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Updates on Human Immunodeficiency Virus (HIV)

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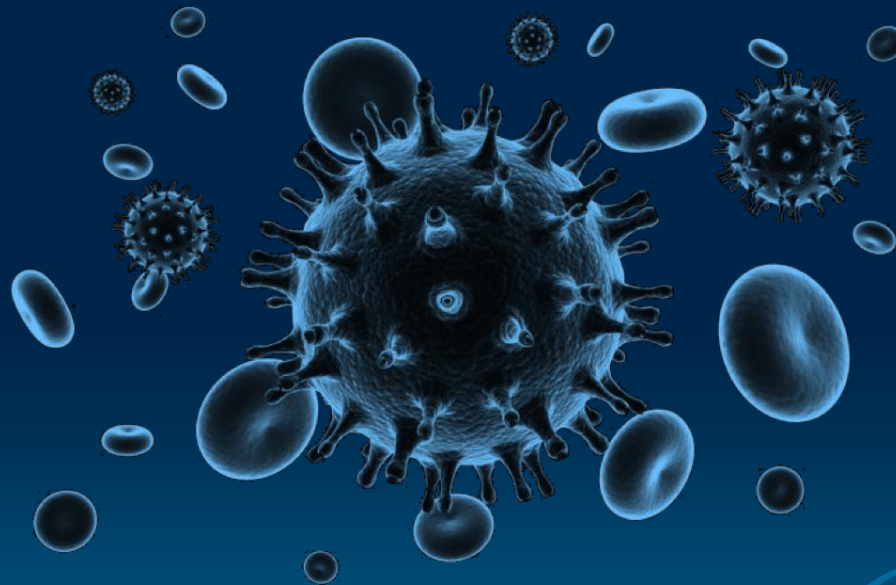
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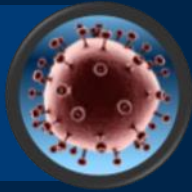
Updates on Human Immunodeficiency Virus (HIV)



Eduardo Martinez, Pharm.D.
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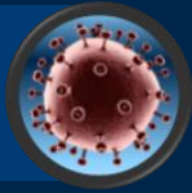
Objectives



- Provide an overview on HIV /AIDS
- Review current antiretroviral treatment strategies
- Recognize recently approved and emerging pipeline agents for the treatment of HIV
- Summarize the most recent guideline updates for the treatment of HIV/AIDS
- Discuss the role of the pharmacist in the treatment of HIV



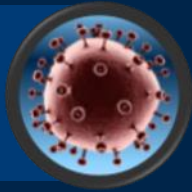
Abbreviations



- **AIDS** – Acquired Immune Deficiency Syndrome
- **ART** – Anti-Retroviral Therapy
- **CD4** – Cluster of Differentiation 4
- **CDC** – Centers for Disease Control and Prevention
- **CCR5** – CC Chemokine Receptor 5
- **GP120** – Glycoprotein 120
- **HIV** – Human Immunodeficiency Virus
- **INSTI** – Integrase Strand Transfer Inhibitor
- **MOA** – Mechanism of Action
- **MSM** – Men who have Sex with Men
- **NNRTI** – Non-Nucleoside Reverse Transcriptase Inhibitor
- **NRTI** – Nucleoside Reverse Transcriptase Inhibitor
- **PEP** – Post-Exposure Prophylaxis
- **PI** – Protease Inhibitor
- **PrEP** – Pre-Exposure Prophylaxis
- **STD** – Sexually Transmitted Disease
- **STR** – Single Tablet Regimen
- **VL** – Viral Load



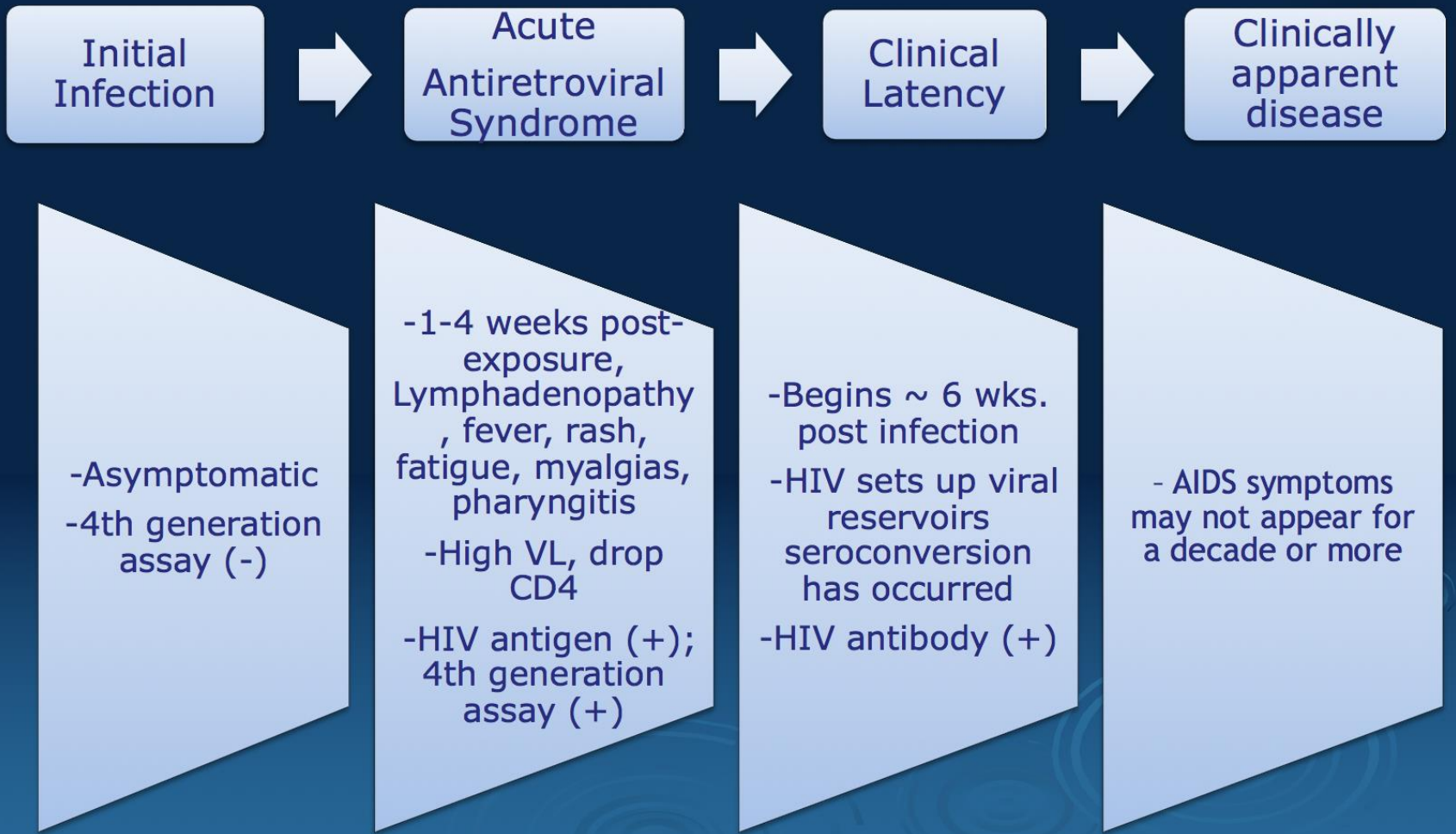
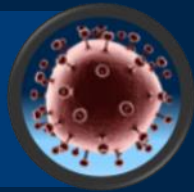
Background



- HIV attacks the body's immune system, specifically the CD4 cells (T cells).
- HIV interferes with the body's ability to fight infection, making a person more vulnerable to other diseases.
- The outlook for people living with HIV has significantly improved over the past two decades.
- Without treatment, HIV infection is likely to develop into AIDS as the immune system gradually wears down.

