

## Clinical Commissioning Policy Statement Dolutegravir/lamivudine for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults and adolescents over 12 years of age (1920) [200301P]

### Commissioning Position

#### Summary

Dolutegravir/lamivudine for the treatment of HIV infected adults and adolescents >12 years of age is recommended to be available as a treatment option through routine commissioning within the criteria set out in this document.

The policy statement is restricted to certain age groups as there is insufficient evidence to confirm safety and/or it is not recommended to be used in those age groups not included in the policy.

### Executive Summary

#### Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

### Plain language Summary

#### About HIV

HIV 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 infection. In some cases, this can lead to acquired immunodeficiency syndrome (AIDS), which is the name given to several life-threatening illnesses that can develop when the immune system has become severely damaged by the HIV virus.

HIV is transmitted through the body fluids of a person with a detectable level of the virus. Most people have flu-like illness several weeks after infection. After this, HIV may not cause any symptoms for several years, but it will still damage the immune system.

There is currently no cure for HIV, but with treatment, most people with HIV will have near normal life expectancy and will not develop AIDS-related illness.

There are 2 main types of HIV – HIV-1 (the most common type) and HIV-2 (relatively uncommon in the UK). This policy covers HIV-1 only as dolutegravir/ lamivudine is not licensed for the treatment of HIV-2.

## About current treatments

It is recommended that treatment with antiretroviral therapy (ART) the medicines used to treat HIV is usually started immediately after a diagnosis to stop the virus replicating in the body. The standard of care is treatment with three drugs. Antiretrovirals are divided into different classes. These drug classes stop HIV reproducing by binding to one of the viral enzymes: reverse transcriptase, protease or integrase.

Standard three-drug regimens usually include two drugs from the nucleoside reverse transcriptase inhibitor (NRTI) class, plus one drug from one other class: a non-nucleoside reverse transcriptase inhibitor (NNRTI) **or** a protease inhibitor (PI) **or** an integrase inhibitor (INI).

## About dolutegravir and lamivudine

Dolutegravir is an INI and lamivudine is an NRTI meaning the combination targets two different steps of the HIV replication pathway.

Typically, HIV treatment includes three different drugs, as described above. Dolutegravir/lamivudine provides an alternative treatment with similar effectiveness to three-drug combinations for both first-line therapy and as a switch option in people already on a three-drug combination who have an undetectable viral load. Dolutegravir and lamivudine can be prescribed as separate tablets or as a fixed dose combination pill as a single tablet.

## What we have decided

NHS England has carefully reviewed the evidence to treat HIV with dolutegravir/lamivudine in adults and adolescents >12 years of age. We have concluded that there is enough evidence to make the treatment available at this time.

## Links and updates to other Policies

This document updates or is informed by the following documents:

- NHS England (2018) Clinical Commissioning Policy: Immediate antiretroviral therapy for treatment of HIV 1 in adults and adolescents
- NHS England (2018) Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infection (all ages)
- NHS England (2019) Clinical Commissioning Policy: Dolutegravir/rilpivirine for treating HIV-1 in adults
- Best Practice in HIV Prescribing and Multidisciplinary Teams (2019)
- NHS England (2013) Specialised Human Immunodeficiency Virus (HIV) Services (Adult)

## Committee discussion

The Clinical Panel considered the policy proposition based on three evidence papers. The evidence base was considered which demonstrated effectiveness, achieving viral load targets, reduced toxicity and reported adverse events. See the committee papers [\(link\)](#) for full details of the evidence.

## The condition

HIV is a virus that damages the CD4 cells of the immune system, leaving the body less able to fight off infection and disease. In some cases, the damage caused to the immune system by HIV leads to AIDS, which is the collective name given to several illnesses that can be life threatening for people with HIV. HIV cannot be cured; however, effective management of HIV reduces its impact on the immune system and can prevent people with the virus from developing AIDS.

