Towards a Functional Cure for HIV Infection: 
The Potential Contribution of Therapeutic Vaccination

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1. Introduction

Human immunodeficiency virus (HIV-1) currently infects 33.3 million people globally. In 2009, 1.8 million people died from acquired immunodeficiency syndrome (AIDS) marking a decline in AIDS deaths by 19% since 1999, the estimated peak of the pandemic. This is largely due to the introduction of combination antiretroviral therapy (ART) in 1996 and its expanding access in recent years. However, despite continued efforts to improve ART availability worldwide, only 5 of the estimated 15 million people living with HIV-1 in low- and middle-income countries have access (UNAIDS, 2010). Furthermore, the number of new infections continues to outpace the number of people being put on ART each day. ART is costly, and places a formidable financial burden on healthcare services. This in turn compromises efforts for universal access.

Combination ART has made a significant impact on HIV-1 morbidity and mortality (Vittinghoff et al., 1999, Palella et al., 2006) and represents the ‘gold standard’ for HIV-1 treatment. Despite early optimism that combination ART could potentially eradicate infection (Perelson et al., 1996, Ho, 1997), it has since become clear that virus invariably returns if ART is stopped. As a result, ART remains a daily lifelong treatment requiring a high level of compliance to avoid the development of (multi) drug resistance.

Where ART is available, the diagnosis ‘AIDS’ becomes less frequent, and HIV-1 infection may no longer be considered a irrevocable terminal disease but rather a chronic manageable infection. However, recent studies have observed that ART does not restore life expectancy completely (Neuhaus et al., 2010a; The Antiretroviral Therapy Cohort, 2008). Furthermore, as those living with HIV-1 do become older, age-related toxicities emerge (Powderly, 2007, 2010) as well as other ART co-morbidities such as increased risk of cardiovascular disease, metabolic disorders, neurocognitive abnormalities, liver and renal disease, bone disorders, malignancy and frailty (Deeks & Phillips, 2009).

Untreated HIV-1 infection is characterised by a substantial depletion of CD4+ T-cells in the mucosa as well as a gradual progressive decline of CD4+ T-cells in peripheral blood. When CD4+ T-cell levels in peripheral blood fall below 200 cells/mm³, immune competence is reduced leading to susceptibility to opportunistic infections and conditions that characterise AIDS as well as significant increases in viral load (Levy, 2007). It is primarily the level of CD4+ T-cells in peripheral blood that determines the requirement for ART (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2011).
In recent years it has become apparent that disease progression in HIV-1 infection is not simply due to a loss of CD4+ T-cells as a result of chronic cytopathic viral infection. Instead, HIV-1 infection is accompanied by a progressive generalised immune activation (Neuhaus et al., 2010b; Kuller et al., 2008). Indeed, expression of the activation marker CD38 particularly on CD8+ T-cells has been found to be more predictive of disease progression than viral load (Giorgi et al., 1993; Hazenberg et al., 2003). Although immune activation may be reduced on effective ART, it is not completely absent but remains higher than in uninfected individuals. This may in part explain the loss and/or lack of optimal gain in CD4+ T-cell counts despite effective viral suppression below the level of detection (Hunt et al., 2003). It is intriguing that a similar immune activation is also observed in rhesus macaques infected with simian immunodeficiency virus (SIVsmm or SIVagm) but not in the natural host for these viruses, the sooty mangabey and African green monkey respectively, despite high viral loads (Silvestri et al., 2003). Furthermore, HIV-2 in contrast to HIV-1, is associated with slower disease progression and lower levels of immune activation (Sousa et al., 2002).

