AIDS: Evolution of an Epidemic (2007)
Lecture One—From Outbreak to Epidemic
Bisola O. Ojikutu, M.D., M.P.H.

1. Start of Lecture 1 (00:00)

[music] [ANNOUNCER:] From the Howard Hughes Medical Institute, The 2007 Holiday Lectures on Science. This year's lectures, "AIDS: Evolution of an Epidemic" will be given by Dr. Bruce Walker, Howard Hughes Medical Institute investigator and director of the Center for AIDS Research at Harvard University. And Dr. Bisola Ojikutu, director of the Office of International Programs in the Division of AIDS at Harvard Medical School. The first lecture is titled "From Outbreak to Epidemic." And now to introduce our program, the president of the Howard Hughes Medical Institute, Dr. Thomas Cech.

2. Welcome by HHMI President Dr. Thomas Cech (01:09)

[DR. CECH:] Welcome to the Howard Hughes Medical Institute and the 2007 Holiday Lectures on Science. We're webcasting live from our headquarters in Chevy Chase, Maryland and our auditorium here is filled with high school students from the greater Washington, DC area. The Holiday Lectures is one of many Institute activities dedicated to biomedical discovery and science education. To learn more about HHMI's many research and educational activities please visit our web site, www.hhmi.org. This lecture series focuses on HIV and AIDS. And we've lined up two experts: Dr. Bruce Walker who's an HHMI investigator at the Massachusetts General Hospital and Harvard Medical School in Boston, and his colleague, Bisola Ojikutu. They will combine basic research and clinical and public health work in their talks just as they do in their everyday work lives. Both speakers are M.D.s who do research and spend significant time with patients, but they don't see patients just in the Boston area, they go back and forth between Harvard University and the South African province of KwaZulu-Natal, a place where nearly one in five people is infected with the virus that causes AIDS. In these lectures Bruce and Bisola will take you from the microscopic realm of the virus and virus-infected cells to the realities of testing and providing AIDS therapies to people around the world in a case of limited resources. Many of you viewing these lectures have grown up in an era where AIDS has been well known, but in her first lecture Bisola will take us back to a time when only a handful of doctors in the U.S. began seeing patients with an odd constellation of symptoms. The first cases of what came to be known as AIDS were very puzzling. Was this really a new disease? What caused it? And how did it spread? Bisola will show us how the combined efforts of primary care physicians, epidemiologists and basic researchers put the puzzle pieces together. So we'll now have a brief video to introduce Bisola before her lecture.

3. Profile of Dr. Bisola Ojikutu (03:44)

[music] [DR. OJIKUTU:] So I'm a clinician, I'm an infectious disease specialist. I have a clinic at Mass General Hospital and I primarily treat patients with HIV. It's probably 50/50... HIV infection as well as other infectious diseases. Hi. - Hi doctor. - How are you doing? I see patients, I examine them, I treat them, I admit them to the hospital if necessary and that's very important to me, I enjoy that experience. And also from the HIV standpoint I like still being invested in the epidemic here at home and making linkages between what's happening here at home to what's happening overseas. So secondly there's the public health piece. I work as the director of the Office of International Programs at the Division of AIDS and we have a team that's made up of... really a diverse group of people. *We also did it in Botswana...* What we do here is we develop programs, we do research, we mentor medical students, we work on programs for young doctors, the residents and the fellows, and we work as a team, you know even though we're all sort of working on our different projects, we work as a pretty cohesive team. Oh! Yeah, yeah. What I hope is that the students will walk away realizing just how complex HIV is. Not just from the scientific standpoint, but

from the social standpoint, from the economic standpoint. It's such a multi-disciplinary disease and I think that's a good thing and it's a bad thing. It's a good thing because many different people can make a difference. The bad thing is that even if there was a vaccine available, that doesn't mean that the problem will be solved.

4. 1980 and the first signs of the coming epidemic (05:39)

So good morning everyone and thank you for coming. So I hope you got from the video that I'm a public health practitioner and a clinician so it's a little bit different that I'm speaking and giving a science lecture. But what I want you to get from my experience and what I'm going to tell you is that really what we're talking about is a very multi-disciplinary disease. The HIV AIDS epidemic has really shown that we can have an interplay between all the different aspects of science, both the basic science, the public health piece and the clinical medicine. Really science has sort of pushed the clinical piece and the need for new public health interventions has pushed science. So I'm hoping that if you decide to look into this field in the future, that you will realize that there are many different roles that you can play. All right, so let's begin. So I'm pretty sure that most of you were not born in the 80s, so let me take you back. There were a lot of strange things going on back then. An extra-terrestrial was actually the star of one of the highest grossing movies. A bunch of cats were actually a hit on Broadway. An actor was just voted in as president, and interestingly the U.S. beat Russia in hockey in the Olympics. Now I'm not a hockey fan, but apparently this was a big deal. So at the same time that all these strange things were happening, a strange new disease was brewing. Something that would change our world forever. It all started in Los Angeles in 1980 and at the time patients were presenting with sort of vague symptoms. Weight loss, lack of energy, diarrhea, fevers, sweats, rashes and swollen lymph nodes. So what did this mean? I mean these were all vague symptoms, I'm sure you've all had them, and it could be caused by any viral illness. So when these patients would present to their primary care doctors, often times they'd be sent home. But what's unique about this and what these patients were experiencing was that these symptoms didn't go away. They were chronic, they were progressive, and they were debilitating.

