NHS England Evidence Review:

Fostemsavir for the treatment of HIV-1 infection

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of fostemsavir containing antiretroviral therapy (ART) regimens, for individuals with multi-drug resistant (MDR) human immunodeficiency virus 1 (HIV-1) infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART.

Fostemsavir is a prodrug of temsavir, which is a HIV-1 gp120-directed attachment inhibitor. Temsavir has a unique mechanism of action; it binds directly to the HIV viral envelope gp120 close to the CD4 binding site, locking gp120 into a closed state that prohibits the conformational change necessary for initial interaction between the virus and CD4 cell-surface receptors, thereby preventing attachment and subsequent entry into host T cells and other immune cells.

HIV attacks the immune system destroying CD4 positive (CD4+) T cells. The reduction of these cells leaves people living with HIV less able to fight off infections (immunosuppressed) and makes them susceptible to other diseases including cancers. If HIV is untreated, a high viral load (high level of virus) can be seen, meaning the HIV is not suppressed (under control). This can increase the chance that HIV is spread, as well as cause significant morbidity (poor health) and mortality (death) for the person living with HIV.

HIV is treated with ART started immediately after a diagnosis to limit viral replication. Current clinical management involves life-long ART, which stops the virus replicating in the body and destroying CD4+ T cells. There is no cure for HIV, but ART enables most people to live a long and healthy life with an undetectable viral load, which eliminates the risk of passing on the infection. ART is a combination of drugs (usually three) as a single active drug does not offer effective therapy. The choice of which ART combination is used is complex and individualised. ART requires a very high level of concordance (taking the required dose, ideally greater than 95% of the time) to avoid drug resistance and to control the virus.

In addition, the review Patient, Intervention, Comparator and Outcomes (PICO) document included the identification of possible subgroups of patients within the included studies who might benefit from treatment with fostemsavir more than others, as well as the criteria used by the included studies to confirm a diagnosis of HIV-1 infection.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of fostemsavir containing ART regimens, for individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy. The searches for evidence published since 1 January 2011 were conducted on 10 June 2021 and identified 144 references. The titles and abstracts were screened and seven full text papers were obtained and assessed for relevance.

One clinical trial was identified for inclusion; a multicentre, two-cohort, phase three clinical trial including a total of 371 patients (the BRIGHTE study reported in three publications: Ackerman et al 2021, Kozal et al 2020 and Lataillade et al 2020). The study included a non-randomised cohort of 99 adults who had no fully active, approved antiretroviral options remaining because of exhaustion[1] of at least four of six antiretroviral (ARV) classes, and a randomised cohort of 272 adults who had the option of receiving at least one fully active, approved antiretroviral drug in at least one but no more than two ARV classes. The BRIGHTE study was carried out at 108 international investigational sites across Africa, Asia-Pacific, Europe, North America, and South America.

In terms of clinical effectiveness:

- **Virological suppression (virologic response: HIV-1 RNA <40 copies/mL) (critical outcome)**. One multicentre, two-cohort, phase three clinical trial provided very low certainty evidence on the proportion (%) of patients who had a virological response at weeks 24, 48, 72 and 96. The proportion (%) of patients who had a virological response following additional treatment with fostemsavir increased in patients with one or two fully active ARVs remaining but remained comparable over time in patients with no remaining ARV options up to 96 weeks. No measures of statistical significance were reported.
- **Virological suppression (virologic failure: HIV-1 RNA ≥400 copies/mL) (critical outcome)**. The multicentre, two-cohort, phase three clinical trial provided very low certainty evidence that failure rates remained similar across different timepoints (up to 96 weeks) following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and patients with one or two fully active ARVs remaining. No measures of statistical significance were reported.
- **Reduction in viral load (change in HIV-1 RNA $\log_{10}$) (critical outcome)**. The randomised cohort in the multicentre, phase three clinical trial, comprising heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining, provided very low certainty evidence that there was a statistically significant reduction in viral load in patients receiving blinded fostemsavir compared to patients receiving blinded placebo at day 8 of treatment ($p<0.0001$)[2].
- **Mortality (critical outcome)**. One multicentre, two-cohort, phase three clinical trial provided very low certainty evidence for rates of mortality following additional treatment with fostemsavir in adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining up to 96 weeks. The three study publications reported different mortality rates, with the proportion of deaths in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options

[1] Exhaustion was defined as elimination of all agents within a given class as a fully active option because of resistance, previous side effects, contraindications, or unwillingness to use enfuvirtide (a twice daily injectable agent) (Kozal et al 2020).
[2] Different p-values were reported in the main text (Kozal 2020, pg. 1234) and supplementary appendix (Table S3, pg. 11) and the figure reported in this evidence review has been taken from the appendix.

ranging between15% and 17% and between 3% and 4% in patients with one or two fully active ARVs remaining.

- **Increase in baseline CD4+ T-cell count (cells/μL) (important outcome)**. One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that there were improvements in CD4+ T-cell counts following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining from baseline through to 48 weeks. No measures of statistical significance were reported.
- **Quality of life (important outcome)**. One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that there were positive changes (indicating benefit) in quality of life (QoL) measured by the overall Functional Assessment of HIV Infection (FAHI) score and the physical and emotional wellbeing domain scores following additional treatment with fostemsavir for both adults with MDR HIV-1 with one or two fully active ARVs remaining and those with no remaining ARV options at 96 weeks. No measures of statistical significance were reported. Negative changes were reported following additional treatment with fostemsavir in adults with no remaining ARV options and adults with one or two fully active ARVs remaining in the function or global wellbeing, social wellbeing, and cognitive function subscales for the FAHI. However, no statistical data or measures of statistical significance were reported for these subscales. QoL measured using EQ-5D-3L showed a positive improvement in adults with MDR HIV-1 with one or two fully active ARVs remaining at 96 weeks, but this was not reflected in adults with MDR HIV-1 with no remaining ARV options. However, no statistical data or measures of statistical significance were reported for these subscales.
- **Treatment failure (withdrawal due to lack of efficacy) (important outcome).** One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence for withdrawals due to lack of efficacy[3] following additional treatment with fostemsavir, that is, between 4% and 6% in both heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and those with one or two fully active ARVs remaining up to 96 weeks follow-up.
- **Treatment adherence (withdrawal due to non-adherence) (important outcome).** One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence for withdrawals due to treatment non-adherence following additional treatment with fostemsavir, that is, between 4% and 6% in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and those with one or two fully active ARVs remaining up to 96 weeks follow-up.

In terms of safety:

- **Adverse events**. One multicentre, two-cohort phase three clinical trial (BRIGHTE study provided very low certainty evidence that adverse event rates were similar during the 8-day double-blind period of the randomised cohort between the two treatment groups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (fostemsavir versus placebo; 43% and 35%, respectively). Overall, most patients in both cohorts (heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining) reported having at least one adverse event following additional treatment with fostemsavir up to 96 weeks follow-up. The most common adverse events were self-reported diarrhoea, nausea, and headache and were generally considered low grade. Higher rates of grade 3 or 4 adverse events and events leading to discontinuation

[3] Change in OBT due to lack of efficacy was classified as treatment failure (Ackerman et al 2021).

following additional treatment with fostemsavir were reported in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options compared to adults with MDR HIV-1 with one or two fully active ARVs remaining.

- **Serious adverse events**. One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that the rate of serious adverse events[4] following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options was48% up to 96 weeks and 34% in adults with MDR HIV-1 with one or two fully active ARVs remaining.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- The randomised cohort provided very low certainty evidence for outcomes in different groups of patients with MDR HIV-1 with one or two fully active ARVs remaining, reporting that the proportion (%) of patients who had a virological response to fostemsavir plus optimised background therapy (OBT) were similar for most pre-specified baseline characteristics up to week 96. Virologic response rates were lowest following additional treatment with fostemsavir in patients with baseline viral load of 100,000 copies/mL or more and patients with baseline CD4+ T-cell count less than 20 cells/µL at all timepoints (up to week 96). Improvements in CD4+ T-cell count following additional treatment with fostemsavir were also reported across all subgroups, including in the most immunosuppressed patients at baseline up to week 96. In terms of evidence for subgroups based on OBT susceptibility scores, the randomised cohort, comprising patients with MDR HIV-1 with one or two fully active ARVs remaining, showed an association between the proportion (%) of patients who had a virological response following additional treatment with fostemsavir and overall susceptibility score-new (OSS-new) at week 96, but no clear association with other susceptibility scores or number of fully active antiretrovirals (#FAA) according to study entry criteria.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

No comparative studies were identified which considered the clinical effectiveness or safety of the addition of fostemsavir to the ART regimen compared with standard care in individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy. The authors acknowledged the inability to include a comparator group beyond the initial 8 day analysis in the randomised cohort and the confounder of highly individualised OBT as limitations of the trial. However, the authors also highlighted that these limitations were unavoidable due to the complexities of patients with MDR HIV-1 who have limited treatment options. Factors relating to the design and conduct of the BRIGHTE study included in this review meant that it was at high risk of bias. Certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

The BRIGHTE study included information about study participants in terms of baseline demographic and clinical details, highlighting the diversity in all patients in relation to, for example, race and gender. Heavily treatment-experienced adults with MDR HIV-1 with no

[4] Serious adverse events did not include deaths and the authors reported that the majority of serious adverse events were associated with infections or complications associated with advanced AIDS (Kozal et al 2020).

remaining ARV options were older compared to patients with MDR HIV-1 with one or two fully active ARVs remaining.

The follow-up periods in the included study ranged from eight days in the randomised cohort for the blinded comparator period (fostemsavir versus placebo) up to 48 or 96 weeks for different outcomes. It was unclear whether patients in the randomised cohort met the inclusion criteria for this evidence review as the authors described treatment during the initial eight days as functional monotherapy, with patients receiving failing antiretroviral regimen rather than an optimised background regimen of other ART agents. Overall, the number of patients who discontinued from the study up to week 96 for reasons including, for example, adverse events, lack of efficacy and non-adherence included 22% of adults with MDR HIV-1 with one or two fully active ARVs remaining and 38% of adults with MDR HIV-1 with no remaining ARV options.

Measures of statistical significance were not reported for all outcomes, including changes in virological suppression, measures of QoL and safety outcomes. The scales used to assess QoL outcomes were self-report measures which may introduce bias. In addition, statistical data were not reported for all FAHI subscale scores, and measures of statistical significance were not reported. The BRIGHTE study did not comment on what Minimum Clinically Important Difference thresholds would be for any of the outcomes reported.

Conclusion:

The BRIGHTE study identified for this review provided very low certainty evidence suggesting that the addition of fostemsavir to the ART regimen in individuals with MDR HIV-1 infection with limited treatment options increases the proportion (%) of patients who have virological and immunological responses up to week 96 and may improve measures of QoL. There is little evidence for the clinical significance of many of these measures to patients. Most patients reported at least one adverse event following additional treatment with fostemsavir up to 96 weeks, with a greater proportion of patients with MDR HIV-1 with no remaining ARV options reporting grade 3 or 4 adverse events, serious adverse events, deaths, and adverse events leading to discontinuation compared to patients with MDR HIV-1 with one or two fully active ARVs remaining. The serious limitations of the BRIGHTE study reduces the reliability of conclusions about the treatment effects and the lack of comparative data (which the authors acknowledged and stated was unavoidable given the nature of the complexities of this patient cohort) means that it is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of addition of fostemsavir to the ART regimen compared with standard care.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In individuals with multi-drug resistant (MDR) HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy (ART), what is the clinical effectiveness of the addition of fostemsavir to the ART regimen compared with standard care?

2. In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy (ART), what is the safety of the addition of fostemsavir to the ART regimen compared with standard care?

3. In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy (ART), what is the cost effectiveness of the addition of fostemsavir to the ART regimen compared with standard care?

4. From the evidence selected, are there any subgroups of patients that may benefit from the addition of fostemsavir to the existing ART regimens more than the wider population of interest?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2019).

