

**DEAR READER**

Not long after the introduction of highly active antiretroviral therapy (HAART) and the subsequent dramatic decreases in AIDS death rates, clinicians and patients alike became very interested in stopping HIV therapy. Once the notion of viral eradication under HAART was deemed impossible and the specter of viral drug resistance to potent HIV therapy was confirmed, our therapeutic paradigm for HAART changed. We realized that, depending on a patient's disease status, HIV drugs may be less like the lifelong, uninterrupted therapy we were first told about and more like a precious resource that must be used wisely to attain maximum benefit. Unfortunately, drug toxicities complicated the HIV therapy equation even more.

Consequently, a veritable explosion of treatment interruption research studies ensued. Reasons behind studying treatment interruptions have varied from "autovaccination" (the hypothesis that alternately starting and stopping HAART might enhance immune responses to HIV) to minimizing drug toxicities and side effects. Throughout the past half dozen or so years that such research has been conducted, we have learned a great deal about what works and what does not work when interrupting HAART. This issue of *RITA!* reviews the research conducted to date and some insights that such research has given us.

Although the abbreviation "STI" has been defined as "structured treatment interruption," "strategic treatment interruption," and even "supervised treatment interruption," it has now earned a permanent place in the lexicon of HIV/AIDS terminology. The question of when to stop or interrupt therapy is now considered by many to be as important as when to start therapy. Faced with increasingly limited resources and growing healthcare costs, national and local government could benefit from knowledge about when best to use HAART.

Perhaps what STI research underscores most is that HAART is imperfect. While HAART has clearly saved lives, it does not eradicate the virus from the human body and its use is associated with both short-term and long-term dangers. One might argue that, for some people, HAART could be considered a cure for AIDS (the most advanced stage of HIV disease). But now many HIV-infected people without AIDS diagnoses suffer from medication-related maladies or illnesses that, while not a direct result of HIV infection, are related to or complicated by HIV's effects on the immune system. We still need a cure for HIV.

Finally, you may have heard that one of The CFA's founders and a director for many years, Joel Martinez, died on November 12. Joel was a committed activist, a prolific writer, and a true inspiration for those who had the opportunity to work with him (see page 22). Joel was the father of this publication and the great driving force behind HIV treatment advocacy in Houston. He was loved greatly and will be missed terribly. The CFA's legacy is to continue the work of HIV research/treatment information and advocacy (both locally and nationally), to which Joel dedicated his life. Joel's mantra "Think*Cure!*" has never rung more loudly. As human beings, we must beat AIDS—and we must beat it soon.

Very truly yours,
The Center for AIDS:
Hope & Remembrance Project

A handwritten signature in brown ink that reads "Tom".

Thomas Gegeny, MS, ELS
Senior Editor

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HIV treatment interruptions: A review

By Jennifer Newcomb-Fernandez, PhD

INTRODUCTION

The widespread use of highly active antiretroviral therapy (HAART) has had a significant impact on HIV by reducing mortality and morbidity.¹ Unfortunately, long-term use of antiretroviral treatment is associated with several limitations and drawbacks. Currently available antiretrovirals are unable to completely eradicate the HIV infection, and infectious virus continues to reside and to replicate latently in reservoirs. As a result, most patients will be on antiretroviral therapy for the rest of their lives, a situation that could potentially cause severe side effects and drug toxicity. These include, but are certainly not limited to, high triglyceride and cholesterol levels, insulin resistance, diabetes, and redistribution of body fat—many of which increase the likelihood of suffering a cardiac event. Adherence is difficult because of the daily, long-term drug dosing requirements and incidence of side effects, and there is a continuous risk of an emergence of drug-resistant HIV.^{2,3} Finally, because of the extremely high cost of antiretroviral treatment, 95% of HIV-infected individuals worldwide do not have access to HAART.⁴

Because of these limitations, HIV researchers are exploring alternative treatment strategies, such as “structured treatment interruptions” (STIs), by using a variety of dosing schedules, antiretroviral regimens, and patient populations. In some cases, treatment is interrupted according to a scheduled time frame, while other studies have used CD4 T cell counts or viral load as indicators of when to stop or re-initiate therapy. Alternatively, one research group has investigated the novel idea of continuous therapy, but with alternating HAART regimens.⁵

Still other researchers have simply documented the effects of treatment interruption on virologic and immunologic control from case studies whereby patients discontinued treatment temporarily for various reasons (eg, side effects, other health concerns, cost of drug, or poor compliance).

There are 3 main applications for the potential utility of STIs. First, STIs may enable a patient to receive less total drug, resulting in decreased drug-related toxicity, reduced cost of patient health management, and improved quality of life for the patient. Second, many studies have explored the concept of “autovaccination” or “autoimmunization” in conjunction with treatment interruption. Though antiretroviral therapy has enabled immunologic control of HIV and viral suppression, the use of HAART is associated with decreased HIV-specific immune responses, particularly in patients with chronic HIV infection.^{6,7} Once treatment is interrupted, viral load increases shortly afterward.⁸⁻¹⁰ Researchers hypothesized that in patients who maintained successful viral suppression with HAART for a sustained period of time, controlled and limited interruption of treatment would enable short bursts of autologous virus to boost HIV-specific immune responses, potentially resetting the viral set-point to a lower level. Repeating these on-treatment and off-treatment cycles could possibly lead to better control of the virus by the patient’s own immune system, even allowing the infected individual to suppress virus in the absence of antiretroviral therapy.^{2,11} Third, STIs may be useful and beneficial in a salvage therapy regimen whereby HIV has become multi-drug resistant and patients have lim-

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ited treatment options. Here, an STI may allow for the repopulation of wild-type, drug-susceptible virus, therefore improving the chances of successful salvage therapy after the interruption.^{3,12,13}

Numerous studies have investigated treatment interruptions as an alternative approach to HIV therapy. This article will present an overview of the various strategies researchers are employing to alter the HIV therapeutic landscape with the use of treatment interruptions, and the effect these interruptions have on immunologic and virologic control of HIV. However, the benefits of STI are questionable and sometimes difficult to interpret. Comparison between studies is complicated because of varying patient populations with different treatment, immunologic, and virologic histories and characteristics. STI duration and design are discrepant: in particular, the triggers for re-initiating therapy (pre-determined schedule, viral load rebound, or drop in CD4 T cell count). In addition, definitions of viral suppression and virologic failure are variable.

