HIV/AIDS and Opportunistic Infections

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Objectives

• Provide an overview of human immunodeficiency virus, acquired immunodeficiency syndrome, and opportunistic infections
• Describe the history of the disease state, its etiology, and epidemiological trends
• Describe various prevention strategies and testing/screening methods used to control the incidence of disease
• Discuss pertinent information concerning the various drug classes of antiretroviral therapy, treatment initiation options and prevention mechanisms
Human Immunodeficiency Virus (HIV)

- HIV is a retrovirus (virus that contains enzymes that can turn RNA into DNA)
- It weakens a person’s immune system by destroying important cells that fight disease and infection
- Causes **acquired immunodeficiency syndrome (AIDS)**, a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections
- World’s most serious pandemic
HIV-1 vs. HIV-2

- **HIV-1**
  - More virulent and infective form of the virus and is the cause of the majority of HIV infections globally

- **HIV-2**
  - Immunodeficiency seems to develop more slowly and to be milder
  - Those with HIV-2 are less infectious early in the course of infection
  - It is predominantly found in Africa and tends to be associated more so with AIDS wasting
These are the facts!!

- More than 1.2 million people in the US are living with HIV, and 1 in 8 of them don’t know it.
- From 2005 to 2014, the annual number of new HIV diagnoses declined 19%.
- Gay and bisexual men, particularly young African American gay and bisexual men, are most affected.
Number of people receiving ART and percentage of all people living with HIV receiving ART in low- and middle-income countries overall and by WHO region, 2013

TOTAL: 11.7 MILLION

36% [34–38%]

- African Region
- Region of the Americas
- South-East Asia Region
- European Region
- Eastern Mediterranean Region
- Western Pacific Region
- High-income countries

*aCountry income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Rates of Adults and Adolescents Living with Diagnosed HIV Infection
Year-end 2014—United States and 6 Dependent Areas

N = 970,319  Total Rate = 360.0

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data are based on address of residence as of December 31, 2014 (i.e., most recent known address).
### Diagnoses of HIV Infection among Adults and Adolescents, by Transmission Category
2015—United States and 6 Dependent Areas

<table>
<thead>
<tr>
<th>Transmission category</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-male sexual contact</td>
<td>26,646</td>
<td>66.7</td>
</tr>
<tr>
<td>Injection drug use (IDU)</td>
<td>2,460</td>
<td>6.2</td>
</tr>
<tr>
<td>Male-to-male sexual contact and IDU</td>
<td>1,215</td>
<td>3.0</td>
</tr>
<tr>
<td>Heterosexual contact&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9,515</td>
<td>23.8</td>
</tr>
<tr>
<td>Other&lt;sup&gt;b&lt;/sup&gt;</td>
<td>84</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td><strong>39,920</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

*Note.* Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category.

<sup>a</sup> Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

<sup>b</sup> Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

<sup>c</sup> Because column totals for numbers were calculated independently of the values for the subpopulations, the values in each column may not sum to the column total.
# Diagnosed HIV Infections Attributed to Male-to-Male Sexual Contact by Race/Ethnicity, 2015—United States and 6 Dependent Areas

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>120</td>
<td>0.5</td>
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<tr>
<td>Asian</td>
<td>729</td>
<td>2.7</td>
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<tr>
<td>Black/African American</td>
<td>10,318</td>
<td>38.7</td>
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<tr>
<td>Hispanic/Latino(^a)</td>
<td>7,271</td>
<td>27.3</td>
</tr>
<tr>
<td>Native Hawaiian/other Pacific Islander</td>
<td>64</td>
<td>0.2</td>
</tr>
<tr>
<td>White</td>
<td>7,572</td>
<td>28.4</td>
</tr>
<tr>
<td>Multiple races</td>
<td>570</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Total(^b)</strong></td>
<td><strong>26,646</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

*Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary and based on 6 months reporting delay. Data have been statistically adjusted to account for missing transmission category.*

\(^a\) Hispanics/Latinos can be of any race.

\(^b\) Because column totals for numbers were calculated independently of the values for the subpopulations, the values in each column may not sum to the column total.
Number and Percentage of HIV-Infected Persons Engaged in Selected Stages of The Continuum of HIV Care

OVERALL: Of the 1.1 million Americans living with HIV, only 25 percent are virally suppressed.

- Diagnosed: 82%
- Linked to Care: 66%
- Retained in Care: 37%
- Prescribed ART: 33%
- Virally Suppressed: 25%
YOU CAN GET HIV VIA...

- Sex without a condom
- Passed from mother to baby
- Sharing injecting equipment
- Contaminated blood transfusions & organ transplants

HIV IS NOT TRANSMITTED BY...

- Insect bites
- Toilet seats
- Kissing
- Sharing cutlery
- Touching
Transmission of HIV: Sexual Intercourse

- Vaginal, anal, or oral

- Can be found in semen and cervical secretions

- Male to male sexual contact holds the highest risk of transmission
Pathophysiology: HIV Replication

1. Fusion of HIV to the host cell surface.
2. HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
3. Viral DNA is formed by reverse transcription.
4. Viral DNA is transported across the nucleus and integrates into the host DNA.
5. New viral RNA is used as genomic RNA and to make viral proteins.
6. New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.
7. The virus matures by protease releasing individual HIV proteins.
Monitoring Parameters

- **Viral load** can be used as a prognostic factor to monitor disease progression and effects of treatment
  - Undetectable viral load is desired
  - Can vary based upon the laboratory company
- **Number of CD4 lymphocytes** is a surrogate marker of disease progression
  - Normal level 500-1600 cells/mm³
Main symptoms of Acute HIV infection

Systemic:
- Fever
- Weight loss

Central:
- Malaise
- Headache
- Neuropathy

Pharyngitis
Mouth:
- Sores
- Thrush

Lymph nodes:
- Lymphadenopathy

Skin:
- Rash

Esophagus:
- Sores

Muscles:
- Myalgia

Liver and spleen:
- Enlargement

Gastric:
- Nausea
- Vomiting
Prevention

- No Cure!!!
- Abstinence or celibacy
- Barrier methods
- Eliminating high-risk behaviors
- Decreasing sex partners reduce risk
- Stopping IV drug abuse
- Personal protective equipment (PPE) in health care settings prevents parenteral transmission

- Get tested and know your partner’s status
- Use condoms consistently and correctly
- Prenatal and perinatal medication use
- Preexposure prophylaxis
- Postexposure prophylaxis
- Screening all pregnant mothers and providing antiretroviral therapy reduces perinatal transmission
Treatment as Prevention

- ART should be offered to pts at risk of transmitting HIV to sexual partners, including heterosexuals and other risk groups

- **HPTN 052**
  - 1763 heterosexual serodiscordant couples in resource-constrained countries randomized to start ART early or defer until CD4+ count <250 cell/mm³
  - A total of 39 HIV-1 transmissions were observed
    - Of these, 28 were virologically linked to the infected partner
  - Early initiation of ART reduced rates of sexual transmission of HIV-1 and clinical events
Baseline Laboratory Evaluation of Newly Diagnosed HIV Patient

- HIV antibody testing
  - If prior documentation is not available
  - If HIV RNA is below the assay’s limit of detection
- CD4 T-cell count
- Plasma HIV RNA
- Complete blood count
- Chemistry profile
- Transaminase levels
- Blood urea nitrogen (BUN)
- Creatinine

