Medicinal Chemistry
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Anti - Viral Agents Part – 1

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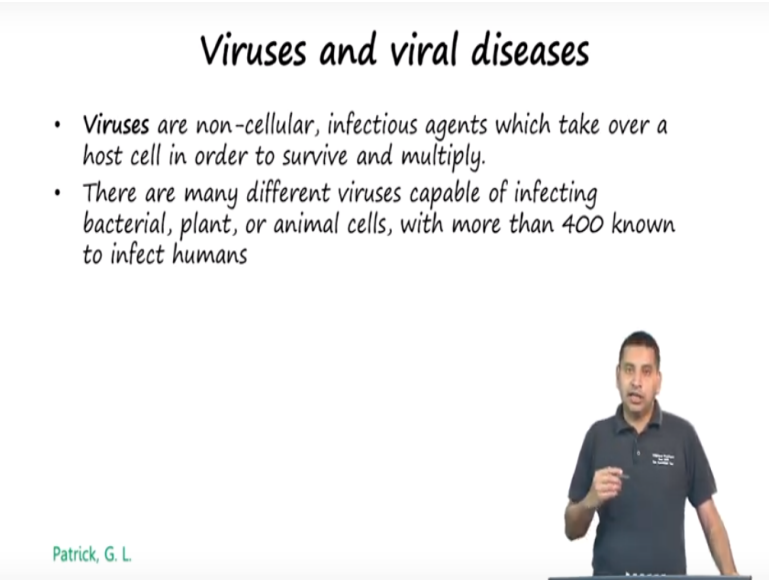

So in today's lectures we will look at the various antiviral agents, so to begin with viruses are actually very interesting organisms they are actually non-cellular infectious agents and they need a host cell for them to survive and multiplied, so there are of course you know wide variety of viruses which are capable of infecting bacterial, plant or unable cells and there about four hundred that are known to infect humans.

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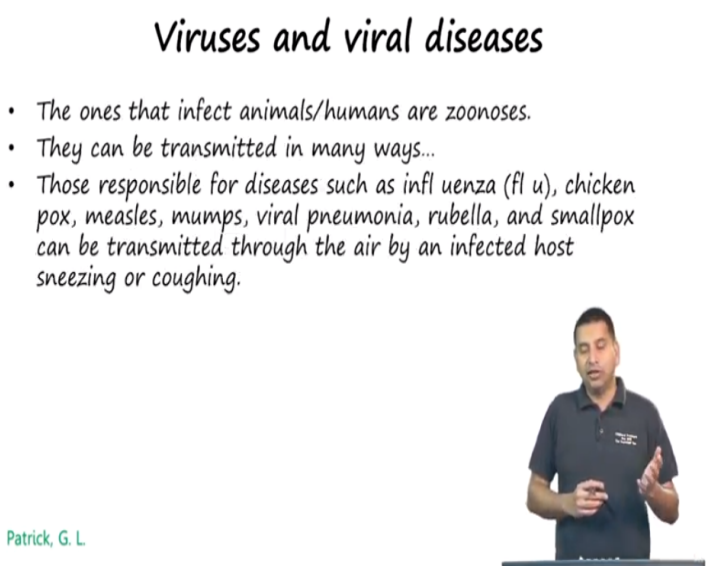

So the once that are infecting humans or animals are called as Zoonoses, that can be transmitted in many ways, so the most common you know viral infection can be many of us can uncoated the follow which is basically the common cold which is influence and there are also other viruses which we may have uncoated in one of a family members which is chicken pox, measles, mumps are also not very uncommon and you have viral pneumonia you have another diseases called is rubella and of course the major disease which is encoated in past which is smallpox and all of these can be transmitted through the air.

So by sneezing or coughing, so if one get enclosed proximity to infected person then there is a good chance that we would acquire this through or acquire this virus through a sneezing or coughing, so which is why these diseases are actually quite contiguous.

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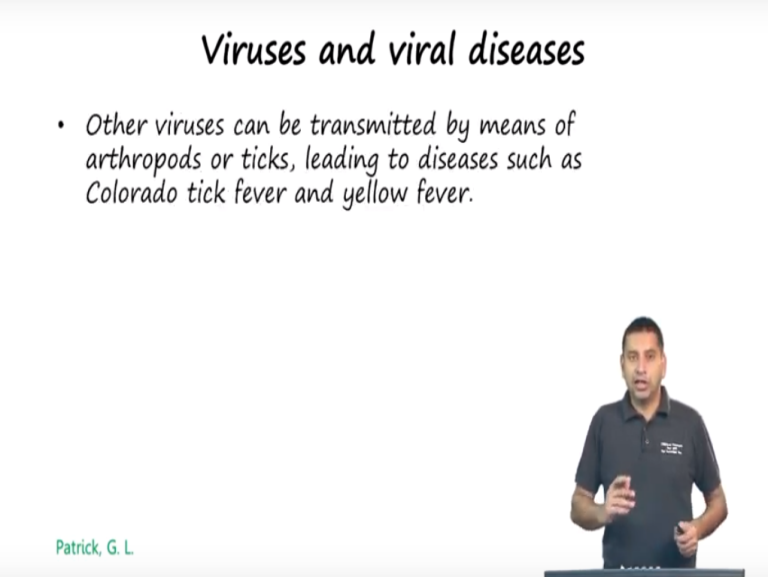

There are other kinds of viruses which can be transmitted by the means of carrier just like you have malaria which can be transmitted mosquitoes there are also other viral infection which can be transmitted through arthropods or ticks, so the example for this Colorado tick fever and yellow fever which is actually transmitted by these organisms.

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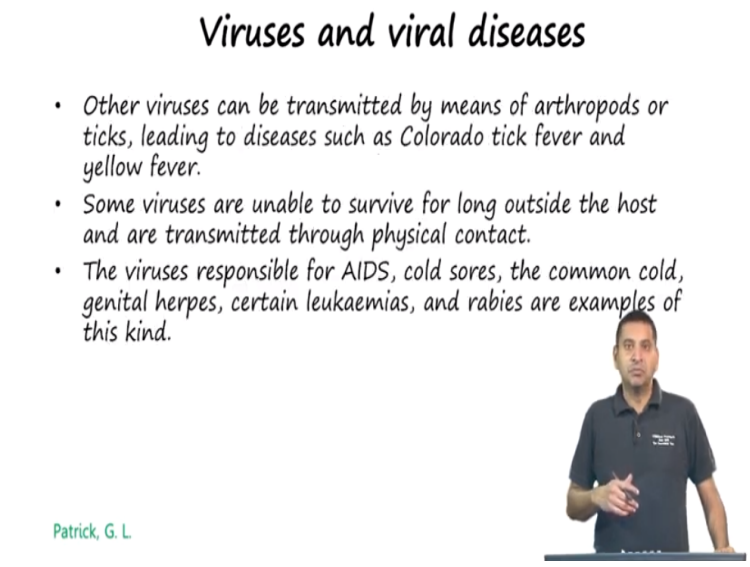

Some viruses are unable to survive are long outside the host and are transmitted through physical contract, so for example the measure epidemic in the world which is AIDS which is affected you know millions of peoples in past 30 years is actually transmitted through physical contact or

through blood transmission and the common cold is also gone through physical contact genital herpes certain kinds of Leukaemias and rabies are examples of transmitting the virus through physical contact.

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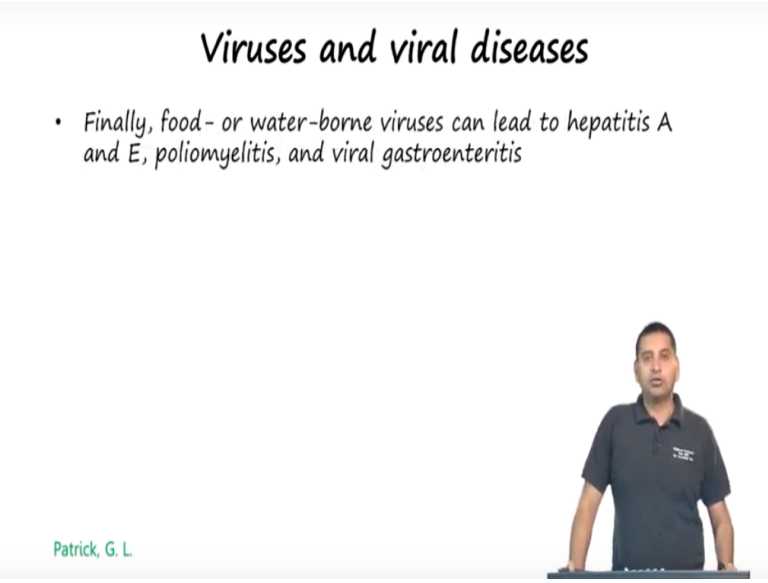

Finally they can also be food or water borne diseases which are such hepatitis A and E, a poliomyelitis which is again you know it is been eradicated in India through vaccination but it is a water borne infection and you can also have viral gastroenteritis, which is quite common occurrence in during floods and heavy rains.

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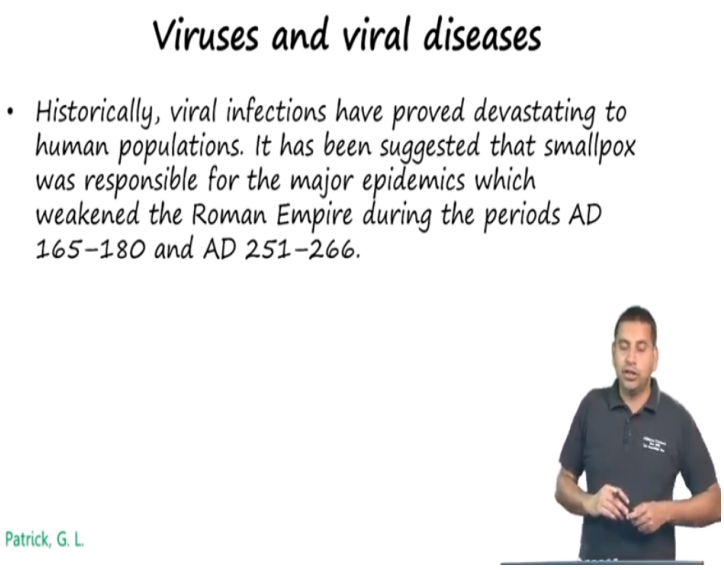

Historically viral infections have proved devastating and it is related to the death to the millions of people, so the small pox for example is been suggested to be one of the reasons why the Roman empire which was very strong which was first century and it was started declining because of smallpox.

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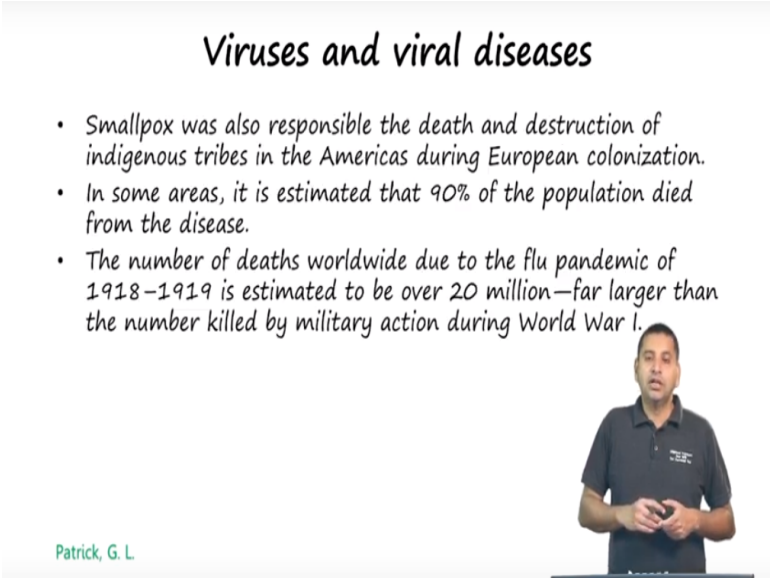

Small pox was also responsible for the death and destruction of a number of indigenous tribes during European colonization so what happens was specially in south America you know small pox was not prevalent and when the colonization the European occurred there was a lot of death

and destruction association because this virus was transmitted to the population in some areas it is estimated as 90 percent of the population died from this disease another major historical event which happens in 20 century is the flu pandemic in which about 20 million people died this happened in the years 1918 to 1919.

And it is still fresh in the memory of our medical community at these number which is 20 million is far more then what was whether the number of people who are killed during world war 1, so just to think about this put this in perspective this kind of disease can cause death and destruction to millions of people and which is much more then what would happen if there is a military conflict so therefore there is a you know possibility that large population of people you know country wiped out you know infection is quite similar.

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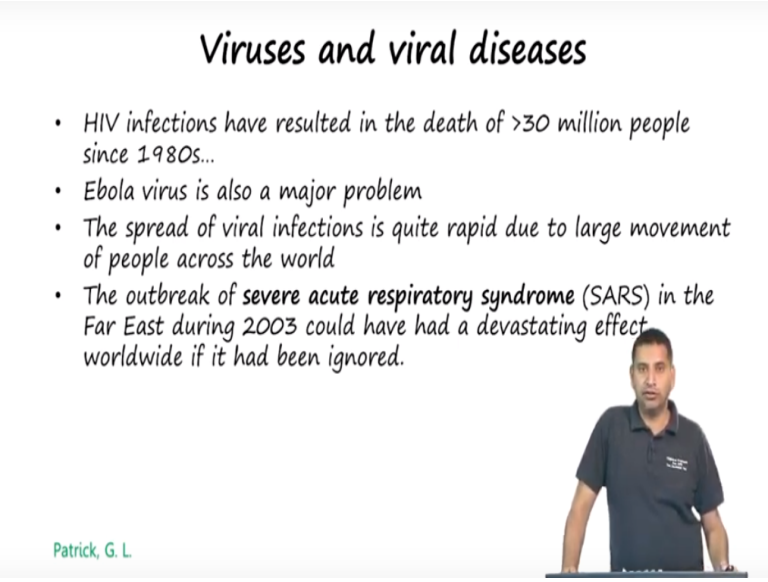

So HIV infections for example which leads to AID's has be around for about 30-40 years and it is resulted in the death of more than 30 million peoples, the Ebola virus for example is another major problem in specially in Africa and the spread of viral infection is now a days quite large because of globalization and there is large number of people who are sort of travelling you know daily basis across the world and so if there is a section population which is affected by a virus today they can quickly spread to another far region because of the rapid movement of the people across the world.

