It's (not so) Complicated: Antiretroviral Therapy and Monitoring for Complications

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Objectives

- Identify common complications associated with antiretroviral therapy
- Discuss management options for adverse effects
- Review patient cases to demonstrate potential complications with antiretroviral therapy

Complication vs. Side Effect

- Differentiating between complications of medications, side effects, and complications of HIV disease itself

  - ***Complication:*** a secondary disease or condition that develops in the course of a primary disease or condition and arises either as a result of it or from independent causes.

  - ***Side effect:*** an often harmful and unwanted effect of a drug or chemical that occurs along with the desired effect

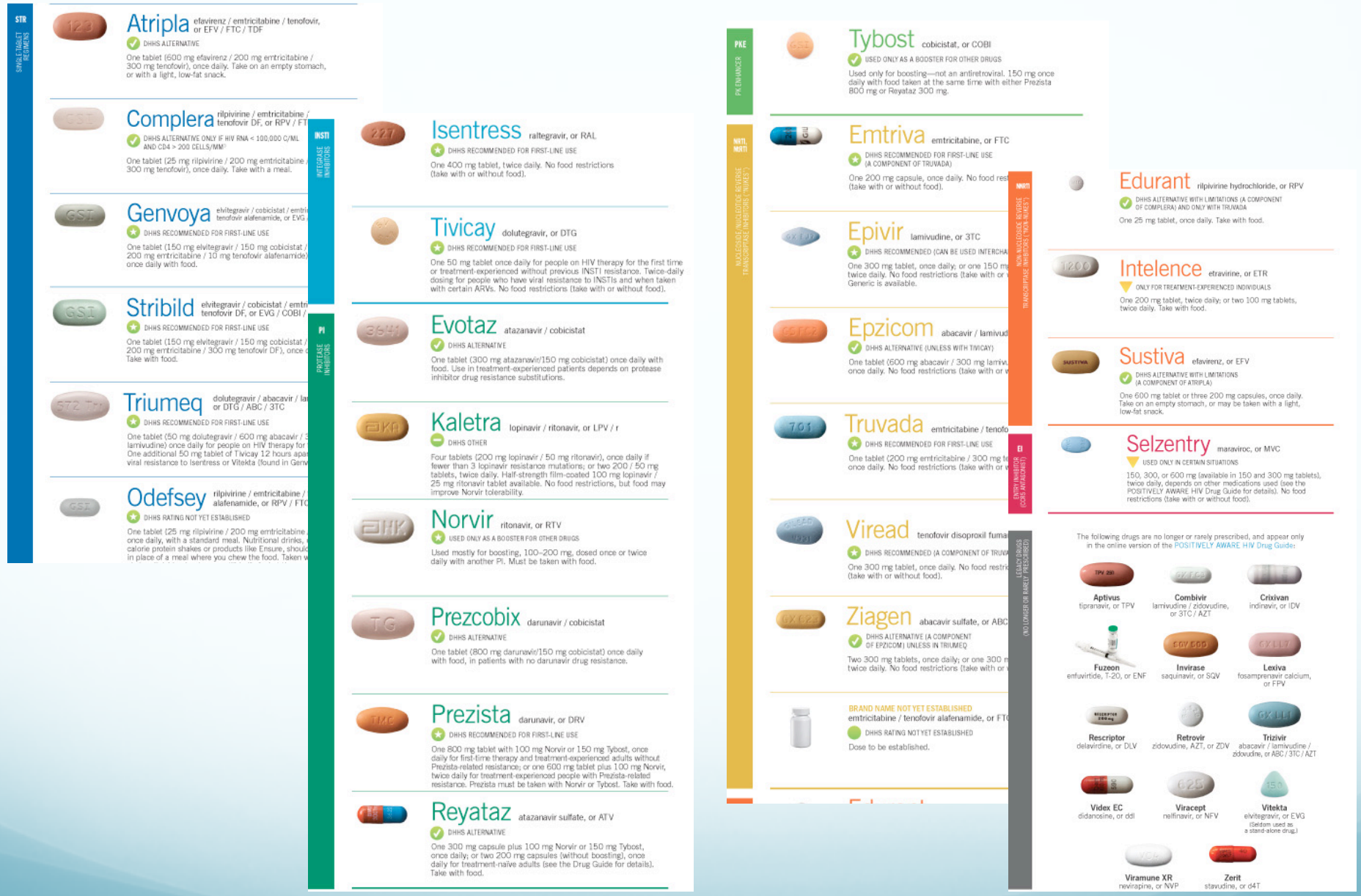
It's (not so) Complicated

- When antiretrovirals first came to market, for most, the benefit outweighed the risk of adverse effects and complications.
- People just 'dealt' with it, because these medications were literally life-saving. Or life-prolonging
- As recently as 2015, the guidelines still suggested that people could wait until their CD4 count dropped below 350-500 cells/mm^3 before starting ARVs.

