Bias in HIV prevalence estimates from refusals to be tested in seroprevalence surveys

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Abstract

Nationally-representative HIV seroprevalence surveys are increasingly being relied upon for HIV prevalence estimates. We explore the potential for bias in these estimates because of non-response due to the refusal to be tested. The few studies on this topic have failed to identify any substantial bias, but they typically ignore bias due to refusals that are informed by prior knowledge about one's HIV status. In a sample of respondents from Malawi that had been tested before, we find that HIV positives are five times more likely to refuse a subsequent test than HIV negatives. We use this parameter in simulations that further rely on empirical data from the Demographic and Health Surveys and demonstrate that this factor alone may lead to significant bias in HIV prevalence estimates; particularly in urban areas where HIV prevalence, refusal rates, and coverage of VCT are often higher.

< first draft of the paper with preliminary results >

Background

Most published estimates of HIV prevalence in sub-Saharan Africa are based on inputs from sentinel surveillance data in antenatal clinics (ANC). Because of the importance of reasonably accurate HIV prevalence figures for policy formulation and resource allocation, the validity of these estimates have been subject to extensive scrutiny and often found overestimate true prevalence [1-13]. Bias in ANC-based HIV prevalence estimates is attributed to the representativeness of women attending antenatal clinics and/or the under-representation of remote rural areas in surveillance systems. The identification of biases have led to the development of correction schemes to improve extrapolations from ANC surveillance data [2, 14-16], but questions continue to surround the uniform applicability of adjustment procedures in a variety of settings [12].

Expanding resources and progress in medical technology has brought HIV testing increasingly within reach of nationally representative household surveys and that has generated new prospects of resolving the type and magnitude of bias in ANC sentinel surveillance estimates or to provide a new gold standard for HIV prevalence estimates altogether [10, 17-20]. The inclusion of HIV serostatus testing in several Demographic and Health Surveys (DHS) is pushing the agenda in that respect. Data from such community-based surveys are indeed a valuable addition to ANC estimates, but they are also subject to bias due to limitations of the sampling frame (e.g., the exclusion of high risk groups in army barracks, prisons or migrant worker hostels) and non-response because of population mobility and refusal. The association of population mobility with HIV infection has been documented extensively [12, 21-28]. In comparison, relatively little is known about the relationship between refusal and HIV infection in community-based studies [10, 18, 20]. A number of small-scale studies in STD and antenatal clinics most often conclude that refusals are positively associated with HIV status [29-37]. A few studies remain inconclusive about the nature of the relationship or suggest the opposite pattern [38-40].

In aggregate, population-based seroprevalence surveys are believed to underestimate true HIV prevalence, but the studies that have addressed this issue failed to identify significant bias due to non-response [13, 20, 41, 42]. These studies do not, however, account for the possibility that individuals refuse testing based on prior knowledge of HIV status. We hypothesize that HIV+ individuals who are aware of their HIV status are much less likely to consent to testing in a seroprevalence survey than those who previously tested negative and those who have not had a previous HIV test. Furthermore, we claim that this form of selective refusal may bias HIV seroprevalence estimates based on nationally representative serosurveys; particularly in settings where HIV prevalence, refusal rates, and VCT coverage are relatively high.

First we describe levels of prior testing and refusal rates in a number of Demographic and Health Surveys (DHS) in sub-Saharan Africa and explore their relationship with HIV prevalence. Secondly, we investigate the relationship between prior knowledge of HIV status and consent for testing using longitudinal survey data from Malawi with multiple rounds of HIV testing. We then develop a model of bias in HIV seroprevalence surveys that is based on HIV prevalence, the level of prior testing in a population, the refusal rate and the relationship between prior knowledge and consent for testing. Using that model, we simulate bias in estimates of HIV prevalence and the sex ratio of infections using empirical values of refusal and prior testing rates that we derive from the DHS surveys.