So in descent memory the outbreak of severe acute respiratory syndrome which is SARS is something that we would want to discuss, so this happened in the far east in the year pretty much in the year 2003 and there was immediate action taken by the medical community and that resulted in a lessor of an effect but if it had be ignored then it is quite possible at much larger number of people would have been affected by the disease.

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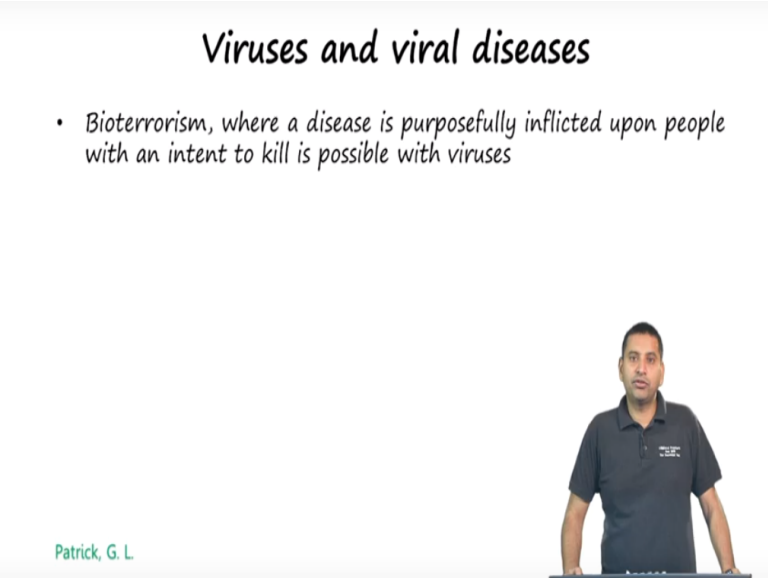

So this brings us to the possibility of bioterrorism, so here what can happen, so that it could be terrorist who could introduce a disease into a population with the intent to killed the population or terror of population with viruses, so which is why we need to keep our guard up and we need to be able to developed effective antivirus even vaccine for that matter, so that we can countered the possible of that this kinds of virus can cause.

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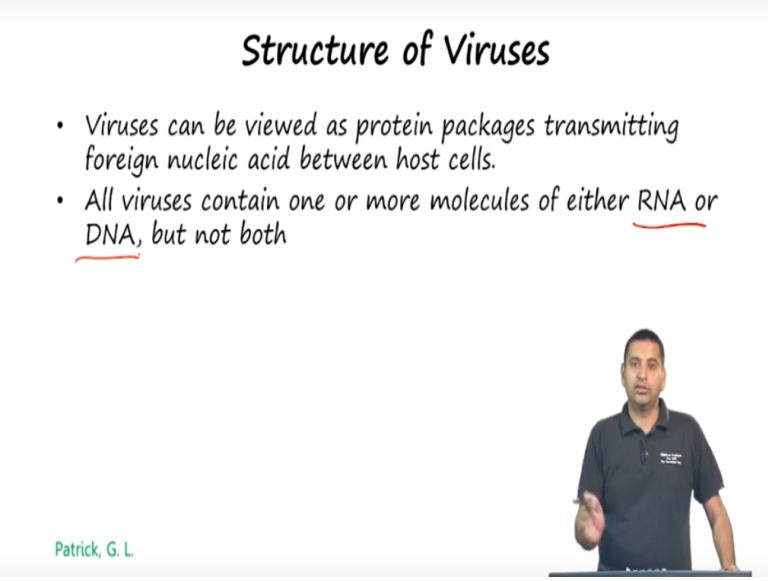

So let us start with general understanding of viruses and viruses are basically protein packages and this can transmit for a nucleic acid between host cells, so this is how we can very simplistically look at it there are mainly two kinds of viruses one is the Raibon nucleic acid or RNA virus and the other one is the DNA virus, so the virus will not contain both that either RNA or DNA.

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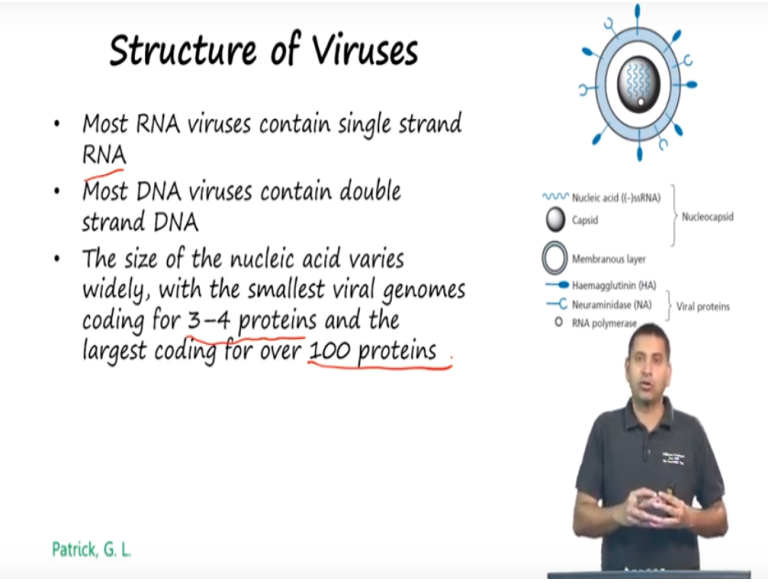

So here is a structure of a virus that general structure of a virus and most RNA viruses contain a single strand of virus RNA and most DNA viruses contain double strand DNA, so that is pretty

much what is there in our mammalian sell the size of the nucleic acid varies widely with the smallest viral genomes coding only for three to four protein, so imagine an organism such as a virus where you have the genetic coat coding only for three to four proteins and they are sufficient to go into a host cell.

Inside the host cell and take over the host cell machinery at lead to potentially fatal consequences in the largest coding virus is over 100 proteins so these are far lower then what a single cellular organism that we are familiar with can actually coat for, so viruses are extremely simple molecules or simple organism but they can have devastating consequences.

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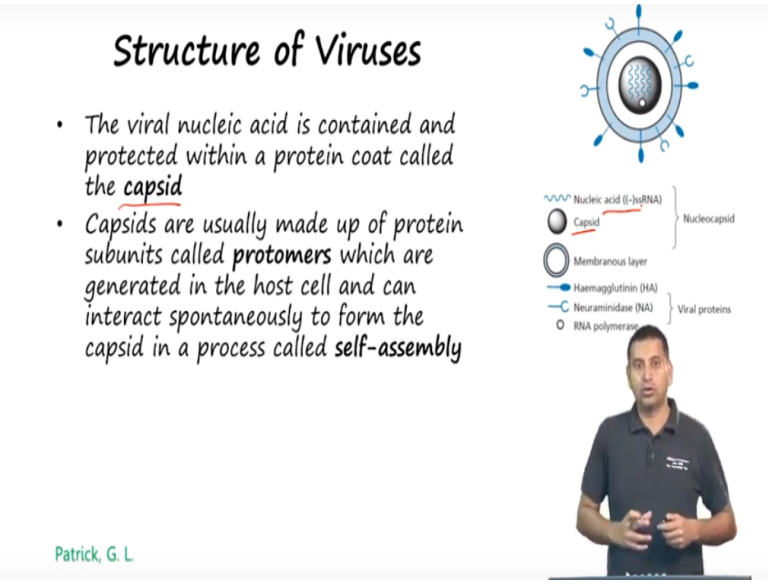

The viral nucleic is contained and protected within a protein coat called as the capsid, capsid are usually made of protein subunits called as Protomers, which are generated in the host cell and can interact spontaneously to form the capsid in a process of called self-assembly so here is the capsid and these one are able to coat the nucleic acids.

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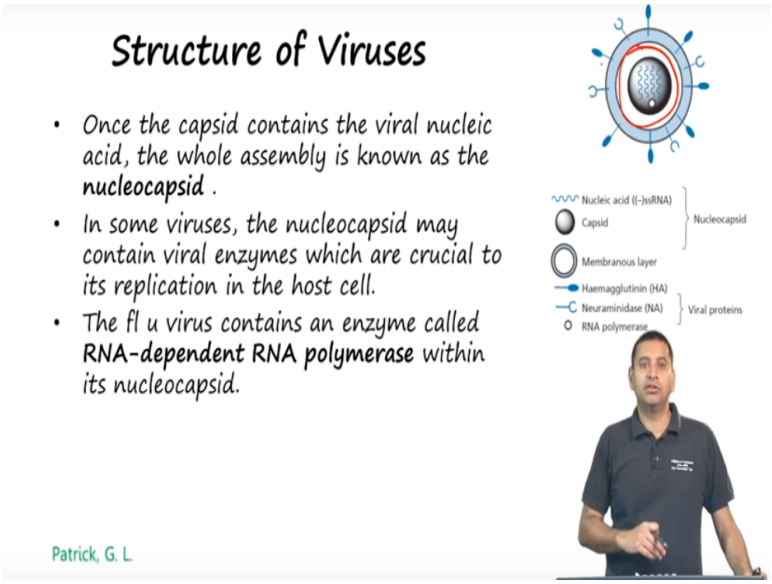

So once the capsid that contained the viral nucleic acid then the whole assembly is known as the Nucleocapsid, so these is called the nucleocapsid and in some viruses the nucleocapsid may contain viral enzymes which are critical to replication in the host cell, the flu virus contains an enzyme called as RNS dependent RNA polymerize within it is nucleocapsid.

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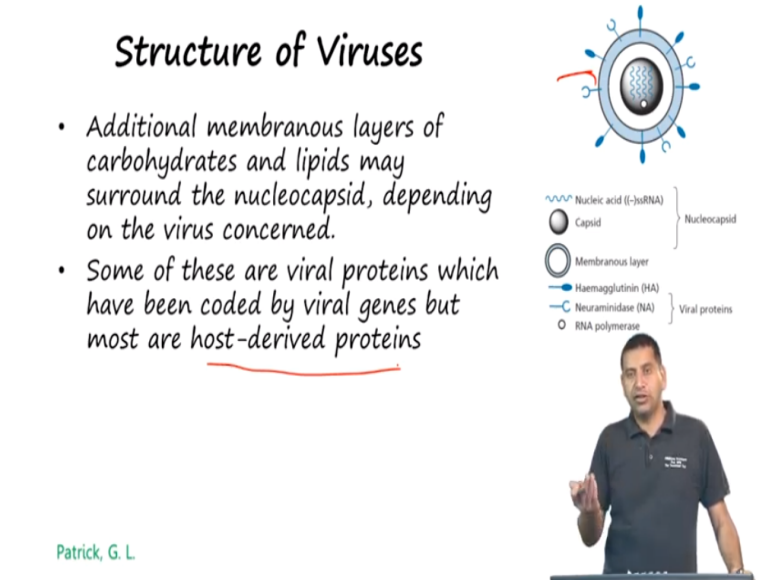

There could be addition membranous layers of carbohydrates and lipids surrounding the nucleocapsid which is shown here and basically there would be variation depending on the virus

concerned, some of these are viral proteins which have been coated by viral genes but most are host derived protein, so these is a general structure of a virus.

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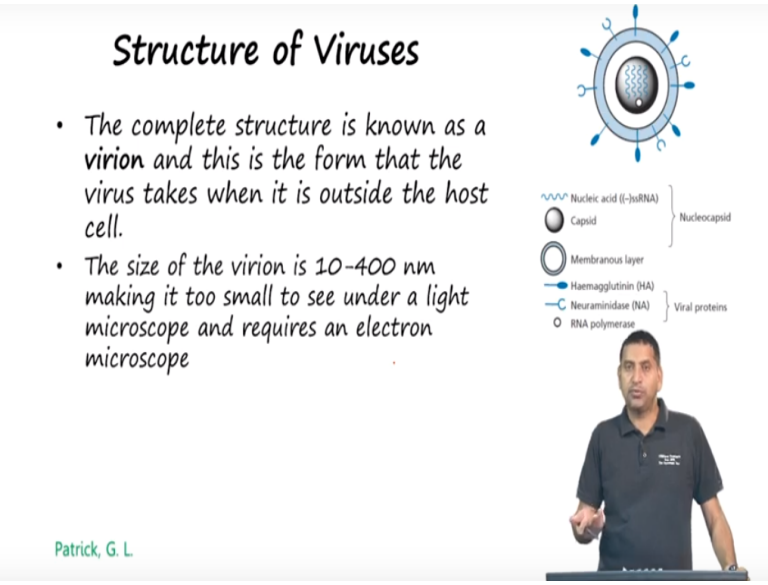

The complete structure is known as a virion and this is the form that the virus takes when it is outside the host cell, so the size of this virion is between 10 and 400 Nano meter and so if you want to look at it under a light microscope it is not possible so you would need an electron microscope to take the presents of viruses.

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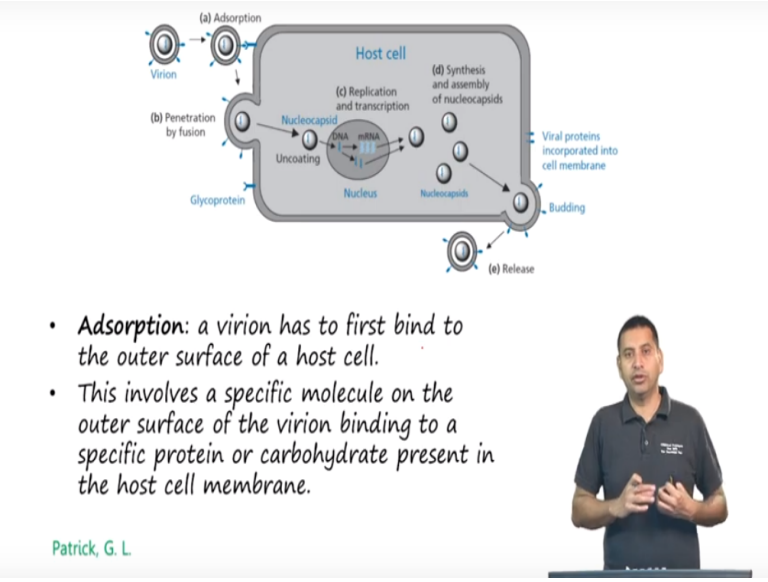

Now let us look at the various stages in with the infection occurs the first step is known as adsorption, so adsorption is when the virion is go and bind to the outer surface of the host cell, so this involve very specific interactions and specific molecules on the outer surface of the virion that helps with binding to the specific routine or carbohydrate that is present on the host cell membrane.

