Clinical Education Initiative
Support@ceitraining.org

ECHO: A REVIEW AND UPDATE ON HSV THERAPEUTICS

Tara Babu, MD, **MSCI**

1/12/2024

ECHO: A Review and Update on HSV Therapeutics
[video transcript]

00:07
So with that, I'll pass it to Dr. Tia Babu. To do our presentation today.

00:15
Yeah. So today I'm going to present a review and an update on HSV, otherwise known as herpes simplex virus therapeutics. And I have no financial disclosures. In terms of the learning objectives, I'm going to review the epidemiology and burden of HSV disease. And then I'm going to describe the available therapies for HSV and the current guidelines for treatment of HSV. This is just an outline of my presentation, I'll go over some of the epidemiology virology. briefly discuss the current therapeutics, which I think a lot of you've are probably already familiar with. And then I will go into a little bit about vaccines and then end with HSV resistance. So I'm sure you're familiar with these slides from the CDC. But STIs are on the rise. And this is from 2018. So in 2018, it's estimated that one in five people in the United States have had have an STI. That totals nearly 68 million infections in the year 2018. In terms of new infections, the estimate was 26 million new sexually transmitted infections in 2018. And almost half of these new cases were in young people ages 15 to 24. In the US, STIs really do have a big financial burden for the medical system. New STIs totaled nearly 16 billion direct medical costs in 2018. And just to give a breakdown of the STIs prevalence and incidence in the United States, here you can see the purple is prevalence. So that is how many cases there are at any given time. And then incidence is the number of new cases and so this is for 2018. You can see by and large, the highest prevalent STI is HPV human papilloma virus which is associated with, you know, genital warts, cervical cancer or pharyngeal cancers at 42 Point 5 million and has a high incidence of 13 million new cases. The second STI is HSV two, and it has a high prevalence rate of 18 point 6 million but a lower incidence rate of new cases. 572,001 thing that I would note here is that these are for reportable infectious diseases, but HSV one is not reportable. And so if you added HSV, one to HSV, two, the prevalence would be much higher and would also increase the incidence. And just to provide context, you can see here chlamydia prevalence is about 2.4 million gonorrhea, HIV and then syphilis down here. So it just be two second highest prevalence STI in the United States. And before we go into therapeutics, I do want to talk just a little bit about HSV one and two, so they are in the herpes Vira day family they are herpes simplex virus one and two. They have the property of all herpes Vira day infections or viruses and that they can go into a latent state. So once you are infected with a herpes virus, a virus you basically have the infection for like herpes associated with oral herpes, genital herpes, it can also infect the eye, you can have Author ware infections, you can have encephalitis that goes to the brain. And then also, there is a very serious fulminant Hepatitis that really can occur with herpes both HSV one and two may cause genital HSV. I think back in the day used to be taught above the diaphragm was HSV. One and below was HSV. Two but that is really not the case. And we definitely are

