



e doença de órgão
–O desafio a longo prazo

CICLO DE REUNIÕES TEMÁTICAS

Patologia Renal

Hospital de Cascais

A DOENÇA RENAL ASSOCIADA AO VIH

O QUE MUDOU NOS ÚLTIMOS 30
ANOS

SUMÁRIO

1. Doença Renal e VIH
2. HIVAN e outras Glomerulopatias associadas ao VIH
3. Doenças Tubulointersticiais associadas ao VIH
4. Contribuição da TARV para a Doença Renal
5. A Mudança da Epidemiologia da Doença Renal associada ao VIH

1 DOENÇA RENAL E VIH

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ASSOCIATED FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

T. K. SREEPADA RAO, M.D., EDWARD J. FILIPPONE, M.D., ANTHONY D. NICASTRI, M.D.,
SHELDON H. LANDESMAN, M.D., ELLIOT FRANK, M.D., C. K. CHEN, M.D., AND ELI A. FRIEDMAN, M.D.

Nephrotic Syndrome, Progressive Irreversible Renal Failure, and Glomerular “Collapse”: A New Clinicopathologic Entity?

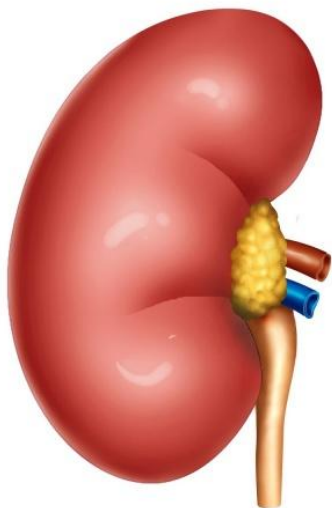
Mark A. Weiss, MD, Eleanor Daquioag, MD, E. Gordon Margolin, MD, and Victor E. Pollak, MD

● Six patients are reported with nephrotic syndrome and relatively rapid progression to irreversible renal failure. The renal histologic findings are unusual. The most striking changes are collapse of glomerular capillary loops, such as might occur with glomerular hypoperfusion; significant tubulointerstitial damage is also seen. These patients appear to have a clinicopathologic entity hitherto unreported. Its differentiation from other causes of progressive glomerular damage, and particularly from focal and segmental glomerulosclerosis, is discussed.

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INDEX WORDS: Nephrotic syndrome; irreversible renal failure; glomerular capillary collapse.

O espectro da Doença Renal na infeção VIH é diverso.



Expressão
intrarrenal dos
genes do VIH

Desregulação do
sistema imunitário

-Co-infeções

Co-morbilidades

-Nefrotoxicidade
farmacológica

I. Glomerular-dominant^a

- a. Podocytopathies (all characterized by extensive foot process effacement)^b
 - i. Classic HIVAN
 - ii. FSGS (NOS) in the setting of HIV
 - iii. Minimal change disease in the setting of HIV
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- b. Immune complex-mediated glomerular disease^b
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 - vii. Fibrillary or immunotactoid glomerulonephritis in the setting of HIV
 - viii. Other immune complex disease in the setting of HIV

II. Tubulointerstitial-dominant^a

- a. Tubulointerstitial injury in the setting of classic HIVAN
 - i. Hyaline droplet tubulopathy
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- c. Drug-induced tubulointerstitial nephritis (other than ART)
 - i. Antibiotics
 - ii. Proton pump inhibitors
 - iii. NSAIDs
 - iv. Other
- d. Direct renal parenchymal infection by pathogens (bacterial, viral, fungal, protozoal, etc.)
- e. Immunologic dysfunction-related tubulointerstitial inflammation
 - i. Diffuse infiltrative lymphocytosis syndrome (DILS)
 - ii. Immune reconstitution inflammatory syndrome (IRIS)
- f. Other tubulointerstitial inflammation in the setting of HIV

III. Vascular-dominant^a

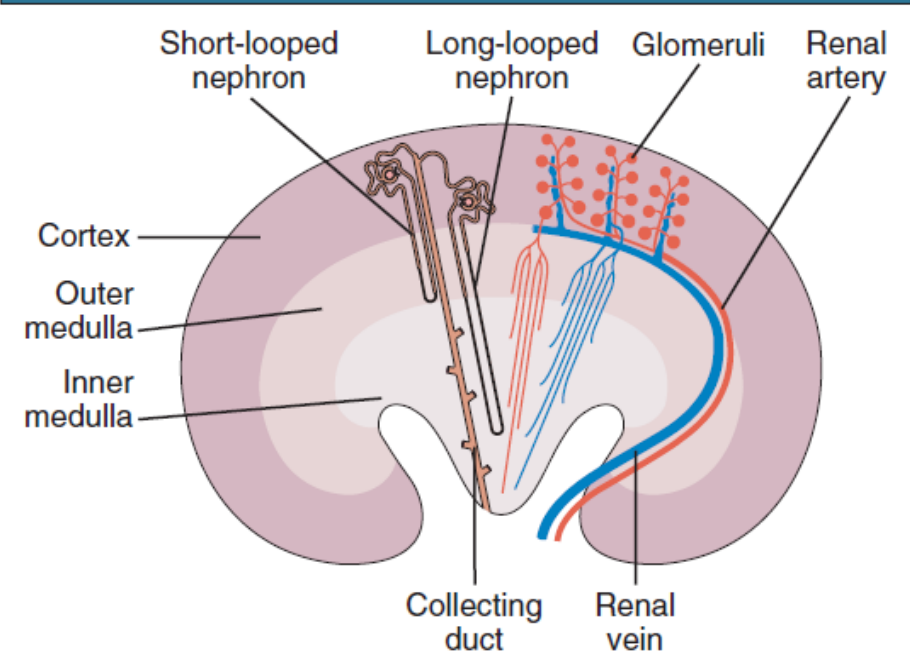
- a. Thrombotic microangiopathy in the setting of HIV
- b. Arteriosclerosis

IV. Other, in the setting of HIV infection

- a. Diabetic nephropathy
- b. Age-related nephrosclerosis

- I. Glomérulos
- II. Túbulos
- III. Interstício
- IV. Vasos

Coronal Section Through a Unipapillary Kidney



Kopp JB, Naicker S. Human Immunodeficiency Virus Infection and the Kidney. In: Feehally J, Floege J, Tonelli M, Johnson RJ. Comprehensive Clinical Nephrology. Elsevier; 2019. p679-688.

