OPTIMIZING OUTCOMES FOR WOMEN LIVING WITH HIV: MOVING CLINICIANS FROM KNOWLEDGE TO ACTION

EXPERT perspectives

OVERVIEW

Sally Hodder, MD, and Paul Sax, MD, provide their expert perspectives on best practices in managing women with HIV. They consider current antiretroviral therapy (ART) recommendations for women with HIV; review emerging clinical data for novel combinations; and discuss benefits and risks associated with ART in pregnancy.

CONTENT AREAS

- Recent approvals
- Emerging clinical data
- Opportunities for HIV testing
- Initial ART for treatment-naïve women
- Benefits and risks of ART in pregnancy
- Best practices in initiating ART
- Considerations in therapy selection
- Postpartum management

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CE STATEMENT

Target Audience

The target audience is HIV specialists, infectious disease specialists, obstetricians/gynecologists, primary care clinicians, and other health care providers who care for women with HIV or at risk of HIV.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Evaluate the clinical data on novel therapeutic regimens for the treatment of HIV
- Recognize special considerations that affect ART initiation in women with HIV
- Implement personalized management strategies for women living with HIV

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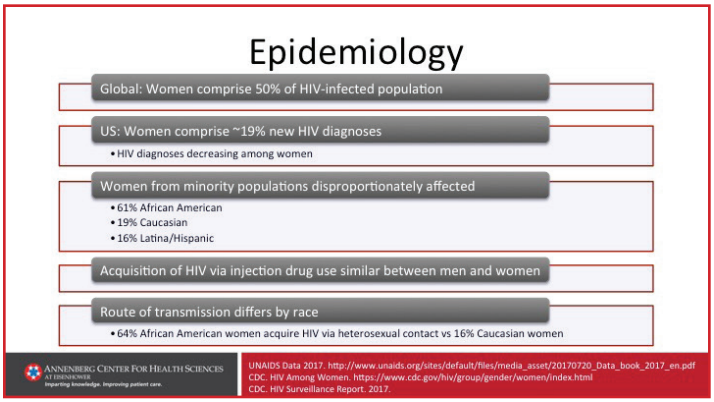
Module 1:

Guideline Recommendations and Current Regimens

We want to evaluate the clinical data on novel therapeutic regimens for the treatment of HIV, recognize the special considerations that affect ART initiation in women with HIV, and implement personalized management strategies for women living with HIV. I'm going to start us off with this first module, and this one is on guidelines recommended and current regimens, as well as a look forward to regimens that may be coming soon.

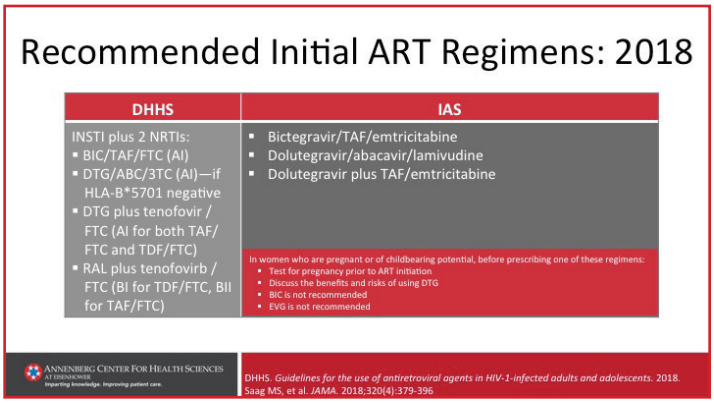
Epidemiology

Globally, women comprise approximately half the people living with HIV. However, in the United States, it has always been a disease that has predominately affected men. Right now, women comprise approximately 19% of new HIV diagnoses. HIV diagnoses in women have actually declined over time. However, still 1 out of 5 is a significant proportion of those with HIV and hence we need to understand how best to treat them. One thing that has been consistent from the beginning of the epidemic, is that women are disproportionately affected with HIV if they come from communities of color. Sixty-one percent of the women with HIV in the United States are African American vs 12%-13% of the general population. Ninteen percent are Caucasian and 16% are Latino or Hispanic. Acquisition of HIV rates and the route of transmission does appear to differ by race. Sixty-four percent of African American women acquire HIV via heterosexual contact vs only 16% of Caucasian women with HIV.



ART Regimens

What are now the recommended initial antiretroviral regimens? All of them are based on the same principle. They include 2 nucleoside reverse transcriptase inhibitors, tenofovir and emtricitabine, or abacavir lamivudine. And then they include an unboosted integrase inhibitor, either bictegravir or dolutegravir. The Department of Health and Human Services guidelines recommend bictegravir, TAF, FTC; dolutegravir, abacavir, 3TC; dolutegravir plus tenofovir, FTC or TAF FTC; and raltegravir plus tenofovir FTC or TAF FTC. Now these are much more inclusive guidelines than those in the International AIDS Society, which were updated in 2018.



Here, just 3 regimens are recommended, all of them containing unboosted integrase inhibitors. Again, bictegravir, TAF, FTC; dolutegravir, abacavir, lamivudine; or dolutegravir plus TAF, emtricitabine. The main difference in these 2 guidelines is that they no longer include raltegravir since it is a 2-pill-a-day regimen and is not formulated. In addition, dolutegravir and bictegravir have higher resistance barriers. One thing the guidelines stress is that women who are pregnant or of childbearing potential, before prescribing one of these regimens, we should test for pregnancy before ART initiation, discuss the benefits and risks of using dolutegravir, which is an important drug for initial therapy—we'll cover that more in the course of this lecture. Remember that bictegravir is not recommended for women who are pregnant because there are very little data on the use of bictegravir in pregnancy. And also, the boosted integrase inhibitor, elvitegravir, should not be used during pregnancy because there are inadequate drug levels, in particular, of cobicistat.

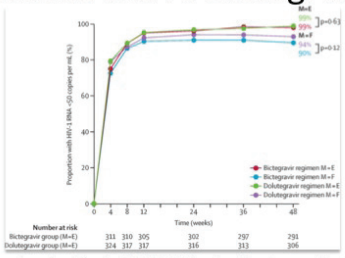
Clinical Data

Let's take a look at a recent clinical trials data on the use of bictegravir as initial therapy. This is a study that was conducted . . . a multinational study, that I was the lead investigator on. It compared bictegravir, TAF, FTC vs dolutegravir, TAF, FTC. The results were very] similar. About 90% of patients were successfully treated in both treatment arms. If you look at the protocol analysis, 99% were successfully treated by week 48. Importantly, in neither study arm, was there any resistance in any study subject. I think what this study shows us is that with our currently recommended regimens, essentially all of the people who were taking their medications successfully, with good adherence, are going to be suppressed, virally suppressed.

