HIV-RELATED MALIGNANCIES:
FROM DESPAIR TO GENE THERAPY

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[video transcript]

[00:00:07] - [Jessica] Good afternoon, and welcome to This Month in HIV. Our January presentation is HIV-Related Malignancies: From Despair to Gene Therapy and will be presented by Dr. Ariela Noy, who's a member and attending physician in the Hematology Division and Lymphoma Service at Memorial Sloan-Kettering Cancer Center. My name is Jessica, I'm the program coordinator for HIV/AIDS education training department with the Mount Sinai Institute for Advanced Medicine. And before I officially introduce our speaker, I would like to thank our funder, The New York State Department of Health AIDS Institute Clinical Education Initiative. The Mount Sinai Institute for Advanced Medicine serves as a co-sponsor of This Month in HIV. So, a couple housekeeping notes. For the duration of this presentation, all lines will be muted to ensure that there will be no distraction during Dr. Noy's presentation. At the end of the presentation, we will unmute all phone lines with a Q and A session. However, if you do not have a question for the presenter or if you're not speaking, please do make sure that your line is muted, otherwise it could be distracting. And please, also, don't put your line on hold as that function can disturb the webinar as it causes music to start playing in the background. If you do have questions for Dr. Noy, you can hold them until the end or you can type them into your WebEx Chat Box directed to either the full group or to me and I can read them at the end. A quick note about the evaluation process: at the end of today's presentation, you will receive an email with instructions on how to evaluate today's presentation and claim your CME or CNE credit. Please remember that This Month in HIV is supported via our New York State Department of Health CEI grant and your participation in the evaluation process helps to keep this program free of charge for all attendees.

So, at this point, I'd like to introduce our speaker, Dr. Ariela Noy. Dr. Noy is a board-certified hematologist and medical oncologist with a major focus on treating cancers of the lymphoid immune system, in particular, Hodgkin and non-Hodgkin lymphomas and certain forms of leukemia. HIV-related lymphomas are one of her main areas of interest. To provide the best treatment to each patient with these diseases, Dr. Noy works very closely with a team of expert specialists. Her research interests include HIV-related cancers, especially lymphoma, molecular detection of minimal disease in patients on lymphoma trials, and a variety of other lymphoma-related projects, including new treatments, imaging, and quality of life. At a national level, she serves as the chair of the Lymphoma Working Group for The AIDS Malignancy Consortium, an NCI-sponsored research group. Dr. Noy serves on two NIH committees that oversee the national lymphoma research agenda and she also reviews for a number of journals. At Memorial Sloan-Kettering, she is a member of The Department of Medicine Quality Assurance, Minimal Residual Disease in Hematology, and Fertility Preservation Committee. In addition, Dr. Noy enjoys her role as a mentor to students from high school through to the post graduate level. So, at this time, Dr. Noy, I would like to turn it over to you and you can go ahead and begin your presentation.

[00:03:17] - [Dr. Noy] Well, my high school student is sitting right here, so. Thank you for that lovely introduction. This is my researching funding.
We'll be discussing today what the elevated risks are for different types of cancers for people who have HIV and we'll be talking about some of the current and potential future treatment paradigms for those patients.

So, I'm sure I'm bringing coals to Newcastle, but it's always important to remember how many people are living worldwide with HIV and that two million people in North America are living with HIV. As you know, there are big racial disparities, geography disparities. One of the hotspots in Manhattan actually have a 20 percent prevalence, which is in Chelsea. And in addition, 20 percent of patients who have HIV in the US do not even know they're infected. And you'll see that not knowing you're infected if you have an HIV-related cancer is really a problem.

So, HIV increases the risk of developing cancer due to a number of factors, probably the most important is immune surveillance of tumors. There are also direct HIV effects and in some of the types of cancers co-virus infection is not only possible, but it is directly related to the development of cancer. So, it's absolutely necessary to have both HIV and the co-virus. HIV cancers occur at an increased rate, even in the absence of AIDS. So, it's a very common misunderstanding that if you do not have a low CD4 count, you are essentially at no increased risk. And then treatment without HIV cancer, without HIV treatment, just the cancer alone, rarely works and patients will typically relapse from the cancer, which is why it's so important to know that they have HIV. However, ongoing stigma surrounding HIV infection prevents accurate diagnosis and treatment. As a vignette, I will tell you that I'm working someone up who is actually slated for prostate cancer surgery. And the day of his treatment, his surgery, he was found to be anemic two weeks ago, went to see one of my colleagues and only then told that person that he actually had an HIV infection. And it turns out he has lymphoid malignancy in addition to his prostate cancer.

