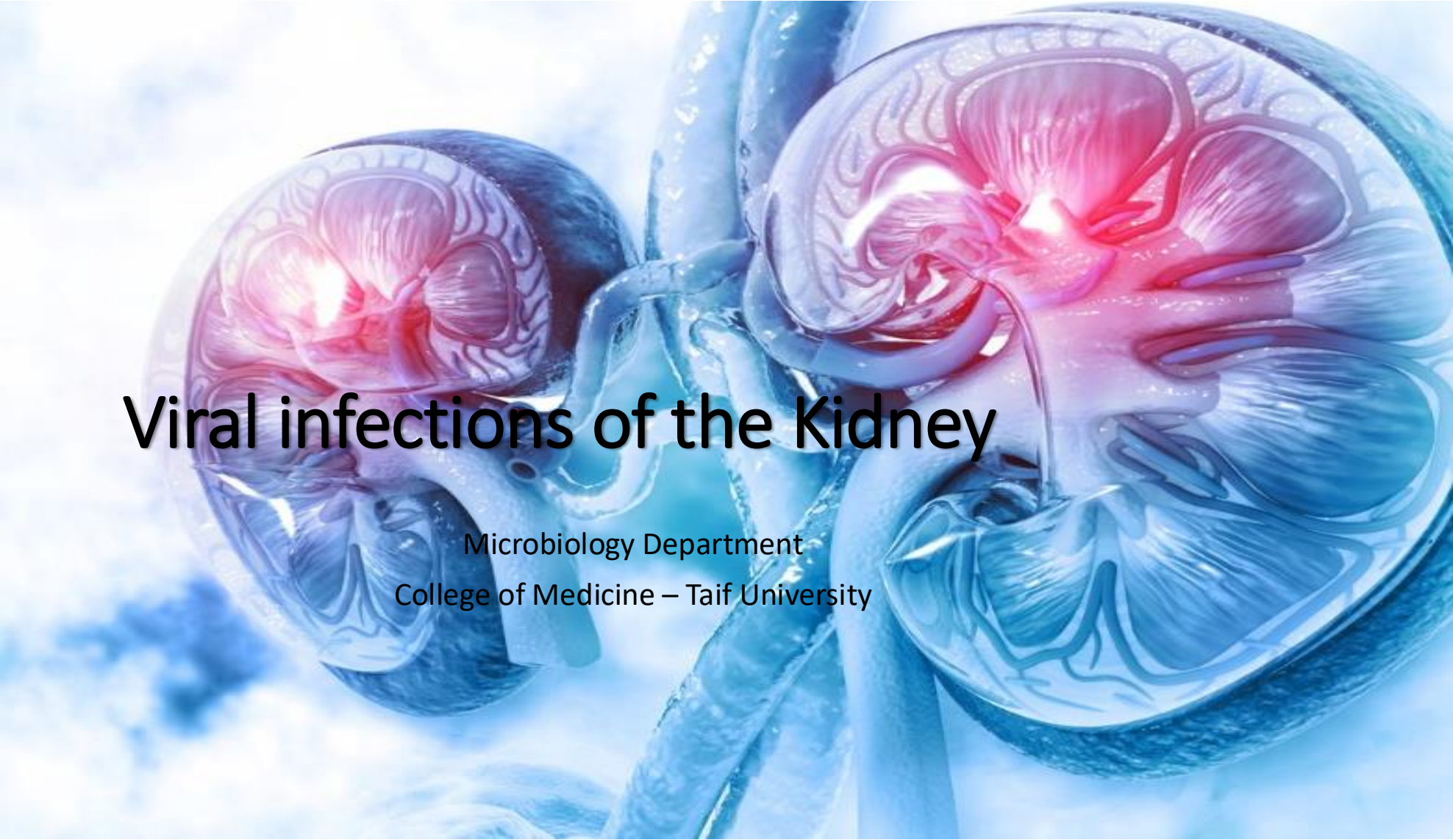
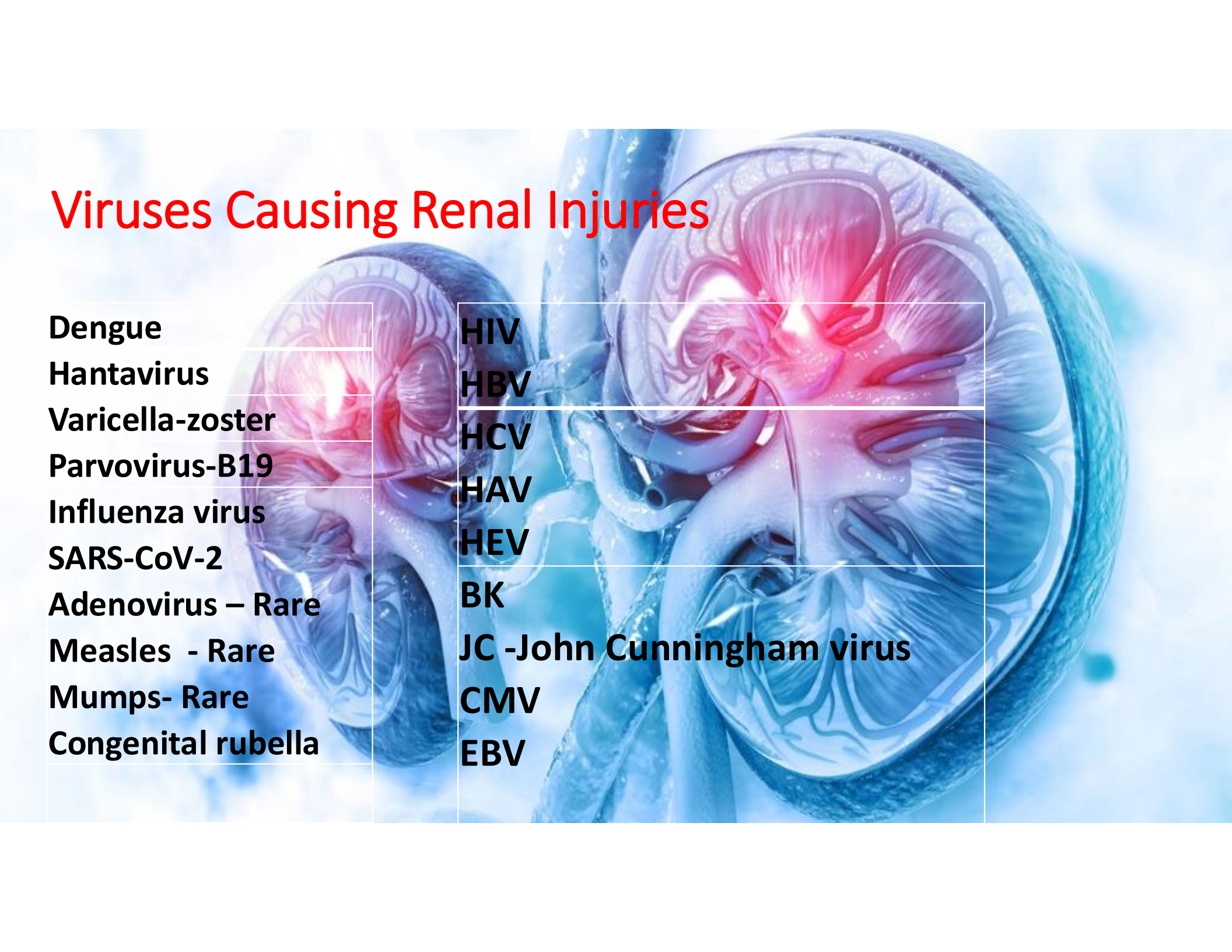




Viral infections of the Kidney

Microbiology Department
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Viruses Causing Renal Injuries



Dengue

Hantavirus

Varicella-zoster

Parvovirus-B19

Influenza virus

SARS-CoV-2

Adenovirus – Rare

Measles - Rare

Mumps- Rare

Congenital rubella

HIV

HBV

HCV

HAV

HEV

BK

JC -John Cunningham virus

CMV

EBV

Viral infections

- Viral infections can induce acute kidney injuries (AKI) by various mechanisms
 - Direct cytopathic effects by virus replication
 - Vasculitis
 - immune complex mediated glomerulonephritis (GN).
 - Affect the innate and cellular immunity as in infection-related glomerulonephritis (IRGN)
 - cryoglobulinemia
- About 40% of patients who recover from acute kidney injuries (AKI) have persistent renal dysfunction and many develop chronic kidney disease (CKD).
- Infection of patients with pre-existing CKD, rapid disease progression may result in end stage renal disease (ESRD).



