NHS England Evidence Review:

Lenacapavir for multi-drug resistant Human Immunodeficiency Virus 1 (HIV-1)

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of lenacapavir plus optimised antiretroviral treatment (ART) compared with optimised ART alone in people 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.

In addition, the review scope included the identification of possible subgroups of people within the included studies who might benefit from adding lenacapavir to the optimised ART regimen more than the wider population of interest.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of lenacapavir plus optimised antiretroviral treatment (ART) compared with optimised ART alone in people 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. In addition, the review scope includes the identification of possible subgroups of people within the included studies who might benefit from the addition of lenacapavir to their optimised ART regimens more than the wider population of interest.

The searches for evidence published since January 2014 were conducted on 11th and 12th January 2024 and identified 139 references. The titles and abstracts were screened and 9 full text papers were obtained and assessed for relevance.

Two papers were identified for inclusion in the evidence review (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023). Both papers report the 52-week phase 2/3 CAPELLA study, which assessed the licensed dosage of lenacapavir (3 oral loading doses followed by subcutaneous maintenance treatment 6-monthly) in 2 cohorts of people with MDR HIV-1 (n=72 in total). Participants in cohort 1 were randomised 2:1 to receive lenacapavir plus their current failing ART (n=24) or placebo plus current failing ART (n=12) for 14 days. Participants in both groups in cohort 1 subsequently received open label lenacapavir plus optimised ART from day 15. All participants in cohort 2 (n=36) received open label lenacapavir plus optimised ART from day 1.

Primary and secondary efficacy endpoints were evaluated in cohort 1 of CAPELLA. Efficacy in cohort 2 was not included in the prespecified endpoints because cohort 2 was designed primarily to provide access to lenacapavir for individuals who met the same eligibility criteria as those in cohort 1 but were not eligible for random assignment. Results presented at 26 and 52 weeks in the uncontrolled single arm phase of the trial are for cohorts 1 and 2 combined.

In terms of clinical effectiveness:

Critical outcomes

- Virological suppression. The single arm phase of CAPELLA (cohorts 1 and 2 combined) provides very low certainty evidence that maintenance treatment with lenacapavir plus optimised ART suppresses viral load to less than 50 copies per millilitre and to less than 200 copies per millilitre in about 80% of people with MDR HIV-1 at 52 weeks. No comparator was available at this time point.
- Reduction in viral load. The randomised controlled phase of CAPELLA provides very low certainty evidence that statistically significantly more participants achieve a clinically significant reduction in viral load (the primary outcome) at 15 days with loading doses of oral lenacapavir plus failing ART compared with placebo plus failing ART. About 90% of people with MDR HIV-1 taking lenacapavir had a clinically important reduction compared with about 20% of people taking placebo ($p<0.001$). The CAPELLA study also provides very low certainty evidence that ongoing maintenance treatment with subcutaneous lenacapavir 6-monthly plus optimised ART reduces mean viral load in people with MDR HIV-1 at week 52. No comparator was available at this time point and this outcome was exploratory only.
- Increase in baseline CD4 counts. The CAPELLA study provides very low certainty evidence that ongoing maintenance treatment with lenacapavir plus optimised ART improves CD4 counts in people with MDR HIV-1 by a clinically important amount at

week 52. No comparator was available at this time point and this outcome was exploratory only.

Important outcomes

- Mortality. Very low certainty evidence from CAPELLA suggests lenacapavir does not impact mortality in people with MDR HIV-1 over 52 weeks. However, mortality was not a prespecified outcome.
- Quality of life. No evidence was identified for this outcome.
- Treatment failure. The CAPELLA study provides very low certainty evidence that lenacapavir resistance may emerge within 26 weeks in people with MDR HIV-1 receiving lenacapavir plus optimised ART. Of 22/72 participants who met the prespecified criteria for resistance analysis, 8 had resistance-associated mutations to lenacapavir by week 26 and a further person (9 in total) by week 52. No comparator was available at these time points and this outcome was exploratory only.
- Treatment adherence. In the CAPELLA study, there were no reports of lack of adherence to lenacapavir treatment. However, 5/9 participants who had resistance-associated mutations to lenacapavir were found to lack adherence to their optimised ART. This outcome was exploratory, and the evidence provided by CAPELLA is of very low certainty.

In terms of safety:

- Frequency of adverse events. The CAPELLA study provides very low certainty evidence that, over 52 weeks, two thirds of people with MDR HIV-1 experience injection site reactions with lenacapavir (including swelling, pain, erythema and subcutaneous nodules), and a quarter experience other lenacapavir-related adverse events (including nausea, diarrhoea, headache, myalgia, pyrexia, rash, somnolence and vomiting).
- Frequency of serious adverse events. No serious adverse events considered related to lenacapavir were reported in CAPELLA. The study provides very low certainty evidence that, over 52 weeks, most adverse events related to lenacapavir are likely to be mild or moderate in people with MDR HIV-1.
- Frequency of adverse events leading to discontinuation. The CAPELLA study provides very low certainty evidence that, over 52 weeks, adverse events seen with lenacapavir rarely lead to treatment being stopped in people with MDR HIV-1 (1 person only).
- Frequency of grade 3 to 4 laboratory abnormalities. The CAPELLA study provided very low certainty evidence that, over 52 weeks, grade 3 or 4 treatment-emergent adverse events occur in about 30% of people with MDR HIV-1 who are taking lenacapavir in combination with ART.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients who would benefit more from treatment with lenacapavir.

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

Limitations

Quality assessment found the randomised controlled phase of CAPELLA was at low risk of bias in most domains. However, it is possible that investigators could become aware of participants' treatment allocation, and there were differences in baseline characteristics between the lenacapavir and placebo groups, both of which raised concerns. There were also some inconsistencies in data between the 2 papers and the reasons for this are unclear.

The groups in cohort 1 were small (lenacapavir n=24 and placebo n=12) and statistical analysis was powered and reported for the primary outcome only. All participants continued their failing ART for the first 14 days, and it is not known if the results at day 15 would have been the same if ART had been optimised. Nevertheless, failing ART was appropriately used to avoid confounding and show that any improvement in viral load at 15 days was likely to be because of lenacapavir, not a change in ART.

The lack of comparator in the second phase of the study means it is unclear how lenacapavir affected outcomes measured at weeks 26 and 52; for example, whether any participants in the study improved because of lenacapavir or because of the optimised ART regimen alone. Also, the trial protocol states that the outcomes in cohort 2 were exploratory. Therefore, they cannot be relied upon and should be considered hypothesis generating only.

The CAPELLA study included only 72 participants and, of these, only 66 completed the study. This means that less common adverse events may not have been identified and the safety profile of lenacapavir is uncertain. MDR HIV-1 is rare so there are few eligible participants for studies. Also, resistance profiles and background treatment regimens differ substantially and are often amended. This means it is difficult to conduct high quality, controlled studies. Nevertheless, the trial was designed in accordance with relevant regulatory guidance.

The median age of participants in CAPELLA was 52 years (range 23 to 78 years). No evidence was identified for children and lenacapavir is not licensed for use in children. It is unclear if the study population is representative of the population with MDR HIV-1 in the UK, and whether the treatment regimens used in the study were the same as those currently used in the UK.

Little information is available in CAPELLA on adherence to treatment. Maintenance treatment with lenacapavir is given subcutaneously every 6 months so adherence to this medicine may be better than for a daily oral treatment. However, lenacapavir is licensed for use in combination with oral ARTs. Oral treatment regimens for MDR HIV-1 are complex and adherence is often suboptimal, especially outside of a clinical trial. Poor adherence to a treatment regimen increases the risk of treatment failure and emergence of resistance.

Conclusion

CAPELLA provides very low certainty evidence that treatment with lenacapavir plus optimised ART suppresses viral load to less than 50 or 200 copies per millilitre in about 80% of people with MDR HIV-1 at 52 weeks. The randomised controlled phase of the study provides very low certainty evidence that oral lenacapavir plus failing ART statistically significantly reduces viral load by a clinically important amount at 15 days compared with placebo plus failing ART. CAPELLA also provides very low certainty evidence that ongoing maintenance treatment with lenacapavir plus optimised ART continues to reduce viral load at week 52, and improves CD4 counts by a clinically important amount at that time point.

Very low certainty evidence from CAPELLA shows that lenacapavir resistance may emerge within 26 weeks in people with MDR HIV-1 receiving lenacapavir plus optimised ART. In the study, there were no reports of lack of adherence to lenacapavir treatment, probably because

maintenance treatment is given by subcutaneous injection every 6 months. However, lack of adherence to optimised background ART regimens was reported. The study data suggest resistance and subsequent treatment failure may be driven by a lack of other fully active ARTs in the optimised background regimen and/or poor adherence to optimised ART.