- Urinalysis
- Serologies for hepatitis A, B, and C viruses
- Fasting blood glucose and serum lipids
- Genotypic resistance testing
  - At entry into care, regardless of whether ART will be initiated immediately
  - For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful
Diagnosis: HIV Testing

- There are three broad types of tests available:
  - **Antibody tests**
    - OraQuick HIV Test
    - Home Access HIV-1 Test System
  - **Combination or fourth-generation tests**
  - **Nucleic acid tests (NAT)**
- HIV tests may be performed on blood, oral fluid, or urine
Combination, or 4\textsuperscript{th} Generation, Test

- Looks for both HIV antibodies and antigens
- Antigens are foreign substances that cause your immune system to activate
- The antigen is part of the virus itself and is present during acute HIV infection
- If you’re infected with HIV, an antigen called p24 is produced even before antibodies develop
Combination, or 4th Generation, Test

- Combination screening tests are now recommended for testing done in labs
- Becoming more common in the United States
- This test can pick up both acute and chronic HIV infection
  - If you suspect acute HIV infection at the time of testing, order HIV viral load as well
Goals of Treatment

- Reduce HIV-related morbidity; prolong duration and quality of survival
- Restore and/or preserve immunologic function
- Maximally and durably suppress HIV viral load
- Prevent HIV transmission
Tools to Achieve Treatment Goals

- Selection of ARV regimen
- Maximizing adherence
- Pretreatment resistance testing
Improving Adherence

- Support and reinforcement
- Simplified dosing strategies
- Reminders, alarms, timers, and pillboxes
- Ongoing patient education
- Trust in primary care provider
DHHS HIV Treatment Guidelines

- U.S. Department of Health and Human Services (DHHS) established guidelines to treat those affected by HIV
- **Goal of guidelines:**
  - Provide guidance to care practitioners on the optimal use of antiretroviral agents for the treatment of HIV infection
- In July 2016, the DHHS issued updates to guidelines
Key Updates to Guidelines

- **What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient**
  - The approval of 3 fixed-dose combination products containing tenofovir alafenamide (an oral prodrug of tenofovir) and emtricitabine (TAF/FTC) prompted several changes in the What to Start section

- **Regimen Switching**
  - Based on the most current data, this section was simplified to focus on switch strategies for virologically suppressed patients.
    - Strategies with Good Supporting Evidence
    - Strategies Under Evaluation
    - Strategies Not Recommended
Key Updates to Guidelines

- **HIV-Infected Women**
  - ART is recommended for all HIV-infected patients, including all HIV-infected women
  - Early treatment for HIV-infected women during pregnancy and continuation of ART after pregnancy is important
  - New data on interactions between antiretroviral (ARV) drugs and hormonal contraceptives
Key Updates to Guidelines

- **Hepatitis B Virus (HBV)/HIV Coinfection**
  - Included TAF/FTC as a treatment option for patients with HBV/HIV coinfection
  - No longer recommends adefovir or telbivudine as options for HBV/HIV coinfected patients, as there is limited safety and efficacy data on their use in this population

- **Hepatitis C Virus (HCV)/HIV Coinfection**
  - Updates regarding the potential pharmacokinetic (PK) interactions between different ARV drugs and the recently approved hepatitis C drugs **daclatasvir** and the fixed-dose combination product of **elbasvir and grazoprevir**
  - Peginterferon alfa and ribavirin were removed from Table 12, as these agents do not have significant PK interactions with ARV drugs
Key Updates to Guidelines

- *Tuberculosis (TB)/HIV Coinfection*
  - Updates to treatment of latent tuberculosis infection (LTBI) in HIV-infected persons
  - This section addresses the data from the TEMPRANO and START studies demonstrating a potential role of ART in reducing TB disease
  - The recommendations and discussion regarding when to initiate ART in patients with active TB were simplified
  - As rifamycins are potent inducers of P-glycoprotein (P-gp), and TAF is a P-gp substrate, coadministration of TAF and rifamycins is not recommended
Drug Resistance Testing for Treatment Naïve Patients

- Recommended for persons with HIV infection at entry into care
  - If therapy is deferred, repeat testing may be considered at the time of ART initiation
- Genotypic testing is recommended
- In special circumstances, ART initiation should not be delayed while awaiting resistance testing results
  - Regimen can be modified once results are reported
Drug Resistance Testing for Treatment Naïve Patients

- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes.
- If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers should ensure that genotypic resistance testing also includes INSTI genotype testing.
Drug Resistance Testing: For Treatment Experienced Patients

- HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ART regimens.
- When a patient experiences virologic failure while receiving an INSTI-based regimen, genotypic testing for INSTI resistance should be performed.
- Drug-resistance testing due to virologic failure should be performed:
  - While the person is taking prescribed ARV drugs.
  - Within 4 weeks after discontinuing therapy.
Drug Resistance Testing: For Treatment Experienced Patients

- If more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing may still provide useful information to guide therapy
  - Previously selected resistance mutations can be missed
- Genotypic testing is recommended as the preferred resistance testing in patients with:
  - Suboptimal virologic response
  - Virologic failure while on first- or second-line regimens
- Phenotypic testing is preferred for persons with known or suspected complex drug-resistance mutation patterns
Recommendations for Initiating ART

- ART should be initiated as soon as possible
  - On a case-by-case basis, ART may be deferred because of clinical and/or psychological factors
- Patients should understand that indefinite treatment is required
- ART does not cure HIV
- Address strategies to optimize adherence
HIV Treatment
Treatment

- Highly active antiretroviral therapy (HAART)
  - Increasing life expectancy and quality of life

- Classes of Antiretrovirals (ARVs)
  - Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
  - Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
  - Protease Inhibitors (PIs)
  - Integrase Inhibitors
  - Fusion Inhibitors
  - CCR5-receptor Antagonists
Antiretroviral Mechanism of Action

http://depts.washington.edu/nwaetc/Pill_Chart.pdf
### Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Ziagen</td>
<td>ABC</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>FTC</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>3TC</td>
</tr>
<tr>
<td>Tenofovir Alafenamide</td>
<td>Descovy</td>
<td>TAF</td>
</tr>
<tr>
<td>Tenofovir Disoproxil Fumarate</td>
<td>Viread</td>
<td>TDF/TFV</td>
</tr>
</tbody>
</table>

- Stavudine, Didanosine, and Zidovudine are rarely used
NRTIs

- **Mechanism of Action (MOA)**
  - Target reverse transcriptase causing termination of DNA chain elongation acting as false nucleoside analogues
- **Neuropathy, Pancreatitis**
  - Associated with didanosine, stavudine
- **Myelosuppression**
  - Associated with zidovudine
- **Abacavir**
  - HLA-B*5701 screening recommended for hypersensitivity reaction; hepatic adjustment
- **Advantages of Dual-NRTI Pairs**
  - Established backbone of combination therapy
  - Minimal drug interactions
Adverse Effects: NRTIs

- All NRTIs:
  - Lactic acidosis and hepatic steatosis
    - Highest incidence with Stavudine, then Didanosine and Zidovudine, lower with TDF, ABC, 3TC, and FTC
  - Lipodystrophy (higher incidence with d4T)

- Abacavir
  - Hypersensitivity reaction
  - Rash
  - Possible increased risk of MI

- Tenofovir
  - Renal impairment
  - Decrease in bone-mineral density
  - Headache
  - GI intolerance
## Protease Inhibitors (PIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>ATV</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Prezista</td>
<td>DRV</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva</td>
<td>FPV</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Kaletra</td>
<td>LPV/RTV</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>/r</td>
</tr>
</tbody>
</table>

