

Reagents for HIV/SIV Vaccine Studies

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Progress in developing a vaccine against HIV has been much slower than expected. There are many reasons why development of a vaccine against HIV is extremely difficult.

- There is no clear protective immunity even after natural infection
- The virus is highly variable
- The virus is able to escape aspects of the immune pressure
- It can infect different cell types over the course of infection
- Not all infected cells are recognizable by the immune system
- The virus affects cells of the immune system itself
- There is a risk of inducing infection-enhancing antibodies
- There is no perfect animal model for the infection

In spite of years of research into HIV, much is still unknown about the virus. What exactly makes it so pathogenic? What are the mechanisms that appear to protect some people against infection? What determines the dramatically different rates of progression to AIDS after infection? An important part of the research into these questions is done using animal, mostly primate, models. Unfortunately, no single primate model is ideally suited for the job.

Chimpanzees are the primates genetically most closely related to humans. They can be infected with HIV, but progress to AIDS very slowly after HIV infection. Thus far, only one chimpanzee has died from an AIDS-like illness, ten years after infection with HIV-1 (Villinger et al., 1997). This is a drawback in the light of recent discussions about the lack of necessity for sterilizing immunity (the total prevention of infection, as opposed to partial immunity, where infection after vaccination can occur but is less severe). Even a vaccine that does not prevent infection may still boost the immune system enough to prevent or delay disease in the event of infection. In fact, vaccines that protect against other viral diseases generally do not induce sterilizing immunity (polio, measles, varicella, smallpox). Since chimpanzees develop disease only very slowly, this effect cannot easily be studied using chimpanzee models. In addition, chimpanzees are a threatened species, they are very expensive, they cannot be put down unless they are extremely ill, and since HIV usually does not make them sick they must be kept in isolation for their lifetime, up to 40 years. Being HIV-infected, they pose a risk for their caretakers. Finally, the use of chimpanzees in potentially lethal experiments gives rise to complicated ethical considerations. After the initial, disappointing results involving HIV-1 vaccines (usually subunit vaccines) based on lab strains, the chimpanzee trials have largely been abandoned in favor of the cheaper and less demanding macaque monkey.

Macaques in the wild are not natural hosts for SIV, and most SIV strains are highly pathogenic to them, so they provide a very good model system to study pathogenesis. HIV-2, which is much more similar to SIV than HIV-1, quickly produces an AIDS-like disease in the pig-tailed macaque, *M. Nemestrina*. This is also the only macaque species that can be productively infected with HIV-1, although thus far without developing AIDS (Heeney, 1996). Challenge strains used in macaques are most frequently derived from SIV_{sm}, usually after several passages in macaques. A recent development is the use of chimeric SIV/HIV (SHIV) viruses that can infect macaques, cause an AIDS-like disease just like other SIVs, but share a varying number of genes with HIV-1. Only in the last few years have SHIV strains become available that are sufficiently pathogenic to be used as challenge strains in vaccine trials (see Fig. 1c).

In many cases the results of vaccine trials are different in different animal models. It is not always known when this is a virus effect (SIV vs. HIV), and when the host immune system responds differently to different immunizations and challenges. This problem obviously makes the interpretation

