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Clinical evidence review of dolutegravir-rilpivirine for treating human immunodeficiency virus type 1 (HIV-1) in adults

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About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers dolutegravir-rilpivirine for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least six months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Four studies published in 4 papers are included in this review. Evidence of the efficacy of dolutegravir-rilpivirine comes from the pooled results of 2 identically designed randomised controlled non-inferiority trials (SWORD-1 and SWORD-2) and a substudy of the randomised controlled trials. The aim of the main studies was to demonstrate that dolutegravir-rilpivirine was non-inferior to existing treatments for the trial population. A paper of 2 case reports provided additional data on treatment adherence and caregiver burden.

Effectiveness

The evidence suggests that dolutegravir-rilpivirine is statistically significantly non-inferior (that is, it is no less effective) than existing antiretroviral therapies for the primary effectiveness outcomes. Use of dolutegravir-rilpivirine in the SWORD studies did not result in more participants with a viral load of 50 copies or more per mL at 48 weeks compared with existing antiretroviral therapies. The number of participants with a viral load of 50 copies or more per mL remained low at 100 weeks, however, this was not compared with existing antiretroviral therapies.

The SWORD studies also reported on CD4 cell count, however, it was not possible to determine from the evidence whether dolutegravir-rilpivirine was any more or less effective than existing antiretroviral therapies at increasing CD4 cell count.

Participants in the SWORD studies reported similar levels of satisfaction with the use of dolutegravir-rilpivirine compared with existing antiretroviral therapies. Participants who switched to dolutegravir-rilpivirine reported less distress linked to their HIV and

medication symptoms compared with those who remained on existing antiretroviral therapies.

The case reports stated that the use of dolutegravir-rilpivirine relieved the burden on caregivers as it did not need to be crushed or prepared as an oral suspension.

Safety and tolerability

It is not clear from the evidence whether dolutegravir-rilpivirine is safe and well tolerated.

Use of dolutegravir-rilpivirine in the SWORD studies was associated with similar changes to blood lipid levels as existing antiretroviral therapies.

The SWORD substudy reported a greater increase in bone mineral density with dolutegravir-rilpivirine compared with existing antiretroviral therapies.

The SWORD studies also reported on adverse events, renal function, treatment adherence and viral resistance, however, it was not possible to determine from the evidence whether there was a statistically significant difference in these outcomes in the participants that switched to dolutegravir-rilpivirine compared with those who remained on existing antiretroviral therapies.

Evidence gaps and limitations

The evidence base is limited to pooled data from 2 randomised controlled trials (RCTs), a substudy of the RCTs, and 2 case reports. The SWORD studies were open label in design, which may have introduced bias in the reporting of outcomes.

Some of the participants in the SWORD studies were from the UK, however, it is not clear how similar the rest of the study population would be to the UK population.

The published comparative data is limited to a follow up of 48 weeks. People with HIV may be using dolutegravir-rilpivirine for longer than 48 weeks, but the efficacy of dolutegravir-rilpivirine compared with existing antiretroviral therapies after this time is not known. It is also not clear which existing antiretroviral therapies dolutegravir-rilpivirine was being compared with.

Table of contents

Abbreviations 5
Medical definitions 5
1 Introduction 6
Disease background 6
Focus of review 6
Epidemiology and needs assessment 6
Product overview 7
Treatment pathway and current practice 7
2 Evidence 8
Literature search 8
Overview of included studies 9
Key outcomes 11
Evidence gaps and limitations 17
3 Related NICE guidance and NHS England clinical policies 26
4 References 27
Appendix 1 Search strategy 28
Appendix 2 Study selection 30
Appendix 3 Evidence tables 35
Appendix 4 Results tables 45
Appendix 5 Grading of the evidence base 56

Abbreviations

Term	Definition
ART	Antiretroviral therapy (drugs that treat HIV)
BMD	Bone mineral density
HIV	Human immunodeficiency virus. Please note that there are two main types of HIV – HIV-1 (the most common) and HIV-2 (relatively uncommon and less infectious). This evidence review covers HIV-1 only.
INI	Integrase inhibitor (a class of antiretroviral drug)
NNRTI	Non-nucleoside reverse transcriptase inhibitors (a class of antiretroviral drug)
NRTI	Nucleoside reverse transcriptase inhibitors (a class of antiretroviral drug)
PI	Protease inhibitors (a class of antiretroviral drug)

Medical definitions

Term	Definition
CD4 cell	A type of white blood cell that kills viruses in the body
Viral load	A measure of the number of viral particles in the body, reported as copies per millilitre of blood (copies/mL)
Virological failure	A term used to describe when the viral load in someone with HIV is greater than 200 copies/mL despite the use of antiretroviral therapy.
Virologically suppressed	A term used to describe when the level of HIV in the body is too low to be detected. This is usually when there are less than 50 copies of HIV-1 virus per ml of blood.

1 Introduction

Disease background

1.1 HIV (human immunodeficiency virus) is a virus that damages a type of white blood cell in the immune system called a CD4 cell. Damaging CD4 cells weakens the body's ability to fight off infection and disease, leaving people with HIV vulnerable to opportunistic infection. In some cases this can lead to acquired immunodeficiency syndrome (AIDS), which is the collective name given to several life-threatening illnesses that can develop when the immune system has become severely damaged by the HIV virus. There is currently no cure for HIV, but with treatment, most people with HIV will live a long and healthy life, and will not develop AIDS-related illness. HIV is transmitted from person to person through the body fluids of an infected person. Most people have flu-like illness several weeks after infection. After this, HIV may not cause any symptoms for a number of years, but it will still damage the immune system.

Focus of review

1.2 In line with the marketing authorisation, the focus of this review is on dolutegravir-rilpivirine for the treatment of HIV-1 infection in adults who are virologically-suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Epidemiology and needs assessment

1.3 In the UK, 93,385 people received treatment for HIV in 2017 and 4,363 people were newly diagnosed with the condition (Public Health England, 2018). Over 98% of all people with HIV in the UK in 2017 were on antiretroviral therapy, and 97% of those had a viral load of less than 200 copies per mL (Public Health England, 2018).

Product overview

Mode of action

1.4 Dolutegravir is an integrase inhibitor (INI). It binds to HIV integrase (an HIV enzyme used to insert HIV DNA into the DNA of the CD4 cells) to prevent HIV DNA being inserted into uninfected CD4 cells.

1.5 Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It binds to HIV reverse transcriptase (an HIV enzyme used to convert HIV genetic code into DNA, so that it can be injected into the CD4 cell) to prevent HIV DNA replicating.

Regulatory status

1.6 Dolutegravir-rilpivirine has a marketing authorisation for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of virological failure and no known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Dosing information

1.7 The SPC for dolutegravir-rilpivirine states that the recommended dose is 1 tablet, taken orally, once daily. Each tablet contains dolutegravir sodium equivalent to 50mg dolutegravir and rilpivirine hydrochloride equivalent to 25mg rilpivirine.

Treatment pathway and current practice

1.8 Once a diagnosis of HIV is made, treatment with antiretroviral therapy is started, to stop the virus replicating in the body. A combination of drugs is usually used because the disease can adapt and become resistant. Types of drugs include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase inhibitors (INIs). All drugs have the aim of stopping the virus replicating in the body, but have different processes for doing this:

- NRTIs: The HIV virus uses an enzyme known as reverse transcriptase to convert HIV genetic code (RNA) into DNA, which then allows it to infect CD4 cells and replicate itself. NRTIs contain faulty versions of the building blocks used by the HIV virus to convert its RNA into DNA, which means the conversion into DNA is not completed properly, stopping the HIV genetic material being added to healthy CD4 cells
- NNRTIs: Attach themselves to reverse transcriptase, which stops the HIV genetic material from infecting the healthy cell.
- PIs: After the CD4 cell has been infected with HIV, the virus tells the infected cell to make new HIV genetic material and HIV proteins, to replicate itself. To make functional HIV proteins so that the HIV virus can replicate, they must be cut up by an enzyme known as HIV protease. PIs block HIV protease so the HIV protein cannot be cut properly, which stops functional copies of the HIV virus being replicated. These types of drugs are usually 'boosted' with ritonavir or cobicistat, which helps to improve levels of PI and reduces the risk of drug resistance.
- INIs: After the HIV RNA has been converted into DNA, it must be inserted into the CD4 cell DNA. INI's block this process.

1.9 Usually treatment consists of 3 drugs, made up of 2 NRTIs and either a ritonavir/cobicistat-boosted PI, an NNRTI, or an INI. Possible combinations include 2 drugs out of tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine, abacavir, and lamivudine, with either darunavir, raltegravir, rilpivirine, efavirenz, dolutegravir, elvitegravir/cobicistat, or bictegravir.

2 Evidence

Literature search

2.1 A literature search identified 166 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 26 full text references were obtained and assessed for relevance. The company submission also highlighted an additional unpublished

manuscript (Aboud et al.). Full text inclusion and exclusion criteria were applied to the identified papers and 4 studies, including the unpublished Aboud et al. manuscript, were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of papers excluded at full text with reasons). Some of the evidence from the Aboud et al. manuscript is confidential (denoted by yellow marking). This is because the manuscript has not yet been published in a peer-reviewed publication. It is anticipated that the manuscript will be published in a peer-reviewed journal before NHS England makes a final commissioning decision on dolutegravir-rilpivirine.

Overview of included studies

2.2 Two identically designed randomised controlled trials (RCTs) named SWORD 1 and SWORD 2 were presented in 2 papers (Llibre et al. 2018 and Aboud et al. TBC). In the SWORD studies, participants who were on antiretroviral therapy were either switched to dolutegravir-rilpivirine or continued with their existing treatment. Existing treatment varied however, at baseline around 70% of participants were taking tenofovir disoproxil fumarate and/or emtricitabine and around half of the participants were taking an NNRTI as a third-agent. Llibre et al. 2018 (SWORD 1 and 2 studies) presents data comparing dolutegravir-rilpivirine with existing antiretroviral therapies for 48 weeks. Aboud et al. TBC presents data for participants that used dolutegravir-rilpivirine for 100 weeks, but does not compare it to existing antiretroviral therapies. This second paper also reports non-comparative data for an additional group of participants who took dolutegravir-rilpivirine for 48 weeks.

