PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Missed opportunities for HIV testing among patients newly presenting for HIV care at a Swiss university hospital: a retrospective analysis
AUTHORS	Lhopitallier, Loïc; Moulin, Estelle; Hugli, Olivier; Cavassini, Matthias; Darling, Katharine

VERSION 1 – REVIEW

REVIEWER	Karen Champenois Laboratoire de recherche, EPS Maison Blanche, Paris, France
REVIEW RETURNED	02-Nov-2017

GENERAL COMMENTS	This manuscript presents the retrospective analysis of contacts for care collected in medical records of patients who attended HIV care in Switzerland. Although the monocentric design and the relatively small sample of patients, the authors found proportions of missed opportunities for HIV testing based on clinical indicator conditions in agreement with other European studies. This study shows that recommendations to test for HIV more frequently people from the population groups the most vulnerable to HIV is few or not followed by care providers. As the authors discussed it, care providers are not used to address sexuality and HIV with their patients (and nothing has changed since the study of Champenois et al. carried out in 2010). Perhaps also, they are not aware of this recommendation of repeated testing for at-risk populations (up to every 3 months for MSM in UK or in France) that lead to offer an HIV test at almost each contact with care. An important work to inform and train care providers, GPs and physicians from specialties other than infectious diseases to identify HIV indicator conditions (clinical and non-clinical) is a major issue to extend and improve the efficiency of HIV testing. As a monocentric study, it may underestimate the missed opportunities based on clinical indicator conditions because it didn't catch the medical encounters in GPs, or other hospital or medical centers. In another hand, it may overestimate the missed opportunities based on risk group because a contact with care at hospital is punctual for a specific health event (in particular in emergency department) and HIV testing may be considered by hospital physicians (rightly or wrongly) as taking part of a regular follow-up. Detailed comments - Too much abbreviations: ADI, PICT, FOPH, LHU, …. - The manuscript is clear and well written. It may be reviewed by a native English speaker Article summary, strengths and limitations: the authors could add the

	limitation that the study caught visits to their hospital only. Methods - Authors could provide examples of “HIV ICs in which HIV prevalence is considered to be >0.5%”. HIDES and OptTest studies may be cited (in Methods and / or Discussion) as references of an European work to optimize HIV testing based on indicator condition. - A question: did the history of HIV testing could be taken into account? for example a visit of MSM at the hospital but an HIV test performed 2 months ago makes this visit is not a missed opportunity. Results - Page 8, line 23: the authors give the proportions of patients who had missed opportunities from one, two or three categories. It may be interesting to know how many patients had an epidemiological indicator condition and a clinical indicator condition or two / three clinical indicator conditions which supposed to lead more likely to an HIV test. - Page 8, line 45: it lacks details about 46% and 33% - Page 8, line 54: 119 patients were late presenters of whom 74% were enrolled in the cohort. It seems that only late presenters could be enrolled in the cohort; in Methods it is written that all new HIV patients can choose to enter into the cohort. - Page 9, MO and LP: Late presenters were less likely to have a missed opportunity in the five years prior to HIV diagnosis. MSM were less likely to be late presenters but had more likely to have a missed opportunity for testing because they were MSM and have not been tested. All these results are probably linked together and MSM may be a confounding factor in this last analysis. Is the analysis to assess the association between LP and MO was adjusted for the population group? Table 1 - Errors in percentage calculation remain (female, other origin) - For patients with and without missed opportunities, percentages would be presented in column rather than in row that makes them easier to interpret. - In the column univariate, what the “*” means for MSM and previous HIV test >1 year ago? - How to explain that Sub-Saharan Africa origin was not significantly associated with missed opportunities in the univariate analysis and became significant in the multivariate analysis? - a few demographic variables were not significantly associated with MO in the multivariate model. Did results change if these variables were removed from the model? Table 2: 30 patients were diagnosed at the acute HIV infection stage and 36 have been tested because of acute HIV infection signs. Does it mean that all acute infections were symptomatic? Figure: Percentage should be added on the Figure 1B. Discussion Page 10, line 46 and after, about the reverse association between late presenters and having missed opportunities: the authors may

	consider also the possible confounding role of being MSM (as said above). Could the authors calculate the total number of visits at the hospital for people who presented late and other (regardless MO)? This could help confirm or refute the assumption made on line 56 i.e. their late presentation was their only presentation. The authors discussed results and had appropriate conclusions. Now that the findings are made, what have the authors planned to do to improve the MO situation in their hospital? I invite the authors to read the European study OptTest and tools developed during this study to help them improve HIV knowledge of other specialty physicians and improve HIV testing policies inside their hospital.

