

Syphilis (Part 1)
HIV Testing Overview (Part 2)
Peter Leone, M.D.

PART 1

SLIDE 1

Hello, I'm Peter Leone. I'm the Medical Director for HIV and STD for Communicable Diseases in North Carolina. I'm also Professor of Medicine at the University of North Carolina. We're going to cover 2 topics today. We'll spend the first portion of this session talking about syphilis- a little bit about the natural history of syphilis, treatment, and the implications around syphilis for HIV, and then we'll segway into HIV, in particular, focusing on HIV testing and our goal to identify all folks living with HIV and to link them into care. The last part of the HIV talk, we'll actually be talking about acute HIV. It's the very earliest stage of HIV in which we see folks who are infected, but antibodies aren't detected. And then we'll sort of wrap up with a general summary. So, with that, I'll go ahead and begin.

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Syphilis is an old disease. It's been around for thousands of years. It's a very complicated organism, but simplistic in how it initially causes infection. Syphilis is a mucosally-transmitted infection—it requires skin to skin contact—a lesion coming into contact with somebody else's mucosal surface, and the organism then transferring across and causing infection. The first stage is for this corkscrew organism to actually invade through the epithelial cells and enter into the lymphatic system. It will then set up a localized infection just below the skin surface itself.

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Now, when we look at the organism itself, it looks snake-like. It actually has a lipid outer membrane with what we call a flagella, that causes this corkscrew motility. That lipid outer membrane sort of reduces the response that we see to the organism in terms of antibody response. It also will drag other fatty acids into the person's body and set up an initial response with antibodies that are self-identifying antibodies.

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So, the antibody response to syphilis stimulates these cells, which produce antibodies. The antibodies are specific for lipids on the surface and they may be directed against particular proteins, but they aren't sufficient to actually get rid of infection in many, if not most, individuals who are infected with syphilis.

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When we talk about syphilis, we really talk about the clinical stages. Now, this is a complicated slide that lays out the course of syphilis over years. From a public health standpoint, our concern is that first year of infection. The reason for that is transmission occurs when there are lesions on the skin.

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Now, if you look, you can see there are several phases here in which we can find organisms. We refer to syphilis (or at least I do) as obeying the rules of three. There are three stages and most of these stages are separated by either three weeks or three months.

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The first stage is infection. The primary stage –what we will see—is a lesion that appears on the skin surface where contact occurred. Typically, that lesion occurs about three weeks after a person is infected, but may take as long as three months. The general incubation period is about 10-60 days. What appears first is a chancre. That will resolve in about three weeks, and untreated, will go away. Most of these lesions do not hurt; they have a clean base to them; they don't cause any purulence and, as a result, can be missed. But they occur anywhere that person may have come in contact with another infected lesion. So, though we typically see them on the genitals (and this one is actually on the shaft of the penis), they can occur on the lips, the tongue, the anal mucosa, inside the vagina, or on the cervix, depending on where that initial contact occurred. And, of course, untreated, this will go away, even though infection has not been cleared. After that primary stage, we're looking at a time period of around 1-3 months where a person will go into secondary syphilis.

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Now, the rash that occurs with secondary syphilis is one that can be mistaken for all sorts of conditions or illnesses. It is a very non-specific rash. It's what's called a flat rash. It's a macular papular rash that can have hyper-keratotic areas. On the skin of people who have color, it may be missed entirely, or if people present, and most folks with symptoms due to syphilis do present during the secondary stage, these rashes can be mistaken for a drug rash, a non-specific viral illness, and as a result, again, can be missed. So, it's important, at least in STD clinics where we have someone who comes in with a rash, we should be thinking about secondary syphilis. Acute HIV, as we'll talk about later, may present with a rash very similar to this.

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It can also involve the palms of the hands and the soles of the feet. They used to get a lot of strange looks in the STD clinics when patients came in and we would take a sexual history and, it became part of the physical exam, I'd say "I need to take a look at your hands. And, oh, by the way, can you take your shoes and socks off ?." And they'd look at me like, well, I didn't have sex with my feet! But the rash for secondary syphilis does involve frequently the palms of the hands and the soles of the feet, so it's important again, as part of an exam, to be aware of that and to look over the entire body surface.

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Along with the rash, we can see, in some cases, what we call condyloma lata. It only occurs during the secondary stage of syphilis, but it is a highly infectious lesion. These

are flat, white- appearing lesions that pop up over the course of several days or weeks, may persist for a couple of weeks and, then again, without treatment, will clear if this person isn't diagnosed properly. These lesions don't hurt and can be mistaken for genital warts. They typically appear on moist, mucosal surfaces—so, in between the buttocks, under the arm, inner part of the thigh, the vagina. In individuals with HIV, these lesions may be much more extensive. The reason why we're concerned about these lesions, again—people may present and these are highly infectious and may transmit syphilis to other folks.