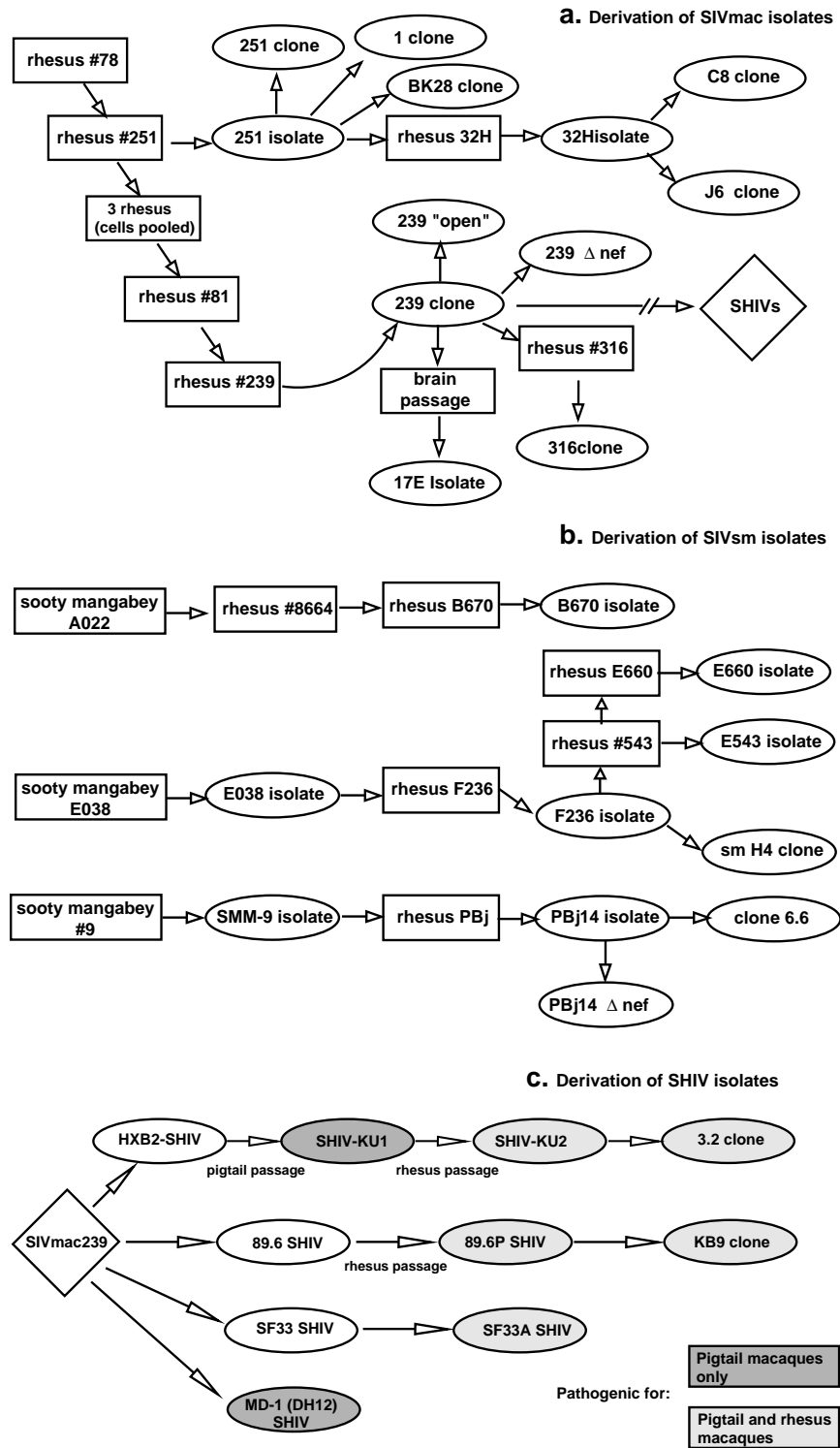


Figure 1. An overview of the derivation of SIVmac (a), SIVsm (b) and SHIV (c) strains. Rectangles indicate passages in a rhesus macaque, ovals indicate isolates or clones derived from these. Figures 1a and 1b were updated from (Schultz & Hu, 1993); Figure 1c was produced by Dr. Alan Schultz (NIAID) based on information from the original references. The figures were reprinted with permission. References: SIVmac (Figure 1a): 251/BK28 (Kornfeld et al., 1987); 1A11 (Marthas et al., 1990); 32H-C8 (Rud et al., 1992); 32H-J5 (Rud et al., 1992); 239 (Kestler et al., 1990); 239 derivatives (Desrosiers et al., 1998); 17E (Anderson et al., 1993); 316 (Mori et al., 1992). SIVsm (Figure 1b): B670 (Conway et al., 1991); H4 (Novembre et al., 1993); PBJ14 (Dewhurst et al., 1990); PBJ14- Δ nef (Novembre et al., 1996); E543 (Hirsch et al., 1997). SHIV (Figure 1c): KU1 (Joag et al., 1996); KU2 (Raghavan et al., 1997); 3.2 clone (Sodroski, unpublished); 89.6 (Reimann et al., 1996b); 89.6P (Reimann et al., 1996a); KB9 (Karlsson et al., 1997); SF33 (Luciw et al., 1995); SF33A (Luciw, unpublished); DH12 (Shibata et al., 1997a).

of vaccine studies in animal models difficult. Furthermore, subtle differences in the design of the vaccine (adjuvants, quantity and variability of antigens) and the trials (frequency and timing of inoculations, timing and severity of challenge, virus type, cell-free or cell associated) all can influence the outcome.

