

Immunotherapies and Vaccines

Hermancia S. Eugene and Ted M. Ross
*University of Pittsburgh
United States*

1. Introduction

Human Immunodeficiency Virus (HIV) was first isolated in 1983 by Barre-Sinoussi and Gallo in parallel at two independent institutions (Barre-Sinoussi, Chermann et al. 1983; Gallo, Sarin et al. 1983). The following year, HIV was established as the causative agent of Acquired Immunodeficiency Syndrome (AIDS). Given such a monumental discovery, there were expectations that an effective vaccine or treatment was not far from being marketed. Unfortunately these expectations have yet to become reality and HIV has become a global epidemic. In 2010, the World Health Organization (WHO) reported that 33.3 million individuals worldwide were living with HIV/AIDS (World Health Organization 2009). The discovery of HIV as the causative agent of AIDS stimulated many areas of basic virological and immunological research. Researchers continue to stress the need for more integrated approaches for development of HIV antiviral treatments and vaccines. In this chapter, the viral and immune challenges, criteria for evaluating clinical studies, candidate therapies and vaccines will be reviewed.

1.1 Viral and immune challenges

Several factors have contributed to the delay of HIV vaccines and therapeutics. These factors can be grouped into two main categories; 1) intrinsic viral characteristics and 2) viral and host interactions. The intrinsic viral properties of HIV, such as rapid replication and virus mutation, virus recombination and viral integration have been obstacles in drug and vaccine development (Aaron N. Endsley 2008; Montagnier 2010). One of the major problems in HIV vaccine development is the high sequence variability of viral isolates (Monteiro, Alcantara et al. 2009; Cuevas, Fernandez-Garcia et al. 2010). The classification of HIV into clades is covered in the HIV nomenclature proposal now found on the Los Alamos HIV Sequence database website (Robertson, Anderson et al. 2000). A major contributor to the high variability of the virus is the lack of proof reading activity present in the viral polymerase (reverse transcriptase) combined with rapid replication rate. Such a combination allows for emergence of viral isolates that can evade the immune response elicited to older viral sequences. The constant escape from immune surveillance results in a constant need for “catch up” by the immune response. Another reason for increase variability is the ability of the virus to genetically recombine (Brown, Peters et al. 2011). Due to the possibility of superinfection, viruses from different clades can be present in the same cell during replication and may result in recombinant viruses. For example, a virus classified A/E has an envelope derived from a clade A virus and Gag proteins derived from a clade E virus.

The other major viral property that works against effective of therapy and viral clearance is viral integration. HIV contains a viral integrase responsible for integration of the HIV provirus into the DNA of an infected cell (Delelis, Carayon et al. 2008). Provirus integration is an essential part of replication (Engelman, Englund et al. 1995). This integrated viral DNA results in both establishment of viral reservoirs in the host and disruption of the immune responses against the infecting virus (Finzi, Blankson et al. 1999; Miedema 2008; Carter, Onafuwa-Nuga et al. 2010; Virgin and Walker 2010). These viral reservoirs are a source of actively replicating viruses in individuals who have controlled infection and have undetectable levels of virus (Wong, Hezareh et al. 1997; Chun, Nickle et al. 2008; Lerner, Guadalupe et al. 2011). Authors Siliciano J.D and Siliciano, R F discuss HIV reservoirs and how they contribute to the lack of virus eradication and the need for continuous HAART therapy by HIV infected individuals to prevent virus rebound (Siliciano and Siliciano 2004). The lack of a defined correlate(s) of protection for HIV is a major obstacle in vaccine and therapeutic development. Humoral immune responses were initially proposed as a correlate of protection. Studies in experimental animals have shown that passively administering anti-HIV antibodies results in protection from infection (Prince, Reesink et al. 1991; Putkonen, Thorstensson et al. 1991; Emini, Schleif et al. 1992). The first prophylaxis vaccine to enter phase III trials, AIDSVAX by VaxGen, induced antibodies to HIV vaccine components but vaccine was not efficacious (Ltd. 2003). The failure of the initial studies has not changed the viewpoint of everyone on the role of humoral responses as the correlate of protection. The antigens used in these studies, monomeric gp120 and monomeric gp160, are not the functional unit of the HIV envelope. The HIV envelope is trimeric on the surface of the virus particle. Studies using trimeric envelope immunogens have been used to improve the humoral responses (Nkolola, Peng et al. 2010; Sundling, Forsell et al. 2010; Sundling, O'Dell et al. 2010). Also, the recent vaccine trial in Thailand, has provided some data to support the possibility that humoral responses may be the HIV correlate of protection (Rerks-Ngarm, Pitisuttithum et al. 2009).

Many investigators are designing preventative vaccines for HIV that induces cellular response (Nanjundappa, Wang et al. 2011; Ranasinghe, Eyers et al. 2011; Sistigu, Bracci et al. 2011). Data from preclinical studies, as well as infected individuals, showed that an effective cellular response was able to control viral replication and resulted in reduce progression to diseases (Wilson, Keele et al. 2009; Streeck and Nixon 2010). Coming off the heels of failed humorally-driven trials, the certainty of developing a preventative vaccine is questioned and some in the field believed that preventing progression to disease to be a viable alternate focus. Vaccines aimed at eliciting cellular responses for preventing infection or disease progression have also not been successful. In 2007, the Merck HIV vaccine trial used adenovirus to deliver HIV genes *gag*, *pol* and *nef*. The trial was stopped after intermediate data analysis showed no supportive evidence to continue (Sekaly 2008). It appears that pre-existing immune responses to the adenovirus may have increased susceptibility to infection. Other alternative theories of the immune correlates of HIV/AIDS protection need to be considered. The immune correlate(s) for preventing infection and prevention of disease symptoms (*i.e.* control of infection) may be different (Jose Esparza 1996). In the case of preventative vaccines, an effective initial response to the virus is needed. At the time of the initial assault, the immune system is not dysfunctional. In contrast, during HIV therapy the immune system is in a state of dysregulation due to the constant tug of war with the virus infection. HIV infection causes a dysregulation of the immune response (Kuhrt, Faith et al.

2010; Sabado, O'Brien et al. 2010; Kolte, Gaardbo et al. 2011). Therefore, the HIV immunotherapeutic field does not only have to establish the correlate for preventing disease progression but has to overcome the immune dysfunction caused by the viral infection. The moderate success of the Thailand study and the failure of the STEP trial have brought into question both humoral and cellular immunity as the correlates of protection. New vaccine designs are now aimed at inducing both of humoral and cellular responses. The key to overcoming these obstacles faced by drug and vaccine development is continued research not only in terms of treatment, but also basic research of HIV and human immunology.

1.2 Evaluation of immunotherapies and vaccines in human trials

Since there is a lack of protective correlate(s), standardized evaluation of clinical responses is needed to develop preventative AIDS vaccines and improved immunotherapies (Pantaleo and Koup 2004). Usually, when a correlate of protection is lacking, a vaccine's ability to provide clinical benefit by reducing mortality and morbidity gives precedent for licensing. Due to the availability of an FDA approved therapy, HAART, any therapy that will be approved is compared to benefits given by HAART. HAART reduces viral loads and restores some level of CD4+T cells in individuals that benefit from therapy. In a clinical setting, the hallmarks or surrogate markers of efficacy are reduction in viral loads and increase in the number of CD4+ T cells (Peto 1996; Peters 2000). While CD4 +T cells increase during HAART therapy leads to better prognosis of disease. Recent Proleukin (rIL-2) clinical trials, SILCAAT and ESPRIT volunteers showed increase in CD4 +T cells but the time to disease progression was not increased. These results have brought into question the validity of increase CD4+T cells as a readout for better disease outcome (Peters and Samuel 2010). The composition of the CD4+ T cell population recovered after therapy was evaluated at the end of the study to determine if the increase CD4+ T cells population was any different from populations seen after HAART therapy. Other T cells have also come into light in the last few years, Th17 cells and cells that secrete IL-21 may play a role in the non-disease progression seen in African green monkeys and Sooty Mangabeys (Ciccione, Greenwald et al. 2011; Hartigan-O'Connor, Hirao et al. 2011; Milush, Mir et al. 2011). These trends are also being reported in long-term non-progressors and elite controllers (Hartigan-O'Connor, Hirao et al. 2011; Salgado, Rallun et al. 2011; Salgado, Rallun et al. 2011). Results in animal studies have shown the possible role of Th17 cells in the gut mucosa in reduced bacterial translocation and slower disease progression (Cecchinato, Trindade et al. 2008; Maloy and Kullberg 2008; Hofer and Speck 2009).

There is a lack of consensus on the hallmarks or surrogate markers for preventative vaccine trials. The ideal standard for a preventative HIV vaccine would be sterilizing protection. Sterilizing protection is complete protection from HIV infection, no detectable HIV at any time and no transmission of HIV. In 2007 an NIH workshop on vaccine efficacy resulted in a report by Follman et al. which stated three parameters for evaluating HIV vaccine efficacy (Follmann, Duerr et al. 2007). The three parameters for evaluating vaccine efficacy are 1) reduction in risk of acquiring HIV 2) the reduction in cumulative risk of progressing to AIDS from the time of infection to diagnosis and 3) reduction in the risk of transmission of HIV to others. Vaccine endpoints are based on years of clinical studies (Peto 1996; Follmann, Duerr et al. 2007; MacLachlan, Mayer et al. 2009). Preclinical (usually NHP) studies have established surrogate markers for vaccine efficacy. Thus far, the most relevant marker identified as a determinant of disease

outcome is the reduction of plasma HIV genome RNA levels following infection (Lavreys, Baeten et al. 2006). The viral set point is a consistent marker for determining disease progression; i.e. the higher the viral set point, the more likely a patient will progress to AIDS (Lavreys, Baeten et al. 2006; Kelley, Barbour et al. 2007). The levels of CD4+ T cells in the blood of infected individuals can also act as a surrogate of disease progression (Chouquet, Autran et al. 2002). However, the correlation between CD4+ T cell levels in the blood and disease progression becomes more significant closer to the onset of AIDS. Modeling studies have concluded that a reduction in blood viral titers of 1-1.5 log₁₀ compared to peak infection leads to a significantly positive impact on progression to disease (Davenport, Ribeiro et al. 2004). The other aspect to a preventative vaccine is reduction of viral load leading to reduce transmission. A vaccine that results in a reduction in the rate or probability of transmission would have a positive impact on the HIV global epidemic. In the absence of a sterilizing vaccine, to have a vaccine, that not only lowers viral set point, but also reduces transmission rate would be beneficial (Gurunathan, Habib et al. 2009).