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Now, we are seeing in North Carolina a resurgence of both syphilis and HIV. In fact, this is a national issue. We're looking at newly diagnosed syphilis cases also having HIV infection at the same time. These co-infections really create a negative effect from a public health standpoint. It's what we call a win-win-lose relationship. Syphilis affects HIV by increasing the amount of virus in the blood. The more virus in the blood, the more rapidly HIV can progress, so we can see a decrease in the CD4 count in individuals who acquire syphilis and have HIV. In addition, those lesions that we see actually increase the amount of HIV that can be shed in general secretions and syphilis itself can increase the amount of HIV in the blood. That increases the risk of transmitting HIV. In addition, having the lesion, if you're not HIV-infected, increases your risk of acquiring HIV if you come in contact with someone else who has HIV.²The HIV effects on syphilis is that we're seeing more folks present with neurosyphilis, syphilis meningitis in particular, at an earlier stage, and these folks, we believe, are at greater risk for serologic failure; which means that we may require more treatment or, at least, more extensive follow-up. How do you make the diagnosis? What do we do in order to make sure we don't miss cases of syphilis as they present? Well, one of the first things we have to do is look at the lesions. Realizing that folks may come in and they may actually put medication on or treat the lesion themselves. The problem with that is that it actually reduces our yield of being able to find an organism.

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We talked about that window period being about 3 weeks after exposure to infection and it turns out that the antibody response may be delayed and, in fact, that chancre may appear before a person actually has a chance to develop antibodies that we can detect through testing. So, we can take fluid from those lesions and look at it under a darkfield microscope. In doing that, we can see the organism in some cases and, if it's moving through that field of vision, and it looks like a corkscrew organism and sort of slinks through, we can say that that person has a positive darkfield evaluation and we would presumptively say that that person has syphilis. That's whether or not their blood test is positive.

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Now we should be doing a blood test using a non-treponemal test like a VDRL, RPR, or a TRUST, but that test may be negative even though the lesion is present. The bottom line is if you suspect syphilis, we would recommend in North Carolina where we still have significant numbers of cases, that we treat these people presumptively and then

bring them back in for further evaluation in a couple of weeks. The test for syphilis that we recommend as a screening test is a non-treponemal test. It is measured out, and as you will see on the slide, it's measured out as titers and what is done in the lab is that they'll take the serum from that person's blood test and they'll mix it with antibodies in a reagent and look for a response where there will actually be a dropping out of whatever particle is in there to cause a cloudy or granular appearance on the card. Where that stops, we say that stops and we look at how many dilutions it takes to get to that point.

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So the RPR, the VDRL, the TRUST are measured out in titers—1:1, 1:2, 1:4, etc. It's important because that is the test that we use to look for following and monitoring clinical response. As we already talked about, in the primary stage where the chancre first appears, that blood test is positive about 80-90% of the time, meaning about 10-20% of the time, the person can have syphilis, present with a chancre, and their blood test is negative. In the secondary stage, it's virtually 100% positive. So we can rely on the blood tests in the early stages as being helpful, but recognize you still may have a negative blood test with primary disease. That sets the benchmark then for looking for a clinical response. Now, the blood test will remain positive for years in a person who was not treated, but may end up coming down over time. As we'll talk about later, we will treat someone with syphilis presumptively, and then we'll actually follow that response at about 6 months to a year out to make sure that they've had a decline in the titer. An appropriate decline in titer is a four-fold decrease from the initial value. So again, think about syphilis; presumptive treatment is indicated in folks that we suspect are presenting with a primary lesion, and that blood test becomes an important benchmark for looking at clinical response.

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Now again, if we go back and look at lab tests for syphilis, we want to confirm the initial screening test or what we call a treponemal serologic test. The two tests that are typically used are what we call a TP-PA and/or a FTA antibody test. Screening test is very sensitive, but non-specific, so we can have false positives in the VDRL, the RPR, and the TRUST and we want to be able to confirm that. The problem with the treponemal serologic test is that it does not come back as a titer; it's read as either positive or negative, and usually once a person is positive on that test, they're positive for life. So we can't follow the clinical response. We still use it, again, for confirmation. We use it in some cases for screening, as I'll talk about next. So, there really is this new dilemma with new tests that are available and some of you viewing this talk may say, well, we don't use the RPR, the TRUST, or the VDRL as our screening test. The lab that we work with actually does a treponemal specific test as the initial screen.

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There are two currently licensed tests for serologic screening and confirmation. There's the Trinity Captiva syphilis test; there's also a Trepchek test. These are IgG antibody-based tests. Some of them may actually contain IgM detection as well. They are EIA, so it's a specific type of antibody test. Some labs are using these as screening because they're relatively cheap and because of large volume labs, these can be done in an

automated fashion and doesn't require a technician to set up a card for reading. The problem with the test is, again, it doesn't correlate with clinical response and we believe that there may be false positive antibody tests. So, this has created a real dilemma for clinicians to be able to figure out does this person have syphilis or not. Again, it's a quantitative, non-treponemal test that would be used for guiding response to treatment.

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The CDC has sort of recognized that this becomes a problem in terms of interpretation if we invert the recommended non-treponemal screening test with treponemal specific antibody confirmation versus using that very specific antibody test as the first screening test. So this algorithm that you're looking at right now breaks it down into a person having a positive treponemal EIA. If they're positive, that should be reflexively rolled over to doing a quantitative non-treponemal test; ie: either an RPR or a TRUST. If that second test is positive, that's consistent with syphilis. It may be an old syphilis, or it could be a new syphilis, that has to be based on clinical findings. But that person usually should be treated. The dilemma becomes what if that non-treponemal test is negative.

