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Summary — Prior to Simian Immunodeficiency Virus (SIV)-infected macaques becoming the 'model of choice' in the 1990s, chimpanzees were widely used in AIDS vaccine research and testing. Faced with the continued failure to develop an effective human vaccine, some scientists are calling for a return to their widespread use. To assess the past and potential future contribution of chimpanzees to AIDS vaccine development, databases and published literature were systematically searched to compare the results of AIDS vaccine trials in chimpanzees with those of human clinical trials, and to determine whether the chimpanzee trials were predictive of the human response. Protective and/or therapeutic responses have been elicited in chimpanzees, via: passive antibody transfer; CD4 analogues; attenuated virus; many types and combinations of recombinant HIV proteins; DNA vaccines; recombinant adenovirus and canarypox vaccines; and many multi-component vaccines using more than one of these approaches. Immunogenicity has also been shown in chimpanzees for vaccinia-based and peptide vaccines. Protection and/or significant therapeutic effects have not been demonstrated by any vaccine to date in humans. Vaccine responses in chimpanzees and humans are highly discordant. Claims of the importance of chimpanzees in AIDS vaccine development are without foundation, and a return to the use of chimpanzees in AIDS research/vaccine development is scientifically unjustifiable.

Key words: *AIDS, chimpanzee, HIV,* Pan troglodytes*, vaccine.*

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Introduction

Over decades, billions of dollars have been dedicated to the development of an AIDS vaccine, only to result in disappointment and failure (1, 2). The exact number of vaccines tested pre-clinically and clinically is difficult to determine, but recent reviews have suggested over 30–40 vaccines in over 85 clinical trials involving almost 20,000 volunteers (3–7). The US National Institute of Allergy and Infectious Diseases (NIAID) report over 50 preventive vaccines in over 100 clinical trials (8), and 30-plus therapeutic trials. This analysis indicates that the figures are even greater, with no vaccine affecting disease progression (9, 10) or approved for use.

Initial optimism, such as that shown in 1984 when the US Health and Human Services secretary declared that a vaccine would be available within two years, has given way to a realisation that the virus will not be beaten easily. In some quarters, it is acknowledged that animal models of questionable relevance are culpable (for comprehensive cited examples and examples of expert opinion, see [11] and other cited references throughout this review). These animal models include the use of macaques infected with Simian Immunodeficiency Virus (SIV) or hybrids of SIV and Human Immunodeficiency Virus (HIV). President Clinton's 2007 goal for the development of an AIDS vaccine has now passed, with notable high-profile failures such as VaxGen's AIDSVAX and Merck's V520 vaccines. In 2004, the AIDS Vaccine Advocacy Coalition (AVAC) acknowledged that there would be no vaccine available by 2007, foreseeing a 'long haul' (12); and optimistic experts predict that it will be over a decade before the first vaccine is available — while others predict half a century (13).

In the light of these statistics and recent high-profile failures, many scientists are advocating changes to AIDS vaccine development. A small number involved in chimpanzee research believe that chimpanzees have been, and will remain, important, and thus advocate a return to their use (14).

This recommendation requires evidence that chimpanzees played a crucial role when their use in the late 1980s and early 1990s was common. This is the scope of this study: to assess whether their responses to previous vaccines correlated with human responses and to compare the immunogenic and prophylactic natures of those vaccines in chimpanzees and humans. The *a priori* argument is that if the vaccines behaved similarly, the resumed use of chimpanzees may be scientifically justifiable, independent of ethical considerations; but if the chimpanzee results proved erroneously predictive, there would be no scientific basis upon which to call

for the reinstatement of chimpanzees in AIDS research.

Summary of Vaccines and Clinical Trials

A prerequisite for comparing human and chimpanzee responses to AIDS vaccines is a comprehensive assessment of which vaccines have been involved in clinical trials to date. This was achieved by consulting the National Library of Medicine's *ClinicalTrials.gov* database (*http://www.clinicaltrials.gov/*), for which registration of clinical trials has been required for several years by the International Committee of Medical Journal Editors. The search was performed by using the operators 'AIDS OR HIV' (*Disease or Condition* field), and 'Vaccine' (*Experimental Treatment* field). It included all trials that were no longer recruiting patients. Though this database may not constitute an exhaustive repository of information regarding all trials of HIV vaccines to date, it currently describes around 47,000 trials sponsored by the National Institutes of Health (NIH), other US federal agencies and private industry, conducted in 151 countries. For the purposes of this investigation, it can be regarded as the most complete source of HIV clinical trial data which is readily available. The International AIDS Vaccine Initiative (IAVI) database (http://www.iavireport. org/trialsdb/default.asp) was also used to obtain vaccine details.

All the clinical trials located are summarised in Table 1. The 197 clinical trials of AIDS vaccines registered involved 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning that strain MN recombinant gp120 was considered to be a separate vaccine from strain SF-2 recombinant gp120).

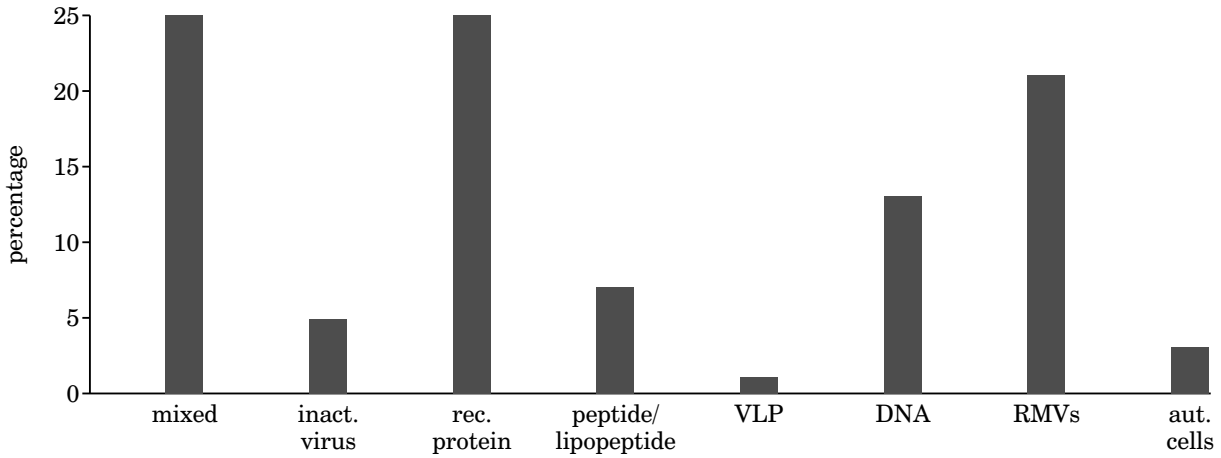
Figure 1 indicates the types and prevalence of vaccines tested clinically in the 197 trials: 49 trials (25%) were of recombinant protein vaccines; 41 trials (21%) were of recombinant microbial vaccines (RMVs); and 50 trials (25%) used a combination of two or more approaches. These trials and the others constituting the remaining 29%, are discussed below.

Figure 2 provides a breakdown of the types of vaccines in the RMV class. Of 41 trials, 13 (32%) involved canarypox vectors, closely followed by adenovirus vectors (12 trials [29%]). Eight trials (20%) were based on vaccinia virus vaccines, and the remaining 19% involved a variety of viruses and bacteria, as detailed in the text.

Of the trials, 143 (72%) were Phase I trials (Figure 3), which involve a relatively small number of volunteers (typically 20–100) over a two-year period, in which humans encounter the vaccine for the first time. Twenty-four (12%) were Phase II trials, in which vaccine candidates that appeared promising in Phase I investigations are tested in up to 300 people, including those at high risk of HIV infection or who are HIV-positive (HIV^+). Sixteen (8%) Phase I/II trials were also registered (i.e. Phase I and Phase II trials performed in parallel).

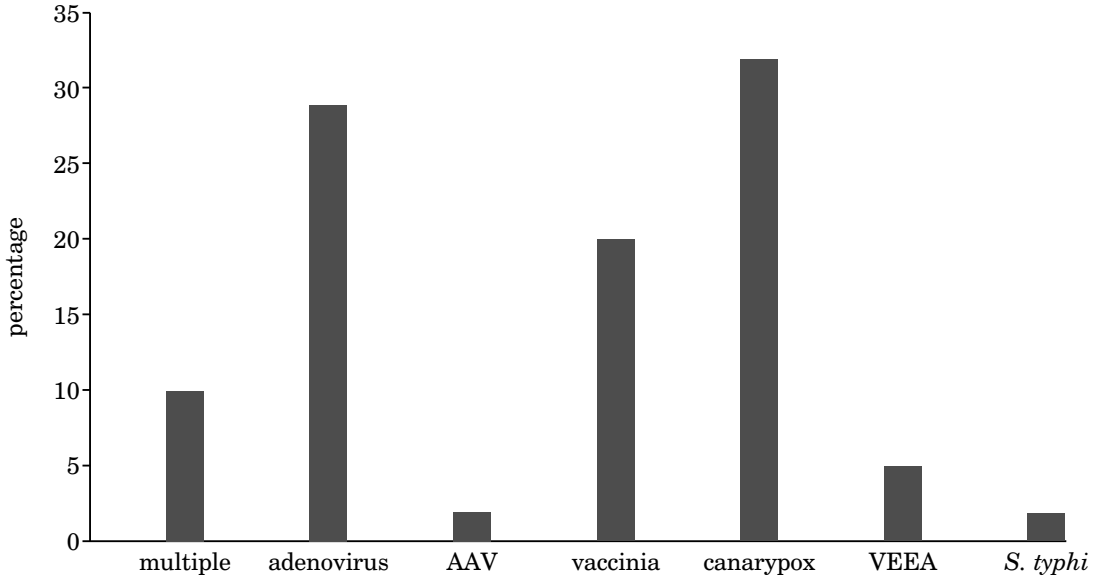
Just seven of the 197 clinical trials progressed to Phase III (the final stage of testing prior to licens-

Figure 1: AIDS vaccines in clinical trials



A total of 197 trials were registered with ClinicalTrials.gov, *up to and including 11 November 2007.*
Mixed = combinations of two or more vaccines; inact. virus = inactivated virus vaccines; rec. protein = recombinant protein vaccines; VLP = virus-like particles; DNA = DNA-based vaccines; RMVs = recombinant microbial vaccines; aut. cells = autologous cell vaccines.

Figure 2: RMV vaccines in clinical trials



Up to and including 11 November 2007, 41 trials involving recombinant microbial vectors were conducted, as identified by ClinicalTrials.gov. *Multiple = combinations of two or more RMV vaccine types; AAV = adeno-associated virus; VEEA = Venezuelan Equine Encephalitis alphavirus;* S. typhi = Salmonella typhi.

ing), in which the vaccine is tested typically in up to 3000 people, involving individuals at higher risk. A further seven trials did not specify the phase.

Figure 4 summarises the status of the registered trials as of summer 2007. A total of 106 trials (54%) had reached an end, of which 95 trials (48% of the total) had been completed, with a further ten terminated and one suspended. Fifty-eight trials (29%) were 'no longer recruiting'; 33 were either actively, or about to begin, recruiting (24 trials and nine trials, respectively).

Detailed Analysis and Human *Versus* Chimpanzee Comparison

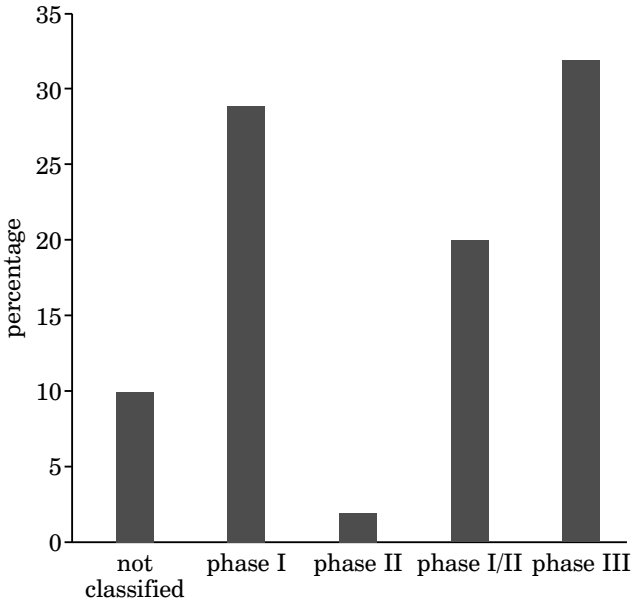
Vaccines and clinical trials were analysed in detail to assess whether those that failed in humans provided protection from HIV infection and/or therapeutic benefits in chimpanzees. A comprehensive analysis was performed of the recent history and current situation surrounding vaccine development in chimpanzees (see Table 2 for trial information) and humans (Table 1), and to compare results and information from each species. Full use was made of the Nonhuman Primate HIV/SIV Vaccine Trials (NHPVT) Database (http://www.hiv.lanl.gov/content/vaccine/home.html). In these Tables, the interventions are shown in plain text, underlined, or bold text, to indicate which specific vaccines were tested in both species (see Table legends).

Passive approaches

Many of the early experiments in HIV vaccine research centred on passively transferring HIV and SIV-specific antibodies from infected to non-infected animals, to see if this protected the recipients from infection following a subsequent viral challenge (for reviews, see 15–19). Five such trials in chimpanzees are registered in the NHPVT database, and are summarised in Table 2.

The search of the *ClinicalTrials.gov* database did not locate any human trials of passive antibodies to protect against or to treat HIV infection, but many reports of pre-clinical and clinical investigations of passive therapies for HIV/AIDS do exist. The NHPVT database contains five entries for trials of this type, and all but the earliest (NHP .361; registered in 1988) either prevented or controlled HIV infection in chimpanzees (Table 2). Murthy *et al*. (17) referred to passive immunisation studies in chimpanzees involving a total of five different antibodies. Four of them were protective; the one that was not protective did, however, delay the onset of infection (20). HIV human hyperimmune immunoglobulin (HIVIG) had been shown to protect chimpanzees from HIV challenge when administered both pre- and post-exposure (21), an observation that prompted the authors to conclude that induction of humoral immunity was a pre-requisite for any HIV vaccine, but that cell-mediated immunity may not be needed — a conclusion that is

Figure 3: Phases of AIDS vaccine clinical trials



Percentage of vaccine candidates in different phases of clinical trials, as of 11 November 2007. Not classified = phase not specified. N = 197.

unfounded in humans. Stiehm *et al*. (22), in contrast, assessed the effects of HIVIG in 30 HIV+ children, where CD4 cell levels, plasma RNA copy number, cellular virus load, immunoglobulin levels, and neutralising antibody titres were only minimally affected and clinical status was not changed.

A soluble CD4 analogue called 'CD4-IgG' (also known as CD4 immunoadhesin, in which CD4 is combined with an immunoglobulin for stability) was also protective in chimpanzee experiments (23). Trials in humans, however, suggested no evidence of clinical benefit: for example, a Phase I trial revealed that CD4-IgG did not augment the effects of the HIV inhibitor drug, azidothymidine (AZT; 24), and a Phase I/II investigation revealed a slight improvement of T-helper cell function, but no clinical benefit (25). Arguably, these difficulties may be expected, because HIV+ individuals have high levels of soluble CD4 in their blood, even in quite advanced AIDS, suggesting it has little or no effect on progression of the disease.

