3.1 Marty St. Clair: Discovery of AZT as the First Anti-HIV Drug

**Marty St. Clair:** Let’s get started right away. I always like to start with just putting people back in the day when HIV first came to be in this country. Like I always like to start with, June 5th, 1981 when Michael Gottlieb reported an MMWR, those few cases of gay white men with pneumocystis pneumonia. (1) It was reported at MMWR, and I think everybody now knows the story that he actually called up [00:00:30] New England Journal of Medicine and said, “I think I have something for you.” New England Journal of Medicine said, “If you don’t publish it quickly, you’re going to get scooped.” That’s why it ended up in MMWR.

In the next couple of slides you’ll notice that I do have some yellow type, and the yellow type is for CDC tabulation of the new disease in this country. I do this because it takes you back in the era. It, actually, hopefully, for those of you who lived it, will help you [00:01:00] feel it again. For those of you who didn’t live it, will help take you back, and realize what was happening in public hysteria on this new disease that was causing so much trouble. The first report was 1981, August 1981, just a couple of months after Michael Gottlieb’s report in MMWR where the CDC reported 108 cases in the United States.

We went from 3 to 108 in 2 months. June 30th, 1982 [00:01:30] was a big day for me, and for probably everybody in this room, because now we actually knew that HIV/AIDS was caused by an infectious agent, and not by any of the practices that were reputed back in the time that were associated with certain demographics, or part of the reason why we had such a stigma in this country. To have this be caused by an infectious agent, all of a sudden made those of us who deal with infectious diseases feel like this is something we can deal with.

We understand infectious agents. [00:02:00] This was actually a big thing for us. July 15th, 1992, CDC reported 413 cases in the United States with 155 deaths. Then July 27th, 1982, we actually had a name for our syndrome, Acquired Immune Deficiency Syndrome or AIDS. Once again, a really good thing. We can stop having all of these non politically correct names for this disease based on the [00:02:30] population that came into this country. We’ve been fighting all these years’ stigma, and having appropriate names, certainly is one way to fight stigma.

September 1982, CDC reported 593 cases of AIDS in the United States with 243 deaths. For those people who are paying attention, we’re talking about a 50% fatality rate. Yes, there is some fear going around the country. Probably more than [00:03:00] there is scientific analysis, which is always unfortunate. Then January of 1983, the CDC reported cases of AIDS in female sex partners of males with AIDS. That was a good thing because it’s not just going from male to male, but it can go from male to female. In fact, now we know it goes female to female and female to male. As long as there is transmission of bodily fluids, this disease can spread, and it is not a disease of a certain demographic. [00:03:30]

Did I go—two? I seem to have missed—Let me go, I’m going to go back a slide because I think I have a slide out of order here.

May 1983, Luc Montagnier reported in Science, isolating a virus he called lymphadenopathy virus (LAV) associated with AIDS. (2) Lymphadenopathy virus is a retrovirus, and this is a big thing [00:04:00] for me because I wanted to be a virologist ever since I was 13. When I was a senior in college at Oregon State University, I actually worked for a year in a retrovirus lab. It was an avian retrovirus lab, but it was just like, “Oh my gosh, this is what I want to do with my life.” I learned how to replicate the virus. I learned how to isolate reverse transcriptase. I learned how to assay reverse transcriptase. All of these things I learned as an undergraduate not realizing [00:04:30] what an impact it would have on my career later.

January 1984, CDC reported 3,000 cases of AIDS in the United States with 1,283 deaths. At this point, there really was a great deal of fear overcoming this country, to the point that even healthcare providers were afraid to treat people with HIV.

As with many of you in this room, I’m oftentimes asked to talk at World AIDS Day (every December 1st) events. I went to Pittsburgh, [00:05:00] probably three years ago, I guess, and talked at a World AIDS Day event. When I was finished talking, a woman came up to me. She said her brother had HIV/AIDS. He got appendicitis and he went to the hospital. His appendix ruptured in the hospital, and he died of a ruptured appendix because no healthcare providers would treat him. I was just like, “Oh my God, I cannot imagine how horrible it was back here that healthcare providers would allow somebody to die rather than treat them.”

