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CD4 CD8 CELL RATIOS IN INDIVIDUALS WITH ACUTE AND EARLY HIV INFECTION

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CD4 CD8 Cell Ratios in Individuals with Acute and Early HIV Infection
[video transcript]

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[Jim] Welcome to Physicians' Research Network. I'm Jim Brawn the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease, as well as its co-infections and complications. We hope this recording of Martin Hoenigl's presentation CD4/CD8 Cell Ratios in Individuals with Acute and Early HIV Infection will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not-for-profit organization, dedicated to peer support and education for physicians, nurse practitioners, and physician assistants and membership is open to all interested clinicians nationwide at our website, prn.org. And now, allow me to introduce, Martin Hoenigl, Assistant Research Scientist at the Antiviral Research Center of the University of California San Diego, in San Diego California.

- Thanks very much. I'm super happy to be here. Obviously, thanks so much to the organizers for inviting me and for letting me present a little bit about, shortly, our acute HIV screening program in San Diego, with some new findings there. And also a little bit on the role of symptoms during acute HIV infection of acute retroviral syndrome. And then move on to the main topic of my talk, which is really focusing on CD4/CD8 ratios, which were hugely popular, I think, before my time as a practitioner, 15, 20 years, were used a lot before we had effective, highly effective ART available. But somehow got less used and less important, during the recent years, and also less a hot topic in research, until now. Where really, in the last three to four years, a lot of papers came out on the importance, not just to look at CD4 counts, but really also on CD8 counts. And, particularly, on the ratios of CD4/CD8.

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I will focus on one of our studies, where we correlated CD4/CD8 ratios with severity of acute retroviral syndrome, in patients with acute HIV infection. And also focus on the dynamic of this ratio under antiretroviral therapy, in acute HIV infection. I'm coming from San Diego. You've probably heard a few speakers in the past come from there, such as Susan Little, who is my mentor. Or also Scott Letendre, or also Sarah Chinela. And what we are doing, basically, for a long time, but in this algorithm since 2007

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is that we test everybody who is testing in our program, which is a community based program. We are testing everybody for acute HIV infection. Our algorithm is, because we are community based, patients just walk in from the street, because they want to get tested or they got referred. We initially need a point of care test. We do an antibody test, a rapid antibody test, so we immediately pick out those with established issue of infection. Everybody who is negative, down here, gets to a qualitative HIV NAT. Everybody who is antibody negative, we do a qualitative NAT to really also diagnose people with acute HIV infection. Obviously in those where the qualitative NAT is negative, those are then uninfected versus those with a positive NAT, have acute HIV infection. You may think, how big is this program?

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We are approximately making, recently, more than 5000 tests per year, the vast majority among men who have sex with men. Many of those who test with us are really new individuals who test with us every year. Obviously, when looking at repeat testing rate, this is higher in MSM than in other, which is really reflecting the recommendations that you want to test MSM repeatedly for HIV infection.

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As a total, majority of tests about 70% in MSM and if you look on diagnoses, it's nearly 89%. And particularly interesting, when you look here on this blue bar, this is the acute HIV infections we diagnosed in this period of five or six years, and you see it's all in MSM. That's really the reason, also, why the San Diego HIV epidemic, pandemic, is driven by MSM. That's also why most of our studies are focusing on, MSM exclusively, because, really, we see rarely acute HIV infections in other people who test with us. I'll go rather quickly over the next two or three slides, that are just an evaluation of cost-effectiveness that may be particularly interesting for policy makers, where we looked on different approaches to see whether it is cost-effective to test everybody for acute infection.

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We basically compared four algorithms in community based settings and our outcome was costs per acute HIV infection diagnosis and costs per transmission averted, so infection averted.

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These are the algorithms used to early test. This is actually the algorithm we really use in our setting, and then we created a few other algorithms that would be feasible for community based testing, where we need point of care results immediately. Like an architect algorithm, with initial rapid antibody test. Because we really want to diagnose as many as possible, when they are first in, to really reduce loss of follow up, which is an issue in community based settings. Determine which is a point of care, p24 based assay, which is not very good, unfortunately. That would be, definitely, the thing we want to go. We want to have good assays available that could diagnose HIV point of care, acute HIV infection point of care. And conventional antibody only, where we just do antibody tests, and those who are negative, tell them, "Okay, you're antibody negative. You probably don't have HIV." Two outcomes. One, the cost per acute HIV diagnosis. We really could show that up to an HIV prevalence per test, so if you perform 100 tests, 1000 tests, if you have one positive test per 1000 tests, it seems to be cost-effective to test for acute HIV infection.

