MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
08/01/2020

Agenda Item No	4.1
National Programme	Blood and Infection
Clinical Reference Group	HIV CRG
URN	1920

Title
Dolutegravir /lamivudine for the treatment of Human Immunodeficiency Virus (HIV 1) infected adults and adolescents >12years of age

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Routinely Commissioned 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). HIV is transmitted through the body fluids of a person with a detectable level of the virus. 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 proposition covers HIV 1 only as dolutegravir/ lamivudine is not licensed for the treatment of HIV 2. 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. Until now the standard of care is treatment with three drugs. These three 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).

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

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Not reported
2.	Progression free survival	Not reported
3.	Mobility	Not reported
4.	Self-care	Not reported

5.	Usual activities	Not reported
6.	Pain	Pain can sometimes be caused by the medication taken to control HIV. The one of the studies reported that 5% of participants in the dual therapy group and 4% in the triple therapy group experienced back. Arthralgia (joint pain) was reported by 2% of participants in the dual therapy group and 4% in the triple therapy group. Headache was reported by 10% of participants in both the dual and triple therapy groups. The statistical significance of the difference between the groups was not reported. It is not possible to determine from the evidence whether dolutegravir/lamivudine makes a difference to feelings of pain during treatment compared to other antiretroviral therapies. However, the proportions of participants reporting pain were similar in both dual and triple therapy groups. It is not clear how generalisable the results are to the UK as although most of the participants in the main study were countries similar to the UK population, only 3% of the dual therapy group and 3% of the triple therapy group were UK participants.
7.	Anxiety / Depression	Anxiety is a feeling of unease and can include symptoms such as feeling restless or worried, having trouble concentrating or sleeping, and dizziness or heart palpitations. Depression is a mood disorder characterised by low mood, feelings of sadness, and a loss of interest in activities that used to be enjoyable. The main study reported that less than 1% of participants in both the dual therapy group and the triple therapy group experienced anxiety and/or depression, with 2% in both study groups also reporting suicidal ideation and behaviour. However, it should be noted that over half of the participants reporting suicidal ideation and/or behaviour had a previous history of depression, suicidal ideation and/or behaviour. There were two deaths, both in the dual therapy group, neither of which were considered to be related to study medication. It is not possible to determine from the evidence whether dolutegravir/lamivudine improves anxiety or depression compared to other antiretroviral therapies. See the final paragraph of row 6 ‘Pain’ for the limitations with this evidence.

8.	Replacement of more toxic treatment	There is no direct evidence for dolutegravir/lamivudine replacing a more toxic treatment, however, there is limited evidence of its effect on renal function and bone mineral density (see row 3 'Renal function' and row 5 'Bone mineral density' in the table below).
9.	Dependency on care giver / supporting independence	Not reported
10.	Safety	Adverse events are unintentional and undesirable signs and symptoms reported during a study. If an event is thought to be related to the drugs being used in a study, it is known as a drug-related adverse event. In the main study in treatment naïve participants, drug-related adverse events were reported by 18% in the dual therapy and 24% in the triple therapy participants respectively, broadly explained by a lower level of grade 1 nausea. There was a similar proportion at 2% in both dual therapy and triple therapy for adverse events leading to permanent discontinuation of study drug. In the main study in treatment experienced participants, drug-related serious adverse events were reported by less than 1% of participants in both Phase 1 and Phase 2 leading to drug interruption only in one Phase 1 participant. The evidence suggests there is no difference in the number of drug-related adverse events with dolutegravir/lamivudine compared to other antiretroviral therapies. See the final paragraph of row 6 'Pain' for the limitations with this evidence.
11.	Delivery of intervention	Not reported