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Within a few weeks of infection, HIV may cause a flu-like illness with fever, headache, muscle aches and joint pain, sore throat and swollen lymph glands. This can last for a few weeks, after which there may be no specific signs or symptoms of HIV for several years. As the virus continues to destroy cells in the immune system, people with HIV may develop mild infections or other signs and symptoms, including fever, fatigue and weight loss. If untreated, HIV progresses to AIDS, which is characterised by certain conditions such as tuberculosis, cytomegalovirus, candidiasis, cryptococcal meningitis, toxoplasmosis, cryptosporidiosis, and different types of cancer, particularly Kaposi's sarcoma and lymphoma. AIDS can be characterised by wasting syndrome, neurological complications such as dementia, and kidney disease.

HIV is transmitted from person to person through the body fluids of an infected person with a detectable viral load. It can affect people of any age, family origin, sex or sexual orientation.

### **Current treatments**

Currently HIV is usually managed with a combination of three drugs including two nucleoside reverse transcriptase inhibitors (NRTIs; tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine, abacavir, lamivudine) and either a protease inhibitor (PI; darunavir, atazanavir, lopinavir) boosted with ritonavir or cobicistat, a non-nucleoside reverse transcriptase inhibitor (NNRTI; rilpivirine, efavirenz, doravirine ) or an integrase inhibitor (INI; dolutegravir, elvitegravir/cobicistat, raltegravir, bictegravir).

People typically start on a three-drug regimen and only move to another if there is lack of virological response, treatment failure, or tolerability issues. Additional issues include pill burden and dose frequency which may affect adherence. Considerations related to potential for drug-drug interactions are particularly relevant as people with HIV are living longer, which means they may become more likely to take medication for age-related comorbidities.

### **Proposed treatments**

Dolutegravir/lamivudine is a combination regimen which allows treatment with two drugs rather than three: dolutegravir (an INI), and lamivudine (an NRTI). It is licenced as a treatment option in those who are naïve to antiretroviral treatment who have no viral resistance to dolutegravir or lamivudine and whose viral load is <500,000 copies/ml of blood. It is also an option for people whose disease is currently being controlled (HIV-1 RNA <50 copies/ml) with a stable antiretroviral regimen for at least 6 months, with no history of virological failure, and no known or suspected resistance to any NRTI inhibitor or INI. Dolutegravir/lamivudine also provides an alternative treatment option to NNRTIs for people who have concerns about the toxicity of NNRTIs.

The Summary of Product Characteristics (SPC) for dolutegravir/lamivudine states that it is not recommended during pregnancy. For other contraindications to use, please refer to the [SPC](#).

## **Epidemiology and Needs Assessment**

The latest available data shows that in 2018 there were around 96,000 people in England being seen for HIV care (Public Health England, 2019). The estimated prevalence of HIV in England was 2.4 per 1,000 population aged between 15-59 years old (Public Health England, 2019) and around 4,500 people in England were newly diagnosed with the condition in 2018 (Public Health England, 2019).

In 2017 there were around 73,000 adults with HIV in England who were on antiretroviral treatment and had a viral load of less than 50 copies/ml (Public Health England, 2018). Considering the annual incidence of HIV, this number is likely to increase to 77,000 adults in 2018/19. It is estimated that approximately 65% of these people would meet the marketing authorisation for dolutegravir/lamivudine. This suggests approximately 47,450 adults and adolescents would be eligible for treatment with dolutegravir/ lamivudine in 2018/19, if they were to start or switch from their existing antiretroviral therapy. However, fewer people would receive

dolutegravir/lamivudine in clinical practice, because of the eligibility criteria, and the availability of alternative treatment regimens.

## Evidence summary

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

### Clinical trial evidence

Three papers were presented for review with appropriate population, intervention and comparators and primary outcomes (see Table 1 at Appendix 1). Paper 1 is two multi-centre, double-blind, randomised non-inferiority Phase 3 trials. Paper 2 is an open-label, single arm, multi-centre trial. Paper 3 is a systematic review of seven studies of dual therapy regimens.

