**Supplementary Material** for the 2026 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Antiviral Treatment for Mild to Moderate COVID-19 in Infants, Children, and Adolescents

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REFERENCES


## METHODS

### Panel formation and conflicts of interest

The chair and vice chair of the guideline panel were selected by the leadership of the Infectious Diseases Society of America (IDSA). Twenty-six additional panelists comprised the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, critical care medicine, pulmonology, maternal fetal medicine, and pharmacology, as well as biostatistics. Guideline methodologists oversaw all methodological aspects of the guideline development, including the identification and summarization of scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guidelines Subcommittee (SPGS) Chair, and if necessary, the Conflict of Interests Ethics Committee. This assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of the guideline for the disclosures reported to IDSA.

**Practice recommendations**

Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA clinical practice guideline handbook].

**Review and approval process**

Feedback was obtained from two external individual peer expert reviewers as well as the endorsing organizations. The IDSA Standards and Practice Guidelines Subcommittee (SPGS) and Board of Directors reviewed and approved the guideline prior to publication.

**Process for updating**

IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

**Clinical questions**

Each clinical question was formatted according to the PICO style: Patient/Population (P), Intervention/Indicator (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated for their relative importance for decision-making.

**Literature search**

Literature searches were conducted in Ovid Medline, Embase, and Cochrane Library in September 2024 and June 2025. Searches were limited to studies published in English.

Search strategy:

(((("nirmatrelvir and ritonavir drug combination"[Supplementary Concept] OR "nirmatrelvir"[Supplementary Concept] OR "remdesivir"[Supplementary Concept] OR nirmatrelvir[tiab] OR "nirmatrelvir and ritonavir drug combination"[tiab] OR Paxlovid[tiab] OR remdesivir[tiab] OR Veklury[tiab]) AND (("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "randomized"[tiab] OR "placebo"[tiab] OR "drug therapy"[Subheading] OR "trial"[tiab] OR "groups"[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])) AND (("2023/01/01"[dp] : "3000/12/31"[dp]) OR ("2023/01/01"[crdt] : "3000/12/31"[crdt]))) NOT ("address"[Publication Type] OR

"autobiography"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "Book Illustrations"[Publication Type] OR "Case Reports"[Publication Type] OR "Comment"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "editorial"[Publication Type] OR "Expression of Concern"[Publication Type] OR "interactive tutorial"[Publication Type] OR "interview"[Publication Type] OR "lecture"[Publication Type] OR "legal case"[Publication Type] OR "legislation"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "overall"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narrative"[Publication Type] OR "portrait"[Publication Type] OR "hascommenton"[All Fields] OR "Cartoons as Topic"[Mesh] OR "case history"[tiab] OR "case histories"[tiab] OR "case report"[tiab] OR "case reports"[tiab]"case studies"[tiab]OR "case study"[tiab]))

**Study selection**

Inclusion and exclusion criteria were pre-defined. The eligibility criteria below were used.

Inclusion criteria:

- *Patient population*- Patients with mild or moderate COVID-19
- *Intervention*- Nirmatrelvir/ritonavir or remdesivir
- *Comparator*- No nirmatrelvir/ritonavir or no remdesivir, respectively
- *Outcomes*- Hospitalization, symptom resolution, serious adverse events
- *Study design***-** RCTs

Exclusion criteria:

- *Patient population*- Patients without severe or critical COVID-19
- *Intervention*- N/A
- *Comparator*- N/A
- *Study design***-** Review articles, case reports

**Data extraction and analysis**

Guideline methodologists, with panelist assistance, extracted the data for each pre-determined patient-important outcome. If a relevant publication was missing raw data for an outcome prioritized by the panel, an attempt was made to contact the author(s) for the missing data.

