

# HIV Pathogenesis and Prospects for Vaccine Development

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*As the HIV pandemic continues to gather force, there is a widening gap in access to care in developed and developing countries. The persistence of this sobering reality was highlighted in major presentations on the opening and closing days of the 8th Conference on Retroviruses and Opportunistic Infections in Chicago. An effective vaccine might one day lessen this discordance, and data presented on vaccine trials in animals give reason to be optimistic. In addition, unraveling the factors that contribute to the typically relentless progression of HIV infection may in the end not only aid in the development of effective vaccines, but may also help to stem the progression of disease. This review summarizes important progress made in understanding HIV pathogenesis and discusses these advances in the context of exciting new data presented in the realm of candidate HIV vaccines.*

## Acute Infection

Accumulating data suggesting that early events in acute HIV infection may influence the ultimate progression of disease necessitate a better understanding of the initial events following exposure to virus. Studies over the past 2 years have shown that T helper cell responses to HIV are diminished or absent in persons with progressive chronic HIV infection, and additional studies at this Conference underscore this defect (Abstracts 154, 156, 158, and 160). The reasons for this lack of T helper cell responses have been unclear, but a study in macaques supports the notion that early immune damage is occurring, in that active memory cells appear to be the primary target for simian immunodeficiency virus (SIV) in acute infection (Veazey et al, Abstract 506). By analogy, one would expect to see something similar in acute HIV infection, and such studies are clearly warranted.

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Since most acute infections worldwide occur across a mucosal barrier, dendritic cells (DCs) in the lamina propria have long been thought to play an important role. The potential role of a recently described surface molecule preferentially expressed on DCs was reviewed in a State-of-the-Art Lecture by van Kooyk (Abstract L10). Termed DC-SIGN for DC-specific, ICAM-3-grabbing non-integrin, this molecule is thought to mediate DC trafficking and T cell binding. It is a type II mannose-binding C-type lectin that recognizes carbohydrates and serves as the major HIV receptor on DCs through a specific interaction with gp120. It does not mediate virus entry, so it is distinct from CD4 and CCR5. Instead, it enhances infection of activated T cells. It can stabilize HIV-1 for more than 4 days, because binding to DC-SIGN protects HIV from proteases that are present in plasma. This then likely allows for transport of the virus to regional lymph nodes, where infection can be propagated further. Whether targeting of DC-SIGN with specific therapies would have an antiviral effect remains to be determined, but is becoming an active area of investigation.

Other factors potentially influencing transmission and subsequent progression were also suggested in a variety of studies. At the time of acute infection plasma viremia is quite high—one study showed an average of over 10 million viral particles per milliliter of plasma when acute patients were first evaluated (Walker, State-of-the-Art Lecture, Session 37). At these early times prospects for transmission are high. One study indicated that sexual transmission may actually precede the symptoms of acute infection (Pilcher et al, Abstract 411). The investigators examined 5 cases in which sexual transmission occurred during acute HIV infection in the source patient. Their findings suggest that transmission can occur up to 2 days before the onset of symptoms, and the finding of clusters of cases transmitted by persons with acute infection provides even more impetus for the early identification of these individuals. Another study suggested that preseroconversion levels of T cell receptor rearrangement excision circles (TRECs) may influence disease progres-

sion, with low TREC content associated with more rapid disease progression (Zhang et al, Abstract 373). The potential mechanisms involved remain to be defined.

One study of acute infection is worthy of special mention. Rizzardi and coworkers (Abstract 759) treated persons with acute HIV infection with 8 weeks of the immunosuppressive agent cyclosporin A (CSA) and then followed them longitudinally. Comparison was made to persons treated with highly active antiretroviral therapy (HAART) alone. This therapy rapidly and effectively increased CD4+ cell counts, and HIV-specific CD8 immune responses were maintained. One potential explanation for

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this finding would be that virus is less able to infect the CSA-treated cells since this compound has an antiproliferative effect. Further studies will be needed to determine the effects of this intervention on long-term outcome, including the ability to use supervised treatment interruption (STI) with the intention of gaining immune control of infection.

