Manuscript reference number: THELANCETHIV-D-16-00151

Title: Global, regional, and national incidence, prevalence, and mortality for HIV, 1980‒2015: estimates from the Global Burden of Disease Study 2015

# EDITORIAL POINTS

***1, Please include the author list with affiliations in the revised paper.***

We are putting together the final author list and will have it to you as soon as possible and at the latest by June 10th, as we had previously agreed.

***2, The revised paper must also include Contributors and Declaration of interest statements as outlined in our information for authors.***

We plan to send the forms together with the author list.

***3, Please add the additional details of the systematic review sent to me by email last week in a revised appendix; the appendix must be formatted according to our guidelines (as a single page-numbered pdf), where you refer to the appendix in the main text please include a page number (or range) where the relevant information is contained.***

We have made the change in the appendix.

***4, The research in Context panel, Evidence before this study should include details of a short search strategy (databases, search terms, language and date restrictions) used to identify previous evidence.***

We have added this section to clarify the search strategy for the literature review. Further details on this is provided in the appendix on page 6-9.

***5, In the Methods section, cite the revised appendix where you mention the Systematic review and give the relevant page number in the appendix.***

We have made the change.

***6, While we don't need you to repeat the methods if they have been published before, please make sure that someone reading this paper, would know where in the appendix or what references to seek out to find detailed description of the methods.***

We have further clarified the methods section with proper reference and added details in appendix.

***7, At the end of the Methods section, a short paragraph with the heading "Role of the funding source" with the standard wording "The funder(s) of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication." Amend this wording to accurately reflect the role of the study sponsor or any restrictions in access to data.***

We have added the suggested paragraph at the end of the Methods section.

***8, As previously discussed, the paper is longer than we had hoped, but reading it through again cuts are going to be difficult. If you can shorten the text please do, we can probably also help during the editing phase. As previously mentioned, avoid repetition of data in the main text if it is available in tables and, although the Discussion should start with a brief description of the main finding of your paper avoid major repetition of findings in the Discussion section.***

We have made the related changes.

***9, Please remove the subheadings from the Results and Discussion sections.***

We have removed the subheadings from these sections.

***10, Please see the end of this email for a list of signed statements from authors and people named in your paper that we will need before we can consider your paper further. Please scan and upload signed author statements and ICMJE conflict of interest forms for all authors with your revised submission.***

No authors have conflicts of interest, and the conflict of interest forms will be submitted with author forms on Friday, June 10th, as mentioned above.

## Reviewers' comments:

## Reviewer #1:

***There is one spelling mistake where mortality is spelled as morality Abbreviation not defined: ST-GPR, UI, PrEP, DHS Please add the reference for: More details of the method have been thoroughly documented in the GBD 2015 Mortality and Causes of Death capstone paper.***

We made the correction to the misspelling of mortality and added defined acronyms to ST-GPR, UI, PrEP, and DHS when they are first mentioned in the paper. We also added a reference for the GBD 2015 Mortality and Causes of Death capstone paper.

***Suggest that 95% UI is included every time where the 95%UI is given in brackets. It is used the first time and after that the UIs are merely given in brackets. Readers could easily think this refers to ranges and not UIs.***

We agree with the reviewers concern that readers might confuse our 95% uncertainty interval brackets for ranges. To clarify this, we added 95% UI to the portions of the text that include 95% uncertainty intervals.

***Page 7, line 225. Where the rates are given, add per 100,000.***

We have made the change to line 225 and verified that all rates list per 100,000 appropriately.

***This is a complicated paper with lots of detail. It is dense to read. In addition, many abbreviations are used that makes it even harder to read. Could the authors consider writing out some of the abbreviations to aid in readability. For example VR.***

We appreciate the reviewers comment on the detailed nature of the paper. To enhance readability of the text, we have removed the abbreviation VR and replaced it with vital registration. We have also omitted the abbreviation ANC and replaced it with antenatal care clinic through the text.

***Line 255: In patients over the age of 50, 9.5% (8.8-10.2%) of deaths occurred in men 256 and 5.8% (5.3-6.3%) in women. 100% of the deaths should occur in men and women combined and this adds up to 15.3. Please rephrase the sentence to make clear what the percentage refers to.***

Thank you point this out. We have rephrased the sentence to avoid any confusion.

***Line 267: "however, due to the time between incidence due to AIDS and death, mortality increased."***

***This sentence does not make sense. Please clarify***

We have rephrased the sentence.

***Paragraph starting at Line 305. This paragraph does not make a coherent point, but jumps from one topic to another. Please rewrite and focus the points more coherently. It jumps from universal ART, to the link between deaths and prevalence, to scaling up detection of new infections, to the quality of ART in the third 90.***

We have edited the paragraph to make it more coherent.

***Line 309: It would be nice to add how much extending ART would cost.***

This is an important topic but one that is beyond the scope of this paper.

***Paragraph starting at line 321 says 4 times that incidence is high or stable. Can this be rewritten to not repeat the same point several times?***

We have edited the paragraph.

