HIV Treatment & Prevention

PRESENTED BY:

HOLLY R. MURPHY, PHARMD, AAHIVP, BCPS

Learning Objectives

At the completion of this activity, pharmacists will be able to:

- 1. Recognize major individual and drug class toxicities
- 2. Identify drug-drug interactions and provide and appropriate recommendation to manage
- 3. Recommend an appropriate pharmacotherapy option for PrEP & PEP

At the completion of this activity, pharmacy technicians will be able to:

- 1. List modes of HIV transmission and discuss prevention methods
- 2. Differentiate between treatment for HIV & PrEP
- Identify barriers to patient adherence

Important Abbreviations:

(+) and (-) = positive and negative

ARV = Antiretroviral

MSM = Men who have Sex with Men

OI = Opportunistic Infection

PCP = Pneumocystis jirovecii

Px = Prophylaxis

Tx = Treatment

VL = Viral Load

HIV 101

AN INTRODUCTION TO HIV

Introduction: HIV Virus Types

HIV-1

More virulent and pathogenic

Many subtypes (strains)

Found all over the globe

HIV-2

Less virulent and pathogenic, but still documented to cause AIDS

Also several subtypes

Mostly contained to Africa



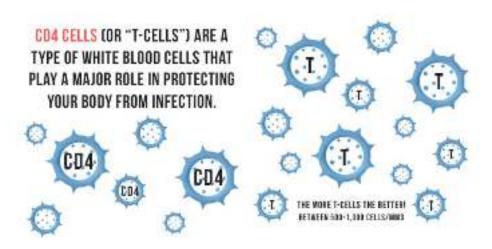
We will primarily focus on HIV-1!

HIV – Human Immunodeficiency Virus

- HIV is an infection that attacks the human immune system
- Specifically targets CD4 cells

CD4 Cells and Viral Load

- CD4 cells are similar to "generals" in an army
 - CD4 cell count should be as high as possible
- Viral Load (VL) is the amount of VL per mL of blood
 - $\,{}^{\circ}\,$ VL should be as low as possible



AIDS – Acquired Immunodeficiency Syndrome

- An advanced form of HIV
- Typically, a patient is diagnosed with AIDS when one of the following criteria are met:
 - CD4 Count of less than 200 cells/mm³
 - History of an AIDS defining illness regardless of CD4 count
- Without treatment, a patient can progress to AIDS within 8 to 10 years of the initial infection

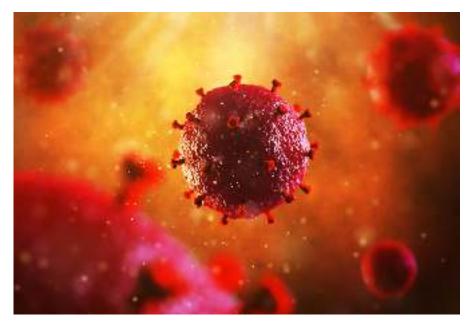


Image source: https://www.cdc.gov/dotw/hiv-aids/index.html

- 1.Attaches to human CD4 cells
 - Uses gp41 and gp120 to attach
- 2. Replicates using reverse transcriptase
 - HIV is an RNA retrovirus
- 3. Viral release or "budding" from CD4 cells as a new virus
- 4.CD4 cell death
- 5.Infection of other CD4 cells

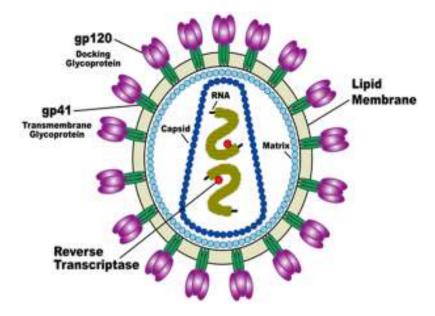


Image source: https://www.pbs.org/wgbh/pages/frontline/aids/virus/virus.html

Attaching to CD4 cells has such an impact on our immune system because:

- 1. CD4 cells activate macrophages
- 2. CD4 cells activate cytotoxic T helper cells (CD8)
- 3. CD4 cells activate B-cells, which make antibodies

When HIV kills CD4 cells, it causes IMMUNE SYSTEM SUPPRESSION

- Additionally, co-infection with other pathogens makes each separate infection worse
- HIV + various lung or brain pathogens
- HIV + TB
- HIV + Hepatitis

