Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials

Andrew M. Hill, Nikkita Mitchell, Sophie Hughes, and Anton L. Pozniak

Purpose of review
Results from nonrandomized cohort studies suggest higher risks of CNS adverse events for dolutegravir, versus other ARVs. There have been two case reports of myocarditis on dolutegravir. Integrase inhibitors have been associated with IRIS in two cohort studies. Meta-analysis of randomized trials can be used to cross-check potential safety signals. This systematic review of drug safety used an EMBASE and MEDLINE search combined with serious adverse event (SAE) reports on the website www.clinicaltrials.gov. Cardiovascular, CNS or IRIS-associated adverse events were analysed for dolutegravir versus other ARVs. Relative risks for the comparison between dolutegravir and other antiretrovirals were calculated for each adverse event. Meta-analyses applied Mantel–Haenszel random-effects models.

Recent findings
There was a higher risk of Grade 1–4 insomnia adverse events for DTG (6.1%) versus other ARVs (4.5%; P = 0.02). There was no significant difference between DTG and other ARVs in the risk of cardiovascular serious adverse events. In the SINGLE and SPRING-1 trials comparing DTG with efavirenz, there were 5/465 patients with reported suicidality SAEs on DTG (1.1%) versus 6/469 (1.3%) on EFV. In other studies, serious adverse events of suicidality were reported for 15/2250 patients on DTG (0.7%) versus 9/2257 patients on other ARVs (0.4%). Risks of IRIS were low, but event rates were low and the main trials excluded CDC stage C disease.

Summary
In this meta-analysis, there was no significant effect of dolutegravir on the risk of cardiac, IRIS or suicide-related serious adverse events. There was a higher risk of insomnia for DTG. Other completed randomized trials should be included in new evaluations of DTG safety. Continued pharmacovigilance, with regular meta-analyses, should be used to monitor safety.

Keywords
adverse events, antiretroviral treatment, dolutegravir, efavirenz, integrase inhibitors

INTRODUCTION
World Health Organization (WHO) guidelines currently recommend first-line treatment for HIV with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC) and either the non-nucleoside efavirenz (EFV) or the integrase inhibitor dolutegravir (DTG) [1]. Treatment guidelines in high-income settings have recently been revised to recommend first-line use of integrase inhibitors in preference to EFV [2–4].

A single generic tablet containing tenofovir, 3TC and DTG is becoming available in low-income and middle-income countries for US $75 per year [5,6], which is cheaper than efavirenz-based first-line
Dolutegravir is becoming a first-line antiretroviral treatment option in several low-income and middle-income countries, because of its clinical advantages and its reduced cost as a generic fixed-dose combination.

Observational study reports suggest there may be increased risk of cardiac, CNS and IRIS-related adverse events with use of dolutegravir.

There is limited published safety data from randomized trials for dolutegravir, particularly for at-risk populations (pregnant women, those with tuberculosis co-infection, CDC stage C disease and/or low CD4 counts).

This meta-analysis of 6647 patient-years of follow-up showed increased risk of Grade 1–4 insomnia for DTG versus other ARVs, with no significant difference in risk of cardiac, suicidality or IRIS-related adverse events.

Independent pharmacovigilance could be improved by the publication of standardized adverse event data from randomized trials, including all severity grades, frequency and cause.

KEY POINTS

- Dolutegravir is becoming a first-line antiretroviral treatment option in several low-income and middle-income countries, because of its clinical advantages and its reduced cost as a generic fixed-dose combination.
- Observational study reports suggest there may be increased risk of cardiac, CNS and IRIS-related adverse events with use of dolutegravir.
- There is limited published safety data from randomized trials for dolutegravir, particularly for at-risk populations (pregnant women, those with tuberculosis co-infection, CDC stage C disease and/or low CD4 counts).
- This meta-analysis of 6647 patient-years of follow-up showed increased risk of Grade 1–4 insomnia for DTG versus other ARVs, with no significant difference in risk of cardiac, suicidality or IRIS-related adverse events.
- Independent pharmacovigilance could be improved by the publication of standardized adverse event data from randomized trials, including all severity grades, frequency and cause.

