AIDS: Evolution of an Epidemic (2007)
Lecture Three—Drugs and HIV Evolution
Bisola O. Ojikutu, M.D., M.P.H.

1. Start of Lecture 3 (00:04)

[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 third lecture is titled "Drugs and HIV Evolution." And now to introduce our program, the grants program director of the Howard Hughes Medical Institute, Dr. Dennis Liu.

2. Welcome by HHMI Program Director Dr. Dennis Liu (01:11)

[DR. LIU:] Good morning and welcome back to the Howard Hughes Medical Institute and the Holiday Lectures on Science. This morning's speaker will be Bisola Ojikutu. In her previous lecture Bisola took us back to the dramatic days when AIDS first emerged as a brand new disease and then she talked about how it grew to become a global plague of unprecedented proportions. As a physician Bisola was drawn from a concern to helping individual patients to helping communities of patients and once Bisola became interested in HIV it was natural for her to be concerned with public health policy issues and health care delivery, especially for underserved communities. Now in this lecture Bisola will talk about how treatment for HIV infection has turned this disease from a death sentence to a manageable chronic illness. But she's also going to point out that although we have good treatments for HIV, people who need treatment often don't get it and she'll talk specifically about programs in South Africa that she's designed to help deliver treatment to some of the most underserved and stressed communities. And now we'll have a brief video to introduce Bisola.

3. Dr. Bisola Ojikutu in South Africa (02:30)

[music] [DR. OJIKUTU:] I've been working in South Africa for the last three some odd years and what I've done over that course of time is worked on developing programs and sustaining programs that increase access to care and treatment for patients there who are in dire need of treatment. We're coming up with a research agenda where we're going to be looking at outcomes for the kids, the orphans who are going to start anti-retroviral therapy. Some of them have already started. There's a lot we don't know about adherence in that population, about access to care in that population. Working in South Africa I've been inspired by the people and the places that I've been exposed to. I think it's been an awesome experience and I have thoroughly enjoyed it. I've learned a lot and it hasn't just been me giving back, I've certainly gotten a lot from the experience, both the patients, the doctors, and the nurses who I've worked with. I do feel hopeful. You know when I first went to South Africa, that was in 2003, there were just a couple thousand people on highly active anti-retroviral therapy, and today, by last count, 300,000 people are on medications. My concern is that if there isn't HIV is it just going to be something else? You know, some other infectious disease or some other chronic disease that's going to disproportionately impact these communities, these resource-poor settings where the health care infrastructure isn't good enough to manage it. So while we're dealing with HIV I think that we need to be rebuilding the health care infrastructure in most of these countries for the future.

4. Antiretroviral therapy can halt progression to AIDS (04:23)

So good morning everyone and welcome to your second day of lectures. I just wanted to start by telling you that when I was a first year in medical school I shadowed one of the doctors at the hospital where I was, and

we would go around the AIDS ward, because at that particular hospital they had a AIDS ward, they had a cardiac ward and they had a cancer ward, so each disease had its own little place. And what was so sad about working in the AIDS ward was that there was very little that we could really do for those patients so they were just extremely sick and we just sort of watched them die. But by the time I was a fourth year in medical school, so just merely three years later, there really was no AIDS ward, they actually closed it, just because, you know, there really weren't that many AIDS patients who actually needed to be admitted to the hospital. So what happened there? You know, what really changed things? It was the development of anti- retroviral therapy, or the medication that we use to treat HIV. So let's look at disease course in HIV and sort of review what we talked about yesterday. So most patients who are infected with HIV will develop AIDS and their disease course is characterized by a decrease in helper T cell count and an increase in viral level. Once they develop AIDS they'll have those opportunistic infections that we spoke about yesterday and eventually they're going to die. So what do you do to stop this lethal disease course? Well, you stop viral replication.

5. Video: Benefits of antiretroviral therapy (05:52)

So you guys met Zinhle yesterday and you know that she's HIV positive. But she's also on anti- retroviral medications, so let's see what that's done in her life.

6. AZT: The first antiretroviral used to fight HIV (07:44)

Okay, so let's look at our AIDS timeline which you probably remember from yesterday. So the epidemic was first noticed in 1981 and we had cultured the virus two years later, then two years following that we had the first commercial test to actually detect antibodies to HIV. And then it was sort of miraculous because six years after noting five patients in an ER in Los Angeles, we actually had a medication that would treat this virus. The medication was called AZT. So what is AZT? So it's basically very similar to thymidine which is a building block of DNA. So what's different about it is that AZT has an azide side chain as opposed to the hydroxyl side chain of thymidine. And the interesting thing is that back in the 60s, you know, some researchers said, "well, you know, let's synthesize a drug "that maybe we can use in cancer." And they synthesized AZT and it just didn't work. So they put it on the shelves and now when HIV came up, somebody said, "Hmm, let's try this for HIV."

7. AZT's mechanism of action (08:50)

So how would this work? So HIV RNA is reverse transcribed to a growing strand of DNA. So of course you see at the top, the HIV RNA and what happens as it's being built is you have nucleotides coming in and binding to the hydroxyl group that you see there. So when AZT comes in, it looks like a nucleotide, binds to the hydroxyl group, but you have this azide side chain. So it blocks further extension of the chain because the other nucleotides can't bind to it. So that makes sense. So let's look at an AZT animation.