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Now you have a discrepancy. You have a specific antibody test and a non-treponemal test that don't agree. The roll over on that is to do another non-treponemal test different than the initial one. If it's positive, we would say that that person probably has an old case of syphilis. They may have been treated. They may have been unrecognized, and we usually will err on the side of treatment. If that second treponemal test comes back negative, we would say that person does not have syphilis and doesn't require further evaluation or treatment. This is again going to be an issue as a lot of places are using these treponemal tests as screening tests, in particular, in pregnancy. You can imagine the dilemma of having someone who's been in a long-term relationship who is pregnant who comes in and gets a routine screen because we recommend syphilis screening (in fact, that's the law that syphilis testing be done in pregnancy), and this treponemal test comes back positive. It's important to counsel this person that it may be a non-specific reaction to antibodies that cross-react. We see this often in pregnancy and the person may not have syphilis. We need to actually sort this thing out through the algorithm that was there.

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Now, what about treatment? Make a diagnosis and we would say great, what do we do? Treatment is old time. We've had the same antibiotic as our most effective strategy and, of course, for treatment for syphilis for over 50 years. And it still is...guess what? Penicillin. We break syphilis into early and late stages so that we can understand potential for infection as well as response to treatment. So, for primary, secondary, and early latent syphilis, the recommendations are to use Benzathine Penicillin, 2.4 million units given as a one-time IM injection. If that person is allergic to penicillin, and by allergy, I'm referring to someone who has hives, shortness of breath, may have dropped their blood pressure, but a significant reaction, what we would call an urticarial reaction. We would not recommend using penicillin, and the alternative choice is to use

doxycycline, however that has to be taken twice a day for 2 weeks. If an individual is pregnant, and you're dealing with a pregnant woman with syphilis and she has an allergy to penicillin, you still need to use penicillin. In those cases, those women have to be admitted into a hospital where they can be observed, de-sensitized to penicillin, and given penicillin for treatment. The other issue that comes up is what about HIV-infected individuals. The current recommendations that will be coming out in the 2010 STD Treatment Guidelines, is that for early stage syphilis, the same treatment be used as a non-HIV infected individual. That is, a single dose of Benzathine Penicillin.

So, in summary again, for syphilis, it's common. We're still seeing it in North Carolina. You have to think about it with certain clinical presentations. Blood tests are useful, but aren't necessarily 100% perfect. So, in the primary stage, recognize that the person may have a negative blood test, so you would still treat presumptively and bring them back in for repeat testing. In the secondary stage, we would expect the blood test to be positive. And for primary, secondary, or early latent syphilis, that first year of being infected with syphilis, the treatment is still the same as it's been for years--penicillin. We want to follow these folks up and make sure their partners are brought in for screening and treatment that's appropriate for either their stage or their exposure.

PART 2...HIV Testing Overview

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So with that, I'm going to go ahead and segway into HIV testing and give you an overview of why we want to expand HIV testing and identify every single person living with HIV. The issue with HIV is that about 21% of individuals living in the US with HIV do not know their status, yet they account for about half of all transmissions. And, even though we recommend HIV testing, it had been pegged in the past to risk assessment. Now, that's great if we have plenty of time and people were honest in either providing information or actually knew what their risk was. But we know that a significant number of individuals don't have any risks themselves, but their partners do. So, we may assess risk based on their own history, but that doesn't tell us whether or not they've been exposed to HIV from their steady partner and, believe me, we see folks who've had one monogamous partner for years, yet acquire HIV from that person who either didn't know that they were infected or didn't disclose it. Secondly, although we like to think we're open and not judgmental as a society, we're not. And we're not comfortable talking about sexuality. So, although I might frame it in the right way, ask good questions, a person might not be so willing to say that, oh yeah, by the way, I was having an affair or, oh, by the way, although I look like I'm heterosexual, I'm not. I don't want to be judged, so I'm not going to tell you about these other activities. As a result, we've really tried to move away from risk assessment as a reason for doing an HIV test.

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The current CDC recommendations are that every single adult in the US should know their status. And, for high risk individuals, they should be tested probably at least on an annual basis, if not more frequently. The third part is that we should be moving away from a separate written consent for HIV testing. It is no longer required as a separate written consent in North Carolina. A general consent for care is sufficient, provided that

a person is told that HIV may be part of the package. And, although I believe in counseling, we no longer believe that counseling and testing have to be wedded at the same time. Certainly, anyone who wants counseling or should be given information about how to reduce their own risks, we should be providing that in the most expert way we can. But there isn't enough time in busy medical settings to do that. As a result, we think getting the test is important. If you provide counseling and you never do the test, we haven't accomplished our goal. If we get the test and a person is negative, at least we've identified that person is not HIV-infected and we can spend more time with them, if we have it, for counseling. But we want to identify every single person with HIV, so it's important to get the test done. So again, testing and counseling don't have to be linked; they can be separated out. Pre-test counseling is no longer required for an HIV test, and post-test counseling is only required for those that are HIV positive. Now, why did we make these changes in HIV testing and counseling recommendations ?

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The rationale behind this, again, is that many individuals don't access care until they're sick and by that point, they may have transmitted HIV to other folks, or they may be so far advanced that they die. And this is a disease that we can turn into a non-progressive, chronic illness. We have effective treatment; it's available. We know that just knowing your status, knowing that you're HIV-infected, reduces risk activity by at least 40%, whether or not this person actually comes into care. There is inconclusive evidence about prevention benefits...for folks just coming in who test negative...which is why we're not saying every single person with a negative test should be counseled. And again, there's a great deal of experience with HIV testing, including rapid tests, that we think is translated into moving HIV testing to be a part of regular, routine care...no different than getting your blood pressure checked or having your cholesterol screened. So we really want to move HIV testing forward and say this is about being healthy. It's about sexual health. It's not about deciding if you're a good person or a bad person; there shouldn't be any judgment attached to this. It should just be something that we do. In our STD clinics, we recommend that every single person coming in to be seen for any STD evaluation have a HIV test done every single time they come in. In pregnancy, in North Carolina, the recommendations are for two HIV tests to be done in pregnancy. For any sexually active adult, we would say, know your status!

