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When is TAF not TDF?

…. When is cobicistat not ritonavir?

managing drug interactions when choosing ART

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Drug interactions and antiretrovirals….

Fun, fascinating, or just plain annoying?

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Drug interactions - what to consider

Pharmacokinetic:

- Absorption
  - Chelation
  - P-glycoprotein
- Distribution
  - Protein binding
  - Transporter proteins
- Metabolism
  - Liver enzymes
- Elimination
  - Biliary
  - kidney

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Pharmacodynamic:

- two drugs have additive or antagonistic pharmacologic effects
  - Alcohol and sedatives
  - Historical ART example:

Using thymidine analogues stavudine and zidovudine together

Significant drug interactions to consider

Absorption:

- **Cationic chelation**
  Integrase inhibitors
- **P-glycoprotein**
  Ritonavir, cobicistat inhibit

  tenofovir substrate

Metabolism:

- **Cytochrome P450**
  induced by: NNRTI, ritonavir

  inhibited by: PIs + cobicistat

  substrates: maraviroc, PIs, NNRTIs, elvitegravir, dolutegravir
- **UGT - glucuronidation**
  ritonavir induces

  Integrase inhibitors are substrates

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Elimination:

- **biliary**
  atazanavir and bilirubin
- **renal transporters**
  Tenofovir substrate

  Inhibitors:

  cobicistat, ritonavir

  dolutegravir

  rilpivirine

distribution:

Transporters blood- hepatocyte

fusidic acid inhibits OAT1B1

statins can't get into hepatocytes- toxicity…

Significant drug interactions to consider

Absorption:

- **Cationic chelation**
  - Integrase inhibitors
- **P-glycoprotein**
  - Ritonavir, cobicistat inhibit
  - tenofovir substrate

Metabolism:

- **Cytochrome P450**
  - induced by: NNRTI, ritonavir
  - inhibited by: PIs + cobicistat
  - substrates: maraviroc, PIs, NNRTIs, elvitegravir, dolutegravir
- **UGT - glucuronidation**
  - ritonavir induces
  - Integrase inhibitors are substrates

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Elimination:

- **biliary**
  - atazanavir and bilirubin
- **renal transporters**
  - Tenofovir substrate
  - Inhibitors:
  - cobicistat, ritonavir
  - dolutegravir
  - rilpivirine

distribution:

Transporters blood- hepatocyte

- fusidic acid inhibits OAT1B1
- statins can't get into hepatocytes- toxicity…

Tenofovir… isn't it drug interaction free?

Tenofovir DF

- Consider pharmacodynamic interactions
  - kidney toxicities
- Atazanavir interaction
  - Should boost atazanavir when using with tenofovir DF
  - Atazanavir 300mg/ritonavir 100mg + tenofovir DF:
    - Atazanavir AUC ↓ 25% compared to boosted atazanavir + NO tenofovir - unknown mechanism
    - Tenofovir AUC ↑ 37% - probable p-glycoprotein inhibition
- Is a p-glycoprotein substrate, but 300mg drug outweighs any effect of efflux by p-gp

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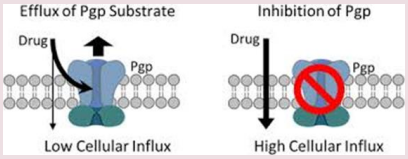
P- glycoprotein

- A multidrug transporter protein
- Pumps xenobiotics out of cells

- Found:
  - Blood brain barrier
  - Liver-bile ducts
  - Small intestine
  - Testes
  - Ovaries
  - Placenta
  - Kidney tubules



Inhibitors: Cobicistat, ritonavir, verapamil
Inducers: Phenytoin, carbamazepine, rifampicin
Substrates: digoxin, dabigatran, tenofovir

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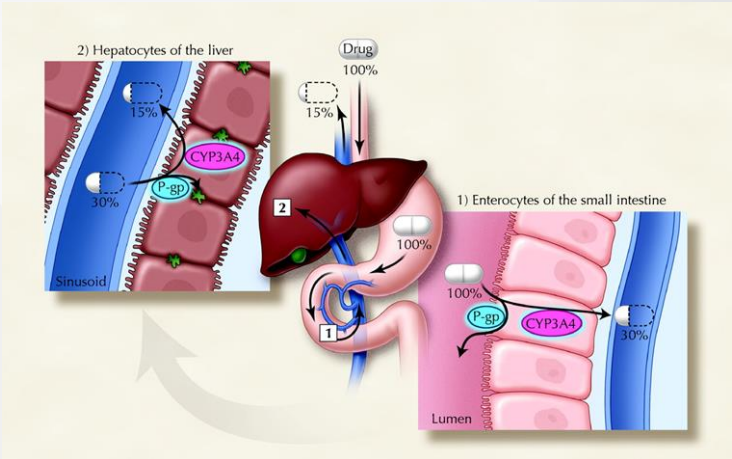
P- glycoprotein