Current Recommendations

- Start comprehensive antiretroviral therapy (cART) in all HIV positive patients **regardless of CD4 count**
- First-line Recommended Regimens:

1. *Dolutegravir/abacavir/lamivudine (Triumeq)*
2. *Dolutegravir + tenofovir disoproxil fumerate/emtricitabine*
3. *Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (Genvoya)*
4. *Elvitegravir/cobicistat/tenofovir disoproxil fumerate/emtricitabine (Stribild)*
5. *Raltegravir + tenofovir disoproxil fumerate/emtricitabine*
6. *Darunavir/ritonavir + tenofovir disoproxil fumerate/emtricitabine*



http://positivelyaware.com/hivdrugchart

Current Options

- Currently we have ~40 FDA approved medications for the management of HIV.
  - Six single tablet regimens (STL)
  - Many potential combinations
  - Compare to 2006: twenty-two FDA approved agents
- Only **SEVEN** are part of recommended first line regimens
- Great to have many options, but some options are better than others – all are efficacious
  - Many drugs that are no longer recommended had heavy side effect profiles. Fears of these prominent side effects still prevent some people from starting therapy

Complications with 'older' antiretrovirals

- Neuropathy – indinavir (Crixivan)
- Lipoatrophy/lipodystrophy – stavudine (Zerit)
- Hepatotoxicity – nevirapine (Viramune)
- Dyslipidemia – protease inhibitors
- Bone marrow suppression – zidovudine
- Lactic acidosis – nucleoside reverse transcriptase inhibitors

Stavudine	Raltegravir
(greater than 10% CNS: headache 25-46% Dermatologic: rash 18-30% Gastrointestinal: nausea, vomiting, diarrhea 30-45% Hepatic: hyperbilirubinemia 65-68%, increased AST 42-53%, increased ALT 40-50% Neuromuscular: peripheral neuropathy 8-21%	(greater than 10%) Hepatic: Increased ALT 1-11% Other: CNS: insomnia 4% Hematologic: thrombocytopenia 1-3% Neuromuscular: increased creatine phosphokinase 3-4%

Complications and Side Effects Associated with all Antiretrovirals

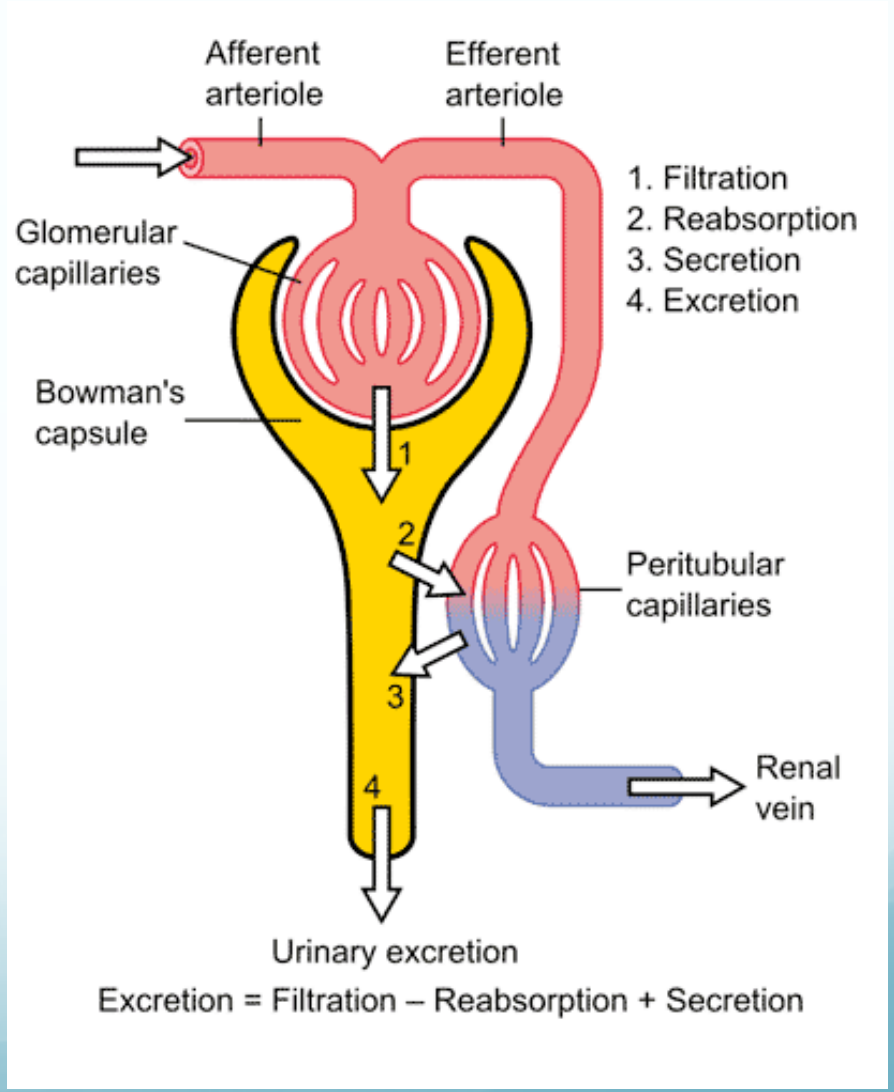
- Lipodystrophy/fat redistribution
- Decrease in bone mineral density
- Gastrointestinal issues
- Metabolic complications
  - Lipodystrophy
  - Dyslipidemia

