



Clinical Education Initiative
Support@ceitraining.org

PREVENTION OF ANAL CANCER IN HIV-POSITIVE MEN AND WOMEN: AN EVOLVING LANDSCAPE

Joel M. Palefsky, MD, FRCP(C)
Professor of Medicine, Division of Infectious Diseases
UCSF School of Medicine, San Francisco, CA

9/11/2018

Prevention of Anal Cancer in HIV-Positive Men and Women: An Evolving Landscape **[video transcript]**

[00:00:01] Welcome to Physicians Research Network. I'm Jim Braun 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 coinfections and complications. We hope this recording of Joel Palefsky's presentation 'Prevention of Anal Cancer in HIV Positive Men and Women: an Evolving Landscape' will be helpful to your daily practice. And we 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. Membership is open to all interested clinicians nationwide at our website PRN.org. Now allow me to introduce Joel Palefsky, Professor of Medicine in the Division of Infectious Diseases at the University of California San Francisco School of Medicine.

[00:00:55] Thanks for having me back Jim. I'm going to be talking about prevention of anal cancer and then we're going to be hearing about what happens when we don't prevent anal cancer. So what I want to do with you this evening is to discuss the epidemiology of anal cancer, pre-cancer, and HPV infection and particularly how it's changing. I've talked about this a few times here and it is an evolving landscape. And we'll talk about the ways in which it is changing. Give you a little update on current methods for prevention of anal cancer in HIV positive individuals. And then talk a little bit about the ANCHOR study, that's the Anal Cancer/HSIL Outcomes Research study, the ANCHOR study. Now I gave you a little bit of information about it the last time and now we're well into it, and I'll tell you where we're at.

[00:01:48] So first important point for tonight is that cancer has now emerged as the number one cause of death amongst HIV positive people. Now that individuals are living longer with HIV on effective antiretroviral therapy, lifespans have greatly increased they are normal now or close to normal, sometimes longer than normal. And as this has happened, the spectrum of diseases that cause mortality has changed and cancer has now emerged as number one. I think this is something that is not widely appreciated in the medical community. I think you're well aware that the distribution of cancers has changed. So the green ones were the AIDS defining cancers, the ones that are associated most with immune suppression meaning there are hardly ever found in the normal population, these have come down. They are K.S., non-Hodgkin's lymphoma, cervical cancer. Interestingly though cervical cancer hasn't really come down. And then it's the non-AIDS defining malignancies that have become more prominent percentage wise and have actually been slowly increasing over time. So the action in the cancer arena is primarily in the non-AIDS defining arena. On this side of the slide is the distribution of some of those non-AIDS defining ones, where the HPV associated ones are in gray. And you'll see that they are also slowly creeping up as a percentage of the cancers that are occurring.

[00:03:26] So we're here to talk about anal cancer. Just a very quick reminder, I know you know this, but the area that we're talking about here is of course at the end of the GI tract just distal to the rectum. And the anus as an organ is I think it's a great organ to study because it's got lots of interesting flexible features. One of which is that it combines some of the elements of the cervix inside the canal, because it's mucosal epithelium, and some elements of the vulva, because it's a keratinized epithelium on the perianus. And the anus begins at the squamocolumnar junction at the end of the rectum and goes all the way out to about five centimeters in the perianal area. So when you're doing an anal exam and when you're talking about anal cancer, you're talking about cancers that can occur anywhere within that rather large piece of real estate.

[00:04:29] Now one of the things that's interesting about anal cancer is in the general population it has been slowly increasing. Cervical cancer has come down because we have an active screening program. We don't have an active screening program for anal cancer. And since the 1970s, this cancer has been increasing by about 2 percent per year in both men and women. We don't really know why, some people think it may reflect changes in sexual behavior that began in the 60s. People having more partners, more potential exposures, not entirely clear but it is very consistent. I'll show you some data from some other countries. But it's also important to realize that the absolute number of cases is rather small as is the incidence as expressed by the rate per hundred thousand cases per year. So we're really still in the general population only talking about 2 per 100000 or so. What is more disturbing is that if you look at the five year relative survival since 1975 it has improved, but rather minimally. Went from 64 percent to nearly 69 percent. So despite improvements in treatment, which you'll be hearing about, the overall survival rate really hasn't budged all that much.

