Author's response to reviews

Title: Implications of the HIV testing protocol for refusal bias in seroprevalence surveys

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Author's response to reviews: see over
Johannesburg, 10 December 2008.

Dear Editor,

Please find enclosed our revised manuscript “Implications of the HIV testing protocol for refusal bias in seroprevalence surveys”. Below we have laid out our responses to the second set of reviewers’ comments. We thank the reviewers for their continued commitment to improve the quality of our manuscript.

With best regards,

Georges Reniers
Tekebash Araya
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**Reviewer: Patty J Kissinger**

The paper is improved and the purpose better stated. However, there are a few things that are distracting:

1. the authors state that population-based studies are underestimated because of testing techniques, but this study is not population-based, it is hospital-based. They should really only talk about hospital-based studies.

   We are well aware that our sample is not representative for a population-based study, and that is acknowledged in the methods section (4th paragraph), and repeated in the discussion (2nd & 3rd paragraphs). However, our aim is to establish the relationship between the study protocol and the relative magnitude of bias in HIV prevalence estimates. We find that the protocol that most resembles the one from the DHS (and many other population-based surveys), is also the protocol that leads to smallest bias in HIV prevalence estimates in our sample. It is likely that this relationship also holds in a population-based sample, but we do not have the data to test this (we are not aware of a population-based dataset that could be – or has been– used for this purpose).

   Given the concerns of the reviewer, we have now included an additional clarification and disclaimer in the methods and in the conclusion.

   Methods 4th paragraph: “The downside of a medical facility-based study is that it is not necessarily representative of the determinants of participation in population-based surveys (e.g., levels of –undisclosed– prior knowledge of one’s
HIV status may be higher in a health facility sample, and prior knowledge of HIV positive status has been identified as a source of bias in HIV prevalence estimates [28]). Therefore, our estimates of absolute levels of refusal per se cannot be extrapolated to general population surveys, but a health facility-based sample is probably satisfying to identify the type of post-test counseling protocol that minimizes bias (i.e., the relative magnitude of refusal bias under different study protocols).”

Conclusion: “To date, most population-based surveys have followed a protocol that did not involve the return of HIV test results. To the extent that the results from this study can be extrapolated to non-health facility-based settings, they suggest that by not returning HIV test results to respondents, these population-based surveys have minimized the potential for refusal bias”.

2. on page 4, they present a great deal of references for the association between mobility and HIV. This is is not relevant as the paper is not dealing with HIV, but rather acceptance of HIV testing. Did they mean that migration effects estimates of HIV testing rates? This point needs clarification.

Migration or mobility is discussed as one possible source of non-response bias, refusals being another. The point is well taken, however, and the number of references to the literature on mobility and HIV infection have been reduced to four.

3. Even though this is an international setting, the authors could incorporate into their discussion the new CDC guidelines for testing in hospital facilities. Since others may follow suit. The use of the classifications of testing seem to change in the methods. Isn't this study really about opt-out vs. mandatory counseling. If so, stating it as such would make the findings and conclusion clearer.

The 2006 CDC guidelines stipulate recommendations for providing testing and counseling as part of the provision of medical care. While we agree that this is an interesting and potentially contentious issue, we rather not engage in that debate as the focus of our paper is on the implication of the testing protocol for estimates of HIV prevalence (i.e., epidemiological assessment rather than medical practice).

4. On page 12, the sentence "these variables are of little substantive interest in the application and are simply chosen to maximize the predictive power of the regression equation" need further clarification. Like me, many of the readers may be unfamiliar with the Heckman model

In this fragment we indicate that we are not interested in gaining a better understanding of the risk factors of HIV infection (therefore, the effects of these regression coefficients are not discussed any further). We simply defined our regression model so as to maximize the explained variance in HIV status.
5. on page 14, there should be more discussion of why there was so much variability in acceptance by counselor. Was it just personality or were there some structural issues?

The variable consent rates by counselor are indeed interesting. Because counselors were assigned in clusters to wards (two to four counselors covering each ward), the variability in consent rates by counselor is difficult to distinguish from other factors (e.g., admission diagnosis). In addition to personality issues, other structural factors that may have played a role in varying consent rates by counselor are gender (the only male counselor had much lower consent rates), and experience (one counselor who just started service prior to the initiation of the study had the lowest consent rates). Only after the fieldwork was over, we realized that we could have randomly assigned counselors to wards (the analyses presented in this manuscript were not envisioned at the time of the fieldwork planning). In any case, the number of counselors was fairly small to give us statistical power to investigate this further, and we simply use counselor as a statistical control in the analyses.

