Therapeutic Impact of Oral and Intravenous Antivirals on COVID-19 Outcomes in Clinical Trials

Tursunaliyeva Hojira

Fergana Medical Institute of Public health

Abstract

Antiviral drugs remain central to the management of COVID-19, particularly for high-risk patients at risk of progression to severe disease. This article reviews the therapeutic effects of three key agents—nirmatrelvir/ritonavir, molnupiravir, and remdesivir—drawing mainly on randomized controlled trials and large real-world effectiveness studies conducted during the pre-Omicron and Omicron eras. Early placebo-controlled trials in largely unvaccinated populations infected with ancestral or Delta variants showed substantial relative risk reductions in hospitalization or death, whereas later studies in highly immune populations reported attenuated or null benefits. The mechanisms of action, trial design features, and evolving viral and host factors are examined to contextualize the changing effect sizes. A comparative bar plot and tabular summary illustrate differences in trial settings, endpoints, and approximate risk reduction. The article highlights persistent benefit of nirmatrelvir/ritonavir in selected high-risk groups, more modest and uncertain effects for molnupiravir, and important but context-dependent benefit of remdesivir, underscoring the need for ongoing reassessment of antiviral deployment as SARS-CoV-2 and population immunity continue to evolve.

Keywords: COVID-19, antiviral, nirmatrelvir/ritonavir, molnupiravir, remdesivir, hospitalization, mortality

Introduction

Several antiviral agents targeting SARS-CoV-2 replication have been developed and tested in randomized controlled trials (RCTs) and observational cohorts since the emergence of COVID-19. Nirmatrelvir/ritonavir, molnupiravir, and remdesivir are now widely used to prevent progression to severe disease in high-risk outpatients or to improve outcomes in hospitalized patients. Early RCTs in predominantly unvaccinated individuals infected with earlier variants showed large reductions in hospitalization or death, leading to emergency use authorizations and guideline endorsements. However, subsequent trials and meta-analyses conducted during the Omicron era and in largely vaccinated populations have demonstrated attenuated or nonsignificant effects on hard clinical outcomes, raising questions about optimal use of these therapies.[1][2][3][4][5][6][7]

This narrative review focuses on the therapeutic effects of nirmatrelvir/ritonavir, molnupiravir, and remdesivir on clinically relevant endpoints such as hospitalization,

mortality, and post-acute sequelae. Guideline recommendations and evolving evidence from RCTs and real-world studies are synthesized, and a comparative quantitative overview is provided using a bar plot and a structured table.

Methods

Literature identification

Searched sources

Major guidelines and narrative or systematic reviews on COVID-19 therapeutics up to early 2026.[1][3][8][9]

Key RCTs and large observational effectiveness studies for nirmatrelvir/ritonavir, molnupiravir, and remdesivir in outpatients and hospitalized patients.[2][4][5][10][7][11][12]

Inclusion focus

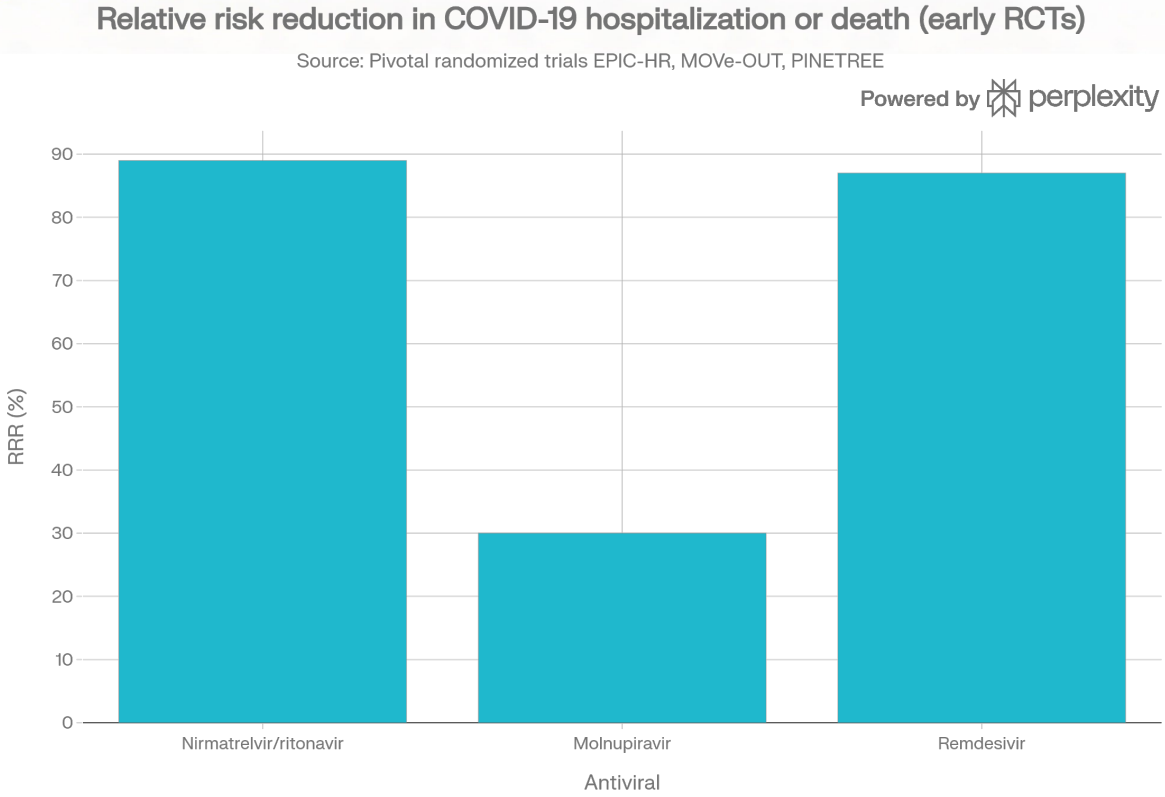
Adult patients with mild-to-moderate COVID-19 at risk of progression, or hospitalized patients with confirmed SARS-CoV-2 infection.