[00:05:49] So this just shows you what's happening in other countries and these are mostly countries where there are decent registry data. Part of the problem is in Africa and many other areas of developing countries, they don't keep very reliable cancer data. And in the places where they do, they often don't distinguish for instance between rectal cancer and anal cancer. So it's very difficult to interpret those data. But in some of the countries where they do keep reliable data, there are very clear increases in the incidence of anal cancer from the 70s onward in both men and women in the general population. Something else that I think is not widely appreciated in the general population is that male anal cancer is predominantly a disease of women. We in this room have done so much work on HIV positive people where as you know the incidence is so much higher, anal cancers tended to become a little conflated with HIV and particularly with men who have sex with men. But in fact in the general population in terms of absolute number of cases, it's more common in women than it is in men.

[00:06:56] Now I've shown you variations of this over the years and this is kind of our current understanding of the natural history from acquisition of HPV infection through pre-cancer and ultimately development of cancer. And over the years I've made this more colorful and added all these things to reflect the fact that we now understand that it is the norm to have multiple HPV types. It isn't

unusual, it's the norm. And in fact if you do some of the most modern sequencing methodologies, Next-Gen sequencing, you actually find in a single person thousands of variants of HPV. We're still wrapping our head around that, this is a big surprise. But the point is that we almost all get HPV when we're sexually active at some point in time and we get it quickly, we get it within our first few sexual partners. And unless you're extremely unlucky you'll probably get HPV first before you get HIV, so you'll have HPV established. Many of us, myself included, believe that we never clear HPV from the body. It goes latent in most people after a good immune response and in most people never causes a problem. But in some people they don't control it well or they become immune compromised later and then the virus that was acquired decades earlier can then reactivate.

[00:08:26] So you get your HPV first and in the setting of HIV if it's not controlled, if you're not on any antiretroviral medicine, your immune system continues to deteriorate. HPV replicates more, you see higher levels of it and you start to get disease. Now in the olden days we used to think that people would go from normal to low grade squamous intra-epithelial lesions, which are not precancerous, to high grade squamous intra-epithelial lesions which are considered precancerous and then cancer. We now know that's probably not true, what probably in fact happens is that when you get a viral infection it decides to go down one of two pathways but not both. The first pathway which is actually the more common is the LSIL pathway, and that really is just highly active replicating virus. It is what viruses most want to do, which is make more of themselves. So an LSIL lesion is just a ton of virus, not very much by way of transformation of the cells. On the other hand, in a smaller percentage of cases, the virus will instead of making a lot more virus will turn its attention to expressing oncogenic genes. And instead of getting a ton of virus, what you get is a lot of malignant transformation or pre-malignant transformation.

[00:09:44] So it's the HSIL of course that we're most worried about and what we most want to find and remove before cancer can develop. And we also used to think that it took time, a lot of time, to go from normal to high grade and then eventually you would pop to cancer. Well we do think that the thing that helps it to pop are an accumulation of genetic changes, just the right or wrong combination of genetic changes. Like we know from the Bert Vogelstein colon cancer model, when you go from a benign adenoma to progressively higher grades of precancer, usually you had one more big genetic change along each step of the way. That is probably happening here and it's probably facilitated by HPV, because HPV causes genetic instability. But what we can now say is that the HSIL lesion actually develops very quickly, probably within two years or so. We knew this actually from the cervix, but we've now shown it in the anus because we just completed a study in the AIDS Malignancy Consortium of young HIV positive MSM, 16 to 26 years old most of them were in their late teens and early 20s, and most of them only sexually active for a few years. And when we screened over 150 of them, more than a third of them already had a high grade lesion. And over the next two years a follow up, those who didn't forty percent of them developed a high grade lesion. So the high grade lesion is developing quickly and then that is what's sitting there for a long time accumulating those genetic changes, which ultimately leads the development of cancer.