What are the causes of death? Patients who are on HAART, previously to HAART therapy, 10 percent of HIV deaths were related to cancer but in the HAART era, there's an increase in contribution of cancer-related deaths. In fact, we know that the life expectancy of someone who is living with HIV now approaches or is equal to the general population. Which means that there is more time for HIV-related cancer to develop and there is more time for non-AIDS-defining cancers which would happen in that population due to aging habits like smoking and ongoing exposure to the co-infections. So, for an example, in France, the causes of deaths in 2000 were compared to pre- and post-HAART eras and 28 percent of the HIV-associated deaths were from cancer and that breaks down to 15 percent, which were AIDS-defining and non-AIDS-defining.

Alright, so what are the AIDS-defining cancers? So just to remember that the CDC definition of actually having AIDS includes things like opportunistic infections, low CD4 count, but also includes a
list of malignancies. And those lists of malignancies were specifically fixed at that time, being non-Hodgkin lymphoma, Kaposi’s sarcoma, and cervical cancer. What has been increasingly important is that additional types of cancer risks are quite extent and important in patients who have HIV. But due to really political reasons, the CDC has no desire to expand the definition of an AIDS-defining malignancy, the argument being that it would cloud the literature, which I think is kind of specious. But we know that patients have Hodgkin lymphoma, HPV, the human papillomavirus cancers, including anal and oral cancer, which I will show you is very similar, biologically, to cervical cancer, smoking-related lung cancer, and hepatitis B and most importantly, hepatitis C, hepatocellular cancer. So, if you have a patient who has Hodgkin lymphoma, they may be as sick as someone who has non-Hodgkin lymphoma but they will technically not have an AIDS-defining diagnosis.

This is just to show you as an example of how much better patients are doing on HAART. So, these are pre-HAART numbers and post HAART numbers, I think they’re self-explanatory. So, you know, rarely do we see patients now dying of Kaposi’s sarcoma, for example, and the non-Hodgkin lymphoma cure rates are at least twice as good.

So, concentrating a little bit on non-Hodgkin lymphoma first, the incidence rates have been all over the place. Recently, this is our conglomerate of four different studies conducted both in France, The UK, Germany, and The United States. Estimated risks of non-Hodgkin lymphoma increased 25 to 150-fold, affected by the severity and duration of the CD4 nadir by ongoing viremia. And also, most importantly, the interruptions in HAART, which were scheduled in the US SMART Study, which was to try to decrease the risk of ongoing exposure to HAART therapies, that that study, having been stopped, due to increased fatalities in the interruption arm, that study showed a three-fold increase in cancer. And accounted for about half the deaths that those patients were experiencing.

So, another group out of the NCI disputes that incident rate and it’s dramatically different, right? So, this shows only an 11-fold increase, and a 17-fold increase for AIDS-defining cancers. So, even if that is the number, 11-fold increase translates to anywhere between four and 10 percent lifetime risk of developing lymphoma while you are on HAART therapy. So, this is still a very important health issue for people who have HIV.

Lymphoma diagnosis in HIV patients can be missed. And this is because patients and their providers may be reluctant to biopsy, particularly lymph nodes, thinking that it’s just related to their HIV. That is probably true to some extent, but patients who are not viremic typically will not have lymphadenopathy. Also, sometimes I see patients who are referred for a scan and if the scan doesn’t look particularly aggressive, they may say, "Oh, this is probably just viremia." Yes, that does happen. We also have patients, for example, who have syphilis and they, you know, after having lymphoma, so we know they no longer have lymphoma, but they have a positive PET scan and it turns out they have a
positive VDRL. So, it can be confusing, but there has to be some vigilance to obtaining biopsies and most of the time, at least a core biopsy is preferable to an FNA because you can get very confused by a fine needle aspirate that has very minimal material on it.

