



Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents

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Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents

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Policy Statement

NHS England will commission dolutegravir for treatment of HIV-1 in adults and adolescents 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

Throughout the production of this document, due regard has been given 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 in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Dolutegravir is an HIV drug that was approved in Europe in January 2014. This is a relatively new type of HIV drug called an integrase inhibitor (INI). It is the third drug in this class.

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 other HIV drugs. This includes a much lower risk of common side effects such as mood changes, depression, anxiety, disrupted sleep and suicidal thoughts. Overall, this means the treatment is better tolerated and improves patient safety.

Approximately 10% of HIV positive people cannot use the standard first line treatment (efavirenz) because of these side effects and approximately another 10% change treatment because of them up to two years after starting. These side effects affect quality of life and can reduce adherence, with a risk of drug resistance. A further 10% of patients experience problems with their treatment for whom dolutegravir provides an alternative or even the only option of effective treatment.

The evidence for these benefits came from large randomised studies. Studies looking at switching people on stable therapy are still ongoing.

1. 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), an NNRTI or an integrase inhibitor (INI) [1].

Effective antiretroviral treatment (ART) requires 95% 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. In 2012, the proportion of patients on treatment with an undetectable viral load was very high: 92% had a viral load of less than 200 copies and 86% had less than 50 copies [2]. Current standard treatment is therefore effective for many people. The availability of generic efavirenz has reduced the cost of standard treatment considerably. New drug treatments need to demonstrate both clinical and cost effectiveness over current 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 licence for treatment in HIV-1 infected adults and adolescents in January 2014.

HIV drugs are not currently reviewed by NICE to determine their clinical and cost effectiveness.

2. 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 a recommended first line 3rd agent, given in combination with either tenofovir and emtricitabine or lamivudine and abacavir, and for reasons of clinical effectiveness and cost is the 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 to 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.

3. 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.

4. Epidemiology and needs assessment

The HIV epidemic continues to pose a public health risk in England. By the end of 2012, an estimated 98,400 (CI 93,500-104,300) people were living with HIV in the UK; approximately one in five (21,900, 22% [18%- 27%]) of whom were undiagnosed and unaware of their infection [5]. Whilst HIV-1 remains a life-threatening disease, effective antiretroviral (ARV) medicines mean that it can be managed as a chronic long term condition. In 2012 there were 71,800 HIV positive

patients in England in HIV services (78,000 in the UK), of whom 61,107 (85.1%) were receiving ART [2]. The annual increase in patients receiving ART between 2011 and 2012 was 4,749 (8.5%). Estimated new patients receiving ART in 2013, 2014 and 2015 are 5,153, 5,591 and 6,166 respectively.

British HIV Association Treatment guidelines currently recommend [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.

It is estimated that between 10 – 20 % of patients starting therapy are unable to take efavirenz based regimens and will require initiation on alternative second line therapies in the first 2 years. Up to 10% of patients on treatment also experience treatment failure or resistance requiring use of new or integrase based regimens to achieve viral suppression.

Dolutegravir offers an additional option to all recognised second line therapies.

5. 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).
- 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.
- Dolutegravir has reduced side effects and improved tolerability compared with 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 results 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 anti-viral drug 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].

No trial data is currently available on switching to dolutegravir in patients who are currently stable on treatment.

A dolutegravir named-patient programme has been available since 2011 for patients with integrase resistant mutations, and has been accessed by a small number of patients to date.

6. Rationale behind the policy statement

For up to 20% of patients starting their first treatment, it will not be possible to take or continue efavirenz-containing regimens due to resistance, mental health issues, toxicity or intolerance. These patients will require alternative regimens and dolutegravir is at least clinically equivalent to existing alternatives and is broadly of equivalent cost.

Up to 10% of patients on treatment require a new regimen due to treatment failure. Dolutegravir provides another treatment choice and in some cases may be the only option available.

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.

7. Criteria for commissioning

Dolutegravir will be routinely commissioned in HIV-1 infected adults and adolescents 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 as agreed in the MDT (expected to be no more than 20% in the first two years of treatment). Dolutegravir is a treatment option for this patient group.

Where used, this policy recommends use of dolutegravir with the lowest cost, clinically indicated backbone. This is generally abacavir and lamivudine.

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:

- In treatment experienced and Integrase inhibitor naïve patients at a dose of 50mg daily.
- In treatment experienced and integrase resistant patients at a dose of 50mg twice daily.

Dolutegravir should be combined with at least two other anti-viral drugs to which the virus is sensitive.

All patients for whom dolutegravir is considered a treatment option for failure and resistance **must be considered in an HIV specialist treatment multidisciplinary**

(MDT) meeting and the decision of the MDT recorded.

The manufacturer provides dolutegravir to NHS organisations according to the price agreed in confidence with the Department of Health Commercial Medicines Unit and NHS England.

Exclusions

- Patients switching to dolutegravir who have not been referred to and discussed in the HIV specialist treatment MDT meeting or where the decision about their treatment is not recorded.
- Patients stable on treatment **should not be** switched to dolutegravir. There are no published trial data for switching stable patients on to dolutegravir.
- Use of dolutegravir by providers who are not commissioned by NHS England to provide HIV care and treatment services.
- An increase in the price of dolutegravir would require a review of this policy.

Where clinicians consider switching to dolutegravir for patients not covered in the circumstances above, an Individual Funding Request may be considered where the patient's case is exceptional. The MDT discussion should be included in the IFR.

8. 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.

9. Governance arrangements

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.

10. 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.

11. Audit requirements

All patients considered for treatment with dolutegravir **must** be referred to and

discussed in, an HIV MDT. Recommendations for treatment must be recorded.

Commissioners will review the audits. This policy will be reviewed by the CRG annually.

12. 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.

13. 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).

14. Date of review

This policy will be reviewed in April 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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