

Conference on Retroviruses and Opportunistic Infections
CROI XVIII – Feb 27 – Mar 2, 2011
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Introduction

CROI is one of the largest conferences on HIV/AIDS in the world, with over 4,000 researchers, clinicians and a handful of community members and activists attending. This year, there were over a thousand abstracts featured as reports, symposia, posters and discussion groups. And once again, the zeitgeist is summed up in steps infinitesimally incremental, many sadly of marginal or no clinical significance whatsoever. Such trial and error efforts may yet yield a cure for HIV disease. However, the current model of drug discovery is increasingly problematic, riddled with the draining conflicts and corruption of patent drug makers. This model impedes discovery, inhibits communication between scientists and funnels clinical research down the rabbit hole of marketing rather than genuine assessment of clinical outcomes and risks.

As ever, many comprehensive reports have already been generated from the conference. A few are listed below. IN this report, I endeavor to provide information not reviewed in those and, where there is overlap, sometimes a slightly different perspective. The best reports are:

www.natap.org (very comprehensive; look also for Mark Mascolini's reports)

www.aidsmeds.com (Tim Horn's reports in particular)

www.hivandhepatitis.com (Liz Highleyman is one of the best)

www.thebody.com (Nelson Vergel has an excellent review)

Nutrition—Vitamin D: Make no Bones about it—levels are too damn low!

Index: 80, 823, 826, 706, 822, 827, 829, 828, 824, 79LB (LB=late breaker)

An astonishing thirteen abstracts were presented at this conference that discussed vitamin D. (Sadly, the 13 come up when you search the term "Vitamin" in the abstract body—and INCLUDE ALL 14 previous conferences!! Either their search engine is faulty or this is an indictment of a very skewed, unscientific approach to medicine and HIV disease.)

These 13 studies reviewed plasma levels in people with HIV as well as a few that evaluated administering vitamin D3 (cholecalciferol) in different populations to assess various outcomes. Risks were identified for individuals with low vitamin D levels, which is common among people with HIV. This can range from insufficiency of D (blood level below 30 ng/ml) to severe deficiency (below 10). (Some argue that a healthy level of vitamin D3 should be *at least* 40 or 50 ng/ml.) Benefits seen in clinical trials included reducing the risk of tenofovir-associated bone damage, lowering parathyroid hormone and reducing the risk of diabetes when vitamin D3 was given.

In Abstract 706, the issue of adolescents suffering from depleted bone density was highlighted. These are people around 17 years of age who started life with HIV. Of the 64 people studied, 45 were on ARV with 46% on tenofovir-containing regimens. 31% had low vitamin D levels (defined as <30 ng/ml). Not getting enough protein and vitamin D in the diet was strongly associated with having a reduced total bone mineral content. Overall, a full third of the adolescents had a lower bone mineral density than one would expect for their age.

Abstract 80 reviewed a study of 203 patients randomized to either placebo or 50,000 IU of vitamin D every 4 weeks for 12 weeks (3 directly observed oral doses). This was among patients on a tenofovir-containing regimen (TDF), which can cause osteopenia leading to osteoporosis (with the increased associated risk of bone fractures). Here, the outcome was the level of parathyroid hormone. The parathyroid is a gland—a set of usually four spots found on the back of the thyroid gland—that releases this hormone in response to plasma calcium levels. Increased levels that get too high (hyperparathyroidism) are not uncommon in HIV—especially when on drug regimens that contain tenofovir or efavirenz (like Truvada, Viread and Atripla). High levels are a marker for osteopenia. Among these 18-24 year-old people, those on the vitamin D3 arm saw their level drop significantly while the no-D arm had an increase in their parathyroid hormone level.

An entire poster session, comprising posters 822-829, covered D. I shall cover the highlights briefly; for more details, either email me or see the abstract on the CROI website (<http://www.retroconference.org/AbstractSearch/Default.aspx?Conf=20>).

822- Researchers investigated Vitamin D levels among women in the Chicago area: "The majority were African American (71%), but 23% were white, and 5% were Hispanic." They found low levels of D regardless of season, 59% in fall/winter and 54% in spring/summer of the cohort were deficient. African American women bore the worst brunt of deficiency. Median levels of the group were shockingly low, ranging from a summer high of only 21.12 ng/ml to an extremely low 13.5 ng/ml in the winter. (Sun exposure is one of the best ways for the body to synthesize vitamin D.)