Patient Case 1

- Patient LA presents for her regular follow up in your clinic. She has been on Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disproxil fumerate) for about three years. Her most recent labs show that her viral load serum creatinine has increased from 0.9mg/dL to 1.15mg/dL. Urinalysis also shows proteinuria.
- You suspect one of her meds is currently altering her kidney function. Which of the following agents is likely responsible for this change?
- A. elvitegravir
- B. cobicistat
- C. emtricitabine
- D. tenofovir

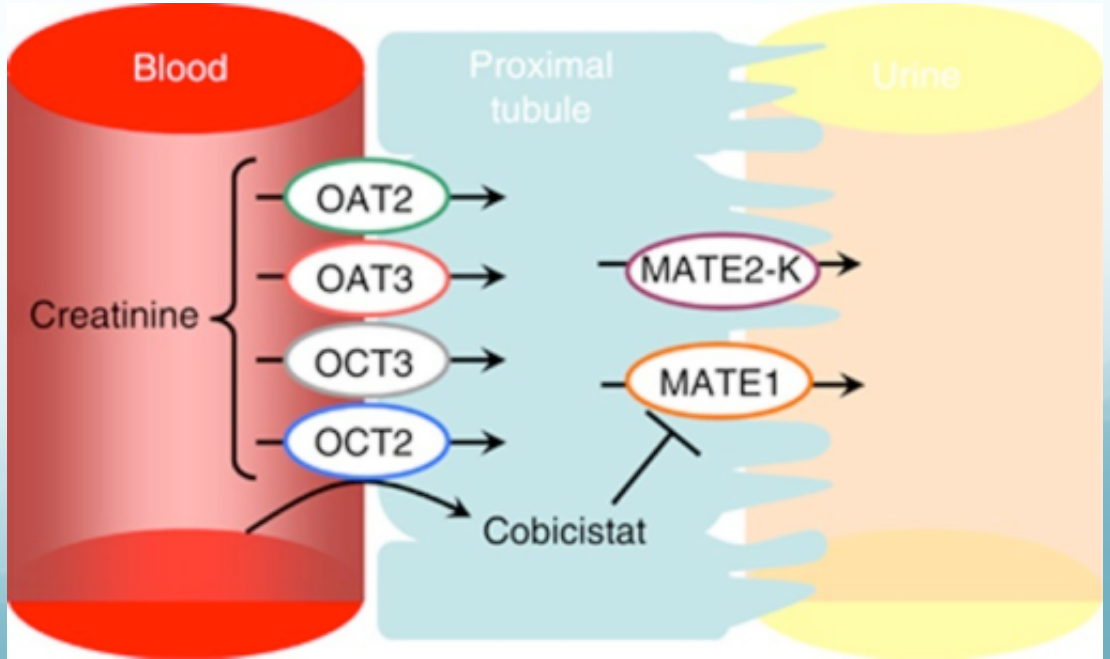
Renal Complications

- Impact on serum creatinine (SCr) vs. actual change in kidney function/glomerular filtration
  - Remember, SCr is a **surrogate marker** to **estimate** creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR)



Renal Complications - Cobicistat

- Pharmacokinetic booster with no antiretroviral activity, but a part of many cART regimens
- Inhibits renal tubular secretion of creatinine, thus increasing SCr level
- However, there is no impact on actual glomerular filtration rate.

