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HIV in Women Throughout the Lifespan Kaiser Family Foundation July 26, 2012

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BEATRIZ GRINSZTEJN: My name is Beatriz Grinsztejn; I am a clinical investigator from Rio de Janeiro, Brazil, having been working with HIV and AIDS for more than 20 years now, and have always had a special focus on HIV and women issues. I want very much to welcome you to this great session in which we will talk about different aspects of the struggles of women living with HIV/AIDS. We have really wonderful speakers with us today. I want to pass now to my co-chair, Dr. Sharon Hillier.

SHARON HILLIER: Thanks, and welcome to all of you and thanks for joining us today towards the end of what's been an exciting meeting. We do have a wonderful opportunity to think about the breadth of issues facing women. We'll have four presentations, and then we've allowed time at the end to have a discussion so the other speakers will join us at the front at the conclusion of the talk.

What we'd like to do today is introduce our first speaker who is Dr. Linda-Gail Bekker. Linda-Gail, I think everyone who works in women's health or who works in HIV knows Linda-Gail very well. She's a tireless advocate for both treatment and prevention. She works with the HPTN, the Microbicide Trials Network, with the Adolescent Trials Network.

I hear her described as a behavioral researcher, as a biomedical researcher, as a clinical trialist, as an advocate

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for women and adolescents, which I think makes her the perfect person inasmuch as she really makes everyone feel that she is engaged in all aspects of this work. So it's a great pleasure to introduce Dr. Bekker who comes to us from the University of Cape Town, and who will be sharing with us her perspectives on adolescents, women and HIV.

LINDA-GAIL BEKKER: Thank you very much Sharon and Beatriz. I'm delighted that we kick off this great session with adolescent woman. Thank you for the introduction. I was just thinking, I think I'd describe myself as a Jane of all trades going forward, but yes, starting with adolescent girls and HIV.

Today's generation of young people is the largest in human history. There are almost 2 billion people between the ages of 10 and 24, which makes up a quarter of the world, a third of Africa and about 31-percent of South Africa's population. So what is an adolescent and why are they different? Well, we can think about them in terms of their age, obviously, the enormous physical differences that are occurring at this time, the psycho-social transition that is happening and, of course, the cognitive impact.

So, WHO, who really influences a lot in the region where I come from, think of this as an age group of 11 to 19. There is, as you know, enormous hormonal changes going on at the time of puberty. In fact, estrogen levels increase eight-

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fold during puberty in young women. This leads to physiological changes which we describe as the tenor stages that happen over this period.

Any of you who are bringing children through this period of adolescence will know that the adolescent brain is a work in progress, and sometimes a terrain that we, as adults, perhaps have forgotten to understand. So if we divide up this age group, pre-adolescence to early adolescence - 10 to 13 years - there are bodily changes, preoccupation with self-image and normality, same sex peer group pressures, high levels of mood swings and concrete - we think of adolescents in this age group as being concrete thinkers.

Middle adolescence is a time for asserting independence; again, a physical concern, increased risk taking and sexual experimentation at this time, and the formation of a more operational way of thinking.

Late adolescence now, the 17 to 20 year olds, there are major concerns about career now, thinking into the future, lifestyle relationships, a degree of independence is established and more realistic body image and sexual identification is established.

As we think about all of that background and the impact of HIV infection, we also need to recognize that today's youth actually haven't known a world without AIDS. Half of all new infections, we're told by UNAIDS, occur in the 10 to 24 year

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old age group, and there are upwards of 10 million youth living with HIV now - two-thirds of them occurring in the region from where I come. And, in fact, we have now come to notice or to recognize that perinatal infected children are growing up into adolescence - those long-term survivors - and definitely now increasing the population of adolescents who are living with HIV.

This paper, written by authors in South Africa, looking at the effect of early initiation of anti-retroviral treatment in infants concluded by saying, "The changes in our guidelines for infants will have a significant impact on pediatric AIDS mortality, but further efforts are required to reduce the substantial growing AIDS mortality in older children." This really, is our challenge. We know that this predominantly falls in young women in terms of the epidemiology.

This is South Africa's burden. Many of you will have seen the pitiful data from 2004; extraordinary numbers of young women becoming infected with HIV. On your far left, these are surveys that we've carried out in Cape Town, and you can see there an awesome 10.6-percent mean prevalence in young women in one particular township. So there's no doubt, and this is not the subject of this afternoon's talk, but we do need to think about our prevention package for this age group.

We now sit with more than 50-percent of the world's infected population being women and girls. What we've noticed

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in South Africa over time is that there's an increasing age group of perinatally infected children growing up, becoming adolescent, and a younger age group of adolescents requiring anti-retrovirals filling out this group of adolescents. So in South Africa there is a, I think, conservative estimate of 14,000 adolescents on ART, a projected 106,000 requiring ART, and you can see this is making up a significant number of the people requiring anti-retrovirals.

In my adolescent clinic I see both perinatally infected youth and sexually infected youth, and they have different requirements, so equal ratio of males to females in perinatal, tending to be younger, physically tending to be underdeveloped, more treatment experienced, often not disclosed to, and transitioning from pediatric care.

The sexually infected youth are often referred to us from antenatal care clinics; females outnumbering males, older, treatment naive in many instances, aware of their status, precocious in their outlook and in their behavior and transitioning instead into adult care. So it's really a very different environment that we find ourselves.

The first challenge is that of testing and linkage. It certainly has been shown in numerous studies around the world that uptake of HIV counseling and testing is low in adolescents. The subsequent linking into care is poor, and often perinatally youth are going undiagnosed presenting

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severely immune suppressed. Once diagnosed, few engage with the health care system.

We have looked at data from a township in Cape Town where we noticed that very few of what we expected to be on anti-retroviral in the adolescent population had actually got on to anti-retroviral. I think this speaks to our reluctance to test this age group, so we as providers, actually need to change our paradigm and really actively seek out youth who need to be tested.

Of course, then linking into care is very important, and there are numerous programs that have been thought about. I just put this one out that we've been working on in Cape Town which is called Schlaganine [misspelled?] and its group intervention to engage newly diagnosed youth. It's lay-facilitator lead; it's modular and really enables young people to come to terms with their disease, think about where they are and then link safely into care.

What about living with HIV? There are specific complexities for specifically perinatally infected youth. Body image, they've lived with their disease for a long time, they may have delayed puberty and they may have already experienced a lot of side effects. Intellectual delay has been described; knowledge of their mothers' infection, leading to all kinds of socio-psychological difficulties, lack of support structure and, of course, orphaning being a very important factor.

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In terms of generally living with HIV, we find a high level of denial of disease, enormous amounts of depression - often undiagnosed - uncertainty about futures, of preoccupation with death and a lack of understanding of disease, with a huge amount of nihilism in the population.