## Persistence of Viral Reservoirs

Lifelong therapy will almost certainly be required to treat HIV disease, since viral eradication is not likely to occur. This sobering point was further emphasized in a State-of-the-Art Lecture from Siliciano (Abstract L5), who showed essentially no decay in the latent viral reservoir in persons highly adherent to their medication regimens. With follow-up now out to 4 or 5 years in these individuals, there has still been no change in reservoir size compared to initial values. In fact, his studies suggest that the survival of latently infected cells is

the same as their uninfected counterparts. Maintenance of viral species in the reservoir is very persistent, such that resistance mutations can be deposited in this reservoir and will likely persist for the life of the individual. The persistence of drug-resistant mutations that enter this reservoir was further demonstrated in persons undergoing STIs (Deeks et al, Abstract 292; Hance et al, Abstract 293). Even though the half-life of infected cells in the reservoir may be shortened on more intensive regimens (Ho et al, Abstract S17; Ramratnam et al, Abstract 502), and decay rates of cell-associated infectivity may be more rapid in persons treated earlier after acute infection (Wong et al, Abstract 503), such regimens are not practical and the likelihood of eradication does not appear to be increased.

Another issue that is still to be adequately addressed is the possible presence of other reservoirs. At this meeting, the kidney was revealed as a potential haven for HIV. Virus was identified in mesangial cells in persons who have HIV-related nephropathy (Marras et al, Abstract LB3). The possibility that this represents a separate sanctuary was suggested by the finding of divergent evolution of viruses obtained from kidney and peripheral blood. Another possible reservoir is the macrophage, but studies presented indicated that the decline of virus in macrophages very closely paralleled the decline in CD4+ cells, suggesting against this as a proposed mechanism of the slower second-phase decline in plasma viremia (Bucy et al, Abstract 507). Instead, these data were interpreted to suggest that the slow decline after the first week might be due to slow release from tissue sanctuary sites yet to be defined. The brain is one potential site, an argument supported by data showing divergent evolution of viruses obtained from cerebrospinal fluid compared to blood and other tissues (Ellis, Abstract S19).

A number of studies addressed viral dynamics, and highlighted controversies still have not been fully rectified. Using deuterated glucose to label the DNA of proliferating cells, 4 normal subjects and 7 controls were examined by Mohri and colleagues (Abstract 269). Lymphocyte turnover rates were accelerated by several-fold in HIV infection compared with uninfected controls, and this was true for both CD4+ and CD8+ cells. With institution of HAART, these turnover rates rapidly decline and reach near normal levels by 1 year. These results were interpreted to

mean that the low CD4+ cell count in AIDS is a consequence of increased cell death rather than decreased cellular regeneration. However, other studies presented suggest that increased cell turnover and decreased thymic output both contribute to the inability to maintain normal cell numbers (Douek et al, Abstract 270).

### Immune Responses to HIV

The role of the immune system in controlling HIV replication was further defined through a number of presentations at this meeting. In particular, exciting data presented provide evidence that may facilitate eventual induction of effective neutralizing antibody responses. Desrosiers in the Bernard Fields Memorial Lecture (Abstract L1) presented data from studies of the role of envelope glycoprotein in avoidance of antibody-mediated recognition. Using SIV and simian-human immunodeficiency virus (SHIV) model systems to study mutations in the V1-V2 region that affect carbohydrate attachment of gp120, he demonstrated that removal of carbohydrates can enhance neutralization sensitivity and that antibodies elicited by such mutant viruses can confer augmented immune control following subsequent pathogenic viral challenge, as evidenced by a lower viral set point. Although there were few additional studies of neutralizing antibodies at the meeting, this lecture alone served to fuel enthusiasm that effective neutralizing antibody induction might still be a reality.