2.3 This review also includes a substudy of the SWORD studies (McComsey et al. 2018) and a case report of 2 patients who switched to dolutegravir-rilpivirine (Suzuki et al. 2017).

2.4 A summary of the characteristics of the included studies is shown in table 1 (see evidence tables in appendix 3 for full details).

Table 1 Summary of included studies

Paper and study	Population	Intervention and comparison	Primary outcome
Llibre et al. (2018) RCT SWORD 1 and SWORD 2 at 48 weeks	Adults with HIV-1 infection (n=1024) Virologically suppressed (<50 copies/mL) Stable ART regimen for at least 6 months No history of virological failure No known or suspected resistance to any NNRTI or INI	Dolutegravir and rilpivirine (n=513) Any other ART (n=511)	Number of participants with viral load <50 copies/mL at week 48
Aboud et al. (TBC) SWORD 1 and SWORD 2 at 100 weeks	As for Llibre et al. (2018) study above (n=990)	Dolutegravir-rilpivirine at week 100 (n=513) Dolutegravir-rilpivirine at week 48 (n=477) No comparator	Number of participants with viral load <50 copies/mL at week 48
McComsey et al. (2018) Bone mineral density substudy of SWORD 1 and SWORD 2	Adults with HIV-1 infection receiving tenofovir disoproxil fumarate (n=81) Virologically suppressed (<50 copies/mL) Stable ART regimen for at least 6 months No history of virological failure No known or suspected resistance to any NNRTI or INI	Dolutegravir and rilpivirine (n=46) Any other ART (n=35)	Increase in hip BMD at week 48
Suzuki et al. (2017) Case report	Adults with HIV-1 infection and dysphagia (n=2) Virologically suppressed (<50 copies/mL) Stable ART regimen for at least 6 months No history of virological failure	Dolutegravir and rilpivirine (n=2) No comparator	Adherence and care burden
Abbreviations: ART, antiretroviral therapy; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RCT, randomised controlled trial			

Key outcomes

2.5 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

2.6 The SWORD 1 and SWORD 2 studies were two separate but identical studies designed to comply with regulatory guidance. Before the studies started, it was agreed that the results from SWORD 1 and SWORD 2 would be pooled. In the published papers, the treatment differences are only reported for the pooled data. Viral load and virological non-response outcomes were intended to demonstrate non-inferiority. All other outcomes were intended to prove superiority.

Effectiveness

Virological outcomes

2.7 The number of participants with a viral load <50 copies/mL at week 48 in the SWORD studies was statistically significantly non-inferior in the group that switched to dolutegravir-rilpivirine (94.7%) compared with the group that remained on their existing ART (94.9%, adjusted treatment difference of -0.2%, 95% CI -3.0 to +2.5, non-inferiority margin of 4%). Around 89% of the participants that switched to dolutegravir-rilpivirine had a viral load <50 copies/mL at week 100.

2.8 The number of participants with a virological non-response at week 48 in the SWORD studies was statistically significantly non-inferior in the group that switched to dolutegravir-rilpivirine (n=3, <1%) compared with the group that remained on their existing ART (n=6, 1%; adjusted treatment difference of -0.5%, 95% CI -1.4 to +0.5, non-inferiority margin of 4%). Around 3% of participants that switched to dolutegravir-rilpivirine had a virological non-response at week 100.

CD4 cell count

2.9 There was an increase in median CD4 cell count from baseline to week 48 in the SWORD studies in both the group that switched to dolutegravir-rilpivirine (increase of 28.0 cells per µL) and the group that remained on their existing ART (increase of 22.0 cells per µL). The statistical significance of the difference in these increases is not reported. By week 100, the median CD4 cell count in participants who had switched to dolutegravir-rilpivirine had increased by 33 cells per µL compared with baseline.

Health related quality of life and caregiver burden

2.10 The HIV Treatment Satisfaction Questionnaire is completed by people with HIV and measures satisfaction with treatment. It includes subscores on lifestyle/ease and general satisfaction/clinical. There was no statistically significant change in mean HIV Treatment Satisfaction Questionnaire total score in the SWORD studies for participants who switched to dolutegravir-rilpivirine compared with those that remained on their existing ART (from baseline to week 48, p value not reported). There was also no statistically significant difference in the change in the mean general satisfaction/clinical subscore, however, there was a statistically significant greater increase in the mean lifestyle/ease subscore for participants who switched to dolutegravir-rilpivirine compared with participants who remained on their existing ART ($p<0.0001$).

2.11 The Symptom Distress Module was completed by people with HIV and measures distress linked to HIV and ART-related symptoms. There was a statistically significant greater decrease from baseline to week 48 in mean symptom bother score in the SWORD studies for participants who switched to dolutegravir-rilpivirine compared with participants who remained on their existing ART ($p=0.014$).

2.12 The Suzuki et al. (2017) case reports (n=2) stated that there was a reduced burden on caregivers when patients switched to dolutegravir-rilpivirine because the tablets could be taken without crushing or preparing them in an oral suspension.

Safety and tolerability

Adverse events

2.13 In the SWORD studies, at least 1 adverse event was reported by week 48 in 77% of the participants that switched to dolutegravir-rilpivirine and 71% of the participants that remained on their existing ART (statistical significance between groups not reported). By week 100, 88% of participants that switched to dolutegravir-rilpivirine had reported at least 1 adverse event.

2.14 The majority of adverse events in both groups in the SWORD studies were mild (grade 1). The most frequently reported adverse events at week 48 were nasopharyngitis (10% of both groups), headache (8% intervention, 5% comparator), and upper respiratory tract infection (5% intervention, 7% comparator). Other adverse events by week 48 included diarrhoea (6% intervention, 5% comparator), back pain (3% intervention, 6% comparator), bronchitis (4% intervention, 3% comparator), influenza (3% in both groups), arthralgia (joint pain, 4% intervention, 2% comparator), insomnia (3% intervention, 2% comparator), depression (3% intervention, 1% comparator), anxiety (2% in both groups), and abnormal dreams (1% intervention, no cases in comparator group). By week 100, the most commonly reported adverse events in the intervention group were psychiatric disorders (17%), viral upper respiratory tract infection (15%), headache (12%), upper respiratory tract infection (10%), diarrhoea (9%), back pain (6%), bronchitis (7%), arthralgia (7%), syphilis (6%), and nasopharyngitis (2%).

2.15 Drug-related adverse events by week 48 in the SWORD studies were reported in 19% for the intervention group and 2% for the comparator group. Serious drug-related adverse events were reported in 1% of participants in the switch group and <1% in the non-switch group. The statistical significance of the differences in drug-related adverse events between the groups was not reported. By week 100, drug-related adverse events were reported in 20% of the participants that switched to dolutegravir-rilpivirine.

2.16 In the SWORD studies, there was 1 death (<1%) in both dolutegravir-rilpivirine and comparator groups (statistical significance not reported) by week 48. There were 2 further deaths (<1%) in the dolutegravir-rilpivirine group between week 48 and week 100. None of the deaths were considered to be related to the study drugs.

Blood lipids

2.17 Mean changes in total cholesterol, HDL cholesterol, calculated LDL cholesterol, triglycerides and total:HDL cholesterol from baseline to 48 weeks were reported in the SWORD studies. 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.

2.18 Changes in total cholesterol, HDL cholesterol, LDL cholesterol, and total:HDL cholesterol 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)

Renal function

2.19 Changes in mean levels of cystatin C, retinol binding, beta-2-microglobulin, C-reactive protein, D dimer, fatty acid binding protein, glucose, interleukin-6, soluble CD14, soluble CD163, soluble vascular cell adhesion molecule-1, and estimated glomerular filtration rate were reported at week 48 in the SWORD studies. The study paper stated that there was 'no consistent pattern of change' for these outcomes. The statistical significance of the differences in changes between the group that switched to dolutegravir-rilpivirine and the group that remained on their existing ART was not reported.

2.20 There was a statistically significant decrease in median retinol binding protein/creatinine level from baseline to week 100 in participants in the SWORD studies who switched to dolutegravir-rilpivirine (p<0.001).

2.21 There was a statistically significant decrease in median urine beta-2-microglobulin:creatinine from baseline to week 100 in participants in the SWORD studies who switched to dolutegravir-rilpivirine and who were on tenofovir disoproxil fumarate at baseline ($p<0.001$). There was no change in median urine beta-2-microglobulin:creatinine for participants who were not on tenofovir disoproxil fumarate at baseline.

Bone density

2.22 There was a statistically significant greater increase in total hip bone mineral density in the SWORD substudy for the group that switched to dolutegravir-rilpivirine compared with the group that remained on their existing ART (baseline to week 48, difference in adjusted change of +1.29%, 95% CI 0.27 to 2.31, p=0.014).

2.23 There was a statistically significant greater increase in lumbar spine bone mineral density in the SWORD substudy for the group that switched to dolutegravir-rilpivirine compared with the group that remained on their existing ART (baseline to week 48, difference in adjusted change of +1.32%, 95% CI 0.07 to 2.57, p=0.039) (McComsey et al. 2018).

2.24 There were statistically significant greater increases in total hip T score (baseline to week 48, difference in adjusted change of +0.09%, 95% CI 0.02 to 0.16, p=0.016) and lumbar spine T score (baseline to week 48, difference in adjusted change of +0.12%, 95% CI 0.00 to 0.23, p=0.049) in the SWORD substudy for the group that switched to dolutegravir-rilpivirine compared with the group that remained on their existing ART.

2.25 The 10 year probability of hip fracture in the SWORD substudy was reduced for the group that switched to dolutegravir-rilpivirine (baseline to week 48, -0.08%) and increased for the group that remained on their existing ART (baseline to week 48, +0.03%). The 10 year probability of osteoporotic fracture in the SWORD substudy was reduced in both the switch group (baseline to week 48, -0.12%) and non-switch group (baseline to week 48, -0.04%). The statistical significance of the difference in these changes was not reported.

