Steven Deeks, MD
Professor – Department of Medicine
University of California - San Francisco (UCSF)

Prof. Steven Deeks

Steven G. Deeks, MD, is a Professor of Medicine in Residence at the University of California, San Francisco (UCSF) and a faculty member in the Positive Health Program (AIDS Program) at San Francisco General Hospital. Dr. Deeks has been engaged in HIV research and clinical care since 1993. He is an expert on the role of chronic inflammation in untreated and treated HIV disease. Dr. Deeks has published over 300 peer-review articles, editorials and invited reviews on these and related topics. He has been the recipient of several NIH grants. He is the principle investigator of NIH-funded international collaboratory aimed at developing therapeutic interventions to cure HIV infection (DARE). He is the co-chair of the "Towards an HIV Cure" International Working Group and a member of the Office of AIDS Research Advisory Council (ORAC). He was elected to the American Society for Clinical Investigation (ASCI). In addition to his clinical and translational investigation, Dr. Deeks maintains a primary care clinic for HIV infected patients, and is a member of the Department on Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents.

"I think the most interesting studies were those that showed (1) ART during "hyperacute" HIV might be curative (as shown in NHP model, the "LA baby" and the PrEP screen failure), (2) HIV integration into growth genes might stimulate decades of homeostatic proliferation, (3) that HIV is enriched in cells that express CCR5, PD-1, LAG-3 and perhaps activation markers, (4) some broadly neutralizing antibodies might stimulate ADCC, (5) HDAC inhibitors and other anti-latency drugs fail to produce protein

(when used alone), (6) vorinostat induces long-term changes in gene expression patterns and (7) CTL escape mutations are deposited early, and persist during ART".

Compared with healthy HIV-negative people, a group with HIV had significantly lower numbers and diversity of gut microbiota. Reduced microbiota richness and diversity correlated with microbial translocation, monocyte activation, and immune dysfunction in this small comparative study. Researchers from the Karolinska Institute and colleagues from other centers noted that the intestinal mucosal barrier endures abnormalities during progressive HIV infection, with changes including translocation of microbial products and subsequent chronic systemic inflammation. (Microbial translocation is movement of viable bacteria or bacterial products across the intestinal wall and into the lymphatic system, liver, spleen, kidney, or peripheral circulation). To determine how gut microflora are altered in people with HIV infection--and how antiretroviral therapy may affect that process--these investigators prospectively compared gut microbiota in 32 HIV-positive people and 9 healthy HIV-negative controls. They did not include people taking antibiotics or probiotics in the past 2 months or people with infectious diarrhea. Among people with HIV, including 3 elite controllers, median CD4 count stood at 355 (interquarile range 120 to 2470). (Elite controllers maintain a high CD4 count and low viral load without antiretroviral therapy.) The researchers collected plasma and fecal samples from all participants at a baseline visit and a median of 10 months later in 19 people who had started antiretroviral therapy. The researchers used deep sequencing of the 16S rRNA gene to evaluate microbiota composition. They also evaluated soluble markers of microbial translocation and monocyte activation. Numbers and alpha diversity of observed bacterial species were lower in HIV-positive participants than in HIV-negative controls. Reduced baseline microbiota richness and alpha diversity in people with HIV correlated with markers of microbial translocation, monocyte activation, and immune dysfunction. Baseline alpha diversity correlated significantly with CD4 percent ($r = 0.42$, $P = 0.01$) and CD8 percent ($r = -0.37$, $P = 0.03$). Twelve HIV-positive people with a detectable viral load and low microbiota diversity had significantly lower CD4 counts than 19 viremic patients with high microbiota diversity (about 250 versus 400, $P = 0.01$). Microbiota of the 3 elite controls resembled microbiota of healthy controls. Compared with viremic HIV-positive people, elite controllers had an increased relative abundance of bacteroidetes. Elite controllers and HIV-negative controls had lower levels of actinobacteria than viremic HIV-positive people. In the 16 people who started antiretroviral therapy, gut flora abnormalities persisted after a median of 10 months and alpha diversity of microbiota declined significantly from baseline measures ($P = 0.006$). Because starting antiretroviral therapy did not restore microbiota diversity, the researchers proposed that adjuvant therapy may be needed to reshape microbiota in people with HIV infection. Similar gut microbiota in HIV-positive elite controllers and HIV-negative controls suggested to the investigators "that a healthy state of gut microbiota may be associated with delayed disease progression." Delaying antiretroviral therapy (ART) for as few as 3 days during the "hyperacute" phase of simian immunodeficiency virus (SIV) infection in macaque monkeys resulted in 10- to 100-fold higher viral reservoir sizes, according to results of a 22-monkey study at the Oregon National Primate Research Center. Afam Okoye and colleagues concluded that ART begun before peak viral replication "limits systemic virus dissemination and seeding of the reservoir in peripheral and extralymphoid mucosal compartments." Reports of the Mississippi baby, the Long Beach baby, and the adult VISCONTI cohort suggest that ART very early in the course of infection can block HIV from long-lived reservoirs or greatly limit reservoir size. In light of this and other research, the Oregon team asked if HIV reservoirs established before peak viral replication differ in size or quality from those established later. To address that question they assessed HIV RNA in plasma, cells, and tissue and SIV DNA in cells and tissue of macaques infected intravenously with a highly virulent SIV strain, SIVmac239. ART involved four antiretrovirals, tenofovir, emtricitabine, dolutegravir, and ritonavir-boosted darunavir. Two monkeys