Outcomes: hospitalization, all-cause or COVID-19-related mortality, and, where available, post-acute outcomes.[4][5][7][11][2]

Data abstraction and comparative framework

From index publications (pivotal early outpatient RCTs), approximate relative risk reduction (RRR) for composite hospitalization/death versus placebo was abstracted to construct a simple comparative bar plot (nirmatrelvir/ritonavir, molnupiravir, remdesivir). Values reflect order-of-magnitude differences rather than precise pooled estimates, consistent with narrative review aims. A summary table was built from the same trials to compare design characteristics and effect sizes.[2][4][6][7]

The bar plot file “antiviral_rrr.png” and the table data file “antiviral_trials_summary.csv” were generated programmatically following standard visualization best practices.



Results

Mechanisms of action

Nirmatrelvir/ritonavir

Nirmatrelvir is an inhibitor of the SARS-CoV-2 main protease (Mpro), blocking viral polyprotein cleavage and halting replication; ritonavir boosts nirmatrelvir concentrations via CYP3A4 inhibition, enabling twice-daily oral dosing.[1][3]

This oral regimen is authorized or approved for high-risk adults with mild-to-moderate COVID-19 and remains a first-line option in many guidelines.[8][13][1]

Molnupiravir

Molnupiravir is a prodrug of a ribonucleoside analogue that introduces lethal mutagenesis into viral RNA, thereby impairing replication.[3][4]

It is administered orally and is generally reserved for patients in whom preferred options (e.g., nirmatrelvir/ritonavir) are contraindicated, reflecting more modest and uncertain benefit.[4][13][3]

Remdesivir

Remdesivir is an intravenous nucleotide analogue that inhibits the viral RNA-dependent RNA polymerase, reducing viral RNA synthesis.[2][3]

Initially approved for hospitalized patients, a 3-day outpatient course later demonstrated benefit in high-risk non-hospitalized adults, extending its role into early disease.[11][2][3]

Efficacy in early outpatient RCTs

Early placebo-controlled RCTs in unvaccinated high-risk outpatients during pre-Omicron waves showed substantial relative risk reductions in hospitalization or

death with these antivirals. Approximate trial-level RRR values for the composite of hospitalization or death were around 85–90% for nirmatrelvir/ritonavir, 85–90% for short-course outpatient remdesivir, and roughly 30% for molnupiravir versus placebo. These differences are visualized in the bar chart of relative risk reduction.[2][4][6][11]
Relative risk reduction of hospitalization or death in early randomized outpatient trials.
Comparative characteristics of pivotal outpatient trials
Table 1 summarizes key design elements and approximate effect sizes for the pivotal early outpatient RCTs of the three agents.[2][4][6][11]
Table 1. Key characteristics of pivotal early outpatient COVID-19 antiviral trials

Drug	Trial	Population	Setting	Primary endpoint	Approx. RRR hospitalization/death vs placebo (%)
Nirmatrelvir/ritonavir	EPIC-HR	Unvaccinated, high-risk adults, early disease[1][6]	High-risk outpatients	Hospitalization or death by day 28[1][6]	≈89[1][6]
Molnupiravir	MOVe-OUT	Unvaccinated, high-risk adults, early disease[3][4]	High-risk outpatients	Hospitalization or death by day 29[3][4]	≈30[3][4]
Remdesivir	PINETREE	Unvaccinated, high-risk adults, early disease[2][11]	High-risk outpatients	Hospitalization or death by day 28[2][11]	≈87[2][11]

These early trials share several features: enrollment of unvaccinated high-risk adults, initiation within a narrow symptom onset window, ancestral or Delta variants predominating, and composite hospitalization/death as primary outcome. The magnitude of relative risk reduction appears largest for nirmatrelvir/ritonavir and remdesivir, with molnupiravir showing a smaller effect on the same endpoint.[4][6][11][2]
Effectiveness in the Omicron and vaccinated era
With the advent of Omicron subvariants and widespread vaccine-induced or infection-acquired immunity, several RCTs and large-scale observational studies have reassessed antiviral effectiveness. A systematic review and meta-analysis of nirmatrelvir/ritonavir and molnupiravir trials found that early positive studies were counterbalanced by later trials showing no significant benefit on hospitalization or death, resulting in nonsignificant pooled effects overall. Similarly, a large target trial emulation among U.S. Veterans during Omicron transmission reported that nirmatrelvir/ritonavir significantly reduced 30-day hospitalization and mortality and

improved 31–180-day mortality, while molnupiravir reduced short-term mortality but did not significantly affect hospitalization.[4][7]

