Essentials in Immunology

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Module No. # 18

Lecture No. # 35

Host response mechanisms during infectious diseases - part 2

In the previous class, we had studied the response of the host to various intercellular infections. The primary one being mycobacterium and the effects on fungus. In today's class, we will be studying two main types. One is viral infections and the other is new emerging diseases and I think it is fitting end to this part because you can see how the different host factors play an important role in modulating disease.

This is a very important aspect and you can see that there is no single mechanism. You have multiple mechanisms that are in place and this is perhaps the reason why the immune system mechanisms are so redundant. You have innate, you have adaptive and within each of these you have different sub compartments.

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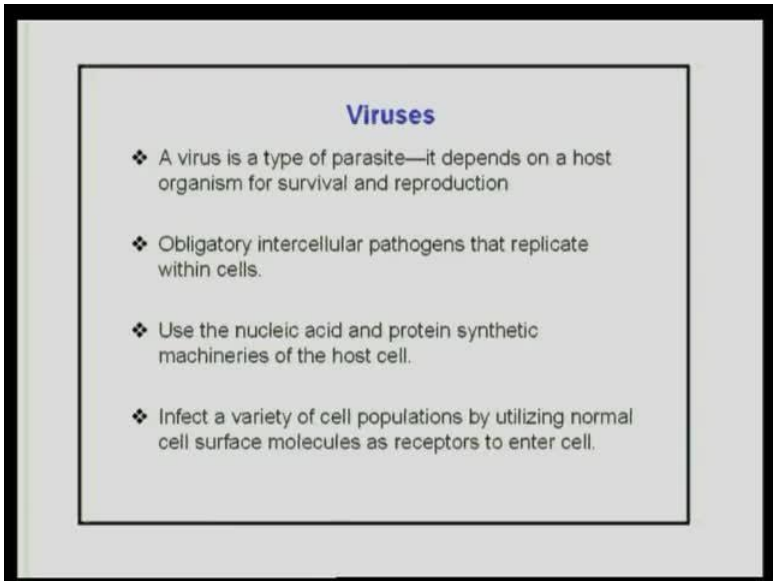

So, if we go to the first part on viruses, so what are viruses? So, these are sort of inert protenacious particles which replicate based on plant cells or animal cells. In our case, they it would mainly animal cells and what are some of the things they do is that they use the nucleic acid and protein by synthetic machineries to replicate in the host.

Life is about replication because you would need to increase your progeny, so that you can spread it. That is what biology is all about and if you are unable to do it, then it does not quite work out. So, it is very important for pathogens or organisms to find mechanisms by which they can replicate. It is also important for host the host to take care of itself and prevent this take over by different pathogens including viruses and this interaction between the two is what is we study in this part known as the immune system.

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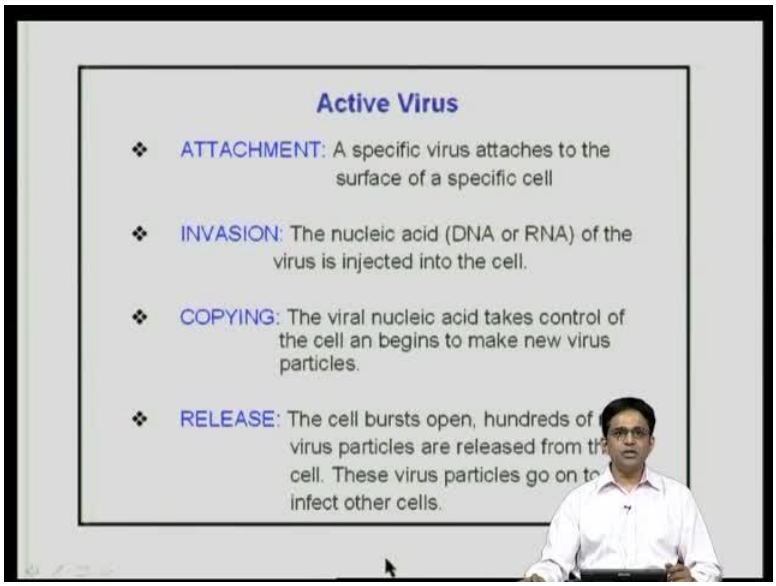

The one of the ways by which viruses infect is by utilizing cell surface molecules to gain entry in. So, essentially if we were to take a look at the different steps in terms of viruses there are mainly four. One is attachment. Virus attaches to the surface of a specific cell, often it is through binding of a particular receptor. The most famous, of course is your HIV virus which you are I am sure you have heard of where GP120 of the virus attaches to CD4 and that sort of helps in the entry of it.

Now, there are co-receptors involved in this. We will be studying some of these chemokine receptors that are involved in this but the specific interaction is between a viral protein and a specific receptor on the host cell. Now, after attaching an entry with the DNA or RNA

whatever type the virus belongs to is injected into the cell. You need to copy and as I have copying is very important because replication is the hall mark of life.

Viral nucleic acids take control and begin to make new virus particles. So, what happens is if it is RNA, then it is converted into DNA and then back into RNA and ultimately, into proteins and if it is DNA, then back into RNA and then into proteins. Now, the viral particles are formed and then the cell bursts open and releases hundreds of these and with the hope that these will be able to find host cells by which in which they can replicate and spread the progeny.

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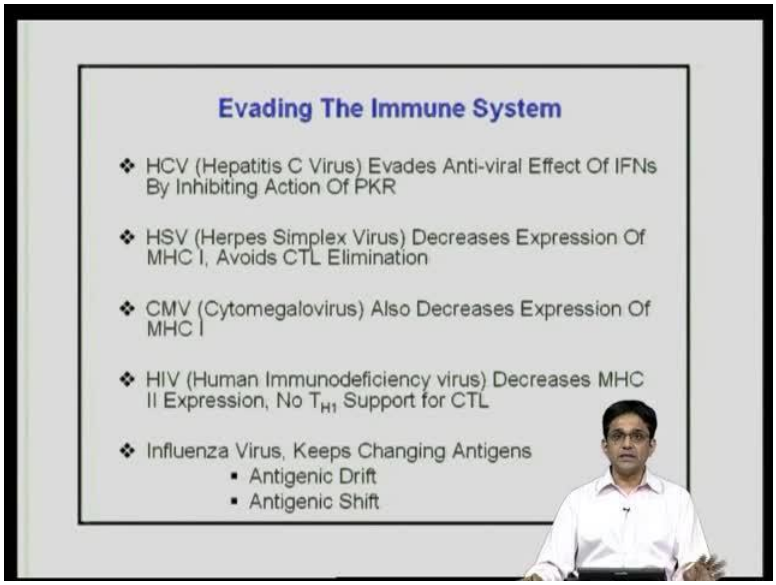

Now, in terms of evading the immune system, you have different viruses that have got different mechanisms or have used different mechanisms. For example, the hepatitis C virus inhibits interferons. We will be discussing little bit about interferons by inhibiting the action of PKR or protein kinase R, HSV or herpes. Simplex viruses decrease expression of MHC class 1 avoids CTL elimination.

Cytomegalovirus also decreases expression of MHC class 1. So, what has happened is since the MHC class 1 response is so important in terms of infecting in terms of fighting viruses, the virus, the particles have evolved in such a way that means the species that are able to down regulate MHC class 1 are you know have a more likelihood of spreading.

So, that is what has happened is the environment condition is such is that you are you are looking for progeny that can bypass the immune system. One of the best ways by which they can do it is to try and decrease MHC class 1, you will get a lower CD8 response and that helps. Then you have HIV which decreases MHC class 2 expressions, then you do not have large majority of CD4 positive cells are destroyed. As a result of which the helper activity is less and therefore, the CTLs that are generated are often not fully functional.

In case of influenza, it is little bit different because they keep changing the antigens and that is goes by antigenic drift or shift.

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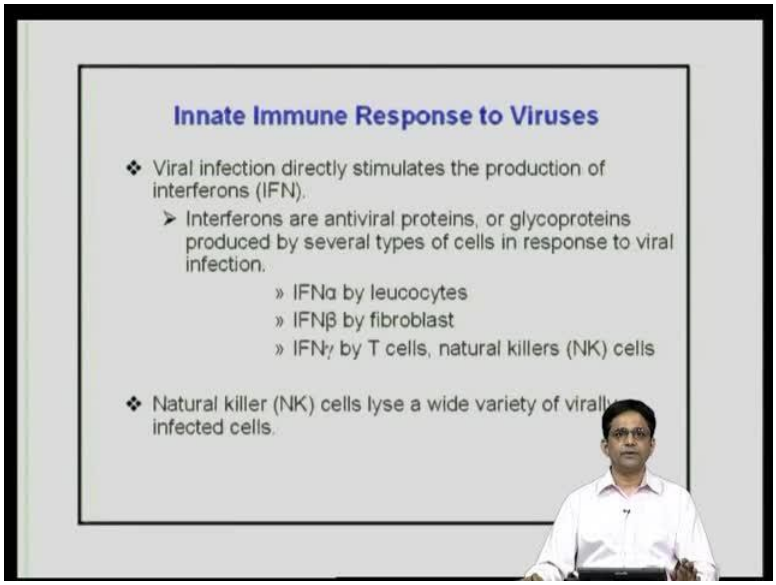

Now, one of the important ways by which the host controls viruses is by the production of interferon. So, we will spend a few slides on interferons. Now, interferons were discovered several years ago in the 1950s by Isaac and Lindeman because they found the fact that interferes or a host factor that interfere with the replication of viruses.

Subsequently, these were purified and we know there are three broad types. Interferon alpha is produced by leukocytes and interferon beta by fibroblast. Both alpha and beta bind to a particular receptor known as a type 1 interferon receptor.

Now, type 2 is interferon gamma which is produced by T cells and natural killer cells. The receptor for the interferon gamma is distinct from that of interferon alpha and beta. So, these two have different signal transaction pathways and we will discuss that a little bit later.

You have natural killer cells which will lies a wide variety of viral infected cells because if you remember natural killers cells kill cells that where you have lowered MHC class 1. Also, NK cells have NK receptors and you have different types of whether they are inhibitory or activating type and in case, NK ligands are expressed on these virally infected cells, NK cell will kill these viral infected cells.

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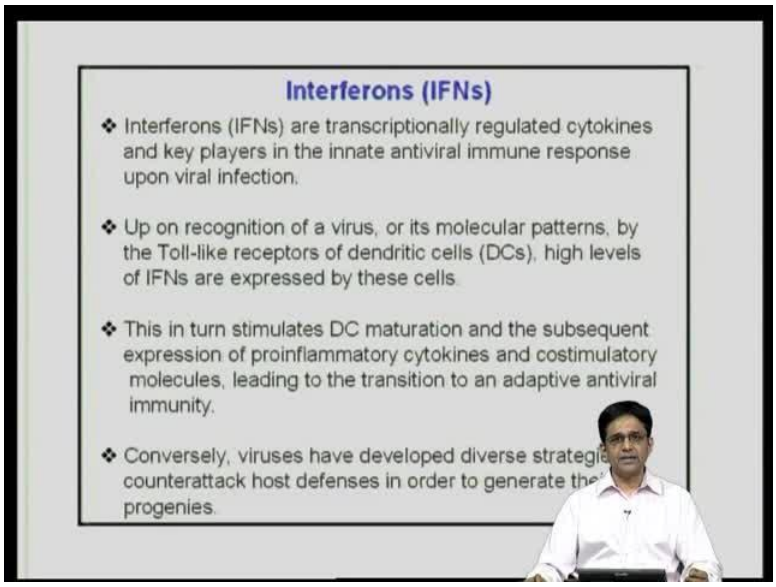

So, little bit about interferons now. Interferons are transcriptionally regulated cytokines and they play a very important role in modulating immune responses, especially antiviral immune responses. What happens in this case based upon recognition toll like receptors on dendritic cells and high amounts of interferons are expressed by dendritic cells. You have other types of cells also that were shown that can produce interferons. What this does is the production of interferons modulates the adaptive immune response and that is the most important part. Now, as a result of this effect of interferon's viruses have developed different strategies to counter it.

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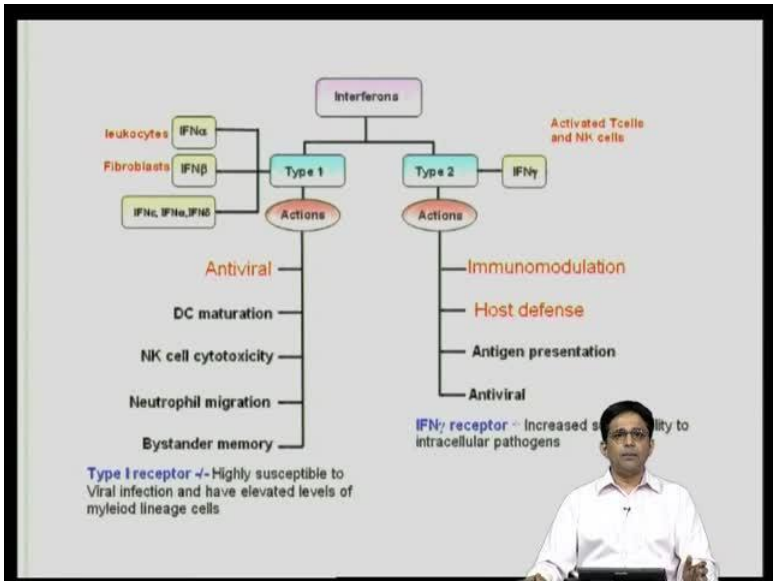

In general, as I mentioned there are two types of interferons Type 1, the IFN alpha beta and these are primarily antiviral in nature. They are involved in dendritic cell maturation. NK cell cytotoxicity, they increase NK cell cytotoxicity, neutrophil migration. If you look at the phenotype of the receptor of individuals that lack the type 1 interferon receptors, they are highly susceptible to viral infections and they have elevated levels of myeloid lineage cells that is primarily because interferons are probably inhibiting this particular lineage cells and in the absence of it, these cells sort of take off.

So, they might have some growth regulatory property but the primary effects of Type 1 interferons are antiviral. That is how they were discovered and it is very important that we understand that.

The other type of interferon which is the interferon gamma, it is produced by activated T cells and NK cells. As we mentioned, they are immuno-modulatory. They are very important for host defence, so as those previously discussed. In that interferon gamma lacking mice are highly susceptible to infections by intercellular pathogens like salmonella mycobacteria. We also talked about BCG versus if you remember correctly in the past lecture that interferon gamma knockout mice are highly sensitive to intercellular pathogens.