HIV 101: HIV Transmission

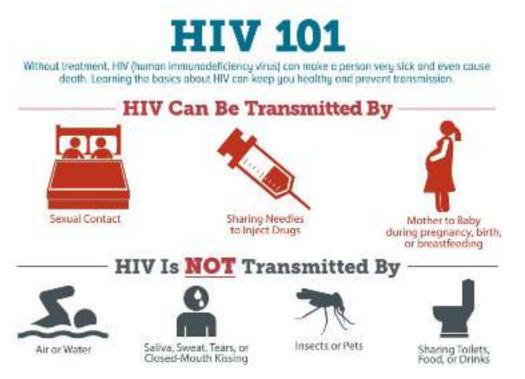


Image source: CDC 2018

HIV 101: HIV Transmission

Transmission occurs through 4 bodily fluids:

- 1. Blood
- 2. Breast Milk
- 3. Semen
- 4. Vaginal Fluid

Clinical Pearls for Pregnancy/Breast Feeding:

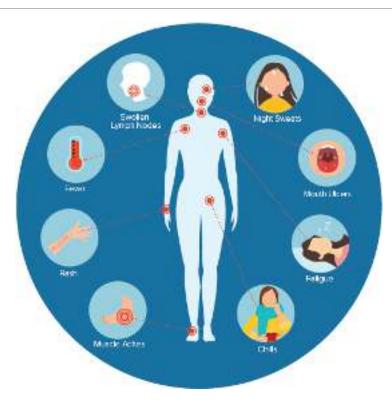
- HIV rarely crosses the placenta
- Baby is at highest risk for infection during vaginal birth
- HIV(+) mothers should NOT breast feed (in the United States)

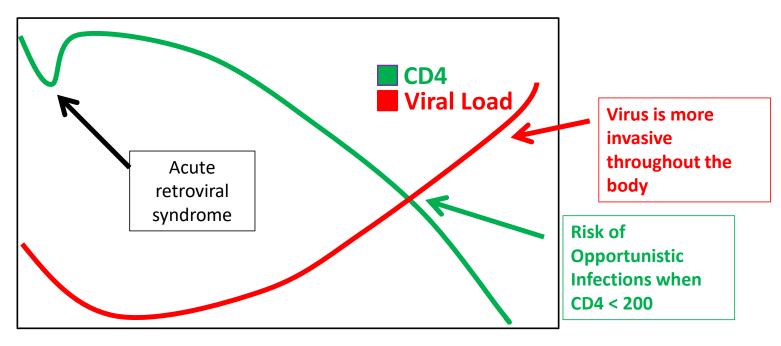
HIV 101: The "Window" Period

An HIV(+) individual will not test (+) on a test IMMEDIATELY after infection:

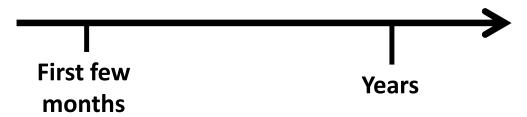
- It takes time to build up reservoirs of virus and produce antibodies
- HIV tests react to HIV antibodies in the blood
- Most people develop detectable antibodies in 2 to 8 weeks
 - 97% of people will develop antibodies within the first 3 months of infection

Signs & Symptoms of Acute HIV Infection





Clinical Course of HIV to AIDS



HIV 101: Prevention

- 1. Practice safe sex or abstinence
 - Definition: A sexual activity that protects a person from infection
 - Includes ALL sex (anal, vaginal, and oral)
 - Use latex or polyurethane condoms only (NO lambskin!)
- 2. Utilize standard blood-borne precautions
- 3.Be educated



Epidemiology across the Globe

HIV IS THE WORLD'S LEADING INFECTIOUS KILLER

Approximately 36.9 million people worldwide were living with HIV/AIDs at the end of 2017

- 1.8 million were children < 15 years old
- Majority (66%) live in Sub-Saharan Africa

Only 75% know they are HIV(+)

21.7 million (59%) were receiving ART

Less than half have an undetectable VL



The vast majority of people living with HV are in law- to middle-income countries, particularly in Sub-Saharan Africa.



Epidemiology in the US

More than 1.1 million people in the US are HIV(+)

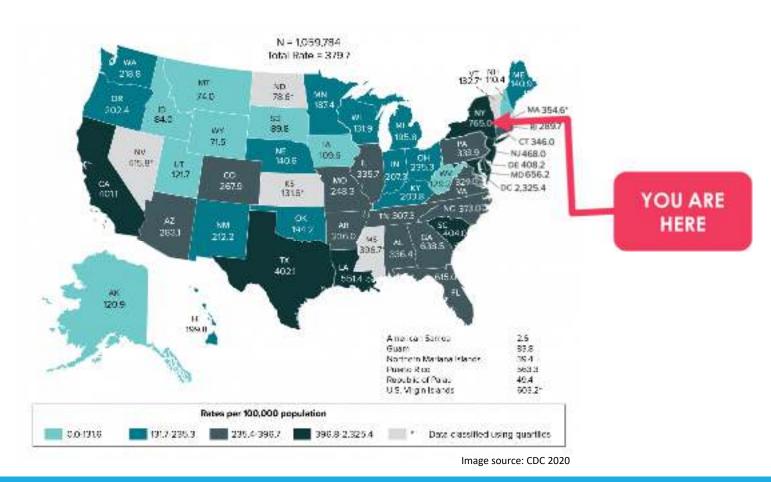
- 1 in 7 (14.2%) are unaware of their infection
- Gay, Bisexual, and other MSM groups are most seriously affected
- Blacks/African Americans face the most severe burden of HIV