seeing an increasing proportion of new HSV one genital infections, and that's particularly in young people and in men who have sex with men. There have been studies that have shown that greater than 50% of the new genital HSV has been due to HSV one. The fortunate news is that HSV One, genital herpes does have fewer recurrences and not to have lower transmission risk than HSV two. And here is just an image of the herpes virus. It's a DNA virus. It's an envelope virus. And then I just want to draw your attention to these glycoproteins. So there are several glycoproteins on the herpes virus and these are particularly important for the virus infecting cells, but also when we talk about vaccine targets and antigens for vaccination. And this is just a brief slide on the pathogenesis of HSV. So firstly, the virus you're inoculated with a virus. It is neurotropic. So it goes along the sacral ganglion if it's genital herpes, and then it goes to the dorsal root ganglion in your spinal cord. And the virus replicates. Here you can see the purple circles. Once the virus replicates, it then goes back and it spreads to the skin mucosa and you see the vesicles and ulcers. The important thing with herpes is once this symptomatic infection is over, you still have the virus present in the dorsal root ganglion, so it never goes away. And it can reactivate. And now that we've reviewed just some of the brief epidemiology and pathogenesis, I'm really gonna focus on the management for herpes. Really, the management is twofold. One is the prevention of symptoms and recurrences and it really does improve quality of life for patients to have less frequent recurrences and less symptoms. And then the second piece is prevention, prevention of transmission to sexual partners and particularly cero discordant couples. So these are the treatments. I'm sure many of you are familiar with them. I think the first thing I will say is that we've had the same drugs for 20 to 25 years for herpes. They do work, but hopefully we will have future therapeutics in the pipeline. The drugs that are typically recommended are Valley cycle, Vir, famciclovir, and Acyclovir. And in the 2021 treatment guidelines, the dosing were unchanged from the 2015. general principles are really for, for genital herpes, episodic versus suppressive therapy, which I will talk about. And it's important to just briefly review the mechanism of how these drugs work because I'm going to talk about resistance in a few slides. So here you can see Acyclovir valacyclovir, is a pro drug to Acyclovir. So it converts Acyclovir and goes through the same pathway. And famciclovir has a similar pathway, where it requires the herpes viral kinase, the tyrosine kinase to phosphorylate it so Acyclovir is not active until it has this tri phosphorylation step. But the important thing is that the herpes, actual the herpes viral kinase is the first step for phosphorylation. And then the cell that's infected the cellular kinases do the next two steps. So if you do not have this tyrosine kinase, step to phosphorylate Acyclovir can't be activated and cannot go and inhibit the DNA preliminary polymerase for the for the replication of the virus. So when we talk about resistance here, this is the step that the virus doesn't either have a tyrosine kinase or there's a polymorphism. There's some sort of change here where encyclopedia cannot be phosphorylated. And that's when we see resistance for herpes. So here's a case of a 40-year-old man never previously had a diagnosis of HSV. Two had antibody tightening or antibody serology testing during a previous STI clinic visit that was negative, and now presents with one to two days of painful blisters on his penis, on exam, you know, someone went in when all went

bad, not that the and he doesn't miss having three new partners in the past one to two months and really uses condoms. So you do a PCR test on the lesion and it's positive for HSV two. So this case would be a primary episode. This is the first clinical episode of this patient having HSV genital lesions but also the first time that it sounds like that this patient actually converted to HSV two and this is just to show the natural history of herpes. So you have the blisters which and also rate and then eventually crossed over and that can happen anywhere from four to 20 days

10:06
with the progression of the virus and this is from the mm WR the recommended regimens for treatment are either Acyclovir famciclovir rally cycle here and typical treatment is seven to 10 days. I will highlight that this is a recommendation dosing for both HIV and non-HIV patients. However, with HIV patients, sometimes they do require longer treatment until the regions have resolved. And I would also mention that ngulia Kylie Jenner, genital herpes can cause a prolonged clinical illness. Patients can have severe also ulcerations and they can have neurologic involvement. Even if this is their first episode, and it's very mild. The recommendation is to treat a primary episode for genital herpes. And I just put this quote in from Christine Johnson's article and 2022 and Cid really choosing between these treatments, dosing strategies that are the most feasible for the patient adherence should be prioritized. So when you choose which regimen to use, it's really important to also take into consideration what the patient can do, what medications are easily available and what the financial burden might be. So this is a second case you have a 30-year-old woman she's HIV negative. She does have a known history of HS two genital lesions and now presents with one to two days of pain in her genital area. She was diagnosed over the past year and has been having outbreaks almost monthly to bi monthly but has never sought out a carrier to actually take medications during the outbreaks. And here you can see some of the ulcerations in this picture. So this case highlights considerations for suppressive versus epithet episodic therapy. So suppressive therapy is therapy that a patient would take medication every day to suppress symptomatic recurrences, and also suppress viral shedding if they are concerned about transmission. Episodic therapy requires the patient to take the medication during an episode. Typically, these are patients who actually know they're going to have an episode have like a prodrome feeling that these symptoms are coming on. And I think the key if a patient is going to do episodic therapy is they actually need to have the prescription and they need to have the medication on hand in order to be successful at taking it when they have an episode. Things to consider are the severity of disease and the patient preference, what's important to them. It is good to know and good to counsel your patients that there really is good long term safety data in patients who take Acyclovir valacyclovir or famciclovir chronically, and there really is no evidence of emergence of resistant strains and people who have immuno competent mewn systems. It's more that we see resistance in the immunocompromised host, which I will talk about. And then in terms of the long term, it's important to continue to revisit once you put a patient on suppressive therapy, it's important to