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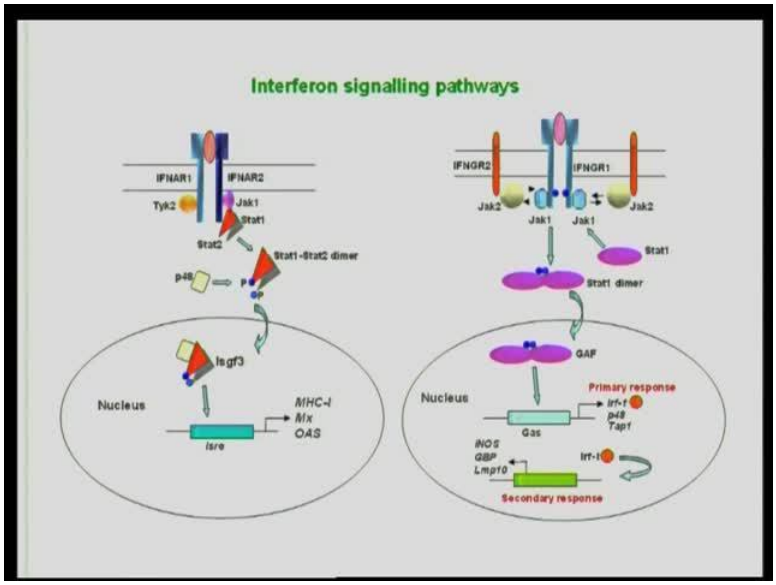

A little bit about their signal transduction pathways. What is shown over here is the Type 1 signal transduction pathway shown here and over here interferons function through what is known as the Jak Stat pathway. Jak stands for janus kinase and is a tyrosine kinase and Stat is a signal transducer and activator of transcription. So, what happens over here and what will be shown is upon binding upon interferon with its receptor, you have activation of the Jak or the janus kinase and which phosphorylates the Stats.

The Stats upon phosphorylation, they bind with each other or bind with other molecules and they enter the nucleus where they transcribe several genes. So, the mechanisms by which interferons function is primarily through transcriptional regulation and how this works is via through the Jak Stat pathway, very important. I will just briefly mention, so here you have the type 1 interferon receptors. There are two sub units over here IFNAR 1 and they are 2 and these are associated with the Jak 1 and Tyk 2, both these two are tyrosine kinases.

Now, these two will bind to the Stat 1 and 2. Upon phosphorylation, the Stat 1 Stat 2 you know dimerise, they bind together with another molecule known as p48, enter the nucleus and they form this complex known as Isgf3 and they will bind to Isre or interferon responsive elements which is present in certain genes. The ones that are shown over here are this is the Mx gtpases MHC class 1 and the oligo adrenolytic synthase which is important in antiviral responses ok.

So, it is very important that interferons you understand the way interferons function. It is mainly via transcriptional regulation and that transcription of different genes that are involved in the response and this function through the Jak and the Jak Stat pathway.

The other interferon that we talked about the type 2 interferon was interferon gamma and this binds to again the interferon gamma sub units. The IFN gamma R1 R2 and over here the tyrosine kinases, you have Jak 1 and Jak 2.

Now, Jak 1, Jak 2 upon coming together after binding to interferon gamma, what happens over here? You have phosphorylation of Stat 1. The Stat 1 dimerises and then enters the nucleus and it enters the nucleus to form a gamma activated factor. So, the gamma activated factor binds to the gamma activated sequence which is present in the promoters of several primary responses of genes like Irf-1, p48, Tap 1 and you know p48 is a same one that is present over here. The interferon responsive factor goes and then binds to other gene which is shown and they are a part of the second response.

So, in with respect to interferon gamma you have two types of responses. Again, you have the Jak Stat pathway thus playing an important role but over here you have the primary response and Irf-1, then goes on and bind to other in the promoters. It is also another it is a transcription factor it is and it binds to other promoters of other genes and which are part of the secondary responsive.

So, you can differentiate the primary and the secondary responsive because the secondary responsive genes will be sensitive, will require protein synthesis, therefore will be sensitive to cycloheximide treatment whereas Irf-1, p48, Tap 1 for example, these are primary responsive and will be insensitive to cycloheximide treatment. So, it is very important that students understand primary and secondary responsive genes and the way of differentiating them using a protein synthesis inhibitor, you could also use daptomycin d which is the RNA transcription inhibitor. So, we will now move to ok.

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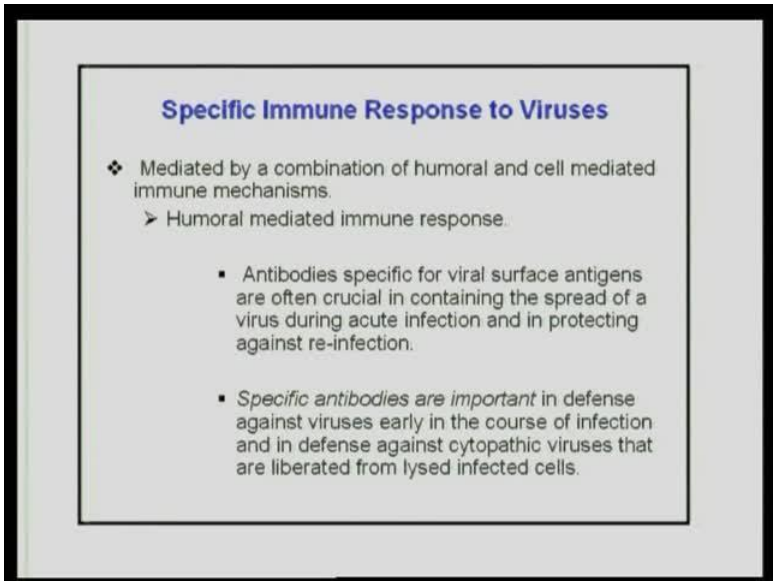

So, now if we look at specific immune response to viruses, there are interferons certainly one but as mentioned the immune system has different pathways that play an important role and you have it is a combination of both humoral and a cell mediated. Now, in the humoral mediated one, very important aspect is the generation of neutralizing antibodies. If you are able to generate neutralizing antibodies against the particular virus or bacteria, then you have a good chance that you will be able to mediate protective effects.

As was mentioned that most of the effect, most of the good vaccine are the ones that generate very good neutralizing antibody. In this case, smallpox is a good example and the fact that we have been able to eradicate smallpox is because of the fact that you we generate that you are able or one is able to generate a good neutralizing antibody against this particular virus. So, the ability of good neutralizing antibody is really key.

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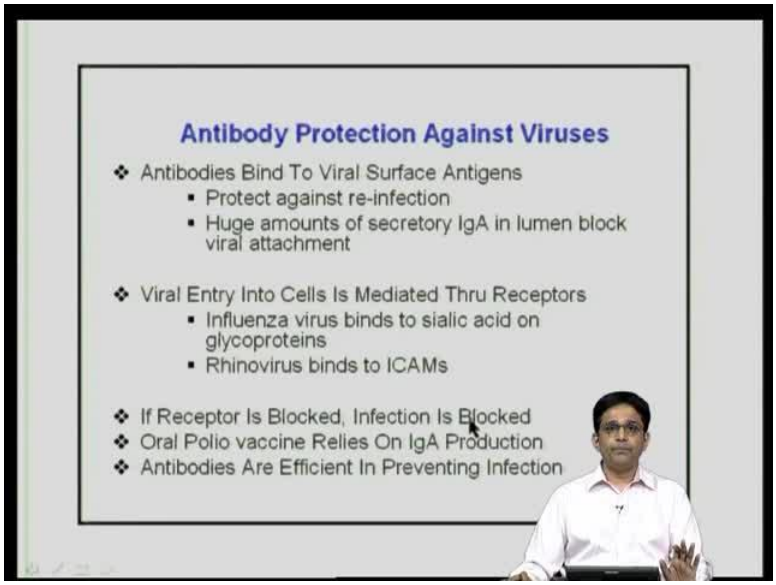

So, what these antibodies do is that they would bind to the viral capsid particles. They would inhibit the binding of them to its receptor and more importantly, it would allow they would fix complement and as a result of which complement mediate lyses would take place. It would also help in opsonisation where antibody bound a viral particles would be taken up by macrophages or phagocytic cells and phagocytes.

So, there are different mechanisms by which this works so and some of the ones are shown over here. If the receptor is blocked, infection is blocked. In case of oral polio vaccine, it realises on the production of IgA production and so you have a good mucosal immune system that is generated. Antibodies are efficient in preventing infection.

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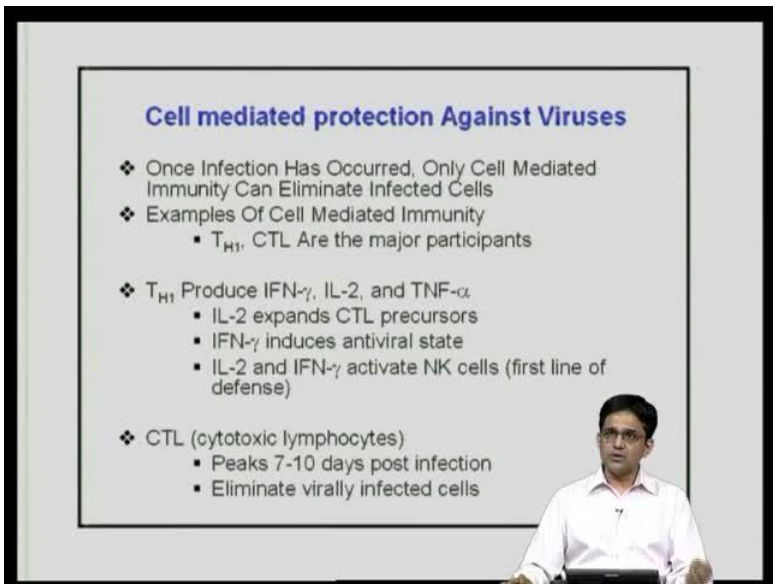

Now, you have also cell mediated protective mechanisms as one of the ones that was discussed is a good robust CD8 positive response because CD8 positive response will lyse the viral infected cells. Now, in order to generate a good CD8 positive response, you also need to have CD4 helper around and so, you need both of which would be required for this State. On top of that you have natural killer cell because natural killer cells would kill the viral infected cells. What is also shown over here, IL-2 is important because interleukin 2 1 T cells are activated. They would produce IL-2; hence IL-2 is important for expansion of CTL precursors and so on.

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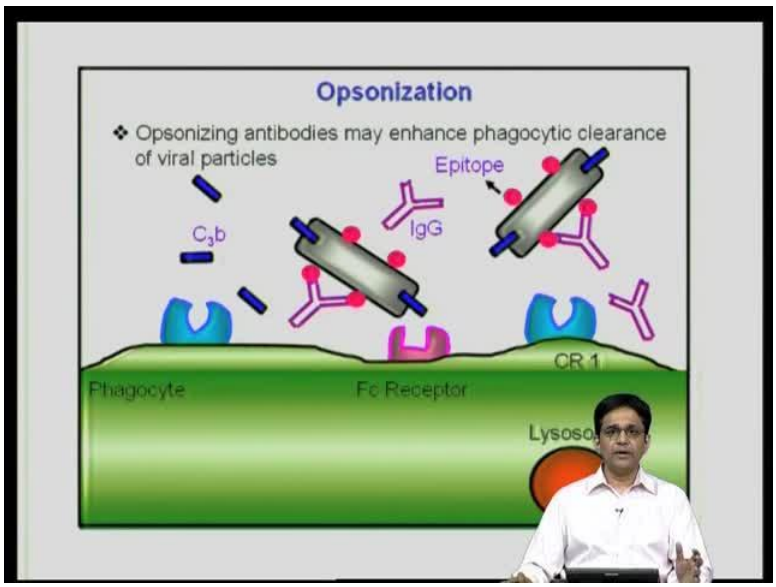

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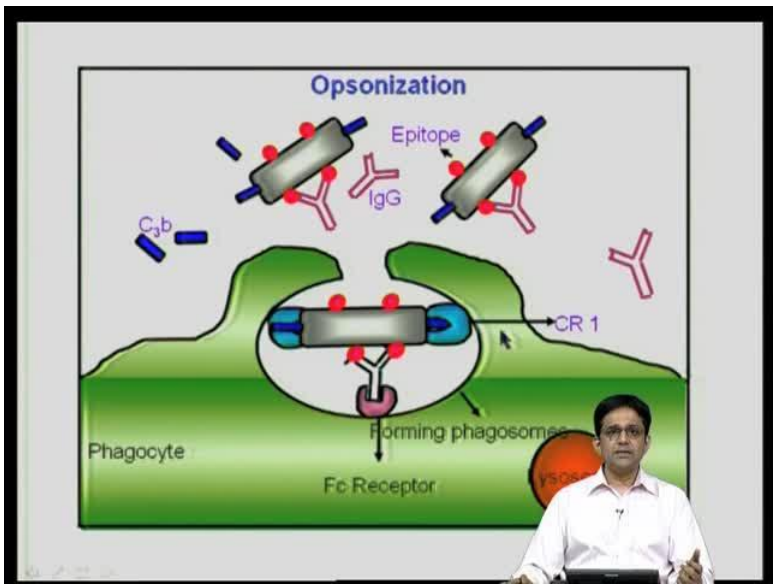

What I am going to show you over here is the process of opsonisation and these are viruses coated particles that are bound with antibodies. You can see that these antibodies help opsonise, means they help the uptake of these viral coated particles into phagocytes.

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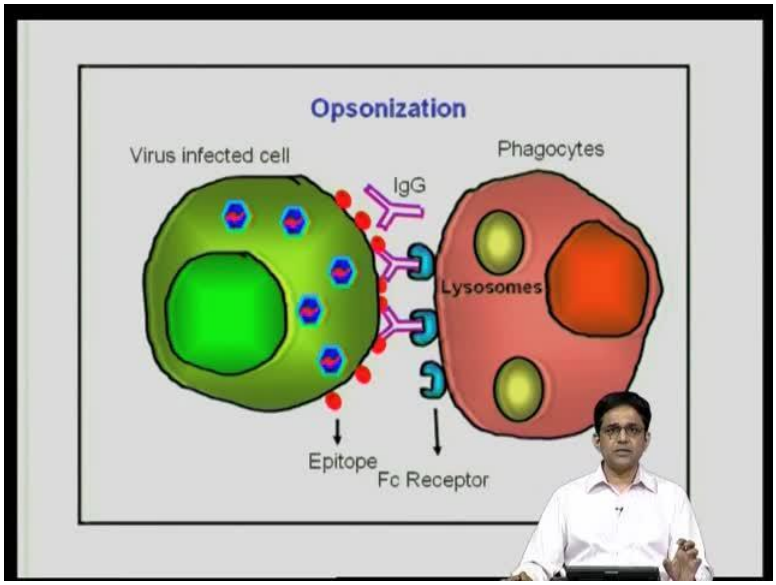

Then these phagocytes are taken up and then they are sort of they are engulfed and they are degraded in lysosomal compartments.