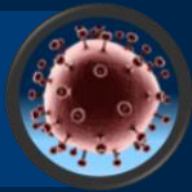


Course of HIV





Risk of Exposure

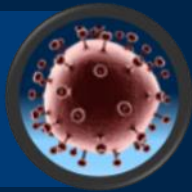


HIV IS **NOT** TRANSMITTED BY...

Insect bites Toilet seats Kissing Sharing cutlery Touching



Transmission



YOU CAN GET HIV VIA...



Sex without
a condom



Passed via
pregnancy



Sharing injecting
equipment

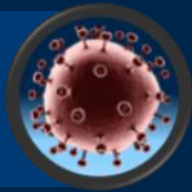


Contaminated blood
transfusions &
organ transplants

Decrease Percent Infection by Transmission Route



Diagnosis



HIV Testing:

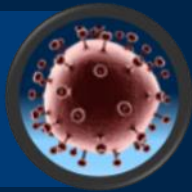
- 4th generation antigen/antibody combination test
 - Highly infectious acute stage
- p24
 - Newly infected individuals

AIDS Diagnosis :

- A positive test for HIV antibodies or antigen **and** one or more of the following:
 - CD4 T cells <200 (or CD4 percentage <14%),
or
 - Any of the 25 "*AIDS defining conditions*"



Diagnosis



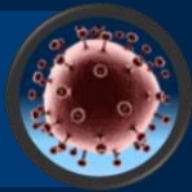
OraQuick HIV Test

- In-vitro diagnostic home-use test
- Pain-free testing with oral fluid
- Detects HIV infection if used 3 months after a risk event





Epidemiology

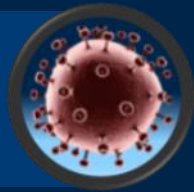


- Approximately 1.1 million people in the U.S. are living with HIV today
- About 15% of them are unaware they are infected
- An estimated 39,000 Americans became newly infected with HIV in 2016
- Gay, bisexual, and other MSM bear the greatest burden by risk group
 - 26,000 of new HIV infections per year



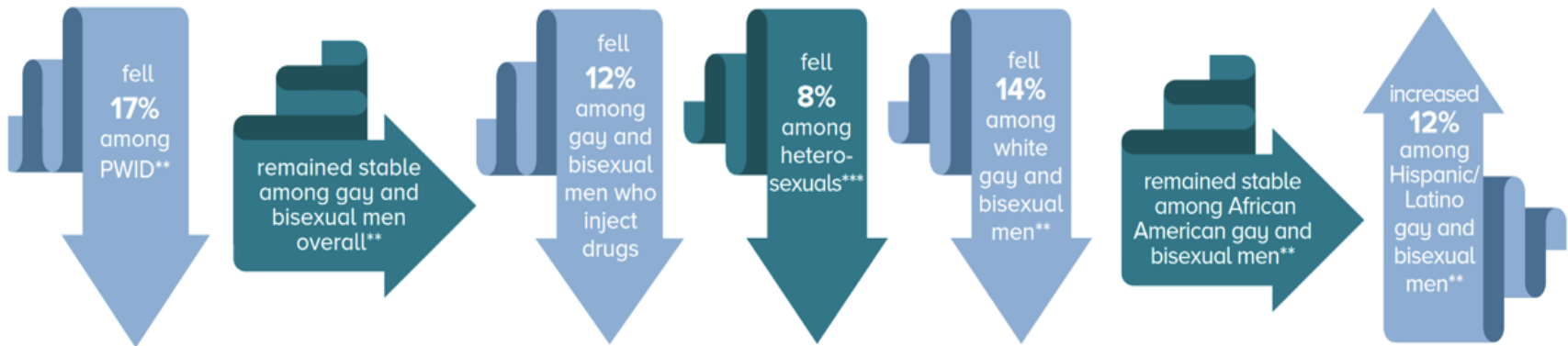


HIV Diagnoses

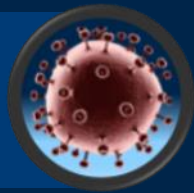


- In 2017, 38,739 people received an HIV diagnosis in the U.S.

