Hot News

What Have we Learned from Recent CD4-Guided Treatment Interruption Studies?

During August 2006, four studies on CD4-guided therapy interruption were reported: SMART (abstracts WEAB0203 and WEAB0204), BASTA (abstract WEAB02002), and ANRS 116 SALTO (abstract WEAB0205) during the International AIDS Conference in Toronto, and STACCATO (Ananworanich, et al. Lancet 2006;368:459-65). They are all highly relevant for clinical practice, and their results to some extent provide contradictory messages. Without doubt they have initiated one of the hottest discussion subjects in HIV therapy. The contradiction lies in the fact that the SMART study showed inferior clinical outcomes using the strategy of episodic CD4-guided treatment interruptions to relieve drug adverse events, while the conclusions of the other three studies pointed to the safety and efficacy of this approach under certain circumstances.

This over simplistic contradiction can to some extent be explained by the differences in the designs of the studies. While the STACCATO trial included 430 patients, BASTA 114 patients, and SALTO only 99 patients, the SMART study enrolled a massive number of 5472 patients, giving it the statistical power to assess minor differences in clinical outcome. Another important difference was the threshold of CD4+ cell counts for restarting and interrupting therapy. For the three studies showing no important clinical differences between the two arms, these thresholds were: STACCATO, a restart threshold of CD4+ count 350 cells/µl, and interruption after a minimum of 12 weeks on therapy and a confirmed CD4+ count > 350 cells/µl; for BASTA, restart and interruption thresholds were 400 and 800 CD4+ cells/µl, respectively; for SALTO, restart and interruption thresholds were 300 and > 450 CD4+ cells/µl, respectively. All of these are higher than the CD4+ threshold for SMART: i.e. restart at 250 and interruption at 350 cells/µl. As a consequence, the patients on SMART were kept at lower CD4+ counts for longer periods, thus increasing the risk for disease progression. In fact, after adjustment for proximal CD4+ count and viral load levels (latest CD4+ count and viral load before an adverse event), the hazard ratio (therapy interruption arm/continuous treatment arm) for disease progression was reduced from 2.5 ($p < 0.001$) to 1.4 ($p = 0.12$).

However, while the proximal CD4+ count and viral load are correlated with the number of adverse events in both arms of the SMART study, they do not entirely explain all the cases of disease progression or the discordance between the studies. In the subsets of patients with proximal CD4+ counts of 350-499 and > 500 cells/µl, the rate of opportunistic disease or death was still significantly higher in the treatment interruption arm ($p < 0.05$), thus raising the possibility that something more than just the absolute CD4+ count is involved. With this in mind, the STACCATO team commented that according to the CD4+ counts observed, it was expected to have "about 17 AIDS-defining opportunistic events or deaths in the STACCATO scheduled treatment interruption group"; however they found none. Such estimates are based on statistical data including patients starting therapy at various CD4+ counts. Remarkably, restarting and interrupting therapy at higher CD4+ thresholds was an important difference of the STACCATO compared to the SMART study. Moreover, it has been reported that some CD4+ cell functionalities are impaired in patients that have experienced lower CD4+ nadirs (Siddique MA, et al. J Infect Dis 2006;194:661-5). Perhaps more adverse events can be expected during equal absolute CD4+ counts in patients starting therapy at lower CD4+ thresholds, implying that the quality (and not only quantity) of CD4+ recovery, or the level of immune activation and inflammatory responses, may be more predictive for the occurrence of adverse events than the absolute proximal CD4+ count.

In conclusion, the strategy of CD4-guided therapy should not be entirely abandoned. More studies with a design taking into account all the available knowledge are still needed to further clarify this issue. But while we wait for those studies, the CD4+ count threshold for therapy initiation should again be brought into debate. All the four studies concluded that the CD4+ nadir is predictive for time off-therapy and the rate of CD4+ decrease after treatment interruption. In addition, from the considerations mentioned above, it may be that the SMART study is teaching us that there is an increased risk for opportunistic disease or death, even when CD4+ counts are at high levels in patients where (re-)initiation of therapy was at low CD4+ counts (250 cells/µl). Indeed, several immunologic studies suggest a better prognosis for immune recovery when therapy is started at higher CD4+ counts. At the same time, drug adverse reactions and the risk for resistance development cautioned us to start therapy too early. However, the drug regimens available have much improved in recent years. The precarious balance between immune recovery prospects and risks associated with lifelong treatment may have shifted. In

my opinion, what the results of the recent CD4-guided treatment-interruption studies are teaching us is that the discussion of "when to start therapy" is open again.