***Line 324: How does awareness of HIV among the general population lead to incidence not declining much? Can this be rewritten to be clearer or be omitted?***

We have rewritten the sentence to avoid any confusion.

***Line 334: Consider deleting "Much of the initial faster decline in global incidence may have been due to the natural epidemic curve". This point has already been made in Line 323.***

Thank you for your suggestion. We have deleted the sentence mentioned.

***Line 391: antenatal has been used up to this point and now the abbreviation ANC is brought in. Consider abbreviating from the beginning or not at all.***

We thank the reviewer for noting this inconsistency. We have spelled out antenatal care clinic each time it is mentioned.

***Line 400. Repeat. Consider deleting "also different between men and women where the utilization of treatment is much common" and replace with higher to create one sentence:***

***In addition, the utilization of ART treatment is higher among women as indicated by the higher ART coverage for women in 2015."***

We have made the suggested change.

***Table 1 using the abbreviation LWH, rather be consistent and use PTWH.***

We have made the title of Table 1 clearer.

## Reviewer #2:

***This update of GBD estimates for HIV around the world is welcome and important. Compared with earlier iterations, there are various enhancements and improvements, particularly in estimating mortality separately by ART status. This is likely to become an increasingly important part of understanding the HIV pandemic in its (hopefully) declining years.***

***However, in order to model HIV-related mortality by ART status, obviously separate modelling parameters have to be developed for people on/off ART, and it is mentioned briefly (lines 131-133) that this was accomplished by undertaking systematic reviews - firstly an update of a similar GBD 2013 process for off-ART and a new review for on-ART. These systematic reviews thus obviously become foundational elements for this manuscript, yet as far as I can see neither has ever been systematically written up with PRISMA-compliant documentation, peer-review and publication. The brief description on page 5 of the Web Appendix is completely inadequate in this respect - these reviews should have been previously published as part of the normal step-by-step scientific process in order to use them as foundations of this modelling. The failure to do this also means that the current manuscript does not in fact comply fully with the GATHER guidelines for estimates, since not all the inputs are adequately documented.***

We acknowledge the concern the reviewer has regarding the input on- and off-ART mortality used as input to our HIV/AIDS estimation process. We would like to highlight that the methods used in producing On-and Off-ART mortality from published and unpublished cohort data used in our study have been peer reviewed and published in The Lancet in 2014 (Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 1005–70.).

To provide timely updates of Global Burden of Diseases estimates (GBD) for over 300 diseases and injuries in a coherent analytical framework is a significant undertaking. We have not separately published literature reviews for each disease and injury previously as this process would make both the inputs and results of GBD outdated by the time that they would be published. It is the standard in the GBD to include in each cycle of estimation updates of both published and unpublished data that are used in the assessment. For example, for HIV the vast majority of data used in estimating the epidemic such as antenatal clinic data or prevalence surveys are not published in journals but are made available through datasets collated by UNAIDS or from governments and other data providers through survey microdata. We seek to make the GBD, including the HIV/AIDS estimation, GATHER compliant, which given the nearly 60,000 sources included in the GBD is a major undertaking.

We have added to the appendix complete details on the methods used in synthesizing cohort data for on- and off-ART mortality in addition to the search terms we have used in the literature review and complete lists of literature included in both on- and off-ART mortality analysis (Appendix Tables 3 and 4).

For this study, and for GBD 2015 in general, we will make all computer code accessible by posting them online on our website. Data documentation following GATHER will also be available through the Global Health Data Exchange (GHDx). GATHER compliance has been a huge undertaking, and these will only be ready at the time of the publication, not at the time of submission. The GATHER guidelines have not yet been published, but we have made the decision to make the GBD 2015 GATHER compliant in anticipation of their publication. Given that we are anticipating these guidelines, the posting of computer codes and the data files will only be feasible in time for publication.

***The wording of the title is inappropriate in describing the manuscript as "results" rather than "estimates". This may be a semantic point, but some readers will take "results" to reflect conventional epidemiological surveillance processes of accounting for individuals, which is far from the case here.***

Thank you for the comment. We have changed the title to reflect the reviewer’s suggestion.

***Figures 5a and 5b are useful depictions of differences between GBD 2015 and UNAIDS 2014 estimates, but I couldn't find any reference to or discussion of these figures in the main text. It would also be appropriate to show Lin's correlation concordance coefficients as metrics for these comparisons, overall and perhaps by super-region.***

We have included in the text already the intra-class correlation coefficient which is a widely used metric for comparison of two quantities. The Lin concordance coefficient is an alternative method to capture the same construct; in this case the ICC for prevalence is 0.997 and the Lin concordance correlation coefficient is 0.996. We prefer to report the more widely used measure of the ICC.

***Table 1 and Appendix Tables 1 and 2 are all headed "Country-specific estimates..." but inexplicably include sub-national estimates for regions in the United Kingdom. There is no clear justification for this - and the inter-regional variations as shown are not even interesting. This should be removed so that the United Kingdom is shown on the same basis as other countries.***

We thank the reviewer for their comment. We have dropped UK subnational units in the report as the reviewer has suggested.