One other regimen worth mentioning that is not on the guidelines yet, except as an alternative, is doravirine. Doravirine is a new, non-nucleoside reverse

Recently Approved INSTI: Bictegravir

- Approved as fixed dose, single-pill combination
- Resistance not reported in clinical trials



Percentage of participants with HIV-1 RNA less than 50 copies per mL by visit

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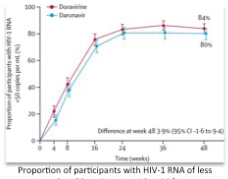
Sax PE, et al. *Lancet HIV*. 2017; 390:2073-2082.

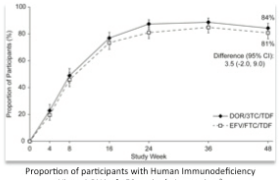
transcriptase inhibitor, approved in September of 2018. It has been shown to have comparable virologic efficacy with efavirenz and darunavir as part of initial regimens in the data shown here on the slide. It's known to have fewer CNS adverse events than efavirenz and a better lipid profile within both efavirenz and darunavir. There are very few women enrolled in these clinical trials, and as a result, we do not have any experience

Recently Approved NNRTI: Doravirine

- New NNRTI approved September 2018
- Comparable virologic efficacy with efavirenz- and darunavir-based regimens in randomized trials
- Fewer central nervous system side effects than efavirenz
- Better lipid profile than efavirenz and darunavir



Proportion of participants with HIV-1 RNA of less than 50 copies per mL by visit[1]



Proportion of participants with Human Immunodeficiency Virus–1 RNA of <50 copies/mL over time[2]

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1. Molina JM, et al. *Lancet HIV*. 2018;5(5):e211-e220.
2. Orkin C, et al. *Clin Inf Dis*. 2018.

with doravirine in pregnancy. I should mention, though, that the NNRTI class . . . there is a long-standing use of NNRTIs in pregnancy and it's possible that doravirine will have a role for treatment of HIV-infected women of childbearing potential in the future.

GEMINI 1 and GEMINI 2: 2018

Phase 3 data for dolutegravir + lamivudine presented 2018*

Study	DTG/3TC, %	DTG/TDF/FTC, %
GEMINI 1	90	93
GEMINI 2	93	94
AEs		
*Headache	10	10
*Diarrhea	9	11
*Nasopharyngitis	8	11
Drug-related AEs	18	24
Emergent drug resistance	0	0

For treatment-naïve patients who cannot take tenofovir or abacavir

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*Cahn P, et al. Presented at the 22nd International AIDS Conference (AIDS 2018), 23-27 July 2018, Amsterdam, The Netherlands.
Cahn P, et al. *Lancet*. 2018. Epub ahead of print.

What about 2-drug combination regimens for initial therapy? The best data come from the GEMINI I and GEMINI II studies which were identical. They compared a 2-drug regimen of dolutegravir lamivudine vs the 3-drug regimen of dolutegravir plus TDF and FTC. As demonstrated in the table, virologic response rates were excellent, again in the low 90% range. There were no patients who developed treatment-emergent resistance during the course of the study.

One thing that's important is that the DHHS guidelines now list this regimen, dolutegravir lamivudine, as an important option for treatment-naïve patients who cannot take tenofovir or abacavir. Because this is really changing the paradigm of HIV therapy, going from 3 drugs to 2 drugs, we await further follow-up data of this regimen to ensure that patients do not develop resistance or other problems.

One other 2-drug regimen to mention as a suppressive regimen is cabotegravir and rilpivirine. This is only for

2-Drug Regimens in Clinical Trials: Cabotegravir + Rilpivirine

- Safety and efficacy of monthly dosing in treatment-naïve and treatment-experienced patients
- First Long-Acting Injectable Regimen (FLAIR) = cabotegravir + rilpivirine vs abacavir/dolutegravir/lamivudine
- Antiretroviral Therapy as Long-Acting Suppression (ATLAS) = cabotegravir + rilpivirine vs any triple-drug combination
  - Non-inferior to oral therapy*

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*https://www.viivhealthcare.com/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen.aspx

treatment-experienced patients who are virologically suppressed. It's a long acting injection of cabotegravir and rilpivirine and the first of these studies. The FLAIR studies and the ATLAS study, we know from a press release that these are noninferior to continued oral therapy. When I talked about changing the paradigm with 2-drug treatment, and the dolutegravir lamivudine GEMINI studies, this particular regimen, once monthly injection of 2 different antivirals, really does change the way we approach treatment. We await data on this in this population that we're discussing today, HIV-infected women. There are some data that cabotegravir may have a longer half-life, slower rate of elimination than in women than it does in men.

Additional clinical trials of dolutegravir and lamivudine should be mentioned, including a small pilot study that I was involved in called ASPIRE, which showed that patients who are switched from a triple-therapy regimen, the dolutegravir lamivudine, did maintain virologic suppression. A much larger study called TANGO is currently ongoing and we expect to see data on this strategy from this study later this year.

Summary

To summarize some of the data; many regimens are recommended for women with HIV. In fact, women with HIV should be treated with essentially the same regimens that men with HIV have. However, with women of childbearing potential, especially women who express the desire for pregnancy, we should definitely test them for pregnancy before starting and discuss the benefits and risks of using dolutegravir.

Module 2:

Special Consideration for ART Initiation in Women

Testing is really the foundation for access to treatment and care. It is the gateway, and it's absolutely essential. The US Preventive [Services] Task Force recommendations for HIV screening are shown, and you should know that these are actually under revision, and new guidelines should be forthcoming soon.

HIV Testing Guidelines

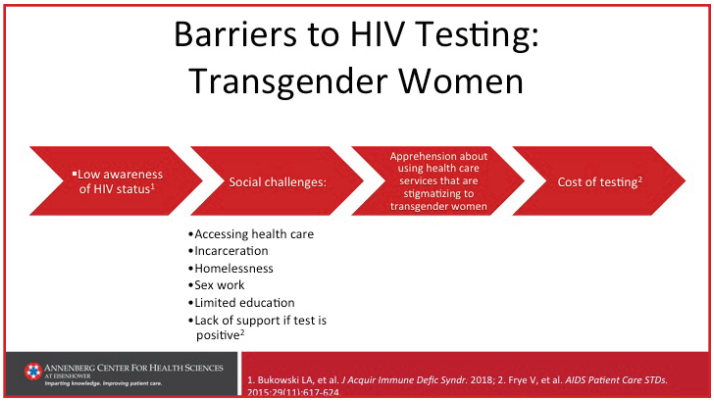
The current guidelines recommend screening adolescents and adults age 15-65, screening pregnant women for HIV, and recent Department of Health and Human Services perinatal guidelines recommend that women should be tested for HIV as early as possible in the pregnancy.

