

# HAART is Associated with Improved Kidney Function Despite Early GFR Reductions

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## Centers for AIDS Research Network of Integrated Clinical Systems (CNICS)

### Background

- HIV is associated with a spectrum of kidney disorders, including HIV-associated nephropathy (HIVAN).
- The natural history of kidney disease among HIV infected persons is incompletely understood.
- Antiretroviral therapy (ART) preserves or improves kidney function among HIV infected patients, and modifies the natural history of HIVAN.
- Antiretroviral renal toxicity has been reported including:
  - Tenofovir: renal insufficiency and proximal tubular dysfunction. Also associated when co-administered with: didanosine, amprenavir or ritonavir.
  - Indinavir: nephrolithiasis and renal insufficiency.

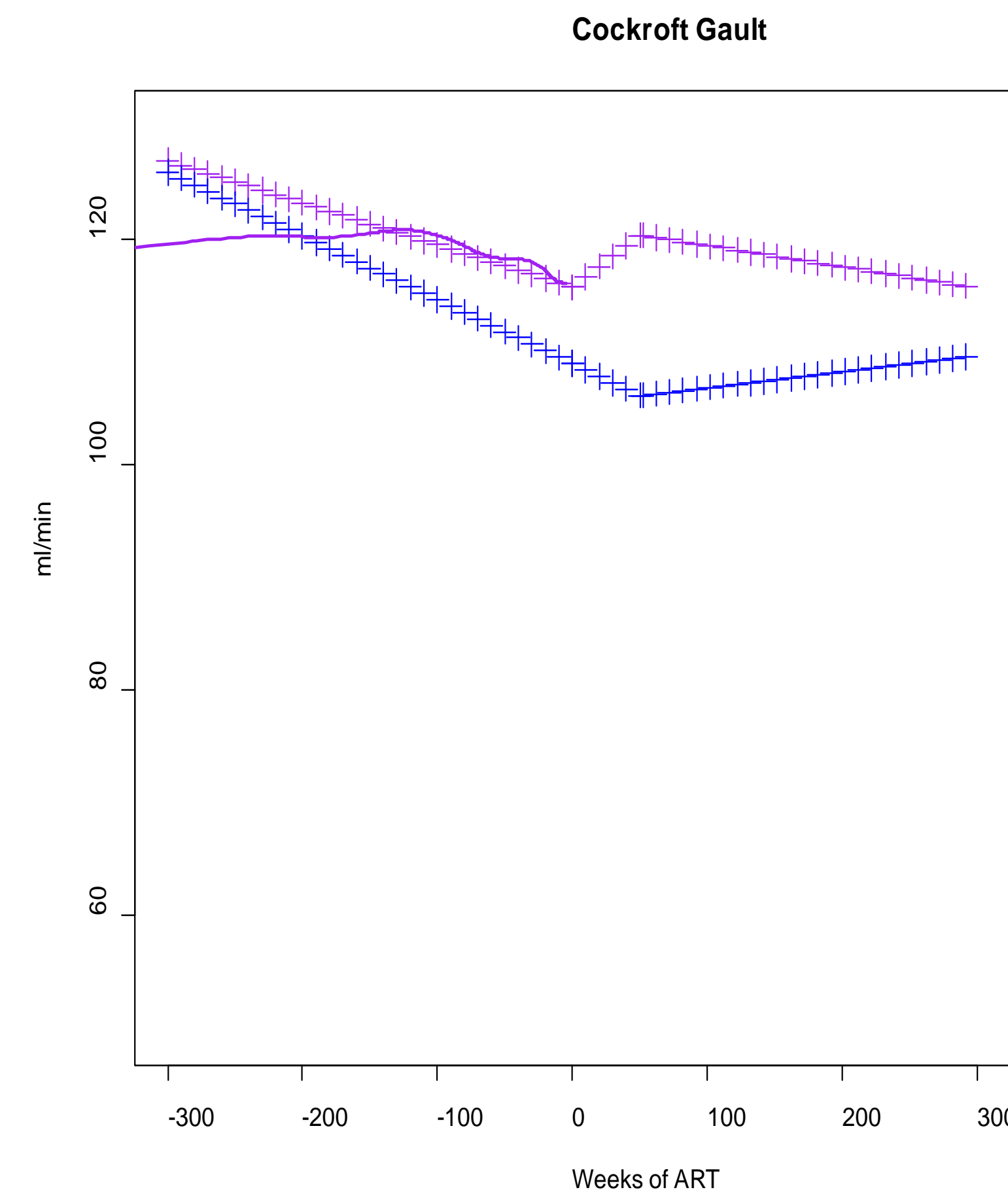
### Objectives

- To examine the effects of ART on kidney function by comparing GFR slopes before & after ART.
- To identify correlates of GFR slope before and after ART among demographic, viral & immune factors & between specific antiretroviral agents & combinations.

### Methods

- Prospective, multicenter cohort of ART naive patients beginning their 1<sup>st</sup> regimen (≥ 3 drugs as 2 NRTIs plus either a PI, NNRTI or third NRTI).
- Mixed-effects, multivariable models of GFR slope by Cockcroft Gault (CG) or MDRD. Estimates of non-linear GFR slopes were afforded by linear spline models that included knots (inflection points) at weeks 0 & 52 of ART giving slope estimates as: pre-ART & post-ART: yr1 & >yr1.
- Models were adjusted for age, sex, race (black vs not black), HCV, HBV, AIDS (by CDC Class C), first log<sub>10</sub> viral load, nadir CD4 cell count, & pharmacologically treated hypertension & diabetes.
- Renal measurements were censored after any change in the first regimen.