By far the best protection against both cell-free and cell-bound infection with HIV and SIV so far has been obtained using live attenuated virus vaccines. The protection is not type-specific, and SIV-vaccinated monkeys can even be protected against superinfection with virulent SHIV strains (Heeney, 1996). Live attenuated virus vaccines basically establish an infection, which appears to be the best way to prime the immune system to react to the presence of an alien invader; both humoral and cellular immune responses are optimized in this situation. However, there are many risks associated with the use of attenuated virus vaccines. First of all, it is uncertain that the attenuated virus is really non-pathogenic. It has been reported some time ago that virus that was apathogenic in adult monkeys could cause disease in neonates (Ruprecht et al., 1996). According to a recent report (Cohen, 1997), several adult monkeys that have been vaccinated with an attenuated virus several years ago have now also fallen ill. Apparently, this is not a matter of repair of the crippling mutations, but rather an inability of the immune system to control even very weak immunodeficiency viruses in the long run. However, even if this approach is ultimately deemed to be too dangerous, vaccine trials using attenuated SIV variants provide very important insights into the nature of protective immunity against immunodeficiency viruses.

In recent years, many successes have been reported using attenuated and SHIV based vaccines. Without striving for completeness, we cite some examples of successful vaccination attempts here. Successful protection from vaginal challenge in rhesus macaques has been reported by Miller et al. (1997). Dunn et al. (1997) reported that macaques infected with the SIVmac251 clone BK28 were protected against subsequent challenge with a chimeric strain, SHIVsbg. No virus could be recovered from three of the five challenged monkeys, although SHIV-infected cells were found. Two monkeys did develop viremia, but the viral load was 100-fold reduced compared to unvaccinated control animals. Comparable results were reported by Stephens et al. (1997) using attenuated SIVmac or SHIV as a vaccine and a pathogenic SHIV-KU1 for challenge. Interestingly, animals in this study that were productively infected with a pathogenic virus were later unable to fend off superinfection with a second virulent strain. Quesada-Rolander reported protection of monkeys vaccinated with SHIV-4 against rectal challenge with a virulent SIVsm (Quesada-Rolander et al., 1996). From two out of four monkeys, no virus could be recovered a year after challenge; two other showed initial viremia, which was later suppressed. Linhart et al. reported on an attempt to use attenuated viruses in a post-exposure vaccination, using simultaneous inoculation. The study showed no effect of co-injection of a non-virulent variant along with a virulent one (Linhart et al., 1997). An attempt was made to prevent infection of newborn macaques by vaccinating pregnant monkeys with the attenuated strain SIVmac1A11. Two out of three newborns were protected against mucosal challenge after birth (Van Rompay et al., 1996). Stahl-Hennig et al. reported sterilizing immunity in 4 out of 8 macaques vaccinated with the attenuated strain 32H-C8 (Stahl-Hennig et al., 1996). Putkonen et al. report protection of cynomolgous monkeys against SIV challenge using an attenuated HIV-2 strain as a vaccine (Putkonen et al., 1995). Other successful vaccinations have been reported using SIVmac1A11 (Otsyula et al., 1996), SIVmac316- Δ nef and 239- Δ 3 (Wyand et al., 1996) and several other attenuated SIV strains.

The number of different viral strains used in vaccine research is rapidly growing. In Figures 1–3 we present an overview of the virus strains that are frequently used in these studies, and their derivation. A distinction must be made between strains used for vaccination, which obviously must be non-pathogenic, and strains used for challenge, which tend to be pathogenic. However, it should be mentioned that some strains have been used both as vaccine and as challenge strains. Pathogenicity is a relative concept, and depends on the virus, the host species, and the individual host (most probably on characteristics of the MHC). For example, SIVsm is not pathogenic in its natural host, the sooty mangabey, but can be highly pathogenic to macaques.

SIVmac viruses are used most extensively in these studies. The SIVmac isolates 251 and 32H both have a reduced pathogenic counterpart, clones 1A11 and C8, respectively. These clones are genetically very similar to the quasispecies they were derived from, but they have one or more attenuating genetic

