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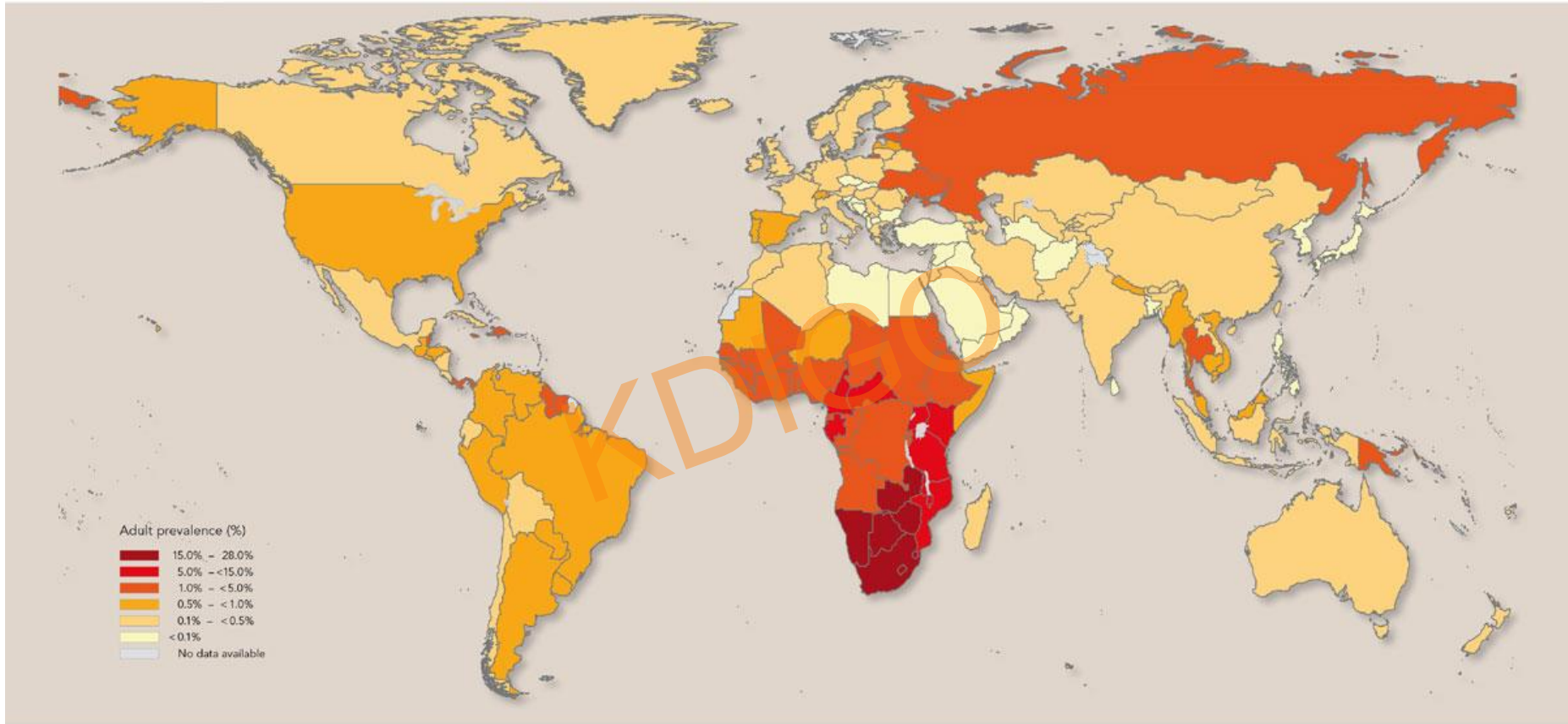
HIV–associated nephropathy (HIVAN)

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Kidney Center
Heidelberg University Hospital

SIMPOSIO KDIGO
October, 8th 2019

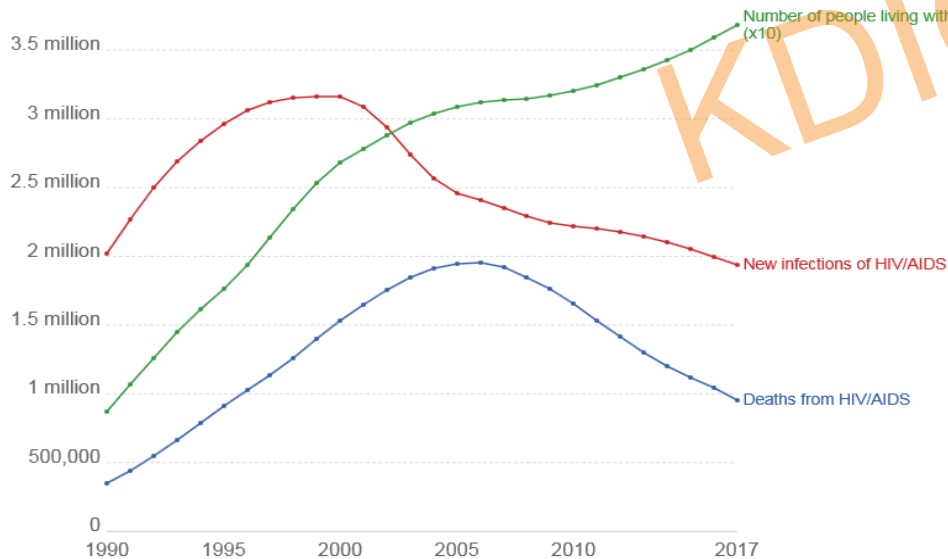
The extent of HIV worldwide I



The extent of HIV worldwide II

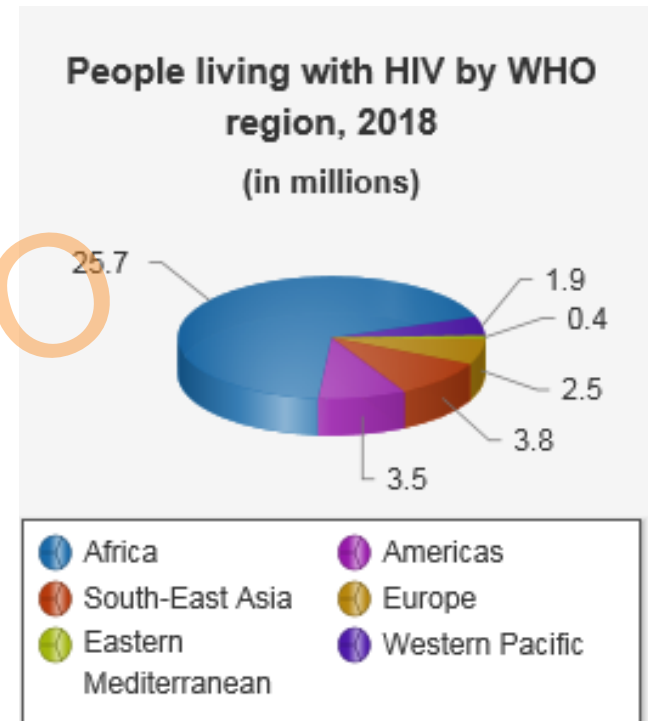
In 2018:

- 37.9 million people living with HIV
- 1.7 million newly infected people
- 0.77 million HIV-related deaths
- 79% of people with HIV know their status

