A Clinical Compendium on HIV Treatment Selection: Real Cases, Real Challenges, Real Solutions

OVERVIEW

Substantial progress in the realm of HIV treatment has been made over the past few decades. Antiretroviral therapy (ART) has changed the treatment of HIV, allowing most people living with HIV (PLWH) to achieve life expectancies similar to those of the general population. However, the many new ART regimens available have made shared decision making increasingly important for patients and clinicians. In this activity, Melissa Badowski, PharmD, MPH, and James Sosman, MD, review 4 case studies inspired by real-world challenges encountered in routine clinical practice. Their discussions delve into recent clinical advances in the use of ART as well as the mitigation and management of adverse events.

TARGET AUDIENCE

This activity is intended for HIV specialists, infectious disease specialists, primary care physicians, nurse practitioners, nurses, and other healthcare professionals who care for persons living with HIV.

LEARNING OBJECTIVES

- Describe the impact of weight gain on the health outcomes of persons living with HIV (PLWH)
- Detail the latest data on treatment-related adverse events associated with antiretroviral therapies (ART) for treatment-naïve and treatment-experienced patients
- Employ strategies to lower the risk for ART-associated adverse events in PLWH, especially those at risk for suboptimal health outcomes
- Create individualized HIV treatment strategies for PLWH based on patient- and treatment-specific factors

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PROGRAM INTRODUCTION

The goal of antiretroviral therapy (ART) is to prevent adverse outcomes in people living with HIV (PLWH) and reduce the risk of HIV transmission. ART has revolutionized the medical management of HIV, allowing most patients who are virally suppressed to achieve life expectancies comparable with the general population.[1] However, the broad range of ART available to clinicians has introduced considerable complexity into treatment decision making. Newer antiretrovirals (ARVs) have been associated with less frequent dosing and improved tolerability, but recent studies suggest that some of these regimens may be associated with adverse effects, such as weight gain and lipodystrophy.[2]

A shared decision-making approach is an important way for clinicians to facilitate treatment selection and switching discussions. There are 5 steps of shared decision making: (1) seek patient participation, (2) help patients explore and compare treatments, (3) assess patient values and preferences, (4) collaborate with patients to reach a decision, and (5) evaluate patient decisions.[3] As a part of step 2, it is important for clinicians to be familiar with the different features of various ART regimens for both treatment-naïve and -experienced patients as well as the most up-to-date guidance published by the DHHS.[1]

In this case-based, question and answer–style program, experts review details from 4 cases of PLWH, with an emphasis on the factors that can influence treatment selection and switching across diverse patient populations.

References

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Q&A

Case 1 Question 1

Case background

Samuel, a 40-year-old man with newly diagnosed HIV presents for selection of initial ART. Laboratory results reveal HIV-1 RNA 68,700 copies/mL, CD4+ T-cell count of 390 cells/µL, and negative for HBV coinfection. His body mass index (BMI) is 30.8 kg/m^2 (obesity). He is initiated on bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC).

Within 6 months, Samuel's viral load is undetectable, and his CD4+ T-cell count has increased to 620 cells/µL. However, Samuel notes that he is unhappy with his levels of recent weight gain. Since his ART initiation visit, he has gained 9.1 lbs (4.1 kg), and his BMI has increased to 31.9 kg/m^2.

Question 1

Which of the following of Samuel's ART components have been linked with weight gain?

a. BIC and FTC
b. BIC and TAF
c. FTC and TAF
d. None of the above

Answer rationale

The correct answer is B.

- Newer ART regimens have been associated with higher levels of weight gain than older ART regimens.[1]
- Compared with protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) have been associated with increased risk of weight gain. Newer, second-generation INSTIs (ie, BIC and dolutegravir [DTG]) are associated with more weight gain than elvitegravir.[1]
- With BIC/TAF/FTC, average weight gain within the first 48 weeks of treatment is about 3.0 kg.[2]
- There is also evidence that TAF is associated with pronounced weight gain in both treatment-naïve and treatment-experienced patients.[3,4] In the ADVANCE clinical trial, which enrolled treatment-naïve PLWH, regimens of DTG and FTC with either TAF or tenofovir disoproxil fumarate (TDF) were compared. Patients who received TAF had significantly greater weight gain compared with those who received TDF (6.4 vs 3.2 kg).[3]

Faculty Discussion

In this case, the correct answer is really B which is bictegravir and TAF or tenofovir/alafenamide. And we know that it is true that many of the newer regimens have been associated with a higher degree of weight gain than some of the older antiretroviral therapy. And compared, interestingly, with protease inhibitors and non-nucleosides or NNRTIs and integrase inhibitors, they've all been associated with some increased weight gain and the newer, for example, second generation integrase inhibitors, such as bictegravir and dolutegravir—as opposed to elvitegravir and raltegravir—are associated

with more weight gain. And there's also evidence that TAF, ironically, is associated with pronounced weight gain, both in treatment-naive [patients] and people that are treatment experienced that are on it. There was actually a clinical trial called ADVANCE which randomized a few thousand patients to various regimens. These were all treatment-naive patients, done, actually, in Africa. And it showed that those regimens that contain dolutegravir and FTC or emtricitabine with either TAF or TDF were compared, and what they found was that the TAF-containing regimens, in this group, actually had significantly more weight gain than those on TDF. Now, everybody gained weight on the regimen. They had been treatment-naive so they all gained some weight, possibly a return to health effect, but those on TAF gained more weight, 6.4 kg as opposed to 3.2 kg. We're really seeing a fair amount of weight gain in these newer regimens.

And that's something I also see in my practice is the weight gain that also is from a lot of these newer drugs and from that perspective, not just looking at the medications as a whole, but really what you mentioned was that return to health effect and especially in patients who are getting started on antiretroviral therapy, we see a lot of that. I would agree with that.

References

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3. Venter WDF et al. *N Engl J Med*. 2019;381(9):803-815. doi:10.1056/NEJMoa1902824
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Case 1 Question 2

Case background

Which of the following has been associated with increased risk of weight gain after ART initiation in this patient?

a. Baseline HIV-1 RNA ≤100,000 copies/mL
b. Black race
c. CD4+ T-cell count ≥200 cells/μL
d. Male sex

Answer rationale

The correct answer is B.

- Black race is strongly associated with weight gain following initiation of ART. Compared with people of other races in pooled clinical trial data, Black people gained an average of 0.99 kg more in the first 96 weeks of ART (*P* <.001). Black people also had a higher rate of weight increase of 10% or more than people of other races.[1]
- In a pooled analysis of randomized controlled trials, women had greater BMI gains than men in the first 96 weeks of ART initiation (1.91 vs 1.39 kg/m^2).[2]
- Lower baseline CD4+ T-cell count (ie, <200 cell/μL) and higher HIV-1 RNA levels (ie, >100,000 copies/mL) have been associated with more weight gain.[1]

Faculty Discussion

The most appropriate answer here is option B, Black race. This is based off of a pooled analysis of 8 randomized, controlled clinical trials that occurred between 2003 and 2015 in treatment-naive patients living with HIV.

Interestingly, weight gain was greater in some of those more recent clinical trials as well as those using newer antiretroviral agents, so a lot of the ones that came to market in the last about 10 years or so. Black race was a strong predictor for weight gain once antiretroviral therapy was started when compared to baseline therapy. Weight gain was approximately 1 kg more over about 96 weeks of the first time of starting antiretroviral therapy and although baseline viral load and CD4 counts are associated with increased weight gain, this was more common if the viral load was more than 100,000 or if the CD4 count was lower. If there was perhaps an AIDS diagnosis being less than 200 cells/mL.

When looking at sex as a risk factor, being female was associated with weight gain, and although the mechanism of weight gain in this population is rather unknown, the trend appears to be pretty similar with the trends that we see in just the regular population where we see a higher prevalence of obesity in Black women across the United States. Being a female is a risk factor for weight gain not only in general, but in those living with HIV as well.

It's interesting that we're definitely seeing, as you mentioned, weight gain in our practice mirroring really what we're seeing on epidemiologic studies. And to tell you the truth, just like you said, in the review of 8 trials that Paul Sax was lead author on, and a number of other co-authors just like that, we're seeing in a number of large and small, certainly epidemiologic studies, that there's a signal that people are gaining weight. We think a little, as you mentioned, with TAF and some of the newer integrase inhibitors, but we're seeing it in general. There's some signal as to those, but it's really a phenomenon that we're dealing with right now for the last few years and probably for the next few years.

