HIV JournalView


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Got Blips?

Lower is better when it comes to taxes, rap music and HIV viral load. However, research suggests that an occasional, transient low-level rise in HIV viremia among patients who otherwise have viral loads below the limit of assay detection, so-called "blips," may not be such a bad thing. For example, in AIDS Clinical Trials Group (ACTG) study 343,[1] a large trial of induction and maintenance antiretroviral therapy begun in 1997, subjects with occasional blips did not have higher failure rates than those with persistently undetectable viral loads. This was true even though patients with blips (detected through the use of extra-sensitive assays) tended to have viral loads closer to 50 copies/mL than those without blips. Likewise, in studies looking at differences in clinical outcomes among those with and without blips,[1-4] transient viral load increases were not associated with the development of major drug-resistance mutations or CD4+ cell-count compromise. The reasons why some people blip and others don't and the differences between the two remain unclear. However, two recently published studies tackle these questions and examine this phenomenon from distinct vantage points.

Miller LG, Golin CE, Liu H, et al. No evidence of an association between transient HIV viremia ("blips") and lower adherence to the antiretroviral medication regimen. J Infect Dis. April 15, 2004;189(8):1487-1496.

The possible causes of blips are the same factors that have been said to cause outright virologic failure of HIV therapy: suboptimal regimen potency, baseline drug resistance, variable pharmacokinetics, host immune responses and non-adherence.

Adherence, in particular, has been one of the obvious targets blamed for blips, since suboptimal adherence to antiretrovirals is known to be prevalent.

To examine the relationship between medication adherence and blips in viral load, Miller and colleagues at the University of California in Los Angeles (UCLA) performed a case-control study using data from a prospective cohort study of adherence to new antiretroviral therapy.

The cohort's 128 patients, who either initiated HIV treatment or started a new antiretroviral regimen, underwent monthly measurements of plasma HIV-RNA levels, CD4+ cell count and

antiretroviral adherence. Adherence was measured using pill count, self-reporting and electronic monitoring devices (EDEMs). A composite adherence score, which relies primarily on the EDEM data, was derived using techniques the investigators developed and described previously.[5]

The adherence score of the cases, which was defined as people who had a viral load increase of between 40 and 1,000 copies/mL, sandwiched between two measurements of <40 copies/mL, was compared with that of the controls who had no evidence of blips. The patients who had blipped and the controls were matched for time from initiation of regimen to the blip and treatment-naive status at entry. Baseline HIV viral load level and CD4+ cell count, however, were not included in the matching scheme, although these parameters have been identified as predictors of therapy response. Adherence of cases before, during and after a blip was also examined.

A quarter of the cohort (32 subjects) experienced a blip during a mean of 48 weeks of on-study follow up. Four of these subjects had insufficient adherence data available and were excluded from analysis. Among the remaining 28 subjects, the mean viral load at the time of a blip was 128 copies/mL. The mean time from regimen initiation to blip was 27 weeks. There were no significant differences between the cases and controls with regard to composition of antiretroviral regimen, duration of HIV infection or virologic outcomes. Importantly, among the cases, therapy was not changed before, during or immediately after a blip. Adherence of the cases to HIV therapy prior to, at the time of and during the month following the blip was 86%, 84% and 80%, respectively -- indicating no decrease in overall adherence preceding a blip. The controls had adherence scores during the corresponding intervals of 77%, 79% and 75%, respectively. Thus, the cases had significantly (p=0.046) *better* rather than poorer adherence compared to subjects in the control group!

Nine case and nine control subjects experienced virologic failure, defined as a viral load >40 copies/mL (for cases, this did not include the blip). An examination of overall adherence among the 19 cases who had complete EDEM data, found that, at the time of a blip, adherence was better than it had been during periods of sustained undetectable viral load results. Dose timing was evaluated and there was no association found between medication timing error and blips.

Until you consider both sides of a blip -- the rise *and* the fall -- this seems like a counter-intuitive result. The increase in viremia can clearly be imagined to be rooted in patients' non-adherence. A patient slacks on adherence and his or her viral load goes up -- but what about the subsequent fall in viral load? Increases in viremia induced by non-adherence usually beget more viremia. To make this a blip, rather than a blast-off, there must be pressure from therapy to (re)suppress the virus.

In other words, it makes sense that patients with blips are taking their medication, for if they didn't take it, their viral loads would continue to rise rather than fall immediately. If, as has been suggested previously, patients with blips have a relatively higher, yet still undetectable (<50 copies/mL), viral load than patients who do not blip (for reasons that remain unclear), it could be that these patients may require greater adherence to their therapy to maintain control of their viremia. The ability of "blippers" to do as well as they do despite this potential virologic handicap may be a product of their better adherence. If they had poorer adherence, they would never have been able to sustain viral loads below 50 copies/mL in the first place. The result of this interesting study therefore become less surprising than at first glance.