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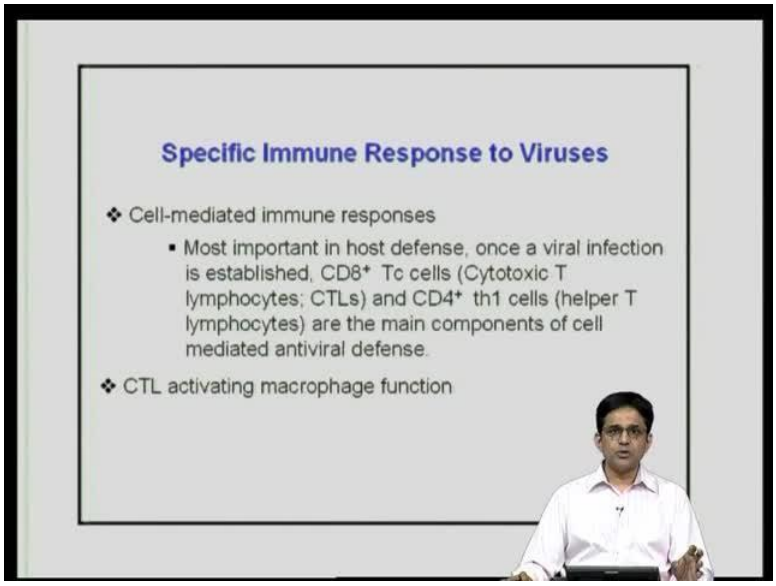

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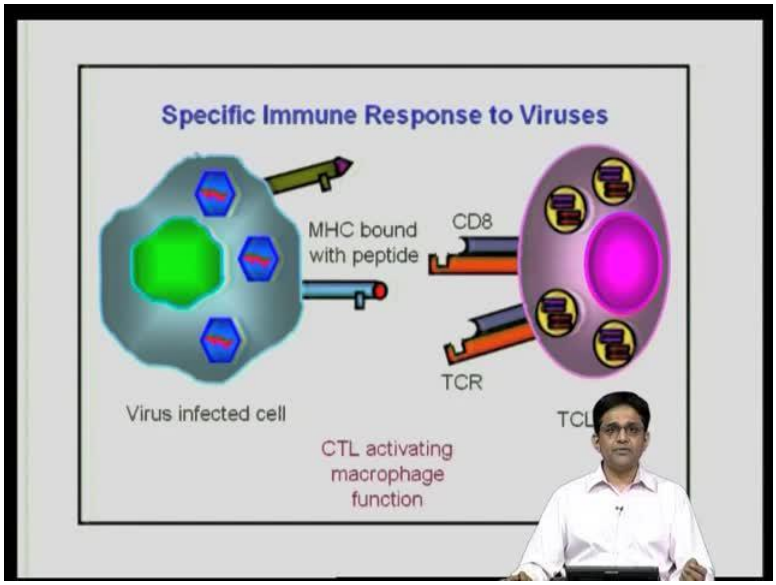

Both CD4 and CD8 responses are important in case of viruses and these are and there is there is no doubt about it because in case you have a compromised CD4 response, you will be unable to generate a good CD8 response and if you do not have a good CD8 response, you are unable to kill these viruses. So, it involves a combination of the two and that is pretty much what is shown over here. You have a virally infected cell and you have the specific T cell receptor.

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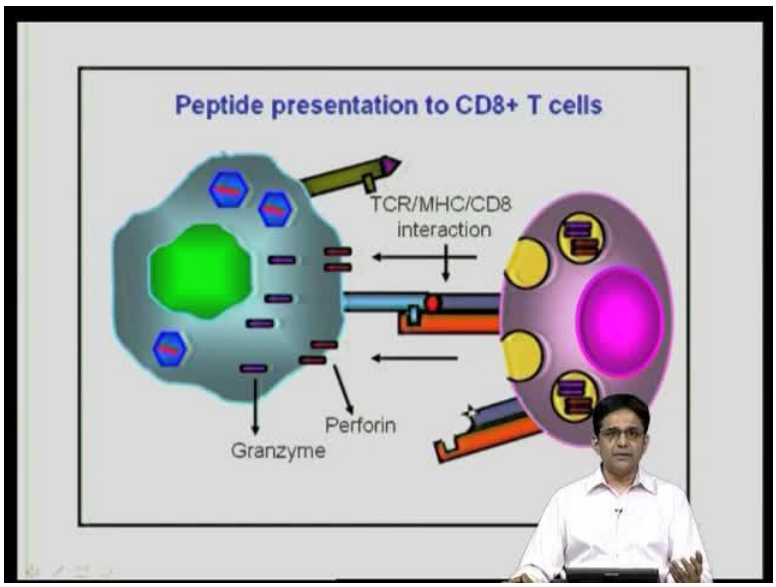

This requires good recognition that particular T cell has to recognize a virally infected cell expressing the MHC and along with some viral encoded peptide, the TCR needs to be specific for it. So, you are able to generate a good response and then the perforins and the

granzymes are secreted by the CD8 positive T cells which would kill these viral infected cells.

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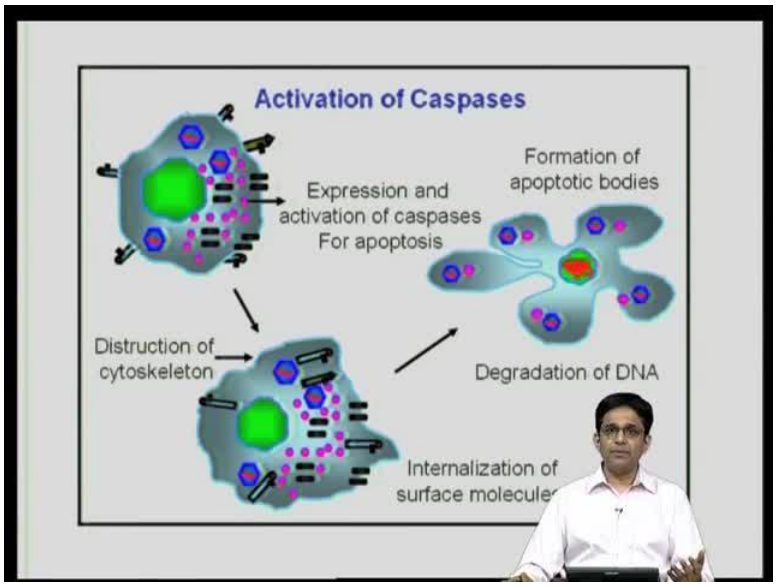

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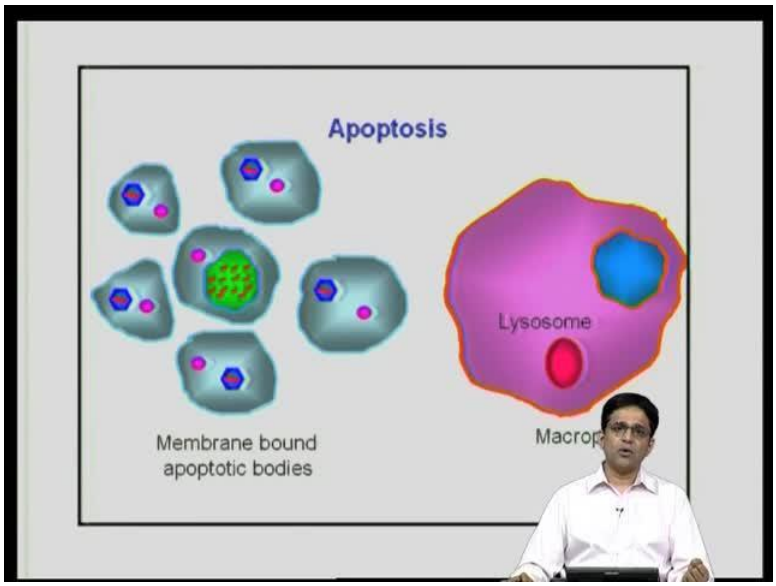

What would also happen along with this is that you have activation of caspases and the virally infected cells. You would form, you would trigger apoptosis in these and they would be degraded and after degradation, they would be broken up into apoptotic bodies which would be phagocytosis. This we had discussed these this the efficient cleaning up of phagocytic cells in our class on T cell survival.

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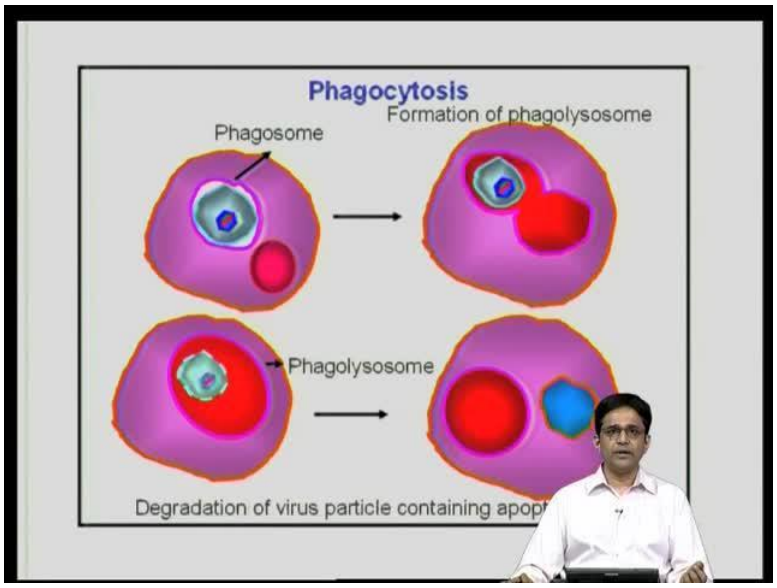

That is precisely what is shown over here that you have good phagocyte cells which do an efficient job of cleaning up apoptotic bodies.

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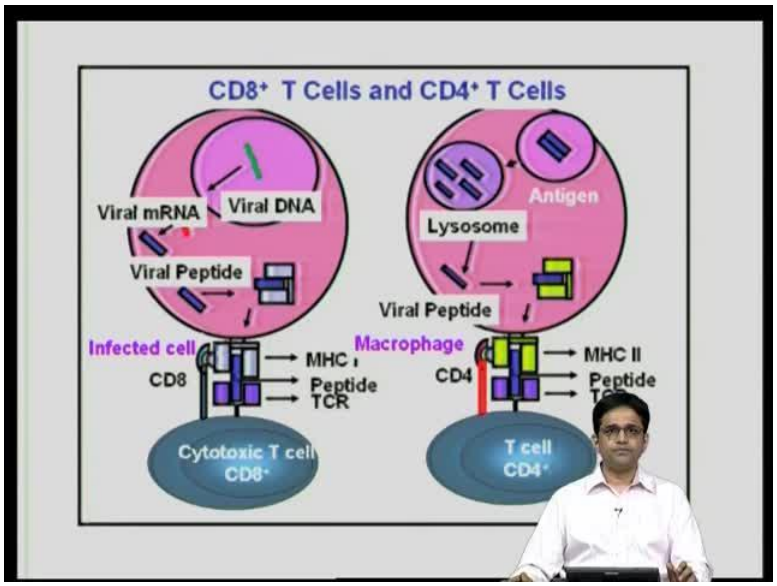

What is shown over here is the two paths that is important over here. You have the CD4 positive cell which is recognizing, which are the TCR that recognizes MHC class 2 and you have a CD8 positive cell that recognizes MHC class 1 and both of these are required but what is important to note over here is that often in this case, in case of the class 1 response of the CD8 positive response, you have viral DNA. It is made into mRNA and this mRNA is

transcribed in two viral proteins in the cytosol and a part of these are then broken down and transported into the Er and where they get loaded on MHC class 1 and then they are shown up over here.

So, you can see then we had discussed our class 1, MHC class 1 MHC class 2 this is why it is so important that you have the two parts over here. Over here, if the viral proteins are made in the cytosol, then perhaps our some of them are degraded and the peptides are transported into the Er where they get loaded on MHC class 1. However, if they if some of them are digested in lysosomal compartments or MHC 2 like compartments, then chances are high that some of the viral peptides are loaded on MHC class 2 and will be showing those particular peptides to CD4 positive cells. Suffice to say you need a good both CD4 as well as the CD8 response to generate good antiviral T cell responses.

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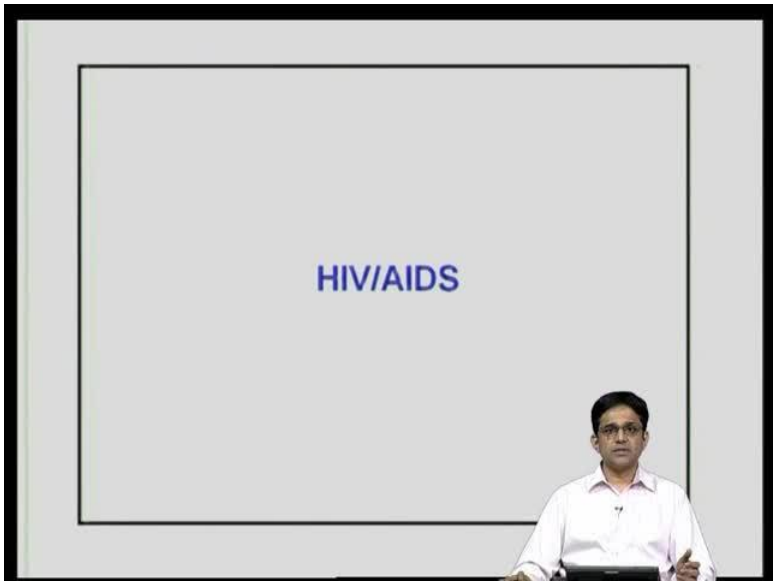

We will now discuss a particular virus which is extremely important and something that I am sure that you are all familiar with.

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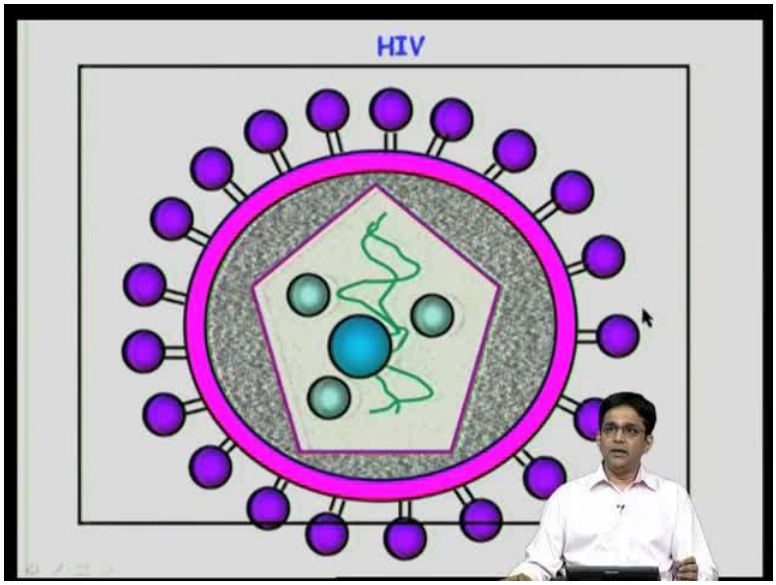

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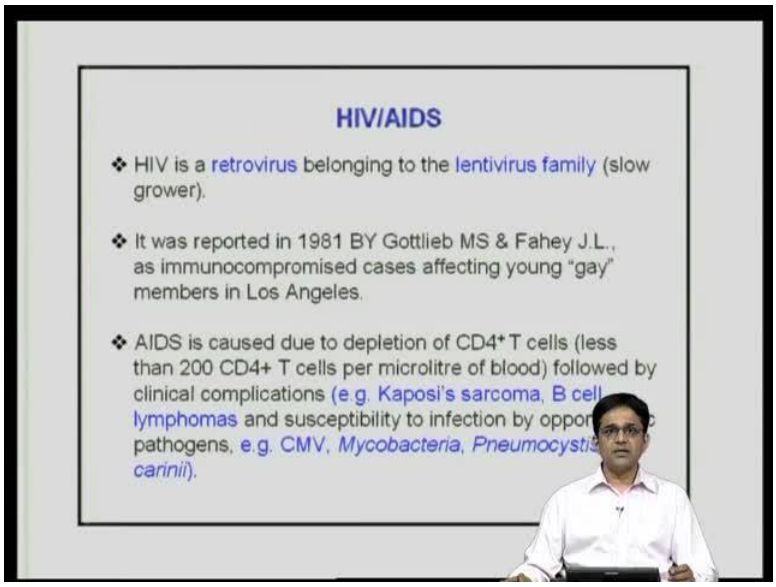

This is the human immuno-deficiency virus known as HIV. Now, HIV is the retrovirus belonging to the lentivirus family which slow grower. A retrovirus means, it is made up of RNA and it needs to transcribe and it uses reverse transcriptase to get into DNA and then again to form its particles.

