Clinical Commissioning Policy
Fostemsavir for multi-drug resistant HIV-1 infection (adult) (URN 2108) [201008P]

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Commissioning position

Summary

Fostemsavir is recommended to be available as a routine commissioning treatment option for individuals with multi-drug resistant HIV-1 infection, when a viral suppressive regimen cannot be constructed with remaining antiretroviral agents within the criteria set out in this document.

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.

This policy is applicable to adults, due to the evidence base and the summary of product characteristics for fostemsavir. Post pubescent access is permitted as outlined in NHS England Policy 170001/P Commissioning Medicines for Children in Specialised Services.

Executive summary

This policy is focused on multi-drug resistant (MDR) human immunodeficiency virus type 1 (HIV-1) infection and the use of fostemsavir, a new drug which is added to remaining antiretroviral drugs (ART) used to treat HIV-1 infection.

The independent evidence review returned evidence for fostemsavir, which is presented for a routine commissioning position.

Plain language summary

Human immunodeficiency virus type 1 (HIV-1) infection

Human immunodeficiency virus (HIV) attacks the immune system destroying CD4 positive (CD4+) T cells, a type of white blood cell that is vital for fighting infection. The reduction of these cells leaves people living with HIV less able to fight off infections (immunosuppressed) and makes them susceptible to other diseases including cancers. If HIV is untreated, a high viral load (high level of virus) can be seen, meaning the HIV is not supressed (under control). This can increase the chance that HIV is transmitted, as well as cause significant morbidity (poor health) and mortality (death) for the person living with HIV.

There are two main types of HIV. Most cases within the UK are HIV-1 type which is considered more transmissible than HIV-2.

Multi-drug resistant HIV-1 infection

Treatment for HIV-1 involves life-long antiretroviral treatment (ART), which stops the virus replicating in the body and destroying CD4+ T cells. There is no cure for HIV, but ART enables most people to live a long and healthy life with an undetectable viral load, which eliminates the risk of transmitting the infection. Combination antiretroviral therapy has transformed HIV-1 infection into a manageable chronic condition for many people living with HIV. However, for some individuals finding effective ART is not always possible. A viable (suitable) regimen may no longer exist because of multidrug resistance (MDR), meaning the virus does not respond or only partially responds to the drugs. Contraindications (factors which stop a drug being used), previous intolerance to ART, treatment history, concordance issues, drug-to-drug interactions or drug resistance patterns with current antiretrovirals are other reasons why an individual might have multi-drug resistant HIV-1 infection.

Current treatment in MDR HIV-1 infection

There are currently no treatment options for MDR HIV-1 infection other than attempting to optimise the remaining ART options. The care of MDR-HIV-1 patients is outlined in the British HIV Association (BHIVA) guidelines (BHIVA. 2016).

Fostemsavir as a treatment in multi-drug resistant HIV-1 infection

Fostemsavir is a new drug, which is targeted against the HIV viral envelope, it works by inhibiting (stopping) the attachment and entry of HIV virus into the host T cells and other immune cells. It is added to the current ART drugs and not used in isolation. If the treatment works, a reduction in the viral load will be seen, aiming for the virus to be supressed. The immune cells will also recover, with an increase in the CD4/CD8 cells, which reduces the chance of immunosuppression, infection, certain types of cancers and dying. When the virus is supressed, it also reduces the ability to transmit (pass on) the virus to others.

What we have decided

NHS England has carefully reviewed the evidence to treat MDR HIV-1 infection with fostemsavir. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

This policy is linked to:

- Best Practice in HIV Prescribing and Multidisciplinary Teams (NHS England. 2019)
- Service Specifications B06/Sa Specialised Human Immunodeficiency Virus (HIV) Services (adults) and B06/Sb (children). (NHS England. 2013).
- Clinical Commissioning Policy 170028P: Immediate antiretroviral therapy for treatment of HIV-1 in adults and adolescents (NHS England. 2018).
- Clinical Commissioning Policy 200301P: Dolutegravir/lamivudine for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults and adolescents over 12 years of age (NHS England. 2020).
- Clinical Commissioning Policy 200210P: Dolutegravir/rilpivirine for treating HIV-1 in adults (NHS England. 2020).
- Clinical Commissioning Policy F03/P/b: Cobicistat as a booster in treatment of HIV in adults and adolescents. (NHS England. 2018)
- Clinical Commissioning Policy 190137P: Doravirine for the treatment of HIV-1 in adults (NHS England. 2019).
- Clinical Commissioning Policy F03/P/a: Elvitegravir/cobicistat/emtricitabine/tenofovir for treatment of HIV-1 in adults (NHS England. 2015).
- Clinical Commissioning Policy B06/P/a: Dolutegravir for treatment of HIV-1 infection (all ages) (NHS England. 2019)

- Clinical Commissioning Policy 16043/P: Tenofovir Alafenamide for treatment of HIV-1 in adults and adolescents (NHS England. 2016).
- Clinical Commissioning Policy 170131P: Bictegravir-emtricitabine-tenofovir alafenamide for the treatment of HIV-1 in adults (NHS England. 2019).

