Author's response to reviews

Title: Monitoring Entry into Care of Newly Diagnosed HIV-Infected Persons: San Francisco 2006-2007

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Version: 2 Date: 21 July 2008

Author's response to reviews: see over
July 16, 2008

Dr Mark Todd  
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Re: Re-submission of manuscript 8954899671942409 entitled “Monitoring Entry into Care of Newly Diagnosed HIV-Infected Persons: San Francisco 2006-2007” after revision

Dear Dr Todd:

We are submitting the revised manuscript “Monitoring Entry into Care of Newly Diagnosed HIV-Infected Persons: San Francisco 2006-2007”. We are also attaching the point-by-point response to the reviewers and the additional required documents.

We have performed changes to this version of the manuscript that we feel incorporate all the reviewer’s comments.

Please feel free to contact me with any further questions.

Sincerely,

Nicola M. Zetola, MD, MPH

Reviewer 1
Major revisions:

1. My first comment is about the word choice and changing of the word from "entry" to "accessing" HIV medical care. I've been looking through my papers to find the article that demonstrates that many people access care, i.e. have that first visit and never return to receive results of CD4 and viral load tests or have other visits. Therefore, it is difficult to say that these individuals have entered HIV medical care. In other articles "entry into care" is defined as at least 2 visits within 6 months or in a year (some other time frame) with the same HIV medical care provider(s)/clinic. If the authors prefer to use the term “entry into care” then they should define it early -- even briefly in the abstract. Their definition is not written until page 6.

We agree with Reviewer 1 in this regard. However, we chose the word “entry” for exactly that same reason. We felt that the phrase “accessing medical care” was most commonly used for patients who remain in care after their first contact with a health care provider. Without a definition clearly stated in the manuscript, both words/phrases could be misleading. Therefore, we are now defining what we considered “entry to care” in the abstract and expand that definition in the methods sections of the manuscript. Although the selection of words might be arbitrary, we feel that the reader has a clear idea of what we are referring when we talk about “entry to care”.

2. My second comment is that the authors do not tell the reader in the introduction/background the rationale for why looking at CD4 and viral load tests are a good marker for accessing care. This rationale is not presented distinctly until the first paragraph of the discussion, page 9: "CD4 T cell counts and HIV plasma viral load are used to determine stage of disease and are commonly obtained on the first visit of HIV care. Therefore, CD4 T cell counts and HIV plasma viral load could potentially serve as a surrogate marker to evaluate entry into care, and determine unmet health care needs in various communities.” I would suggest the authors move this to the beginning of the article.

That paragraph has been moved to the background section.

3. My third comment is about the validity of self reported medical care visits. As part of the case-management efforts, newly diagnosed HIV infected persons were contacted. During this interview they were asked if they had entered HIV medical care. This response is subject to bias since it is socially acceptable to answer that they were in care. Since self reported entry into care is an acceptable end point, I believe your finding of confirmed entry into care may be overestimated. The authors would strengthen their manuscript and give credence to the case management practice if they present data on the percentage of these self reports that were confirmed by contacting medical care providers or finding a subsequent CD4 or HIV viral load test that corresponds to dates of case's self reported visit.

We agree that the text was not clear regarding the fact that all cases that were initially confirmed to have accessed care by self-report were then corroborated by CD4 counts and/or viral load. Now that paragraph is more explicit in that regard. It now reads: “One hundred and one (101 out of 160 new HIV-infected cases, 63%) patients were initially reported to enter HIV primary care after diagnosis by self-report or by a health provider. The entry into HIV care of all of these 101 patients was corroborated by having records of CD4 T cell counts or plasma HIV viral loads.”

