HIV and AIDS Academic Half Day
(adapted from UC)

Case #1
A 27 y/o previously healthy male presents with 2 days of mild fever, sore throat, generalized malaise. You note cervical and axillary lymphadenopathy, mild meningismus, and a diffuse maculopapular rash on his trunk and neck. On further history he notes an episode of unprotected intercourse roughly 2 weeks prior. He had otherwise not been sexually active for many months.

1) How does Acute HIV present and what else should be in your differential?

*Symptoms of **acute HIV** can include acute malaise, myalgias, anorexia, weight loss, GI upset, aphthous ulcers, lymphadenopathy, pharyngitis, and rash. This is a very similar presentation to many other acute viral illnesses. Oftentimes, individuals have non-specific or mild symptoms and do not come to the attention of healthcare providers during the acute phase.*

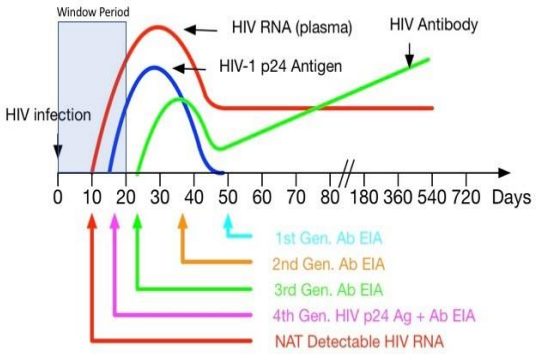
Suspect acute HIV as a possible etiology in patients with " fever and rash presentation", "aseptic meningitis presentation", " flu-like syndrome", and "infectious mono like syndromes" among others.

Differential Diagnosis:
Most Common: EBV, Influenza, Strep pharyngitis, Viral/Noninfectious gastroenteritis, Viral URI
Less Common: Acute Viral Hepatitis, Drug Reaction, Primary Herpes Simplex, Secondary Syphilis
Uncommon: Acute CMV, Disseminated Gonococcemia, Primary Immunodeficiencies, Measles, Travel Related Diseases – Malaria, Typhoid

2) You suspect Acute HIV. What is the best test to order at this time and why?

*There are two different approaches that you can take to diagnose acute HIV. With both methods you have to consider the **window period** (Ab not detectable). If a patient is having symptoms then they likely have a positive RNA, but may not have a detectable Ab or Ag:*

a) *Order 4th generation HIV Ag/Ab test – This test detects the p24 antigen, which is detectable approximately 15-20 days after HIV exposure, or 5-7 days after viral RNA is detectable. In a case of acute HIV you would expect for the Ab to be negative (because it doesn't form until 3-5 weeks post-exposure) and the Ag to be positive. If the test is negative, but you still have a high suspicion for acute HIV then you can repeat the test in 2-4 weeks. The benefit of this test is that it is less expensive than the viral PCR.*



b) *Order HIV Viral RNA- This test turns positive sooner after HIV exposure (after 5 days for the ultrasensitive test).*

But this test may take up to 5 days to be resulted!

If high suspicion perform a rapid 4th generation, and send the blood for Viral load to lab at the same time.

3) You check the lab discussed above. What do you think this patient's CD4 count, RNA PCR, HIV Antibody testing to show?

RNA PCR / Viral Load – Elevated. High viremia means that the patient is very contagious.
CD4 Count – Variable in acute HIV
HIV Antibody – May not be present yet due to window period. p24 antigen might be positive, though

4) You discuss the patient's HIV infection as well as Anti-Retroviral Therapy (ART). Who should be treated with ART? After initial diagnosis, what other baseline labs should he receive?

