ART in Renal Failure

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Disclosures

No conflicts of interest or relationships to disclose.

Outline

- Potential causes of creatinine elevation in PWH
- Workup of creatinine elevation in PWH
- ART in renal failure

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Case

- 65-year-old man with HIV, HFrEF, obesity, and hypertension
- Last CD4 391 cells/mm^3, HIV RNA undetectable
- On TAF/FTC + DTG + r/DRV since 2016
- Baseline Cr over past few years has ranged from 0.94-1.3 mg/dL

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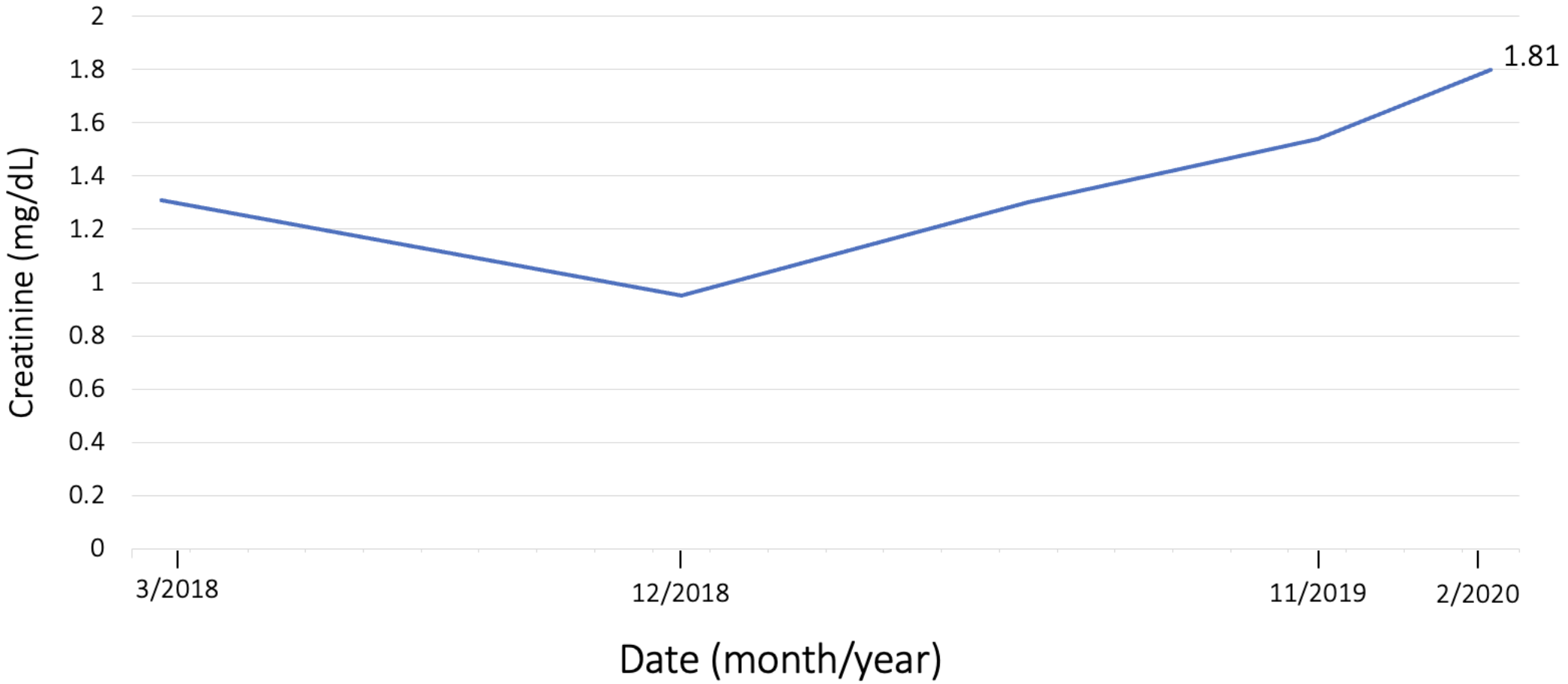
Case: Creatinine Trend



Creatinine Monitoring in HIV

The 2020 HIVMA Primary Care Guidance recommends:

- “Chemistry panels should be monitored on a regular basis as needed to assess medication toxicity and to monitor potential or existing comorbid conditions”
- “Frequency of monitoring depends on the underlying medical conditions and the need to monitor for ART toxicities, depending upon the regimens chosen”
- “Biannual monitoring for renal function and urinary abnormalities is warranted for patients who receive tenofovir”

Thompson MA, CID, 2020.