Safety analysis for dolutegravir

Dolutegravir: Safety Analyses in Nonrandomized Cohort Studies

There was a report of two cases of myocarditis on dolutegravir [16], with one additional case of myocarditis in the FLAMINGO trial, part of the Phase 3 development programme [10]. Data from two recent studies from nonrandomized cohort studies in France and the Netherlands reported an association between the use of integrase inhibitors and a higher risk of Immune Reconstitution Inflammatory Syndrome (IRIS) [17,18]. Results from nonrandomized cohort studies suggest a higher risk of CNS adverse events for dolutegravir compared with other integrase inhibitors [19–22]; insomnia was a particular issue in these studies. Cohort studies are not randomized trials, so there is the potential for bias and confounding in the reported association with these
adverse events. There was evidence for ‘channeling bias’ in the OPERA cohort: patients with preexisting CNS conditions were more likely to be treated with dolutegravir, which could contribute to the higher risks of CNS adverse events seen [23]. It is possible that these reports of adverse events in the observational studies were unusual findings, not seen consistently in other studies.

The European Summary of Product Characteristics (SPC) for dolutegravir lists IRIS as an uncommon adverse event, which could occur in 0.1–1% of treated patients [24]. Insomnia, abnormal dreams and depression may occur in 1–10% of treated patients, according to the SPC; suicidal ideation, or suicide attempt (particularly in patients with a preexisting history of depression or psychiatric illness) may occur in 0.1–1% of treated patients. However, it is not clear from the SMPC whether these risks are higher than would be expected when using other, alternative ARVs.

Randomized clinical trials of ARVs normally include 200–400 patients per treatment arm. These sample sizes can be too small to detect treatment-related effects on rare adverse events. The increased risk of suicide-related adverse events for efavirenz was only seen when a meta-analysis of clinical trials was conducted, including over 6000 patients [25].

Given the need for independent evaluation of safety, a systematic review and meta-analysis was conducted to evaluate whether dolutegravir is associated with increased risks of cardiovascular, CNS or IRIS-related adverse events, which have been identified as potential issues from observational studies.

**METHODS**

Embase and Medline databases were searched in line with PRISMA guidelines from the earliest available date until 20th April 2017. This was supplemented by a search of clinical trials presented at the International AIDS Society Conference in Paris in July 2017.

Trials with a randomized controlled design were included, if they had an intervention arm containing dolutegravir at the standard dose of 50 mg once daily versus a control arm with another ARV. Non-standard doses of dolutegravir were not included. Criteria for exclusion of trials were populations with HIV-2 infection, single-arm or cross-over designs, no active control arms and under 24 weeks of randomized treatment. Trials with dolutegravir in all treatment arms were also excluded.

For each clinical trial, data on the number of patients with key adverse events were recorded wherever available. Serious adverse events (SAEs) were collected from the database www.clinicaltrials.gov wherever available, or from the supplementary appendices of trial publications. For cardiac disorders, all SAEs listed under the system organ class ‘cardiac disorders’ were recorded. For suicide-related disorders, three SAEs were recorded: suicidal ideation, attempted suicide and completed suicide. For insomnia, Grade 1–4 adverse event information from clinical trial publications were recorded. For IRIS, all adverse event information available was recorded.

Relative risks for the comparison between dolutegravir and other ARVs were calculated for each adverse event. Meta-analyses applied Mantel–Haenszel random-effects models. The meta-analyses of suicide-related SAEs was stratified by the use of efavirenz, which has been associated with a higher risk in another meta-analysis [25]. The meta-analysis of insomnia was also stratified according to the design of the studies (switch versus nonswitch design). This was because patients already stable on a current treatment might be more likely to show new adverse events whenever switched to a new treatment, versus remaining on their current treatment.

To minimize the risk of publication bias, all completed trials of dolutegravir, which had been registered on www.clinicaltrials.gov were checked for availability of results from at least one source. The results were collected independently by two authors (A.H. and N.M.) and cross-checked.

