HIV ENFEKSİYONU İLE İLİŞKİLİ BÖBREK TUTULUMU

Dr. Nurgül Ceran

OLGU 1

50 yaşında erkek hasta

Ateş yüksekliği,

bulantı, kusma,

kanlı idrar yakınmalarıyla acil servise getirildi

Acil serviste yapılan tetkiklerde

Lökosit:20000/mm^3 , Kreatin: 4.57mg/dl (GFR:15 ml/dk),

Yapılan USG'de: Renal parankim ekojenitesi Grade 2 diffüz artmış

OLGU 1

Hasta ***ARY ve Pyelonefrit*** ön tanıları ile dahiliye kliniğine yatırılmış

OLGU 1

Yatış sonrası ayrıntılı sorgulamasında yakınmalarının 20 gündür devam ettiği öğrenildi.

Bu süre içinde başka bir merkeze başvurduğu, orada da kreatinin değerinin yüksek olduğu söylenmiş.

Hastalık öncesi oral alımında azalma, analjezik kullanımı, bitkisel ilaç kullanımı anamnezi yok.

Özgeçmişinde astım tanısı dışında özellik yok. Düzenli olarak aldığı ilaç yok

OLGU 1

Fizik Muayenede:

Genel durum orta, bilinç açık, koopere, oryante

Ateş: 37.8°C, NDS: 85/dk, TA: 110/70 mmHg,

Solunum sistemi muayenesinde ekspiryumda uzama dışında patolojik bulgu yok

OLGU 1

Kalp sesleri ritmik, ek ses, sufl yok

Batı rahat, barsak sesleri normoaktif, organomegali yok

Kostovertebral açı hassasiyeti +/+

Pretibial ödem yok

Patolojik LAP yok

OLGU 1

Hastanın idrar ve kan kültürü alındıktan sonra Seftriakson 1*2 gr/gün IV dozda başlanmış

Üriner USG'de: Parankim ekojenitesi Grade 2 artmış. Kortikomedüller ayrım net olarak yapılabilmekte, kalkül, kitle, pelvikaliektazi izlenmedi. Mesane dolumu homojen

OLGU 1

TİT: 80 eritrosit, 2 lökosit, 4+proteinüri

24 saatlik idrarda protein: 1. 2 g/gün

GFR: 9ml/dk

OLGU 1

Nefroloji konsültasyonu sonucu: Kontrastsız Batın BT, KRY açısından tetkiki önerildi

Proteinüri saptanması sonrası nefroloji uzmanınca renal biyopsi planlanması, biyopsi öncesi 3 gün hemodialize alınması önerildi

OLGU 1

Hemodializ öncesi istenen rutin testlerde AntiHIV pozitif bulundu, HBsAg ve AHCV: Negatif

PPD: 10mm,

İdrarda ARB: Negatif,

CMV DNA: Negatif

OLGU 1

Hasta 9. gün AntiHIV pozitifliği sonrası Enfeksiyon hastalıkları Kliniğine nakledildi

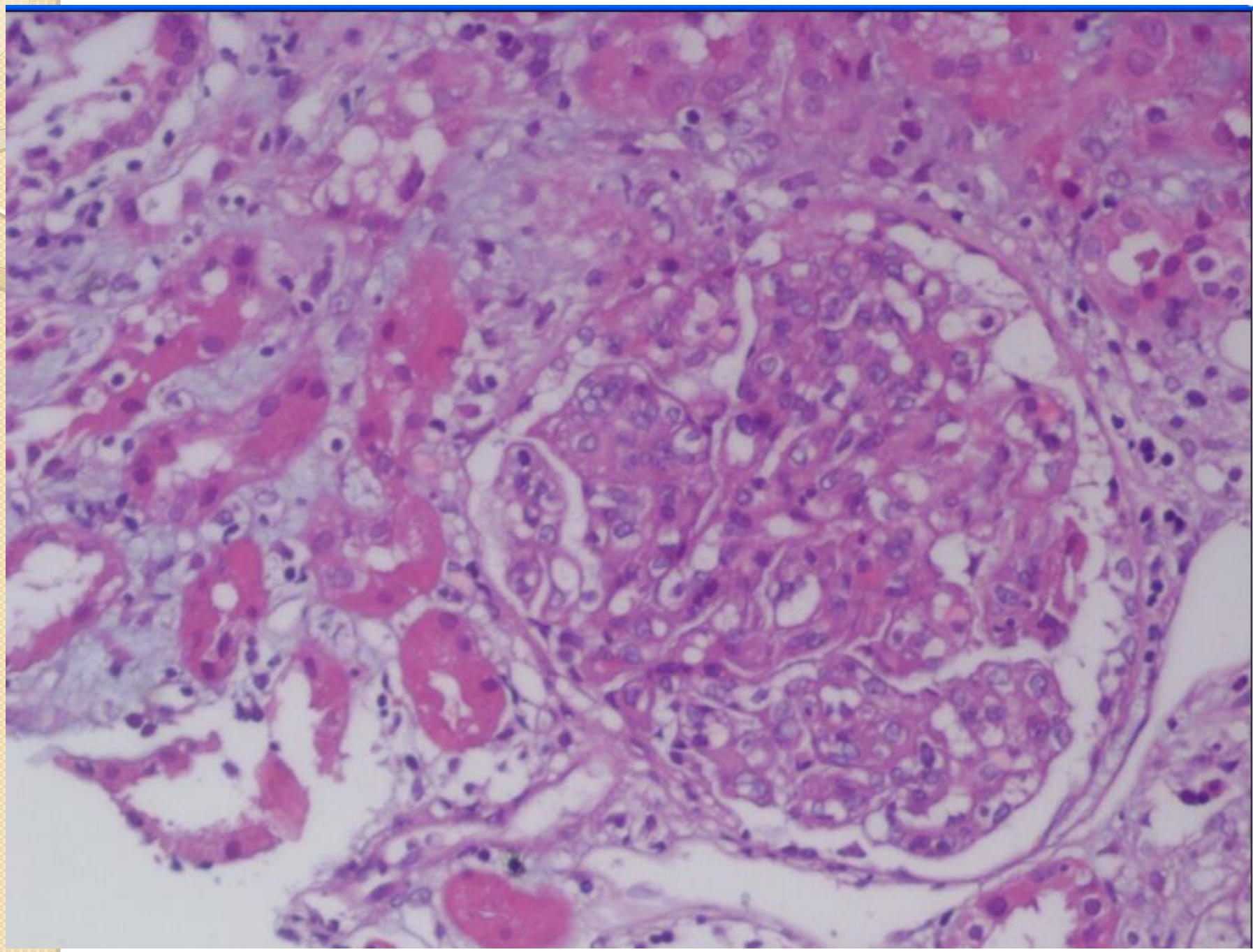
Hastanın son bir yılda 10-15 kilo kaybı olduğu öğrenildi

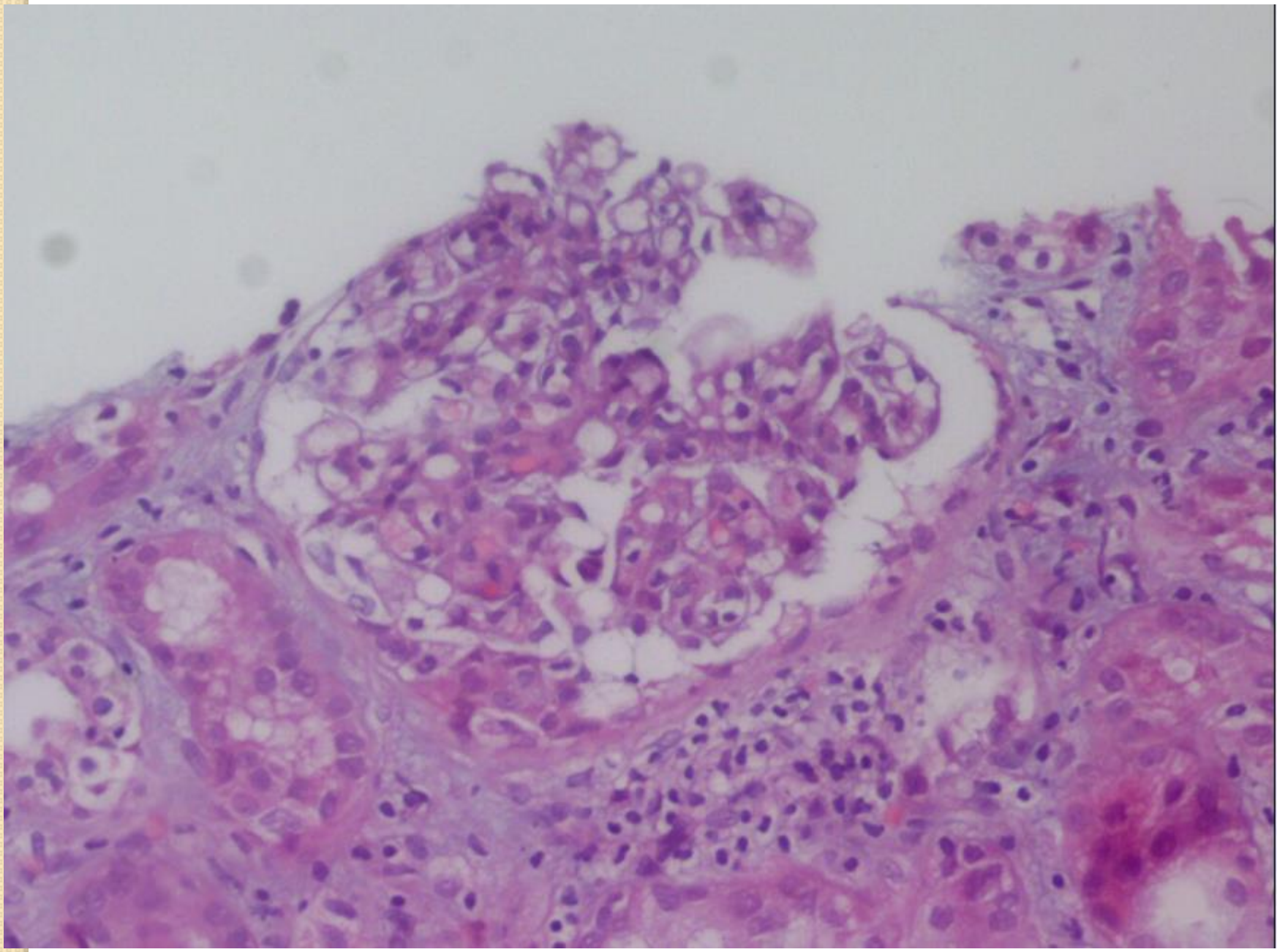
OLGU 1

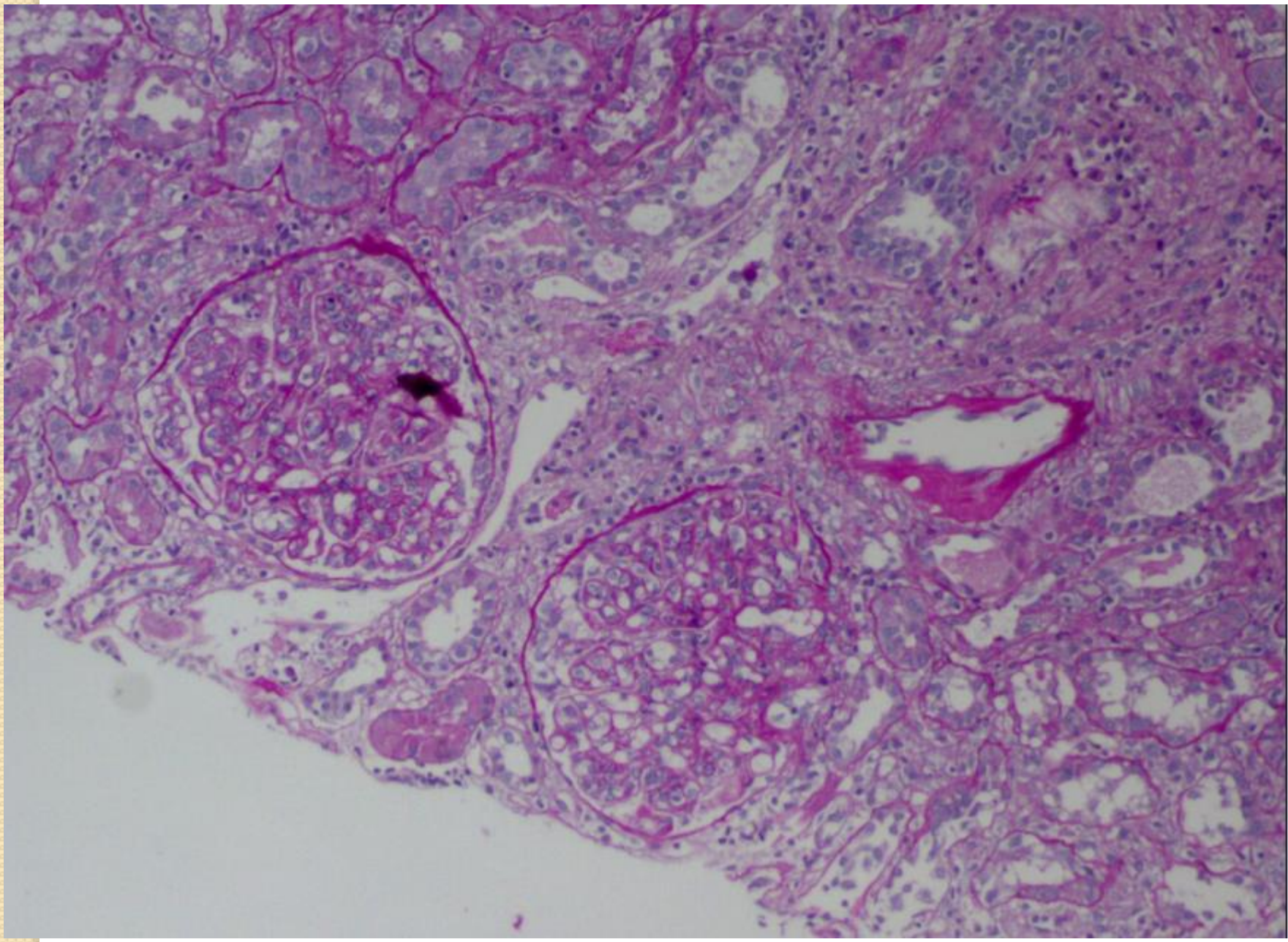
HIV RNA:1 487 636 IU/ml, (670000 kop/ml)