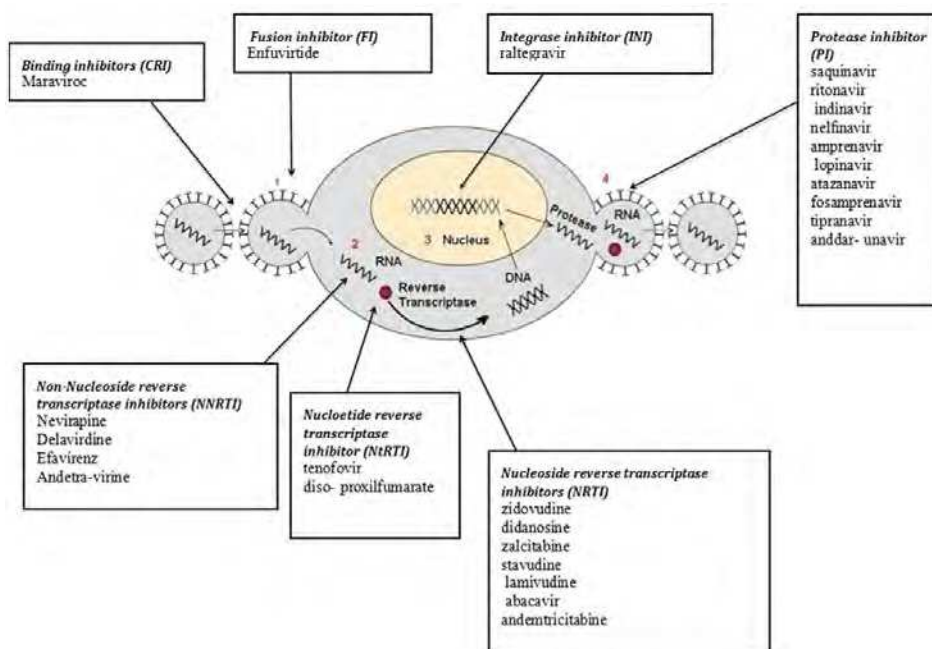
2. Immunotherapies

2.1 Highly Active Antiviral Therapy (HAART)

Two years after the discovery of the causative agent of AIDS, the first sign of possible treatment was reported in 1985 with the development of the first antiretroviral compound (Mitsuya, Weinhold et al. 1985). This compound was called Retrovir (zidovudine, AZT) and became the first drug in the family of nucleoside reverse transcriptase inhibitors (NRTI). AZT targets the reverse transcription process of HIV's replication cycle. Since AZT, several NRTI and other families of drugs targeting the replication cycle of HIV have been discovered. As of 2010, the FDA has licensed twenty-five antiretroviral drugs. These drugs can be grouped based on the mode of action and are placed into one of the following groups: nucleoside reverse transcriptase inhibitors (NRTI), nucleotide reverse transcriptase inhibitor (NtRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), co-receptor inhibitor (CRI), integrase inhibitor (INI), and fusion inhibitor (FI) (De Clercq 2010). Figure 1 highlights licensed drugs and the mode of action of each group of drugs.

In 1996, the first use of combination drug therapy was attempted using a protease inhibitor that was combined with an NRTI (Gulick, Mellors et al. 1997). Combinational therapy confirmed that there was a longer period of undetectable or reduced viral loads as well as recovery of CD4+T cells in the blood. Combination therapy or HAART is now the treatment of choice for HIV infected individuals and results in various clinical outcomes (Greenbaum, Wilson et al. 2008; Crabtree-Ramirez, Villasis-Keever et al. 2010). Individuals on HAART need to be monitored at all times to ensure the combinational therapy is effective and does not result in viral mutants. Individuals on HAART will need their treatment regimen adjusted upon development of viral resistance (Paci, Martini et al. 2011; Von Kleist, Menz et al. 2011). In addition to viral resistance, HAART is highly toxic to patients resulting in reduced patient compliance (John, Moore et al. 2001; Kronenberg, Riehle et al. 2001). Moreover, HAART treatment is expensive and therefore people living in developing countries have less access to drugs even though these are the locations where the epidemic is greatest. Based on surveys and clinical research the WHO has identified factors that need to be considered to determine HAART treatment in an adult

(World Health Organization 2006) : 1) suitability of drug combination, 2) licensing of drugs by national regulatory department and recommended dose, 3) toxicity profile of the drug, 4) availability of laboratory monitoring, 5) potential of maintenance and adherence to treatment , 6) prevalence of co-existing infections (e.g. Tuberculosis), 7) child bearing age, 8) availability of local and international manufacturers, and 9) price and effectiveness of drug.



Stages of replication cycle where drugs act: 1) Receptor binding and membrane fusion, 2) RNA genome reverse transcribed into DNA, 3) Provirus integration, 4) Virion egress and maturation.

Fig. 1. Diagram showing the licensed antiretroviral HIV drugs and the step in the replication cycle they act on.

One of the complications that an individual can experience on HAART is immune reconstitution inflammatory syndrome (IRIS) (Letang, Miro et al. 2011). IRIS is seen in individuals recovering from immunodeficiency. Criteria for IRIS 1) Response to antiviral therapy by: viral loads >1 log₁₀/ml decrease in RNA level 2) clinical deterioration of inflammatory of infectious condition upon antiviral treatment and 3) symptoms cannot be alleviated by: clinical course of treatment, medication side effects or toxicity, treatment failure or complete non adherence (Tappuni 2011). IRIS is also recorded in individuals with HIV co-infections such as tuberculosis (Lin, Lai et al. 2010). Additionally, individuals on HAART develop other diseases such as cardiac and metabolic complications that are affiliated with aging (Broder 2010). The side effects of HAART treatment and limited availability in HIV endemic areas are the drive for development of new immunotherapies for HIV.

2.2 Expanding HIV therapy from HAART

During HIV infection, the immune system does provide a defense aimed at eradicating the infection. This mounted immune response is insufficient and allows the viral infection to impair the immune system and persist. The use of therapeutics in infected individuals is aimed at overcoming the immune systems impairment to allow for viral control leading to decrease progression to AIDS. Human studies of long term non-progressor and elite progressors have observed a slower progression to disease in these individuals (Rodes, Toro et al. 2004; Okulicz and Lambotte 2011). Long term non-progressors are characterized based on absence of disease, low viral loads, and stable or increasing CD4 T cells.(Paroli, Propato et al. 2001). There is great need for drugs and vaccine strategies that reduce viral loads in infected individuals. Development of an effective HIV therapy needs to incorporate the knowledge that the immune system of an infected individual is dysfunctional. Figure 2 below simplifies the current knowledge of immune dysfunction and pathogenesis of HIV infection and table1(Fernandez, Lim et al. 2009). Immune dysfunction has been identified in Lymphocytes (T and B cells), NK cells, macrophages and even cytokine secretion.

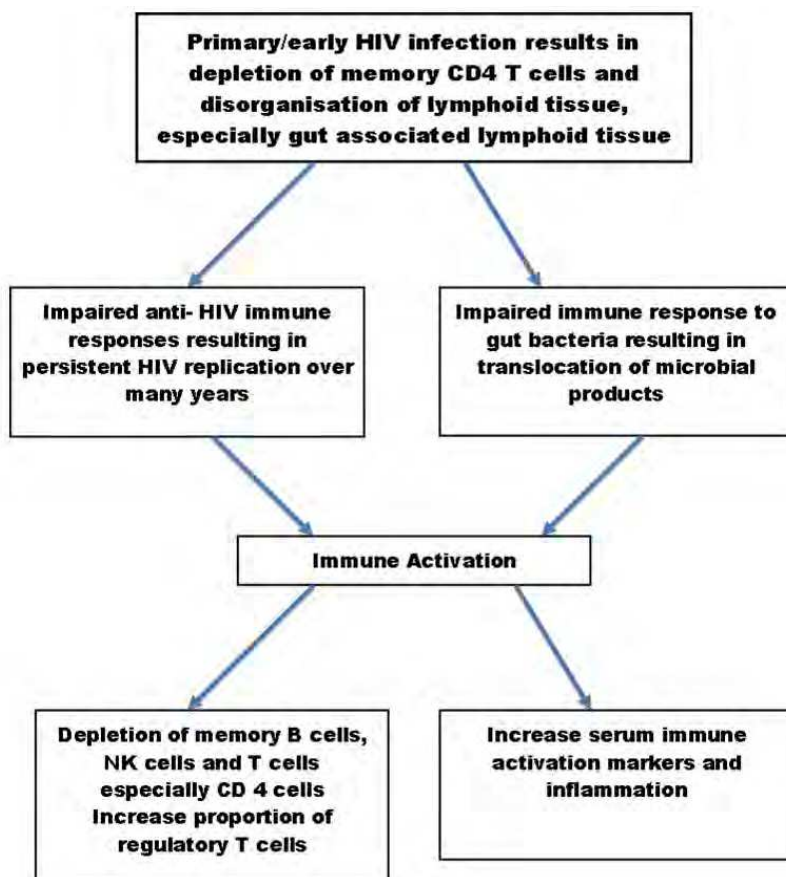


Fig. 2. Pathogenesis of immune dysfunction associated with HIV (Fernandez, Lim et al. 2009)

Dysfunction	References
The frequency of CD4+ T cells infected by HIV in vivo is too low to account for the CD4 T cell loss	(Chun, Carruth et al. 1997),(Douek, Brenchley et al. 2002)
Most apoptotic CD4+T cells in peripheral blood and lymph nodes of patients with chronic HIV infection are infected HIV	(Finkel, Tudor-Williams et al. 1995)
Naïve CD8+T cells, memory B and NK cells as well as CD4+T cells decline in HIV infection	(D'Orsogna, Krueger et al. 2007),(Fauci, Mavilio et al. 2005),
SIV-infected macaques exhibit a persistently activated immune system and rapidly progress to AIDS, while SIV-infected sooty mangabeys show normal T cell division rates and do not progress to AIDS.	(M Roederer 1995)
HIV-2 infection is associated with lower levels of immune activation, which may explain the slower decline of CD4+Tcells compared with HIV-1 infection	(Michel, Balde et al. 2000)
In mice, TLR7 stimulation unrelated to a virus infection induces immune activation and immunopathology similar to that in HIV infection	(Baenziger, Heikenwalder et al. 2009)

Table 1. Evidence of dysfunction of the immune system of HIV infected individuals (Fernandez, Lim et al. 2009)

Current experimental therapies are grouped based on components and or modes of action, such as the HIV viral proteins targeted, the components of the immune system effected, fusion inhibitors, viral inhibitors, and HIV regulatory protein inhibitors, (Kilby 1999; Peters 2000; Pett 2009). Examples of these can be seen in Table 2.

Type of Immunotherapy	Examples
HIV Viral Protein	Remune, rgp160 (VaxSyn), rgp120, p24VLP, ALVAC1452
Components of Immune Systems	rIL-2, rIL-7, primed dendritic cells
Fusion inhibitors	T-20, T-1249
Viral inhibitors	sCD4 , Indinavir, nevirapine
HIV regulatory protein inhibitors	
DNAzymes	DzV3-9

Table 2. Some examples of Immunotherapies

HIV viral proteins used for immunotherapy include the viral envelope protein, core protein (Gag), reverse transcriptase, tat, nef, polymerase, as well as the whole killed virus (Tsoukas, Raboud et al. 1998; Gorse, Simionescu et al. 2006; Ensoli, Bellino et al. 2010). Viral proteins have been delivered as recombinant proteins, DNA vaccines, on virus-like-particles or in viral vectors (Buonaguro, Tornesello et al. 2009; Rosenberg, Graham et al. 2010). CD8+ T cells with cytolytic activity appeared to control viral titers in both non-human primate

models, as well as infected individuals with HIV (O'Connell, Bailey et al. 2009). In an effort to induce more cytotoxic T lytic (CTL) responses viral vectors, such as canarypox virus and DNA vaccination, were implemented (Kutscher, Allgayer et al. 2010; Rosario, Bridgeman et al. 2010). One example of the use of recombinant canarypox virus vaccine to deliver viral proteins is the vaccine VCP1452 (ALVAC1452). ALVAC1452 was used to carry the HIV-1 genes: gag, pol, env and nef.