Now, the first reported case of AIDS was in 1981 by Gottlieb and Fahey who realized that there were lot of immuno-compromised cases that were affecting young gay members in the Los Angeles community. Now, the cases that when they first came were usually found to be observed or these infection were associated with people in advance age older old people whose immune system was compromised.

Now, what was surprising over here that these cases were being were showing up in a particular in younger people and further investigations reveal that this younger people belong to a particular community, the gay community. That is how really you have to give credit to the doctors and the scientists who are able to make this association and the first report appeared in mortality and morbidity report which is some sort of a classic. Students must be a little close attention as to the characteristics and to the acuteness of the physicians and the scientist who are able to pin point and transfigure this out because this is the first time that this was being was being shown up.

So, we went from our world without AIDS to AIDS all of a sudden and you have to give credit to the doctors and the scientists to be able to who are able to distinguish this. So, what happens in case of AIDS is caused depletion of CD4 positive cells which means you have less than 200 CD4 positive T cells per micro litre of blood and this because of the lowered CD4 number of cells. You have clinical complications, you have Kaposi sarcoma, it is a type of tumour that takes over and you have B cell lymphomas. You see your immunity is compromised.

So, now you know your tumour cells as well as infections and susceptibility to infections increases. So, you have infections by opportunistic pathogens like cytomegalovirus, mycobacteria, pneumocystis and carinii etcetera. Students should also learn to differentiate between HIV positive and AIDS. This is a very important distinction. When you have HIV positive means you have been exposed to HIV and you have been tested to HIV positive by either RT-PCR or ELISA but it does not mean you are AIDS. You go from HIV positive to AIDS or acquired immunodeficiency syndrome once you have CD4 count drops.

So, it is very important to understand that HIV whether you have HIV positive or negative depends on the detection by RT-PCR ELISA and once you have CD4 count drops and that can be determined by using specific antibodies and using flow cytometry. Once you have CD4 count drop that is when you start becoming susceptible to tumours and other infections common infections that occur. Very important for students to pay close attention to this.

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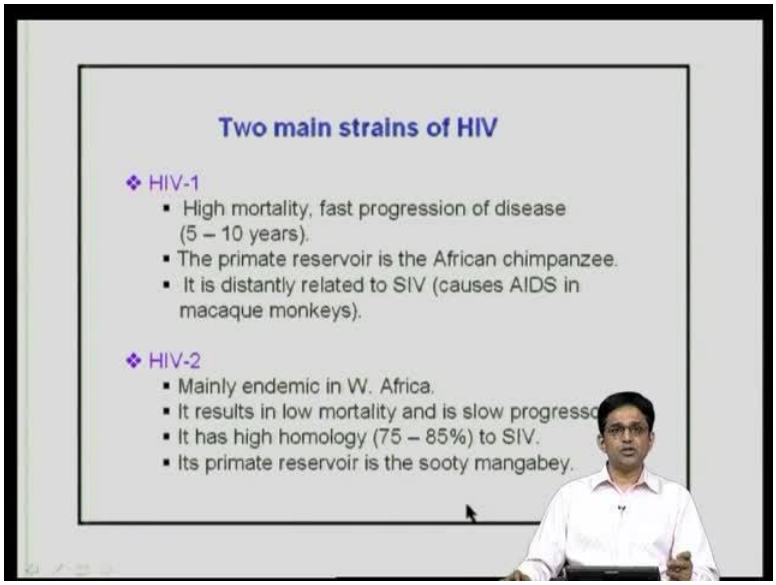

There are two main strains of HIV 1 and HIV 2. HIV 1 is a faster progressing one, has higher mortality, whereas HIV 2 has low mortality somewhat slow progressing and in case in both these cases, the primary reservoirs are somewhat different. In HIV 1, the primary reservoir is the African chimpanzee, whereas it is a sooty mangabey in the HIV 2. In HIV 1, it is distinctly related to the simian immunodeficiency virus, whereas HIV 2 is more closely related to this immunodeficiency virus.

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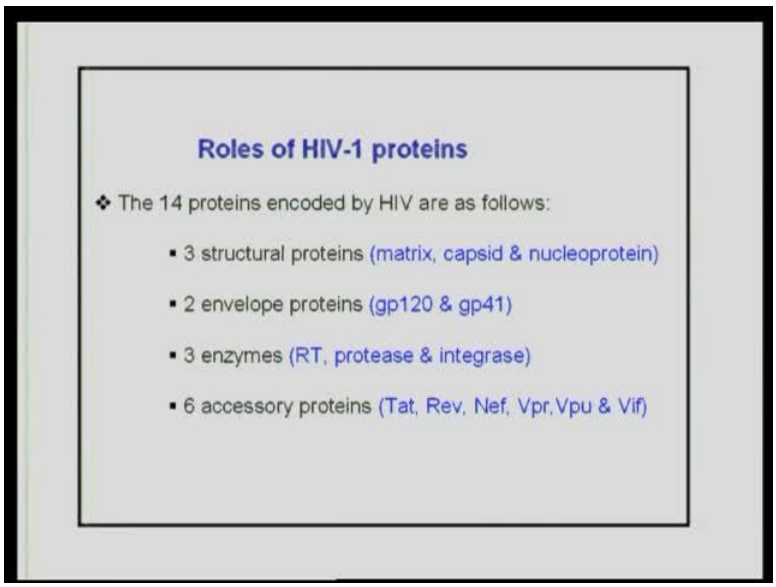

Now, there are several proteins that are encoded by HIV. Remember, HIV is the virus and several of the proteins are polyproteins. You have structural proteins, the matrix capsid nucleoprotein, you have envelop protein, gp120, gp41, gp120 as you know is important in

binding CD4 which is a receptor the enzymes the reverse transcriptase protease and integrase. Remember, proteases are target of and proteases are important because it is important in cleaving these polyproteins. So, proteases also a target as a drug target and you have different accessory protein like you have the Tat, Rev, Nef and so on we will be studying a little bit about these.

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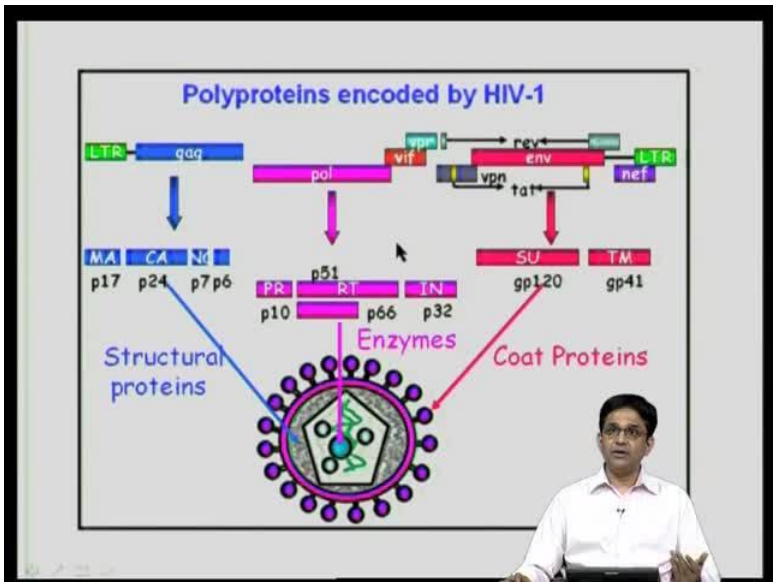

What is shown over here is you have these different polyproteins encoded by HIV and you can see that they are broken down over here. So, you can see you have pol which is actually broken down into reverse transcriptase, integrase and the protease. Again, that is how the viral in several viruses, the proteins are transcribed as polyproteins and then they get broken down and that is where the protease part is very important over here because it is important in breaking down these proteins, so that they can function properly. Now, the targets of HIV you know which will be coming to are again reverse transcriptase and the protease which is very important.

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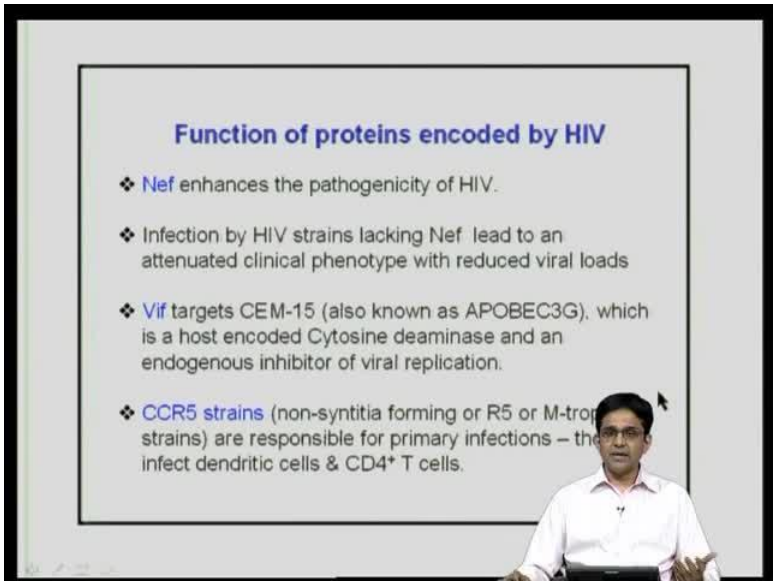

I said we would be discussing a little bit about this. Now, Nef protein enhances the pathogenicity of HIV, so if you have HIV lacking Nef, it leads to attenuated clinical phenotype. They reduce with reduced viral loads. Now, Vif is important. Vif is important because it targets cytosine deaminase known as CEM-15. So, if we have virus particles, so what it will target that now? If you have HIV that lacks Vif or encodes the non-functional Vif, then what happens is that you have a high rate of mutations in this.

So, it is the cytosine deaminase is a host response to take care of such kind of particles and that is why, perhaps HIV has evolved in such a way that it encodes or it is been selected for these molecules like Vif which will target the cytosine deaminase and as it is a endogenous activator of viral applications.

Now, you have in terms of HIV, you have different types of viruses. You have the R type and you have the R5 type and you have the R4 type. Now, the primary infections in HIV occur through the macrophages or the M-tropic or the M-tropic stands for macrophages tropic. They are responsible for clinical infections and they infect dendritic cells and so on. So, once you have infection from the M-tropic and the co-receptors over here is the CCR5 receptor and then subsequently as HIV evolves in the particular body, they turn from R5 into R4 or M-tropic to a T-tropic because then they start infecting T cells. So, it is a very important transition and again student should be important should realise this.

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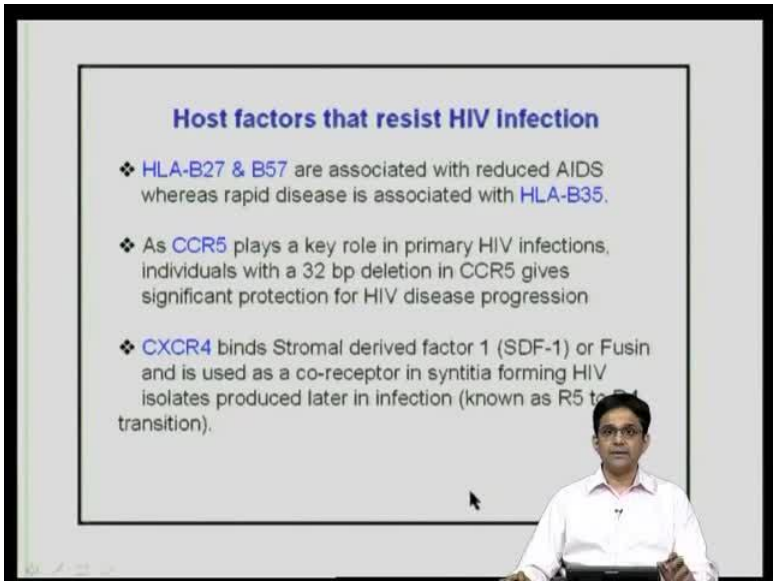

So, in fact that is why I said CCR5 plays an important role over here. So, if you have individuals that lack CCR5 or a 32 based per deletion, in fact high very high number almost 10 percent of occasions they have a deletion in CCR5 and that gives them significant protection against HIV because what happens in this case is even though they are exposed to HIV, HIV is not able to primarily infect them because of the lack of CCR5. So, you see apart from gb120 binding to CD4, you also need CCR5 though as co-receptors and together this helps the entry of the virus. If you do not have it, then it is a problem.

What happens later on is from CCR5 from R5, it becomes R4 because now you have it needs to bind another co-receptor which is the CCR4 receptor or the stromal derived factor 1 or the fusin which is important in syntitia forming HIV isolates and this as I said occurs later in infection. Now, apart from the chemokine receptors, you also have the MHC molecules, the HLA-B27 B57 you know which play an important role. So, for example B27 B57, these are MHC class 1 molecules. They are associated with reduced AIDS that means they are they are more protective, whereas rapid disease is associated with HLA-B35.

