Author’s response to reviews

Title: Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study

Authors:

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Author’s response to reviews: see over
17 December 2011

Dear Professor Andrea De Luca and the editorial team of BMC Infectious Diseases,

Please find uploaded to the BMC submission pages our revised manuscript for the following original research article:

**Trends in missed presentations and late HIV diagnosis in a UK teaching hospital: a retrospective comparative cohort study**

We have corrected formatting of images and manuscript as requested and responses to the reviewer’s comments are given below (numbered for convenience).

I look forward to your response. If I can provide any other information please do not hesitate to contact me.

Yours sincerely,

Jared Wohlgemut  
on behalf of co-authors Dr. Tim Lawes and Dr. Robert Laing
Major compulsory revisions:

1. The abstract is not easy to follow. Different outcomes are presented: missed indications for HIV testing, late diagnosis (CD4 < 350 cells/mm3), time to diagnosis, missed presentation (same as missed presentation?), but only late diagnosis is defined.

We appreciate the potential for confusion in outcomes. We would wish to report all outcomes as we feel these provide different ways of assessing progress in diagnosis in the clinical environment. Therefore,

(i) We have defined each outcome in the abstract as follows:
“Missed presentations (failure to diagnose ≤ 1 month of a clinical or non-clinical indicator for testing), late diagnosis (CD4 < 350 cells/mm3), and time to diagnosis (months from first presentation to diagnosis) were compared between cohorts using χ² and log-rank tests.

(ii) We intended missed opportunities for testing / missed indications for testing / missed presentations to mean the same. We realise the potential for confusion and therefore use “missed presentation” throughout the paper.

2. In my opinion paragraph reporting the analysis on clinical aspects (last paragraph of Results) is not clear and should be rewritten. In particular:

a) Does the first paragraph refer to an overall description of the study population?

We appreciate this may not be clear to readers. This section assessed disease progression after missed presentation in two ways. (i) By comparing the clinical stage, presence/absence of AIDS defining illness and No. of clinical indicators for testing between first (missed) presentation and (eventual) diagnosis in those with missed presentation only (n=36). (ii) By comparing CD4 counts at diagnosis in those with a missed presentation and those diagnosed at first presentation (total cohort).

To clarify this we have:

i) Added to the methods section to clarify statistical analysis as follows:
“Finally, in patients with a missed presentation we assessed disease progression by time of diagnosis by comparing the number of clinical indicators for testing, clinical stage and presence or absence of AIDS defining illness at first presentation and diagnosis using related-samples Wilcoxon-signed rank tests. Likelihood of immunologically advanced disease (CD4 < 200 cells / mm3) at diagnosis was compared between patients with and without missed presentation by logistic regression adjusting for baseline characteristics”

ii) Clearly indicated in the results which patients the findings refer to:
“In those patients with a missed presentation (n=36), the median number of clinical indicator diseases increased significantly from 1 at first presentation to 3 at diagnosis (Related-samples Wilcoxon-Signed rank tests, P < 0.001). Progression to AIDS (25%) or higher WHO clinical staging (53%) was common between missed presentation and diagnosis. Compared
with those diagnosed at first presentation, patients with ≥1 missed presentation were also substantially more likely to have immunologically advanced disease (CD4 < 200 cells/mm³) at diagnosis: 74% vs. 30% (OR = 6.9, 95% CI: 3.0 to 16.2; P < 0.001).

b) What do the authors mean by progression to AIDS? prevalence of clinically diagnosed AIDS?

AIDS was clinically diagnosed using AIDS-defining illnesses as defined by WHO. Progression to AIDS referred to a patient without AIDS-defining illness at first (missed) presentation who subsequently developed AIDS by time of diagnosis. To clarify this point we have, in the methods:

i) Described how AIDS was defined:
“HIV clinical staging, and clinical diagnosis of AIDS, at first presentation and diagnosis were defined by World Health Organisation (WHO) criteria [16].”

ii) Described how we assessed progression to AIDS.
“Finally, in patients with a missed presentation we assessed disease progression by time of diagnosis by […] presence or absence of AIDS defining illness at first presentation and diagnosis using related-samples Wilcoxon-signed rank tests”

iii) Results now read:
“Progression to AIDS (25%) or higher WHO clinical staging (53%) was common between missed presentation and diagnosis”

c) Why do the authors use WHO staging? The may wish to consider not to include this classification as it may be redundant when CD4 cell count is available.

