PREVENTION AND TREATMENT OF HIV:
POLITICS, PREVENTION, AND PHARMACOTHERAPY OF A PLAGUE

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I. INHERENT DIFFICULTIES IN CONTROLLING HIV

A. Spreads via pleasurable and social activities: Sex, and needle sharing are positively reinforcing and intimate.

B. Remains Active in Body for Life: Efforts to avoid transmission-prone behavior must also continue lifelong. Permanent change is more difficult than temporary; relapse is extremely common.

C. Uses the system that is supposed to destroy it, for its reproduction, transport and transmission: It progressively destroys critical CD4 cells, rides macrophages as buses throughout the body and even into the brain, and uses these and other immune system cells for maintenance and as factories for replication.

D. Has an unusually long incubation period: For up to 10-15 years, you cannot tell if you (or your partners) have it, and you may be transmitting for years before it causes symptoms. As a slow, insidious enemy, it does not cause recognition and alarm like the immediate type of threat that mammals recognize and react to instinctively.

E. Continually mutates surface proteins to evade antibodies: The virus evades both natural antibodies caused by infection, and vaccines, by continually "altering the target" (mutating its surface antigens). As a result, the push for an HIV vaccine has been unsuccessful to date, frustrating numerous researchers.

F. Remains latent within protected sanctuaries: HIV, and RNA virus, produces a DNA copy within the cell's nucleus, where it is impervious to the immune system, able to persist in a latent state for up to the lifetime of the cell, and ready to begin replication if the cell's reproduction is stimulated. It also hides within protected niches such astrocyte cells in the brain.

G. Usual public health methods are difficult to apply to HIV: For most communicable diseases public health strategies depend on an environmental "fix," a vaccine to supplement natural immunity, treatment of infected persons to make them non-infectious (as well as to cure the disease), and/or isolation/quarantine to separate infected from uninfected persons. The first two are not available. Although there is no cure, treatment can theoretically cause less viral shedding by infected persons; however, treatment guidelines in recent years (now being

reconsidered) have called for treatment to be delayed until CD4 counts fall to levels that can take many years (see IV.A.1 below), which has worked against the use of antiviral medications as a public health control measure. In addition, patients anticipating reduced infectiousness have resumed unsafe behaviors, possibly neutralizing such protection. Any type of quarantine (i.e., official restrictions on certain activities by infected persons) would have to be lifelong, creating practical as well as political objections, although this strategy has been applied to some degree in Cuba.

H. "Viral reproductive rate," R_0, must be <1 for prevalence to gradually decrease, but this is especially difficult to achieve with HIV: A viral reproductive rate or <1 means that the average infected person will infect less than new person during an entire lifetime of infection. If R_o is even minimally greater than 1, incidence and prevalence continue to rise exponentially, until the population of susceptibles is becoming depleted, which in a homogeneously exposed population does not occur until about half the population is infected. Yet because of the extremely long incubation period before symptoms develop, by the time a person has symptoms of infection, the virus has usually been passed on already. Therefore, infected persons need early knowledge of their status, e.g., through partner notification. Even so, maintenance of lifelong safer behavior is difficult.

II. POLITICAL DIFFICULTIES IN CONTROLLING HIV

A. Techniques that are scientifically feasible have not been politically possible: Examples of public health control techniques successfully used for some other communicable diseases, which have met resistance in the case of HIV, include:

1. **Routine testing for the disease.** Routine HIV testing, without written consent requirements unique to this diseases, has been recommended for the healthcare setting by the Centers for Disease Control (CDC) only since September 2006, but is not yet legal in seven states including New York. The "opt-out" testing that CDC recommends requires specific advance notification of the patient of the intent to test and an opportunity to refuse. California's law permits testing without written consent, but only after specific information is provided as well as the opportunity to orally refuse is offered.

2. **Reporting by name to public health.** Name-based HIV reporting only became nationwide in 2007, after over two decades in which only cases meeting the criteria for AIDS were reportable, and several years of experiments with reporting earlier HIV cases by anonymous codes in key states (including those with the most cases). Meanwhile, AIDS is an increasingly irrelevant, arbitrarily defined concept (CD4 count <200 or one of a specific list of opportunistic diseases) for relatively advanced HIV disease.

3. **Contact investigation and partner notification.** In many parts of the U.S., such services are routinely provided for syphilis but are not routine for HIV. Being reported as a case does not lead to such contact investigations by public health, except in a few locations like New York where legislation has provided such a linkage. In October 2008, CDC recommended a common standard for such "partner services" for HIV, syphilis, gonorrhea, and Chlamydia, which for the first time implied that the services for HIV could be triggered by reporting; these recommendations have not yet been implemented nationwide.

