insomnia being a listed mental health comorbidity and in fact I imagine it gets listed as a concern in many inpatient admissions (see concern 3). This needs to be listed as a limitation.

Response:

We included “insomnia” in psychiatric disorders because insomnia (or sleep disturbance) is common in PLWH as well as other psychiatric problems (e.g., depression, anxiety, mania). However, as you point out, the prevalence of psychiatric disorders may be biased if it includes many patients with insomnia because inpatients are more likely to have insomnia than outpatients. Therefore, we additionally calculated the number of patients with each disease classified under the same comorbidity category (i.e., for vascular diseases and psychiatric disorders), and provided the results in Supplementary Table 2. The results showed that only 17 patients had insomnia, implying that it is unlikely that psychiatric disorders over-represent those of inpatients. One possible reason for the very small numer is because the length of hospitalization may be short and few inpatients required medications for insomnia during hospitalization. We hope that these added data would be useful for readers to obtain more information on diseases classified under these two comorbidity categories.

Nonetheless, we acknowledge that comorbidities in this study may include acute conditions because we defined them by one disease record (ICD-10 code). In addition, although comorbidity profiles may differ between inpatients and outpatients, they were not examined separately in this study. Therefore, as you point out, some comorbidity categories may over-represent those of inpatients more than those of outpatients. We agree that these are important limitations of this study, so we have added this point to the limitations (Page 25-26).

3. I think there is an overlap of acute vs chronic which is a significant limitation of this paper. The title implies chronic comorbidity but many of the medications are acute, as I and one other reviewer have noted. I still really struggle with electrolyte replacement being a co-medication, as well as the fact that we do not really know whether some of these prescriptions are in patient for 30 days or outpatient 30 day prescriptions. As such, this paper struggles to identify the chronic management of people living with HIV. This should be acknowledged. Perhaps the title should read simply comorbidity and comedication use among a cohort of people living with HIV and receiving care in hospital settings in Japan, or something.

Response:

We acknowledge that an overlap between acute and chronic is one major limitation of this study. Thus, we have now added in the limitation that, because of our definitions, 1) some acute conditions may be treated as chronic comorbidities, and 2) co-medications are not necessarily those for treatment of chronic conditions (Page 25). Furthermore, as you suggest, we have also changed the title to simply write “comorbidity” instead of “chronic comorbidity”.

In this study, to understand frequently used medications by PLWH, we examined all medications during the whole study period irrespective of whether they were inpatient or outpatient prescriptions, so co-medications were not examined separately between inpatients and outpatients. However, considering that both comorbidity and co-medication profiles may differ between them, our results may be biased. Therefore, we now state in the limitations that because of this reason our results may not accurately represent comorbidity/co-medication profiles of the general population living with HIV (Page 25-26).

As in your comment, perhaps “oral electrolyte replacers” should not be considered as “co-medications.” However, it should also be reminded that this is a subcategory name and A07 not only includes, or does not necessarily include, “oral electrolyte replacers,” but it can include all the following drugs: “intestinal anti-infective antidiarrhoeals,” “intestinal adsorbent antidiarrhoeals,” “intestinal anti-inflammatory agents,” “antidiarrhoeal micro-organisms,” “oral electrolyte replacers,” “motility inhibitors,” and “all other antidiarrhoeals,” although we acknowledge that all of these A07 drugs seem to be used more for acute bowel or intestinal problems. Besides, “oral electrolyte replacers” here do not include intravenous preparations, which are classified under the category of K (a class of “hospital solutions”). In the original manuscript we only wrote subcategory names and it was confusing to readers, so we have added the ATC code for each of the top 10 co-medications (Page 18). We hope that this helps to remind readers that co-medications were classified based on the 2nd level of ATC codes, which is a broad classification.

Moreover, to provide additional information regarding co-medications between patients with different health status, we separately examined co-medications of patients with a hospital admission record (n=324) and those without (n=1121), and provided the results in Supplementary Table 3. In the table, we marked the classes of “hospital solutions” because some readers may be concerned about agents mainly used for inpatients. Co-medications ranked in the top 10 were similar between the two groups, but some medications (e.g., antacids/antiflatulents/anti-ulcerants and systemic antibacterials) were much more frequently used by patients with a hospital admission. We understand that the analysis was between those with or without a hospital admission record and co-medications of the 324

patients also include outpatient prescriptions, so it still does not reveal the differences between co-medications used by inpatients only during hospitalization and those used by outpatients. Yet, we believe that the added data can still provide interesting information to readers.

4. It is unsurprising that comorbidities increase with increasing age among this cohort of people living with HIV or any other cohort for that matter, so I'm not sure too much should be made of this. Clearly DDI are important across age groups for people living with HIV in this cohort as all are on ART and the vast majority are on other medications.

Response:

Because this is the first study to describe the comorbidity and co-medication profiles of PLWH in Japan by age group, we considered it to be meaningful to report the differences in results by age group. However, we agree that it is not surprising that older patients have more comorbidities than younger patients. Therefore, after considering your comments, we have revised the summary sentence in the conclusion to write that chronic comorbidities and co-medications were common among PLWH in Japan taking antiretrovirals, especially among older patients, who more frequently used co-medications (Abstract & Page 26).