TREATMENT INTERRUPTION IN PATIENTS WITH PHI AND TREATMENT-NAÏVE PATIENTS

Patients treated with HAART during primary HIV infection (PHI) provide a unique opportunity to examine the effects of STIs on immunologic and virologic control and HIV dynamics, particularly the viral set-point. Data suggest that early antiretroviral therapy is beneficial in patients diagnosed during PHI; however, this early and sustained treatment may lead to health problems caused by the long-term drug exposure. Controlled treatment interruptions in this patient population may be a feasible alternative to minimize drug-related toxicity. Additionally, a hypothetical STI-induced autoimmunization achieved during PHI could potentially lead to an enhanced HIV-specific immune response, lowered viral set-point, and optimal viral control even in the absence of continuous antiretroviral treatment.^{2,11}

Several small studies have shown that interruption of antiretroviral treatment in this population is not detrimental, though it is uncertain if any benefits are derived. Whether treatment interruptions afford more than just a break from treatment by actually altering the dynamics of HIV and lowering the viral set-point is unclear. For patients treated during PHI, data from a variety of studies and case reports suggest that viral suppression can be maintained for at least 6 months, and in some cases, for up to 2 years after treatment interruption,^{11,14-17} though HIV RNA was still detectable, indicating that the virus had not been eradicated.¹⁶ Studies of STIs in patients treated with HAART during early infection, rather than during the acute PHI phase, have also observed viral suppression for 1 to 2 years after treatment interruption.¹⁸⁻¹⁹ In addition to sustained viral suppression, robust and broad HIV-specific immune responses that were positively associated with durable viral suppression have been detected in a small number of patients following an STI.^{16,19} Indeed, one small study observed plasma viral rebounds that became smaller and smaller with each successive interruption.¹¹

HIV-infected patients who have previously been antiretroviral treatment naïve also appear to suffer no harm from an interruption in treatment. An early report examined the effect of a single, 28-day treatment interruption after patients were treated for 28 days to investigate the effects of an occasional unscheduled interruption.⁷ Though viral load increased once treatment was interrupted, it quickly returned to baseline levels once treatment was re-initiated, and no drug-resistance mutations were detected. Moreover, in a similar patient population, Lori and colleagues²⁰ observed an increase in the time to rebound after each successive treatment interruption. In fact, a lower viral set-point was induced and maintained for several months in 2 patients.

TREATMENT INTERRUPTION IN PATIENTS WITH CHRONIC HIV INFECTION

The benefits of STIs, including the potential to induce autovaccination, have been studied extensively in patients chronically infected with HIV. Initially, researchers hypothesized that asymptomatic, chronically HIV-infected individuals who had good, long-term immunologic and virologic control under HAART could experience continued suppression in the absence of antiretroviral therapy. Unfortunately, most data have not supported this concept. Some studies have reported such viral suppression, but only in a small percentage of patients.²¹⁻²³ Thus far, only Dybul and colleagues,²⁴ using an STI schedule of 7 days on treatment followed by 7 days off treatment, observed sustained viral suppression (HIV RNA less than 500 copies/mL) for up to 68 weeks in all 8 patients who remained on study. In addition, no newly emergent drug-resistance mutations were detected, and patients experienced significant decreases in cholesterol and triglyceride levels. While these findings suggested that shorter treatment interruptions may be optimal because the virus may not have an opportunity to rebound, the randomized Staccato study failed to replicate these results using the same STI design.²² Though patients were successfully treated with HAART prior to treatment interruption, over half of the patients who participated in the treatment-interruption arm experienced virologic failure. Consequently, that arm of the study was prematurely terminated.

Several larger studies have examined an STI schedule that involves interrupting current HAART therapy for 2 weeks, resuming HAART for 8 weeks, and stopping treatment at week 40 until re-initiation of treatment becomes necessary.^{6,21,25} In contrast to patients with PHI,^{11,16} patients chronically infected with HIV did not experience an autovaccination event in a manner that enhanced viral control or lowered the viral set-point.^{6,21} However, a small per-

centage of patients maintained viral suppression (defined as viral load less than 5,000 copies/mL) for up to 3 months (17%) and 1 year (8%) after stopping treatment, and only 1 patient developed drug resistance that required salvage therapy,²¹ though viral rebound (HIV RNA greater than 100 copies/mL) was detected within 8 days in the majority of patients.²⁵ Predictors of response were low pre-HAART viral load and no or few incidences of viral rebound during first 40 weeks of the study.²¹

Longer cycles of intermittent HAART show no benefit in terms of immune control or a reduction in adverse events when patients are off treatment for 4 weeks followed by 8 weeks of HAART.²⁶ In fact, 3 patients in the STI arm showed evidence of newly emergent drug resistance, a finding that has been reported by other research groups.²⁷ However, others found that drug-resistance mutations detected during STIs were intermittently present and not persistent. Moreover, detection of these mutations did not predict failure to resuppress virus once treatment was re-initiated with the same antiretroviral agents.²⁸

In addition to interrupting treatment based on a prescheduled timeline, studies have also tested the idea of stopping and starting therapy based on CD4 T cell counts and viral load in patients chronically infected with HIV. As such, patients would stop treatment once their CD4 T cell counts reached a predetermined value and restart therapy once that value dropped to a specified level. The same principles are applied to STIs based on viral load; interrupting treatment once suppression is achieved and re-initiating treatment once viral rebound occurs. One of the largest trials in the history of any infectious disease, known as the **Strategies for the Management of Anti-Retroviral Therapy (SMART)** study, was designed by investigators with the Community Programs for Clinical Research on

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AIDS (CPCRA) and will compare a strategy of delayed, episodic HIV therapy against one of immediate, uninterrupted therapy in patients who are treatment naïve and treatment experienced. The study will follow 6000 HIV-infected subjects for as long as 8 years. The episodic treatment arm (also referred to as the “wait group”) involves stopping or deferring treatment until CD4 T cell counts fall below 250 cells/mm³, at which point subjects will initiate treatment to increase CD4 counts to at least 350 cells/mm³ for 2 consecutive visits, after which treatment would be interrupted again. In the other study arm (referred to as the “go group”), subjects immediately begin therapy regardless of CD4 T cell count and remain on antiretroviral therapy (changing regimens as needed to suppress virus) for the duration of the trial.²⁹

