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Lecture title: Anti-Viral Drugs

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Summary:

1- Learning what is the anti-viral drugs

2- The most common Types of anti- viral drugs used

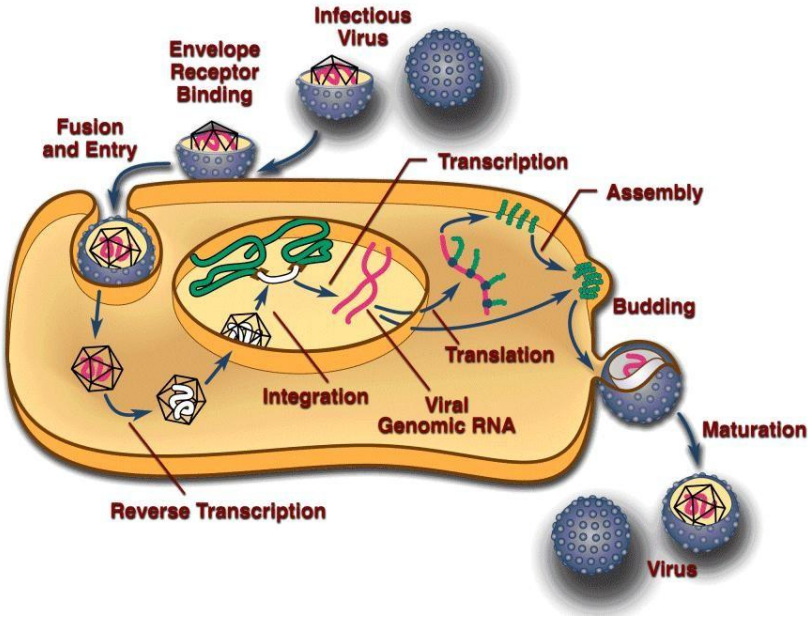
3- Considerations in the clinical development of antiviral agents

Antiviral agent

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead, they inhibit its development.

Most of the antiviral drugs now available are designed to help deal with HIV, herpes viruses (best known for causing cold sores and genital herpes, but actually the cause of a wide range of other diseases, such as chicken pox), the hepatitis B and C viruses, which can cause liver cancer, and influenza A and B viruses. Researchers are working to extend the range of antivirals to other families of pathogens.

Designing safe and effective antiviral drugs is difficult because viruses use the host's cells to replicate. This makes it difficult to find targets for the drug that would interfere with the virus without harming the host organism's cells. Moreover, the major difficulty in developing vaccines and anti-viral drugs is due to viral variation.



Virus life cycle and targets of antivirals

Types of anti-viral drugs mode of action

1. Before cell entry

One anti-viral strategy is to interfere with the ability of a virus to infiltrate a target cell. The virus must go through a sequence of steps to do this, beginning with binding to a specific "receptor" molecule on the surface of the host cell and ending with the virus "uncoating" inside the cell and releasing its contents. Viruses that have a lipid envelope must also fuse their envelope with the target cell, or with a vesicle that transports them into the cell, before they can uncoat.

A. Entry inhibitor

A very early stage of viral infection is viral entry, when the virus attaches to and enters the host cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight HIV. HIV most heavily targets the immune system's white blood cells known as "helper T cells", and identifies these target cells through T-cell surface receptors designated

"CD4" and "CCR5". Attempts to interfere with the binding of HIV with the CD4 receptor have failed to stop HIV from infecting helper T cells, but research continues on trying to interfere with the binding of HIV to the CCR5 receptor in hopes that it will be more effective.

B. Uncoating inhibitor

Inhibitors of uncoating have also been investigated.

