Incomplete Modeling of the Effect of Antiretroviral Therapy on the Risk of Cardiovascular Events

TO THE EDITOR—The paper by Desai and colleagues [1] presents some difficulties for the reader.

The authors represent exposure in their marginal structural models as the current use of a single specific drug or drug combination. The idea that the current risk of a cardiovascular disease (CVD) event depends on a single current antiretroviral drug or combination is biologically implausible [2–4]. The authors implicitly acknowledge this when they report that some exposures appear to have nonlinear cumulative effects. Although this is far more plausible, they do not present these results. The authors note that assuming a linear cumulative effect could lead to misleading results, but it is hard to see why assuming an even simpler dose response relationship will give results that are any less misleading. The solution to this problem is to carry out flexible cumulative exposure modelling [5].

The authors use the approach of Cole and Hernan to select variables for modeling treatment initiation and censoring. Cole and Hernan conclude that selecting these variables "requires a thoughtful process," and they encourage authors to present the results of sensitivity analysis using different sets of variables [6]. The reader has no idea of the variables that these authors considered when modeling treatment initiation and censoring and the sensitivity of results to the choices made. Their SAS code suggests that the authors used only the most recent CD4 cell count and viral load for every drug and combination. In our work we found that exposure to abacavir depended on variables such as dyslipidaemia, lipodystrophy, and a previous CVD event and that prescribing behavior changed after the D:A:D published their findings on abacavir in 2008 [7]. Residual confounding seems likely if the authors used the same simple model for every drug and combination.

The authors include a large number of variables in their Cox models. Full results are not given, but it seems as if these models contained 30 to 40 covariates. The resulting estimates are probably too precise, because seldom used drugs and drug combinations are omitted, and their effects are then ignored [8] and probably somewhat inflated because of small sample bias (especially with myocardial infarction as the outcome) [9]. A better solution to the problem of multiple exposures is hierarchical modeling, with additional modeling of likely associations between the effects of drugs in the same drug class or between the effects of combinations that share components, and with an explicit acknowledgement of residual effects due to exposures omitted from the model [8]. In this way, the authors might have been able to identify combinations whose effect differed from the sum of its components.

Some of the variables used in these Cox models had many missing values. Missing values were replaced using multiple imputation, but the reader does not know what imputation model was used, or how results changed when missing values were replaced, or the sensitivity of results to other plausible imputation models [10].

So what should a prudent reader conclude? That some common antiretroviral combinations contain drugs that elevate the risk of CVD? – Yes, but we knew that. That some combinations are more or less risky than the sum of their components? – In our opinion there is little evidence here to support such conclusions. Marginal structural modeling, multiple regression, and multiple imputation are delicate tools that can account for time-dependent confounding, multiple exposures, and missing data. But modeling these complexities requires careful thought—one cannot simply rerun a SAS macro.

Note

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