5. Pneumocystis pneumonia (PCP) found in affected patients (07:52)

So some of the patients actually presented with shortness of breath, really horrible shortness of breath. And a deep dry cough, and those patients would often times present to the emergency room and upon further investigation what they found is that these patients had a rather rare fungal infection called *Pneumocystis carinii* pneumonia, or PCP. Prior to this time we didn't see PCP in many patients. We saw it in patients who were immunosuppressed, usually from cancer chemotherapy. So what does that mean? That means that *Pneumocystis carinii* pneumonia is an opportunistic infection. An opportunistic infection is an infection that basically take the opportunity when your immune system is depleted, to cause disease. So when a patient presents with shortness of breath and cough, what's your knee jerk reaction? What do you do? Well, you get a chest x-ray. Well, first you examine the patient, then if you know something's wrong and you feel like you need to go further you get a chest x-ray. So, on the left you see a normal chest x-ray and you have clear lung fields and nice clean heart border. Next to that you have a chest x-ray that shows somebody who has *Pneumocystis carinii* pneumonia or PCP and basically they have an infiltrate in the lower right, which you see highlighted and the next step is to ask the patient for a sputum sample. So the patient coughs up sputum and you take it to the lab and you stain it and you might see some fungal pathogen which will lead you toward the direction and the diagnosis of PCP.

6. PCP outbreaks and the CDS (09:30)

So, were these new infections happening just in Los Angeles? Well no, we actually saw cases in New York City too. Now remember this is rare, so why are we seeing it now in New York City? So who noticed this spike in cases? Because remember I said primary care doctors saw them, ER doctors saw them, individual

doctors. How did we figure out that something new was happening? Well the Centers for Disease Control and Prevention is a public health institute that's located in Atlanta. And what they do is really outbreak investigation. So if you eat a hamburger at a fast-food restaurant and then somebody else eats a hamburger at a fast-food restaurant and you both get sick, the CDC goes and tries to figure out why you're sick. They also stock rare medications, so things that people don't normally need and can't go to CVS and get from the pharmacy. So what they noticed at the CDC at this time is that there was a spike in a rare medication called Pentamidine. Now at the time, remember we didn't see that many cases of PCP and Pentamidine treats PCP, so when they saw this spike they were like, "What's going on here?" What do we need to do to investigate to figure out what's going on?

7. Video: First AIDS patient (10:47)

So what they did is they sent some CDC officers out to the places where they saw these spikes and one of the places that they went was L.A. and they worked with Dr. Michael Gottlieb. Now Dr. Michael Gottlieb was a young assistant professor who was an infectious disease specialist and an immunologist working at UCLA, University of California, Los Angeles and he was one of the people to see some of these first cases of PCP or *Pneumocystis carinii* pneumonia. So let's hear from him first hand. So this patient had weight loss and fever and appeared quite ill and we thought that he would have something ordinary, something that's already in the textbook so we did not pay huge attention to him initially. But when he developed *Pneumocystis* pneumonia we got much more interested because people coming in from the community with pneumonia, it was highly unusual if not unheard of to come in with *Pneumocystis* pneumonia and that indicated that he had a severe immune deficiency, but the question was why.

8. Similar infections in the first set of patients (11:57)

So in order to get a better sense of why, Dr. Gottlieb said, "Well, you know, I'm a clinician but I'm going to "write up these cases, I'm going to put them together "and then put them in the literature so that people "see that something new is happening" and this paper that he wrote for the *MMWR* or Morbidity--which is disease, Mortality--death, Weekly Report that came out in June of 1981 was really the first report of this new disease manifestation, new disease entity that we have in our literature. So he as one clinician was able to make a significant contribution that led to further investigation into this disease process. So I said that this is a case report or a case series, so it's a series of patients that have commonalities, you basically write up the commonalities and you try to figure out using just simple deduction what's going on with a group of patients. So in this particular case series there were five patients. So four out of five were previously healthy, so that's good to know. One of them had Hodgkin's, which is a lymphoma, but basically he had chemotherapy about three years ago so in general he was well now. All five were active homosexuals. All five had this *Pneumocystis carinii* pneumonia or PCP.

