



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
Main Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2018

Baseline Genotype Testing to Assess Drug Resistance Before Beginning HIV Treatment-Reply

Saag, Michael S ; Günthard, Huldrych F ; Smith, Davey M

DOI: <https://doi.org/10.1001/jama.2018.15946>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-161798>

Journal Article

Published Version

Originally published at:

Saag, Michael S; Günthard, Huldrych F; Smith, Davey M (2018). Baseline Genotype Testing to Assess Drug Resistance Before Beginning HIV Treatment-Reply. *JAMA : the Journal of the American Medical Association*, 320(20):2154.

DOI: <https://doi.org/10.1001/jama.2018.15946>

The difference in MACE numbers was 15 between the placebo group (n = 61) and escitalopram group (n = 46), in line with the differences in depression remission. The difference in MACE occurrence appearing beyond 1 year after randomization is a reasonable concern. However, a meta-analysis of 16 studies of depression following ACS found that differences in MACE occurrence became prominent after 1 year and over longer follow-up intervals⁴; this is in keeping with our findings, although we agree that further replication should be sought.

Dr Zimmermann and colleagues raise concerns about the cumulative incidence figures in the article. The data in Figure 2 have been rechecked, and we found that the cumulative event curves were matched erroneously to the numbers at risk. This was our mistake and an error that arose during the revision process after the original submission and unconnected to other analyses. The article has been corrected online, and we apologize for the oversight. In addition, numbers at risk have also been revised for Figures 2 and 3, taking into account the censoring date as well as end points. Regarding mortality definitions, all-cause mortality was chosen as a component of the MACE outcome at an early stage of protocol development, was recorded in the body of the protocol, and was used in a prior publication² as well as in the current analysis. However, the change was not applied in the synopsis by mistake.

We appreciate Dr Rust's concerns about placebo controls. Because of the lack of evidence for the effect of depression treatment shortly following ACS at the time the study was designed, the EsDEPACS trial was judged both by funders and by an independent ethics review panel to be addressing an issue of clinical equipoise.⁵ In addition to providing study drugs, research psychiatrists met with all participants for at least 30 minutes at every visit and addressed psychological symptoms through supportive intervention as well as promoting cardiac treatment. Participants could withdraw from the trial for any reason. For participants without remission after the trial, further treatment was facilitated when requested. All participants were approached for evaluation of psychiatric outcomes 1 year after baseline evaluation.⁶ We agree that findings from our studies^{3,5} support further active control and stepwise intensification trials.

Jae-Min Kim, MD, PhD

Robert Stewart, MD, FRCPsych

Jin-Sang Yoon, MD, PhD

Author Affiliations: Department of Psychiatry, Chonnam National University Medical School, Republic of Korea (Kim, Yoon); Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England (Stewart).

Corresponding Author: Jae-Min Kim, MD, PhD, Department of Psychiatry, Chonnam National University Medical School, 160 Baekseoro, Dong-gu, Gwangju 61669, Republic of Korea (jmkim@chonnam.ac.kr).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Stewart reported receiving grants from Janssen and Roche and co-supervision of a PhD candidate with GlaxoSmithKline. No other disclosures were reported.

1. Kim JM, Bae KY, Kang HJ, et al. Design and methodology for the Korean observational and escitalopram treatment studies of depression in acute

coronary syndrome: K-DEPACS and EsDEPACS. *Psychiatry Investig*. 2014;11(1):89-94. doi:10.4306/pi.2014.11.1.89

2. Kim JM, Stewart R, Kim JW, et al. Serotonin transporter gene association between anxiety and long-term cardiac outcomes in acute coronary syndromes. *J Am Coll Cardiol*. 2018;71(23):2706-2707. doi:10.1016/j.jacc.2018.04.006

3. Kim JM, Stewart R, Lee YS, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA*. 2018;320(4):350-358. doi:10.1001/jama.2018.9422

4. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry*. 2013;203(2):90-102. doi:10.1192/bjp.bp.112.111195