In contrast to the paucity of presentations related to humoral immune responses, numerous presentations addressed the role of cellular immune responses in control of viremia and pathogenesis of infection. The breadth of the cytotoxic T lymphocyte (CTL) response was shown to extend beyond the traditionally studied epitopes in Gag, reverse transcriptase, Env, and Nef. Using new techniques to quantitate interferon gamma (IFN- $\gamma$ ) release by CD8+ cells as a measure of CTL activity, it was demonstrated that significant responses can be detected to Tat and Rev (Addo et al, Abstract 167), as well as the accessory proteins Vif, Vpr, and Vpu (Altfeld et al, Abstract 168). These techniques have also allowed for the comprehensive assessment of responses to all of the expressed proteins of HIV, showing that 18 of 18 persons studied over a wide range of viral loads and CD4+ cell counts had detectable responses (Betts et al, Abstract 272). However, in contrast to previous published reports of a correlation

between viral load and CTL magnitude when A2 restricted responses alone are studied, these more comprehensive studies failed to show any significant correlation. Other studies examined CTL epitope density in different regions of the virus, including p17 and Nef, and identified a clear correlation between predicted proteasomal cleavage sites and actual epitope boundaries (Yusim et al, Abstract 271). Such studies begin to address the issue of relative immunodominance of CTL responses, an issue of critical relevance to vaccine design.

CD8+ cells have been shown to lyse infected cells but also to release soluble inhibitory factors that include beta chemokines that inhibit R5 viruses as well as other factor(s) that inhibit X4 viruses. The precise characterization of the elusive X4 inhibitory factor(s) remains to be determined. There was relatively little presented at the meeting relating to this response. Persons who are treated in the acute stage of infection appear to develop particularly robust CD8+ cell noncytotoxic activity, and the ability of this response to inhibit viral replication appears to be best when there is direct cell-to-cell contact (Chun et al, Abstract 504). However, full characterization of the factor remains elusive.

In the past 2 years numerous publications have indicated a role for virus-specific CD4+ T helper cells in effective control of chronic HIV infection, and additional data at this meeting further support this notion, although not without persisting controversies.

The relationship between CD4+ T helper cells and CTLs was further evidenced by a macaque immunization model, in which induction of CTLs was associated with the induction of strong CD4+ T helper cells directed against the virus (Belyakov, Abstract S5). Such relationships were also implied in studies of natural infection in humans (Imami et al, Abstract 158; Autran et al, Abstract 160). The delineation of this relationship between CD4+ T helper cell responses and CTL function should be important, since it will help to guide immunotherapeutic interventions for persons who are already infected.

A number of studies addressed the important issue of what factors contribute to the lack of immune control in chronic infection. Insights into the lack of T helper cell responses to HIV in persons with chronic infection were provided by studies using proliferation assays, IFN- $\gamma$  and interleukin 2 (IL-2) ELISPOT assays, and major

histocompatibility complex (MHC) class II tetramers. Subjects studied included those undergoing STIs. Virus-specific T helper cells were found to persist during periods of viremia, but to be incapable of proliferation (McNeil et al, Abstract 156). A second study also found that defects in proliferation may be independent of the ability to secrete IFN- $\gamma$  (Pires et al, Abstract 157). The demonstration of HIV-specific class II tetramers that allow for direct staining of the antigen-specific cells should help to further resolve these issues (Yassine Diab et al, Abstract 155). Assessment of reasons for immune failure of CTL responses included the potential inability of HAART to restore DC number and function (Donaghy et al, Abstract 40) and lack of effective maturation of CTLs into fully functional effector cells (Champagne et al, Abstract 274; Van Baarle et al, Abstract 275; Papagno et al, Abstract 276). The demonstration of skewed maturation of CTLs in HIV infection compared to cytomegalovirus infection in the same individuals suggests that there are specific factors that impair differentiation selectively, such as perhaps a lack of sufficient HIV-specific T helper cell function (Abstracts 274 and 275).