9. Opportunistic infection: Cytomegalovirus (13:18)

And all five had CMV. Now what is CMV? CMV stands for cytomegalovirus and it's a herpes virus and it's also an opportunistic infection. Cytomegalovirus is something that probably about 60% of the adult population in the United States is exposed to. So it's quite common but it doesn't manifest itself as a disease necessarily until you actually develop immune dysfunction. And when someone has immune dysfunction they can actually present with CMV or cytomegalovirus retinitis which is an inflammation at the back of the eye. So what you're seeing on the left is a normal retina, the back of the eye. In the middle you have a cytomegalovirus-infected retina and they're basically pointing at the dark brown areas which are hemorrhages and areas of inflammation because that's what cytomegalovirus causes, and then you see some CMV particles and that's underneath an electron microscope.

10. Opportunistic infection: Candidiasis (14:28)

So four out of five of these patients also had something called candidiasis. Now what's candidiasis? Well you guys have probably heard something about candida before. It's a fungal infection and some people have it in their mouths, normal healthy people, they'll just have some candidia in their mouths, they'll have it in their gastrointestinal tract and again it doesn't really cause a problem. It's when your immune system has a dysfunction that you actually see some manifestation of disease. So what is this? An opportunistic infection. So in this particular patient on the left you basically have overgrowth of candida on the tongue and we call that thrush. And then you have some fungal cells that have been stained on your right.

11. Opportunistic infection: Kaposi's sarcoma (15:14)

So this one is really interesting. This is Kaposi's sarcoma and this is another disease manifestation that we saw a spike in cases in back in the early 80s. Sarcoma so it's a cancer and what would happen is that these patients presented with purplish vascular-type lesions on their skin. Now prior to this time we really only saw Kaposi's sarcoma in patients who were over 60 and they were Mediterranean or of Eastern European descent. Not sure why it was particularly in that population, but that's who we saw it in. So when we saw it in these patients who were young, pretty much, we wondered what's going on here? So on your left you have the cutaneous lesions, the lesions of the skin, those purplish vascular lesions and then you have what we'll call Kaposi's sarcoma herpes virus because this particular cancer is caused by a herpes virus.

12. Opportunistic infection: Herpesvirus (16:15)

So I'm sure you all know what this is. This is just herpes simplex virus and it causes a cold sore in lots of people, probably about 20% of the population has been exposed to herpes simplex. So what would happen in these particular patients is that they would have recurrent cold sores, you know just wouldn't go away or would just come right back again, and that's because again, their immune system was depleted and sometimes in these patients they would actually have herpes virus that would spread and it would go to the esophagus or it would go to the brain. So we had these interesting pieces of this puzzle. We know that it primarily affects previously healthy young gay men. We know that these are a constellation of opportunistic infections, so a lot of different opportunistic infections, not one. We have geographic clustering in Los Angeles and New York and this disease was highly fatal. So two out of five people had actually died who were reported in this *Morbidity and Mortality Weekly Report*, two out of five. So we had this group of patients, we had this, you know, disease process. We have to give it a name.

13. AIDS defined (17:30)

So the CDC decided to call it by 1982 Acquired Immune Deficiency Syndrome. Acquired, because it didn't come from birth, they developed it later in life. Immune deficiency, because we had this constellation of opportunistic infections and a syndrome, because there were a lot of different things that were going on with these patients, not one thing. Once we had a name we came up with a case definition. So remember we said Kaposi's sarcoma was confirmed with something that we saw in these patients more often, so in the case definition we had to have Kaposi's sarcoma confirmed by biopsy in patients under 60. These patients had life-threatening opportunistic infections, again confirmed by biopsy, so basically they just took whatever tissue it was affecting, they just took a piece and actually looked at it under a microscope. There was also an absence of other illness or immunosuppressive therapy. So why was the case definition important? So when you have a disease don't you want to get a diagnosis and usually what we do is we have a diagnostic test. So for this disease, because this is a new rare entity we had no diagnostic test yet. So we had to come up with a case definition which is what I just read to you that will allow rapid identification of new cases, allow for tracing of the people who actually have disease and allow for identification of people with AIDS. So what else do you need to do? Well, you draw blood on patients and that's like, you know, obviously that's sort of a

standard thing that people do, and you find interesting things when you draw blood on patients. But in these particular patients they had a decrease of very important immune system cells called T helper cells.

14. Cells of the immune system (19:13)

I'm going to just give you a little bit of an introduction to the immune system. Dr. Walker is going to talk about it extensively in the next lecture, but just so you have a taste of what he's going to talk about, we have B cells and B cells react to antigens by producing antibodies. And when they produce antibodies those antibodies go on to neutralize different pathogens. We have two different types of T cells, cytotoxic T cells and helper T cells. The helper T cells are cells that conduct the immune system, the cytotoxic T cells actually recognize antigen on cells and actually kill those cells directly. And then we have antigen-presenting cells.

15. Antigen-presenting cells and helper T cells (19:55)

So antigen-presenting cells actually engulf foreign pathogens like a virus, process it in the cell and then present antigen on their surface. And antigen is just protein that actually stimulates or actually, you know, recognizes and becomes a part of the immune system so it can actually target other cells. So what's happening with helper T cells? So the helper T cells recognize the antigen that's on the surface of the antigen-presenting cell. They actually stimulate cytokine production and cytokines actually work as messengers within the immune system and the cytokines stimulate other cells like B cells, other T helper cells, cytotoxic T cells.