**Evidence to decision**

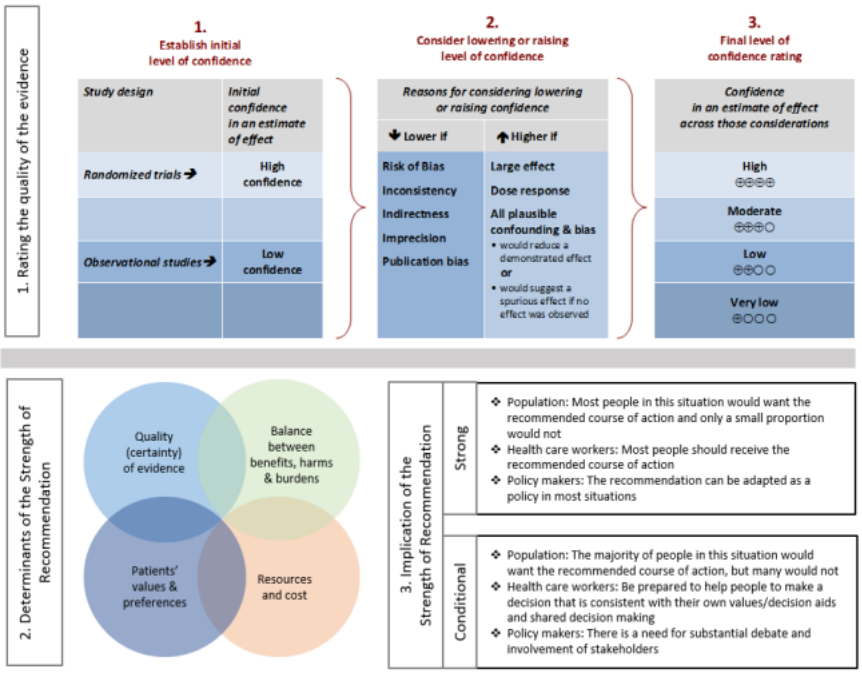
Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. Risk of bias was assessed by using the Cochrane Risk of Bias tool for RCTs [Higgins 2011]. The certainty of evidence was determined first for each critical and important outcome and then for each recommendation using the GRADE approach for rating the confidence in the evidence [Guyatt 2008, GRADE Handbook/Schunemann]. Evidence profiles were developed using the GRADEpro Guideline Development Tool [Guyatt 2008] and reviewed by panel members.

The Evidence to Decision framework [GRADEpro] was used to translate the evidence summaries into a practice recommendation. All recommendations are labeled as either “strong” or “conditional” according to the GRADE approach. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. Supplementary Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention” (either not using a specific treatment or a diagnostic test).

All members of the panel participated in the preparation of the draft guideline and approved the recommendation.

**TABLES AND FIGURES**

**Supplementary Figure 1.** Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology (unrestricted use of figure granted by the U.S. GRADE Network)