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Common Causes of CKD in PWH

- Usual causes, including non-ART medication side effects
- Hepatitis B or C
- Benign medication effect from ART
- Tenofovir-associated nephrotoxicity
- HIV-associated nephropathy (HIVAN)

Cohen SD, NEJM, 2017.

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

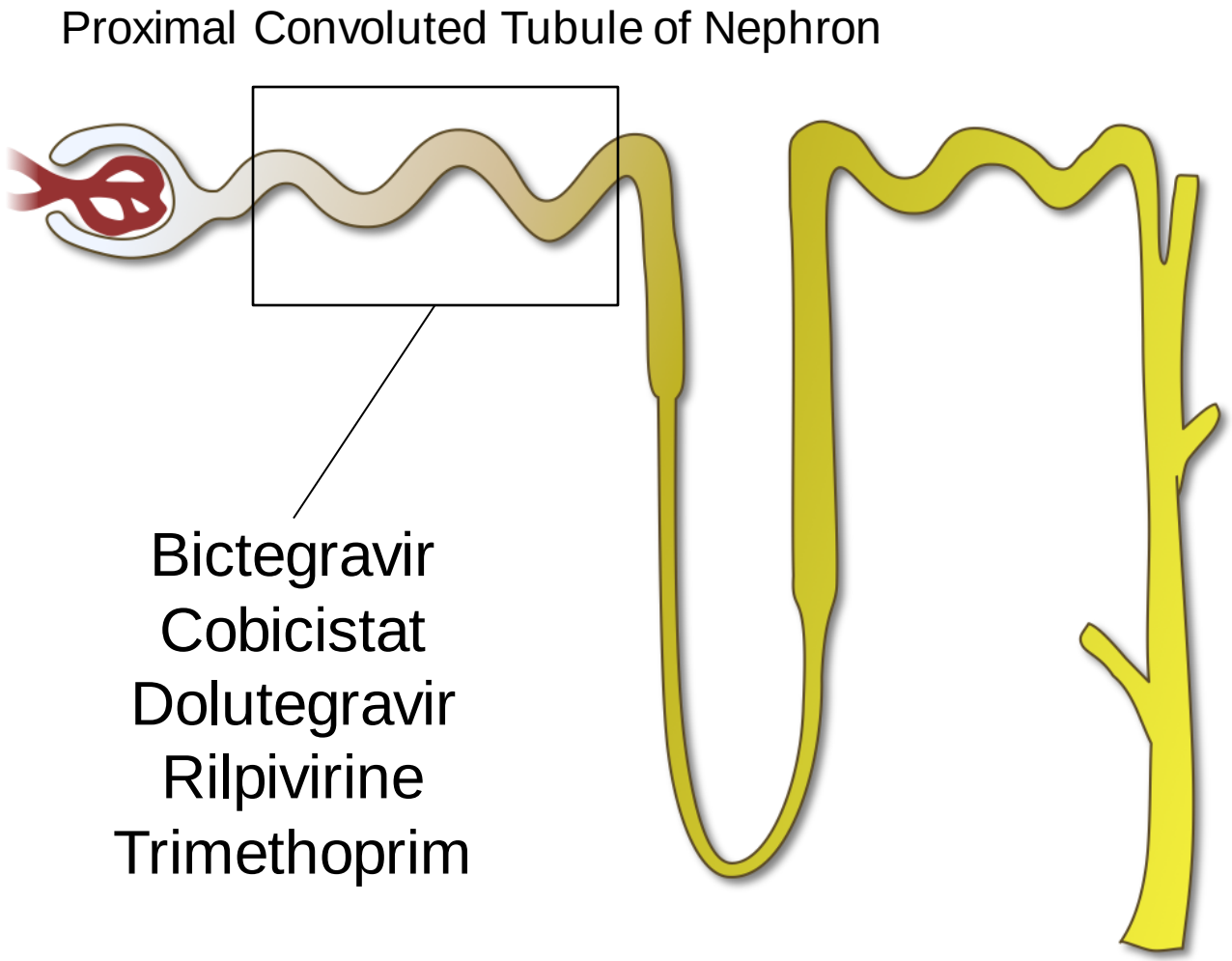
Julie R. Ingelfinger, M.D., *Editor*

Kidney Diseases Associated with Human Immunodeficiency Virus Infection

Scott D. Cohen, M.D., M.P.H., Jeffrey B. Kopp, M.D., and Paul L. Kimmel, M.D.