4. **Case management to help prevent further transmission.** For HIV, programs funded by the Ryan White CARE Act offer social workers who serve as case managers for benefits like housing and social services, but are generally not trained or authorized to address prevention. CDC has developed effective prevention programs for HIV positives, under names such as "Prevention with Positives," but they are not linked with reporting and few infected individuals find their way into them.

5. **Sanctions on unsafe behavior.** Laws exist in some jurisdiction against intentional transmission of HIV, but this is almost impossible to prove. Negligent transmission can generally only be legally addressed by civil lawsuits. AIDS activists around the world have castigated such laws as criminalization of HIV infection, rather than accepting them as efforts to protect public health by encouraging responsibility by the infected not to infect others.

6. **Mandatory or routine and universal screening; and isolation/quarantine.** This approach is typical for tuberculosis control in the U.S. For HIV, it has been used rather successfully for HIV in Cuba, but is politically anathema in the U.S.

B. **A cynical definition of public health in a democratic society (don't quote this on exams!):** "The application of the democratic political process to the selection and management of health problems of the population." Unfortunately, the democratic political process can in turn be defined as "the sum total of self-interests, myths, prejudices, and delusions, balanced by the often less-expressed common sense, wisdom, ideals and practical experience, of all factions of the population." Public health programs need public mandates, public funding, and thus are inherently political.

C. **Ironic comparisons with hepatitis C:** HIV has lots of public funding but has legal restrictions on testing, was not reportable in many states for the first 25 years of the epidemic, and in most jurisdictions faces political restrictions on public health outreach to reported cases for prevention. Hepatitis C, which is far more prevalent in the U.S., does not face any such restrictions, but has minimal public funding.

D. Additional ironies: how opposing sides converged to frustrate the public health agenda: During the early years of the HIV/AIDS epidemic, the agendas of both AIDS activists and their conservative opponents often conflicted with traditional public health approaches. The activists opposed reporting, partner notification, and routine testing. The conservatives objected to socially explicit messages thought necessary for HIV/AIDS education, to sex education and condom availability for teenagers, to condoms for prisoners, and to permitting clean needles to be available without prescription. These attitudes persist to a lesser extent today, and still serve as barriers to legislation and public policy.

III. WHAT CAN WORK FOR PREVENTION?

A. The five stages of prevention as applied to HIV: Reducing exposure is always more "primary" and more effective than mitigating the effects of exposure. If risk behavior causing exposure continues unchanged, no method can be fully effective at avoiding infection. On the other hand, if exposure is avoided (stage 1 prevention), infection risk can be eliminated. The second stage of prevention is to mitigate the acquisition of disease due to exposure which continues. Measures that aim at mitigating disease acquisition without otherwise reducing exposure are sometimes referred to as "harm reduction." The third stage of prevention is to detect early disease and to prevent it from advancing as well as spreading (if infectious) to other persons. The fourth stage is to prevent complications resulting from advanced disease. The fifth and last stage of prevention is to avoid death from complications. In all of these stages, the appropriate target population must be identified.

B. Public health measures to control the disease at the source: As with other diseases, much of the prevention effort can be cost-effectively directed at identifying infected persons and helping to prevent further transmission. With TB, for example, we don't have everyone wear respirators as they walk down the street, we try to find and treat the small minority of people who are infected. But with HIV, for years we primarily asked everyone to wear condoms rather than identifying and working with the people who were infected. See also II.A above regarding the political barriers that have obstructed or delayed the adoption of the following strategies. These measures involve stages 1, 2, and 3 of prevention as just described, but are targeted at persons already infected and their contacts who are at risk.

1. **Reporting by laboratories and physicians** brings those who are infected to the attention of public health officials responsible for HIV prevention. However, if no preventive outreach is done, the reporting serves only general epidemiological purposes rather than helping to control transmission.

2. **Preventive outreach to infected persons** can include partner services (see below), referrals to "Prevention with Positives" or prevention case

management services, referrals to early and expert medical care if not already being followed by an HIV provider, assistance with adherence to antiretroviral regimens to prevent emergency of drug-resistance strains, and notifications about mental health services, ADAP program, and other programs available to HIV-infected patients.