## Reviewer #3:

***Main comments***

***The topic of this paper is important and in terms of global estimates of the burden of HIV, it is useful to have at least two different sets of estimates, with slightly different methods, assumptions and data.***

We thank the reviewer.

***In the previous set of GDB estimates (2013) there was an overall difference of 6 millions in the prevalence of HIV worldwide between the GBD and the UNAIDS estimates, the former being 6 millions lower, including one third of differences arising from high income countries, even is this is not the most affected area of the world (North America, Europe, Australasia and Central Europe), as shown in Hallett TB et al (Embracing different approaches to estimating incidence, prevalence and mortality. AIDS 2014;8 (Suppl 4):S523-S532) and in Supervie et al (GBD 2013 and HIV incidence in high income countries. Lancet 2015; 385: 1177). differences were also noted for China (Jia Z et al. HIV incidence and mortality in China. Lancet 2015;385:1510). New (2015) estimates are higher, but still highly unrealistic for high-income countries. As an example in UK, Public Health England reports that 103,700 people (95% credible interval: 97,500-112,700) were living with HIV (PLWHIV) in 2014 with an increase from 2010 when the figure was 91240, and 76900 of those are on treatment, that is 75% of PLWHIV (Skingsley A, Yin Z, Kirwan P, Croxford S, Chau C, Conti S, Presanis A, Nardone A, Were J, Ogaz D, Furegato M, Hibbert M, Aghaizu A, Murphy G, Tosswill J, Hughes G, Anderson J, Gill ON, Delpech VC and contributors. HIV in the UK - Situation Report 2015: data to end 2014. November 2015. Public Health England, London.), In the GDB 2015, corresponding figures are: 30580 (9820-63970) PLWHIV, with a decreasing age standardized prevalence from 2005, and a null incidence! All these results are highly implausible.***

In GBD 2015, we have systematically utilized the most reliable source on HIV/AIDS burden, the HIV cause specific mortality from vital registration systems, for countries with working vital registration systems after correcting for garbage codes and HIV cause of death miscoding. Details on these methods are described in Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 1005–70.

In addition, we have developed the Cohort Incidence Bias Adjustment (CIBA) model to ensure that mortality from vital registration systems, for countries such as the UK and France, is consistent with the incidence and prevalence estimates generated by Spectrum given our assumptions of on- and off- ART mortality and other program data such as ART coverage. However, the performance of CIBA-Spectrum depends also on the input incidence estimates to CIBA-Spectrum and these incidence curves are from the UNAIDS country files. In the case of incidence estimates for the UK in our manuscript, the incidence rate input from UNAIDS is zero starting in the year 2009, which leads to severely underestimated incidence and prevalence even after the application of cohort incidence bias adjustment.

We thank the reviewer for pointing this out and have corrected this mistake in the UNAIDS input files. Our updated estimates show that there are 52.7 thousand PLWH and number of new infection are 2.1 thousand for 2015. These estimates, however, are still different from the figures the reviewers quoted from the Public Health England 2015 report. Yet, it is important to note that, the figures from the Public Health England report are estimates from a “multi-parameter statistical model fitted to a range of surveillance and survey data”( Skingsley A, Yin Z, Kirwan P, Croxford S, Chau C, Conti S, Presanis A, Nardone A, Were J, Ogaz D, Furegato M, Hibbert M, Aghaizu A, Murphy G, Tosswill J, Hughes G, Anderson J, Gill ON, Delpech VC and contributors. HIV in the UK - Situation Report 2015: data to end 2014. November 2015. Public Health England, London). To fully understand the difference in the estimates between GBD 2015 and those from Public Health England, further analysis needs to be done. The researchers at GBD are conducting a joint analysis with UNAIDS reference group to disaggregate the differences between estimates from UNAIDS and GBD. We plan to conduct similar analysis with Public Health England with whom we already have a close collaboration on GBD in general.

Based on the comments from Jia et al as the reviewers pointed out and our collaborators from China Center for Disease Control and Prevention, in the current study we have improved our estimates for China by using CIBA-Spectrum and the use of two series of HIV mortality data from China: 1. The National Notifiable Infectious Disease Reporting System (NIDRS), and 2. The Disease Surveillance Points System (DSP). NIDRS is a national system with great quality on reported HIV mortality in the most recent years and DSP, although not population-based and nationally representative, shows a consistent and plausible trend in reported HIV mortality over time. We have combined the two systems by applying the ratio of numbers of deaths from NIDRS to DSP from years between 2010 and 2014 to the entire DSP series. We then used this adjusted HIV mortality together with the incidence estimate from UNAIDS as inputs to CIBA-Spectrum. Our new mortality estimate for China in 2013 is 28006 which is much higher than what is reported by Murray et al. in GBD2013.