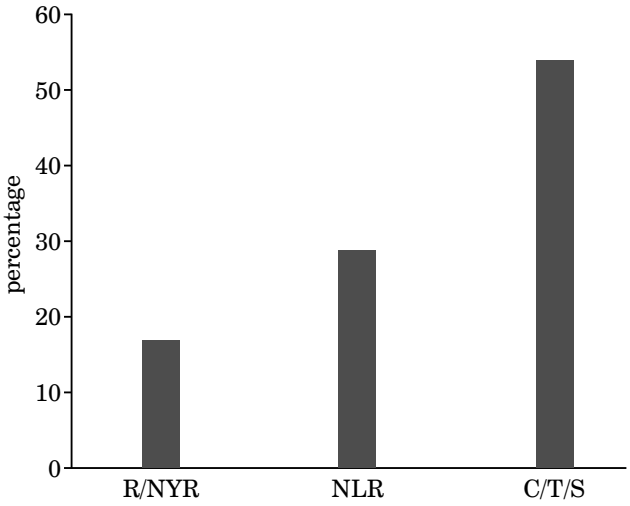
More recently, Armbruster *et al*. (26, 27) described Phase I clinical trials of three human monoclonal antibodies (hMAbs), in which they were safe and well tolerated. One of these antibodies had been shown to delay seroconversion in chimpanzees some time previously (16), and a paper reported a proof-of-principle human study (though the evidence is considered to be 'circumstantial'; 28), showing that a cocktail of the same hMAbs could delay viral rebound in HIV-infected patients whose antiretroviral therapy has been interrupted. There were major caveats, however: the trial was neither randomised nor blinded; only two of eight chronically infected patients showed rebound delay; the antibodies used had to be highly potent and used at a high dose; and, there was evidence of rapid escape.

Nevertheless, in spite of these caveats, it is claimed that the findings from these experiments, in which the transferred antibodies protected chimpanzees against HIV-1 infection when administered immediately prior to or after viral challenge, directed the initial push toward an HIV vaccine involving recombinant HIV envelope proteins to induce the production of HIV neutralising antibodies (29, 30). The status of this approach to vaccine development is considered in detail below (see 'Recombinant Proteins').

Attenuated/inactivated virus vaccines

Live attenuated virus vaccines have historically been used with great success against many diseases (including measles, mumps and rubella), due to their induction of strong and broadly reactive humoral and cell-mediated immune responses (31). Despite this, putative AIDS vaccines of this class have been limited to NHP studies and have not entered clinical trials (32, 33). This is due to concerns over reversion to virulence, recombination with other virions to form new, potentially highly-

Figure 4: Status of AIDS vaccine clinical trials



Summary of the status of registered clinical trials of AIDS vaccines, as of 11 November 2007. R/NYR = trials recruiting or not yet recruiting; NLR = trials no longer recruiting; C/T/S = completed, terminated or suspended trials. N = 197.

pathogenic strains, and the dangerous consequences of integration of the attenuated virus genetic material into the host genome (summarised by Van der Ryst; 29). Although these concerns are largely based on the results of macaque experiments, there are convincing human data: immunosuppression has occurred in humans exposed to attenuated HIV via blood transfusions; and residual infectivity caused over 200,000 people to be infected by live polio virus during vaccination in the infamous Cutter incident (30).

Inactivated AIDS vaccines, however, have been tested clinically. Ten trials are registered, including two in 2005 for the Remune vaccine (formerly known as HIV-1 Immunogen), which comprises whole HIV particles that have been chemically and radioactively inactivated, with their envelopes removed to preclude the infection of T-cells. The rationale is to use this vaccine as a therapeutic intervention, probably in tandem with anti-retroviral drugs, in people already infected with HIV, in order to control the activity of the virus by stimulating cell-mediated immunity and thus reduce the rate of progression of AIDS.

However, Remune has failed to produce promising results in human subjects. Two of the ten trials (the most recent of which was registered in 2005) were terminated, and a large Phase III study failed to find any additional benefit from Remune, when used to augment anti-HIV drugs (10). Even more recently in July 2007, Remune's manufacturer (Immune Response Corporation) announced the discontinuation of its HIV Vaccine Development Program altogether, following a disappointing clinical trial of Remune *and* its second-generation successor vaccine, IR103 (consisting of Remune and an adjuvant known as Amplivax) (34). The results of human trials have therefore prompted negative opinions concerning this approach in a number of reviews, for example, "…inactivated viruses have not been capable of inducing adequate immunoresponse" (35).

There is evidence of enhanced immune response in chimpanzees following vaccination with a gp120-depleted inactivated HIV-1 (36), and the NHPVT database contained one record of a chimpanzee trial of this type of vaccine (Table 2). In 1993, inactivated whole HIV-1 was tested along with three different adjuvants (37), in three groups of three chimpanzees — but even the group with the 'best' immune responses became infected when challenged shortly after their sixth immunisation. It is therefore assumed that vaccines of this type may have proceeded to clinical trials based on more-positive results from experiments with other species.

Recombinant proteins

Immunogenic proteins have constituted a significant area of AIDS vaccine research, accounting for 49 (25%) of the 197 registered trials, though just seven of them have been registered since 2004. These 49 trials have tested just nine different vaccines (or 15 vaccines, if similar proteins from different strains of HIV are included). Vaccines tested have comprised the following: gp160 (expressed in Vero cells [epithelial cells from African green monkeys], in *Sf9* cells by using recombinant baculovirus, and from strains IIIB and LAI-2); gp120 (strains SF2, MN, IIIB, A244 and W61D, and also Env 2-3 [a yeast-derived gp120 combined with an adjuvant emulsion]); NefTat fusion protein; Tat protein; EnvPro (an engineered and stabilised form of gp160 with adjuvant); and p24 protein (from the *gag* gene). Other proteins, such as the viral polymerase and regulatory proteins Rev and Vpr, have also been subject to evaluation. Perhaps the best-known candidate vaccines from this class are the AIDSVAX vaccines (AIDSVAX B/B and AIDSVAX B/E), each comprising two gp120 proteins from different HIV clades.

The relatively high number of trials for the number of recombinant protein vaccines is due to combination of the immunogenic proteins with a variety of adjuvants, as well as the testing of different routes of administration. Notably, just nine of the total of 49 trials have not been completed. Of the 40 completed trials, just four had progressed beyond Phase I. Of the nine trials that had not been completed, three were prematurely terminated. Almost all of the trials (45/49) involved recombinant envelope protein, since this protein is the primary target for neutralising antibodies in infected persons (38). Although invariably immunogenic, the antibodies induced have tended to be very clade-specific and have failed to neutralise primary isolates of HIV derived from the blood of patients. Another major problem with the use of stand-alone vaccines of this type was quickly revealed — they rarely induced the cell-mediated arm of the immune system, which has been regarded as an essential requirement for an HIV vaccine for some years (39).

Seven chimpanzee trials of recombinant proteins were listed in the NHPVT database, in which eight vaccines were tested (Table 2). All eight tests showed the vaccines to be immunogenic (though one test gave mixed results). Three of the eight tests did not result in protection (involving two gp120 and one gp160 vaccine), whereas three tests did result in protection (all of which involved gp120 vaccines). One of the tests (with a gp120 vaccine) gave mixed results (where one animal was protected, but another was not protected completely), and another test did not assess protection from infection.

Notable vaccines reported in the scientific literature include recombinant gp120 vaccines that protected chimpanzees from subsequent challenge (40–42), but that failed to show protection in

Table 1: Clinical trials of AIDS vaccines listed in the *ClinicalTrials.gov* database

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
Attenuated/inactivated virus						
1999	NCT00000943	A study to test if giving Remune (an HIV vaccine) can improve the immune systems of HIV-positive patients who are also participating in ACTG 328	HIV-1 immunogen	—	C	T
1999	NCT00001445	Phase I study to evaluate the safety and immunogenicity of HIV-1 immunogen in children with HIV-1 infection	HIV-1 immunogen (gp120-depleted inactivated HIV-1 preparation in Incomplete Freund's Adjuvant (IFA)	I	C	T
1999	NCT00002172	An expanded access, open-label, compassionate use protocol of Remune in HIV-1-infected adults with CD4 count less than 300 cells/ml	HIV-1 immunogen (Remune)	—	C	T
1999	NCT00002173	An expanded access, open-label protocol of Remune (HIV-1 immunogen) in HIV-1-infected adults with CD4 count 550 cells/ml and greater	HIV-1 immunogen (Remune)	—	C	T
1999	NCT00002359	A multicentre, double-blind, phase III, adjuvant-controlled study of the effect of 10 units of HIV-1 immunogen (Remune) compared to IFA alone every 12 weeks on AIDS-free survival in subjects with HIV infection and CD4 T-lymphocytes between 300 and 549 cells/μl regardless of concomitant HIV therapies	HIV-1 immunogen (Remune)	III	C	T
2000	NCT00005001	A pilot, phase II, double-blind study to assess the virologic effect of Remune *versus* IFA in patients who are infected with Human Immunodeficiency Virus Type 1 (HIV-1), have a plasma HIV-1 RNA level less than 50 copies/ml, are receiving Highly Active Antiretroviral Therapy (HAART), and who subsequently discontinue their HAART regimen	HIV-1 immunogen (Remune)	II	C	T
2000	NCT00005002	A randomised, double-blind, adjuvant-controlled, multicentre study to compare the virologic and immunologic effect of HAART plus Remune *versus* HAART plus (IFA) in antiretroviral-naïve patients infected with Human Immunodeficiency Virus Type 1 (HIV-1)	Remune	III	NLR	T
2000	NCT00006153	Effectiveness of adding Remune to the current anti-HIV drug combination	HIV-1 immunogen (Remune)	I	T	T
2005	NCT00021762	Effects of immunisation with HIV-1 immunogen plus anti-HIV treatment interruption on the levels of HIV	HIV-1 immunogen (Remune)	II	T	T
2005	NCT00238459	Immunopathogenesis of acute and early HIV infection and the role of HIV-specific CD4 T-cell responses and the effect of their enhancement by potent antiretroviral drugs and an HIV vaccine	HIV-1 immunogen	—	R	T

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
Recombinant protein						
1999	NCT00000632	A phase I clinical trial to evaluate the safety and immunogenicity of 100μg of Env 2-3 in MF59	Env 2-3	I	C	P
1999	NCT00000633	A phase I multicentre clinical trial to evaluate the safety and immunogenicity of Immuno-AG recombinant HIV gp160 in asymptomatic HIV seropositive individuals	**gp160 vaccine (Immuno-AG)**	I	C	T
1999	NCT00000667	A phase I/II dose escalation study of intradermal gp160 to evaluate safety, delayed type hypersensitivity (skin test) responses and immunogenicity in asymptomatic HIV seropositive patients with more than 400 $CD4^+$ cells	gp160 vaccine (MicroGeneSys)	I	C	T
1999	NCT00000745	A phase I multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of HIV-1 recombinant envelope glycoprotein gp160	gp160 vaccine (MicroGeneSys)	I	C	P
1999	NCT00000749	A phase I clinical trial to evaluate the safety and immunogenicity of 200μg of gp120 (CHO) BIOCINE in MF59 emulsion *versus* the emulsion control: three injections at 0, 1, and 6 months	**rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00000755	A phase I/II trial of vaccine therapy of HIV-1 infected individuals with 50–500 CD4 cells/mm^3	**rgp120/HIV-1MN**	I	C	T
1999	NCT00000757	A phase I multicentre trial to evaluate the safety and immunogenicity of HIV-1 recombinant envelope glycoprotein gp160	gp160 vaccine (MicroGeneSys)	I	C	P
1999	NCT00000762	A placebo-controlled, phase I clinical trial to evaluate the safety and immunogenicity of recombinant envelope proteins of HIV-1 gp160 and gp120 in children ≥ 1 month old with asymptomatic HIV infection	**rgp120/HIV-1MN** **rgp120/HIV-1 SF-2** gp160 vaccine (MicroGeneSys)	I	C	T