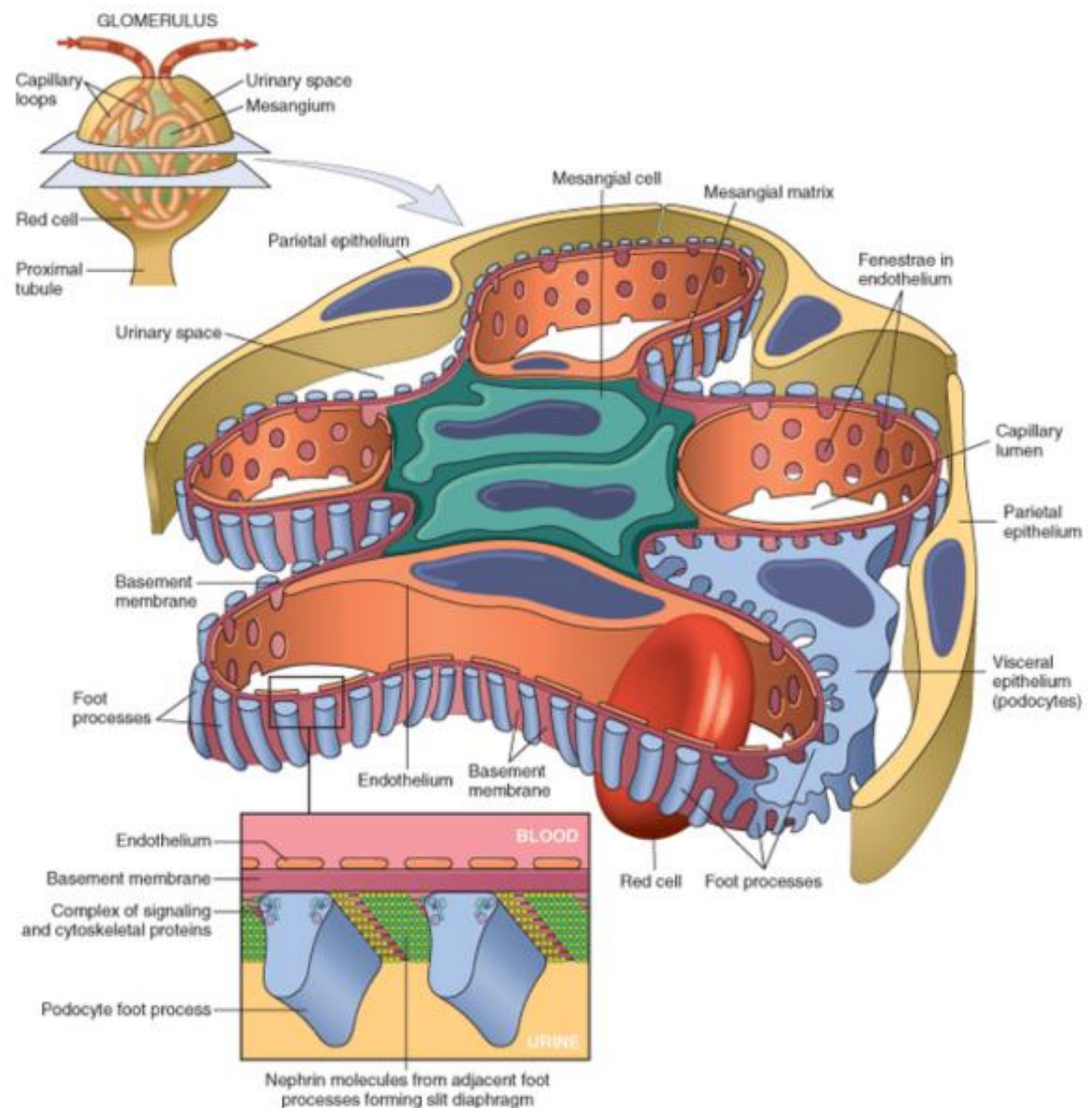


Table 1 | Pathologic classification of HIV-related kidney diseases

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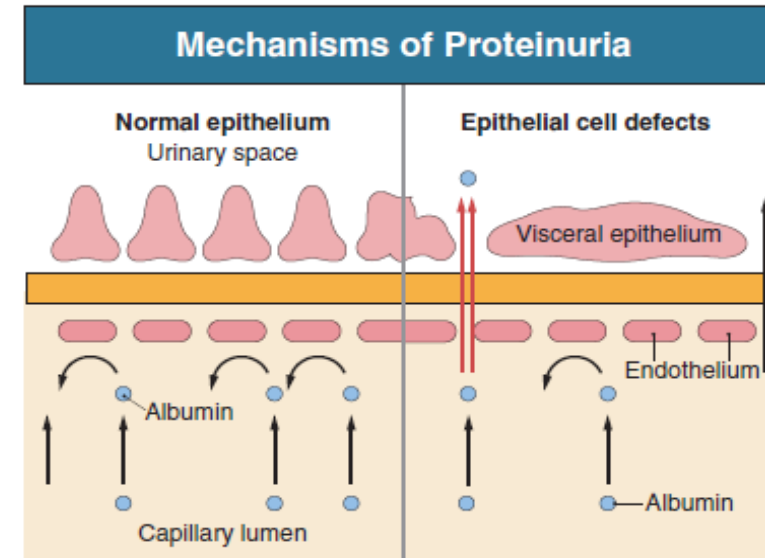
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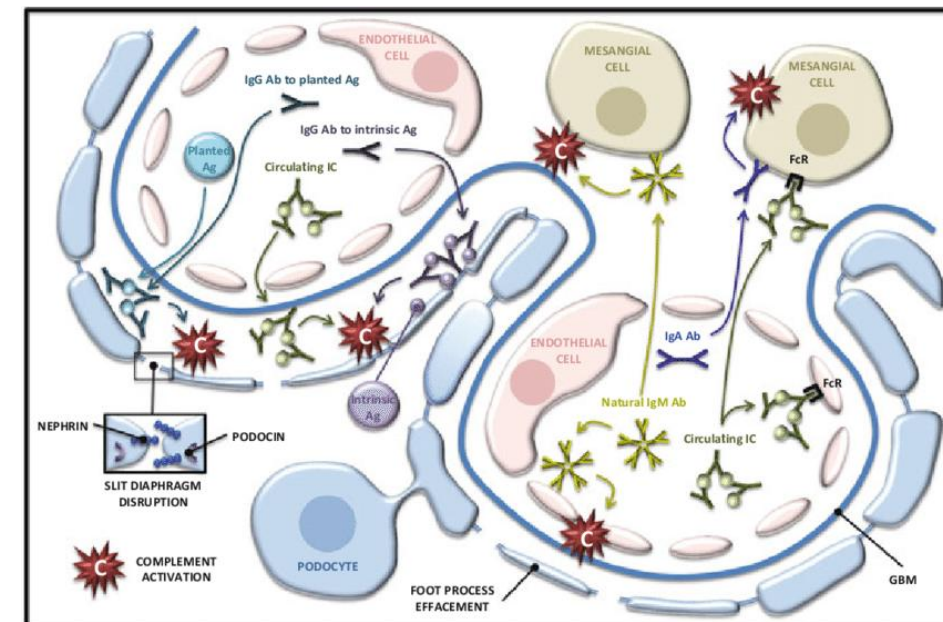
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Swanepoel CR, Atta MG, D'Agati VD, Estrella MM, Fogo AB, Naicker S, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney International* (2018) 93, 545–559