2.3 Remune

Remune, is a whole killed virus with a clade A envelope and a clade G gag depleted of gp120 administered in conjunction with incomplete Freund's adjuvant. This vaccine was shown to be safe and resulted in a maintenance of CD4+T cells in volunteers in a two year follow up study (Sukeepaisarncharoen, Churdboonchart et al. 2001). Remune clinical trial is covered in detail in the article by Fernandez -Cruz et al (Fernandez-Cruz, Navarro et al. 2003). The gp120 component of the virus was removed in an effort to present the more conserved antigens to induce T cell responses. In phase II clinical trials this vaccine was combined with HAART, where Remune was administered intramuscularly every 3 months. Trial participants had a mean CD4+T cell count of 586 cells /mm³ and a mean viral load of 953 RNA copies /ml. Peripheral blood mononuclear cells (PBMC) were collected from trial participants. Following stimulation with Env gp120 depleted virus or recombinant Gag p24, PBMCs proliferate was observed in vaccine volunteers compared to a negative control group that was vaccinated against Candida. In addition, there was proliferation following HIV-specific antigen proliferation in isolated CD8+T, CD4+T and NK cells. Predominantly, memory CD4+T and CD8+T proliferated to HIV antigen stimulation.

Remune / HAART combination therapy entered phase III trials, but it was terminated after an intermediate evaluation of the data showed no significant benefit of Remune to the individuals receiving the therapeutic vaccine (Moss, Wallace et al. 1999). Additional studies using only Remune elicited significant increases in CD4+ T cells and reduced viral loads following vaccination (Fernandez-Cruz, Navarro et al. 2003). However, Remune /ALVAC did not elicit significant increases in the cytotoxic T cell activity or enhanced CD4+ T cell compared to ALVAC alone. (Angel, Routy et al. 2011). Remune did not meet criteria for evaluation by the FDA as an Immunotherapy. Although these studies with Remune did not result in licensing, these studies contributed to the knowledge of the field with a better appreciation that increases in specific T cell responses measured by *in vitro* assays do not always correlate with the efficacy of vaccination. Since increase in CD4+ T cells numbers do not correlate with better prognosis better surrogates or immune markers of vaccine efficacy are needed.

2.4 Proleukin (recombinant IL-2/rIL-2)

Another form of immunotherapy being investigated for HIV is the use of components of the immune system, including cytokines, innate cells, or T cells (Pett 2009). Investigation of cytokine levels identified IL-2 to be reduced in HIV infected individuals with greatest reduction seen in individuals who progress to disease. (Lane and Fauci 1985; Kannanganat, Kapogiannis et al. 2007). IL-2 is known to be a T cell derived cytokine needed for stimulation of cell proliferation and enhancement of cytolytic activity (Malek and Castro 2010). In the early 20th century, recombinant IL-2 (rIL-2) was administered to individuals with high and low CD4+T cell counts and low viral loads either intravenously or subcutaneously. IL-2 administration resulted in an increased numbers of CD4+T cell counts, which may be

clinically beneficial especially in late stage disease (Arno, Ruiz et al. 1999; Davey, Chaïtt et al. 1999; Levy, Capitant et al. 1999). Two rIL-2 trials called SILCAAT and ESPRIT is covered by the report of Peters B. and Samuel M (Peters and Samuel 2010).

The rIL-2, termed Proleukin, was given subcutaneously in both these studies. The SILCAAT trial was designed for late stage HIV infected volunteers as defined by CD4+T cells between 50 and 299 cells/mm³ and the ESPRIT trial was designed for early stage infected individuals, defined by CD4+T cells counts above 300 cells /mm³ (Committee 2009). The endpoints for both trials were effect of treatment on disease progression and death. HAART was administered alone or in combination with Proleukin. There was a significant increase in CD4+T cell numbers in patients treated with the combination of HAART/Proleukin compared to HAART alone. Over a period of 7-8 years, there was an increase in cell numbers. Nonetheless, this increase did not translate to clinical benefits since there was not a reduction in incidence to AIDS or length of time to AIDS in individuals who received HAART/Proleukin versus HAART alone. Further analysis of these results showed that these up-regulated CD4+T cells following HAART/Proleukin treatment were different from CD4+T cells activated by HAART alone. The HAART/Proleukin treatment resulted in increased numbers of naïve and central memory CD4+T cells. Treatment with HAART alone resulted in increase of effector memory CD4+T cells. Fewer regulatory T cells were present with the HAART alone versus HAART/Proleukin treatment. Furthermore, Proleukin treatment resulted in toxicity in some individuals. Even though the Proleukin treatment increased CD4+T cell numbers, a surrogate maker for vaccine efficacy, the level of toxicity of this drug does not justify its use (Peters and Samuel 2010). Similar to the Remune trials, the use of Proleukin increased CD4+T cells a surrogate marker for vaccine efficacy. The discovery of cytokines linked to HIV immune dysfunction continue. Therefore, the use of interleukins as therapies both directly and as adjuvants need to be carefully considered (Clerici 2010).

In addition to cytokines, other immune system components were investigated as immunotherapies. One such immune component is serum Gc factor the precursor for macrophage activating factor (MAF) (Mosser 2003). During HIV infection, gp120 prevents deglycosylation of Gc factor affecting production of MAF and results in lack of macrophage activation (Nobuto Yamamoto 2009). The use of serum Gc factor as a therapy is a potent macrophage activator and has no side effects in humans (Mosser 2003; Yamamoto, Ushijima et al. 2009). Another immune component being used is dendritic cells (DC). Dendritic cells (DC) are potent professional antigen presenting cells and are ideal for priming T cells for cytotoxic activity (Van Gulck 2010). DC primed with HIV specific antigens stimulates T cells that can destroy HIV infected cells. In addition to DC primed T cells, direct use of T cells as therapy is being investigated. The use of genetically engineered T cells with modified CCR5 receptors demonstrate that these strategies increase CD4+T cells with engineered T cells/HAART compared to HAART alone (Gulick, Lalezari et al. 2008). As seen in previous studies, the populations of CD4+T cells increased need to be investigated as increase in CD4+T cells may not lead to better disease outcome.

Pharmacological compounds are another area of HIV therapeutic development. New targets of HIV therapeutics is covered in a review by Jiang, Yan; Liu, Xinyong; De Clercq, Erik (Jiang 2011). These compounds target different stages of HIV replication cycle including viral entry, reverse transcription and viral exit. Most of the compounds initially developed were targeted at reverse transcriptase and fall under the categories of NRTI and NNRTI. Additional compounds have been developed that target other viral proteins and parts of the replication cycle. There are now compounds that target the HIV receptor CD4, the co-

receptors CCR5 and CXCR4, integration of virus into the host genome, and viral membrane fusion (Latinovic, Le et al. ; Ferain, Hoveyda et al. 2011).

2.5 Enfuvirtide (T20)

One of the initial fusion proteins to enter clinical trials was called T20 (Kilby 1999). Following receptor/co-receptor binding, the viral envelope mediates fusion of the cell and viral membrane via the gp41 domain of the HIV envelope. The gp41 heptad repeat sequence is responsible for membrane fusion and is highly conserved between viruses of all clades. A therapy targeted at the fusion domain should overcome the challenge of virus diversity. Initial peptides DP107 and DP178 corresponding to the heptad repeat sequences were found to inhibit viral infectivity in cell culture (Wild, Oas et al. 1992; Wild, Shugars et al. 1994). To further support the theory that disruption of the fusion domain leads to lack of virus infectivity, mutations in the supercoil/heptad repeat region was performed. These mutant viruses could not infect permissive cells. The next step in development of this drug was determining the concentration needed *in vivo* to inhibit membrane fusion. Based on the DP178 peptide a 36 amino acid peptide was formulated and called T20. This peptide was confirmed to have inhibitory activity *in vitro*. After *in vitro* studies, dosing and safety studies were performed using T20 followed by clinical trials using this fusion inhibitor (Wild, Greenwell et al. 1993).

Sixteen HIV-infected adult volunteers were given T20 intravenously for 14 days (Kilby, Hopkins et al. 1998). Subjects were chosen based upon CD4⁺ T cell counts greater or equal to 100 cells/mm³ and viral loads of 10,000 or more copies of RNA/ml of plasma. All participants were newly infected and not on therapy or were using antiretroviral therapy but ceased treatment for the trial. People were given 3mg to 100mg intravenous doses. No participants reported any adverse effects or toxicity. A few individuals had elevated temperatures and mild headaches. The drug had a half-life of 1.83 hours. Overall, there was a significant decrease in RNA plasma levels, with the fusion peptide can decrease viral infectivity and indirectly reduce viral load.

In a follow up study, increasing doses of T20 over time were used (Kilby, Lalezari et al. 2002). Volunteers with viral loads greater than 5000 copies of RNA/ml of plasma were placed on T20 therapy. Volunteers received either intermittent injection or were fitted with a device to allow for continuous drug infusion instead of intravenous dosing. The trial took place over 28 days of outpatient treatment. Adverse effects were seen in some individuals fitted with the infusion device. The pump used in treatment had frequent alarming caused tender nodules under the skin when infusion took place. Because of this side effect some individuals were taken off the pump and changed to the injection arm of the study. In the case of toxicity one individual withdrew from the study on that basis. Following 28 days of treatment, there was a dose-dependent decline in RNA levels. The best results were seen in individuals receiving intermediate dose of 30mg of T20. Potential T20 resistant-viruses showed the development of multiple point mutations in the present of T20 treatment. Therefore, several conclusion were made: 1) a more user friendly outpatient device is needed for administering treatment, 2) understanding and characterizing possible resistant virus need to be carefully monitored and 3) correct combination of other antiretroviral therapies and fusion inhibitors need to be considered.

T20 was moved to a large phase III clinical trial performed in the United States (TORO1) and Europe/Australia (TORO2) (Joly, Jidar et al. 2010) . TORO1 consisted of 491 individuals who had more than 6 months of therapy including NRTI, NNRTI or protease inhibitors.

TORO 2 enrolled 504 volunteers with patients having had treatment with one or more of the same groups of antiretroviral (NTRI, NNRTI and PI). Volunteers in both studies had viral loads greater than 5000 copies/ml of plasma. Patients were treated with 90mg of T20 with HAART therapy or therapy alone. After 48 weeks, there was a significant drop in viral loads in the T20 plus antiretroviral therapy versus the antiretroviral treatment alone. The volunteers in the T20/HAART arm of the study had a 2-fold increase in CD4+ T cells counts from baseline compared to HAART alone that lasted greater than 96 weeks. At that point all individuals in the study were placed on T20/HAART. However the responses of the individuals originally on HAART alone never reached the levels of the individuals who received T20/HAART. This outcome indicated that T20 should be given early in treatment. T20 is now called Enfuvirtide and has been licensed by the FDA as the first fusion inhibitor to be used for HIV therapy.

This positive step forward in the immunotherapy field fuels the continuous research to find better and safer HIV immunotherapies. Other therapies being investigated include HIV frameshift efficiency modulators, DNAzymes and the theory of alloimmunity. The first two therapies are still early in development. Alloimmunity was observed in a NHP study where animals were protected from virus challenge. After investigation it was concluded that the protection observed because the virus was grown in human PBMCs (Langlois, Weinhold et al. 1992). The use of alloimmunity in the field of HIV vaccines has expanded since the initial finding. Thomas Lehner et al published a report covering discussions during a NIH workshop on the use of alloimmunity as a strategy for HIV vaccines (Lehner, Shearer et al. 2000)

3. Prophylaxis

Some of the earliest HIV/AIDS vaccines were based upon the envelope protein of the virus (Lasky, Groopman et al. 1986; Arthur, Pyle et al. 1987; Redfield, Birx et al. 1991). Soluble portion of envelope (gp120) or the entire gp160 envelope protein was used as recombinant proteins to vaccinate humans and induce a humoral response (Wintch, Chagnat et al. 1991; Pincus, Messer et al. 1993). HIV envelope subunit vaccines elicited neutralizing antibody responses following vaccination without toxic side effect in human volunteers. The first phase III clinical trial in pursuit of an effective HIV vaccine was done by VaxGen using their vaccine called AIDSVAX and consisted of a bivalent subunit recombinant gp120 envelope proteins (Francis DP 1998).

