



Clinical Commissioning Policy: Elvitegravir/cobicistat/ emtricitabine/tenofovir for treatment of HIV in adults

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Contents

1	Executive summary	4
	Policy Statement	4
	Equality Statement	4
	Plain Language Summary	5
2	Introduction	5
3	Definitions	7
4	Aim and objectives	8
5	Epidemiology and needs assessment.....	8
6	Evidence base	9
7	Rationale behind the policy statement	14
8	Criteria for commissioning.....	14
9	Patient pathway	15
10	Governance arrangements	15
11	Mechanism for funding.....	16
12	Audit requirements	16
13	Documents which have informed this policy.....	16
14	Links to other policies.....	16
15	Date of review	17
	References	17

1 Executive summary

Policy Statement

NHS England will commission elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (hereafter tenofovir) for the treatment of HIV-1 in adults 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

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

Elvitegravir/cobicistat/emtricitabine/tenofovir is a fixed dose medicine for the treatment of HIV in adults. Its trade name is Stribild®. It was approved in Europe in May 2013.

HIV treatment usually involves taking three or more medicines in combination. However, sometimes two, three or four of these drugs are combined in a single pill. In this combination, three of the medicines are anti-HIV drugs; the fourth (cobicistat) is a medicine used to boost one of the other drugs (elvitegravir). Tenofovir and emtricitabine are from a group of drugs called 'reverse transcriptase inhibitors' (RTIs) and have been used for many years. Elvitegravir is from a group of drugs called integrase inhibitors (INI). It was the first to be available for use 'once-daily' and must be given with cobicistat to work effectively.

Elvitegravir/cobicistat/emtricitabine/tenofovir has the potential to improve care in the following ways:

- It reduces levels of virus in the body as well as current standard HIV drugs. In common with other integrase inhibitors, it does this more quickly than other types of HIV medicines. This is the main aim of HIV treatment.
- It causes fewer side effects than many other HIV drugs. This includes a lower risk of some common side effects of the most widely used drug (efavirenz), such as dizziness and abnormal dreams.

Regimens that involve taking medicines together once a day may help some people take their treatment more consistently and avoid the risk of forgetting to take part of their HIV treatment.

2 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

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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 regimens. Development of new ARV medicines often focuses on improvements in tolerability, reductions in toxicity and fewer drug-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 been commonly 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].

Elvitegravir/cobicistat/emtricitabine/tenofovir is combined in a single tablet or fixed dose combination (FDC) containing three active drugs (tenofovir, emtricitabine, elvitegravir) and a pharmacokinetic enhancer or 'booster' (cobicistat). Elvitegravir was the second INI to be approved and the first that could be taken once daily.

Elvitegravir/cobicistat/emtricitabine/tenofovir is licensed for treating adults over 18 years. There are limited pharmacokinetic data on use in young people aged 12 – 18 years, showing similar drug handling to that seen in adults, but insufficient data on safety and efficacy to be able to recommend a dose in those aged between 6 and 18 years. It should not be used in children aged 0 – 6 years.

Elvitegravir/cobicistat/emtricitabine/tenofovir is included in the British HIV Association (BHIVA) guidelines. The process used by BHIVA to produce its UK national

guidelines has been accredited by the National Institute for Health and Care Excellence (NICE).

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

3 Definitions

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

- **Antiretroviral therapy (ART):** This usually consists of a combination of three antiretroviral drugs. A backbone of two 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.

4 Aim and objectives

This policy aims to identify the evidence and cost implications of routine commissioning of Elvitegravir/cobicistat/emtricitabine/tenofovir for specific patient groups.

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

Elvitegravir/cobicistat/emtricitabine/tenofovir is price comparative with second line therapies. This policy aims to identify those patients that would benefit from this regimen as a second line therapy choice where first line treatment is not clinically indicated, or where it represents a clinically appropriate option to manage intolerance or toxicities.

5 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 ART means that it can be managed as a chronic long term condition. In

2012 there were 71,800 registered HIV positive patients in England, of whom 61,107 (85.1%) were receiving ART [6]. 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.

BHIVA treatment guidelines [1] currently recommend:

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

These guidelines are under constant review in view of the availability of new data. Elvitegravir/cobicistat/emtricitabine/tenofovir offers an additional option to other second line therapies. It also offers an alternative to first line treatment where patients are unsuitable for or are unable to tolerate efavirenz or require an alternative for toxicity, tolerability or adherence reasons.

As HIV treatment is lifelong, and its success is dependent on a high level of adherence, ART selection is individualised to achieve the most clinically appropriate, cost-effective option.

6 Evidence base

Key clinical trials in ARV-naïve patients.