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And per HIV infection averted, we basically showed the same. That really testing MSM populations, sexually active MSM populations for acute HIV infection really pays for itself over the long run. That's really something that we should keep in mind. Because, of course, we have this clear recommendation

for hospital and clinic-based testing, where now architect is recommended to also diagnose acute HIV infection, but in community-based settings, the recommendations are not so clear yet. Our analysis and other analyses show that probably we should test people at risk, MSM at risk, sexually active MSM for acute HIV infection routinely. If you can't do that, obviously, that's always one big argument.

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Why don't you just use risk tools for predicting incident or acute HIV infection? This is one tool we developed in our cohort. This works pretty well in our cohort, but the major issue with all these risk tools is that you can't use them in all other different cohorts. For example, our tool works good in our cohort. It's mostly meth is a major risk factor, mostly sexual risk behavior. It also worked pretty good in San Francisco, when we tested it with Susan Buff in her cohort, and they're using it, actually. But when we went on to Amarillo University to Atlanta, where the whole HIV epidemic is very different. It's mostly black MSM who acquire HIV infection, and really, in Atlanta, risk behavior is not really the main driver of HIV infection. It's more that so many black MSM are already HIV infected, the underlying HIV prevalence there, that even low-risk behavior in those people does not prevent them from getting HIV infection. So it did not work well in Atlanta, as did many other scores. There's many different variables, which also make a point that we really maybe want to test everybody for acute HIV infection.

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And the other big thing, obviously, when we always think about acute HIV infection, is acute retroviral syndrome. We think, okay, we make some analysis, we ask people, do they have any signs and symptoms? Such as fatigue, headache, pharyngitis, skin rash, lymphadenopathy, GI symptoms, night sweats, myalgia. So very unspecific symptoms, obviously. Together with some exposure, some recent exposure, which we, at least in our MSM community, who is testing with us in San Diego, nearly always find. There's always lots of this exposure. We wanted here really to focus on the signs and symptoms. And we decided to look on this in a study over the last 10 years or so, how good signs and symptoms were an indicator of acute HIV infection. And really, when we focused on our 90 people who were diagnosed with acute HIV infection with routinely obtained tests for acute HIV infection.

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We really saw that only 50% had ongoing signs or symptoms at the time they tested with us. So if we would have used signs or symptoms to decide who we test for acute HIV infection, we would have missed 50% of acute HIV diagnosis and on the other hand, obviously, when thinking back about these unspecific symptoms, probably, we would've tested still a lot of people who, at the end, didn't have acute HIV infection.

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When going back 14 days, so not just asking about ongoing symptoms, but symptoms during the last two weeks, obviously the sensitivity increased a little bit to 80% in total. But, there were still about 20% who either developed signs or symptoms of acute retroviral syndrome later or never. Because we followed up with these patients and these patients all enrolled into our studies and followed up and we repeatedly asked them for signs and symptoms until three months after enrollment.

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Now, moving on to CD4 and CD8 ratios. What we found, very importantly, I went over that. There's a

lot of studies that really show that the severity of acute retroviral syndrome is a surrogate marker of HIV one disease progression. When we really looked on CD4 cell count, if this correlated somehow in acute HIV infection, with severity of acute retroviral syndrome, we did not find any correlation. In contrast, of course, to viral loads. Really, the question for us remained: what about correlation with CD4/CD8 ratios? Maybe there's a correlation of acute retroviral syndrome as a surrogate marker of disease progression, with CD4/CD8 ratios, while there is none with CD4 counts and acute infection.

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Coming to the concept of CD4/CD8 cell ratios as a marker of immunosuppression and non-AIDS morbidity and mortality in HIV infection. Of course, there have been big improvements over the last decade with ART now being highly effective in improving health and survival. Also, toxicities of ART have gone down highly significantly. But, despite all these advances, we still know that even people treated and suppressed on ART who live with HIV, have still higher non-AIDS morbidity and mortality than the general population. This is, of course, mainly associated with immune dysfunction, and may also persist despite suppressive antiretroviral treatment. When we think about which markers we use in people, at the time of HIV diagnosis, but then also as follow up markers, of course we use viral load. But then we also use CD4, T-cell count.