5. Kim JM, Bae KY, Stewart R, et al. Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2015;76(1):62-68. doi:10.4088/JCP.14m09281

6. Kim JM, Stewart R, Bae KY, et al. Effects of depression co-morbidity and treatment on quality of life in patients with acute coronary syndrome: the Korean Depression in ACS (K-DEPACS) and the Escitalopram for Depression in ACS (EsDEPACS) study. *Psychol Med*. 2015;45(8):1641-1652. doi:10.1017/S003329171400275X

Baseline Genotype Testing to Assess Drug Resistance Before Beginning HIV Treatment

To the Editor In the updated Recommendations of the International Antiviral Society–USA Panel for the treatment and prevention of human immunodeficiency virus (HIV) infection in adults,¹ the recommendations for laboratory monitoring have been revised to include the use of baseline HIV genotype to assess transmitted drug resistance. The panel recommended testing only for nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors, and reserved testing for integrase strand-transfer inhibitor (InSTI) resistance to cases of suspected exposure to a partner with InSTI resistance. All preferred regimens are InSTI-based, favoring dolutegravir and bictegravir and, when those are not available, raltegravir and elvitegravir/cobicistat.¹

Although the transmission of signature mutations for InSTIs (such as Y143R/C, N155H, or Q148K/R/H) is extremely infrequent—hence we agree there is generally no need to monitor for these mutations prior to treatment initiation—there is no rarity of InSTI polymorphisms that can reduce InSTI activity. Casadellà et al² reported a 14% prevalence of such substitutions in Europe on the basis of samples collected in treatment-naïve patients between 2006 and 2007. In our own institution, prevalence was also 14% in treatment-naïve patients with acute or recent (<6 months postinfection) HIV infection diagnosed in 2015 and 2016. The most frequently found substitution was the E157Q polymorphism, and all patients were infected with subtype B strains, suggesting that it is unrelated to specific recombinant forms or subtypes.³ Antiretroviral-naïve patients carrying viruses with such a polymorphism have been reported to experience virologic failure with raltegravir⁴ and elvitegravir/cobicistat⁵-based regimens. In fact, Charpentier et al⁵ reported that 2 of 8 antiretroviral-naïve patients starting elvitegravir/cobicistat-based antiretroviral treatment had experienced virologic failure.

In this context, we believe that testing baseline InSTI genotype might be considered in particular epidemiologic settings if such polymorphisms are reported to be frequent in a given

population, region, or HIV risk group, particularly if raltegravir or elvitegravir/cobicistat are the available or chosen INSTIs. Regimens with bictegravir or dolutegravir would not be affected by such polymorphisms.

Juan Ambrosioni, MD, PhD
Mar Mosquera, MD
José M. Miró, MD, PhD

Author Affiliations: Infectious Diseases Service, Hospital Clinic of Barcelona, Barcelona, Spain (Ambrosioni, Miró); Service of Microbiology, Hospital Clinic of Barcelona, Barcelona, Spain (Mosquera).

Corresponding Author: José M. Miró, MD, PhD, Infectious Diseases Service, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain (jmimiro@ub.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Miró reported receiving personal fees and academic and research grants from Abbvie, Angelini, Contrafact, Cubist, Genentech, Gilead Sciences, Jansen, Medtronic, Merck, Novartis, Pfizer, and ViiV Healthcare. No other disclosures were reported.

1. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA Panel. *JAMA*. 2018;320(4):379-396. doi:10.1001/jama.2018.8431
2. Casadellà M, van Ham PM, Noguera-Julian M, et al; SPREAD Programme. Primary resistance to integrase strand-transfer inhibitors in Europe. *J Antimicrob Chemother*. 2015;70(10):2885-2888. doi:10.1093/jac/dkv202
3. Ambrosioni J, Nicolás D, Manzardo C, et al. Integrase strand-transfer inhibitor polymorphic and accessory resistance substitutions in patients with acute/recent HIV infection. *J Antimicrob Chemother*. 2017;72(1):205-209. doi:10.1093/jac/dkw376
4. Charpentier C, Descamps D. Resistance to HIV integrase inhibitors: about R263K and E157Q mutations. *Viruses*. 2018;10(1):E41. doi:10.3390/v10010041
5. Charpentier C, Malet I, Andre-Garnier E, et al. Phenotypic analysis of HIV-1 E157Q integrase polymorphism and impact on virological outcome in patients initiating an integrase inhibitor–based regimen. *J Antimicrob Chemother*. 2018; 73(4):1039-1044. doi:10.1093/jac/dkx511

