
Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

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Clinical/Medical**

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Infections
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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products² regulated by CDER and CBER for the treatment of cancer.³ Specifically, this guidance includes recommendations regarding the inclusion of patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, the availability of adequate safety data, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and

¹ This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For the purposes of this guidance, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

³ Topics of the other three guidances are related to eligibility criteria for patients with brain metastases, for patients with organ dysfunction or prior or current malignancies, and regarding minimum age considerations for inclusion of pediatric patients.

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lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.^{4,5}

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice and should be considered to avoid jeopardizing patient safety.

Trial design and methodological approaches are important considerations when enrolling a broader population and are addressed elsewhere^{6,7} and are not addressed in this guidance because the considerations are not specific to enrolling patients with HIV, HBV, or HCV infections.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HIV and HBV infections can be chronically managed and HCV infections can be cured with contemporary antiviral therapy. These viral infections may increase the risk of development of several malignancies. However, exclusion of patients with HIV, HBV, or HCV infections from cancer clinical trials remains common in most studies of investigational drugs. Expanding cancer clinical trial eligibility to be more inclusive of patients with HIV, HBV, or HCV infections is justified in many cases, and may accelerate the development of effective therapies in cancer patients with these chronic infections. Designing cancer clinical trials that include patients with HIV, HBV, or HCV infections and including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

⁴ Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, *NEJM*, 376:1504-1505.

⁵ Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, *JCO*, 35(33): 3737-3744.

⁶ See the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁷ Jin S, Pazdur R, Sridhara R, 2017, Re-Evaluating Eligibility Criteria for Oncology Clinical Trials: Analysis of Investigational New Drug Applications in 2015, *JCO*, 35(33): 3745-3752.

III. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients infected with HIV, HBV, or HCV in cancer clinical trials. Eligibility criteria that address requirements regarding relevant concurrent antiviral and other therapies (e.g., antibiotic prophylaxis) and degree of immunocompetence in patients with HIV, HBV, or HCV infections should be designed in a manner that is appropriate for a given cancer, investigational drug (for instance taking into account immunosuppressive potential), and intended use population.⁸ In cases where there is a strong rationale for exclusion, the rationale should be addressed in the trial protocol.

The following recommendations for eligibility criteria for patients with cancer and concurrent HIV infection are focused on evaluation of immune function and HIV therapy. The following recommendations for eligibility criteria for patients with cancer who have evidence of chronic HBV or with history of chronic HCV or virologically suppressed on HCV treatment are focused on liver-related laboratories and HBV/HCV therapy.

A. Recommendations for patients with HIV infection

1. Evaluation of immune function

- **Eligibility based on CD4+ T-cell counts**
 - Patients with CD4+ T-cell (CD4+) counts \geq 350 cells/uL should generally be eligible for any study.
 - Patients with a lower CD4+ count ($<$ 350 cells/uL) should generally be eligible if the patient has a potentially curable malignancy or for interventions in a later stage of development that have demonstrated prior activity with a given cancer.
- **Eligibility based on history of AIDS (acquired immunodeficiency syndrome)-defining opportunistic infections**
 - Patients without a history of AIDS-defining opportunistic infections should generally be eligible for any study.
 - Patients with a history of AIDS-defining opportunistic infections may be eligible, taking into account the time frame and cancer type:
 - In general, patients should be eligible if they have not had an opportunistic infection within the past 12 months.

⁸ Uldrick T, Ison G, Rudek M, et al., 2017, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group, JCO, 35(33): 3774–3780.

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- For studies of patients with a history of AIDS-defining cancers (e.g., Kaposi's sarcoma, aggressive B-cell lymphoma, and invasive cervical cancer) with curative potential, exclusion of patients with uncontrolled opportunistic infections may be appropriate.
- Patients on prophylactic antimicrobials should be included, although patients taking specific antimicrobial drugs where there may be drug-drug interactions or overlapping toxicities should if appropriate, be changed to an alternative antimicrobial, or if not, be excluded.

2. *HIV therapy*⁹

- **Timing of antiretroviral therapy (ART) initiation** – Eligibility criteria specifying timing of initiation of ART should be based on study goals and take into consideration patients recently diagnosed with HIV or patients not on effective ART. Effective ART is defined as a drug, dosage, and schedule associated with reduction and control of the viral load.
 - **For advanced cancer settings in which there is not curative intent:** To ensure that effective ART is tolerated and that toxicities are not confused with investigational drug toxicities, trial participants should be on established ART for at least four weeks and have an HIV viral load less than 400 copies/mL prior to enrollment.
 - **For therapies given in a potentially curative setting:** Participants should agree to adhere to ART based on protocol defined treatment guidelines taking into account any evidence for multidrug resistance.
- **Exclusion of specific ART drugs** – It may be necessary or appropriate to exclude patients taking certain ART drugs based on demonstrated or predicted drug-drug interactions that affect absorption, distribution, metabolism, and excretion of the investigational drug (or the ART) or for potential overlapping toxicities.
 - Drug-drug interactions with ART occur via many mechanisms, with cytochrome P450 3A4 (CYP3A4)-mediated interactions being the most common. The absorption, distribution, metabolism, and excretion data known to date for the investigational drug should be assessed. Exclusion of patients on specific ART drugs should then be based on the potential for clinically significant drug-drug interactions using known information (see Appendix 2). The protocol should include tables of any drugs, including ART and other drugs, that are prohibited

⁹ See Appendix 1 for references regarding management of concurrent HIV infection.