The underlying causes of the generalised immune activation associated with HIV-1 infection are presently not fully understood, but are probably associated with multiple mechanisms. These may include reactivation of latent viruses during HIV-1 infection, such as cytomegalovirus (CMV) or Epstein-Barr virus (EBV). The most widely considered mechanism is based on the significant depletion of CD4+ T-cells in the mucosa leading to a disruption of the gut lining and translocation of microbial flora to the systemic immune system (Brenchley et al., 2006). HIV-1 is known to incorporate host human leukocyte antigens (HLA) into its envelope during budding, that may play a role in immune activation. Furthermore, the conserved C5 region of gp120 may also be involved in immune activation (Cadogan & Dalgleish, 2008) by virtue of similarity with the peptide binding domains of HLA molecules. This region of gp120 has been shown to bind peptide and promote activation of antigen-specific T-cell clones (Sheikh et al., 2000).

A small percent (<5%) of individuals have been found to control HIV-1 infection for long periods in the absence of ART. Virus levels, although very low – are never eliminated in these individuals (Hunt et al., 2011). These elite and viraemic controllers (that have a low viral load) have been shown to have narrow cell-mediated immune responses preferentially targeting Gag, and lower immune activation (Rosenberg et al., 1997; Zuniga et al., 2006; Walker, 2007; Saez-Cirion et al., 2007; Binley et al., 1997; Kiepiela et al., 2007). The fact that some individuals can control HIV-1 viraemia suggests that long-term immunological control of HIV-1 infection is possible. This therefore provides credence to the concept of therapeutic vaccination as a means to confer relevant immune stimulation that can ultimately lead to a sustained virological response, emulating a long-term nonprogressor status where the risk of virus transmission is reduced. As a result, more focus will need to be directed to understanding the mechanism(s) behind the control of HIV-1 in elite and viraemic controllers (Autran et al., 2011).

Long-term control of HIV-1 infection in the absence of ART forms the basis for the term ‘functional cure’ where virus and immune activation levels become equivalent to that found in elite controllers or natural virus suppressors (Jeffries, 2010). In contrast, a ‘sterilising cure’ relates to HIV-1 eradication, that is, the permanent removal of the HIV-1 by the complete elimination of viral reservoirs. The eradication concept has been inspired by ‘The Berlin Patient’ who received a bone marrow transplant from a donor that had the CCR5Δ32 mutation rendering the cells resistant to virus strains using this co-receptor for infection (Hütter et al., 2009). The Berlin patient has remained virus-free for four years to date (Allers et al., 2011).
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Therapeutic vaccines have the advantage of being able to penetrate sanctuary sites less well accessed by ART such as lymphoid tissue (Pantaleo et al., 1991; Fox et al., 1991) and the central nervous system (Alexaki et al., 2008), that represent regions for viral persistence. This relates to therapeutic interventions targeting both the virus itself as well as HIV-associated immune activation. This chapter will discuss the potential contribution of therapeutic vaccination to achieve a functional cure for HIV-1 infection.

2. HIV-1 persistence in reservoirs

The failure of ART to eradicate HIV-1 infection lies in the observation that HIV-1 remains quiescent in latent reservoirs. Latently infected resting CD4+ cells (either naive or long lived memory cells) carry transcriptionally silent HIV-1 and represent the predominant reservoir of HIV-1 infection. Other cells may also act as reservoirs (Reviewed in Alexaki et al., 2008) such as macrophages, dendritic cells and astrocytes (where HIV-1 infection occurs via a CD4-independent mechanism). It is these latent reservoirs that represent the major challenge to eradication of HIV-1 infection. More than 80% of individuals on suppressive ART have persistent viraemia below the level of detection (Maldarelli et al., 2007). This low level viraemia is not reduced further despite ART intensification (Dinoso et al., 2009) supporting the concept that HIV-1 rebounds on ART cessation from the rapid reactivation of virus from latently infected cells rather than from continuous ongoing low level replication (Joos et al., 2008). Long lived memory cells comprise approximately 1 cell per million with an extremely low decay rate explaining why 73 years is required to eliminate HIV-1 from infected individuals (Finzi et al., 1999, Siliciano, 2010).