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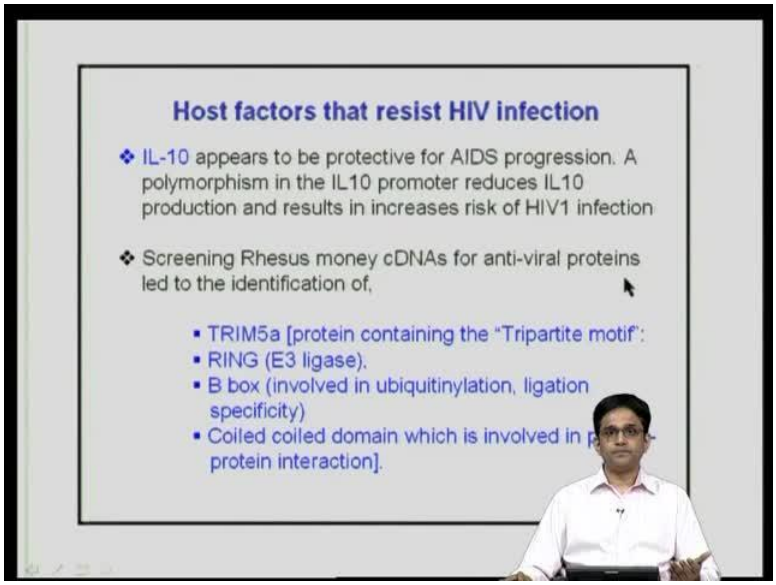

IL10 is also important for AIDS protection. A polymorphism in the IL10 promoter reduces IL10 and results in increase HIV. So, if you produce high amounts of IL10, chances are better for you in terms of getting or being less susceptible to AIDS. Now, studies have also shown that a particular molecule known as the tripartite motif or TRIM5a is an important molecule in encoding resistance. Now, how does this work? So, the reason this class is about host mechanisms and so that is why we are going to pick a few like CEM-15 and then TRIM5a as to how they help.

Now, TRIM is known as tripartite motif because it has different motives and there are three main ones that are important. One is it encodes a ring motif. A ring stands for really interesting new genes and these are primarily E3 ubiquitin ligases. E3 ubiquitin ligases are important players in the ubiquitin proteasome system. So, what this is? It shows it is E3 ubiquitin ligases. It is important in the degradation of proteins using the cytosolic proteins degradation rule. It also has a B box which is involved in ubiquitination ligation specificity and you have the coiled-coiled domain which is involved in protein-protein interaction.

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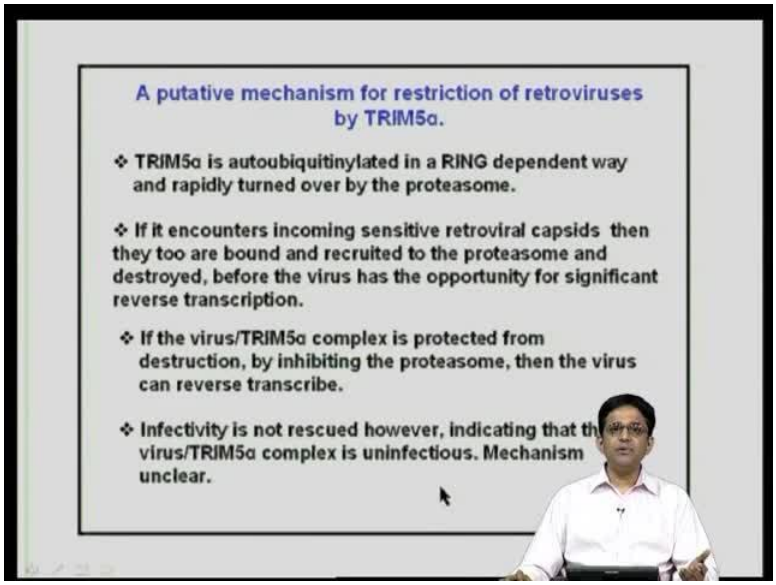

So, what happens in this case is that TRIM is rapidly auto-ubiquitinylated and gets degraded by the proteasome. Now, once a TRIM what it also does is it binds to these are viral capsids and once it upon binding of these viral capsids, then it gets degraded and so along within the viral capsids are also degraded. So, it is a way by which the molecule is produced. It binds to viral capsids and gets degraded and along with it, degrades the viruses also.

Now, in fact this is done before the virus can reverse transcribe and if you inhibit the proteasome part, then of course TRIM cannot function because it is not degraded. So, that is an important aspect that is shown up over here. So, you have TRIM5a. It is ubiquitinated and it gets degraded by the proteasome.

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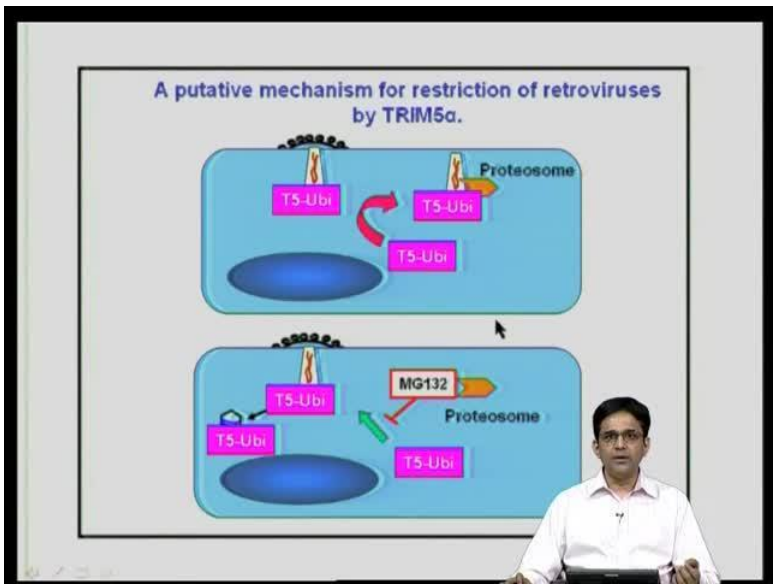

Now, in case you are inhibiting the proteasome, then it is not degraded and you have these viral capsids being produced over here is degraded, so the viral capsids are not being produced here. The proteasome part is being blocked and therefore, you have viral capsids being produced. So, it is an important aspect on how the host has also evolved mechanisms to take care of viruses.

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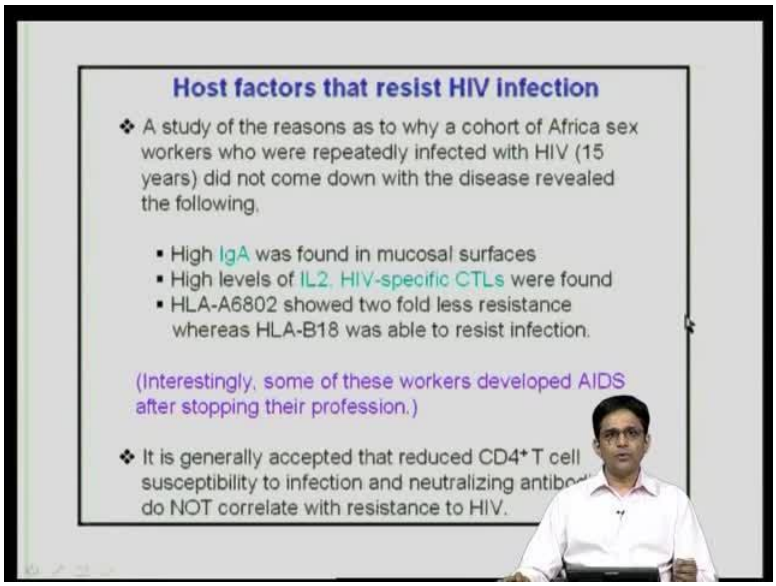

Now, this is an interesting study that was done among a cohort of sex workers in Africa who are repeatedly infected with HIV for 15 years but did not come down with disease. So, then scientists tried to find as to what made them resistant to HIV. What was found is very interesting. What was found is that they had high IgA in mucosal surfaces, so good IgA responses you know may be throw out a HIV infection. They had high levels of IL-2 and HIV specific cytotoxic T lymphocytes were found.

Now, also what was found is that their MHC phenotype was little bit different. HLA-A6802 showed two fold resistance whereas HLA-B18 was able to resist infection. So, perhaps it was the combination of these factors, the MHC, the ability to generate CTLs, the ability to generate good mucosal immunity because of high titus of IgA together gave them immunity.

What is interesting is that some of these workers develop AIDS after stopping their profession. So, why do you think? So, I think students should think a little bit about it what is happening is when they were continuing this profession they were being exposed to the antigen, as the result of which the immune system was getting stimulated constantly.

Now, what happened is once I stop the profession, the exposure to antigen became less and perhaps there was some down modulating of their immune system. As the result, some endogenous viruses that were kept inactive, you know sort of become that would latent in fact they sort of re-emerged and they were able to may be takeover. So, it is very important that you know constant triggering with antigen may play an important role in keeping our immune system active.

Now, it is generally accepted that reduced CD4 positive T cells susceptibility to infection and neutralizing antibodies do not correlate with resistance to HIV.

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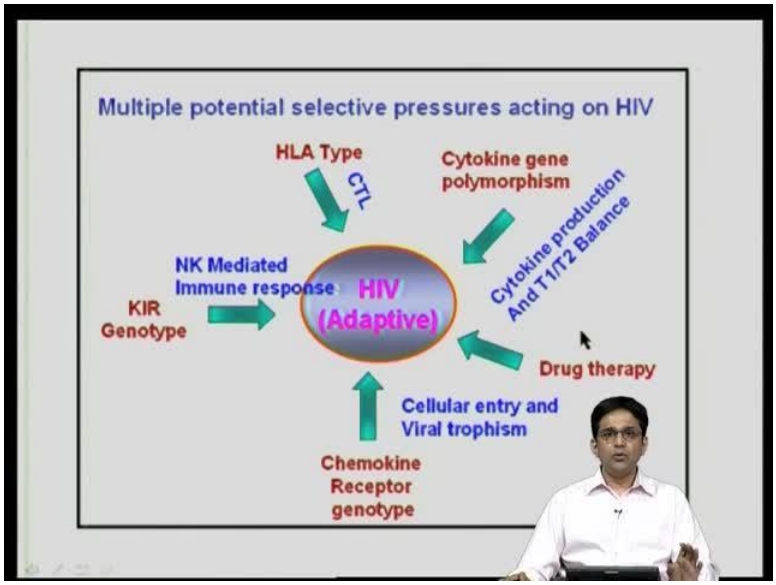

So, therefore it is important to understand that there are different factor that are sort of playing a role over here and that is what is shown over here. You have the HLA type which plays an important role, you have cytokine gene polymorphisms and you have drug therapy immune while because you know you are giving drug therapy, so you are selecting for certain types of viruses. You have chemokine receptor. We talked about the 32 the deletion in 32 base pairs in the CCR5 and then you have the NK receptor genotype. So, there are different combinations that play an important role in finally determining the outcome of HIV and it is very important to understand these different factors.

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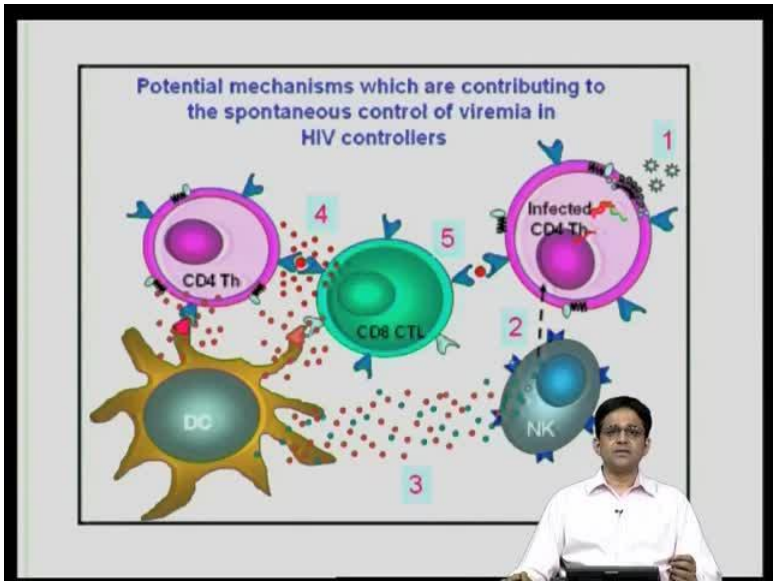

So, again what is shown over here is you have different players. You have the NK cells, you have the CD4 positive cells, the dendritic cells. You know all sort of coming together to play important role.

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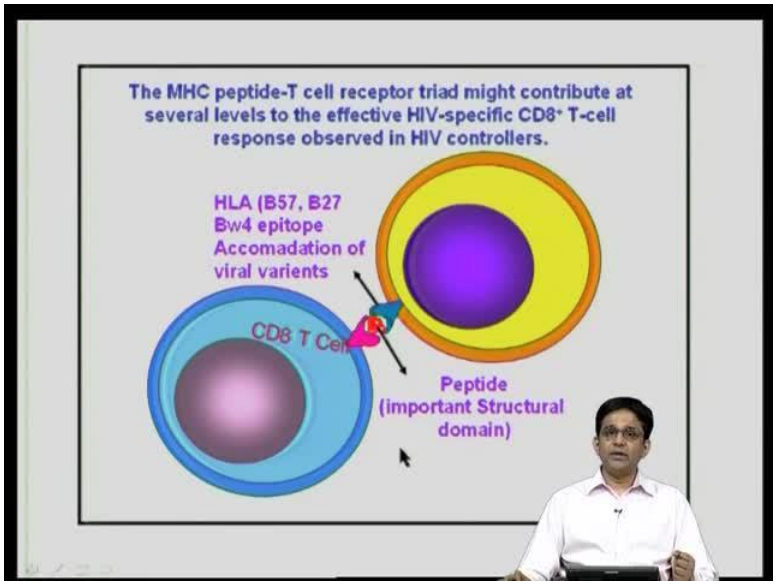

What is shown over here is the interaction between a particular MHC and a viral. This is MHC class 1 which is shown on which is being recognized by CD8 positive T cells and if you have the appropriate combination, may be some viral peptides bind preferentially to certain MHC class 1 and may help in generating productive response whereas there are other ones, other MHC molecules that are going to bind, some of these unable to generate efficient productive responses.

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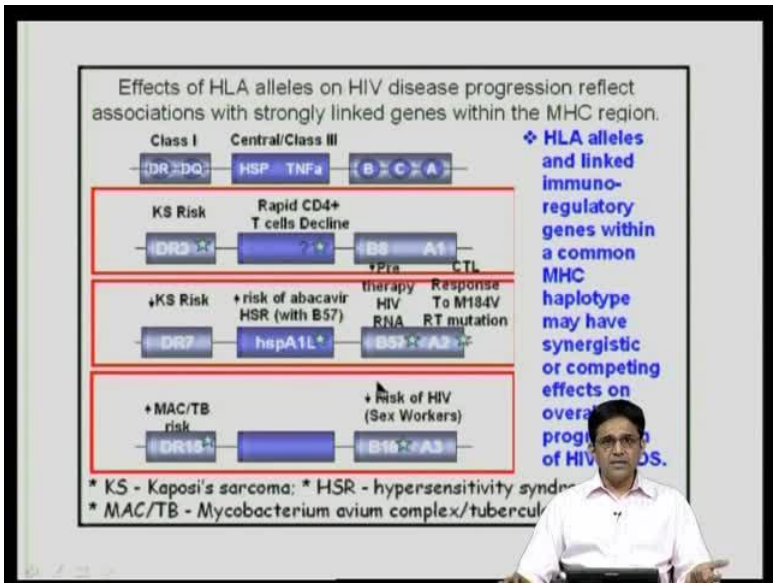

This is again shown over here in terms of the MHC class 1 and so what is shown over here is these particular ones, they reduce the risk of HIV whereas some others are involved with Kaposi sarcoma risk so on. So, there is combination of factors that are that are involved. Suffice to say that the HLA alleles or the MHC alleles are linked with immuno-regulatory genes and there are several variety of them which are important in determining susceptibility.