#### Paper 1: Cahn et al, 2018

##### **Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in anti-retroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multi-centre, double-blind, randomised, non-inferiority, phase 3 trials.**

The paper by Cahn et al, 2018, reports twin multi-centre double-blinded RCTs GEMINI-1/GEMINI-2 comparing the use of dolutegravir 50mg plus lamivudine 300mg (two-drug regimen (2DR)) against dolutegravir 50mg plus tenofovir disoproxil fumarate 300mg plus emtricitabine 200mg (three-drug regimen (3DR)), in 1441 treatment naïve patients with HIV-1. Non-inferiority of the 2DR compared to 3DR was demonstrated in both individual studies with a pooled adjusted difference within a pre-specified non-inferiority of greater than -10% in the proportion of participants with plasma viral load (pVL) <50 copies per ml by week 48 (-1.7%, (95% CI -4.4 to 1.1)). There was no evidence of viral resistance in 10 participants identified as having virological failure. The proportion of participants experiencing any or serious adverse events (AEs) were similar between the 2DR and 3DR arms, whilst a smaller proportion of participants in the 2DR arm experienced treatment related AEs, largely due to reduced nausea.

#### Paper 2: Joly et al, 2018

##### **Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL)**

The paper by Joly et al, 2018, reports a single-arm, open label, multi-centre trial (LAMIDOL) in which 110 3DR-treatment experienced patients with HIV-1 were switched to a 2DR of dolutegravir 50mg plus lamivudine 300mg. The study reported therapeutic and strategy success with ≤10 participants not achieving viral load suppression of <50 copies per ml by week 48. One participant had confirmed virological failure and with no evidence of resistant mutations. There were nine participants that experienced serious AEs during the study, two of which (both suicidal ideation) were attributed to the 2DR treatment.

#### Paper 3: Comi et al, 2018

##### **Dolutegravir plus lamivudine as simplification dual therapy in virologically suppressed HIV-1 infected subjects**

The paper by Comi et al, 2018, is a systemic review of published studies in which participants were switched from a 3DR to a 2DR of dolutegravir plus lamivudine. The review included the LAMIDOL study amongst a total of eight studies. The other seven studies included two randomised trials and five clinical cohorts, all focusing on treatment experienced participants. The review concluded that the 2DR had substantial evidence of both efficacy and tolerability.

Overall, the evidence from the three papers suggests that the combination of dolutegravir plus lamivudine has good efficacy in reducing and maintaining suppressed viral load in both treatment naïve and treatment experienced patients with HIV-1. The evidence also suggests

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that the combination of dolutegravir plus lamivudine in the treatment naïve and treatment experienced patients with HIV-1 is not associated with development of viral resistance. There is insufficient evidence presented to conclude that there are non-inferior changes to CD4+ count between the 2DR of dolutegravir plus lamivudine compared to a 3DR because these were not reported. The 2DR of dolutegravir plus lamivudine appears to have a similar, adverse event profile compared to a 3DR.

However, the evidence should be interpreted with caution when applying in clinical practice in England due to the following considerations:

- Single-entity tablets of dolutegravir and lamivudine were used as the 2DRs and therefore bio-equivalence from a fixed-combination formulation containing dolutegravir 50mg plus lamivudine 300mg would need to be demonstrated in application of the current evidence.
- Very few participants in the included studies were from the UK. The only studies to include UK participants were GEMINI-1 and GEMINI-2 with a total of 37 (3%) participants (21 (3%) in 2DR and 16 (2%) in 3DR).
- Most studies within the evidence review included only participants with little or no virological failure and/or viral resistance, and therefore the use of dolutegravir and lamivudine in patients with a history of either should be avoided.

### **Effectiveness**

#### ***Viral load***

The proportion of participants with plasma HIV-1 RNA of less than 50 copies per ml at week 48 of follow up was the primary outcome in the GEMINI-1 and GEMINI-2 studies in treatment naïve patients.

For each of GEMINI-1 and GEMINI-2, assuming a true response rate of 87% for 2DR and 89% for 3DR, a sample size of 347 participants per treatment group had 90% power to detect non-inferiority at a one-sided  $\alpha$  level of 2.5%. Non-inferiority was concluded if the lower boundary of the two-sided 95% CI for the difference in response (2DR minus 3DR) was greater than -10%.

The primary outcome in the LAMIDOL study in treatment experienced patients was the absence of both virological and strategy failure up to week 48. Virological failure was defined as pVL > 50 copies per ml confirmed in a second sample taken 2-4 weeks later, and strategy failure as discontinuation of the strategy for  $\geq 30$  days due to AEs, participant, or investigator decision, or loss to follow up. Each study was powered based on the primary outcome.