3.1 Vaxgen (AIDSVAX B/B and B/E) vaccine clinical trial

After showing protection in chimpanzee after homologous and heterologous challenges, the Vaxgen vaccine moved into clinical trials. The primate study was not very well powered and complete protection was not achieved in a suboptimal HIV animal model (Berman, Gregory et al. 1990). The initial VaxGen studies were done with a monovalent vaccine either from the HIV strain MN or IIIB (Migasena, Suntharasamai et al. 2000). Both these envelopes were from lab adapted virus strains. The recombinant proteins envelope MN and IIIB gp120s were produced in engineered bacteria. The phase I and II clinical trials showed that AIDSVAX was well tolerated with irritation just at site of injection. Six individuals acquired HIV during the trial. The vaccine that was sent into phase III clinical trial was bivalent with both clade B envelopes MN and IIIB in an effort to deal with virus diversity. The vaccine trials took place in the US with a total of 5000 at-risk women and homosexual men and

parallel studies were conducted in Thailand with intravenous drug users (Francis DP 1998). The vaccines were tailored to the trial sites. In the US, the vaccine consisted of envelopes from clade B. The Thailand vaccine was made from envelopes from clade B and E. Trials were powered to determine efficacy and were scheduled for three years allowing for long-term follow up. The endpoints designated for the trials were infection as measured by seroconversion and viral load as measured by polymerase chain reaction. In 2003, VaxGen reported the failure of its vaccine trial (Profile 2003). There was no significant decrease in infection in individuals who received the vaccine when all individuals were considered. However, the company reported that the vaccine was more immunogenic and produced higher levels of antibody responses in Black and Asian volunteers. Because of this finding, the AIDS VAX was included in a future study in combination with ALVAC-HIV-vCP1521 in Thailand.

Since the beginning of the VaxGen trials, HIV prophylaxis vaccines designed to elicit humoral response have increased in sophistication. Vaccine designs used to induce effective neutralizing antibodies is covered in a review by Vaine et al. (Vaine, Lu et al. 2009). Vaccine designs include use of envelopes with variable loops deleted, glycosylation mutated, epitope grafting, envelope trimers and centralized sequences. Our lab has been involved in studies to increase antibody response to envelope. The initial studies performed used the molecular adjuvant in combination with sgp120 to increase antibody titers (Green, Montefiori et al. 2003). Results from that study showed that DNA vaccination with sgp120 linked to three copies of C3d efficiently increase antibody tiers in rabbits compared to non-C3d constructs. This work was expanded to link C3d3 to a more native envelope structure. Trimerize envelopes stabilized by the bacteriophage fibritin and linked to C3d showed better cross neutralizing titers to primary isolates compared to trimers without C3d. Both groups of mice vaccinated with envelope trimers with and without C3d induced high anti-envelope responses (Bower, Yang et al. 2004). Our lab has also used virus-like particles (VLP) in an effort to present envelope in its native form (Young, Smith et al. 2004). Responses of mice vaccinated with the HIV VLP when compared to soluble gp120 or trimers had higher envelope titers and broader immune responses (McBurney, Young et al. 2007). The VLP induced both mucosal and systemic responses.

In parallel with developing vaccines to eliciting antibody responses vaccines aimed at eliciting T cell responses were being developed (Egan, Pavlat et al. 1995). Both animal and human studies have indicated that CD8+T cells were linked to reduce viral load and led to development of vaccines aimed at producing the ideal cellular responses (Asquith and McLean 2007). Several viral vectors have been used to elicit cellular responses to HIV proteins including poxvirus vectors, vaccinia virus vectors, adenovirus vectors, alphaviruses vectors, avipoxvirus vectors, poliovirus vectors and rhabdovirus vectors (Polo and Dubensky 2002). Viral vectors allow for 1) high production levels of antigens directly into cells, 2) potential adjuvant effect on the immune response given the viral nature of the system and 3) the particular characteristic allows for efficient uptake of vaccine by professional antigen presenting cells to stimulate the immune response. Viral vectors can be mucosal adjuvants. Mucosal stimulation is an asset in HIV vaccine development as most infection takes place via the mucosa (Chenine, Siddappa et al. 2010). There is a major disadvantage to viral vectors, the possibility of pre-existing immunity may lead to adverse effects and reduced immune response directed at the vaccine antigens (Gudmundsdotter, Nilsson et al. 2009; Pine, Kublin et al. 2011). Other strategies that have been investigated for inducing a cellular response include using various vaccine regimens. One of the vaccine

regimens that had proved successful in primates to stimulate a cellular response is a DNA prime followed by protein or viral vector boost (Barnett, Burke et al. 2010; Jaoko, Karita et al. 2010; Keefer, Frey et al. 2011).

3.2 Merck clinical trial

The Merck vaccine consisted of three recombinant adenoviral vectors of different serotype expressing the genes *gag*, *pol* and *nef* (Shiver, Fu et al. 2002). Preclinical trials in macaques vaccinated with the modified Ad5 expressing *gag*, *pol* and *nef* showed immunogenicity. When monkeys were challenge with SHIV and SIVmac239, animals had reduced viral loads. Further analysis identified the animal's HLA type as a major factor in the outcome of vaccination and efficacy seen. With reduced viral loads in the primate model after challenge the vaccine was moved into clinical trials. During clinical trials phase I and II the vaccine was safe and induce cellular immune responses measured by interferon gamma enzyme-linked assay. Interferon gamma enzyme-linked assay (INF gamma ELISPOT) used is the standardize assay for cellular responses in a vaccine setting. STEP phase III trial enrolled a total of 3,000 healthy individuals. The endpoints for the STEP trial as with the VaxGen study were infection and viral load. Each volunteer received three injections of the three genes and received vaccinations two and three 6 months apart from each other. The STEP trial was stop after analysis of data collected from the ongoing study. The study was stopped due to the results pointing to increase rate of infectivity in vaccine groups. This outcome was unexpected as the volunteers in the vaccine arm of the study had quality cellular responses. Quality cellular responses were defined by moderate to high total INF gamma producing cells ELISPOT and the CD8+T cells generated were polyfunctional by ICS staining after stimulation with HIV antigens. The polyfunctional nature of the CD8+T cells was thought to be needed for the ideal response to viral load (Betts and Harari 2008; Hanke 2008). However, the STEP results had an additional element that complicated the outcome. Volunteers who had pre-existing immunity to Ad5 had a trend for higher rates of infectivity (Sekaly 2008). The failure of the STEP trial brought into scrutiny both the use of viral vectors and cellular responses as a correlate of protection. To overcome the hurdle of pre-existing immunity ways to modifying vector delivery and engineering vectors has been under investigation.

After the failure of the STEP vaccine trial, the results of the next phase III vaccine trial was of great interest. The vaccine components had a potential for inducing both cellular and humoral responses. Inducing both humoral and cellular responses to HIV antigens had been investigated as early as 1986 when recombinant vaccinia virus was used to delivery envelope gp41 and gpII0 induced both humoural and cellular responses in macaques (Zarling, Morton et al. 1986).

3.3 ALVAC and AIDSVAX clinical trial

The ALVAC and AIDSVAX clinical trial in Thailand enrolled 16402 healthy men and women between the ages of 18-30 years into the study(Rerks-Ngarm, Pitisuttithum et al. 2009). The ALVAC vaccine contains a clade E envelope and a *gag/pol* from clade B. The AIDSVAX vaccine is the B/E vaccine covered in the previous section. The vaccine trial covered multiple centers and the individuals were randomized into placebo or vaccine groups. Vaccine groups received four injection of the canarypox virus vector vaccine ALVAC, followed by two boost injections with the AIDSVAX B/E recombinant gp120. The endpoints for the trials were HIV infection and early viral loads after the first 6 months and

every 6 months thereafter for 3 years. Measurement of cellular immunogenicity was done by interferon gamma ELISPOT and intracellular cytokine staining (ICS) for antigens gag and envelope. Humoral responses were measured for binding antibodies to various gp120 envelopes and p24 (gag core). T cell responses via ELISPOT showed a 19.7 % in vaccinated individuals 6 months after the final vaccination. In addition greater cytokine responses were measured in the CD4+ T cells of vaccinated individuals. Binding antibodies to the envelopes MN and A244 present in the vaccine were similar and had a GMT-1 of 31,207 and 14588 respectively. There were only mild to moderate adverse effects mainly at the site of injection as in preliminary studies. When it came to trial endpoints there was no significant difference in viral loads of individuals who got infected whether or not they got the vaccine. Nonetheless there was a silver lining, the study recorded a 31.3% protection rate using a 95% confidence interval. This outcome resulted in ripples across the world. This was the first time any efficacy was reported in an HIV vaccine trial. However, a study did not result in the elucidation of a correlate of protection for HIV. The only immune parameter measured that should any potential as a correlate of protection was antibody binding to envelopes. This vaccine trial infused a new hope into the HIV vaccine field, showing that protection from infection was possible.

Besides establishing correlates of protection the HIV vaccine field has other hurdles to overcome. These challenges include (Moutsopoulos, Nares et al. 2007) vaccine design to overcoming variability and induce the appropriate immune response at the mucosal surface. The two main strategies being used to overcome virus variability are using centralized sequence usually based on envelopes of one or multiple clades, mosaic antigens and polyvalent vaccines consisting of multiple genes of HIV from one or multiple clades (McBurney and Ross 2008) (Santra, Korber et al. 2008; McElrath and Haynes 2010). Our lab have used consensus envelopes in an effort to expand HIV immune responses breath when compared to monovalent vaccines or a polyvalent primary envelope VLP mixture (McBurney and Ross 2009). In a review by Gao F et al. the use of centralized envelopes (consensus, center of the tree and ancestral) to induce HIV specific immune responses is covered (Gao 2007). The use of the centralized immunogens resulted in a superior breadth of cellular and humoral immune response (Kothe, Li et al. 2006; Liao, Sutherland et al. 2006; Kothe, Decker et al. 2007; Santra, Korber et al. 2008). In regard to generating mucosal immunity different vaccine strategies including vaccination at oral or vaginal in primates and use of adjuvants are being investigated to establish protective immune response at the mucosa (Peters, Peng et al. 2003; Duerr 2010; Sui, Zhu et al. 2010). To better direct the mucosal vaccine development investigation of the immune environment during infection and what is needed to prevent infection is being done (Gurney, Elliott et al. 2005; Moutsopoulos, Nares et al. 2007; Burgener, Boutilier et al. 2008; Schulbin, Bode et al. 2008).

4. Moving forward

Collaborative efforts between basic research, pharmacology, vaccinology and immunology are moving the HIV search for treatment forward. Trials aimed at investigating new drugs and therapeutic vaccines are being done worldwide (Choudhary and Margolis 2011). WHO and world governments continue to devote money to clinical trials for potential preventative measures in an effort to curb the HIV/AIDS global epidemic. The phase II and III clinical trials of preventative vaccines sponsored by National Institute of Allergy and

Infectious Diseases (NIAID) are ran by different clinical networks. The clinical networks include: 1) AIDS clinical trials groups, 2) HIV prevention trials network, 3) HIV vaccine trials Network 4) International maternal pediatric Adolescent AIDS Clinical trials, 5) International network of strategic initiatives in global HIV trials and 6) Microbicide trials network volunteers. Ongoing clinical trials can be found at the AIDSinfo website (<http://www.aidsinfo.nih.gov/Vaccines>).