2.26 There was a statistically significant greater reduction in bone-specific alkaline phosphatase type, osteocalcin type, procollagen type 1 N-terminal propeptide, and type 1 collagen C-telopeptide from baseline to week 48 in the SWORD studies in the group that switched to dolutegravir-rilpivirine compared with the group that remained on their existing ART ($p<0.05$).

2.27 From baseline to week 100 there was a statistically significant decrease in mean bone-specific alkaline phosphatase type, osteocalcin, and type 1 collagen C-telopeptide for participants who switched to dolutegravir-rilpivirine in the SWORD studies. There was a statistically significant increase in mean procollagen type 1 N-terminal propeptide in the same group.

Treatment adherence

2.28 Patient reported treatment adherence by week 48 in the SWORD studies 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. Treatment adherence at week 100 was not reported.

2.29 The 2 participants included in the Suzuki et al. (2017) case reports maintained treatment adherence after switching to dolutegravir-rilpivirine.

Viral resistance

2.30 There was 3 reported cases of a viral mutation after the use of dolutegravir-rilpivirine for 100 weeks in the SWORD studies. 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 decrease susceptibility or not. No cases of viral resistance were reported by week 48 in the group that remained on their existing ART.

Evidence gaps and limitations

2.31 The evidence base is limited to pooled data from 2 randomised controlled trials, a substudy of the trials, and 2 case reports.

2.32 The SWORD studies were open label in design. This means that both the researchers and the participants in the trial knew whether the participant received dolutegravir-rilpivirine or not. This may have introduced bias in the reporting of outcomes.

2.33 The SWORD studies included participants from 12 countries, including the UK. It is not clear how many participants were from the UK and how many were from the other countries: Argentina, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, and the USA. The SWORD substudy included participants from 6 countries, including the UK. It is not clear how many participants were from the UK and how many were from the other countries: Argentina, Belgium, Canada, Spain, and the USA. The 2 case reports in the Suzuki et al. (2017) paper were from Japan and it is not clear how applicable these would be to the UK population.

2.34 The effects of dolutegravir-rilpivirine after more than 100 weeks of use are unknown. The SWORD studies and the SWORD substudy reported data at 48 weeks and 100 weeks, and the case reports were followed up for 12 months. The 100 week data from the SWORD studies is limited because it is not compared with data from existing antiretroviral therapies. Patients with HIV are expected to use antiretroviral medication for the rest of their lives and so are likely to be using dolutegravir-rilpivirine for longer than the follow up period in the included studies.

2.35 The SWORD studies do not clearly report which existing antiretroviral therapies participants were using, so it is not clear what dolutegravir-rilpivirine was being compared with in the SWORD studies.

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Viral load <50 copies/mL	Llibre et al. (2018)	8/10	Directly applicable	A	Viral load is a measure of how much of the HIV virus there is in the blood, measured by the amount of HIV genetic material (RNA) present in the body. The measurement is given as the number of copies of the virus per millilitre of blood (copies/mL). If there are high levels of HIV in the blood, the risk of the person with HIV becoming ill from other infections increases. The aim of antiretroviral therapy is to reduce viral load to less than 50 copies/mL to lower the risk of the person with HIV acquiring other infections. In addition, when viral load is less than 50 copies/mL, the risk of HIV being passed on to another person is extremely low, even during unprotected sexual intercourse. The SWORD 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%). The result remained statistically significantly non-inferior for subgroup analyses by third-line agent treatment at baseline, baseline CD4 cell count, age, sex and ethnicity. 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. 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 generalizable 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.
	Aboud et al. (TBC)	8/10	Directly applicable		

CD4 cell count	Llibre et al. (2018)	8/10	Directly applicable	A	CD4 cells are white blood cells that fight infections in the body. The higher the number of CD4 cells in the body, the more capable the body is of fighting infection. A CD4 cell count of over 500 indicates that the body is able to effectively fight most infections. A CD4 cell count of below 200 indicates that the body is at high risk of developing serious illnesses. The HIV-1 virus kills CD4 cells, increasing the risk of the person with HIV developing serious illnesses. The SWORD 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 per µL compared with baseline. It is not possible to determine from the evidence whether dolutegravir-rilpivirine had a greater or lesser effect on CD4 cell count compared with 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 generalizable 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.
	Aboud et al. (TBC)	8/10	Directly applicable		
Renal function	Llibre et al. (2018)	8/10	Directly applicable	B	Renal function is a measure of how well the kidneys are working. The kidneys filter toxins and waste products from the blood and release hormones to regulate blood pressure, produce red blood cells, and help the body absorb calcium. HIV can result in kidney disease and kidney failure (known as HIV-associated nephropathy). Some antiretroviral therapy can have a negative effect on the kidneys. The SWORD 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 with 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 generalizable 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.
Blood lipids	Llibre et al. (2018)	8/10	Directly applicable	A	Blood lipids are fats in the blood, such as fatty acids and cholesterol. 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. HIV infection and treatment with some HIV medicines can increase the risk of hyperlipidaemia. The SWORD studies reported on the changes in total cholesterol, mean HDL cholesterol, mean calculated LDL cholesterol, mean triglycerides, and mean total:HDL cholesterol from baseline to 48 weeks. The study paper does not provide an estimate of the difference in the change between the group that switched to dolutegravir-rilpivirine and the group that remained on their existing ART for any of these outcomes. The difference in the change between the groups was reported to be not statistically significant for all of the outcomes, although the p values were not reported. Changes in total cholesterol, HDL cholesterol, LDL cholesterol, and total:HDL cholesterol 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. 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 generalizable 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.
	Aboud et al. (TBC)	8/10	Directly applicable		

Bone mineral density	McComsey et al. (2018)	9/10	Directly applicable	B	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. Low bone mineral density is also an indirect indicator of osteoporosis. Bone loss occurs faster in people with HIV than in people without HIV. Both the HIV infection and some HIV medicines may increase the rate of bone loss. A substudy of the SWORD studies reported a statistically significant greater increase in total hip BMD and lumbar spine BMD from baseline to 48 weeks in participants who switched to dolutegravir-rilpivirine compared with participants who remained on their existing ART. The increase in total hip BMD was 1.29% greater in participants who switched to dolutegravir-rilpivirine compared with those who remained on their existing ART (95% CI +0.27% to +2.31%, p=0.014). The increase in total lumbar spine BMD was 1.32% higher with dolutegravir-rilpivirine compared with those who remained on their existing ART (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 with other antiretroviral therapies. The results should be interpreted with caution because it is not clear how generalizable 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.
Treatment adherence	Llibre et al. (2018)	8/10	Directly applicable	B	Treatment adherence describes the extent to which someone acts on medical advice about their treatment. This can include taking the recommended dose of medication each day, taking medication at recommended times of day, and taking medication for a recommended period of time. Poor adherence to ART is associated with less effective suppression of the HIV-1 virus, resulting in a higher viral load of HIV in the body. A higher viral load of HIV increases the risk of a person becoming ill from other infections. Poor adherence to ART can also lead to permanent resistance of HIV to a particular drug or class of drugs. The SWORD 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
	Suzuki et al. (2017)	5/10	Directly applicable		

					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 with other antiretroviral therapies because statistical significance was not reported. 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 generalizable 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. In addition, the data from the case reports were limited to 2 patients from Japan. It is not clear whether the participants in the case reports fully reflect the marketing authorisation of dolutegravir-rilpivirine as it is not reported whether they had a known resistance to NNRTIs or INIs.
Viral resistance	Llibre et al. (2018)	8/10	Directly applicable	A	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. Viral resistance is caused by a mutation in a virus gene. Frequent mutations occur in the HIV-1 virus because it replicates very quickly and does not correct any mutations that occur when it replicates. The frequent mutations in the HIV-1 virus increases the risk of it becoming resistant to drugs. The SWORD studies reported that 3 participants out of 513 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

	Aboud et al. (TBC)	8/10	Directly applicable		dolutegravir-rilpivirine, however, it was not reported whether the other two participants showed a decrease 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 with 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 generalizable 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.
Health related quality of life	Llibre et al. (2018)	8/10	Directly applicable	B	Health related quality of life is the perceived quality of a person's daily life based on their health. This can include a person's physical and mental health. Two scales were used to assess health related quality of life in the included studies. 1. The HIV Treatment Satisfaction Questionnaire (HIVTSQs) measures satisfaction with treatment for people who have HIV. It is completed by participants and has 10 items. Scores range from 0 to 6 for each item. It provides an overall (total) score as well as subscores on lifestyle/ease and general satisfaction/clinical. 2. The Symptom Distress Module (SDM) measures distress linked to HIV or ART-related symptoms. It is completed by participants and has 20 items. Scores range from 0 to 4 for each item. It provides an overall score, known as the symptom bother score. The SWORD studies reported that total score on the HIVTSQs increased from 54.4 at baseline to 55.9 at week 48 in the group that switched to dolutegravir-rilpivirine, and from 53.9 at baseline to 54.3 at week 48 for the group that remained on their existing ART. The study paper reported that the difference in increases between the groups was not statistically significant (p value not reported). The same study paper reported a decrease in mean symptom bother score on the Symptom Distress Module from 9.6 at baseline to 8.2 at week 48 in the group that switched to dolutegravir-rilpivirine, and from 11.0 at baseline to 10.3 at week 48 in the group that remained on their existing ART. The difference in decreases between the groups was reported to be statistically significant, with the participants who switched to dolutegravir-rilpivirine reporting a greater decrease

					in symptom bother score than the participants who remained on their existing ART (p=0.014). The results suggest that dolutegravir-rilpivirine had a similar effect on total HIVTSQs score as other antiretroviral therapies. The results suggest that dolutegravir-rilpivirine decreased symptom bother score more than 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 generalizable 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.
Burden on caregiver	Suzuki et al. (2017)	5/10	Directly applicable	C	Burden on caregiver is the strain or load taken on by a person who cares for someone who is chronically ill. It can include physical, emotional, social and financial factors. 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. The 2 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.
Adverse events	Llibre et al. (2018)	8/10	Directly applicable	A	Adverse events are unintentional and undesirable signs and symptoms reported during a study. Adverse events can occur in both the intervention and control groups of a study. They may be related to drugs being used in the study or they may be caused by other factors, such as natural progression of an existing condition. They can be mild or serious. 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. The SWORD studies reported that the proportion of participants who had a drug-related adverse event by week 48 was 19% in the group that switched to dolutegravir-rilpivirine and 2% in the group that remained on their existing ART. By week 100, 88% of the participants who switched to dolutegravir-rilpivirine had reported at least 1 adverse event. The most frequently reported adverse events at week 48 were nasopharyngitis

