Therapeutic Approach to the HIV-Positive Patient

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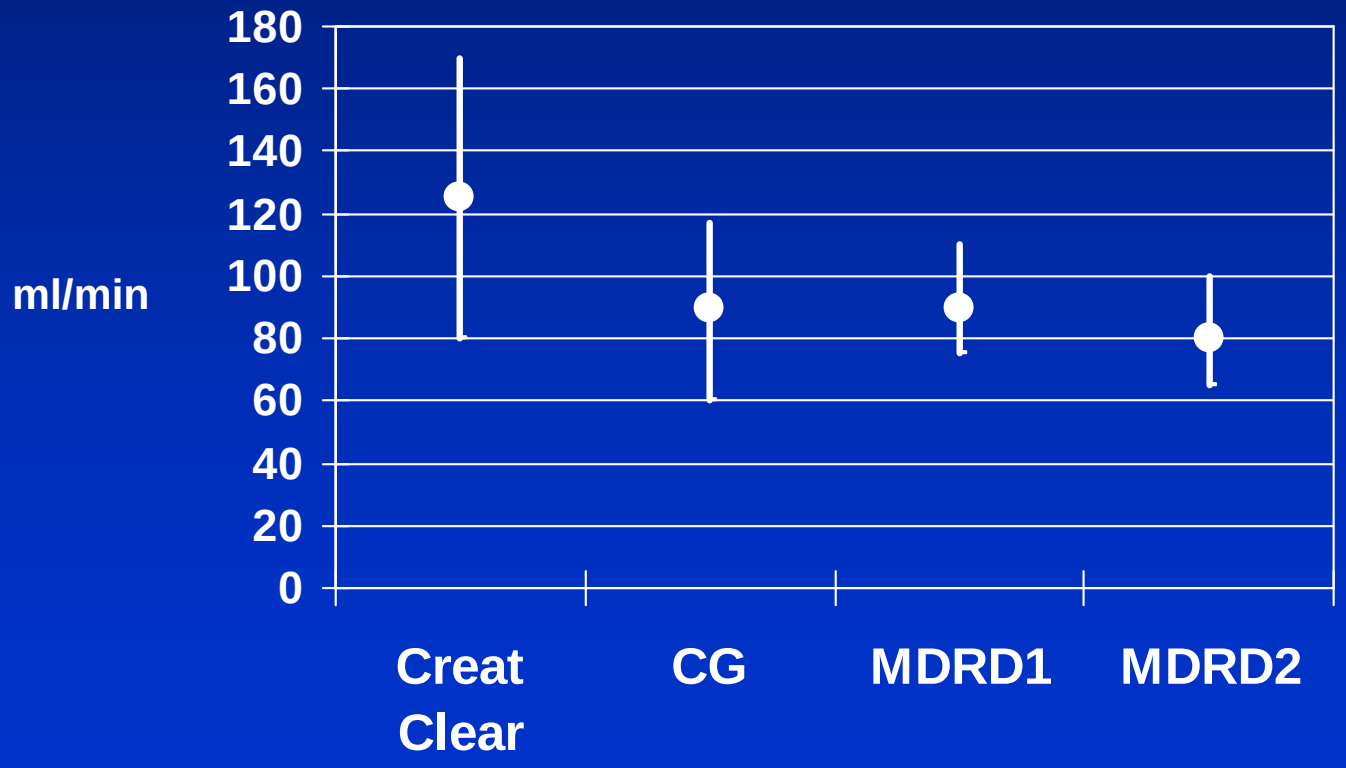
Topics

- Assessing GFR
- HIVAN treatment
- TTP/TMA
- Dialysis
- Nephrotoxicity of HIV therapies