Amantadine and rimantadine, have been introduced to combat influenza. These agents act on penetration/uncoating. They are M2 inhibitors which block the ion channel formed by the M2 protein that spans the viral membrane. The influenza virus enters its host cell by receptor-mediated endocytosis. Thereafter, acidification of the endocytotic vesicles is required for the dissociation of the M1 protein from the ribonucleoprotein complexes. Only then are the ribonucleoprotein particles imported into the nucleus via the nuclear pores. The hydrogen ions needed for acidification pass through the M2 channel. Amantadine and rimantadine block the channel.

2. During viral synthesis

A second approach is to target the processes that synthesize virus components after a virus invades a cell.

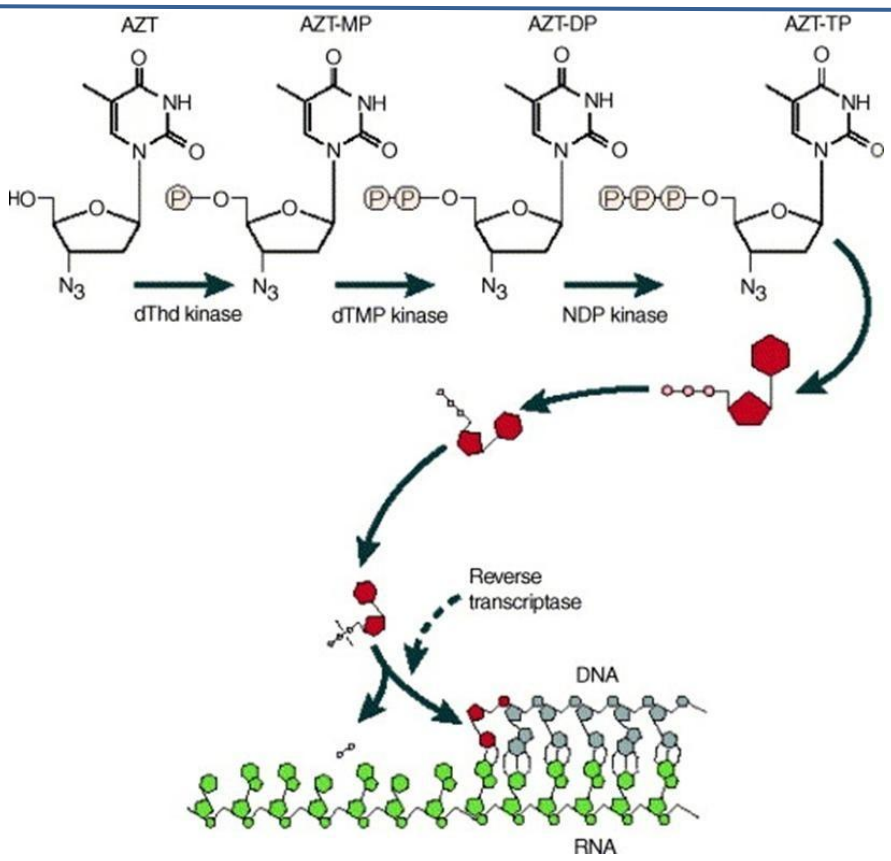
A. Reverse transcription

One way of doing this is to develop nucleotide or nucleoside analogues that look like the building blocks of RNA or DNA, but deactivate the enzymes that synthesize the RNA or DNA once the analogue is incorporated. This approach is more commonly associated with the inhibition of reverse transcriptase (RNA to DNA) than with "normal" transcriptase (DNA to

RNA). An improved knowledge of the action of reverse transcriptase has led to better nucleoside analogues to treat HIV infections. One of these drugs, lamivudine, has been approved to treat hepatitis B, which uses reverse transcriptase as part of its replication process. Researchers have gone further and developed inhibitors that do not look like nucleosides, but can still block reverse transcriptase.

Another target being considered for HIV antivirals include RNase H-which is a component of reverse transcriptase that splits the synthesized DNA from the original viral RNA.

