

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiological factors associated with the absence of previous HIV testing among HIV-positive persons in Singapore, 2012 to 2017
AUTHORS	Ang, Li Wei; Toh, Matthias Paul Han Sim; Boudville, Irving; Wong, Chen Seong; Archuleta, Sophia; Lee, Vernon; Chow, Angela; Leo, Yee-Sin

VERSION 1 – REVIEW

REVIEWER	Champenois, Karen Inserm U995, ATIP-Avenir
REVIEW RETURNED	07-May-2021

GENERAL COMMENTS	<p>Review BMJ Open 2021 Missed opportunities for early HIV diagnosis: Epidemiological factors associated with the absence of previous HIV testing among HIV-infected persons in Singapore, 2012 to 2017 bmjopen-2021-050133</p> <p>Review submitted 7/05/2021</p> <p>Based on national surveillance data, the manuscript describes characteristics of people newly diagnosed with HIV in Singapore in 2012-17, especially according to the presence of previous HIV test and stage of HIV infection at diagnosis. The manuscript is clear, the methods are adapted to meet the objectives. This manuscript contributes few to the general knowledge on the topic but is certainly important to understand the local epidemic.</p> <p>I have concerns about the wording: - Diagnosis at an early stage of HIV infection was defined by the authors as CD4 at diagnosis >200/mm³. We usually define late stage when CD4>350/mm³; this threshold represents a loss of chance for patients' health. Furthermore, authors add no precision on acute stage of disease when CD4 could be under 200. - In the published papers on missed opportunities for HIV testing, a missed opportunity is defined as a contact with care in which the provider does not offer an HIV test despite an HIV indicator (clinical or behavioral).</p> <p>The objectives is "This study seeks to elucidate epidemiological factors associated with the absence of previous HIV testing prior to their diagnosis among cases diagnosed at both early and late stages of HIV infection"</p>
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	<p>The authors assumed that people had different characteristics depending on the stage of infection at diagnosis (that is certainly right). Except for the multivariate analysis, patients included in the analysis were described together without any adjustment for this variable.</p> <p>Detail comments</p> <ul style="list-style-type: none"> - Patients with no CD4 count at diagnosis or with no information on HIV testing history were excluded (12% of the initial sample). They should be compared on the main characteristics with those enrolled to assess the potential selection bias - It seems a lot of information was collected at the mandatory declaration. The authors should specify how these data were collected from patients: self-administered questionnaire, face-to-face interview with the physician, It can be interesting to interpret some results - Exclusive classification has been made for the type of partners, this should be specified in the methods part - I am surprised by some of the results: 75% of people aged 15-24 reported a previous HIV testing; 95% of patients were men with "only" 60% of homo/bisexuality; and women had less likely to be tested before diagnosis than men (despite antenatal screening). It's not the same epidemiology that in Europe! - 93% of people who had ever been tested reported a negative test. What about the other 7%? Were they report positive results? It might be interesting to describe these patients to understand why they retested. Were they lost to follow-up and use testing to come back into care (at what stage?) or it's to check a recent positive test? - Figure 2 is not clear (and quite few informative) - One of limitation enounced is the "The cross-sectional design of our study did not allow us to make inference about the causality of having had no previous HIV testing and the associated factors". I am not sure we expect causality in this kind of context. - "Individuals, especially those at high risk of STIs and HIV, would benefit from having better knowledge about HIV and the symptoms related to acute or advanced HIV infection, as well as the benefits of early diagnosis and linkage to care." I agree with this, but the authors could discuss how spread the information to these people, how improve their risk perception, how enhance their empowerment in health, ... - Discussion may gain in quality in comparing the results with other studies on the topic from other countries (external validity).
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REVIEWER	Girardi, Enrico National Institute for Infectious Diseases "L. Sapienza", Epidemiology
REVIEW RETURNED	12-May-2021

