with men). Half of them received daily oral tenofovir/emtricitabine (TDF/FTC) as PrEP and the other half received LA-CAB 600 mg intramuscularly every 2 months. After 2 years of follow-up, 72 out of 2248 individuals using LA-CAB versus 25 out of 2244 on TDF/FTC became infected with HIV (HR 0.34; CI 95% 0.22-0.54; $p < 0.001$).

Interestingly, only seven breakthrough infections in the LA-CAB arm occurred in subjects despite on-time dosing, appearing the rest in persons with delayed injections. Furthermore, new incident HIV infections depicted an unusual delayed antibody production and low viral load values (*Marzinke et al. J Infect Dis 2021*), which precluded to introduce antiretroviral therapy earlier and favored the selection and accumulation of integrase resistance mutations. These results reinforce the need to check periodically plasma HIV-RNA and HIV antigen/antibody in all subjects on PrEP. In persons receiving LA-CAB as PrEP, viral load testing is now recommended every 2 months, along with each intramuscular injection. Nevertheless, due to its high efficacy, LA-CAB as PrEP should still be considered in settings where HIV-RNA screening is not readily available.

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Unexplained hepatitis in children after lifting COVID-19 pandemic restrictions

Since January 2022, almost 150 cases of acute hepatitis with epidemic features have been reported among children aged 1-15 years old, mostly below 5 years old. A wide range of symptoms has appeared, but a subset of these children has progressed to liver failure and required liver transplantation and at least one death has been reported already.

Common hepatitis viruses that cause food-borne (hepatitis A or E viruses) or nosocomial infections (hepatitis B, C, or D viruses) have been ruled out. Furthermore, a possible relationship with COVID-19 vaccines has similarly been excluded, since all these children had not been vaccinated. Other less probable causes, including poisoning, seem unlikely.

Recent evidences suggest that infection by human adenoviruses (HAdV) is the most likely cause of these unexplained childhood hepatitis. Adenoviruses could be involved in up to 80% of cases that were tested. (*Christie B. BMJ 2022; 377:o982*). The fact that this idiopathic hepatitis has been identified in countries that first lifted social restrictions to control the COVID-19 pandemic support an epidemiological link. This is the case for the United Kingdom, Denmark, The Netherlands, Holland, the United States, and Spain.

HAdVs are double-stranded non-enveloped DNA viruses, well known to be associated with pediatric illnesses. More than 100 different types of HAdV have been described, designated by consecutive numbers, which are grouped into seven species, designated by letters from A to G. Adenoviruses are capable of infecting a diverse number of human cells, hence their use as vaccine vectors (for example, those from Astra-Zeneca, Janssen or Sputnik for COVID-19 vaccines). Interestingly, distinct HAdV species may display a differential cellular tropism.

The transmission of HAdV is similar to that of other respiratory viruses, by drops or aerosols, or through direct inoculation in the conjunctiva or oral-nasal mucosa. Moreover, infection may occur throughout the fecal-oral route or through contact with contaminated objects. After an incubation period of 2-14 days, acute self-limited infection occurs. Occasionally, HAdVs can persist in the respiratory or digestive tracts, and reactivate after long periods of host latency.

HAdVs can produce very different clinical manifestations, depending on the age group, community setting, immune status, and viral species. Primary infection by HAdV usually occurs after 6 months of birth and within the first 5 years of life, following the steadily vanishment of the protection given by passively transferred maternal anti-HAdV antibodies. The most characteristic HAdV infections in young children are acute respiratory tract infections. They are often accompanied by gastrointestinal symptoms. Most childhood HAdV infections are mild; however, especially in older children, they can depict more severe manifestations, including non-purulent conjunctivitis, hemorrhagic cystitis, and mesenteric adenitis. Occasionally, they evolve with respiratory sequelae such as prolonged bacterial bronchitis or bronchiectasis.