3. **Notification and targeted prevention for exposed contacts:** Many people have no idea that they have been exposed. Notification and referral of contacts to testing and counseling leads either to the identification of new infections before they have been further transmitted, or to alerting individuals that they are at risk so that they can prevent becoming infected. Partner services have generally been sporadic or limited to the contacts of cases identified or followed at public health-related clinics. Since infected persons may acquire additional seronegative partners over time and not inform or adequately advise them about prevention, partner services should not necessarily be a one-time matter; HIV positives should be asked on an ongoing basis about new partners.

C. **Population-based public health approaches:** The target population for some measures may be the entire community, certain age groups, or risk-defined groups.

1. **Routine and universal testing** can identify almost everyone who is infected. This is a population-based approach, but it is also the starting point for a source-based approach outlined above, which can be initiated once the testing identifies cases. Everyone who has been sexually active, has used drugs associated with HIV transmission, or has had occupational or traumatic exposure to blood should be tested. Frequency of testing should increase and efforts to test should be intensified for persons who have already been involved in transmission-prone behavior.

2. **Education** is generally accepted as an essential part of HIV prevention, but should not be confused with behavior change. Many people are fully informed about HIV risk, but continue to engage in risk-prone behavior. Nevertheless, everyone who could potentially acquire HIV in their lifetimes (virtually the entire population) should be armed with knowledge about the disease and how to prevent it. Education can vary in complexity, and more detailed messages should be targeted to those at greater risk, e.g., information about the risks of specific sexual practices and the benefits of condoms is appropriate for all adolescents and adults but not children; information on cleaning needles is most appropriate for actual injection drug abusers; detailed information on HIV treatment is needed by persons who are already infected.

D. **Population-based approaches involving change of cultural sexual norms to reduce risk:** The **"A-B-C"** concept has been successfully used in Uganda,

where HIV incidence and prevalence have decreased, and has been adopted for U.S.-supported programs abroad, but not within the U.S.:

1. **Abstinence** is always the safest. Includes delaying first sexual activity among young people, which may have been the factor most responsible for HIV reduction in Uganda. Secondary abstinence of previously sexually active people is also important. This is a stage 1 prevention measure.

2. **Be Faithful,** if already sexually active. (Faithfulness should be with someone of the same serological HIV status, so routine testing is an important enhancement to this strategy if there is a significant prevalence of infection in the population.) A reduction in extramarital and other outside affairs has been a significant contributor to HIV reduction in Uganda. This is either a stage 1 or 2 prevention measure, depending on the certainty that neither partner in the relationship is already infected, and that additional exposure to others can be prevented.

3. **Condoms**, if abstinence is not practical and mutual monogamy cannot be depended on. Continuing high-risk sexual exposure but using condoms is a "harm reduction" strategy. In Uganda, this has made the least contribution of the three pillars of the A-B-C program, but in the U.S., it is the predominant strategy. This is a stage 2 prevention measure, which can be classed as "harm reduction."

E. Population-based approaches for Prevention and treatment of injection drug use: The "**D**" to supplement the A-B-C program.

1. **Prevention of exposure** means effective programs to keep kids from starting drug habits (stage 1 prevention), and getting addicts into treatment (if the addicts are already infected, this is a stage 3 measure; if not, it is stage 1 if abstention can be achieved).

2. **Needle exchange** is a controversial "harm reduction" (stage 2 prevention) strategy if drug use continues. Every supplied clean needle becomes a dirty needle the moment it is used. Making clean needs and syringes available without prescription at pharmacies is an alternative, which avoids using public health agencies or funds to distribute the means of continuing a dangerous and illegal practice.

4. **Ongoing prevention counseling** should be part of the continuing medical care of HIV-infected persons. This is a stage 3 prevention measure.

F. Other population-based "harm reduction" (stage 2) approaches:

1. **Promotion of circumcision** may play an increasing role as a population-based prevention strategy, because circumcision significantly reduces both infection of and transmission by males.

2. **Barrier protection for sex other than intercourse** is a potentially valuable strategy for prevention of multiple STDs. Condom use in populations has almost entirely been limited to vaginal and anal intercourse. Increased use of flavored condoms for fellatio, and of plastic wrap or latex dams for cunnilingus, can further reduce HIV transmission as well as that of genital herpes, HPV, pharyngeal gonorrhea, and labial syphilis. The development of latex or polyethylene panties that incorporate a female condom or that surround a male condom is a promising area for prevention (see www.zebrafoundation.org).

IV. CURRENT DRUG TREATMENTS FOR PATIENTS WITH HIV

(References used include multiple Web sources, package inserts, Epocrates, etc.)

A. Antiretroviral drugs to directly suppress HIV: Since 1996, standard treatment has consisted of "cocktails" of at least 3 drugs, from at least two different classes, to increase effectiveness and to slow resistance (HAART, or highly effective antiretroviral therapy).