Again, we know this is a time of rule-breaking, and it also occurs in the patients we find in our clinics: risk taking behavior with a sense of invincibility, a sense of outliving the disease regardless, and then, of course, the impact of peer pressure and social norms. With HIV being highly stigmatizing, clearly not cool to take medicines that separate one from one's peers.

The HIV clinic really needs to supply support, support and more support. Patients need to be screened for other infections, to have regular CD-4 counts; I can't emphasize enough how important. We have a lifetime of anti-retrovirals for these patients, and we need to be sure that we preserve treatment options. Mental health screens, STI screening, and then, of course for these young women, family planning and good counseling around safer sex, reproductive intent, nutrition and healthy lifestyles. Importantly, we should provide this as a one-stop shop so that these young women can get their services where they need.

As we think about anti-retrovirals, when do we need to start, particularly in the treatment naïve? We tend to use, as

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per WHO guidelines, adult start criteria - particularly for the post-pubertal. We may use pediatric guidelines for the pre-pubertal adolescent, and CD-4 normal ranges are similar to what we find in adults. Dosing is based on the ton of scores.

Outcomes on anti-retroviral programs: Looking back, this has been somewhat dismal, showing poor retention and poor adherence to treatment. In a sub Saharan Africa study, adolescents were 1.5 times less likely to be viral-logically suppressed at one year.

When we've looked in our own programs, and this is a large clinic in Gugulatou [misspelled?], you can see the green line in terms of survival compared to the blue line which is pediatric and the red line which is adult. The adolescents are surviving, more or less, at the rate that adults are, but when you look at the retention and care, the adolescents are definitely doing less well than the other two groups.

Following on this data, we decided to put an adolescent clinic together at Hannan Crusaid, and so now we have an adolescent specific anti-retroviral clinic. We went back after one year to see what was happening there, and you see similar rates of mortality and loss to follow up in adolescents and adults.

However, poorer rates of viral-logical suppression and higher rates of viral-logical failure in adolescents compared to adults; however, again, speaking to their youthful immune

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systems, more robust CD-4 responses. We think the poorer viral-logical outcomes may be due to behavioral or biological factors, although we couldn't tell that from this retrospective look. You see here the adjusted hazard ratio for viral-logical failure in adolescents versus adults.

So what do we start with? The guidelines are always written for adults and adolescents. Again, three drugs are a minimum. Perinatally infected adolescents may be very treatment experienced already, and of course, in low income settings this poses an enormous challenge. RTIs or PI based regimens are up for use, and we tend to avoid [inaudible] in girls where reproductive intent may be an important concept.

Rapid initiation in pregnancy and advanced HIV is obviously advised. One group that should have genotyping and frequent monitoring of viral load and CD-4 is this group. I would really advocate that we need to step out of the adult paradigm for adolescents and really [inaudible] for more monitoring of this population.

So what anti-retrovirals? Well again, one can look in your guidelines for guidance on this, but we want to avoid lipodystrophic and lipohydrophobic drugs if at all possible and really simplify regimens that make it easy to adhere to. In the interest of time, I'm going to move on and just remind you that the challenges of adherence come because of the denial and fear of HIV infection, misinformation, distrust of the medical

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establishment, fear and lack of belief, low self-esteem, chaotic lifestyle, lack of support and unavailable or inconsistent access to care.

What makes things better? It's really the opposite of all of those: understanding the importance of adherence, belief, feeling comfortable and keeping clinic appointments as well as managing side effects.

What do we know causes suboptimal adherence? Regimen complexity, active drug use or alcoholism, mental illness - very important that we actively diagnose and deal with mental illness - and you see the other predictors there.

How can we improve adherence? Peer support and a caring team, again, cannot be emphasized enough. The kids that come, the adolescents that come to our unit, love the nurses that care of them, and it's very important one establishes those relationships. Manage side effects, educate, honesty - the BS there is bullshit. Adolescents don't manage well with dishonesty and so it's very important that we do this.

I'm going to end with a few quotes from adolescents. I also want to emphasize sexual and reproductive services, contraceptive choices, discussion about reproductive intent, couples counseling if possible, counseling and management of safer conception and treatment adjustments for pregnancy.

We asked adolescents what they thought, and here are a few quotes: "You must take your medication; when you drink your

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medication it will help the soldiers of your body." "The medication makes your soldiers, strengthens your immune system, but if don't eat them your immune system can die and you go to stage four."

On being a teenager: "You see when the schools are open I take them correctly, but when their closed I tend to forget. Maybe I oversleep. Who doesn't know a teenager who won't do that, so I miss taking pills?" "I get angry and sometimes I refuse to take the pills. The others in the house are not drinking pills. I'm the only one who's drinking pills, and sometimes I cannot eat. I need to wait for some hours."

We need to remember that an adolescent occurs within the adolescent context. Perinatal infected adolescents need to be disclosed to. They may have treatment burnout, loss and bereavement. Parent peers: the etiology of HIV is important that we describe it to them and they understand it, and that complicated emotions are dealt with.

Disclosure is very important to adolescents so that they can deal with their infection and move forward. I just want to remind you that psychiatric prevalence is high, and affected youth with rates similar to that we see in HIV infected youth. Increased psychiatric hospitalization, and you see the list of common diagnoses that need to be dealt with. In terms of treatment, it may need pharmacological treatment, but therapy should also be considered under these

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circumstances. It's very important that we think of the transition from pediatric into adult care.

An ideal adolescent clinic has an infrastructure that may be separate or it may occur within an adult system, but it needs to be consciously devised for adolescent care. My preference is that of a one stop shop where all of these attributes are present. That is, adolescent friendly, nonjudgmental, and we have such a place and I invite you to follow us on Facebook and see a youth clinic in operation in Cape Town.

Finally, this can result in hope for the future. Again, some quotes from adolescents: "I will finish school, I'll take my medication, I want to marry and have children." That's the difference that can come with this. I want to pay tribute to a wonderful group of young people who help us do this right called the Future Fighters, and to a number of people who helped me put this talk together. Thank you very much. [Applause].

SHARON HILLIER: I think she just set a new world record for a number of slides in 16 minutes. [Laughter]. So in addition to being a Jane of all trades, you're a superwoman in terms of your speed. Our next presentation we're very pleased to invite Elizabeth Stringer. I've known Elizabeth for many years. She's been a tireless advocate for women's health as an obstetrician/gynecologist, who has spent much of her

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career in Zambia - in Lusaka, Zambia - where she's done some of the most seminal work on the effect of contraceptives on HIV progression. She's also done a lot of work locally within Zambia on HIV screening and really expanding the cervical cancer screening programs in Zambia. She's now at the University of North Carolina in Chapel Hill. We're very pleased to hear from Elizabeth on cancer, HIV and women. Thank you.