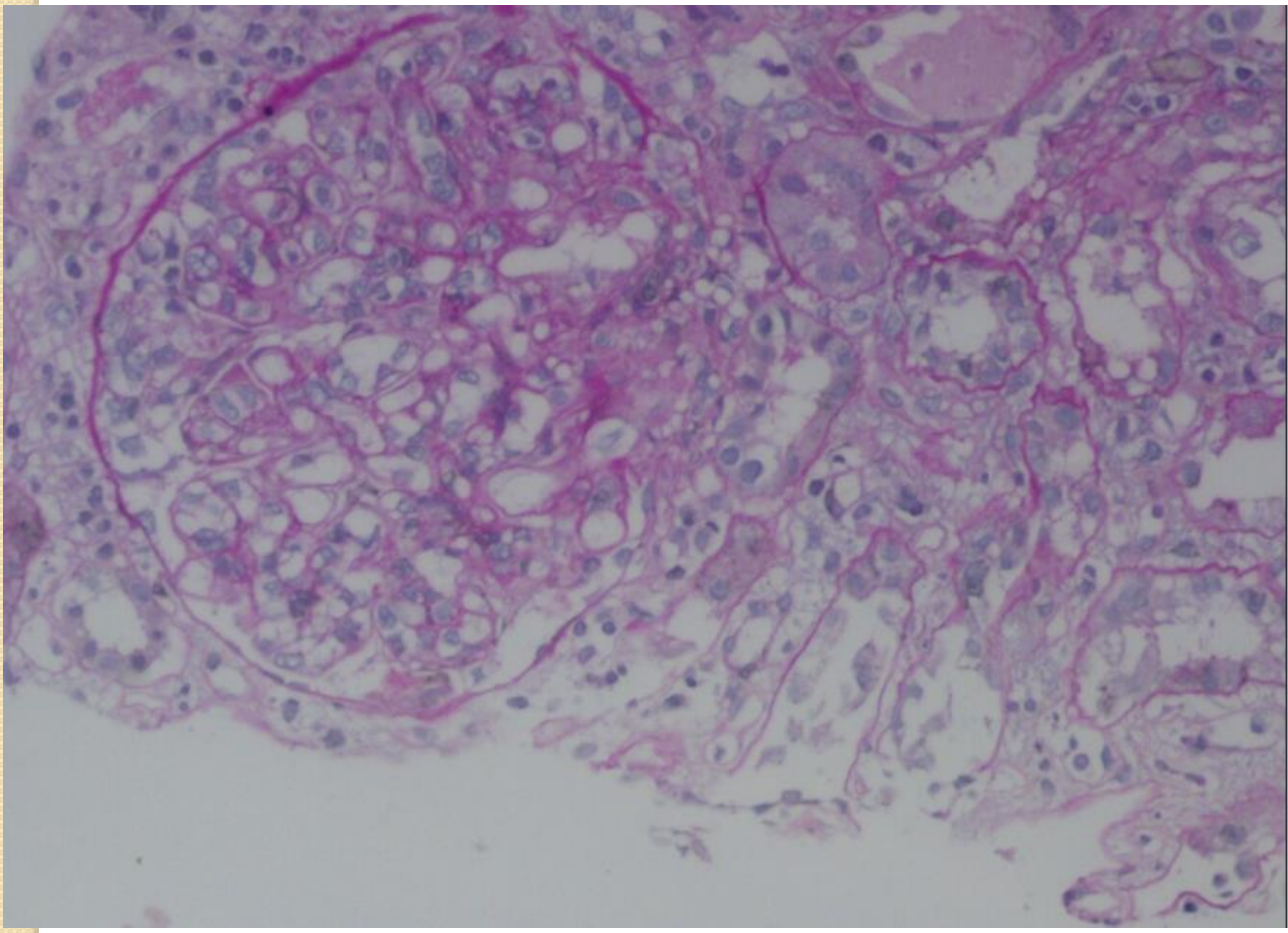
CD4: 227 mm^3

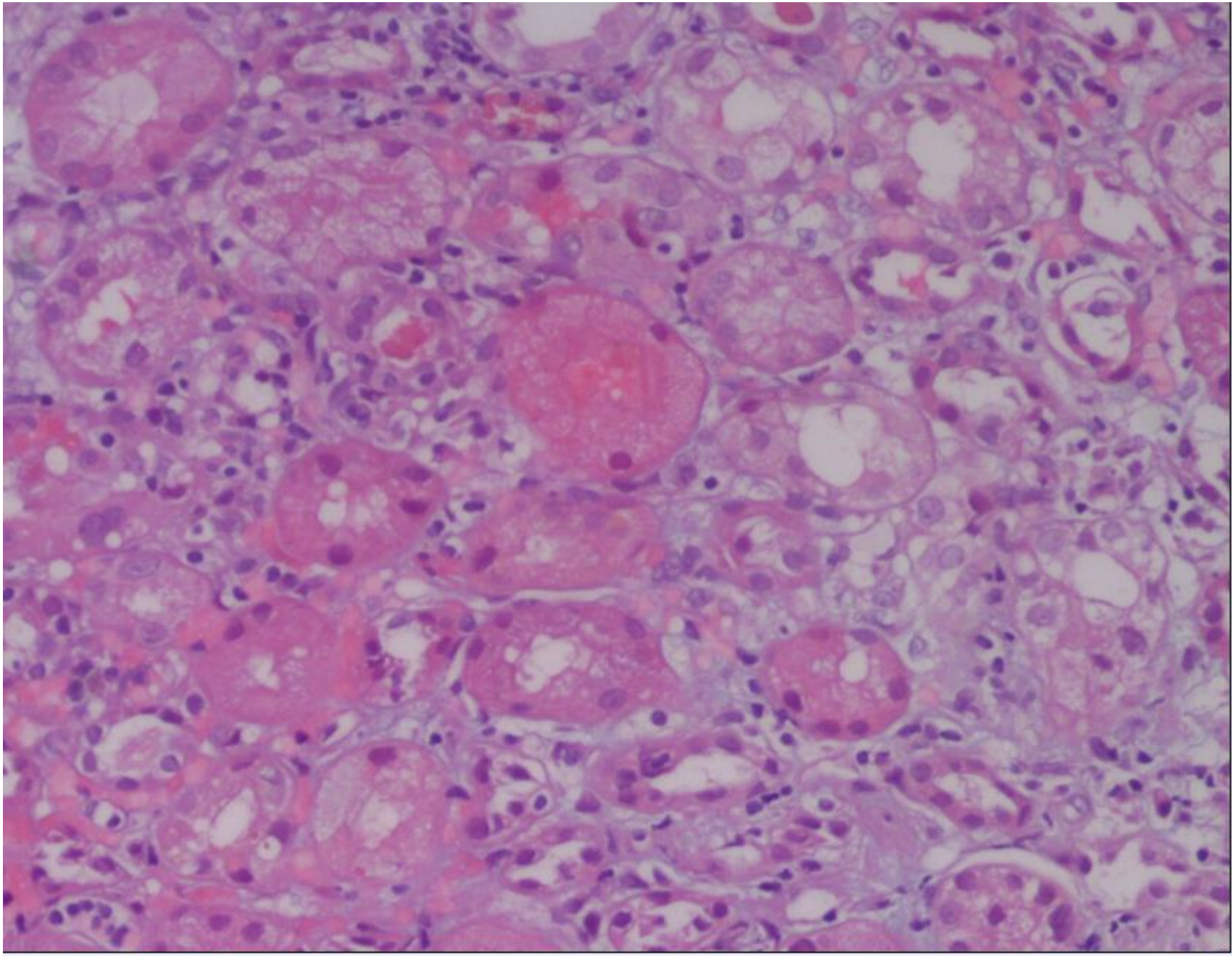
Hasta haftada 3 gün HD'e devam etti.
Yatışının 13. gününde böbrek biopsisi yapıldı.

