A step forward for HIV vaccines

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See Articles page e366

Development of a safe and effective HIV vaccine will probably be essential to achieve a durable end to the HIV pandemic.[1,2] However, only four HIV vaccine regimens have been assessed for clinical efficacy in the 35-year history of the HIV epidemic.[2] The main challenges facing the development of an HIV vaccine are scientific and are unprecedented in the history of vaccinology, including the need to protect against globally diverse virus strains and unclear immune correlates of protection. In *The Lancet HIV*, Linda-Gail Bekker and colleagues report an important next chapter in the quest to develop an HIV vaccine.[3]

In 2009, the RV144 trial showed the first, and to date only, positive results from an HIV vaccine efficacy trial in human beings.[4] This vaccine included priming with canarypox ALVAC vectors and boosting with alum-adjuvanted envelope (env) gp120 proteins, and it provided 31% efficacy in a low-risk population in Thailand. Although not sufficient for licensure, these data catalysed a wave of enthusiasm to understand the immune correlates of protection and to try to improve this vaccine. Findings from an immune correlates analysis indicated that antibodies against env variable loops 1 and 2 (V1V2) correlated inversely with infection risk,[5] and a sieve analysis similarly showed vaccine-induced immune pressure on env V1V2.[6] These data led to a hypothesis that vaccine-elicited binding antibodies against V1V2 might have accounted for the protection observed in RV144. Additional potential correlates of protection that emerged from RV144 included IgG3 responses and CD4+ T-cell responses. A validated and predictive immune correlate of protection would be a major advance for the HIV vaccine field. Thus, a key priority has been to test this potential V1V2 immune correlate prospectively in another study.

Bekker and colleagues aimed to adapt the RV144 vaccine regimen to the clade C epidemic in South Africa. New ALVAC vectors (vCP2438, expressing clade C *env gp120* and clade B *env gp41/gag/pro*) and bivalent clade C env gp120 proteins (TV1/1086) were manufactured, and instead of the alum adjuvant used in RV144, the more potent squalene-based adjuvant MF59 was used. Bekker and colleagues assessed the safety and immunogenicity of this new vaccine in the HIV Vaccine Trials Network (HVTN) 100 trial[3]—a placebo-controlled, randomised, double-blind, phase 1/2 trial in South Africa. A late boost was added to the RV144 vaccine schedule at 12 months, with vaccine administered at months 0, 1, 3, 6, and 12. Thus, the RV144 and HVTN 100 trials differed by many variables. Binding antibody responses were of a higher magnitude and cellular immune responses were of a higher frequency in HVTN 100 compared with RV144, but V1V2-specific antibody responses were lower in HVTN 100 than in RV144. The reasons for these differences are not entirely clear but could be related to the specific env strains selected for the vaccines and the more potent adjuvant used in HVTN 100.

The findings of HVTN 100 are important because prespecified immunological go/no-go criteria were achieved, including IgG antibody binding and CD4+ T-cell responses, which led to initiation of a phase 2b/3 efficacy trial (HVTN 702) to ascertain the capacity of this vaccine to protect against HIV acquisition in South Africa (NCT02968849). HVTN 702 will also test prospectively whether vaccine-elicited V1V2-binding antibodies correlate with protection. Validation of this immune correlate would be useful because it could then be used as a surrogate biomarker that would greatly accelerate HIV vaccine development moving forward.

As the area of HIV vaccine research awaits efficacy results from HVTN 702, additional HIV vaccine candidates are also being pursued. These include adenovirus vectors expressing mosaic immunogens with an env gp140 protein boost, cytomegalovirus vectors that induce persistent T-cell responses, native-like env trimers, and sequential env immunisation approaches that aim to induce broadly neutralising antibodies.[2] One lesson from the RV144, HVTN 100, and HVTN 702 trials is that the time and resources needed to bring a vaccine candidate into efficacy trials are substantial. However, only such clinical efficacy trials can establish if a vaccine candidate protects humans. Moreover, efficacy data in humans helps to refine preclinical models and immunological assays. Therefore, we need to increase the number of efficacy trials to test a broad range of ideas for vaccines if we are to achieve the ultimate objective of developing an HIV vaccine and ending the HIV pandemic.

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Time for action on methamphetamine use and HIV

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See **Articles** page e379

For more than a decade, we have repeatedly learned about the associations between HIV infection among men who have sex with men (MSM) and methamphetamine use, so-called chemsex parties, in which group sex and recreational drug use happen concurrently, and seeking casual sex partners on the internet.[1–3] In *The Lancet HIV*, Phunlerd Piyaraj and colleagues[4] carefully created a conceptual framework of HIV incidence among MSM on the basis of theoretical assumptions and statistical associations between variables found in a cohort of MSM in Bangkok. Participants were enrolled from April, 2006, to December, 2010, and followed up until March, 2012. The framework highlighted once again the associations between methamphetamine use and HIV infection among MSM. Mutual risk factors for both methamphetamine use and HIV infection, including finding casual sex partners on the internet and attendance of chemsex parties, were also identified among MSM in this cohort.

Piyaraj and colleagues did not discuss in much detail potential interventions to tackle methamphetamine use and HIV infection, or associated risk factors, among MSM. Decriminalisation of recreational drugs to move away from suppressive and punitive policies to more pragmatic ones has been progressing in Thailand.[5] Effective implementation, however, would need substantial investment in reforming mindsets of law enforcement officers and health-care professionals at large.

MSM who engage in methamphetamine use and chemsex parties probably perceive themselves to be different from traditional drug users. Consequently, they might not feel that conventional harm reduction services provided by health-care professionals and community-based organisations that mainly serve traditional drug users are right for them. At the same time, health-care professionals and community-based staff in conventional settings might also not have the familiarity to manage MSM who use drugs confidently. Reported barriers to access health support that have restricted MSM who use drugs include fear of judgment or concern about expertise.[6]

The evidence base and clinical guidelines for effective screening and harm reduction interventions for MSM who use drugs are limited, despite being urgently needed worldwide.[7,8] Innovative approaches to address these needs should promptly be put in place. In Thailand, it was not until 2017 that members from key populations including MSM, transgender women, sex workers, and people who use or inject drugs came together to address the interconnected concerns on drug use and HIV. Such concerted efforts have enlarged networks of trained medical professionals and community-based staff who can serve various groups of people who use drugs and who can advocate for more appropriate harm reduction interventions. A syndemic of depression, drug use, chemsex-risk sexual behaviours, HIV, and sexually transmitted infections (STIs) among MSM means that harm reduction services need to include management of mental health problems and bacterial and viral STIs.[9]

In a community-led test-and-treat cohort of 648 MSM in Bangkok conducted during 2015–18, HIV incidence has remained disturbingly high at 6·6 per 100 person-years (unpublished data), increasing from the incidence reported by Piyaraj and colleagues of 6·0 per 100 person-years during 2006–12. Piyaraj and colleagues did not discuss how pre-exposure prophylaxis (PrEP), if implemented effectively, would affect the twin epidemics of methamphetamine use and HIV infection among MSM. However, evidence from big cities where these epidemics are similarly observed among MSM has shown the impact