ELIZABETH STRINGER: Thank you Sharon. Good afternoon. I've been asked to speak about women, HIV and cancer. At first glance this seems like a really big topic, but if you drill down, the only cancers of which women who are HIV infected are at risk of acquiring are those related to HPV. This includes cervical cancer, vaginal cancer and vulvar cancer. For the next 15 minutes I'll talk primarily about cervical cancer because that one is the most important one and the one that is most extensively studied.

This slide is from the Interagency Research on Cancer. The red represents incident, and the blue is mortality. You can see that breast cancer is the number one cancer in women world wide, although it's not related to HIV so I'm not going to discuss that so much today. If you look at cervical cancer, you can see that the mortality in cervical cancer in less developed regions approximates that of breast cancer. In some countries it's even higher.

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There's a huge discrepancy between cervical cancer in more developed regions and less developed regions, both for incidents and mortality, and this is primarily linked to cervical cancer screening programs. Gakido [misspelled?] and Colleagues looked at the coverage of cervical cancer screening world wide in 57 countries, they analyzed household surveys as part of the world health surveys.

Women were asked if they had ever had a pelvic exam, and they were categorized as having crude coverage, which is in the blue. Women were also asked if they had ever had a pelvic exam and a pap in the past three years, and if they had that it was considered effective coverage, which is in the green. You can see if you look at the left hand part of the slide, that women in the poorest countries have much lower levels of coverage of cervical cancer screening, which is not surprising.

The culprit for cervical cancer infection is the human papilloma virus. In the 1970s zur Housen prostrated a role for HPV in cervical cancer. In the '80s he cloned subtype 16 and 18, and was awarded the Nobel Prize in physiology or medicine in 2008. This cartoon is a review from *Nature Medicine* and it shows the progression of cervical disease from an initial state of normal epithelium on left - that's the squamous epithelium of the cervix - and through stages of inter-epithelial Neoplasia, and then ultimately cervical cancer.

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HPV is a causative agent. In most women, an infection with HPV is cleared quickly, but in women who have risk factors such as smokers or women who are immunocompromised, HPV can persist and lead to a dysplasia over a period of years. A pap test is a screening test where the cervix is scraped and then the epithelium is looked for dysplasia under the microscope.

There are other low-cost methods such as VIA, or visual inspection of the cervix with acetic acid - I'll speak about that a little bit more in a minute - and then an HPV test is a molecular test that looks for oncogenic strains of HPV in a sample taken from the cervix or the vagina.

There are over 100 HPV subtypes, but only about 14 are known to cause cervical cancer. Smith and Colleagues performed a Meta analysis that included over 14,000 from all over the world who had undergone HPV testing and they looked at correlates with cervical cancer. They found that, by far, the most common cancer associated HPV types were HPV 16 and HPV 18. These account for approximately 70-percent of all cervical cancers. Interestingly, and contrary to some suspicion, the distribution of these subtypes did not differ substantially between Africa and other parts of the world.

So what is the unique relationship between HPV and HIV co-infection? Soon and Wright [misspelled?] described some of these differences by looking at HIV positive and HIV negative women. HIV infected women were more likely to have prevalent

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HPV. They were more likely to be co-infected with multiple HPV subtypes, they were less likely to have spontaneous regression of the HPV infection and they also had a higher rate of recurrence or persistence after treatment.

In some settings, it has not been possible to perform pap smears because of logistics. This slide shows visual inspection with acetic acid. On the left part of the slide you see the cervix before application of the acetic acid, and on the right is the cervix after application of the acetic acid or vinegar, showing white lesions which are the areas that are most concerning.

Three studies in Kenya, India and Nigeria have looked at the performance of Pap smear and visual inspection with acetic acid among HIV positive women. You can see in this slide the VIA has a comparable, if not better, sensitivity as the Pap smear.

Our group in Zambia in 2005 looked at 150 HIV infected women presenting to the ART clinic; all women had a CD-4 of less than 200 cells and they underwent a pap smear. If you look at this slide, you can see that almost 33-percent of the women had a high grade lesion, and 20-percent of the women had cancer. So 50-percent of the women had a high grade lesion or cancer. Only seven percent of the women had a normal pap smear.

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This is one of the reasons that members of our team - including Dr. Parham and Dr. Monahanmuntu [misspelled?] helped start the Zambian Cervical Cancer Prevention Program. It was established in 2006 as a collaboration between academic, research and public sector. It's a nurse led cancer screening program using VIA and digital cervicography, which is taking a picture of the cervix with a camera and then blowing it up on a computer screen. The approach is see and treat using cryotherapy; so women who have mild to moderate lesions are treated then and there at the clinic, and they also establish a referral system for high grade pre-cancer and invasive cancer lesions.

This is a picture of Dr. Parham showing one of the nurse's VIA, and here is a nurse performing cryotherapy in one of the clinics. This takes about 10 to 15 minutes. Here we see the cumulative enrollment of women in the Zambian Cervical Screening Program between 2006 and 2010. Over 50,000 women have been screened for cervical cancer, and since 2010 thousands of more women have been screened.

Around the same time that Zambia was developing their Cervical Cancer Screening Program, Denning, Soon and Wright [misspelled?] performed a randomized control trial looking at screen and treat approaches for cervical cancer prevention in low resource settings. They randomized over 6,000 women to either HPV screening or VIA screening.

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There was a second randomization to either immediate colposcopy after a positive HPV test, immediate colposcopy after an abnormal VIA or delayed intervention. The outcomes were biopsy determined, CIN-2, or moderate dysplasia at six and twelve months. This slide shows the results at six months from HPV testing, and in the VIA group, and you can see that both detected more cases of CIN-2 than the delayed evaluation group.

In a sub-analysis of 956 HIV positive women, Hoon and Colleagues looked at the performance of the HPV and VIA and the sensitivity and specificity. HPV was 95-percent sensitive compared to VIA which was 64-percent sensitive, although HPV had a lower specificity at 65-percent.

These investigators took HPV screening to a new level in rural India. Their objective was to measure the effect of a single round of screening by HPV, cytology or VIA on the incidents of cervical cancer. It was a very large cluster randomized trial with over 130,000 women in 52 clusters in rural India.

The primary outcomes were cervical cancer incidents, cervical cancer death and the secondary outcomes were cervical cancer stage distribution and survival and case fatality rates. These are the primary results of this study which showed that women who were randomized to the HPV testing arm had a 50-

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percent reduced hazard of a stage two or higher cancer as well as a 50-percent reduction in death.

The ACTG-5282 study is taking an interesting look at prophylactic cryotherapy in HIV infected women. This study is currently enrolling and women who are HIV infected and greater or equal to 18 years are eligible. They undergo VIA; if they have no lesions on VIA then an HPV DNA test is taken. If the woman has a high risk type of HPV, she is randomized to either Arm A - immediate cryotherapy - or Arm B - which is a cytology based strategy.