What are the subtypes of non-Hodgkin lymphoma associated with HIV? They vary by CD4 count. So, Diffuse Large B-Cell Lymphoma is the most common. And it is independent of CD4 count, and I’ll show you some data about treatment of DLBCL. Primary effusion lymphomas and B cell CNS lymphomas are very rare in patients that do not have extremely low CD4 counts. So, here in Manhattan, we hardly ever see those patients, whereas some of my colleagues in the AMC who work more in more indigent areas, county hospitals, they still see these patients. I haven’t seen more than one primary effusion lymphoma in five years and I have not seen a B cell CNS lymphoma in probably 10. Burkitt’s and atypical Burkitt’s, or Burkitt’s like is a very aggressive type of lymphoma and it’s also independent of CD4. And plasmablastic lymphoma is typically independent of CD4 count.

So what happens when these patients come? Before HAART, it became dogmatic that you should not treat patients aggressively with chemotherapy, and that was because of underlying infections and in fact, a randomized trial demonstrated that the patients did better when you did not treat them appropriately for the lymphoma but treated them palliatively. In the HAART era, the patients typically come in without prior opportunistic infections, even if they have a low CD4 count, or they're having one current infection which triggers the diagnosis of HIV and that can be easily treated. And we know patients that have signs of the virus will have recovery of CD4 count. So, the current paradigm is to treat patients aggressively. Typically, this is a mistake, I’m sorry. This should be R-EPOCH typically over RCHOP. It’s a much more complicated regimen, it’s a five-day infusion. But in non-randomized trials, the Complete Response rates have improved from 40 to 85 percent. We keep in mind that both the HIV-related factors, such as low CD4 or opportunistic infections, as well as the tumor-related factors, such as poor performance status or advanced stage, interact. So, patients do worse the more they have that.

So here we see if a patient has a response to chemotherapy and then has immune recovery, we expect them to live much better, longer lives than if they do not have immune recovery. So, we can’t always predict. I mean, there are patients who come in who are HAART naive, and do not recover their CD4 count after chemotherapy, those patients are rare. But then they have ongoing advanced AIDS problems, such as CMV retinitis, et cetera.

This is another trial, this is from the UK, this is for someone who was from Italy, and this shows the expected survival in a patient who has good HIV parameters and good lymphoma parameters compared to patients that have poor parameters. So, clearly, a dramatic disparity between those two groups of patients.
So this is the five-day infusion for Diffuse Large B Cell Lymphoma. The baseline CD4 predictive of a poor outcome and in this patient population, you can see like an 85 percent cure rate. And this trial was first published by the NCI but has been replicated by the Aids Malignancy Consortium in a multicenter fashion.

This shows similarly that in this subtype of patients, the difference does not vary between patients that have HIV or no HIV.

One of the controversies has been whether to hold anti-retroviral therapy. The NIH is very dogmatic about this and they insist that all their patients stop HAART. What happens is a reproducible increase in the HIV viral load, which then comes back down after completion of therapy, and a decrease in the CD4 count, which takes about six to 12 months to recover. In data that we submitted from an AMC study, which is under publication review, we showed that the patients who were taking concurrent HAART not only had no worsening of their CD4 count, I can't show you the data yet because it's in review. But they actually had immune reconstitution immediately, even if they had some decrease, they had immune reconstitution and their CD4 counts were back to baseline by three months. Now, whether that really has an impact on overall survival from the tumor, a decrease in opportunistic infection, or any other salient feature is unknown because the study was too small to generate a difference.

So the most important advance in the treatment of C cell lymphomas was a drug that was directed against B cell lymphoma, which was an antibody that coats the cells and makes them chemotherapy-sensitive. Early studies suggested an increased risk, especially of patients who had a CD4 count less than 50. And this was replicated when the treatment was changed from the one day treatment to the five-day treatment. But then there was a conflicting study that actually showed possibly increased efficacy.

So, what we have done is created a second trial where all of these patients actually get prophylactic antibiotics if they have a CD4 count less than 100 and this is just recently enrolled, adding a chemotherapy sensitizer to the backbone of Rituximab-EPOCH, so I'll have to see what that data looks like in terms of infection. In the Phase I, we do not see excess toxicity. But the Phase II data will be more robust.