<b>n</b>	4770
Women n (%)	988 (21%)
Black	1893 (40%)
HCV	776 (16%)
HBV	256 (5%)
Pharmacologically treated Diabetes	167 (4%)
Pharmacologically treated Hypertension	776 (16%)
AIDS (CDC Category C diagnosis)	1472 (30%)
CKD before ART	70 (2%)
Age at ART initiation (yrs), <b>median (IQR)</b>	39 (36, 41)
Nadir CD4 (cells/cm <sup>3</sup> )	186 (55, 299)
First LVL (log <sub>10</sub> cop/mL)	4.6 (3.7, 5.2)
Pre-ART f/u (wks)	17 (5, 96)
Post-ART f/u (wks)	169 (65, 313)



**Figure 1:** Model derived GFR estimates ‘+++’ compared to a smoothing line based on weighted averages ‘—’ in patients who received neither tenofovir nor ritonavir (purple; n=1905) or tenofovir + ritonavir (blue; n=949); 591 received ritonavir without tenofovir & 1325 received tenofovir without ritonavir.

### CG

	Pre-ART slope	Yr1 ART slope	P-value Yr1 vs. PreART slope	>yr1 ART slope
<b>No CKD</b>	-2.1 (-2.6, -1.5)	1.1 (-0.8, 2.9)	<.001	-0.2 (-2.9, 2.4)
<b>CKD</b>	-13.1 (-25.8, -0.4)	13.2 (-19.3, 45.7)	0.02	-0.6 (-33.6, 32.4)
<b>TDF-/RTV-</b>	-1.9 (-3.6, -0.3)	4.7 (0.6, 8.9)	<.001	-1.0 (-6.1, 4.2)
<b>TDF-/RTV+</b>	-3.4 (-5.6, -1.2)	1.4 (-5.7, 8.6)	0.06	0.0 (-9.1, 9.2)
<b>TDF+/RTV-</b>	-1.6 (-2.3, -1.0)	2.0 (-1.3, 5.2)	0.01	0.1 (-4.6, 4.9)
<b>TDF+/RTV+</b>	-2.9 (-4.0, -1.9)	-3.0 (-6.4, 0.5)	0.50	-1.0 (-6.1, 4.2)

### MDRD

	Pre-ART slope	Yr1 ART slope	P-value Yr1 vs. PreART slope	>yr1 ART slope
<b>No CKD</b>	-1.0 (-1.5, -0.5)	-3.1 (-4.8, -1.3)	0.004	-1.2 (-3.5, 1.2)
<b>CKD</b>	-15.9 (-22.0, -9.7)	14.3 (-4.9, 33.5)	<.001	-0.4 (-20.8, 20.0)
<b>TDF-/RTV-</b>	-0.7 (-1.8, 0.3)	0.1 (-3.0, 3.2)	0.27	-0.8 (-4.7, 3.1)
<b>TDF-/RTV+</b>	-3.6 (-6.2, -1.0)	-5.1 (-11.7, 1.6)	0.29	-1.9 (-9.7, 5.9)
<b>TDF+/RTV-</b>	-0.7 (-1.2, -0.2)	-1.4 (-4.0, 1.1)	0.27	-0.8 (-4.6, 3.0)
<b>TDF+/RTV+</b>	-1.2 (-1.8, 0.3)	-9.1 (-12.6, -5.6)	<.001	-1.7 (-6.4, 3.1)

**Table 2:** Model derived GFR slope estimates (95% CI) as: pre-ART, yr1 & >yr1 by CG & MDRD according to a preART diagnosis of chronic kidney disease (CKD), and receipt of tenofovir (TDF) &/or ritonavir (RTV). **YELLOW** fill indicates significant slope reduction from preART slope; **GREEN** indicates a significant improvement ; **NO FILL COLOR** indicates no significant change.

**Table 1:** Patient characteristics

### Results

- Among patients with **CKD**, ART was associated with a significant early (**yr1**) GFR slope improvement followed by a stable **>yr1** GFR slope (not significantly different from zero).
- Among patients **without CKD**, early (**yr1**) GFR slopes differed according to the GFR estimating equation, with:
  - significant ↑ in **yr1** slope by CG (-2.1 to 1.1 ml/min);
  - significant ↓ in **yr1** slope by MDRD (-1.0 to -3.1 ml/min\*1.73m<sup>2</sup>);
- TDF & RTV** use was associated with early (**yr1**) GFR slope differences, but not with later (**>yr1**) differences in GFR slope.
- Patients who received **neither TDF nor RTV** had:
  - significant ↑ **yr1** GFR slope by CG, but no change in **yr1** slope by MDRD;
  - stable **>yr1** slopes;
- Patients who received **TDF combined with RTV** had:
  - attenuated GFR improvements during the first year of ART (unchanged by CG, reduced by MDRD);
  - stable **>yr1** GFR slopes;
- Patients who received **either TDF or RTV (not both)** were more similar to those without exposure to these agents.
- Correlates of the rate of GFR decline prior to ART included: lower nadir CD4 cell counts, black race, hypertension, & an AIDS diagnosis.
- Correlates of the rate of GFR improvement in association with ART included: lower nadir CD4 cell counts, viral suppression to < 500 cop/ml after 1 yr of ART & the absence of hypertension.

### Conclusions

- Tenofovir combined with ritonavir was associated with attenuated GFR improvements during the first year of ART, but not with GFR slope differences after 1 yr.
- We continue to explore associations with other ART medications in this cohort and explore differences between GFR estimating equations.