References

1. Sax PE et al. *Clin Infect Dis*. 2020;71(6):1379-1389. doi:10.1093/cid/ciz999
2. Bares SH et al. *J Womens Health (Larchmt)*. 2018;27(9):1162-1169. doi:10.1089/jwh.2017.6717

Case 1 Question 3

Question 3

Which of the following has been proposed as the cause of weight gain with INSTIs?

a. Antagonism of GLP-1 receptors
b. Decrease in physical activity due to adverse events
c. Restoration of weight following long-term systemic inflammation
d. All of the above

Answer rationale

The correct answer is C.

- The precise mechanism of weight gain following ART initiation has not yet been identified, and several theories have been proposed.[1]
- One theory for weight gain following ART initiation is that weight is simply being restored to the level that it would be if patients had not been living with HIV and exposed to systemic inflammation.[1]
- The extra weight gain associated with INSTI-based regimens has been attributed to direct effects on adipocytes and adipose tissue along with mediation of insulin resistance.[2]
- There is no evidence that weight gains are caused by changes in caloric intake or resting metabolic rate, which correlates with physical activity. In a small study of 30 PLWH who primarily initiated INSTI-based regimens, weight increased by an average of 3.8 kg at 6 months, but no significant change in resting metabolic rate or diet was noted.[3]

Faculty Discussion

And the answer that we were looking for in this case was C, restoration of weight following long-term systemic inflammation. And this would be the so-called return to health phenomenon. The idea that certainly in treatment-naive patients with higher viral loads, as we heard from Melissa, lower CD4 counts, there is some ethnicity and racial differences, but clearly, as they return to health, starting on antiretroviral therapy, pretty much most antiretroviral therapy, we will see weight gain. But we're also seeing this in folks that are switching to certain medications, meaning they're well-controlled and then they've switched, and where possibly this idea of reduction in system inflammation or return to health has a little less cachet in terms of explaining that.

At this moment, the precise mechanism of the weight gain with antiretroviral therapy has not been identified, even though that's one of the theories that the extra weight, likewise that we see specifically with some of the newer generation integrase inhibitors, has been attributed, possibly, and these are biologically plausible theories, [to the] effects on adipocytes and maybe adipose tissue, along with mediation of insulin resistance. There's been a number of small sample studies looking at things like insulin resistance. Other receptors that are endocrinologically being studied that might have to do with energy metabolism and imbalance with that and there are some in vitro studies that seem to imply, hey, maybe integrase has a role here, maybe TAF might have a role with some of these, but these are really, right now, hypothesis-generating, and unfortunately there's a lot of them. We don't really have the mechanism there.

There was a small study, interestingly, that did look, even though as I said there's some understanding that may be a blockage of a receptor involved in energy metabolism, that integrase might have a role in that, especially dolutegravir. But then, on the contrary, there's a small study of about 30 women living with HIV, where they were looking at weight gain and changes in caloric intake and exercise. And they were really able to show that the caloric intake and so-called energy differential and caloric differential really wasn't different between those that gained weight and those that didn't in HIV-negative folks. More to come regarding that. I agree. I think there's a lot of research that's been generated from this and I think there's just going to continue to be more in trying to figure out the exact mechanism of why we're seeing a lot of weight gain with these newer agents specifically.

References

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Case 1 Question 4

Question 4

Samuel is at risk for which of the following long-term outcomes based on this short-term weight gain?

a. Diabetes
b. Hepatocellular carcinoma
c. Osteoporosis
d. Thyroid disease

Answer rationale

The correct answer is A.

- In an analysis of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study, short-term increase in BMI was associated with an 11% increase in risk for diabetes over a 5.3-year median follow-up for all patients, regardless of pre-ART BMI. In this study, there was an increase in risk for cardiovascular disease (CVD) among patients with normal pre-ART BMI but not for those who were underweight or overweight at baseline. It is possible that longer follow-up and additional studies may reveal a direct correlation between short-term weight gain and CVD across all BMIs.[1]
- Weight gain with INSTI initiation has been correlated with increased hemoglobin A1c (A1C) levels, providing additional support for the link between INSTI-mediated weight gain and development of diabetes.[2]

Faculty Discussion

And the most appropriate option is option A, diabetes. We have clearly elucidated a relationship between newer antiretroviral agents as well as weight gain, but longer-term outcomes are only beginning to emerge at this point. Metabolic effects secondary to weight gain was demonstrated through long-term follow-up thanks to the D:A:D cohort, so D:A:D stands for the Data Collection on Adverse Events in Anti-HIV Drugs, so it's a little bit easier to say the D:A:D cohort, during the study. And it showed that there was a risk of diabetes over a median of about 5 years. The integrase inhibitors were associated with weight gain and so we've seen that in our patient that we're currently talking about over the 6 months that he's been on treatment. And it's also been associated with increases in hemoglobin A1c levels. Therefore, we should be monitoring all of our patients who are on antiretroviral therapy, especially these newer agents, for metabolic effects of antiretroviral therapy, especially when we're starting therapy for them. We should at least have a baseline and that's in line with the guidelines, but we should be following up with them at each follow-up visit. In my practice, what we're doing, aside from the hemoglobin A1c testing, although we may not be doing that at every single visit, we are getting fasting blood glucose, whether it's through the Chem 7 or also called the basic metabolic panel.

This isn't something that just needs to be followed by a primary care provider. Since we're using these drugs in our setting, we should also be monitoring that and following up. The impetus should be on us, as well. If it is elevated, we begin to start the discussion with the patient, are you having any symptoms of diabetes, are you having increased thirst, hunger, are you having more frequent urination in the evening time, just as an example. And this is also the time for us where we start to talk about some of the dietary interventions as well as exercise.

What are your eating habits? Do you exercise regularly? I think that's something that we should start to have that conversation earlier on rather than when weight gain has already occurred. And what do you do in your practice, Jim?

I couldn't agree more with what you were saying meaning that we can't just, if our general practice is really ID-focused, we do HIV, we really can't just leave that necessarily to the patient to bring up with their primary care clinician because they may not be aware of it. This is pretty new information we've been dealing with, and I think we've really got to take on the role of doing a fair amount of screening, active screening around diabetes, and kind of early management because they may not be seeing their primary care doc, ironically, on a regular basis. I agree with what you said. This is really team-based care. You know, I'll do some, certainly my nurse will pick up, and our HIV-specialty pharmacists all have a pretty big role in that.

References

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Case 1 Question 5

Additional case information

Samuel is frustrated with his weight gain and asks whether it merits changing his therapy, as he doesn't want to gain more weight.

Question 5

Based on DHHS guidelines, how do you counsel Samuel?

a. Improving adherence may decrease weight gain
b. Substituting TAF for TDF is the recommended next step
c. Switching to a new therapy can reverse weight gain
d. Switching to a new therapy is not recommended

Answer rationale

The correct answer is D.

- DHHS guidelines recommend against switching effective ART on the basis of weight gain alone. Instead, clinicians should counsel patients about the importance of physical activity and nutrition.[1]
- Furthermore, with BIC/TAF/FTC, the greatest weight gain has been reported during the first year (~3 kg), followed by yearly increases of 0.5 to 0.7 kg per year, which is consistent with changes in weight in the general population.[2]
- However, as a part of shared decision making, patient values and preferences should be assessed, and clinicians should collaborate with patients to reach a treatment decision. In some cases, patients may prefer to switch ART despite guideline recommendations.[3]

Case conclusion

Together, you and Samuel decide to switch his regimen to an alternative regimen (eg, an RPV-based regimen), which may be more weight neutral, to attempt to prevent additional weight gain. You discuss recommendations for healthy nutrition, including increasing the amount of plant-based foods and limiting fatty foods. Additionally, you discuss strategies for increasing physical activity.

Faculty Discussion

With this patient, Samuel, as you read, he is pretty frustrated about the weight gain and wants to know about switching therapy. Not an uncommon scenario. We're definitely seeing this. And this is controversial right now. When we look at question 5, based on the DHHS guidelines, how do you counsel Samuel? And really the answer here would be D, which is switching to a new therapy, isn't recommended. Right now, we know that the DHHS guidelines are kind of a so-called living document and that a steering committee, an expert panel, is always reviewing present data in real time and making modifications. They tend to come out at least yearly, sometimes semiannually they might modify some of their recommendations. They're kind of holding, so it'll be interesting to see what they do either later this year or next summer when they usually come out with their annual modifications.