In the discussion section we have modified the paragraph discussing the counselor effect: “The largest variation in consent is accounted for by the counselors, which suggests that studies interested in minimizing non-response must be careful in the selection and training of their fieldwork team. Unfortunately our study was not designed to assess the possible reasons for the variable study enrollment rates by counselor (e.g., via the randomization of counselors across wards). We have no reason, however, to suspect significant bias in HIV prevalence estimates due to variability in consent attributable to counselors.”

6. Table 1, still seems irrelevant to me. The authors have not justified keeping it in.

The methodology for adjusting for selection bias rests on the identification of a variable that correlates well with HIV status, and is also observed for patients who refuse the test. The admission diagnosis is a variable that gives us that statistical leverage, and Table 1 demonstrates the correlation between the admission diagnosis and the likelihood of being HIV positive. We’d be willing to move Table 1 to an annex, but since reviewer 2 argues for more detail on this issue, we retained it in the current version of the manuscript.

7. All tables need to include the N in the title.

Where relevant, the N’s are reported in the tables. The N’s sometimes vary by analysis or column, and it is therefore difficult to report them in the title.

8. Is it really valid to look at counselors 3, 5, 6 since the numbers were so few?
We simply report on all data, irrespective of the number of patients approached by each counselor. It is true that because of the small number problem, the effects for some of the counselors cannot be estimated (for example in Table 4). By not a priori excluding any counselor, we utilize the maximum available information in each statistical model.

9. On table 4 they present Odds ratios for one and Relative risks for another. This needs clarification. It seems to me that this study is really a cross-sectional, since rapid tests were performed, and not really prospective. Participants were enrolled prospectively. I guess it is arguable, but the statistics should reflect the study design.

The exponentiated form of coefficients – exp(b) – in a multinomial logistic model are “relative risk ratios”; in a binomial logistic regression they are “odds ratios”. A clarification to that effect is now included in the column headers of Table 4.

**Reviewer: Michael Sweat**

The revision of the draft is significantly improved. The paper continues to be of likely interest, largely in the contribution the analysis makes to better understanding potential bias of sampling strategies with HIV seroprevalence surveys. The paper would be enhanced if there were a better description / justification for the assumption that ICD codes correlate with HIV infection status in an unbiased manner. Additionally, the discussion would be enhanced if the limits of generalizing these results beyond hospital-based settings were made more strongly.

- **Major Compulsory Revisions**

(1) The methodology used in the study is strongly predicated on having valid estimates of HIV prevalence estimates across ICD codes. The paper would be much improved with a more detailed justification for how this was derived.

As part of the previous revision, we reformulated the methods section to give more detail as to how we derived estimates of the likelihood of infection for each category of admission diagnosis: “For each entry in Table 1, we calculated the HIV prevalence among those who agreed to test. These percentages are considered a measure of the likelihood of infection, and used as a predictor in an analysis of the covariates of consent. We therefore assume that in each group of conditions listed in Table 1, HIV status is not correlated with the willingness to be tested (e.g., that the HIV prevalence in patients with pneumonia is the same for those who accepted and those who refused the test).” If this is not clear, we are willing to follow the advice of the reviewer as to how to reformulate this fragment.

As for the validity of our approach and assumptions, our justification does not rest on purely theoretical grounds. Instead, we choose an empirical route for testing
the assumptions (as well as possible flaws in statistical models for adjusting refusal bias). The empirical test is presented as Scenario 1 in Table 5. In that scenario, we pretend as if we do not know the HIV status in those who accepted testing without the return of test results, and compare the selection-adjusted estimates of HIV prevalence with observed HIV prevalence. That comparison suggests that the selection-adjusted estimate of HIV prevalence is indistinguishable from the true value.

(2) The discussion and conclusions section would be enhanced by not generalizing the results to non-hospital settings. It is very likely that hospital patients would be much more likely to already know their HIV infection status than in population-based surveys, and already knowing your infection status is likely associated with consent to be tested. Thus, the results of this study would very likely be quite different if conducted in a population setting.

We entirely agree with the remark about differences in prior testing rates in a hospital compared to a random population sample, and their implications for refusal bias in HIV prevalence estimates (see Reniers & Eaton forthcoming in AIDS for a more detailed discussion of prior testing and refusal bias in HIV prevalence estimates). We are not arguing, however, that the absolute magnitude of refusal bias will be the same in a health facility and a random population sample. Instead, we simply argue that bias will be larger in studies with a protocol whereby the return of test results is a condition for study participation compared to a protocol wherein patients or respondents can test without post-test counseling or the return of test results. We find evidence for that in a health facility-based setting, and suggest (with the necessary disclaimers) that the same holds in a random population sample. See also our response to the first query of P.Kissinger.

