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## What's New in HIV Treatment? New Medications and Guidelines Update

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WHAT'S NEW IN HIV TREATMENT?  
NEW MEDICATIONS AND GUIDELINES UPDATES

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This session seeks to intensively examine the newest antiretroviral agents used in the management of HIV and AIDS. These drugs are discussed within the context of the latest treatment recommendations, including pertinent counseling points for patients. In addition, the session seeks to broadly discuss the epidemiology and common modes of transmission for the HIV virus and to evaluate various mechanisms for infection control. Pertinent applications specific to the state of Florida are incorporated into this discussion, including the current applicable laws as related to the testing and confidentiality of HIV/AIDS testing and the role of pregnancy in the statutes.

### Learning Objectives

#### Pharmacist

- 1 Identify new antiretroviral agents and their role in the management of HIV/AIDS
- 2 Recognize pertinent treatment updates to the adult and adolescent antiretroviral therapy guidelines
- 3 Identify first-line antiretroviral recommendations for patients who are antiretroviral-naive
- 4 Provide pertinent counseling points to a patient receiving new antiretroviral agents as it relates to dosing, administration, and potential side effects and drug interactions

- 5 Identify the epidemiology and modes of transmission for the HIV virus and mechanisms for infection control
- 6 Recognize common secondary infections associated with HIV/AIDS
- 7 Identify current applicable laws in the state of Florida as related to the testing and confidentiality of HIV/AIDS testing and the role of pregnancy in the statutes.

#### Pharmacy Technician

- 1 Identify new antiretroviral agents and their role in the management of HIV/AIDS
- 2 Recognize first-line antiretroviral recommendations for patients who are antiretroviral-naive
- 3 Recognize dosing, administration, and potential side effects and drug interactions with new HIV/AIDS therapies
- 4 Identify pertinent treatment updates to the adult and adolescent antiretroviral therapy guidelines
- 5 Identify the epidemiology and modes of transmission for the HIV virus and mechanisms for infection control

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## Target Audience

Pharmacists, Pharmacy Technicians, Nurses

## Universal Activity Number

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## Introduction

Few could have imagined the extent and reach of AIDS when it was first recognized as a disease in 1981. Practitioners and researchers alike were puzzled by the increasing number of patients presenting with unusual opportunistic infections and rare malignancies. Eventually, it would be determined that a retrovirus (human immunodeficiency virus type 1 (HIV-1)) was responsible for the sharp acceleration of such clinical symptoms. This discovery would forever change the face of medicine for decades to follow. To date, more than 60 million individuals have been infected with the HIV virus.<sup>10</sup> Today, the acronyms 'HIV' and 'AIDS' are much too familiar acronyms among most social circles. The mere mention of the acronyms, for many, conjures jaded perceptions that may or may not be based upon factual evidence. As a precursor, then, to any discussion on the topic, a fundamental understanding of the epidemiology and modes of transmission of the HIV virus is paramount.

AIDS is primarily considered to be a sexually transmitted disease. Statistics show that approximately 80% of adults become infected with HIV following exposure at mucosal surfaces.<sup>10</sup> However, HIV is not exclusively transmitted sexually. Transmission may occur anytime infected blood or other potentially infectious material (OPIM) enters the body of a person who is not infected. In addition to sexual transmission, infection may also occur via:<sup>11</sup>

- Birth (neonatal exposure)
- Sharing of needles or syringes
- Direct contact with the blood or open sores of an infected person
- Needle sticks or other sharp related injuries

The latter mechanism of transmission (needle sticks and sharps related injuries) was recognized early on as being a potential hazard for healthcare workers and for patients, who may face the potential of transmission from an infected healthcare worker. This occupational hazard led to OSHA's introduction of the Bloodborne Pathogen Standard in 1991. The standard applies to all workers who face exposure to bloodborne pathogens during their regular work duties. The introduction of the Bloodborne Pathogen Standard required that employers actively seek new ways to isolate or remove the BBP hazard from the workplace, through the use of items such as:<sup>12</sup>

- Sharps disposal containers
- Self-sheathing needles
- Safer medical devices
- Needless systems
- Fume Hoods
- Biosafety Cabinets

The concept of 'universal precautions' was adopted as part of the code of federal regulations. The 'universal precautions' provision simply states that *"all human blood and certain human body fluids are treated as if known to be infectious for HIV, HBV, and other bloodborne pathogens."* [29 CFR 1910.1030(b)] Unless visibly contaminated with blood, OSHA excludes urine, feces, nasal secretions, vomit, perspiration, sputum and saliva (except during dental procedures) from its definition of 'other potentially infectious materials for this purpose.<sup>13</sup>

If a healthcare worker becomes exposed to blood (or other potentially infectious material), puncture sites from needlesticks or cuts should be washed immediately with soap and water. Flush any splashes to the nose, mouth, or skin with water and irrigate the eyes using an appropriate eye wash station. The exposed individual should seek immediate medical attention. The CDC recommends prophylaxis for ALL occupational exposures to HIV. All exposure incidents should be reported to the facility's OSHA Officer. It may be helpful to call the post-exposure prophylaxis hotline at 1-888-448-4911 for advisement when an exposure occurs.<sup>13</sup>

In addition to the more traditional preventative measures for HIV infection, pre-exposure prophylaxis (PrEP) has emerged as a way to significantly reduce the transmission of HIV. When taken appropriately, daily PrEP regimens may reduce the risk of getting HIV from sex by more than 90%!<sup>11</sup> Among those who inject drugs, it reduces the risk by more than 70%.<sup>11</sup> PrEP is a powerful tool in reducing transmission and should be included in discussions with patients who may benefit from the use of these regimens.