CAPELLA provides very low certainty evidence that, over 52 weeks, lenacapavir is generally well tolerated in people with MDR HIV-1, although mild to moderate injection site reactions occur in two thirds of people. The study also suggests lenacapavir does not impact mortality at 52 weeks. However, the study may have been too small and too short to detect rare events.

No evidence was identified to determine how lenacapavir affects the quality of life of people with MDR HIV-1, or for the cost effectiveness of the treatment. Also, no evidence was found to identify subgroups of patients who may benefit from the addition of lenacapavir to the existing ART regimens more than the wider population of interest. That said, data from CAPELLA suggest that people without virological suppression at week 52 were most at risk of developing lenacapavir resistant mutations. When the number of ART options available to participants were compared, the efficacy of lenacapavir was generally similar regardless of the number of fully active ARTs in the optimised background ART regimen.

People with MDR HIV-1 have very few treatment options left and, when viral replication is not suppressed to an undetectable level, they are at increased risk of disease progression, AIDS and ultimately death. In CAPELLA, 46% of participants had resistance to at least 2 ARTs in all 4 main classes and 17% had no fully active ART in their optimised background regimen. Resistance to newer treatments for MDR HIV-1 was also seen (ibalizumab 30% and fostemsavir 32%). The findings of the evidence review are important because they suggest lenacapavir has antiviral activity for up to 52 weeks and can be added to ART in adults with MDR HIV-1 who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART. In CAPELLA, no major safety concerns were identified with lenacapavir use for up to 52 weeks, but it is not known whether rare adverse events will be identified in future.

Interpretation of the data is limited by the small number of participants, the relatively short follow up period, the complexity of the study population and the variety of ART regimens used to overcome treatment resistance. After 14 days, CAPELLA was a single arm study and, therefore, could not assess causality. Also, many of the outcomes were exploratory and should be considered hypothesis generating only.

Adherence to treatment is generally better in a clinical trial than in the real world and, if lenacapavir is used, it will be important for people with MDR HIV-1 to take their optimised ART as prescribed.

3. Methodology

Review questions

The review question(s) 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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
4. From the evidence selected, are there any subgroups of patients who may benefit from adding lenacapavir to the optimised ART regimen more than the wider population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 11th and 12th January 2024.

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 document. Full text of potentially relevant studies 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

Two papers were identified for inclusion in the evidence review (Segal-Maurer S et al. 2022 and Ogbuagu O et al. 2023). Both papers report the CAPELLA study (at 26 weeks and 52 weeks respectively), which included 2 cohorts of people with MDR HIV-1. Participants in the first cohort were randomised 2:1 to receive lenacapavir (n=24) plus failing ART or placebo plus failing ART (n=12) for 14 days. Participants in both groups in cohort 1 subsequently received open label lenacapavir plus optimised ART from day 15 onwards. All participants in the second cohort (n=36) received lenacapavir plus optimised ART from day 1.

Table 1 provides a summary of the CAPELLA study and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Segal-Maurer et al. (2022) Ogbuagu et al. (2023) 52-week phase 2/3 CAPELLA trial 1 cohort in the trial was randomised, placebo controlled and double blind for 14 days 42 sites in 11 countries	72 people aged 12 years or more with stable failing ART (HIV-1 RNA ≥400 copies per mL) for at least 8 weeks and • documented resistance to at least 2 ARTs from at least 3 of the 4 main ART classes • only 1 or 2 fully active ARTs from the 4 main classes that could be combined to form a viable regimen Cohort 1 included the first 36 participants with stable viraemia (decrease of <0.5 log_{10} copies per mL confirming lack of response to ART) and HIV-1 RNA ≥400 copies per mL between the visits Cohort 2 included 36 participants with reduced viraemia (decrease of ≥0.5 log_{10} copies per mL) and/or HIV-1 RNA <400 copies per mL between the visits, and participants eligible for cohort 1 after that cohort was filled In the total trial population: • median age of participants was 52 years (range 23 to 78 years), 75% were male and 41% were white • median HIV-1 RNA was 4.5 log_{10} copies per mL and median CD4 count was 150 cells per mm^3 • 46% of participants had resistance to at least 2 ARTs in all 4 main classes • resistance to recently approved ART for MDR HIV-1 was also seen (ibalizumab 30%, fostemsavir 32%) • 17% had no fully active ART in their optimised background regimen	**Cohort 1** Participants in cohort 1 were randomised 2:1 to receive lenacapavir plus failing ART (n=24) or placebo plus failing ART (n=12) for 14 days All participants subsequently received open label lenacapavir and optimised ART **Intervention** Oral lenacapavir 600 mg on days 1 and 2, and 300 mg on day 8, plus failing ART From day 15, open label SC lenacapavir 927 mg every 6 months plus optimised ART **Comparator** Matching oral placebo on days 1, 2 and 8 plus failing ART From day 15, open label oral lenacapavir (600 mg on days 15 and 16, and 300 mg on day 22), followed by SC lenacapavir 927 mg every 8 months plus optimised ART **Cohort 2** Open label oral lenacapavir (600 mg on days 1 and 2, and 300 mg on day 8), followed by SC lenacapavir 927 mg every 6 months from day 15 plus optimised ART	**Critical outcomes** • Virological suppression • Reduction in viral load • Increase in CD4 counts **Important Outcomes** • Mortality • Treatment failure • Treatment adherence **Safety**

Abbreviations

ART, antiretroviral treatment; CD4, cluster of differentiation 4; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant; RNA, ribonucleic acid; SC, subcutaneous

5. Results

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 and safety of adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?

Outcome	Evidence statement
Clinical effectiveness	
Critical outcomes	
Virological suppression **Certainty of evidence:** Very low	Virological suppression is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. If virological suppression is achieved, an individual has zero 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. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to virological suppression measured at 26 weeks and 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. At week 52 in cohort 1 in the single arm phase of CAPELLA, virological suppression of less than 50 copies per millilitre HIV-1 RNA occurred in 30/36 participants receiving lenacapavir (83%, 95% CI 67% to 94%). A less strict virological suppression of less than 200 copies per millilitre occurred in 31/36 participants (86%, 95% CI 71% to 95%). Similar results were seen at week 26. No comparator was available for this time point and statistical analyses could not be undertaken for these secondary outcomes. **(VERY LOW)** At week 52 in cohorts 1 and 2 of CAPELLA combined, virological suppression of less than 50 copies per millilitre HIV-1 RNA occurred in 56/72 participants receiving lenacapavir (78%, 95% CI 66% to 87%). A less strict virological suppression of less than 200 copies per millilitre occurred in 59/72 participants (82%, 95% CI 71% to 90%). Similar results were seen in cohorts 1 (above) and 2 individually. No comparator was available for this time point and statistical analyses could not be undertaken. Also, outcomes in cohort 2 (and, therefore, the total population) are exploratory only. **(VERY LOW)** **The single arm phase of CAPELLA provides very low certainty evidence that maintenance treatment with lenacapavir plus optimised ART suppresses viral load to less than 50 copies per millilitre and to less than 200 copies per millilitre in about 80% of people with MDR HIV-1 at 52 weeks. No comparator was available at this time point.**
Reduction in viral load **Certainty of evidence:** Very low	Reduction in viral load is important to patients because 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. A reduction in viral load of 0.5 $\log_{10}$ copies per millilitre is considered to be clinically important. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to viral load measured at 15 days, 26 weeks and 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. At day 15 in the randomised controlled phase of the CAPELLA trial (cohort 1), a statistically significant and clinically important reduction in viral load of at least at least 0.5 $\log_{10}$ copies per millilitre HIV-1 RNA from baseline was seen with lenacapavir compared with placebo (primary outcome). In the lenacapavir group, 21/24 participants