The searches for evidence were informed by the PICO document and were conducted on 10th June 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three papers reporting outcomes for patients with MDR HIV-1 infection with limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART were identified for inclusion (Ackerman et al 2021, Kozal et al 2020, Lataillade 2020). The three papers related to one multicentre, two-cohort, phase three clinical trial (the BRIGHTE study) including a total of 371 patients; 272 patients with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes and 99 patients with no fully active, approved antiretroviral options. Table 1 provides a summary of the included papers and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Ackerman et al 2021 Multicentre, 2-cohort, phase 3 clinical trial 108 sites in 23 countries on six continents	See Kozal 2020 Subgroups: outcomes reported on the basis of age, gender, race and geographic region, and by initial OBT:#FAA; OBT:OSS-new; OBT:S-GSS; OBT:GSS; OBT:PSS; OBT:OSS	**Intervention** See Kozal 2020 **Comparison** See Kozal 2020	**Critical outcomes** • Virological suppression: Virologic response (HIV-1 RNA <40 copies/mL) at 96 weeks • Mortality at 96 weeks **Important outcomes** • Increase in baseline CD4+ T-cell count, mean (cells/µL) at 96 weeks • Treatment failure: withdrawal due to lack of efficacy at 96 weeks • Treatment adherence: withdrawal due to non-adherence at 96 weeks
Kozal et al 2020 Multicentre, 2-cohort, phase 3 clinical trial 108 sites in 23 countries on six continents	N=371 adults with MDR HIV-1 infection Female/male: 10/89 (10%/90%) Median age at time of study: 50 years (range 17 to 72) History of AIDS diagnosis: 89 (90%) Haller index: 5.46 ± 8.26 Subgroups: outcomes reported on the basis of age, gender, race, and geographic region, and for patients with baseline HIV-1 RNA >1,000 copies/mL	**Intervention** Non-randomised cohort: open-label fostemsavir 600 mg twice daily plus OBT Randomised cohort: Day 1 to 8 Blinded fostemsavir 600 mg twice daily plus failing ART Day 8 to end of study: open-label fostemsavir 600 mg twice daily plus OBT **Comparison** No relevant comparator. Randomised cohort: Day 1 to 8 Blinded placebo twice daily plus failing ART	**Critical outcomes** • Virological suppression: Virologic response (HIV-1 RNA <40 copies/mL) at 24 and 48 weeks • Virological suppression: Virologic failure (HIV-1 RNA ≥400 copies/mL) at 48 weeks • Reduction in viral load (change in HIV-1 RNA $\log_{10}$) day 1 to 8 • Mortality at 48 weeks **Important outcomes** • Increase in baseline CD4+ T-cell count, mean (cells/µL) at 24, 36 and 48 weeks • Safety: Any adverse event; grade 2 to 4 adverse event; drug-

Study	Population	Intervention and comparison	Outcomes reported
			related grade 2 to 4 adverse event; grade 3 or 4 adverse event; adverse event leading to discontinuation at 48 weeks • Safety: Serious adverse event (not including death); CDC Class C AIDS-defining event; drug-related serious adverse event at 48 weeks
Lataillade et al 2020 Multicentre, 2-cohort, phase 3 clinical trial 108 sites in 23 countries on six continents	See Kozal 2020 Subgroups: outcomes reported for patients on the basis of gender, age, race, geographic region, and baseline viral load (copies/mL); baseline CD4+ T-cell count (copies per µL); and number of fully active antiretrovirals in initial OBT	**Intervention** See Kozal 2020 **Comparison** See Kozal 2020	**Critical outcomes** • Virological suppression: Virologic response (HIV-1 RNA <40 copies/mL) at 72 and 96 weeks • Virological suppression: Virologic failure (HIV-1 RNA ≥400 copies/mL) at 96 weeks • Mortality at 96 weeks **Important outcomes** • Increase in baseline CD4+ T-cell count, mean (cells/µL) at 96 weeks • Quality of life: FAHI score (total; physical wellbeing; emotional wellbeing) at 96 weeks • Safety: Any adverse event; drug-related grade 2 to 4 adverse event; adverse event leading to discontinuation at 96 weeks • Safety: Serious adverse event (not including death); CDC Class C AIDS-defining event; drug-related serious adverse event at 96 weeks

Abbreviations

AIDS – acquired immune deficiency syndrome, ART – antiretroviral therapy, CDC – Centres for Disease Control and Prevention, #FAA - fully active antiretrovirals, FAHI – functional assessment of HIV infection, GSS – genotypic susceptibility score, HIV – human immunodeficiency virus, OBT – optimised background therapy, OSS – overall susceptibility score, PSS – phenotypic susceptibility score, RNA – ribonucleic acid, S-GSS – standard genotypic susceptibility score

5. Results

In individuals with MDT HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART, what is the clinical effectiveness and safety of the addition of fostemsavir to the ART regimen compared with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Virological suppression:[5] virologic response (HIV-1 RNA <40 copies/mL) **Certainty of evidence:** Very low	This outcome is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. When virological suppression is achieved, an individual has negligible ability to transmit the virus to others and low risk of disease progression. If virological failure is seen, consideration is given to alter the current ART regimen to achieve viral suppression. Two papers reporting the multicentre, two-cohort, phase three clinical trial known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for the proportion (%) of patients who had a virological response following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Virologic response was defined as HIV-1 RNA <40 copies/mL and measured up to 96 weeks. In adults with no fully active, approved ARV options • Kozal et al 2020 (n=99) reported that following additional treatment with fostemsavir, 37% of patients had a virological response at week 24 and 38% at week 48. Of the 15 patients who received ibalizumab in their initial OBT, 8 (53%) had a virological response at weeks 24 and 48. No measures of statistical significance were reported. **(VERY LOW)** • Lataillade et al 2020 (n=99) reported that 35% of patients had a virological response following additional treatment with fostemsavir at week 72 and 37% at week 96. No measures of statistical significance were reported. **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=272) reported that, following additional treatment with fostemsavir, 53% of patients had a virological response at week 24 and 54% at week 48. Patients receiving fostemsavir in the initial blinded phase of the randomised cohort reported that 57% of patients had a virological response at week 48 compared to patients initially receiving placebo who reported that 45% of patients had a virological response at week 48. No measures of statistical significance were reported. **(VERY LOW)** • Lataillade et al 2020 (n=272) reported that 53% of patients had a virological response following additional treatment with fostemsavir at week 72 and 60% at week 96. No measures of statistical significance were reported. **(VERY LOW)**

[5] In the intention-to-treat (ITT) population (all patients who had received at least one dose of a trial regimen), virologic response rate was determined using the Food and Drug Administration Snapshot algorithm, whereby patients who had missing HIV-1 RNA values or who changed the composition of their OBT were classified as having had virologic failure.

Outcome	Evidence statement
	One multicentre, two-cohort phase three clinical trial (known as the BRIGHTE study) with 371 patients provided very low certainty evidence that the proportion (%) of patients who had a virological response increased over time (up to 96 weeks) following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (randomised cohort). The proportion (%) of patients who had a virological response following additional treatment with fostemsavir remained comparable at each timepoint in patients with no remaining ARV options (non-randomised cohort). No measures of statistical significance were reported for either cohort at any timepoint.
Virological suppression: virologic failure (HIV-1 RNA ≥400 copies/mL)[6] **Certainty of evidence:** Very low	This outcome is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. When virological suppression is achieved, an individual has negligible ability to transmit the virus to others and low risk of disease progression. If virological failure is seen, consideration is given to alter the current ART regimen to achieve viral suppression. Two papers reporting the multicentre, two-cohort, phase three clinical trial known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for virologic failure following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Virologic failure was defined as HIV-1 RNA ≥400 copies/mL or HIV-1 RNA level above the Nadir (i.e. ≥40 copies/mL) and measured up to 96 weeks. In adults with no fully active, approved ARV options • Kozal et al 2020 (n=99) reported virologic failure following additional treatment with fostemsavir in 46% patients when defined as HIV-1 RNA ≥400 copies/mL and 53% when defined as HIV-1 RNA ≥40 copies/mL at 48 weeks. No measures of statistical significance were reported. **(VERY LOW)** • Lataillade et al 2020 (n=99) reported virologic failure following additional treatment with fostemsavir in 49% patients when defined as HIV-1 RNA ≥400 copies/mL at 96 weeks. No measures of statistical significance were reported. **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=272) reported virologic failure following additional treatment with fostemsavir in 18% patients when defined as HIV-1 RNA ≥400 copies/mL and 38% when defined as HIV-1 RNA ≥40 copies/mL at 48 weeks. No measures of statistical significance were reported. **(VERY LOW)** • Lataillade et al 2020 (n=272) reported virologic failure following additional treatment with fostemsavir in 23% patients, when defined as HIV-1 RNA ≥400 copies/mL at 96 weeks. No measures of statistical significance were reported. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that virologic failure rates remained similar across different timepoints following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and patients with one or two**

[6] Before 24 weeks, virologic failure was defined as an HIV-1 RNA value of at least 400 copies/mL after previous confirmed suppression to <400 copies/mL or an increase of at least 1.0 $\log_{10}$ in the HIV-1 RNA level above the nadir (that is, ≥40 copies/mL). During or after 24 weeks, virologic failure was defined as an HIV-1RNA level of at least 400 copies/mL.

Outcome	Evidence statement
	fully active ARVs remaining. No measures of statistical significance were reported.
Reduction in viral load (*change in HIV-1 RNA log_{10})* **Certainty of evidence:** Very low	This outcome is important to patients as it reflects a measure of clinical effectiveness of the treatment. A reduction in viral load correlates with reducing the risk HIV transmission to others and a lower risk of disease progression. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020) provided evidence for the reduction in viral load following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=270)[7]. Reduction in viral load was defined as change in HIV-1 RNA log_{10} and measured from day 1 to 8. In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=270)[7] reported a mean[8] (SE) reduction from baseline to day 8 in HIV-1 RNA level of 0.79 (0.05) log_{10} copies/mL in the fostemsavir group and 0.17 (0.08) log_{10} copies/mL in the placebo group. This reflected a statistically significant benefit of fostemsavir compared with placebo (a between group difference of -0.63 log_{10} copies/mL [95% CI -0.81 to -0.44]; p<0.0001)[9]. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence from 201 patients with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes, that at day 8 of treatment there was a statistically significant reduction in viral load in patients receiving blinded fostemsavir compared to patients receiving blinded placebo.**
Mortality **Certainty of evidence:** Very low	Mortality is important to patients as individuals with advanced HIV have a high mortality rate due to progressive viral replication and advanced immunosuppression. Interventions which improve the survival outcome are important markers of effective HIV treatment. Three papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Ackerman et al 2021, Kozal et al 2020, Lataillade et al 2020) provided evidence for mortality rates following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Mortality was measured up to 96 weeks. In adults with no fully active, approved ARV options • Kozal et al 2020 (n=99) reported 14 (14%) deaths at week 48 following additional treatment with fostemsavir. **(VERY LOW)** • Lataillade et al 2020 (n=99) reported 17 (17%) deaths at week 96 following additional treatment with fostemsavir. **(VERY LOW)** • Ackerman et al 2021 (n=99) reported 15 (15%) deaths at week 96 following additional treatment with fostemsavir. **(VERY LOW)**

[7] Two patients (both from the fostemsavir treatment group) had missing Day 1 HIV-1 RNA values and were not included in the analysis.
[8] Mean adjusted by Day 1 log10 HIV-1 RNA.
[9] Different p-values were reported in the main text (Kozal 2020, pg. 1234) and supplementary appendix (Table S3, pg. 11) and the figure reported in this evidence review has been taken from the appendix.

Outcome	Evidence statement
	In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=272) reported 11 (4%) deaths at week 48 following additional treatment with fostemsavir. **(VERY LOW)** • Lataillade et al 2020 (n=272) reported 12 (4%) deaths at week 96 following additional treatment with fostemsavir. **(VERY LOW)** • Ackerman et al 2021 (n=272) reported 9 (3%) deaths at week 96 following additional treatment with fostemsavir. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence for rates of mortality following additional treatment with fostemsavir. However, there were unexplained discrepancies in rates of mortality reported at week 48 (Kozal et al 2020) and week 96 (Ackerman et al 2021), with more deaths reported at 48 weeks compared to 96 weeks. In addition, the two publications (Ackerman et al 2021, Lataillade et al 2020) reported different mortality rates at week 96. The authors did not provide explanations for the discrepancies in reported death rates at similar timepoints.**
Important outcomes	
Increase in baseline CD4+ cell counts (cells/mm^3) Certainty of evidence: Very low	Increase in CD4+ counts is important to patients as it reflects the overall immune function of a person living with HIV. The CD4+ measurements are critical in establishing thresholds for initiation and discontinuation of opportunistic infection prophylaxis. Increased CD4+ counts correlate with the reduced risk of disease progression and reduced rates of death. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020) provided evidence for CD4+ T-cell counts (cells/mm^3) following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). CD4+ T-cell counts were measured at 24, 36 and 48 weeks. In adults with no fully active, approved ARV options • Kozal et al 2020 (n=87) reported a mean CD4+ T-cell count of 41 cells/mm^3 at 24 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. **(VERY LOW)** • Kozal et al 2020 (n=83) reported a mean CD4+ T-cell count of 60 cells/mm^3 at 36 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. **(VERY LOW)** • Kozal et al 2020 (n=83) reported a mean CD4+ T-cell count of 64 cells/mm^3 at 48 weeks following additional treatment with fostemsavir. This reflected a mean increase over time of 63.5 cells/mm^3. No measures of statistical significance were reported. **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=247) reported a mean CD4+ T-cell count of 90 cells/mm^3 at 24 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. **(VERY LOW)** • Kozal et al 2020 (n=234) reported a mean CD4+ T-cell count of 110 cells/mm^3 at 36 weeks following additional treatment with fostemsavir. No measures of statistical significance were reported. **(VERY LOW)** • Kozal et al 2020 (n=228) reported a mean CD4+ T-cell count of 139 cells/mm^3 at 48 weeks following additional treatment with fostemsavir. This reflected a mean increase over time of 139 (SD 135) cells/mm^3. No measures of statistical significance were reported. **(VERY LOW)**

Outcome	Evidence statement
	One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that there were important improvements in CD4+ T-cell counts following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining from baseline through to 48 weeks. No measures of statistical significance were reported.
Quality of life Certainty of evidence: Very low	Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. One paper reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Lataillade et al 2020) provided evidence for quality of life following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Quality of life was measured using the FAHI score and EQ-5D-3L up to week 96. In adults with no fully active, approved ARV options • Lataillade et al 2020 reported a positive change following additional treatment with fostemsavir from baseline to week 96 in mean total score (4.9 [95% CI -1.8 to 11.5]) and in subscales for physical wellbeing (1.7 [95% CI -0.2 to 3.6]) and emotional wellbeing (1.6 [95% CI -0.6 to 3.8]). **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Lataillade et al 2020 reported a positive change following additional treatment with fostemsavir from baseline to week 96 in mean total score (5.3 [95% CI 2.0 to 8.5]) and in subscales for physical wellbeing (2.1 [95% CI 1.1 to 3.2]) and emotional wellbeing (3.0 [95% CI 1.9 to 4.1]). **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that there were positive changes (indicating benefit) in QoL following additional treatment with fostemsavir, measured by the overall FAHI score and the physical and emotional wellbeing scores at 96 weeks for both adults with MDR HIV-1 with one or two fully active ARVs remaining and adults with MDR HIV-1 with no remaining ARV options. No measures of statistical significance were reported. However, both cohorts reported little (or small negative) changes in the function or global wellbeing, social wellbeing, and cognitive function subscales for the FAHI. QoL measured using EQ-5D-3L showed a small positive improvement following additional treatment with fostemsavir in adults with MDR HIV-1 with one or two fully active ARVs remaining at 96 weeks, but this was not reflected in adults with MDR HIV-1 with no remaining ARV options. No statistical data or measures of statistical significance were reported for these subscales.**
Treatment failure Certainty of evidence: Very low	This outcome is important to patients as it reflects the effectiveness of the intervention. Clinical conditions occur in advanced HIV disease as a consequence of failure to achieve viral suppression and with advanced immunosuppression. These conditions are associated with significant patient morbidity and mortality. One paper reporting the multicentre, two-cohort, phase three clinical trial (Ackerman et al 2021) provided evidence for treatment failure following additional treatment with fostemsavir in heavily treatment-experienced adults