Other smaller studies have already reported results using these types of strategies in patients with chronic HIV infection. The Staccato study also investigated a CD4-guided STI and preliminary data show that no patient has failed this treatment arm to date.²² In contrast, another study detected viral rebound in patients within 2 to 3 weeks after interrupting treatment based on either CD4 T cell counts or viral load, though the patients had previously maintained viral suppression for more than 2 years with HAART.³⁰ However, the definition of viral rebound differs dramatically from study to study. For example, the Staccato study²² defined virologic failure as HIV RNA greater than 500 copies/mL, while virologic failure was defined as HIV RNA greater than 50 copies/mL in the study conducted by Davey and colleagues.³⁰ Other studies using viral load as an indicator of treatment re-initiation detected viral rebound within a few days to 1 month after interrupting treatment in the majority of patients. However, these levels became undetectable once treatment was re-initiated,^{23,31,32} and drug-resistance mutations were rarely detected.^{31,32} Observations from patient case studies have reported similar findings, observing rapid viral rebound

that quickly drops to undetectable levels once treatment is restarted.⁹ Importantly, one study reported that each consecutive STI was associated with more control of viral replication. Moreover, an increase in HIV-specific CD8 T cell responses was also detected, but only in about one-third of patients.²³

TREATMENT INTERRUPTION IN MULTI-DRUG-EXPERIENCED PATIENTS

Treating multi-drug-experienced patients is challenging because many of these patients have exhausted all treatment options as a result of broad cross-resistance. Continuing suboptimal treatment may maintain CD4 T cell counts but also allow the emergence of additional drug-resistance mutations, further limiting treatment options. The concept of STIs in this patient population stems from the hypothesis that interrupting treatment may enable a rebound in wild-type, drug-susceptible virus and perhaps elicit an HIV-specific immune response. As a result, the patient would experience enhanced virologic suppression once a salvage regimen was started after the interruption. Temporary reversal of drug-resistance mutations can occur and, while transient, may provide an opportunity for salvage therapy to work with some increased efficacy. Further, it was anticipated that immunologic control could be maintained for brief periods without treatment because of preserved CD4 T cell increases from previous therapy.^{3,12}

One large, randomized trial (CPCRA 064) examined the effects of a 4-month STI followed by the initiation of an optimized regimen based on the presence of drug-resistance mutations in individual patients.³³ Though 64% of patients in the STI group experienced a shift to wild-type virus by 4 months, there were significantly more cases of disease progression in the STI group, compared to the control group. CD4 T cell counts decreased during interruption, and though they recovered on therapy, values were consistently lower in the STI group

during follow-up, compared to the control group. Similarly, the randomized Retrogene study examined the efficacy of combining several drugs, commonly referred to as “mega highly active antiretroviral therapy” or “mega-HAART,” after a 3-month STI.³⁴ Complete reversion to wild-type HIV was detected in 35% of patients in the STI group, though reversion was not associated with viral suppression in this study.

In contrast, other smaller studies have reported positive effects of STIs prior to initiating salvage therapy.^{10,13,35} A multiple-drug (approximately 8 drugs) salvage regimen, referred to as GIGHAART, initiated after an 8-week STI demonstrated a significant virologic and immunologic benefit up to 48 weeks.³⁵ Moreover, the inclusion of an agent in a salvage regimen to which the subjects’ virus was still susceptible was beneficial and led to a durable virologic response.^{10,13} These data support the idea that patients with drug-resistant HIV could benefit from an STI prior to salvage therapy, particularly if a drug to which they are not resistant is included. Another report found that viral suppression after an STI was associated with decreased viral load at the time of treatment interruption, inclusion of new drugs when re-initiating treatment, and fewer drugs to which the patient had reduced susceptibility.³⁶ Moreover, a shift to wild-type virus was associated with subsequent viral suppression, though patients still experienced viral rebound and a drop in CD4 T cell levels once treatment was interrupted.³⁶

Why the GIGHAART study and the studies by Deeks and colleagues reported positive effects from STIs while other studies^{33,34} found no real benefit to STIs (and even detrimental effects) is not quite clear. Choice of salvage regimen and the number of drugs included in the salvage regimen could be factors. In addition, duration of STI and degree of immunosuppression in the study sample may be responsible.¹²

ALTERNATING HAART REGIMENS— A DIFFERENT TYPE OF INTERRUPTION

Recently, a strategy of proactively alternating regimens while HIV is suppressed has been explored.⁵ Typically, an antiretroviral regimen is changed only after it fails. Alternating treatment before it fails may provide a way to reduce viral replication capacity and accumulation of drug-resistance mutations. Older studies performed prior to the introduction of HAART studied the effects of alternating mono- or dual-therapy, but none examined this strategy with HAART. In the SWATCH study (SWitching Antiviral Therapy Combination against HIV-1), treatment-naïve subjects alternated two 3-drug regimens every 3 months with continuous administration of HAART (see Figure on page 10). Researchers found that virologic failure was significantly delayed in patients who alternated treatment, compared to those subjects who received the same regimen consistently. These findings suggest that this strategy may be beneficial in HIV-infected patients, though it should be noted that this study included a somewhat small sample size and improved regimens are now available compared to the older drug regimens used in this study.

TREATMENT INTERRUPTION IN THE SETTING OF IMMUNE-BASED THERAPY

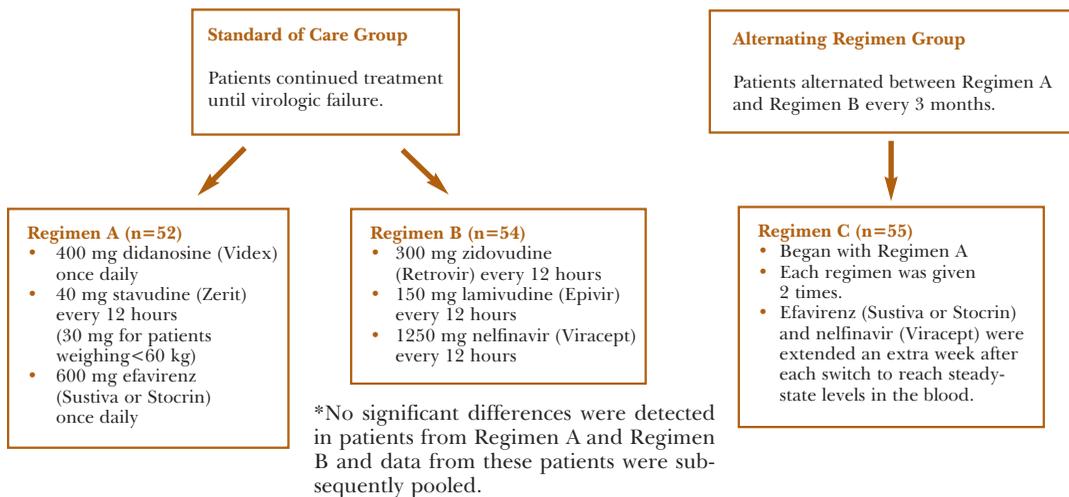
The addition of various immune-modulating agents has also been investigated in conjunction with treatment interruption. Recombinant human granulocyte macrophage-colony stimulating factor (GM-CSF) was initially developed to treat chemotherapy-induced neutropenia. Research suggests that GM-CSF may stimulate immune responses and improve viral control in HIV patients. When given to chronically HIV-infected patients during an STI, GM-CSF blunted viral rebound and substantially prevented decreases in CD4 T cells in the absence of antiretroviral treatment.³⁷