Then April 1984, DHH (Department of Health and Human Services, HHS) secretary [Margaret Heckler (1931–2018)] announced that Bob Gallo discovered the virus he called HTLV-III or
human T-cell leukemia virus 3 is the cause of AIDS, and expected the vaccine within 2 years, which we don't have yet. Now I want to go back to this slide that I just jumped over. This is a retrovirus. This is lymphadenopathy virus, or HTLV-III, or HIV, which it is known now.

I always show this slide, and I know everybody in this room knows this, but a lot of people back in the day were afraid to go through doors where the doorknob might have been touched by somebody with HIV/AIDS. This is my illustration why that is, and totally an unscientific fear. HIV is an enveloped virus. When it buds out of the cell, it picks up the lipid bilayer from the cell. That lipid bilayer has to be intact for that virus to be infectious. If that virus, which very unlikely would be anyway, were deposited on the doorknob, it's going to dry. The lipid bilayer is going to disintegrate, and that virus is no longer infectious. There's absolutely no reason for anybody to fear going through a door where they touch a doorknob that might've been touched by somebody with HIV/AIDS. There's certainly no reason to fear hugging somebody with HIV/AIDS. It isn't transmitted this way.

Oops. Oh. I'll get there. Really I will.

Back to our CDC numbers. June, 1984, the CDC reported 4,918 cases of AIDS in the United States with 2,221 deaths.

That was the same month that Burroughs-Wellcome, which became Glaxo Wellcome, then GSK (GlaxoSmithKline). Those of us who were actually with Burroughs Wellcome back then now work for a company called ViV [Healthcare], which actually is owned by GSK, and sits on GSK property, but we consider ourselves to be separate. The only disease area we work in is HIV/AIDS, and so I am now a ViV employee and incredibly happy.

June 1984, Burroughs-Wellcome scientists were screening compounds for anti-HIV activity. Then, November 1984, the CDC reported 6,993 cases of AIDS in the United States with 3,343 deaths. And that is the month that we first discovered the activity of AZT (azidothymidine).

Now, I’m going to move specifically into the discovery of AZT as a drug to be used against HIV/AIDS. What was the situation in 1984? I pretty much just told you what the situation in 1984 was. There were fewer than 5,000 cases of AIDS in the United States. We didn't know it was caused by a retrovirus. As you all know, retrovirus double-stranded DNA is matriculated into the cellular DNA, such that, that virus, that cell is always infected, and daughter cells from that infected cell are also infected. If you can put yourself back into 1984, you will realize that, back then, the scientific community did not think that we could attack HIV/AIDS with an antiretroviral for that reason. Neither did the pharmaceutical industry think that you would be successful in discovering a drug that could be used against HIV/AIDS.

With the exception of us. We had—well, being Burroughs Wellcome—had just gotten the approval of acyclovir for herpesviruses. In fact, when I started working for Burroughs Wellcome in 1976, my job was to elucidate the mechanism of action of acyclovir. I worked with herpes viruses from 1976 until 1984. I gained a lot of experience. I gained a lot of drug discovery, and specifically drug experience with acyclovir, but we knew about retroviruses. We assumed HIV was similar to the other retroviruses in that it infects cells with the appropriate proteins on the exterior of the cell. The core is freed from the lipid bilayer, the two strands of RNA are through activity of reverse transcriptase made into a double stranded DNA, which is then intercalated into the cellular DNA using integrase. From that way forward, it goes on through normal biology processes creating new viruses that bud out of the cell.

Remember, we had just finished a very successful drug development program with acyclovir, which, once phosphorylated, inhibits herpes simplex virus DNA polymerase. We believed we would be successful in HIV doing exactly the same thing. When we started our screening process, we emphasized nucleosides for the purpose of inhibiting reverse transcriptase.

As I just said, we had experience and success in antivirals—shouldn't be plural, singular, acyclovir—and we initiated screening of nucleosides. By we, I pretty much mean me. There were a group of about four of us that were involved in this. We’re a small company, somewhere around 400 to 500 people in RTP (Research Triangle Park, North Carolina) in our little funny shaped building that we call Burroughs Wellcome. When the company made the decision that we would initiate a drug discovery development process for HIV/AIDS, I raised my hand because remember, I'd had experience with retroviruses as an undergraduate, and I had just spent from 1976 to 1984, working with herpes viruses. Believe me, I was sick to death of herpes viruses. So I said, “Please, can I be part of this effort, so I can work with retroviruses again, which is really what I want.”

