NHS England

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

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Evidence Review:

Comparison of tenofovir alafenamide and tenofovir disoproxil fumarate.

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Contents

1. 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?

2. 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

3. 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

Table 3: Bioequivalence

Bioequivalence

<table>
<tr><th>Level of Evidence</th><th>Study design & Intervention</th><th>Outcome measure(s)</th><th>Results</th><th>Reference</th><th>Comments</th></tr>
<tr>
<td>1-*</td>
<td><u>Study Design</u>
Phase 1b, randomized, partially blinded dose ranging study.

<u>Number of patients, their characteristics</u>
38 antiretroviral naïve or experienced HIV-1 infected adults. Baseline characteristics were similar in most aspects except for viral load (TAF 8mg & 25mg: 4.5 log_{10} copies/mL, TAF 40mg: 4.3 log_{10} copies/mL, TDF: 5.0 log_{10} copies/mL, and placebo: 4.2 log_{10} copies/mL).
All but one subject was male.

<u>Intervention</u>
Treatment group 1: TAF 8mg daily for 10 days (n=9)
Treatment group 2: TAF 25mg daily for 10 days (n=8)
Treatment group 3: TAF 40mg daily for 10 days (n=7)

<u>Comparator</u>
Treatment group 4: TDF 300mg daily for 10 days (n=6, not blinded)
Treatment group 5: Placebo (n=7)

All patients were followed for 11 days after the end of dosing (21 days in total)

All doses were taken in a fasted state in the morning.</td>
<td><u>Secondary</u>
TFV-DP concentration in peripheral blood mononuclear cells (PBMC)

PK parameters: Maximum observed plasma concentration of drug (C_{max}), time of maximum observed plasma concentration (T_{max}), AUC, and elimination half-life</td>
<td>
<table>
<tr><th colspan="5">TFV Multiple dose PK day 10</th></tr>
<tr><th></th><th>TAF 8mg (n=9)</th><th>TAF 25mg (n=8)</th><th>TAF 40mg (n=8)</th><th>TDF 300mg (n=6)</th></tr>
<tr><td>AUC_{tau} (ng•h/mL), mean, (%CV)</td><td>65.5 (23.5)</td><td>267.7 (26.7)</td><td>405.8 (12.7)</td><td>1918.0 (39.4)</td></tr>
<tr><td>C_{max} (ng/mL), mean (%CV)</td><td>4.2 (24.7)</td><td>15.7 (22.1)</td><td>28.3 (8.7)</td><td>252.1 (36.6)</td></tr>
<tr><td>C_{tau} (ng/mL), mean (%CV)</td><td>2.1 (33.8)</td><td>9.2 (26.1)</td><td>13.3 (16.0)</td><td>38.7 (44.7)</td></tr>
<tr><td>T_{max} (h),median(Q1,Q3)</td><td>1.50 (1.00,1.98)</td><td>1.50 (1.25, 1.75)</td><td>1.29 (1.04, 1.50)</td><td>1.25 (0.58, 2.00)</td></tr>
<tr><td>$T_{1/2}$, (h),median (Q1, Q3)</td><td>30.77 (26.90, 55.61)</td><td>40.19 (29.98, 44.84)</td><td>35.95 (26.38, 42.90)</td><td>14.86 (12.18, 16.81)</td></tr>
<tr><th colspan="5">PBMC TFV-DP multiple dose PK</th></tr>
<tr><td>AUC_{tau} (µM•h), mean (%CV)</td><td>3.5 (77.1)</td><td>21.4 (76.9)</td><td>74.5 (92.7)</td><td>3.0 (119.6)</td></tr>
</table>
</td>
<td>Ruane et al, 2013</td>
<td>

All three doses of TAF provided decreased plasma levels of TFV compared to TDF 300mg.
TAF 8mg and TDF 300mg resulted in similar intracellular levels of TFV-DP.
TAF 25mg and 40mg resulted in higher intracellular TFV-DP than TDF 300mg.
Study is limited by its small study groups.
No statistical analyses of the pharmacokinetics were reported.
The TDF 300 mg group was not blinded
All but one of the included subjects was male.

</td>
</tr>
</table>

Bioequivalence

<table>
<tr><th>Level of Evidence</th><th>Study design & Intervention</th><th>Outcome measure(s)</th><th>Results</th><th>Reference</th><th>Comments</th></tr>
<tr>
<td>1-*</td>
<td><u>Study Design</u>
Phase 1/2 randomized, double-blind, active controlled, dose escalation study

<u>Number of subjects, their characteristics</u>
30 HIV-1 infected antiretroviral treatment naïve adults.
Median baseline viral load was similar in both TAF groups (4.64 & 4.61 log_{10} copies/mL) but higher in the TDF group (5.06 log_{10} copies/mL)

<u>Intervention</u>
Treatment group 1: TAF 40mg plus placebo daily for 14 days (n=10)

Treatment Group 2: TAF 120mg plus placebo daily for 14 days (n-10)