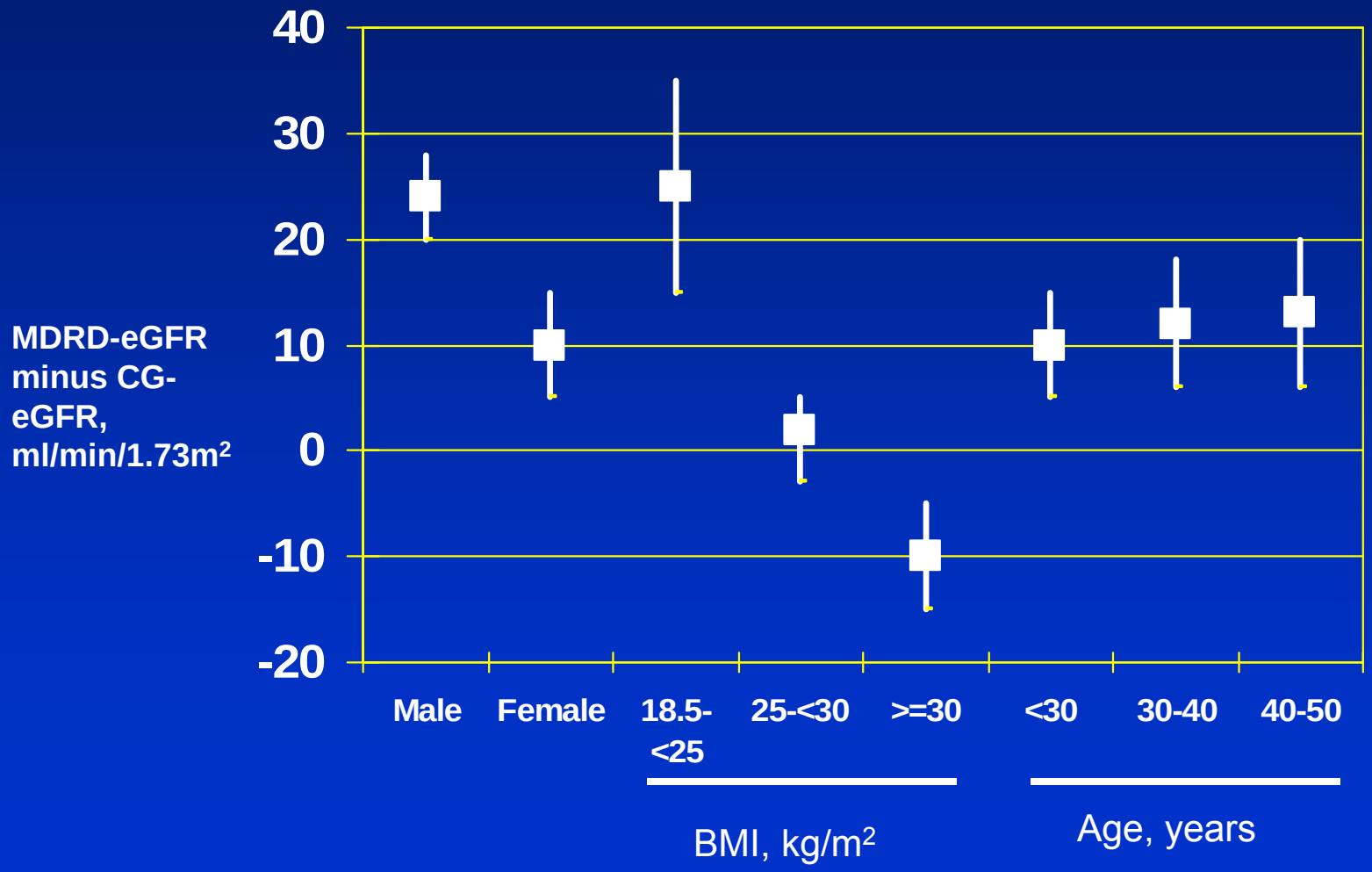
Estimating GFR in HIV Patients

Comparison of GFR Estimates



From Ravasi, et al. HIV Medicine 2009

Estimating GFR in African HIV-Infected Patients



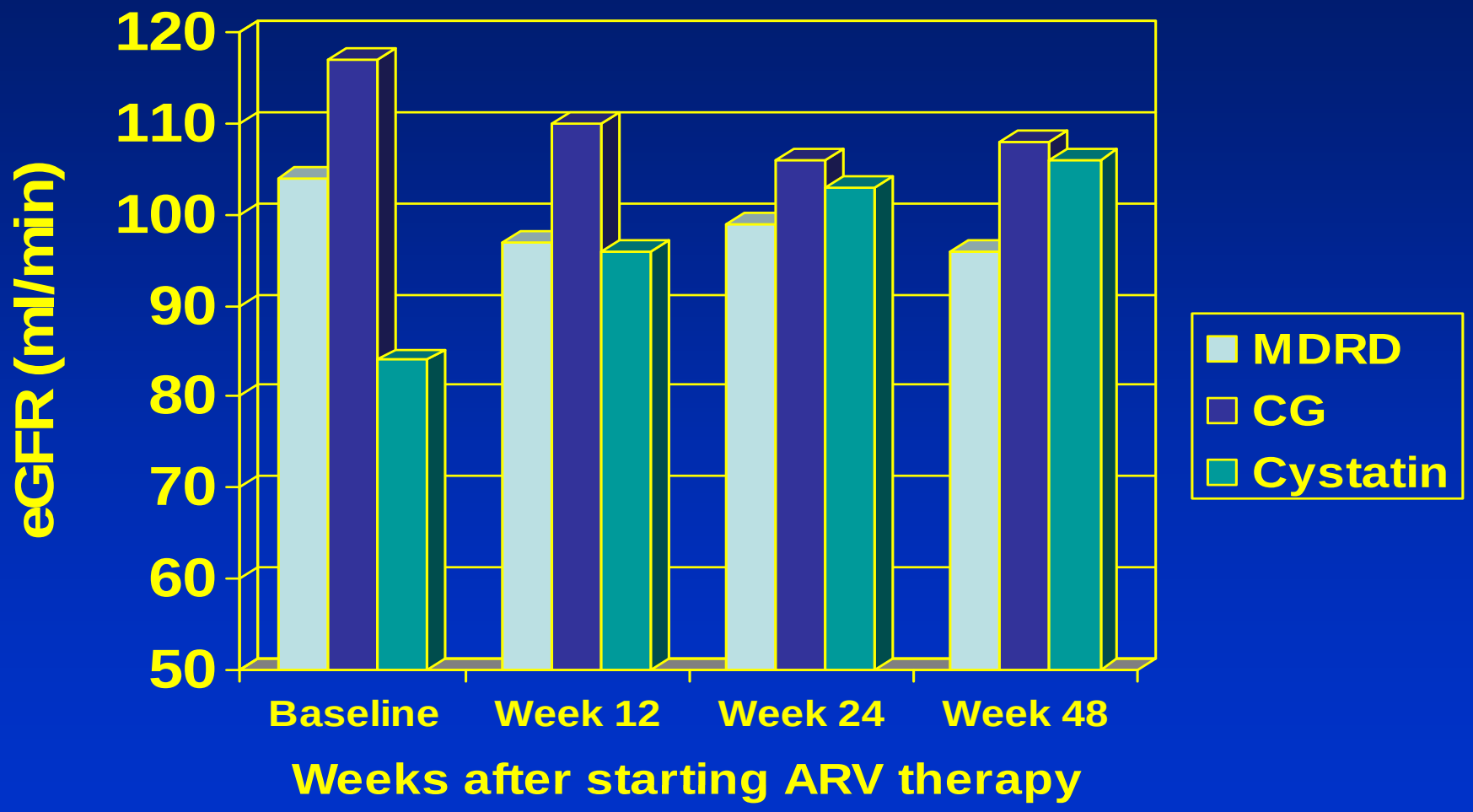
From Stöhr, et al. Antiviral Ther 2008

Cystatin C in HIV Patients

- Higher levels in HIV-infected patients compared to controls with comparable creatinine levels and other GFR measures
- Higher levels with higher viral load
- HAART lowers and interruption of HAART increases cystatin C levels acutely

- Are changes in cystatin C indicative of non-renal effects on cystatin C or measures of subtle HIV renal involvement?

Estimating GFR in HIV patients



From Mauss, et al. Antiviral Ther 2008

Estimating GFR in HIV Patients

- Among a population of mostly male, Caucasian, reasonably healthy HIV-infected patients on HAART:
  - Compared various GFR estimates to Tc-99m Pentetate-GFR
    - Bias: eGFR – nuclear GFR
    - Relative accuracy: % of estimates within 30% of nuclear GFR
  - MDRD: fair bias (-10), good relative accuracy (89%)
  - CG: minimal bias (-4) but only fair relative accuracy (70%)
  - 24-hour creatinine clearance: low bias (+6), good relative accuracy (88%)
    - More likely to be within 10 and 20% of nuclear GFR than MDRD
  - Cystatin C: most bias (-29) and lowest relative accuracy (41%); most tended to underestimate GFR

From Barraclough, et al. 2009