HIV Diagnoses in the U.S. and Dependent Areas, 2012–2016

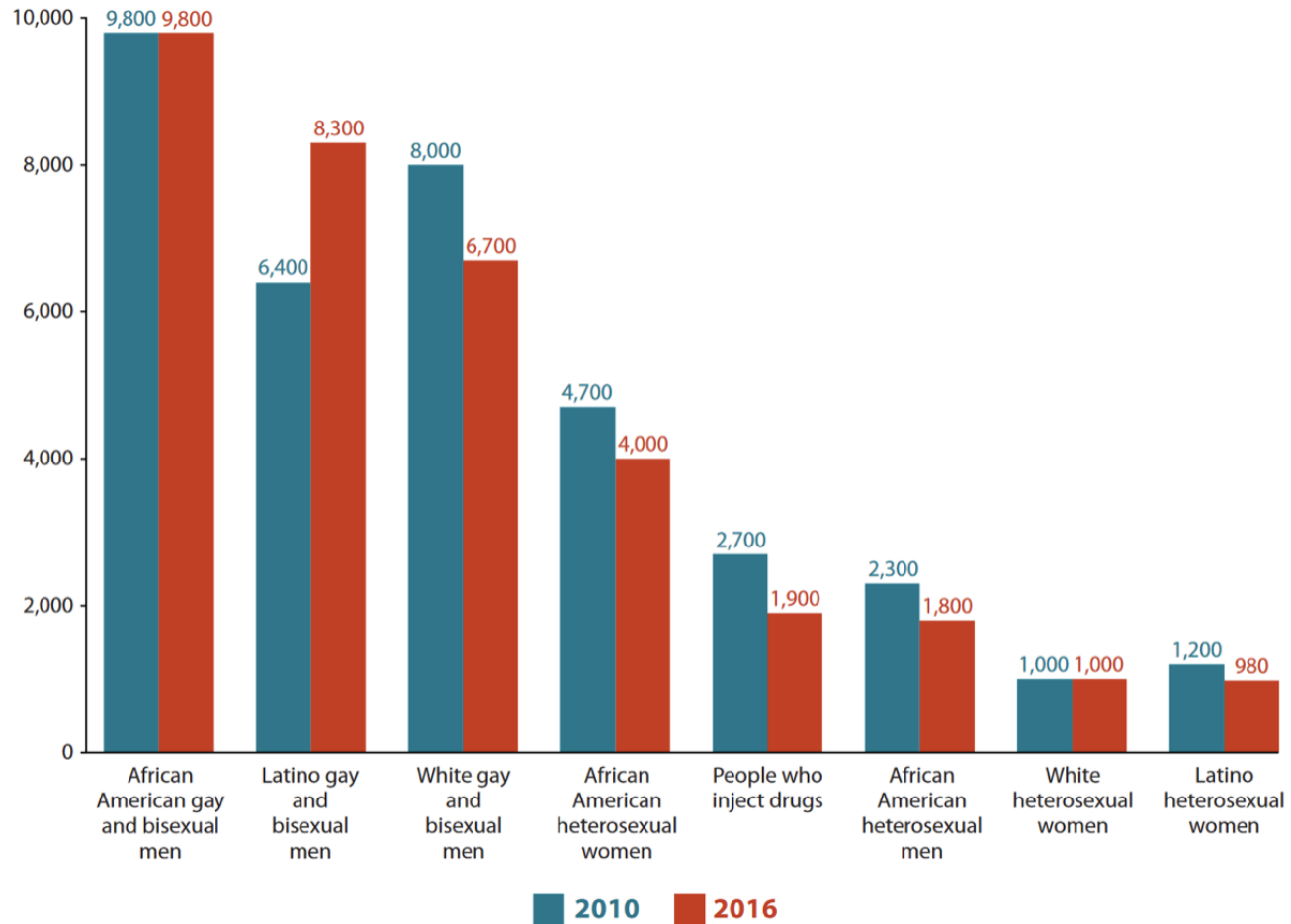


Source: CDC, *HIV in the United States and Dependent Areas*, Jan. 2019.

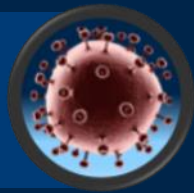


HIV Incidence

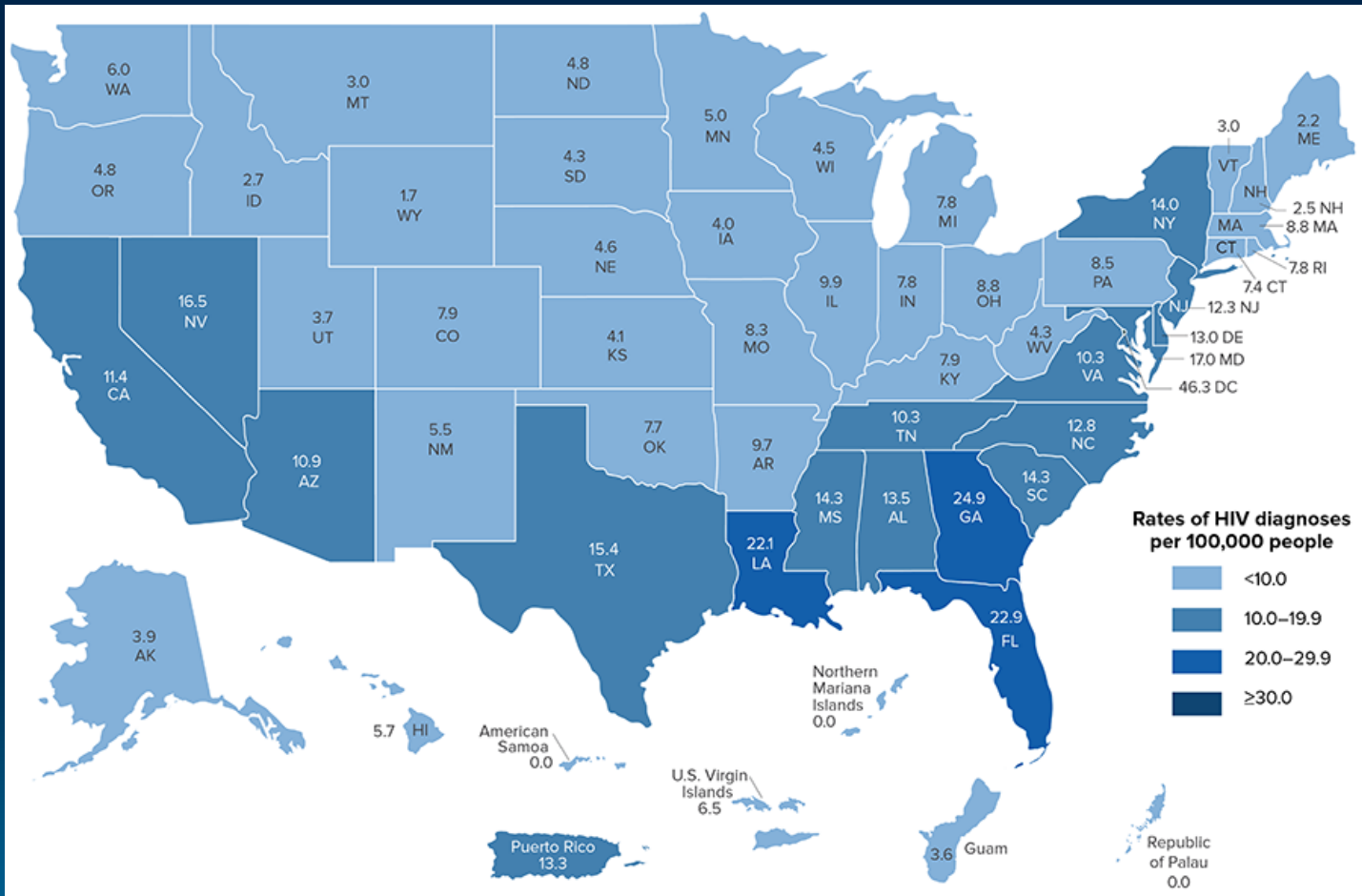
New HIV Infections by Race and Transmission Group, U.S. 2010 vs. 2016:

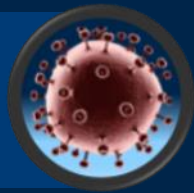


Source: CDC, *HIV Incidence: Estimated Annual Infections in the U.S., 2010-2016*, Feb. 2019.

