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Clinical research linking Paxlovid® to a lower risk of Long COVID

On November 6, 2022, the U.S. Department of Veterans Affairs (VA) issued a press release reporting the findings from a study showing the medication Paxlovid® (ritonavir-boosted nirmatrelvir) can reduce the risk of symptoms of post-acute sequelae of COVID-19, or "Long COVID."

Background[3]

Recovery from COVID-19 infection can vary from person to person. Most individuals seem to recover quickly and completely however some report symptoms that persist or emerge weeks or even months later. These sets of conditions are referred to as "Long COVID." Long COVID - the disease encompassing the post-acute sequelae of SARS-CoV-2 (PASC) - affects millions of people around the world. Prevention of PASC is an urgent public health priority.

Current Study[2]

The VA study, which included more than 56,000 Veterans with a positive SARS-CoV-2 test, showed that ***those given the oral antiviral medication Paxlovid® in the first 5 days of a COVID-19 infection had a 25% decreased risk of developing 10 of 12 different Long COVID conditions studied***, including heart disease, blood disorders, fatigue, liver disease, kidney disease, muscle pain, neurocognitive impairment and shortness of breath. The decreased risk of Long COVID associated with Paxlovid® treatment exists regardless of whether it was a participant's first infection or a reinfection and regardless of whether the participant was unvaccinated, vaccinated or boosted.

Study Limitations[2]

This study has several limitations, including:

1. The demographic composition of the study cohort (majority White and male) may limit generalizability of study findings
2. Misclassification bias and residual confounding cannot be ruled out as investigators did not capture Paxlovid® use outside the VA system or if large number of people in the control group used Paxlovid® outside the VA, which may bias the results toward the null
3. Analyses were focused on a pre-specified set of 12 sequelae and did not examine all sequelae of COVID-19
4. As the virus continues to mutate and as new variants emerge and as vaccine uptake improves, it is possible that the real-world effectiveness of Paxlovid® may also change over time
5. *Importantly, this study has not been published in any medical journal at this time. It is available for review as a preprint only, which is a preliminary report of work that has not been certified by peer review. Preprints should not be relied on to guide clinical practice or health-related behavior and should not be reported in news media as established information.*

Future Studies[2]

Paxlovid® was approved in the U.S. for the treatment of acute COVID-19 illness in people with one or more risk factors for progression to severe disease. The results evaluating the risk of PASC according to number of baseline risk factors suggest that the benefit was evident in people who had 1 to 2 baseline risk factors, progressively increased in a graded fashion as the number of risk factors increased, and was most pronounced in people with 5 or more risk factors. These analyses suggest that those who are at most risk will likely derive the most benefit. Whether the salutary benefit of Paxlovid® extends to people without risk factors for progression to severe disease (who would not qualify for Paxlovid® under the current FDA emergency use authorization and were not included in our analyses) remains to be tested in future randomized trials.

The author notes that their results suggested risk reduction for some but not all the pre-specified post-acute sequela in this analysis. It is possible that various sequelae are mediated by various mechanisms including some that may be affected by the receipt of antivirals and others that may not. Participants in our study were treated in the acute phase with a 5-day course of Paxlovid®; it remains unclear whether longer duration or higher dose or both may have resulted in more reduced risk of post-acute sequelae. It is also unclear whether initiation of treatment in the post-acute phase of COVID-19 reduces the risk of Long COVID.

Current Paxlovid® Prescribing Information[4]

Paxlovid® is authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid® is a combination of two medications, nirmatrelvir and ritonavir. Paxlovid® has been shown to lower the risk of hospitalization and death COVID-19 in infected patients. Paxlovid® has to be prescribed within five days of symptoms, and it is important for individuals to contact their health care providers if they test positive for COVID-19 to see if they would benefit from being prescribed lifesaving oral antiviral treatments.

In the National Institutes of Health COVID-19 treatment guidelines for the therapeutic management of nonhospitalized adults with COVID-19, ***Paxlovid® is the preferred initial therapy*** (Strong recommendation, based on moderate quality of evidence), followed by remdesivir, for patients who are at high risk of progressing to severe COVID-19. Of note, molnupiravir is listed as an alternate therapy, for use when the preferred therapies are not available, feasible to use, or clinically appropriate. This is due to lower efficacy than the other options recommended by the panel. Additionally, it is not recommended for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated.

Paxlovid® does carry some significant drug interactions and requires renal dose adjustment:

1. Paxlovid® Drug Interactions
2. Paxlovid® Renal Dosing Information

**Full Paxlovid® prescribing information can be found here.

IHS Test to Treat Initiative

The IHS continues to prioritize utilization of the IHS COVID-19 Test to Treat Initiative and encourages all sites to participate. Criteria for participation and distribution to Test to Treat I/T/U sites includes:

1. Sites requesting oral antivirals (Paxlovid® and molnupiravir) as part of the IHS Test to Treat Initiative will undertake a self-assessment of readiness to administer the product (including current policies and procedures in place) before submitting a distribution. At a minimum, elements of self-assessment shall include the following;
    - Adherence to all components of Emergency Use Authorizations (EUA)
    - Access to COVID-19 testing and pharmacy services
    - Testing logistics (order, result, reporting, prioritized case investigation & contact tracing)
    - Treatment logistics (provider order, cross-check for contraindications, pharmacy dispensing)
    - Process for tracking & reporting Adverse Drug Events to MedWatch in accordance with EUA
2. Attestation and completed request submitted in HHS Health Partner Ordering Portal (HPoP)
3. Sites will participate in all storage, dispensing, utilization, inventory management, and other reporting requirements per HHS and IHS policy related to the Test to Treat Initiative.

More information on the IHS Test to Treat Initiative can be found here.

References:

1. U.S. Dept. of Veterans Affairs. Office of Public and Intergovernmental Affairs. Paxlovid® reduces risk of Long COVID, Published online Nov 6, 2022.
2. Xie Y, Choi T, Al-Aly Z. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19. *MedRxiv*. Posted online Nov 5, 2022.
3. Indian Health Service. IHS Coronavirus (COVID-19) Webpage. Available at: Long COVID
4. National Institutes of Health, COVID-19 Treatment Guidelines, Therapeutic Management of Nonhospitalized Adults With COVID-19, Last updated online December 28, 2022