Reviewer: 3

Reviewer Name: Pablo Perez

Institution and Country: Imperial College London, United Kingdom

Please state any competing interests or state ‘None declared’: None declared

I commend the considerable effort and time dedicated by the authors to address the issues and challenges raised in the previous round of reviews. It's encouraging to receive a much improved version of the manuscript.

Minor comments for the present version are as follows:

1. Page 6 - ines 28/29: changes on PK/PD are not necessarily a cause of increased number or NCDs. Does this statement refer to the case of alterations in lipid and/or glucose profiles? If it does, such effect is not age-bound, but an adverse effect of specific ART drugs.

Response:

Thank you very much for re-reviewing the manuscript and providing us with important suggestions.

We regret that our writing was confusing. In the sentence you point out, we intended to mean that age-associated chronic comorbidities are now concerns to older PLWH because of age-related physiological changes in general, just like they are to older people without HIV. Then, in the next sentence, we mentioned that, in addition to such normal age effects, older PLWH may have more comorbidities because of the influences of HIV and HIV treatement.

As you point out, although age-related physiological changes can cause organ dysfunction and lead to disease, the resulting changes in pharmacokinetics/pharmacodynamics are not necessarily the causes of comorbidities. Thus, to properly express our intended meanings and avoid confusing readers, we have now revised the relevant part of the text (Page 6).

2. Page 8 - lines 40 to 46: the authors clearly defined the issue of acute care hospitals in the context of Japan. They also comment that demographic and clinical variables were extracted from the database. They should, thus, clearly express the proportion of patients that, during the study, required: 1) admission for an AIDS-defining illness; 2) admission for another acute-care reason; and 3) were stable, ambulatory patients. This will enrich the discussion and conclusions, as it would allow to flesh out the strength vs limitation of using the claims database to answer the research questions.

Response:

We agree that hospitalization status is important information for an understanding of our study patients. Thus, we have now added the following data in Table 1 (Page 15): 1) patients without hospital admission (patients with outpatient data only); 2) patients with hospital admission for any cause; 3) patients with hospital admission for at least one AIDS-defining condition, and 4) patients with hospital admission for non-AIDS-defining conditions only, during the study period.

For the reasons for hospital admission, we relied on disease names recorded under “the disease that led to hospital admission,” and it is difficult to appropriately define any single individual disease an “acute disease.” Thus, we are unable to provide the number of patients with hospital admission for any acute-care reasons other than AIDS-defining conditions. Instead, we now provide the number of patients with hospital admission for non-AIDS-defining conditions only (Table 1) and a full list of these non-AIDS-defining illnesses that led to hospital admission is provided in Supplementary Table 1. We believe that added information regarding hospitalization helps to provide more background information of our study population.

3. The dominion of academic written English by the authors is very good. Minor copy-edditing, however, could strengthen coherence and cohesion throughout. Particularly, shorter and more succinct paragraphs will increase the clarity and strength of messages conveyed.

Response:

Thank you for your advice. The manuscript had been copy-edited throughout by professional English copyeditors prior to every submission, but based on your comments, we also had the revised parts copy-edited again this time. We believe our manuscript is now easier to read.

Additional comments to reviewers

In the previous revision, we conducted reanalysis using the revised definitions of “kidney failure” and “vascular diseases,” and reported that these did not result in changes in the prevalence of the two comorbidities. However, there was an error in the program, so we have now corrected the miscalculation and reflected the changes in the manuscript. Changes were made to the prevalence of “kidney failure” and “vascular diseases” and the number of comorbiditities (Table 1 & Figure 2). Our manuscript now reports correct data, and the correction did not result in changes in the overall trends and conclusion drawn from the results. However, we are genuinely sorry that we responded to your previous comments based on incorrect data.

Another thing that we’d like to inform you is that we revised the definition of AIDS-defining conditions and AIDS-defining cancers because our original definitions missed some conditions that should definitely be considered as AIDS-defining conditions/cancers. Thus, some results have been updated, although it did not cause major changes in the overall results of this study. We highly appreciate your understanding for our changes at this stage.

VERSION 3 – REVIEW

REVIEWER	Pablo Perez Imperial College London, United Kingdom
REVIEW RETURNED	10-May-2018

GENERAL COMMENTS	I sincerely thank the authors for the time and effort put to address the challenges raised both by reviewer #2 and myself. This draft provides a very clear snapshot of the population under study, their co-morbidities profile and co-medications used. Given the cross-sectional nature of the design, rather than prospective/retrospective cohort, I believe the objectives are addressed by the methods and the results and discussions are balanced and adequately funded. The newly included Supplementary tables disentangle the confusion around the level and degree of contamination of the results (i.e. given hospital admissions and co-medications specifically used for in-patients). Furthermore, areas of knowledge gaps, where future research is necessary (e.g. a cohort or a case-control inpatients vs outpatients), can now be easily identified from this study's limitations. I appreciate and have enjoyed the opportunity of reviewing your work. Best regards.