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COVID-19 vaccination and HIV-1 acquisition

Susan P Buchbinder and colleagues[1] express concern that COVID-19 vaccines utilising replication-defective adenovirus vectors of human serotype 5 (HAdV-5) might increase the risk of HIV-1 acquisition. Such concern has prompted hesitancy to deploy available, safe, and efficacious adenovirus-based COVID-19 vaccines in countries with high HIV-1 incidence.

Currently, two COVID-19 vaccines use HAdV-5 vectors, the first being Sputnik V developed by the Gamaleya Research Institute (Moscow, Russia), which consists of an HAdV-5 vector boost given after priming with an adenovirus vector of human serotype 26 (HAdV-26), and the other being the CanSino Biologics product (Tianjin, China), which uses two sequential doses of an HAdV-5-vectored vaccine. Other COVID-19 vaccines employ different adenovirus serotypes—the single-dose vaccine from Janssen uses an HAdV-26 vector and the vaccine from AstraZeneca uses the same chimpanzee-derived adenovirus vector for each of the two doses.

Concern about the use of HAdV-5 vectors for mass vaccination stems from Merck's phase IIb STEP and Phambili AIDS vaccine trials in North, central, and South America, Australia, and South Africa in 2007–08. These trials tested three doses of an HAdV-5 vector carrying HIV-1 *gag*/*pol*/*nef* genes. The vaccine was administered to individuals at high risk for HIV-1 infection and showed little efficacy, together with a small but significant and sustained increase in HIV-1 infections in a subset of men who were not circumcised and had baseline titres of more than 1:200 of HAdV-5-specific neutralising antibodies.[2–4] By contrast, a follow-up AIDS vaccine trial using a DNA prime followed by an HAdV-5 boost with constructs that carried *gag*/*pol*/*nef* and *env* of HIV-1 in circumcised, homosexual men, negative at baseline for HAdV-5 neutralising antibodies, showed no increase in HIV-1 acquisition rates.[5] It was also shown that previous infection with HAdV-5 does not, of itself, increase vulnerability to HIV-1,[6] nor does a live HAdV-4/7 vaccine, which has been given orally since the 1970s to US army recruits.[7] Furthermore, no increase in HIV-1 infection rates was reported for the HAdV-26 COVID-19 vaccine during large-scale trials[8] or in widespread use following emergency authorisation.

High prevalence rates of neutralising antibodies to both HAdV-5 and HAdV-26 have been reported among people residing in some countries of sub-Saharan Africa,[9] and several hypotheses have been formulated to explain why immunisation with HAdV-5 vectors might render men with pre-existing neutralising antibodies to this virus more susceptible to HIV-1 infection. It was speculated that adenovirus-specific neutralising antibodies complex the vaccine vector to Fc receptors on dendritic cells, resulting in activation of $CD4^+$ T cells, which then become more susceptible to HIV-1 infection.[10] This interpretation is unlikely as the adenovirus vectors bind not only serotype-specific neutralising antibodies, but also the even more prevalent non-neutralising antibodies, which are highly cross-reactive between different human and chimpanzee adenovirus serotypes.[11] Alternatively, T cells specific to antigens of the HAdV-5 vector were held responsible.

In support of this view, it was shown that HAdV-5-specific $CD4^+$ T cells are particularly sensitive to HIV-1 infection,[12] leading to the hypothesis that humans with high neutralising antibody titres to HAdV-5 develop high frequencies of HAdV-5-specific $CD4^+$ T cells. These $CD4^+$ T cells, it was postulated, would migrate to the genital tract and the rectal mucosa, thereby increasing numbers of HIV-1 susceptible cells at the ports of viral entry. However, T cells cross-react between different human-origin and chimpanzee-origin adenovirus serotypes.[13] Thus, if the increased HIV-1 acquisition in the STEP and Phambili trials was indeed caused by adenovirus-specific T cells, it should not have been specific to HAdV-5 and should also affect other adenovirus vector vaccines, including Janssen's HAdV-26-based COVID-19 vaccines or AstraZeneca's chimpanzee adenovirus vector product. Moreover, a T cell-based effect should not correlate to baseline titres of HAdV-5 neutralising antibodies, as these do not predict frequencies of HAdV-5-specific $CD4^+$ T cells.[14] Others have argued that any vaccine that increases activated $CD4^+$ T cells will promote HIV-1 infection.[15] Perhaps, more pertinently, one study showed that individuals with high baseline HAdV-5-specific neutralising antibody titres, who became infected with HIV during the STEP trial, had a qualitatively different antibody response to adenovirus at baseline compared with individuals who remained uninfected, leading the authors to conclude that they were immunologically less responsive, and, thereby, more susceptible to infections regardless of the vaccine.[16]

In the end, we still do not know what caused the slightly increased HIV-1 infection rates in HAdV-5 seropositive men in the STEP and Phambili trials. However, it is important to note that the increase in HIV-1 infection in these studies was only observed in very small numbers of individuals.[2,4]

To date, more than 7·2 billion doses of COVID-19 vaccines have been given to over 3·1 billion humans, many of whom have received adenovirus vector vaccines, which have some advantages over mRNA-based products. In particular, they can be formulated for prolonged storage at 4°C and are among the most affordable COVID-19 vaccines, facilitating deployment in resource-poor countries. Rare serious adverse events have been reported after immunisations with the AstraZeneca or Janssen vaccines, most notably cerebral venous sinus thrombosis with thrombocytopenia

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and Guillain-Barré syndrome, but not one of the COVID-19 vaccines has been linked to increased rates of HIV-1 acquisition in the billions of vaccine recipients.

Nonetheless, in October, 2021, South Africa and Namibia suspended the use of Sputnik V over concerns that it might increase male vaccinees' susceptibility to HIV-1 infection. This suspension was made despite the fact that Sputnik V underwent extensive clinical testing and was found to be safe and highly effective in preventing disease, hospitalisations, or death due to COVID-19,[17–19] and is now being used in 70 countries. At present, no trial or empirical evidence suggests that Sputnik V, or any other COVID-19 vaccine, increases susceptibility to HIV-1 infection. Spain, Belgium, and Italy have implemented age-related or sex-related target groups for individual COVID-19 vaccines to minimise very rare adverse events observed upon emergency-use authorisation, notably cerebral venous sinus thrombosis in young women after immunisation with the adenovirus-based AstraZeneca and Janssen vaccines, or myocarditis in young men after immunisation with Moderna's mRNA COVID-19 vaccine. Similarly, recommending a target group for adenovirus-based vaccines in countries with high HIV-1 prevalence could be an option for regulatory bodies to take the most prudent and cautious path. The individual patient's age and self-reported sexual behaviours that contribute to personal HIV-1 risk could be considered in vaccine allocation.

Due vigilance and monitoring of adverse events, including HIV-1 infection rates, are absolutely crucial in the pandemic response and the roll-out of vaccines, but still, we would urge global health authorities to license and distribute any efficacious and safe vaccines that are available especially while access to COVID-19 vaccines in low-income countries remains insufficient.

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