

# Clinical Commissioning Policy Tenofovir alafenamide for treatment of HIV 1 in adults and adolescents

## Policy statement

NHS England will commission tenofovir alafenamide for Human Immunodeficiency Virus type 1 (HIV-1) treatment in adults and adolescents in accordance with the criteria outlined in this document and its marketing authorisation, as detailed in <https://www.medicines.org.uk/emc>. 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**

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.

## Plain language summary

### Anti-retroviral therapy

Treating HIV with anti-retroviral therapy (ART) has transformed the outlook for people living with HIV. ART allows most people with HIV to live a normal life, with a normal life expectancy.

As people get older, some medical concerns become very important. These include:

* Heart disease
* Kidney problems
* Bone problems

Some HIV drugs have side effects that affect these medical problems which happen as people get older. Until a cure is found, ART is a life-long treatment, with most people taking ART for decades. This means it is very important to minimise the long-term side-effects, and at the same time, make sure the ART is still effective.

### Tenofovir alafenamide

An evidence review looked at how safe and effective tenofovir alafenamide (or TAF) was. Tenofovir alafenamide was compared to another drug called tenofovir disoproxil fumarate[[1]](#footnote-2) or TDF. Like TDF, TAF is an effective drug. TAF appears to have a lower risk of kidney and bone side effects in the short-term. However, we do not know if it is lower in the long-term.

TAF is used in combination with other HIV drugs. The evidence review (conducted in 2016) evaluates the combination known as elvitegravir/cobicistat/emtricitabine/TAF or E/C/F/TAF with a review of cost. TAF is available in different fixed dose combinations with one or more additional HIV drugs.

### **What we have decided**

NHS England has carefully reviewed the evidence for treatment of HIV-1 infection in adults and adolescents with tenofovir alafenamide. We have concluded that there is enough evidence to make the treatment available at this time.

## Documents which have informed this policy

* B06/S/a Specialised Human Immunodeficiency Virus (HIV) Services (Adult) – service specification
* B06/S/b Specialised Human Immunodeficiency Virus (HIV) Services (Children) – service specification
* Clinical commissioning policy: Reimbursement for the use of generic drugs for pre exposure prophylaxis (PrEP) for the prevention of HIV.

## Introduction

HIV treatment (antiretroviral therapy, ART) has improved greatly over the last two decades and standard of care now involves two or three drug agents. Three drug options typically include 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). Recommended two drug regimens include one NRTI with an INI or a PI/b.

ART requires good adherence (>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 2021, of people receiving ART where a viral load result was reported, 98% were virally suppressed (UK Health Security Agency (UKHSA), 2022). Current standard treatment is therefore effective for many people. New drug treatments therefore need to demonstrate clinical and cost effectiveness and improved safety profiles compared to current standard treatments.

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

Tenofovir alafenamide (TAF) is licensed as a treatment for HIV-1 infection in adults and adolescents. TAF is available in fixed dose combinations, with one or multiple other HIV drugs.

This policy considers the use of TAF as a bioequivalent of TDF in appropriate individuals. TAF will be delivered 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.

It is expected that prescribers will construct a regimen containing TAF in combination with other HIV drugs, which is the most clinically effective at the lowest acquisition cost. Advice for the most effective cost combinations can be determined from the national prescribing algorithm.

## Aims and objectives

This policy aims to identify the evidence and cost implications of routine commissioning of a TAF-containing product 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 patients who would benefit from TAF. This includes a defined group of people in whom TDF is contraindicated at treatment initiation or who develop complications during treatment. In both patient cohorts TAF is determined to be an appropriate alternative and is used with other ART drugs to construct a viable ART regimen. This policy covers TAF within fixed dose combinations. It is anticipated that prescribers will select the most clinical effective regimen at the lowest acquisition cost.

## Epidemiology and needs assessment

In 2018, the joint United Nations Programme on HIV and AIDS (UNAIDS)[[2]](#footnote-3) set a goal to eliminate HIV transmission by 2030. In 2021 the UK committed to the HIV action plan (2022-2025) to reduce HIV transmission, AIDS- and HIV-related deaths as well as reducing HIV-related stigma. To achieve these aims, a combination prevention approach will be implemented with a focus on prevent, test, treat and retain (UKHSA. 2022). In 2020, an estimated 97, 740 (95% credible interval (Crl) 96,400 to 100,060) people were living with HIV infection in England, of these, 4,660 (95% Crl 3,640 to 6,980) were estimated to be unaware of their HIV status (UKHSA. 2022).