As part of the PrEP regimen, a combination of two HIV medications is taken daily to help prevent an HIV-negative person from getting HIV from a sexual or injection-drug-using partner who is positive. Federal guidelines recommend that PrEP be considered for people who are HIV-negative and in an ongoing sexual relationship with an HIV-positive partner. This recommendation also includes anyone who:<sup>11</sup>

- isn't in a mutually monogamous relationship with a partner who recently tested HIV-negative, *and*
- is a . . .
  - gay or bisexual man who has had anal sex without using a condom or been diagnosed with an STD in the past 6 months, *or*
  - heterosexual man or woman who does not regularly use condoms during sex with partners of unknown HIV status who are at substantial risk of HIV infection (for example, people who inject drugs or women who have bisexual male partners).

PrEP is also recommended for people who have injected drugs in the past 6 months and have shared needles or been in drug treatment in the past 6 months.<sup>11</sup>

While the focus on this monograph lies within the therapeutic applications of HIV management, the preventative pharmaceuticals used in PrEP regimens overlap with this arena as well. The applications of PrEP will be discussed in detail in a future monograph activity.

In addition to the complex management of the primary infection, those infected with HIV are more prone to opportunistic infections. These infections tend to occur much more frequently and severely in patients with weakened immune systems. As patients become better managed, the incidence of these opportunistic infections tends to decrease. Nonetheless, opportunistic infections add another level of complexity to appropriate HIV management. According to the CDC, these are the most common opportunistic infections associated with HIV infection:<sup>11</sup>

Candidiasis of bronchi, trachea, esophagus, or lungs	A type of fungal infection, often occurring in the mouth and vagina. Candidiasis is only considered an OI when it infects the esophagus or lower respiratory tract, such as the trachea and bronchi, or deeper lung tissue.
Invasive cervical cancer	Starts within the cervix, then spreads to other parts of the body. Regular examinations of the cervix are recommended.

Coccidioidomycosis	Caused by the fungus <i>Coccidioides immitis</i> . It most commonly acquired by inhaling fungal spores, which can lead to a pneumonia.
Cryptococcosis	Caused by infection with the fungus <i>Cryptococcus neoformans</i> . The fungus typically enters the body through the lungs and can cause pneumonia. It can also spread to the brain, causing swelling of the brain. It can infect any part of the body, but (after the brain and lungs) infections of skin, bones, or urinary tract are most common.
Cryptosporidiosis, chronic intestinal (greater than one month's duration)	Caused by the protozoan parasite <i>Cryptosporidium</i> . Symptoms include abdominal cramps and severe, chronic, watery diarrhea.
Cytomegalovirus diseases (particularly retinitis) (CMV)	A virus that can infect multiple parts of the body and cause pneumonia, gastroenteritis, encephalitis of the brain, and sight-threatening retinitis. People with CMV retinitis have difficulty with vision that worsens over time. CMV retinitis is a medical emergency because it can cause blindness if not treated promptly.
Encephalopathy, HIV-related	Can occur as part of an acute or chronic HIV infection.
Herpes simplex (HSV): chronic ulcer(s) (greater than one month's duration); or bronchitis, pneumonitis, or esophagitis	HSV can cause painful viral cold sores in or around the mouth, or painful ulcers on or around the genitals or anus. In people with severely damaged immune systems, HSV can also cause infection of the bronchus, pneumonia, and esophagitis.
Histoplasmosis	<i>Fungal histoplasma</i> most often infects the lungs and produces symptoms that are

	similar to those of influenza or pneumonia. Progressive disseminated histoplasmosis can last a long time and involves organs other than the lungs.
Isosporiasis, chronic intestinal (greater than one month's duration)	Caused by the parasite <i>Isospora belli</i> , which can enter the body through contaminated food or water. Symptoms include diarrhea, fever, headache, abdominal pain, vomiting, and weight loss.
Kaposi's sarcoma (KS)	Cancer caused by a virus called Kaposi's sarcoma herpesvirus (KSHV) or human herpesvirus 8 (HHV-8). KS causes capillaries to grow abnormally and may occur anywhere in the body. KS appears as firm pink or purple spots on the skin that can be raised or flat. KS can be life-threatening when it affects organs inside the body, such as the lungs, lymph nodes, or intestines.
Lymphoma, multiple forms	Cancer of the lymph nodes and other lymphoid tissues in the body.
Tuberculosis (TB)	Caused by the bacteria <i>Mycobacterium tuberculosis</i> . TB can be spread through the air when a person with active TB coughs, sneezes, or speaks. Breathing in the bacteria can lead to infection in the lungs. Symptoms of TB in the lungs include cough, tiredness, weight loss, fever, and night sweats.

*Mycobacterium avium* complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary. Other *Mycobacterium*, disseminated or extrapulmonary.

Caused by infection with different types of mycobacterium: *Mycobacterium avium*, *Mycobacterium intracellulare*, or *Mycobacterium kansasii*. In people with

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severely damaged immune systems, infections with these bacteria may spread throughout the body and can be life-threatening.

*Pneumocystis carinii* pneumonia (PCP)

Caused by a fungus called *Pneumocystis jirovecii*. The first signs of infection are difficulty breathing, high fever, and dry cough.

Pneumonia, recurrent

Lung infection caused by a variety of bacteria, viruses, and fungi. Symptoms include cough (with mucous), fever, chills, and difficulty breathing. One of the most common opportunistic and life-threatening causes of pneumonia is infection with the bacteria *Streptococcus pneumoniae*, also called *Pneumococcus*. There are now effective vaccines that can prevent infection with *Streptococcus pneumoniae* and all persons with HIV infection should be vaccinated.