	Aboud et al. (TBC)	8/10	Directly applicable		(10% of both groups), headache (8% intervention, 5% comparator), and upper respiratory tract infection (5% intervention, 7% comparator). Other adverse events by week 48 included diarrhoea (6% intervention, 5% comparator), back pain (3% intervention, 6% comparator), bronchitis (4% intervention, 3% comparator), influenza (3% in both groups), arthralgia (joint pain, 4% intervention, 2% comparator), insomnia (3% intervention, 2% comparator), depression (3% intervention, 1% comparator), anxiety (2% in both groups), and abnormal dreams (1% intervention, no cases in comparator group). By week 100, the most commonly reported adverse events in the intervention group were psychiatric disorders (17%), viral upper respiratory tract infection (15%), headache (12%), upper respiratory tract infection (10%), diarrhoea (9%), back pain (6%), bronchitis (7%), arthralgia (7%), syphilis (6%), and nasopharyngitis (2%). The proportion of participants with a serious drug-related adverse event by week 48 was 1% in the group that switched to dolutegravir-rilpivirine and <1% in the group that remained on their existing ART. The study paper reported that none of the fatal events were considered related to the study drugs. The statistical significance of the difference between the groups for any of the adverse event outcomes was not reported. 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 with 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 generalizable 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.

3 Related NICE guidance and NHS England clinical policies

NHS England and NICE have not issued any guidelines or policies on managing HIV with dolutegravir-rilpivirine.

There is related guidance from NHS England:

- HIV testing: encouraging uptake (2017) NICE quality standard 157
- HIV testing: increasing uptake among people who may have undiagnosed HIV (2016) NICE guideline 60
- Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil) (2016) NICE evidence summary 78
- Deep dermal injection of non-absorbable gel polymer for HIV-related lipoatrophy (2013) NICE interventional procedures guidance 439

There are related policies from NHS England:

- Dolutegravir for treatment of HIV-1 in adults and adolescents (2018) NHS England
- Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents (2018) NHS England
- Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents (2017) NHS England
- Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV in adults (2015) NHS England
- Use of cobicistat as a booster in treatment of HIV infection (all ages) (2015) NHS England

There are related guidelines from the European AIDS Clinical Society and the British HIV Association:

- EACS Guidelines 2018 version 9.1 (2018) European AIDS Clinical Society

- BHIVA guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2015 (2016 interim update) (2016) British HIV Association

4 References

Aboud et al. TBC – to be added after publication in a peer reviewed journal

Llibre J M, Hung C C, Brinson C et al. (2018) Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet vol 391 (10123): p839-849

McComsey G A, Lupo S, Parks D et al. (2018) Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health. AIDS vol 32 (4): p477-485

Suzuki T, Hara N, Osa M, Misawa K, Imai K, Fujikura Y, Maeda T, Sonehara W, and Kawana A (2017) Efficacy of switching to dolutegravir plus rilpivirine, the small-tablet regimen, in patients with dysphagia: two case reports. Journal of Pharmaceutical Health Care & Sciences vol 3: p23

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 – 04 Sep 2018
Search date: 05/09/2018
Number of results retrieved: 20 (Medline) 11 (In process) 0 (epub ahead of print) 0 (daily update)
Search strategy:

Database: Ovid MEDLINE(R) <1946 to September 04, 2018>
Search Strategy:
---
1 HIV-1/ (74256)
2 ("hiv-1" or "hiv-i" or "hiv type 1" or "hiv type i").tw. (70536)
3 ("immunodeficiency virus" adj4 (I or i)).tw. (639)
4 or/1-3 (91384)
5 Rilpivirine/ (280)
6 rilpivirine.tw. (403)
7 or/5-6 (440)
8 dolutegravir.tw. (410)
9 7 and 8 (51)
10 juluca.tw. (0)
11 9 or 10 (51)
12 4 and 11 (20)

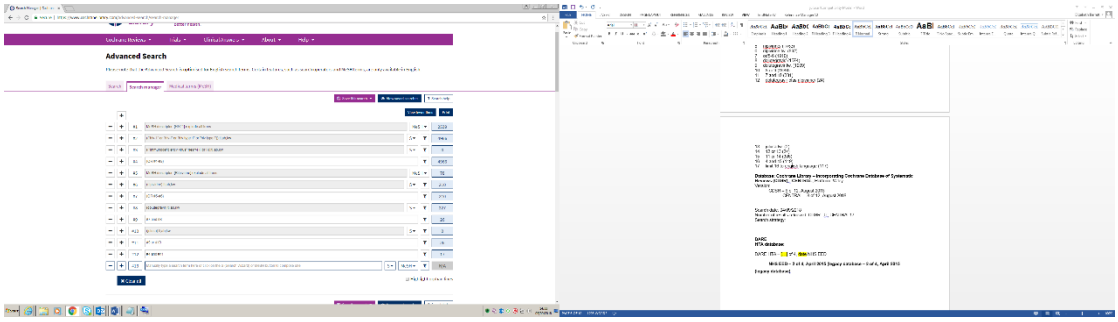
Database: Embase
Platform: Ovid
Version: 1974 to 2018 September 04
Search date: 05/09/2018
Number of results retrieved: 117
Search strategy:

Database: Embase <1974 to 2018 September 4>
Search Strategy:
---
1 exp Human immunodeficiency virus 1/ (73814)
2 ("hiv-1" or "hiv-i" or "hiv type 1" or "hiv type i").tw. (88557)
3 ("immunodeficiency virus" adj4 (I or i)).tw. (918)
4 or/1-3 (107013)
5 rilpivirine/ (1763)
6 rilpivirine.tw. (892)
7 or/5-6 (1910)
8 dolutegravir/ (1574)
9 dolutegravir.tw. (1009)
10 8 or 9 (1680)
11 7 and 10 (381)
12 dolutegravir plus rilpivirine/ (24)
13 juluca.tw. (2)
14 12 or 13 (24)
15 11 or 14 (386)
16 4 and 15 (119)

17 limit 16 to english language (117)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR);; CENTRAL; Platform: Wiley
Version:
CDSR – 8 of 12, August 2018
CENTRAL – 8 of 12, August 2018

Search date: 04/09/2018
Number of results retrieved: CDSR –0 ; CENTRAL17 –.
Search strategy:



DARE
HTA database;
EED 0
Platform: CRD
Search date: 05/09/2018

Results: DARE 1 HTA 0 , NHS EED 0

2 searches (1) juluca (2) rilpivirine and dolutegravir

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 166 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	**Inclusion**	**Exclusion**
Population	Adults with HIV-1 infection who: - are virologically suppressed (HIV-1 RNA <50 copies/mL) and - are on a stable antiretroviral regimen for at least 6 months with no history of virological failure and - did not have known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor	Healthy volunteers Non-humans
Intervention	Dolutegravir-rilpivirine (Juluca) as a once daily fixed-dose combination single tablet regimen	
Comparator	Any other antiretroviral therapy	
Outcomes	- Percentage of patients with an undetectable HIV-1 viral load (<50 copies/mL) - Change in CD4 cell count - Change in HIV-1 RNA count - Renal function - Blood lipids - Bone density - Medication adherence - Treatment-emergent resistance - Survival and progression free survival - Health related quality of life - Replacement of more toxic treatment - Dependency on care giver/supporting independence - Safety (including adverse effects) - Delivery of intervention	
Other		Abstracts, editorials, opinion pieces and commentaries Epidemiological studies Non-English language Duplicates