In therapeutic research, studies are expanding to include drugs targeted at eliminating viral reservoirs (Huelsmann, Hofmann et al. 2011; Kovochich, Marsden et al. 2011). Follow up studies of individuals on HAART are being done to evaluating health and treatment efficacy (Mahdavi, Malyuta et al. 2010; Torti, d'Arminio-Monforte et al. 2011). Findings from these evaluations will be use to better treatments and evaluate possible side effects of long term drug use (Boyd and Hill 2010; Kranzer, Lewis et al. 2010; Shapiro, Hughes et al. 2010; Shrestha, Sudenga et al. 2010). Another area of HIV therapy receiving increase attention is the use and effectiveness of HAART in individuals with cancer and bacterial/virus co-infections such as tuberculosis, HPV (Crane, Sirivichayakul et al. 2010; Hermans, Kiragga et al. 2010; Minkoff, Zhong et al. 2010).

New strategies or modification of old strategies are being used for vaccine development as more knowledge of the virus and the immune response to the virus continue to be dissected. Table 3 shows vaccine strategies used over the years and their limitations. One example is seen in a paper by Somogyi, E., J. Xu, et al where a VLP is used to present 15 antigens(Somogyi, Xu et al. 2011). While this vaccine is design for therapeutic purposes the platform could be applied to prophylaxis vaccines as well. As with therapeutics, clinical trials for preventative vaccines are continuous taking place. The trials that are currently being done by HIV vaccine network can be found at <http://www.hvtn.org/science/trials.html>.

Vaccine Design	Limitations
Live, attenuated virus	Pathogenicity in vaccines
Inactivated viruses with adjuvants	Restricted specificity of neutralizing antibodies, absence of CTLs
Recombinant envelope protein	No neutralizing antibodies for patient isolates of HIV-1; absence of CTLs
Plasmid DNA	Limited immunogenicity in humans
Live, recombinant vectors: Poxviruses Vaccinia MVA, NYVAC Canary pox	Dissemination in immunosuppressed vaccines Limited experience in humans Limited immunogenicity in humans at achievable dosages
Gene-deleted adenovirus	Pre-existing immunity to adenovirus may limit immunogenicity
Alphaviruses, adeno-associated virus	Limited experience in humans
Envelope subunit immunogens	No elicitation of neutralizing antibodies

Table 3. HIV-1 vaccine design adapted from " Strategies for an HIV vaccine" by Norman L. Letvin (Letvin 2002)

Besides the strategies seen in the table prophylaxis treatment being investigated are topical microbicides, combination therapy of vaccines and microbicides and the use of antivirals as preventative treatment (PrEP) (Chirenje, Marrazzo et al. 2010; Mayer and Venkatesh 2010; Brinckmann, da Costa et al. 2011; Oh, Price et al. 2011). In areas where women are prohibited from use of condoms the use of effective microbicides would allow these women to protect themselves from infection. In the case of microbicides time of application is an essential part of evaluation.

The use of antiviral as post exposure treatment for healthcare workers is also under investigation. PrEP has been expanded to other individuals, including men who have sex with men. A national clinical trial was completed and results of trial were reported this year (2011). The PrEP was safe and resulted in partial efficiency in reducing HIV acquisition (DK Smith 2011). One concern of PrEP is the development of drug resistant viruses due to therapy prior to infection (Abbas, Hood et al. 2011).

The war against HIV continues to be fought with scientific innovation together with continued funding from both government and private agencies. With such continued efforts the road to epidemic control and /eradication may be closer than it was over twenty- five years ago.

5. References

- Aaron N. Endsley, N. N. S., Rodney J.Y. Ho (2008). "Combining Drug and Immune Therapy: A Potential Solution to Drug Resistance and Challenges of HIV Vaccines?" *Current HIV Research* 6: 401-410.
- Abbas, U. L., G. Hood, et al. (2011). "Factors Influencing the Emergence and Spread of HIV Drug Resistance Arising from Rollout of Antiretroviral Pre-Exposure Prophylaxis (PrEP)." *PLoS ONE* 6(4): e18165.
- Angel, J. B. a., J.-P. b. Routy, et al. (2011). "A randomized controlled trial of HIV therapeutic vaccination using ALVAC with or without Remune." *AIDS* 25(6): 731-739.
- Arno, A., L. Ruiz, et al. (1999). "Efficacy of Low-Dose Subcutaneous Interleukin-2 to Treat Advanced Human Immunodeficiency Virus Type 1 in Persons with $\geq 250/\text{CE}^{\circ}\text{L}$ CD4 T Cells and Undetectable Plasma Virus Load." *Journal of Infectious Diseases* 180(1): 56-60.
- Arthur, L. O., S. W. Pyle, et al. (1987). "Serological responses in chimpanzees inoculated with human immunodeficiency virus glycoprotein (gp120) subunit vaccine." *Proceedings of the National Academy of Sciences* 84(23): 8583-8587.
- Asquith, B. and A. R. McLean (2007). "In vivo CD8+ T cell control of immunodeficiency virus infection in humans and macaques." *Proceedings of the National Academy of Sciences* 104(15): 6365-6370.
- Baenziger, S., M. Heikenwalder, et al. (2009). "Triggering TLR7 in mice induces immune activation and lymphoid system disruption, resembling HIV-mediated pathology." *Blood* 113(2): 377-388.
- Barnett, S. W., B. Burke, et al. (2010). "Antibody-Mediated Protection against Mucosal Simian-Human Immunodeficiency Virus Challenge of Macaques Immunized with Alphavirus Replicon Particles and Boosted with Trimeric Envelope Glycoprotein in MF59 Adjuvant." *J. Virol.* 84(12): 5975-5985.

- Barre-Sinoussi, F., J. C. Chermann, et al. (1983). "Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)." *Science* 220(4599): 868-871.
- Berman, P. W., T. J. Gregory, et al. (1990). "Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160." *Nature* 345(6276): 622-625.
- Betts, M. R. and A. Harari (2008). "Phenotype and function of protective T cell immune responses in HIV." *Current Opinion in HIV and AIDS* 3(3): 349-355
310.1097/COH.1090b1013e3282fbaa1081.
- Bower, J. F., X. Yang, et al. (2004). "Elicitation of Neutralizing Antibodies with DNA Vaccines Expressing Soluble Stabilized Human Immunodeficiency Virus Type 1 Envelope Glycoprotein Trimers Conjugated to C3d." *J. Virol.* 78(9): 4710-4719.
- Boyd, M. A. and A. M. Hill (2010). "Clinical Management of Treatment-Experienced, HIV/AIDS Patients in the Combination Antiretroviral Therapy Era." *PharmacoEconomics* 28: 17-34 10.2165/11587420-000000000-000000000.
- Brinckmann, S., K. da Costa, et al. (2011). "Rational design of HIV vaccines and microbicides: report of the EUROPRIME network annual conference 2010." *Journal of Translational Medicine* 9(1): 40.
- Broder, S. (2010). "The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic." *Antiviral Research* 85(1): 1-18.
- Brown, R. J. P., P. J. Peters, et al. (2011). "Inter-compartment recombination of HIV-1 contributes to env intra-host diversity and modulates viral tropism and sensitivity to entry inhibitors." *J. Virol.*: JVI.00131-00111.
- Buonaguro, L., M. L. Tornesello, et al. (2009). "Short Communication: Limited Induction of IL-10 in PBMCs from HIV-Infected Subjects Treated with HIV-VLPs." *AIDS Research and Human Retroviruses* 25(8): 819-822.
- Burgener, A., J. Boutilier, et al. (2008). "Identification of Differentially Expressed Proteins in the Cervical Mucosa of HIV-1-Resistant Sex Workers." *Journal of Proteome Research* 7(10): 4446-4454.
- Carter, C. C., A. Onafuwa-Nuga, et al. (2010). "HIV-1 infects multipotent progenitor cells causing cell death and establishing latent cellular reservoirs." *Nat Med* 16(4): 446-451.
- Cecchinato, V., C. J. Trindade, et al. (2008). "Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques." *Mucosal Immunol* 1(4): 279-288.
- Chenine, A. L., N. B. Siddappa, et al. (2010). "Relative Transmissibility of an R5 Clade C Simian- Human Immunodeficiency Virus Across Different Mucosae in Macaques Parallels the Relative Risks of Sexual HIV-1 Transmission in Humans via Different Routes." *Journal of Infectious Diseases* 201(8): 1155-1163.
- Chirenje, Z. M., J. Marrazzo, et al. (2010). "Antiretroviral-based HIV prevention strategies for women." *Expert Review of Anti-infective Therapy* 8(10): 1177-1186.
- Choudhary, S. K. and D. M. Margolis (2011). "Curing HIV: Pharmacologic Approaches to Target HIV-1 Latency." *Annual Review of Pharmacology and Toxicology* 51(1): 397-418.

- Chouquet, C., B. Autran, et al. (2002). "Correlation between breadth of memory HIV-specific cytotoxic T cells, viral load and disease progression in HIV infection." *AIDS* 16(18): 2399-2407.
- Chun, T.-W., L. Carruth, et al. (1997). "Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection." *Nature* 387(6629): 183-188.
- Chun, T.-W., D. C. Nickle, et al. (2008). "Persistence of HIV in Gut-Associated Lymphoid Tissue despite Long-Term Antiretroviral Therapy." *Journal of Infectious Diseases* 197(5): 714-720.
- Cicccone, E. J., J. H. Greenwald, et al. (2011). "CD4+ T Cells, Including Th17 and Cycling Subsets, are Intact in the Gut Mucosa of HIV-1 Infected Long-Term Non-Progressors." *J. Virol.*: JVI.02643-02610.
- Clerici, M. a. b. (2010). "Beyond IL-17: new cytokines in the pathogenesis of HIV infection." *Current Opinion in HIV & AIDS* 5(2): 184-188.
- Committee, T. I. E. S. G. a. S. S. (2009). "Interleukin-2 Therapy in Patients with HIV Infection." *New England Journal of Medicine* 361(16): 1548-1559.
- Crabtree-Ramirez, B., A. Villasis-Keever, et al. (2010). "Effectiveness of Highly Active Antiretroviral Therapy (HAART) Among HIV-Infected Patients in Mexico." *AIDS Research and Human Retroviruses* 26(4): 373-378.
- Crane, M., S. Sirivichayakul, et al. (2010). "No Increase in Hepatitis B Virus (HBV)-Specific CD8+ T Cells in Patients with HIV-1-HBV Coinfections following HBV-Active Highly Active Antiretroviral Therapy." *J. Virol.* 84(6): 2657-2665.
- Cuevas, M. T., A. Fernandez-Garcia, et al. (2010). "Short Communication: Biological and Genetic Characterization of HIV Type 1 Subtype B and Nonsubtype B Transmitted Viruses: Usefulness for Vaccine Candidate Assessment." *AIDS Research and Human Retroviruses* 26(9): 1019-1025.
- D'Orsogna, L. J. a., R. G. b. Krueger, et al. (2007). "Circulating memory B-cell subpopulations are affected differently by HIV infection and antiretroviral therapy." *AIDS* 21(13): 1747-1752.
- Davenport, M. P., R. M. Ribeiro, et al. (2004). "Predicting the Impact of a Nonsterilizing Vaccine against Human Immunodeficiency Virus." *J. Virol.* 78(20): 11340-11351.
- Davey, R. T., D. G. Chaitt, et al. (1999). "A Randomized Trial of High-versus Low-Dose Subcutaneous Interleukin-2 Outpatient Therapy for Early Human Immunodeficiency Virus Type 1 Infection." *Journal of Infectious Diseases* 179(4): 849-858.
- De Clercq, E. (2010). "Antiretroviral drugs." *Current Opinion in Pharmacology* 10(5): 507-515.
- Delelis, O., K. Carayon, et al. (2008). "Integrase and integration: biochemical activities of HIV-1 integrase." *Retrovirology* 5(1): 114.
- DK Smith, M., RM Grant, MD, PJ Weidle, PharmD, A Lansky, PhD, J Mermin, MD, KA Fenton, MD, PhD, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC. (2011). Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR Weekly, Centers for Disease Control and Prevention (CDC)*. 60: 65-68.