At this point, they recommend against switching based solely on weight gain. And instead, they want us to really try the things like counseling, the importance of physical activity and nutrition. I would say, you know, a fair number of colleagues, anecdotally, aren't always doing that, but what we do try to do is at least some shared decision-making with our patient, meaning if we're going to switch to a medication, right now that might be implicated, like a TAF-containing regimen or bictegravir and/or dolutegravir. Then mentioning there has been some weight gain so we really want you to look at things to make sure your weight isn't going up too much and let us know about that. And certainly, some proactive counseling is really where we'll go with that at most. I'm not switching right at this moment. And to tell you the truth, when we look at people in certain studies that are starting, like bictegravir, TAF, FTC, the greatest weight gain in some clinical trials, up to 3 kg, has really been front-loaded, within the first 6 to 12 months, and then after the first year, the weight gain is much flatter. We really, many times, might expect earlier weight gain and then less going forward. That is what some studies are seeming to imply. We just don't know if [this is the case]. At this point, we're not recommending switching formally.

A lot of our patients will, you know, want to weigh the options and, honestly, it is the shared decision-making that I couldn't stress more. We lay out various plans for them and what do they want to do, you know, what is their buy-in because I don't have any hard evidence. But, anecdotally, patients who are choosing what they want to do—whether they want to try diet and exercise—are really embarrassed by the weight gain and they want nothing to do with these medications anymore. A lot of times, you know, we have to have what do they want to do. And I think unless we have their buy-in, it's going to be very hard for us to continue therapy. Sometimes, you know, when we start to think about potential down-the-road, yes these may be side effects, but are these side effects precluding them from taking any of the medications, would that cause further loss of virologic suppression? I think really bringing the patient into their care gives them more freedom to choose what they want to do, as well.

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Case 2 Question 6

Question 6

Case Background

Janelle, a 28-year-old woman with HIV infection recently found out that she is 14 weeks pregnant with an unplanned pregnancy. Janelle was diagnosed 2 years ago and has a viral load of 43 copies/mL on dolutegravir/lamivudine (DTG/3TC). She presents for follow-up and says that her OB/GYN instructed her to discuss whether any changes to her ART are necessary during pregnancy.

Question 6

Which of the following potential adverse events may be associated with DTG?

a. Fetal cardiac abnormalities
b. Neural tube defects
c. Preterm birth
d. Spontaneous abortion

Answer rationale

The correct answer is B.

- The Botswana Tsepamo study was developed to evaluate the risk of neural tube defects (NTDs) in women receiving ART. In an unplanned preliminary analysis conducted in May 2018, investigators found that the rate of NTDs among women receiving DTG was 0.94%.[1] A March 2019 update revealed a lower rate of NTDs among those receiving DTG; although, the rate was still elevated relative to those receiving non-DTG ART (0.30% vs 0.10%).[2]
- In the most recent analysis of the Tsepamo study conducted in April 2020, the rate of NTDs with DTG decreased to 0.19%. While this was significantly higher than the rate of NTDs among women without HIV (0.07%), it is not significantly higher than the rate in those receiving any non-DTG ART (0.11%).[3]
- According to DHHS guidelines, DTG can be continued in patients who become pregnant while on a DTG-based regimen due to the low absolute risk of NTDs; nonetheless, engaging patients in an informed risk-benefit discussion is a key component of shared decision making.[4]

Faculty Discussion

In terms of the following potential adverse events for this patient who is newly pregnant, the one that we are most concerned with is option B, neural tube defects. This adverse event wasn't something that we knew about until post-marketing data became available. And this was based off of a study or a signal, the Tsepamo study that was conducted in Botswana. And this signal that neural tube defects were occurring in women in this region at 0.94%, almost 1% of patients, initially. That caused great alarm in the medical community. Should we be leaving patients on dolutegravir-based therapy because of this risk? But then there were subsequent analyses and data that emerged that demonstrated that the incidence of neural tube defects in dolutegravir-containing regimens did decrease and that was to 0.19%. The incidence of neural tube defects is still higher than women who do not have HIV, but when they looked at antiretroviral therapy across the board, there wasn't really any difference.

When we think of women of child-bearing potential who have HIV within our own practices, we have to think about and talk about are you at risk for becoming pregnant? Do you want to become pregnant? Is pregnancy something that is a goal of yours? Maybe it's not now, maybe it's in the future, but it's always important to have that ongoing conversation with our patients.

The important take-home message from this is that dolutegravir, according to the guidelines, can still be continued in those who are pregnant or who plan to become pregnant based off of the rate of neural tube defects being lower than what was initially anticipated. And again, it's in accordance with our national guidelines, but ultimately bringing the patient into it, having this risk vs benefit discussion, with each of our patients. And they should be informed and then that shared decision-making should be part of the discussion that you have.

This is something that's been implemented in our own practice where we discuss various antiretroviral options with the patient. If they're new to therapy, if things in their life change, maybe they have a new partner that maybe in the past they weren't thinking of becoming serious or having children, but it's an ongoing evaluation of pregnancy risk. I think making sure that we do this with our patients, not just a one time or being once we see them for the first time in our practice, is very important.

And, additionally, if they are concerned or they think that they may want to become pregnant in the future, we should be talking with our patients about folic acid supplementation. Starting them on a prenatal vitamin, but again we can't just start this prenatal vitamin if they're on an integrase-based therapy, so we would want to make sure that we educate them that they should be separating it if they're on integrase-based therapy. I'm going to turn it back to you, Dr. Sosman. Dolutegravir, in your practice, is it something that is a concern or that you're continuing patients on?

That's a good question and I think, in general, like we're seeing, if the woman is already suppressed on dolutegravir, we certainly do a lot of counseling regarding family planning, birth control. And if they are, I wouldn't really switch. We may modify, depending on what agents they're linked with. But, in general, we'll continue it. It seems well-tolerated.

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Case 2 Question 7

Question 7

Based on DHHS guidelines, which of the following is a recommended treatment change to the regimen of DTG/3TC during pregnancy?

a. Add DRV/r
b. Add ATV/r
c. Switch to DTG/ABC/3TC
d. No change recommended

Answer rationale

The correct answer is C.

- There are no data on the use of 2-drug regimens, including DTG/3TC, during pregnancy. Therefore, the DHHS recommends either switching regimens or adding a third antiretroviral to this treatment option.[1]
- DTG/ABC/3TC is a preferred INSTI-based regimen during pregnancy. This is because it is a single-tablet regimen administered once per day. It is also useful when a PI-based regimen may not be ideal due to risk for preterm delivery or drug-drug interactions.[1]
- ATV/r and DRV/r are preferred agents for PI-based regimens in pregnancy; however, they should be combined with a preferred dual-NRTI backbone such as ABC/3TC, TDF/FTC, or TDF/3TC.[1]

Faculty Discussion

And the answer here would really be C which is switching to dolutegravir, abacavir and 3TC or lamivudine and why is that. First of all, she's right now on a 2-drug regimen and we just don't have enough information about that. We know we want to keep that viral load undetectable and it was, in this patient, but with pregnancy, the changes hormonally and with bioavailability of certain medications, we just don't have enough information.

It seems that we should go to a more standard regimen, combination pill with a more traditional backbone and anchor medicine, like, in this case, abacavir, 3TC and dolutegravir. And those are, that integrase combination is coformulated in a single pill and we know that, with single pills, adherence is better, convenience. This has a very good side effect profile and then, likewise, not a lot of drug interactions or bioavailability issues and concentration issues in pregnancy that we know of. That's really a why. The atazanavir/ritonavir boosted PI and darunavir/ritonavir are actually preferred regimens, but they should really be with a preferred dual NRTI backbone like abacavir/3TC, TDF/FTC or TDF and 3TC. Actually, TAF, we just don't have enough information right now. We're concerned about that during pregnancy until we have more information.

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Case 2 Question 8

Additional case information

Janelle is positive for HLA-B*5701, precluding switch to an ABC-containing regimen. After a discussion of the risks and benefits of DTG-based treatment and the recommendation to switch to a 3-drug regimen, you and Janelle decide to change her regimen to TDF/3TC plus DRV/r.

She returns to the clinic 1 month later for viral load monitoring (20 weeks gestation). Her viral load has increased from 43 to 350 copies/mL with a CD4 count of 511 cells/μL. She has no symptoms of diseases that might increase viral load (eg, respiratory illness).

Question 8

Which of the following is a likely cause of Janelle's elevated viral load?

a. Nonadherence to drug regimen
b. Lower plasma drug exposure during pregnancy
c. Regimen switch
d. Elevated CD4 count

Answer rationale

- The most common reason for lack of viral suppression is nonadherence to ART.[1]
- A meta-analysis of studies evaluated adherence to ART during pregnancy internationally, with 27% of studies coming from the United States. More than one-quarter of pregnant people had inadequate (≤80%) ART adherence.[2]
- The most common reason for missing doses is forgetfulness, reported in 57% of nonadherent pregnant people taking ART.[3]
- Factors associated with suboptimal adherence in pregnancy include unplanned pregnancy, depression, a history of intimate partner violence, and a lack of awareness about ART preventing perinatal transmission.[3-5]

Faculty Discussion

Janelle did test positive for the HLA-B*5701 and the regimen had to be changed. We didn't have any single-tablet regimens that were a viable option, so based on this question the most appropriate answer is option A, nonadherence to her drug regimen. This becomes a major concern for us because we are concerned for vertical transmission between the mother to child. Our goal is to make sure that we prevent HIV transmission to the child at all costs. This is really where we start to think about the importance of being undetectable so the mother can't transmit it over to the child and so we really need to focus on how can we get Janelle to be taking her regimen without missing anything and making sure that she is fully adherent to it.