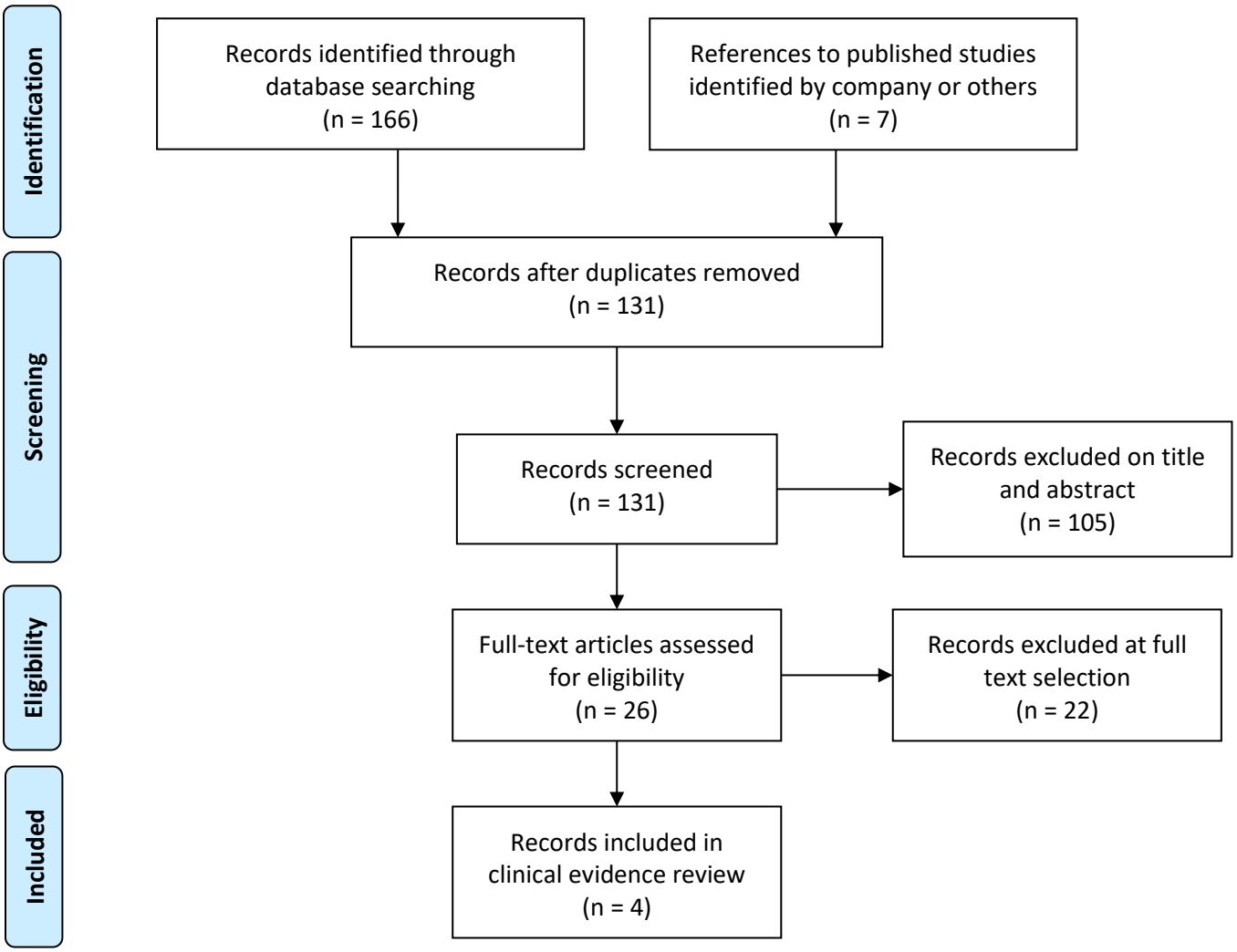
Table 3 Studies excluded at full text

Study reference	Reason for exclusion
Anonymous (2018) Erratum: Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies (The Lancet (2018) 391(10123) (839-849) (S0140673617330957) (10.1016/S0140-6736(17)33095-7)). The Lancet 391(10138), 2416	Erratum to the print version of Llibre et al. (2018). The version of the Llibre et al. (2018) paper included in the current evidence review has already been corrected.
Boswell R, Foisy M M, and Hughes C A (2018) Dolutegravir Dual Therapy as Maintenance Treatment in HIV-Infected Patients: A Review. Annals of Pharmacotherapy 52(7), 681-689	Review article with no new data or meta-analysis. Included studies have been considered separately for inclusion.
Capetti A F, Astuti N, Cattaneo D, and Rizzardini G (2017) Pharmacokinetic drug evaluation of dolutegravir plus rilpivirine for the treatment of HIV. Expert Opinion On Drug Metabolism & Toxicology 13(11), 1183-1192	Review article with no new data or meta-analysis. Included studies have been considered separately for inclusion.
Capetti A F, Cossu M V, Paladini L, and Rizzardini G (2018) Dolutegravir plus rilpivirine dual therapy in treating HIV-1 infection. Expert Opinion on Pharmacotherapy 19(1), 65-77	Review article with no new data or meta-analysis. Included studies have been considered separately for inclusion.
Capetti A F, Cossu M V, Sterrantino G, Barbarini G, Di Giambenedetto , S , De Socio , G V, Orofino G, Di Biagio , A , Celesia B M, Rusconi S, Argenteri B, and Rizzardini G (2018) Dolutegravir Plus Rilpivirine as a Switch Option in cART-Experienced Patients: 96-Week Data. Annals of Pharmacotherapy 52(8), 740-746	This paper provides 96 week follow up data for a study that was excluded from the review (Capetti et al. 2016).
Capetti A F, Sterrantino G, Cossu M V, De Socio , G V, Di Giambenedetto , S , Celesia B M, Argenteri B, Di Biagio , A , Orofino G C, Barbarini G, and Rizzardini G (2016) Dolutegravir plus rilpivirine in cART-experienced subjects: An observational cohort. Journal of the International AIDS Society 19 (Supplement 7), 81	Abstract. Full text has been considered separately for inclusion.
Capetti A F, Sterrantino G, Cossu M V, Orofino G, Barbarini G, De Socio , G V, Di Giambenedetto , S , Di Biagio , A , Celesia B M, Argenteri B, and Rizzardini G (2016) Switch to Dolutegravir plus Rilpivirine Dual Therapy in cART-Experienced Subjects: An Observational Cohort. PLoS ONE [Electronic Resource] 11(10), e0164753	Not all participants in this study reflect the marketing authorisation for dolutegravir-rilpivirine, and results are not reported separately for the participants that do.
Casado J L, Monsalvo M, Rojo A M, Fontecha M, and Rodriguez-Sagrado M A (2018) Dolutegravir and rilpivirine for the maintenance treatment of virologically suppressed HIV-1	Review article with no new data or meta-analysis. Included studies have been

infection. Expert Review of Clinical Pharmacology 11(6), 561-570	considered separately for inclusion.
Cattaneo D, Minisci D, Cozzi V, Riva A, Meraviglia P, Clementi E, Galli M, and Gervasoni C (2017) Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect? Antiviral Therapy 22(4), 353-356	Not all participants in this study reflect the marketing authorisation for dolutegravir-rilpivirine, and results are not reported separately for the participants that do.
Gantner P Cuzin L, Allavena C, Cabie A, Pugliese P, Valantin, and Dat'AIDS study group (2017) Efficacy and safety of dolutegravir and rilpivirine dual therapy as a simplification strategy: a cohort study. HIV Med 18(9), 704-708	Letter to the editor
Gantner P, Lee G Q, Rey D, Mesplede T, Partisani M, Cheneau C, Beck-Wirth G, Faller J P, Mohseni-Zadeh M, Martinot M, Wainberg M A, and Fafi-Kremer S (2018) Dolutegravir reshapes the genetic diversity of HIV-1 reservoirs. Journal of Antimicrobial Chemotherapy 73(4), 1045-1053	Does not report relevant outcomes and only one participant received dolutegravir with rilpivirine.
Gubavu C, Prazuck T, Niang M, Buret J, Mille C, Guinard J, Avettand-Fenoel V, and Hocqueloux L (2016) Dolutegravir-based monotherapy or dual therapy maintains a high proportion of viral suppression even in highly experienced HIV-1-infected patients. Journal of Antimicrobial Chemotherapy 71(4), 1046-50	Only 11/52 participants received intervention of interest. Results for these participants are not reported separately.
Kelly S G, Nyaku A N, and Taiwo B O (2016) Two-Drug Treatment Approaches in HIV: Finally Getting Somewhere? Drugs 76(5), 523-531	Review article with no new data or meta-analysis. Included studies have been considered separately for inclusion.
Mehta R, Wolstenholme A, Di Lullo , K , Fu C, Joshi S, Crauwels H, Givens N, Vanveggel S, Wynne B, and Adkison K (2018) Bioequivalence of a Fixed-Dose Combination Tablet of the Complete Two-Drug Regimen of Dolutegravir and Rilpivirine for Treatment of HIV-1 Infection. Antimicrobial Agents & Chemotherapy 62(9),	Participants did not have HIV-1 infection.
Merli M, Galli L, Marinaro L, Ariaudo A, Messina E, Foppa C U, Castagna A, Lazzarin A, Bonora S, and Hasson H (2016) Pharmacokinetics of dolutegravir and rilpivirine in combination with SMV and SOF. Topics in Antiviral Medicine 24 (E-1), 177	Abstract
Orkin C, Khuong-Josses M A, Lutz T, Baker D, Rubio R, Blair E, Kahl L, Angelis K, Underwood M, Wynne B, Shah R, Vandermeulen K, and Aboud M (2018) Safety and efficacy of DTG+RPV in the phase III SWORD-1 and SWORD-2 studies: 48-week subgroup analysis by baseline third agent class and geographic location. HIV Medicine 19 (Supplement 2), S28-S29	Abstract
Orkin C, Libre J, Kahl L, Blair E, Wynne B, Curtis L, Angelis K, Shah R, Aboud M, and Gartland M (2018) Renal, Inflammatory and bone biomarkers following switch to the DTG + RPV	Abstract

2-drug regimen: The SWORD-1 and SWORD-2 studies. HIV Medicine 19 (Supplement 2), S17	
Palacios R, Mayorga M, Gonzalez-Domenech CM, Hidalgo-Tenorio C, Galvez C, Munoz-Medina L, de la Torre J, Lozano A, Castano M, Omar M, and Santos J (2018) Safety and Efficacy of Dolutegravir Plus Rilpivirine in Treatment-Experienced HIV-Infected Patients: The DORIVIR Study. Journal of the International Association of Providers of AIDS Care 17, 1-4	Not all participants in this study reflect the marketing authorisation for dolutegravir-rilpivirine, and results are not reported separately for the participants that do.
Punekar Y, Oglesby A, Angelis K, Antela A, Aboud M, Blair E, Kahl L, Gartland M, Wynne B, Lopes S, and Murray M (2018) Impact of reasons for switch and prior regimen on patient reported outcomes (PROs) in the SWORD studies. HIV Medicine 19 (Supplement 2), S25	Abstract
Revuelta-Herrero J L, Chamorro-de-Vega E, Rodriguez-Gonzalez C G, Alonso R, Herranz-Alonso A, and Sanjurjo-Saez M (2018) Effectiveness, Safety, and Costs of a Treatment Switch to Dolutegravir Plus Rilpivirine Dual Therapy in Treatment-Experienced HIV Patients. Annals of Pharmacotherapy 52(1), 11-18	Not all participants in this study reflect the marketing authorisation for dolutegravir-rilpivirine, and results are not reported separately for the participants that do.
Sebaaly J C, and Kelley D (2017) Single-Tablet Regimens for the Treatment of HIV-1 Infection. Annals of pharmacotherapy 51(4), 332-344	A review article that does not look at dolutegravir-rilpivirine.
Todd S E. J, Rafferty P, Walker E, Hunter M, Dinsmore W W, Donnelly C M, McCarty E J, Quah S P, and Emerson C R (2017) Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. International Journal of STD and AIDS 28(11), 1074-1081	It is not clear whether patients received the intervention of interest.