Indications for ART:

- *All patients with HIV should be offered ART regardless of CD4 count and it should be initiated as soon as possible.*
    - *Reduces serious AIDS- and non-AIDS-related complications.*
    - *Reduces risk of AIDS-related morbidity and mortality in CD4 < 350*
    - *Reduces risk of transmission*
- *Prior to initiating ART make sure that the patient is agreeable to the medication and willing to commit to a lifelong daily medication regimen. Suboptimal adherence reduces effectiveness and can induce permanent resistance to antiretroviral medications. Also make sure that there are no financial barriers to obtaining the medication – link patients to social services, case management, HIV education, and counseling as indicated.*
    - *If there are barriers to treatment then address these barriers prior to starting ART.*

Baseline Labs:

- *Comorbidities & ART Monitoring: CBC, Renal Function (HIV Nephropathy), Hepatic Function, Lipid Profile (increased risk of cardiac events in HIV and effects of ART), Glucose*
- *Disease Baseline: HIV RNA level and CD4 count*
- *Resistance Testing: HIV Genotyping*
- *Infectious Screening:*
    - *Toxoplasma IgG – if future low CD4 < 100 then will need prophylaxis with Bactrim*
    - *Syphilis Testing – Trepia if no history of syphilis and RPR if positive history of syphilis*
    - *Gonorrhea/Chlamydia - swab all orifices (vagina or urine, anal, throat)*
    - *Hepatitis B – HIV quickens liver damage of HBV and if co-infected with HBV then this affects ART regimen selection.*
    - *Hepatitis A and C*
    - *PPD or Quantiferon – for PPD Induration > 5 mm is positive in the HIV+ population*
- *Side Effects*
    - *G6PD – Test in patients of Mediterranean or African origin*
    - *HLA-B*5701 – Test before initiation of abacavir due to risk of hypersensitivity reaction*
- *Pregnancy test – alters treatment regimen and is an absolute indication for treatment.*

5) How are you going to monitor their HIV and potential complications?

Serial CD4 Counts and Viral Loads – Every 3 to 6 months. Newest guidelines (2018) say viral load q 3 months until <50, for one year, then q 6 months. A bit more controversial is CD4 count q 6 months until >250 for a year, then stop checking CD4 unless viral load increases.

<u>Co-infection screening:</u> GC/Chlamydia, Syphilis screening, HCV yearly. The annual HCV testing is only for high risk population (all MSM and active drug users).

6) What preventative care items need to be addressed in patients with HIV?

<u>Vaccinations:</u> Have learners note what vaccines (live) are contraindicated in patients with low CD4 counts. Can discuss why prevnar should be given prior to pneumovax. Prevnar, PCV13 is a conjugated vaccine whereas pneumovax, PPSV, is a polysaccharide vaccine. PCV is recognized as T cell dependent, stimulating antibody response, mucosal immunity, and immunologic memory. PCV stimulates memory B cells and can "prime" the immune system for an enhanced secondary immune response to PPSV.

	HIV Infection with CD4 < 200	HIV Infection with CD4 >=200 for 6 months
Influenza (inactivated)	**1 dose annually**	
Influenza (live)	**Not recommended**	
Tdap	**1 dose Tdap then Td or Tdap booster every 10 years**	
MMR	**Not recommended**	**2 doses**
Varicella	**Not recommended**	**2 doses**
Shingrix	**No recommendation**	
Zostavax	**Not recommended**	**No recommendation**
HPV	**3 doses through age 26**	
PCV13	**1 dose**	
PPSV23	**1st – 8 weeks after PCV13, 2nd – 5 years later, 3rd – after age 65 and 5 years from previous PPSV23**	
Hep A	**2 or 3 doses depending on vaccine**	
Hep B	**2 or 3 doses depending on vaccine**	
MenACWY	**2 doses 8 weeks apart and then Q5Years**	
MenB	**Recommended if another risk factor or indication**	
Hib	**Recommended if another risk factor or indication**	

<u>Cancer Screening</u> – Typical screening per age. However, recommendations state that women with HIV should have more frequent pap smear testing initially after diagnosis (every 6 months – 1 year until 3 consecutive negative tests then can space).
Anal cancer screening in HIV+, MSM 35 or older by anal pap smear is recommended.