**Supplementary Table 1.** Characteristics of included studies

| Author Year | Country/ Hospital | Study design | N (intervention/ comparator); % female | Age mean (SD)/Median (IQR) | Severity of disease | Intervention (study arms) | Comparator | Co-interventions | Outcomes reported | Funding source |
|---|---|---|---|---|---|---|---|---|---|---|
| Hammond 2024 (Epic-SR) | USA, UK, Mexico, Turkey, Argentina, Brazil, Thailand, Bulgaria, Ukraine, Romania, Malaysia, Slovakia, Poland, Hungary, Czech Republic, South Africa, Japan, South Korea, Spain, Puerto Rico, Poland, Colombia/NA | RCT | 1296 (Nirmatrelvir-ritonavir: 658/Placebo:638);<br><br>54% female | 42 (18-87) | Outpatient adults with RT-PCR or rapid antigen confirmed SARS-CoV-2 infection and associated signs and symptoms of COVID-19 occurring ≤5 days before randomization | Nirmatrelvir (300 mg) and ritonavir (100 mg) every 12 hours for 5 days | Placebo with inactive filler every 12 hours for 5 days | N/A | Time to sustained alleviation of all COVID-19 symptoms through day 28, COVID-19 related hospitalization or death from any cause through day 28, Number of medical visits and number of days in hospital/ICU through day 28, Day 5 viral load, Day 10 or 14 viral load rebound, Symptom rebound, Side-effect profile | Pfizer |
| Hammond 2022 (Epic-HR) | USA, South Africa, Turkey, Argentina, Mexico, Bulgaria, Russia, Ukraine, Thailand, Colombia, Czech Republic, Malaysia, Japan, | RCT | 2246 (Nirmatrelvir-ritonavir 1120/ Placebo 1126);<br><br>53.2% female | 45 (18-86) | Asymptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe disease | Nirmatrelvir (300 mg) and ritonavir (100 mg) every 12 hours for 5 days + placebo after completion | Matching placebo capsules for 5 days | N/A | COVID-19 related hospitalizations through day 28, Viral load from baseline through day 14, Incidence of adverse effects | Pfizer |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Poland, Hungary/NA | | | | | | | | | |
| Liu 2023 | China: 5 COVID-19-designated hospitals | Parallel RCT | 264 (132/132);<br><br>46.2% female | Mean (SD):<br><br>Paxlovid + standard care: 71.50 (11.61)<br><br>Standard treatment: 69.20 (14.43) | Hospitalized patients 18-90 years with severe comorbidities, confirmed SARS CoV-2 infection by real-time PCR within the previous 48 h, duration from symptoms onset to hospital admission <5 days or SARS-CoV-2 nucleic acid Ct value ≤25 by RT-PCR<br><br>Severe defined as severe comorbidities, SOFA or Charlson score ≥2. Severe comorbidities defined as immunosuppressive disease or immunosuppressive status, chronic obstructive pulmonary disease, hypertension complicated with target organ injury, acute and chronic cardiac insufficiency, chronic renal insufficiency, etc. | Received Paxlovid at a dose of 300 mg nirmatrelvir (two tablets) + 100 mg ritonavir (one tablet), orally administered every 12 h for 5 days | Standard care including antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc. | Standard care including antivirus, anticoagulant therapy, prone position ventilation, awake prone positioning, corticosteroid therapy, and nutrient support, etc. | 28-day all-cause mortality,<br>Risk of death assessed in subgroup participants based on duration since symptoms onset to hospital admission,<br>Efficacy included in-hospital mortality,<br>Proportion of progress to severe COVID-19 within 14 days,<br>Proportion of acute exacerbation from the chronic disease within 14 days,<br>SARS–CoV-2 RNA clearance within 7 days and 14 days,<br>Duration of SARS–CoV-2 RNA clearance, length of hospital and ICU stay,<br>Organ support days to 28 days,<br>Adverse events occurring during and after treatment period | National Natural Science Foundation of China |

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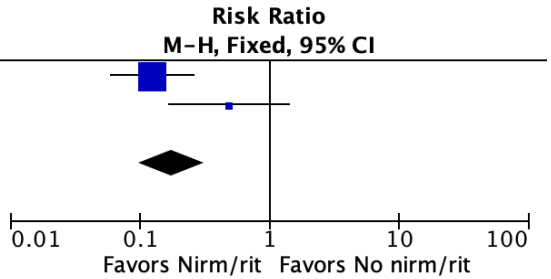
|---|---|---|---|---|---|---|---|---|---|---|
| Beigel 2020 | USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore/ 60 trial sites and 13 subsites | RCT | 1062<br><br>(541/521);<br><br>35.6% female | Mean: 58.9 (15) | Met 1 of the following suggestive of lower respiratory tract infection at time of enrollment: radiographic infiltrates by imaging study, $SpO_2$ ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation | Remdesivir 200 mg loading dose once day 1, 100 mg maintenance dose once daily days 2-10 | (1) Placebo 200 mg once day 1, 100 mg once daily days 2-10 | Supportive care according to the standard of care for the trial site hospital; if a hospital had a written policy or guideline for use of other treatments for COVID-19, patients could receive those treatments | Mortality at day 14, Number of recoveries, Time to recovery (days), Hazard ratio of mortality, Hospital discharge, Adverse events | National Institute of Allergy and Infectious Diseases<br><br>National Institutes of Health, Bethesda, MD<br><br>Governments of Japan, Mexico, Denmark, and Singapore<br><br>Seoul National University Hospital<br><br>United Kingdom<br><br>Medical Research Council |
| Spinner 2020 | United States, Europe, and Asia/ 105 hospitals | RCT | 584<br><br>(193/191/200);<br><br>% female not reported | N/A | Moderate COVID-19 pneumonia (any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air) | Remdesivir (5-Day Group) 200 mg once daily day 1, 100 mg once daily days 2-5 via IV | (1) Remdesivir (10-Day Group): 200 mg once daily day 1, 100 mg once daily days 2-10 via IV<br><br>(2) SoC | Steroids, HCQ, Lopinavir-ritonavir, TCZ, AZ | Day 11 clinical status on 7-point scale, No. (%) (Includes Mortality at Day 11), Clinical improvement (at day 5, 7, 11, 14, 28), Recovery (at day 5, 7, 11, 14, 28), Adverse events | Gilead Sciences |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gottlieb 2022 | 64 sites in US, Spain, Denmark, and UK | RCT | 562 (279/283); 47.9% female | 50 (15) | SARS CoV-2 PCR positive within 4 days prior to screening with ≥1 symptom and symptom onset ≤7 days | Remdesivir 200 mg x 1 day, then 100 mg daily for 2 days | Placebo | None | Mortality,<br>All cause hospitalization,<br>COVID-19 related hospitalization,<br>COVID-19 related medically attended visits,<br>Change in nasopharyngeal viral load,<br>Serious adverse events | Gilead |
| Sise 2024 | 55 sites in Brazil, Portugal, Spain, UK, and US | RCT | 243 (160/80);<br><br>42.8% female | 69 (14) | Age ≥12 years, ≥40kg, hospitalized with COVID-19, oxygen saturation ≤94%, and either severely reduced kidney function or kidney failure | Intravenous remdesivir 200 mg on day 1, 100 mg daily up to day 5 | Saline placebo | Corticosteroids, monoclonal antibodies | All-cause death or invasive mechanical ventilation through day 29,<br>All-cause death through day 29,<br>Clinical status assessed by an 8-point ordinal scale at days 15 and 29,<br>Adverse events,<br>Serious adverse events,<br>Plasma concentrations of remdesivir | Gilead Sciences |