***Also in France, the general social insurance scheme (CNAMTS), which covers 87% of the French population, including mostly private and public salaried workers (the rest being covered by other public smaller schemes), had published that in 2014, 110040 individuals were covered by the so-called 'affection de longue durée' system because of HIV infection and had HIV related health care costs paid by social security this year (***[***http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/prevalence/prevalence-des-ald-en-2014.php***](http://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/affection-de-longue-duree-ald/prevalence/prevalence-des-ald-en-2014.php)***), while the estimated prevalence by GDB 2015 for France is 79170 in 2015, even if the uncertainty interval is compatible with the social security figures (being 175700). I suspect the problems also exist in other countries of this category (quite likely Group 2A countries mainly), as for the 2013 estimates. This is never discussed, although the fact that GBD do not use data from the surveillance system in high-income countries is noted in the discussion.***

In GBD 2015, we have made significant efforts in providing internally consistent estimates of incidence, prevalence and mortality for countries with working vital registration systems through the utilization of HIV cause-specific data and the new Cohort Incidence Bias Adjustment model. In GBD 2013, the estimate for prevalence in France for year 2013 was 69,636, and with the use of CIBA, this has increased to 79,170 in GBD 2015. As pointed out by the reviewer, we have not yet incorporated data from HIV surveillance and case reporting data that exist in many of the countries with vital registration system and we have noted this in the discussion – namely, the desirability of expanding the methods to use alternative sources like this.

***There are several issues in using cause of deaths statistics in high-income countries (more or less Group 2A countries), or in any country with relatively high ART coverage, to derive incidence and prevalence estimates:***

***\* As shown in France, the cause specific vital registration system underestimates the number of deaths in PLWHIV, because the physician fulfilling the death certificates is not necessarily aware of the HIV status and because more and more deaths in PLWHIV are not from an AIDS-defining cause or even an HIV-related cause (see Lewden C, Jougla E, Alioum A, Pavillon G, Lièvre L, Morlat P, Salmon D, May T, G Chêne G, Costagliola D and the Mortalité 2000 Study Group. Number of deaths among HIV-infected adults in France in 2000, three-source capture-recapture estimation. Epidemiol Infect 2006; 134(6): 1353-1359 for underestimation estimates, and Morlat P, Roussillon C, Henard S, Salmon D, Bonnet F, Cacoub P, Georget A, Aouba A, Rosenthal E, May T, Chauveau M, Diallo B, Costagliola D, Chêne G; for the ANRS EN20 Mortalité 2010 Study Group. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 2014; 28(8):1181-91 for evolving proportion of deaths from AIDS defining and non AIDS defining causes). In 2000, it was estimated that only 76% of deaths in PLWHIV could be traced in the National Registration System, and given the changing pattern in the causes of death in PLWHIV, it is likely that this percentage did not increase since 2000. The authors should define what they called cause specific mortality due to HIV/AIDS from vital registration system (which ICD codes were used).***

The reviewer effectively raises two issues: a) the distinction between deaths in HIV positives and deaths attributable to HIV and b) is there mis-classification of HIV related deaths in other causes. For the first point, in the GBD we follow the rules of the ICD - namely we assign deaths to underlying cause. So our estimates of deaths are not all deaths in HIV positives but deaths that are HIV-related. In other words, a myocardial infarction in an HIV positive is assigned to myocardial infarction following ICD rules for underlying cause. The more important issue in terms of our study is whether there are deaths that are HIV-related that are misclassified and assigned to other causes of death either with proper ICD codes or garbage codes. We identify deaths directly coded to HIV and deaths that are assigned to some causes that are often used for HIV misclassification, particularly in earlier years of the epidemic.

To account for the various erroneous coding for HIV related deaths, three distinctive process are applied to arrive at accurate count of deaths due to HIV for populations with vital registration systems, namely HIV-related garbage redistribution, redistribution to HIV as part of overall garbage redistribution, and HIV misclassification correction.

1. Before garbage code redistribution for all cause specific deaths, specific HIV-related garbage redistribution is performed to account for the disparate nature of HIV/AIDS mortality among geographies and over time. To capture such distribution, age band (under 1 month, 1-59 months, 5-19 years, 20-49 years, 50-59 years, 60-69 years , 70-79 years, and 80 plus years), time (five year time period) and sex specific target proportions are generated for each garbage code group. The redistribution of death from garbage code groups is based on the regional increase in mortality rate of death rate in the garbage code group relative to the death rates observed in the period 1980 to 1984. Any relative increase exceeding 5% is deemed to come from deaths related to HIV/AIDS and these excess death exceeding 5% are redistributed to HIV/AIDS. If the increase is smaller than 5%, then the excess deaths are all redistributed to reminder target that is non-HIV related.
2. We also apply the general non-HIV related garbage code redistribution. This in general has minor impact on the final HIV-related mortality. Details of the method are described in Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 1005–70.
3. As we have observed in many vital registration systems, specific causes of deaths that are commonly comorbid with HIV/AIDS such as tuberculosis have age patterns that deviate from those observed in country-years without the HIV/AIDS epidemics. Such deviations are likely due to the trends in HIV/AIDS mortality. In this study, we follow the method developed by Birnbaum et al (Birnbaum, Jeanette Kurian, Christopher JL Murray, and Rafael Lozano. "Exposing misclassified HIV/AIDS deaths in South Africa." *Bulletin of the World Health Organization* 89.4 (2011): 278-285.) To correct misclassified causes of death to HIV-related deaths. Essentially, we generate global standard relative risk due to specific causes of deaths by age using all vital registration data from country years with HIV prevalence lower than 1%. The reference in generating the relative age pattern is the average mortality rates in age groups 65-69, 70-74, and 75-79. Using these global relative age patterns, expected cause and specific mortality rate can be generated using the observed cause-specific mortality rate in the reference age groups (ages 65-79). We then compare these expected age specific rates with the observed age-specific mortality rates for specific causes of death. The excess age-specific mortality, which is the difference between observed and expected age-specific rate, from a specific cause of death is reallocated to HIV/AIDS.