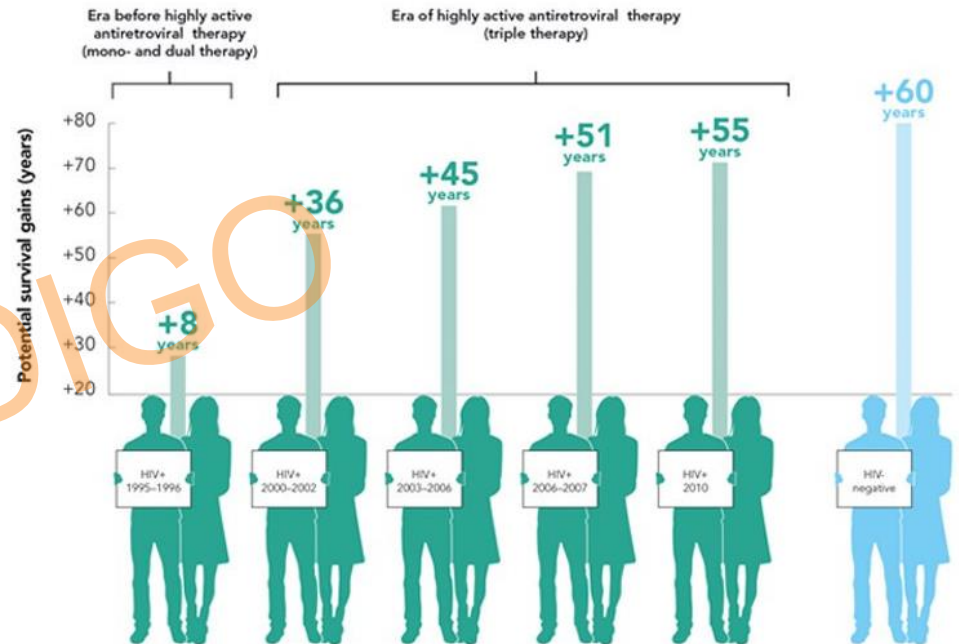
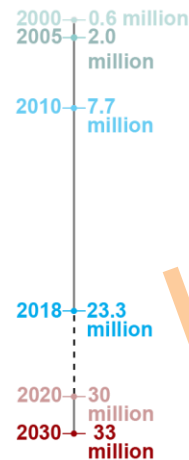
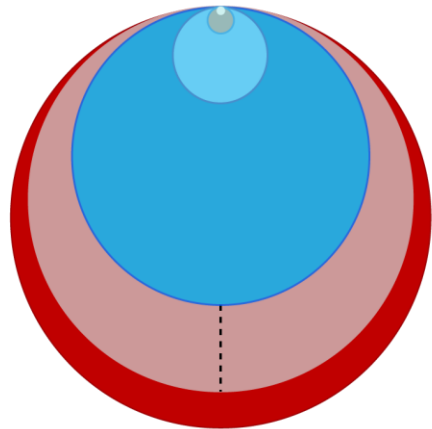


Source: IHME, Global Burden of Disease

CC BY



The extent of HIV worldwide III



Source: Adapted from Lohse et al, 2007; Hoog et al, 2008; May et al, 2011 & Hogg et al, 2013.

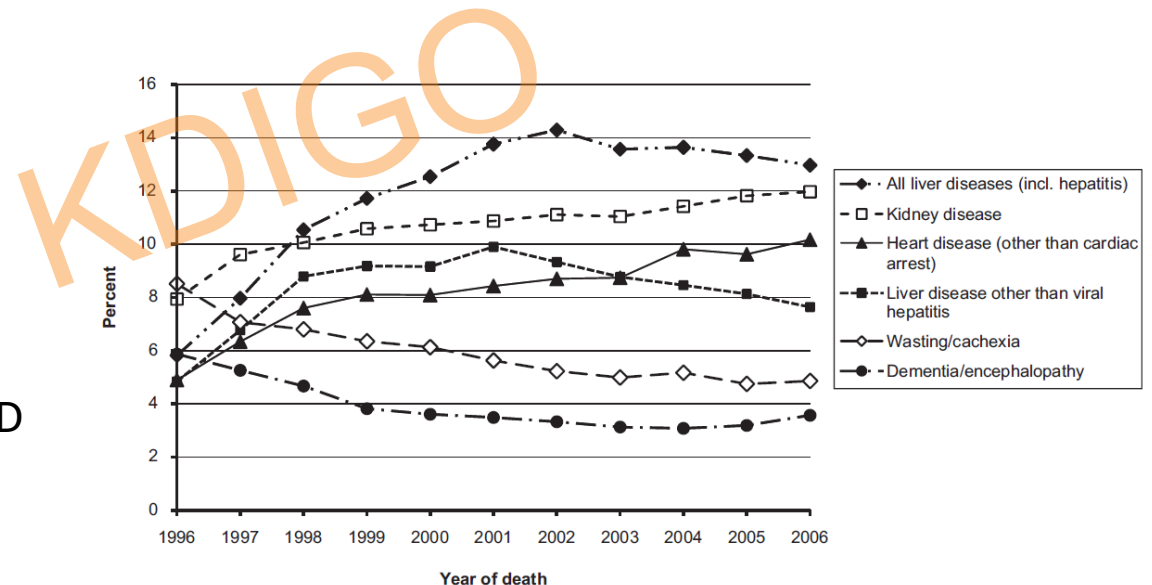
Approx. 62% on medication (2018)

↑ life expectancy

The extent of HIV worldwide IV

Increase of renal disease in HIV infected patients

- Prevalence of CKD in HIV-infected individuals varies broadly
 - Africa: 38% Nigeria, 20% Uganda, 11.5% Kenya
 - Asia: 16.8% Hong Kong, 27% India
 - Americas: 7%
 - Europe: 1%
- HIV as etiologic factor of CKD
 - Spain: 0.5-1.1%
 - Cameroon: 6.6%
 - South Africa: 28.5%



HIV-associated nephropathy

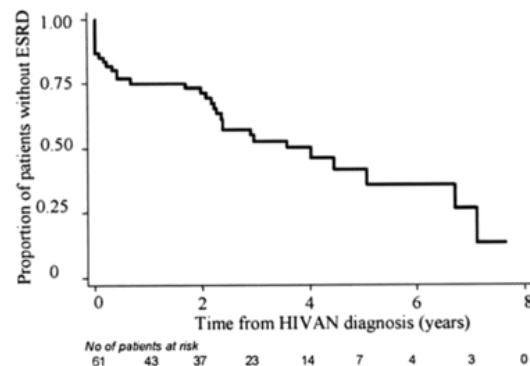
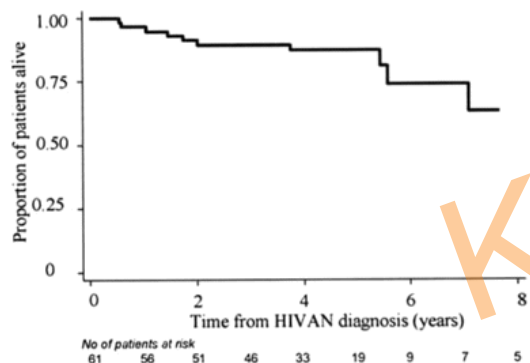
Associated Focal and Segmental Glomerulosclerosis in the Acquired Immunodeficiency Syndrome

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.

- **AIDS-associated nephropathy**
 - First described in early 1980s associated with AIDS
 - Aggressive form of FSGS in African-Americans
- **HIV-associated nephropathy (HIVAN)**
 - Appears in a progresses HIV infection
 - Major cause of ESRD in HIV patients
 - Characterized by significant proteinuria and progressive kidney failure.
 - Prevalence
 - 1% to 10% im HIV-infected patients
 - HIVAN histology in 50% of HIV positive patients
 - 90% of HIVAN patients are of African descent.