- Indinavir, Nelfinavir, Saquinavir, and Tipranavir are not commonly used
Protease Inhibitor: Ritonavir

- PIs are almost always prescribed with a boosting agent that allows less frequent dosing and less food interactions

- **Drug interactions:**
  - CYP3A4 >2D6 substrate
  - Potent 3A4, 2D6 inhibitor
  - Inducer of CYPs 1A2, 2C8, 2C9, and 2C19 and UGT1A1

- **Adverse effects:**
  - GI intolerance
  - Hyperlipidemia, hyperglycemia
  - Hepatitis
Pharmacokinetic Enhancer: Cobicistat

- PIs are almost always prescribed with a boosting agent that allows less frequent dosing and less food interactions

**Drug interactions:**
- Strong inhibitor of 3A4, 2D6, and P-glycoprotein
- Interactions are very similar to Ritonavir
- Many drug-drug interactions

**Adverse effects:**
- GI intolerance
- Increase in serum creatinine
- May cause or worsen renal impairment
PIs

- **MOA**
  - Inhibits viral budding from the CD4 cell

- **Class-wide effects**
  - Hyperlipidemia, lipodystrophy, hepatotoxicity
  - GI intolerance
  - Possibility of increased bleeding risk for hemophiliacs

- **Drug interactions**
  - Inhibitors of CYP 3A4
  - Minimal risk of cross resistance and most are boosted with Ritonavir (strong inhibition effects)
Adverse Effects: PIs

- Atazanavir
  - Hyperbilirubinemia
  - PR prolongation
  - Nephrolithiasis, cholelithiasis

- Darunavir
  - Rash
  - Liver toxicity
Advantages and Disadvantages of PIs

Advantages
- Higher genetic barrier to resistance
- PI resistance uncommon with failure of boosted PIs

Disadvantages
- Metabolic complications
- GI intolerance
- Potential for drug interactions (CYP450), especially with RTV
- No single-pill combination regimens
PI Drug Interactions

- All PIs are metabolized in the liver via CYP450, 3A4 substrates
- Most PIs are strong inhibitors of 3A4
- **Contraindications for ALL PIs:**
  - Lovastatin, Sildenafil, Simvastatin, St. John’s wort
- Avoid rifampin
- **There are many drugs that interact with PIs**

Selected PI Drug Interactions

- **Warfarin:**
  - can decrease the INR due to 2C9 induction

- **Phosphodiesterase-5 inhibitors:**
  - increase level
  - risk of toxicity

- **Hormonal contraceptives:**
  - Ritonavir can decreased levels

- **Statins:**
  - PIs can increase levels

- **Atazanavir:**
  - Caution with the use of acid-suppressive agents
Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>EFV</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Intelence</td>
<td>ETR</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>NVP</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Edurant</td>
<td>RPV</td>
</tr>
</tbody>
</table>
NNRTIs

• MOA
  • Act at the site of reverse transcriptase, binding to and inhibiting enzymatic activity, preventing viral conversion from RNA to DNA

• Class-wide adverse effects
  • Rash, including Stevens-Johnson syndrome
  • Hepatotoxicity (especially NVP)

• Drug interactions
  • Mostly inducers of CYP 3A4 (some have inhibition actions)

• Cross-resistance possible among class
Adverse Effects: NNRTIs

- **Efavirenz**
  - Neuropsychiatric
  - Teratogenic in nonhuman primates
  - Dyslipidemia

- **Rilpivirine**
  - Depression

- **Nevirapine**
  - Higher rate of rash
  - Hepatotoxicity

- **Etravirine**
  - Severe skin rash
  - Fat maldistribution
  - Peripheral neuropathy
Advantages of NNRTIs

- Long half-lives
- Less metabolic toxicity (dyslipidemia, insulin resistance) than with some PIs
- Single-pill combination regimens available with EFV and RPV
Disadvantages of NNRTIs

- Low genetic barrier to resistance – single mutation
- Cross-resistance among most NNRTIs
- Potential drug interactions (CYP450)
- Transmitted resistance to NNRTIs more common than resistance to PIs
- Rash:
  - Steven’s Johnson Syndrome
  - Toxic Epidermal Necrolysis
- Hepatotoxicity
Disadvantages of NNRTIs

- **EFV:**
  - High rate of CNS-related side effects
  - Teratogenicity risk: need to use 2 forms of birth control to prevent pregnancy
  - Birth defects typically occur prior to diagnosis of pregnancy

- **RPV:**
  - Lower efficacy if HIV RNA >100,000 or CD4 <200
  - Food requirement (400 cal)
  - PPIs are contraindicated; use H2 antagonists (12 hrs)
NNRTI Drug Interactions

- All NNRTIs are cleared non-renally and metabolized in the liver via CYP450
- They are all 3A4 substrates and may be an inducer, inhibitor or both
- **Avoid the following medications:**
  - Clopidogrel, carbamazepine, oxcarbazepine
  - Phenobarbital, phenytoin, rifampin, St. John’s wort
NNRTI Drug Interactions

- **Rilpivirine:**
  - Must not combine with proton pump inhibitors
  - Must separate from H2 blockers and other acid reducing agents
  - If H2 blockers are used, must at least 12 hours before or 4 hours after
  - Avoid clopidogrel, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and St. John’s wort
## Integrase Inhibitors (INSTIs)

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<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>Tivicay</td>
<td>DTG</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Vitekta</td>
<td>EVG</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Isentress</td>
<td>RAL</td>
</tr>
</tbody>
</table>
INSTIs

• **MOA**
  - Inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle

• **Adverse effects**
  - Headache
  - Insomnia
  - Rash
  - Nausea/diarrhea
Adverse Effects: INSTIs

- **Dolutegravir**
  - Headache
  - Insomnia
  - Rash, hypersensitivity reaction

- **Elvitegravir**
  - Decreased CrCl
  - Increased risk of TDF-related nephrotoxicity
  - Nausea, diarrhea

- **Raltegravir**
  - Nausea
  - Headache
  - Diarrhea
  - CPK elevation, myopathy, rhabdomyolysis
  - Rash
Advantages of INSTIs

- Virologic response noninferior to EFV
- Fewer adverse events than with EFV or PIs
- RAL, DTG have fewer drug-drug interactions than with PIs or NNRTIs (not true of EVG/COBI)
- Single-pill combination regimens available with DRV, EVG/COBI
Disadvantages of INSTIs

- Lower genetic barrier to resistance than PIs
  - DTG does not
- Myopathy, rhabdomyolysis, skin reactions reported with RAL (rare)
- Depression and suicidal ideation
  - (rare; usually in patients with preexisting psychiatric conditions)
INSTI Drug Interactions

- Should be taken 2 hours before or 6 hours after cation-containing antacids, sucralfate, iron or calcium supplements
- PPIs do not pose an interaction with INSTIs
- **Raltegravir:**
  - Rifampin can decrease its levels
- **Elvitegravir:**
  - May decrease plasma concentrations of 2C9 substrates
CCR5 Receptor Antagonists

- Maraviroc (Selzentry®)
  - Approved in 2007
- Dosage: 300mg BID
  - 150mg BID in combination with 3A4 inhibitors
  - 600mg BID in combination with 3A4 inducers
- MOA:
  - Bind to CCR5 protein on CD4 cell to prevent virion binding
- Adverse effects
  - Hepatotoxicity, coughing, dizziness and GI effects