In Gilead-sponsored studies 102 [7,8] and 103 [9,10], STRIBILD (n=348 and 353 respectively) was studied for 144 weeks against components:

- study 102: (tenofovir, emtricitabine, efavirenz) (n=352)
- study 103: atazanavir/r + (tenofovir, emtricitabine) (n=355)

Both trials were phase 3, randomised, double-blind, double dummy active-controlled interventional studies in treatment-naïve, HIV-1 infected adult subjects:

Inclusion criteria: ART-naïve adult subjects, HIV RNA >5,000 copies/mL, no CD4 restrictions, Cockcroft-Gault (creatinine clearance) >70 mL/min

Trial endpoints for both studies were:

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- Primary endpoint: HIV RNA concentration of < 50 copies/mL after 48 weeks (according to the US FDA snapshot algorithm), with a 12% non-inferiority margin
- Secondary and tertiary endpoints: achievement and maintenance of viral suppression, pure virological failure and change in CD4 cell count

Efficacy:

Study 102

- Virological success was maintained in both groups at high rates through week 144: 80.2% (279/348) versus 75.3% (265/352), difference +4.9% (95% CI: -1.3% to 11.1%)

Study 103

- High rates of virologic success (HIV-1 RNA, <50 copies/mL) in both groups were maintained at week 144: Elvitegravir/cobicistat/emtricitabine/tenofovir: 77.6% (274/353) vs atazanavir/r + tenofovir, emtricitabine) 74.6% (265/355) (difference: 3.1%; 95% CI: -3.2% to 9.4%)
- The proportion of subjects with virologic failure was similar in both groups at week 96 (6.8% vs 7.3%) and week 144 (7.9% vs. 7.3%)

Safety:

Elvitegravir/cobicistat/emtricitabine/tenofovir was generally well tolerated, as demonstrated by the low discontinuation rate: <6% across both 102 & 103 studies. Elvitegravir/cobicistat/emtricitabine/tenofovir has reduced side effects and improved tolerability compared with current alternatives, mainly due to fewer neuropsychiatric complications than efavirenz.

Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance without affecting renal glomerular function. Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3mg/dL) from baseline should be closely monitored for renal safety.

Although the most common first line regimens used in the UK contain efavirenz, a significant 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].

Resistance:

In the UK, the virological failure rate on current first-line regimens in 2008–2009 was approximately 10% at one year [11]. Around 3% of patients have evidence of triple-class resistance [12]. BHIVA recommend 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 circulating integrase resistance as currently it is not routinely screened for in the treatment naïve population, and may only be tested in those failing INI-based therapy.

Primary (transmitted) drug resistance affecting response to integrase inhibitors is likely to be extremely uncommon in the UK; however around 10% of patients in the UK have evidence of one or more drug resistance mutations at the time of diagnosis. The SWITCHMRK-1 and -2 studies [13], in which patients with an undetectable viral load on a boosted protease inhibitor regimen were randomised to switch to raltegravir or stay on their current regimen, showed a high rate of virological failure in patients with previous virological failure or drug resistance if switched to raltegravir. These data from patients treated with a different integrase inhibitor, together with the lack of clinical trial data on elvitegravir/cobicistat/emtricitabine/tenofovir use in the context of drug resistance, suggest that it should normally be avoided in patients who have proven or suspected drug resistant virus.

Stable switch:

Several studies have demonstrated the non-inferiority of elvitegravir/cobicistat/emtricitabine/tenofovir when switching patients who are virologically suppressed on another regimen (NNRTI, PI or INI), including the following Gilead-sponsored clinical trials:

NNRTI switch - Study 0121 [14]

- Elvitegravir/cobicistat/emtricitabine/tenofovir was non-inferior in maintaining viral suppression at week 48 following a switch from NNRTI + (tenofovir, emtricitabine) in virologically suppressed patients; 93% vs. 88% (95% CI for difference, – 0.5% to 12.0%).
- There was no treatment-emergent resistance.

PI/r switch - Study 0115 [15]

- Elvitegravir/cobicistat/emtricitabine/tenofovir was non-inferior in maintaining viral suppression at week 48 following a switch from PI+RTV+ (tenofovir, emtricitabine) in virologically suppressed patients; 94% vs. 87% group (95% CI for difference, – 0.4% to 13.7%).
- There was no treatment-emergent resistance.

INSTI switch - Study 0123 [16]

- Patients who switch to elvitegravir/cobicistat/emtricitabine/tenofovir from a raltegravir-containing regimen maintain viral suppression, with 100% of patients with HIV RNA<50mL at week 12 through week 48.

Adherence:

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.