No	Metric	Summary from evidence review
1.	Viral load	Viral load is a measure of how much HIV virus is in the blood. Higher levels of HIV in the blood increase the risk of a person with HIV becoming ill from other infections and passing the virus on to other people. The aim of antiretroviral therapy is to reduce viral load to less than 50 copies/mL. The main study 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 dual therapy group compared to the triple therapy group (91% vs 93%, adjusted treatment difference of -0.7%, 95% CI -4.3% to +2.9%). The evidence suggests that dolutegravir/lamivudine is as effective as other antiretroviral therapies in maintaining a viral load of less than 50 copies/mL in both treatment naïve and treatment experienced patients with HIV-1. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
2.	CD4 cell count	CD4 cells are white blood cells that fight infections in the body. The HIV-1 virus kills CD4 cells, increasing the risk of the person with HIV developing serious illnesses. The main study did not present changes in CD4+ count from baseline to primary endpoint despite this being a pre-specified secondary outcome nor did the other studies report changes in CD4+ count. It is not possible to determine from the evidence whether dolutegravir/lamivudine had a greater or lesser effect on CD4 cell count compared to other antiretroviral therapies. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
3.	Renal function	Renal function is a measure of how well the kidneys are working. If the kidneys are not working well, this has a negative effect on the filtration of toxins and waste products from the blood, the release of hormones that regulate blood pressure, the production of red blood cells, and the absorption of calcium. The main study reported change in renal biomarkers from baseline to week 48, with favourable outcomes in the dual therapy group but overall statistical significance was not reported. The study looking at two-phase switch reported that when dolutegravir was introduced, there was a limited decrease in eGFR which stabilised after initiation. The evidence suggests that there is an increase in mean change in renal biomarkers when using dolutegravir/lamivudine and this could be because of the absence of tenofovir disoproxil fumurate which is associated with impaired renal function.

		See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
4.	Blood lipids	Blood lipids are fats in the blood, such as fatty acids and cholesterol. Generally, the presence of elevated or abnormal levels of lipids or lipoproteins in the blood (hyperlipidaemia) increases the risk of developing heart disease, gall bladder disease and pancreatitis. The main studies reported on changes in total cholesterol, LDL-cholesterol and total triglycerides at baseline and week 48 with increases in the dual therapy group and decreases in the triple therapy group. Differences between groups was significant. HDL-cholesterol significantly increased in the dual therapy group compared to the triple therapy group. Overall cholesterol to HDL ratio was lower in the triple therapy group compared to the dual therapy group. Absolute values were not presented. In the review study, limited data were presented on lipid changes, with two studies demonstrating that participants switching to dual therapy had statistically significant reductions in total cholesterol, LDL-cholesterol and triglycerides and increases in HDL-cholesterol not reaching statistical significance. The limited evidence is not conclusive for the effects of dolutegravir/lamivudine on the blood lipid profile. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
5.	Bone Mineral Density	Bone mineral density (BMD) is the amount of bone mineral in bone tissue. A decrease in bone mineral density, also known as bone loss, is associated with a higher risk of bone fracture and is an indirect indicator of osteoporosis. One of the studies reported serum bone-specific alkaline phosphatase, serum osteocalcin, serum procollagen 1 N-terminal propeptide and serum type 1 collagen C-telopeptide increases in both dual and triple therapy groups bone biomarkers favouring the dual therapy regimen, but overall statistical significance was not reported. The other two studies did not report changes in bone biomarkers. The evidence suggests that there is an increase in mean change in bone biomarkers when using dolutegravir/lamivudine and this could be because of the absence of tenofovir

		disoproxil fumurate which is associated with impaired bone health. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
6.	Viral resistance	Viral resistance refers to when a virus is no longer affected by a drug that used to be effective against it. It means that a virus will continue to multiply despite the presence of a drug that would usually kill it. The main study reported that 10 participants (6/719) [0.8%] in the dual therapy group and 4/722 [0.6%] in the triple therapy group) developed virological failure but no samples that were tested (9/10) showed any virological resistance. There was no evidence of virological resistance due to dual therapy in the participants in the other two studies. The evidence suggests that dolutegravir/lamivudine in treatment naïve and treatment experienced populations is not associated with development of virological resistance. However, it should be noted that all studies excluded participants with any pre-existing evidence of major viral resistance therefore should be interpreted with caution. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.
7.	Health related quality of life	Health related quality of life is the perceived quality of a person's daily life based on their physical and mental health. The main study reported high scores for quality of life measured using EQ-5D-5L health state utility for both dual therapy and triple therapy groups at baseline and week 48, with non-significant between-group differences from baseline to week 48. The results suggest that dolutegravir/lamivudine has a similar effect on health-related quality of life compare to other antiretroviral therapies. See the final paragraph of row 6 'Pain' in the table above for the limitations with this evidence.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The clinical commissioning policy proposition recommends the use of dolutegravir/lamivudine for the treatment of naïve (i.e. never treated) Human Immunodeficiency Virus (HIV) infected adults and adolescents >12years of age. Either a fixed dose combination or the separate products can be used depending on their relative costs. This is its licensed indication and it is excluded from tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Blood and Infection PoC Assurance Board on the 05/12/2019