2024 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Management of COVID-19: Anti-SARS-CoV-2 Neutralizing Antibody Pemivibart for Pre-Exposure Prophylaxis

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ABSTRACT. This article provides a focused update to the clinical practice guideline on the treatment and management of patients with COVID-19, developed by the Infectious Diseases Society of America. The guideline panel presents a recommendation on the use of the anti-SARS-CoV-2 neutralizing antibody pemivibart as pre-exposure prophylaxis. The recommendation is based on evidence derived from a systematic literature review and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Information on pemivibart is included in the U.S. Food and Drug Administration Emergency Use Authorization for this agent.

Keywords. COVID-19; SARS-CoV-2; pemivibart; pre-exposure prophylaxis; guideline

Posted online at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ on August 12, 2024. COVID-19 management guidelines may change rapidly with evolving virus variants and ongoing research, so please check the website for most updated version of this guideline.

As the pandemic evolves, new SARS-CoV-2 variants emerge with varying susceptibility to available anti-SARS-CoV-2 neutralizing antibodies. For current information, please refer to the CDC COVID-19 Data Tracker (Summary of Variant Surveillance) [1].

In moderately or severely immunocompromised persons 12 years or older, should pemivibart compared to no pemivibart be used for pre-exposure prophylaxis?

Recommendation: In moderately or severely immunocompromised individuals 12 years or older at risk for progression to severe COVID-19, the IDSA guideline panel suggests pre-exposure prophylaxis with pemivibart when predominant regional variants are susceptible to the agent *(conditional recommendation, low certainty of evidence)*.

Remarks:

- The anticipated benefit is likely greatest in people who are the most immunocompromised because they have the highest risk of inadequate immune response and progression to severe disease. See Table 1 for examples of individuals with varying degrees of immunosuppression. See Figures 1 and 2 for information from the FDA EUA.
- The anticipated benefit may be lower in patients aged 12 to 17 years, who have less severe COVID-19 outcomes than adults, as reflected by lower rates of hospitalization.
- As the evidence is based on immunobridging and circulating variant susceptibility is evolving, additional clinical and laboratory data may impact this recommendation.
- Patients who place a higher value on potential harms, specifically, the observed 0.6% risk of anaphylaxis, and a lower value on the uncertain benefits of prevention of severe COVID would reasonably decline pemivibart.
- Per the FDA EUA, pemivibart is authorized to be given at 4,500 mg IV every 3 months.
- Per the FDA EUA, in individuals who have recently received a COVID-19 vaccine, pemivibart should be administered at least 2 weeks after vaccination.

Figure 1. FDA Emergency Use Authorization (EUA) criteria for the use of pemivibart for pre-exposure prophylaxis of COVID-19 in moderately or severely immunocompromised patients [2]

According to the FDA Emergency Use Authorization of pemivibart, medical conditions or treatments that may result in moderate to severe immune compromise include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Hematologic malignancies associated with poor responses to COVID-19 vaccines regardless of current treatment status (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
- Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppressive therapy)
- Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, and biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Figure 2. FDA EUA criteria for the use of pemivibart for pre-exposure prophylaxis of COVID-19 [2]

This EUA for the use of the unapproved products pemivibart for pre-exposure prophylaxis in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are:

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and
- Who have moderate-to-severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and are unlikely to mount an adequate response to COVID-19 vaccination.

Table 1. Broad categorization of example immunocompromised status based on medical condition or immunosuppressive treatment. Thresholds by which this categorization has been determined have been derived from cohort studies beginning in the Omicron era of COVID-19; however, this may not be representative of currently evolving variants.

The risk of progression to severe COVID-19 is a continuum influenced by various factors, including the degree of immunosuppression. The categorization of risk and the examples provided in the table below are illustrative, based on a few studies, and are not exhaustive or a thorough list of all conditions [3,4].