Outcome	Evidence statement
	with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Treatment failure was defined as withdrawal due to lack of treatment efficacy[10] and measured at 96 weeks. In adults with no fully active, approved ARV options • Ackerman et al 2021 (n=99) reported withdrawal due to lack of treatment efficacy in six patients at 96 weeks following additional treatment with fostemsavir. **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • The randomised cohort, including adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes (Ackerman et al 2021) (n=272) reported withdrawal due to lack of treatment efficacy in 12 patients at 96 weeks following additional treatment with fostemsavir. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that withdrawal due to lack of efficacy was low in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs remaining up to 96 weeks following additional treatment with fostemsavir.**
Treatment adherence Certainty of evidence: Very low	Adherence to treatment is an important to patients as it provides an indication of how the treatment is tolerated. Effective treatment requires long-term therapy with ART regimens to achieve viral suppression and immune regulation. If a treatment has adherence challenges it can increase the risk of treatment failure and add to viral resistant strain development and transmission. One paper reporting the multicentre, two-cohort, phase three clinical trial (Ackerman et al 2021) provided evidence for treatment adherence following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). Treatment adherence was defined in the study as withdrawal due to non-adherence and measured at 96 weeks. In adults with no fully active, approved ARV options • Ackerman et al 2021 (n=99) reported withdrawal due to treatment non-adherence in six (6%) patients at 96 weeks following additional treatment with fostemsavir. **(VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Ackerman et al 2021 (n=272) reported withdrawal due to treatment non-adherence in 11 (4%) patients at 96 weeks following additional treatment with fostemsavir. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence that rates of withdrawal due to treatment non-adherence were low (between 4% and 6%) in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and adults with MDR HIV-1 with one or two fully active ARVs**

[10] Change in OBT due to lack of efficacy was classified as treatment failure (Ackerman et al 2021).

Outcome	Evidence statement
	remaining up to 96 weeks following additional treatment with fostemsavir.
Safety	
Adverse events Certainty of evidence: Very low	Safety of fostemsavir is an important to patients as it allows comparison of interventional approaches. Two papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for safety outcomes following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). In adults with no fully active, approved ARV options • Kozal et al 2020 (n=99) reported that 97% of patients had had at least one **adverse event** at 48 weeks following additional treatment with fostemsavir (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache)**;** 85% were assessed as **grade 2 to 4 adverse events**; 22% as **drug-related grade 2 to 4 adverse events**; 47% as **grade 3 or 4 adverse events**; and 13% resulted in **discontinuation of trial drug**. **(VERY LOW)** • Lataillade et al 2020 (n=99) reported similar findings at week 96; 98% of patients had had at least one **adverse event** following additional treatment with fostemsavir (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache); 22% were assessed as **drug-related grade 2 to 4 adverse events;** and 12% resulted in **discontinuation of trial drug. (VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=247) reported that 43% of patients receiving blinded fostemsavir and 35% of patients receiving blinded placebo had had at least one adverse event up to day 8 (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache). **(VERY LOW)** • Kozal et al 2020 (n=247) reported that, following additional treatment with fostemsavir, 91% of patients had had at least one **adverse event** at week 48 (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache); 76% were assessed as **grade 2 to 4 adverse events**; 20% as **drug-related grade 2 to 4 adverse events**; 26% as **grade 3 or 4 adverse events**; and 5% resulted in **discontinuation of trial drug**. **(VERY LOW)** • Lataillade et al 2020 (n=272) also reported similar findings at 96 weeks follow-up; 92% of patients had had at least one **adverse event** (the most common being self-reported diarrhoea, nausea, upper respiratory tract infection and headache); 21% were assessed as **drug-related grade 2 to 4 adverse events**; and 5% resulted in **discontinuation of trial drug**. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence for safety. Adverse event rates were reported to be similar during the 8-day double-blind period of the randomised cohort between the two treatment groups (fostemsavir versus placebo; 43% and 35%, respectively). Overall, most patients in both cohorts reported having at least one adverse event up to 96 weeks follow-up. Higher rates of grade 3 or 4 adverse events and events leading to discontinuation were reported in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options**

Outcome	Evidence statement
	compared to adults with MDR HIV-1 with one or two fully active ARVs remaining.
Serious adverse events (not including death) Certainty of evidence: Very low	Safety of fostemsavir is an important to patients as it allows comparison of interventional approaches. Two papers reporting the multicentre, two-cohort, phase three clinical trial, known as the BRIGHTE study (Kozal et al 2020, Lataillade et al 2020) provided evidence for safety outcomes following additional treatment with fostemsavir in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options (non-randomised cohort: n=99), or with one or two fully active ARVs remaining (randomised to fostemsavir or placebo on days 1 to 8, followed by fostemsavir: n=272). In adults with no fully active, approved ARV options • Kozal et al 2020 (n=99) reported that 30% of patients had had at least one **serious adverse event** at 48 weeks following additional treatment with fostemsavir; 14% were assessed as **CDC Class C AIDS-defining events**; and 3% were assessed as **drug-related**. **(VERY LOW)** • Lataillade et al 2020 (n=99) reported that 48% of patients had had at least one **serious adverse event** at 96 weeks following additional treatment with fostemsavir; 15% were assessed as **CDC Class C AIDS-defining events;** and 3% were assessed as **drug-related. (VERY LOW)** In adults with the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes • Kozal et al 2020 (n=247) reported that 27% of patients had had at least one **serious adverse event** at 48 weeks following additional treatment with fostemsavir; 9% were assessed as **CDC Class C AIDS-defining events**; and 3% were assessed as **drug-related**. **(VERY LOW)** • Lataillade et al 2020 (n=272) reported that 34% of patients had had at least one **serious adverse event** at 96 weeks following additional treatment with fostemsavir; 8% were assessed as **CDC Class C AIDS-defining events**; and 3% were assessed as **drug-related**. **(VERY LOW)** **One multicentre, two-cohort phase three clinical trial (BRIGHTE study) provided very low certainty evidence for safety. Serious adverse events did not include deaths and the authors reported that the majority of serious adverse events were associated with infections or complications associated with advanced AIDS. Rates of serious adverse events following additional treatment with fostemsavir increased from 48 to 96 weeks in both cohort populations; from 27% to 34% respectively in heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options and from 30% to 48% respectively in adults with MDR HIV-1 with one or two fully active ARVs remaining.**

Abbreviations

AIDS – acquired immune deficiency syndrome, ART – antiretroviral therapy, ARV – antiretroviral, CDC – Centres for Disease Control and Prevention, CI – confidence interval, FAHI – functional assessment of HIV infection, HIV – human immunodeficiency virus, MDR – multidrug resistance, N/A – not applicable, OBT – optimised background therapy, RNA – ribonucleic acid, SD – standard deviation, SE – standard error, VAS – visual analogue scores.

In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing antiretroviral therapy, what is the cost effectiveness of the addition of fostemsavir to the ART regimen compared with current standard treatment?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from the addition of fostemsavir to the existing ART regimens more than the wider population of interest?

Outcome	Evidence statement
Subgroup – baseline characteristics **Certainty of evidence:** Very low	The randomised cohort in the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) reported outcomes for subgroups of patients with one or two fully active ARVs remaining (Kozal et al 2020) (n=272). At week 48: • The randomised cohort compared **virologic response (HIV-1 RNA <40 copies/mL)** following additional treatment with fostemsavir in pre-specified subgroups (Kozal et al 2020) (n=272). The proportion (%) of patients who had a virological response at week 48 were similar across most subgroups but were higher for patients aged 50 years or older (59%), females (61%), and patients self-reported as black race (65%); higher response rates were reported among patients who had one fully active antiretroviral drug in their initial OBT (56%). In contrast, patients who had a high baseline viral load (≥100,000 copies/mL) or a low baseline CD4+ T-cell count (<20 cells/mm^3) showed a reduced response rate (35% for both subgroups). No statistical measures were reported. **There was evidence that that the proportion (%) of patients who had a virological response varied for some pre-specified baseline characteristic subgroups. The randomised cohort reported higher rates in older patients, females, patients self-reported as black race, and patients who had one fully active ARV drug in their initial OBT. Reduced response rates were reported in patients who had a high baseline viral load (≥100,000 copies/mL) or a low baseline CD4+ T-cell count (<20 cells/mm^3).**
Subgroup – baseline viral load (copies/mL) **Certainty of evidence:** Very low	The randomised cohort in the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) reported outcomes for subgroups of patients with one or two fully active ARVs remaining (Lataillade et al 2020) (n=272). At week 96: • The randomised cohort compared **virologic response (HIV-1 RNA <40 copies/mL)** following additional treatment with fostemsavir in subgroups of patients by baseline viral load (copies/mL) (Lataillade et al 2020) (n=272). The lowest virological response rate was reported in patients with baseline viral loads of ≥100,000 copies/mL (49%). By comparison, the response rate in patients with baseline viral loads of <1,000 copies/mL was 74%. No statistical measures were reported. • **Virologic response rates** at week 96 were similar across most baseline subgroups, including between patients with one or two fully active antiretrovirals in their initial OBT.

Outcome	Evidence statement
	There was evidence that the proportion (%) of patients who had a virological response was similar for most pre-specified baseline characteristic subgroups. The randomised cohort reported lowest response rates in patients with baseline viral loads of ≥100,000 copies/mL.
Subgroup – baseline HIV-1 RNA >1,000 copies/mL **Certainty of evidence:** Very low	The randomised cohort in the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for **reduction in viral load** in heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Kozal et al 2020) (n=239). Reduction in viral load was defined as change in HIV-1 RNA log_{10} and measured from day 1 to 8. At day 8 in the randomised cohort: • The randomised cohort subgroup of patients with baseline HIV-1 RNA >1,000 copies/mL (Kozal et al 2020) (n=239) reported a **mean (SE) reduction from baseline to day 8 in HIV-1 RNA level** of 0.86 (0.05) log_{10} copies/mL in the fostemsavir group and 0.20 (0.09) log_{10} copies/mL in the placebo group. This reflected a between group difference of -0.66 log_{10} copies/mL [95% CI -0.87 to -0.46]; p=n/a. • There was no effect on between-group differences in the decrease in HIV-1 RNA level on the basis of age, gender, race, or geographic region. **There was evidence that reduction in viral load was similar between patients receiving fostemsavir or placebo up to 8 days for subgroups based on baseline characteristics, although a difference between treatment groups was reported between patients with baseline HIV-1 RNA >1,000 copies/mL.**
Subgroup – baseline characteristics and viral susceptibility and availability to initial OBT[11] [12] **Certainty of evidence:** Very low	The randomised cohort in the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for the **virologic response (HIV-1 RNA <40 copies/mL)** and **increases in CD4+ T-cell count** in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Ackerman et al 2021) (n=272). At week 96 in the randomised cohort: • Subgroup outcomes for **virologic response (HIV-1 RNA <40 copies/mL)** following additional treatment with fostemsavir in patients by initial OBT:OSS-new (Ackerman et al 2021) (n=272) showed that the lowest proportion (%) of patients who had virological response was in patients with an OSS-new score of 0 for their initial OBT (31% at 96 weeks) compared to patients with an OSS-new score of >2 (88% at 96 weeks). • There was no clear association between increased **virologic response** rate at week 96 and S-GSS, GSS, PSS, OSS or #FAA. • In the randomised cohort, increases in **CD4+ T-cell count** from baseline to week 96 following additional treatment with fostemsavir were generally similar across subgroups (Ackerman et al 2021) (n=213), with the exception of a greater mean increase among patients aged less than 35 years compared with those aged 35 to less

[11] For genotypic susceptibility scores (GSS), phenotypic susceptibility scores (PSS) and overall susceptibility scores (OSS), each ARV agent in the OBT was assigned a susceptibility rating based, respectively, on the genotypic susceptibility rating (GSR), phenotypic susceptibility rating (PSR) or net susceptibility rating (OSR) results from the Monogram assays (1.0 = full activity, 0.5 = partial activity, 0 = resistance) and the susceptibility ratings were summed. 'OSS-new' was a variation of OSS in which ARV agents previously used by the patient contributed an OSR of 0. Stanford GSS (SGSS) was determined using the Stanford University HIV Drug Resistance Database algorithm applied to sequence data from the Monogram genotypic assays (Ackerman et al 2021).

[12] Number of fully active ARVs according to study entry criteria (#FAA), including availability in terms of the patients' tolerance to, eligibility for, and willingness to take the FAA (Ackerman et al 2021).

