PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Peer-mediated HIV assisted partner services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol
AUTHORS	Monroe-Wise, Aliza; Mbogo, Loice; Guthrie, Brandon; Bukusi, David; Sambai, Betsy; Chohan, Bhavna; Scott, John; Cherutich, Peter; Musyoki, Helgar; Bosire, Rose; Dunbar, Matthew; Macharia, Paul; Masyuko, Sarah; Wilkinson, Eduan; De Oliveira, Tulio; Ludwig-Barron, Natasha; Sinkele, Bill; Herbeck, Joshua; Farquhar, Carey

VERSION 1 – REVIEW

REVIEWER	Gabriel Culbert University of Illinois at Chicago
REVIEW RETURNED	01-Aug-2020

GENERAL COMMENTS	Thank you for the opportunity to review manuscript 2020-041083, entitled, Peer-mediated assisted partner notification services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol. Partner notification for PWID is clearly an area where research evidence is needed. The protocol as described here, however, is insufficiently detailed to allow other researchers to replicate the study and raises a number of ethical concerns that are inadequately addressed. Eligibility criteria and recruitment procedures are unclear. Partner notification procedures also are vague. It's not clear whether or not partners are actually "notified" of having shared an HIV exposure. The use of biometric identification to reduce re-enrollment in a research study seems like an over-engineered solution to a minor problem and raises significant risks without providing much discernible benefit. The study is described alternately as a cohort study and a comparative efficacy study? If the latter, what are the two groups being compared? Authors state (page 8) that APNS has not been well-studied among PWID, at least one previous study utilized a very similar peer-driven model: Levy JA, Fox SE. The outreach-assisted model of partner notification with IDUs. Public Health Reports. 1998;113(Supp. 1). Authors state (page 8) that "cellular telephones…are the typical modality for APNS". Can the authors provide a citation for this? Several previous studies have used in-person notification (e.g., Brown et al, 2011). Also, on page 9, authors describe APNS as a process that usually occurs by phone. WHO guidelines describe several methods (e.g., in-person, letters, dual referral). Authors mention (page 8 and 9) that cell phone ownership is low among

	PWID in Kenya. Even if true (a citation would be good), would not in-person notification be desirable from the standpoint of ensuring that the identity of the partner is confirmed and the right person gets notified? Also, authors write later that cell phones will be used for the initial contact. Why are different procedures used to notify sex and drug-injecting partners? How are these procedures different? What is the sex partner is also an injecting partner? Page 10, why is HCV testing offered only when test kits are available. Should not all “index participants” receive HCV testing? The eligibility criteria and description of recruitment and screening procedures are a bit muddled. The Authors state, “PE’s work with clinicians at each site…” How are potential index patients identified? Do researchers approach people in a waiting room? Are all NSP clients approached or just those whose HIV+ status is known to clinic staff? How is confidentiality protected when PWID are initially approached? Why would PE’s be looking for index patients? Are these PWID who were identified as potential participants through a chart review? On page 16, authors state that, "All index and partner participants who were positive for HIV or HCV complete a six-month follow-up visit.” Aren’t index patients by definition HIV-positive? As described here, the recruitment process is not replicable. The use of an iris-scanning biometric device to ensure that a participant does not enroll more than once is not well justified. The risks to participants from the use of this sort of technology seem to outweigh the benefit to subjects or researchers. Why not use a government-issued ID, or name date of birth? What would be the reason (or harm) for participants to enroll more than once? Did the researchers examine the acceptability (potential for loss of privacy) of this technology beforehand? Why would partners consent to biometric identification before even knowing the reason for having been approached by researchers/PE’s? Have any other studies utilized biometric identification? Beyond preventing re-enrollment, how will this information be used or stored? Biometric identification should be included in Figure 2. What is the rationale for using a 3-year contact tracing period? Does the 3 years refer to the 3 years before the index patient was diagnosed? Can a person enroll if he has been sexually inactive or had no drug injecting partners in the last 3 years? What about people who say that all their partners have been notified? How much will researchers know about a person’s sex/drug-injecting history before they decide whether or not the person is eligible to participate? Are index patients given any choice as to which, if any, of their partners will be notified and how their partners will be notified? WHO recommends offering multiple PN options. What are index patients told will happen to their partners? The “firewall” between those who do partner elicitation and those who do notification is well conceived. Barcodes to link index patients to their partners is appropriate.

	More information about the types of information that will be elicited on questionnaires (enrollment and follow-up) would be helpful. The procedures for notifying partners does not conform to partner notification. The authors state (page 14), Using a standardized script, PEs inform potential participants that they have been identified as an individual who might be eligible for a research study on HIV and HCV." Why aren't all partners notified that they may have shared an exposure to the virus? Why is this information withheld, especially given the importance of this information in making a decision about whether or not to test? What is the definition of "notified" in this study? What about partners who don't want to join a research study or prefer not to travel to the study site? Should delivery of APNS depend on the partner's interest and willingness to participate in the research? Won't partners wonder why they are being approached to participate in an HIV study? At what point are partners told that they may have shared an exposure with someone who is HIV-positive? What are the procedures for confirming the identity of the partner before recruiting him/her? How many attempts will be made to locate/contact partners before abandoning attempts to notify? Authors state that the first contact with partners will be by phone, but this contradicts what was said earlier about this being an in-person PN intervention. The process for enrolling "partners" as "index patients" results in a less clean study design. How will the researchers address this in the statistical analysis? If the partner (now an index patient) names the original "index patient", what will the researchers do with that information? Little justification is provided for excluding people with a history of IPV. Also, what is the time frame for the IPV assessment (1 month? 1 year?) A recent study from Kenya, for example, suggested that APS is safe and effective for people with a remote history of IPV. Goyette MS, Mutiti PM, Bukusi D, Wamuti BM, Otieno FA, Cherutich P, Golden MR, Spiegel H, Richardson BA. HIV assisted partner services among those with and without a history of intimate partner violence in Kenya. Journal of acquired immune deficiency syndromes. 2018 May 1;78(1):16. Authors state, "Any potential partner who is classified as high IPV risk…" This sentence in confusing. What is a "potential partners"? How will partners be able to appraise their anticipated risk of IPV in the study, if they don't yet know what the study is about or why they specifically have been approached to join? The choice of outcomes makes sense for a larger clinical effectiveness trial. However, there are a number of unanswered questions that warrant investigation in the context of a pilot study. Will PWID consent to join the study? How many partners can they name from the past 3 years? For how many partners will they be able to provide identifying and locating information. Will they consent for their partners to be notified? If yes, how do they want their partners to be notified? Can partners be located from the information that index patients provided? What is the minimum information that index patients must provide to be able to locate partners? A better cascade might be #partners named/#partners with complete contact information/# partner located and notified/ #