Women in the cytology based strategy then undergo a polposcopy and biopsy and further treatment if needed. Both Arm A and B have polposcopies with biopsies at weeks 26, 78 and 130. They all come as CIM-2 and we're really looking forward to the results of this trial.

I can't really talk about cervical cancer without talking about HPV vaccines. They are two licensed prophylactic vaccines; they're a virus-like particle technology. One of them is called Cervarix which is for HPV 16 and 18, and the other one is Gardasil. They have excellent safety tolerability and immunogenicity, and there is high efficacy for prevention of high grade pre-cancers caused by vaccine related HPV types.

Campus and Colleagues look at the reduction in lifetime risk of cervical cancer with different strategies. They looked at women over the age of 30 as well as pre-adolescent girls.

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On the X-axis you can see VIA, HPV, a number of different tests for HPV as well as the vaccine. In women over the age of 30, they determined that three HPV screenings in their lifetime could potentially reduce their risk of cancer by 30 to 40-percent. In pre-adolescent girls, the vaccine and one HPV screening has the potential to reduce their lifetime risk of cancer by 50-percent.

I'm only going to briefly talk about vulvar cancer. There's very little data reported worldwide. It is a problem that we see. It's caused by HPV. It's preventable if pre-cancerous lesions are recognized, and vulvar cancer progresses in much the same way that cervical cancer does. It's treatable with early diagnosis, but it requires special surgical training to take care of these lesions.

So what are the components - I've talked about a lot of different things, and what are the components of a successful cervical cancer eradication program? I haven't discussed community awareness, but this is a really key component to eradicating cervical cancer. Women need to know the importance of screening and the frequency and they need to come to the clinic. There needs to be primary prevention with HPV vaccine. You need to have a screening program that can reach a lot of women and treat women when they're at the clinic.

The treatment needs to be available for both low and high grade lesions. Women need to be able to access treatment

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for early cancers, which is access to hysterectomies, and treatment for moderate cancers, which is extended hysterectomies or a radical hysterectomy. This specialized surgery needs a lot more training in low resource areas. Women also need access to radiation and chemotherapy for treatment of advanced cancers.

I'd like to acknowledge the Citer Cervical Cancer Team [misspelled?], particularly Dr. Groesbeck Parham and Dr. Melinda Monahan Muntu, Dr. Carlo Cheboycha [misspelled?] and the CDC who's been helping fund the cervical cancer program in Zambia. If it hadn't been for Marco Terrace [misspelled?] many years ago when he first gave that money, I'm not sure it would be what it is today.

In conclusion, just as we used early PMTCD infrastructure to build HIV care and treatment services for women, we now have the opportunity to extend cervical cancer screening as well. Service integration and a holistic approach is the future of HIV care and treatment. In resource limited settings, cervical cancer control should be a central component of our efforts. Thank you very much. [Applause].

BEATRIZ GRINSZTEJN: It's my great pleasure now invite Dr. Kathy Anastos to do the next talk. Dr. Anastos is from the Albert Einstein College of Medicine. She has been a great leader on HIV research in women's health in the United States.

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She is also doing seminar work in Rwanda. Dr. Anastos will present us on the aspects related to aging in women with HIV.

KATHRYN ANASTOS: Thank you very much. Let me thank the conference organizers both for having this session and for inviting me to speak. Just to give us perspective, this graph shows the projection of the proportion of people with HIV infection who will be over the age of 50 by the year 2017. This is applicable both to women and men; this is in the United States.

However, we need to recognize that when we talk about aging in HIV women, or in effect when we talk about anything in HIV infected women, that the greatest burden of disease, overwhelmingly, is carried in communities of African descent. African women represent 85-percent of the women living with HIV today. That will be true going into the future as we age.

We're going to have a very brief foray into talking about aging and HIV infected women, and I'm primarily focusing on the biologic- what we understand and what we don't understand. We'll talk a little bit about menopause as an inflammatory state. Menopause is a threshold event in aging for women, and until the last decade was extremely poorly studied.

In some areas it remains very poorly studied. For example, the mucosal immunology or any immunology of the genital tract; and I'm not going to touch on that. We will

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touch on three clinical conditions that are felt to be inflammation related; cardiovascular disease, bone disease and neurocognition; each of these is known to have sex differences. Then in very broad terms we'll discuss the research agenda going forward.

Because most of the data I'm going to show is from WIHS, I just want to briefly describe it. WIHS has six sites clinically across the country plus a data center here in Baltimore and will soon add a southern site to represent the evolution of the HIV epidemic in the United States.

WIHS enrolled twice and is currently enrolling again. This is the cohort as of the end of 2011 when 3,800 women were enrolled, of whom, 74-percent were HIV positive and 26-percent were HIV negative. I want to stress that this HIV negative comparison is extremely important. We don't know if something is caused by HIV or whether it's caused by normal aging if we can't compare it HIV negative women.

WIHS enrolled in '94-'95; the women were approximately 35 years old, so those women are now 18 years older than that on average, and the second cohort was slightly younger and they are about 10 years older. I will not present demographic characteristics again, but all my studies I show will be drawn from this population.

We know that menopause causes increased levels of pro-inflammatory site at times. This actually happens in men also,

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but in men it's a linear increase, where as in women there's a bump that occurs right at menopause. We also operate with a paradigm that HIV causes high levels of these same inflammatory cytokines. However, most of that data is in men, not in women.

I want to draw your attention to this study in WIHS that had this finding that IL-6, after being treated with heart, falls in men but does not show a change in women. So IL-6 is shown here along the bottom, the men are in the middle column, the women are on the right. What you really see is that IL-6 wasn't high in the women to begin with. It is not a marker that goes up in HIV infected women; at least not in women in the WIHS.

Here I'm showing you other markers of inflammation that are felt to be particularly important in cardiovascular disease. This is all women, and it's the HIV positive women compared to uninfected women. You can see that several markers of either inflammation or clotting - the clotting parameters - are higher. Some get better with treatment and TNF alpha stays high throughout. However, let me give you a little more data.

This is from the cardiovascular disease investigations within WIHS that are led by Robert Kaplan who kindly shared all his slides. I'm going to show you TNF alpha over time. This is a study that is centered on heart initiation and then looked at specimens going backwards and specimens going forward to see

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what happened to inflammatory markers in these 120 HIV negative women and 120 HIV positive women.

What you can see is that, indeed, TNF alpha here three visits prior to heart initiation - this is the uninfected women here - the TNF alpha is quite a bit higher in the HIV positive women. After heart initiation it declines, but it does not go back down to the same level as the HIV negative women; it remains significantly elevated.

