Current aspects of renal diseases in HIV infection

Eric DAUGAS
Service de Néphrologie
Hôpital Bichat – Paris
France
1996 = HAART
highly active antiretroviral therapy
combination of three antiretroviral agents
two RTI + one PI or
three RTIs
EPIDEMIOLOGY
of
renal diseases
in HIV infected patients
HIV is a CKD risk factor

**Table 2. Characteristics of the HERS cohort by the end of research visit 5**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HIV-positive (N = 885) N (%)</th>
<th>HIV-negative (N = 425) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of follow-up, visits 1–5</td>
<td>21.0 months</td>
<td>21.3 months</td>
</tr>
<tr>
<td>Women with clinical AIDS</td>
<td>44 (5.0)</td>
<td>—</td>
</tr>
<tr>
<td>Women with renal abnormalities, by race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>192 (21.7)</td>
<td>28 (6.6)*</td>
</tr>
<tr>
<td>African-American</td>
<td>153/538 (28.4)</td>
<td>19/225 (8.4)ab</td>
</tr>
<tr>
<td>White</td>
<td>20/183 (10.9)</td>
<td>6/134 (4.5)b</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18/152 (11.8)</td>
<td>2/62 (3.2)b</td>
</tr>
<tr>
<td>Other</td>
<td>1/12 (8.3)</td>
<td>1/4 (25.0)</td>
</tr>
</tbody>
</table>

## High prevalence of CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Proteinuria %</th>
<th>Stage 3-5 CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szczech LA, Kidney Int, 2002</td>
<td>2057 (w)</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Gupta SK, Clin Nephrol, 2004</td>
<td>487</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Overton E, CROI 2007</td>
<td>847</td>
<td>29</td>
<td>4%</td>
</tr>
<tr>
<td>Fernando SK, Am J Med Sci 2008</td>
<td>400</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>
CKD is associated with uncontrolled HIV

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Viral load</td>
<td>• CD4 ≤ 200 mm$^3$</td>
</tr>
<tr>
<td>• CD4 ≤ 200 mm$^3$</td>
<td>• Viral load</td>
</tr>
<tr>
<td>• Afro-american</td>
<td>• Hypertension</td>
</tr>
<tr>
<td>• HCV</td>
<td>• Hypoalbuminemia</td>
</tr>
</tbody>
</table>

Szczech LA, Kidney Int, 2002
**CKD = 3rd death risk factor in this study**


<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio adjusted$^a$</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.2 per 10 years</td>
<td>(0.96, 1.45)</td>
<td>.11</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White vs. black</td>
<td>1.3</td>
<td>(0.89, 1.81)</td>
<td>.19</td>
</tr>
<tr>
<td>Hispanic/other vs. black</td>
<td>1.3</td>
<td>(0.89, 1.84)</td>
<td>.18</td>
</tr>
<tr>
<td>CD4 cell count &gt;500 vs. &lt;200</td>
<td>0.3</td>
<td>(0.18, 0.48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CD4 cell count 200–500 vs. &lt;200</td>
<td>0.4</td>
<td>(0.30, 0.57)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Viral load from 500 to 10,000 vs. &lt;500</td>
<td>1.8</td>
<td>(0.84, 3.70)</td>
<td>.13</td>
</tr>
<tr>
<td>Viral load above 10,000 vs. &lt;500</td>
<td>3.5</td>
<td>(1.68, 7.44)</td>
<td>.002</td>
</tr>
<tr>
<td>Clinical AIDS</td>
<td>4.1</td>
<td>(2.99, 5.50)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HAART use vs. other ART or no ART</td>
<td>0.7</td>
<td>(0.44, 1.03)</td>
<td>.07</td>
</tr>
<tr>
<td>Hepatitis C antibody positivity</td>
<td>1.5</td>
<td>(1.07, 2.01)</td>
<td>.02</td>
</tr>
<tr>
<td>Injection drug use at enrollment</td>
<td>1.1</td>
<td>(0.81, 1.49)</td>
<td>.53</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.2</td>
<td>(1.10, 4.35)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.9</td>
<td>(1.21, 2.84)</td>
<td>.004</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>2.5</td>
<td>(1.90, 3.32)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Acute renal failure

Prospective data from 754 patients between 2000 and 2002

- incidence = 5.9 %/year
- #100 x Population générale

Risk factors
- <200 T4/mm³
- Detectable viral load
- AIDS
- HCV

Franceschini et al. Kidney Int, 2005
Modifications of renal diseases profile in HAART era
New profile of kidney diseases in HAART era

- Improved control of HIV
- Control of HIV-related renal diseases
- Prolonged life with a continuous exposure to HIV and to therapies
- Immune reconstitution
HIV-related
Directly due to HIV (group 1)
- HIVAN
- TMA
- Immune complexe GN
Related to immune deficiency (group 2)
Infiltrative interstitial nephritis (Lymphomas, DILS…)
- Infectious interstitial nephritis
- Infectious GN
- Amyloidosis?