GENERAL COMMENTS	<p>This paper presents factors associated with having a previous negative HIV test in persons diagnosed with HIV AIDS in Singapore</p> <p>This piece of information may be relevant for planning control activity in the country. Data analysis and presentation and comment of results however, have significant limitations</p> <p>The main issue is that the analysis of the association between previous testing and individual characteristics is performed in the whole population and separately for those with early and late diagnosis. No rationale is provided for this second analysis and no</p>
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	<p>specific discussion of the results of these analyses are included in the paper.</p> <p>Specific point Title: The inclusion of the term missed opportunities is inappropriate since the paper does not focus for missed opportunities for early HIV diagnosis such as testing in STI clinics or in ED or the like Abstract :The results section is confused and should be focused on the results related to the main objective of the study Introduction: The statement “In recognition of the major consequences of undiagnosed HIV infection, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and partners launched the 90–90–90 targets” looks inaccurate. The 90-90-90 targets reflect mainly the recognition of the “treatment as prevention” principle</p> <p>Methods: Classification for mode of HIV transmission, occasion of first testing and reasons for not having previous test should be reported. More importantly it should be reported how this information were obtained, eg. though a structured questionnaire, an interview etc. be reported</p> <p>The discussion needs to be completely restructured. It does not effectively summarize the study results or discuss these results in relation of previous published findings Some conclusions are not based on the results : eg “ This study highlights the missed opportunities for early diagnosis in persons at risk of HIV infection who do not undergo regular testing” – there are no data on missed opportunities . “This study demonstrated the usefulness of anonymous testing as an avenue to facilitate early diagnosis of HIV in Singapore” there is no analysis of the role of anonymous testing in facilitating early diagnosis.</p>
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VERSION 1 – AUTHOR RESPONSE

COMMENTS TO AUTHOR:

Reviewer: 1

Dr. Karen Champenois, Inserm U995

Comments to the Author:

Review BMJ Open 2021

Missed opportunities for early HIV diagnosis: Epidemiological factors associated with the absence of previous HIV testing among HIV-infected persons in Singapore, 2012 to 2017

bmjopen-2021-050133

Review submitted 7/05/2021

Based on national surveillance data, the manuscript describes characteristics of people newly diagnosed with HIV in Singapore in 2012-17, especially according to the presence of previous HIV test and stage of HIV infection at diagnosis.

The manuscript is clear, the methods are adapted to meet the objectives. This manuscript contributes few to the general knowledge on the topic but is certainly important to understand the local epidemic.

I have concerns about the wording:

- Diagnosis at an early stage of HIV infection was defined by the authors as CD4 at diagnosis >200/mm³. We usually define late stage when CD4>350/mm³; this threshold represents a loss of chance for patients' health. Furthermore, authors add no precision on acute stage of disease when CD4 could be under 200.

Reply: We note that there are varying definitions for late-stage infection, which limits the comparability between studies [a,b]. Some studies used a combination of laboratory-based definitions, such as CD4 count <200 cells/mm³ [c] or <350 cells/mm³ [d], and a clinical definition based on the occurrence of an AIDS-defining event in three months [c], six months [d,e] or one year [f,g] following HIV diagnosis. We have added the following in relation to the definition of late-stage HIV infection in the Methods section:

"To ensure accuracy in classifying late-stage HIV infection based on CD4 count <200 cells/mm³, efforts were taken to exclude acute infection through the process of contact tracing interviews, which include questions about previous HIV tests. Recency assays to document or confirm acute infections were not done routinely or universally for all persons newly-diagnosed with HIV."

References:

- a) Adler A, Mounier-Jack S, Coker RJ. Late diagnosis of HIV in Europe: definitional and public health challenges. *AIDS Care* 2009; 21(3):284-93.
- b) Antinori A, Coenen T, Costagiola D, Dedes N, Ellefson M, Gatell J, et al; European Late Presenter Consensus Working Group. Late presentation of HIV infection: a consensus definition. *HIV Med.* 2011;12(1):61-4.
- c) Jeong SJ, Italiano C, Chaiwarith R, Ng OT, Vanar S, Jiamsakul A, et al. Late Presentation into Care of HIV Disease and Its Associated Factors in Asia: Results of TAHOD. *AIDS Res Hum Retroviruses.* 2016;32(3):255-61.
- d) Mocroft A, Lundgren J, Antinori A, Monforte Ad, Brännström J, Bonnet F, et al; Late presenters working group in COHERE in EuroCoord. Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. *Euro Surveill.* 2015;20(47). doi: 10.2807/1560-7917.ES.2015.20.47.30070.
- e) Longo B, Pezzotti P, Boros S, Urciuoli R, Rezza G. Increasing proportion of late testers among AIDS cases in Italy, 1996-2002. *AIDS Care.* 2005;17(7):834-41.
- f) Rosinska M, Janiec J, Niedźwiedzka-Stadnik M. Increase of new HIV diagnoses among men who have sex with men in Poland, 2000 to 2011. *Euro Surveill.* 2013;18(48):20642.
- g) Dai SY, Liu JJ, Fan YG, Shan GS, Zhang HB, Li MQ, et al. Prevalence and factors associated with late HIV diagnosis. *J Med Virol.* 2015;87(6):970-7.

