NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Clinical evidence review of bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) for the treatment of human immunodeficiency virus type 1 (HIV-1) in adults

NHS England Unique Reference Number 1702 / CSP ID010

First published: June 2018

Updated: [Not applicable]

Prepared by: National Institute for Health and Care Excellence on behalf of NHS England Specialised Commissioning.

About this clinical evidence review

Clinical evidence reviews provide a summary of the best available evidence for a single technology within a licensed indication for which the responsible commissioner is NHS England. The clinical evidence review supports NHS England in producing clinical policies but are **not NICE guidance or advice**.

Summary

This evidence review considers bictegravir-emtricitabine-tenofovir alafenamide (B/F/TAF) as a treatment for human immunodeficiency virus (HIV-1) positive adults.

Evidence review

A literature search was undertaken, which identified 15 references (see appendix 1 for search strategy). The company also provided a submission of evidence. Six studies, 6 published were included in the review.

Results

Evidence of the efficacy of B/F/TAF comes from 5 randomised controlled trials (RCTs). One RCT with 629 previously untreated HIV-1 participants compared B/F/TAF with dolutegravir, abacavir and lamivudine (DTG/ABC/3TC), (Gallant et al. 2017). Two additional RCTs by Sax et al. (2017a) containing 645 previously untreated HIV-1 participants and (2017b) containing 98 participants compared B/F/TAF with dolutegravir, emtricitabine and tenofovir alafenamide (DTG/F/TAF). Two recently published RCTs were also submitted by the company: one compared participants switching to B/F/TAF from boosted protease inhibitor-based regimens (Daar et al. 2018) and dolutegravir, abacavir and lamivudine (Molina et al. 2018). Patient reported outcomes from patients in the Gallant et al. and Molina et al. RCTs were also reported over 48 weeks in Wohl et al. (2018).

Effectiveness

Primary Outcomes – Previously untreated

The studies by Gallant et al. (2017) and Sax et al. (2017a and b) showed that B/F/TAF works as well as both DTG/ABC/3TC and DTG/F/TAF in reducing the HIV-1 RNA plasma levels to below 50 copies per ml at 48 weeks follow up. Results from all of the studies showed that there was no statistically significant difference in the proportion of people with fewer than 50 copies of HIV-1 RNA per ml of plasma (viral load) at 48 weeks follow up who received any of the

following treatments: B/F/TAF, DTG/ABC/3TC or DTG/F/TAF. A decrease in HIV-1 RNA plasma levels to below 50 copies per ml is an indication that the antiretroviral medication is working effectively.

Gallant et al. (2017) and both Sax et al. (2017a and b) studies showed that B/F/TAF works as well as both DTG/ABC/3TC and DTG/F/TAF in increasing the average CD4 cell count from the start of treatment (baseline) to 48 weeks follow up. Results from all of the studies showed that there was no statistically significant difference in the average change of CD4 cell counts from baseline for people who received any of the following treatments: B/F/TAF, DTG/ABC/3TC or DTG/F/TAF. An increase in CD4 cell count is both an indication that the immune system is improving in health (as the HIV-1 virus infects these cells) and that the antiretroviral medication is working.

Secondary Outcomes

The study by Gallant et al. (2017), measuring average percentage change in bone mineral density (hip and lumbar spine) from the beginning of treatment (baseline) to 48 weeks follow up, showed that B/F/TAF was as good as DTG/ABC/3TC in reducing the loss of bone mineral density during treatment. The study showed there was no statistically significant difference in the average percentage change in bone mineral density for people who received either B/F/TAF or DTG/ABC/3TC. Reduced bone density can be an indication of osteoporosis and increases the risk of fracture.

Study drug adherence was reported by Gallant et al. (2017) and both Sax et al. (2017a and b). Both studies showed equal levels of adherence for those achieving lower than 50 copies of HIV-1 RNA per ml of plasma who received B/F/TAF, DTG/ABC/3TC or DTG/F/TAF. The studies showed a non-statistically significant difference in people who received B/F/TAF, DTG/ABC/3TC or DTG/F/TAF. A high level of drug adherence indicates the patient has correctly followed the medical advice and taken the medicine as prescribed.

No treatment emergent resistance, where the virus becomes resistant to the treatment being given resulting in the medicine not having its desired effect, to B/F/TAF, DTG/ABC/3TC or DTG/F/TAF treatments was reported in either Gallant et al. (2017) or the Sax et al. (2017a and b) studies.

Safety and tolerability

The study by Gallant et al. (2017) reported fewer overall adverse events in people receiving B/F/TAF when compared with DTG/ABC/3TC although Sax et al. (2017a) reported more when compared with DTG/F/TAF. Both studies reported fewer drug-related adverse events (an undesired experience associated with the use of the medicine) in people who received B/F/TAF when compared with DTG/ABC/3TC or DTG/F/TAF. There was no difference in the number of drug-related serious adverse events for people who received B/F/TAF when compared with DTG/ABC/3TC (Gallant et al. (2017)).

There was no statistically significant difference in any adverse event leading to study drug discontinuation between people who received B/F/TAF when compared with either DTG/ABC/3TC or DTG/F/TAF. The most common adverse events, measured over 48 weeks which did not lead to discontinuation, consisted of diarrhoea, nausea, headache, arthralgia and fatigue.

Primary Outcomes – Treatment switching

The studies by Molina et al. (2018) and Daar et al. (2018) showed that B/F/TAF works as well as both DTG/ABC/3TC and protease inhibitor-based regimens in maintaining HIV-1 RNA plasma levels below 50 copies per ml at 48 weeks follow up following treatment switching. Results from both studies showed that there was no statistically significant difference in the proportion of people with fewer than 50 copies of HIV-1 RNA per ml of plasma (viral load) at 48 weeks follow up who received any of the following treatments: B/F/TAF, DTG/ABC/3TC or protease inhibitor-based regimen. Maintaining HIV-1 RNA plasma levels below 50 copies per ml is an indication that the antiretroviral medication is working effectively.

Molina et al. (2018) and Daar et al. (2018) studies showed that B/F/TAF works as well as both DTG/ABC/3TC and protease inhibitor-based regimens in increasing the average CD4 cell count from the switching of treatment (baseline) to 48 weeks follow up. Results from both studies showed that there was no statistically significant difference in the average change of CD4 cell counts from switching baseline for people who received any of the following treatments: B/F/TAF, DTG/ABC/3TC or protease inhibitor-based regimens. An increase in CD4 cell count is both an indication that the immune system is improving in health (as the HIV-1 virus infects these cells) and that the antiretroviral medication is working.

Secondary Outcomes

The study by Molina et al. (2018), measuring average percentage change in bone mineral density (hip and lumbar spine) from the switching of treatment (baseline) to 48 weeks follow up, showed that B/F/TAF was as good as DTG/ABC/3TC in reducing the loss of bone mineral density during treatment. The study showed there was no statistically significant difference in the average percentage change in bone mineral density for people who received either B/F/TAF or DTG/ABC/3TC. Reduced bone density can be an indication of osteoporosis and increases the risk of fracture.

Study drug adherence was reported by Molina et al. (2018) which showed equal levels of adherence for those achieving lower than 50 copies of HIV-1 RNA per ml of plasma who received either B/F/TAF or DTG/ABC/3TC. The difference between the treatments was not statistically significant. A high level of drug adherence indicates the patient has correctly followed the medical advice and taken the medicine as prescribed.

No treatment emergent resistance, where the virus becomes resistant to the treatment being given, resulting in the medicine not having its desired effect, to B/F/TAF or DTG/ABC/3TC was reported in Molina et al. (2018). Daar et al. (2018) also reported no treatment emergent resistance to B/F/TAF but did report 1 to ritonavir-boosted darunavir with abacavir plus lamivudine.

Safety and tolerability

Molina et al. (2018) and Daar et al. (2018) reported no difference in overall adverse events in people switching to B/F/TAF when compared with remaining on DTG/ABC/3TC or boosted protease inhibitor-based regimens. Molina et al. reported fewer drug-related adverse events (an undesired experience associated with the use of the medicine) in people who switched to B/F/TAF when compared with DTG/ABC/3TC whereas Daar et al. reported greater events when switching to B/F/TAF compared with remaining on boosted protease inhibitor-based regimens. There was a very small increase in the number of drug-related serious adverse events reported for people who switched to B/F/TAF when compared with remaining on either DTG/ABC/3TC (Molina et al.) or boosted protease inhibitor-based regimens (Daar et al.)

There was no statistically significant difference in any adverse event leading to study drug discontinuation between people who received B/F/TAF when compared with either DTG/ABC/3TC or boosted protease inhibitor-based regimens. The most common adverse events, measured over 48 weeks which did not lead to discontinuation, consisted of upper respiratory tract infection, headache, diarrhoea, and nasopharyngitis.

A more detailed presentation of the effectiveness, safety and tolerability evidence for all studies can be found in the key outcomes section.

Patient report outcomes

Wohl et al. (2018) reported a lower percentage of bothersome symptoms reported by patients treated with B/F/TAF compared to DTG/ABC/3TC in both treatment naïve patients and patients who switched to B/F/TAF compared with those remaining on DTG/ABC/3TC. Among treatment-naïve patients, statistically significant differences ($p<0.05$) in fatigue/loss of energy, dizzy/light-headedness, nausea/vomiting and difficulty sleeping were observed at least 2 time points in the adjusted or unadjusted logistic models, with the lower prevalence of bothersome symptoms in patients receiving B/F/TAF compared with those taking DTG/ABC/3TC. For virologically

suppressed participants, switching to B/F/TAF from DTG/ABC/3TC compared to staying on DTG/ABC/3TC was associated with a statistically significantly lower prevalence of nausea/vomiting, sad/down/depressed, nervous/anxious and difficulty sleeping in at least 2 time points in the adjusted or unadjusted logistic models compared with patients who remained on DTG/ABC/3TC.

Evidence gaps

No published studies provided evidence regarding the potential advantages of taking a single tablet compared with multiple tablets.

Table of contents

Abbreviations

Term	Definition
ART	Antiretroviral Therapy
ARV	Antiretroviral
B/F/TAF	bictegravir, emtricitabine and tenofovir alafenamide
BHIVA	British HIV Association
DTG/ABC/3TC	dolutegravir, abacavir and lamivudine
DTG/F/TAF	dolutegravir, emtricitabine and tenofovir alafenamide
EMA	European Medicines Agency
EPAR	European Public Assessment Report
GFR	Glomerular Filtration Rate
HBV	Hepatitis B virus
HIV-1	Human Immunodeficiency Virus type 1
HLA-B5701	Human Leukocyte Antigen allele (B 5701)
INI	Integrase Strand Transfer Inhibitor
LSM	Least square mean
MDT	Multidisciplinary Team
NICE	National Institute for Health and Care Excellence
NRTI	Nucleoside analog reverse-transcriptase inhibitor
PHE	Public Health England
PI	Protease inhibitor
STR	Single tablet regimen

Medical definitions

Term	Definition
Arthralgia	Joint pain
Bone Mineral Density	The amount of mineral matter per square centimetre of bones.
HLA-B*5701 positive	A genetic test, which if positive, indicates the individual is possibly allergic to abacavir
NRTI 'backbone'	The combination of Nucleoside analog reverse-transcriptase inhibitors to which a third drug is added in antiretroviral therapy
Nasopharyngitis.	Swelling of the nasal passages and the back of the throat

Introduction

Disease background

HIV, or human immunodeficiency virus, is the virus that causes AIDS (Acquired Immunodeficiency Syndrome). HIV attacks the immune system by destroying CD4 positive (CD4+) T cells, a type of white blood cell that is vital to fighting infections. The destruction of these cells leaves people living with HIV vulnerable to other infections, diseases and other complications. HIV treatment with antiretroviral therapy (ART) has transformed the outlook for people living with HIV from that of a significantly shortened lifespan to a manageable long term chronic condition. Without treatment, HIV causes progressive damage to the immune system that ultimately results in serious ill health and death. ART prevents damage to the immune system through suppression of the HIV virus and reduces the risk of a wide range of serious complications which are more frequent in untreated, HIV-infected individuals. (National Institute of Allergy and Infectious Diseases)

Focus of review

In line with the marketing authorisation, the focus of this evidence review is B/F/TAF for the treatment of HIV-1 in adults (aged 18 years and over).