8. Animation: AZT blocks reverse transcriptase (09:35)

So if you look at reverse transcriptase you see that HIV RNA is reverse transcribed into a growing strand of DNA. You have the purple nucleotides coming in, building on the DNA and the yellow molecules are RNA that's being degraded. So what happens when reverse transcriptase is inhibited by AZT? So here you have reverse transcriptase, and you have the HIV RNA coming in, the nucleotides getting built on so that you have the growing DNA strand, but then you see these green molecules. So the green molecule is AZT and here we can compare it side to side with thymidine. So again you're seeing an azide side chain on the AZT and a hydroxyl side chain on the thymidine. And of note, both are triphosphoralated before they're incorporated. So here you see AZT coming in and reverse transcriptase thinks it's a nucleotide. It incorporates, chain termination ensues, and the life cycle is disrupted.

9. Drug development and approval process (10:55)

So when you have a new drug it actually has to go through a pretty extensive process before it gets on the market. So what happens first is you do pre-clinical testing and that's in animals. If things look good you do safety testing and that's phase I, small group of patients. You can also figure out dosing when you do that. If things look good there you do a phase II trial which is larger. Again you're looking at safety but you're also looking at efficacy, so does it really work? And phase III trials actually have a larger group of patients but you're still really looking at safety and efficacy. So at that point if things look good from your trials, you go to approval and you do post-market testing. So it doesn't sound too complicated but this can really take more than 15 years.

10. AZT's initial clinical results were encouraging (11:42)

So let's look at the AZT phase I trial that was performed at the National Institutes of Health and Duke University. So in the phase I AZT clinical trial they were given AZT for six weeks. These are patients with HIV obviously and what they saw was that there was a significant increase in T helper cells. So this is great, looks good. Most people didn't have too much toxicity, though AZT can cause anemia so some people did have that, but it wasn't too bad. So AZT went on to phase II trial and here it was compared to a placebo, or an inactive drug that's basically used as a comparison. And here what they saw was that the patients on AZT had a lower proportion of opportunistic infections than the people who were on placebo. So that's good. But I think the most striking thing about this was that they looked at mortality. And in the treatment group 1 in 145 people died, but in the placebo group 16 out of 137 people died. So they noticed this at 7 months into the trial. They halted the trial, they unblinded it, meaning that the researchers and the patients now know if they're really getting drug or not, and then because of these striking results, everybody got AZT. So this is really, you know, sort of a remarkable story.

11. HIV evolves to become resistant to a drug (13:14)

But let's go back to that first chart or graph that I showed you. Is there something strange about this? There's something strange. Okay. So basically there's a spike, an increase in opportunistic infections at 22 weeks. So what's going on there? So basically HIV is becoming resistant to AZT. So how does that happen? As HIV RNA is reverse transcribed into the growing DNA strand, reverse transcriptase is just really sloppy and it makes a lot of errors. So in a patient's blood you actually don't just see normal virus, you actually can have mutant virus, just because of the sloppiness of reverse transcriptase and it doesn't have a proofreading mechanism. So if you give one drug, like AZT, basically you lower the amount of virus in the blood but virus is still replicating because you don't lower it enough. If you keep giving the drug, then under selective pressure you're going to get more resistant virus.

12. Treating with multiple drugs to battle resistance (14:21)

So what's the natural thing to do then? Well why don't you just give them more than one drug? So trials went on where we gave people more than one drug, two drugs that were actually in the same category of reverse transcriptase inhibitors and they worked to a certain extent. There was less virus in the blood, less mutations, but really the best thing to do based on the trials that we did, is to give people three drugs. And when you give people three drugs, virus by the test that we take in the blood system show that it's undetectable. You give people more drugs to get the virus low so it's not doing a lot of replication. So if you need more drugs then how do you figure out what kind of drug you're going to make and where do you go in terms of a drug target? Well in this case we looked at the protease enzyme. So let's look at this animation.

13. Animation: Protease inhibitor (15:22)

So when HIV buds from a cell it's not in a mature form. Its proteins are actually in a multi-linked chain, so protease comes in and it cleaves the proteins in several different places. So the proteins undergo a conformational change and they're actually... HIV becomes mature and the life cycle goes on. So when protease is inhibited by a medication, called Ritonavir in this case, it's a protease inhibitor, it binds to the active site in protease so now it can't cleave the protein. So if it can't cleave the protein then HIV can't become mature and the life cycle is inhibited.

14. Triple-drug therapy sustains low viral levels (16:28)

So now we have the sense that basically two drugs won't work or at least they won't work for very long, so there's two drugs, but if you give three drugs, so two of the first kind of drugs, or two of the AZT-type drugs, plus a protease inhibitor, you can actually see a sustained decrease in the amount of virus in the blood. And you can also see an increase in T helper cell level. So this is all good stuff that we're seeing.

15. Triple-drug therapy and drop in U.S. AIDS deaths (17:02)

So if you go back to the AIDS timeline, we had the first anti-retroviral drug, AZT in 1987 and then the first protease inhibitor in 1995 and now we know that you really need three drugs to treat HIV. So here in the United States from 1987 to 1995 we saw an increase in the number of deaths amongst people who were living with HIV because we weren't really treating them, or we weren't treating them adequately. So when we learned that you actually need three drugs you saw this steep decrease in the people who were dying, and this is actually what I saw, you know, when I was in medical school.

