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EDITORIAL

Therapeutic drug monitoring
*David Back, PhD, Saye Khoo, MD,
and Sara Gibbons, MPhil*

SHORT COMMUNICATIONS

**Men who have had sex with men and blood donation:
Is it time to change our deferral criteria?**
*Marc Germain, MD, FRCPC, PhD, and
Graham Sher, MB, BCh, FRCPC, PhD*

**Clinical correlates to muscle biopsy findings in
HIV patients experiencing fatigue: A case series**
Steven C. Zell, MD, and Surl Nielsen, MD

ORIGINAL PAPER

**Can structured treatment interruptions (STIs)
be used as a strategy to decrease total drug
requirements and toxicity in HIV infection?**
*Sharon Walmsley, MD, FRCPC, and
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D. William Cameron, MD, FRCPC
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Editorial 84 Therapeutic drug monitoring
*David Back, PhD, Saye Khoo, MD,
and Sara Gibbons, MPhil*

Short Communications 86 Men who have had sex with men and blood donation:
Is it time to change our deferral criteria?
*Marc Germain, MD, FRCPC, PhD, and
Graham Sher, MB, BCh, FRCPC, PhD*

90 Clinical correlates to muscle biopsy findings in
HIV patients experiencing fatigue: A case series
Steven C. Zell, MD, and Surl Nielsen, MD

Original Paper 95 Can structured treatment interruptions (STIs)
be used as a strategy to decrease total drug
requirements and toxicity in HIV infection?
*Sharon Walmsley, MD, FRCPC,
and Mona Loutfy, MD, FRCPC*

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Therapeutic drug monitoring

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Highly active antiretroviral therapy (HAART) can suppress viral replication and substantially prolong patient life. It can also fail for a number of reasons, including poor adherence, insufficient drug potency, emergence of resistance, cellular factors, and pharmacokinetic factors. Although many antiretroviral drugs are now available, a limited number of combinations has been proven effective for individual patients. With sequential treatment failures, the durability of virologic response tends to decrease with subsequent treatment regimens until the patient is left with few or no therapeutic options. There is evidence that many treatment-naïve patients will switch from their initial regimen within one year. It is imperative that we adopt strategies that will optimize the use of available therapies, so as to achieve long-term viral suppression.

Monitoring the course of HIV infection has been an essential component of patient management. CD4 counts help track the immunological status of a patient, and viral load assays are used to monitor the antiviral activity and durability of a regimen, and to guide treatment changes. Resistance assays are becoming a standard element of care despite issues around interpretation of results. With emerging evidence linking drug exposure to both antiviral efficacy and toxicity, attention is being focused on the role of monitoring plasma drug levels in patients receiving HAART. If inadequate drug levels—arising from poor adherence, inherent pharmacokinetic factors, or drug interactions—are a major cause of treatment failure, then monitoring these levels and having an intervention strategy seems a logical approach to improve the success rate of therapy. Likewise, high drug levels may relate to toxicity, either in the patient at that time or somewhere down the line.

Managing the therapeutic regimen of a patient on the basis of measured drug concentrations is referred to as therapeutic drug monitoring (TDM). In virtually all cases, TDM is applied to drugs exhibiting a narrow therapeutic window in order to optimize efficacy and/or avoid toxicity. This diagnostic approach has been used for many years with anticonvulsants, immunosuppressants, aminoglycoside antibiotics, and some cytotoxics. In the setting of HIV management, the potential role of TDM is receiving increasing attention. There are clearly several features of current antiretroviral therapy that suggest TDM may have benefit. As pointed out by Flexner and Piscitelli in a recent editorial,¹ generally the most important aspect of HIV therapy that draws us to consider the role of TDM is the lifelong treatment. We still have relatively few options despite the 16 licensed antiretrovirals, so getting it right (ensuring there is enough drug for efficacy, but not too much for toxicity) is surely a major goal. Care providers need to know that drug concentrations achieved in a patient have a high probability of chronically suppressing HIV replication without generating drug resistance or problematic toxicities. They also need to remember that drug levels may more accurately correlate acute, rather than chronic or cumulative toxicities.

A major confounder when considering TDM in a clinical setting is adherence. Patients who do not take their antiretroviral therapy on schedule, or who do not comply with food requirements would be expected to have low plasma drug concentrations and consequently a poor outcome. However, those patients may have apparently “normal” plasma levels if they take the dose just before a hospital visit. A patient failing therapy for poor adherence would appear to have a normal drug level in any outcome analysis. Hence, a thorough assessment of adherence is essential within any TDM program to facilitate interpretation of concentrations, and to ensure good outcome. It is also critical to know the accurate timing of a blood sample in relation to when the dose was taken.

Another important consideration in TDM is setting the target drug concentrations. There is some degree of confidence that we know minimum effective concentrations (MECs), values that are generated and extrapolated from patient studies or *in vitro* studies, at least in treatment-naïve patients. There is much less confidence surrounding maximum concentrations with the exception of indinavir and possibly efavirenz. The presence of drug-resistant virus for an antiretroviral drug means that it is not rational to use the same set of target concentrations for patients harboring drug-sensitive and drug-resistant virus. This is where relating drug concentrations to the patient viral isolate becomes a much more attractive option than TDM on its own. The use of inhibitory quotients (IQ), virtual IQ (vIQ), or normalized IQ (nIQ) is currently being clinically evaluated for a number of different drugs. Data presented at the 9th Conference on Retroviruses and Opportunistic Infections (CROI)^{2,3} gives grounds for optimism that this approach may prove of considerable benefit, and probably better than TDM on its own. There is literally a price to pay for the advance in technology, and the issue of reimbursement is likely to prove a considerable stumbling block to the widespread access to the test. Clearly what we need is good economic evaluation of the cost-benefit factors surrounding the use of TDM with or without resistance testing. In absolute costs TDM is "inexpensive" (US\$50 to US\$60 per sample), compared with resistance testing (genotype US\$300, virtual phenotype US\$450).

Defining the clinical situations in which TDM will have the greatest use is a priority. The recent interim analysis of the ATHENA trial⁴ has suggested that dose adjustment of indinavir reduced toxicity, and maintained patients on the indinavir-containing regimen. On the other hand, TDM of nelfinavir identified patients with low plasma concentrations. By either ensuring the drug was taken with food or dose modification, the TDM arm showed better virological outcome at 12 months.

Despite the lack of randomized controlled trial data, there are probably a number of other specific situations in addition to indinavir and nelfinavir that warrant TDM. The use of lopinavir plus ritonavir (Kaletra) with amprenavir gives rise to a complex interaction of three drugs, and monitoring the levels of both lopinavir and amprenavir may be important. The use of once daily regimens can also lead to trough plasma concentrations that are close to the MEC, which is true of saquinavir plus ritonavir. Thus, TDM will identify any individuals with low and potentially problematic levels.

Certain patient groups are clearly at increased risk for unpredictable and potentially damaging pharmacokinetic profiles, and could benefit from TDM. This includes patients with liver or renal damage, pediatric and pregnant patients, and patients with complex drug interactions. Much remains to be learned, and there are a number of challenges facing the introduction of TDM into clinical practice. If we can benefit *some* patients by ensuring efficacy or limiting toxicity simply by taking a couple of extra blood samples, we should vigorously standardize and validate this approach. ■

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Men who have had sex with men and blood donation: Is it time to change our deferral criteria?

