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Slide 1. Antiretroviral Drugs in the Treatment and Prevention of HIV Infection

Slide 2. Uses of Antiretroviral Agents: Antiretroviral agents (ART) have revolutionized the treatment of chronic HIV infection. These development of these agents represents some of the most important pharmacological advances of the last century. Their use in combination regimens has resulted in tremendous declines in HIV-associated mortality. Most often, we think of antiretrovirals in the context of their use for the treatment of chronic HIV infection. This will be the focus of this lecture. However, antiretroviral agents have other important uses – notably in the prevention of HIV transmission – and we will discuss these issues as well. On this slide, you will see the topics to be covered: bold text represents established uses of ART, whereas the lighter text represents emerging or experimental uses of ART.

Slide 3. Antiretroviral Drugs: General Principles. There are currently 7 classes of FDA-approved antiretroviral agents and 22 individual drugs. Antiretrovirals must be used in combination to be effective. This combination is often referred to as HAART - Highly Active Antiretroviral Therapy.

Slide 4. FDA approved antiretroviral classes are listed on this slide. You will need to be familiar with each of the classes' unique characteristics. In general, you will not be required to memorize the names of individual drugs. However, in classes where only one drug exists I will refer to the individual drug by its name.

Slide 5. Location of action of the ART drug classes in the viral replication cycle. Every stage in the viral life cycle is a potential target for antiviral therapy. This slide graphically illustrates the stage in the viral life cycle where each of the ART classes work.

Slide 6. These are pictures of some nucleoside analogues. The point of this slide is to show the similarity in structure to host nucleotides.

Slide 7. Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)

Slide 8. Nucleotide reverse transriptase inhibitors work almost identically to NsRTIs. Clinically, they are used interchangeably.

Slides 9, 10. These slides illustrate the mechanism of action of, and resistance to, NRTI's. As can be seen in the illustration, NRTI's act as

competitive inhibitors of reverse transcriptase by competing with host nucleotides for incorporation into the elongating DNA chain. Incorporation of these agents into the viral DNA chain results in chain termination.

Slide 11. NNRTIs

Slides 12, 13. Mechanism of action and resistance to NNRTIs: As can be seen in the illustration, NNRTI's act as non-competitive inhibitors of reverse transcriptase. By binding to the enzyme at a site different from the active site, a conformational change occurs which prevents further incorporation of host nucleotides into the growing viral DNA chain.

Slide 14. NNRTIs have multiple drug-drug interactions and adverse effects. The slide summarizes what you need to know about these characteristics.

Slides 15, 16. Protease Inhibitors

Slide 17. Entry inhibitors: This is an umbrella term for two classes of FDA approved agents: 1) the fusion inhibitor *enfuvirtide* and 2) the CCR5 antagonist *maraviroc*.

Slide 18. Mechanism of action of *enfuvirtide*, the only FDA approved fusion inhibitor. As can be seen in this slide, the fusion inhibitor works by binding to a viral envelope glycoprotein gp41. Gp41 anchors the virus to the CD4+ cell. A conformational change in gp41 structure allows the surface of the virus to come into proximity with the host cell. This is depicted on the lower left hand of the slide. The fusion inhibitor binds to gp41 and prevents this conformational change, thereby preventing the viral surface from coming into proximity with the host cell – viral-cell fusion is thus aborted. Resistance to this agent emerges through mutations in the gp41 protein that prevent proper binding of the fusion inhibitor.

Slide 19. Mechanism of action of *maraviroc*, the single agent in the CCR5 antagonist class. HIV requires the presence to the CD4 receptor *and an additional coreceptor*, in order to bind and fuse with the host cell. Two chemokine coreceptors have been identified: CCR5 and CXCR4. Most new HIV infections are caused by viruses utilizing the CCR5 coreceptor. These are known as *R5 tropic* viruses. The CCR5 antagonist binds to CCR5 thus preventing the virus from utilizing the coreceptor. This class of agents is *not* active against CXCR4 tropic virus.

Slide 20. Maraviroc was designed and approved for HIV-infected patients with multidrug resistant virus. However, there is now interest in studying this drug in newly infected and treatment naïve individuals. On this slide

you can see data from various cohorts of HIV infected patients – naïve and experienced – and the proportion of R5 tropic virus identified in each of the cohorts. As the slide clearly illustrates, patients who are treatment experienced (and therefore have presumably been infected longer and with more advanced disease stages) have lower prevalence of pure R5 tropism. Remember that the CCR5 antagonist is NOT active against X4 or X4/R5 (dual/mixed) tropic virus.

Slides 21, 22. Integrase Inhibitor.

Slide 23. Treatment of Chronic HIV Infection: When to Start? Although this seems like a straightforward question, this is an area of active debate and flux amongst HIV providers.

Slide 24. When to initiate antiretroviral therapy in the course of HIV infection is one of the biggest questions facing patients and clinicians. On this slide you will see the main factors contributing to our decision to recommend initiation of treatment. In bold are the major factors, and in lighter text are additional factors that may sway the patient and clinician to initiate therapy. In terms of clinical measures, there is general consensus that any patient who is symptomatic must be treated. Likewise, patients whose CD4 counts have dipped below 350 cells/ml should be offered treatment. The decision to treat must be a collaborative decision between clinician and patient. In asymptomatic patients with high CD4 counts (greater than 350) some factors may favor initiation of treatment – these are listed on the slide in light text. There are no RCTs to guide us in terms of the perfect time to initiate treatment. However, population based observational studies have shown that waiting until the CD4 count has dropped below 200 is associated with greater morbidity and mortality. Early treatment must be balanced by a recognition of potential for long term toxicities and the commitment of the patient to a lifetime of treatment.