1. **Former philosophy was to "hit early, hit hard."** NIH and other guidelines since 2001 call for **delay in treatment until CD4 count (normally about 1000) is below 350 (recently increased to 500), or the patient is symptomatic**, because of side effects and the potential to develop drug resistance over time. However, earlier onset of treatment could help reduce transmission (due to less virus in sexual secretions and blood), and there is an ongoing debate about whether it might have better long-term results. NIH Director Anthony Fauci has recently called for a "test and treat" approach that would revive the early treatment strategy.

2. **Treatment goals include undetectable "viral load" (HIV titer in blood) and an increase in CD4 cell count (which without treatment steadily decreases over time).** Three benefits of reducing viral load are delayed progression of HIV due to fewer circulating viral particles and fewer new cells infected; reduced viral shedding which can decrease infectiousness; and delayed development of resistance, since the risk of mutations is proportional the number of viruses reproducing. The higher the CD4 count, the greater the level of immunity against opportunistic conditions (AIDS is defined by a count of under 200). **Adherence to treatment regimens benefits public health as well as the individual,** because the development of multi-drug resistant strains can negate the value of all the research to develop these treatments, and can frustrate the global effort to provide treatment to infected persons. All of the above slow the progression of HIV, which not only prevent disability and death, but also can reduce the overall healthcare budget. Reducing healthcare

expenses for HIV/AIDS is a public benefit since public funds provide a major portion of the expenses of treatment.

3. **The currently available drug categories are discussed below.** The number of available drugs has expanded by 8 from 2003 to the present, with one new NNRTI, four new protease inhibitors, and one new drug each in the new classes of fusion inhibitors, CCR5 antagonists, and integrase inhibitors (month and year of approval listed below). More options are in clinical trials or earlier stages of investigation. As with bacteria and antibiotics, there is a continual race between the ability of the organism to develop resistance by mutation and the development of new drugs to fight it.

4. **Nucleoside reverse transcriptase inhibitors (NRTIs), the first class developed. Available agents:**
   a) **Zidovudine (Retrovir)**, the original antiretroviral drug, first shown to prolong life and to reduce opportunistic infections in 1987; still commonly referred to as "AZT." Many long-term survivors took this alone (five times a day) or with one other drug and their virus is now resistant to this drug. Can cause severe anemia. Very effective in preventing infection of newborns, so is added to regimens for pregnant women. Usual dose in combination with other antiretrovirals is one 300 mg tablet twice a day, without food restrictions; also available as a liquid.
   b) **Lamivudine (Epivir)**, also known as 3TC. Well-tolerated and can be combined with any other NRTI, but resistance develops rapidly. Can also be helpful for chronic hepatitis B (see 1.B.4 below). Traditional dosage was one 150 mg tablet twice a day; but once-daily dosage of 300 mg has also been found effective. Also available in oral solution.
   c) **Emtricitabine (Emtriva)** is very similar in action and sensitivity to lamivudine. It was approved for once-daily use before lamivudine was. Usual dosage is 200 mg daily. Also available in oral solution.
   d) **Stavudine (Zerit)**, also known as d4T; should not be used with AZT. Usually well-tolerated, however more strongly associated with lipodystrophy and pancreatitis than most other antiretrovirals, which has led to reduced usage. No known mutations identified by genotyping to cause resistance, but phenotypic resistance does occur. Usual dose is one 40 mg capsule twice a day, which is convenient. Also available in oral solution.
   e) **Didanosine (Videx)**, also known as ddI. Pancreatitis risk 1-9% (fatal in 6% if occurs) and neuropathy risk 5-12%, both increased if stavudine is also given. Alcohol may also increase toxicity. Until recently, given in two 200 mg chewable tablets once a day on an empty stomach; now available as a once daily capsule (Videx EC 400 mg), an advantage for compliance. Also available as a powder for solution.
   f) **Zalcitabine (Hivid)**, also known as ddC. Similar to didanosine, and must not be used together with it; also should not be used with lamivudine or stavudine, which limits usefulness. Apparently higher risk of pancreatitis

and other toxicity than with didanosine; now rarely used. Usual dose is one 75 mg tablet every 8 hours, without food restrictions except to avoid concomitant antacids.

g) **Abacavir (Ziagen),** also known as ABC, can be combined with any of the above, and shows little cross-resistance. Severe allergic reactions with fever, occur in 2-3% of recipients, are potentially fatal if drug is not quickly discontinued. Usual dose is one 300 mg tablet twice a day. Also available in oral solution.