<u>Other Screening</u> – Typical guidelines for AAA screening, osteoporosis, AAA, depression, etc.

Case #1 Continued

Your patient moves to Florida and loses touch with the medical system. 12 years later he presents as a 39 year old male with a generalized tonic-clonic seizure. Prior to this, he had a 2-3 week history of fevers and headaches. His CD4 count is 14, His HIV RNA is >500,000. He is confused, and has a temperature of 101. He has no nuchal rigidity. On a cursory neurologic exam he has no focal abnormalities.

6) What study would you like? What is on your differential? What do you think is most likely?

CT Scan without Contrast – QR code on next page. Shows discrete low-attenuation lesions in the basal ganglia and hippocampus

MRI with Gadolinium – QR code on next page. We see a ring enhancing lesion on imaging.

Differential Diagnosis - Most concerning given his CD4 count is Toxoplasmosis or CNS Lymphoma. Toxoplasmosis often has multiple ring-enhancing lesions. Brain abscess and tuberculosis are also on the differential, but less likely. If the lesion had been enhancing on only T2 with flair then PML (JC virus reactivation) would be on the differential diagnosis.

7) How would you further evaluate him? How would you proceed to treat and/or differentiate between etiologies of your differential?

<u>Toxoplasmosis serology studies</u> – If negative then unlikely to be toxoplasmosis. NPV for this test in this setting is better than PPV.
<u>CD4 Count</u> – If high CD4 count then unlikely to be toxoplasmosis. Toxoplasmosis reactivation typically occurs when CD4 < 100.
<u>Toxoplassma gondii PCR</u>- Detection of T. gondii *by PCR in cerebrospinal fluid has demonstrated high specificity (96 to 100 percent), but variable sensitivity (50 to 98 percent)]. Treatment also affects diagnostic sensitivity. Thus, a positive PCR result establishes the diagnosis of TE, but a negative one does not rule it out.*
<u>Brain Biopsy (open or stereotactic)</u> – This is the only way to definitively tell the difference between toxoplasmosis and CNS lymphoma.

***If history, PE and imaging is suggestive of toxo, then start empitic Toxo treatment (a positive Toxo serology is helpful but not required). Treatment is with pyrimethamine (+leucovorin to prevent marrow suppression) and sulfadizine. Look for clinical improvement within several days and follow for radiologic improvement in 2-3 weeks. If no improvement then move towards brain biopsy.*

8) How could this complication have been prevented in this patient? What are the indications for prophylaxis against Toxoplasmosis in patients with HIV?

*Patients with a **CD4 count <100 AND positive Toxoplasma IgG** should be given prophylaxis.*

*First line is **TMP-SMX 1 DS tab daily**. Alternative regimens include dapsone + pyrimethamine + leucovorin or atovaquone +/- pyrimethamine + leucovorin.*
Prophylaxis can be discontinued once CD4 >200 sustained over 3 months on ART.

Questions for the Expert

Break

Case #2

32 y/o M presents with 2 weeks of shortness of breath, dyspnea on exertion, and cough. He has a 25 lb weight loss over the past 2-3 months. He was diagnosed with HIV in 2006 and had a "pneumonia" five months ago. He takes only OTC medications. When he had "pneumonia", his CD4 was 135, HIV Quant 329,000 copies

Vital Signs: T 101F, HR 132, BP 80/40, RR 24, SaO2 80% on RA.

Physical Exam: He is thin, tacky mucous membranes, tachycardic, in moderate respiratory distress, has a mildly productive cough, no lymphadenopathy, and has some minor diffuse crackles in his lungs bilaterally.

1) What do you think is going on? How will you confirm your diagnosis?