For those women who test HIV-negative initially, repeat testing in the third trimester is recommended for those who are at risk for acquiring HIV during the pregnancy, and specifically, it's recommended that women be tested in the third trimester, as well, if they are in a facility that has an HIV incidence of greater than 1 for 1,000 cases. HIV testing should be offered to women at other times, particularly those who are diagnosed with sexually transmitted diseases, those who inject drugs, commercial sex workers, and women from countries with high HIV prevalence, such as sub-Saharan Africa. Also noteworthy is that women with an HIV-infected partner, or a partner who is at high risk for acquiring HIV, should be tested as well.

Barriers to Testing

Barriers to HIV testing among African American and other populations of women, include lack of access to health care services, internalized stigma and fear about a reactive HIV test result, and concerns about privacy and confidentiality.

Many women face the risk of intimate partner violence in the event of an HIV diagnosis. Specific barriers have been identified among immigrant women. For instance, a study in Washington, DC, that assessed barriers among women immigrating from East Africa, showed that many women do not wish to be tested

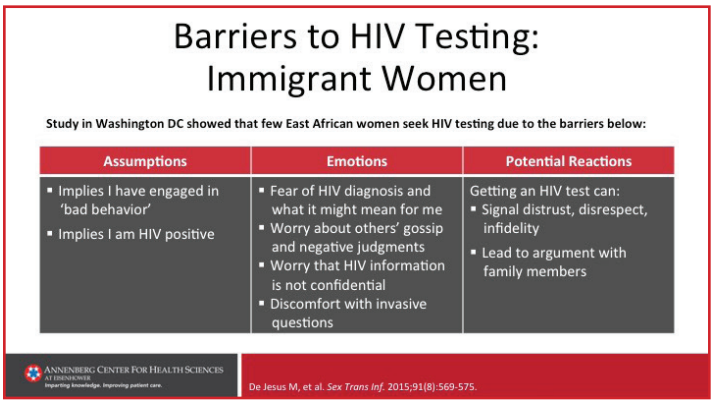


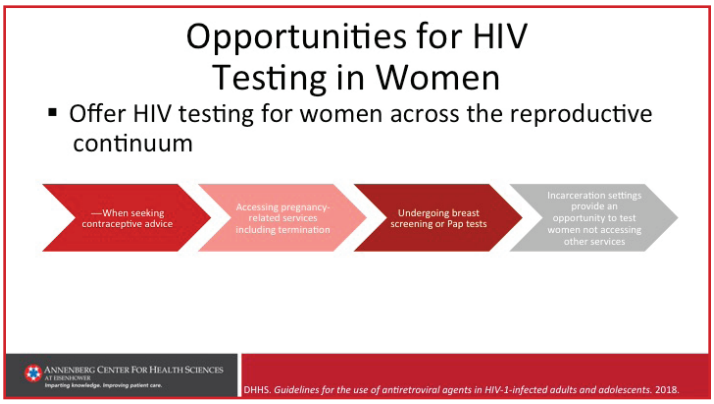
for HIV because of assumptions that others might have about them, regardless of the result. Emotions associated with the fear of diagnosis, discomfort about the presumed judgment of others or about potentially invasive questions, as well as the potential reactions of family and friends, all posed barriers to testing among this subpopulation. Effective strategies to facilitate testing among women, including African American women, include improving access to health care, increasing women's knowledge about HIV and available treatment, including HIV testing alongside testing for sexually transmitted infection, and building social norms and problem-based coping skills among this population.

Transgender women have a very high prevalence of HIV infection and also have a very high prevalence of undiagnosed HIV infection, well in excess of 2-times the general population in the US. And I think therefore this is a really important group to consider. There are social challenges shown there. This was based on a study of transgender women that associated incarceration, homelessness, sex work, and limited education, with decreased access to HIV testing. Other factors have been identified as well, such as a lack of support if the tests were to be positive. I think it's critically important to understand that transgender women are an important group in which HIV testing should be done, and that there may be special barriers affecting testing in that group of individuals.

Opportunities for Testing

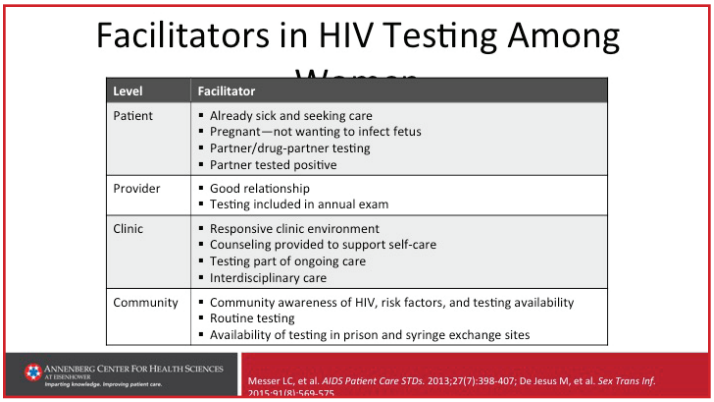
There are a lot of opportunities for HIV testing among women. I think often, in busy practices, we miss those. And some of those are shown here: at the time of





contraceptive prescription, accessing pregnancy relating services, or ongoing preventive care, such as breast screening and pap smears. In addition, incarceration settings also provide an opportunity to test women who may not have availability of HIV testing services at other times.

The factors shown have been demonstrated to be facilitators of HIV testing among women. I think that it's important ... there are important critical times in individual's lives such as when they're pregnant and not wanting to infect [the] fetus, that an individual may be more receptive to HIV testing. I think as providers, it's incumbent that testing be included in annual exams, sort of the routinization of HIV testing is critically important. And I think it goes without saying, obviously, a trusting, good relationship between the health care provider and the patient is really essential to facilitate testing.