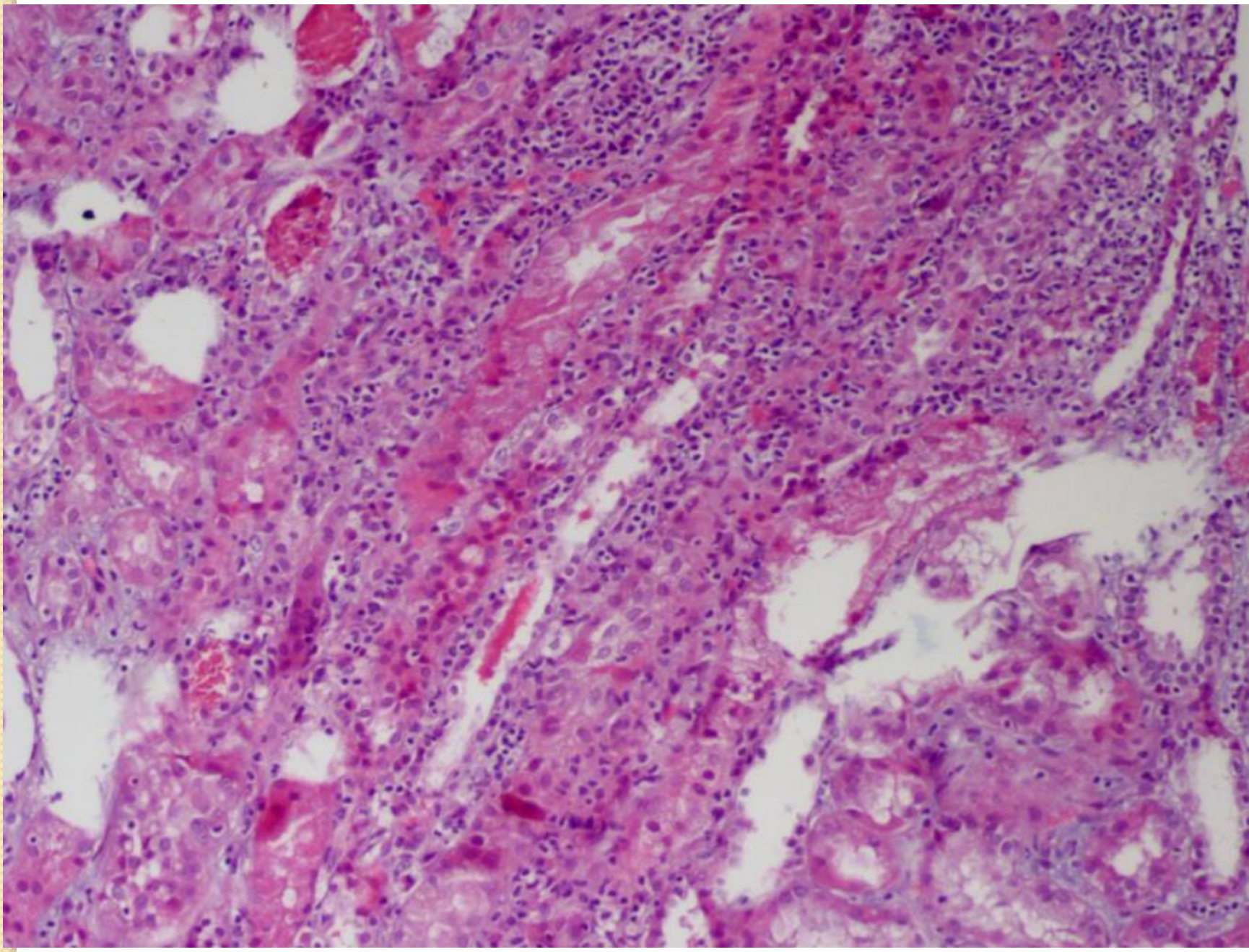


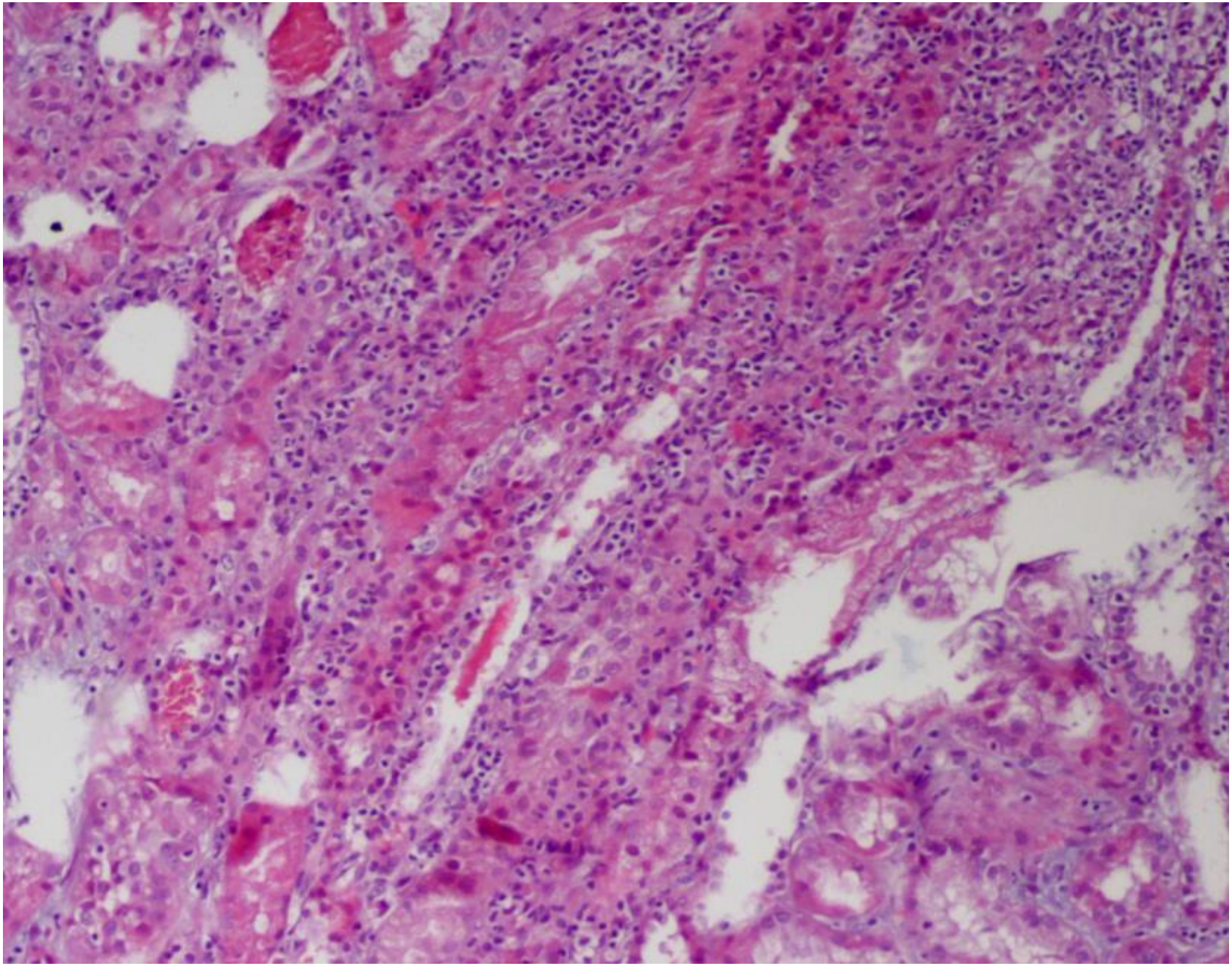


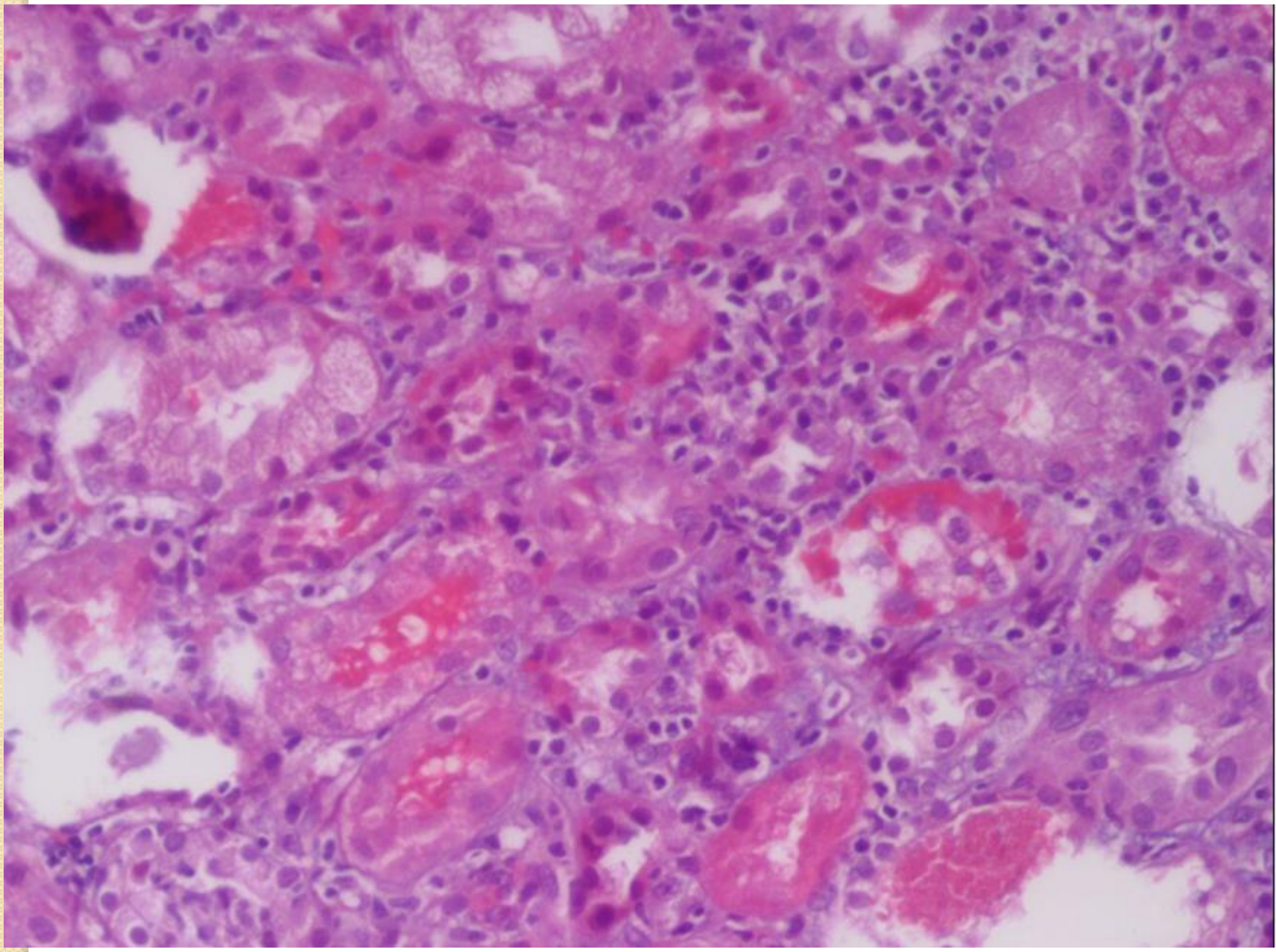


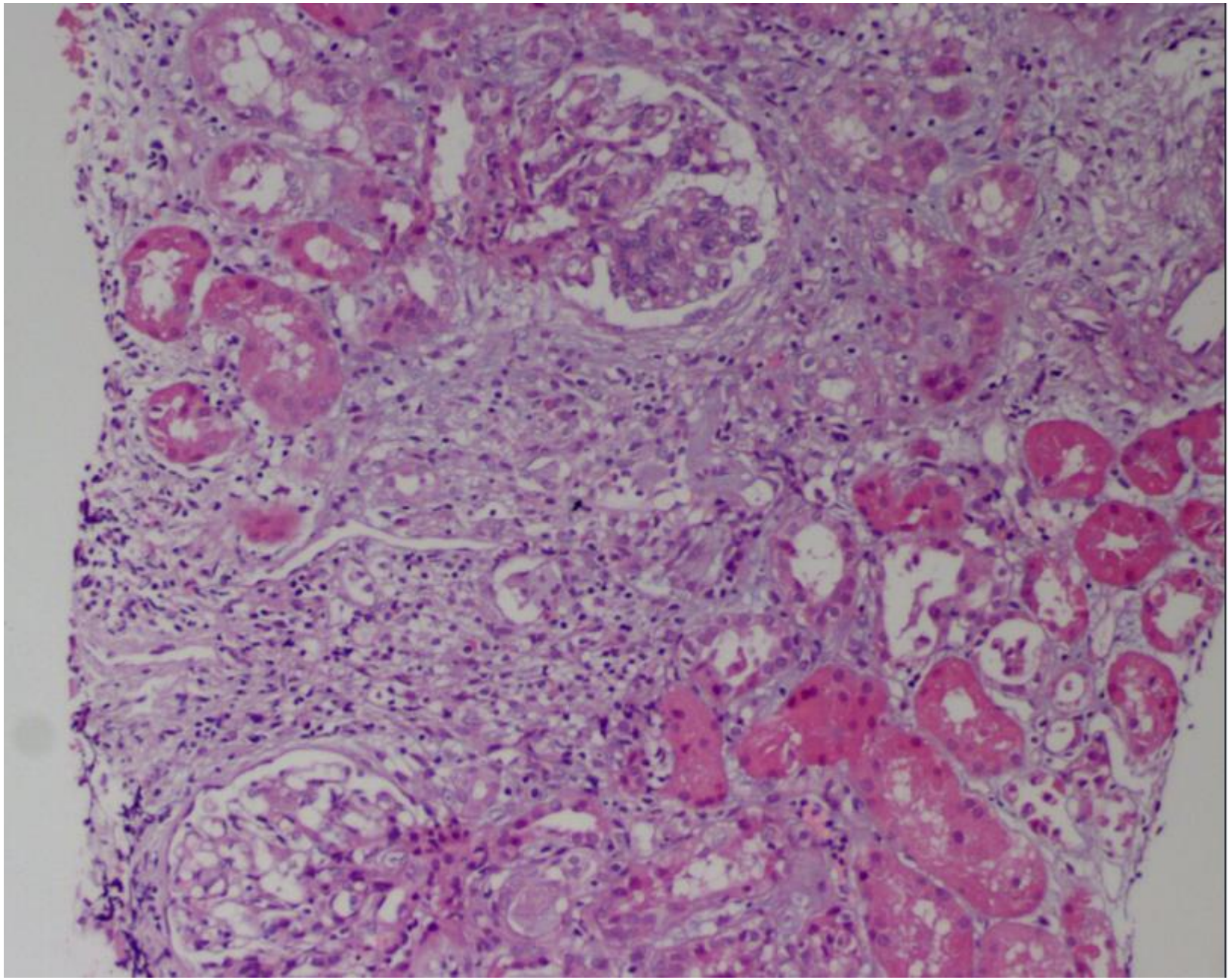


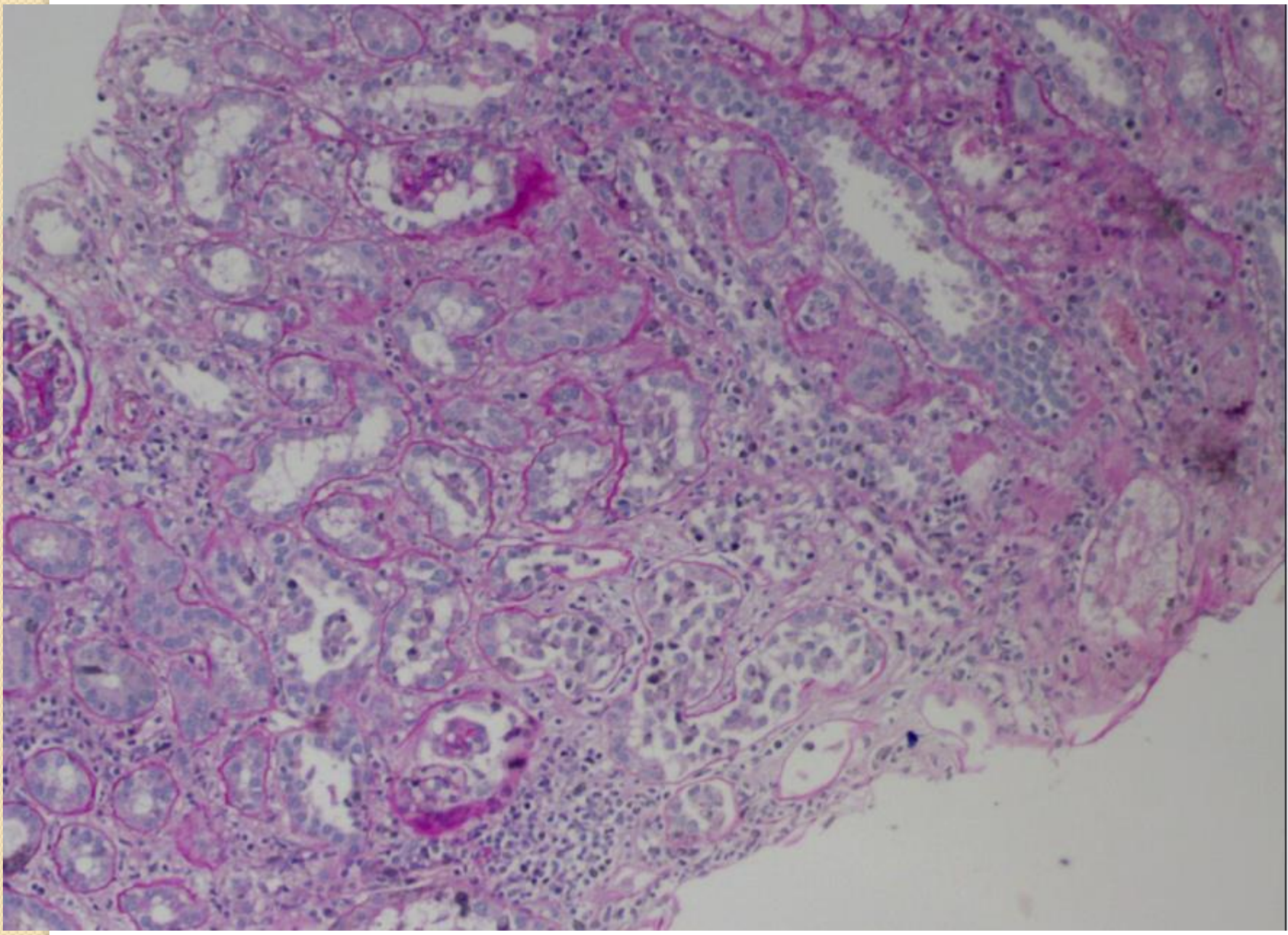


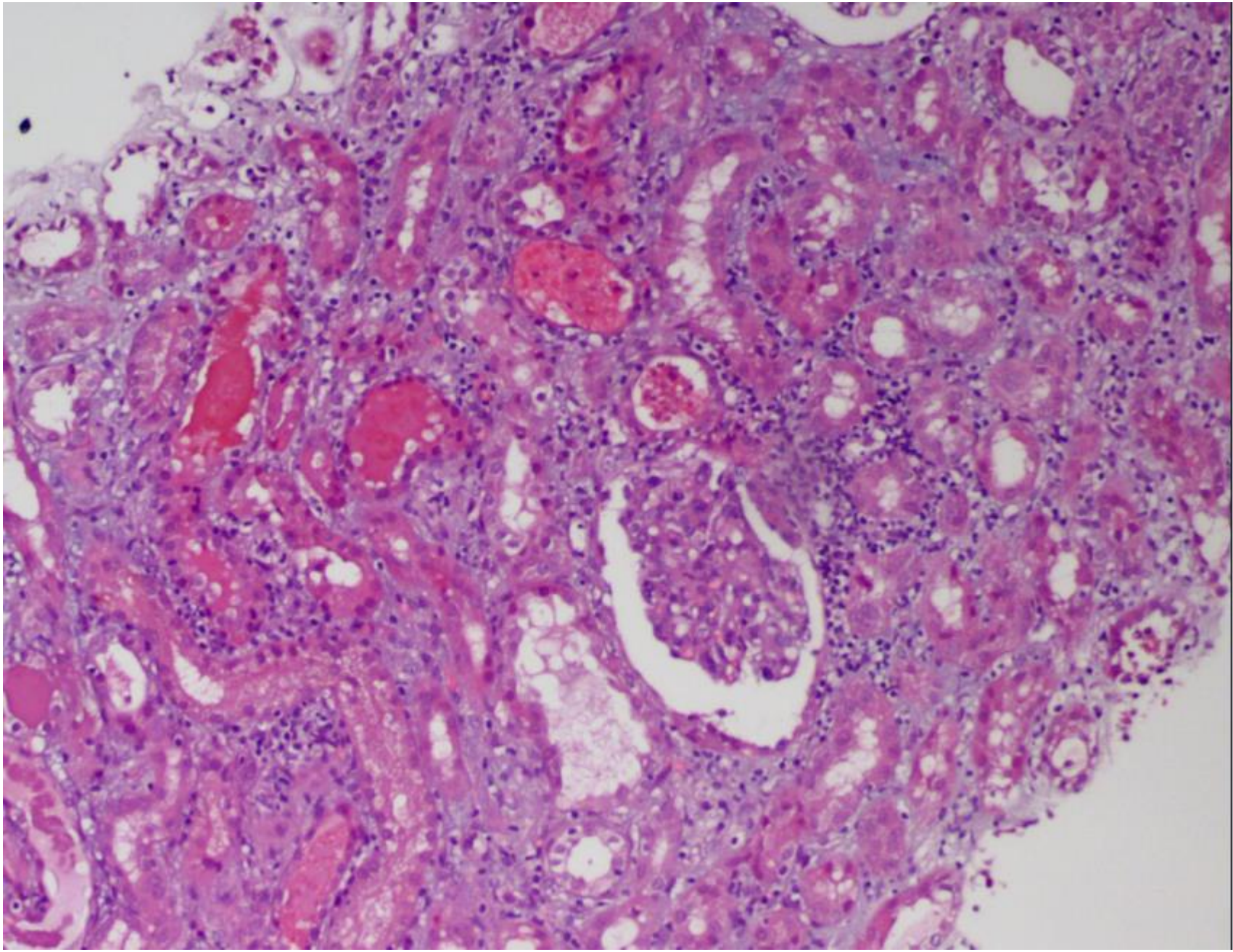












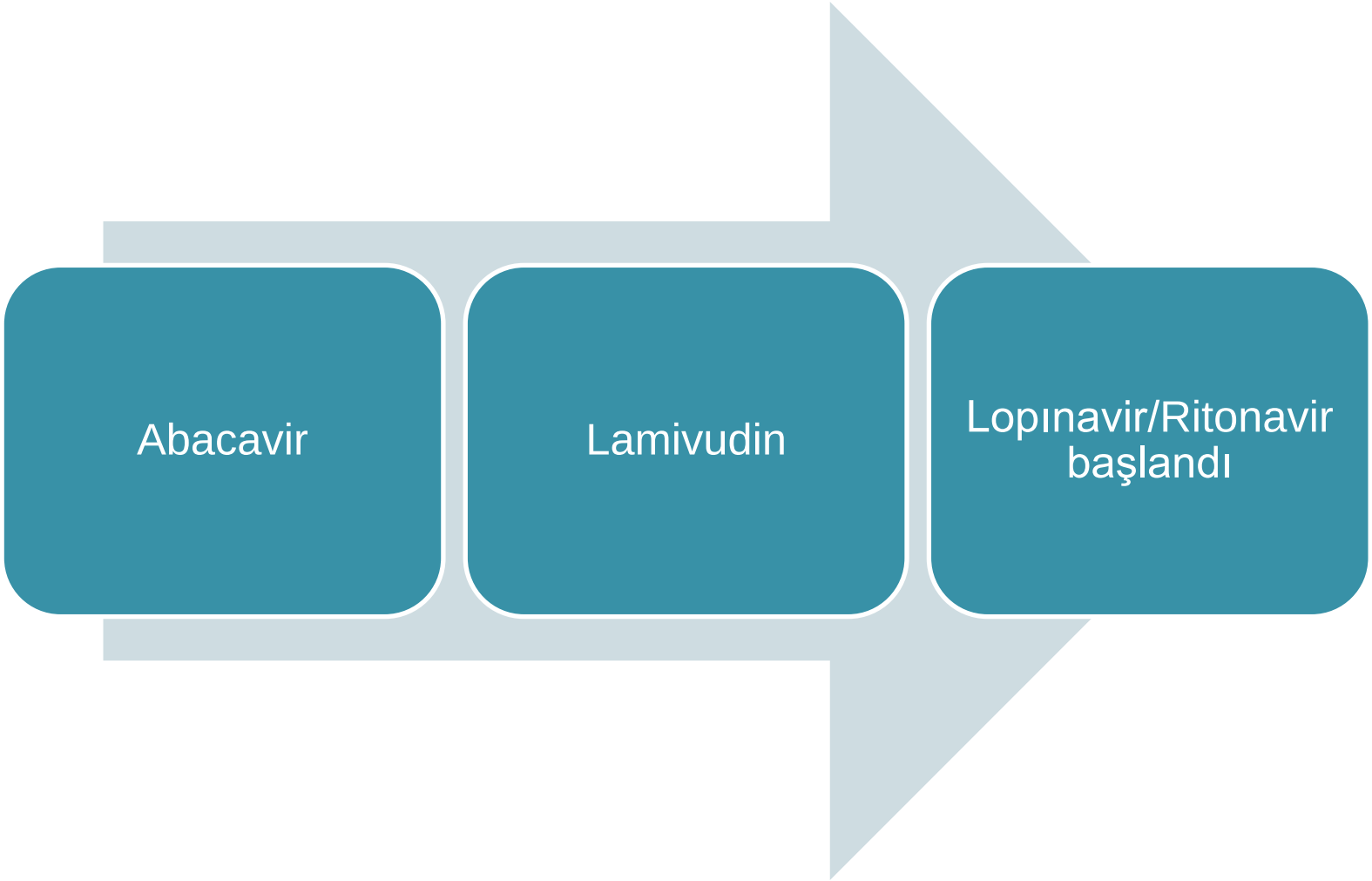
Histopatolojik Rapor

- Glomerüllerde endokapiller hücre proliferasyonu
- 3 glomerülde küçük selüler kresent
- Tübüler zedelenme
- Mikst interstisyel inflamasyon

Histopatolojik Rapor

Glomerül ve tubulointerstisyel değişiklikler , spesifik olmamakla birlikte HIV ile İlişkili nefropati – HIVAN- ile uyumludur

OLGU 1



OLGU 1

Lopınavir/Ritonavir

Raltegravir

OLGU 1

Hasta haftada 2 gün hemodializ programına devam etmesi

1mg/kg prednisolon tedavisinin bir ay daha devamı

ART tedavilerinin devamı önerildi

OLGU 1

Hastanın son durumu: Hasta 1.5 yıldır takipte

Hasta, ART tedavi başlandıktan 3 ay sonra kreatin değeri: 1.25, GFR:65 ml/dk

Tedavinin 5. ayında kreatin değeri: 0.97, GFR:87 ml/dk

Halen: Kreatin 0.92 mg/dl, GFR: 93ml/dk

HIV RNA: Negatif

Tarih	Kreatin	GFR	CD4 (%)	HIV RNA
20.05.2015	4.77	9.31 ml/dk		
28.05 2015	3.74	18 ml/dk	227(15.8)	1 487 636
25.06.2015	4.66	14 ml/dk		
29.06.2015	5.71	11 ml/dk		
02.07.2015	5.09	13 ml/dk		
06.07.2015	5.21	13 ml/dk		
23.07.2015	1.75	44 ml/dk	399(25.3)	5177
07.09.2015	1.25	65 ml/dk		
09.11.2015	0.97	87 ml/dk	854 (32.6)	Negatif
10.02.2016	1.05	79 ml/dk		
04.04.2016	1.09	76 ml/dk	725(25.8)	<100
31.08.2016	0.91	94 ml/dk	765 (30.5)	<100
22.11.2016	0.92	93 ml/dk	1002(34)	Negatif


Aybilgi.net

OLGU 2

86 yaşında erkek hasta

12 yıldır(1999 yılından beri) HIV pozitifliği nedeniyle kliniğimiz takibinde

12 yıl önce ilk başvurduğu sırada klinik bulgu yok,

OLGU 2

HIV RNA: 350 000 kop/ml, CD4:180mm^3

12 yıl süresince hiç hospitalize edilmedi

Fırsatçı enfeksiyon atağı olmadı, düzenli poliklinik takiplerine geldi

OLGU 2

Tedavinin başlangıcında zidovudin + lamivudin + ritonavir,

Zidovudin +lamivudin + indinavir,

Tenofovir/emtricitabin + indinavir tedavileri aldı

Tenofovir/emtricitabin+Lopinavir/Rit. (İndinavir tedavisinin 6. yılından sonra kan şekerinde yükselme gözlendiği için İndinavir tedavisi Lopınavir/Ritonavir ile değiştirildi.)

OLGU 2

3 aylık aralarla poliklinik takibi ve rutin tetkikleri yapıldı

2 yıl sonra (2013 yılında) poliklinik kontrolünde kreatin değeri 4 mg/dl saptandı (3 ay önceki kontrolde 1.07 mg/dl, GFR:70 ml/dk)

OLGU 2

Renal yetersizliğe neden olabilecek tanılar gözden geçirildi.

Batın USG, Batın BT, TİT, idrar kültürü, idrarda ARB

USG: Renal parankim ekojenitesi hafif artkın. Renal parankimal hastalık

OLGU 2

Hastada ilaca bağlı nefrotoksisite düşünüldü.

Tenofovir/Emtricitabin tedavisi kesildi.

Lamivudin + zidovudin + Lop/R tedavisi doz ayarlayarak devam edildi.

OLGU 2

Kretain değeri 4 ay sonunda 2.59 mg/dl

Raltegravir tedavisi kullanıma girince(2013 yılında) tedavi Lop/R + Raltegravir olarak devam etti

OLGU 2

- Hastada kreatin değeri 2-2.3(GFR: 29-34 ml/dk), arasında değişti.
- Elektrolit değerleri normal
- İdrar volümü normal
- Düzenli takip dışında aldığı ilaç yok
- İlaca bağlı nefrotoksisite ve KRY