REVIEWER	Cristina Agustí Benito Centre for epidemioogical studies on HIV and STIs of Catalonia - Public Health Agency of Catalonia (Spain)
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	General comments: You presented an interesting retrospective study about missed opportunities for HIV testing in patients newly diagnosed with HIV in an HIV outpatient clinic at a Swiss tertiary hospital. You suggested a definition of missed opportunity based on the Swiss HIV testing recommendations. In my opinion the presented manuscript is interesting for the readership of the journal but some modifications should be included in order to meet all acceptance criteria of BMJ Open. The objectives of the study are well defined and the methodology is clear, the results are well presented but in my opinion the study has important limitations that are not enough discussed by the authors. In the Discussion you explain the limitations of the study due to the study design that only comprises one hospital located in a region of Switzerland that is not representative of the epidemics in the country. You have not taken into account all potential missed opportunities of Primary Care, STI clinics, specialist clinics, etc. On the other hand you have not described the Swiss health care system and the barriers to access to HIV testing and care for migrants and people with low income. Introduction The manuscript will benefit with a detailed description about the Swiss health care system, is there universal access? Is HIV testing provided free of charge? Is it necessary a prescription of a physician? Barriers to access the health care system could play an important role that from my point of view are not enough discussed in the manuscript. What about Primary care? In most countries the big majority of population attends almost exclusively to this services and it is the front line of the health care system. Could you please describe the use of Primary care in the region? In my opinion not having had into account Primary Care is the most important limitation of the study. Definitions Did you take into account the refusal rate of the patient to get tested for HIV? Do you have access to this information? How do you know if the physician recommend and HIV test and the patient didn't do it (because he or she didn't want to get tested or because they cannot afford the cost)? If you haven't had this information into account please include it as a limitation. Why do you define ICs as one with an HIV prevalence of 0,5% instead of 0,1% as stated in Sullivan A, et al. (2013) Feasibility and Effectiveness of Indicator Condition Guided Testing for HIV: Results

	from HIDES I (HIV Indicator Diseases across Europe Study). PLOS ONE 8(1) and in the European Guidelines for HIV testing in health care settings developed by HIV in Europe? Could you please better explain epidemiological risk? You mention for instance MSM, what is the frequency recommended for this group? Once a year? Please specify. Study design Please specify if information was collected about HIV tests performed out of the hospital. Was this information collected? Is possible that the test was not performed because the patient reported has been tested in other setting? MOs could be overestimated. Please include it in the limitations of the study. Why do you include parental status? In my opinion this information is not relevant. Results Could you please specify what was the total number of patients newly presenting for HIV during the study period in your clinic? What was the proportion of patients with complete electronic records? Figure 1: I suggest represent the data in a table, it's not necessary a figure. Table 1: Do you have information about transgender people? Could you explain which were the most frequents MOs in the ED? Discussion Please, re-write the limitations of the study and adapt the discussion of the obtained results to them. Improving health care access would impact in the early diagnosis of HIV. Eliminating barriers for HIV testing is crucial to do that. You suggest that offering non-targeted screening in ED, as recommended in US, would have enabled diagnosis of 86% of the patients of your sample. Have you calculated how many tests would have been performed during the study period? Have you estimated the number of positive tests you would have found? Do you think it would be a cost-effective intervention? Please take into account the role of Primary Care in early diagnosis of HIV. You said that "many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis", can you assure that these individuals haven't attend Primary Care? Do you have information about it?

REVIEWER	David Chadwick James Cook University Hospital Middlesbrough UK
REVIEW RETURNED	22-Nov-2017

GENERAL COMMENTS	This is an interesting manuscript reporting a single centre analysis of potential missed opportunities (MO) for HIV testing amongst a cross-section of patients diagnosed with HIV. Whilst I think the study is potentially suitable for publication, there is one major problem with the cohort studied which I mention below. 1.The authors have included 30 patients with primary HIV infection in their various analyses. By definition these patients had very recently acquired HIV and would not have tested HIV positive if tested weeks, months or years earlier. In various parts of the manuscript it seems these patients have been assumed to have potential missed opportunities to diagnose earlier, for example in final conclusion paragraph of discussion – 'we observe that 47% of the patient…… could have been tested and diagnosed at an earlier stage.' This is clearly not correct for these 30 patients. I would

	advise that the analysis is repeated excluding these patients and only these results shown, or that results for both populations (201 or 171 patients) are shown and it made clear that the results for the 201 patients don't have the same implications for earlier testing. 2. In the discussion the authors briefly mention the limitation of not being able to fully assess potential MOs for testing in primary care, and hence this study has potentially underestimated MOs. It is clearly the experience of several studies, including the Dutch one in primary care cited, as well as our experience in the UK showing that when it is possible to review primary care records a significant proportion or the majority of MOs are found to occur in primary care. Hence I think that unless the system of using primary care in Switzerland is very different to Holland or the UK, the likelihood of underestimation should be more forcefully stated in the discussion. I personally believe that most studies showing lower levels of MOs (e.g. reference 11) grossly underestimate MOs through not having had access to primary care or other relevant records. A recent BHIVA audit (see '2016: Review of Late Diagnosis' at http://www.bhiva.org/NationalAuditReports.aspx) of 773 adults presenting late (CD4<200), showed 46% had clear MOs, however many units taking part did not have good access to primary care records.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Karen Champenois
Institution and Country: Laboratoire de recherche, EPS Maison Blanche, Paris, France
Competing Interests: None declared