I started screening in June. There are some people in this room that are as old as me, so you might remember. When I talk to scientists today, nobody believes that this is the truth, but what we did for our assays, we made a cell sheet of cells in the bottom of a petri dish. I have to hold up my hand like this. That's what a petri dish looks like, because nobody even knows what a petri dish is anyway. If you have your cell sheet on the bottom of petri dish, you can infect your cell sheet with viruses. For every place that a virus infects the cell, it will infect adjoining cells, cells die, they fall off. At the end of your assay, when you stain that cell sheet, and our stain was purple, the
every Friday, when my assay was done, and it was about 350 plates, which, like today the way we do things, in the first place, we wouldn't have 350 plates. In the second place, we would assay hundreds more compounds that I could in my petri dishes doing everything by hand. Every Friday, I'd be sitting at my desk. I'd hold these plates up to the light, and I'd count the plaques, and they all had 100. I would do about 350 plates [00:13:00] per assay, so every Friday I'd count about 350 plates, and they all had 100.

Until Friday, November 16th, 1984, when I was counting my plates. I came to 16 that had no plaques. I said to my manager, who was in the office right next door, and I said, "Hey, Phil [Furman], come over and look at this. Out of this great big old assay, I have these 16 plates that have no plaques at all. Do you suppose I forgot to put the virus in these 16 plates?" To which he responded, "Yes, right, that makes a lot of sense. 350 plates [00:13:30] and you forgot to put the virus in these 16, which all have the same compound on them?"

Obviously, Phil [Furman] knew, and I told our department head. Dave Barry (1944–2002), and I think I might have told Sandy [Nusinoff] Lehrman on that day. Monday morning, when I came back into work, my phone mail was completely full of messages from people around the company who said, "Did we hear it right? Did you find something that could be used against HIV/AIDS?" [00:14:00] Because we were a little company and there weren't many of us doing this, but everybody knew what we were doing, and the news spread like wildfire. Between late Friday afternoon and first thing Monday morning, just about everybody in the company had heard. But of course, like everybody in this room, I'm a scientist, I never believe anything that's done the first time, so I immediately stuck back into another assay, using much lower concentrations, of course. On November 24th, 1984, we got the IC50 for [00:14:30] AZT in the system with this virus, which was not HIV, of 4 nM, which is, like, 1000 times lower than IC50 for aciclovir against herpes viruses. It was in this system—AZT does not have that low IC50 in other more relevant systems—but it was in the system.

That was the end of 1984. What happened in 1985? [00:15:00] The first thing that happened in the end of 1984, is that people who know about this stuff did a patent search. We found that AZT actually existed in the literature. There is a paper from the NCI (National Cancer Institute) looking at a whole list of compounds for anti-cancer activity. AZT is one of that whole list of compounds, has no activity in that assay. The fact that it was published is prior art. So we couldn't apply for a compound patents and intellectual property (IP) [00:15:30] so our patent for AZT was the use of AZT against HIV/AIDS. Anybody can use AZT for any other disease area and not violate our patent. Our patent was specifically for the use of AZT against HIV/AIDS.

We sent AZT out to several different collaborators, some of which are actually in this room today, under code, and said, "Can you stick this compound in your assay, and see if you have any activity against HIV?" Remember, we actually weren't assaying [00:16:00] at this time, HIV. We were using a murine leukemia virus (MLV) as a virus. We were not using HIV. So we sent it under code to people who actually were working with HIV, and said, "Please, excuse me, stick this compound in your assay and tell us what you found." In fact, everybody found that it had activity.

Remember, I told you that I was doing the mechanism of action for aciclovir, which is phosphorylated to the triphosphate, so all of those experiments, all those assays, all those procedures [00:16:30] were fresh in my mind. I could pretty much stick AZT in similar procedures. I found out that AZT is phosphorylated too, to the triphosphate, similar to acyclovir is, and then inhibits reverse transcriptase.