actually talk to them again at a year and then to continue to discuss whether they want to stay on suppressive therapy or not. We do know that recurrences do decrease many years out after the first infection. And depending on how the patient feels, they may want to discontinue suppressive therapy at some point. And then also to discuss short term suppressive therapy. For instance, if there are times where they want to take suppressive therapy, for instance of vacation, or they're going on their honeymoon, and then really to discuss their concern for being in a discordant zero discordant relationship if they have a partner who doesn't have HSV. And these are the regiments for suppressive therapy for persons who do not have HIV and this is from the MN WR article, and has several options for treatment for suppressive therapy. And this is the recommended episodic therapy for non-HIV patients from the MWR as well and there aren't Really a lot of good head to head data for these medications. But I think a lot of people probably aren't familiar with Acyclovir and valacyclovir. And valacyclovir does have very good bioavailability. And Acyclovir does have a very high area under the curve, which we talked about when we talk about treatment and coverage for an infection. And I just wanted to add this as a reference for the recommendation for suppression and genital herpes in patients who have HIV infection, and the dosing can be higher, and also for episodic therapy longer. So I just wanted to show this study that we actually published in 2023, we were looking at whether Acyclovir inhibiting herpes can actually have an effect on BV score. But the reason I wanted to show this is because it's just really, like all the studies shows that suppressive. antiviral therapy is really effective. And so this study was in 41 women who had known HSV, two and then also had BV. This was the day of observational period when they actually weren't taking any medication. So for 28 days, they were swabbing they were doing anal genital swabs. And you can see here this is the proportion of positive HSV tests during that observational period. So is fairly high. These patients had known recurrences of HSV, to be in the study, but they actually did have a pretty high shutting rate. And then these are the days of Val Acyclovir suppression. And basically there was a 94% reduction in HSV shedding with patients taking 500 milligrams of LSI kobir daily.

17:12
And I think when you talk about herpes suppression, a lot of people refer to the quarry study in 2004. This was really a seminal study, and not only with the transmission but also looked at with AD symptomatic disease for HSV. Two, and so in this study, they had 1498 monogamous, heterosexual HSV, two zero discordant couples, the source, the couple member with the with the infection had to have symptomatic a history of symptomatic recurrent HSV two genital infection and patients were randomly assigned. So the source patient was in each couple was randomly assigned to either receiving 500 milligrams of Le Segovia once daily or placebo and these patients were followed for eight months. And this study showed that if the couple member who had HSV two genital infection took Valley Segovia daily for suppressive therapy, there was a 48% reduction in transmission. I will also mention that the mean recreates rates of recurrence were point one per month without Acyclovir are with Acyclovir valacyclovir and point four per month without so definitely there was a decrease in symptomatic recurrence, and also a