	partners who accept HIV/HCV testing/ #partners who test positive/# of new diagnoses/#linked to care. The sample size and power analysis section describes the expected number of partners given the researchers assumptions and under ideal circumstances. The basis for these assumptions (e.g., each index will identify on average two partners) is not specified and it's not truly a power analysis. Suggest revising. Are partners who are HIV+ and HCV+ counted twice? Page 21: This study is described variously as a cohort study and a 2-arm comparative efficacy study. What type of study is this and where is the comparison arm? Given the relative newness of APS for PWID and the lack of detail regarding confidentiality protections, notification procedures, etc., this study can hardly be described as minimal risk (page 21). Please revise to include a full discussion of the anticipated risks, including the risk of psychological distress, social or economic hardship, criminal penalties (for example if notification leads to identifying someone as a PWID), loss of privacy and/or confidentiality. What are the plans for monitoring for social harms? See, for example: Ayala G, Bahati M, Balan E, Chang J, Do TD, Fokeerbux NA, Hassan A, Kerboghossian J, Poonkasetwatana M, Saavedra J, Spieldenner A. Partner notification: a community viewpoint. Journal of the International AIDS Society. 2019 Jul;22(Suppl Suppl 3).

REVIEWER	Dr Van Thi Thuy Nguyen WHO Country Office in Viet Nam
REVIEW RETURNED	26-Aug-2020

GENERAL COMMENTS	Assisted partner notification services (APNS) has been demonstrated as an acceptable and effective approach in identifying HIV cases and linkage to care. Important role of peer educators in delivering APNS has also been reported. This proposed study aims to examine if APNS can be adapted to find, test, and link to HIV and HCV care the sexual and injecting partners of HIV-positive PWID using a network of community-embedded peer educators and identify transmission patterns and risks for onward transmission in phylogenetic analysis. Overall, the protocol is well designed and written. However, I have several comments for improvement: 1. The title: The title of the paper does not truly reflect the study as described in the methodology. APNS in this study is only for HIV index cases not HCV index cases. In addition, partners of HIV index cases including injecting and sexual partners. Thus, not all HIV and HCV positive are people who inject drugs as stated in the title. 2. The methodology: The method described in the protocol showed that APNS is only applied for HIV index cases. HCV testing is just an add in test for all HIV index cases and their partners. This clearly shown in the Figure 2. Thus, this should be very clear in the protocol. If the authors would like to explore and report whether APNS works for PWID with HCV then all the PWID who tested for HIV should also be tested for HCV and those positive with anti-HCV will be considered as HCV index cases and APNS can be offered to these HCV index cases. 3. Other comment:

	• The abstract: objective of the study should also mention the second objective of identification of transmission patterns and risks for onward transmission using phylogenetic analysis. • Only strengths of the study were presented but not limitations in the section of Strengths and limitations of this study. • Confidentiality and safety: The authors stated that sexual partners will be brought to independent facilities which are local health care clinics that serve the general population. It is unclear if any of the health care providers in these clinics will be participated in the study or trained on service delivery for this group of patients. • HCV counselling and care: it may be good to clarify how long would it take to get the HCV RNA results from the central laboratory. • General ethical consideration: the authors stated that the safety monitoring board will meet biennially to discuss study progress and review data including IPV monitoring data. Should the safety monitoring board meet more frequent (quarterly if not monthly) to address any safety issue occurred in a timely manner?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer 1

Authors state (page 8) that APNS has not been well-studied among PWID, at least one previous study utilized a very similar peer-driven model:
Levy JA, Fox SE. The outreach-assisted model of partner notification with IDUs. Public Health Reports. 1998;113(Supp. 1).

Thank you for bringing this article to our attention. We have referenced it when we comment that APNS among PWID has not been extensively studied.

Authors state (page 8) that “cellular telephones…are the typical modality for APNS”. Can the authors provide a citation for this? Several previous studies have used in-person notification (e.g., Brown et al, 2011). Also, on page 9, authors describe APNS as a process that usually occurs by phone. WHO guidelines describe several methods (e.g., in-person, letters, dual referral). Authors mention (page 8 and 9) that cell phone ownership is low among PWID in Kenya. Even if true (a citation would be good), would not in-person notification be desirable from the standpoint of ensuring that the identity of the partner is confirmed and the right person gets notified? Also, authors write later that cell phones will be used for the initial contact.

We have clarified our language around APNS using cellular phones and added several references in the last paragraph of the Introduction section. To our knowledge there are no existing publications describing telephone ownership or usage in this population.

Why are different procedures used to notify sex and drug-injecting partners? How are these procedures different? What is the sex partner is also an injecting partner?

Thank you for informing us that this was not clear. We have clarified our meaning by re-writing that sentence as follows:

“Additionally, our protocol involves referrals to different facilities for injection partners and for sexual partners, as a precaution to ensure safety and confidentiality of index participants.”
Page 10, why is HCV testing offered only when test kits are available. Should not all “index participants” receive HCV testing?

The sentence on HCV testing on page 10 (page 8 in our version) describes routine HCV testing at our study sites that occurs outside of study procedures, to set the stage for what these settings are like and what services are offered at baseline. We do HCV testing on all index participants as part of study procedures, as described under “Index recruitment and enrollment.” We have clarified this as follows:

“All recruitment sites offer routine HCV testing when kits are available through specific donor-driven projects.”