Summary: Estimating GFR

- Cystatin C least accurate
  - Uncertainty regarding changes due to HAART on GFR
- Abbreviated MDRD and 24-hour creatinine clearance provide reasonable (and similarly) accurate assessments of GFR
- Though somewhat less accurate, drug dosing recommendations are still mostly based on Cockcroft-Gault calculations
- Remains to be well studied in African Americans, less healthy HIV(+) patients
  - Protein/creatinine ratio validated in children with HIV—not tested in adults

Drug Dosing Considerations

- Some HAART agents need dose adjustments for reduced GFR and dialysis
  - Especially NRTIs (other than abacavir)
- PK data often sparse
- Drug combinations
- No information on clinical impact of PK-based dosing changes
- Potential for drug-drug interactions

Spectrum of Glomerular Disease in HIV-Infected Patients

- HIVAN-Collapsing FSGS
- Immune-complex GN
- Idiopathic FSGS
- HCV and cryoglobulinemia
- TMA
- Membranous
  - HBV
  - Malignancy
- Minimal change nephropathy
- IgA nephropathy
- Post-infectious GN
  - Infectious endocarditis
  - Other infections

HIVAN and ACE Inhibition

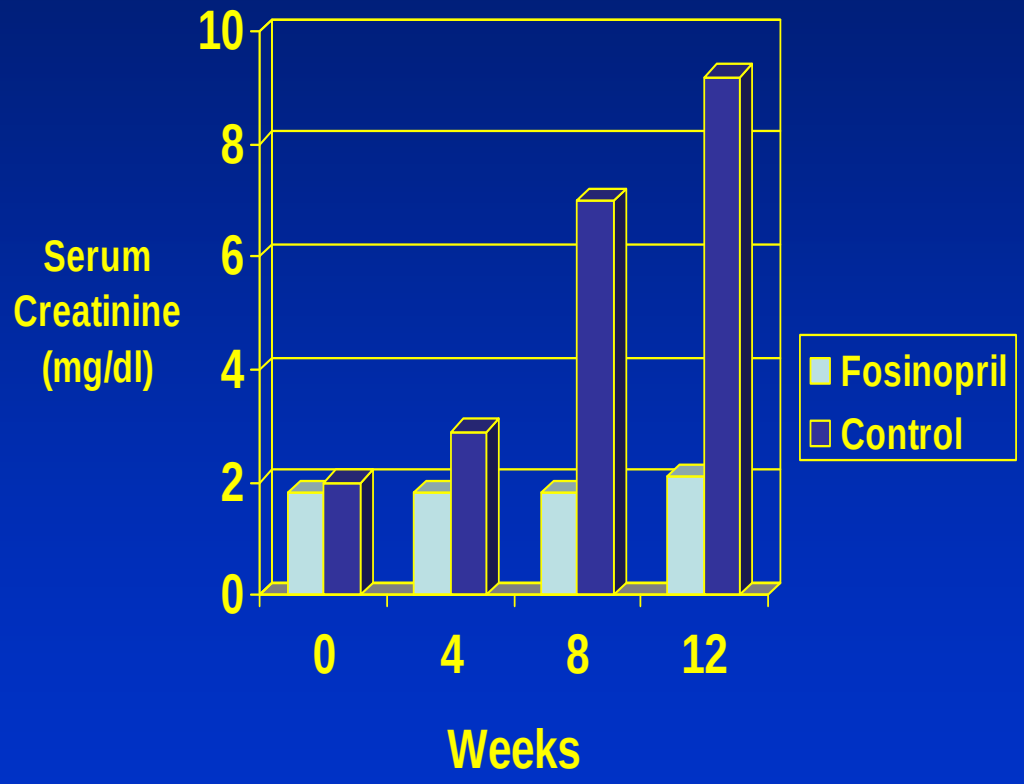
- Angiotensin II worsens podocyte injury of HIVAN in murine models
- ACE inhibition inhibits development and progression of HIVAN in murine models
  - No protection provided with other BP medications
  - Independent of BP lowering effect

