

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A comparison of effectiveness between oral rapid testing and routine serum-based testing for HIV in an outpatient dental clinic in Yuxi prefecture, China: a case-control study
AUTHORS	Li, Shifu; Su, Shu; Li, Shunxiang; Gao, Liangmin; Cai, Ying; Fu, Jincui; Guo, Chunyuan; Lu, Wei; Cheng, Feng; Jing, Jun; Chen, Liang; Zhang, Lei

VERSION 1 - REVIEW

REVIEWER	Carmen Figueroa World Health Organization
REVIEW RETURNED	26-Oct-2016

GENERAL COMMENTS	<p>Congratulations on how the manuscript is written.</p> <p>In my opinion there is enough evidence already comparing standard testing versus rapid testing provided by a health care workers.</p> <p>My suggestion is that you re-structure your research to find an innovative way to offer patients rapid testing, or that you explore other uses of rapid testing such as self-testing or self-sampling or other providers such as lay providers.</p> <p>One comment on the design, please provide reason why participants were recruited in different phases for each approach and potential bias this will introduce in the study.</p>
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REVIEWER	Anthony J. Santella Hofstra University Hempstead, New York USA
REVIEW RETURNED	10-Nov-2016

GENERAL COMMENTS	<p>Overall, good study and manuscript, however, there are points that need to be clarified:</p> <ol style="list-style-type: none">1. There is a considerable body of literature on rapid HIV testing in the dental setting and I don't see any of that literature in your background section. Dental provider studies have taken place and been published from the US, Canada, Australia, UK, Korea, India and CHINA! specific to the dental setting. Patient studies in the US have also been published. I don't see any of these studies included in the Background.2. I'd like more surveillance data on the HIV/AIDS epidemiology not only in China but also specific to the geographic location where the hospital where dental patients were surveyed.3. I'm confused by the study design--the case/control description
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	<p>doesn't make sense the way it's currently laid out.</p> <p>4. Did the inclusion criteria include having to be a dental patient at that hospital?</p> <p>5. Are there concerns about the generalizability of the results because of the one study location?</p> <p>6. Commentary on preference for oral rapid HIV test but you only sampled dental patients?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Carmen Figueroa

Institution and Country: World Health Organization

Competing Interests: None declared

Dear authors

Congratulations on how the manuscript is written.

Response: Thanks for the encouragement.

In my opinion there is enough evidence already comparing standard testing versus rapid oral testing provided by a health care workers.

Response: Thanks. Although there have been multiple studies on rapid oral HIV tests, most of these were conducted in the developed country settings. This research is one of the first studies conducted in China. For the Chinese population, this idea is quite new, and the acceptance rate of rapid HIV testing is unclear as it is associated with the various factors according to the previous studies.

Therefore, it is important to explore and accumulate evidence for PITC in this particular setting. We have added more introduction about the research setting in the background to explain the necessity as below.

“A number of studies from the developed countries like US, Canada, UK and Australia, and other Asian countries such as India and Korea have proved the superior effectiveness of the rapid oral HIV testing method compared with the blood HIV testing method²³⁻²⁹. Recently, a few studies have conducted the evaluation of rapid oral HIV testing in the east part of China^{30 31}, but no studies have been reported in the less developed area of China, like our study setting in Southwest. This location has various ethnic minorities gathered, and the vast majority of illicit drugs in China are trafficked through Yunnan from the 'Golden triangle' of opium production. Thus, injecting drug behaviour is one of the main HIV transmission routes in this area, resulting in one of the highest HIV rates in China^{2 32}. The number of people living with HIV in Yunnan province was 79,915 (1.70‰ of total population) by the end of October 2014, accounting for about one-sixth of the national infected population³³. However, an estimation indicates that nearly half of PLHIV remained undiagnosed in China³⁴. This region may have the possible huge unidentified HIV-positive cases as well, so it is urgent to implement an effective HIV testing method in a general clinical setting to increase the HIV diagnosed rate. Moreover, the acceptance of rapid oral HIV testing among susceptible populations depends on the various factors^{35 36}. So the previous results in other areas cannot represent the residents here, this study is necessary for appropriate health care providers to identify the effects and efficiency of the rapid oral HIV testing method.

Yuxi, with 2.3 million residents, is the third-largest city in Yunnan province in Southwest China. The city is located 100 kilometres south of Kunming, the capital of Yunnan Prefecture, and approximately 300 kilometres north of Vietnam³²”.

My suggestion is that you re-structure your research to find an innovative way to offer patients rapid testing, or that you explore other uses of rapid testing such as self-testing or self-sampling or other providers such as lay providers.