Effective antiretroviral therapy (ART) means for many individuals HIV can be managed as a chronic long-term condition, allowing them to live a near normal life. Lifesaving treatments and ongoing transmission means that the number of people seen for HIV care continues to rise; a 16% increase from 84,817 in 2014 and a 3% increase from 95,472 in 2018 to 98,552 in 2019 (PHE. 2020). In 2021, a total of 91,432 people accessed HIV care compared to 88, 786 in 2020, (UKHSA. 2022). In 2021, almost all (99%) of people engaged in HIV care were receiving antiretroviral therapy (ART) treatment of whom, 98% were virally supressed (UKHSA. 2022).

British HIV Association (BHIVA) treatment guidelines for adults currently recommend the following first-line (BHIVA. 2022):

* **Recommended for most people with HIV**:
	+ tenofovir disoproxil and emtricitabine or tenofovir alafenamide and emtricitabine or abacavir and lamivudine plus dolutegravir
	+ tenofovir alafenamide and emtricitabine and bictegravir
	+ Lamivudine and dolutegravir
	+ **Recommended in some clinical situations**: Darunavir plus cobicistat or ritonavir plus emtricitabine plus tenofovir alafenamide or tenofovir disoproxil
	+ Doravirine plus emtricitabine or lamivudine plus tenofovir alafenamide or tenofovir disoproxil
	+ Efavirenz plus emtricitabine or lamivudine plus abacavir or tenofovir alafenamideor tenofovir disoproxil (only in pregnancy or during tuberculosis treatment)
	+ Raltegravir plus emtricitabine plus tenofovir AF or tenofovir DX

Of note, several other regimens are recommended for switch and maintenance. o When clinically appropriate, lamivudine and emtricitabine can be considered interchangeable.

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 (TAF) offers some additional benefits in the short term in terms of reduced toxicity for particular patient groups.

## Evidence summary

Tenofovir alafenamide (TAF) and tenofovir disoproxil 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 or higher active levels in cells but with much lower plasma concentrations of tenofovir, thought to be an important 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 fixed dose combinations (FDCs) with elvitegravir/cobicistat/emtricitabine**

The safety and efficacy of TAF compared to TDF has been assessed in one phase 2 RCT (Sax et al 2014), 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 (Sax et al 2015). 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 (Mills et al 2015).

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. TAF usage has been associated with weight gain relative to TDF in clinical trials and cohorts (BHIVA. 2022).

## Implementation

The criteria below set out when TAF, as part of the TAF-containing ART regimen, will be routinely commissioned. The expectations are that TDF will be utilised unless the following high or medium risk factors are identified at either treatment initiation or treatment review.

NHS England will routinely commission a tenofovir alafenamide regimen in accordance for patients meeting the following criteria:

### Inclusion criteria

**All patients:**

* Decisions to offer TAF are made by appropriately qualified members following a clinical assessment and that ongoing monitoring is performed in accordance with national service specifications, British HIV Association (BHIVA. 2022) guidelines and/or local best practice guidance **AND**
* Prescribers should refer to the Summary of Product Characteristics (SPC) for detailed information regarding safety and suitability for TAF and TDF **AND**
* Prescribers should consider other suitable ART options dependent on concurrent patient factors (e.g. cardiovascular disease or co-existing hepatitis) to construct the most clinically effective and suitable regimen at the lowest acquisition cost.

**AND** Individuals meet either high risk **OR** medium risk factors for TDF:

1. **High risk factors for TDF:**
	* Moderate or severe reduction in glomerular filtration (Estimated Glomerular Filtration Rate[[3]](#footnote-4) (eGFR) ≤ 49 ml/min2 ) and clinical assessment suggests that TAF would have a lower risk profile than TDF **OR**
	* Individuals with proven renal toxicity[[4]](#footnote-5) with TDF (acute or chronic) **OR**
	* Individuals with confirmed osteoporosis on DEXA or a high risk[[5]](#footnote-6) of a major fracture as determined by an appropriate fragility risk score.

**OR**

1. **Medium risk factors for TDF:**

All medium risk patients must be discussed at a Multi-disciplinary Team (MDT) meeting and the alternative regimen agreed and meet the inclusion criteria as either:

* Individuals who are < 25 years[[6]](#footnote-7) **OR**
* Individuals with an eGFR ≥ 50 ml/min2 in which:
	+ A progressive reduction in glomerular filtration rate[[7]](#footnote-8) on TDF is seen **AND**
	+ Significant concurrent medical issues, monitoring/prescribing concerns or significant patient factors (e.g. intolerance, concordance) suggest TAF would have a lower risk profile to TDF.