Cryoglobulinemia

- Cryoglobulinemia refers to the presence of one or more immunoglobulins in the serum, which clump together at temperatures below 37C.
- These immunoglobulins dissolve again when the serum is reheated.
- These gelatinous protein clumps can obstruct blood circulation, which can damage skin, joints, nerves and organs esp. **kidneys** and liver

Types of cryoglobulinemia

Type 1 cryoglobulinemia: monoclonal immunoglobulin (Ig) M and associated with lymphoproliferative disorders (10—15% of cases).

Type 2 cryoglobulinemia: mixed immune complexes formed by monoclonal IgM and polyclonal IgG.

It is seen in viral infections—such as HCV (most common), hepatitis B virus (HBV), cytomegalovirus, HIV, Epstein-Barr, toxoplasmosis and malaria.

Type 3 cryoglobulinemia: mixed immune complexes typically formed by polyclonal IgM, and it represents 25—30% of cases.

It is associated with autoimmune diseases: lupus, rheumatoid arthritis and Sjogren syndrome.

Dengue virus

- It is related to family *Flaviviridae*, genus *Flavivirus* (+) sense ssRNA enveloped virus.
- Five virus serotypes (DENV-1-5)
- Some antigenic heterogeneity occurs among strains of each serotype.
- Infection by one serotype provide brief cross protection to other serotypes (6-12 Wk) after which immunity remains to the infecting serotype only.



Transmission

- Mosquito bite [Main route] mainly by female *Aedes aegyptii*.
- Organ transplants or blood transfusions from infected donors
- Infected pregnant mother to her fetus [rare].

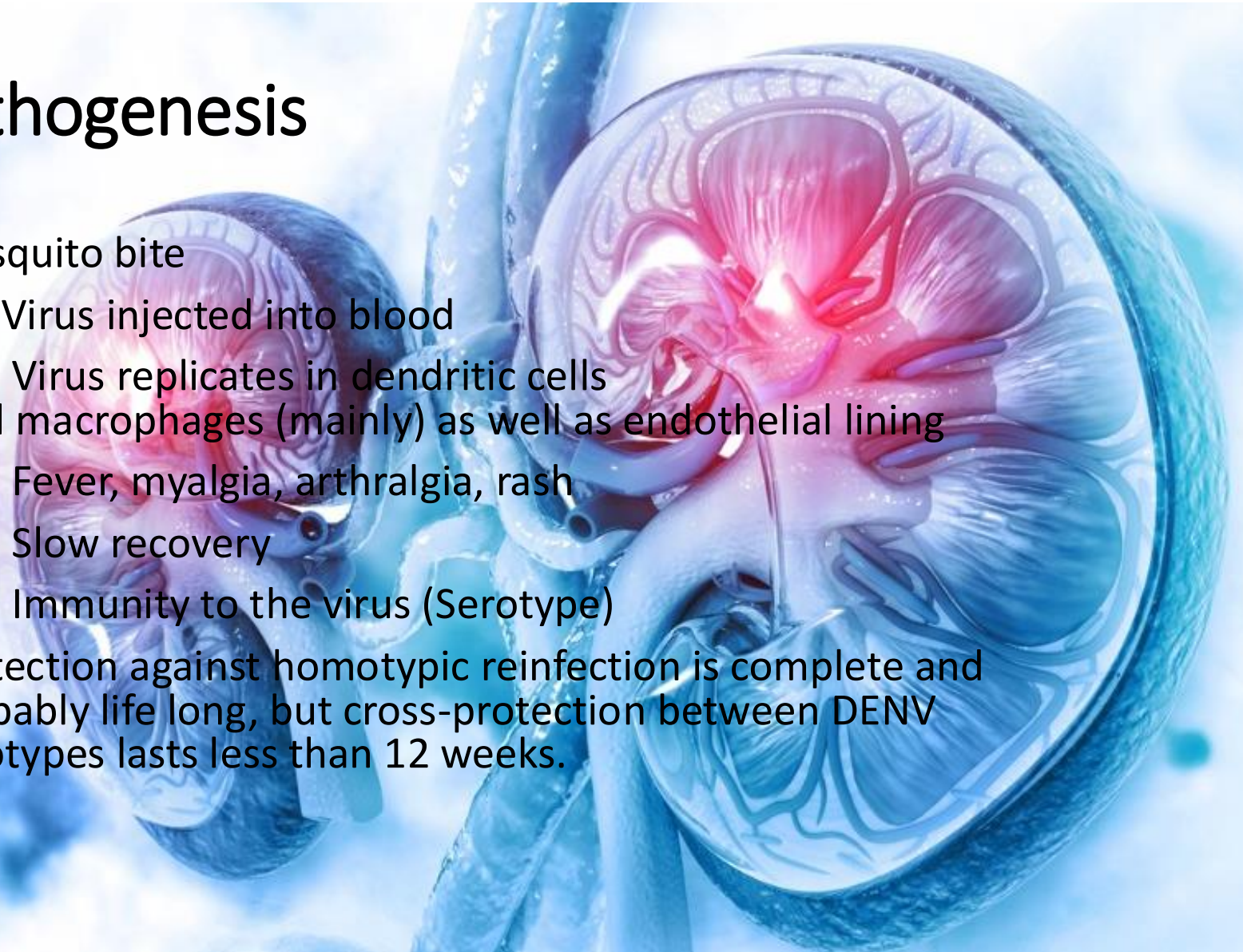
Clinical Disease Forms:

- Dengue is classified into specific syndromes:
 - dengue fever..... Flu like symptoms, muscle pain and positive torniquet test
 - dengue haemorrhagic fever.....haemorrhages
 - dengue shock syndrome.



Pathogenesis

- Mosquito bite
 - → Virus injected into blood
 - → Virus replicates in dendritic cells and macrophages (mainly) as well as endothelial lining
 - → Fever, myalgia, arthralgia, rash
 - → Slow recovery
 - → Immunity to the virus (Serotype)
- Protection against homotypic reinfection is complete and probably life long, but cross-protection between DENV serotypes lasts less than 12 weeks.



Kidney lesion

Acute kidney injuries (AKI) occurs in ~10–33% of patients and is primarily associated with dengue haemorrhagic fever and dengue shock syndrome.

AKI results from

Acute tubular necrosis (ATN).....from hypovolemia and capillary leak.

Glomerulonephritis immune-complex deposition
direct virus infection of renal tissue

The presence of haematuria and proteinuria helps distinguish glomerulonephritis from typical ATN.

Treatment : Supportive management.

Prevention: A tetravalent, live-attenuated dengue vaccine (Dengvaxia®) 9-45 years of age giving in three doses.

LABORATORY DIAGNOSIS

- Peripheral white leukopenia with absolute granulocytopenia, and the platelet count may fall to less than $100,000$ per mm^3 .
- RT-PCR
- Serologic diagnosis of DENV infection is problematic because of the extensive cross-reactivity among DENV serotypes and with other flaviviruses.
- The most useful assay is the IgM-ELISA.