823- Again found low levels of D and high parathyroid hormones, this effect being more pronounced among Ethiopian women than Caucasian Israeli women. Low intake of D₃, calcium and less exposure to sunlight were likely explanations, as well as the increased degree of bone loss found in those more deficient.

824- Trying to understand the damage to kidneys seen among a proportion of users of TDF, a low serum D₃ level was associated with higher parathyroid hormone numbers and consequently increased bone loss but also TDF-associated tubular damage to the kidneys.

825- Also found hyperparathyroidism to be associated with TDF use. This also was independent of the concurrently observed low levels of D (hypovitaminosis D, defined as <30 ng/ml). Having a more normal level of D in this cohort of 371 patients was associated with a reduced odds (OR-0.7).

826- Took a more general look of the impact of ARV on vitamin D levels. Here, TDF was seen to have a protective effect on D levels while AZT (zidovudine, Retrovir) and efavirenz (Sustiva) were associated with an increased risk of a low vitamin D level.

827-SUPPLEMENTATION DECREASES THE RISK OF DIABETES

Here, 1574 patients were evaluated in a retrospective study among a prospectively evaluated cohort of HIV-infected individuals living in Modena, Italy. Those at baseline who took vitamin D had a reduced risk of developing diabetes mellitus in contrast to those patients who did not supplement with D. A fasting glucose ≥ 126 mg/dl was considered incipient diabetes and some individuals were recommended to take at least 30,000 IU of vitamin D₃ a week. 232 or 14.7% reported consistent intake of the supplement. Of the 74 cases of DM identified in the cohort, only 2 were in the D supplementing group while the other 72 were among those not using vitamin D. These data need to be replicated in larger, prospective, randomized controlled trials.

828- Based on studies suggesting low levels of vitamin D are associated with more rapid disease progression of HIV and increased risk for TB, they did a test tube study of monocyte-derived macrophages, a type of cell that identifies and kills invading infections like TB bacteria. They found that when the cells were provided with vitamin D, it suppressed the co-infection of cells by HIV and TB. In the cells, vitamin D also actively inhibited the replication of both HIV and TB in the cells in which they were found.

829- A small study of 45 HIV+ adults were randomized to receive either placebo or 4000 IU daily of vitamin D₃ over a short period of 12 weeks. At the end, those using D had moderately increases of D of 5.0 ng/ml versus (whereas in the placebo arm, there were actually declines in the levels of vitamin D). Of note, those on efavirenz who took D saw a blunted response, achieving only 3.6 ng/ml increase. There was no benefit seen in this short study on flow-mediated brachial artery dilation (FMD) from the use of vitamin D.

Of course, there was an obligatory drug comparison study (79LB): our drug (TMC278) doesn't wipe out D levels like efavirenz does! Which does raise the point that low vitamin D levels are related both to HIV-related disease progression as well as some antiretrovirals, including the NNRTI efavirenz (a/k/a Sustiva). In the ECHO study, this new NNRTI from Tibotec, so far known as TMC278, was shown to have a salutary effect on at least not

causing D levels to drop further. While these kind of “market positioning” studies are nice as far as they go, they also strike me as having a somewhat unsavory side insofar as saying it’s a better drug because it DOESN’T do something, leaving open the question of what side effects it DOES cause. Efavirenz doesn’t mess with your kidneys so much—but it can raise LDL, cause nightmares and other psych issues and may deteriorate bones. What problems this new drug may cause are not yet clear—but at least it doesn’t cause levels of D3 to drop (which may bode well, one might hope, for not inducing osteopenia (bone deterioration)).

Basic Science

Abstract 435, researchers evaluated the role of oxidative stress in the development of HIV-associated neurologic disease (HAND). While assessing whether other phenomena were at the root of the inflammatory responses, such as protein folding, they determined that the attenuation of the pro-oxidant state that induces oxidative stress helped to reduce the development of HAND, at least in the *in vitro* model they used (evaluating the effects of macrophages, which are significant contributors to the pathology of neuroAIDS). *After all these decades of research underscoring the impact of oxidative stress on various aspects of HIV disease and ARV side effects, it seems incomprehensible that the NIH is incapable of constructing clinical trials assessing combination antioxidants that might address these underlying issues—studies that would, perhaps in factorial design, assess the effects of a multivitamin/mineral with N-acetylcysteine, alpha lipoic acid, fish oil, vitamin D3, etc. in combinations.* It’s not like they’re dangerous, toxic agents.