<u>Comparator</u>
Treatment group 3: TDF 300mg plus placebo for 14 days (n=10)

Subjects were followed for up to 21 days after the end of dosing (35 days in total), depending on treatment groups

All doses were taken in a fasted state in the morning.</td>
<td><u>Secondary</u>
TFV-DP concentration in peripheral blood mononuclear cells (PBMC)

PK parameters: Maximum observed plasma concentration of drug (C_{max}), time of maximum observed plasma concentration (T_{max}), AUC.</td>
<td>
<table>
<tr><th colspan="4">TFV Single dose PK, fasting state</th></tr>
<tr><th></th><th>TAF 40mg (n=10)</th><th>TAF 120mg (n=10)</th><th>TDF 300mg (n=10)</th></tr>
<tr><td>$AUC_{0-\infty}$ (ng•h/mL), mean, (%CV)</td><td>279+-129 (46.5)</td><td>1150+-662 (57.4)</td><td>1810+- 628 (34.6)</td></tr>
<tr><td>C_{max} (ng/mL), mean (%CV)</td><td>13+-4.53 (35)</td><td>41.9+-14.1 (33.7)</td><td>207+-42.0 (20.3)</td></tr>
<tr><td>T_{max}</td><td>0.25</td><td>2.00</td><td>0.25-2.00</td></tr>
<tr><th colspan="4">PBMC TFV-DP multiple dose PK (day 14)</th></tr>
<tr><td>AUC_{tau} (µM•h),</td><td>8.2</td><td>16.9</td><td>0.9</td></tr>
</table>
</td>
<td>Markowitz et al 2014</td>
<td>

Both doses of TAF produced lower mean plasma concentrations of TFV compared to TDF 300mg
Both doses of TAF produced higher intracellular levels of TFV compared to TDF 300mg.
Study is limited by its small study groups. The authors suggest that the group size was adequate to provide stable estimates of the population means for pharmacokinetic variables of interest, but provide no power calculations.
Baseline viral load was higher in the TDF group than both TAF groups.
No statistical analyses of the pharmacokinetic trial aspects were reported.

</td>
</tr>
</table>

Bioequivalence					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	Study Design Phase 2 randomized, double blind, double dummy active controlled study to assess safety and efficacy. Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening. Trough and population PK samples were collected on all subjects at various points throughout the study. An intensive PK sub study (n=26) was performed at weeks 4 and 8. Number of subjects, their characteristics 171 HIV-1 infected, antiretroviral naïve adults. 17% of E/C/F/TAF and 28% E/C/F/TDF subjects had HIV-1 RNA >100,000 copies/mL. Intervention *Treatment group 1:* single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo (n=112). Comparator *Treatment group 2:* single tablet containing E/C/F/TDF 150 mg/150 mg/ 200mg/ 300 mg once daily plus placebo (n=58).	Secondary: TFV-DP concentration in peripheral blood mononuclear cells (PBMC) PK parameters: Maximum observed plasma concentration of drug (C_{max}), time of maximum observed plasma concentration (T_{max}), AUC, and elimination half-life	**Pharmacokinetic substudy (n=26)** • Plasma TFV exposure was 91% lower in the TAF group compared to the TDF group. • Intracellular tenofovir diphosphate levels were 5.3 fold higher with TAF than TDF. • Raw figures and other results of this substudy are not reported.	Sax et al, 2014	• Due to presence of cobicistat, TAF bioavailability is increased so 10mg TAF is equivalent to 25mg TAF when used as monotherapy. • The pharmacokinetic substudy is limited by its small size (n=26) • The PK substudy appears to show that TAF confers a large reduction in plasma TFV compared to TDF, along with improved intracellular levels, though the scant reporting of results makes this difficult to verify. • Methods of selection of patients for the PK study are not reported. • Baseline characteristics or details of the substudy population are not clearly reported. • Substudy statistical analysis is not reported.

Bioequivalence

<table>
<tr><th>Level of Evidence</th><th>Study design & Intervention</th><th>Outcome measure(s)</th><th>Results</th><th>Reference</th><th>Comments</th></tr>
<tr>
<td>1+</td>
<td><u>Study Design</u>
Two identical phase 3, randomised, double-blind, active-controlled multicenter studies to assess safety and efficacy of TAF compared to TDF in combination with (E/C/F). Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or 100,000 - ≤ 400,000 copies/mL or >400,000 copies/mL), region, and CD4 count (<50 cells per µL, 50-199 cells/µL or ≥200 cells per µL at screening

A PK sub-study (n=65) was performed at weeks 4 and 8.

<u>Number of subjects, their characteristics</u>
1733 HIV-infected, antiretroviral treatment naïve adults with an HIV-1 RNA concentration of at least 1000 copies/mL and an estimated GFR of at least 50mL/min.

<u>Intervention</u>
Treatment group 1: single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo (n=866).