WIHS also conducts studies that are more clinically focused. This is actually a very large study that's, again, in WIHS and Max - Max is a cohort of men - that looks at carotid ultrasound over time. This is an ultrasound probe measuring right before the bifurcation of the carotid artery. It's measured over four visits, and soon we will have very good data to help us understand what happens at least in the carotid arteries over time in HIV infected women.

The cross-sectional data, both in women and in men, indicates that with lower CD-4 counts there is a rising rate of carotid lesions. This is lesions in the carotid artery, and it is independent of HIV therapy; so it is correlated with CD-4 count, not with whether or not the person is being treated. It is similar in women and men.

Finally in cardiovascular disease, let me just say something about lipids - HDL cholesterol and LDL cholesterol - because this is frequently talked about as if - LDL cholesterol

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goes up in everybody who takes PIs. It goes up to higher than our levels would be if we were not HIV infected. In fact, what this shows from WIHS data, which again is longitudinal data, is that the LDL is lower in women when they are untreated.

When they become treated the LDL rises back to the level of the HIV negative women. Also of note, is how high the HDLs are. These are very high HDLs. That's in part because WIHS women are mostly of African descent, and people of African descent have higher HDLs. Therefore, looking at HDL in women compared to men is highly confounded by ancestry.

Let's move on to bone disease. Bone disease is also felt to be mediated by inflammation. Why do we care about bone density, the things we measure? Because they're a marker for fracture risk. Bone strength is, in fact, fairly complex, and related to this list of physiologic events that occur.

The evolution of our bone mass in everybody is that in general we peak at around the age of 20; that men peak at a higher rate than women - this is felt to be testosterone mediated - and that starting in our mid-30s our bone mass starts to decline. Women always have a lower bone mass than men on average, and there's this more precipitous decline right here which is menopause.

So hypothetically, what happens in HIV infection is that at the point of HIV infection there's some more rapid decline, but relatively mild. That at the point of ART

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initiation there's a little dip again, and that then in men there's a steady decline and in women there would be again this decline here. This is, in fact though, hypothetical.

We know that in post-menopausal women the cortical thickness is thinner - you can see how much thinner that is than it is right here - but, in fact, when we look at fractures there's a difference between women and men even though these look the same. This is fractures in HIV positive women and in HIV negative women; and then fractures in HIV positive men and HIV negative men. What I want you to notice is that the relative increase of the fracture rate in women is higher - that's an underlying fact among all populations - but that the percent increase is really well under a doubling rate. It's probably about 50 to 60-percent, whereas in men it's a tripling.

This I really think may be a sex difference. You see it again here; that here in the Hobbs Cohort which is predominantly men, there's more than a doubling, whereas in WIHS it's about a 20-percent increase in the fracture rate which even with a relatively large sample size was not statistically significant.

Bone metabolism is very complex and here in HIV we talk about the virus, the host and the therapy, but I want to focus just for a second on this hypogonadism. In fact, even though women in general have lower bone mass, men have greater

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hypogonad as a result of HIV infection, and it is their testosterone that is protecting their bones so that the hypogonadism in HIV infected men may really be putting them at greater risk of bone disease than is occurring in women.

Finally, let me address neurocognitive function. The Y studies in neurocognitive function are led by Pauline Mackey. We're relatively early in these studies, but I want to show you the data that we do have. These are cross-sectional findings and I'll address three questions: do HIV infected women have greater risk for menopausal symptoms, does menopausal stage influence depressive symptoms in HIV infected women and do menopausal symptoms influence cognitive functioning.

This shows the symptom domains of menopause: mood, sleep, vasomotor, somatic and vaginal, and you can see that, as expected, early in perimenopausal are more likely to be symptomatic. The only symptom that was HIV related was night sweats.

With depressive symptoms there was an interaction of HIV infection with depression so that depressive symptoms were increased in the early menopause in HIV infected women who were not treated, but not among women who were well treated.

There was also an interaction between symptoms and learning. In fact, a decline in cognitive function with aging is one of the most frightening aspects of aging. We found that women with more anxiety related symptoms during the

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perimenopause were also more likely to have poorer learning. This learning was measured as a verbal acquisition skill.

As we go forward and want to study HIV infection in women, one of our difficulties is actually that we can't define menopause very well. We define it retrospectively after there's been 12 months of missed menses. In fact, we know that HIV infected women miss menses more frequently even when they are not actually post menopausal as measured by FSH.

There is a new test that we might have soon. We used this in WIHS; this work is led by Ruth Greenblatt. It's anti-malarian hormone which is a growth factor that is made in the ovarian granulosa cells of the primary follicles. It is indicative of the primary follicle pool, so as we lose our primary follicles, that's essentially when we go through menopause. This, therefore, might be a measure.

I want to show you one, what I think, is a tantalizing, slide, although you might think I need to get a life if this is tantalizes me [laughter]. This is HIV positive women on the left, HIV negative women on the right, stratified by CD-4 count above or below 500.

First notice that there's really not much difference between the positive and negative women, but that women with lower CD-4 counts have a lower AMH, even in their younger years, and that is true even in the HIV negative women. It may

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be that this is giving us some clue as to the function of the CD-4 cells during normal aging.

In summary, let me just say that studying men does not inform us adequately about disease in women. This is the X and the Y chromosome. I would have thought there were more differences between these chromosomes than their shape. This difference in chromosomes defines a vast array of physiologic differences. There are sex steroid receptors in every single cell of the body. Many cells have many different kinds of receptors, and therefore men are not just like women except have additional appendage. There really are differenced in our immune system and the way we respond to disease.

Going forward we need to look at sex differences in HIV induced inflammation. We really need to know what's happening in HIV infected women, and not think that when we study men we know what's going on. In addition, the studies of HIV infected women really must include African women - who carry the greatest burden of HIV infections - but must also occur in countries where the metabolic and cardiovascular disease burden is high.

These two groups will overlap in the future. The epidemiologic shift from infectious disease to metabolic disease in Africa will put HIV infected women at risk of metabolic disease also. There really must be clinical

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international studies that cross the full age range of women and that use menopause as part of the definition.

I want to thank all the WIHS sites and investigators. WIHS is funded through several agencies of national institutes of health. I particularly want to thank Robert Kaplan, Polly Mackey, Michael Yun [misspelled?] and Ruth Greenblatt, and finally, the WIHS participants, most of whom joined WIHS when they thought they were not going to be living with HIV; they thought they were going to die with HIV. They have been dedicated through almost 20 years, and we hope that until we get larger studies in Africa their experience can also inform what will happen to the larger group of women worldwide living with HIV. Thank you. [Applause].