For the LAMIDOL study, assuming a true response rate of 90%, a sample size of 95 had a 90% power to detect non-inferiority of the 2DR over the 3DR at a one-side  $\alpha$  level of 2.5%. Non-inferiority was concluded if  $\leq 10$  participants failed in phase 2, including a maximum of 5 with virological failure.

#### **Single entity tablets in treatment naïve population**

In GEMINI-1 the proportion of participants achieving a pVL < 50 copies per ml at week 48 in intention to treat analysis was 90% (320/356) in the 2DR and 93% (332/358) in the 3DR (adjusted treatment difference -2.6%, 95% CI -6.7 to 1.5). In GEMINI-2 the proportion of participants achieving a pVL < 50 copies per ml at week 48 in intention to treat analysis was 93% (335/360) in the 2DR and 94% (337/359) in the 3DR (adjusted treatment difference -0.7%, 95% CI -4.3 to 2.9). In the pooled analysis, 655 [91%] of 716 in the two-drug regimen vs 669 [93%] of 717 in the three-drug regimen achieved a pVL < 50 copies per ml at week 48 (pooled adjusted treatment difference -1.7%, 95% CI -4.4 to 1.1). Most participants achieved a plasma HIV-1 RNA < 50 copies per ml by week 4. Both studies met the primary efficacy endpoint of non-inferior virological efficacy at week 48 as the lower boundary of the two-sided 95% CI for the difference was greater than -10%.

The primary outcome by subgroups was generally consistent with the overall efficacy for baseline HIV-1 RNA  $\leq 100\ 000$  copies per ml and  $> 100\ 000$  copies per ml, HCV serostatus,

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age group, gender, ethnicity, and HIV subtype. For CD4+ counts  $\leq 200$  cells per  $\mu\text{l}$ , only 79% (50/63 participants) in the 2DR achieved  $< 50$  copies per ml compared to 93% (51/55 participants) in the 3DR. However only three of 13 participants had HIV-1 RNA  $\geq 50$  copies per ml and most of the failures in this subgroup were said to be participant factors unrelated to efficacy or treatment failure.

### **Single entity tablets in treatment experienced population**

In LAMIDOL therapeutic success at week 48 was achieved in 101 out of 104 participants included in phase 2, 97% (95% CI 94-100). From the original 110 participants entering phase 1, 6 did not enter phase 2 (3 due to AEs, and 3 due to pVL  $> 50$  copies/ml). The study was deemed to have reached the primary efficacy end point as  $< 10$  participants had therapeutic or strategy failure.

In LAMIDOL, no subgroup analysis was conducted.

The systematic review by Comi et al (2018) concluded substantial virologic efficacy of dual therapy with dolutegravir /lamivudine.

### **CD4+ T cell count**

#### **Single entity tablets in treatment naïve population**

In GEMINI-1 and GEMINI-2 change in CD4+ cell count from baseline to w48 was a pre-specified secondary outcome but was not presented in the main report or supplementary material.

#### **Single entity tablets in treatment experienced population**

In LAMIDOL, from D0 to week 48, CD4 count significantly increased by 54.7 cells/mm<sup>3</sup> (95% CI 22.2 to 88.2;  $p < 0.01$ ) and CD4/CD8 ratio by 0.04 (95% CI 0.007 to 0.07,  $p < 0.05$ ).

In the systematic review by Comi et al (2018) changes in CD4+ counts were not presented.

### **Safety and tolerability**

#### **Viral resistance**

In GEMINI-1 and GEMINI-2 virological withdrawal was defined by a second and consecutive HIV-1 RNA value of:

- Decrease from baseline of less than one log copies per ml (unless  $< 200$  copies per ml by week 12)
- Confirmed plasma HIV-1 RNA of  $\geq 200$  copies per ml at week 24
- Confirmed rebound from  $< 200$  to  $\geq 200$  copies per ml

These participants were discontinued from the study and genotypic/phenotypic resistance tests were performed.

In LAMIDOL virological failure was defined as first pVL  $> 50$  copies per ml confirmed on second sample 2-4 weeks later.

In the systematic review by Comi et al (2018) virological failure was not clearly defined for individual studies.