This manuscript presents the retrospective analysis of contacts for care collected in medical records of patients who attended HIV care in Switzerland. Although the monocentric design and the relatively small sample of patients, the authors found proportions of missed opportunities for HIV testing based on clinical indicator conditions in agreement with other European studies. This study shows that recommendations to test for HIV more frequently people from the population groups the most vulnerable to HIV is few or not followed by care providers. As the authors discussed it, care providers are not used to address sexuality and HIV with their patients (and nothing has changed since the study of Champenois et al. carried out in 2010). Perhaps also, they are not aware of this recommendation of repeated testing for at-risk populations (up to every 3 months for MSM in UK or in France) that lead to offer an HIV test at almost each contact with care. An important work to inform and train care providers, GPs and physicians from specialties other than infectious diseases to identify HIV indicator conditions (clinical and non-clinical) is a major issue to extend and improve the efficiency of HIV testing.
As a monocentric study, it may underestimate the missed opportunities based on clinical indicator conditions because it didn't catch the medical encounters in GPs, or other hospital or medical centers. In another hand, it may overestimate the missed opportunities based on risk group because a contact with care at hospital is punctual for a specific health event (in particular in emergency department) and HIV testing may be considered by hospital physicians (rightly or wrongly) as taking part of a regular follow-up.

Detailed comments
- Too much abbreviations: ADI, PICT, FOPH, LHU, ….

The manuscript has been reviewed and many abbreviations removed to improve the readability. We have kept PICT as it is commonly-used and it used in all our previous publications (and appears several times in this manuscript) and ED (emergency department), for the same reasons.

- The manuscript is clear and well written. It may be reviewed by a native English speaker

Article summary, strengths and limitations: the authors could add the limitation that the study caught visits to their hospital only.

We mention 'monocentric study' in the list of strengths and limitations of this study and describe this more fully in the limitations section of the Discussion: 'As we reviewed medical notes only from our institution, the number or categories of MO may be prone to bias'.

Methods
- Authors could provide examples of "HIV ICs in which HIV prevalence is considered to be >0.5%". HIDES and OptTest studies may be cited (in Methods and / or Discussion) as references of an European work to optimize HIV testing based on indicator condition.

Thank you for the comment. We have a updated the manuscript and added a few examples of HIV ICs and cited the HIDES and OptTest studies.

- A question: did the history of HIV testing could be taken into account? for example a visit of MSM at the hospital but an HIV test performed 2 months ago makes this visit is not a missed opportunity.

The history of the last negative HIV test was taken into account and was included in a categorical fashion in the multivariate analysis.

Results
- Page 8, line 23: the authors give the proportions of patients who had missed opportunities from one, two or three categories. It may be interesting to know how many patients had an epidemiological indicator condition and a clinical indicator condition or two / three clinical indicator conditions which supposed to lead more likely to an HIV test.

24 (29%) of patients with missed opportunities due to epidemiological risk (n = 84) also had a clinical indicator condition. We do not have data on the number of discrete clinical indicator conditions only on their presence or not at each consultation.

- Page 8, line 45: it lacks details about 46% and 33%

The manuscript was modified to included these details and present the data in a more intelligible manner.

- Page 8, line 54: 119 patients were late presenters of whom 74% were enrolled in the cohort. It seems that only late presenters could be enrolled in the cohort; in Methods it is written that all new HIV patients can choose to enter into the cohort.

The manuscripts was modified and the reference of 74% of LPs patients enrolled in the cohort was removed in order to enhance clarity of the information.

- Page 9, MO and LP: Late presenters were less likely to have a missed opportunity in the five years prior to HIV diagnosis. MSM were less likely to be late presenters but had more likely to have a missed opportunity for testing because they were MSM and have not been tested. All these results

are probably linked together and MSM may be a confounding factor in this last analysis. Is the analysis to assess the association between LP and MO was adjusted for the population group?

In order to assess the association between LP and MO we performed a multivariate logistic regression looking at the risks of being a LP. This analysis was confounded by demographic, clinical and epidemiological (including being MSM) factors. I have added this precision to the Methods (data and statistical analysis) to enhance clarity.

Table 1
- Errors in percentage calculation remain (female, other origin)
- For patients with and without missed opportunities, percentages would be presented in column rather than in row that makes them easier to interpret.

We have presented percentages per row for each category so that we can easily compare, for a given category, the percentage with and without missed opportunities. For the first column, percentages were presented per column to reflect the distribution of patients. This layout was confusing. We have therefore opted for removing the percentages (per column) for all patients.

- In the column univariate, what the "*" means for MSM and previous HIV test >1 year ago?

The "*" represented statistical significance. (ie. p value < 0.05). We have made this clearer in the manuscript.

- How to explain that Sub-Saharan Africa origin was not significantly associated with missed opportunities in the univariate analysis and became significant in the multivariate analysis?