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Figure. Design of the SWATCH Study

- Treatment-naïve subjects were recruited from 15 hospital-based outpatient clinics in Spain and Argentina.
- Subjects were randomly assigned to one of the following groups:



RESULTS

- Virologic failure over 48 weeks (HIV RNA >400 copies/mL) was significantly delayed in the Alternating Regimen Group compared to the Standard of Care Group.
- Significantly more patients in the Alternating Regimen Group had HIV RNA levels <400 copies/mL while receiving treatment.
- Detection of drug-resistance mutations was more frequent in the Standard of Care Group.
- CD4 and CD8 T cell levels were similar in all groups.
- Quality of Life scores, drug adherence, and frequency of adverse events were similar in all groups.

Other studies have looked at STIs with interleukin-2 (IL-2). In particular, the combination of exogenous interleukin-2 (IL-2) and HAART is associated with a reduction in the number of latently infected CD4 T cells.³⁸ IL-2 may assist in altering the dynamics of HIV during an STI by increasing the HIV-specific immune response. Moreover, patients with a history of IL-2 therapy may also derive benefits from an STI, compared to patients who have never received exogenous IL-2.²⁴ However, studies that have investigated the effect of IL-2 therapy in conjunction with an STI have shown no substantial benefit. Indeed, all such patients experienced viral rebound within 2 to 3 weeks of treatment interruption, regardless of whether they had

previously received IL-2.³⁰ When combined with HAART, no significant differences were detected between patients who received IL-2 versus those patients who received HAART alone, in terms of eliciting an HIV-specific immune response²³ or in terms of persistent viral suppression after treatment discontinuation.³⁹

The addition of hydroxyurea (HU, also known as hydroxycarbamide) has provided some benefit to patients when given in conjunction with an STI. HU possesses antiviral and cytostatic effects⁴⁰ and may blunt viral rebound during STIs.³⁷ The combination of IL-2 + HU + HAART prior to treatment interruption in patients with PHI was signif-

icantly associated with virologic suppression (HIV RNA less than 5000 copies/mL).¹⁷ Case reports of patients recently infected with HIV who were treated with antiretroviral therapy combined with HU have also reported viral suppression for a year or longer following treatment interruption.^{16,18} HU was associated with persistent control of HIV in a small percentage of patients with PHI in one study.⁴¹ Importantly, 2 treatment-naïve patients experienced an increase in the time to rebound after each successive treatment interruption and the induction and maintenance of a lower viral set-point for several months.²⁰ The addition of HU in chronically HIV-infected patients led to more cases of viral suppression, compared to patients who received HAART alone.⁴⁰ Both groups experienced increased immune responses, regardless of treatment arm, indicating that HU does not have a substantial effect on HIV-specific immune responses. However, patients in the HU group achieved a lower peak viral load rebound and lower viral load set-point.

Taken together, these findings suggest that many of these agents may be beneficial in maintaining viral suppression and perhaps lowering the viral set-point in the absence of antiretroviral therapy. However, these studies tend to have a small sample sizes and response to treatment occurred in an even smaller number of patients. In addition, many of these agents are associated with frequent, and sometimes severe, side effects. Treatment with IL-2 caused a temporary flu-like syndrome,²³ and pain, redness, and swelling were observed in the majority of patients at the sites of GM-CSF injection.³⁷ More serious events, such as diarrhea, hypotension, malaise, pharyngitis, periorbital edema, and back pain were also observed in patients who received GM-CSF.³⁷ In one study investigating the effect of HU, over half of the subjects stopped taking HU because of intolerable side effects, including peripheral neuropathy and oral ulcerations.⁴¹

FACTORS ASSOCIATED WITH RESPONSE TO STIs

Why some studies report benefits with STIs, while others report detrimental effects is not clear. Patient population plays a large part in this outcome and as discussed in an editorial by Aiuti and Giovannetti,³ patients with good immunologic and virologic control, who were treatment naïve before starting HAART and who are currently being treated with effective drug combinations, will probably have the best outcomes with STIs. Patients with PHI who undergo treatment interruptions fare far better than those who are multi-drug resistant or who have been chronically infected with HIV for years. Nevertheless, identifying factors that influence immunologic or virologic control during an STI would provide a means to predict whether treatment interruptions would be beneficial to specific patients.

Obvious predictive factors include pretreatment CD4 T cell nadir, plasma HIV RNA levels, and presence of drug-resistance mutations. Pretreatment CD4 T cell nadir correlates with the ability to suppress virus during an STI.^{3,14} In the BASTA study, patients with high CD4 T cell nadirs remained on STIs longer than those with low CD4 T cell nadirs. The researchers concluded that STIs may be safe in patients with CD4 T cell nadirs greater than 500 cells/mm³ and that patients with low CD4 T cell nadirs (less than 200 cells/mm³) are at high-risk and should not participate in any type of treatment interruption.⁴² In fact, the rate of viral rebound is increased in patients with advanced HIV infection (defined on the basis of low CD4 T cell counts).⁴³ Plasma HIV RNA level is also a critical factor in determining how well an individual will be able to suppress virus once treatment is discontinued,^{3,14} as well as presence of drug-resistance mutations prior to STI.²⁴

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Other, not-so-obvious factors that are associated with virologic suppression during STIs include levels of endogenous IL-15 and tumor necrosis factor- α , (but not levels of endogenous IL-2, IL-7, or interferon- α).⁴⁴ An abstract at the 10th Conference on Retroviruses and Opportunistic Infections presented data showing that lower pre-treatment HIV-*envelope* nucleotide sequence diversity and amino acid diversity were associated with improved viral control after an STI.⁴⁵ Finally, exogenous factors such as prior antiretroviral regimens³ and the specific HAART regimen used during the re-initiation component of the STI strategy also appear to be important. For example, in the Staccato study, only 1 out of 8 patients taking an efavirenz (Sustiva)-based HAART regimen experienced virologic failure.²²

CONCLUSION

While an abundance of studies have examined the concept of treatment interruption in HIV-infected patients with various degrees of immunosuppression and disease state, drawing any conclusions is virtually impossible except that the STI strategy is still experimental and could be dangerous in some patient populations. With the exception of studies conducted in multi-drug-experienced patients, most studies tend to be performed in low-risk patients with good immunologic and virologic control and few drug-resistance mutations. In addition, the majority of studies include small sample sizes.