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00000774	A phase I study to evaluate the safety and immunogenicity of recombinant HIV-1 envelope antigen in children born to HIV-infected mothers	**rgp120/HIV-1MN** **rgp120/HIV-1 SF-2**	I	NLR	P/T
1999	NCT00000777	Active immunisation of HIV-1 infected, pregnant women with CD4 lymphocyte counts ≥ 400/mm^3: A phase I study of safety and immunogenicity of VaxSyn recombinant gp160 (Note: some patients receive placebo)	gp160 vaccine (MicroGeneSys)	I	C	P/T
1999	NCT00000779	A phase I comparative blinded trial of several HIV-1 derived immunogens in infected individuals with ≥ 500 CD4 cells/mm^3	**rgp120/HIV-1IIIB** **rgp120/HIV-1MN** **rgp120/HIV-1 SF-2** Env 2-3	I	C	T
1999	NCT00000782	A phase I/II study of Delayed-Type Hypersensitivity (DTH) reactions to intradermal HIV envelope antigen	**gp160 vaccine (Immuno-AG)** gp160 vaccine (MicroGeneSys)	I	C	T
1999	NCT00000809	Safety and effectiveness of two different formulations of an HIV vaccine in infants born to HIV-infected women	MN rsgp120/HIV-1	I	T	T
1999	NCT00000822	A phase I/II double-blind controlled trial to determine the safety and immunogenicity of HIV-1 MN rgp160 Immuno-AG vaccine therapy in HIV-infected individuals with ≥ 500/mm^3 CD4$^+$ T-cells and 200–400/mm^3 CD4$^+$ T-cells	**gp160 vaccine (Immuno-AG)**	I	C	T
1999	NCT00000832	A randomised, placebo-controlled, double-blinded phase I safety and immunogenicity trial of recombinant envelope protein, HIV-1 SF-2 rgp120 (BIOCINE), combined with MF59 in HIV-1 uninfected adult volunteers	**rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00000853	A phase I, multicentre, randomised, double-blind, placebo-controlled HIV-1 vaccine trial to evaluate the safety and immunogenicity of low dose MN rsgp120/HIV-1 (Genentech) in combination with QS21 adjuvant or alum in healthy adults	**rgp120/HIV-1MN**	I	C	P
1999	NCT00000956	A phase I multicentre trial to evaluate the safety and immunogenicity of HIV-1 recombinant envelope glycoprotein gp160	gp160 vaccine (MicroGeneSys)	I	C	P
1999	NCT00000957	A phase I multicentre clinical trial to evaluate the safety and immunogenicity of vaccinia derived HIV-1 recombinant envelope glycoprotein (gp160) of Human Immunodeficiency Virus: Evaluation of accelerated schedules	**gp160 vaccine (Immuno-AG)**	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00000958	A placebo-controlled, phase I, pilot clinical trial to evaluate the safety and immunogenicity of Env 2-3, a yeast-derived recombinant envelope protein of HIV-1, in combination with MTP-PE/MF59 in individuals with HIV infection (placebo patients receive MF59 emulsion only)	Env 2-3	I	C	T
1999	NCT00000968	A phase I multicentre clinical trial to evaluate the safety and immunogenicity of vaccinia-derived HIV-1 recombinant envelope glycoprotein (gp160)	**gp160 vaccine (Immuno-AG)**	I	C	P
1999	NCT00000972	A phase I clinical trial to evaluate: Part A. The safety of MTP-PE/MF59 adjuvant emulsion Part B. The safety and immunogenicity of Env 2-3, a yeast-derived recombinant envelope protein of HIV-1, in combination with MTP-PE/MF59	Env 2-3	I	C	P
1999	NCT00000977	Active immunisation of asymptomatic, HIV-infected individuals with recombinant gp160 HIV-1 antigen: A phase I/II study of immunogenicity and toxicity	gp160 vaccine (MicroGeneSys)	I	C	T
1999	NCT00001019	Safety of and immune response to an HIV vaccine (SF-2 gp120) with or without MTP-PE/MF59 adjuvant	**rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00001020	A phase I study of the safety and immunogenicity of rgp120/HIV-1IIIB vaccine in healthy adult subjects (Note: study extended only for subjects who have previously received rgp120/HIV-1IIIB or rgp120/HIV-1MN on VEU 006 or VEU 006 rollover study)	**rgp120/HIV-1IIIB** **rgp120/HIV-1MN**	I	C	P
1999	NCT00001021	A phase I multicentre study of the safety and immunogenicity of MN rgp120/HIV-1 vaccine given either alone or in combination with IIIB rgp120/HIV-1 vaccine in healthy adult subjects (Note: original study extended only for patients previously enrolled on VEU 009)	**rgp120/HIV-1IIIB** **rgp120/HIV-1MN**	I	C	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00001031	A phase II clinical trial to evaluate the immunogenicity and reactogenicity of the recombinant HIV-1 envelope vaccines SF-2 rgp120 (CHO) [Chiron vaccines] in MF59 adjuvant and MN rgp120/HIV-1 [VaxGen] in alum adjuvant in healthy adults	**rgp120/HIV-1MN rgp120/HIV-1 SF-2**	II	C	P
1999	NCT00001037	A phase I, multicentre, clinical trial to evaluate the safety and immunogenicity of vaccinia-derived MN HIV-1 recombinant envelope glycoprotein (rgp160) of HIV at two different vaccination schedules	**gp160 vaccine (Immuno-AG)**	I	C	P
1999	NCT00001041	Active immunisation of HIV-1 infected, pregnant women with CD4 lymphocyte counts ≥ 400/mm^3: A phase I study of safety and immunogenicity of MN rgp120/HIV-1 vaccine (Note: some patients receive placebo)	**rgp120/HIV-1MN**	I	C	T
1999	NCT00001042	A phase I, randomised, double-blind, placebo-controlled, clinical trial to compare the safety and immunogenicity of recombinant envelope protein rgp120/HIV-1SF2 (BIOCINE) combined with seven adjuvants in healthy HIV-1 uninfected individuals	**rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00001043	A phase I, multicentre, randomised trial to evaluate the safety and immunogenicity of vaccinia-derived MN HIV-1 recombinant envelope glycoprotein (rgp160) of human immunodeficiency virus at two different vaccination schedules	**gp160 vaccine (Immuno-AG)**	I	C	P
1999	NCT00001044	A phase I, multicentre, randomised, double-blind, placebo-controlled HIV-1 vaccine trial to evaluate the safety and immunogenicity of rgp120/HIV-1MN (Genentech) in combination with QS21 adjuvant and/or alum in healthy adults	**rgp120/HIV-1MN**	I	C	P
1999	NCT00001046	Active immunisation of HIV-infected pregnant women: A phase I study of safety and immunogenicity of a rgp120/HIV-1 vaccine (Note: some patients receive placebo)	**rgp120/HIV-1 SF-2**	I	T	T
1999	NCT00001052	A phase I, multicentre, randomised, double-blind, placebo-controlled HIV-1 vaccine trial to evaluate the safety and immunogenicity of MN recombinant soluble gp120/HIV-1 (rsgp120/HIV-1) (Genentech) in combination with QS21 adjuvant and/or alum in healthy adults	**rgp120/HIV-1MN**	I	C	P
1999	NCT00001056	A phase I multicentre clinical trial to evaluate the safety and immunogenicity of vaccinia-derived HIV-1 recombinant envelope glycoprotein (gp160) of human immunodeficiency virus: Evaluation of a 200μg dose	**gp160 vaccine (Immuno-AG)**	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00001096	A phase I, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of HIV-1 MN rsgp120 and bivalent AIDSVAX B/E (HIV-1 MN rgp120/A244 rgp120) in combination with QS-21 with or without alum in healthy HIV-1 uninfected adults	MN rgp120/HIV-1 and A244 rgp120/HIV-1 **rgp120/HIV-1MN**	I	NLR	P
1999	NCT00001992	A phase I study of the safety and immunogenicity of rgp120/HIV-1IIIB vaccine in HIV-1 seropositive adult volunteers	**rgp120/HIV-1IIIB**	I	C	P
1999	NCT00002204	A phase I, observer-blind, placebo-controlled study of the chiron vaccine HIV p24/MF59 administered to healthy HIV-seronegative adults	HIV p24/MF59	I	C	P
1999	NCT00002402	A phase I/II trial to evaluate the safety and immunogenicity of AIDSVAX B/B and B/E vaccines in the USA	**AIDSVAX B/B and AIDSVAX B/E (MN rgp120/HIV-1 and GNE8 rgp120/HIV-1) and (MN rgp120/HIV-1 and A244 rgp120/HIV-1)**	I/II	C	P
1999	NCT00002441	A phase III trial to determine the efficacy of bivalent AIDSVAX B/B vaccine in adults at risk of sexually transmitted HIV-1 infection in North America	**AIDSVAX B/B (MN rgp120/HIV-1 and GNE8 rgp120/HIV-1)**	III	C	P
2000	NCT00006327	A phase III trial to determine the efficacy of AIDSVAX B/E vaccine in intravenous drug users in Bangkok, Thailand	**AIDSVAX B/E (MN rgp120/HIV-1 and A244 rgp120/HIV-1)**	III	C	P
2001	NCT00027365	An investigational combination vaccine given to people who are not infected with HIV	Combination vaccine (NefTat and gp120 W61D) NefTat **gp120 W61D**	I	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2002	NCT00031109	The effectiveness of human antibodies in influencing an AIDS-like disease in monkeys	**gp160 MN/LAI-2**	—	NLR	P
2004	NCT00076947	Safety of the EnvPro HIV vaccine in healthy volunteers	EnvPro	I	C	P
2005	NCT00117429	A phase I, randomised, double-blind clinical trial of the HIV gp120/NefTat/ AS02A vaccine candidate in subjects with well-controlled chronic HIV-1 infection on HAART	HIV gp120/NefTat/AS02A vaccine	I	R	T
2005 (comp. 2003)	NCT00122564	Phase I study evaluating the systemic and mucosal safety and immunogenicity of a recombinant HIV-1 gp160 (MN/LAI) administered by transmucosal (nasal or vaginal) routes, alone or formulated with DC-Chol, in HIV negative volunteers (ANRS VAC14)	**HIV-1 gp160**	I	T	P
2006	NCT00369031	A phase I, open-label, parallel group trial to evaluate safety and immunogenicity of three nasal immunisations using a fixed dose-level of HIV gp140 V2 loop deleted protein adjuvanted with LTK63 followed by intramuscular boosting with HIV gp140 V2 loop deleted protein adjuvanted with MF59 when administered to healthy adults	Human Immunodeficiency Virus glycoprotein 140 (vaccine)	I	NLR	P
2006	NCT00412477	A phase I study of safety and immunogenicity of the WRAIR HIV-1 vaccine LFn-p24 administered by the intramuscular (IM) route in healthy adults	HIV LFn-p24	I	C	P
2007	NCT00505401	A phase I safety and immunogenicity trial of recombinant HIV-1 tat in HIV-1 infected adult volunteers	Recombinant HIV-1 Tat protein	I	C	T
2007 (comp. 2004)	NCT00529698	A phase I safety and immunogenicity trial of recombinant HIV-1 tat protein in HIV-1 uninfected adult volunteers	Biologically active recombinant Tat protein (ISSP-001)	I	C	P
Peptide/Lipopeptide						
1999	NCT00000775	A phase I safety and immunogenicity trial of UBI SynVac (HIV-1 MN octameric V3 peptide vaccine)	**rgp120/HIV-1MN** Monovalent octameric V3 peptide vaccine	I	C	P
1999	NCT00000795	A phase I safety and immunogenicity trial of UBI multivalent HIV-1 peptide immunogen in HIV-1 seronegative human subjects	HIV-1 peptide immunogen, multivalent	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00000798	A phase I safety and immunogenicity trial of UBI microparticulate monovalent HIV-1 MN peptide immunogen in HIV-1 seronegative human subjects	HIV-1 peptide vaccine, microparticulate monovalent	I	C	P
1999	NCT00000845	A phase I safety and immunogenicity trial of UBI HIV lipopeptide vaccine component P3C541b in HIV-1 seronegative human subjects	P3C541b lipopeptide	I	C	P
1999	NCT00000846	A phase I trial to evaluate the safety and immunogenicity of the UBI HIV-1MN PND peptide immunogen, given by IM injection, in combination with the UBI microparticulate monovalent HIV-1 MN branched peptide given orally, in HIV-1 uninfected volunteers	HIV-1 peptide vaccine, microparticulate monovalent HIV-1 peptide immunogen, multivalent	I	C	P
1999	NCT00000886	A phase I safety and immunogenicity trial of HIV-1 gp120 C4-V3 hybrid polyvalent peptide immunogen mixed in mineral oil containing mannose mono-oleate (IFA)	HIV-1 C4-V3 polyvalent peptide vaccine	I	C	P
1999	NCT00001060	A phase I trial of HIV-1 C4-V3 polyvalent peptide vaccine in HIV-1 infected persons	HIV-1 C4-V3 polyvalent peptide vaccine	I	C	T
1999	NCT00001386	Phase I protocol for the evaluation of the safety and immunogenicity of vaccination with synthetic HIV envelope peptides in patients with early human immunodeficiency virus infection	PCLUS 3-18 MN PCLUS 6.1 MN	I	C	T
1999	NCT00002353	A phase I safety and immunogenicity trial of UBI HIV lipopeptide immunotherapeutic P3C541b in HIV-1 seropositive human subjects	P3C541b lipopeptide	I	C	T
2000	NCT00005779	Safety of the candidate vaccine C4-V3 alone or with interleukin-12 (IL-12) in HIV-infected patients receiving effective anti-HIV drug therapy	HIV-1 C4-V3 polyvalent peptide vaccine	I	C	T
2004	NCT00076037	Safety of and immune response to a new HIV CTL MEP	HIV CTL MEP	I	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00121758	Randomised double-blinded phase II AIDS vaccine study comparing immunogenicity and safety of 3 doses of lipopeptide (LIPO-5) *versus* placebo in non-infected HIV volunteers (ANRS VAC 18)	LIPO-5	II	NLR	P
2005	NCT00195234	A phase I multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of an HIV CTL multi-epitope peptide vaccine formulated with RC529-SE and GM-CSF given to HIV-1 positive adults on stable HAART	HIV CTL MEP	I	C	T
2006	NCT00381875	A pilot study to investigate the safety and immunogenicity of a peptide vaccine for HIV infected HLA-A2 individuals designed to impede the development of antiretroviral resistance	E1M184V peptide vaccine	I	R	T
Virus-like particles						
1999	NCT00000835	A multicentre, randomised, placebo-controlled, double-blind trial to evaluate the safety and immunogenicity of an HIV-1 pseudovirion vaccine	HIV-1 pseudovirion vaccine	I	T	P
1999	NCT00001053	A phase I safety and immunogenicity study of HIV p17/p24:Ty-VLP in HIV-1 seronegative subjects	HIV p17/p24:Ty-VLP	I	C	P
DNA vaccines						
1999	NCT00001088	A phase I safety and immunogenicity trial of the facilitated HIV-1 Gag-Pol DNA vaccine (APL-400-047, Apollon, Inc.) given intramuscularly by needle and syringe or Biojector 2000 needle-free jet injection system in HIV-1 uninfected adult volunteers	APL 400-047	I	NLR	P
1999	NCT00001538	A phase I study of APL 400-003, a candidate HIV vaccine, in HIV-negative volunteers	APL 400-003	I	C	P
1999	NCT00002231	GENEVAX-HIV (APL 400-003), a candidate DNA vaccine: A pilot dose escalation study of GENEVAX-HIV delivered intramuscularly using the Biojector 2000 in HIV seronegative volunteers	GENEVAX-HIV (APL 400-003)	I	C	P
1999	NCT00002232	GENEVAX-HIV (APL 400-003), a candidate DNA vaccine: A pilot study of GENEVAX-HIV given by intramuscular or intradermal administration in HIV seronegative volunteers	GENEVAX-HIV (APL 400-003)	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00002350	A phase I trial of APL 400-003 vaccine: Safety and immune response evaluations of multiple injections at escalating doses in asymptomatic HIV infected patients	APL 400-003	I	C	P
2001	NCT00009685	HIV-1 vaccine test in uninfected adult volunteers	VRC4302	I	C	P
2002	NCT00043511	Safety of an HIV DNA vaccine given to HIV uninfected adults	pGA2/JS2	I	C	P
2002	NCT00045838	HIV-1 vaccine test in uninfected adult volunteers	VRC-HIVDNA006-00-VP	I	C	P
2002	NCT00047931	A phase I clinical trial to evaluate the safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, VRC-HIVDNA009-00-VP, in uninfected adult volunteers	VRC-HIVDNA009-00-VP	I	NLR	P
2003	NCT00052182	Safety of and immune system response to an HIV vaccine (EP HIV-1090) in HIV infected patients	EP HIV-1090	I	C	T
2003	NCT00054860	Safety of and immune system response to an HIV vaccine (EP HIV-1090) in HIV uninfected adults	EP HIV-1090	I	C	P
2003	NCT00069030	A phase I clinical trial to evaluate the safety and immunogenicity of the HIV-1 DNA vaccine VRC-HIVDNA009-00-VP (Gag-Pol-Nef-multiclade Env) with the plasmid cytokine adjuvant VRC-ADJDNA004-IL2-VP (IL-2/Ig)	VRC-HIVDNA009-00-VP (Gag-Pol-Nef-multiclade Env)	I	NLR	P
2003	NCT00071851	Safety of and immune response to an HIV-1 DNA vaccine (VRC HIVDNA009-00-VP) in HIV uninfected adults	VRC-HIVDNA009-00-VP	I/II	C	P
2004	NCT00089531	Candidate HIV vaccine	VRC-HIVDNA016-00-VP	I	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00111605	A phase I clinical trial to evaluate the safety and immunogenicity of an HIV-1 *gag* DNA vaccine with or without IL-12 DNA adjuvant, boosted with homologous plasmids in healthy, HIV-1 uninfected adult participants	HIV-1 *gag* DNA	I	NLR	P
2005	NCT00115960	A phase I clinical trial to evaluate the safety and immunogenicity of HIV-1 *gag* DNA vaccine alone or with IL-15 DNA, boosted with HIV-1 *gag* DNA + IL-15 DNA or HIV-1 *gag* DNA + IL-12 DNA, in healthy, HIV-1 uninfected adult participants	HIV-1 *gag* DNA	I	R	P
2005	NCT00125099	Safety of and immune response to a DNA HIV vaccine (VRC-HIVDNA009-00-VP) in HIV infected individuals with acute HIV infection	VRC-HIVDNA009-00-VP	I/II	NLR	T
2005	NCT00141024	Safety of and immune response to the experimental preventive HIV vaccine, EP HIV-1090, in healthy, HIV-1 uninfected adults	EP HIV-1090	I	NLR	P
2005	NCT00187148	Evaluation of the tolerability and safety of a recombinant HIV-1 multi-envelope DNA plasmid vaccine (EnvDNA) in healthy adults	EnvDNA	I	NLR	P
2005	NCT00195312	A phase I multicentre, randomised, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of an HIV-1 *gag* DNA vaccine administered alone or with escalating doses of IL-12 DNA or IL-15 DNA molecular adjuvants to HIV-1 positive adults receiving stable HAART	HIV-1 *gag* DNA	I	T	T
2005 (comp. 2003)	NCT00249106	A randomised, placebo-controlled, dose-escalating, double-blinded phase I study to evaluate the safety and immunogenicity of a clade C DNA vaccine ADVAX e/g + ADVAX p/n-t (ADVAX) administered intramuscularly to HIV uninfected, healthy volunteers	ADVAX e/g ADVAX p/n-t (ADVAX)	I	NLR	P
2005	NCT00270205	A phase I/II, randomised, double-blind study to evaluate the safety, tolerability, and immunogenicity of LC002, a DermaVir vaccine, in HIV-1 infected subjects currently under treatment with HAART	LC002	I/II	R	T
2007	NCT00528489	A phase I clinical trial to evaluate the safety and immunogenicity of PENNVAX-B (Gag, Pol, Env) given alone, with IL-12 DNA, or with a dose escalation of IL-15 DNA, in healthy, HIV-1 uninfected adult participants	PennVax B(Gag, Pol, Env)	I	NYR	P
2007	NCT00532974	A phase I safety and immunogenicity study of the Pharmexa-Epimmune HIV-1 CTL epitope-based DNA vaccine (EP HIV-1090) administered using a Biojector 2000 needle-free immunisation device in HIV-1 infected individuals receiving potent Combination Antiretroviral Therapy	EP1090	I	R	T

