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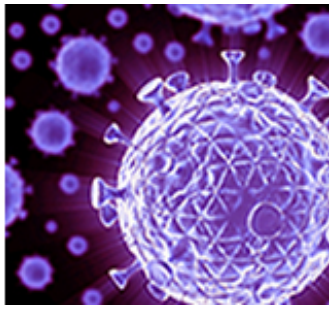

VOLUME 2 — ISSUE 4: TRANSCRIPT

Featured Cases: New Recommendations for HAART in HIV

Our guest author is Joel Gallant, MD, MPH, Adjunct Professor of Medicine, in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. Dr. Gallant is also Associate Medical Director of Specialty Services at Southwest Care in Santa Fe, New Mexico.

After participating in this of this activity, the participant will demonstrate the ability to:

- List the currently recommended antiretroviral regimens and discuss the data supporting their use.
- Discuss the approach to patients with absolute or relative contraindications to nucleoside analogs.
- Describe a patient for whom a protease inhibitor-based regimen might be chosen for initial antiretroviral therapy

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of HAART in HIV in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 3 *eHIV* Review newsletter— New Recommendations for HAART in HIV.

Unlabeled/Unapproved Uses: Dr. Gallant has indicated that there will be references to the following agents and combinations of agents not approved at the time this podcast was recorded: a once-daily formulation of raltegravir; a dolutegravir/abacavir/lamivudine single tablet co-formulation; tenofovir/alafenamide (TAF) in various co-formulations; and doravirine, also known as MK-1439. **Please note the dolutegravir/abacavir/lamivudine single tablet co-formulation is now FDA approved.**

Faculty Disclosure: Dr. Gallant has indicated he has received grant and or research funding from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck & Co., Sangamo BioSciences, Vertex Pharmaceuticals, and ViiV Healthcare. He has served as a consultant or advisor to Bristol-Myers Squibb, Gilead Sciences, and Janssen Therapeutics, and he has been a paid member of the committee/panel/board at Takara Bio.

MEET THE AUTHOR

Joel Gallant, MD, MPH
Associate Medical Director of Specialty Services
Southwest CARE Center
Santa Fe, New Mexico
Adjunct Professor of Medicine, Division of Infectious Diseases
Johns Hopkins University School of Medicine

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CME INFORMATION

⇩ PROGRAM BEGINS BELOW

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September 25, 2014; activities expire 2 years from the date of publication.

Length of Activity: 30 minutes

INTENDED AUDIENCE

The target audience (clinicians) for this initiative includes infectious disease (ID) specialists, primary care physicians (PCPs), nurse practitioners (NPs), physician assistants (Pas), and other health care practitioners whose work/practice includes treating patients with HIV.

STATEMENT OF NEED

- As the demographics of HIV have shifted to include many older adults, clinicians require education regarding the treatment of common comorbidities.
- Clinicians may be unclear about issues specific to the diagnosis and treatment of women with HIV.
- Many clinicians require education regarding current treatment and new emerging hepatitis C medications in patients coinfected with HIV/HCV who require antiretroviral therapy.
- Clinicians may need an update on current recommendations for the treatment of HIV with HAART.

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HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

MR. BOB BUSKER: Welcome to this *e*HIV Review Podcast.

Today's program is a follow-up to our newsletter issue on "New Recommendations for HAART in HIV." With us today is that issue's author, Dr. Joel Gallant, Adjunct Professor of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. Dr. Gallant is also Associate Medical Director of Specialty Services at Southwest Care in Santa Fe, New Mexico.

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Learning objectives for this audio program include:

- List the currently recommended antiretroviral regimens and discuss the data supporting their use.
- Discuss the approach to patients with absolute or relative contraindications to nucleoside analogs.
- Describe a patient for whom a protease inhibitor-based regimen might be chosen for initial antiretroviral therapy.

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I'm Bob Busker, managing editor of *e*HIV Review. Dr. Gallant, thank you for joining us today.

DR. JOEL GALLANT: I'm happy to be here, Bob, thank you.

MR. BUSKER: : In your newsletter issue, doctor, you reviewed the current guidelines for initial antiretroviral therapy in patients infected with HIV, as well as some of the recent studies describing more effective, better tolerated, and more convenient first-line ART treatment options. Today I'm going to ask you to translate how some of those new findings can be incorporated into clinical practice. So if you would, Dr. Gallant, start us off with a patient description.