<u>Comparator</u>
Treatment group 2: single tablet containing E/C/F/TDF 150 mg/ 150 mg/200 mg/ 300 mg once daily plus placebo (n=867)</td>
<td><u>Secondary:</u>
TFV-DP concentration in peripheral blood mononuclear cells (PBMC)

PK parameters: Maximum observed plasma concentration of drug (C_{max}), time of maximum observed plasma concentration (T_{max}), AUC, and elimination half-life</td>
<td><u>Pharmacokinetics Substudy (n=65)</u>
<table>
<tr><th colspan="3">TFV Multiple dose PK</th></tr>
<tr><th></th><th>E/C/F/TAF (n=36)</th><th>E/C/F/TDF (n=29)</th></tr>
<tr><td>AUC_{tau} (ng•h/mL), mean, (%CV)</td><td>297 (20)</td><td>3410 (25.0)</td></tr>
</table>
Intracellular TFV-DP was 4.1 fold higher in the TAF group compared to the TDF group.
</td>
<td>Sax et al, 2015 (2)</td>
<td>
The pharmacokinetic substudy is limited by its small size (n=65)
TAF, in combination with E/C/F, produced lower mean plasma concentrations of TFV compared to TDF.
TAF produced 4.1- fold higher intracellular levels of TFV compared to TDF
Selection of patients into the pharmacokinetic substudy was non randomised.
Substudy statistical analysis is not reported.
</td>
</tr>
</table>

Table 4: Clinical effectiveness

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	Study Design Phase 1b, randomized, partially blinded dose ranging study. Number of patients, their characteristics 38 antiretroviral naïve or experienced HIV-1 infected adults. Baseline characteristics were similar in most aspects except for viral load (TAF 8mg & 25mg: 4.5 log_{10} copies/mL, TAF 40mg: 4.3 log_{10} copies/mL, TDF: 5.0 log_{10} copies/mL, and placebo: 4.2 log_{10} copies/mL). All but one subject was male. Intervention Treatment group 1: TAF 8mg daily for 10 days (n=9) Treatment group 2: TAF 25mg daily for 10 days (n=8) Treatment group 3: TAF 40mg daily for 10 days (n=7) Comparator Treatment group 4: TDF 300mg daily for 10 days (n=6, not blinded) Treatment group 5: Placebo (n=7) All patients were followed for 11 days after the end of dosing (21 days in total) All doses were taken in a fasted state in the morning.	Primary Time weighted average change from baseline to study day 11 in plasma HIV-1 RNA ($DAVG_{11}$) (log_{10} copies per mL) Secondary Change in HIV-1 RNA at day 11. Median first-phase decay slope	• Median $DAVG_{11}$ was -0.76 for TAF 8mg, -0.94 for TAF 25mg, -1.08 for TAF 40mg, -0.48 for TDF 300mg, and -0.01 for placebo. The differences between 25mg and 40mg TAF groups and TDF were significant (p=0.017 and p=0.006 respectively). • Median decrease in HIV-1 RNA followed a similar pattern. TAF 8mg resulted in similar decreases (-1.08), whilst 25mg and 40mg TAF resulted in significantly larger decreases compared to TDF (-1.46, p=0.024 and -1.73, p=0.003 respectively) • Median first-phase decay slopes were -0.305 for TAF 8mg, -0.455 for TAF 25mg, -0.511 for TAF 40mg, and -0.183 for TDF 300mg. The differences between 25mg and 40mg TAF groups and TDF were significant (p=0.012 and p=0.006 respectively.)	Ruane et al, 2013	• It is unclear whether other medicines were being used during the study. • All three doses (as well as TDF) were significantly better than placebo. • Only the 25mg and 40mg TAF doses were statistically better than TDF 300mg. • Study is limited by its small study groups. Eight patients per group were required to provide 90% power to detect a difference of 0.75log10 copies/mL of DAVG11 in HIV-1 RNA between at least one of the three TAF groups and the placebo group. This was not achieved in all groups. • The TDF 300 mg group was not blinded • All but one of the included subjects was male.