Abstract 468 – here they looked at “elite controllers” or people who for at least a DECADE or more have maintained low or even undetectable viral loads and stable CD4 counts in normal ranges. They examined the transcripts of the viruses infecting these individuals and elucidated that at least a subset of the N – 125? patients *may have achieved a functional cure*. This research bears closer scrutiny!!

Inflammation was the buzzword of the day (Schacker, Abstract 73). He gave a presentation that was both a relief as much as it was frustrating. With the exception of some advancements in our understanding of the details, it is something many of us have worked on and Fred Bingham of DAAIR days really focused in on as early as 1993. That is: Inflammation is a serious issue that causes a lot of trouble!

Put a little more scientifically, there are a variety of factors that conspire to enhance and perpetuate a pro-inflammatory state. HIV-related damage to the gut causes the epithelial lining to lose integrity, resulting in mucosal translocation of lipopolysaccharides (LPS). That is, these LPS molecules spill out of the blood and stimulate intense inflammatory responses. Other cells, like neutrophils, accumulate in crypts (part of the lining of the intestinal tract) and this is observed even among people on ARV with undetectable viral loads. Persistent activation of the immune system is thus a result of ongoing viral replication, even at low levels, as well as reactivation from latency (or stimulation of infected resting T cells or macrophages that have slow growing virus).

In addition, concurrent infections by herpes viruses like herpes simplex I or II (HSV), CMV, Epstein-Barr, etc. Further, the translocation of LPS from the gut into the peripheral blood results in an inflammatory cytokine storm, leading to tissue damage in the gut, thymus, lymph nodes and endothelial cells. This tissue damage in turn leads to further T cell loss along with all the associated clinical sequelae such as accelerated aging, dementia, etc. This sets up a vicious cycle that Fred Bingham and we basically discussed as a model of AIDS pathogenesis. (Indeed, I wrote a white paper for ACT UP for the 1993 International Conference on AIDS in Berlin, Germany that distinguished the pathogenesis of HIV (i.e., the viral “lifecycle”) from the pathogenesis or development of AIDS. Unfortunately, Peter Duesberg misinterpreted this as saying HIV wasn’t the cause of AIDS. He even CALLED me and I had to disabuse him of this notion telling that, while I agreed with him that HIV does indeed exist it was indeed also the cause of AIDS—not drug use or whatever other flaky, wholly unsupported notions he was entertaining.)

As HIV and infected cells invade lymph nodes, the T-cell zone is increasingly disrupted, and the network of trafficking of cells for antigen presentation and activation is also disrupted and deteriorates. The cells in the germinal center become increasingly isolated and unable to communicate with each other while increasing numbers of naïve CD4+ cells undergo apoptosis. Fibrosis or scarring in the T-cell zone of the lymph node

predicts CD4 decline. This is mediated by the cytokine, TGF-beta, and these events occur early after infection. Desmin+ cells are increasingly displaced by collagen (scar tissue) that further disrupts lymph node architecture. (Desmin is a protein associated with muscle cells and is also associated with mitochondrial function. See, e.g., <http://en.wikipedia.org/wiki/Desmin>.)

Gut-associated lymphoid tissue (GALT) fibrosis, or scarring, limits immune reconstitution (so addressing gut function and integrity makes sense; for us, the primary agents for improving this, aside from diet, includes a good multi, NAC as well as L-glutamine and probiotic therapy, as well as addressing any pathogens that may be there such as candidiasis, or herpes infections such as CMV, HHV-8 (the cause of Kaposi's sarcoma) or parasites like amoebae).

Viral fibrosis and other infections induces the release of LPS which leads to inflammation and further collagen deposition (i.e., scarring or fibrosis formation) which impedes the FRC network and increase increasing T-cell apoptosis (cell suicide, which accounts for a significant amount of destruction of uninfected T cells).

For Schacker, he had a rather limited menu of therapeutic options to address these issues, including:

- Better ARV (or hell, how about a cure...);
- latent reservoir—flushing it out and eliminating it;
- treating underlying OIs/Herpes/CMV infections;
- Antifibrotic therapy in SIV model—can slow/stop collagen and sig CD4 impact (didn't specify therapy?);
- IL-7.

One interesting study suggested that, while central adiposity (fat accumulation around the organs of the trunk) is associated with increased mortality and other cardiovascular risks, lipoatrophy in the limbs (loss of fat) is not. By contrast, limb wasting where the muscle volume and strength deteriorates IS associated with increased mortality (Scherzer, 76). A clarion cry for sustaining a good resistance exercise program!