It is clear that to achieve a functional cure, therapeutic vaccination will need to induce not only effective antigen-specific immune responses but also combat the generalised immune activation induced by HIV-1.

3. The concept of a functional cure

The ultimate aim of a functional cure for HIV-1 infection is to induce long-term remission by depleting virus reservoirs to such an extent that a ‘controller’ status is achieved. In this way virus is maintained at low levels for long periods of time in the absence of ART, equivalent to that observed in known HIV-1 controllers (Lambotte et al., 2005) natural virus suppressors (Sajadi et al., 2007) and elite controllers (Deeks & Walker, 2007). This concept can be compared to achieving a sustained virological response for hepatitis C virus (HCV) infection following interferon/ribavirin treatment. If a sustained virological response is observed for HCV (undetectable virus for at least 6 months), the patient is considered cured. The potential for curing HCV infection is theoretically greater than for HIV-1 since HCV, a separate genus Hepacivirus within the virus family Flaviviridae, replicates solely in the cytoplasm of infected cells. As such, on cell division, the virus may remain in only one of the daughter cells. In contrast, HIV-1 is a retrovirus that integrates into the host genome and as such, on cell division will be automatically present in both daughter cells.

A sustained virological response for HIV-1 could be envisaged as either:

a. Indefinite virus control below the limits of detection (<50 copies HIV-1 RNA/ml) (equivalent to a sterilising cure/eradication).

b. Long-term low level virus replication, as for a natural virus suppressor or long-term non progressor, with concomitant low levels of immune activation (equivalent to a functional cure).
Approaches towards eradication include attempts to purge reservoirs by selective activation of latently infected cells (such as memory cells) in the presence of ART such that released virus may not infect and replicate in neighbouring cells (Richman et al., 2009). Agents include histone deacetylase inhibitors, cytokines, such as IL-2 and IL-7, as well as bryostatin, the protein kinase C activator (Kovochich et al., 2011). However, such interventions may also be associated with side effects, resistance and high cost.

Maintaining HIV-1-infected cells in a continuously latent (transcriptionally silent) state, akin to true latency characteristic of herpesviruses, represents the opposite extreme that has received less attention. HIV-1 is produced from activated CD4+ T-cells. At present it is not clear how HIV-1 can be maintained transcriptionally silent whilst still allowing for the CD4+ T-cell activation required to mount an immune response.

### 3.1 Functional cure and treatment interruption

In order to demonstrate a sustained virological response (functional cure) for patients that are well controlled on ART, treatment will ultimately need to be stopped in order to show that virus levels remain controlled (low/undetectable).

Treatment interruption has been intensely investigated in the past as a means to overcome the limitations of lifelong ART which include side effects, drug resistance and high cost. Today, treatment interruption *per se*, is viewed with scepticism due to safety concerns arising from the SMART study, the largest treatment interruption study to date (El-Sadr et al., 2006). In the SMART study and numerous previous smaller studies, ART was interrupted without any additional immunological support. Treatment interruption in the SMART study was CD4-guided, where ART was discontinued when CD4 levels rose above 350 cells/mm$^3$ and resumed if CD4 counts fell below 250 cells/mm$^3$. However, the study was prematurely halted since patients in the treatment conservation group (treatment interruption) experienced greater side effects and adverse events than those in the continuous ART arm. The SMART study therefore concluded that treatment interruption was not safe and that ART should remain a continuous life-long treatment. These safety concerns have affected the design of all treatment interruption trials including those for therapeutic vaccines. Interestingly, a more recent large study of the Swiss Cohort, has suggested that treatment interruption of up to six months can be safely tolerated particularly if patients are well monitored (Kauffman et al., 2011).