**Supplementary Figure 2.** Forest plot for the outcome of hospitalizations for nirmatrelvir/ritonavir

| Study or Subgroup | Nirmatrelvir/ritonavir Events | Total | No nirmatrelvir/ritonavir Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hammond 2022 | 8 | 1039 | 65 | 1046 | 86.4% | 0.12 [0.06, 0.26] |
| Hammond 2024 | 5 | 654 | 10 | 634 | 13.6% | 0.48 [0.17, 1.41] |
| **Total (95% CI)** | | **1693** | | **1680** | **100.0%** | **0.17 [0.10, 0.31]** |
| Total events | 13 | | 75 | | | |

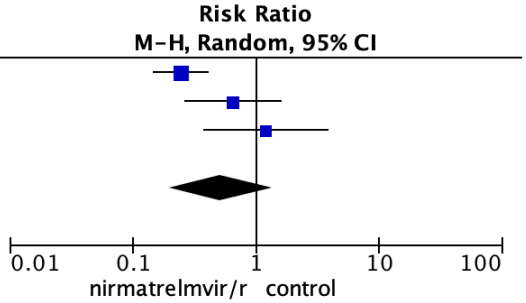
Heterogeneity: $Chi^2 = 4.38$, df = 1 (P = 0.04); $I^2 = 77\%$
Test for overall effect: Z = 5.87 (P < 0.00001)




**Supplementary Figure 3.** Forest plot for the outcome of serious adverse events (SAEs) for nirmatrelvir/ritonavir

| Study or Subgroup | Nirmatrelvir/ritonavir Events | Total | No nirmatrelvir/ritonavir Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Hammond 2022 | 18 | 1109 | 74 | 1115 | 40.1% | 0.24 [0.15, 0.41] |
| Hammond 2024 | 8 | 654 | 12 | 634 | 32.6% | 0.65 [0.27, 1.57] |
| Liu 2023 | 6 | 132 | 5 | 132 | 27.2% | 1.20 [0.38, 3.84] |
| **Total (95% CI)** | | **1895** | | **1881** | **100.0%** | **0.52 [0.20, 1.35]** |
| Total events | 32 | | 91 | | | |

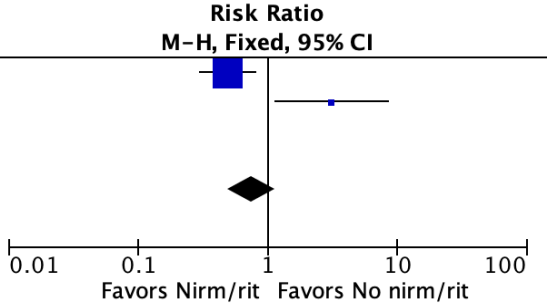
Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = 8.06$, df = 2 (P = 0.02); $I^2 = 75\%$
Test for overall effect: Z = 1.34 (P = 0.18)




