Transcript Details
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Rapid Initiation: Getting Newly Diagnosed HIV-1 Patients on ARV Treatment Quickly

Announcer:
You're listening to ReachMD. This industry feature is sponsored by Janssen Infectious Diseases, the marketer and distributor of SYMTUZA®(darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets for oral use. See the full Prescribing Information, including Boxed WARNING for SYMTUZA® at www.SYMTUZAhcp.com. The following program is intended for US healthcare professionals only and is not certified for continuing medical education. Your host today is Dr. Jennifer Caudle and your guest is Dr. Moti Ramgopal, who is a paid consultant for Janssen Therapeutics, Division of Janssen Products, LP.

Dr. Caudle:
Beginning treatment immediately after an HIV-1 diagnosis can come with a variety of benefits. And thanks to recent advancements, there are now therapeutic options available that can be prescribed to newly diagnosed patients—even if you don't have their resistance testing records.

This is ReachMD, and I'm your host Dr. Jennifer Caudle. Joining me today is Dr. Moti Ramgopal, an infectious disease specialist in Fort Pierce, Florida, who's been in practice for more than 20 years. Together we'll discuss the single-tablet regimen, SYMTUZA®, and its clinical trial results in rapid initiation for treating newly diagnosed HIV-1 patients prior to resistance testing records being available.

Dr. Moti Ramgopal, thanks so much for being here today.

Dr. Moti:
Of course, thank you for having me.

Dr. Caudle:
Of course, so before we dive into our discussion, let's review the indication for SYMTUZA®, along with the Boxed WARNING.

Dr. Moti:
So SYMTUZA® is a single-tablet regimen indicated for the treatment of HIV-1 infection in adults who have no prior antiretroviral treatment history or who are virologically suppressed on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

The Boxed WARNING for SYMTUZA® is regarded severe acute exacerbations of hepatitis B that have been reported in patients who are coinfected with HIV-1 and hepatitis B and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate and may occur with discontinuation of SYMTUZA®. it's important to closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and Hep B virus and discontinue SYMTUZA®. If appropriate, antihepatitis B therapy may be warranted.

In addition, SYMTUZA® is contraindicated with certain medications due to the potential for serious and/or life-threatening events, or the loss of therapeutic effect and possible development of drug resistance. It's important to consult the full Prescribing Information at www.SYMTUZAhcp.com for potentially serious drug interactions prior to and during SYMTUZA® therapy.

Dr. Caudle:
So great, and thanks for breaking that down for us Dr. Ramgopal. Now, as a physician who's been treating patients living with HIV-1 for over 20 years, I imagine you've seen a great deal of change in the way HIV is diagnosed and treated. With that in mind, what can you

tell us about the diagnostic and treatment goals that exist today for HIV?

Dr. Moti:
Well, despite the gains made in HIV care over the last few decades, there's still a lot of work to be done as it relates to treatment of patients with HIV-1. You know, the United Nations actually has a goal to end the AIDS epidemic by 2030, known as the 90-90-90 treatment goal–meaning that by 2020, 90% of patients with HIV will be diagnosed, 90% will be receiving ARV therapy, and 90% of patients on treatment will be virologically suppressed. Achieving the 90-90-90 goal is important because it may not only end the AIDS epidemic by 2030, it will also generate profound health and economic benefits.

Dr. Caudle:
So, with the 90-90-90 treatment goal in mind, what would you say needs to be done in order to have that become a reality, in particular with patients receiving ARV therapy?

Dr. Moti:
Well, as providers, one thing we need to do is minimize the time it takes between HIV-1 diagnosis and start of therapy for newly diagnosed patients. This is where rapid initiation comes in, which is a model of care that involves starting ARV therapy before baseline laboratory and resistance tests are available or come back. The benefits of engaging and rapidly treating people who are newly diagnosed with HIV may include increased rates of virologic suppression and retention in care, as well as decreased time to achieve virologic suppression and decreased morbidity and mortality. Patients deserve to have the option of taking control of their HIV as early as possible, and the good news is that rapid initiation models of care are quickly gaining traction.

Dr. Caudle:
That's really great to hear, Dr. Rampogal. How do you decide what ARV to start in patients you want to rapidly initiate on therapy?