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2007	NCT00545987	Evaluation of local and systemic reactogenicity following serial administration of ADVAX, a clade C DNA vaccine, ADVAX e/g + ADVAX p/n-t, by Ichor TriGrid™ *in vivo* electroporation to HIV uninfected, healthy volunteers	ADVAX-EP	I	R	P
Recombinant microbial vaccines *Adenovirus*						
2004	NCT00080106	Effectiveness of and immune response to HIV vaccination followed by treatment interruption in HIV infected patients	MRK Ad5 HIV-1 gag	II	NLR	T
2004	NCT00083330	A phase I clinical trial to evaluate the safety and immunogenicity of a recombinant multiclade HIV-1 adenoviral vector vaccine, VRC-HIVADV014-00-VP, in uninfected adult volunteers	VRC-HIVADV014-00-VP	I	NLR	P
2004	NCT00091416	Safety of and immune response to an HIV-1 vaccine boost (VRC-HIVADV014-00-VP) in HIV uninfected adults who participated in HVTN 052	VRC-HIVADV014-00-VP	I	NLR	P
2004	NCT00095576	Investigation of V520 in an HIV vaccine proof-of-concept study	V520	II	T	P
2005	NCT00102089	A phase I clinical trial to evaluate the safety and immunogenicity of a booster dose of a recombinant multiclade HIV-1 adenoviral vector vaccine, VRC-HIVADV014-00-VP, in uninfected subjects who were previously immunised with VRC-HIVDNA009-00-VP in VRC 004	VRC-HIVADV014-00-VP VRC-HIVADV014-00-VP booster	I	C	P
2005	NCT00108654	A phase I clinical trial to evaluate the safety and immunogenicity of a booster dose of a recombinant multiclade HIV-1 adenoviral vector vaccine, VRC-HIVADV014-00-VP, in uninfected subjects who were previously immunised with VRC-HIVDNA016-00-VP in VRC 00	VRC-HIVADV014-00-VP	I	NLR	P
2005	NCT00119873	Safety of and immune response to an experimental HIV vaccine (VRC-HIVADV014-00-VP) in HIV uninfected adults	VRC-HIVADV014-00-VP	I	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00183261	A randomised phase II study of therapeutic immunisation and treatment interruption among subjects who began potent antiretroviral therapy within 30 days of diagnosis of acute or recent HIV infection	MRKAd5 HIV-1 gag/pol/nef	II	NLR	T
2006	NCT00350623	Investigation of V520 in a HIV vaccine dose refinement study	V520	II	T	P
2006	NCT00413725	A multicentre double-blind randomised placebo-controlled phase IIB test-of-concept study to evaluate the safety and efficacy of a three-dose regimen of the clade B-based Merck adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in HIV-1 uninfected adults in South Africa	MRKAd5 HIV-1 gag/pol/nef	II	S	P
2007	NCT00479999	VRC 012: A phase I clinical trial of the safety and immunogenicity of an HIV-1 adenoviral vector serotype 35 dose escalation as a single agent and prime–boost schedules with an HIV-1 adenoviral vector serotype 5 vaccine in uninfected adults	VRC-HIVADV027-00-VP VRC-HIVADV038-00-VP	I	R	P
2007	NCT00486408	A phase IB open-label clinical trial to expand the characterisation of the immune responses to the Merck adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in healthy, HIV-1 uninfected adult participants	MRKAd5 HIV-1 gag/pol/nef	I	S	P
Recombinant microbial vaccines *Adeno-associated virus*						
2007 (comp. 2003)	NCT00482027	A phase I randomised, placebo-controlled, double-blind dose-escalation trial to evaluate the safety and immunogenicity of tgAAC09, a gag-PR-RT AAV HIV vaccine	tgAAC09	I	C	P
Recombinant microbial vaccines *Vaccinia*						
1999	NCT00000767	A multicentre, randomised, placebo-controlled, double-blind trial to evaluate the safety and immunogenicity of a recombinant vaccinia-HIV-1 IIIB env/gag/pol vaccine (TBC-3B)	TBC-3B vaccine	I	C	P
2003	NCT00051922	Development of a new HIV vaccine	PolyEnv1	I	NLR	P
2005	NCT00187044	Evaluation of the safety of a polyvalent vaccinia virus-HIV-1 envelope recombinant vaccine (PolyEnv1) in healthy adults	PolyEnv1	I	NLR	P
2005	NCT00189930	A single-blind, randomised, controlled, phase II study to evaluate immunogenicity and safety of two doses of the MVA-nef HIV vaccine in HIV-1 infected patients with CD4 > 250/μl	MVA-nef MVA-BN	II	NLR	T