Clinical Effectiveness

Level of Evidence	Study design & Intervention	Outcome measure(s)	Results	Reference	Comments
1-*	Study Design Phase 1/2 randomised, double-blind, active controlled, dose escalation study Number of subjects, their characteristics 30 HIV-infected, antiretroviral treatment naïve adults. Median baseline viral load was similar in both TAF groups (4.64 & 4.61 log_{10} copies/mL) but higher in the TDF group (5.06 log_{10} copies/mL) Intervention *Treatment group 1:* TAF 40mg plus placebo daily for 14 days (n=10) *Treatment Group 2:* TAF 120mg plus placebo daily for 14 days (n-10) Comparator *Treatment group 3:* TDF 300mg plus placebo for 14 days (n=10) Subjects were followed for up to 21 days after the end of dosing (35 days in total), depending on treatment groups All doses were taken in a fasted state in the morning.	Primary Time weighted average change from baseline to study week 2 in plasma HIV-1 RNA ($DAVG_2$) (log_{10} copies per mL) Secondary Change in HIV-1 RNA at day 11. Change from baseline in CD4 cell counts (cells/mm^3)	• $DAVG_2$ not reported. • Mean changes in HIV-1 RNA were -0.94 log_{10} copies/mL (-1.66 to 0.02, median -0.96) for the TDF group, -1.57 log_{10} copies/mL (-2.21 to -0.65, median -1.65) for the TAF 40mg group, and -1.71 log_{10} copies/ml (-2.24 to -1.33; median -1.68) in the TAF 120mg group. The difference between both the 40mg and 120mg TAF groups and TDF group was significant (p=0.025) • There were no significant differences in mean HIV-1 RNA change between TAF 40mg AND 120mg (p=0.68) • Median first-phase decay slopes were -0.36 for TAF 40mg, -0.63 for TAF 120mg, and -0.64 for TDF 300mg. The differences between both TAF groups and TDF were significant (p=0.0003). • Mean changes from baseline in CD4 counts were 15 (-143 to 99, median 25) for 300mg TDF, 91 (-120 to 249, median 97) for the TAF40mg group, and 33 (-58 to 120, median 31) for TAF 120mg. There were no statistically significant differences between groups.	Markowitz et al, 2014	• It is unclear whether other medicines were being used during the study. • Despite the differences in baseline viral load between groups, both TAF doses led to a significant reduction in HIV-1 viral load and CD4 counts compared to TDF 300mg. • Results from this study support the hypothesis that higher intracellular TFV levels lead to improved clinical efficacy. • Study is limited by its small study groups. It was adequately powered to detect a 1.0 log10 copies/mL difference in HIV-1 RNA between the TDF group and at least one of the TAF groups. • Baseline viral load was higher in the TDF group than both TAF groups.

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	Study Design Phase 2 randomised, double blind, double dummy active controlled study to assess safety and efficacy. Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening. Number of subjects, their characteristics 171 HIV-1 infected, antiretroviral naïve adults. 17% of E/C/F/TAF and 28% E/C/F/TDF subjects had HIV-1 RNA >100,000 copies/mL. Intervention *Treatment group 1:* single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo (n=112). Comparator *Treatment group 2:* single tablet containing E/C/F/TDF 150 mg/150 mg/ 200mg/ 300 mg once daily plus placebo (n=58).	Primary: Virologic response (Proportion of subjects with HIV-1 RNA <50 copies/mL at weeks 24). Secondary: Proportion of subjects with HIV-1 RNA <50 copies/mL at weeks 48. Change in CD4 count (cells/ µL) at weeks 24 and 48.	• Virologic response was 87.5% in the E/C/F/TAF group and 89.7% in the E/C/F/TDF group at week 24. The baseline HIV-1 RNA stratum-weighted difference in the response rate between the two treatment groups was −3.7% (95% CI: -14.4% to 7.0%, p =0.48). • At week 48, virologic response was 88.4% in the E/C/F/TAF group and 87.9% in the E/C/F/TDF group.The baseline HIV-1 RNA stratum-weighted difference in the response rate between the two treatment groups was −1.0% (95% CI: −12.1% to 10.0%, p=0.84). • The mean change in CD4 cell count from baseline to week 24 was +177 in the E/C/F/TAF group and +204 in the E/C/TDF group (p=0.41), and at week 48 the corresponding changes were +230 and +206, respectively (p=0.43).	Sax et al, 2014	• In HIV-infected, antiretroviral treatment naïve subjects, TAF in combination with E/C/F resulted in comparable rates of virologic suppression and increase in CD4 cell count to E/C/F/TDF • Modest, but not statistically significant differences between groups were observed.