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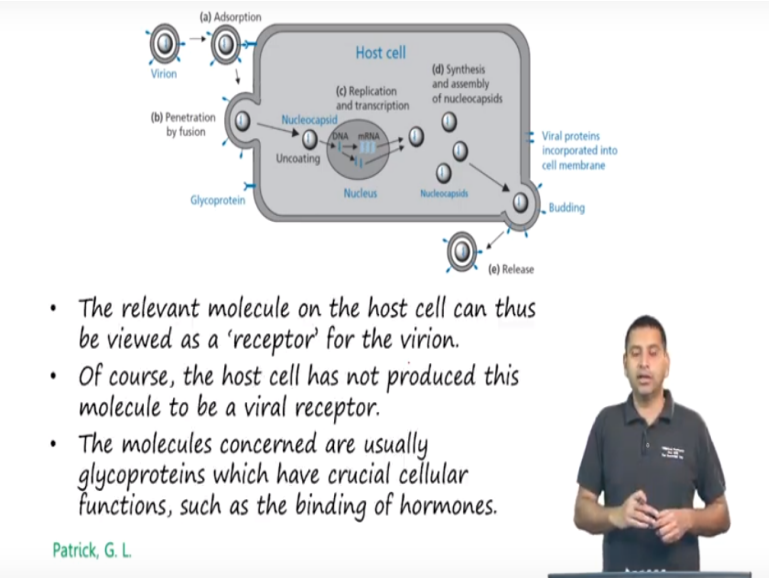

So the host cell protein or carbohydrate can be called as a receptor for the virion, and the host cell has not produce this molecule to be a viral receptor of course but it can serve as a vain which the viruses is going to interact with the host cell and start getting solved and these molecule which we already know are called as glycoproteins and we have crucial cellular function such as binding of hormones, so this is place where you know some of the hormones you are going to interact with the cells of it and help of it signal transmission.

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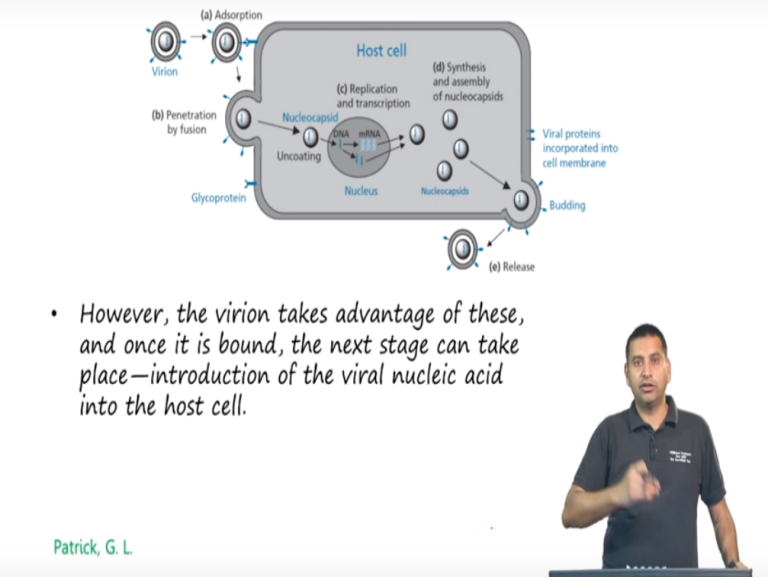

So the virion takes advantage of these and once it is bound the next stage can takes place which is introduction of the viral nucleic acid of the host cell.

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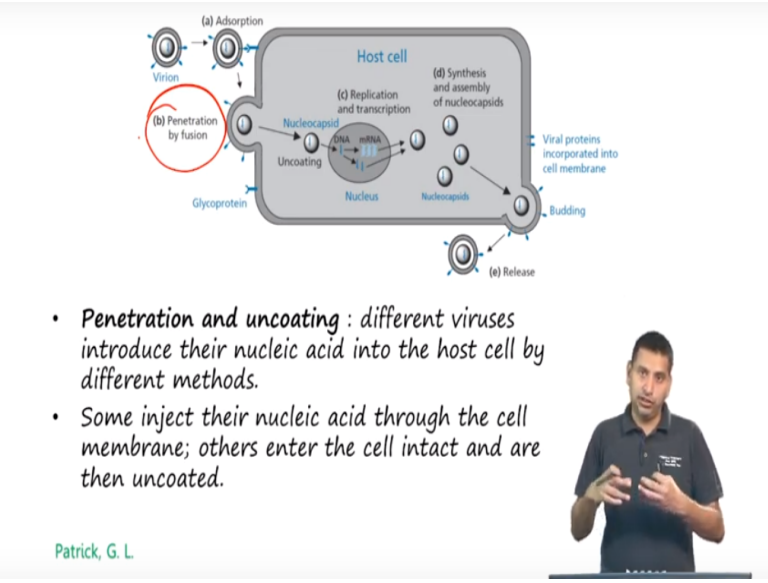

So the next stage is penetration and fusion so different viruses introduce their nucleic acid by different methods, some of them inject the nucleic acid through the cell membrane others enter the cell intact and then they are uncoated, so depending on what the type of viruses this mechanism will change.

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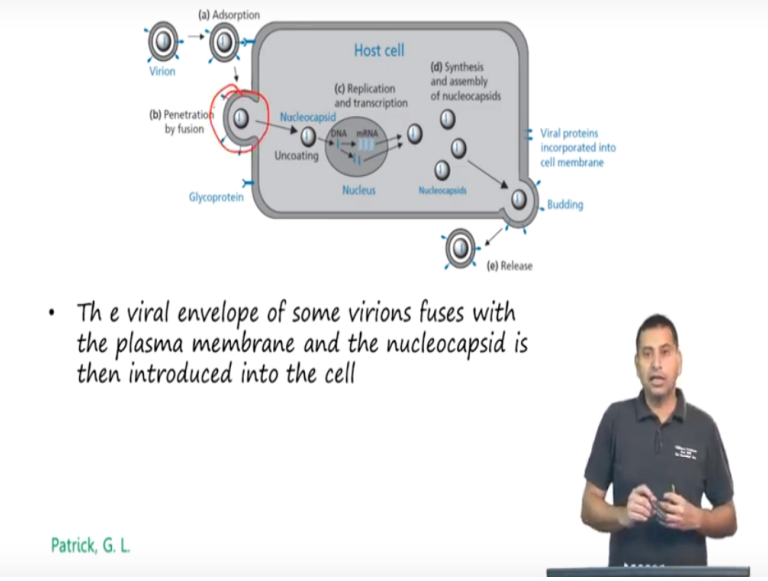

So the viral envelope of some virions fuses with the plasma membrane and the nucleocapsid is then introduced into the cell so these is a process of fusion and then once it get sit is uncoated and goes to the endosomes.

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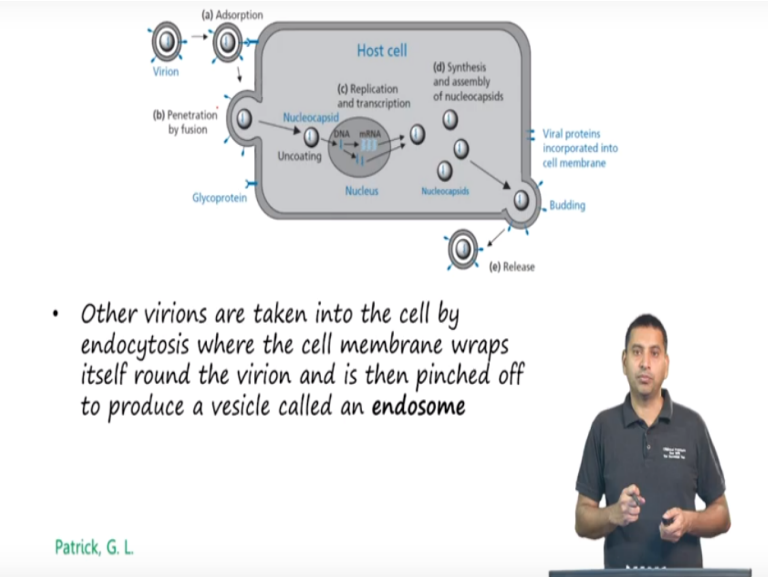

So after are takes place then the cell membrane wraps itself around the virion and is then pinched off to produce a vesicle called an endosome.

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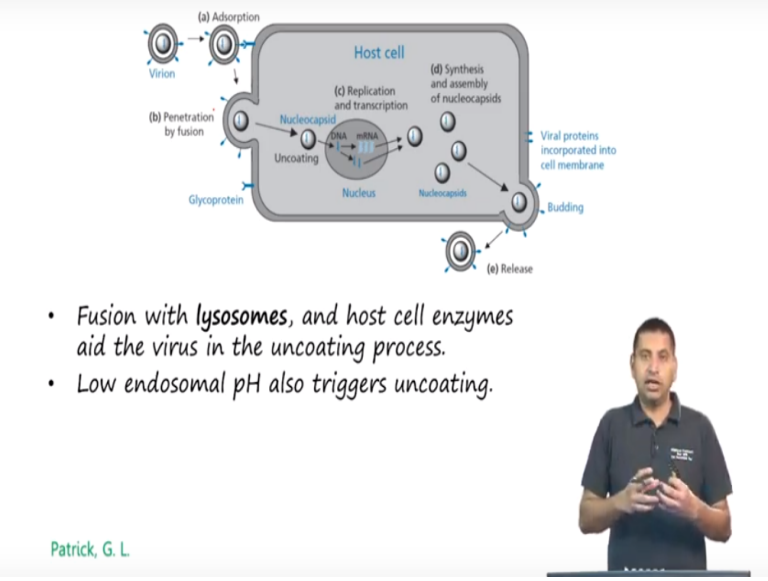

Then fusion of this endosome with lysosomes and host cell enzyme aid the virus in the uncoating process and since we have discuss previously the endosome has a lower PH and it also triggers the uncoating.

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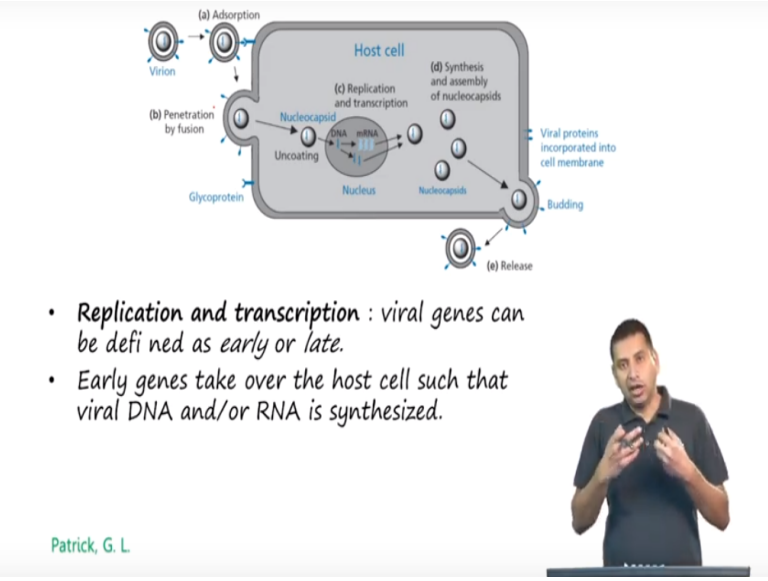

Then come's measure process of replication and transcription so the viral genes you know that can be define us in two stages one is early stage and the second one is late stage, so the early genes take over the host cell such that the viral DNA or RNA is synthesized, so here is the

process in which the virus is going to use it is machinery incorporate itself into the host machinery and replicate and divide and produce a larger number of viral particles.

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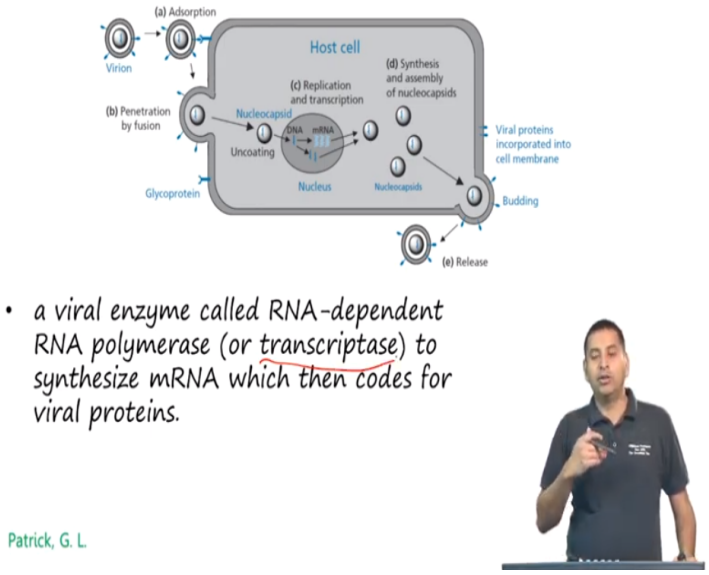

So the viral enzyme which is called as RNA dependent, RNA polymerase or transcriptase is now going to help with synthesizing the MRNA, and these MRNA coat for viral proteins, so this is the key step that we are discussing right now which replication and transcription.

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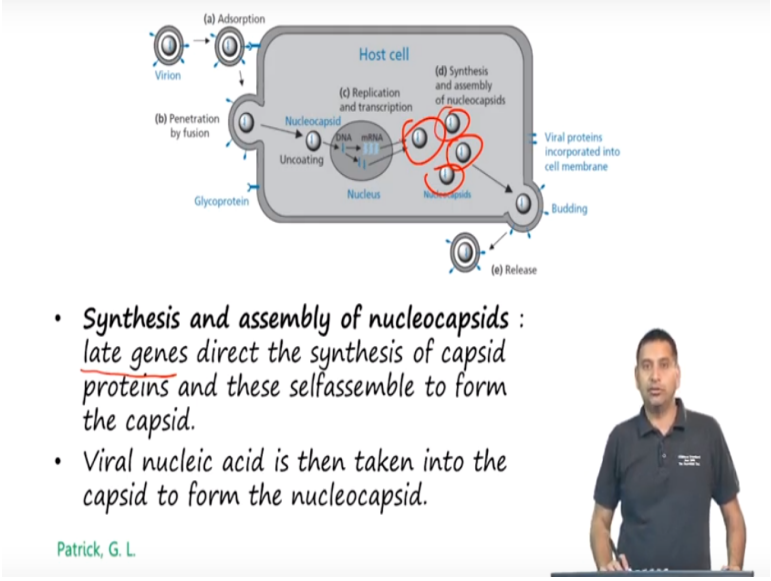

Then what happens is that you have after these proteins are synthesis then you have the synthesis and assembly of nucleocapsids, so we already discuss the neucleocapsids are out of membrane which is important for holding the nucleic acids and so these are also synthesize and these are done by the so called late genes, so the late genes direct the synthesis of capsid proteins and then there is a process of self-assemble which form the capsid, the viral nucleic acid is then taken into the capsid which is showed here and they form a nucleocapsid.