Dr. Moti:
Dr. Caudle, in my practice, I often rapidly initiate clinically appropriate patients who I have diagnosed with HIV-1. SYMTUZA® is also the only evidence-based single-tablet regimen recommended by the DHHS guidelines for rapid initiation. It was studied in a Phase 3 clinical trial for rapid initiation, called the DIAMOND study. So for patients I rapidly initiate on therapy, I often prescribe SYMTUZA®.

Dr. Caudle:
We are back with ReachMD. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Moti Ramgopal about SYMTUZA ® and its role in rapid initiation for treating newly diagnosed HIV-1 patients.

Announcer:
SYMTUZA® is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults:

- who have no prior antiretroviral treatment history or
- who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months and have no known substitutions associated with resistance to darunavir or tenofovir.

IMPORTANT SAFETY INFORMATION
BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- Severe acute exacerbations of hepatitis B (HBV) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of SYMTUZA®.

  Action: Monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue SYMTUZA®. If appropriate, antihepatitis B therapy may be warranted.

Dr. Caudle:
So, Dr. Ramgopal, you just mentioned SYMTUZA® is the only STR to have been studied in a Phase 3 clinical trial for rapid initiation. So, let's talk about that in more detail. First, what can you tell us about how this study was designed?

Dr. Moti:
So the DIAMOND trial was a Phase 3, open-label, single-arm, multicenter, prospective trial that evaluated the efficacy and safety of SYMTUZA® over 48 weeks in patients, n of 96 patients, who were rapidly initiated on treatment. DIAMOND was not a registrational trial.

The patients in the trial were treatment-naïve adults diagnosed with HIV who were then treated with SYMTUZA® over 48 weeks. Resistance testing were available after initiation of treatment. The study looked at the proportion of patients with viral loads less than 50 copies per milliliter at Week 48.

Another interesting key endpoint of this study was to assess patient-reported outcomes by using a validated instrument called the HIV Treatment Satisfaction Questionnaire status version, or HIVTSQs.

As baseline labs became available, results were assessed against predefined safety or resistance stopping rules to determine if patients should remain on treatment. For example, these included parameters around renal function, hepatic function, or certain HIV drug resistance patterns. For the safety stopping rules, there were three patients who discontinued treatment due to preexisting lab abnormalities prior to starting SYMTUZA®. For the resistance stopping rules, there were no patients who discontinued treatment in this study.

Dr. Caudle:
You know thanks for sharing this, Dr. Ramgopal. Let's get started by discussing the patient satisfaction endpoint you just mentioned. What can you tell us about the patient satisfaction outcomes seen with SYMTUZA®?

Dr. Moti:
Well, Patient Reported Outcomes for treatment satisfaction were evaluated using the HIV Treatment Satisfaction Questionnaire, or as I mentioned before, HIVTSQs. The HIVTSQs is a validated 10-item patient reported questionnaire that measures patient satisfaction with antiretroviral treatment. Each question is scored on a 6-point scale, where a score of 6 indicates high favorability and a score of 0 indicates low favorability. Responses to all questions are then added up to give one total treatment satisfaction score, and that can range from 0 to 60.

In the DIAMOND study, patient satisfaction was evaluated at Weeks 4, 24, and 48. Ninety-six patients who were rapidly initiated on treatment with SYMTUZA®, completed the HIVTSQs at Week 48. Overall high treatment satisfaction scores were reported, with a mean score of 58 out of 60 at Week 48. At Week 48, 97% of patients who rapidly initiated SYMTUZA® reported they were satisfied with their treatment, which was in response to the following question on the questionnaire: "How satisfied are you with your current treatment?", where satisfied equated to those patients who responded with a score of 5 or 6. Patients who scored a 5 or 6 on individual satisfaction items from the 10-item HIVTSQs ranged from 87.5% to 99% at Week 48.

Patient-reported outcomes data in rapid initiation scenarios are limited, the results from the HIVTSQs provide patients' perspective with respect to their level of treatment satisfaction.