Hepatitis C

I attended a full session on the treatment of hepatitis C, much of which focused on just two drugs, boceprevir and telaprevir. These appear to be the furthest along in clinical trials. Boceprevir is a protease inhibitor that targets the NS3 protease of Hep C. It considerably improves the chances for a sustained viral response (SVR), the most relevant measure, clinically, of outcomes for these drugs. SVR response rates are also improved with both drugs among those of us with the tougher to treat subtypes of Hep C (HCV) known as genotypes 1A, 1B and, to a lesser extent epidemiologically speaking, 4. My take on it basically was that they were more or less equivalent in their outcomes but telaprevir's side effect profile (rashes in some people that in some cases resulted in discontinuation of the drug), were much less harsh than boceprevir, which seemed to enhance the background adverse events of the pegylated interferon and ribavirin backbone that studies so far have included. That is, there were more discontinuations and otherwise just higher percentages of people with anemia and neutropenia in the boceprevir studies, not seen with telaprevir.

Procrastination being the better part of valor, I'm finishing this segment of my CROI report somewhat late—and after the European (EASL) conference with its pretty significant announcement of cure rates using ALL oral agents, even among people who not only had genotype 1 infection but had previously failed therapy. (In these latter cases, addition of IFN/riba cinched the deal for complete SVR among all participants—albeit, the total number in the trial was VERY small—11). A NATAP note from EASL:

As NATAP's Jules Levin reported from EASL: *So just completed was the last oral session at this year's EASL, the Late Breaker session where as expected the BIG news was presented. In the BMS null-responder study where patients received 2 oral HCV drugs alone, the BMS HCV protease + the BMS NS5A inhibitor without peg/rbv, 4/11 patients achieved a cure. This is considered by everyone here at the meeting as 'proof of concept' that we can cure HCV at least for some patients perhaps all without peg/rbv. This is the big news we have been waiting for. But for the patients who did not achieve SVR they got mutations BUT when giving peg/rbv to these patients they then went to undetectable, and essentially 100% of null-responders in this study who received quad therapy, peg/rbv+the BMS protease+the BMS NS5A achieved a cure.*

NeuroAIDS→Microbicides?

This is a term used to describe the range of problems that may arise as a result of HIV infection. It includes damage both to the brain (central nervous system) and nerves (including peripheral neuropathy), as well as co-infections that may attack the brain, such as *Cryptococcus neoformans*, syphilis and toxoplasmosis.

Neuropathic pain—associated with HIV and some antiretrovirals—is a chronic and common problem. It usually begins in the soles of the feet and may work its way up the legs, causing, burning, tingling and numbness. Cannabinoids found in marijuana have been shown to have some benefit in treating this, particularly in the form of smoked marijuana.

The body has receptors for the active ingredients of marijuana known as cannabinoid receptors one and two (CB1 and CB2). The CB2 receptor is found in the periphery, like in the gut, as well as to a lesser degree in the brain. THC found in pot is the stuff that gets us high and binds to either CB1 (found in the brain) and to CB2. Well, the body also makes its own THC-like substances—*endogenous ligands*. Endogenous means within the body. Ligand means the protein or substance that binds to the receptor and activates it. The body makes anandamide as (one of several) natural “endocannabinoid” compounds. Well, a surprising *in vitro* study, paper 179, further showed that agonism (“activation” as opposed to inhibition) of one of the two common cannabinoid receptors, CB2, by the endogenous ligands, including anandamide, actually inhibited HIV infection of CD4 cells!

One wonders if hash oil might not be just a fine lubricant that may work as a microbicide? (One would probably have to use a plastic condom since latex may be damaged by oil-based lubricants. And THC and such are fat soluble and might well need an oil carrier. This is just a hypothesis but pot does tend to grow like a weed...)

Prevention

Sadly, a great deal of time was wasted burbling on about the wonders of “pre-exposure prophylaxis” or PREP. While in and of itself, finding microbicides that protect people is vitally important, the use of “Truvada” or the two-drug containing pill that includes tenofovir and emtricitabine, has not in my view been either established as either efficacious or safe. Nonetheless, many spoke about “proof of principle” when I believe “evidence of principle” is about as far as one might go....let’s break this down a bit. I more completely review this here: <http://www.fiar.us/PREP-HYPE.html>

Efficacy

The two large studies that are pointed to establish efficacy are the Iprex and CAPRISA studies. The CAPRISA study used a tenofovir-containing gel and was studied among women in Africa vs. placebo. The “take-home” message continually repeated is a 39% reduction in risk. But where does this come from? Lets look at the data. The data below is abstracted from the original study, published at / www.sciencexpress.org / 19 July 2010 / Page 1 / 10.1126/science.1193748.