BEATRIZ GRINSZTEJN: Thank you. Thank you very much Dr. Anastos, for such a comprehensive talk. It's my great honor now to introduce to you Mrs. Siphwe Hlophe. She's a woman living with HIV from Swaziland. She's the founder of the Swaziland Positive Living and the vice-chair of the ICW; that is the International Community of Women Living with HIV/AIDS. She is also the southern African chairperson for ICW. She has received a number of awards for her engagement and leadership in the women living with HIV agenda in Africa.

SIPHIWE HLOPHE: Thank you. Good afternoon ladies and gentlemen. It is my pleasure to be here. I said to my colleagues here, if only treatment in the hospital was like

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conducting these studies. The studies are so efficient as compared to the treatment we are accessing at the hospital we wouldn't be here. I'm a woman living with HIV and AIDS. I'm going to present the experiences of a young woman entering the reproductive health years, and also an older woman, like me, who is aging with HIV and AIDS. The presentation is divided into two parts. The first part is on young women in their reproductive years, and the second one is on older women, aging and HIV and AIDS.

Young women in their reproductive years - I've talked about the issue of access to treatment. In most of our country's coverage on PMTCT services it is pleasing and has made treatment services accessible to women living with HIV and AIDS. We are now proud of saying we are getting or we are having negative barriers, so we are proud of the PMTCT rollout in our countries. [Applause]. We also talk about access to family planning information that addresses contraception in relation to HIV and AIDS.

No information on the use of various contraceptives and their interaction with HIV and AIDS; we don't have enough information for these young women. We don't have enough information on how the treatment of ART interacts with the contraceptive that we are being given. No information is available to women about methods to improve the safety of contraception and child birth, especially women living with HIV

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and AIDS to fall pregnant. We talk about the sperm washing methods; that is very expensive for young women. We talk about the cesarean section during childbirth; it's all expensive to these young women.

We talk about family planning and maternal clinics that are often a woman's only contact with a developing country health system, but as you get there to the system or to the health care, you don't get the exact or the expected reception you wanted to get as a young woman living with HIV and AIDS. Most of the time you would get a negative attitude from the health workers.

You still have a parallel care system in Africa. This is inefficient, reinforces the stigma and creates a [inaudible] of health care workers uninvolved in meeting basic needs. You go to an AMC as young woman, you are diagnosed HIV/AIDS positive, and then within that health care clinic we don't get all their services that are supposed to be there. You are referred to another health care - a bigger one - where they usually say oh, you can go and get treatment from B. The period from A to B, again, you'll find that most of the young women are giving birth along the way before they access their treatment.

What are we saying? We are saying young women or the hospitals; we must have a one stop shop where you are diagnosed or you are tested, where you are given a treatment and the baby

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is treated, not to be referred to a hospital where sometimes we find that you don't have enough money to continue.

We have another issue. It is a new issue during the era of HIV and AIDS. The first is sterilization. This sterilization to these young women, it happens during the time of vulnerability when you are in labor pains. The health worker will talk to you and say A, B, C, D; can you sign this consent form. You will sign the consent form, but this sterilization should at least be taught to these young women - what it means, what services are there - than to sign when you are in labor pains.

Hostile attitude towards HIV positive women who seek to have children. I remember in Swaziland I was invited by one of the sisters in a clinic, and we talked and I said to her I'm going to talk about these young women having a right to have a baby or a child. She said, oh, I was going to tell you that you should go and tell these women not to have rights, not to have babies. I said, oh, you are infringing in their rights. These health workers [inaudible]. It doesn't give a relationship between a young woman who's HIV positive and them. We expect that. When I arrived with my documents, the health worker must look at it and observe my status and we start a relationship so we know all of what I'm supposed to be getting. Many of these violate [inaudible] are in the provision of the

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health services and are perpetrated by health services personnel.

Aging with HIV and AIDS. I'm now under 60 with HIV, so we older women have a special disease burden. The treatment requires special expertise. For instance, research and information is needed to learn where the anti-retroviral treatment could interfere with drugs that older women might be taking for other chronic diseases such as diabetes; I'm a diabetic person.

We need to know very well, as an older woman, how are these drugs interacting with each other, then to present yourself and then you give them that oh, I'm HIV positive, the first thing, they look at me, how? This one is an older woman, how did she get the positive. Those are the issues - those should be the secondary issues. We are looking at how we are going to use the diabetic medicine together with the ARVs in our bodies.

The question of improving the quality of life and survival of aging women with HIV is ignored. [Inaudible] national planning and rolling it in treatment care and aging positive women. You know when countries or national governments are making their plans; usually there are no plans for aging women with HIV and AIDS. It is very important that when we make our country plans we do have women who are like me, who are HIV positive.

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How do we incorporate their needs or how do we plans for them for the part of our nationally strategic framework? We have the issue of stigma and discrimination. We should stop playing as if everything is okay. It's not okay. It's seriously not okay. There is a stigma within us and within the society we are living with. There is discrimination. The way they look at an older woman who's HIV positive.

The first thing before you present yourself, the health worker will call another one to record you and then before you are even treated, you find that you have three or four health workers looking at your papers, and then you go home. At home in the society, they don't expect you to be, old as I am, to be HIV positive. These are the issues that we should look at as we remain as people or as the society where we are saying we do care for women living HIV and AIDS.

Challenges: cervical cancer, as Linda or Kathryn who was presenting on AIDs. Cervical cancer is creating problems in lower resources countries are difficult to implement and maintain for a variety of reasons, including cost, including adequate [inaudible] facilities to provide the services.

I'll put an example of my country, Swaziland. We have been mobilizing women to go for the test or screening of cervical cancer. You know one said, you know, Siphwe, the way you mobilize the women, but we don't even have a swab, so you are saying, but we are talking the problems and coins of having

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the cervical cancer, if the hospital doesn't have that, a swab, a small swab, where you can use it, so it's a big problem. Adherence to treatment. We talk about the drug store counts, inconvenient dosing frequency pill [inaudible].

You know, in Swaziland last year, we had this problem whereby those that were on treatment were given a consignment of two weeks and then you talk of a person who doesn't have money to go and refill after two weeks. It's giving us a problem and then you talk of the dosage and then the regiments were changed left and right and said, oh, you can have these drugs, meanwhile we address this. So we had to push very hard to the government and say, what is happening here in this country? It's not supposed to be happening to those who are on treatment.

Dietary restriction versus food insecurity. Usually the health worker or the doctor would say, you must eat a balanced diet, but you think of a woman in the rural or in the countryside who doesn't have enough to eat, we had also another woman who was eating a condom in our country in order to take her antiretroviral drugs, she was in ASPC in south Africa, on news and so on, is dead! Of the country resolving what is happening. There is the dishes lying.

So you are saying, as women living with HIV and AIDS, we're experiencing a lot of problem, the medical swab, that can be solved by our government. Side effects. When you present

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yourself and say I've developed A, B, C, D, you are not treated where you get the drugs, you are referred to another hospital where you have to pay for to be treated for the side effects.