HIV-associated nephropathy

- Key features/parameters of HIVAN
 - Advanced HIV disease
 - Heavy proteinuria
 - Rapid decline in kidney function



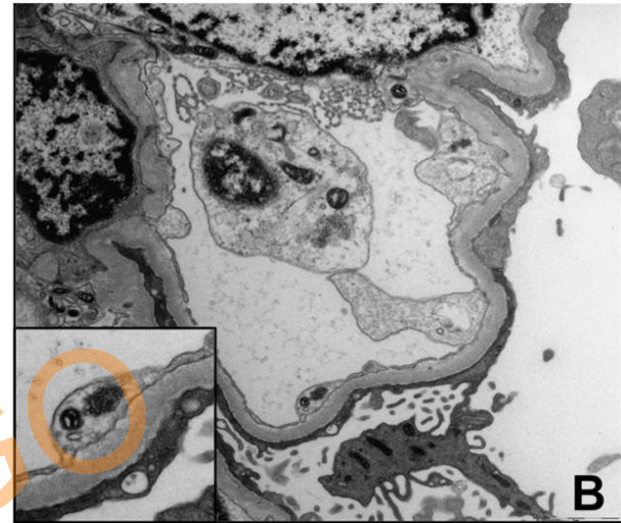
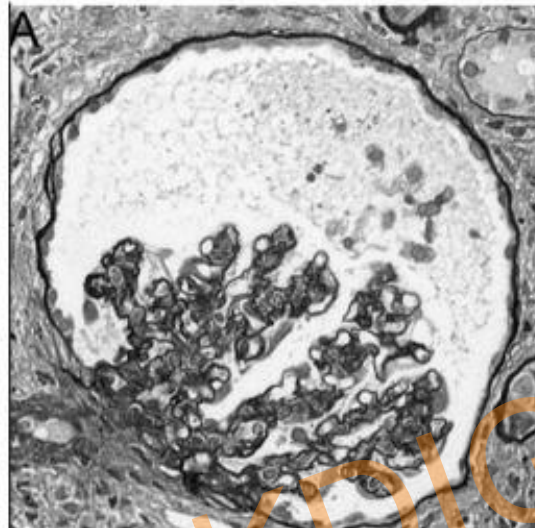
Variable	All patients (n = 61)
Male sex	32 (52)
At HIVAN diagnosis	
Age, mean years	36.1
Ethnicity	
Black African	48 (79)
Black British/Caribbean	13 (21)
HIV risk (n = 60)	
Heterosexual	57 (95)
Homosexual/bisexual	3 (5)
Hepatitis B surface Ag	4 (7)
Hepatitis C antibody	0 (0)
Diabetes mellitus	1 (2)
Hypertension	4 (7)
AIDS (CDC stage C)	29 (48)
CD4 ⁺ T cell count, median cells/ μ L (IQR)	66 (29–147)
HIV-1 RNA level, mean log copies/mL	5.2
Serum creatinine level, median mg/dL (IQR)	3.4 (2.1–7.9)
GFR, median mL/min (IQR)	21 (9–37)
Proteinuria level, median g/24-h period (IQR)	5.4 (3.4–8.9)

HIVAN Pathophysiology

FSGS

Collapsing
glomerulopathy

Foot process
effacement

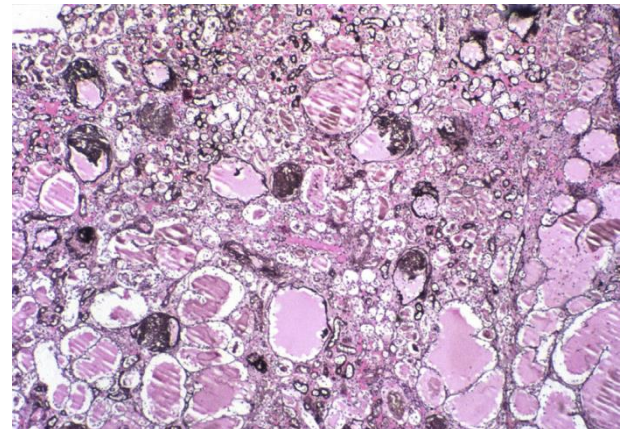
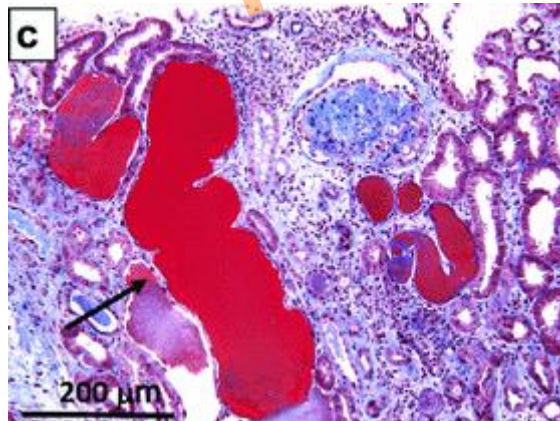


Tubulointerstitial Nephritis

Microcystic dilations

Tubular atrophy +
proteinaceous casts

Immune infiltrate

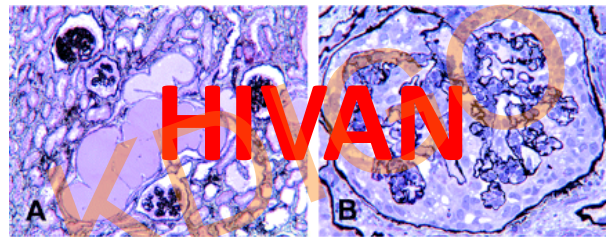
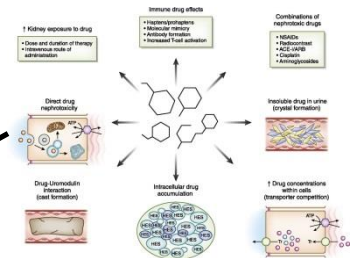


HIVAN risk factors

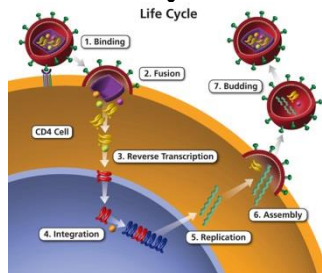
Genetic predispositions



cART-related kidney toxicity



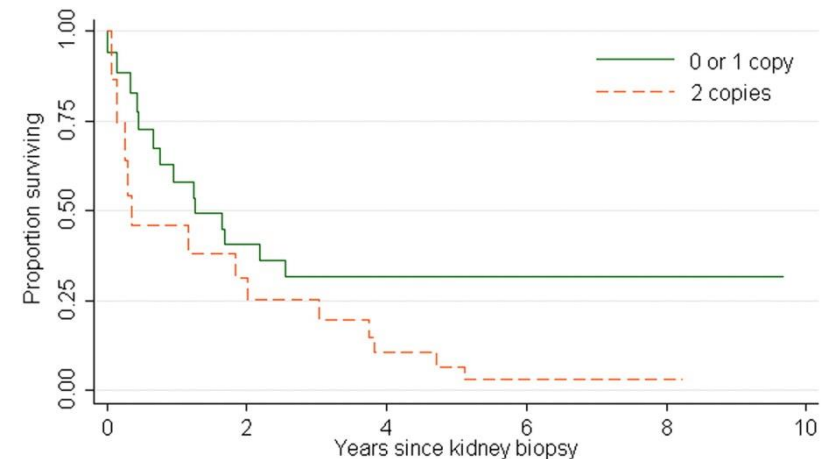
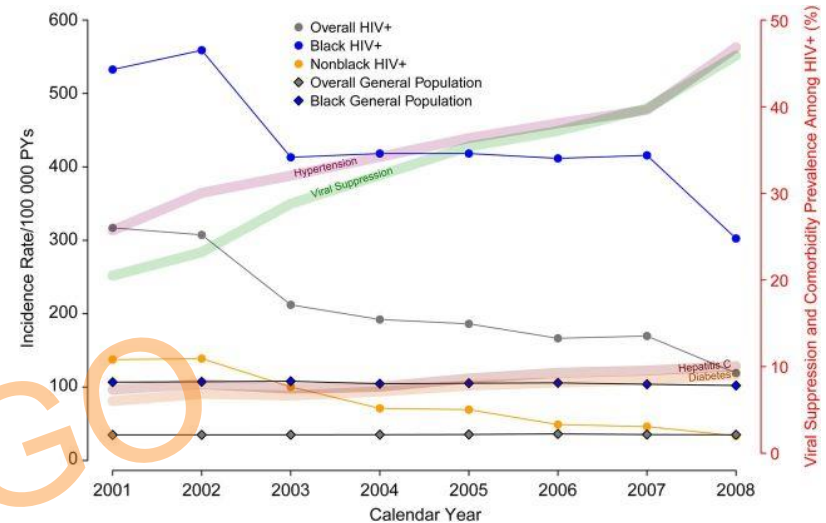
Direct viral effects



