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Expert Interviews

National HIV Curriculum Podcast

LATITUDE Study: Interim Findings and Implications

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Dr. Aadia Rana, University of Alabama Birmingham Professor of Medicine and LATITUDE Study Chair, discusses the LATITUDE Study's key findings to date and considerations for prescribing long-acting ART for individuals who struggle to take oral medications or who have detectable viral loads.

Topics:

- CAB/RPV
- injectable ART
- oral ART

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Transcript

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introduction**[00:00] Introduction**

Hello everyone, I'm Dr. Brian Wood from the University of Washington in Seattle. Welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

The HIV treatment option, long-acting injectable cabotegravir with rilpivirine (CAB/RPV), was approved by the FDA based on randomized trials that enrolled people who had suppressed viral loads while taking oral ART [antiretroviral therapy]. However, recently, we saw results of an interim analysis from a randomized controlled trial (RCT) that actually aimed to engage people with HIV who had a history of difficulty taking oral ART. This study, known as ACTG 5359 (or the LATITUDE Study) is really a landmark study. It challenges paradigms of who should be included in research trials, and the findings we have seen to date are highly clinically relevant. Today, I'm honored to be joined by Dr. Aadia Rana to discuss the LATITUDE Study and the key findings to date and also to discuss considerations for prescribing long-acting ART for individuals who struggle to take oral medications or who have detectable viral loads.

Dr. Aadia Rana is Professor of Medicine in the Division of Infectious Diseases at the University of Alabama Birmingham, also called UAB. She's also senior scientist with the UAB Center for AIDS Research (or CFAR) where she is the director of the Implementation and Community Sciences Core. She served as chair for the LATITUDE Study, which we will discuss in detail today, and she has extensive experience researching disparities in access to care and disparities in adherence to treatment for people with HIV. She has also studied biomedical interventions to help support treatment adherence, has been involved in clinical trials for investigational HIV and hepatitis C drugs, and has many community and public health partnerships aimed to help improve HIV care outcomes. Welcome, Aadia.

Dr. Rana

Thank you so much for having me, excited to be here.

importance-study**[02:07] Importance of Study**

Dr. Wood

I'm honored to be able to talk to you about this today and we will get right into it, starting with the LATITUDE trial, which you were intimately involved with. Maybe you could start with your perspective on why it was important to conduct a randomized controlled trial of long-acting cabotegravir/rilpivirine for people who have difficulty taking oral ART.

Dr. Rana

Absolutely. So, I think, as the audience may know, sort of the gold standard for when we're testing a new drug or therapy is the randomized clinical trial. So, whether we're comparing it to placebo, or a sugar pill, or the current standard of care, to truly determine whether the new therapy is as effective, or more effective, than what's currently used is the randomized control trial, whereby a flip of a coin, people are given one treatment

or the other. In this design for new therapies, often the people who are selected for those studies, who are considered excellent study candidates meaning they always take their medications, they always show up for visits, they have no challenges with keeping study visits. And so, this is a population that often excludes exactly the population we are trying to study, and so this population does not benefit from that gold standard, which is unfortunate.

And so, we make a lot of assumptions as to whether this treatment is better or that treatment is better, but we don't often include the people who are most vulnerable or who may benefit the most, so I think an RCT was important for that standpoint. Separate from that, we are testing a new paradigm of treatment; we're studying two drugs versus the three-drug regimen for antiretrovirals, which we know has a great durability when it comes to both safety and efficacy. But what about these two drugs, in particular, in patients who have had virologic failure on either similar agents or not? What is the safety and efficacy of this regimen in this population? So, I think the only way to truly answer this question would be a randomized control trial, and it was wonderful that we were able to conduct this.

Dr. Wood

Really wonderful. I'm guessing it took a lot of work to plan and prepare.

study-participants**[04:36] Study Participants**

Dr. Wood

In response to what you just said, Aadia, for listeners who are less familiar with the data, the individuals included in LATITUDE were different than those included in the early registrational trials, the early registrational RCTs that led to the FDA approval, correct?