	(88%) experienced the reduction compared with 2/12 participants (17%) in the placebo group (absolute difference 71%; 95% CI 35% to 90%, p<0.001). **(VERY LOW)** At week 52 in the single arm phase of the study in cohort 1, mean viral load was reduced from baseline by a mean –2.57 (SD 1.0) log_{10} copies per millilitre HIV-1 RNA (exploratory outcome). No comparator was available for this time point and statistical analyses could not be undertaken. **(VERY LOW)** **The randomised controlled phase of CAPELLA provides very low certainty evidence that statistically significantly more participants achieve a clinically significant reduction in viral load at 15 days with 3 loading doses of oral lenacapavir plus failing ART compared with placebo plus failing ART. About 90% of people with MDR HIV-1 taking lenacapavir had a clinically important reduction compared with about 20% of people taking placebo. All participants continued their failing ART for this period and it is not known if the results would have been the same if ART had been optimised.** **The CAPELLA study also provides very low certainty evidence that ongoing maintenance treatment with subcutaneous lenacapavir 6-monthly plus optimised ART reduces mean viral load in people with MDR HIV-1 at week 52. No comparator was available at this time point and this outcome was exploratory only.**
Increase in baseline CD4 cell counts **Certainty of evidence:** Very low	Increase in CD4 counts is important to patients because 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 occurrence of AIDS defining illnesses and reduced rates of death. A 30% change in the absolute CD4 count or an increase or decrease of 3% is considered to be clinically important. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to CD4 counts measured over 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. At week 52 in the single arm phase of CAPELLA, CD4 counts increased from baseline to week 52 by a mean of 82 cells per microlitre (95% CI 43 to 122 cells per microlitre) in cohort 1 and 113 cells per microlitre (95% CI 70 to 156 cells per microlitre) in cohort 2 (exploratory outcome). These improvements from baseline are likely to be clinically important. No comparator was available for this time point and statistical analyses could not be undertaken. **(VERY LOW)** **The CAPELLA study provides very low certainty evidence that ongoing maintenance treatment with subcutaneous lenacapavir 6-monthly plus optimised ART improves CD4 counts in people with MDR HIV-1 by a clinically important amount at week 52. No comparator was available at this time point and this outcome was exploratory only.**
Important outcomes	
Mortality **Certainty of evidence:** Very low	Mortality is important to patients because individuals with advanced HIV have a high mortality rate because of progressive viral replication and advanced immunosuppression. Interventions which improve the survival outcome are important markers of effective HIV treatment. Mortality was not a prespecified outcome in the phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) included in the evidence review. However, the number of deaths was reported. No deaths were reported in cohort 1 of CAPELLA. In cohort 2, 1 person died from cancer at week 10 and another died from pneumonia at week 82. Neither of the deaths was considered related to lenacapavir treatment. **(VERY LOW)**

	Very low certainty evidence from CAPELLA suggests lenacapavir does not impact mortality in people with MDR HIV-1 over 52 weeks. However, the study may have been too small and too short to detect rare events.
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients because 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. **No evidence was identified for this outcome.**
Treatment failure **Certainty of evidence:** Very low	Treatment failure is important to patients because it reflects the effectiveness of the intervention. Consideration and analysis in those with treatment failure can assist with understanding of developing genotypic and phenotypic resistance patterns to ART agents. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to treatment failure measured at 26 weeks and 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. Of 22/72 participants (11 in each cohort) who met the prespecified criteria for resistance analysis, 8 had resistance-associated mutations to lenacapavir by week 26 and a further person by week 52 (9 in total, 4 in cohort 1 and 5 in cohort 2). Of these, 4/9 had no fully active drugs in their optimised ART and 5/9 had inadequate adherence to ART (including the person who developed emerging resistance between week 26 and week 52). Despite emerging resistance, 4/9 resuppressed (HIV-1 RNA less than 50 copies per millilitre) while continuing lenacapavir (2 with a change in optimised ART and 2 without a change in ART). **(VERY LOW)** At week 52, 16 participants did not have HIV-1 RNA of less than 50 copies per millilitre. Of these, 10 had HIV-1 RNA of 50 copies per millilitre or more suggesting virological suppression was incomplete or failing. **(VERY LOW)** **The CAPELLA study provides very low certainty evidence that lenacapavir resistance may emerge within 26 weeks in people with MDR HIV-1 receiving lenacapavir plus optimised ART**. **Resistance and subsequent treatment failure may be driven by a lack of other fully active ARTs in the optimised background regimen and/or poor adherence to optimised ART. No comparator was available at this time point and this outcome was exploratory only.**
Treatment adherence **Certainty of evidence:** Very low	Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. Effective treatment requires long-term adherence to ART regimens to achieve viral suppression and immune regulation. Poor adherence can increase the risk of treatment failure and add to viral resistant strain development and transmission. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to treatment adherence measured at 26 weeks and 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. 5/9 participants with emerging resistance to lenacapavir had inadequate adherence to their optimised ART (determined from plasma concentrations of key ARTs). 1 person in cohort 2 was withdrawn by the investigator at week 16 because of 'non-compliance'. **(VERY LOW)** **In the CAPELLA study, there were no reports of lack of adherence to lenacapavir treatment, probably because maintenance treatment is given by subcutaneous injection every 6 months. However, lack of adherence to optimised background ART regimens was reported, which may increase the risk of lenacapavir resistance**

	emerging and subsequent treatment failure. This outcome was exploratory, and the evidence provided by CAPELLA is of very low certainty.
Safety	
Frequency of adverse events **Certainty of evidence:** Very low	Safety of lenacapavir is an important to patients because it allows comparison of interventional approaches in this highly complex patient cohort. Treatment-emergent adverse events are those that occur during treatment, which were not present beforehand or which worsen during the study. However, they may not be due to the treatment being studied (lenacapavir). For example, they may be due to the person's condition worsening or another treatment they are taking. Treatment-related adverse events are adverse events that the investigators think have definitely or probably been caused by the treatment they are studying (a side effect of lenacapavir). One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to safety of lenacapavir over 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. In the placebo controlled 14-day period in cohort 1, at least 1 treatment-emergent adverse event was reported in 9/24 participants (38%) in the lenacapavir group and in 3/12 participants (25%) in the placebo group. In that period, nausea was the only adverse event reported in more than 1 participant taking lenacapavir (3/24 participants, 13% compared with 0/12 participants taking placebo). No statistical analyses were reported. **(VERY LOW)** In cohorts 1 and 2 combined over 52 weeks, 47/72 participants (66%) had at least 1 injection site reaction with lenacapavir, including swelling (26/72, 37%), pain (22/72, 31%), erythema (22/72, 31%) and SC nodules (18/72, 25%). **(VERY LOW)** Excluding injection site reactions, 17/72 participants (24%) had at least 1 treatment-related adverse event over 52 weeks. These were nausea, diarrhoea, headache, myalgia, pyrexia, rash, somnolence and vomiting (all n=2, except nausea n=3). **(VERY LOW)** **The CAPELLA study provides very low certainty evidence that, over 52 weeks, around two thirds of people with MDR HIV-1 experience injection site reactions with lenacapavir, and around a quarter of people experience other lenacapavir-related adverse events.**
Frequency of serious adverse events **Certainty of evidence:** Very low	Serious treatment-emergent adverse events include those that result in death or hospitalisation, or cause persistent or significant disability or incapacity. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to safety of lenacapavir over 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. In the placebo controlled 14-day period in cohort 1, no serious adverse events were reported in either group. **(VERY LOW)** In cohorts 1 and 2 combined over 52 weeks, 10 participants had serious adverse events, none of which were considered related to lenacapavir**. (VERY LOW)** **No serious adverse events considered related to lenacapavir were reported in CAPELLA. The study provides very low certainty evidence that, over 52 weeks, most adverse events related to lenacapavir are likely to be mild or moderate in people with MDR HIV-1. However, the study may have been too small and too short to detect rare adverse events.**

Frequency of adverse events leading to discontinuation **Certainty of evidence:** Very low	Stopping treatment because of adverse events is important to patients with MDR HIV-1 because it limits their treatment options further. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to safety of lenacapavir over 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. In the placebo controlled 14-day period in cohort 1, no participants in either group discontinued treatment because of an adverse event. **(VERY LOW)** In cohorts 1 and 2 combined over 52 weeks, only 1 participant discontinued treatment because of an adverse event related to lenacapavir (a subcutaneous nodule, grade 1). **(VERY LOW)** **The CAPELLA study provides very low certainty evidence that, over 52 weeks, adverse events seen with lenacapavir rarely lead to treatment being stopped in people with MDR HIV-1. However, the study may have been too small and too short to detect rare adverse events.**
Frequency of grade 3 to 4 laboratory abnormalities **Certainty of evidence:** Very low	Grading is another way of reporting adverse events, which relates to the intensity of the adverse event, rather than the actual outcome of the event. Grade 3 adverse events are severe and undesirable adverse events, such as those needing hospitalisation, and grade 4 adverse events are life threatening. One phase 2/3 study (Segal-Maurer et al. 2022 and Ogbuagu et al. 2023; CAPELLA) provided evidence relating to safety of lenacapavir over 52 weeks. Participants in cohort 1 were randomised to receive oral lenacapavir or placebo plus their current failing ART for 14 days then, from day 15, all participants received subcutaneous lenacapavir 6-monthly and optimised ART. All participants in cohort 2 received lenacapavir plus optimised ART. In the placebo controlled 14-day period in cohort 1, no adverse events of grade 3 or higher were reported. **(VERY LOW)** In cohorts 1 and 2 combined over 52 weeks, grade 3 or higher laboratory abnormalities occurred in 23/72 participants (32%). Of the 5 participants with grade 4 laboratory abnormalities, 2 had elevated aspartate aminotransferase, 2 had elevated creatinine, and 1 had fasting hyperglycaemia). **(VERY LOW)** **The CAPELLA study provided very low certainty evidence that, over 52 weeks, grade 3 or 4 treatment-emergent adverse events occur in about 30% of people with MDR HIV-1 who are taking lenacapavir in combination with ART.**
Occurrence of new or recurrent clinical event(s) indicating severe immunodeficiency **Certainty of evidence:** Not applicable	**No evidence was identified for this safety outcome.**

Abbreviations

ART, antiretroviral treatment; CD4, cluster of differentiation 4; CI, confidence interval; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant; p, p-value; RNA, ribonucleic acid; SC, subcutaneous; SD, standard deviation

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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified regarding the cost effectiveness of lenacapavir for individuals with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART.**

Abbreviations

ART, antiretroviral treatment; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant

From the evidence selected, are there any subgroups of patients who may benefit from lenacapavir more than the wider population of interest?

