Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infection (all ages)

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Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 infection (all ages)

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Contents

Policy statement

NHS England will commission dolutegravir for treatment of HIV-1 infection (all ages) in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

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

Dolutegravir is an HIV drug that was first approved in Europe in January 2014. This is a type of HIV drug called an integrase inhibitor (INI). It is the third drug in this class. In September 2014, a fixed dose combination drug combining dolutegravir, abacavir and lamivudine also received approval.

HIV treatment usually involves taking three or more drugs in a combination. However, sometimes two, three or four of these drugs are combined in a single pill.

Dolutegravir has the potential to improve care because:

a) It reduces levels of HIV virus in the body quickly. This is the main aim of HIV treatment.
b) It causes fewer side effects than some other HIV drugs. This includes a lower risk of common side effects such as diarrhoea, mood changes, depression and anxiety. Overall, this means the treatment is well-tolerated and safe, improving choice for people living with HIV, particular those that experience side effects on other drugs.

The evidence for these benefits came from large randomised studies.

Introduction

HIV treatment has improved greatly over the last two decades and standard of care now involves triple therapy, typically with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) plus one of the following: a ritonavir-boosted protease inhibitor (PI/r), a non nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI) [1].

Effective antiretroviral treatment (ART) requires high adherence to drug regimes. Development of new ARV medicines often focuses on improvements in tolerability, reductions in toxicity and drug to drug interactions.

Effectiveness of ART is measured by an undetectable viral load. The proportion of treated individuals with a viral load less than 50 has improved (94% in 2016) which may be driven, at least in part, by improvements in drug choice. Current standard treatment is therefore effective for many people. The availability of generic ART has reduced the cost of standard treatment considerably. New drug treatments need to demonstrate both clinical and cost effectiveness over standard treatments.

Despite the success of current standard treatment in terms of clinical outcomes, neuropsychiatric side effects have commonly been reported with efavirenz which is currently the most widely prescribed drug. People with a history of psychiatric disorders appear to be at greater risk of serious psychiatric side effects. These may include suicidal ideation and possible increased risk of suicide [3, 4].

Dolutegravir is produced by ViiV Healthcare UK Ltd and is the third HIV integrase strand transferase inhibitor (INI) to be approved. It is the first INI that can be taken as once daily dosing without boosting with a pharmacokinetic enhancer. Dolutegravir received an EU license for treatment in HIV-1 infected adults and adolescents in January 2014. A fixed dose combination tablet combining dolutegravir, abacavir and lamivudine received approval in September 2014. A license indication extension to cover children diagnosed with HIV-1 aged 6-12 years old was granted in March 2017.HIV drugs are not currently reviewed by NICE to determine their clinical and cost effectiveness.

Definitions

The key terms used in this policy and their definitions are:

Antiretroviral therapy (ART): This usually consists of a combination of 3 antiretroviral drugs. A backbone of 2 nucleoside reverse transcriptase inhibitors (NRTI) and a 3rd agent from one of the following classes of drugs: non- nucleoside reverse transcriptase inhibitors (NNRTI), ritonavir boosted protease inhibitors (PI/r) and integrase inhibitors (INI).

Fixed dose combination (FDC): Single tablets which combine a number of agents.

First line therapy: Efavirenz is one of the recommended first line 3rd agents, given in combination with either tenofovir and emtricitabine or lamivudine and abacavir, and for reasons of clinical effectiveness and cost is a preferred first line option.

NRTI / NNRTI backbone and 3rd Agent: These include individual agents often used in fixed dose combinations including: abacavir and lamivudine; tenofovir and emtricitabine; tenofovir with efavirenz and emtricitabine; tenofovir, rilpivirine and emtricitabine; and tenofovir, elvitegravir, cobicistat and emtricitabine.

Second line therapy: The use of alternative 3rd agents where efavirenz cannot be used for reasons of potential or actual intolerance or transmitted HIV drug resistance. Alternative 3rd agents include: the NNRTIs rilpivirine and nevirapine, the INIs raltegravir, elvitegravir/cobicistat and dolutegravir, and the PI/rs darunavir/ritonavir and atazanavir/ritonavir. Drug selection depends on side effects profile, tolerability, resistance profile, drug-drug interactions and cost.