We determined that AZT was safe in animal models. That's a relative term, isn't it? We submitted the IND (Investigational New Drug application) to the FDA. Then we announced our discovery at ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy). Does anybody remember ICAAC 1985, it was in Minneapolis? Do you guys remember? [00:17:00] We submitted abstracts, and our collaborators that we sent AZT to, submitted abstracts, and the organizers of ICAAC put them all in one session. We all had oral presentations. While I'm old and experienced now, I was really young and scared to death back then, and had never talked to more than five people at once in my life.

The night before I went to see what room our session was in, and it was in the basketball [00:17:30] stadium, which holds 30,000 people. Oh my God, I was absolutely terrified. I talked to Trudy. People know [Gertrude B.] Elion (1918–1999), she's a Nobel laureate (1988). She is actually the person who hired me at Burrough Wellcome all those years ago. We had an event the night before the session, and Trudy and I were at the event. I talked to Trudy and I said, "Oh my God, it's in a basketball stadium. I can't do this." Trudy said to me, [00:18:00] she said, "If you aren't nervous or anxious, or in some way up, you aren't going to do a good job. Use that, use the fact that you're nervous about speaking in front of all of these people, and you'll do a better job."

I don't know that I did a better job or not, but I do know the entire front row was full of reporters with...
all those big klieg lights, which nobody sees anymore because everybody usually just uses their cell phones now. I couldn't see a thing. I could not see anybody behind all those klieg lights, which was like, [00:18:30] "Phew, I actually made it through that." Sometimes this goes forward, and sometimes it doesn't. Now it does.

I hope people are paying attention to dates here because this development program would not occur today.

The activity of AZT was first discovered November 16th, 1984. We started a Phase I safety study July 3rd, 1985. The first 19 patients were reported in Lancet March 15th [00:19:00] 1986. (3) We found out that AZT was well tolerated, once again, that's a relative term, and crossed the blood-brain barrier. Phase II, so everybody knows you don't get drugs approved on Phase II studies, but here we go. We did the double-blind, placebo-controlled Phase II study of AIDS patients. These were very advanced patients who would have died had they not gotten onto this study. It began February 18th, 1986. [00:19:30] 281 patients were enrolled by June 30.

When you consider there were maybe 6,000 patients in this country with HIV/AIDS, we enrolled 281 patients by June 30. That's amazing. The data safety and monitoring board stopped the study on September 19th, 1986 because at that time, 16 placebo patients had died, and 1 AZT patient had died.

When you consider that every year, on that date, until she died, she would call me, or send me a letter, or write me an email or something because she thought that was an important enough date that it shouldn't be forgotten.

Do you remember me telling you there were 400 to 500 people at Burroughs Wellcome and RTP at this time? We barely made enough AZT for this study. We certainly didn't make enough AZT to supply all the placebo [00:20:30] patients. And we absolutely did not make enough AZT to provide to anybody in the United States who would have qualified for this study. We literally depleted the entire world's supply of thymidine making AZT. At this time, I was actually doing reverse transcriptase assays, which I monitored with tritiated thymidine triphosphate. I could not buy thymidine triphosphate. Burroughs Wellcome literally depleted the entire world's supply of thymidine making AZT. Ultimately, 5,000 [00:21:00] patients received AZT free of charge through the treatment IND.

[coughing]

FDA gave AZT top priority, 1AA. They asked us to provide them data. I'm just going to say again, this was a phase II study. We did not do a phase III study. We did not do a dose-escalation study. We had one study done with the highest concentration of AZT that we thought people could tolerate because, in fact, we were enrolling [00:21:30] incredibly advanced patients. The FDA wanted us to supply our data to them under an NDA, and we said, "We're writing reports now." They said, "Send us what you got when you get it." We made our first installment October 17th, 1986.

I always tell people this because, in the days of Twitter and Facebook and all this, people don't realize that, back then, we didn't have email. You had to actually print 12 [00:22:00] copies of each report, put them in a truck, and drive the truck from RTP up to Washington DC. That's what I mean when I say first installment. I mean the first truck went up there. Several trucks went up there until the final truck rolled up to Washington, DC on December 2nd, 1986. Then on January 16th, 1987, we had a FDA advisory panel, which I attended. To which I wore my scared to death suit, which I

[laughter]

[00:22:30] The FDA advisory panel voted 10 to 1 for approval. The one negative vote was for safety, and as we all know, FDA's first responsibility is to safety. As I already told you, AZT did not undergo a dose-response or a dose-escalation study. We chose what we thought was the highest dose that people could tolerate and in fact, they actually couldn't. That one dissenting vote was for safety and a completely appropriate vote. Then the FDA approved AZT for use [00:23:00] in HIV positive people on March 19th, 1987, which my mom actually thought was such an important date that every year, on that date, until she died, she would call me, or send me a letter, or write me an email or something because she thought that was an important enough date that it shouldn't be forgotten.