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Men who have had sex with other men even once, since 1977, are permanently deferred as blood donors. This policy was put in place several years ago when it was recognized that men who have sex with men (MSM) represented a group at risk for HIV. The policy is not unique to the United States and Canada, since most industrialized countries apply the same rule, or one that is very similar. Many have expressed the view that such a policy, while it may have been justified in the early days of the HIV epidemic, is now overly cautious and has the unfortunate effect of stigmatizing gay men who would donate blood.

According to some, the policy is biased because it appears to be based on a person's sexual preferences rather than the sexual practices and partners that might put someone at risk for infection. It is also seen as setting a double standard by which certain behaviors in heterosexuals only bring a temporary deferral, while male-to-male sex entails lifetime exclusion.

The American Association of Blood Banks (AABB), an independent organization that represents the transfusion community, endorses a relaxation of the current deferral policy for MSM.¹ The AABB argues that highly sophisticated tests are now used to screen blood donations for HIV and other transfusion transmitted diseases (TTDs), making it unnecessary to apply such a restrictive policy. It suggests imposing a temporary deferral of one year for male-to-male sex, similar to deferrals that are applied for other activities at risk for TTDs. In theory,

asking donors to focus on the recent past might also improve their ability to recall events that are more relevant to the risk posed by window period donations. This revised policy would also have the benefit of increasing the pool of eligible donors.

Not surprisingly, this question of MSM and blood donations is rather controversial, and it has been the object of heated debates for a number of years and in various jurisdictions. While recognizing the following discussion will most certainly not put an end to the argument, it represents our personal opinions and positions on this issue, not that of the organizations we represent.

All blood donations are tested for the presence of antibody and/or antigen of transfusion-transmitted infections, including hepatitis C virus (HCV), HIV, hepatitis B virus (HBV), syphilis, and human T-lymphotrophic virus (HTLV). In recent years, nucleic acid testing (NAT) for HCV and HIV has been added to the traditional arsenal of serological tests, as an attempt to reduce the risk of transfusing blood collected from donors who might be in the early phase of infection.² The transfusion industry has also been transformed into a highly regulated environment, in which processes are highly controlled and safeguards are put in place to make sure that these screening tests are being performed and documented with the highest possible level of proficiency.³

Given all that, one may ask whether current tests are more than sufficient as a way of safeguarding the blood supply. Why bother screening donors on the basis of their self-reported risk factors, if testing has become so effective? One obvious answer is the health questionnaire currently remains our only line of defense against certain TTDs, such as malaria and Chagas disease, but also for other conditions that may be detrimental to transfusion recipients or to the donors themselves. If

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only for this reason, the health questionnaire will always remain a necessary step in the donor screening process. The second reason is, even with the advent of nucleic acid testing, there remains the possibility that some donors will test negative if they donate during the window period of early infection. Recent experience has shown that this can happen even with all donations being subjected to NAT.^{4,5} This is due to the intrinsic limit that nucleic acid tests have in their ability to detect infections in the earliest phase of viremia.

It is widely agreed, even with the most sensitive screening assays in place, donors should be deferred temporarily if they report recent behaviors that put them at risk for certain TTDs. Why impose a permanent deferral for behaviors that may have happened only once or a few times in the distant past in the case for male-to-male sex? The transfusion community remains divided on this particular issue.

Some argue the goal of the donor interview is not only to exclude donors who are in the window period of infection, but also to reduce as much as possible the prevalence of TTDs in the donor population, even if screening tests can easily detect such donors. The main contention is there should be an effort to reduce as much as possible the number of infected donations that come into the system in the first place because of potential failures of the overall screening process. Since the prevalence of HIV is much higher in MSM in comparison with the general population, a more inclusive deferral policy should be applied to this group of people. In fact, other groups at higher risk for TTDs, such as intravenous drug users and those who accept money or drugs in exchange for sex, are also permanently deferred for similar reasons. In spite of the apparent discrepancy in the level of stringency that is imposed on the MSM population in comparison with other groups at risk for TTDs, the proponents of the current policy believe that it remains a sensible risk reduction strategy. Is this a legitimate argument?

Published data shows that the process of screening blood donations is fallible. Testing errors can produce false-negative test results.⁶ Clerical and administrative errors may lead to the inappropriate release of infectious blood components.¹ Such errors are now extremely rare because of the increasing level of control in the process of screening and handling donations. On the other hand, one cannot assume that these mishaps never happen. Blood products sometimes need to be transfused on an emergency basis, prior to laboratory screening for transmissible diseases. One of us (M.G.) conducted an analysis in which the impact of a relaxation of the current deferral policy for MSM was modelled, taking into consideration these various factors.⁷ The results showed, if 12-month

abstinent MSM were allowed to donate blood, the additional number of HIV-positive donations that would escape detection and find their way into the inventory would be extremely small, in the order of 1:11,000,000. Consider the following to put this estimate in perspective. With current test procedures, the residual risk of acquiring HIV from a blood transfusion is estimated at 1:1,000,000, at worst.² The risk of changing to a 12-month deferral policy for male-to-male sex represents less than 10 percent of that current risk. A more lenient deferral policy for MSM would also have the benefit of increasing the number of eligible donors by about 1 percent. This is small but maybe not insignificant, considering the difficulties recruiting and retaining a stable number of active blood donors.

With these numbers in hand, what should be done about the current deferral policy for MSM? Given today's paradigm in blood safety, even the minuscule increment in risk that would result from the revised policy appears unjustified and undesirable to many, especially to those in need of blood. Even the prospect of a positive impact on the availability of blood donors does not appear to make a difference to those who are exquisitely concerned about blood safety. In this context, it becomes very difficult for those who manage and regulate the blood system to make a strong argument in favor of a change in the MSM deferral policy, considering the perspective of those in need of blood products.

In November 2001, Canadian Blood Services and Héma-Québec hosted a consensus conference that addressed the broader question of blood donor screening based on reported risk factors for TTDs. Not surprisingly, the controversial question of male-to-male sex and blood donation was one of the issues that triggered the conference. A panel of experts and stakeholders was asked to reflect on these issues and produce a consensus statement that could guide the policy makers in their decision-making process. In that statement, which will soon be published in its totality along with the proceedings from the conference, the panel did not make any specific recommendation concerning the MSM deferral policy. However, the panel did provide some guidelines as to the scientific, societal, and ethical principles upon which the donor screening process should be based. It was agreed that certain constraints could be imposed on individuals when a significant risk exists, on condition that the risk can be effectively mitigated by such constraints. In addition, the economic costs and the burdens to certain individuals or groups of individuals should be reasonable when compared with the benefits that these constraints will bring to society in general. Finally, these restrictions should be fairly distributed among the general population.

Without trying to second-guess the consensus panel, it is our opinion that the current MSM deferral policy adheres to these principles, albeit tenuously in some respects. We firmly believe that a temporary deferral of male-to-male sex will always remain a minimum requirement to safeguard the blood supply, as long as sexually transmitted diseases and the HIV epidemic continue to disproportionately afflict the MSM population. On the other hand, we also believe that the calculable margin of safety that is gained by the current policy is extremely small when compared to a policy that would only impose a temporary deferral for male-to-male sex. This safety margin also comes with the cost of having to defer a fairly large number of men who could potentially contribute safe donations to a blood supply that is periodically difficult to sustain. This balance between safety increments (even marginal ones) and adequacy of the donor base will continue to challenge the transfusion industry, including operators, regulators, and stakeholders. Prior to any change to the current policy regarding MSM being promoted or imposed, there should be a very clear consensus that such a change is both justified and necessary. This consensus must be broadly based, and should not only come from those who feel unjustly treated by the current policy. In seeking such consensus, we believe that if priority should be given anywhere, it should be to the opinion of those who have the most to lose or to gain from this change, namely the transfusion recipients themselves. This is reasonable, given the rights of recipients of blood transfusions to expect their therapeutic intervention to be optimally safe. ■

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Clinical correlates to muscle biopsy findings in HIV patients experiencing fatigue: A case series

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Abstract

Muscular fatigue may result from HIV infection, and may be associated with antiretroviral drug treatment. Clinical features linked to muscle biopsy findings may assist in determining etiology, and guide treatment decisions.