Comorbidity disease

Genetic predispositions

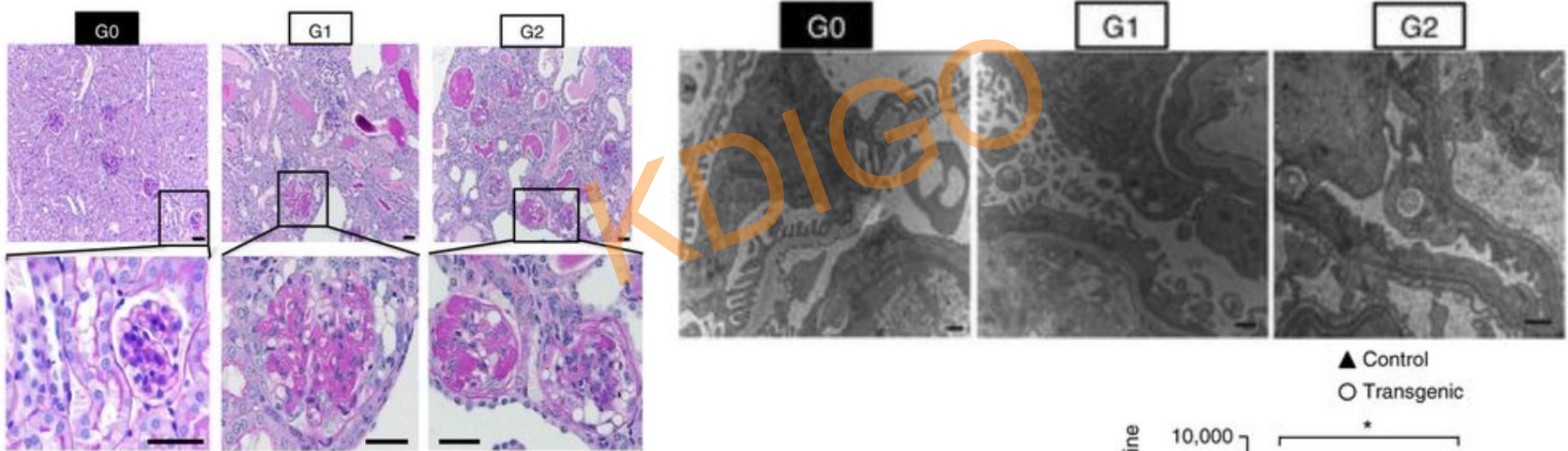
- 18- to 50-fold higher prevalence of HIVAN in black HIV patients
- **APOL1 G1 and G2 risk variants**
 - Frequency
 - Both 22%
 - Single 45%
 - Strongly associated with development of FSGS and HIVAN
 - 5-fold higher odds of proteinuria
 - 3.5 fold higher odds of HIVAN
 - 3-fold higher risk of progressing to ESRD
 - 29- to 89-fold higher odds of HIVAN (both alleles)



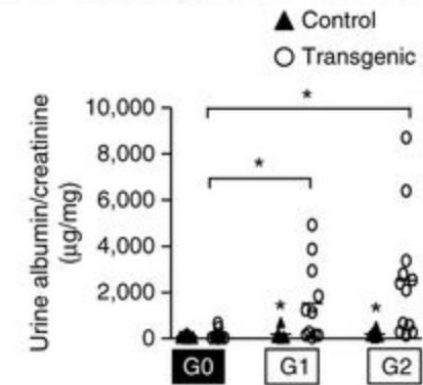
Mechanisms of APOL1-mediated disease

Limited data:

- Higher expression of APOL1 variants in glomeruli and podocyte
- Expression of APOL1 variants in transgenic mouse cause proteinuria, glomerulosclerosis and podocyte effacement



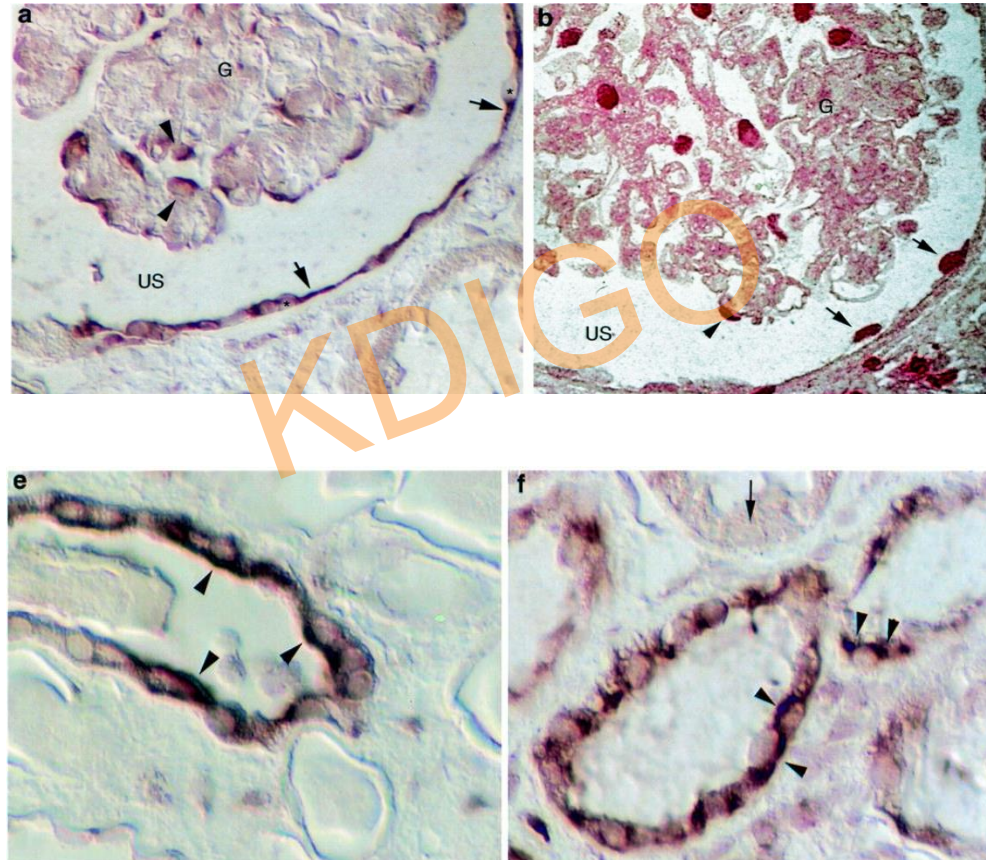
- The estimated lifetime risk with both *APOL1* alleles
 - 50% for HIV+
 - 4% for HIV-