The graphs below shows the raw numbers of death due to HIV based on originally assigned HIV mortality in the vital registration systems from France and Russia, and the impacts of HIV related redistribution procedures on the final HIV related deaths in our analysis.





For the HIV garbage redistribution, the following table shows by time period what code groups are being redistributed to HIV related deaths in France:

|  |  |
| --- | --- |
| **Year Range** | **Garbage codes targeted to HIV** |
| 2000-2004 | A31-A319, A42-A449, B37-B409, B42-B469, B49-B499, B58-B599, C46-C4652, C467-C469, D80-D849, D898-D899 |
| 2005-2009 | A31-A319, A42-A449, B37-B399, B41-B419, B44-B469, B49-B499, B58-B599, C46-C4652, C467-C469, D80-D849, D898-D899 |

***The authors should explain more precisely how they corrected the cause of death data for coding error and, more importantly, on HIV misclassification. Was the correction country dependent, year dependent? How does it account for the fact that some so-called 'non HIV-related causes' are none the less more frequent in PLWHIV?***

The methods the correct for cause of death coding errors have been descried in details in Murray CJL, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 1005–70. We have added additional sections in the web appendix (p5-6)to the current article on both garbage code redistribution and HIV misclassification correction.

On HIV misclassification correction, the correction is indeed country and year dependent where for each country, year, age and sex, the HIV misclassification correction depends on both the global relative death rates and those observed in the country and year of interest. We do not as of yet capture the increased risk of some non-communicable causes of death in HIV positives. This notion of excess mortality in HIV positives for other causes is akin to the increased risk in individuals suffering with diabetes and some cardiovascular outcomes. Given our focus on ICD defined underlying cause, this mortality is not captured. We have added to the discussion that we do not quantify this component of excess mortality.

***\* Nowadays in high income countries, death from AIDS defining causes or considered to be HIV related are more a reflect of late presentation than a reasonable starting point for estimating HIV incidence.***

We are not sure we understand the comment. We use the data from Antiretroviral Therapy Cohort Collaboration which provides observed deaths rates due to HIV and the number of HIV related deaths and back estimate the implied HIV prevalence and incidence. These are internally consistent with each other.

***\* Finally It is highly unlikely to get precise estimates for incidence in 2015 from the deaths reported in 2015, while there is so little information on recent incidence trends given the current life expectancy in PLWHIV, in particular under ART (see Wandeler et al, Current opinion in HIV/AIDS 2016, death may occur decades after infection), but even without ART (a decade or so). Estimates of the 2015 situation are more driven by the model assumptions than by true trends on the field, and therefore highly imprecise, even more than shown by current uncertainty estimates.***

The reviewer raised a valid point. Even with the cohort incidence bias adjustment method we have developed, it is hard to estimate/adjust the incidence in the most recent years precisely because of the duration from infection to mortality. This is a research area we need to improve in the upcoming GBD iteration. We have added this limitation to the discussion/limitation section. We also would like to note that this limitation applies to all existing estimates of HIV incidence, including those produced by UNAIDS.

*Detailed comments*

***The technical quality of reporting is poor (missing information, errors, ...)***

We have made the changes related to the points the reviewer has raised.

***In the abstract, report uncertainty intervals***

We have added uncertainty intervals to all quantities we have reported in the abstract and the main text.

***Research in context, implications paragraph: I do not see on which strong and convincing arguments GBD authors states that their estimates are the most comprehensive and internally consistent assessments, while it is obviously flawed for probably most Group 2A countries, which is an important issue, even though this is not the most affected region of the world.***

While we acknowledge that improvements still need to be made to the methodologies used in incidence estimation for countries with vital registration systems especially those in group 2A as the reviewer pointed out, to our knowledge, no other research group, including UNAIDS, has provided comparable estimates series that are as comprehensive [UNAIDS reports country estimates for less than 120 countries] and internally consistent. While there may be ways to improve estimates for Group 2A countries, we do not think that our estimates suffer from systematic bias in one direction or another.