No evidence was identified regarding any subgroups of patients who would benefit more from treatment with lenacapavir than the wider population of interest. However, 2 subgroup analyses provide additional data to support decision-making.

Subgroup	Evidence statement
Those who become virologically supressed (<50 copies HIV RNA per mL) compared with those who remain virologically unsuppressed (>50 HIV RNA copies per mL)	At week 52 in cohorts 1 and 2 of CAPELLA combined, virological suppression (less than 50 copies per millilitre HIV-1 RNA) occurred in 56/72 participants receiving lenacapavir (78%). Of the 16 participants (22%) who did not have virological suppression at week 52 while receiving lenacapavir, 10 had HIV-1 RNA of 50 copies per millilitre or more. Of these, 1 had virological rebound (viral load at least 50 copies per millilitre after a previous measure of less than 50 copies per millilitre), 5 never had virological suppression, and 4 later resuppressed with no change in optimised background ART. Of the other 6, 4 discontinued treatment (3 with last available HIV-1 RNA of less than 50 copies per millilitre; 1 with last available HIV-1 RNA of at least 50 copies per millilitre), 1 died and 1 had missing data. Resistance analysis showed 9 people (4 of whom later resuppressed) in the study had lenacapavir resistant mutations at week 52. All 9 were at high risk of developing resistance because of a lack of fully active background ART options or poor adherence. **From the CAPELLA study data, it is likely that most people without virological suppression at week 52 had developed lenacapavir resistant mutations.**
People with no ART options available compared with those with 1 or 2 ART fully or partially virological suppressed ART options available	In cohorts 1 and 2 in the CAPELLA study at week 52, HIV-1 RNA was less than 50 copies per millilitre in 9/12 participants (75%) with no fully active ARTs available, 20/26 participants (77%) with 1 fully active ART available, and 27/34 participants (80%) with at least 2 fully active ARTs available. **Results of the CAPELLA study suggest that the efficacy of lenacapavir was generally similar regardless of number of fully active ARTs in the optimised background ART regimen. Resistance analysis showed that a lack of fully active background ART options was a risk factor for developing lenacapavir resistance.**

Abbreviations

ART, antiretroviral treatment; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant; RNA, ribonucleic acid

6. Discussion

This evidence review includes a phase 2/3 trial (CAPELLA) that studied the safety and efficacy of lenacapavir in 2 cohorts of people with MDR HIV-1, and reported outcomes at 15 days, 26 weeks (Segal-Maurer et al. 2022) and 52 weeks (Ogbuagu et al. 2023). The trial has many limitations.

Only cohort 1 was randomised and placebo controlled, and then only for 14 days. Participants in cohort 1 received 3 loading doses of oral lenacapavir or matching placebo alongside their failing ART until day 15. At this point, ART was optimised and participants in the lenacapavir group began 6-monthly subcutaneous maintenance treatment and participants in the placebo group switched to lenacapavir treatment (oral then subcutaneous; the open label single arm phase of the trial). All participants in cohort 2 received lenacapavir plus optimised ART throughout the study. The baseline characteristics of the cohorts 1 and 2 were generally similar.

Primary and secondary efficacy endpoints were evaluated in cohort 1 of CAPELLA. Efficacy in cohort 2 was not included in the prespecified endpoints because cohort 2 was designed primarily to provide access to lenacapavir for individuals who met the same eligibility criteria as those in cohort 1 but were not eligible for random assignment.

Quality assessment found the randomised controlled phase of CAPELLA was at low risk of bias in most domains. However, it is possible that investigators could become aware of participants' treatment allocation, and there were some differences in baseline characteristics between the lenacapavir and placebo groups, both of which raised concerns. For example, the median overall susceptibility score was 2.0 in the lenacapavir group and 1.5 in the placebo group meaning HIV in participants in the placebo group was less susceptible to background ART. There were also some inconsistencies in data between the papers and the reasons for this are unclear.

The groups in cohort 1 were small (lenacapavir n=24 and placebo n=12) and statistical analysis was powered and reported for the primary outcome only. Even for the primary outcome, it is possible that powering was inadequate because the number of participants in the placebo group may have been too small for sufficient events to occur within the 14-day time period. Outcomes at day 15 were downgraded because failing ART was used rather than optimised ART, which was specified on the PICO. Nevertheless, failing ART was appropriately used to avoid confounding and show that any improvement in viral load at 15 days was likely to be because of lenacapavir, not a change in ART.

Outcomes at 26 and 52 weeks in the second phase of the study were downgraded because there was no comparator, increasing the risk of bias. The lack of comparator means that it is unclear how lenacapavir affected outcomes; for example, whether any participants in the study improved because of lenacapavir or because of the optimised ART regimen alone. Also, the trial protocol states that the outcomes in cohort 2 were exploratory, which means they cannot be relied upon and should be considered hypothesis generating only. Nevertheless, the efficacy outcomes assessed were objective and, therefore, less likely to be biased by unblinded assessment than subjective outcomes.

The CAPELLA study included only 72 participants and, of these, only 66 completed 52 weeks. This means that less common adverse events may not have been identified and the safety profile of lenacapavir is uncertain. MDR HIV-1 is rare so there are few eligible participants for studies. Also, resistance profiles and background treatment regimens differ substantially and are often amended. This means it is difficult to conduct high quality, controlled studies.

Nevertheless, the trial was designed in accordance with relevant regulatory guidance (European public assessment report for lenacapavir).

Participants in CAPELLA were treatment-experienced with MDR HIV-1 and some had experienced treatment failure. In the total study population, 46% of participants had resistance to at least 2 ARTs in all 4 main classes and 17% had no fully active ART in their optimised background regimen. Resistance to newer treatments for MDR HIV-1 was also seen (ibalizumab 30% and fostemsavir 32%). At baseline, median HIV-1 RNA was 4.5 $\log_{10}$ copies per millilitre and median CD4 count was 150 cells per cubic millimetre meaning participants were at risk of complications from HIV.

The median age of participants in CAPELLA was 52 years (range 23 to 78 years). No evidence was identified for children and lenacapavir is not licensed for use in children (Summary of product characteristics). Little evidence is available for females because 75% of participants in CAPELLA were male. The study was undertaken in 11 countries including the USA, Canada and Europe (but not the UK) and 41% of participants were white. It is unclear if the study population is representative of the population with MDR HIV-1 in the UK, and whether the treatment regimens used in the study were the same as those currently used in the UK.

Little information is available in CAPELLA on adherence to treatment. Maintenance treatment with lenacapavir is given subcutaneously every 6 months so adherence to this medicine may be better than for a daily oral treatment. However, lenacapavir is licensed for use in combination with oral ARTs. Oral treatment regimens are complex and adherence is often suboptimal, especially outside of a clinical trial. Poor adherence to a treatment regimen increases the risk of treatment failure and emergence of resistance.

No evidence was identified to determine how lenacapavir affects the quality of life of people with MDR HIV-1, or for the cost effectiveness of the treatment.

7. Conclusion

The study assessed the licensed dosage of lenacapavir, which consists of 3 oral loading doses followed by subcutaneous maintenance treatment 6-monthly. It included a randomised controlled phase in which participants took lenacapavir or placebo plus failing ART for 14 days, followed by a single arm phase in which all participants took lenacapavir and optimised ART for 52 weeks.

CAPELLA provides very low certainty evidence that treatment with lenacapavir plus optimised ART suppresses viral load to less than 50 copies per millilitre and less than 200 copies per millilitre in about 80% of people with MDR HIV-1 at 52 weeks. The randomised controlled phase of the study provides very low certainty evidence that oral lenacapavir plus failing ART statistically significantly reduces viral load by a clinically important amount at 15 days compared with placebo plus failing ART (88% compared with 17% respectively, $p<0.001$). CAPELLA also provides very low certainty evidence that ongoing maintenance treatment with lenacapavir plus optimised ART continues to reduce viral load (mean reduction –2.57 $\log_{10}$ copies per millilitre HIV-1 RNA) at week 52, and improves CD4 counts by a clinically important amount (around 100 cells per microlitre) at that time point.

Very low certainty evidence from CAPELLA shows that lenacapavir resistance may emerge within 26 weeks in people with MDR HIV-1 receiving lenacapavir plus optimised ART. In the study, there were no reports of lack of adherence to lenacapavir treatment, probably because maintenance treatment is given by subcutaneous injection every 6 months. However, lack of adherence to optimised background ART regimens was reported. The study data suggest resistance and subsequent treatment failure may be driven by a lack of other fully active ARTs in the optimised background regimen and/or poor adherence to optimised ART.