This case series examined HIV patients in an ambulatory HIV clinic who received antiretroviral therapy, and complained of unexplained muscular fatigue. Clinical features with measurement of acid-base status, levels of lactate, aminotransferases, triglycerides and creatine kinase were correlated to light and electron microscopic results of muscle biopsy.

Three patients with acquired mitochondrial changes on biopsy shared common features of lactatemia, elevated aminotransferases and triglycerides, and ultrasonographic hepatic steatosis. A fourth patient with normal mitochondria had myositis with fibrosis, but no systemic symptoms. Biochemical parameters were unremarkable, except for a high creatine kinase.

Acquired mitochondrial disease may manifest as systemic illness and muscular fatigue. Unique metabolic changes and other organ dysfunction may precede overt physical signs of HIV myopathy.

Key Words: antiretrovirals, lactic acidosis, HIV infection, mitochondrial diseases, drug toxicity

Introduction

Muscle fatigue in the HIV-infected patient, defined in this case series as diminished exercise tolerance and subjective muscle fatigue, may result from diverse etiologies that often present with a similar clinical picture.

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Overt physical evidence of myopathy may come late in the disease process. The ability to correlate unique and early biochemical findings to specific histopathologic results on muscle biopsy may shed light on the physiologic basis of observed laboratory abnormalities preceding overt myopathy. Despite advances in HIV management, muscle fatigue still often occurs as a result of inflammatory responses to HIV itself, or as a consequence of antiretroviral therapy.¹ Nucleoside analogs inhibit mitochondrial DNA polymerase- γ , leading to disruption of oxidative metabolism.² A mitochondrial myopathy, initially noticed with zidovudine in the late 1980s, was attributed to reductions in mitochondrial DNA.³ Recently, other nucleoside agents have been implicated in producing mitochondrial dysfunction, characterized by a more systemic syndrome of lactic acidosis, lipid alterations, and metabolic disruption of active organs, resulting in pancreatitis and hepatic steatosis.^{4,5}

Little is known about the correlation of clinical findings to specific muscle biopsy findings. Knowledge of early changes in clinical and biochemical parameters in relationship to pathologic findings is necessary. Potential interventions in HIV-associated muscle fatigue may vary from discontinuation of antiretroviral therapy in the setting of mitochondrial toxicity, to treatment intensification and use of adjunct anti-inflammatory therapy for patients manifesting HIV-associated polymyositis.^{6,7}

Methods

Patients were recruited from an HIV ambulatory clinic, Northern Nevada HOPES, between April 2000 and August 2001. During this period, 2,250 patients were seen for both routine and urgent visits. Those who complained primarily of diminished exercise tolerance and subjective muscle fatigue underwent a directed neuromuscular exam (by S.C.Z.) that assessed strength, reflexes, presence of atrophy or fasciculations, and a targeted physical exam to screen for opportunistic infections. In the absence of physical causes for a complaint, selective laboratory testing was done to

Table 1. Clinical features at time of diagnosis in HIV patients with muscle fatigue

<i>Patient number</i>	<i>Age</i>	<i>CD4 cell count (cells/mm³)</i>	<i>Plasma viral load (copies/ml)</i>	<i>Current antiretroviral agents (cumulative months patient exposure)</i>
1	52	1,023	163	EFV(5)/ddI (17)/d4T(44)
2	38	273	97	NVP(9)/ddI(9)/d4T(9)
3	37	4	104,820	RTV(12)/IDV(12)/d4T(42)/3TC(42)
4	34	688	<50	NVP(19)/d4T(16)/3TC(16)

Note: EFV=efavirenz; ddI=didanosine; d4T=stavudine; NVP=nevirapine; RTV=ritonavir; IDV=indinavir; 3TC=lamivudine

screen for common etiologies of fatigue in the clinic population. This included a complete blood cell count to exclude anemia; serologic screening to rule out recent acquisition of viral hepatitis of types A, B and C; a total testosterone level to assess gonadal function; and a thyroid profile consisting of a thyroid-stimulating hormone and free thyroxine levels.

Patients who complained of muscle fatigue without discernible cause by history, physical exam, and screening laboratory evaluation underwent further laboratory testing which measured acid-base status (room air arterial blood gases, and venous plasma lactate), and fasting triglycerides, creatine kinase, and aminotransferase levels. All patients underwent hepatic ultrasonography. If the plasma lactate level was elevated, antiretroviral therapy was halted out of a concern for symptomatic hyperlactatemia. Patients were hospitalized for supportive care only if acidosis was significant, or they required intravenous rehydration. No other specific interventions were performed. All patients underwent muscle biopsy of the deltoid within three weeks of their initial presentation. Biopsy specimens were examined using routine light microscopy (LM), histochemistry and electron microscopy (EM) by a neuropathologist (S.N.) at Sutter Medical Center in Sacramento, California.

Results

Four patients met the criteria of unexplained muscle fatigue, and following informed consent, underwent the aforementioned laboratory testing with subsequent muscle biopsy. The patients were male with CD4 lymphocyte counts ranging from 22 to 1,023 μ L, and on highly active antiretroviral therapy (HAART) with two nucleoside analogs at the time of their illness. All had received stavudine (d4T) with mean treatment duration of 27 months. Other nucleosides included didanosine (ddI), and lamivudine (3TC). Table 1 gives important immunologic parameters of CD4 cell count and viral load at presentation, and a description of prescribed antiretroviral drugs and duration of therapy. On biopsy, three patients had evidence of an acquired mitochondrial myopathy, and one patient had histologic changes of polymyositis.

Table 2 relates key clinical parameters to biopsy findings. Those with acquired mitochondrial myopathy tended to have a systemic clinical syndrome with metabolic changes consisting of low-level lactatemia, a significant rise in triglycerides, and aminotransferase levels. Plasma lactate for this group was high on repeat sampling. Fatty infiltration on liver ultrasound was noted in two of three patients with acquired mitochondrial myopathy. All patients with acquired mitochondrial myopathy noted resolution of symptoms over three to four weeks with discontinuation of antiretroviral therapy. Patient 3 had significant acidosis complicated by diarrhea and bicarbonate loss, and required hospitalization for intravenous fluid administration for two days. Patient 4 with polymyositis had an isolated high creatine kinase level. His plasma lactate was marginally elevated, but was normal upon repeat testing the next day with normal acid base parameters, suggesting the initial increase was possibly a lab error. The patient received electromyography that showed changes classic for polymyositis, and was treated with oral prednisone therapy after a muscle biopsy.

In Figure 1A, the Modified Trichome Stain on the frozen muscle biopsy specimen from Patient 1 shows uniform fibers without individual fiber necrosis, and absence of ragged-red fibers or inflammatory response by light microscopy. However, the electron microscopic picture on the biopsy from this patient shows the prominent increase in number and size of the mitochondria in Figure 1B. There is also close association of these abnormal mitochondria with increased number of lipid droplets. The myofibers are otherwise intact. In contrast, the inflammatory myopathic features seen on the muscle biopsy from Patient 4 are demonstrated in the light microscopic field from the Modified Trichome stained material in Figure 1C. There is wide variation in fiber size associated with individual fiber necrosis, interstitial mononuclear inflammation, and extensive fibrosis. The electron microscopic findings in Figure 1D, in contrast to Patient 1, reveal nonspecific changes characterized by a uniform number, distribution, and size of muscle mitochondria.