Comparison of ART characteristics that may be relevant when individualising therapy:

	Once daily if no resistance	No. tabs*	Drug-drug interactions (+ = Low)	Indicated if VL> 100,000 copies/ml	Indicated if renal impairment [†]	Dietary requirement
Atripla [§]	Y	1	+++	Y	N	N [^]
Eviplera [§]	Y	1	++	N	N	Y
Elvitegravir/ cobicistat/ emtricitabine/	Y	1	++++	Y	N	Y

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	Once daily if no resistance	No. tabs*	Drug-drug interactions (+ = Low)	Indicated if VL > 100,000 copies/ml	Indicated if renal impairment [†]	Dietary requirement
tenofovir						
Dolutegravir	Y	2	+	Y	Y	N
Raltegravir	N	3	+	Y	Y	N
Atazanavir/r	Y	3	+++++	Y	Y	Y
Darunavir/r	Y	3	++++	Y	Y	Y

*including (tenofovir, emtricitabine) or Kivexa backbone if not single tablet regimen (STR)

[†]dose adjustment or change of backbone not possible with FDC

[^]effective without regard to food, but side effects may be reduced if taken on an empty stomach

[§]efavirenz and rilpivirine can also be given as third agents with a separate NRTI backbone

	Neuropsychiatric side effects*	Gastrointestinal side effects*	Hyperlipidaemia*
Atripla	+++	++	++
Eviplera	++	++	+
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir	++	++	++
Dolutegravir	++	++	+
Raltegravir	++	+	+
Atazanavir/r	+	+++	+++
Darunavir/r	++	+++	+++
Atripla	+++	++	++

*including (tenofovir, emtricitabine) or Kivexa backbone if not STR

The level of adherence to once daily elvitegravir/cobicistat/emtricitabine/tenofovir compared with twice daily raltegravir has not been assessed in studies.

Several studies have shown higher adherence rates with once daily dosing of ART compared with twice daily [17,18].

7 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 or adherence problems. These patients require alternative regimens.

Elvitegravir/cobicistat/emtricitabine/tenofovir is one alternative and has been shown to be non inferior to existing alternatives and is broadly of equivalent cost.

This commissioning policy proposes routine commissioning of Elvitegravir/cobicistat/emtricitabine/tenofovir for specific patient groups based on evidence that exists to demonstrate 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 elvitegravir/cobicistat/emtricitabine/tenofovir. The cost of the drug is comparable with other second line treatment.

8 Criteria for commissioning

Elvitegravir/cobicistat/emtricitabine/tenofovir will be routinely commissioned in HIV-1 infected adults in the following clinical scenarios:

- Patients who are unable to take efavirenz due to toxicity, intolerance or adherence issues as agreed in the HIV specialist multidisciplinary team (MDT), or
- Patients who are unable to take other first or second line treatments due to toxicity, intolerance or adherence issues as agreed in the HIV specialist multidisciplinary team (MDT).

Modelling suggests not more than 30% of a total patient cohort should require alternatives to first line therapy. Elvitegravir/cobicistat/emtricitabine/tenofovir is one of a number of treatment options for this patient group.

Exclusions

- Patients starting therapy for the first time who are able to tolerate efavirenz based regimens.

- Patients with renal dysfunction that would require dose adjustment of tenofovir and emtricitabine.
- Patients switching to elvitegravir/cobicistat/emtricitabine/tenofovir who have not been referred to and discussed in the HIV specialist MDT meeting or where the decision about their treatment is not recorded.
- Patients stable on treatment switching to this regimen. Whilst there are published trial data showing non-inferiority for switching stable patients, this policy does not actively support patient switching unless it is in line with the commissioning criteria which is for patients who are not stable as a result of demonstrated intolerance and toxicity issues.
- Patients with proven or suspected resistance to any of the component drugs in elvitegravir/cobicistat/emtricitabine/tenofovir.
- Use of elvitegravir/cobicistat/emtricitabine/tenofovir by providers who are not commissioned by NHS England to provide HIV care and treatment services.
- Any increase in the price of elvitegravir/cobicistat/emtricitabine/tenofovir would require a review of this policy.

Cost

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

9 Patient pathway

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

10 Governance arrangements

All patients identified who might benefit from treatment with the combination of elvitegravir/cobicistat/emtricitabine/tenofovir 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.

11 Mechanism for funding

NHS England is responsible for funding the use of all antiretroviral medicines. Trusts are required to separately identify spending on different ART regimens. Funding to the provider will be in accordance with their agreed tariff arrangements.

12 Audit requirements

All patients considered for treatment **must** be referred to and discussed in, an HIV specialist MDT. Recommendations for treatment with elvitegravir/cobicistat/emtricitabine/tenofovir must be recorded. Commissioners will review the audits. This policy will be reviewed by the CRG annually.

13 Documents which have informed this policy

- Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification
- Clinical commissioning policy statement: Stribild[®] for the treatment of HIV-1 infection in adults.
- Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents

14 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).

15 Date of review

This policy will be reviewed in 2016/2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

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