Outcome	Evidence statement
	than 50 years [292 cells/μL; 95% CI 225 to 359 vs 166 cells/μL; 95% CI 133 to 199] and patients from Europe [306 cells/μL; 95% CI 219 to 392] compared with those from North America [147 cells/μL; 95% CI 112 to 182]. • Subgroup outcomes for **CD4+ T-cell count (cells/μL)** for patients by viral susceptibility to initial OBT (Ackerman et al 2021) (n=213) showed comparable outcomes for #FAA, S-GSS, GSS, PSS, OSS, and OSS-new. • Patients with **CD4+ T-cell count <20 cells/μL** at baseline had a mean increase of 240 cells/mm^3 to week 96. **There was evidence that the OSS-new score was associated with virologic response rates following additional treatment with fostemsavir, but there was no clear association between S-GSS, GSS, PSS, OSS or #FAA and virologic response rates. CD4+ T-cell counts were generally similar across subgroups, with the exception of age and geographical location, and CD4+ T-cell counts increased up to week 96 in patients with CD4+ T-cell count <20 cells/μL at baseline but no measures of statistical significance were reported.**
Subgroup – baseline CD4+ T-cell count (copies/μL) **Certainty of evidence:** Very low	The randomised cohort in the multicentre, two-cohort, phase three clinical trial (BRIGHTE study) provided evidence for the **increases in CD4+ T-cell count (cells/μL)** in subgroups of heavily treatment-experienced adults with MDR HIV-1 with one or two fully active ARVs remaining (Lataillade et al 2020) (n=213). At week 96 in the randomised cohort: • In the randomised cohort, increases in **CD4+ T-cell count (cells/μL)** from baseline to week 96, following additional treatment with fostemsavir, were generally similar across subgroups (Lataillade et al 2020) (n=213) including patients with <20 cells/μL at baseline. **There was evidence that CD4+ T-cell counts were generally similar across subgroups of patients by baseline CD4+ T-cell counts, with most patients maintaining or improving their CD4+ count category from baseline to week 96, following additional treatment with fostemsavir.**

Abbreviations

AIDS – acquired immune deficiency syndrome, ART – antiretroviral therapy, ARV – antiretroviral, CDC – Centres for Disease Control and Prevention, CI – confidence interval, #FAA - fully active antiretrovirals, FAHI – functional assessment of HIV infection, GSS – genotypic susceptibility score, HIV – human immunodeficiency virus, MDR – multidrug resistance, N/A – not applicable, OBT – optimised background therapy, OSS – overall susceptibility score, PSS – phenotypic susceptibility score, RNA – ribonucleic acid, SD – standard deviation, SE – standard error, S-GSS – standard genotypic susceptibility score.

6. Discussion

This review considered the evidence for the clinical effectiveness, safety and cost-effectiveness of fostemsavir in addition to the existing ART regimen compared with standard care, in individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART. The critical outcomes of interest were virological suppression, reduction in viral load, and mortality. The important outcomes of interest were increase in baseline CD4+ T-cell counts, QoL (as measured by, for example, EQ-5D-3L or FAHI), treatment failure, treatment adherence, and safety. Evidence was also sought on cost effectiveness.

Evidence was available from one multicentre, two-cohort phase three clinical trial including a total of 371 patients, known as the BRIGHTE study, which was reported in three publications (Ackerman et al 2021, Kozal et al 2020 and Lataillade et al 2020). No relevant comparative studies were identified. The study was at high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

The BRIGHTE study included a non-randomised cohort comprising adults who had no fully active, approved antiretroviral options remaining because of exhaustion[13] of at least four of six ARV classes (nucleoside reverse-transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, integrase inhibitors, protease inhibitors, CCR5 antagonists, and entry inhibitors). The BRIGHTE study also included a randomised cohort of adults who had the option of receiving at least one fully active, approved antiretroviral drug in at least one but no more than two antiretroviral classes. The study was carried out at 108 international investigational sites across Africa, Asia-Pacific, Europe, North America, and South America. Research conducted across different countries and cultures may reduce the generalisability of the findings to the NHS in England because of potential challenges associated with comparability or equivalence of the findings due to differences in, for example, healthcare systems and socio-economic status.

Demographic details were reported in the BRIGHTE study, including age, gender, geographical region and race, in addition to baseline clinical details including history of AIDS, duration of prior ART, number of prior ART regimens, HIV-1 RNA levels, and CD4+ T-cell counts (Ackerman et al 2021, Kozal et al 2020 and Lataillade et al 2020). The demographic and clinical information highlighted the diversity across all patients in terms of race and gender. In addition, adults with MDR HIV-1 with no remaining ARV options were older compared to adults with MDR HIV-1 with one or two fully active ARVs remaining.

Information on disease history for patients in the included cohorts indicated that most patients (86%) had a previous history of AIDS (85% in adults with MDR HIV-1 with one or two fully active ARVs remaining and 90% in adults with MDR HIV-1 with no remaining ARV options) and most patients had received five or more prior ART regimens (85% in total; 83% in adults with MDR HIV-1 with one or two fully active ARVs remaining and 91% in adults with MDR HIV-1 with no remaining ARV options). The duration of prior ART ranged from 10 years or less (12% in total; 15% in adults with MDR HIV-1 with one or two fully active ARVs remaining and 5% in adults with MDR HIV-1 with no remaining ARV options) to over 20 years (40% in total; 34% in adults with MDR HIV-1 with one or two fully active ARVs remaining and 59% in adults with MDR HIV-1 with no remaining ARV options).

[13] Exhaustion was defined as elimination of all agents within a given class as a fully active option in addition to fostemsavir because of resistance, previous side effects, contraindications, or unwillingness to use enfuvirtide (a twice daily injectable agent) (Kozal et al 2020).

To meet the PICO eligibility criteria, studies were required to compare fostemsavir in combination with an optimised background regimen of other ART agents versus optimised ART regimens which do not feature fostemsavir. The BRIGHTE study included a non-randomised cohort in which all patients with no remaining antiretroviral options received open-label fostemsavir plus OBT (i.e., there was no comparator treatment arm). In the randomised cohort, patients with the option of using at least one fully active, approved antiretroviral drug in at least one but no more than two antiretroviral classes, received fostemsavir or placebo in addition to their failing regimen for eight days. It was unclear from the study whether these patients met the inclusion criteria as the authors described the initial eight days treatment as functional monotherapy, with patients receiving failing antiretroviral regimen rather than an optimised background regimen of other ART agents, as stated in the PICO. The authors acknowledged the inability to include a comparator group beyond the primary analysis in the randomised cohort as a limitation of the trial. However, they also highlighted that this was unavoidable due to the complexities of patients with MDR HIV-1 who have limited treatment options.

The authors reported that the lack of standardised OBT reflects current practice (Kozal et al 2020) and the highly individualised background therapies required by this population (Lataillade et al 2020). In addition, patients with no remaining ARV options were permitted to enrol in other trials of antiretroviral drugs. As such, although 81% of patients had no fully active antiretroviral drug in their initial OBT, 19 patients had one fully active antiretroviral drug, including 15 patients who received investigational ibalizumab.

Follow-up periods in the BRIGHTE study ranged from day eight in the initial randomised cohort blinded period to 96 weeks in the non-randomised cohort and open-label phase of the randomised cohort (Ackerman et al 2021, Kozal et al 2020 and Lataillade et al 2020). Outcomes were analysed differently: the ITT-E population and safety population included all patients who received at least one dose of study treatment; virologic response rates were assessed using Snapshot analysis of the ITT-E population, with missing HIV-1 RNA or change in OBT due to lack of efficacy classified as treatment failure (Ackerman et al 2021).

The randomised cohort showed that the addition of fostemsavir to the ART regimen in individuals with MDR HIV-1 infection with limited treatment options had a statistically significantly greater decrease in the HIV-1 RNA level compared to placebo up to eight days of treatment with fostemsavir (Kozal et al 2020). Although p-values reported by Kozal et al (2020) were not consistent for the main publication ($p<0.001$) and supplementary appendix ($p<0.001$), the difference does not change the interpretation of the data for the outcome as both p-values are considered statistically significant. Efficacy was reported to have been maintained in adults who had the option of receiving one or two fully active ARVs between weeks 24 and 48 (Kozal et al 2020) and up to 96 weeks (Lataillade et al 2020). Progressive improvements with fostemsavir were also reported in the CD4+ T-cell count up to week 48 in adults who had the option of receiving one or two fully active ARVs , including patients with the greatest level of immunosuppression at baseline (Kozal et al 2020) and through to week 96 (Lataillade et al 2020).

The proportion (%) of patients who had virological and immunological responses increased or were maintained over time in adults who had no remaining ARV options and adults who had the option of receiving one or two fully active ARVs..

The BRIGHTE study reported patient-reported QoL measured by the FAHI score and EuroQoL visual analogue scale (EQ-5D-3L) (Lataillade et al 2020). Baseline QoL scores were low for all patients, although baseline FAHI scores were higher in patients who had the option of receiving one or two fully active ARVs (123, SD 29) compared to patients who had no remaining ARV options (114, SD 34), indicating a better QoL. Changes in FAHI

scores up to week 96 suggested improvements in overall QoL, measured by the FAHI total score, in patients who had the option of receiving one or two fully active ARVs and physical and emotional wellbeing subscales. Positive changes were also reported by patients who had no remaining ARV options, in terms of overall QoL and physical and emotional wellbeing subscales. However, no statistical data were reported for the subscale scores and measures of statistical significance were not presented. Furthermore, the open-label nature of the trial and the subjectivity of patient-reported outcomes reduces the reliability in interpretation of the findings.

The BRIGHTE study reported that most patients (in both cohorts) had experienced at least one adverse event up to 96 weeks, although few adverse events resulted in discontinuation of the trial drug. The most common adverse events were diarrhoea, nausea, and headache and were generally considered low grade. A greater proportion of patients who had no remaining ARV options reported grade three or four adverse events, serious adverse events, deaths, and adverse events leading to discontinuation compared with patients who had the option of receiving one or two fully active ARVs (Lataillade et al 2020). Overall, there was a high number of patients who discontinued from the study for reasons such as adverse events, lack of efficacy and non-adherence up to week 96; 22% of adults who had the option of receiving one or two fully active ARVs and 38% of adults who had no remaining ARV options. However, there were unexplained discrepancies in rates of mortality reported at week 48 (Kozal et al 2020) and week 96 (Ackerman et al 2021), with more deaths reported at 48 weeks compared to 96 weeks. In addition, the two publications (Ackerman et al 2021, Lataillade et al 2020) reported different mortality rates at week 96. There was an unexplained discrepancy in the rates of mortality reported in two publications (Ackerman et al 2021 and Lataillade et al 2020) which contributes to uncertainty about the results: 15 patients versus 17 patients, respectively, reported for adults who had no remaining ARV options and 9 patients versus 12 patients, respectively, reported for adults who had the option of receiving one or two fully active ARVs.

Regarding evidence for subgroups, the randomised cohort, comprising adults who had the option of receiving one or two fully active ARVs, reported that most pre-specified baseline characteristics did not affect virologic response to fostemsavir and OBT up to week 48, although higher rates were reported in older patients, females, patients self-reported as black race, and patients who had one fully active ARV drug in their initial OBT (Kozal et al 2020). At week 96, the randomised cohort, comprising adults who had the option of receiving one or two fully active ARVs, showed that virologic response rates were similar for most pre-specified baseline characteristic subgroups; response rates were lowest at all timepoints in patients with baseline viral load of 100,000 copies/mL or more and those with baseline CD4+ T-cell count less than 20 cells/µL (although confidence intervals were wide for most findings). Improvements in CD4+ T-cell count were also reported across all subgroups up to week 96, including in the most immunosuppressed patients at baseline (Ackerman et al 2021; Lataillade et al 2020). In terms of evidence for subgroups based on OBT susceptibility scores, the randomised cohort, comprising adults who had the option of receiving one or two fully active ARVs, showed an association between virologic response rates and OSS-new at week 96, but no clear association with GSS, S-GSS, PSS, OSS or #FAA. However, the authors note that these scores are limited as they are based on drug susceptibility analyses at trial screening. The scores therefore do not account for the possible presence of previous drug-resistant virus, which is pertinent to the BRIGHTE study as it includes patients with high levels of previous exposure to all antiretroviral classes (Ackerman et al 2021).

The BRIGHTE study did not comment on what Minimum Clinically Important Difference thresholds would be for any of the outcomes reported. The study provided demographic and clinical information about the patients, which highlighted the diversity across all

patients. The study administered open-label fostemsavir which may introduce bias in the interpretation of the findings, and patients with no remaining ARV options were permitted to receive investigational ibalizumab. Furthermore, outcomes were analysed differently: the ITT-E population and safety population included all patients who received at least one dose of study treatment; virologic response rates were assessed using Snapshot analysis of the ITT-E population, with missing HIV-1 RNA or change in OBT due to lack of efficacy classified as treatment failure (Ackerman et al 2021). The limitations, in addition to the small sample size and lack of relevant comparator, add potential biases due to risk of threat to internal validity and distorting results of the study and outcome assessment. However, it is acknowledged that such limitations (i.e. small sample size and the inability to include a comparator group) reflect the complexities of patients with MDR HIV-1 who have limited treatment options.

No evidence was identified on the cost-effectiveness of the addition of fostemsavir to the ART regimen.

7. Conclusion

This review includes one multicentre, two-cohort, phase three clinical study (known as the BRIGHTE study, reported in three publications) which provided very low certainty evidence for critical and important outcomes for the addition of fostemsavir to the ART regimen in individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART.

The BRIGHTE study included information about study participants in terms of baseline demographic and clinical details, highlighting the diversity in patients with MDR HIV-1 with no remaining ARV options and patients with MDR HIV-1 with one or two fully active ARVs remaining, including diversity in background regimens. The duration of prior ART ranged from 10 years or less in 12% of patients to over 20 years in 40% of patients.

In adults with MDR HIV-1 with one or two fully active ARVs remaining, there was evidence suggesting that the addition of fostemsavir to the ART regimen increased the proportion (%) of patients who had a virologic response between weeks 24 and 48, and improvements were reported in the CD4+ T-cell count through to week 48 in these patients. However, between 22% and 38% participants were lost to follow up (22% of adults with one or two fully active ARVs remaining and 38% of adults with no remaining ARV options.

In heavily treatment-experienced adults with MDR HIV-1 with no remaining ARV options, virological and immunological responses increased over time following treatment with fostemsavir. Evidence based on subgroups indicated that virologic response to fostemsavir and OBT were similar for most pre-specified baseline characteristics, and improvements in CD4+ T-cell count were reported across all subgroups up to week 96. The randomised cohort, comprising adults with one or two fully active ARVs remaining, provided evidence for subgroups based on OBT susceptibility scores, reporting an association between virologic response rates and overall susceptibility OSS-new at week 96, but no clear association with other OBT susceptibility scores or #FAA.