Slide 25. Treatment of Chronic HIV Infection: What to Start? This slide describes some of the pre-treatment variables that need to be evaluated when choosing an initial antiretroviral regimen. None of these are absolute guides for the use of a particular drug or drug class but may sway your choice towards a particular combination.
-Resistance testing is now recommended at baseline due to significant rates of resistance in treatment-naïve patients. This type of resistance is called “primary resistance” and signifies that the individual was infected with a drug resistance strain (as opposed to “acquired resistance” which develops as a consequence of non-suppressive use of ARTs).
-Some agents are contraindicated in pregnancy (namely efavirenz - an NNRTI) while some agents have been shown to definitively decrease

mother to child transmission. This issue should be explored before deciding on a regimen.
-There is a high prevalence of viral hepatitides among HIV-infected patients. Chronic HBV can be treated with certain (but not all) NRTIs. Therefore, in an HIV/HBV coninfected individual, choice of NRTIs should include those which also treat hepatitis B. No antiretroviral agents are active against hepatitis C. However, there are overlapping toxicities between certain antiretrovirals and antiviral agents used in the treatment of hepatitis C. Thus, if HCV treatment is planned certain ART agents should be avoided to prevent overlapping toxicities.
-There is a growing awareness that certain antiretroviral agents, notably the protease inhibitors, are associated with metabolic derangements and coronary artery disease.

Slide 26. First line Antiretroviral Therapy: In general, combination ART (cART, also known as HAART) is composed of : 2 NRTI's with EITHER an NNRTI OR a ritonavir-boosted protease inhibitor. The slide represents this graphically.

Slide 27. Goals of Antiretroviral Therapy

Slide 28. Phases of Viral decay. This slide shows the various phases of viral response to medications. Viral load decreases rapidly and substantially in the first 2-4 weeks of treatment when viral replication in productively infected CD4+ T cells is inhibited. Because of this rapid action, viral load measurements are used to monitor treatment response early in the course of treatment. By 16-24 weeks of treatment, the viral load should be undetectable, as viral replication in latently infected cells is inhibited.

Slide 29. Limitations of Currently Available ART are listed on this slide

Slide 30. Causes of treatment failure. In bold, the most common causes of treatment failure, including the emergence of drug resistance and treatment non-adherence. These two phenomena are linked to one another. It is rare for viral resistance to emerge in fully adherent patients on a HAART regimen. Other less common causes of viral resistance are listed in lighter text.

Slides 31, 32. HIV Resistance: Underlying Concepts and Implications

Slide 33. Annual death rates due to HIV in the United States 1987-2005. As you can see from the slide, a tremendous dip in deaths around 1995 coincided with introduction of HAART.

Slides 34, 35. Prevention of mother to child transmission and trends in perinatally acquired AIDS in the United States.

Slide 36. Post-exposure prophylaxis is divided into two types of uses: occupational and non-occupational. In the course of your career as physicians you may experience an occupational exposure or be around someone who has had an occupational exposure. There is very little data on the efficacy of ART in preventing transmission in this context because rates of transmission are extremely low. At this stage, an RCT cannot be ethically conducted. Our data is based on a case-control study of AZT monotherapy conducted in the pre-HAART era that showed an 80% decrease in transmission. The current standard of care is to provide 28 days of cART. Non-occupational exposure - as in the case of sexual assault, barrier method failure, or injection drug use exposure - is an indication to provided non-occupation PEP (nPEP). If data about the source patient can be obtained PEP can be tailored accordingly. Time is of the essence! The sooner the better for PEP. Efficacy after 72 hours is unknown but thought to be substantially diminished.

Slide 37. Treatment of Acute HIV infection. Acute HIV refers to the stage of infection following exposure but prior to the development of HIV-specific antibodies. This stage is characterized by a viral-like illness and extremely high viral loads. The slide describes the rationale for considering treatment during acute HIV. Treatment at this stage is not considered standard practice. Trials are underway to determine whether treatment of acute HIV is beneficial.

Slide 38. Pre-exposure prophylaxis: This is a controversial use of ART. PrEP refers to the use of antiretrovirals *prior to* a potential exposure to HIV. In other words, ART use is timed with sexual intercourse between serodiscordant couples. This strategy has not been proven effective in preventing HIV transmission in clinical trials. In general, it has been studied mostly in mathematical models. The use of ART-containing microbicides should also be mentioned although it is not usually considered a form of PrEP. However, I think it is important for you to know that antiretroviral agents are being investigated in use for topical microbicides as a strategy to prevent HIV transmission.

Slide 39. Antiretroviral Treatment in the Control of the HIV Epidemic. It has been suggested by some researchers that ART can be used to reduce transmission on a community level. This hypothesis is based on the observation that risk of transmission is proportional to the degree of viremia in the infected patient – in other words the higher the viral load the higher the infectiousness. Extrapolating from this data, mathematical models have hypothesized that the propagation of an epidemic is proportional to the mean HIV RNA level in the community. The

reproduction number (R0) is a measure of the ability of an epidemic to propagate – the higher the R0 the more likely the epidemic is to spread. If R0 is proportional to the mean community viral load, perhaps reduction of viral load through universal treatment might control the HIV epidemic? This strategy, which is highly controversial, has been termed the “test and treat” strategy – in other words, universal treatment for all HIV infected individual will be provided as a public health intervention. In a recent publication from the World Health Organization, researchers calculated that this type of approach may eliminate a generalized epidemic such as ones found in sub-Saharan Africa. However, whether this strategy is feasible and acceptable is unknown.

Slide 40. Summary