Immunity against HAdV depends on innate mechanisms, as well as adaptive immunity, both humoral and cellular immune responses. Immune protection against HAdV begins from the 1st year of life and is strengthened with successive infections until it becomes

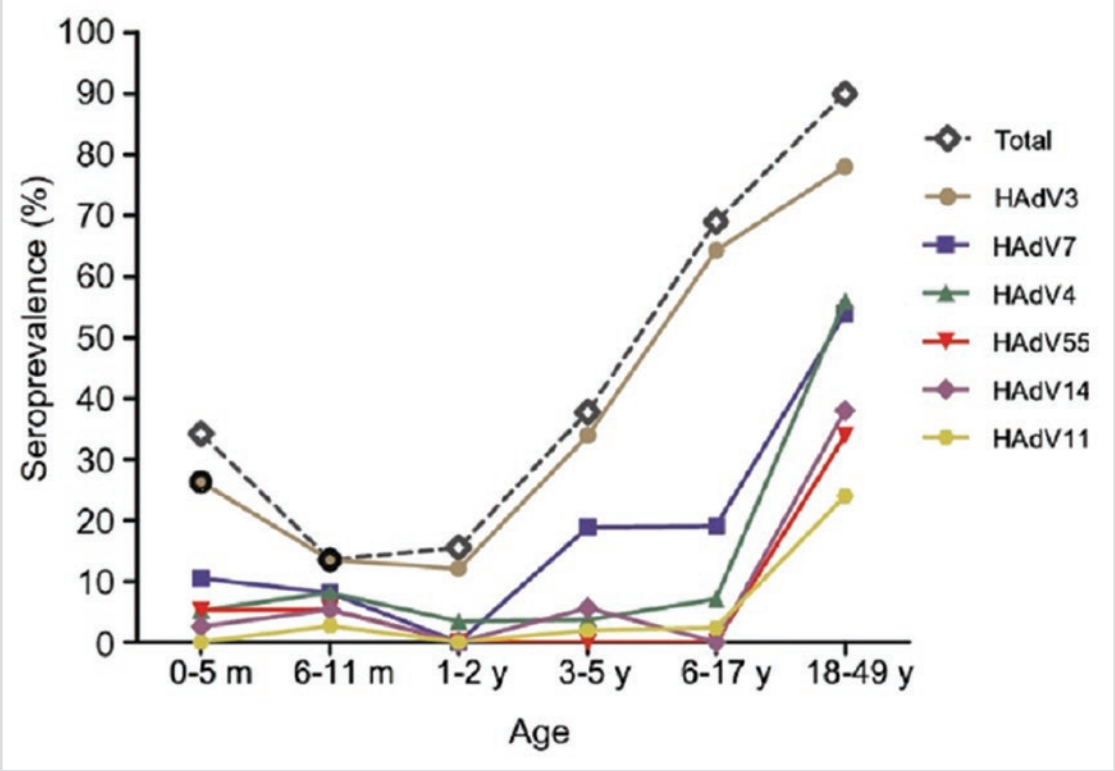

Figure 1. *Seroprevalence of human Adenovirus infection in different age groups. From: Tian X, et al. Virologica Sinica 2021; 36:373-381*