16. Early epidemic signs in the U.S. (20:45)

So once you know this about the immune system, you know that there's this problem with T helper cells and you have T helper cell decline, then what else do you want to do? Well you want to find out, is this really a new disease entity? Or is this something that's just been around for a long time and we haven't noticed it? So what the CDC did, they asked doctors to actually go back in their records to 1979 and pull out all the cases of people who they saw at that time with these different opportunistic infections. And what you see from 1979 is that there are some cases of these opportunistic infections, not that many, but this is more than you'd normally see. And in 1980 you see even more. And in 1981 you see even more cases of opportunistic infections. This basically says, look, we have a new disease process here and we need to investigate it further.

17. Tracing individuals to determine the spread of the epidemic (21:41)

So we need to find out how this disease is actually being transmitted because at the time we don't know yet. We do know that amongst those early cases, most of them were men who have sex with men. So there's some indication that this is sexually transmitted. So then how do you really figure out whether that's what's going on? Well, you do contact tracing. So the CDC basically went to all the people who actually met that case definition and they asked them very specific questions about their sexual history. How many people did they have sex with? What was the gender of those people? Where did those people live? And it was through that process that they encountered who we will call Patient Zero. So Patient Zero was a flight attendant, he lived in Canada but he worked for an airline and flew from New York to Los Angeles on a regular basis. He basically during his interview with the CDC, told them that he had had 250 sexual partners each year for the last three years. Yeah. Sorry. **[laughter]** So it's a lot and what happened at the time was that the CDC said, "Okay, how are we going to get in "touch with all of these people? "I mean does he even know all these people?" And he didn't. He had been engaging in some anonymous sex, he wasn't using condoms, but he did have a little black book. And inside his little black book he had about 72 names of the, you know, like, 750 cases that he had over that time period. And so the CDC went to those 72 that were in that book and they

tried to see who had opportunistic infections of those cases. And what they found from their tracing was that eight people actually had opportunistic infections. They had KS or PCP or other opportunistic infections. The line here connecting those cases just means that there was a sexual interaction. So if you notice carefully four of them were in New York and four of them were in LA. So that's what we mean by Patient Zero, that he was possibly one of the people who connected those two locations where we initially saw cases being reported. So what do you do at that point? You go to each one of those contacts and you ask them who have they slept with. And what they found was that a number of them also had opportunistic infections. Go to those contacts, find out who they slept with, and a number of them also had opportunistic infections and met the case definition of AIDS. And then you go to those contacts until you have this web of people who have AIDS and what does that tell you? Well, one, it tells you that the disease is sexually transmitted or at least it gives you more evidence in that direction. But two, it also tells you some common sense, okay? If you sleep with one person you sleep with everybody that they slept with. So I think that those are two principles to walk away with as far as the contact tracing is concerned.

18. More pieces of the AIDS puzzle (25:02)

So we started out with a few pieces of the puzzle and now we have a few more. We have the fact that this disease, this new disease entity affects previously healthy young men who have sex with men. We have the fact that these people have a constellation of opportunistic infections. We have geographic clustering in Los Angeles as well as New York. We have the fact that it's highly fatal, remember I told you a lot of people in that case report were actually passed away by the time that case report came out. Then I mentioned that we had depleted helper T cells and now given the fact that we have that contract tracing we know that there's evidence of sexual transmission. So I can stop and take some questions.

19. Q&A: Is Kaposi's sarcoma a deadly cancer? (25:55)

Yes?

[STUDENT:] For the Kaposi's sarcoma, you said it's a cancer caused by the herpes virus, but it's not a deadly cancer?

[DR. OJIKUTU:] So those first cases that we saw of Kaposi's sarcoma were interesting because they were different from the cases that we had seen before. So the previous cases were in men who were, you know, in their 60s or older and they had those vascular lesions. And those men usually didn't die, okay? So they actually did fine. Maybe they had chemotherapy but they actually did fine. But with these patients who we now saw presenting, some of them did fine and some of them had progressive disease so that sort of links it as an opportunistic infection. That's a good question and you know you get a t-shirt if you ask a good question. But you know what, you are way up there, okay, so I'm coming really close and then I need an assist from one of you guys.

20. Q&A: Are opportunistic infections worse in AIDS patients? (26:58)

[STUDENT:] The opportunistic infections that people had in the beginning, were they much more severe than other cases that didn't have AIDS?

[DR. OJIKUTU:] So I think it really sort of depends on which ones we're talking about because, you know, you see patients who are on cancer chemotherapy and who are immunosuppressed and they can have really bad opportunistic infections too. The commonality is the immunosuppression, okay? So I think that what happens, it just... it's a matter of the immune system, it's not so much a matter of okay, well, this particular AIDS virus necessarily causes the worst opportunistic infections.