Aybilginet

OLGU 3

50 yaşında erkek hasta

İşe giriş taraması sırasında AntiHIV pozitifliği saptanmış

Bilinen DM'u var oral antidiabetik kullanıyor

OLGU 3

Anamnezinde ateş, kilo kaybı, ishal yok

Şiddetli kuru öksürükten yakınıyor

OLGU 3

- HIV RNA: 255 000 IU/ml, (114000 kop/ml)
- CD4: 229 mm^3 ,
- HBA1C: 9.9,
- Kan şekeri: 354 mg/dl
- PPD:10 mm,
- Akciğer grafisinde hiluslar dolgun

OLGU 3

- Toraks BT'de parankimal lezyon saptanmadı.
- TİT: Özellik yok
- Göz muayenesinde patoloji yok
- INH proflaksisi başlandı
- Tenofovir/emt + Dolutegravir tedavisi başlandı

OLGU 3

Tedavinin 1. ayı sonunda HIV RNA<100 IU/ml, rutin biyokimyaları normal bulundu

Tedavinin 3. ayında rutin kontrol sırasında Kreatin: 3.44 mg/dl saptandı

OLGU 3

Nefroloji konsültasyonu istendi

Tedavisi Lop/Rit + Raltegravir olarak değiştirildi

Nefroloji tarafından yapılan tetkiklerde patoloji aydınlatılamadı. Böbrek biopsisi önerildi. Hasta bugüne kadar biyopsi yapılmasını kabul etmedi

Halen kreatin düzeyi 2.31 mg/dl

OLGU 3

Tarih	Kreatin	GFR	HIV RNA	CD4 (%)
18.5.2016	0.99	85 ml/dk	1 017 000	229(11.9)
19.07.2016	1.04	80 ml/dk	350	255(16.4)
18.09.2016	3.44	20 ml/dk		
17.10	3.11	23 ml/dk	<100	256(18.3)
27.12	2.66	27 ml/dk		
01.02.	2.31	32 ml/dk	Negatif	336(17)

OLGU 3

Hastada ilac toksisitesine bağlı gelişen Akut böbrek hasarı düşünüldü

Risk faktörü: Diabet

HIV İle İlişkili Böbrek Hastalıkları

- HIV pozitif hastalarda hem akut hem de kronik böbrek hastalığı riski vardır
- İlaçlara bağlı nefrotoksisite
- HIV ile ilişkili nefropati (HIVAN)
- İmmun kompleks böbrek hastalığı
- Trombotik mikroanjiopati

Kidney Disease in HIV

HIV İNFEKSİYONUNDA RENAL HASTALIKLAR

- 77 Renal biyopsi (1999-2003) (John Hopkins, USA)
  (%89 Afrika kökenli)
- HIVAN %40
- FS(non-collapsing)GN %17
- İmmun kompleks GN %34
- İnterstisyel nefrit %5
- Trombotik MA %1
- Amiloidozis %1
- Hypertansif nefropati %1

Haas et al, Kidney Int 67:1381(2005)

- 99 Renal biyopsi 2003-2004 (Baragwanath Hospital, South Africa)
- HIVAN %27
- FS(non-collapsing)GN %3
- İmmun kompleks GN %34
- Membranöz GN %13
- Post-infesiyöz/IgA GN %13
- Diğer GN %15
- Diğer %10

Gerntholtz et al, Kidney Int 69: 1885 (2006)

HIV ve Akut Böbrek Hasarı

- HIV ile enfekte kişilerde daha yaygındır
- Advers sonuçlarla ilişkilidir
- Etyoloji

-Sepsis ARY için en belirgin risk faktörü olarak kalmıştır

-ARY ile ilişkili diğer faktörler DM, HTN, KRY, KC hastalığı

Nadkarni et al, JAIDS 2015

Acute Kidney Injury (AKI) in HIV

- More common in HIV patients
  - OR 2.8 in hospitalized patients*
- Associated with increased mortality
  - OR 5.8 in hospitalized patients*
- Risk factors: chronic kidney disease (CKD), advanced HIV, hepatitis C co-infection

Franceschini *et al*. KI 2005
Wyatt *et al*. AIDS 2006*
Roe *et al*. CID 2008

Common Causes of AKI in HIV

- Infection (52%)
  - 76% AIDS-defining
- Drugs (32%)
  - Antibiotics
  - ARV (indinavir & tenofovir)
  - NSAIDS, radiocontrast, lithium
- Liver Failure (10%)
  - 90% Hepatitis C

Franceschini *et al*. KI 2005

Table 2. Univariate and multivariable analysis for factors associated with acute renal failure.