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And then we just spent one slide on CD4s. Of course we used them daily. Hallmark of immunosuppression. And, very importantly, despite that CD4 counts are, for sure, very useful for monitoring our patients, it has to be said very clearly that T-cell activation, exhaustion, and responsiveness often fails to normalize fully, despite CD4 cell counts fully normalized at about 800 cells. It might not be that CD4 is a very good marker for T-cell activation and exhaustion. On another side, when looking on CD4 cells alone at ART initiation and during ART as follow-up parameters, we really see more and more studies that show that CD4 cells are really an imperfect predictor of immune recovery. And, therefore, just focusing on CD4 may confound our day to day management of HIV positive individuals, as well as, of course, in the predation of clinical trials.

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When we look on CD8 cells we see, of course, quite the opposite, so we have the inversion of the CD4/CD8 ratio, CD4 with HIVs going down, CD8 usually is going up. So the CD8 T-cell count increases in HIV infection and this expansion which is caused by multiple factors, immunology factors, and also by gut microbial translocation and immune modulation. It's really a driver of increased morbidity and mortality in HIV infection. And, very important, in contrast to CD4 counts, which we nearly always see in effective ART, if people take the medication, if it works, CD4 counts increase rapidly. CD8 T-cell counts often stay elevated, despite effective antiretroviral treatment. There's still a lot of research going on to factor why this is the case. There's theories that it might be low level HIV replication, which is the cause, or low level microbial translocation, or if the infection is ongoing, lymph node fibrosis. Most likely, it's a factor of multiple different mechanisms that leads to this continuously increased CD8 cell counts, during effective antiretroviral therapy. Here, I'll also show you something. And that's one of the major points of my talk, that really the only thing we can do to decrease CD8 cell counts is to initiate ART as early as possible. So this is here, the solid black line, where you see really ART initiated in primary HIV infection leads to this significant decrease over time, in this CD8 T-cell count, while the later you start antiretroviral therapy, here, these other lines, the less decrease you see.

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This inverted ratio between CD4 and CD8 T-cells, CD4/CD8 cell ratio is really a hallmark of immunosuppression and I talked a little bit about a few of these factors influencing this ratio: inflammation, as seen here, as shown with elevated biomarkers of inflammation, such as increased Interleukin-6, or increased sCD14. Then, also, other factors that activate CD8 T-cells, and on the other hand we have the CD4 immune reconstitution, which is mainly also influenced by the late initiation of ART. And when we look on all these factors and you see, in the center of all this is always the gut, that I mentioned, the microbial translocation. Then we see this direct disregulation and this inverted ratio of CD4/CD8 ratio, where we suddenly have higher CD8s and lower CD4s. And they really, as I'll show you later, may also influence HIV reservoir and non-AIDS events as our main outcome.

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When thinking about the CD4/CD8 ratio below one, then we basically have to say, what is normal? Is this normal? No, it's not normal. Normally range is usually around two. If you increase it maybe around 1.0 to 6.0 of CD4/CD8 ratio. And very importantly, when you think about our patients, when the patients get older, the CD4/CD8 ratio goes down. So, with older patients, we see lower CD4/CD8 ratios, as shown here in this graph. While, with younger patients, we see higher CD4/CD8 ratios. And is it just AIDS which can intervene and AIDS which can result in low CD4/CD8 ratios below one? No, it's also many other underlying diseases, which we may see not as often, always, in our HIV focused clinical practice, but we could still think about bone marrow suppression, anemia, multiple sclerosis, myasthenia gravis, or other chronic infections that are also associated with a low CD4/CD8 ratio. But now, moving back to our patients, who are HIV positive and on ART, we really have to say that even in those patients who are responding to ART, who have normal CD4 counts, if we don't focus only on CD4 counts, but also look on CD4/CD8 ratio and we find that the CD4/CD8 ratio is low,

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then this is associated with poor clinical outcomes, increased morbidity and mortality, with T-cell dysfunction, increased viral reservoir and increased inflammation. So it's really useful to look in our patients not only on CD4 counts and be okay, if this is normalized and the viral load is suppressed, but really also take a look on the CD8 cell count and calculate the CD4/CD8 ratio, if your lab isn't doing it. Because this is relevant. When we look on the correlation between CD4/CD8 ratio and non-AIDS morbidity, there is recently relayed in the last two years,

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there is a number of papers coming out that clearly show that low CD4/CD8 ratio is a strong predictor of non-AIDS malignancies, cardiovascular events, kidney, liver disease.

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Here one of the first recent studies in 2014 that we have here in green, people without any non-AIDS event that had clearly higher CD4/CD8 ratios, when compared to other people with non-AIDS malignancies, with any non-AIDS event. Or also in different sub-entities. Like ischemic heart disease, where we will see a difference of higher ratios in those without any non-AIDS event versus those with some. And this was also shown in a number of other studies that already are published. There will be even more studies when you listen to what researchers have still not submitted or poster presentations There will be even more big studies that is coming out, that will show this association. How can we now

influence really the CD4/CD8 cell ratio? How is the ratio developing, once we initiate antiretroviral therapy?