- Douek, D. C., J. M. Brenchley, et al. (2002). "HIV preferentially infects HIV-specific CD4+ T cells." *Nature* 417(6884): 95-98.
- Duerr, A. (2010). "Update on mucosal HIV vaccine vectors." *Current Opinion in HIV and AIDS* 5(5): 397-403 310.1097/COH.1090b1013e32833d32832e32839.
- Egan, M. A., W. A. Pavlat, et al. (1995). "Induction of Human Immunodeficiency Virus Type 1 (HIV-1)-Specific Cytolytic T Lymphocyte Responses in Seronegative Adults by a Nonreplicating, Host-Range-Restricted Canarypox Vector (ALVAC) Carrying the HIV-1MN env Gene." *Journal of Infectious Diseases* 171(6): 1623-1627.
- Emini, E. A., W. A. Schleif, et al. (1992). "Prevention of HIV-1 infection in chimpanzees by gp120 V3 domain-specific monoclonal antibody." *Nature* 355(6362): 728-730.
- Engelman, A., G. Englund, et al. (1995). "Multiple effects of mutations in human immunodeficiency virus type 1 integrase on viral replication." *J. Virol.* 69(5): 2729-2736.
- Ensolli, B., S. Bellino, et al. (2010). "Therapeutic Immunization with HIV-1 Tat Reduces Immune Activation and Loss of Regulatory T-Cells and Improves Immune Function in Subjects on HAART." *PLoS ONE* 5(11): e13540.
- Fauci, A. S., D. Mavilio, et al. (2005). "NK cells in HIV infection: Paradigm for protection or targets for ambush." *Nat Rev Immunol* 5(11): 835-843.
- Ferain, T., H. R. Hoveyda, et al. (2011). "Agonist-induced internalization of CCR5 as a mechanism to inhibit HIV replication." *Journal of Pharmacology and Experimental Therapeutics*.
- Fernandez, S., A. Lim, et al. (2009). "Immune activation and the pathogenesis of HIV disease: implications for therapy.(LEADING ARTICLE)(Report)." *Journal of HIV Therapy* 14(3): 52(55).
- Fernandez-Cruz, E., J. Navarro, et al. (2003). "The potential role of the HIV-1 immunogen (Remune γ Æ) as a therapeutic vaccine in the treatment of HIV infection." *Expert Review of Vaccines* 2(6): 739-752.
- Fernandez-Cruz, E., J. n. Navarro, et al. (2003). "The potential role of the HIV-1 immunogen (Remune γ Æ) as a therapeutic vaccine in the treatment of HIV infection." *Expert Review of Vaccines* 2(6): 739-752.
- Finkel, T. H., G. Tudor-Williams, et al. (1995). "Apoptosis occurs predominantly in bystander cells and not in productively infected cells of HIV- and SIV-infected lymph nodes." *Nat Med* 1(2): 129-134.
- Finzi, D., J. Blankson, et al. (1999). "Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy." *Nat Med* 5(5): 512-517.
- Follmann, D. P., A. M. D. P. M. P. H. H. Duerr, et al. (2007). "Endpoints and Regulatory Issues in HIV Vaccine Clinical Trials: Lessons From a Workshop." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 44(1): 49-60.
- Francis DP, G. T., McElrath MJ, Belshe RB, Gorse GJ, Migasena S, Kitayaporn D, Pitisuttitham P, Matthews T, Schwartz DH, Berman PW (1998). "Advancing AIDSVAX to phase 3. Safety, immunogenicity, and plans for phase 3." *AIDS Res Hum Retroviruses.* 14(Suppl 3): S325-331.

- Gallo, R. C., P. S. Sarin, et al. (1983). "Isolation of Human T-Cell Leukemia Virus in Acquired Immune Deficiency Syndrome (AIDS)." *Science* 220(4599): 865-867.
- Gao, F. L., Hua-Xin; Hahn, Beatrice H.; Letvin, Norman L.; Korber, Bette T.; Haynes, Barton F. (2007). "Centralized HIV-1 Envelope Immunogens and Neutralizing Antibodies." *Current HIV Research* 5: 572-577.
- Gorse, G. J., R. E. Simionescu, et al. (2006). "Cellular Immune Responses in Asymptomatic Human Immunodeficiency Virus Type 1 (HIV-1) Infection and Effects of Vaccination with Recombinant Envelope Glycoprotein of HIV-1." *Clin. Vaccine Immunol.* 13(1): 26-32.
- Green, T. D., D. C. Montefiori, et al. (2003). "Enhancement of Antibodies to the Human Immunodeficiency Virus Type 1 Envelope by Using the Molecular Adjuvant C3d." *J. Virol.* 77(3): 2046-2055.
- Greenbaum, A. H., L. E. Wilson, et al. (2008). "Effect of age and HAART regimen on clinical response in an urban cohort of HIV-infected individuals." *AIDS* 22(17): 2331-2339
2310.1097/QAD.2330b2013e32831883f32831889.
- Gudmundsdotter, L., C. Nilsson, et al. (2009). "Recombinant Modified Vaccinia Ankara (MVA) effectively boosts DNA-primed HIV-specific immune responses in humans despite pre-existing vaccinia immunity." *Vaccine* 27(33): 4468-4474.
- Gulick, R. M., J. Lalezari, et al. (2008). "Maraviroc for Previously Treated Patients with R5 HIV-1 Infection." *New England Journal of Medicine* 359(14): 1429-1441.
- Gulick, R. M., J. W. Mellors, et al. (1997). "Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy." *New England Journal of Medicine* 337(11): 734-739.
- Gurney, K. B., J. Elliott, et al. (2005). "Binding and Transfer of Human Immunodeficiency Virus by DC-SIGN+ Cells in Human Rectal Mucosa." *J. Virol.* 79(9): 5762-5773.
- Gurunathan, S., R. E. Habib, et al. (2009). "Use of predictive markers of HIV disease progression in vaccine trials." *Vaccine* 27(14): 1997-2015.
- Hanke, T. (2008). "STEP trial and HIV-1 vaccines inducing T-cell responses." *Expert Review of Vaccines* 7: 303-309.
- Hartigan-O'Connor, D. J., L. A. Hirao, et al. (2011). "Th17 cells and regulatory T cells in elite control over HIV and SIV." *Current Opinion in HIV and AIDS* 6(3): 221-227
210.1097/COH.1090b1013e32834577b32834573.
- Hermans, S. M., A. N. Kiragga, et al. (2010). "Incident Tuberculosis during Antiretroviral Therapy Contributes to Suboptimal Immune Reconstitution in a Large Urban HIV Clinic in Sub-Saharan Africa." *PLoS ONE* 5(5): e10527.
- Hofer, U. and R. Speck (2009). "Disturbance of the gut-associated lymphoid tissue is associated with disease progression in chronic HIV infection." *Seminars in Immunopathology* 31(2): 257-266.
- Huelsmann, P., A. Hofmann, et al. (2011). "A suicide gene approach using the human proapoptotic protein tBid inhibits HIV-1 replication." *BMC Biotechnology* 11(1): 4.
- Jaoko, W., E. Karita, et al. (2010). "Safety and Immunogenicity Study of Multiclade HIV-1 Adenoviral Vector Vaccine Alone or as Boost following a Multiclade HIV-1 DNA Vaccine in Africa." *PLoS ONE* 5(9): e12873.

- Jiang, Y. L., Xinyong; De Clercq, Erik (2011). "New Therapeutic Approaches Targeted at the Late Stages of the HIV-1 Replication Cycle." *Current Medicinal Chemistry* 18: 16-28.
- John, M., C. B. Moore, et al. (2001). "Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy." *AIDS* 15(6): 717-723.
- Joly, V., K. Jidar, et al. (2010). "Enfuvirtide: from basic investigations to current clinical use." *Expert Opinion on Pharmacotherapy* 11(16): 2701-2713.
- Jose Esparza, W. L. H., Saladin Osmanov (1996). "HIV Vaccine Development." *AIDS* 10(suppl): S123-S132.
- Kannanganat, S., B. G. Kapogiannis, et al. (2007). "Human Immunodeficiency Virus Type 1 Controllers but Not Noncontrollers Maintain CD4 T Cells Coexpressing Three Cytokines." *J. Virol.* 81(21): 12071-12076.
- Keefer, M. C., S. E. Frey, et al. (2011). "A phase I trial of preventive HIV vaccination with heterologous poxviral-vectors containing matching HIV-1 inserts in healthy HIV-uninfected subjects." *Vaccine* 29(10): 1948-1958.
- Kelley, C. F., J. D. Barbour, et al. (2007). "The Relation Between Symptoms, Viral Load, and Viral Load Set Point in Primary HIV Infection." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 45(4): 445-448 410.1097/QAI.1090b1013e318074ef318076e.
- Kilby, J. M. (1999). "Therapeutic potential of blocking HIV entry into cells: focus on membrane fusion inhibitors." *Expert Opinion on Investigational Drugs* 8(8): 1157-1170.
- Kilby, J. M., S. Hopkins, et al. (1998). "Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry." *Nat Med* 4(11): 1302-1307.
- Kilby, J. M., J. P. Lalezari, et al. (2002). "The Safety, Plasma Pharmacokinetics, and Antiviral Activity of Subcutaneous Enfuvirtide (T-20), a Peptide Inhibitor of gp41-Mediated Virus Fusion, in HIV-Infected Adults." *AIDS Research and Human Retroviruses* 18(10): 685-693.
- Kolte, L., J. C. Gaardbo, et al. (2011). "Dysregulation of CD4+CD25+CD127lowFOXP3+ regulatory T cells in HIV-infected pregnant women." *Blood* 117(6): 1861-1868.
- Kothe, D. L., J. M. Decker, et al. (2007). "Antigenicity and immunogenicity of HIV-1 consensus subtype B envelope glycoproteins." *Virology* 360(1): 218-234.
- Kothe, D. L., Y. Li, et al. (2006). "Ancestral and consensus envelope immunogens for HIV-1 subtype C." *Virology* 352(2): 438-449.
- Kovochich, M., M. D. Marsden, et al. (2011). "Activation of Latent HIV Using Drug-Loaded Nanoparticles." *PLoS ONE* 6(4): e18270.
- Kranzer, K., J. J. Lewis, et al. (2010). "Treatment Interruption in a Primary Care Antiretroviral Therapy Program in South Africa: Cohort Analysis of Trends and Risk Factors." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 55(3): e17-e23 10.1097/QAI.1090b1013e3181f1275fd.
- Kronenberg, A., H. M. Riehle, et al. (2001). "Liver failure after long-term nucleoside antiretroviral therapy." *The Lancet* 358(9283): 759-760.
- Kuhr, D., S. A. Faith, et al. (2010). "Evidence of Early B-Cell Dysregulation in Simian Immunodeficiency Virus Infection: Rapid Depletion of Naive and Memory B-Cell Subsets with Delayed Reconstitution of the Naive B-Cell Population." *J. Virol.* 84(5): 2466-2476.