Viral load: plasma HIV RNA levels are used to monitor response to antiretroviral therapy. Patients on effective therapy sustain a plasma HIV RNA level of <50 copies/ml (undetectable). Patients who fail to achieve an undetectable viral load or experience a confirmed viral load rebound above 50 copies/ml are deemed to be experiencing virological failure.

Intolerance: patients 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.

Stable patients: patients who continue to experience an undetectable viral load and who are not experiencing any intolerance to their medication are deemed to be stable.

Aim and objectives

This policy aims to identify the evidence and cost implications of routine commissioning of dolutegravir for specific patient groups.

The objectives are to enable access to dolutegravir where its use is supported by clinical evidence and where it is demonstrated to represent good value.

Dolutegravir is price comparative to second line therapies. This policy aims to identify those patients that would benefit from dolutegravir as a second line therapy choice where first line treatment is not clinically indicated, or where patients are experiencing treatment failure or are experiencing intolerance.

Epidemiology and needs assessment

The HIV epidemic continues to pose a public health risk in England. By the end of 2016, an estimated 89,400 (CI 87,200-94,700) people were living with HIV in the England; approximately one in eight (10,400) of whom were undiagnosed and unaware of their infection [5]. Whilst untreated HIV-1 infection remains a life-threatening disease, effective antiretroviral (ARV) medicines mean that it can be managed as a chronic long term condition. Overall in 2016, 96% of the 91,987 people in the UK living with a diagnosed HIV infection received ART, compared to 94% in 2015 and 74% in 2007. The number of people starting ART has increased from 4,800 in 2012 to 6,700 in 2015 dropping slightly to 5,700 in 2016.

British HIV Association Treatment guidelines currently recommend, as preferred first – line therapy [1]:

- NRTI backbone: tenofovir and emtricitabine
- Third agent: EITHER atazanavir/ritonavir, OR darunavir /ritonavir, OR efavirenz, OR raltegravir OR elvitegravir/cobicistat

These guidelines remain under review in view of new outcome data, the expiry of patents for standard of care drugs and the availability of new agents.

Up to 30% of patients requiring ART will be unable to take first line therapies or will require treatment choices to manage demonstrated toxicity, intolerance, adherence, treatment failure or resistance. These patients require alternative regimens. Dolutegravir offers an additional option to all recognised second line therapies.

Evidence base

Dolutegravir is the third HIV integrase strand transferase inhibitor (INI) to be made available and has advantages over the other two. In randomised studies it has shown superiority over two other commonly used third agents, efavirenz and boosted darunavir [6, 7]. It has also shown activity against integrase resistant strains of HIV [8]. In summary:

- In antiretroviral naïve patients, dolutegravir has been shown to be non-inferior to raltegravir (Spring 2 study) and superior to tenofovir with efavirenz and emtricitabine, when combined with abacavir and lamivudine (Single study).
- In treatment experienced but integrase naïve patients, dolutegravir has been shown to be superior to raltegravir (Sailing study).
- Dolutegravir has been shown to be superior to boosted darunavir irrespective of the nucleoside backbone that it is combined with (Flamingo study) and also to boosted lopinavir (Dawning Study).
- Dolutegravir has been shown to be an effective treatment option in patients with integrase resistant virus (Viking 3 study). The dolutegravir dose in integrase resistance is 50mg twice daily.
- In a number of trials, dolutegravir was combined with abacavir/lamivudine including at high viral loads, which was previously a restriction when using abacavir/lamivudine with other drugs.
- Trials have shown that dolutegravir has reduced side effects and improved tolerability compared with some current alternatives.

Dolutegravir is a once-daily drug that can be taken with or without food. Treatment adherence is considered to be an important factor in achieving good clinical outcomes and preventing drug-resistance within drug classes. Issues such as tolerability, pill burden, dose frequency, side effects, safety concerns and access to adherence support may impact on a patient's ability to adhere to their treatment regimen.

Several studies have shown higher adherence rates with once daily dosing of ART compared with twice daily [9,10].

Dolutegravir has a good tolerability profile. In phase III studies, approximately 2% of patients stopped the drug due to adverse events compared with 10% taking tenofovir with efavirenz and emtricitabine [6] and 4% taking darunavir/ritonavir [7]. Discontinuation rates were similar compared to raltegravir.