16. Problems with triple-drug therapies and a search for new drugs (17:50)

But at the same time giving people that much drug is probably going to cause side effects, they're probably not going to want to take it, and so we're always looking for new drugs, new drug targets. So how do you look for new drug targets? Well sometimes it's really good, and I think it's good in general to listen to your patients, but sometimes it's really, really good to listen hard because they can give you the clues.

17. Video: Steve Crohn: HIV free despite exposure (18:18)

So Steve Crohn is a gentleman who lives in New York and he's a man who has sex with other men and basically he's been exposed to HIV multiple times. So let's hear his story.

[NARRATOR:] But despite repeated exposures to HIV, Steve Crohn remained uninfected.

[MR. CROHN:] I don't know why I was surviving. I remember talking about it with somebody at a family party and they said, "Well why aren't they studying you?" Like when you look at families and all the children have some malfunction or bone disorder, some genetic disease or whatever they study the child that does not. In most of the studies we're not studying HIV-negative people at all.

18. People who have mutant CCR5 co-receptors avoid infection (19:02)

[DR. OJIKUTU:] So the observation with Steve Crohn was that certain people are not infected with HIV even after repeat exposure. So then one hypothesis that somebody might have is that a genetic mutation in their immune system actually stops HIV from entering the cells. So the experiment would then be to actually look at the receptors in their immune system and figure out why they don't actually have the binding and the entry that normal people have. So you probably remember this picture from yesterday. So it's HIV binding to CD4 receptor, and then that's the chemokine co-receptor because HIV doesn't bind unless it has two sites to bind to, or two different receptors to bind to, and that's CCR5. So in someone who's normal, doesn't have a

genetic mutation, that's what it looks like. But in someone who actually has a mutation, Steve Crohn for instance, HIV doesn't bind to this chemokine co-receptor, the CCR5 and therefore it doesn't enter into the cell, so he doesn't become infected.

19. New class of drugs that inhibits CCR5 (20:32)

So this sounds like a pretty decent drug target then, because if you inhibit CCR5, seems like Steve Crohn is doing fine, you're not hurting him, but you're inhibiting HIV from entering into the cell. So going back to our timeline again. So we have this triple-drug therapy and I said that sometimes, you know, it's too cumbersome, there's too many pills that people are taking, you have side effects, so we're always looking for new drug targets, and about six weeks ago, a little more, the first CCR5 inhibitor, Maraviroc, was actually approved. So we can go to questions. Okay.

20. Q&A: Is the CCR5 inhibitor drug working well? (21:18)

[STUDENT:] How has that new drug been progressing, like is there any...

[DR. OJIKUTU:] So I actually, I've spent a lot of time with clinical patients, I actually started my first patient on it probably about two weeks ago and he's doing fine. Before that we actually couldn't even get it in a pharmacy. So in clinical trials it did very well, particularly for patients who were sort of on failure regimens, meaning they had already failed. So we're not really using it in patients who haven't been on medications before. So thus far it seems like it's doing well.

21. Q&A: Does AZT also affect cellular replication? (21:54)

[STUDENT:] When you said you introduced the AZT and it blocks, wouldn't that also, wouldn't our body also use it for the RNA in healthy cells, it would use AZT and it would inhibit certain proteins that we would need?

[DR. OJIKUTU:] Yeah, that's a really good question. So DNA polymerase does actually see AZT as a nucleotide, but it doesn't see it very well. Okay, so it doesn't work, and that's kind of why it didn't work in cancer, okay so it doesn't really incorporate, so that's why it can be used in this case.

22. Q&A: Do age groups differ in HIV drug resistance? (22:28)

[STUDENT:] Can different age groups of HIV patients show variation in resistance to drugs?

[DR. OJIKUTU:] Can different age groups show variation in resistance? From what I've seen I think people are pretty standard in their resistance to a particular medications, most of my patients are tolerating medications regardless of their age group. So I haven't really seen that people of different age groups are having major problems and I haven't seen that in the literature either. Okay.

23. Q&A: How common is the CCR5 mutation? (22:59)

[STUDENT:] How common was the mutation for the CCR5 receptor?

[DR. OJIKUTU:] Okay, so from what I've seen in the literature, the homozygous version of it, is less than 1% in Caucasian populations. So I don't think... the heterozygous you see in other people, but I've seen pretty much homozygous in Caucasians.

24. Q&A: Do the drugs have side effects? (23:22)

[STUDENT:] Okay so you said that you give the patients three medicines, right? But the side effects with it, and not wanting to take it and different things, but was there anything seriously, like, ill with them, or they did just not want to take it?

[DR. OJIKUTU:] Some of the medications have toxicities that we've learned about over the years. So for instance with AZT, you know, it does cause anemia and that anemia can be quite profound, meaning that people can actually be short of breath, and be in the hospital. Another thing we've seen with some of these patients is that they'll develop lactic acidosis and come in really sick on some of these medications. Some patients end up with lipodystrophy, meaning they get wasted in here, and they sort of develop a stomach and a buffalo hump. So these medications have toxicities that stop people from taking them, so what we're doing is just trying to find drugs that have the least amount of toxicity. Over here.

