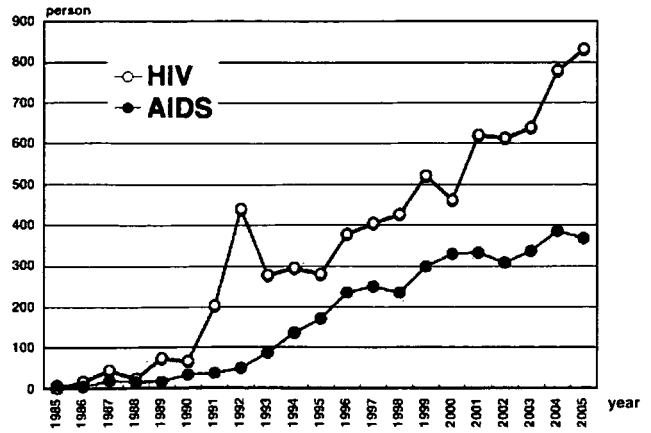

Fig. 2. Reported numbers of HIV-infected people and AIDS patients in Japan from 1985 through 2005 (adapted from [5]).

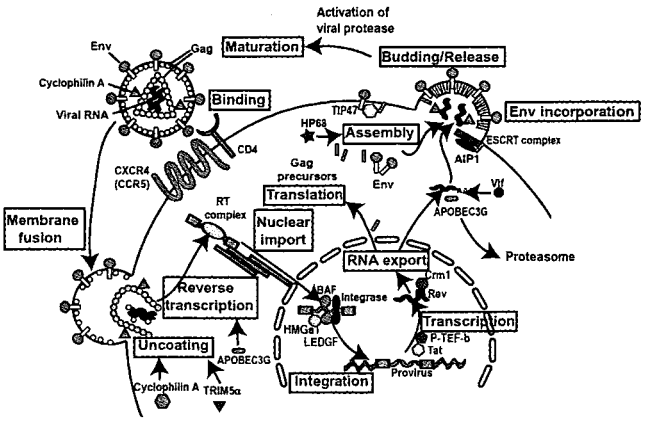

Fig. 3. The HIV replication cycle and host factors. HIV infection starts with the adsorption of virions that target cells through the interaction of CD4 and chemokine receptors (CXCR4 or CCR5) (binding). HIV enters cells by pH-independent membrane fusion between virions and target cells (membrane fusion). After partial uncoating of incoming virions (uncoating), reverse transcription of viral RNA into viral DNA occurs in the cytoplasm of infected cells (reverse transcription). Double-stranded viral DNA is transported into the nucleus (nuclear import), where integration of viral DNA into host chromosomal DNA is performed by viral integrase and several factors such as BAF, HMGa1, and LEDGF (integration). Synthesis of viral and mRNAs from the integrated viral DNA (called a "provirus") is mediated by action of both viral protein Tat and cellular P-TEF-b (transcription). Unspliced RNA or partially spliced mRNA is exported from the nucleus to the cytoplasm through the interaction of the viral Rev protein, RRE, and cellular protein Crm 1. Viral proteins are synthesized in the cytoplasm (translation) and viral envelope glycoproteins (Env) are incorporated into virions with the assistance of the cellular TIP47 protein (Env incorporation). After assembling the viral components, HIV eventually buds and is released from the plasma membrane through the interaction of several cellular factors such as ESCRT complex and AIP1. Subsequent processing by the virion-encoded protease yields mature virus particles (maturation). (Adapted from [9].)

coverage and prevention programs such as education on safer sex and recommendation of condom use and screening/surveillance nationwide to detect the potentially HIV-infected. Care and prevention must be taken especially among both young men and women.

3. HIV and Host Factors

Viruses such as HIV cannot replicate other than *in vivo* within living cells because they have only the viral genome (DNA or RNA) and a very limited number of proteins. Below, we introduce the host or cellular factors involved – either required or restrictive – in HIV replication, then discuss genetic factors that affect the course of HIV. We conclude this section by reviewing a recent trial involving HIV-infected people who are resistant to the disease progression.