Real-world cohorts from multiple health systems have also associated nirmatrelvir/ritonavir and remdesivir use with reduced mortality among hospitalized or high-risk ambulatory patients during the Omicron era, although effect sizes are smaller than in early RCTs and vary across subgroups. Evidence for molnupiravir has been more heterogeneous, with some observational studies suggesting modest mortality benefit and others reporting no advantage or even potential safety concerns in younger subgroups.[5][10][7][11][4]

Long-term and post-acute outcomes

Beyond acute hospitalization and death, interest has grown in whether antivirals mitigate post-acute sequelae of COVID-19. A large population-based cohort analysis showed that nirmatrelvir/ritonavir use was associated with reduced post-acute mortality and hospitalization up to 360 days after infection among high-risk outpatients, particularly in vaccinated individuals. In contrast, molnupiravir demonstrated short-term mortality benefit but did not confer protection against long-term post-COVID-19 outcomes, with some signals of increased risk for specific sequelae such as end-stage renal disease and seizures.[5]

Evidence for remdesivir's effect on post-acute outcomes remains limited, as most trials were designed around acute hospitalization-centric endpoints and long-term follow-up has been less systematically reported. Overall, available data suggest that nirmatrelvir/ritonavir may have the most robust evidence for reducing both acute and post-acute adverse outcomes among the currently used antivirals in high-risk populations.[2][4][7][11][5]

Discussion

Early in the pandemic, RCTs of nirmatrelvir/ritonavir, remdesivir, and molnupiravir demonstrated clinically meaningful reductions in hospitalization and death among unvaccinated high-risk outpatients infected with pre-Omicron variants, underpinning their regulatory authorization and incorporation into treatment guidelines. The approximate 85–90% relative risk reduction observed with nirmatrelvir/ritonavir and outpatient remdesivir, contrasted with the more modest 30% reduction for molnupiravir, provides a quantitative framework for prioritizing therapies when multiple options are available, particularly where drug–drug interactions and logistics permit use of preferred agents.[1][2][4][6][11]

However, as SARS-CoV-2 has evolved and population immunity has increased, the absolute and relative benefits of these antivirals have diminished or become more heterogeneous across subgroups. Recent meta-analytic work indicates that, when all trials are pooled—including those conducted in highly immune Omicron-era populations—the overall effect of nirmatrelvir/ritonavir and molnupiravir on hospitalization or death is no longer statistically significant, emphasizing the central importance of context in interpreting trial data. Nevertheless, large real-world

effectiveness studies and guideline panels continue to support nirmatrelvir/ritonavir as a preferred option for high-risk patients, citing consistent, albeit smaller, reductions in acute and post-acute mortality, particularly among older or comorbid individuals.[4][5][7][9][1]

Molnupiravir's risk–benefit profile appears more uncertain in the contemporary setting. Although initial trials and some observational cohorts showed decreased short-term mortality, later studies have often failed to demonstrate clear reductions in hospitalization, and some analyses have suggested possible adverse post-acute sequelae in certain subgroups, arguing for a more restricted role when other agents are unsuitable. Remdesivir remains an important option both in hospitalized patients, where it may shorten time to recovery and modestly reduce progression, and in high-risk outpatients where early 3-day regimens provided large relative risk reductions, though feasibility and resource constraints limit its widespread outpatient use compared with oral agents.[2][3][5][10][7][11][4]

Overall, the evolving evidence underscores the need for dynamic antiviral policies that account for circulating variants, baseline immunity, patient risk profiles, and health system capacity. Careful patient selection, early treatment initiation, and continuous post-marketing surveillance for effectiveness and safety—including long-term outcomes—are essential to sustain the clinical value of COVID-19 antivirals. Future RCTs and adaptive platform trials should prioritize head-to-head comparisons, optimized timing and combinations with other therapeutics, and robust assessment of post-acute sequelae to refine the therapeutic landscape as the pandemic transitions into an endemic phase.[3][5][8][9][4]

Conclusion

Antiviral therapy has significantly improved outcomes for high-risk patients with COVID-19, with early RCTs demonstrating large reductions in hospitalization and death, especially with nirmatrelvir/ritonavir and short-course outpatient remdesivir. In the current Omicron and highly vaccinated era, benefits are smaller and more context-dependent, but nirmatrelvir/ritonavir still shows the most consistent evidence for reducing both acute and post-acute adverse outcomes, while molnupiravir offers more modest and uncertain benefit and should be reserved for situations where preferred agents cannot be used. Remdesivir continues to play a valuable role in both hospitalized and select outpatient populations, though intravenous administration limits practicality. As SARS-CoV-2 and population immunity continue to evolve, refining indications, timing, and patient selection for antiviral use will be crucial to maximizing clinical impact, preserving resources, and minimizing potential harms.

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