DR. GALLANT: The first patient is a 36 year old accountant with recently diagnosed HIV infection. He has a CD4 count of 532 and a viral load of 136,500. His genotype shows wild-type virus, and he has a negative hepatitis C antibody and a negative hepatitis B surface antigen, with normal liver enzymes and kidney function. He's otherwise healthy but takes over-the-counter omeprazole for gastroesophageal reflux disease, and he also takes a multivitamin. He's single but sexually active with male partners. He's been consistently using condoms since learning of his HIV diagnosis and he's willing to start antiretroviral therapy if it is recommended and feels he could be adherent but would like a simple, easily tolerated regimen.

MR. BUSKER: So he's willing to begin ART. Would you recommend it for this patient?

DR. GALLANT: I definitely would. Antiretroviral therapy is recommended for all patients in the United States who have HIV infection, regardless of CD4 count and viral load. Obviously, we can defer therapy in patients who don't seem to be ready for treatment, but in this case the person seems to be willing and ready to take therapy. He already takes some medication anyway, so he has a good sense of his ability to be adherent. Maybe the fact that he's an accountant predicts that he's likely to be adherent, but that might be a stereotype.

In addition, ART is recommended to reduce transmission of HIV infection to sexual partners, and we know that this man has several sexual partners. Although he is using condoms, this further reduces the risk of transmission.

MR. BUSKER: Which ART regimens would you consider in this patient?

DR. GALLANT: Based on recent studies, integrase inhibitor-based regimens seem to have advantages over other regimens and are generally now my first choices, unless there's a compelling reason to use something else. We've seen this in studies using each of the three currently approved integrase inhibitor-based regimens. In some cases they are noninferior to standard regimens and in other cases they are actually superior, but in all cases they seem to have definite advantages in terms of tolerability and toxicity.

As an example, the single-tablet coformulation of tenofovir/emtricitabine (FTC)/elvitegravir/cobicistat, which used to be called "the quad," would be a reasonable choice. He asked for something simple, and this is one pill once a day. It's well tolerated, effective at high viral loads as well as low viral loads, and effective at low CD4 counts, as well as high CD4 counts. He has a high CD4 count, but his viral load is above 100,000, so that's a consideration when choosing therapy.

Dolutegravir plus either tenofovir/emtricitabine or abacavir/lamivudine (3TC) would also be reasonable choices. The dolutegravir-based regimens have the advantage of fewer drug interactions compared to the quad regimen. In addition, there is now a single-tablet dolutegravir/abacavir/lamivudine coformulation. Of course, that would only be indicated if his HLA-B*5701 test were negative.

One of those two would probably be my first choice. If I had more concerns about his adherence, I might consider a protease inhibitor-based regimen until he proved that he was adherent, because it's very hard to become resistant to protease inhibitor-based regimens even if you are nonadherent. However, I get a sense that's not going to be the case with this patient.

MR. BUSKER: Let me flip that question around and ask you which regimens would you NOT consider for this patient?

DR. GALLANT: Tenofovir/emtricitabine/rilpivirine is a very nice, well tolerated, single tablet regimen that is recommended in the guidelines but is not recommended in a patient like this for two reasons. One, he has a baseline viral load of above 100,000, and two, he uses a proton pump inhibitor, which interferes with rilpivirine absorption. So that would be off my list for this particular patient.

Tenofovir/emtricitabine/efavirenz is a widely used recommended regimen. However, I don't tend to start therapy with this regimen anymore because there are better alternatives in terms of tolerability. So while I still have many patients who are taking it and are doing well, it's not something that I start off with, though it is still recommended in current guidelines.

Tenofovir/emtricitabine plus boosted darunavir would be an acceptable regimen, and as I mentioned before, it would be a good choice if you had doubts about this patient's adherence. But he did ask for something simpler, and I think someone who is likely to adhere to therapy can get away with a single-tablet regimen.

Raltegravir plus tenofovir/emtricitabine would also be acceptable and is very well studied, but it doesn't have real advantages over the dolutegravir-based regimens and does have to be taken twice a day at the moment, although a once a day formulation of raltegravir is in trials now.