Table 2. Correlates of laboratory and hepatic ultrasonography to muscle biopsy findings

Patient number/age	Arterial blood gas (pH/pCO ₂ /O ₂)	Plasma lactate (mmol/L) ref: 0.7-2.5	AST level (relative fold increase) ref: 3-45 IU/L	Serum triglyceride (mmol/L) ref: 0.4-2.8	Creatine kinase (U/L) ref: 38-174	Hepatic steatosis on ultrasound	Final microscopic diagnosis
1 (52)	7.43/35/93	4.7	194 (2.4)	7.60	86	Present	Acq. Mito.*
2 (38)	7.44/27/79	3.0	66 (2.2)	3.25	235	Absent	Acq. Mito*
3 (37)	7.18/9/107	5.4	286 (3.6)	3.88	68	Present	Acq. Mito*
4 (34)	7.41/39/69	3.2	159 (1.04)	1.76	1027	Absent	PM [†]

Note: *Acquired mitochondrial myopathy (electron microscopic evidence of large, unusually shaped mitochondria, and unremarkable light microscopy). [†] Polymyositis (light microscopy with a severe inflammatory mononuclear cell infiltrate, fibrosis and replacement of muscle fibers, without abnormal mitochondria).

Discussion

Skeletal muscle involvement occurs in all stages of HIV infection. Muscle weakness associated with overt physical signs may be seen during wasting and cachexia, or accompany systemic opportunistic infections and HIV-related malignancies.⁸ Determining the etiology of muscle fatigue, especially when chronic and unexplained by physical exam, remains a challenge. In the physical exam, differentiating an HIV-associated myopathy from an acquired drug-related mitochondrial myopathy is important. The latter, first recognized as a complication of zidovudine therapy, presumably results from the ability of nucleoside analogs to alter mitochondrial function through inhibition of DNA polymerase- γ , and impairment of oxidative phosphorylation. Early reports of mitochondrial myopathy associated with zidovudine usage do not describe a systemic metabolic syndrome.^{1,9} Reasons likely include a prior emphasis on muscle weakness, unawareness of potential biochemical changes due to toxicity of nucleoside analogs, and the unique tissue uptake of zidovudine, favoring its effect in muscle over other metabolically active organs such as the liver.¹⁰ More recently, there is a growing awareness of mitochondrial toxicity as a systemic syndrome, which is a chronic or cumulative toxicity of long-term treatment with drugs such as stavudine and zalcitabine (ddC) that inhibit DNA polymerase- γ to a greater degree.¹¹

Case series of symptomatic lactic acidosis have shown consistent lipid abnormalities in association with hepatic steatosis, and occasionally pancreatitis. The latter syndrome has been associated primarily with stavudine, and discontinuation of the drug has coincided with a resolution of symptoms and acidosis.¹² All our patients with acquired mitochondrial myopathy had received stavudine for a considerable time, and had demonstrated abrupt increases in their fasting triglyceride levels. This has been attributed to impairment of beta-oxidation of fatty acids associated with mitochondrial dysfunction.¹³

It is unclear whether the steatosis suggested by hepatic ultrasonography results from deposition of fat within the liver, or from primary hepatocellular dysfunction. The proclivity towards a more systemic syndrome seen with stavudine, as opposed to zidovudine's primary muscle effect, may result from differences in each drug's affinity for forms of thymidine kinase. Thymidine kinase phosphorylates thymidine nucleoside analogs, and has tissue specific forms and a distribution that may account for the specific organ toxicities of nucleoside analogs.^{14,15}

The physical appearance of patients with mitochondrial toxicity was unremarkable in these cases. All had preserved muscle mass without deficits in strength, and fatigability was not demonstrable upon physical examination despite complaints of diminished exercise tolerance. Waiting for clear-cut physical evidence of myopathy would have not been in the best interest of these patients who were all systemically ill. Those with acquired mitochondrial disease showed a low CO₂ with moderate anion gap elevation, suggesting chronic respiratory compensation for a low-level systemic acidosis. In contrast, the sole patient with polymyositis had only a high creatine kinase level. Physical examination showed no focal deficit in strength, but lean body cell mass was below normal with less than 35 percent, compatible with his biopsy findings of severe fibrosis replacing muscle fibers. Overall, Patient 4 presented with a nonsystemic picture, pointing towards specific muscle disease based upon his high creatine kinase level and loss of muscle mass.

Conclusion

Acquired mitochondrial disease may manifest systemically in the setting of antiretroviral therapy. Patients without metabolic changes, but demonstrating evidence of primary muscle weakness or wasting, should be screened with a serum creatine kinase level. An elevated level may lead to a consideration of an electromyography

Figure 1. Contrasting light microscopy (LM) and electron microscopy (EM) photomicrographs of mitochondrial toxicity and polymyositis in HIV infection

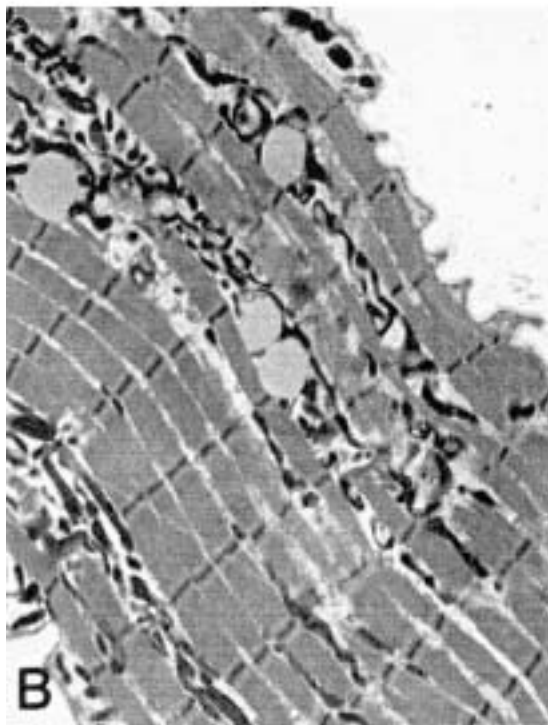
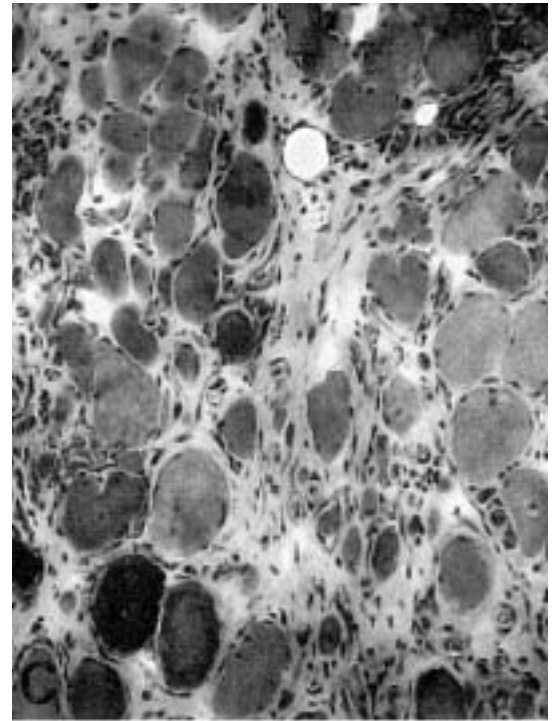
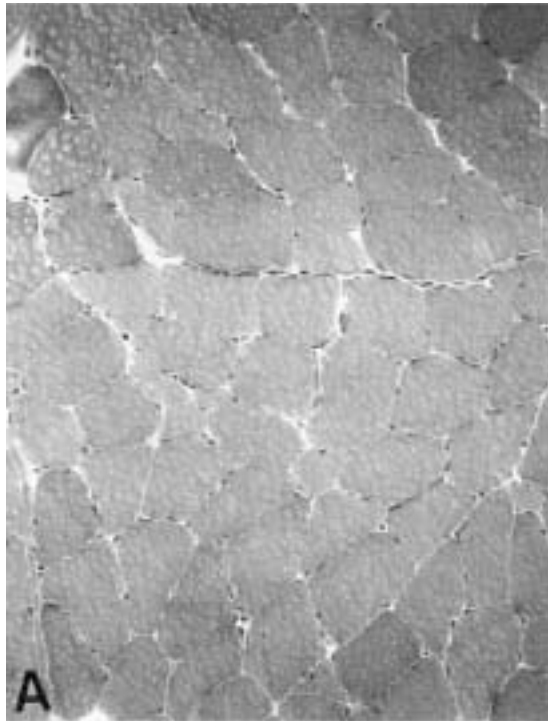