Unrelated to HIV context (group 4)
Diabetic nephropathy,
Vascular nephropathy
HCV-related…

Related to HAART (group 3)
Direct nephrotoxicity
Indirectly: IRIS

pre-HAART era

1996

HAART era

Time
HIVAN: HIV-Associated Nephropathy

Kimmel, Barisoni and Kopp; Ann Intern Med; 2003
Beneficial effect of Zidovudine on HIVAN course in pre-HAART era

- Michel C., Nephron 1992
- Ifudu O., Am J Nephrol 1995
HIVAN and HAART

Dialysis

Proteinuria
10 g/d

Creatinine
132 µmol/L

Proteinuria
#1g/d

Wali et al; Lancet 1998
HIVAN and HAART

Creatinine 557 µmol/L
Proteinuria 17 g/d

Creatinine 124 µmol/L
Proteinuria 1.5 g/d

Winston et al; NEJM 2001
HIVAN/HAART in African American

Lucas et al, AIDS, 2004

Fig. 1. The incidence of HIV-1-associated nephropathy by calendar period and AIDS status. Brackets represent 95% confidence intervals.

Fig. 2. HIV-1-associated nephropathy incidence stratified by AIDS status and antiretroviral use. White bars, no antiretroviral use; blue bars, NRT alone; purple bars, HAART.
HIVAN/HAART in African American

Schwartz et al, JASN, 2005
HIVAN / HAART in Paris

HIVAN on histology

126 patients in pre-HAART era
Mean creatinine 496µmol/L

versus

33 patients HAART
Mean creatinine 592µmol/L

Laradi et al, JASN 1998 and Burckle et al; Am Soc Nephrol; 2002
Guidelines for HIVAN treatment

**Recommendation 4.** Patients with (B-II). HAART should not be withheld from patients simply because of the severity of their renal dysfunction (B-III).

Gupta SK et al. Clin Infect Dis 2005
Immune glomerulonephritis

- Caucasians
- Numerous nosologic entities

- IgA nephritis: 8% prevalence in Beaufils et al NDT 1995
  Eluted immune complex including IgA anti-HIV: Kimmel et al, NEJM 1992
  Treatment with HAART????
Thrombotic microangiopathy

Decreased incidence in HAART era

Gervasoni et al, Clin Infect Dis, 2002
Becker et al, Clin Infect Dis, 2004

Direct and indirect effect of HIV containment by HAART
Renal toxicity of HAART
Indinavir

Renal and urological disorders related to crystalluria

Daudon M et al Lancet. 1997 May 3;349(9061):1294-5
Indinavir (Crixivan°)

- Clinical manifestations
  - Renal colic / Flank pain / Dysuria / Gross hematuria
  - Urolithiasis / radiolucent calculi
  - Renal parenchymal defect / Papillary necrosis
  - Crystalluria / Leukocyturia / Microhematuria / Mild proteinuria
  - Acute renal failure / Chronic renal failure
  - Hypertension

- Histological findings
  - Tubulointerstitial nephritis with indinavir crystals in tubules

Discontinuation in 33% of patients
Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America

- Patients receiving indinavir should drink at least 1.5 L of water daily to prevent stone formation.
- Periodic monitoring of renal function and pyuria should be performed during the first 6 months of indinavir therapy and biannually thereafter,
- although routine screening for crystalluria is not warranted unless there is a suspicion of nephrolithiasis.
- Indinavir need not be withheld from patients with reduced renal function.
- In patients who develop indinavir nephrolithiasis, it would be reasonable to restart indinavir therapy once rehydration is achieved.
- Patients who develop indinavir-induced hypertension, pyuria, rhabdomyolysis, or renal insufficiency (acute or chronic) should permanently discontinue use of this drug.