Risk category	Example health condition	Example therapeutics
Higher risk immunocompromised patients	• Stem cell transplant <2 years • Graft versus host disease, grade 3 or 4 • Hematological malignancy on therapy • Lung transplant • Fewer than 1% peripheral B-cells assessed in past 6 months	• B-cell depleting agents in past 12 months (e.g., rituximab, ofatumumab, ocrelizumab, others) • CAR-T therapy in past 12 months • Abatacept
Moderate risk immunocompromised patients	• Solid organ transplant other than lung • Solid tumor on treatment • Congenital agammaglobulinemia • Graft versus host disease, grade 1 or 2	• Tyrosine kinase inhibitor (e.g., ibrutinib, acalabrutinib, others) • High-dose corticosteroids (>20 mg prednisone or equivalent for >4 weeks) • Anthracycline derivates

	• HIV infection with CD4 <200 • Other severe primary immunodeficiency	
Lower risk immunocompromised patients	• HIV infection with CD4 >200 • Inflammatory bowel disease • Cirrhosis • ESRD • Solid tumor (treatment >12 month prior)	• Anti-TNF • Anti-IL-6 • Anti-IL12 and 23 • Corticosteroids ≤10 mg long-term, or <20 mg for <4 weeks • Intra-articular steroids

BACKGROUND

Monoclonal antibodies (mAbs) directed at the receptor-binding domain of SARS-CoV-2 spike protein have been employed as prophylactic and therapeutic agents for COVID-19. Animal models, including those using the parent mAb for pemivibart, adintrevimab, have demonstrated the ability of these antibodies to inhibit viral replication in the lower respiratory tract, thereby reducing virus-induced pathology [5,6].

An advantage of an anti-SARS-CoV-2 mAb is its ability to provide protection for individuals who do not respond to vaccination. Additionally, this protection begins immediately after the infusion. The FDA previously issued an Emergency Use Authorization (EUA) for tixagevimab/cilgavimab (Evusheld) as pre-exposure prophylaxis for COVID-19 [7,8]. However, as the pandemic progressed, new SARS CoV-2 variants emerged with reduced neutralizing susceptibility to various anti-SARS-CoV-2 mAbs in assays performed using infectious (also referred to as authentic) and pseudotyped viruses. There is evidence that the results of these *in vitro* neutralization assays can predict the efficacy of prophylactic or therapeutic anti-SARS-CoV-2 mAb activity [9,10]. The FDA has employed these and other immunobridging studies to determine the withdrawal and authorization of anti-SARS CoV-2 mAbs [2,11]. The FDA defines immunobridging as a method to infer vaccine (or by extension, monoclonal antibody) effectiveness by comparing immune responses, such as antibody levels, from a new vaccine (or antibody) to those of an approved vaccine or antibody under different conditions. This approach is useful when direct efficacy trials are impractical due to low disease incidence or ethical issues. Immunobridging

allows for quicker and more cost-effective vaccine (and monoclonal) approvals, which is critical during public health emergencies like the COVID-19 pandemic. It has been used for evaluating COVID-19 vaccines across different age groups and for booster doses. In the case of pemivibart immunobridging, serum neutralization titer was utilized to compare pemivibart to previous mAbs [2,12,13].

While vaccination remains the first-line approach for the prevention of COVID-19, there are some immunosuppressed individuals who may not mount an adequate protective response to COVID-19 vaccines. Certain immunocompromised patients (examples listed in Table 1) are at particularly high risk for complications of COVID-19. Immunosuppressed individuals may benefit from pre-exposure prophylaxis (PrEP). Anti-SARS-CoV-2 mAbs have track records of efficacy for both treatment and prevention of COVID-19. In March 2024, the FDA conferred emergency use authorization for pemivibart for the pre-exposure prophylaxis of COVID-19 in adults and adolescents (12 years of age and older weighing at least 40 kg) based on immunobridging data from the CANOPY study, which suggests pemivibart should have similar efficacy against the newer Omicron subvariants as was previously seen with adintrevimab (the parent mAb of pemivibart) in the setting of circulating Delta variants and other anti-SARS-CoV-2 mAbs (See Tables 1 and 2 on the FDA EUA Factsheet [2]. FDA authorization was based on immunobridging; the serum neutralization titer was used to compare pemivibart to other anti-SARS CoV-2 mAbs that showed clinical efficacy.

In this focused update to the 2023 guideline [14], a recommendation and remarks are provided for pemivibart as pre-exposure prophylaxis. The primary audience for this recommendation is clinicians managing moderately or severely immunocompromised persons 12 years or older.

METHODS

The panel's recommendation is based upon evidence derived from a systematic review and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach

(Supplementary Figure 1) [15]. The recommendation has been endorsed by the Pediatric Infectious Diseases Society, the Society of Infectious Diseases Pharmacists, the Society for Healthcare Epidemiology of America, and the Society of Critical Care Medicine.