HIVAN and ACE Inhibition

- Captopril in 9 patients (creatinine 3.4 mg/dl, urine P/C 5.3) and 9 matched controls (creatinine 3.7 mg/dl, urine P/C 9.6) with HIVAN (Kimmel 1996)
  - Most on AZT +/- ddI or ddC
    - 5 untreated
  - 17 developed ESRD
  - Mean renal survival 156 vs. 37 days
    - Median survival 83 vs. 30 days
    - Urine protein not systematically studied

HIVAN and ACE Inhibition

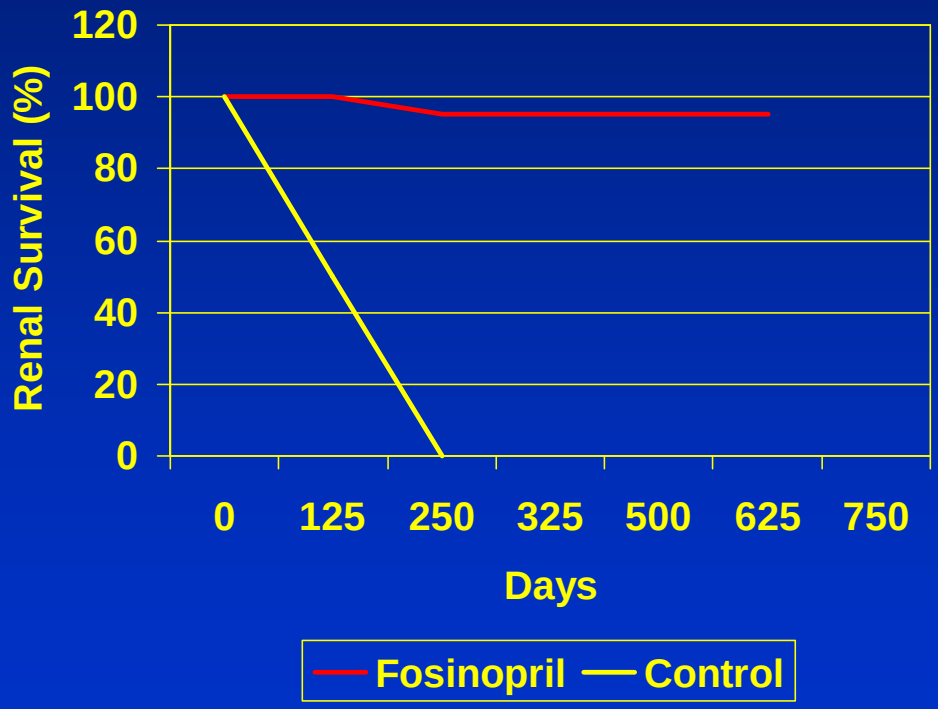
- Burns (1997): 20 patients with HIVAN (Nephrotic and non-nephrotic)
  - 12 agreed to treatment with fosinopril for 12-24 weeks
    - 7 patients treated with ARV therapy
  - Treated patients had stable or improved serum creatinine and proteinuria
  - Untreated patients had worsening renal function and proteinuria
    - 0/5 treated patients with NS → ESRD
    - 4/4 untreated patients with NS → ESRD by 4 mos



From Burns, et al KI 1997

HIVAN and ACE Inhibition

- Wei (2003): 44 patients with HIVAN
  - 28 received fosinopril, 16 served as controls
    - Serum creatinine ≤ 2 mg/dl
    - FU to 5.1 yrs
    - ~50% treated with ARV therapy
  - Median renal and overall survival
    - Treated: 480 days, 1 ESRD, 87.5% survival
    - Untreated: 147 days, all ESRD, 21.4% survival



From Wei, et al. KI 2003

HIVAN and ACE Inhibition

- Small observational studies
- No randomized controlled trials
- No studies with modern ARV therapy

- Seems like a reasonable thing to do
  - With proteinuria regardless of pathology
  - No studies of ACEi + ARB or ACEi vs. ARB
  - No studies of ACEi/ARB + spironolactone