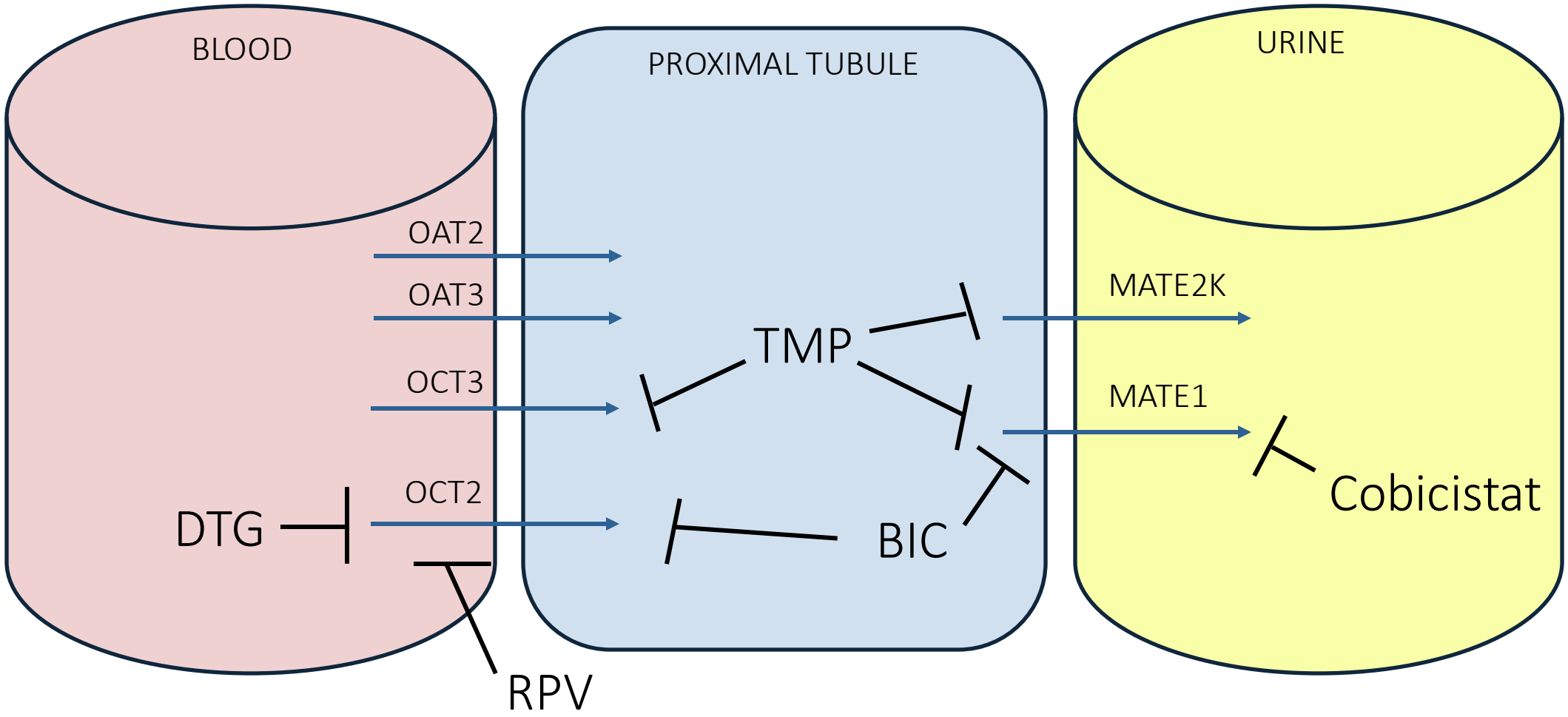
Benign Effects of ART on Creatinine

- BIC, DTG, RPV, cobicistat, and TMP inhibit proximal tubular secretion of creatinine (Cr), which may increase serum Cr without changing the GFR
- May expect a 10-20% (or 0.1-0.2 mg/dL) increase in Cr, usually within first few weeks of therapy, then plateaus
- Check creatinine 1 month after starting any of these medications to establish a new baseline



National HIV Curriculum. Image credit: David Spach, MD.