Discuss differential: Concerning for PCP Pneumonia** – why? Subacute +/- acute decompensation, SOB, dry cough, fever, diffuse bilateral infiltrate. CXR can be normal in 1/3 of cases, High Res CT often has ground glass opacities. **Bacterial Pneumonia? Tuberculosis? Histoplasmosis?

Definitive diagnosis can only be made by demonstration of organism in tissue, sputum, or BAL fluid.
***Induced Sputum: Sensitivity 50-90%.** Consider obtaining if bronch is delayed. (needs expert lab interpreter- not routinely performed at LHH)*
***Bronchoscopy: Staining with Direct fluorescent antibody is most commonly used. PCR testing also available. Sensitivity 96-98%** by obtaining samples for PCR.*

Discuss empiric treatment vs definitive diagnosis.

***What about other possible tests?** Beta d glucan (a cell wall component of all fungi) has a high sensitivity and NPV for patients with PJP. Some learners may mention LDH, used to be present in 90% of HIV infected patients with PJP (in the age before ART).*

Can discuss management of respiratory failure and sepsis here as well – *the patient needs an ABG, both for grading severity of his respiratory failure (regardless of etiology) and for management decisions related to his likely PJP. He also needs to be started on sepsis protocol with fluid resuscitation due to his low blood pressure and tachypnea (Q-SOFA).*

2) You obtain the appropriate test and your suspicion was confirmed. How do you grade severity? How can you treat this infection?

See chart for treatment on next page. Need ABG to eval A-a Gradient. LDH useful correlates to severity/prognosis.

Moderate-to-severe disease is defined by ***room air pO2 <70 mm Hg*** *or* ***A-a O2 gradient ≥35 mm Hg***

Discuss who gets steroids and why. Patients can clinically worsen on the 2nd and 3rd days of treatment, thought to be due to inflammation due to dying organisms. Steroids can decrease the mortality and respiratory failure associated with PJP. Compared with placebo, the risk ratios for overall mortality in patients receiving adjunctive corticosteroids were 0.56 at one month and 0.59 at three to four months of follow-up. Corticosteroids for patients with moderate to severe disease.

Drug	Dosage
Preferred regimen	
TMP-SMX	TMP-SMX (15 to 20 mg/kg/day of the trimethoprim component) orally or IV given in three or four divided doses* ¶
Alternative regimens	
TMP **plus** dapsone Δ	TMP: 5 mg/kg orally three times daily ¶
	Dapsone: 100 mg orally once per day
Primaquine Δ **plus** clindamycin*	Primaquine: 30 mg (base) orally once per day
	Clindamycin: 900 mg IV every 8 hours **OR** 600 mg IV every six hours **OR** 600 mg orally three times daily **OR** 450 mg orally four times daily
Atovaquone suspension	750 mg orally twice daily (must be taken with food)
Pentamidine ◇	4 mg/kg IV once daily ¶
Adjunctive glucocorticoids §	
Prednisone	40 mg orally twice daily for 5 days, followed by 40 mg orally once daily for 5 days, followed by 20 mg orally once daily for 11 days

Adverse effects:

TMP-SMX: rash, fever, neutropenia, hyperkalemia, transaminase elevation
Pentamidine: nephrotoxicity, hyperkalemia, hypoglycemia, hypotension, pancreatitis, dysrhythmias, transaminitis
Atovaquone: rash, fever, transaminitis
Dapsone: rash, fever, GI upset, methemoglobinemia, hemolytic anemia (G6PD Deficiency)
Primaquine: rash, fever, methemoglobinemia, hemolytic anemia (G6PD Deficiency)

Clindamycin: rash, diarrhea, C diff colitis, abdominal pain

3) He is now nearing discharge. What prophylactic medications should this patient be discharged home with? What pathogens will be covered?