Dr. Rana

That is correct. So, the early registrational trials, known as a FLAIR, which was for people who had been either newly diagnosed or not previously on treatment, or ATLAS for those who were stable on treatment. Obviously, included just those same excellent candidates as I mentioned. So, either they had already been stable on their treatment, that was for the ATLAS study, or were anticipated to be stable, were going to come into the study, take oral therapy for 20 weeks, and then be randomized. And we were actually looking for almost the opposite, in the sense of in our inclusion criteria, we wanted people who had demonstrated either currently having challenges, evidence of viremia at the time of enrollment in the study, as well as having episodes of viremia just within the past year. So, we were really looking for almost *the* most challenging participants for this study, and a lot of those studies' conditions, such as active substance use, or unstable housing, or being unhoused, are often considered exclusions. Those were not exclusions for our study.

And overall, participants who had low CD4 counts or severe immunosuppression were excluded often in these types of studies, and they were not excluded for our study as well. So, we really wanted to try to get the population that all of us who do clinical practice are trying to do better for and improve outcomes, and our inclusion criteria reflected that. Now, we wanted to, based on the safety and efficacy data that was available to us. I'll remind our listeners that when we developed the initial inclusion criteria for this study, that was prior to any safety or efficacy data being available from those registrational trials, ATLAS and FLAIR. And so, we were doing it based on phase 2 studies, so LATTE, LATTE-2, and as well as some of preliminary data that we were getting from these registrational trials.

Now, as we got more safety and efficacy data, we were able to modify some of our inclusion criteria, but we still had to limit it, certainly, to people who had no history of resistance to the agents, of course, and then certainly if they had hepatitis B. So, neither of these agents treat hepatitis B. If you have hepatitis B, you need an additional antiretroviral in order to treat that, and we thought that if we allowed those people to participate, that would impair our ability to clearly look at the impact of these agents on viral suppression.

Dr. Wood

Absolutely. Thank you for outlining that. And I just want to add, I think it's so fantastic you were able to successfully do a study in which people who often are not reached and engaged in research, and who really could benefit from this new therapy, really were included. So, I just want to highlight to you and the whole team, how important I think this is, and hopefully it's a paradigm and model for future research as well.

study-phases--design**[08:04] Study Phases & Design**

Dr. Wood

But let's talk about the design. So, you mentioned who was included. I know the study happened in several phases, and it was a bit more complex than some CTs [clinical trials]. Can you outline for us the phases and the design of the study?

Dr. Rana

Absolutely. So, there were four steps officially for this study. It's in Step 1, which is our first phase of this study, was the phase at which after participants who were eligible entered and were started on oral antiretrovirals in order to achieve virologic suppression, which we ultimately defined as less than 200 copies. Again, the duration of this changed as we got more safety and efficacy data on the long-acting. So, we started off with participants needing to be suppressed for a minimum of 20 weeks on oral antiretrovirals, but we were able to shorten it up to a minimum of four weeks. So almost, essentially, as soon as they were suppressed, they could then be eligible for randomization. During this Step 1, participants, of course, received support for adherence to oral therapy. There were monthly visits. And in addition to your typical study remunerations that you receive for blood draws, et cetera, they also received conditional economic incentives for achieving virologic benchmarks.

So, once they achieved those, they were then eligible for randomization, that would then commence Step 2. And so, we were randomized to either continue on oral antiretroviral therapy or then start the long-acting treatment, and that also was modified. Initially, everyone had to receive one month of the oral cabotegravir and rilpivirine. Once the FDA changed that requirement, it became optional. So, sites, with their participants, would decide whether or not to do that lead-in. That phase is where we have our primary outcome determined, is a total of 52 weeks. After Step 2, if you were suppressed at the end of Step 2 on *either* arm, you were then eligible to enter Step 3. And Step 3 was actually a growth in after discussion with our global community advisory board in the ACTG [AIDS Clinical Trials Group]. And their feedback for that was that they felt that there would be participants who would be very disappointed in not being randomized to injectable therapy.

And so, having the opportunity to cross over could be a way to help people stay engaged with the study, as well as show them, "Look, even if you don't get this, please continue on, and you may be eligible in the future." So that allowed us to give a crossover for this population. And then, for those who are already on long-acting, it allows us to answer a question of durability of this strategy. So now, in Step 3, which is also 52 weeks so an additional year, we will also be able to define how long people were able to sustain what were essentially monthly injections. And then the final phase was Step 4, which is developed essentially to monitor for the development of resistance. So, there's a lot of concern mentioned earlier about how this is a two-drug regimen in people who have been previously exposed to antiretrovirals. There's a lot of concern about loss to follow-up and an explosion of resistance virus that could develop.