very significant decrease in transmission. And I'd previously referred to Christine's article, but this is a really nice summary of the evidence and what the data is that drives, recurrences and transmission and suppressive therapy. So here you can see the symptomatic HSV. Two, by and large has the most data for prevention of recurrences. So it's a Level A which is a high certainty and benefits. So it's very data driven, that we know that if people who have genital HSV two genital lesions are symptomatic, if you put them on suppressive therapy, they will have less recurrences. And this is true for both people with and without HIV. There is no data on patients who have asymptomatic HSV. Two and for HSV. One, there isn't data, strong data to say this, but there is that that for patients who are symptomatic with genital HSV one if they are having many recurrences, that there would be some sort of benefit for being on suppressive therapy. In terms of transmission for HSV, two symptomatic the strongest data are for people who are not infected with HIV. And again, as I showed you the data from their quarry study, the transmission risk was decreased about 50%. In fewer discordant couples when this worst patient took Valley cycle Vir. I will also just mention there are there is a study that shows in Sierra discordant couples also zero discordant with HIV, that suppressive therapy did not decrease transmission of HSV. So, this is not a highly data driven place and should be discussed with, you know, patients as well. And part of the toolkit should also be consideration for use of condoms. If there's concern for HSV transmission. And for transmission again here for HSV. One there is there is no data to suggest the suppressive therapy decreases transmission. So now that I went through some of the literature on therapeutics, I do want to just mention some of these vaccines because I think this is a place right now that is very exciting. There have been previous HSP vaccines but currently there are three candidates right now that are in phase one, phase one, two trials. Bio and tech, I believe has completed their HSV vaccine, study and hope we're hoping that or it was completed enrollment and we're hoping for interim data this year. And they are looking at an mRNA vaccine that has several glycoproteins and this is a prophylactic vaccine because in HSV vaccines, there are candidates that are prophylactic and they're candidates that are therapeutic prophylactic means they prevent people from getting infection therapeutic is when people actually have for instance, HSV two genital disease taking vaccine could decrease their recurrences and viral shedding. They're also currently enrolling for the Moderna study, which is an mRNA vaccine and the GSK study, which is a recombinant protein vaccine, and it has an adjuvant similar to the Shingrix vaccine. And both of these vaccines are actually therapeutic. So they're enrolling participants who actually have previous HSV, two genital infections. And this is just from the Herpes Cure advocacy website. To give you an idea that there are several other vaccines out there that are in preclinical studies, which are animal studies, and there's quite a range. There's a Live Attenuated Vaccine, which means it's a weakened virus platform vaccine. There's mRNA, as I mentioned, there is actually an intranasal vaccine by blue Villa Willow, that's in preclinical trials. And several of these vaccines are therapeutic and some are prophylactic to evaluate in patients who have not been infected with HSV. And lastly, I was going to just mention herpes resistance. So this is a 28 year old woman who has a history of HIV her CD for count is less than 100. Viral load about 200,000 copies who inconsistently takes her AR team

that presents with recurrent herpetic Whitlow refractory to valley cyclo virotherapy. So this is a case I would be concerned for herpes resistance. She's immunocompromised host. Her CD for count is less than 100. And she is on suppressive therapy and continuing to have outbreaks. So we talked about Acyclovir and its mechanism of being phosphorylated. It works on the DNA polymerase here. Other drugs that do not require that that phosphorylation by the tyrosine kinase or cidofovir, foscarnet brincidofovir. And these are medications that we do use if somebody does have herpes resistance. And then there is a whole new class of medications there are helicase primase inhibitors. So instead of inhibiting a DNA polymerase, which helps with replication, it actually inhibits the helicase primase complex which unwinds the DNA before the DNA polymerase acts on the DNA. And these medications are being studied for herpes resistance and for resistance Acyclovir resistance and first class resistance to valley cycle Vir and famciclovir. alternative therapies that can be used are foscarnet, as I mentioned, and cidofovir however, they are very nephrotoxic. And if they're on foscarnet, they need to be in the hospital. There are case reports though, and I put these in here of using topical therapies for genital herpes. There are case reports of successfully treating with a nipple mod, and also to have a topical cidofovir. However, I would also mention that the topical cidofovir needs to be compounded in a pharmacy. But these were able to treat resistant herpes and a few of the case reports mentioned. And lastly, I'm just going to talk about patella Vir that that new helicase primase inhibitor. So this study was actually published a few years ago. But the primary endpoint it's a phase two study where they randomized people to either get patella Vir