The eligibility criteria and description of recruitment and screening procedures are a bit muddled. The Authors state, “PE’s work with clinicians at each site…” How are potential index patients identified? Do researchers approach people in a waiting room? Are all NSP clients approached or just those whose HIV+ status is known to clinic staff? How is confidentiality protected when PWID are initially approached? Why would PE’s be looking for index patients? Are these PWID who were identified as potential participants through a chart review? On page 16, authors state that, "All index and partner participants who were positive for HIV or HCV complete a six-month follow-up visit.” Aren’t index patients by definition HIV-positive? As described here, the recruitment process is not replicable.

Thank you for noting that our description of the recruitment process was unclear. We have added some language under “Index recruitment and enrollment” to clarify that we use existing clinical data on HIV-positive clients at each site to identify potential index participants. Additionally, any client who tests positive for HIV during routine testing is invited to participate. PWID are typically initially approached by clinicians who are already aware of their HIV status. We have also clarified that PEs sometimes help clinicians in recruitment efforts by finding individuals in the community if the individuals are not regular clients at the site. We have also clarified the language about who completes 6-month follow-up visits by saying “all indexes and any partners who were positive for HIV or HCV…”

The use of an iris-scanning biometric device to ensure that a participant does not enroll more than once is not well justified. The risks to participants from the use of this sort of technology seem to outweigh the benefit to subjects or researchers. Why not use a government-issued ID, or name date of birth? What would be the reason (or harm) for participants to enroll more than once? Did the researchers examine the acceptability (potential for loss of privacy) of this technology beforehand? Why would partners consent to biometric identification before even knowing the reason for having been approached by researchers/PE’s? Have any other studies utilized biometric identification? Beyond preventing re-enrollment, how will this information be used or stored? Biometric identification should be included in Figure 2.

Re-enrollment of PWID in both academic and government research efforts in Kenya has been a major concern over the past decade, as PWID are motivated by research reimbursement and generally do not have government-issued ID cards. Names can be falsified and many people are not aware of their dates of birth. As such, all serious efforts at studying this population have involved biometrics over the past decade, including academic and government programs. The largest study of PWID in Kenya to date prior to ours, an R01 called the TLC-IDU study, also used biometrics (see link below). We did not

want people to enroll as index participants repeatedly because this would make it difficult for us to analyze our data. The use of biometrics in key populations in Kenya are discussed in the following publications:

https://www.standardmedia.co.ke/sci-tech/article/2001349675/biometrics-system-for-identifying-people-living-with-hiv-ready

https://www.fhi360.org/sites/default/files/media/documents/resource-linkages-uic-guidance.pdf

https://www.iavi.org/phocadownload/userupload/National%20Implementation%20Guidelines%20for%20HIV%20and%20STI%20Programming%20among%20YKPs%202018.pdf

https://www.researchgate.net/publication/237199975_Estimates_of_the_Size_of_key_populations_at_risk_for_HIV_infection_Men_who_have_sex_with_men_female_sex_workers_and_injecting_drug_users_in_Nairobi_Kenya

Kurth AE, Cleland CM, Des Jarlais DC, Musyoki H, Lizcano JA, Chhun N, Cherutich P. HIV Prevalence, Estimated Incidence, and Risk Behaviors Among People Who Inject Drugs in Kenya. J Acquir Immune Defic Syndr. 2015 Dec 1;70(4):420-7. doi: 10.1097/QAI.0000000000000769. PMID: 26226249; PMCID: PMC4624615.

What is the rationale for using a 3-year contact tracing period? Does the 3 years refer to the 3 years before the index patient was diagnosed? Can a person enroll if he has been sexually inactive or had no drug injecting partners in the last 3 years? What about people who say that all their partners have been notified? How much will researchers know about a person's sex/drug-injecting history before they decide whether or not the person is eligible to participate?

We used a 3-year window because this is a commonly used period of time for partners for APNS. The 3-year period is 3 years from the date of enrollment, not from HIV diagnosis. We have changed the word "past" to "three years prior to enrollment" to clarify this. One of our inclusion criteria for index participants is "Willing and able to provide locator information for sexual and/or injecting partners;" hence, a person who has no sexual or injection partners for the previous 3 years would not be eligible. We have never encountered a person who has stated that all partners have been notified, but such a person would still be eligible as our aim is not just to notify and test partners, but also to ensure they are linked to and engaged in care. We ask only the questions required to assess eligibility criteria.

Are index patients given any choice as to which, if any, of their partners will be notified and how their partners will be notified? WHO recommends offering multiple PN options. What are index patients told will happen to their partners?

Index participants may withhold contact information on any individual partners from study staff in the case that they do not want specific partners notified. We have added a sentence in the "Index recruitment and enrollment" section stating that indexes who wish to notify partners themselves are given a 2-week window in which to do so, after which partners are contacted by study staff.

The "firewall" between those who do partner elicitation and those who do notification is well conceived. Barcodes to link index patients to their partners is appropriate.

Thank you; this is noted.

More information about the types of information that will be elicited on questionnaires (enrollment and

follow-up) would be helpful.

We would be glad to include more detailed information about questionnaires in supplementary files if this would be helpful.

The procedures for notifying partners does not conform to partner notification. The authors state (page 14), Using a standardized script, PEs inform potential participants that they have been identified as an individual who might be eligible for a research study on HIV and HCV." Why aren't all partners notified that they may have shared an exposure to the virus? Why is this information withheld, especially given the importance of this information in making a decision about whether or not to test? What is the definition of "notified" in this study? What about partners who don't want to join a research study or prefer not to travel to the study site? Should delivery of APNS depend on the partner's interest and willingness to participate in the research? Won't partners wonder why they are being approached to participate in an HIV study? At what point are partners told that they may have shared an exposure with someone who is HIV-positive? What are the procedures for confirming the identity of the partner before recruiting him/her? How many attempts will be made to locate/contact partners before abandoning attempts to notify? Authors state that the first contact with partners will be by phone, but this contradicts what was said earlier about this being an in-person PN intervention.

You have raised many valid concerns regarding the partner notification procedures and we have clarified the rationale behind these procedures, as well as what happens if an individual does not accompany the HA to the study office, on page 13 in the section "Peer-educator mediated assisted partner services and partner recruitment."