When we say undetectable, we typically mean, per the guidelines, it's less than 200 copies/mL, but in the instance of most of our labs that are being drawn, an undetectable viral load would be less than 20 copies/mL. Just kind of for a frame of reference. Additionally, now that we've gone away from a single-tablet regimen, and so Janelle is on tenofovir disoproxil fumarate, so TDF, the lamivudine and then plus boosted darunavir. Boosted darunavir technically should be twice daily and so the darunavir that counts as 1 tablet twice daily as well as the ritonavir that it's boosting it with, so another 2 drugs. We now have 5 medications that Janelle has to take on a daily basis and now split it into twice daily dosing.

That becomes a lot harder to remember how to take it. Maybe, you know, in the busy life that she forgets her second dose in the evening time. There's a whole host of other concerns that we think about. She's juggling responsibilities and she's maybe just merely forgetting that she has to take this medication. We know that vertical transmission, thanks to the advent of antiretroviral therapy, has significantly decreased over time and so that is, you know, just having that prevents mother-to-child transmission, but then in terms of adherence, we have to think of other factors. We know that this was an unplanned pregnancy, so are there other factors that are going on? Is Janelle depressed? Is she experiencing any sort of abuse in her relationship? These are all questions that we should be asking or observing within Janelle.

The other thing, in terms of making sure to educate patients on this, the need for adherence, at any point in time with HIV therapy, this is the most important time and I cannot stress that to our patient enough because of that reduction of HIV transmission that we want to make sure. Another point of education that I make sure to tell our patients is that during pregnancy we want to make sure that you're also making sure that you're not picking up any sexually-transmitted infection. That's another thing that we counsel on [and that] is to make sure to continue to use appropriate protection. And so, within our guidelines, if you're living in an area that has high prevalence of HIV or sexually transmitted infections, a patient who is pregnant will typically be tested during their first trimester as well as their third trimester to make sure that there's no additional sexually-transmitted infections that were picked up. But if there is still ongoing risk beyond that third trimester, a lot of times during delivery a patient will be tested for HIV again, during active delivery as well, if there is any risk for other sexually-transmitted infections. We want to make sure that we are treating this before the child comes into the world.

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Case 2 Question 9

Additional case information

On questioning, Janelle notes that she is taking her medications "most of the time" but not every day.

Question 9

How would you initially manage Janelle's suboptimal adherence?

a. Educate her about how to take her medications
b. Refer her to her pharmacist for medication counseling
c. Switch to a 2-drug regimen
d. Ask her why she is not taking her medications as prescribed

Answer rationale

- Brief conversations with patients are the best way to address ART adherence. Together with patients, clinicians can uncover barriers, develop strategies, and individualize goals to increase ART adherence.[1]
- Compared with patients who were aware that ART can decrease the risk of perinatal transmission, those who lacked this knowledge had a 6-fold higher likelihood of nonadherence.[2]
- Maternal use of ART reduces the risk of perinatal HIV transmission, regardless of CD4 count and HIV RNA levels by reducing the concentration of HIV in blood and genital secretions. In people with undetectable viral loads, the risk of HIV transmission is very low. To prevent perinatal transmission in pregnant patients with HIV RNA levels higher than 1000 copies/mL, the DHHS recommends a scheduled cesarean delivery at 38 weeks.[3]
- Furthermore, there is evidence that HIV viral load higher than 10,000 copies/mL prior to pregnancy is associated with a greater risk of pregnancy loss compared with those with HIV viral load less than 40 copies/mL.[4]

Case conclusion

You ask Janelle if anything specific is going on when she misses her ART doses. She notes that she is stressed between her work schedule and the pregnancy. You talk with her about ways to help her remember her pills and discuss the importance of adherence to prevent perinatal transmission and avoid the need for a planned cesarean delivery.

Faculty Discussion

The answer to this next question would be D, which is to ask her why she's not taking her medications as prescribed. And, as you just said, it's really having that conversation. And, as opposed to putting up the barrier for us as clinicians, what we really should do is [realize that] even having a brief conversation with the patient can really do a lot. And it many times can start like asking them what they think might be the best way to address their adherence, meaning you might, as opposed to us talking at them, really hearing them and really engaging them and they might come up with a creative idea or uncover a barrier that we were just not aware of.

And then developing strategies and when they have buy-in to that, I think, you know, data shows it's much more likely that they'll follow the new adherence kind of plan. But you can do that in piecemeal. A bunch of smaller, briefer conversations as opposed to having to take a half hour with this. And the rest of the team members can help.

The other interesting thing is the idea of knowledge. Like we assume our patients, especially if they've already been diagnosed with HIV, on therapy, may already know some of these things, that antiretroviral therapies, as we just heard from Melissa, really have been a major game-changer. In fact, maternal antiretroviral therapy was the first biomedical intervention to prevent the spread of HIV that was successful. Preventing it from mother-to-child transmission, vertical transmission. And we know that folks that got pregnant when they weren't on antiretroviral therapy, had a higher viral load, were more likely to [have] a greater chance of losing the pregnancy compared to someone that had an undetectable viral load at the time of conception.

And then, likewise, when those women that are pregnant are aware that antiretroviral therapy really decreases the rate of transmission to their child and dramatically decreases that rate by 99-plus percent, if they're aware of that, they're much more likely, in fact 6 times more likely, so to speak, to take their medications than someone not [aware of that]. There, the risk of nonadherence is much lower.

And likewise, as we just heard, if they have an undetectable viral load through gestation, at the time of delivery, they can deliver without other interventions, so-called naturally, and if they have a detectable viral load, we're monitoring that, and if it's above 1,000, they probably qualify for a planned cesarean delivery. But really, when it's undetectable, as we just heard, the chance of transmission is very close to zero, really quite low. It's really, really been incredible.

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Case 3 Question 10

Case background

Susanne, a 59-year-old postmenopausal woman with HIV was diagnosed 5 years ago. She has been receiving EVG/c/TAF/FTC and has maintained an undetectable viral load for the past few years. Susanne was recently diagnosed with dyslipidemia, hypertension, and osteopenia.

Question 10

Which of the following components of Susanne's regimen can increase the risk for dyslipidemia?

a. EVG/c and FTC

b. EVG/c and TAF

c. FTC and TAF

d. EVG/c, TAF, and FTC

Answer rationale

The correct answer is B.

- All INSTIs, including EVG/c, have been associated with an elevated risk of the development of dyslipidemia compared with NNRTIs. However, compared with PIs, INSTIs tended to cause less dyslipidemia.[1]
    - Of the various INSTIs, EVG/c has been associated with a higher rate of dyslipidemia than DTG (incidence rate, 1.20).[1]
- EVG has been shown to impair adipogenesis, interfere with adipocyte metabolism, and promote proinflammatory cytokine expression.[2]
- TAF is associated with a greater risk for dyslipidemia than TDF. In a randomized controlled trial comparing 144 weeks of TAF and TDF in coformulations with EVG/c/FTC, TAF was associated with greater increases than TDF in levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (P <.001 for all).[3]
- There is also evidence that switching from TDF to TAF results in lipid level increases. However, this effect may be reversible, as switching back to TDF from TAF returned lipid levels roughly to baseline.[4]

Faculty Discussion

The correct answer was B and what we found more recently in the last few years is that all of the integrase inhibitors may be associated with some dyslipidemia compared with the non-nucleosides, efavirenz, rilpivirine, nevirapine, that class. However, compared to protease inhibitors, the integrase inhibitors tended to cause less dyslipidemia. And this data really was amplified in the RESPOND study which was combining multiple cohorts together, at least 15 to 17 cohorts. And they were looking at this epidemiologic data of this cohort study. This was not a randomized, controlled trial. And when they did that, some of these factors did significantly fall out, meaning protease, dual-boosted protease inhibitors [being] probably the most likely to cause dyslipidemia followed by integrase and then non-nucleoside as the anchor, so to speak, within a regimen.