	Crude IRR (95% CI)	P	Adjusted IRR (95% CI)	P
Characteristics				
Age at HIV diagnosis (per 10 year older)	1.47 (1.28–1.70)	<0.001	1.04 (0.87–1.24)	0.66
Sex				
Male	1			
Female	0.81 (0.59–1.11)	0.20	Excluded	
Ethnicity				
White/other	1			
Black	1.30 (0.96–1.77)	0.10	Excluded	
HIV acquisition				
Heterosexual	1		1	
IVDU	2.80 (1.76–4.46)	<0.001	1.50 (0.75–2.91)	0.26
MSM	0.74 (0.48–1.14)	0.17	1.03 (0.66–1.61)	0.89
AIDS diagnosis				
Yes	19.78 (13.40–29.21)	<0.001	Excluded	
Hepatitis B coinfection				
Yes	1.91 (1.15–3.17)	0.01	1.09 (0.50–2.42)	0.83
Hepatitis C coinfection				
Yes	1.81 (1.17, 2.80)	0.01	1.36 (0.76, 2.44)	0.31
cART exposure status (time-updated)				
No cART	1		1	
Indinavir-containing cART	7.37 (3.18–17.06)	<0.001	1.81 (0.53–6.76)	0.32
Tenofovir-containing cART	1.01 (0.61–1.66)	0.97	1.06 (0.46–2.43)	0.89
Atazanavir-containing cART	1.27 (0.32–5.01)	0.74	1.05 (0.20–5.49)	0.96
cART not containing indinavir, tenofovir or atazanavir	1.41 (0.76–1.72)	0.53	1.11 (0.54–2.30)	0.78
Latest CD4 cell counts (cells/μl) (time-updated)				
>350	1		1	
201–350	1.84 (1.23–2.75)	0.01	1.56 (0.97–2.48)	0.07
101–200	4.54 (2.98–6.93)	<0.001	2.08 (1.11–3.91)	0.02
51–100	9.82 (5.85–16.46)	<0.001	6.38 (3.18–12.78)	<0.001
0–50	19.89 (13.11–30.19)	<0.001	10.29 (5.11–20.98)	<0.001
Latest updated HIV RNA (copies/ml) (time-updated)				
<400	1			
>400	1.29 (0.97–1.70)	0.08	Excluded	
Latest eGFR (ml/min/1.73 m^2) (time-updated				
≥90			1	
75–89	1.38 (0.90–2.11)	0.13	1.46 (0.86–2.49)	0.16
60–74	4.81 (3.07–7.54)	<0.001	4.19 (2.37–7.42)	<0.001
<60	36.02 (24.45–53.07)	<0.001	27.00 (16.13–44.95)	<0.001

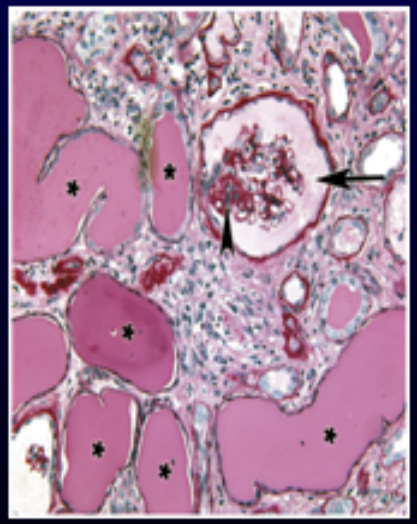
HIVAN

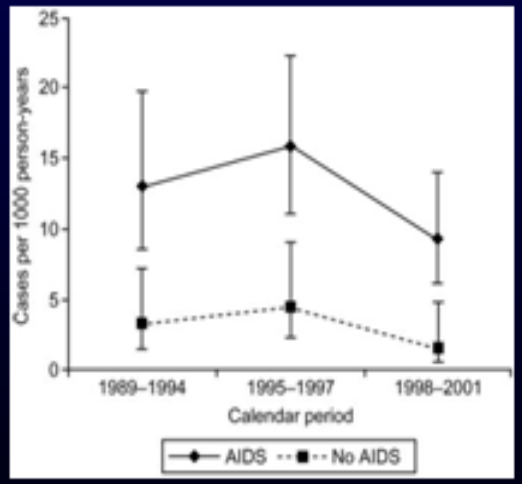
- HIV enfeksiyonu ile ilişkili böbrek hastalığıdır
- AIDS'in bir komplikasyonu olarak 1984 yılında tanımlanmıştır
- Afrika kökenlilerde beyazlara oranla çok daha yüksek oranda görülür
- Renal sendrom progresif renal yetmezlik ve proteinüri ile karakterizedir

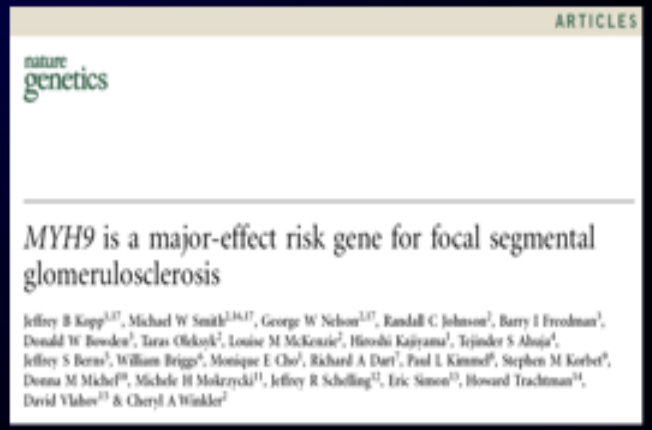
HIV-Associated Nephropathy (HIVAN)

- Black ethnicity
- CD4 <250 cells/μL
- Large, echogenic kidneys
- Heavy proteinuria

Associated Focal and Segmental Glomerulosclerosis in the Acquired Immunodeficiency Syndrome
T. K. Sreepada Rao et al.
N Engl J Med 1984; 310:669-673






ARTICLES

nature genetics

MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis

Jeffrey B Kopp[1,17], Michael W Smith[2,16,17], George W Nelson[3,17], Randall C Johnson[3], Barry I Freedman[3], Donald W Bowden[3], Taras Oleksyk[2], Louise M McKenzie[2], Hiroshi Kajiyama[1], Tejinder S Ahuja[4], Jeffrey S Berns[5], William Briggs[6], Monique E Cho[7], Richard A Dart[7], Paul L Kimmel[8], Stephen M Korbet[9], Donna M Michel[10], Michele H Molkrzycki[11], Jeffrey R Schelling[12], Eric Simon[13], Howard Trachtman[14], David Vlahov[15] & Cheryl A Winkler[2]

AIDS 2004; 18: 541-6, Nat Genet. 2008; 40: 1175-84

HIV/ESRF in UK CHIC

CONCISE COMMUNICATION

Clinical epidemiology of HIV-associated end-stage renal failure in the UK

Loveleen Bansi[a], Amelia Hughes[b], Sanjay Bhagani[c], Nicola E. Mackie[d], Clifford Leen[e], Jeremy Levy[b], Simon Edwards[a], John Connolly[c], Steve G. Holt[f], Bruce M. Hendry[g,h], Caroline Sabin[a], Frank A. Post[g,h], on behalf of the UK CHIC/ESRF study group

AIDS 2009; 23: 2517-21

All patients with permanent RRT in UK CHIC (1998-2007)

- **68 (0.31%) of 21,948 patients had ESRF**

- **Black patients (44)**
  - HIVAN 36
  - Vascular/HPT 1
  - Glomerulonephritis 2
  - Diabetes 2
  - Congenital 2
  - Unknown 1
  - ***Confirmed*** ***57%***

- **White/other patients (24)**
  - Vascular/hypertension7
  - Glomerulonephritis 5
  - Diabetes 4
  - Amyloid 3
  - Congenital 2
  - Unknown 3
  - ***Confirmed*** ***63%***

Patient characteristics (N=21948)			
	ESRF	No ESRF	P-value
N	68	21883	
Yaş, median	36(31-41)	34(30-40)	0.13
Kadın,N(%)	20(29.4)	4707(21.5)	0.13
Afrika köken, N(%)	44(64.7)	5418(24.8)	<0.0001
AIDS tanılı, N(%)	25(38.5)	4902(22.4)	0.005
CD4 sayısı	72(27-157)	179(71-300)	<0.0001
HBV+, N(%)	4(5.9)	1679(7.7)	0.58
HCV+, N(%)	5(7.4)	1594(7.3)	0.98

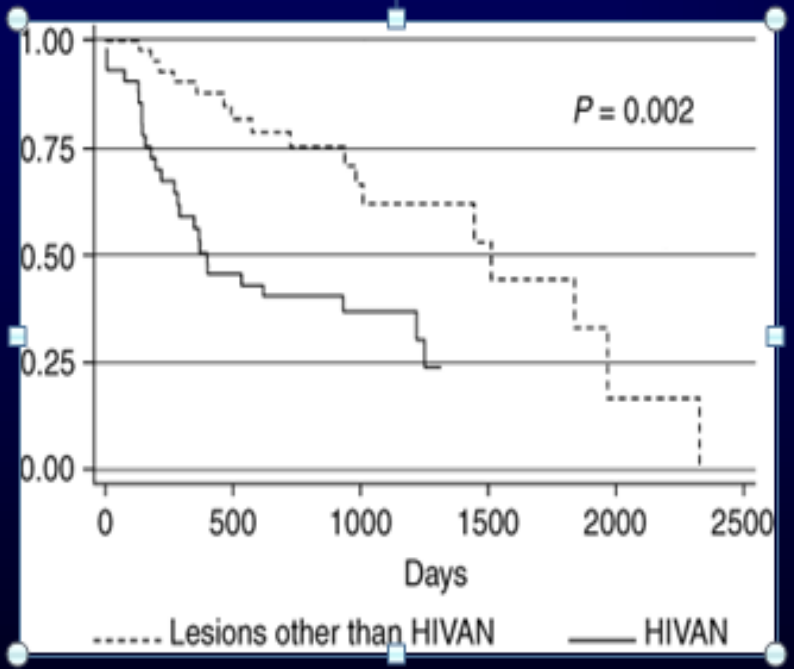
AIDS 2009; 23:2517-21

Characteristics of those with ESRF by HIVAN status(N=65)			
	HIVAN	Diğer	P-value
N	35	30	-
Yaş, median	**35(29, 39)**	**42(37, 48)**	**0.001**
Kadın, N(%)	**15 (42.9)**	**4 (13.3)**	**0.01**
Afrika Köken, N(%)	**35 (100)**	**7(23.3)**	**<0.0001**
AIDS tanısı, N(%)	**16 (45.7)**	**9 (30)**	**<0.0001**
CD4 sayısı, median	70(29-144)	72 (25-190)	0.67
HBV +, N(%)	2(5.7)	2(6.7)	0.87
HCV+, N(%)	1(2.9)	4(13.3)	0.11
Başlangıç GFR(ml/dk)	**11**	**50**	**0.01**
HIV süresi- RRT	196(0-1035)	2171(1574-3668)	<0.0001

AIDS 2009; 23:2517-21

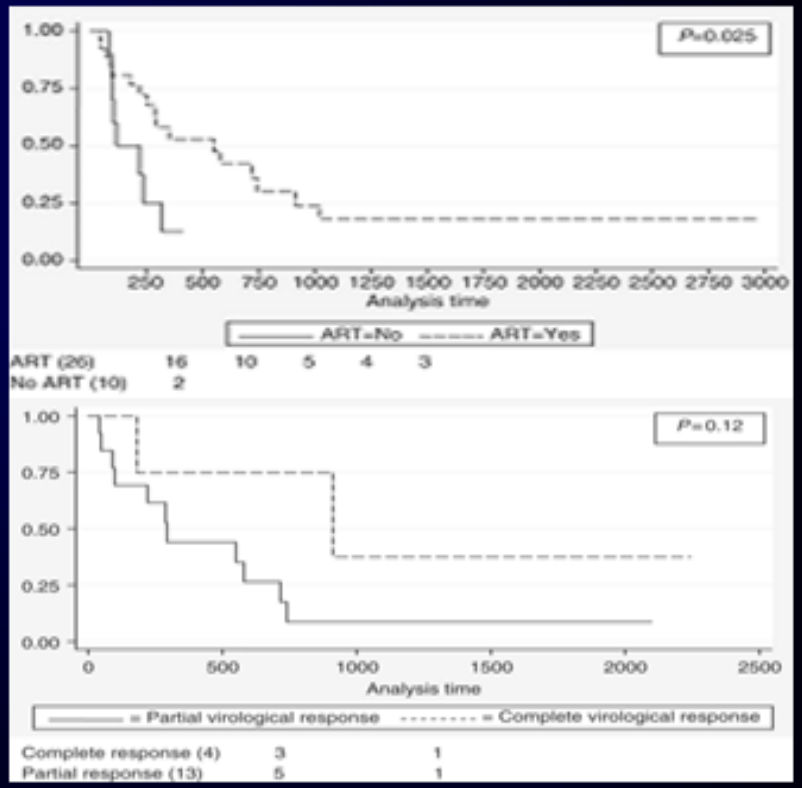
Natural History of HIVAN

- Cohort of 42 patients with HIVAN and 47 patients with renal diseases other than HIVAN



- Use of HAART associated with slower progression to RRT

- Cohort of 36 patients with HIVAN



- Complete suppression of HIV replication may slow progression to RRT

Kidney Int 66: 1145 (2004)

Nephrol Dial Transplant 2006; 21: 2809

PATOGENEZ

- HIV ile böbrek epitel hücrelerinin enfeksiyonudur
- Enfekte böbrek hücreleri içinde HIV genleri bulunur. Transgenik fare modelinde bazı HIV genleri özellikle Nef ve Vpr'nin patogenezde rolü olduğu düşünülür
- Genetik duyarlılığı içeren konak faktörleri. Afrika kökenlierde 12 kat daha sık tutulum (APOL 1 geninde HIVAN riskinde artmayla ilişkili tek nükleotid polimorfizmi saptanmış)