**RESULTS**

The PUBMED /EMBASE search identified a total of 496 reports. There were 150 studies identified on www.clinicaltrials.gov, of which 8 trials were eligible for analysis. There was one additional study presented at IAS 2017 which was included in the analysis (NEAT 022). Table 1 shows a summary of the nine randomized trials included in this meta-analysis. There was a total of 6647 patient-years of follow-up in these nine randomized studies.

Two studies, SPRING-2 and SAILING, compared dolutegravir with another member of the integrase inhibitor class (raltegravir). There were five studies in treatment-naïve patients (SINGLE [9**], SPRING 1 [26], SPRING 2 [13], FLAMINGO [10] and ARIA [11]), one in treatment experienced patients (SAILING [27]) and three switch studies for patients with HIV RNA suppression at baseline (STRIIVING [28], NEAT 022 [29**] and SWORD 1/2 [30]). For the SWORD 1 and 2 studies, there was no serious adverse event data available; only adverse events leading to discontinuation and those recorded for at least 5% of patients in one treatment arm were reported. Therefore, the SWORD studies were not included in the analysis of cardiac SAEs, and only partial information about suicide-related SAEs could be included (only...
those leading to discontinuation). In the STRIIVING study [28], randomized treatment was for 24 weeks, after which time all patients received dolutegravir: only the initial 24-week randomized phase was included in the meta-analysis. Full safety data were available for only two of the nine studies – SINGLE and NEAT 022. For the other studies, the results included serious adverse events, adverse events leading to discontinuation, and all Grade 1–4 adverse events recorded in at least 5% of patients in one treatment arm. (SPRING-1 was the exception, with data available at a threshold of at least 3% of patients.) Therefore, other adverse events, which were not reported as SAEs or occurring in fewer than 5% of patients, cannot be assessed in this meta-analysis. In addition, all nine studies excluded patients with CDC stage C disease at baseline. CDC stage C disease is associated with a higher risk of IRIS.

Table 2 shows the three completed studies and five ongoing studies of dolutegravir, which could not

### Table 1. Randomized trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>ABC/3TC/DTG TDF/FTC/EFV</td>
<td>833</td>
<td>Naıve</td>
<td>144 weeks</td>
</tr>
<tr>
<td>SPRING-1</td>
<td>2NRTI+DTG</td>
<td>101</td>
<td>Naıve</td>
<td>96 weeks</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>2NRTI/DTG</td>
<td>822</td>
<td>Naıve</td>
<td>96 weeks</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>2NRTI/DTG</td>
<td>484</td>
<td>Naıve</td>
<td>96 weeks</td>
</tr>
<tr>
<td>ARIA</td>
<td>2NRTI/DTG</td>
<td>495</td>
<td>Naıve</td>
<td>48 weeks</td>
</tr>
<tr>
<td>SAILING</td>
<td>OB + DTG OB + RAL</td>
<td>719</td>
<td>Experienced</td>
<td>48 weeks</td>
</tr>
<tr>
<td>STRIIVING³</td>
<td>2NRTI/DTG</td>
<td>551</td>
<td>Switch</td>
<td>24 weeks</td>
</tr>
<tr>
<td>NEAT 022</td>
<td>OB + DTG OB</td>
<td>410</td>
<td>Switch</td>
<td>48 weeks</td>
</tr>
<tr>
<td>SWORD²</td>
<td>RPV + DTG Current</td>
<td>1024</td>
<td>Switch</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

DTG, dolutegravir; EFV, efavirenz; OB, optimized background regimen.

³Limited data available from SWORD studies on insomnia and adverse events leading to discontinuation. No data on cardiac SAEs.

²From weeks 24-48, the control arm switches to DTG.