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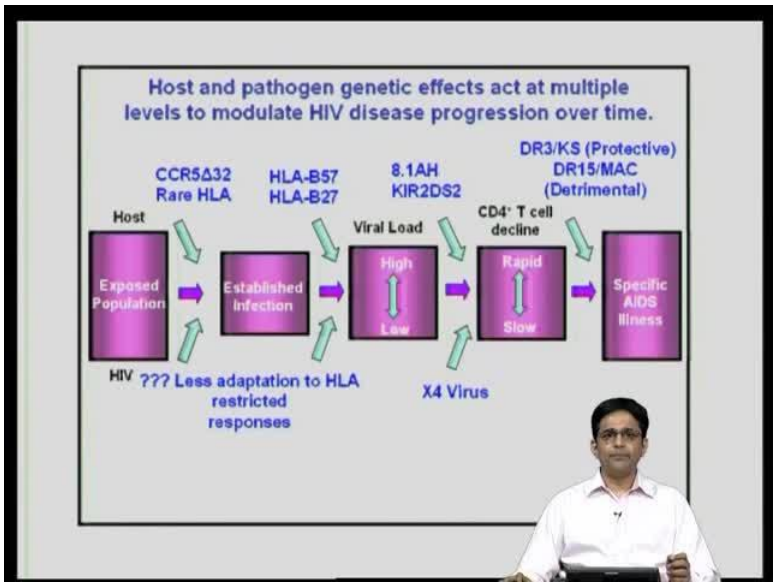

Some more are shown over here. You have the host is exposed population, here is the CCR5 delta 32, you have rare HLA's over here and so these are important and establishment of

infections. So, upon once you establish then you have the MHC class 1 molecule that are important.

Subsequently, you have the KIRs which is the killer inhibitor receptors which is the NK receptors which play an important role and then you have the DRs or the MHC Class 2 which are important in generation of a different responses. So, at different parts you have this modulation of the host responses along with the viruses and then you have different aspects which contribute to susceptibility.

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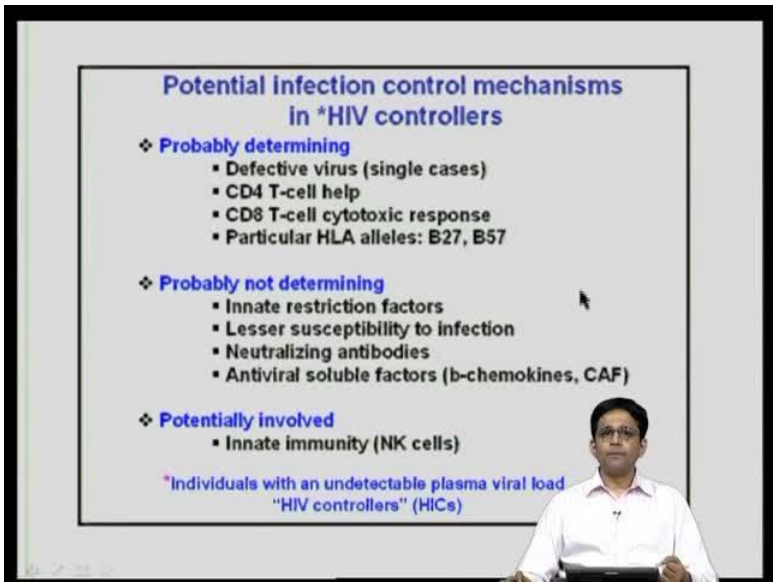

Overall, it would appear that if that CD4, without doubt CD4 positive T cell helps CD8 and particular HLA leads like B27 are important in determining susceptibility to HIV and the once that are may be not that important in neutralizing antibodies because it is very hard to generate in neutralizing, a good neutralizing antibodies against HIV. You are soluble factors, innate restriction factors and the once that NK cells are probably potentially involved over here but clearly once that seem to be important are here the once listed over here because remember, in case of HIV the primary response that is generated is the cellular response. So, you have to focus on that. You have CD4 positive response, CD8 positive response and the particular HLA alleles.

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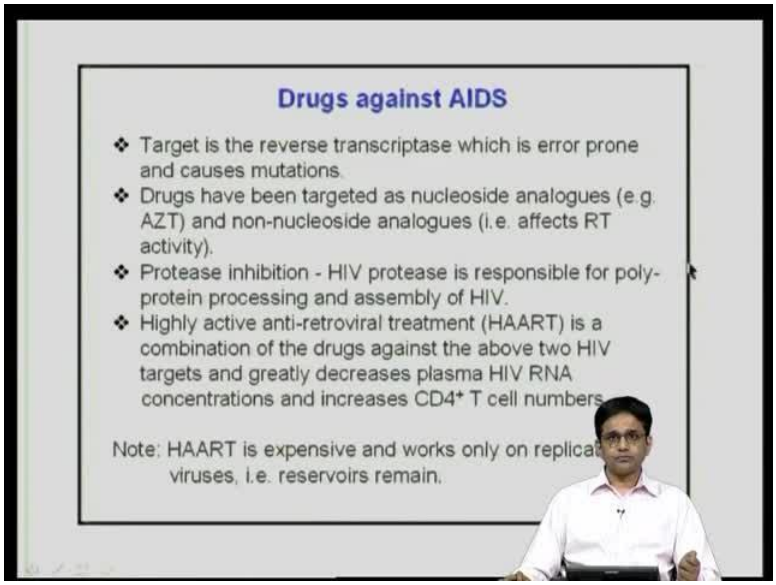

Now, I am just briefly going to talk about the drugs against HIV and the mechanisms are as I have said, you have once that mainly effect the RT or the reverse transcriptase. You have nucleoside analogs and which will affect the reverse transcriptase activity and then you affect the protease and I have mentioned the way by which it works because you need to target, you need to cleave HIV proteins into polyproteins.

Now, the highly active anti-retroviral treatment is the combination of these drugs, both the anti-RT and the anti-protease which is required to reduce the HIV numbers. Now, the fact is these drugs work and they work they reduce HIV numbers. Remember, heart is expensive, it works on replicating viruses but the reservoirs remember remain but the drugs work but they are highly expensive. So, what about vaccines against AIDS?

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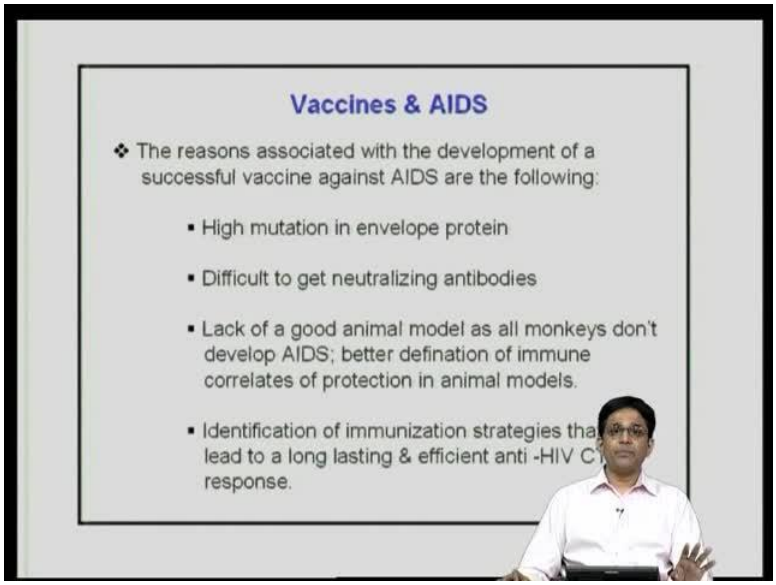

Now, the problem with vaccines is that HIV mutates a lot. It is a very smart viruses, it mutates. It has a very high mutation frequency, therefore to generate a good antibody response, by the time antibody response is generated, the epitope is changed. So, it has become difficult to manage the new viruses and so that is one of the big problems which have the high mutation in the envelope protein. It is difficult to get neutralizing antibodies.

The other important parts is there is a lack of a good animal model as all monkeys do not develop AIDS and identification of immune strategies that lead to long lasting and efficient anti-HIV CTL responses. These are these are all important aspects.

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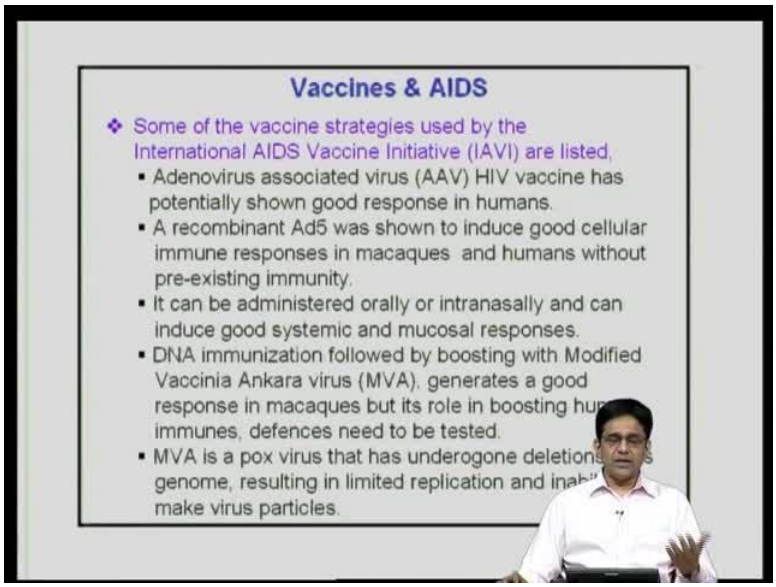

So, there are different strategies that have been listed to target AIDS or HIV and different strategies have been followed but there have you know there is always been some problem or the other. One hopes that better study will lead to mechanisms by which we understand this in a much better way.

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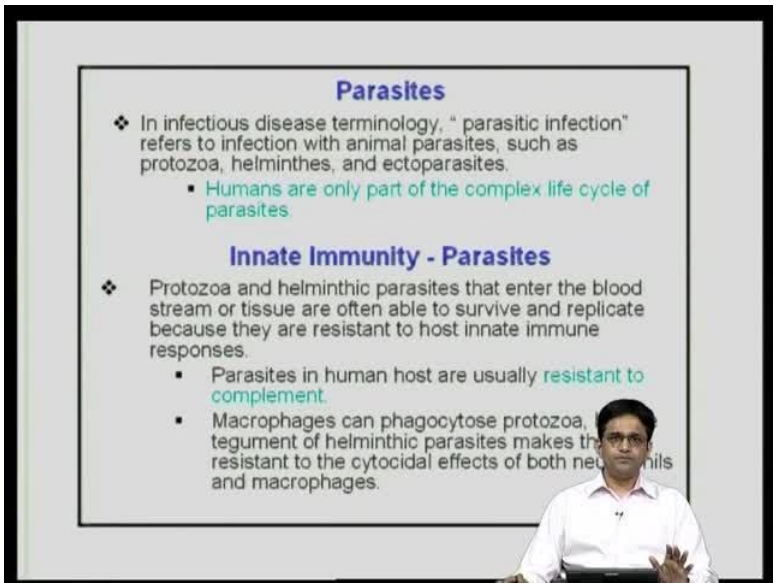

So, we should be hopeful. We you know instead of being completely cynical, we should be hopeful that better work may lead to strategies by which we can control HIV which is a very important disease. So, we will now move on to some other aspects. So, apart from viruses I will try and cover parasites and the newly emerging diseases.

So, in case of parasites, the parasitic infections, now protozoa helminthic parasites, now these sort of enter the blood stream and they are able to survive. Several of these, you know target the gastrointestinal tract and where they reside and they play important role worms for example. Some of the features are that parasites in the human host are usually resistance to complement and macrophages can phagocytoes protozoa and but somehow they are resistant to these to macrophages complement so on. So, that makes it a little bit difficult.

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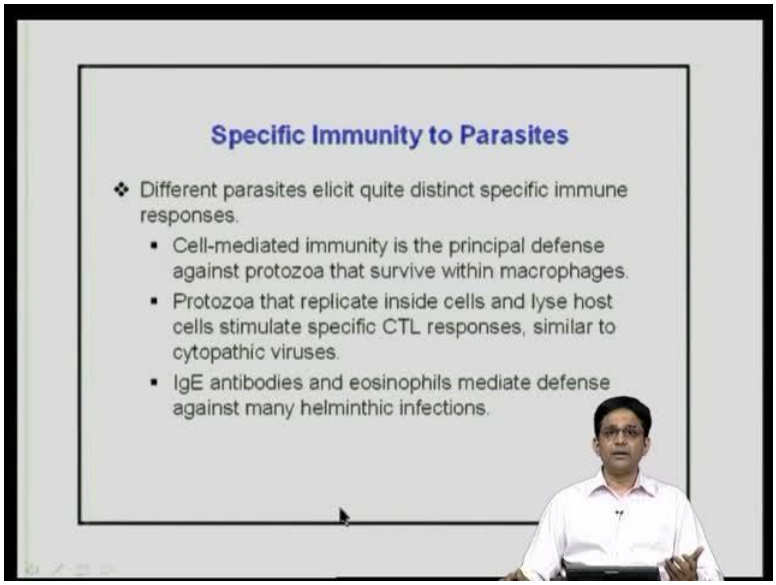

Now, cell mediated immunity is a primary defence against protozoa that is a why within a macrophages. So, they replicate and they are able to generate a specific CTL response. Now, IgE antibodies and eosinophils mediate defence against many helminthic infections, so again IgE responses are very important. Remember, for to get a IgE response, you would need a good Th2 response, so that is that is again important.

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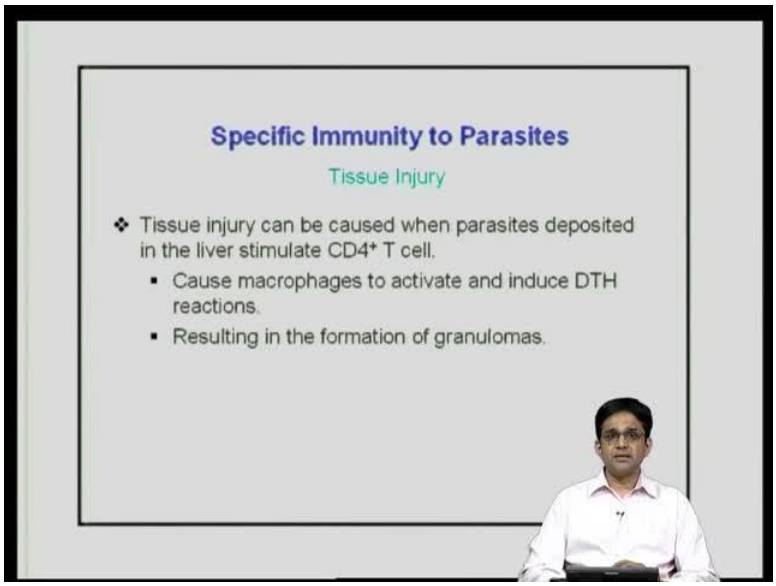

Now, one should also be a little bit careful that when you are generating these responses, it can be to tissue injury because macrophages can get activated and they can induce delayed type hypersensitivity response and it results in the formation of granulomas.