[00:11:22] So in the bad days before we had A.R.T., there was not sufficient time for those lesions to progress, people died of other HIV related comorbidities and that was one of the things that kept the incidence of anal cancer a little bit controlled. Now the good news/bad news story is of course, it's great news that people are doing better they're living longer now. In the absence of screening the opportunity for HSIL to progress to cancer is now there because there is now the time. So what does that translate into? So one of the biggest cohort studies in North America reported that from the beginning of the A.R.T. era through 2007, the incidence of anal cancer which in the general population you heard was about 2 per hundred thousand. In men who had sex with men before the HIV epidemic i.e. HIV negative MSM the incidence of anal cancer was estimated to be as high as about 30 to 35 per hundred thousand. So a lot higher than the general population. But as you can see, quite a bit lower than when HIV came onto the scene. So in 2007 it was estimated that the incidence was 131 per hundred thousand among HIV positive MSM. So if you think about it, HIV positive MSM are about 80 fold higher rate of anal cancer than the general population. Men who have sex with women who in theory don't have any particular mechanism of getting HPV into their anal canal are at high risk of anal cancer, 46 per hundred thousand. And then women are also at high risk, 30 per 100000. To put this into context, in our screened population the incidence of cervical cancer in this country is about 8 per 100000. So anal cancer is more common in this population than cervical cancer is. In Australia and the general population, they're estimating that by 2030 because they do such a good job at controlling cervical cancer, and again nobody's doing anything to prevent anal cancer, they estimate that by 2030 anal cancer will be more common in the general population of women than cervical cancer will be.

[00:13:56] So anal cancer in all of these groups is unacceptably high. We would never accept these kinds of rates of cervical cancer in this country and they shouldn't be accepted anywhere. Now here's a better piece of news which is that increase that I just told you about, it's not been reversed but at least seems to have stopped. It seems to have leveled out. So from the data that I showed you before were through 2007, the most recent data which now take us through 2012 show actually a decline in the incidence of anal cancer. It's not actually statistically significant, but I think it's safe to say is that at least we can say that the rapid rate of increase seems to have stopped and now it's leveled off at a rate that's still too high. So that's one thing.

[00:14:53] The other thing about anal cancer, in terms of absolute number of cases, is in that analysis where they showed the slight decline in anal cancer in the last few years, they looked at some of the trends in the AIDS and cancer registry match. The methodology that they used was a little bit different from the NA-ACCORD, here they actually looked at cancer registries and then did a match with HIV registries to see who was in both of them. And what they found, not surprisingly, was that the incidence rate is the highest in MSM and about the same when you were an MSM who is an IDU and then progressively lower rates, similar to what we saw with the NA-ACCORD, if you were a male heterosexual or female. If you were older, the rates of anal cancer increased. If you were white, you were at higher risk than being black or Hispanic. And if you had a prior AIDS diagnosis, that was one of the strongest risk factors, so probably having a low CD4 nadir and having a history of OIs was a strong risk factor for

developing anal cancer. And also when you were diagnosed, also made a difference. If you're diagnosed earlier then you were at increased risk of anal cancer.

[00:16:20] What this slide shows, I hope you can see the yellow line in the back, is basically that the trends if you're looking at calendar period between 1996 to 2000 or 2009 to 2012 are basically not that different. So it's just a different graphical way of showing you that the likelihood of developing cancer has not changed all that much in the last set of post-ART years. So it shows you that in that period there were 1568 cases of anal cancer. And what you can, see compared to some of the other most common cancers, were there were more lung cancers in this period, but there were more anal cancers than there were prostate cancers. And what that says is that anal cancer is not the most common cancer, but it is the most common preventable or we think preventable cancer in the HIV positive population. So we really do think this deserves attention.

