CPAG Summary Report for Clinical Panel – URN1806
Clinical evidence review of dolutegravir-rilpivirine for treating human immunodeficiency virus type 1 (HIV-1) in adults

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported
5.	Usual activities	Not reported
6.	Pain	Pain can sometimes be caused by the medication taken to control HIV. The main studies reported that 3% of participants in the dolutegravir-rilpivirine group and 6% in the existing ART group experienced back pain by week 48. By week 100, 6% of the participants in the dolutegravir-rilpivirine group reported back pain. Arthralgia (joint pain) was reported by 4% of participants in the dolutegravir-rilpivirine group and 2% of the existing ART group by week 48. By week 100, arthralgia was reported by 7% of participants in the dolutegravir-rilpivirine group. Headache was reported by 8% of participants in the dolutegravir-rilpivirine group and 5% of the existing ART group by week 48. By week 100, headache was reported by 12% of participants in the dolutegravir-rilpivirine group. The statistical significance of the difference between the groups was not reported. It is not possible to determine from the evidence whether dolutegravir-rilpivirine makes a difference to feelings of pain during treatment compared to other antiretroviral therapies. The results should be interpreted with caution because the studies were open label in design (both the participant and the researcher knew whether each participant received dolutegravir-rilpivirine or not). This may have introduced bias. It is not clear

		how generalisable the results are to the UK as although some of the participants were from the UK, it is not clear many participants from other countries in the studies were similar to the UK population.
7.	Anxiety / Depression	Anxiety is a feeling of unease and can include symptoms such as feeling restless or worried, having trouble concentrating or sleeping, and dizziness or heart palpitations. Depression is a mood disorder characterised by low mood, feelings of sadness, and a loss of interest in activities that used to be enjoyable. The main studies reported that 2% of participants in the dolutegravir-rilpivirine group and 2% in the existing ART group experienced anxiety by week 48. Depression was reported by 3% of participants in the dolutegravir-rilpivirine group and 1% of the existing ART group by week 48. The statistical significance of the difference between the groups was not reported. It is not possible to determine from the evidence whether dolutegravir-rilpivirine improves anxiety or depression compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ for the limitations with this evidence.
8.	Replacement of more toxic treatment	There is no direct evidence for dolutegravir-rilpivirine replacing a more toxic treatment, however, there is evidence of its effect on renal function and bone mineral density compared to TDF-containing regimens (see row 3 ‘Renal function’ and row 5 ‘Bone mineral density’ in the table below).
9.	Dependency on care giver / supporting independence	Burden on caregiver is the strain or load taken on by a person who cares for someone who is chronically ill. When caring for someone with HIV, this may include helping them to take their medications at the correct time and taking them to healthcare appointments. Two case reports stated that switching to dolutegravir-rilpivirine reduced the burden on caregivers at home in patients with difficulty swallowing. The results should be interpreted with caution because they are limited to case reports from 2 Japanese participants. It is not clear how applicable

		these results would be to the UK population. It is not clear whether the participants fully reflect the marketing authorisation of dolutegravir-rilpivirine as it is not reported whether they had a known resistance to NNRTIs or INIs.
10.	Safety	Adverse events are unintentional and undesirable signs and symptoms reported during a study. If an event is thought to be related to the drugs being used in a study, it is known as a drug-related adverse event. In the main studies, 19% of the group that switched to dolutegravir-rilpivirine and 2% of the group that remained on their existing ART had a drug-related adverse event by week 48. These were serious in 1% and <1% of the groups respectively, and no deaths were related to the study drugs. Adverse events leading to withdrawal by week 48 were reported in 17 (3%) participants in the dolutegravir-rilpivirine group and 3 (1%) participants in the existing ART group. The statistical significance of the difference between the groups for any of the adverse event outcomes was not reported. By week 100, 88% of the participants who switched to dolutegravir-rilpivirine had reported at least 1 adverse event. Please note that subjects in both arms were on a stable ART for at least 6 months prior to either remaining on that treatment, or switching to dolutegravir-rilpivirine. People remaining on their existing regimen may be less likely to experience an adverse event (compared with those switching treatments) because they have already demonstrated some tolerance to it. It is not possible to determine from the evidence whether there was a difference in the number of drug-related adverse events with dolutegravir-rilpivirine compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ for the limitations with this evidence.
11.	Delivery of intervention	Dolutegravir-rilpivirine is a small oral tablet. There is no comparative evidence of the benefits of taking a smaller tablet compared to existing ART, however, there is evidence from two case reports that

		switching to dolutegravir-rilpivirine allowed patients with dysphagia (difficulty swallowing) to take tablets without having to crush them or prepare them in an oral suspension.

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Viral load	Viral load is a measure of how much HIV virus is in the blood. Higher levels of HIV in the blood increase the risk of a person with HIV becoming ill from other infections and passing the virus on to other people. The aim of antiretroviral therapy is to reduce viral load to less than 50 copies/mL. The main studies reported that the number of participants who had a viral load of less 50 copies/mL at week 48 was statistically significantly non-inferior in the group that switched to dolutegravir-rilpivirine than in the group who remained on their existing ART (94.7% vs 94.9%, adjusted treatment difference of -0.2%, 95% CI -3% to +2.5%, non-inferiority margin of 4%). Around 89% of the participants that switched to dolutegravir-rilpivirine had a viral load of <50 copies/mL at week 100. The evidence suggests that dolutegravir-rilpivirine is as effective as other antiretroviral therapies in maintaining a viral load of less than 50 copies/mL. See the final paragraph of row 6 ‘Pain’ in the table above for the limitations with this evidence.
2.	CD4 cell count	CD4 cells are white blood cells that fight infections in the body. The HIV-1 virus kills CD4 cells, increasing the risk of the person with HIV developing serious illnesses. The main studies reported that CD4 cell count increased from baseline to week 48 by 28.0 cells/µL in the dolutegravir-rilpivirine group and 22.0 cells/µL in the group that remained on their existing ART. The statistical significance of the difference in the increases between the groups is not reported. By week 100, the median CD4 cell count in participants who had switched to dolutegravir-rilpivirine had increased by 33 cells/µL compared to baseline.