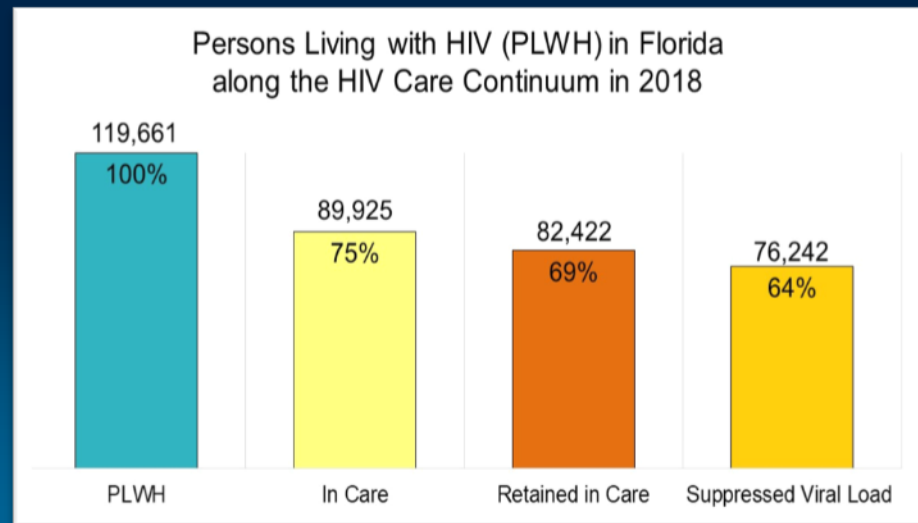
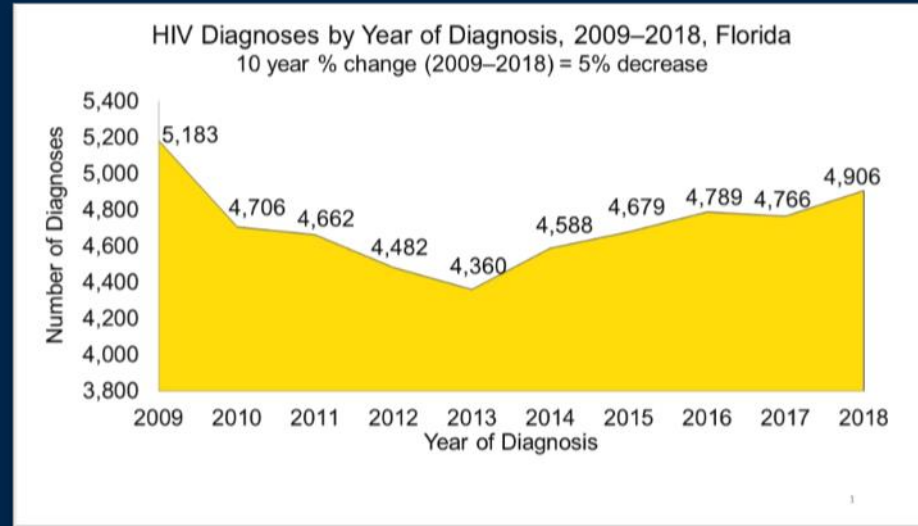


HIV in the U.S.



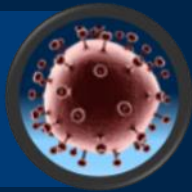


HIV in Florida





Nationwide Initiative



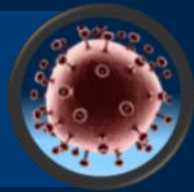
Ending the HIV Epidemic: A Plan for America

Key strategies:

- **Diagnosing** all individuals with HIV as early as possible after infection.
- **Treating** HIV rapidly and effectively after diagnosis to achieve sustained viral suppression.
- **Protecting** individuals at risk for HIV using proven prevention approaches.
- **Responding** rapidly to detect and respond to growing HIV clusters and prevent new infections.



A Plan for America



GOAL:

75%
reduction in new
HIV infections
in 5 years
and at least
90%
reduction
in 10 years.



Diagnose all people with HIV as early as possible after infection.

Treat the infection rapidly and effectively to achieve sustained viral suppression.



Protect people at risk for HIV using potent and proven prevention interventions, including PrEP, a medication that can prevent HIV infections.

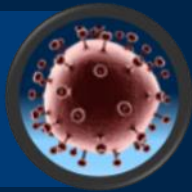
Respond rapidly to detect and respond to growing HIV clusters and prevent new HIV infections.



HIV HealthForce will establish local teams committed to the success of the Initiative in each jurisdiction.



True or False



Antiretroviral therapy is recommended for all HIV positive patients regardless of CD4 count to reduce morbidity, mortality, and transmission.

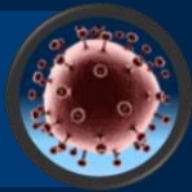


OR





True or False



Antiretroviral therapy is recommended for all HIV positive patients regardless of CD4 count to reduce morbidity, mortality, and transmission.

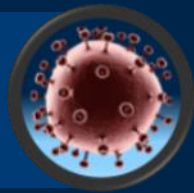


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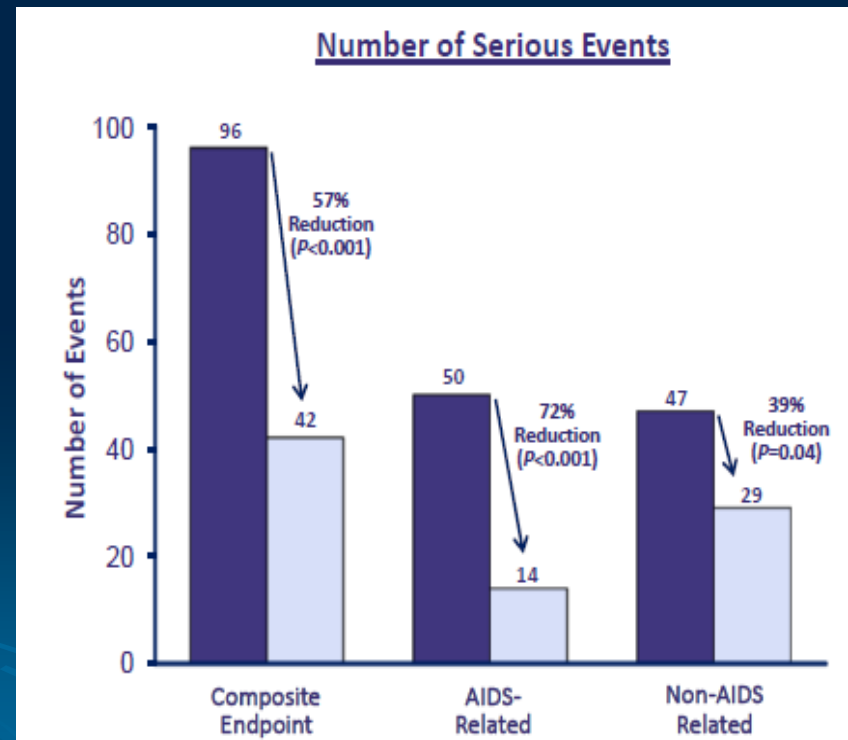
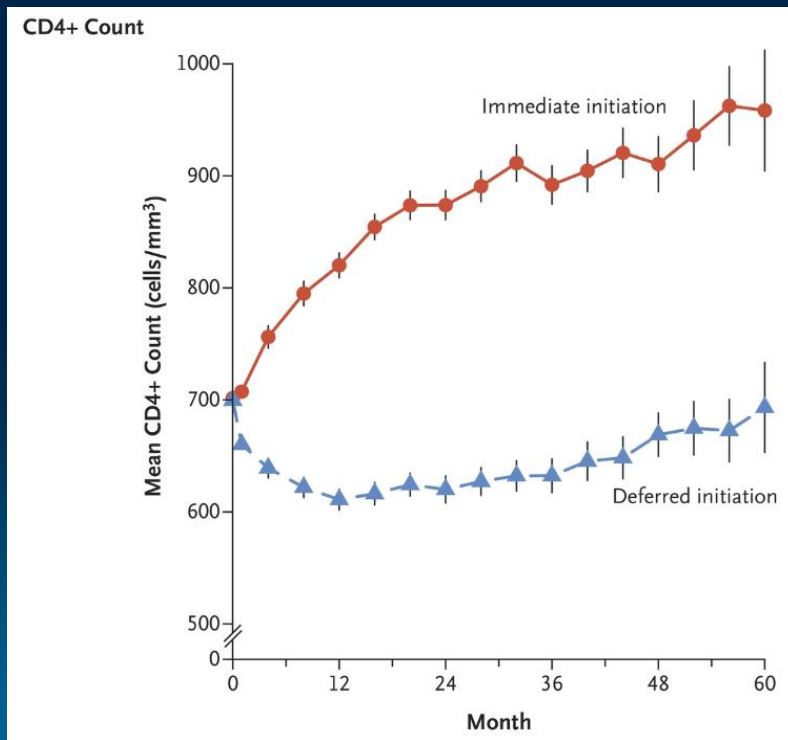