HIV incidence has remained stable at about 39,000 new infections every year

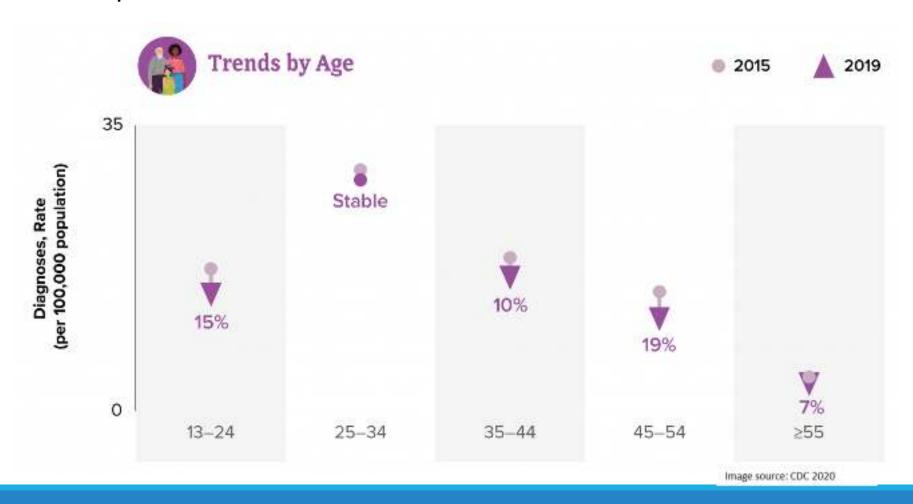
- Some groups bare the burden more than others (IE: MSM groups)
- 2016: 38,700 individuals diagnosed HIV (+)



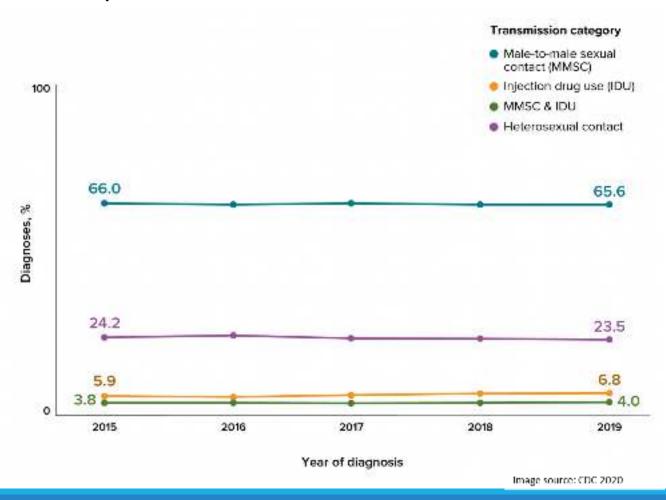
Rates of Adults and Adolescents Living with Diagnosed HIV Infection, Year-end 2019—United States and 6 Dependent Areas



Rates of Diagnoses of HIV Infection among Adults and Adolescents, by Age at Diagnosis, 2015-2019 – United States and 6 Dependent Areas



Percentages of Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2015-2019 – United States and 6 Dependent Areas



Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category, 2019 – United States and 6 Dependent Areas