### Table 2. Randomized trials to be included in future meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Duration/complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAWNING</td>
<td>2NRTI + DTG</td>
<td>627</td>
<td>Experienced</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Gilead 1489</td>
<td>2NRTI + LPV/r</td>
<td>629</td>
<td>Naıve</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Gilead 1490</td>
<td>2NRTI + DTG</td>
<td>645</td>
<td>Naıve</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Ongoing studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSPRING</td>
<td>2NRTI + EFV</td>
<td>125</td>
<td>Naıve</td>
<td>48 weeks/1Q2018</td>
</tr>
<tr>
<td>ADVANZ-4</td>
<td>2NRTI + PI/r</td>
<td>108</td>
<td>Naıve</td>
<td>48 weeks/1Q2018</td>
</tr>
<tr>
<td>NAMSAL</td>
<td>TDF/3TC/DTG TDF/3TC/EFV</td>
<td>606</td>
<td>Naıve</td>
<td>96 weeks/4Q2018</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>TDF/FTC/DTG TAF/FTC/DTG TDF/FTC/EFV</td>
<td>1110</td>
<td>Naıve</td>
<td>96 weeks/1Q2019</td>
</tr>
<tr>
<td>D2EFT</td>
<td>DTG + DRV/r</td>
<td>610</td>
<td>Experienced</td>
<td>48 weeks/4Q2019</td>
</tr>
<tr>
<td>VESTED</td>
<td>TAF/FTC/DTG TDF/FTC/DTG TDF/FTC/EFV</td>
<td>549</td>
<td>Naıve</td>
<td>50 weeks postpartum</td>
</tr>
</tbody>
</table>

DTG, dolutegravir; EFV, efavirenz.
be included in this analysis. The three completed studies – DAWNING [12], Gilead 1489 [14] and Gilead 1490 [15] – have been presented publicly. However, the detailed safety data is not available on the website www.clinicaltrials.gov or as a supplement to the main publication of the trial (for the two Gilead studies). The approximate dates of completion of the ongoing studies – INSPIRING [31] & ADVANCE [34] & D2EFT [35] and VESTED [36] – are listed in Table 2.

### CARDIAC SERIOUS ADVERSE EVENTS

The SINGLE, SAILING, FLAMINGO, SPRING-1, SPRING-2, ARIA, STRIVING and NEAT 022 trials were included for analysis (Table 3). There was a

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG arm</th>
<th>Cardiac SAEs</th>
<th>Control arm</th>
<th>Cardiac SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE, 144 weeks</td>
<td>DTG: 4/414</td>
<td>Congestive cardiac failure - Not considered drug-related.</td>
<td>EFV: 2/419</td>
<td>Atrial fibrillation - Not considered drug-related.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pericarditis - Not considered drug-related.</td>
<td></td>
<td>- Cocaine use immediately prior to events. PMHx of prior atrial dysrhythmia following cocaine use, angina pectoris, hypertensive cardiomyopathy, cardiac failure congestive.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Chest pain, hospitalized. Treated with ibuprofen and resolved. RF: nil Cardiac failure - Not considered drug-related.</td>
<td></td>
<td>- RF: cocaine abuse.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Right ventricular failure - Not considered drug-related.</td>
<td></td>
<td>- Coronary artery disease - Not considered drug-related.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Considered secondary to sleep apnoea syndrome and hypertensive heart disease).</td>
<td></td>
<td>- Chest pain, stress ECG-induced angina. Investigations revealed coronary heart disease with raised left ventricular pressure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PMHx of right heart failure. RF: hypertension, hyperglycaemia, obesity.</td>
<td></td>
<td>- RF: smoker.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Severe angina, underwent PCI. PMHx of previous MI. RF: hypertension, hypertriglyceridaemia, hypercholesterolaemia.</td>
<td></td>
<td>- Shortness of breath, greatly reduced ejection fraction. PMHx of previous cardiomyopathy. RF: hypertension.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Atypical chest pain, investigations revealed dilated cardiomyopathy with left ventricular dysfunction.</td>
<td></td>
<td>- Shortness of breath, greatly reduced ejection fraction. PMHx of previous cardiomyopathy. RF: hypertension.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Considered viral cause. RF: nil Coronary artery disease - Not considered drug-related.</td>
<td></td>
<td>- Coronary artery disease - Not considered drug-related.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acute coronary syndrome, underwent PCI. RF: hypertension, hypertriglyceridaemia, FHx of MI (Father).</td>
<td></td>
<td>- Acute chest pain, investigations revealed multiple coronary artery stenoses. Underwent PCI. PMHx: possible previous TIA. RF: Previous smoker, hypercholesterolaemia, hypertriglyceridaemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Myocarditis - Not considered drug-related.</td>
<td></td>
<td>- Previous smoker, hypercholesterolaemia, hypertriglyceridaemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Chest pain, myocarditis revealed on MRI.</td>
<td></td>
<td>- Underlying cause not reported. Resolved. RF: smoker, hypertension, hypertriglyceridaemia, Alcoholic cardiomyopathy - Not considered drug-related.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Underlying cause not reported.</td>
<td></td>
<td>- Acute respiratory failure due to exacerbation of COPD, cardiomyopathy and hypventilation. PMHx of angina. RF: hypertension, hypercholesterolaemia, hypertriglyceridaemia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- RF: Diabetic on insulin.</td>
</tr>
</tbody>
</table>
wide range of cardiac SAEs reported, with no clear trend for a particular type of cardiac SAE on dolutegravir. There was one case of myocarditis recorded, in the FLAMINGO trial.