*Requires a tropism test to detect presence of CCR5-tropic virus prior to use
# Fixed-Dose Combinations

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine/Lamivudine</td>
<td>Combivir®</td>
</tr>
<tr>
<td>Emtricitabine/Tenofovir Alafenamide</td>
<td>Descovy®</td>
</tr>
<tr>
<td>Lamivudine/Abacavir</td>
<td>Epzicom®</td>
</tr>
<tr>
<td>Atazanavir/Cobicistat</td>
<td>Evotaz®</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Kaletra®</td>
</tr>
<tr>
<td>Darunavir/Cobicistat</td>
<td>Prezcobix®</td>
</tr>
<tr>
<td>Zidovudine/Lamivudine/Abacavir</td>
<td>Trizivir®</td>
</tr>
<tr>
<td>Tenofovir/Emtricitabine</td>
<td>Truvada®</td>
</tr>
</tbody>
</table>
## Single Tablet Regimens (STR)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz/Tenofovir/Emtricitabine</td>
<td>Atripla®</td>
<td>EFV/TDF/FTC</td>
</tr>
<tr>
<td>Rilpivirine/Tenofovir/Emtricitabine</td>
<td>Complera®</td>
<td>RPV/TDF/FTC</td>
</tr>
<tr>
<td>Elvitegravir/Cobicistat/Tenofovir/Alafenamide/Emtricitabine</td>
<td>Genvoya®</td>
<td>EVG/COBI/TAF/FTC</td>
</tr>
<tr>
<td>Emtricitabine/Rilpivirine/Tenofovir/Alafenamide</td>
<td>Odefsey®</td>
<td>FTC/RPV/TAF</td>
</tr>
<tr>
<td>Elvitegravir/Cobicistat/Tenofovir/Emtricitabine</td>
<td>Stribild®</td>
<td>EVG/COBI/TDF/FTC</td>
</tr>
<tr>
<td>Dolutegravir/Abacavir/Lamivudine</td>
<td>Triumeq®</td>
<td>DTG/ABC/3TC</td>
</tr>
</tbody>
</table>
Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 INSTI + 2 NRTIs
  - 1 PK-boosted PI (RTV/c) + 2 NRTIs
  - 1 NNRTI + 2 NRTIs

- Few clinical end points to guide choices: recommendations based mostly on rates of HIV RNA suppression and severity of adverse effects

- Advantages and disadvantages to each type of regimen

- Individualize regimen choice
Factors to Consider When Selecting an Initial Regimen

- Pre-treatment viral load and CD4 count
- Genotype results
- HLA-B*5701 status
- Anticipated adherence
- Comorbidities
- Pregnancy potential

- Barrier to resistance
- Potential adverse effects
- Potential drug interactions
- Convenience
  - Pill burden
  - Dosing frequency
  - Food requirements
- Cost/access
## DHHS Recommended Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI based</td>
<td>• DTG/ABC/3TC^</td>
</tr>
<tr>
<td></td>
<td>• DTG (QD) + TDF/FTC or TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>• EVG/COBI/TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>• EVG/COBI/TDF/FTC*</td>
</tr>
<tr>
<td></td>
<td>• RAL + TDF/FTC or TAF/FTC</td>
</tr>
<tr>
<td>PI based</td>
<td>• DRV/r (QD) + TDF/FTC or TAF/FTC</td>
</tr>
</tbody>
</table>

- Note: 3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency
- ^ = if HLA-B*5701 negative
- *= only if pre-ART CrCl >70 mL/min
# DHHS Alternative Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI based</td>
<td>▪ EFV/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>▪ EFV + TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>▪ RPV/TDF/FTC or RPV/TAF/FTC^</td>
</tr>
<tr>
<td>PI based</td>
<td>▪ (ATV/c or ATV/r) + TDF/FTC or TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>▪ (DRV/c or DRV/r) + ABC/3TC*</td>
</tr>
<tr>
<td></td>
<td>▪ DRV/c + TDF/FTC or TAF/FTC</td>
</tr>
</tbody>
</table>

- Note: 3TC can be used in place of FTC and vice versa; TDF: caution if renal insufficiency
- ^ = only if pre-ART HIV RNA <100,000 copies/mL and CD4 >200 cells/µL
- * = only if HLA-B*5701 negative
### DHHS Other Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>If HIV RNA $&lt;100,000$ copies/mL and HLA-B*5701 negative:</td>
<td>- (ATV/c or ATV/r) + ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>- EFV + ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>- RAL + ABC/3TC</td>
</tr>
<tr>
<td>Others to consider when TAF, TDF, or ABC cannot be used</td>
<td>- DRV/r + RAL (BID)$^\text{^}$</td>
</tr>
<tr>
<td></td>
<td>- LPV/r + 3TC</td>
</tr>
</tbody>
</table>

Note: 3TC can be used in place of FTC and vice versa

$^\text{^} =$ only if HIV RNA $<100,000$ copies/mL and CD4 $>200$ cells/$\mu$L
What Not to Use: Regimens

- **Monotherapy with NRTI**
  - Does not demonstrate potent and sustained antiviral activity

- **Dual-NRTI regimens**
  - Does not demonstrated potent and sustained antiviral activity

- **Triple-NRTI regimens**
  - Other than ABC/3TC/ZDV and possibly 3TC/ZDV + TDF
  - Suboptimal virologic activity
## Initial Therapy: Dual-NRTI Pairs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/3TC</td>
<td>• Once-daily dosing</td>
</tr>
<tr>
<td></td>
<td>• Co-formulated with DTG in a single-pill regimen</td>
</tr>
<tr>
<td></td>
<td>• Use only for patients who are negative for HLA-B*5701</td>
</tr>
<tr>
<td></td>
<td>• Possible risk of cardiovascular events; caution in patients with CV risk factors</td>
</tr>
<tr>
<td></td>
<td>• Possible inferior efficacy if baseline HIV RNA &gt;100,000 copies/mL</td>
</tr>
</tbody>
</table>
## Initial Therapy: Dual-NRTI Pairs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC</td>
<td>- Once-daily dosing</td>
</tr>
<tr>
<td></td>
<td>- In several single-pill regimen coformulations</td>
</tr>
<tr>
<td></td>
<td>- High virologic efficacy</td>
</tr>
<tr>
<td></td>
<td>- Active against HBV</td>
</tr>
<tr>
<td></td>
<td>- Renal and bone toxicity is less common than with TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>- Approved for eGFR $\geq$30 mL/min</td>
</tr>
<tr>
<td></td>
<td>- In some combinations, use supported by bioequivalence/bioavailability studies or randomized switch studies</td>
</tr>
<tr>
<td></td>
<td>- No randomized comparisons with ABC/3TC</td>
</tr>
</tbody>
</table>
## Initial Therapy: Dual-NRTI Pairs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| TDF/FTC  | ▪ Once-daily dosing  
▪ In several single-pill regimen coformulations  
▪ High virologic efficacy  
▪ Active against HBV  
▪ Potential for renal and bone toxicity (more than with TAF)  
▪ Avoid if CrCl <60 mL/min |
### Specific Scenarios and ART Regimen Considerations