Little evidence was identified for mortality. Although very low certainty evidence from CAPELLA suggests lenacapavir does not impact mortality in people with MDR HIV-1 over 52 weeks, the study may have been too small and too short to detect rare events. No evidence was identified to determine whether or not lenacapavir affects quality of life.

CAPELLA provides very low certainty evidence that, over 52 weeks, the adverse events seen with lenacapavir are usually mild or moderate and rarely lead to treatment discontinuation. Over 52 weeks, two thirds of people with MDR HIV-1 experienced injection site reactions with lenacapavir (including swelling, pain, erythema and subcutaneous nodules), and a quarter experienced other lenacapavir-related adverse events (including nausea, diarrhoea, headache, myalgia, pyrexia, rash, somnolence and vomiting). Grade 3 or 4 treatment-emergent adverse events occurred in around a third of people taking lenacapavir plus optimised ART.

No evidence was identified regarding the cost effectiveness of lenacapavir for people with MDR HIV-1 infection who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART. Also, no evidence was found to identify subgroups of patients who may benefit from the addition of lenacapavir to the existing ART regimens more than the wider population of interest. That said, data from CAPELLA suggest that people without virological suppression at week 52 were most at risk of developing lenacapavir resistant mutations. When the number of ART options available to participants were compared, the efficacy of lenacapavir was generally similar regardless of the number of fully active ARTs in the optimised background ART regimen. However, resistance analysis showed that a lack of fully active background ART options was a risk factor for developing lenacapavir resistance.

People with MDR HIV-1 have very few treatment options left and, when viral replication is not suppressed to an undetectable level, they are at increased risk of disease progression, AIDS

and ultimately death. The findings of the evidence review are important because they suggest lenacapavir has antiviral activity for up to 52 weeks and can be added to ART in adults with MDR HIV-1 who have limited or no therapeutic options available to construct a fully suppressive viral regimen from existing ART. In CAPELLA, no major safety concerns were identified with lenacapavir use for up to 52 weeks, but it is not known whether rare adverse events will be identified in future.

Interpretation of the data is limited by the small number of participants, the relatively short follow up period, the complexity of the study population and the variety of ART regimens used to overcome treatment resistance. After 14 days, CAPELLA was a single arm study and, therefore, could not assess causality. Also, the trial protocol states that many of the outcomes were exploratory; therefore, they cannot be relied upon and should be considered hypothesis generating only.

Adherence to treatment is generally better in a clinical trial than in the real world and, if lenacapavir is used, it will be important for people with MDR HIV-1 to take their optimised ART as prescribed.

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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
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 adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?
4. From the evidence selected, are there any subgroups of patients who may benefit from adding lenacapavir to the optimised ART regimen more than the wider population of interest?

P-Population and Indication	People living with HIV-1 infection with limited or no therapeutic options available to construct a fully suppressive viral regiment from existing ART Inability to construct a fully suppressive viral regimen is due to multi-drug resistant HIV. Multi-drug resistance[1] can be due to the following: • Intrinsic multi-drug resistance, where the virus has genetic mutations that render certain ART ineffective (either transmitted at the time of infection, or developed with treatment exposure) AND/OR • Functional multi-drug resistance which affects the ability to use certain ART due to ART tolerability, ART availability, ART safety concerns or contraindications to remaining ART agents Subgroups of interest: • Those who become virologically supressed (<50 copies HIV RNA per mL) compared with those who remain virologically unsuppressed (>50 HIV RNA copies per mL)

[1] NHS England has also defined MDR HIV-1 as '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'

	• No ART options available compared with 1 or 2 ART fully/partially virological suppressed ART options available [**Limited treatment options or no therapeutic options** could be defined as either: • No fully active antiretrovirals (because of either intrinsic or functional multi-drug resistance) **OR** • One or two fully active antiretrovirals that is not causing viral load suppression 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	Lenacapavir [Lenacapavir is used as an additional agent to other standard antiretrovirals. It is given as an oral tablet initially, and then as a subcutaneous injection. It is not used as a sole medication (monotherapy), it needs to be combined with an optimised background regimen of other ART agents]
C-Comparator	Optimised background ART regimens which do not feature lenacapavir [An 'optimised' regimen is usually determined by the multidisciplinary team (MDT). This is 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	**<u>Clinical Effectiveness</u>** *<u>Critical to decision-making:</u>* • **Virological suppression** *Virological suppression is important to patients because it reflects treatment effect (either suppression or failure) of an ART regimen. If virological suppression is achieved, an individual has zero 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 viraemia of HIV RNA <200 copies per mL another pre-defined threshold [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 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 **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 **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 **Low-level viraemia:** A persistent HIV RNA viral load level of between 50-200 copies per mL **Virological blip**: After viral suppression, a single HIV RNA viral load between 50-200 copies per mL followed by an undetectable result] • **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 viral load correlates with reducing the risk HIV transmission to others and a lower risk of disease progression* Examples include but not limited to: ○ 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)][2] • **Increase in baseline CD4 cell counts** *Increase in CD4 counts is important to patients as it reflects the overall immune function of a person*

[2] 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.

	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 occurrence of AIDS defining illnesses 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] [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[3]] [Thresholds which define immunological failure: CD4 count at or below 250 cells/mm following clinical failure [4]OR Persistent CD4 levels below 100 cells/ µL 20 OR CD4 level falls to baseline or below] *<u>Important to decision-making:</u>* • **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* • **Quality of life** *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*

[3] 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

[4] 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/

	Examples include, but not limited to: ○ EQ visual analogue scale and the Functional Assessment of HIV Infection (FAHI) ○ EuroQoL 5-dimension 3-level instrument (EQ-5D-3L); ○ A generic health status measure including descriptive metrics • **Treatment failure** *Treatment failure is important to patients as it reflects the effectiveness of the intervention. Consideration and analysis in those with treatment failure can assist with understanding of developing genotypic and phenotypic resistance patterns to ART agents* Examples include but not limited to: ○ emergence of new resistant mutations or recurrent clinical event(s) indicating severe immunodeficiency (WHO clinical stage 4 conditions after 6 months of effective treatment[5] • **Treatment adherence** *Adherence to treatment is important to patients as it provides an indication of how the treatment is tolerated. Effective treatment requires long-term adherence to ART regimens to achieve viral suppression and immune regulation. Poor adherence can increase the risk of treatment failure and add to viral resistant strain development and transmission* Examples include, but not limited to: ○ Missed doses (observed by research staff review of medication/returned medication) ○ Self-reported adherence measures (e.g., questionnaire methods) ○ Patients opting to remain on lenacapavir ○ Interview methods **<u>Safety</u>** *Safety of lenacapavir is important to patients as it allows comparison of interventional approaches in this highly complex patient cohort.* Examples include, but not limited to:

[5] 1 WHO defined clinical conditions which occur with advanced or severe HIV disease associated with immunodeficiency. WHO Consolidated HIV guidelines. 2016. Annex 10, page 386

	○ Frequency of adverse events ○ Frequency of serious adverse events ○ Adverse events leading to discontinuation ○ Grades 3–4 laboratory abnormalities ○ Occurrence of new or recurrent clinical event(s) indicating severe immunodeficiency ○ Death
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
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2014 to 2024
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
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 English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 11th and 12th January 2024

Database search strategies

Database: Medline ALL

Platform: Ovid

Version: Ovid MEDLINE(R) ALL <1946 to January 10, 2024>

Search date: 11th Jan 2024

Number of results retrieved: 75

Search strategy:

1 (lenacapavir* or sunlenca*).af. (78)

2 limit 1 to english language (75)

3 animals/ not humans/ (5150947)

4 2 not 3 (75)

Database: Embase

Platform: Ovid

Version: Embase <1974 to 2024 January 11>

Search date: 12th Jan 2024

Number of results retrieved: 126

Search strategy:

1 lenacapavir/ (208)

2 (lenacapavir* or sunlenca*).af. (219)

3 1 or 2 (219)

4 limit 3 to english language (211)

5 nonhuman/ not human/ (5363933)

6 4 not 5 (188)

7 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5809704)

8 6 not 7 (126)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley

Version:

CDSR – Issue 1 of 12, January 2024

CENTRAL – Issue 1 of 12, January 2024

Search date: 12th Jan 2024

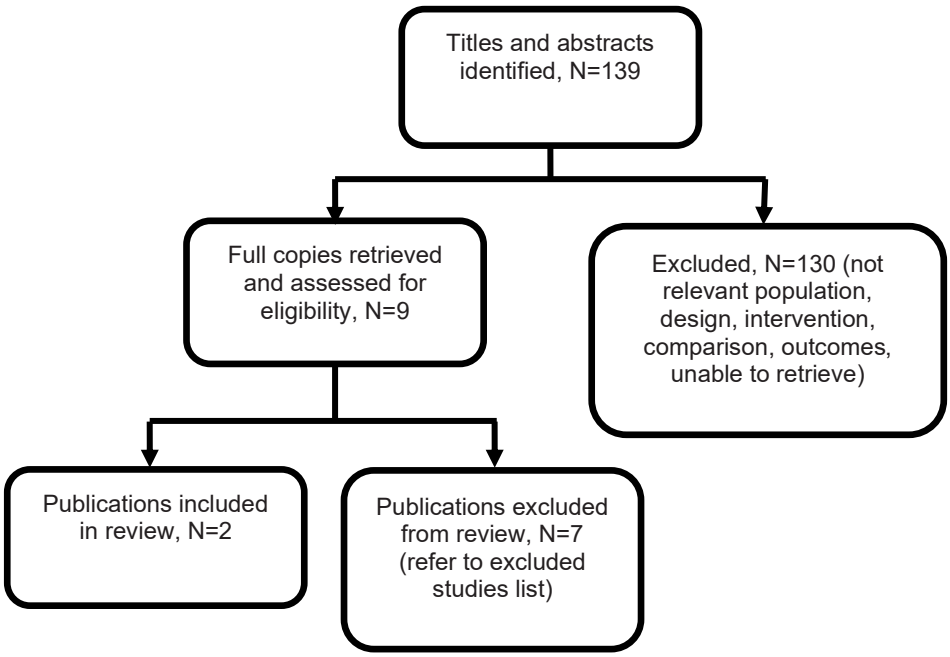
Number of results retrieved: CDSR – 0; CENTRAL – 5.

- #1 lenacapavir* or sunlenca* 32
- #2 "conference":pt or (clinicaltrials or trialsearch):so 725740
- #3 #1 not #2 5

Appendix C Evidence selection

The literature searches identified 139 references. These were screened using their titles and abstracts and 9 references were obtained in full text and assessed for relevance. Of these, 2 references are included in the evidence summary. The remaining 7 references were excluded and 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
Segal-Maurer S, DeJesus E, Stellbrink H-J et al. for the CAPELLA Study Investigators (2022) Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med 386(19): 1793-1803. doi: 10.1056/NEJMoa2115542	Included
Ogbuagu O, Segal-Maurer S, Ratanasuwan W et al. GS-US-200-4625 investigators (2023) Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV 10(8): e497-e505. doi: 10.1016/S2352-3018(23)00113-3	Included
Gupta SK, Berhe M, Crofoot G et al. (2023) Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial. Lancet HIV 10(1): e15-e23. doi: 10.1016/S2352-3018(22)00291-0	Excluded: incorrect population (treatment naïve people)

Appendix D Excluded studies table

Study reference	Reason for exclusion
Chatzidaki I, Curteis T, Luedke H et al. (2023) Indirect Treatment Comparisons of Lenacapavir Plus Optimized Background Regimen Versus Other Treatments for Multidrug-Resistant Human Immunodeficiency Virus. Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 26(6): 810-22	Type of study (unanchored indirect treatment comparison requiring strong assumptions and at high risk of systemic bias)
Gupta SK, Berhe M, Crofoot G et al. (2023) Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial. Lancet HIV 10(1): e15-e23	Incorrect population (treatment naïve people)
Kuritzkes, DR (2023) Kuritzkes, Daniel R (2023) Broadly neutralizing antibodies and long-acting antiretroviral drugs as treatments for HIV. Current opinion in HIV and AIDS 18(4): 225-8	Type of publication type (review article)
Lee NE and Sutherland RK (2023) Lenacapavir and the novel HIV-1 capsid inhibitors: an emerging therapy in the management of multidrug-resistant HIV-1 virus. Current opinion in infectious diseases 36(1): 15-9	Type of publication (review article)
Margot N, Naik V, Vanderveen L et al. (2022) Resistance Analyses in Highly Treatment-Experienced People With Human Immunodeficiency Virus (HIV) Treated With the Novel Capsid HIV Inhibitor Lenacapavir. The Journal of infectious diseases 226(11): 1985-91	Additional analysis of CAPELLA with no additional prespecified PICO outcomes
Margot N, Vanderveen L, Naik V et al. (2022) Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study. The Journal of antimicrobial chemotherapy 77(4): 989-95	Type of study (in vitro)
Margot N, Pennetzdorfer N, Naik V et al. (2022) Cross-resistance to entry inhibitors and lenacapavir resistance through Week 52 in study CAPELLA. Antiviral therapy 28(6): 13596535231220754	Additional analysis of CAPELLA with no additional prespecified PICO outcomes

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Segal-Maurer S, DeJesus E, Stellbrink H-J et al. for the CAPELLA Study Investigators (2022) Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med 386(19): 1793-1803 Ogbuagu O, Segal-Maurer S, Ratanasuwan W et al. GS-US-200-4625 investigators (2023) Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV 10(8): e497-e505 **Study location** 42 sites in 11 countries (USA, Thailand, Italy, France, Canada, Japan, Dominican Republic, Spain, Germany, Taiwan and South Africa) **Study type** 52-week phase 2/3 trial 1 cohort in the trial was randomised, placebo controlled and double blind **Study aim** The study assessed the efficacy and safety of lenacapavir plus ART in people with MDR HIV-1 infection **Study dates** November 2019 to January 2021	**Inclusion criteria** People aged 12 years or more with a stable failing ART (HIV-1 RNA ≥400 copies per mL) for at least 8 weeks and • documented resistance to at least 2 ARTs from at least 3 of the 4 main ART classes • only 1 or 2 fully active ARTs from the 4 main classes that could be combined to form a viable regimen **Exclusion Criteria** These included active serious infections such as tuberculosis, and hepatitis **Total sample size** 72 people were enrolled in 1 of 2 cohorts, according to the change in HIV-1 RNA level between screening and cohort selection visits (14 to 30 days apart) Cohort 1 included the first 36 participants with stable viraemia (decrease of <0.5 log_{10} copies per mL confirming lack of response to ART) and HIV-1 RNA ≥400 copies per mL between the visits Cohort 2 included 36 participants with reduced viraemia (decrease of ≥0.5 log_{10} copies per mL) and/or HIV-1 RNA <400 copies per mL between the visits	**Cohort 1** **Intervention** Oral lenacapavir 600 mg on days 1 and 2, and 300 mg on day 8, plus failing ART From day 15, open label SC lenacapavir 927 mg every 6 months plus optimised ART **Comparator** Matching oral placebo on days 1, 2 and 8 plus failing ART From day 15, open label oral lenacapavir (600 mg on days 15 and 16, and 300 mg on day 22), followed by SC lenacapavir 927 mg every 8 months plus optimised ART **Cohort 2** Open label oral lenacapavir (600 mg on days 1 and 2, and 300 mg on day 8), followed by SC lenacapavir 927 mg every 6 months from day 15 plus optimised ART	Primary and secondary efficacy endpoints were evaluated in cohort 1. Efficacy in cohort 2 was not included in the prespecified endpoints because cohort 2 was designed primarily to provide access to lenacapavir for individuals who met the same eligibility criteria as those in cohort 1 but were not eligible for random assignment 52-week results have been reported in cohorts 1 and 2 combined because the baseline characteristics of the cohorts are generally similar **Critical outcomes** **Virological suppression** Cohort 1 at week 52 (secondary outcomes): • 30/36 participants (83%, 95% CI 67% to 94%) had HIV-1 RNA <50 copies per mL • 31/36 participants (86%, 95% CI 71% to 95%) had HIV-1 RNA <200 copies per mL Total trial population at week 52 (exploratory outcomes): • 56/72 participants (78%, 95% CI 66% to 87%) had HIV-1 RNA <50 copies per mL • 59/72 participants (82%, 95% CI 71% to 90%) had HIV-1 RNA <200 copies per mL **Reduction in viral load** Cohort 1 at day 15 (primary outcome) 21/24 participants (88%) in the lenacapavir group and 2/12 participants (17%) in the placebo group had a decrease in viral load from baseline of at least 0.5 log_{10} copies per mL by day 15 (absolute difference 71%; 95% CI 35% to 90%, p<0.001) At week 52, the mean change in HIV-1 RNA from baseline was –2.57 (SD 1.0) log_{10} copies per mL (exploratory outcome) **Increase in baseline CD4 counts** (exploratory outcome) CD4 counts increased from baseline to week 52 by a mean of: • 82 cells per mm^3 (95% CI 43 to 122 cells per mm^3) in cohort 1 (mean at baseline 161 cells per mm^3, 51% increase) • 113 cells per mm^3 (95% CI 70 to 156 cells per mm^3) in cohort 2 (mean at baseline 258 mm^3 cells per mm^3, 44% increase)	This study was appraised using the Cochrane risk-of-bias tool for randomised trials. Note that this quality assessment tool is relevant to the randomised initial phase of the study, but less suitable for the uncontrolled phase of the study. Limitations for the second phase are descriptive Domain 1: Risk of bias arising from the randomization process 1.1 Yes (computer generated number) 1.2 Probably no (participants were blinded during the initial phase, but investigators may have been able to identify treatment assignment) 1.3 Yes (there are several differences between the baseline characteristics of the lenacapavir and placebo groups) Risk of bias judgement: some concerns Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) 2.1 No (not during the initial phase, but all participants received open label lenacapavir in the second phase of the study) 2.2 No (not during the initial phase, but all participants received open label lenacapavir in the second phase of the study) 2.3 Probably no 2.4 Not applicable 2.5 Not applicable 2.6 Yes 2.7 Not applicable