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00252148	A randomised, placebo-controlled, dose-escalating, double-blinded phase I study to evaluate the safety and immunogenicity of a Modified Vaccinia Ankara (MVA) expressing HIV-1 clade C *env/gag-pol* and *nef-tat* fusion genes (ADMVA) vaccine administered intramuscularly to HIV uninfected, healthy volunteers	ADMVA	I	R	P
2006	NCT00376090	A phase I double-blind, randomised, dose-escalating, placebo-controlled study of safety and immunogenicity of WRAIR/NIH live recombinant MVA-CMDR (HIV-1 CM235 env/ CM240 gag/pol) administered by IM or intradermal route in HIV uninfected adults	MVA-CMDR	I	R	P
2006	NCT00386633	A phase I, open, sequential vaccination study on safety and tolerability of two different doses of a recombinant MVA HIV polytope vaccine (MVA-mBN32) in HIV-negative 18–50 year old healthy volunteers	MVA-mBN32	I	NLR	P
2006	NCT00390078	Single-blind, randomised, controlled, phase I/II vaccination study on safety and immunogenicity of a recombinant MVA-HIV polytope vaccine (MVA-mBN32) in HIV-1 infected patients with CD4 counts > 250/μl	MVA-mBN32 MVA-BN	I/II	R	T
Recombinant microbial vaccines *Canarypox*						
1999	NCT00000904	Safety and effectiveness of anti-HIV vaccines in HIV-negative adults	ALVAC(2)120(B,MN)GNP (vCP1452) **gp160 MN/LAI-2** ALVAC(1)120(B,MN)GNP (vCP1433) ALVAC-HIV MN120TMG (vCP205)	I	C	P
2000	NCT00001136	A study of the effectiveness of an HIV vaccine (ALVAC vCP205) to boost immune functions in HIV-negative volunteers who have already received an HIV vaccine	ALVAC-HIV MN120TMG (vCP205)	I	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2000	NCT00006291	Safety and effectiveness of adding either an HIV vaccine, interleukin-2, or both to a patient's anti-HIV drug combination	ALVAC(2)120(B,MN)GNP (vCP1452)	II	C	T
2000	NCT00007423	Safety and effectiveness of the vaccine ALVAC-HIV vCP205 in HIV-negative adult volunteers in Uganda	ALVAC-HIV MN120TMG (vCP205)	I	C	P
2001	NCT00011011	Vaccine (ALVAC-HIV vCP1452) use and intermittent withdrawal of anti-HIV drugs in patients with HIV	ALVAC(2)120(B,MN)GNP (vCP1452)	I/II	C	T
2001	NCT00013572	HIV candidate vaccine, ALVAC-HIV-1, administration in HIV-negative adults	ALVAC-HIV MN120TMG (vCP205)	I	NLR	P
2001	NCT00013663	Immune therapies and anti-HIV therapy withdrawal in controlling viral load	ALVAC(2)120(B,MN)GNP (vCP1452)	II	C	T
2001	NCT00026624	Safety/immunogenicity of immunisations of ALVAC-DC-SC *vs* ALVAC-SC	ALVAC(2)120(B,MN)GNP (vCP1452)	I	NLR	T
2001	NCT00027261	Safety and immune response study of high-dose canarypox ALVAC-HIV vaccine in healthy, HIV uninfected adults	ALVAC(2)120(B,MN)GNP (vCP1452)	I	NLR	P
2003	NCT00056797	Therapeutic HIV vaccine and interleukin-2 to increase the immune system's response to HIV	ALVAC HIV vaccine (vCP1452)	II	C	T
2004	NCT00076817	Safety and effectiveness of administering an HIV vaccine in the groin *versus* the arm	ALVAC-HIV (vCP205)	I	NLR	P
2004	NCT00098163	A phase I study to evaluate the safety and immunogenicity of ALVAC-HIV vCP1521 in infants born to HIV-1 infected women in Uganda	ALVAC-HIV vCP1521	I	NLR	P
2005	NCT00219362	A phase II, randomised, placebo-controlled study to evaluate the immunogenicity and the safety of 2 schedules of an homologous prime–boost with the ALVAC-HIV vCP1452 in chronically HIV infected patients	vCP1452	II	NLR	T
Recombinant microbial vaccines *Venezuelan Equine Encephalitis alphavirus*						
2003	NCT00063778	Safety of an HIV vaccine (AVX101) in HIV uninfected volunteers in the USA and South Africa	AVX101	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2004	NCT00097838	A phase I, dose escalation, safety, and immunogenicity trial of an alphavirus replicon HIV-1 subtype C gag vaccine (AVX101) in healthy HIV-1 uninfected adult participants	HIV-1 subtype C gag vaccine, AVX101	I	NLR	P
Recombinant microbial vaccines Salmonella typhi						
2003	NCT00062530	Development of an oral prime–boost AIDS vaccine to elicit broadly neutralising antibodies against HIV-1	SCBaL/M9 (oral recombinant *Salmonella typhi* HIV-1 gp120 vaccine)	I	NYR	P
Recombinant microbial vaccines *Multiple*						
2004	NCT00083603	Safety of and immune response to two HIV vaccine formulations (rMVA-HIV and rFPV-HIV) alone or in combination in HIV uninfected adults	rMVA-HIV (rMVA-HIV env/gag + rMVA-HIV tat/rev/nef-RT) FPV-HIV (rFPV-HIV env/gag + rFPV-HIV tat/rev/nef-RT)	I	NLR	P
2005	NCT00107549	A phase I, open-label study to evaluate the safety and tolerability of recombinant HIV-1 vaccines in HIV-1 infected young adults with control of HIV-1 replication and on stable HAART	rMVA-HIV (env/gag [TBC-M358] + tat/rev/nef-RT [TBC-M335]) rFPV-HIV (env/gag [TBC-F357] + tat/rev/nef-RT [TBC-F349])	I	S	T
2006	NCT00301184	A phase I clinical trial to evaluate the safety and immunogenicity of pGA2/JS7 DNA vaccine and recombinant Modified Vaccinia Ankara/HIV62 vaccine in healthy, HIV-1 uninfected adult participants	pGA2/JS7 DNA Modified Vaccinia Ankara/HIV62	I	R	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
Autologous cells						
2001	NCT00019266	Pilot study of autologous T-cell transplantation with vaccine driven expansion of anti-tumour effectors after cytoreductive therapy in metastatic paediatric sarcomas	Therapeutic autologous dendritic cells	II	C	T
2003	NCT00056758	HIV vaccine designed for HIV infected adults taking anti-HIV drugs	Autologous dendritic cell HIV vaccination	I	C	T
2003	NCT00058734	Therapeutic vaccination followed by treatment interruption in HIV infected patients	Dendritic cells pulsed with HIV antigens [peptides]	I	C	T
2006	NCT00402142	Phase II study of autologous myeloid dendritic cells as a 'cellular adjuvant' for a therapeutic HIV-1 vaccine in early stage HIV-1^+ patients (DCV-2)	Dendritic cell vaccine	I/II	R	T
2006	NCT00407836	Phase II study of efficacy, tolerability and safety of CD4-specific T-cell vaccine in HIV infection	T-cell vaccination	II	R	T
2007	NCT00510497	Phase I/II evaluation of therapeutic immunisation with autologous dendritic cells pulsed with autologous, inactivated HIV-1 infected, apoptotic cells	Autologous HIV-1 ApB DC vaccine	I/II	R	T
Multi-component vaccines *DNA/protein*						
2003	NCT00061243	Safety of and immune response to polyvalent HIV-1 vaccine in HIV uninfected adults	HIV-1 DNA vaccine with protein vaccine boost (multiple Env antigens in both parts)	I	NLR	P
2003	NCT00073216	Safety of and immune response to a combination HIV vaccine regimen in HIV uninfected adults	Clade B *gag* DNA/PLG and *env* DNA/PLG microparticles Clade B recombinant, oligomeric gp140/MF59 adjuvant	I	NLR	P
Multi-component vaccines *Canarypox/DNA*						
1999	NCT00001090	A multicentre, randomised, placebo-controlled, double-blinded, phase I trial to evaluate the safety and immunogenicity of live recombinant canarypox ALVAC-HIV vCP205 combined with GM-CSF in healthy, HIV-1 uninfected volunteers AMENDMENT 4/30/99: To study the safety of following 4 ALVAC immunisations with a nucleic acid gag/pol HIV-1 immunogen (APL-400-047, Wyeth-Lederle)	APL 400-047 ALVAC-HIV MN120TMG (vCP205)	I	C	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
Multi-component vaccines *Fowlpox/DNA*						
2003	NCT00051454	Evaluation of the safety of and immune response to an HIV vaccine in healthy adults	HIV DNA plasmid vaccine plus recombinant fowlpox vector	I/II	C	P
2006	NCT00333424	A randomised, placebo-controlled, double-blind, phase I clinical trial to evaluate the safety and immunogenicity of a candidate prophylactic pHIS-HIV-AE DNA prime and rFPV-HIV-AE boost HIV vaccination strategy	*Prime*: (pHIS-HIV-AE) encoding the HIV-1 AE antigens, modified Gag, Pol, Tat/Rev and Env *Boost*: non-replicating, recombinant fowlpox virus (rFPV-HIV-AE) encoding the HIV-1 AE antigens, modified Gag, Pol, Tat/Rev and Env	I	NYR	P
2007	NCT00476749	A randomised, placebo-controlled, double-blind, phase I clinical trial to evaluate the safety and immunogenicity of a candidate prophylactic pHIS-HIV-AE DNA prime and rFPV-HIV-AE boost HIV vaccination strategy	pHIS-HIV-AE DNA prime rFPV-HIV-AE booster vaccine	I	R	P
Multi-component vaccines *Adenovirus/DNA*						
2005	NCT00109629	VRC 008: A phase I clinical trial of a prime–boost HIV-1 vaccination schedule: Multiclade DNA vaccine, VRC-HIVDNA016-00-VP, followed by multiclade adenoviral vector vaccine, VRC-HIVADV014-00-VP, in uninfected adult volunteers	VRC-HIVDNA016-00-VP VRC-HIVADV014-00	I	NLR	P
2005	NCT00123968	A phase I/II clinical trial to evaluate the safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, VRC-HIVDNA016-00-VP, boosted by a multiclade HIV-1 recombinant adenovirus-5 vector vaccine, VRC-HIVADV014-00-VP, in HIV uninfected adult volunteers in East Africa	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP	I/II	R	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00124007	Safety of and immune response to an adenoviral HIV vaccine (VRC-HIVADV014-00-VP) with or without a plasmid HIV vaccine (VRC-HIVDNA016-00-VP) in HIV uninfected adults	VRC-HIVADV014-00-VP VRC-HIVDNA016-00-VP	I	NLR	P
2005	NCT00125970	A phase II clinical trial to evaluate the safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, VRC-HIVDNA016-00-VP, followed by a multiclade recombinant adenoviral vector HIV-1 vaccine boost, VRC-HIVADV014-00-VP, in HIV-1 uninfected adult participants	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP	II	NLR	P
2005	NCT00270218	A phase I clinical trial to evaluate immune response kinetics and safety of two different primes, adenoviral vector vaccine (VRC-HIVADV014-00-VP) and DNA vaccine (VRC-HIVDNA009-00-VP), each followed by adenoviral vector boost in healthy, HIV-1 uninfected adults	VRC-HIVADV014-00-VP VRC-HIVDNA009-00-VP	I	NLR	P
2005	NCT00270465	VRC101: A phase I clinical trial to evaluate the safety and immunogenicity of a prime–boost HIV-1 vaccination schedule of a 6-plasmid multiclade HIV-1 DNA vaccine, VRC-HIVDNA016-00-VP, followed by a recombinant multiclade adenoviral vector HIV vaccine	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP	I	NLR	T
2006	NCT00321061	VRC 011: A phase I clinical trial of intramuscular, subcutaneous and intradermal administration of an HIV-1 multiclade DNA vaccine, VRC-HIVDNA016-00-VP, and an HIV-1 multiclade adenoviral vector vaccine, VRC-HIVADV014-00-VP, in uninfected adult volunteers	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP ('rAd5 vaccine')	I	NLR	P
2006	NCT00384787	A phase IB clinical trial to compare the safety, tolerability, and immunogenicity of an HIV-1 adenoviral vector boost administered intramuscularly, intradermally, or subcutaneously after an HIV-1 DNA plasmid vaccine prime administered intramuscularly to healthy adenovirus type 5 seropositive HIV-1 uninfected adults	VRC-HIVDNA009-00-VP VRC-HIVADV014-00-VP	I	R	P
2006	NCT00415649	A phase II, randomised, placebo-controlled, double-blind trial to evaluate the safety and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine followed by recombinant, multiclade HIV-1 adenoviral vector vaccine in healthy adult volunteers at risk for HIV infection	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP	II	NYR	P
2007	NCT00472719	A phase IB clinical trial to evaluate the safety and immunogenicity of recombinant adenoviral serotype 35 (rAd35) and serotype 5 (rAd5) HIV-1 vaccines when given in heterologous prime–boost regimens or as a boost to a recombinant DNA vaccine in healthy, HIV-1 uninfected adult participants with pre-existing immunity to adenovirus serotype 5 infection	VRC-HIVADV027-00-VP VRC-HIVADV038-00-VP VRC-HIVDNA044-00-VP	I	R	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2007	NCT00498056	A phase IIB test-of-concept, randomised, double-blind, placebo-controlled, international clinical trial to evaluate the efficacy, safety, and immunogenicity of a multiclade HIV-1 DNA plasmid vaccine, VRC-HIVDNA016-00-VP, followed by a multiclade recombinant adenoviral vector vaccine, VRC-HIVADV014-00-VP, in HIV uninfected persons	VRC-HIVDNA016-00-VP VRC-HIVADV014-00-VP	II	NYR	P
Multi-component vaccines *Vaccinia/DNA*						
2007	NCT00428337	A phase I clinical trial to evaluate the safety and immunogenicity of DNA vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in a combined prime–boost regimen, when given to healthy, vaccinia-naïve, HIV-1 uninfected adults	EP-1233 MVA-mBN32	I	R	P
2007	NCT00490074	A phase I/II trial to compare the immunogenicity and safety of 3 DNA-C prime followed by 1 NYVAC-C boost to 2 DNA-C prime followed by 2 NYVAC-C boost	DNA-C NYVAC-C	I/II	R	P
Multi-component vaccines *Vaccinia/recombinant protein*						
1999	NCT00000630	Phase I safety and immunogenicity trial of vaccinia-HIV envelope recombinant vaccine (HIVAC-1e) in combination with soluble recombinant envelope vaccine (gp160; VaxSyn)	HIVAC-1e gp160 vaccine (MicroGeneSys)	I	C	P
1999	NCT00000631	A phase I randomised trial to evaluate the safety and immunogenicity of vaccinia-HIV envelope recombinant vaccine (HIVAC-1e) in combination with soluble recombinant envelope vaccine (VaxSyn)	HIVAC-1e gp160 vaccine (MicroGeneSys)	I	C	P
1999	NCT00000683	A phase I multicentre, randomised, double-blind trial to evaluate the safety and immunogenicity of recombinant vaccinia virus expressing the envelope glycoproteins of human immunodeficiency virus	HIVAC-1e gp160 vaccine (MicroGeneSys)	I	C	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00000746	A phase I, multicentre, randomised trial to evaluate the safety and immunogenicity of a recombinant vaccinia-HIV envelope vaccine (HIVAC-1e) in combination with a panel of subunit recombinant HIV envelope vaccines	**rgp120/HIV-1 SF-2** Env 2-3 HIVAC-1e	I	C	P
1999	NCT00000866	A multicentre, randomised, placebo-controlled, double-blind trial to evaluate the safety and immunogenicity of the Therion recombinant vaccinia-HIV-1 IIIB ENV/GAG/POL vaccine (TCB-3B) and MN rgp120/HIV-1 in alum	**MN rgp120/HIV-1** TBC-3B vaccine	—	C	P
1999	NCT00001026	A phase I, multicentre, randomised trial to evaluate the safety and immunogenicity of a recombinant vaccinia-HIV envelope vaccine (HIVAC-1e) in combination with a panel of subunit recombinant HIV envelope vaccines in vaccinia-naïve individuals	**gp160 vaccine (Immuno-AG)** **rgp120/HIV-1IIIB** **rgp120/HIV-1MN** **rgp120/HIV-1 SF-2** HIVAC-1e	I	C	P
1999	NCT00002261	A comparative phase I clinical study of HIVAC-1e and smallpox (vaccinia) vaccines in previously (vaccinia) vaccinated and unvaccinated volunteers	HIVAC-1e gp160 vaccine (MicroGeneSys)	I	C	P
Multi-component vaccines *Fowlpox/recombinant protein*						
2006	NCT00332930	An extension study to protocol VIR-NCHR-01 to assess the antiretrovirological properties of a therapeutic HIV vaccine candidate based on recombinant fowlpox virus (rFPV) (ITV extension study)	Recombinant fowlpoxvirus (rFPV) expressing HIV gag-pol antigens HIV gag-pol antigens and interferon-gamma (IFN-γ)	I/II	C	T
Multi-component vaccines *Canarypox/recombinant protein*						
1999	NCT00000813	A phase I safety and immunogenicity trial of live recombinant canarypox-gp160 MN (ALVAC vCP125, HIV-1 gp160 MN) in HIV-1 uninfected adult volunteers	ALVAC-HIV gp160MN (vCP125) **rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00000847	A phase I safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV (vCP205) and HIV-1 SF-2 rgp120 in HIV-1 uninfected adult volunteers	ALVAC-HIV MN120TMG (vCP205) **rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00000871	A phase II safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV vCP205 with or without HIV-1 SF-2 rgp120 in HIV-1 uninfected adult volunteers	**MN rgp120/HIV-1 and GNE8 rgp120/HIV-1** **MN rgp120/HIV-1 and A244 rgp120/HIV-1** ALVAC-HIV MN120TMG (vCP205) **rgp120/HIV-1 SF-2**	II	NLR	P

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00000879	A study of the effects of giving two anti-HIV vaccines to babies of HIV-positive mothers	ALVAC(2)120(B,MN)GNP (vCP1452) **MN rgp120/HIV-1 and GNE8 rgp120/HIV-1** ALVAC-HIV MN120TMG (vCP205)	I	NLR	P/T
1999	NCT00000884	A randomised phase I safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV vCP205 delivered by alternate mucosal routes in HIV-1 uninfected adult volunteers	**MN rgp120/HIV-1 and GNE8 rgp120/HIV-1** ALVAC-HIV MN120TMG (vCP205)	I	NLR	P
1999	NCT00000946	A study to test the safety of three experimental HIV vaccines	HIV p24/MF59 vaccine ALVAC-HIV MN120TMG (vCP205) **rgp120/HIV-1 SF-2**	I	NLR	P
1999	NCT00001055	A phase I safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV (vCP205) in HIV-1 uninfected adult volunteers	ALVAC-HIV MN120TMG (vCP205) **rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00001072	A phase I safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV vCP300 and HIV-1 SF-2 rgp120 in HIV-1 uninfected adult volunteers	ALVAC-HIV MN120TMGNP (vCP300) **rgp120/HIV-1 SF-2**	I	C	P
1999	NCT00001076	A phase I safety and immunogenicity trial of live recombinant canarypox ALVAC-HIV (vCP205) and HIV-1 SF-2 rgp120 in HIV-1 uninfected volunteers to evaluate accelerated vaccine schedules	ALVAC-HIV MN120TMG (vCP205) **ALVAC-RG rabies glycoprotein (vCP65)** **rgp120/HIV-1 SF-2**	I	C	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
1999	NCT00004579	A phase I, dose-ranging trial of the Pasteur Merieux Connaught (PMC) oligomeric HIV-1 gp160MN/LAI-2 vaccine alone or primed with live recombinant ALVAC-HIV (vCP205) in HIV seronegative adults	**gp160 MN/LAI-2** ALVAC-HIV MN120TMG (vCP205)	I	C	P
2000	NCT00006509	A study of the safety and effectiveness of an HIV vaccine for HIV-positive patients receiving anti-HIV drugs for at least 2 years	ALVAC(2)120(B,MN)GNP (vCP1452) **gp160 MN/LAI-2**	I	NLR	T
2000	NCT00007332	Safety and immune response study of the vaccine ALVAC vCP1452 alone or in combination with AIDSVAX B/B	ALVAC(2)120(B,MN)GNP (vCP1452) **MN rgp120/HIV-1 and GNE8 rgp120/HIV-1**	II	C	P
2001	NCT00011037	ALVAC-HIV vCP1452 alone and combined with MN rgp120	ALVAC(2)120(B,MN)GNP (vCP1452) **MN rgp120/HIV-1**	II	NLR	P
2005 (comp. 2003)	NCT00223080	A phase III trial of Aventis Pasteur live recombinant ALVAC-HIV (vCP1521) priming with VaxGen gp120 B/E (AIDSVAX B/E) boosting in HIV uninfected Thai adults	ALVAC-HIV vCP1521 **AIDSVAX gp120 B/E**	III	NLR	P
2006	NCT00337181	Extended evaluation of the virologic, immunologic, and clinical course of volunteers who become HIV-1 infected during participation in a phase III vaccine trial of ALVAC-HIV and AIDSVAX B/E	ALVAC-HIV (vCP1521) **AIDSVAX B/E: bivalent HIV gp120**	—	R	P
Multi-component vaccines Salmonella typhi/*recombinant protein*						
1999	NCT00000868	A study to evaluate the safety and effectiveness of HIV-1 LAI gp120 (an HIV vaccine) given with or without HIV-1 MN rgp120 (another HIV vaccine) to HIV-negative volunteers	*Salmonella typhi* CVD 908-HIV-1 LAI gp120 (VVG 203) **rgp120/HIV-1MN**	I	C	P
Multi-component vaccines *Canarypox/inactivated virus*						
2000	NCT00005758	Effectiveness of giving an HIV vaccine (Remune) to HIV-positive patients receiving an anti-HIV drug combination	ALVAC(2)120(B,MN)GNP (vCP1452) HIV-1 immunogen	III	C	T
2000	NCT00006495	Immune responses in HIV-positive patients receiving an anti-HIV drug combination when given the HIV vaccines Remune and vCP1452	ALVAC(2)120(B,MN)GNP (vCP1452) HIV-1 immunogen (Remune)	I	C	T