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**

1+	Study Design Two identical phase 3, randomised, double-blind, active-controlled multicenter studies to assess safety and efficacy of TAF compared to TDF in combination with (E/C/F). Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or 100,000 - ≤ 400,000 copies/mL or >400,000 copies/mL), region, and CD4 count (<50 cells per µL, 50-199 cells/µL or ≥200 cells per µL at screening Number of subjects, their characteristics 1733 HIV-infected, antiretroviral treatment naïve adults with an HIV-1 RNA concentration of at least 1000 copies/mL and an estimated GFR of at least 50mL/min. Intervention *Treatment group 1:* single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo (n=866). Comparator *Treatment group 2:* single tablet containing E/C/F/TDF 150 mg/ 150 mg/200 mg/ 300 mg once daily plus placebo (n=867)	Primary: Virologic response (Proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. Secondary: Treatment responses by subgroups (inc missing=failure, Missing= excluded, and full analysis set) Proportion of subjects with HIV-1 RNA <50 copies/mL at 48 weeks CD4 count change from baseline (cells/µL)	• At week 48, a virologic response was achieved in 92.4% of subjects in the E/C/F/TAF group and 90.4% of subjects in the E/C/F/TDF group (snapshot analysis, ITT). The difference in response rate between the two treatment groups was 2% (95% CI: -0.7% - 4.7%, p=0.13) • Virologic failure with resistance occurred in 0.8% of subjects in the E/C/F/TAF group and 0.6% in the E/C/F/TDF group; resistance mutation development was similar between treatment groups. • 84.4% of subjects in the E/C/F/TAF group and 84.0% in the E/C/F/TDF group achieved an HIV-1 RNA of <20 copies/mL. The difference between treatment groups was 0.4%. (95% CI -3.0% - 3.8%) • Viral suppression was high in both groups (98% for TAF vs 97% for TDF, adjusted difference 0.8% (95% CI -1.0% - 2.5%, per protocol analysis.) Results followed a similar pattern for secondary efficacy endpoints. • The mean change in CD4 cell count (cells/µL) from baseline to week 48 was +230 in the E/C/F/TAF group and +211 in the E/C/F/TDF group.	Sax et al, 2015	• These large, well-conducted studies met its primary objective of demonstrating non-inferiority of TAF vs. TDF as a component of an E/C/F combination product in HIV-infected, antiretroviral treatment naïve subjects; though no non-inferiority level was pre-specified in the report, virologic response was 2% higher in the TAF group. • Both treatment combinations resulted in similar PK profiles. • The baseline characteristics of the study population were consistent with those reported from other studies in HIV-1 infected, antiretroviral treatment naïve subjects. • There were no significant deviations from trial protocol • Modest, but not statistically significant differences between groups were observed. • 96 week data is not yet published.

Clinical Effectiveness

Level of Evidence	Study design & Intervention	Outcome measure(s)	Results	Reference	Comments
1+	Study design Phase 3, open label, randomised, active controlled, multicenter non-inferiority study to assess safety and efficacy of switching to TAF, in combination with E/C/F, from various TDF-containing regimens. Number of subjects, their characteristics 1443 HIV-1 infected, virologically suppressed (HIV-1 RNA <50 copies/mL) taking a TDF-containing regimen and with an estimated GFR of at least 50mL/min. 26% of subjects in the TAF group and 17% of subjects in the TDF group were of Hispanic/latino origin (p=0.0006) Intervention *Treatment group 1:* E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day (n=959). Comparator Treatment group 2: Continue on existing TDF-containing regimen (n=477). • E/C/F/TDF (n=153) • Efavirenz/ emtricitabine/ TDF (n=125) • Cobicistat-boosted atazanavir, emtricitabine and TDF (n=69) • Ritonavir-boosted atazanavir, emtricitabine and TDF (n=130)	Primary Virologic response (Proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. Secondary Virologic response (Proportion of subjects with HIV-1 RNA <50 copies/mL at week 96. CD4 count change from baseline (cells/µL)	• At week 48, a virologic response was achieved in 97% of subjects in the TAF group and 93% of patients in the TDF group (p=0.0002) (snapshot analysis). The difference in response rate, adjusted by previous treatment regimen, was 4.1% (95%CI 1.6-6.7) • Virologic failure occurred in 1% of subjects in both groups. One subject had virologic failure with genotypic resistance to a component of their treatment regimen. • The mean change in CD4 cell count from baseline to week 48 was +35 (SD165) in the TAF group and +24 (SD 156) for the TDF group.	Mills et al 2015	• Patients with an $eGFR_{CG}$ of <50mL/min were excluded • This large, well-conducted study met its primary objective of demonstrating non-inferiority of TAF vs. TDF as a component of an E/C/F combination product in subjects switched from a TDF containing regimen E/C/F/TAF. Statistical superiority was also established. • The open-label nature of the study increases the risk of bias.

Table 5: Safety

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	Study Design Phase 1b, randomized, partially blinded dose ranging study. Number of patients, their characteristics 38 antiretroviral naïve or experienced HIV-1 infected adults. Baseline characteristics were similar in most aspects except for viral load (TAF 8mg & 25mg: 4.5 $\log_{10}$ copies/mL, TAF 40mg: 4.3 $\log_{10}$ copies/mL, TDF: 5.0 $\log_{10}$ copies/mL, and placebo: 4.2 $\log_{10}$ copies/mL). All but one subject was male. Intervention Treatment group 1: TAF 8mg daily for 10 days (n=9) Treatment group 2: TAF 25mg daily for 10 days (n=8) Treatment group 3: TAF 40mg daily for 10 days (n=7) Comparator Treatment group 4: TDF 300mg daily for 10 days (n=6, not blinded) Treatment group 5: Placebo (n=7) All patients were followed for 11 days after the end of dosing (21 days in total) All doses were taken in a fasted state in the morning.	Secondary Adverse events and concomitant medicines Physical examinations Fasting laboratory parameters Electrocardiogram Measured at various points through the study period.	• The most common AEs (≥ 2 subjects) were nausea (2 subjects in TAF 40 mg group vs 0 in TDF group), and fatigue ((2 subjects in TAF8mg group vs 0 in TDF group) • One SAE occurred in the 25mg TAF group but it was considered unrelated to study medication. All other AEs in the TAF and TDF groups were mild or moderate in severity. • Treatment emergent laboratory abnormalities were mainly mild or moderate in severity. It is not possible to determine whether rates were similar in all groups due to inadequate reporting. • There were no treatment-emergent changes in serum creatinine, phosphate, or urine glucose. • Graded urine protein laboratory abnormalities were similar in each group (data not reported) • ECG results were not reported.	Ruane et al 2013	• Limited by short time frame and small sample size • It is unclear whether other medicines were being used during the study. • Both TAF and TDF were well tolerated. No AEs related to study drugs occurred in ≥1 subject. • Study is limited by its small study groups. • The TDF 300 mg group was not blinded • All but one of the included subjects was male.