ART

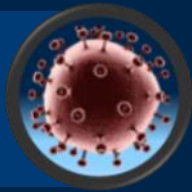


Rapid ART initiation, including starting ART on the same day as HIV diagnosis, can lead to improved clinical outcomes.




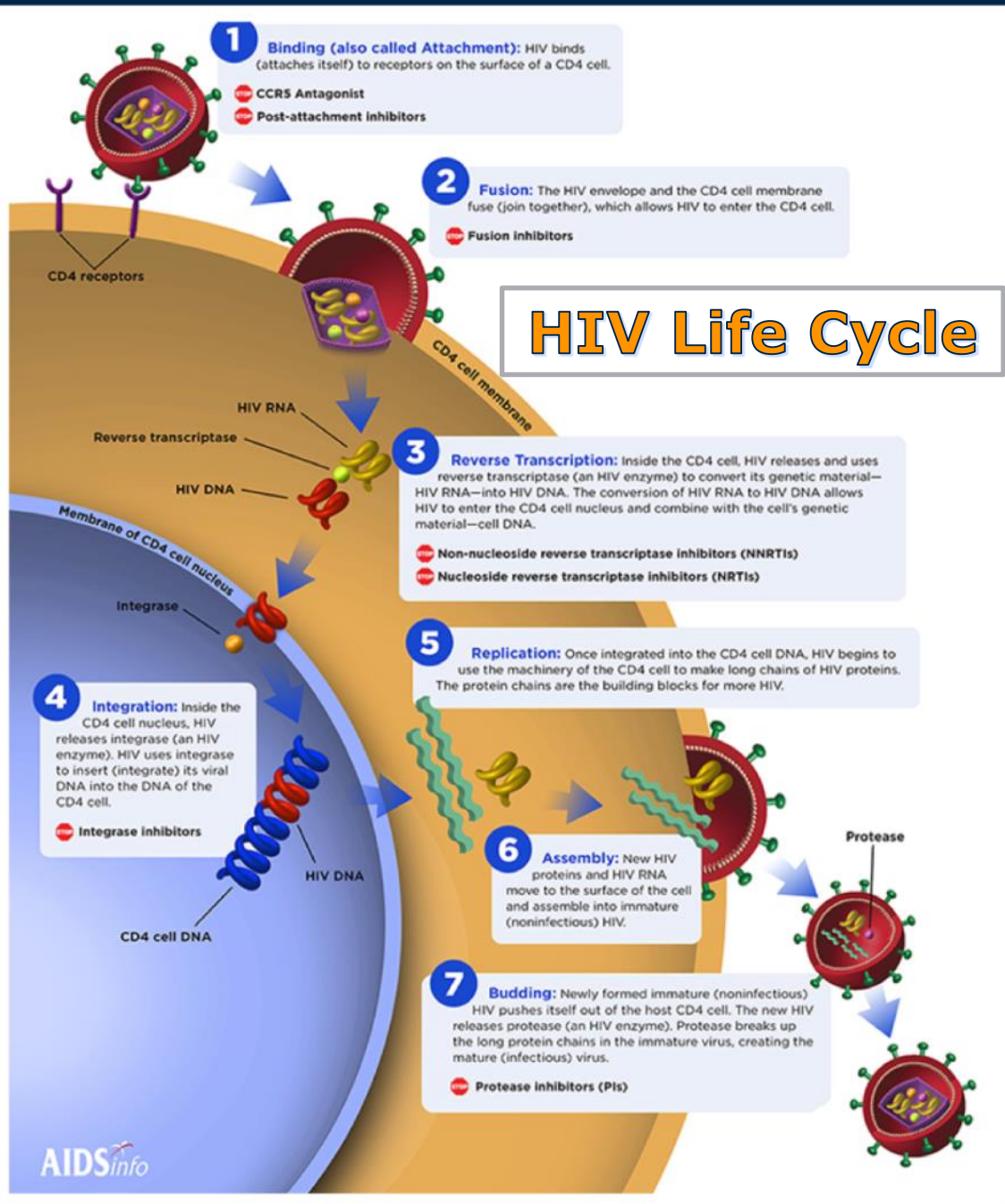


HIV Transmission



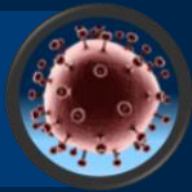
Transmission of HIV Infection in 2016

Percentage of People with HIV	Status of Care	Accounted for x% of New Transmissions
15%	Didn't know they had HIV	38%
23%	Knew they had HIV but weren't in care	43%
11%	In care but not virally suppressed	20%
51%	On medications for HIV and virally suppressed	 0%

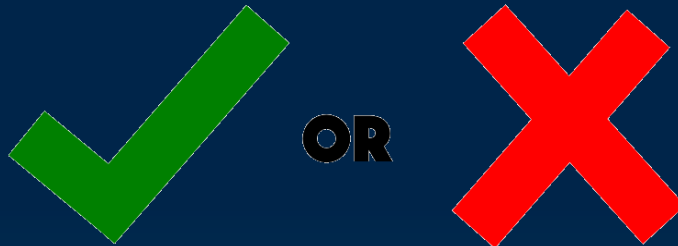




True or False

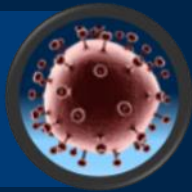


The initiation of a regimen containing two non-nucleoside reverse transcriptase inhibitors (NNRTIs) is common and recommended in HIV patients.