Attenuated SIV Strains

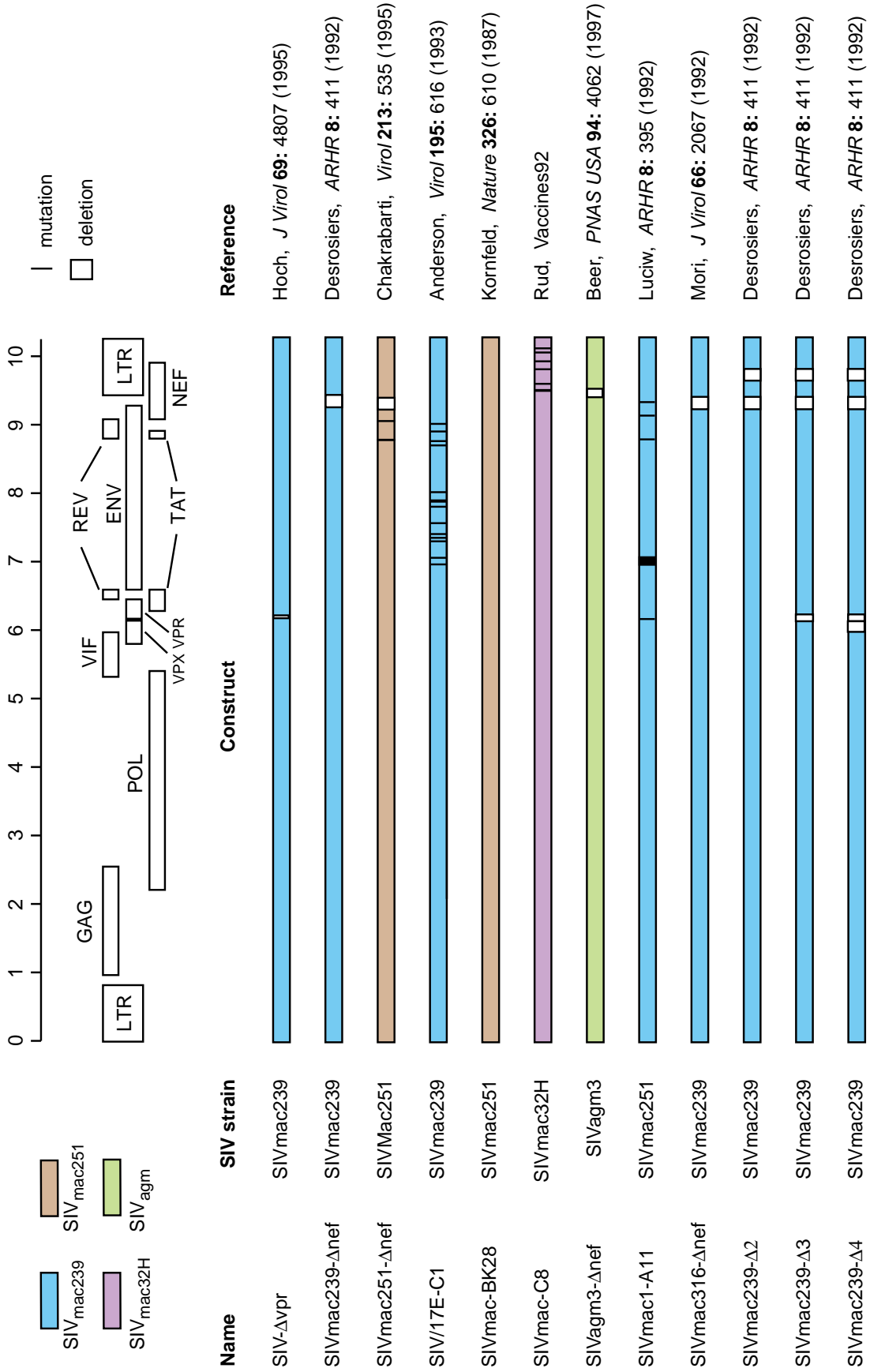
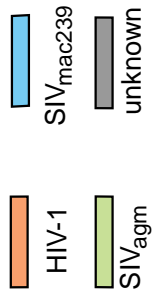
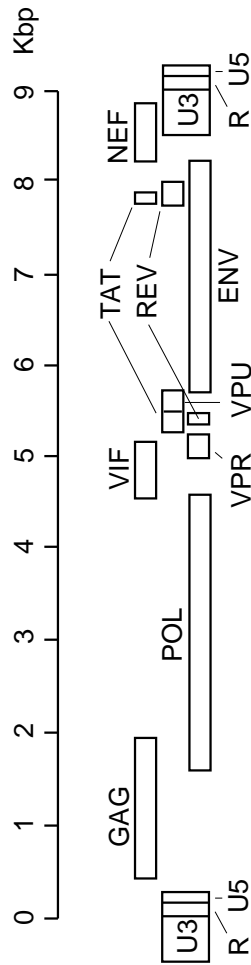


Figure 2. Schematic representation of common attenuated SIV strains used in vaccine research. Deletions are indicated in white, mutations are shown as black lines. Mutations may include insertion or deletion of a stop codon.