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	Study Design Phase 1/2 randomised, double-blind, active controlled, dose escalation study Number of subjects, their characteristics 30 HIV-infected, antiretroviral treatment naïve adults. Median baseline viral load was similar in both TAF groups (4.64 & 4.61 log_{10} copies/mL) but higher in the TDF group (5.06 log_{10} copies/mL) Intervention *Treatment group 1:* TAF 40mg plus placebo daily for 14 days (n=10) *Treatment Group 2:* TAF 120mg plus placebo daily for 14 days (n-10) Comparator *Treatment group 3:* TDF 300mg plus placebo for 14 days (n=10) Subjects were followed for up to 21 days after the end of dosing (35 days in total), depending on treatment groups All doses were taken in a fasted state in the morning.	Secondary Adverse events and concomitant medicines Physical examinations Fasting laboratory parameters Electrocardiogram Measured at various points through the study period.	• No discontinuations due to AEs • The most common AEs (≥subjects) were headache (50%), nausea (27%), and flatulence (23%). The incidences were spread evenly over all groups. • Insomnia was reported in 10% of patients, all of whom were in the TDF group. • One SAE occurred (severe gingival bleeding) in the TDF group. This was not considered to be related to the drug. • Laboratory test abnormalities were similar in all three arms. • There were no significant changes in serum creatinine between any groups (mean change 0.00 for 40mg TAF, 0.05 for 120mg TAF, and 0.007 for 300mg TDF.	Markowitz et al, 2014	• It is unclear whether other medicines were being used during the study. • Study is limited by its small study groups. • Limited by short duration • Both TDF and TAF appeared well tolerated • No significant changes in creatinine measurements between groups, though there was a trend for less change in the TAF groups. • Baseline viral load was higher in the TDF group than both TAF groups.

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
1-*	<u>Study Design</u> Phase 2 randomised, double blind, double dummy active controlled study to assess safety and efficacy. Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening. <u>Number of subjects, their characteristics</u> 171 HIV-1 infected, antiretroviral naïve adults. 17% of E/C/F/TAF and 28% E/C/F/TDF subjects had HIV-1 RNA >100,000 copies/mL. <u>Intervention</u> *Treatment group 1:* single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo (n=112). <u>Comparator</u> *Treatment group 2:* single tablet containing E/C/F/TDF 150 mg/150 mg/ 200mg/ 300 mg once daily plus placebo (n=58).	<u>Secondary:</u> Change from baseline in eGFR and renal parameters Change from baseline in bone and renal biomarkers at weeks 24, 48, and 96. Incidence of AEs	• 170 out of 171 subjects received study medication and were included in the safety dataset. • Through 48 weeks, 94.6% of E/C/F/TAF and 94.8% of E/C/F/TDF subjects reported at least one treatment emergent AE, the majority of which were mild to moderate in intensity. • SAEs occurred in 9.8% of subjects receiving E/C/F/TAF compared to 5.2% of patients in the E/C/F/TDF group • The most common AEs (≥10%) were: nausea (TAF group 21% vs TDF group 12%), diarrhoea (TAF group 18% vs TDF group 16%), URTI (TAF group 15% vs TDF group 21%) fatigue, (TAF group 14% vs TDF group 9%) headache (TAF group % vs TDF group 14%), cough (TAF group 10% vs TDF group 10%). • Grade 3 or 4 LDL cholesterol elevations were more common in the TAF group (9%) than the TDF group (3%). • There was a rise in serum creatinine and a decline in creatinine clearance in both arms. Changes in eGFR (Cockroft Gault) were -5.5mLs for the E/T/F/TAF group and -10.1mLs for the E/C/F/TDF group (p=0.041) • Changes in spine bone mineral density were smaller in the TAF group compared to the TDF group (change from baseline -1.00% and -3.37% respectively, p<0.001) • Changes in hip bone mineral density were smaller in the TAF group compared to the TDF group (change from baseline -0.62% and -2.39% respectively, p<0.001)	Sax et al., 2014.	• The incidence of TEAEs was generally comparable between treatment groups, except for the notably higher incidence of nausea in the TAF group; however, it did not result in study drug interruption or discontinuation in any patient in the TAF group. • TAF resulted in significantly smaller losses in both hip and spine bone mineral density. • Subjects in the TAF group had less of a decrease in GFR compared to those in the TDF group. • Other laboratory abnormalities were similar for both groups • Patients taking TAF had higher increases in total cholesterol, LDL, and HDL, but there was no change in TC:HDL ratio in either group. • This study provides early evidence of an improved safety profile of TAF compared to TDF, though there are some limitations.