Ricardo Camacho
Virology Laboratory
Centro Hospitalar de Lisboa Ocidental
Lisbon, Portugal

New IAS Antiretroviral Treatment Guidelines – August 2006

The International AIDS Society (IAS) released on August 16, 2006 updated recommendations for the treatment of adults with HIV (Hammer, et al. JAMA 2006;296:827-43). The table summarizes the recommended regimens as initial therapy of HIV infection.

Given the high degree of comparability in terms of potency of the components of the regimens recorded in the table in antiretroviral-naive persons with drug-susceptible viruses, the choice of drugs should be based on acceptability, predicted tolerance, pill burden, comorbid conditions (viral hepatitis, lipid abnormalities), reproductive status, concomitant medications, short- mid- and long-term adverse event profiles, and successful alternatives should the initial regimen fail and drug resistance emerge.

Drug-resistance testing should be performed in all subjects before initiating antiretroviral therapy. Assuming the presence of fully drug-susceptible virus, the choice of the dual NRTI component relates to the toxicity profiles and predicted tolerance of zidovudine, abacavir, or tenofovir. All should be given with either lamivudine or emtricitabine, which should be considered as bioequivalent. Differentiating adverse effects for the three distinct NRTI include: headache, nausea, anemia, and lipoatrophy for zidovudine; hypersensitivity reactions with abacavir; and renal dysfunction in patients with baseline renal compromise with tenofovir. As a fixed-dose, zidovudine/lamivudine (Combivir®) is given twice daily, while abacavir/lamivudine (Kivexa®) and tenofovir/emtricitabine (Truvada®) are given once daily.

Triple nucleoside regimens are inferior to PI- and NNRTI-based regimens, and therefore should generally not be recommended as first-line therapy. Some combinations of NRTI are contraindicated, such as zidovudine/stavudine, didanosine/stavudine, tenofovir/didanosine, and abacavir/tenofovir. The reasons for these decisions are based on antiviral competition and overlapping, synergistic toxicities.

Although no definitive data support the use of specific third-drug components, many experts prefer a ritonavir-boosted PI over a NNRTI in very advanced HIV disease with high viral loads because of the higher genetic barrier to resistance and slower rate of mutation selection seen with PI. The results of the ACTG 5142, the first head-to-head prospective comparison of lopinavir/ritonavir versus efavirenz plus two nucleosides seem to confirm the superiority of PI for increasing CD4+ counts at the cost of slightly lower virologic efficacy.

Table. Antiretroviral regimens as initial HIV therapy

2 NRTI	3rd drug
Tenofovir + Emtricitabine	Efavirenz or Nevirapine
Zidovudine + Lamivudine	Lopinavir/r or Atazanavir/r or Fosamprenavir/r or Saquinavir/r
Abacavir + Lamivudine	

Hammer, et al. JAMA 2006;296:827-43.

Efavirenz use requires adequate contraception in women of child-bearing potential, given its teratogenic risk in the first trimester. Nevirapine has virologic activity similar to efavirenz and is safe for the fetus in all stages of pregnancy. There is a risk of hepatotoxicity particularly using nevirapine in women with CD4+ counts > 250 cells/µl and men with counts > 400 cells/µl. Nevirapine is also recommended in patients in whom the central nervous system toxicity of efavirenz is not tolerated or does not abate within two to three weeks of starting treatment.

Of the ritonavir-boosted PI, more data exist for lopinavir/ritonavir, but hyperlipidemia and other metabolic disturbances may favor the use of atazanavir/ritonavir. The most common adverse event with the latter is asymptomatic hyperbilirubinemia, which does not reflect liver injury. Other acceptable alternatives are fosamprenavir/ritonavir and saquinavir/ritonavir.