These granulomas you could see the tuberculosis is actually you know tuberculosis during infection. Tuberculosis, actually they are granulomas and you know they are host response and it causes damage host damage.

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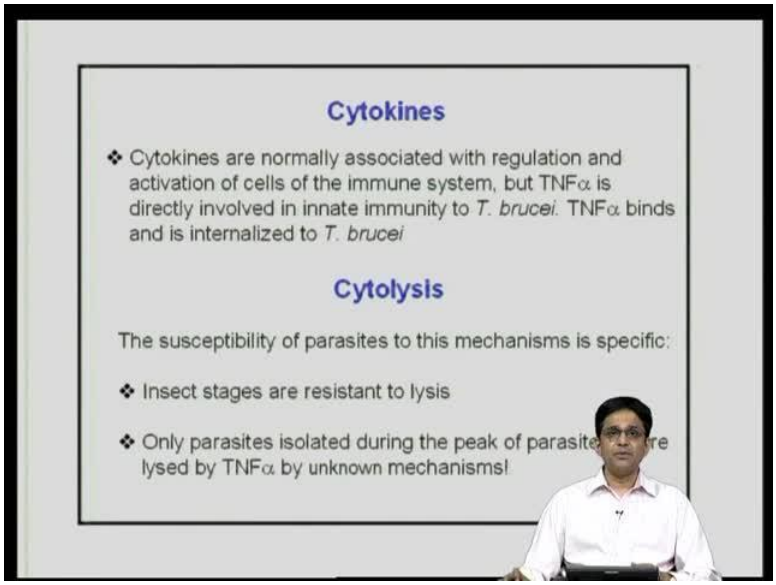

Now, cytokines are important like now in like TNF alpha is very important against innate immunity to T brucei and now what happens is this TNF alpha binds and it is internalize by T brucei. Now, what is interesting is only parasites are isolated during the peak of parasitemia are lysed by TNF alpha but the mechanism are unclear over here.

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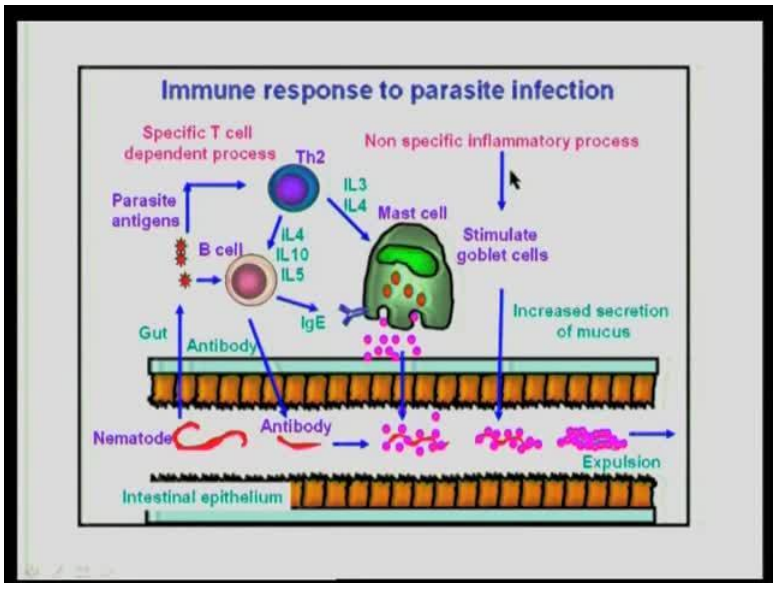

Now, this one is to show you the different mechanisms by which that are involved. So, this is to a parasite infection and you can primarily see that what you need, what you have is expulsion and to get expulsion, you need increasing secretion of the mucus. So, this is what I meant this you need expulsion over here.

Now, to now for increase secretion of the mucus your cytokine profile has to be primarily Th2. So, which is shown over here, you have generating specific T cell response. You have non-specific inflammatory stimulate which secrets goblet cells. They increase secretion of mucus; you have these IL4, IL10, IL 5. These are all Th2 producers, these produce antibodies and these nematodes are produced. The mass cells stimulate IgE production and what you are doing is trying to stimulate them and expel them.

So, now what would happen if you had a Th1 response for example? Now, what a Th1 response would be pro-inflammatory. What it would do is it would actually oppose secretion of the mucus and so on. So, what would happen is it would they would remain stuck and you would generate inflammatory reaction and you would have granuloma formation over there where things would be stuck. It would cause enormous damage and hurt to the host.

So, a Th2 response in this case, what it does? It helps expulsion of eggs, it helps expulsion of nematode, so that there is increase secretion and these are expelled off but of course it is conducive for the nematodes to be there and replicate and try and spread that progeny because you have Th2 response. So, it is very important to understand and it also signifies how the Th1, Th2 are important in playing an important role in this processes.

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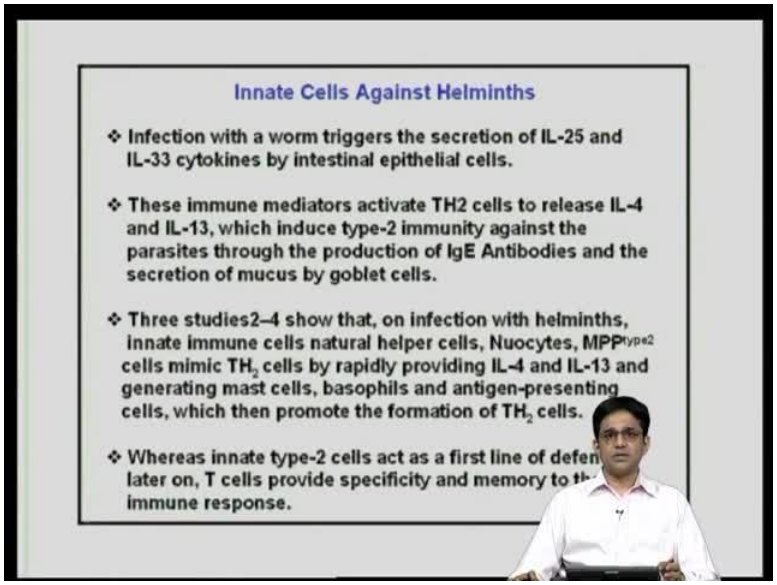

That is what is shown over here. You have different cytokines being involved but primarily it is a Th2 response which through the generation of IgE, they help in secretion of the mucus by the goblet cells and as the result which helps the expulsion.

Now, what is also important is the innate cell act as the first line of defence and later on the T cells come in for specificity and they help in this particular process.

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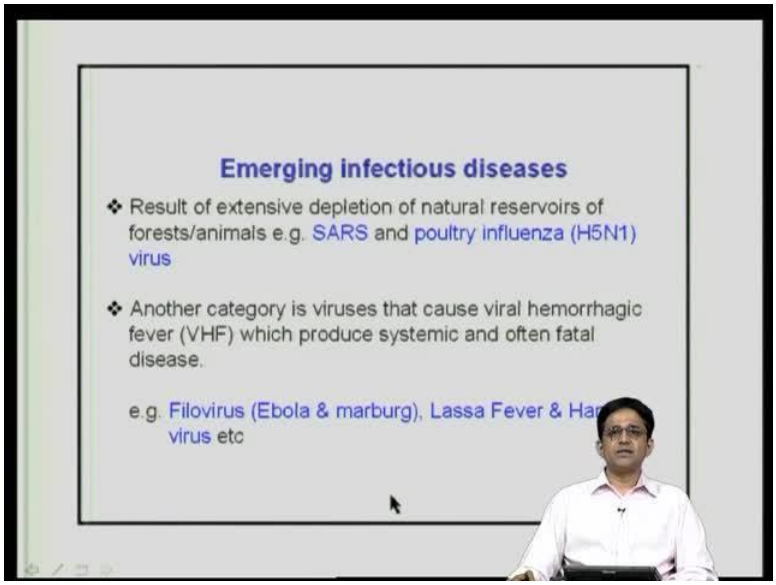

Now, we will talk a little bit about emerging in infectious diseases. Why is this important? Now, if you have read the newspapers, you know in recent days you have these newer diseases that are coming up. You have the SARS and then you have the H1, H1N1, you have H5N5. Why are these coming? I think students should think a little bit about this. Why is it all that you have you know every 2-3 years a new disease that is emerging or new virus that is emerging?

One of the thoughts is that as the human population is expanding, we are venturing into areas and trying to take over areas where viruses have lived in some sort of equilibrium with their environment. Now, as our numbers increase and we cannot disturb that they are also making changes and in response to the changes in their environment and what they are trying to do is they are trying to do is to expand repertoire and trying to jump.

So, in case some of these are successful. What they will do is they are successful in jumping in infecting humans, so what happens as the result of which you have newer diseases. So, this is some aspect that students should be thinking about because as we venture into newer environments, as our population increases we are moving into you know newer territory and this is exactly what happens.

If you remember in the last class, I gave you an excellent example, what happened to the endogenous American Indian population who are never exposed to mycobacterium tuberculosis or mycobacterium leprae 4? When the Europeans invaded or entered America for the first time, they came along, they also brought with them diseases. So, a lot of the

endogenous American Indians had very poor resistance to mycobacterium tuberculosis, mycobacterial diseases for and several of them were actually, they got this disease and they were highly susceptible to these diseases. You had several people dying because of their inability to generate a proper host response because they were not been exposed to it whereas we have been sort of living along with the mycobacterium tuberculosis are immune system is exposed to it. So, we sort of having height and immune response whereas these people were not exposed to it and they were highly susceptible to these, to these pathogens, something that to remember.

So, what is happening now is pretty much the same. The different influences of viruses or viruses are sort of mutating and changing over, changing over their host preferences from pigs you know or from birds to humans. As the result of the changes that are occurring in their environment and also given the fact that these days people travel a lot and so you can move into different countries very quickly, so that you carry the disease along with you. This is again an important aspect that we should all be careful about.

Now, emerging infectious diseases are important and in fact, you have the centre for disease in Atlanta which sort of monitors this. One of the areas that they have been actively monitoring is a virus that causes or a group of virus that causes viral hemorrhagic fever or VHF and over here it produces systemic and often fatal diseases.

Now, the folio viruses, Ebola, Marburg, lass fever you know these belong to this category and I thought, we would end it with a little bit look into the future about emerging infection diseases because it has potential for students to sort of think about you know something that might happen in the future also.

There have been books written on Ebola and I think there is a book known as a hot zone which again students should read. It is about what happens in a place where a chimpanzees centre near Washington DC. This is actually in the State of Virginia where you have an outbreak and how the cdc combine with other scientist try to contain that other break because if it goes out of control, then the disease will spread. Then cause fear and panic which you do not want but it is a very interesting book and it is something that students should also look and think about because apart from course work, you should be thinking about these other different possibilities that may be occurring.

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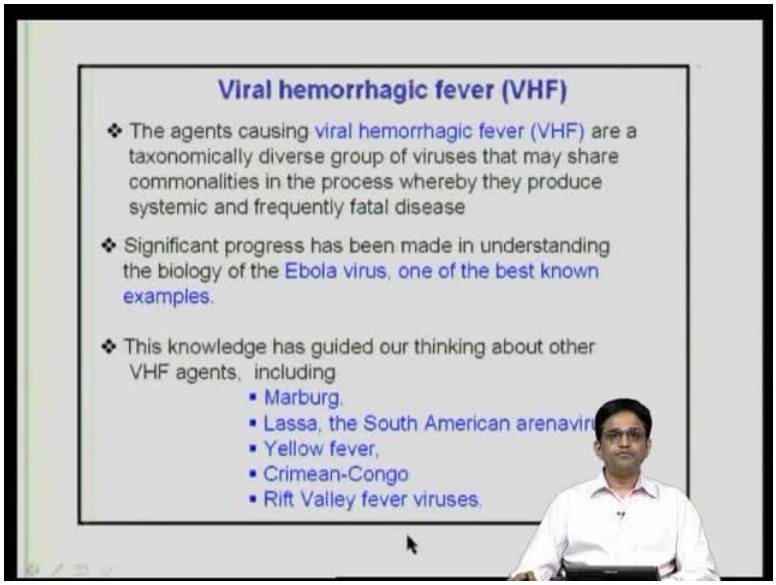

So, little bit about viral hemorrhagic fever. So, they are different group of viruses and they what they do is they cause systemic and frequently fatal disease. Now, the best virus that is known is the Ebola. Now, but there are different other members of it, you have Marburg, Lassa fever, Yellow fever, Rift Valley fever virus so on.

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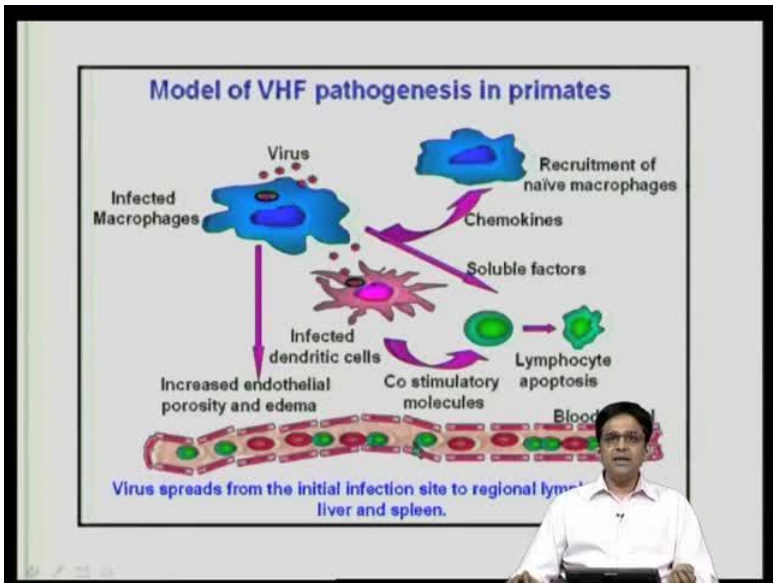

So, what is seen over here is you have the virus and it causes increased endothelial porosity edema and lymphocyte apoptosis very quickly and in systemic infection that takes place.