So, any participant who got at least one injection and then stopped injectable therapy for whatever reason, was encouraged to enroll in this observational Step [4], where they are followed for one year and, at the end of that year, are monitored for any development of resistance. So, only limited to those who got injections, at least one. And then even if they didn't continue in the study but continued injections, say commercially, once they were FDA-approved, they didn't need to enroll in this step. This was only for those who discontinued the

injections.

Dr. Wood

Really helpful to hear you outline it like that and to hear the input that you gathered from the Global Community Advisory Board.

role-economic-incentives**[12:25] Role of Economic Incentives**

Dr. Wood

I have several other questions we'll come back to, but next I'd like to ask you about the conditional economic incentives because I know that gets discussed a lot, and there's pros and cons and controversy around it. Can I just ask you what role you think that played? You described it in Step 1 as an additional reimbursement for achieving virologic benchmarks. What role do you think it played in this study?

Dr. Rana

I will say that in developing this study, the first of its kind in the ACTG really targeting this population, one of the things to really bring home is when we're talking about people with challenges with adherence, you don't want to bring them back in the system that failed them to begin with. So, we have to see what *we* can do differently, not what t*hey* can do differently, but what we can collectively do differently that will change the outcome. Now we're bringing them back in, and we're asking them to take oral therapy again, which, by the way, had not been successful previously. So now, the slight difference is that we have a carrot at the end of the stick, which is the opportunity for injectable. And so what we, as a study team, did, is reviewed the literature on what are successful adherence interventions. One of the interventions that we looked at were these conditional economic incentives. And, the thing that was fairly persistent, or redundant with the literature on conditional economic incentives, are actually two things. They work while you give them, i.e., as a time-limited intervention, and if you need to administer them, as soon as the good behavior that you are trying to achieve is done. And so that's exactly how we wanted to propose this time-limited intervention. So, only during Step 1, what's the goal? We want to get them below 200. In using oral therapy, which had not succeeded previously for them, and in order to then make them eligible for randomization. So CTN-001, the HOPE study, which studied conditional economic incentives versus patient navigation, or both, or standard of care in active substance users, found just this—only worked as a time-limited intervention. So that is what we were trying to use it as, only during Step 1, to get them eligible for randomization.

In terms of how effective we think it is, I think that is something we'll parse through in a little bit more detail. We had proposed initially to the ACTG to randomize the conditional economic incentives as well so that we could clearly answer this question: Are they truly needed beyond the wraparound services that clinics will already provide, beyond the additional monthly visits that they're getting? Unfortunately, from a budgetary standpoint and a sample size standpoint, we were unable to facilitate that within the ACTG. But the good news is the ACTG has approved a protocol, a qualitative protocol, where we will attempt to parse out the impact of the conditional economic incentives in participants who either were successfully randomized or not successfully randomized. The additional conditional economic incentives ended at Step 1; they did not continue in Step 2 or Step 3. And so, what we're seeing really in the duration, I think, of those who were eligible to randomize, are truly the impact of the long-acting injectables themselves.

randomization-eligibility**[16:00] Randomization Eligibility**

Dr. Wood

I see. So then, turning to Step 2 and the randomization to long-acting injectables or oral ART, a question for you about this phase. You mentioned to be eligible for randomization, a participant needed to achieve a viral load below 200 copies, but my understanding is some individuals actually started injectables with viral loads

higher than that. Is that correct?

Dr. Rana

That is correct and I think really speaks to the challenges these patients experience. So, you did have to be less than 200 to become eligible, and then you had four weeks to get randomized, a month, less than a month in certain cases to get randomized.

Dr. Wood

I see.

Dr. Rana

At that randomization visit, we did collect a viral load, did not impact your randomization, but we wanted to see where our participants were. Seventeen percent of the people who eventually got randomized to long-acting were already viremic. Four weeks! And 10% of those who were randomized into the oral arm were already viremic. And I think, again, just speaks to that oral therapy is a challenge for this population. Of those 17% of the 294, they are randomized and were in the long-acting arm; eight of them even had a viral load greater than 10,000, so within four weeks. And so absolutely, we did have even that viremic population included in the Step 2 for our primary analysis.