Andrés Ruiz
Hospital Carlos III
Madrid, Spain

Results of the KLEAN Study

Data from the recently completed lopinavir/r *vs.* fosamprenavir/r with lamivudine and abacavir in antiretroviral-naive patients were published last August (Eron, et al. Lancet 2006; 368: 476-82) and presented at the International AIDS Conference the same month in Toronto, Canada. This randomized, 48-week study has compared ritonavir-boosted fosamprenavir with the (up to now preferred) ritonavir-boosted protease inhibitor, lopinavir, both coad-

ministered with the fixed-dose NRTI combination of abacavir and lamivudine. The findings showed no significant difference between the two therapies in terms of efficacy, tolerability, and toxicity.

The trial recruited 878 antiretroviral-naive patients, who were randomized to receive either fosamprenavir/r 700/100 mg twice daily or lopinavir/r 400/100 mg twice daily, both with a once-daily dose of abacavir-lamivudine 600/300 mg (Kivexa® in Europe; Epzicom® in North America). Primary endpoints at week 48 were either HIV-RNA < 400 copies/ml or discontinuation on account of adverse events. Virologic failure was defined as viral load > 400 copies/ml at week 24, or rebound of viral load > 400 copies/ml. At the end of the study, 73% (n = 315) of patients on fosamprenavir/r attained the targeted viral load of < 400 copies/ml and 71% (n = 317) of patients on lopinavir/r attained the same end-point. The proportion of subjects with HIV-RNA < 50 copies/ml was very similar in both the fosamprenavir and lopinavir groups (66 and 65%, respectively). Virologic failure of 4 and 5%, respectively, was also comparable. Patients experienced few adverse events, mainly nausea, diarrhea, and abacavir hypersensitivity. The rates were again similar in the two groups at 12% with fosamprenavir/r and 10% with lopinavir/r. The abacavir hypersensitivity was 6% overall.

Thus, patients did equally well in both treatment arms of the study and no patients developed resistance to either PI/r. Therefore, the two treatments regimens should be considered equally interchangeable with no differences in terms of efficacy, toxicity or emergence of resistance. This information is important for clinical decisions when making the choice of therapy for antiretroviral-naive patients, and fosamprenavir should be considered as an equally preferred PI option.

Pablo Barreiro
Department of Infectious Diseases
Hospital Carlos III
Madrid, Spain

The PD-1/PDL-1 Pathway: Another Magic Bullet for HIV Therapy?

An effective immune response to pathogens results from activation of T-cells by antigen-presenting cells. The T-cell activation is positively regulated by T-cell receptor ligation and the interaction of the CD28/B7 and other co-stimulatory molecules. Negative regulators include the CTLA-4/B7 and the PD-1/PDL-1 molecules (see Figure).

The responses of T-cells are important in the control of HIV infection, and accumulating evidence suggests that the function of HIV-specific T-cells is impaired during the course of the disease. Recent information suggests that in fact the PD-1/PDL-1/2 interaction (Okazaki, et al. Trends Immunol 2006;27:195-201) may represent a novel mechanism underlying the inability of HIV-1-specific T-cells to control viral replication, as suggested in several reports in press (Day, et al. Nature 2006; Petrovas, et al. J Exp Med 2006; Trautmann, et al. Nat Med 2006). The PD-1, a TNFα family member receptor, is expressed by activated B-cells and T-cells as well as monocytes, and is the receptor for its ligands PDL-1/2. Also, PDL-1 is constitutively expressed on monocytes and is induced on T-cells and B-cells following antigen activation. In contrast, PDL-2 is more tightly regulated and is expressed mainly on activated antigen-presenting cells. Interestingly, both PDL-2 and PDL-1 are also expressed in tumors and their expression may favor escape from immune recognition of cancer cells. The importance of these negative regulatory pathways in self-tolerance is demonstrated by the finding that CTLA-4 and PD-1 knockout mice both develop severe autoimmunity. Furthermore, PDL-1 knockout mice have a milder phenotype, suggesting that PDL-1 function may be redundant.

