Clinical Commissioning Policy Proposition: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents

Reference: NHS England F03X08

First published: Month Year

Prepared by NHS England Specialised Services Clinical Reference Group for HIV CRG

Published by NHS England, in electronic format only.

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Equality Statement

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Plain Language Summary

HIV treatment (antiretroviral therapy or ART) has transformed the outlook for people living with HIV. ART enables most HIV positive people to be able to live a normal life with a normal life expectancy.

As people age, some medical concerns become very important. These include heart, kidney and bone disease. Some HIV drugs have side effects that overlap complications of ageing.

Until a cure is found, ART is lifelong. This means that most people will take ART for decades. It is therefore essential to minimise long-term side effects while making sure ART is still effective.

An evidence review looked at the safety and efficacy of Tenofovir alefenamide (TAF) compared to tenofovir disoproxil fumarate (TDF). These are used in combination with others HIV drugs to make up combination therapies. The evidence review also looked at drug pricing.

After reviewing evidence from research, the policy concludes two main things.

1. That TAF, when used as part of ART, is as effective as TDF-based treatment.
2. TAF appears to have a lower risk of kidney and bone side effects in the short term although long term data is not available.

Introduction

HIV treatment (antiretroviral therapy, ART) 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/cobicistat-boosted protease inhibitor (PI/r), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor (INI) [2].

ART requires good adherence (perhaps >95%) to avoid drug resistance and once commenced should be continued lifelong. 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 its ability to reduce viral load to undetectable levels on routine tests (usually to less than 50 copies/mL). In England in 2014, 95% of patients on treatment had a viral load of less than 200 copies/mL. [1]. Current standard treatment is therefore effective for very many people. New drug treatments therefore need to demonstrate clinical and cost effectiveness and improved safety profiles compared to current standard treatments.

Tenofovir alafenamide (TAF) received an EU license for treatment in HIV-1 infected adults and adolescents in November 2015 as a component of the fixed dose combination (FDC) Genvoya ® (cobicistat, elvitegravir, emtricitabine and tenofovir alafenamide).

Currently TDF is available as a single drug product, as part of a dual formulation with emtricitabine (Truvada ®), and in three FDCs: Atripla ® (efavirenz, emtricitabine, TDF) Eviplera ® (rilpivirine, emtrictabine, TDF) and Stribild ® (cobicistat, elvitegravir, emtricitabine, TDF).

TAF is manufactured by Gilead Sciences who also manufacture all these coformulated products.

TAF was approved in the EU based on studies showing similar efficacy but an improved safety profile compared with TDF.

The manufacturer has offered TAF at a commercially confidential price. Assuming that TAF is provided at the same price or lower than that offered to NHS England and agreed with the Commercial Medicines Unit, the availability of TAF as a treatment option would potentially benefit patients who would otherwise be treated with TDF and for patients for whom TDF was previously contraindicated because of underlying renal or bone disease. It will also be of wider short-term benefit to the NHS in terms of commissioning for value programmes.

It is anticipated that when additional TAF containing fixed dose combination products receive regulatory approval and become available the evidence review and commissioning criteria for TAF will be updated.

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

effectiveness.

2 Proposed Intervention and Clinical Indication

The use of tenofovir alafenamide as part of combination antiretroviral therapy for the treatment of HIV 1 in adults and adolescents infected with HIV-1 immunodeficiency virus-1 (HIV-1). Adolescents are defined as children 12 years of age, or older and with a body weight in excess of 35kg

3 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 or cobicistat boosted protease inhibitors (PI/r) and integrase inhibitors (INI).

Fixed dose combination (FDC): Single tablets that combine a complete ART combination into one pill.

NRTI backbone: The two NRTIs that are the basis of a combination. Two backbones are currently recommended for first line therapy: abacavir plus lamivudine (alternative in current guidelines [2]; available as separate tablets or in a combination pill and TDF plus emtricitabine (preferred in current guidelines [2]; available as separate tablets or in a combination pill); Both of these backbones are available in some 'all in one' tablets combined with other drugs.

Viral load: HIV RNA levels in plasma are used to monitor response to ART. Patients on effective therapy sustain viral load <50 copies/ml (undetectable). Patients in whom who fail to achieve an undetectable viral load is not sustained or who experience a confirmed viral load rebound to above 50 copies/ml are deemed to be experiencing virological failure.

