Article details: 2014-0101	
Title	Declining Suicide Mortality among Persons living with HIV/AIDS who Initiated Highly Active Antiretroviral Therapy in British Columbia, Canada
Authors	Gurm, Jasmine; Samji, Hasina; Nophal, Adriana; Ding, Erin; Strehlau, Verena; Zhu, Julia; Montaner, Julio; Hogg, Robert; Guillemi, Silvia
Reviewer 1	Sinyor, Mark
Institution	Sunnybrook Health Sciences Centre, Psychiatry
General comments	Thank you for the opportunity to review this interesting paper. It examines changing rates of suicide in a large sample of HAART treated HIV/AIDS patients and tries to identify factors associated with suicide in this group. Strengths of the study include the large cohort and the large number of variables examined including biological measures such as CD4 count/viral load. It is deserving of publication but I have the following specific comments: The introduction is succinct and makes a good case for the rationale for this study. The methods are generally appropriate and well described. Comments/queries on the methods: 1. HOMER appears in the abstract but the full term should also appear the first time it shows up in the main text (methods sentence 2) 2. Can the authors comment on the reliability of linkage with DTP and vital statistics? 3. **There is a body of literature suggesting that many deaths ruled as "accidental poisoning" or "poisoning with undetermined intent" are actually suicide and the** authors do well to account for this (I think – according to my reading these were included but please clarify). However many deaths in these categories may not be **suicides. Do the results of the analysis change significantly if a stricter "self-inflicted"** only definition is used? This is relevant since injection drug users may be at a much higher risk of true accidental poisoning while abusing drugs. 4. It may seem obvious but the last 2 sentences of the methods come out of the blue. I would orient the reader that data on the BC population in general was collected to compare/provide context for the rates in the HOMER group. Comments/queries on the results: 5. Here and in Table 1 - **Can "younger age" (at the end of follow up –** a phrase that **doesn't appear in the results text) really be considered a factor associated with suicide?** If they died and hence **weren't around for more years of follow up compared to the alive group, I'm not sure if this is of value/how to interpret it. Similarly in Table 2, older** people are almost always more likely to die from all cause mortality compared to **suicide. I'm not saying this shouldn't be presented but maybe I wouldn't highlight it in the text** especially as an "associated **factor".** **6. 4th paragraph "Never having had an AIDS defining illness(Adjusted Hazard Ratio** [AHR] = 4.45; CI [1.62 – 12.25]) or having a history of injection drug use (AHR = 3.95; CI [1.99 **– 7.86]) was independently associated with an increased rate of suicide." Should read "WERE** independently associated". **7. I am not an expert in ARV treatment and can't comment on the clinical** implications/utility of table 5. If it is useful, the authors should explain why in the interpretation. If not, they could remove the table and simply state that this was examined and there were no meaningful differences. Comments/queries on the discussion: 8. I would favour an expanded limitations section. There are several points not addressed including a. The lack of a control group without HIV/AIDS b. The lack of a control group with HIV/AIDS not currently in treatment – this is a crucial point as this may be a self selected group of people who are engaged with life and their own health care which may substantially mitigate suicide risk and explain the results **c. The large number of "unknown" values e.g. 30% of suicide victims had unknown** injection drug use hx d. Difficulty interpreting the directionality of the associations – did lack of adherence cause suicide victims to get mentally or physically sicker and then they died from suicide **or were they already depressed/hopeless and contemplating suicide and that's why they** stopped adhering e. How many people joined HOMER in each year of the study? Is it possible that most joined in the late 90s and all those people prone to suicide died early on leaving a group less susceptible which explains the precipitous decline? 9. I also think the authors could say more about the implications of these results. The **drop in suicides is probably the most dramatic I've ever seen in any sample. They talk about why such a drop might happen but don't emphasize its magnitude or how that** could be explained. Why did the results differ from the Swiss and Danish samples (likely