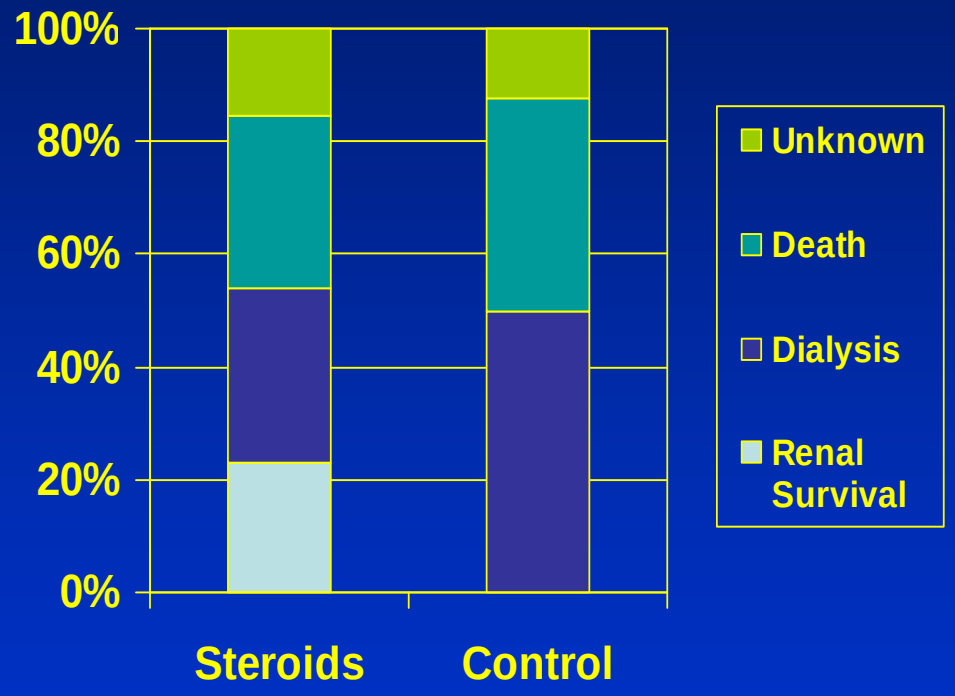
- Should be an adjunct to HAART

HIVAN and Corticosteroids

- Smith (1996): prospective study, 20 patients
  - Most with creatinine > 2 mg/dl and urine protein > 2 g/d
    - Most on AZT and/or ddI; 17 with biopsy HIVAN
  - Prednisone 60 mg daily for 2-14 wks
  - 17/19 with elevated creatinine had ≥ 20% decline in creatinine with prednisone
    - 8.1 → 3.0 mg/dl
    - 2 patients: no response → HD
    - 9 “relapsed”: 5 retreated with improvement
    - Proteinuria improved in 12/13 studied
  - 14/19 with azotemia died, on dialysis, lost to follow up
    - Longest FU 83 weeks

HIVAN and Corticosteroids

- Eustace (2000): retrospective cohort study, 21 patients with HIVAN and creatinine > 2 mg/dl
  - Prednisone 60 mg daily for 1 month, tapered
  - 13 treated; 8 eligible but not treated
  - At 3 mos:
    - 3/8 → ESRD vs. 0/13
  - At 12 mos:
    - 3/13 alive off dialysis with steroids vs. none in control group



HIVAN and Corticosteroids

- No randomized controlled trials
- No studies with modern HAART
- No studies with ACEi/ARB therapy
- Unclear if sustained vs. transient responses
- Risk of opportunistic infections

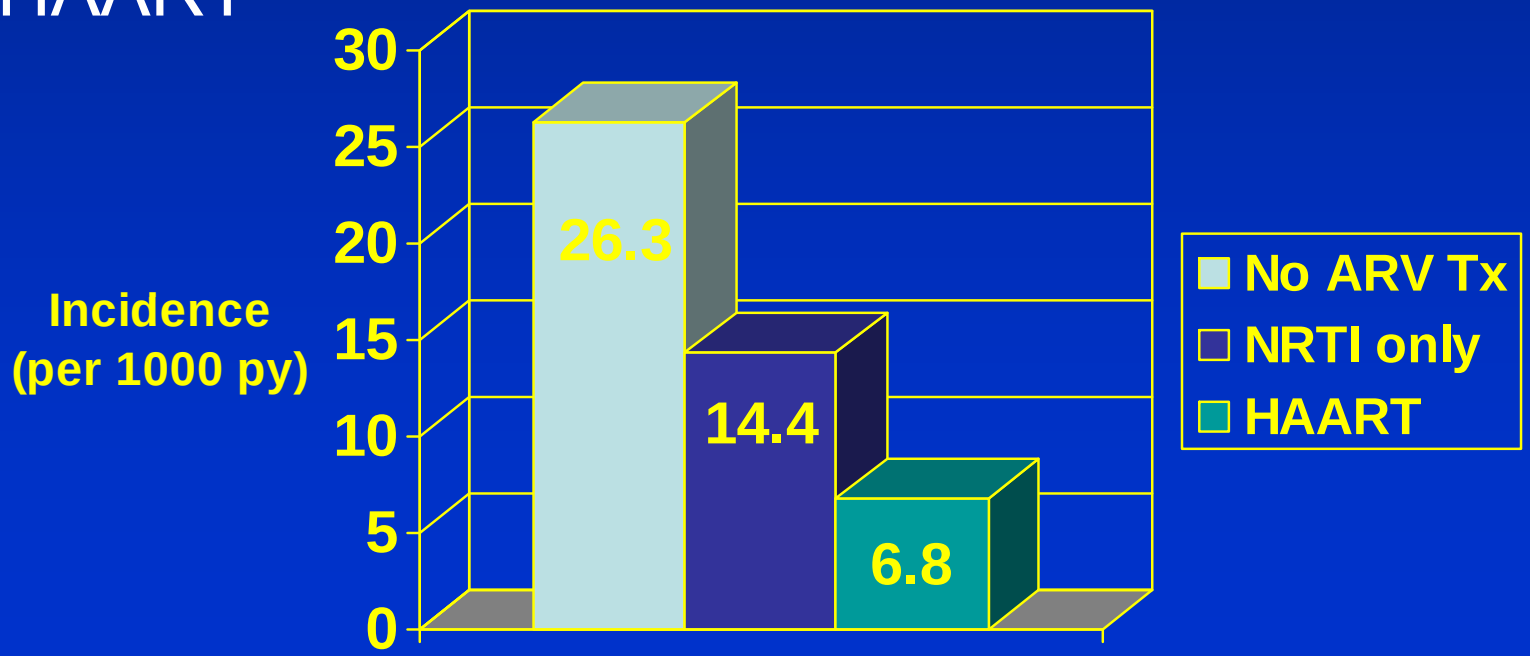
- Might consider if rapidly progressive disease or severe NS with HIVAN despite appropriate HAART, ACEi/ARB and low risk of infection