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**

Safety

Level of Evidence	Study design & Intervention	Outcome measure(s)	Results	Reference	Comments
1+	Study Design Two identical phase 3, randomised, double-blind, active-controlled multicenter studies to assess safety and efficacy of TAF compared to TDF in combination with (E/C/F). Randomization was stratified by HIV RNA level (≤ 100,000 copies/mL or 100,000 - ≤ 400,000 copies/mL or >400,000 copies/mL), region, and CD4 count (<50 cells per µL, 50-199 cells/µL or ≥200 cells per µL at screening A PK sub-study (n=65) was performed at weeks 4 and 8. Number of subjects, their characteristics 1733 HIV-infected, antiretroviral treatment naïve adults with an HIV-1 RNA concentration of at least 1000 copies/mL and an estimated GFR of at least 50mL/min. Intervention *Treatment group 1:* single tablet containing E/C/F/TAF 150 mg/ 150 mg/200 mg/ 10 mg per day plus placebo for (n=866). Comparator *Treatment group 2:* single tablet containing E/C/F/TDF 150 mg/ 150 mg/200 mg/ 300 mg once daily plus placebo (n=867)	Secondary: Percentage change in hip bone mineral density Percentage change in spine bone mineral density Change in serum creatinine Treatment-emergent proteinuria--	• All 1733 subjects receiving study medication were included in the safety dataset. • Through 48 weeks, 40% of E/C/F/TAF, and 42% of E/C/F/TDF subjects experienced at least one AE considered to be related to study treatment; the majority of which were mild to moderate intensity. • SAEs occurred in 8% of subjects receiving E/C/F/TAF compared to 7% of patients on E/C/F/TDF; Only a small proportion of those were considered to be related to study treatment. (0.3% and 0.2%) Five patients died, two in the TAF group and three in the TDF group. These deaths were not deemed related to study drugs. • The most common AEs (≥10%) were: diarrhoea (TAF 17% vs TDF 19%), nausea (TAF 15% vs TDF 17%), headache (TAF 14% vs TDF 13%), and upper respiratory tract infection (TAF 11% vs TDF 13%) • Fewer patients discontinued TAF therapy than did TDF (0.8% vs 1.3% respectively) • Other common AEs were evenly matched between groups. • Five patients discontinued TDF treatment due to renal AEs. There were none in the TAF group. • Serum creatinine results are not adequately reported. There was a significant ($p<0.001$) difference in the percentage of patients with a ≥25% decrease in eGFR between the groups (12 % in the TAF group vs 26% in the TDF group, Cockroft-Gault) • Subjects in the TAF group had a significantly lower urine protein to creatinine ratio (TAF group -3 vs TDF 20, $p<0.0001$) • Changes in spine bone mineral density were smaller in the TAF group compared to the TDF group (change from baseline -1.30% and -2.85% respectively, $p<0.0001$) • Changes in hip bone mineral density were smaller in the TAF group compared to the TDF group (change from baseline -0.66% and -2.95% respectively, $p<0.0001$)	Sax et al, 2015	• In these large studies, the nature and incidence of AEs through to week 48 was comparable between treatment groups. The number of patients who discontinued study drugs due to AEs was slightly higher in the TDF group. • The most frequently reported AEs were consistent with those expected in the subject population and are in accordance with the known safety profiles of the study drugs. • There seems to be a decreased incidence of renal AEs, though reporting is inadequate. • TAF appeared to result in less bone mineral density decreases in both the hip and spine. • 96-week data is not yet published.

4. Summary of Evidence

Available pharmacokinetic studies support the hypothesis that TAF, either alone or in combination products results in lower plasma TFV and higher intracellular TFV-DP levels compared to TDF. TAF 10mg, in combination with E/C/F may therefore be considered bioequivalent to TDF 300mg in the same combination. In the seven available studies, the pharmacokinetics translated into similar or slightly improved virologic response.