Although the most common first line regimens used in the UK contain efavirenz [9], a proportion of patients are unable to tolerate it due to severe psychiatric side effects that include mood changes, anxiety, depression, sleep disturbance, suicidal ideation and possible increased risk of suicide [3,4].

Dolutegravir has a lower propensity for the development of resistant mutations during treatment compared with raltegravir [11,12].

Dolutegravir does not require pharmacokinetic boosting which may result in complex drug-drug interactions and it does not need to be taken with food [13].

In the UK, the virological failure rate on current first-line regimens in 2008–2009 was approximately 10% at one year [14]. Around 3% of patients have evidence of triple-class resistance [15]. BHIVA recommend that patients with triple-class resistance switch to a new ART regimen containing at least two, and preferably, three fully active agents; an integrase inhibitor is normally required as part of this [1]. Relatively little is known about transmitted integrase resistance as it is not routinely screened for in the treatment naïve population [16], and may only be tested in those failing integrase inhibitor-based therapy.

The proportion of patients who may require a switch from efavirenz ranges from 11% to up to 30% at four years [17,18].

The STRIIVING study [19] randomised 533 individuals on stable ART to continue their current regimen or switch to a single tablet regimen of abacavir/lamivudine/dolutegravir and demonstrated non-inferiority for switch. It is therefore appropriate to switch suppressed individuals to dolutegravir-based ART where it is clinically appropriate and the rational clearly documented, particularly if there are less expensive alternatives available.

A fixed dose combination tablet combining dolutegravir, abacavir and lamivudine received approval in September 2014. The approval was based on bioequivalence data for dolutegravir in a combined product compared to its component agents [20].

Rationale behind the policy statement

Up to 30% of patients requiring ART will be unable to take first line therapies or will require treatment choices to manage demonstrated toxicity, intolerance, adherence, treatment failure or resistance. These patients require alternative regimens.

Dolutegravir offers an additional option to all recognised second line therapies. This commissioning policy proposes routine commissioning of dolutegravir for specific patient groups based on evidence that exists to demonstrate superiority and non-inferiority compared with some existing therapies and where this would be cost effective to do so.

NHS England has been offered a commercial in confidence discount for dolutegravir. The cost of the drug is comparable to a second line treatment.

Criteria for commissioning

Dolutegravir (single agent and FDC) will be routinely commissioned for the treatment of HIV-1 infection in the following clinical scenarios:

Patients unable to tolerate first line therapy

Patients who are not suitable for or who do not tolerate efavirenz based first line therapy due to demonstrated toxicity, intolerance or adherence concern. Where regional, cost-based antiretroviral guidelines do not require MDT approval for dolutegravir use then, as long as dolutegravir is clinically appropriate and the rationale for choice is clearly documented in the clinical notes, MDT discussion is not mandatory.

This policy recommends that where dolutegravir is used, it should be combined with the lowest cost, clinically indicated backbone.

Patients failing treatment and those with resistance

Dolutegravir is approved for use in these patients requiring an integrase inhibitor due to recorded treatment failure or resistance. All patients with resistance should be discussed at an MDT:

- In treatment experienced and Integrase inhibitor naïve patients at a dose of 50mg daily.
- In treatment experienced and integrase resistant patients or those requiring concomitant treatment with cytochrome p450 inducing drugs such as antituberculous medication at a dose of 50mg twice daily.

Dolutegravir should be combined with at least one other anti-viral drug to which the virus is fully sensitive.

All patients with resistance, complex co-morbidities or complex drug-drug interactions for whom dolutegravir is considered a treatment option **must be considered in an HIV specialist treatment multidisciplinary** (MDT) meeting and the decision of the MDT recorded.

Children aged 6-12 years

In March 2017, Dolutegravir received a license extension to include treatment of children aged 6-12 years with diagnosed HIV-1.

Prescribing of Dolutegravir in this cohort of patients should be in line with local prescribing guidelines and PENTA prescribing guidance.

Dolutegravir is not licensed for the treatment of children under 6 years of age. Where there is felt to be a clinical indication for use should be discussed and agreed with paediatric clinical network lead MDTs prior to prescribing.