This study does not answer the question of why blips occur, but it strongly suggests that we can stop pointing a wagging finger at the patient and should cross non-adherence off from our list of suspected causes.

Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. AIDS. April 30, 2004;18(7):981-989.

So, now that we have established that it is not the lack of adherence that causes viral load blips, could it be that there are host immune factors that help explain both why these blips occur and why they don't appear to cause obvious harm?

In this study, conducted at the University of California in San Francisco (UCSF), investigators described the immunologic profile of three groups of patients receiving antiretroviral therapy who had varying degrees of HIV viremia during the preceding year:

A. Those who had sustained suppressed viremia with 100% of all viral load results below the limits of assay detection (n=13);

B. Those who had infrequent (less than 50% of all determinations) blips of 50 to 1,000 copies/mL (n=15); and
C. Those who had persistent viremia (greater than 50%) between 50 and 1,000 copies/mL (n=18).

At study entry, subjects with suppressed viremia were found to have significantly higher CD4+ cell counts than subjects who had intermittent or persistent viremia. However, median counts were high in all groups, and ranged from 460-674 cells/mm^3.

During a median of 27 months of on-study follow up, confirmed virologic failure (increase in viral load to greater than 1,000 copies/mL) occurred in 10 of 18 subjects with persistent low-level viremia. In contrast, only one subject in the group with blips, and none of the patients with suppressed viremia, experienced virologic failure. Phenotypic resistance testing was performed in the persistently viremic patients. The results revealed that most of the persistently viremic patients had evidence of drug resistance at baseline, which increased on-study while they had been on stable HIV therapy.

HIV-specific T-cell (CD8+) responses, as measured by interferon-gamma production in response to major HIV proteins, were almost 10-fold greater among those with blips and 12-fold greater among those with persistent viremia compared to those with sustained viral suppression. Further, the breadth of the response to HIV antigens was greatest among patients who experienced intermittent or persistent viremia. Interestingly, even at times when patients with occasional blips had undetectable viremia, their HIV-specific immune responses were more robust than those measured in patients with sustained suppressed viremia.

Immunophenotyping was performed to quantify circulating activated T cells. Both patients with blips and those with suppressed viremia were found to have low levels of activated CD8+ cells, 9% and 6%, respectively, while patients with persistent viremia had much higher levels (16%). Among patients with blips, T-cell activation tended to be highest around the time of a blip, compared to when viral loads were undetectable.

People with blips can therefore be accused of having their cake and eating it too. Compared to patients who maintain consistently undetectable viral loads, patients who blip have significant increases in the magnitude and breadth of their HIV-specific immune responses -- increases that are similar to those in patients with persistent viremia, but *without* the damaging effects of viremia and subsequent T-cell activation.

This finding suggests that the pattern of HIV exposure dictates whether heightened immune activation occurs. That blips do *not* lead to increased T-cell activation may explain why these patients have more favorable outcomes than what is seen in patients with persistent viremia, since T-cell activation has been associated with CD4+ cell decline and is believed to better support viral replication and evolution. That T-cell activation appeared to be greatest around the time of a blip may suggest that bursts of immune activation may trigger viremia, although it is unclear what happens first -- viremia or activation -- and, in any case, this was not addressed by this investigation.

Beyond providing insight into the etiology of blips, this study provides practical information regarding the management of patients with HIV. Currently, there is no consensus on how aggressively to chase low-level HIV viremia. Some clinicians are pursuing antiretroviral modification plus adherence counseling and others are taking more of a watch-and-wait approach. In the UCSF study, persistent low-level viremia was associated with immune activation, viral evolution and cultivation of resistance mutations -- all findings that support aggressive modification of therapy in such patients. In addition, the UCLA study demonstrates that adherence is unlikely to be the reason blippers blip. Together, the results of these studies suggest that the hands-off approach with patients who experience blips is justified.

Reversal of Lipoatrophy

Lipoatrophy is a disfiguring complication of HIV therapy that dramatically impacts a patient's self-esteem, medication and adherence. Further, confidentiality can be compromised when facial fat loss prompts a seemingly endless stream of questions regarding health (i.e., "You look like you are losing weight, are you okay?"). For many patients, lipoatrophy is the most dreaded of the long-term complications of HIV therapy. For other patients, it is a price to pay for successful suppression of their virus. Either way, few of those affected would not be interested in a therapy to reverse the loss of fat, especially in the face. Unfortunately, to date, there has been only one intervention that has clearly been demonstrated to begin to improve lipoatrophy -- the cessation

of stavudine (d4T, Zerit) or zidovudine (ZDV, Retrovir). The Mitochondrial Toxicity (MITOX) Study was one of several studies to demonstrate that a switch from stavudine and, among a smaller number of patients, zidovudine to abacavir (ABC, Ziagen) was associated with modest improvements in peripheral fat wasting.[6] An extension of this study has permitted longer-term follow-up to determine the rate and extent of the reversal of lipoatrophy.