This is due to the introduction of all the confounding variables in the multivariate logistic regression. In the univariate analysis other demographic and clinical factors were all confounding the analysis, diminishing the effect of Sub-Saharan Africa origin on the risk of presenting missed opportunities.

- a few demographic variables were not significantly associated with MO in the multivariate model. Did results change if these variables were removed from the model?

Thank you for your comment. We have removed these variables from the model in order to improve clarity. Their absence does not influence the statistical significance of the association between other variables and the risk for MO in the multivariate model.

Table 2
30 patients were diagnosed at the acute HIV infection stage and 36 have been tested because of acute HIV infection signs. Does it mean that all acute infections were symptomatic?

24 of the 30 patients (80%) diagnosed at the acute infection stage had symptoms of acute HIV infection. Acute infection was defined as an HIV seroconversion with an incomplete Western Blot. Table S3 displays the reasons for testing in patients with acute infection. We have added the definition of acute HIV infection to the manuscript as well the data on the percentage of symptomatic acute HIV infections.

Figure:
Percentage should be added on the Figure 1B.

The changes have been done.

Discussion:
Page 10, line 46 and after, about the reverse association between late presenters and having missed opportunities: the authors may consider also the possible confounding role of being MSM (as said above).
Could the authors calculate the total number of visits at the hospital for people who presented late and other (regardless MO)? This could help confirm or refute the assumption made on line 56 i.e. their late presentation was their only presentation.

We have adapted the manuscript to show an additional analysis (Results – Clinical presentation at diagnosis, site of testing and reason for testing) showing that there is a significant difference in the number of consultations at the hospital between late presenters and others. This helps confirm our assumption.

The authors discussed results and had appropriate conclusions. Now that the findings are made, what have the authors planned to do to improve the MO situation in their hospital? I invite the authors to read the European study OptTest and tools developed during this study to help them improve HIV knowledge of other specialty physicians and improve HIV testing policies inside their hospital.

Thank you for this comment and indeed this invitation to give our opinion beyond our immediate results. We have added some plans to the discussion section which are in line with the OptTest Project

Reviewer: 2
Reviewer Name: Cristina Agustí Benito
Institution and Country: Centre for epidemioogical studies on HIV and STIs of Catalonia - Public Health Agency of Catalonia (Spain)
Competing Interests: None declared

General comments:
You presented an interesting retrospective study about missed opportunities for HIV testing in patients newly diagnosed with HIV in an HIV outpatient clinic at a Swiss tertiary hospital. You suggested a definition of missed opportunity based on the Swiss HIV testing recommendations.
In my opinion the presented manuscript is interesting for the readership of the journal but some modifications should be included in order to meet all acceptance criteria of BMJ Open.

The objectives of the study are well defined and the methodology is clear, the results are well presented but in my opinion the study has important limitations that are not enough discussed by the authors.

In the Discussion you explain the limitations of the study due to the study design that only comprises one hospital located in a region of Switzerland that is not representative of the epidemics in the country. You have not taken into account all potential missed opportunities of Primary Care, STI clinics, specialist clinics, etc. On the other hand you have not described the Swiss health care system and the barriers to access to HIV testing and care for migrants and people with low income.
Introduction

The manuscript will benefit with a detailed description about the Swiss health care system, is there universal access? Is HIV testing provided free of charge? Is it necessary a prescription of a physician? Barriers to access the health care system could play an important role that from my point of view are not enough discussed in the manuscript.

We have added a brief description of the Swiss health care system in our manuscript, emphasizing that co-payments are the main factor for limiting access to care and HIV testing. HIV testing in Switzerland is dependent on a doctor's prescription as the recommendations are based a physician initiated counselling and testing model.

What about Primary care? In most countries the big majority of population attends almost exclusively to this services and it is the front line of the health care system. Could you please describe the use of Primary care in the region? In my opinion not having had into account Primary Care is the most important limitation of the study.

We have added to the introduction the fact that over 98% of the population has health insurance coverage and that access to care is excellent. We do not have data on the use of primary care but we have added references reporting lower use of primary care physicians among patients presenting to the emergency department at our centre.

Definitions

Did you take into account the refusal rate of the patient to get tested for HIV? Do you have access to this information? How do you know if the physician recommend and HIV test and the patient didn't do it (because he or she didn't want to get tested or because they cannot afford the cost)? If you haven't had this information into account please include it as a limitation.

Having reviewed all the consultation notes available we have not identified a situation in which a patient refused to be tested for HIV. It remains possible however that such a refusal was not documented. However non-documentation is very unlikely due to the Swiss Federal Office of Public Health HIV testing recommendations of 2013 which state that not offering a test puts in jeopardy the due diligence of the attending physician. We have specified this information in the manuscript.

Why do you define ICs as one with an HIV prevalence of 0,5% instead of 0,1% as stated in Sullivan A, et al. (2013) Feasibility and Effectiveness of Indicator Condition Guided Testing for HIV: Results from HIDES I (HIV Indicator Diseases across Europe Study). PLOS ONE 8(1) and in the European Guidelines for HIV testing in health care settings developed by HIV in Europe?