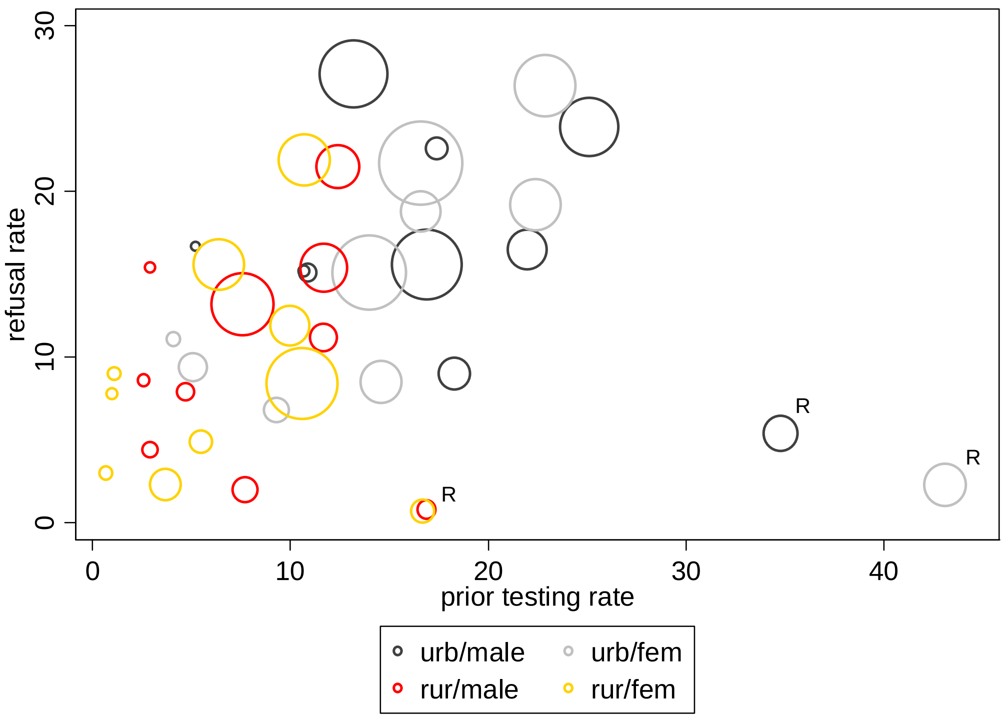
Levels of prior testing and refusal rates in sub-Saharan Africa

The relationships between the prior testing rate, HIV prevalence (size of the circle) and the refusal rate by urban/rural residence and gender for 10 African countries where the DHS have included HIV tests is illustrated in figure 1. Refusal rates range from under 1% for the rural population in Rwanda to close to 30% for males in urban Lesotho. Refusal rates vary quite importantly by urban/rural residence: the median refusal rates in urban and rural areas are 15.4% and 8.5% respectively. The differences in terms of the refusal rates by gender are less substantial. HIV prevalence rates range from 0.4% for males in urban Senegal to 26.3% for urban females in Zambia. As is well described in the literature, HIV prevalence tends to be higher in urban compared to rural areas and to a lesser extent for women compared to men. Rates of prior testing vary from under 1% for females in rural Guinea to 43% for females in urban Rwanda. The median rate of prior testing in urban areas is 16.6% compared to 7.0% in rural areas.

Figure 1 is also very suggestive of a three-way aggregate-level relationship between HIV prevalence, prior testing and refusal. The only deviation from that pattern is Rwanda. It stands out as the country with high prior testing rates and relatively low refusal rates (The observation points for Rwanda in figure 1 are labeled with an ‘R’). Excluding Rwanda, the correlation between either of these variables is greater than 0.5. Provided that the relationship between prior testing and refusal is not spurious[1], that could mean that refusal to be tested in HIV prevalence studies is informed by prior knowledge about one’s HIV status. The fact that refusal rates increase with HIV prevalence as well, further suggests that it is HIV positive individuals in particular who are more likely to refuse. That assertion, however, cannot be verified using DHS data because the HIV status of those who do not consent to testing is unknown (one just knows whether the respondent has been tested before or not).

[1] We verified the ecological correlation in five DHS surveys. The odds of a refusal are between 1.38 and 2.29 times higher among respondents that have been tested before compared to those who have never been tested for HIV.

Figure 1: Prior testing and refusal rates in 10 sub-Saharan African countries by HIV prevalence (size of the circle) , disaggregated by rural/urban residence and sex (in %)



Notes: countries included in the graph are Cameroon (2004), Ethiopia (2005), Ghana (2003), Guinea (2005), Kenya (2003), Lesotho (2004), Malawi (2004), Rwanda (2005), Senegal (2005), and Zambia (2002). Rwanda (the circles labeled with an 'R') stands out with relatively high prior testing rates (particularly in urban areas) and relatively low refusal rates. Source: Demographic and Health Surveys