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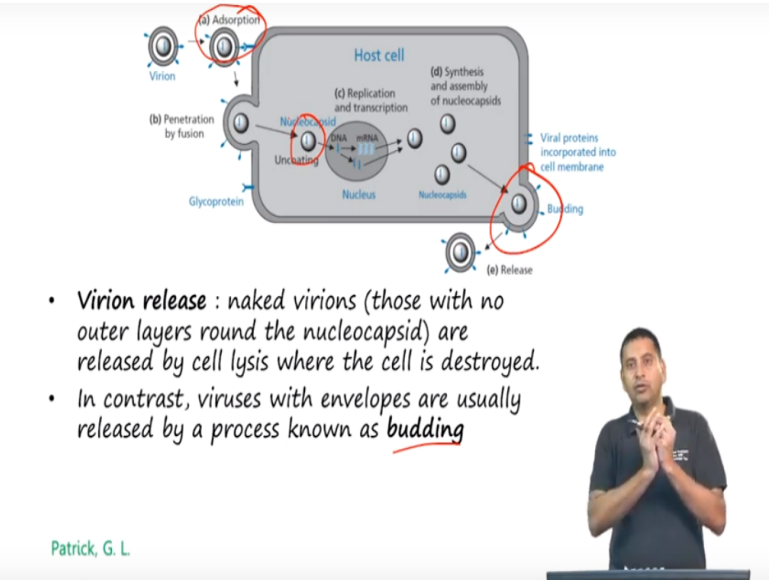

Then comes a next process which is basically the virion release so the naked virion that is with no outer layer around the nucleocapsid are then released by cell lysis and then the cell is actually destroyed of these process and this can be done by a process known as budding, so here is the budding process which is in going to result in the released of the virion, so just to recap the first step here is absorption where in some of the cells of his receptor are recognized by the virion and the virion goes on bind to this.

Once it is binding then it forms it penetrates in fuses it is also possible that the nucleic acid injected into the cell but in this example what we are looking at it is the entry of the entire virus, so once it gets in there is an uncoating that happens and then it incorporate into the host nucleic acid a machinery and then there is replication and transcription, now this replication and transcription results in the generation of multiple copies of the virion and this is now it is coated

by nucleocapsid and then by the process of budding it actually released and in this process the host cell is lysed and therefore the host is dead.

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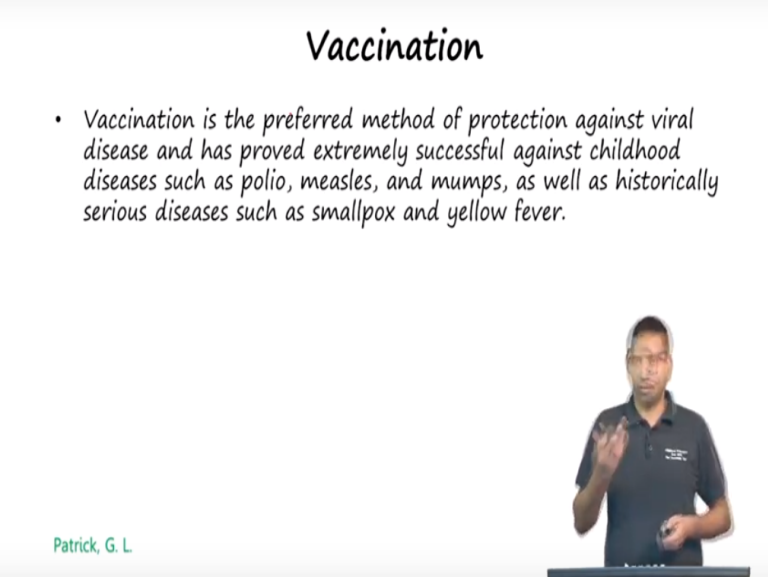

So one of the ways in which we can protect our cells from viral disease is to use from vaccination and number of disease that we looked at such as polio measles and mumps are actually mainly targeted by vaccination, so smallpox and yellow fever are also are sort of serious diseases which are countered by vaccination.

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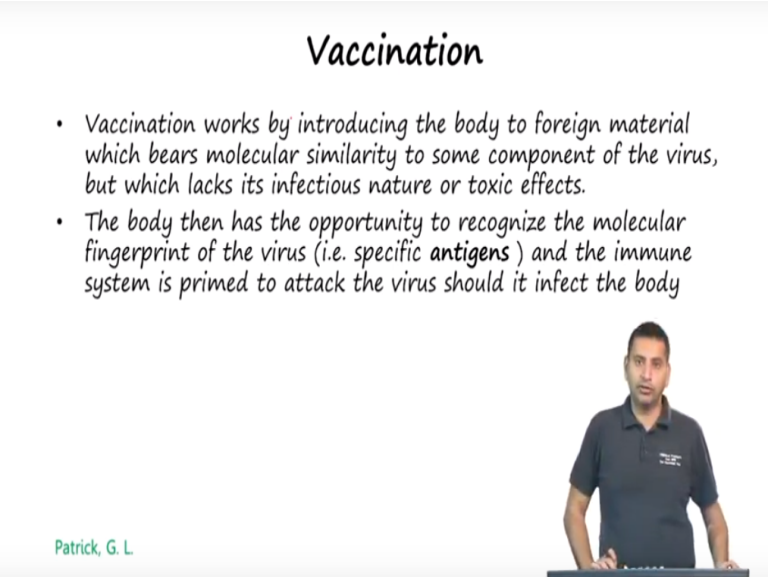

So vaccination works by introducing the body to foreign material, and this foreign material has very similar molecular structure or it has the component of the virus, so what happens is that our immune system generates or recognize this are foreign start generating antibodies for eliminating this new material, so therefore we provide the opportunity for the molecular finger print of the virus to be able to encountered immune system and now the immune system is now primed to attacked the virus and which can infect the body, so this is one of the ways in which we can effectively countered viruses.

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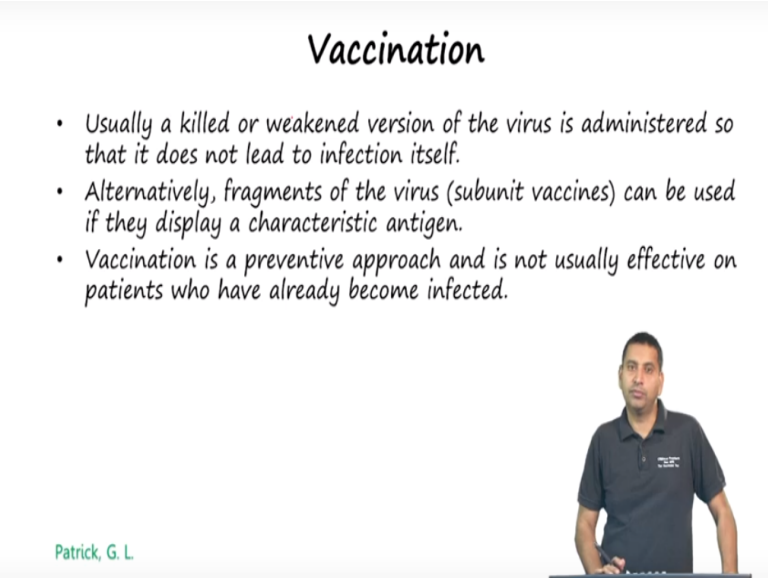

So this vaccine can also contained killed or weakened version of the virus, so therefore this itself will not lead to infection, but it can introduce into the body a structure which is now going to be a recognized by our immune system to produce the corresponding antibody they can also be fragments of the virus which are known as sub unit vaccine which can be used and typically this is a highly preventive approach and once the person is actually infected with the virus one cannot vaccinate this individually.

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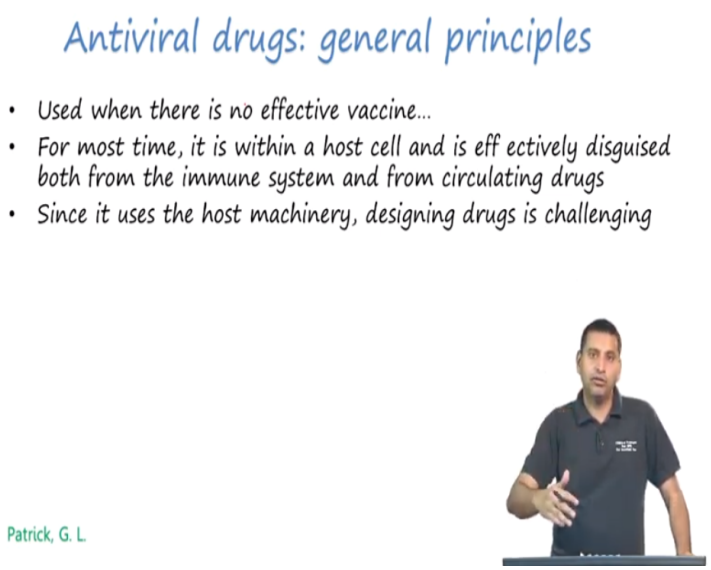

Now if the person if affected by a viral infection then since we cannot vaccinate at that stage we need to starts administering antiviral drugs so now we will look at how this drug have been developed, so there are a few disease where there are no affective vaccine and so therefore we need to use a drug so for the most time the virus is effectively dis-guide from the immune system and from circulating drugs, so since it is uses the host machinery, designing new drugs is actually quite challenging because we do not want to killed the host as well as the virus but beyond to only killed the virus.

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So again as we looked at previously there are two kinds of viruses one is the DNA virus and the other one is the RNA virus and so now we look at some of the antiviral drugs which are used against DNA viruses, so most of the drugs which are active again DNA viruses have developed against herpes viruses and this combat diseases which are cold sores, genital herpes, chicken pox, shingles, eye diseases, mononucleosis, Burkitt's lymphoma and Kaposi sarcoma, so here nucleoside analogue have been particularly effective.

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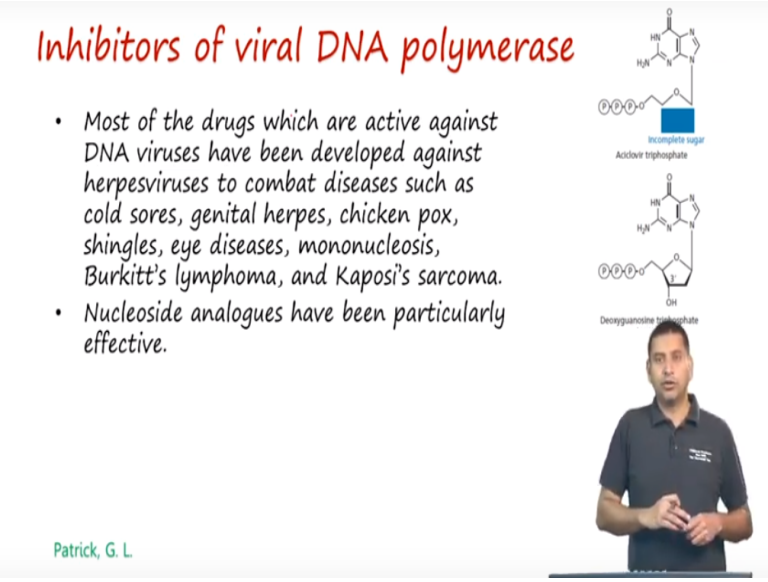

So the first class of drugs that we are going to encountered are inhibitors of viral DNA polymerase, so the first drug we are going to look at is Aciclovir.

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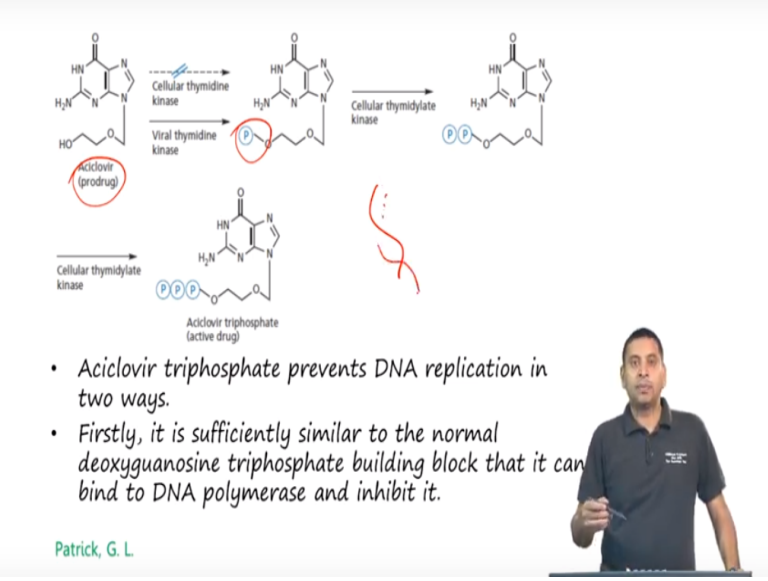

So Aciclovir triphosphate what we have already looked the previously is an incomplete nucleic acid and therefore it is going to be it is going to prevent you know DNA replication, so the way in which is happens is that there is a product it get phosphate related and then it encounters the DNA prevent double stand and then replication and then it prevents the replication from occurring.

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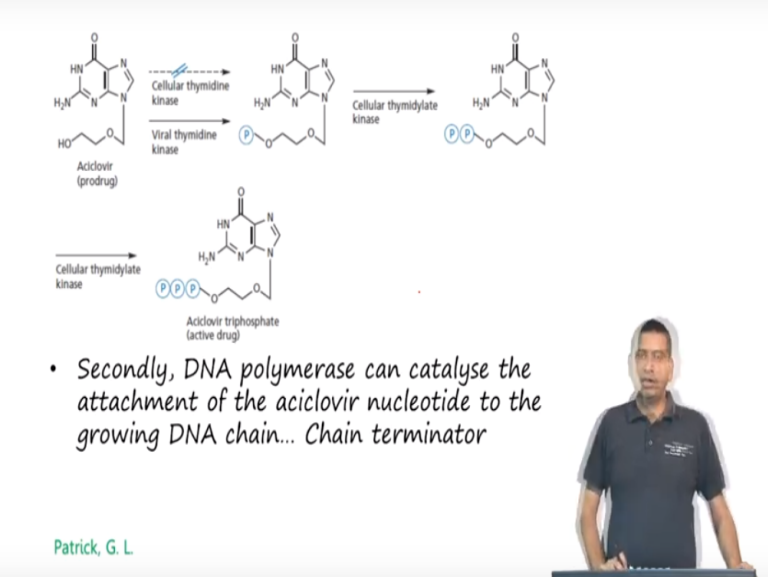

So this is the classic example of the chain terminator.