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 4 Llibre et al. (2018) (SWORD studies)

Study reference	Llibre et al. (2018)
Unique identifier	NCT02429791 – SWORD 1 NCT02422797 – SWORD 2
Study type (and NSF-LTC study code)	Open label, non-inferiority studies (P1 study)
Aim of the study	To evaluate the efficacy and safety of dolutegravir-rilpivirine compared with continuation of current ART regimen for 48 weeks in a large randomised population with suppressed viral load.
Study dates	April 2015 to November 2016
Setting	Centres in 12 countries: Argentina, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, UK, USA
Number of participants	N=1024 A sample size of 952 participants was needed to provide 90% power with a non-inferiority margin of -10% for the primary outcome.

Population	Age: median 43 years, range 21 to 79 years <50 years, n=735 Male: 796 (78%) Female: 228 (22%) Ethnicity - White: 819 (80%) - Asian: 88 (9%) - Black or African American: 84 (8%) - American Indian or Alaska Native: 28 (3%) - Mixed race: 3 (<1%) - Pacific Islander: 2 (<1%) Baseline CD4 cell count (cells per µL) - Dolutegravir-rilpivirine group: median 611 (range 3 to 1774) - Non-switch group: median 638 (range 9 to 1671) Centre for Disease Control Category - A (symptomatic, lymphadenopathy, or acute HIV): 785 (77%) - B (symptomatic, not AIDS): 123 (12%) - C (AIDS): 115 (11%) - Missing: 1 (<1%) Baseline ART third-agent class - NNRTI: 553 (54%) - PI: 269 (26%) - INI: 202 (20%) Most common ART at baseline - Tenofovir disoproxil fumarate: 733 (72%) - Emtricitabine: 693 (68%) Demographic and key characteristics reported to be 'well-balanced' across the groups (p values not reported)

Inclusion criteria	- 18 years and older - On their first or second ART regimen at baseline - Stably suppressed (viral load <50 copies per mL) for 6 months or longer at screening
Exclusion criteria	- Participants who switched to a second-line regimen because of virological failure on the first-line regimen (defined as confirmed plasma HIV-1 RNA ≥400 copies per mL after initial suppression to <50 copies per mL) - Any major resistance-associated PI, INI, NRTI or NNRTI mutation or integrase resistance-associated substitution R263K - Severe hepatic impairment (Child-Pugh C) - Concurrent hepatitis B infection - Anticipated need to receive hepatitis C therapy in the first 48 weeks and interferon-based hepatitis C therapy throughout the study - Substantial suicidality risk as determined by site investigator - QT interval corrected according to Bazett's formula of 450 ms or longer - Pregnancy or breastfeeding
Intervention(s)	Dolutegravir 50mg and rilpivirine 25mg once daily
Comparator(s)	Current ART regimen
Length of follow-up	48 weeks
Outcomes	Primary outcome: - Number of participants with plasma viral load <50 copies/mL
	Secondary outcomes: - Change in CD4 cell counts - Change in HIV Treatment Satisfaction Questionnaire - Treatment adherence
	Safety outcomes: - Incidence and severity of adverse events, including drug-related adverse events - Change in serum concentrations of blood lipids - Change in serum concentrations of bone-turnover biomarkers - Change in inflammatory and cardiovascular biomarkers - Number of participants with viral resistance
Source of funding	ViiV Healthcare and Janssen Pharmaceutica NV

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Research aims and design are clearly stated

2. Is the research design appropriate for the aims and objectives of the research?	1/2	Randomised controlled trial. Design is appropriate for the aims of the research but the open label design may bias the results.
3. Are the methods clearly described?	2/2	The methods are clearly described.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	The data are adequate to support the authors' interpretations and conclusions.
5. Are the results generalisable?	1/2	The study was conducted in 12 countries in Europe, South America, North America and Asia. It is not clear how many participants were recruited from each country. It is not clear whether the results would be generalizable to the UK population, for example, the ethnicity of the study participants may not reflect that of the UK population.
Total	8/10	
Applicability	Directly applicable	The participants in the study matched the marketing authorisation of the intervention

Table 5 Aboud et al. (TBC) (SWORD 100 week data)

Study reference	Aboud et al. (TBC)
Unique identifier	NCT02429791 – SWORD 1 NCT02422797 – SWORD 2
Study type (and NSF-LTC study code)	Open label, non-inferiority studies (P1 study)
Aim of the study	To present the 100 week results of the combined analysis of the SWORD 1 and SWORD 2 studies that evaluate maintenance of virological suppression, longer term safety, and the possible development of resistance substitutions.
Study dates	Participants were screened from April 2015 to October 2015 for SWORD 1 and SWORD 2. Data cut off for week 100 was November 2017.

Setting	Centres in 12 countries: Argentina, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, UK, USA
Number of participants	N=990 513 participants switched to dolutegravir-rilpivirine at the start of the SWORD studies and continued with it to week 100 477 participants remained on their existing ART until week 48 of the SWORD studies and then switched to dolutegravir-rilpivirine to week 100
Population	Age: median 43 years, range 21 to 79 years in early switch group and 22 to 76 years in late switch group <50 years, n=710 (72%) Male: 774 (78%) Female: 216 (22%) Ethnicity - White: 793 (80%) - Asian: 87 (9%) - Black/African American: 80 (8%) - American Indian or Alaskan Native: 25 (3%) - Mixed race: 3 (<1%)Pacific Islander: 2 (<1%) Baseline CD4 cell count (cells per mm^3) - Early switch group: median 611 - Late switch group: median 661 Centre for Disease Control Category - A (symptomatic, lymphadenopathy, or acute HIV): 760 (77%) - B (symptomatic, not AIDS): 119 (12%) - C (AIDS): 111 (11%) - Missing: 0 Baseline ART third-agent class - NNRTI: 542 (55%) - PI: 254 (26%) - INI: 194 (20%) Patient demographic and key baseline clinical characteristics were reported to be similar between the early and late switch groups (p values not reported).
Inclusion criteria	As reported in Llibre et al. (2018)
Exclusion criteria	As reported in Llibre et al. (2018)
Intervention(s)	Dolutegravir 50mg and rilpivirine 25mg from baseline to week 100 Dolutegravir 50mg and rilpivirine 25mg from week 52 to week 100

Comparator(s)	None
Length of follow-up	100 weeks for 513 participants 48 weeks for 477 participants
Outcomes	Primary outcome: - Number of participants with viral load <50 copies/mL
	Secondary outcomes: - Change in CD4 cell counts
	Safety outcomes: - Incidence and severity of adverse events, including drug-related adverse events - Change in serum concentrations of blood lipids - Change in serum concentrations of bone-turnover biomarkers - Number of participants with viral resistance
Source of funding	ViiV Healthcare and Janssen Pharmaceutica NV

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Research aims and design are clearly stated
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Longer term follow up of a randomised controlled trial, with cross over from the comparator arm into the intervention arm. Design is appropriate but a comparative study would have been more useful.
3. Are the methods clearly described?	2/2	The methods are clearly described.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	The data are adequate to support the authors' interpretations and conclusions.
5. Are the results generalisable?	1/2	The study was conducted in 12 countries in Europe, South America, North America and Asia. It is not clear how many participants were recruited from each country. It is not clear whether the results would be generalizable to the UK population, for example, the ethnicity of the study

		participants may not reflect that of the UK population.
Total	8/10	
Applicability	Directly applicable	The participants in the study matched the marketing authorisation of the intervention

Table 6 McComsey et al. (2018) (SWORD substudy)

Study reference	McComsey et al. (2018)
Unique identifier	NCT02478632 – substudy of SWORD 1 and SWORD 2
Study type (and NSF-LTC study code)	Open label, parallel-group substudy of an RCT (P1)
Aim of the study	To evaluate changes at week 48 in bone mineral density and bone turnover biomarkers after switching from a three-drug regimen containing tenofovir disoproxil fumarate to the NRTI-sparing dolutegravir with rilpivirine regimen.
Study dates	June 2015 to November 2016
Setting	32 centres in 6 countries (Argentina [4 centres], Belgium [3 centres], Canada [4 centres], Spain [12 centres], UK [2 centres], USA [7 centres])
Number of participants	N=102 A sample size of 100 participants was needed to provide 77% power with a treatment difference of 1.9%.
Population	Median age: - Dolutegravir-rilpivirine: 43 years (range 21 to 62 years) - Non-switch group: 46 years (range 22 to 76 years) ≥50 years or older: 31 (30%) Women: 53 (52%) White ethnicity: 84 (82%) Body mass index at baseline (mean, SD, range), kg/m^2 - Dolutegravir-rilpivirine= 25.2 (SD 3.9) (18.7 to 33.3) - Current ART= 25.8 (SD 4.8) (18.9 to 38.7) Baseline third-agent class

	- NNRTI= 65 (64%) - INI= 14 (14%) - PI= 23 (22%)
Inclusion criteria	- Participants in SWORD 1 or SWORD 2 who were receiving a stable ART regimen containing tenofovir disoproxil fumarate - Received at least 1 dose of dolutegravir-rilpivirine or current ART
Exclusion criteria	- Less than 3 vertebra in the L1-L4 range suitable for BMD measurement - Bilateral hip replacement - Uncontrolled thyroid disease - Male hypogonadism - Endocrine diseases - Fragility fracture history - Severe osteoporosis - Body mass index <18 kg/m^2 or ≥40 kg/m^2 - 25-hydroxy vitamin D <15ng/mm^3 - Current use of or intent to initiate tamoxifen, bone-related treatment or anabolic steroids (except testosterone if started before study and no plans to discontinue use during study) - Treatment with or intent to initiate anticonvulsant therapy or other hormonal therapy (unless started before study and no plans to discontinue use during study)
Intervention(s)	Dolutegravir 50mg with rilpivirine 25mg once daily
Comparator(s)	Current ART
Length of follow-up	48 weeks
Outcomes	Primary outcome: - Change in total hip BMD
	Secondary outcomes: - Change in lumbar spine (L1-L4) BMD - Change in total hip and lumbar spine BMD - Change in fracture risk score - Change in bone turnover biomarkers
	Safety outcomes: - Adverse events related to the DXA scan procedure
Source of funding	ViiV Healthcare and Janssen Pharmaceutica NV