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Now, what are the hurdles or pitfalls for expanded HIV testing? There are several and we've tried to address some of these in the talk and some of these in policies and principles. As I've already said, we've changed state law so that separate consent is no longer required, but we also recognize that the test and treat model is not going to be enough. We have to make sure that if we're providing a test, we have linkages to care. Now, in places that aren't having a HIV provider, or, if you're a clinician, you're not comfortable providing HIV care, those things can be set up through regional support in the state where we can make sure you have a name or a person to refer that person to for care. We also know that institutional policies can vary from place to place. So, if you're working in a hospital or university setting, please make sure you know what your institutional rules and laws are.

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For local health directors, we're interested in working with you, working with the hospitals in your area, to actually make sure that their rules and regulations begin to fall in line with the state administrative code. And that is that opt-out HIV screening in medical settings be provided for all pre-natal and STD visits; that pre-test counseling is not required as part of testing; that post-test counseling is required only for positives; that HIV tests at the first pre-natal visit and third trimester occurs; and to recognize that clinicians understand that if no HIV test with results can be found or documented in the medical record at the time of labor and delivery, that HIV testing is mandated in this state and that woman, if she absolutely refuses, then we would do a test on the newborn. The goal here is to reduce transmission from an infected mother to an infant to zero. We're not there yet. We average about two neonatal cases a year in North Carolina. We believe that passage of this twice testing in pregnancy has cut neonatal transmission in half. So, we've seen a reduction over the last two years of about 2-3 cases a year of neonatal HIV. It's a significant improvement, but it's not zero, so we really need to continue to push to make sure that we make the change.

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Now all of this really falls under a rubric of saying what is our integrated response for HIV. Should prevention and treatment be linked? The North Carolina approach to this is really one of integration. The objective is to improve HIV care provisions all across North Carolina and to make sure that testing and entry into care is linked; that you have the information you need, and that treatment is provided as a way of not only prolonging the life of the individual, but making sure that we reduce the risk of transmission from person to person.

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Our efforts to expand HIV testing have worked. If you look at the number of tests that occurred in the state lab, we've doubled over a 4-5 year period the number of tests that we've done every single year. So that in 2008-2009, we're looking at a quarter of a million-- 250,000 tests done through the state lab. Obviously this number doesn't include all the additional tests that were sent out to reference labs. It's a big step forward, but we're dealing with very hard to get populations. So, as we start reducing the number of folks who don't know their status, you know what? It's going to be difficult to do unless we take a look at the impact of our screening initiatives, especially at our non-traditional testing sites, and expand testing to get the folks who may be outside of care. Now, we've talked about healthcare reform at the national level, but we still don't have universal access to healthcare. Even if we did, I know for a fact, of being a male, that 20-25 year old guys don't routinely go in for healthcare. And yet, this is a group of men in which we find about half of all new infections for HIV. If we're going to get to these individuals, we're going to need to find linkages outside the traditional medical care setting to make sure that testing is done. Again, we do see individuals access into urgent cares and emergency rooms for healthcare. In fact, a lot of folks use emergency rooms as primary care settings. As a result, we've taken initiative in this state to try to

expand HIV testing in emergency rooms and in medical centers. Part of this, again, is to say... what are we doing? Is it cost effective? We believe that it is.

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We think it's important to do, and as a result, North Carolina has taken an opt-out testing approach in several emergency rooms. Again, we want to move away from that separate written consent. We believe it's cost effective to do so. We think it reduces the amount of time. In addition, without having to do a risk management assessment as part of testing, we protect confidentiality in the environment in which disclosure is an issue. That magic curtain that goes around you in the ER doesn't necessarily prevent any sound from moving from one bed to the next. So again, routinizing HIV testing is important.

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I've said that we'd look at expanding for testing and we think it's important to go find folks. If we look at the data just in North Carolina—looking at data out of the UNC clinic and self-reported delays in testing-- we ask folks when they believe they may have acquired HIV, and when did they finally come in for testing. About one quarter of patients reported waiting four years after when they thought they acquired HIV to get their first HIV test. That's got to change. We really need to do much better than that. In addition, if we look at patients reporting HIV infection in more recent calendar years, we found that this has been shortened, but we're still not getting folks to come in routinely as part of their own healthcare to get HIV testing.

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There are a lot of barriers for patients. A lot of this has to do with their own assessment of their own risk. There's still stigma associated with an HIV diagnosis; less so to the test, but more so with the diagnosis. As a result, it's easy for folks to break down into them and me, meaning, it's all those other folks. They're the ones who get HIV. They're the ones taking the risks. And even though I've seen plenty of young men who've engaged in high risk activity, to a person, almost none of them believed that they were going to be at risk for HIV with their current activities. So, we're humans. We find that people don't recognize their own behavior as risky; people who viewed their behavior as very low risk, even though they've engaged in high risk activity. And they thought their exposure to HIV was unlikely even if they recognized that some of their activity was high risk because they just didn't think that the other folks had HIV because they looked healthy, because they were nice, because they, quote unquote, "looked clean". You can't tell someone's status by looking at them. And, as a result, we need again, to move toward sexual health as being a part of routine healthcare and HIV being incorporated into that. Now the barriers don't just exist for patients.