25. Q&A: Do CCR5 mutations have an effect on people? (24:19)

[STUDENT:] What you're saying is that this mutation in the gene has no effect on the person at all?

[DR. OJIKUTU:] Yeah. It seems like it has absolutely no effect on people. Steve Crohn is obviously doing well, the other people who have these mutations seem to be doing well. It's almost like a good mutation, you know, it stops them from getting HIV and there's nothing harming their immune system. It's actually, you know, the first drug that we have that is actually targeting the immune system to stop HIV from infecting. Uh-huh?

26. Q&A: Is caution need with ART due to HIV mutations? (24:50)

[STUDENT:] Is there a chance you have to be really careful with these drugs for the sake of HIV evolution? Like is there a chance that the virus could evolve so that this won't matter anymore?

[DR. OJIKUTU:] Well, so we've found resistance patterns for all these drugs, I mean, you can look for resistance in anything, so with, like, CCR5, the question is whether or not the virus will then turn and be tropic or want to go into the cell using a different mechanism and that has been found and pretty much for all the HIV drugs there's some way of resistance that the virus gets around so it can actually infect people. So yeah, that does happen. Over here.

27. Q&A: Can you take CCR5 inhibitor without other drugs? (25:31)

[STUDENT:] If people don't have the CCR5 inhibitor, does that mean that they don't have to take the other three drugs so they just take that one?

[DR. OJIKUTU:] No, it's actually, it's a failure regimen meaning that when you start a patient on a group of drugs and you start to see resistance then you sort of have to look at their genotype and figure out what their resistance pattern is and then you put them on a whole group of drugs that have some sensitivity. So Maraviroc or the CCR5 inhibitor you add to drugs. Okay, so it's a group of drugs, it's not by itself. Okay, last question.

28. Q&A: Can using different classes of drugs lower mutation rate? (26:06)

[STUDENT:] I saw some drugs that they were reverse transcriptase inhibitors coupled with protease inhibitors and a lot of the nucleotide replacing medicines going together. Wouldn't it be beneficial then to have the nucleotide inhibitors go and get the HIV and lower the population? That would lower the mutation rate because they're starting to choose their nucleotides better and then put a protease inhibitor in?

[DR. OJIKUTU:] Well that's what we're doing. I know I went through that kind of fast, but basically AZT was the first drug, a reverse transcriptase inhibitor and then they came up with other ones, you know, that look similar but had a different sort of change or different change to them. So certainly you put them together and then you add a protease inhibitor and that's your triple drug regimen, so it's exactly how you're looking at it.

29. Video: Adhering to an antiretroviral regimen (26:58)

Okay, so I want to introduce you to Adam Barrett, and actually he came up yesterday so you guys are familiar with him. He's a nurse at Mass General Hospital where I work, and he's also HIV-positive and he takes a very complicated regimen. So let's hear Adam's story.

[MR. BARRETT:] The current regimen that I'm on, I had been on a triple-drug regimen which I think is the regimen most people are used to hearing individuals talk about. The reason my drug regimen is now a seven-drug regimen is because of the level of viral resistance that I developed to treatment early on. So what I meant by it's a full time job, I start the day at 5:00 a.m. because some of the meds, DDI in particular, requires that you take it on an empty stomach and then other meds in the regimen, Inverase, 3TC, Vireed and Norvair all require that you take their drugs with food. So you really have to balance your medication regimen with your diet regimen as well as a pretty strict timeframe for when you take your medications.

30. Why adherence to HIV medications is crucial (28:11)

[DR. OJIKUTU:] So people who are on such a complicated regimen and even people who are on the regimens that I talked about, can often times have problems with adherence, okay, so adherence is really, really key. And when I'm explaining adherence to my patients, what I tell them is that, you know, when you take your medications that's going to increase the amount of drug in your blood and you have to keep at that level to keep the amount of virus down low so it's not replicating that much. If you actually skip a dose and the amount of drug in your blood goes down, then you end up having replication and when you have replication you end up with mutations and resistant HIV. So this is why adherence is so important because you don't want people to have resistant HIV and then they'll be on medication regimens like Adam--seven drugs.

31. Relationship of adherence to virologic failure (29:09)

So what is good adherence? So basically in this study they just looked at patients and they said, "well, you know what, let's figure out what level of "adherence they need to have to have a low amount of virologic "failure," meaning a low amount of actual... this mutation, all of these sort of resistant virus coming on and what they found is that you really have to have 95% or more adherence to your medication in order to be in a good situation, in order to keep the virus low. So 95% adherence, that's pretty good, I mean that's pretty hard to do. That means, you know, you're not skipping too many pills a month, I mean it's a difficult thing to do and I'm not sure any of my patients have that much adherence.

32. Demo: Student adherence activity (30:00)

So we asked you guys to participate in activities so you understand how important adherence is, and we also had a group of students from North Miami Beach Senior High School participate in this activity and what we asked you to do was to pretend that you were an HIV- infected person and you had to take medications on a regular basis and we put you in different groups. There was a group of students who were in the complicated group, that's right here. So the complicated group is somebody who's on like a failure regimen, that's what this would be, okay so they actually have to inject themselves twice a day, okay, and then they

also have to take pills. So that was the complicated group. And then the second group, actually just had four pills to take once a day, so that's not too bad. And then the third group had our simplest regimen. Okay, this is like the best thing to patients. It's one pill, once a day, it has three drugs in it. Okay, so this is the easy thing.