I would not use an atazanavir-based regimen or a lopinavir-based regimen, as darunavir seems to have advantages over both protease inhibitors. Also, atazanavir is a problem in a person taking a proton pump inhibitor, again because of decreased absorption. So if I were going to use a PI it would be darunavir, but in this patient I won't be using a PI.

MR. BUSKER: If for whatever reason you were not going to use a single tablet co-formulated regimen, how would you decide between abacavir/lamivudine and tenofovir/emtricitabine?

DR. GALLANT: He appears to have no contraindications to either of those two nucleoside backbones, such as kidney disease, bone disease, or cardiac risk factors. I've discussed those issues in the newsletter. At high viral loads, tenofovir/emtricitabine has been preferred when it's combined with either efavirenz or a boosted PI and that's based on the result where tenofovir/emtricitabine was more effective than abacavir/lamivudine at viral loads of above 100,000.

With dolutegravir there is less concern about high viral loads, because in a study comparing dolutegravir with abacavir/lamivudine vs efavirenz/tenofovir/emtricitabine, we didn't see the difference in efficacy in patients with high viral loads. So I would consider

using abacavir/lamivudine if I were going to use dolutegravir, but otherwise my choice would be tenofovir/emtricitabine.

MR. BUSKER: And we'll return, with Dr. Joel Gallant from the Johns Hopkins University School of Medicine, in just a moment.

JEANNE KERULY: Hello. I'm Jeanne Keruly, assistant professor of medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the program directors of *e*HIV Review.

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MR. BUSKER: Welcome back to this eHIV Review podcast. I'm Bob Busker, managing editor of the program. Our guest, from the Johns Hopkins University School of Medicine, is Dr. Joel Gallant. And our topic is: "New Recommendations for HAART in HIV."

We've been discussing how some of the new information Dr. Gallant reviewed in his newsletter issue can be applied in clinical practice. So to continue, please bring us another patient now.

DR. GALLANT: This patient is a 54 year old schoolteacher who is infected with HIV. She takes tenofovir/emtricitabine plus boosted atazanavir with a viral load of less than 20 and a CD4 count of 852. She has no history of resistance, she is also taking metformin for type 2 diabetes with a hemoglobin-A1c of 6.2 percent. She is on losartan and hydrochlorothiazide for hypertension, which is well controlled, and atorvastatin with an LDL cholesterol of 95. She smokes a half a pack of cigarettes per day and now she has an estimated GFR of 52 with 1+ proteinuria.

MR. BUSKER: So now in this patient — before you make any changes to her treatment plan, what other information would you would want to get?

DR. GALLANT: This is a common scenario, and evaluation of her kidney disease is complicated by the fact that she has hypertension and diabetes. She is also on tenofovir, which can affect kidney function and cause proteinuria. It is important to try to find out whether she has any evidence of proximal tubulopathy, which is fairly specific for tenofovir nephrotoxicity. Some of the ways you can do that are to look at phosphorus excretion, specifically using the fractional excretion of phosphate, which is calculated using a simultaneous urine and serum creatinine and phosphorus.

In her case, her microalbumin was moderately elevated and she had a fractional excretion of phosphate of 25 percent. In someone with a low serum phosphorus, any fractional excretion above 10 is abnormal because with a low serum phosphorus, the kidney should be holding on to phosphorus. She has a normal phosphorus, so I would consider her fractional excretion of over 20 to be abnormal, suggesting tenofovir-related proximal tubulopathy.

I would consider HLA-B*5701 testing, and in her case the test was negative, but there are relative contraindications to abacavir that I discussed in the newsletter, so even with a negative HLA-B*5701 test I'm a hesitant to use abacavir in this patient.

MR. BUSKER: So with those results, what would your next step be?

DR. GALLANT: Some people would argue for reducing the dose of tenofovir/emtricitabine—giving it to her every other day—but I would not do that in this patient because she has evidence of tenofovir-induced tubulopathy with the high fractional excretion of phosphate. You might consider that if you thought the kidney issues were not caused by tenofovir but were due to some other process, but when you believe the patient has kidney disease due to tenofovir, I don't think it makes sense to keep giving it, even at a reduced dose.