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We also understand that there are barriers to accessing healthcare. Most individuals accept HIV testing when it's offered to them. If it's viewed as being something that's routinely offered, not based on risks, but just something that we do, it de-stigmatizes the testing process and also increases the acceptability of it. So, in our STD clinics, we find

that about 90-95% of individuals will accept an HIV test when they're told that we do this as a routine part of the evaluation. We had one dental practice recently that did a survey of all folks coming in to their dental practice and asking them if they offered an HIV test in that setting, would they accept it. Over 70% said they would. So, it turns out that promoting expanded testing works. It allows people to not have to identify their own risk activity, and in particular, this is an issue in the Southeast where there are problems around access to care. I've mentioned Emergency Rooms (ER) and folks coming in and why we're trying to work with ERs. I'm going to challenge folks to try and figure out who our natural partners are; to try to actually expand our safety net for testing.

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If you look at our neighbors in South Carolina, they reviewed over 4,000 cases of HIV that were reported between 2001 and 2005. About 40% of those individuals had been diagnosed with HIV within a year of an AIDS diagnosis, meaning they'd been infected probably for at least 5 years, if not longer. When you look at those folks in particular, you find out that, on average, they had entered into healthcare about 4 times, and yet no HIV test was offered for the majority of those folks. So, it's not that we don't have contact with folks who are at risk for infection. We do, it's just that we haven't made HIV testing part of our routine care and we haven't made that link. So again, we know we'd like to work with ERs. We'd like to be able to provide testing in those places. Those partnerships should really exist between health departments and ERs. And, in fact, we can look at new and innovative ways to try and reduce the burden for ERs and follow-up. Meaning it is legitimate and legal in North Carolina to have testing done in the ER and have those results referred to a local health department for folks to find out their results. Obviously, if those folks are negative and don't show up, there's no responsibility to go find them and identify them. If they're positive, well obviously, if they don't show up, we want to be able to go out and get them and it's the state's process to do that.

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So, in conclusion, we want to increase awareness of the importance of HIV testing. We want to find that intersection of HIV to those that are at risk for infection. Opt-out testing can and will increase testing. And there really are ways of reducing delay for entering into care. And a large proportion of our patients who suspect they have HIV are delaying coming in. So, more outreach and education should be coupled with any initiative that we take. So this really summarizes HIV testing and I'm now going to talk about acute HIV.

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The slide that's up right now is a complicated slide. We're not going to go through all the little stages here, but the initial phase, the eclipse phase, and the early antibody phase of HIV, antibodies may not be present while that big line and surge up that's shown on this slide is when HIV ramps up dramatically in the blood and in general secretions. Turns out that early stage of HIV within the first 4-8 weeks is the most infectious stage of HIV. And yet, our antibody test may often miss this very early stage.

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We're going to start off with an example. We had a patient who actually developed some symptoms. Young man, sexually active, presented with fever, headache; went to a local ER, was seen there, actually had a lumbar puncture (LP) that was done and was sent out with a possible diagnosis of Rocky Mountain Spotted Fever, not an unreasonable thing to consider. Headache and fever in spring or summertime in North Carolina is Rocky Mountain Spotted Fever until proven otherwise. However, that wasn't the right diagnosis. He got worse. Came back into another hospital, was admitted, was worked up, actually had an HIV test done...it was negative because it was an antibody test...and was discharged. He then came in contact with another one of his friends, Partner B, actually engaged in sexual intercourse with this person over about a 2-3 week period. They then met up with Partner C, who was a steady sexual partner of Partner B, and they engaged in a three-way. Now, these three individuals were connected through a sexual network. Turns out then that Partner B developed symptoms. He had a sore throat and a fever. He went and saw his local medical physician; he was given a prescription for Azithromycin, and in a week or two, he got better. Then, Partner C, about 2 weeks later, developed a headache, fever, sore throat. He was also given a prescription for Azithromycin and no one asked sexual history and no HIV testing was offered. They both got better. They then met up with Partner D and engaged in sexual intercourse with Partner D. Guess what. A few weeks after this, Partner D got sick. Sounds familiar. He actually went in to an urgent care setting. He developed symptoms similar to Partners B and C. He had fever, rash, swollen lymph nodes; actually presented with a little bit of thrush. Went in requesting to be screened for STDs and an HIV test, was told he could have an STD evaluation, but not an HIV test done. Went back in when he got worse, was referred over to a local medical center, had an HIV test done at that point. He came back HIV positive, was actually ELISA positive, Western blot indeterminate. Turns out he had acute HIV. He then notified his previous two partners, B and C, that they may have been exposed. They came in to a testing event that we had and turned out to be HIV positive. I actually interviewed these two. They told me about Partner A. We went out and found Partner A and, guess what? Turns out he was HIV-infected. So what we had here was acute HIV transmission from person to person. We missed the first case, even though the person entered into care, because the diagnosis wasn't considered initially and the wrong test was ordered. We now know we missed at least 6 infections from this initial missed individual. So what is this? What are we dealing with here? This is acute HIV and this is why it's important.