[00:17:24] So again the numbers zoomed up, leveled off. I think they are still about the same. And now the question is, where do we go from here? There's lots of moving parts. And one of those moving parts is age, because it's well-known that HPV related cancers, anal cancer and cervical cancer, typically don't occur until later in life. Typically in the late 50s and early 60s for anal cancer, late 40s and early 50s for cervical cancer. And what that means is that as more people get old enough to be in that age group, that might be one of those factors that is going to just by itself increase the risk of developing anal cancer. This is an example in the general population of women, showing how the anal cancer incidence goes up with age in women. But in the setting of HIV there's a bit of a double whammy because we also think that, number one more HIV positive people are thankfully living to be that age, and then there may be some accelerated aging. I'll show you in just a moment.

[00:18:41] So what about the demographics? Well in 2015 it was estimated that more than half of people living with HIV were already over the age of 50 years, and that translates into more than 300000 people in 2012. And of course that number has gone up since then. As far as the biological age of people as opposed to their chronological age, we know that HIV is associated with low level chronic inflammation. Some of that appears to be related to increased risk of age related cardiovascular disease, neurological disease, liver disease, neurocognitive decline. All of these things that indicate that somebody may be biologically a little bit older than their chronological age. So this may potentially play into an increased risk of cancer going forward.

[00:19:33] We also know that people who are HIV positive present earlier with these cancers. So for example, the median age when you weight the general population is 51 years for anal cancer and then if you're HIV positive the median age is 47 years. So that's not a huge number difference in years, but it is highly statistically significant.

[00:20:00] So what I've done on this slide is sort of put together a list of things that could go in either direction as we move forward. And what I've done is I've put some of these various factors and different colors corresponding to the things that we have some control over and the things that we don't have control over. So the things in red are things that we don't have very much control over. Orange we have a little bit of control over, and green we do have some control. So increasing age, we have no control over that. And I think that that is likely going to increase the incidence of cancer as potentially will accelerated biological aging, unless we can figure out a way to get rid of HIV reservoirs and remove that chronic inflammation. Lower nadir CD4 level, I showed you some data on the increased risk of cancer associated with that. I put it in orange because we do have some control over that and we have been doing a little bit better with that. We've changed the recommendations over the years so that people who have higher CD4 levels are now starting ART. That's a great thing, but unfortunately if you think about it from the point of view of cancer prevention, at least in the U.S. HIV population, the impact of that change is going to be relatively minor because the vast majority of HIV positive people will have started ART at a level below where we would do it today and may already have sustained at least some of the increased risk associated with that. So it's not clear how in the big picture that's going to impact positively on anal cancer, it's a very good thing obviously for people who are being newly diagnosed, but on a population level it's not clear that we're going to see much of an improvement in anal cancer due to that change in recommendation. Current CD4 levels are definitely things that we can modulate with ART therapy. So there is some data just that concurrent low CD4 levels maybe associated with increased risk of anal cancer. Time on effective ART is something that appears to be reducing the risk of cancer, so the longer you're on good ART there's some data to suggest that your risk goes down and that is something that we can control. Earlier initiation of ART, again I put that into the possible area of control given the various issues identified with finding people at the right time to initiate ART. Now in green at the bottom we have two other important things, we have screening for and removal of HSIL. Now I've put that of course into the decreased incidence of cancer category and I put it as definitely for cervical because we know it works, but we do not know that it works yet for anal. I'm hoping it's going to work. That's what the ANCHOR study is about. So I put it as possibly, I'm hoping it'll get upgraded to probably and by the end of the ANCHOR study to definitely, but you can't say that at this point. We just don't know.

