NHS England

DRAFT

Clinical Commissioning Policy: Stribild® for the treatment of HIV-1 infection in adults

Reference: NHS England B06/P/x

Clinical Commissioning Policy:

Stribild® for the treatment of HIV-1 infection in adults

First published:

Prepared by NHS England Clinical Reference Group for HIV

Published by NHS England, in electronic format only.

Contents

Policy Statement

NHS England will commission Stribild® 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

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 the Equality Act 2010) and those who do not share it.

Plain Language Summary

Stribild® is the trade name for a tablet containing four medicines (tenofovir, emtricitabine, elvitegravir and cobicistat) for the treatment of HIV. 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 (like Stribild®).

Three of the medicines in Stribild® 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.

Stribild® has the potential to improve care in the following ways:

1. 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.
2. 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.

Stribild® is a 'single tablet regimen' (one tablet, taken once daily). 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.

Stribild® will therefore be recommended as an alternative 1st line therapy where patients are unable to use standard first line options and as subsequent therapy where it is considered to be the best clinical option for the patient.

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 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].

Stribild® is a single tablet or fixed dose combination (FDC) containing three drugs (tenofovir, emtricitibine, 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.

Stribild® 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.

Stribild® 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.

2. 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; tenofvir 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 Stribild® for specific patient groups.

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

Stribild® is price comparative with second line therapies. This policy aims to identify those patients that would benefit from Stribild® as a second line therapy choice where first line treatment is not clinically indicated, or where Stribild® represents a clinically appropriate option to manage intolerance or toxicities.

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 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, the expiry of patents for standard of care drugs and the availability of new agents.

Stribild® 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. Stribild® may also offer an additional option to other second line therapies.

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.

5. 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: Atripla® (tenofovir, emtricitabine, efavirenz) (n=352)
- study 103: atazanavir/r + Truvada® (tenofovir, emtricitabine) (n=355)

Both trials were phase 3, randomised, double-blind, double dummy active-controlled interventional studies in treatment-naive, HIV-1 infected adult subjects:
Inclusion criteria: ART-naive adult subjects, HIV RNA >5,000 copies/mL, no CD4 restrictions, Cockcroft-Gault (creatinine clearance) >70 mL/min

Trial endpoints for both studies were:

- 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: Stribild®: 77.6% (274/ 353) vs atazanavir/r + Truvada®: 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:

Stribild® was generally well tolerated, as demonstrated by the low discontinuation rate: <6% across both 102 & 103 studies. Stribild® 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 Stribild® use in the context of drug resistance, suggest that Stribild should normally be avoided in patients who have proven or suspected drug resistant virus.

Stable switch:

Several studies have demonstrated the non-inferiority of Stribild® 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]

- Stribild® was non-inferior in maintaining viral suppression at week 48 following a switch from NNRTI + Truvada® 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]

- Stribild® was non-inferior in maintaining viral suppression at week 48 following a switch from PI+RTV+ Truvada® 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 Stribild® 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
Stribild	Y	1	++++	Y	N	Y
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 Truvada 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	++	++	+
Stribild	++	++	++
Dolutegravir	++	++	+
Raltegravir	++	+	+
Atazanavir/r	+	+++	+++
Darunavir/r	++	+++	+++

*including Truvada or Kivexa backbone if not STR

The level of adherence to once daily Stribild® 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].

6. 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. Stribild® 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 Stribild® 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 Stribild® . The cost of the drug is comparable with a second line treatment.

7. Criteria for commissioning

Stribild® will be routinely commissioned in HIV-1 infected adults in the following clinical scenarios:

Patients unable to tolerate first line therapy and requiring

Patients who are unable to take efavirenz or other first or second line treatments due to toxicity, intolerance or adherence issues as agreed in the HIV specialist multidisciplinary team (MDT) meeting (expected to be no more than 30% of a total patient cohort). Stribild® is one treatment option 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 Stribild® 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 Stribild® .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 Stribild® .
- Use of Stribild® by providers who are not commissioned by NHS England to provided HIV care and treatment services.

- Any increase in the price of Stribild® would require a review of this policy.