HIVAN and HAART

- Observational studies suggest ARV therapies may be beneficial
  - Transient remission of nephrotic syndrome with zidovudine; rapid progression to ESRD when treatment stopped (Babut-Gay 1989)
  - Indinavir compliant patients with stable renal function vs. noncompliant patients who progressed rapidly to ESRD (Ifudu 1995)
  - Recovery from ESRD and reversal (improvement) of histopathologic features of HIVAN (Wali 1998)
  - Reversal of ESRD in HIVAN with ARV therapy (Kirchner 2002, Scheurer 2004)
  - Relapse of HIVAN when HAART interrupted (Scialla 2007)

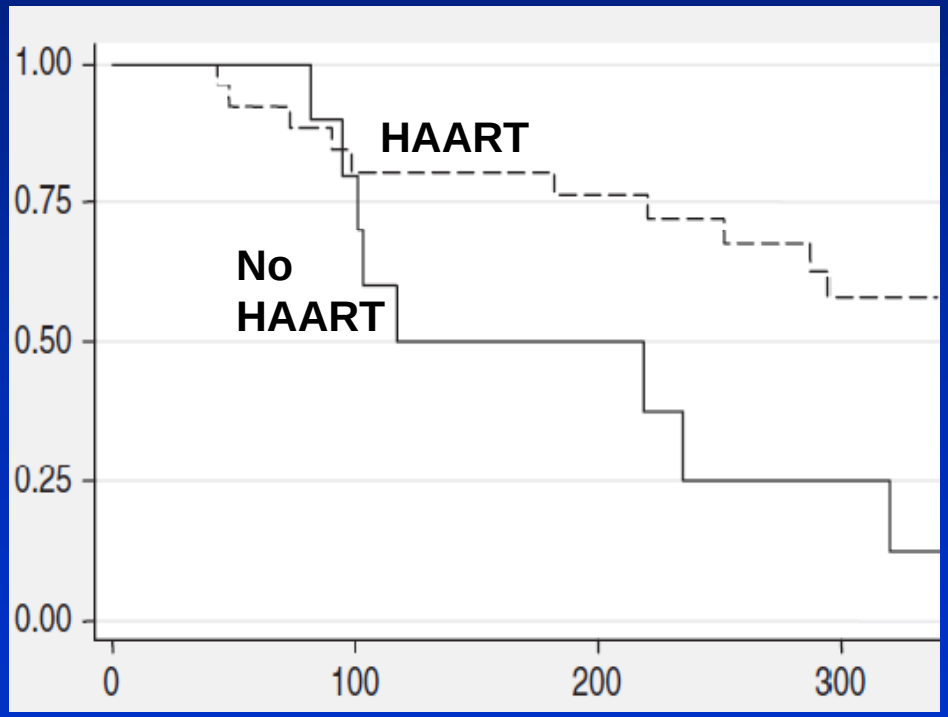
HIVAN Incidence with HAART

- Lucas (2004): Observational clinical cohort study
- HAART reduced HIVAN risk by 60%; no patients without AIDS developed HIVAN on HAART

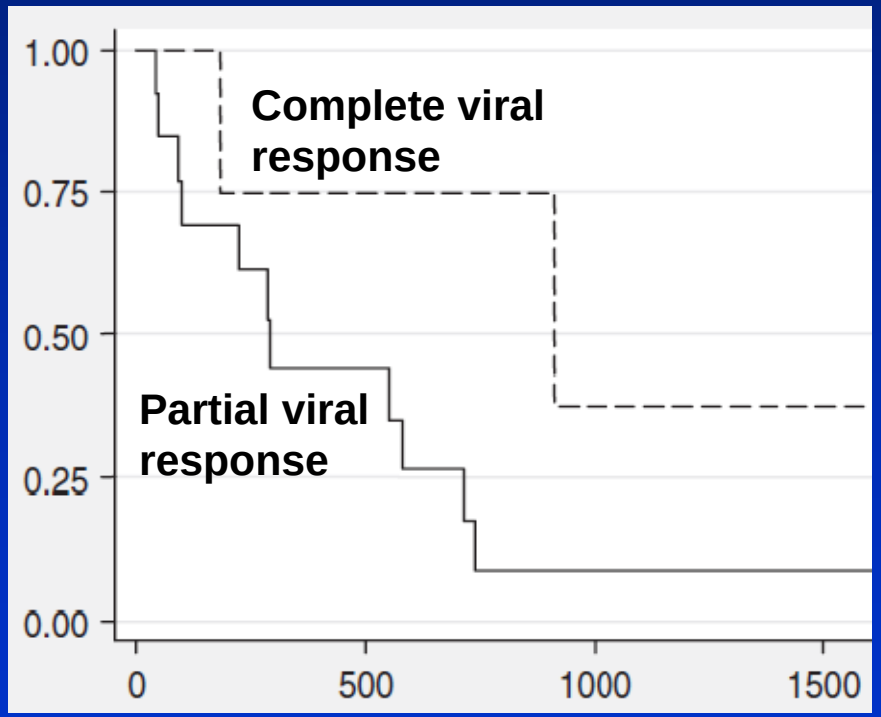


HIVAN Treatment with HAART

Renal survival HIV-infected cohort with HIVAN



Follow Up (days)