Response: We appreciate reviewer's comment. However, in a real-life clinical setting in China, we need first to ensure PITC works. To our best knowledge, there are 810,000 PLHIV in China and 436,817 were diagnosed, indicating 46.1% PLHIV remained undiagnosed. As part of China's HIV surveillance network, our priority is to ensure PLHIV diagnosed in the most efficient and convenient way. We acknowledge that healthcare provider initiated HIV tests might not be the most innovative approach as similar approaches have been implemented in the international settings, but it represents a critical first step for the Chinese HIV surveillance system to integrate a feasible and reliable approach for HIV testing. We would like to argue that in the current Chinese setting, this is something we can practically conduct and promote. We also acknowledge other new approaches or skills, such as self-testing, lay providers perform HIV testings and opt-out method which could increase HIV testing acceptance rate, these will be our future investigation.

One comment on the design, please provide reason why participants were recruited in different phases for each approach and potential bias this will introduce in the study.

Response: Thanks. The reason for conducting the study this way is to avoid confusion to patients and nurses/doctors. Please note that the study was conducted in a single dental clinic. We have the only venue for this exploratory study. So we could not conduct the same study in parallel in two hospitals for comparison. Besides, there would be heterogeneity between two clinics even we do so. We have considered other possibilities: we randomise the testing approach to the patients, that is, at one time, some receive routine tests, and some receive the rapid tests. As the patients shared the same waiting area, it was hard to approach patients privately. That means the next patients would have the preference if they learn about the options they can choose from. Besides, randomising create confusion for nurses and doctors, as they have to remember which group the patients belong to and conduct the appropriate procedures. Based on these considerations, we recruited the two groups of patients in two different period. Further, our comparison in Table 1 showed no differences regarding demographical characteristics between these two groups, so we are confident that our sampling methods do not contribute to variations that undermine our findings. We have updated the method section as follows.

Method: "This case-control study was conducted at the dental clinic in the Yuxi People's Hospital. This hospital has the best and largest dental clinic in Yuxi, which attracts thousands of patients visit each year. The study was conducted in two consecutive periods for performing routine HIV testing and rapid HIV testing separately. The reason for this design is because we have the only venue for this exploratory study, so we cannot conduct the same study in parallel in two hospitals for comparison. Besides, there would be heterogeneity between two clinics even we do so. We have considered other possibilities: we randomise the testing approach to the patients, that is, at one time, some receive control, some receive the rapid test. However, as the patients were in the same waiting room, it is hard for them not to approach each other privately. That means the next patients would have the preference if they learn about the options they can choose from. Besides, randomising create confusion for nurses and doctors, as they have to remember which group the patients belong to and conduct the appropriate procedure. Based on these considerations, we decided to perform the testings separately in two periods."

Reviewer: 2

Reviewer Name: Anthony J. Santella

Institution and Country: Hofstra University, Hempstead, New York, USA

Competing Interests: None declared

Overall, good study and manuscript, however, there are points that need to be clarified:

Response: Thanks for the positive comments, we have responded and clarified each point as below.

1. There is a considerable body of literature on rapid HIV testing in the dental setting and I don't see any of that literature in your background section. Dental provider studies have taken place and been published from the US, Canada, Australia, UK, Korea, India and CHINA! specific to the dental setting. Patient studies in the US have also been published. I don't see any of these studies included in the Background.

Response: Thanks. We have now added more similar studies from other countries and China to have a comparison in the background.

"A number of studies from both developed and developing countries, such as US, Canada, UK Australia, India and South Korea have demonstrated the benefits of the rapid oral HIV testing method compared with routine serum HIV testing 23-29. Recently, two studies have been conducted to evaluate rapid oral HIV testing in the more developed eastern areas of China^{30 31}. In contrast, whether the same approach can achieve similar level of acceptance and outcomes in the less developed southwestern area of China remained unknown. The region is a home to various ethnic minorities and a major route for illicit drug trafficking in China. As a result, HIV prevalence is far higher than other Chinese regions ^{2 32}. The number of people living with HIV in Yunnan province was 79,915 (1.70‰ of total population) by the end of October 2014, accounting for about one-sixth of PLHIV of the country ³³. As nearly half of PLHIV remained undiagnosed in China³⁴, Yunnan have potentially the largest unidentified HIV cases, suggesting an urgency for effective scale-up of HIV testing in the general population. Further, the acceptance of rapid oral HIV testing in susceptible populations depends on the multiple factors ^{35 36}, and previous findings in other parts of China may not be representative here, this study is necessary for healthcare providers to identify the effects of the approach in the local settings".

2. I'd like more surveillance data on the HIV/AIDS epidemiology not only in China but also specific to the geographic location where the hospital where dental patients were surveyed.

Response: Thanks for pointing this. We have found two references to the local surveillance data on the HIV/AIDS epidemiology and added the content in the background part.