# Renal toxicity of antiproteases

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (Reyataz®)</td>
<td>Interstitial nephritis, urolithiasis</td>
</tr>
<tr>
<td>Indinavir (Crixivan®)</td>
<td>Cristalluria, renal colic, AKI and CKD</td>
</tr>
<tr>
<td>Nelfinavir (Viracept®)</td>
<td>Urolithiasis, renal colic</td>
</tr>
<tr>
<td>Ritonavir (Norvir®)</td>
<td>AKI</td>
</tr>
</tbody>
</table>

Daugas E et al., Kidney International, 2005
Izzedine H et al. AIDS, 2007
Nucleotide reverse transcriptase inhibitors: tenofovir

Dose dependent nephrotoxicity
Exacerbated by
  advanced HIV disease,
  reduced GFR, no dosage adaptation to reduced GFR
  concurrent ritonavir or ddi,
  other nephrotoxic
5 to 12 months after starting tenofovir
Tenofovir (Viread° Truvada°)

- Proximal and distal tubular cells dysfunction
- Total or partial Fanconi’s syndrome
  - Earlier manifestations: Glucosuria and hypophosphatemia
  - Nephrogenic diabetes insipidus
- Acute renal failure
- One case including nephritic syndrome

Discontinuation
Total or (rarely) partial reversibility several months after discontinuation

Verhelst et al Am J Kidney Dis 2002
Rare in patient without prior kidney disease

The Safety of Tenofovir DF for the Treatment of HIV Infection: The First 4 Years
M Nelson,¹ D Cooper,² R Schooley,³ C Katlama,⁴ J Montaner,⁵ S Curtis,⁶ L Hsu,⁶ B Lu,⁶ S Smith,⁶ J Rooney,⁶ and the Viread Global Expanded Access Program

<table>
<thead>
<tr>
<th></th>
<th>EAP (n = 10,343)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(3,700 person years)</td>
</tr>
<tr>
<td></td>
<td># of patients</td>
</tr>
<tr>
<td>Any Renal SAEb</td>
<td>56</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>32</td>
</tr>
<tr>
<td>Renal Other</td>
<td>11</td>
</tr>
<tr>
<td>Serum Creatinine Inc / Inc BUN</td>
<td>10</td>
</tr>
<tr>
<td>Fanconi / Tubular / Hypophos / Glyco</td>
<td>7</td>
</tr>
<tr>
<td>Nephrogenic DI</td>
<td>1</td>
</tr>
<tr>
<td>Nephritis</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>0</td>
</tr>
</tbody>
</table>

http://www.natap.org/
Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America

Patients receiving tenofovir

- who have a GFR <90 mL/min per 1.73 m²,
- patients receiving other medications eliminated via renal secretion (e.g., adefovir, acyclovir, ganciclovir, or cidofovir),
- patients with other comorbid diseases (e.g., diabetes or hypertension),
- or patients receiving ritonavir-boosted protease inhibitor regimens

should be monitored at least biannually for measurements of renal function, serum phosphorus, and urine analysis for proteinuria and glycosuria.

- Dosage adaptation to reduced GFR.

Renal IRIS

Differential diagnosis of HAART renal toxicity
Immune restoration inflammatory syndrome (IRIS)

Patient with severe immune deficiency

Silent spread of infectious agent

HAART initiation

Immune restoration

“Paradoxical” inflammatory response
IRIS

Up to 1/3 of patients coinfected with Mycobacterium tuberculosis, MAC or Cryptococcus neoformans

Time between HAART and IRIS: #6-7 weeks

Risk factors

- male gender
- long duration and deep immunodeficiency
- first introduction of HAART
- short delay between treatment of opportunistic infection and HAART
- marked increase of CD4 T cell count and reduction of HIV RNA level

Shelburne SA et al; AIDS, 2005;19:399
IRIS: infectious agents and clinical manifestations

• Wide spectrum of pathogens
• General manifestations
• Visceral manifestations (hepatitis, pneumonitis, encephalitis, lymphadenopathies, splenomegaly..)
• Life threatening in most severe cases
• Management: continuation of HAART and antiinfectious treatment, addition of antiinflammatory therapy: steroid therapy