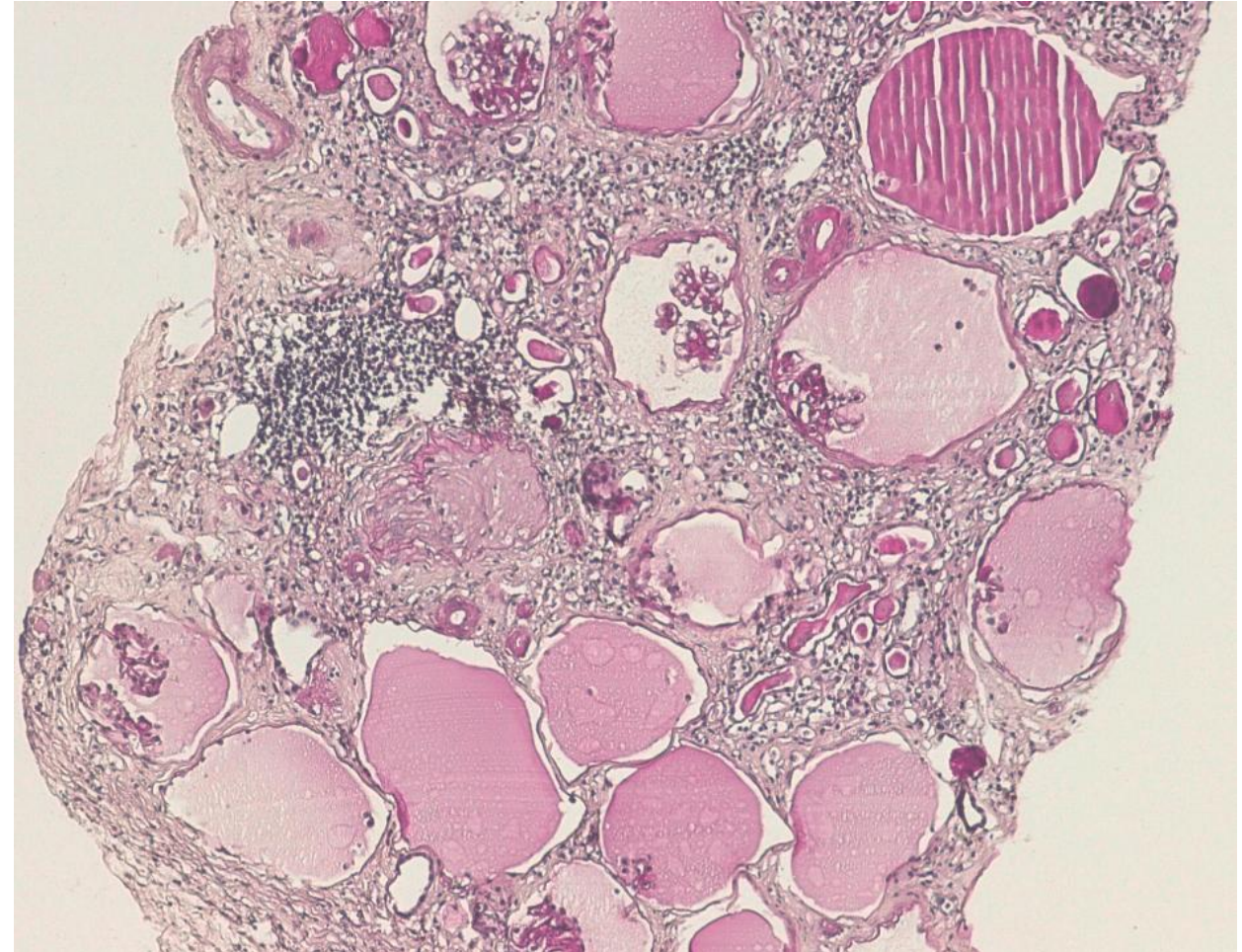
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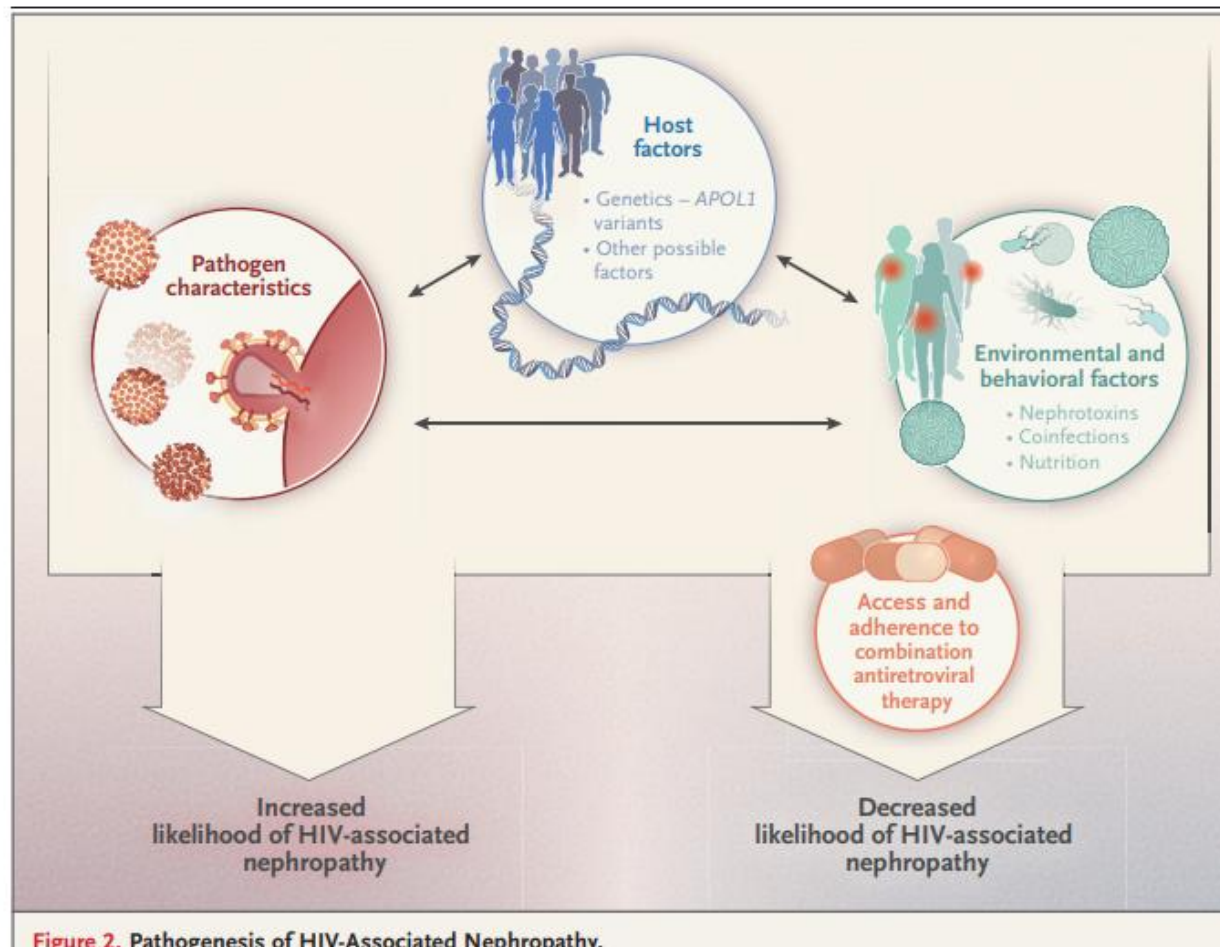
https://www.researchgate.net/figure/Antibody-mediated-glomerular-injury-occurs-through-multiple-mechanisms-Antibody-may-bind_fig4_309304847

2 HIVAN E OUTRAS GLOMERULOPATIAS ASSOCIADAS AO VIH

- A **Glomerulopatia clássica** associada à infecção VIH é GESF colapsante ou HIVAN (*HIV associated nephropathy*).
- Patologia glomerular, mas também tubulo-intersticial: associada a microcistos tubulares e inflamação intersticial.



A patogénese do HIVAN envolve uma complexa interação entre o vírus, hospedeiro, ambiente e o acesso a TARV.