Epidemiology

Human Immunodeficiency Virus (HIV) is a disease of major importance in the UK. Public Health England (PHE) – National HIV surveillance data 2017 - reported that 85,537 (84,551 adults and 986 children) people were being seen for HIV care in England at the end of December 2017 with 3,973 new cases of HIV diagnosed in the same year.

PHE also reported that 83,585 people in England were receiving antiretroviral therapy (ART) at the end of 2017, representing 98% of the population seen for HIV care in England. In 2017, more than a third (39%; 33,144/85,537) of people accessing HIV care in England were aged 50 years and above, compared with 17% in 2007. HIV is a lifelong condition and the prevalence of

comorbidities, including cardiovascular (CV) disease, chronic kidney disease (CKD), mental health disorders and osteoporosis is higher in patients living with HIV (PLWHIV), compared with non-infected individuals (Bagkeris 2018). HIV services should continue evolving to meet the changing needs of people living with HIV including the management of comorbidities and other complex health conditions.

Product overview

Mode of action

Bictegravir is a HIV-1 integrase strand transfer inhibitor (INI), a type of antiretroviral drug designed to block the action of integrase, a viral enzyme that inserts the genome of the HIV-1 virus into the DNA of specific human white blood cells called T-helper cells. Since integration is a vital step in the virus reproducing itself, blocking it can stop it replicating and causing further damage to the infected person's immune system.

Regulatory status

B/F/TAF does not currently have a marketing authorisation in the UK for treating HIV-1 but does have a Committee for Medicinal Products for Human Use (CHMP) positive opinion from the EMA (26/04/18): "Biktarvy is indicated for the treatment of adults infected with human immunodeficiency virus 1 (HIV 1) without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir". It has been studied in clinical trials in people who have no antiretroviral treatment history and those who are virologically supressed.

Dosing information

Oral film coated tablets given once daily containing a fixed dose combination of bictegravir (50mg), emtricitabine (200mg), tenofovir alafenamide (25mg)

Treatment pathway and current practice

The overall goal of treatment is HIV-1 viral suppression (maintaining a low viral count). British HIV Association Treatment guidelines (BHIV) for adults currently recommend the following first-line treatment (Waters et al. 2016):

- One of the following nucleoside analog reverse-transcriptase inhibitor (NRTI) backbones:

    1. tenofovir disoproxil fumarate and emtricitabine: recommended for individuals who do not show established or significant risk factors for kidney or bone problems. OR

    2. tenofovir alafenamide and emtricitabine: preferred option if the individual has established or significant risk factors for kidney or bone problems. OR

    3. abacavir and lamivudine: alternative option, although an individual should not be given abacavir if they are HLA-B*57:01 positive. AND

- a third drug: of which the preferred options are atazanavir/ritonavir, or darunavir /ritonavir, or raltegravir or elvitegravir/cobicistat or rilpivirine, or dolutegravir. An alternative option is efavirenz.

Current commissioning criteria

There are currently 2 published (TAF published July 2016 [updated February 2017] and Dolutegravir published in 2014 [updated August 2018]) commissioning criteria which could be of relevance to B/F/TAF. A summary of the commissioning criteria can be found below.

Tenofovir alafenamide (TAF)

Tenofovir alafenamide is routinely commissioned in adults with HIV-1 who have definite contra-indications for tenofovir disoproxil fumarate (TDF), such as chronic kidney disease and/or osteoporosis, or those with relative contra-indications such as approaching thresholds of osteoporosis and renal markers

of disease (see Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents.) Patients with proven or suspected resistance to the component drugs in TAF should not be given this medication.

Dolutegravir

Dolutegravir is routinely commissioned in adults with HIV-1 who are unable to tolerate the first line therapy of efavirenz, or who develop treatment failure or resistance (requiring an integrase inhibitor). It should be combined with the lowest cost, clinically indicated backbone and at least 2 other anti-viral drugs to which the virus is sensitive. MDT agreement for dolutegravir use is not required where dolutegravir is clinically appropriate, the rationale for choice is clearly documented in the clinical notes, and is compliant with regional cost-based ART prescribing algorithms (which will outline MDT requirements across all ARTs). For commissioning exclusion criteria please see Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents.

Evidence base

Identification of studies

A literature search was undertaken, which identified 15 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 4 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 3 studies were included for previously untreated individuals in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons). Two further studies regarding switching to B/F/TAF in virologically supressed individuals were also included in this review, as was a study which included patient reported outcome data on treatment naive patients and patients switching from DTG/ABC/3TC compared to patients remaining on DTG/ABC/3TC.

Results

Overview of included studies

Three randomised controlled trials (RCTs) were identified from the search (Gallant et al. 2017, along with 2 studies by Sax et al. (2017a) and (2017b). Gallant et al. (2017) compared participants receiving B/F/TAF with those receiving dolutegravir, abacavir and lamivudine whereas both studies by Sax et al. (2017) compared B/F/TAF with dolutegravir, emtricitabine and tenofovir alafenamide. Two studies compared participants switching to B/F/TAF from boosted protease inhibitor-based regimens (Daar et al.) and dolutegravir, abacavir and lamivudine (DTG/ABC/3TC) (Molina et al.). Wohl et al. (2018) reported patient-reported symptoms over 48 weeks in people with HIV-1 who were either treatment naïve or virologically suppressed and randomised to receive B/F/TAF or DTG/ABC/3TC and included the patients from Gallant et al. 2017 and Molina et al. 2018, respectively.

A summary of the characteristics of the studies can be found in Table 1. More detailed evidence and results can be found in appendices 3 and 4.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Daar et al. (2018) Non-inferiority open label RCT	Adults (aged ≥18 years) with virologically supressed HIV-1 infection (n=577)	50 mg bictegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide vs Boosted protease inhibitor-based regimens	Proportion of participants with plasma HIV-1 RNA of less than 50 copies per ml at week 48

Study	Population	Intervention and comparison	Primary outcome
Gallant et al. 2017 Non-inferiority RCT	Adults (aged ≥18 years) with HIV-1 infection who were previously untreated (n=629)	Fixed dose combination bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg vs Fixed dose combination dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg, with matching placebo.	Proportion of participants with plasma HIV-1 RNA concentrations less than 50 copies per ml at week 48
Molina et al. (2018) Non-inferiority RCT	Adults (aged ≥18 years) with virologically supressed HIV-1 infection (n=563)	50 mg bictegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide vs 50 mg dolutegravir, 600mg abacavir and 300mg lamivudine (as a fixed-dose combination or multi-tablet regime)	Proportion of participants with plasma HIV-1 RNA of less than 50 copies per ml at week 48
Sax et al. 2017 Non-inferiority RCT	Adults (aged ≥18 years) with HIV-1 infection who were previously untreated (n=645)	Fixed dose combination bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg; vs dolutegravir (50 mg) in combination with fixed dose combination emtricitabine (200 mg) and tenofovir alafenamide (25 mg)	Proportion of participants with plasma HIV-1 RNA of less than 50 copies per ml at week 48
Sax et al. 2017 RCT	Adults (aged ≥18 years) with HIV-1 infection who were	75 mg bictegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25	Proportion of participants with plasma HIV-1 RNA concentrations of less than 50 copies per ml at week 24

Study	Population	Intervention and comparison	Primary outcome
	previously untreated (n=98)	mg tenofovir alafenamide vs 50 mg dolutegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide	
Wohl et al. 2018 Patient reported outcomes through 48 weeks and logistic regression analysis and longitudinal modelling.	Adults (aged ≥18 years) with HIV-1 infection who were previously untreated and HIV-1 supressed	Fixed dose 50 mg bictegravir 200 mg emtricitabine and 25 mg tenofovir alafenamide vs Fixed dose 50 mg dolutegravir, 600mg abacavir and 300mg lamivudine	HIV symptom index (HIV-SI), % reporting for each of the 20 symptoms

Key outcomes

The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 3 provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study can be found in appendices 3 and 4.

Effectiveness – Previously untreated

Plasma HIV-1 virus levels

The proportion of participants with plasma HIV-1 RNA less than 50 copies per ml at 48 weeks follow up was reported as the primary outcome in the Gallant et al. (2017) (n=629) and as a secondary outcome in Sax et al. (2017a) (n=645) and Sax et al. (2017b) (n=98). Gallant et al. (2017) reported that 92.4% of participants receiving B/F/TAF had less than 50 copies of HIV-1

per ml of plasma compared with 93% of those receiving DTG/ABC/3TC, with a treatment difference of [-0.6% (95% CI: -4.8 to 3.6) p=0.78]. Both treatments worked equally well in reducing HIV-1 viral copies but the difference between them was not statistically significant. Both Sax et al. (2017a and b) studies also reported no statistically significant difference in the proportion of participants achieving less than 50 copies of HIV-1 per ml of plasma in those receiving B/F/TAF when compared with DTG/F/TAF. Sax et al (n=645) reported 89.4% of participants receiving B/F/TAF obtaining less than 50 copies of HIV-1 RNA per ml of plasma copies compared with 92.9% of those receiving DTG/F/TAF, treatment difference of [-3.5% (95% CI: -7.9 to 1.0) p=0.12], and Sax et al (n=98) with 97% of participants compared with 91% obtaining less than 50 copies of HIV-1 RNA per ml of plasma. , treatment difference [6.4% (95% CI: -6.0 to 18.8) p=0.17].

Change in CD4 cell counts

The average change in the number of CD4 cells from the beginning of treatment (baseline) to 48 weeks follow up was another primary outcome in Gallant et al. (2017) and Sax et al. (2017a) (n=645), but reported as a secondary outcome in Sax et al. (2017b) (n=98). Gallant et al. (2017) reported an increase of 233 cells per microlitre (µl) (SD ± 185.2) of plasma in participants receiving B/F/TAF compared with an increase of 229 cells per µl (SD ± 188.8) in those receiving DTG/ABC/3TC showing no statistically significant difference between treatments (p=0.81). Both Sax et al. studies also reported no statistically significant difference in the increase of CD4 cells for participants receiving B/F/TAF when compared with DTG/F/TAF. Sax et al. (2017a) (n=645) reported an increase of 180 cells per µl (SD ± 166.6) from baseline in participants receiving B/F/TAF compared with an increase of 201 cells per µl (SD ± 166.4) in those receiving DTG/F/TAF (p=0.10). Sax et al. (n=98) showed an increase of 258 cells per µl (SD ± 221.7) in participants receiving B/F/TAF compared with an increase of 192 cells per µl (SD ± 242.0) in those receiving DTG/F/TAF giving a treatment difference, in least square mean (LSM), of [72 cells per µl (95% CI: -30 to 174) p=0.16].