The process for enrolling "partners" as "index patients" results in a less clean study design. How will the researchers address this in the statistical analysis? If the partner (now an index patient) names the original "index patient", what will the researchers do with that information?

We enroll partners any time an index mentions them, regardless of whether they have been an index in the past. We designed the study this way because if we excluded eligible individuals as indexes because they have been partners before, we would bias the data. We can perform data analysis any way we want: we can exclude anyone who has been enrolled as an index from the partner analysis, or we can exclude those who have enrolled multiple times as partners.

Little justification is provided for excluding people with a history of IPV. Also, what is the time frame for the IPV assessment (1 month? 1 year?) A recent study from Kenya, for example, suggested that APS is safe and effective for people with a remote history of IPV. Goyette MS, Mutiti PM, Bukusi D, Wamuti BM, Otieno FA, Cherutich P, Golden MR, Spiegel H, Richardson BA. HIV assisted partner services among those with and without a history of intimate partner violence in Kenya. Journal of acquired immune deficiency syndromes. 2018 May 1;78(1):16.

Thank you for the reference—this paper was written by some of the members of our team, and we have referenced it in our section on general ethical considerations. In the cited study, people with high risk of IPV were excluded, and this study defined "high risk" in the same way that we do—those who report experiencing IPV in the previous month are considered "high risk." Given that essentially all previous published studies on APNS have excluded those with high risk of IPV from being index participants out of a concern for their safety in the post-notification period, it would be ethically questionable to include these participants, despite the evidence that APNS is safe for those who report moderate risk of IPV, as you've noted.

Authors state, "Any potential partner who is classified as high IPV risk…" This sentence in confusing. What is a "potential partners"? How will partners be able to appraise their anticipated risk of IPV in the

study, if they don't yet know what the study is about or why they specifically have been approached to join?

IPV questions are asked during the screening process as we mention in the first paragraph of section 8: Intimate Partner Violence Monitoring. Because we have not yet enrolled these participants but are screening them for enrollment, we refer to them as "potential partners." We have changed the wording to "potential partner participants" to clarify that they are potential participants rather than potential partners. Potential participants, both index and partners, are not appraising their own anticipated risk of IPV in the study—we, the researchers, are appraising their risk during the screening process. After screening they undergo informed consent, during which they learn the procedures of the study and can choose not to enroll if they feel they may be at risk.

The choice of outcomes makes sense for a larger clinical effectiveness trial. However, there are a number of unanswered questions that warrant investigation in the context of a pilot study. Will PWID consent to join the study? How many partners can they name from the past 3 years? For how many partners will they be able to provide identifying and locating information. Will they consent for their partners to be notified? If yes, how do they want their partners to be notified? Can partners be located from the information that index patients provided? What is the minimum information that index patients must provide to be able to locate partners? A better cascade might be #partners named/#partners with complete contact information/# partner located and notified/ # partners who accept HIV/HCV testing/ #partners who test positive/# of new diagnoses/#linked to care.

Please note that this manuscript describes the protocol for an NIH R01-funded research study that is currently in progress. Although we agree that the stated questions are interesting (and we will be able to address some of them in our data analysis), we have described the protocol and research questions that we included in our initial proposal in this manuscript.

The sample size and power analysis section describes the expected number of partners given the researchers assumptions and under ideal circumstances. The basis for these assumptions (e.g., each index will identify on average two partners) is not specified and it's not truly a power analysis. Suggest revising. Are partners who are HIV+ and HCV+ counted twice?

We have revised our sample size section to clarify that our sample size is calculated based on precision of prevalence estimates among partners.

Page 21: This study is described variously as a cohort study and a 2-arm comparative efficacy study. What type of study is this and where is the comparison arm?

We apologize for the confusion. The study is a cohort study. In the Statistical Analysis section, we describe using GEE methods to compare the two study arms. We have removed the language "to compare the two arms of the study" as that is not the intent or design of the study.

Given the relative newness of APS for PWID and the lack of detail regarding confidentiality protections, notification procedures, etc., this study can hardly be described as minimal risk (page 21). Please revise to include a full discussion of the anticipated risks, including the risk of psychological distress, social or economic hardship, criminal penalties (for example if notification leads to identifying someone as a PWID), loss of privacy and/or confidentiality. What are the plans for monitoring for social harms? See, for example: Ayala G, Bahati M, Balan E, Chang J, Do TD, Fokeerbux NA, Hassan A, Kerboghossian J, Poonkasetwatana M, Saavedra J, Spieldenner A. Partner notification: a community viewpoint. Journal of the International AIDS Society. 2019 Jul;22(Suppl Suppl 3).

Thank you for raising this concern. We have changed the language in the second paragraph of the

“General ethical concerns” section to read: “There are a number of potential risks to participants. Risks of conducting APNS include psychological distress, social or economic hardship, criminal penalties, and loss of privacy and/or confidentiality. Study procedures, including confidentiality and counseling procedures, are specifically designed to minimize these risks to participants.” Additionally, we have clarified that our safety monitoring board reviews data on social harms twice per year.

Reviewer 2

1. The title: The title of the paper does not truly reflect the study as described in the methodology. APNS in this study is only for HIV index cases not HCV index cases. In addition, partners of HIV index cases including injecting and sexual partners. Thus, not all HIV and HCV positive are people who inject drugs as stated in the title.

Thank you for pointing this out. While we agree that APNS in this study is only for the HIV index cases and not the HCV index cases, we are nevertheless identifying and linking to care HCV-positive people who inject drugs through our APNS procedures. The title refers to the partners identified, rather than the index inclusion criteria.

2. The methodology: The method described in the protocol showed that APNS is only applied for HIV index cases. HCV testing is just an add in test for all HIV index cases and their partners. This clearly shown in the Figure 2. Thus, this should be very clear in the protocol. If the authors would like to explore and report whether APNS works for PWID with HCV then all the PWID who tested for HIV should also be tested for HCV and those positive with anti-HCV will be considered as HCV index cases and APNS can be offered to these HCV index cases.

We agree, and we may explore whether APNS works for HCV-positive indexes to identify HCV-positive partners in the future.

3. Other comment:
• The abstract: objective of the study should also mention the second objective of identification of transmission patterns and risks for onward transmission using phylogenetic analysis.