And when we look at the various integrase inhibitors, there was actually enough power and size in this study to show that elvitegravir/cobicistat might have been associated with the highest degree of dyslipidemia and even slightly higher than dolutegravir. But those were small, small but significant differences.

Why? We don't know. Again, there are some hypotheses. One is that elvitegravir has been shown in some in vitro studies to impair adipogenesis, maybe interferes with adipocyte metabolism and might actually, ironically, induce proinflammatory cytokine expression. It seems a little contrary to what we thought, but it might, and it could be doing it around adipocytes, which might lead to that.

Ironically, we're also seeing, based on more of the backbone medicines, TAF is associated with greater dyslipidemia than TDF and that seems hard to explain, but we're definitely observing that, in this study and in others. And especially when they were coformulated in combinations with elvitegravir, cobicistat, FTC, TAF, was associated with greater levels of all cholesterol, total cholesterol, triglycerides, HDL, and LDL. Interesting observations and signals for us to study further.

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Case 3 Question 11

Question 11

Why would a switch to EVG/c/TDF/FTC be inappropriate for Susanne?

a. ABC is preferred due to presence of hypertension
b. TDF should be reserved for patients with genotypic resistance mutations to TAF
c. TDF has been associated with decreased bone mineral density
d. All of the above

Answer rationale

The correct answer is C.

- Compared with TAF, TDF has been associated with significantly higher rates of bone mineral density (BMD) loss. In a randomized controlled trial comparing TAF and TDF in coformulations with EVG/c/FTC, hip BMD loss from baseline at week 144 was -3.36% with TDF and -0.75% with TAF (*P* <.001). Similar differences in BMD loss were reported for the lumbar spine.[1]
- Although the precise mechanism of TDF-related BMD loss is unknown, it may be related to subclinical renal tubulopathy and aberrant vitamin D metabolism.[2]

Faculty Discussion

The most appropriate option or answer is option C where TDF has been associated with decreased bone mineral density. We've known this for a very long time that TDF has been associated with a reduction in bone mineral density. We know that with the TDF portion being high, TAF still does cause abnormalities in bone mineral density, but it's to a much less effect. We do still see a small reduction in bone mineral density in the spine and hip compared to TDF.

This mechanism, again, is not fully known, but there is some thought that TAF has less systemic effects and that's due to less circulation of tenofovir diphosphate circulating within the body. And so TAF requires smaller doses compared to TDF which ultimately is associated with lower drug concentrations throughout the body as well as less drug exposure for the bones. There are other potentially proposed mechanisms of this, of why there is the reduction, and it may be due to some of the subclinical kidney effects or even abnormal vitamin D metabolism. I think really our take-home is that we've known for some time tenofovir has been associated with bone mineral density reduction, but what we end up seeing is that it's just a little bit lower with TAF. I think making sure that we're letting our patients know about this is something that's very important and, even in my clinical setting, if we talk to a patient about potentially going on to a TDF-based therapy, some patients will ask me, am I going to have an increased risk for fracture, am I going to have that increased risk for broken bones? You know, I've been reading, there's been stuff on television. We tell them that it's something that we definitely have to make sure that we keep an eye on, but if patients have risk factors for osteoporosis, maybe we should be considering other regimens for our patients.

Dr. Sosman, in your practice, do you have a lot of patients who are coming to you that are concerned about osteoporosis as they're aging and if so, what are you doing?

We know that the fastest growing part of our population, especially those living with HIV, is those over 50 and we knew a lot more about bone health among women. Now we're learning much more about it in men, whether they have HIV or not. But HIV disease has really spurred that understanding to a greater degree. It's definitely something we now screen for in our men and women and certainly ask a lot of questions and are pretty cognizant of TDF's concern about that, maybe through a tubular mechanism in the kidneys and, and bone loss.

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Case 3 Question 12

Additional case information

During a shared decision-making discussion, you and Susanne discuss starting DTG/ABC/3TC as a single-tablet regimen.

Question 12

Which of the following adverse events should be discussed with Susanne prior to initiation of DTG/ABC/3TC?

a. Cardiovascular events
b. Weight gain
c. Neuropsychiatric adverse events
d. All of the above

Answer rationale

The correct answer is D.

- In some studies, ABC has been associated with increased risk of CVD, while others have shown a lack of association.1 Nonetheless, it is appropriate to discuss the potential risk for CVD in patients initiating ART.
    - In an analysis of the D:A:D study, which enrolled 33,347 patients for a total of 157,912 person-years, recent use of ABC within the last 6 months increased the risk of myocardial infarction (MI) by 90% compared with no recent use of ABC (*P* =.0001). Cumulative use of ABC was n ot related to MI risk.[2]

- In a meta-analysis of randomized controlled trials comparing ABC-containing ART with non-ABC-containing ART, ABC was not associated with an increased risk of MI or other cardiovascular events.[3]

- In addition to weight gain, neuropsychiatric events have been reported in patients treated with DTG. These include headaches, insomnia, depression, suicidal ideation, panic attacks, nightmares, and dizziness. Cohort studies have shown that overall rates of neuropsychiatric adverse events leading to discontinuation range from less than 1% to 5%.[4-6]

Faculty Discussion

And of these, the correct answer is actually D, all of the above.

And taking these one at a time, cardiovascular events, for quite a while we've seen signals that abacavir may be related to MIs and one of the first studies to show this was the D:A:D study that Melissa had talked about.

That signal, though, is really front-loaded, meaning we don't think we're seeing it in people that have been on abacavir much longer. Otherwise, other studies, when they looked at other cohort studies, haven't really found that signal. The D:A:D study, which is incredibly large and powerful in that respect, does show it, does show that a signal in cardiovascular risk is front-loaded. Other studies haven't. There's been some in vitro work that seems to imply maybe abacavir increases cardiovascular risk through its effect on platelet aggregation, potentially increasing that. But, if someone does have some cardiovascular risks, [when] thinking about starting abacavir-based regimen, it's certainly a factor that I enter into that. She's going to be starting this, she's a woman of a certain age right now, had some dyslipidemia. We definitely want to discuss that.

The weight gain, I'll delay, I'll forego because we talked dolutegravir and weight gain issues, but the neuropsychiatric adverse events, that not everybody will be aware of. We're certainly seeing some in a small number, 1% to at most maybe 5% of people that start dolutegravir and it might be as mild as insomnia, headaches, some depression, and there's even been some suicidality with it, panic attacks, that have been identified.

In my empiric experience, it's a lot less than we used to see with efavirenz when that was the anchor of our preferred 3-drug or so regimens. In that case, it just seemed anecdotally much higher. This is much lower, but it's still something we want to counsel about and have them aware of to let us know anything about that.

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Case 3 Question 13

Additional case information

During a shared decision-making discussion, you and Susanne discuss starting DTG/ABC/3TC as a single-tablet regimen.

Question 13

Which of the following steps should be taken prior to initiating a new regimen to decrease the risk of ART-related adverse effects?

a. Genotypic resistance testing
b. Liver function tests
c. Review of prescription and over-the-counter medications
d. All of the above

Answer rationale

The correct answer is C.

- Drug-drug interactions with ART are common and can alter levels of drug exposure, which may affect the toxicity profile or efficacy of drugs.[1]
- DHHS recommends a thorough review of any prescription and over-the-counter medications to avoid undesirable drug-drug interactions.[1]

Faculty Discussion

The most appropriate answer here is option C, review of prescription, over-the-counter medications. For me, this is one of the most important conversations that I can have with any of my patients, making sure that we have an updated medication history because all too often, a lot of our patients think about prescription medications when we ask for what medications they're currently taking, but they don't often realize the over-the-counter medications. And it's because somebody isn't prescribing it for them and so they don't always have that moment where they're like, oh I'm taking this medication over the counter.

I kind of ease into my talk with them and I ask them, so say you get a headache, what do you take to alleviate your headache? And most of the time they'll say acetaminophen or ibuprofen and they sit there for a second and then that lightbulb goes off and they're like, oh I am taking over-the-counter medications and they may not have realized it. Then kind of the floodgates open and they start talking about all the over-the-counter medications they've taken, other supplements or herbal medications that they're taking, and so we go through everything and I tell them I want to know everything that they're taking, or even something that they're anticipating taking. A lot of times we'll have those conversations and while they're sitting in clinic with me, we'll go through their medication list and I also like to provide a visual for them. I'll take out one of my drug interaction checkers, whether it's something that's institutional-based or free online, and we'll go through their medications together so that they can start to see some of the drug interactions that are possible.