This is an example of things that we tried to do in the AMC, so it's a little bit of a complicated slide. But what this shows is that this is supposed to be HIV and these are host genes that develop into proteins that are integrated into the virus and prevent HIV replication. But the virus has another protein which then drags this complex into a degradation proteasome. And then the drug that we're giving for lymphoma, Bortezomib, actually restores this and so you get reintegration of the host antiviral protein.
So, while we're studying the drug in lymphoma, we're also studying to see if it has an effect on viral replication.

**[00:20:18]** What happens when patients relapse? So, unfortunately even with an 80 or 85 percent cure rate, you're going to have a relapse rate. And many centers have done studies to see if the standard of care, which was high dose chemotherapy, has an effect in those patients and was not too toxic. This is direct evidence that coming from the pre-HAART era, which was sort of a desperation time, like, why would you treat someone for cancer? Now we're offering patients intensive chemotherapy, typically five days in the hospital, 14 days of recovery before they can actually leave the hospital and be transfusion independent. Sometimes prolonged outpatient transfusions are required. And yet, we see that in patients who have relapsed or refractory lymphoma, even they are enjoying an 85 percent cure rate. Now this trial is very biased because of sort of the quality of the patients that gone on the study. We don't see rates as successful as that in the HIV negative population.

**[00:21:30]** They did do a comparison to their population of HIV positive and negative and there was no difference.

**[00:21:38]** And recently, the AIDS Malignancy Consortium partnered with the Bone Marrow Transplant Consortium and we published a paper. It just came out actually in Blood showing that patients could be treated in centers that were not experts in HIV care necessarily, but that they could receive standard chemotherapy for a transplant and have outcomes that were as good as the ones that were preliminarily shown in the City of Hope and in other centers.

**[00:22:12]** Now this is the gene therapy part and this is a very exciting, cutting edge type of thing. So here, these are patients who are actually getting lymphoma therapy and they relapsed and they're getting a stem cell transplant and we take out the CD34 cells and we add antivirus vectors to them. So, this is the first study looking at this. It was only done in four patients but the point was that it was doable, they didn't lose a lot of the stem cells and they were able to transduce the cells and show that there was antiviral transcript a year after the transplant. So, the AMC is partnered with University of Southern California at Davis, and we have an ongoing trial where patients can be referred to any of one of four California centers currently. And we have a new antiviral vector which has many advantages over the original one, including higher transduction rates and we're hoping to see basically if one's immune reconstitution occurs, can we withdraw HIV therapy and demonstrate that the patients will not have viral replication and essentially be cured of their HIV. In theory, if this works, you could envision treating HIV infection with autologous stem cell transplant and gene therapy.
This shows you that in some subtypes of lymphoma which are driven by viruses. In this one, human herpesvirus-8, if you direct therapy simply at the virus without any chemotherapy, you have complete resolution of the malignant fluid. And although this is the short-term follow-up in this paper, this patient never relapsed.

Similarly, in primary CNS lymphoma, I told you it's very rare, but there's no real clear treatment for those patients. Initially, patients received palliative radiation therapy with limited benefit.

And now there are many trials looking at new drugs but also some with experimental therapy with antivirals alone. Some of those trials showed some benefit and unfortunately, it's just hard to accrue those patients. So, they were terminated just for accrual, not for lack of efficacy.

What about Burkitt lymphoma? So, we published this comparison retrospectively, showing that patients treated in the pre-HAART era with non-intensive chemotherapy had a relatively low survival of 40 percent, which seems to be almost doubled in the antiviral era treated with this much more intensive regimen.

And that spear-headed a national study which I ran, showing that modifying this chemotherapy simply for tolerability seems to be safe and effective. You don't have relapses, really, after year one. So we have about a 75 percent cure rate and that is comparable to the HIV negative population studied in Europe in a multicenter trial.

Similarly, in plasmablastic lymphoma, we originally looked at retrospective data and we now have an ongoing prospective study. This rare and aggressive type of lymphoma was originally reported in the late 1990s as universally fatal. And we showed retrospectively that we had survivors irrespective of HIV status. This is actually the HIV negative one, it's not a statistical comparison, but this just shows that it's curative and we have data that should be coming out of a national study shortly. So, moving to, oh, I should just say one other thing. Which is that we're looking at this simpler regimen, it's continuing to enroll both HIV and HIV negative patients for Burkitt's and preliminarily, that data looks a little bit better than this and might end up supplanting our original program.