Change in bone mineral density levels

Gallant et al. (2017) reported the average percentage change in bone mineral density of both the hip and lumbar spine as a secondary outcome. The study showed a decrease in hip bone density of -0.78% (SD ± 2.22) in participants receiving B/F/TAF compared with a decrease of -1.02% (SD ± 2.31) for those receiving DTG/ABC/3TC giving a non-statistically different treatment difference of [0.238% (95% CI: -0.151 to 0.626) p=0.23]. A non-statistically significant treatment difference was also reported for lumbar spine bone mineral density with a reduction of -0.83% (SD ± 3.19) for those receiving B/F/TAF and -0.60% (SD ± 3.10) for those receiving DTG/ABC/3TC, treatment difference [-0.235% (95% CI: -0.766 to 0.297) p=0.39].

Study drug adherence

Study drug adherence, as a subgroup analysis (<95% and ≥95% adherence) of participants who achieved less than 50 HIV-RNA copies per ml of plasma at week 48 follow up, was reported by both Gallant et al. (2017) and Sax et al. (2017a) (n=645). Gallant et al. stated that, of those participants who reported <95% adherence, 81% who received B/F/TAF and 86% who received DTG/ABC/3TC achieved a viral load below 50 HIV-RNA copies per ml (p=0.65). They also stated that, of those reporting ≥95% adherence, 97% who received B/F/TAF and 96% who received DTG/ABC/3TC achieved a viral load below 50 HIV-RNA copies per ml (p=0.66) showing no statistically significant differences in either subgroup. Sax et al. stated that, of those reporting <95% adherence, 84% who received B/F/TAF and 90% who received DTG/F/TAF achieved lower than 50 HIV-RNA copies per ml (p=0.35). They also stated that, of those reporting ≥95% adherence, 94% in both groups achieved lower than 50 HIV-RNA copies per ml (p=1.00) showing no statistically significant differences in either subgroup.

Treatment emergent resistance

Gallant et al. (2017) and both Sax et al. (2017a and b) studies reported no treatment emergent resistance to B/F/TAF, DTG/ABC/3TC or DTG/F/TAF in the study participants.

Safety and tolerability

Gallant et al. (2017) stated that drug related adverse events were higher in participants receiving DTG/ABC/3TC compared with B/F/TAF. Very small numbers of either drug-related serious events or those leading to study drug discontinuation were reported in both groups (see table 2). Sax et al. (2017a) stated that participants receiving B/F/TAF reported fewer drug related adverse events compared with DTG/F/TAF. Again, low numbers of adverse events which led to study drug discontinuation were reported in both groups (see table 2). Sax et al. (2017b) (n=98) reported 55 (85%) of the 65 participants receiving B/F/TAF reported an adverse event with 1 (2%) reported as being any adverse event or death leading to study drug discontinuation. This compared with 22 (67%) of the 33 participants receiving DTG/F/TAF with no events leading to discontinuation in this group. The 2 largest studies (Gallant et al. (n=629) and Sax et al. (2017a) (n=645)), reported the most common adverse events as being nausea, diarrhoea and headache.

Table 2: Adverse events (%)

Study	Drugs compared	Drug-related adverse events	Drug-related serious adverse events	Adverse events leading to discontinuation
Gallant et al, (2017) n=629	B/F/TAF	26%	<1%	0%
	DTG/ABC/3TC	40%	<1%	1%
Sax et al. (2017a) n=645	B/F/TAF	18%	Not reported	2%
	DTG/F/TAF	26%	Not reported	<1%

Effectiveness – Treatment switching

Plasma HIV-1 virus levels

The proportion of participants with plasma HIV-1 RNA less than 50 copies per ml at 48 weeks post switching follow up was reported as the primary outcome in both Molina et al. (2018) and Daar et al. (2018). Molina et al. (2018) reported that 93.6% of participants who switched to B/F/TAF had less than 50 copies of HIV-1 per ml of plasma at 48 weeks follow up compared with 95.0% of those who remained on DTG/ABC/3TC, with a treatment difference of [-1.4% (95% CI: -5.5 to 2.6) p=0.59]. Both treatments worked equally well in maintaining HIV-1 viral copies below 50 copies per ml of plasma but the difference between them was not statistically significant. Daar et al. (2018) also reported no statistically significant difference in the proportion of participants achieving less than 50 copies of HIV-1 per ml of plasma at 48 weeks follow up in those switching to B/F/TAF when compared with DTG/F/TAF. They reported 92.1% of participants switching to B/F/TAF maintaining less than 50 copies per ml compared with 88.9% of those remaining on boosted protease inhibitor-based regimens, giving a treatment difference of [3.2% (95% CI: -1.6 to 8.2) p=0.20].

Change in CD4 cell counts

The average change in the number of CD4 cells from treatment switching (baseline) to 48 weeks follow up was another primary outcome in Molina et al. (2018) and Daar et al. (2018). Molina et al. reported a statistically significantly difference between treatment groups (−31 (SD±181.3) cells/μL in participants switching to B/F/TAF vs 4 (SD±191.0) cells/μL in participants remaining on DTG/ABC/3TC), giving a treatment difference in LSM of [−35 cells/μL (95% CI: −67 to −3), p=0.031]. After adjusting for baseline CD4 cell count, the difference in the mean CD4 count changes from baseline at week 48 for the between treatment groups was not statistically different with a treatment difference in LSM of [−21 cells/μL (95% CI: −51 to 9), p=0.18]. Daar et al. (2018) reported an increase of 25 cells per microlitre (μl) (SD ± 151.2) of plasma in participants switching to B/F/TAF compared with 0 cells per μl

(SD ± 159.4) in those remaining on boosted protease inhibitor-based regimens, showing no statistically significant difference between treatments (p=0.068).

Change in bone mineral density levels

Molina et al. (2018) reported the average percentage change in bone mineral density of both the hip and lumbar spine as a secondary outcome. The study showed an increase in hip bone density of 0.78% in participants switching to B/F/TAF compared 0.30% for those remaining on DTG/ABC/3TC giving a non-statistically significant difference (p=0.47). A non-statistically significant difference was also reported for lumbar spine bone mineral density with an increase of 0.69% for those switching to B/F/TAF and 0.42% for those remaining on DTG/ABC/3TC (p=0.33).

Study drug adherence

Study drug adherence, as a subgroup analysis (<95% and ≥95% adherence) of participants who achieved less than 50 HIV-RNA copies per ml of plasma at week 48 after switching treatment, was reported by Molina et al. (2018). Of those patients who reported <95% adherence (41/282 for the B/F/TAF arm and 64/282 for the DTG/ABC/3TC ARM), 93% (38/41) in the B/F/TAF arm achieved less than 50 HIV-RNA copies per ml of plasma compared to 88% (56/64) in the DTG/ABC/3TC arm (p=0.52). Similarly in those reporting ≥95% adherence, the proportion achieving less than 50 HIV-RNA copies per ml of plasma was 94% (226/240) in the B/F/TAF arm compared to 97% (211/217) in the DTG/ABC/3TC (p=0.17) showing no statistically significant differences in either subgroup.

Treatment emergent resistance

Molina et al. (2018) reported no treatment emergent resistance to B/F/TAF or DTG/ABC/3TC in the study participants. Daar et al. (2018) reported no treatment emergent resistance to B/F/TAF but 1 was reported in a participant who was receiving ritonavir-boosted darunavir with abacavir plus lamivudine.

Safety and tolerability

Molina et al. (2018) stated that drug related adverse events were higher in participants who remained on DTG/ABC/3TC compared with switching to B/F/TAF. Very small numbers of either drug-related serious events or those leading to study drug discontinuation were reported in both groups (see table 3). Daar et al. (2018) stated that participants switching to B/F/TAF reported greater drug related adverse events compared with those who remained on boosted protease inhibitor-based regimens. Again, low numbers of adverse events which led to study drug discontinuation were reported in both groups (see table 3). Molina et al. and Daar et al. reported the most common adverse events as being upper respiratory tract infection, headache, diarrhoea, and nasopharyngitis.

Table 3: Adverse events (%)

Study	Drugs compared	Drug-related adverse events	Drug-related serious adverse events	Adverse events leading to discontinuation
Daar et al, (2018) n=577	B/F/TAF	19%	<1%	1%
	Boosted PI regimens	2%	0%	<1%
Molina et al. (2018) n=563	B/F/TAF	8%	<1%	2%
	DTG/ABC/3TC	16%	0%	1%

Patient reported outcomes

Wohl et al. (2018) described patient reported outcomes from 2 prospective, randomised double-blind studies comparing the differences in HIV symptom scores in newly treated (Gallant et al. 2017) and HIV-1 supressed patients (Molina et al. 2018). Patient reported outcome measures were administered at baseline and weeks 4, 12, and 48. Treatment differences were assessed using unadjusted and adjusted logistic regression and longitudinal modelling

techniques. Statistical significance was assessed using $p<0.05$. Across both populations, bothersome symptoms were reported by fewer patients receiving B/F/TAF compared with DTG/ABC/3TC.

In treatment-naïve adults, there were statistically significant differences between B/F/TAF and DTG/ABC/3TC, with fewer reports of fatigue/loss of energy, nausea/vomiting, dizziness/light-headedness, and difficulty sleeping at 2 or more time points seen in the B/F/TAF group ($p<0.05$) in the adjusted logistic regression model. In the longitudinal models, there were statistically significant differences in the fatigue and nausea/vomiting domains with fewer reports in B/F/TAF group.

In HIV-1 supressed patients, there were statistically significant differences between B/F/TAF and DTG/ABC/3TC, with fewer reports of nausea/vomiting, sad/down/depressed, nervous/anxious, and poor sleep quality (from the PSQI) in the B/F/TAF arm at 2 or more time points in the adjusted logistic regression model, as well as in the longitudinal models.

Evidence gaps

None of the published studies provided evidence on the potential benefits of B/F/TAF as a single tablet regimen compared with taking multiple tablets. Within the Gallant et al. (2017) study, participants in each treatment group received 2 tablets, once daily. In both Sax et al. (2017a and b) studies, participants in each treatment group received 3 tablets, once daily. It should be noted that this was required to ensure participants, investigators, study staff giving the treatment and those assessing the outcomes were all masked to group assignment.

Key ongoing studies

Treatment switching

Trial NCT02603120: Safety and Efficacy of Switching From Dolutegravir and ABC/3TC or ABC/DTG/3TC to B/F/TAF in HIV-1 Infected Adults Who Are

Virologically Suppressed. Status: Active. Estimated completion date: July 2019.

Trial NCT03110380: Switching to a Fixed Dose Combination of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in HIV-1 Infected Adults Who Are Virologically Suppressed. Status: Active. Estimated completion date: December 2020.

Adolescents and children

Trial NCT02881320: B/F/TAF FDC in HIV-1 Infected Virologically Suppressed Adolescents and Children. Status: Active. Estimated completion date: January 2019.