In Reply As stated in the panel's report,¹ the relative absence of resistance-conferring mutations for INSTI drugs supports the recommendation to not test routinely for INSTI resistance before start of HIV treatment. A summary of existing data regarding the relative lack of transmission of INSTI resistance-conferring mutations was published this year.²

As discussed by Dr Ambrosioni and colleagues, the relatively high prevalence of INSTI polymorphisms is of some concern. We agree that it is worth monitoring the effect of INSTI polymorphisms over time, especially as they may potentially affect the efficacy of 2-drug, INSTI-based therapy. To date, however, there are few data indicating that these mutations have meaningful clinical effect on virologic response, especially to INSTI agents recommended for initial therapy.

One of the main reasons the recommendations are updated every 2 years is to incorporate new data that emerge regarding treatment of patients with and at risk for HIV infection. Since relevant and important data often emerge quickly in this dynamic field, we are grateful to Ambrosioni and colleagues for putting this issue on the “watch list” for future recommendations.

Michael S. Saag, MD
Huldrych F. Günthard, MD
Davey M. Smith, MD

Author Affiliations: School of Medicine, University of Alabama at Birmingham (Saag); University Hospital Zurich, Zurich, Switzerland (Günthard); University of California, San Diego, La Jolla (Smith).

Corresponding Author: Michael S. Saag, MD, School of Medicine, University of Alabama at Birmingham, 845 19th St S, BBRB 256, Birmingham, AL 35294 (msaag@uabmc.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Saag reported receiving grants and personal fees from Merck, Gilead, and ViiV. Dr Günthard reported receiving grants from the National Institutes of Health, Swiss National Science Foundation, Swiss HIV Cohort Study, University of Zurich, Yvonne Jacob Foundation, Systems X, Gilead, and Roche and receiving personal fees from Merck, Gilead, Sandoz, and Teva. No other disclosures were reported.

1. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA panel. *JAMA*. 2018;320(4):379-396. doi:10.1001/jama.2018.8431
2. Günthard HF, Calvez V, Paredes R, et al. Human immunodeficiency virus drug resistance: 2018 recommendations of the International Antiviral Society–USA panel. *Clin Infect Dis*. 2018;67:1-11.

CORRECTION

Incorrect Data in Figures: In the Original Investigation entitled “Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial,” published in the July 24/31, 2018, issue of *JAMA*,¹ errors occurred in figures. In Figure 2, incorrect data curves were published in the graph, and in Figures 2 and 3, incorrect numbers at risk were shown. This article has been corrected online.

1. Kim JM, Stewart R, Lee YS, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome: a randomized clinical trial. *JAMA*. 2018;320(4):350-358. doi:10.1001/jama.2018.9422

Unclear Sentence and Incorrect Number in Figure: The Research Letter entitled “Lethality of Civilian Active Shooter Incidents With and Without Semiautomatic Rifles in the United States,”¹ published in the September 11, 2018, issue of *JAMA*, contained an unclear sentence. The second sentence should have been worded as follows: “Many weapons were banned in 1994 under the federal assault weapons ban but were reintroduced to the public marketplace in 2004.” In addition, the Figure should have reported the number of active shooter incidents with a semiautomatic rifle as n = 61. This article was corrected online.

1. de Jager E, Goralnick E, McCarty JC, Hashmi ZG, Jarman MP, Haider AH. Lethality of civilian active shooter incidents with and without semiautomatic rifles in the United States. *JAMA*. 2018;320(10):1034-1035. doi:10.1001/jama.2018.11009