In Hodgkin lymphoma, the story's a little bit different because the risk of developing non-Hodgkin lymphoma, I told you, goes down as your CD4 count goes up. But mysteriously, there's this, believe it or not, this is actually a mathematical curve, if your CD4 count is very low, you're not likely to develop HIV-associated Hodgkin's. And this is sort of where the bulk of it is, and it may have to do with the fact that the immune system is actually necessary to support the Reed-Sternberg cell.
This is a study out of Europe demonstrating that there are significant characteristic differences between patients who have HIV Hodgkin or not in the general population. So for example, these symptoms are twice as common: anemia is twice as common, low albumin is twice as common, bone marrow involvement is 10 times more likely. And advanced stage is three times as likely. So, these things add up into something called the International Prognostic Index Score. Anyone who has a score of between three and seven has a marked decrease in anticipated survival. So you can see here that 70 percent of patients compared to 26 percent in the general population have high risk scores. Now, oddly enough, it turns out that they may be doing just as well with ABVD which is counterintuitive and we don’t know why because in a general population, this IPS score is very predictive.

And that I’m showing here, the overall survival, you know, probably similar, if not the same.

Similar to non-Hodgkin lymphoma, if you have a HAART response with antivirals at the completion of chemotherapy, you do much better than patients who do not take HAART. And this is something that oncologists tell their patients, they’re contracting to go on HAART therapy, even if they didn’t want to take it before.

So what are we doing to make this a little bit better? We have a drug that is FDA approved for relapse refractory Hodgkin lymphoma and it’s targeting an antibody that sticks to the cancer cell, is internalized, and brings very high levels of intracellular chemotherapy into the tumor.

And you can see here, this is called a waterfall plot. So this shows every single line as a patient, how much tumor reduction they had. All the yellow lines are FDG PET negative remission. So this is an astoundingly potent drug. And so, there’s an ongoing trial combining this drug with parts of the ABVD regimen, the AVD part, to see if it is better than the standard chemotherapy.

That trial is accruing, it mirrors the same trial that was done randomly in an international study, which excluded HIV patients. And this is a common problem if the patients are excluded, but there’s really very little rationale for them to be excluded, it’s in some ways, just a bias. So far, what we know is that the first six patients who were treated on the phase I dose are all in remission and they’ve had a follow-up already of two years.

So in summary, you may have unique presentations in terms of extranodal disease. HAART usually is given concurrently, except at the NIH. Immune status pre- and post-treatment are critical to both controlling opportunistic infections and most importantly, allowing the patients most likely to have
immune surveillance after their chemotherapy is completed so that they have the best chance for a good overall survival. Optimal regimens are under investigation and clinical trial participation is encouraged.

[00:31:33] I don't know if you wanna take any questions before I go to the NHL or do you wanna hold them? I mean for the Kaposi's Sarcoma.

- [Jessica] I think we'll hold them 'til the end.

- [Dr. Noy] Okay.

[00:31:44] In Kaposi's Sarcoma-- It is the most common AIDS-associated cancer still in the US, although the morbidity is very low because most patients have cutaneous disease that's easily controlled. It is an extremely common problem, especially in men who have sex with men in developed countries, but it is a huge, huge, huge problem in Sub-Saharan Africa. It is improving with HAART therapy. HHV-8, which is the synuclein virus that is required, is transmitted early in childhood using multiple routes, including premastication of food, which was demonstrated in an amazingly elegant epidemiologic study. So, one of the things that people have done in terms of global health is to try to get the mothers not to chew the baby food right before they give it to the children. And again, if we can control HIV, obviously.

[00:32:57] So the pathogenesis is that the very complicated, large virus has numerous oncogenes, and they affect things like inflammation, and they also carry growth factors, which specifically increase the cell's proliferation. And then affect things in the micro environment that allow the endothelial precursor cells to proliferate and recruit more vasculature into the area to allow for tumor formation. And lastly, the virus is very tricky, so it has anti-apoptosis, so prevention of programmed cell death and mechanisms of immune escape to the HHV-8 virus. So, it's really a tour de force of viral evolution.