21. AIDS timeline (27:35)

So let's get back into our story and go back to the AIDS timeline. So in 1981 the epidemic was first identified by those first five cases and the *MMWR*. But what happened next? Did it spread? I told you that it was in New York. But where did it go from there? So let's take a look at an animation and see where it goes.

22. Animation: U.S. AIDS epidemic (28:03)

So each dot represents cases. In the next few years we had cases in Chicago, Houston, and Miami. Then over the course of the 80s and the early 90s we basically had cases spreading all throughout the United States. And when you get to 1997 and you add all the AIDS cases that we saw since 1981 we had reached 600,000.

23. Early groups affected by AIDS (28:32)

So let's take a moment and think about some of these early groups who were affected. So I mentioned that we were talking about initially young men who have sex with men and I'm sure you can imagine that there was a lot of fear and anxiety within that population at the time, given the fact that, you know, their friends were dying, their partners were dying, we didn't know what this disease was, we didn't have a test to really diagnose it and we certainly didn't have any treatment at the time. And there was also a lot of stigma. One of my patients was telling me a story about his partner, one of his early partners back in 1985 who actually died and he died at home. The reason why he died at home instead of dying at the hospital is because nobody would admit him to the hospital. Health care workers were scared. So then cases started to be reported in other groups, not just men who have sex with men, but Haitians. Case reports came out from Haiti and of course that put a lot of stigma on them too because then people didn't want to look at issues of immigration. Then cases came out in people who were using IV drugs, and you had to think to yourself, some people probably felt, okay, this is in men who have sex with men. I'm not a man who has sex with men. This is in Haitians, I'm not a Haitian. And this is in people who are IV drug abusers, and that's not really me. So this isn't necessarily my problem. But I think that there was an increased concern about this when the cases came out that were in hemophiliacs. These were people that got blood transfusions. And what does that mean? That means it's in the blood supply and basically anybody who gets a blood transfusion can get it.

24. Early theories on what caused AIDS (30:20)

So we have that it's AIDS, we have a name, and then we have a lot of people who are trying to figure out what's going on. What were some of the early theories about AIDS? Well one of the first theories to come out was that this was an autoimmune reaction to foreign sperm antigens. So what does that mean? So basically the first cases were in men who had sex with men and the thought was that sperm in another man might cause an auto-immune reaction. Now this fell by the wayside very quickly because obviously it doesn't really sound legitimate but then you also had cases in people who weren't men who had sex with men. And then there was a question of whether or not immune dysfunction was caused by something called amyl nitrite. That's an inhalant that people use to have euphoria and have increased pleasure during sex. So let me make it clear to you all what was going on. So a lot of these drugs, particularly this amyl nitrite was used sort of in clubs and people would use them at night, you know, when they were having sex and it was something that people just sometimes did. So in some of those case reports that initially came out, people reported a history of having used this drug. So they said, okay, that's a common factor, so maybe that's what's causing the whole problem. And it clearly wasn't because there were lots of other people who were, you know, not using any sorts of drugs that actually had problems.

25. Gallo and Montagnier discover the AIDS virus (31:49)

So then the question was, maybe this is an old pathogen that's just presenting in a new way. So I mentioned cytomegalovirus and that's something that's, you know, been around for awhile and people knew about cytomegalovirus and it does cause some transient immune dysfunction, but remember what I said, 60% of the population had been exposed to CMV so why weren't those people also having opportunistic infections? It didn't make sense. So then the question was, is this a new disease caused by a recently described lymphotropic virus? So what does that really mean? So Dr. Robert Gallo who is at the National Cancer Institute. He was working on these newly described lymphotropic viruses and he actually cultured the first one and he thought, well, because these lymphotropic viruses actually impacted T cells, that maybe because we remember that there's a T helper cell decline with this AIDS virus, maybe it's the same family. So at the same time Luc Montagnier who was at the Pasteur Institute, he was doing some similar work and both of them sort of said, okay, maybe this is the same type of virus, so let's culture it, let's work on it. So why is it important to actually find the pathogen? To actually find which virus this is? It's of primary importance because you need a diagnostic test. Remember we still don't have one. So at this point I'm actually going to go to a test demonstration of one of the diagnostic tests that we developed and we're going to come back to this issue of culturing the virus.

26. Demo: Rapid AIDS virus test (33:33)

So one of the tests that we have to diagnose the AIDS virus actually detects antibodies to the pathogen. You get results in about 20 minutes, it's 99.8% accurate and it's very low cost. So it's great for follow up of patients, they can just sit there and get their test, they don't have to leave, because a lot of patients actually do leave and never find out their test result. So Zinhle Thabethe is here and she's one our colleagues from South Africa and she's said that she doesn't mind getting tested for HIV. So this is Zinhle, she's worked with us for a long time. And I need a nurse. Adam. Why don't you come up? So Adam Barrett is a nurse at Massachusetts General Hospital which is the hospital where Dr. Walker and I work. And Adam is going to actually do a test on both Zinhle and I. Adam's putting on gloves because that's universal precautions. You don't want to expose yourself to patient fluids irrespective of what you know about them. Okay, so Adam is looking at the expiration date because it's important doing a diagnostic test, we need to make sure that it's fresh. So he's got out the reagent. Which one of you will be tested first? I'll be first. Okay so now he's got an alcohol pad. Now you get nervous. That's what I was feeling when you pulled out the alcohol pad. So now he's going to stick me. Okay. Okay so now he's putting some of the blood on a little loop. Okay. Okay. Now he's adding our testing strip to the reagent that now has the blood in it. Okay, Zinhle is next. Putting the lancet in a nice safe container so nobody else gets stuck. **[laughter]** All set? Okay. So we're going to let those percolate, we'll come back to it at the end.