Progressive multifocal leukoencephalopathy

Caused by the JC (John Cunningham) virus. It is rare and seen almost exclusively in persons whose immune systems have been severely damaged by HIV. Symptoms may include loss of muscle control, paralysis, blindness, speech problems, and an altered mental state. This disease often progresses rapidly and may be fatal.

*Salmonella* septicemia, recurrent

*Salmonella* are a kind of bacteria that typically enter the body through ingestion of contaminated food or water. Infection with salmonella usually causes a self-limited illness with nausea, vomiting, and

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diarrhea. *Salmonella* septicemia is a severe form of infection in which the bacteria circulate through the whole body and exceeds the immune system's ability to control it.

#### Toxoplasmosis of brain

Caused by the parasite *Toxoplasma gondii*, which is carried by warm-blooded animals including cats, rodents, and birds and is excreted by these animals in their feces. Humans can become infected with it by inhaling dust or eating food contaminated with the parasite. *Toxoplasma* can also occur in commercial meats, especially red meats and pork, but rarely poultry. Infection with toxo can occur in the lungs, retina of the eye, heart, pancreas, liver, colon, testes, and brain. Although cats can transmit toxoplasmosis, litter boxes can be changed safely by wearing gloves and washing hands thoroughly with soap and water afterwards. All raw red meats that have not been frozen for at least 24 hours should be cooked through to an internal temperature of at least 150°F.

<https://www.cdc.gov/hiv/basics/livingwithhiv/opportunisticinfections.html>

### **Treatment of HIV/AIDS**

Over the past 30 years, numerous advances to antiretroviral therapy (ART) have emerged with single tablet regimens (STRs) being at the forefront of therapy (Table 1).<sup>1</sup> Although STRs have proven beneficial for patients with improved adherence and reduced toxicities with newer formulations, it is imperative to know what each combination is composed of in order to avoid duplicate therapy, additive toxicities, and drug-drug interactions. Over the past two years, new combination products, brand and generic, have been introduced to the market as well as a new first in its class monoclonal antibody (Table 2).<sup>1</sup> With the ever-evolving field of HIV, it is important for

pharmacists, technicians, and nurses to stay up-to-date on new and novel treatments available for HIV.

Table 1. HIV Medications Approved by the FDA<sup>1</sup>

'85- '89	<b>1987</b> Zidovudine (NRTI)				
'90- '94	<b>1991</b> Didanosine (NRTI)	<b>1992</b> Zalcitabine (NRTI)	<b>1994</b> Stavudine (NRTI)		
'95- '99	<b>1995</b> Lamivudine (NRTI) Saquinavir (PI)	<b>1996</b> Indinavir (PI) Nevirapine (NNRTI) Ritonavir (PI)	<b>1997</b> Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	<b>1998</b> Abacavir (NRTI) Efavirenz (NNRTI)	<b>1999</b> Amprenavir (PI)
'00- '04	<b>2000</b> Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC)	<b>2001</b> Tenofovir DF (NRTI)	<b>2003</b> Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	<b>2004</b> Epzicom (FDC) Truvada (FDC)	
'05- '09	<b>2005</b> Tipranavir (PI)	<b>2006</b> Atripla (FDC) Darunavir (PI)	<b>2007</b> Maraviroc (CA) Raltegravir (INSTI)	<b>2008</b> Etravirine (NNRTI)	
'10- '14	<b>2011</b> Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI)	<b>2012</b> Stribild (FDC)	<b>2013</b> Dolutegravir (INSTI)	<b>2014</b> Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)	
'15- '19	<b>2015</b> Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC)	<b>2016</b> Descovy (FDC) Odefsey (FDC)	<b>2017</b> Juluca (FDC)	<b>2018</b> Biktarvy (FDC) Cimduo (FDC) Delstrigo (FDC) Doravirine (NNRTI) Ibalizumab-uiyk (PAI) Symfi (FDC) Symfi Lo (FDC) Symtuza (FDC) Temixys (FDC)	<b>2019</b> Dovato (FDC)

**Drug Class Abbreviations:**

**CA:** CCR5 Antagonist; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor; **PAI:** Post-Attachment Inhibitor

**Note:** Drugs in gray are no longer available and/or are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines. These drugs may still be used in fixed-dose combination formulations.



Table 2. Newly Approved Antiretroviral Agents for the Treatment of HIV/AIDS

Brand Name	Generic Name	Drug Classes	Indication

Juluca	Dolutegravir 50 mg/rilpivirine 25 mg	Dolutegravir – INSTI	2-drug regimen (2DR) to replace current ART in patients who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen for at least 6 months with no history of treatment failure or resistance to DTG or RPV
		Rilpivirine – NNRTI	
Biktarvy	Bictegravir 50 mg/ Emtricitabine 200 mg/ Tenofovir alafenamide 25 mg	Bictegravir – INSTI	<ul style="list-style-type: none"> <li>• Antiretroviral-naïve</li> <li>• To replace current ART in patients who are virologically suppressed (HIV-1 RNA &lt; 50 copies/mL) on a stable regimen for at least 3 months with no history of treatment failure or resistance to the individual components of Biktarvy</li> </ul>
		Emtricitabine – NRTI	
		Tenofovir alafenamide – NRTI	
Cimduo and Temixys	Lamivudine 300 mg/ Tenofovir disoproxil fumarate 300 mg	Lamivudine – NRTI	<ul style="list-style-type: none"> <li>• Indicated in combination with other antiretroviral agents for HIV-1 in adults and children weighing <math>\geq</math> 35 kg</li> <li>• Generic</li> </ul>
		Tenofovir disoproxil fumarate – NRTI	
Delstrigo	Doravirine (DOR) 100 mg/ Lamivudine 300 mg/ Tenofovir disoproxil fumarate 300 mg	Doravirine – NNRTI	3-drug regimen for HIV-1 infection in adults
		Lamivudine – NRTI	
		Tenofovir disoproxil fumarate – NRTI	
Symfi	Efavirenz 600 mg/ Lamivudine 300 mg/ Tenofovir	Efavirenz – NNRTI	<ul style="list-style-type: none"> <li>• 3-drug regimen for HIV-1 infection in adults and children <math>\geq</math> 40 kg</li> <li>• Generic</li> </ul>
		Lamivudine – NRTI	
		Tenofovir disoproxil fumarate – NRTI	