[00:34:00] So, in the beginning stages, it may be driven by this one protein but then the excess of inflammation actually keeps adding to this and then, as I mentioned, a deficient immune response.

[00:34:18] The most common clinical presentation is in the skin. However, oral involvement is frequent and it can look just like advanced dark spots in the mouth. Patients will have a disease burden that can result in very painful lymphedema. They can have lymph node involvement so that it can be confused with lymphoma. And in the advanced stages, they can have gastrointestinal involvement which may be asymptomatic, pulmonary involvement, which usually is a trigger for symptoms, and then in other organs with the brain being rare.
[00:35:01] So this is a picture of you know a spectrum because this is not a life-threatening problem. It's certainly not something that people enjoy having on their skin. It has not only aesthetic problems with it, but can have social consequences, especially if someone has it on their face and if they aren't comfortable with their HIV status, this can be very difficult for someone to explain to a family member, or in the workplace, or whatever. So, Cutaneous KS, even though it is not life-threatening, has significant burden. This is the same process at a point where a patient developed lymphedema. And this is actually moderate. You could have patients who are unable to walk because they have such significant edema. They look like patients who have elephantiasis. And the disease is much easier to treat in this stage than it is when it develops into this stage.

[00:36:12] This is an example of pulmonary KS early, and then you can see here a very diffused pulmonary process. I've seen patients die of this, it is, they're suffocating to death so it is very significant.

[00:36:29] Similar to lymphoma, both the tumor stage and the immune status interact. Patients in the HAART era are mostly affected by the tumor stage and their symptoms because the immune system is well-controlled.

[00:36:47] This is an example of survival. These would be patients that have relatively low tumor burden and good HIV scores, and these would be patients that have advanced tumor scores and poor HIV parameters.

[00:37:04] So what would be the management of Kaposi's sarcoma? Right now, we do not have treatment that is actually directed against Kaposi's sarcoma virus, which is unfortunate because you would think if that is the kernel of the disease, the treatment directed against the virus is the most logical. It's just a difficult virus to target, although there are ongoing studies to look at some of that. Currently, the first line is to optimize HIV therapy and we and others in a study, they did, I don't know, like 18 years ago, demonstrated that you can control about one quarter of early KS by just giving HIV therapy. So there should not be a rush to treat oncologically. There are also some tried and true treatments for early relatively asymptomatic disease. Sometimes, this is the first treatment that was published without the interferon, but you can use topical retinoids, you can give radiation therapy, and there's almost always an ongoing trial of a more pathogenesis-directed therapy for patients who are interested in enrolling in a clinical trial. In the setting of advanced symptomatic visceral Kaposi's sarcoma, these are the mainstay of chemotherapy: this drug can be given, it’s liposomal doxorubicin, can be given for even years in patients getting a treatment, then taking a treatment break, and then retreating. So it is a very useful type of therapy. Paclitaxel, a little more complicated because you can develop an associated neuropathy. And again, we typically have at least one ongoing AIDS malignancy trial for investigational therapy for refractory disease.
The newest approaches would be trying to target KSHV itself. Again, difficult, because of the lack of existing antiviral drugs. The fact that the virus itself is latent, meaning that a lot of gene expression is going on in most of the tumor, it’s just sitting there and then can get activated. But there are attempts to either make the genes active and lyse the infected cells, or using antiviral products. We did do a study of Imatinib, which is a drug that targets a protein, called tyrosine-kinase, and that study showed about a 30 percent response rate. It was not meant as an FDA registration trial, but it is available to patients that have KS and this way they can take a pill instead of taking chemotherapy.

Looking at HPV: Anal and Cervical Cancer. So, similar to Kaposi's sarcoma, where a virus is absolutely necessary, this is human papillomavirus.

And what we see here is that there's a very similar program that occurs in the cervix, which is that cervical cancer is an age-defining cancer, again anal cancer is not. But here, the pre-malignant dysplasia turns into cervical cancer, and the hypothesis is that anal dysplasia turns into anal cancer.