Earlier clinical studies have shown that upon cessation of ART, and in the absence of therapeutic immunisation, CD4+ T-cell counts and virus load rebound to preART levels (i.e. the preART set point) (Oxenius et al., 2002a; Wit et al., 2005; Oxenius et al., 2002b; Mata et al., 2005). However, not all patients have available preART viral load information and therefore efforts have been made to identify alternate markers that may predict where the viral load may settle on treatment interruption in the absence of any other intervention. This is necessary in order to determine whether an intervention has lowered the viral load set point in a subject. Proviral DNA levels at baseline have been shown to correlate with the preART viral load, (Yerly et al., 2005), however, this approach will require further validation before it can be taken in to routine use. Until alternative markers are available, preART RNA values will remain the best predictor of the viral load set point that may be obtained on treatment interruption in the absence of therapeutic immunisation. Consequently, the effect of different therapeutic interventions on the viral load will therefore be compared to the preART values.
CD4+ T-cell counts represent the major parameter that determines the need for ART initiation. For this reason, earlier efforts within therapeutic vaccination aimed to improve CD4+ T-cell counts in order to slow disease progression. However, in light of the SILCAAT and ESPRIT studies that focused on improving CD4+ T-cell counts using IL-2 (which provides nonspecific immune stimulation unlike a therapeutic vaccine that is antigen-specific), the conclusion was that improving CD4 counts per se was not associated with clinical benefit (INSIGHT-ESPRIT and SILCAAT Study groups, 2009). Consequently, reducing viral load now represents the unequivocal major endpoint for any therapeutic vaccine or intervention aimed at effecting a functional cure or ultimately eradication.

The current scepticism regarding treatment interruption means that inclusion criteria for patients in such studies will take into consideration both preART and nadir (lowest ever) CD4+ T-cell counts since this has been shown to be a critical parameter in determining the outcome of treatment interruption (Willberg & Nixon, 2007). In subjects with low CD4+ T-cells nadir (200-250 cells/mm^3), CD4+ T-cell levels fall rapidly on treatment interruption requiring earlier re-initiation of ART (Toulson et al., 2005). Patients selected may therefore be relatively newly infected and have robust preART CD4+ T-cell levels and less well established viral reservoirs.

3.1.1 Functional cure scenario 1: Long lasting remission on ART interruption

One approach towards a functional cure could involve therapeutic vaccination in combination with ART followed by treatment interruption with the aim of providing long lasting sustained virological suppression. The advantage of immunising individuals in the presence of ART is that patients have usually regained CD4+ T-cell counts, including naive CD4+ T-cells that can be stimulated to target HIV-1. Furthermore, virus replication is controlled allowing for immunisation in the absence of circulating virus. The immunisation itself will provide some immune activation as CD4+ T-cells harbouring virus become activated leading to a virus burst which would nevertheless be contained by ART. It would therefore be important to allow for vaccine-induced immune activation to subside before stopping ART. Antigen-specific therapeutic vaccines inducing cell-mediated immune responses against gene products from multiply spliced RNA such as Tat may function in the presence of ART and remove infected cells. This is because these early gene products are not targeted by current antiretroviral therapy. Furthermore, Tat expression is not dependent on the activation state of the infected cell and is therefore also synthesized in quiescent T-cells in the absence of virus replication (Wu & Marsh, 2001). In contrast, for therapeutic vaccines targeting products requiring the expression of structural genes such as Gag and Env, ART would need to be stopped in order for the immune system to identify HIV-1 infected cells expressing these antigens.

Therapeutic vaccination using antigen-specific immune stimulation could be combined with other interventions to provide a long-lasting reduction of HIV-1-associated generalised immune activation and consequently reduce the level of viral rebound even further. The aim would be that when patients are removed from ART, CD4+ T-cell counts would remain sustained and a virus set point would be established at a level compatible with a long-term non-progressor, or elite controller for a significant period of time (Figure 1). The therapeutic vaccine may also attenuate the height of the initial peak rebound so that it does not necessarily overshoot the preART value. This scenario may be most beneficial for newly infected subjects that have robust CD4 T-cell counts.
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Fig. 1. Scenario 1: Therapeutic vaccination in combination with ART leading to sustained virological response (long-lasting remission). Viral rebound may not necessarily overshoot the preART viral load. CD4+ T-cell levels would remain above the level of 350 cells/mm³ that necessitates a return to ART according to current guidelines.