Table 2. Impact of adherence and non-endpoint HIV infections on the effectiveness of tenofovir gel in HIV prevention in the CAPRISA 004 tenofovir gel trial.

	Tenofovir	Placebo	N	Incidence Rate Ratio	Effectiveness	P
All women	38/680.6	60/660.7	889	0.61	39%	0.017

Looks good! There’s the 39% under effectiveness and the p value is “statistically significant” at 0.017.

But let’s look a little closer:

	Tenofovir	Placebo	N	Incidence Rate Ratio	Effectiveness	P
Rural women	25/484.7	42/461.2	611	0.57	43%	0.023
Urban	13 / 195.9	18/199.5	278	0.74	26%	0.380

Among rural women it seemed to work quite well! But among urban women, the effectiveness plummeted to statistical (and clinical) irrelevance (p=0.380). Why might this be? Well, it’s not entirely clear. At baseline, there

were several statistically significant differences between the urban and rural women. While the urban women reported a stable partner, they were slightly older (25.1 vs 23.3) and reported more lifetime partners (6.0 vs 2.1). It may be that the urban women having more partners abrogated the benefit of the gel.

The other major study of course was the iPREX study that used the oral tablets of tenofovir/emtricitabine to see if it would reduce the risk of HIV infection among high-risk individuals (mostly men who have sex with men, some sex workers). The intent-to-treat analysis suggested a 44% RELATIVE risk reduction in the initial paper. This translates to needing to treat 45 people to prevent one infection for a YEAR. At what cost? When at least 10 million HIV+ people are currently clinically eligible and NEED these drugs to survive? Indeed, although this is unheard of for any other study I've ever encountered, even Anthony Fauci touted a substudy that suggested highly adherent individuals achieved a 90% risk reduction. But this is a strange game to play given it is extremely unscientific (and the vicissitudes of presumptions of adherence were underscored in abstract 95LB). And unfortunately, according to abstract 92, the 44% that is scientifically valid saw a small deterioration to 42%.

This must be taken in the context of the ABSOLUTE risk reduction for the whole cohort. That is, the total number of people infected over the course of the study was tiny. From my report on www.fiar.us :

They looked at a total of 2499 participants 1251 in the FTC-TDF arm and 1248 in the placebo arm. There were a total of 110 infections in the study, but 10 appeared to have been seroconversions at the start of the trial, so the study authors used a modified intent-to-treat that ignored those 10. (Intent-to-treat is a statistical measure to assess data based on the initial treatment intent, "[not on the treatment eventually administered.](#)")

So there were 100 infections over a median of 1.2 years on the drugs: 36 in the drug arm and 64 in the placebo arm. The 44% we hear about is the difference of $100 - 36/64$ or 44%. But another way to look at it is the ABSOLUTE RISK. That is, 36 out of 1251 people in the drug arm became HIV+ over a median of 1.2 years. The calculation of $36/1251$ yields about 2.87% risk of becoming infected on the drugs, but that is a rough estimate. According to lead author, Robert Grant: *The annual incidence was 3.86 in the placebo group and 2.16 in the FTC/TDF group.* (This was during an email exchange with Dr. Grant prior to a conference call with Dr. Grant and others on 12/3/10.)

In terms of Safety, there is also concern. Abstract 93 and late-breaker abstract 94 both underscored a small but significant decline in bone mineral density among those receiving drug. This may also suggest an effect on kidney function as well. At the very least, clinicians responding to the request for tenofovir/emtricitabine by HIV-negative individuals should also prescribe high dose vitamin D3 to offset the impact on BMD and kidney function. Clearly, however, this will only be an intervention available to wealthy individuals.

By contrast, the use of Post-Exposure Prophylaxis (PEP) may make more sense. This is a question that needs to be explored more comprehensively than I can do here.