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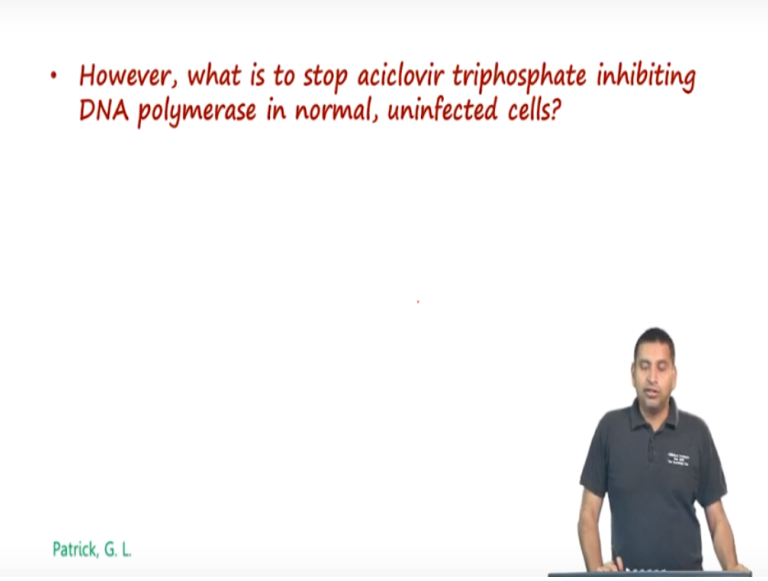

Now the question is that we would need to address this how is this molecule to be selective that is how is not going to be affect DNA polymerase in normal uninfected cells.

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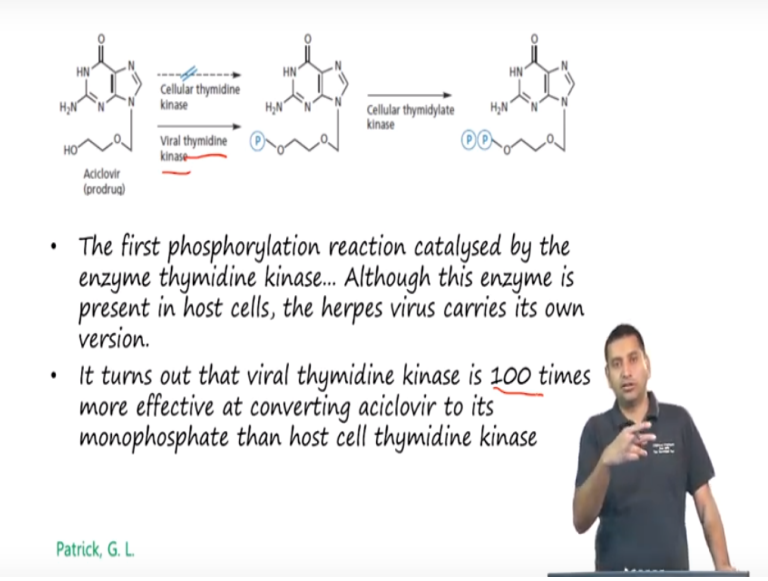

So the first phosphorylation reaction that occurs by this enzyme known as thymidine kinase and here this enzyme is present in host as well as the herpes virus but turns out that the selectivity towards the herpes viral thymidine kinase is 100 fold higher, so therefore the thymidine kinase which is present in viruses is actually more effective in doing this phosphorylation relation, so compare to the host cell and therefore this is one reason why it is selective.

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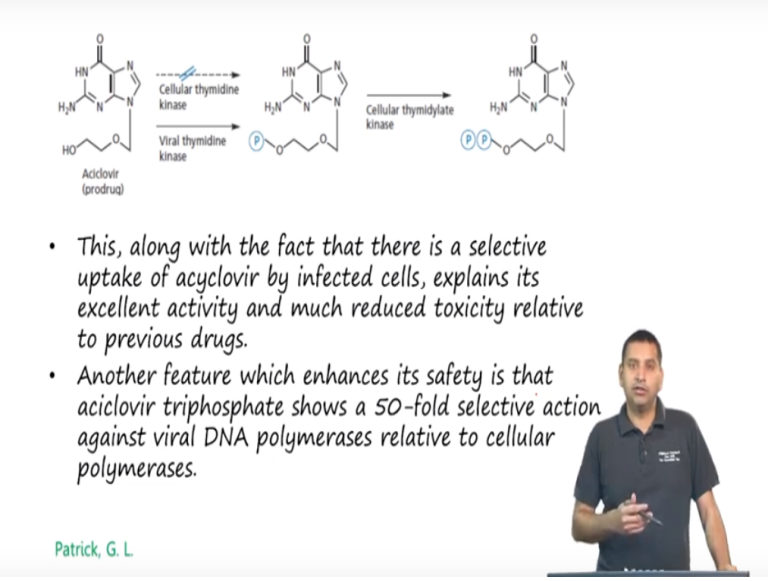

Also there is selective uptake of acyclovir in infected cells and together this explains it is excellent activity and reduce toxicity relative to the previous drugs developed this area, another feature is that it shows a 50 fold selective action against viral DNA polymerase relative to cellular polymerases, so therefore this drugs is one of the most important drugs have been developed against herpes viruses.

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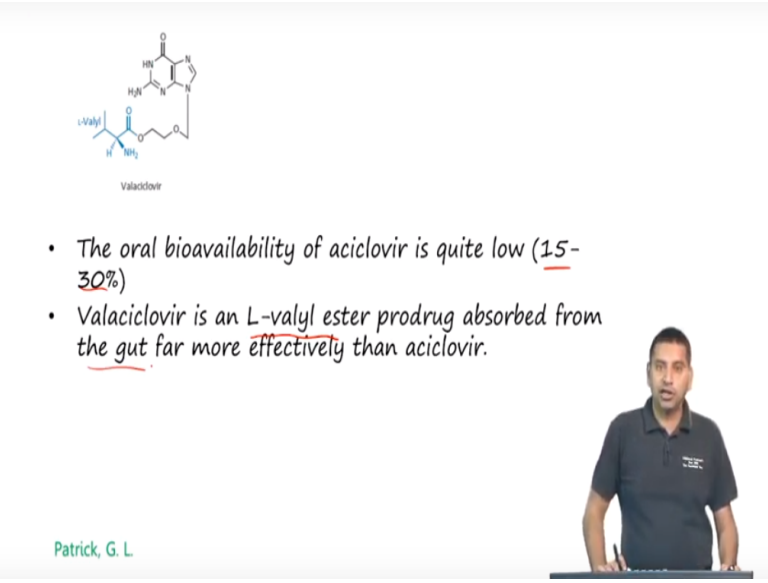

One of the problems with aciclovir is that it is it has very low oral bioavailability, it is only about 15 to 30 percent, so again just to recall oral bioavailability is basically after once consumes a

drug how of the drug is available in a blood stream, so therefore about 85 to 70 percent of the drug is not available right, so in order to addressed this another analog which is the L valyl ester of the molecule was actually generated, so this molecule has the better absorption from the gut compare to acyclovir.

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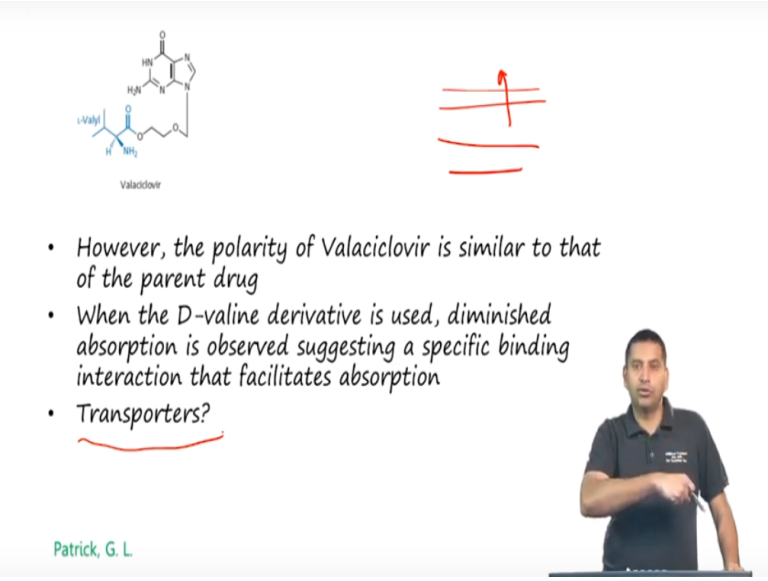

However the polarity of this molecule is similar to that of the parent drug, now when we use the D-valine derivative then what happens is we observed diminished absorption, so this observation suggest that there must be a specific binding interaction that facilitate absorption across the gut, so now together what these means is that it is possible that this drugs access certain transporters because the L-valyl molecule is recognized better by the transporter it is pulled and the D-valine derivative is used there is diminished absorption it is possibly due to poor binding of the molecule of the transporter.

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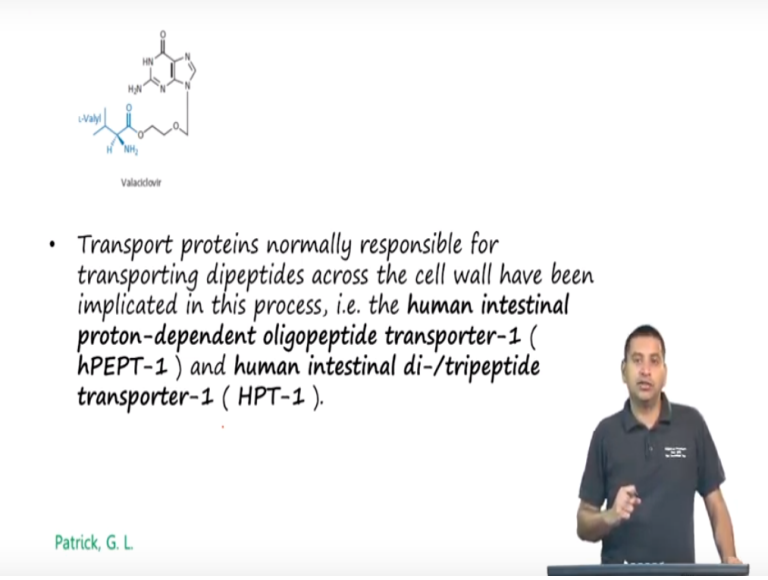

The transport proteins that are present in the gut that are responsible for transporting dipeptides across the cell wall and this example this HPEPT 1 and HPT 1 these are di-peptide and tri-peptide transporter which are possibly the one which are taking this transport.

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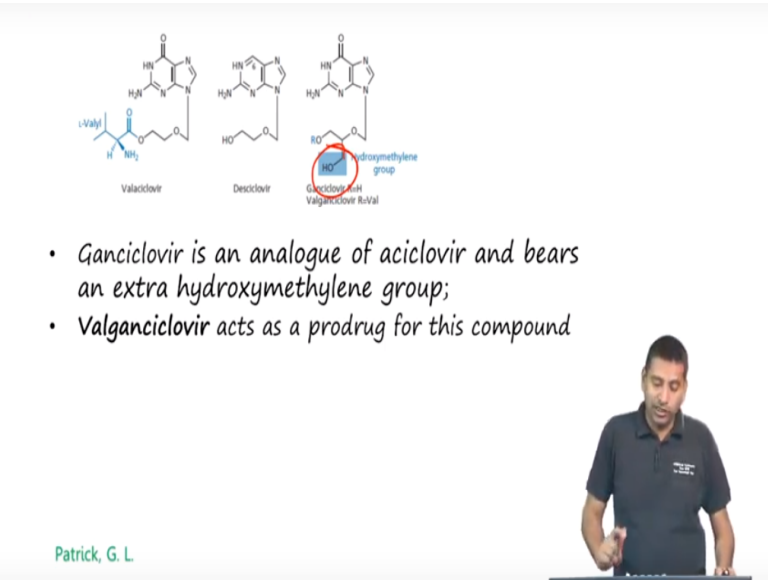

The next molecule in these series is Desciclovir and this lacks the carbonyl group that is present here so if you look at this structure it does not have the carbonyl group, so once it enters in the blood supply there is an enzyme which is known as xanthine oxidase which oxidase this position to give you the carbonyl derivative, so therefore this molecule is actually a product, the next

class of molecules is the Ganciclovir which is again an analogue of acyclovir and it has an extra hydroxymethylene group, I shown here so and there is another version of these which is Valganciclovir which acts as a pro-drug for this molecule it has the raline ester of this the structure.

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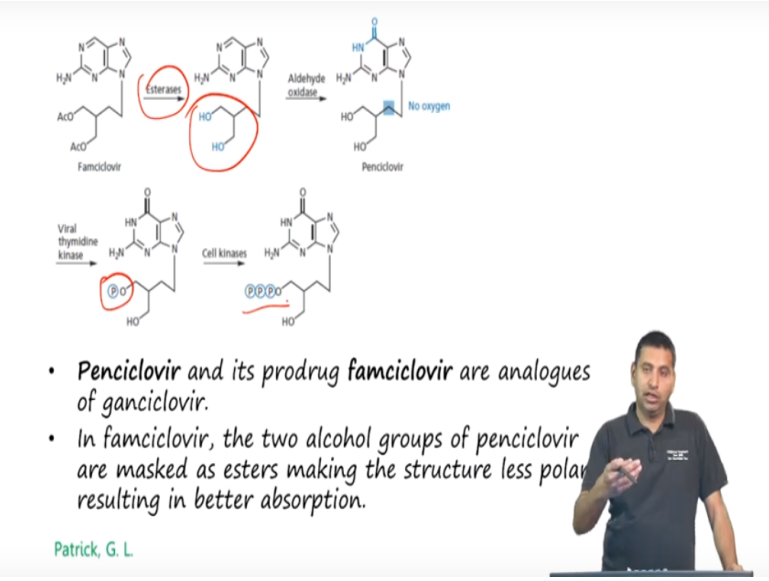

So there is another molecule which is again a of pro-drug which has a dia-acitate molecule derivative and so this dia-acitate by esterase to produce the free diole which is then subsequently you know incubating the transcription, so again the viral thymidine kinase is going to phosphor relate here and then subsequently it generate the triphosphate, so the two alcohol groups is there masked as ester and this makes the structure less polar and there for it is better observe.