In patients with PHI or who are treatment naïve, STIs apparently are not detrimental and may alter the dynamics of HIV, potentially lowering the viral set-point in a select group of patients. However, this has not been shown definitively and though no obvious detriment was detected in the short term, the long-term effects of not suppressing virus fully and continually are not known and may affect clinical outcome and survival.

Overall, data from studies conducted in patients with chronic HIV infection suggest that while they experience viral rebound quickly after treatment

interruption, suppression often occurs quite easily after treatment is resumed, thus suggesting no detriment to immunologic or virologic control. However, STIs have not been shown as beneficial in this patient population because most studies, with the exception of Dybul and colleagues,²⁴ report sustained viral suppression only in a minority of patients, if any. Possible reasons for the positive findings observed by Dybul and colleagues²⁴ include different HAART study regimens, shorter treatment interruption, absence of drug-resistance mutations prior to study enrollment, higher CD4 T cell nadir, and history of IL-2 treatment in the majority of patients (patients in other comparable studies had no history of IL-2).²⁵ It must be stressed that several reports show STIs to be detrimental in patients with chronic HIV infection.^{22,26,27} The data are also mixed regarding multi-drug-experienced patients; however, the CPCRA 064 study observed significantly more cases of disease progression in the STI group, compared to the control group.³³ Importantly, data suggest that increased viremia experienced during an STI potentially increases the risk of HIV transmission,⁴⁶ a situation that could lead to substantial increases in HIV transmission if STIs became a routine part of clinical care.

Though the concept of STI-induced autovaccination appears to have little merit any more (see page 16), the idea of reduced total drug exposure in the absence of large drops in CD4 T cell count or unrecoverable viral rebound is still attractive as a way to reduce drug toxicity and the prohibitive costs of antiretroviral treatment. However, the assumption that less drug will automatically result in less toxicity, lower costs, and improved adherence has not been validated.² After more than 5 years of STI research, many questions still remain. However, one thing is certain—antiretroviral treatment, though beneficial and potentially lifesaving, is only one part of the HIV therapeutic equation. The immune system plays a part as well. Perhaps during windows such as STIs, the dynamics between immunity and virus can continue to be characterized, but with a safety net afforded by HAART.

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Trying to make sense of treatment interruptions

By Dorothy E. Lewis, PhD, and Richard E. Sutton, MD, PhD
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DO TREATMENT INTERRUPTIONS MAKE IMMUNOLOGIC SENSE?

Controlled treatment interruptions seemed like a reasonable idea a few years ago. From a historical viewpoint, by 1996, the message was, “Now that we have better and more effective drug regimens, we might actually be able to rid the body of HIV.” Several years later, the hope (or hype) was gone and a new challenge arose. Remember, this is HIV—there is always a new challenge. The newer drugs contained HIV better, but they came with new or more blatant clinical side effects such as problems with fat redistribution or worse. Not to mention the long-term expense of the medications.

At about the same time, immune studies showed that HIV-specific CD4 T cells could be found, especially in the newly infected and in those treated early after infection. These new assays were based on measuring antigen-specific cytokine production in both CD4 and CD8 T cells from HIV-infected people. Curiously, T cells that made cytokines after antigen exposure *in vitro* were detected most abundantly in those with fairly intact immune systems and some viremia. Previous assays for cellular immunity required antigen-specific T cells to proliferate and in the 1980s, numerous investigators showed that very few HIV antigen-specific CD4 T cells could be detected. However, the new, short-term, antigen-specific cytokine assays did not require such proliferation to demonstrate T cell function.

Therefore, based on the promise of heightened immune responses in the presence of viremia in some patients (as measured by these cytokine assays), some thought that perhaps a good strategy

to bolster HIV immunity would be to provide an opportunity for small, controlled quantities of HIV to be made—ostensibly to provide antigen and to drive the immune response. This was to be done in a structured, monitored way so that if viremia spiked, the drugs could be re-instated. Many variations on this basic idea have been put into trials in the last 5 or 6 years. Early promising results suggested that in early infection, the immune response after such interruption of therapy seemed to contain HIV longer than thought possible. Indeed, a consensus is that if the immune system is still fairly intact, therapy interruption might indeed boost CD8 T cell responses, which likely contain HIV longer.

However, from an immunologist’s perspective, the idea that antigen was needed to bolster the immune response never made much sense. Even when viral replication is halted, which vastly reduces the amount of circulating HIV, the amount of non-replicating HIV trapped in the lymph nodes all over the body should provide plenty of antigen for a continued immune response. In addition, if memory T cells had been formed (rather than short-term, cytokine-producing, HIV-specific T cells), then they should be capable of mediating ongoing HIV-specific immune responses, even in the *absence* of viremia. This notion is complicated because there is preferential HIV infection of HIV-specific CD4 T cells, perhaps crippling future HIV-specific antibody and/or CD8 responses. However, the reality is that most infected people make sufficient and even robust antibody and CD8 T cell responses to HIV. The quality of the response seems to be the problem and a rationale is that while many HIV-specific T cells are generated, too many do not become long-

term memory cells. This eventually allows the virus to escape containment. Indeed, recent data show that in those who have multi-drug resistant virus, therapy interruption is actually a bad idea because it allows HIV to mutate even further.

DO TREATMENT INTERRUPTIONS MAKE VIROLOGIC SENSE?

During acute or chronic infection, many HIV-infected individuals who are not on drug treatment have high levels of circulating virus that is ostensibly wild type; the virus has no detectable mutations that would make it resistant to drugs like tenofovir (Viread) or lopinavir/ritonavir (Kaletra). But don't be fooled: the virus is under tremendous selective pressure from the immune system and is trying (and largely succeeding) to stay at least a step ahead of neutralizing antibodies and CD8 T cells (and probably other aspects of the immune response). A tremendous amount of virus is produced and destroyed each day, and because of the errors made during replication of the virus, mutations arise constantly that are subject to selective pressures. Anyone infected with HIV is essentially a microcosm of Darwinian evolution. Each virus has a certain fitness, and the dynamics of the host immune response ensure that the virus needs to keep "moving."

