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Consensus recommendations for the use of novel antiretrovirals in persons with HIV who are heavily treatment-experienced and/or have multidrug-resistant HIV-1: Endorsed by the American Academy of HIV Medicine, American College of Clinical Pharmacy: An executive summary

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SPECIAL ARTICLE

Consensus recommendations for the use of novel antiretrovirals in persons with HIV who are heavily treatment-experienced and/or have multidrug-resistant HIV-1: Endorsed by the American Academy of HIV Medicine, American College of Clinical Pharmacy: An executive summary

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Abstract

Treatment options are currently limited for persons with HIV-1 (PWH) who are heavily treatment-experienced and/or have multidrug-resistant HIV-1. Three agents have been approved by the U.S. Food and Drug Administration (FDA) since 2018, representing a significant advancement for this population: ibalizumab, fostemsavir, and lenacapavir. However, there is a paucity of recommendations endorsed by national and international guidelines describing the optimal use (e.g., selection and monitoring after initiation) of these novel antiretrovirals in this population. To address this gap, a modified Delphi technique was used to develop these consensus recommendations that establish a framework for initiating and managing ibalizumab, fostemsavir, or lenacapavir in PWH who are heavily treatment-experienced and/or have multidrug-resistant HIV-1. In addition, future areas of research are also identified and discussed in the main document.

KEYWORDS
anti-HIV agents, antiretrovirals, attachment inhibitor, capsid inhibitor, drug resistance, HIV, post-attachment inhibitor

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For affiliations refer to page 357.

TABLE 1 Summary of consensus questions and recommendations for the use of novel antiretrovirals in persons with HIV-1 (PWH) who are heavily treatment-experienced (HTE) and/or have multidrug-resistant (MDR) HIV-1.

Ibalizumab

Question 1: In which PWH should ibalizumab be used or considered?

R1. For adult PWH who are HTE with MDR HIV-1 and unable to achieve or maintain virologic suppression on their current ART, we recommend adding ibalizumab to an optimized background regimen (OBR), which should include at least one fully active agent.
(rating 100% agree)

Question 2: What baseline and follow-up laboratory testing, including frequency, should be performed to monitor safety and effectiveness of ibalizumab?

R1. For adult PWH who are HTE with MDR HIV-1 eligible for ibalizumab, we do not recommend resistance testing for ibalizumab before initiation (*conditional recommendation due to lack of currently available platform and interpretive criteria*). Resistance testing remains necessary to determine the components of the OBR.
(rating 100% agree)

R2. We recommend plasma HIV-1 RNA monitoring every 4–8 weeks, but no later than 12 weeks, for PWH receiving ibalizumab to assess virologic response.
(rating 100% agree)

R3. For PWH receiving ibalizumab who experience a loss of virologic suppression (e.g., detectable viremia after virologic suppression), genotypic testing is not recommended (*conditional recommendation due to lack of currently available platform and interpretive criteria*). There are insufficient data on the continued use of ibalizumab in PWH who do not experience sustained reduction in plasma HIV-1 RNA or virologic suppression.
(rating 100% agree)

R4. For PWH receiving ibalizumab, we recommend CD4 count monitoring every 3–6 months to assess immunologic response.
(rating 100% agree)

Question 3: What clinical factors should be considered before initiating ibalizumab?

R1. For adult PWH who are HTE with MDR HIV-1, we do not recommend that previous treatment with attachment inhibitors (e.g., maraviroc, fostemsavir) impact candidacy for ibalizumab.
(rating 100% agree)

R2. We do not recommend adjustment for initial or maintenance doses of ibalizumab in those with hepatic dysfunction or renal dysfunction, including hemodialysis. There is insufficient evidence for or against dosing modification based on body weight.
(rating 100% agree)

R3. We recommend evaluating acceptability, feasibility, and barriers before initiation of ibalizumab due to intravenous administration.
(rating 100% agree)

R4. We do not recommend evaluating ibalizumab for potential CYP-mediated or drug transporter interactions due to its pharmacokinetic profile. Evaluation for drug interactions remains necessary for the components of the OBR.
(rating 100% agree)

Question 4: What factors should be considered for select populations receiving ibalizumab?

R1. For persons who are HTE with MDR HIV-1 who are less than 18 years old, of childbearing potential not using an effective method of contraception, or pregnant, there is insufficient evidence for or against using ibalizumab.
(rating 100% agree)

Fostemsavir

Question 1: In which PWH should fostemsavir be used or considered?

R1. For adult PWH who are HTE with MDR HIV-1 and unable to achieve or maintain virologic suppression on their current ART, we recommend adding fostemsavir to an OBR that includes at least one other active drug. If another active drug cannot be included, then the OBR should include partially active agents (preferably several).
(rating 100% agree)

Question 2: What baseline and follow-up laboratory testing, including frequency, should be performed to monitor safety and effectiveness of fostemsavir?