Thank you for pointing out this omission. We have modified the language in the first paragraph of the abstract to include the second objective.

• Only strengths of the study were presented but not limitations in the section of Strengths and limitations of this study.

Thank you for pointing out this omission as well. We have added limitations of the study to the Strengths and limitations section.

• Confidentiality and safety: The authors stated that sexual partners will be brought to independent facilities which are local health care clinics that serve the general population. It is unclear if any of the health care providers in these clinics will be participated in the study or trained on service delivery for this group of patients.

Sexual partners are members of the general population and clinicians in these facilities are trained to deliver services to the general population. Clinicians at these sites are not participating in the study: the study’s health advisors collect data from participants at the sites.

• HCV counselling and care: it may be good to clarify how long would it take to get the HCV RNA results from the central laboratory.

We have added a sentence to the HCV counseling and care section describing the typical turnaround time.

• General ethical consideration: the authors stated that the safety monitoring board will meet biennially to discuss study progress and review data including IPV monitoring data. Should the safety monitoring board meet more frequent (quarterly if not monthly) to address any safety issue occurred in a timely manner?

Based on our previous work on APNS in different settings, we believe APNS to be a safe procedure when conducted carefully and conscientiously. Given that our study is not a clinical trial and that our APNS procedures are designed to minimize potential risks, we believe that biennial SMB meetings are adequate.

VERSION 2 – REVIEW

REVIEWER	Gabriel Culbert University of Illinois at Chicago, U.S.
REVIEW RETURNED	08-Nov-2020

GENERAL COMMENTS	RE: Manuscript bmjopen-2020-041083.R1 Peer-mediated assisted partner notification services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol. Thank you for the opportunity to read the revision of this manuscript. In general, the authors have done a good job of responding to my comments. MAJOR 1. The authors have described this as a study of assisted partner notification services (APNS) for HIV; however, no partners are actually notified. Partners are never told that they may have shared an HIV exposure with someone who was HIV-diagnosed unless they refuse participation in the study or are notified by index patients themselves and without the assistance of PE's/HA's. In explaining their decision to withhold this critical information, the authors say that PE's were uncomfortable notifying partners; however, this lack of preparation is a training issue (PE"s receive one day of training only, which perhaps is why they are uncomfortable serving as notifiers), and not a reason to forgo the most important step in partner notification. Also the ethical issue of denying people information that could save their life or at least help them make informed decisions is not addressed. Notifying people that they have shared an exposure to the virus can increase their risk awareness and lead to HIV risk reduction even if the person never tests for HIV – that's why partner notification guidelines emphasize the importance of explicitly telling partners the name of the virus and that the public health department [or researchers in this case] have credible information that the person may have been exposed to HIV. The authors acknowledge the purpose of APNS (page 7) is to "alert [partners] to their exposure and arrange testing". The approach described here (contacting partners and inviting them to participate in a research study without ever telling

	them that they were named as a partner by a person diagnosed with HIV) is not partner notification; and authors are requested, therefore, to revise the title, abstract, and manuscript to make clear that notification of partners was not included in the study protocol (except for those who refused participation). 2. It's unclear what PE's say to partners to encourage them to accompany the PE back to the healthcare facility; yet this is a key step in the protocol. Request to include the IRB approved recruitment script as an appendix. MINOR Please include the contact tracing period (3 years before study enrollment) in the abstract. Authors state in response letter that a 3-year contact tracing period is commonly used but do not say why? Please provide a rationale for the contact tracing period. The first paragraph under Strengths and Limitations (page 4) describes this as a study investigating APNS for HIV and HCV in PWID. However, contact tracing (not actually APNS since partners were not notified) was only offered to people living with HIV. Might it be clearer to say, "This study investigated PE-assisted contact tracing for HIV and HCV in HIV-positive PWID in Kenya"? In revising the title and abstract, please note that HCV contact tracing was only performed for those with HIV infection. Also, please clarify in the abstract and manuscript whether HCV testing was offered to all partners or only to partners of HCV+ index patients? Please revise for grammar and punctuation (e.g., page 4, "They and are known and trusted within the PWID community [to] conduct partner…") Please revise the phrase "elusive target" (page 5, Introduction). Are the authors referring to gaps in the HIV treatment cascade? If so, please state and, if possible, provide more recent data for regional cascade, including for PWID in East Africa or Kenya if available. According to 2019 data on AVERT, care cascade for Kenya is 90%-82%-92% (https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/kenya). If possible, please provide an estimate for DAA coverage in Kenya or citation to support the statement. "Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of HCV-infected individuals living with HCV have been treated, prompting attention to micro-elimination strategies." Page 7: Statement, "…we will see differences in HIV and HCV testing…" is vague. Do the authors mean increases in HIV testing? Compared to what? The phrase "unique transmission patterns and risks…" is also vague. What hypotheses drive the phylogenic analysis? Page 6: The statement, "Similar to FSW and MSM, PWID engage in behavior that is criminalized…" is perhaps too broad a characterization given the considerable variation between countries in criminal statutes related to sex work, same-sex behaviors, and drug use/possession.