I would switch her from atazanavir to another agent, probably darunavir, an integrase inhibitor or an NNRTI depending on her resistance profile because atazanavir has also been associated with nephrotoxicity. In her case I would not use abacavir because of the high cardiac risk. As I discussed in the newsletter, this is a controversial association, but we have enough studies now showing an association that until we know for sure, it's better to avoid abacavir in a patient like this who's a smoker and has hypertension and diabetes. I would consider a nucleoside-sparing regimen even, though those have not been well tested.

MR. BUSKER: A nucleoside sparing regimen — which would you choose for this patient?

DR. GALLANT: It's a great question. There's a reason that there is no recommended regimen in the guidelines, because there is really no perfect nucleoside sparing regimen based on clinical trial data. Every regimen that has been studied has some problem, whether it's a problem of efficacy or a problem of toxicity and tolerability. I do think that based on limited data and extrapolation from the trials we have, the best nucleoside sparing regimens have included a boosted protease inhibitor with lamivudine, and you could probably extrapolate that to FTC.

As I said, there is no specific regimen recommended in the guidelines, but I do think that the fact that this patient's viral load is already suppressed probably increases the likelihood of success for any regimen you could pick. So to answer the question, I would use boosted darunavir once a day in combination with at least one other agent. One option would be to add lamivudine or emtricitabine. The GARDEL study showed that lopinavir/ritonavir, a different protease inhibitor, plus lamivudine, was as effective as lopinavir/ritonavir plus two nucleosides. So we have at least some data we can extrapolate from for this patient. However, I wouldn't use lopinavir in this patient because of her metabolic issues.

Another possibility would be to also include an integrase inhibitor. For example, you could use boosted darunavir plus either lamivudine or emtricitabine plus either dolutegravir or raltegravir. Once cautionary note with dolutegravir is it can increase metformin levels, which can be an issue in patients with diabetes.

A third option would be boosted darunavir plus etravirine, perhaps with lamivudine or emtricitabine. We have a lot of clinical trial data on darunavir and etravirine as a combination in patients who are more heavily treatment experienced, but we don't have data for this combination used as a nucleoside-sparing regimen. However, at least we know those two drugs seem to go well together. And to extrapolate from a different study, ACTG 5142, we have data showing that the combination of lopinavir/ritonavir plus efavirenz, another PI plus NNRTI combination, was quite effective in a large ACTG study, but poorly tolerated. So perhaps this different PI plus NNRTI combination would be as effective and better tolerated.

We're having to base decisions on some assumptions and extrapolation from other studies, which we don't like to do. On the other hand, I think there are real concerns with using either tenofovir or abacavir in a patient like this, so sometimes our hands are tied. I know not everyone would agree with me here, and some people would use a better-tested regimen containing nucleosides, despite the potential risk.

MR. BUSKER: Thank you for that case and discussion, doctor. And let me ask you to bring us one more patient now if you would, please.

DR. GALLANT: This patient is a 35 year old woman who was diagnosed with HIV infection five years ago. She's had multiple hospitalizations for HIV and substance abuse related problems but has never kept follow-up appointments in the HIV clinic. She's never taken antiretroviral therapy. She has a history of depression and bipolar disorder but has been very erratic with psychiatric follow-up and is currently on no psychiatric medications.

She admits she's depressed, she has a CD4 count of 35 with a viral load of 213,000, and her baseline genotype showed wild-type virus. She now comes to clinic for an appointment one week after hospitalization for *Pneumocystis* pneumonia. She is taking trimethoprim-sulfamethoxazole and azithromycin, which were prescribed at discharge, but she continues to use crack cocaine several times a week, denying active injection drug use. She knows several people who have died of AIDS and wants to start ART, preferably with something easy.

MR. BUSKER: This patient obviously has a lot of complications to consider aside from her HIV infection. What are your thoughts about starting her on antiretroviral therapy right away?

DR. GALLANT: This is challenging question. We know from an ACTG trial that the prognosis for people with *Pneumocystis* is better when they start antiretroviral therapy prior to hospital discharge. Ideally, we do that, but this is obviously a very challenging patient. However, her prognosis is very poor if she does not start antiretroviral therapy soon. In fact, if you look back at data from the pre-HAART era, people with CD4 counts below 50 generally had a life expectancy of less than six to 12 months without treatment.