- In the published papers on missed opportunities for HIV testing, a missed opportunity is defined as a contact with care in which the provider does not offer an HIV test despite an HIV indicator (clinical or behavioral).

Reply: We have revised the title of the manuscript and removed the description of "missed opportunity" accordingly.

The objectives is "This study seeks to elucidate epidemiological factors associated with the absence of previous HIV testing prior to their diagnosis among cases diagnosed at both early and late stages of HIV infection"

The authors assumed that people had different characteristics depending on the stage of infection at diagnosis (that is certainly right). Except for the multivariate analysis, patients included in the analysis were described together without any adjustment for this variable.

Reply: As the stage of infection was used as a stratifying variable, it could not be included in the multivariable regression analyses.

Detail comments

- Patients with no CD4 count at diagnosis or with no information on HIV testing history were excluded (12% of the initial sample). They should be compared on the main characteristics with those enrolled to assess the potential selection bias

Reply: We have added a supplementary table on comparison of the 391 HIV-positive persons who were excluded from our study and the 2188 who were included in the analysis. We have also added a paragraph to compare the characteristics between these two groups.

- It seems a lot of information was collected at the mandatory declaration. The authors should specify how these data were collected from patients: self-administered questionnaire, face-to-face interview with the physician, It can be interesting to interpret some results

Reply: We have added how the information was collected from the HIV/AIDS cases in the Methods section.

- Exclusive classification has been made for the type of partners, this should be specified in the methods part

Reply: We have specified the mutually exclusive classification of the type of sexual partners in the Methods section.

- I am surprised by some of the results: 75% of people aged 15-24 reported a previous HIV testing; 95% of patients were men with "only" 60% of homo/bisexuality; and women had less likely to be tested before diagnosis than men (despite antenatal screening). It's not the same epidemiology that in Europe!

Reply: In Singapore, the proportion of women diagnosed with HIV/AIDS has been extremely low (<10%), which is in stark contrast to that of the Southeast Asian region where women constitute about 40% of HIV diagnoses. MSM tend to be younger and are more likely to go for HIV testing. We have added the following observation in the Results section:

"There was a significant decreasing trend in the age-specific proportion having prior test(s) before HIV diagnosis; this proportion declined from 74.5% in age group of 15-24 years to 23.0% in those aged 55-64 years and 7.4% in elderly persons aged 65 years or older (p for trend <0.0005)."

- 93% of people who had ever been tested reported a negative test. What about the other 7%? Were they report positive results? It might be interesting to describe these patients to understand why they retested. Were they lost to follow-up and use testing to come back into care (at what stage?) or it's to check a recent positive test?

Reply: We have added the following paragraph in the Results section:

"Of the remaining 80 HIV-positive persons who had previous HIV tests but last test prior to diagnosis was not negative, 59 reported positive result (24 tested overseas, 23 tested at anonymous test sites,

4 at other places and 8 were unknown) and 21 reported indeterminate results (no information on the test site). Of the 59 HIV-positive persons with previous positive test result for HIV, 30 (50.8%) were detected via voluntary screening, 17 (28.8%) via medical care, 8 (13.6%) via routine programmatic HIV screening and 4 (6.8%) via other modes. The median duration from the last positive test to HIV diagnosis was 1.1 years (IQR 0.2–5.9).”

We do not have information on the reason for subsequent testing after their previous positive result.

- Figure 2 is not clear (and quite few informative)

Reply: We have removed Figure 2 from the revised manuscript.

- One of limitation enounced is the “The cross-sectional design of our study did not allow us to make inference about the causality of having had no previous HIV testing and the associated factors”. I am not sure we expect causality in this kind of context.