Dr. Wood

I see. We will come back, and I'll ask you later, what we know about how those individuals who had detectable viral loads, viral loads above 200 or above 10,000, did with the long-acting injectable therapy.

study-outcomes**[17:50] Study Outcomes**

Dr. Wood

But first, stepping back for a sec, maybe you could just describe for listeners what the primary and secondary outcomes of the analysis were.

Dr. Rana

Absolutely. So, the focus, in terms of the primary analysis, is we were looking at what's considered a composite outcome. So, that means we defined our outcome as the proportion of patients who experienced virologic failure or treatment discontinuation for any reason. And, of course, that's in both arms, so whether that happened in the long-acting arm, or whether that happened in the standard-of-care arm. And we combined it for the reason that we're not just interested in whether this strategy works or was better based on the number of people who were suppressed, but it also allows us to capture if there was impact on things like loss to follow-up or disengagement with care. And so, when you include treatment discontinuation, beyond just virologic failure, it really allows you to assess the overall strategy and its impact rather than just looking at whether you were able to capture virologic failure or not. So that's our primary analysis.

At the same time, though, we do want to individually see what is the impact just on virologic failure as well. And so that is a separate outcome that we looked at, in terms of our secondary outcomes, so overall virologic failure.

And then an additional outcome that we wanted to look at secondarily was treatment discontinuation related to adverse events. So, we have the data from ATLAS and FLAIR and the adverse events that were experienced in that population. Are they any different for this population? Are there different experiences or tolerabilities of these agents that we will see in a population that may have lower CD4 counts, which is

something that we saw, or higher viral loads to begin with, as it were, that we wouldn't have seen in that population? We wanted to make sure with our outcomes, that we were able to separately capture those as well.

Dr. Wood

It's helpful to hear you describe that.

interim-efficacy-analysis**[20:00] Interim Efficacy Analysis**

Dr. Wood

So, turning to outcomes, my understanding is there was a pre-planned efficacy analysis that has given us some data. I believe you presented it at the CROI [Conference on Retroviruses and Opportunistic Infections] conference, and there was a lot of buzz around it, there was a lot of excitement. I'd love if you could describe to listeners, what were the findings of this pre-planned efficacy analysis and what do we know to date about outcomes?

Dr. Rana

I'll just preface, as you mentioned, this was a pre-planned efficacy analysis by our independent Data Safety Monitoring Board (DSMB) once we've had at least 67% of our anticipated enrolled randomized participants achieve an endpoint. So, it was already there, and this meeting happened on February 12th. At that time, we had enrolled 434 participants into the study, and 294 had been randomized. And the population is, I think, very similar to what we see in our clinic. So, there's about 20%, I think, were under the age of 30, 30% female, 64% African American, and 14% either current or prior injection drug use. And so, we think fairly reflective of the U.S. population, we were enrolling in 34 sites from around the United States, including Puerto Rico. And, what the main finding at this interim efficacy analysis that the Data Safety Monitoring Board reviewed was in the primary outcome, there were a total of 28 regimen failures in the long-acting arm and 47 in the standard-of-care arm.

So, as a reminder, for a Data Safety Monitoring Board, what they're looking at, or what they're defining it for significance, is not what we think our primary analysis, planned analysis are. They are deciding whether or not they stop the study, so it's a fairly stringent stopping criteria. Now, this independent Data Safety Monitoring Board has been looking at this data since the beginning, so once we started enrolling, our prior pre-planned interim efficacy analysis, any additional interim efficacy analysis they see. So, they see not just what's in the moment, but they also see what the trend has been. And so, on that pre-planned, for the one in February, that difference—24% in the long-acting arm and 38.5% in the standard-of-care arm—had a difference of 14.5%, which was just outside of the significance in terms of the stopping criteria, which is a 98.5% confidence interval.