Table 1: continued

Date reg'd	Trial ID	Official title	Interventions	Phase	Status	Preventive/ therapeutic
2005	NCT00212888	A pilot study to determine the impact of therapeutic HIV vaccination followed by a scheduled interruption of antiretroviral therapy on HIV-specific immune function and virologic rebound in patients with prolonged viral suppression	Remune ALVAC	I/II	R	T
Multi-component vaccines *Canarypox/peptide or lipopeptide*						
2004	NCT00076063	A study of LIPO-5 and ALVAC-HIV (vCP1452) as possible HIV vaccines	ALVAC-HIV (vCP1452) LIPO-5	I/II	NLR	P
2005	NCT00196651	Randomised study on HIV immune and virological responses following the administration of IL-2 either alone or combined to ALVAC-HIV 1433 and HIV lipopeptides (LIPO-6T) in patients treated early with HAART during primary infection. ANRS 095 PRIMOVAC	LIPO-6T ALVAC HIV 1433 IL-2	II	T	T
Multi-component vaccines *Virus-like particles/peptide*						
1999	NCT00002428	A phase I/II safety and immunogenicity trial of UBI microparticulate monovalent (HIV-1 MN) branched peptide vaccine in HIV-1 seronegative human subjects	HIV-1 peptide vaccine, microparticulate monovalent rgp120/HIV-1MN monovalent octameric V3 peptide vaccine	I/II	C	P
Unknown						
2007	NCT00434512	A dose-ranging study to compare the safety and immunogenicity of a candidate HIV vaccine 732461, adjuvanted or not, administered according to a 0, 1, 6 months schedule to healthy adult HIV seronegative volunteers	HIV vaccine 732461	I/II	NLR	P

Data were considered, up to and including 11 November 2007. Records of AIDS vaccine clinical trials retrieved from http://www.clinicaltrials.gov. *A search was performed by using the operators 'AIDS OR HIV' in the* Disease or Condition *field and 'vaccine' in the* Experimental Treatment *field, and it included all trials that were no longer recruiting patients. This search produced 197 results, detailing clinical trials involving 85 different vaccine products (strain specificity of recombinant proteins, for example, was taken into account, meaning strain MN recombinant gp120 was considered a separate vaccine from strain SF-2 recombinant gp120). The date the trial was registered is not necessarily the date the trial commenced; where both dates are known, these are given, with the earliest being 1999 when the database was initiated, though trials may have begun prior to this date (comp. = [trial] completed). For trial status, C = Completed, T = Terminated, S = Suspended, NLR = No Longer Recruiting, NYR = Not Yet Recruiting, R = Recruiting. The final column indicates whether the vaccine was primarily preventive (P) or therapeutic (T). Interventions are shown in plain text, underlined, or bold text, to indicate which vaccines were previously tested in chimpanzees, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for prior testing in chimpanzees; Underlined text = similar but not identical to vaccine tested in chimpanzees (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in chimpanzees.*

human trials (43). The ability of recombinant gp160 protein to confer protection was also shown in chimpanzees (44, 45), as it was in other studies where a variety of vaccines were also protective to chimpanzees, such as whole inactivated virus, recombinant vaccinia-gp160, the recombinant proteins p18 *gag*, p27 *nef* and p23 *vif*, and peptide immunogens (46, 47). This protection in chimpanzees extended to challenge with HIV-infected lymphocytes, as well as with free virus (48). Recombinant gp160 protein was also protective in chimpanzees when boosted with V3 peptides (49, 50).

Also, one of the two aforementioned AIDSVAX vaccines, produced by VaxGen, was the first candidate HIV vaccine to complete a Phase III trial (43), closely followed by the other. AIDSVAX B/B (comprising gp120 envelope proteins from two clade B strains of HIV, MN and GNE8) failed to protect more than 5000 trial participants (mainly gay men) at high risk of HIV infection (51), and AIDSVAX B/E (comprising gp120 from strains MN and A244 [clade E]) failed to provide protection against HIV infection for over 2500 users of injected drugs in Thailand (52), despite repeated booster immunisations throughout the study. These failures occurred despite the fact that AIDSVAX achieved the greatest immune response of any vaccine of this type (35).

The dearth of active clinical trials of this kind of vaccine, coupled with high-profile failures, has prompted some to consider that the concept of the induction of neutralising antibodies as an HIV vaccine strategy has 'run aground' (53). Evidence suggests this was recognised by many scientists some time ago, there having been a distinct re-focusing of efforts to develop an effective vaccine toward other approaches, as well as an admission that recombinant proteins could be used only as part of a 'prime–boost' vaccine regimen.

Peptide/lipopeptide vaccines

Peptide/lipopeptide vaccines constitute 14 (7%) of the 197 registered clinical trials, and involve nine different vaccines. They contain small fragments of HIV proteins, rather than the complete molecules, which makes them simpler and cheaper. These fragments often contain the most immunogenic parts of the HIV proteins, targeting an immune response to dominant T-cell epitopes and neutralising determinants (54), and several peptides from different strains of HIV can be contained in one vaccine. More recently, they have been combined with lipid molecules to form 'lipopeptides', in order to increase their immunogenicity (55).

In common with recombinant protein vaccines, most trials of peptides/lipopeptides were registered, and therefore took place, in and around 1999. Just four trials have been registered since 2004. All but one (13/14) of the trials are Phase I trials; the exception is a Phase II trial of the LIPO-5 vaccine, which is listed as no longer recruiting participants. As may be expected due to the lack of trial progression, and in common with trials of recombinant protein vaccines, success has not been reported (2, 35, 56, 57), despite, for example, reports of potent and long-lasting B-cell and T-cell responses to lipopeptide immunisation in chimpanzees (58).

No chimpanzee trials of this type of vaccine were listed in the NHPVT database.

Virus-like particles

Virus-like particles (VLPs, also known as 'pseudovirions') can be generated by the *in vitro* or *in vivo* (such as in transfected cells) production of HIV-1 viral proteins, which can spontaneously assemble into particles. Only two registered trials were found in *ClinicalTrials.gov*, which were both Phase I trials registered in 1999. One of these ('HIV-1 Pseudovirion' vaccine) was terminated prior to completion.

Young *et al*. (31), however, report that the other vaccine (HIV p17/p24:Ty-VLP) has also been tested in a Phase II trial (59). In contrast to results obtained in mice, vaccinated individuals had low levels of both humoral and cell-mediated immunity. This vaccine also showed no significant effect on disease progression in HIV-infected volunteers in a long-term follow-up study (60). Young *et al*. (31) also cite another Phase I trial with VLPp24 vaccine, which failed to augment immunity to HIV in infected patients (61).

No chimpanzee trials of this type of vaccine were listed in the NHPVT database.

DNA vaccines

Twenty-five (13%) of the 197 registered trials involved 14 different DNA vaccines, whereby plasmids containing HIV genes are used to induce immunity to the virus when injected intramuscularly. Cells exposed to such plasmids 'ingest' the DNA, which is then transcribed and translated by the host cells to produce the cognate viral proteins. When 'proof of concept' was initially demonstrated by injecting DNA into the muscles of mice (62), it was subsequently shown that proteins produced in this manner could induce significant humoral and cellular immune responses (63–65).

The NHPVT database contained three records of DNA vaccine trials in chimpanzees (NHP .226, NHP .202 and NHP .71), all of which demonstrated immunogenicity. One trial provided protection from HIV infection to an uninfected chimpanzee, and one vaccine induced an indefinite decrease in viral load, when used as a therapeutic vaccine for infected chimpanzees. The other trial was also ther-

apeutic in nature, and also decreased viral load, though this effect was transient.

Twenty-five (13%) of the 197 registered trials examined 14 DNA vaccines. All but three of these 25 trials were Phase I trials, with the remaining three being Phase I/II trials. Just eight of the 25 trials had been completed at the time of writing, and one trial of a *gag* DNA vaccine registered in 2005 has already been terminated.

Many researchers thought that DNA vaccination would revolutionise vaccine development for many diseases, not just for HIV. The first human trial involved HIV-1 strain MN *env* gp160 and *rev* genes (66), and although marginal increases in anti-gp160 cytotoxic T-lymphocyte (CTL) activity were observed in a small number of volunteers, there was no change in $CD4^+$ T-cell count or plasma viral load. Subsequent trials have continued to fall short: for example, plasmids encoding *nef*, *tat* or *env* genes have been only slightly immunogenic (67, 68), and just three of the trials are anything other than Phase I trials (i.e. Phase I/II). This disappointment is reflected in the opinions of authors of several recent reviews on the topic: "Although immunisation with DNA plasmids that contain HIV inserts has elicited substantial cellular responses in mice and nonhuman primates, these products have been poorly immunogenic in humans." (5); "Plasmid DNA constructs have proved to be effective immunogens in mice for eliciting cellular immune responses and for priming antibody responses. It is now clear, however, that DNA vaccines are less immunogenic in nonhuman primates than they are in mice, and even less immunogenic in humans than in non-human primates." (69); and "Although DNA vaccines are immunogenic in mice and monkeys (including neonates), current vaccines are poorly immunogenic when administered alone to people." (70).

There is ample supporting evidence for such opinions. DNA vaccination has been shown in numerous studies to produce strong virus-specific immune responses, and to be protective against HIV infection in chimpanzees (71–74).

The initial failures with 'native' DNA vaccines have led to efforts to augment vaccine DNA expression by using co-expressed cytokines (notably interleukin [IL]-12 and IL-15; 5) and adjuvants (55, 75, 76; see Table 1), by improving DNA delivery techniques (77, 78), by using the DNA vaccines in a combination 'prime–boost' approach, and by using a variety of genetic techniques, such as promoter modification and codon optimisation (79, 80).

Recombinant microbial vaccines (RMVs)

RMV trials constitute 21% (or 41/197) of all registered clinical trials, and involve the use of microorganisms that have been genetically engineered to include HIV genes. Almost all of the vectors are viral, though the bacterium, *Salmonella typhi,* has also been used. The principle involves using the microorganism to carry the HIV genes into the cells of the vaccinated individual, where those genes are expressed and rendered subject to host immune responses via presentation on the host cell-surface in association with Major Histocompatibility Complex (MHC) Class I molecules.

Thirty-seven of the 41 trials have been of *individual* vaccines, and four involved more than one type of vaccine in this class. Collectively, 24 different vaccines have been tested in these trials, with 27 Phase I, 11 Phase II, two Phase I/II and one Phase III trials initiated. RMVs are a relatively new approach to the development of an HIV vaccine, reflected in the fact that just ten clinical trials have reached a conclusion, and that, excluding the canarypox class of vaccines, all but one of the trials were registered in or after 2003. It seems, however, that the primary emphasis of HIV trials has moved toward this approach (5), given the recent high profile failures of recombinant-protein vaccines in Phase III trials, for example (81–83).

Of the concluded trials, seven of the ten were completed, two were terminated, and one was suspended.

Adenovirus

Twelve trials involving five adenovirus vaccines (based on the 'common cold' virus) are registered, constituting 29% of all the trials involving RMVs. This approach has received much attention, for a number of reasons: adenoviruses induce mucosal immunity, which should help prevent HIV infection at genital/rectal sites; they infect dendritic cells, leading to the efficient presentation of viral antigens; and they elicit long-term humoral and cell-mediated immunity (84). They have also given successful results, including protection from HIV infection, in studies in several non-human species, including non-human primates, for example macaques (85) and chimpanzees (86–88). A combination approach, involving recombinant adenovirus-gp160 and gp120 proteins, was also successful in chimpanzees, protecting them from even high-dose challenges of HIV after only a few immunisations (89–91).

Clinical work in this area is fairly advanced, with half of these trials being in Phase II, though two of them have been terminated. These terminated trials involved Merck's V520 vaccine, which comprises a recombinant Ad5 adenovirus containing the HIV *gag*, *pol* and *nef* genes. Despite being widely considered by experts as "one of the most promising to be tested on people so far" (92), trials of the vaccine were terminated in September 2007, when an interim analysis prior to the planned completion in 2008 concluded that the vaccine simply wasn't working. It had failed to protect thousands of

Table 2: Chimpanzee AIDS vaccine trials listed in the nonhuman primate HIV/SIV vaccine trials database

Date	Trial ID	Title/description (reference)	Intervention(s)	Outcome: Immunogenic?	Outcome: Protective/therapeutic?	Notes
Passive (e.g. antibody-mediated)						
1988	NHP .361	Failure of human immunodeficiency virus (HIV) immune globulin to protect chimpanzees against experimental challenge with HIV (146)	**HIVIG**	—	✘	Passive antibody, intravenous
1990	NHP .241 NHP .243	Antibody-mediated *in vitro* neutralisation of human immunodeficiency virus type I abolishes infectivity for chimpanzees (20)	N/A	—	✔/✘	Challenge inocula mixed with neutralising antibody prior to infection
1991	NHP .156	Prevention of HIV-1 IIIB infection in chimpanzees by CD4 immunoadhesin (23)	**CD4 Immunoadhesin (CD4-IgG)** **CHO-SIVgp120**	—	✔	Soluble CD4 analogue, which competes for CD4 binding to the HIV gp120 envelope glycoprotein
1992	NHP .152.1 NHP .152.2	Prevention of HIV-1 infection in chimpanzees by gp120 V3 domain-specific monoclonal antibody (15)	**CB1 anti-V3**	—	✔	Hybrid mouse–human antibody to the V3 loop of HIV-1 strain IIIB
1999	NHP .84	Postexposure immuno-prophylaxis of primary isolates by an antibody to HIV receptor complex (147)	mAb B4	—	✔	Monoclonal antibody directed against HIV receptor complex
Whole inactivated virus						
1993	NHP .204	Immune response of chimpanzees after immunisation with the inactivated whole immunodeficiency virus (HIV-1), three different adjuvants and challenge (37)	Whole inactivated HIV-1 IIIB	✔	✘	
Recombinant protein						
1988	NHP .242	Human immunodeficiency virus type I challenge of chimpanzees immunised with recombinant envelope glycoprotein gp120 (148)	**rgp120**	✔	✘	Vaccine from CHO cell line
1989	NHP .247	Challenge of chimpanzees (*Pan troglodytes*) immunised with human immunodeficiency virus envelope glycoprotein gp120 (149)	**gp120**	✔	✘	Vaccine purified from HIV-infected cell-lines Strain IIIB

Table 2: continued

Date	Trial ID	Title/description (reference)	Intervention(s)	Outcome: Immunogenic?	Outcome: Protective/therapeutic?	Notes
1990	NHP .267	Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160 (40)	**gp120**	✔	✔	Vaccine produced in CHO cells
			gp160		✘	
1991	NHP .362	Immunisation of chimpanzees with the HIV-1 glycoprotein gp160 induces long-lasting T-cell memory (44)	**rgp160**	✔	—	
1995	NHP .193	Resistance of chimpanzees immunised with recombinant gp120SF2 to challenge by HIV-1SF2 (42)	**rgp120**	✔/✘	✔/✘	Strain SF2, expressed in CHO cells
1996	NHP .198	Protection of MN-rgp120-immunised chimpanzees from heterologous infection with a primary isolate of human immunodeficiency virus type 1 (41)	**HIV-1.MN rgp120**	✔	✔	
2001	NHP .21	Protection from secondary human immunodeficiency virus type 1 infection in chimpanzees suggests the importance of antigenic boosting and a possible role for cytotoxic T cells (150)	**HIV-1 W6.1D gp120**	✔	✔	Recombinant gp120 protein from strain W6.1D
DNA vaccines						
1997	NHP .226	Protection of chimpanzees from high-dose heterologous HIV-1 challenge by DNA vaccination (71)	DNA vaccine encoding env, rev and gag/pol	✔	✔	
1997	NHP .202	DNA vaccination as anti-human immunodeficiency virus immunotherapy in infected chimpanzees (151)	pCMN160 HIV-1.MN env-rev	✔	✔	DNA plasmid vaccine expressing *env* and *rev*