	Follow-up procedures for index patients who choose to notify partners themselves (i.e., self-notification or passive referral) are unclear. How will researchers follow-up with partners who are notified by index patients themselves within the 2 week period and without assistance form PE's or HA's? Presumably, at least some partners notified via passive referral will know that they were exposed to HIV and thus possibly more incentivized to complete HIV testing. How will researchers account for this difference in evaluating HIV testing rates in partners notified using passive referral versus those referred by PE's and tested by HA's? Page 7: Authors state, "Typically, APNS is conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone to alert them to their exposure and arrange testing ." Please revise to make clear that WHO guidelines do not specifically endorse any particular method (in-person, cell phone, email) for the initial contact. For example, some U.S. health departments require in-person notification to prevent misidentification and breaches of confidentiality. Please clarify how PE's will confirm that they have correctly identified the partner before inviting him/her to enroll as a partner and which partner identifiers (e.g., name, physical description, date of birth) will be used. The explanation about why sex partners are referred to community clinics (to avoid revealing possibly that the index person was a PWID) is somewhat clearer and justifies having separate referral processes for persons named as sex and drug-injecting partners. However, it's not clear (page 7-8) what the safety issues are or how referral to separate facilities will address those issues. Why not give partners a choice as to where they want to receive testing and care? What if someone is both a sex and drug-injecting partner? Page 8: Authors state, "All participants who are diagnosed with either HIV- or HCV-infected then complete a 6-month follow-up visit to assess linkage to and engagement in care." The authors have written that HCV contact tracing was only for index participants with HIV infection. The words "either…or" in this sentence are confusing because it makes it sound as if people who are HIV+ or HCV+ can enroll and will complete a 6-month follow-up. Perhaps, "All participants, including any partners diagnosed with HIV or HCV through the study, completed a 6-month…" Page 8: Please revise "…who works with the study team to ensure that indexes are HIV-positive." Perhaps, "…works with researchers to ensure that only participants with documented HIV infection are enrolled?" How? Page 8: "…medically assisted therapy (MAT)" Are the authors referring to medication-assisted treatment (MAT) for opioid dependence with methadone or buprenorphine? Page 9: "This study includes index participants and their sexual and injecting partners". Please consider revising as "..and/or drug-injecting partners".

	Page 9: “As such, partners need not be PWID or HIV-positive but are defined by their relationships with indexes.” This statement seems redundant since researchers have no information about partners prior to contacting them except what they were told by index patients, which is only used to recruit the partner, not to establish eligibility. Please clarify the study eligibility criteria for partners here or just remove this statement and instead reference Table 1. In Table 1, it appears that partners are eligible who “injected with the index patient…or had sexual intercourse with the index in the last three years [typo “HIV positive”]. Are “drug-injecting” and “sexual intercourse” defined for the participant? Are partners who engaged only in oral sex eligible to participate? What about minors (less than 18 years of age) who are named as partners? Page 10: “…women who inject drugs are more easily accessed by women PEs.” Please consider revising as “…women who inject drugs may be more easily accessed by women PEs.” Page 10-11: Authors write, “…PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study.” One day seems like a short time to train PE’s to be notifiers. How were PE’s trained, monitored, and supervised to ensure fidelity? Authors state that “all potential indexes are re-tested using HIV rapid tests…to confirm HIV status”. Is confirmatory testing done by researchers or non-study clinicians? If HIV confirmatory testing is done by non-study clinicians, how do researchers verify that index participants are HIV-positive? Page 12: What do authors mean by “…engagement history”? Page 14: “…linked to HIV and HCV prevention services before leaving the study site.” How can participants be linked to prevention services before they have left the study site? Perhaps, “…provided information about HIV and HCV prevention services before leaving the study site.” Page 15: Please clarify, “The purpose of this visit is to assess whether engagement in care has changed following APNS procedures.” Does this refer to the index patient or partner? Page 17: Unclear what authors mean by, “Once notified…” Does this mean once the participant is notified of his/her HCV PCR test results? Please clarify. Page 19: What does “offset by…” mean? Please use appropriate statistical terminology here. Page 20: Please provide ClinicalTrials.gov registration number where it is mentioned. Page 22: Suggest revising the dissemination plan to not include the names of conferences where findings might be presented in the future unless the authors have already had abstracts accepted. Page 23: Please double check the name of funding agency (NIDA). Should read, “National Institute on Drug Abuse”. Institute is

	singular unless referring to the National Institutes (plural) of Health (NIH).

VERSION 2 – AUTHOR RESPONSE

MAJOR

1. The authors have described this as a study of assisted partner notification services (APNS) for HIV; however, no partners are actually notified. Partners are never told that they may have shared an HIV exposure with someone who was HIV-diagnosed unless they refuse participation in the study or are notified by index patients themselves and without the assistance of PE's/HA's. In explaining their decision to withhold this critical information, the authors say that PE's were uncomfortable notifying partners; however, this lack of preparation is a training issue (PE"s receive one day of training only, which perhaps is why they are uncomfortable serving as notifiers), and not a reason to forgo the most important step in partner notification. Also the ethical issue of denying people information that could save their life or at least help them make informed decisions is not addressed. Notifying people that they have shared an exposure to the virus can increase their risk awareness and lead to HIV risk reduction even if the person never tests for HIV – that's why partner notification guidelines emphasize the importance of explicitly telling partners the name of the virus and that the public health department [or researchers in this case] have credible information that the person may have been exposed to HIV. The authors acknowledge the purpose of APNS (page 7) is to "alert [partners] to their exposure and arrange testing". The approach described here (contacting partners and inviting them to participate in a research study without ever telling them that they were named as a partner by a person diagnosed with HIV) is not partner notification; and authors are requested, therefore, to revise the title, abstract, and manuscript to make clear that notification of partners was not included in the study protocol (except for those who refused participation).

We apologize for the confusion, and we have re-worded section 4 under "study procedures" to reflect that our study staff do inform potential participants of their possible exposure to HIV and/or HCV prior to enrolling them into the study. We are providing assisted partner services, which in Kenya has been called assisted partner notification services, as all partners who are contacted are also informed of their potential exposure. Based on these comments, we will change the wording of title and of the intervention to the term "assisted partner services" (APS) rather than APNS.

2. It's unclear what PE's say to partners to encourage them to accompany the PE back to the healthcare facility; yet this is a key step in the protocol. Request to include the IRB approved recruitment script as an appendix.

Please see our modifications under "Peer educator mediated assisted partner services." We have changed this wording to reflect the process that the peer educators use when contacting partners. Although they were trained using a standardized script, they only loosely follow this script and are encouraged to allow the conversation to progress naturally. The modifications in the manuscript clarify this.

MINOR

Please include the contact tracing period (3 years before study enrollment) in the abstract. Authors state in response letter that a 3-year contact tracing period is commonly used but do not say why? Please provide a rationale for the contact tracing period.

A 3-year contact tracing period is thought to include the most active recent partners, but does not extend long enough to be problematic for recall or tracing of partners who are mobile. When you extend much beyond 3 years, efforts to trace partners can be greater for little success.