	disoproxil fumarate 300 mg		
Symfi Lo	Efavirenz 400 mg/ Lamivudine 300 mg/ Tenofovir disoproxil fumarate 300 mg	Refer to Symfi	<ul style="list-style-type: none"> <li>• 3-drug regimen for HIV-1 infection in adults and children <math>\geq</math> 35 kg</li> <li>• Generic</li> </ul>
Symtuza	Darunavir 800 mg/ Cobicistat 150 mg/ Emtricitabine 200 mg/ Tenofovir alafenamide 10 mg	Darunavir – PI	<ul style="list-style-type: none"> <li>• Antiretroviral-naïve</li> <li>• To replace current ART in patients who are virologically suppressed (HIV-1 RNA &lt; 50 copies/mL) on a stable regimen for at least 6 months with no history of treatment failure or resistance to the individual components of darunavir or tenofovir</li> </ul>
		Cobicistat – PK enhancer	
		Emtricitabine – NRTI	
		Tenofovir alafenamide – NRTI	
Trogarzo	Ibalizumab-uiyk	Post-attachment inhibitor	Indicated in combination with other antiretrovirals in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen
Dovato	Dolutegravir 50 mg/ lamivudine 300 mg	Dolutegravir – INSTI	<ul style="list-style-type: none"> <li>• 2DR</li> <li>• Antiretroviral-naïve</li> </ul>
		Lamivudine – NRTI	

Acronyms: INSTI (Integrase strand transfer inhibitor), NRTI (Nucleoside reverse transcriptase inhibitors), NNRTI (Non-nucleoside reverse transcriptase inhibitors), PI (Protease inhibitor), PK enhancer (Pharmacokinetic enhancer)

Patient Case 1

- An otherwise healthy 47 year-old male living with HIV has been virologically suppressed on tenofovir disoproxil fumarate/emtricitabine/rilpivirine for the past 12 months and is interested in reducing the number of ARVs taken.
- The patient is a peer educator and is concerned with his kidney function and bone health.
- The patient does not have any HIV-1 mutations/resistance and has NKDA.
- The patient reports taking omeprazole 20 mg and amlodipine 5 mg daily.
- Can we simplify this patient to once daily dolutegravir/rilpivirine?

### **Dolutegravir/Rilpivirine (JULUCA)**

Late in 2017, the first 2-drug regimen (2DR) single tablet regimen was approved for use in patients living with HIV/AIDS based on meeting non-inferiority from SWORD-1 and SWORD-2 studies.<sup>2</sup> These studies enrolled participants with a HIV-1 RNA (viral load) < 50 copies/mL for at least 6 months without history of virologic failure to either dolutegravir/rilpivirine (n= 513) or to continue their current ART consisting of 3-4 drugs (n= 511). Each group had 95% virologic suppression. Although treatment guidelines still recommend 3-drug regimens, the use of dolutegravir/rilpivirine as a STR may be considered in patients with demonstrated medication adherence. In addition, some prescribers may use this medication in combination with other antiretrovirals for patients with documented resistance.

#### **Patient Case 2**

- A 52 year-old female was newly diagnosed with HIV (NKDA, CD4 count = 629 cells/mm<sup>3</sup>, HIV RNA = 500,238 copies/mL, HIV-1 genotype = no resistance associated mutations). She denies the use of preexposure prophylaxis (PrEP) or any antiretroviral therapy (ART). She is otherwise healthy.
- What initial regimen could be considered for this patient based on national treatment guidelines?

### **Bictegravir/Tenofovir alafenamide/Emtricitabine (BIKTARVY)**

Early in 2018, a new INSTI-based STR was approved and quickly adopted into the national guidelines as a preferred treatment option for most people living with HIV/AIDS (PLWHA). While BIKTARVY is not currently indicated in the pediatric population, recent data presented at the Conference on Retroviruses and Opportunistic Infections (CROI) demonstrated safety and efficacy in patients as young as 6 years of

age and weighing  $\geq 25$  kg.<sup>3</sup> This medication is one of the smallest STR without food requirements and does not require allele testing prior to initiation. Since tenofovir and emtricitabine are components of this STR, hepatitis B infection status should be determined prior to initiation. Although the fixed dose combination of bictegravir/tenofovir alafenamide/emtricitabine demonstrated non-inferiority against boosted PI regimens, dolutegravir plus abacavir/lamivudine, dolutegravir plus tenofovir alafenamide/emtricitabine in treatment-naïve and switch populations, when evaluated for patient-reported symptoms against dolutegravir/abacavir/lamivudine, bictegravir/tenofovir alafenamide/emtricitabine was associated with a lower prevalence of bothersome symptoms (i.e. fatigue, nausea/vomiting, dizziness/lightheadedness, insomnia, nervousness, and depressed mood) in both treatment-naïve and virologically suppressed patients.<sup>4</sup> Based on the safety, tolerability, efficacy, and durability of recently approved INSTIs, the use of a bictegravir-based regimen is likely to be seen frequently in patients receiving ART.