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
<td>• HIV RNA; CD4 count</td>
</tr>
<tr>
<td></td>
<td>• HIV resistance test results</td>
</tr>
<tr>
<td></td>
<td>• HLA-B*5701 status</td>
</tr>
<tr>
<td></td>
<td>• Patient preferences</td>
</tr>
<tr>
<td></td>
<td>• Anticipated adherence</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>• Cardiovascular disease, hyperlipidemia, renal disease, osteoporosis, psychiatric illness, others</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy or pregnancy potential</td>
</tr>
<tr>
<td></td>
<td>• Coinfections: HCV, HBV, TB</td>
</tr>
<tr>
<td>Regimen Characteristics</td>
<td>• Genetic barrier to resistance</td>
</tr>
<tr>
<td></td>
<td>• Potential adverse effects</td>
</tr>
<tr>
<td></td>
<td>• Drug interactions with other medications</td>
</tr>
<tr>
<td></td>
<td>• Convenience (pill #, dosing frequency, fixed-dose combinations, food requirements)</td>
</tr>
<tr>
<td></td>
<td>• Cost</td>
</tr>
</tbody>
</table>
## Specific Scenarios and ART Regimen Considerations

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| CD4 <200                                      | Do not use: higher rate of virologic failure  
  - Rilpivirine-based ART  
  - Darunavir/r + RAL |
| HIV RNA >100,000                              | Do not use: higher rate of virologic failure  
  - Rilpivirine-based ART  
  - Abacavir/Lamivudine + Efavirenz or Atazanavir/r  
  - Darunavir/r + Raltegravir |
| HLA-B*5701 positive                           | Do not use Abacavir  
  - Risk of hypersensitivity                                    |
| Must treat before resistance test results are known | Avoid NNRTI-based regimens: transmitted resistance more likely than with PI or INSTI  
**Recommended:**  
  - Darunavir/r + TAF/FTC or TDF/FTC  
  - Dolutegravir + TAF/FTC or TDF/FTC |
## Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-pill regimen</td>
<td>▪ Dolutegravir/Abacavir/Lamivudine</td>
</tr>
<tr>
<td></td>
<td>▪ Efavirenz/Tenofovir/Emtricitabine</td>
</tr>
<tr>
<td></td>
<td>▪ Elvitegravir/c/TAF/FTC or TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>▪ Rilpivirine/TAF/FTC or TDF/FTC</td>
</tr>
<tr>
<td>Food effects</td>
<td>Should be taken with food:</td>
</tr>
<tr>
<td></td>
<td>▪ Atazanavir</td>
</tr>
<tr>
<td></td>
<td>▪ Darunavir</td>
</tr>
<tr>
<td></td>
<td>▪ Elvitegravir/c/TAF/FTC or TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>▪ Rilpivirine/TAF/FTC or TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>Should be taken on empty stomach:</td>
</tr>
<tr>
<td></td>
<td>▪ Efavirenz</td>
</tr>
</tbody>
</table>
## Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease (eGFR &lt; 60 mL/min)</td>
<td>▪ Avoid Tenofovir DF; use Abacavir or TAF</td>
</tr>
<tr>
<td></td>
<td>▪ ABC not associated with renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>▪ TAF has less impact on renal function and proteinuria than TDF; may be used if eGFR &gt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>▪ Options when ABC or TAF cannot be used:</td>
</tr>
<tr>
<td></td>
<td>▪ LPV/r + 3TC</td>
</tr>
<tr>
<td></td>
<td>▪ DRV/r + RAL (if HIV RNA &lt; 100,000 copies/mL and CD4 &gt; 200 cells/µL)</td>
</tr>
<tr>
<td>Liver disease with cirrhosis</td>
<td>▪ Some ARVs contraindicated or require dosage modification</td>
</tr>
<tr>
<td></td>
<td>▪ Evaluation by expert in advanced liver disease is recommended</td>
</tr>
</tbody>
</table>
## Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| Osteoporosis           | - Avoid TDF: associated with greater decrease in BMD, osteomalacia, urine phosphate wasting  
                        |   - **Use ABC or TAF**  
                        |   - Associated with smaller decreases in BMD  
                        |   - ABC may be used if HLA-B*5701 negative (if HIV RNA > 100,000 copies/mL, do not use with EFV or ATV/r) |
| Psychiatric illness    | - Consider avoiding EFV and RPV: can exacerbate psychiatric symptoms; may be associated with suicidality                                      |
| HIV-associated dementia| - Avoid EFV  
                        | - Favor DRV- or DTG-based regimens                                                   |
### Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cardiac risk</td>
<td>▪ Consider avoiding ABC and LPV/r: increased CV risk in some studies</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Adverse effects on lipids:</td>
</tr>
<tr>
<td></td>
<td>▪ PI/r or PI/c</td>
</tr>
<tr>
<td></td>
<td>▪ EFV</td>
</tr>
<tr>
<td></td>
<td>▪ EVG/c</td>
</tr>
<tr>
<td></td>
<td>Beneficial lipid effects:</td>
</tr>
<tr>
<td></td>
<td>▪ TDF</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>▪ See Perinatal Guidelines</td>
</tr>
</tbody>
</table>
## Selecting Initial ART Regimen: Selected Clinical Scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
</table>
| **HBV**  | - Use TDF or TAF with FTC or 3TC, whenever possible: use 2 NRTIs with activity against both HIV and HBV  
           - If TDF and TAF are contraindicated: treat HBV with FTC or 3TC + entecavir + suppressive ART regimen |
| **HCV**  | - Consult current recommendations |
| **TB**   | - TAF not recommended with rifamycins  
           - If rifampin is used:  
             - EFV: no dosage adjustment needed  
             - RAL: increase RAL to 800 mg BID  
             - DTG: 50 mg BID (only if no significant INSTI mutations)  
             - If PI-based regimen: use rifabutin in place of rifampin |
### ARVs Not Recommended in Initial Treatment

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>High rate of early virologic failure</td>
<td>- ddI + TDF</td>
</tr>
<tr>
<td>Inferior virologic efficacy</td>
<td>- ABC + 3TC + ZDV as 3-NRTI regimen</td>
</tr>
<tr>
<td></td>
<td>- ABC + 3TC + ZDV + TDF as 4-NRTI regimen</td>
</tr>
<tr>
<td></td>
<td>- ddI + (3TC or FTC)</td>
</tr>
<tr>
<td></td>
<td>- Unboosted ATV, FPV, or SQV</td>
</tr>
<tr>
<td></td>
<td>- DLV</td>
</tr>
<tr>
<td></td>
<td>- NFV</td>
</tr>
<tr>
<td></td>
<td>- TPV/r</td>
</tr>
<tr>
<td>High incidence of toxicities</td>
<td>- ZDV + 3TC</td>
</tr>
<tr>
<td></td>
<td>- d4T + 3TC</td>
</tr>
<tr>
<td></td>
<td>- ddI + TDF</td>
</tr>
<tr>
<td></td>
<td>- NVP</td>
</tr>
<tr>
<td></td>
<td>- IDV/r</td>
</tr>
<tr>
<td></td>
<td>- RTV as sole PI</td>
</tr>
</tbody>
</table>
## ARVs Not Recommended in Initial Treatment

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential for drug-drug interactions</td>
<td>- EVG/COBI/TDF/FTC + other ARV drugs</td>
</tr>
<tr>
<td>High pill burden/dosing inconvenience</td>
<td>- LPV/r + 2NRTIs</td>
</tr>
<tr>
<td></td>
<td>- IDV (unboosted)</td>
</tr>
<tr>
<td></td>
<td>- SQV/r</td>
</tr>
<tr>
<td>Lack of data in initial treatment</td>
<td>- ABC + ddl</td>
</tr>
<tr>
<td></td>
<td>- FPV/r</td>
</tr>
<tr>
<td></td>
<td>- DRV (unboosted)</td>
</tr>
<tr>
<td></td>
<td>- ENF (T-20)</td>
</tr>
<tr>
<td></td>
<td>- ETR</td>
</tr>
<tr>
<td>No benefit over standard regimens</td>
<td>- 3-class regimens</td>
</tr>
<tr>
<td></td>
<td>- 3 NRTIs + NNRTI</td>
</tr>
<tr>
<td></td>
<td>- MVC</td>
</tr>
</tbody>
</table>
Opportunistic Infections
What are Opportunistic Infections?