h) **Combinations of NRTIs** can increase compliance and thereby possibly slow development of resistance (as has been done for TB with Rifater, which combines three TB drugs and can be taken once daily). **Combivir** combines zidovudine 300 mg with lamivudine 159 mg in a twice-daily tablet. **Trizivir** adds abacavir 300 mg to the other two, also twice daily, for a "protease-sparing" regimen, however it is no longer considered adequately effective without adding a drug from another class. **Epzicom** combines abacavir 600 mg with lamivudine 300 mg, and can be given once a day. Any of these combination drugs can be taken without regard to meals. See also **Atripla** below, a combination of an NRTI with a slightly different class of drug.

5. **Nucleotide reverse transcriptase inhibitors**. Similar to NRTIs but chemically preactivated and thus requires less biochemical processing in the body to become active. Only one drug in this class has been released**.**

   a) **Tenofovir (Viread)**, also known as TDF, the only available member of this group so far, is well-tolerated and has become widely used both for treatment and post-exposure prophylaxis. Raises blood level of didanosine. Usual dose is 300 mg tablet once daily (helpful for compliance, and making this drug a typical component of once-daily regimens). Tenofovir should be taken with food, preferably a full meal that contains some fat.

   b) **Combinations** of tenofovir with one or more drugs of other classes have been developed by the Gilead company. **Truvada** combines 300 mg of tenofovir with emtricitabine 200 mg, and is taken as one tablet daily. **Atripla** includes those same two drugs (tenofovir 300 mg and emtricitabine 200 mg), together with efavirenz (a drug made by a different manufacturer, see below) 600 mg, and provides complete therapy from three different classes in a single pill per day.

6. **Protease inhibitors (PIs), considered the most powerful class of antiretroviral drugs**, but also the class with the most side effects and drug interactions (the latter mostly due to the cytochrome P450 system).
   Available agents:

   a) **Saquinavir (Fortovase)** has largely supplanting the earlier poorly absorbed Invirase formulation of saquinavir, but requires twice as many pills). Usual dose is six 200 mg capsules 3 times a day, with a meal or up to 2 hours after a meal.

b) **Ritonavir (Norvir)**, a powerful PI but also the one with the very most side effects, drug interactions, and liver toxicity. Increases the blood levels of most other PIs, permitting them to be given in lower dosages. Use of ritonavir in small doses (usually 100 mg per day) for this effect is a concept called "boosting," and one other protease inhibitor comes combined with it (see Kaletra below). Usual dose is six 100 mg capsules twice a day, without food restrictions, but may be better tolerated with food. Also available as an oral solution.

c) **Nelfinavir (Viracept)**, popular because of *relative* convenience of dosage and *relative* freedom from special side effects except for 20-30% diarrhea risk. Usual dose is five 250 mg tablets twice a day with food; also available as powder for solution. Also available as an oral powder.

d) **Indinavir (Crixivan)**, widely prescribed because of good published results, but requires at least 8 glasses or 48 ounces of water a day to reduce a 5-15% risk of kidney stones, often with blood in the urine. Usual dose is two 400 mg capsules every 8 hours, with liquid but at least 1 hour before or two hours after a meal. This makes compliance somewhat difficult. Unlike other PIs, indinavir should not be combined with ritonavir.

e) **Lopinavir** was approved in 9/00, and is supplied as **Kaletra,** which includes in the same pill a small dose of ritonavir to increase lopinavir blood levels). Little cross-resistance with other PIs so can be tried when another PI has failed. Lopinavir is extremely potent against non-mutated ("wild") HIV. Well-tolerated except for 10-20% diarrhea risk. Usual dose is three capsules (each with 400 mg lopinavir and 100 mg ritonavir) twice a day. Also available as an oral solution.

f) **Fosamprenavir (Lexiva)** is a pro-drug converted to amprenavir. It was approved in 10/03 and replaced amprenavir itself (which was formerly available under the name Agenerase), because it was longer-acting and required fewer pills a day. Might have less adverse impact on lipids than with other PIs; HDL generally rises along with modest rises in more harmful fractions. Usual dosage is two 700 mg tablets twice daily, but when boosted with ritonavir the same dose can be taken once daily, or half the dose twice a day.