Prior knowledge of HIV positive status and consent for testing

In order to obtain an empirical estimate of the relationship between prior knowledge of HIV status and consent for testing, we rely on data from the Malawi Diffusion and Ideational Change Project (MDICP). These are longitudinal survey data in three rural district of Malawi whereby respondents were approached for testing in wave three (MDICP3, 2004) and wave four (MDICP4, 2006). The original MDICP sample that was taken in 1998 included around 1,500 ever-married women and their spouses. In MDICP3, the sample was augmented with a group of adolescents (both sexes). In MDICP3, a total of 2,864 individuals were tested using OraSure® saliva swabs. These were processed in the UNC Lilongwe lab with ELISA and Western Blot diagnostics[2]. Post-test counseling was offered in VCT tents in or close by the villages of the respondents one to three months after testing. The second round of HIV testing and counseling took place in 2006, this time using a finger-prick rapid tests (Determine® and UniGold). The respondents

[2] A description of the MDICP project, the data and survey instruments can be found at http:\\www.malawi.pop.upenn.edu. The testing protocol for MDICP3 is described in 43. Bignami-Van Assche S, Smith K, Reniers G, Anglewicz P, Thornton R, Chao LW*, et al.* **Protocol for biomarker testing in the 2004 Malawi Diffusion and Ideational Change Project**. In: *Social Networks Project Working Papers (6)*. Philadelphia: University of Pennsylvania; 2004.

choose the testing location (either in the home or in a VCT tent in the village) and post-test counseling was done 20 to 30 minutes after the test. Respondents were given the option to be tested and counseled about their HIV status or just to provide a drop of blood for research purposes but without post-test counseling or disclosure of the test results.

Of the 2,878 respondents that were tested in MDICP3, 1,954 or 71.8% came back for post-test counseling (1,828 HIV negatives 117 HIV positives and 9 with undetermined result). Of these, 1,444 HIV negatives and 56 HIV positives were contacted again for testing in MDICP4. In this group of respondents, the relative risk of a refusal was 4.94 times higher among HIV positives than in among HIV negatives (95%-CI: 2.55 – 9.57, see Annex I) .

Simulations of bias in HIV prevalence rates in national seroprevalence rates

The finding that refusals are informed by prior knowledge of HIV positive status does not automatically mean that refusals are a source of substantial bias in national or local estimates of HIV prevalence. Both levels of refusal and especially levels of prior testing have been relatively low in many sub-Saharan African countries and the magnitude of bias may therefore be negligible. In order to evaluate the magnitude of this bias, we carry out simulations designed to model the sampling process of individuals for a stratified population-based serological survey such as a DHS.

The model creates a large fictitious population stratified by urban/rural residence and assigns each individual an HIV status and whether or not the individual knows his or her HIV status from a previous HIV test. These individual characteristics are assigned such that the population level aggregates match the estimate obtained in the DHS. That is, if the DHS in Ghana estimates that urban females have HIV prevalence of 2.5 percent, then urban females in the simulated population will have prevalence of 2.5 percent. Similarly if 4.7 percent of rural males in the DHS have had a previous HIV test and received the result, then in the simulated population 4.7 of all rural males will know their HIV status. [3]

The model currently assumes that HIV status and having had an HIV test prior to the survey are independently assigned. This assumption is almost certainly not true; several studies have suggested that individuals who are HIV positive are more likely to know their status [44]. Under this assumption, the model will thus provide conservative estimates of bias in HIV prevalence. In future versions of the model we may seek to quantify and include the relationship between HIV status and knowledge about one's status.

From this large simulated population a stratified random sample is drawn of the same size as in the corresponding DHS. In the case of Ghana, for example, a sample of 11,294 individuals was drawn to match the 2003 DHS. The sample is stratified such that males and females are sampled in equal proportions and individuals are sample proportionally from urban and rural areas following the distribution reported for the year 2000 in the World Urbanization Prospects [45].

Of the sampled population, a random set individuals are identified as 'absent' at the time of testing such that the proportion of missing individuals matches that recorded in each group in the DHS survey. In the

[3] <We are working on a model where the values that we observe from the seroprevalence surveys are 'biased' values, and the outcome from the model the corrected value. Currently we consider the DHS prevalence the true prevalence and the simulated outcomes the observed (biased) values>

model, being absent is assumed to be independent of HIV status. This is also likely to be untrue (Cfr. Infra), but again, this leads to conservative estimates of bias in HIV prevalence.

Finally, for sampled individuals who are 'present at the time of interview' the model probabilistically assigns whether or not each individual refuses to be tested depending on the individuals' HIV status as well as their knowledge about their HIV status. For each individual a random number between zero and one is generated. Those who are unaware of their HIV status 'refuse the test' if the random number is smaller than the proportion in the HIV status naïve population in the corresponding DHS that refused. If the number is greater, then the individual in the simulated sample participates in the HIV test. For example, in the Ghana 2003 DHS 14.35 percent of all urban HIV status naïve men refused. If an urban male in the simulated sample generated a random number of 0.063452 then he would refuse, if the generated random number is 0.44241, then he would accept the test. In aggregate, 14.35 percent of the HIV status naive urban males sampled will refuse the test, although the exact refusal rate will vary slightly for each model draw.