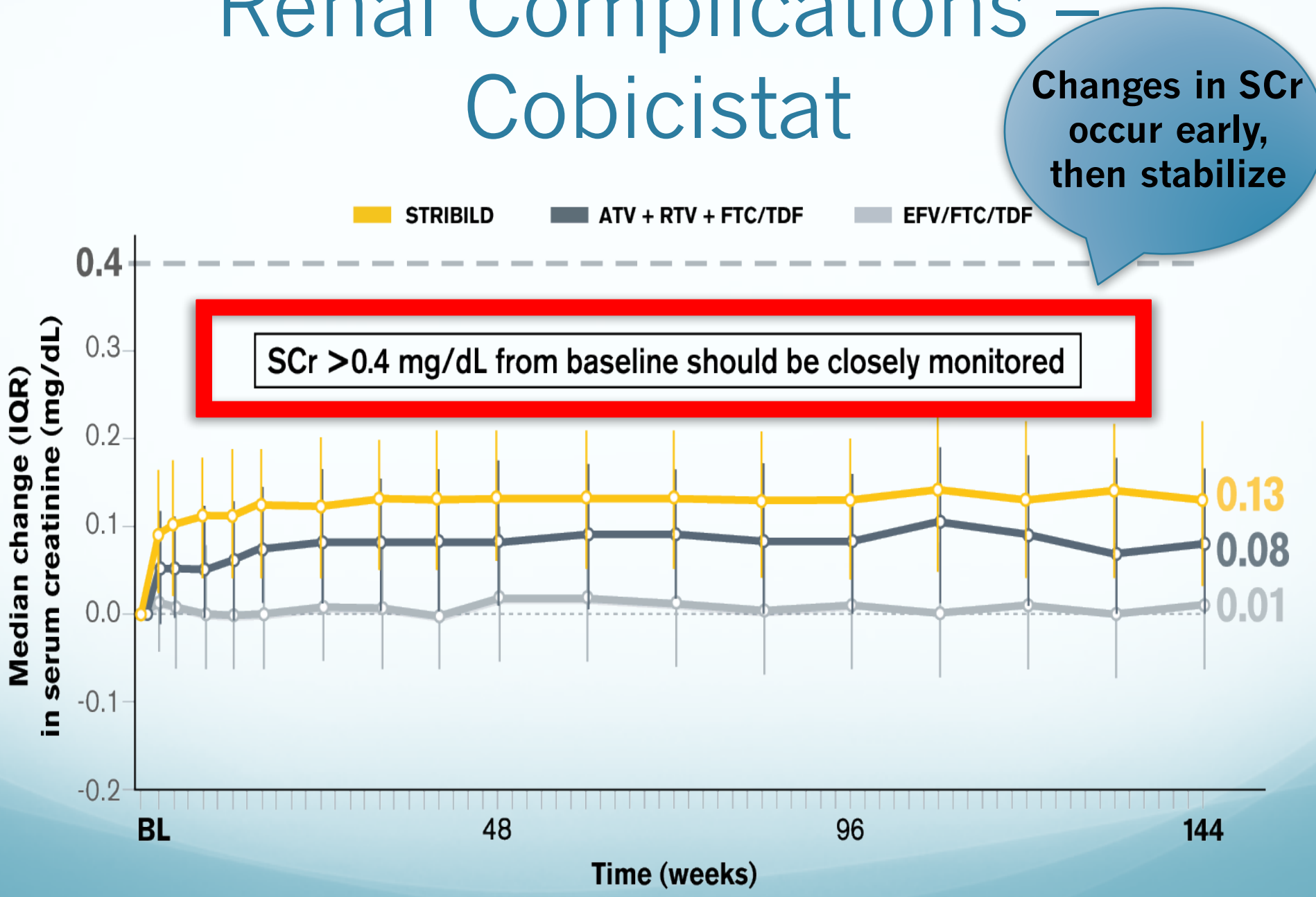


Renal Complications – Cobicistat

- Study by German et al. looked at the effects of ritonavir and cobicistat over 7 days.

	Ritonavir	Cobicistat
Mean change **SCr** @ day 7 from baseline	-0.11%	23.0%*
Mean change **SCr** @ day 14 from baseline (7d post d/c)	-3.76	4.11%*
Mean change in **actual GFR** @ day 7	1.8%	-5.0%
Mean change in **eGFR (Crockcroft-Gault)** @ day 7	1%	-17.5%
* Denotes statistically significant		

Renal Complications – Cobicistat



Renal Complications – Cobicistat

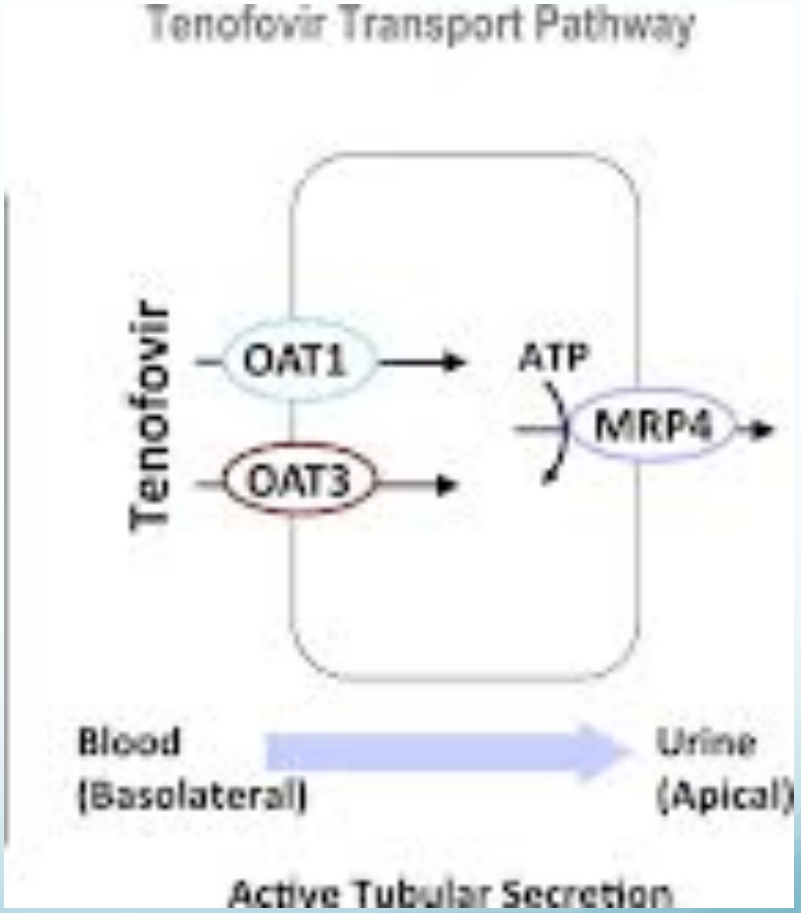
- Bottom Line
  - Increases in serum creatinine do not necessarily translate to impaired renal function
  - Changes in SCr occur early, then stabilize
- Management
  - Discontinue if serum creatinine continues to rise
  - Manage drug-drug interactions that increase levels of other nephrotoxic drugs (TDF!)
- Monitoring
  - Monitor SCr, specifically
  - Re-evaluate therapy if SCr increases more than the anticipated 0.4mg/dL baseline