Table 4: Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Proportion of patients with HIV-1 RNA <50 copies per ml of plasma (48 weeks follow up)	Gallant et.al. (2017)	9/10	Directly applicable	A	This outcome is a measurement of how effective the treatment has been in reducing the number of HIV-1 RNA copies per ml (viral load) in the patient's blood plasma. Suppression of plasma HIV-1 RNA viral load to less than 50 copies per ml is associated with durable clinical and immunological benefits and is considered the recommended goal of antiviral therapy. Gallant et al. (2017) showed that B/F/TAF was as good as DTG/ABC/3TC in reducing the HIV-1 RNA plasma levels to below 50 copies per ml (92.4% vs 93% of people treated respectively). This was not statistically significant with a difference of -0.6% (95% CI: -4.8 to 3.6), p=0.78 at 48 weeks follow up. This result was supported by 2 RCT studies by Sax et al. (2017a and b) both showing no statistically significant difference in people receiving B/F/TAF when compared with DTG/F/TAF. The evidence suggests that receiving B/F/TAF treatment is comparable in reducing the level of detectable HIV-1 RNA in blood plasma (viral load) to below 50 copies per ml when compared with DTG/ABC/3TC or DTG/F/TAF at 48 weeks follow up.
	Sax et al. (2017) n=645	9/10	Directly applicable		
	Sax et al. (2017) n=98	8/10	Directly applicable		
	Daar et al. (2018) n=577	8/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
	Molina et al (2018) n=563	9/10	Directly applicable		Evidence regarding previously untreated individuals should be interpreted with caution because one study (Sax et al. 2017b) (n=98) was not sufficiently powered due to the numbers involved. Therefore the statistics associated with those particular findings should be treated as descriptive only. Molina et al. (2018) showed that B/F/TAF was as good as DTG/ABC/3TC in maintaining the HIV-1 RNA plasma levels below 50 copies per ml, 48 weeks post treatment switching (93.6% vs 95% of people treated respectively). Treatment difference of [-1.4% (95% CI: -5.5 to 2.6), p=0.59]. Daar et al. (2018) also showed that B/F/TAF was as good as boosted protease inhibitor-based regimen in maintaining the HIV-1 RNA plasma levels below 50 copies per ml, 48 weeks post treatment switching (92.1% vs 88.9% of people treated respectively). Treatment difference [3.2% (95% CI: -1.6 to 8.2), p=0.20] Evidence suggests that receiving B/F/TAF treatment is comparable in maintaining the level of detectable HIV-1 RNA in blood plasma (viral load) below 50 copies per ml when compared with DTG/ABC/3TC and boosted protease inhibitor-based regimens 48 weeks after treatment switching.

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
Mean change in CD4 cell count from baseline (48 weeks follow up)	Gallant et.al. (2017)	9/10	Directly applicable	A	This outcome is a marker of likely disease progression which is independent of viral load. A decline in the CD4 cell count of an individual is caused by HIV-1 infection with an increase in cell count indicating that the HIV-1 viral load has been reduced. Gallant et al. (2017) showed that B/F/TAF was as good as DTG/ABC/3TC at increasing the mean CD4 cell count from the start of treatment (baseline) to 48 weeks follow up: 233 per µl (SD ± 185.2) vs 229 per µl (SD ± 188.8) respectively. This was not statistically significant (p=0.81) and was supported by 2 RCT studies by Sax et al. (2017a and b) both showing no statistically significant difference in people receiving B/F/TAF when compared with DTG/F/TAF. The evidence suggests that receiving B/F/TAF treatment is comparable in increasing mean CD4 cell counts from baseline when compared with DTG/ABC/3TC or DTG/F/TAF at 48 weeks follow up. Evidence should be interpreted with caution because one study (Sax et al. 2017b) (n=98) was not sufficiently powered due to the numbers involved. Therefore the statistics associated with those particular findings should be treated as descriptive only. Molina et al. (2018) showed that B/F/TAF was as good as DTG/ABC/3TC in increasing the mean CD4 cell count, 48 weeks post treatment switching. Treatment difference [-21 cells per µl (95% CI: -51 to 9) p=0.18.
	Sax et al. (2017) n=645	9/10	Directly applicable		
	Sax et al. (2017) n=98	8/10	Directly applicable		
	Daar et al. (2018) n=577	8/10	Directly applicable		
	Molina et al (2018) n=563	9/10	Directly applicable		

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					Daar et al. (2018) also showed that B/F/TAF was as good as boosted protease inhibitor-based regimen in increasing mean CD4 cell count, 48 weeks post treatment switching: +25 per µl (SD ± 151.2) vs +0 per µl (SD ± 159.4) respectively. p=0.068 Evidence suggests that receiving B/F/TAF treatment is comparable in increasing mean CD4 cell counts from baseline when compared with DTG/ABC/3TC and boosted protease inhibitor-based regimens 48 weeks after treatment switching.
HIV symptom index	Wohl et al. 2018	8/10	Directly applicable	B	The outcome is a HIV disease specific validated tool which uses patient elicitation to capture changes in 20 symptoms (see tables 12 and 18) which are indicative of improvements in their condition. Each symptom is assessed on a 5 point scale: (0) "I don't have this symptom;" (1) "I have this symptom and it doesn't bother me;" (2) "I have this symptom and it bothers me a little;" (3) "I have this symptom and it bothers me;" (4) "I have this symptom and it bothers me a lot." For the logistical models, the scores from the HIV symptom index were then split into 2 categories: "not bothersome" for scores 0 and 1, and "bothersome" for scores 2, 3, and 4.

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					Wohl et al. (2018) showed that in general a greater percentage of patients receiving DTG/ABC/3TC reported these symptoms as bothersome compared to those receiving B/F/TAF. Most differences were not statistically significant. But where there were statistically significant differences, these were in the favour of the B/F/TAF group (with the exception of hair loss/changes). For the treatment naïve population, statistically significant differences in favour of B/F/TAF were found at 2 or more time points ($p<0.05$) in the adjusted logistic regression model in the following domains: fatigue/loss of energy, dizziness/light headedness, nausea/vomiting, and difficulty sleeping. In the longitudinal models, there were statistically significant differences in the fatigue and nausea/vomiting domains with fewer reports in B/F/TAF group. For the HIV-1 suppressed population, significant differences in favour of B/F/TAF were found at 2 or more time points in the adjusted logistic regression model, as well as in the longitudinal models in the following domains: nausea/vomiting, sad/down/depressed, nervous/anxious, and difficulty sleeping (from the Pittsburgh Sleep Quality Index). A statistically significant difference in favour of DTG/ABC/3TC was found at 4 weeks in both logistic models for hair loss for this patient group.

Outcome measure	Study	Critical appraisal score	Applicability to decision problem	Grade of evidence	Interpretation of evidence
					A statistically significant time by treatment interaction in the longitudinal model was found for headaches, bloating, and changes in body composition. The limitations of study relate to the population included which was mostly male and white, therefore may not be generalisable to other populations. The study population was also considered to be relatively healthy for this disease group. The limitations of patient reported outcomes as opposed to investigator-reported symptoms such as a lack of standardisation of grading is also a concern. These results suggest that over approximately 1 year of follow-up after starting or switching antiretroviral treatment to B/F/TAF, some statistically significant improvements in HIV symptoms were evident, compared to those receiving ABC/DTG/3TC. These differed between the treatment naïve and suppressed population and according to modelling technique used.

Relevance to guidelines and NHS England policies

NICE have not issued any guidelines or policies on the treatment of HIV-1 in adults.

The following NHS England policies have published regarding HIV-1:

- Clinical Commissioning Policy: Dolutegravir for treatment of HIV-1 in adults and adolescents. January 2015 [updated August 2018]. NHS England Reference B06/P/a.
- Clinical Commissioning Policy: Elvitegravir /cobicistat /emtricitabine /tenofovir for treatment of HIV in adults. July 2015. NHS England Reference F03/P/a
- Clinical Commissioning Policy: Tenofovir Alafenamide for treatment of HIV 1 in adults and adolescents. July 2016 [updated February 2017]. NHS England Reference 16043/P.
- Clinical Commissioning Policy: Use of cobicistat as a booster in treatment of HIV positive adults and adolescents. July 2015. NHS England Reference F03/P/b.

References

Public Health England. United Kingdom National HIV Surveillance Data Tables. 2017.

Waters L, Ahmed N, Angus B et al (2015) BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy (2016 interim update). http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf.

NICE (2015) Clinical guidance CG182. Chronic kidney disease in adults: assessment and management (last updated Jan 2015). https://www.nice.org.uk/guidance/cg182

NICE (2012) Clinical guideline CG146. Osteoporosis: assessing the risk of fragility fracture. August 2012. https://www.nice.org.uk/guidance/cg146/chapter/1-Guidance

NOGG (2014) National osteoporosis guideline group: Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK (updated March 2014). https://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf

NOGG (2016) National osteoporosis guideline group: Osteoporosis – clinical guidelines for prevention and treatment. Updated Jan 2016. https://www.guidelines.co.uk/nogg/osteoporosis

Included studies

Bagkeris E, Burgess L, Mallon PW, Post FA, Boffito M, Sachikonye M, Anderson J, Asboe D, Garvey L, Vera J, Williams I, Johnson M, Babalis D, De Francesco D, Winston A, and Sabin CA (2018) Cohort profile: The Pharmacokinetic and clinical Observations in PeoPle over fiftY (POPPY) study. International Journal of Epidemiology 47(5):1391-1392e

Daar E, DeJesus E, Ruane P et al. (2018) Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed HIV-1 infected adults: a randomised, open-label, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV 5(7):e347-e356

Gallant J, Lazzarin A, Mills A et al. (2017) Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. The Lancet 390(10107): 2063-2072

Molina JM, Ward D, Brar I et al. (2018) Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed HIV-1 infected adults: a randomised, double-blinded, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV 5(7):e357-e365

Sax P, Pozniak A, Montes M L et al. (2017) Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. The Lancet. 390(10107):2073-2082

Sax P, DeJesus E, Crofoot G et al. (2017) Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial. Lancet HIV 4(4):e154-e160

Wohl D, Clarke A, Maggiolo F et al. (2018) Patient‐Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double‐Blind, Phase III Non-inferiority Trials of Adults with HIV on Co‐formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co‐formulated Abacavir, Dolutegravir, and Lamivudine. Patient 11(5):561-573

Appendix 1: Search strategy

Database search strategies

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to March 27, 2018>
Search date: 28th March 2018
Number of results retrieved: 7
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to March 27, 2018>
---
1 (bictegravir and emtricitabine and tenofovir and alafenamide).tw. (7)
2 (BFTAF or "B F TAF" or "BF TAF" or B-F-T-A-F or BF T-A-F or "B-F T-A-F" or “B-F TAF”).tw. (0)
3 biktarvy.tw. (1)
4 or/1-3 (7)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 27, 2018>
Search date: 28th March 2018
Number of results retrieved: 3
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 27, 2018>
---
1 (bictegravir and emtricitabine and tenofovir and alafenamide).tw. (3)
2 (BFTAF or "B F TAF" or "BF TAF" or B-F-T-A-F or BF T-A-F or "B-F T-A-F" or “B-F TAF”).tw. (0)
3 biktarvy.tw. (1)
4 or/1-3 (3)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <March 27, 2018>
Search date: 28th March 2018
Number of results retrieved: 1
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <March 27, 2018>
---
1 (bictegravir and emtricitabine and tenofovir and alafenamide).tw. (1)

2 (BFTAF or "B F TAF" or "BF TAF" or B-F-T-A-F or BF T-A-F or "B-F T-A-F" or “B-F TAF”).tw. (0)
3 biktarvy.tw. (0)
4 or/1-3 (1)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update March 27, 2018
Search date: 28th March 2018
Number of results retrieved: 0
Search strategy

Same as Medline

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2018 Week 13>
Search date: 28th March 2018
Number of results retrieved: 15
Search strategy:

Database: Embase <1974 to 2018 Week 13>
---
1 (bictegravir and emtricitabine and tenofovir and alafenamide).tw. (11)
2 (BFTAF or "B F TAF" or "BF TAF" or B-F-T-A-F or BF T-A-F or "B-F T-A-F" or “B-F TAF”).tw. (0)
3 biktarvy.tw. (0)
4 bictegravir plus emtricitabine plus tenofovir alafenamide/ (7)
5 or/1-4 (15)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 0 hits
DARE – 0 hits 2 of 4, April 2015 (legacy database)
CENTRAL – 8 hits (Issue 2 of 12, February 2018)
HTA – 0 hits 4 of 4, October 2016 (legacy database)
NHS EED 0 hits – 2 of 4, April 2015 (legacy database)
Search date: 28th March 2018
Search strategy:

ID Search Hits
#1 bictegravir and emtricitabine and tenofovir and alafenamide:ti,ab,kw (Word variations have been searched) 8
#2 BFTAF or "B F TAF" or "BF TAF" or B-F-T-A-F or BF T-A-F or "B-F T-A-F" or "B-F TAF":ti,ab,kw (Word variations have been searched) 0

#3 biktarvy:ti,ab,kw (Word variations have been searched) 0
#4 #1 or #2 or #3 8

Trials registry search strategies

Clinicaltrials.gov

Search date: 28/03/2018
Number of results retrieved: 13
Search strategy and results page:

bictegravir AND hiv

Search date: 28/03/2018
Number of results retrieved: 21
Search strategy and results page:

B/F/TAF AND hiv

Clinicaltrialsregister.eu

Search date: 28/03/2018
Number of results retrieved: 2
Search strategy and results page:

bictegravir AND hiv

Search date: 28/03/2018
Number of results retrieved: 1
Search strategy and results page:

B/F/TAF AND hiv

Appendix 2: Study selection

The search strategy presented in Appendix 1 yielded 34 studies. Following de-duplication, 15 records were subsequently screened on titles and abstract in EPPI Reviewer according to the following inclusion/exclusion criteria.