3.1.2 Functional cure scenario 2: Remission following intermittent ART

It is possible that on treatment interruption as in scenario 1, viral load levels may stabilize at a lower set point, but not sufficiently low to be compatible with an HIV controller. This may be the case for individuals that started ART later on in disease course, where the number of viral reservoirs is greater, and the CD4+ T-cell nadir lower. To address this, therapeutic vaccination may be used to allow ART to become safely intermittent and where the viral set point may be sequentially reduced following multiple cycles of ART and booster immunisations with the therapeutic vaccine (Figure 2). In such a scenario, due to the safety concerns, the duration of the ART-free period should not exceed the 6 month time period shown to be safe in the Swiss cohort study (Kauffman et al., 2011). This approach of intermittent ART in combination with therapeutic immunisation and booster immunisations has not been investigated to date and may be viewed with scepticism due to the safety concerns arising from the SMART study. However, the underlying basis for the SMART study, i.e. a need to combat ART side effects, drug resistance and high cost remain relevant issues that need to be resolved.

Similarly to scenario 1, therapeutic vaccination may also attenuate the size of the initial peak of rebound during the first treatment interruption allowing the set point to establish below the preART level. Following subsequent booster immunisations on ART in this scenario, as the viral load set point is lowered, CD4+ T-cell decline would also become less marked and would ultimately stabilise above the level necessitating ART (350 cells/mm³).
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Stippled line at 350 indicates CD4 count below which ART should be initiated. Thick solid line: CD4 count. Thin line: viral load (VL). Dashed line: PreART viral load

Fig. 2. Scenario 2: Functional cure over time: intermittent ART supported by therapeutic vaccination, where viral rebound achieves a lower set point for each successive treatment interruption with a concomitant slower CD4+ T-cell decline over time

Any therapeutic vaccination approach involving treatment interruption involves concerns that viral reservoirs would become repopulated. It is interesting to note that viral reservoirs are also repopulated in elite controller patients since they never manage to eliminate their virus despite maintaining a viral set point below the level of detection (Hunt et al., 2011).

3.1.3 Functional cure scenario 3: On continuous ART
Although potentially applicable to all patient categories, this third scenario for achieving a functional cure on continuous ART may be particularly suited for subjects where treatment interruption is not considered a viable option due to poor CD4+ T-cell reconstitution on ART, low CD4+ T-cell nadir or a very high preART viral load set point. This approach could involve combining continuous ART with therapeutic vaccination and reservoir purging agents (Figure 3).

In this scenario, subjects would be maintained on continuous ART. Therapeutic vaccination would be carried out in the presence of ART as in scenarios 1 and 2 with the aim of generating more effective responses to HIV-1. However, instead of removing patients from ART as in scenarios 1 and 2, reservoir purging agents would be used to reverse latency and allow for the expression of viral genes. Viral replication and spread would be hindered due to the presence of ART. Expression of viral genes would render infected cells ‘visible’ to the immune system allowing for their removal as a consequence of the improved immune responses resulting from therapeutic immunisation. However, to show ultimately that viral reservoirs have been reduced significantly or even fully depleted, subjects will need to be removed from ART.
3.2 Functional cure and treatment naive patients

Therapeutic vaccination of individuals that are treatment naive would be an attractive proposition in regions where ART availability is incomplete and where the financial burden to sustain life long treatment is greatest. In this case, subjects would be immunised in the presence of circulating virus to improve and direct immune responses to important epitopes such that viral load is decreased, CD4+ T-cell numbers have the potential to increase and the initiation of treatment delayed. However, therapeutic vaccination itself may result in a transient immune activation that could result in the seeding of further reservoirs with functional and ‘fit’ (replication competent) virus.