### Progress in Vaccine Studies

The opening and closing sessions of this Conference were marked by lectures describing in vivid detail the desperate global situation with respect to the HIV pandemic, which continues to gather force. The need for a vaccine has never been greater, and important progress toward this goal was presented at the Conference. This included not only the aforementioned success with induction of neutralizing antibodies (Desrosiers, Abstract L1), but also a number of other animal models in which protection from disease was a common theme.

One of a number of impressive immunization studies was presented by Robinson and colleagues (Abstract 24). This group had previously demonstrated that DNA immunization followed by boosting with a modified vaccinia virus Ankara (MVA) vector resulted in induction of strong immune responses, and here presented the results of challenge studies. Following the MVA boost, impressive levels of CD8 responses were obtained—up to 18% of CD8+ cells by tetramer analysis. This study design was impressive because the investigators waited 6 months after the final booster immunization until they chal-

lenged with a pathogenic virus. This meant that the immune responses were in memory at the time of encounter with virus. All animals became infected upon challenge, but all vaccinated animals had preservation of CD4+ cell number and most animals were able to control viremia at levels below 1000 copies/mL plasma. All 24 vaccinated animals remained clinically healthy, with vigorous virus-specific cellular immune responses and absence of detectable virus in lymph nodes by *in situ* hybridization. Clinical trials in humans are slated for later this year.

Other impressive studies also showed that although complete protection from viral challenge could not be obtained, viral set point could be dramatically influenced. One approach involved the use of phage-displayed peptides, in which 4 of 5 challenged animals maintained low viral loads despite becoming infected (Chen et al, Abstract 26). Another involved the use of vesicular stomatitis virus recombinant vectors (Rose et al, Abstract 23). Although follow-up is brief in these animals, the early data indicate a 100-fold or greater decrease in viral load in the vaccinees compared to controls. New delivery methods for a variety of candidate vaccines (Otten et al, Abstract 27; Marovich et al, Abstract 29) and development of polyvalent constructs (Cho et al, Abstract 28) may enhance the ability to achieve broader and more durable vaccine-induced immune responses. In addition, some of these approaches are being adapted for use as therapeutic vaccines, an approach for which there is presently considerable enthusiasm and yet few firm data.

Most studies of vaccines have examined immune responses in peripheral blood, but induction of mucosal immune responses may be particularly relevant to the development of an effective vaccine. Belyakov and colleagues (Abstract S5) presented data in a murine model of virus infection, in which mice are immunized with a peptide-based vaccine and then challenged with a vaccinia virus expressing HIV proteins. Intrarectal immunization resulted in induction of CTLs in Peyer's patches and intestinal lamina propria, and in CD8+ T cell-mediated protection, whereas subcutaneously immunized animals developed CTLs in the spleen and not the gut, and were not protected. Extension to a macaque model confirmed the advantage to intrarectal immunization when the animals were challenged with a pathogenic SHIV, in that the intrarectally immunized monkeys had more effective

clearance of plasma viremia and greater preservation of CD4+ cell counts despite infection. Studies examining mucosal T cell responses in humans should facilitate assessment of candidate vaccines (McElrath, Abstract S6).

Although the animal trial data presented are impressive, human data are most eagerly awaited. Promising candidates include alphavirus vectors (Johnston, Abstract S7) and a polyepitope vaccine (Hanke, Abstract S8), both of which are slated to be in larger human clinical trials in the near future. The initial phase of testing of the polyepitope vaccine, presented in the context of a DNA and MVA vector, is already in phase I trials in humans. The vectors mentioned in the animal trials above are also all on paths toward clinical development, and initial data from some of these can be anticipated at the Retrovirus Conference in 2002.