Now throw antiretroviral drugs into the mixture. Clearly, the 23 antiretroviral medications approved thus far have changed the face of HIV disease and AIDS forever. The drugs, when prescribed and taken properly, dramatically and rapidly reduce the amount of circulating virus down to "undetectable" levels. In most circumstances, if one looks hard enough, there is evidence that the virus is still probably replicating at very low levels in immune-privileged sites such as the brain and testes and in secondary lymphoid organs. That means that the virus can (and does) still mutate, but at a much slower rate. That also means less chance of viral escape from the medications.

Now remove the drugs, either in a prescribed way (a treatment interruption) or because of lack of compliance. One little-considered fact is that drugs have different half-lives in the body: each is cleared at a

different rate. Thus, during treatment interruption the virus may be exposed to only a single agent, perhaps just for a day or two. Because the virus replicates constantly, even such brief exposure can allow drug-resistant viral species to be selected. This has been shown in Africa, where pregnant women who were given a single dose of nevirapine (Viramune) during labor developed nevirapine-resistant virus. In the absence of antiretroviral drugs, the virus is free to mutate within the confines of a depleting immune system. But the more replication and mutation allowed, the greater chance that drug-resistant virus will develop. If that occurs, then the virus is already a step ahead when a drug regimen is restarted.

Surprisingly, drug-resistant viral mutants already exist in the virus population (ie, the virus does not suddenly decide to develop resistance to a drug it encounters). However, the mutants are present at such low levels that we cannot detect them, and in general they are less fit than wild-type virus and so do not replicate to the same extent. Sometimes such viral mutants are simply "archived" in a resting T cell or macrophage, only to appear when that cell is activated. But once the virus is exposed to drug, selective pressure favors the drug-resistant virus (even though it may be less fit). A clinical example of this is with viral resistance to lamivudine (Epivir): the emergent virus has the reverse transcriptase mutation M184V, rendering it less fit than wild-type virus and, therefore, less prone to cause a decline in CD4 T cells.

We all know that interruptions in treatment give the patient a break from complex regimens and the increasing number of side effects and toxicities. But we also know that treatment interruptions give the virus a break as well, allowing increased replication and favoring the development of drug resistance that only becomes apparent after the medications are restarted. That is why more patients are failing treatment interruptions in terms of rapidly rising viral loads and falling CD4 counts, and why more clinicians are looking away from STIs toward other creative treatment options.



Is autovaccination dead?

By Bernard Hirschel, MD

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“Long-term non-progressors have a strong cellular anti-HIV immune response.” Thus starts many a review article on HIV immunology. And many readers therefore conclude, “After induction of a strong anti-HIV immune response, an ordinary patient with HIV infection will be transformed into a long-term non-progressor.”

But how to induce a strong anti-HIV immune response? In the absence of effective HIV vaccines, the virus itself will have to do. Stop HAART, have the virus rebound, start treatment again, and repeat the stop-start cycle a few times. This schedule would expose patients to several pulses of HIV antigen, and presumably jolt the immune system into responding. Such “autovaccination” would be followed by withdrawal of HAART. Hopefully, the newly stimulated immune system would then contain the virus without drugs.

Too good to be true? Despite widespread skepticism, data from experiments in monkeys with Simian Immunodeficiency Virus (SIV), as well as isolated case reports, suggested that the idea might have merit.

It has now been put to the test in 133 patients recruited in Switzerland and Spain. HAART was interrupted for 2 weeks, then restarted and given for 8 weeks. The off-on cycle was repeated 4 times. After week 40, treatment was suspended indefinitely, unless CD4 T cell counts dropped dangerously or viral loads became excessive. The level of post-trial viremia after 12 weeks off therapy was measured and compared to the level before HAART, with the hope that viremia post-trial would be lower than pre-HAART.

Anti-HIV immune responses were indeed stimulated, as measured by the number of lymphocytes reacting to HIV antigens, which rose from 300 to 2000 per million. But the treatment interruptions did not significantly influence the post-trial viremia, which rose close to the level before HAART. Moreover, a strong anti-HIV immune response in no way predicted low post-trial viremia; to the contrary, patients with strong stimulation of anti-HIV immune responses tended to have higher, not lower, viremia after interruption of therapy.

These results provide strong arguments against the hypothesis that “autovaccination” helps to improve immune control of HIV. They also cast a shadow of doubt on the prospects of therapeutic vaccination. Indeed, the immune response induced by the treatment interruptions was stronger than the most vigorous immune responses induced so far by experimental vaccines, and of course, the “vaccine” and the “challenge” viruses were exactly the same—no worries regarding mutants and variations in subtypes! If such an immune response is ineffective, so would a less vigorous response induced by a heterologous therapeutic vaccine.

Is autovaccination dead? Pretty much so, at least for the vast majority of patients who started therapy during chronic HIV infection. The concept of intermittent therapy may still have value—not because it provides effective autovaccination, but because lowering exposure to HAART might diminish side effects and diminish costs. Prospective trials comparing intermittent with continuous treatment are ongoing.



Treatment interruptions in the salvage setting: What have we learned?

By Veronica Miller, PhD
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Patients with multi-drug-resistant virus are still facing the dilemma of putting together an effective treatment regimen that is tolerable. Ideally, strategies for managing treatment in such patients would be based on introducing new treatments, those specifically designed to inhibit HIV with accumulated drug-resistance mutations, such as enfuvirtide (Fuzeon), or experimental compounds like tipranavir, TMC114, and TMC125. However, such new agents usually are available one at a time because they are developed by different companies and have different timelines for research and development. This leaves clinicians and patients with the problem of how to put together a complete regimen with more than one optimally active drug.

The early reports of what happens to multi-drug-resistant virus populations when treatment is interrupted (the well-known shift to wild-type virus) raised much hope that this could be an effective strategy for dealing with the problem of resistant viruses: just let them disappear and be replaced by wild-type virus. What we have learned, however, is that this may not be such a good strategy after all. Clinically, patients may be better off staying on treatment, as shown by the CPCRA 064 study recently reported by Jody Lawrence and her co-investigators (see data review, page 5). The reasons for this notion include basic principles of drug-resistance selection, viral fitness, resulting shifts in viral population, and the benefits of treatment even for patients with “treatment failure.” Perhaps much of the optimism associated with the implementation of this treatment-interruption strategy was based on a misunderstanding of what the shift in the viral population actually represents.