4. My fourth comment concerns other exclusions for CD4 and HIV viral load laboratory tests. The authors excluded individuals who had laboratory tests done on the same date as their first HIV diagnostic test. If the authors are looking for indicators for access to primary HIV medical care then laboratory tests should be restricted to those that were ordered from these medical care centers and excluded if lab tests are ordered at ER visits and/or hospitalizations. The authors should discuss if they can determine who ordered the tests and if they can confirm if this is a primary care practice or
some other medical service. Again, not excluding testing at ER visits or hospitalizations would overestimate the number of cases who have entered into primary HIV medical care. For this analysis we excluded persons with HIV laboratory tests ordered on same day of diagnosis (n=26), assuming these may represent individuals with longstanding infections who underwent HIV testing to document status for services. CD4 T cell counts or HIV viral loads obtained at the emergency department or during a hospitalization were not considered surrogates of entry to HIV primary care. This is now clearly stated in the methods section.

5. My fifth comment is simply sticking to the same terminology throughout the paper. The first is referring to CD4 cell counts and HIV viral loads which are sometimes referred to as CD4 tests, CD4 T cell counts, HIV viral loads, plasma HIV viral loads, plasma HIV-1 viral loads, plasma viral loads, and viral load tests. When first introduced, the most formal names should be used; and in parentheses, the simple names you'll be using throughout the rest of the text can be introduced: for example, CD4 T cell counts (CD4 tests) and plasma HIV viral loads (viral loads). Secondly, the case management intervention in the abstract is called an “interview by SFDPH staff”, in the last sentence of the background a “patient contact”, and in the methods it is described as many things: a “contact, disclosure, and referral”. Yet, there appears to be a difference between contact through letters and an interview with a case manager for a referral. I strongly suggest that the definition/wording of intervention of interest be clearly used. One suggestion for use is “case-manager interview and referral to HIV medical care”, because it is not the interview or the contact itself that is leading to entry into care.

We agree with Reviewer 1 and we have adopted the term “case-manager interview and referral to HIV medical care” throughout the manuscript. Similarly, the formal terminology for “CD4 T cell counts and plasma HIV viral load” is used consistently throughout the text.

Discretionary revisions

a) In the abstract, page 2, methods, second sentence, “Self report from patient, reports by medical providers, confidential laboratory and visits reports were used to determine the date of the initial health care visit after HIV diagnosis.” Same term is used on page 6 Definition of outcomes. What is a visit report? It is unclear throughout the article whether there is a systematic review of medical records? Should this read ... “reports by medical providers, mandatory laboratory reports and medical record reviews were used to determine the date of the initial health care visit after initial HIV diagnosis.”?

The text has been modified following the Reviewer’s suggestion

b) I would include a table or statement that showed to what extent all forms of reporting entry into HIV medical care overlapped. This would give some credence to the reporting systems.

We feel that a detailed report of the reporting system is beyond the scope of our article and will distract the reader from the main points we want to communicate. We feel that enough information is provided to understand how the reporting system worked. Instead we have extended the explanation and details of the modifications and changes implemented to improve the reporting system.

c) Page 4 Background, beginning of paragraph 3 makes the case for why using CD4 and viral load would be useful, see comment b) above. Then go on with ... 3rd paragraph.

Page 4 Background, third paragraph needs editing. One suggestion is: “At the public health level, Collecting initial CD4 cell counts and HIV viral loads can determine the stage of HIV infection at diagnosis entry into medical care. Although several studies have used CD4 T cell counts tests or viral load results as markers of care, these studies have not used these laboratory tests as a surveillance tool for surveillance for to assess linkage to HIV medical care in the public health setting. (2,5,6). Surveillance of laboratory reports of CD4 T cell counts and plasma HIV viral loads
could be used by public health agencies as surrogates for linkage to HIV care after diagnosis, allowing the design, evaluation and improvement of HIV testing and linkage to care programs. Currently …. Viral loads.” The meaning of the end of the last sentence was not clear; either clarify or omit.