EPİDEMİYOLOJİ

- Etkin ART'lerin tedavide kullanılmasıyla HIVAN'a bağlı son evre böbrek hastalıklarının insidansı azalmıştır
- Biyopsiyle doğrulanmış HIVAN oranı 1997'de %80 iken 2004 yılında %30'a gerilemiştir

Am J Neph 2008;28:478

KLİNİK BULGULAR

- Afrika kökenliler (>%90)
- İlerlemiş HIV hastalığı
- Ağır proteinüri (Ortalama 4.1 g/gün, %14'ü <1.5 gr/gün, mikroalbuminüri de olabilir)
- Böbrek fonksiyonlarında hızlı bozulma (ortalama GFR 10 ve 20 ml/dk)
- Hematüri (%45-75)
- Hipertansiyon (%12-26)
- Ödem (%22-59)

TANI

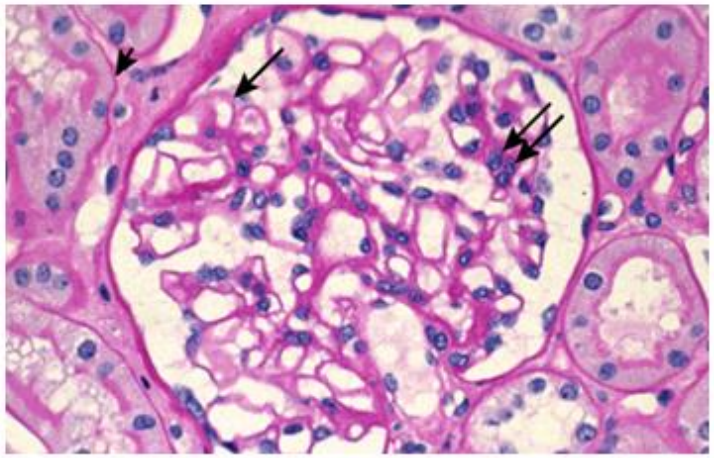
- Klinik bulgular HIVAN'ı düşündürüyorsa tanı böbrek biyopsi ile olmalıdır
- HIVAN düşünülen hastaların %40'ında alternatif tanılar saptanır

Semin Nephrol 1998; 18:406

HİSTOLOJİK BULGULAR

- Kollapsing fokal segmental glomeruloskleroz karakteristiktir
- Tubüllerde dilatasyon
- Yoğun intestisyel inflamasyon
- Tubuloretiküler inklüzyonlar

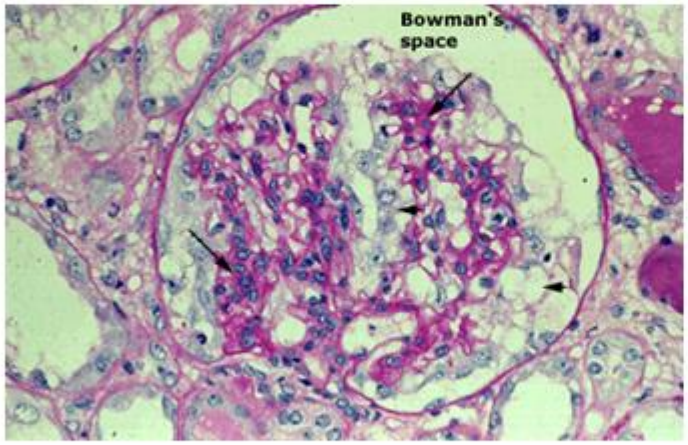
HİSTOPATOLOJİK BULGULAR



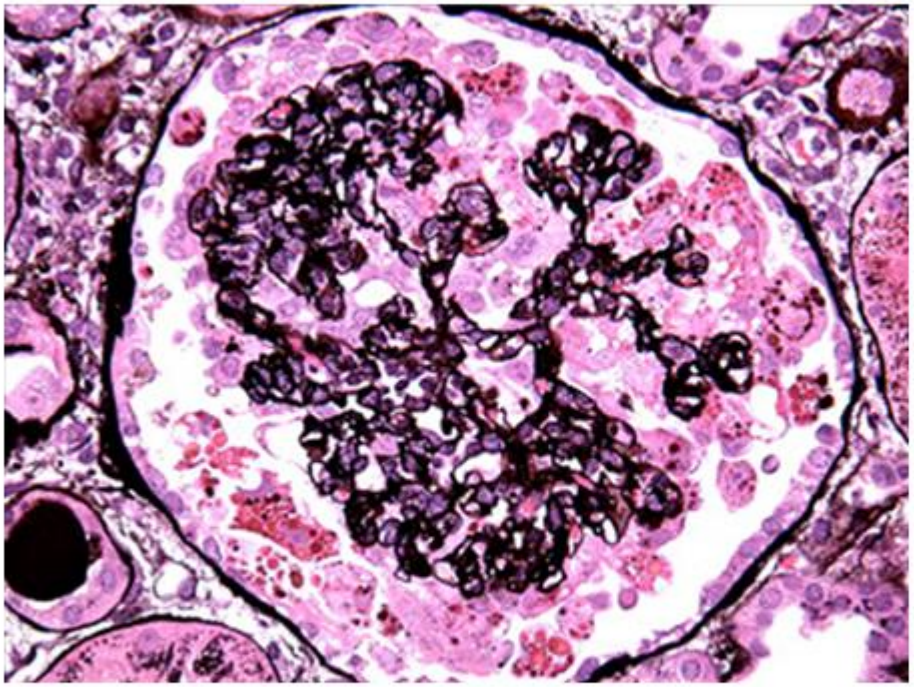
Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

HİSTOPATOLOJİK BULGULAR

Light micrograph showing collapsing FGS

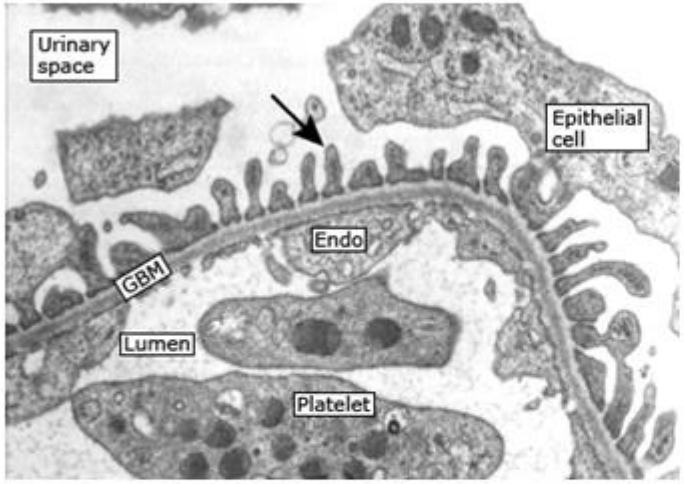


HİSTOPATOLOJİK BULGULAR



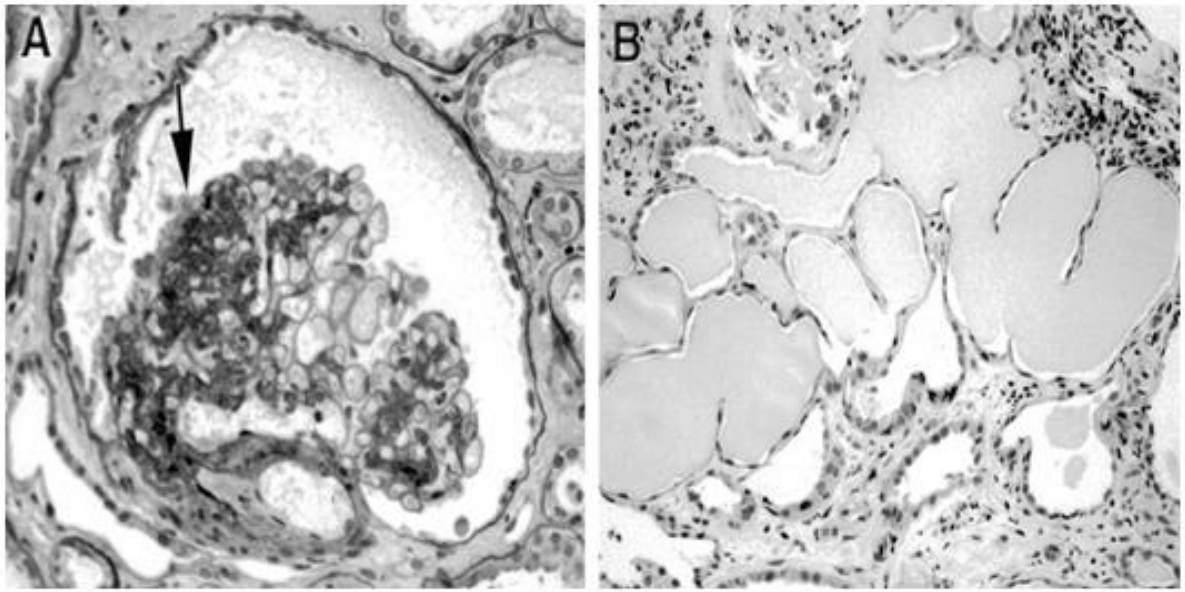
The glomerular capillary lumina are obliterated by collapse of glomerular basement membranes, with hypertrophy and hyperplasia of overlying glomerular epithelial cells containing numerous protein resorption droplets (Jones' methenamine silver, 400x).

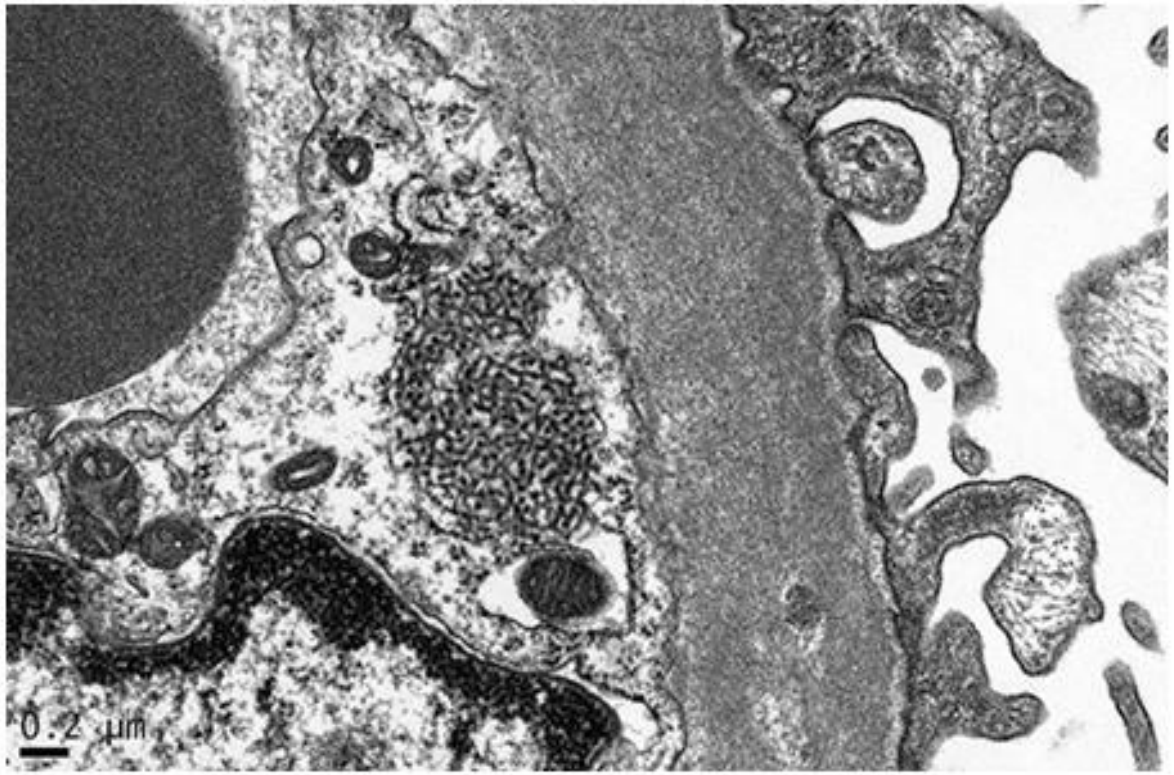
Electron micrograph of a normal glomerulus



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

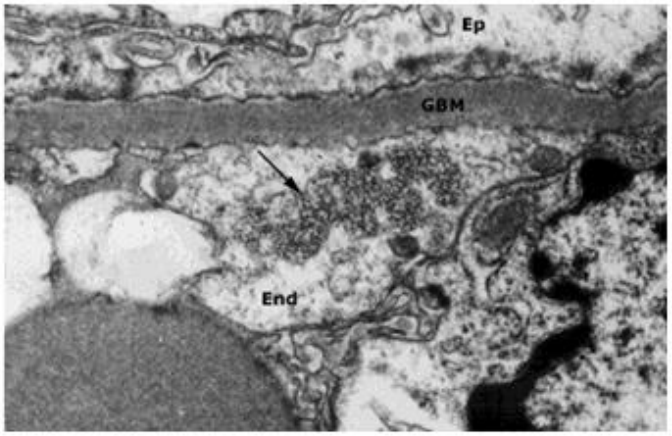
Collapsing FGS and Microcystic Dilatation of the Tubules





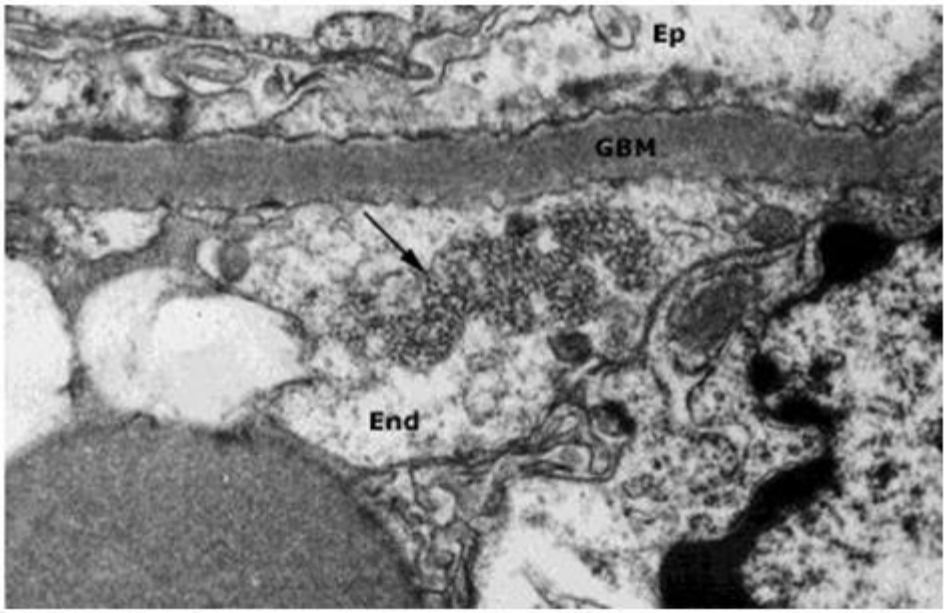
A large tubuloreticular inclusion is seen within a glomerular endothelial cell (electr
micrograph, x40,000).