Overall, there were 15/2202 (0.7%) patients with cardiovascular SAEs on DTG versus 8/2215 (0.4%) on other ARVs [relative risk (RR) = 1.69, NS; Table 4]. There were 25 cardiac SAEs recorded in 23 patients: of these, 1 was considered drug-related (DTG arm of SPRING-2); 1 other cardiac SAE was considered unlikely-drug related (DTG arm of SPRING-1).

Additional case information was available for 19 of the 23 patients with cardiac SAEs. Seventeen of 19 patients had underlying cardiac risk factors (89%).

### Table 3 (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG arm</th>
<th>Cardiac SAEs</th>
<th>Control arm</th>
<th>Cardiac SAEs</th>
</tr>
</thead>
</table>
| SPRING-1, 96 weeks | DTG: 1/51 | Acute myocardial infarction  
- Considered unlikely drug-related.  
Right coronary artery 100% stenosed.  
RF: [considered most likely cause] smoker, borderline dyslipidemia | EFV: 0/50    |              |
| SPRING-2, 96 weeks | DTG: 1/411 | Arrhythmia  
- Considered drug-related.  
Episodic dizziness & weakness at Day 196. Short runs of VT & ventricular ectopics on investigation, considered to be right ventricular outflow tract ventricular tachycardia. Treated & withdrawn from study. Resolved within 2 days & at later follow-up. Found to have acute hepatitis C.  
RF: smoker, COPD. | RAL: 0/411    |              |
| ARIA, 48 weeks       | DTG: 2/248 | Acute coronary syndrome  
- Not considered drug-related.  
Chest pain and hypertensive emergency. Resolved and blood pressure drugs adjusted.  
RF: hypertension, hypercholesterolemia, hypertriglyceridaemia, vascular disorder, type 2 diabetes, previous smoker.  
Acute myocardial infarction  
- Not considered drug-related.  
Acute chest pain. PMHx of MI, cardiac stents, angina pectoris, left ventricular hypertrophy.  
RF: Smoker, hypertension, diabetes, hypercholesterolaemia, hypertriglyceridaemia. | ATV/r: 0/247  |              |
| STRIVING, 24 weeks<sup>b</sup> | DTG: 1/275 | Congestive cardiac failure  
- Not considered drug-related.  
Shortness of breath. Considered escalation of chronic cardiac failure.  
RF: hypertension, cardiomyopathy. | CAR: 0/276    |              |
| NEAT 022, 48 weeks   | DTG: 1/204 | ST-elevation myocardial infarction  
- Not considered drug-related. | PI: 3/208    | Atrial fibrillation  
- Not considered drug-related.  
ST-elevation myocardial infarction  
- Not considered drug-related.  
Acute myocardial infarction without ST involvement  
- Not considered drug-related. |

**Total** 15/2202 (0.7%) 8/2215 (0.4%)

CAR, current antiretroviral regimen; COPD, chronic obstructive pulmonary disorder; DTG, dolutegravir; EFV, efavirenz; FHx, cardiac family history; MI, myocardial infarction; PCI, percutaneous coronary intervention; PMHx, cardiac past medical history; RF, cardiac risk factor(s); VT, ventricular tachycardia.