Table 7
Prophylaxis to prevent first occurrence of opportunistic infections in HIV/AIDS patients

Infection	Indication	Recommended Treatment	When to Discontinue
Pneumocystis pneumonia	CD4 count <200 or oropharyngeal candidiasis	TMP-SMX 1 DS tab daily OR 1 SS tab daily	CD4 count >200 for 3 mo
Toxoplasmosis	Toxoplasma IgG-positive patients with CD4 count <100	TMP-SMX 1 double-strength daily	CD4 count >200 for 3 mo
Mycobacterium tuberculosis	Positive screen for latent TB, or close contact with TB-infected person	Isoniazid 300 mg with pyridoxine 25 mg daily for 9 mo	After treatment
Mycobacterium avium complex	CD4 count <50	Azithromycin 1200 mg weekly	After treatment course (usually 12 mo, if needed) and CD4 count >100 for 3 mo

Alternative regimen for PJP: Dapsone 100 mg daily (check for G6PD)

Histoplasmosis: Can discuss. Not routinely done – this is a good question for the expert. ***Itraconazole at a dose of 200 mg daily*** *can be considered for patients with CD4 counts <150 cells/mm3 who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years). Ask the expert about indications in our patients.*

Case #3
45 year old F with history of AIDS (recent PCP Pneumonia) who presents with headache and fever for 2 weeks. Her boyfriend brought her in because today she was confused, didn't know where she was, and wasn't answering questions appropriately. Her temperature is 101 and she has some neck rigidity and grimaces when trying to flex her neck.

1) What is on your differential diagnosis?

Cryptococcal meningitis. Clinically has a subacute picture like above. Confirmation is by spinal tap. CSF examination is significant for lower WBC than cases of bacterial meningitis. More than 50% of AIDS patients with acute cryptococcal meningitis will have a CSF wbc count of less than 20.

Toxoplasma? Less likely as more than 90% of patients with AIDS with Toxoplasma encephalitis will have one or more mass lesion observed on contrast brain CT Scan. (YOU did not give us imaging results here!). So without that Toxo is also likely but less so and imaging would clarify diagnosis.

PML? The clinical presentation for PML does not include fever. CT is typically normal, but brain MRI would show extensive white matter lesions. Patient commonly presents with neurologic deficits including altered mental status.

CNS Lymphoma? Most patients with CNS lymphoma present with a focal finding and evidence of a mass lesion on brain imaging

2) What test helps to make the diagnosis?

<u>Cryptococcal antigen test</u> – CSF or Serum. Serum antigen test is positive >95% of patients with active crypto meningitis. Lumbar puncture is important to eval for bacterial meningitis and both Indian ink staining and antigen tests can be used to diagnose. (Indian ink faster but with low sensitivity, crypt antigen better sensitivity).

<u>Opening pressure</u> should always be measured and often is the clue that suggests cryptococcal meningitis. In a study among 221 patients, 54% had an opening pressure greater than 250mm H20 and 27% had an opening pressure greater than 350mm Hg H20.

Case #3 (Continued)

A CT is obtained which shows mild atrophy, but no mass lesions. A lumbar puncture is performed and analysis of the CSF shows 7 wbc/mm^3, glucose of 41 mg/dL, and a negative gram stain. The opening pressure is 310 mmH20. CD4 count is 12. Toxoplasma shows IgG is positive, and IgM is negative.

3) How do you treat the infection?

Start <u>induction therapy</u> with amphotericin B (0.7mg/kg) IV PLUS Flucytosine (100mg/kg PO daily) x 2 weeks. Liposomal amphotericin B preparation 3-5 mg/kg IV (preferred due to lesser side effects)

Then <u>consolidation</u> <u>therapy</u> fluconazole 400mg po daily x 12 weeks. Prior to moving to consolidation, patient must have substantial clinical improvement and a negative CSF fungal culture on repeat lumbar puncture.

Then step down to <u>Maintenance therapy</u>, fluconazole 200mg po daily. Therapy remains lifelong at 200mg daily unless patient has completed initial course of therapy, has no symptoms of cryptococcosis, and the patient's CD4 count >200 for at least 6 months.