**Supplementary Figure 4.** Forest plot for the outcome of adverse events leading to treatment discontinuation for nirmatrelvir/ritonavir

| Study or Subgroup | Nirmatrelvir/ritonavir Events | Total | No nirmatrelvir/ritonavir Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hammond 2022 | 23 | 1109 | 47 | 1115 | 90.2% | 0.49 [0.30, 0.80] |
| Hammond 2024 | 16 | 654 | 5 | 634 | 9.8% | 3.10 [1.14, 8.42] |
| Liu 2023 | 4 | 132 | 132 | 0 | | Not estimable |
| **Total (95% CI)** | | **1895** | | **1749** | **100.0%** | **0.75 [0.50, 1.13]** |
| Total events | 43 | | 184 | | | |

Heterogeneity: $Chi^2 = 10.58$, df = 1 (P = 0.001); $I^2 = 91\%$
Test for overall effect: Z = 1.39 (P = 0.16)

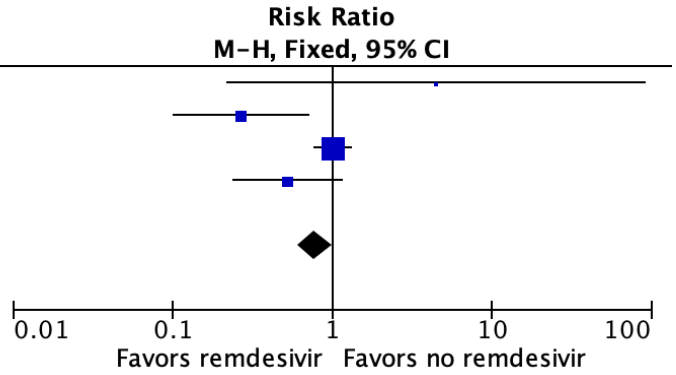


**Supplementary Figure 5.** Forest plot for the outcome of serious adverse events (SAEs) for remdesivir

| Study or Subgroup | Remdesivir Events | Remdesivir Total | No remdesivir Events | No remdesivir Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Beigel 2020 | 2 | 55 | 0 | 49 | 0.6% | 4.46 [0.22, 90.78] |
| Gottlieb 2021 | 5 | 279 | 19 | 283 | 20.8% | 0.27 [0.10, 0.70] |
| Sise 2024 | 82 | 163 | 40 | 80 | 59.2% | 1.01 [0.77, 1.31] |
| Spinner 2020 | 9 | 191 | 18 | 200 | 19.4% | 0.52 [0.24, 1.14] |
| **Total (95% CI)** | | **688** | | **612** | **100.0%** | **0.78 [0.61, 1.00]** |
| Total events | 98 | | 77 | | | |

Heterogeneity: $Chi^2 = 10.50$, df = 3 (P = 0.01); $I^2 = 71\%$

Test for overall effect: Z = 1.95 (P = 0.05)



**Supplementary Table 2.** Risk of bias assessment for randomized controlled trials

| Study | Bias in randomization process | Bias due to deviations from intended interventions | Bias due to missing outcome data | Bias in measurement of outcome | Bias in selection of the reported result |
|---|---|---|---|---|---|
| Liu 2023 | | | | | |
| Hammond 2022 | | | | | |
| Hammond 2024 | | | | | |
| RECOVERY Collaborative Group 2025 | | | | | |
| Beigel 2020 | | | | | |
| Gottlieb 2022 | | | | | |
| Sise 2024 | | | | | |
| Spinner 2020 | | | | | |
| Wang 2020 | | | | | |
| Butler 2023 | | | | | |
| Caraco 2022 | | | | | |
| Fischer 2021 | | | | | |
| Jayk Bernal 2021 | | | | | |
| Khoo 2023 | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Sinha 2022 | | | | | |
| Zou 2022 | | | | | |
| Arribas 2022 | | | | | |
| Guan 2023 | | | | | |

| Low | High | Unclear |
|---|---|---|

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Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet **2023**; 401(10373):281-93.

Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 trial of molnupiravir for treatment of Covid-19 in nonhospitalized adults. NEJM Evid **2022**; 1(2):EVIDoa2100043.

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