26:08
who had HSV two general lesions symptomatically or PrEP patella Vir and then they don't wash out period and then they got Valley cycle of your suppressive therapy or they got valleys like revere a washout period and then patella Vir and the thought was that they would be able to look at shedding rates and symptomatic disease within participants as a control and the primary endpoint was intended to treat within participant HSV shedding they actually randomized 91 participants 45 to receive patella via first 46 to receive la cycle Vir however, there was a safety signal and preclinical study and the FDA pause the study and the sponsor eventually ended the study early. So from the data that was analyzed 74% participants were able to complete their first treatment period and 56% were able to complete both. And this just shows the percent of HSV swabs for shedding overall and here's orange, which is patella Vir and valley Segovia overall there was a significant decrease in shedding for subclinical so it's symptomatic shunning there was about a 50 50% reduction with patella veer versus Valley sacro very suppressive therapy. And then for patients with lesions, they shed about the same. There wasn't a significant difference between patella Vir and valley sacred bear for HSV two shedding. And within participants, these are swabs with HSV detected and these are non lesional And here you can see the dark is Valley cyclo Vir. The white is patella Vir and overall patella Vir fared pretty well there were a couple participants that did have a lot of shedding during their Portello Vir arm and you can see in the non lesional arm there was less but there were just a few participants that

had that had shedding in the patella via arm. So he'll craze prime ACE inhibitors are not FDA approved, but there is currently an open label study for immunocompromised persons. And I included the clinical trial number which is on clinical trials.gov. And there is an early active access program to protect severe if you have a patient who you think would benefit. So in conclusion, antiviral suppressive medication decreases symptomatic infection and transmission and non HIV patients with HSV. Two genital infections, new vaccines with new antigens and new platforms are really on the horizon. And he'll a case primates inhibitors are continuing to be evaluated particularly for resistant herpes. Thank you.

29:06
Thanks very much. That was That was great. And one of the reasons I asked you to do this was the television. Right, so I'm glad that you were able to include that that. I just want to make a comment that you mentioned in the very beginning about herpes being a reportable condition and that is true in Washington State. But it's not true in New York state. So for our audience, who probably I'm guessing is mostly New York, herpes is reportable only in the newborn, but genital herpes is not reportable. So it really varies state by state. So the CDC numbers are even lower than what you showed. So we do have several questions. One was why take short term suppressive therapy for a job interview.

30:03
It's a scenario that's actually thought for somebody before. It was like a travel job interview where they were traveling out of state, and they were concerned. So

30:13
just didn't want to feel ill. And,

30:15
yeah, do you think it's really, I think a lot of this is shared decision making, deciding between episodic and suppressive therapy, but that was actually a real scenario.

30:28
Okay, and then there was a question of what treatments so that was really that came in, in the very beginning. So you address that? Do you personally recommend 500 milligrams or a full gram for episodic treatment? When using Valley cyclic beer?

30:44
That's a good question. I think it's, I think it probably varies depending on clinicians, I would say. But I think I think it depends on the expense of whether somebody can get the medication. I think the other thing is that I am personally someone who likes to potentially push the dose of

the medication. So I think that plus the patient themselves, so if I think that they're not doing well, with the 500, I will give them a gram.

31:25
How about you, Daniel,

31:26
do I usually use a gram? Yeah, me

31:30
too. I think because we're infectious disease specialists, we tend to see only people who don't do well, with. So like our bias is to maybe push the dose a bit, because we tend to see resistant cases that get referred because they've failed. But you know, the studies are either the side effects to the treatment, does age matter? Or just the immune system?

32:08
Um, in terms of the side effects for a psychopath, or is that the question? I

32:13
think that's the question, right? Would you be more concerned with an older person?