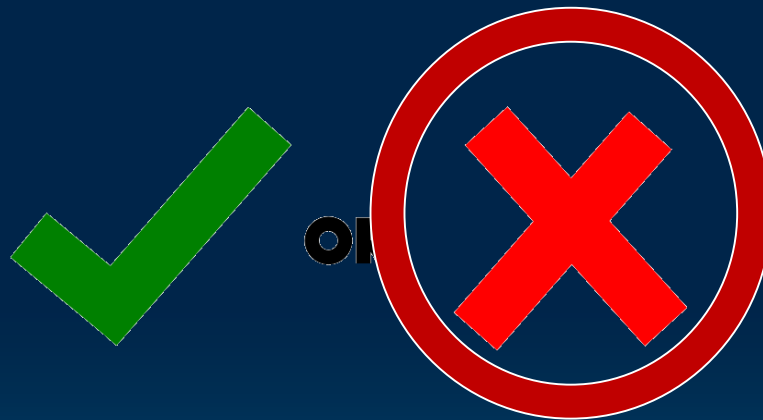




True or False

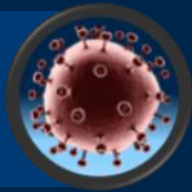


The initiation of a regimen containing two non-nucleoside reverse transcriptase inhibitors (NNRTIs) is common and recommended in HIV patients.





Therapy



2 NRTIS

Abacavir (ABC)/Lamivudine (3TC)- EPZICOM
Tenofovir Disoproxil fumarate (TDF)/Emtricitabine (FTC)- TRUVADA
Tenofovir alafenamide (TAF)/Emtricitabine (FTC)- DESCOVY



NNRTI

Efavirenz (EFV)- SUSTIVA
Rilpivirine (RPV)- EDURANT
Etravirine (ETR)- Intelence
Doravirine (DOR)- Pifeltro

BOOSTED PI

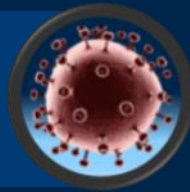
Darunavir with Ritonavir (DRV/r)- PREZISTA/NORVIR
Atazanavir with Ritonavir (ATV/r)- REYATAZ/NORVIR
DRV/COBI- PREZCOBIX
ATV/COBI- EVOTAZ

INSTI

Dolutegravir (DTG)-TIVICAY
Raltegravir (RAL)- ISENTRESS
Elvitegravir(EVG)- VITEKTA
Bictegravir (BIC)



Therapy

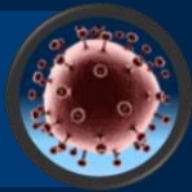


- Integrase inhibitor based regimens are recommended for most patients.

Agent	Advantages	Disadvantages
Dolutegravir	<ul style="list-style-type: none">• Few drug interactions• Single-tablet formulation• Higher barrier to resistance• May be use during pregnancy	<ul style="list-style-type: none">• Co-formulated with abacavir and lamivudine• Risk of neural tube defects
Bictegravir	<ul style="list-style-type: none">• Few drug interactions• Single-tablet formulation• Higher barrier to resistance	<ul style="list-style-type: none">• Lack of data in pregnancy
Raltegravir	<ul style="list-style-type: none">• Few drug interactions• Preferred ARV in pregnancy	<ul style="list-style-type: none">• Not available as a single-tablet formulation• Lower barrier to resistance
Elvitegravir	<ul style="list-style-type: none">• Single-tablet formulation• Can be used for rapid ART start	<ul style="list-style-type: none">• Lower barrier to resistance• Avoid in pregnancy (inadequate drug levels in the 2nd/3rd trimesters)



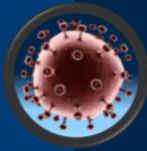
Single Tablet Regimen



- **Biktarvy**- bictegravir/ emtricitabine/TAF (INSTI + 2 NRTIs)
- **Triumeq**- abacavir/dolutegravir/lamivudine (INSTI + 2 NRTIs)
- **Atripla**- efavirenz/tenofovir/TDF (NNRTI + 2 NRTIs)
- **Stribild**- elvitegravir/cobicistat/emtricitabine/TDF (boosted INSTI + 2 NRTIs)
- **Genvoya**- elvitegravir/cobicistat/emtricitabine/TAF (boosted INSTI + 2 NRTIs)
- **Complera**- emtricitabine/ rilpivirine/ TDF (NNRTI + 2 NRTIs)
- **Odefsey**- emtricitabine/ rilpivirine/ TAF (NNRTI + 2 NRTIs)
- **Symfi**- efavirenz/lamivudine/TDF (NNRTI + 2 NRTIs)
- **Symtuza**- darunavir/cobicistat/emtricitabine/ TAF (boosted PI + 2 NRTIs)



Individualized Treatment



Among a sample of HIV patients, incidence of comorbidities increased (2003 to 2013):

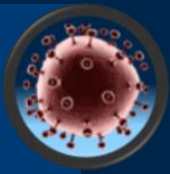
- Hypertension rose from 11.6% to 25%
- Hyperlipidemia rose from 9.5% to 21.9%
- Diabetes rose from 6.4% to 9.4%

Must consider the patient's entire medical history when recommending or prescribing ART.





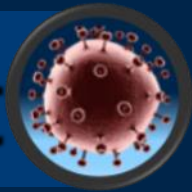
Individualized Treatment



Condition	Consider Avoiding	Rationale
Dementia	Efavirenz	Potential overlap of symptoms
Opioid dependence	Efavirenz	May precipitate withdrawal
Cardiovascular (CV) Risk	Abacavir, lopinavir/ritonavir	Increased CV risk
Dyslipidemia	Boosted protease inhibitors, efavirenz, elvitegravir/cobicistat, tenofovir disoproxil fumarate (TDF)	Increased lipids



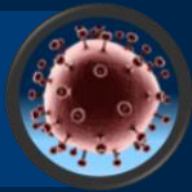
Individualized Treatment



Condition	Consider Avoiding	Rationale
Chronic kidney disease (<u>CrCl \leq 60 mL/min</u>)	Tenofovir disoproxil fumarate (TDF) <u>unless end stage renal disease (ESRD)</u>	Risk of proximal renal tubulopathy
Cirrhotic liver disease	Abacavir, Symfi® (efavirenz/lamivudine/TDF), atazanavir, darunavir, elvitegravir	Not recommended in severe liver disease
Osteoporosis	Tenofovir disoproxil fumarate (TDF)	Risk of decreasing bone mineral density
Psychiatric illness	Efavirenz, rilpivirine	Possible exacerbation of symptoms / suicidal risk



New Agents



Recently approved ART and agents in the pipeline:

Doravirine

Cabotegravir/
rilpivirine

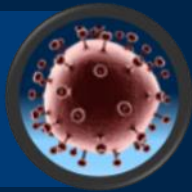
Broadly neutralizing
antibodies

Ibalizumab

Fostemsavir



Doravirine



MOA:

- Non-nucleoside reverse transcriptase inhibitor

Dose:

- 100 mg orally daily

Adverse Effects:

- Fatigue, nausea, headache

Points to consider:

- Concern with neuropsychic and lipid abnormalities
- STR: Delstrigo (TDF + 3TC + DOR)

NNRTI

Efavirenz (EFV)-
SUSTIVA

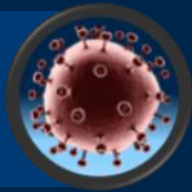
Rilpivirine (RPV)-
EDURANT

Etravirine (ETR)-
Intelence

Doravirine (DOR)-
Pifeltro



Ibalizumab



MOA:

- Binds to CD4 and interferes with post-attachment

Dose:

- 2000 mg intravenous (IV) loading dose
- 800 mg IV every 14 days

Adverse Effects:

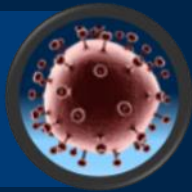
- Infusion reactions, rash, dizziness, diarrhea

Points to consider:

- Monoclonal antibody
- For use in salvage therapy
- Miss dose > 3 days, restart cycle with loading dose



BNAbs



Body Neutralizing Antibodies (*BNAbs*)

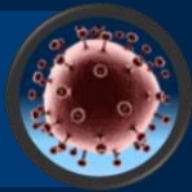
- Passive immunity
- Use alone or a combination
- Instant protection
- Must be regularly “re-dosed” to maintain protection



BNAbs trials could be an important step toward designing an HIV vaccine.