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for patients while participating in the study, and therefore would be considered part of the exclusion criteria for the study. For sensitive CYP3A4 substrates, patients who are using concurrent strong CYP3A4 inhibitors (e.g., ritonavir, cobicistat) or strong CYP3A4 inducers could be switched to an alternate effective ART regimen (with minimal drug-drug interaction potential) before study participation or should be excluded from the study if their regimen cannot be altered. Otherwise eligible study participants could be switched to an alternate effective ART regimen before study participation.

- Consider exclusion of patients on specific ART drugs based on toxicity (e.g., tenofovir (renal dysfunction), atazanavir (PR prolongation and AV block), efavirenz (depressed mood)) if overlapping toxicities with investigational drugs are expected and it is not possible to switch to an alternative effective ART regimen during treatment with the investigational drug.
- **Exceptions to concurrent ART** – Although effective ART is recommended in patients with HIV infection, exceptions to concurrent ART could be considered in both development of eligibility criteria and conduct of studies, as follows:¹⁰
 - In studies enrolling patients with curable malignancies where cancer therapy requires prioritization, eligibility criteria should permit enrollment, since treatment interruption or deferred initiation of ART is appropriate in curable malignancies when ART may compromise intended full-dose cancer therapy with investigational drug(s).
 - For treatment interruptions for toxicity management.
 - For treatment interruptions to meet scientific objectives of the study.

B. Recommendations for patients with evidence of chronic HBV infection or patients with history of chronic HCV or virologically suppressed on HCV treatment

1. Liver-related laboratories

- Liver-related laboratory eligibility criteria should generally be the same as that for the general population.
 - Exception: AST/ALT and bilirubin criteria may be less stringent in patients with cancers such as hepatocellular carcinoma and

¹⁰ Uldrick T and Little R, 2015, How I Treat Classical Hodgkin Lymphoma in Patients Infected with Human Immunodeficiency Virus, *Blood*, 125(8):1226-1235.

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cholangiocarcinoma in whom hepatic function based on Child-Pugh score should be used.

2. *HBV/HCV therapy*

- **HBV:** HBV reactivation can occur in chronic carriers of HBV infection (HBsAg-positive, undetectable or low HBV DNA, and normal ALT) who are not on HBV therapy, or in individuals who have serologic evidence of a resolved prior HBV infection (i.e., HBsAg-negative and anti-HBc-positive). While HBsAg-negative, anti-HBc-positive patients are at lower risk of HBV reactivation compared with HBsAg-positive patients, risk of HBV reactivation should be considered in all patients and the need for anti-HBV prophylaxis should be carefully assessed prior to the initiation of anticancer therapy.¹¹ Eligibility criteria for patients with chronic HBV infection with active disease who meet the criteria for anti HBV therapy should require the patient be on a suppressive antiviral therapy prior to initiation of cancer therapy.¹²
- **HCV:** Eligibility criteria for patients with a history of HCV infection should generally require patients to have completed curative antiviral treatment and require HCV viral load below the limit of quantification. A patient who is HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution should be eligible. For incurable cancers, patients with untreated HCV may be enrolled if the HCV is stable, the patient is not at risk for hepatic decompensation, and the investigational cancer treatment is not expected to exacerbate the HCV infection.
- **HCV:** Eligibility criteria for patients on concurrent HCV treatment should generally require patients to have HCV below the limit of quantification.

¹¹ Terrault NA, Lok AS, McMahon BJ, et al., 2018, Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance, *Hepatology*, 67(4): 1560-1599.

¹² Reddy K, Beavers K, Hammond S, et al., 2015, American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy, *Gastroenterology*, 148(1): 215-219.

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APPENDIX 1: REFERENCES FOR MANAGEMENT OF CONCURRENT HIV AND HEPATITIS B

1. HIV - Department of Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV¹³
2. HIV - HHS Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV¹⁴
3. HBV – Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance¹⁵

¹³ Available at <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0>, accessed June 23, 2020.

¹⁴ Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf, accessed June 23, 2020.

¹⁵ Terrault NA, Lok ASF, McMahon BJ, et al., 2018, *Hepatology*, 67(4): 1560-1599.

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APPENDIX 2: REFERENCES FOR AVAILABLE ANTIRETROVIRAL, HEPATITIS B, AND HEPATITIS C DRUGS AND RELEVANT PHARMACOLOGY TO AVOID DRUG-DRUG INTERACTIONS

1. HIV - Literature^{16,17}
2. HIV - University of Liverpool HIV Drug Interaction Website Searchable Database¹⁸
3. HIV - FDA's Website – HIV Treatment Information for Adults¹⁹
4. HBV and HCV - University of Liverpool HEP Drug Interaction Website Searchable Database²⁰
5. HCV – HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C²¹

¹⁶ Rudek M, Flexner C, Ambinder R, 2011, Use of Antineoplastic Agents in Patients with Cancer Who Have HIV/AIDS, *Lancet Oncol*, 12(9): 905-912. The article includes tables on drug interaction potential of antiretroviral drugs.

¹⁷ Berretta M, Caraglia M, Martellotta F, et. al., 2016, Drug-Drug Interactions Based on Pharmacogenetic Profile between Highly Active Antiretroviral Therapy and Antiblastic Chemotherapy in Cancer Patients with HIV Infection, *Front. Pharmacol.*, epub March 30, 2016, doi: 10.3389/fphar.2016.00071.

¹⁸ Available at <https://www.hiv-druginteractions.org/>, accessed June 23, 2020.

¹⁹ Available at <https://www.fda.gov/drugs/hiv-treatment/hiv-treatment-information-adults>, accessed June 23, 2020.

²⁰ Available at <https://www.hep-druginteractions.org/>, accessed June 23, 2020.

²¹ Available at <https://www.hcvguidelines.org/evaluate/monitoring>, accessed June 23, 2020.