Hantavirus

- Hantaviruses belong to the Order *Bunyavirales*; Family *Hantaviridae*
- They are enveloped virus contains **three segments** of single stranded negative sense RNA.
- Reservoir: rodents
- The first virus was detected in Russia 1913, however the virus was named after Hantaan river in South Korea, in 1978.



Mode of transmission

- People may also get infected via:
 - Inhalation of the virus in aerosolised rodents' excreta.
 - Being bitten by infected rodents
 - Eating food contaminated with infected rodent's urine, droppings or saliva
 - Touching the eyes, nose and mouth after contacting articles contaminated with an infected rodent's urine, droppings or saliva
- Human to human transmission is extremely rare.

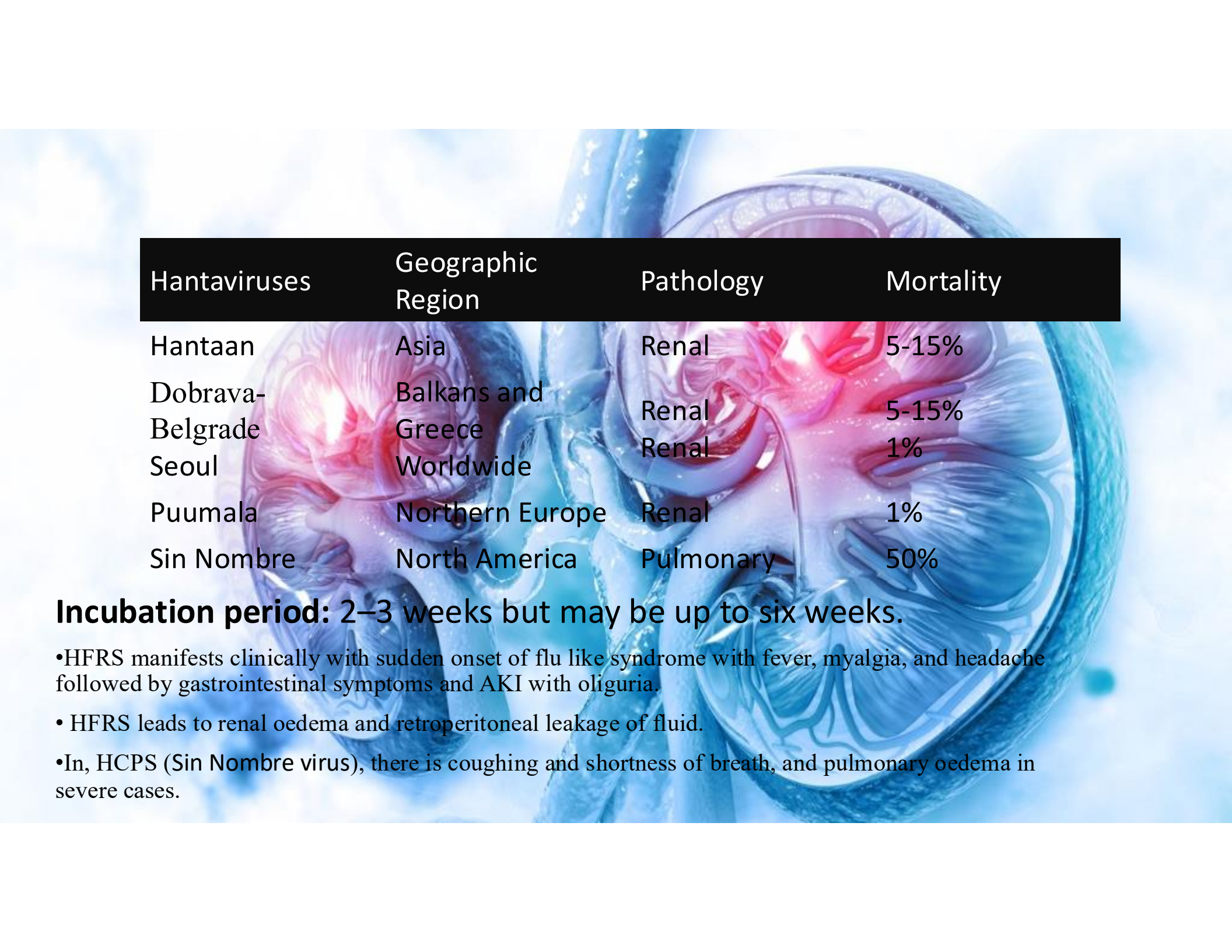


Clinical features

- Haemorrhagic fever with renal syndrome (HFRS), mainly in Europe and Asia- Old World-Hantaviruses
- Hantavirus cardiopulmonary syndrome (HCPS), in the Americas- New World-Hantaviruses

The clinical features in patients with hantavirus disease are quite variable, from asymptomatic to severe.

Feature	HFRS	HCPS
Major target organ	Kidney	Lung
First phase	Febrile	Febrile “prodrome”
Second phase	Shock	Shock, pulmonary edema
Evolution	Oliguria, diureses, convalescence	Diureses, convalescence
Mortality	1-15%	50%



Hantaviruses	Geographic Region	Pathology	Mortality
Hantaan	Asia	Renal	5-15%
Dobrava-Belgrade	Balkans and Greece	Renal	5-15%
Seoul	Worldwide	Renal	1%
Puumala	Northern Europe	Renal	1%
Sin Nombre	North America	Pulmonary	50%

Incubation period: 2–3 weeks but may be up to six weeks.

- HFRS manifests clinically with sudden onset of flu like syndrome with fever, myalgia, and headache followed by gastrointestinal symptoms and AKI with oliguria.
- HFRS leads to renal oedema and retroperitoneal leakage of fluid.
- In, HCPS (Sin Nombre virus), there is coughing and shortness of breath, and pulmonary oedema in severe cases.

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- Renal involvement may occur up to 30–40% of cases.
 - Acute tubulointerstitial nephritis is the most prominent finding in the renal histopathology.
 - Recovery usually begins during the second week of illness and is accompanied by improvement of urinary output resulting in polyuria.
 - Full recovery takes weeks.
 - Longer-lasting complications are rare:
 - glomerulonephritis
 - Guillain-Barré syndrome
 - Hypopituitarism
 - hypertension.