First-line therapy: The first combination that someone is prescribed. 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. (see section 5)

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 NNRTI rilpivirine, the INIs raltegravir, elvitegravir/cobicistat and dolutegravir, and the PI/rs darunavir/ritonavir or cobicistat and atazanavir/ritonavir or cobicistat. Drug selection depends on side effects profile, tolerability, resistance profile, drug-drug interactions and cost.

Intolerance: when patients either (i) experience side effects, or (ii) have been assessed to be at high risk of side effects.

Stable patients: patients who have a sustained undetectable viral load on ART and who are not experiencing side effects.

4 Aims and Objectives

This policy aims to identify the evidence and cost implications of routine commissioning of TAF containing products for treatment of HIV 1 in adults and adolescents.

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

This policy aims to identify those patients who would benefit from TAF. This includes people in whom TDF would be indicated as a component of ART, those who are currently taking a TDF-containing regimen who would benefit from switching and those for whom TDF would be contra-indicated.

5 Epidemiology and Needs Assessment

The HIV epidemic continues to pose a public health risk in England. By the end of 2014, an estimated 103, 700 (CI 97,500-112,700) people were living with HIV in the UK; of whom 17% (18,100) were undiagnosed and unaware of their infection [1]. Whilst HIV-1 remains a life-threatening disease, effective antiretroviral therapy (ART) means it can be managed as a chronic long term condition and treatment outcomes in the England are good and compare very favorably to other European countries. In 2014 there were 78,317 HIV positive patients attended HIV services in England (85,489 in the UK), of whom 70,641 (91%) were receiving ART [1]. Of those receiving ART 95% had sustained viral suppression. There continues to be just over 6000 patients newly diagnosed with HIV in the UK per year and thus the number of patients attending HIV services and requiring ART continues to rise, (approximate 5% increase from 2013 to 2014). In the UK in 2010, 57,867 patients were on ART, rising to 76,462 patients in 2014. Ensuring patients continue to receive good and effective care but at the same time ensuring best use of resources is of high importance.

British HIV Association Treatment guidelines for adults currently recommend the following first-line [2]:

- **NRTI backbone:** tenofovir disoproxil fumarate and emtricitabine is the preferred option.
- **Third drug:** preferred options are atazanavir/ritonavir, or darunavir /ritonavir, or raltegravir or elvitegravir/cobicistat or rilpivirine, or dolutegravir. An alternative option is efavirenz. At the time of writing efavirenz is the least expensive 3rd agent so despite its alternative standing in the BHIVA guidelines it is a preferred option in regional prescribing pathways.

These guidelines remain under regular review for any new outcome data, the expiry of patents for standard of care drugs and the availability of new drugs. Where new drugs become available they need to have similar or better efficacy and safety profiles than current ARVs and should either be cost comparative or contribute

significantly to commissioning for value programmes.

Tenofovir is a safe and widely used ARV. Evidence shows the new compound offers some additional benefits in the short term in terms of reduced toxicity for particularly patient groups; in addition the proposed pricing structure may contribute substantially to commissioning for value programmes in the short-term. The likely significant price reductions as generic versions of TDF come to market must also be considered.

6 Evidence Base

Tenofovir alafenamide (TAF) and tenofovir disproxil fumarate (TDF) are both pro-drugs of tenofovir. TDF is already one of the most widely used HIV drugs, especially in combination with emtricitabine. Both TAF and TDF need to be converted inside cells to the active version of tenofovir (tenofovir diphosphate). The difference between the two pro-drugs is that TDF is converted to tenofovir in the plasma which then enters cells to undergo the activation step; TAF, however, mainly enters cells in the TAF form and is then broken down to tenofovir followed by conversion to the active form. TAF results in similar active levels in cells but with much lower plasma concentrations of tenofovir, thought to be the main predictor of tenofovir-associated toxicity. Renal impairment and reduced bone mineral density are the most important reported tenofovir toxicities and TAF, by virtue of the lower plasma tenofovir levels, is associated with lower rates of abnormal markers (serum creatinine, estimated GFR, markers of proteinuria) for both side effects compared with TDF. TAF-based regimens are at least as effective as TDF-based treatments for first-line treatment and for treatment switch. TAF is associated with a less favourable lipids profile than TDF with greater rises in total-, LDL- and HDL-cholesterol; numerical differences are, however, small and when compared as Cobicistat, elvitegravir, emtricitabine, TDF vs elvitegravir/cobicistat/emtricitabine/TAF the average total:HDL-cholesterol ratio is the same for both. A summary of the trials investigating TAF-based HIV treatment follows:

Studies of TAF vs TDF in FDCs with elvitegravir/cobicistat/emtricitabine

- The safety and efficacy of TAF compared to TDF has been assessed in one phase 2 RCT [3], in two phase 3 RCTs in ART naïve patients and in one phase 3 RCT in stable patients switching to TAF.
- GS-104 and GS-111 compared elvitegravir/cobicistat/emtricitabine/TDF FDC with elvitegravir/cobicistat/emtricitabine/TAF [E/C/F/TAF] FDC for first-line HIV treatment. In terms of efficacy, the TAF-based regimen was non-inferior to TDF-based treatment at 48 weeks. [4] There were low rates of resistance in both arms. The TAF-based group had significantly reduced impact on a range of biomarkers for renal and bone toxicity. Both FDCs are effective across a range of baseline viral loads.
- In GS-109 patients who were suppressed on TDF-based combinations either continued treatment or switched to E/C/F/TAF FDC. Individuals switching treatment were as likely to maintain viral suppression (97% vs 93%) and

experienced significant improvements in biomarkers for renal health. Bone mineral density at the spine and hip increased in the TAF group [5].

In summary, TAF is tolerated well and is an effective nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 infection when used in combination antiretroviral therapy. TAF is associated with improved renal and bone markers compared to TDF.

7 Proposed Criteria for Commissioning

The criteria below sets out when TAF as part of the combination of elvitegravir/cobicistat/emtricitabine/TAF [E/C/F/TAF] will be routinely commissioned.

As TAF (compared to TDF) offers clinical benefit for specific patients groups with defined renal, bone or drug contra-indications, these criteria will be relevant to future consideration of use of TAF(compared to TDF) when it is included in combinations with other widely used drugs:

1. **Patients unable to tolerate first-line* therapy**

- Patients who are unable to take efavirenz (as current first line in regional guidelines) due to toxicity, resistance, intolerance or adherence issues as agreed in the HIV specialist multidisciplinary team (MDT); or
- Patients who are unable to take first- or other second-line treatments due to toxicity, intolerance or adherence issues as agreed in the HIV specialist multidisciplinary team (MDT). This includes patients who have either not tolerated other first or second line regimens or who for reasons of potential tolerability, toxicity and adherence issues should not be prescribed first or other second line regimens.

2. **Stable patients switching from alternative ART regimens**

- Patients stable on elvitegravir/cobicistat/emtricitabine/TDF can switch to elvitegravir/cobicistat/ emtricitabine/TAF; or
- Patients stable on other combinations can switch to Elvitegravir/cobicistat/emtricitabine/TAF where this is cost-neutral or cost-saving; and
- Where there has been clinical assessment that switch to TAF will deliver additional clinical benefit and that it is clinically appropriate and safe to do so; and
- The rationale for switch must be explained to the patient and be clearly documented in the notes, available for audit. This should include a discussion about the potential need to switch back should the TAF-based product become more costly than the TDF equivalent (and there are no contra-indications to TDF) must be documented

3. **Patients with definite or relative contra-indications to alternative NRTI backbones**

- Patient with osteoporosis (FRAX >10% or confirmed osteoporosis on DEXA) who have a definite contra-indication to TDF; or
- Patients approaching these thresholds of osteoporosis who may be considered as having a relative contra-indication to TDF); or

- Patients with renal disease based on NICE definitions (chronic kidney disease stage G3, or chronic kidney disease stage G1/2 plus stage A3 proteinuria or nearing this threshold) or renal toxicity or other intolerance secondary to TDF (TAF does not have a licensed indication for CKD stage 4 or 5) who have a definite contra-indication to TDF; or
- Patients who are HLA-B5701 positive, who have cardiovascular disease or high estimated risk of cardiovascular disease in accordance with BHIVA guidelines who have a definite contraindication to abacavir