		It is not possible to determine from the evidence whether dolutegravir-rilpivirine had a greater or lesser effect on CD4 cell count compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ in the table above for the limitations with this evidence.
3.	Renal function	Renal function is a measure of how well the kidneys are working. If the kidneys are not working well, this has a negative effect on the filtration of toxins and waste products from the blood, the release of hormones that regulate blood pressure, the production of red blood cells, and the absorption of calcium. The main studies reported ‘no consistent pattern of change’ from baseline to 48 weeks across 12 different measures of renal function, including estimated glomerular filtration rate. The statistical significance of the difference in changes between the group that switched to dolutegravir-rilpivirine and the group that remained on their existing ART was not reported. It is not possible to determine from the evidence whether dolutegravir-rilpivirine had a greater or lesser effect on renal function compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ in the table above for the limitations with this evidence.
4.	Blood lipids	Blood lipids are fats in the blood, such as fatty acids and cholesterol. Generally, the presence of elevated or abnormal levels of lipids or lipoproteins in the blood (hyperlipidaemia) increases the risk of developing heart disease, gall bladder disease and pancreatitis. The main studies reported on changes in total cholesterol, mean HDL cholesterol, mean calculated LDL cholesterol, mean triglycerides, and mean total:HDL cholesterol from baseline to 48 weeks. The difference in the change between the group that switched to dolutegravir-rilpivirine and the group that remained on their existing ART was reported to be

		not statistically significant for all of the outcomes, although the p values were not reported. Changes from baseline to week 100 in the dolutegravir-rilpivirine group of the SWORD studies were reported to show 'no clinically relevant effect' (p values not reported). The evidence suggests that the change in blood lipids with dolutegravir-rilpivirine was similar to the change in blood lipids when using other antiretroviral therapies. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
5.	Bone mineral density	Bone mineral density (BMD) is the amount of bone mineral in bone tissue. A decrease in bone mineral density, also known as bone loss, is associated with a higher risk of bone fracture and is an indirect indicator of osteoporosis. One of the studies reported a statistically significant improvement by 48 weeks with dolutegravir-rilpivirine compared to existing tenofovir disoproxil fumarate based ART for total hip BMD (+1.29%, 95% CI +0.27% to +2.31%, p=0.014) and total lumbar spine BMD (+1.32%, 95% CI +0.07% to +2.57%, p=0.039). The evidence suggests that there is a greater increase in bone mineral density in the hip and spine when using dolutegravir-rilpivirine compared to continuing with tenofovir disoproxil fumarate based antiretroviral therapies. The results should be interpreted with caution because it is not clear how generalisable the results are to the UK. Although some of the participants were from the UK, it is not clear many participants from other countries in the studies were similar to the UK population.
6.	Treatment adherence	Treatment adherence describes the extent to which someone acts on medical advice about their treatment, such as taking the recommended dose of medication each day. Poor adherence to ART can increase a person's viral load, which puts them at increased risk of becoming ill from other infections. Poor adherence can also lead to permanent

		resistance of HIV to a particular drug or class of drugs. The main studies reported that patient reported treatment adherence by week 48 was 97.9% in the group that switched to dolutegravir-rilpivirine and 98.3% in the group that remained on their existing ART. The statistical significance of the difference between the groups was not reported. The 2 case reports reported that adherence was maintained for 12 months after switching to dolutegravir-rilpivirine in patients with difficulty swallowing. Although numerically treatment adherence was similar in both groups, it is not possible to conclude from the evidence whether dolutegravir-rilpivirine resulted in better or worse treatment adherence compared to other antiretroviral therapies because statistical significance was not reported. See the final paragraphs of rows 6 ‘Pain’ and 9 ‘Dependency on caregiver’ in the table above for the limitations with this evidence.
7.	Viral resistance	Viral resistance refers to when a virus is no longer affected by a drug that used to be effective against it. It means that a virus will continue to multiply despite the presence of a drug that would usually kill it. The main studies reported that 3 participants out of 513 (0.6%) who switched to dolutegravir-rilpivirine developed a viral mutation by week 100. At least one of the participants with a mutation did not show a decreased susceptibility to dolutegravir-rilpivirine, however, it was not reported whether the other two participants showed a decreased susceptibility or not. No cases of viral resistance were reported by week 48 in the group that remained on their existing ART. It is not possible to determine from the evidence whether dolutegravir-rilpivirine resulted in more or fewer cases of viral resistance compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ in the table above for the limitations with this evidence.

8.	Health related quality of life	Health related quality of life is the perceived quality of a person's daily life based on their physical and mental health. The main studies reported that there was no statistically significant difference in change in satisfaction with HIV treatment (as measured by the HIV Treatment Satisfaction Questionnaire) when comparing dolutegravir-rilpivirine (54.4 to 55.9) with existing ART (53.9 to 54.3). There was a statistically significant improvement in symptom bother score (as measured by the Symptom Distress Module) with dolutegravir-rilpivirine (9.6 to 8.2) compared to existing ART (11.0 to 10.3). The results suggest that dolutegravir-rilpivirine had a similar effect on total HIV Treatment Satisfaction Questionnaire score as other antiretroviral therapies. The results suggest that dolutegravir-rilpivirine improved symptom bother score more than other antiretroviral therapies. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.