33. Demo: Student adherence results (31:10)

All right so let's look at the results. So 95% remember, I told you that was good adherence. So congratulations to Miami, 30% of them or a little bit less were actually able to have good adherence. But you guys, you guys had about maybe 25% somewhere around there. But let's compare it to a group of patients in the United States who are actually HIV infected. You both did better. So what I'm trying to figure out is what happened here. **[laughter]** So half of you guys didn't even participate and I'm wondering, and maybe we could talk about it a little bit, did you start taking it and maybe stop? Was it hard to take? How many of you actually did the activity? Okay that actually looks like more than...hmmm, okay.

34. Demo: Students discuss their adherence issues (32:02)

So somebody tell me what was hard about it?

[STUDENT:] Well it was hard because you had a daily schedule that changes but the medication has to always be on the same schedule. So, like, I went out for Thanksgiving and we stayed at my grandparents house and it was 9:00 and I realized, oh, I missed my medication and I hadn't....

[DR. OJIKUTU:] It's tic-tacs! Just kidding. I know, I think that that's a really good…reason.

[STUDENT:] When you need to go someplace and it's a couple hours before you have to take a drug you don't realize you're going to be out until after you're supposed to take them.

[DR. OJIKUTU:] That's perfect actually. So which group were you in?

[STUDENT:] The second one.

[DR. OJIKUTU:] The middle group. So who was in the one tablet per day? You all had better be in this group right here.

[STUDENT:] I had protocol one and it was really difficult to try to manage the whole Kool-aid and the tic-tacs. **[laughter]** You had to carry around like a bottle of water with you wherever you went.

[DR. OJIKUTU:] Okay. Okay. So at least you weren't injecting anything! So no, that's totally a valid... I've heard that from many patients, if it's complicated, it's complicated.

[STUDENT:] For me I think it was more like I didn't take it as seriously because I knew that there weren't any real adverse effects, but I feel like if I would have, you know, had HIV, I probably would have been more on top of taking the medication all the time. But since I wasn't taking it as seriously maybe. I mean not that it wasn't, you know, a serious experiment or whatever, but I knew that, you know.

[DR. OJIKUTU:] Well there's some of my patients who don't take it seriously either honestly, so yeah, that's completely valid. Anybody else have a different experience, up in the back?

[STUDENT:] It was actually difficult for me, I had the third protocol.

[DR. OJIKUTU:] That's one pill, once a day! A tic-tac! **[laughter]**

[STUDENT:] Well I was always hungry, and I had to take it without food and so it was very difficult for me not to eat, like, two to three hours before I actually took the pill.

[DR. OJIKUTU:] Okay, okay, I see. There were different, you know, food arrangements that had to be made, so okay, all right. Okay. So let me just go back and kind of finish up. Okay.

35. HIV prevalence growing in certain U.S. populations (34:19)

So remember what I was saying about the U.S. and how only 25% of the people in that particular study were actually able to have good adherence, so this is a major problem because we have 1.3 million people who are infected here in the United States and 46,000 new cases per year. I think it's interesting to refer this back to my first lecture where I was talking about the early groups affected and see how the epidemic has actually changed here in the United States. Well, men who have sex with men are still the most likely group to be infected with HIV, so that piece hasn't changed so much. But what's interesting is if you look at things from a racial and ethnic perspective and you actually see that over time the number of cases of AIDS in the white population has actually gone down and that in the black population has gone up and then sort of, you know, leveling off, I suppose, or looks like it is and then it's a little bit slightly up in the Hispanic population. So that's different from what the epidemic looked like initially. So then I think it's also important to notice that more women are becoming infected with HIV and if you just estimate over time the numbers have gone up.

36. Statistics on the global HIV/AIDS epidemic (35:34)

But you know even though we have this problem here in the United States I think the key or the piece to take home is that we have millions of people who are living with HIV around the world, 33.2 million in total. And of course in sub-Saharan Africa which is the region most highly impacted, which we discussed yesterday, we have 22.5 million people who are infected.' So all those people don't actually need medications. When you need medications your CD4 cell count is down at 200, okay, so those are the people who we really want to get medications to now. Some of the other issues—opportunistic infections—they also indicate that you need medications. But around the world right now we have seven million people who are HIV-positive and who need treatment. So a lot of good things have happened over the last 3 or 4 years and two million of those people actually have medications and I think, you know, people say, well, you know, things aren't going well, but this is a huge, huge increase over what we had previously in terms of who had access to care and treatment, so this is good. But of course there's still 70% total unmet need so there's a lot of work that remains to be done.

37. South African HIV/AIDS statistics (36:50)

So if you look at South Africa in and of itself, there are 5.4 million people infected, 1.1 million people need anti- retroviral therapy, 290,000 are actually getting it and because not that many people are getting antiretroviral therapy, 950 people die per day. So over the course of one year you have 350,000 people dying in one country of one disease per year. So in South Africa AIDS is a part of life. You have graveyards and, you know, people basically outside their houses, you have people who, you know, bury their family members who have died, and, you know, there was a recent survey that came out that basically said that South Africans spend more time at funerals than they actually do grocery shopping. That's how bad things are.