27. Isolating the AIDS virus from lymph cells (37:52)

So let's go back to this issue of viral culture. Remember I said Dr. Rob Gallo and Luc Montagnier wanted to culture virus to figure out if they could identify it as something new. So what they observed, remember back to the very beginning of the lecture is that some of these patients presented with swollen lymph nodes. And these patients weren't necessarily overcome with opportunistic infections. Remember this was part of the original list. So if that's the case then maybe the hypothesis should be that AIDS is caused by a virus concentrated in the lymph nodes that then destroy helper T cells. So then the experiment is going to be to culture a virus from the lymph node. So what they did was they took a lymph node specimen from a healthy volunteer which is on the left and from an infected volunteer or a patient who actually had symptoms of AIDS on the right. They ground it up and they added a growth factor called IL2 which is something that Dr. Gallo was using before when he discovered that new family of lymphotropic viruses. So this was great because that made the lymphocytes actually grow. So what you see on the right is actually really bizarre looking. Basically it's just aggregates of cells that are infected. They look kind of like giant cells and it's basically syncytia formation. So this just highlights, okay, here's a normal cell and here's actually one of those great big giant cells.

28. HIV the retrovirus that causes AIDS (39:28)

So when they actually looked at this, they basically saw that it was teeming with viruses and they looked at it under electron microscope and what they saw was a retrovirus, and so a retrovirus is a little bit different from a normal virus and I'll get to that in a second, but what you're seeing here is just a picture, an EM of the HIV virus basically budding off of a cell. So if you look at that schematic, it's a retrovirus, they actually had to give it a name and the name was HIV which is what we know today, or human immunodeficiency virus. And it took years of work to actually sort all this out but basically you had an envelope protein, you had the all-important reverse transcriptase, which made RNA from the virus into DNA. You have integrase which is another enzyme. You actually have the RNA which differentiates this retrovirus from a regular virus and you have protease.

29. Antibodies to HIV found in infected people (40:28)

So if AIDS is caused by a virus, if it's caused by this HIV virus, does the body launch an immune response? Why are these people still sick? You're not still sick with a cold for years. So let's go back to this issue of B cells. So B cells recognize antigen, so they recognize a pathogen. They make antibodies and they neutralize a pathogen, meaning they get rid of it so they get it out of your body. So what was happening in these men who have sex with men? Well, some of them with AIDS had antibodies against HIV, but some of them without AIDS also had antibodies. The point is that virus could be cultured from anybody who had antibodies. So what is that telling you? It's basically telling you that the antibody response isn't sufficient in HIV.

30. Development of an antibody-based test for HIV (41:27)

So okay, let's go back to our AIDS timeline. The epidemic was first identified in 1981. HIV was cultured in 1983 and now because we have a virus we can now develop a diagnostic test to determine just how extensive the epidemic was. And that first commercial test to detect HIV was developed in 1985. So you saw one version of the test, that's a quick version. What we use at the hospital where I work is an ELISA, or an enzyme-linked immunosorbant assay and it's confirmed with a Western blot and the theories of both of them are similar so I just want to focus your attention in this lecture on the ELISA.

31. How the ELISA test works (42:13)

So what happens? Well, patient blood from patients are put in a well and in that well you basically have inactive HIV protein that's anchored by albumin beads at the bottom of the well. You add the patient blood and if there's anti-HIV antibody in the patient's blood, that's going to bind to the antigen in the well. Then you add chemically tagged antibody that labels human antibodies so it just has a chemical tag on the end and then you add a chemical that's actually going to react with the chemical tag. And at the end of the day you just want to be able to see that there are antibodies in these wells. And if you look at the well clearly there is a difference between those that are brown and have antibody and those that are white and don't have antibody.

32. Detecting HIV in samples preserved before the outbreak (43:02)

So once you have a diagnostic test there are lots of things that you can do. The data in this study right here comes from a group of men who have sex with men in San Francisco who are in a hepatitis B study. In that hepatitis B study they were basically collecting blood from them and then storing it at different time points. So what you could do is actually run the test on these samples over time and see how many of these people actually developed HIV. And amazingly they found that 70% of the cases within this particular group, men

who have sex with men in San Francisco actually developed HIV between 1978 and 1984. So that was a huge finding.