Pipeline Agents



Lerinomab (PRO140)

MOA:

- Humanized monoclonal antibody that blocks entry via CCR5 binding

Likely place in therapy:

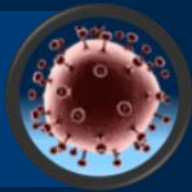
- Salvage, switch after oral

Points to consider:

- Weekly subcutaneous (subQ) injections
- High viral rebound at various doses



Pipeline Agents



UB-421

MOA

- Broadly neutralizing monoclonal antibody targeting CD4 binding

Likely place in therapy:

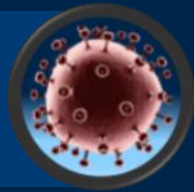
- Treatment failure

Points to consider:

- Weekly or 2 times weekly subQ injections



Pipeline Agents



Fostemsavir

MOA:

- Attachment inhibitor binds to GP 120

Dose:

- 600 mg orally twice daily

Adverse effects:

- Nausea, diarrhea, immune reconstitution inflammatory syndrome (IRIS), fatigue

BRIGHTE Week 96 Update (2019)

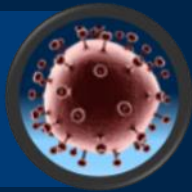
Likely place in therapy:

- Salvage

Randomized cohort (n=272)	Non-randomized cohort (n=99)
≥ 1 fully active ARV agent but cannot construct viable regimen w/remaining agents	No remaining ARV classes and no fully active approved ARV agents
Failing regimen + fostemsavir <i>versus</i> Failing regimen + placebo	Fostemsavir added to optimized background; investigational drugs ok
HIV < 40 copies/mL: 60%	HIV < 40 copies/mL: 37%



Pipeline Agents



Cabotegravir/rilpivirine

MOA:

- Integrase strand transfer inhibitor + non-nucleoside reverse transcriptase inhibitor

Dose:

- 30 mg/25 mg orally daily for 4 weeks, then 400/600 mg intramuscularly (IM) monthly

Adverse effects:

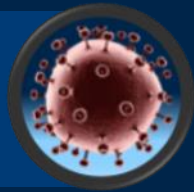
- Nausea, injection site reaction, fatigue, pyrexia

Likely place in therapy:

- Under study for treatment naïve patients and PrEP

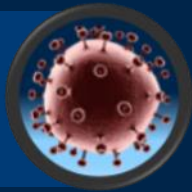


Pipeline Agents



Cabotegravir/rilpivirine

	Population	Criteria	48 week outcomes
FLAIR	<i>Treatment naïve</i> <ul style="list-style-type: none">- HIV RNA > 1000 c/mL- HBSAg (-)- No NNRTI mutations	All started abacavir/lamivudine/dolutegravir first, then randomized to continue (n=283) versus switch to CAB/RPV (n=283)	<u>HIV RNA < 50</u> ABC/3TC/DTG: 93.3% CAB/RPV: 93.6%
ATLAS	<i>Treatment experienced</i> <ul style="list-style-type: none">- PI, NNRTI, or INSTI based regimen with 2 NRTIs	Randomized 1:1 to continue (n=308) versus switch to CAB/RPV (n=308)	<u>HIV RNA > 50</u> CAR: 1.0% CAB/RPV: 1.6%



PrEP vs. PEP

<p>PrEP stands for pre-exposure prophylaxis.</p>	<h2>What's it called?</h2>	<p>PEP stands for post-exposure prophylaxis.</p>
<p>Before HIV exposure. PrEP is taken every day, before possible exposure.</p>	<h2>When is it taken?</h2>	<p>After HIV exposure. In emergency situations, PEP is taken within 72 hours (3 days) after possible exposure.</p>
<p>PrEP is for people who don't have HIV and:</p> <ul style="list-style-type: none">• have a sex partner with HIV• have sex with people whose HIV status is unknown• share injection drug equipment	<h2>Who's it for?</h2>	<p>PEP is for people who don't have HIV but may have been exposed:</p> <ul style="list-style-type: none">• during sex• at work through a needlestick or other injury• by sharing injection drug equipment• during a sexual assault



PrEP: STD in the past 6 months



PrEP vs. PEP



- Pre-Exposure Prophylaxis (PrEP)
 - **Truvada** -TDF /emtricitabine
 - **Descovy** - TAF / emtricitabine

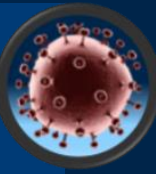


- Post-Exposure Prophylaxis (PEP)
 - **Truvada** -TDF /emtricitabine *plus* **Raltegravir**





Pre-Exposure Prophylaxis



Over 1 million Americans are at substantial risk for HIV,
but only 90,000 PrEP prescriptions were filled in 2015

The number of PrEP users grew by 30% from 2017 to 2018

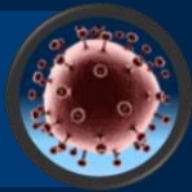
However...

- 94% of all PrEP users are men (16x more PrEP users are men than women)
- 25-34 year olds account for most new infections, but only 60% of PrEP use
- The South accounts for 50% of all new infections, but only 30% of PrEP use

Overcoming these disparities and expanding PrEP use is essential



True or False



The new Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV suggest screening for substance abuse disorders as routine part of clinical care.

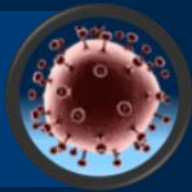


OR





True or False



The new Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV suggest screening for substance abuse disorders as routine part of clinical care.