Exclusions

- Patients starting therapy for the first time who are able to tolerate efavirenz based regimens.
- Patients prescribed or switching to dolutegravir who have not been referred to and discussed in the HIV specialist treatment MDT meeting where this is required by regional, cost-based or in the absence of cost-based regional guidance.
- Patients prescribed or switching to dolutegravir where the decision about their treatment is not recorded in the clinical notes.
- Use of dolutegravir by providers who are not commissioned by NHS England to provided HIV care and treatment services.
- An increase in the price of dolutegravir would require a review of this policy.

Patient pathway

Commissioned HIV care and treatment providers who meet the service specification initiate and monitor HIV drug treatment. Prescription and monitoring of dolutegravir is in line with the existing patient pathway.

Governance arrangements

All patients identified who might benefit from dolutegravir can receive it within regional policy as long as rationale for choice is documented, otherwise must be referred to and discussed at a specialist HIV MDT and recommendation recorded.

Mechanism for funding

NHS England is responsible for funding the use of all antiretroviral medicines. Funding for ART is currently on a pass through basis reported to Area Teams. Trusts will be required to separately identify spend on dolutegravir.

Audit requirements

Regional prescribing polices should be agreed by appropriate commissioners and shared with the HIV CRG.

All antiretroviral decisions, including rationale for drug choice, should be documented in the clinical notes.

Regular audit of prescribing against regional guidelines is expected.

Documents which have informed this policy

B06/S/a Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification

B06/S/b Specialised Human Immunodeficiency Virus (HIV) Services (Children) – service specification

B06/PS/a Clinical commissioning policy statement: Stribild for the treatment of HIV-1 infection in adults

Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

Date of review

This policy will be reviewed when further information is received which indicates a review is required.

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Errata summary

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Patients who are not suitable for or who do not tolerate efavirenz based first line therapy due to demonstrated toxicity, intolerance, or adherence concerns, treatment failure or resistance. Where regional, cost-based antiretroviral guidelines do not require MDT approval for dolutegravir use then, as long as dolutegravir is clinically appropriate and the rationale for choice is clearly documented in the clinical notes, MDT discussion is not mandatory.	Patients who are not suitable for or who do not tolerate efavirenz based first line therapy due to demonstrated toxicity, intolerance or adherence concerns, where regional, cost-based antiretroviral guidelines do not require MDT approval for dolutegravir use then, as long as dolutegravir is clinically appropriate and the rationale for choice is clearly documented in the clinical notes, MDT discussion is not mandatory.	Page 11 Section 7 Criteria for Commissioning Paragraph 2	The cost of Dolutegravir is now comparable to other second line treatments and new guidance would say that MDT agreement would not be required for those unable to tolerate / not suitable for first line therapy and that MDT approval would only be needed for those failing treatment or with resistance	Laura Jane Waters	Dec 2018
Dolutegravir should be combined with at least two one other anti-viral drugs to which the virus is fully sensitive. All patients with resistance, complex co-morbidities or complex drug-drug interactions for whom	Dolutegravir should be combined with at least one other anti-viral drugs to which the virus is fully sensitive. All patients with resistance, complex co-morbidities or complex drug-drug interactions for	Page 11 Section 7 Criteria for Commissioning Paragraph 5	Rationale here is to avoid update when dual policies done + often, for treatment-experiences patients, not all backbone drugs will be fully active	Laura Jane Waters	Dec 2018

dolutegravir is considered a treatment option (including those with toxicity, intolerance, adherence, treatment failure and resistance) must be considered in an HIV specialist treatment multidisciplinary (MDT) meeting and the decision of the MDT recorded.	whom dolutegravir is considered a treatment option must be considered in an HIV specialist treatment multidisciplinary (MDT) meeting and the decision of the MDT recorded.				
All patients identified who might benefit from dolutegravir must be referred to and discussed at a specialist HIV MDT and the recommendation recorded. This includes the cohorts identified for routine commissioning as well as any exceptional cases.	All patients identified who might benefit from dolutegravir can receive it within regional policy as long as rationale for choice is documented, otherwise must be referred to and discussed at a specialist HIV MDT and the recommendation recorded.	Page 12 Section 9 Governance arrangements Paragraph 1	The cost of Dolutegravir is now comparable to other second line treatments and new guidance would say that MDT agreement would not be required for those unable to tolerate / not suitable for first line therapy and that MDT approval would only be needed for those failing treatment or with resistance	Laura Jane Waters	Dec 2018