The process is similar for individuals who know their HIV status. Each individual is assigned a random number. However the likelihood of accepting the test will now depend on the individuals HIV status. Based on the MDICP data, an individual who knows he is HIV positive is 4.94 times as likely to refuse as an individual who knows he is HIV negative. The likelihoods of refusal for each of these two groups is calculated so that in aggregate approximately the proportion of individuals who refuse is the same as the proportion of individuals who knew their status in the DHS survey refused. For example, if the HIV prevalence is 15 percent and the refusal rate among those that have been tested before is 10 percent, then a simple calculation reveals that about 31 percent of the individuals who know they are positive must refuse and 6.3 percent of those who know they are negative must refuse.

Finally, the HIV prevalence is calculated amongst the individuals who accepted to participate in the sero-survey. The bias can be assessed by comparing the sample prevalence to the actual fixed HIV prevalence in the population from which the sample is drawn. The comparison may be made across the entire population or within each stratified subgroup.

The model is considered in three different scenarios, where individuals who know they are positive are 2.55, 4.94 and 9.57 times as likely to refuse as individuals who know they are negative (corresponding to the relative risk point estimate and the 95% confidence interval limits). For each country the model is run 500 times for each scenario, producing a distribution of HIV prevalence estimates.

Results <to be completed>

Preliminary simulation results are presented for the Malawi 2004 DHS. Table 1 shows the relevant parameters recorded in the DHS. A total of 7868 individuals were eligible for HIV testing in the DHS. Of these 9.7 percent were not available at the time of testing. Of those present for the household survey, 13.4 percent reported that they had previously received the result of an HIV test. Of those who had been tested previously, 22.1 percent refused to be tested, and of those who had not been tested previously 24 percent refused to be tested for HIV[4]. The national adult HIV prevalence estimated by the DHS is 11.6

[4] Note that in the Malawi 2004 DHS, individuals who had been tested previously were overall *less* likely to refuse than individuals who had not been tested previously. In fact, out of the 10 countries with DHS surveys including HIV testing reported above, Malawi is the only country for which this is true. However, this does not affect the hypothesis that *amongst individuals who know their status*, HIV positive individuals are more likely to refuse than those who have tested negative.

percent. For the purposes of parameterizing the simulation model, each of these figures is stratified by gender and urban/rural residence. These can be seen in Table 1.

Table 1: Parameters reported in Malawi 2004 DHS

	Males		Females		Total		
	Urban	Rural	Urban	Rural			
% Tested Previously	25.1	12.4	22.9	10.7	13.4	**Sample Size =**	7868
% Refusal - Tested Previously	25.4	19.7	27.1	21.7	22.1	**% Urban =**	15.1
% Refusal - Not Tested Previously	28.6	23.5	28.9	23.0	24.0		
% Absent	19.8	13.1	7.0	5.1	9.7		
DHS Sample HIV Prevalence	16.3	8.8	18.0	12.5	11.6		

Table 2 shows the results of the sample simulations based on the Malawi 2004 DHS parameters in Table 1. The first column shows the actual HIV prevalence in the simulated population, for the entire population and each sub-group. Columns two through four give the mean estimate of HIV prevalence in the sample drawn over 500 simulations for the ‘low’, ‘medium’, and ‘high’ assumptions about the likelihood of refusing for individuals who know their HIV status. The ‘low’ scenario corresponds to the assumption that individuals who know they are HIV positive are 2.55 times more likely to refuse than individuals who have tested negative, the ‘medium’ to 4.94 times, and the ‘high’ to 9.57 times. Columns five through seven represent the ratio of the actual population prevalence to the estimate of the prevalence produced by the sample.

In the sample population, the true population prevalence is 11.63 percent, but under the ‘medium’ assumption the sample prevalence is 10.48 percent. The stratified sample underestimates the actual population by about 11 percent. Under the low assumption, the bias is a relatively modest five percent, and under the high assumption the sample prevalence is about 16 percent too low.

However, the amount of bias is considerably greater for selected subpopulations that are more likely to have been tested previously and have high HIV prevalence and refusal rates. For example, while urban males make up only 7.55 percent of the entire population, the sample underestimates prevalence in this group by 23 percent under the medium assumption. Thus, while the bias may be modest in the national estimates of HIV prevalence, it is likely much more severe for subgroups of the population. This finding has potentially severe consequences for appropriately allocating resources for local ARV and VCT programs and generally providing healthcare services to populations that might have a greater burden of disease than that projected by national serological surveys. Furthermore, this suggests that the amount of bias in nationally representative serological surveys may increase in the future as VCT and ARV programs rollout and testing becomes more common.