Diagnosis

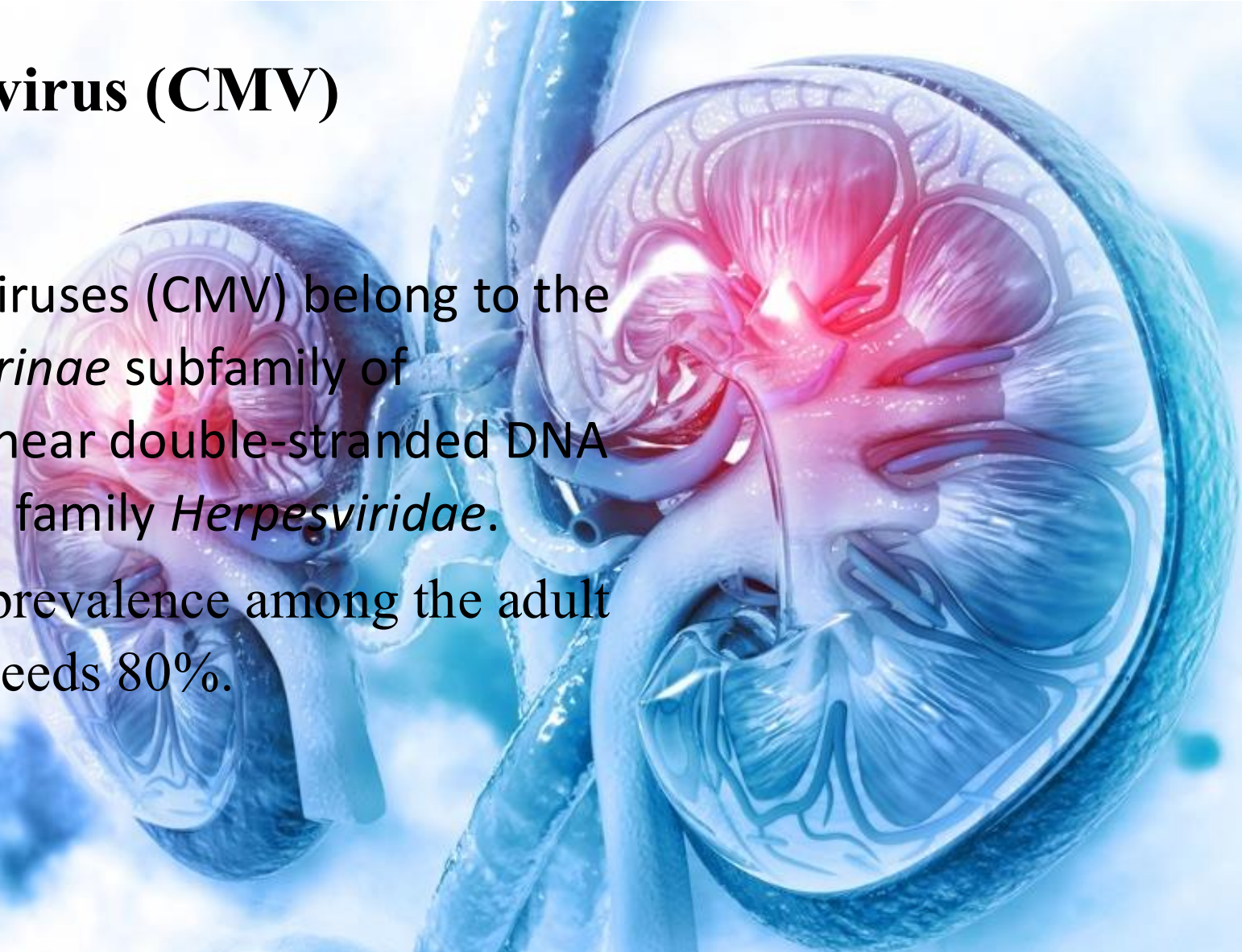
- Presence of hantavirus-specific IgM antibodies or a 4-fold or greater increase in IgG antibody titers or hantavirus-specific IgG seroconversion.
- Reverse transcriptase-polymerase chain reaction (RT-PCR) results for hantavirus RNA

Treatment: Conservative treatment.



Cytomegalovirus (CMV)

- Cytomegaloviruses (CMV) belong to the *Betaherpesvirinae* subfamily of enveloped, linear double-stranded DNA viruses in the family *Herpesviridae*.
- CMV's seroprevalence among the adult population exceeds 80%.



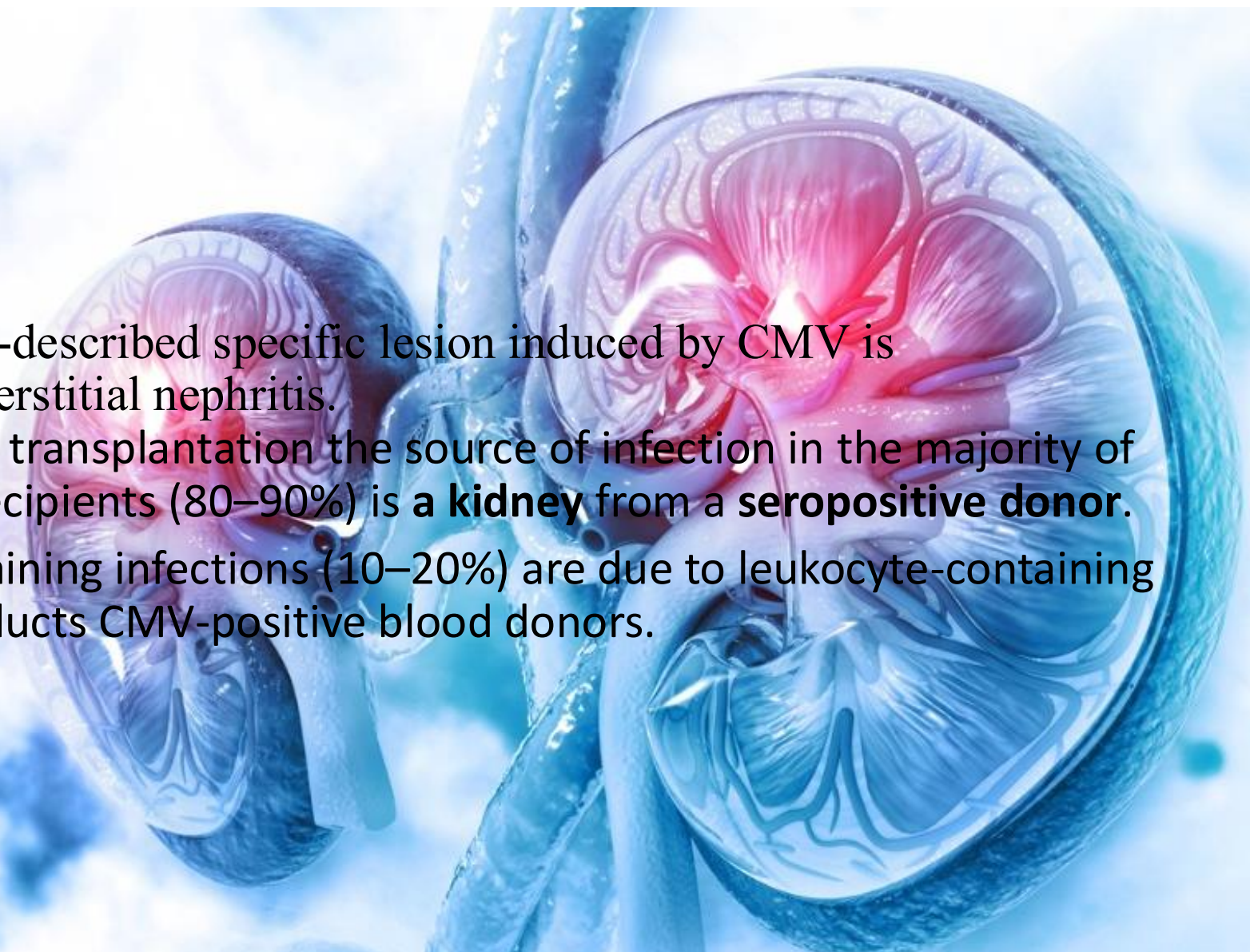
- As other herpes viruses, CMV establishes lifelong latency within the host, with the possibility of reactivation, more common in immunocompromised individuals

There are three paths to CMV infection:

- primary CMV infection,
- CMV infection reactivation
- superinfection.



- It often leads to mild, nonspecific symptoms in immunocompetent patients, but remains a major problem in immunocompromised hosts.
- It is one of the most frequent viral pathogens associated with renal transplantation.
- Acute kidney injuries may be frequently associated with CMV replication in kidney transplant recipients (KTR)

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- The best-described specific lesion induced by CMV is tubulointerstitial nephritis.
 - In kidney transplantation the source of infection in the majority of allograft recipients (80–90%) is a **kidney** from a **seropositive donor**.
 - The remaining infections (10–20%) are due to leukocyte-containing blood products CMV-positive blood donors.