Treatment naive individuals currently represent a study population where the effects of therapeutic vaccination on viral load and CD4+ T-cell counts can be readily observed. However, clinical trials involving treatment naive subjects will likely involve enrolment of patients that are early in disease course and where ART is not yet indicated. Such patients would likely have robust CD4+ T-cell counts and viral loads below 100 000 copies/ml. It is likely that viral reservoirs in these patients would be less well established. The more robust the CD4+ T-cell count, the more likely that the patient may provide an immunological response to the therapeutic vaccine.

4. Approaches to therapeutic vaccination in clinical development

A number of different approaches to HIV-1 therapeutic vaccination are currently in clinical development, although not necessarily at this point in time directly aiming to achieve a
functional cure (Tables 1-3). The majority of products aim to induce T-cell immunity whereas a minority aim to induce antibody responses to specific viral antigens. The viral antigens used as therapeutic vaccine candidates include peptides, polypeptides, fusion proteins, recombinant proteins, DNA, RNA either alone or with viral vectors such as poxviruses or adenoviruses, as well as inactivated autologous virus. These antigens can be injected directly or via \textit{ex vivo} bombardment of autologous dendritic cells that are re-infused into the patient. The overall objective of therapeutic vaccine candidates is to reduce viral load, although some also aim to concurrently sustain CD4+ T-cell counts upon ART interruption.

The potency of \textit{ex vivo} stimulation of dendritic cells with inactivated autologous virus was first appreciated following the original studies by Lu et al., (2004) and Garcia et al., (2005) where subjects experienced a significant although transient reduction of viral load. Such approaches require access to autologous virus prior to ART initiation either for purification and inactivation or use as the basis for amplification of viral genes. This approach requires access to advanced technology and may require intermittent boosting to maintain the effect.

Therapeutic vaccines are also being developed that aim to target dendritic cells \textit{in situ}. This usually involves intradermal administration. Since intradermal injection requires trained personnel, alternative approaches are being developed to target dendritic cells such as topical patches/plasters.

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<tr>
<th>Company</th>
<th>Product</th>
<th>Clinical phase</th>
<th>Technology</th>
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<tbody>
<tr>
<td>Argos Therapeutics</td>
<td>AGS-004</td>
<td>II</td>
<td>Autologous DCs co-electroporated with amplified \textit{in vitro} transcribed RNA encoding CD40L and autologous HIV-1 antigens derived from the patient’s own plasma taken immediately prior to the initiation of ART.</td>
</tr>
<tr>
<td>Baylor University/ANRS</td>
<td>DC Vaccine</td>
<td>I</td>
<td>DALIA study: \textit{Ex vivo} administration of Lipopeptides to Nef, Gag and Env to DCs followed by reinfusion to patient</td>
</tr>
<tr>
<td>Bionor Pharma</td>
<td>Vacc-4x</td>
<td>IIb</td>
<td>Peptides to conserved domains of HIV p24 injected intradermally with GM-CSF.</td>
</tr>
<tr>
<td>Genetic Immunity</td>
<td>LC002</td>
<td>II</td>
<td>Clade B DNA in nanoparticles and delivered to DCs in a patch (Dermavir).</td>
</tr>
<tr>
<td>NIAID/Profectus Biosciences</td>
<td>MRK Ad5 HIV-1 gag</td>
<td>II</td>
<td>Replication defective adenovirus vector carrying HIV-1 gag.</td>
</tr>
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Table 1. Therapeutic vaccine candidates immunising subjects on ART with a treatment interruption phase in the study. DC: dendritic cell, TI: treatment interruption. NCT provides the clinical trial identifier for trials listed on www.clinicaltrials.gov

Viral vectors derived from adenoviruses or poxviruses have also been extensively used to deliver DNA-based vaccines most often in a prime boost strategy. For such approaches it
will likely be necessary to determine the serological status of vaccine recipients to the 
viruses that have been used as a basis for these vectors since prior immunity may negatively 
affect vaccine efficacy. Similarly, maintenance of vaccine effect may require boosting using a 
heterologous virus vector, to avoid inhibitory effects of prior vaccine-induced immunity to 
the original vector.