3.1. Cellular Factors Involved in the HIV Replication Cycle (Fig. 3)

HIV, whose genome is about 10 kbp encoding structural proteins such as Gag, Env, and Pol and several accessory proteins, cannot replicate without interacting with cellular machinery like other viruses. As is discussed in the anti-HIV therapy section, host factors involved in HIV replication cycle have been extensively studied since the virus was characterized at the molecular level and many cellular factors, mostly proteins, have been found. Detailed analysis of the interaction between HIV and cellular factors is crucial for understanding the pathogenesis of HIV and for developing new approaches to control the virus infection [8–11].

a) Virus entry

HIV entry into target cells requires two cell surface molecules – CD4, an immunoglobulin superfamily member, and chemokine receptors such as CCR5 and CXCR4. This seven membrane-spanning-G-protein-coupled family of chemokine receptors functions as coreceptors for the virus entry. Recent studies revealed that another molecule known as dendritic cell-specific ICAM-3 (intercellular adhesion molecule 3)-grabbing nonintegrin (DC-SIGN) promotes the virus infection by trapping the virus through interaction with gp120 molecules in some types of cells.

b) Uncoating and reverse transcription

After entry, cores of viral particles are partially disassembled – also called uncoating – in the cytoplasm and start reverse transcription. Recent studies demonstrated that a cellular protein called TRIM5α is a restriction factor for HIV-1 infection in cells of some primates such as rhesus macaques. Restriction occurs at uncoating and/or reverse transcription by targeting the capsid (CA) of the virus core. Although human TRIM5α itself does not strongly block the reverse transcription of

HIV-1, it is considered that the protein plays a role in this process. Another cellular factor, cyclophilin A, which also targets HIV-1 CA, modulates the susceptibility of HIV-1 to unknown restriction factors in human cells. Recently, the host factor named apolipoprotein B mRNA-editing enzyme, catalytic polypeptide 3G (APOBEC3G) was found to block HIV reverse transcription if the protein is incorporated into virions. This enzyme has cytidine deaminase activity by which it converts cytosines to uracils during reverse transcription, resulting in degradation of newly synthesized viral DNA or G-to-A hypermutation in the integrated DNA. To combat this host factor, HIV has an accessory protein called viral infectivity factor (Vif). The Vif protein protects the HIV genome by binding to APOBEC3G, and Vif-APOBEC3G complexes are degraded proteasome-dependently.

c) Integration

After reverse transcription, viral DNA associated with viral and cellular protein – called the preintegration complex (PIC) – is transported into the nucleus (nuclear import). The viral genome is then inserted into host chromosome DNA by viral enzyme integrase (IN) (integration). Cellular factors facilitating integration include the barrier to auto-integration factor (BAF); the high mobility protein HMGa1; and lens epithelium-derived growth factor (LEDGF/p75) that links IN and the host chromatin.

d) Transcription

Transcription from integrated viral DNA, called a provirus, is done through collaboration with the viral transactivator protein (Tat) and cellular proteins. Tat potentially activates transcription from the HIV long terminal repeat (LTR) by interacting with certain RNA called the transactivation response (TAR) element, although Tat alone is not enough for activation. Recent studies showed that recruitment of positive transcription elongation factor b (P-TEF-b) consisting of cyclin-dependent kinase (CDK9) and Cyclin T by Tat stimulates transcriptional elongation.

e) Viral RNA export

Unspliced RNA, including viral genomic RNA and mRNA for structural proteins, or partially spliced mRNA is exported from the nucleus to the cytoplasm through interaction of the viral Rev protein, Rev-response element (RRE), and a cellular protein chromosome region maintenance (Crm 1).

f) Assembly and Env incorporation

HIV Gag proteins themselves are necessary and sufficient for forming virus-like particles (VLP), but several cellular factors are believed to be involved in this important "assembly" process. Recent studies show that a cellular protein called HP68 (also ABCE1) appears to be critical for proper assembly of the HIV-1 capsid, a major player in assembly among Gag proteins. Incorporation of envelope glycoproteins (Env) is essential for forming infectious virus particles because Env proteins are used by the virus to attach and fuse with the target cell membrane. Interaction between Gag and Env proteins is required for Env incorporation into virions and the involvement of cellular factors has been suggested. Recent findings have revealed that a cellular protein named tail-interacting protein of 47 KDa (TIP47) bridges between Gag and Env proteins and is responsible for Env incorporation into virions [12].