Direct viral effects

Kidney as site of HIV infection

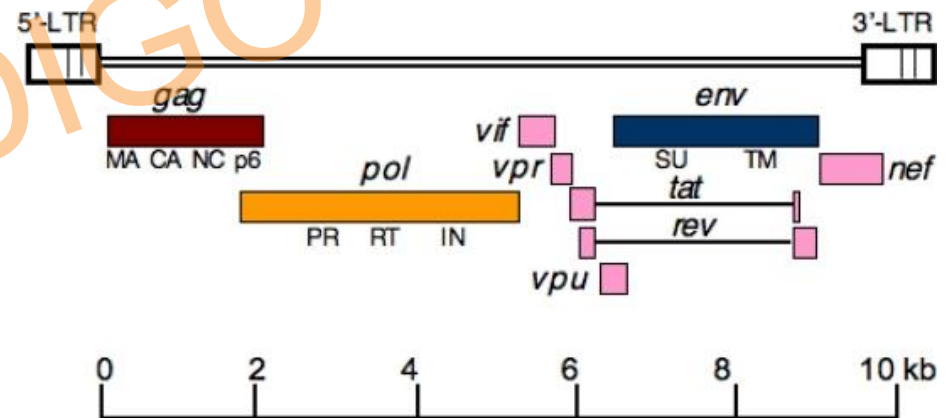
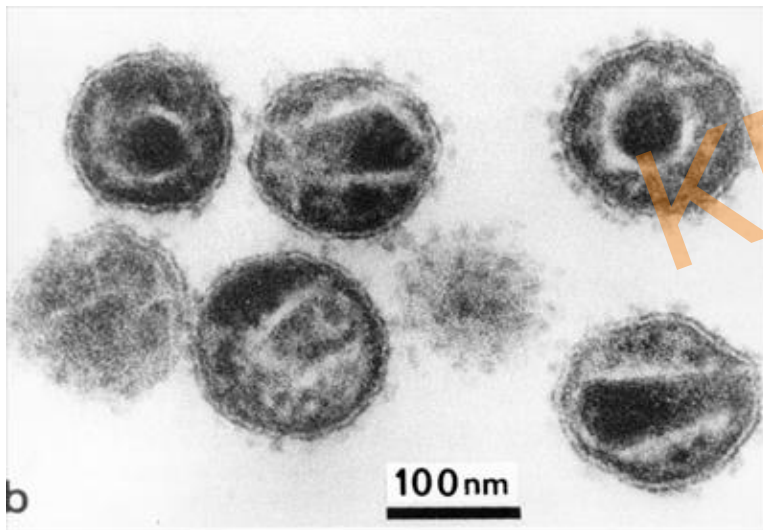
- Renal epithelial cells are infected by HIV



Direct viral effects

Kidney as site of HIV infection

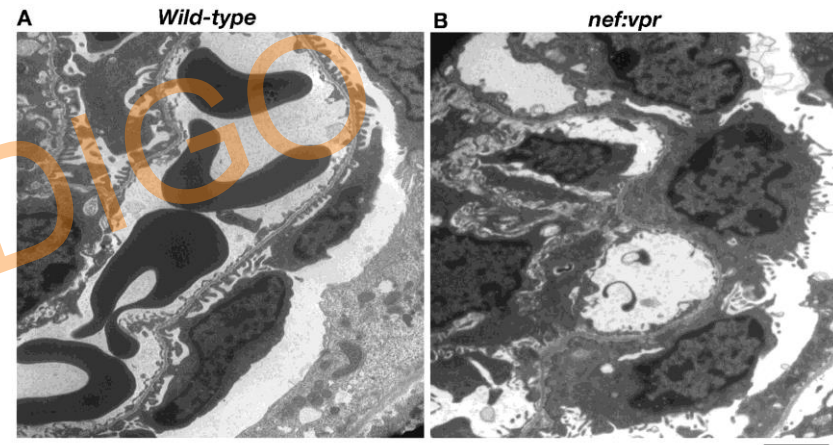
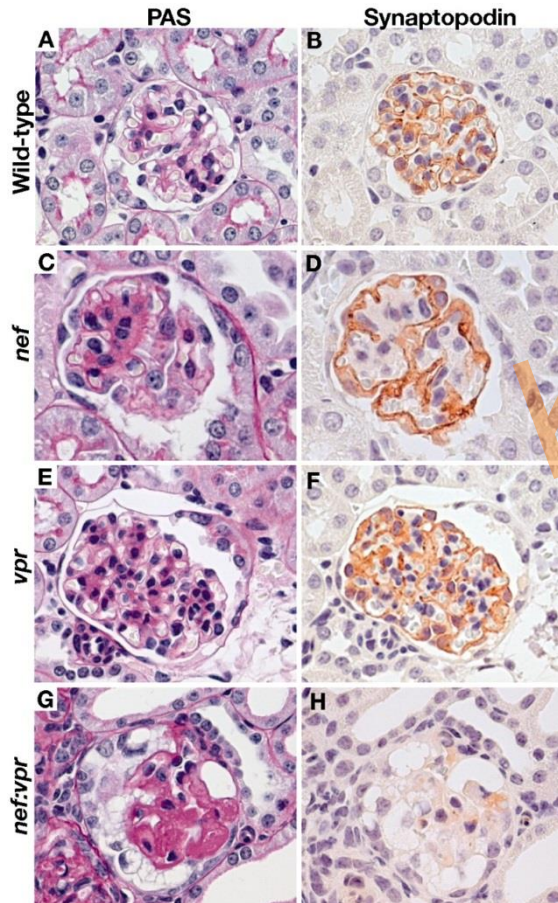
- Role of accessory proteins in disease pathogenesis
 - *vpr*, *nef*



Direct viral effects

Kidney as site of HIV infection

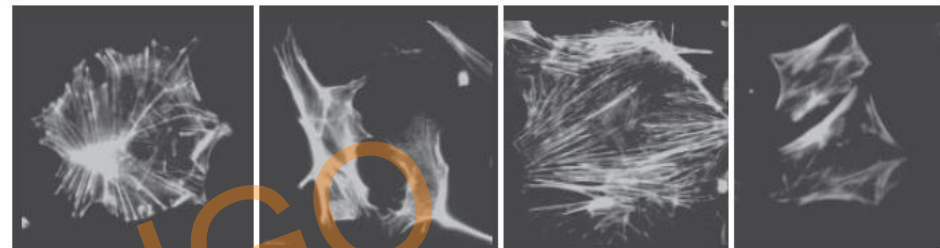
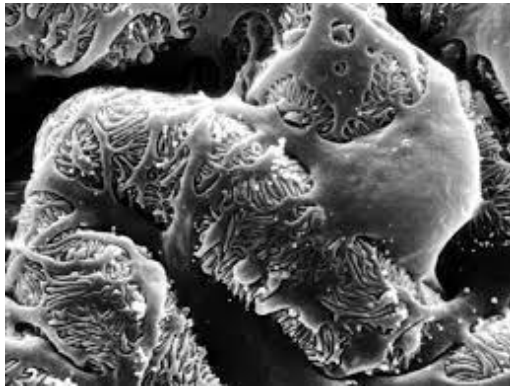
- transgenic mice expressing *nef* and *vpr* in podocytes



Direct viral effects

Kidney as site of HIV infection

- Expression of *nef* in human podocytes in vitro

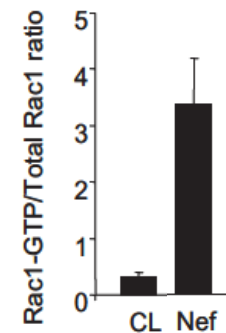
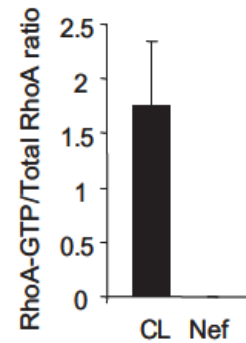
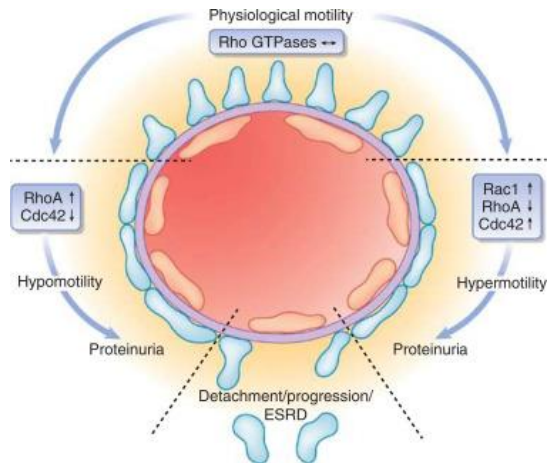