Appendix – A couple of abstracts:

Session 50-Poster Abstracts

[HIV Entry and Cell-Cell Transmission](#)

Monday, 2-4 pm; Hall D

Paper # 179

Agonism of Cannabinoid Receptor 2 Attenuates HIV-1 Infection in CD4⁺ T Cells

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Background: Agents that activate cannabinoid receptor pathways have been tested as treatments for cachexia, nausea, or neuropathic pain in HIV/AIDS patients. Both the HIV fusion co-receptors (CXCR4 and CCR5) and the cannabinoid receptors (CB1 and CB2) are members of the highly conserved family A of G protein coupled receptors (GPCR). Coordinate activation of family A GPCR can lead to cross-desensitization, changes in receptor localization, and loss of intended physiological outcome. We hypothesized that cannabinoid drugs modulate chemokine co-receptor activity and alter HIV infectivity.

Methods: We challenged primary CD4 T cells with cannabinoids prior to either cell-free or cell-associated infection. Productive viral infection and viral transfer were measured using GFP-expressing variants of the

CXCR4-tropic HIV-1 clone NL4-3. Cells were subject to treatment with dual cannabinoid receptor agonists, receptor-selective agonists, receptor-selective antagonists, and the endo-cannabinoids.

Results: We found that CB2, but not CB1, agonism reduced infection in primary CD4 T cells following cell-free exposure to R4 tropic virus. We tested a panel of commercially available CB2 selective agonists, which each reduced HIV-1 productive infection by approximately 30 to 50% without altering cellular fitness. The endogenous cannabinoids anandamide and 2-arachidonoylglycerol were also sufficient to inhibit HIV infection. This decrease in HIV permissiveness was dose-dependent and CB2-receptor specific. In a cell-associated model of viral spread, CB2 activation did not alter viral transfer to treated target cells, but did significantly reduce productive infection. Inhibition was 2-fold greater in unstimulated cells than in activated cells. To further investigate the mechanism of this action, we assayed the capacity of CB2 to down-regulate CXCR4 signaling. We found that CB2 agonism decreased chemokine-mediated CXCR4 internalization and MAP kinase phosphorylation.

Conclusions: These findings suggest that cannabinoid activation via the CB2 in CD4 T cells can inhibit the cellular processes required for productive infection following either cell-free or cell-associated viral acquisition. Our data indicate that CB2 can interrupt CXCR4 function and that this allosteric modulation reduces infection by HIV-1. Therefore, the clinical use of cannabinoids could inhibit viral replication in HIV-1-infected patients.

Session 99-Poster Abstracts

[Host Genomics](#)

Wednesday, 2-4 pm; Hall D

Paper # 468

Transcriptional Profiling of CD4 T Cells Identifies Distinct Subgroups of HIV-1 Elite Controllers

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Background: Elite controllers (EC) represent a rare group of HIV-1-infected persons who maintain undetectable viral loads in the absence of ART, but their underlying immunological characteristics may vary. Mechanisms contributing to the spontaneous viral control in these patients remain unclear.

Methods: We performed microarray-based whole-genome transcriptional profiling of sorted HLA-DR CD4 T cells from a cohort of EC (n = 12), HIV-1⁻ persons (n = 9), and HIV-1-infected persons effectively treated with HAART (n = 14), using the Illumina microarray platform. Simultaneously, the total magnitude of HIV-1-specific CD8 T cells was determined by IFN- γ ELISpot using overlapping peptides spanning the entire HIV-1 proteome, and residual HIV-1 viremia was assessed using an ultra-sensitive PCR protocol with single-digit resolution.

Results: A total of 1159 transcripts were differentially expressed between HIV-1 ART-treated persons and HIV-1⁻ individuals. Of these transcripts, n = 124 were also differentially expressed between HIV-1⁻ persons and EC. None of the known HIV-1 restriction factors or other genes involved in the intrinsic resistance of CD4 T cells against HIV-1 were differentially expressed in EC. Interestingly, we observed that the gene expression signatures from EC were split in 2 distinct subgroups: The majority of EC (n = 8) clustered with ART-treated persons, as opposed to the gene expression pattern of a smaller subgroup of EC (n = 4) that clustered with HIV-1⁻ persons. The latter group of patients differed from other EC by higher CD4 T cells counts ($p = 0.01$) and a smaller magnitude of total HIV-1-specific CD8 T cells ($p = 0.03$), but not in terms of residual HIV-1 viremia, expression of HLA-B57 or -B27 or chemokine receptor polymorphisms.

Conclusions: These data identify a specific subgroup of EC whose immunological and gene expression characteristics approximate those of HIV-1⁻ persons, and who may have achieved a true functional cure of HIV-1 infection.