"The region is a home to various ethnic minorities and a major route for illicit drug trafficking in China. As a result, HIV prevalence is far higher than other Chinese regions ^{2 32}. The number of people living with HIV in Yunnan province was 79,915 (1.70‰ of total population) by the end of October 2014, accounting for about one-sixth of PLHIV of the country ³³. As nearly half of PLHIV remained undiagnosed in China³⁴, Yunnan have potentially the largest unidentified HIV cases, suggesting an urgency for effective scale-up of HIV testing in the general population."

"Yuxi, with 2.3 million residents, is the third-largest city in Yunnan province in Southwest China. The city is located 100 kilometres south of Kunming, the capital of Yunnan Prefecture, and approximately 300 kilometres north of Vietnam³²".

3. I'm confused by the study design--the case/control description doesn't make sense the way it's currently laid out.

Response: Thanks. It is a case-control study, but the study was conducted in two consecutive phases. We have explained the approach in method section elaborately as below.

Method: "This case-control study was conducted at the dental clinic in the Yuxi People's Hospital. This hospital was the largest dental clinic in Yuxi and attracted thousands of outpatient visits every year.

The study was conducted in two consecutive phases, each for routine serum HIV testing and rapid oral HIV testing, respectively. We designed the study this way for a number of reasons. We had only one venue for this exploratory study, so we could not conduct the same study in parallel in two clinical settings for comparison. Besides, heterogeneity could be introduced if two clinics were chosen. We have considered other possibilities: such as randomising the type of HIV testing the patients were to receive. However, as the patients shared the same waiting area, it is hard to approach each patient privately. That means the next patients would develop their preference based on other patients' decisions. Besides, randomisation may also create confusions for nurses and doctors to try to remember the group each patient belongs to and conduct the appropriate procedure. Based on these

considerations, we decided to conduct testings in two separate phases”.

4. Did the inclusion criteria include having to be a dental patient at that hospital?

Response: We conducted the study in the dental clinic of the hospital, all the patients here were dental patients, since many manifestations of AIDS started with oral disease. We have mentioned it in the method section.

“This case-control study was conducted at the dental clinic in the Yuxi People's Hospital.”

“As the initial symptoms of AIDS often include oral candidiasis, herpes zoster, herpes simplex, oral bacteria or fungal infection, and recurrent oral ulcer, we chose a dental clinic as our study site for a higher chance to diagnose HIV-infected patients.”

5. Are there concerns about the generalizability of the results because of the one study location?

Response: Thanks. The hospital in our study was the best and largest dental clinic in Yuxi, thousands of patients receive treatment here each year. The participants in the clinic were from various socio-economical and ethnic background so the sample is representative of the local general population in Southwest China. However, we acknowledge that the study may not be representative to the national China, We have added more information to introduce the study setting in the method section. However, multiple research settings may further reduce the selection bias; the future study could consider this point. We have added it as one of the limitations in the discussion.

Method: “The hospital patients were from a diverse socio-economic and ethnic background hence the collected sample is representative of the local general population in Southwest China”.

Discussion: “Fourth, although the study sample is representative of the local general population in Southwest China, the findings may not be generalizable to the whole country”.

6. Commentary on preference for oral rapid HIV test but you only sampled dental patients?

Response: We sampled the dental patients with oral discomfort and sought for medical care. The population may have a higher HIV prevalence than the general patients. In this way, we hope to diagnose more positive cases and evaluate the accuracy of the testing approach in the study. But this approach can be widely used in general clinics. We have explained the reason of the study setting selection in the method.

“As the initial symptoms of AIDS often include oral candidiasis, herpes zoster, herpes simplex, oral bacteria or fungal infection, and recurrent oral ulcer, we chose a dental clinic as our study site for a higher chance to diagnose HIV-infected patients.”

VERSION 2 – REVIEW

REVIEWER	Anthony Santella Hofstra University USA
REVIEW RETURNED	13-Jan-2017

GENERAL COMMENTS	In your responses you indicated that per my earlier suggestion additional studies were added, however, no new references were added. At the minimum, I suggest you review Wang et al in Plos One. There are also numerous studies out of India which can translate to China as well.
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VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Anthony Santella

Institution and Country: Hofstra University, USA

Competing Interests: None declared

In your responses you indicated that per my earlier suggestion additional studies were added, however, no new references were added. At the minimum, I suggest you review Wang et al in Plos One. There are also numerous studies out of India which can translate to China as well.

Response: we appreciated this valuable comments. We have added more studies from India, included all relevant published studies from China, and revised the content of the introduction as below:

“The oral fluid-based test for HIV in India is particularly shown to perform better than the finger stick test, accurate and well accepted by hospital participants 24 30. More recently, two independent studies on rapid oral HIV testing have been conducted in China^{31 32} and demonstrated a high acceptance of oral HIV testing in dentists and willingness to integrate the testing procedure in their clinical practice.”