g) Budding and Release

After the viral components are assembled, HIV eventually buds and is released from the plasma membrane. Several cellular factors play a role in this very last step of the virus replication cycle. Proteins required for HIV budding and release include endosomal sorting complex required for transport (ESCRT) –I. II, III; apoptosis-linked gene (ALG)2-interacting protein 1 (AIP1); ATPase associated with cellular activities vacuolar protein sorting protein 4 (Vps4). Thus, HIV hijacks endosomal sorting machinery to get out from infected cells.

3.2. Host Factors Influencing the Course of HIV Infection

Epidemiological studies show that two phenotypes resistant to HIV infection exist among infected individuals. One involves those exposed but non-infected; the other involves those infected but protected against disease progression to AIDS. Genetic analyses revealed that certain genetic backgrounds correlate with these phenotypes [13, 14]. Concretely, a mutated allele of CCR5 – one of the major HIV coreceptors – called CCR5 delta32 has a 32bp deletion in the coding sequence of the receptor that prevent it from being transported to the cell surface. Most people homozygous for CCR5 delta32 are resistant to HIV-1 infection and suffer no health deficits, although CCR5 is considered important for the immune response in human. In addition, AIDS onset is delayed 2 to 4 years in individuals heterozygous for CCR delta32. These surprising findings suggest that an antiviral targeting CCR5 is feasible without severe side effects.

Another example of resistance to HIV infection is the V64I polymorphism of CCR2 receptor. V64I mutation in CCR2 was found to be associated with a delay in progression to AIDS. V64I polymorphism affects the stability of the CCR2A isoform, resulting in the downregulation of CCR5. The frequency of the CCR5 delta32 allele is highest in northern European populations, whereas that of CCR2 V64I polymorphism is common across ethnic populations.

3.3. Elite HIV Controller vs. Viremic Controller

Although most people infected with HIV eventually experience a reduction in CD4+ cells and increased viral loads, small subset maintains viral loads of less than 50 RNA copies/ml in plasma without undergoing antiretroviral treatment. These individuals, who are called elite HIV controller are estimated to number 1 in 300 HIV-infected persons [15]. Another subgroup, called viremic controllers, maintains viral loads of fewer than 2,000 copies/ml without therapy. A viral load of fewer than 2,000 copies is accompanied by a dramatically reduced risk of virus transmission and disease progression.

Table 1. Anti-HIV drugs approved in Japan.

- Nucleoside reverse transcriptase inhibitors (NRTI)
  - Zidovudine (AZT)
  - Didanosine (ddI)
  - Zalcitabine (ddC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Abacavir (ABC)
  - Tenofovir (TDF)
  - Emtricitabine (FTC)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Nevirapine (NVP)
  - Efavirenz (EFV)
  - Delavirdine (DLV)
- Protease inhibitors (PI)
  - Saquinavir (SQV)
  - Ritonavir (RTV)
  - Indinavir (IDV)
  - Nelfinavir (NFV)
  - Amprenavir (APV)
  - Lopinavir (LPV)
  - Atazanavir (ATV)
  - Fosamprenavir (FPV)

Dr. B. Walker of Harvard Medical Center and others set up the HIV controller consortium to conduct haplotype and whole genome sequence analysis on 1,000 elite controllers and 1,000 viremic controllers in the six months after the 16th International conference on AIDS (August 2006, Toronto). Understanding immunological and genetic factors among these controllers promise to provide useful information on new immunotherapeutic approaches and vaccines.

4. Anti-HIV Therapy

Until an effective vaccine has become available, the best weapon against HIV/AIDS is antiretroviral therapy (ART). The introduction of combination of anti-HIV drugs called highly active antiretroviral therapy (HAART) into the clinical setting dramatically reduced mortality from AIDS and AIDS-related diseases in developed countries since 1996. HAART features combinations of three drugs consisting at least two different types. The three classes of licensed anti-HIV drugs currently available in Japan [16] are (1) nucleoside reverse transcriptase (RT) inhibitors (NRTI), (2) non-nucleoside RT inhibitors (NNRTI), and (3) protease inhibitors (PI). The first two inhibitors act on HIV RT, a unique enzyme that catalyzes the reaction of viral DNA synthesis from the viral RNA genome. Protease inhibitors exert its antiviral activity by inhibiting the viral protease (**Table 1**).