Two identical phase 3 studies (n=1733 level 1++), and a supportive phase 2 trial (n=171, level 1+) provide the primary evidence for the safety and efficacy of TAF as part of a single tablet regimen containing E/C/F (Genvoya®) in HIV-1 infected antiretroviral naïve adults. (Sax et al, 2015, Sax et al, 2014). All three studies were randomised, double-blind, multicentre, active controlled trials and were identical in design except for sample size, duration, and minor differences in eligibility criteria. The baseline characteristics of the study populations were consistent with those reported from other studies in antiretroviral treatment naïve subjects. At week 48 in the phase 3 studies, 92.4% of subjects in the E/C/F/TAF group achieved a virologic response (HIV RNA <50 copies/mL) compared with 90.4% in the E/C/F/TDF group (Sax et al, 2015). The baseline HIV-1 RNA stratum-weighted difference in response rate between the two treatment groups was +2% (95% CI -0.7-4.7%), demonstrating the primary objective of non-inferiority of E/C/F/TAF vs. E/C/F/TDF as the lower bound of the 95% confidence interval was greater than the pre-defined -12% non-inferiority margin. The rates of virologic failure were low and comparable between the two treatment groups (4% in both groups). Both groups also demonstrated similar increases from baseline in CD4 cell counts (+230 vs. +211 cells/ µL, respectively). Week 96 and 144 results are yet to be published. In an open label phase 3 trial, 97% of patients switched from various TDF-containing regimens to E/C/F/TAF had a virologic response, compared with 93% of patients who remained on a TDF-containing regimen. In this study, TAF was shown to be non-inferior, and statistical superiority was also established. (Mills et al, 2015(2)) In the phase 2 study at week 24, TAF or TDF, along with E/C/F resulted in comparable rates of virologic suppression (87.5% vs 89.7% respectively) and increase in CD4 cell count (+177 and +204 cells/ µL respectively. (Sax et al, 2014, HIV/AIDs bureau, 2014). Week 48 results were consistent with those reported at week 24.

In long term phase 2 and 3 studies, a total of 1437 HIV-infected antiretroviral treatment naïve adults received E/C/F/TAF and 1310 received E/C/F/TDF. (Sax et al, 2014) (Sax et al 2015.) Both treatment groups had a similar overall incidence of treatment- emergent AEs and AEs considered to be related to study drug. Diarrhoea, nausea, headache, and URTIs were amongst the most frequently reports AEs. TAF resulted in significantly smaller changes in renal markers, though longer term trials are required to determine whether this will translate into fewer cases of renal adverse effects. TAF resulted in smaller decreases in hip and spine bone mineral density compared to TDF. Discontinuation due to an AE was relatively low in either treatment group with no notable differences between the two groups.

Overall, these data support the use of TAF as a well-tolerated and effective nucleoside reverse transcriptase inhibitor. It appears to be equally as effective as TDF both as a monotherapy and as a combination product. It remains to be seen

whether the improvements in renal and bone markers seen in studies up to 48 weeks will translate to less serious adverse reactions in the longer term.

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Appendices

Appendix 1 - Search strategy

Question(s)
What is the clinical efficacy, clinical effectiveness, clinical safety and cost-effectiveness of: TAF compared to TDF E/C/F/TAF (Genvoya) compared to E/C/F/TDF (Stribild) in the treatment of patients with HIV-1 infection?
Search strategy *Indicate all terms used in the search* *Search term (indicative):* • *HIV,* • *treatment*, therap*, medication, medicines, drug*, antiretroviral,* • *'pharmacokinetic enhancer', booster, enhance*,* • *TAF (GS-7340)* • *TDF (Viread)* • *E/C/F/TAF (Genvoya)* • *E/C/F/TDF (Stribild)* *Limits:* • *Humans* • *English language*

P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	*Children (aged 12 years and above) or adults with HIV infection* *Sub-groups may include previously treated/treatment-naïve adults, those with co-infections or co-morbidity; risk groups for acquiring HIV e.g. men who have sex with men (MSM), people who inject drugs, sex workers*
I – Intervention Which intervention, treatment or approach should be used?	Antiretrovirals containing TAF compared with those containing TDF either alone or in combination, but focussed on comparing the differences between TAF and TDF in particular. Fixed dose combination tablet of either:, E/C/F/TAF or E/C/F/TDF
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	TAF compared with TDF E/C/F/TAF (Genvoya) compared with E/C/F/TDF (Stribild)

O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	<u>Critical to decision-making:</u> 1. Treatment response (viral load): viral suppression (RNA levels <50 copies/ml) at 48/96 weeks[1] 2. Proportion with virological failure (viral load >400 copies/ml on consecutive visits) 3. Proportion with drug resistance 4. Proportion discontinuing for adverse events e.g. bone, lactic acidosis, hepatic and renal, with particular attention to renal failure with E/C/F/TAF (Genvoya) 5. Proportion with grade 3 / 4 adverse events <u>Important to decision-making:</u> • Treatment emergent AIDS defining illness • Measures of cost-effectiveness e.g. incremental cost-effectiveness ratio (ICER) • Measures of adherence to treatment regime • Quality of life measures (including physical and social functioning) Measures of unplanned health care e.g. emergency admissions
Assumptions / limits applied to search *e.g. date limits, inclusion and exclusion criteria (study type or aspect of topic)*	

[1] BHIVA defines treatment response as the proportion of patients with an undetectable viral load of <50 copies/ml at 6 months (24 weeks) and12 months (52 weeks) after starting ART. However, this may vary between different published papers and BHIVA also state that treatment response at 48/96 weeks is a critical outcome.