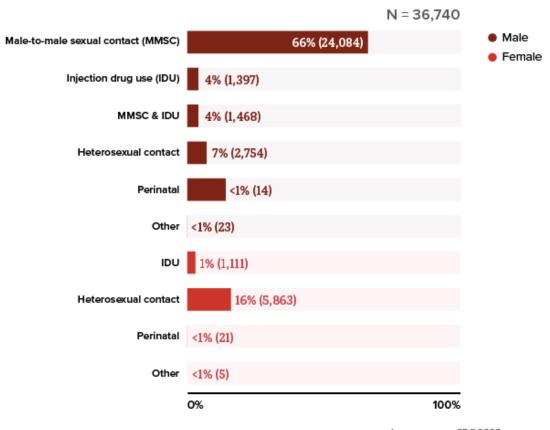


Image source: CDC 2020

Epidemiology in the US

Blacks represent 13.4% of total US population

2017: 40.3% of all HIV infections

Hispanics/Latinos represent 18.5% of total US population

2017: 24.7% of all HIV infections

Total: 65% of All HIV Infections

New HIV Infections

HIV incidence by race/ethnicity, 2019

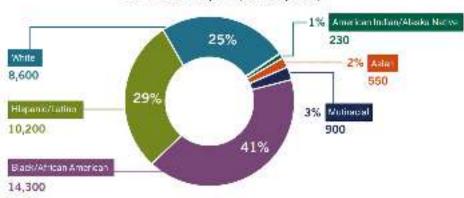


Image source: CDC 2020

Antiretroviral Therapy

GOALS OF TREATMENT & TREATMENT CONSIDERATIONS

Goals of Antiretroviral Therapy

Maximally & durably suppress plasma HIV VL

Reduce HIV-associated morbidity, & prolong survival

Improve QOL

Restore and preserve immune function

So, indirectly the CD4 count will hopefully improve

Prevent HIV transmission

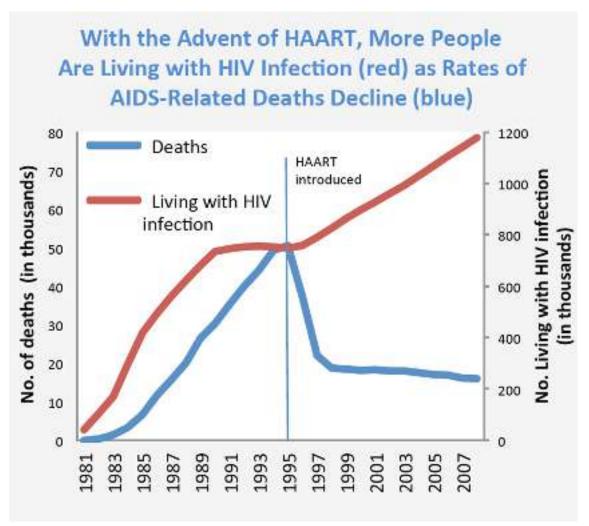


Image source: https://www.publichealth.org/public-awareness/hiv-aids/research-treatment/

Starting Therapy

Recommendation	Strength
AIDS-Defining Illness	A-I
CD4 < 350	A-I
Pregnancy, combination treatment	A-I
HIV-Associated Nephropathy (HIVAN)	A-II
Hepatitis B Virus (HBV) co-infection [when HBV treatment is indicated]	A-III
CD4 350-500	A-II
CD4 > 500	B-III

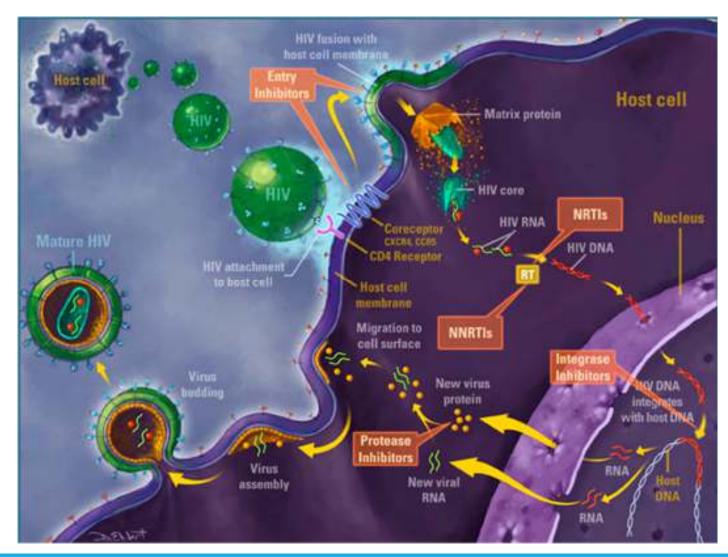
cart is recommended for all HIV (+) individuals.

Strength of this recommendation depends on CD4 count.

When to Initiate HIV Treatment

Patients initiating ARV should be <u>willing and able</u> to commit to lifelong treatment and should <u>understand</u> the benefits and risks of therapy and the <u>importance of adherence</u>.

Patients <u>may choose to postpone therapy</u>, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.



Source: Kalapila, Aley G. and Jeanne M Marrazzo. "Antiretroviral Therapy for Prevention of Human Immunodeficiency Virus Infection." The Medical clinics of North America 100 4 (2016): 927-50. Courtesy of David H. Spach, MD, University of Washington, Harborview Medical Center, Seattle, WA.