We could not agree more with this comment. However the Swiss testing recommendations state 0.5% prevalence although they are based on HIDES 1 recommendations and a 0.1% prevalence to define indicator conditions. As we opted to use these recommendations for our definition of a missed opportunity we maintained the reference to 0.5% prevalence. We have inserted this reference mid-sentence to make this clear.

Could you please better explain epidemiological risk? You mention for instance MSM, what is the frequency recommended for this group? Once a year? Please specify.

Epidemiological risk represents patients who:

- Belong to a group with a high prevalence of HIV
- Have an at-risk sexual behaviour with either a known –positive person or an individual who belongs to a group with high prevalence.

The Swiss Federal Office of Public Health does not specify a frequency of testing in this group.

Study design

Please specify if information was collected about HIV tests performed out of the hospital. Was this information collected? Is possible that the test was not performed because the patient reported has

been tested in other setting? MOs could be overestimated. Please include it in the limitations of the study.
We obtained the date of the previous HIV test for our patients, regardless of the setting where it was performed. This was obtained by questioning our patients during the initial consultation. However we did that have information on consultations and testing outside of our hospital which could lead to bias regarding the estimation of MO, as we have mentioned in the limitations section of the Discussion.

Why do you include parental status? In my opinion this information is not relevant.
We have removed this information from the manuscript.

Results
Could you please specify what was the total number of patients newly presenting for HIV during the study period in your clinic? What was the proportion of patients with complete electronic records?

We had complete electronic records for 100% of the patients (n=201) who presented at our clinic during the study period.

Figure 1
I suggest represent the data in a table, it's not necessary a figure.

We would prefer to keep this figure as it depicts patients with chronic disease who are followed up over a series 10 clinical episodes before an HIV test is performed.

Table 1:
Do you have information about transgender people?

We did not identify any transgender patient during our study period.

Could you explain which were the most frequents MOs in the ED?

As with the sample as a whole, most ED MOs were related to epidemiological risk +/- HIV indicator conditions. This has been added to the manuscript.

Discussion
Please, re-write the limitations of the study and adapt the discussion of the obtained results to them. Improving health care access would impact in the early diagnosis of HIV. Eliminating barriers for HIV testing is crucial to do that.

You suggest that offering non-targeted screening in ED, as recommended in US, would have enabled diagnosis of 86% of the patients of your sample. Have you calculated how many tests would have been performed during the study period? Have you estimated the number of positive tests you would have found? Do you think it would be a cost-effective intervention?

The ED receives about 40,000 patients a year. This would amount to 240,000 tests over the study period. The incidence of HIV in Switzerland in 2015 was 6/100.000. We would have anticipated 14.4 positive tests using a blanket testing approach. We doubt this would be cost-effective but this does not take in account the beneficial effects resulting from increased counselling and awareness secondary to blanket testing.

Please take into account the role of Primary Care in early diagnosis of HIV. You said that “many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis”, can you assure that these individuals haven’t attend Primary Care? Do you have information about it?

Thank you for your comment. Such data is not routinely collected to due to the absence of a centralized database for the whole of the cantonal (or even federal) health care system. We have only made an assumption. The manuscript was edited to make the hypothetical nature of this statement clearer.

Reviewer: 3
Reviewer Name: David Chadwick
Institution and Country: James Cook University Hospital, Middlesbrough, UK
Competing Interests: None declared

This is an interesting manuscript reporting a single centre analysis of potential missed opportunities (MO) for HIV testing amongst a cross-section of patients diagnosed with HIV. Whilst I think the study is potentially suitable for publication, there is one major problem with the cohort studied which I mention below.

1.The authors have included 30 patients with primary HIV infection in their various analyses. By definition these patients had very recently acquired HIV and would not have tested HIV positive if tested weeks, months or years earlier. In various parts of the manuscript it seems these patients have been assumed to have potential missed opportunities to diagnose earlier, for example in final conclusion paragraph of discussion – ‘we observe that 47% of the patient…… could have been tested and diagnosed at an earlier stage.’ This is clearly not correct for these 30 patients. I would advise that the analysis is repeated excluding these patients and only these results shown, or that results for both populations (201 or 171 patients) are shown and it made clear that the results for the 201 patients don't have the same implications for earlier testing.

We thank you for this very important comment which led to intense debate within the study team.
1) Our definition of a MO is MO for testing (and associated counselling) and not for diagnosis. Therefore if a patient is seronegative for HIV but has an indication for HIV testing and is not tested we consider this a MO. We have reformulated the manuscript to make this clearer.
2) Our study population only consisted of seropositive patients as a denominator, which could lead to confusion. However we consider that an individual who presents with acute HIV and belongs to a risk group should have been tested in the 5 years pre-seroconversion if he presented to care. We hypothesize that the counselling associated with testing whilst the patient was still seronegative might have diminished his/her risk of acquiring HIV.

3) All analysis regarding late presentation excluded acute infections. This is now stated in the Methods section.