Follow Up (days)

Modified from Atta, et al NDT 2006

HIVAN Treatment with HAART

- Initiation of HAART → GFR improvement
  - Associated with suppression of HIV replication and suppression of viremia
  - Most evident in patients with lower eGFR and CD4 count < 200 cells/μL at baseline
  - GFR improvement also seen in patients with higher CD4 counts but not directly related associated to an effect on viral replication
  - Independent of race

(Kalayjian et al 2008)

Conclusions—HIVAN

- Antiretroviral therapy should be started when HIVAN is diagnosed—may improve kidney function and reduces progression of HIVAN → ESRD
  - International AIDS Society-USA Panel
  - US Health and Human Services
- HAART does not appear to benefit non-HIVAN renal diseases
- Non-nephrotic proteinuria with/without azotemia
  - Unknown benefit of “early” treatment
- Use ACE inhibitor/ARB
- Steroids in selected patients on HAART?

TTP/TMA in HIV-Infected Patients

- Typical features as seen in others with TTP
- Need to exclude other causes
  - Malignant hypertension
  - Disseminated Kaposi sarcoma
- Incidence may be lower in HAART era
  - 1-7% of patients with nearly 100% mortality
  - More recently < 0.5% of patients; mostly not on HAART

TTP/TMA in HIV-Infected Patients

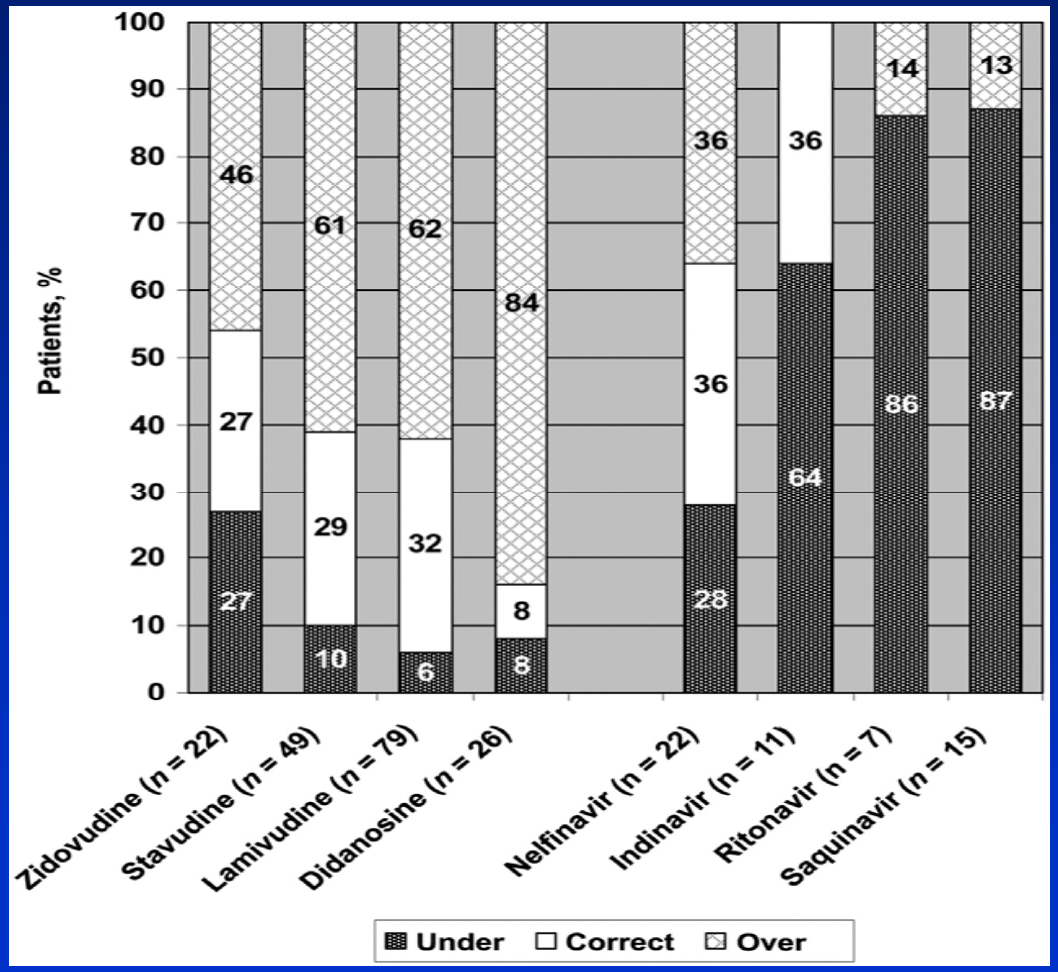
- ADAMTS13
  - Very low activity in 45-70% of patients
    - May be due to HIV-mediated endothelial infection and injury
    - vWF levels tend to be high in HIV patients
  - Inhibitors in $\leq$ 50% of patients
    - Severely reduced ADAMTS13 levels without inhibitors may be poor
    - prognostic marker
  - Outcome better in patients with lower activity