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- The virus transmission is prevented by **transfusing leukocyte-depleted blood products**, which is consistent with the fact that CMV is a **leukocyte-associated pathogen**.
 - For this reason, **all immunocompromised** patients are given CMV-seronegative or leukocyte-depleted blood products.

Diagnosis

- Tests of antigenemia or DNAemia are preferred over serologic testing or cell cultures.
- The histological hallmark of CMV infection is the presence **of Cowdry Type A viral inclusions, also known as “Owl Eye Inclusions”**

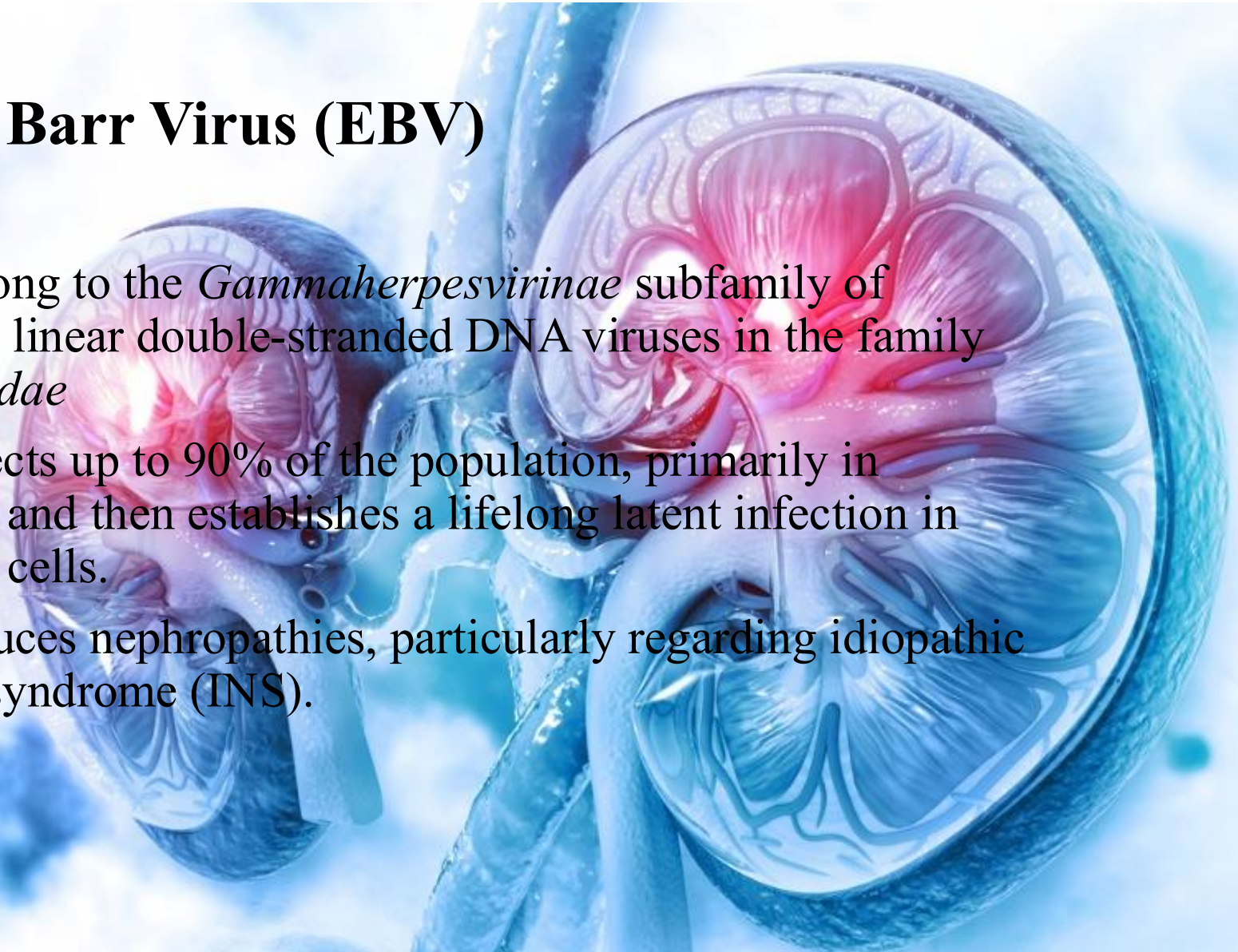
Treatment:

Ganciclovir

Foscarnet, an antiviral drug used in cases of resistance mutations to ganciclovir, **is a major source of nephrotoxicity.**

Epstein Barr Virus (EBV)

- EBV belong to the *Gammaherpesvirinae* subfamily of enveloped, linear double-stranded DNA viruses in the family *Herpesviridae*
- EBV infects up to 90% of the population, primarily in childhood, and then establishes a lifelong latent infection in memory B cells.
- EBV-induces nephropathies, particularly regarding idiopathic nephrotic syndrome (INS).



- One explanatory hypothesis is that B lymphocytes could be self-reactive and produce **anti- Epstein Barr Nuclear antigen (EBNA)** antibodies that cross-react with certain podocytes (**cells that cover the outer surfaces of glomerular capillaries**) proteins.
- Tubulointerstitial nephritis with polyclonal immune infiltrate has also been reported as a cause of AKI during EBV infection.
- Finally, some cases of glomerulonephritis and thrombotic microangiopathy have also been reported in the setting of primary EBV infection

Polyomaviruses

BK Polyomavirus

- BK polyomavirus is a nonenveloped, double-stranded DNA virus belonging to the *Polyomaviridae* family.
- BK are the initials of the first patient from which the virus was isolated.

Primary infection

- The virus leads to mostly asymptomatic infections during childhood but sometimes upper respiratory symptoms in one third of children.
- It has a seroprevalence of around 80–90%.

Latency

- BK virus persists as latent virus in the renal tubular epithelial cells and the uroepithelium.

Reactivation

- The BK polyomavirus associated nephropathy occurring as a consequence of a deeply immunocompromised state at **early post-transplantation.**

- Early, following hematopoietic stem cell transplantation (HSCT), urinary BK polyoma virus replication leads to haemorrhagic cystitis.
- These further develop to tubular-cell necrosis and inflammation, then tubular atrophy and interstitial fibrosis, that lead to allograft function.
- The reduction of the immunosuppression is the best treatment to reduce the BK polyomavirus nephropathy but can unfortunately lead to allograft rejection.

JC Virus

- The JC virus was described the same year as BK virus.
- Similarly, it has a tropism for urothelial epithelial cells and can reactivate during an immunocompromised state.
- However, contrary to BK polyomavirus, JC virus reactivation usually does not coincide with viral nephropathy, and almost never affects kidney allograft function.
- JC-virus-related nephropathy can occur both **early and late** following transplantation, unlike BK polyomavirus associated nephropathy, which typically occurs in the **early post-transplant** period.
- In about 50% of JC-virus-related nephropathies, allograft function seemed to be impacted, and moderate to severe tubulitis was noted.



Hepatitis C virus

HCV is an Enveloped virus contains ssRNA virus + sense genome.

- The virus is related to Family, *Flaviviridae* , Genus *Hepacivirus*
- Seven genotypes 1:7 and several subtypes with **high rate of virus heterogenicity.**
- HCV is associated glomerular disease due to viral antigen-immune complex formation with their deposition on glomerular basement membrane.
- The pathologic hallmark is type 1 MPGN with or without type 2 mixed cryoglobulinemia.



1- Mixed cryoglobulinemia with membranoproliferative glomerulonephritis (MPGN)

It ranges from asymptomatic proteinuria or hematuria to nephrotic or nephritic syndrome, which can progress to chronic renal insufficiency.

- The diagnosis is often made by low serum concentrations of complement levels (C1q, C4, and C3) and the presence of anti-HCV antibodies and HCV RNA.