Control podocyte

HIV-1

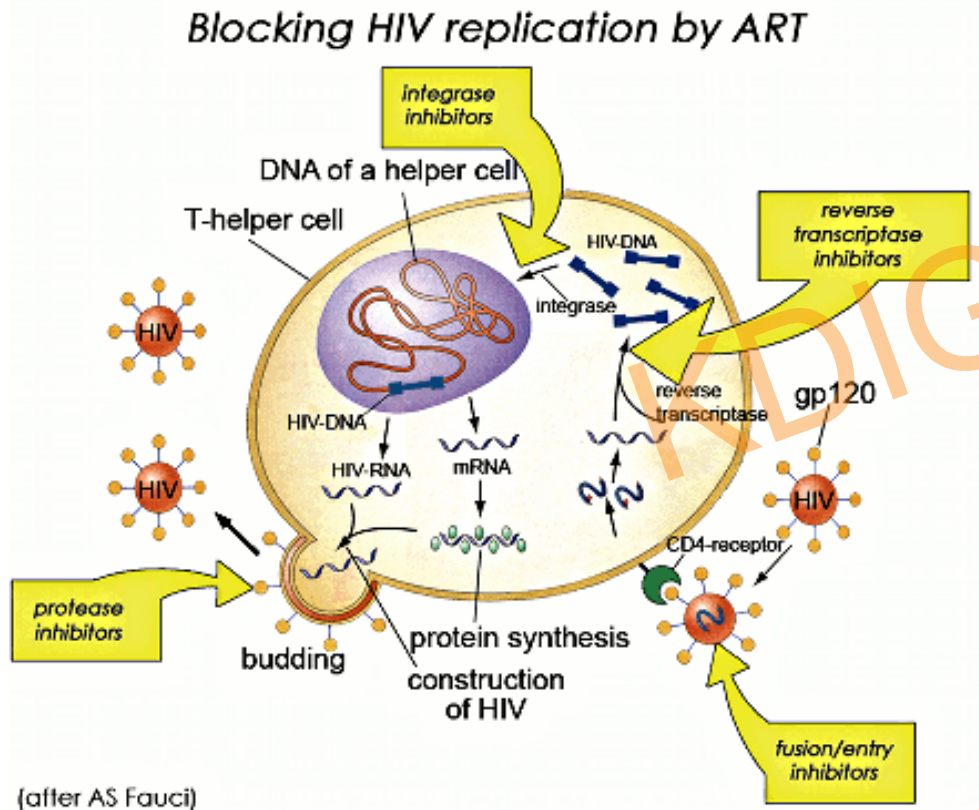
HIV-1 Δ Nef

Nef



cART-related kidney toxicity

Combined antiretroviral therapy



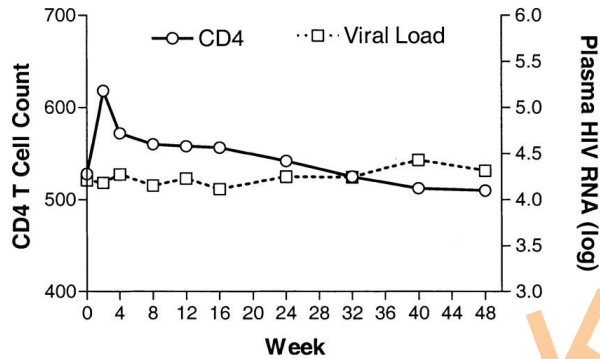
Drug classes:

1. Entry inhibitors
2. RT inhibitors
3. Integrase inhibitors
4. Protease inhibitors

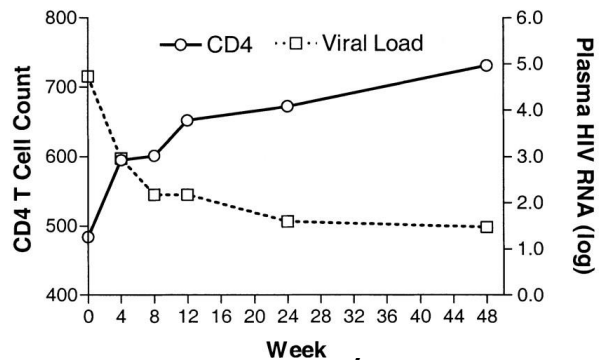
cART-related kidney toxicity

Combined antiretroviral therapy

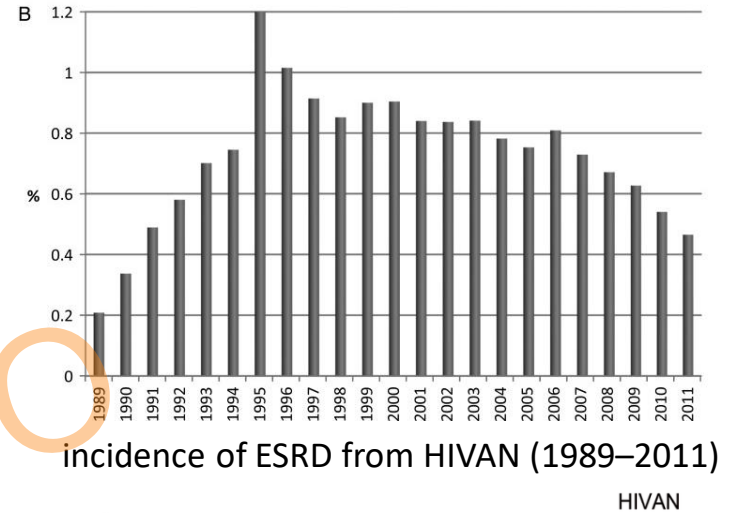
A Untreated



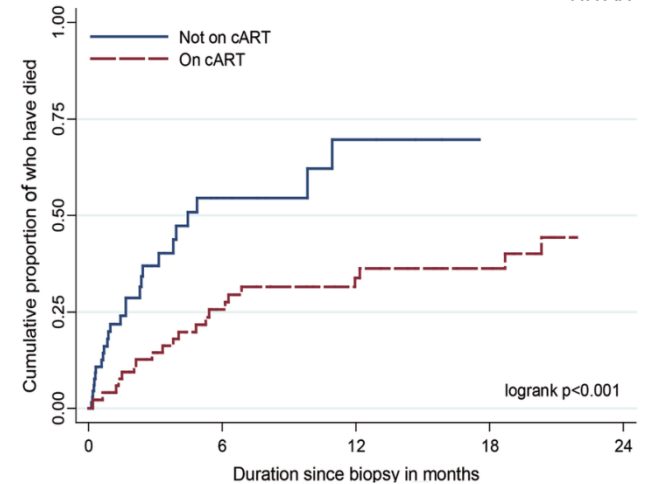
C Antiretroviral Treated



HIV RNA <200 copies/mL CD4 count > 350 cells/ μ l

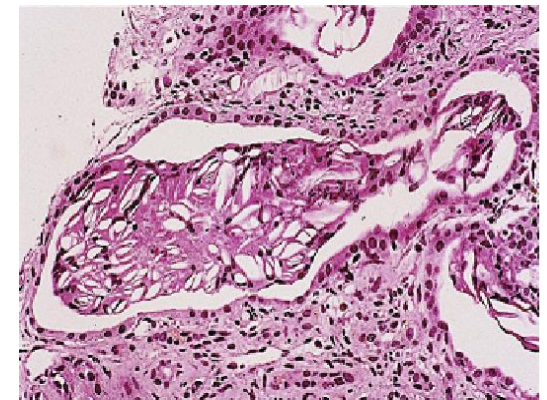
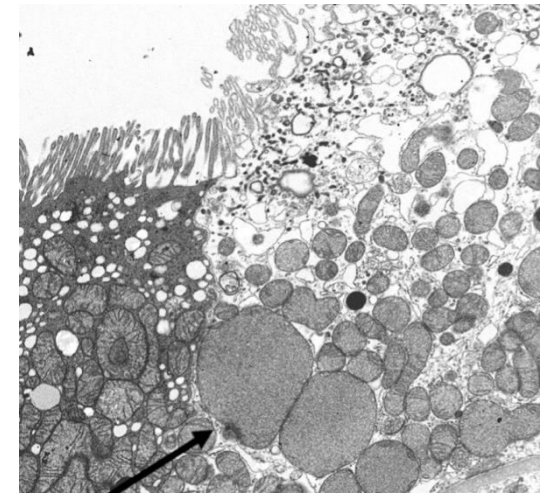


incidence of ESRD from HIVAN (1989–2011)
HIVAN



cART-related kidney toxicity

- Kidney injuries due to reverse transcriptase (RTI) and protease (PI) inhibitors are reported
- **Tenofovir (RTI)**
 - 33% higher risk of CKD
 - characterized by Fanconi syndrome
 - tubular accumulation and mitochondria injury
 - recovery can be incomplete
- **Atazanavir (PI)**
 - 20% higher CKD incidence
 - Crystalluria, tubulointerstitial nephritis
 - Poorly soluble → crystal formation, inflammation
 - Persistent risk for kidney injury