<sup>a</sup>Event occurred during the trial along with atrial fibrillation and atrial flutter.

<sup>b</sup>From weeks 24-48, the control arm switches to DTG.

NEAT 022 case narratives unavailable.

SWORD 1 and 2 SAE data not yet publicly available.

### Suicide-Related Adverse Events

In the SINGLE and SPRING-1 trials, there were 5/465 patients with reported suicidality SAEs on DTG (1.1%) versus 6/469 (1.3%) on EFV (RR = 0.87, NS; Table 4). In the SAILING, FLAMINGO, SPRING-2, ARIA, STRIVING, SWORD and NEAT 022 trials, SAEs of suicidality were reported for 15/2250 patients on DTG (0.7%) versus 9/2257 patients on other ARVs (0.4%; RR = 1.58, NS, Fig. 2 and Table 5).

### Insomnia

The risk of Grade 1–4 insomnia was higher for DTG (Table 6 and Fig. 3): There were 165/2716 patients with Grade 1–4 insomnia on dolutegravir (6.1%).
versus 124/2727 on other ARVs (4.5%; RR = 1.30; P = 0.02, Fig. 3). There was no significant difference in risk of insomnia between the studies with a continue versus switching design, and head-to-head studies in naïve or experienced patients (Fig. 3).

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**

IRIS was reported in 1/414 participants on DTG versus 2/419 participants on EFV in SINGLE, 6/354 (DTG) versus 3/361 (RAL) in SAILING, and 1/465 (1.1%) vs. 6/469 (1.3%) in SPRING-1 (Table 4).

**Table 4.** Suicide-related serious adverse events in randomized clinical trials of dolutegravir versus efavirenz

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG arm</th>
<th>Suicidality SAEs</th>
<th>Control arm</th>
<th>Suicidality SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Suicide attempt [3]</td>
<td></td>
<td>Suicide attempt [2]</td>
</tr>
<tr>
<td>SPRING-1</td>
<td>DTG: 0/51</td>
<td>EFV: 1/50</td>
<td></td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>Total</td>
<td>5/465 (1.1%)</td>
<td>6/469 (1.3%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DTG, dolutegravir; EFV, efavirenz.

**FIGURE 1.** Meta-analysis of cardiac serious adverse events in randomized trials of dolutegravir.

**FIGURE 2.** Meta-analysis of suicide-related serious adverse events in randomized trials of dolutegravir.
Table 5. Suicide-related serious adverse events in randomized clinical trials of dolutegravir versus other antiretrovirals

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG arm</th>
<th>Suicidality SAEs</th>
<th>Control arm</th>
<th>Suicidality SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAILING</td>
<td>DTG: 6/357</td>
<td>Suicidal ideation (4)</td>
<td>RAL: 2/362</td>
<td>Suicidal ideation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suicide attempt (2)</td>
<td></td>
<td>Depression suicidal</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG: 4/242</td>
<td>Suicide attempt (3)</td>
<td>DRV/r: 0/242</td>
<td>Completed suicide</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>DTG: 2/411</td>
<td>Suicide attempt (2)</td>
<td>RAL: 6/411</td>
<td>Suicide attempt (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suicidal ideation (2)</td>
<td></td>
<td>Completed suicide</td>
</tr>
<tr>
<td>ARIA</td>
<td>DTG: 0/248</td>
<td>AtV/r: 0/247</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRIVING*</td>
<td>DTG: 1/275</td>
<td>Suicide attempt</td>
<td>CAR: 0/276</td>
<td></td>
</tr>
<tr>
<td>SWORD 1 and 2*</td>
<td>DTG: 1/513</td>
<td>Suicidal ideation</td>
<td>CAR: 1/511</td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>NEAT 022</td>
<td>DTG: 1/204</td>
<td>Suicidal ideation</td>
<td>Pt: 0/208</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15/2250 (0.7%)</td>
<td>9/2257 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