#### **Single entity tablets in treatment naïve population**

In GEMINI-1 and GEMINI-2, virological withdrawal definitions were met by 10 participants overall, 6 in 2DR and 4 in 3DR (w16 n=1, w24 n=7, w48 n=2). No samples showed emergence of resistance to integrase strand transfer inhibitors although 1 of 10 samples was not analysed. All were classified as virological rebounds.

Reasons for discontinuation of treatment other than virological withdrawal were similar between 2DR (9% (66 of 719) and 3DR (7% (52 of 722) and included loss to follow up (2%), discontinuation due to AEs (2%), and withdrawn consent (2%). Additionally, withdrawals due to

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protocol deviation occurred in 1% for 2DR and <1% for 3DR, most commonly due to non-compliance with protocol procedures. Two participants in each of 2DR and 3DR groups became pregnant.

### **Single entity tablets in treatment experienced population**

In LAMIDOL, there were 3 cases of therapeutic failure. One participant had pVL of 84 copies per ml at week 4 and 83 copies per ml 18 days later, and with trough dolutegravir and lamivudine plasma levels in therapeutic range at time of failure. There was no evidence of INSTI resistant mutations. A second participant was lost to follow up at week 32, and a third participant was switched back to 3DR despite virological blip, rather than virological failure occurring, based on a subsequent pVL of 44 copies/ml. In this participant dolutegravir plasma concentrations were below therapeutic levels. Three viral blips were also observed in two participants (week 24 pVL 51, week 40 pVL, 67, week 48 pVL 130 – all returning to <50 copies per ml within 3-4 weeks). One of these participants had low trough dolutegravir concentrations. Resistance-associated mutations were not detected.

Excluding the LAMIDOL study results, in the systematic review by Comi et al (2018), three studies reported 5/256 participants receiving 2DR experienced virological failure (n=1/29, 1/44 and 3/183) and four studies reported no virological failures (n=27, 203, 105 and 32).

### **Adverse events**

#### **Single entity tablets in treatment naïve population**

In GEMINI-1 and GEMINI-2, any-cause AE was reported by 76% in the 2DR and 81% in the 3DR. Fewer participants reported drug-related AEs with 18% in the 2DR and 24% in the 3DR broadly explained by a lower level of grade 1 nausea. There was a similar proportion at 2% in both 2DR and 3DR for AEs leading to permanent discontinuation of study drug, and a similar proportion of serious AEs at 7% for 2DR and 8% for 3DR with 1% related to the drugs (cholelithiasis, hepatotoxicity, psychiatric disorder, rhabdomyolysis, substance-induced psychotic disorder, and suicide attempt (n=1 for each) and suicidal ideation (n=2). Two deaths were reported in the 2DR (n=1 Burkitt's Lymphoma and n=1 acute myocardial infarction) and neither were believed to be attributable to the study drugs. AE profile was similar between GEMINI-1 and GEMINI-2.

#### **Single entity tablets in treatment experienced population**

During phase 1 of LAMIDOL, one participant had dolutegravir interruption due to depression with suicidal ideation, believed to be related to the drug. In phase 2, eight participants reported serious adverse events (hospitalisation n=3, viral polyarthritis n=1, acute hepatitis C n=1, grade 4 increase in creatine kinase due to fitness activity n=2, depression leading to hospitalisation n=1). Only the two depressive episodes were thought to be associated with dolutegravir, and only one of which had the drug discontinued.

The systematic review by Comi et al (2018) noted that overall very few short-term adverse events leading to treatment discontinuation were observed in the included studies. Excluding the LAMIDOL study results, in the remaining seven studies, 17 treatment discontinuations due to adverse events were reported in three studies (n=1/44, 5/203 (mostly muscle aches) and 11/183) and four studies reported no treatment discontinuations due to adverse events (n=29, 27, 105 and 32). 38 participants reported adverse events in 4 studies (n=2/44, 3/27, 12/203 and 21/183) and no participants reported adverse events in 3 studies (n=29, 105 and 32).

### **Blood lipids**

#### **Single entity tablets in treatment naïve population**

In GEMINI-1 and GEMINI-2 total cholesterol, LDL-cholesterol and total triglycerides increased from baseline to week 48 in the 2DR and decreased in the 3DR. The difference between groups was significant for each. HDL-cholesterol significantly increased in the 2DR compared to 3DR.

