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The Role of Antivirals in COVID-19 Rebound Infections

Announcer:
COVID-19: On The Frontlines

Dr. Turck:
COVID-19 viral rebound infections continue to impact patients and challenge clinicians. Why do some patients experience it? And what kind of role does antiviral medication have?

You're listening to *COVID-19: On The Frontlines* on ReachMD. I'm Dr. Charles Turck. And joining me today to talk about COVID-19 viral rebound is Dr. Jonathan Li, the Director of the Harvard/Brigham Virology Specialty Laboratory, the Director of the Harvard University Center for AIDS Research Clinical Core, and member of the NIH COVID-19 treatment guidelines panel.

Dr. Li, welcome to the program.

Dr. Li:
Thanks, Charles. I'm really happy to be here.

Dr. Turck:
To start us off, Dr. Li, how has the antiviral treatment nirmatrelvir/ritonavir played a role in rebound infections?

Dr. Li:
Well, that's a great question. Nirmatrelvir/ritonavir, otherwise known as Paxlovid to most of my patients is the most commonly prescribed antiviral for outpatients with COVID-19, and it right now plays, I think, the critical role in how we keep our patients healthy and prevent them from progressing to severe disease. But as you and I'm sure that your listeners have seen, over the last year we've heard a lot of anecdotal reports of patients with symptom and viral rebound after taking Paxlovid and it's made the news, I think, a lot because there's been some prominent people who have reportedly had this Paxlovid rebound including, you know, President Biden and Tony Fauci. And, I would say that, unfortunately, this concern about rebound has really made some of our patients hesitant about taking Paxlovid, and I think we all know that you have to take anecdotal reports with a grain of salt. And, you know, I recall earlier in the pandemic before we had Paxlovid of hearing about several patients in the hospital who had experienced biphasic disease courses. They would tell me that they were initially getting better and then taking a turn for the worse. And this got me thinking about, you know, wondering about how common rebound was in the absence of antiviral therapy because I think only by knowing kind of this baseline rate can we really understand how much more common rebound is with Paxlovid.

Dr. Turck:
Well, let's dive into your research. Would you tell us about your study and its goals?

Dr. Li:
Yes, so, our goal was to determine the rates of symptom and viral rebound during the natural course of COVID-19 recovery, so without any antiviral medications. And, you know, in order to do that you need a pretty unique study that includes both intensive monitoring of symptom scores and of nasal swab viral loads, and we found that in the ACTIV-2 study. So ACTIV-2 is an NIH-funded platform trial that tested a number of antiviral therapies for COVID-19. Now this trial did not study Paxlovid, but we were able to use the placebo recipients of this trial to evaluate the rates of symptom and viral rebound during natural COVID-19 recovery. And I would say that one of the strengths of the study is that participants recorded their symptoms daily and also took daily nasal swabs for viral load testing. I mean, this is a pretty selfless group of volunteers who were part of this study. But having this intensively collected data set really gave us a detailed granular view of what was happening during natural COVID-19 recovery.

Dr. Turck:
Turning to the results, Dr. Li, would you share some of your key findings with us?

Dr. Li:
Yeah. We were actually frankly pretty surprised at what we found. Our results showed that symptom or viral rebound kind of individually was actually quite common even in the absence of antiviral therapy. We found that symptom rebound occurred in about one in four individuals and viral rebound was also fairly common. Our definition of viral rebound was that the viral load had to increase at least half a log from the prior viral load and in particular we wanted to focus on high-level viral rebound, and we defined that as having a viral load increase that reached an absolute threshold of at least 5 logs/mL from the nasal swabs. And we chose kind of 5 logs because this level of viral rebound is where we tend to start seeing culture positivity, and culture positivity is an indication of having infectious virus and increases risk for transmission, and our results showed that high-level viral rebound was happening in about one in eight individuals, so symptom rebound one in four, high-level viral rebound one in eight. But on the other hand, if you look at the combination of symptom and high-level rebound, actually, that was actually quite rare, so these two kind of events were happening largely kind of in different patient populations. The combination of symptom and high-level viral rebound was only happening in less than 3 percent of the participants, so very rare. So I would say one of the, you know, take-home points here is that in patients who have kind of symptom relapse, that most of them actually don't seem to have any increase in their virus and viral load shedding especially not at the high levels that would indicate an increased risk of transmission.

Dr. Turck:
For those just tuning in, you're listening to *COVID-19: On The Frontlines* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jonathan Li about his research on SARS-CoV-2 viral rebound in untreated patients.

Let's dive deeper into these keep findings. Dr. Li, what do these results tell us about the road to recovery for these patients?

Dr. Li:
That's a great question, Charles. I think the results really highlight that symptom resolution, so the, you know, kind of symptom improvement over time in acute COVID is often times not a linear process. The recovery sometimes can be a little bumpy in that the symptoms can wax and wane over time and that symptom relapse is not unexpected even without treatment. I would say that luckily the symptom relapse is only rarely linked with viral rebound and viral resurgence.

Now, I do want to be clear about what our data does not show. Our data does not mean that Paxlovid rebound is not real or not important because we didn't study Paxlovid patients. We studied patients really during the natural recovery from COVID-19. And I do think that there's actually some data out there that suggests that viral rebound could be more common after Paxlovid treatment, but the data at this point at least in my mind is not conclusive. What these results do show is that, baseline rates of symptom and viral relapse in untreated individuals really need to be accounted for when you're studying what happens after treatment. In other words, you really do need a control group of untreated individuals when you're studying rates of Paxlovid rebound.

Dr. Turck:
How can we better prevent the risk of rebound in patients who've taken nirmatrelvir ritonavir?

Dr. Li:
Yeah. There's so much that we still don't know about rebound after nirmatrelvir/ritonavir, or Paxlovid treatment. I think right at the top of the list is we need to get a better handle on how much more common it is compared to untreated infection, but we also don't know, you know, whether the timing of treatment affects outcomes. You know, if you took Paxlovid on day 1 or 2 of infection, would your rate of rebound be different if you took it on days 4 or 5? I don't know that. I don't think anyone knows that answer. And, you know, there's also no data on whether longer courses would help as that hasn't been studied either. So I would say right now there's still more questions than answers when it comes to preventing rebound after nirmatrelvir.

What I would say is that patients should remain vigilant for the week or so after they finish treatment. If their symptoms do recur and they are positive again on an antigen test, they should follow the CDC guidelines and reisolate. Our data that we've generated as part of a different study, suggests that individuals who do rebound after Paxlovid can have very high levels of viral rebound and also have culture positivity suggesting that they may be able to transmit the rebounding virus to others. So I think following the CDC guidelines at this point still makes a lot of sense.

Dr. Turck:
And, finally, do you have any key takeaways you'd like to share with our audience?

Dr. Li:
Well, I think I would really like to urge those patients who are at high risk of severe COVID, that for those individuals, don't let the news

of Paxlovid rebound, I would say, scare you from taking this lifesaving medicine. Rebound cases in general are mild, and for the vast majority of patients, they represent more of a nuisance than anything. Clinical trials of Paxlovid show that it is incredibly effective at preventing hospitalizations or death despite viral or symptom rebound, and in the end, I would say that is what we care about. Right? We care about keeping our patients healthy and out of the hospital.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Jonathan Li, for sharing his research and insights on COVID viral rebound.

Dr. Li, thank you for speaking with me today.

Dr. Li:
Thank you so much for having me. This has been a blast.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit ReachMD.com/COVID19 where you can be Part of the Knowledge. Thanks for listening.