Reply: We have removed this sentence from the revised manuscript.

- “Individuals, especially those at high risk of STIs and HIV, would benefit from having better knowledge about HIV and the symptoms related to acute or advanced HIV infection, as well as the benefits of early diagnosis and linkage to care.” I agree with this, but the authors could discuss how spread the information to these people, how improve their risk perception, how enhance their empowerment in health, ...

Reply: We have added the following in the Discussion section:

“The Singapore Health Promotion Board has been working with partner organisations to conduct programmes and campaigns targeted at high-risk individuals to urge them to go for early and regular HIV testing. Various educational programmes on HIV prevention and management are conducted using a lifestyle approach in order to reach out to at-risk individuals through social settings.”

- Discussion may gain in quality in comparing the results with other studies on the topic from other countries (external validity).

Reply: We have cited a few more studies and references in the Discussion section.

Reviewer: 2

Dr. Enrico Girardi, National Institute for Infectious Diseases "L. Sapienza"

Comments to the Author:

This paper presents factors associated with having a previous negative HIV test in persons diagnosed with HIV AIDS in Singapore This piece of information may be relevant for planning control activity in the country. Data analysis and presentation and comment of results however, have significant limitations The main issue is that the analysis of the association between previous testing and individual characteristics is performed in the whole population and separately for those with early and late diagnosis. No rationale is provided for this second analysis and no specific discussion of the results of these analyses are included in the paper.

Reply: We have added in the revised manuscript that the factors associated with no previous HIV

testing were deemed to differ depending on the stage of infection at diagnosis, hence separate analysis was conducted for those with early and late diagnosis. Moreover, the stage of infection was deemed as more of an outcome variable rather than a factor for having no prior HIV tests prior to positive diagnosis.

In the Discussion section, we first mentioned the four common risk factors that were associated with no previous HIV testing in multivariable analyses for both early and late stages of HIV infection at diagnosis, followed by the two additional risk factors identified in the separate analysis for early-stage HIV infection (women and Malay ethnicity). We have restructured the discussion and elaborated more on the key results.

Specific point

Title: The inclusion of the term missed opportunities is inappropriate since the paper does not focus for missed opportunities for early HIV diagnosis such as testing in STI clinics or in ED or the like

Reply: We have revised the title of the manuscript and removed the description of “missed opportunity” accordingly.

Abstract :The results section is confused and should be focused on the results related to the main objective of the study

Reply: We have revised the results section of the Abstract to focus on the independent risk factors identified in the multivariable logistic regressions.

Introduction: The statement “In recognition of the major consequences of undiagnosed HIV infection, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and partners launched the 90–90–90 targets” looks inaccurate. The 90-90-90 targets reflect mainly the recognition of the “treatment as prevention” principle

Reply: We have removed the first part of the statement “In recognition of the major consequences of undiagnosed HIV infection”.

Methods: Classification for mode of HIV transmission, occasion of first testing and reasons for not having previous test should be reported. More importantly it should be reported how this information were obtained, eg. though a structured questionnaire, an interview etc. be reported

Reply: We have included the classifications and described how the information was obtained in the Methods section.

The discussion needs to be completely restructured. It does not effectively summarize the study results or discuss these results in relation of previous published findings Some conclusions are not based on the results : eg “ This study highlights the missed opportunities for early diagnosis in persons at risk of HIV infection who do not undergo regular testing” – there are no data on missed opportunities . “This study demonstrated the usefulness of anonymous testing as an avenue to facilitate early diagnosis of HIV in Singapore” there is no analysis of the role of anonymous testing in facilitating early diagnosis.

Reply: We have restructured the Discussion section.

The description on “missed opportunities” has been removed from the title and the revised

manuscript.

We have removed the sentence on the usefulness of anonymous testing as an avenue to facilitate early diagnosis of HIV, as it has been alluded to in another sentence “At-risk individuals who go to anonymous test sites are more likely to have HIV testing on a regular basis or at a shorter inter-test interval.”

VERSION 2 – REVIEW

REVIEWER	Girardi, Enrico National Institute for Infectious Diseases "L. Sapienza", Epidemiology
REVIEW RETURNED	02-Aug-2021
GENERAL COMMENTS	The issues raised in my previous review have been adequately addressed