CAR, current antiretroviral regimen; DTG, dolutegravir; EFV, efavirenz; SAE, serious adverse event.
*STRIIVING adverse events included up to 24 weeks only (from weeks 24–48, the control arm switches to DTG).
*STRIIVING adverse events reported at a frequency threshold of greater than 3%.
*STRIIVING adverse events leading to withdrawal only.

Table 6. Grade 1–4 insomnia adverse events in randomized trials of dolutegravir

<table>
<thead>
<tr>
<th>Trial</th>
<th>DTG arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINGLE</td>
<td>DTG: 7/414</td>
<td>EFV: 5/419</td>
</tr>
<tr>
<td>SAILING</td>
<td>DTG: 12/357</td>
<td>RAL: 14/362</td>
</tr>
<tr>
<td>FLAMINGO</td>
<td>DTG: 19/242</td>
<td>DRV/r: 16/242</td>
</tr>
<tr>
<td>SPRING-1</td>
<td>DTG: 6/513</td>
<td>EFV: 6/50</td>
</tr>
<tr>
<td>SPRING-2</td>
<td>DTG: 25/411</td>
<td>RAL: 19/411</td>
</tr>
<tr>
<td>ARIA</td>
<td>DTG: 10/248</td>
<td>AtV/r: 8/247</td>
</tr>
<tr>
<td>STRIVING*</td>
<td>DTG: 10/276</td>
<td>CAR: 1/277</td>
</tr>
<tr>
<td>SWORD 1 and 2*</td>
<td>DTG: 2/513</td>
<td>CAR: 0/511</td>
</tr>
<tr>
<td>NEAT 022</td>
<td>DTG: 7/204</td>
<td>Pt: 8/208</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>165/2716 (6.1%)</td>
</tr>
</tbody>
</table>

CAR, current antiretroviral regimen; DTG, dolutegravir; EFV, efavirenz.
*SIncludes adverse events grades 1-4, frequency threshold for reporting greater than 5%, except the following.
**SPRING-1 adverse events reported at a frequency threshold of greater than 3%.
**SWORD 1 and 2 adverse events leading to withdrawal only.

411 (DTG) versus 0/411 (RAL) in SPRING-2. There were no reported cases of IRIS in SPRING-1, FLAMINGO, STRIIVING or NEAT 022. There was no significant difference in the risk of IRIS between DTG and other ARVs. However, all the randomized trials excluded patients with CDC grade C disease at baseline.

CONCLUSION

In this meta-analysis of randomized trials in 6647 patient-years of follow-up, there was a higher risk of Grade 1–4 insomnia adverse events for DTG (6.1%) versus other ARVs (4.5%; P = 0.02).

There was no significant difference in the risk of cardiac SAEs between DTG and other ARVs. All cardiac SAEs except two were considered to be

FIGURE 3. Meta-analysis of insomnia adverse events in randomized trials of dolutegravir.
unrelated to study medications by the trial investigators, one was possibly drug-related and one was unlikely to be drug-related; 89% of total participants had underlying cardiac risk factors.

The analyses of suicidality are currently inconclusive. Risks of IRIS were low, but event rates were low and the main trials excluded CDC stage C disease.

There are several limitations to this meta-analysis. Of the nine studies included, only two (SINGLE and NEAT 022) had detailed data on all adverse events by treatment arm available for analysis. For the other studies, the only results available were for serious adverse events, common Grade 1–4 adverse events (>5% in any treatment arm) and those leading to discontinuation. However, a more detailed analysis of less common adverse events, not categorized as SAEs or leading to discontinuation, could lead to other conclusions.