So, why do we think that? Because the histology is very similar in the anal and cervical patients when you look at that microscopically. The cancer arises in what's called a transformation zone, which is where the external epithelium meets the internal epithelium. And that there's an ongoing long latency period between initial infection, pre-invasive lesions, and then the development of invasive cancer. And this suggests that patients who have increasing survival will also have an opportunity to develop invasive cancer.

So, what do we know further about this? That there are two high-risk subtypes, that they are frequently exposed or obtained early in sexual activity, and so that it's important to consider vaccination in, at most likely, pre-puberty or early puberty area, rather than wait for patients who now have HIV and probably have the high-risk serotype.

The virus similar to KSHV has specific oncoproteins, which increase the cells going into cycling and also decrease the ability to repair DNA damage. This is a synuclein of tumor development because then you continue to make additional oncogenic changes in the host cell.

HPV in women increase, you have like a disparity here because in the early parts of adulthood is where you have the highest prevalence of HPV, a high risk.
And then this an example showing the difference between the general population and HIV infection. A highest prevalence of actual cervical or anal cancer in men who have sex with men who are HIV infected and cervical cancer in HIV infected patients.

So what should we do? What we want to do is we want to increase immune surveillance to prevent progression to cancer. We want to get rid of the HPV infection, if possible, through vaccination. Although the vaccination studies originally were done in people who had no HIV. And if anything, if there's something that we can do here to take people who have persistent HPV with low-grade lesions and convert them into HPV negative.

This shows you that the lower your CD4 count, the more prevalent you are to have persistent HPV infection if you are female. So, these patients compared, for example, CD4 counts less than 200 compared to CD4 counts greater than 500 have a higher rate of HPV persistent infection in the anus, which is the yellow bar. And you can see much higher rates in the cervix.

The lower your CD4 count, the more likely it is—these are the low and these are the normal CD4 counts—the more likely it is prevalent that you will have abnormal cervical cytology and that is thought to be because of the persistent virus.

And this is relatively newer data showing that the same holds true in the anus. So if you think about this, we're looking at 75 percent of women who have a CD4 count less than 200 having an abnormal pap smear in the anus. It's a very simple test to do but many providers don't know about it and they don't do it.

And now why do we care? Because the hypothesis is that some time between anogenital infection, creating a low-grade lesion with further immune suppression and further genetic changes will become a high-grade lesion and this will develop anal cancer. The different between cervical cancer and anal cancer is that we do not know what the rates of this are and how long it takes. And that, I will show you, is important.

Cervical cancer mortality was never studied in a randomized trial. And what happened was pap smears were instituted in The UK and The US in the 50s, and the risk of developing invasive cervical cancer in both countries dropped dramatically. But if you look in Sub-Saharan Africa, cervical cancer that's invasive, or in India, cervical cancer is the number one cancer killer of women. So, the argument has been that we should develop anal cancer screening and the AIDS Malignancy Consortium has a very
large study now. I'm looking at that question, which is that when we note someone having high grade anal dysplasia, they are randomized to extremely close surveillance versus intervention.

[00:46:52] Why would you not intervene on all of these patients? The answer is that in cervical cancer, intervention is relatively simple. There are algorithms that are well known, depending on the type of lesion, repeat pap smears, colposcopy, and there's a vaccine that is being developed that is actually therapeutic with preliminary efficacy.

[00:47:22] However, in the anus it is not as simple. Yes, the pap smear is simple. Doing a high resolution anoscopy, with directed biopsy is simple. However, treatment is not.

[00:47:35] So, let me move on to this slide, showing that you would have to actually ablate anal tissue using either acetic acid, cryotherapy, laser therapy, cautery, or surgery. Now, I am not going to show you pictures, I have seen these pictures. This is not a pleasant therapy for patients and they have very, very severe pain and you can imagine that in the perioperative period, it is not easy to take care of bathroom needs. So, preventing anal cancer would be a lot better. If we know that we have to treat lesions and the question becomes: Is it justified to treat a high-grade lesion with laser to prevent invasive cancer? How many patients do we have to treat? What is the morbidity? And this large study hopefully will address that.

[00:48:35] Once the patient has invasive disease, these are things that can be done. Infrared coagulation is again, a relatively morbid procedure. There's some efficacy for antivirals or immune modulation.