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If we look at the natural history of HIV invading the body, this is a cross-section of vaginal mucosa. HIV will bind to CD4 CD8 positive cells, the virus will move to the local lymph nodes where it will replicate, break out, and then, within about 2-3 weeks, disseminate throughout the whole body and can be associated with fever, rash, and swollen lymph nodes. Sounds a lot like secondary syphilis, may look like it, but also can be mistaken for all sorts of things, including mononucleosis, hepatitis, non-specific drug rash.

SLIDE 40

So this syndrome of a non-specific viral illness is actually, what we call in the case of HIV, acute retroviral syndrome. It occurs, we think, in about 90% of individuals, and yet, most of these are missed because they either don't come in or, if they do come into care, they're misdiagnosed. This usually begins about 1-4 weeks after exposure; on average we're looking at about 2-3 weeks, and the symptoms resolve in about 14 days.

SLIDE 41

It's hard to say what are the specific signs and symptoms. All the things that are listed here are pretty non-specific—fever, lethargy, myalgias, rash, headache, pharyngitis, swollen lymph nodes. They're the most common symptoms, but they can be presenting in any way with all sorts of illnesses like this.

SLIDE 42

And if we look at GI symptoms, we can actually find that in North Carolina about 40% of individuals present with nausea, vomiting, or diarrhea, along with these other systemic symptoms. The bottom line here is that when young adults present with a non-specific viral illness, HIV needs to be considered in the differential.

SLIDE 43

So, if we're talking about Rocky Mountain Spotted Fever in the differential, you should be ordering an HIV test. If you're thinking about mononucleosis, make sure an HIV test is ordered. If you think the person has gastroenteritis, and you don't have a definitive diagnosis for it, HIV should be considered. We've already said that about half of all the newly diagnosed syphilis cases in North Carolina in men are HIV co-infected. Any case of suspected syphilis or proven syphilis should also have an HIV test. The problem we get into is that the test may be negative in the very early stages. So, consider HIV and then you have to make sure the right test is ordered. Now, how do we approach this in North Carolina? What do we do? How do we make the diagnosis?

SLIDE 44

Well, once again is, where is the entry point? We should be working with ERs, urgent care centers, or in high prevalence settings with primary care physicians who might serve our populations, like adolescent health clinics and STD clinics, to make sure they understand and look for the signs and symptoms of acute HIV. We found that about 78% of folks presented with symptoms and actually were missed early on. About 65% sought medical evaluation; about half of these went into EDs or ERs. And if you look at the breakdown in terms of differential, about one third were diagnosed with a bacterial infection, one third were given a diagnosis of a non-specific viral illness, and only 15% were diagnosed with acute HIV. So, we've got a long way to go to make sure that it's recognized. Now, why is it being missed? Where is the problem here? It really goes two-fold.

SLIDE 45

Patients may not recognize that they have HIV. Who wakes up in the morning and says, "I have a headache and fever...I think I might have HIV." So, a lot of individuals at risk

for HIV are not even aware that this syndrome exists. We're trying to make sure there are educational efforts, in particular to men who have sex with men, to recognize signs or symptoms so that if they present with a fever, rash, swollen lymph nodes that last more than 2-3 days, and they know they've had unprotected sexual intercourse within the last 2-3 weeks, they need to think about HIV as a cause for this and they should go in and make sure they're tested. Raising awareness is important and making sure that the right technologies are available for testing is also important. A negative antibody test during this phase doesn't rule out acute HIV.

SLIDE 46

Again, if we look at the stages of HIV-- this is laid out in the course of years-- we're only going to focus on that first phase...very high viral load that peaks at about 6-8 weeks. We're talking about copies that can be in the millions of copies per mil. It will then come down where we enter a clinical latency phase. If this acute phase is missed, these individuals may go on without symptoms for years. And, of course, they are infectious to partners and their HIV will progress. So we have reason to believe that folks are presenting to medical settings with acute HIV and we're missing it. The dilemma is not only that we're missing transmission during the acute phase, we're delaying diagnosis of these folks so that we no longer see people presenting late.

SLIDE 47

Now the tests that we order for this have traditionally been antibody tests and I'll talk about where we are currently. We are on our third generation EIA assays that reduce that window period down to about 3-4 weeks. We know that virtually everyone will seroconvert with third generation antibodies by about 8 weeks. This idea that a person infected may take up to 6 months to develop antibodies is no longer true. But we're still stuck with a window period, again in third generation assays, of about 3-4 weeks. In North Carolina, our public health lab, we roll over all negative antibody tests into pooled nucleic acid testing. That reduces the window down to about 1-2 weeks. We also now have a 4th generation assay that has a similar window period to pooled nucleic acid.

SLIDE 48

We care about this phase because it is the most infectious period; the diagnosis is missed. From an individual perspective, there are some benefits here. If we treat aggressively very early, we think we can lower the viral set point. We may be able to turn some of these folks into long-term non-progressors. Currently, there is mounting data to suggest that these individuals, who start treatment early, do better. We also believe though, that we can link them into care. Our own experience at UNC and at Duke has been that about 85-90 % of these folks with acute HIV that we link into care remain in care after that first contact. That's incredibly high and would suggest that our efforts in finding these folks and bringing them in are really paying off. In addition, if we can change behavior for that first 2-3 months, we can get them through this most infectious phase and reduce their risk of transmitting HIV to other partners.