### **Lamivudine/Tenofovir Disoproxil Fumarate (CIMDUO and TEMIXYS)**

2018 found approval of branded generics closely related to the components of TRUVADA (tenofovir disoproxil fumarate/emtricitabine). Like their predecessor, these branded generics should be used in combination with NNRTI, PI, or INSTI to ensure complete ART. The same dosing, administration, side effects, and drug interactions should be considered when using this agent in combination with other ARVs. It is also important to note that this agent has not been approved for the use of preexposure prophylaxis (PrEP).

### **Doravirine (PIFELTRO) and Doravirine/Tenofovir Disoproxil Fumarate/Emtricitabine (DELSTRIGO)**

A new NNRTI, doravirine, was approved in the 3<sup>rd</sup> quarter of 2018 as both a STR and a single agent to be combined with other ARVs. Doravirine has a few notable benefits such as a unique resistance pathway, fewer drug-drug interactions, no food restrictions, and fewer CNS side effects when compared to other NNRTIs. Although non-inferiority was met when evaluating the fixed dose combination of doravirine/lamivudine/tenofovir disoproxil fumarate compared to efavirenz/emtricitabine/tenofovir disoproxil fumarate, doravirine-based therapy was associated with significantly fewer neuropsychiatric events and a more favorable lipid profile.<sup>5</sup> Non-inferiority was also met when tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudine was administered with either doravirine 100 mg daily or darunavir 800 mg plus ritonavir 100 mg daily.<sup>6</sup> The use of

doravirine should not be combined with other NNRTI agents since other NNRTIs are considered CYP3A4 substrates and would reduce the serum concentration of doravirine.

### **Efavirenz/Lamivudine/Tenofovir disoproxil fumarate (SYMFI and SYMFI LO)**

Another branded generic introduced to the market in 2018 is the only available generic STR. The components of SYMFI are closely related to the generic equivalent of ATRIPLA. The only difference being the substitution of lamivudine for emtricitabine. Both lamivudine and emtricitabine are interchangeable since they are both well-tolerated and select for the same M184I/V mutation. The advantage of lamivudine and tenofovir disoproxil fumarate use within this formulation is that both are currently available as generics as well as efavirenz.

One of the more notable aspects of the SYMFI LO approval was the use of a lower dose of efavirenz within the STR. Instead of the traditional 600 mg of efavirenz, this formulation is 400 mg of efavirenz. The ENCORE1 study group demonstrated virologic and safety non-inferiority between efavirenz 400 mg and 600 mg when combined with tenofovir and emtricitabine over a 96-week period when used as first-line ART. The study also noted fewer efavirenz-related adverse events with the use of efavirenz 400 mg.<sup>7</sup> Although this branded generic is available, the national treatment guidelines recommend against the use of efavirenz-based therapies as initial therapy in the United States due to concerns with safety, tolerability, and the development of resistance.

### **Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide (SYM TUZA)**

Another first in 2018, was the approval of a PI-based STR. Although the use of darunavir-based therapy has been reserved for initiation in certain clinical situations (i.e. rapid start after diagnosis, unknown genotype while waiting for results, or intermittent adherence) due to its durable activity against HIV-1, the utility of a STR for patients requiring PI-based therapy offers the simplicity of consolidating ART into a single pill. Similar to most PI-based therapies requiring PK enhancement, numerous drug-drug interactions and contraindications to therapy are present since darunavir is a major substrate of CYP3A4 and a strong inhibitor of CYP3A4 along with cobicistat. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide demonstrated non-inferiority through week 48 in terms of safety and efficacy when compared to darunavir/cobicistat + emtricitabine/tenofovir disoproxil fumarate in treatment-naïve patients as well as in virologically suppressed patients receiving this newly approved drug compared to emtricitabine/tenofovir disoproxil fumarate with either boosted (cobicistat or ritonavir)

darunavir, atazanavir, or lopinavir/ritonavir. This STR is a potent and durable treatment for HIV-1 in patients where medication adherence may not always be ensured.

#### Patient Case 3

- A patient with an extensive history of ART non-adherence developed resistance to NRTIs, NNRTIs, PIs, enfuvirtide, and maraviroc.
- The medical team decides to initiate dolutegravir and ibalizumab-uiyk based on resistance findings and the patient's viral load of 5987 copies/mL.
- Is this an appropriate use of ibalizumab-uiyk?

### **Ibalizumab-uiyk (TROGARZO)**

A new drug class was introduced to the market in 2018. Ibalizumab is a humanized monoclonal antibody that exerts its mechanism of action by working a post-attachment inhibitor (PAI). This agent blocks HIV-1 from infecting CD4 cells by binding to domain 2 of the CD4 cell and interferes with post-attachment steps necessary for entry of HIV into host cells and, thus, prevents viral transmission from cell-cell fusion. It is important to note that this agent should not be used as monotherapy in the management of HIV and will have to be coupled with other antiretroviral agents. Ibalizumab is only available as an intravenous preparation and should not be administered as an IV push or bolus. This agent requires a loading dose that should be run over no less than 30 minutes to assess for any infusion-associated reactions. If no infusion-associated reactions are observed, subsequent infusions may be reduced to no less than 15 minutes. The maintenance dose of ibalizumab should be administered every 14 days. If the maintenance dose of ibalizumab is missed by  $\geq 3$  days, a loading dose should be administered as soon as possible.