4) Your patient is started on the above therapy and ARTs. At admission your patient initially improves, but then over the next 24-48 hours her mental status waxes and wanes. Her nurse calls you to the bedside to evaluate the patient – she is worried your patient may be seizing. What could be going on?

*Among other things, the patient could have symptoms from **increased intracranial pressure**. They may require **serial lumbar puncture taps**, especially if the patient is symptomatic. **Goal CSF pressure is <20cm H2O.***
Daily monitoring for headache or other signs of increased intracranial pressure is needed for patients with crypt meningitis and many need daily LP to control the intracranial pressure. Not treating increased intracranial pressure leads to worsen outcome. Rare patients may need lumbar or ventricular drains.

5) The patient improves with your treatment and is discharged on all of her medications with plans to complete therapy for her crypto meningitis. Several days later she returns with severe headache, nausea, vomiting, and malaise, and myalgia. She has had low grade fevers at home. She's been taking all of her medications, what could be going wrong?

She could have Immune Reconstitution Inflammatory Syndrome.
*Consider IRIS when i**nflammatory signs or symptoms occur after recent initiation, re-initiation, or change** to a more effective combination ARV therapy with associated **increase in CD4 cell** count and/or decrease in viral load and the following have been excluded:*

- *Worsening of known infections due to inadequate or inappropriate therapy*
- *New infections not known to be associated with IRIS (e.g., bacterial sepsis)*
- *Medication reaction*

Case #4
You are on Long Call one Wednesday night when one of your co-interns comes up to you and appears anxious. They tell you that they were performing an I&D on a patient with an arm abscess. When they were capping the needle after injecting lidocaine they accidentally poked their finger with the needle. They cleansed the area, but are now unsure what else to do and come to you for advice.

1) What is the risk of HIV transmission from an occupational needlestick exposure? What about other infectious bloodborne pathogens?

Results from a prospective study of occupational exposures to HIV showed:
Percutaneous Exposure – 0.33% risk
Mucosal Exposure – 0.09% risk
Intact Skin Exposure – <0.1% risk
Risk of Hepatitis B acquisition after percutaneous exposure was 6-30% and Hepatitis C risk was 1.8%.

Table 1
Human immunodeficiency virus transmission risks from exposure to an HIV-positive source with a nonsuppressive viral load

Risk Level	Exposure Category	HIV Transmission Risk from a Source with Nonsuppressed HIV Infection
High	Blood transfusion	92.5%
	Mother-to-child (vertical) transmission	22.6%
	Receptive anal intercourse	1.38%
	Needle sharing for injection drug use	0.63%
Moderate	Needlestick injury	0.23%
	Insertive anal intercourse	0.11%
	Vaginal intercourse (receptive)	0.08%
	Vaginal intercourse (insertive)	0.04%
Low	Insertive or receptive oral intercourse	No estimate
	Sharing sex toys	
	Blood on compromised skin	

Data from Tan DHS, Hull MW, Yoong D, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. *Can Med Assoc J*. 2017;189(47):E1448-E1458; and Patel P, Barkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. *AIDS*. 2014;28(10):1509-1519.

2) Who should your co-intern contact regarding this needlestick injury?

Northwell Employees: During Business Hours should go to Employee Health Services. After hours report to the ED.

3) What labs should be done on the source patient? What about on your co-intern?

Baseline SOURCE tests should include: Hepatitis B surface Ag, Hepatitis B core IgM, Hepatitis C Ab, Rapid HIV.

Baseline EXPOSED PERSON tests should include: Hepatitis B surface Ag, Hepatitis B surface Ab, Hepatitis B core Ab, Hepatitis C Ab, 4th Generation HIV

4) Should your co-intern be started on any medications at this time? What are the indications for post-exposure prophylaxis? How are the recommendations different between occupational and non-occupational exposures?