Committee discussion

The Panel debated the evidence at some length and concluded there was some evidence of effectiveness, albeit low, in this target population.

See the committee papers (link) for full details of the evidence.

The condition

The proposed use of fostemsavir is for individuals with MDR HIV-1 infection who have limited or no therapeutic options, and therefore a fully viral suppressive regimen cannot be constructed. These individuals might have some ART options which are fully or partially active, but the virus will not be controlled and they will have a detectable virus within their blood tests. If a regimen of different active drugs cannot be constructed, it may lead to virological failure which in turn leads to immunosuppression, morbidity and mortality as well as the risk of onward transmission.

The health-related quality of life (HRQoL) for these treatment-experienced individuals is often low because of a combination of poor health status as a consequence of viral replication leading to advanced immunosuppression, and accumulating side-effects from multiple antiretrovirals and concomitant medications to prevent the complications of immunosuppression. For this population, there is a continued need for the development of new classes of antiretrovirals with novel mechanisms of action that are well tolerated and do not have cross-resistance to available therapies. This allows individuals with MDR HIV-1 infection, and individuals with limited ART options, new opportunities to achieve viral suppression which can improve their clinical and health related quality of life outcomes.

Current treatments

HIV is treated with ART started immediately after a diagnosis to limit viral replication. 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 inhibitors. The standard of care is treatment with two or three drugs.

People typically start on a two or three-drug regimen and only move to another if there is lack of virological response (the virus is not supressed) or tolerability issues. Additional issues include pill burden and dose frequency which may affect concordance. Considerations related to potential drug-drug interactions are particularly relevant as people with HIV are living longer, which means they may need to take medication for age-related comorbidities.

Effective treatment is one that suppresses viral replication and maintains an undetectable viral load. In addition to preventing progression of HIV infection to immunosuppression and life-threatening illness, effective treatment also prevents HIV transmission.

Proposed treatment

Fostemsavir is a new drug, which is the first to belong to this class of drugs for HIV treatment. The active metabolite of fostemsavir is temsavir, which is a HIV-1 gp120-directed attachment inhibitor. Fostemsavir has a unique mechanism of action, binding directly to the HIV viral envelope gp120, close to the CD4 binding site, locking gp120 into a closed state. This prohibits the conformational change necessary for initial interaction between the virus and

CD4 cell-surface receptors, thereby preventing attachment and subsequent entry into host T cells and other immune cells.

Fostemsavir has no in-vitro cross-resistance with other antiretroviral classes, and is active against CCR5-tropic, CXCR4-tropic, and dual-tropic strains of HIV-1. Further details regarding fostemsavir are available in the Summary of Product Characteristics (SPC) EMEA/H/C/005011 (European Medicine Agency (EMA). 2021). It holds EU and UK approval.

It is proposed that fostemsavir will be added to an optimised background ART regimen and initiated under the advice of a HIV specialist multidisciplinary team, in line with the British HIV Association (BHIVA) guidelines (BHIVA. 2016) for the treatment of individuals with multiple class virological failure (with or without) extensive drug resistance.

Epidemiology and needs assessment

Public Health England (PHE) data from 2019 established that of the 98,552 people diagnosed with HIV in the UK, 96,886 (98%) were on treatment. The estimated number of people on treatment, engaged in care with a reported viral load more than 200 copies per millilitre (>200c/ml, a marker of virological failure) was 2,400. A proportion of these individuals will have MDR HIV-1.

The UK HIV drug resistance database is the national surveillance of HIV-1 drug resistance. Analysis of treatment-experienced patients who have experienced virological failure provide insights into the extent of resistance within and across drug classes and estimates of the number of individuals with multi-class resistance. In 2016, among treatment-experienced patients with a detectable level of HIV virus 32% had resistance to any class of ART and 3% had resistance to protease inhibitors. The latter is likely to be a marker of MDR HIV-1 and extrapolating this data to the PHE data of 2,400 patients with a detectable HIV-RNA provides an estimate of about 70 patients who are likely to be eligible for this intervention.