Renal Complications – Tenofovir disproxil fumerate

- Tenofovir disproxil fumerate (TDF) is a prodrug for tenofovir
  - Part of the majority of first line regimens
  - Active even in presence of M184V mutation
  - Also plays major role in, PrEP, PEP
- Most commonly used ARV, most complications?
  - Truvada, Atripla, Complera, Stribild

Renal Complications – Tenofovir disoproxil fumerate

- Proposed mechanism
  - Build-up of intracellular tenofovir in the proximal tubules
  - Can be reversible (AKI) or permanent (CKD)

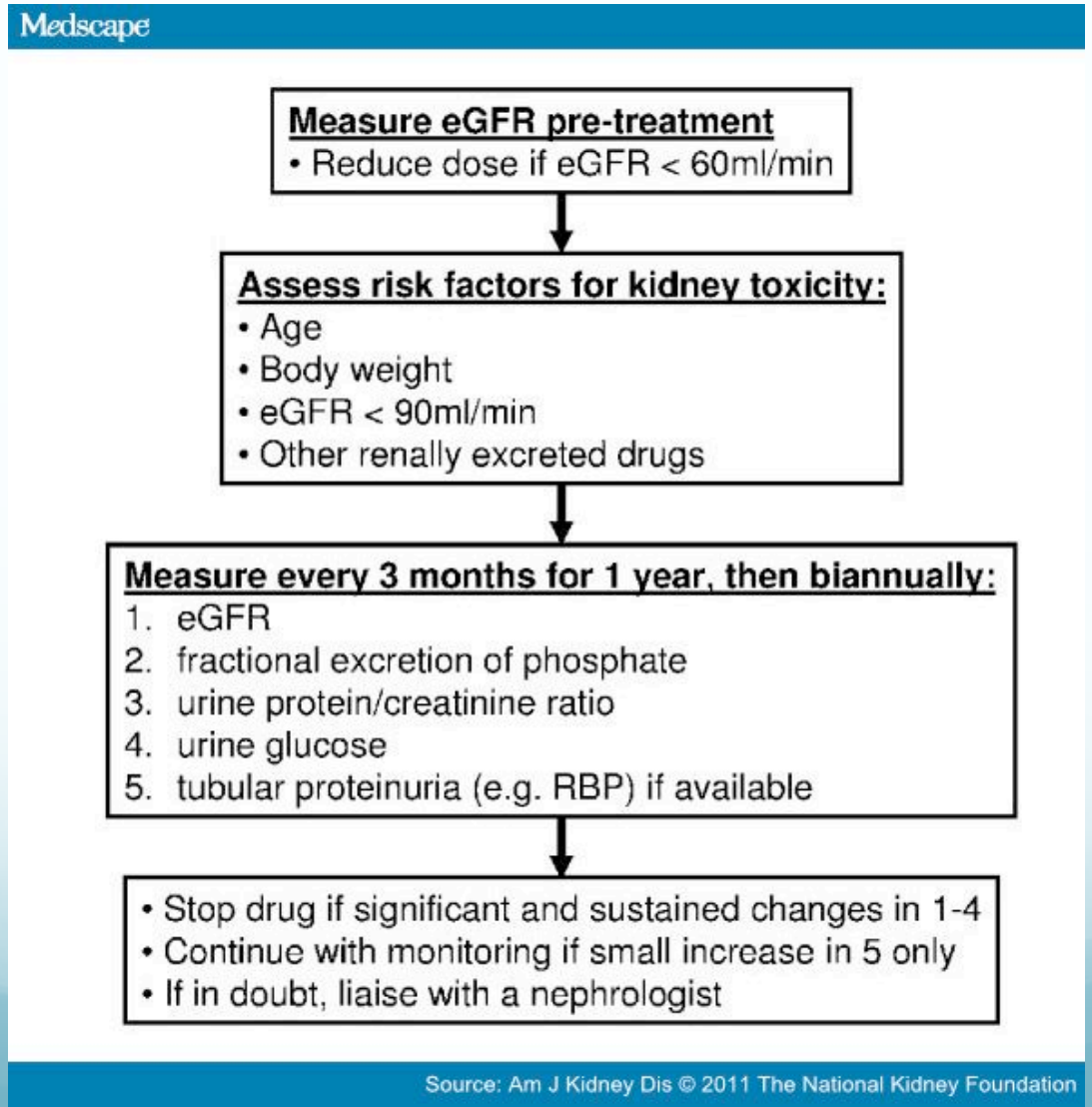


https://www.researchgate.net/figure/264904325_fig1_Effect-of-various-drugs-on-tubular-creatinine-secretion-17-Tubular-secretion-of

Renal Complications – Tenofovir disproxil fumerate

- Fanconi's Syndrome
  - Rare
  - Proximal renal tubule dysfunction
  - Normal reabsorption of electrolytes impaired
  - Thus, spillage of electrolytes into urine
  - Objective findings
    - Increased urine proteincreatinine ration (PCR)
    - Glucosuria with normal blood glucose
    - Hypophosphatemia

Suggested Algorithm for Monitoring TDF Toxicity



Renal Complications – Tenofovir disproxil fumerate

- Bottom line
  - TDF well known to cause actual nephrotoxicity
  - Close, regular monitoring
