Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

accelerated progression to a new AIDS-defining condition or death. Deayton did not look at CMV-related organ-endpoint disease, but, importantly, attempted to define variables that would be useful in the assessment of HIV-infected individuals for disease progression. The results were independent of age and HIV RNA load.

Although Deayton and colleagues' findings point to a possible relation between CMV and HIV, they beg the question of what are we as clinicians to do with this information? The availability of this simple tool (PCR for assessment of blood specimens) could provide a useful addition to the management of HIV patients. Specifically, patients failing current HIV treatments could be probed for persistent detection of CMV DNA. Clearly such a strategy is not without expense. However, the potential benefits to individuals with HIV disease must be considered, particularly with existing orally bioavailable drugs such as valganciclovir or new antivirals, that approach clinical development, including maribavir. However, before such recommendations can be endorsed, Deayton and colleagues' findings need to be verified in additional and larger clinical trials, in different populations around the world. With verification of these data, a randomised trial must be done in individuals known to be persistently PCR-positive for CMV DNA to assess the clinical benefit.

I have no conflict of interest to declare.

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Mucosal immunisation and immunoprophylaxis as potential strategies for prevention of SARS

See pages 2122 and 2139

Severe acute respiratory syndrome (SARS) is a rapid-onset atypical pneumonia that was first identified in epidemic proportions in China in 2002.[1] WHO recently announced the containment of the latest outbreak, which was centred on the National Institute of Virology in Beijing.[2]

In today's *Lancet*, Alexander Bukreyev and colleagues show that a single intranasal immunisation in African green monkeys with the attenuated bovine/human parainfluenza virus type 3 (BHPIV3), into which the envelope spike (S) protein from the SARS coronavirus (SARS-CoV) has been expressed, induced neutralising antibodies to SARS-CoV in serum, and protected against subsequent live-viral challenge with SARS-CoV.

This finding is important since it brings together known yet innovative technologies, knowledge, and skills to address prevention of an emerging infectious disease. If applicable generally, the result could represent a major step forward for simplifying mass immunisation in at-risk human populations. On the basis that the S protein of other coronaviruses induced virus-specific immunity and, in some cases, protection against subsequent challenge in animal models,[3] Bukreyev and colleagues used a well-documented carrier vector, BHPIV,[3,4] to create a live-attenuated vaccine that protects monkeys against challenge with SARS-CoV.

Several animal viruses display the type of stable host-range restriction that led to the development of the Jennerian approach to live-attenuated vaccines, as used in creating the BHPIV3 vector. This chimeric vector has important potential in inducing protective immune responses against respiratory syncytial virus (A and B) and human parainfluenza virus (type 3) in rhesus monkeys and hamsters.[5,6] Human trials show that the live-attenuated bovine parainfluenza virus type 3 (BPIV3) is safe, immunogenic, and stable in infants and children,[7] and BHPIV3 produces enhanced immunogenicity against disease in rhesus monkeys.[6] Data are not yet available on the use of the BHPIV3 chimeric vector in human trials.

Intranasal live-attenuated viral vectors offer the best possibility of inducing sustainable protective immunity via the mucosal route. In the host-restricted approach to attenuation, it has been seen that: powerful adjuvants are not required;[6] that both systemic and mucosal immune responses are generated;[7] and that exacerbation of disease after natural exposure does not seem to occur.[8] Additionally, mucosal immunisation offers the advantage that mucosal immune mechanisms seem to mature earlier in young children and wane later in elderly people than with systemic immune mechanisms.[9]

Despite the promise demonstrated by the Jennerian approach and in particular the BHPIV3/SARS-S intranasal vaccine, we need to know the lag before both mucosal and systemic immune mechanisms are effective, and also the duration of immunity induced. Bukreyev and colleagues only report challenging the monkeys with SARS-CoV at 28 days after immunisation. Whilst the immunisation gave excellent protection from viral shedding at 28 days, the serum concentration of antibody in immunised animals was not greater at 28 days post-challenge than that measured in non-immunised animals. Further studies examining which mucosal immune responses are induced to SARS-CoV and which of these have any role in immune protection need to be done. Dose-response studies for both immunisation and challenge will also be needed before this model can be adopted for human trials.