Clinic environments are important. Those environments that really offer privacy as well as counseling to promote self-care are important. And then community awareness is critically important. There have been a number of media campaigns in recent years in various areas that have shown to be an effective in increasing HIV testing. I would add also that given the increase in some areas of the country with injection drug use, syringe exchange sites are a very important site where individuals at risk and increased risk for HIV infection can be tested.

Summary

In summary, barriers to HIV testing often delay or prevent access to care for women, and it's important to offer HIV testing to women across the reproductive health continuum with the opportunities spanning from the time when you're seeking contraception, to pregnancy, to menopausal care, to routine health care, and I think that all of those opportunities ought to be considered.

Module 3:

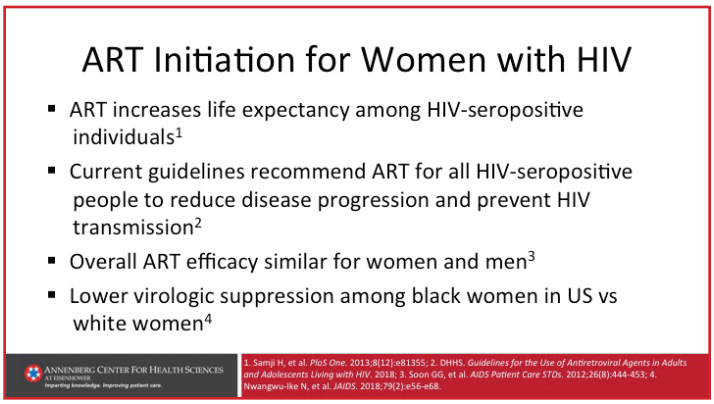
Best Practices in Initiating Therapy in Women

Hannah-Therapy Initiation in Treatment Naïve Patient

Hannah is a 24-year-old African American woman who recently received a diagnosis of HIV while being evaluated for a 10-day history of an acute viral syndrome and an abdominal rash. She has no other significant medical history. She is an attorney, single, lives alone, and has never been pregnant. What is the optimal approach to therapy for this patient?

ART Initiation

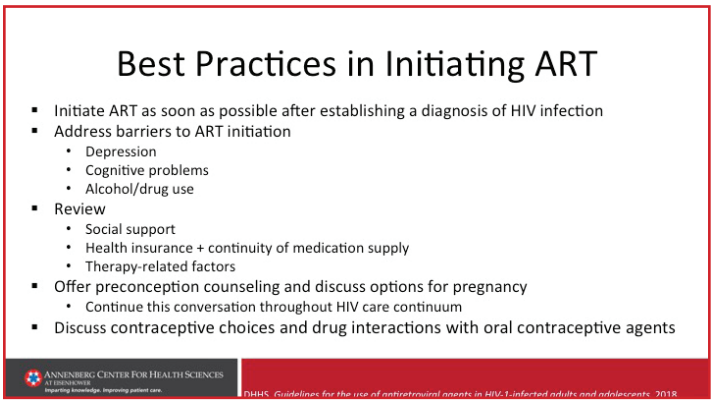
Multiple studies have demonstrated that early treatment with antiretroviral therapy (ART) reduces disease progression, prevents HIV transmission, and increases life expectancy among HIV-infected individuals. Current 2018 Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* recommend initiation treatment for all HIV-seropositive persons. Overall, studies have shown similar efficacy of ART among men and women, though a number of studies have demonstrated lower virologic suppression rates among black women in the United States vs white US women. It is important to initiate ART as soon as possible after establishing a diagnosis, and, if possible, the same day. Both DHHS and International AIDS Society guidelines recommend integrase inhibitors, the newest class of antiretroviral agents, which are associated with excellent tolerability and convenience for patients.



Bictegravir, dolutegravir, and raltegravir are recommended in combination with 2 nucleoside reverse transcriptase agents, either tenofovir or abacavir, and then either 3TC or FTC. Prior to ART selection, clinicians are advised to discuss a plan for contraception with women who have no plans to conceive and provide counseling about safe sex practices. A pregnancy test should be conducted in all women before prescribing antiretroviral therapy.

Best Practices in ART Initiation

A number of best practices that have been identified in initiating antiretroviral therapy among women are shown on this slide. It has, in recent years, become important to initiate antiretroviral therapy as soon as possible after establishing a diagnosis. Indeed, there are successful programs that initiate antiretroviral therapy the same day as diagnosis. However, I would say that it is critically important to personalize that to the individual situation of the patient and the availability of doing this in any particular community.



Three barriers that are important to address before antiretroviral initiation, are shown: depression, cognitive problems, and substance use and alcohol. Also important is a review of social support, health insurance, and the ability to assure continuity of antiretroviral therapy once prescribed. Nothing is worse for the patient than to get a prescription and then subsequently find that the health insurer will not cover that particular drug. It's incumbent on us to figure those things out ahead of time.

Also important for women of childbearing age is a discussion of options for pregnancy if pregnancy is desired, and certainly the availability of contraception, if that is a choice of the women. It's important that these things are identified before initiation of treatment because they effect selection of the antiretroviral agent, as we'll discuss.

Shown in this slide are the most recent recommendations for initiation of antiretroviral therapy. On the left side is the Department of Health and Human Services, the US recommendations, and on the right are the International AIDS Society, and they're remarkably similar. All ... both sets of recommendations really are focusing on integrase inhibitors, the newest class of antiretroviral agents, and they've been a class that's really been associated with excellent tolerability and convenience.

The alphabet soup is showing, but basically, if you look at the DHHS, bictegravir, dolutegravir, raltegravir, are the 3 integrase inhibitors that are recommended in combination with 2 nucleoside reverse transcriptase agents, either tenofovir or abacavir, and then either 3TC or FTC. And as you can see, they're remarkably similar to the IAS recommendations.

In the discussion before selection of antiretroviral therapy, when clearly the woman has said she has no plans to conceive, and I would suggest that no plans to conceive really includes then a plan for contraception, or obviously, in the event if the woman is not really of childbearing potential, if she has had a hysterectomy or tubal ligation, I think that counseling about safe sex practices is really critical, and a pregnancy test should be conducted in all women before prescribing antiretroviral therapy.

The choice should be guideline-driven. I think some important points that should be considered when prescribing antiretroviral therapy to the women with no plans for conception, and I would add that that then means that there is a plan for contraception, or that perhaps she's not of childbearing potential, perhaps she's had a tubal ligation or a hysterectomy. But this is clearly for the individuals who are not planning to conceive.