Client healthcare provider relationship. It's what we are demanding. It's what we are saying, we need it to be friends. All the doctors who are treating us so we can sit down and say, you have developed A, B, C, D, how do you treat me? But you just come in and the doctor said, oh you are HIV positive, oh! You are suffering from headache! You go out. So you can't sit down and then we don't sit down and talk and say, this is what is happening, this is what is happening, can we get the relationship so that the doctor knows how am I feeling, how should I be, how should I be treated?

And then the system of care. You know the system of care is deteriorating. That's why I've said, if only treatment in the hospitals was like conducting the studies that are being presented here, we wouldn't be here or we wouldn't be where we are with what is happening in us, but the system of care, it's so much that it desired to be looked into. Thank you, ladies and gentlemen. [Applause]

SHARON HILLIER: Thank you. We would really like to invite all the speakers to take their places up at the podium and then we'll ask you to come the microphone. Please identify yourself and then we'll direct the questions to those on the panel.

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KATIE GOTTFRIED: Hi, I'm Katie Gottfried from the Division of AIDS. Really great, great panel discussion, thank you so much. This is a question for Elizabeth and it's more of a comment and reflection than a question. One of the things we're noticing more and more is this issue of HPV-related anal cancer and I think in the future, in the near future, as women are living longer and HPV-related anal cancer is more of a field infection, so women don't have to have to have specific risk factors for anal dysplasia, I think this is really going to be a growing problem in resource limited settings and I wanted to know what your thoughts were about a screening out that might be effective or which day do you think we should be going? Just an opinion about that and I'd open that to the rest of the panel because I think that everyone up there has a really important opinion.

ELIZABETH STRINGER: I didn't talk about anal cancer, but I agree. It probably is rising and in my experience working in clinical care in Zambia in a large gynecological setting, we didn't see a lot of that. We did have a lot of women who reported anal intercourse, but we didn't really talk about anal cancer. It's possible if HPV screening becomes more standard of care and the vaccine, that will have more of an impact, but I don't have much of experience with that, so I can't comment on that as well.

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KATHLEEN GOTTFRIED: I think what I'm getting at as well as women live longer, they'll survive cervical cancer with appropriate screening, they'll survive AIDS-related complications, but then they'll have – I think it's the spectrum coming through.

KATHRYN ANASTOS: So I may be an outlier in this opinion, but I'm a primary care doctor. The principles of screening are really well-established and we're not even close to meeting the principles of screening when we talk about anal cancer. Maybe we're unable to do that, but we don't know that making intervention changes the outcome in anal cancer.

We don't even really know if all this high grade anal dysplasia we're seeing developed into a cancer that would impact on the person's life. I recognize that the population based cancer statistics do indicate that there is a substantial increased hazard of many folds, by tenfold, of increased hazard of many cancer in HIV-infected men in particular compared to the standard general population, I'm not sure how good the population based statistics are in knowing the sero-status of the other group, but whether or not we can alter that outcome with a screening and treatment program, we have a long way to go in my opinion.

MALE SPEAKER 1: Thank you very much. [Inaudible] from South Africa. One is to Elizabeth. I don't know much, I'd like to know from you in the Human Papillovirus vaccine and the

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role it could play or what is there already in assisting young girls in prevention of cervical cancer because I understand the role it can play. If then it was such a problem, advocating for that or so, and also just to stand to the issues of screening?

It's okay to say that yes, we are screening less, especially in less developed countries, but can't you be able to make changes as a country, a very strong one because with the coming of HIV, we are seeing more and more younger women contracting cervical cancer in particular. Thank you.

ELIZABETH STRINGER: So I'll talk a little bit about what I know and then other people can chime in. I know different strategies have been looked at for HPV vaccine. Mostly in schools or age-based and I believe that the school based programs are seeming to capture more girls than just going by the age based and it's recommended that girls can receive that as early as nine years of age and I think people have been targeting fifth grade, at least in places within the United States.

I also think that Rwanda has a flagship program for scaling up the vaccine and Zambia is now lobbying for trying to scale it up, but there are a lot of logistics. How do you give it the coal chain and so you need to be in place before it's scaled up, but GAVI has, I believe, put it on its list and it is becoming more affordable and the prices are really

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dramatically dropping so I think in the near future, it is going to be more accessible to girls in low resource settings.

LINDA GAIL-BEKKER: So I'll give a perspective from South Africa. Thank you for raising it. It was a bullet there, but I would absolutely endorse the fact that as a preventative tool, it makes a lot of sense to get it into pre-pubical girls and boys actually. South Africa is one of the first countries to register it both for young men and women.

With South Africa is one of our big issues has been the cost. It's a three vaccine dose and it's expensive, but as you've heard, the cost is being negotiated down. We are not a GAVI country, so that is an additional complication, but I know that our Ministry is certainly looking at a school-based program., Certainly there are countries, Australia comes to mind where programs have been extraordinary and I think this is something that we as globally need to be advocating for.

SHARON HILLIER: We'll take your question please.

KAYA MARGOSA: Good afternoon. My name is Kaya Margosa [misspelled?] I am from Sultan [misspelled?], Southern Africa. My question is to Madame Siphwe Hlophe. Once again thank you, Madame Hlophe, for the good work that you are doing in South Africa. You have been the voice of the voiceless and I really want to appreciate the good that you are doing in that country.

My question is, what do you think will be the roll of man in supporting, particularly men living with HIV, in the

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country like Swaziland, which is very patriarchal in nature? My second point or question to you again, your experience of women who are positive and then you find that the man is negative, discordance, what has been the practice and what has been done in the country to address discordancy, particularly to support women? I thank you.

SIPHIWW HLOPHE: Thank you, Mr. Margosa. I think the second question of a woman or a man who is positive should be answered by you, since you are the one doing that. But on the issues on the issues of the roll of man in supporting the women, it is much important that we do that, but looking into the culture of how we are in Swaziland, the way our culture is, it doesn't give enough space for the support to each other.

We are what we call its culture identity, Swazilo in custom, having more than one wife and many girlfriends, so the way it is, it doesn't give enough space for the men to support the women, although now, as an organization, a support, we're started a men's organization in our organization where we started a men's department where we want to educate and empower men how to support the women that they are living with. We hope, it's just at a teaching stage, we hope that it will grow up as we continue, that everybody will be supported on that, but if you're taking into the consideration the way Swazis are.

MUTIMOR SHAJEMA: Thank you very much. My name is Muti Morra Shajem [misspelled?] from Rwanda. My question is going

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to be directed to Elizabeth. In Rwanda as an organization [inaudible] have done a lot of work on several kinds of screening programs and have screened over 3,000 women for the last several years and the national program has implemented a primary prevention and soon there will be a national route on several kinds of screening. There are a lot of details about that.