R1. For adult PWH who are HTE with MDR HIV-1 eligible for fostemsavir, we do not recommend resistance testing for fostemsavir before initiation (*conditional recommendation due to lack of currently available platform and interpretive criteria*). Resistance testing remains necessary to determine the components of the OBR.
(rating 100% agree)

R2. We recommend plasma HIV-1 RNA monitoring every 4–8 weeks, but no later than 12 weeks, for PWH receiving fostemsavir to assess virologic response.
(rating 100% agree)

R3. For PWH receiving fostemsavir who experience a loss of virologic suppression, resistance testing to evaluate gp120 resistance-associated mutations with decreased susceptibility to temsavir is not recommended (*conditional recommendation due to lack of currently available platform and interpretive criteria*). There are insufficient data on the continued use of fostemsavir in PWH who do not experience sustained reduction in plasma HIV-1 RNA or virologic suppression.
(rating 100% agree)

(Continues)

TABLE 1 (Continued)

R4. For PWH receiving fostemsavir, we recommend CD4 count monitoring every 3–6 months to assess immunologic response.
(rating 100% agree)

Question 3: What clinical factors should be considered before initiating fostemsavir?

R1. For adult PWH who are HTE with MDR HIV-1, we do not recommend that previous treatment with attachment inhibitors (e.g., ibalizumab, maraviroc) impact candidacy for fostemsavir.
(rating 100% agree)

R2. We do not recommend fostemsavir dosage adjustment for low or high body weight, hepatic dysfunction, or renal dysfunction, including hemodialysis.
(rating 100% agree)

R3. We recommend evaluating fostemsavir for potential CYP-mediated or drug transporter interactions. Evaluation for drug interactions remains necessary for the components of the OBR.
(rating 100% agree)

Question 4: What factors should be considered for select populations receiving fostemsavir?

R1. For persons who are HTE with MDR HIV-1 who are less than 18 years old, of childbearing potential not using highly effective methods of contraception, or pregnant, there is insufficient evidence for or against the use of fostemsavir.
(rating 100% agree)

Lenacapavir

Question 1: In which PWH should lenacapavir be used or considered?

R1. For adult PWH who are HTE with MDR HIV-1 and unable to achieve or maintain virologic suppression on their current ART, we recommend adding lenacapavir to an OBR that includes at least one other active drug. If another active drug cannot be included, then the OBR should include partially active agents (preferably several).
(rating 100% agree)

Question 2: What baseline and follow-up laboratory testing, including frequency, should be performed to monitor safety and effectiveness of lenacapavir?

R1. For adult PWH who are HTE with MDR HIV-1 eligible for lenacapavir, we do not recommend resistance testing for lenacapavir before initiation (*conditional recommendation due to lack of currently available platform and interpretive criteria*). Resistance testing remains necessary to determine the components of the OBR.
(rating 100% agree)

R2. We recommend plasma HIV-1 RNA monitoring within 4 weeks of the oral administration phase and every 8–12 weeks during the subcutaneous administration phase to assess virologic response.
(rating 100% agree)

R3. For PWH receiving lenacapavir who experience a loss of virologic suppression, resistance testing is not available and is not recommended (*conditional recommendation due to lack of currently available platform and interpretive criteria*). There are insufficient data on the continued use of lenacapavir in PWH who do not experience sustained reduction in plasma HIV-1 RNA or virologic suppression.
(rating 100% agree)

R4. For PWH receiving lenacapavir, we recommend CD4 count monitoring every 3–6 months to assess immunologic response.
(rating 100% agree)

Question 3: What clinical factors should be considered before initiating lenacapavir?

R1. For adult PWH who are HTE with MDR HIV-1, we do not recommend that previous treatment with any antiretroviral therapy impact candidacy for lenacapavir.
(rating 100% agree)

R2. We do not recommend lenacapavir dosage adjustment in mild to moderate renal impairment (CrCl ≥15 mL/min) or mild to moderate hepatic dysfunction (Child-Pugh Class A or B). There is insufficient evidence for or against lenacapavir dosing modification based on body weight, severe hepatic dysfunction (Child-Pugh Class C), or end-stage renal disease, including hemodialysis.
(rating 100% agree)

R3. We recommend evaluating acceptability, feasibility, and barriers that may be related to subcutaneous administration before initiating lenacapavir.
(rating 100% agree)

R4. We recommend evaluating lenacapavir for potential CYP-mediated or drug transporter interactions. Evaluation for drug interactions remains necessary for the components of the OBR.
(rating 100% agree)

Question 4: What factors should be considered for select populations receiving lenacapavir?