P-glycoprotein in drug absorption and distribution



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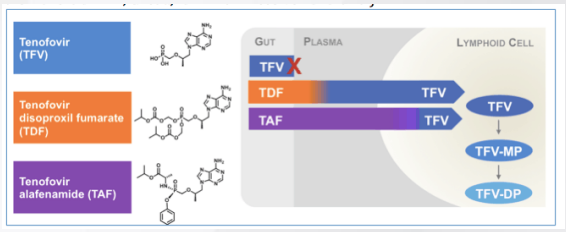
Tenofovir… isn't it drug interaction free?

Tenofovir AF….



- The salt is removed at lymphocyte surface
  - Significantly **less** tenofovir in TAF products
    25mg or 10mg
- Efflux by p-glycoprotein *does* come into effect
  - Standard dose of 25mg allows absorption of sufficient drug to attain therapeutic effect

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Tenofovir… isn't it drug interaction free?

Tenofovir AF….

- Efflux by p-glycoprotein *does* come into effect
  - Standard dose of 25mg allows absorption of sufficient drug to attain therapeutic effect

- Questions:
  - When is 10mg tenofovir AF used?
  - When should tenofovir AF ***not*** be used?

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Tenofovir AF drug interactions

1. Do not use TAF with strong p-gp inducers
   - Rifampicin, rifabutin
   - Carbamazepine
   - Phenytoin
   - St John's wort
2. Use the 10mg strength with inhibitors
   - Ritonavir
   - Cobicistat
   - Consider also: ketoconazole, itraconazole, verapamil
3. Genvoya® has broader interactions to consider

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Tenofovir AF drug interactions- p-glycoprotein inducers

- many interactions NOT studied
- Gilead has data on carbamazepine:
  - 300mg BD carbamazepine @steady state + TAF/emtricitabine
  - decreased tenofovir AF AUC by 55% compared to TAF/FTC alone (GS-US-311-1387 study)
  - Likely p-glycoprotein induction
- "There is an urgent need for research to better understand drug–drug interactions between rifampicin and the next-generation antiretrovirals"
  Maartens G, Boffito M, Flexner C. Curr Opin HIV AIDS 2017, 12:355–358

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Tenofovir AF drug interactions

1. Do not use TAF with strong p-gp inducers
   - Rifampicin, rifabutin
   - Oxcarbazepine …carbemazepine
   - Phenytoin
   - St John's wort

2. Use the 10mg strength with p-gp inhibitors
   - Ritonavir
   - Cobicistat
     - Consider also: ketoconazole, itraconazole, verapamil

3. Genvoya® has broader interactions to consider

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Where will you find Tenofovir AF?

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Tenofovir AF drug interactions

Odefsey ®

Tenofovir AF (25mg)- emtricitabine- rilpivirine

•Drug interactions:

consider *both* rilpivirine and the TAF

- Rilpivirine and antacids
- TAF and p-gp inducers

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Tenofovir AF drug interactions

Genvoya®

Tenofovir AF (10mg)- emtricitabine- elvitegravir- cobicistat

- Drug interactions: in reality, its *always* the cobicistat to worry about
  - P- glycoprotein inhibitor

    -TAF at 10mg

  - Cobicistat is CYP450 3A4 inhibitor
  - all the usual interactions….
  - Do not add any enzyme inducers
- Also: chelation (elvitegravir)

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Case of interest

Mr LB, 65yrs, well controlled HIV

- Truvada + nevirapine for many years
- co-morbidities include
  - Peripheral neuropathy, COPD, AF, GORD
- Lives in Thailand most of the year (it's cheaper)
- Interested in the 'mark 2' version of Truvada
  - Heard it's better for his bones
- Sees a GP for regular health care needs when in Australia
- Presented to pharmacy for Descovy®
  - off to Thailand in 1 month, can he have 6 months supply now?

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Mr LB: easy swap to TAF?