*Date were considered, up to and including 11 November 2007. Records of AIDS vaccine trials in chimpanzees were retrieved from the Nonhuman Primate HIV/SIV Vaccine Trials Database (*http://www.hiv.lanl.gov/content/vaccine/home.html*). This search produced results of 24 vaccine trials (accounting for duplicates). Column five indicates whether the vaccine was immunogenic in chimpanzees (indicated by a check/cross for yes/no, or a dash where not explicitly measured); column six indicates whether the vaccine was effective in preventing HIV infection or controlling it (indicated by a check/cross for yes/no, or a dash where not explicitly measured). Interventions are shown in plain, underlined, or bold text, to indicate which vaccines were subsequently tested in clinical trials, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for subsequent testing in humans; Underlined text = similar but not identical to vaccine tested in humans (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in humans.*

Table 2: continued

Date	Trial ID	Title/description (reference)	Intervention(s)	Outcome: Immunogenic?	Outcome: Protective/therapeutic?	Notes
2000	NHP .71	Therapeutic immunisation of HIV-infected chimpanzees by using HIV-1 plasmid antigens and interleukin-12 expressing plasmids (72)	pCMN160 HIV-1.MN env-rev pCGag/Pol	✔	✔/✘	DNA constructs expressing MN strain Env and Rev proteins Decrease in viral loads observed, though transient
Recombinant microbial vaccines *Vaccinia*						
1987	NHP .249	Effect of immunisation with a vaccinia-HIV recombinant on HIV infection in chimpanzees (152)	v-env5	✔	✘	Recombinant vaccinia-env virus
1989	NHP .244	Cell-mediated immune proliferative responses to HIV-1 of chimpanzees vaccinated with different vaccinia recombinant viruses (153)	VV160 VV25 VVF	✔/✘	✘	Recombinant vaccinia-gp160 virus (VV160) Recombinant vaccinia-p25 virus (VV25) Recombinant vaccinia-F/3´ orf virus (VVF)
2000	NHP .318	Multi-envelope HIV vaccine safety and immunogenicity in small animals and chimpanzees (154)	Recombinant vaccinia virus-env	✔	—	Vaccinia virus expresses multiple envelope proteins
Recombinant microbial vaccines *Canarypox*						
1997	NHP .225	Challenge of chimpanzees immunised with a recombinant canarypox-HIV-1 virus (155)	ALVAC-HIV-1 vCP250	✔	✘	Recombinant virus expresses gp120 gag and protease gene products
Multi-component vaccines						
1991	NHP .159	Immunisation of chimpanzees confers protection against challenge with human immunodeficiency virus (46)	Whole inactivated virus Purified recombinant proteins Synthetic peptides	✔	✔	

Table 2: continued

Date	Trial ID	Title/description (reference)	Intervention(s)	Outcome: Immunogenic?	Outcome: Protective/therapeutic?	Notes
1998	NHP .167	Fine specificity of anti-V3 antibodies induced in chimpanzees by HIV candidate vaccines (156)	(i) vCP125/gp160 combination (ii) gp160 plus V3 peptide boost	✔	✘	(i) Recombinant canarypox ALVAC (expressing gp160 MN), plus gp160 (MN/LAI strain) (ii) gp160 MN/LAI strain plus synthetic V3 peptide
1998	NHP .141	Vaccine protection against a heterologous, non-syncytium-inducing, primary human immunodeficiency virus (90)	*Prime*: rec. adenovirus-gp160 (MN) *Boost*: gp120 protein (SF2)	✔	✔	
2005	NHP .465	Replicating rather than non-replicating adenovirus–human immunodeficiency virus recombinant vaccines are better at eliciting potent cellular immunity and priming high-titre antibodies (91)	*Prime*: Ad5 and Ad7 adenoviruses, both replication competent and deficient *Boost*: oligomeric gp140 delta V2	✔	—	Sequential priming immunisations with different serotypes of adenovirus env-rev recombinants, and boosting with oligomeric gp140 delta V2 (strain SF162)

*Date were considered, up to and including 11 November 2007. Records of AIDS vaccine trials in chimpanzees were retrieved from the Nonhuman Primate HIV/SIV Vaccine Trials Database (*http://www.hiv.lanl.gov/content/vaccine/home.html*). This search produced results of 24 vaccine trials (accounting for duplicates). Column five indicates whether the vaccine was immunogenic in chimpanzees (indicated by a check/cross for yes/no, or a dash where not explicitly measured); column six indicates whether the vaccine was effective in preventing HIV infection or controlling it (indicated by a check/cross for yes/no, or a dash where not explicitly measured). Interventions are shown in plain, underlined, or bold text, to indicate which vaccines were subsequently tested in clinical trials, given the caveat that the frequent poor quality of vaccine information requires this to be an educated guess: Plain text = no evidence found for subsequent testing in humans; Underlined text = similar but not identical to vaccine tested in humans (e.g. same plasmid containing same HIV gene among other genes; different adjuvant; etc.); Bold text = identical vaccine tested in humans.*

volunteers from HIV infection, and also to reduce HIV levels in people already infected. Disturbingly, more HIV infections were present in those who had been given the vaccine, as compared to those given the placebo (24 *versus* 21, respectively), with those who had been in the trial longer and who had received more injections faring even worse, with 19 cases of HIV infection after vaccination *versus* just 11 after placebo treatment (93, 94).

As this was the first viral-recombinant vaccine to reach this stage of clinical trials, and the first to examine cell-mediated immunity alone in humans (53), some believe that it raises questions about whether the use of RMVs can be successful at all, particularly as vaccines based on adenovirus have appeared to be the most immunogenic in terms of the percentage of human responders and the level and duration of T-cell responses (95).

Adeno-associated virus

Just one trial was identified involving recombinant adeno-associated virus (AAV), which was registered in 2007, although it commenced in 2003. This Phase I trial has been completed, and evaluated an AAV containing clade C *gag*, *pro*, and *rt* HIV sequences.

Vaccinia

Of 40 single-intervention recombinant microbial vaccine trials, eight, involving seven vaccinia-virus based interventions, were identified, though just one trial has been completed. All but two are Phase I trials, with one trial at Phase I/II and another at Phase II.

Three trials involving recombinant vaccinia vaccines in chimpanzees were identified in the NHPVT database. Although all the vaccines were immunogenic, the two trials that took place in the 1980s did not show protection from HIV infection. The other trial took place more recently in 2000, but only assessed immunogenicity.

Modified Vaccinia Ankara virus (MVA) forms the basis of many recombinant vaccinia approaches to an HIV vaccine, because of its high degree of attenuation and consequent good safety profile. Initial results in human trials, however, have been disappointing, with cell-mediated immunity being elicited in only a small minority of individuals (96), despite promising results in macaques (5). Human trials that include MVA vaccines as part of a prime–boost strategy have also been disappointing (6).

Canarypox

Vectors based on the canarypox virus constitute the biggest proportion of trials involving RMVs — altogether around a third of the total (13/41, or 32%), five of which have progressed to Phase II; the remainder are Phase I trials. These trials involved four different vaccines, all based upon the ALVAC vector developed by Sanofi-Pasteur (based on an attenuated strain of canarypox). In principle, these vectors are highly fit-for-purpose: they replicate only in the cytoplasm of infected cells (minimising the risk of integration with the host genome and any ensuing problems); replication is restricted; and they are sufficiently safe and well tolerated in humans (97, 98). Further, they can accommodate large gene insertions (99), and they can stimulate both humoral and cell-mediated immune responses of long duration in humans (100–102).

An early Phase I/II trial ended in disappointment, however, when a gp160 vaccine (ALVAC-HIV) failed to enhance both humoral and cell-mediated immune responses (103). Looking at the register of clinical trials (Table 1), further failures with other ALVAC trials appear to have followed. Focus seems to have shifted to other approaches, signalled by the low number of trials registered in recent years (compared to 1999–2001, for example). This is true, not just for trials solely involving canarypox, but also for the many trials of AIDS vaccines involving recombinant canarypox in combination with other approaches such as the use of DNA and recombinant proteins. In addition, it has been reported that five different canarypox vaccines have been tested in around 11,500 volunteers (5). Though well tolerated, these vaccines did not induce durable immune responses, and were immunogenic in fewer than 20% of the subjects (104).

Canarypox vaccines have also been tested in children, with similarly disappointing results. For example, the vCP205 and vCP1452 vaccines were given to very young infants of HIV^+ mothers; again, they were well tolerated, but produced humoral and cell-mediated immune responses either not at all, or of a very low magnitude (105). Comparison with chimpanzee vaccinations is difficult, as just one such trial is listed in the NHPVT database, involving three animals. In this instance, the vCP250 vaccine was immunogenic, and protected one of the two experimental animals from cell-associated viral challenge. It did not, however, protect this chimpanzee against subsequent infection with cell-free HIV (Table 2).

As mentioned previously, many trials have used canarypox in combination with other vaccine candidates — though this has not resulted in an improvement in efficacy. For example, vCP1452 has been administered with an AIDSVAX B/B boost to infants, but enthusiasm for further trials was limited due to ‘modest immunogenicity’ (70).

Others

Two clinical trials involved the use of Venezuelan Equine Encephalitis alphavirus (VEE) as a vector.

Both Phase I trials, they assessed the vaccine AVX101, which contains the HIV *gag* gene as an immunogen. Another trial, registered in 2003 but not yet recruiting participants, proposes to evaluate a vaccine based on recombinant *Salmonella typhi* containing the HIV gp120 gene.

Three clinical trials, all registered relatively recently (2004–2006), involved more than one type of RMV. Two of the three trials investigated combinations of vaccinia-based (MVA) and fowlpox-based vaccine pairs, each containing the *env*/*gag* and *tat*/*rev*/*nef* HIV genes. The status of the earlier of the two trials is 'no longer recruiting,' though the details state that all vaccinations were discontinued in November 2006, and the other trial has been suspended. The third trial will assess a 'prime–boost' intervention involving an initial DNA plasmid vaccine 'prime', followed by a Modified Vaccinia Ankara (MVA) 'boost' (this approach is described in more detail later in this review).

Autologous cells

Dendritic cells are one of the first ports-of-call for the virus upon infection. They are locally infected at the entry site of the virus, before proceeding to the lymph nodes where they infect $CD4^+$ T-cells — the principal target of the virus, the attrition of which leads to AIDS. Consequently, dendritic cells are central to the induction of the immune response to HIV infection, though their response is known to decline with time (106–109).

With this in mind, six trials have been registered that involve two types of autologous-cell approach to therapeutic HIV vaccination: five with dendritic cells, and the other with T-cells. The former strategy involves harvesting a patient's own dendritic cells and loading them *in vitro* with HIV peptide antigens or inactivated autologous virus. The latter T-cell based vaccine is prepared from autologous T-cells, which have proliferated following exposure to recombinant CD4. The cells are then introduced back into the patient, in the hope that they can better activate immune responses that can control the infection. Early results in humans are considered promising, at least against the same viral strain used to produce the cell-based vaccine (110), though this must be interpreted with caution, as any efficacious vaccine must elicit immune responses against diverse strains of HIV.

No chimpanzee trials of this vaccine type were listed in the NHPVT database, though the immunogenicity in chimpanzees of dendritic cells pulsed with test antigens has been reported in the scientific literature, with somewhat equivocal results (111, 112), and a T-cell vaccine for hepatitis C has been tested in chimpanzees, which elicited immunity against heterologous hepatitis C virus (HCV; 113).

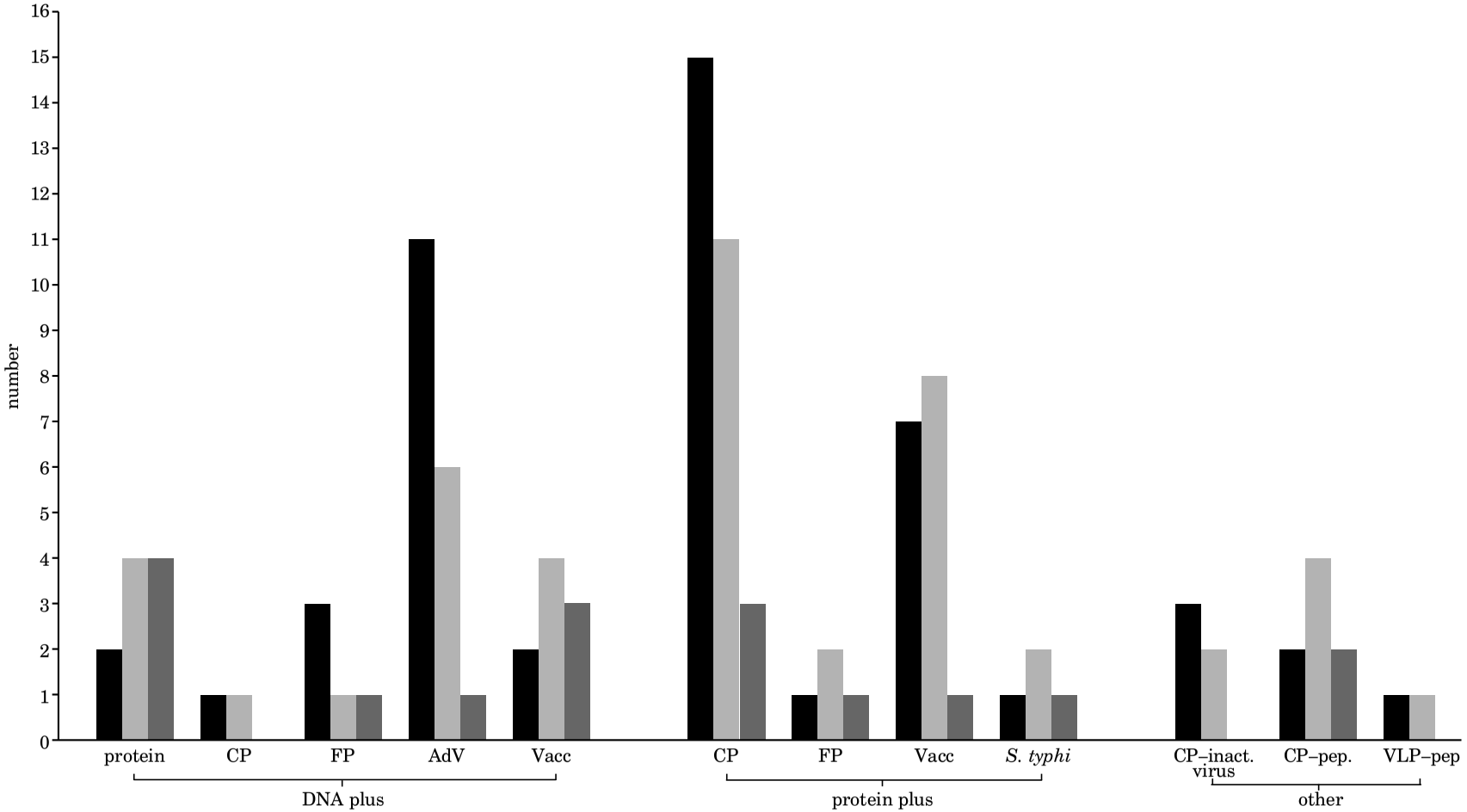
Multi-component vaccines and prime–boost strategies

Due to negative results in many trials involving single vaccines of all types, much focus has shifted toward the development of multi-component vaccines, in so-called 'prime–boost' strategies. This type of intervention aims to enhance the immune response to a particular antigen, and to induce both the humoral and cell-mediated arms of the immune response by administering it in successive, but slightly different, ways — especially when using just one route/vaccine type has not proved sufficiently immunogenic. The rationale is to 'prime' the immune system with the first antigen (for example, a DNA vaccine or recombinant adenovirus or poxvirus), and then to 'boost' the immune response to it by using, for example, another RMV or protein.