- An illness caused by any one of various organisms that occur in individuals with weakened immune systems, including people with HIV/AIDS
- HIV leads to immunosuppression (immunodeficiency) that allows opportunistic pathogens to cause infections in these patients
Opportunistic Infections
Mucosal Candidiasis: Epidemiology

- Oropharyngeal and esophageal candidiasis are common
  - Most common in patients with CD4 count <200 cells/µL
  - Prevalence lower in patients on ART

- Usually caused by Candida albicans; other species (especially C glabrata) seen in advanced immunosuppression, refractory cases
Clinical Manifestations

- Oropharyngeal (thrush):
  - Pseudomembranous: painless, creamy white plaques on buccal or oropharyngeal mucosa or tongue; can be scraped off easily
  - Erythematous: patches on anterior or posterior upper palate or tongue
  - Angular cheilosis

- Esophageal: retrosternal burning pain or discomfort, odynophagia, fever; on endoscopy, whitish plaques with or without mucosal ulceration
Mucocutaneous Candidiasis: Clinical Manifestations

Pseudomembranous candidiasis

Erythematous candidiasis
Mucocutaneous Candidiasis: Clinical Manifestations

Esophageal candidiasis
Mucocutaneous Candidiasis: Diagnosis

- **Oropharyngeal:**
  - Usually clinical diagnosis
  - For laboratory confirmation: KOH preparation; culture

- **Esophageal:**
  - Empiric diagnosis: symptoms and response to trial of therapy (usually appropriate before endoscopy); visualization of lesions + fungal smear or brushings
  - Endoscopy with histopathology and culture
Mucocutaneous Candidiasis: Prevention

- **Preventing exposure**
  - Candida are common mucosal commensals; no measures to reduce exposure

- **Primary prophylaxis**
  - Not recommended: mucosal disease has low mortality; acute therapy is effective; concern for drug resistance, drug interactions, expense
Mucocutaneous Candidiasis: Preventing Recurrence

- ART and immune reconstitution reduce recurrences
- For oropharyngeal or vulvovaginal, chronic suppressive therapy generally not recommended
  - If frequent or severe recurrences, consider fluconazole 100 mg PO QD or TIW (oral); fluconazole 150 mg PO weekly (vaginal)
- For esophageal, consider fluconazole 100-200 mg PO QD or posaconazole suspension 400 mg PO BID
Mucocutaneous Candidiasis: Preventing Recurrence

- Azole-refractory oropharyngeal or esophageal candidiasis: recommended until immune reconstitution on ART (if responded to echinocandins, voriconazole, or posaconazole)
- Stopping chronic suppressive therapy:
  - Reasonable to stop when CD4 >200 cells/µL after ART initiation
Oropharyngeal Candidiasis: Treatment

Preferred (7-14 days)
• Fluconazole 100 mg PO QD
• Clotrimazole troches 10 mg PO 5 times daily
• Miconazole mucoadhesive buccal tablet 50 mg QD to canine fossa

Alternative
• Itraconazole* oral solution 200 mg PO QD
• Posaconazole* oral suspension 400 mg PO BID x 1, then 400 mg QD
• Nystatin suspension 4-6 mL QID or 1-2 flavored pastilles 4-5 times daily
Esophageal Candidiasis: Treatment

**Preferred (14-21 days)**
- Fluconazole 100 mg (up to 400 mg) PO or IV QD
- Itraconazole* oral solution 200 mg PO QD

**Alternative**
- Voriconazole* 200 mg PO BID
- Caspofungin 50 mg IV QD
- Micafungin 150 mg IV QD
- Anidulafungin 100 mg IV x 1, then 50 mg IV QD
- Amphotericin B deoxycholate 0.6 mg/kg IV QD
- Amphotericin B (lipid formulation) 3-4 mg/kg IV QD
Monitoring and Adverse Events

- Majority of patients’ response to therapy is rapid, with improvement in signs and symptoms within 48–72 hours.
- Short courses of topical therapy rarely result in adverse effects, mainly cutaneous hypersensitivity reactions.
- Oral azole therapy can be associated with:
  - Nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations.
- If prolonged azole therapy is anticipated (>21 days), periodic monitoring of liver chemistry studies should be considered (CIII).
Pneumocystis Pneumonia (PCP)

- PCP is an organism that is classified as a fungus but also shares biological characteristics with protozoa.

- **Two types:**
  - Pneumocystis carinii (infects rodents)
  - *Pneumocystis jirovecii* (infects humans)

- Initial infection with PCP usually occurs in early childhood; two thirds of healthy children have antibodies to *P. jirovecii* by age 2-4 y.o.
Pneumocystis Pneumonia (PCP)

- The infection is limited to the lungs in >95% of cases
  - May also infect lymph nodes, spleen, liver, retina, skin, and bone marrow
- The most common underlying conditions associated with PCP are:
  - Leukemia, Hodgkin disease and other lymphomas, primary immunodeficiency's, and organ transplants
Pneumocystis Pneumonia (PCP)

- Approximately 90% of cases occurred among patients with CD4+ counts of <200 cells/mL
- Other factors associated with a higher risk for PCP included:
  - CD4+ cell percentage <14%,
  - Previous episodes of PCP,
  - Oral thrush
  - Recurrent bacterial pneumonia
  - Unintentional weight loss
  - Higher plasma HIV RNA
- Pneumocystis spreads by the airborne route and takes up residence in the alveoli
PCP: Clinical Manifestations

- Progressive exertional dyspnea, fever, nonproductive cough, chest discomfort
- Subacute onset, worsens over days-weeks (fulminant pneumonia is uncommon)
- Chest exam may be normal, or diffuse dry rales, tachypnea, tachycardia (especially with exertion)
- Extrapulmonary disease seen rarely; occurs in any organ, associated with aerosolized pentamidine prophylaxis
PCP: Diagnosis

- Definitive diagnosis requires demonstrating organism:
  - Induced sputum (sensitivity <50% to >90%)
    - Spontaneously expectorated sputum: low sensitivity
  - Bronchoscopy with bronchoalveolar lavage (sensitivity 90-99%)
  - Transbronchial biopsy (sensitivity 95-100%)
  - Open-lung biopsy (sensitivity 95-100%)
  - PCR: high sensitivity for BAL sample; may not distinguish disease from colonization
PCP: Diagnosis

Chest X ray: PCP with bilateral, diffuse granular opacities

Chest X ray: PCP with bilateral perihilar opacities, interstitial prominence, hyperlucent cystic lesions
PCP: Primary Prophylaxis

- **Initiate:**
  - CD4 <200 cells/µL or history of oropharyngeal candidiasis

- **Consider for:**
  - CD4% <14% or history of AIDS-defining illness
  - CD4 200-250 cells/µL if Q 3-month CD4 monitoring is not possible