I would restart the medications that she had been prescribed in the past for her bipolar disorder and depression, because continuing mental illness is a big risk factor for nonadherence and treatment failure. I would refer her to psychiatry, I would refer her to substance abuse treatment if she was interested, and I would refer her to an adherence counselor. But she needs to be started on antiretroviral therapy, so I would probably do it immediately because she's here in the clinic now and I don't know if she'll be back. The longest I would consider waiting would be two weeks because of her low CD4 count, her recent PCP, and her current motivation to start. We often talk about the fact that patients don't do well if they are non-adherent, but even if she were to take meds for a month and stop them after that, that a short course of treatment would prolong her life expectancy. So I don't think we can wait for everything to be perfect before we get her started.

MR. BUSKER: So when you do start her, what treatment regimen would you use?

DR. GALLANT: In this patient I would probably use a boosted protease inhibitor, most likely tenofovir/emtricitabine plus once a day darunavir/ritonavir, because she is unlikely to develop resistance with nonadherence. It is three pills a day, and ideally you'd like to give this patient a one pill a day regimen, but I think that in contrast to NNRTI-based regimens and probably the integrase inhibitor-based regimens, this would be preferred. No matter how nonadherent she is, she is very likely to lose options as a result of taking that regimen.

The other option would be a dolutegravir-based regimen. It does appear to have a higher barrier to resistance than other integrase inhibitors, and in fact, in trials with patients who were treatment naïve, so far we have not seen resistance with dolutegravir, which is also better tolerated than protease inhibitors. It's not clear yet whether it has as high a barrier to resistance as a boosted protease inhibitor. We'll need longer-term clinical experience to know whether that's the case.

So my choice would be a boosted PI, but if she came back to me with GI side effects from the PI that were interfering with adherence, I would switch her to dolutegravir.

MR. BUSKER: Very specifically, doctor — in this patient, which regimens would you not consider using?

DR. GALLANT: I would definitely not use an efavirenz-based regimen. Efavirenz is less well tolerated, there's a high risk of resistance with nonadherence, and she already has significant mental health issues that efavirenz could exacerbate. I would not use the rilpivirine coformulation. It is very well tolerated but it is not recommended in patients with advanced disease, which she clearly has, and there appears to be even higher risk of resistance than with efavirenz.

I probably would not use the elvitegravir/cobicistat "quad" regimen, either. It is a single tablet and is easier to take, but I think there is a greater risk of resistance there than with dolutegravir.

MR. BUSKER: As far as new agents and new therapies that are in development — which of those might change your approach to a patient with these kinds of complications?

DR. GALLANT: We have tenofovir alafenamide (TAF) coming. The hope is that it will be a new form of tenofovir that has less kidney and bone toxicity than the current form of tenofovir, TDF. That could eliminate the need for the nucleoside-sparing regimens that we discussed in case two, and it's likely to have less renal and bone toxicity than tenofovir, without the concern about cardiac risks associated with abacavir. It is also likely to be coformulated with emtricitabine, with elvitegravir/cobicistat/emtricitabine, with rilpivirine/emtricitabine and

possibly also with darunavir/cobicistat/emtricitabine. In that last patient, where adherence was such a big issue, the darunavir/cobicistat/emtricitabine/TAF coformulation would be ideal for such a patient because of its simplicity and high barrier to resistance.

Finally, we still may learn more about the cardiac risk of abacavir in future cohort studies, which could either confirm the association or suggest that it isn't actually an issue. That may also help us in patients like the second patient, where we might feel more comfortable using abacavir if future cohort studies don't show an association with myocardial infarction.

MR. BUSKER: While we're on the subject of potential new therapies, Dr. Gallant — let me ask your opinion about some of the presentations at the recent CROI meeting. Which ones struck you as most important?

DR. GALLANT: One of the most important studies presented at CROI was the ACTG 5257 study, which was a randomized comparison of boosted darunavir, boosted atazanavir and raltegravir, each combined with tenofovir/emtricitabine. The results were interesting. From a pure efficacy or virologic outcomes standpoint, there really wasn't a significant difference between the three. But when you looked at the combination of efficacy and tolerability, then raltegravir clearly had the advantage and was superior to the other two arms. And among the protease inhibitors, darunavir was superior to atazanavir mainly because of less jaundice and less GI toxicity.

