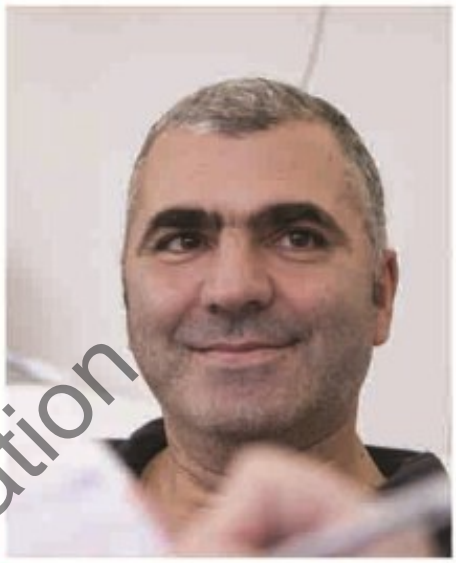
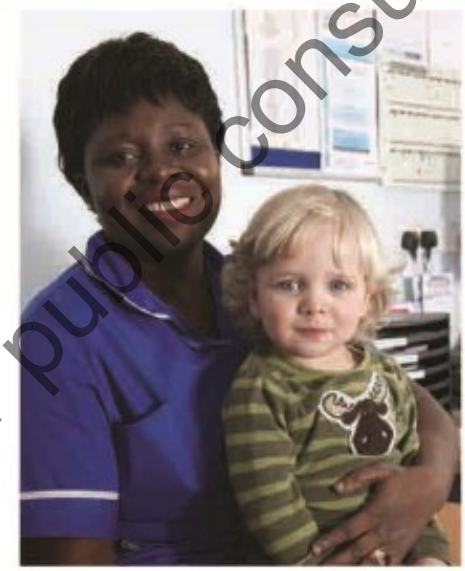
NHS England

Evidence Review: Comparison between tenofovir alafenamide and tenofovir disoproxil fumarate.

February 2016





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NHS England

Evidence Review:

Comparison of tenofovir alafenamide and tenofovir disoproxil fumarate.

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Contents

1. Introduction

Introduce the evidence review topic (Provide information on the epidemiology for the appropriate geographical area for the use of the treatment/condition. Include information on estimates of incidence and prevalence of condition, current demand etc. Include information on current alternative treatments if any and the proposed treatment etc.)

2. Research Questions

The British HIV Association (BHIVA) recommends tenofovir (TFV) as part of its preferred antiretroviral regime for treatment-naïve adults living with HIV-1. Along with emtricitabine, it forms a nucleoside reverse transcriptase inhibitor (NRTI) backbone which is usually combined with either a ritonavir-boosted protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, or an integrase inhibitor (BHIVA 2015).

Traditionally, tenofovir has been administered orally as the prodrug tenofovir disoproxil fumarate (TDF). TDF is converted into TFV in the plasma, which is then distributed intracellularly where it is phosphorylated to its active form tenofovir diphosphate (TFV-DP). (Wong, 2015)

TDF is licensed in combination with other antiretroviral products for the treatment of HIV-1 infected adults. (Gilead 2015) It is available as a single component product (Viread®) as well as in three combination products:

- Atripla® (tenofovir disoproxil fumarate, efavirenz, and emtricitabine)
- Eviplera®▼(tenofovir disoproxil fumarate, emtricitabine, and rilpivirine hydrochloride)
- Stribild®▼ (tenofovir disoproxil fumarate, emtricitabine, elvitegravir, and cobicistat)

TDF is effective and generally well tolerated, but in rare cases its use may be limited by renal adverse effects or decreased bone density. This presents a particular problem given the long-term nature of antiretroviral treatment. (Gilead 2015, Wong 2015).

Tenofovir alafenamide (TAF) is a newer prodrug of TFV. It is converted to both TFV and TFV-DP intracellularly, which means less TFV circulating in plasma. It is postulated that this may lead to a decreased likelihood of serious adverse effects compared to TDP, making it more suitable for longer term prescribing.