***Background***

***Reference 1 to 5 are all from GDB, while UNAIDS estimates would also lead to the same conclusion.***

We respectfully disagree with this comment. While UNAIDS provides estimates for HIV/AIDS, it does not provide a comprehensive view of burden of all diseases and injuries that can show the relative importance of HIV/AIDS in each country. GBD is the only source for up-to-date and comprehensive mortality and burden estimates for over 300 causes of deaths which are also comparable across countries and over time.

***Reference 7 is quite exotic.***

We have removed reference #7 from the manuscript.

***Line 95 to 103, when alluding to differences between UNAIDS and GDB estimates, the authors should cites articles and letters which have highlighted issues in their 2013 estimates (see above).***

We have added the citations as the reviewer suggested.

***Methods***

***Overall the methods are quite difficult to understand. Perhaps providing an example of the various steps in the supplementary material would be helpful for instance one for a group 1 country and one for a group 2A country.***

We thank the reviewer for this great suggestion and added in the appendix two country examples: Canada and Botswana.

***Please define abbreviation the first time they are used: Line 124 VR (vital registration).***

Based on the feedback from Reviewer 1 on the readability of the text, we chose to omit the abbreviation VR from the text and have replaced it with vital registration.

***Why to cite reference 3 when discussing the collaboration with ART-CC, while reference 3 do not relate to mortality on ART? The authors were probably thinking to reference 3 of the text which was provided secondarily: on off ART methods description and tables.***

We have corrected the reference to ART-CC.

***Line 138, state the abbreviation for Space-Time Gaussian Process regression (ST-GPR) as it will be used later on.***

We have made the changes.

***Explain how incompleteness and misclassification of causes of death, in particular HIV related, were corrected (see above)***

As mentioned above, we have added additional section in the appendix on these topics.

***Please state in the text that a list of the countries per group (such as defined in lines 143-148) is provided in the supplementary appendix, and provide a list of the countries by income category (as high income is used in particular in Figure 4B) and by SDI (as SDI is used in the result section and in Table 1). A simplification of the different groups would be welcomed.***

We understand the reviewer’s concern and have added a table to the appendix (Appendix Table 7) which lists all GBD countries by region (including those that are classified as high-income) and their SDI values in 1980, 1985, 1990, 1995, 2000, 2005, 2010, and 2015.

***Incidence and prevalence estimates***

***The sentence, lines 171-172, is a declaration of faith but is not sustained by any convincing arguments. The time from infection to death is long (around 10 years), even longer when on successful ART (may be decades), depends strongly on ART coverage at the population level, and PLWHIV dye more and more from non HIV-related causes, when ART coverage is high. So good sense would state against this assertion. I suspect that basing estimates on combining all available data in a Bayesian framework would be a better methodology. Second, GBD estimates for many of the most affected countries do not rely on VR data. Besides, this is not method, but comment, so should not appear in the method section anyway.***

We respectfully disagree with the reviewer. HIV cause-specific data from vital registration systems even for countries where vital registration systems are not complete are by far one of the most reliable sources for estimating burden of HIV. Unlike approximation of the fraction of the population belonging to high-risk groups, vital registration systems in countries where they are complete, capture all deaths. For countries in the developed world, HIV cause-specific mortality, with proper adjustment for misclassification and garbage coding, is more reliable to gauge the trend and level of the epidemic comparing to case report data (of which completeness is hard to assess and the time of infection is hard to back-cast) and prevalence data which are rarely available in most nations with VR systems. For incidence assessment, death from HIV provides the best source of information to help generate sensible incidence estimates. The statement provides the background for why VR is used in estimating burden of HIV/AIDS in all group 2 countries.

***The Cohort Incidence Bias Adjustment method is never clearly explained (even in the supplementary material).***

To aid the description of CIBA, we have added a country example in the appendix.

***Line 196-197. The GATHER guideline is not available on line yet making the reader left with no way to verify this assertion, besides the reference should be one journal only even if it will be published in several journals.***

The reviewer is correct in pointing out that GATHER guideline has not been published yet. However, we have committed to make this study, and GBD 2015 more generally, GATHER compliant in anticipation of their publication. This is why we commit to make all data documentation available through the Global Health Data Exchange in time for publication, but not at the time of the submission of this study. We are developing a checklist to describe how we have met each aspect of the GATHER guidelines that will be provided prior to publication, should the manuscript be expected.

***Figures and Table legends and contents***

 ***Figure 1. The text should be (line 470): the fourth panel present estimates of percent of people, not number of people living with HIV receiving ART.***

We have made title of the fourth panel clearer.

 ***Figure 2 B and 3B. Specify that presented results are country results***

We have made the changes to the titles to clarify that the results are country level.

 ***Figure 2 A and 3A; Why to specify high-income North America, for North America?***

High-income North America is one of the 21 GBD regions.

***Table 1. Define what SDI (socio-demographic index) means and provide la list of countries in each categories. Sub-country regional estimates are reported for UK only, if I red Table 1 correctly. Does it make sense to provide such estimates for one country only? Besides given that the estimated incidence in this country was estimated to be 0***

We have further clarified the definition and construction of SDI. We have also removed the subnational units of UK from table 1.