2- MPGN without cryoglobulinemia

3- Other Related Glomerulopathies like MesPGN, focal proliferative GN, and IgAN have also been reported.

- In aggressive disease like cryoglobulinemic vasculitis with impending organ failure, immunosuppressive agents may be used to save the kidney.

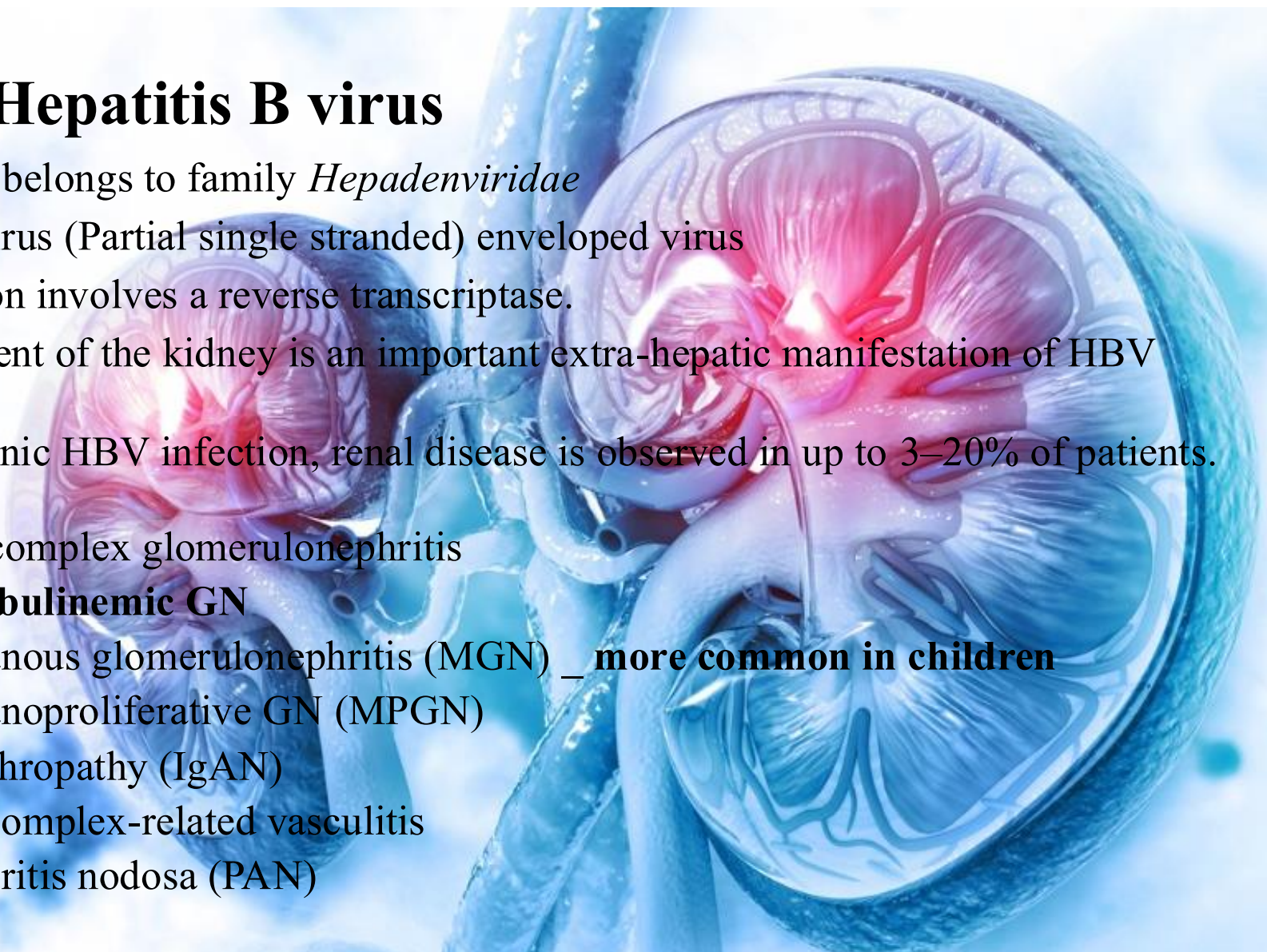
The prognosis of HCV-associated glomerulopathies is poor because of a high incidence of cardiovascular diseases and infections.

Hepatitis B virus

- The virus belongs to family *Hepadenviridae*
- dsDNA virus (Partial single stranded) enveloped virus
- Replication involves a reverse transcriptase.
- Involvement of the kidney is an important extra-hepatic manifestation of HBV infection.
- With chronic HBV infection, renal disease is observed in up to 3–20% of patients.

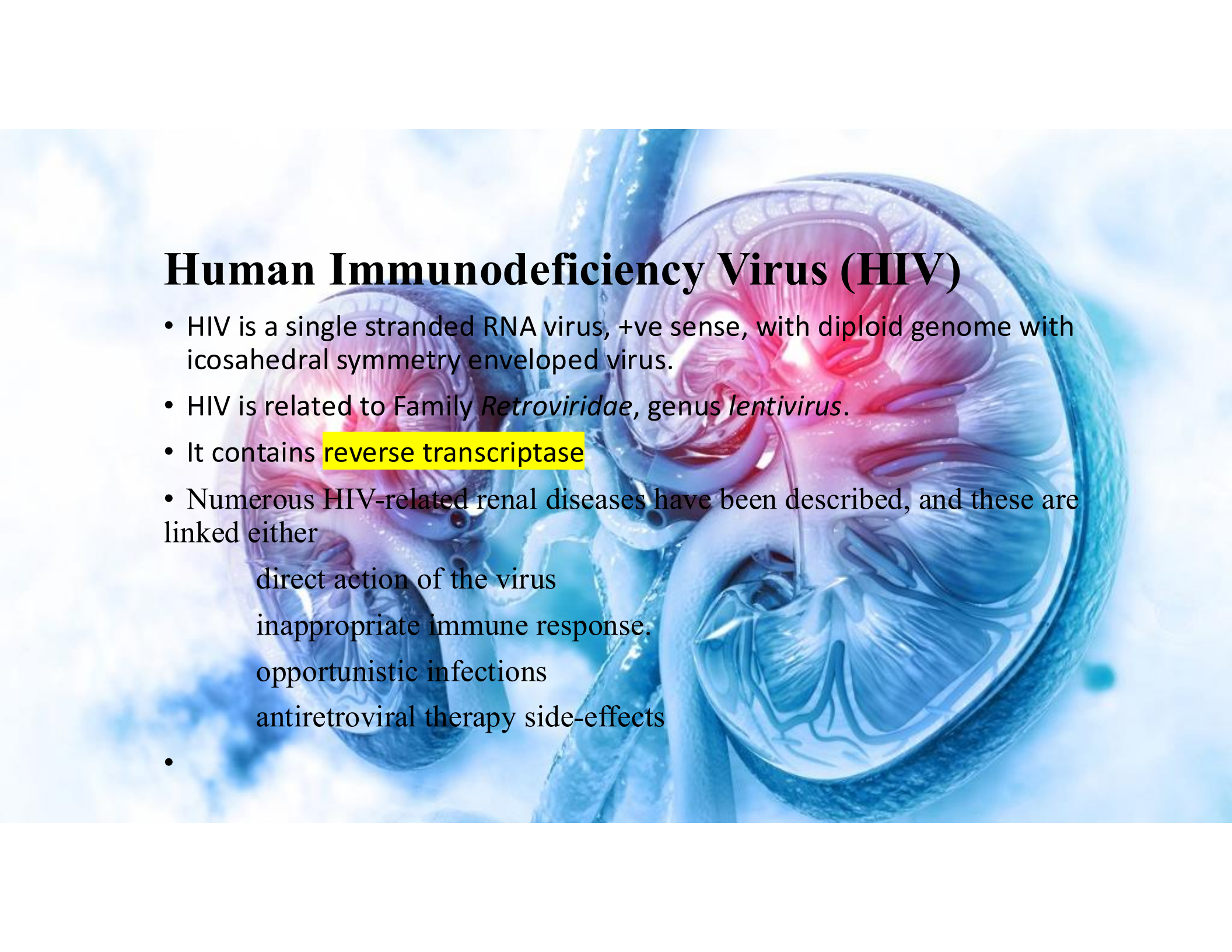
Lesions:

- Immune-complex glomerulonephritis
- **cryoglobulinemic GN**
- membranous glomerulonephritis (MGN) _ **more common in children**
- membranoproliferative GN (MPGN)
- IgA nephropathy (IgAN)
- Immune complex-related vasculitis
- polyarteritis nodosa (PAN)



Treatment

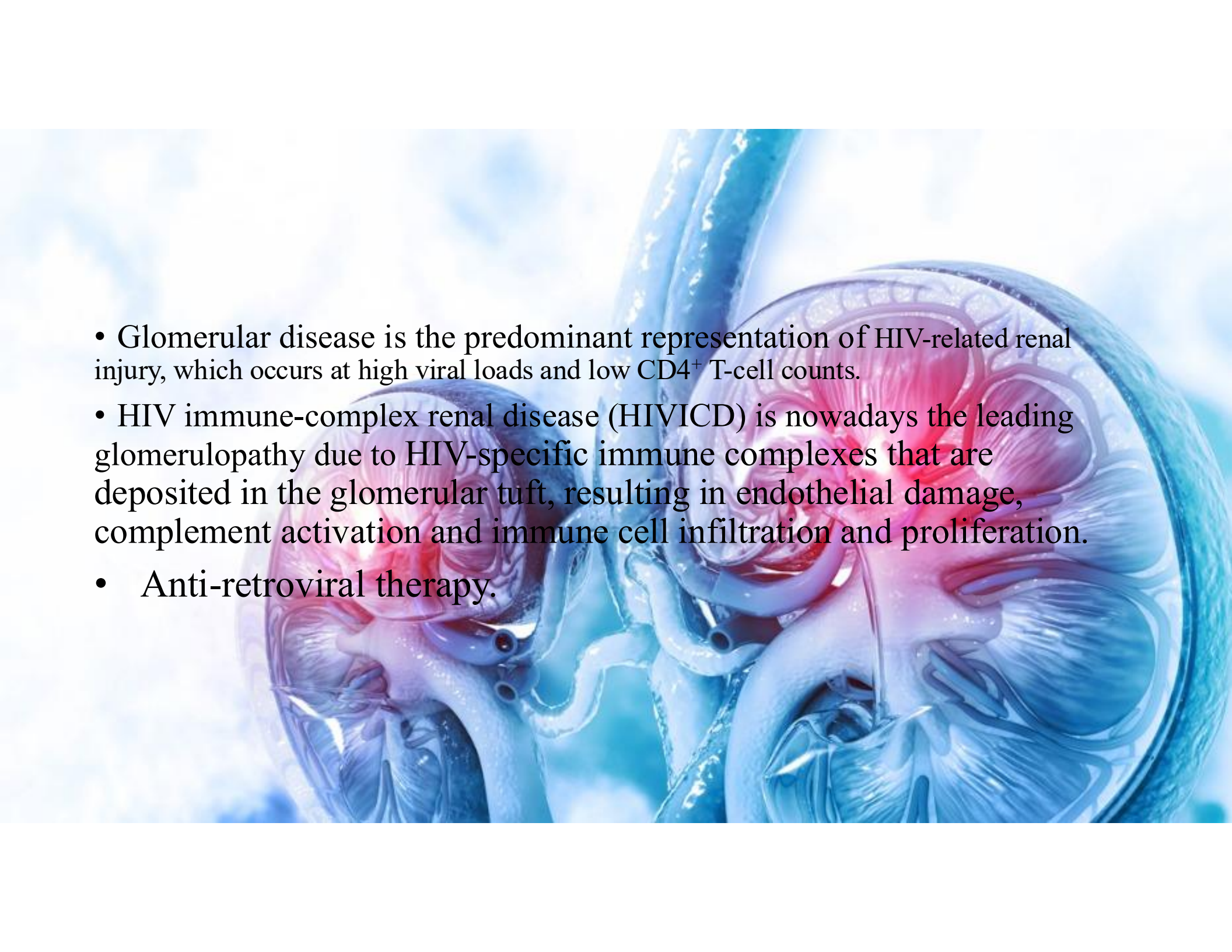
- Interferon and lamivudine (reverse transcription inhibitors) are used for treatment of HBV related GN and vasculitis.
- Corticosteroids may be given for a period of < 6 months without a significant effect on liver disease, HBV viremia, or patient morbidity or mortality
- Dose adjustment of drugs according to creatinine clearance should always be kept in mind.
- Universal vaccination has decreased childhood cases of HBV membranous nephropathy related to horizontal transmission of the virus.



Human Immunodeficiency Virus (HIV)

- HIV is a single stranded RNA virus, +ve sense, with diploid genome with icosahedral symmetry enveloped virus.
- HIV is related to Family *Retroviridae*, genus *lentivirus*.
- It contains reverse transcriptase
- Numerous HIV-related renal diseases have been described, and these are linked either
 - direct action of the virus
 - inappropriate immune response.
 - opportunistic infections
 - antiretroviral therapy side-effects

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- Glomerular disease is the predominant representation of HIV-related renal injury, which occurs at high viral loads and low CD4⁺ T-cell counts.
 - HIV immune-complex renal disease (HIVICD) is nowadays the leading glomerulopathy due to HIV-specific immune complexes that are deposited in the glomerular tuft, resulting in endothelial damage, complement activation and immune cell infiltration and proliferation.
 - Anti-retroviral therapy.

Hepatitis E virus

Taxonomy: *Hepeviridae*, Genus *Hepevirus*, non enveloped, 27-34 nm particles containing a ssRNA genome positive sense.

Transmission

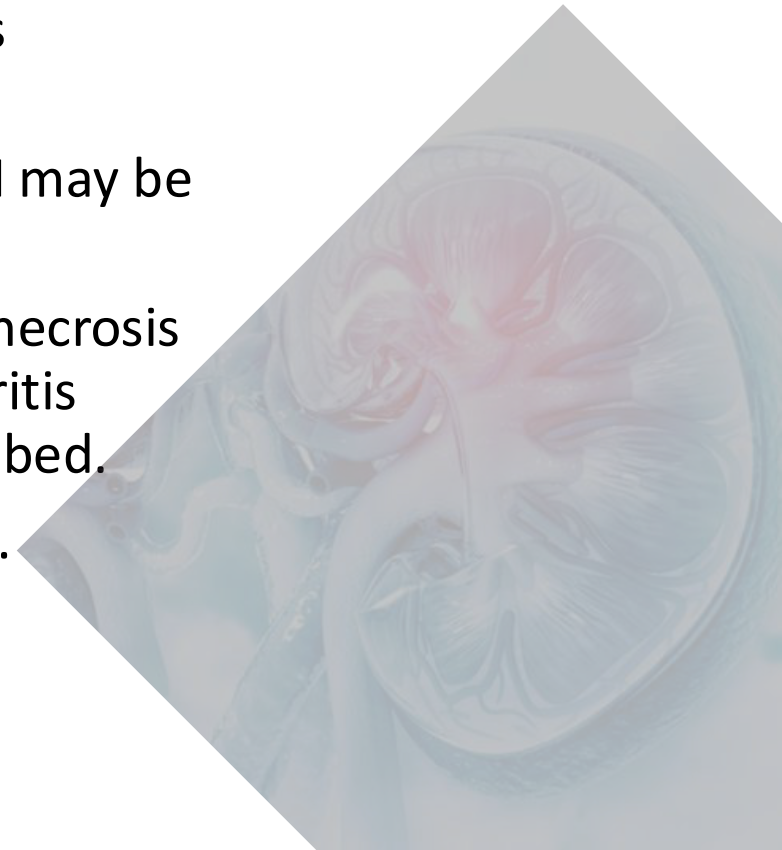
- Enterically transmitted disease.
- Contaminated food, water (e.g., infected food handlers, raw shellfish)
- HEV infection is reported to be associated with different renal syndromes and HEV particles are isolated from the urine of infected patients.
- Renal injury is related to direct cytopathic injury due to the viral replication or related to immune-mediated mechanisms.