Figure 1A/Figure 1B
In Patient 1, LM (Modified Trichrome Stain x 100) and EM (x 5,000) shows uniform myofibers without abnormal structure in Figure 1A, but numerous and enlarged mitochondria with associated lipid droplets in Figure 1B.

Figure 1C/Figure 1D
In Patient 4, LM (Modified Trichrome Stain x100) shows inflammatory myopathic changes in Figure 1C, and EM (x3000) shows nonspecific myofiber degeneration, but normal mitochondria in Figure 1D.

Photos courtesy of Surl Nielsen

(EMG). Accompanying biochemical derangements of mitochondrial toxicity may herald overt muscle disease, and physical signs of weakness may not be present. Useful tests for detecting this syndrome are fasting triglyceride and aminotransferase levels, both of which may abruptly increase during prodromal stages. Ultrasonography of the liver that demonstrates steatosis may also serve as a noninvasive marker of mitochondrial dysfunction.

When mitochondrial dysfunction is present in the setting of chronic nucleoside analog therapy, physicians need to make a choice about continuing these drugs. Physicians can choose to substitute tenofovir for stavudine. Recent data from *in vitro* cell culture model suggests that tenofovir does not deplete mitochondrial DNA, and has no significant effect in inhibition of DNA polymerase- γ .¹⁶ Surveillance studies are needed to confirm relative safety, but currently tenofovir appears to offer a treatment alternative in the presence of mitochondrial toxicity. For physicians who choose to discontinue nucleoside analogs, dual protease inhibitors using pharmacokinetic enhancement may provide control of viremia. Ritonavir/saquinavir given alone twice daily demonstrate comparable results with the same regimen intensified with nucleoside analogs, suggesting dual protease inhibitor combinations can achieve control of viremia without need for nucleoside combinations for some patients.^{17,18} For patients with insufficient anti-HIV activity on only protease inhibitors, addition of a non-nucleoside drug such as efavirenz or nevirapine may also be carefully considered, provided attention is given to complex drug interactions.

Recognition and management of long-term drug toxicities of anti-HIV therapies is a necessary consequence of the successes of medical treatment of HIV disease. ■

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Can structured treatment interruptions (STIs) be used as a strategy to decrease total drug requirements and toxicity in HIV infection?

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Abstract

Structured treatment interruptions (STIs) are a new strategy under investigation in clinical trials involving a number of different HIV-infected populations. These populations include patients with prolonged HIV RNA suppression who were treated in either seroconversion or later in disease, and patients with virologic failure despite HAART, prior to the initiation of a salvage regimen. The goals of STI vary in each of these groups. Until the results of clinical trials are available, the use of STIs must be considered experimental. There are a number of potential risks, including the loss of a significant number of CD4 cells with the development of opportunistic infections, rebound of HIV RNA, emergence of drug resistance, and reseeding of viral reservoirs. However, STIs also hold the promise for decreasing antiretroviral drug burden and toxicity, and improving quality of life. Given that much of the world's population infected with HIV does not have access to continuous HAART, the development of strategies that could decrease overall drug burden and cost is important.

This paper provides an update of the recently published and presented studies on the use of STIs in various populations of HIV-infected patients. In particular, it discusses what is known and unknown about the relative risks and benefits of this approach, and what studies are ongoing.

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Lastly, it identifies how the use of STIs could decrease drug burden and toxicity in patients receiving therapy.

Key Words: *structured treatment interruption, antiretroviral therapy, drug toxicity, HIV, HAART*

Introduction

Over the past several years, there has been growing interest in treatment interruption in HIV infection.¹⁻⁴ To date, few questions have been fully answered since most of the information comes from retrospective, non-controlled cohort studies in which data and conclusions are frequently misinterpreted. The structured treatment interruption strategy remains in a state of equipoise, and until the relative benefits and risks can be fully measured in randomized clinical trials, the use of STIs should be considered experimental and not part of routine practice. For many patients, the potential for a treatment interruption, structured or not, is often considered beneficial, primarily to decrease the burden and toxicity associated with continuous therapy. Patients need to be counselled on the potential risks and benefits of such an approach before it is recommended in clinical management.

Highly active antiretroviral therapy (HAART) has significantly improved HIV-associated morbidity and mortality.⁵⁻⁷ However, long-term suppression of plasma viremia is unlikely to eradicate HIV,⁸⁻¹⁰ and benefits come with considerable short-term and increasingly recognized long-term toxicity.¹¹⁻¹³ Long-term adherence is also problematic.¹⁴ Similar to HAART, the balances between the risks and benefits are different for each

patient, and the use of STIs will likely need to be individualized once clinical consequences are more fully understood.¹⁵

Although anti-HIV treatments are increasingly available, consistent long-term therapy is either impractical or not affordable for the majority of HIV-infected individuals in the world. New strategies are needed to increase adherence, and to decrease cost and toxicity. In a setting of chronic therapy, STI may offer an alternative to continuous HAART.

What are STIs?

Several different names have been used for “STIs,” including structured, strategic, or supervised treatment interruptions. STI is a strategy that discontinues all antiretroviral agents for defined periods of time under careful medical observation, while prophylactic therapies are continued or initiated for opportunistic infection. Antiretroviral (ARV) therapy with the same or a new combination is reinitiated at some future point.

This strategy is not to be confused with treatment discontinuations that form the basis of many of the cohort studies published in the literature. These non-STIs frequently occur in practice, initiated by the doctor or more frequently by the patient. They are precipitated by problems with adherence, short-term or long-term toxicities, pill fatigue, hospitalization, economics, access, or futility.^{16,17} In these settings, there are typically no preplanned criteria for the reinitiation of therapy, and prophylaxis for opportunistic pathogens is also frequently discontinued. Given the heterogeneous nature of the studied populations, and the reasons for and duration of the interruption, the interpretation of the outcomes is difficult.

What are the goals of STIs?