There was evidence of improvements in QoL scores assessed by patients with one or two fully active ARVs remaining, and changes were also reported by patients with no remaining ARV options, but the clinical significance of these findings is unclear.

Evidence for safety showed that most patients reported at least one adverse event up to 96 weeks, with a greater proportion of patients with no remaining ARV options reporting grade 3 or 4 adverse events, serious adverse events, deaths, and adverse events leading to discontinuation compared to patients with one or two fully active ARVs remaining.

The evidence from the BRIGHTE study must be regarded as very low certainty due to the design, conduct, and reporting. No relevant comparative studies were identified (as acknowledged by the authors who highlighted the inability to include a comparator group due to the nature of the complexities of the patient population) and there was no evidence for cost effectiveness.

The BRIGHTE study provides evidence to suggest that the addition of fostemsavir to the ART regimen in individuals with MDR HIV-1 infection with limited treatment options increases virological and immunological response rates up to week 96 and may improve measures of QoL. There is little evidence for the clinical significance of many of these measures to patients. Most patients reported experiencing at least one adverse event, although these were reported to be low grade, self-limiting, and did not interrupt study treatment. Given the limitations of the evidence and the complexities of this patient cohort, it

is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of the addition of fostemsavir to the ART regimen compared with standard care.

Appendix A PICO Document

The review questions for this evidence review are:

1. In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART, what is the clinical effectiveness of the addition of fostemsavir to the ART regimen compared with standard care?
2. In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART, what is the safety of the addition of fostemsavir to the ART regimen compared with standard care?
3. In individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART, what is the cost effectiveness of the addition of fostemsavir to the ART regimen compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from the addition of fostemsavir to the existing ART regimens more than the wider population of interest?

P –Population and Indication	People with MDR HIV-1 infection with limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART. Subgroups of interest: • Virally supressed (< 50 copies HIV RNA per mL) compared with virally unsuppressed (> 50 HIV RNA copies per mL individuals. • No remaining ART options available compared with 1-2 fully/partially virally suppressed ART options available. [**MDR HIV-1 infection**: treatment-experienced individuals with HIV-1 infection who have limited remaining approved and fully active antiretrovirals (ART) to form a viable ART regimen which induces viral suppression. This could be as a result of drug resistance (screening or historical resistance or both) *AND/OR* factors which affect the ability to use remaining ART regimens. This includes ART tolerability; ART availability; ART safety concerns or contraindications to remaining ART agents.] [**Limited treatment or no therapeutic options** defined as either: • No fully active antiretrovirals remaining **OR** • One or two fully or partially active antiretrovirals. Despite having one or more treatment options the viral load is not supressed on the existing therapy.] [**Suppressive viral regimen** defined as: • Virological suppression: Achieving and maintaining a HIV-1 RNA of < 50 copies per mL.] [The population might be described as having a “failing” ART regimen. This is a regimen which has not induced viral load suppression as described above.]
I – Intervention	Fostemsavir [Fostemsavir is used as an additional agent to other standard antiretrovirals. The usual dose of fostemsavir is 600mg twice per

	day, delivered orally. Fostemsavir is not used as a sole medication (monotherapy), it needs to be combined with an optimised background regimen of other ART agents.]
C – Comparator(s)	Optimised ART regimens which do not feature Fostemsavir [An "optimised" regimen is usually determined by the multi-disciplinary team (MDT). This the best combination of remaining ART options constructed from a standard ART regimen. It is expected to be highly individualised, with multiple included drug combinations used.]
O – Outcomes	**Clinical Effectiveness** Minimal Clinically Important Differences (MCIDs) are not known unless stated. *Critical to decision-making:* • Virological suppression *Virological suppression is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. When virological suppression is achieved, an individual has negligible ability to transmit the virus to others and low risk of disease progression. If virological failure is seen, consideration is given to alter the current ART regimen to achieve viral suppression.* Examples include but not limited to: ○ Number of patients achieving viral suppression (HIV RNA < 50 copies per mL). ○ Number of patients achieving another pre-defined threshold of viral suppression e.g. detecting low-level of viraemia. [Common definitions: **Virological failure**: Incomplete virological response after commencing treatment or evidence of confirmed virological rebound of a HIV-1 RNA ≥ 200 copies per mL[14] **OR** HIV viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test[2] **Incomplete virological response**: Two consecutive HIV RNA viral loads of > 200 copies per mL after 24 weeks without ever achieving a HIV viral load of < 50 copies per mL[15] **Virological rebound**: Failure to maintain a HIV RNA viral load below the limit of detection (ordinarily < 40-50 copies/mL) on two or more consecutive occasions[3] **Low-level viraemia**: A persistent HIV RNA viral load level of between 50-200 copies per mL[16] **Virological blip**: After viral suppression, a single HIV RNA viral load between 50-200 copies per mL followed by an undetectable result[3]] • Reduction in viral load *Reduction in viral load is important to patients as it reflects a measure of clinical effectiveness of the treatment. A reduction in*

[14] Department of Health and Human Sciences. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.
[15] World Health Organisation (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016. Available at: https://www.who.int/hiv/pub/arv/arv-2016/en/
[16] British HIV Association (BHIVA). 2016. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy.

	viral load correlates with reducing the risk HIV transmission to others and a lower risk of disease progression. Examples include but not limited to: o Mean change (or log change) in HIV-1 RNA from baseline [MCIDs: The minimal change in viral load considered to be statistically significant (2 standard deviations) is a three-fold change (equivalent to a 0.5 log_{10} copies/mL change)[17]] • Mortality *Mortality is important to patients as individuals with advanced HIV have a high mortality rate due to progressive viral replication and advanced immunosuppression. Interventions which improve the survival outcome are important markers of effective HIV treatment.* *Important to decision-making:* • Increase in baseline CD4 cell counts *Increase in CD4 counts is important to patients as it reflects the overall immune function of a person living with HIV. The CD4 measurements are critical in establishing thresholds for initiation and discontinuation of opportunistic infection prophylaxis. Increased CD4 counts correlate with the reduced risk of disease progression and reduced rates of death.* Examples include but not limited to: o Mean change in CD4 count from baseline. o Number of patients achieving treatment target CD4 threshold o Increase in the CD4/CD8 ratio. [MCIDs: A change of (2 standard deviations) between 2 tests is approximately a 30% change in the absolute count, or an increase or decrease in CD4 percentage by 3 percentage points[11]] [MCIDs: CD4/CD8 ratio has been identified as a marker of risk for both AIDS-related and non-AIDS-related morbidity and mortality, independent of CD4 cell count. A ratio of more than 0·45 has been associated with a two-fold decrease in risk of progression to severe non-AIDS-defining event or death compared with a ratio less than 0·30[18]] [Thresholds which define immunological failure: CD4 count at or below 250 cells/mm^3 following clinical failure[19] **OR** Persistent CD4 levels below 100 cells/mm^3[20] **OR** CD4 level falls to baseline or below[14]] • Quality of life

[17] Murray JS, Elashoff MR, Iacono-Connors LC, Cvetkovich TA, Struble KA. The use of plasma HIV RNA as a study endpoint in efficacy trials of antiretroviral drugs. AIDS 1999;13:797-804.
[18] Mussini C, Lorenzini P, Cozzi-Lepri A, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV 2015; 2: e98–106
[19] Clinical failure includes a list of conditions which occur with advanced or severe HIV disease associated with immunodeficiency. World Health Organisation (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016. Annex 10, page 386. Available at: https://www.who.int/hiv/pub/arv/arv-2016/en/
[20] World Health Organisation (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2016. Available at: https://www.who.int/hiv/pub/arv/arv-2016/en/

	Quality of life is important to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. [Examples include, but not limited to: o EQ visual analogue scale and the Functional Assessment of HIV Infection (FAHI) o EuroQoL 5-dimension 3-level instrument (EQ-5D-3L) o A generic health status measure including descriptive metrics o Interview methods]. • Treatment failure *Treatment failure is important to patients as it reflects the effectiveness of the intervention. Clinical conditions occur in advanced HIV disease as a consequence of failure to achieve viral suppression and with advanced immunosuppression. These conditions are associated with significant patient morbidity and mortality.* [Examples include but not limited to: o New or recurrent clinical event (s) indicating severe immunodeficiency (WHO clinical stage 4 condition)[21] after 6 months of effective treatment]. • Treatment adherence *Adherence to treatment is an important to patients as it provides an indication of how the treatment is tolerated. Effective treatment requires long-term therapy with ART regimens to achieve viral suppression and immune regulation. If a treatment has adherence challenges it can increase the risk of treatment failure and add to viral resistant strain development and transmission.* [Examples include but not limited to: o Missed doses (observed by research staff review of medication/returned medication) o Self-reported adherence measures (e.g. questionnaire methods) o Interview methods] **Safety** Safety of fostemsavir is an important to patients as it allows comparison of interventional approaches. [Examples include, but not limited to: o Frequency of adverse events o Frequency of serious adverse events o Adverse events leading to discontinuation o Grades 3–4 laboratory abnormalities] **Cost effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.

[21] WHO defined clinical conditions which occur with advanced or severe HIV disease associated with immunodeficiency. WHO Consolidated HIV guidelines. 2016. Annex 10, page 386.

Language	English only
Patients	Human studies only
Age	All ages
Date limits	2011-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, and pre-publication prints.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in the English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were excluded.

One search was conducted for fostemsavir for MDR resistant HIV-1 infection.

Search dates: 1 January 2011 to 10th June 2021

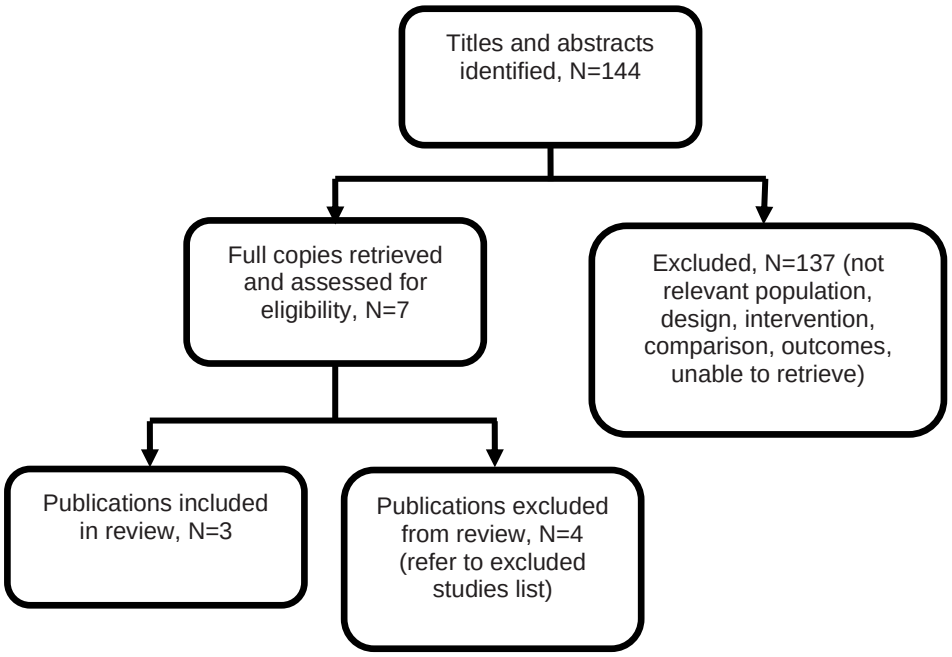
Medline search strategy:

# ▲	**Searches**
1	HIV-1/
2	exp HIV Infections/
3	(hiv or human immunodeficiency virus or human immune deficiency virus).ti,ab,kw.
4	1 or 2 or 3
5	(fostemsavir or rukobia).mp.
6	((gp120 or gp 120) adj3 inhibitor?).ti,ab,kw.
7	5 or 6
8	4 and 7
9	exp animals/ not humans/
10	8 not 9
11	limit 10 to (english language and yr="2011 -Current")

Appendix C Evidence selection

The combined literature searches for fostemsavir for MDR resistant HIV-1 infection identified 144 references. These were screened using their titles and abstracts and seven references relating to people with MDR HIV-1 infection with limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART were obtained in full text and assessed for relevance. Of these, three references are included in this evidence review. The 4 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Lataillade M, Lalezari JP, Kozal M, Aberg JA, Pialoux G, Cahn P, Thompson M, Molina JM, Moreno S, Grinsztejn B, Diaz RS, Castagna A, Kumar PN, Latiff GH, De Jesus E, Wang M, Chabria S, Gartland M, Pierce A, Ackerman P, Llamoso C. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV. 2020 Nov;7(11):e740-e751. doi: 10.1016/S2352-3018(20)30240-X	Included
Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina JM, Grinsztejn B, Diaz R, Castagna A, Kumar P, Latiff G, DeJesus E, Gummel M, Gartland M, Pierce A, Ackerman P, Llamoso C, Lataillade M; BRIGHTE Trial Team. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection N Engl J Med. 2020 Mar 26;382(13):1232-1243. doi: 10.1056/NEJMoa1902493	Included
Thompson M, Lalezari JP, Kaplan R, Pinedo Y, Pena OAS, Cahn P, Stock DA, Joshi SR, Hanna GJ, Lataillade M; AI438011 study team. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in antiretroviral-experienced patients: week 48 analysis of AI438011, a Phase IIb, randomized controlled trial. Antivir Ther. 2017;22(3):215-223. doi: 10.3851/IMP3112	Excluded Population do not meet the PICO criteria for multidrug-resistant HIV-1; treatment experienced (defined as current or previous exposure to ≥1 week of ≥1 antiretroviral drug).