### Immune Augmentation in HIV Infection

The demonstration that some persons are able to coexist with the virus for 20 years or longer without developing disease has sparked intense interest in the mechanisms by which virus is held in check. As indicated above, compelling evidence now exists for immune-mediated control of virus in these individuals. Three additional factors have fueled interest in immune reconstitution as a therapeutic intervention: (1) the demonstration that HAART leads to increases in naive cells, (2) the demonstration that early treatment of acute infection leads to augmented T helper cell responses, and (3) anecdotal reports that treatment interruption after treated acute infection has been associated with long-term control of viremia. Together, these factors have fostered a new area of investigation, which is controversial enough already that it merited its own session at the Conference. This is variably termed "supervised treatment interruption" or "structured treatment interruption."

It is important in any discussion of STI to discuss the settings in which it is being applied, since the objectives in these settings may be very different. Table 1 lists the 3 different objectives to STI that have been discussed. This review will deal with all 3, but will focus in particular on the use of STI to enhance immune responses, since this is the approach that has been most extensively tested thus far.

Data were presented in which STI was used with the objective of boosting immune function in both acute and chronic infection. This distinction appears to be important in assessing the results of the studies presented, since the results thus far in acute infection appear more impressive. In addition, one must be aware that there is no accepted definition for acute cohorts, and they are actually quite different among different studies. One acute study presented involved subjects with an average plasma viral load of 10 million HIV RNA copies/mL at the time of enrollment (Walker, State-of-the-Art Lecture, Session 37), whereas another examined persons with an average viral load of less than 100,000 HIV RNA copies/mL (Markowitz et al, Abstract 288). One must also make a distinction between treatment cessation and treatment interruption in order to ensure objective comparisons.

The effects of STI in acute infection indicate that at least transient control of viremia may be possible with this approach (Walker, State-of-the-Art Lecture, Session 37). In follow-up of the first 8 persons to undergo repeated cycles of therapy interruption, a total of 14 subjects were presented. Treatment was interrupted after at least 8 months of successful therapy, and reinstated for a viral load persistently above 5000 copies/mL (for greater than 3 weeks) or a single viral load of greater than 50,000 copies/mL. Of the first 14 subjects, 4 were able to persistently control viremia after a simple treatment cessation, 2 were able to persistently control after a second treatment interruption, and 1 was reported to maintain viral load at less than 5000 copies/mL after a third interruption. The longest follow-up is now over 400 days, with some persons able to maintain viral loads of less than 500 copies/mL. Of the 14 subjects, 7 remain off therapy and are considered successes, and 6 are still involved in the second, third, or fourth STI and cannot yet be evaluated. There is only 1 person who underwent 4 STIs in whom viremia was not controlled, and treatment would be considered a failure. However, this person has a viral load of 7445 copies/mL after 128 days off therapy for the fourth time, and has chosen not to resume therapy because of the recent changes in the treatment guidelines.

Another trial of immune control following treatment of acute infection was one in which persons decided on their own to discontinue medications, and is therefore a treatment termination study. These individuals, some of whom had received ther-

apeutic immunizations while on HAART, had lower initial viral loads (less than 100,000 copies/mL) at the time they were diagnosed with acute infection. After a mean of 258 days off therapy, viral loads range from 2.9 to 4.2 log<sub>10</sub> copies/mL in those remaining off therapy. Two persons have maintained viral loads of less than 1000 copies/mL, but 7 of 14 have resumed HAART. There was no evidence that the immunization had a beneficial effect. Thus treatment termination, particularly in early as opposed to acute infection, does not appear to confer as clear an effect on set point viral load.