38. Barriers to treatment in South Africa (37:46)

So why is this the situation? So I can't talk for hours, you know, about all the sorts of details, but I'll just give you a little bit of a snapshot, just from more personal experience more than anything else. So the patients that I see in South Africa and in other places of the world, it's a simple issue of transportation. Literally you have people who live 20 miles from a clinic and yet they have to go there once a month. So can you imagine having AIDS and having to walk 20 miles to get some care and treatment? And then there are lots of people around the world who are poverty stricken and what does that really mean? Well, it means that often times if you're poor and you're trying to get food you're really not going to put HIV and AIDS and this sort of thing at the top of your list, and this is just my own personal experience with patients and what I'll tell you in South Africa is that about 50% of the people actually live in poverty. In one of the clinics where I work they actually have a situation where there's only one nurse who sees about 60 patients per day, by herself, a couple of counselors, people who do, like, counseling and testing for HIV and a doctor who comes by, like, half a day a week. And that's the situation. I mean you literally sit all day waiting for care and I mean it's a really big issue all around the world that there aren't trained health care workers. So when I was in South Africa that's a lot of what we did, was actually train the health care workers about HIV and how to treat HIV and now... that was 2003 to 2004 and now a lot of them are actually experts and, you know, can do probably a better job than anybody here in treating patients.

39. AIDS orphans and the "gogo" (39:30)

So who are the most vulnerable? Well, AIDS orphans, it's a huge issue. There are 12 million young children who have been orphaned in sub-Saharan Africa. One in ten have lost at least one parent, and in South Africa alone there are 1.2 million AIDS orphans. So just to show you a little bit about what's going on in these families, basically you have the grandmother or the *gogo* who's leading the family and that's fine, I mean, a lot of people are lucky to have somebody because a lot of the kids are actually on the street, or you'll have, like, ten-year-olds taking care of a household of, like, five other little kids. But the problem here is that a lot of these women, they're elderly, they're debilitated themselves and they just... HIV is not something that they even talk about or know much about and they're living out in some remote rural area taking care of like ten kids. So the average household in one of the areas that I work in is called KwaXimba has ten members in a small single-room house. Six of them are children, and half of them are orphans of AIDS. So that's pretty typical. Unemployment 68%, 72% have a chronically-ill adult and 60% are hungry.

40. *Umndeni* "Family" Care Program (40:45)

So the program that I run is called the *Umndeni* family care program, *Umndeni* is the Zulu word for family and it's a collaboration between Harvard University, Habitat for Humanity and a local non-governmental organization called Valley Trust. And basically the goal of the program is to build capacity to address both HIV and poverty in families that are caring for AIDS orphans in KwaZulu-Natal which is the province where the community is located. So we have about 400 children. I think an important thing here is that, though these kids are orphans of AIDS, and I'll explain it to you later about a mother to child transmission, 95% of them have not even been tested for HIV. So we do a lot in this program because we're trying to be comprehensive and we do HIV testing in the home, we link to treatment sites through community health workers. We do a lot of social support and I think the interesting thing about it is that because a lot of these people are living in these households where, you know, you have a single room, there's no flush toilets, and that sort of thing, they actually get a new house. And that's the linkage with Habitat for Humanity.

41. Mother-to-child HIV transmission is preventable (41:54)

Okay, so, from treatment at community-based programs to issues of prevention. So perinatal transmission, that's mother-to-child transmission. So why is this so important? So in KwaZulu-Natal which is the province that I'm talking about where Durban is located, there are 100,000 children who are HIV infected and this is completely preventable because most of these kids, their infection is a result of mother-to-child

transmission. So if you look at mother-to-child transmission it can actually occur at three different time points. In utero or during pregnancy, during delivery or intrapartum, or through breast feeding. So it happens probably about 30% of the time, somewhere between 25% and 30%, and at these three stages. So this is data actually from the United States and the reason why I'm showing you this data is because I want to sort of hammer home the point that we know how to prevent this, we know how to do this, it's just not happening. So this is, I think this was 1992. These women were not given any medication and basically they found that the rate of peri- natal transmission, the rate of mother-to-child transmission was 24.7%. So in the next study they actually gave AZT to these women, they were actually in labor, they gave it during labor and then they gave it to the baby afterwards and the rate of transmission went to 7.6 and then in the last study these women actually got that triple drug combination that I was talking about and plus they gave them some extra antiretroviral therapy. So basically they dropped the rate of mother-to-child transmission from 24.7 down to 1.5. So because of this we don't really have that much perinatal transmission here in the United States. I mean you see how far it's gone down. So this is a huge success story. But globally, literally, we have two million women who are pregnant with HIV in 2005 and only 11% got anything in terms of antiretroviral therapy. And so the question is, we know what to do, why isn't it happening and why aren't we doing it? And the interesting thing is this is really actually simple to decrease. I mean, literally, you can give a mom some antiretroviral medication during birth, give it to the baby and that in and of itself can decrease transmission probably in half. So it's just one of those things that's just, you know it's sort of striking. So just some conclusions. So I think that strides have been made in global access to treatment for HIV. I showed you some barriers and access to care but, you know, I think we can overcome those. And I really think that interventions to improve prevention of mother-to-child transmission should be a primary goal, but at the end of the day I think that there is hope. **[applause]**

42. Q&A: How long does a newborn have to take ARVs? (45:15)

[STUDENT:] For preventing mother- to-child transmission, when you give the child the drugs, how long do they have to take that?