Everybody is not going to experience a drug-drug interaction, but again I like to talk to them about what they should start to look for. If this medication interacts, maybe you will start to feel this side effect or that side effect. Just to kind of give them something to think about. What I tend to think about is, you know, drug interactions are very, very prevalent, but again if they're thinking about going onto a medication, I want to encourage them to talk to their pharmacist, talk to their provider about taking anything over-the-counter, contact us first or contact their provider first. Now, it doesn't have to be for every single thing, but for some of the medications I give them, I start to list off some other medications that they should think about. A lot of times, if they're taking antacids, they're going to potentially interact with some of the first-line regimens. For some of our Tums or Rolaids, they may think that it's insignificant, but again I tell them to make sure that you're separating it if you're taking an integrase-based regimen. I don't want to put them at risk for developing resistance if the medication regimen is suboptimal, but I also don't want to increase their risk for any side effects.

Aside from the DHHS guideline which is an excellent resource for looking at their tables for what happens with drug-drug interaction, most of our patients won't necessarily go there, but there are free [sources]. University of Liverpool is another example of a great resource to look up drug-drug interactions and not only in a clinical setting. It is free for patients online. It may be a little bit cumbersome for them to review that data, but if there's not a pharmacist in your clinic or in your clinical setting, this is an excellent resource to use. And it gives you medications that you should avoid or the clinical management and the data behind that clinical management. I think that's really important to take into consideration as you're using any of these antiretroviral regimens and some people may not be familiar with all the antiretroviral regimens that are available for use, but I think just knowing some of the drug interaction checkers are really important and valuable for ourselves, our patients and then for some of those over-the-counter medications that they encounter.

Melissa, I couldn't agree more. It's amazing when you actually get kind of an inventory of everything our patients are taking and for some they may be thinking if this isn't prescribed or this is gotten in a health food store or something else, it's pretty natural and not an issue. And it can really, you know, make me break out into a cold sweat at times. It is really important advice.

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Case 3 Question 14

Additional case information

Susanne initiates DTG/ABC/3TC. When she returns 6 months later for a follow-up appointment, she has gained 5 lbs (1.4 kg) and her BMI has changed from within the normal range to overweight.

Question 14

Which of the following steps would be a reasonable intervention to help Susanne with weight management?

a. Encourage healthy nutrition and physical activity
b. Recommend she take an over-the-counter weight loss medication
c. Refer to psychiatrist for cognitive behavioral therapy to improve impulse control
d. Switch her ART regimen to one without an INSTI

Answer rationale

The correct answer is A.

- DHHS recommends against switching ART due to weight gain, as there is no evidence that weight gain is reversible with drug switching. Instead, clinicians should discuss lifestyle modifications, including physical activity and nutrition, for weight management.[1]
- Overall, any amount of physical activity makes a difference, even if incorporated in small amounts into daily activities. DHHS guidelines for Americans recommend the following minimum levels of physical activity to achieve substantial health benefits:[2]

- 150-300 minutes of moderate-intensity aerobic activity per week
- 75-150 minutes of vigorous-intensity aerobic activity per week
- Moderate- or vigorous muscle-strengthening activities on ≥2 days per week

- Nutrition counseling should include a discussion of healthy foods, such as fruits and vegetables, and the importance of limiting intake of added sugars, saturated fats, and sodium.[3]
- As appropriate, providers may consider referral to a dietician, physical therapist, and/or an obesity specialist for weight management support.[4]

Faculty Discussion

The answer here would be A which is really to encourage healthy nutrition and physical activity. That sounds easy, but it definitely takes counseling, just like everything else we do. This is really the recommendation right now from DHHS regarding weight gain which is really physical activity, nutrition, weight management and these are things we should all take to heart, not just our HIV patients, but certainly this is who we're focusing on. And the interesting thing is that there have been some studies more recently that have really shown that exercise and diet can actually achieve that. When we look at the amount that's recommended of exercise, it's doable, but if your patient doesn't move, then it's going to take so-called baby steps getting them active.

And if they have the ability to use smart watches or things like that, if they have that resource or smart phones to kind of assess their movement, that can really be motivating, at least, personally, I find it motivating.

Other things like nutrition counseling, actually there have been studies, and I think Reed and others have done some studies, that really have shown that nutrition counseling and weight loss recommendations can really go far. And I think, in that cohort of HIV-positive individuals, in that study, they were actually shown that nutrition counseling really helped them lose weight. It's been validated within an HIV population. And usually it's around limiting saturated fats, sugars, sodium and really heart-healthy diets and calorie consumption.

And likewise, I think it's really important to expand our team, not just the doc or other clinician, HIV specialty pharmacist, social worker, nurse, but we've got to bring in, you know, physical therapist, trainer. A lot of times, if they're not used to movement or they've got some gait abnormalities and we need them to move aerobically, we might need them to attend physical therapy. And the nutritionist, I think today it's so different than 20 years ago or so when we were dealing with the nutritionist to help them gain weight because we were dealing with cachexia and weight loss. Now, it's like the rest of us, we're dealing with weight gain. So, the nutritionist, as part of our care team, is going to be essential.

And I think it will be great if there was some way, somehow that we could actually prescribe fresh fruits and vegetables for our patients because, in so many instances, when I'm counseling our patients about what to eat and how to eat healthier, a lot of times fruits and vegetables are expensive and a lot of times it's easier to grab something that's fast food because it's cheaper and will fill them up. I think we don't do it all at once, any of the changes. We say, hey, can you maybe switch out drinking soda and go to water or switch out drinking juice or do something else and it's just little changes over time that we try to implement that actually helps, again, anecdotally.

The other thing that I've looked into is that there are some insurances that will cover gym memberships. Maybe not all of it but if you're living in certain states that might be another resource that we can share with our patients, depending on the type of insurance that they have. I think any way that little, small things that we can do to increase activity and healthy eating is something to try at the very least.

I think that's a great idea. This concept of the brief counseling. As opposed to going on and on —which I can sometimes do—about what they should do, it's more like hey, little problem-solving, like you said getting people to have far less sugared drinks can really make a difference. And fruits and vegetables, as you said.

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Case 4 Question 15

Case background

Chang, a 57-year-old man with HIV and bipolar disorder presents to you for potential modification of his ART regimen. He was diagnosed with HIV 14 years ago and is currently on a stable regimen of ATV/r plus TDF/FTC. He has several historic resistance mutations due to inconsistent adherence to his previous ART regimens. He has been working to better adhere to both his ART and bipolar disorder medications, which has improved his virologic control over the past several years.

He recently had an acute manic episode requiring a change of his medication for bipolar disorder to quetiapine. On initiation of quetiapine, he experienced rapid and severe weight gain of 13 lbs (5.9 kg) within 6 weeks. The patient says that the weight gain makes him unmotivated to take his medications, and his adherence has slipped recently. His viral load is 420 copies/mL.

Question 15

Chang's rapid weight gain is likely due to a drug interaction between quetiapine and which of the following?

a. ATV/r
b. TDF
c. FTC
d. All of the above

Answer rationale

Correct answer is A.

- Ritonavir and cobicistat are CYP3A4 inhibitors that can lead to higher systemic exposure of drugs that are metabolized by CYP3A4, such as quetiapine.[1,2]
- Similarly, atazanavir is also a CYP3A4 inhibitor.[1]
- Ritonavir and cobicistat are also known to have effects on other CYP enzymes and UGT drug transporters, which can further exacerbate drug-drug interactions.[1]

Faculty Discussion

The most likely reason for this weight gain is option A, the role of boosted atazanavir. And again, it's going back to that interaction with the medication of quetiapine. Any time you see basically I like to say any antiretroviral agent, over time, I start to recognize which medications should or should not be used together, but if it's something that you don't commonly see, always just take a second to look it up. I know it's easier said than done, but I think 30 seconds putting it into a drug interaction checker could save your patient some of these side effects that occur. We know that boosters or protease inhibitors or even NNRTIs can be very high-risk for a drug-drug interaction, but again with this case, we know that atazanavir and ritonavir are both CYP3A4 inhibitors. We want to make sure that when we do recognize these, especially in the presence of quetiapine, there is a major, major drug interaction here.

We want to make sure to educate the patient again on potential side effects and so the concentration of quetiapine may be increased so much that we are seeing this rapid weight gain. We start to see CNS effects. We may even see QTC prolongation. We want to make sure that we are looking at this before putting a patient on it.

The provider may not be within the HIV context, so if it is their psychiatrist, a lot of times what I see is that when the patient comes in and I do that medication reconciliation, that's when I find out that the patient is on a new medication. In this case it would the quetiapine for this patient.