(group A) began treatment 7 days after SIV infection, before peak viral replication; 2 (group B) began treatment 10 days after infection, at or near peak viral replication; and 18 (group C) began treatment 42 days after infection, early in chronic infection. In group A macaques plasma viral load continued rising after ART began, peaked at day 12 at an average 71,000 copies/mL, then dropped below the 30-copy detection limit after 6 weeks of therapy. In group B plasma viral load peaked at day 12 at an average 1.8 million copies/mL and did not become undetectable until 18 weeks after treatment began. Group C macaques, the 18 chronically infected animals, reached peak plasma viral load at an average 14 million copies/mL 12 to 14 days after infection. Twenty weeks after ART began, 7 of these monkeys still had detectable SIV RNA in plasma. Group A animals had no detectable SIV RNA in peripheral blood mononuclear cells (PBMCs) 20 weeks after infection, while 1 of the 2 group B animals still had detectable SIV RNA in PBMCs 32 weeks after infection, and all 18 group C animals still had detectable SIV RNA in PBMCs at that point. Thirty-two weeks after infection, SIV RNA became undetectable in small intestine of the 2 group A macaques, undetectable in 1 of 2 group B macaques, and detectable in all group C macaques. One of 2 group A macaques had no detectable SIV RNA in lymph nodes 32 weeks after infection, whereas all animals in groups B and C had detectable SIV RNA in lymph nodes at that point. SIV RNA was detectable at low levels in PBMCs and bone marrow of group A animals and detectable at higher levels in group B and C animals. Thirty-two weeks after infection, SIV DNA in PBMCs averaged 2.5 log (about 300 copies) per 100 million cells in the group A macaques (treated 7 days after infection), 3.5 log (about 3000 copies) in the group B macaques (treated 10 days after infection), and 4.4 log (about 25,000 copies) in group C animals (treated 42 days after infection). SIV DNA was also lower in group A animals than in groups B or C in lymph nodes, bone marrow, and small intestine. Peak plasma viral load correlated positively with SIV DNA in PBMCs 32 weeks after SIV infection ($r = 0.44$, $P = 0.03$). Coculture could not detect replication-competent SIV in the 4 macaques treated 7 or 10 days after infection but remained detectable in macaques treated 42 days after infection. However, adoptive transfer of lymphocytes from animals treated 7 days after infection to 2 antiretroviral-naive macaques induced productive infection. And when ART stopped in the 4 macaques treated 7 to 10 days after infection, SIV RNA promptly rebounded in plasma. Okoye and colleagues proposed several conclusions: SIV reservoirs become established early during acute infection in CD4 memory cells; SIV DNA increases exponentially in PBMCs and tissues 7 to 10 days after infection; delaying ART for as few as 3 days in the "hyperacute" phase of infection results in 10- to 100-fold higher SIV levels in tissue reservoirs after treatment begins; ART begun before peak SIV replication limits seeding of reservoirs in various compartments; virus from reservoirs established during acute SIV infection can induce rapid viremia in untreated animals and in treated animals after treatment stops. The Oregon team proposed that "aggressive monitoring for acute HIV infection with immediate introduction of ART could profoundly influence treatment outcomes and enhance viral eradication strategies." It is worth remembering that 10 years ago Bruce Walker and colleagues reported failure of off-treatment HIV control in 14 people who began ART between 9 and 33 days after the onset of acute infection symptoms. During the Q&A John Mellors said: "outstanding study, I'm struck by a couple of things, that you had rebound viremia and you could adoptively infect animals despite not being able to detect any replication competent virus from blood in any of the assays that were used, and that really strongly suggests that our assays are incapable of detecting replication competent virus that can fuel rebound or in your instance result in adoptive infections, so the entire field has to reconcile that". And Deborah Persuad said "the data suggests 7 days is too late, we need to figure out what is that window of opportunity for early therapy to prevent reservoir establishment rather than just diminishing it to a point that I couldn't tell f she said we can or can't detect it but once therapy is stopped there is rebound viremia, so do you have plans to narrow that window, this is relevant to perinatal infection, in terms of how early should we treat to accomplish not minimal reservoir but complete blockage of reservoir forma-