- Ação directa do vírus
- Expressão Vpr, Nef »» lesão celular
- **Infeção VIH avançada, não tratada**

- Raça africana (>90%)
- Variantes de risco do gene APOL1 »» ↑ risco de **HIVAN/ pior prognóstico**
- Sistema imunitário

Manifestações clínicas:

- Proteinúria na faixa nefrótica;
- PA normal (HTA presente em 12-20%);
- Rins de dimensões aumentadas e hiperecogénicos (microcistos).

Progride rapidamente para DRC terminal se não for tratada.

Fatores de mau prognóstico:

- Descendência africana/ genotipo APOL1 de risco;
- Disfunção renal grave basal;
- Proteinúria;
- Histologia » ++ glomerulos esclerosados/ sinais de cronicidade.

A maioria dos doentes VIH com proteinúria têm um diagnóstico alternativo.

GN MEDIADA POR IMUNOCOMPLEXOS (HIVICK)

Nefropatia IgA

GN pós-infecciosa

GN mesangio-proliferativa

GN Lupus-like

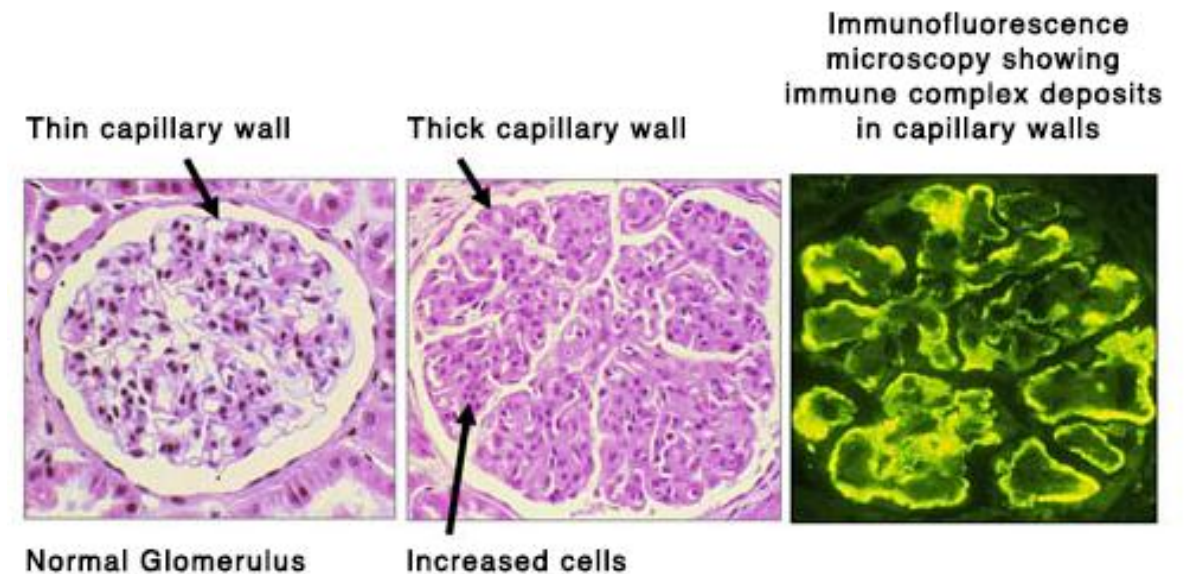
GN membrano-proliferativa

GN por criglobulinas

Outras GN

Patogénese complexa:

- Reconstituição imunológica induzida pela TARV;
- Formação de imunocomplexos – antigénios VIH/ expansão policlonal de linfócitos B;
- Depósitos glomerulares/ activação do complemento;
- Lesão celular.



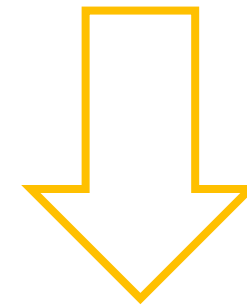
<https://unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/mpgn/>

Manifestações clínicas:

- ⑩ Proteinúria nefrótica/ subnefrótica
- ⑩ Sedimento urinário ativo – hematúria e cilindros hemáticos;
- ⑩ HTA (~79%)
- ⑩ C3 diminuído (~40%)
- ⑩ ANA + (~21%)

- ⑩ Cargas virais + baixas;
- ⑩ CD4⁺ + elevados;
- ⑩ Menor relação com TARV (?)
- ⑩ Diabetes e HTA.