PEP (Post-Exposure Prophylaxis) is indicated to healthcare personnel with a percutaneous, mucous membrane, or intact skin exposure to blood or bloody bodily fluids of a patient with known HIV infection.

If the source patient's HIV status is unknown then PEP may be administered while awaiting HIV testing– particularly if the patient is high risk (i.e. IVDU, high-risk sexual activities) or has symptoms of HIV infection.

If the exposure happened in a high risk setting (i.e. needlestick from sharps container and patient cannot be identified) then also offer PEP.

PEP Regimens should be started ASAP (within 1-2 hours of injury):

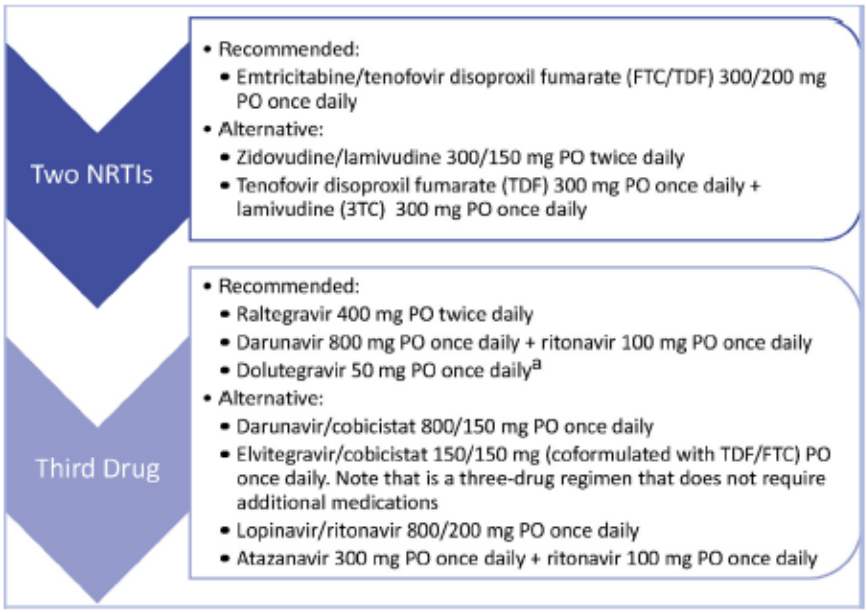


Fig. 1. Antiretroviral therapy options for PEP, favoring a 3-drug approach combining 2 NRTIs and an integrase inhibitor or a protease inhibitor. NRTIs, nucleoside reverse transcriptase inhibitors. [a] Dolutegravir should not be used in pregnant women and women of childbearing age, given the potential risk of neural tube defects.[20,21]. (*Data from* Refs. [7,14,16,24])

Duration of PEP is for 28 days. If the source patient's HIV testing comes back negative then the PEP may be discontinued prior to the completion of a 28 day course.
For non-occupational exposures (i.e. sharing needles, sexual assault, MSM, etc), patients should complete a full 28-day course of PEP since the source often cannot necessarily be tested.

5) The source patient is an injection drug user, but luckily they are HIV negative. They ask you how they can reduce their risk of acquiring HIV in the future. What advice would you give them?

PrEP is Pre-Exposure Prophylaxis for HIV. This is the proactive use of ART in HIV-negative individuals to mitigate the risk of HIV acquisition in those at greatest risk for infection. It has been shown to reduce HIV transmission at both an individual level and a population level.

Truvada (emtricitabine/tenofovir disoproxil fumarate) has been approved for use in PrEP. Descovy (emtricitabine/tenofovir alafenamide) is also approved for use in PrEP except in individuals who have receptive vaginal intercourse due to lack of efficacy data in this population.

If a patient is considering PrEP then the physician should also counsel on other methods to decrease the risk of HIV transmission (condoms, clean needles, etc.). Baseline labs include CBC, LFTs, Creatinine, HIV screening, Hepatitis A, B, and C screening, and STI screening.