4.1. Anti-HIV Drugs Approved in Japan

(1) Nucleoside RT inhibitors (NRTI)

The nucleoside RT inhibitors (NRTI) act as a competitive inhibitor for dNTPs after being phosphorylated in the host cell and cause premature DNA chain termination. Inhibitors are 2', 3'-dideoxynucleoside analogs of host 2'-dideoxynucleosides incorporated into the DNA chain. If the 3'-OH group of a nucleoside is replaced by an azido group or hydrogen, the viral DNA elongation is blocked due to the lack of 3' OH onto which the next nucleoside is supposed to be added. NRTI include zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), stavudine (d4T), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC).

(2) Non-nucleoside RT inhibitors (NNRTI)

Unlike NRTI, non-nucleoside RT inhibitors (NNRTI) bind to the RT molecule near its active site, causing major conformational changes to the molecule inactivating the enzyme activity. NNRTI include nevirapine (NVP), efavirenz (EFV), and delavirdine (DLV). Based on binding features, NNRTI are divided into (1) EFV as a tight binding inhibitor, and (2) NVP and DLV as rapid-equilibrium inhibitors. With NNRTI, the inhibition of RT is specific to HIV-1; the RT of HIV-2 is not inactivated by NNRTI. Although EFV is the most frequently used HAART NNRTI component in Japan, this drug has disadvantages such as side effects and rapid emergence of the resistant viruses.

(3) Protease inhibitors (PI)

Eight protease inhibitors (PI) approved and used since 1995 in Japan are saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nelfinavir (NFV), amprenavir (APV), lopinavir (LPV), atazanavir (ATV), and fosamprenavir (FPV). The processing of HIV proteins by viral protease is essential for the virus replication because HIV cannot form mature or infectious virions without this step – which is why PI are highly effective against HIV.

HAART therapy that uses different classes of compounds is considered the most effective because it maximizes antiviral efficacy and minimizes side effects. A key factor to success with ART is "adherence." If a patient cannot adhere to anti-HIV drug use, this increases the chance of the resistant viruses emerging. In fact, it was difficult to do it at the beginning of the HAART because the numbers of tablets are too much. When HAART was first started, in fact, the number of tablets used was too high, resulting in incomplete adherence to anti-HIV drugs. Advances in anti-HIV drug development have, however, enabled to cut administration to a daily basis, e.g., the combination of ATV/rtv plus TDF/FTC is recommended for this administration. Decreasing the number of drugs administered improves patient adherence to drug regimens and enhances their quality of life.

4.2. New Anti-HIV Drugs Under Development

Although HAART therapy has dramatically reduced AIDS and AIDS-related disease mortality, serious problems remain with side effects and the emergence of drug-resistant viruses. Solving these issues involves two approaches – developing new types of RTI or PI, or finding new classes of HIV inhibitors. An example of types of new protease inhibitors is TMC114 (darunavir) approved by the US Federal Drug Administration (FDA) in June 2006. TMC114 is active against HIV-1 strains highly resistant to PI. The second approach finding new classes of HIV inhibitors includes entry inhibitors, integrase inhibitors, and maturation inhibitors (**Table 2**) [17, 18].

1) Entry inhibitors

a) Fusion inhibitors

Table 2. Candidates for new anti-HIV drugs.