4) Table S3 shows the results of the multivariate logistic regression performed to identify risk factors for missed opportunities excluding patients with acute HIV infection. The main differences observed are decreased risk for patients > 30 years of age and the loss of statistical significance in the association between MSM and MOs. (this is probably due to the fact that 17 of the 30 acute infections were in MSM increasing the variability in the data by reducing the denominator).

5) We have opted to maintain the acute infections in the final analysis as we believe that these patients had missed opportunities for HIV testing (and counselling) although they were seronegative.

However the analysis performed without the 30 acute infections could be presented in a supplementary table.

2. In the discussion the authors briefly mention the limitation of not being able to fully assess potential MOs for testing in primary care, and hence this study has potentially underestimated MOs. It is clearly the experience of several studies, including the Dutch one in primary care cited, as well as our experience in the UK showing that when it is possible to review primary care records a significant proportion or the majority of MOs are found to occur in primary care. Hence I think that unless the system of using primary care in Switzerland is very different to Holland or the UK, the likelihood of underestimation should be more forcefully stated in the discussion. I personally believe that most studies showing lower levels of MOs (e.g. reference 11) grossly underestimate MOs through not having had access to primary care or other relevant records. A recent BHIVA audit (see '2016: Review of Late Diagnosis' at http://www.bhiva.org/NationalAuditReports.aspx) of 773 adults presenting late (CD4<200), showed 46% had clear MOs, however many units taking part did not have good access to primary care records.

Thank you for pointing this out. We have completed the discussion and added the reference to the BHIVA audit which corroborates the fact that many MO must occur in primary care but that our study design does not allow us to obtain this information.

VERSION 2 – REVIEW

REVIEWER	David Chadwick James Cook University Hospital, Middlesbrough, UK
REVIEW RETURNED	27-Dec-2017

GENERAL COMMENTS	I think the authors have answered my questions.

REVIEWER	Cristina Agustí Centre for epidemiological studies on HIV and STIs of Catalonia-Public Health Agency of Catalonia. Spain
REVIEW RETURNED	22-Jan-2018

GENERAL COMMENTS	General comments: The authors have taken into account most of the suggested comments but some relevant ones have not been considered. In my opinion some important issues are not enough discussed in the second version of the manuscript. And the Discussion should be re-rewritten. Introduction You added to the 2nd version of the manuscript a detailed description about the Swiss health care system however, there is some missing information: Do undocumented immigrants have access to the health care system? Is HIV testing provided free of charge?, if not, what's the cost of a test? Is it necessary a prescription of a physician? As I previously commented, barriers to access the health care system could play an important role that from my point of view that are not enough discussed in the manuscript. Definitions In the reviewed version of the manuscript the authors mentioned that "We did not identify any situations in which HIV testing was recommended and not accepted by the patient". Testing refusal is

	collected in the clinical records? You did not explain why do they define ICs as one with an HIV prevalence of 0,5% instead of 0,1% as stated in Sullivan A, et al. (2013) Feasibility and Effectiveness of Indicator Condition Guided Testing for HIV: Results from HIDES I (HIV Indicator Diseases across Europe Study). PLOS ONE 8(1) and in the European Guidelines for HIV testing in health care settings developed by HIV in Europe. Could you please clarify why did you take into account 0.5%instead 0.1%? Could you please better explain epidemiological risk? Study design Could you please clarify if any information was collected about HIV tests performed out of the hospital? Was this information collected? There is the possibility that an HIV test was recommended but it was not performed because the patient reported that he or she has already been tested in other setting. MOs could be overestimated. Please include it in the limitations of the study. Why do you include parental status? In my opinion this information is not relevant. Discussion Page 11 line 24-30. You say “In patients under regular follow up, there may be the assumption by the hospital physician that the patient’s general practitioner GP has performed an HIV test and vice versa”. I don’t disagree but in my opinion you’re missing the possible lack of knowledge on risk factors for HIV and ICs among health professionals. Page 11 line 41. You say “In Switzerland, physicians frequently do not discuss sexual behaviour with their male patients, potentially missing those with risk factors”. Are you referring to all specialties, only GPs? What about female patients? Do physicians discuss among them about their sex life? Page 11 last paragraph: Please take into account the biggest limitation of your study, not taking into account primary care, it’s probable that most of the included patients had gone to Primary Care before going to the hospital, you are not analyzing missed opportunities in primary care, please mention this issue in this paragraph, not only in the limitations section. Page 12 line 19. You mention that HIV testing implies expenditure by the patient. Could you please better explain? Do you mean that HIV testing is not provided for free in the Swiss health care system? What’s the cost? Page 12 line 19. You suggest that offering non-targeted screening in ED, as recommended in US, would have enabled diagnosis of 86% of the patients of your sample. Have you calculated how many tests would have been performed during the study period? Have you estimated the number of positive tests you would have found? Do you think it would be a cost-effective intervention? Please take into account the role of Primary Care in early diagnosis of HIV. You said that “many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis”, can you assure that these individuals haven’t attend Primary Care? Do you have information about it? Tables and figures: Table 1: Please specify the region, country and study period. Please delete (next to 33.Please substitute IDU by “people who inject drugs (PWID). Figure 1: I suggest represent the data in a table, it’s not necessary a figure. I suggest deleting “As 94 patients presented MOs,…”. Please specify the region, country and study period.