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However, overall cholesterol to HDL ratio was lower in the 3DR than the 2DR. Absolute values were not presented.

Unfavourable changes to renal and bone biomarkers were seen in both regimens but significantly lower in the 2DR compared to the 3DR.

### **Single entity tablets in treatment experienced population**

Lipids were not reported as an outcome in LAMIDOL study.

The systematic review by Comi et al (2018) reported that following the switch to 2DR, two studies (n=203 and n=27) found limited reductions in median triglycerides (-31 mg/dL (p=0.012) and -66 mg/dL (p< 0.001)), median LDL-cholesterol (-7 mg/dL (p=0.335) and -15 mg/dL (p=0.009)) and total cholesterol (-7 mg/dL (p=0.047) and -24 mg/dL (p<0.01)) and an increase in HDL cholesterol (+4 mg/dL (p=0.047), n=27), noting that the clinical implications of these changes remain unclear.

## **Implementation**

### **Criteria**

Dolutegravir/lamivudine should be prescribed in accordance with local, regional and national drug algorithms. Where regional, cost-based antiretroviral guidelines do not require a multi-disciplinary team (MDT) approval for dolutegravir/lamivudine use then, as long it is clinically appropriate and the rationale for choice is clearly documented, MDT discussion is not mandatory.

Dolutegravir/lamivudine should be considered in treatment naïve people or for switch where it is considered clinically appropriate and does not incur additional cost compared to other clinically appropriate options. It should be considered in those with HIV VL of <500 000 copies/ml.

Specific situations include:

- 1) where current, or anticipated, drug-drug interactions limit the suitability of other HIV medications.
- 2) where there are contraindications or potential problems with NRTI backbone drugs e.g. abacavir and increased cardiovascular risk or tenofovir-DF and reduced eGFR.
- 3) intolerance of other agents.
- 4) Where an HIV MDT recommends its use. It is recommended MDT discussion takes place if there are possible adherence issues due to risks of increased development of tolerance to two classes of ART through poor compliance.

A fixed dose combination (single-tablet regimen) or the individual products can be used.

Contra-indications/exclusions/cautions:

- 1) Dolutegravir/lamivudine should not be used in people who have active hepatitis B without an additional HBV-active drug.
- 2) People with proven or suspected resistance to dolutegravir or lamivudine.
- 3) Use and reimbursement of this product by providers who are not commissioned by NHS England to provided HIV care and treatment services.
- 4) Dolutegravir/lamivudine should not be taken with any other medicinal products containing dolutegravir or lamivudine, except where a dose adjustment of dolutegravir is indicated due to drug-drug interactions.

Dolutegravir/lamivudine should not be used in:

- a. individuals with very high viral load (more than 500,000 copies/ml) as they were excluded from the GEMINI trials.

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- b. people with a low CD4 count (less than 200 cells/mm<sup>3</sup>); dolutegravir/lamivudine underperformed relative to the three-drug comparator arm in the GEMINI trials in people with low baseline CD4. Although this was driven by non-treatment related discontinuations, more data is required.
- c. People with AIDS-defining illnesses who, with the exception of cutaneous Kaposi's sarcoma, were excluded from the GEMINI trials.

Any increase in the price of this product or price reduction of alternative treatments may require a review of this policy.

### **Patient Pathway**

Treatment with dolutegravir/lamivudine can be considered for adults and adolescents >12 years of age for first-line treatment or as a switch option where they are virally suppressed on an alternative combination. Prescription of dolutegravir/lamivudine is in line with the existing pathway for people with HIV who are on antiretroviral treatment and should be in line with cost-based, regional prescribing guidelines. Monitoring of dolutegravir/lamivudine is in line with existing pathways for people with HIV who are on antiretroviral treatment and should be in line with national guidelines and standards.

### **Governance Arrangements**

In accordance with the 2013/14 NHS Standard Contract for Specialised Human Immunodeficiency Virus Services (Adults), people with HIV must have ongoing assessment, monitoring and management when starting, switching and remaining on antiretroviral therapies. This is to be undertaken by an appropriately qualified MDT.