Many of the adverse events will not be directly drug-related. Cardiac events may be attributable to other medications taken by participants, HIV-associated chronic inflammation that remains even in treated individuals [37], as well as lifestyle factors such as recreational drug use, alcohol and smoking [38]. HIV is a risk factor for suicide among other psychiatric disorders, which may be a result of social stigma, as well as lifestyle factors [39]. Case narratives for SAEs are not in the public domain, therefore, their nature and cause cannot be determined.

Information regarding drug-relatedness of adverse events was not consistently available. For those adverse events that were deemed unrelated, additional data from multiple trials would help to provide confirmation. Medical journals should request that more detailed study reports be made available, in the format of the publication of the SINGLE trial in the New England Journal of Medicine.

Three completed clinical trials had no results available on the website www.clinicaltrials.gov. Whenever a clinical trial is published in a medical journal, the more detailed safety data should be posted on this website at the same time. This would allow for independent analysis of the safety results in a standardized format.

Finally, there are ongoing randomized trials, conducted by independent research groups and with less restrictive inclusion and exclusion criteria. These clinical trials could improve our knowledge of the safety of dolutegravir in patients with CDC C disease, HIV-TB co-infection and pregnancy.

There are plans to switch millions of patients onto dolutegravir-based treatment in sub-Saharan Africa within the next 18 months. This transition needs to be supported by careful analysis of drug safety. Other completed randomized trials should be included in new evaluations of DTG safety: DAWNING (n = 627), SWORD 1 and 2 (n = 1024), Gilead trial 1489 (n = 629) and Gilead trial 1490 (n = 645). Continued pharmacovigilance, with regular meta-analyses, should be used to monitor safety. A recent analysis of the psychiatric disorders reported to the World Health Organization pharmacovigilance database suggests a higher risk of depression, suicide and self-injury for dolutegravir and raltegravir, compared with elvitegravir [40]. Analyses of this type need to be repeated regularly and checked for potential confounding factors.

Acknowledgements
None.

Financial support and sponsorship
The ongoing analyses of safety were supported by a research grant from the World Health Organization.

Conflicts of interest
A.H. has received consultancy payments from Janssen, not connected with this project. A.P. has received consultancy payments from Gilead, Janssen, BMS, Merck and ViV and Cipla, not connected with this project. N.M. and S.H. report no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
□ of outstanding interest

9. Most recent WHO guidelines outlining potential risks and benefits of transitioning to dolutegravir-containing HIV treatment regimens.

10. Walsme S, Baumgarten A, Berenguer J, et al. Brief report: dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy naïve patients: week 96 and week 144 results from the SINGLE randomised clinical trial. J Acquir Immune Defic Syndr 2015; 70:515–519. Randomized trial with the longest patient follow-up time on dolutegravir. SINGLE was also one of the two trials providing detailed publicly available adverse event information in this report.


18. Duterte M, Cuzin L, Pugliese P, et al. Initiation of ART based on integrase inhibitors increases the risk of IRIS. In: Conference on Retroviruses and Opportunistic Infections (CROI) 2017, Seattle [abstract 732]. Cohort study that observed severe IRIS leading to hospitalization occurring more frequently in participants exposed to integrase inhibitor-containing ART compared with those on other ART regimens.


29. Gatell J, Assoumou L, Moyle G, et al. Switching from a boosted protease inhibitor (PI)/based regimen to a dolutegravir (DTG) regimen in virologically suppressed patients with high cardiovascular risk (Framingham score > 10% or age > 50 years) is noninferior and decreases lipids: The NEAT 022 study [oral abstract].

In this report, NEAT 022 was one of the two trials providing detailed publicly available adverse event information.


An ongoing trial that will provide safety data on use of dolutegravir versus efavirenz in HIV/TB infection.


A large, ongoing trial that will provide safety data on use of dolutegravir in a resource-limited setting.


An ongoing trial that will provide safety data on use of dolutegravir versus efavirenz during pregnancy.