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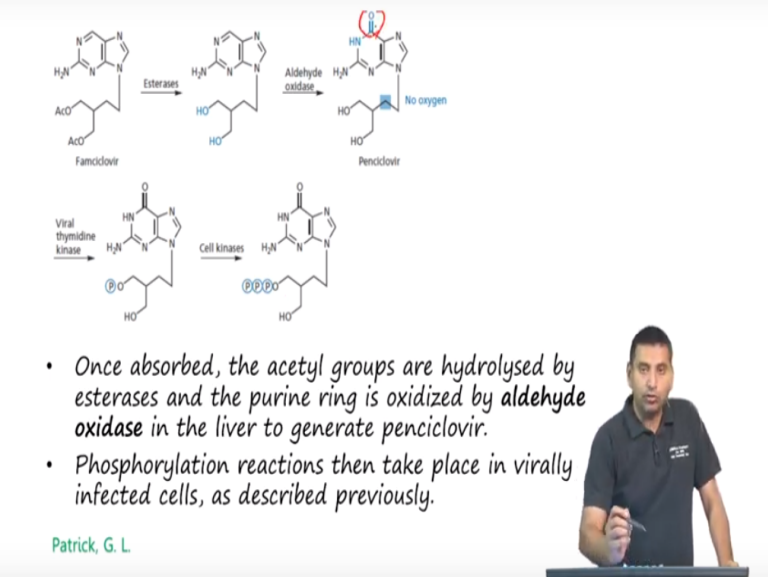

So once it is observe there is an enzyme called as aldehyde oxidase is, which there oxidase is to give you the final molecule which has the carbonyl group.

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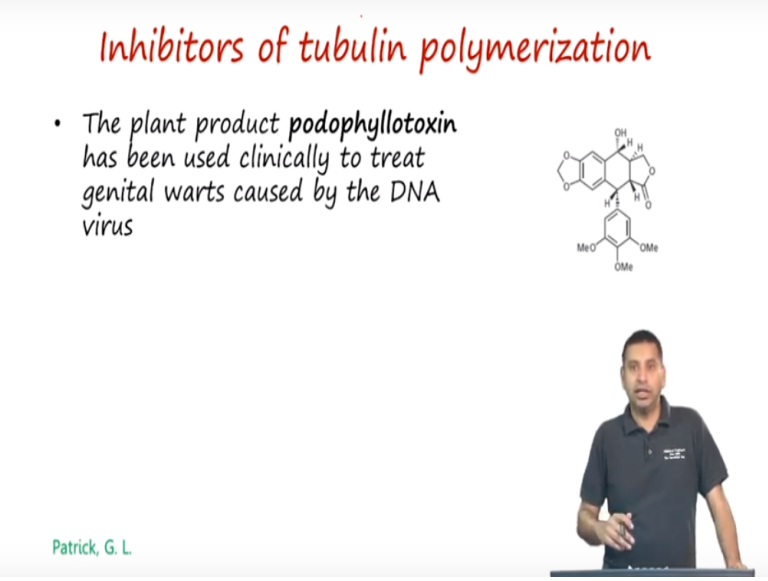

One can also think about inhibiting tubulin polymerization we have looked at this previously and this can be one method by which you can inhibit viruses and this is the molecule that we are looking at which is podo phylo toxin and this is been used in clinically to treat genital warts caused by DNA virus.

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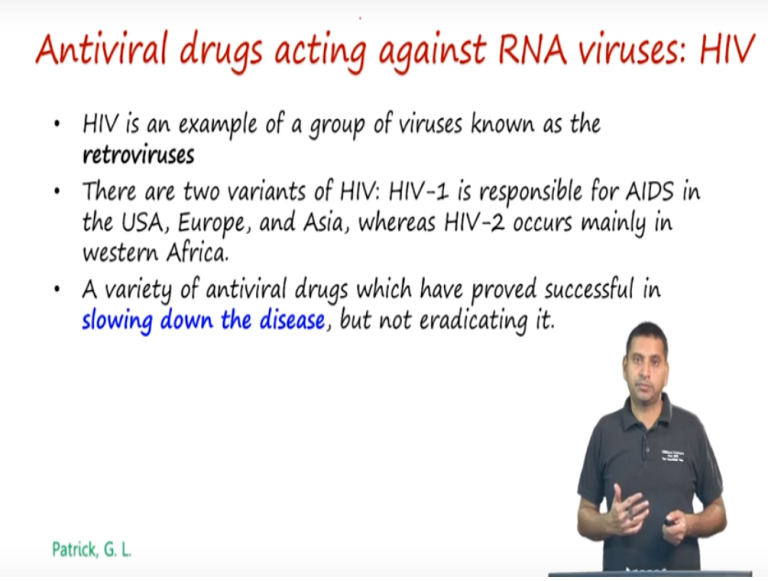

There are antiviral drugs which act against RNA viruses which is second class of viruses and here we will specifically locate HIV, so HIV is an example of viruses for group of viruses it is known as retroviruses and there two measure variants one is HIV 1 which is responsible for AIDS in much of America Europe and Asian and there is another one which is HIV 2 which mainly occur in Western Africa.

So number of antiviral drug developed in the past 30 years or so and these help in slowing known the disease but they do not completely eradicated recently it has been shown that two people have been completely cured of HIV and these are very promising this looks very promising and therefore it is possible in future we may be able to completely eradicate this disease.

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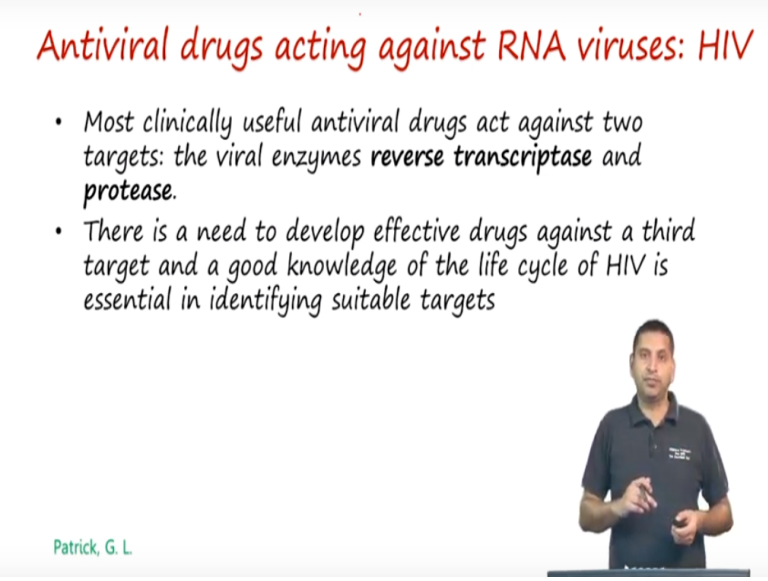

So most clinically useful drugs target the viral enzyme known as reverse transcriptase is in protease, so here we need to developed effective drugs against a third target and for this we need to have a good knowledge of the life cycle of HIV.

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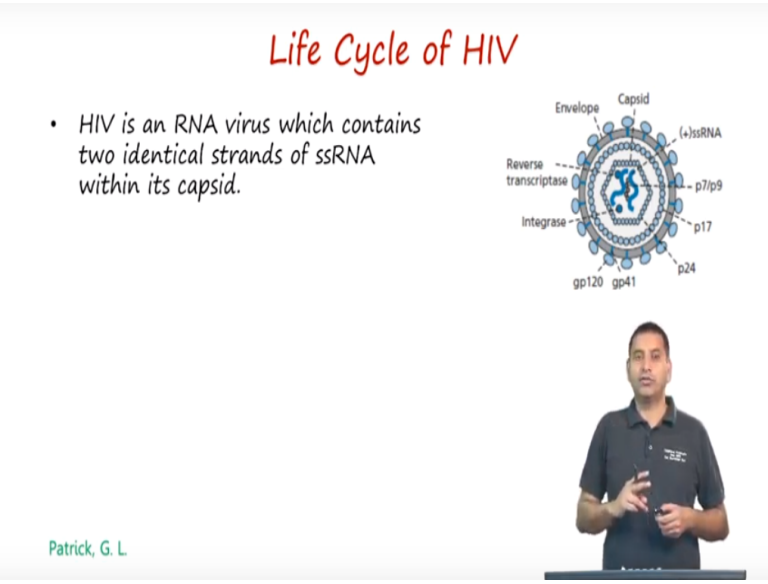

So let us look at this briefly HIV is a RNA virus which contains a single strand of RNA and there are two identical strands of this single strand RNA.

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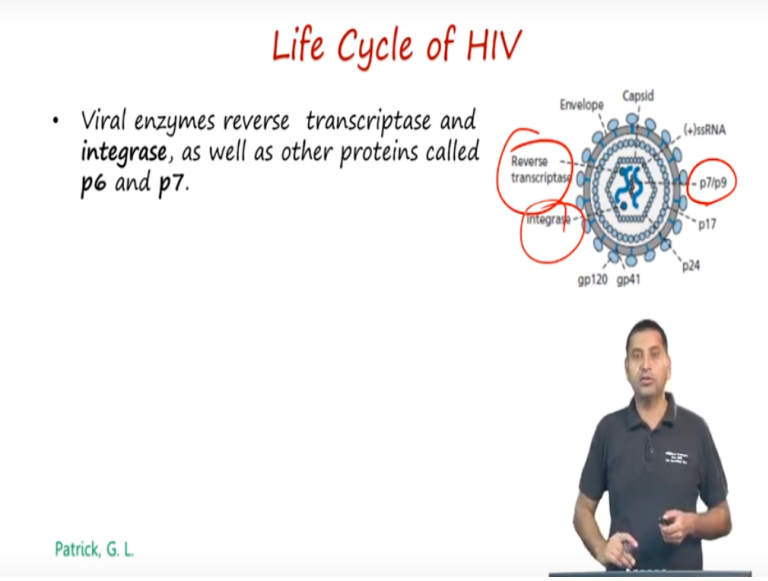

And the viral enzymes reverse transcriptase in integrase as well as other proteins called s P6 and P7, so this are all enzymes which are present in this virus.

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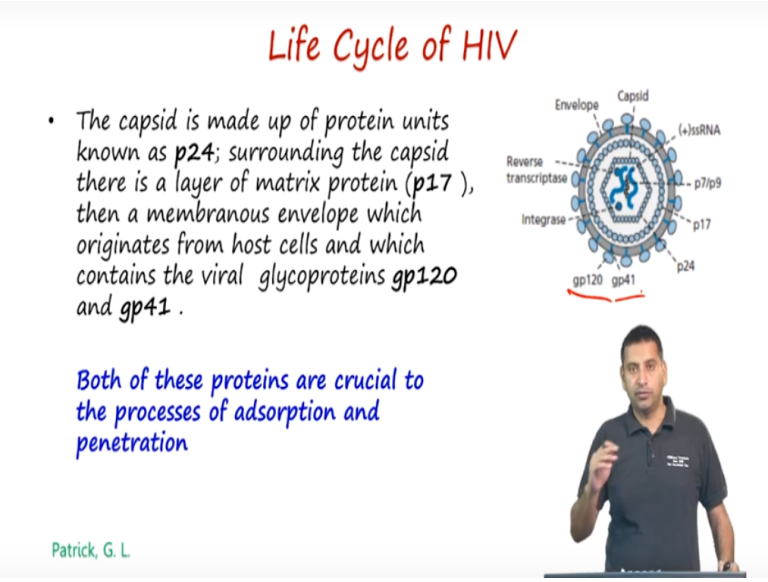

The capsid is made up of protein units known as P24. And surrounding the capsid there is a layer of matrix protein known as P17 and then a membranous envelope which originates from the host cells and which contains the viral glycoproteins GP120 and GP41, both of these proteins are crucial to the processes of adsorption and penetration.

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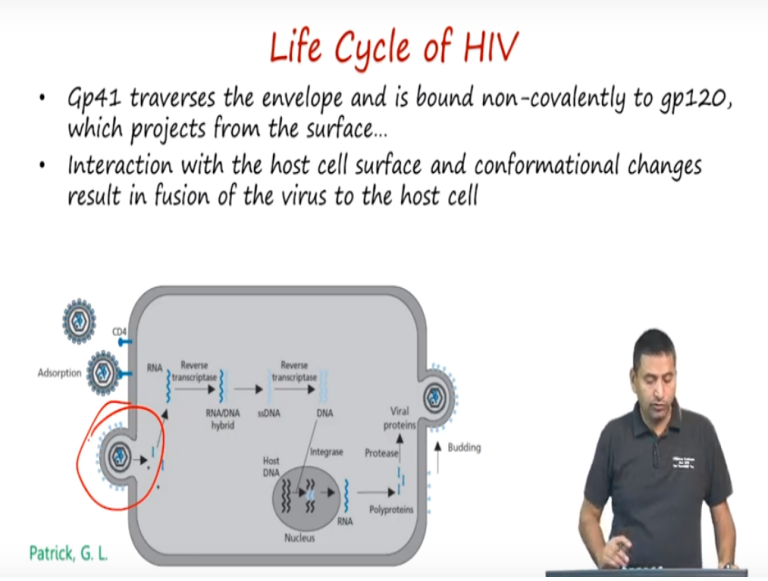

Now what happens is that GP 41 traverses the envelope it is bound non-covalently to GP120 and then interaction with the host cell surface and subsequent conformational changes result in fusion of the viral particle.

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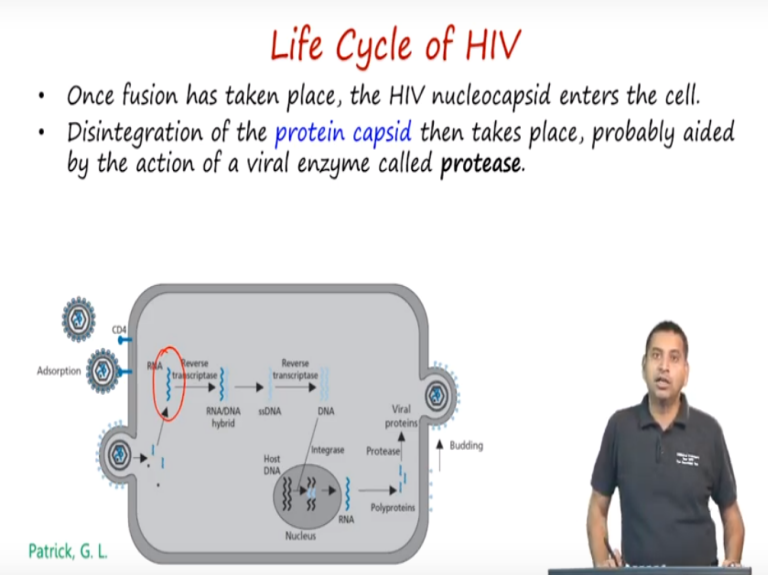

So then once fusion has taken place it releases the single strand RNA before that you need the enzyme called as protease which breaks down the protein capsid.

