

Lenacapavir PrEP Works Well for People Who Use Substances

Drug use and binge drinking did not affect safety or adherence to twice-yearly PrEP injections.

December 19, 2025 By [Liz Highleyman](#)

Twice-yearly lenacapavir (Yeztugo) pre-exposure prophylaxis (PrEP) can be a safe and effective HIV prevention option for people who use drugs or drink heavily, according to study results presented at [IDWeek 2025](#).

Many cisgender gay and bisexual men, transgender men and women, and gender-diverse people who use substances are at high risk for HIV acquisition, but social, structural and individual barriers can make daily oral PrEP use a challenge. Injectable PrEP administered once every six months may help overcome these barriers.

The Food and Drug Administration [approved lenacapavir PrEP in June](#), making it the longest-acting HIV prevention option. The approval is supported by two large studies showing that the biannual injections dramatically reduced HIV acquisition. The Phase III [PURPOSE 1 trial](#) found that twice-yearly lenacapavir PrEP was 100% effective for young cisgender women in Africa. [PURPOSE 2](#) showed that lenacapavir injections reduced the risk of HIV acquisition by 96% relative to background incidence for cisgender men and gender-diverse people who have sex with men in the United States and six other countries.

Jesse Clark, MD, of the University of California Los Angeles, and colleagues looked at lenacapavir PrEP adherence and safety among PURPOSE 2 participants who recently used drugs or engaged in binge drinking.

Among the more than 2,000 total trial participants, the median age was 28 years, and a third were ages 16 to 25. The population was racially diverse: 37% Black, 33% were white, 12% were Asian and 63% were Latino. Nearly a quarter identified as transgender or nonbinary.

More than a third (37%) reported any drug use—including cocaine, amphetamine-type stimulants, opioids sedatives, or hallucinogens but not cannabis—within the past three months, and 41% reported at least monthly consumption of six or more drinks on a single occasion. Stimulant use was most common (20%); less than 2% said they used opioids, and less than 1% reported injection drug use.

The researchers found that adherence, defined as on-time injections within 28 weeks after the previous shot, was high overall. What's more, it was comparable both between people who did and did not use drugs or binge drink and across different types of substance use. Adherence to the third shot at 52 weeks exceeded 90% across the board and reached 100% for the 14 opioid users expected to receive this injection.

The frequency of adverse events was also similar regardless of substance use. As seen in the full study population, the most common side effect was injection site reactions, reported by more than 80%.

This study also assessed drug interactions between lenacapavir and fentanyl. Lenacapavir is a moderate CYP3A inhibitor, and fentanyl is partially metabolized by this enzyme, so it could potentially increase fentanyl concentrations. However, laboratory data predicted only a weak interaction between lenacapavir shots and IV fentanyl. Preliminary modeling based on known fentanyl metabolism pathways, previous literature on fentanyl metabolism and in vitro data suggested no clinically meaningful interactions are expected.

"Twice-yearly lenacapavir is a favorable option for people who use drugs or binge drink," the researchers concluded.

To learn more, the ongoing Phase II [PURPOSE 4](#) trial ([NCT06101342](#)) is studying lenacapavir PrEP and tenofovir disoproxil fumarate/emtricitabine (Truvada) daily oral PrEP specifically for people who inject drugs in the United States. It is expected to be completed in late 2028.

Click here for [more news about PrEP](#).

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