SLIDE 49

So, finding folks is important and making the diagnosis is important. There's also a public health perspective to finding individuals with acute HIV. Recognizing that when you have a case of acute HIV, there's someone else out there that's transmitting HIV. So, we can identify the network and we can look at behaviors, geography, and other activities that may actually have contributed to transmission and target our interventions. In a time of limited resources, that's really important. Secondly, we can get those individuals to reduce risks, even if it's for a short period of time and, hopefully, reduce transmission in the population. Multiple studies would now suggest that acute HIV accounts for anywhere from 14-50% of transmission of HIV. Think about it. Four to eight week period may contribute to half of all transmission events. We really should be working much harder to make sure we don't miss any of these individuals. So, we've talked about signs and symptoms. We talked about entry points. I've now talked about the importance of finding these folks. STD clinics are important because we know that an STD facilitates HIV transmission. If a person engages in activities that allow them to contract gonorrhea or syphilis, they may have acquired HIV at the same time. So, offering an HIV test is important during that first phase, especially in our STD clinics.

SLIDE 50

If we look at stage of transmission, again, high probability of transmission during the early phase. In fact, during the acute phase of HIV, we know that the risk of transmission may be 10-20 times higher than any other stage of HIV. Although we talk about very high viral loads during this early phase, it also appears that the efficiency of transmission of HIV during this early phase, sexually, is much higher, so that even a low amount of virus in general secretions during that first 2-3 months may be much more easily transmitted to partners.

SLIDE 51

If we look at studies that have looked at the stages of HIV, and the transmission potential by stage, we find the highest risk of transmission, again, occurs within that first 6 month period. So, we want to find everyone with HIV. Don't get me wrong. It's important to not miss a single person with HIV. But the acute phase becomes an important public health effort to identify these folks, bring them into care, and reduce downstream transmission of HIV.

SLIDE 52

We talked about other STDs as being important and again, why am I saying if anyone has a STD, we should be making sure they are tested for HIV? And it doesn't matter if they had a HIV test done 4 weeks ago or 8 weeks ago and was negative. If they're now presenting with another STD, get another test. If we look at classic sexually transmitted infections—gonorrhea, trich, chlamydia, syphilis, even herpes (now this is incident herpes)—and we look at the period of time from incubation to symptoms, it overlaps with HIV and, in particular, with acute HIV, so that we can see someone present with gonorrhea and they may be in the acute phase for even a week or two after they've acquired gonorrhea, the same thing with trich and chlamydia. So making sure a test is done, but also making sure we're offering a test that will identify folks during that early phase, becomes critical.

SLIDE 53

Another way of looking at this is what is the yield of offering a test that will pick up the acute phase? It's a very busy slide. What I want to focus on is the far right hand part of this slide. This is looking at the increased percentage of individuals with HIV that were picked up because they were in their acute phase when screening was done. In general, we're looking at around a 4-6 % increase yield of those that are infected. But in some settings, and in particular, in settings in which there are large numbers of men who have sex with men entering into care, it can be anywhere from 13 to nearly 20% of individuals living with HIV. So if we look at, in particular, one clinic in New York City that serves an area where there's lots of MSM in that area, it was about 25% of all their HIV-infected individuals who presented during this acute phase. So if we only offered antibody testing, we would miss anywhere from 4-6 % of folks living with HIV up to about a quarter. Significant, and again, suggests that we need to think differently about the tests that we're offering.

SLIDE 54

In North Carolina, our current strategy, which I anticipate will change over the next year or two, is to do what we call "pooling". That's to take a portion of blood from those that are testing negative and do a two-step pooling process to do testing on only one sample. The advantage of that is that it allows us to do it at a reduced cost; we can do it on everyone. The disadvantage is that you have to have a large volume of blood; you lose a little bit of the sensitivity, and there's a delay in making the diagnosis. In North Carolina right now, we're looking at about a 10-14 day delay from the time when the blood is drawn to when we can identify an acute HIV infection.

SLIDE 55

Now, how so we do that in North Carolina? Our two-stage pooling works like this. The first top of the slide where you see all those dots refers to individual folks that were tested based on antibody tests and they were all negative. We then take a portion of blood from 10 of those individuals and put it into one tube and we do this nine times. We then take those and combine it into one master pool so that bottom dot at the bottom represents a portion of blood from 90 individuals. That one tube then is tested for HIV RNA—a very sensitive test that can pick up a low number of copies. If it's positive, we have to go back and de-construct it to figure out which one is positive. The two-step process allows us to reduce that number down to about 21-22 tests as opposed to having to test 90 individuals. If it's negative, we assume that all the bloods that were contributing to that pool were negative and that's the end of the story. Now this is useful in that it allows us to identify positives. The algorithm that the state uses is on the next slide.

SLIDE 56

If they're antibody positive, we do a Western blot currently for confirmation. If it's negative on the EIA, we do the pooling. If the pool identifies a positive, we identify the individual. We go out and find that individual. We have DIS across the state, Disease Intervention Specialists, who go out and find that person and bring them into care.

SLIDE 57

We then have bi-weekly discussions on all of these cases to make sure that we're identifying people correctly; that we're finding the partners and understanding their status. The linkage to care on this is almost universal. We get to these folks, on average, in about 48 hours. And, as already mentioned, the retention in care is enormously high. It's a very useful and powerful tool for helping us control the HIV epidemic in North Carolina. So what's on the horizon? Pooling is one method, but it's not the end all. As I mentioned before, there is a 4th generation assay that is now FDA-approved. We anticipate a 2nd test being approved in 2011.