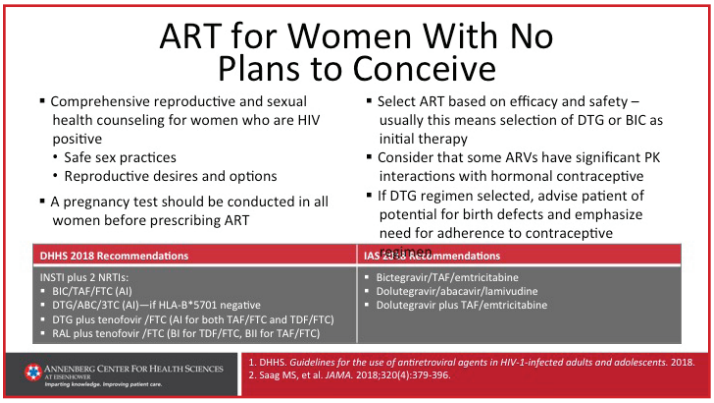
A pregnancy test, however, should be conducted in all women before prescribing antiretroviral therapy. If oral contraceptives or hormonal contraceptives are to be prescribed, one needs to consider that some antiretroviral agents, most commonly the boosted protease inhibitors or efavirenz, may have drug interactions with some antiretroviral agents, though by and large, one of the attractive issues with integrase inhibitors is they have fewer drug-drug interactions. If a dolutegravir regimen is selected, the patient should be advised to the potential birth defects that have been recently associated with this drug, and we will discuss those in just a minute.

Other considerations when selecting an antiretroviral therapy should be the pill burden. There are many 1 pill, once-a-day regimens, though some, even in the DHHS recommended guidelines, have more than 1 pill. Dosing frequency. We talked about the potential for drug interactions. But there are others, for example comorbidities. Some antiretrovirals, for example, the bictegravir, tenofovir alafenamide, and emtricitabine, is not recommended in individuals who have a creatinine clearance less than 30. So it's important to really identify if any comorbidities exist.

Also important is to identify the presence of resistance to antiretroviral agents. Even though individuals may not have been on antiretroviral agents in the past—it's a new diagnosis—it is not infrequent that there is transmission of drug resistance at the time of HIV acquisition, and so a resistance test should be done for all individuals. And then special considerations, there are some regimens, though none of those on the top recommended list for CD4 and viral load requirements, so one needs to bear that in mind. And the other is that the HLA-B*5701 testing must be done in the event that you are planning to prescribe abacavir. HLA-B*5701 actually predicts occurrence of a hypersensitivity which can be a life-threatening complication, so it's important to remember that.

No Plans to Conceive

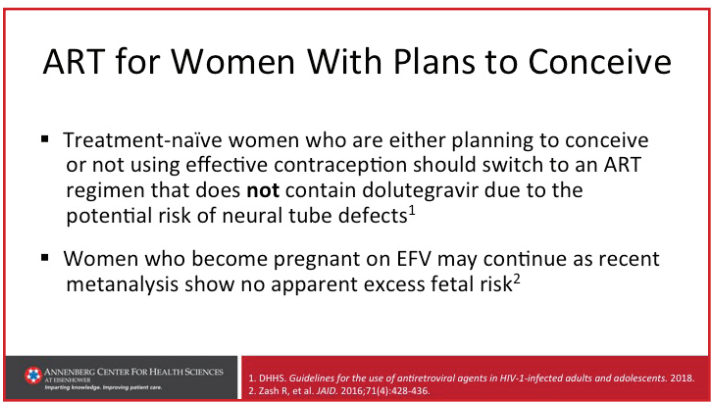
I think antiretroviral selection for women who plan to conceive, and this includes women who say, "Yes, I would like to get pregnant in the near future," but also the women who say, "I have no plans to get pregnant," but who have no form of contraception, and I think that you really need, in that case, to also consider that it is not infrequent that an individual will conceive. Treatment-naïve patients who are planning to conceive, and are not using contraception, should switch to an antiretroviral regimen that does not contain dolutegravir. And this is because, as we'll show in a minute, there's been a recent association with dolutegravir and neural tube defects in the infant when dolutegravir was taken at the time of contraception.



Women who become pregnant on efavirenz may continue, as recent analysis has shown no apparent fetal risk of neural tube defect. Animal studies in the drug development of efavirenz demonstrated neural tube defect. However, data now, for years, suggest that that does not appear to really be... to put the fetus at increased risk for development.

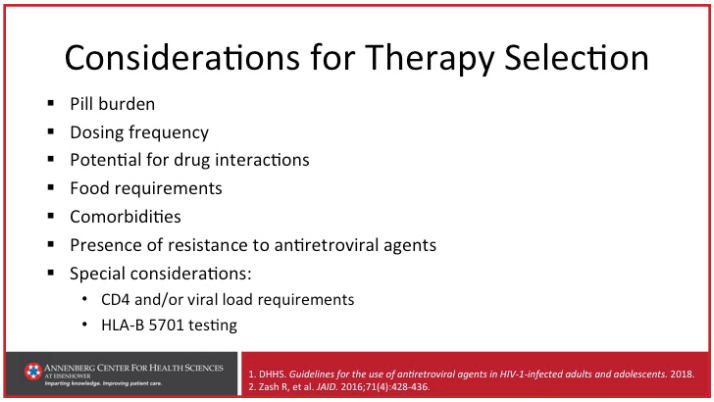
Plans to Conceive

There has been a recent association of dolutegravir at conception with neural tube defects. The Botswana and Harvard partnership actually changed in 2016 to routinely providing dolutegravir regimens for all individuals starting on antiretroviral therapy. An unplanned review of outcomes in the spring of 2018 demonstrated that individuals who ... women who were on dolutegravir at conception had a much higher risk for having an infant with a neural tube defect.



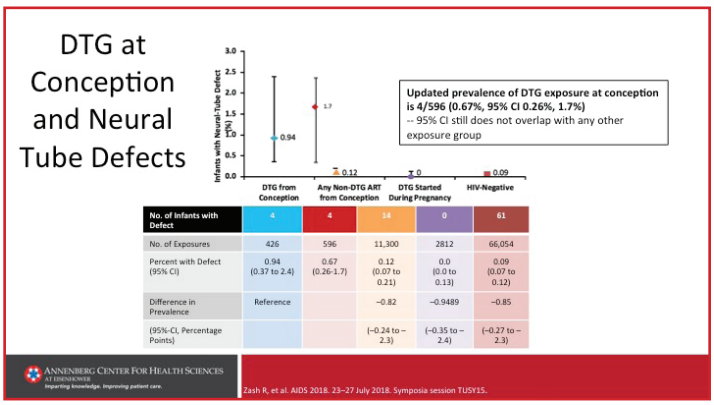
DTG + NTD Risk

Neural tube closure occurs in the third to fourth week following conception or the fifth to sixth week of gestation; therefore, the most vulnerable period for the development of neural tube defects (NTDs) is in preconception and first trimester exposures to antiretroviral therapy (ART).