Appendix D Excluded studies table

Study reference	Reason for exclusion
Hiryak K, Koren DE. Fostemsavir: A Novel Attachment Inhibitor for Patients with Multidrug-Resistant HIV-1 Infection. Annals of Pharmacotherapy. 2021;55(6):792-7.	Not a systematic review; no meta-analysis of results and studies not relevant based on all treatment arms including fostemsavir, or participants not multidrug-resistant.
Lalezari JP, Latiff GH, Brinson C, Echevarria J, Trevino-Perez S, Bogner JR, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug BMS-663068 in treatment-experienced individuals: 24 week results of AI438011, a phase 2b, randomised controlled trial. The Lancet HIV. 2015;2(10):e427-37.	Population do not meet the PICO criteria for multidrug-resistant HIV-1; treatment experienced (defined as current or previous exposure to ≥1 week of ≥1 antiretroviral drug). [Linked to Lataillade 2018 and Thompson 2017]
Lataillade M, Zhou N, Joshi SR, Lee S, Stock DA, Hanna GJ, et al. Viral Drug Resistance Through 48 Weeks, in a Phase 2b, Randomized, Controlled Trial of the HIV-1 Attachment Inhibitor Prodrug, Fostemsavir. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2018;77(3):299-307.	Population do not meet the PICO criteria for multidrug-resistant HIV-1; treatment experienced (defined as current or previous exposure to ≥1 week of ≥1 antiretroviral drug). [Linked to Lalezari 2015 and Thompson 2017]
Thompson M, Lalezari JP, Kaplan R, Pinedo Y, Pena OAS, Cahn P, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in antiretroviral-experienced patients: week 48 analysis of AI438011, a Phase IIb, randomized controlled trial. Antiviral Therapy. 2017;22(3):215-23.	Population do not meet the PICO criteria for multidrug-resistant HIV-1; treatment experienced (defined as current or previous exposure to ≥1 week of ≥1 antiretroviral drug). [Linked to Lalezari 2015 and Lataillade 2018]

Appendix E Evidence Table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Ackerman P, Thompson M, Molina JM, Aberg J, Cassetti I, Kozal M, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS. 2021;35(7):1061-72. **Study location** 108 sites in 23 countries on six continents **Study type** Multicentre, 2-cohort, phase 3 clinical trial **Study aim** To investigate how demographic and	**Study inclusion criteria** See Kozal 2020. **Study exclusion criteria** See Kozal 2020. **Total sample size** See Kozal 2020. **Baseline characteristics** See Kozal 2020.	**Intervention** See Kozal 2020 **Comparison** See Kozal 2020	Participants remaining in the study at week 96 data cut-off: randomised cohort[22]: 213/272 (78%) non-randomised cohort[23]: 61/99 (62%) **Critical outcomes** ***Virological suppression[24]*** ***Virologic response (HIV-1 RNA <40 copies/mL)[a]*** <u>Randomised cohort – subgroup outcomes for patients by initial OBT:OSS-new, n (%) [95% CI]</u> At week 96 (n=272): 0 (n=35): 11 (31) [19 to 48] >0 to 1 (n=105): 61 (58) [49 to 67] >1 to 2 (n=101): 69 (68) [59 to 77] >2 (n=17): 15 (88) [66 to 97] The authors reported that there was no clear association between virologic response rate at week 96 and S-GSS, GSS, PSS, OSS or #FAA. ***Mortality, n (% calculated)*** <u>Non-randomised cohort</u> At week 96 (n=99): 15 (15)	See Kozal 2020. **Other comments**: See Kozal 2020. [a] Subgroup outcomes (randomised cohort): Virologic response rates at week 96 were similar across subgroups for age, gender, race and geographic region. [b] Subgroup outcomes (randomised cohort): Increases in CD4+ T-cell count from baseline to week 96 were generally similar across subgroups with the exception of greater mean increased among patients aged less than 35 years compared with those aged 35 to less than 50 years [292

[22] Participants who had at least one remaining fully active antiretroviral drug in at least one but no more than two antiretroviral classes at baseline (with no protocol-defined requirement for inclusion of fully active antiretrovirals).
[23] Participants who had no remaining approved fully active antiretroviral drug available to use as ART.
[24] In the intention-to-treat (ITT) population (all patients who had received at least one dose of a trial regimen), virologic response rate was determined using the Food and Drug Administration Snapshot algorithm, whereby patients who had missing HIV-1 RNA values or who changed the composition of their OBT were classified as having had virologic failure.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
treatment-related factors impact responses to fostemsavir-based regimens in heavily treatment-experienced adults with HIV-1. **Study dates** Patients were enrolled between February 2015 to May 2016			Randomised cohort At week 96 (n=272): 9 (3) **Important outcomes** ***Increase in baseline CD4+ T-cell count, mean (cells/µL)[b]*** Randomised cohort – subgroup outcomes for patients by initial OBT:#FAA, n [95% CI] At week 96 (n=213): 1 (n=120): 206 [174 to 238] 2 (n=87): 195 [153 to 238] Randomised cohort – subgroup outcomes for patients by initial OBT:S-GSS, n [95% CI] At week 96 (n=213): >0 to 1 (n=34): 236 [178 to 293] >1 to 2 (n=121): 210 [173 to 248] >2 (n=55): 169 [125 to 213] Randomised cohort – subgroup outcomes for patients by initial OBT:GSS, n [95% CI] At week 96 (n=213): >0 to 1 (n=45): 224 [180 to 268] >1 to 2 (n=112): 215 [174 to 255] >2 (n=53): 165 [120 to 210] Randomised cohort – subgroup outcomes for patients by initial OBT:PSS, n [95% CI] At week 96 (n=213): >0 to 1 (n=7): 206 [157 to 254] >1 to 2 (n=99): 209 [170 to 248] >2 (n=93): 201 [159 to 242] Randomised cohort – subgroup outcomes for patients by initial OBT:OSS, n [95% CI]	cells/µL; 95% CI 225 to 359 vs 166 cells/µL; 95% CI 133 to 199] and patients from Europe [306 cells/µL; 95% CI 219 to 392] compared with those from North America [147 cells/µL; 95% CI 112 to 182]. Patients with CD4+ T-cell count <20 cells/µL at baseline had a mean increase of 240 cells/mm^3 to week 96. **Source of funding:** See Kozal 2020.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			At week 96 (n=213): >0 to 1 (n=22): 201 [155 to 247] >1 to 2 (n=100): 206 [167 to 245] >2 (n=82): 202 [157 to 248] <u>Randomised cohort – subgroup outcomes for patients by initial OBT:OSS-new, n [95% CI]</u> At week 96 (n=213): 0 (n=21): 142 [75 to 210] >0 to 1 (n=85): 219 [179 to 258] >1 to 2 (n=83): 192 [148 to 237] >2 (n=15): 270 [145 to 395] ***Treatment failure (withdrawal due to lack of efficacy), n*** <u>Non-randomised cohort</u> At week 96 (n=99): 6 <u>Randomised cohort</u> At week 96 (n=272): 12 ***Treatment non-adherence (withdrawal due to non-adherence), n*** <u>Non-randomised cohort</u> At week 96 (n=99): 6 <u>Randomised cohort</u> At 96 (n=272): 11	
Kozal M, Aberg J, Pialoux G, Cahn P, Thompson M, Molina	**Study inclusion criteria**	**Intervention**	Participants remaining in the trial at week 48 data cut-off: randomised cohort[29]: 15/272 (79%)	This study was appraised using the JBI checklist for

[29] Participants who had at least one remaining fully active antiretroviral drug in at least one but no more than two antiretroviral classes at baseline (with no protocol-defined requirement for inclusion of fully active antiretrovirals).

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
JM, et al. Fostemsavir in Adults with Multidrug-Resistant HIV-1 Infection. New England Journal of Medicine. 2020;382(13):1232-43. **Study location** 108 sites in 23 countries on six continents **Study type** Multicentre, 2-cohort, phase 3 clinical trial **Study aim** To investigate the efficacy of fostemsavir in patients with multidrug-resistant HIV-1 infection **Study dates**	Adults aged at least 18 years and undergone multiple treatments for HIV-1 infection. Failure of current antiretroviral regimen[25] and no viable antiretroviral combination therapy available because of exhaustion[26] of at least 4 of 6 antiretroviral classes[27] **Study exclusion criteria[28]** Patients with chronic untreated HBV (patients with chronic treated HBV were eligible); HIV-2 infection; ALT or AST > 7 x ULN; Alkaline Phosphatase > 5 x ULN; bilirubin ≥ 1.5 x ULN (unless patient currently on atazanavir	Non-randomised cohort[a] All patients received open-label fostemsavir 600 mg twice daily plus OBT (n=99) Randomised cohort: Day 1 to 8[b] Patients received fostemsavir 600 mg twice daily plus failing ART (n=203)	non-randomised cohort[30]: 67/99 (68%) **Critical outcomes** **Virological suppression**31 **Virologic response (HIV-1 RNA <40 copies/mL), n (%) [95% CI]** Non-randomised cohort At week 24 (n=99): 37% At week 48 (n=99): 38, 38 (29 to 48) Among patients (n=15) who received ibalizumab in their initial OBT, 8 (53%) had a response at weeks 24 and 48. Randomised cohort[c] At week 24: *Total (n=272): 53%* At week 48: Fostemsavir (n=203): 115, 57 (50 to 63) Placebo (n=69): 31, 45 (34 to 57) *Total (n=272): 146, 54 (48 to 60)*	randomised controlled trials. 1. No 2. Yes 3. No 4. Partly 5. Unclear 6. Unclear 7. No 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments**: [a] Patients in the non-randomised cohort were permitted to enrol in other antiretroviral drug trials to include additional investigational antiretroviral drugs in the

[25] Defined as HIV-1 RNA count of ≥400 copies per ml.
[26] Defined as the elimination of all agents within a given class as a fully active option to pair with fostemsavir because of resistance, previous side effects, contraindications, or unwillingness to use enfuvirtide.
[27] Nucleoside reverse-transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, integrase inhibitors, protease inhibitors, CCR5 antagonists, and entry inhibitors.
[28] Data source: ClinicalTrials.gov website (available at: https://clinicaltrials.gov/ct2/show/NCT02362503).
[30] Participants who had no remaining approved fully active antiretroviral drug available to use as ART.
[31] In the intention-to-treat (ITT) population (all patients who had received at least one dose of a trial regimen), virologic response rate was determined using the Food and Drug Administration Snapshot algorithm, whereby patients who had missing HIV-1 RNA values or who changed the composition of their OBT were classified as having had virologic failure.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Patients were enrolled between February 2015 to May 2016	and has predominantly unconjugated hyperbilirubinemia) **Total sample size** N=371 (non-randomised cohort: n=99; randomised cohort: n=272) **Baseline characteristics** Non-randomised cohort: (n=99) • Female/male: 10/89 (10%/90%) • Median age at time of study: 50 years (range 17 to 72) • History of AIDS diagnosis: 89 (90%) HIV-1 RNA – log_{10} copies/mL: • Mean (SD) log_{10} copies/mL: 4.2 (0.9) • Distribution, n (%): <400 copies/mL: 5 (5) 400 to <1,000 copies/mL: 4 (4)	Day 8 to end of trial All patients received open-label fostemsavir 600 mg twice daily plus OBT (n=272) **Comparison** No relevant comparator. Randomised cohort: Day 1 to 8 Patients received placebo twice daily plus failing ART (n=69)	***Virologic failure[32] (HIV-1 RNA ≥400 copies/mL), %[d]*** Non-randomised cohort At week 48 (n=99): 46 Randomised cohort At week 48 (n=272): 18 ***Virologic failure (HIV-1 RNA above the nadir, i.e. ≥40 copies/mL), n (%)*** Non-randomised cohort At week 48 (n=99): 52 (53) Randomised cohort At week 48 (n=272): 104 (38) ***Reduction in viral load (change in HIV-1 RNA log_{10}), adjusted mean[33] (95% CI), SE*** Randomised cohort At day 8 Fostemsavir (n=201): -0.791 (-0.885 to -0.698), 0.0474 Placebo (n=69): -0.166 (-0.326 to -0.007), 0.0809 Difference between groups:[e] -0.625 (-0.810 to -0.441), p<0.0001	OBT; 15 patients received investigational ibalizumab. [b] It was unclear whether the intervention received by patients in the randomised cohort for the initial 8 days met the inclusion criteria as the authors described the treatment as functional monotherapy, with patients receiving failing antiretroviral regimen rather than an optimised background regimen of other ART agents, as stated in the PICO document. [c] Response rates at week 48 were similar across most pre-specified subgroups in the randomised cohort. Response rates were numerically higher among patients aged 50 years or older (59%), females (61%), and patients of black race (65%); higher