The population of HIV within a patient comprises quasispecies with the high diversity and rapid evolution of viral genomes characteristic of RNA viruses; this forms the basis for the efficient selection of drug-resistant mutants observed under suboptimal treatment conditions. As long as antiretroviral drugs exert selective pressure, the drug-resistant strains of HIV will have the upper hand. But, resistance mutations frequently affect enzyme activity and result in reduced fitness of the resistant HIV strains compared to wild-type viruses—when compared in drug-free conditions. This explains why, as soon as the selective pressure of the drugs is removed, the wild-type population will outgrow the resistant one(s). This phenomenon is observed *in vivo*, indicating that wild-type virus has been archived during the on-treatment period—just as drug-resistant strains will be archived during the off-treatment period (see also essay, page 14). The key is that neither population may ever be completely eradicated in any one individual over a lifetime of being treated; therefore, re-initiation of treatment may well lead to reselection of the resistant strains present in the archived collection of viruses. However, the virus with reduced fitness may be less harmful to the patient and thus the overgrowth of wild-type virus may not be the desired effect either. Each of these points has been documented with data derived from clinical samples.

Perhaps the most useful information that has come out of this line of research is the understanding that the “failing” treatment does provide clinical benefit, although the patient clearly may be experiencing

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virologic failure. One of the first indications of this premise was the observation that viral loads increase and CD4 T cell counts fall in patients stopping therapy. The association between clinical benefit and antiretroviral treatment may be indirect (attributable to changes in the fitness of mutant viruses) or direct (attributable to the residual activity of the “failing” regimen). Evidence for the “fitness” effect comes from the temporal association between loss of resistance phenotype and the steepest changes in surrogate markers. Studies by Stephen Deeks and colleagues have also given credence to this hypothesis. However, surrogate marker changes have been observed even in patients whose viral populations did not exhibit the “shift,” indicating that residual antiviral activity (in spite of drug resistance) may play a role. Surprisingly, support for this notion has come from testing the effect of removing single drugs from a failing regimen—in particular, nucleoside reverse transcriptase inhibitors (NRTIs).

Three recently reported studies of partial or single-drug interruption indicate that a failing drug may not be completely devoid of activity in patients whose virus carries resistance-associated mutations to that drug. Frank Maldarelli and colleagues from the National Institutes of Health (NIH) reported that interruption of stavudine (Zerit) in 3 patients who were receiving it as part of a failing regimen resulted in significant increases in viremia. The patients’ baseline viral genotypes had multiple mutations associated with stavudine resistance. Upon resumption of stavudine treatment, HIV-1 RNA levels declined to baseline, leading the authors to conclude that stavudine contributed to antiviral activity in this regimen.¹ Similarly, Tom Campbell and his colleagues from the University of Colorado demonstrated that interruption of lamivudine (Epivir) in 4 patients on a failing regimen resulted in a 0.5 log increase of HIV-1 RNA, independent of an M184V → M switch. Thus, lamivudine appears to contribute to antiviral activity independently of the M184V effects on viral fitness and susceptibility to

zidovudine (Retrovir).² Finally, in a study of partial treatment interruption presented by Stephen Deeks, interruption of the NRTI component of a failing regimen resulted in rapid increases of HIV-1 RNA levels.³ These data help explain why patients on treatment (particularly those “salvage” patients who are heavily treatment experienced with several drug-resistance mutations), no matter how high the viral load or low the CD4 T cell count, appear to do better clinically than patients who are off treatment.^{4,5} In the final analysis, each of the 2 mechanisms—viral fitness and residual antiviral activity—are likely to contribute to clinical benefit.

Only 1 of the 3 controlled clinical trials described above was powered to assess the clinical impact of a treatment strategy that includes a period of treatment interruption. As described in the literature review in this issue of *RITA!* (see page 5), the conclusions reached by investigators of treatment interruption are often in disagreement with each other.

All 3 studies described above documented changes with regard to which viral variants comprised the predominant or majority population. Interestingly, however, the CPCRA 064 study demonstrated that patients with a shift in predominant viral population towards wild-type virus did have better virologic and immunologic responses, confirming the earlier observations from observational studies and the GIGHAART study (see data review, page 5). But the surrogate marker responses did not translate into a clinical benefit. The decrease in CD4 T cell count prior to re-initiation of treatment may have been sufficient to put the patients at risk for clinical progression, regardless of the subsequent response. An estimated median of 4.9 months passed for the CD4 T cell count to exceed baseline values in the treatment-interruption group.

The study with the most positive conclusions (a significant benefit for treatment interruption in terms of surrogate marker responses) was GIGHAART,

which used the shortest interruption time and the highest number of drugs in the new treatment regimen. If residual drug activity plays a therapeutic role, as indicated by the single-drug interruption studies, then the effects of such antiviral activity would have a greater chance of being detected if more drugs are used in treatment combinations. However, the clinical impact of having extremely reduced CD4 T cell counts for too long may override the effect of a superior virologic response offered by multiple agents.

The basic concepts of drug-resistance selection and viral fitness, together with the documented benefit of staying on treatment, should guide patient management decisions. In situations where treatment interruption is necessary, the interruption times should be as brief as possible, with careful monitoring of CD4 T cell counts during the interruption interval. The available data suggest that the composition of the new treatment regimen should be based on including a maximum number of truly “active” drugs.

So, where should research in this area now be focused? The best overall strategy will be one that helps us avoid situations that foster the development of multi-drug resistance and intolerable long-term toxicities. Whether this problem of multi-drug resistance will continue to be prevalent after years of HAART remains to be seen, especially considering the many current patients who are survivors from the pre-HAART treatment era and who therefore have likely been exposed to suboptimal therapy. Has HAART really been as effective in preventing resistance development as we had predicted? We should continue assessing the prevalence and characteristics of multi-drug resistance over time. Finally, the assessment of each drug’s contribution to the benefit sustained by a “failing” regimen is another area that should be developed, as is the use of immune-based therapies that may provide protection during periods off treatment.

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FACT SHEET on Structured Treatment Interruption

WHAT IS A STRUCTURED TREATMENT INTERRUPTION (STI)?

An STI is the complete and abrupt stopping of HIV medications under medical supervision; it begins on a day agreed upon by physician and patient and usually lasts for a fixed amount of time.

WHAT IS THE PURPOSE OF AN STI?