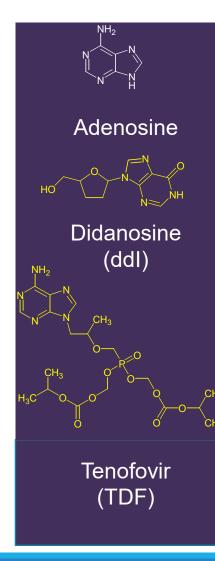
NRTI: Nucleoside Reverse Transcriptase Inhibitors

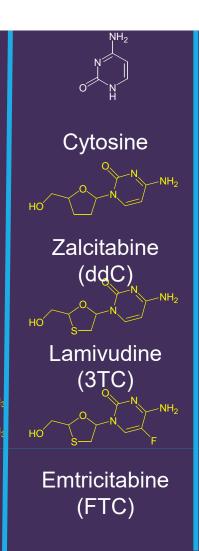
THE "NUKES"

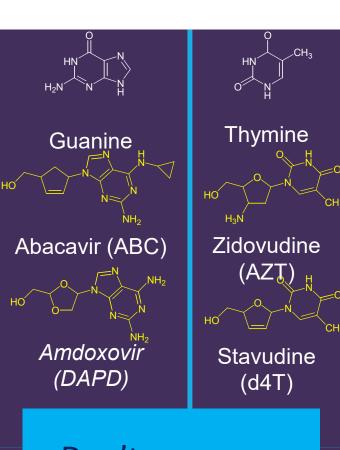
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Mechanism of Action:

• Incorporates into the DNA of the virus by mimicking nucleosides and stopping replication







Don't use more than one from each column!

NRTIs - Class Information

Considered the backbone of ARV therapy

Renal dose adjustments required

All except Abacavir

All have black box warnings

Class Wide: hepatotoxicity (hepatic steatosis) and lactic acidosis (mitochondrial dysfunction)

Short term side effects are mostly GI related

ABC (Abacavir) Ziagen®

Tablet, oral solution

300mg BID or 600mg Q Day

Generally well tolerated

- Cardiovascular issues (controversial)
- HLA-B*5701 (test for hypersensitivity)
- Hypersensitivity is a combination of symptoms
 - Group 1 Fever (not resolved by acetaminophen)
 - Group 2 Rash
 - Group 3 GI symptoms
 - Group 4 General ill feeling, extreme tiredness, achy
 - Group 5 SOB, cough, or sore throat
- Less efficacy noted in pts with higher VL (>100,000 copies), except when used w/ DTG



Patients usually have 2 or more

FTC (Emtricitabine) Emtriva®

Cytosine analog

Capsule, Oral solution

- 200mg daily
- No food restrictions

Well tolerated

- Less side effects (headache, nausea)
- Hyperpigmentation/skin discoloration (rare, ~2%)

Has activity against Hepatitis B, but not FDA approved for treatment



3TC (Lamivudine) Epivir®

Cytosine analog

Tablet, Oral solution

- 150mg BID or 300mg daily
- No food restrictions

Well tolerated

Less side effects (headache, nausea)

Has activity against Hepatitis B



TDF (Tenofovir Disoproxil Fumarate) Viread®

Adenosine analog

Tablet

- 300mg Daily
- No food restrictions, although generally taken with food

Well tolerated

- GI related side effects, especially gas
- Headache
- Bone Demineralization
- Renal insufficiency, Fanconi syndrome

Activity against Hepatitis B

FDA approved 2012 for Pre Exposure Prophylaxis (PrEP) in combination with emtricitabine



TAF (Tenofovir Alafenamide) Vemlidy®

NEWEST FORMULATION OF TENOFOVIR!!!

Pro-drug of Tenofovir

- Concentrates INSIDE cells
- 90% LOWER plasma concentrations

Less ADEs/SEs:

- Less Renal Toxicity
- Less Bone Demineralization
- Less GI Side Effects
- BETTER TOLERABILITY
- Weight gain***

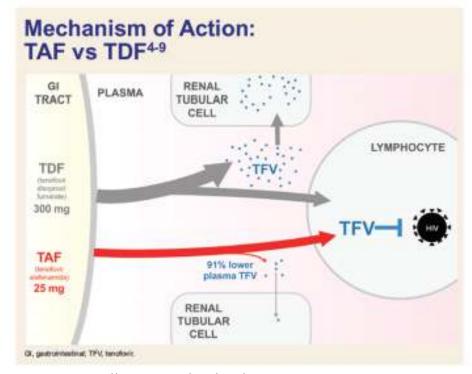


Image Source: https://www.natap.org/2015/EACS/EACS_17.htm

Other NRTIs

Stavudine

Didanosine

Zidovudine







Important Resistance Information

M184V

Complete resistance to: FTC, 3TC

Partial resistance to: ABC

Increased susceptibility to: TDF

K65R

Resistance to: all NRTIs (specifically TDF) except AZT

NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors

THE "NON-NUKES"

Patient Case #1

AL is a 67 y/o WM with history of HIV, HTN.