Hirsch HH et al, Clin Infect Dis 2004;38:1159-
<table>
<thead>
<tr>
<th>References</th>
<th>Jehle et al</th>
<th>Daugas et al</th>
<th>Daugas et al</th>
<th>Izzedine et al</th>
<th>Salliot et al</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial CD4-cell count (/mm³)</strong></td>
<td>69</td>
<td>26</td>
<td>11</td>
<td>37</td>
<td>88</td>
</tr>
<tr>
<td><strong>Initial RNA viral load (copies/ml)</strong></td>
<td>1,247,786</td>
<td>56,732</td>
<td>169,850</td>
<td>&lt;750,000</td>
<td>177,504</td>
</tr>
<tr>
<td><strong>Infectious agent</strong></td>
<td>TB</td>
<td>TB</td>
<td>MAC</td>
<td>TB</td>
<td>TB</td>
</tr>
<tr>
<td><strong>Time from OI treatment to HAART (days)</strong></td>
<td>15</td>
<td>30</td>
<td>4</td>
<td>-90</td>
<td>45</td>
</tr>
<tr>
<td><strong>Time from HAART to IRIS (days)</strong></td>
<td>60</td>
<td>4</td>
<td>70</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td><strong>CD4-cell count (/mm³)</strong></td>
<td>82</td>
<td>97</td>
<td>299</td>
<td>148</td>
<td>326</td>
</tr>
<tr>
<td><strong>RNA viral load (copies/ml)</strong></td>
<td>104</td>
<td>373</td>
<td>162</td>
<td>&lt;200</td>
<td>494</td>
</tr>
<tr>
<td><strong>Creatinine level (µmol/l)</strong></td>
<td>433</td>
<td>143</td>
<td>252</td>
<td>346</td>
<td>700</td>
</tr>
<tr>
<td><strong>Others IRIS-related symptoms</strong></td>
<td>Worsening of pulmonary infiltrate</td>
<td>Fever, abdominal lymphadenopathy, salpingitis, ascitis</td>
<td>Fever, weight loss, severe cholestasis</td>
<td>Erythematous skin lesions, lymphadenopathy, splenomegaly, cholestasis</td>
<td>None</td>
</tr>
<tr>
<td><strong>Kidney biopsy</strong></td>
<td>Granulomatous interstitial nephritis</td>
<td>Interstitial nephritis</td>
<td>Liver biopsy: extensive granulomatous inflammation</td>
<td>Granulomatous interstitial nephritis</td>
<td>Granulomatous interstitial nephritis</td>
</tr>
<tr>
<td><strong>Steroid therapy (1 mg/kg/day) duration (months)</strong></td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Healthy with normal renal function</td>
<td>Healthy with normal renal function</td>
<td>Healthy</td>
<td>Healthy with normal renal function</td>
<td>Healthy with normal renal function</td>
</tr>
</tbody>
</table>
Case report

51-year-old Chinese man
No previous medical history

Disseminated tuberculosis revealed HIV-1
CD4 cell 80/mm³
RNA viral load 177,504 copies/ml
GFR 92 mL/min/1.73 m² (creatinine: 62 µmol/L)
Antituberculosis therapy

HAART including tenofovir

RNA viral load (copies/ml)
Creatinine level (µmmol/l)
CD4-cell count (/mm³)
Acute renal failure with tubulointerstitial nephropathy syndrome

Antituberculosis therapy

HAART including tenofovir
Acute renal failure with tubulointerstitial nephropathy syndrome

Tenovir toxicity? IRIS?

Antituberculosis therapy

HAART including tenofovir

Time (months)

Serum creatinine level (µmol/l)

Creatinine level (µmol/l)

CD4-cell count (/mm³)

RNA viral load (copies/ml)
Antituberculosis therapy

HAART including tenofovir

Acute renal failure with tubulointerstitial nephropathy syndrome

Tenofovir toxicity? IRIS?

Renal biopsy
J Vérine, Hôpital Saint-Louis, Paris
Antituberculosis therapy

HAART including tenofovir

RNA viral load (copies/ml)
Creatinine level (µmol/l)
CD4-cell count (/mm³)
Antituberculosis therapy

HAART including tenofovir

Prednisone
However HAART is beneficial
The Strategies for Management of Antiretroviral Therapy (SMART) trial

5472 patients, HIV, >350 CD4+/mm³

Open randomized controlled trial

- Continuous HAART
  « viral suppression group »
- Episodic HAART
  if CD4<250/mm³ until > 350/mm³
  « drug conservation group »

SMART study group, NEJM, 2006
After a mean followup of 16 months...

SMART study group, NEJM, 2006
After 16 months (instead of 6 years) enrollment was stopped because of a safety risk in the drug conservation group.
Conclusion
Main treatment strategy for CKD is HAART

HAART at all stages including stage 5

HAART as early as possible
HIV: yet a more severe renal threat than diabetes in black patients in HAART era

<table>
<thead>
<tr>
<th></th>
<th>eGFR change per year</th>
<th>Multivariate hazard ratio for ESRDb</th>
<th>Multivariate hazard ratio for deathb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HIV or diabetes</td>
<td>−0.1 (−0.1, −0.1)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>HIV</td>
<td>−0.4 (−1.3, 0.5)</td>
<td>0.68 (0.26–1.76)</td>
<td>2.21 (1.57–3.13)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−1.4 (−1.4, −1.3)</td>
<td>1.97 (1.86–2.08)</td>
<td>1.23 (1.21–1.26)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HIV or diabetes</td>
<td>−0.8 (−0.9, −0.7)</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Diabetes</td>
<td>−2.3 (−2.4, −2.1)</td>
<td>1.78 (1.63–1.93)</td>
<td>1.06 (1.00–1.12)</td>
</tr>
</tbody>
</table>

Choi et al, Kidney Int, 2007
Thank you