STIs are currently being evaluated in clinical trials in three different HIV-infected populations, and the goals differ in each context. These three groups include:

- 1) Acute HIV infection—patients who have a relatively intact immune system with early and prolonged HIV suppression following treatment in seroconversion.¹⁸
- 2) Chronic HIV infection—patients with prolonged HIV RNA suppression when treatment was initiated long after seroconversion.¹⁹
- 3) Virologic failure—patients with virologic failure of HAART who are considering salvage therapy.^{20,21}

The goals of STI in these three scenarios differ and must not be confused. In patients with controlled viral load suppression after treatment in seroconversion, brief STIs are being studied as a means of “autoimmunization” with the hope of inducing long-term immune control, eventually enabling control of HIV infection in the

absence of treatment. Although the autoimmunization approach may also be evaluated in chronically infected patients with well-treated HIV infection, STIs are more commonly considered to decrease drug toxicity or to give the patient respite from continuous HAART. There is hope that these patients can limit their exposure to HAART and decrease toxic effects without jeopardizing long-term efficacy on re-treatment. In patients with virologic treatment failure, STIs are being studied as a strategy to improve HIV RNA responses to subsequent salvage therapy. During the STI, it is hypothesized that drug-sensitive virus will evolve or reemerge without drug pressure, and the proportion of drug-resistant virus will decrease, enabling better responses to subsequent salvage therapy. Early evidence suggests that patients in whom the predominant HIV RNA genotype reverts to wild type will have a better response to the salvage therapy.²⁰

What are the potential risks of STIs?

While these potential benefits are being evaluated in clinical trials, it must be recognized that STIs may be accompanied by risks. HIV suppression with HAART does not result in reconstitution of HIV-specific immune responses.²² It is well recognized that during the STI, viral replication will increase, typically with the emergence of the “more fit” wild type virus.^{23,24} This reemergence of virus can lead to “reseeding” of the viral reservoirs, and the eventual decrease in the CD4 count and functional immune competence.^{25,26} The time of this reemergence of viremia and the kinetics of viral replication varies, likely related both to the size of the viral reservoir, and HIV-specific immunity. For patients with control of HIV viral replication by current assays of plasma viremia (less than 50 copies/ml), the reemergence of viremia usually occurs within two to four weeks after discontinuation of treatment.²⁷ Rebound viremia kinetics is uncharacterized when treatment is stopped after plasma viremia has been suppressed to a greater extent (eg, less than three copies/ml).

Another major risk is the change in plasma viremia and CD4 cell count during STI may not be regained to the previous levels after treatment is reinitiated.

A patient may develop “a viral rebound” syndrome during STI like the acute seroconversion syndrome.²⁸ This may present with fever, headache, lymphadenopathy, rash, myalgia, and aseptic meningitis. As well as precipitous declines in the CD4 cell count, the emergence of more pathogenic wild type virus, and the development of opportunistic infections have been reported during STI. Therefore, it is important that appropriate primary and secondary prophylaxis for opportunistic infections be initiated or maintained during STIs.

Table 1. Potential risks, benefits, and opportunities to decrease drug burden and toxicity of structured treatment interruption (STI) in different HIV patient populations

<i>Patient group</i>	<i>Rationale for STI</i>	<i>Potential benefits of STI</i>	<i>Potential risks of STI</i>	<i>Potential to decrease drug burden and toxicity</i>	<i>References</i>
Patients treated during seroconversion	Autoimmunization Boosting of waning HIV-specific immunity	Induce long-term immune control without antiretroviral agents	Failure to control viral replication during STI Reseeding of reservoirs	High for a few selected patients	18, 31-43
Patients treated during chronic infection	Intermittent treatment to sustain CD4 counts or decrease HIV RNA to specified levels	Decrease drug burden Decrease drug toxicity Improve quality of life	Failure to control HIV RNA Emergence of resistance Complex regimens Decreased quality of life Increased transmission risk during STI	Low with single interruption High for repeated interruptions	19, 23, 27, 45-51
Patients with virologic failure despite HAART		Allowing for a better HIV RNA response to salvage therapy Improved CD4 cell response to salvage therapy	Loss of CD4 cell count during STI Inability to recapture loss of CD4 cell count, or gain in HIV RNA during STI Viral rebound syndrome, or opportunistic infection during STI	Low	20,21, 52,53

There is a potential public health risk of STIs. Given the significant increases in viral replication, the patient could be at greater risk of HIV transmission during the rebound if safer sex, or injection drug-use practices lapse during STI.²⁹

For patients with previous resistant strains, there are concerns for the reemergence of archived drug-resistant strains with reintroduction of drug treatment.

Finally, the emergence of antiretroviral drug resistance with cessation and subsequent reinitiation of treatment is also a major concern. There is the potential for new resistant mutations to develop during periods of sub-therapeutic drug concentrations.

Can STIs autoimmunize and allow successful discontinuation of antiretroviral therapy?

Structured treatment interruption is a strategy used in patients who are treated with HAART in acute infection,

and who are managed with a single or repetitive treatment interruption. The objective is to determine whether HIV RNA replication can be controlled for extended periods of time without antiretroviral agents. It is based upon the hypothesis that early treatment of HIV results in clearance of HIV antigen, loss of immunologic memory, and waning of HIV specific immunity. By employing STI, autologous HIV antigen resurges, resulting in stimulation of HIV-specific T-helper and cytotoxic T-lymphocyte responses.³⁰ A similar approach can be taken by using HIV candidate vaccines such as Remune,³¹ or ALVAC³² to stimulate the immune system. In addition, cytokines such as interleukin-2 (IL-2), immune modulators such as granulocyte-macrophage colony-stimulating-factor (GM-CSF), hydroxyurea (HU), and mycophenolic acid are also being evaluated.³³

The initial observation that led to this hypothesis was based on a case report published in 1999 that described the "Berlin patient."³⁴ This patient was treated early after

HIV infection with didanosine (ddl), indinavir (IDV), and hydroxyurea, and was able to control HIV replication after cycling on and off treatment twice, for more than 176 days. Since the "Berlin patient," there have been other reports in the literature evaluating this strategy with mixed results.³⁵⁻³⁷

The concept of autoimmunization is further supported by animal data. In a randomized controlled trial, macaques, acutely infected with simian immunodeficiency virus (SIV), were treated with phosphonylmethoxypropyl adenine (PMPA), ddl, and HU with a fixed scheduled STI of three weeks on, three weeks off. HAART was able to suppress viral replication for six months after treatment withdrawal.³⁸ Animals in the STI group exhibited increases in virus specific T-cell responses, and control of rebound viremia during subsequent interruptions. In contrast, viral specific immunity did not increase, and SIV rebounded after treatment withdrawal in animals in the control group on continuous HAART.

What data support the autoimmunization approach?

A number of clinical investigators are testing this approach in controlled clinical trials. Rosenberg and colleagues¹⁸ administered one or two STIs to eight patients. The patients presented with symptomatic acute HIV infection with positive HIV RNA in plasma, but negative or weakly positive antibody tests, and were started on HAART within 72 hours of diagnosis (one to 34 days). They had consistent suppression of HIV RNA less than 50 copies/ml for at least eight months. During STI, ARV treatment was reinitiated if weekly measurement of plasma viremia increased greater than 5,000 copies/ml for three weeks, or greater than 50,000 copies/ml on one occasion. Despite the rebound, all patients were able to achieve at least a transient steady state for leveling of plasma viremia off therapy. Five out of eight subjects had plasma viremia less than 500 copies/ml after a median of 6.5 months (five to 8.7 months). All patients had increased HIV-specific cytotoxic T-lymphocytes, and maintained HIV-specific T-helper cell responses.