Pode ser clinicamente indistinguível do HIVAN

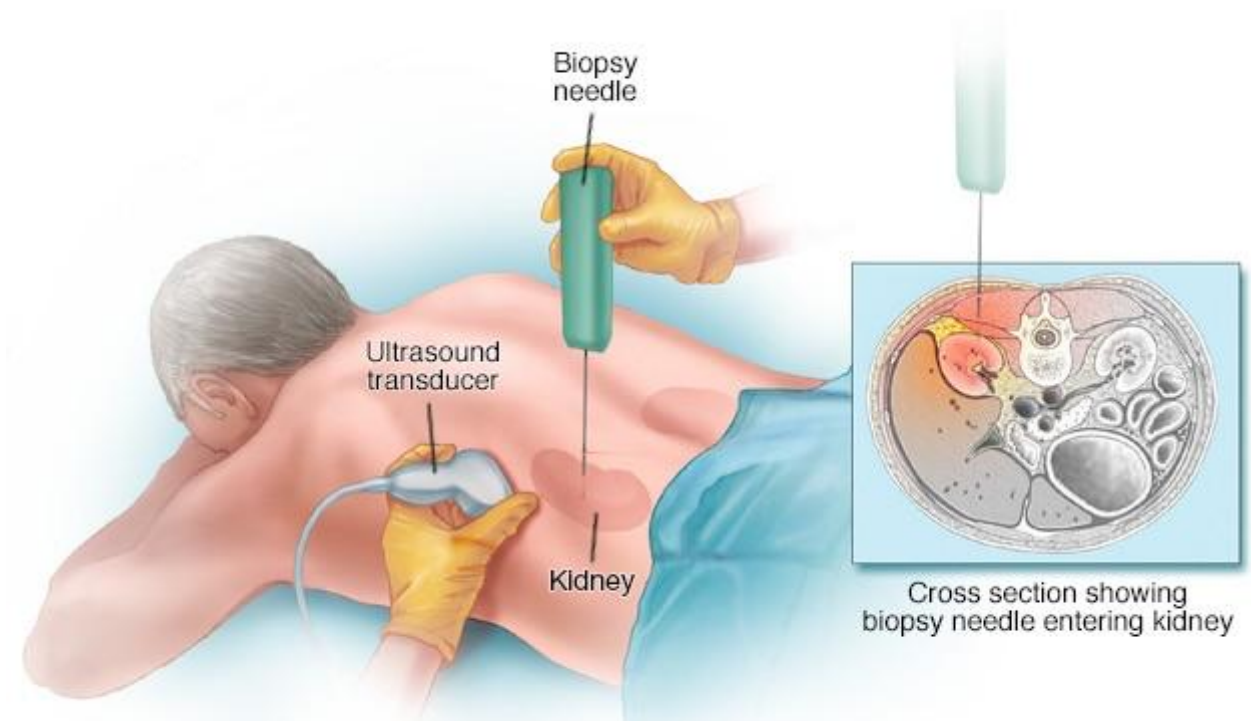


Biópsia renal

Diagnóstico definitivo »» Biópsia Renal

Indicações:

- Lesão renal aguda
 - Sedimento urinário activo
 - Proteinúria nefrótica
 - Doença renal crónica inexplicável
- Possibilidade da biópsia influenciar a terapêutica
- Condições do doente para tolerar a terapêutica



<https://www.mayoclinic.org/tests-procedures/kidney-biopsy/about/pac-20394494>

Opções terapêuticas

Treatment	Condition	Evidence of effectiveness
ART	HIVAN	Case-series and epidemiological studies showed cessation/ reversal of eGFR decline and decreased HIVAN incidence
	HIVICK	Large case-series showed conflicting associations with CKD progression
ACE-i or ARB	HIVAN/ HIVICK	Small case-series showed slower progression to ESKD in those treated with ACE-i/ ARB
Corticosteroids	HIVAN/ HIVICK	Two small case-series: One showed variable improvement in SCr and proteinuria, with similar risk of death over 12 months of follow-up. Second series showed improvement in SCr but not in proteinuria.
Cyclosporine	HIVAN/ HIVICK	Small case-series: Proteinuria improved or stabilized in all 3 patients who received cyclosporine.

Treatment strategies for specific kidney diseases in the setting of HIV

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ART, combination antiretroviral therapy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HIVAN, HIV-associated nephropathy; SCr, serum creatinine.

3 DOENÇAS TUBULOINTERSTICIAIS ASSOCIADAS AO VIH

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- f. Other tubulointerstitial inflammation in the setting of HIV

Lesão Renal Aguda

Pré-Renal

Renal

Pós-Renal

Necrose Tubular
Aguda

- Isquémica
- Tóxica

Nefrite Intersticial
Aguda

- AINEs
- Antibióticos
- IBPs
- TARV
- Alopurinol
- Infecções

Nefropatia Cristais

- Aciclovir
- TARV

Microangiopatias
trombóticas

Lesão Renal Aguda

Pré-Renal

Renal

Pós-Renal

Necrose Tubular
Aguda

- Isquémica
- **Tóxica**
 - **Tenofovir**

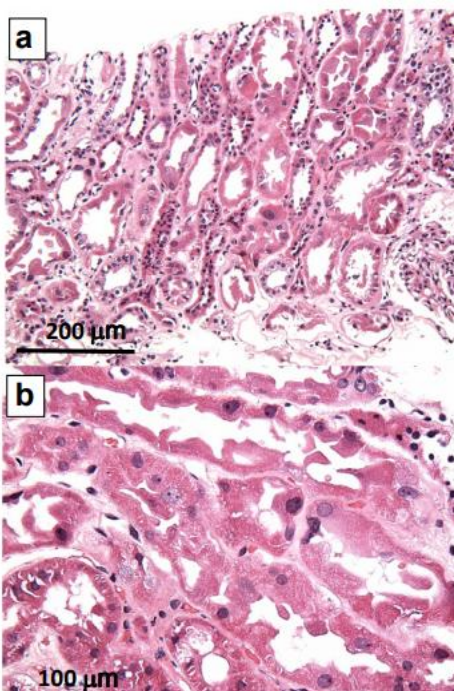
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- Aciclovir
- TARV

Microangiopatias
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Lesão Renal Aguda

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Nefropatia Cristais

- Anfotericina B
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- TARV

Microangiopatias
trombóticas

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Necrose Tubular
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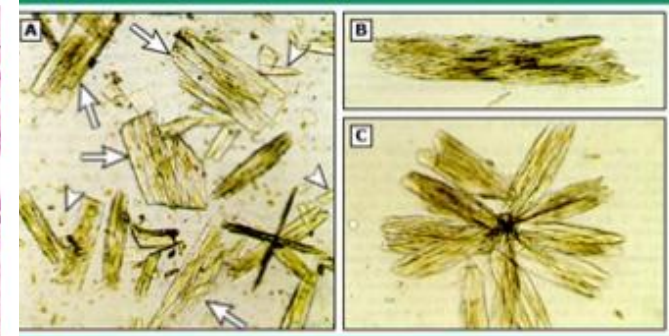
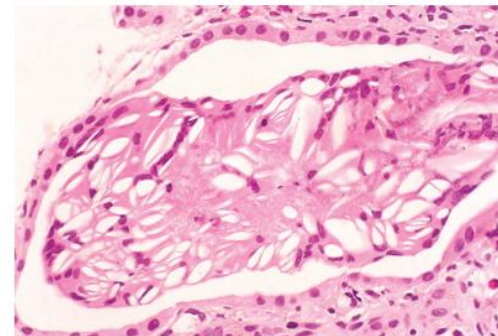
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Nefropatia Cristais