32:18
Um, I think it's a good question, because the studies are mostly on younger, healthier people. But I wouldn't be I don't think concerned it depending on the comorbidities. If they have a history of renal insufficiency, then I would be more concerned.

32:37
So and that's actually the next question. Do these drugs require root renal dose adjustment?

32:44
I believe they, they do this? Yeah, I don't I don't have the Creatinine clearance slide. But yes, they do. Especially if they're going to chronically be on them for renal dysfunction.

33:01
I think you'll get a feel for sort of mucosal or mucocutaneous infection, there's more leeway, because you're not using such a high dose, like a one gram three times a day or something. You're already doing lower than that. And so I'm pretty sure as long as your creatinine clearance is over 30. But you don't have to make an adjustment. But 30 and under I think you do.

33:27

Right. I think that's

33:32
I have one question for okay. So it's happened a few times where patients are sent to me because in the process of STI screening, they get these herpes antibodies ordered. And I think a lot of folks don't understand kind of the implications, the strengths and limitations of the tests. But sometimes, it seems like people are being placed on perfect prophylactic agents just by antibody testing, and it looks like from your slide, there's no evidence for that, if you've never had an outbreak. So how might you approach sort of either peeling it off or continuing it in that scenario?

34:16
So would this be the seropositive? asymptomatic is? Yeah, yeah. Now, I think it's a good question, because I, I think it again, has to be discussed. You know, I'm sure you have these discussions with the patient. And I'm sure some of them feel very strongly about being on this suppressive therapy. And so I think, you know, being completely transparent that we don't have any data on it is helpful. You know, I think the other thing though, is we don't, we do know that even people who are asymptomatic do share All right. And so I think part of what I've seen with looking in the literature and other you know, people talking about HSV, is I think that there is this whole group of people who have HSV. Two, don't know it, but are not asymptomatic. And so I think there's also this piece of education of what symptoms are for HSV. Two, because we do find that when we actually discuss symptoms, some, some patients will actually realize that they are symptomatic. And they may have not realized that before. And so I think there is a bucket of people who are asymptomatic, but then there is a large group of people who just don't know, and once they're educated on the symptoms, find that they actually are symptomatic. And they just didn't realize that those were symptoms of herpes before.

35:59
Yeah, that's a great point. I think that's very, very true that the symptoms are so mild, and just sort of irritants that are self limited, that people ignore them, and don't realize it's her pelvic. Alright, two more questions have come in. You mentioned doing a PCR for a diagnosis, how reliable is that test? And is the reliability different with presence of lesions or, or after the lesion is healed, I think is what they need. Yeah,

36:29
so it's a very sensitive test for picking up HSV. But once the lesion is healed, it goes down. So the best time to do it is when it's a vesicle. That's one of the AQa viruses there. And if you look at even I think the portal of your study shows it, you can see that when people have lesions, they're positive for herpes. So that's the best time to do it before it would request over.

37:00
Yeah, and what about, can you just discuss the blood test?

37:06
Um, I can I know there's a new recommendation in the 2021. But so it's a two-stage test. So we do the zero logic test, but then it needs to be confirmed by a Western Blot. And it's similar to other infections that we test, we test for both.

37:27
So it's testing for antibody, not antigen, antibody.

37:34
Testing for the genetic material

37:39
that two step tests that they recommend in the guidelines, you can't actually get that additional test anywhere in the US except I think, perhaps Washington. Yes, it's not one that's FDA approved in New York, so you can't even draw it and send it out. Oh, that's really interesting. I didn't know that. Or it's, I guess, I should say, it's not FDA approved. So it's not cleared for use in New York. Because it's, I think it's maybe a homegrown test or something like that. So right now in New York, outside of somebody with a history of symptoms, I'm just using it as screening with no history of symptoms or a positive partner. There's not really a clear role for it yet. Until that test becomes more widely available. Thank you. Glee.

38:35
Okay, thanks so much, Tia. I really appreciated all the questions.

[End Transcript]