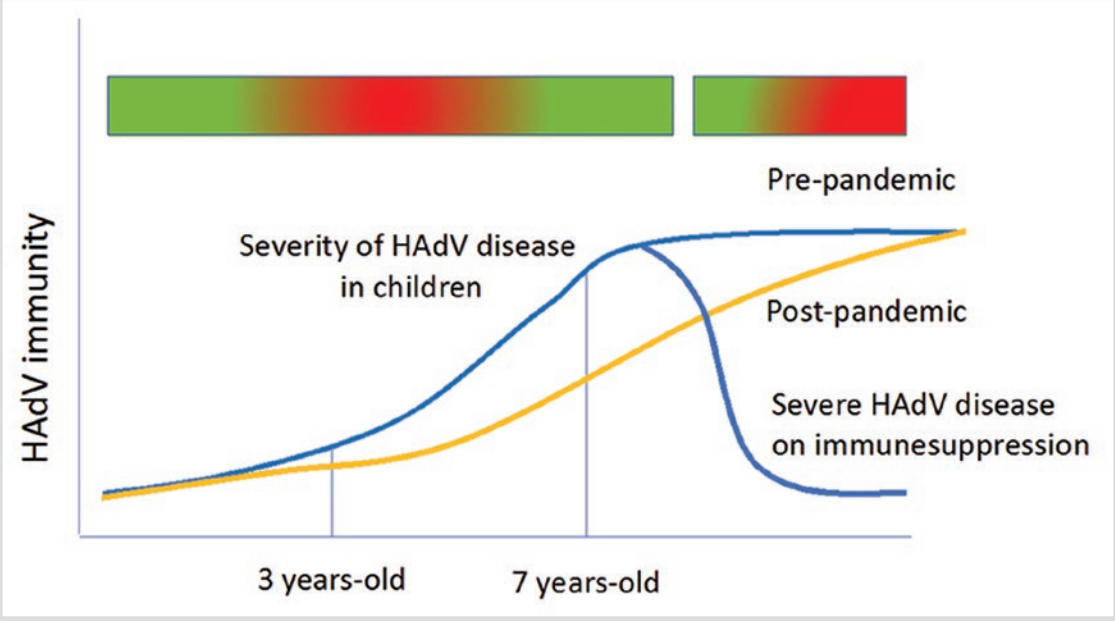

Figure 2. *Hypothesis. Pathogenesis of unexplained childhood hepatitis.*

robust enough from approximately the 6th year of life (Fig. 1) (*Tian X, et al. Virologica Sinica 2021; 36: 373-81*). Furthermore, the development of immunity against one HAdV species appears to provide some cross-immunity against others. Loss of T-cell responses against HAdVs is associated with more severe infections, particularly in children. In these cases, the most frequent HAdV species is C, which is usually associated with hepatitis (*Lion T. Clin Microb Rev 2014; 27: 441-62*).

In light of these data, the HAdV hypothesis for unexplained childhood hepatitis gains strength. The period of social isolation of more than 2 years caused by the COVID-19 pandemic has reduced natural exposure to HAdVs. In children between 1 and 7 years of age, in whom immunity against HAdVs has to be strengthened by repeated infections, the level of protection would nowadays be deficient. As social life returns to normal, new HAdV infections would be more severe in a subset of unexposed young children between 2 and 6 years old. For those older than 7 years old, the immunity acquired before the COVID-19 pandemic still would be robust enough to protect against severe HAdV disease (Fig. 2). The recognition of HAdV type 41F, usually causing gastrointestinal disease, as the most likely responsible for these cases of hepatitis supports this hypothesis.

More definitive data are needed before accepting the adenovirus hypothesis for the current unexplained childhood hepatitis. The causal relationship has not yet been reliably confirmed, and whether other specific HAdV variants or types may be particularly responsible. It is important to clarify these aspects, since confirmation might support the threat of rebounds for other illnesses (allergies, infections, etc.) following lifting restrictions and prolonged social isolation.

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International outbreak of monkeypox in men having sex with men

On May 17, seven patients with monkeypox were reported in the United Kingdom (*Mahase E. BMJ 2022*). Since that time, more than 2500 cases have been reported in 30 non-African countries, including Spain, Portugal, Italy, Sweden, USA, Canada, and Australia by the end of June 2022. Almost all are gay men under the age of 40. In Spain, the Ministry of Health has already confirmed 120 cases and there are another 50 suspects. Almost all have been diagnosed in Madrid.

Monkeypox virus (MPXV)

It is a double stranded DNA virus that belongs to the orthopoxvirus family. Rodents (rats, squirrels, etc.) are its main reservoir. Monkeys – like humans – become infected from these animals, so it is a zoonosis. The virus was first isolated in 1958 in monkeys that fell ill at a research facility in Denmark (*Cho C & Wenner H. Bacteriol Rev 1973*).

The first human case of MPXV infection was described in 1970 in a child from the Democratic Republic of the Congo, formerly Zaire (*Ladnyj I, et al. Bull WHO 1972*). MPXV is similar to the virus that caused smallpox, the only infectious disease that has been eradicated from the world to date. The WHO considered it extinct by 1980.

People vaccinated against smallpox depicts some protection against monkeypox. Therefore, almost all current cases have been described in young people, all of whom being unvaccinated against smallpox.

Transmission

Monkeypox is a rare viral infection in humans. A hundred cases are reported each year in West African countries, such as Nigeria, Cameroon, the Central African Republic, and the Republic of the Congo. In Nigeria alone, 241 cases have been confirmed since 2017, eight of which have died (*Nguyen P et al. Emerg Infect Dis 2021*). So far in 2022, 15 more cases have been diagnosed in Nigeria. Outside of West Africa, reported cases are almost always related to travel to endemic areas.

Transmission usually occurs when humans come into close contact with infected animals or contaminated meat. Small skin wounds or mucosal exposure facilitate contagion. In 2003, there was an outbreak in the U.S. with 47 affected. The source of the contagion was squirrels sold as pets from a farm near Chicago, where they had grown up alongside rodents imported from Ghana, which turned out to be infected with MPXV (*Reed K, et al. N Engl J Med 2004*).

Clinical manifestations

The disease usually self-limits in less than a month, with the appearance of fever, headache, arthromialgias, neck adenopathies, and characteristic