The results, both anecdotal and published, of successful control of viremia following treatment of acute infection have fueled additional studies in chronic infection. The largest trial to date is the Swiss-Spanish Intermittent Treatment Trial, presented by Fagard and colleagues (Abstract 357). This trial included 128 subjects, who were successfully treated with HAART and then underwent 4 cycles of 2 weeks off therapy and then 8 weeks on therapy. At 40 weeks into the trial medications were discontinued until viral load rose above 5000 copies/mL. Twelve weeks after stopping therapy, only 9 of 54 subjects who could be evaluated had an HIV RNA level below 5000 copies/mL, and those who did remain off therapy were more likely to have initiated therapy early after diagnosis of acute infection. In the end the strategy appears to have worked for about 1 in 6 subjects, and again durability is not yet known, nor is it clear how much this is different from what would be expected without any intervention. In another trial of STI in chronic infection (García et al, Abstract 289), baseline viral load decreased an average of 0.54 log<sub>10</sub> copies/mL in the STI group, whereas the control group experienced an increase of 0.24 log<sub>10</sub> copies/mL over the same

time. The mean HIV RNA load in the STI group was approximately 10,000 copies/mL, compared to 50,000 copies/mL in the controls. Both higher HIV-specific T helper cell responses and higher CTL responses were seen in the group that underwent STI. These differences, although small, are statistically significant, but still do not demonstrate a clinical benefit of this strategy. In a field in which there has been little consensus, the consensus emerging from the meeting is that STI must remain in the research realm for the time being, and is not ready for clinical practice.

Other approaches to immune augmentation were also presented at the meeting. The use of IL-2 plus HAART clearly leads to greater increases in CD4+ cell count than HAART alone (Levy et al, Abstract 344), results in greater restoration of immune function to memory antigens (Durier et al, Abstract 345), and is associated with a greater increase in thymic production even in advanced patients (Saint-Mezard et al, Abstract 350). Long-term IL-2 therapy is able to maintain high CD4+ cell numbers, even when the frequency of administration is decreased (Chaitt et al, Abstract 347). However, clear demonstration of clinical benefit remains elusive. Coupling IL-2 therapy with treatment interruption may ultimately enhance the ability to see a beneficial effect, if one is induced (Smith et al, Abstract 360). IL-2 therapy along with HAART and HIV immunogen as therapeutic vaccine does induce T helper cell responses (Hardy et al, Abstract 349), but again clinical benefit of such strategies remains to be shown.

## Conclusions

There seems to be little question now that the immune response plays a major role in containing HIV, even though it is ultimate-

**Table 1. Objectives of Supervised Treatment Interruption (STI)**

Intended Objectives of STI	Clinical Setting
To enhance immune responses	Acute infection Chronic infection
To limit drug toxicities	Acute infection Chronic infection Treatment failure
To repopulate with wild-type virus	Chronic infection Treatment failure

ly unable in most cases to prevent disease progression in the absence of therapy. Encouraging results with early treatment of acute infection demonstrate that critical immune responses can be effectively boosted in infected persons and that the host-virus relationship can be manipulated. This finding should provide encouragement to continue to explore methods to obtain meaningful and durable immune enhancement as an adjunct to HAART in HIV infection. Moreover, the demonstration that control of viremia can be achieved following immunization offers further evidence that AIDS viruses can be contained by the immune system. Although a vaccine that prevents infection seems to remain an elusive goal, there appears to be a realistic hope that a vaccine to prevent or delay disease may become a reality.

## Conference Abstracts Cited in the Text

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- 293.** Characterization of Minority Viral Populations Expressing Protease Resistance Mutations in Patients Undergoing Structured Treatment Interruptions (STI). A. Hance, V. Lemiale, J. Izopet, D. Lecossier, V. Joly, P. Massip, F. Mammano, D. Descamps, F. Brun-Vezinet, and F. Clavel.
- 344.** Effect of Subcutaneous (SC) IL-2 Therapy Combined with HAART in HIV-Infected Patients. Results of the ANRS 079 Randomized Trial. Y. Levy, C. Capitant, A. S. Lascaux, C. Durier, C. Michon, L. Weiss, E. Oksenhendler, J. A. Gastaut, C. Goujard, C. Rouzioux, J. P. Aboulker, J. F. Delraissy, and the ANRS 079 Study Group.
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