[coughing]

I am going to go through this quickly. Everybody knows this. These are the other nucleosides that were approved. These are NNRTI's (non-nucleoside reverse transcriptase inhibitors) that are approved. [00:23:30] These are PI's (protease inhibitors), and their dates that they were approved. Everybody has seen this slide.

This is a slide that the CDC put together (Estimated AIDS Deaths and Prevalence, United States, 1985–1999) that I think truly, is probably the best representation of the value of pharmaceuticals.
That in fact, and I can do—Look at this. I can actually do this—maybe I can't—In fact, the incidents of HIV/AIDS during this drug development time [00:24:00] did not change.

What changed with the advent of HAART, highly active antiretroviral therapy—primarily two nuc's (nucleoside analogues) and an NNRTI or two nuc's and a PI—what changed is the death rate. We didn't change the number of people with this disease, we changed the number of people who died with this disease.

It's been an incredible journey. I'm still on this journey. I will work with HIV until the day I decide to stop working, which isn't going to be any time soon, but every journey has to start with one step. [0 0:24:30] In this journey, our one step was AZT.

[applause]

**John Mellors** (moderator): Thank you, Marty. I'm glad. We're all glad you studied retroviruses in college.

[laughter]

Questions? Bruce.

**Bruce Walker:** Marty, was there any pushback at the company about developing HIV drugs, given [00:25:00] the stigma with the disease and such, or was not there not an issue?

**Marty:** That's actually a good question. I don't think there was. As I said, my first assay that I saw activity the following morning, I had multiple phone calls from people. Everybody was behind us. Everybody knew what we were doing. Everybody believed we could do it, and it was just a matter of time when it happened. I don't remember hearing any dissension within the company, but I might have been so high that I didn't hear it. [00:25:30]

[laughter]

**Michael Gottlieb:** Marty, how many compounds did you screen before you found those 16 plates?

**Marty:** Actually, not that many. Remember, although it was a whole lot of plates to count, it wasn't a whole lot of compounds per assay. It was certainly less than 500 by the time we saw AZT. Also, remember we were very targeted. We pretty much looked at nucleosides.

**Michael Gottlieb:** Did you ever find any others?

**Marty:** I'm sorry?

**Michael Gottlieb:** Did you ever find any others? [00:26:00]

**Marty:** Yes, yes. In fact, actually, ddI (didanosine, Videx) and d4T (stavudine, Zerit), which were approved next, actually went through our assay. We saw the activity, but in that assay, neither one of them was active as AZT, and so we didn't go any further with those.

**John:** Robin.

**Robin Weiss:** I must say it's very nice to hear this story in retrospect, personally, from you. Just a question on this last slide, that [00:26:30] the deaths seem to have plateaued before HAART was introduced. Was that because you'd already began testing on about a quarter of the patients?

**Marty:** This is because this is 1999 at the end of this slide, and everybody knows that this graph wouldn't look like that today. I think that we have much better, much safer drugs today than we did back in 1999.

**John:** I think Robin's asking the plateau in [00:27:00] deaths before the introduction of HAART, was that due to the nucleoside analogs?

**Marty:** Oh, that? Yes. I would say yes.

**John:** Mark.

**Mark Harrington:** There's good evidence from the Vancouver group that also—Pneumocystis prophylaxis and MAC (mycobacterium avium complex disease) prophylaxis also played a role in reducing death in that pre-HAART period. But I wanted to ask you why didn't Burroughs Wellcome proceed to do the dose-ranging [00:27:30] studies after you got approval and started charging $10,000 a year, which was the most expensive drug ever approved? Because we had to call Gina Kolata (b. 1948, science journalist) who published an article about it in The New York Times in December 27th, 1989, which resulted in the FDA three weeks later, reducing the dose by half. (4)

Why didn't you guys do—In those intervening four years, when people were exposed to a very high
dose of AZT, which was very toxic to many of them requiring them to get [blood] transfusions [00:28:00] if they were lucky, or infections if they were unlucky, why didn't your company just do that research anyway since it was making so much money off of AZT?