We are also starting to form some kind of partnership with Elizabeth's colleagues in Zambia by teaching doctor, Faham [misspelled?], and so I would like to know your views on sustainable programs and issues around what are your views in terms of pro-Zambia [inaudible] has a screening program as a primary prevention procedure, because we already talked about a potential vaccination program in young girls. Thank you.

ELIZABETH STRINGER: Thank you. Excellent work in Rwanda. That's great. I think sustainability is always a big challenge and especially when it involves cervical cancer screening because in Zambia right now, we have extra nurses who are screening many, many women every day to take the burden away from the nurses in the health facilities.

I think there are some exciting things coming down the pipeline, potentially screening with HPV testing or even self-HPV DNA testing, so you can triage out the women who may not need a specum exam and that can reduce the burden on the health facilities, so it is a challenge, but I definitely think it's

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workable and it's something that we need to have to strive to figure out how to integrate cervical cancer screening in all of our countries.

LIZZIE SCHMIDT: This is Lizzie Schmidt from Philadelphia. This is a follow up question for Elizabeth. If the nurses are the ones who are mostly doing the treating with cryotherapy, what's the training involved for them to do this task sharing?

ELIZABETH STRINGER: I actually haven't gone through their training, but we were looking at some of our nurses for ACTG 52 and so I was enquiring about how long the training was to do VIA and Cryo and Dr. Cariam [misspelled?] told me in three to four weeks with a nurse working hand in hand with another nurse that he would feel that she would be relatively competent to do it on her own with some form of backup, so maybe you can also comment.

KATHRYN ANASTOS: So I'm one of the founders of We Act Rwanda and we had to start from scratch, right? We had nobody trained and actually it was Dr. Muti Morra [misspelled?] who helped direct this training, but it is a really important question because the issue of how to do VIA is dependent upon knowing what you're looking at.

So you have to look at really just hundreds of cervixes to be able to know what's abnormal and what's normal and what to treat and what not to treat and therefore it is really

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important that the training, if you're starting Denova [misspelled?] when you don't have a program like where you guys have where you can just put someone in with another provider for three to four weeks.

You do three to four weeks of intensive training that has classroom component, has a computer based component where there's just slide after slide of, is this a normal cervix? What's this cervix show? What's happening on this cervix? Truly, it's important to develop a group of patients who will be screened during that period who are at greater likelihood of having cervical disease, which actually means screening HIV-positive women during a training period is highly valuable both for the trainee and for the women.

I would like to ask a question, if I may.

ELIZABETH STRINGER: Can I add one more thing to that? Another really important component of the ongoing cervical cancer screening program is that every Friday afternoon, they have a weekly conference where they actually go over pathologies from the previous week and they bring the nurses there and they're talking about what they saw and it's an ongoing learning thing, so I think that's an important component of it.

KATHRYN ANASTOS: The constant monitoring and evaluation of, the value of taking a picture it is really that

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you can then go over it and learn from that. Dr. Muti Morra, did you want to add a comment here?

MUTI MORRA: I just have a different question, particularly for you, different question.

KATHRYN ANASTOS: So I find the study from India very sobering that what made a difference in outcomes was HPV testing. VIA maybe is equal to a pap smear. A pap smear is a lousy test. The reason it works so well in preventing cervical cancer in developing countries is that we do it over and over again.

We used to do it at intervals that were ludicrous, every year, which is really totally unnecessary in most women, so we were very good at lowering the death rate from cervical cancer, but if we're talking about doing something from once every ten years, once every five years, shouldn't we be doing HPV testing? I'd really like to know more about that.

ELIZABETH STRINGER: I think that we seem to be heading in that direction.

SHARON HILLIER: I think just because our time is nearly up, we have two more questions, and then our other moderator will have the last word and the last question.

MUTI MORRA: Thank you. My name is Muti Morra, as I said. My question is going to be for Kathryn, particularly I want to know, I know there are a lot of going on in terms of potential reasons behind aging and HIV in women. I saw in your

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good presentation that pejorative changes and disparities that exist between men and women and particularly cardiovascular profiles, HDR, RDR, [inaudible], do you have particular reasons or is it possible, has it been explored enough the reason behind these changes particularly between men and women and [inaudible] and rest of the [inaudible]?

KATHRYN ANASTOS: So as I understand, the question is have we adequately explored the sex differences and markers of inflammation and cardiovascular mucosal markers and what accounts for them? The short answer is clearly no. I welcome this opportunity just to say what I'm trying to communicate here is that we have a paradigm of HIV infection and what happens pathophysiologically and the pathophysiology is extremely important in understanding the complications, understanding the ultimately how to eradicate and the paradigm is built almost entirely from data in men and we know there are sex differences in these areas, so that we, as in every other disease, with few exceptions, we really need a much better exploration of how much of this is the same in women and men.

There are things we know that are very similar. For example, there's the efficacy of the ARVs, we know they work, right? We know they work in women, we know they work in men. We may not know as well as we want to know about certain kinds of differences, but we know they're saving lives. On the other hand, these differences in diseases that have both a sex

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difference and race difference and an ancestry difference to begin with.

For example, diabetes in the United States is twice as common in people of African of descent compared to people of European descent, so what's going to happen in Africa potentially if there's an epidemic of diabetes related both to economic development and to HIV, but maybe that won't happen. What I'm saying is, we don't know and therefore there's a huge amount of work that remains to be done. Thanks.

MICHELLE KAHN: My name is Michelle Kahn [misspelled?] from the University of California, San Francisco. Thank you all for your presentation. My question is for Dr. Anastos, regarding menopause and whether there's any data suggesting that that impacts on HIV-related disease as opposed to other primary care considerations.

KATHRYN ANASTOS: Is there an association of menopause with HIV disease progression, is your question, right? We don't really know. One, we have a hard time defining menopause. Second, most studies pre-treatment were in women had not aged past menopause, so therefore we don't have a lot of information, but we do know that in normal menopause, the CD4 falls, the same way you see that decrease in bone, there's a decrease in CD4.

Normal aging has a slight decrease in CD4 count, however the impact of treatment is so powerful that it will

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overcome whatever that difference is in my opinion, the same way if you look at studies with ART-treated individuals, that age effect essential disappears and that's because the treatment is so miraculously powerful that it overcomes those differences and therefore I think we will never know because we will not study.

BEATRIZ GRINSZTEJN: Quick comment on the HPV testing. So we have just published work from the perspective from a mid-income country and we show it to be very cost effective in a cost effectiveness analysis to incorporate HPV testing outward in the HIV positive women, so yeah, okay.

That has been a great pleasure to have you all here and I think it has been a very productive session with excellent speakers and a very good discussion. Unfortunately we came time to close our sessions and thank you very much for coming here and thank you very much for our presenters and Dr. Hillier.

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