Drug	Mechanism of action
Fusion inhibitors T-20 (Enfuvirtide)	Synthetic peptide that mimics the part of gp41 and blocks virus-cell fusion (approved by FDA, USA)
CCR5 inhibitors Maraviroc Aplaviroc Vicriviroc TAK-220, TAK-652	Binds to extracellular loop or transmembrane domains of CCR5 and blocks gp120-CCR5 interaction
CXCR4 inhibitors AMD070 KRH-1636, KRH-2731	Binds to extracellular loop domains of CXCR4 and blocks gp120-CXCR4 interaction
Integrase inhibitors MK-0518 JTK-303 (GS9137)	Inhibits virus-specific enzyme and blocks integration of viral DNA into host genomic DNA
Maturation inhibitors PA-457 (Bevirimat)	Inhibits the very last step of Gag processing and blocks virus maturation

A fusion inhibitor named T-20 (enfuvirtide) approved by the US FDA in 2003, blocks membrane fusion between HIV virions and the target cell membrane. T-20 is a synthetic peptide of 36 amino acids that mimicks the part of gp41 responsible for virus-cell fusion. Although the mechanism of this drug is new and it showed significant efficacy in clinical trials, it has the drawbacks of not being usable orally, having a relatively short half-life, and resulting in the rapid emergence of the drug resistant viruses when treatment failed.

b) Chemokine receptor (coreceptor) inhibitors

To enter cells, HIV must bind to a chemokine receptor called CCR5 or CXCR4 after binding to a CD4 receptor. Both chemokine receptors are seven transmembrane G protein-coupled receptors. The advantage of inhibitors targeting host proteins such as CCR5 and CXCR4 is that they make it more difficult for HIV to escape from the drug-host protein interaction compared to drugs targeting HIV-encoded proteins. Searching for host factors involved in HIV replication cycle started soon after the virus was characterized at the molecular level and many cellular factors – most of which are proteins – has been found, as detailed in Section 3. Theoretically, all interactions between host factors and HIV are novel targets for anti-HIV therapy, but another rationale exists for CCR5 inhibitors to be developed. As described earlier, the majority of people homozygous for CCR5 delta32 are resistant to HIV-1 infection and suffer no health deficits [14], AIDS onset is delayed 2 to 4 years in individuals heterozygous for CCR delta32. Three CCR5 inhibitors developed by foreign pharmaceutical companies are maraviroc (Pfizer), aplaviroc (GlaxoSmithKline), and vicriviroc (Shering-Plough). All bind to part of an extracellular or transmembrane domain of the CCR5 receptor and block interaction between an HIV Env protein called gp120 and the receptor. The development of aplaviroc was terminated due to hepatic toxicity. Takeda, the largest pharmaceutical company in Japan, is developing CCR5 inhibitors TAK-220, and TAK-652, both of which bind to the transmembrane domain of CCR5 [19]. Induction and selection of viruses resistant to TAK compounds is reported to be time-consuming or infeasible in *in vitro* culture. All CCR5 inhibitors above are orally bioavailable.

Another type of coreceptor inhibitors is the CXCR4 inhibitor. In 1997, we reported the first chemokine antagonist, a peptide called T22 [20], that has an antiparallel β-sheet structure similar to that of SDF-1, a natural ligand of CXCR4. This peptide specifically inhibits infection of X4 HIV using CXCR4 as a coreceptor. A low molecular weight compound, the bicyclam AMD3100 also reportedly blocks HIV-1 entry and infection via CXCR4. One of the derivatives, AMD070, which is available in oral form, has been announced to have entered Phase Ib/IIa clinical trials. We recently reported that a small CXCR4 antagonist KRH-1636 has potent anti-X4 HIV activity both *in vitro* and *in vivo* [21]. KRH-2731, a KRH-1636 drivative reportedly is a more potent and orally bioavailable inhibitor of X4 HIV both *in vitro* and *in vivo*. CXCR4 inhibitor binding sites are located in the extracellular loops (ECL) of CXCR4. The interaction between the V3 loop of HIV gp120 and ECL of the receptor is thought to be blocked by the CXCR4 inhibitors. Unlike targeting CCR5, blocking the CXCR4 receptor includes concerns about side effects by inhibitors due to the fact that SDF-1 or CXCR4 knockout in mice causes severe birth defects such as abnormal hematopoiesis and cerebral development, and gastrointestinal tract vascularization.