### Exclusion criteria

* Individuals with contra-indications or the potential for significant drug interactions to tenofovir alafenamide, as outlined by the Summary of Product Characteristics (SPC) **OR**
* Individuals determined to be not suitable by MDT assessment of medium risk factors **OR**
* The use and reimbursement of TAF-based products by providers who are not commissioned by NHS England to provide HIV care and treatment services.

### 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.

**Governance arrangements**

All patients identified who might benefit from starting TAF will (in medium risk cases) be referred to and discussed at specialist HIV MDTs and the recommendation recorded in accordance with national prescribing ART guidance.

All patients identified who might benefit from switching to TAF, should be managed in accordance with the national guidance for switching ARVs including prescribing for the best clinical efficacy at the lowest acquisition cost.

For patients deemed suitable for a 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.

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**

Reimbursement for use of ART for individuals meeting the criteria in this policy is provided via Specialised Commissioning teams. Off-label use is not routinely commissioned.

## **Audit requirements**

1. Number of medium risk patients referred to MDT

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

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

## Policy amendments

First published July 2016. Updated and republished February 2017.Updated November 2022.

## 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

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| 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).   |
| First line therapy | The first combination that someone is prescribed to treat HIV. Tenofovir disoproxil and emtricitabine or tenofovir alafenamide and emtricitabine the NRTIs recommended for most people. Lamivudine or lamivudine/abacavir are also recommended in combination with dolutegravir. When clinically appropriate, lamivudine and emtricitabine can be considered interchangeable (BHIVA. 2022). |
| Fixed dose combinations (FDC) | FDC are single tablets that combine a complete ART regimen into one pill. |
| Intolerance | Intolerance is when patients either (i) experience side effects, or (ii) have been assessed to be at high risk of side effects. |
|  Second line third agents | The use of alternative non-NRTIs agents where first line options cannot be used for reasons of potential or actual intolerance, drug-drug interactions or transmitted HIV drug resistance. Alternative 3rd agents include: the NNRTI rilpivirine or nevirapine, the INIs elvitegravir/cobicistat, and the PI/r lopinavir/ritonavir or atazanavir/ritonavir or cobicistat. Drug selection depends on side effects profile, tolerability, resistance profile, drug-drug interactions and cost. |
| People with stable HIV | Stable patients have a sustained undetectable viral load on ART and are not experiencing side effects. |
| Viral load | HIV RNA levels in plasma are used to monitor response to ART. Patients on effective therapy sustain a viral load of <50 copies/ml (undetectable). Patients who do not achieve an undetectable viral load or who experience a confirmed viral load rebound to above 50 copies/ml are deemed to be experiencing virological failure. |

## References

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1. Tenofovir disoproxil can be formulated with different salts, those with fumarate are referred to as TDF. TDF is used throughout this policy due to the evidence base returned. Other tenofovir disoproxil salts are covered within this policy. [↑](#footnote-ref-2)
2. UNAIDS has a vision of zero new HIV infections, zero discrimination and zero AIDS-related deaths, and a principle of leaving no one behind”. They agreed to end AIDS as a public health threat by 2030 through meeting a series of Fast-Track commitments including treatment for all, eliminating childhood AIDS, ensuring access to HIV prevention, championing the rights of girls, women and key populations, social protection and delivery by communities, financing the AIDS response and realising human rights. [↑](#footnote-ref-3)
3. This policy uses eGFR to define renal thresholds as this estimation of renal function as it is more frequently used in clinical practice. It is noted that Creatinine Clearance (CrCl) is used in the Summary of Product Characteristics (SPC). Prescribers should consider situations where eGFR is a poor approximation for renal function, such as in the extremes of body mass. Further details are available from the Medicines and Healthcare products and Regulation Agency (MHRA) 2019. [↑](#footnote-ref-4)
4. Renal toxicity defined as a progressive, sustained decline in renal function or development of renal tubular acidosis, attributable to TDF. Toxicity could also include development or worsening of existing proteinuria without another reversible or explained cause. It is expected that prescribers can consult renal specialists if there is diagnostic uncertainty. [↑](#footnote-ref-5)
5. High fracture probability defined as >10% (major osteoporotic or hip fracture absolute risk), with NICE recommending QFracture or FRAX scores. [↑](#footnote-ref-6)
6. SPC information for TD-FTC mentions uncertainties associated with the long-term renal and bone effects of tenofovir disoproxil during the treatment of HIV-1 infection in the paediatric population. The HIV positive population most at risk of bone disease include children and young people below the age of peak bone mass (aged approx. 25 years). [↑](#footnote-ref-7)
7. A reduction in eGFR of 15ml/min in the past 12 months or 25% reduction in eGFR in the past 12 months were determined to be significant threshold measures by HIV CRG working group. [↑](#footnote-ref-8)