Exclusions

1. Patients starting therapy for the first time who are able to tolerate efavirenz based regimens (or other less expensive first line regimens as per local/regional prescribing policies) as an alternative to elvitegravir/cobicistat/emtricitabine/TAF
2. Patients with proven or suspected resistance to any of the component drugs in elvitegravir/cobicistat/emtricitabine/TAF
3. Patients 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 already on elvitegravir/cobicistat/emtricitabine/TDF will not need additional discussion to switch to elvitegravir/cobicistat/emtricitabine/TAF
4. Use and reimbursement of elvitegravir/cobicistat/emtricitabine/TAF or by providers who are not commissioned by NHS England to provided HIV care and treatment services.
5. Any increase in the price of elvitegravir/cobicistat/emtricitabine/TAF would require a review of this policy, as would any reduction in price of alternative combinations.
6. Patients for whom the drug is contra indicated or data for use in that patient sub group does not exist to support the prescribing eg: HIV/HBV co-infection at the time of writing; these exclusions will likely change as more date becomes available

Approach to future TAF-containing drugs

TAF is prescribed as part of combination therapy and market authorisations are due to be completed for two other formulations containing TAF and other widely used ARVs during the first half of 2016.

This policy has been produced following completion of an evidence review for TAF as a new agent and its use in E/C/F/TAF. No further evidence reviews or new policies will be produced in relation to new combinations unless

a) the combination contains TAF and another new drug agent or formulation

b) new data emerges to demonstrate superiority over existing treatments, or

c) the combination requires investment which needs to be considered as part of annual prioritisation

New policies will follow the process for policy development.

In all other cases, where TAF is combined with routinely used ARVs, NHS England will review the evidence to demonstrate that new combination products are bio-equivalent to existing regimens and will then assess the cost impact of routine commissioning for specific, defined patient groups who will achieve additional benefit over existing treatments for the same or lower cost than current treatments. Following approval through the appropriate governance route, guidance will then be issued on the approved commissioning arrangements and this policy document updated as required.

8 Proposed Patient Pathway

Commissioned HIV care and treatment providers who meet the service specification initiate and monitor HIV drug treatment. Prescription and monitoring of TAF containing fixed dose combination products is in line with the existing patient pathway.

9 Proposed Governance Arrangements

All patients identified who might benefit from starting TAF as a part of the fixed dose combination products cobicistat/elvitegravir/emtricitabine/TAF will in most cases be referred to and discussed at specialist HIV MDTs and the recommendation recorded in accordance with regional/locally agreed ART prescribing guidance

All patients identified who are currently on TDF as part of cobicistat/elvitegravir/emtricitabine/TDF or and who might benefit from switching to TAF as part of cobicistat/elvitegravir/emtricitabine/TAF fixed dose products respectively should be managed by regional/locally agreed best practice guidance for switching ARVs. Those switching from other products should be discussed at MDT.

Individuals deemed suitable to start emtricitabine/TAF based therapy because of intolerance or relative contraindication to other NRTI backbones will not require discussion at MDT unless there is a requirement to do so for other components of the regimen in accordance to existing NHSE commissioning policies. However the indication to start should be clearly documented to enable audit of emtricitabine/TAF use.

Patients deemed suitable for switch following medical review, this, must be undertaken with a planned approach to ensure no drug wastage occurs.
(For guidance on role and responsibilities of MDT meetings see HIV CRG guidance February 2016).

This includes the cohorts identified for routine commissioning as well as any exceptional cases.

10 Proposed 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 Commissioning

Hubs.

11 Proposed Audit Requirements

1. Patients on cobicistat/elvitegravir/emtricitabine/TAF

2. Estimated GFR changes in patients commencing TAF-based ART

3. Patients with contraindications to other NRTI backbones switched to F/TAF

12 Documents That Have Informed This Policy Proposition

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

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

In addition, the following references:

1) Skingsley A, Kirwan P, Yin Z *et al*. HIV new diagnoses, treatment and care in the UK 2015 report: data to end 2014. October 2015. Public Health England, London.

2) Churchill D, Waters L, Ahmed N *et al*. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. Accessed 5th February 2016 at http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

3) Sax P, Zolopa A, Brar I et al. 2014. Tenofovir alafenamide vs tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomised phase 2 study. J Acquire Immune Defic Syndr, 67(1), pp. 52-58

4) Sax PE, Wohl D, Yin MT *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015; 385: 2606-15.

5) Mills A, Arribas JR, Andrade-Villaenueva J *et al*. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet ID 2015; 16: 43-52.

13 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by May 2016).

END