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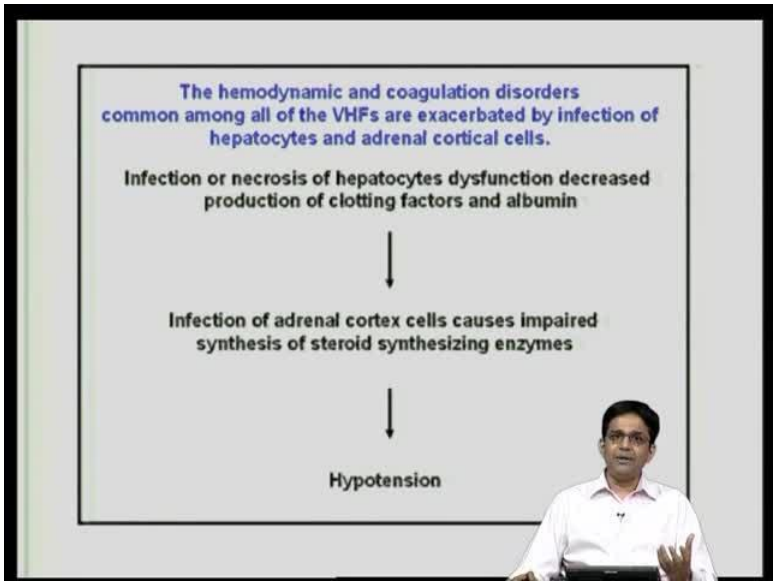

That what it does is basically what is happening is you have decrease production of clotting factors. As result of which you have hyper tension because your blood pressure drops rapidly.

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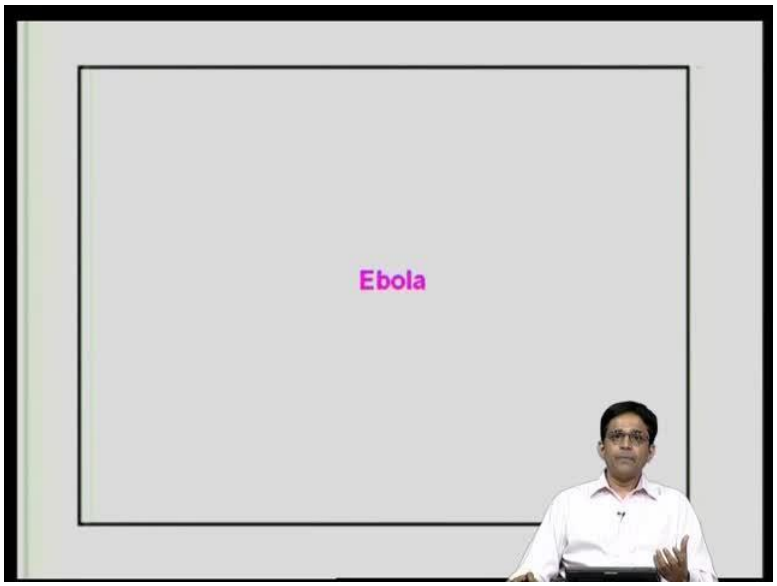

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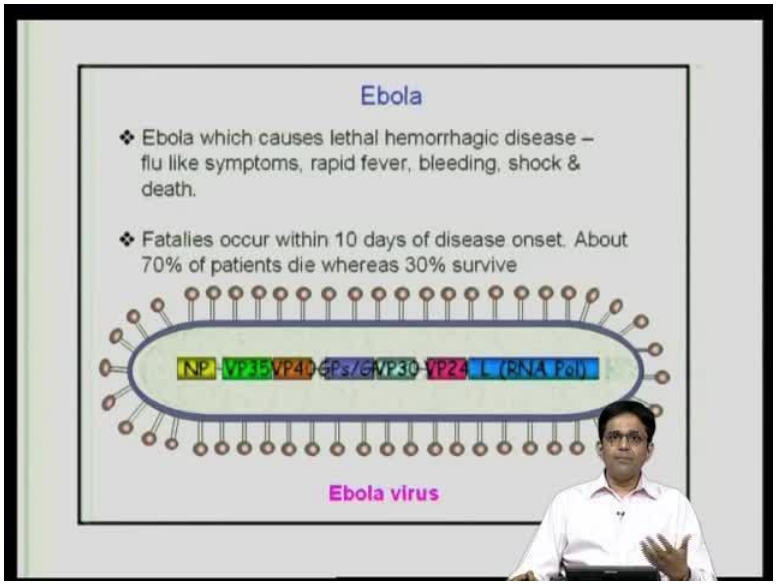

The example is Ebola which we will discuss and it causes lethal hemorrhagic diseases flu like symptoms rapid fever, bleeding, shock, death but now, what is surprising over here is about 70 percent of the patients die whereas 30 percent survive. So, a question that can be asked is how come 30 percent of the patients survive? What how are the survivors different form the ones that are susceptible?

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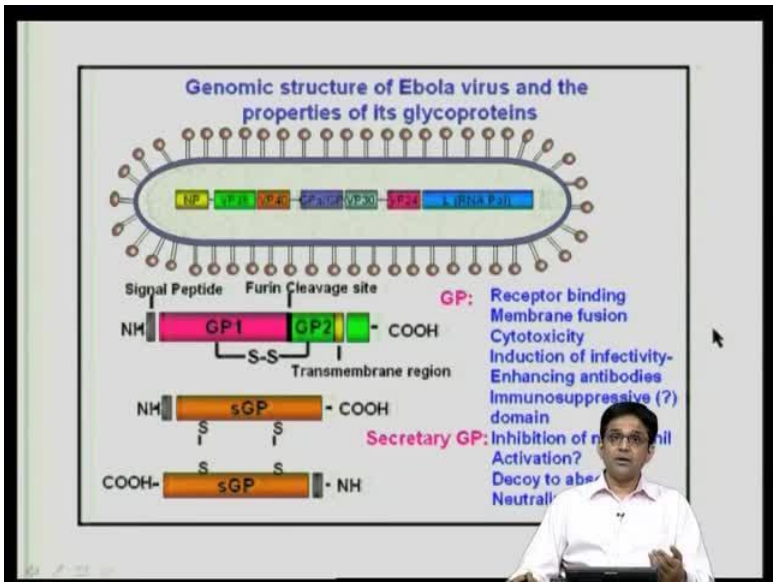

It is very important for us as immunologist, people who are interested in host response to be asking what differentiates this group, this cohort from the other and if we understand this, then you know it might shed some light.

In fact, this is precisely the type of studies that were done with HIV where you found that a person who is being repeatedly in contact with HIV positive people were not was not coming with the disease and not coming down with disease because of the mutation in CCR5. In fact, that is how that 32 base pair deletion was found out and you know because it can shed important light as to how what makes or what are the attributes of survivors or what are the attributes of a person who is more susceptible?

So, if you understand that may be there could be ways by which you could you could make the person who is more susceptible into and reduce the susceptibility, so increase the chances of survival. So, it is very important in terms of research and it has translational applications. So, this is the structure of Ebola virus. I think the whole idea is that it causes rapid cytotoxicity as mentioned very high fever, there is lot of bleeding and a study on susceptibility were actually done.

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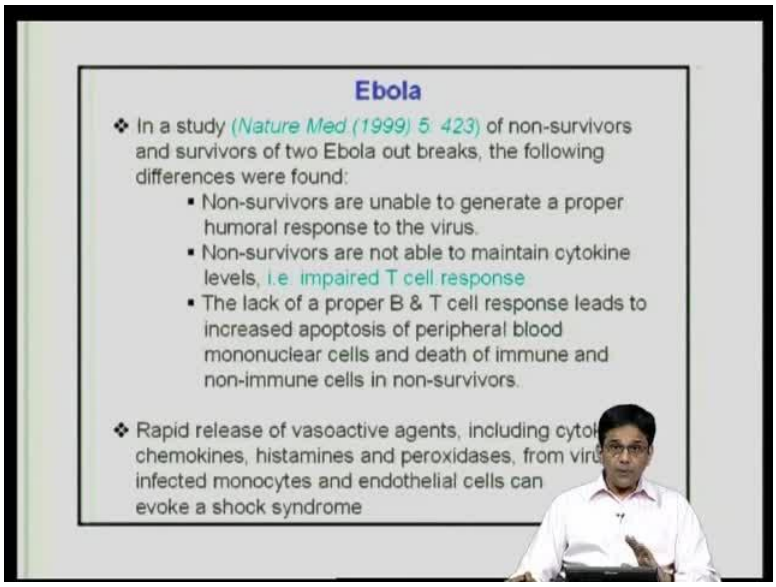

In fact, in a study that was published in nature medicines several years back, what was found is that the non-survivors were unable to generate a proper humoral response to the virus. A very rapid fast humoral response the also the non-survival is not able to maintain cytokine levels that is they had an impaired T cell response and the lack of a proper B and T cell response led to increase apoptosis of peripheral blood mononuclear cells and death of immune and non-immune cells in non-survivals.

What was also happened is you have also rapid release of vasoactive agents including cytokines, chemokines and histamines and as a result you had what is known as a shock like syndrome. We had discussed this you know in our studies on septic shock during innate immunity class. So, it is very important.

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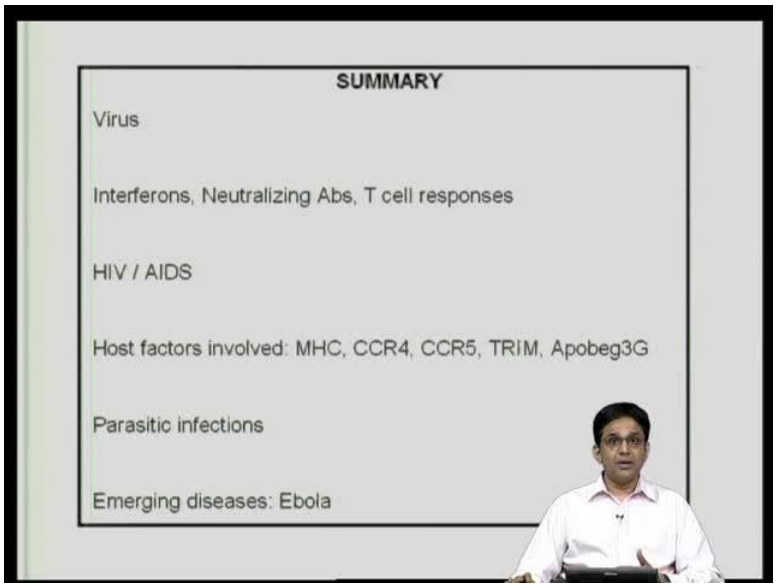

So, it is very important for students to able to understand this. So, Ebola was important in our study because it is an emerging virus and the last part of it was to tell you about the cohort of survival. The differences between the survivors and the non-survivors and it tells us these sort of studies will may lead to better ways by which you can increase the survivability of the group that are non-survivors because once you understand what are the factors that make it. Perhaps, we can think of better ways may be use adjuvants, vaccines by which you can boost the immunity.

So, over all this class sort of dealt with the host response. In fact, the previous as well as this is very important because actually the entire immune system is coming together. You can see that you know CD4 cells are important, CD8 cells are important, NK cells are important. These cells are terribly important because they are very important generating neutralizing antibody responses and over all you have these players but it is also important to understand some of the key ones that we discussed.

We discussed the Jak Stat pathway which is very important in terms of responses to interferon, very you know it is and certain chemokine receptors that are important in

generating our ability to be résistance to certain viruses CCR5. These are important aspects because they are important players and trying to understand how we resist. You know resist different pathogens that we are surrounded with.

So, I will just briefly you know summarize this class. So, we first started off with viruses and we discussed, you know the fact that they must replicate to try and spread and there are different ways by which you can target. You can target the receptor, you can target the progeny, you can target the reverse transcriptase and you can the protease so on so forth, the different ways by which you can do that.

We also talked about the interferons, the neutralizing ability to generate interferons the Jak Stat pathway and the way Type 1 interferons versus the Type 2 interferons. The Type 1s are primarily antiviral and the Type 2 interferon gamma is against intercellular infections. If you do not have interferon gamma or its receptor, you are highly susceptible to BCG infection with that was discussed.

Now, in terms of viral or in terms of vaccine, the ability to generate neutralizing antibodies is really the key and this cannot be over emphasized. All the successful vaccines are the ones where you generate very good neutralizing antibodies. We also looked at the role of T cells, you need both CD4 and CD8 to play an important role in generating this response.

We studied HIV in great detail and I want students to be very aware of the difference between the HIV positive and AIDS positive. You turned from HIV positive to AIDS positive only once your CD4 count goes down. So, the assays to determine these two are different. For HIV positive, you can do it by RT RT-PCR or ELISA, for AIDS, you would have to find the numbers of CD4 for positive cells which is why you need to understand the importance of cell surface antibodies and the use of flow cytometry over here.

Now, what this does is the lower CD4 count makes you highly susceptible to tumours, to endogenous tumours and susceptibility to intercellular pathogens. In fact, some common opportunistic pathogens that we live with once that immunity goes down this sort of take over.

Now, in the host factor that is important we discussed the important role of MHC. You could see that having such MHC was protective whereas you know more susceptible. We studied

the importance of chemokine receptors, the CCR5 to CCR4 transition, the infection of HIV starts of CCR5, the m tropic and then the virus changes over to CCR4 or the T-tropic viruses.

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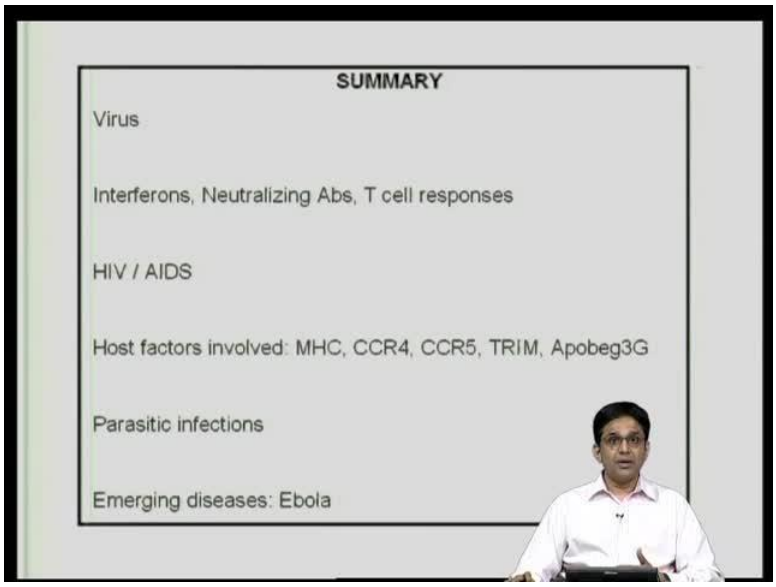

We studied the importance of TRIM5 a proteins which is important because they sort of target, they bind to the viral capsids and target it for proteasomal destruction.

We also studied how the virus encodes the factor known as Vif which binds to CEM-15 which is a cytosine deaminase which is important. So, these are important. You can see this evolving nature of pathogens and the host proteins which play an important role. We also studied the role of parasitic infection, especially nematodes with the important role of Th2 type and secretion of mucus; so that you can you extrude these organisms. Then finally, we studied emerging diseases with Ebola being an important component and the difference between the survivors and non-survivors.

So, over all I hope this is been very useful to you and I hope you will be whenever you read newspaper, articles on disease out breaks and all you will be thinking about this class and you will be able to link it together. If you are able to do that, then that will mean that this class has been successful.

Thank you so much.