Example of the mechanisms of antivirals: Mechanism of action of azidothymidine (AZT). AZT needs to be phosphorylated, in three steps, to the triphospate form before it can interfere with the reverse transcriptase reaction



B. Integrase

Another target is integrase, which splices the synthesized DNA into the host cell genome. There appears to be no functional equivalent of the enzyme in human cells. The biochemical mechanism of integration of HIV DNA into the host cell genome involves a carefully defined sequence of DNA tailoring (3'-processing) and coupling (joining or integration) reactions. In spite of some effort in this area targeted at the discovery of therapeutically useful inhibitors of this viral enzyme, there are no drugs for HIV/AIDS in clinical use where the mechanism of action is inhibition of HIV integrase. However there are several promising candidates in several classes of compounds, including nucleotides, dinucleotides, oligonucleotides and miscellaneous small molecules such as heterocyclic systems, natural

products, diketo acids and sulfones, that have been discovered as inhibitors of HIV integrase.

C. Transcription

Once a virus genome becomes operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins. Production of mRNA is initiated by proteins known as transcription factors. Several antivirals are now being designed to block attachment of transcription factors to viral DNA. Kao et al. recently identified a compound called nucleozin via random screening, which was found to inhibit influenza by interacting with influenza NP. Nucleozin causes the NPs to aggregate abnormally, and consequently inhibits normal viral transcription, crippling the replication cycle by extension. Examination of a nucleozin analogue revealed that the compound functions by binding to two copies of NP and forming abnormal dimers, causing the proteins to aggregate and preventing them from functioning normally. Nucleozin was also shown to inhibit influenza virus in vitro and in a mouse model, making it a promising candidate for a new antiviral drug.

D.Translation/antisense

Genomics has not only helped find targets for many antivirals, it has provided the basis for an entirely new type of drug, based on "antisense" molecules. These are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes, and the binding of these antisense segments to these target sections blocks the operation of those genomes. A phosphorothioate antisense drug named fomivirsen has been introduced, used to treat opportunistic eye infections

in AIDS patients caused by cytomegalovirus, and other antisense antivirals are in development.

E. Translation/ribozymes

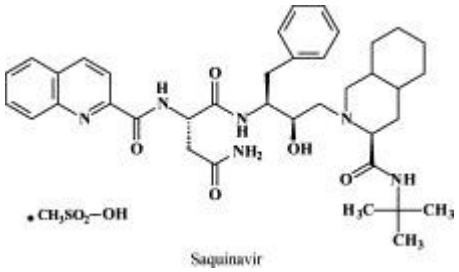
Yet another antiviral technique inspired by genomics is a set of drugs based on ribozymes, which are enzymes that will cut apart viral RNA or DNA at selected sites. In their natural course, ribozymes are used as part of the viral manufacturing sequence, but these synthetic ribozymes are designed to cut RNA and DNA at sites that will disable them.

A ribozyme antiviral to deal with hepatitis C has been suggested, and ribozyme antivirals are being developed to deal with HIV. An interesting variation of this idea is the use of genetically modified cells that can produce custom-tailored ribozymes. This is part of a broader effort to create genetically modified cells that can be injected into a host to attack pathogens by generating specialized proteins that block viral replication at various phases of the viral life cycle.

F. Protease inhibitors

Some viruses include an enzyme known as a protease that cuts viral protein chains apart so they can be assembled into their final configuration, such as Saquinavir (Figure 4). HIV includes a protease, and so considerable research has been performed to find "protease inhibitors" to attack HIV at that phase of its life cycle. Protease inhibitors became available in the 1990s and have proven effective, though they can have unusual side effects, for example causing fat to build up in unusual places.

Improved protease inhibitors are now in development.



Saquinavir

Protease inhibitor antiviral Saquinavir. : Structure: cis-N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl3(S)-[[N-2-quinolylcarbonyl-l-asparaginyl]-amino]butyl]-(4aS-8aS)-isoquinoline-3(S)-carboxamide methane sulfonate, hard gel capsules, Invirase®, also available as soft gelatin capsules (Fortovase®).Activity spectrum: HIV (types 1 and 2).Mechanism of action: transition-state, hydroxyethylene-based, peptidomimetic inhibitor of HIV protease

Release phase

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers. Two drugs named zanamivir (Relenza) and oseltamivir (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named neuraminidase that is found on the surface of flu viruses, and also seems to be constant across a wide range of flu strains.