	Figure 2: Please specify the region, country and study period. I suggest including the percentages. Table S2: Please specify the region, country and study period. Do you have information about transgender people?

VERSION 2 – AUTHOR RESPONSE

Editorial Comments:
Can you clarify why table S3 was included as a supplementary file for editors only as opposed to including it as a supplementary file (and citing/ discussing it in the main manuscript)?

- Table S3 was included to answer the question of reviewer 3 regarding the inclusion of patients with acute HIV infection in the multivariate logistic regression. However, as it was not possible to include it in the online reply, it was therefore included as a supplementary table. We have now removed this table from our submission

Reviewers' Comments to Author:
Reviewer: 2
Reviewer Name: Cristina Agustí

General comments:
Introduction
You added to the 2nd version of the manuscript a detailed description about the Swiss health care system however, there is some missing information:
Do undocumented immigrants have access to the health care system?

- Undocumented migrants do have access to the health care system through cantonal social services. In our canton, the canton of Vaud, this is managed by EVAM (Etablissement Vaudois d'Acceuil aux Migrants) which pays for health insurance for migrants and arranges for a consultation in a specialized migrant health service. Referrals to specialist services can then be made as required.

Is HIV testing provided free of charge?, if not, what's the cost of a test? Is it necessary a prescription of a physician?

- HIV testing, when prescribed by a physician, is covered under the mandatory health insurance law (LAMal). The cost of a test is 10 CHF (Swiss Francs) and the associated counselling is 60 CHF, so the overall cost charged to the patient is 70 CHF. Patients may have to pay for it out of pocket depending on the level of cover they have with their health insurer. HIV testing can also be accessed without a physician prescription in voluntary counselling and testing centres. In such cases, expenses are covered out of pocket by the patient.

As I previously commented, barriers to access the health care system could play an important role that from my point of view that are not enough discussed in the manuscript.

- We thank you for your comments, we have developed the aspects mentionned above in the text of the Introduction and Discussion.

Definitions
In the reviewed version of the manuscript the authors mentioned that "We did not identify any situations in which HIV testing was recommended and not accepted by the patient". Testing refusal is collected in the clinical records?

- The 2013 Swiss HIV testing recommendations (reference 7) emphasize the legal responsibility of a physician in ordering an HIV test in certain circumstances. Not recommending testing when indicated is now considered misconduct and, as such, testing refusal is documented in clinical records. This has been added to the text following the sentence you quote.

You did not explain why do they define ICs as one with an HIV prevalence of 0,5% instead of 0,1% as stated in Sullivan A, et al. (2013) Feasibility and Effectiveness of Indicator Condition Guided Testing for HIV: Results from HIDES I (HIV Indicator Diseases across Europe Study). PLOS ONE 8(1) and in the European Guidelines for HIV testing in health care settings developed by HIV in Europe. Could you please clarify why did you take into account 0.5%instead 0.1%?

- We are fully aware of the HIDES I study and agree with the reviewer that the figure mentioned by Sullivan et al is 0.1% rather than 0.5%. The conditions listed in the table in question in the Swiss FOPH testing recommendations refer not only to the HIDES indicator diseases but to other conditions and the table was compiled by HIV specialists throughout Switzerland. We need to cite this table as it formed the basis of one category of missed opportunities. However, we agree with the reviewer that citing the precise % stated in the recommendations is confusing. The compromise we therefore propose is to change this category to 'HIV indicator conditions' without citing 0.1% or 0.5%. We have made this change throughout the text (where we subsequently refer to 'indicator conditions' or 'ICs').

Could you please better explain epidemiological risk?

- In this paper, epidemiological risk is defined in the top paragraph of page 7. It is defined in accordance with the Swiss FOPH HIV testing recommendations of 2015 (reference 8). It is defined as belonging to or having a sexual partner from a high-risk group: men who have sex with men [MSM], people who inject drugs [PWID] and individuals originating from a high-prevalence region, notably, sub-Saharan Africa).

Study design
Could you please clarify if any information was collected about HIV tests performed out of the hospital? Was this information collected?

- Out of hospital HIV testing was mentioned in clinic letters for some of the patients, and this information was used to determine the date of the last HIV test performed. However, 1) as this information was not uniformly available for all patients and 2) was potentially prone to recall bias, we did not include such data in our analyses. As described in the Discussion, not having access to such information is a limitation of this study.

There is the possibility that an HIV test was recommended but it was not performed because the patient reported that he or she has already been tested in other setting. MOs could be overestimated. Please include it in the limitations of the study.

- As mentionned previously, due to the legal implications of not performing a recommended test we believe that previous relevant testing, even out of hospital, would be included in the clinic letter. However, as such data may be subject to recall bias, we have added this limitation to the discussion.