- Kutscher, S., S. Allgayer, et al. (2010). "MVA-nef induces HIV-1-specific polyfunctional and proliferative T-cell responses revealed by the combination of short- and long-term immune assays." *Gene Ther* 17(11): 1372-1383.
- Lane, H. C. and A. S. Fauci (1985). "Immunologic Abnormalities in the Acquired Immunodeficiency Syndrome." *Annual Review of Immunology* 3(1): 477-500.
- Langlois, A. J., K. J. Weinhold, et al. (1992). "Detection of Anti-Human Cell Antibodies in Sera from Macaques Immunized with Whole Inactivated Virus." *AIDS Research and Human Retroviruses* 8(9): 1641-1652.
- Lasky, L., J. Groopman, et al. (1986). "Neutralization of the AIDS retrovirus by antibodies to a recombinant envelope glycoprotein." *Science* 233(4760): 209-212.
- Latinovic, O. a., N. a. Le, et al. "Synergistic inhibition of R5 HIV-1 by maraviroc and CCR5 antibody HGS004 in primary cells: implications for treatment and prevention." *AIDS*.
- Lavreys, L., J. M. Baeten, et al. (2006). "Higher Set Point Plasma Viral Load and More-Severe Acute HIV Type 1 (HIV-1) Illness Predict Mortality among High-Risk HIV-1-Infected African Women." *Clinical Infectious Diseases* 42(9): 1333-1339.
- Lehner, T., G. M. Shearer, et al. (2000). "Alloimmunization as a Strategy for Vaccine Design against HIV/AIDS." *AIDS Research and Human Retroviruses* 16(4): 309-313.
- Lerner, P., M. Guadalupe, et al. (2011). "The Gut Mucosal Viral Reservoir in HIV-Infected Patients Is Not the Major Source of Rebound Plasma Viremia following Interruption of Highly Active Antiretroviral Therapy." *J. Virol.* 85(10): 4772-4782.
- Letang, E., J. M. Miro, et al. (2011). "Incidence and Predictors of Immune Reconstitution Inflammatory Syndrome in a Rural Area of Mozambique." *PLoS ONE* 6(2): e16946.
- Letvin, N. L. (2002). "Strategies for an HIV vaccine." *The Journal of Clinical Investigation* 110(1): 15-27.
- Levy, Y., C. Capitani, et al. (1999). "Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial." *The Lancet* 353(9168): 1923-1929.
- Liao, H.-X., L. L. Sutherland, et al. (2006). "A group M consensus envelope glycoprotein induces antibodies that neutralize subsets of subtype B and C HIV-1 primary viruses." *Virology* 353(2): 268-282.
- Lin, J.-N., C.-H. Lai, et al. (2010). "Immune reconstitution inflammatory syndrome presenting as chylothorax in a patient with HIV and Mycobacterium tuberculosis coinfection: a case report." *BMC Infectious Diseases* 10(1): 321.
- Ltd., A. I. (2003). "HIV gp120 Vaccine - VaxGen: AIDSVAX(TM), AIDSVAX(TM) B/B, AIDSVAX(TM) B/E, HIV gp120 Vaccine - Genentech, HIV gp120 Vaccine AIDSVAX - VaxGen, HIV Vaccine AIDSVAX - VaxGen." *Drugs in R&D* 4(4): 249-253.
- M Roederer, J. G. D., M T Anderson, P A Raju, L A Herzenberg, and L A Herzenberg (1995). "CD8 naive T cell counts decrease progressively in HIV-infected adults." *J Clin Invest.* 95(5): 2061-2066.
- MacLachlan, E., K. H. Mayer, et al. (2009). "The Potential Role of Biomarkers in HIV Preventive Vaccine Trials." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 51(5): 536-545 510.1097/QAI.1090b1013e3181adcbbe.

- Mahdavi, S., R. Malyuta, et al. (2010). "Treatment and disease progression in a birth cohort of vertically HIV-1 infected children in Ukraine." *BMC Pediatrics* 10(1): 85.
- Malek, T. R. and I. Castro (2010). "Interleukin-2 Receptor Signaling: At the Interface between Tolerance and Immunity." *Immunity* 33(2): 153-165.
- Maloy, K. J. and M. C. Kullberg (2008). "IL-23 and Th17 cytokines in intestinal homeostasis." *Mucosal Immunol* 1(5): 339-349.
- Mayer, K. H. and K. K. Venkatesh (2010). "Chemoprophylaxis for HIV Prevention: New Opportunities and New Questions." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 55: S122-S127 110.1097/QAI.1090b1013e3181fbc1094c.
- McBurney, S. P. and T. M. Ross (2008). "Viral sequence diversity: challenges for AIDS vaccine designs." *Expert Review of Vaccines* 7(9): 1405-1417.
- McBurney, S. P. and T. M. Ross (2009). "Human immunodeficiency virus-like particles with consensus envelopes elicited broader cell-mediated peripheral and mucosal immune responses than polyvalent and monovalent Env vaccines." *Vaccine* 27(32): 4337-4349.
- McBurney, S. P., K. R. Young, et al. (2007). "Membrane embedded HIV-1 envelope on the surface of a virus-like particle elicits broader immune responses than soluble envelopes." *Virology* 358(2): 334-346.
- McElrath, M. J. and B. F. Haynes (2010). "Induction of Immunity to Human Immunodeficiency Virus Type-1 by Vaccination." *Immunity* 33(4): 542-554.
- Michel, P., A. T. Balde, et al. (2000). "Reduced Immune Activation and T Cell Apoptosis in Human Immunodeficiency Virus Type 2 Compared with Type 1: Correlation of T Cell Apoptosis with $\alpha 2$ Microglobulin Concentration and Disease Evolution." *Journal of Infectious Diseases* 181(1): 64-75.
- Miedema, F. (2008). "A brief history of HIV vaccine research: stepping back to the drawing board?" *AIDS* 22(14): 1699-1703.
- Migasena, S., P. Suntharasamai, et al. (2000). "AIDSVAX- μ E (MN) in Bangkok Injecting Drug Users: A Report on Safety and Immunogenicity, Including Macrophage-Tropic Virus Neutralization." *AIDS Research and Human Retroviruses* 16(7): 655-663.
- Milush, J. M., K. D. Mir, et al. (2011). "Lack of clinical AIDS in SIV-infected sooty mangabeys with significant CD4+ T cell loss is associated with double-negative T cells." *The Journal of Clinical Investigation* 121(3): 1102-1110.
- Minkoff, H., Y. Zhong, et al. (2010). "Influence of Adherent and Effective Antiretroviral Therapy Use on Human Papillomavirus Infection and Squamous Intraepithelial Lesions in Human Immunodeficiency Virus, μ Positive Women." *Journal of Infectious Diseases* 201(5): 681-690.
- Mitsuya, H., K. J. Weinhold, et al. (1985). "3'-Azido-3'-deoxythymidine (BW A509U): an antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro." *Proceedings of the National Academy of Sciences* 82(20): 7096-7100.
- Montagnier, L. (2010). "25†years after HIV discovery: Prospects for cure and vaccine." *Virology* 397(2): 248-254.

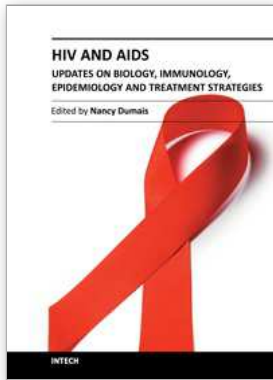
- Monteiro, J. P., L. C. J. Alcantara, et al. (2009). "Genetic variability of human immunodeficiency virus-1 in Bahia state, Northeast, Brazil: High diversity of HIV genotypes." *Journal of Medical Virology* 81(3): 391-399.
- Moss, R. B., M. R. Wallace, et al. (1999). "Phenotypic Analysis of Human Immunodeficiency Virus (HIV) Type 1 Cell-Mediated Immune Responses after Treatment with an HIV-1 Immunogen." *Journal of Infectious Diseases* 180(3): 641-648.
- Mosser, D. M. (2003). "The many faces of macrophage activation." *Journal of Leukocyte Biology* 73(2): 209-212.
- Moutsopoulos, N. M., S. Nares, et al. (2007). "Tonsil Epithelial Factors May Influence Oropharyngeal Human Immunodeficiency Virus Transmission." *The American Journal of Pathology* 171(2): 571-579.
- Nanjundappa, R. H., R. Wang, et al. (2011). "GP120-specific exosome-targeted T cell-based vaccine capable of stimulating DC- and CD4+ T-independent CTL responses." *Vaccine* 29(19): 3538-3547.
- Nkolola, J. P., H. Peng, et al. (2010). "Breadth of Neutralizing Antibodies Elicited by Stable, Homogeneous Clade A and Clade C HIV-1 gp140 Envelope Trimers in Guinea Pigs." *J. Virol.* 84(7): 3270-3279.
- Nobuto Yamamoto, N. U., and Yoshihiko Koga (2009). "Immunotherapy of HIV-Infected Patients With Gc Protein-Derived Macrophage Activating Factor (GcMAF)." *Journal of Medical Virology* 81: 16-26.
- O'Connell, K. A., J. R. Bailey, et al. (2009). "Elucidating the elite: mechanisms of control in HIV-1 infection." *Trends in Pharmacological Sciences* 30(12): 631-637.
- Oh, C., J. Price, et al. (2011). "Inhibition of HIV-1 infection by aqueous extracts of *Prunella vulgaris* L." *Virology Journal* 8(1): 188.
- Okulicz, J. F. and O. Lambotte (2011). "Epidemiology and clinical characteristics of elite controllers." *Current Opinion in HIV and AIDS* 6(3): 163-168
110.1097/COH.1090b1013e328344f328335e.
- Paci, P., F. Martini, et al. (2011). "Timely HAART initiation may pave the way for a better viral control." *BMC Infectious Diseases* 11(1): 56.
- Pantaleo, G. and R. A. Koup (2004). "Correlates of immune protection in HIV-1 infection: what we know, what we don't know, what we should know." *Nat Med* 10(8): 806-810.
- Paroli, M., A. Propato, et al. (2001). "The immunology of HIV-infected long-term non-progressors--a current view." *Immunology Letters* 79(1-2): 127-129.
- Peters, B. S. (2000). "HIV immunotherapeutic vaccines." *Antiviral Chemistry & Chemotherapy* 11(5): 311-320.
- Peters, B. S. and M. Samuel (2010). "Implications of the SILCAAT and ESPRIT trials and the future for HIV immunotherapy.(LEADING ARTICLE)(human immunodeficiency virus)(enhanced suppression of the platelet IIb/IIIa receptor with integrilin therapy)(study of interleukin-2 in people with low CD4+ T cell counts on active anti-human immunodeficiency virus therapy)(Report)." *Journal of HIV Therapy* 15(1): 15(13).
- Peters, C., X. Peng, et al. (2003). "The Induction of HIV Gag-Specific CD8+ T Cells in the Spleen and Gut-Associated Lymphoid Tissue by Parenteral or Mucosal