[00:23:23] And then there is HPV vaccination. So we know the vaccine works, and when we say that what we mean is we know it prevents high grade disease. Prevents cervical high grade disease, it prevents anal high grade disease. So why did I say likely and not definitely? The only definitely here is for cervical screening. And the only reason I did that, because I'm trying to be as objective as possible, as enthusiastic as I am about vaccination is that we still don't actually have proof that we're reducing cancer. We know that we're reducing high grade disease, but it's going to take a few more decades before we see that reduction in high grade disease translate into a reduction in cancer because of that long latency period that I talked about before. So it's just too early to say. We think it will, but when we talk about the vaccine preventing cancer what we frankly really mean is the vaccine preventing high grade disease which we expect will translate into a reduction in cancer.

[00:24:27] Now the other things that we need to consider in thinking about where anal cancers are going to go are what we call the future indicators. If you don't have anal HPV infection, you're not going to get anal cancer. If you don't have anal HSIL, if you're a believer in this paradigm that I showed you, you're not going to get anal cancer. So what do the data look like right now as far as what people have as far as anal HPV infection and anal HSIL? Well basically the numbers are pretty bad when it comes to HPV infection, almost everybody has HPV infection. This is the SUN study, it replicates data that we generated as well. Basically in MSM 96 percent of the men had anal HPV infection in one single testing, 90 percent of the women had anal HPV infection in one single testing. 59 percent of the men had sex with women had anal HPV infection at one single testing. If you test people repeatedly, those numbers go up. Multiple HPV types. Thousands of variants as I was saying before. You may be asking yourself 'why do women get anal HPV infection? Why are 90 percent of them getting it?' 90 percent of women are not having anal intercourse. It's common, but it's not 90 percent. And what we now believe is that some women get anal HPV infection because of the way that they wipe themselves after going to the toilet. Very nice study was done in Tasmania where they showed that women who wipe themselves from front to back like their moms taught them to do to prevent a urinary tract infection were at higher risk of getting anal HPV infection than women who didn't. So you really can blame your mother for this. Now I'm not suggesting that we teach girls to wipe the other direction, you probably have to do a formal cost benefit analysis because perhaps does have an impact on UTIs. I don't know. Just saying that it is absolutely credible if a woman has anal cancer, anal HSIL, or anal HPV infection and she says she's never had anal intercourse before, it is totally believable. And the same is true for men who have sex with women. You know I have occasional guys in my office, California Highway Patrol the most macho, you know what I'm talking about, and swearing up and down that they haven't done anything and some of them haven't.

[00:27:03] The other fascinating thing to me is that actually anal HPV infection is more common than cervical HPV infection in HIV positive women and in high risk HIV negative women too. 42 percent in the HIV negative for the anus, 27 percent for the cervix. So the anus is a terrific reservoir. I think it's a great place for HPV hang out. But having said that, it is less transformable than the cervix. If you compare for instance the rate of progression to cancer associated with HPV-16 in the anus versus the cervix, the cervix wins hands down on a per HPV-16 infection basis. There's more cervical cancer. So there are other sites specific factors that are playing a role here, but obviously there are still too many transforming events in the anus.

[00:28:02] What about these high grade lesions? Basically what we're finding is that in just about any study these days, this was the first and I think only community based study where we did random digit dialing, we found 43 percent of the HIV positive MSM having an anal lesion. And in the most recent studies most of them are hover around 50 percent or a little bit more even. So roughly half the HIV positive population of MSM have anal HPV infection at any one time, it waxes it wanes but mostly it waxes.

[00:28:42] And then we're also appreciating, thanks to a recent AMC study, that the prevalence of anal high grade in women is higher than we thought. In this study about 30 percent of the women had anal high grade disease. So now you may be asking yourself, 'how often do these high grade lesions progressed to cancer?' Well nobody's ever done that prospective study until we started the ANCHOR, so I'll have some data for you in about 10 more years. But our best back of the envelope calculations are that roughly one in four hundred HSILs in an HIV positive person will progress to cancer every year. So that doesn't sound like a lot if you're on an individual basis, but if you are multiplying that by the number of years at which a person may be at risk, our best lifetime estimate for a person may be as high as 10 percent for an anal cancer which is a lot. Is it going to be that high? I'm guessing probably not, but it's still going to be I think predicting going to be between 5 and 10 percent of lifetime risk of cancer. And it's such a bad cancer as you're going to hear before that I think that is really unacceptable.

