Author's response to reviews

Title: QTc interval prolongation in HIV-infected patients: a case-control study by 24-hour Holter ECG recording

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Author's response to reviews: see over
To the Editor of
BMC Cardiovascular Disorders

Sir,

enclosed please find the revised manuscript of our work entitled “QTc interval prolongation in HIV-infected patients: a case-control study by 24-hour Holter ECG recording”, with the following responses to the reviewers’ concerns:

REFEREE 1

1) QUESTION: Please clarify in the methods and in figure 1 how your final control population included 64 controls (see also Associate Editor’s question 3).

ANSWER: We selected 64 HIV infected subjects with normal QTc interval as assessed by standard and Holter ECG, matched by gender and age (± 5 years) with the 32 cases. Forty patients came from the original group II, and 24 were consecutive HIV-infected patients with normal QTc interval at standard and Holter ECG recording.

This was specified in the Methods section, page 3, lines 15-19, and in the figure 1.

2) QUESTION: No echocardiographic data are provided by the authors. This is a clear limitation. It should be recognized as a limitation if data are unavailable. (see also Associate Editor’s question n.1)

ANSWER: we added at the end of the DISCUSSION section the following sentence: “Our work presents some limitations: the number of patients in both groups is limited, and the statistical differences marginal; moreover, no echocardiographic data are provided. However, to the best of our knowledge, this seems to be the largest group of adult HIV-infected patients ever studied by 24-hour Holter ECG recording”.

3) QUESTION: The authors should better specify if the patients complained of symptoms such as angina or dyspnoea.

ANSWER: “Neither cases nor controls complained of angina or dyspnoea”.
This was added in the RESULTS section, page 6, lines 11-12.

4) QUESTION: Did the authors find any other ECG abnormality between the two groups of patients?

ANSWER: “Thirteen out of 32 cases (41%) and 17 out of 64 controls (26%) presented ectopic ventricular beats (p=0.2); 14 patients among cases (44%) and 30 among controls (47%) presented ectopic supraventricular beats (p=0.9)”.
This was added in the RESULTS section, page 6, lines 12-14.

5) QUESTION: does a prolonged QTc carry any prognostic implication? Which is the follow-up of the two cohorts? How did a prolonged QTc influence the follow-up of the patients?

ANSWER: we thank the reviewer for this suggestion; in the RESULTS section, page 6, lines 17-19, the following sentences have been added: “Among cases, after a mean follow-up of 4.8±0.9 years 5 patients resulted dead and 27 were still alive; among controls, after a mean follow-up of 4.1±1.1 years 2 patients resulted dead and 62 were still alive (p=0.04).”
In the DISCUSSION section, page 8, lines 5-8, the following sentences have been added: “Our group of HIV-infected patients with prolonged QTc showed at follow-up an increased risk of death when compared to patients with normal QTc (p=0.04). Interestingly, none of the patients died for heart-related diseases. Our data suggest a possible association between QTc prolongation and all-cause mortality also in HIV-infected patients, likewise previously described among other non-HIV populations [32].”
Finally, a new reference [32] has been added in the REFERENCE section, page 13:
1) **QUESTION**: The number of patients in both groups is small, and the statistical differences marginal. This should be specified in the limitation section. (see also the question n. 2 of Referee 1)

**ANSWER**: We added at the end of the DISCUSSION section (page 8, lines 19-22) the following sentences: “Our work presents some limitations: the number of patients in both groups is limited, and the statistical differences marginal; moreover, no echocardiographic data are provided. However, to the best of our knowledge, this seems to be the largest group of adult HIV-infected patients ever studied by 24-hour Holter ECG recording”.

2) **QUESTION**: Which other cardiac parameters were obtained from the 2 groups? What were the differences if any? Were there differences in symptoms, specifically arrhythmia-related? (see also question 3 and 4 of Referee 1)

**ANSWER**: “Neither cases nor controls complained of angina or dyspnoea. Thirteen patients among cases (41%) and 17 among controls (26%) presented ectopic ventricular beats (p=0.2); 14 patients among cases (44%) and 30 among controls (47%) presented ectopic supraventricular beats (p=0.9).”

This was added in the RESULTS section, page 6, lines 11-14.

3) **QUESTION**: It is not clear how the controls were selected. Were patients consecutive? (see also question 1 of referee 1)

**ANSWER**: We selected 64 HIV infected subjects with normal QTc interval as assessed by standard and Holter ECG, matched by gender and age (± 5 years) with the 32 cases. Forty patients came from the original group II, and 24 were consecutive HIV-infected patients with normal QTc interval at standard and Holter ECG recording.

This was specified in the Methods section, page 3, lines 15-19, and in the figure 1.

4) **QUESTION**: It is noted in the text that differences in relation to AZT and FTC were significant, yet p values were not, please correct or explain

**ANSWER**: we report in the RESULTS section, page 6, lines 20-24, that “antiretroviral drugs were not associated with QTc prolongation at a statistically significant level (table 2). However, patients treated with zidovudine (AZT) presented QTc prolongation more
frequently than patients not treated with AZT (34% vs 19%; OR 2.27 and 95% C.I. 0.78-6.62; p=0.15). Moreover, patients receiving emtricitabine (FTC) were less likely to have a QTc prolongation than patients not receiving FTC (12% vs 31%; OR 0.31 and 95% C.I. 0.08-1.12; p=0.08).”
Therefore in the text we have already specified that the differences in relation to AZT and FTC were not statistically significant.

MINOR COMMENT
QUESTION: in methods, please correct “Spectral estimates of R-R….. artifacts”
ANSWER: in the methods section, page 4, line 21, we substituted “artifacts” for “artefacts”

EDITORIAL REQUEST
Requesting ethics statement: name of ethics committee.
ANSWER: we specified in the Methods section, page 5, lines 15-16, that “The research was approved by the Ethics Committee of “L. Spallanzani” National Institute for Infectious Diseases, Rome (Italy).”

PLEASE NOTE that the following sentences have been added in the COMPETING INTERESTS section (page 10, lines 1-3): NP received speaker’s honoraria from Pfizer, MSD, Gilead, Novartis, Carefusion, Johnson & Johnson, Bristol Myers Squibb, Sanofi Aventis. All other authors declare that they have no competing interests.

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Kind Regards.
Rome, November 28th, 2012
Pierangelo Chinello, MD