As indicated by Bukreyev and colleagues, the approach they used of a replicating chimeric viral vector with protein inserts from a common human respiratory pathogen might be limited to infants and small children, because of interference from neutralising antibodies developed through natural infection.[10] Further investigations are warranted to establish a vector construct that would be effective in all age groups, especially because of the increased mortality rate from SARS in elderly people.[11]

Possibilities for immuoprophylaxis and treatment of high-risk individuals who have become exposed to SARS-CoV are outlined in a Research letter, also in today's *Lancet*, by Jan ter Meulen and colleagues. These researchers describe preliminary experiments in the ferret, a species that can be naturally infected with SARS-CoV. They found that prophylactic treatment of infected animals with a human monoclonal antibody (directed against the cell-surface spike glycoprotein of SARS-CoV) abrogated viral shedding from the pharynx, and prevented the development of macroscopic lung disease in infected animals. Extrapolation to human beings of a prophylactic treatment that reduced viral shedding and lung lesions would probably reduce transmission and the high morbidity associated with the disease.

Such a strategy, in combination with immunisation during a SARS outbreak, would offer potential treatment and prophylactic applications. However, before the monoclonal antibody approach suggested by ter Meulen can be applied to human beings, several further studies are required. Of particular importance are experiments relating to the efficacy of immunoprophylaxis and treatment in the presence of an established infection, appropriate dose-response and safety studies, and, critically, study of the effect of circulating antibody on vaccine efficacy.[12]

Bukreyev, ter Meulen, and their colleagues have shown that SARS can be effectively prevented by immunisation of the mucosa of the respiratory tract and immunoprophylaxis in animal models. Whilst further studies are required before these concepts can be applied to human beings, the findings provide exciting strategies for the prevention of disease in target communities and treatment of at-risk individuals.

We have no conflict of interest to declare.

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Sharing is caring, except when it comes to HLA-class-I alleles in HIV-1 transmission

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One of the key unanswered questions about human infection with HIV-1 is why some individuals resist infection, despite repeated exposure to virus. The basis for this inter-individual variability in susceptibility is unknown. However, growing evidence suggests that differences in genetic make-up have an influential role. For example, polymorphisms in genes that influence the cell entry of HIV, such as CC chemokine receptor 5, are associated with variations in the risk of acquiring HIV infection.[1,2]

Human leucocyte antigens (HLA), critical modulators of the adaptive immune response to HIV, have also been proposed as important risk factors affecting susceptibility to infection. At face value, this suggestion is both paradoxical and counter-intuitive. HLA proteins, although displayed on the cell surface, are not cofactors for entry of HIV into the cell, and are involved in immune responses that are typically generated well after cell entry has occurred. So, in the context of heterosexual HIV transmission, what are the potential mechanisms by which HLA-mediated responses might influence virus acquisition? There is evidence for at least three, non-mutually exclusive, mechanisms. Interaction of HLA with the natural-killer receptors of the innate immune system might influence transmission, and although a role for this interaction in disease progression is established,[3] the contribution to transmission is less well understood.[4] Alternatively, HLA-class-I disparity between sexual partners might induce cellular or humoral allogenic immune responses that reduce the probability of transmission. Conversely, viruses that have escaped HLA-mediated immune recognition in a donor (transmitter) might be preferentially acquired in a recipient host (seroconverter) who has similar antigen-presenting molecules—ie, HLA type. However, there are no large well-designed studies to support these conjectures in the context of heterosexual transmission of HIV.

In today's *Lancet*, Tevfik Dorak and colleagues fill in some of the gaps in our knowledge. They looked at the distribution of HLA-class alleles in 125 couples initially discordant for HIV status and in 104 persistently discordant Zambian couples. These researchers found that if the sexual partners shared one or both *HLA-B* alleles, the risk of transmission in the seroconverting partner increased by around two-fold. This increase was independent of non-genetic risk factors that can promote heterosexual transmission, including the index partners' viral mRNA levels.

Why is Dorak and colleagues' study important? First, it is a tour de force. These investigators selected two groups with similar epidemiological and other characteristics for their analyses. The participants came from the largest cohort of cohabiting couples who were initially discordant for HIV (n=1300). These individuals were followed up quarterly for 6 years for relevant behavioural and epidemiological characteristics, which is even more remarkable given that this region of the world is a challenging one in which to do studies that include inquiring about the frequency of intercourse. Second, the results drive home the point that,