	because those are national registries with many people who aren't in treatment)? Should we be directing suicide screening to all HIV/AIDS patients or particularly to those with a history of IV drug abuse? What should we take away from these findings? **10. I'm not sure I fully follow the reasoning at the bottom of page 11 about "healthier"** people being at higher risk of suicide. The suicide victims did have higher CD4 counts than those who died from other causes but they had lower CD4 values/higher viral load compared to those who remained alive. **11. Bottom of page 12 "mental health illness". This is an awkward term -"mental illness" might be better.** Other minor points: 1. In several places including table titles the phrase "committed suicide" is used. **"Commit" evokes the idea of a crime which may be unempathic/stigmatizing. The preferred nomenclature currently** in the suicide literature is simply **"died from suicide", "died by suicide" or "suicide death".** **2. Similarly the phrasing "78% of all suicides were male" in paragraph 2 of the results is not ideal. The suicides aren't male, the people were. Better here and throughout the text would be "suicide victims" or "people who died from suicide".**
Reviewer 2	Colman, Ian
Institution	University of Ottawa, Department of Epidemiology & Community Medicine
General comments	This well-written paper describes the trend in suicide rates among 5,229 HIV-positive individuals being treated with HAART in British Columbia from 1996 to 2012, and investigates predictors of suicide in the cohort. The authors observed a dramatic decrease in suicide over this time period, and identified increased risk of suicide among injection drug users and those who have never experienced an AIDS defining illness. The authors identify a key limitation – they have no data on mental illness diagnoses. The results are consistent with other studies, but nevertheless these findings are important in the Canadian context. A few suggestions for improving the manuscript: 1. Figure 1 is very compelling. Nevertheless, a time trend analysis demonstrating the decline in suicide rate is statistically significant would be helpful, particularly given the small numbers of suicides included. 2. More details about the cohort would be helpful to assess the generalizability of the results. Are all individuals who receive HAART in BC during the study period **included in the cohort? It's not entirely clear from the Methods if this is** the case. 3. The authors include accidental poisoning deaths as suicide, which is consistent with other studies. Some readers, however, may object to this considering some of these deaths may truly be accidental. Presumably there are some inadvertent overdose deaths in this population. It would be useful to know how many of the suicides received this cause of death, and if the results are the same if these deaths are removed in a sensitivity analysis. 4. The analysis of predictors of suicide is interesting, but the results are somewhat expected. What would be very interesting would be to see if the trend in suicide rate is changing among particular subgroups (i.e., an interaction between time and subgroup). 5. **Please avoid using the term "committed suicide". It is a pejorative term;** suicide has not been a crime in Canada for 40 years. 6. **It would be helpful to define what an "AIDS defining illness" is, particularly** given how important it is in the context of the results. 7. Table 5 is very difficult to interpret for those who do not work in the field of HIV. Please describe the treatment regimens in better detail.
Author response	Reviewer: 1 These is a detailed study on suicide and HIV infection with detailed full records for an area in Canada and covering a key time period from 1997 to 2010 (11). The authors have tracked rates, compared these over time, showed a distinct decline and also showed elevations compared to teh general population. It is really rare for me to read a paper and have very little criticism or comment. Congratulations to the authors. I belive this is really important and deserves publication. I would only ask that the authors add a brief paragraph in their discussion speculating on the relationship between this and other suicidal behaviours (thoughts, ideation, attempts). As this is the severest end of the spectrum some acknowledgement of the array of suicide behaviours may be relevant. Overall this is a really neat well done study, important findings and good subanalysis (despite the very low numbers) relating to efaverenz (or NNRTIs in general). Authors are aware of the limitations and biases and these are clearly set out. Response: Thank you for the comment. We have added information regarding the array of suicide behaviours to **page 18 of the discussion section, as follows: "Lastly, suicide** itself - as discussed here in the current study - can be seen as the severest endpoint of a spectrum. We did not collect data for other suicidal or self-harming behaviours but acknowledge that they are closely related as they represent the array of suicidal

behaviours that exist." NB: We have shortened the response from the previous submitted version and moved it to the limitation section as suggested by the editor in her last communication.