### **Mechanism for funding**

Reimbursement for the use of ART for individuals meeting the criteria in this policy is provided via NHS England Specialised Commissioning Teams. Antiretrovirals should be prescribed in line with NHS England clinical commissioning policies in addition to agreed regional prescribing initiatives.

### **Audit requirements**

All people identified who might benefit from dolutegravir/lamivudine must be referred to and their treatment discussed in an HIV MDT or in line with regional, cost-based guidelines. Recommendations for treatment must be recorded. Commissioners will review the audits.

### **Policy review date**

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting [england.CET@nhs.net](mailto:england.CET@nhs.net)

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

## Definitions

• <b>Antiretroviral therapy (ART):</b>	a combination of drugs that treat HIV
• <b>Integrase inhibitors (INIs):</b>	a class of antiretroviral drug that prevents HIV DNA being inserted into the DNA of CD4 cells.
• <b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs):</b>	a class of antiretroviral drug that stops HIV DNA being added to healthy CD4 cells.
• <b>Nucleoside reverse transcriptase inhibitors (NRTIs):</b>	a class of antiretroviral drug that prevents the replication of HIV DNA.
• <b>Protease inhibitors (PIs):</b>	a class of antiretroviral drug that prevents HIV from replicating.
• <b>Viral load:</b>	a measure of the number of viral particles in the body, reported as copies per millilitre of blood (copies/ml).
• <b>Virological failure/non-response:</b>	when the viral load in someone with HIV is greater than 200 copies/ml on 2 consecutive tests despite the use of antiretroviral therapy.
• <b>Virologically suppressed:</b>	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.
• <b>Naïve:</b>	people who have not received any antiretroviral therapy previously.
• <b>Stable:</b>	people who continue to experience an undetectable viral load and who are not experiencing any intolerance to their medication are deemed to be stable.
• <b>Intolerance:</b>	people who are either assessed to be at high risk of adverse effects or experience adverse effects that will or have led to drug discontinuation are deemed to be intolerant.

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Appendix 1: Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary Outcome
GEMINI-1 and GEMINI-2 Cahn et al (2018)  Two Non-inferiority double-blind phase 3 RCTs	1441 treatment naïve patients with HIV-1 randomised to 2DR (n=719) or 3DR (n=722); participants had no evidence of pre-existing major viral resistance to NNRI, NNRTI, PI	Intervention: Once daily two-drug regimen of dolutegravir 50mg plus lamivudine 300mg  Comparison: Once daily three-drug regime of dolutegravir 50mg plus tenofovir disoproxil fumarate 300mg plus emtricitabine 200mg	Non-inferior virological efficacy <sup>1</sup> of the 2DR compared to the 3DR with primary end point the proportion of participants with plasma HIV-1 RNA of less than 50 copies per ml at w48 using the FDA snapshot algorithm in the intention to treat exposed population.
LAMIDOL Joly et al (2018)  Single-arm open label phase 2 trial	110 treatment experienced patients with HIV-1; Participants were virologically suppressed on first line cART, not previously had change of regimen due to virological failure, and no changes in treatment in previous 6 months	Phase 1: (week-8 to D0) 3DR third agent replaced by Dolutegravir (50mg) Phase 2: 2DR (D0 to W48) NRTI backbone replaced by Lamivudine (300mg)	Absence of both virological failure (pVL>50 copies/ml confirmed in a second sample 2-4 weeks later) and strategy failure (discontinuation of the strategy for >=30 days due to AEs, participant or investigator decision, or loss to follow up) up to W48
Comi et al 2018  Systematic review  Included 8 studies; three clinical trials and five cohort studies	Population of individual studies varied 29-203; 727 in total	Intervention:  Any intervention in which a triple cART is switched to a 2DR of dolutegravir plus lamivudine.  Comparison: Various – only two included studies were randomised	Not clearly specified for individual studies

<sup>1</sup> Non-inferiority was concluded if the lower boundary of the two-sided 95% CI for the difference in response (2DR minus 3DR) was greater than -10%.

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		clinical trials; another was a single arm open label trial (LAMIDOL), and the other studies included were prospective or retrospective cohorts.	
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