It is recommended that if your patient is on any inhibitor in the presence of quetiapine, that you reduce the dose by 1/6 of the normal dose in a patient. And so that would be much, much smaller than what the patient is currently already receiving. But the other thing to think about is let's say the patient on antiretroviral medication, such as atazanavir, with that booster ritonavir, is switched or stopped, then we need to make sure that if they do remain on quetiapine that they do go up by a factor of 6, that 6-fold increase, because we don't want to put the patient into another manic episode. A lot of times we abate the drug-drug interaction, but then we have to make sure that we're making sure to dose-adjust what's needed to make sure that we're not putting the patient at risk for another consequence.

There are also other pathways that are responsible for drug-drug interactions, especially with those pharmacokinetic enhancers or boosters such as the ritonavir or cobicistat. Any time I see that, my knee-jerk reaction is always, always, always double check if there's any drug interaction that's possible. The other thing is, you know, when we empower our patients to tell us about these side effects, we're not necessarily having them wait until their next follow-up visit. Maybe we just saw them 2 weeks ago and they're not coming back for a month, they can just pick up the phone or send a note through their EHR and let us know that they're having additional side effects. And maybe we can pinpoint this and figure it out a little bit sooner. But again, it's always that team-based approach.

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Case 4 Question 16

Case background

Chang, a 57-year-old man with HIV and bipolar disorder, presents to you for potential modification of his ART regimen. He was diagnosed with HIV 14 years ago and is currently on a stable regimen of ATV/r plus TDF/FTC. He has several historic resistance mutations due to inconsistent adherence to his previous ART regimens. He has been working to better adhere to both his ART and bipolar disorder medications, which has improved his virologic control over the past several years.

Question 16

Which of the following next steps should be pursued to optimize outcomes in this patient?

a. Contact the patient's psychiatrist to determine next steps
b. Discontinue ART
c. Discontinue quetiapine
d. Switch ART to INSTI instead of boosted PI

Answer rationale

Correct answer is A.

- Polypharmacy is becoming increasingly common among PLWH, and many ARVs are associated with drug-drug interactions. As such, a multidisciplinary approach is a critical component of treating PLWH.[1,2]
- Particularly for patients with comorbidities and for those who are older, clear and effective communication across specialties is critical. Non-HIV specialists may not be as familiar with potential drug-drug interactions stemming from ART.[2]
- The multidisciplinary care team for PLWH can include primary care providers, non-HIV specialists, and pharmacists.[1]
- ART should not be discontinued in this patient, as viral suppression is critical to preventing adverse outcomes and HIV transmission.[2]

Faculty Discussion

It should really be A which is to contact the patient's psychiatrist to determine the next steps, meaning I would not just discontinue the quetiapine, as you mentioned, and I wouldn't discontinue the antiretroviral therapy. It's critical that we try to keep them maximally virally suppressed, their CD4 count high or we're going to create a more critical and different issue.

They're on a new medication from their psychiatric provider or their mental health provider. It takes not one person in a silo; it's an interdisciplinary approach to making sure that we're uncovering a lot of these drug-drug interactions for the patient because if a patient has a side effect, then we're putting them at risk for maybe wanting to stop their medication, not telling us and then they lose virologic suppression which can ultimately cause them to transmit the virus to somebody else. There's so many different factors that we think about when we're managing drug-drug interactions.

I agree the recognition of polypharmacy is really important. The irony in that is as we've gone in HIV, polypharmacy 25 years ago would've been the boatload of antiretroviral therapy that people were taking. Now, it can be as simple— depending on the drug—as one pill once a day, and the polypharmacy is really coming in through all of the other things we're doing for comorbidities. Certainly people with mental health disease, complex mental health disease, they're usually on combination therapy and then all of the other things we're doing as our group of patients continue to age, live into their 50s, whether it's managing hypertension, diabetes. A lot of times, those are, dyslipidemia, that's combination therapy just for those regimens. We're really dealing with a lot and recognizing that we really need a multidisciplinary approach to this [since it] is really critical for our patients. And that should not just include us, our nurse and our pharmacist. It's really got to include the primary care clinician, in this case the psychiatrist, and it might be that they're also seeing a cardiologist, but we've got to think of that team as more, as embracing the kind of the specialists that are also involved in that. It was really going to be important to reach out to the psychiatrist and see what we can do in terms of making a change.

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Case 4 Question 17

Additional case information

After review with the psychiatrist, the quetiapine is discontinued, and aripiprazole is initiated. The patient is maintained on his ART regimen. At a 3-month follow-up visit he is feeling happier with his weight and regimen. His viral load has increased to 800 copies/mL.

He returns 6 months later, and his weight has returned to baseline. However, his viral load is 1600 copies/mL, and his CD4 count has decreased to 210 cells/µL. He reports suboptimal adherence to his medication, indicating he occasionally misses doses due to forgetfulness, missing up to 3 or 4 doses per week.

Question 17

Which of the following tests should be performed?

a. Genotypic resistance testing
b. HBV testing
c. Pill count for adherence
d. Therapeutic drug monitoring

Answer rationale

Correct answer is A.

- Persistently elevated HIV RNA levels over 200 copies/mL increase the risk of developing resistance mutations, with a stronger association for levels over 500 copies/mL.[1]
- DHHS recommends drug resistance testing for patients with virologic failure and HIV RNA levels over 1000 copies/mL.[2]
- Pill counts and therapeutic drug monitoring are used to determine patient adherence; however, pill counts are not generally recommended for routine use due to the ease with which they can be altered by patients and their confrontational nature.[3]

Faculty Discussion

Of these options, it's really A which is genotypic resistance testing. And we know that these are not what we would call viral blips that this patient is having which is that occasionally the viral load will get to detectable but 200 or less copies of RNA/mL. They might sustain some blips for a while. Those patients, in studies, epidemiologic and otherwise, that have blips, actually do pretty well. They maintain CD4 count. It might make us a little anxious, but they can actually do very well.

These, however, are not blips. There is the viral load is rising and he's really getting viral loads over 500. And we know that when we start seeing that, in this case it was quite a bit over 500, we know that there is a much higher risk of resistance developing, many times from, like in this case, nonadherence. When the viral load is above actually 1,000 copies per mL, we're pretty confident that the commercially and other available resistance genotypic tests are going to be able to pick up resistance mutations. They'll be able to run the test. It'll be a valid test. If it's below 1,000 copies per mL, it may not be. That doesn't mean I don't run it. A lot of times I will still run it if it's above 500, but, and we might get lucky there, but it may not show much, or the test may come back as inadequate because of that. But, in his case, we should be able to run that.

Other things you might do in terms of monitoring that we have here, like pill count for adherence therapy to drug monitoring. To tell you the truth, we don't do much of that. It's not particularly easy to do. It can be a little confrontational for the patient. Using things like MEMS caps, you know, which are automated, we don't tend to use in clinical practice right now. That certainly was instrumental in a lot of formative adherence work that informed us of these issues. Not infrequently, we will check with pharmacy, make sure that refills were picked up, things of that nature and sometimes, depending on the pharmacy, we're given a heads-up if that doesn't happen, even if we don't go soliciting that. But a lot of times, we're trying to be less confrontational about that, but really discussing other modalities to help with adherence.

In going on to our resistance thought frame, we know that we're thinking of switching therapy because mutations were uncovered and so we want to make sure that we never put somebody on a medication that they're resistant to. There are certain indications where maybe we might want to keep a single mutation around, but we won't go into that. But there, for purposes of this, we want to make sure that we avoid the medications that this patient is resistant to. So, notably, the boosted atazanavir.

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Case 4 Question 18

Additional case information

Genotypic resistance testing is performed and reveals new M46I/M and I84V mutations, suggesting an evolving mutation landscape leading to resistance to ATV/r, with cross-resistance to other ritonavir-boosted PIs. His historical resistance mutations include K103N, which precludes use of efavirenz and nevirapine.

The patient is currently taking aripiprazole for his bipolar disorder. You consider switching him to an INSTI-based regimen.

Question 18

How might the administration of a BIC- or DTG-based regimen influence the blood level of his antipsychotic?

a. Increased antipsychotic concentrations
b. Decreased antipsychotic concentrations
c. No effect on antipsychotic concentrations
d. Effects on antipsychotic concentrations have not been established

Answer rationale

Correct answer is C.

- Compared with earlier INSTIs (eg, RAL, EVG/c), the second-generation INSTIs, DTG and BIC, have been associated with low rates of drug-drug interactions.[1]
    - The long-acting INSTI cabotegravir (CAB) has not been extensively evaluated for drug-drug interactions at this time.[1]
- No drug-drug interactions with antipsychotics have been noted with DTG or with BIC.[1]

Faculty Discussion

For this question, the most appropriate response is that it's option C, that there's no effect on antipsychotic concentration and so when I see bictegravir and dolutegravir, there are minimal drug-drug interactions, but for the most part it makes me [take] a little bit of a breath of relief because there's not as many drug-drug interactions that we think about. But obviously the first thing we needed to do was make sure that there would not be resistance to any of the medications we are considering putting the patient on. And the reason that we look at bictegravir and dolutegravir is because they do have genetic barriers to resistance compared to the first-generation integrase inhibitors, being elvitegravir, as well as raltegravir.