ARVs include:

• Rilpivirine/Tenofovir AF/Emtricitabine

Presents to clinic with worsening s/s of GERD

You are asked to select which agent to be prescribed.

What recommendation would you make?

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Mechanism of Action:

Binds to reverse transcriptase in a way that inhibits the enzyme's activity directly

NNRTIs - Class Information

Class wide side effects:

- Rash
- Hepatotoxicity
- **Caution: This class is known for cross resistance**
- If one drug develops resistance, it is likely the others will have resistance as well

EFV (efavirenz) Sustiva®

Tablet

- 600mg Daily
- Preferably administered QHS

MUST take on an empty stomach – lipophilic drug

Can cause false positives for THC and benzodiazepines

Adverse Effects:

CNS Effects (Vivid dreams)

Pregnancy Category D



RPV (rilpivirine) Edurant®

Tablet

25mg Daily

MUST take with food

Adverse Effects:

- Insomnia
- Headache



Do not use in patients with a VL >100,000 copies/mL

QTC Prolongation!!



DOR (Doravirine) Pifeltro

100 mg Daily, combo tablet is Delstrigo (DOR/3TC/TDF)

Taken with or without food

Adverse Effects:

- Nausea
- Dizziness
- Headache
- Fatigue
- Diarrhea
- Abdominal pain
- Abnormal dreams

Drug interactions with CYP inducers



Other NNRTIs

Etravirine

Nevirapine

Delavirdine

Important Resistance Information

K103N

Complete resistance to: EFV, NVP

Y181C/I/V

Resistance to: all NNRTIs

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You are asked to select which agent to be prescribed.

What recommendation would you make?

Pls: Protease Inhibitors

Protease Inhibitors (PIs)

Mechanism of Action:

- Binds to the active site of the viral protease enzyme
 - This prevents the processing of viral proteins into their functional conformations
 - Viral particles are still produced but they are not effective at infecting new cells

Pls- Class Information

Most are administered with ritonavir – a "booster" that inhibits CYP3A4

Because of this, lots of drug-drug interactions!!

Class wide side effects:

- Generally GI related
- High incidence of diarrhea
- Metabolic abnormalities

ATV (atazanavir) Reyataz®

300mg capsule with 100mg tablet of ritonavir daily

400mg (requires 2 of the 200mg capsules) daily

MUST take with food

Adverse Effects:

- Hyperbilirubinemia
- Scleral Icterus/Jaundice
- Prolonged QTc
- Nephrolithiasis

Drug interactions with antacids/acid reducing agents (PPIs, H2's)

Use caution with other agents the prolong the QTc (verapamil, etc)





DRV (darunavir) Prezista®

600mg tablet with 100mg tablet of ritonavir BID

800mg tablet with 100mg tablet of ritonavir daily

No food requirements, but generally taken with food

Adverse Effects:

- Rash
- GI issues (diarrhea)
- Headache
- Hepatotoxicity

Caution use in sulfa allergy (drug has a sulfa moiety)



LPV/r (lopinavir with ritonavir) Kaletra ®

400/100mg tablets - 2 tablets BID or 4 tablets daily

No food requirements – generally taken with food

Adverse Effects:

- Nausea
- Vomitting
- DIARRHEA
- QT Prolongation
- Asthenia



^{**}Oral solution contains approx. 42% alcohol***

Other Pls

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Tipranavir

Integrase Inhibitors

THE NEWEST KIDS ON THE BLOCK

Integrase Inhibitors

Mechanism of Action:

• Interfere with the incorporation of reverse-transcribed HIV DNA into the chromosomes of host cells by blocking the enzyme Integrase

Integrase Inhibitors – Class Information

Very well tolerated

Minimal drug-drug interactions

Minimal side effects

RAL (raltegravir) Isentress®

400mg tablet BID

No food requirements

Well tolerated

- Nausea
- Diarrhea
- CPK elevation (monitor CPK levels)

This drug is not metabolized through CYP

Metabolized via glucoronidation instead



EVG (elvitegravir) Vitekta®

85mg or 150mg tablet

EVG/COBI/TDF/FTC (Stribild®/Genvoya®)

Generally taken with food

Well tolerated

Adverse effects related to co-formulated agents:

- Nausea
- Diarrhea
- Proteinuria
- Elevated SCr





DTG (dolutegravir) Tivicay®

50mg tablet daily (BID dosing when used with potent UGT or 3A4 inhibitors)

No food requirements

Well tolerated

- Hypersensitivity
- Insomnia
- Headache

IMPORTANT DRUG DRUG INTERACTIONS:

- Metformin Max of 1000mg per day
- MVI Take with food or separate!
- Tums AVOID USE or separate!