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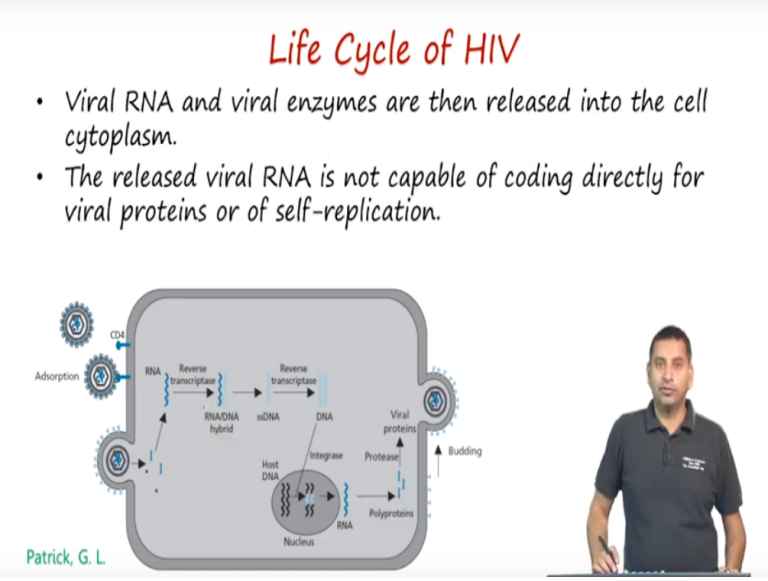

And then once it is broken then you need to have you know reverse transcriptase, so the release viral RNA is not capable for coding directly for viral proteins or for self-replication instead it is converted to DNA host machinery.

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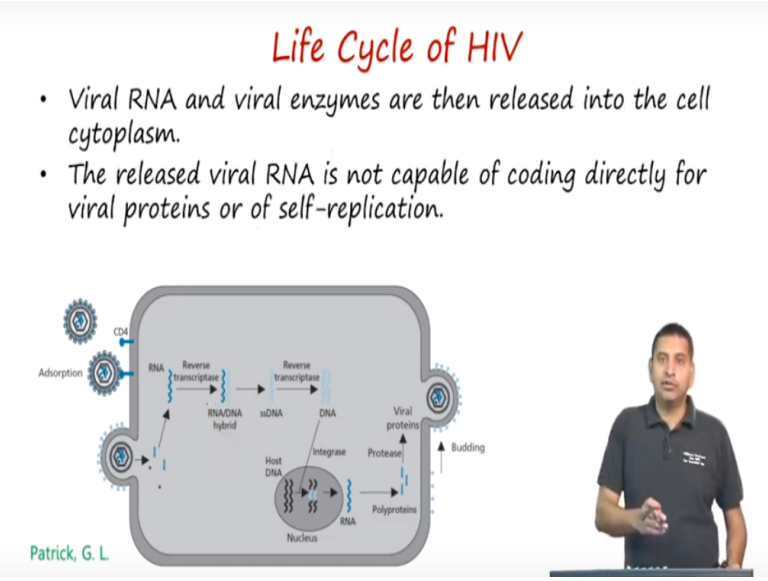

So viral RNA and enzyme are then release into the cell cytoplasm.

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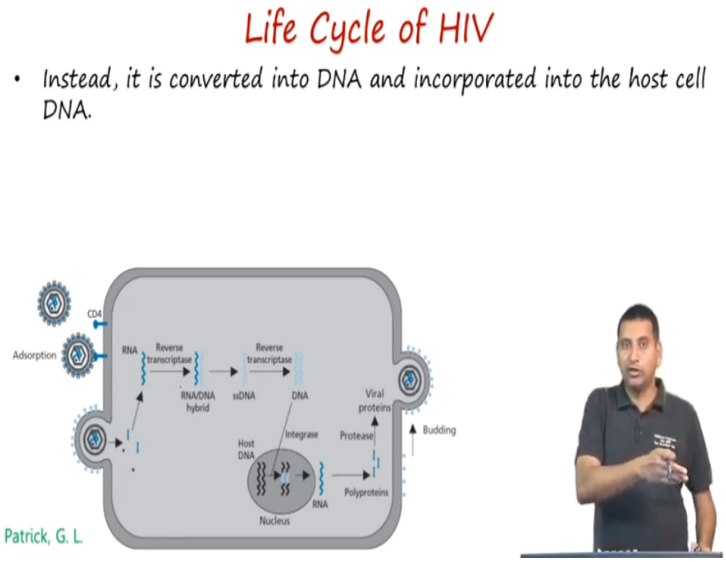

And then it is converted into DNA and incorporated into the host cell DNA.

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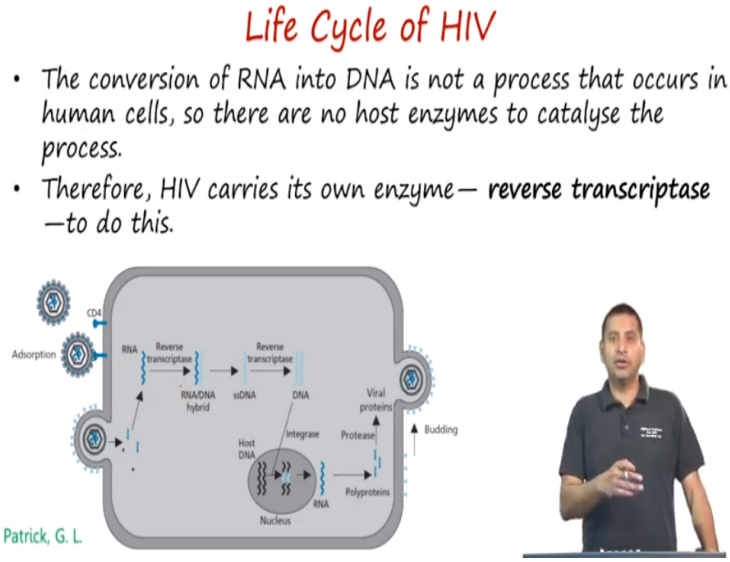

So the conversion of RNA into DNA is not a process that occurs in human cells, and there for there are no host enzymes to catalyze the process, HIV carries it is own enzyme known as reverse transcriptase in order to carries is out.

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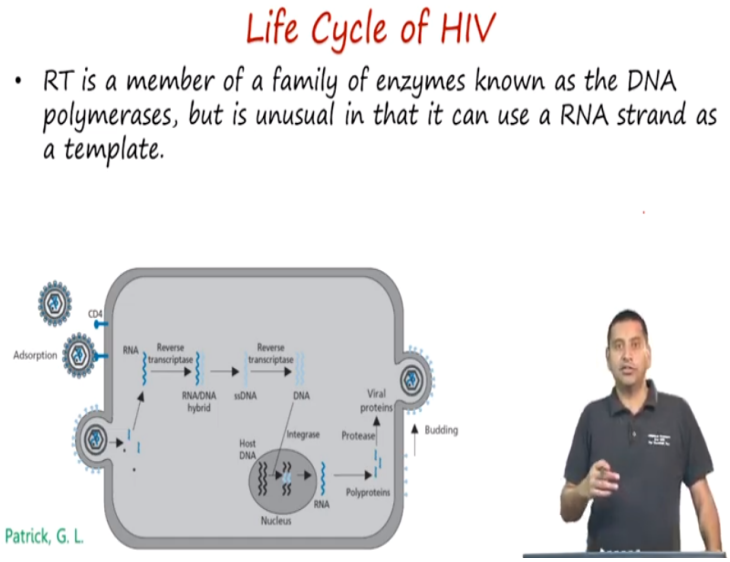

Reverse transcriptase is a member of a family of enzyme known as the DNA polymerases but it is unusual that it can use RNA stand as a template.

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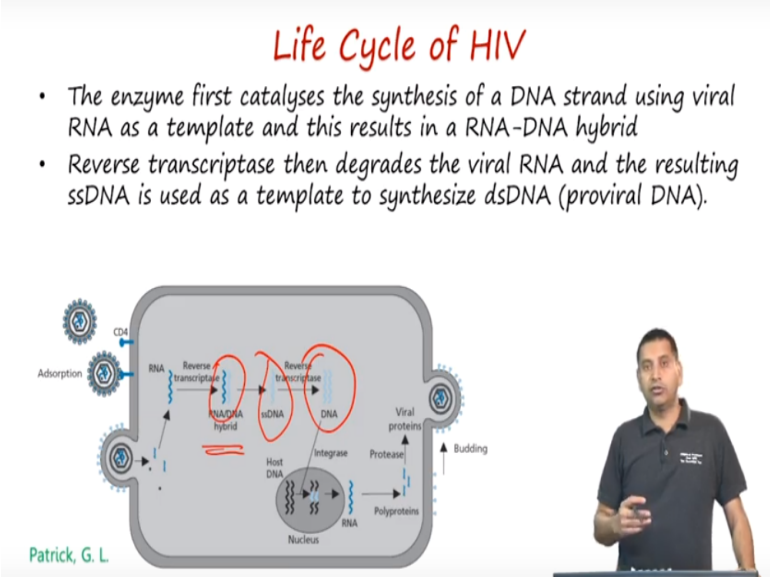

The enzyme first catalyzes the synthesis of a DNA strand using viral RNA as a template and this result in a DNA RNA hybrid, then reverse transcriptase degrades the viral RNA resulting in a single strand it DNA, now this single strand it DNA is used at template to generate a double strand it DNA which is also known as pro-viral DNA.

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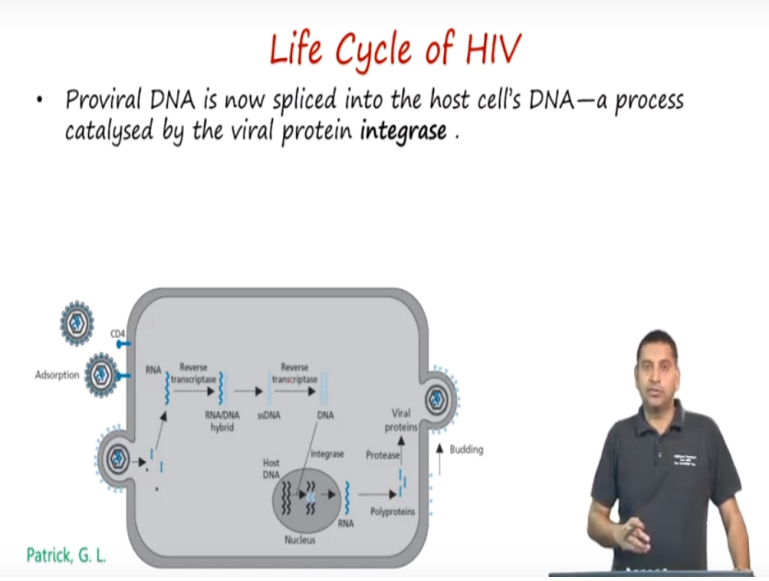

Pro-viral DNA is then spliced into the host cell's DNA by an enzyme known as viral protein integrase.

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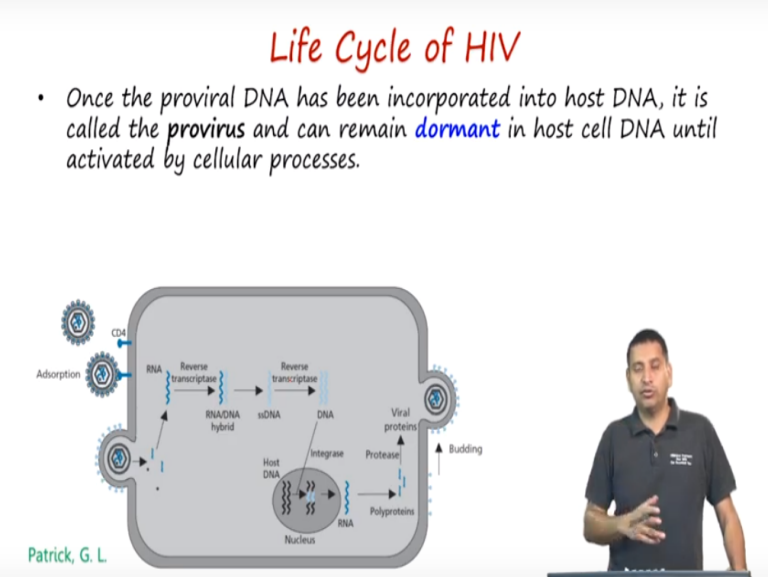

Once the pro-viral DNA has been incorporated into the host cell DNA, it is called the provirus and this can remain dormant for weeks or even months or years together until there are certain cellular processes which are activating it.

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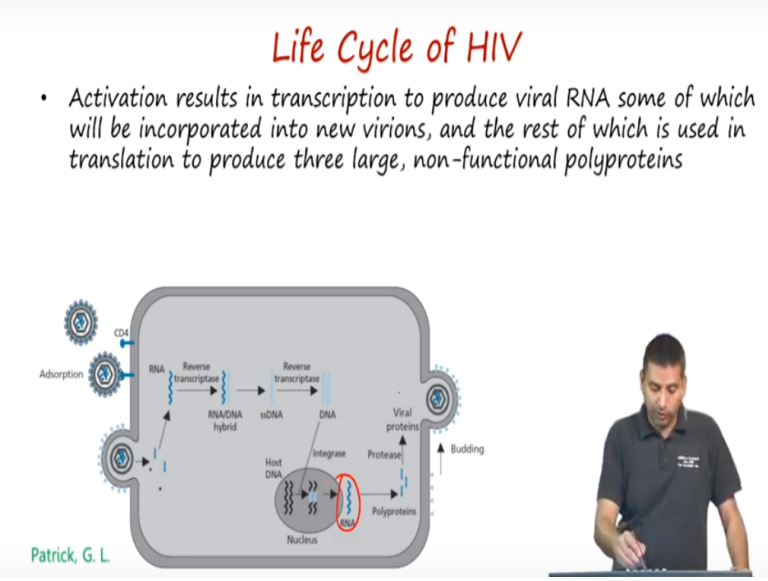

So once is activation happens then it results in transcription to produce viral RNA which is shown here and this is viral RNA some of which will be incorporated into new virions, and the rest of which is used in transcription to produce three large non-functional poly-proteins.