Why do you include parental status? In my opinion this information is not relevant.

- We agree and have removed it.

Discussion
Page 11 line 24-30.

You say “In patients under regular follow up, there may be the assumption by the hospital physician that the patient’s general practitioner GP has performed an HIV test and vice versa”. I don’t disagree but in my opinion you’re missing the possible lack of knowledge on risk factors for HIV and ICs among health professionals.

- Thank you for this comment. We nonetheless believe that there are two aspects that have led to better knowledge of HIV testing recommendations among health professionals in Switzerland:
1) The legal responsibility of not performing a recommended test was widely publiziced within the physician community and has led to greater awareness of HIV testing recommendations.
2) GPs and hospital physicians are required to regularly attend continuous medical education events, where HIV testing is frequently discussed.
Further, we have another manuscipt in preparation describing a study in which we observe ‘patient follow-up elsewhere’ as one of the principal reasons for not proposing HIV testing.

Page 11 line 41. You say “In Switzerland, physicians frequently do not discuss sexual behaviour with their male patients, potentially missing those with risk factors”. Are you referring to all specialties, only GPs? What about female patients? Do physicians discuss among them about their sex life?

- Studies regarding disclosure of sexual behaviour to physicians in Switzerland were performed using questionnaires administered in an outpatient setting. The speciality of the physician was not specified. Two studies were performed and only male patients (references 30 & 31) were included, now added on page 11. We believe that sexuality must also be discussed with female patients (especially in certain specialities such as obstetrics and gynecology) but we lack data on this population. However, as this sentence reads oddly, we have removed ‘male’ as we agree that it suggests that this is only a problem with male patients.

Page 11 last paragraph: Please take into account the biggest limitation of your study, not taking into account primary care, it’s probable that most of the included patients had gone to Primary Care before going to the hospital, you are not analyzing missed opportunities in primary care, please mention this issue in this paragraph, not only in the limitations section.

- We agree with the reviewer that mentioning this main limitation whilst presenting the conclusions of the study will give a better insight to the reader. As such we have added a sentence at the end of the paragraph (top of page 12).

Page 12 line 19. You mention that HIV testing implies expenditure by the patient. Could you please better explain? Do you mean that HIV testing is not provided for free in the Swiss health care system? What’s the cost?

- HIV testing when ordered by a physician is covered under the mandate of the federal basic health insurance (LAMal). However, for patients with low health expenditures, this might require out-of-pocket expense if they have a high franchise in order to have lower premiums. In this case, as mentionned above, the cost of the test is 10 CHF plus the consultation (70 CHF total).

Page 12 line 19. You suggest that offering non-targeted screening in ED, as recommended in US, would have enabled diagnosis of 86% of the patients of your sample. Have you calculated how many tests would have been performed during the study period? Have you estimated the number of positive tests you would have found? Do you think it would be a cost-effective intervention?

- The ED receives around 40,000 patients a year. This would amount to 240,000 tests over the study period. The incidence of HIV in Switzerland in 2015 was 6/100.000. We would have anticipated 14.4 positive tests using a blanket testing approach. We doubt this would be cost-effective but this does

not take in account the beneficial (preventive) effects resulting from increased counselling and awareness secondary to blanket testing, notably, with respect to the prevention of onward transmission. We have added a comment on the lack of data on cost-effectiveness at the end of this paragraph.

Please take into account the role of Primary Care in early diagnosis of HIV. You said that “many individuals who need to be tested do not access health care before the event that leads to HIV diagnosis”, can you assure that these individuals haven’t attend Primary Care? Do you have information about it?

- Such data is not routinely collected due to the absence of a centralized database for the whole of the cantonal (or even federal) health care system. We have had to make an assumption as described in the limitation section of the Discussion, and the lack of information regarding primary care remains the main limitation of the study. The manuscript was edited to make the hypothetical nature of this statement clearer.

Tables and figures:
Table 1: Please specify the region, country and study period. Please delete (next to 33.Please substitute IDU by “people who inject drugs (PWID).

- We have performed the suggested modifications.

Figure 1: I suggest represent the data in a table, it’s not necessary a figure. I suggest deleting “As 94 patients presented MOs,…”. Please specify the region, country and study period.

- We have added the region, country and study period but prefer presenting the data as a figure, given that the other reviewers did not object to our choice.

Figure 2: Please specify the region, country and study period. I suggest including the percentages.

- We have performed the suggested modifications.

Table S2: Please specify the region, country and study period.

- We have performed the suggested modifications.

Do you have information about transgender people?

- Yes; there were no transgender individuals among the 201 patients included. We now state this explicitly as an annotation in Table 1.

VERSION 3 – REVIEW

REVIEWER	Cristina Agustí Centre for Epidemiological Studies on HIV/AIDS and STIs of Catalonia, Spain
REVIEW RETURNED	26-Mar-2018

GENERAL COMMENTS	The authors have taken into account my suggested comments. I suggest publishing the manuscript without further revision