R1. For persons who are HTE with MDR HIV-1 who are less than 18 years old, of childbearing potential not using highly effective methods of contraception, or pregnant, there is insufficient evidence for or against the use of lenacapavir.
(rating 100% agree)

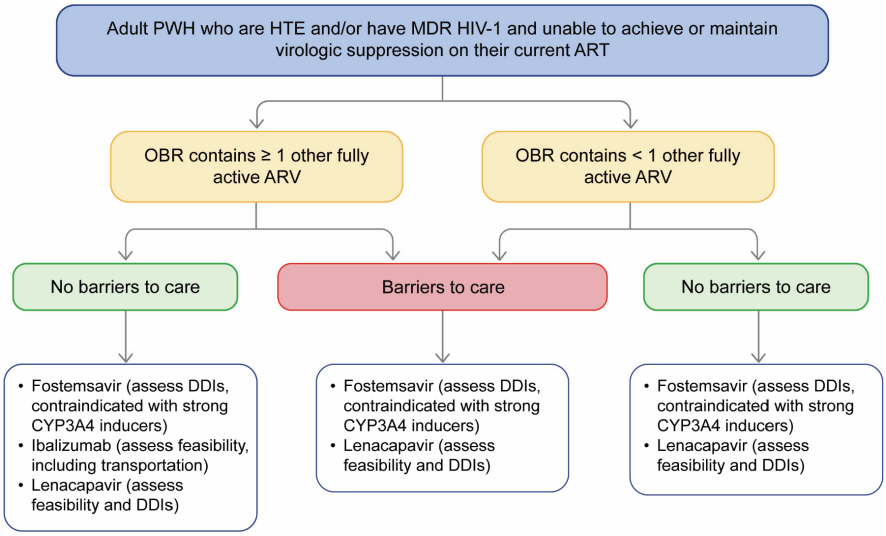

FIGURE 1 Algorithmic approach to major decisions for selecting novel antiretrovirals (ARVs) for PWH who are heavily treatment-experienced (HTE) and/or have multidrug-resistant (MDR) HIV-1. This algorithm, based on these consensus recommendations, provides the framework for the selection of novel ARVs for PWH who are HTE and/or have MDR HIV-1. This process involves the consideration of crucial decision points, which include evaluating the activity of the components of the optimized background regimen (OBR) and identifying potential barriers to care. The ideal approach associated with improved virologic response rates involves combining the novel ARV with an OBR that includes at least one fully active agent. If this is not feasible, the novel ARV can be combined with an OBR that contains at least one additional ARV with partial activity. The decision-making process encompasses patient-specific characteristics, comorbidities, potential drug interactions (DDIs), resistance profiles, tolerability, and considerations related to medication access (e.g., limitations with transportation or geographic proximity) and adherence, including route and frequency of administration (e.g., twice-daily dosing with fostemsavir), as well as social and environmental factors. A resistance interpretation system should be utilized to determine the overall susceptibility scoring and activity of ARVs when constructing an OBR. It is important to note that the listing of reasonable novel ARVs for each scenario is presented in alphabetical order, signifying no preference. Additionally, this figure encompasses the major decision points for selecting novel ARVs, but its applicability may vary across patient-specific or clinical scenarios. PWH who are HTE and/or have MDR HIV-1 are diverse, which highlights the importance of shared decision-making and collaboration between clinicians and patients when choosing novel ARVs. This process should consider the patient's individual experiences, knowledge, goals, needs, medical history, severity of illness and treatment burden, social support, and ability to follow treatment. Copyright Shelly Saboo.

1 | EXECUTIVE SUMMARY

Antiretroviral therapy (ART) for persons with HIV-1 (PWH) has evolved, introducing new agents, formulations, and regimens. Nevertheless, drug resistance, adverse effects, and limited options still pose challenges. These challenges limit therapeutic options and can have dire consequences, including higher risks of treatment failure, worsened clinical outcomes, increased transmission of HIV, and higher mortality rates.

The use of enfuvirtide and maraviroc, previously used for PWH who are heavily treatment-experienced (HTE) and/or have multidrug-resistant (MDR) HIV-1, was limited by pretreatment requirements, efficacy, and safety. The recent approval of novel antiretroviral agents for PWH who are HTE and/or have MDR HIV-1 offers encouraging options for virologic suppression and immune restoration in this population. However, integrating these agents into practice is complex and is further limited by the scarcity of recommendations from national and international guidelines and the lack of commercially available resistance testing. These are major barriers for clinicians selecting, managing, and monitoring ART for these patients.

To address these limitations, a diverse panel of authors with expertise in HIV pharmacotherapy, biostatistics, and scientific research were assembled and utilized a modified Delphi technique to develop consensus questions and recommendations for the utilization of ibalizumab, fostemsavir, and lenacapavir in PWH who are HTE and/or have MDR HIV-1. A summary of the questions and recommendations is shown in Table 1. Based on these consensus recommendations, an algorithm was developed to provide an overview of considerations for selecting novel ARVs for PWH who are HTE and/or have MDR HIV-1 (Figure 1). Please refer to the main document[1] for evidence summaries for each respective recommendation, future directions with each agent, and references.

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CONFLICT OF INTEREST STATEMENT

Author personal and financial relationships with industry and other entities are detailed in Appendix 1.

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APPENDIX 1

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