The first paragraph under Strengths and Limitations (page 4) describes this as a study investigating APNS for HIV and HCV in PWID. However, contact tracing (not actually APNS since partners were not notified) was only offered to people living with HIV. Might it be clearer to say, “This study investigated PE-assisted contact tracing for HIV and HCV in HIV-positive PWID in Kenya”? In revising the title and abstract, please note that HCV contact tracing was only performed for those with HIV infection. Also, please clarify in the abstract and manuscript whether HCV testing was offered to all partners or only to partners of HCV+ index patients?

Our study does provide HIV assisted partner services as defined by WHO and the Kenyan Ministry of Health and as described above. We agree that we are not providing assisted partner services for those with HCV. We modified the first Strength and Limitations bullets to ensure that is clear.

Please revise for grammar and punctuation (e.g., page 4, “They and are known and trusted within the PWID community [to] conduct partner…”)

This bullet has been modified.

Please revise the phrase “elusive target” (page 5, Introduction). Are the authors referring to gaps in the HIV treatment cascade? If so, please state and, if possible, provide more recent data for regional cascade, including for PWID in East Africa or Kenya if available. According to 2019 data on AVERT, care cascade for Kenya is 90%-82%-92% (https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/kenya).

We are referring to the global care cascade in this sentence, which is why we said “the most elusive target worldwide.” The point of the sentence is to demonstrate that new ways to find high-risk individuals are necessary worldwide. The citation for that statistic is from 2016. We have modified our language in that sentence for clarity.

Kenya recently published its 2018 HIV report (KENPHIA) showing a lag in testing behind the other two targets, and we have included a reference to this.

If possible, please provide an estimate for DAA coverage in Kenya or citation to support the statement. “Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of HCV-infected individuals living with HCV have been treated, prompting attention to micro-elimination strategies.”

To our knowledge, there are no published data on this. We have included several references to documentation of the small pilot programs that have occurred in Kenya (one as part of a study in which 90 participants were treated, another as part of a pilot in which 88 people were treated).

Page 7: Statement, "…we will see differences in HIV and HCV testing…" is vague. Do the authors mean increases in HIV testing? Compared to what? The phrase "unique transmission patterns and risks…" is also vague. What hypotheses drive the phylogenic analysis?

For "differences in HIV and HCV testing," the end of the sentence explains the differences we are expecting, i.e. "between sexual and injection partners" but we have moved this term to the beginning of the sentence to clarify. We have also added some additional language to clarify the phylogenetic analysis hypothesis.

Page 6: The statement, "Similar to FSW and MSM, PWID engage in behavior that is criminalized…" is perhaps too broad a characterization given the considerable variation between countries in criminal statutes related to sex work, same-sex behaviors, and drug use/possession.

We have modified this sentence to state "behavior that is criminalized in many parts of the world"

Follow-up procedures for index patients who choose to notify partners themselves (i.e., self-notification or passive referral) are unclear. How will researchers follow-up with partners who are notified by index patients themselves within the 2 week period and without assistance form PE's or HA's? Presumably, at least some partners notified via passive referral will know that they were exposed to HIV and thus possibly more incentivized to complete HIV testing. How will researchers account for this difference in evaluating HIV testing rates in partners notified using passive referral versus those referred by PE's and tested by HA's?

We have added clarifying language about passive referral under "Index recruitment and enrollment."

Page 7: Authors state, "Typically, APNS is conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone to alert them to their exposure and arrange testing ." Please revise to make clear that WHO guidelines do not specifically endorse any particular method (in-person, cell phone, email) for the initial contact. For example, some U.S. health departments require in-person notification to prevent misidentification and breaches of confidentiality.

We have changed the wording of this sentence to state "While there are many ways to provide partner services, APS in Kenya is often conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone or physically trace them to alert them to their exposure and provide testing."

Please clarify how PE's will confirm that they have correctly identified the partner before inviting

him/her to enroll as a partner and which partner identifiers (e.g., name, physical description, date of birth) will be used.

We have added a sentence describing the verification process under the section entitled “Peer-educator mediated assisted partner services and partner recruitment.”

The explanation about why sex partners are referred to community clinics (to avoid revealing possibly that the index person was a PWID) is somewhat clearer and justifies having separate referral processes for persons named as sex and drug-injecting partners. However, it’s not clear (page 7-8) what the safety issues are or how referral to separate facilities will address those issues. Why not give partners a choice as to where they want to receive testing and care? What if someone is both a sex and drug-injecting partner?

We have clarified the safety issues for index partners at the end of the “Approach” paragraph. Partners have a choice of where they receive testing if they choose not to participate in the study; however, the study can only operate in the sites that we work with, so if they choose to undergo testing as part of the study, they have to do so in the study sites.

Page 8: Authors state, “All participants who are diagnosed with either HIV- or HCV-infected then complete a 6-month follow-up visit to assess linkage to and engagement in care.” The authors have written that HCV contact tracing was only for index participants with HIV infection. The words “either…or” in this sentence are confusing because it makes it sound as if people who are HIV+ or HCV+ can enroll and will complete a 6-month follow-up. Perhaps, “All participants, including any partners diagnosed with HIV or HCV through the study, completed a 6-month…”

In our study, those completing 6 month follow-up visits are all participants who are positive for either HIV or HCV. By definition this includes all index participants, as they are all HIV-positive. This also includes any partner who has been diagnosed with either HIV or HCV. We have changed the wording to the following: “All index participants, as well as all partners participants who are diagnosed with HIV or HCV, complete a 6-month follow-up visit to assess linkage to and engagement in care.”

Page 8: Please revise “…who works with the study team to ensure that indexes are HIV-positive.” Perhaps, “…works with researchers to ensure that only participants with documented HIV infection are enrolled?” How?

We have changed the sentence to read “works with researchers to ensure that only participants with documented HIV infection are enrolled as indexes, verifying HIV status through re-testing if documentation is not provided.”

Page 8: “…medically assisted therapy (MAT)” Are the authors referring to medication-assisted treatment (MAT) for opioid dependence with methadone or buprenorphine?

We are referring to treatment for opioid dependence with methadone and have changed this to “medication assisted treatment (MAT).”