Table 2: Preliminary Simulation Results for Malawi 2003 DHS

	Population Prevalence	**Sample HIV Prevalence**			**Population Prev/Sample Prev**		
		Low	Medium	High	Low	Medium	High
Malawi	*11.63*	*11.03*	*10.48*	*10.02*	*1.05*	*1.11*	*1.16*
Urban Males	16.30	14.57	13.25	12.08	1.12	1.23	1.35
Rural Males	8.80	8.48	8.04	7.67	1.04	1.09	1.15
Urban Females	18.00	16.29	15.03	13.76	1.10	1.20	1.31
Rural Females	12.50	12.07	11.61	11.19	1.04	1.08	1.12

<Similar results are to be presented for other DHS scenarios, in particular to compare the amount of potential bias in populations with much lower HIV prevalence, prior testing and refusal than Malawi>

Discussion - <to be completed>

- This is merely a suggestive model. It does not replace the need for in depth comparisons of responders and non-responders and is NOT meant to be extrapolated as an adjustment for DHS or other population based sero-surveys

- Weaknesses;
  - only 1 available sample to estimate parameter for the likelihood of refusal based on prior knowledge
  - parameter may vary with the level of refusal: in populations where the refusal rate is higher, it may be less selective, and, in other words to a lesser degree informed by prior knowledge
  - parameter may vary with urban/rural residence and gender
  - so far we only account for refusal conditional on an interview (usually precedes the testing), future models should also include the group of respondents who refused the interview

- In short, this likely value of this parameter needs to be considered on a case by case basis, and much more empirical work needs to be done to grasp how it varies with age, time, sex, residence, and other demographic and behavioral covariates.

- In spite of the uncertainty about this parameter, a wide range of parameters (between 2.55 and 9.57) are tested in the model and at least modest bias is found in each case.

- The simulation model is *conservative* in its assumptions that may lead to increased bias.
  - The model likely underestimates bias because individuals who are HIV positive are more likely to be tested
  - It likely underestimates bias because individuals who are positive are more likely to be absent at the time of testing.
  - A similar phenomenon may be occurring amongst individuals who have not been tested, i.e. individuals who have not been tested but *perceive* themselves to be at higher risk for infection may be more likely to refuse to be tested. Previous work on self-assessed risk of infection has had mixed results, but indeed this relationship should be investigated more.

- Refusal is not the only source of bias in DHS type surveys needs to be analyzed.
  - Sampling frame (no good way to do this…)
  - Mobility ---- USE DSS! Usually records mobility regularly separate from HIV testing.

Annex 1: relative risk of refusal in MDICP4 (t_2) by prior test result (conditional on post-test counseling in MDICP3 (t_1))

```
                 |     t1 HIV+    t1 HIV- |      Total
-----------------+------------------------+------------
      t2 refusal |         9         47   |         56
      t2 consent |        47       1397   |       1444
-----------------+------------------------+------------
           Total |        56       1444   |       1500
                 |                        |
            Risk |  .1607143    .0325485  |   .0373333
                 |                        |
                 |      Point estimate    |    [95% Conf. Interval]
                 |------------------------+------------------------
 Risk difference |         .1281658       |        .03154    .2247917
      Risk ratio |          4.93769       |      2.548762    9.565734
 Attr. frac. ex. |         .7974761       |      .6076527    .8954602
 Attr. frac. pop |         .1281658       |
                 +-------------------------------------------------
                                  1-sided Fisher's exact P = 0.0001
                                  2-sided Fisher's exact P = 0.0001
```

Alternative estimate using poisson regression:

```
. poisson refusalt2 hivt1 if hivt1<8 & postvctt1==1, irr

Iteration 0:   log likelihood = -236.25674
Iteration 1:   log likelihood = -233.44745
Iteration 2:   log likelihood = -233.42932
Iteration 3:   log likelihood = -233.42931

Poisson regression                                Number of obs   =       1500
                                                  LR chi2(1)      =      13.38
                                                  Prob > chi2     =     0.0003
Log likelihood = -233.42931                       Pseudo R2       =     0.0279

------------------------------------------------------------------------------
   refusalt2 |        IRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       hivt1 |   4.937699   1.796586     4.39   0.000     2.419993    10.07477
------------------------------------------------------------------------------
```

Gives the same point estimate but slightly larger confidence intervals

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