- Aciclovir
- **TARV**
 - **Indinavir**

Microangiopatias
trombóticas



Doenças Tubulointersticiais Crónicas

Síndrome de
Fanconi

Diabetes
Nefrogénica

Nefrite intersticial
crónica

- Glicosúria
- Fosfatúria > hipofosfatémia
- Uricosúria
- Aminoacidúria
- Proteinúria tubular

4 CONTRIBUIÇÃO DA TARV PARA A DOENÇA RENAL

- Tratamento da infecção VIH está recomendada em todos os indivíduos com VIH +, sendo o controlo virológico uma estratégia essencial na redução da incidência de lesão renal aguda e nefropatias associadas ao VIH.
- Contudo, TARV é responsável por uma variabilidade de efeitos nefrotóxicos incluindo lesão renal aguda e doença renal crónica.
- A lesão renal aguda relacionada com TARV é mais frequente no primeiro ano de terapêutica.



Table 2. Manifestations of antiretroviral toxicity [10, 13, 33, 34, 73]

Antiretroviral group	Kidney damage mechanism	Kidney manifestations
NRTI		
Abacavir Didanosine Lamivudine Stavudine Zidovudine	Inhibition of mitochondrial DNA polymerase; oxidative phosphorylation and endogenous nucleotide kinases	AKI, AIN (case report) Fanconi or Fanconi-like syndrome Type B lactic acidosis Nephrogenic diabetes insipidus (case reports)
NtRTI		
Tenofovir	Direct proximal tubular epithelial cells toxicity Intracellular accumulation Mitochondrial depletion	Fanconi syndrome Nephrogenic diabetes insipidus AKI Osteomalacia
NNRTI		
Efavirenz Nevirapine	Unknown Hypersensitivity	Minimal change disease (case report) Urolithiasis (case report) AKI (case reports)
Protease inhibitors		
Indinavir Atazanavir Nelfinavir Amprenavir Saquinavir Lopinavir Ritonavir	Intratubular drug precipitation due to poor solubility (mainly for indinavir, atazanavir)	AKI and CKD Acute and chronic interstitial nephritis Nephrolithiasis, asymptomatic crystalluria, crystal nephropathy Papillary necrosis
Integrase inhibitors		
Raltegravir	Skeletal muscle toxicity	Rhabdomyolysis and AKI (case reports)

NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase; NNRTI, non-nucleoside reverse transcriptase inhibitor; AKI, acute kidney injury; AIN, acute interstitial nephritis; CKD, chronic kidney disease.

Tratamento:

- Alteração do regime terapêutico
- Corticoterapia (?)