Dolutegravir in Pregnancy

Summer 2018 – Warnings of neural tube defects from a study in Africa

Spring 2019 – Unlikely association, recommendation is not to use in women of childbearing age without proper counseling.

Other Integrase Inhibitors may also be impacted in the future

BIC (Bictegravir)

50mg of bictegravir only found in combination with FTC/TAF

Taken with or without food

Well tolerated

Adverse effects typically related to co-formulated agents:

- Nausea
- Diarrhea
- Renal Impairment, etc.

Similar DDIs to Tivicay – MVI, Metformin



Pharmacokinetic Enhancers

THE "BOOSTERS"

RTV (ritonavir) Norvir ®

MOA: Protease Inhibitor

HOWEVER – used as a boosting agent only due to inhibition of CYP 3A & 2D6

Ritonavir 100mg PO WITH protease inhibitors (generally QD)

Generally taken with food

Side effects include:

Mostly GI related (N/V/D)

DRUG-DRUG INTERACTIONS!!!

Has activity against HIV in high doses (never used)



COBI (cobicistat) Tybost ®

MOA: Inhibits CYP3A & 2D6

- Cobicistat 150 mg daily + atazanavir 300 mg daily
- Cobicistat 150 mg daily + darunavir 800 mg daily
- Also found in Stribild and Genvoya

Generally taken with food

Side effects:

- Mostly GI related (N/V/D)
- Elevates SCr***

DRUG DRUG INTERACTIONS!!!

NO ACTIVITY AGAINST HIV



Other Drugs – Entry Inhibitors

Fusion Inhibitor – Enfuvirtide

CCR5 Inhibitor – Maraviroc

Post-Attachment Inhibitor – Ibalizumab, fostemsavir

*Injectables – Cabotegravir + Rilpivirine

Investigational Agents

Cabotegravir + Rilpivirine



Image Source: Viiv 2022

Combination Products

Atripla® - EFV/TDF/FTC

Prezcobix ® - DRV/COBI

Complera® - RPV/TDF/FTC

Evotaz ® - ATV/COBI

Odefsey ® – RPV/TAF/FTC

Truvada® - TDF/FTC

Triumeg[®] - DTG/ABC/3TC

Descovy ® – TAF/FTC

Stribild® - EVG/COBI/TDF/FTC

Epzicom® - ABC/3TC

Genvoya ® – EVG/COBI/TAF/FTC

Biktarvy ® - BIC/FTC/TAF

Symtuza ® – DRV/COBI/FTC/TAF

Juluca ® - RPV/DTG

Dovato ® – DTG/3TC













Which Agents Do We Use?

REVIEW OF GENOTYPES & PREFERRED FIRST LINE REGIMENS

Assessment Question #2

RW is a 36 y/o HM with history of HTN and anxiety.

Presents to clinic as a newly positive HIV diagnosis x 3 days, referred from PCP office. Ready to start tx after meeting with the prescriber. No resistance panel available, labs from PCP visit WNL and HBV ab +.

You are asked to select which agent to be prescribed.

What recommendation would you make?

Guideline Recommended 1st Regimens for Treatment Naïve Patients

2 NRTI + 1 Integrase Inhibitor

Minimum of 3 drugs! Always 2 or more classes!

However, there are exceptions....

*Tenofovir = both TAF & TDF

Integrase Based Regimens

- Dolutegravir/Abacavir/Lamivudine
- Dolutegravir + Tenofovir/Emtricitabine
- Bictegravir / Tenofovir / Emtricitabine

What is a Genotype?

A report of all ARVs and assessment of susceptibility

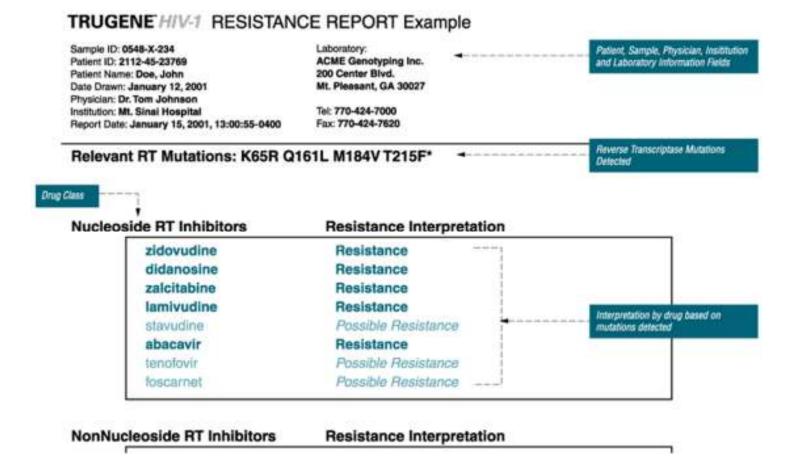
VL must be > 1,000 to order

Order when:

- Initially diagnosed
 - A baseline genotype is recommended
- One month into Tx if VL has not dropped by 2-log
- VL begins to rise in a patient previously controlled on a HAART regimen

Do not order if:

- Non-adherent or lost to care because the genotype is going to look pan-susceptible (false-negative for resistance)
- Genotypes only show resistance of the virus has been put under selective pressure by HAART



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What recommendation would you make?