Reviewer: 2

Thank you for the opportunity to review this interesting paper. It examines changing rates of suicide in a large sample of HAART treated HIV/AIDS patients and tries to identify factors associated with suicide in this group. Strengths of the study include the large cohort and the large number of variables examined including biological measures such as CD4 count/viral load. It is deserving of publication but I have the following specific comments:

The introduction is succinct and makes a good case for the rationale for this study. The methods are generally appropriate and well described.

Comments/queries on the methods:

1. HOMER appears in the abstract but the full term should also appear the first time it shows up in the main text (methods sentence 2)

Response: We have now expanded the acronym HOMER in page 6 of the methods section.

2. Can the authors comment on the reliability of linkage with DTP and vital statistics?

Response: We have now added information to characterize the linkage in the methods section on page 6, as follows: "Cause and date of death were obtained through an ongoing monthly linkage of the BC-CfE registry with the BC Vital Statistics event registry up to June 2012. This linkage significantly minimizes loss to follow-up to less than 4% and allows all deaths that occurred in the sample to be included."

3. There is a body of literature suggesting that many deaths ruled as "accidental poisoning" or "poisoning with undetermined intent" are actually suicide and the authors do well to account for this (I think – according to my reading these were included but please clarify). However many deaths in these categories may not be suicides. Do the results of the analysis change significantly if a stricter "self-inflicted" only definition is used? This is relevant since injection drug users may be at a much higher risk of true accidental poisoning while abusing drugs.

Response: Although we are not able to perform analyses excluding accidental poisoning or poisoning with undetermined intent deaths, since they form the vast majority of deaths, we agree that injection drug users may be at a higher risk of truly accidental poisoning. As such, we did an analysis comparing predictors of suicide among IDU vs. non-IDU, excluding individuals with unknown IDU status. The results remained consistent in this sub-analysis. We suspect that some of the unknown IDU are, in fact, IDU, since injecting drug use is so prevalent among the HIV positive population here in BC.

4. It may seem obvious but the last 2 sentences of the methods come out of the blue. I would orient the reader that data on the BC population in general was collected to compare/provide context for the rates in the HOMER group.

Response: We have included a sentence prior to the last few sentences to contextualize the nature of the comparison, on page 8, as follows: "Suicide rates and general mortality data from HOMER were compared to that of the BC general population to contextualize findings."

Comments/queries on the results:

5. Here and in Table 1 - Can "younger age" (at the end of follow up – a phrase that doesn't appear in the results text) really be considered a factor associated with suicide? If they died and hence weren't around for more years of follow up compared to the alive group, I'm not sure if this is of value/how to interpret it. Similarly in Table 2, older people are almost always more likely to die from all cause mortality compared to suicide. I'm not saying this shouldn't be presented but maybe I wouldn't highlight it in the text especially as an "associated factor".

Response: Thank you for the comment. Younger age has been associated with an increased risk of suicide in this paper and in others, and is one of the leading causes of death among adolescents and young adults. We would suggest that the fact that younger individuals died of suicide and were therefore unable to contribute more follow-up time is significant.

6. 4th paragraph "Never having had an AIDS defining illness(Adjusted Hazard Ratio [AHR] = 4.45; CI [1.62 – 12.25]) or having a history of injection drug use (AHR = 3.95; CI [1.99 – 7.86]) was independently associated with an increased rate of suicide." Should read "WERE independently associated".

Response: Thank you; we have changed that sentence in the text to read were independently associated.