Table 5: Sifting criteria

Sifting criteria	Inclusion	Exclusion
Population	Adults with HIV-1	
Intervention	B/F/TAF as a once daily fixed dose combination (FDC) single tablet regimen (STR).	
Comparator	• dolutegravir/emtricitabine/tenofovir alafenamide • raltegravir/emtricitabine/tenofovir alafenamide • emtricitabine/tenofovir alafenamide • rilpivirine/emtricitabine/tenofovir alafenamide • dolutegravir/abacavir/lamivudine • atazanavir/ritonavir/emtricitabine/tenofovir alafenamide • darunavir/ritonavir/emtricitabine/tenofovir alafenamide • elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide • elvitegravir/cobicistat/emtricitabine /tenofovir disproxil fumarate	
Outcomes	**Efficacy** • Percentage of patients with an undetectable HIV-1 viral load (<50 copies/ml) post naïve initiation and/or switch • Change in CD4 cell count from baseline • Change in HIV-1 RNA count from baseline **Adverse events** • Incidence and severity of adverse events • Discontinuations due to adverse events • Overall adverse events	

	Renal function • Percentage change from baseline in serum creatinine and estimated Glomerular Filtration Rate (eGFR) • Percentage change from baseline in urine retinol binding protein to creatinine ratio • Percentage change from baseline in urine β2-microglobulin to creatinine ratio • Percentage change from baseline in urine albumin to creatinine ratio **Bone density** • Percentage change from baseline in bone mineral density of the hip and lumbar spine **Other** • Medication adherence • Treatment-emergent resistance • The following outcomes are included as standard and will be considered where evidence allows: survival; progression free survival; health related quality of life (including mobility; self-care; usual activities; anxiety/depression); replacement of more toxic treatment; dependency on care giver/supporting independence; safety (including adverse effects); and delivery of intervention.	
Other		Abstracts Editorials Opinion pieces Commentaries Non-humans Healthy volunteers

Table 6: Studies excluded at full text.

Study reference	Reason for exclusion
Sax P E, DeJesus E, Ward D, Benson P, Wei X, White K, Martin H, Cheng A, Quirk E, and Antonucci S. Randomised trial of bictegravir or dolutegravir with FTC/TAF for initial HIV therapy. HIV Medicine: 2017;18 (Supplement 1),17	Conference Abstract

In addition to the study selection above the company submitted 2 recently published studies on treatment switching which are included in this evidence review.

Appendix 3: Evidence tables

Table 7: Daar et al (2018)

Study reference	Daar E, DeJesus E, Ruane P et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed HIV-1 infected adults: a randomised, open-label, multicentre, active-controlled, phase 3, non-inferiority trial. The Lancet. 2018; S2352-3018(18)30091-2 [Epub ahead of print]
Unique identifier	NCT02603107
Study type (and NSF-LTC study code)	Randomised, open label, multicentre, active-controlled, phase 3 non-inferiority trial (P1)
Aim of the study	To assess the efficacy and safety of switching to fixed-dose combination bictegravir, emtricitabine and tenofovir alafenamide to that of remaining on a boosted protease PI regimen in HIV-1 infected, virologically supressed adults.
Study dates	Dec 2015 and July 2016
Setting	Multicentre (n=121) in 10 countries – including the UK
Number of participants	577 virologically supressed HIV-1 infected adults were randomised (1:1) to switch to coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (n=290) or remain on their baseline boosted protease inhibitor regimen (n=287).
Population	HIV-1 infected adults (aged ≥18 years) who were virologically supressed for ≥6 months before screening
Inclusion criteria	Plasma HIV-1 RNA concentrations of 50 copies per mL or less, had an eGFR of ≥50 mL/min (Cockcroft–Gault equation), and had no documented resistance to emtricitabine, tenofovir, abacavir, or

	lamivudine. Participants with chronic hepatitis B infection (unless receiving a non-tenofovir disoproxil fumarate containing regimen) or chronic hepatitis C infection were permitted to enter the study.
Exclusion criteria	None reported
Intervention(s)	Fixed-dose combination of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg with matching placebo
Comparator(s)	
Length of follow-up	48 weeks
Outcomes	Primary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA ≥50 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 after imputation of missing-as-failure and missing-as-excluded values • participants with HIV-1RNA less than 20 copies per mL at week 48 • change in HIV-1 RNA and CD4 cell count from baseline to week 48.
	Secondary outcomes: • percentage changes from baseline in hip and lumbar spine at week 48 • bone mineral density at week 48, • change from baseline in serum creatinine and eGFR at week 48 • percentage changes from baseline in urine retinol binding protein to creatinine ratio at week 48 • urine β2-microglobulin to creatinine ratio at week 48 • urine albumin to creatinine ratio at week 48. • changes from baseline in fasting lipid parameters (total, LDL and HDL cholesterol; total cholesterol to HDL ratio; triglycerides). • numbers of participants who initiated treatment with lipid-modifying agents during the study.
	Safety outcomes: • Incidence and severity of adverse events • treatment-emergent resistance
Source of funding	Gilead Sciences

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Open label studies can be prone to biases
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data reported and analysed appropriately
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria, and the underrepresentation of female participants, reduce this.
Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 8: Gallant et al (2017)

Study reference	Gallant J, Lazzarin A, Mills A et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial
Unique identifier	NCT02607930
Study type (and NSF-LTC study code)	Double-blind, multicentre, active-controlled, randomised controlled non-inferiority trial (P1)
Aim of the study	To assess the efficacy and safety of bictegravir coformulated with emtricitabine and tenofovir alafenamide as a fixed-dose combination versus coformulated dolutegravir, abacavir, and lamivudine in the treatment of HIV-1

Study dates	Nov 2013 and July 2016
Setting	Multicentre (n=122) in 9 countries – including the UK
Number of participants	629 adults with HIV-1 viral infection previously untreated were randomised (1:1) to receive either coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (n=314) or coformulated dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg (n=315) with matching placebo.
Population	HIV-1 infected adults (aged ≥18 years) who were previously untreated
Inclusion criteria	Plasma HIV-1 RNA concentrations of 500 copies per mL or more, no hepatitis B virus infection, were HLA-B*5701-negative, had an eGFR of 50 mL/min or more (Cockcroft–Gault equation), and had no documented resistance to emtricitabine, tenofovir, abacavir, or lamivudine.
Exclusion criteria	None reported
Intervention(s)	Fixed-dose combination of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg with matching placebo
Comparator(s)	Fixed dose combination of dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg, with matching placebo
Length of follow-up	48 weeks
Outcomes	Primary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 • virological efficacy • baseline HIV-1 RNA • baseline CD4 cell count • geographical region • study medication adherence • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 after imputation of missing-as-failure and missing-as-excluded values • participants with HIV-1RNA less than 20 copies per mL at week 48 • change in HIV-1 RNA and CD4 cell count from baseline to week 48.
	Secondary outcomes: • percentage changes from baseline in hip and lumbar spine at week 48 • bone mineral density at week 48, • change from baseline in serum creatinine and eGFR at week 48 • percentage changes from baseline in urine retinol binding

	protein to creatinine ratio at week 48 • urine β2-microglobulin to creatinine ratio at week 48 • urine albumin to creatinine ratio at week 48.
	Safety outcomes: • Incidence and severity of adverse events • treatment-emergent resistance
Source of funding	Gilead Sciences

NSF-LTC

Criteria	**Score**	**Narrative description of study quality**
2. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data reported and analysed appropriately
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria, and the underrepresentation of female participants, reduce this.
Total	9/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 9: Molina et al (2018)

Study reference	Molina J-M, Ward D, Brar I et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed HIV-1 infected adults: a randomised, double-blinded, multicentre, active-controlled, phase 3, non-inferiority trial. The

	Lancet. 2018; S2352-3018(18)30092-4 [Epub ahead of print]
Unique identifier	NCT
Study type (and NSF-LTC study code)	Double-blind, multicentre, active-controlled, phase 3, randomised non-inferiority trial (P1)
Aim of the study	To evaluate the efficacy and safety of switching to fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide compared to that of remaining on dolutegravir, abacavir, and lamivudine in HIV-1-infected, virologically suppressed adults.
Study dates	Dec 2015 and July 2016
Setting	Multicentre (n=96) in 9 countries – including the UK
Number of participants	563 virologically supressed HIV-1 infected adults were randomised (1:1) to switch to coformulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (n=282) or remain on dolutegravir, abacavir, and lamivudine once daily for 48 weeks (n=281).
Population	HIV-1 infected adults (aged ≥18 years) who were virologically supressed for ≥3 months before screening.
Inclusion criteria	Plasma HIV-1 RNA concentrations of 50 copies per mL or less, had an eGFR of ≥50 mL/min (Cockcroft–Gault equation), and had no documented resistance to emtricitabine, tenofovir, abacavir, or lamivudine. Those with chronic hepatitis C infection were permitted to enter the study.
Exclusion criteria	Chronic hepatitis B infection (defined as positive hepatitis B surface antigen [HBsAg] and negative hepatitis B surface antibody [HBsAb], or positive HBcAb and negative HBsAb, regardless of HBV surface antigen status, at screening) were excluded
Intervention(s)	Fixed-dose combination of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg
Comparator(s)	Dolutegravir plus co-formulated abacavir, and lamivudine or the fixed-dose combination of dolutegravir, abacavir, and lamivudine
Length of follow-up	48 weeks
Outcomes	Primary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA ≥50 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 after imputation of missing-as-failure and missing-as-excluded values • participants with HIV-1RNA less than 20 copies per mL at week 48 • change in HIV-1 RNA and CD4 cell count from baseline to

	week 48.
	Secondary outcomes: • percentage changes from baseline in hip and lumbar spine at week 48 • bone mineral density at week 48, • change from baseline in serum creatinine and eGFR at week 48 • percentage changes from baseline in urine retinol binding protein to creatinine ratio at week 48 • urine β2-microglobulin to creatinine ratio at week 48 • urine albumin to creatinine ratio at week 48. • changes from baseline in fasting lipid parameters (total, LDL and HDL cholesterol; total cholesterol to HDL ratio; triglycerides). • numbers of participants who initiated treatment with lipid-modifying agents during the study.
	Safety outcomes: • Incidence and severity of adverse events • treatment-emergent resistance
Source of funding	Gilead Sciences