Where clinicians consider prescribing Stribild® 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 Stribild® is in line with the existing patient pathway.

9. Governance arrangements

All patients identified who might benefit from Stribild® 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 are required to separately identify spending on different ART regimens.

11. Audit requirements

All patients considered for treatment with Stribild® **must** be referred to and discussed in, an HIV specialist 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/PS/a Clinical commissioning policy statement: Stribild® for the treatment of HIV-1 infection in adults.

B06/P/b Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents (consultation draft)

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 September 2016 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. Williams I, Churchill D, Anderson J et al. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (updated November 2013), HIV Medicine (2014), 15 (Suppl. 1), 1–85
2. Public Health England Personal Communication (SOPHID 2012)
3. Mollan KR; Smurzynski M; Eron JJ; Daar ES, Campbell TB, Sax PE, Gulick RM, Na L, O'Keefe L, Robertson KR and Tierney C. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161(1):1-10
4. Summary of product characteristics Efavirenz (25 June 2013). Date accessed 28/1/14 via www.medicines.org.uk
5. Aghaizu A, Brown AE, Nardone A, Gill ON, Delpech VC & contributors. HIV in the United Kingdom 2013 Report: data to end 2012. November 2013. Public Health England, London accessed Dec 13).
6. Public Health England (SOPHID 2012)
7. Sax PE et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomized, double Sax PE et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomized, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet. 2012b;379:2439-48-blind, phase 3 trial, analysis of results after 48 weeks. Lancet. 2012b;379:2439-48.
8. Zolopa A, et al. A Randomized Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results. Journal of Acquired Immune Deficiency Syndromes (JAIDS) 2013; 63: 1: 96–100.
9. DeJesus E, et al., Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, noninferiority trial. Lancet 2012a:379:2429-38.
10. Rockstroh JK, et al. A Randomized, Double-Blind Comparison of Coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF vs Ritonavir-Boosted Atazanavir Plus Coformulated Emtricitabine and Tenofovir DF for Initial Treatment of HIV-1 Infection: Analysis of Week 96 Results; Journal of Acquired Immune Deficiency Syndromes (JAIDS) 2013; 62: 5: 483–486.
11. Pillay D, Dunn D. UK HIV Drug resistance database. Annual Report 2008/09. Available at http://www.ctu.mrc.ac.uk/pdf/HIV_Res_Report09.pdf

12. UK HIV Drug Resistance Database. Prevalence of HIV drug resistance in ART-naïve patients by calendar year. 2007. Available at www.hivrdb.org.uk
13. Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010 Jan 30;375(9712):396-407.
14. Pozniak A, Markowitz M, Mills A, Stellbrink HJ, Antela A, Domingo P, Girard PM, Henry K , Nguyen T, Piontkowsky D, Garner W, White K, Guyer B. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial Lancet Infect Dis. 2014 Jul;14(7):590-9. doi: 10.1016/S1473-3099(14)70796-0. Epub 2014 Jun 5
15. Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, Nguyen T, Ebrahimi R, White K, Piontkowsky D . Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and teno fovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. The Lancet Infectious Diseases, 14(7): 581 – 589.
16. Mills A, Crofoot G, Ortiz R, Rashbaum B, Towner W, Ward D, Brinson C, Kulkarni R, Garner W, Ebrahimi R, Cao H, Cheng A, and Szwarcberg J. Switching From Twice-Daily Raltegravir Plus Tenofovir Disoproxil Fumarate/Emtricitabine to Once-Daily Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in Virologically Suppressed, HIV-1–Infected Subjects: 48 Weeks Data. HIV Clin Trials 2014;15(2):51–56
17. Buscher A, Hartman C, Kallen MA et al. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, HAART naive HIV patients (Int J STD AIDS 2012; 23(5):351-355.
18. Nachega JB,Parienti JJ et al. Effect of once daily dosing and lower pill burden antiretroviral regimens for HIV infection: A Meta-analysis of Randomised Controlled Trials. Abstract PS4/5 14th European AIDS conference October 16th-19th Brussels, Belgium.