Interestingly, the approval of this agent is based on a mere 40 heavily treatment-experienced patients with multidrug resistant HIV-1 with a HIV RNA  $> 1,000$  copies/mL and documented resistance to  $\geq 1$  ARV from each of 3 classes of medications (NRTI, NNRTI, and PI) as measured by resistance testing.<sup>8</sup> In addition, the patients must have been treated with ARVs for  $\geq 6$  months and be failing or had recently failed therapy. This single arm, multicenter study was conducted over 25 weeks and achieved virologic suppression (HIV RNA  $< 50$  copies/mL) in 43% of patients receiving ibalizumab + optimized backbone regimen that was investigator-specific. This medication will not be used in routine clinical practice but is reserved for patients with extensive resistance and treatment failure.

## **Dolutegravir/lamivudine (DOVATO)**

Dolutegravir/lamivudine became the first 2DR approved in April 2019 for use in antiretroviral-naïve populations. This approval was based on 48-week data acquired from the GEMINI 1 and 2 trials comparing once daily dolutegravir (DTG)/lamivudine (3TC) or dolutegravir plus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). Both studies met non-inferiority and demonstrated similar efficacy (HIV-1 RNA < 50 copies/mL) and safety [Gemini-1: DTG/3TC (90%; 320/356) vs. DTG + TDF/FTC (93%; 332/358); Gemini-2: DTG/3TC (93%; 335/360) vs. DTG + TDF/FTC (94%; 337/359). Although, numerically, there were more adverse events in the three-drug regimen group, few participants discontinued therapy in each group due to adverse events.<sup>9</sup> Although not currently in the guidelines, this agent has the potential to offer a regimen with a reduced number of medications that has similar efficacy and tolerability offered by a 3-drug regimen. It will be important to continue to evaluate ongoing safety and efficacy data since triple-drug therapy has been the cornerstone of HIV treatment for more than 20 years.

### **What to Start as Initial Therapy**

Although 2DR have been greatly discussed and debated, treatment guidelines still recommend ART consisting of 2 NRTIs + a 3<sup>rd</sup> active agent (INSTI, NNRTI, or PI with PK enhancer). National treatment guidelines in the United States recommend the third agent (in combination with two NRTIs) to come from the integrase inhibitor class (i.e. bictegravir, dolutegravir) due to its durable virologic efficacy and favorable tolerability and toxicity profiles.

Recommended Initial Regimens for Most People Living with HIV/AIDS	Notes	Counseling Points
1 INSTI + 2 NRTIs		
Bictegravir 50 mg/ Emtricitabine 200 mg/ Tenofovir alafenamide 25 mg (BIKTARVY)		<ul style="list-style-type: none"> <li>• 1 tablet PO once daily</li> <li>• May be taken without regard to food</li> <li>• Supplements containing calcium or iron can be taken together with food</li> <li>• Can be taken under fasting conditions 2 hours before antacids containing Al, Mg or Ca</li> </ul>
Dolutegravir 50 mg/ Lamivudine 300 mg/ Abacavir 600 mg (TRIUMEQ)	HLA-B*5701 negative (must be screened prior to abacavir use)	<ul style="list-style-type: none"> <li>• 1 tablet PO once daily</li> <li>• May be taken without regard to food</li> <li>• Administer TRIUMEQ 2 hours before or 6 hours after taking medications containing polyvalent cations<sup>1</sup>, or buffered medications</li> </ul>
Dolutegravir 50 mg (TIVICAY) + Tenofovir/ Emtricitabine 200 mg (TRUVADA or DESCOVY)	<ul style="list-style-type: none"> <li>• Either tenofovir alafenamide 25 mg or tenofovir disoproxil fumarate 300 mg may be used</li> <li>• Lamivudine 300 mg may be substituted for emtricitabine</li> </ul>	<ul style="list-style-type: none"> <li>• 2 tablets PO once daily</li> <li>• May be taken without regard to food</li> <li>• Administer TIVICAY 2 hours before or 6 hours after taking medications containing polyvalent cations<sup>1</sup>, sucralfate, or buffered medications</li> </ul>

Raltegravir (ISENTRESS) + Tenofovir/Emtricitabine 200 mg (TRUVADA or DESCOVY)	<ul style="list-style-type: none"> <li>• Either raltegravir 400 mg BID or 1200 mg (two 600 mg tablets) once daily</li> <li>• Either tenofovir alafenamide 25 mg or tenofovir disoproxil fumarate 300 mg may be used</li> <li>• Lamivudine 300 mg may be substituted for emtricitabine</li> </ul>	<ul style="list-style-type: none"> <li>• May be taken without regard to food</li> <li>• Co-administration or staggered administration of aluminum or magnesium-containing antacids is not recommended</li> <li>• Co-administration of calcium carbonate antacid with ISENTRESS HD should be avoided</li> </ul>
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1 Polyvalent cations include (Aluminum, Calcium, Iron, Magnesium, and Zinc)

The guidelines also recommend screening for pregnancy prior to ART initiation for women of childbearing potential as preliminary data has raised concerns for increased risk of neural tube defects in infants born to women receiving dolutegravir at time of conception. Therefore, dolutegravir should be avoided and not prescribed for women who are:

- Pregnant and within 12 weeks post-conception
- Childbearing potential and interested in becoming pregnant or not using effective contraception at time of sexual activity

### **Updates to the HIV-1 Guidelines**

Notable medication updates to the guidelines included the addition of bicitgravir/tenofovir alafenamide/emtricitabine (BIKTARVY) as first-line therapy for most people with HIV. The benefits of this STR is the small size, safety, efficacy, lack of food requirements, and durability of the regimen with minimal drug-drug interactions.