This was a very important study, and it joins the list of a number of other studies that indicate that integrase inhibitors seem to be a great choice for initial therapy. If ACTG 5257 were the only study, then it would be hard to extrapolate beyond raltegravir, but, of course we've seen a number of other studies looking at integrase inhibitor-based regimens compared with recommended regimens that show advantages with all of the integrase inhibitors.

While we talk a lot about the importance of once daily therapy, in this study a twice daily regimen outperformed two once daily regimens, suggesting that tolerability trumps convenience when there are big differences in tolerability. There were still some advantages of the protease inhibitor-based regimen, namely that patients who failed therapy on a PI didn't develop resistance, whereas people who failed on raltegravir could develop integrase inhibitor and nucleoside resistance. But the raltegravir based regimen also had less effect on lipids than either of those two relatively "lipid friendly regimens."

At CROI we also heard about doravirine, also known as MK-1439, a new NNRTI now in development. It appears to have some advantages in activity against NNRTI-resistant virus, and we'll look forward to seeing phase III studies in treatment-naïve adults.

Another very important study at CROI was the PARTNER cohort from Europe. We now know that treatment is prevention. This was best demonstrated in HPTN 052, where we saw a 96 percent reduction in sexual transmission when partners infected with HIV were on antiretroviral therapy. The PARTNER study is a large cohort of serodiscordant couples, both heterosexual and homosexual, in which one partner has HIV infection and is on treatment and the other is negative for HIV. These couples were not using condoms, and the trial found no risk of transmission from the positive partner to the negative partner, regardless of the type of sexual activity.

Of course the authors pointed out that you can't prove a negative, and they provided confidence intervals around that zero estimate. But as the study goes on, as more couples are recruited and as they have longer follow-up time, those confidence intervals will shrink. I think this is quite consistent with what we saw in HPTN 052, because although I mentioned that the reported efficacy was 96 percent, in fact, there was only one transmission from a treated positive partner to a negative partner, and that transmission occurred before the positive partner's viral load had been suppressed. You could argue that the efficacy of suppressive antiretroviral therapy was 100 percent in HPTN 052, as it appeared to be in the PARTNER study.

I think these two studies together suggest that there is no more effective form of prevention than antiretroviral therapy when it's effective at reducing viral load.

MR. BUSKER: Dr. Gallant, I want to thank you for sharing your insights today. Let's wrap things up by reviewing what we discussed in light of our learning objectives. So to begin: the currently recommended antiretroviral regimens and the data supporting their use.

DR. GALLANT: First, just to remind everyone that antiretroviral therapy is now recommended in the US for everyone, regardless of CD4 count and viral load. The guidelines list quite a few recommended regimens for all patients and additional options for those specifically with viral loads below 100,000. Among those, the evidence supporting the integrase inhibitor-based regimens is strengthening, but there is still a role for protease inhibitor-based regimens in patients with unreliable adherence.

MR. BUSKER: And our second objective: the approach to patients with absolute or relative contraindications to the nucleoside analogs.

DR. GALLANT: We discussed the rationale for using an NRTI- sparing regimen, primarily in a patient with kidney disease or possibly osteoporosis plus either multiple cardiac risk factors or a positive HLA-B*5701 test. And we discussed the various NRTI-sparing regimens including a boosted protease inhibitor plus lamivudine or emtricitabine plus perhaps something else, but pointed out that none of these are well studied and that none of these are specifically recommended by the guidelines.

MR. BUSKER: And finally: patients for whom a protease inhibitor based regimen might be chosen for initial antiretroviral therapy.

DR. GALLANT: We talked about a patient with a very high risk for nonadherence and the fact that a protease inhibitor-based regimen would be a good choice because of the fact that resistance does not occur with non-adherence and treatment failure. Still, it's important to remember that you can always change to a simpler regimen if the patient turns out to be adherent.

MR. BUSKER: Dr. Joel Gallant, from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine, thank you for participating in this eHIV Review Podcast.

DR. GALLANT: It's been a real pleasure. Thank you for having me.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ehivreview.org/test.

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