The purpose of an STI depends on the needs and conditions of the individual, but the 3 most common reasons for a break in treatment include:

- 1) **Possible stimulation of the immune system against HIV** – Some researchers have believed that complete suppression of HIV (undetectable viral load) may stop the immune system from “seeing” enough virus to stimulate a strong response. During an STI, the viral load rises. By forcing the immune system to contend with periodic bursts of virus, some researchers think it may be possible to strengthen the body’s natural response to HIV. This approach seems to hold the most promise for the small number of individuals who began HIV drugs early—during acute, or primary, HIV infection. However, most research in patients with chronic HIV disease suggests that such immune stimulation or “autovaccination” is not a successful strategy for treating HIV.
- 2) **Relief from the side effects and toxicities of HIV medications** – Although potentially life-saving, HIV drugs can be difficult to take and sometimes dangerous. The drugs are associated with a number of side effects and toxicities, including diarrhea, nausea and vomiting, elevations in blood fat levels, and changes in body shape. An STI may provide temporary relief from some of these problems; it may also relieve the feeling of being tied to a medication regimen.
- 3) **Partial restoration of drug-sensitive (“wild-type”) virus** – For individuals who have taken many HIV medications and developed drug resistance, some investigators have suggested that an interruption in treatment could once again make the virus “drug sensitive.” Even though there may be some truth to this (study results are conflicting), the benefits are limited. Drug-resistant virus never really goes away, and for individuals who have ever had an AIDS diagnosis, an interruption in treatment can mean a dramatic fall in T cell count and a return of symptoms or illness.

WHAT’S THE DIFFERENCE BETWEEN AN STI AND “NON-COMPLIANCE” OR “NON-ADHERENCE”?

During an STI, you completely and abruptly stop taking all of your HIV drugs for a fixed amount of time. Nonadherence, on the other hand, refers to missing doses of medication or only partially taking the medication. It’s the difference between doing something all the way and doing it only part of the way. Nonadherence can cause resistance to HIV medications.

ARE THERE RISKS TO AN STI?

Yes. Depending on your treatment history and medical condition, an STI could produce a sharp decline in your T cell count and a return of illness. This is true for individuals with a T cell “nadir” below 200. (Nadir means the lowest your T cell count has ever been.) For example, if your nadir was less than 200, but your count rose to 500 after you started HIV drugs, your count will likely drop quickly if you interrupt treatment. On the other hand, if your T cell count was 700 to begin with and didn’t go up much after you started treatment, it probably won’t go down very quickly if you interrupt treatment. Nonetheless, close monitoring of your viral load and blood work is important in the first few weeks and months after interrupting treatment.

Also, during periods off treatment, HIV can increase its diversity, which may allow drug resistance to emerge when treatment is restarted. However, the complete story on this is not clear, and more research is needed.

IF I TAKE AN STI, CAN I GO BACK TO TAKING THE SAME REGIMEN?

In all likelihood, yes—assuming that you didn’t stop the regimen because of its side effects or toxicity. (Side effects and toxicities will likely return if you restart the same drugs). If the regimen you were on kept your viral load undetectable, it will likely make it undetectable again. If the regimen didn’t make your viral load undetectable, it probably won’t make it undetectable if you go back to that regimen.

WHAT’S THE BOTTOM LINE?

- 1) **Do not undertake an STI without first consulting your physician.** If you want to take an STI but your doctor seems reluctant, find out why. Although the decision is ultimately yours anyway, it’s always best if you and your physician plan together.
- 2) **Your medical history and past T cell counts are critical in deciding if an STI is right for you.** If you’ve had an AIDS-defining illness, or if your T cell count was ever low (less than 200), an STI may be risky for you. If you decide to take one anyway, talk to your doctor about medications to prevent opportunistic infections. If you were never ill before you started taking HIV medications and if your T cell count was never low, an STI may be safe for you. Remember this: under the current HIV treatment guidelines, if your T cell count has never been less than 350, you probably wouldn’t have started taking HIV medications in the first place.
- 3) **Stay under medical care.** Especially during an STI, it’s important to see your physician every 3 to 4 months for an examination and lab work—even more often in the first couple of months.
- 4) **Brace yourself for a decline in T cell count and a rise in viral load.** If you’ve become accustomed to having an undetectable viral load or a strong T cell count (for example, 700), the initial change in your numbers may cause you to worry.
- 5) **Have a plan.** Know how long the STI will last. Will you go back to the drugs on a certain date or when your T cell count falls to a certain level? Decide at the start when your STI will end.



WHERE CAN I CALL FOR MORE INFORMATION, OR FOR A REFERRAL TO A PHYSICIAN WHO SPECIALIZES IN HIV?

You can call The Center for AIDS at 713.527.8219 or toll free at 888.341.1788.



IN MEMORIAM

L. Joel Martinez

1953–2003

Joel was born in Harlingen, Texas, on January 29, 1953. Throughout his life, he was admired for his amazing combination of intellect, compassion, and achievement. Joel graduated from Rice University *cum laude* in 1976 and Columbia University School of Law in 1977.

With his diagnosis of AIDS in 1986, Joel's life and life's work changed course. Frustrated by the lack of adequate treatment information available to patients and their physicians, Joel became a lay expert on medical issues relating to HIV/AIDS and one of the country's most respected advocates on treatment issues. Joel served as the head of treatment information and advocacy for the Houston Clinical Research Network at the Montrose Clinic from 1993 to 1995. In 1995, Joel founded The Center for AIDS: Hope & Remembrance Project, where he led the organization as director until February 2003. In his new position as director of advocacy at The Center for AIDS, he was involved in the AIDS Treatment Activists Coalition (ATAC), a national coalition of AIDS activists working together to end the AIDS epidemic by advancing research on HIV/AIDS.

Joel was a co-founder of the AIDS Equity League and Body Positive Houston; a volunteer with Project Immune Restoration, a program of Project Inform; and a past trustee of the Texas Human Rights Foundation, the Houston Gay & Lesbian Political Caucus, and Amigos Volunteers in Education and

Service (AVES). He also served as Community Constituency Representative to the American Foundation for AIDS Research (amfar) and the AIDS Clinical Trials Group. He testified before the FDA and was one of only two patients ever to have voting privileges on an FDA panel, the Biological Response Modifiers Advisory Committee. Joel was a member of the Community Constituency Group of the Community Programs for Clinical Research on AIDS (CPCRA), and the cardiovascular focus group of The Forum for Collaborative HIV Research in Washington, DC. He made numerous presentations on HIV/AIDS, as well as authored many articles in various publications including the *Houston Press*, *The Link*, *James White Review*, *Enlace*, *Beta (en español)* and *RITA!*

For his work relating to HIV/AIDS issues, Joel received many awards and honors, most recently the Bradley Scott Award from the Harris County Hospital District. He was also the recipient of The AVES Pyramid Award and the Humanitarian Award of Houston Black Tie Dinner. Despite his own health battles over 17 years and his incredible commitment to his work on HIV/AIDS issues, Joel somehow continued to pursue a wide variety of interests including raising and showing prize-winning dogs, playing classical piano, cooking, writing poetry and short stories, and so much more. Joel will be missed as we continue the struggle to overcome HIV and AIDS.

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