Also because one year, Congress even took, I believe 100 million [dollars] out of Tony Fauci's AIDS research budget and gave it to you guys to pay for AZT, because the federal government didn't want to use taxpayer dollars to pay for it before the Ryan White AIDS Drug Assistance Program was passed. (5)

Marty: Actually, I can answer the first part of your questions, and possibly [00:28:30] not the last part of your question. Yes, AZT was approved at a toxic dose. Everybody in this room knows that. I know that, you know that. A lot of people who received AZT at this dose did have to have transfusions. We know that. AZT dose was reduced, I think, as quickly as it could have, because you had to show not only efficacy, but safety at lower doses, which weren't evaluated in that first study. It was not a phase III study. I think, in fact, [00:29:00] the dose was reduced probably as quickly as it could have been.

Maybe I'm wrong about that. At that time, I was a virologist and today I'm a clinical virologist. I might be able to answer that better if that were done today, but yes, it was expensive. It was toxic. We were aware of both of those things. They both changed.

John: Dan.

John Coffin: Hi, Marty. Very nice to talk. It really, I think, great to hear this story coming out, [00:29:30] from the way it went from the beginning. There was a remarkable piece of luck in there, was there not? In retrospect, many anti-HIV drugs are pretty specific for HIV. The fact that you were able to identify a very active compound using a murine leukemia virus-based assay, have you thought about that over the years, about the remarkable nature of that?

Marty: I've thought about a lot of things. A murine leukemia virus is not a lentivirus [00:30:00] which HIV is, so you're right. They are different. They have different genomes. They have different gene products. You're right, we were lucky. I didn't mention this, we're also lucky in that our company had actually looked at AZT previous to our investigation as an antibacterial. It actually has activity against gram-negative virus-- gram-negative bacteria. I'm a virologist. Everything is a virus to me. Gram-negative bacteria, but the bacteria become resistant overnight. [00:30:30] During that time that that investigation was going forward, a lot of the preclinical work was done.

When we decided then to develop AZT as a drug to be used against HIV, all we had to do was compile those data into reports rather than actually generate the data. That saved a lot of time too. Yes, there was a lot of luck involved.

John Coffin: If I remember correctly, your patent search also turned up another paper which was from a German lab, [00:31:00] (Wolfram) Ostertag (1937–2010, German geneticist). A rather bizarre paper [DL39] in which they actually had used AZT in a Friend [murine] leukemia virus model in mice. (6) The paper was really strange when you read it. I'm just wondering if you remember that or if you have any comments on that.

Marty: I remember that paper, and it came out during litigation. Unfortunately, if you're an inventor on a patent, the only thing that actually means is that you're going to end up in litigation. Do not ever be [00:31:30] an inventor if you have any choice in the matter. I remember that paper, but I also remember being confused about that paper.

Speaker 7: It was very confusing. Actually, I can explain it [inaudible 00:31:39].

Marty: Oh, please do.

John: Bob?

Robert Redfield: I just wanted to make a point. Maybe you didn't emphasize it, but I think a great deal of credit obviously goes to Burroughs Wellcome, and obviously, [Dave] Barry, because if I remember correctly, not only did you use up all the thymidine population which, [00:32:00] at the time, you were getting by purifying DNA from herring sperm, I think.

Marty: Yes.

Robert: Based on that first study by Sam Broder. Dave went to London and had to convince your company to build what I thought was like a $90 million thymidine synthesis plant, or something, to be able to make enough drug to do the later studies. I don't see a lot of pharmaceutical companies doing that anymore.

Marty: Yes. I don't think a pharmaceutical company would even invest in a drug discovery development program for 5000 patients, today, anyway. We wouldn't even have gotten to the place where you [00:32:30] said we wouldn't have done it. Yes, it's an amazing story that I don't think could possibly be repeated today.
John Coffin: One last question, Marty. Who counted the plaques?

[laughter]

Marty: Me. Every single one of them.

[laughter]

John: Okay, well done.

[applause]

[00:32:53] [END OF AUDIO]

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