***Figure 4B. Is this the overall number of deaths in PLWHIV or the number of HIV-related deaths in PLWHIV? This is because there might be an excess number of deaths from non-HIV related causes in PLWHIV for some causes, in particular in high income countries (non-AIDs defining cancers, cardiovascular diseases, ...)***

In the current study and GBD in general, we only count underlying causes of death. As stated earlier, HIV causes of death in GBD include B20-B24.9 in ICD10 and 042-044.9 in ICD9 detail. We also apply three distinctive HIV cause of death correction procedures to the data from vital registration systems which were discussed in response to an earlier question the reviewer has.

***Results***

 ***Global incidence, prevalence, death and people receiving ART***

***Would be useful to provide the new estimates for 2013, as this would allow to discuss the issue of precision for the most recent years and also how much the changes in estimates can be attributed to changes in methods and data used rather than true change in the field.***

We have added our estimates for year 2013 in this section.

***Mortality estimates***

***Line 261, why to cite a reference in the result section? Does the sentence relates to Figure 4B or to other results?***

We have removed the misplaced citation.

***Discussion***

***Incidence and prevalence are estimated to have been higher in men than in women in the nineties, which is not supported by available data. This should be discussed***

We are perplexed by the reviewer’s comment. In the earlier phases of the epidemic a much larger share of transmission was due to transmission in MSM and IDU groups than more recently which is why the incidence and prevalence was more male than more recently. This is entirely consistent with what we know about the evolution of the global epidemic.

***Please discuss the figures for UK, including plausibility of a null incidence***

As suggested by the reviewer earlier, we have added discussion regarding estimation of HIV burden for developed countries. We have also corrected the mistake for UK as pointed out by the reviewer.

***Please discuss the specific issues of estimates from GBD compared to countries estimates in high income countries for instance in countries claiming GBD 2013 estimates were underestimating the true figures, such as Australia, Canada, China, France, Netherlands, UK, USA (see also above).***

As suggested by the reviewer earlier, we have added discussion regarding estimation of HIV burden for developed countries.

***Unclear what CD4 progression ratios means (line 455).***

It refers to the probability of progressing from higher CD4 count category to lower CD4 count category. We have clarified the language in the text.

***Please discuss precision of the estimates in the most recent period and change in the new and previous estimates of the 2013 figures to illustrate this discussion.***

We have added in the discussion based on reviewer’s suggestion.

***Supplementary***

***Title of table 1 and 2 should state more clearly (and earlier in the text) that they are by sex, as the fact that these are by sex table does not appear at the top of the table in the submitted document.***

We have fixed the title issues for table 1 and table 2 in the appendix.

***Figures 3, 4 and 5 are listed twice, the first round should be suppressed as it does not correspond to the provided figures.***

We have corrected the mistake.

***The figure describing the main steps of the modelling is not numbered and has no legend.***

The legend for this figure is provided on the right-hand side of the flowchart. The process numbering has been updated to show the order of processes within each estimation group.

***Please combined the 2 supplementary provided documents (on off ART document and supplementary), and verify the list of references as many references (from 10 to 28 and 31 of the initial supplementary material) are not cited in the text and as some are alluded to in the text but no reference number is provided.***

We have expanded the appendix by incorporating the supplementary document and corrected the issues of references.

***Some of the data used for the on ART mortality can be part of several studies used to estimate mortality on ART (such as several reference from ART-CC or comparing results in ART-CC and South Africa and HIV causal, which have several European cohorts in common with ART-CC. Was this accounted for?***

We have made efforts in removing the duplicated sources. This process is discussed in the expanded appendix.

***Please reorganize the text so that what is being done per group appear only once and not at 2 separate place of the document (page 8-9 and then 12) See also comment above on the utility of providing one or two examples.***

We have made necessary changes as the reviewer suggested. The country examples are also provided.

***List of contributors***

***There are no affiliations and no conflict of interest statement.***

Our initial submission is sent as corporate authorship. Affiliations and conflict of interest information are being provided in the resubmission to Lancet HIV.

## Reviewer #4:

***1. In lines 44 to 49, the paper does not provide a rationale or justification for why the other 2 globally-recognised HIV epidemic models - Optima HIV and the AIDS Epidemic Model. - were not also used in comparing and improving model estimates. Both these models have produced HIV estimates for several countries and such further comparisons would have been most useful for academic purposes, and to explain why Spectrum was used. I would strongly recommend comparisons with other widely-recognized HIV epidemic models for which multi country estimates exist. For revision, (a) these estimates should be included in the web appendices for comparison reasons, and (b) further justification should be provided of why the model structures of other models were not considered, and (c) the paper should describe how their HIV epi model is different in structure and function from these other 2 widely-used models.***

We have provided comparisons between the current study and those from UNAIDS as these two estimation series are the only ones that provide country and global level estimates. However, we thank the reviewer for pointing out the fact that it is important and useful to provide information on Optima and AIDS Epidemic Model. We have expanded our discussion/limitation on aspects of HIV/AIDS modeling that are included in Optima but not in our strategy such infection to detection etc. we have also included in the appendix comparison to the two models for countries where all three estimates series are available (Appendix Table 8).