Dr. Caudle:
Very interesting. You know, it's nice to hear that different endpoints are being included in evaluating newer ARV therapies. When treating patients, tolerability tends to be another key factor for providers in deciding which ARV may be appropriate for patients. So, what can you tell us about the tolerability profile for SYMTUZA® seen within this study? And also, what can you tell us about your own experiences?

Dr. Moti:
Thank you for that question. In the DIAMOND trial, less than 1% of patients discontinued the trial due to adverse events over the 48 weeks. There were also no discontinuations due to diarrhea, CNS, renal, or bone adverse events. The most common adverse drug reactions that were seen in the DIAMOND trial, which occurred in 2% or more of patients of any grade level, were diarrhea, nausea, rash, vomiting, and fatigue. Most adverse events involving treatment with SYMTUZA® were mild to moderate in severity, meaning Grades 1-2. In another Phase III registrational study in treatment naïve patients, the most common adverse drug reactions were diarrhea, rash, nausea, fatigue, headache, and abdominal discomfort, and flatulence. This is not a complete list of all adverse reactions reported with the use of SYMTUZA®. You can refer to the full Prescribing Information for a complete list of adverse drug reactions.

This is a tolerability profile that has worked well for me in my practice. But of course, healthcare professionals should refer to the full Prescribing Information for a complete list of adverse drug reactions to see if they have the same comfort level with this as I do.

Dr. Caudle:
You know patients, of course, want a medication that can help them obtain virologic suppression and get to an undetectable level. So what can you tell us about the efficacy of SYMTUZA® seen in this study?

Dr. Moti:
Thank you, absolutely. In an intent-to-treat analysis of the 109 patients in the study, 84% of patients achieved an undetectable viral load

at Week 48, with viral load being defined as less than 50 copies per milliliter. Of that, 8% of patients experienced virologic failure, meaning they had an HIV RNA >50 copies/mL in the window or at the time of discontinuation, and another 7% of patients had no viral load data. If you exclude the 13 patients with missing data, 96% of the remaining patients achieved an undetectable viral load at week 48. No patients discontinued due to lack of efficacy or protocol-defined virologic failure.

Dr. Caudle:
Dr. Ramgopal, let's now talk about resistance and the importance of a high genetic barrier when you think about different treatment options. Is SYMTUZA® unique?

Dr. Moti:
Well yes, SYMTUZA® is the only STR containing the protective barrier of darunavir. In the DIAMOND study, there were zero treatment-emergent mutations in rapid initiation.
In the AMBER trial, there were 362 treatment-naïve patients taking SYMTUZA®, only 1 patient receiving SYMTUZA® was found to have M184I/V, and this was in a patient who had evidence of this mutation prior to starting SYMTUZA®. The protective barrier of darunavir is supported with over 5500 patients treated with darunavir in 14 clinical trials, with long-term data up to 192 weeks.

Dr. Caudle:
Interesting, you know finally, Dr. Ramgopal, my last question to you, is do you have any other takeaway thoughts for our listeners today?

Dr. Moti:
Yes, I think it's important to individualize treatment for your patients. For a patient I'm looking to rapidly initiate on ARV, SYMTUZA® is an option based on the efficacy and tolerability profile and the patient-reported outcomes seen in the DIAMOND study. Also, the fact that the DHHS guidelines recommends SYMTUZA® as an option for patients in rapid initiation scenarios makes it a strong part of my consideration set when treating patients with HIV. I have years of experience with darunavir and SYMTUZA is the only STR that has the same barrier to resistance as other DRV-containing regimens that I have offered to my patients previously. Based on all this information, I feel very comfortable prescribing SYMTUZA® for patients in rapid initiation scenarios.

Dr. Caudle:
Now, in addition to the Boxed WARNING and contraindications, let's learn more Important Safety Information for SYMTUZA®.

Announcer:
CONTRAINDICATIONS

- Do not coadminister SYMTUZA® and the following drugs due to the potential for serious and/or lifethreatening events or loss of therapeutic effect: alfuzosin, carbamazepine, cisapride, colchicine (in patients with renal and/or hepatic impairment), dronedarone, elbasvir/grazoprevir, ergot derivatives (such as: dihydroergotamine, ergotamine, methylergonovine), ivabradine, lomitapide, lovastatin, lurasidone, oral midazolam, naloxegol, phenobarbital, phenytoin, pimozide, ranolazine, rifampin, St. John's wort (Hypericum perforatum), sildenafil for pulmonary arterial hypertension, simvastatin, and triazolam.

WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) and cases of liver injury, including some fatalities, have been reported in patients receiving darunavir, a component of SYMTUZA®. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities, including severe hepatic adverse reactions.

  Action: Monitor liver function prior to initiating and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases. Patients with evidence of new or worsening liver function should consider discontinuing SYMTUZA®. SYMTUZA® is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

- **Severe Skin Reactions:** In patients receiving darunavir, a component of SYMTUZA®, severe skin reactions may occur, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis. These include conditions accompanied by fever and/or elevations of transaminases.

Action: Discontinue SYMTUZA® immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis, and/or eosinophilia.

- **Risk of Serious Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:** Consult the full Prescribing Information prior to and during treatment for potential drug interactions.
- **Immune Reconstitution Syndrome:** Patients receiving SYMTUZA® may develop new onset or exacerbations of immune reconstitution syndrome.
- **New Onset or Worsening Renal Impairment:** Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs. In clinical trials of SYMTUZA®, there were no cases of proximal renal tubulopathy, including Fanconi syndrome, reported in the SYMTUZA® group through Week 48. SYMTUZA® is not recommended in patients with creatinine clearance below 30 mL per minute. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including nonsteroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

  Action: Prior to initiating or during treatment, on a clinically appropriate schedule, monitor serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue SYMTUZA® in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg/dL should be closely monitored for renal safety.
- **Sulfa Allergy:** Darunavir contains a sulfonamide moiety. The incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

  Action: Monitor patients with a known sulfonamide allergy.
- **Lactic Acidosis/Severe Hepatomegaly With Steatosis:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of SYMTUZA®, and tenofovir disoproxil fumarate (TDF), another prodrug of tenofovir, alone or in combination with other antiretrovirals.

  Action: Discontinue SYMTUZA® in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.
- **Diabetes Mellitus/Hyperglycemia:** New-onset or exacerbations of pre-existing diabetes mellitus and hyperglycemia have been reported in patients receiving protease inhibitors.

  Action: Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required.
- **Fat Redistribution:** Redistribution and/or accumulation of body fat have been observed in patients receiving antiretroviral therapy.
- **Hemophilia:** Patients with hemophilia may develop an increase in bleeding events.

ADVERSE REACTIONS

- The most common clinical adverse reactions (all grades) occurring in at least 2% of treatment-naïve patients were diarrhea, rash,* nausea, fatigue, headache, abdominal discomfort, and flatulence.

*Rash includes pooled reported terms: dermatitis, dermatitis allergic, erythema, photosensitivity reaction, rash, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash pruritic, toxic skin eruption, and urticaria.

Grade 2-4 laboratory abnormalities have been reported in patients receiving SYMTUZA®, including elevations in serum creatinine, liver function tests, triglycerides, total cholesterol, low-density lipoproteins, and glucose levels.

This is not a complete list of all adverse reactions reported with the use of SYMTUZA®. Please refer to the full Prescribing Information

for a complete list of adverse drug reactions.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** SYMTUZA® is not recommended for use during pregnancy and should not be initiated in pregnant individuals because of substantially lower exposures of darunavir and cobicistat during pregnancy.

Lactation: The Centers for Disease Control and Prevention recommends that HIV-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Consult the full Prescribing Information for SYMTUZA® for additional information on the Uses in Specific Populations.

Please visit www.SymtuzaHCP.com for full Prescribing Information, including Boxed WARNING for SYMTUZA®.

Dr. Caudle:
Well, that's a great way to round out today's discussion, and I want to thank my guest, Dr. Moti Ramgopal, for helping us better understand the value of rapid initiation and how SYMTUZA® is a treatment option for rapid initiation.

Dr. Moti Ramgopal, it was great speaking with you today.

Dr. Moti:
Dr. Caudle, it's my pleasure and thank you for having me.

Announcer:
This program was sponsored by Janssen Therapeutics, Division of Janssen Products, LP. If you missed any part of this discussion, visit ReachMD.com/hivhealth. This is ReachMD. Be part of the knowledge.

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