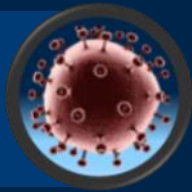


OR





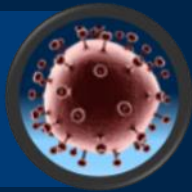
Updates (Dec 18th)



The screenshot shows the AIDSinfo website interface. At the top left is the AIDSinfo logo. To its right is the text "OFFERING INFORMATION ON HIV/AIDS TREATMENT, PREVENTION, AND RESEARCH". A search bar labeled "Search AIDSinfo" is on the top right. A navigation bar below contains links for Home, Guidelines, Understanding HIV/AIDS, Drugs, Clinical Trials, and Research. The "Understanding HIV/AIDS" link is highlighted in green. A white pop-up window is centered on the screen with the title "Updated Adult and Adolescent ARV Guidelines" and a close button (X). The main text in the pop-up reads: "On Wednesday, December 18, 2019, the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents released an updated version of the *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*." Below this, it says: "Feedback on the revised guidelines is welcome. Please email your comments with the subject line 'Comments on the Adult and Adolescent ARV Guidelines' to ContactUs@aidinfo.nih.gov by January 1, 2020." An "OK" button is at the bottom of the pop-up. In the background, the website content is partially visible, including a breadcrumb trail "Home > Guidelines > Ad...", a search bar, and a "What's New in the" section with links like "Panel Roster", "Financial Disclos", "Introduction", "Baseline Evaluat", and "Laboratory Testing".



Updates (Dec 18th)

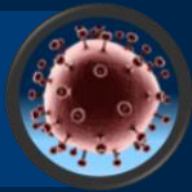


Treatment as prevention (TasP), commonly known as *Undetectable = Untransmittable* or *U = U*.

- Using effective ART to consistently suppress plasma HIV RNA levels to <200 copies/mL.
- Use another form of prevention with sexual partners for at least the first 6 months of treatment and until HIV RNA <200 copies/mL.



Updates (Dec 18th)

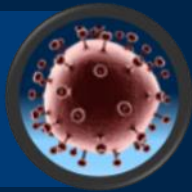


Dolutegravir Recommendations for Individuals of Childbearing Potential

- Prevalence of neural tube defects is lower than initially reported (the rate has been reduced from 0.9% to 0.3%).
- DTG may be used as an alternative ART for individuals who are of childbearing potential and trying to conceive.



Updates (Dec 18th)

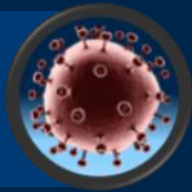


Laboratory Testing for Initial Assessment and Monitoring of People with HIV Receiving Antiretroviral Therapy

- The panel previously recommended monitoring fasting lipid profile and fasting glucose before and after initiation of ART.
- The new recommendation allows for random (non-fasting) tests.

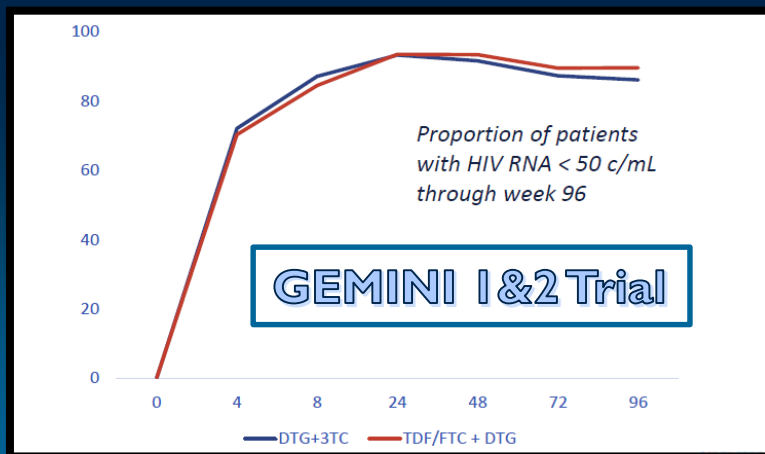


Updates (Dec 18th)



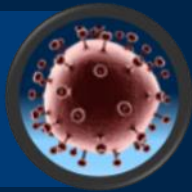
DTG/3TC was added to the list of *Recommended Initial Regimens for Most People with HIV, except for individuals:*

- With pre-treatment HIV RNA $>500,000$ copies/mL
- Who are known to have active hepatitis B virus (HBV) co-infection





Updates (Dec 18th)



Tables

- *Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy*
- *Antiretroviral Therapy-Associated Adverse Events That Can Be Managed with Substitution of Alternative Antiretroviral Agent*

Source: aidsinfo.nih.gov/guidelines.



Pharmacist's Role



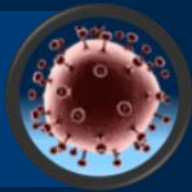
GOAL:

75%
reduction in new
HIV infections
in 5 years
and at least
90%
reduction
in 10 years.

- Empower patients to get tested.
- Identify opportunities to increase compliance.
- Recommend strategies to protect high risk individuals.
- Get involved !!!!



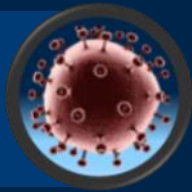
Conclusion



- ❑ Breakthroughs notwithstanding, HIV/AIDS research has not slowed.
- ❑ Despite the progress achieved in the last few decades, HIV incidence remains high throughout the US.
- ❑ Science has provided us the tools to target a goal of reducing new HIV diagnosis by more than 90% in 10 years.
- ❑ Pharmacists are uniquely positioned to contribute to this goal.



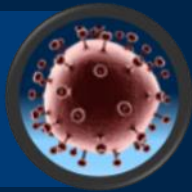
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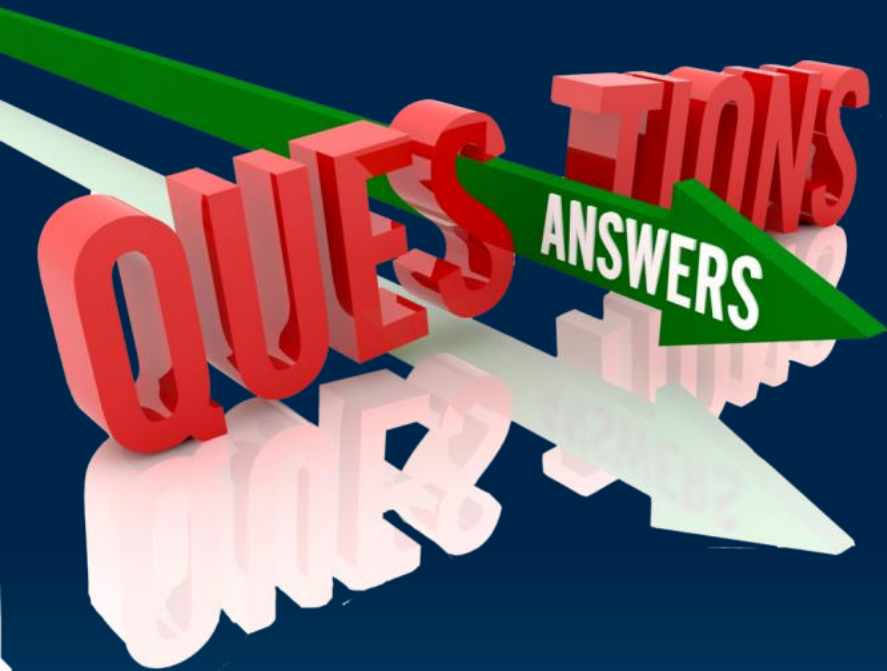
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Updates on HIV



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