Although the induction of neutralising antibodies remains the major goal for an effective 
preventative vaccine, therapeutic vaccines aim to induce antibody responses to other viral 
antigens such as the HIV-1 Tat protein. Earlier studies have shown that loss of antibody 
responses to Tat correlated with disease progression (van Baalen et al., 1997; Rezza et al., 
2005). Such a vaccine may also address pathogenic effects of Tat released from infected cells 
(Ensoli et al., 1993).

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<th>Company</th>
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<tbody>
<tr>
<td>Imperial College</td>
<td>GTU-MultiHIV-B (FIT06)</td>
<td>I n=30</td>
<td>DNA plasmid. Intradermal injections in combination with GM-CSF and IL-2 as well as a growth hormone.</td>
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<tr>
<td>Univ. Oxford Med Research Council</td>
<td>MVA.HIVconsv</td>
<td>I n=20</td>
<td>MVA vector encoding a DNA that carries conserved domains in Gag, Vif, Pol, Env.</td>
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<tr>
<td>University Pennsylvania / Drexel University</td>
<td>PENNVAX B,GENEVA X IL-12-4532, pIL15EAM</td>
<td>I n=38</td>
<td>PENNVAX-B is a DNA vaccine encodes synthetic HIV-1 envelope protein, Gag and Pol. GENEVAX and pIL15 are DNA adjuvants (IL-12 and IL-15)</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>DNA</td>
<td>I n=21</td>
<td>Dendritic cells transfected with vectors encoding consensus (clade B) HIV Gag and Nef mRNA.</td>
</tr>
<tr>
<td>NIAID</td>
<td>HIV Antigens &amp; IL-12</td>
<td>I n=60</td>
<td>Plasmid DNA with IL-12 to enhance the response.</td>
</tr>
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</table>

Table 2. Therapeutic vaccine candidates in clinical development where therapeutic 
vaccination occurs in the presence of continuous ART. DC: dendritic cell. NCT provides the 
clinical trial identifier for trials listed on www.clinicaltrials.gov

5. The challenges facing therapeutic vaccination

No preventative vaccine has yet been developed for HIV-1 infection. This is despite intense 
efforts since the virus was first isolated in 1983 (Barre-Sinoussi et al., 1983). The challenges 
faced by preventative and therapeutic vaccines are similar in that HIV-1 shows extensive 
genetic variation and a propensity for immune escape. Furthermore, human populations are 
also varied and this is characterised by a variety of human leukocyte antigens (HLA). HLA 
function to present HIV-1 epitopes at the surface of infected cells to allow for recognition 
and removal by cytotoxic T-lymphocytes. The association of certain HLA with virus control 
(e.g. HLA-B57) and disease progression (e.g. B35) has recently been highlighted.
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(International HIV Controllers Study Study, 2010). However these HLA alleles are not present in a large proportion of individuals. It has been suggested that patients in clinical studies should be HLA tested to help explain and understand the results (Li et al., 2011).

One salient difference between the preventative and therapeutic vaccines lies in their objectives. At present it is considered remote that a vaccine can be developed that will yield sterilising immunity and complete protection from HIV-1 infection. For this reason, the objective of a preventative vaccine is now to prevent infection as far as is possible, and should infection occur the immune system will be sufficiently primed to ensure that the disease course is milder (Johnston & Fauci, 2007). This was the aim of the STEP trial, which used an adenovirus vector. However, unexpectedly, prior exposure to adenovirus infection resulted in greater susceptibility to HIV-1 infection in study participants (Buchbinder et al., 2008).