Chimeric SIV/HIV Strains



Name	HIV strain	Construct	Reference
SHIV _{sbg}	LAI	[SIV_mac239]	Dunn, <i>Virology</i> 223 : 351 (1996)
SHIV -4	HXBc2	[SIV_mac239]	Li, <i>J AIDS</i> 5 : 639 (1992)
SHIV _{SF33}	SF33	[SIV_mac239]	Luciw, <i>PNAS USA</i> 92 : 7490 (1995)
SHIV _{SF162}	SF162	[SIV_mac239]	Luciw, <i>PNAS USA</i> 92 : 7490 (1995)
SHIV _{w61D}	ACH320.3.1	[SIV_mac239]	Ranjbar, <i>ARHR</i> 13 : 797 (1997)
SHIV _{Han-2}	Han-2	[SIV_mac239]	Ranjbar, <i>ARHR</i> 13 : 797 (1997)
SHIV-89.6	89.6/HXBc2	[SIV_mac239] [HXBc2] [89.6] [8053]	Reimann, <i>J Virol</i> 70 : 3198 (1996)
NM-1	NL43	[SIV_mac239] [NL43]	Shibata, <i>J Virol</i> 65 : 3514 (1991)
NM-2	NL43	[SIV_mac239] [NL43]	Shibata, <i>J Virol</i> 65 : 3514 (1991)
NM-3	NL43	[SIV_mac239] [NL43]	Shibata, <i>J Virol</i> 65 : 3514 (1991)
NM-4	NL43	[SIV_mac239] [NL43]	Shibata, <i>J Virol</i> 65 : 3514 (1991)
NM-5	NL43	[SIV_mac239] [NL43]	Shibata, <i>J Virol</i> 65 : 3514 (1991)

Chimeric SIV/HIV Strains (cont'd)