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As I said, of course we know if initiated appropriate antiretroviral therapy, we see rapid viral suppression and also an increase of the CD4 cell count. In contrast, the normalization of CD8 count is rarely observed. Here we have the CD8, on the other hand, here we have the increasing CD4, and of course the viral suppression. However, and this is something I want to show you here below, if you initiate antiretroviral therapy very early during infection, this may significantly reduce CD8 cell activation. Here, we can only show you is acute HIV infection. We see these very high levels of CD8 cell activation, also higher, a little bit higher compared to chronic HIV infection. But here, and that's maybe one of the main messages today, you see that if you initiate ART very early, and this is not looking at the time of initiation, this is looking at the follow up point, which is much later in the course. That the level of T-cell activation, CD8 T-cell activation is much lower in those who initiated ART very early, versus those here, in orange, who initiated ART later. As I told you, there are a number of factors that may influence CD4/CD8 ratios and now I can also show you a few slides to a very recently accepted paper from Dr. Smith and Sara Gianella, who has been here last year,

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on CMV and CD4/CD8 ratio, where they really looked on 600 PBMC samples from 108 CMV, Epstein–Barr virus, seropositive HIV-infected men, who started ART very early and were followed over nearly 30 months. What they really found is when correlating levels of CMV replication with CD4/8 ratios,

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that those who had high CMV replication had the lowest CD4/CD8 ratios, under antiretroviral therapy, under effective antiretroviral therapy. And then going on and differentiating which really, what was really the cause? Was it CD4, which did just not increase as much in those with CMV infection?

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Or was it CD8, which increased further and therefore led to this lower CD4/CD8 ratio? They really found, very clearly, that it was just CD8. So there was no difference in CD4 if CMV infection, but in those with higher replication of CMV, they found that CD8 was increased further, despite effective antiretroviral therapy. So CMV, obviously another very important factor, as it seems, that is associated with lower CD4/CD8 ratios. There are of course also other determinants of low CD4/CD8 cell ratios in HIV infected patients on antiretroviral therapy.

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I talked about CMV shortly, but, in another study, they also found obviously that long time ART initiation before 1997 versus after 2002, had a higher likelihood of having... Of course, these people have been a longer time infected, of lower CD4/CD8 ratios. So CD4/CD8 ratios decrease with time, and then the lower CD4 T-cell nadir was also a factor associated with lower ratios. And, of course, importantly, a shorter duration of viral suppression. So, at the end, it comes still there that CD8 gives us additional information, but it does not prevent us from keeping our patients virally suppressed, because this is obviously also a factor that is protective against having very low CD4/CD8 ratios.

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So now I want to talk shortly about our study and what we added. The objective of our study was that we know, of course, that early initiation of ART seems to improve CD4/CD8 cell ratio, but really don't know so much about the dynamic of CD4/CD8 ratios during the early HIV infection. And especially in context of early or immediate ART initiation. There is not really a literature on any correlation of the ratio with severity of Acute Retroviral Syndrome. Which of course correlates with the HIV disease progression.

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We analyzed CD4/CD8 cell ratios in relation to signs and symptoms of acute HIV infection and also in context of early versus delayed initiation of antiretroviral therapy. We had this seven year study period and included these 90 individuals with acute HIV infection, who were enrolled into our cohort in this time period.

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When starting on signs and symptoms of Acute Retroviral Syndrome, we really found that the CD4/CD8 cell ratios were significantly lower in individuals who reported signs or symptoms before or at the time of diagnostic testing, versus those who did not report any symptoms of Acute Retroviral Syndrome. That is of course a clear correlation. We certainly see here the median, significantly lower. And, very importantly, when thinking about CD4 and CD8 cell counts alone, we did not see a significant difference. This is really a strength, maybe, of the ratio that it takes into account both measures, and if they are both just not significant, when taking into account both, you actually see a clear effect and correlation.