7. I am not an expert in ARV treatment and can't comment on the clinical implications/utility of table 5. If it is useful, the authors should explain why in the interpretation. If not, they could remove the table and simply state that this was

	examined and there were no meaningful differences. Response: This is a recommendation from all of the reviewers; as such, we have removed table 5. Comments/queries on the discussion: 8. I would favour an expanded limitations section. There are several points not addressed including a. The lack of a control group without HIV/AIDS Response: We did include a comparison of our mortality data to the general population, but certainly, having a control group within our sample would have been beneficial as well. b. The lack of a control group with HIV/AIDS not currently in treatment – this is a crucial point as this may be a self selected group of people who are engaged with life and their own health care which may substantially mitigate suicide risk and explain the results Response: We describe in the limitations how the sample is limited to those who have initiated treatment and have now expanded the sentence on pages 17 and 18 as **follows: "Second, our data pertains to a very specific popula**tion of PLHIV, who have initiated HAART in British Columbia, Canada **–** a universal healthcare setting with free access to treatment and HIV-**related care."** c. **The large number of "unknown" values e.g. 30% of suicide victims had** unknown injection drug use hx Response: We have now listed that limitation in the discussion section on page 18, as **follows: "Fifth, our sample size, information on certain variables such as IDU, and** gender distribution is limited; in addition, we had no access to clinical information regarding previous psychiatric history, particularly depression, or any mental health-**related treatments."** d. Difficulty interpreting the directionality of the associations – did lack of adherence cause suicide victims to get mentally or physically sicker and then they died from suicide or were they already depressed/hopeless and contemplating suicide and **that's why they stopped adhering** Response: We have now added a sentence to page 17 of the limitations describing how we are unable to infer both causality **and direction of associations, as follows: "First, in** the cross-sectional analysis, we are able to highlight associations, but unable to **determine/infer causality or direction of associations."** e. How many people joined HOMER in each year of the study? Is it possible that most joined in the late 90s and all those people prone to suicide died early on leaving a group less susceptible which explains the precipitous decline? Response: Individuals have been joining the HOMER cohort consistently over time **–** unfortunately, it has only been in the last couple years that the number of new HIV diagnoses in BC has plateaued. 9. I also think the authors could say more about the implications of these results. **The drop in suicides is probably the most dramatic I've e**ver seen in any sample. They **talk about why such a drop might happen but don't emphasize its magnitude or how** that could be explained. Why did the results differ from the Swiss and Danish samples (likely because those are national registries with many pe**ople who aren't in treatment)?** Should we be directing suicide screening to all HIV/AIDS patients or particularly to those with a history of IV drug abuse? What should we take away from these findings? Response: Thank you for the feedback. We have now emphasized the dramatic nature of our results and have included theories about why there is such an extreme drop in **the incidence of suicides in the discussion, on page 14, as follows: "Several factors may** have contributed to such a dramatic decline within this cohort. First, as the HAART era progressed, treatment regimens became simpler, more effective, less toxic and better **tolerated18,24 thereby reducing treatment burden and impact on patients' quality of** life. Secondly, initially characterized as a terminal illness **–** and therefore inherently associated with an elevated risk of suicide18,25 – HAART transformed HIV into a chronic-manageable condition9,24. Lastly, public perception of HIV has evolved over time, leading to greater social acceptance of PLHIV and potentially contributing to reduced suicide rates in this population. PLHIV in BC may now be exposed less to established correlates of suicidality such as stigma, marginalization and social exclusion,9,15,17-21 than at the start of the epidemic as a result of public health campaigns and harm-reduction programming that improve access to facilities such as **the supervised injection site, which may have contributed to a reduction in "accidental poisoning", and therefore, a drop in the number of suicides as evaluated in HOMER."** 10. **I'm not sure I fully follow the reasoning at the bottom of page 11 about "healthier" people being at higher risk of suicide.** The suicide victims did have higher CD4 counts than those who died from other causes but they had lower CD4 values/higher viral load compared to those who remained alive. Response: Thank you for the feedback, we have re-worded this sentence on page 16 as

follows: "Lastly, although those who died of suicide may have appeared to be physically healthier (i.e. higher CD4, no ADI), they may not have been healthier from a mental health standpoint."

11. Bottom of page 12 "mental health illness". This is an awkward term -"mental illness" might be better.

Response: Thank you, we have now changed the wording to mental illness rather than mental health illness.

Other minor points:

1. In several places including table titles the phrase "committed suicide" is used. "Commit" evokes the idea of a crime which may be unempathic/stigmatizing. The preferred nomenclature currently in the suicide literature is simply "died from suicide", "died by suicide" or "suicide death".

