Are adenovirus vector vaccines for COVID-19 safe for individuals at high risk for HIV-1 acquisition?

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We wish to respond to an article, published in the *Lancet*, expressing concern that COVID-19 vaccines utilizing replication-defective adenovirus (Ad) vectors of human serotype 5 (HAdV-5) might increase the risk of human immunodeficiency virus (HIV)-1 acquisition.[1] Such

concern has prompted hesitancy to deploy available, safe and efficacious Ad-based COVID-19 vaccines in countries with high HIV-1 incidence.

Currently, two COVID-19 vaccines use HAdV-5 vectors: (i) Sputnik V, developed by the Gamaleya Research Institute (Moscow, Russia), which consists of an HAdV-5 vector boost given after priming with an Ad vector of human serotype 26 (HAdV-26), and (ii) the CanSino Biologics product (Tianjin, China), which uses two sequential doses of an HAdV-5-vectored vaccine. Other COVID-19 vaccines employ different Ad serotypes: the single-dose vaccine from Janssen uses an HAdV-26 vector and the vaccine from AstraZeneca uses the same chimpanzee-derived Ad vector for each of 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, conducted in 2007/2008 in the Americas, Australia and South Africa. These used 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 a lack of efficacy, together with a small but significant and sustained increase in HIV-1 infections in a subset of males, who were not circumcised and had baseline titers > 1:200 of HAdV-5-specific neutralizing antibodies (NAs).[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 males, negative at baseline for HAdV-5 NAs, showed no increase in HIV-1 acquisition rates.[5] It was also shown that prior 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 1970ies 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 authorization.

High prevalence rates of NAs to both HAdV-5 and also HAdV-26 have been reported among subjects residing in some countries of Sub-Saharan Africa,[9] and several hypotheses have been formulated to explain why immunization with HAdV-5 vectors might render males

with pre-existing NAs to this virus more susceptible to HIV-1 infection. It was speculated that Ad-specific NAs 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, since the Ad vectors bind not only serotype-specific NAs, but also the even-more-prevalent non-neutralizing antibodies, which are highly cross-reactive between different human and chimpanzee Ad 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 NA titers to HAdV-5 develop high frequencies of HAdV-5-specific $CD4^+$ T cells. These, it was postulated, would migrate to the genital tract and/or the rectal mucosa thereby increasing numbers of HIV-1 susceptible cells at the ports of viral entry. Again, however, T cells cross-react between different human- and chimpanzee- origin Ad serotypes.[13] Thus, if the increased HIV-1 acquisition in the STEP/Phambili trials was indeed caused by Ad-specific T cells, it should not have been specific to HAdV-5 and should also affect other Ad vector vaccines, including Janssen's HAdV-26-based COVID vaccines or AstraZeneca's chimpanzee Ad vector product. Moreover, a T cell-based effect should not correlate to baseline titers of HAdV-5 NAs, as these do not predict frequencies of HAdV-5-specific $CD4^+$ T cells.[14] Others have argued that any vaccine that increases HIV-1-specific $CD4^+$ T cells will promote HIV-1 infection.[15] Perhaps more pertinently, one study showed that individuals with high baseline HAdV-5-specific NA titers, who became infected with HIV during the STEP trial, had a qualitatively different antibody response to Ad 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 males 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 Ad vector vaccines, which have some advantages over mRNA-based products. In particular, they can be formulated for prolonged storage at 4^{o}C and are among the most affordable COVID-19 vaccines, facilitating deployment in resource-poor countries. Rare serious adverse events have been reported after immunizations with the AstraZeneca or Janssen vaccines, most notably cerebral venous sinus thrombosis (CVST) with thrombocytopenia and Guillain-Barré syndrome, but none of the COVID-19 vaccines has been linked to increased rates of HIV-1 acquisition in the billions of vaccine recipients.

Recently, nonetheless, South Africa and Namibia suspended the use of Sputnik V over concerns that it might increase male vaccinees' susceptibility to an HIV-1 infection. This is despite the fact that Sputnik V underwent extensive clinical testing and was shown to be safe and highly effective in preventing disease, hospitalizations, or death due to COVID-19,[17-19] and is now being used in 70 countries. At present, there is no trial or empirical evidence that it, or any other COVID-19 vaccine, increases susceptibility to HIV-1 infection. Countries specify age- or sex- related target groups for individual COVID-19 vaccines have been implemented in order to minimize very rare adverse events observed upon emergency-use authorization, notably CVST in young women after immunization with the Ad-based AstraZeneca and Janssen vaccines or myocarditis in young men after immunization with the mRNA-based Moderna vaccine. Similarly, recommending a target group for Ad-based vaccines in countries with high HIV-1 prevalence may be an option for regulatory bodies to take the most prudent and cautious path. The individual patient's age and self-reported sexual behaviors 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 mandatory in the pandemic response and the roll-out of vaccines, Still, we would urge global health authorities, to license and distribute whatever efficacious and safe vaccines are available especially while access to COVID-19 vaccines in less developed countries remains limited.

Conflicts of interest: Drs. DML, DAO, WB, EM, NA, CC, and EHC serve as unpaid advisers to the Gamaleya Research Institute. DML: Advisory Boards or ad hoc consultancy Accelerate, Antabio, Centauri, Entasis, Meiji, Menarini, Mutabilis, Nordic, Paion, ParaPharm, Pfizer, QPEX, Shionogi, Summit, T.A.Z., VenatoRx, Wockhardt, Zambon, Paid lectures – bioMérieux, Beckman Coulter, Cardiome, GSK, Hikma, Merck/MSD, Menarini, Nordic, Pfizer, and Shionogi. Relevant shareholdings or options – Dechra, GSK, Merck and Pfizer, amounting to less than 10% of portfolio value. He also has nominated holdings in Arecor, Avacta, Diaceutics, Evgen, Genedrive, Poolbeg, Renalytics AI, Synairgen and Trellus (all with research/products pertinent to medicines or diagnostics) through Enterprise Investment Schemes but has no authority to trade these shares directly. HCJE has equity in Virion Therapeutics. She serves as a Consultant to Biogen, Takeda, Freeline Inc., and Regenxbio. DYL and IVD report patents for a Sputnik V pharmaceutical agent and its method of use to prevent COVID-19.

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