NSF-LTC

Criteria	**Score**	**Narrative description of study quality**
Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
Are the methods clearly described?	2/2	Clear and appropriate.
Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data reported and analysed appropriately
Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria, and the

		underrepresentation of female participants, reduce this.
Total	9/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 10: Sax et al. (2017)

Study reference	Sax P, Pozniak A, Montes M L et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial
Unique identifier	NCT02607956
Study type (and NSF-LTC study code)	Randomised, double-blind, multicentre, placebo-controlled, phase 3, non-inferiority trial (P1)
Aim of the study	To compare initial HIV-1 treatment with bictegravir coformulated with the NRTI combination emtricitabine and tenofovir alafenamide as a fixed-dose combination to dolutegravir administered with coformulated emtricitabine and tenofovir alafenamide.
Study dates	Nov 2015 to July 2016
Setting	Multicentre (n=126) in 10 countries– including the UK
Number of participants	645 adults with HIV-1 viral infection previously untreated were randomised (1:1) to receive either a fixed dose combination of bictegravir 50 mg with coformulated emtricitabine 200 mg, and tenofovir alafenamide 25 mg (n=320) or dolutegravir 50 mg, with coformulated emtricitabine 200 mg and tenofovir alafenamide 25 mg, with matching placebo (n=325)
Population	HIV-1 infected adults (aged ≥18 years) who were previously untreated
Inclusion criteria	Plasma HIV-1 RNA levels of at least 500 copies per mL, with estimated glomerular filtration rate (eGFR) of at least 30 mL per min (calculated by the Cockcroft–Gault equation), and with virological resistance testing showing sensitivity to emtricitabine and tenofovir. Participants with chronic hepatitis B virus or hepatitis C virus infection and previous antiretroviral use for pre-exposure or post-exposure HIV prophylaxis were permitted to enter the study.
Exclusion criteria	None reported

Intervention(s)	Fixed-dose combination of bictegravir 50 mg with coformulated emtricitabine 200 mg, and tenofovir alafenamide 25 mg with matching placebo
Comparator(s)	Fixed dose combination of dolutegravir 50 mg, coformulated emtricitabine 200 mg and tenofovir alafenamide 25 mg with matching placebo
Length of follow-up	48 weeks
Outcomes	Primary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 when imputing missing data as failure (M = F) and missing as excluded (M = E)
	Secondary outcomes: • virological efficacy by age (<50 vs ≥50 years), sex (male vs female), race (black vs non-black), baseline HIV-1 RNA (≤100 000 copies per mL vs >100 000 copies per mL), baseline CD4 count (<200 vs ≥200 cells per mL), geographical region (USA vs outside the USA), and study medication adherence (<95% vs ≥95%) • changes in log10 HIV-1 RNA and CD4 count from baseline • changes from baseline in fasting glucose • changes from baseline in lipid panels • changes from baseline in serum creatinine • changes from baseline in eGFR
	Safety outcomes: • Incidence and severity of adverse events • treatment-emergent resistance
Source of funding	Gilead Sciences

NSF-LTC

Criteria	**Score**	**Narrative description of study quality**
Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.

3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	2/2	Data reported and analysed appropriately
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria and the underrepresentation of female participants, reduce this.
Total	9/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Table 11: Sax et al. (2017)

Study reference	Sax P, DeJesus E, Crofoot G et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, phase 2 trial.
Unique identifier	NCT02397694
Study type (and NSF-LTC study code)	Randomised, double-blind, phase 2 trial (P1)
Aim of the study	To compare Bictegravir plus emtricitabine and tenofovir alafenamide and dolutegravir plus emtricitabine and tenofovir alafenamide
Study dates	March 2015 to May 2016*
Setting	22 outpatient centres in the USA
Number of participants	98 adults with HIV-1 viral infection previously untreated were randomised (2:1) to receive either 75 mg bictegravir (n=65) or 50 mg dolutegravir (n=33) with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide.
Population	HIV-1 infected adults (aged ≥18 years) who were previously untreated
Inclusion criteria	Plasma HIV-1 RNA loads of at least 1000 copies per mL, CD4 counts of at least 200 cells per µL, and had estimated glomerular filtration rates (creatinine clearance estimated with the Cockcroft-Gault method) of at least 70 mL per min at their screening visit.

	Patients who had screening HIV-1 genotypes showing sensitivity to emtricitabine and tenofovir.
Exclusion criteria	Hepatitis B co-infected or hepatitis C co-infected, had new AIDS-defining conditions within 30 days of screening, or were pregnant.
Intervention(s)	75 mg bictegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide. Note: emtricitabine 200 mg, and tenofovir alafenamide 25 mg were given as open label
Comparator(s)	50 mg dolutegravir with matching placebo plus the fixed-dose combination of 200 mg emtricitabine and 25 mg tenofovir alafenamide. Note: emtricitabine 200 mg, and tenofovir alafenamide 25 mg were given as open label
Length of follow-up	12, 24 and 48 weeks
Outcomes	Primary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 24
	Secondary outcomes: • proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at weeks 12 and 48 • participants with HIV-1RNA less than 20 copies per mL at week 48 • proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 when imputing missing data as failure (M = F)
	Safety outcomes: • safety and tolerability at 48 weeks
Source of funding	Gilead Sciences

NSF-LTC

Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.

4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Data reported and analysed appropriately but the study is underpowered.
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria, the giving of emtricitabine and tenofovir alafenamide as open label and the underrepresentation of female participants, reduce this.
Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

*Note : The publication states the 48 week trial dates as being March 23rd 2015 to May 21st 2015 – a reporting error has been assumed and thus amended to 2016

Table 12: Wohl et al. (2018)

Study reference	Wohl D, Clarke A, Maggiolo F et al. Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. https://doi.org/10.1007/s40271-018-0322-8
Unique identifier	N/A
Study type (and NSF-LTC study code)	Secondary analyses of previously reported data (2 double blind randomised studies, NCT02607930 and 02603120) using unadjusted and adjusted logistic regression models and generalised mixed model for longitudinal data (S2)
Aim of the study	To compare patient reported outcomes for fixed dose combination coformulated bictegravir, emtricitabine and tenofovir alafenamide versus coformulated dolutegravir, abacavir, and lamivudine in the treatment of HIV-1
Study dates	See Tables 8 and 9
Setting	See Tables 8 and 9
Number of participants	See Tables 8 and 9
Population	HIV-1 infected adults (aged ≥18 years) who were either previously untreated or virologically supressed

Inclusion criteria	See Tables 8 and 9
Exclusion criteria	See Tables 8 and 9
Intervention(s)	Fixed-dose combination of bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg
Comparator(s)	Fixed dose combination of dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg
Length of follow-up	4, 12, and 48 weeks
Outcomes	Primary outcome: • HIV symptom index (HIV-SI) 1. Fatigue/loss of energy 2. Fevers/chills/sweats 3. Dizzy/light-headedness 4. Pain/numbness/tingling in hands/feet 5. Trouble remembering 6. Nausea/vomiting 7. Diarrhoea/loose 8. Sad/down/depressed 9. Nervous/anxious 10. Difficulty sleeping 11. Skin problems/rash/itching 12. Coughing/trouble breathing 13. Headaches 14. Loss of appetite 15. Bloating/pain/gas in stomach 16. Muscle aches/joint pain 17. Problems with sex 18. Changes in body composition 19. Weight loss/wasting 20. Hair loss/changes
	Secondary outcomes: • Short Form (SF)-36 • Pittsburgh Sleep Quality Index (PSQI) • Work Productivity and Activity Impairment (WPAI)
Source of funding	Gilead Sciences

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	2/2	Clear and appropriate.
2. Is the research design appropriate for the aims and objectives of the research?	2/2	Clear and appropriate.
3. Are the methods clearly described?	2/2	Clear and appropriate.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	Data reported and analysed appropriately. A number of categorical variables (including the dependent variable, HIV-SI), were dichotomised in the analysis and others normalised.
5. Are the results generalisable?	1/2	Although the study population and indication appear generalisable, strict inclusion criteria, and the underrepresentation of female participants, reduce this.
Total	8/10	
Applicability	Directly applicable	The intervention and indication are directly relevant to the decision problem.

Appendix 4: Results tables

Table 13: Daar et al. (2018)

	B/F/TAF (n=290)	Boosted PI (n=287)	Difference (95%CI*)	P value
N=577				
Primary Outcomes (48 weeks)				
Proportion of patients with HIV-1 RNA <50 copies per ml	267 (92.1%)	255 (88.9%)	3.2% (-1.6 to 8.2)	0.20^
Proportion of patients with HIV-1 RNA	5 (1.7%)	5 (1.7%)	-0.0% (-2.5 to 2.5)	1.00

≥50 copies per ml				
HIV-1 RNA <50 copies per ml by missing-equals-failure analysis**	269/290 (92.8%)	261/287 (90.9%)	1.8% (-2.8 to 6.5)	0.45^
HIV-1 RNA <50 copies per ml by missing-equals-excluded analysis**	269/2272 (98.9%)	261/264 (98.9%)	0.0% (-2.2 to 2.4)	1.00^
HIV-1 RNA less than 20 copies per ml	249 (85.9%)	243 (84.7%)	1.2% (-4.7 to 7.1)	0.73^
Mean change in CD4 cell count	+25 per µl (SD ± 151.2)	+0 per µl (SD ± 159.4)	Not reported	0.068^
Secondary Outcomes (48 weeks)				
Mean % change in bone mineral density (hip)	Not reported	Not reported	Not reported	Not reported
Mean % change in bone mineral density (lumbar spine)	Not reported	Not reported	Not reported	Not reported
Change in urine albumin to creatinine ratio (mg/g) from baseline	0.0% (-34.4 to 59.6)	8.9% (-21.6 to 63.5)	Not reported	0.097*
Change in urine β2-microglubilin to creatinine ratio (µg/g) from baseline	-35.1% (-71.5 to -3.0)	24.4% (-22.0 to 146.5)	Not reported	<0.001*
Change in urine retinol binding protein to creatinine ratio (µg/g) from baseline	-14.0% (-50.6 to 23.9)	33.3% (-8.6 to 113.4)	Not reported	<0.001*
Change in Total cholesterol (mg/dL) from baseline	N=261 1 (-17, 20)	N=248 5 (-12,18)	Not reported	0.32
Change in Direct LDL	N=261 0 (-16, 15)	N=248 3 (-14, 18)	Not reported	0.47

(mg/dL) from baseline				
Change in Triglycerides (mg/dL) from baseline	N=260 -6 (-42, 22)	N=247 4 (-29, 38)	Not reported	0.002
Change in HDL (mg/dL) from baseline	N=261 3 (-3, 7)	N=247 1 (-4, 7)	Not reported	0.13
Change in Total cholesterol to HDL ratio from baseline	N=261 -0.2 (-0.6, 0.3)	N=247 0.0 (-0.5, 0.4)	Not reported	0.033
Safety – incidence of event (%)				
Any adverse event	233 (80%)	226 (79%)	Not reported	
Grade 3 or 4 adverse event	13 (4%)	18 (6%)	Not reported	
Serious adverse event	17 (6%)	20 (7%)	Not reported	
Drug-related adverse event	54 (19%)	6 (2%)	Not reported	
Drug-related serious adverse event	1 (<1%)	0	Not reported	
Any adverse event leading to study drug discontinuation	2 (1%)	1 (<1%)	Not reported	
Highest adverse events occurring with ≥5 incidence in either group were Headache (4 to 12%), Diarrhoea (6 to 8%) and Nasopharyngitis (7 to 12%)				

B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. Boosted PI=ritonavir or cobicistat-boosted atazanavir or darunavir plus either emtricitabine and tenofovir disoproxil fumarate or abacavir and lamivudine

^P-value for the superiority test comparing the percentages between treatment groups were from the Fisher exact test. The differences in percentages between treatment groups and their 95.002% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

* P values were from the 2 sided Wilcoxon rank sum test to compare the 2 treatment groups.

