Preventative HIV-1 vaccines Initial HIV vaccines using recombinant envelope proteins Following the traditional vaccine paradigm, the HIV-1 preventative vaccine field first developed over 20 different recombinant envelope proteins from various strains in the late 1980s to mid-1990s, hoping to induce neutralizing antibodies to HIV.It was given as three injections (0, 1, 6.5 months) in two phase 2b trials starting in 2004 ("Step") and 2007 ("Phambili"). Later in 2007, when futility was declared for the efficacy objective of Step, both Step and Phambili discontinued enrolment and vaccination, unblinding participants and continuing safety follow up. Both trials revealed unexpected findings. The Step data, in men who have sex with men (MSM), showed that vaccine-recipients with pre-existing immunity to Ad5 and/or who were uncircumcised had an increased risk of HIV-1 acquisition which waned with time [7]. Phambili, conducted in heterosexual adults, showed no vaccine effect on HIV acquisition during blinded follow-up, but during the unblinded follow-up there was higher HIV-1 [8] phenomenon could not be attributed to circumcision status or baseline Ad5 sero-positivity [9*]. The mechanism of increased HIV-1 acquisition has not been deciphered [10]. Step had further repercussions because it was found that the vaccine produced what were felt to be reasonable levels of CD8+ T-cell responses as well as long-standing immune responses recognizing clades B and C, with no effect on HIV-1 acquisition or viral load set-point. Post-hoc analysis indicated that these CD8+ immune responses were directed at variable, not conserved, regions of the virus. Hence "immune T-cell breadth", like neutralizing antibody breadth, was still an issue that needed to be solved [11].The DNA vaccine (0, 1, 2 months) contained a mixture of six plasmids expressing clade B gag, pol, nef and env proteins from clades A, B, and C, followed by a Ad5 vector boost (month 6) expressing a clade B gag-pol fusion protein and env glycoproteins from clades A, B, and C. The non-human primate model demonstrated protection from low-dose mucosal challenge [12].Genetic sieve analysis of viral isolates from HIV-infected participants revealed that isolates from vaccine-recipients were less likely to possess a lysine at K169 of the env V2 region than placebo-recipients, and vaccine efficacy was significantly higher against HIV-1 manifesting a lysine at K169 than against HIV-1 with a different residue at position 169, suggesting vaccine immune pressure at this region [22].Post-vaccination sera tested against a linear peptide array derived from an HIV strain used in both the vector and gp120 exhibited a high binding pattern to peptides in the V1V2 region, especially the conserved amino acids on the V1V2 crown, residues 163-178.Antibodies from RV144 vaccine-recipients that bound to the K169 V2 region did not neutralize nor capture hard-to-neutralize (tier 2) subtype AE viruses but did bind to env on tier 2 AE virus-infected CD4+ T cells and mediate antibody-dependent cellular cytotoxicity (ADCC).It found 60.5% vaccine efficacy at 1 year and 31.2% vaccine efficacy at 3.5 years with a canarypox vector prime, ALVAC-HIV (vCP1521) expressing clade E env and clade B gag and pro (0, 1, 3, 6 months) followed by protein boosts with alum adjuvant, AIDSVAX(R) clades B/E gp120 (3, 6 months) [17**].The first T-cell vaccine candidate to undergo clinical efficacy trials was a replication-defective recombinant Ad5 vector with HIV-1 clade B gag/pol/nef inserts.The arising hypothesis is that one mediator of the protective anti-HIV-1 antibody effector function induced by the RV144 vaccine was a non-neutralizing and most likely Fc receptor (FcR)-mediated action that included ADCC activity.Pathogenesis studies revealed that the magnitude and breadth of the early CD8+ T-cells markedly influenced early viral control, so cytotoxic T-cell (CTL)-based vaccines were designed

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primarily to control post-infection viremia, but there were also hopes they could prevent HIV acquisition.The strategy to induce CTL responses to HIV proteins was to insert HIV genes into recombinant viral vectors and shuttle these genes into the Class I antigen-presenting pathway [6].

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