g) **Atazanavir (Reyataz**), approved 6/03. Raises unconjugated bilirubin levels, but not due to hepatic mechanism. Usual dose is one 300 mg capsule with ritonavir 100 mg, or one 400 mg (two 200 mg capsules) once daily, with food, if ritonavir is poorly tolerated. It is tempting to combine this drug with tenofovir and/or efavirenz to produce once-daily regimens, however both tenofovir and efavirenz reduce atazanavir levels. Ritonavir-boosted dosage is definitely recommended with these drugs; efavirenz should only be used in treatment-naïve patients, and a 400 mg dose of atazanavir is needed along with ritonavir. If given with an H2 receptor antagonist. or a proton pump inhibitor, complex timing requirements for the latter drugs are recommended, and the latter class is not recommended in treatment-experienced patients. If one of these acid-suppressing drugs is

given with tenofovir, a 400 mg dosage of atazanavir boosted with ritonavir should be used..

h) **Tipranavir (Aptivus)** approved 6/05, first non-peptide-based protease inhibitor, not subject to same mechanisms of resistance as earlier PIs. Recommended for treatment-experienced patients with resistance to other PIs. Usual dose is two 250 mg tablets with ritonavir 200 mg, taken twice a day. Also available as an oral solution.

i) **Darunavir (Prezista),** second non-peptide-based protease inhibitor**,** approved 6/06. For treatment-naïve patients, usual dose is two 400 mg tablets with ritonavir 100 mg, once daily. For treatment-experienced patients, dose is one 600 mg tablet with ritonavir 100 mg, twice daily. Recommended to give with food.

7. **Non-nucleoside reverse transcriptase inhibitors (NNRTIs), one commonly used with two NRTIs as a substitute for protease inhibitor ("protease-sparing regimens"); viral cross-resistance to the first three can be produced by a single mutation.**
   Available agents:
   a) **Nevirapine (Viramune)**, also known as NVP, the first NNRTI commercially available. Single-dose treatment of mother and baby at delivery is an inexpensive and effective regimen for reducing newborn infections that has been widely used in Africa, however this may promote drug resistance. Rash incidence 17%; severe skin or liver reactions within first 8 weeks can be fatal; hypersensitivity reactions may also include fever and joint or muscle pains. Usual dose is one 200 mg tablet twice a day; also available in a suspension.
   b) **Delavirdine (Rescriptor)**, the second NNRTI. Rash incidence 18%; apparently fewer severe or lethal reactions have been reported than with nevirapine. Usual dose is two 200 mg tablets 3 times a day; also available in a powder for solution.
   c) **Efavirenz (Sustiva)**, also known as EFV, the third NNRTI and most potent of the first three. Rash incidence 15-27% and nervous system side effects in up to 52%, usually mild. Usual dose is three 200 mg capsules once daily in the evening, an advantage for compliance. No liquid formulation.
   d) **Etravine (Intelence),** the newest member of the class (approved 1/08). Effective against virus resistant to other NNRTIs, however resistance by a separate mechanism can occur. Recommended only for treatment of strains resistant to other NNRTIs. Generally well-tolerated except for risk of rash, as with other NNRTIs. Usual dose is 200 mg (two 100 mg tablets) twice a day.

8. **Fusion inhibitors:** binds to gp41, an HIV protein that penetrates the cell membrane and interferes with its ability to approximate the two membranes. **Enfuvirtide** (**Fuzeon),** the only available agent in this class so far, was approved 3/03 for treatment-experienced patients (implying resistance to other

drugs, and not using as initial treatment), and can only be given by injection. Usual dose is 90 mg subcutaneously, twice a day. Injection site reactions are common.

9. **CCR5 Antagonists, also called "chemokine receptor antagonists:** bind to a cell receptor called CCR5, preventing an interaction with an HIV surface protein called gp120. Does not work well against HIV viruses that have adapted to find to another type of cell surface receptor, CXCR4. Therefore, an expensive tropism test should be done to determine whether the patient's HIV is exclusively CCR5-tropic, before starting treatment. **Maraviroc (Prezista),** the only available agent in this group so far, was approved 8/07 for treating HIV that is resistant to several other drugs. Usual dose is 150 mg twice a day. **Vicriviroc**, similar to maraviroc, is currently undergoing clinical trials.

10. **Integrase inhibitors** designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. Since integration is a vital step in retroviral replication, blocking it can halt further spread of the virus. **Reltegravir (Isentress)** was approved 10/07 for treatment-experienced patients or multiple drug resistance. Usual dose is one 400 mg tablet twice a day. **Elvitegravir** (Gilead, no brand name yet) is in advanced clinical trials.