This estimate needs to be interpreted with caution as there are significant missing viral load reports within the PHE data, and the UK HIV drug resistance database does not have a complete data set from all clinics. Also, as MDR HIV-1 is diagnosed based on cumulative reports of resistance tests over time, protease inhibitor resistance is a marker, and not definite evidence of MDR HIV-1.

Ending the HIV epidemic is a global Sustainable Development Goal (United Nations 2015). In 2019, the Secretary of State for Health and Social Care set the target for England to become one of the first countries to reach HIV elimination by 2030 (Public Health England (PHE). 2019) Achieving viral suppression for all individuals living with HIV is a key factor to achieve HIV elimination and therefore treatment options for individuals with MDR HIV-1 has an individual benefit and a wider public health purpose.

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. The link to the evidence summary is available here.

Implementation

NHS England will routinely commission fostemsavir in combination with an optimised background regimen of antiretroviral(s) therapy in accordance with the patient pathway for patients meeting the following inclusion criteria:

Inclusion criteria

- Individuals are either:
  - Not virally suppressed with existing ART regimen[1] **OR**
  - Are virally supressed but on a highly complex regimen with concerns of tolerance, resistance or safety where the addition of fostemsavir could simplify the regimen and optimise patient outcome and experience

AND must meet all the following five criteria:

- The use of fostemsavir has been discussed and agreed with the patient (through shared decision making, this can be through various mediums including verbal as well as written shared decision-making tools, translated and Easy Read materials) and the HIV specialist multi-disciplinary team (MDT) **AND**
- Individuals are adult patients[2] **AND**
- Fostemsavir is to be added to an optimised background ART regimen **AND**
- Individuals have multi-drug resistant (MDR)-HIV-1 infection[3] **AND**
- Individuals have limited or no therapeutic ART options remaining[4]

Exclusion criteria

- Individuals with contraindications to fostemsavir, as outlined in the summary of product characteristics (EMA. 2021 EMEA/H/C/005011) **OR**
- Individuals with a past trial of fostemsavir with no clinical response[5] **OR**
- Individuals determined not to be suitable for fostemsavir by the HIV specialist MDT

Stopping criteria

Fostemsavir may be stopped in individuals if they fall into one of the three categories listed below:

No treatment response:

Patients with no treatment response (defined as no change or an increase in the HIV-1 RNA level compared to baseline) assessed at 3-6 months from fostemsavir commencement. Clinicians can reassess the patient in a further 3 months if they feel the lack of response was transient or attributable to a reversible cause (e.g. adherence which is now corrected or a resolved drug interaction). If there is no treatment response, fostemsavir should be stopped and alternative agents considered.

Limited treatment response:

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[1] **Virological suppression:** achieving and maintaining a HIV-1 RNA of < 50 copies per mL

[2] This policy is applicable to adults (≥18 years) due to lack of safety data in children. Post pubescent access is permitted as outlined in NHS England Policy 170001/P Commissioning Medicines for Children in Specialised Services

[3] **MDR HIV-1 infection**: treatment-experienced individuals with HIV-1 infection who have limited remaining approved and fully active antiretrovirals (ART) to form a viable ART regimen. This could be as a result of drug resistance (screening or historical resistance or both) **and/or** factors which affect the ability to use remaining ART regimens. This includes ART tolerability; ART availability; ART safety concerns or contraindications to remaining ART agents

[4] **Limited treatment or no therapeutic options:** defined as either: (1) no fully active antiretrovirals remaining **OR** (2) one or two fully or partially active antiretrovirals

[5] If **no clinical response** was determined to be the result of non-adherence and/or other factors which are now addressed (such as resolved drug interaction or an additional optimised background regimen which is now available) a re-trial could be considered