- Minor Essential Revisions

(1) In the last sentence of the abstract the direction of effects is unclear for the variables listed. For example, rather than “gender”, it should state “female gender”.

The directions of the effects are now included in the abstract: “Other covariates of refusal are age (non-linear effect), gender (higher refusal rates in men), marital status (lowest refusal rates in singles), educational status (refusal rate increases with educational attainment), and counselor.”

(2) Page 5 first full sentence – it should be clarified if ref 33 is referring to a system where clients use the voucher to retrieve existing results, or to be retested.

Done: “Instead, they are given a voucher for retesting at the nearest …”
(3) Page 11 – “Most of these effects remain stable after the introduction of more controls”. The phrase “more controls” is unclear.

Reformulated to: “In Model 2, we introduce a number of additional control variables (i.e., ward of admission, male gender, age, educational level and marital status). The odds of consenting to testing and post-test counseling are twice as high for women as for men. The quadratic effect of age confirms the curvilinear relationship between age and consent described in Table 3. Those with higher educational status are less likely to participate in testing, which confirms the bivariate results in Table 3. In terms of marital status, singles are most likely to consent to testing and post-test counseling. The parameter estimates for the infection likelihood, counselor, and study month, however, hardly change in the presence of these controls.”

(4) First sentence of conclusions is missing the word “of”.

Corrected

- Discretionary Revisions

(1) In the background section, “…are positively associated with HIV status”. Suggest that this read “HIV infection”. The reader cannot currently tell whether the association is with HIV infection or non-infection.

Indeed. Corrected

(2) I interpret many of the findings in the analysis as related to clients deciding to forego an HIV test due to the fact that they already know their HIV infection status. This is especially so given that they are being sampled in a hospital. This possible interpretation is not explored much in the paper. For example, people who know that they are HIV-infected may be willing to provide a blood sample for the study, but do not see the need to be counseled and receive a test result that they already know to be positive.

We could not agree more (see also response to comment #2 and our response to the first comment of P.Kissinger): it is indeed plausible that prior testing rates are higher in a health facility-based study and that may lead to a larger bias compared to a random population sample (again, this is likely to affect absolute levels of bias, not necessarily the relative importance of bias under different study protocols).

Having said that, it is likely that (1) consent for retesting is also lower among those who are aware of their HIV positive status even when the return of test results is not a prerequisite of study participation, and that (2) consent for a survey interview that usually precedes HIV testing in population-based surveys is lower among those who are aware of their HIV positive status.
(3) Page 12 – It is suggested that the rationale for why a comparison between the Heckman probit model and the standard probit model is important to conduct. We’re not sure whether we properly understand this comment, but a comparison of standard probit estimates and (Heckman) selection adjusted probit estimates of HIV prevalence tells us whether or not selection effects result in significant bias. A more formal statistical test of that is presented by $H_0: \rho=0$

(4) Last paragraph of discussion section: “First, we identified a marginally significant downward bias in HIV prevalence estimates under the assumptions of a protocol whereby test results are not returned to respondents”. This is an important finding, and this sentence is too wordy. Suggest a more direct statement, such as, “First, when results are not returned to clients HIV prevalence is lower”.

Reformulated as: “First, we identified marginally significant bias under the assumptions of a protocol whereby test results are not returned to respondents.”

Reviewer: Patrick Sullivan

I appreciate the authors’ responses to my comments and to those of the other reviewers. The manuscript seems much clearer to me in its revision. I would still suggest that the authors consider trying to make very clear the crux of the question and how the Heckman modeling proposes to address the question, as many readers will not be clear about the purpose and what was done without a very focused explanation. Also, the assumption that whether or not a patient has HIV is not related to their willingness to be tested seems problematic. Although the assumption is stated clearly (“HIV status is not correlated with the willingness to be tested”), I think it would be helpful to address whether you think this assumption is true, and how you think it would change your results if it were not true, in the discussion.

We’ve rearranged the discussion section such that the discussion of the main question of interest comes first. In the conclusion, we’ve deleted a fragment that was of secondary interest only and may divert readers’ attention from the main purpose of the study.

In response to the validity of our assumption (and the selection model in general), we refer to the empirical test presented in scenario 1 of table 5. In the paragraph immediately preceding Table 5, we explain that the inclusion of the infection likelihood variable significantly improves our estimates of HIV prevalence.