33. HIV infection precedes AIDS symptoms by years (43:51)

So what would happen to somebody who had HIV over time? So if you look at disease progression, basically you have asymptomatic infection. Over the course of time you have this helper T cell decline and then patients develop AIDS. AIDS is characterized by the opportunistic infections that I mentioned to you already. So how long does that take? Well HIV is really the course of time throughout the whole infection. But it takes eight to ten years to actually develop AIDS and then once you developed AIDS the average time to death is about 18 months.

34. Modes of HIV transmission (44:30)

So the other thing that you can do when you have a test is that you can confirm that the people who you think have risk factors actually are people who are transmitting disease, they have it themselves. So you look at the contact tracing that I showed you before where the cases were connected by sex and you can actually test them for disease so that you know that sexual contact is an issue, it's a mode of transmission. You can look at IV drug users and find out whether or not they have a higher risk. You can look at people who actually get blood transfusions and know that they have a higher risk. I mean, you were using information before but now you have a diagnostic test that actually gives you the information. And then there's also this issue of mother to child transmission and I'm going to talk about that more in my lecture tomorrow. But you can test mom for HIV and then test baby and then you know that transmission has occurred from mother to child and that makes sense because it's exchange of intimate body fluids, almost like with sexual contact, when the baby actually goes through the birth canal.

35. U.S. AIDS infection estimates from mid-1980s (45:39)

So if you look at the United States over time, you know people weren't so worried when they got this information so these are the numbers of cases that we had between 1981 and 1986 and it really wasn't that high, but the CDC made estimates as to where this would go and when they made those estimates they really saw a significantly increased rate of cases by 1991, so about 25,000. And they were actually correct—close to being correct—when they looked at actually the number of cases that we had by the time that we were talking about in 1991 so like the late 80s and then early 90s.

36. Global HIV/AIDS estimates (46:22)

So from that time, from 1991 and 25,000 cases or 20,000 cases we have 33.2 million people who are infected with HIV worldwide this year. So where are those cases? So no corner of the world is immune. There are cases pretty much everywhere but I really want to focus your attention on sub-Saharan Africa because that's where the largest number of cases are. And that's where I spend a lot of my time working. So I think the other point is looking at new infections. Across the globe we have 2.5 million new HIV infections in 2007 and a whopping 1.7 million of them are in sub-Saharan Africa. So I want to conclude with a few numbers that I think are important. Just to re-emphasize that in 2007 we had an estimated 2.5 million people with new HIV infection. Every day more than 6,800 people contract HIV. In 2007 2.1 million people died from AIDS and from those five cases that we saw in Los Angeles back in 1980 and that were reported in 1981, more than 25 million people have died of AIDS. So clearly we have a huge problem and really it's going to take the combined efforts of scientists, clinicians and public health practitioners to bring an end to this epidemic. So I'll stop there.

37. Q&A: What happens after an HIV-positive test result? (47:58)

Let's take some questions. There were some questions over on this side.

[STUDENT:] Usually when the diagnostic test first came out, usually after the test shows positive, what actually happens to the patient? Like what are the next steps?

[DR. OJIKUTU:] Oh, okay, that's a really good question. The whole process of testing is not just about pricking, I mean we did it in a very simple way just to show it. It's not about pricking and putting the blood in the reagent. It's really pre-test counseling, the actual test, then post-test counseling. So, you know, I've seen patients who were just recently diagnosed with HIV and usually what you have to do is sit down and talk to them about what their infection really means and you have to test for those T helper cells that are in the blood and figure out what you can do in terms of helping to manage the disease and this discussion is going to evolve over the next lectures, we'll talk about what the interventions would be. But it is definitely about talking to them and figuring out, do they feel okay about it. Most people, you know, need help in terms of counseling, so it's definitely a process.

38. Q&A: How did the infection get so wide spread? (49:10)

[STUDENT:] You were saying that the 5 cases in 1981 that started in L.A. and New York, what was that connection to the sub-Saharan Africa that, like, what was the strong connection between that to get the 22.5 million with AIDS today.

[DR. OJIKUTU:] Okay, that's a complicated question too. You know I think that basically what we're talking about is an issue of finding out where the first cases were and figuring out how that then spreads and I think that there are just a lot of issues in terms of the type of virus we're talking about, how we're talking about immigration and people migrating and actually giving infection to each other, so I'm going to leave a lot of that discussion up to Dr. Walker's fourth lecture because he's going to be talking about the origins of HIV, the different types of HIV and exactly how the epidemic progressed over the years.

39. Q&A: What is the time from HIV infection to developing AIDS? (49:58)

[STUDENT:] You said that it takes like 8 to 10 years for you to develop AIDS. So has there been any cases where it took a person shorter or longer to develop AIDS?

[DR. OJIKUTU:] Oh definitely, definitely. There are cases of people developing AIDS more quickly, there are certainly people who don't progress and actually don't develop AIDS and again that's another complicated immune system question but it's variable. What I gave you were average numbers, just for the average case.