Electron micrograph showing tubuloreticular structures in HIV nephropathy



Electron micrograph in HIV-induced focal collapsing glomerulosclerosis shows numerous intraendothelial (End) tubuloreticular structures (arrow). These structures are not seen in the

Endothelial Tubuloreticular Inclusions (TRI)



AYIRICI TANI

- HIVAN %56
- Klasik FSGS %21
- MPGN %6
- Amiloidozis %4
- Diabetik nefropati %4
- Lupus benzeri İKGN %4
- Diğerleri %5

TEDAVİ VE TAKİP

- ART almıyosa hemen başlanır,
- ART alan hastaysa toksisite açısından gözden geçirilir/değiştirilir
- ACE inhibitörleri ve Anjiotensin reseptör blokörleri (proteinürik ve/veya hipertansif hastalarda)
- Glukokortikoidler, renal fonksiyonlar ve proteinüri üzerine etkili (Rutin değil)
- Takipte nefrotoksik ilaçlardan sakınmak

PROGNOZ

- Genellikle kötü

  57 hastanın 30'unda ESRD

  6 hasta ex

Tanı konulduğu sırada ART alanlarda ESRD daha belirgin

31 hasta 4.5 yıl izlem,

15 hastada ESRD

Virolojik süpresyon (%70),

ESRD(%48) hastada elde edilmiş)

Black ethnicity and low current CD4 cell count are risk factors for HIV/ESRF

Table: Predictors of ESRF

		Univariate		Multivariate	
Variable		HR (95% CI)	P-value	HR (95% CI)	P-value
Sex	Male	0.59 (0.34, 1.02)	0.06	2.10 (0.98, 4.49)	0.06
Risk group	Heterosexual	1	-	Excluded	
	MSM	0.13 (0.07, 0.24)	<0.0001		
	Other	0.54 (0.26, 1.10)	0.09		
Ethnicity	White	1	-	1	-
	Black	5.50 (3.28, 9.21)	<0.0001	6.93 (3.56, 13.48)	<0.0001
Year of starting pRRT	2003-2007	1	-	Excluded	
	1998-2002	0.62 (0.31, 1.25)	0.18		
Time updated CD4 count	Per 50 cell/mm^3 increase	0.82 (0.75, 0.89)	<0.0001	0.83 (0.76, 0.95)	<0.0001
Time updated VL	<500 copies/ml	0.70 (0.40, 1.22)	0.21	Excluded	
Age	Per 10 year higher	1.01 (0.75, 1.34)	0.97	Excluded	
Started HAART (time-updated)	Yes	1.15 (0.60, 2.18)	0.68	Excluded	
HCV status	Negative	1	-	1	-
	Positive	0.67 (0.24, 1.84)	0.43	1.42 (0.50, 4.09)	0.51
	Unknown	0.18 (0.04, 0.74)	0.02	0.25 (0.06, 1.05)	0.06

pRRT=permanent renal replacement therapy; HCV=hepatitis C

AIDS 2009; 23: 2517-21

Antiretroviral Nephrotoxicity

- Tenofovir (Viread®, Truvada®, Atripla®)
- Indinavir (Crixivan®)
- Atazanavir (Reyataz®) ?
- Boosted PI ?
- Rare case reports with other agents

Kirk *et al*. for EuroSIDA, CROI 2010

KTD in HIV infected patients

284 consecutive HIV patients

Median creatinine clearance 109-123 ml/min

- 22% of 154 on TFV
- 6% of 49 on cART/no TFV
- 12% of 81 no cART

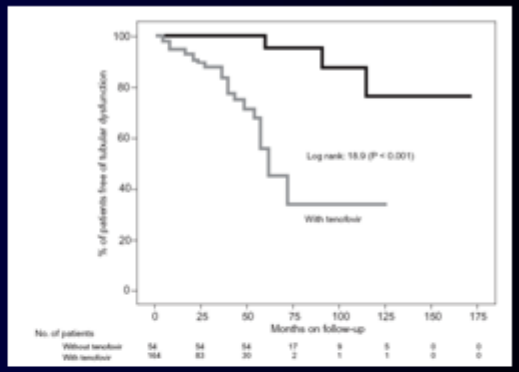


Table 3. Predictors of renal tubular damage in HIV patients.

	Tubular damage		Univariate analysis		Multivariate analysis	
	Yes*	No	OR (95% CI)	*P*	OR (95% CI)	*P*
No. of patients	33	150				
Age (years)	47 (43–52)	44 (39–48)	1.0 (0.9–1.0)	0.26	1.06 (1.0–1.1)	0.01
Male sex (%)	75	85	0.5 (0.2–1.2)	0.18		
Body weight (kg)	65 (57–73)	70 (62–79)	0.9 (0.9–1.0)	0.20		
History of hypertension (%)	26	29	1.0 (0.4–2.3)	0.93		
History of diabetes (%)	50	24	1.8 (0.9–3.6)	0.09		
Plasma HIV-RNA (log copies/ml)	1.7 (1.7–1.7)	1.7 (1.7–1.7)	0.1 (0–11.4)	0.34		
CD4 cell count (cells/μl)	494 (306–784)	506 (351–712)	0.9 (0.9–1.1)	0.07		
Length of ART (months)	76 (39–118)	54 (30–98)	0.9 (0.9–1.1)	0.24		
HAART with TDF (%)	91	71	10.6 (3.0–37.4)	<0.001	21.6 (4.1–113)	<0.001
HAART with PI (%)	64	50	2.3 (1.1–4.8)	0.02		
Concomitant nephrotoxic drugs (%)	21	14	2.2 (0.9–5.1)	0.07		
Serum HCV-RNA positive (%)	35	29	1.4 (0.6–2.9)	0.35		
Serum HBsAg positive (%)	12	6	1.8 (0.6–5.1)	0.28		

AIDS 2009;23:689-96

Table 3. Predictors of renal tubular damage in HIV patients.

	Tubular damage		Univariate analysis		Multivariate analysis	
	Yes*	No	OR (95% CI)	*P*	OR (95% CI)	*P*
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Tenofovir Toxicity

- Classic presentation: proximal tubulopathy
  - Phosphate wasting
  - Metabolic acidosis
  - Euglycemic glycosuria
  - Elevated creatinine
- 1-2% of patients develop significant toxicity
  - More frequent sub-clinical abnormalities

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2005, p. 3361–3366 Vol. 49, No. 8
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.8.3361–3366.2005
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Population Pharmacokinetics of Tenofovir in Human Immunodeficiency Virus-Infected Patients Taking Highly Active Antiretroviral Therapy

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Received 1 March 2005/Returned for modification 22 May 2005/Accepted 31 May 2005

The influence of renal function on tenofovir pharmacokinetics was investigated in 193 human immunodeficiency virus (HIV)-infected patients by the use of a population approach performed with the nonlinear mixed effects modeling program NONMEM. Tenofovir pharmacokinetics was well described by a two-compartment open model in which the absorption and the distribution rate constants are equal. Typical population estimates of apparent central distribution volume (V_c/F), peripheral distribution volume (V_p/F), intercompartmental clearance (Q/F), and plasma clearance (CL/F) were 534 liters, 1,530 liters, 144 liters/h and 90.9 liters/h, respectively. Apparent plasma clearance was related to body weight/serum creatinine ratio (BW/S_{CR}) and to the existence of a tubular dysfunction. Concomitant treatment with lopinavir/ritonavir was found to decrease tenofovir clearance. Individual Bayesian estimates of CL/F were used to calculate the tenofovir area under the concentration-time curve from time zero to 24 h (AUC_{0-24}). In patients without tubular dysfunction, AUC_{0-24} values markedly decreased from 6.7 to 1.4 mg · h/liter for BW/S_{CR} increasing from 0.44 to 1.73. The relevance of a dosage adjustment based on BW/S_{CR} should be further evaluated.

Incomplete Reversibility of Estimated Glomerular Filtration Rate Decline Following Tenofovir Disoproxil Fumarate Exposure

Sophie Jose,[1] Lisa Hamzah,[2] Lucy J. Campbell,[2] Teresa Hill,[1] Martin Fisher,[9] Clifford Leen,[10] Richard Gilson,[3] John Walsh,[4] Mark Nelson,[5] Phillip Hay,[6] Margaret Johnson,[7] David Chadwick,[11] Dorothea Nitsch,[8] Rachael Jones,[5] Caroline A. Sabin,[1] Frank A. Post,[2] for the UK Collaborative HIV Cohort Study Steering Committee

[1]Research Department of Infection and Population Health, University College London, [2]Kings College Hospital National Health Service (NHS) Foundation Trust and King's College London School of Medicine, [3]Mortimer Market Centre, University College Medical School, [4]Imperial College Healthcare NHS Trust, [5]Chelsea and Westminster NHS Foundation Trust, [6]St George's Healthcare NHS Trust, [7]Royal Free Hampstead NHS Trust, and [8]London School of Hygiene and Tropical Medicine, London, [9]Brighton and Sussex University Hospitals NHS Trust, Brighton; [10]The Lothian University Hospitals NHS Trust, Edinburgh, and [11]South Tees Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom

Background. Tenofovir disoproxil fumarate (TDF) has been linked to renal impairment, but the extent to which this impairment is reversible is unclear. We aimed to investigate the reversibility of renal decline during TDF therapy.

Methods. Cox proportional hazards models assessed factors associated with discontinuing TDF in those with an exposure duration of >6 months. In those who discontinued TDF therapy, linear piecewise regression models estimated glomerular filtration rate (eGFR) slopes before initiation of, during, and after discontinuation of TDF therapy. Factors associated with not achieving eGFR recovery 6 months after discontinuing TDF were assessed using multivariable logistic regression.

Results. We observed declines in the eGFR during TDF exposure (mean slopes, −15.7 mL/minute/1.73 m^2/year [95% confidence interval {CI}, −20.5 to −10.9] during the first 3 months and −3.1 mL/minute/1.73 m^2/year [95% CI, −4.6 to −1.7] thereafter) and evidence of eGFR increases following discontinuation of TDF therapy (mean slopes, 12.5 mL/minute/1.73 m^2/year [95% CI, 8.9–16.1] during the first 3 months and 0.8 mL/minute/1.73 m^2/year [95% CI, .1–1.5] thereafter). Following TDF discontinuation, 38.6% of patients with a decline in the eGFR did not experience recovery. A higher eGFR at baseline, a lower eGFR after discontinuation of TDF therapy, and more-prolonged exposure to TDF were associated with an increased risk of incomplete recovery 6 months after discontinuation of TDF therapy.

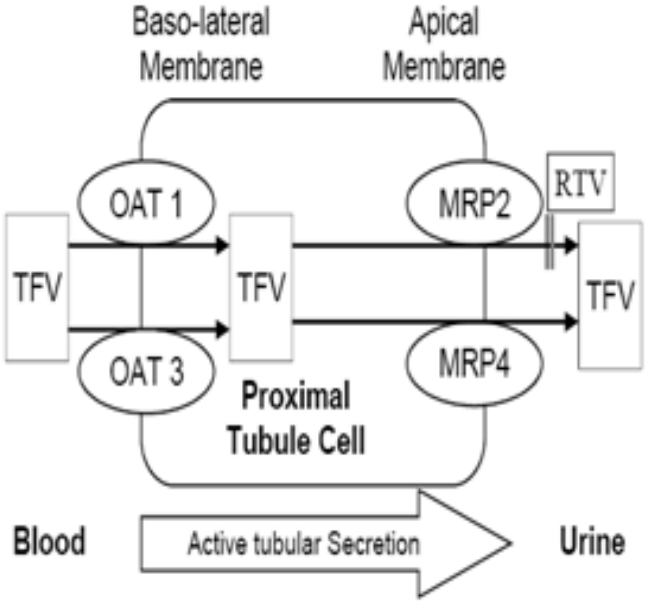
Conclusions. This study shows that a decline in the eGFR during TDF therapy was not fully reversible in one third of patients and suggests that prolonged TDF exposure at a low eGFR should be avoided.

Risk factors for KTD while receiving tenofovir

Role of polymorphisms in genes encoding drug transporters

Table 4. Predictors of kidney tubular dysfunction in human immunodeficiency virus (HIV)–infected patients treated with tenofovir.

