Electronic Supplementary Material 4: GRADE Approach to Drug-Drug Interactions

Experts at the University of Liverpool adapted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group method [1, 2] for assessing the quality of evidence and expressing the strength of recommendations regarding drug-drug interactions with medications used to treat HIV and hepatitis C [3-6]. Table 1 illustrates the four categories used to assess the quality of evidence based on i) a hierarchy of methodological design, and ii) execution of a study, with the ability to up- or downgrade the assessment of evidence quality [5]. Examples of how the GRADE system was applied to HIV drug-drug interactions are provided in Table 2 [6].

Table 1. Modified GRADE method to assess the quality of drug-drug interaction evidence

<table>
<thead>
<tr>
<th>GRADE Equivalent</th>
<th>Downgrade a</th>
<th>Upgrade b</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Evidence obtained from at least 1 properly designed and executed randomized controlled trial.</td>
<td>Study Quality: • Serious limitations (-1) • Very serious limitations (-2) • Important inconsistency (-1 or -2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence obtained from observational studies.</td>
<td>Directness: • Some uncertainty (-1) • Major uncertainty (-2) Sparse or imprecise data (-1)</td>
</tr>
<tr>
<td>Low</td>
<td>High probability of publication bias (-)</td>
<td></td>
</tr>
<tr>
<td>Very Low</td>
<td>Strong Association: • Strong, no confounders, consistent &amp; direct evidence (+1) b • Very strong, no major threats to validity, direct evidence (+2) c • Evidence of dose response gradient (+1) • All plausible confounders would have reduced effect (+1)</td>
<td></td>
</tr>
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GRADE = Grading of Recommendations Assessment, Development and Evaluation

a 1 = move up or down one grade (e.g., from high to moderate); 2 = move up or down two grades (e.g., from high to low)

b A statistically significantly relative risk of >2 (<0.5), based on consistent evidence from two or more observational studies, with no plausible confounders

c A statistically significant relative risk >5 (<0.2) based on direct evidence with no major threats to validity.

The strength of recommendation was framed in the context of the question: Is it safe to administer both drugs? The GRADE equivalents were mapped to symbols representing recommendations in a simple, readily recognizable graphical representation [5, 6]. A red circle indicates, “These drugs should not be co-administered;” an orange square indicates, “Potential interaction – may require close monitoring, alteration of dosage, or timing of administration;” a green diamond indicates, “No clinically significant interaction expected;” and a black star indicates, “There are no clear data, actual or theoretical, to indicate whether an interaction will occur” [3, 4]. Filled symbols indicate further information on the interaction is available on the University of Liverpool drug interaction websites (www.hiv-druginteractions.org or http://www.hiv-druginteractions.org/). Empty symbols indicate the combination has not been studied and that an interaction has been predicted based on the metabolic profiles of the drugs.

References