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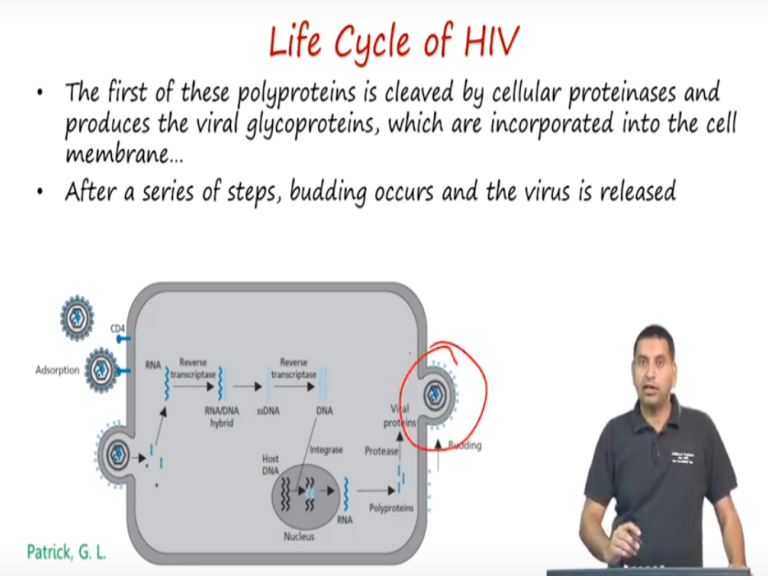

And then the first of this poly-protein is cleaved by cellular proteinases and produces the viral glycoproteins which are incorporated into the cell membrane after a series of step which we will not go the detail about the budding occurs and the virus is released.

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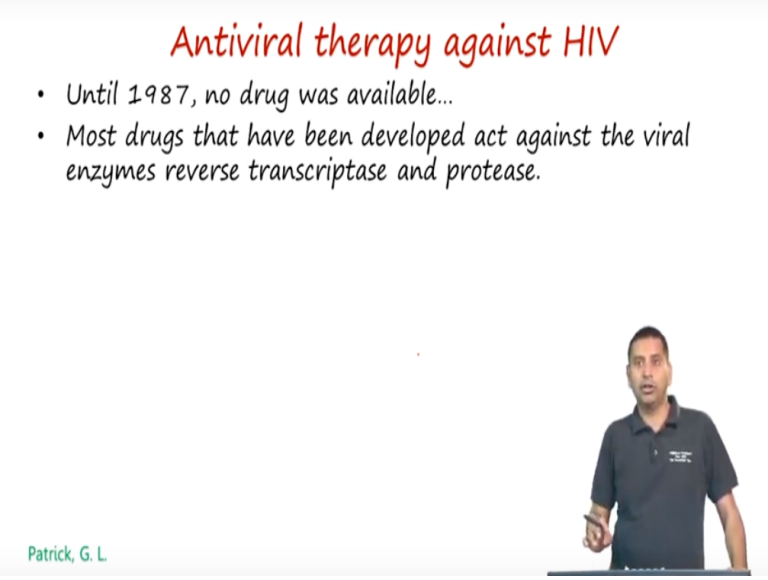

Until 1987 there was no drug available against HIV, most drugs have been developed to act against the viral enzyme reverse transcriptase and rotease.

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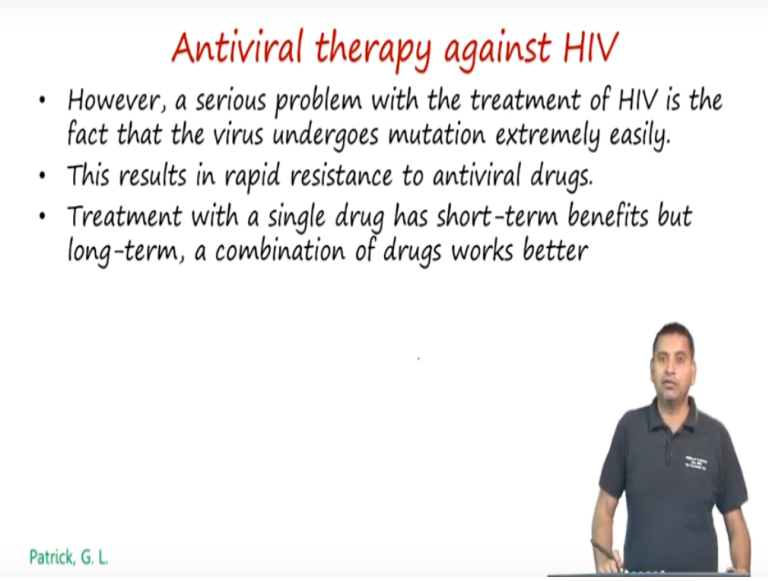

However a serious problem with the treatment of HIV is that the virus undergoes mutation extremely easily and so once a drug has been introduce there is going to be rapid resistance developed to the antiviral drug so therefore treatment with a single drug can have short term benefits however after the drug has been introduce and it benefits are seen since the virus can rapidly mutant in developed resistance it is preferred that in the long term a combination of drug

is actually used, so today HIV therapy consist of a combination of drugs which have given for pretty much for the life time of the individual.

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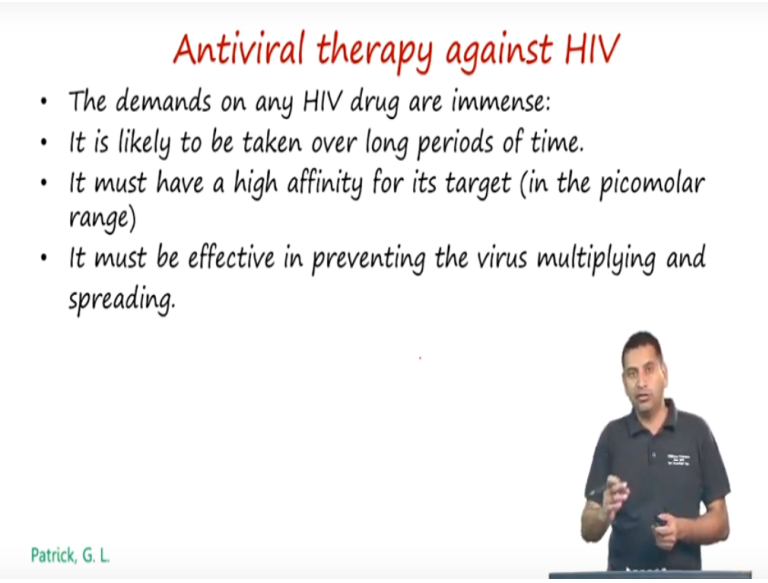

So the demands of any new HIV drug are quite high one it has to be taken over long period of time, so it has to have you know many years or decades even for that matter this drug there is developed must have high affinity for it is target which is in the Picomolar range, it must be effective in preventing the virus multiplying and spreading.

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This new drug should also show low activity against a similar host targets in the cell and it should be safe and well tolerated and it must effective against large variety of viral isolates as possible or else it only serve to select resistant variants.

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Then it also needs to be synergistic with other drugs because we are going to give a combination of this drugs it should be synergistic with them and compatible with other drugs used to treat this opportunistic disease and infections arising from the weakened immune response.

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The drug must stay above the therapeutic levels within the infected cell and in circulation and it also must be capable of being taken orally with a minimum frequency of doses and it should preferably be able to cross the blood-brain barrier in case the virus lurks in the brain and lastly it must be inexpensive, so developing a new drug for HIV is actually quite challenging.

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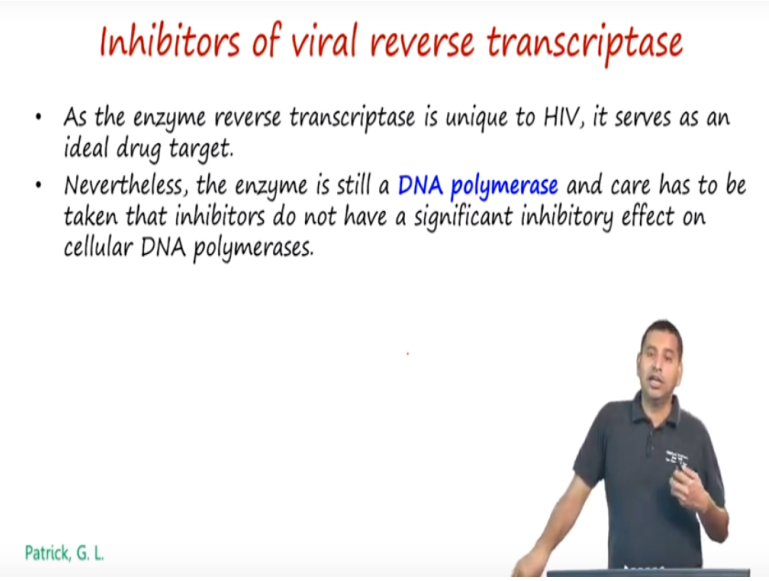

So with that lets us look at inhibitors of viral reverse transcriptase, so as the enzyme reverse transcriptase is unique to HIV, it serves as a very good drug target. However it is still remains a DNA polymerase and therefore one has to be careful about how selective the drug that we are developing is towards in reverse transcriptase rather than are host cell DNA polymerase.

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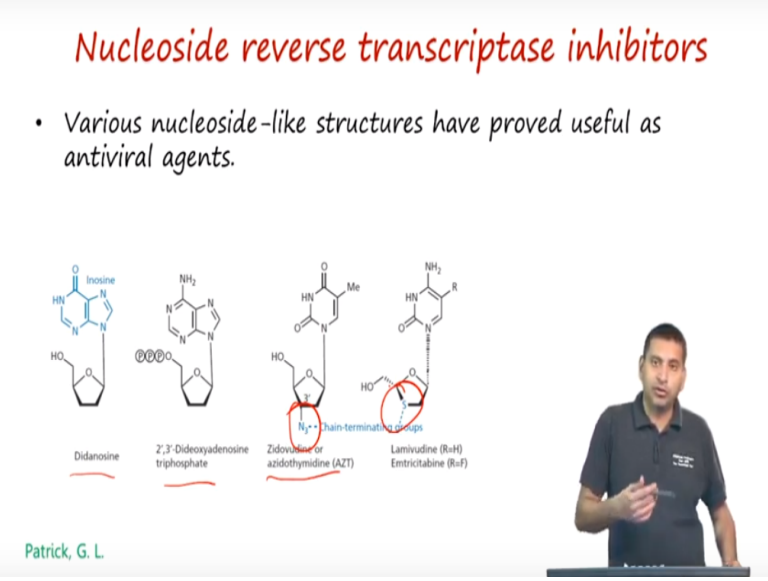

So various nucleoside like structures have been useful as antiviral agents so here are some examples so Didanosine and then this is a Dideoxyadenosine triphosphate and then this is AZT which is one of the first drug that was introduce it contains an AZT ring here or you can have chain terminating group such as a sulphur here and so on, again these are this the broad class mechanism of action of these drug you are already looked at previously and they are inhibitors of reverse transcriptase.

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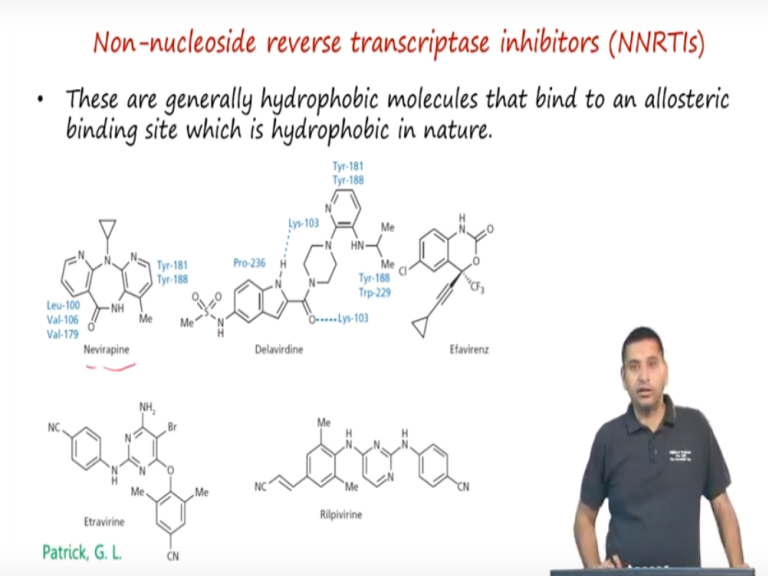

And there are also non-nucleoside reverse transcriptase inhibitors which are known as NNRTI's, and what these do these are generally hydrophobic molecules and they got bind to an allosteric binding site in the enzyme, so they were happen there is an example of this.

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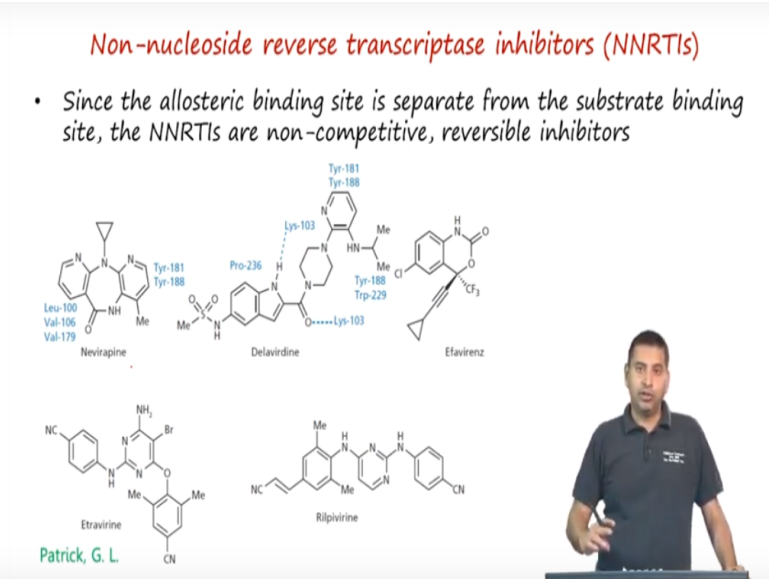

And since the allosteric binding site is separate from the substrate binding site, these are non-competitive reversible inhibitors.