However, when they looked at the key secondary outcomes of virologic failure and treatment-related failure, the difference was significant and quite stark: 7.2% versus 25%, long-acting versus standard of care for virologic failure, 9.6% versus 26.2% for treatment-related failure, comparing long-acting to standard of care. Those were both statistically significant and on-trend. And so, from their perspective, the Data Safety Monitoring Board said it was crystal clear where this was headed, both in terms of the primary outcome and what was already evident in the secondary outcome. And so, at that time, their recommendation to the team and to the ACTG was to halt randomization and then to offer long-acting to all participants, which was something that the network accepted for that reason. I will also highlight, I think, two additional outcomes from the study that are important to mention.

One is that there were two participants in the long-acting arm who had the development of resistance, and both of those participants had fairly high-level integrase resistance evident on their resistance panel. There was also resistance in the standard-of-care arm. There were much higher rates of virologic failure, but only

two, also participants with evidence of resistance, likely reflective of the fact that most of those virologic failures were related to nonadherence rather than actual development of resistance. The other thing that I will highlight is for these monthly injections in this population with challenges with adherence, 93% of the injections were on time. So, these folks came in monthly, and I think that's something also that we would like to tease out in our qualitative work, to see people talk about, and I'm sure we'll talk about every month versus every other month, and was it actually better that they came in monthly, or what could get addressed? But 93% were on time, and these are a lot of injections to give, so very interesting to see.

Dr. Wood

No, that's really impressive. And you were just mentioning some questions, I think those are great questions to look at, and we'll come back to some of those. Aadia, I've heard some different opinions about the trial being stopped because the primary outcome didn't technically reach statistical significance, but you made the point it seemed really clear it was heading that direction, and the secondary outcomes were clearly very different. I just ask your opinion, or your response to anyone who would say, "Well, maybe it shouldn't have been stopped because the primary outcome didn't reach the criteria for stoppage that was planned." What would you say?

Dr. Rana

Yeah, I would say that, again, for this independent Data Safety Monitoring Board that had been tracking this data from the beginning, they are looking at reducing harm and making sure that the participants are having a just and equitable treatment in this study. And so, I think that because they were able to clearly trend where the benchmarks were going, they knew that in some amount of time, this was likely, in their opinion, going to achieve significance. And given what the secondary outcomes were, I think from their perspective, this is where they crossed the line, that we were no longer being equitable in both arms. And I agree. Of course, I'm biased, but the network probably also wanted to accept that recommendation. And so, I think we have to be careful, as I mentioned earlier, stoppage criteria significance versus effectiveness significance, in terms of main analysis or primary analysis.

And that is coming soon, and we hope to report that momentarily. But I think that this has been demonstrated previously. If you recall [HPTN] 083 also had, which was the cabotegravir prevention study, also had a similar outcome and was recommended to be stopped by their Data Safety Monitoring Board, and resulted in a guideline change. So, I think there's precedent where independent Data Safety Monitoring Boards are able to use not just black and white—is this statistically significant or not—but where is this going, and how can this be interpreted in terms of our responsibility to our trial participants?

Dr. Wood

I think those are great points, and appreciate that. And we should be clear to listeners that what we have so far is a pre-planned interim analysis, and as you said, really, the main principle findings of the study are forthcoming, hopefully in the near future. So, I want to be clear about that to everyone. But there are so many important lessons learned here.

virologic-failures**[28:07] Virologic Failures**

Dr. Wood

Let me come back to some other outcomes. You mentioned development of new resistance mutations occurred for two participants in the long-acting injectable arm and also two in the standard-of-care oral ART arm. I am curious for those two individuals who developed new resistance with long-acting cabotegravir/rilpivirine. Did they have detectable viral loads, viral loads above 200 before starting injectable therapy? And what else can you tell us about the volunteers who started injectable therapy with a viral load above 200?

Dr. Rana

So, what I can share, in terms of what I have from the interim efficacy analysis, so we had a total of six who experienced any virologic failure. There was one participant who had treatment discontinuation and then experienced virologic failure; that participant was randomized but had never actually initiated injections. After taking that participant out, the other five who actually initiated injections and then experienced virologic failure at the time of our planned interim efficacy analysis, none of those five had viral loads greater than 200 on entry to Step 2. So, I can only speak to the converse in that when you ask me what happened to those who were viremic, well, none of them are included in that list of five, right?

Dr. Wood

Got it.