  - Despite risk, use of tenofovir does not need to be restricted in the general HIV population
- Management
  - Discontinue if SCr continues to rise
  - Decrease other nephrotoxic agents
  - Manage drug-drug interactions
  - Consider switch to TAF
  - Referral to nephrologist if prolonged impaired renal function
- Monitoring
  - Drug-drug interactions that may increase TDF concentrations
    - Cobicistat, ledipasvir (Harvoni component),
  - Serum creatinine, urinalysis (urine glucose, urine protein), serum phosphate (if suspected)

Bone Mineral Density (BMD) loss

- Bone Mineral Density
  - Used to determine osteoporosis risk via dual-energy x-ray absorptiometry (DXA)
- BMD loss – a complication due to disease as well as antiretroviral therapy
  - Patients living with HIV more likely to have factors affecting BMD (CD4 cell count, higher baseline fasting glucose)
  - HIV disease itself is a risk factor
    - Osteoporosis prevalence may be as high as 3x higher than non infected patients

Bone Mineral Density (BMD) loss

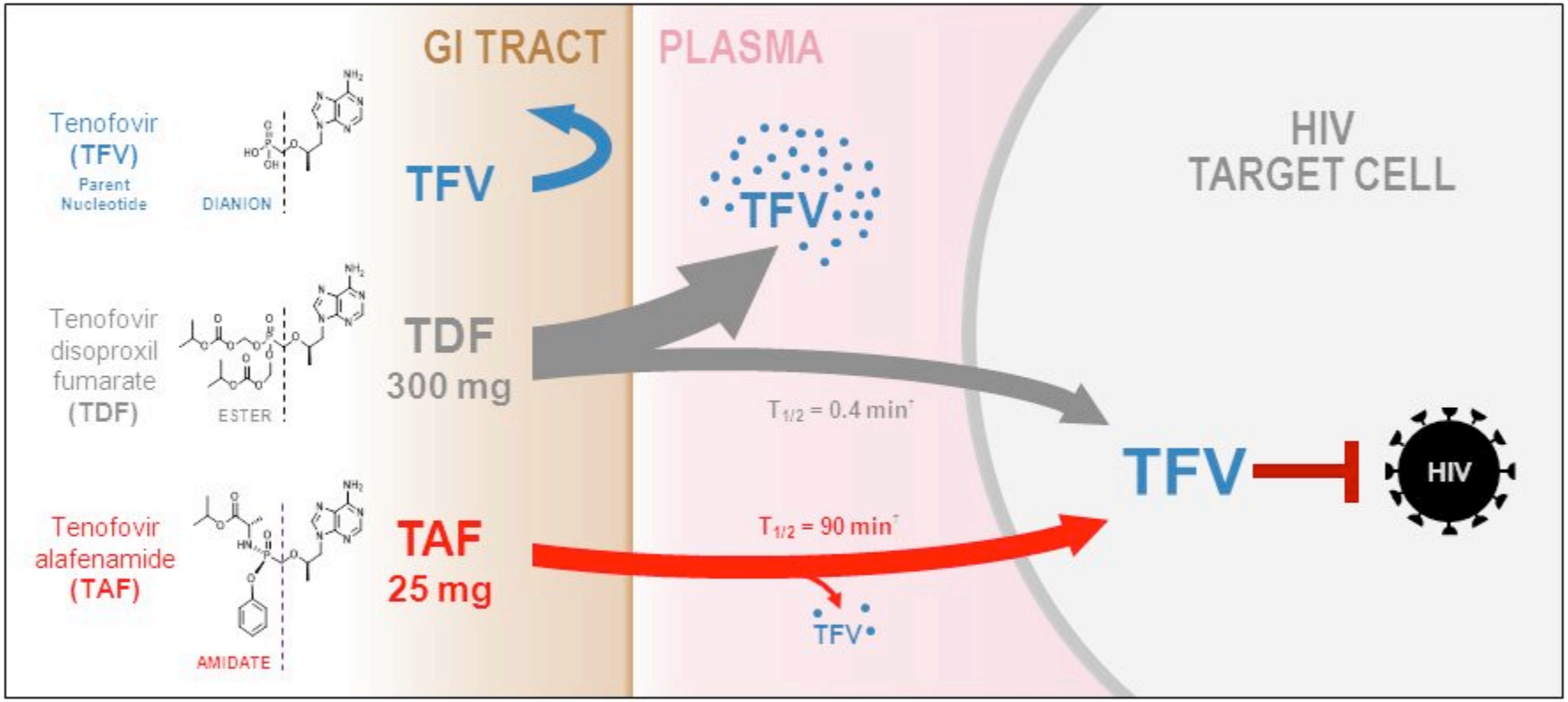
- All ARVs contribute to BMD loss
  - PI > NNRTI
  - TDF > ABC
- Brown, et al
  - ~2.5% BMD loss over 96 weeks. Not significant between ARVs.
- Grace et al.
  - Can be as high as >5% change in patients with other significant risk factors for osteoporosis