Proximal Tubule Renal Transporters



Adapted from Lepist E-I, Kidney Int, 2014.

Combining ART that Block Tubular Secretion of Creatinine

- Paucity of data on the effects of combining ART that block tubular secretion of Cr
  1. Prospective cohort of 288 PWH on different dual regimens (DTG, RPV, c/DRV)[1]
     - No additive effect
  2. Retrospective cohort of 725 PWH on c/DRV plus DTG and/or RPV[2]
     - An additive effect was seen

- The exact effect of combining ART that blocks tubular secretion is unknown and may depend on the receptor and patient

1-Casado JL, HIV Medicine, 2019. 2-Perez Elias MJ, JAC, 2021.

What is a Cystatin C?

- A compound produced by nucleated cells in the body
  - Not affected by muscle mass or by tubular inhibition of medications
  - Can be affected by conditions that cause chronic systemic inflammation

- When to use? If available, can help discern a benign creatinine elevation from a pathologic creatinine elevation.

- How to use? It can be used in conjunction with a serum creatinine, but not in lieu of, to estimate renal function.

Cohen SD, NEJM, 2017.

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Tenofovir-Associated Nephrotoxicity

- Due to TDF more often than TAF
- May or may not reverse with drug discontinuation
- Higher risk with ritonavir-boosted medications, caution with cobicistat

- Use of tenofovir can lead to any of the following:
  1. GFR decline
  2. Proteinuria
  3. Proximal tubulopathy
  4. Fanconi syndrome

Cohen SD, NEJM, 2017. Hamzah L, J Infect, 2017. Cattaneo D, JAIDS, 2018.

What is Fanconi Syndrome?

- Specific proximal tubulopathy that is a type II renal tubular acidosis[1]
  - Characterized by glycosuria, phosphaturia, uricosuria, and aminoaciduria

- If suspected, calculate a fractional excretion of phosphate ($FePO_4$)
  - Order serum creatinine, urine creatinine, serum phosphate, urine phosphate
  - < 10% is normal and > 20% is abnormal

- More often due to TDF, though case reports with TAF exist[2-4]

1-National HIV Curriculum. 2-Bahr NC, Ann Intern Med, 2019. 3-Novick TK, Medicine (Baltimore), 2017. 4-Serota DP, OFID, 2018.

Diagnostic Workup of Creatinine Elevation in PWH

CONSIDER BENIGN ART EFFECT	Did the patient recently start an ART which can lead to an elevation in serum Cr and is the increase < 20% from baseline? If yes, continue medication.
CONSIDER TENOFOVIR EFFECT	Recall TDF >> TAF more likely implicated. If concerned, obtain UA and send urine protein:creatinine ratio. Send urine Cr, urine PO_4, serum Cr, and serum PO4 to calculate a $FePO_4$. If elevated, consider refer to nephrology.
CONSIDER NON-HIV RELATED CAUSES	Comorbid conditions, such as HTN and DM, are increasingly common in PWH. Screen for Hep B and Hep C. Review medication list for nephrotoxic meds.
SEND OTHER DIAGNOSTIC WORKUP	If FePO4 < 20%, patient is not on tenofovir-containing ART, patient has proteinuria, or high suspicion remains, consider renal ultrasound, post-void residual, and nephrology consultation.