- **Discontinue:**
  - On ART with CD4 >200 cells/µL for >3 months

- **Reinitiate:**
  - CD4 decreases to <200 cells/µL
PCP Primary Prophylaxis: Preferred

- Trimethoprim-sulfamethoxazole (TMP-SMX) DS 1 tablet PO QD*
- TMP-SMX SS 1 tablet PO QD
- For patients who experience non life-threatening adverse events, consider desensitization or dosage reduction
PCP Primary Prophylaxis: Alternate

- TMP-SMX DS 1 tablet PO 3 times Q week
- Dapsone 100 mg PO QD or 50 mg BID
- Dapsone 50 mg QD + pyrimethamine 50 mg Q week + leucovorin 25 mg Q week*
- Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg, all Q week*
- Aerosolized pentamidine 300 mg Q month via Respirgard II nebulizer (other devices not recommended)
- Atovaquone 1,500 mg PO QD*
PCP Preferred Treatment

- Duration: 21 days for all treatment regimens
- TMP-SMX is treatment of choice

Moderate-severe PCP

- TMP-SMX: 15-20 mg/kg/day TMP and 75-100 mg/kg/day SMX IV or PO in divided doses Q6-8H

Mild-moderate PCP

- As above, or TMP-SMX DS 2 tablets TID
- Adjust dosage for renal insufficiency
PCP Alternative Treatment

Moderate-severe PCP

- Pentamidine 4 mg/kg IV QD
  - Recommended for patients who cannot tolerate TMP-SMX or experience clinical failure with TMP-SMX; do not combine use
- Primaquine 30 mg (base) PO QD + clindamycin 600 mg IV Q6H or 900 mg IV Q8H or 300 mg PO Q6H or 450 mg PO Q8H
  - More effective than pentamidine, less toxicity
PCP Alternative Treatment

Mild-moderate PCP

- Dapsone 100 mg PO QD + TMP 15 mg/kg/day PO in divided doses TID
  - Similar efficacy, fewer side effects than TMP-SMX, but more pills
- Primaquine 30 mg (base) PO QD + clindamycin 300 mg PO Q6H or 450 mg PO Q8H
- Atovaquone 750 mg PO BID
  - Less effective than TMP-SMX, but fewer side effects
PCP Adjunctive Treatment

- **Corticosteroids**
  - For moderate-to-severe disease (room air PO2 <70 mmHg or A-a gradient >35 mmHg)
  - Give as early as possible (within 72 hours)
  - Prednisone 40 mg BID days 1-5, 40 mg QD days 6-10, 20 mg QD days 11-21, or methylprednisolone at 75% of respective prednisone dosage
PCP: Preventing Recurrence

- Secondary prophylaxis (chronic maintenance therapy) for life unless immune reconstitution on ART
  - Preferred: TMP-SMX 1 DS PO QD, or 1 SS PO QD
  - Alternatives:
    - TMP-SMX DS 1 tablet PO 3 times Q week
    - Dapsone 100 mg PO QD or 50 mg BID
    - Dapsone 50 mg QD + pyrimethamine 50 mg Q week + leucovorin 25 mg Q week
PCP Preventing Recurrence: Alternatives

- Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg, all Q week*
- Aerosolized pentamidine 300 mg Q month via Respirgard II nebulizer (other devices not recommended)
- Atovaquone 1,500 mg PO QD
- Atovaquone 1,500 mg PO QD + pyrimethamine 25 mg QD + leucovorin 10 mg PO QD
Clinical Pearls (PCP)

- TMP-SMX DS daily regimen also provides cross-protection against toxoplasmosis & other bacterial infections
- Primary pneumocystis prophylaxis should be D/C for adult and adolescent patients who have responded to ART with an increase in CD4+ counts to >200 cells/mL for >3 months
- D/C primary prophylaxis among these patients is recommended because prophylaxis adds limited disease prevention
Monitoring and Adverse Events

- TMP-SMX: Rash, fever, leukopenia, thrombocytopenia, hepatitis, and hyperkalemia
- Dapsone/primaquine: methemoglobinemia and hemolysis (especially in those with G6PD deficiency)
- Dapsone: rash and fever
- Pentamidine: azotemia, pancreatitis, hypo/hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia
- Primaquine/clindamycin: anemia, rash, fever, and diarrhea
- Atovaquone: headache, nausea, diarrhea, rash, and transaminase elevations
Toxoplastic encephalitis (Toxoplasmosis)

- Caused by the protozoan Toxoplasma gondii.
- Toxoplasma has an infectious reservoir in almost all animals; humans acquire infection either through
  - Ingestion of tissue cysts contained in undercooked meat (usually pork or lamb)
  - Oocysts on contaminated vegetables
  - Exposure to cat feces containing oocysts

**There is no transmission by person-to-person contact**
Intermediate host:
birds, mammals, humans

Bradyzoites encyst within the CNS and muscle of the infected host.

Oocysts are excreted in cat feces. Contaminated soil is ingested by birds, mammals, and humans.

Tachyzoites infect all nucleated cells in the host, replicate, and cause tissue damage.

Toxoplastic encephalitis

Definitive host

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Toxoplasmosis

- Toxoplasmic encephalitis usually occurs in HIV-infected patients with CD4+ counts <100 cells/μL.
- Seroprevalence varies substantially among different communities (e.g., approx. 15% in the U.S. and 50%–75% in certain European countries)
- The incidence and associated mortality in Europe and the U.S. have decreased substantially with the initiation of ART and the broad use of prophylaxis regimens active against T. gondii
- Clinical disease is rare among patients with CD4+ counts >200 cells/μL (greatest risk occurs when CD4+ count <50 cells/μL)
Clinical Manifestations

- 10-30% of seropositive patients who develop AIDS develop TE
- Involvement of the CNS
- Symptoms:
  - Headache
  - Disorientation
  - Drowsiness
  - Convulsions
  - Loss of memory
  - Focal to major motor seizures
Diagnosing

- Serum Toxoplasma IgG antibody test results are positive in nearly all patients with toxoplasmic encephalitis.
- CNS imaging with computed tomography (CT) typically shows multiple contrast-enhancing mass lesions, but may show a single lesion or no lesions.
- Magnetic resonance imaging (MRI) is more sensitive than CT for CNS toxoplasmosis.
Toxoplasma gondii Encephalitis: Preventing Exposure

- All HIV+ should be tested for IgG to Toxoplasma at baseline, to detect latent infection
- Toxoplasma seronegative: counsel about sources of infection
  - Patients: avoid eating raw or undercooked meat or shellfish; wash hands after handling raw meat and after contact with soil; wash fruits/vegetables; clean cat-litter boxes daily and wash hands afterward; cats should not be fed raw/undercooked meats
Toxoplasma gondii Encephalitis: Primary Prophylaxis

- **Recommended:**
  - TMP-SMX 1 DS QD

- **Alternative:**
  - TMP-SMX 1 DS PO TIW
  - TMP-SMX 1 SS QD
  - Dapsone* 50 mg PO QD + pyrimethamine 50 mg PO Q week + leucovorin 25 mg PO Q week
  - Dapsone* 200 mg PO Q week + pyrimethamine 75 mg PO Q week + leucovorin 25 mg PO Q week
  - Atovaquone 1,500 mg PO QD +/- pyrimethamine 25 mg PO QD + leucovorin 10 mg PO QD
Toxoplasmosis **Preferred:** Treatment