2) Integrase inhibitors

Integrase (IN) is a viral enzyme that catalyzes to join double-stranded viral DNA into host chromosomal DNA,

an enzyme unique to HIV, and a desirable target for anti-HIV drugs along with reverse transcriptase and protease. Despite much effort to develop effective, specific anti-IN inhibitors, such drugs have not reached the clinical stage due to a lack of efficacy *in vivo* and/or side effects from candidate compounds. Two ongoing clinical trials have, however, yielded hopeful results. One involves MK-0518 (Merck) [22], a compound that reduced the viral load to below 400 copies /ml (99% drop) in 80% of treated participants infected with multidrug-resistant HIV. MK-0518 also appeared safe and potent in HIV-infected individuals in a different clinical trial. The other is JTK-303 or GS9137 (JT). Ten-day monotherapy trials with JTK-303 reduced circulating HIV in the blood by as much as 2.0 log10 [23].

3) Maturation inhibitors

PA-457 (Bevirimat), is a new class of anti-HIV inhibitor called a maturation inhibitor [24], blocks HIV maturation by inhibiting the final step in the processing of HIV Gag protein. A multi-dose Phase IIa study done in HIV-infected patients has shown that PA-457 significantly reduced the viral load compared to the placebo. A Phase IIb trial in which the effects of combination therapy in HIV-infected patients are examined is now underway.

At the end of 2003, WHO announced it would provide antiretroviral drugs (ARV) to 3 million HIV-infected persons in developing countries (about half of HIV-infected persons in such countries) by the end of 2005. Only 21 countries met the "3 by 5" target of providing ARV to at least half of those who need treatment, however, although the number of people receiving ARV in developing countries dramatically increased. A large concern when this project started was that widespread use of ARV in developing countries, mainly in Africa, would promote drug resistance. However, HIV-infected persons in these countries have proven to be just as aware of the need to adhere ARV regimens as those in developed countries, and no widespread drug resistance has emerged [25].

5. HIV/AIDS Vaccines

Although HAART therapy markedly reduces HIV-infected and AIDS patients mortality, what is we really needed for preventing HIV infection is a vaccine designed to elicit the human immune responses to prevent or control infection by a pathogen. Two vaccines against HIV infection are thus envisioned – a therapeutic, or treatment, vaccine used to treat people with HIV infection or AIDS, and preventive vaccine that elicits sterilizing immunity among HIV-negative vaccines and controls HIV spread. The therapeutic vaccine boosts the human immune systems against HIV to control the virus infection. If such a vaccine is developed, HIV-infected people will not have to rely solely on antiretroviral therapy. Although neither a therapeutic nor preventive vaccine yet exists, HIV/AIDS vaccine goals are two-fold – ultimately to develop a vaccine that prevents persistent HIV infection, eventually inhibits the initial spread of the virus throughout the body

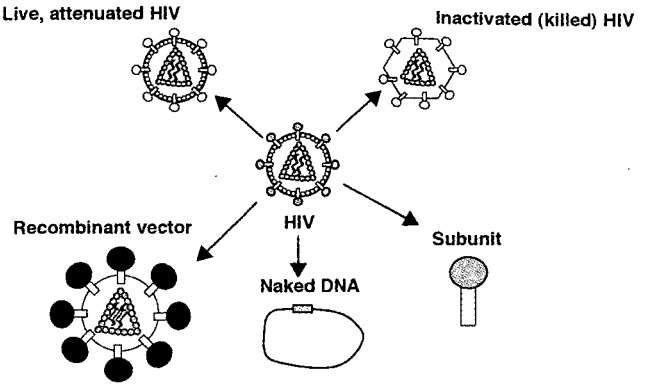

Fig. 4. Types of HIV/AIDS vaccines. Live attenuated HIV: the vaccine contains weakened HIV. Inactivated (killed) vaccine: the vaccine contains HIV killed by chemical reagents. Subunit vaccine: the vaccine consists of purified components of HIV such as gp120. Recombinant vector: the vaccine contains a weakened vector unrelated to HIV, into which HIV gene(s) are inserted. Naked DNA: the vaccine consists of a plasmid DNA that contains HIV gene(s).