The importance of the PD-1/PDL-1 pathway in viral infection has been highlighted by the finding that PD-1 expression was associated with CD8+ T-cell unresponsiveness and with the inability of mice to clear lymphocytic choriomeningitis virus infection (Barber, et al. Nature 2006;439:682-7). In particular and of utmost importance was the finding that blocking PD-1/PDL-1 interaction could restore the effector function of "helpless" virus-specific CD8+ T-cell responses.

In HIV-1 infection, PDL-1 expression is higher in monocytes and B-cells and, importantly, high levels of PDL-1 correlate directly with plasma virus levels and inversely with the CD4+ T-cell counts (Trabattoni, et al. Blood 2003;101:2514-20), suggesting a role for this negative regulatory pathway in progression to AIDS. Recent papers (Okazaki, et al. Trends Immunol 2006;27:195-201; Day, et al. Nature 2006; Trautmann, et al. Nat Med 2006) demonstrate that the PD-1 receptor is also highly expressed on HIV-1-specific CD8+ T-cells. One of these studies was performed on 71 African patients infected with HIV-1 clade C and the others on patients from North America. Functionally, high expressing PD-1+ HIV-1-specific T-cells are impaired in their proliferative potential, and they undergo apoptosis in the presence of the PDL-1 ligand. Curiously, those studies demonstrated that while cytomegalovirus-specific T-cells expressed low level of PD-1, Epstein Barr virus-specific T-cells expressed high level of PD-1-like HIV-1-specific T-cells, which was the case