[00:30:04] So we need to do something about it. Primary prevention is the best obviously, meaning preventing HPV infection. But just like I was saying before about the great thing of starting ART earlier it's going to have a relatively limited impact on the anal cancer rates because almost all the people who are at risk have already been exposed to HPV. This is only for prevention of initial HPV infection. So we must do it. It is essential, and it's certainly important before somebody turns 26. The cutoff for the CDC is 26 years of age. After that it's considered to be not cost effective, you can make an individual decision about what you want to do but by and large the horse is already out of the barn, the longer somebody has been sexually active when you're starting to consider vaccination.

[00:30:54] So you would know that we're now using the nonavalent vaccine which adds the five high risk types shown there to the quadrivalent vaccine that was used before. The vaccine works extremely well. It's safe. It's one of the best vaccines out there and it is also one of the very best public health interventions that we have produced. The news here is twofold, one that for individuals who are healthy not immunocompromised for any reason if they are starting vaccination under the age of 15 they only need two injections and not three. We used to say 0, 2, and 6 months. Now if they fall into that category as long as those injections are six months or more apart, then they only need two. 0 and 6 months or 0 and 12 months. So that should help with uptake. If you're HIV positive or otherwise immune suppressed or if you're starting at the age of 15 or older, you still need three injections. That hasn't changed. For the people who are still in the very healthy end of the spectrum, there's even a move afoot to push towards one injection. This is based on some retrospective data from the Costa Rica vaccine trial population based study where they showed that women who got their first vaccination and never came back for a bunch of reasons turned out to be just as protected as women who had two or three injections. So now there is a prospective study in progress to determine, there are several of them actually around the world, to see if we could get away with just one shot. The vaccine is just that good, provided you're young enough to have that good robust immune response and if you're 50 and you're over the hill.

[00:32:52] For HIV positive people, again this is absolutely a safe vaccine and I can't stress enough that for people under the age of 26 how crucial it is to give it to them. It probably produces lower titers than in HIV negative people, but that's OK because you're still got way overkill as far as protection is concerned. So I wouldn't worry about that. Wouldn't worry about HIV viral loads going off the charts when you're vaccinating people and I wouldn't worry about CD4 changes. It's a safe vaccine.

[00:33:24] So for secondary prevention, this is our model. It's based on the cervical model. Basically it assumes, and I'll talk a little bit about this, the use of cytology as a screening test by primary care providers for at risk people just like we do for cervical screening in women. Big difference is that here if you have any abnormality, including atypical squamous cells of undetermined significance, that should prompt a referral for a high resolution anoscopy. However cytology has problems, as I'll show you in a bit, and there's some other things that we could potentially do. For people who are primary care providers, I think you should consider doing a cytology and/or some HPV testing as I'll show you in your at risk populations and I'll show you who we recommend that for. But also one other thing which is a digital anorectal exam or a DARE. We all know how to do it, we recommend that an HIV positive person have it at least annually. And the goal here is not to get abnormalities that could lead to identification and precancerous lesions, but actually to find prevalent cancers. You feel a hard mass you know it practically right away and it really is complementary to the cytology, which is not designed to screen for cancers it's really designed to screen for pre cancer. So the combination of these two tests use primary care providers during your annual anorectal exam and the cytology in high risk individuals, I think is a great way to go. If people after they have anoscopy with biopsies are shown to have high grade disease, we will do what we can to treat it. If they have low grade disease, we will usually leave it alone unless people are symptomatic or insist on having it out.