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<tbody>
<tr>
<td>Genetic Immunity</td>
<td>LC002</td>
<td>II n=36</td>
<td>Clade B DNA incorporated into nanoparticles and delivered to DCs in a patch (Dermavir).</td>
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<tr>
<td>SEEK (previously PepTcell)</td>
<td>HIV-v</td>
<td>I n=55</td>
<td>Mixture of polypeptide T-cell epitope sequences to conserved domains of HIV (internal proteins). Single subcutaneous injection</td>
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<tr>
<td>Statens seruminstitut, DK, EU clinical trials partnership</td>
<td>AFO-18</td>
<td>I n=20</td>
<td>Peptides representing 3 CD4 and 17 CD8 minimal HIV epitopes. Adjuvant CAF01.</td>
</tr>
<tr>
<td>Thymon</td>
<td>TUTI-16</td>
<td>I/II n=24</td>
<td>Tat Lipopeptide. Subcutaneous injection, acts as own adjuvant.</td>
</tr>
<tr>
<td>FIT Biotech</td>
<td>FIT06 (GTU-MultiHIV-B)</td>
<td>II n=60</td>
<td>DNA plasmid using GTU® Technology patented by FIT Biotech (Gene Transport Unit). Gag, Rev, Nef, Tat. Clade B.</td>
</tr>
<tr>
<td>Hospital Clinic of Barcelona</td>
<td>DCV2</td>
<td>I/II n=60</td>
<td>Autologous dendritic cell pulsed ex vivo with patient’s own virus.</td>
</tr>
<tr>
<td>Istituto Superiore di Sanita</td>
<td>ISS T003</td>
<td>II n=160</td>
<td>Inactivated Tat protein injected intradermally (i.d.) to induce antibodies to Tat. This study is an observational cohort.</td>
</tr>
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Table 3. Therapeutic vaccine candidates in clinical development immunising subjects that are treatment naive.

6. Conclusion

The complexity of HIV-1 infection represents a challenge to achieving a functional cure or ultimately eradication of infection. A number of scenarios have been suggested in this chapter where therapeutic vaccination is combined with ART and also potentially with virus
purging agents. At present it is unlikely that any one scenario will suit all purposes, indeed, the choice of approach will likely depend upon the availability of ART, how far advanced the infection is on diagnosis and when during the disease course ART was initiated since these considerations will influence the size of viral reservoir. It is unlikely that there will ever be a single product that will either prevent HIV-1 infection completely or eradicate HIV-1 infection. Therefore, combinations may be more appropriate. Harnessing the immune system is a rational approach to combine with ART bearing in mind that the immune system may penetrate regions of the body not reached by current therapy. Combination ART has been more successful than monotherapy. Similarly combining ART with therapeutic vaccination and/or virus purging agents will likely be more effective than any of these interventions on their own. The recent Thai study provides is an example where two preventative vaccine candidates that had not shown effect earlier, provided an improved response leading to a marginally significant effect when combined (Reks-Ngarm et al., 2009). Ultimately a therapeutic vaccine will need to confer effective immune responses in all individuals regardless whether they possess HLA compatible with virus control or not. It is therefore important that therapeutic vaccine candidates take into consideration genetic variation in both human and viral populations in order to be able to elicit the most effective responses leading to control of infection. Strictly, the term ‘functional cure’ can be considered misleading since virus is not completely removed from the body, but rather the patient experiences remission from symptoms. The term ‘functional control’ would therefore be more appropriate.

Eradication approaches will require much research and development, where both novel and known compounds will be tested in new ways to determine a potential effect on eradication without incurring too many side effects. It may therefore take significant time before such products are available on the market. In contrast, a functional cure may be achievable in the shorter term and represent a more realistic goal since virus reduction has been shown for a number of therapeutic vaccine candidates. Approaches that aim to successfully combat HIV-1 infection will need to address both the virus (virus-specific approaches including ART and therapeutic vaccines) as well as the generalized immune activation that drives the infection. It is likely that to achieve a functional cure, a combination of different interventions may ultimately be required.

7. Acknowledgments
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8. References


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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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