

Hypothesis

## Clade, Country and Region-specific HIV-1 Vaccines: Are they necessary?

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### Abstract

Today, scientists are often encouraged to custom-design vaccines based on a particular country or clade. Here, we review the scientific literature and then suggest that the overwhelming endeavor to produce a unique vaccine for every world region or virus subtype may not be necessary.

### Clade, country or region-specific vaccines

It is generally agreed that HIV-1 arose decades ago by transfer of virus from chimps to humans [1]. The subsequent travel of infected persons and the continued practice of high-risk behaviors fostered virus transmission to virtually every world region. Once HIV-1 awareness was heightened and HIV-1 sequencing projects were implemented, regional similarities of viral sequences, presumably a consequence of the founder effect, became evident. Clade designations (e.g. clade A, B, C) were then used as a means to categorize viruses based on genetic sequence; thus such clade designations also tended to cluster viruses according to geographical location. Today, due to continuous virus transmission, mutation and recombination,

the demarcation of HIV-1 subtypes has become increasingly blurred, and the categorization of viruses by clade is increasingly difficult [2-5]. Nonetheless scientists are currently encouraged to custom-design vaccines based on a particular country or clade [6-11]. To this end, a single viral sequence may be selected, possibly based on a formula of ancestry or consensus, to represent all other viruses in the targeted category.

Designing vaccines in this way prompts careful consideration: must a unique vaccine be prepared to represent every clade, country or region of the world? If so, how will this be accomplished and for which country should first vaccines be produced? Who will decide? The complexity of

such an undertaking and the many difficulties that attend it encourage a second look at the strategy. Review of the scientific literature may provide reassurance that the seemingly unachievable endeavor to custom-produce a vaccine for every clade, country or region may not be necessary.

### **Do immune responses discriminate between clades?**

While differences in encoded protein sequence may permit discrimination between certain HIV-1 subtypes, successful vaccine development requires that viral proteins elicit protective immune responses, regardless of sequence. It has long been known that clades, as defined by genetic sequence, do not correspond to immunotypes, as defined by mutually exclusive immune responses [12-14]. Both B- and T-cells elicited by a virus from one clade may recognize viruses from other clades. This cross-clade responsiveness is explained by the fact that the B- and T-cells recognize precise epitopes rather than the overall sequence similarity of viruses. Antibody binding depends on three-dimensional structure, and the molecular structures bound by antibodies can occur on proteins that differ widely in primary sequence. T-cells recognize peptides in association with Class I or Class II MHC molecules, but like B-cells, T-cells can cross-react with non-identical targets. Conversely, two viruses may have 99% sequence similarity, yet a particular neutralizing antibody or T-cell receptor may discriminate between them. This discrimination may be due to a single amino acid change within the receptor contact site or in a sequence that alters epitope display [15,16]. Thus it is the detail of epitope and epitope context, not overall sequence similarity that defines lymphocyte specificity.

### **Cross-clade protection is achieved by priming the immune system with diverse viral sequences from a single clade**

The issues described above suggest that although a single-component vaccine may not be sufficient to target *any* clade, a cocktail vaccine, designed to represent the natural diversity of HIV-1, may be sufficient to target *all* clades. The latter point is supported by studies of HIV-1-infected humans and SIV-infected macaques. Although infected subjects cannot clear endogenous virus (due to its sequestration in "privileged" sites, hidden from the immune system), most individuals are resistant to super-infection [17-22]. This protection likely arises as the result of many successive rounds of endogenous viral mutation in the infected host. Each time an immune response is elicited in the periphery of an infected subject, new virus mutants appear [23,24]. The new viruses, by definition, have altered T- and B-cell determinants, allowing escape from the established antibodies and T-cell receptors. Following several rounds of immune response and virus escape, the

B- and T-cells are primed to recognize a broad spectrum of determinants [25]. Thus, superinfections are rare, even in subjects likely to have been serially exposed to viruses from different clades. The rare double infections in humans (explaining the origin of virus recombinants [4]) are perhaps a consequence of (i) drug regimens which block the natural evolution of virus in the infected subject, (ii) repeated HIV-1 exposures prior to maturation of the adaptive immune response, and/or (iii) disease-related immunodeficiency.

The fact that a mature immune response to HIV-1 cannot clear sequestered virus, but can prevent super-infection emphasizes the importance of priming the system preemptively. Similar considerations pertain to the design of vaccines against human herpesviruses (e.g. VZV and EBV), as these viruses provoke both lifelong infections and long-term protective immunity to superinfection. As with the successful VZV vaccine [26], an effective HIV-1 vaccine should be administered before virus exposure, infection and sequestration.

### **Could a cocktail vaccine ever be large enough to prevent HIV-1 infections?**

Perhaps careful vaccine formulation will preclude the need for assembly of enormous cocktails. Consideration that envelope structure is constrained by function suggests that the formulation of an effective envelope-based vaccine is feasible. The virus envelope must bind target cells to mediate infection, and only a few target cell receptor molecules (e.g. CD4, CCR5, CXCR4), have been described. Therefore, the number of discrete envelope shapes that maintain full cell-binding potential and function is likely to be limited [27]. Because the virus envelope is the target of both neutralizing antibodies and T cells, the strengths of both arms of the immune system may be harnessed by an envelope-based vaccine cocktail [28-30]. Diverse proteins need not be cross-inhibitory. In fact, type-specific immune responses have been recognized toward a single envelope construct represented as only 1% of a mixed vaccine [31]. Cocktail vaccines are effective in controlling other diverse pathogens (e.g. pneumococcus, poliovirus), despite early doubts about their prospect of success [32].

### **Clade, Country or Region-specific HIV Vaccines may not be necessary**

The assembly of envelope cocktail vaccines will probably be necessary to represent the natural diversity of HIV-1, even within a single clade. Careful vaccine design may reveal a cocktail formulation able to prevent virus infections in every world region, and to overcome the political and financial dilemmas associated with the production of clade, country or region-specific vaccines.

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