** P-value, difference in percentages, and 95% CI were based on a dichotomized response: HIV-1 RNA < 50 vs. HIV-1 RNA ≥ 50 copies/mL or missing for Missing = Failure analysis or vs. HIV 1 RNA ≥ 50 copies/mL for Missing = Excluded analysis. P-values were from the Fisher exact test to compare the 2 treatment groups. The difference in

percentage of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

Table 14: Gallant et al. (2017)

	B/F/TAF (n=314)	DTG/ABC/3TC (n=315)	Difference (95%CI*)	P value
N=629				
Primary Outcomes (48 weeks)				
Proportion of patients with HIV-1 RNA <50 copies per ml	290 (92.4%)	293 (93%)	-0.6% (-4.8 to 3.6)	0.78^
HIV-1 RNA <50 copies per ml by missing-equals-failure analysis	290/314 (92.4%)	294/315 (93.3%)	-0.9% (-5.1 to 3.2)	0.65^
HIV-1 RNA <50 copies per ml by missing-equals-excluded analysis	290/292 (99.3%)	294/301 (97.7%)	1.6% (-0.7 to 4.0)	0.10^
HIV-1 RNA less than 20 copies per ml	275 (87.6%)	275 (97.3%)	0.4% (-4.8 to 5.6)	0.87^
Mean change in CD4 cell count	+233 per µl (SD ± 185.2)	+229 per µl (SD ± 188.8)	Not reported	0.81^
Secondary Outcomes (48 weeks)				
Mean % change in bone mineral density (hip)	-0.78% (SD ± 2.22)	-1.02% (SD ± 2.31)	0.238% (-0.151 to 0.626)	0.23**
Mean % change in bone mineral density (lumbar spine)	-0.83% (SD ± 3.19)	-0.60% (SD ± 3.10)	-0.235% (-0.766 to 0.297)	0.39**
Study drug adherence (%) -subgroup analysis of participants reaching <50 HIV-RNA copies per ml				
< 95%	81%	86%	Not reported	0.65
≥ 95%	97%	96%	Not reported	0.66

Change in serum creatinine (mg/dL) from baseline	0.11 (0.03 to 0.17)	0.11 (0.03 to 0.18)	Not reported	0.78**
Change in eGFR (ml/min) from baseline***	-10.5 (19.5 to 0.2)	-10.8 (-21.6 to -2.4)	Not reported	0.20**
Change in urine albumin to creatinine ratio (mg/g) from baseline	0.6% (-32.0 to 48.9)	6.2% (-23.6 to 57.7)	Not reported	0.11**
Change in urine β2-microglubilin to creatinine ratio (µg/g) from baseline	-23.0% (-57.2 to 19.8)	-18.1% (-54.2 to 17.4)	Not reported	0.40**
Change in urine retinol binding protein to creatinine ratio (µg/g) from baseline	13.6% (-20.9 to 63.6)	19.9% (-16.0 to 58.9)	Not reported	0.34**
Safety – incidence of event (%)				
Any adverse event	265 (84%)	283 (90%)	Not reported	
Grade 3 or 4 adverse event	23 (7%)	24 (8%)	Not reported	
Serious adverse event	19 (6%)	25 (8%)	Not reported	
Drug-related adverse event	82 (f)	127 (40%)	Not reported	
Drug-related serious adverse event	1 (<1%)	1 (<1%)	Not reported	
Any adverse event leading to study drug discontinuation	0	4 (1%)	Not reported	
Highest adverse events occurring with ≥5 incidence in either group were Nausea (10 to 23%), Diarrhoea (13%) and Headache (11 to 14%)				

B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine.

* Difference (95·002% CI for snapshot analysis, 95% CI for missing-equals-failure and missing-equals-excluded analyses) based on Mantel–Haenszel proportions adjusted by baseline HIV-1 RNA (≤100 000 vs >100 000 copies per mL) and region (USA vs ex-USA). ^ p value based on the Cochran–Mantel–Haenszel test, stratified by baseline HIV-1 RNA (≤100 000 vs >100 000 copies per mL) and region (USA vs ex-USA).

Data are median (IQR), unless otherwise specified. eGFR=estimated glomerular filtration rate. **p values for B/F/TAF versus DTG/ABC/3TC from two-sided Wilcoxon rank-sum tests. ***Calculated with the Cockcroft–Gault formula.

For adherence, only subjects who returned at least 1 bottle and had calculable drug adherence were included in the percentage and p-value calculations.

Table 15: Molina et al. (2018)

	B/F/TAF (n=282)	DTG/ABC/3TC (n=281)	Difference (95%CI*)	P value
N=563				
Primary Outcomes (48 weeks)				
Proportion of patients with HIV-1 RNA <50 copies per ml	264 (93.6%)	267 (95.0%)	-1.4% (-5.5 to 2.6)	0.59[*]
Proportion of patients with HIV-1 RNA ≥50 copies per ml	3 (1.1%)	1 (0.4%)	0.7% (-1.0 to 2.8)	0.62*
HIV-1 RNA <50 copies per ml by missing-equals-failure analysis	268/282 (95.0%)	268/281 (95.4%)	-0.3% (-4.1 to 3.4)	1.00[**]
HIV-1 RNA <50 copies per ml by missing-equals-excluded analysis	268/269 (99.6%)	268/268 (100.0%)	-0.4% (-2.1 to 1.1)	1.00[**]
HIV-1 RNA less than 20 copies per ml	254 (90.1%)	257 (91.5%)	-1.4% (-6.4 to 3.5)	0.66[*]
Mean change in CD4 cell count	-31 per µl (SD ± 181.3)	+4 per µl (SD ± 191.0)	-35 per µl (-67 to -3)	0.031
Mean change in CD4 cell count (post adjustment for baseline counts)	Not reported	Not reported	-21 per µl (-51 to 9)	0.18
Secondary Outcomes (48 weeks)				
Mean % change in bone mineral density (hip)	0.16	0.30	Not reported	0.47^
Mean % change in bone mineral density (lumbar spine)	0.69	0.42	Not reported	0.33^

Study drug adherence (%) -subgroup analysis of participants reaching <50 HIV-RNA copies per ml				
< 95%	93%	88%	Not reported	0.52
≥ 95%	94%	97%	Not reported	0.17
Change in urine albumin to creatinine ratio (mg/g) from baseline	14.3% (-21.6 to 62.9)	8.7% (-20.3 to 66.0)	Not reported	0.74
Change in urine β2-microglubilin to creatinine ratio (µg/g) from baseline	20.9% (-19.4 to 84.0)	16.5% (-33.6 to 95.9)	Not reported	0.53
Change in urine retinol binding protein to creatinine ratio (µg/g) from baseline	19.6% (-7.0 to 71.8)	29.1% (-5.6 to 75.1)	Not reported	0.31
Change in Total cholesterol (mg/dL) from baseline	N=264 0 (-17, 18)	N=259 2 (-17,18)	Not reported	0.77
Change in Direct LDL (mg/dL) from baseline	N=264 1 (-13, 18)	N=259 2 (-14, 14)	Not reported	0.42
Change in Triglycerides (mg/dL) from baseline	N=264 -5 (-34, 23)	N=259 3 (-23, 30)	Not reported	0.028
Change in HDL (mg/dL) from baseline	N=264 -1 (-6, 4)	N=259 0 (-4, 6)	Not reported	0.13
Change in Total cholesterol to HDL ratio from baseline	N=264 0.0 (-0.4, 0.4)	N=259 0.0 (-0.5, 0.4)	Not reported	0.56
Safety – incidence of event (%)				
Any adverse event	225 (80%)	225 (80%)	Not reported	
Grade 3 or 4 adverse event	16 (6%)	10 (4%)	Not reported	

Serious adverse event	15 (5%)	22 (8%)	Not reported	
Drug-related adverse event	23 (8%)	44 (16%)	0.006	
Drug-related serious adverse event	1 (<1%)	0	Not reported	
Any adverse event leading to study drug discontinuation	6 (2%)	2 (1%)	Not reported	
Highest adverse event occurring with ≥1% incidence in either group were Headache (2 to 3%)				

B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine.

* P-value for the superiority test comparing the percentages between treatment groups were from the Fisher exact test. The differences in percentages between treatment groups and their 95.002% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

** P-value, difference in percentages, and 95% CI were based on a dichotomized response: HIV-1 RNA < 50 vs. HIV-1 RNA ≥ 50 copies/mL or missing for Missing = Failure analysis or vs. HIV 1 RNA ≥ 50 copies/mL for Missing = Excluded analysis. P-values were from the Fisher exact test to compare the 2 treatment groups. The difference in percentage of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on an unconditional exact method using 2 inverted 1-sided tests.

^ P-value were from the ANOVA model including treatment as a fixed effect

Table 16: Sax et al. (2017a)

	B/F/TAF (n=320)	**DTG/F/TAF (n=325)**	**Treatment difference (95% CI*)**	**P value**
N=645				
Primary Outcomes (48 weeks)				
Proportion of patients with HIV-1 RNA <50 copies per ml (Intention To Treat analysis)	286/320 (89.4%)	302/325 (92.9%)	-3.5% (-7.9 to 1.0)	0.12^
HIV-1 RNA <50 copies per ml (per-protocol analysis)	279/282 (99%)	296/297 (99.7%)	-0.7% (-2.6 to 1.2)	0.33^
HIV-1 RNA ≥50 copies per ml	14 (4%)	4 (1%)	Not reported	
HIV-1 RNA <50 copies per ml by missing-equals-failure analysis	288/291 (99.0%)	304/306 (99.3%)	-0.4% (-2.3 to 1.6)	0.63 ^

HIV-1 RNA <50 copies per ml by missing-equals-excluded analysis	288/320 (90.0%)	304/325 (93.5%)	-3.4% (-7.7 to 0.9)	0.12^
HIV-1 RNA less than 20 copies per ml	263/320 (82.2%)	283/325 (87.1%)	-3.9% (-9.4 to 1.5)	0.16^
Mean change in CD4 cell count	+180 per µl (SD ± 166.6)	+201 per µl (SD ± 166.4)	Not reported	0.10^
Secondary Outcomes (48 weeks)				
Study drug adherence (%) - subgroup analysis of participants reaching <50 HIV-RNA copies per ml				
< 95%	84%	90%	Not reported	0.35
≥ 95%	94%	94%	Not reported	1.00
	Median (Q1,Q3)	**Median (Q1,Q3)**		
Change in serum creatinine (mg/dL) from baseline	N=287 0.10 (0.03, 0.18)	N=304 0.11 (0.04, 0.19)	Not reported	0.096**
Change in eGFR (ml/min) from baseline***	N=286 -7.3 (-17.3, 0.1)	N=303 -10.8 (-20.0, -1.7)	Not reported	0.0181**
Change in Total cholesterol (mg/dL) from baseline	N=278 12 (-3, 30)	N=295 15 (1, 31)	Not reported	0.14**
Change in Direct LDL (mg/dL) from baseline	N=278 9 (-6, 25)	N=295 12 (-3, 25)	Not reported	0.21**
Change in Triglycerides (mg/dL) from baseline	N=278 3 (-21, 31)	N=295 7 (-14, 35)	Not reported	0.23**
Change in HDL (mg/dL) from baseline	N=278 5 (0, 11)	N=295 5 (-1, 12)	Not reported	0.68**
Change in Total cholesterol to	N=278 -0.1 (-0.5, 0.3)	N=295 -0.1 (-0.6, 0.4)	Not reported	0.70**

HDL ratio from baseline				
Change in Glucose (mg/dL) from baseline	N=287 2 (-4, 10)	N=304 4 (-3, 11)	Not reported	0.0435**
Safety – incidence of event (%)				
Any drug related adverse event	57 (18%)	83 (26%)	Not reported	
Any adverse event leading to study drug discontinuation	5 (2%)	1 (<1%)	Not reported	
Highest adverse events occurring with ≥5 incidence in either group were Headache (3 to 4%), Diarrhoea (3%) and Nausea (3 to 5%)				

B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/F/TAF=dolutegravir, emtricitabine, and tenofovir alafenamide.