11. **Investigation/experimental agents (Reference: Wikipedia: Entry Inhibitors)**
    Other agents are under investigation for the ability to interact with some component of HIV entry and the possibility they may serve as entry inhibitors.
    a) **TNX-355**, a monoclonal antibody that binds CD4 and inhibits the binding of gp120.
    b) **PRO 140**, a monoclonal antibody that binds CCR5.
    c) **BMS-488043**, a small molecule that interferes with the interaction of CD4 and gp120.
    d) **Epigallocatechin gallate**, a substance found in green tea, appears to interact with gp120 as do several other theaflavins.
    e) **b12** is an antibody against HIV found in some long-term nonprogressors. It has been found to bind to gp120 at the exact region, or epitope, where gp120 binds to CD4; b12 seems to serve as a natural entry inhibitor in some individuals. It is hoped that further study of b12 may lead to an effective HIV vaccine.
    f) **Griffithsin**, a substance derived from algae, appears to have entry inhibitor properties.
    g) **TRI-1144** is a candidate from Trimeris to begin a new generation of fusion inhibitors, to overcome the shortcomings of enfuvirtide.
    h) **DCM205** is a small molecule based on L-chicoric acid which is capable of directly inactivating HIV-1 in vitro. DCM205 is thought to act primarily as an entry inhibitor and represents a promising new microbicide candidate for the prevention of HIV-1/AIDS.

12. **Side effects of antiretroviral drugs:** Gastro-intestinal symptoms (nausea, diarrhea), neuropathy (pain, tingling, and/or numbness along nerves), skin rashes, and lipodystrophy (redistribution of body fat) are common to a number of antiretroviral drugs, and to HIV itself. Hyperlipidemia (elevations of cholesterol and triglycerides) and diabetes occur with a number of the drugs, and increase the risk of heart disease and stroke now that HIV patients are living long enough for these to occur. Individual drugs have additional special risks, some of which are listed above. Concern about such adverse effects has led to the recommendations to delay treatment.

13. **Compliance and resistance problems with antiretroviral drugs:** Resistance mutations develop rapidly when only one or two drugs are given, or if dosage is irregular or reduced.
    a) Resistance is rising rapidly even in the United States, and a Dutch study suggests only 50% of patients in a developed country take medications as prescribed (see separate handouts).
    b) Concerns regarding supply of these drugs to Third World include whether consistent implementation of multi-drug regimens are possible with little health care infrastructure; if not, possible massive development of resistance could make all known drugs useless worldwide.

14. **Antiretroviral Medications are not a cure.** They do not eradicate HIV, generally need to be taken indefinitely once they are indicated, and because of the risk of eventual viral resistance, there is no guarantee of permanent effectiveness.

B. <u>Antimicrobials to prevent or treat opportunistic infections (prophylaxis) that are the hallmark of AIDS</u>:

References: MMWR 51 (RR08): 1-46, June 14, 2002; Annals of Internal Medicine (120:11): 932-944, June 1, 2004

1. **Primary prevention (before apparent infection has occurred); examples:**
    a) **Prevention of *Pneumocystis carinii* (PCP) pneumonia**, using trimethoprim-sulfamethoxazole (Bactrim or Septra or generic); also effective against toxoplasmosis and bacterial pneumonias: given when CD4 count is less than 200/ml (a count that also defines AIDS). Also used as secondary prevention. Usual dose is one double-strength tablet daily, for primary or secondary prevention; but dosing only three times a week or using single-strength tablets daily generally works for primary prevention. This drug has the added advantages of also preventing toxoplasmosis and most bacterial pneumonia. Alternatives: dapsone 100 tablet daily (not effective for toxoplasmosis); dapsone 50 mg daily plus weekly pyrimethamine 75 mg and leucovorin 25 mg (effective also for toxoplasmosis); or aerosolized pentamidine using Respirgard II nebulizer,

300 mg once monthly. May be discontinued when CD4 count has remained above 200 for 3 months.

b) **Primary prevention of *Mycobacterium avium intracellulare* (MAI)**, using weekly azithromycin (Zithromax); given when CD4 count is less than 50/ml; may be discontinued if CD4 count remains above 100 for 3 months. Usual dose 1200 mg once a week. Alternatives: clarithromycin (Biaxin); rifabutin (Mycobutin) 300 mg daily; latter interacts with protease inhibitors. Also used as secondary prevention after resolution of disseminated or symptomatic gastrointestinal disease.