Page 9: “This study includes index participants and their sexual and injecting partners”. Please consider revising as “..and/or drug-injecting partners”.

This has been revised.

Page 9: “As such, partners need not be PWID or HIV-positive but are defined by their relationships with indexes.” This statement seems redundant since researchers have no information about partners prior to contacting them except what they were told by index patients, which is only used to recruit the partner, not to establish eligibility. Please clarify the study eligibility criteria for partners here or just remove this statement and instead reference Table 1.

This sentence has been removed.

In Table 1, it appears that partners are eligible who “injected with the index patient…or had sexual intercourse with the index in the last three years [typo “HIV positive”]. Are “drug-injecting” and “sexual intercourse” defined for the participant? Are partners who engaged only in oral sex eligible to participate? What about minors (less than 18 years of age) who are named as partners?

Yes, both sexual intercourse and drug injecting are defined for the participant. We have added these definitions to the section “Index recruitment and enrollment” for clarification. Minors less than 18 years of age do not meet the inclusion criteria for partners listed in table 1 (i.e. 18 years of age or older). The typo “HIV positive” has been removed.

Page 10: “…women who inject drugs are more easily accessed by women PEs.” Please consider revising as “…women who inject drugs may be more easily accessed by women PEs.”

This has been revised.

Page 10-11: Authors write, “…PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study.” One day seems like a short time to train PE’s to be notifiers. How were PE’s trained, monitored, and supervised to ensure fidelity?

Peer educators were not trained to be notifiers, but rather to be locators and chaperones, so one day of training was adequate. As we mention in the following sentence, PEs attend quarterly sessions with study leadership so that study-related issues can be addressed. We have added additional clarification:

“PEs are supervised by clinic managers, who are all collaborators in the study.”

Authors state that “all potential indexes are re-tested using HIV rapid tests…to confirm HIV status”. Is confirmatory testing done by researchers or non-study clinicians? If HIV confirmatory testing is done by non-study clinicians, how do researchers verify that index participants are HIV-positive?

The sentence before the one quoted reads “For this study, HIV rapid testing is performed by COs and takes place as part of standard clinic procedures.” We have added the term “non-study” to this sentence to clarify. We have modified the following sentence to read: “If HIV-positive, either newly diagnosed or known to be positive, clinicians approach potential indexes with one of two strategies. Either the clinicians discuss the study directly with potential participants or engage PEs to find individuals and bring them to the study office if they are not regular clients at the site.” In other words, HIV-confirmed clients are referred to the study staff by the clinicians.

Page 12: What do authors mean by “…engagement history”?

This has been modified to read “history of engagement in HIV care.”

Page 14: “…linked to HIV and HCV prevention services before leaving the study site.” How can participants be linked to prevention services before they have left the study site? Perhaps, “…provided information about HIV and HCV prevention services before leaving the study site.”

This has been revised.

Page 15: Please clarify, “The purpose of this visit is to assess whether engagement in care has changed following APNS procedures.” Does this refer to the index patient or partner?

This refers to both indexes and partners. We have clarified that language.

Page 17: Unclear what authors mean by, “Once notified…” Does this mean once the participant is notified of his/her HCV PCR test results? Please clarify.

Yes, this has been clarified.

Page 19: What does “offset by…” mean? Please use appropriate statistical terminology here.

Offset terms are statistical features of both GLM and Poisson equations: https://rpubs.com/Shaunson26/offsetglm

Page 20: Please provide ClinicalTrials.gov registration number where it is mentioned.

This has been added.

Page 22: Suggest revising the dissemination plan to not include the names of conferences where findings might be presented in the future unless the authors have already had abstracts accepted.

This has been removed.

Page 23: Please double check the name of funding agency (NIDA). Should read, “National Institute on Drug Abuse”. Institute is singular unless referring to the National Institutes (plural) of Health (NIH).

This has been corrected.

Thank you again for taking the time to review our manuscript. Please feel free to contact me with any additional questions.

VERSION 3 – REVIEW

REVIEWER	Gabriel Culbert University of Illinois at Chicago
REVIEW RETURNED	22-Jan-2021

GENERAL COMMENTS	I would like to thank the authors for responding to the previous comments and revising the paper. The authors have thoughtfully addressed most of the substantive criticisms. The addition of details regarding recruitment and notification are much clearer. To be even more clear, the authors may wish to include the scripts that were used to guide recruitment and notification of partners as appendices. I appreciate the need for PE's and HA's to be flexible in their approach; however, notification is arguably the most important step and also the step where breaches of confidentiality or other protocol violations are likely to occur. Also, notification is often the step with which providers are least experienced or comfortable and the use of scripts aids greatly in ensuring fidelity and that partners receive the correct information - i.e., partners are told that they were named as partners by someone diagnosed with HIV. The inclusion of recruitment and notifications scripts would also be useful for reproducibility. Thank you for the opportunity to review the revised manuscript and I wish the authors success with this very important work.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Dr. Gabriel Culbert, Politeknik Negeri Jakarta
Comments to the Author:
I would like to thank the authors for responding to the previous comments and revising the paper. The authors have thoughtfully addressed most of the substantive criticisms. The addition of details regarding recruitment and notification are much clearer. To be even more clear, the authors may wish to include the scripts that were used to guide recruitment and notification of partners as appendices. I appreciate the need for PE's and HA's to be flexible in their approach; however, notification is arguably the most important step and also the step where breaches of confidentiality or other protocol

violations are likely to occur. Also, notification is often the step with which providers are least experienced or comfortable and the use of scripts aids greatly in ensuring fidelity and that partners receive the correct information - i.e., partners are told that they were named as partners by someone diagnosed with HIV. The inclusion of recruitment and notifications scripts would also be useful for reproducibility. Thank you for the opportunity to review the revised manuscript and I wish the authors success with this very important work.

Reviewer: 1
Competing interests of Reviewer: None declared.

In response to the reviewer's request for scripts used to train health advisors and peer educators on how to conduct partner notification, we have uploaded the scripts, entitled "Appendix A: Health Advisor Introduction Script" and "Appendix B: Peer Educator Introduction Script" as additional files.

Thank you again for taking the time to review our manuscript. Please feel free to contact me with any additional questions.