Another notable change to the updated set of HIV-1 guidelines was the recommendation on the use of elvitegravir/cobicistat/tenofovir alafenamide or tenofovir disoproxil fumarate/emtricitabine (GENVOYA; STRIBILD). This STR option is now only recommended for initial regimens in *certain clinical situations* and has become the only INSTI-based therapy not recommended as initial therapy for most people with HIV due to its number of drug-drug interactions associated with cobicistat, food requirements, and lower barrier resistance with elvitegravir compared to bicitgravir and dolutegravir. If

a patient is virologically suppressed and tolerating this agent without any issues (i.e. access to food, drug-drug interactions) there is no need to change the patient to another agent unless an issue is identified.

The combination of doravirine + tenofovir alafenamide/emtricitabine or the STR option doravirine/tenofovir disoproxil fumarate/emtricitabine was recently approved and recommended as an initial regimen for HIV-1 in certain clinical situations.

Finally, the use of the 2DR, dolutegravir 50 mg daily + lamivudine 300 mg daily, may be considered when abacavir or tenofovir, either formulation, cannot or should not be used (i.e. resistance, side effects, HLA-B\*5701 positivity with abacavir). With the promise of 2DR, expect to see the approval of more novel combinations.

### **The Regulatory Aspect of HIV/AIDS Diagnosis – Florida Practitioners**

The complex social and therapeutic elements surrounding the detection, treatment and prevention of HIV infection has, in many states, introduced legislation that directly impacts healthcare workers. In the state of Florida, informed consent must be obtained before HIV testing may be performed. Providers may NOT perform an HIV test based on a "general consent" from a patient to draw blood. Health care providers must, by law, convey three pieces of information as part of the process of obtaining informed consent:<sup>14</sup>

- Disclose that the provider is required by law to report the test subject's name to the local county health department if the HIV test results are positive
- Alert the patient that as an alternative, the patient may secure the HIV test at a site that tests anonymously. Locations of such facilities must be made available.
- Relate the extent of the confidentiality rights that adhere to the test results in the provider's patient records.

Minors in Florida are considered adults for the purposes of consenting to HIV testing and treatment. The state specifically forbids telling parents the fact of the minor's consultation, examination or treatment for a sexually transmissible disease, including HIV infection, either directly or indirectly (such as by billing a parent or their insurer for an HIV test without the child's permission). This, of course, has broad implications for permissible discussions with family members at the pharmacy level. Infants and young children, however, are treated as unable to make an informed decision and consent of their parents or legal guardian is required.<sup>14</sup>

Florida law imposes an “opt out” testing in which pregnant women are advised that the health care provider attending to them will conduct an HIV test but they maintain the right of refusal. The Department has two administrative rules that address the testing of pregnant women. Prior to testing, practitioners must notify the woman of the tests that will be conducted and of her right to refuse any and all tests. Permissible exceptions to Florida’s requirement for informed consent for HIV testing includes specifically defined emergencies, therapeutic privilege, sexually transmitted diseases among specific populations, criminal acts, organ and tissue donations, research, abandoned infants, significant exposures, repeat HIV testing, and judicial authority. Testing for HIV without proper consent may lead to disciplinary action in addition to exposing the provider to the possibility of civil suit. <sup>14</sup>

## **Conclusion**

The discussion of HIV and AIDS is an extremely broad topic with many facets, ranging from clinical discussions to social discussions to legal discussions. Healthcare providers should be aware of the sensitivities and perceptions that are inherently assumed when discussing this topic with patients. Becoming familiar with state regulations surrounding testing and consent are simply one piece of a much larger paradigm. In a subsequent monograph, the focus will shift from that of using pharmaceuticals as treatment vehicles to using pharmaceuticals as preventative tools in PrEP regimens. As options become more diverse and extensive for patients with HIV and AIDS, it is more important than ever before that healthcare providers become versed in these options and lead as the patient’s advocate in both treatment and preventative pharmacologic options. We hold more tools than ever before to push the care of our patients in the right direction.

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### What's New in HIV Treatment? New Medications and Guidelines Update

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LESSON EVALUATION

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1a. PHARMACISTS ONLY: Does this lesson meet the learning objectives? (Circle choice).

Identify first-line antiretroviral recommendations for patients who are antiretroviral-naive	YES	NO
Recognize common secondary infections associated with HIV/AIDS	YES	NO
Recognize pertinent treatment updates to the adult and adolescent antiretroviral therapy guidelines	YES	NO
Provide pertinent counseling points to a patient receiving new antiretroviral agents as it relates to dosing, administration, and potential side effects and drug interactions	YES	NO
Identify the epidemiology and modes of transmission for the HIV virus and mechanisms for infection control	YES	NO

Identify current applicable laws in the state of Florida as related to the testing and confidentiality of HIV/AIDS testing and the role of pregnancy in the statutes.

Identify new antiretroviral agents and their role in the management of HIV/AIDS

1b. TECHNICIANS ONLY: Does this lesson meet the learning objectives? (Circle choice).