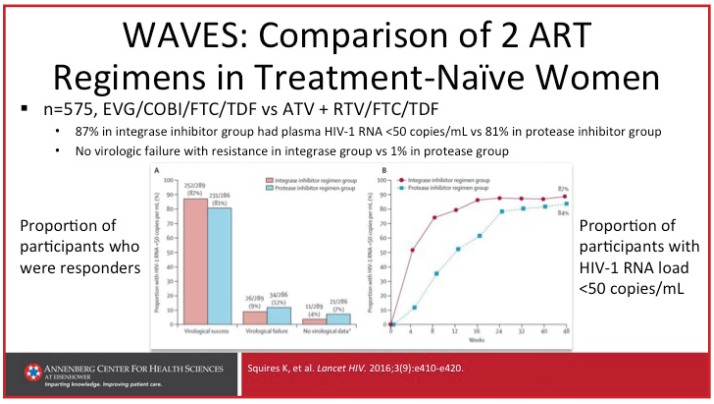


In 2018, a large study in Botswana reported that 4 infants with NTDs were born to HIV-infected women with HIV using dolutegravir (DTG) at conception.[1] Subsequent studies have examined this putative link between antiretroviral therapy (ART) and NTD. Data from the Canadian Perinatal HIV Surveillance Program, and other small cohorts in Frankfurt and Eastern/Central Europe, presented at HIV Glasgow, confirmed no additional association between DTG and NTDs.[2-4] However, researchers caution that sample sizes are small and additional data are required.

Switching gears a bit and looking at a comparison of antiretroviral regimens among naïve women. Over the past couple of years, there have been just a few trials done exclusively among women, and that's important because historically, antiretroviral trials had small percentages of women on the order of 10% or 20%. The data shown in the WAVES study compared 2 regimens. One was the integrase regimen, elvitegravir, boosted with cobicistat, and emtricitabine, and tenofovir, compared with a ritonavir-boosted atazanivir along with tenofovir and emtricitabine. And as you can see, both groups had a high rate of viral suppression that were not significantly different, and there was no virologic failure with resistance in the integrase group vs 1% in the protease group.



On the graph of viral suppression, the integrase group showing in red does actually attain virologic suppression sooner, and that is really seen across the class of integrase inhibitors compared with older, either non-nucleoside reverse transcriptase or a protease regimen.



Given the previous discussion of dolutegravir, it begs the question what do we know about neural tube defects among other integrase inhibitors? We don't have a lot of data about that. In fact, one of the issues is newly approved antiretroviral agents usually do not have substantial pregnancy data for years after they are approved, and often it's the antiretroviral pregnancy registry [that] is critically important to be able to understand whether these drugs are safe or not.

Similarly, at present, there is no evidence of increased NTDs risk with integrase inhibitors elvitegravir (EVG)- or bictegravir (BIC)-containing products during pregnancy. Analysis of a global safety database with 630 pregnancies exposed to EVG found no prospective cases of NTDs.[5] One retrospective case was reported of an NTD in a pregnancy of a woman exposed to EVG prior to conception. The same study reported no cases of NTDs among 25 BIC-exposed pregnancies. Pharmacovigilance monitoring is ongoing.

Summary

In summary, antiretroviral therapy should be initiated as soon as possible after establishing a diagnosis, with the caveat that consideration, as we discussed, with other conditions or comorbidities that require being addressed, do get addressed. Integrase inhibitors are recommended for initial therapy, along with 2 nucleoside reverse transcriptase inhibitors, and clearly, the recommended list of dolutegravir, bictegravir, or raltegravir, may be used with established safety for women with no plans to conceive. This means women who either are on a contraceptive regimen or who have had a hysterectomy or tubal ligation and they're not of reproductive potential.

The potential for the neural tube defects with dolutegravir requires a discussion among women who are initiating dolutegravir on the importance of adhering to contraceptive regimen, and I think that it's important to note that while there is no evidence currently associating other integrase inhibitors with neural tube defects, in fact, the numbers with newer agents such as bictegravir are very small, and so there's no definitive evidence either way.

Module 4:
HIV and Pregnancy

Shelley: Newly Diagnosed During Pregnancy

Shelley is a 28-year-old woman who recently discovered she was pregnant. She was offered an HIV test as part of pregnancy counseling. She tested positive for HIV and is estimated to be approximately 14 weeks gestation based on the date of her last menstrual period and ultrasound. She has never had a prior HIV test and is asymptomatic, with a normal physical exam. She is currently sexually active with the father of the baby and he is HIV-negative by report. Shelley is aware that the treatment of HIV during pregnancy prevents the transmission of HIV to the newborn and is eager to start HIV therapy as soon as possible.

Therapeutic Goals

The goals of antiretroviral therapy (ART) in pregnancy are to reduce perinatal transmission and treat maternal disease. In resource-rich countries such as the United States, ART initiation in pregnancy has reduced the HIV transmission rate to newborns from approximately 30% to <1%-2%. The risk of perinatal transmission declines with decreasing levels of material HIV RNA; therefore, ART is recommended in pregnancy to achieve full viral suppression.

ART in Pregnancy

You are probably aware that many women with HIV are diagnosed in the context of pregnancy because HIV testing is recommended universally for pregnant women. It's also known that women who already have an established diagnosis of HIV may become pregnant during the course of their HIV treatment. We have been extraordinarily successful in reducing the rate of HIV transmission to the newborn using antiretroviral therapy. At baseline, without any treatment, it's about 30% transmission. Now it's <1% and it's essentially 0 for women who are adherent to their treatment.

At our hospital, which is called Brigham and Women's Hospital—and by the name you can guess has a very large obstetrical service—we have not had a transmission among women who are HIV-positive in many, many, many, many years to their newborn because of ART given during pregnancy. So, we know that starting HIV treatment during pregnancy is recommended. If you have someone, for example, in first trimester, some have said, well you might want to delay a bit, but most guidelines recommend initiating

treatment right away. That's because there is some intrauterine transmission. There are also some dosing changes that are warranted for pregnant women because of a larger volume of distribution and some lower levels of certain drugs during pregnancy. For example, atazanavir instead of 300 mg a day is given at 400 mg a day along with low dose ritonavir 100 mg. The twice daily darunavir ritonavir strategy is recommended for pregnant women over the once-daily strategy.