Strong recommendations are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations are made when the suggested course of action would apply to the majority of people with many exceptions and shared decision making is important.

A literature search was conducted in May 2024 as part of a systematic review. Key eligibility criteria at both the topic and clinical question levels guided the selection of studies for inclusion. For this clinical question, immunocompromised persons 12 years or older were included. The primary comparator of interest was pemivibart vs. no pemivibart; however, other mAbs were also considered.

A critical appraisal of the evidence according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach, along with an assessment of the benefits and harms of care options informed the recommendation(s) [15,16]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

One ongoing randomized controlled trial (RCT) was identified studying pre-exposure prophylaxis (PrEP) with a single dose of 4,500 mg IV pemivibart administration in adults ≥18 years of age at increased risk of SARS-CoV-2 infection or inadequate response to COVID-19 vaccination [17] (Supplementary Table 1). Results of the effect of pemivibart in preventing symptomatic COVID infections are expected later in 2024. In the interim, to inform anticipated clinical benefits of pemivibart, the panel relied on indirect evidence from an RCT of adintrevimab (see Table 2), the ancestral neutralizing antibody from which pemivibart was derived, previous studies evaluating other anti-SARS-CoV-2 mAbs, and immunobridging evidence [2,10].

158 **Table 2.** GRADE Evidence Profile: In moderately or severely immunocompromised persons 12 years or older, should pemivibart compared to no
159 pemivibart be used for pre-exposure prophylaxis?

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pemivibart	No pemivibart	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
No data												
Symptomatic infections (as inferred by immunobridging neutralization study of pemivibart 4,500 mg IV based on titers against JN.1 at day 28)												
1[2,17]	non-randomised studies	serious[a]	not serious	serious[b]	not serious	none	Immunobridging is established if the lower limit of the 2-sided 90% CI of the ratio of the geometric mean titer value is greater than 0.8. Results: the geometric mean ratio between the calculated titer for pemivibart against JN.1 (based on an authentic virus neutralization assay EC50 value of 63.6 ng/mL) and the calculated titer for adintrevimab against Delta (based on a similar authentic virus neutralization assay EC50 value of 7 ng/mL) was 0.82 (90% CI: 0.80-0.85). The authors conclude that the calculated pemivibart serum neutralizing antibody titers were consistent with the titer levels associated with efficacy in prior clinical trials of adintrevimab and certain other monoclonal antibody products previously authorized for the prevention of COVID-19.				⨁◯◯◯ Very low	IMPORTANT
Symptomatic infections (as inferred by indirect evidence from adintrevimab 300 mg PrEP cohort) (follow-up: 3 months)[c]												
1[18]	randomised trial	not serious	not serious	serious[d]	serious[e]	none	12/752 (1.6%)	40/728 (5.5%)	**RR 0.29** (0.15 to 0.55)	**39 fewer per 1,000** (from 47	⨁⨁◯◯ Low	CRITICAL

										fewer to 25 fewer)		
Anaphylaxis												
1[2,17]	non-randomised studies	not serious	not serious	not serious	not serious	none	4/623 (0.6%)	0/162 (0.0%)	not estimable	**6 more per 1,000** (from 0 more to 12 more)[f]	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. No control group comparison (see Supplementary Table 2)

b. Not based on patient-important outcomes. Neutralizing activity only.

c. Adintrevimab is the ancestral neutralizing antibody which is no longer active against circulating virus but was used to create pemivibart

d. Several layers of indirectness are present: 1) Indirect data from parent monoclonal antibody against SARS CoV-2 variant that is no longer in circulation; 2) indirectness whether JN.1 will be susceptible to pemivibart to the same degree, i.e. uncertainty of remaining effect estimate at currently circulating variants; 3) uncertainty of baseline risk: over time, the proportion of symptomatic infections have declined and whether the historical 5.5% symptomatic infection rate seen with adintrevimab (enrollment in 2021) within 3 months is still applicable is unknown. With declining baseline risk for symptomatic infections, the absolute risk difference of downstream patient important outcomes (hospital admission, severe COVID etc.) resulting from pemivibart declines as well and may become less clinically relevant over time.

e. Fragility present; low number of events

f. Anaphylaxis was observed in 4/263 (0.6%) participants receiving pemivibart, 2 of which were described as life-threatening.