Martin A, Smith DE, Carr A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS. April 30, 2004;18(7):1029-1036.

The MITOX Study[6] randomized 111 patients who had moderate to severe lipoatrophy while receiving either stavudine or zidovudine. One group switched its thymidine analogue to abacavir, while the other group continued its pre-study therapy for 24 weeks, at which point patients could elect to switch to abacavir.

This widely reported study found a gain in DEXA-imaged limb fat among patients who switched to abacavir (85% of those switching were on stavudine) compared to the negligible limb fat increase in patients who maintained their pre-study regimen. However, the modest increase (0.4 kg) in peripheral fat gain among those who switched was not well appreciated by the participants, as indicated by their responses to a body image questionnaire 24 weeks after the switch.

The MITOX Study extension examined the outcomes of subjects from the original MITOX Study for an additional 80 weeks. A total of 111 patients had been originally randomized and, of these, 85 patients reached the 104-week follow up. Subjects were assigned to one of three groups:

A. Those who had switched their thymidine analogue to abacavir at the start of the initial study;
B. Those who had originally been randomized to continue pre-study therapy but switched to abacavir at week 24; or
C. Those who had originally been randomized to continue pre-study therapy, but at week 24 elected not to switch to abacavir.

At week 104, DEXA examination revealed that the mean increase in limb fat from baseline was 1.26 kg in the pooled abacavir groups, compared to a paltry 0.49-kg increase in the thymidine analogue continuation arm (p=0.008).

Unfortunately, the authors focused on an intent-to-treat analysis, in which comparisons were made according to the original randomization, rather than also presenting an on-treatment analysis. The subjects who switched to abacavir at week 24 were therefore lumped in with those who continued on stavudine or zidovudine throughout the study. This is typically a preferred approach, but given that half of the control subjects crossed over at week 24 to the experimental intervention (that is they switched to abacavir), it would have been helpful to exclude these subjects from some analyses and/or provide more information regarding the differences between those who switched to abacavir early versus those who switched later. For example, according to one graph, it is evident that patients who switched to abacavir at study entry experienced significantly greater increases in fat than patients who switched to abacavir at week 24 (~1.4 kg versus ~0.5 kg).

In contrast to the 24-week report from this investigation, at week 104 there was evidence of subjective appreciation of body shape improvement among patients who switched to abacavir. Differences in body shape perception were significant within the abacavir-switch group, but not in the control arms or between arms. Multivariate analysis found a correlation between baseline body mass index (BMI) and limb fat gain (the higher the BMI, the greater the limb fat mass at study end).

The amount of visceral adipose tissue (deep abdominal fat) was not found to be different between the study arms during the study. In addition, bone mineral density was not significantly different between the arms initially. However, the arm analysis found a significant loss of bone density among the subjects treated with the thymidine-analogue. Again, this analysis groups control subjects with those who had switched to abacavir at week 24, potentially obfuscating a more profound difference between the control and early abacavir-switch arm.

Although switching to abacavir was virologically safe, abacavir hypersensitivity reactions (HSRs) did occur, as expected. HSR was diagnosed in five patients in the original study, as well as four additional subjects who switched at week 24 to abacavir.

This study paints a much more optimistic picture than the original 24-week report by these authors. Overall, patients' limb fat increased by 36% following their switch to abacavir -- an impressive response for a problem for which, prior to this study, and since then, no other intervention has been found to be effective. (Note: This same group of investigators recently reported the negative results of a trial of rosiglitazone for lipoatrophy.[7]) The patients' relatively underwhelming appreciation for this change during the open-label study even after two years following the switch may be a consequence of the inherent difficulty of conducting such subjective evaluations in which participant expectation at the onset is likely to be high. In addition, body shape surveys can only detect so much. As much as we HIV clinical scientists adore quantitative data, qualitative assessments may have yielded more robust data on body shape.

This and similar studies also provide insights into the etiology of lipoatrophy accompanying HIV therapy. The improvement in body fat with the simple discontinuation of (mostly) stavudine[8] supports the now widely appreciated link between stavudine and lipoatrophy. However, it is also notable that this improvement was seen independent of other metabolic parameters, such as triglycerides and other lipids, insulin, glucose and visceral fat. Therefore, the effects of thymidine analogue therapy seem isolated in this particular investigation.

Armed with these data, clinicians would be prudent to avoid the agents most closely associated with lipoatrophy and, certainly coincident with MITOX and similar studies,[8] stavudine use has waned. There are data beyond this study, however, that support a role for the ubiquitous zidovudine in fat wasting[9] -- although arguably at a much lower rate than stavudine. With time, as newer agents with minimal body shape effects become further integrated into standard care, it may well be that lipoatrophy will be a relic of an early period of the HAART era. Until then, there is increasing benefit to switching and no apparent downside.