Dr. Rana

I can't specifically answer to you what happened to those 17% who were long-acting, what was their outcome. I can't specifically answer that, but I can say in terms of virologic failure, the five who initiated injections, none of them had a viral load greater than 200.

Dr. Wood

I see.

Dr. Rana

The other thing I will point out, for those five who initiated injections and had virologic failure, only two of those five had significant resistance-associated mutations. None of them had missed injections, and three of them did have a delay in their injections, but none of them were delayed by greater than a week in terms of the window. Most were just within a day or two. So, the pharmacokinetics (PK), I think, will be interesting to see. As you know, there's predictors that include BMI and subtype, as well as archived resistance, so we will be investigating that as well. But I also thought that was very interesting, that we had no missed. So, we're talking about mostly on-time injections, no missed injections, and yet still, we do have the emergence of resistance in very few, but still cases, so something to consider, and again, speaks to the importance of this RCT.

Dr. Wood

Absolutely. And it does seem in line with what we know from the prior RCTs. My understanding is somewhere in the range of 1-2% of individuals, despite on-time injections of long-acting cabotegravir/rilpivirine, do develop virologic failure. But sounds like you will be looking at PK data and looking to see if there were any other factors contributing to the risk for virologic failure. Is that right?

Dr. Rana

And it'll be similar, in that we won't have that many, just like in the combined ATLAS, FLAIR, ATLAS-2M analyses, but we will certainly look for similar factors that were included in that model as well and perhaps ascertain if there's any additional ones that are additional for this particular population.

lessons-learned**[31:34] Lessons Learned**

Dr. Wood

But also, 93% on-time injections is really impressive and, in my mind, comes back to what you were saying

before. You posed it as, "Well, what can we, as a medical and research community, do differently?" And it seems like what you offered and did here really worked, and people engaged. And with the support, people got their injections, and a lot were really successful. So again, a lesson here that I'm taking is, look, we should never assume a person is not going to be able to come for their injections, and we, as a medical community, can do things a lot better to help people engage. But I'll ask for your reflections on that, and then what other important lessons do you think listeners should take from the findings of LATITUDE thus far?

Dr. Rana

I think that that's spot-on, that the assumptions that we make that a person shouldn't be offered this novel, new, potentially expensive, whatever you might say, therapy based on their past behavior, when in fact, this new therapy may actually support them in changing their behavior. I think as practitioners and providers, we really need to hit ourselves on the head with a two-by-four sometimes when we think about it. I know that this is being discussed even more as we have new agents with new modalities, and more extensive durations being developed and potentially approved, and then how are we ensuring equitable distribution of these new agents? And so, the one thing I will always say every time people ask me the most important lesson learned from LATITUDE for me, and I call this study a labor of love for everyone who, back 10 years ago now, first proposed this study to the ACTG, which as a paradigm shift of every frame that you can think of, in both, not just what we were testing, who we were testing, what we were including in terms of support.

So, the big lesson learned is, please do not exclude people with challenges with adherence in your phase 3 or even phase 2 investigational trials. They are motivated to participate. They want to do better. They want to feel better as well. And, understanding the limitations of FDA approvals and how that pathway works. But for industry and people who are developing these agents, to at least formulate how can we, very early on, not as phase 4, but very early on, include this population who would probably most benefit and potentially have the biggest impact on the epidemic, is paramount. And I think this study, where we screened 900 people, enrolled 434, randomized 300, we can do it, right? We can do it. And 93% on-time injections, and in terms of those, and few, lower than expected loss to follow up, we can be fluid, we can make these changes. We just can't expect everyone to follow the same paradigm that we had originally planned. So, for me, that's always going to be one of the most important lessons that we learned from this study.

Dr. Wood

Such an important lesson and paradigm shift. And I think your research and findings, and other data, and other experience, has really shown us that even for individuals who historically have struggled to take oral ART or come to visits, for some, especially those with low CD4 counts, this really can be life-saving therapy. There's a lot to consider, obviously, but really, it can be life-saving, so I appreciate those lessons very much.

clinical-practice-integration**[35:32] Clinical Practice Integration**

Dr. Wood

So, maybe in the last part of our conversation, Aadia, I'm just curious to hear how you've taken the findings of LATITUDE thus far and integrated them into clinical practice and what you think that should look like for clinicians, for people who care for people with HIV on a day-to-day in clinical practice. How would you translate these lessons into counseling for patients, and decision-making, and prioritization of cabotegravir/rilpivirine?