Identify the epidemiology and modes of transmission for the HIV virus and mechanisms for infection control	YES	NO
Recognize first-line antiretroviral recommendations for patients who are antiretroviral-naïve	YES	NO
Identify new antiretroviral agents and their role in the management of HIV/AIDS	YES	NO
Recognize dosing, administration, and potential side effects and drug interactions with new HIV/AIDS therapies	YES	NO
Identify pertinent treatment updates to the adult and adolescent antiretroviral therapy guidelines	YES	NO

2. Was the program independent & non-commercial? YES NO

3. Relevance of topic

	Low Relevance					Very Relevant	
	1	2	3	4	5	6	7

4. What did you like MOST about this lesson? \_\_\_\_\_

\_\_\_\_\_

5. What did you like LEAST about this lesson? \_\_\_\_\_

\_\_\_\_\_

6. How would you improve this lesson? \_\_\_\_\_

\_\_\_\_\_

**PLEASE MARK THE CORRECT ANSWER(S)**

1. Which of the following antiretroviral regimens is considered first-line for most patients living with HIV/AIDS?
  - a. Bictegravir/Emtricitabine/Tenofovir alafenamide
  - b. Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide
  - c. Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide
  - d. Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate

2. A patient with CXCR4 virus and complete reverse transcriptase (NRTI and NNRTI) and integrase resistance has darunavir/ritonavir as the only active antiretroviral agent. Which of the following antiretrovirals would be most appropriate to initiate?
  - a. Bictegravir
  - b. Doravirine
  - c. Ibalizumab
  - d. Maraviroc
  
3. Which of the following antiretroviral combinations is contraindicated with the use of a proton pump inhibitor?
  - a. Dolutegravir/rilpivirine
  - b. Doravirine/Emtricitabine/Tenofovir disoproxil fumarate
  - c. Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide
  - d. Dolutegravir/lamivudine
  
4. Which of the following is a two-drug, single tablet regimen approved for patients who are antiretroviral-naïve with no underlying resistance?
  - a. Darunavir/cobicistat
  - b. Dolutegravir/lamivudine
  - c. Dolutegravir/rilpivirine
  - d. Emtricitabine/Tenofovir alafenamide
  
5. A patient is initiating dolutegravir/lamivudine/abacavir. Which lab test is essential to obtain prior to initiation?
  - a. Glucose-6-phosphate dehydrogenase enzyme test
  - b. HLA-B\*5701 screen
  - c. Phenotype
  - d. Trofile co-receptor tropism assay
  
6. A 36-year old newly diagnosed male living with HIV (antiretroviral-naïve, NKDA, CD4 = 176 cells/mm<sup>3</sup>, HIV-1 RNA = 123,002 copies/mL) is also starting treatment for active tuberculosis with rifampin, isoniazid, pyrazinamide, and ethambutol. Which of the following antiretroviral regimens would be most appropriate?
  - a. Dolutegravir 50 mg/rilpivirine 25 mg once daily
  - b. Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg once daily
  - c. Dolutegravir 50 mg/lamivudine 300 mg /abacavir 600 mg once daily
  - d. Raltegravir 800 mg twice daily + Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg once daily
  
7. Which of the following agents works extracellularly and is considered a post-attachment inhibitor?
  - a. Dolutegravir
  - b. Doravirine
  - c. Enfuvirtide
  - d. Ibalizumab-uiyk

8. In which of the following clinical scenarios should dolutegravir use be avoided?
- A 26-year old female patient contemplating pregnancy.
  - A 37-year old male with a CD4 count of 27 cells/mm<sup>3</sup>.
  - A 57-year old female with a HIV-1 viral load of 521,362 copies/mL.
  - A 48-year old male currently using injection drugs.
9. When compared with other NNRTIs, which of the following is a benefit of doravirine?
- May be taken without regards to meals.
  - Is associated with fewer drug-drug interactions and CNS side effects.
  - Offers a unique resistance pathway.
  - All of the above are benefits of doravirine.
10. A patient is initiating Bicittegravir/Emtricitabine/Tenofovir alafenamide, which of the following education points is necessary to counsel upon?
- This agent must be taken with food.
  - The use of proton pump inhibitors is contraindicated.
  - Supplements containing calcium or iron can be taken together with food.
  - This agent can be taken under fasting conditions 30 minutes before antacids containing Al, Mg or Ca.
11. The transmission of the HIV virus may occur via:
- Sexual transmission
  - Sharing of needles or syringes
  - Needlesticks in the healthcare setting
  - All of the above are correct
  - None of the above are correct
12. The idea that “all human blood and certain human body fluids are treated as if known to be infectious with bloodborne pathogens” is known as:
- Universal precautions
  - PrEP
  - NNRTI
  - OSHA
13. Patients with compromised immune systems are more likely to acquire secondary infections, including:
- Tuberculosis
  - Pneumonia
  - Diabetes mellitus, type 2
  - Both ‘A’ and ‘B’ are correct
  - All of the above are correct

14. In the state of Florida, mandatory HIV testing is required in all pregnant women to reduce neonatal exposure to infants.
- True
  - False
15. In the state of Florida, healthcare workers must disclose the following information as a part of the process of obtaining informed consent for HIV testing:
- The test subject's name will be reported to the local county's health department if the test result is positive
  - There are no options for anonymous testing in the state of Florida
  - Positive test results become a matter of public record in the state of Florida
  - Both 'A' and 'B' are correct
  - All of the above are correct
16. 'Three drug regimens' for the treatment of HIV-1 include all of the following EXCEPT:
- Symfi®
  - Delstrigo®
  - Dovato®
  - Biktarvy®
17. By knowing to know what each combination product is composed of, pharmacists may help prevent unnecessary \_\_\_\_\_.
- duplicate therapies
  - additive toxicities
  - drug-drug interactions
  - All of the above are correct
18. \_\_\_\_\_ is a monoclonal antibody indicated in combination with other antiretrovirals in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.
- Trogarzo®
  - Biktarvy®
  - Juluca®
  - Symfi®
19. One of the more notable aspects of the SYMFI LO® approval was the use of a lower dose of \_\_\_\_\_.
- Lamivudine
  - Efavirenz
  - Tenofovir
  - Cobicistat

20. Ibalizumab:

- a. is only available as an intravenous preparation
- b. should be administered as a single bolus dose
- c. should be administered every 30 days as a maintenance dose
- d. All of the above are correct