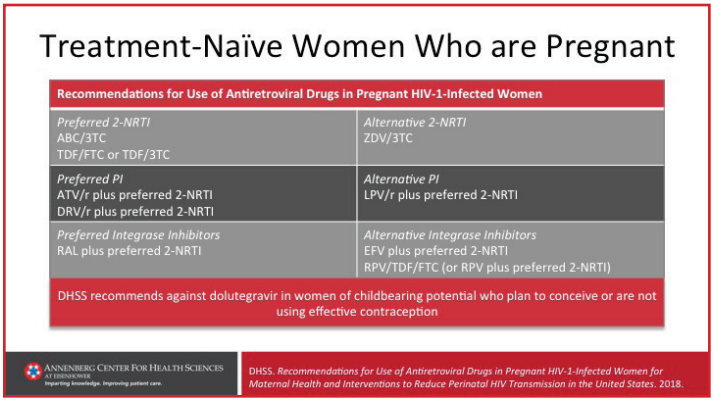
ART Adherence

Pregnancy does have effects on adherence. Many studies have been done showing that pregnant women are more likely to be adherent to ART during pregnancy. I think a lot of this is that it's a very motivating condition for them. Even some of our very difficult-to-treat patients have been able to take ART during pregnancy, and that's very encouraging. It gives them a motivation to take it even after pregnancy, it shows that they can do it. We know that the benefits of ART are pretty clear. Obviously having an uninfected baby is, as I mentioned, a huge motivating factor, and then also women want to stay healthy so that they can care for their babies and live to be healthy mothers.

Efficacy and Safety Data

Recommended ART Regimens

Although much of the data concerning ART efficacy involve women in resource-limited settings, in general, these data show that combination regimens are more effective in reducing HIV transmission than single-drug regimens, and starting ART earlier in pregnancy is more effective in reducing perinatal transmission than initiating ART later in pregnancy. Although some patients might prefer to delay ART until after completion of the first trimester, ART may be less effective in reducing in utero HIV transmission when initiated later in pregnancy.

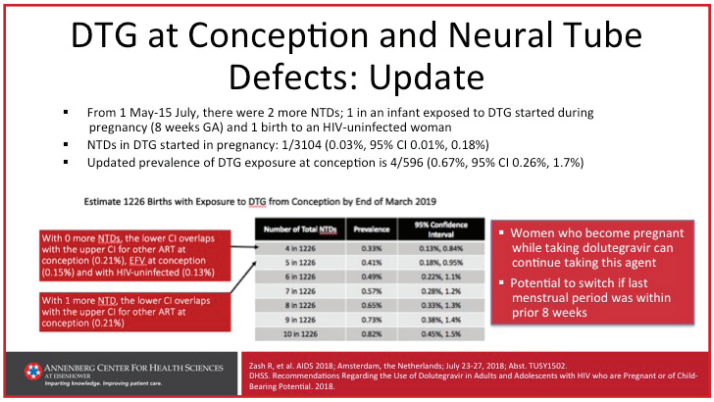


The United States Department of Health and Human Services perinatal guidelines recommend ART for all treatment-naïve pregnant women diagnosed with HIV to reduce the risk of perinatal transmission and optimize maternal health. Optimally, ART initiation should occur as soon as HIV is diagnosed in pregnancy. The choice of ART regimen is informed by current adult treatment guidelines, with decisions made in discussion with patients.

Considerations in Therapy Selection

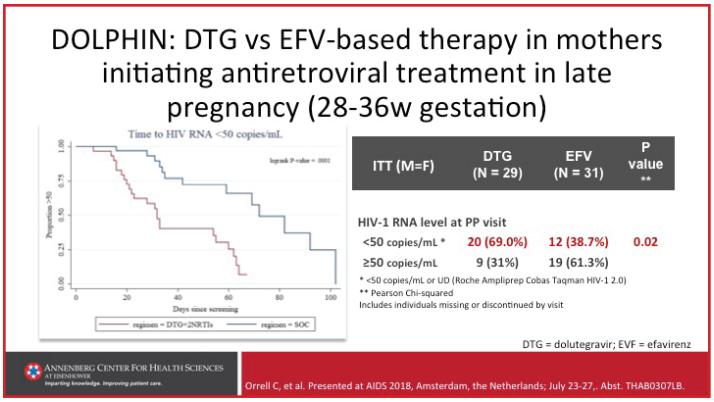
Considerations in therapy selection include virus resistance profile, efficacy and safety of available combination regimens, adherence potential of particular regimens, tolerability, other comorbidities, drug-drug interactions, and pharmacokinetic data in pregnancy. Some regimens that are preferred in the general population, such as bictegravir and tenofovir alafenamide, are not preferred for pregnant women because pharmacokinetic data or experience in this population is unavailable. In addition, some agents are contraindicated in pregnancy, such as cobistat and full-dose ritonavir. Some pharmacokinetic changes in pregnancy may require increased or more frequent dosing, eg, twice daily raltegravir.

I want to update us on the data from dolutegravir taken at the time of conception and neural tube defects. After the initial publication of the data that Sally presented, there were 2 more babies who had neural tube defects. One in an infant who was exposed to dolutegravir started during pregnancy, very early on. And it's hard to know whether that's related to this adverse event. The second was in a woman who was HIV-uninfected and so obviously she did not receive dolutegravir. So this lowered the estimate of neural tube defects in dolutegravir-exposed women who conceived while receiving dolutegravir somewhat.

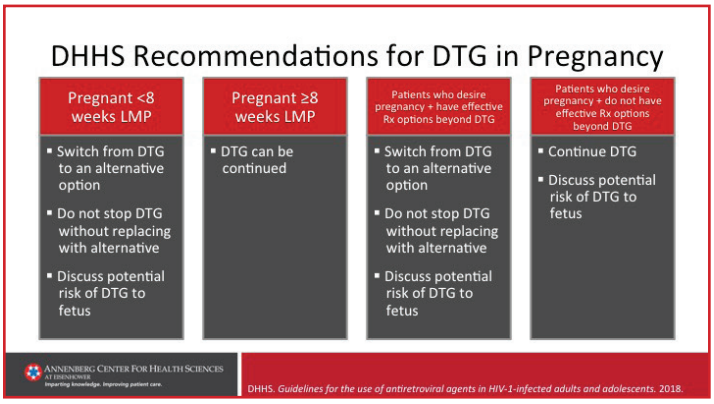


They've now projected that if there's no more cases, then the upper bound of the confidence might overlap with efavirenz. Even if there is 1 more case it might overlap with other ART. This data is that the data on dolutegravir and neural tube defects are out there. It's a small number of cases—4. We don't know about causality yet and I think we really need to await further data before making any definitive conclusions.