In the presence of aripiprazole, there's no change in the antipsychotic concentration and so we can use that with very much confidence that likely we could go back to a single-tablet regimen for this patient. It'll be a little bit easier on their adherence. The other thing that's not so much on the horizon, it's here, is the long-acting injectable of cabotegravir. At this point, it's not something that's potentially recommended in this situation just because we don't have many drug-drug interaction data for this, but I anticipate in the future there will be more data that is emerging and so that might be an even better option in the future for our patients, especially where adherence may be an issue, but for the purposes of the long-acting injectable with cabotegravir and rilpivirine, it's only indicated in those who are virologically suppressed, so as a switch modality, not as something that we're going to initiate in somebody who may not have adequate adherence.

Again, we would not want the patient to be on medication that can increase their risk for side effects or increase their risk for loss of virologic suppression, so he's already unsuppressed here. We want to make sure that we're durably suppressing this patient in this instance and so taking the thought of any drug-drug interactions out of this makes us all sleep a little bit easier at night. One of the other things is our patient does have resistance to protease inhibitors and protease inhibitors are pretty hard to pick up resistance to. We know that the patient was likely nonadherent for some time and since protease inhibitors are so robust, we want to make sure that our patient can be adherent and tolerate bictegravir- as well as dolutegravir-containing regimens because those have really high genetic barriers to resistance. But now we may be taking, if a patient fails this therapy, we may be taking once-daily regimens off the plate for this patient as well as that single-tablet regimen option that we've now been able to put the patient on.

What we do tend to tell our patients is that starting and stopping the medication is probably the worst thing that you can do. While I don't want them to just stop a medication regimen, I'd want them to do it basically cold turkey without taking it every other day because then, at least if they stop it all at once, there's less likely a chance for resistance to develop. Whereas if they are taking it every other day, every couple of days, the virus is really smart and can detect low levels within the body and so that's where it's going to increase their chance for resistance.

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Case 4 Question 19

Question 19

In addition to modifying the patient's ART regimen based on the resistance results, which of the following should be done next to optimize patient adherence to treatment?

a. Screen for neurocognitive impairment and neuropsychiatric comorbidities
b. Switch to a once-daily ART regimen
c. Connect the patient with support resources
d. All of the above

Answer rationale

Correct answer is D.

- Reducing the pill burden and frequency of ART administration can improve patient adherence. If possible, once-daily administration is the preferred dosing schedule for its ease of use.[1]
- Multidisciplinary resources are often helpful for improving ART adherence. It is important to match those resources with patient needs to help them overcome barriers to regular ART use.[1]
- Psychiatric barriers can have effects on patient adherence.1 HIV-associated neurocognitive disorder (HAND) is particularly prevalent in people who were diagnosed with HIV early in the epidemic and in those with virologic failure.[2]

Faculty Discussion

In this scenario, the most appropriate option is D, all of the above. I'll kind of go through it in a stepwise manner, but I think the first thing for me, and the most important thing, is how we can keep it as simple as possible for our patients. We want to make sure that we are offering a single-tablet regimen where possible, ensuring that their medication insurance is able to cover it and so we know that with single-tablet regimens, it's going to improve medication adherence the most for our patients.

One of the other things to consider is, say a patient does go into the hospital, what does that formulary look like? Do they have single-tablet regimens available to them because I know not every hospital has a full stock of all the single-tablet regimens that are available or all the combination formulations that are available. I'm sure that a lot of these first-line medication regimens are on formulary at most hospitals, but bictegravir-containing regimens, there's nothing that is available that you're able to split that regimen apart. Really being able to make sure that a lot of these are on formulary, where possible, is really important.

We've seen a lot of medication errors in that inpatient setting where maybe the medication regimens aren't being split appropriately or if a medication is supposed to be boosted, maybe the booster isn't being given with the medication that's being boosted and our cobicistat-containing formulations, they're together with our elvitegravir-containing regimen, as well as some of our PI-containing regimens, so that makes it a little bit easier so we don't have to worry about those boosting properties. But ideally, we want to give all of the antiretroviral reg, or all of the antiretroviral agents together, where possible.

The other thing that we need to think about are some of the neurocognitive abilities as well as neuropsychiatric comorbidities. Ideally our patients should be screened for neurocognitive impairment and if there's any mental health concerns, especially in people who lack virologic suppression. Maybe they have a low CD4 nadir and, as Jim had mentioned, a lot of our HIV population is growing older. They are at increased risk for developing HIV-associated neurocognitive disorders. Patients with this may have problems that manifest as concentration issues, memory impairment or even just as simple as lack of motivation.

Really effective antiretroviral therapy, and many years ago, HIV-associated dementia was much more commonly seen. Nowadays, it's less than 5% of our patient population, thanks to the advent of newer and more effective antiretroviral agents, but it is still something that we should be screening for. And even some of the mild neurocognitive impairment should be screened for because, still, up to 50% of our patients may be experiencing that.

Additionally, some of the psychiatric barriers may exist and impair our antiretroviral therapy adherence. Up to 50% of patients are living with a mental health condition, whether it's depression, bipolar disorder, schizo-affective disorder, you know we just really need to make sure that we're identifying this in our patients and screening appropriately.

Finally, another mechanism that we need to be cognizant of for our patients are to support resources. Think about a patient who may be getting prescribed a medication or switching to a newer antiretroviral agent, and they go to their pharmacy to pick it up and it's not covered, it requires a prior authorization and the patient doesn't necessarily know what that means, and they may feel defeated and they're just like, okay, well I'm just going to continue on my medication. Their refills may end up lapsing.

One of the things that I make sure that we are doing as a service for our patients that we see in clinic is any time there's a new start or there's a switch in therapy, when the order is put in, I will educate the patients about their new medication, but then I'm also, once I finish that session, I tend to pick up the phone, call the pharmacy to see if it's covered, if there's any issues that are occurring, do I need to do a prior authorization, is there going to be a substantial copay and if there is a copay, I discuss with the patient can you afford it. And if they're unable to afford it, making sure to activate a copayment card as long as they're eligible for it or do they need patient assistance or do they need to be enrolled in an HIV drug assistance program.

I think making sure that I identify any intervention that's needed before they walk out the door is just half the battle for the patient.

The other concern could be privacy. Maybe nobody knows their status, so maybe they don't want their medications that are delivered home or they maybe are concerned about going and picking them up and one of the people in their community seeing that they're picking up medication. We can always potentially have it sent somewhere else, a mail order pharmacy, or maybe a 90-day supply so it reduces the number of trips that a patient has to go to their pharmacy.

These are all little factors that I try to overcome. And one of the last things that I do for our patients, if we're switching therapy, I tend to put it on the comment section, is that this is replacing whatever their previous regimen is because then this will trigger the pharmacy of where it's getting dispensed, if a patient is trying to fill their old regimen and then usually the pharmacy will contact us or tell the patient to contact us so we can maybe troubleshoot if they're having side effects to their medication. We tend to call a patient when they've switched over just to make sure that they're doing okay on the regimen.

Melissa, everything you said and a few things we also just let them know, even if there's a resource that we hadn't thought of and many of our patients know we have a lot of resources, fortunately, in our clinical program, but we just say if anything happens, also reach out to us even though we're proactive. Because they may be in-between a job and just not have the money for that prescription. Every late fall, at this time, is the timing for changes in re-anteing up their insurance, if they [didn't renew their] insurance, they could end up going to the pharmacy in January, and that just didn't happen, and they get a large bill. This'll be, you know, $1,000. And they might just leave it, they're embarrassed to maybe contact us. We just try to lower that pressure.

The other issue is neurocognitive stuff. Right now, prevention is obviously continuing their antiretroviral therapy for a patient and also really addressing the cardiovascular risks. Not unlike what we do in the general population, managing and preventing hypertension, weight gain, preventing diabetes, treating dyslipidemias, getting exercise. All of those things have independently been shown to reduce neurocognitive changes in the general population ages. In HIV, because of inflammation and other things going on, even some unchecked, we're worried about neurocognitive stuff happening much earlier in our patients.

And other than screening, which we have to be cognizant of, unfortunately I think over this next decade, as our patients are continuing to get older, I think this is going to be the really big next thing we'll want to deal with. I don't think we have answers right now, but we're certainly going to be screening more for it.

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