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What is more, not even just occurrence of Acute Retroviral Syndrome was associated with lower CD4/CD8 cell ratios, but also the duration of signs and symptoms, with lower ratios observed in those with longer duration of symptoms and the severity of signs and symptoms. Those who had such severe symptoms of ARS that they needed to seek medical attention because of their symptoms had lower CD4/CD8 ratios, versus those who said, yeah, they had some signs and symptoms but it was not that bad that they had to seek medical attention because of that. They were just testing routinely with us and got diagnosed. When focusing on the influence of antiretroviral therapy on the CD4/CD8 ratio and the timing of initiation

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of antiretroviral therapy in persons with acute HIV infection, on how this is influencing the CD4/CD8 ratio. We had really around 30% of people who started antiretroviral therapy within 30 days of acute HIV infection diagnosis. Which is according to Fiebig around 30 days, within 40 days of the estimated date of infection. Which we categorized as early ART, and then 41 people started ART later, categorized as delayed ART. Really, among those with early ART, we saw that the CD4/CD8 ratios did not, and this was really our main finding, did not differ between the time the people tested positive and the time they started ART, because obviously this time period was not so long. But, when looking on those on delayed ART, who started ART later, we found clearly that at the time they tested positive for acute HIV infection with NAT, the CD4/CD8 ratios were still okay. But at the time they initiated ART, mostly, a few months later, the CD4/CD8 ratios went down significantly.

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This I can show you here. It's a little bit small, but there was a significant difference between the time of the initiation of ART in those with delayed ART, versus there was no difference in those with early ART. And why is this relevant? Even when we followed up people 36 weeks, 36 after ART initiation,

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we found of course that in both groups, in those who initiated ART. Early ART and those initiated late ART, the CD4/CD8 ratios increased after 36 weeks of ART, compared to the time of ART initiation. But when looking back to the time of diagnosis, we saw that in those with early ART obviously there was a significant increase from the time of diagnosis to week 36 of ART, at this difference, there was a significant increase while in those with delayed ART, due to the initial drop while they were not on ART, there was no significant increase of the CD4/CD8 ratio So this really tells us, we cannot make up for this time, for this CD4/CD8 cell ratio, which is happening because we delay ART. We really should start ART as early as possible, to keep people, our patients on a relatively high CD4/CD8 cell ratio, increase from there and not just wait until the CD4/CD8 ratio goes further down. Because we won't increase more.

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Shortly, just a little bit also, about early and chronic HIV infection, I told you, this all is now acute HIV infection, so diagnosed within 10 days of actual infection, according to phebic, according to our definition, but also then focusing on early HIV infection which we define as infection with an estimated date of infection lower than 130 days. So still pretty early, we found that actually the CD4/CD8 cell ratios increased significantly once ART is initiated. So, this is time from estimated infection to ART, 90 days immediate, and we see the significant increase, and also, if you diagnose people with chronic HIV infection of course you want to treat them, because this also results in an increase of the CD4/CD8 ratio.

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So, when looking over several recent studies and also focusing on our studies we found that the CD4/CD8 ratios were generally lower in individuals with symptomatic acute HIV infection and with severe and long lasting symptoms of ARS, compared to those with less symptomatic acute HIV infection, and also our data indicate that CD4/CD8 ratios decline rapidly during acute HIV infection. If we don't treat or there's a rapid decline in this ratio until we start treatment, enter ART treatment, and early ART initiated as soon as possible in our study within 40 days of estimated date of infection was associated with a significant increase in CD4/CD8 ratios. Which, when you think about the bottom hand once there is this increase it probably remains.

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And conclusions, really, acute retroviral syndrome, and that's also one of the questions, is only helpful for diagnosing about 50% of acute HIV infection cases that you would diagnose if you would just use routine screening for acute HIV infection, everybody, in MSM. But of course, in ARS it's important, because the severity, we should still ask for symptoms, because the severity really correlates with HIV disease progression. Low CD4/CD8 ratios are associated with higher non-AIDS morbidity and mortality risks. And, CD4/CD8 ratios really correlate with ARS severity in acute HIV infection. They decline rapidly during acute HIV infection, but may increase significantly once ART is initiated. And really the take home message: very early initiation of ART does a lot of good things. Which is in part also displayed by the significant increase in CD4/CD8 ratios, which may be a sign of lower viral reservoir, for example, lower inflammation. So, that's really the way to go.

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And, acknowledgements, very shortly. I came to San Diego in 2014, from Austria, this was one of the opportunities I had, one of the fellowships I got from a New York based foundation, the Max Kade Foundation, which is an Austrian-American Foundation, now I stayed here. And to end, I showed on the first slide, I showed Arnold Schwarzenegger but right now we have a much more popular Austrian, in our... she's really a star and a hero of our patient collective, and this is Conchita Wurst, obviously, and we are very proud of that. And with that I want to thank you for your attention.
[Video End]