BENEFITS

In the EVADE RCT conducted in unvaccinated individuals, symptomatic COVID infections occurred in 40/728 (5.5%) patients receiving placebo compared to12/752 (1.6%) patients receiving adintrevimab (RR 0.29, 95% CI 0.15, 0.55) [18]. Additionally, prior studies found that *in vitro* neutralizing titers of anti-SARS CoV-2 mAbs, including adintrevimab and other anti-SARS CoV-2 mAbs, were associated with clinical benefit [2,10]. *In vitro* neutralizing activity of pemivibart appears retained with currently circulating variants as of June 2024 [19].

HARMS

In the CANOPY trial, serious adverse events included anaphylaxis, which was observed in 4/623 (0.6%) participants receiving pemivibart, 2 of which were described as life threatening (absolute risk increase of 6 more anaphylactic reactions in 1,000, 95% CI, from 0 more to 12 more) [2].

OTHER CONSIDERATIONS

The panel's suggestion for the use of pemivibart is based on the following lines of evidence: the track record of success of anti-SARS-CoV-2 mAbs for both treatment and prevention; the phase 2/3 randomized controlled trial of the parent mAb adintrevimab demonstrating a 71% protection from symptomatic COVID-19; and immunobridging data.

The panel agreed the overall certainty of evidence for this recommendation was low (Table 2) due to concerns about: indirectness of evidence, given that efficacy of pemivibart is derived from immunobridging studies compared to adintrevimab and other anti-SARS-CoV-2 mAbs; uncertainty that pemivibart is active against the currently circulating variants; uncertain risks of pemivibart, including anaphylaxis; uncertainty regarding likelihood of symptomatic infections leading to hospitalizations and severe COVID-19 because of a lower risk of progression in 2024 than earlier in the pandemic when the

adintrevimab study was conducted; lack of peer review for the immunobridging study; study risk of bias (Supplementary Table 2) in the CANOPY results reported; and imprecision due to the low number of symptomatic infections in the indirect data from adintrevimab. An additional source of uncertainty in adolescents is indirectness related to the inclusion of just 9 participants <18 years of age in the pre-exposure prophylaxis cohort of the EVADE trial and no participants <18 years of age in the CANOPY trial, necessitating extrapolation from adult data.

In the CANOPY study, 4/623 (0.6%) of participants were diagnosed with anaphylaxis, including 2 who were considered to have a severe reaction requiring Emergency Department visit and/or hospitalization. Due to the small number of participants who have received pemivibart in this trial, the true frequency of severe anaphylaxis remains unclear.

EQUITY CONSIDERATIONS

Efforts should be made to provide equitable access to this therapy for patients who may benefit, including those from marginalized communities, underserved populations, and diverse socioeconomic backgrounds. These include addressing barriers such as geographical disparities, financial constraints, language accessibility, and cultural considerations to ensure that all individuals have fair and inclusive opportunities to receive this treatment.

CONCLUSIONS AND RESEARCH NEEDS

The guideline panel issued a conditional recommendation for PrEP with pemivibart in moderately or severely immunocompromised individuals. Due to the limited clinical evidence, the resulting net benefit remains unknown for adults and may be clarified when final randomized trial evidence is available; it will remain unknown for patients aged 12 to 17 years since they were not included in the trial. Detailed data on the efficacy of pre-exposure prophylaxis specifically in immunocompromised individuals who have

received COVID-19 vaccines are needed. Additionally, data regarding safety, serum neutralizing against emerging variants, clinical efficacy, and pharmacoeconomic analyses are needed.

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Drs. Adarsh Bhimraj and Rajesh T. Gandhi are chair and vice chair of the panel, respectively. The Immunocompromised subgroup, under the leadership of Dr. Arthur Kim, led the development of the recommendation and associated remarks. Remaining panelists assisted with interpretation of data, as well as drafting, revising, and approving the recommendation and manuscript. Drs. Yngve Falck-Ytter, lead methodologist, and Rebecca Morgan, methodologist, were responsible for designing and performing the data analyses and leading the panel according to the GRADE process. Jennifer Loveless, methodologist, was responsible for project planning and management, including revisions to and final approval of the recommendation and manuscript.

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Additional Information: More detailed information on the analysis and development of recommendations is available in the Supplementary Material.

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