The text has been modified following the Reviewer’s suggestion.

d) Page 5, a suggestion for a re-write of the last paragraph background: In this report we describe the characteristics of patients having a newly diagnosed HIV infection between July 1, 2006 and June 30, 2007 who entered into HIV medical care. Secondly, we demonstrate an additional yield obtained by using laboratory surveillance of CD4 tests and HIV viral loads as a marker for entry into HIV medical care after initial diagnosis. Lastly, we show an effect of having had a case manager interview and referral to medical care after a first positive HIV test on the likelihood of entering medical care within 3 months of the initial HIV diagnosis.

The text has been modified following the Reviewer’s suggestion.

e) Page 6, Documentation of entry into care: Were laboratories mandated to report only HIV viral loads or both viral loads and CD4 cell counts? The laboratories were mandated to report viral loads. CD4 cell count reports were not mandated. This is clarified in the current version of the manuscript.

f) Page 6, Documentation of entry into care: Try to make sentences more concise. For example, second and third sentence suggestions are “Laboratories are required by law to report all viral load tests to the health department. Additionally, CD4 test results were collected by health department staff from major San Francisco hospitals and through medical records review. Since July 1, 2006, the SFDPH began recording the initial primary HIV care visit as part of standard HIV case management practice.”

The text has been modified following the Reviewer’s suggestion.

g) Page 6, Definition of outcome, last sentence may be more clear if you write: Date of first HIV diagnosis, date of first primary care visit and date of first CD4 and/or HIV viral load test were used in our analysis to determine the timing from diagnosis to entry into HIV care.

The text has been modified following the Reviewer’s suggestion.

h) Statistical Analysis section is very confusing. First you describe the multivariate analysis before the univariate or descriptive analysis, which is backward. In your univariate analysis, you mention comparing mean CD4 and Viral load tests using a t-test but this is not presented anywhere, and CD4 are presented categorically in Table 1. You present categorical data in table 1 and use a Z-test to compare proportions across groups; a chi-square test across all categories would be more appropriate or univariate odds ratios if you wanted a statistic for each category relative to a reference category.

The Z tests is the appropriate test to compare the proportions from two independent groups to determine if they are significantly different from one another, which is exactly what we were trying to determine. On the other hand, the chi-square test requires the use of numerical values and does not allow the use of percentages, proportions or ratios. Similarly, we feel that the comparison between percentages (proportions) is easier to understand than the use of ratios. Although chi-square tests and logistic regression would be appropriate statistical tests to describe the differences between groups had the data been presented differently (e.g. as plain numbers or ratios), we feel that the differences are easier to understand when presented as percentages.

I strongly suggest placing your analysis strategy by order of your tables; you should describe your analysis plan as:
A) Descriptive statistics and a comparison of persons who were confirmed to have entered care and who had not entered care (Table 1); again the analysis would be either 1) Chi square tests or 2) odds ratios.

We agree that the univariate analysis should be described before the multivariate analysis, and we have changed the Statistical Analysis section to read in the same order as the tables. We no longer mention using t-tests to assess differences in mean CD4 and viral load tests.

B) Comparison of the timing from diagnosis to entry into care for individuals identified as in care by interview versus as in care by CD4 or viral load test (figure 2). Since I don’t see a statistical test I’m not sure if there is any importance to this figure. But I would suggest one of two: you can test the average number of days using a t-test or mean and 95% confidence intervals, or if you want to keep it categorical, collapse the data to <60 days and >60 days and do a Chi square test; use fisher exact statistic since you’ll have a small cell size.

C) Table 2 is your multivariate analysis; in your text you state that the potential risk or confounding factors included in your analysis are: sex, sexual orientation, age, site of testing, race/ethnicity, substance abuse, and CD4. Why is your main variable case-management interview and referral, as in your model, not listed? You also use an acronym in your table that means nothing to the reader, e.g. SFGH; I'd suggest writing this out. There are also other variables, e.g. co-morbidities, and CD4< 200 vs. CD4>200.

We have changed the text to include the case-management interview and referral variable, and we have spelled out the acronym in the table. We did not explicitly list CD4 category in the table because it was not significant in the model; however, the table notes that the odds ratios were adjusted for CD4 category and several other possible confounders.