	(n=3), and participants eligible for cohort 1 after that cohort was filled (n=33) **No. of participants in each treatment group** Participants in cohort 1 were randomised 2:1 to receive lenacapavir plus failing ART (n=24) or placebo plus failing ART (n=12) for 14 days All participants subsequently received open label lenacapavir and optimised ART All participants in cohort 2 received open label lenacapavir. **Baseline characteristics** In cohort 1: • median age of participants was 54 years (range 24 to 71 years), 72% were male and 46% were white • at baseline, median viral load was lower and median CD4 count was higher in the lenacapavir group than in the placebo group (HIV-1 RNA 4.2 $\log_{10}$ copies per mL versus 4.9 $\log_{10}$ copies per mL and 172 cells per mm^3 versus 85 cells per mm^3 respectively) • participants had undergone previous treatment with a median 9 ARTs • 17% had no fully active ART in their optimised background regimen • resistance to at least 2 ARTs in all 4 main classes of ART was reported in 58% of participants in the		**Important outcomes** **Mortality** (not a prespecified outcome) No deaths were reported in cohort 1. In cohort 2, 1 person died from cancer at week 10 and another died from pneumonia at week 82. Neither of the deaths was considered related to lenacapavir **Quality of life** Not reported **Treatment failure** (exploratory outcome) Of 22/72 participants (11 in each cohort) who met the prespecified criteria for resistance analysis, 8 had resistance-associated mutations to lenacapavir by week 26 and a further person by week 52 (9 in total, 4 in cohort 1 and 5 in cohort 2) Of these, 4/9 had no fully active drugs in their optimised ART and 5/9 had inadequate adherence to ART (including the person who developed emerging resistance between week 26 and week 52) Despite emerging resistance, 4/9 resuppressed (HIV-1 RNA <50 copies per mL) while continuing lenacapavir (2 with a change in optimised ART and 2 without a change) At week 52, 16 participants did not have HIV-1 RNA of less than 50 copies per millilitre. Of these, 10 had HIV-1 RNA ≥50 copies per mL **Treatment adherence** (exploratory outcome) 5/9 participants with emerging resistance to lenacapavir had inadequate adherence to their optimised ART (determined from plasma concentrations of key ARTS) at week 52 1 person in cohort 2 was withdrawn by the investigator at week 16 because of 'non-compliance' **Safety** (secondary outcome) **Frequency of adverse events** In the placebo controlled 14-day period, at least 1 adverse event was reported in in 9/24 participants (38%) in the lenacapavir group and in 3/12 participants (25%) in the placebo group In the placebo controlled 14-day period, nausea was the only adverse event reported in more than 1 participant taking lenacapavir (3/24, 13% compared with 0/12 participants taking placebo) In the total population at 52 weeks, excluding injection site reactions, 17/72 participants (24%) had at least 1 adverse event considered related to lenacapavir. These were nausea, diarrhoea,	Risk of bias judgement: low risk Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention) 2.1 No (not during the initial phase, but all participants received open label lenacapavir in the second phase of the study) 2.2 No (not during the initial phase, but all participants received open label lenacapavir in the second phase of the study) 2.3 Not applicable 2.4 Probably no 2.5 Probably no 2.6 Not applicable Risk of bias judgement: low risk Domain 3: Missing outcome data 3.1 Yes (no participants lost to follow up in phase 1 and 3 lost to follow up in phase 2) 3.2 Not applicable 3.3 Not applicable 3.4 Not applicable Risk of bias judgement: low risk Domain 4: Risk of bias in measurement of the outcome 4.1 No (validated and objective outcomes) 4.2 Probably no 4.3 No (not during the initial phase, but all participants received open label lenacapavir in the second phase of the study) 4.4 Not applicable 4.5 Not applicable Risk of bias judgement: low risk

	lenacapavir group and 25% of participants in the placebo group • median overall susceptibility score for optimised ART was 2.0 in the lenacapavir group and 1.5 in the placebo group[a] In the total trial population: • median age of participants was 52 years (range 23 to 78 years), 75% were male and 41% were white • median HIV-1 RNA was 4.5 log_{10} copies per mL • median CD4 count was 150 cells per mm^3 • 46% of participants in the trial had resistance to at least 2 ARTs in all 4 main classes • resistance to recently approved ART for MDR HIV-1 was also seen (ibalizumab 30%, fostemsavir 32%) • 17% had no fully active ART in their optimised background regimen		headache, myalgia, pyrexia, rash, somnolence and vomiting (all n=2, except nausea n=3). Most adverse events seen with lenacapavir were reportedly mild or moderate 47/72 participants (66%) had at least 1 injection site reaction with lenacapavir, including swelling (26/72, 37%), pain (22/72, 31%), erythema (22/72, 31%) and SC nodules (18/72, 25%) **Frequency of serious adverse events** In the placebo controlled 14-day period, no serious adverse events were reported in either group In the total study population at week 52, 10 participants had serious adverse events, none of which were considered related to lenacapavir **Adverse events leading to discontinuation** In the placebo controlled 14-day period, no participants discontinued treatment because of an adverse event in either group In the total study population at week 52, only 1 participant discontinued treatment because of an adverse event related to lenacapavir (SC nodule) **Grade 3–4 laboratory abnormalities** In the placebo controlled 14-day period, no adverse events of grade 3 or higher were reported In the total study population at week 52, grade 3 or higher laboratory abnormalities occurred in 23/72 participants (32%) Of the 5 participants with grade 4 laboratory abnormalities, 2 had elevated aspartate aminotransferase, 2 had elevated creatinine, and 1 had fasting hyperglycaemia). **Occurrence of new or recurrent clinical event(s) indicating severe immunodeficiency** Not reported	Domain 5: Risk of bias in selection of the reported result 5.1 Yes 5.2 No 5.3 No Risk of bias judgement: low risk Overall risk of bias judgement: **some concerns** Other comments: the randomised controlled phase of the study was low risk in most domains, although there were some differences in baseline characteristics between the lenacapavir and placebo groups which raises some concerns. Participants received failing ART in this phase of the study, rather than optimised ART All participants received open label lenacapavir in the second phase of the study, which increases the risk of bias. However, the efficacy outcomes assessed were objective and, therefore, less likely to be biased by unblinded assessment compared with subjective outcomes. The study included only 72 participants and only 66 completed the study; therefore, less common adverse events may not have been identified. There were some inconsistencies in data between the papers and the reasons for this are unclear Source of funding: Gilead Sciences (the marketing authorisation holder for lenacapavir)

Abbreviations

ART, antiretroviral treatment; CD4, cluster of differentiation 4; CI, confidence interval; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant; mL, millilitre; mm^3, cubic millimetre or microlitre; p, p-value; RNA, ribonucleic acid; SC, subcutaneous; SD, standard deviation

a The drug susceptibility score to an individual ART was determined according to a proprietary algorithm, with 1.0 indicating full susceptibility, 0.5 partial susceptibility, and 0 no susceptibility. The overall susceptibility score of the optimised background ART was the sum of the individual scores.

Appendix F Quality appraisal checklists

Cochrane risk-of-bias tool for randomized trials checklist

Domain 1: Risk of bias arising from the randomization process	
1.1 Was the allocation sequence random?	
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1. Were participants aware of their assigned intervention during the trial?	
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 3: Missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	

Risk-of-bias judgement	Low / High / Some concerns
Domain 4: Risk of bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	
Risk-of-bias judgement	Low / High / Some concerns
Domain 5: Risk of bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	
5.2.... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	
5.3... multiple eligible analyses of the data?	
Risk-of-bias judgement	Low / High / Some concerns
Overall risk-of-bias judgement	Low / High / Some concerns

Appendix G GRADE profiles

Table 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 clinical effectiveness and safety of adding lenacapavir to the optimised ART regimen compared with the optimised ART regimen alone?