[00:35:20] Here's one of my colleagues Michael Berry doing HRA uses a colposcope. It's I think a pretty fun technique to do, very challenging takes a long long time to get really good at it. And then there's a digital anorectal exam. This slide unfortunately is out of date because I don't think any San Francisco Giants fan could put the number one sign up there for now years.

[00:35:50] So our screening list is here and it includes all HIV positive people, regardless of their sex or their risk factor. It also includes women with high grade cervical or vulvar disease or cancer. And then anybody who's immune suppressed for any reason or who has perianal disease of any kind associated with HPV, be it Bowen's disease or condyloma should be considered. The one thing is please don't do it until somebody has reached a minimum age and in that case we recommend 25 years if you're HIV positive. You do not need, despite what I told you about the AMC study, to screen the 20 year old HIV positive MSM. Why? They're probably going to have high grade disease eventually and they might even have it now, but they're not going to get cancer. So let's leave them alone, not traumatize them physically and psychosocially, and leave them alone until their risk of cancer is high enough that it's time to intervene. And we think 25 years is a safe cutoff. So leave them alone until 25 and using the same

reasoning we think you could probably even put off screening an immunocompetent person until they're 40.

[00:37:03] The challenges are that the technology is not great. Cytology has limited sensitivity, perhaps better in HIV positive people because the lesions tend to be bigger. And as you know we've been working towards incorporating more HPV testing in the cervical world and we're talking about it in the anus too. HPV testing is probably more sensitive than cytology, but it's also got a lot lower specificity. I just told you that almost everybody is positive. So it's got limited utility in some ways. So what you can do is actually consider a reflex approach. This was a study that we haven't published yet but basically here we're using one HPV test called Aptima, which is an RNA test, and if you're positive which is a basket of types and you have a normal cytology then your risk of having HSIL, which is what it's all about, is quite a bit higher. It's tenfold higher, but the absolute risk is still pretty low. If you have an LSIL with a positive Aptima test your absolute risk of having high grade disease is about 30 percent, it increases the relative risk by about 2.6 fold. So the increase is less marked but the absolute risk is higher. And then if you get even more fancy and specifically pull out the worst HPV type, like HPV-16, if your Aptima HPV-16 positive with a normal cytology you have a 40 percent chance of having a high grade lesion. Again a nearly tenfold higher risk of having high grade disease compared to being negative for HPV-16 and so on. So we're not ready to formally recommend this yet, but I think we're moving in this direction and we will probably recommend some reflex screening approaches to try and get that good balance of predictive value and sensitivity.

[00:38:57] For the treatment of HSIL, it's all about prevention of cancer and relief of symptoms. It's a difficult thing to do because the lesions in HIV positive people tend to be multifocal, tend to be large, they recur a lot. And our primary approaches are hyfrecation versus infrared coagulation. These two methods are pretty equivalent in terms of their success rate. The problem is that we get a lot of people who have what's called metachronous disease which are lesions that pop up in areas where we didn't treat them before, probably due to those latent infections. I call it anal whack a mole. And so patients need to be followed for a long time.

[00:39:40] Steve Goldstone led a lovely study through AIDS Malignancy Consortium which was actually the very first randomised controlled trial of infrared coagulation and did show that IRC was successful, from a statistical point of view, in causing clearance of more HSIL than no treatment at all. It was a little surprising actually how many people seemed to clear their HSIL over a one year period, 30 percent. Personally I'm not sure I believe that, I think that a lot of people will be diagnosed again with HSIL if we follow them longer. This was just one year follow up.