– a goal that will be difficult to attain and a long time in coming – and, more realistic and tentatively to design a vaccine that markedly reduces viral load and slows progression to AIDS or one that significantly suppresses HIV transmission. Even partially effective vaccines could dramatically benefit public health. In this regard, T. Quinn et al., of Johns Hopkins Medical Institute, reported that HIV transmission per coital act was highest during early-stage infection when the viral load of the index partner is high [26], suggesting a correlation between HIV transmission and viral load. If this is the case, HIV/AIDS vaccines that only reduce viral loads on vaccinees must be developed and could reduce HIV spread.

5.1. Types of HIV/ AIDS Vaccines

Many different approaches exist in vaccine production (**Fig. 4**) [27].

a) Live attenuated vaccine

An attenuated vaccine consists of whole viral particles whose virulence is reduced but which retain their ability to elicit a host immune response. Although this type of vaccine exposes epitopes for both T cells and B cells, and is cost-effective and has less requirements for booster shots (an additional dose or doses of a vaccine taken after the initial dose to enhance the immune response to the vaccine), the vaccine is considered too dangerous to use due to probable reversion by high mutation rate of HIV.

b) Inactivated (killed) vaccine

An inactivated vaccine is made using viral particles treated by a chemical reagent such as formaldehyde. This type of vaccine also provokes immunity mediated by both T and B cells but requires large amounts of vaccine and booster shots compared to the live attenuated vaccine.

c) Subunit vaccine

A subunit vaccine consists of purified components of pathogens such as viral proteins or synthetic peptides that are part of the whole protein. Two efficacy trials using recombinant gp120, expected to induce neutralizing antibodies against gp120, as an immunogen was completed but vaccine failed to prevent HIV infection.

d) Recombinant vector vaccine

Administration of a recombinant vector vaccine that contains DNA encoding the desired protein antigens can induce large amounts of immunogen in a vaccinee. An advantage of this is that the vaccine directly expresses immunogens to specific sites targeted by the vector used. This vaccine induces both helper and cytotoxic T-cell responses through endogenous antigen prersentation and cross-presentation of immunogen. This approach is now being used for prime vaccination in HIV/AIDS vaccine study as described later.

e) Naked DNA vaccine

The naked DNA vaccine involves direct injection of a plasmid DNA encoding the desired protein antigens, which, surprisingly induces both helper and cytotoxic T-cell responses although large amounts of plasmid DNA are required for effective uptake.

5.2. Status of Ongoing Clinical Vaccine Trials

There are three phases of preventive HIV vaccine trials:

Phase I- involves a small number of HIV-negative volunteers tested for safety and dosages of vaccine and usually takes 12 to 18 months.

Phase II- involves hundreds of HIV-negative volunteers tested for safety and immune responses of vaccine and usually takes 2 to 4 years.

Phase III- involves thousands of HIV-negative volunteers are tested for safety and effectiveness of vaccine and usually takes 3 to 4 years.

As of this writing, over 30 HIV vaccine candidates are in ongoing Phase I/IIa trials [28]. Phase IIb/III candidates are being investigated in two clinical trials. One, canarypox vector prime (env, gag, and pol) plus a subunit gp120 boost (Phase III), is being conducted in Thailand fully enrolled with over 16,000 volunteers. The objective of this trial is assessing whether canarypox vector prime plus subunit gp120 boost can elicit cellular-helper and humoral responses for preventing HIV infection and/or reducing the viral load. The other one is replication-defective adenovirus type 5 (Ad5) vector expressing three HIV genes (gag, pol, and nef) (Phase IIb). This trial, called the STEP study is being conducted in the United States, Australia, Brazil, etc., enrolling 3,000 subjects. Multiclade (A, B, C) prime/Ad5 boost (Phase II, NIH-VRC) is a runner-up. The objectives of the last two trials are to obtain more information about the safety of the vaccine in humans and to determine whether the vaccine elicits cell-mediated immune (CMI) response to the HIV antigens used. So far, the majority of the AIDS vaccine candidates including the above phase IIa/III trials focus on eliciting the CMI response, mainly because studies in humans and monkeys indicate that the CMI response is a key to reducing viral load, which eventually decreases virus transmission. We have not, however, obtained data on whether a particular vaccine-induced CMI response correlates with the prevention of HIV infection although some vaccine candidates indeed induce substantial CMI responses. More importantly, it is apparent that the CMI-based vaccine cannot block the infection itself because it only acts on cells after infection is established. It thus appears that additional strategies incorporating neutralizing antibody- [29, 30] and innate immunity-based vaccinations are needed.