My preference is to have a table with 2 columns: one with the univariate odds and 95% CI for all variables and the second column with a multivariate model showing all adjusted Odds ratios with 95% CIs; you can bold the statistically significant ones. I don’t think you need p-values too, unless this is the journal’s preference.

We feel that presenting separate tables for the univariate and multivariate analyses is a clearer way to illustrate our findings to the reader.

You do not need to mention that a two sided p-value < 0.05 is statistically significant or that a confidence interval not including 1 is statistically significant; the reader should know this.

This sentence was deleted.

i) Discussion, page 10, second paragraph: Are references 5 and 8 for the prior reports you refer to in the first sentence “Importantly, and contrary to prior reports”? If not, you need a reference for these reports or you should leave the phrase out and just state “We found ....”

The references refer to prior reports that contrast with our findings. We have left the text and references as they were in the prior version of the manuscript.

Minor suggestions:
2. Page 4, paragraph 1 last line, insert word “care” --- “lower health care cost (3).”
3. Avoid redundancy and wordiness, for example repeating the phrase “after initial HIV diagnosis”; once stated it is known throughout a paragraph of text.

All these suggestions have been incorporated into the new version of the manuscript.

Reviewer 2
Reviewer's report:
This paper is concerned with the importance of early entry to care for HIV-infected patients, for individual and public health benefits. The authors present the result of a year-long observational study, in which the timing of entry to care for newly diagnosed patients is associated with their characteristics, in particular where they were diagnosed and whether they were contacted by public health workers afterwards. I feel that this topic is important and the findings would be of interest to many readers. However, my understanding and appreciation of the work was unfortunately limited by somewhat inadequate descriptions of the context, study design and analysis method. To those working in the San Francisco Public Health Department, the set-up will be very familiar, but to those in other settings, further explanations may be required. A diagram showing the flow of patients from diagnosis, to ‘case contact’, to presentation at a clinic, with CD4 testing etc would be useful. This would enable the authors to clearly illustrate what they are most concerned with (i.e. not timing from infection to diagnosis, or continued follow-up after initial appointment) and where unfamiliar things (case contact, various sorts of information on timing of visits) fit in.

While we understand that most of our readers do not work for the San Francisco Department of Public Health, we feel that the flow of patients from diagnosis to entry into care is similar to other health-department settings. We also feel that the details of patient flow are not central to the paper, and presenting a diagram on this would distract the reader from the more important analysis at hand.

Throughout the manuscript, there was a tendency to use ‘jargon’ type words without explanation that added to this difficulty in reading this manuscript (especially Introduction and Methods). For instance – what is the ‘HIV/AIDS surveillance registry’, what does ‘legal’ mean in this context, write ‘CD4 cell count and viral load DATA’.

We have reviewed the manuscript and replaced the technical words for simpler ones when possible. However, we feel that the words/sentences suggested by Reviewer 2 were simple enough to be understood by the reader. “HIV/AIDS surveillance registry” is a registry of the surveillance of HIV/AIDS cases, “legal” means required by law, and “CD4 cell count and viral load DATA” refers to the values and dates of the CD4 cell count and viral loads. We feel that further explanation of those terms would add unnecessary wordiness to the text.

I also felt there was a tension in the manuscript between interpreting these results to assess what kind of things promote individuals connecting to care sooner rather than later and issues about surveillance. The former is an important public health question, which the authors can address: e.g. people tested at particular facilities and with contact to health workers come sooner. That should be mentioned prominently in the ‘conclusions’ section, and more of the discussion devoted to outlining possible reasons for those relationships. But, at the same time, the authors make another point about CD4 data at first entry to care as being used in surveillance. I don’t really understand why monitoring the distribution of CD4 count at the stage is useful since it’s confounded by the timing of HIV diagnosis as well as the general physiology which varies between population sub-groups, and is anyway a very noisy signal at the best of times.