- Treatment:
  - HAART
  - Plasma infusion
  - Plasma exchange—especially if low ADAMTS13 activity
  - Relapse if HAART interrupted

Dialysis Outcomes in HIV-Infected Patients

- Mortality rate among HIV-infected dialysis patients declined after 1995, the year HAART was introduced, in most but not all studies
- In French study comparing HIV (+) patients with other HD patients without HIV or DM—nearly identical 2-year survival (~90%)
  - Viral load, no HAART, H/O opportunistic infections = mortality risk factors
  - Tourret, et al. CJASN 2006
- Important issues: HCV co-infection, IVDU, HAART use and dosing

HAART Dosing Errors in HD Patients

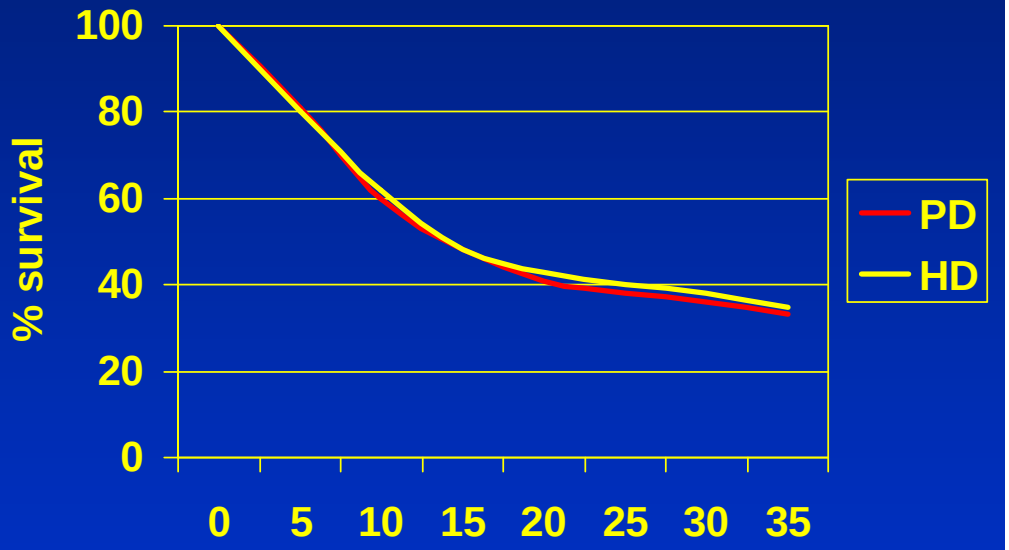


- Underdosed patients had loser CD4+, more severe HIV disease, and poorer survival

Tourret, et al 2007

Dialysis Outcomes in HIV-Infected Patients

- Similar outcomes with PD compared to HD
- Patient survival on PD depends mostly on HIV status and treatment
  - More peritonitis
  - Higher hospitalization rates
  - HIV survival in PD fluid for up to 7 days and in tubing for up to 2 days



From Ahuja, et al, 2003

Hemodialysis Access in HIV Infected Patients

- AV fistula survival similar in HIV (+) and control patients
- Higher AV graft thrombosis rate
  - One-year thrombosis-free graft survival lower
    - 17% vs. 62% in controls (Mitchell 2007)
    - 49% vs. 77% in controls (Curi 1999)
  - Lower cumulative graft survival
  - Higher graft infection rate—especially with history of IVDU but also in patients without IVDU history
- Catheter-related bacteremia not more common than in control patients
  - Polymicrobial and GNR infection may be more common
  - Catheter survival similar

Nephrotoxicity of Antiretroviral Therapies

- Crystal-related injury
  - Indinavir
  - Atazanavir
    - Rare case reports with other PI and efavirenz (NNRTI)
  - IV acyclovir
  - Sulfadiazine
- Tenofovir
  - AKI
    - May be progressive and only partially reversible
  - Fanconi syndrome
  - Nephrogenic DI (rare)
  - Mitochondrial toxicity due to DNA depletion, inhibition of DNA polymerase γ
- Lactic acidosis
  - NRTI
  - May be asymptomatic or severe
  - Associated with liver disease, other organ systemic involvement
- Others—mostly isolated reports
  - AIN/CIN
  - Fanconi syndrome
  - RTA
  - DI
  - Rhabdomyolysis

Conclusions

- GFR estimation:
  - MDRD and 24-hr creatinine clearance most accurate
    - Cystatin C least accurate
    - Drug dosing recommendations still mostly based on Cockcroft-Gault calculations
- HIVAN treatment
  - ARV therapy should be started when HIVAN is diagnosed
  - HAART does not benefit non-HIVAN renal diseases
  - ACE inhibitor/ARB
  - Steroids in selected patients—remains uncertain
- Dialysis
  - Short-term patient survival similar to other ESRD patients
  - Outcomes with PD and HD are similar
  - AV fistula survival similar to other HD patients
  - Higher AV graft thrombosis and infection risk
  - Catheter-related BSI not more common but more polymicrobial and Gram (-) infection