Dr. Rana

So again, with LATITUDE, for our study sites, we wanted to make sure that they were empowered to treat this population and to enroll this population. And what that ended up translating to, in addition to the conditional economic incentives, of course, was are they co-located, or in relation with, say, a clinic that does offer wraparound services, for example, a Ryan White clinic, or an FQHC [Federally Qualified Health Center], or

something of that nature, in that way. And the truth is, is that the majority of patients living with HIV are often served in those exact settings. And so, when I think about now, this findings from LATITUDE, and again, we'll parse this out a little bit more in the qualitative work, but the resources that were really needed for these patients are often the same resources I offer to my clinic patients, whether it's referrals to substance use support, or mental health counseling, or just overall counseling in general, transportation support, as it were.

The big difference often was the treatment that they were getting and the attention that they're getting from it. So, I would say my takeaway from these findings is right now, we have who are currently FDA-approved for these drugs, now no longer study drugs, but now FDA-approved. And I would consider offering these agents to people who have challenges with adherence. And it will be a question of implementation and resources at your site—how you strategically move through your patient population to prioritize. And I think this is going to be a very healthy and robust discussion as to where we should go. Guidelines have recently changed to consider this in sort of our most vulnerable population, low CD4 count, absolutely intolerant of oral ART. But I think once we sort of have that, which are there but are not, luckily, as many people, we know that engagement and adherence is a dynamic process.

You can be adherent one month and nonadherent the next month, and that can change, and so I would challenge us to consider these agents in that population, as well. So, people who've historically had challenges, who may be doing okay right now, but may, at some point, then benefit from this being part of their treatment strategy, as well. And so that's how I'm looking at it, is potentially prioritizing our most vulnerable, and then in a fairly rapid way, as our structure allows, broadening it and expanding offering it to the population that is interested, who actually says, "I want to do this."

Dr. Wood

Absolutely. And I don't know your local experience, but my local experience here, and I think the experience of many, is because of limited resources, because it does take a lot to both get the cabotegravir/rilpivirine approved and in hand, and then administer, and help monitor and support the on-time injection visits. Most clinics do have to prioritize.

Dr. Rana

That's right, absolutely.

Dr. Wood

Most clinics cannot prescribe and successfully offer this therapy to everyone who is interested and could benefit. So, as you mentioned, clinicians and clinics have to decide how to prioritize their resources, so it's helpful to hear how you outlined the considerations.

dosing-considerations**[39:45] Dosing Considerations**

Dr. Wood

And I'm just wondering, other considerations or words of wisdom, clinicians are reaching for injectable cab-rilpivirine for individuals who've struggled to take oral ART for whatever reason. For example, coming back to every one- versus every two-month dosing, or other practical considerations based on your trial or clinic experience?

Dr. Rana

Certainly, in this study, one of the limitations of this study is we only tested monthly. We didn't test every other month. And we are, I believe, the only country that is actually regulatory-approved for monthly injections, so that is a limitation. And of course, we only did this in U.S. settings, and we had the requirement

for eligibility for randomization to be less than 200. Although, as we discussed earlier, we did have a not insignificant portion be viremic, so I think we'll be able to make fairly good deductions, in addition to some of the clinical experience that we have that's also been published on that use. I would say, based on what we currently have in terms of data from the LATITUDE Study, Ward-86 [UCSF HIV clinic], and other settings, for those with challenges with adherence, I would actually recommend starting off with monthly injections for some duration, anywhere from three to four months as it were. Of course, the first two sets of injections are one month apart anyway, but in some settings, and I think the sense is that these monthly injections will allow both the patient as well as the provider to feel comfortable with engagement and also potentially have more frequent opportunities to address separate challenges that the patient may be experiencing, and then transition them, once safety tolerability has been, to every other month. So, I think that is a good paradigm to potentially consider *if* your clinic infrastructure can support that.