Other groups studied STIs in patients treated in seroconversion with variable outcome.^{37,39-43} Hermans et al⁴⁰ evaluated 15 patients initiated on therapy within two to six months after seroconversion. After a mean duration of antiretroviral therapy from five to 43 months and an STI, plasma HIV RNA was less than 50 copies/ml for four to 37 months. Over time, nine patients had a rebound of viremia: six to a level less than 3 log₁₀ copies/ml, two to a level less than 3.5 log₁₀ copies/ml, and one to a level greater than 4 log₁₀ copies/ml.

It would appear that the autoimmunization approach for a few carefully selected patients may allow for periods

of time with control of HIV replication in the absence of drug therapy. However, this observation is inconsistent, leading to the following questions:

- 1) How early in infection do patients need to be treated in order to gain benefit from STI? It is believed the earlier the treatment, the more preserved the immune system, but the more rapid the clearance of "immunizing" HIV antigen.
- 2) How long does the plasma viremia need to be suppressed prior to treatment interruption? Most studies have not evaluated patients unless the HIV RNA is less than 50 copies/ml for more than six months to one year.
- 3) How long should STI be, and what should prompt the reinitiation of treatment? Should it be for a specified time, to a certain HIV RNA level, or until a certain CD4 cell count decline? Fixed-cycled approaches would be easier to administer to a large group of patients in a clinical setting.
- 4) Should there be a single, or multiple interruptions before evaluation of treatment discontinuation?

The answers to these questions require further study.

Can repeated STI in patients treated in chronic infection be useful?

By the time a patient is chronically infected, the immune system is damaged and immunity may not be as responsive to autologous boosting as in the early stages.⁴⁴ Nonetheless, there may be a role for STI in this setting to decrease drug burden.

Fauci et al⁴⁵ conducted a pilot study in which HIV-positive patients with HIV RNA less than 50 copies/ml, and a CD4 count greater than 300 copies/ml received repeated cycles of seven days on HAART, then seven days off HAART. These patients had not initiated their HAART therapy during their seroconversion illness, but had suppression of HIV RNA to less than 500 copies/ml for six months, and less than 50 copies/ml at enrollment. The median time on HAART prior to the entry to this trial was 13.5 months (range seven to 43 months). All of the eight patients who remained on this regimen were able to maintain suppression of viremia for 32 to 68 weeks. There was no increase in HIV proviral DNA, or replication competent HIV in peripheral CD4 cells. Given the short cycle, it was anticipated that there would be insufficient time for viremia to rebound and, therefore, there was no anticipation of stimulation of the immune system by autoimmunization. Two patients who had interruptions of therapy for 10 to 21 days had significant increases in HIV RNA. No changes were noted in CD8 T-cells, or in the number of CD4 or CD8 cells with activation markers. There were no changes in T-cell responses to p24 antigens. There were no changes in CD4 counts at 24 weeks. No individual on a short cycle of HAART developed new drug resistance

that conferred genotypic mutations, albeit using insensitive assays.

Not surprisingly, there was some improvement in the toxicity profile. A significant decrease in the mean serum cholesterol of 22 percent (220 to 171 mg/dl) occurred during the 24 weeks of the intermittent therapy. There was also a decrease in the mean low density protein (LDL) cholesterol from 142 mg/dl to 118 mg/dl, and a significant decrease in the mean serum triglyceride from 270 to 113 mg/dl during STI.

It is necessary to perform large randomized trials to determine the clinical applicability of such an approach in HIV therapy. This approach may have no impact on incidence of long-term toxic effects such as lipoatrophy or lipodystrophy, but if used early, it could delay their onset. If successful, this approach could also decrease the total drug intake, provide relief from a continuous medication schedule, and potentially decrease adverse events and costs. The practicability of this approach in a clinical setting is questionable, given the importance of careful monitoring by both the physician and the patient, and the short cycling period.

The Swiss and Spanish Intermittent Treatment Trial (SSITT) is one of the largest cohorts of patients in which STI is being evaluated in patients who initiated HAART during chronic infection.⁴⁶ The trial enrolled 133 patients. The patients had stable antiretroviral treatment, with HIV RNA less than 50 copies/ml for least six months, CD4 counts greater than 300/mm³, and no prior non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment. Patients were treated with cycles of STI for two weeks, followed by resumption of HAART for eight weeks. After four cycles, treatment was suspended indefinitely, unless the viral load rebounded to greater than 5,000 copies/ml. At 52 weeks, three months after treatment was discontinued, 23 subjects (17 percent) were responders. By 96 weeks, only 11 percent were responders. The current results of this ongoing study suggest that many patients can be safely managed without drugs for several months, potentially decreasing adverse events and costs. They also suggest the goal of persistent low-level viremia without treatment is unlikely to be achieved.

Lori et al⁴⁷ recently reported on a cohort of chronically infected patients, known as PANDAs. They had been treated with ddI and hydroxyurea, and had suppressed but detectable viremia over two years. The patients had normalized the percentages of naïve CD4 and CD8 lymphocytes, and exhibited vigorous HIV-specific T-helper responses. In this observational study, the PANDA group was matched with a control group of asymptomatic patients with similar CD4 counts and viral loads before the initiation of HAART therapy. Nine

PANDAs and seven control patients agreed to interrupt therapy for eight weeks. Therapy was reinitiated if the HIV RNA rebounded above 10,000 copies/ml on two occasions, or if the CD4 cell count decreased below 200 cells/mm³ at any time. None of the PANDA group had to restart treatment before eight weeks. After reinitiating therapy, the group returned to similar levels before the interruption. In contrast, four out of seven patients treated with HAART had to reinitiate therapy early. It is hypothesized that the strong HIV-specific T-helper cell response, detected in the selected patients treated with hydroxyurea and ddI, played an important role in controlling viral replication off therapy. The PANDA group had maintained a low but detectable level of HIV for several years on therapy that may have exposed the immune system to autologous antigen needed to induce T-cell immunity. However, this was a non-randomized study, and different outcomes may have been due to other factors.

Other groups have not shown control of viral load replication, nor delay in viral load rebound in small numbers of patients treated with repeated STI.⁴⁸

Patients with chronic infection are a heterogeneous group, so it might be expected that responses to STI would be variable. Using STI in this setting requires better elucidation of reliable predictors of response to it such as pre-HAART viral load and CD4 count, HIV proviral load, rate of viral HIV rebound, and cytotoxic T-lymphocytes. An observational study of five patients³⁵ demonstrated that patients with stronger cellular immune response at the beginning of a given interruption period had longer delays of viral load rebound. It also appeared that the duration of the on/off cycle may have been crucial to the success of this approach.

Is there a role for a single STI in chronic infection?

Multiple studies in the literature have evaluated single STIs or treatment discontinuations after long-term suppression of HIV RNA after initiation of HAART in chronic infection. In the majority of cases, there is typically a viral rebound to pre-HAART levels accompanied by a decline in CD4 counts. Reinitiation of therapy is often successful in re-suppressing HIV viremia.^{23,27,49-51} This approach is usually associated with only a short period off therapy, and is unlikely to have much impact on total drug burden or toxicity. For some patients, a break from therapy is occasionally necessary. Before this can be recommended, more research is necessary to determine safety, especially immune competence lost during the interruption, and the risk of the emergence of resistance.

What is the role of STI in salvage therapy?

A retrospective study of 48 patients suggested that a treatment interruption (mean of 121 days, range from 54

to 322 days) prior to the initiation of salvage antiretroviral therapy resulted in an increased proportion of patients suppressing viral replication with the initiation of the salvage therapy.²⁰ This response appeared to be the most significant in the 28 patients who had reversion of the viral genotype to wild type during the treatment interruption. Sixty-seven percent of these patients were able to suppress viral replication to less than 500 copies/ml by 629 days after initiation of the salvage therapy. These conclusions may only generate hypotheses because of unspecified reasons for the treatment interruption, length of the interruption, use of opportunistic infection prophylaxis, and number of new agents available in the salvage therapy.