Brown, Todd T., Grace A. Mccomsey, Martin S. King, Roula B. Qaqish, Barry M. Bernstein, and Barbara A Da Silva. "Loss of Bone Mineral Density After Antiretroviral Therapy Initiation, Independent of Antiretroviral Regimen." *JAIDS Journal of Acquired Immune Deficiency Syndromes* 51.5 (2009): 554-61. Web.

Bone Mineral Density (BMD) loss

- Bottom line:
  - HIV disease itself can contribute to BMD loss
  - All ARVs contribute to BMD loss to some extent
- Management
  - Avoid TDF regimens in patients w/ history of osteoporosis/osteopenia
  - Bisphosphonates
  - Vitamin D supplementation - if level low
- Monitoring
  - Monitor for fragility fractures
  - Vitamin D levels
  - DXA – ideally, but not practically

Tenofovir disproxil (TDF) vs tenofovir alafenamide (TAF)



- **91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV**

† $T_{1/2}$ based on *in vitro* plasma data.

1. Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. 2. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. 3. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. 4. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. 5. Sax P, et al. *JAIDS* 2014. 2014;67(1):52-8. 6. Sax P, et al. *Lancet* 2015;385:2606-15.

Tenofovir disproxil (TDF) vs tenofovir alafenamide (TAF)

Patient Case - 2

- A 60 year old man with a 10 year history of HIV presents to your clinic ready to start antiretroviral therapy for the first time. He is s/p MI two years ago. Other patient meds include: metoprolol 100mg, aspirin 81mg daily, and atorvastatin 40mg.
- Which of the following would be a reasonable option for his patient's ARV regimen? Patient has no major drug resistance mutations and is HLAB5701 Negative
  - A. Triumeq
  - B. Atripla
  - C. Tivicay + Truvada
  - D. Atazanavir/ritonavir + Truvada

Cardiovascular Complications - Abacavir

- Abacavir – does it or doesn't it?
  - D.A.D Study (2008)
    - Association between 'recent' abacavir exposure and acute MI (HR 1. 89)
    - Association was strong in those with underlying CV risk factors – bias?
  - No association: ACTG, French Hospital Database on HIV, US Veterans, etc.
  - Confusion!
    - US Veterans Cohort: three analysis – no association, statistically significant association with CV events
  - Meta Analysis
    - Also conflicted
  - No clear mechanism identified.
  - Again, may be a combination of antiretroviral complication plus complication of actual disease state.

Llibre, Josep M., and Andrew Hill. "Abacavir and Cardiovascular Disease: A Critical Look at the Data." *Antiviral Research* 132 (2016): 116-21. Web. D:A:D Study Group, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008 Apr 26;371(9622):1417-26.

Cardiovascular Complications - Abacavir

Table 2
Main findings of prospective randomized clinical studies and meta-analysis of randomized clinical trials assessing the potential association between abacavir exposure and acute myocardial infarction in HIV-1 infected individuals.