Special Populations

Assessment Question #3

TJ is a 21 y/o AAF with history of multiple STIs, otherwise healthy.

Presents to clinic requesting STI screening. Expresses interest in PrEP after discussing risks/benefits with the medical team.

HIV ag/ab 4th gen negative, all other labs WNL.

You are asked to select which agent to be prescribed.

What recommendation would you make?

Guideline Recommended Agents During Pregnancy

In general, the same regimens as recommended for treatment of non-pregnant adults should be used in pregnant women unless benefits outweigh risks

NRTI Backbone Combinations

- ABC + 3TC
- TDF or TAF + FTC
- TDF or TAF + 3TC

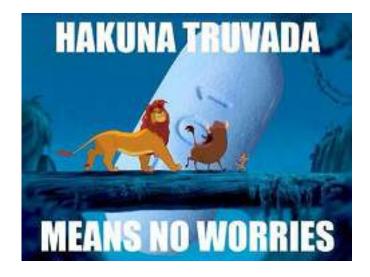
Other Active Agents To Be Used In Combination With NRTI Backbone

- Atazanavir + Ritonavir
- Darunavir + Ritonavir
- Raltegravir
- Dolutegravir

Pre-Exposure Prophylaxis (PrEP)

Truvada and Descovy are the only currently FDA-approved <u>oral</u> agents for the PREVENTION of HIV infection in high-risk patient populations

- Serodiscordant couples: one (+) partner and one (-) partner
- Engagement in sexual activity in a high-risk area
 - Inconsistent or no use of condoms
 - STI diagnosis
 - Sex trade worker
 - Illicit drug use or alcohol dependence
 - Incarcerated
- Rx of PrEP is only ONE component of HIV prevention/risk reduction.
- Descovy can only be used in individuals assigned male at birth



*NEW IN 2022: Cabotegravir 600mg injection for PrEP Q 60 Days!!

Post Exposure Prophylaxis (PEP & nPEP)

nPEP: Non-occupational Post Exposure Prophylaxis

PEP: Occupational Post Exposure Prophylaxis

- Patients who have had sexual, IVDU, or other exposures to potentially infectious fluids of persons known to be HIV infected
 - Includes healthcare workers, sexual assault victims, etc.
- Only to be used within 72 hours of exposure
- If possible, source persons should be interviewed to determine his or her HIV status (if unknown) and use of ARVs

Preferred ARV Regimens:

- TDF/FTC or TDF/3TC plus
- DTG or RAL

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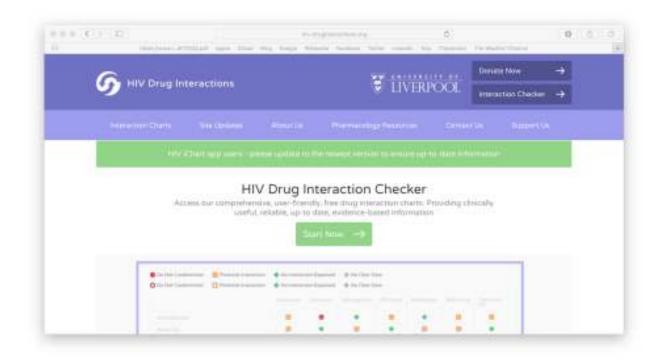
What recommendation would you make?

Helpful Resources

Web Resources of Interest

- -DHHS Guideline Tables
 - http://www.aidsinfo.nih.gov/guidelines/
- Northeast Caribbean AIDS Education and Training Center
 - http://www.necaaetc.org/
- University of Liverpool
 - www.hiv-druginteractions.org
- -Toronto HIV Clinic
 - http://www.hivclinic.ca/main/home

www.hiv-druginteractions.org



References

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf. Accessed April 2022.

Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. Dominguez, KL, Smith, DK, Vasavi T, et al.. April 18, 2016, Update (May 23, 2018). https://stacks.cdc.gov/view/cdc/38856. Accessed April 2022.

New York State Department of Health AIDS Institute. HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault New York, NY: New York State Department of Health AIDS Institute; 2014: available at http://www.hivguidelines.org/clinical-guidelines/post-exposure-prophylaxis/hiv-prophylaxis-following-non-occupational-exposure/. Accessed April 2022.

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Please contact me with questions!

HIV Treatment & Prevention

PRESENTED BY:

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