Other groups have made similar observations.^{21,52,53} Typically, there will be decreases in CD4 counts, and increases in viremia during the variable interruptions. These markers may not always return to base line after reinitiating salvage therapy. Given the potential for improved virologic responses, these observations have led to the development of clinical trials for patients who have treatment options that are numerous such as Canadian HIV Trials Network (CTN) study 164, or that are few such as Options in Management with Antiretrovirals (OPTIMA), and the French GIGHAART study (ANRS 097). Some of these studies have also employed the use of anti-HIV treatment with five or more drugs (mega-HAART) in the salvage regime.⁵³

What are the other potential risks and benefits of STI in clinical practice?

Can STIs be used to decrease drug burden and toxicity in chronic infection? Some investigators believe that STI in chronic infection cannot autoimmunize, nor control HIV replication, but may be used to decrease drug burden and toxicity. Another STI strategy currently under investigation—Tibet study, Strategies for Management of Anti-Retroviral Therapy (SMART) study, Community Programs for Clinical Research on AIDS (CPCRA)—compares the strategy of continuous HAART versus STI to enable “acceptable” immunologic and virologic control.

In this strategy, patients are treated with HAART until the CD4 count increases above a certain threshold and HIV RNA is suppressed. HAART therapy is discontinued at this point until the CD4 count declines to a lower threshold, or there is a significant virologic rebound. This approach uses criteria for the reinitiation of HAART similar to those used for the initiation of HAART in the antiretroviral-naïve subjects. The emergence of wild type virus and the decline of CD4 cell counts can be precipitous, and careful medical follow-up is necessary.

If demonstrated to be safe and effective, this strategy would decrease the total drug burden while maintaining

adequate immunologic control without selecting for resistance. It could potentially be adapted to the clinical setting after addressing questions of emergence of drug resistance, and the quality and quantity of reconstitution of the immune system. Although STIs can transiently mobilize HIV-specific T-cells, there is rapid depletion of the T-cell population with viral replication. This raises concern about the quality of the immune reconstitution^{44,54,55} and the potential for reseeding viral reservoirs.

What about the risk of the emergence of drug resistance during STI? The emergence of resistance is a major clinical concern, leading to questions about whether all the agents should be discontinued at the same time, given variability in biological half-life. If one agent with a low genetic barrier to resistance and a long half-life such as NNRTI is stopped at the same time as the reverse transcriptase inhibitors, there is a concern that the patients may have exposure to the NNRTI alone, for a few hours to days. This could be sufficient to allow for emergence of resistance, thereby decreasing its usefulness in further treatment.

Multiple studies in the literature evaluate STIs following HIV RNA suppression with HAART treatment during chronic infection. The rebound of viral load replication typically re-suppresses to below the limits of detection of the assay in the majority of cases, implying that significant emergence of resistance does not occur.^{23,27,48-51}

During antiretroviral therapy, it is hypothesized that new uninfected target cells arise and escape infection due to the presence of antiretroviral drugs. The period of greatly increased viral replication in STI could be a particularly dangerous period for the development of resistance with even transient low levels of the drug.⁵⁶

A greater concern is the risk of STIs in patients who already harbor resistant viruses.^{21,57-59} In the absence of drugs, a resistant mutation may confer a fitness cost relative to wild type. In the presence of drugs, the fitness of wild type viruses decreases, and if reduced below that of resistant viruses, the resistant viruses may outgrow the wild type strains. The resistant virus would be expected to increase faster during periods of drug treatment than during drug-free periods. Therefore, an STI with long treatment phases and short STI phases would delay, but not prevent, the development of resistance.¹⁵ One study of 20 multi-drug resistant patients with virologic failure demonstrated genotypic reversion to wild type was common and increased with the duration of interruption, but the previous mutations reemerged quickly with the reinitiation of salvage therapy.⁵⁹

A study of 12 patients undergoing three STIs by Picado et al⁶⁰ demonstrated the emergence of the M184V mutation (lamivudine (3TC) resistance mutation) in two patients after their second or third STI. There was a stepwise increase in the proportion of mutations in the virus population with each STI. Both patients had been on a previous regime that included 3TC.

A shift from drug-resistant to wild type genotype can regularly be shown in patients with virologic failure on STI using conventional genotyping, but minority resistant populations can be demonstrated in a large proportion of patients using sensitive polymerase chain reaction (PCR) techniques.⁶¹

What is the impact of STI on adherence and quality of life? Poor adherence is a major factor associated with virologic failure of HAART therapy, as well as in the development of drug resistance.⁶²⁻⁶⁴ STIs potentially increase or decrease adherence to treatment when they are reintroduced following the drug-free period.

Patients may approach reinitiation of therapy with better adherence if relieved of toxicity and fatigue of HAART, and if they recognize the risks of an STI with rising viral load and declining CD4 count off therapy. In contrast, adherence can be negatively affected by an STI if treatment reinitiation is associated with the recurrence of acute adverse events such as nausea, vomiting, diarrhea, or other toxicity.

STIs can have a positive or negative impact on quality of life. They may be a cause of stress because of a possible rebound in viremia, or a substantial CD4 decrease. On the other hand, relief from drug toxicity can improve quality of life. More careful follow-up during STI and the increase in monitoring can also negatively affect the quality of life, and increase the "medicalization" of their illness.

One small prospective study assessed the psychological impact of four STI cycles (maximum 30 days) in 12 patients.⁶⁵ The quality of life was better in patients interrupting therapy than in controls during the second and fourth reintroduction of HAART. Adherence to medication was greater after the first interruption of therapy in experimental subjects, although no differences were found after the following interruptions. In the experimental group, there was no overall increase in quality of life off treatment, but there was a decrease in quality of life at therapy reintroduction.

Conclusions

In conclusion, interest continues to grow in the potential role of STIs to decrease total antiretroviral drug requirements, and to decrease toxicity in patients with

HIV infection. Until the results of clinical trials are complete, STIs remain experimental, and not part of routine clinical practice. It is premature to pass judgement on STI based on observational, uncontrolled studies.

For patients treated in seroconversion, STIs may be used to autoimmunize and to allow some patients to control HIV viral replication periodically off drugs. This strategy will only be applicable for a few patients because most are not diagnosed or treated during seroconversion.

The results from short cycle on/off therapy are encouraging. With a short cycling period, rebound of plasma viremia is less likely to occur, and the risk of the emergence of drug-resistant virus is lower. This approach could decrease the total drug exposure time by half and decrease acute toxicity, but it is complex and requires careful adherence by patient and physician which would likely be difficult to implement in a large clinical setting. The potential for delaying long-term adverse drug effects such as lipodystrophy warrants further study.

The use of an STI prior to the initiation of a salvage regimen appears to increase virologic response rates, especially if there is reversion of the genotype to wild type. However, the durability of the response may be compromised by the regrowth of drug-resistant mutants, requiring further data. STI in this setting is typically brief, and it is unlikely to have much impact on drug burden or toxicity issues.

Another exciting potential use of STI awaits the results of clinical trials. In these trials, HAART is stopped and reinitiated to maintain the CD4 cell count within certain parameters. Although appealing in principle, more needs to be learned about the safety of this approach in terms of the quality and quantity of immune reconstitution, risk of drug resistance, and impact on adherence and quality of life. If found to be safe, this strategy could be particularly important in resource-constrained treatment settings. ■

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