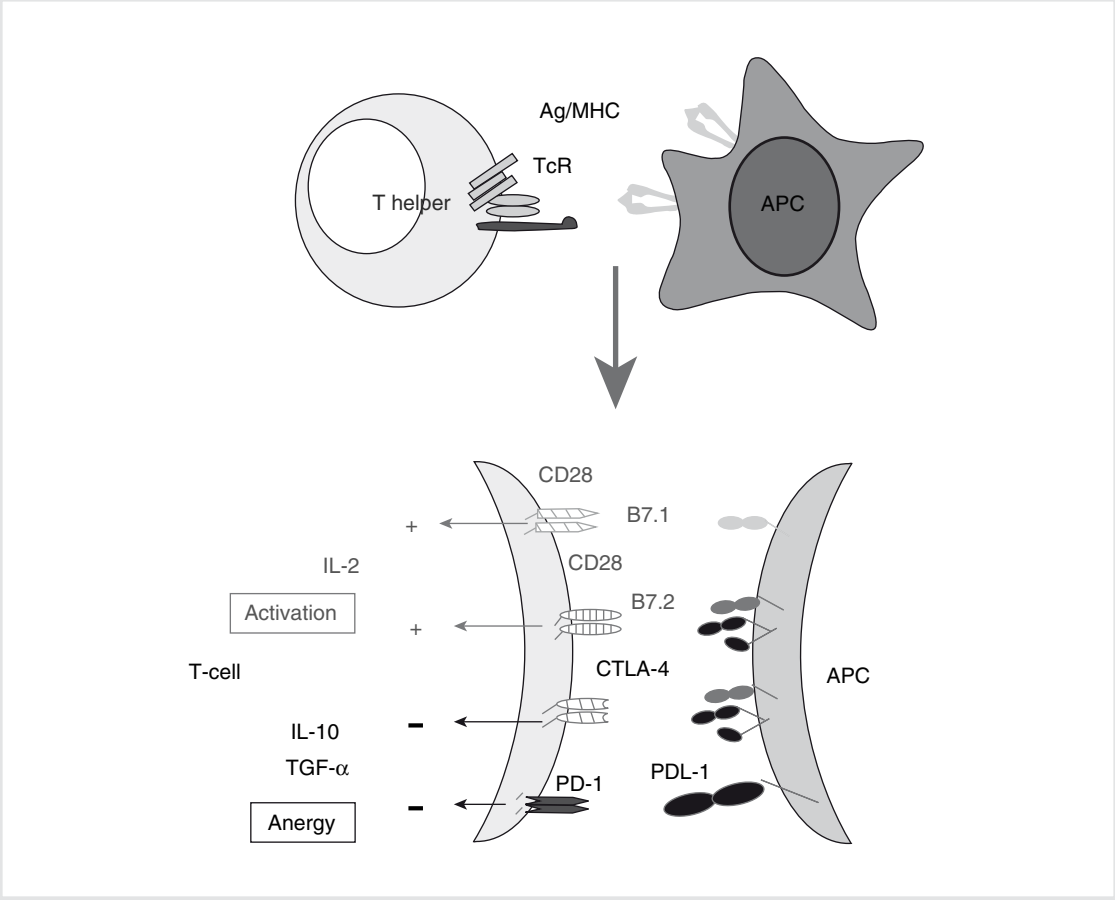

Figure. *T-cell activation is mediated by the interaction between TcR and the antigen presented by APC. Co-stimulatory as well as inhibitory molecules expressed on T-cells and APC regulate the strength of the signal and its outcome. CD28 binding to B7.1/B7.2 on APC mediates T-cell proliferation, IL-2 production and immune activation, while CTLA-4 and PD-1, through the interaction with their specific ligands, limit T-cell response. CTLA-4 binds to B7.1/B7.2 with higher affinity than CD28. Signal transduction through CTLA-4 and ligation of PDL-1 to PD-1, together with the production of inhibitory cytokines such as IL-10 and TGF, induce tolerance/anergy of T-cells. APC: antigen presenting cells; TcR: T-cell receptor; MHC: major histocompatibility complex; TGF: transforming growth factor; PD-1: programmed cell death-1; CTLA: cytotoxic T lymphocyte antigen.*

in both HIV-1+ and HIV-1-negative individuals. Because the level of cytomegalovirus and Epstein Barr virus replication/expression in these patient cohorts has not been associated with PD-1 expression, it remains unclear how high-level of PD-1 expression relates to the ability of these cells to control Epstein Barr virus and cytomegalovirus replication.

Further studies are therefore required to assess whether the PD-1/PDL-1-negative regulatory pathway represents an important therapeutic target for the treatment of HIV infection. Neutralizing antibodies to the human PDL-1 and blocking antibodies to the human PD-1 are available. Their cross-reactivity with the equivalent molecules encoded by the genomes of rhesus macaques provides an opportunity to test, in the preclinical setting, the importance of this negative regulatory pathway in the pathogenesis of SIV/HIV infection.

Mario Clerici
University of Milan
Milan, Italy
Monica Vaccari, Adriano Boasso, Valentina Cecchinato, Gene Shearer, Genoveffa Franchini
National Cancer Institute
Bethesda, MA, USA

Is There Any Risk of Intracranial Hemorrhage Using Tipranavir?

Ritonavir-boosted tipranavir is indicated for antiretroviral treatment of adult patients infected with

HIV-1 with evidence of viral replication and who are treatment-experienced or have HIV-1 strains resistant to protease inhibitors.

The FDA and Boehringer Ingelheim have recently warned healthcare professionals regarding the potential risk for fatal and nonfatal intracranial hemorrhage in patients receiving 500 mg of tipranavir (Aptivus®) boosted by 200 mg of ritonavir twice daily. A retrospective analysis of clinical trials including 6840 HIV-infected patients has concluded that ritonavir-boosted tipranavir was linked to 14 reports of intracranial hemorrhage events, including eight fatalities. The median time to the complication after initiation of therapy was 525 days. However, most cases occurred in patients with contributing risk factors for intracranial hemorrhage such as central nervous system lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or concomitant therapy with anticoagulants and antiplatelet agents.

Accordingly, ritonavir-boosted tipranavir should therefore be used with caution in patients with factors that increase the risk for bleeding. The FDA also noted that although tipranavir was found to inhibit human platelet aggregation *in vitro* at levels consistent with those used in clinical studies, and high doses were linked to multiple organ bleeding and death in rodents, this effect was not observed in canine studies and its cause remains unclear. Moreover, in humans, advanced HIV/AIDS has been previously linked to an increased risk for intracranial hemorrhage, and its causal relationship remains under investigation. Because no pattern of abnormal coagulation parameters was observed in patients receiving tipranavir in general or prior to development of intracranial hemorrhage, routine measurement of coagulation parameters should not be recommended in patients taking tipranavir.

Ivana Maida
University of Sassari
Sassari, Italy