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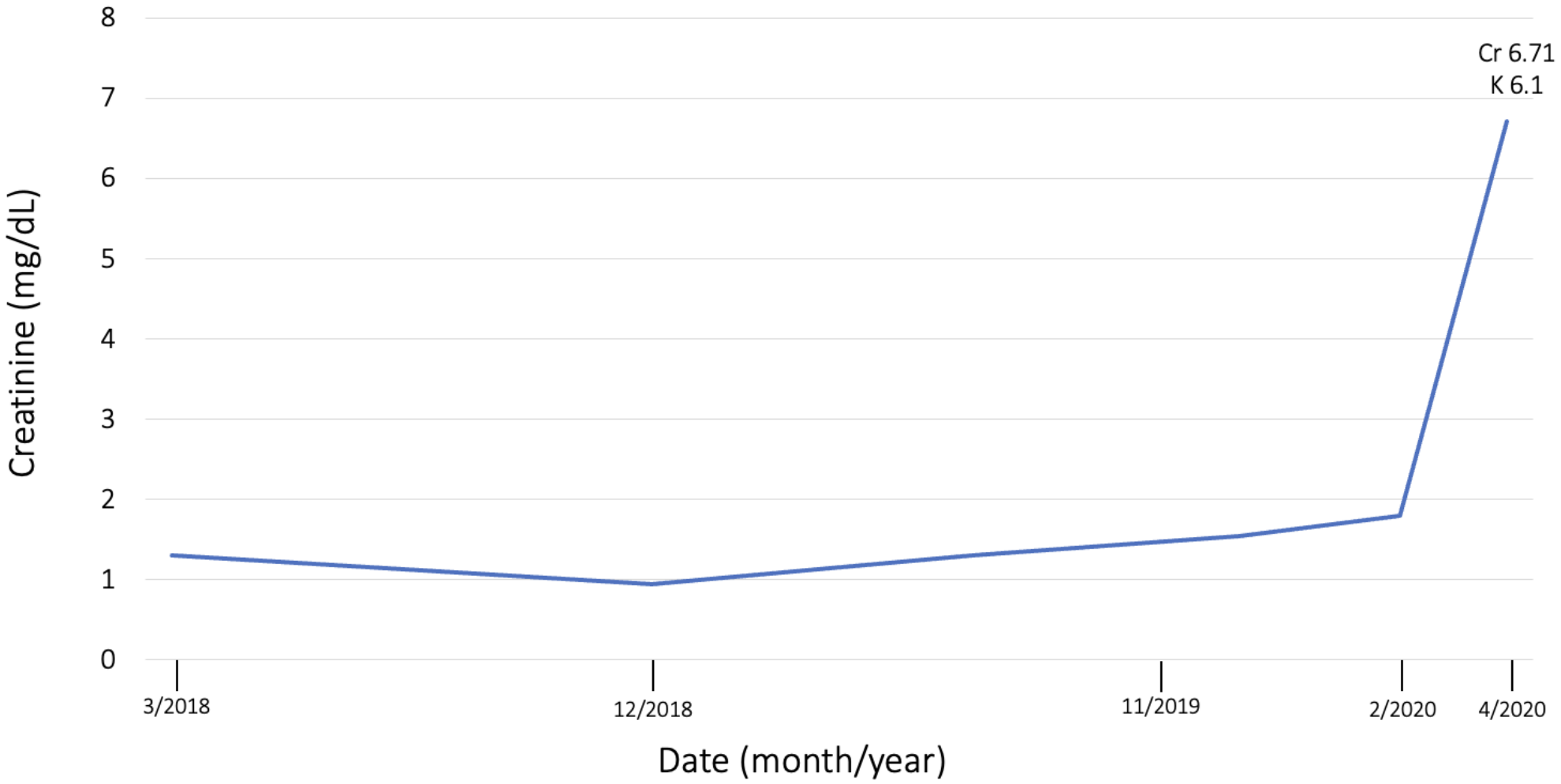
Indications for Referral to Nephrology

- GFR decline more than 25% from baseline and to a level less than 60 mL/min/1.73 m^2 that fails to resolve with removal of any potential nephrotoxic drugs
- Albuminuria greater than 300 mg/day
- Hematuria with either proteinuria or elevated blood pressure
- Advanced kidney disease with GFR less than 30 mL/min/1.73 m^2
- Or sooner, if your clinical setting requires

Case continued



Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults with Renal or Hepatic Insufficiency

Generic Name (Abbreviation) *Trade Name*	Usual Dose[a]	Dosing in Adults with Renal Insufficiency			Dosing in Adults with Hepatic Impairment
Abacavir (ABC) *Ziagen*	ABC 300 mg PO twice daily *or* ABC 600 mg PO once daily	No dose adjustment necessary.			*Child-Pugh Class A:* ABC 200 mg PO twice daily (use oral solution) *Child-Pugh Class B or C:* **Contraindicated**
Abacavir/Lamivudine (ABC/3TC) *Epzicom*	One tablet PO once daily	Not recommended if CrCl <30 mL/min. Instead, use the individual component drugs and adjust 3TC dose according to CrCl.			*Child-Pugh Class A:* Patients with mild hepatic impairment require a dose reduction of ABC. Use the individual drugs instead of the FDC tablet in these patients. *Child-Pugh Class B or C:* **Contraindicated** due to the ABC component
Emtricitabine (FTC) *Emtriva*	FTC 200-mg oral capsule once daily *or* FTC 240-mg (24-mL) oral solution once daily	**Dose by Formulation**			No dose recommendation.
		30–49	200 mg every 48 hours	120 mg every 24 hours	
		15–29	200 mg	80 mg every 24	