Other risk factors

Cohort study:

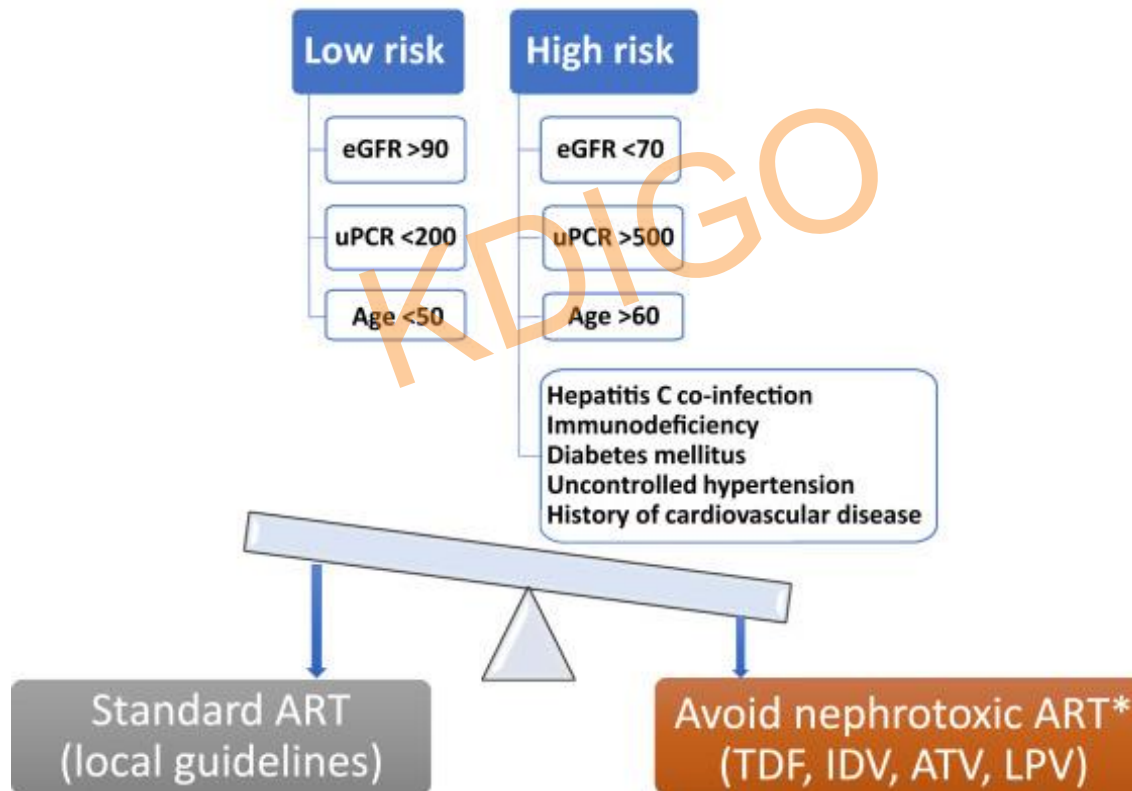
22,156 HIV-infected patients

366 developed ESRD

	No ESRD (n=21,790)	ESRD (n=366)	P value
Age (y)	45 +/- 10	45 +/- 8	0.9
Female	2.2%	2.2%	0.9
Race			<0.001
White	36%	13%	
Black	42%	85%	
Other	4%	3%	
Unknown	18%	0%	
Body Mass Index (kg/m ²)	24.9 +/- 4.5	24.6 +/- 4.4	0.6
eGFR <60 ml/min/1.73m²	5%	46%	<0.001
Proteinuria			<0.001
0 mg/dL	84%	32%	
30–100 mg/dL	15%	43%	
300–1000 mg/dL	1%	26%	
Hypertension	30%	67%	<0.001
Diabetes	5%	20%	<0.001
Cardiovascular Disease	5%	8%	0.01
Dyslipidemia	8%	8%	0.7
CD4 Count (cells/mm³)	285 (289)	236 (243)	0.008
Viral Load (copies/mL)	82,009 (166,484)	96,007 (146,947)	0.5
Hepatitis C Virus Infection	20%	30%	<0.001
Hypoalbuminemia**	18%	37%	<0.001
Antiretroviral Therapy	25%	21%	0.06
Statin Use	2%	1%	0.09
ACE Inhibitor Use	2%	4%	0.02

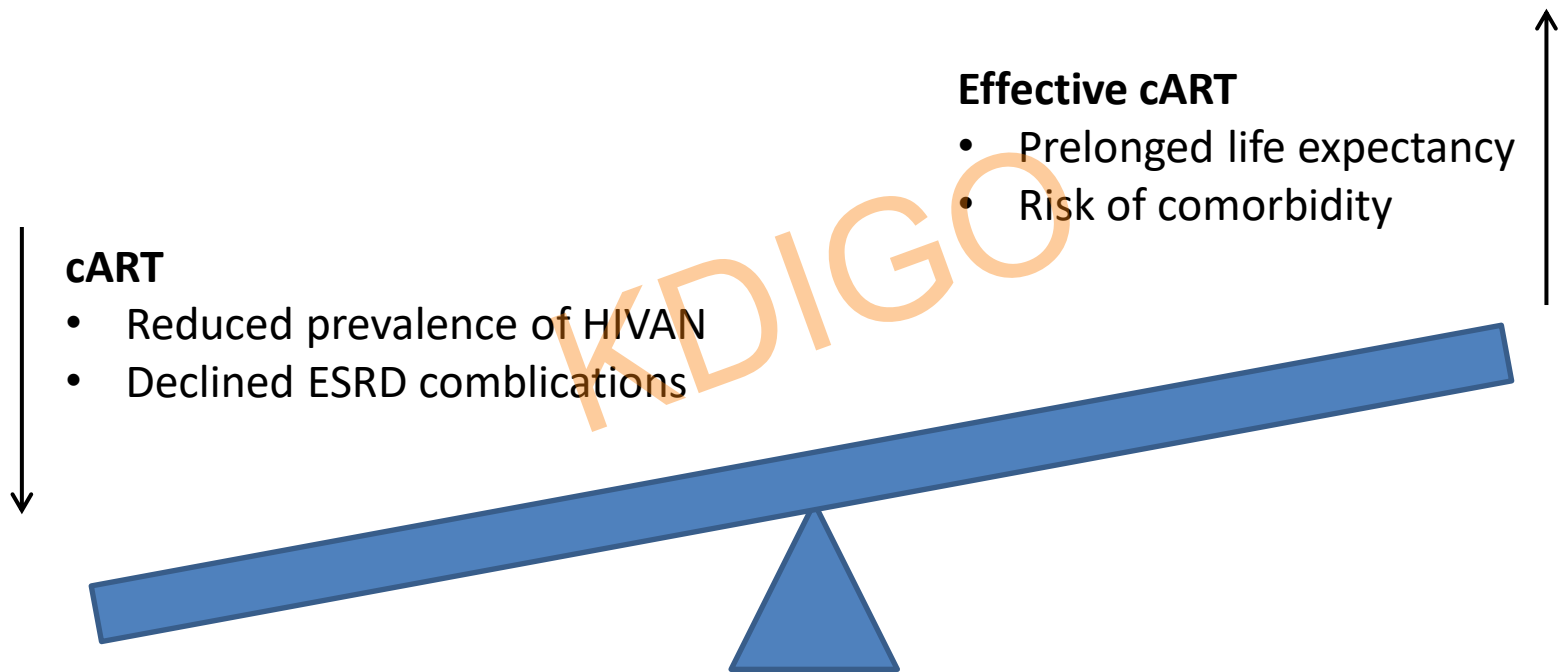
HIVAN Treatment

- No specific HIVAN treatment available
- Assessment of CKD risk scores:



Management of ESRD in HIV Infected Persons

Risk of renal disease in HIV infected individuals

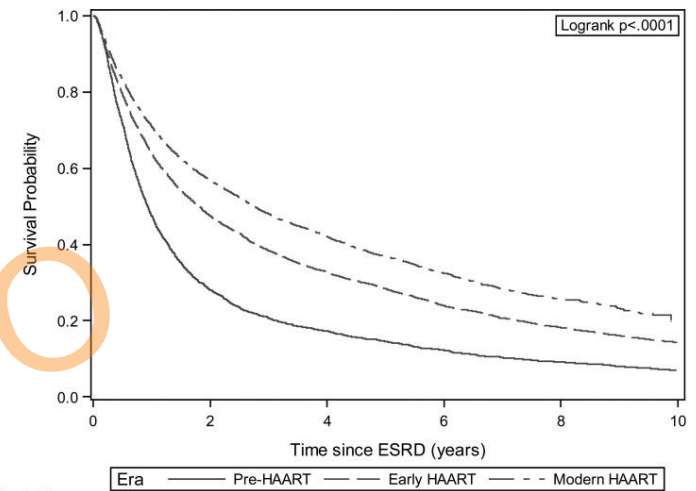
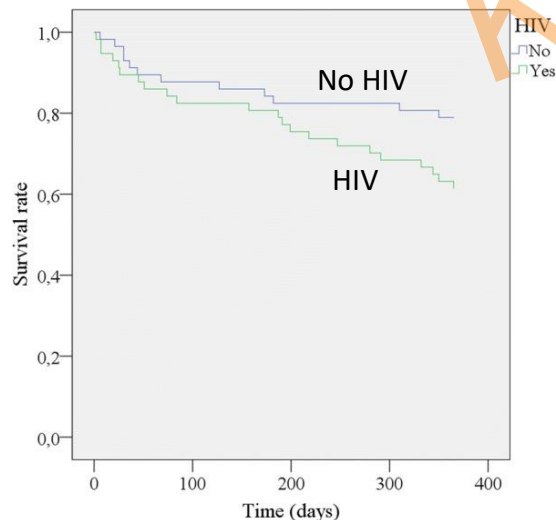


→ Increase need of HIV+ patients for dialysis and kidney transplantation

Management of ESRD in HIV Infected Persons

1. Dialysis

Country (reference)	Year	Total number of patients on dialysis	Prevalence of HIV infection (%)
United States ¹⁰	1985	ND	0.3
	2002	263,820	1.5
Europe ^{11,12}	1984-1986	> 4000	0-5
	1990	152,658	0.12
Italy ¹³	1990	21,500	0.11
	1995	27,000	0.13
France ^{14,15}	1997	22,707	0.36
	2002	27,577	0.67
Spain ^{16,17}	2004	4962	1.15
	2006	14,876	0.54
Egypt ¹⁸	1991	5000	1.64



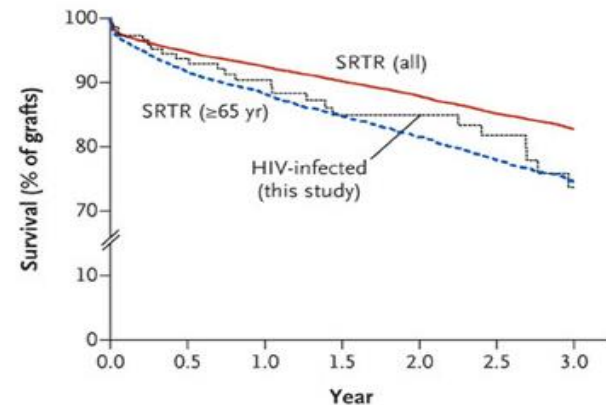
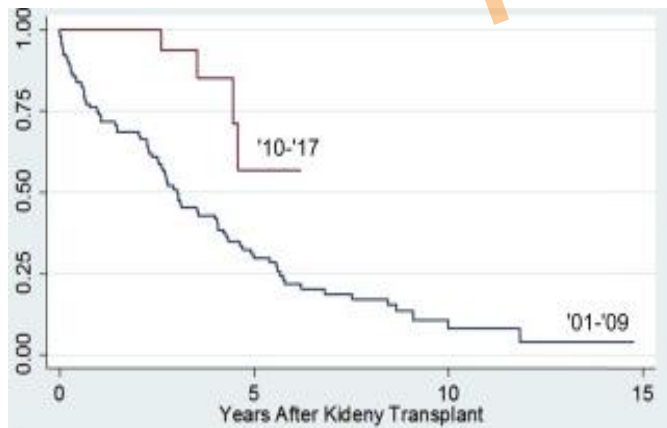
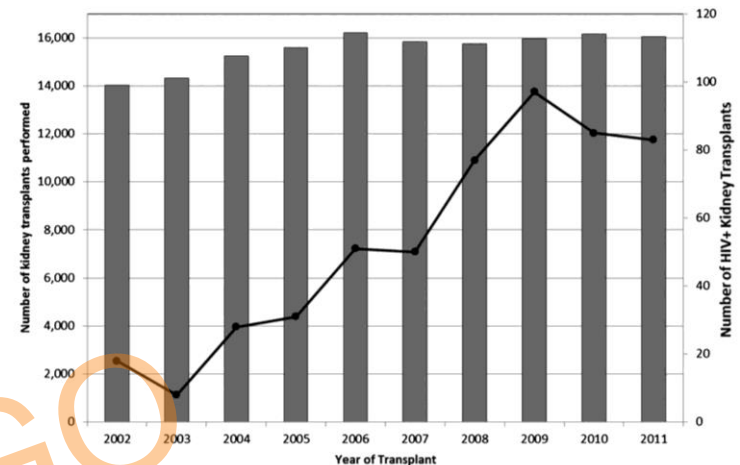
Main risk factors:

- Ineffective control of viral load (41%)
- Side infections

Management of ESRD in HIV Infected Persons

2. Transplantation

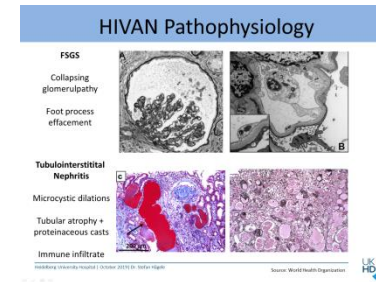
- **Criteria:**
 - Effective HIV suppression for ≥ 6 months
 - Undetectable plasma HIV-1 RNA
 - CD4+ cell count > 200 cells/mm³
- **Risks:**
 - Immunosuppressiva and low CD4 count
 - Interactions of Immunosuppressiva with cART



Summary

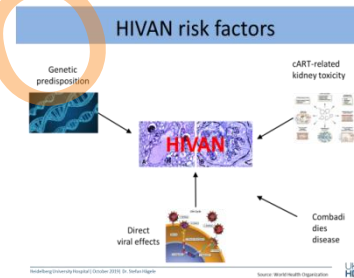
1. HIV can cause kidney injury

- Control of kidney parameters
- Biopsy if required



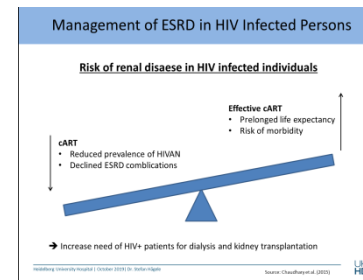
2. Risk factors:

- Genetic depositions
- Direct viral effects
- Drug nephrotoxicity



3. Therapy

- Adjustment of cART
- Dialysis
- Transplantation



Thank you for your attention



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