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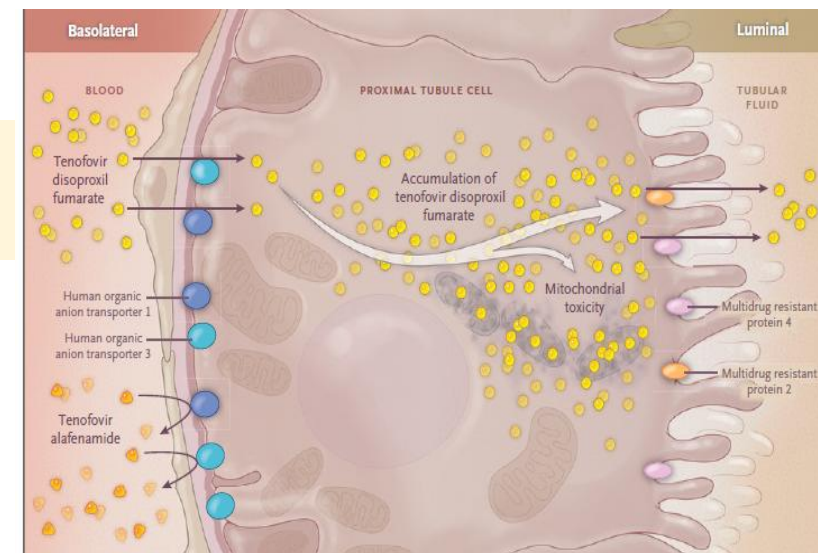
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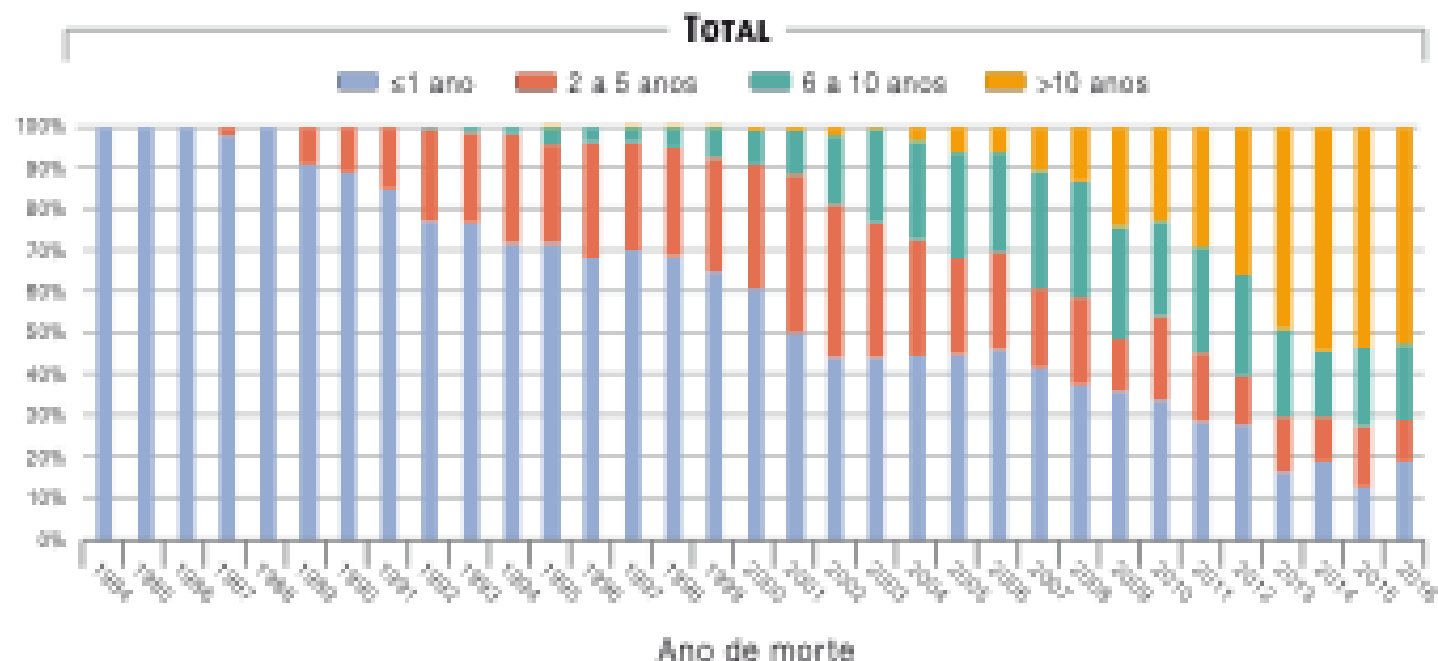
Cohen SD, Kopp JB, Kimmel PL. Kidney Diseases Associated with Human Immunodeficiency Virus Infection. N Engl J Med. 2017 377:24.

TENOFOVIR DISOPROXIL FUMARATO VS. TENOFOVIR ALAFENAMIDO

5 A MUDANÇA DA EPIDEMIOLOGIA DA DOENÇA RENAL ASSOCIADA AO VIH

Nos últimos 30 anos

TERAPÊUTICA ANTI-RETROVIRAL »»» AUMENTO DA ESPERANÇA MÉDIA DE VIDA



Nos últimos 30 anos

TERAPÊUTICA ANTI-RETROVIRAL »»» AUMENTO DA ESPERANÇA MÉDIA DE VIDA

↓ de HIVAN

↑ GESF não colapsantes »»
evolução sub-aguda/ crónica

↑ HIVICK

↑ Síndrome metabólica

↑ Diabetes Mellitus

↑ HTA

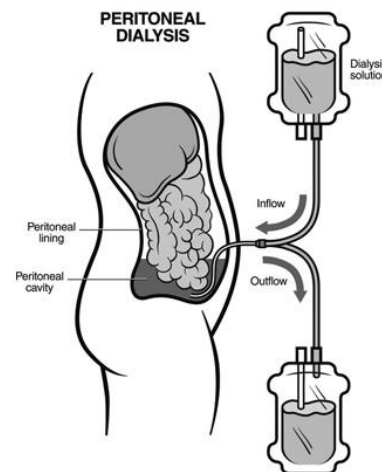
Nefropatia associada TARV

↑ Doença Renal Crónica

Nos últimos 30 anos

TERAPÊUTICA ANTI-RETROVIRAL »»» AUMENTO DA ESPERANÇA MÉDIA DE VIDA

- Maior incidência de DRC terminal a necessitar de terapêutica de substituição da função renal (TSFR).
- VIH não é contra-indicação para nenhuma das modalidades de TSFR.
- Sobrevida da população VIH ~ população em geral sob diálise.



EM SUMA ...

- ✓ Infecção VIH tornou-se numa doença crónica com o advento da TARV.
- ✓ Maior e melhor expectativa de vida, mas aumento das co-morbilidades.
- ✓ Mudança do padrão da doença renal associadas ao VIH.
- ✓ A doença renal é frequente nos doentes VIH, pelo que a monitorização e triagem regular está recomendada.

OBRIGADA!

Table 1. Possible renal effects of novel ARV drugs

ARV drug	Renal effect
Raltegravir	Inhibition of tubular secretion of serum creatinine by organic cation transporters Rhabdomyolysis Possible reduction in true GFR
Elvitegravir	None reported
Dolutegravir	Inhibition of tubular secretion of serum creatinine by organic cation transporters
Cobicistat	Inhibition of tubular secretion of serum creatinine by MATE 1 Increase in serum concentration of TDF with potential risk for enhancement of TDF tubular toxicity if co-administered (not proven)
Tenofovir alafenamide fumarate	No renal toxicity reported
Atazanavir	Renal stones Acute tubular injury (interstitial nephritis)

MATE1, multidrug and toxin extruder protein 1; TDF, tenofovir disoproxil fumarate. Ritonavir (often included in combination therapy as a booster) partially inhibits MATE1 and may therefore increase serum TDF.