(See also response to 2 a) above). CD4 count was only available at diagnosis. We wished to provide some indication of disease progression between missed presentation and diagnosis at X months after the initial indication for testing (missed presentation). To do this we chose 3 indicators. (i) No. of clinical indicators for testing as defined by national guidelines (ii) WHO staging and (ii) presence / absence of AIDS defining illness. In practice we acknowledge CD4 count is used to stage at diagnosis (locally CDC criteria are used). We also acknowledge that a missed presentation by definition will not have been subject to thorough specialist review and therefore interpretation of staging at this point should be treated with caution. Nevertheless our aim was to illustrate the impact on immunological and clinical disease progression associated with missed presentations.

We feel it is important to retain the information on WHO staging alongside CD4 counts to illustrate this progression and also to illustrate disparity in findings of (a) reduced missed presentation + less clinically advanced disease at diagnosis in the later cohort and (b) a lack of significant change in CD4 count at diagnosis. We question this finding and suspect that staging and history of presentations may be incomplete where previous clinical history is undocumented (in the increasing HIV population from overseas or working in international industry in our region). See discussion:
“The disparity between reductions in missed presentation and non-significant decline in late or very late diagnosis may reflect shifts in demographics of all patients. In particular under-diagnosis and lack of documented health contact outside the UK create challenges to detection of HIV in migrants”.

d) What do the author mean with progression after missed presentation? No numbers are provided on this aspect (last sentence of the paragraph)
(See also response to 2 a) above). The difference in risk of clinical or immunological progression associated with missed presentation was not significantly different between periods so we feel this sentence is best removed to avoid confusion (it adds little to our message)

We have removed this sentence: “Clinical and immunological progression after missed presentation was more common in the later cohort, despite reduced time to diagnosis”.

3. In the results section The following sentence me “The proportion of patients diagnosed within one year of first presentation was 77% in the earlier cohort and 92% in the later cohort (HR = 1.36, 95% CI: 0.96 to 1.94; P = 0.084)” is unclear To me; how the HR was calculated? Does the comparison refer to the one year data only?

This was referred to (perhaps not clearly enough) in the methods section as a multivariate Cox-regression. To clarify how we analysed time to diagnosis we have changed the methods and results to read as follows:

i) Methods:
“Further comparison of time to diagnosis between cohorts was made using Kaplan-Meier curves and multivariate Cox-regression adjusting for case-mix”.

ii) Results:
“Kaplan-Meier curves reflected a higher proportion of diagnoses made at first presentation in the later cohort as well as reduced time to diagnosis in those missed at first presentation (median delay 10 vs. 34 months; p = 0.005) – figure 3. A multivariate Cox-regression model revealed a non-significant improvement in rate of (time to) diagnosis (adjusted HR = 1.36, 95% CI: 0.96 to 1.94; P = 0.084) after adjusting for case-mix: the proportion of patients diagnosed within one year of first presentation was 77% in the earlier cohort and 92% in the later cohort.”

Minor essential revisions

4. The definition of “time to diagnosis” should be included in the “Definitions” paragraph.

Agree. We have clarified the primary outcome as missed presentation and defined all secondary outcomes (‘late diagnosis, ‘very late’ diagnosis and ‘time to diagnosis). The methods now read:
“The primary outcome was 'missed presentation', defined as failure to diagnose HIV within one month of a clinical or non-clinical indicator for testing. Secondary outcomes included, 'late' diagnosis (CD4 count < 350/mm3 at diagnosis), 'very late' diagnosis (CD4 count < 200/mm3 at diagnosis) and time to diagnosis (months from first presentation to diagnosis).”

Discretionary Revisions

5. In Background: “Universal 'opt-out' testing in all general healthcare settings” has been recommended in some countries, but I would not say that it has been “adopted”.

Agreed and changed to read: “Many countries, including the USA and Canada have recommended universal 'opt-out' testing in all general healthcare settings."