There is a publication, small, from Mississippi, of 12 patients, where they didn't have the infrastructure to support every-month injection. So even for these very challenged treatment-experienced people, they went straight to Q2 [every 2] month. And again, small, 12 patients, but that's what they could do. And so far, those patients are doing well. So, it is a little bit of a reflection of what your capacity is in your clinic. The only other additional thing I would say is because BMI has been an issue, is to be sure that we're using two-inch needles, particularly in those with a BMI greater than 30, as well. And so, whether you're starting off monthly or every other month, either way, to be very careful because we have certainly had experiences with failures that may be related to that.

viral-load--cabrpv-switch**[42:30] Viral Load & CAB/RPV Switch?**

Dr. Wood

And coming back to LATITUDE for a moment, obviously, the goal, as you described in Step 1, was to achieve a viral load below 200, and you mentioned some of the other data and experience that's out there from Mississippi, from Ward 86. We've seen data from other places as well regarding starting long-acting cabotegravir/rilpivirine with detectable viral load, sometimes very high viral load. So, practically speaking, in your practice, is there a viral load you really hope or aim to achieve before switching to the long-acting therapy, or is it really a case-by-case decision?

Dr. Rana

I think, at this point, it is going to be more of a case-by-case decision for those with a very high viral load. So, as we know, right now, rilpivirine, for example, is not recommended for use as a three-drug regimen in patients with a viral load greater than 100,000. And so, if we extrapolate that, wow, don't ever use this in anybody who has a viral load greater than 100,000. But we have case reports where cab plus rilpivirine has been used effectively in that population. But the thing is, is that those people also fit the other criteria of low CD4 count, really no other option, or unwilling to take oral. So, at that point, you're almost on a compassionate use kind of basis at that, you're trying to really just save their lives. And so, I think that's where it gets to a case-by-case basis.

I think when you don't fit those other criteria, then of course, it's more of a, "All right, do I think this regimen, is this regimen expected to work?" Meaning they don't have exposure to rilpivirine the past, or no predicted NNRTI [non-nucleoside reverse transcriptase inhibitor] resistance, or no predicted cabotegravir resistance. Now I feel a little bit more comfortable with higher viral loads, even in the potentially 1,000s, 10,000s, as it were, but that will have to be, I think, a careful consideration. A lot of these clinics, where they are using injectables in viremic, they do have experts at their clinic reviewing those cases, often ends up being a review of their treatment history more than anything, a careful review of treatment history and resistance profile prior, more so than a deciding based on viral load. So, a little bit of nuance, I think, and I think will certainly play a role in the speed of scale up at sites.

Dr. Wood

Absolutely a lot to consider in those situations.

future-research**[45:00] Future Research**

Dr. Wood

So, Aadia, I feel like I could talk to you about this all day, but we will wrap up shortly. And maybe as a final part of this conversation, you could just tell me and tell listeners what you would like to see as the future of research for long-acting therapy. You've mentioned a couple outstanding research questions that could be looked at, Q2 month, for example, instead of Q1 [every 1] month. What else would you like to see happen in this area in the future?

Dr. Rana

Yeah, so I think a couple of things. One, I think any study on treatment using any new modality, I mentioned this before, please include this population in your investigational studies phase 3 before approval. I think the other thing that would be of interest is whether or not testing behavioral strategies alongside these long-acting strategies. I think that we were unable to do that for this, for LATITUDE specifically, as it relates to the conditional economic incentives. But any behavioral strategy, whether it's additional counseling, whether it's motivational interviewing, we all know that all of those things work. It'd be interesting to see how they work in concert with some of these biomedical strategies as well. So, this biomedical behavioral truly being tested together, and then we don't have to guess, "Hey, which one was the one that won over today?" I think that would be wonderful to see, and that our behavioral scientists have so much to add and so much to contribute in what we've done, and to really sort of see that validated in a large clinical trial would be fantastic.

Dr. Wood

That would be phenomenal. Aadia, we've talked about a lot. I want to thank you for your time and expertise and for all the work that you do.

Dr. Rana

Thank you so much. It was such a pleasure to be able to discuss this with you this afternoon, and we really look forward to getting the primary analysis out to you all very soon.

Dr. Wood

I look forward to it. Thank you, Aadia.

Dr. Rana

Thank you.

credits**[47:00] Credits**

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