[DR. OJIKUTU:] So they can actually just take one dose on that regimen that primarily we're using overseas. I mean here sometimes we give it to them for a week, and, you know, then stop it. The issues that then come up is does that then breed resistance in them because, you know, they have a drug that's working against the virus. And we found resistance mutations, sometimes they go away, you know, so I think it's an issue that's evolving in these cases.

43. Q&A: Does a C-section remove the need for perinatal ARVs? (45:48)

[STUDENT:] Could you avoid, during intra- partum, could you avoid giving the child HIV by performing a C-section?

[DR. OJIKUTU:] Well it doesn't cut the risk to zero, but it definitely cuts it down significantly, but then you have to think, in a lot of these settings, is that really safe, especially in sort of developing settings. But it can. What we found, though, is that if you have a viral load that's undetectable, you really don't need to do that.

44. Q&A: Can helper T cells be artificially enhanced (46:17)

[STUDENT:] Building off the correlation between low helper T cell count and HIV, is there any way that, like, cytotoxic T cells or helper T cells can be, like, artificially enhanced and administered in any way?

[DR. WALKER:] I'll talk about that a little bit in the next lecture. It's a very good question about the possibility that you might be able to enhance immunity to get a better control of the virus.

45. Q&A: Can CCR5 inhibitors prevent initial infection? (46:49)

[STUDENT:] CCR5 inhibitors, for women, if that was given to women, is it possible when they're pregnant, is it possible for the baby to essentially stop producing CCR5 in the white blood cell count. Because it's being inhibited and can affect the baby at that time, so is that possible?

[DR. OJIKUTU:] So I haven't seen any studies on CCR5 in women and a lot of these drugs people don't study in women because of the fact that it can you know be toxic and teratogenic. So I don't think we'll see that for a while but I think it's an interesting idea. Okay so way up in the back.

46. Q&A: Can CCR5 inhibitors be made into a vaccine? (47:30)

With the CCR5, since it prevents the HIV from getting into the cell do you think it would be possible to develop that into a vaccine to prevent it?

[DR. OJIKUTU:] Yeah, they're definitely looking at that. Do you know a lot of details? Go ahead Bruce.

[DR. WALKER:] Well just again it's one potential mechanism, if you could generate something through a vaccine that would target in the same way that a drug does, you might be able to have an effect, so it's a very good question, but not something that's been realized yet.

[DR. OJIKUTU:] So over there. You guys pick.

47. Q&A: Why were the initial U.S. cases in homosexual men? (48:08)

[STUDENT:] It said in one of the packets that the first cases of HIV infection were found among homosexual men. Why is it more common to find it among homosexual men? Is it a genetic reason?

[DR. OJIKUTU:] So I don't think the first cases of HIV were found amongst homosexual men. I think that we were talking about the United States and we were saying the initial epidemic was pretty much in homosexual men. No, I totally understand what you're saying so I think that there are a couple issues that I can tell you about and then also in the panel later Adam does a lot of prevention work amongst men who have sex with men. But I think that one thing you need to look at is the route of transmission and if you're talking about anal receptive sex, that's... of the sexual activities, gives you the highest risk of transmission. What actually happens is that the mucosa is quite friable, meaning that it can break down, so HIV has an easier time of getting in, so that's one issue. And when you're talking about that time when we actually had those initial first cases I think that there was a lot of sexual liberation that was going on. We talked about patient zero and how many actual sexual contacts he had. You know, I mean, he was a little off the chart, you know, but I think there were a lot of people who were engaging in sex without using condoms and that was sort of a thing that was happening at the time and I also think that if you really go back and look at the numbers I would bet that a lot of cases weren't found in these other populations because a lot of these people sort of had barriers in access to care. Like I'm wondering how many cases there really were in Haiti and if you look back there were more cases in Haiti and other places, but, you know, maybe it was found in that particular population because that particular population had more access to actual care and treatment. And some of that is speculation.

48. Q&A: What are governmental barriers to treatment? (49:58)

[STUDENT:] Have you seen a government or political influence has created a barrier to the treatment of AIDS?

[DR. OJIKUTU:] Oh, of course. Of course, I mean in South Africa you probably know that you know there's been a lot of barriers created by the government and the initial barrier was just kind of spreading the idea that HIV didn't necessarily have anything to do with AIDS and that the treatment that we were using here in the United States and other places didn't even work and kind of encouraging people to use medications that don't work. So I think political will is an important... you can't move, in terms of moving forward with treatment programs, unless you have good political will. So I'll just take somebody up there.

49. Q&A: What preventive measures do health-care workers take? (50:40)

[STUDENT:] What kind of preventative actions do people take in South Africa to workers? What kind of preventative actions do they take?

[DR. OJIKUTU:] Well I think that's a really huge issue. You know some of the places where I worked it is something where people, you know, actually know about universal precautions, and you know they're wearing gloves, but when you're talking about places that are resource-constrained out in rural areas, people aren't necessarily wearing gloves, you know, people aren't wearing masks for tuberculosis, which is much more transmittable than HIV. So I think that it's really an issue of resources and it's also an issue of knowledge spread. Okay.

