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# Letters to the Editor

## *RE: "LESSONS LEARNED FROM THE DESIGN AND IMPLEMENTATION OF MYOCARDIAL INFARCTION ADJUDICATION TAILORED FOR HIV CLINICAL COHORTS"*

We read with interest the article by Crane et al. (1) concerning myocardial infarction reporting and adjudication in their large observational human immunodeficiency virus (HIV) cohort study. We wish to share our experience and lessons learned as members of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) Endpoint Review Committee (ERC), evaluating acute myocardial infarction (AMI) and other serious non-AIDS (SNA) disease endpoints in our international HIV clinical trials network.

Our studies support the importance of standard case definitions. SNA event criteria in INSIGHT include both confirmed and probable criteria (2). Confirmed criteria for AMI, which reflect a higher degree of diagnostic certainty (typically with laboratory confirmation), are also adapted from the universal definition of myocardial infarction (3). Probable AMI criteria are based upon clinical criteria and/or less definitive criteria, such as a compatible clinical syndrome with characteristic electrocardiographic changes.

We also agree from our experience with the need for multiple reviewers and a process of adjudication. In INSIGHT, all suspected events are reported on a standard case form, which is reviewed by 3 expert members of the ERC, who are blinded to study drug treatment status. If not all reviewers agree on diagnostic certainty, a process of adjudication (typically by e-mail) occurs until consensus is reached. An ERC nurse coordinator manages the flow of each reported event to help ensure that it is reviewed in a timely manner.

Supporting the need for expert review and adjudication, when we reviewed SNA events for the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) (a study of interleukin-2 treatment for HIV patients on antiretroviral therapy with CD4+ counts $\geq$300 cells/mm$^3$) (4), we found that of 83 reports of AMI, 33 (40%) required adjudication. Ultimately, 55 (66%) were adjudicated as meeting confirmed criteria, 3 (4%) were adjudicated as meeting probable criteria, and 25 (30%) were rejected as not meeting case criteria (2). We also found that clinical judgment is often required in assessment of source documentation to determine whether criteria are met, supporting the importance of using reviewers with clinical expertise in the disease being evaluated.

We strongly agree with the need for original supporting source documentation from the medical record and/or treating clinician, allowing for full independent evaluation by ERC reviewers. To facilitate this process, our case report forms for each event include a checklist of the required documentation; local site investigators should be familiar with endpoint criteria and required supporting material.

Cardiovascular disease and other SNA events are increasingly being recognized as major causes of morbidity and mortality in persons with HIV (5, 6). These events were in large part the motivation for the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial (7). Thorough reporting and review procedures are crucial for obtaining accurate information on the occurrence of myocardial infarction and other SNA events in HIV studies.

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### References

1. Crane HM, Heckbert SR, Drozd DR, et al. Lessons learned from the design and implementation of myocardial infarction adjudication tailored for HIV clinical cohorts. *Am J Epidemiol*. 2014;179(8):996–1005.
2. Lifson AR, Belloso WH, Davey RT, et al. Development of diagnostic criteria for serious non-AIDS events in HIV clinical trials. *HIV Clin Trials*. 2010;11(4):205–219.
3. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116(22):2634–2653.
4. The INSIGHT-ESPRIT Study Group and SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. *N Engl J Med*. 2009;361(16):1548–1559.
5. Phillips AN, Neaton J, Lundgren JD. The role of HIV in serious diseases other than AIDS. *AIDS*. 2008;22(18):2409–2418.
6. Miller CJ, Baker JV, Bormann AM, et al. Adjudicated morbidity and mortality outcomes by age among individuals with HIV infection on suppressive antiretroviral therapy. *PLoS One*. 2014; 9(4):e95061.
7. Babiker AG, Emery S, Fatkenheuer G, et al. Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clin Trials*. 2013; 10(1 suppl):S5–S36.

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