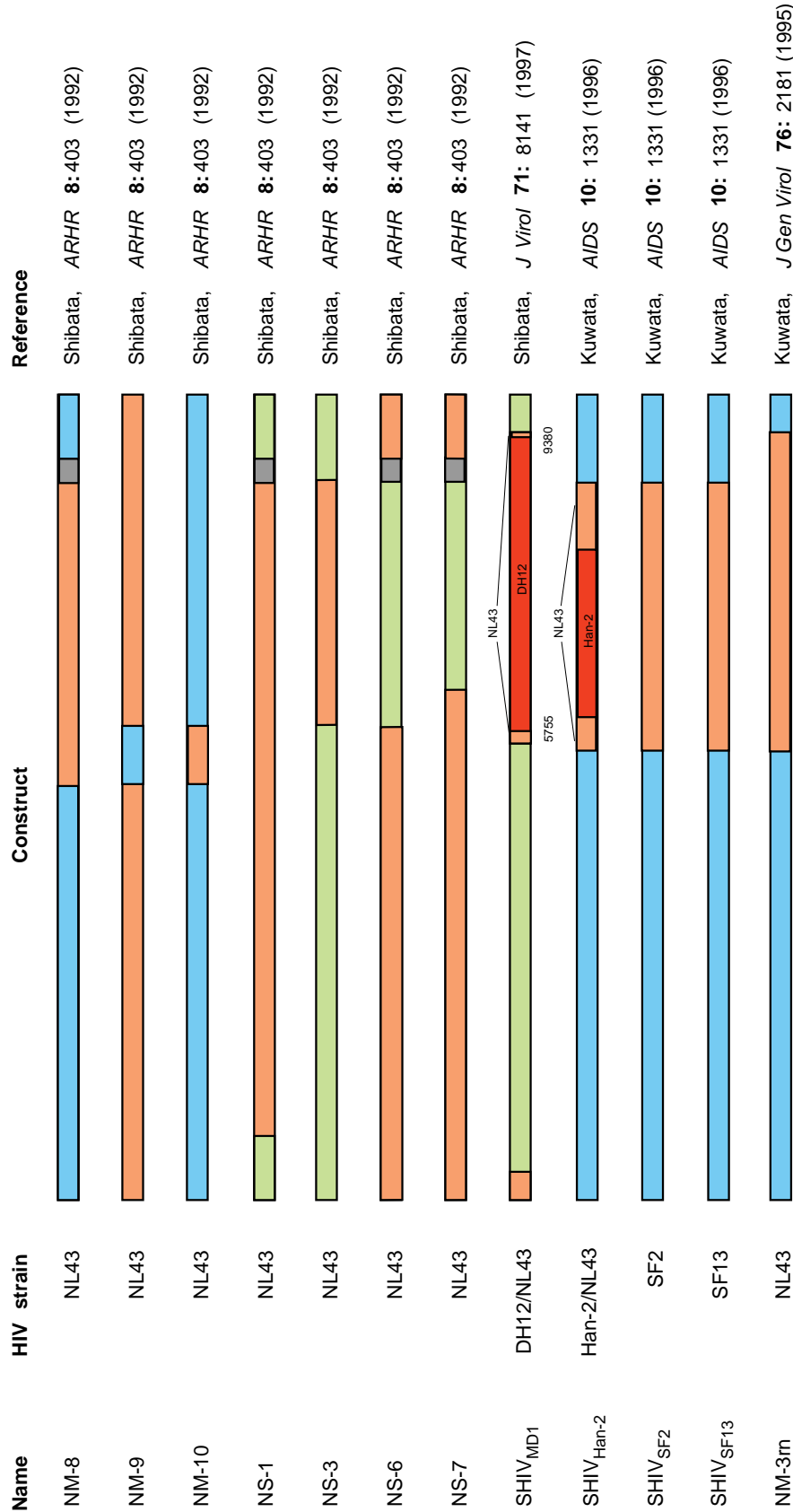


Figure 3. Schematic representation of common chimeric HIV/SIV strains used in vaccine research. The information was obtained from the references shown in the Figure. Although every attempt was made to contact the authors to clarify ambiguities, in some cases the exact location of the borders between HIV and SIV could not be established. The uncertain regions are shown in gray. The HIV genes used in these constructs are from the clones HXB2, 89.6, SF33, and DH12.

deletions. Another important SIVmac isolate, 239, is a clonal isolate from rhesus monkey #239. SIVmac239 is pathogenic, but a long series of reduced- or non-pathogenic strains with varying number of deletions in the genome has been derived from it. These strains cover a spectrum of pathogenicity, ranging from highly pathogenic to apparently non-infectious (unable to replicate in the host) (Desrosiers et al., 1998). It has recently become apparent that monkeys infected with SIVmac239- Δ 3, in the lower mid range of the pathogenicity spectrum, do develop AIDS after several years (Cohen, 1997). Two macrophage-tropic variants have also been derived from SIVmac-239: SIVmac316 and 17E (see Figure 1a).

SIVsm isolates can be highly pathogenic to macaques. Pathogenic challenge stocks in this group are usually bulk (rather than clonal) isolates, passaged in one of several macaques. Genetic clones of this group (such as SIVsmH4) tend to be much less pathogenic. An important and highly pathogenic strain is SIVsmPBj14, which kills a majority of infected macaques at primary infection, within a few weeks; monkeys that survive primary infection usually die of an AIDS-like illness within two years. Other isolates that have been used as challenge stocks are B670 and E660. Derivation of commonly used isolates from this group is shown in Figure 1b.

SHIV strains have recently been developed that are highly pathogenic. SHIV strains have traditionally been used for both protection and challenge. Especially SHIVs that have been composed from a CXCR4-using HIV strain appear to be pathogenic. The viruses usually are pathogenic only in their derivative form, after passage in several monkeys. Derivation of some frequently used SHIV strains is shown in Figure 1c.

In recent years the repertoire of non-pathogenic vaccine strains has been extended by the creation of artificially attenuated virus variants. This is usually done either by creating stop codons in non-vital sections, or deleting sections from the genome of a virulent strain. Since these attenuated virus strains often are not included in Genbank, we have produced an alignment for them. The alignment itself is not reproduced here, but it will be made available on the web page (<http://hiv-web.lanl.gov>). Instead, Figure 2 shows a schematic representation of attenuated SIV strains. The diagram shows where changes have been made or documented with respect to the wild type. The number of SHIV chimeras is also growing rapidly; a fairly large number of pathogenic SHIV strains is now available. The diagram in Figure 3 gives an overview of SHIV strains that are presently in use in the vaccine field, and indicates which section of the genomes are derived from HIV-1 (and which strain of HIV-1), and which from a SIV strain.

Notes

SIVmac239, a frequently used pathogenic strain, contains a stop codon (TAA) in *nef*.

BK28 is a clone from the SIVmac251 bulk isolate; it is the only sequence available from SIVmac251.

SHIV KU1 and KU2 are passages of SHIV-4.

SHIV 89.6P and KB9 are passages of SHIV89.6.

SF33A is a passage of SF33.

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