50. Q&A: Is there hesitation in being tested? (51:21)

[STUDENT:] Is there a hesitation in your experience among the public for, like those who come into HIV clinics, do you think they have some kind of hesitation of just being tested?

[DR. OJIKUTU:] Of course.

[STUDENT:] You know if they even get tested and receive medication intravenously maybe they'll acquire AIDS just through that.

[DR. OJIKUTU:] Well I think there's a lot of resistance to getting tested and that can be for multiple different reasons, you know. Some people just don't want to know that they're HIV infected. You know when I started working in South Africa I think a huge problem was the fact that people didn't know that treatment was really available, so if you don't think treatment is available, why would you want to know that you're actually HIV positive? And then there's the issue of stigma, you know. I mean who necessarily wants to know that they're HIV positive, if they know that their neighbor will then stigmatize them and not want to speak to them if they happen to know. So I think it's a huge issue, it's something that I'm not sure people are really dealing with as much as they should and Zinhle did you want to say anything about that?

[MS. THABETHE:] Stigma is still going to be a huge issue since there's a lot of interventions and myths around HIV and just because there has been a lot of debate, and like Bisola has been saying, if there is no political will, if the leaders are saying "HIV does not cause AIDS," and it is confusing to people, and also there is also traditional belief that maybe this kind of illness is coming from bewitchment or traditional related illnesses, so there is a little bit of stigma, but there has been progress in terms of looking into that. Particularly that we have been seeing a lot of people getting better with ARVs.

[DR. OJIKUTU:] Okay, so I think we're just going to take a couple more questions.

51. Q&A: What has U.N. done about mother-to-child transmission? (53:07)

[STUDENT:] It seems like the role of education could really help the mother-to-child transmission. What is the international community, specifically the UN and the World Health Organization done about this?

[DR. OJIKUTU:] Well they've put out guidelines, they put together programs, I think people are working hard at this. I don't think that... I think that people are aware that mother-to-child transmission occurs but I think that there are a lot of issues on the ground in terms of what's happening and in terms of systems of care at these clinics where you have women coming in and they're just so overwhelmed that they don't get tested, even if they're in labor. Or they forget to hand them the nevirapine, or they forget to document in the chart that they were supposed to get a pill to go home with. So I think that it's a multi-factorial thing and your government agencies can only do so much. It's really what's happening on the ground that needs to be tackled. Okay, up there.

52. Q&A: How does a child avoid infection from the mother (54:02)

[STUDENT:] I have a question about how... cause mothers share most of their bodily fluids with their child, how do they not transmit... like, even without the treatment it's so few compared to what you would think of all their bodily fluids kind of being shared. How does that not happen? How do they not very often get AIDS, the child get HIV from their mother?

[DR. OJIKUTU:] Well I think one piece of it is the viral load of the mother. It's not necessary that every mother has a viral load of over 100,000. So there are variables and factors here. There was a study that was done by Professor... his name is Jerry Coovadia and he's a pediatrician in South Africa and, you know what he found was that the women that were transmitting more virus actually had lower CD4 counts too and they were sicker. So maybe... basically what he's saying is that a younger, you know, healthier woman who has a higher CD4 count and maybe has a lower viral load, those factors then lead to less transmission. So I think it's a really variable process.

53. Q&A: Why are more women being infected in the U.S.? (55:13)

[STUDENT:] Why do you think that more women in the United States are being infected with HIV?

[DR. OJIKUTU:] Here in the United States?

[STUDENT:] Yes.

[DR. OJIKUTU:] So I think that it's a multi-factorial piece. I mean, you know, there's the biomedical portion of it that actually... a lot of sexually transmitted diseases are more common in certain populations here in the United States including black women and one of them particularly is herpes simplex virus, and you know this is something that's come out in many, many reports and it's something that people maybe haven't been paying as much attention to which means that HIV can actually be transmitted more efficiently when you actually have genital lesions. So I think there's the health piece to it, there's a portion of that that's also psycho-social, you know, actually not being aware that this is a huge issue in our community and maybe not using condoms as often or having multiple sexual concurrent partnerships, meaning multiple partners at the same time. There's a researcher at UNC who's doing a lot of work with black women to try and figure out exactly why there's a higher rate in that population and one of the issues is this issue of multiple sexual concurrent partnerships. You know I think it's... like I said, it's multi-factorial and I think it's something that a lot of people are talking about and trying to sort out.

[DR. LIU:] Thank you Bisola. Thank you for your talk. **[applause]**

54. Closing remarks by HHMI Program Director Dr. Dennis Liu (56:43)

Thanks for that talk Bisola, actually it's a good time to remind people to visit BioInteractive.org and the Ask a Scientist feature where you can continue to ask questions. I was particularly struck to see the adherence data, I thought that was one of the most interesting parts of the program and how just taking your medicine can be so difficult. In the final lecture, the next lecture, Bruce Walker is going to return and he's going to talk about strategies for creating a vaccine against HIV. You've seen how successful the drug story has been, so Bruce will help explain why in 25 years we still don't have an effective vaccine against HIV and yet there's hope that that's still coming. **[music]**