Source	Type of analysis	Subjects included	Subjects exposed to ABC	AMI events	Type of exposure to ABC analysed	HR for ABC use (95% CI)[a]	AMI events/ p/y	Additional analysis done	Era
GSK (Brothers et al., 2009)	Meta-analysis of randomized clinical trials	14,174	9502	27	Cumulative	0.52 (0.15–1.79)	1.9/ 1000	Absence of association in the whole RCT data set (0.813 [0.38 to 1.75])	1997 –2006
STEAL Study (Martin et al., 2009)	Randomized clinical trial	357	179	4	Cumulative, 96 weeks	**8.33 (1.02–50)**	22/ 1000		2007 –2008
Cruciani et al. (Cruciani et al., 2011)	Meta-analysis of randomized clinical trials	9233	4376	31	Cumulative	0.73 (0.39–1.35)	3.0/ 1000	Cardiovascular events RR 0.95 (95% CI 0.62 –1.44); Overall mortality RR 1.20 (95% CI 0.63 –2.27)	1996 –2010
FDA (Ding et al., 2012)	Meta-analysis of randomized clinical trials	9868	5028	46	Cumulative	1.02 (0.56–1.83)	4.7/ 1000	Risk difference between ABC containing and non-ABC regimen is 0.008% (95% CI: –0.26%, 0.27%).	1996 –2010

ABC: abacavir. P/y: patient/year. GSK: Glaxo Smith and Kline. FDA: Food and Drug Administration, US. CVE: Cerebrovascular events.
[a] Boldface highlights positive findings between abacavir exposure and AMI.

D:A:D Study Group, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008 Apr 26;371(9622):1417-26.

Cardiovascular Complications - Abacavir

- Bottom line:
  - Overall, evidence is still conflicting on whether abacavir contributes significantly to CV events
- Management:
  - Consider avoiding abacavir in patients with a history of CV disease or CV events
- Monitoring:
  - Monitor for increased risk factors for CV disease or new development of

D:A:D Study Group, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008 Apr 26;371(9622):1417-26.

Patient Case - 3

- Patient Mmis a 54yo male here for follow up 6 weeks after switching from Atripla to Triumeq. Today, he complains that he's become very grumpy lately and has been spending more time alone at home because he doesn't have the motivation to go spend time with his friends like he used to. He asks you to prescribe something 'for his mood'. What do you do?

A. Tell him the Atripla is still in his system, so he may be having residual side effects

B. Tell him to see a psychologist

C. Tell him that you will prescribe a low dose antidepressant

D. Tell him it there might be an association with dolutegravir, so he should discontinue the drug immediately.

E. None of the above

Psychiatric Complications

- Efavarinez
  - Well documented, experienced by many patients, and they will tell you!
  - Vivid dreams, agitation, feeling ‘hung-over’ or ‘groggy’ the following morning
  - Exacerbation of existing psychiatric disorders

Psychiatric Complications

- Dolutegravir??
  - Kheloufi and colleagues report 4 cases of patients switching to dolutegravir and experiencing new onset pysch symptoms or exacerbations. 2/4 pts did not have history of psychiatric disease.
    1. 56yo female; RAL → DTG d/t simplification;
       - After 1 week: dizziness, fatigue, 'feeling drunk'
       - Symptoms disappeared after d/c; no psych hx

    2. 43yo female; ATZ → DTG d/t metabolic adverse effects
       - After 1 month: headache, mentally depressed, irritability, angriness
       - Symptoms resolved 2 weeks post d/c

    3. 51yo female; ATZ → DTG d/t dyslipidemia
       - After a few days: feeling 'high'; 1 month: anxiety; 3 months: physician consulted d/t depressive syndrome and psychological distress.
       - Symptoms disappeared when switched back to atazanavir

    4. 64yo male; ATZ → DTG d/t dyslipidemia
       - After a few days: headaches, which resolved. 1 month: exacerbation of anxiodepressive symptoms with suicidal idealations
       - Symptoms resolved after a few months, DTG continued; Hx of severe psychological disease w/ no medications.

Kheloufi, Farid, Julie Allemand, Saadia Mokhtari, and Anne Default. "Psychiatric Disorders after Starting Dolutegravir." *AIDS* 29.13 (2015): 1723-725. Web.

Psychiatric Complications

- Bottom line
  - EFV has a well established high rate of significant psychiatric side effects
  - DTG may have associated psych effects not previously expected
- Management
  - EFV:
    - take on empty stomach to avoid increased concentrations with food
    - Avoid in patients with psychiatric history
    - Switch patient to first line recommended regimen
  - DTG:
    - Consider switch to alternative regimen
- Monitoring
  - Patient voiced complaints
  - Significant changes in mood or behavior
  - Monitor for drug-drug interactions

Complications due to Patients

- Is resistance a complication of long-term ARV use?
- Complications due to inappropriately taking meds
  - missing doses
  - Not taking entire regimen (i.e. once daily vs twice daily or Truvada only)
  - Separating medication throughout day (i.e. Prezista in the morning, ritonovir at night, Truvada at night)
- Complications due to drug-drug interactions?
  - (not only due to patients!)
  - Stay tuned for next week's webinar!

Questions?


That's all Folks!