Fifty clinical trials were identified in this category (Figure 5), with the most prevalent combinations being canarypox–protein (15 trials), adenovirus–DNA (11 trials) and vaccinia–protein (7 trials). Given the relatively recent nature of this type of approach, the majority of the trials are Phase I trials (31/50), with just seven Phase II and two Phase III trials. One of the Phase II trials, involving a canarypox–lipopeptide vaccine (ALVAC HIV-1433 and LIPO-6T), was terminated, and a recent publication revealed that HIV-specific $CD4^+$ T-cell responses did not change in immunised patients relative to controls, that the vaccination had only a transient effect on interferon-gamma-producing CD8 responses, and that the viral rebound after treatment interruption was similar in immunised patients and controls (114). The Phase III trial, involving a canarypox–inactivated virus vaccine (vCP1452 and Remune), was registered in 2000 and has been completed (without success), and the other trial, involving a canarypox–protein vaccine combination (vCP1521 and AIDSVAX gp120 B/E), commenced in 2003 and is no longer recruiting.

Despite this Phase II termination and the lack of reported success surrounding the Phase II trials, much hope is held in some quarters for this strategy, largely based on pre-clinical studies in monkeys, where prime–boost vaccines are often more potent than either vaccine alone (55). The NHPVT database lists four chimpanzee trials of multi-component vaccines, one of which tested two different vaccine combinations. All five combinations were immunogenic. One of the trials (NHP .465), involving an adenovirus prime and an oligomeric gp140 boost, did not assess protection from infection, but all the other vaccines demonstrated protection, except one, which comprised a vCP125/gp160 combination (trial NHP .167). In addition to those studies registered with the NHP database, Girard *et al*. (47) reported the protection of chimpanzees from HIV infection following immunisation with "a variety of HIV-1 immunogens — followed by rgp160 and V3 peptides", including combinations of enve-

Figure 5: Vaccine combinations involved in multi-component clinical trials



Data were considered, up to and including 11 November 2007. Bars are clustered into three groups identified by the labels under the chart: the first group shows vaccines involving a plasmid DNA component; the second, vaccines involving a recombinant protein component; and the third shows vaccines not fitting into either category. Vaccines are identified as follows: CP = canarypox; FP = fowlpox; AdV = adenovirus; Vacc = vaccinia; S. typhi = Salmonella typhi*; inact. virus = inactivated whole virus; pep = peptide/lipopeptide; VLP = virus-like particle. For each vaccine combination, there are three bars: the black bar represents the number of clinical trials involving that particular combination identified in the database; the light grey bar shows the total number of different vaccines involved in those trials; and the dark grey bar reveals how many of the 'total' vaccines in those trials were 'new' vaccines that had not been tested singly in other trials. N = 49 (not including one vaccine for which the classification was not available).*

■ = *trials;* ■ = *total vaccines;* ■ = *new vaccines.*

lope antigens. This all contrasts with findings in humans, however, where "observations in early phase clinical trials in humans have not been promising", due to adverse reactions and lack of diversity in the immune response (115).

Naturally, not all the vaccines tested in chimpanzees have provided protection against HIV challenge. One of the vaccine combinations tested by Girard *et al*. (47), for example, described a combination strategy involving recombinant gp160–canarypox and recombinant gp160 protein, that failed, although the low dose of the vaccine was postulated as a factor.

Summary and Discussion

To date, 85 candidate AIDS vaccines have been tested in 197 clinical trials, comprising several main types — from inactivated virus vaccines through DNA plasmids to recombinant proteins and viruses. Just 12% of these trials have reached Phase II, only seven (3.5%) have reached Phase III, and altogether, 18 trials were prematurely terminated. None has been successful.

Early optimism has transformed into a realisation that we are decades away from even a partially effective vaccine in humans. The monumental financial and human resources allocated to vaccine development have resulted in dozens of safe and effective vaccines *only* for chimpanzees and monkeys with laboratory-induced infections. Hope that the use of NHPs will lead to the successful development of a vaccine for humans is tempered by the recent, high-profile failures of the AIDSVAX and V520 (Merck) candidates in extensive and late-stage clinical trials. Notably, the latter increased the risk of HIV infection compared to the placebo — and it is not alone in this respect: previously, gp120-based vaccines increased the risk that vaccinated people would develop an infection or progress to AIDS post-infection (116).

Furthermore, the limited critical appraisal to date of the favoured SIV/chimeric SIV–Human Immunodeficiency Virus (SIV/SHIV)-macaque model, has been unfavourable (35, 53, 56, 117–121), stimulating a desire for models of greater relevance. While some scientists associated with chimpanzee research advocate a resumption of their use, such use must be objectively and independently evaluated.

Poor performance of the chimpanzee model in the development of AIDS vaccines

This analysis expands on previous data that underlined the poor performance of chimpanzees as models in HIV/AIDS research, evidenced by a large number of negative opinions and comments toward it and by the significant withdrawal of NIH funding for it. The evidence provided, based on a comparison of human and chimpanzee responses to AIDS vaccines, gives further argument against a return to chimpanzee-use in this field.

Contrary to claims that chimpanzees play a "critical role in the testing of potential [HIV] vaccines" and that they "are still important for testing vaccines aimed at preventing HIV-1 infection or reducing the virus load in infected individuals"(14), this review shows that neither claim has any scientific foundation. Many vaccines of many types have been tested in chimpanzees prior to clinical trials, and their correlation to, and predictive nature for, the human response is demonstrably poor. Chimpanzees have been protected from HIV infection passively via the transfer of antibodies (both pre- and post-exposure), which prompted the (now highly unlikely) suggestion that cell-mediated immunity is not necessary. Passive protection has also been induced by a soluble CD4 analogue. Neither approach has been successful in humans. Attenuated vaccines have provided protection in chimpanzees, but have not been tested clinically due to safety concerns. Inactivated-virus vaccines have disappointed clinically, and while results were similarly negative in chimpanzees, these results were of little relevance and did not prevent inactivated-virus vaccines from progressing to clinical trials. Negative results with recombinant protein vaccines in chimpanzees (Table 2) also did not stop these vaccines progressing to further testing and clinical trials (122).

While RMVs have been disappointing in humans, including the Phase III AIDSVAX trials, many (excluding a couple of early efforts) provided protection from HIV infection in chimpanzees. Clinical trial success with peptide and lipopeptide vaccines has not been reported, despite prior evidence of potent and persistent cell-mediated immune responses in chimpanzees. Both preventive and therapeutic DNA vaccination have been successful in chimpanzees. Optimism for success in humans was high, but poor immunogenicity has led to recent disparaging comments. Recombinant adenovirus vaccines have elicited protection from HIV infection in chimpanzees, both alone and in combination with recombinant HIV proteins. However, the situation in humans may be grave, with possibly "the most promising [vaccine] tested on people so far", in the form of Merck's V520 vaccine, not only ending in the termination of its Phase IIb trial, but increasing the risk of HIV infection for its recipients.

Due to the diminished use of chimpanzees in pre-clinical testing for reasons discussed above, some types of vaccines have not been widely tested in chimpanzees. Immunogenicity has been demonstrated in chimpanzees with vaccinia-based vaccines, however — which is true in only a small minority of humans in clinical trials so far. Similarly, canarypox vaccines have induced pro-

tection from cell-associated (but not cell-free) virus challenge in chimpanzees, but several vectors have been immunogenic in a small proportion of clinical-trial volunteers, including children, even as part of prime–boost regimens — and then only poorly so. Some prime–boost vaccines, involving a variety of immunogens, have proven positive in chimpanzees, again in contrast to humans, in which the results have been disappointing, replete with adverse reactions and lack of diversity in the immune response.

Problems with the chimpanzee model: Reasons for its lack of relevance

Researchers continue to rely on results largely from macaques infected with SIV or SHIV (an SIV/HIV hybrid), despite important differences between SIV-infected macaques and HIV-infected humans (53, 117). Significant disparities exist in virulence, pathology, genetics, protein function, infection and host response (118). Two recent reviews stated that, "efficacy of HIV-1 based vaccines cannot be directly evaluated in the SIV model" (119) and that, "this has not proven a practical animal model for studying vaccines" (35), the latter citing significant supporting evidence (56, 121, 122). A 2007 review stated, "When it comes to testing HIV vaccines, only humans will do" (53); another cited, "the persistent view held by many that there is no predictive animal model for HIV infection in humans" (123), and another that, "No animal models faithfully reproduce... HIV-1 infection and disease in humans, and the studies of experimental vaccines in animal models... have yielded disparate results" (124).

Yet the rhesus macaque became the model of choice following the discovery in 1987 that SIV caused an AIDS-like disease in these animals (125). It replaced the chimpanzee, widely used in AIDS research for several years previously but which had "had problems from the get-go" (125) — *vis-à-vis* practicality (the significant costs of using and maintaining chimpanzees, including user's fees of $50,000+ per animal), statistical significance (few animals could be used in each experiment, giving unreliable results), and species differences (HIV infection rarely progresses to AIDS-like illness in chimpanzees) "undermining the model's reliability" (125). The latter problem of scientific unreliability is, from a human perspective, most worrying. If years of chimpanzee use in HIV/AIDS research have not led to tangible progress and improvements clinically, then they represent a waste of limited resources and have done little to alleviate human suffering, as there is still no AIDS vaccine and none is imminent. A brief summary of the known differences between human and chimpanzee HIV infection and ensuing pathology may explain why.

Chimpanzees have higher baseline levels of $CD8^+$ T-cells and a higher ratio of $CD8^+/CD4^+$ T-cells, and their percentage of beta-chemokine-positive $CD8^+$ T-cells and natural killer (NK) cells is significantly higher than in uninfected humans. Chimpanzees do not typically produce increased numbers of these cells following HIV infection, unlike humans (126). As these are the cells that attempt to control infection, and the latter are the cells infected by HIV-1 and subsequently destroyed by the virus, this is critical. Unlike in humans, it is difficult to routinely isolate HIV from the plasma and sera of infected chimpanzees (127), and chimpanzee $CD4^+$ cell numbers do not drop dramatically over the course of HIV infection, with remarkably few exceptions. Instead, detectable plasma HIV decreases and eventually becomes undetectable (117). With perhaps only one exception, HIV infection of chimpanzees does not result in a significant decline in $CD4^+$ T-cell levels, immunodeficiency and AIDS-like illness, as in humans. The exception was Jerom ('Chimpanzee C499'), who was infected with three different isolates of HIV-1 over ten years and suffered a progressive decline in $CD4^+$ T-cells and developed AIDS-like symptoms, caused by a quasispecies of HIV that had mutated to become more pathogenic (128). Notably, Jerom's blood, though it caused a similar decline in $CD4^+$ T-cells in other chimpanzees transfused with it, did not cause them to develop a similar disease (129).

These differences, difficulties, and the lack of a vaccine led many scientists to conclude that chimpanzees should have no place in the quest for an AIDS vaccine. In 1994, the *Handbook of Laboratory Animal Science* called primate models of AIDS "unsuccessful" (130). The NIH AIDS Research Program Evaluation Task Force cited the "limited utility of the chimpanzee model" and recommended "redirecting monies currently expended in the less relevant chimpanzee model" (131). The latter was put into practice: AIDS-related chimpanzee studies fell from almost 30 studies in 1998 to four in 2005. Thomas Insel M.D., former director of the Yerkes Regional Primate Center, noted that 15 years of work in chimpanzees has produced little data relevant to humans, stating "I can't tell you what it is that those [chimpanzee] studies have given us that has really made a difference in the way we approach people with this disease [HIV/AIDS]" (132); and a review article in 2000 opined "Defending the usefulness of the chimpanzee as a model for HIV research has not only become a difficult task, but also a controversial one" (133).

These realisations came too late. At least 198 chimpanzees were deliberately infected with HIV prior to 1997 (134), and around 1,300 chimpanzees are currently in US laboratories, due in large part to over-breeding for AIDS research in anticipation of their use in this area, and despite a breeding moratorium being in place for the past decade.

Ethical issues associated with chimpanzee use

Ethics must be considered alongside scientific relevance, because of the cost of chimpanzee use, and because chimpanzees are a 'special case', testified to by public and scientific opinion, and policies and laws in the US and throughout the world. The passage of the CHIMP (Chimpanzee Health Improvement, Maintenance and Protection) Act in the USA in 2000, as well as the fact that many countries ban or restrict the use of great apes, acknowledges a different moral status for chimpanzees. Both scientists and the public acknowledge that chimpanzees have advanced cognitive abilities, and social and emotional needs. They are capable of reasoned thought, abstraction, generalisation and symbolic representation; have a concept of self; exhibit a broad range of emotions; experience mental as well as physical pain; and can be taught to communicate in human languages such as American Sign Language, and demonstrate complex nonverbal communication patterns among themselves (135–142). In captivity, they show a range of behavioural abnormalities and measurable signs of distress (psychopathology; 143, 144). The widely-respected researcher and advocate for chimpanzee welfare, Jane Goodall, stated in a letter to *Science* that, "It is their humanlike behaviours that most fascinate people: their tool-using and making abilities, the close supportive bonds among family members… and their complex social interactions — the cooperation, the altruism, and the expression of emotions like joy and sadness" (145).

Conclusions

The evidence presented in this study includes:

— substantial differences between chimpanzee and human responses to HIV infection and the course of the disease;

— expert opinion;

— past failures as a vaccine model;

— progression of vaccines to clinical trials despite negative results in chimpanzees;

— increasing knowledge of chimpanzees' cognitive and emotional capacities; and

— increased ethical issues surrounding chimpanzee research.

From this evidence, it is concluded that chimpanzees have no justifiable role in AIDS vaccine research and testing. Advocating the resumption of their use defies the burden of scientific evidence of repeated failures involving their use. If chimpanzees were not reliable, predictive and fit for purpose from 1990 to 2008, what justification is there for a resumption of their use? A 2006 review of AIDS vaccine testing, when referring to chimpanzee trials of inactivated-virus and DNA vaccines, concluded "it proved difficult to examine the effect of these vaccines, due to the general lack of clinical progression to immunodeficiency in this animal model and the prohibitive cost of these experiments" (7).

Some twenty years after chimpanzees were the mainstay of AIDS vaccine testing, an efficacious vaccine for human use remains unavailable and not imminent. The use of chimpanzees has largely been abandoned for scientific and cost–benefit reasons. As millions of humans continue to become infected or die each year, the continued use of chimpanzees in AIDS research is scientifically unwise and ethically unjustifiable.

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