To achieve the ultimate goal for an AIDS vaccine – in other words, to prevent establishment of persistent HIV infection, which would eventually inhibit the initial spread of the virus throughout the body – we must overcome many challenges. First, HIV isolates are hypervariable due to the high mutation rate, recombination, and rapid replication of the virus. This hypervariability allows the virus to escape from the host immune system, such as neutralizing antibodies and T-cell-mediated immunity. Studies are thus required on how the virus mutates and causes recombination and how it escapes from the immune system. Second, unlike infection by other viruses such as polio and measles, HIV infection does not usually induce a broad spectrum of neutralizing antibodies. There are several approaches to make effective antigens and achieve this purpose. These include the production of antigens that mimic the shape of HIV Env proteins, the production of antigens that better expose neutralizing epitopes, and the production of mimetopes that bind to a broad spectrum of neutralizing antibodies, Third, there is no immune correlates of certain immune responses with protection from HIV infection, although effective vaccines against other diseases have been developed with lack of known immune correlates of protection. We still do not know which adaptive immune response – neutralizing antibodies, T-cell-mediated immunity or mucosal immunity – is necessary for an effective HIV vaccine. As mentioned, a subset of HIV-infected individuals called elite HIV controllers has controlled virus infection for several years without undergoing antiretroviral therapy. Detailed analysis of the immune responses of these people against the virus may enable us to identify important immune responses. Fourth, it is not clear which HIV antigens (immunogens) are required to induce an efficient immune response against HIV infection. The fact that live attenuated SIV vaccines induce high degree of vaccine efficacy indicates that multiple viral proteins are required as antigens and as components for effective HIV vaccine candidates although the above question has not been addressed in both human and nonhuman contexts. Fifth, there is no ideal animal model for HIV infection and AIDS in human because HIV infects only humans and causes AIDS. The SIV-rhesus macaque model is used as a surrogate, but SIV infection causes AIDS-like immunodeficiency more rapidly in rhesus macaques than HIV infection in humans. A SIV/HIV hybrid, in which only critical regions of HIV that are targeted by restriction factors such as TRIM5α and APOBEC3G in simian cells are replaced

by those of SIV in the context of an HIV background, has been made independently by the two research groups [31, 32]. The hybrid SIV/HIV could efficiently replicate in simian cell cultures. These viruses may cause immunodeficiency closer to human AIDS in rhesus macaques and can be used for immunogens, although the immunogenic regions of HIV in the rhesus macaques may not reflect those in humans due to the difference in MHC.

5.3. New Approaches to HIV Prevention

Although tremendous effort has gone into developing effective AIDS vaccines, it will take a long time to establish mainly due to HIV hypervariabilty. Among alternative approaches being tried to prevent the epidemic is the ABC behavior change approaches in which A stands for abstinence; B for being faithful; C for correct and consistent condom use. Other approaches include (1) male circumcision, (2) female diaphragms as cervical barriers, (3) pre-exposure prophylaxis (PreP) or post-exposure prophylaxis (PEP) with antivirals, (4) microbicides as female-controlled prevention, and (5) the control of sexually transmitted diseases (STDs) other than HIV infection, e.g., herpes simplex virus.

6. Conclusions

Given that we do not know yet whether an effective vaccine against HIV /AIDS can be developed, we must address two issues to overcome or stop the global AIDS epidemic. First, we must strengthen HIV prevention, especially female-controlled prevention such as female diaphragms, Prep with ART, and microbicides. Second, we must increase access to treatment – not only ART but also drugs that prevent opportunistic infections – by HIV-infected victims to the maximum extend possible. To prevent an AIDS pandemic in Japan will require a broad ongoing educational program involving the government, schools, and the mass media to provide people in Japan – especially young people – with correct knowledge on HIV/AIDS and recommending safer sex using condoms.

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