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	2/2	Research aims and design are clearly stated
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Design is appropriate for the aims of the research. Unlike in the primary study, in this substudy the assessors were blinded to drug allocation.
3. Are the methods clearly described?	2/2	The methods are clearly described.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	The data are adequate to support the authors' interpretations and conclusions.
5. Are the results generalisable?	1/2	It is unclear in which countries the study was conducted. It is not clear whether the results would be generalizable to the UK population, for example, the ethnicity of the study participants may not reflect that of the UK population.
Total	9/10	
Applicability	Directly applicable	The participants in the study matched the marketing authorisation of the intervention

Table 7 Suzuki et al. (2017)

Study reference	Suzuki et al. (2017)
Unique identifier	Not included on clinicaltrials.gov
Study type (and NSF-LTC study code)	Case reports (P3)
Aim of the study	To describe 2 cases of HIV-1 infected patients whose comorbidities involving the central nervous system and/or aging led to difficulty swallowing retroviral tablets.
Study dates	Not stated
Setting	1 hospital in Japan
Number of participants	N=2
Population	Case 1

	- Male, 66 years old, Japanese - HIV-1 infection and multiple system atrophy, characterised by cerebella ataxia, Parkinsonism, and autonomic dysfunction. Progressive symptoms of dysphagia. - Undetectable viral load at baseline - No history of virological failure - Before switching to dolutegravir-rilpivirine, treated with levodopa/carbidopa and taltirelin hydrate. These were oral tablets that were crushed. Switched to dolutegravir-rilpivirine as unable to swallow levodopa/carbidopa and taltirelin hydrate as whole tablets. Case 2 - Female, 36 years old, Japanese - HIV-1 infection and neurologic sequelae with progressive multifocal leukoencephalopathy showing fatal subacute demyelinating disease of the brain - Undetectable viral load at baseline - No history of virological failure - Before switching to dolutegravir-rilpivirine, treated with EFV plus ABC/3Tc as crushed tablets via a feeding tube. Switched to dolutegravir-rilpivirine as she was extubated and able to resume oral feeding, but EFV plus ABC/3Tc tablets were too large to take orally. Note: The paper does not report whether the participants had a known or suspected resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.
Inclusion criteria	Not stated
Exclusion criteria	Not stated
Intervention(s)	Dolutegravir-rilpivirine
Comparator(s)	Previous ART
Length of follow-up	12 months
Outcomes	- HIV-1 viral load - CD4 cell count - Adherence - Burden on caregivers
Source of funding	None stated

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	2/2	The research questions/aims and design are clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Case report. The research design is appropriate for the aims of the research. However, a randomised controlled trial with patient interviews would have provided more reliable data.
3. Are the methods clearly described?	1/2	The study dates are not reported and it is not clear how cases were identified for inclusion in the paper.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The conclusions are in line with the data, however, the conclusions are more strongly stated than the data suggests they should be. There is no acknowledgement of the limitations of the study design in the paper.
5. Are the results generalisable?	0/2	It is not clear if the results are generalizable to the UK population as there were only two participants.
Total	5/10	
Applicability *	Directly applicable	The intervention and participants matched the marketing authorisation of the intervention. However, it is not clear whether these participants had a resistance to any non-nucleoside reverse transcriptase inhibitor or integrase inhibitor.

Appendix 4 Results tables

Table 8 Llibre et al. (2018) (SWORD studies)

	Dolutegravir-rilpivirine	Current ART	Analysis
N	**513***	**511****	
Primary outcome			
Number of participants with plasma viral load <50 copies per mL at week 48	486 (94.7%)	485 (94.9%)	DR was non-inferior to current ART, with a non-inferiority margin of 4%. Adjusted treatment difference of -0.2% (95% CI -3.0 to 2.5). Adjusted for baseline ART third-agent class and age group (<50 or ≥50 years). No statistically significant difference in viral load between subgroups based on third-agent treatment class at baseline, baseline CD4 cell count, age, sex or ethnicity (data presented on a graph only – point estimates and p values not provided).
Number of participants with virological non-response by week 48	3 (<1%)	6 (1%)	Dolutegravir-rilpivirine was non-inferior to current ART with an inferiority margin of 4%. Adjusted treatment difference of -

				0.5% (95% CI -1.4 to 0.5) Adjusted for baseline ART third-agent class and age group (<50 or ≥50 years).
Secondary outcomes				
Changes in median CD4 cell counts at week 48		Increase of 28.0 cells per µL (IQR -55.0 to 112.5)	Increase of 22.0 cells per µL (IQR -46.0 to 108.08)	Statistical significance of difference in increases is not reported.
Change in patient-reported outcomes on the HIV Treatment Satisfaction Questionnaire, status version (HIVTSQs) from baseline to week 48	Total score	Mean 54.4 (SD 6.4) to mean 55.9 (SD 7.0)	Mean 53.9 (SD 6.6) to 54.3 (SD 6.0)	No statistically significant difference between the groups
	Lifestyle/ease subscore	Mean 27.5 (3.2) to mean 28.3 (3.0)	Mean 27.2 (3.3) to mean 27.3 (3.7)	P<0.0001
	General satisfaction/clinical	Not reported	Not reported	No statistically significant difference between the groups
Symptom Distress Module from baseline to week 48	Symptom bother score	Mean 9.6 (10.0) to mean 8.2 (8.1)	Mean 11.0 (11.2) to mean 10.3 (9.2)	P=0.014
Patient reported treatment adherence by week 48		97.9% (SD 4.22)	98.3% (SD 3.91)	P value not reported
Safety outcomes				
At least 1 adverse event by week 48 (number of participants)		395 (77%)	364 (71%)	Statistical significance and p values not reported
Nasopharyngitis		49 (10%)	50 (10%)	Statistical significance
Headache		41 (8%)	23 (5%)	

Upper respiratory tract infection		24 (5%)	37 (7%)	and p values not reported
Diarrhoea		32 (6%)	27 (5%)	
Back pain		15 (3%)	31 (6%)	
Bronchitis		23 (4%)	15 (3%)	
Influenza		14 (3%)	17 (3%)	
Arthralgia		21 (4%)	9 (2%)	
Insomnia		17 (3%)	10 (2%)	
Depression		17 (3%)	6 (1%)	
Anxiety		11 (2%)	8 (2%)	
Abnormal dreams		6 (1%)	0	
Adverse events by week 48 by grade (number of participants)	Grade 1	247 (48%)	244 (48%)	Statistical significance and p values not reported
	Grade 2	116 (23%)	100 (20%)	
	Grade 3	27 (5%)	17 (3%)	
	Grade 4	5 (1%)	3 (1%)	
Adverse events leading to withdrawal from the study by week 48 (number of participants)		17 (3%)	3 (1%)	Most common adverse events leading to withdrawal were psychiatric disorders, gastrointestinal disorders and neoplasms.
Drug-related adverse events by week 48 (number of participants)		97 (19%)	9 (2%)	Those reported by 2% or more of participants were headache and diarrhoea.
Serious adverse events by week 48 (number of participants)	Total	27 (5%)	21 (4%)	Statistical significance and p values not reported None of the fatal events were considered related to study drugs
	Drug-related	4 (1%)	1 (<1%)	
	Fatal	1 (<1%)	1 (<1%)	
Change in mean serum concentrations of lipids from baseline to week 48	Total cholesterol (mg/dL)	184.3 to 186.1	186.7 to 187.0	No significant difference in change from baseline between the groups (changes and p values not reported)
	HDL cholesterol (mg/dL)	52.3 to 54.1	53.3 to 54.7	
	Calculated LDL cholesterol (mg/dL)	107.2 to 109.0	108.8 to 107.5	
	Triglycerides (mg/dL)	126.4 to 118.0	126.3 to 125.8	

	Total:HDL cholesterol	3.78 to 3.67	3.73 to 3.65	
Change from baseline in mean serum concentrations of bone-turnover biomarkers at 48 weeks	Bone-specific alkaline phosphatase type	15.9 to 12.9	16.2 to 17.1	P<0.0001
	Osteocalcin type	23.8 to 19.0	24.0 to 23.1	P<0.0001
	Procollagen type 1 N-terminal propeptide	53.0 to 45.6	55.3 to 54.7	P<0.0001
	Type 1 collagen C-telopeptide	0.66 to 0.49	0.69 to 0.63	P<0.0001
Change in inflammatory and cardiovascular biomarkers from baseline to week 48 [note: it is not clear if these are mean or median values] [note: the number of participants at baseline and week 48 for each biomarker varied – the n reported here is the number of participants at week 48]	Cystatin C, mg/L	N=483	N=482	Statistical significance of differences between group or changes within groups not reported
		Baseline 0.70 Change of 0.00 (min -0.4 to max 0.5)	Baseline 0.70 Change of 0.00 (min -0.4 to max 0.4)	
	Retinol binding, nmol/L	N=453	N=455	
		Baseline 5.61 Change of -1.87 (min -189.98 to max 17.92)	Baseline 5.13 Change of -0.76 (min -169.06 to max 186.73)	
	Beta-2-microglobulin, nmol/L	N=161	N=174	
		Baseline 14.41 Change of -3.39 (min -11129.69 to max 125.42)	Baseline 14.41 Change of 0.00 (min -333.05 to max 3411.03)	
	C-reactive protein, mg/L	N=480	N=482	
		Baseline 1.30 Change of 0.0 (-0.60 to 0.70***)	Baseline 1.30 Change of 0.00 (-0.50 to 0.90***)	
	D dimer, nmol/L FEU	N=463	N=466	
		Baseline 1.15 Change of 0.00 (-0.05 to 0.38***)	Baseline 1.10 Change of 1.10 (-0.11 to 0.27***)	
	Fatty acid binding protein 2, ng/mL	N=478	N=478	
		Baseline 2.25 Change of -1.46 (-2.61 to -0.67***)	Baseline 2.37 Change of -1.03 (-2.02 to -0.34***)	
	Glucose, mmol/L	N=469	N=462	
		Baseline 5.00	Baseline 5.00	