* Difference (95·002% CI for snapshot analysis, 95% CI for missing-equals-failure and missing-equals-excluded analyses) based on Mantel–Haenszel proportions adjusted by baseline HIV-1 RNA (≤100 000 vs >100 000 copies per mL) and region (USA vs ex-USA). ^ p value based on the Cochran–Mantel–Haenszel test, stratified by baseline HIV-1 RNA (≤100 000 vs >100 000 copies per mL) and region (USA vs ex-USA).

Data are median (IQR), unless otherwise specified. eGFR=estimated glomerular filtration rate. **p values for B/F/TAF versus DTG/ABC/3TC from two-sided Wilcoxon rank-sum tests. ***Calculated with the Cockcroft–Gault formula.

All sensitivity analyses were prespecified except the posthoc modified snapshot analysis, which excluded 7 patients with no post baseline HIV-1 RNA results.

Per-protocol analysis excluded patients in full analysis set who were off study drug at Week 48 or had low adherence, ie, adherence ≤2.5th percentile among those in study

M=F and M=E analyses included patients who discontinued study drug, but remained in study, including those treated with other antiretrovirals

For adherence, only subjects who returned at least 1 bottle and had calculable drug adherence were included in the percentage and p-value calculations.

Table 17: Sax et al. (2017b)

	B/F/TAF (n=65)	**DTG/F/TAF (n=33)**	**Treatment difference (95% CI*)**	**P value**
N=98				
Primary Outcomes (24 weeks)				
Proportion of patients with HIV-1 RNA <50 copies per ml of plasma	97%	94%	2.9% (-8.5 to 14.2)	0.5
Secondary Outcomes (12 weeks)				
HIV-1 RNA <50 copies per ml	93.8%	93.9%	-1.3% (-12.9 to 10.2)	0.79

Secondary Outcomes (48 weeks)				
HIV-1 RNA <50 copies per ml	97%	91%	6.4% (-6.0 to 18.8)	0.17
HIV-1 RNA <50 copies per ml by missing-equals-failure analysis	96.9%	93.9%	Not reported	0.43
HIV-1 RNA less than 20 copies per ml	50/65 (90.8%)	29/33 (87.9%)	2.8% (-11.9 to 17.5)	0.67
Mean change in CD4 cell count	+258 per µl (SD ± 221.7)	+192 per µl (SD ± 242.0)	[difference in least squares mean] 72 cells per µl (-30 to 174)	0.16
Median adherence to treatment	97% (IQR 94-99)	96% (IQR 90-99)	Not reported	
Safety – (48 weeks) incidence of event (%)				
Any adverse event	55 (85%)	22 (67%)	Not reported	
Any adverse event or death leading to study drug discontinuation	1 (2%)	0	Not reported	
Highest adverse events occurring with ≥5 incidence in either group were Diarrhoea (12%), Nausea (8 to 12%), Arthralgia (6%) and Fatigue (6%) No treatment related serious adverse events or deaths occurred				

B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/F/TAF=dolutegravir, emtricitabine, and tenofovir alafenamide. *analysis of variance model. IQR = Interquartile range

Table 18: Wohl et al. (2018)

	4 weeks		12 weeks		48 weeks	
% reporting symptom	**B/F/TAF (n=311)**	**DTG/ABC/3TC (n=313)**	**B/F/TAF (n=307)**	**DTG/ABC/3TC (n=309)**	**B/F/TAF (n=293)**	**DTG/ABC/3TC (n=298)**
Treatment naïve population % figures are from unadjusted logistic regression model						
+ Fatigue/loss of energy	✓ **37.7**	**47.1**	✓ **33.6**	**41.7**	✓ **32.8**	**41.4**
Fevers/chills/sweats	20.4	18.7	14.0	15.5	15.4	14.8
Dizzy/ lightheaded	✓ 17.6	23.5	15.0	17.6	✓ **13.0**	**21.5**
Pain/ numbness/ tingling in hand/feet	14.7	16.8	16.4	17.5	19.1	19.6
Trouble remembering	20.1	19.0	23.8	20.4	20.8	21.5
+ Nausea/vomiting	✓ **13.7**	**23.9**	✓ **7.5**	**15.6**	9.6	12.4
Diarrhoea/ loose bowels	20.8	21.3	15.6	18.8	11.6	14.8
Sad/ down/ depressed	31.9	35.5	33.2	32.4	27.6	31.3
Nervous/ anxious	31.9	32.9	27.8	30.1	28.8	30.2
Difficulty sleeping	32.9	35.8	✓ **29.1**	**38.2**	✓ 29.4	36.2
Skin problems/ rash/ itching	21.7	25.8	19.5	22.3	20.8	22.1
Coughing/ trouble breathing	13.4	14.0	14.4	13.9	12.7	14.1
* Headaches	20.8	22.7	18.6	21.0	✓ **13.0**	**22.9**
+ Loss of appetite	13.4	16.6	✓ **10.5**	**18.1**	9.6	12.8
* Bloating/ pain/ gas in stomach	24.4	24.4	20.2	22.0	✓ **18.5**	**25.3**
Muscle aches/ joint pain	19.2	21.1	23.6	22.3	21.6	25.3
Problems with sex	18.6	17.2	18.0	16.2	17.5	18.9
* Changes in body composition	14.7	12.3	17.4	15.2	19.5	22.9
Weight loss/ wasting	9.6	9.4	✓ 7.2	11.4	11.6	11.4
Hair loss/ changes	6.7	9.4	6.9	8.4	5.5	8.8
PSQI			#			

HIV-1 supressed population % figures are from unadjusted logistic regression model						
	4 weeks		**12 weeks**		**48 weeks**	
% reporting symptom	**B/F/TAF (n=281)**	**DTG/ABC/3TC (n=280)**	**B/F/TAF (n=278)**	**DTG/ABC/3TC (n=278)**	**B/F/TAF (n=266)**	**DTG/ABC/ 3TC (n=266)**
Fatigue/loss of energy	✓ 30.7	35.7	35.7	36.5	34.6	38.3
Fevers/chills/sweats	12.9	8.9	14.7	14.5	10.5	11.7
+ Dizzy/ lightheaded	✓ 10.0	13.9	14.4	16.2	12.0	14.3
Pain/ numbness/ tingling in hand/feet	17.8	20.4	20.3	23.2	✓ 21.9	25.9
Trouble remembering	21.1	16.4	22.3	25.0	24.4	23.3
+Nausea/ vomiting	6.4	7.5	✓ 4.0	7.9	✓ 4.5	8.6
Diarrhoea/ loose bowels	15.0	16.8	15.8	16.3	11.7	13.9
+ Sad/ down/ depressed	✓ 19.6	22.9	22.7	26.0	✓ **23.0**	**30.9**
+ Nervous/ anxious	✓ 17.9	20.7	✓ 20.1	25.1	✓ 23.4	28.6
+ Difficulty sleeping	32.7	33.9	✓ 31.3	38.8	32.0	35.3
Skin problems/ rash/ itching	14.6	14.6	17.7	20.3	22.6	21.5
Coughing/ trouble breathing	13.6	12.9	13.7	11.9	15.9	17.8
Headaches	17.9	17.6	17.3	18.3	18.1	16.7
+ Loss of appetite	6.8	8.6	✓ **5.4**	**10.9**	6.4	8.3
Bloating/ pain/ gas in stomach	20.8	24.4	✓ 17.3	21.9	19.3	19.4
Muscle aches/ joint pain	22.9	22.9	30.0	28.5	28.3	25.2
Problems with sex	16.5	14.0	18.1	20.9	20.4	21.6
Changes in body composition	19.6	18.6	22.7	22.7	28.7	22.0
Weight loss/ wasting	7.2	5.7	11.2	9.0	10.6	6.4
Hair loss/ changes	**7.5**	✗ **3.2**	4.3	6.5	9.4	9.1
+ PSQI	#		#			

Bold - Figures in **bold** show where there was a significant difference between B/F/TAF and DTG/ABC/3TC

(✓) indicates significant difference favouring the B/F/TAF group in the adjusted logistic regression model

(✗) indicates a statistically significant difference favouring the DTG/ABC/3TC group in the adjusted logistic regression model.

(+) next to the symptom denotes that there was a statistically significant difference favouring the B/F/TAF group in the longitudinal model.

(*) denotes that this symptom had a statistically significant time by treatment interaction in the longitudinal model.

(#) indicates that there was a statistically significant difference in PSQI in favour of the B/F/TAF group in the longitudinal model.

HIV-SI consists of 20 symptoms, each was modelled separately as the dependent variable

Baseline figures are not shown but these showed no significant differences between the two treatments with the exception of a statistically significant higher % of weight loss/ wasting in the B/F/TAF group.

The adjusted logistic regression model was adjusted for age, sex, race (white compared with non-white), baseline bothersome symptom count, VACS index score, medical history of serious mental illness (yes vs no), baseline SF-36 PCS, baseline SF-36 MCS, and years since HIV diagnosis (for the supressed group only).

The PSQI was an additional analysis where it was the dependent variable with baseline SF-36 and baseline PSQI as the covariates. A hat

Appendix 5: Grading of the evidence base

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

NSF-LTC scoring notes

1. Are the research questions/aims and design clearly stated?	Score 2 points if the research aims and design are both clearly described Score 1 point if either the research aim or research design is clearly described Score 0 points if neither are clearly described
2. Is the research design appropriate for the aims and objectives of the research?	Score 2 points if the research design (e.g. RCT, cohort, before and after) is appropriate to the objectives Score 1 point if the research design is not clearly described but it can be inferred and appears appropriate, or if it is partially appropriate Score 0 points if it is not appropriate or very unclear
3. Are the methods clearly described?	Score 2 points if the methods are described and appropriate. Consider randomisation methods, blinding methods, the methods for handling bias and confounding, and the methods for calculating sample size, where appropriate Score 1 point if the methods are not clearly described but they can be inferred and appear appropriate, or if they are partially appropriate Score 0 points if they are not appropriate or very unclear
4. Are the data adequate to support the authors' interpretations / conclusions?	Score 2 points if the data supports the conclusions and issues of bias, confounding and study power have been sufficiently accounted for (either in study methods or analysis) Score 1 point if the data partially supports the conclusions Score 0 points if the data do not support conclusions or very unclear

5. Are the results generalisable?	Score 2 points if the study results are fully generalisable to the UK setting Score 1 point if the study results are partially generalisable Score 0 points if the results are not generalisable or very unclear

Overall grading by outcome

For each key outcome, studies were grouped and the following NSF-LTC criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.
- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.