[00:40:20] So I just want to finish off by just talking about the ANCHOR study because this is really the very definitive study that we're looking for to determine whether everything that I've been blathering

on about should become standard of care. And the reason that it's necessary is because we are in the era of evidence based medicine. And I can treat that high grade lesion and I can make it go away and my patient might not get anal cancer, but I will never know whether it's because of something I did or whether that person was never going to get cancer in the first place. So the people who do their very best to avoid paying us for procedures often tell us 'we're not going to pay you unless you give us the evidence that it works.' Just to complain a bit, nobody ever asked the cervical people to do that. In fact you know we just went willy nilly, if you'll pardon the expression, into cervical screening and treating for decades. Millions of women before anybody actually showed that it led to a reduction in cervical cancer. Fortunately it did, but now we can't do that. So we finally convinced the NIH to give us money to do what I think is what most people would consider pretty ballsy study, which is to do a randomized controlled trial comparing treatment to no treatment. So we basically look for people who are at the highest risk, HIV positive people over the age of 35, and screen them and if they have biopsy proven high grade disease randomise them 50/50 to treatment versus what we call active monitoring. And then we follow them a minimum of every six months, sometimes more commonly or more often if the clinician feels it's necessary, and we count up the number of cases of anal cancer both arms. We have a data safety monitoring board and of course if somebody is diagnosed with anal cancer in either arm they are immediately removed from the study and treated. But the DSMB is monitoring the number of cases of cancer in both arms and if we see a diversion earlier than we thought or no diversion in the opposite direction, they will stop the study.

[00:42:34] Anyway, the other thing that's very exciting about this study is that it is the last chance that we will ever have to study from a biological point of view the progression at the molecular level the events that are occurring between HSIL and cancer. Cause in the cervix if you have a woman with high grade disease you have to treat her, you can't repeatedly sample her to see what changes if she develops cancer. But we're taking samples from every single person in this study, some of them in retrospect will have progressed to cancer. We will have their tissues before and after they develop cancer, and some of the biomarkers a progression that we hope to find will we think also be relevant for cervical disease or even oropharyngeal disease because they're are essentially the same disease. So this study I think will have very broad implications beyond just the anus. So this is the study schema which I just told you. Just to give you an idea of the numbers, 17000 people we estimate we're going to have to screen nationwide to enroll 5058 people. And follow people for five years or more. So until the last person is in, we're going to be following people for five years. And our best estimate given the kinds of numbers I told you about are that probably fewer than 50 will develop cancer over the course of the study.

[00:44:02] This is our map of ANCHOR sites. We have three in the New York area now. Cornell, Steve Goldstone's laser surgery and Bronx Montefiore. And we will soon be opening a fourth at Rutgers in New Jersey. And then you can see we're largely on the East Coast and also pretty heavily concentrated in the southeast where a lot of the epidemic is currently raging and the worst. Just a few numbers, so as of a few days ago when we actually screened collectively more than 6000 people and we've enrolled

2368. And we're very proud actually of the diversity, the racial and ethnic diversity in the study. We have a very high proportion of African-Americans Latinas, Latinos. So we're very pleased at that. We aimed to have 20 percent women and we're not quite there, it's about 18 percent. Still really, really good. So far not a single study related serious adverse event. Lots of adverse events it's a very high risk challenged study population, but nothing related to what we've done to them. And we're also going to be measuring their quality of life to see how we're hopefully not ruining their lives. We have seen cancers both in screening as we expected given the numbers and we've also seen some cancers in follow up. It's too early to say anything at this point about what the data mean. So I'll stop there about that.

[00:45:45] So to summarize, anal cancer is increasing in the general population and it will remain, for the foreseeable future unless something changes in some unanticipated way, the most common preventable cancer in HIV positive men and women. Primary prevention is a great way to go, highly efficacious, great for younger people who have not yet initiated sexual activity or 26 and under. So please vaccinate people at that age and have a serious conversation with people who are around that age, maybe still a little bit too old for cutoff but may still benefit. For secondary prevention, anal HSIL can be sought and it can be treated. Please do your digital anorectal examination. We think HPV testing will be gradually incorporated into screening algorithms. The treatment can be challenging, those of us who do it do feel that we are preventing anal cancer. But we have to prove it. And that's what the ANCHOR study will hopefully do for us. So with that I will stop and thank you very much for your attention.

[End]