- Pyrimethamine 200 mg PO 1 dose, then:
  - For weight ≤60 kg: pyrimethamine 50 mg PO QD + sulfadiazine 1,000 mg PO Q6H + leucovorin 10-25 mg PO QD
  - For weight >60 kg: pyrimethamine 75 mg PO QD + sulfadiazine 1,500 mg PO Q6H + leucovorin 10-25 mg PO QD
- Duration: ≥6 weeks, longer if extensive disease or incomplete response at 6 weeks
Toxoplasmosis Alternative Treatment

- Pyrimethamine as above + clindamycin 600 mg IV or PO Q6H + leucovorin as above
- TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or PO BID
- Atovaquone 1,500 mg PO BID + pyrimethamine, as above + leucovorin as above
- Atovaquone 1,500 mg PO BID + sulfadiazine (weight-based as above)
- Atovaquone 1,500 mg PO BID (variable absorption)
- Pyrimethamine as above + azithromycin 900-1,200 mg PO QD + leucovorin as above
Toxoplasmosis Alternative Treatment

- Adjunctive corticosteroids only if indicated for treatment of mass effect; monitor closely and discontinue as soon as possible
- Anticonvulsants if history of seizures; continue at least through period of acute therapy
  - Should not be given prophylactically to all patients
Toxoplasma gondii Encephalitis: Monitoring and Adverse Events

- **Pyrimethamine:**
  - rash, nausea, bone marrow suppression
  - May be reversed with increase in leucovorin dosage

- **Sulfadiazine:**
  - rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, crystalluria

- **Clindamycin:**
  - rash, fever, nausea, diarrhea (including Clostridium difficile colitis), hepatotoxicity
Toxoplasma gondii Encephalitis: Monitoring and Adverse Events

- **TMP-SMX:**
  - rash, fever, leukopenia, thrombocytopenia, hepatotoxicity
- **Atovaquone:**
  - nausea, vomiting, diarrhea, rash, headache, hyperglycemia, fever
Toxoplasmosis Secondary Prophylaxis

- **Preferred:**
  - Pyrimethamine 25-50 mg PO QD + sulfadiazine 2,000-4,000 mg PO daily in 2-4 divided doses + leucovorin 10-25 mg PO QD

- **Alternative:**
  - Clindamycin 600 mg PO Q8H + pyrimethamine 25-50 mg PO QD + leucovorin 10-25 mg PO QD (not effective as PCP prophylaxis)
  - TMP-SMX DS 1 tablet BID
  - Atovaquone 750-1,500 mg PO BID + pyrimethamine 25 mg PO QD (+ leucovorin 10 mg PO QD)
  - Atovaquone 750-1,500 mg PO BID + sulfadiazine 2,000-4,000 mg PO daily in 2-4 divided doses
  - Atovaquone 750-1,500 mg PO BID
Mycobacterium avium complex

- M. avium is the etiological agent in >95% of patients with AIDS who acquire disseminated MAC disease
- The mode of transmission is thought to be through:
  - Inhalation
  - Ingestion
  - Inoculation via the respiratory or gastrointestinal tract (person-to-person unlikely)
Disseminated MAC: Epidemiology

- Usually occurs in people with CD4 count <50 cells/µL
- Incidence: 20-40% in patients with advanced AIDS who are not on effective ART or MAC prophylaxis
- Other risk factors: plasma HIV RNA >100,000 copies/mL, previous opportunistic infections, previous colonization with MAC
- 10-fold decrease in incidence in areas with effective ART
MAC: Clinical Manifestations

- Usually a disseminated multiorgan infection
  - Symptoms: fever, night sweats, weight loss, fatigue, diarrhea, abdominal pain

- Localized manifestations most common in persons on ART:
  - lymphadenitis (cervical or mesenteric), pneumonitis, pericarditis,
  - osteomyelitis, skin or soft tissue abscesses, genital ulcers, CNS infection
Disseminated MAC: Diagnosis

- Confirmed diagnosis: compatible signs and symptoms plus isolation of MAC from blood, bone marrow, lymph node, or other normally sterile tissue or fluid
- Other studies may support diagnosis (eg, AFB smear and culture of stool or tissue biopsy, radiographic imaging)
Disseminated MAC: Prevention

- Preventing exposure
  - No recommendations; MAC organisms are common in the environment

- Preventing disease
  - Recommended for all with CD4 count <50 cells/µL
  - Before prophylaxis, rule out disseminated MAC disease (clinical assessment +/- blood culture)

- Stopping prophylaxis
  - Discontinue in patient on ART with increase in CD4 count to >100 cells/µL for ≥3 months

- Restart prophylaxis
  - if CD4 count decreases to <50 cells/µL
Disseminated MAC: Prevention

**Primary prophylaxis:**
- Azithromycin 1,200 mg PO Q week
- Clarithromycin 500 mg PO BID
- Azithromycin 600 mg PO TIW

**Alternative:**
- RFB 300 mg PO QD (adjust dosage based on interactions with ARVs)
  - Rule out active TB before use
  - Significant interactions with PIs and NNRTIs
Disseminated MAC: Prevention

- Clarithromycin + RFB not more effective than clarithromycin alone
  - Should not be used

- Azithromycin + RFB more effective than azithromycin alone:
  - Higher cost, adverse effects
  - Risk of drug interactions
  - No demonstrated survival benefit
  - Not recommended
Disseminated MAC: Treatment

• Initial treatment (≥12 months)
  • At least 2 drugs, to prevent resistance

Preferred

• Clarithromycin 500 mg PO BID + ethambutol 15 mg/kg PO QD

• Azithromycin 500-600 mg PO QD + ethambutol 15 mg/kg PO QD (when drug interactions or intolerance precludes use of clarithromycin)
Disseminated MAC: Treatment

- Consider adding 3rd or 4th drug, if CD4 count < 50 cells/µL, high mycobacterial load, in absence of effective ART, or if drug resistance likely
- Clarithromycin + ethambutol + rifabutin improved survival and reduced emergence of resistance in earlier studies; no data in context of effective ART
- Alternatives to rifabutin, or possible 4th agents: amikacin, streptomycin, levofloxacin, moxifloxacin
Disseminated MAC: Treatment

- Rifabutin interacts with many ARVs:
  - Some combinations are contraindicated
  - Some require dosage adjustment
- Efavirenz may decrease clarithromycin levels
  - Increase level of active metabolite
  - Clinical significance is unknown
Disseminated MAC: Monitoring

- Clinical improvement and decrease in quantity of MAC in blood or tissue are expected within 2-4 weeks after start of appropriate therapy; may be delayed if extensive disease or advanced immunosuppression
- If little or no clinical response to therapy: repeat MAC blood culture 4-8 weeks after initiation of therapy
Disseminated MAC: Adverse Events

- Clarithromycin, azithromycin: nausea, vomiting, abdominal pain, abnormal taste, transaminase elevations, hypersensitivity
  - Clarithromycin doses >1 g per day for MAC treatment are associated with increased mortality, should not be used
- Rifabutin doses ≥450 mg/day: higher risk of adverse interactions with clarithromycin or other inhibitors of cytochrome P450 3A4; possible higher risk of uveitis, neutropenia, other adverse effects
Summary

- Patient compliance is vital for survival
- HIV infects CD4+ T4 helper lymphocytes and can lead to the development of opportunistic infections
- OIs usually present in people with AIDS status
- Early detection of the virus can prevent complications
- Education is key!!!
References

- https://www.cdc.gov/hiv/basics/
- https://www.avert.org/hiv-transmission-prevention/myths