- Immunization with Recombinant *Listeria monocytogenes* HIV Gag." *The Journal of Immunology* 170(10): 5176-5187.
- Peto, T. (1996). "Surrogate markers in HIV disease." *Journal of Antimicrobial Chemotherapy* 37(suppl B): 161-170.
- Pett, S. L. (2009). "Immunotherapies in HIV-1 infection." *Current Opinion in HIV & AIDS* 4(3): 188-193.
- Pincus, S. H., K. G. Messer, et al. (1993). "Differences in the antibody response to human immunodeficiency virus-1 envelope glycoprotein (gp160) in infected laboratory workers and vaccinees." *The Journal of Clinical Investigation* 91(5): 1987-1996.
- Pine, S. O., J. G. Kublin, et al. (2011). "Pre-Existing Adenovirus Immunity Modifies a Complex Mixed Th1 and Th2 Cytokine Response to an Ad5/HIV-1 Vaccine Candidate in Humans." *PLoS ONE* 6(4): e18526.
- Polo, J. M. and T. W. Dubensky (2002). "Virus-based vectors for human vaccine applications." *Drug Discovery Today* 7(13): 719-727.
- Prince, A. M., H. Reesink, et al. (1991). "Prevention of HIV Infection by Passive Immunization with HIV Immunoglobulin." *AIDS Research and Human Retroviruses* 7(12): 971-973.
- Profile, A. R. D. (2003). "HIV gp120 Vaccine - VaxGen: AIDSVAX(TM), AIDSVAX(TM) B/B, AIDSVAX(TM) B/E, HIV gp120 Vaccine - Genentech, HIV gp120 Vaccine AIDSVAX - VaxGen, HIV Vaccine AIDSVAX - VaxGen." *Drugs in R&D* 4(4): 249-253.
- Putkonen, P., R. Thorstensson, et al. (1991). "Prevention of HIV-2 and SIVsm infection by passive immunization in cynomolgus monkeys." *Nature* 352(6334): 436-438.
- Ranasinghe, C., F. Eyers, et al. (2011). "A comparative analysis of HIV-specific mucosal/systemic T cell immunity and avidity following rDNA/rFPV and poxvirus-poxvirus prime boost immunisations." *Vaccine* 29(16): 3008-3020.
- Redfield, R. R., D. L. Birx, et al. (1991). "A Phase I Evaluation of the Safety and Immunogenicity of Vaccination with Recombinant gp160 in Patients with Early Human Immunodeficiency Virus Infection." *New England Journal of Medicine* 324(24): 1677-1684.
- Rerks-Ngarm, S., P. Pitisuttithum, et al. (2009). "Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand." *New England Journal of Medicine* 361(23): 2209-2220.
- Robertson, D. L., J. P. Anderson, et al. (2000). "HIV-1 Nomenclature Proposal." *Science* 288(5463): 55.
- Rodes, B., C. Toro, et al. (2004). "Differences in disease progression in a cohort of long-term non-progressors after more than 16 years of HIV-1 infection." *AIDS* 18(8): 1109-1116.
- Rosario, M., A. Bridgeman, et al. (2010). "Long peptides induce polyfunctional T cells against conserved regions of HIV-1 with superior breadth to single-gene vaccines in macaques." *European Journal of Immunology* 40(7): 1973-1984.
- Rosenberg, E. S., B. S. Graham, et al. (2010). "Safety and Immunogenicity of Therapeutic DNA Vaccination in Individuals Treated with Antiretroviral Therapy during Acute/Early HIV-1 Infection." *PLoS ONE* 5(5): e10555.

- Sabado, R. L., M. O'Brien, et al. (2010). "Evidence of dysregulation of dendritic cells in primary HIV infection." *Blood* 116(19): 3839-3852.
- Salgado, M., N. I. Rallun, et al. (2011). "Long-term non-progressors display a greater number of Th17 cells than HIV-infected typical progressors." *Clinical Immunology* 139(2): 110-114.
- Salgado, M., N. I. Rallun, et al. (2011). "Long-term non-progressors display a greater number of Th17 cells than HIV-infected typical progressors." *Clinical Immunology* 139(2): 110-114.
- Santra, S., B. T. Korber, et al. (2008). "A centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys." *Proceedings of the National Academy of Sciences* 105(30): 10489-10494.
- Schulbin, H., H. Bode, et al. (2008). "Cytokine Expression in the Colonic Mucosa of Human Immunodeficiency Virus-Infected Individuals before and during 9 Months of Antiretroviral Therapy." *Antimicrob. Agents Chemother.* 52(9): 3377-3384.
- Sekaly, R.-P. (2008). "The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?" *The Journal of Experimental Medicine* 205(1): 7-12.
- Shapiro, R. L., M. D. Hughes, et al. (2010). "Antiretroviral Regimens in Pregnancy and Breast-Feeding in Botswana." *New England Journal of Medicine* 362(24): 2282-2294.
- Shiver, J. W., T.-M. Fu, et al. (2002). "Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity." *Nature* 415(6869): 331-335.
- Shrestha, S., S. Sudenga, et al. (2010). "The impact of highly active antiretroviral therapy on prevalence and incidence of cervical human papillomavirus infections in HIV-positive adolescents." *BMC Infectious Diseases* 10(1): 295.
- Siliciano, J. D. and R. F. Siliciano (2004). "A long-term latent reservoir for HIV-1: discovery and clinical implications." *Journal of Antimicrobial Chemotherapy* 54(1): 6-9.
- Sistigu, A., L. Bracci, et al. (2011). "Strong CD8+ T cell antigenicity and immunogenicity of large foreign proteins incorporated in HIV-1 VLPs able to induce a Nef-dependent activation/maturation of dendritic cells." *Vaccine* 29(18): 3465-3475.
- Somogyi, E., J. Xu, et al. (2011). "A plasmid DNA immunogen expressing fifteen protein antigens and complex virus-like particles (VLP+) mimicking naturally occurring HIV." *Vaccine* 29(4): 744-753.
- Streeck, H. and D. F. Nixon (2010). "T Cell Immunity in Acute HIV-1 Infection." *Journal of Infectious Diseases* 202(Supplement 2): S302-S308.
- Sui, Y., Q. Zhu, et al. (2010). "Innate and adaptive immune correlates of vaccine and adjuvant-induced control of mucosal transmission of SIV in macaques." *Proceedings of the National Academy of Sciences* 107(21): 9843-9848.
- Sukeepaisarncharoen, W., V. Churdboonchart, et al. (2001). "Long-term follow-up of HIV-1-infected Thai patients immunized with Remune monotherapy." *HIV Clinical Trials* 2(5): 391-398.
- Sundling, C., M. N. E. Forsell, et al. (2010). "Soluble HIV-1 Env trimers in adjuvant elicit potent and diverse functional B cell responses in primates." *The Journal of Experimental Medicine* 207(9): 2003-2017.

- Sundling, C., S. O'Dell, et al. (2010). "Immunization with Wild-Type or CD4-Binding-Defective HIV-1 Env Trimers Reduces Viremia Equivalently following Heterologous Challenge with Simian-Human Immunodeficiency Virus." *J. Virol.* 84(18): 9086-9095.
- Tappuni, A. R. (2011). "Immune Reconstitution Inflammatory Syndrome." *Advances in Dental Research* 23(1): 90-96.
- Torti, C., A. d'Arminio-Monforte, et al. (2011). "Long-term CD4+ T-cell count evolution after switching from regimens including HIV nucleoside reverse transcriptase inhibitors (NRTI) plus protease inhibitors to regimens containing NRTI plus non-NRTI or only NRTI." *BMC Infectious Diseases* 11(1): 23.
- Tsoukas, C. M., J. Raboud, et al. (1998). "Active Immunization of Patients with HIV Infection: A Study of the Effect of VaxSyn, a Recombinant HIV Envelope Subunit Vaccine, on Progression of Immunodeficiency." *AIDS Research and Human Retroviruses* 14(6): 483-490.
- Vaine, M., S. Lu, et al. (2009). "Progress on the Induction of Neutralizing Antibodies Against HIV Type 1 (HIV-1)." *BioDrugs* 23(3): 137-153. 110.2165/00063030-200923030-200900001.
- Van Gulck, E. F. V. T., Viggo; N. Berneman, Zwi; Vanham, Guido (2010). "Role of Dendritic Cells in HIV-Immunotherapy." *Current HIV Research* 8(4): 310-322.
- Virgin, H. W. and B. D. Walker (2010). "Immunology and the elusive AIDS vaccine." *Nature* 464(7286): 224-231.
- Von Kleist, M., S. Menz, et al. (2011). "HIV Quasispecies Dynamics during Pro-Active Treatment Switching: Impact on Multi-Drug Resistance and Resistance Archiving in Latent Reservoirs." *PLoS ONE* 6(3): e18204.
- Wild, C., T. Greenwell, et al. (1993). "A Synthetic Peptide from HIV-1 gp41 Is a Potent Inhibitor of Virus-Mediated Cell-Cell Fusion." *AIDS Research and Human Retroviruses* 9(11): 1051-1053.
- Wild, C., T. Oas, et al. (1992). "A Synthetic Peptide Inhibitor of Human Immunodeficiency Virus Replication: Correlation between Solution Structure and Viral Inhibition." *Proceedings of the National Academy of Sciences of the United States of America* 89(21): 10537-10541.
- Wild, C. T., D. C. Shugars, et al. (1994). "Peptides Corresponding to a Predictive C₁-Helical Domain of Human Immunodeficiency Virus Type 1 gp41 are Potent Inhibitors of Virus Infection." *Proceedings of the National Academy of Sciences of the United States of America* 91(21): 9770-9774.
- Wilson, N. A., B. F. Keele, et al. (2009). "Vaccine-Induced Cellular Responses Control Simian Immunodeficiency Virus Replication after Heterologous Challenge." *J. Virol.* 83(13): 6508-6521.
- Wintsch, J., C.-L. Chagnat, et al. (1991). "Safety and Immunogenicity of a Genetically Engineered Human Immunodeficiency Virus Vaccine." *Journal of Infectious Diseases* 163(2): 219-225.
- Wong, J. K., M. Hezareh, et al. (1997). "Recovery of Replication-Competent HIV Despite Prolonged Suppression of Plasma Viremia." *Science* 278(5341): 1291-1295.

- World Health Organization, W. (2006). ANTIRETROVIRAL THERAPY FOR HIV Infection in adults and adolescents: Recommendations for a public health approach W. H. A. Programme, World Health Organization 1-134.
- World Health Organization, W. (2009). "Global summary of the AIDS epidemic." Retrieved 02.11.2011, 2011, from http://www.who.int/hiv/data/2009_global_summary.png.
- Yamamoto, N., N. Ushijima, et al. (2009). "Immunotherapy of HIV-infected patients with Gc protein-derived macrophage activating factor (GcMAF)." *Journal of Medical Virology* 81(1): 16-26.
- Young, K. R., J. M. Smith, et al. (2004). "Characterization of a DNA vaccine expressing a human immunodeficiency virus-like particle." *Virology* 327(2): 262-272.
- Zarling, J. M., W. Morton, et al. (1986). "T-cell responses to human AIDS virus in macaques immunized with recombinant vaccinia viruses." *Nature* 323(6086): 344-346.



HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies

Edited by Dr. Nancy Dumais

ISBN 978-953-307-665-2

Hard cover, 694 pages

Publisher InTech

Published online 26, October, 2011

Published in print edition October, 2011

The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, "From the laboratory to the clinic," and the second part, "From the clinic to the patients," represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Hermancia S. Eugene and Ted M. Ross (2011). Immunotherapies and Vaccines, HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies, Dr. Nancy Dumais (Ed.), ISBN: 978-953-307-665-2, InTech, Available from: <http://www.intechopen.com/books/hiv-and-aids-updates-on-biology-immunology-epidemiology-and-treatment-strategies/immunotherapies-and-vaccines>

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