- GN with and without mixed cryoglobulinemia have been reported.
- Decline in estimated glomerular filtration rate with HEV infection has been shown in renal allograft recipients.
- There is an improvement in renal function and decrease in proteinuria level following HEV clearance.

Hepatitis A Virus (HAV)

- HAV is a nonenveloped single-stranded RNA virus belonging to the *Picornaviridae* family.
- Extra-hepatic manifestations rarely occur, but AKI may be present in 5% of patients.
- Reported renal injuries are mostly acute tubular necrosis (ATN), but cases of acute tubulo-interstitial nephritis (AITN) and glomerular nephritis have been described.
- in renal transplant recipients has been suggested.

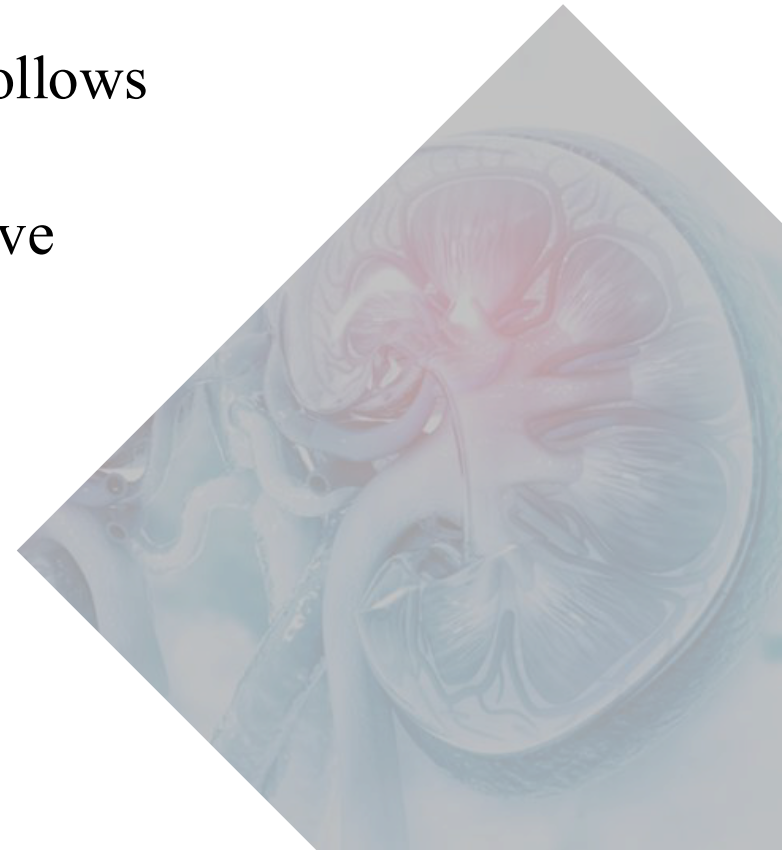


B19

- B19 belongs to the Family *Parvoviridae* [ssDNA naked virus].
- Infection with parvovirus B19 causes several clinical syndromes
 - fifth disease- skin rash in children
 - transient aplastic crisis-pure red cell aplasia
 - hydrops fetalis

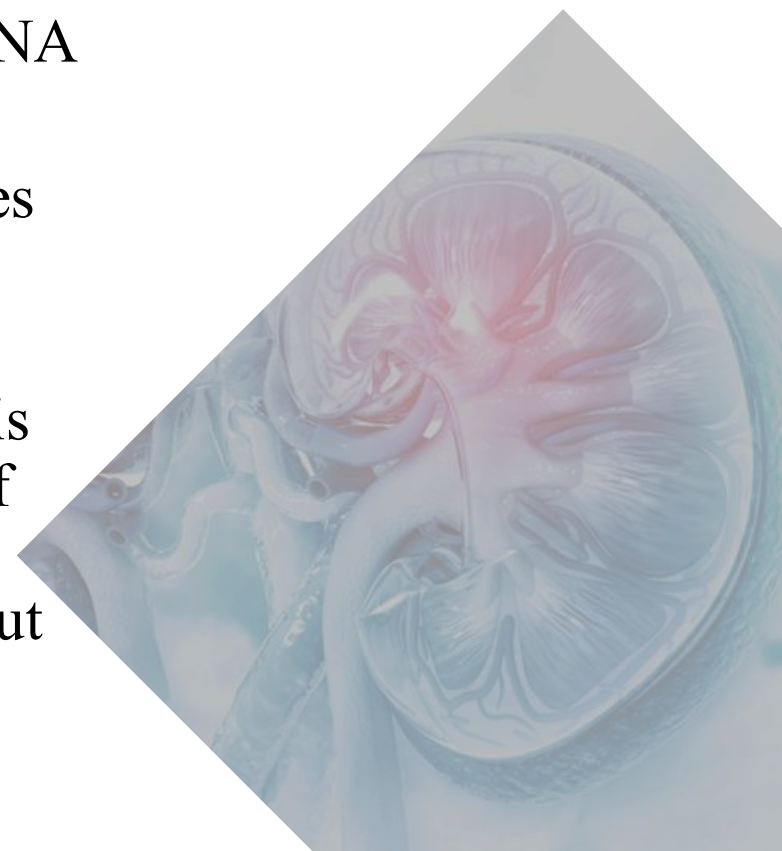


- **Acute nephritic syndrome with hypocomplementemia** and proteinuria often follows fever, rash, and arthritis.
- Spontaneous recovery is common, but some have persistent renal dysfunction and/or proteinuria



Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

- SARS-CoV-2 is an enveloped, single-stranded RNA virus belonging to the *Coronaviridae* family.
- The frequency of acute kidney injury (AKI) varies from 5% to 50%, depending on the severity of infection.
- The main cause of AKI was acute tubular necrosis (ATN) which was present in approximately 50% of cases and coincided with multiple factors (hemodynamic changes, nephrotoxic drugs, etc.) but was possibly a direct viral injury.



- Angiotensin-converting enzyme 2 (ACE2) is the major cellular receptor for SARS-CoV-2 spike protein.
- Such receptor is expressed on proximal tubular cells and podocytes.
- SARS-CoV-2 infection may locally promote the production of inflammatory mediators that lead to AKI.
- The other major cause of AKI is the development of collapsing ***focal segmental glomerulosclerosis*** (FSGS) in 25 to 40% of cases.

Influenza Virus

- Influenza virus is an enveloped, single-stranded, fragmented RNA virus belonging to the *Orthomyxoviridae* family.
- AKI was observed in approximately 50% of patients hospitalized in intensive care units and was associated with significantly worse outcomes
- The causes are likely multiple, involving a variety of factors, such as infection-related hypovolemia, drug toxicities and possible aggressive fluid accumulation.
- In addition, a few cases of glomerulonephritis or thrombotic microangiopathy have been described.