Single Tablet Regimens Are Difficult to Administer in Renal Failure

Fixed Dose Combinations NOT recommended with the following CrCl…	
CrCl < 70 mL/min	Elvitegravir-Cobicistat-Tenofovir DF-Emtricitabine (*Stribild*)
CrCl < 50 mL/min	Efavirenz-Tenofovir DF-Emtricitabine (*Atripla*), Rilpivirine-Tenofovir DF-Emtricitabine (*Complera*), Doravirine-Tenofovir DF-Lamivudine (*Delstrigo*), Tenofovir DF-Emtricitabine (*Truvada*)
CrCl < 30 mL/min	Dolutegravir-Lamivudine (*Dovato*), Abacavir-Lamivudine (*Epzicom*), Dolutegravir-Abacavir-Lamivudine (*Triumeq*)
CrCl < 30 mL/min and NOT on HD	Bictegravir-Tenofovir alafenamide-Emtricitabine (*Biktarvy*), Tenofovir alafenamide-Emtricitabine (*Descovy*), Elvitegravir-Cobicistat-Tenofovir alafenamide-Emtricitabine (*Genvoya*), Rilpivirine-Tenofovir alafenamide-Emtricitabine (*Odefsey*), Darunavir-Cobicistat-Tenofovir alafenamide-Emtricitabine (*Symtuza*)

DHHS ART Guidelines 2024.

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NRTIs & Renal Failure

- Tenofovir containing NRTIs
  - TAF
    - AVOID TAF/FTC with CrCl ≤ 30 mL/min
    - AVOID TAF with CrCl ≤ 15 mL/min
    - OK to use with HD
  - TDF
    - AVOID TDF with CrCl ≤ 60 mL/min, but dose adjust as follows:
      - CrCl 30-49 mL/min q48h
      - CrCl 10-29 mL/min twice weekly
      - HD once weekly

- 3TC (lamivudine) and FTC (emtricitabine) require dose adjustment with CrCl < 50 mL/min
- No dose adjustments needed with abacavir

DHHS ART Guidelines 2024.

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Can you use TAF after TDF-associated nephrotoxicity?

- Hamzah et al.[1]
  - Study Design: Randomized, open-label trial to either take FTC/TAF or continue current ART
  - Population: 31 PWH with prior history of tubulopathy from TDF
  - Primary outcome: Urine protein:creatinine ratio (PCR)
  - Result: 12-week exposure to TAF did not affect uPCR

- Campbell et al.[2]
  - 31 individuals from the above study remained on TAF through week 96
  - None developed glycosuria or proximal renal tubulopathy

- Case report of TDF-associated Fanconi resolving with switch to TAF[3]

1-Hamzah L, HIV Medicine, 2020. 2-Campbell L, JAIDS, 2021. 3-Karris MY, AIDS Res Hum Retroviruses, 2017.

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NNRTIs and PIs & Renal Failure

- NNRTIs
  - DOR
    - No dose adjustment necessary but not studied in ESRD or HD
  - RPV
    - RPV alone – no dose adjustment
    - RPV/TAF/FTC – contraindicated < 30 mL/min but if on HD give dose after
    - RPV/TDF/FTC – contraindicated < 50 mL/min, no recommendations regarding HD
    - RPV/DTG – no dose adjustment necessary but if < 30 mL/min monitor for adverse effects
- PIs
  - DRV
    - r/DRV – no dose adjustment
    - c/DRV – if with TDF, contraindicated if CrCl < 70 mL/min
    - TAF/FTC/c/DRV – contraindicated if CrCl < 30 mL/min but if on HD give dose after

INSTIs & Renal Failure

- c/EVG
  - c/EVG/TAF/FTC (10mg TAF) – do not use with CrCl < 30 mL/min but ok to use after HD
  - c/EVG/TDF/FTC (300mg TDF) – do not start with CrCl < 70 mL/min & stop with CrCl < 50mL/min