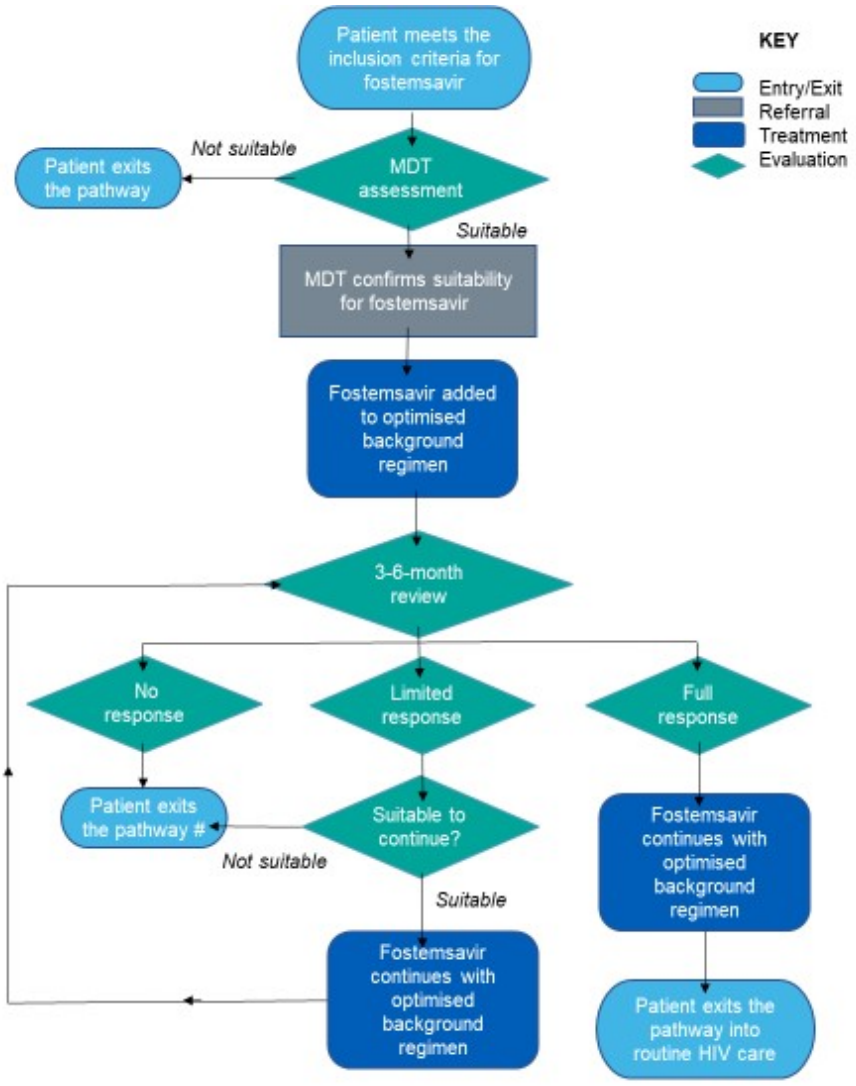
Limited treatment response, defined as patients with a decline in HIV-1 RNA level, but are still not virally supressed after 6 months of treatment. The decision to continue fostemsavir should be reached jointly between the HIV specialist MDT team and the patient, with other alternatives considered and background ART regimen optimised. If fostemsavir is continued, a further assessment should be conducted after 3-6 months and ongoing there-after to ensure this remains the most suitable intervention for the individual.

Fostemsavir is no longer an appropriate intervention:

Individuals who develop significant toxicity or contraindications to fostemsavir or decide to discontinue at any point in the pathway.

Patient pathway

Figure 1-Patient pathway for fostemsavir in MDR-HIV-1 infection



Patients can re-enter the clinical pathway for a retrial for fostemsavir if the clinician determines the limited or no treatment response factors have been addressed. This could include (and is not limited to):

- Resolved adherence issues
- Resolved drug interactions, which warrant retrial with fostemsavir
- New optimised background ART regimen is available which warrants retrial with fostemsavir
- Resolved patient factors which warrant retrial, such as normalised hepatic function

Governance arrangements

The governance arrangements are described in detail within Service Specification B06/Sa Specialised Human Immunodeficiency Virus (HIV) Services (adults) (NHS England. 2013).

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

Audit requirements

Mandatory data collection will be via the existing epidemiological surveillance system operated nationally to monitor population level HIV and AIDS Reporting System (HARS). Additional contractual data collection requirements to secure sufficient supply and to support reimbursement will be agreed nationally and collected locally, such as the prior approval software.

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.

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

Antiretroviral therapy (ART)	ART is a combination of drugs used in HIV treatment. ART drugs are divided into different groups depending on where they act on the HIV virus enzymes (reverse transcriptase, protease or integrase inhibitors).
Fostemsavir	A new drug which is added to ART medication, to try and control the HIV-1 virus.
Human immunodeficiency virus (HIV)	Is a virus which attacks the immune system destroying CD4 positive (CD4+) T cells, a type of white blood cell that is vital for fighting infections. The reduction of these cells leaves people living with HIV less able to fight off infections (immunosuppressed). There is currently no cure for HIV, but most people living with HIV can lead a normal life, as ART medication can control the virus.
Multi-drug resistant HIV-1 infection (MDR-HIV-1)	The HIV-1 virus does not respond or only partially responds to the ART drugs. An individual might also have other medical problems, or reasons why certain types of ART cannot be used.

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