HIV-Associated Cognitive Dysfunction: HAART Helps

HIV-associated dementia is a well-known complication of AIDS. However, much more subtle cognitive impairments have been demonstrated to exist at higher CD4+ cell counts.[10] While HIV therapy can improve, and perhaps even prevent, dementia,[11,12] it is not known whether therapy can impact less obvious cognitive dysfunction.

Robertson KR, Robertson WT, Ford S, et al. Highly active antiretroviral therapy improves neurocognitive functioning. J Acquir Immune Defic Syndr. May 1, 2004;36(1):562-566.

In this study, 48 patients, who either initiated or changed potent antiretroviral therapy, were subjected to a battery of neuropsychological and neurological evaluations before and six months after the start of their regimen.

Cerebrospinal fluid (CSF) was collected at both time points to measure CSF HIV viral load. Only one subject was treatment naive at study entry. Two thirds of the participants were male and 31% were white. The mean baseline CD4+ cell count was 226 cells/mm^3 and the mean plasma HIV RNA was 4.56 log copies/mL. Plasma HIV RNA declined to 2.64 log copies/mL, and CSF HIV RNA declined from 2.74 to 1.36 log copies/mL.

Using a standardized measure of dementia, 69% of the patients were rated as normal, 21% were equivocal and 10% had dementia. At six months, no change in dementia score was detected for most of the subjects (70%); 23% of patients, however, did experience improvement and three patients (6%) experienced a decline in function. Overall, however, all patients demonstrated significant neurological improvement. Among the neuropsychological domains tested, significant improvement was observed in attention, speed, flexibility, visuospatial, verbal and figurative memory, fine motor and language, but no change was shown in gross motor.

These data are critical for several reasons. First, there is concern that combination antiretroviral therapy has variable penetration into the central nervous system, and might therefore not be able to improve HIV-related cognitive problems. This study adds to previously generated data[13,14] regarding the benefit of potent antiretroviral therapy in cases of advanced dementia and indicates that even more subtle cognitive impairment can also respond to HIV treatment.

Second, the improvements demonstrated here, among patients without advanced AIDS, suggest

that HIV-related cognitive dysfunction may need to be considered an indication for the initiation of antiretroviral therapy, regardless of CD4+ cell count and plasma HIV-RNA level. Lastly, although the subjects of this study by and large did not have dementia, their improvement with antiretrovirals indicates that under-recognized cognitive dysfunction was present at baseline. Unfortunately, screening for cognitive impairment is not currently standard clinical practice. Time-consuming and technical assessments make comprehensive neuropsychological evaluation difficult. Abbreviated but sensitive clinic-friendly instruments would clearly come in handy.

A5095 -- Trizivir Versus Efavirenz Combinations

Gulick RM, Ribaudo HJ, Shikuma CM, et al, for the AIDS Clinical Trials Group Study A5095 Team. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. April 29, 2004;350(18):1850-1861.

Finally, if you have not yet heard about ACTG Study A5095, a three-arm, blinded trial comparing Trizivir (zidovudine + lamivudine [3TC, Epivir] + abacavir) *versus* Trizivir + efavirenz (EFV, Sustiva) *versus* Combivir (zidovudine + lamivudine) + efavirenz, it is well past time to wake up Dr. Rip van Winkle.

This ongoing study which was first presented at the International AIDS Society Conference on HIV Pathogenesis and Treatment in Paris in July 2003, has yielded preliminary results that have been reported on this and every other Web site dedicated to HIV management. These important initial findings were published in the New England Journal of Medicine in April and the article is a must-read for anyone who treats HIV infection.

The bottom line is that, after a median of 32 weeks on study, 21% (82) of the 382 subjects receiving Trizivir had experienced virologic failure (two HIV RNA values >200 copies/mL at least 16 weeks after randomization). This compared to only 11% (85) of 765 subjects in the combined efavirenz arms ($p<0.001$) who experienced virologic failure. Differences in virologic efficacy were seen at high (>100,000 copies/mL) and low viral loads. The results led an interim monitoring committee to recommend that the Trizivir arm be stopped and the results presented.

These data clearly indicate that Trizivir is not as effective as an efavirenz-containing regimen. It is important to note that Trizivir did not do poorly, it simply did not do as well as the other arms. An additional distinction that needs to be made is between the performance of Trizivir in this and other studies and the results of several recent trials of other triple-nucleoside combinations[15-17] (e.g., tenofovir [TDF, Viread] + didanosine [ddI, Videx] + lamivudine and tenofovir + abacavir + lamivudine) that had near-universal failure rates. To paint all triple-nucleoside regimens with the same brush is simply not justified. For more on this study, click here.

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