		Change of 0.00 (-0.30 to 0.40***)	Change of 0.20 (-0.10 to 0.50***)	
	Interleukin-6, ng/L	N=478	N=480	
		Baseline 1.61 Change of -0.04 (-0.76 to 0.61***)	Baseline 1.57 Change of -0.05 (-0.65 to 0.59***)	
	Soluble CD14, ng/mL	N=479	N=479	
		Baseline 1677.46 Change of 363.72 (-41.43 to 849.12***)	Baseline 1696.34 Change of 773.83 (336.09 to 1185.67***)	
	Soluble CD163, µg/L	N=477	N=477	
		Baseline 537.70 Change of 52.80 (-31.50 to 139.20***)	Baseline 555.40 Change of 26.00 (-43.70 to 133.80***)	
	Soluble vascular cell adhesion molecule-1, µg/L	N=479	N=480	
		Baseline 1894.63 Change of -21.45 (-412.14 to 341.55***)	Baseline 1871.05 Change of 16.12 (-383.28 to 429.40***)	
	eGFR using cystatin C, TDF at baseline, mL/min/1.73m^2	N=350	N=338	
		Baseline 115.74 Change of 0.00 (-6.96 to 9.42***)	Baseline 115.97 Change of 0.00 (-7.65 to 7.81***)	
	eGFR using cystatin C, no TDF at baseline, mL/min/1.73m^2	N=133	N=144	
		Baseline 119.66 Change of 0.00 (-9.15 to 0.00***)	Baseline 116.81 Change of 0.00 (-3.39 to 8.03***)	
Number of participants that developed viral resistance during the study		1 participant NNRTI resistance-associated substitution K101K/E mixture with no decreased	None	

	susceptibility to rilpivirine. No integrase resistance substitutions or decreases in dolutegravir susceptibility.		

*N=516 assigned to dolutegravir-rilpivirine but 3 did not receive treatment

**N=512 assigned to current ART group but 1 did not receive treatment

***It is not clear in the study paper whether these figures are 95% confidence intervals or ranges.

Table 9 Aboud et al. (TBC) (SWORD 100 week data)

	Dolutegravir-rilpivirine from baseline to 100 weeks	**Dolutegravir-rilpivirine from 52 to 100 weeks**
N	**513**	**477**
Primary outcome		
Number of participants with plasma viral load <50 copies per mL	456 (89%) (95% CI 86.2% to 91.6%)	444 (93%) (95% CI 90.8% to 95.4%)
	Note: Maintenance of viral suppression was consistent across subgroups for age, race, baseline CD4 cell count and sex	
Number of participants with virological non-response	13 (3%)	10 (2%)
Secondary outcomes		
Changes in median CD4 cell counts (cells/mm^3)	+33 (IQR -51 to +143)	+12 (IQR -81 to +99)
Safety outcomes		
At least 1 adverse event (number of participants)	453 (88%)	386 (81%)
Psychiatric disorders	88 (17%)	54 (11%)
Nasopharyngitis	8 (2%)	8 (2%)
Headache	59 (12%)	29 (6%)
Viral upper respiratory tract infection	77 (15%)	49 (10%)
Upper respiratory tract infection	51 (10%)	35 (7%)
Diarrhoea	46 (9%)	21 (4%)
Back pain	30 (6%)	27 (6%)

Bronchitis		38 (7%)	17 (4%)
Arthralgia		37 (7%)	25 (5%)
Syphilis		32 (6%)	25 (5%)
Adverse events by grade (number of participants)	Grade 1	228 (44%)	247 (52%)
	Grade 2	167 (33%)	108 (23%)
	Grade 3	45 (9%)	23 (5%)
	Grade 4	13 (3%)	8 (2%)
Adverse events leading to withdrawal from the study (number of participants)		34 (7%) These were psychiatric (n=12); neoplasms (n=8), gastrointestinal (n=7); nervous system disorders (n=3); hepatobiliary (n=1); respiratory, thoracic, or mediastinal (n=1)	15 (3%) These were psychiatric (n=5), neoplasms (n=2), gastrointestinal (n=3), and nervous system disorders (n=3)
Drug-related adverse events (number of participants)		103 (20%) Most common drug-related adverse events were headache, nausea, and diarrhoea	58 (12%) Most common drug-related adverse events were headache, nausea, and diarrhoea
Serious adverse events (number of participants)	Total	58 (11%)	30 (6%)
	Fatal	3 (<1%)* None of these were considered related to study drugs	0
Change in mean serum concentrations of lipids	Total cholesterol (mmol/L)	Increase of 0.10 from baseline 'No clinically relevant effect'	Increase of 0.06 from week 52 'No clinically relevant effect'
	HDL cholesterol (mmol/L)	Increase of 0.001 from baseline 'No clinically relevant effect'	Decrease of 0.03 from week 52 'No clinically relevant effect'
	LDL cholesterol (mmol/L)	Increase of 0.15 from baseline 'No clinically relevant effect'	Increase of 0.16 from week 52 'No clinically relevant effect'
	Total:HDL cholesterol	Increase of 0.05 from baseline 'No clinically relevant effect'	Increase of 0.11 from week 52 'No clinically relevant effect'
Change from baseline in mean serum concentrations of	Bone-specific alkaline phosphatase type (µg/L)	Decrease in mean of 2.9 from baseline (p<0.001)	Decrease in mean of 4.1 from week 52 (p<0.001)

bone-turnover biomarkers	Osteocalcin (µg/L)	Decrease in mean of 3.8 from baseline (p<0.001)	Decrease in mean of 3.8 from week 52 (p<0.001)
	Procollagen type 1 N-terminal propeptide (µg/L)	Increase in mean of 2.1 from baseline (p=0.107)	Decrease in mean of 2.9 from week 52 (p<0.01)
	Type 1 collagen C-telopeptide (µg/L)	Decrease in mean of 0.1 from baseline (p<0.001)	Decrease in mean of 0.13 from week 52 (p=0.002)
Retinol binding protein/creatinine ratio	TDF at baseline	Decrease in median of 4.86 from baseline (p<0.001)	Decrease in median of 3.26 from week 52 (p<0.001)
	No TDF at baseline	Decrease in median of 2.21 from baseline (p<0.001)	Decrease in median of 2.26 from week 52 (p<0.001)
Urine beta-2-microglobulin: creatinine	TDF at baseline	Decrease in median of 0.01 (p<0.001)	Decrease in median of 0.01 (p<0.001)
	No TDF at baseline	No change	Decrease in median of 0.01 (p=0.245)
Number of participants that developed viral resistance during the study		3 participants developed at least 1 NNRTI resistance-associated substitution No INI resistance-associated substitutions in any participants	Unknown as testing not undertaken
TDF tenofovir disoproxil fumarate * Note: a poster publication of this study reported only 1 fatality in this group			

Table 10 McComsey et al. (2018) (SWORD substudy)

	Dolutegravir-rilpivirine	**Current ART**	**Analysis**
N	**46**	**35**	
Primary outcome			
Percentage increase in total hip BMD (areal density in g/cm^2) including femoral neck, trochanter and intertrochanter areas at week 48	1.34%	0.05%	Difference in adjusted percentage change +1.29% (95% CI 0.27 to 2.31, p=0.014) Greater change with DR observed in all age, sex, baseline body mass index, and baseline third-agent class subgroups, however,

			sample sizes too small for statistical analysis
Secondary outcomes			
Percentage increase in lumbar spine (L1 to L4) BMD (areal density in g/cm^2) at week 48	1.46%	0.15%	Difference in adjusted percentage change +1.32% (95% CI 0.07 to 2.57, p=0.039) Greater change with DR observed in all age, sex, baseline body mass index and baseline third-agent class subgroups, however, sample sizes too small for statistical analysis
Total hip T score at 48 weeks	Not reported	Not reported	Difference in adjusted percentage change +0.09% (95% CI 0.02 to 0.16, p=0.016)
Lumbar spine T score at 48 weeks	Not reported	Not reported	Difference in adjusted percentage change +0.12% (95% CI 0.00 to 0.23, p=0.049)
Total hip Z score at 48 weeks	Not reported	Not reported	P=0.026
Total lumbar spine Z score at 48 weeks	Not reported	Not reported	P=0.013
10 year probability of hip fracture	-0.08%	+0.03%	P value not reported
10 year probability of osteoporotic fracture	-0.12%	-0.04%	P value not reported
Safety outcomes			
No adverse events attributable to DXA scan procedure. 1 participant in the dolutegravir-rilpivirine group had clinically significant loss of BMD (≥5%) at week 48, but did not require pharmacological intervention. 1 participant in current ART group experienced a non-traumatic fracture of the right fibula that was considered not to be related to study treatment.			
Notes Bone biomarkers were also reported in this paper, however, these were also reported in the Llibre et al. (2018) paper for a larger group of participants, including the ones in this paper. Therefore the results for bone biomarkers in this study population are presented in the results table for the Llibre et al. (2018) paper.			

Table 11 Suzuki et al. (2017)

	Dolutegravir-rilpivirine	
	Case 1	**Case 2**
Outcomes at 12 months	Undetectable HIV-1 viral load (<40 copies/mL) CD4 cell count of 474 cells/mL Adherence maintained Reduced burden on caregivers at home Enabled patient to take tablets on his own without crushing them or preparing an oral suspension	Undetectable HIV-1 viral load (<40 copies/mL) CD4 cell count of 289 cells/mL Adherence maintained Tablets could be taken without crushing or preparing an oral suspension

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.