I do want to mention in prospective study, looking at dolutegravir vs efavirenz in women starting therapy in late pregnancy. Remember, integrase inhibitors lower viral load much faster than any other drug class and that's shown in this figure. The women who started dolutegravir-based regimens late in pregnancy had a faster time to achieving viral loads shown in this



Kaplan–Meier curves than those starting efavirenz. Indeed, at a postpartum visit they were significantly more likely to have viral load less than 50, this might translate into a benefit in rapidly gaining virologic control and diminishing the risk of transmission to the newborn. This is, of course, late in pregnancy—28-36 weeks is way beyond the time when the neural tube has been formed so the concerns about the safety of dolutegravir in pregnancy here do not apply.



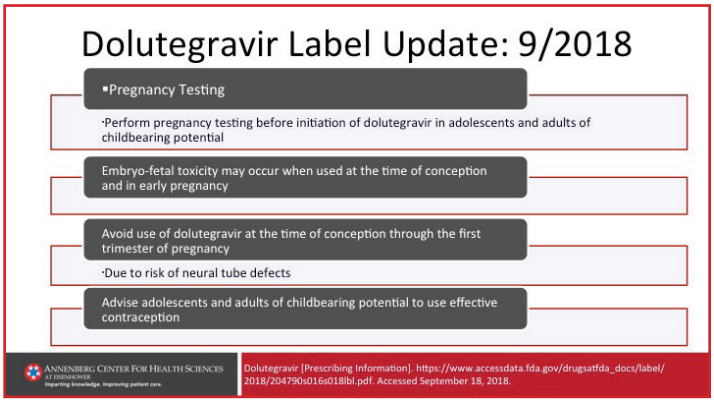
What are the DHHS recommendations for use of dolutegravir in pregnancy? Let's take each of these 4 columns. If a woman is pregnant at less than 8 weeks after her last menstrual period, we recommend switching from dolutegravir to an alternative option but we would not recommend stopping dolutegravir or choosing an alternative. The alternatives, choosing the options really are on that slide, a couple of slides ago, of the recommended regimens. If women are at greater than 8 weeks after their last menstrual period, dolutegravir can be continued because remember the neural tube has already been formed and there is now plenty of data showing that dolutegravir is safe if started during pregnancy.

What about women who say they would like to become pregnant and have effective treatment options aside from dolutegravir? I think that one should discuss the options with the patient and switch from dolutegravir to an alternate option if a woman expresses concern about the safety issues with dolutegravir. I would not mandate this. I would sort of discuss the pros and cons and the limitations of the data as best as we can.

How about women who desire pregnancy and do not have effective options except for dolutegravir? The benefits of continuing a dolutegravir-based regimen greatly exceed the risks and so that should be continued. All in all, I think the message that we keep getting over and over from these particular studies and presentations is that the women really have a right to know the risks and benefits and have a right to also make decisions about their own treatment. Dolutegravir as I've [alluded] to was one of our best treatments for HIV today. If you're doing trade-offs between the benefit for the mom and the potential risk to the newborn, often it may actually fall in favor of the benefit to the mom since the risk to the newborn appears to be very, very small.

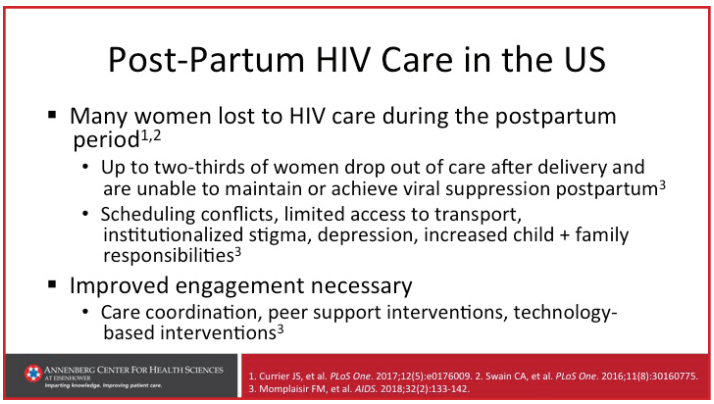
DTG Label Update

On the label for dolutegravir it states the following, this was updated in September of 2018, "perform pregnancy testing before starting dolutegravir in adolescents and adults of childbearing potential." It mentions this embryo fetal toxicity of neural tube defects when used at the time of conception. It does advise against using dolutegravir at the time of conception through the first trimester due to this potential risk of neural tube defects. And then in general, it makes sense to advise adolescents and adults of childbearing potential to use effective contraception while they're receiving a dolutegravir- based regimen.



Post-Partum Care

What happens after delivery? I am going to move away from any specific HIV therapy and then discuss this extremely important issue and that is that many women who are cared for very fastidiously and very closely during pregnancy are then unfortunately lost to HIV care during the postpartum period. In some studies it's been as many as 2/3 of the women, and all kinds of reasons have been cited for this including scheduling conflicts, limited access to transportation, some of the stigma associated with HIV, postpartum depression, more child and family responsibilities. By definition, a woman who's just had a baby has more child and family responsibilities. So we really need to improve our



engagement of these women after they deliver and it really is the time to bring out our best care coordination and peer support interventions, and anything we can to make things easier for women to stay in care after they've had . . . women with HIV to stay in care after they've had their baby.

Summary

Early ART initiation in pregnancy is an effective strategy for achieving viral load suppression and therefore reducing mother-to-child transmission. We would like to recommend avoiding dolutegravir if possible at the time of conception through the first trimester of pregnancy due to the possible increased risk of neural tube defects in the baby. And then after delivery it is critically important for us to improve engagement with our women with HIV who are pregnant, who were pregnant, and to make sure that they have adequate and easy-to-achieve HIV follow-up. So, with that, I would like to thank you for your attention. I hope that this review of HIV treatment in women was educational and entertaining.

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