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Lenacapavir (oral plus failing ART for 14 days then SC plus optimised ART)[a]	Placebo (for 14 days only)[b]	Result (95%CI)		
Virological suppression (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in cohort 1 with HIV-1 RNA <50 copies per mL at week 52 (secondary outcome) (lower HIV-1 RNA is beneficial and <50 copies per mL indicates virological suppression)									
1 single arm trial (cohort 1[c]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	30/36 participants (83%, 95% CI 67% to 94%)	Not applicable	No statistical analysis	Critical	Very low
Number of participants in cohort 1 with HIV-1 RNA <200 copies per mL at week 52 (secondary outcome) (lower HIV-1 RNA is beneficial and <200 copies per mL indicates less strict virological suppression or low-level viraemia)									
1 single arm trial (cohort 1[c]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	31/36 participants (86%, 95% CI 71% to 95%)	Not applicable	No statistical analysis	Critical	Very low

Number of participants in the total population with HIV-1 RNA <50 copies per mL at week 52 (exploratory outcome) (lower HIV-1 RNA is beneficial and <50 copies per mL indicates virological suppression)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	56/72 participants (78%, 95% CI 66% to 87%)	Not applicable	No statistical analysis	Critical	Very low
Number of participants in the total population with HIV-1 RNA <200 copies per mL at week 52 (exploratory outcome) (lower HIV-1 RNA is beneficial and <200 copies per mL indicates less strict virological suppression or low-level viraemia)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	59/72 participants (82%, 95% CI 71% to 90%)	Not applicable	No statistical analysis	Critical	Very low
Reduction in viral load (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in cohort 1 with a decrease in viral load from baseline of at least 0.5 log_{10} copies per mL by day 15 (primary outcome) (lower viral load is beneficial and a reduction in viral load of 0.5 log_{10} copies/mL is considered to be clinically important)									
1 RCT (cohort 1[c]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	Serious limitations[3]	Serious indirectness[4]	Not applicable	No serious imprecision	21/24 participants (88%)	2/12 participants (17%)	Absolute difference 71% (95% CI 35% to 90%, p<0.001)	Critical	Very low
Mean reduction in HIV-1 RNA from baseline to week 52 in cohort 1 (exploratory outcome) (lower HIV-1 RNA and a greater mean reduction is beneficial)									
1 single arm trial (cohort 1[c]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	No serious imprecision	–2.57 (SD 1.0) log_{10} copies per mL	Not applicable	No statistical analysis	Critical	Very low

Increase in baseline CD4 cell counts (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Mean increase in CD4 counts from baseline to week 52 in the total population (exploratory outcome) (higher CD4 count is beneficial and a 30% change in the absolute CD4 count or an increase or decrease of 3% is considered to be clinically important)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	82 cells per mm^3 (95% CI 43 to 122 cells per mm^3) in cohort 1 113 cells per mm^3 (95% CI 70 to 156 cells per mm^3) in cohort 2	Not applicable	No statistical analysis 51% increase from baseline in cohort 1 44% increase from baseline in cohort 2	Critical	Very low
Mortality (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in the total population who died during follow up (not a prespecified outcome)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	2 people died (at week 10 and week 82) Both deaths were considered unrelated to lenacapavir	Not applicable	No statistical analysis	Important	Very low
Treatment failure (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in the total population who met the prespecified criteria for resistance analysis and had resistance-associated mutations to lenacapavir by week 26 (exploratory outcome) (resistant mutations are harmful because they stop the treatment suppressing the HIV virus)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	8/22 participants (36%)	Not applicable	No statistical analysis	Important	Very low

Number of participants in the total population who met the prespecified criteria for resistance analysis and had resistance-associated mutations to lenacapavir by week 52 (exploratory outcome) (resistant mutations are harmful because they stop the treatment suppressing the HIV virus)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	9/22 participants (41%)	Not applicable	No statistical analysis	Important	Very low
Number of participants in the total population with HIV-1 RNA ≥50 copies per mL at week 52 (exploratory outcome) (lower HIV-1 RNA is beneficial and ≥50 copies per mL indicates that virological suppression may be incomplete or failing)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	10/16 participants (63%) who did not have HIV-1 RNA <50 copies per mL	Not applicable	No statistical analysis	Important	Very low
Treatment adherence (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in the total population with inadequate adherence to treatment at week 52 (exploratory outcome) (inadequate adherence is harmful because missing doses reduces suppression of the HIV virus)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	5/9 participants (56%) with emerging resistance to lenacapavir had inadequate adherence to their optimised ART 1 person was withdrawn from the trial because of 'non-compliance'	Not applicable	No statistical analysis	Important	Very low

Safety (1 phase 2/3 study: RCT for 14 days then open label single arm)									
Number of participants in cohort 1 with at least 1 treatment-emergent adverse event at 15 days (higher result indicates harm)									
1 RCT (cohort 1[c]) Segal-Maurer S et al. (2022) Ogbuagu O et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	9/24 participants (38%)	3/12 participants (25%)	No statistical analysis	Safety	Very low
Number of participants in the total population with at least 1 treatment-related adverse event (excluding injection site reactions) considered related to lenacapavir at 52 weeks (higher result indicates harm)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	17/72 participants (24%)	Not applicable	No statistical analysis	Safety	Very low
Number of participants in the total population with at least 1 treatment-related injection site reaction at 52 weeks (higher result indicates harm)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	47/72 participants (66%)	Not applicable	No statistical analysis	Safety	Very low
Number of participants in cohort 1 with at least 1 serious treatment-emergent adverse event at 15 days (higher result indicates harm)									
1 RCT (cohort 1[c]) Segal-Maurer S et al. (2022) Ogbuagu O et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	0/24 participants (0%)	0/12 participants (0%)	No statistical analysis	Safety	Very low

Number of participants in the total population with at least 1 serious treatment-emergent adverse event at 52 weeks (higher result indicates harm)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	10/72 participants (14%) All were considered unrelated to lenacapavir	Not applicable	No statistical analysis	Safety	Very low
Number of participants in cohort 1 with adverse events leading to discontinuation of treatment at 15 days (higher result indicates harm)									
1 RCT (cohort 1[c]) Segal-Maurer S et al. (2022) Ogbuagu O et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	0/24 participants (0%)	0/12 participants (0%)	No statistical analysis	Safety	Very low
Number of participants in the total population with adverse events leading to discontinuation of treatment at 52 weeks (higher result indicates harm)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	1/72 participants (1%, SC nodule)	Not applicable	No statistical analysis	Safety	Very low
Number of participants in cohort 1 with grade 3 or 4 laboratory abnormalities at 15 days (higher result indicates harm)									
1 RCT (cohort 1[c]) Segal-Maurer S et al. (2022) Ogbuagu O et al. (2023)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	0/24 participants (0%)	0/12 participants (0%)	No statistical analysis	Safety	Very low

Number of participants in the total population with grade 3 or 4 laboratory abnormalities at 52 weeks (higher result indicates harm)									
1 single arm trial (cohorts 1 and 2[d]) Segal-Maurer S et al. (2022) Ogbuagu et al. (2023)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	23/72 participants (32%)	Not applicable	No statistical analysis	Safety	Very low

Abbreviations

ART, antiretroviral treatment; CD4, cluster of differentiation 4; CI, confidence interval; HIV-1, Human Immunodeficiency Virus 1; MDR, multi-drug resistant; mL, millilitre; mm^3, cubic millilitre or microlitre; p, p-value; RCT, randomised controlled trial; RNA, ribonucleic acid; SC, subcutaneous; SD, standard deviation

1 Downgraded. No comparator arm. All participants in cohort 1 received open label lenacapavir after day 14 and some outcomes are exploratory only or not prespecified
2 Downgraded. No comparator arm and outcomes in cohort 2 (and, therefore, the total population) are exploratory only
3 Downgraded. Quality assessment raised some concerns about investigators potentially being unblinded and differences in baseline characteristics between the groups. Also, sample sizes are small
4 Downgraded. The controlled phase of the study used failing ART not optimised ART

a Oral lenacapavir 600 mg on days 1 and 2, and 300 mg on day 8, plus failing ART then, from day 15, open label SC lenacapavir 927 mg every 6 months plus optimised ART
b Matching oral placebo on days 1, 2 and 8 plus failing ART then, from day 15, open label oral lenacapavir (600 mg on days 15 and 16, and 300 mg on day 22), followed by open label SC lenacapavir 927 mg every 8 months plus optimised ART
c Cohort 1 included the first 36 participants with stable viraemia (decrease of <0.5 log_{10} copies per mL confirming lack of response to ART) and HIV-1 RNA ≥400 copies per mL between the visits (phase 3 RCT, quality starts at 'high')
d Cohort 2 included 36 participants with reduced viraemia and/or HIV-1 RNA <400 copies per mL between the visits (n=3), and participants eligible for cohort 1 after that cohort was filled (n=33). 52-week results have been reported in cohorts 1 and 2 combined because the baseline characteristics of the cohorts are generally similar (phase 2 open label single arm trial with exploratory outcomes, quality starts at 'low')

References

Included studies

- Ogbuagu O, Segal-Maurer S, Ratanasuwan W et al. GS-US-200-4625 investigators (2023) Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV 10(8): e497-e505
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- Gilead Sciences Ltd 2023 Sunlenca: Summary of product characteristics

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