[32] Before 24 weeks, virologic failure was defined as an HIV-1 RNA value of at least 400 copies/mL after previous confirmed suppression to <400 copies/mL or an increase of at least 1.0 log_{10} in the HIV-1 RNA level above the nadir (that is, ≥40 copies/mL). During or after 24 weeks, virologic failure was defined as an HIV-1RNA level of at least 400 copies/mL.
[33] Mean adjusted by Day 1 log_{10} HIV-1 RNA.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	1,000 to <100,000 copies/mL: 74 (76) ≥100,000 copies/mL: 15 (15) CD4+ T-cell count: • Mean (SD): 99 (131) • Distribution, n (%): <20 cells/µL: 40 (40) 20 to <50 cells/µ/L: 14 (14) 50 to <200 cells/µ/L: 25 (25) 200 to <500 cells/µ/L: 18 (18) ≥500 cells/µ/L: 2 (2) Number of prior ARV regimens, n (%): • 2 to 4: 8 (8) • 5 or more: 90 (91) • Unknown: 1 (1) Fully active ARVs in initial OBT, n (%): • 0: 80 (81) • 1: 19 (19) • 2: 0 (0) • >2: 0 (0) <u>Randomised cohort</u>: Blinded fostemsavir (n=203); blinded placebo (n=69)		<u>Randomised cohort – subgroup outcomes for patients with baseline HIV-1 RNA >1,000 copies/mL</u> At day 8: Fostemsavir (n=180 of 182)[34]: -0.863 (-0.963 to -0.762), 0.0509 Placebo (n=59): -0.198 (-0.373 to -0.023), 0.0889 Difference between groups: -0.665 (-0.867 to -0.463), p=n/a **Mortality, n (%)** <u>Non-randomised cohort</u> At week 48 (n=99): 14 (14) <u>Randomised cohort</u> At week 48 (n=272): 11 (4) **Important outcomes** ***Increase in baseline CD4+ T-cell count, mean (cells/mm^3)*** <u>Non-randomised cohort</u> At week 24 (n=87): 41 At week 36 (n=83): 60 At week 48 (n=83): 64 *Mean increase to week 48: 63.5 cells/mm^3* <u>Randomised cohort</u> Follow-up time point week 24 (n=247): 90 At week 36 (n=234): 110 At week 48 (n=228): 139 *Mean (SD) increase to week 48: 139 (135) cells/mm^3*	response rates were reported among patients who had one fully active antiretroviral drug in their initial OBT (56%). By contrast, patients who had a high baseline viral load (≥100,000 copies/mL) or a low baseline CD4+ T-cell count (<20 cells/mm^3) showed a reduced response rate (35% for both subgroups). [d] In the non-randomised cohort, virological data were not available for 9 (9%) patients. In the randomised cohort, virological data were not available for 17 (8%) patients initially receiving blinded fostemsavir and 5 (7%) patients initially receiving blinded placebo. [e] Subgroup outcomes (randomised cohort): There was no effect on between-group differences (fostemsavir vs placebo from day 1 to day 8) in the decrease in HIV-1 RNA level on the

[34] Two patients (both in the fostemsavir treatment arm) who had missing HIV-1 RNA values on day 1 were not included in the analysis.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Female/male: o Fostemsavir: 60/143 (30%/70%) o Placebo: 12/57 (17/83%) • Median age at time of study: o Fostemsavir: 48 years (range 18 to 73) o Placebo: 45 years (range 19 to 66) • History of AIDS diagnosis: o Fostemsavir: 170 (84%) o Placebo: 61 (88%) HIV-1 RNA – log_{10} copies/mL, mean (SD): • Fostemsavir: 4.4 (1.0) • Placebo: 4.4 (1.2) HIV-1 RNA – distribution, n (%): • <400 copies/mL o Fostemsavir: 14 (7) o Placebo: 7 (10) • 400 to <1,000 copies/mL: o Fostemsavir: 7 (3) o Placebo: 3 (4) • 1,000 to <100,000 copies/mL o Fostemsavir: 125 (62) o Placebo: 35 (51) • ≥100,000 copies/mL:		***Safety, n (%)*** **Adverse events[f]** <u>Non-randomised cohort</u> At week 48 (n=99): Any adverse event: 96 (97) Grade 2 to 4: 84 (85) Drug-related grade 2 to 4: 22 (22) Grade 3 or 4: 47 (47) Leading to discontinuation: 13 (13) <u>Randomised cohort</u> At Day 8: Fostemsavir (n=203): 88 (43) Placebo (n=69): 24 (35); most drug-related adverse events were ≤Grade 2. At week 48 (n=272): Any adverse event: 247 (91) Grade 2 to 4: 206 (76) Drug-related grade 2 to 4: 55 (20) Grade 3 or 4: 70 (26) Leading to discontinuation: 14 (5) **Serious adverse events (not including death)** <u>Non-randomised cohort</u> At week 48 (n=99): 30 (30) CDC Class C AIDS-defining event: 14 (14) Drug-related: 3 (3) <u>Randomised cohort</u> At week 48 (n=272): 74 (27) CDC Class C AIDS-defining event: 24 (9) Drug-related: 7 (3)	basis of age, gender, race, or geographic region. [f] At week 48, the most common grade 3 or 4 adverse events were pneumonia and diarrhoea. The majority of serious adverse events were associated with infections. Of the 10 patients who had a serious adverse event that was deemed to be trial drug related, 7 had one event and 3 had two events. Of the 25 deaths, 17 were due to AIDS-related events or acute infections. According to the investigators, 1 of these deaths was considered to be related to a trial drug. The authors acknowledged the confounder of highly individualised OBT, and the lack of standardised background therapy reflects real-world practice.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	o Fostemsavir: 55 (28) o Placebo: 24 (35) CD4+ T-cell count, mean (SD): • Fostemsavir: 147 (174) • Placebo: 170 (205) CD4+ T-cell count - distribution, n (%): • <20 cells/µL: o Fostemsavir: 55 (27) o Placebo: 17 (25) • 20 to <50 cells/µ/L: o Fostemsavir: 19 (9) o Placebo: 6 (9) • 50 to <200 cells/µ/L: o Fostemsavir: 76 (37) o Placebo: 26 (38) • 200 to <500 cells/µ/L: o Fostemsavir: 42 (21) o Placebo: 16 (23) • ≥500 cells/µ/L: o Fostemsavir: 11 (5) o Placebo: 4 (6) Number of prior ARV regimens, n (%): • 2 to 4: o Fostemsavir: 31 (15) o Placebo: 12 (17) • 5 or more: o Fostemsavir: 169 (83) o Placebo: 57 (83) • Unknown:			**Source of funding:** Bristol-Myers Squibb then ViiV Healthcare and GlaxoSmithKline.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	o Fostemsavir: 3 (1) o Placebo: 0 (0) Fully active ARVs in initial OBT, n (%): • 0: o Fostemsavir: 15 (7) o Placebo: 1 (1) • 1: o Fostemsavir: 108 (53) o Placebo: 34 (49) • 2: o Fostemsavir: 80 (39) o Placebo: 34 (49) • >2: o Fostemsavir: 0 (0) o Placebo: 0 (0)			
Lataillade M, Lalezari JP, Kozal M, Aberg JA, Pialoux G, Cahn P, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. The Lancet HIV. 2020;7(11):e740-e51.	**Study inclusion criteria** See Kozal 2020 **Study exclusion criteria** See Kozal 2020 **Total sample size** See Kozal 2020 **Baseline characteristics** See Kozal 2020	**Intervention** See Kozal 2020 Comparison See Kozal 2020	**Critical outcomes** ***Virological suppression[35]*** ***Virologic response (HIV-1 RNA <40 copies/mL), n (%)*** <u>Non-randomised cohort</u> At week 72 (n=99): 35 (35) At week 96 (n=99): 37 (37) Response rate at week 24 for the 15 patients receiving ibalizumab in their initial OBT was 5 of 15 (53%) compared to those who did not receive ibalizumab (32 of 84 patients; 38%). <u>Randomised cohort</u>	This study was appraised using the JBI checklist for randomised controlled trials. See Kozal 2020 **Other comments**: [a] The most common antiretroviral in the initial OBT for patients in the randomised cohort was dolutegravir (mostly twice a day), taken by 229

[35] In the intention-to-treat (ITT) population (all patients who had received at least one dose of a trial regimen), virologic response rate was determined using the Food and Drug Administration Snapshot algorithm, whereby patients who had missing HIV-1 RNA values or who changed the composition of their OBT were classified as having had virologic failure.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study location See Kozal 2020 **Study type** See Kozal 2020 **Study aim** To evaluate the safety and efficacy of fostemsavir in heavily treatment experienced individuals with multidrug-resistant HIV-1. **Study dates** See Kozal 2020	• Previous exposure to ARV classes, n (%): • Non-randomised cohort: (n=99) • NRTI: 97 (98) • NNRTI: 93 (94) • PI: 97 (98) • INSTI: 94 (95) • CCR5 antagonist: 40 (40) • Fusion inhibitor: 67 (68) • Randomised cohort: (n=272) • NRTI: 270 (99) • NNRTI: 248 (91) • PI: 257 (94) • INSTI: 204 (75) • CCR5 antagonist: 72 (26) • Fusion inhibitor: 107 (39) • ARV classes with no fully active and approved agents, n (%):		At week 72 (272): 144 (53) At week 96 (n=272): 163 (60) <u>Randomised cohort – subgroup outcomes for patients by baseline viral load (copies/mL), n (%)</u> At week 96 (n=272): 163 (60) <1,000 (n=31): 23 (74) 1,000 to <10,000 (n=44): 32 (73) 10,000 to <100,000 (n=117): 69 (59) ≥100,000 (n=80): 39 (49) <u>Randomised cohort – subgroup outcomes for patients by baseline CD4+ T-cell count (cells per µL), n (%)</u> At week 96 (n=272): 163 (60) <20 (n=72): 33 (46) 20 to <50 (n=25): 14 (56) 50 to <100 (n=39): 21 (54) 100 to <200 (n=63): 41 (65) ≥000 (n=73): 54 (74) Virological response rates at week 96 were similar across most other baseline subgroups, including between patients with 1 or 2 fully active antiretrovirals in their initial OBT. ***Virologic failure[21] (HIV-1 RNA ≥400 copies/mL), n (%)*** <u>Non-randomised cohort</u> At week 96 (n=99): 49 (49) patients met the criteria for protocol-defined virological failure. Nadir HIV-1 RNA values after protocol-defined virological failure showed that at week 96, virological suppression to <40 HIV-1 RNA copies per mL was achieved 5 of 49 (10%) patients. <u>Randomised cohort</u>	(84%) patients, this was classified as fully active at screening in 178 (78%) patients). Darunavir (134 [49%] of 272 patients) and tenofovir (116 [43%] patients) were included in the OBT but were classified as fully active at screening for fewer than half of patients. In the non-randomised cohort, the initial OBT included no approved fully active antiretrovirals for 81% of patients. Dolutegravir, darunavir, and tenofovir were the most commonly used antiretrovirals in the initial OBT for the non-randomised cohort; however, in almost all cases (99 [100%] patients) they were not classified as fully active at screening. Four participants had one fully active antiretroviral and were recorded as protocol deviations: enfuvirtide (n=2),

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Non-randomised cohort: (n=99) • NRTI: 99 (100) • NNRTI: 98 (99) • PI: 99 (100) • INSTI: 98 (99) • CCR5 antagonist: 99 (100) • Fusion inhibitor: 97 (98) • Randomised cohort: (n=272) • NRTI: 239 (88) • NNRTI: 221 (81) • PI: 202 (74) INSTI: 79 (29) • CCR5 antagonist: 212 (78) • Fusion inhibitor: 232 (85) • Fully active ARVs in initial OBT, n (%): • Non-randomised cohort: (n=99) • 0 agents: 80 (81) • 1 agent: 19 (19), including 15 patients receiving ibalizumab • 2 agents: 0 (0)		At week 96 (272): 63 (23) patients met the criteria for protocol-defined virological failure. Nadir HIV-1 RNA values after protocol-defined virological failure showed that at week 96, virological suppression to <40 HIV-1 RNA copies per mL was achieved in17 of 63 (27%) patients. ***Mortality, n (%)[b]*** <u>Non-randomised cohort</u> At week 96 (n=99): 17 (17) <u>Randomised cohort</u> At week 96 (n=272): 12 (4) **Important outcomes** ***Increase in baseline CD4+ T-cell count, mean (cells/µL)*** <u>Randomised cohort – subgroup outcomes for patients by baseline viral load (copies/mL), mean (SD); median (IQR)</u> At week 96 (n=272): 163 (60) <1,000 (n=25): 137 (202); 101 (53 to 268) 1,000 to <10,000 (n=38): 147 (190); 133 (81 to 200) 10,000 to <100,000 (n=91): 218 (181); 184 (94 to 288) ≥100,000 (n=59): 250 (190); 222 (124 to 342) <u>Randomised cohort – subgroup outcomes for patients by baseline CD4 T-cell count (copies per µL), mean (SD); median (IQR)</u> At week 96 (n=213): 205 (191) <20 (n=54): 240 (196); 212 (105 to 306) 20 to <50 (n=17): 201 (77); 181 (138 to 222) 50 to <100 (n=26): 199 (124); 171 (125 to 262) 100 to <200 (n=52): 172 (140); 145 (77 to 236) ≥200 (n=64): 205 (255); 150 (40 to 331)	dolutegravir (n=1), and etravirine (n=1). [b] 7 of 29 deaths (24%) were AIDS related; 11 (38%) were acute infections; 6 (21%) were non-AIDS-related malignancies; 5 (17%) resulted from other unspecified conditions. [c] In both cohorts, there was little (or small negative) changes in the function or global wellbeing, social wellbeing, and cognitive function subscales for the FAHI. For EQ-5D-3L analyses, baseline mean single index utility scores and VAS were higher in the randomised cohort compared to non-randomised cohort. At 96 weeks, a small positive improvement was reported in the randomised cohort, but this trend was not seen in the non-randomised cohort.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• ≥2 agents: 0 (0) • Randomised cohort: (n=272) • 0 agents: 16 (6) • 1 agent: 142 (52 • 2 agents: 114 (42) ≥2 agents: 0 (0)		***Quality of life[c]*** **FAHI score** (measured using a 5-point Likert scale (0 = not at all to 4 = very much); with a higher value indicating improvement in QoL)[36] <u>Non-randomised cohort</u> Baseline: mean 114 (SD 34) Mean change from baseline to week 96: Total score: 4.9 (95% CI -1.8 to 11.5) Physical wellbeing: 1.7 (95% CI -0.2 to 3.6) Emotional wellbeing: 1.6 (95% CI -0.6 to 3.8) <u>Randomised cohort</u> Baseline: mean 123 (SD 29) Mean change from baseline to week 96: Total score: 5.3 (95% CI 2.0 to 8.5) Physical wellbeing: 2.1 (95% CI 1.1 to 3.2) Emotional wellbeing: 3.0 (95% CI 1.9 to 4.1) ***Safety, n (%)[d]*** **Adverse events** <u>Non-randomised cohort</u> At week 96 (n=99): Any adverse event: 98 (99) Drug-related grade 2 to 4: 22 (22) Leading to discontinuation: 12 (12) <u>Randomised cohort</u> At week 96 (n=272): Any adverse event: 249 (92)	[d] The most common adverse events were pneumonia, diarrhoea and headache. Greater proportions of patients in the non-randomised cohort reported grade 3 or 4 adverse events, serious adverse events, fatalities, and adverse events leading to discontinuation compared with patients in the randomised cohort. **Source of funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