Considerations in the clinical development of antiviral agents

A total of 37 antiviral compounds (not including interferons or immunoglobulins) have been licensed for the treatment of HIV, HBV, herpesvirus, influenza virus and/or HCV infections. In the preceding sections these compounds have been discussed from the following viewpoints: chemical structure, activity spectrum, mechanism of action, principal clinical indication(s). Other points that need to be considered before the full clinical potential of any given drug could be appreciated are:

(i) duration of treatment, (ii) single- versus multiple-drug therapy, (iii) pharmacokinetics, (iv) drug interactions, (v) toxic side effects and (vi) development of resistance. A particular issue that may be important in the clinical setting is whether the listed anti-HIV agents would be equally suited for the treatment of HIV2 and HIV-1 infections.

As to the duration of treatment, this may vary from a few days (HSV, VZV, influenza virus infections) to several months or years (HIV, HBV and HCV infections), depending on whether we are dealing with an acute (primary (i.e. influenza) or recurrent (i.e. HSV, VZV) infection or chronic, persistent (i.e. HIV, HBV, HCV) infection. For HIV infections it is still being evaluated whether long-term treatment can be interrupted, without loss of benefit (or increased benefit) to the patient (structured treatment interruption, STI).

While the short-term treatment (5–7 days) of HSV, VZV and influenza virus infections, and even the more prolonged treatment of CMV infections, can be based on single-drug therapy, for the long-term treatment of HIV infections combination of several drugs in a triple-drug cocktail (also referred to as HAART for ‘highly active anti-retroviral therapy’) has become the standard procedure, and likewise, the long-term treatment of HBV infections may in the future also evolve from single- to dual- or triple-drug therapy.

Pharmacokinetic parameters to be addressed, when evaluating the therapeutic potential, include bioavailability (upon either topical, oral or parenteral administration), plasma protein binding affinity, distribution through the organism (penetration into the CNS, when this is needed),

metabolism through the liver (i.e. cytochrome P-450 drug-metabolizing enzymes) and elimination through the kidney. Particularly when concocting the multiple-drug combinations for the treatment of HIV infection, possible drug–drug interactions should be taken into account: i.e. some compounds act as P-450 inhibitors and others as P-450 inducers, and this may greatly influence the plasma drug levels achieved, especially in the case of NNRTIs and PIs.

Toxic side effects, both short and long-term, must be considered when the drugs have to be administered for a prolonged period, as in the treatment of HIV infections. These side effects may seriously compromise compliance (adherence to drug intake), and could, at least in part, be circumvented by a reduction of the pill burden to, ideally, once-daily dosing.

Finally, resistance development may be an important issue, again for those compounds that have to be taken for a prolonged period, as is generally the case for most of the NRTIs, NNRTIs and PIs currently used in the treatment of HIV infections. Yet, the nucleoside phosphonate analogues (NtRTIs) tenofovir and adefovir do not readily or rapidly lead to resistance development, even after more than 1 year of therapy (for HIV and HBV, respectively). Resistance has been noted with HBV against lamivudine after long-term therapy (>6 months), but, if resistant to lamivudine, HBV infections remain amenable to treatment with adefovir dipivoxil. As has been occasionally observed in immunosuppressed patients, HSV may develop resistance to acyclovir, and CMV to ganciclovir, but, if based on ACV TK or CMV PK deficiency, these resistant viruses remain amenable to treatment with foscarnet and/or cidofovir. In immunocompetent patients,

treated for an acute or episodic HSV, VZV or influenza virus infection, short-term therapy is unlikely to engender any resistance problems.