2. **Secondary prevention (for prevention of recurrence after an initial bout with infection, or prevention of activation of latent infection):**
   a) **Prevention of recurrences of *Pneumocystis carinii*:** See above.
   b) **Prevention of recurrences of *Mycobacterium avium intracellulare*:** See above.
   c) **Prevention of recurrences of systemic yeast (candidiasis) or serious systemic fungal infections (cryptococcal meningitis; coccidioidomycosis or Valley Fever)**, using fluconazole (Diflucan). Alternative: itraconazole (Sporonox) is effective prophylaxis for yeast or histoplasmosis. Prophylaxis is not recommended to prevent recurrences of oral or vaginal candidiasis, since treatment is not difficult and the risk of drug resistance and side effects from continual treatment outweigh the benefits.
   d) **Prevention of recurrences of cytomegalovirus (CMV) eye infections** with ganciclovir (Cytovene). Not recommended for primary prevention; cost to pharmacist approximately $18,000 per year; highly toxic (teratogenic and carcinogenic in animals). Usual dose is 12 tablets per day in three doses. Valganciclovir (Valcyte), a prodrug of ganciclovir, produces higher plasma levels equivalent to IV ganciclovir, may be given as two 450 mg tablets once daily, at cost to pharmacist of almost $21,000 annually; may replace oral ganciclovir. Alternative medications to these two require injection. Intravitreal implant with gancliclovir or intravitreal injections of fomivirsen (Vitravene) available.
   e) **Prevention of recurrences of herpes simplex,** if outbreaks are frequent or severe, can be achieved by acyclovir 400 mg twice a day, valcyclovir 500 mg twice a day, or famcyclovir 500 mg twice a day.
   f) **Prevention of activation of latent tuberculosis (TB)** in patients who already are infected (have positive tuberculin skin tests), using isoniazid (INH) for 9 months. Alternatives: Rifampin (Rifadin) for 4 months, rifampin plus pyrazinamide (generic) for two months (note: deaths recently reported from liver failure). HIV patients are not the only ones who get this preventive therapy, but they are 100 times more likely to activate latent TB so all HIV positive persons with positive tuberculin tests (5mm or more induration) should be treated. Rifampin interacts with protease inhibitors, so short-course TB preventive therapy is sometimes given before starting HIV treatment.

g) **Prevention of recurrence or of activation of latent toxoplasmosis** can be accomplished using trimethoprim-sulfamethoxazole, which is routinely given for PCP prophylaxis when CD4 count is below 200 (see above). Actually, toxoplasmosis activation is rare above a CD4 count of 100. If the patient is given dapsone instead, and CD4 count is below 100, antibody testing for toxoplasmosis can identify patients who should be considered for pyrimethamine with sulfadiazine for prophylaxis. Following treatment of active toxoplasmosis, maintenance with the latter two drugs is recommended. Dapsone alone is not considered effective, but is in combination with pyrimethamine.

3. **Persons without HIV also get prophylaxis for some infectious diseases:** An example of prophylaxis that is used for travelers but is *not* currently thought to be specially indicated for HIV: prevention of malaria with chloroquine (Aralen) or quinine. (Note, however, that Malarone, a combination drug for malaria prophylaxis, however, has a component (atavoquone) which is a third-line alternative for prophylaxis of *Pneumocystis*.)

4. **Control of chronic hepatitis C, using interferon and ribavirin (Rebetron and new pegylated interferon combinations):** Does not aim at preventing acute disease recurrence, but may in some cases avoid the mutual acceleration of progression of HIV and hepatitis C disease. These drugs have no effect on HIV itself. (Note, however, that one of the drugs besides interferon that is helpful against chronic hepatitis **B**, lamivudine or 3TC, is also one of the NRTI drugs used against HIV.)

C. Controversies Related to HIV-related Medications:

1. **High cost; affordability issues, especially in Third World.** Some countries are refusing to honor patents and trying to produce low-cost drugs themselves. Drug companies, responding to international pressure, are making medications less expensive in Africa.

2. **Advertising techniques have come under fire.** Ads showing healthy, active men supposedly taking the medications are thought to reduce concern for prevention.

D. General Commentary on Current Drug Treatments:

1. **Reduction in mortality:** Since the mid-1990s, there has been remarkable progress in availability of effective medications in developed countries. Death rates there have declined, hospices have emptied, AIDS patients who had been preparing for death have returned to work, and most opportunistic diseases have become less common. But mortality rates have now leveled off, and increased life expectancy means more people living with HIV.

2. **Limitations of treatment**: HIV treatments are not curative; they are extremely expensive and essentially still unavailable in most countries with highest rates; most regimens are complicated to take; they are toxic both acutely and chronically; and resistance is becoming more prevalent. They are not a substitute for prevention, which however is also very difficult.