Response: Thank you for this information. We have changed the wording throughout the paper accordingly.

2. Similarly the phrasing "78% of all suicides were male" in paragraph 2 of the results is not ideal. The suicides aren't male, the people were. Better here and throughout the text would be "suicide victims" or "people who died from suicide".

Response: Thank you, we have changed the wording here as well.

Reviewer: 3

This well-written paper describes the trend in suicide rates among 5,229 HIV-positive individuals being treated with HAART in British Columbia from 1996 to 2012, and investigates predictors of suicide in the cohort. The authors observed a dramatic decrease in suicide over this time period, and identified increased risk of suicide among injection drug users and those who have never experienced an AIDS defining illness. The authors identify a key limitation – they have no data on mental illness diagnoses. The results are consistent with other studies, but nevertheless these findings are important in the Canadian context. A few suggestions for improving the manuscript:

1. Figure 1 is very compelling. Nevertheless, a time trend analysis demonstrating the decline in suicide rate is statistically significant would be helpful, particularly given the small numbers of suicides included.

Response: Thank you. We have added the following text to the methods on page 9: "A test of trend to analyze the change in suicide rates over time was performed; specifically, due to the small number of suicide deaths, the asymptotic test Somers' D **was used." We have also added information on the test results to the results section.**

2. More details about the cohort would be helpful to assess the generalizability of the results. Are all individuals who receive HAART in BC during the study period **included in the cohort? It's not entirely clear from the Methods if this is the case.**

Response: Thank you for the comment. Yes, all individuals who received HAART in BC during the study period are included, and we have now included wording to that effect **in the methods on page 6, as follows: "The BC**-CfE is the centralized distributor of antiretroviral therapy for all individuals accessing **HIV treatment in BC."**

3. The authors include accidental poisoning deaths as suicide, which is consistent with other studies. Some readers, however, may object to this considering some of these deaths may truly be accidental. Presumably there are some inadvertent overdose deaths in this population. It would be useful to know how many of the suicides received this cause of death, and if the results are the same if these deaths are removed in a sensitivity analysis.

Response: Table 1 describes how suicide deaths were categorized, including the number listed as inadvertent overdose deaths. As 73% of suicide deaths were classified as accidental poisoning by and exposure to narcotics and psychodysleptics, we are unable to perform a sensitivity analysis excluding these deaths; nor is there a way to identify which overdose deaths were suicide deaths with our existing data. We have expanded **the limitations section to clarify this as well on page 18 as follows: "Fourth, suicides may** be underestimated as those that occur as a result of self-administered withdrawal of care, or similar, indirect ways often cannot be distinguished as such; however, given the **definition of suicide utilized in this study includes "accidental poisoning" it may also be** possible that the number of suicides is over-estimated, and that some instances of **overdose death are, in fact, not suicides."**

4. The analysis of predictors of suicide is interesting, but the results are somewhat expected. What would be very interesting would be to see if the trend in suicide rate is changing among particular subgroups (i.e., an interaction between time and subgroup).

Response: Thank you for this suggestion. At this time, the authors feel that such an analysis is beyond the scope of the paper; however, we plan to continue exploring the phenomenon of suicide death among HIV positive individuals, and examining interactions and changes in association over time will be an interesting facet of the investigation.

5. **Please avoid using the term "committed suicide". It is a p**ejorative term;

	suicide has not been a crime in Canada for 40 years. Response: Thank you. We have removed this term from the paper. 6. **It would be helpful to define what an "AIDS defining illness" is, particularly** given how important it is in the context of the results. Response: We have now clarified the definition and given examples of AIDS-defining **illnesses on page 8, as follows: "ADI: a condition that, in the setting of a HIV infection,** confirms the diagnosis of AIDS. This includes a list of serious and life threatening **diseases like cancers and infections."** 7. Table 5 is very difficult to interpret for those who do not work in the field of HIV. Please describe the treatment regimens in better detail. Response: Based on overall feedback, we have decided to remove table 5.