The first product containing TAF to receive a positive opinion in Europe is Genvoya®, a combination product containing TAF, elvitegravir, cobicistat, and emtricitabine (E/C/F/TAF) licensed for the treatment of adults and adolescents aged 12 years and older with body weight at least 35kg infected with HIV-1 without any known mutations associated with resistance to the components. (EMA 2015) Genvoya® will therefore represent an alternative to Stribild®. Genvoya® is approved in the US. (FDA 2015) Studies into another fixed dose combination containing darunavir, cobicistat, emtricitabine (D/C/F) and TAF are ongoing.

Research questions are therefore as follows:

- What is the evidence that TAF and TDF in fixed dose combinations (E/C/F/TAF and E/C/F/TDF) are bioequivalent in children (12 years and over) or adults with HIV infection?
- What is the evidence that TAF and TDF in fixed dose combinations (E/C/F/TAF and E/C/F/TDF) are clinically equivalent in children (12 years and over) or adults with HIV infection?
- What is the evidence that TAF results in reduced renal and bone adverse effects compared to TDF in children (12 years and over) or adults with HIV infection?

3. Methodology

Search strategy

Date of Evidence Search: 5th February 2016

Primary literature was identified by searching EMBASE (1974-) and MEDLINE (1946-) through NHS Evidence over the last 10 years up to and including 5th February 2016. All databases were searched using pre-defined terms for English Language articles. The preferred search terms were: Tenofovir alafenamide OR (Genvoya OR TAF) AND tenofovir disoproxil OR (PMPA fumarate OR TDF OR Viread). No methodological filters were applied. Studies in children under 12 years of age were excluded.

In addition to the primary literature searches, the websites of the MHRA, EMA, FDA, NICE, SMC, AWMSG, and other Health Technology Assessment Agencies were searched for relevant assessment reports and safety reviews. A broader search for unpublished research and 'grey literature' was also undertaken using relevant clinical trials registries, horizon scanning resources, major conference proceedings, and commercial Pharma resources. Google was used to search for additional web-based materials. NICE's Medicines Awareness Daily newsletter was checked for relevant newly published information up to and including 5th February 2016.

These searches were supplemented by reviewing the bibliographies of key papers and review articles.

Selected articles were qualitatively evaluated according to methodology and grading system established by the Scottish Intercollegiate Guideline Network (SIGN) levels of evidence (table 1).

Table1: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–*	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance
2+	Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance
2–*	Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance
3	Non-analytical studies (eg case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence (–) should not be used as basis for making recommendations. *Source*: adapted from SIGN (2001).	

Table 2: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence

Grades of recommendations
Grade 'A' At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or*** A systematic review of RCTs or a body of evidence consisting principally of studies rated as

1+ directly applicable to the target population and demonstrating overall consistency of results.
Grade 'B' A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 1++ or 1+
Grade 'C' A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 2++
Grade 'D' Evidence level 3 or 4 ***or*** Extrapolated evidence from studies rated as 2+

Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001

4. Results

A total of eight relevant clinical trials were identified for inclusion in this review. All but one of the trials had been fully published. The results of the included studies are summarized in tables 3,4, and 5. No published economic analyses on the use of tenofovir alafenamide fixed-dose combinations were identified.

Phase 1 studies

- Ruane P, DeJesus E, Berger D et al. 2013. Antiviral activity, safety, and pharmacokinetics/ pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1 positive adults. J Acquire Immune Defic Syndr, 63(4), pp. 449-455

Phase 1/2 Studies

- Markowitz M, Zolopa A, Squires K et al. 2014. Phase I/II study of the pharmacokinetics, safety and antiretroviral activity of tenofovir alafenamide, a new prodrug of the HIV reverse transcriptase inhibitor tenofovir, in HIV infected adults.J Antimicrob Chemother, 69, 1362-1369

Phase 2 Studies

- 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

Phase 3 Studies

- Sax P, Wohl D, Yin M et al. 2015. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for inititial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. The Lancet, 385, pp 2606-2615
- Mills A, Arribas J, Andrade-Villanueva et al. 2015. 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 Infect Dis, published online November 2nd 2015