We feel that the discussion section clearly illustrates the points described above about what kinds of things promote individuals connecting to care (e.g., type of facility, contact with health workers, etc.). The background and discussion sections also make the point that monitoring CD4 count at this early stage is useful for public health surveillance purposes because it can provide evidence of delays in linkage to care. Indeed, a significant proportion of the newly diagnosed cases included in our study had CD4 counts consistent with an AIDS diagnosis.

The assumption regarding all patients that are diagnosed and enter care in the same day being excluded seems to warrant further investigation given that this accounts for a larger share of the overall sample size. Is there any data to support that these tests are merely confirmatory? What is the CD4 cell count distribution for these individuals? The multiple data sources which have been drawn together to assemble the dataset of the other individuals might be able to provide more insights on this issue?
The reasons for the exclusion of these patients have been expanded in the manuscript and detailed in our response to Reviewer 1’s comments. Those data are available and could be provided if the editor feels strongly about it. However, we feel that those CD4 counts and viral loads should not be used as a marker of entry to care (in agreement with Reviewer 1). Providing these data might add confusion and distract the reader from the findings we are trying to communicate.

The Introduction was overly brief, and didn’t, in my opinion, fully explore the benefits of linking diagnosis to care. First, the prevention of infection is important and several modelling studies have indicated that (e.g. Blower et al, Nature, 1990s, Baggaley et al, Emerging Themes in Epidemiology, 2006). Then, the clinical benefits of early entry to care have received close attention from a benefit and cost-benefit perspective (e.g. Badri et al, PLoS Med & Lancet, 2006; Hallett et al, PLoS Med 2008). Timing in entry to care in the Netherlands has recently been analysed (Smit et al, PLoS One, 2008), showing that ‘too late’ diagnosis is the limiting factor for clinical outcomes there. The epidemic in MSM in San Francisco have been studied in many articles, in particular the resurgence in the HAART era (e.g. Truong, STI, 2006)… and in London (Stolte, AIDSA 2003/4).

First, the introduction has been expanded according to Reviewer 1’s suggestions. Second, we agree with Reviewer 2 that there are numerous other benefits to early entry into care after diagnosis. Our paper focuses on the clinical and public health benefits that we feel are most important to the practice of public health departments. We feel that discussion of a cost-benefit perspective, for example, is beyond the scope of this paper.

The choice of the z and t-test requires some justification, since a non-parametric or survival-based approach would seem a more natural choice.

“Linkage to care” should be replaced with “Linkage to care after diagnosis” throughout the manuscript for clarity.

We have changed this phrase in the first paragraph of the background section to read “linkage to care after diagnosis.” After that, we feel that the “after diagnosis” is implied and does not need to be stated explicitly throughout.

First sentence of the introduction after first comma does not make sense. Break into two sentences and quantify how MANY years after infection you mean.

We have edited this sentence following the Reviewer’s suggestion.

Second paragraph of introduction does not flow naturally from first paragraph. Consider re-orderings or adding a linking sentence?

We have edited this paragraph following the Reviewer’s suggestion.

Results: It’s no surprise that ‘sex’ was not statistically significant with only 9 women. This should be stated – or alternatively, the analysis restricted to men only.

We have stated this in the Statistical Analysis section following the Reviewer’s suggestion.

For the ‘not significant at p>0.05 level’, I presume you did some form of backward model selection on Wald tests / Likelihood ratio tests? This should be stated explicitly.

As mentioned in the text, we developed the models manually and did not use automatic procedures like forward, backward or stepwise elimination. We feel these procedures may eliminate confounders from the final model that, although “not significant” should be accounted for given their biological or historical importance.
All numbers should be written in numerals, not words. Currently, this is inconsistent throughout the manuscript.
We wrote out numbers as text only when they were stated at the beginning of a sentence. This is standard practice.

In the discussion, you state that patients from the hospital were more likely to access care than those seen at the STD clinics, DESPITE having lower CD4 cell counts. That seems expected, since patients with clinic symptoms are more likely to recognize the urgency of seeking care.
We have clarified this sentence following the Reviewer’s suggestion.