- BIC/TAF/FTC
  - Do not give in CrCl < 30 mL/min who are not on HD
  - If on HD, ok to dose after HD
  - Guidelines state that if receiving while on chronic HD, should be virally suppressed

Elvitegravir & Bictegravir in Hemodialysis

- c/EVG/TAF/FTC Trial[1]
  - Single arm multicenter phase 3B trial of virally suppressed PWH on chronic hemodialysis (HD)
  - 55 individuals switched to c/EVG/TAF/FTC while on HD
  - c/EVG/TAF/FTC was safe and efficacious to 96 weeks (36 completed the study)

- BIC/TAF/FTC Extension[2]
  - At 96 weeks, patients transitioned from c/EVG/TAF/FTC to BIC/TAF/FTC
  - 55 enrolled, 36 completed c/EVG/TAF/FTC, 10 entered BIC/TAF/FTC extension
  - All 10 participants on BIC/TAF/FTC had viral suppression at 48 weeks

- Six PWH on BIC/TAF/FTC and HD achieved or maintained suppression[3]

1-Eron JJ, Lancet HIV, 2018. 2-Eron JJ, ID Week 2020 #1002. 3-Sidman EF, Am J Health Syst Pharm. 2023.

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Dolutegravir & Renal Failure

- Dolutegravir plasma concentrations decrease in CrCl < 30 mL/min
  - In a trial of 8 persons with CrCl < 30 mL/min compared to 8 matched healthy controls, AUC, C_{max}, and C_{24} of dolutegravir decreased by 40%, 23%, and 43%
  - Recommendation:

> clinically relevant effect on the exposure of dolutegravir. No dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

- OK to use dolutegravir in HD

Dolutegravir Package Insert. Molto J, CROI 2016, #432.

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Injectables in Renal Failure

- CAB-RPV
  - If severe renal impairment or HD, increase monitoring for adverse effects
  - PO CAB for oral lead in or bridge: no dose adjustment necessary

- Lenacapavir
  - No dose adjustment necessary

- Less commonly used
  - Enfuvirtide – no dose adjustment necessary
  - Ibalizumab – no dose adjustment necessary

DHHS ART Guidelines 2024.

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ART in Peritoneal Dialysis

- Paucity of data
- One proposition is to dose for CrCl < 15 mL/min
- Another proposition is to consider like HD and unlikely to need supplemental dosing
- Case report of a PWH on Biktarvy and PD who maintained viral suppression

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Antiretrovirals for People with HIV on Dialysis

Dima Dandachi, MD, MPH,[1] Michela Fabricius, BS,[2] Baraa Saad, MD,[3] Mark T. Sawkin, PharmD,[4] and Kunal Malhotra, MD, MBA[5]

Dandachi D, AIDS Patient Care and STDs, 2022. Partosh D, Int J STD AIDS, 2023.

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Acute Renal Failure in the Hospital

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Managing modern ART in the ICU: overcoming challenges for critically ill people with HIV

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Case Continued

With the acute rise in creatinine, what might you do with his ART?

A. Continue TAF/FTC + DTG + r/DRV

B. Switch to ABC/3TC/DTG

C. Simplify to DTG + r/DRV

D. Switch to DTG/RPV

NRTI: M184V, K70N, L74V
NNRTI: K101E, Y181C, G190S
PI: None
INSTI: None

Hep B cAb positive
Hep B sAg negative
Hep B sAb positive, 23 IU

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My Personal Practice for ART Choice in Renal Failure

- What are things that influence my choice?
  - Drug-drug interactions
  - Absorption concerns
  - Prior ART history, mutations, and potential future ART options
  - Hepatitis B status
  - Trajectory of renal function
  - Viral load, CD4, etc.

- My general approach
  - When needing a tenofovir-sparing regimen, I tend to use DTG + c/DRV or consider DTG-RPV
  - I am awaiting DTG + DOR data in ESRD and HD
  - If patient, provider, and clinic can access CAB-RPV, would like to use this
  - If on HD, I tend to use BIC/TAF/FTC

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Conclusions

1. Causes of creatinine elevation in PWH are multifactorial.
2. Consider use of a cystatin C when working up a creatinine rise in PWH on ART.
3. Fixed dose combinations are difficult to use in renal failure.
4. Use the DHHS Guidelines Appendix B, Table 12 for guidance in ART in renal failure.
5. Each clinical scenario warrants different considerations for ART choice in renal failure.

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