***2. Effect of differential CD4 recovery rates on the on-ART mortality rates: In general, the on-ART mortality estimates have not been described with sufficient detail. Most particularly, it did not seem from the model that CD4 recovery (after being on ART) and in particular,* differential CD4 recovery *(males recovering at different rates than females, and older populations recovering at different rates than younger populations) have been taken into account (see Chakezha et al, 2016, in press). As revision, (a) the on-ART modelling should be described in more detail and (b) the team should build CD4 recovery rates into their on-ART mortality estimates. Even if not possible to build it into the current modelling effort, then it should at least be acknowledged in the Measurement Challenges and Opportunity section (lines 355 to 423).***

We have expand the on-ART mortality estimation process and input data in the appendix as suggested by the reviewers. We should note that while the Spectrum model does not explicitly incorporate CD4 recovery while on ART, the death rates included in our estimation are based on initial CD4 count in cohort studies not concurrent CD4 count, in this way, the death rates based on ART and initial CD4 do reflect the net effect of CD4 recovery. Since we use different death rates by age and sex group it implicitly reflects the differential CD4 recovery. We agree it may be useful in the future to consider explicit modeling of this phenomenon.

***3. Sensitivity analyses in relation to the reduction in infectiousness from being on ART. One of the main drivers of year-on-year changes in Spectrum estimates (and bones of contention relating to these estimates), has always been the effectiveness of ART in real life settings (as opposed to the HPTN 052 92% efficacy in research settings). In Swaziland, for example, in the same year that the SHIMS was published (with 3% HIV incidence amongst the adult population), the country also reported that 85% of its PLHIV population with CD4 counts of 350 and below (over 60% of the PLHICV population) was on ART. Although observational, there are also other studies that shows much more ART effectiveness in real life settings than in the HPTN052 research setting. The paper is not clear on how this was considered and sensitivity analyses performed around this one variable, which is a key driver of new infections in Spectrum.***

Our current study was not able to incorporate a quality measure of ART treatment and uses the same viral load suppression parameter for low and middle income countries as UNAIDS, at about 70%. We agree with the reviewer that such a parameter has important implications for the new infections estimates in Spectrum. However, country-specific data on viral load suppression are not available and as pointed out in the discussion section, future data collection should include viral load tests, like the two recent DHS surveys in Lesotho and Mozambique. In the discussion, we did try to call attention to the point that ART coverage may be overestimated, that viral load suppression may be exaggerated, and that these are important aspects of understanding why incidence has not declined more.

***4. ART adherence rates, and treatment failure rates: with the preponderance of routine ART data and results, a lot more is known about ART failure rates and rates of 2nd line treatment initiation. This paper and the modelling effort could draw more extensively on these data to better inform the modelling efforts. Even if not possible to build it into the current modelling effort, then it should at least be acknowledged in the Measurement Challenges and Opportunity section (lines 355 to 423).***

We thank the reviewer for pointing this issue out. Although this is not explicitly incorporated in our current analysis, adding such a parameter would certainly benefit model performance when country specific data become available. We have added this point to the discussion.

***5. In lines 424 to 457, a comparison is made to the UNAIDS 2014 HIV estimates. Given that UNAIDS just released (on 31 May 2016) their latest 2015 HIV estimates, this section is obsolete and should be rewritten with the 2015 HIV estimates in mind - and the abstract, conclusions, appendices and figures adjusted accordingly.***

The reviewer brought up a valid point. However, UNAIDS only released their global and regional estimates without any details at the country level. We have added relevant estimates at the aggregated level from UNAIDS 2015 in the discussion.

***6. Challenges in future PLHIV detection rates: In the Discussion section, several challenges in achieving the end of AIDS by 2030 are described and discussed. What this section was less critical of (but what is a huge challenge), is the drop in yields from HIV testing. As the sick and females (who typically access health facilities in countries with mostly infectious diseases) were tested first, that population of newly-diagnosed PLHIV has been identified and have been the easy population to identify. HIV testing yields have decreased dramatically in some places (from 1 in 5 persons tested to 1 in 16 persons in South Africa, for example) at a time when detection rates (and thus yields) should increase. Having a situation, as is the case in Malawi, where 69% of HIV tests are repeat testers (personal communications with Malawi AIDS program), is unsustainable - we seem to keep testing the same low-risk populations and not yet good at identifying the high risk We don't just need more testing, we need different and better and more targeted testing and that is an important point to make in this discussion section.***

We completely agree with the reviewer on this point and have added in our discussion to reflect this concern. We should note that the real issue is the number of new cases detected, not just the fraction of those detected that are positive. Expansion of testing may necessarily lead to a decrease in the percentage that is positive, even if increased numbers tested may lead to an increase in the number of positives detected.