[00:48:57] Okay, so what we don't know, is that once the disease is actually not just superficially invasive, but actually invasive in a way that requires resection, you're looking at a pretty morbid therapy. This is an A-P resection is anterior-posterior resection. You know, you're removing a lot of pelvic structures and you may need to have diversion, so this is not something that we want patients to have to go through. The AIDS Malignancy Consortium looks at standard chemoradiotherapy. They added a drug that is supposed to help in this setting, an anti EGFR receptor drug, and there was still a 20 percent recurrence, and notably, one fourth of the patients have grade 4 toxicity. So there is certainly room for improvement.

[00:49:57] I mentioned vaccination, so vaccination is to prevent infection. And also, to reduce the risk of persistence. So, for example, the incident infection rate, the efficacy against HPV-16 and 18, 97 percent effective. They saw no evidence of early invasive lesions if the patients were vaccinated prior to sexual exposure.
This shows similar data in HIV negative men with the anal intraepithelial neoplasia as the end point. You can see here the vaccine is better than placebo in preventing anal intraepithelial neoplasia.

And then, just touching on non-AIDS cancers. So I periodically get these kinds of phone calls, saying, "Oh, I'm treating someone with HIV. What am I supposed to do?" Because people are not educated about this, even in the oncology community. And we look to see, this was a study that we did looking at eight years of non-AIDS defining cancer at MSK, and there were 400 patients. So in a typical year, we expect a small number of patients in solid tumor clinics to have any one of these cancers. Overall, about 40 to 50 new non-AIDS defining cancers per year. And again, it's important because we think that if you treat the HAART, they'll have benefits. It's also good to know that someone may have a lower CD4 count because chemotherapy drugs can make that worse and you don't want somebody to die of a MAC infection while you're treating their cancer. That will serve no purpose.

And lung cancer demands a little bit of a comment because the HIV population for socioeconomic reasons, has at least twice the smoking prevalence that the general population does. So, we need to have awareness in primary care to advise patients who are HIV positive that they are increasing their risk of cancer-related death, not just due to HIV-related problems, but due to smoking and we have a preliminary study looking at a test that shows the patient. Physiologically, you may be 50, but your lungs are 75. And that is to try to get them to go to a quit smoking program.

And then lastly, hepatocellular cancer.

So HIV exasperates the risk of developing hepatocellular cancer that is related to hepatitis B and hepatitis C. And it is a large public health problem in endemic areas. We are not sure but we think that HIV may actually increase the stage of disease. Stage being defined as resectable at diagnosis, or unresectable. And this may have a significant impact. Unfortunately, but most important, talking about a cellular carcinoma, which is sorafenib, another tyrosine kinase inhibitor, was not actually tested in people who have HIV. So, we are in the process of developing a sorafenib program in Sub-Saharan Africa and in The United States. If you have a disease that is not resectable, and you don't have an option to be on this drug, chemotherapy has extremely poor outcome.

So, I'm gonna leave, looks like I have three and a half minutes for questions! These are the people that I primarily work with in the AIDS Malignancy Consortium or have worked with them in the past, and I'm giving special thanks to these people, especially Susan Krown who mentored me in the early parts of my faculty development.
[00:54:48] - [Jessica] I don't believe anybody has any questions. If you do, please chat them in now and let us know to unmute your line. Unfortunately, we had a lot of unmuted lines and there was quite a bit of background noise. But Dr. Noy, thank you so much. That was a fantastic presentation, and we really appreciate your time.

- [Dr. Noy] Thank you so much!

- [Jessica] Yeah! And I wanna thank our funder again, The New York State Department of Health AIDS Institute Clinical Education Initiative. As a reminder to everybody on the line, you will receive an email with instructions on how to evaluate today's presentation and claim your CME or CNE credit. And next month, This Month In HIV Webinar will be on February 15th with Dr. Meagan O'brien, Preventing Cardiovascular Complications Seen In Patients with HIV. Alright, so thank you again, Dr. Noy, and thank you everybody for joining us, and we hope you'll join us next month.

- [Dr. Noy] Have a great day, bye!

- [Jessica] All right, you too, bye!

[Video End]