SLIDE 58

These 4th generation assays detect both antibody and HIV antigen in a single test. The utility of this is that you can test at the individual level, has a similar sensitivity to the nucleic acid test. Not quite as good, but it can pick up about 80-85% of folks that are antibody negative but RNA positive. We believe that this test will replace nucleic acid pooling.

SLIDE 59

Now there are testing algorithms that are decided at the national level. This comes out from a collaborative group that includes the CDC. We anticipate a new algorithm that will include 4th generation assays.

SLIDE 60

This new algorithm involves doing a 4th generation screen. If that person is positive, we know that that person has HIV, but we don't know if they are acutely infected or not. Meaning we don't know if they're reacting to the antibody or antigen component in this test. We would then recommend that a rapid test be done on that blood, or another EIA, looking for just antibodies. If they're antibody positive, then we know they are chronically infected, but indeed, infected. If they are negative on antibodies, we would assume that that person has acute HIV and they should go to the right-hand portion of this slide, meaning they should have an individual nucleic acid test done. We would assume that that person has acute HIV and go out and get them and do the test. If you notice, in this algorithm, Western blot is not contained in here. We're looking at a change in our structure that's going to happen pretty soon over the next couple of years. Meaning that we'll be moving to 4th generation assays as our single, up front test, so we can get past the issue of people who are antibody negative, but still have HIV. We can get past the issue of pooling as a complicated algorithm to find acute HIV infection. We also will be moving away from Western blots because Western blots take 8-12 weeks before they turn positive. So, the problem is you have a very sensitive screening test and a less sensitive confirmatory test. We've got this window period that actually creates problems in terms of confirming a person being infected. So, we're now looking at either doing a 2nd ELISA or nucleic acid test to make sure that that person has HIV and to do confirmation.

SLIDE 61

Now how well does the 4th generation assay work? As I've already mentioned, it can identify about 80-90% of acutes. If you look strictly at folks that are RNA positive and antibody negative, it will identify about 80%. Not 100 %, but this test will allow us to open up screening and identification of acute HIV across the whole state of North Carolina.

SLIDE 62

So what are the considerations and conclusions to 4th generation antigen-antibody combos? We can detect acute infection. It may miss folks with lower copy numbers. We view it as a replacement for RNA pooling. And, in particular, it will shorten the time for diagnosis, meaning that we will have potential for better positive predictive values and lower costs and RNA pooling tests.

SLIDE 63

Confirmatory testing is a point that's worth mentioning here. If we move to 4th generations, we're looking a confirmation with a different RNA. I believe that Western blots will become a thing of the past. If a person in a non-medical setting has a positive EIA, a single positive EIA is not reportable to surveillance, but that person can be referred into HIV clinic for confirmation. Ryan White funding will pay for confirmation evaluations. So we think that in non-traditional testing sites, those linkages to care should happen very early. Our goal is to get 85% of folks into care. Recognize though, that in many of these settings, we use rapid HIV antibody tests. Most of the time, it's not a problem. But when you have an individual who presents with an acute viral illness or to ERs where we have folks frequently presenting with symptoms, rapid antibody tests may miss the acute phase of HIV.

SLIDE 64

So, if you look at 3rd generation EIAs, they can detect about one third of the folks who are RNA positive, but antibody weakly positive. But the other tests have very low sensitivity in terms of picking up folks during the acute phase. So, my own opinion is that we probably should be moving away from doing rapid tests in ERs. Certainly, it makes sense to do rapid tests in non-traditional test sites that are not dealing with sick individuals and it would be worth asking folks as a routine part of an HIV screen if they've had febrile illness that lasted more than a couple of days within the last 2-3 weeks.

SLIDE 65

So, in conclusion, detection of acute HIV is important. It's an important public health issue. We want to identify folks with acute HIV because we believe it will decrease the transmission potential of HIV. We can get these folks into care. We know that earlier linkage to care is better and we should be looking for acute HIV in some high risk settings—STD clinics, ERs, and places that serve MSM populations.

SLIDE 66

So what's important to consider? We've mentioned that acute HIV is important at the individual, as well as at the population, level. Recognize that panels for acute HIV are for acute viral illnesses and should include HIV in that panel. I would actually like to see where a Monospot is ordered, a prompt for an HIV test comes up. Where a syphilis test is ordered, where someone is thinking about secondary syphilis, a prompt for HIV comes up. Where Rocky Mountain Spotted Fever is considered, a prompt for an HIV test is ordered. I believe that the 4th generation assays will make that diagnosis much easier. And again, it's important to screen in all STD clinic populations and in all MSM populations.

SLIDE 67

We have linkages to help guide you through care. There are numbers here for HIV service, for acute HIV program that's a joint collaboration with the state and Duke and UNC Hospitals. Certainly, make sure that folks know about the signs and symptoms of acute HIV.

SLIDE 68

That concludes my two talks on Syphilis and HIV. We think it's an important topic because these diseases are not going away anytime soon. We're still seeing ongoing transmission of HIV in North Carolina and currently we have a co-epidemic of syphilis and HIV. Make sure you think about these illnesses when people of sexually active young age present with acute, non-specific signs or symptoms. And make sure you have all the support you need. We're here at the state to make sure we can help you and I hope you found this presentation helpful. Thank you.