40. Q&A: Does the HIV test detect HIV throughout infection (50:35)

[STUDENT:] So the test you took right now, would that be for AIDS or would it be for the HIV virus? And if it is for the HIV virus, so you could possibly take it at any of the, you know 8 to 10 years that you'd have it and you'd know.

[DR. OJIKUTU:] Yeah, no absolutely. So this test detects antibody to HIV. So antibody to HIV actually comes on when you actually are infected. I mean it takes a while for your body to make that antibody, but you will develop antibody to the virus and that antibody will progress, because remember I told you patients with AIDS have antibody, patients who are asymptomatic and who are on the disease progression also have antibody. So at any point in time you could test for the HIV antibody.

41. Q&A: How was HIV transmitted in Haitian cases? (51:24)

[STUDENT:] The outbreak that occurred in Haiti, were they also homosexual men or was that the first case of heterosexual?

[DR. OJIKUTU:] So most of those cases were actually heterosexual transmission and I think... I don't want to mislead you in thinking that, okay, well, you know, it's just very easy to connect that piece to the other piece, but I think that what went on was that we had these cases in Haiti and they could have been around for a long time but people didn't actually know that they were around. Now some people have tried to say that it was an issue of migration that there were people that were going down to Haiti and having sex and then they brought it back to the United States and then some of that has been a bit disproved. So yes, these people had heterosexual transmitted disease and there was probably also heterosexually transmitted disease in other places in the world. I sort of simplify the story to a certain extent to show you what was happening in the United States. Let me go over to this side. Yes.

42. Q&A: Are opportunistic infections getting worse over time? (52:23)

[STUDENT:] As more and more people are getting HIV and then spreading, are the opportunist diseases getting more and more, like, extreme and more worse and are the time periods shortening where it turns into AIDS and stuff?

[DR. OJIKUTU:] So I don't think that the opportunistic infections are getting worse, I think that there are a lot of people who don't have access to what we'll talk about as treatment for HIV and for AIDS. So you see a lot of opportunistic infections. For example, here in the United States people have access to care, a lot of people do and they actually get treated so we don't see as many of these opportunistic infections. You go overseas to where I go in South Africa in KwaZulu Natal and you see disseminated tuberculosis, you see terrible infections in the brain and you see these incredibly sick people in the hospital and it's not to say that that couldn't happen anywhere else, it's an issue of immune dysfunction. It's really more an issue of barriers and access to care which is something I'll talk about in my next lecture.

43. Results of rapid HIV test (53:32)

Okay. So our test is ready. So here on the left you have Zinhle's test. Here on the right you have my test. So if you look at my test you see that there's a red band at the top near the C. The C is the control band. So basically on this test strip you have two different types of things that are happening here. At the control you have anti-human antibodies and basically all that means is that it's going to react with any antibodies in your system, and everybody has antibodies. So that's the control. At the T is the test, and that's where you actually have synthetic HIV proteins. So that means that if you have antibodies to HIV, the T should turn red. Does that make sense? So, on my strip I have a line at C so there's control that's showing up. So in Zinhle's test she has a line at control and she also has a line at T. So this test is positive.

44. Zinhle Thabethe and her HIV-positive status (54:48)

So Zinhle, did you want to come up and tell us a little about your story. You have a microphone on.

[MS. THABETHE:] Actually I've just taken a moment of reliving what actually happened in 2001. I was diagnosed in 2001 in South Africa so this is not a new story. I've known about it and actually this moment has made me think about that when I was diagnosed I was a little bit, a few years over your ages, I was probably 21 when I contracted the virus but then I discovered when I was 25 years old in 2001. So this is the real story and like Bisola has actually mentioned, you don't just walk in a clinic and they prick you and they tell you you're HIV positive. This was just a demo. You go through a lot of counseling and people helping

you to figure out what you need to do and help you throughout the steps. So I have been there. So I've actually had people like Dr. Ojikutu who have been helping me in South Africa. So yeah, HIV is still around, that's why it's an important opportunity for you young people to know that you're still needed in the fight against HIV, we still need to make more scientists out of you, more doctors because the problem is not over yet, we still need to fight more and we still need to figure a lot of things that are not known to people and not known about HIV at this point and as you see the slide showing that the most, most of the problem is where I am and where I live in South Africa in KZN where Dr. Walker and Dr. Ojikutu are working. There is still a lot to be done and probably you will also have a role to play if you focus in science and get interested in the stories they both tell.

[DR. OJIKUTU:] Thanks Zinhle. **[applause]**

45. Closing remarks from HHMI President Dr. Thomas Cech (56:59)

[DR. CECH:] Well, thank you Bisola for a fascinating lecture and thank you students for your great questions. While it's devastating to think that this plague has continued to grow for 25 years, it's heartening to see how science can contribute to understanding and fighting it. In the next lecture Bruce Walker will reveal how much we've learned about the complex lifestyle of the HIV virus and the epic battle that the immune system continues to fight against infection. **[music]**