[36] The Functional Assessment of HIV Infection (FAHI) is a 47-item disease-specific instrument evaluating Health-Related Quality of Life (HRQL) in people living with HIV. It evaluates physical well-being, functional and global well-being, emotional well-being/living with HIV, social well-being, and cognitive functioning. It yields a total score and individual subscale scores. A higher value FAHI score indicates benefit.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Drug-related grade 2 to 4: 57 (21) Leading to discontinuation: 14 (5) **Serious adverse events (not including death)** <u>Non-randomised cohort</u> At week 96 (n=99): 48 (48) CDC Class C AIDS-defining event: 15 (15) Drug-related: 3 (3) <u>Randomised cohort</u> At week 96 (n=272): 92 (34) CDC Class C AIDS-defining event: 23 (8) Drug-related: 9 (3)	

Abbreviations

AIDS – acquired immune deficiency syndrome, ALT – alanine aminotransferase, ART – antiretroviral therapy, ARV – antiretroviral, AST – aspartate aminotransferase, CDC – Centres for Disease Control and Prevention, CI – confidence interval, #FAA - fully active antiretrovirals, FAHI – functional assessment of HIV infection, GSS – genotypic susceptibility score, HBV - hepatitis B virus, HIV – human immunodeficiency virus, N/A – not applicable, OBT – optimised background therapy, OSS – overall susceptibility score, PSS – phenotypic susceptibility score, RNA – ribonucleic acid, SD – standard deviation, SE – standard error, S-GSS – standard genotypic susceptibility score, ULN – upper limit of normal, VAS – visual analogue scores.

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Randomised Controlled Trials

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

Appendix G GRADE profiles

Table 2a. In individuals with MDR HIV-1 infection who have no fully active, approved ARV options available to construct a fully suppressive viral regiment from existing ART, what is the clinical effectiveness and safety of the addition of fostemsavir to the ART regimen compared with current standard treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Fostemsavir + OBT	Current standard treatment + OBT	Result		
Virological suppression									
Virologic response (HIV-1 RNA <40 copies/mL) at 24 weeks, % (higher value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	37	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 48 weeks, n (%) [95% CI] (higher value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	38 (38) [29 to 48]	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 72 weeks, n (%) (higher value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	35 (35)	Critical	Very low

Virologic response (HIV-1 RNA <40 copies/mL) at 96 weeks, n (%) (higher value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	37 (37)	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 24 weeks, n (%) - subgroup **outcomes for patients who received ibalizumab in their initial OBT (higher value indicates benefit)**									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	None	8 (53)	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 48 weeks, n (%) - subgroup **outcomes for patients who received ibalizumab in their initial OBT (higher value indicates benefit)**									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	None	8 (53)	Critical	Very low
Virologic failure (HIV-1 RNA ≥400 copies/mL) at 48 weeks, % (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	46	Critical	Very low
Virologic failure (HIV-1 RNA level above the nadir, i.e. ≥40 copies/mL) at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	52 (53)	Critical	Very low

Virologic failure (HIV-1 RNA ≥400 copies/mL) at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	49 (49)	Critical	Very low
Mortality									
Mortality at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	14 (14)	Critical	Very low
Mortality at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	17 (17)	Critical	Very low
1 non-randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	15	Critical	Very low
Increase in baseline CD4 cell counts									
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 24 weeks, n (higher value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	87	None	41	Important	Very low

Increase in baseline CD4+ T-cell count, mean (cells/µL) at 36 weeks, n (higher value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	83	None	60	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/µL) at 48 weeks, n (higher values indicate benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	83	None	64	Important	Very low
Quality of life									
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – total composite score (higher value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	4.9 (-1.8 to 11.5)	Important	Very low
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – physical wellbeing domain (higher value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	1.7 (-0.2 to 3.6)	Important	Very low
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – emotional wellbeing domain (higher value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	1.6 (-0.6 to 3.8)	Important	Very low

Treatment failure									
Withdrawal due to Lack of efficacy at 96 weeks, n									
1 non-randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	6	Important	Very low
Treatment adherence									
Withdrawal due to Treatment Non-adherence at 96 weeks, n									
1 non-randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	6	Important	Very low
Safety									
Any adverse event at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	96 (97)	Important	Very low
Any adverse event at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	98 (99)	Important	Very low
Grade 2 to 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	84 (85)	Important	Very low

Drug-related grade 2 to 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	22 (22)	Important	Very low
Drug-related grade 2 to 4 adverse events at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	22 (22)	Important	Very low
Grade 3 or 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	47 (47)	Important	Very low
Adverse events leading to discontinuations at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	13 (13)	Important	Very low
Adverse events leading to discontinuations at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	12 (12)	Important	Very low
Serious adverse events (not including death) at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	30 (30)	Important	Very low

Kozal et al 2020									
Serious adverse events (not including death) at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	48 (48)	Important	Very low
Serious adverse events (CDC Class C AIDS-defining event) at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	14 (14)	Important	Very low
Serious adverse events (CDC Class C AIDS-defining event) at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	15 (15)	Important	Very low
Serious adverse events (drug-related) at 48 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	3 (3)	Important	Very low
Serious adverse events (drug-related) at 96 weeks, n (%) (lower value indicates benefit)									
1 non-randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	99	None	3 (3)	Important	Very low

1. Bias: serious risk of bias due to lack of blinding of patients and clinicians.
2. Serious indirectness due to no relevant comparator and 19/99 patients had one fully active antiretroviral drug, including 15 patients who received ibalizumab in addition to fostemsavir and OBT.

Table 2b. In individuals with MDR HIV-1 infection who have the option of receiving at least one fully active, approved ARV drug in at least one but no more than two ARV classes to construct a fully suppressive viral regiment from existing ART, what is the clinical effectiveness and safety of the addition of fostemsavir to the ART regimen compared with current standard treatment?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Fostemsavir + OBT	Current standard treatment + OBT	Result		
Virological suppression									
Virologic response (HIV-1 RNA <40 copies/mL) at 24 weeks, % (higher value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	53	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 48 weeks, n (%) [95% CI] (higher value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	203	69	Fostemsavir: 115 (57) [50 to 63] Placebo: 31 (45) [34 to 57] *Total: 146 (54) [48 to 60]*	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 72 weeks, n (%) (higher value indicates benefit)									
1 randomised cohort	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	144 (53)	Critical	Very low

Lataillade et al 2020									
Virologic response (HIV-1 RNA <40 copies/mL) at 96 weeks, n (%) (higher value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	163 (60)	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 96 weeks, n (%) - subgroup **outcomes for patients by baseline viral load (copies/mL) (higher value indicates benefit)**									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	<1,000 (n=31): 23 (74) 1,000 to <10,000 (n=44): 32 (73) 10,000 to <100,000 (n=117): 69 (59) ≥100,000 (n=80): 39 (49)	Critical	Very low
Virologic response (HIV-1 RNA <40 copies/mL) at 96 weeks, n (%) [95% CI]- subgroup **outcomes for patients by initial OBT:OSS-new (higher value indicates benefit)**									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	0 (n=35): 11 (31) [19 to 48] >0 to 1 (n=105): 61 (58) [49 to 67] >1 to 2 (n=101): 69 (68) [59 to 77] >2 (n=17): 15 (88) [66 to 97]	Critical	Very low
Virologic failure (HIV-1 RNA ≥400 copies/mL) at 48 weeks, % (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	203	69	18	Critical	Very low
Virologic failure (HIV-1 RNA level above the nadir, i.e. ≥40 copies/mL) at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	203	69	104 (38)	Critical	Very low

Virologic failure (HIV-1 RNA ≥400 copies/mL) at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	203	None	63 (23)	Critical	Very low
Reduction in viral load									
Reduction in viral load (change in HIV-1 RNA log_{10}), from day 1 to day 8, adjusted mean[a] (95% CI) (greater reduction indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	201	69	Fostemsavir: -0.791 (-0.885 to -0.698), SE 0.0474 Placebo: -0.166 (-0.326 to -0.007), SE 0.0809 *Difference between groups: -0.625 (-0.810 to -0.441), p<0.0001*	Critical	Very low
Reduction in viral load (change in HIV-1 RNA log_{10}), from day 1 to day 8, adjusted mean (95% CI) - subgroup outcomes for patients with baseline HIV-1 RNA >1,000 copies/mL (greater reduction indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	180	59	Fostemsavir: -0.863 (-0.963 to -0.762), SE 0.0509 Placebo: -0.198 (-0.373 to -0.023), SE 0.0889 *Difference between groups: -0.665 (-0.867 to -0.463), p=n/a*	Critical	Very low
Mortality									
Mortality at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	11 (4)	Critical	Very low

[a] Mean adjusted by Day 1 log_{10} HIV-1 RNA.

Mortality at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	12 (4)	Critical	Very low
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	9	Critical	Very low
Increase in baseline CD4 cell counts									
Increase in baseline CD4+ T-cell count, mean (cells/µL) at 24 weeks, n (higher value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	247	None	90	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/µL) at 36 weeks, n (higher value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	234	None	110	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/µL) at 48 weeks, n (higher values indicate benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	228	None	139	Important	Very low

Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks - subgroup outcomes for patients by baseline CD4 T-cell count (copies per μL), mean (SD) (higher values indicate benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	<20 (n=54): 240 (196) 20 to <50 (n=17): 201 (77) 50 to <100 (n=26): 199 (124) 100 to <200 (n=52): 172 (140) ≥200 (n=64): 205 (255)	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:#FAA (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	1 (n=120): 206 [174 to 238] 2 (n=87): 195 [153 to 238]	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:S-GSS (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	>0 to 1 (n=34): 236 [178 to 293] >1 to 2 (n=121): 210 [173 to 248] >2 (n=55): 169 [125 to 213]	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:GSS (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	>0 to 1 (n=45): 224 [180 to 268] >1 to 2 (n=112): 215 [174 to 255] >2 (n=53): 165 [120 to 210]	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:PSS (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	>0 to 1 (n=7): 206 [157 to 254] >1 to 2 (n=99): 209 [170 to 248] >2 (n=93): 201 [159 to 242]	Important	Very low

Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:OSS (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	>0 to 1 (n=22): 201 [155 to 247] >1 to 2 (n=100): 206 [167 to 245] >2 (n=82): 202 [157 to 248]	Important	Very low
Increase in baseline CD4+ T-cell count, mean (cells/μL) at 96 weeks, n [95% CI] - subgroup outcomes for patients by initial OBT:OSS-new (higher values indicate benefit)									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	213	None	0 (n=21): 142 [75 to 210] >0 to 1 (n=85): 219 [179 to 258] >1 to 2 (n=83): 192 [148 to 237] >2 (n=15): 270 [145 to 395]	Important	Very low
Quality of life									
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – total composite score (higher value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	5.3 (2.0 to 8.5)	Important	Very low
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – physical wellbeing domain (higher value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	2.1 (1.1 to 3.2)	Important	Very low
FAHI score, mean change from baseline to 96 weeks, mean (95% CI) – emotional wellbeing domain (higher value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	3.0 (1.9 to 4.1)	Important	Very low

Treatment failure									
Withdrawal due to Lack of efficacy at 96 weeks, n									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	12	Important	Very low
Treatment adherence									
Withdrawal due to Treatment Non-adherence at 96 weeks, n									
1 randomised cohort Ackerman et al 2021	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	11	Important	Very low
Safety									
Any adverse event from day 1 to day 8, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	203	69	Fostemsavir: 88 (43) Placebo: 24 (35)	Important	Very low
Any adverse event at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	247 (91)	Important	Very low
Any adverse event at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	249 (92)	Important	Very low

Grade 2 to 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	206 (76)	Important	Very low
Drug-related grade 2 to 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	55 (20)	Important	Very low
Drug-related grade 2 to 4 adverse events at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	57 (21)	Important	Very low
Grade 3 or 4 adverse events at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	70 (26)	Important	Very low
Adverse events leading to discontinuations at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	14 (5)	Important	Very low

Adverse events leading to discontinuations at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	14 (5)	Important	Very low
Serious adverse events (not including death) at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	74 (27)	Important	Very low
Serious adverse events (not including death) at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	92 (34)	Important	Very low
Serious adverse events (CDC Class C AIDS-defining event) at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	24 (9)	Important	Very low
Serious adverse events (CDC Class C AIDS-defining event) at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	23 (8)	Important	Very low

Serious adverse events (drug-related) at 48 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Kozal et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	7 (3)	Important	Very low
Serious adverse events (drug-related) at 96 weeks, n (%) (lower value indicates benefit)									
1 randomised cohort Lataillade et al 2020	Serious limitations[1]	Serious indirectness[3]	Not applicable	Not calculable	272	None	9 (3)	Important	Very low

1. Bias: serious risk of bias due to lack of blinding of patients and clinicians during the open-label treatment periods.
2. Serious indirectness due to no relevant comparator. It was unclear whether the blinded phase of the randomised cohort met the PICO eligibility criteria as it included 8 days blinded placebo prior to open-label fostemsavir plus OBT and fostemsavir described as functional monotherapy (8 days of blinded fostemsavir and failing ARV regimen prior to open-label fostemsavir plus OBT up to 96 weeks).

Glossary

Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or

	condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Ackerman P, Thompson M, Molina JM, Aberg J, Cassetti I, Kozal M, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS. 2021;35(7):1061-72
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