	Bivariate analysis		Multivariate analysis	
Factor	OR (95% CI)	*P*	OR (95% CI)	*P*
Female sex	1.70 (0.5–5.9)	.403		
Age (per year)	1.06 (1–1.1)	**.047**	1.09 (1.02–1.18)	.024
Body weight (per kg)	0.95 (0.9–1)	**.052**	0.93 (0.88–0.99)	.048
Hepatitis C virus coinfection	1.30 (0.4–3.7)	.627	…	
Months receiving tenofovir treatment	1.03 (1–1.1)	**.039**	…	
Plasma HIV RNA level (per log copies/mL)	1.6 (0–6.7)	.334	…	
CD4 cell count (per cells/mL)	1 (0.9–1)	.795	…	
Use of nephrotoxic drugs	2.50 (0.7–8.2)	**.130**	…	
Use of protease inhibitors	2.85 (0.8–9.4)	**.087**	…	
Arterial hypertension	1.17 (0.3–3.7)	.785	…	
Diabetes	2.36 (0.8–6.8)	**.111**	…	
Creatinine clearance (per mL/min)	0.98 (0.9–1)	**.124**	…	
Genetic polymorphisms[a]				
Genotype CC at *ABCC2* −24 (vs. CT and TT)	4.51 (1.2–16.50)	**.023**	5.04 (1.20–21)	.027
ABCC2 1249A allele	1.01 (0.35–2.9)	.977	…	
ABCC2 3563A allele	0.75 (0.15–3.63)	.722	…	
ABCC2 3972T allele	0.43 (0.16 to 1.16)	**.096**	…	
ABCC2 4544A allele	1.09 (0.28–4.26)	.892	…	
ABCC4 669T allele	0.63 (0.2–2.4)	.494	…	
ABCC4 3463G allele	0.28 (0.2–1.6)	.545	…	
ABCC4 4131G allele	1.22 (0.4–3.4)	.696	…	
SLC22A6 453A allele	2.3 (0.8–6.9)	**.138**	…	
SLC22A11 rs11231809 A allele	0.60 (0.2–1.9)	.387	…	
ABCB1 3435T allele	0.806 (0.29–2.6)	.873	…	
ABCB1 1236T allele	0.856 (0.3–2.7)	.796	…	



Curr Opin Infect Dis 2009; 22: 43-48

Clin Infect Dis. 2009;48:e108-16

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Lack of a Clinically Important Effect of Moderate Hepatic Insufficiency and Severe Renal Insufficiency on Raltegravir Pharmacokinetics▽†

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Received 8 September 2008/Returned for modification 15 November 2008/Accepted 1 February 2009

Raltegravir is a human immunodeficiency virus type 1 integrase strand transfer inhibitor with potent activity in vitro and in vivo. Raltegravir is primarily cleared by hepatic metabolism via glucuronidation (via UDP glucuronosyltransferase 1A1), with a minor component of elimination occurring via the renal pathway. Since the potential exists for raltegravir to be administered to patients with hepatic or renal insufficiency, two studies were conducted to evaluate the influence of moderate hepatic insufficiency (assessed by using the Child-Pugh criteria) and severe renal insufficiency (creatinine clearance, <30 ml/min/1.73 m^2) on the pharmacokinetics of raltegravir. Study I evaluated the pharmacokinetics of 400 mg raltegravir in eight patients with moderate hepatic insufficiency and eight healthy, matched control subjects. Study II evaluated the pharmacokinetics of 400 mg raltegravir in 10 patients with severe renal insufficiency and 10 healthy, matched control subjects. All participants received a single 400-mg dose of raltegravir in the fasted state. In study I, the geometric mean ratios (GMR; mean value for the group with moderate hepatic insufficiency/mean value for the healthy controls) and 90% confidence intervals (CIs) for the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the maximum concentration of drug in plasma (C_{max}), and the concentration at 12 h (C_{12}) were 0.86 (90% CI, 0.41, 1.77), 0.63 (90% CI, 0.23, 1.70), and 1.26 (90% CI, 0.65, 2.43), respectively. In study II, the GMRs (mean value for the group with renal insufficiency/mean value for the healthy controls) and 90% CIs for $AUC_{0-\infty}$, C_{max}, and C_{12} were 0.85 (90% CI, 0.49, 1.49), 0.68 (90% CI, 0.35, 1.32), and 1.28 (90% CI, 0.79,

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A Switch in Therapy to a Reverse Transcriptase Inhibitor Sparing Combination of Lopinavir/Ritonavir and Raltegravir in Virologically Suppressed HIV-Infected Patients: A Pilot Randomized Trial to Assess Efficacy and Safety Profile: The KITE Study

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Abstract

A nucleoside reverse transcriptase inhibitor (NRTI) backbone is a recommended component of standard highly active antiretroviral therapy (sHAART). However, long-term NRTI exposure can be limited by toxicities. NRTI class-sparing alternatives are warranted in select patient populations. This is a 48-week single-center, open-label pilot study in which 60 HIV-infected adults with plasma HIV-1 RNA (<50 copies/ml) on sHAART were randomized (2:1) to lopinavir/ritonavir (LPV/r) 400/100 mg BID + raltegravir (RAL) 400 mg BID switch (LPV-r/RAL arm) or to continue on sHAART. The primary endpoint was the proportion of subjects with HIV-RNA <50 copies/ml at week 48. Secondary efficacy and immunologic and safety endpoints were evaluated. Demographics

IDSA GUIDELINE

Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Keywords. HIV-1; chronic kidney disease; clinical practice guideline; HIV-associated nephropathy; kidney transplantation.

EXECUTIVE SUMMARY

Background

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [1]. CKD is common in human immunodeficiency virus (HIV)–

relevant management questions, summarize pertinent data from clinical studies, and offer recommendations for clinical care. The scope of this document is CKD in HIV-infected adults and children in the United States. The guidelines do not address screening, evaluation, or management of HIV-related kidney disease in resource-constrained settings

ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
Proximal tubulopathy with any combination of: 1. Proteinuria: urine dipstick ≥ 1, or confirmed increase in UP/C > 30 mg/mmol[i] 2. Progressive decline in eGFR and eGFR < 90 mL/min[ii] 3. Phosphaturia[iii]: confirmed hypophosphataemia secondary to increased urine phosphate leak	TDF**	**Assessment:** • Tests for proximal renal tubulopathy/renal Fanconi syndrome[iii] • Consider renal bone disease if hypophosphataemia of renal origin: measure 25(OH) vitamin D, PTH, DXA **Consider stopping TDF if:** • Progressive decline in eGFR and no other cause • Confirmed hypophosphataemia of renal origin and no other cause • Osteopenia/osteoporosis in the presence of increased urine phosphate leak
Nephrolithiasis: 1. Crystalluria 2. Haematuria[iv] 3. Leucocyturia 4. Loin pain 5. Acute renal insufficiency	IDV ATV (DRV)	**Assessment:** • Urinalysis for crystalluria/stone analysis • Exclude other cause for nephrolithiasis • Renal tract imaging including CT scan **Consider stopping IDV/ATV if:** • Confirmed renal stones • Recurrent loin pain +/- haematuria
Interstitial nephritis: 1. Progressive decline in eGFR[ii] 2. Tubular proteinuria[iii]/ haematuria 3. Eosinophiluria (if acute) 4. Leucocyte casts	IDV ATV	**Assessment:** • Renal ultrasound • Refer to nephrologist **Consider stopping IDV/ATV if:** • Progressive decline in eGFR and no other cause
Progressive decline in eGFR, but none of the above[v]	TDF** PI/r	**Complete assessment:** • Risk factors for CKD[v] (see Kidney Disease: Definition, Diagnosis and Management) • PRT, UA/C, UP/C (see Kidney Disease: Definition, Diagnosis and Management and Indications and Tests for Proximal Renal Tubulopathy (PRT) • Renal tract ultrasound **Consider stopping ARVs with potential nephrotoxicity if:** • Progressive decline in eGFR and no other cause[v]

* Use of COBI, DTG, RPV, but also PI/r is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

** TAF has shown lower tenofovir-related renal adverse effects due to lower systemic tenofovir exposure. Switch-studies from TDF to TAF suggest

From: **Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America**

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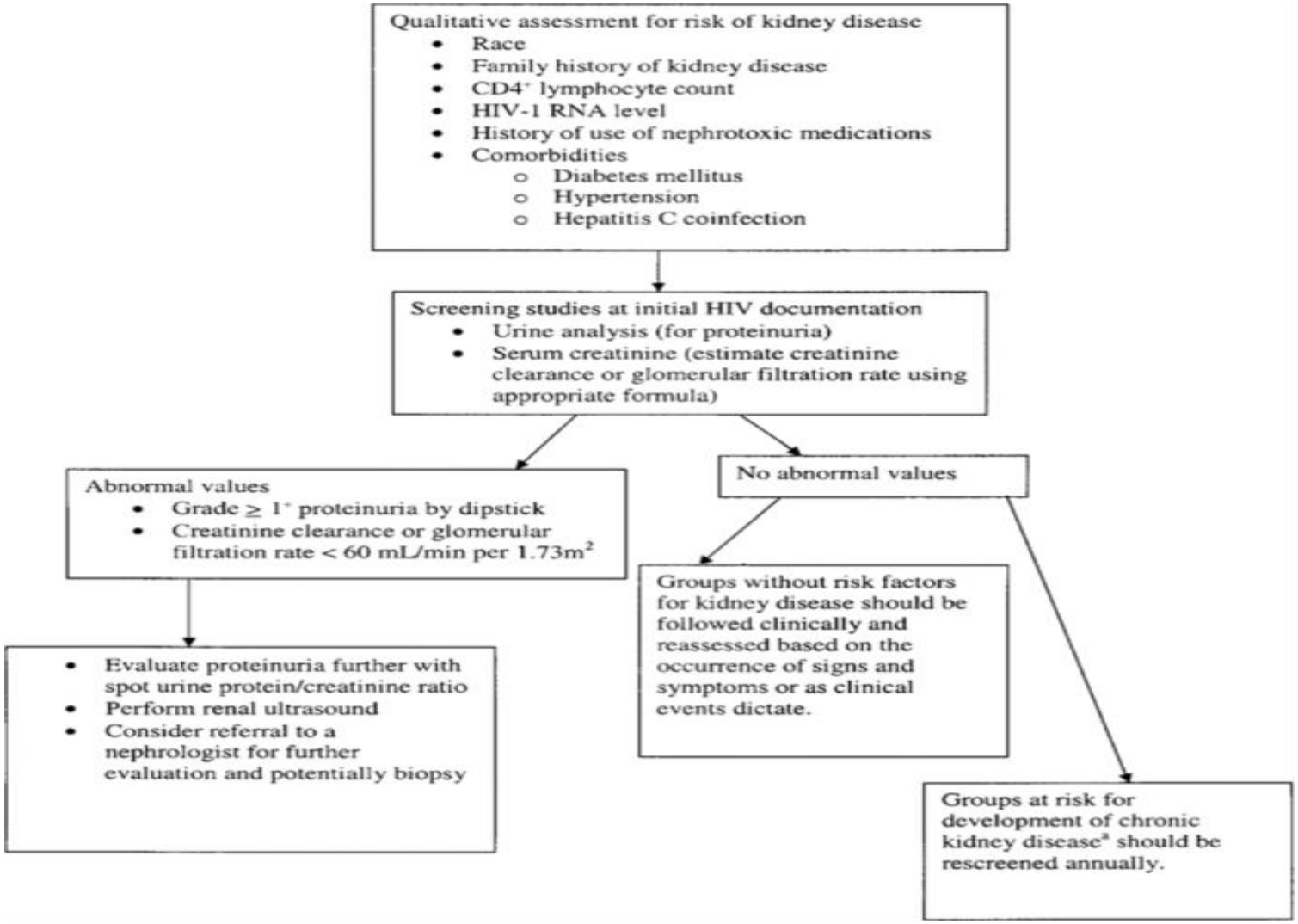

Figure Legend:

Suggested screening algorithm for HIV-related renal diseases. [a]Groups at risk for chronic kidney disease include individuals of African American race; individuals with diabetes, hypertension, or hepatitis C virus coinfection; individuals with $CD4^+$ cell counts <200 cells/mm^3; and individuals with HIV RNA levels >4000 copies/mL.

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Insulin Resistance in HIV Protease Inhibitor–Associated Diabetes

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Abstract

Background—Fasting hyperglycemia has been associated with HIV protease inhibitor (PI) therapy.

Objective—To determine whether absolute insulin deficiency or insulin resistance with relative insulin deficiency and an elevated body mass index (BMI) contribute to HIV PI–associated diabetes.

Design—Cross-sectional evaluation.

Patients—8 healthy seronegative men, 10 nondiabetic HIV-positive patients naive to PI, 15 nondiabetic HIV-positive patients receiving PI (BMI = 26 kg/m^2), 6 nondiabetic HIV-positive

•In summary, diabetes in HIV PI–treated subjects was associated with peripheral insulin resistance and hyperglucagonemia.
•Indinavir did not reduce proteolytic processing of proinsulin to insulin or glucose-induced insulin secretion from [beta]-cells.
•The mechanisms by which peripheral insulin action is impaired in some individuals treated with HIV PIs
remain to be identified.

Indinavir Induces Acute and Reversible Peripheral Insulin Resistance in Rats

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The use of HIV protease inhibitors (PIs) has been associated with several metabolic changes, including lipodystrophy, hyperlipidemia, and insulin resistance. The etiology of these adverse effects remains unknown. PIs have recently been found to cause acute and reversible inhibition of GLUT4 activity in vitro. To determine the acute in vivo effects of indinavir on whole-body glucose homeostasis, glucose tolerance tests were performed on PI-naïve Wistar rats immediately after a single intravenous dose of indinavir. Glucose and insulin levels were significantly elevated in indinavir-treated versus control rats ($P < 0.05$) during the initial 30 min of the glucose tolerance test. Under euglycemic-hyperinsulinemic clamp conditions, indinavir treatment acutely reduced the glucose infusion rate required to maintain euglycemia by 18 and 49% at indinavir concentrations of 14 and 27 μmol/l, respectively. Muscle 2-deoxyglucose uptake was similarly reduced under these conditions. Restoration of insulin sensitivity was observed within 4 h after stopping the indinavir infusion.

GLUT4 activity in vitro, providing a potential mechanism for the insulin resistance observed in HIV-positive patients treated with this class of drugs (4). Glucose transport is the rate-limiting step for whole-body glucose disposal in rodents (5–7) and humans (8). GLUT4 is predominantly expressed in tissues responsible for the bulk of whole-body glucose disposal (skeletal/cardiac muscle and fat) (9–12) and is believed to be the principal transporter isoform mediating insulin-stimulated glucose uptake at these sites. GLUT4 inhibition by PIs is observed acutely in both 3T3-L1 adipocytes and *Xenopus* oocytes heterologously expressing GLUT4, and this inhibition is readily reversible by removal of the drug from the incubation media (4). Therefore, if the insulin resistance observed in the HIV PI-associated lipodystrophy syndrome is caused by GLUT4 inhibition, PIs should be capable of producing acute and reversible effects on whole-body glucose disposal.

Teşekkürler