tion. The presenter responded...they have done some studies...probably within 24-48 hours you probably would not get rebound but after that is probably too late". Antiretroviral therapy (ART) begun soon after HIV infection dampened central nervous system (CNS) inflammation in a study of 26 recently infected people in San Francisco. Cerebrospinal fluid (CSF) markers of inflammation returned to normal about 9 months after these people started ART, whereas ART begun during chronic infection has not had this effect. Markers of CNS inflammation typically remain abnormally high in people responding well to ART begun during chronic HIV infection. Julia Peterson (University of California, San Francisco) and collaborators conducted this study to determine how ART begun soon after HIV infection affects standard markers of inflammation in the CNS. This longitudinal observational study involved antiretroviral-naive people with primary HIV infection, defined as infection within the year after transmission. These people started diverse ART regimens at different intervals after infection for reasons not related to this study. Peterson and colleagues analyzed data from 26 people with pretreatment blood and CSF samples as well as follow-up samples collected at intervals 6 to 12 months after they started ART. The investigators measured the following indicators: CSF/plasma albumin ratio and CSF protein, markers of blood-brain barrier disruption, CSF white blood cells (WBC), a marker of CNS inflammation, CSF and plasma neopterin, markers of immune activation, particularly macrophage activation. The researchers compared these values with those in 20 age-matched HIV-negative controls. The 26 people with HIV had a median age of 37 (interquartile range [IQR] 31 to 44) and had HIV infection for a median of 136 days (IQR 59.5 to 178.3). The HIV group's median CD4 count was significantly lower than that of the 20 HIV-negative controls, but four values were significantly higher in the HIV group: CD8 count, CSF WBC, CSF neopterin, and plasma neopterin. CSF protein and CSF/plasma albumin ratio were nonsignificantly higher in the HIV group. Participants began ART a median of 229 days (IQR 119.5 to 741.8) after HIV infection. The first on-treatment visit came a median of 278.5 days (IQR 199.5 to 369.3) after people started ART. Median antiretroviral CNS penetration effectiveness score of regimens was high at 7 (IQR 7 to 7). Viral load in plasma and CSF both dropped significantly a median of 9.3 months after ART began ($P < 0.0001$). CSF protein also fell significantly after ART began ($P = 0.01$), while the CSF/plasma albumin ratio fell nonsignificantly. CSF WBC declined significantly after ART started ($P < 0.0001$), returning to levels recorded in HIV-negative people (median 2 cells/uL). CSF neopterin fell significantly with ART ($P = 0.001$) to levels equivalent to those in HIV-negative controls. After treatment began, neopterin levels in blood and CSF were lower than those recorded in a historical comparison group of people who began ART during chronic infection. Pre-ART levels of CSF neopterin, plasma neopterin, and CSF/plasma albumin ratio correlated with on-ART CSF neopterin. Peterson and colleague concluded that CNS inflammation markers abnormally high during primary infection returned to normal within 1 year of starting ART. Specifically, they observed that "CNS immune activation markers measured 9 months after early ART were similar to those in HIV-negative controls" and that "CSF neopterin after early ART was lower than that reported after treatment initiated during chronic HIV infection." Noting that these findings contrast with earlier reports of persistent CNS immune activation when treatment begins during chronic infection, the researchers suggested their results may indicate another benefit of starting ART early in the course of infection.