Pharmacist review pre dispensing:
Medication includes:

- amiodarone 100mg mane
- telmisartan 80mg mane
- warfarin (Coumadin) dose as per INR
- thyroxine 50mcg mane
- esomeprazole 20mg mane
- tiotropium 18mcg inh mane
- fluticasone-salmeterol 250-25mcg (Seretide) 1 inh BD via spacer
- salbutamol inhaler 100mcg 2 puffs inh prn
- testogel 10mg/g sachets top 1 daily
- pregabalin 150mg mane, 300mg nocte
- carbamazepine 200mg mane, 400mg nocte
- zolpidem 10mg nocte PRN
- amitriptyline 50mg nocte

Yikes!

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Mr LB: easy swap to TAF?

Question:
- Off to Thailand in 1 month, can he have 6 months supply now?

Answer:
- No!
- Carbamazepine needs review

Subsequently:
- Full GP and pharmacist review at GP clinic
- Continue taking Truvada®

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Tips for prescribers & pharmacists

When starting or swapping to TAF:

1. Check all other medication with the patient or their GP/pharmacy

2. Consider concurrent medication you wish to prescribe

3. Avoid prescribing TAF if patient is taking/needs to take
   - Carbamazepine, phenytoin
   - A rifamycin

4. Use 10mg TAF patient is taking ritonavir or cobicistat boosted protease inhibitor
   - Taken into account with Genvoya®
   - Be wary of extra interactions when using cobicistat or ritonavir!

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What about Cobicistat?

Is it the same as ritonavir?

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What's the difference between cobicistat and ritonavir?

Both utilised to 'boost' other antiretrovirals and allow them to be given less frequently

- Both
  - inhibit cytochrome P450 3A4
  - Inhibit cytochrome P450 2D6 (cobicistat less so)
  - inhibit p-glycoprotein
  - play a role in inhibiting some transporter proteins
- But…..
  - Ritonavir interferes with many *other* liver enzymes
    - Both P450 and UGT systems
    - Inhibits some and can induce others
      - by activating pregane X receptor, ritonavir increases expression of drug metabolising enzymes

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What's the difference between cobicistat and ritonavir?

	Cobicistat	Ritonavir
Enzymes induced	n/a	CYP1A2 CYP2B6 CYP2C9 CYP2C19 UGT1A4
Enzymes inhibited **(descending order)**	CYP3A4 CYP2D6 (weak)	CYP3A4 CYP2D6 CYP2C9 CYP2C19 CYP2A6 CYP1A2 CYP2E1 CYP2B6 (in vitro)
Transporters inhibited	P-glycoprotein OATP1B1 OAT1B3 MATE-1 BRCP	P-glycoprotein (*also can induce) OATP1B1 OAT1B3 MATE-1 BRCP

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UGT- uridine diphosphate glucuronyl transferase, BRCP- breast cancer resistance protein, OATP – organic anion transport protein, MATE – multidrug and toxin extrusion protein

What's the difference between cobicistat and ritonavir?

Cobicistat:

- Weak 2D6 inhibitor
  - less than 2 fold increase in desipramine
- P-gp – weaker than ritonavir but still effective
  - Cobicistat + tenofovir DF: ↑ TDF AUC 30%
  - Cobicistat + tenofovir AF: ↑ TAF AUC 265% !

    - Genvoya has 10mg TAF
- Major interactions are CYP 450 3A4

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Drug interactions + ritonavir…..

Utilised to boost other ARV (3A4 inhibition)

- Care with accidental boosting of something else
  - Statins, Ca channel blockers, rifabutin, vinca alkaloids, sildenafil, some Hep C drugs, rivaroxaban…..

BUT, not only 3A4 to consider……

- Lowers lamotrigine (induces glucuronidation)
- Lowers voriconazole (induction 2C19)
- May lower clozapine (induction 1A2)
- Lowers olanzapine (induction 1A2 +/or glucuronidation)
- increases digoxin (p-glycoprotein inhibition)
- Lowers thyroxine (induces glucuronidation)

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What's the advantage of cobicistat ?

Cobicistat:

- Weak 2D6 inhibitor
  - 'safer' with amphetamines
- Major interactions are CYP 450 3A4
  - We understand these!
- No enzyme induction

Remember: licenced as a once daily boosting agent

- May not overcome affects of any co-administered inducers
- Can *not* be substituted for twice daily ritonavir regimens when an inducer is part of the regimen.
  - eg RED regimen

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Tips for prescribers & pharmacists

1. When starting cobicistat:

- Check all other medication with the patient or their GP/pharmacy
- Consider concurrent medication you wish to prescribe
- change doses or selection of medication metabolised by CYP 3A4
- Avoid prescribing if patient is taking/needs to take
  - Carbamazepine, phenytoin
  - A rifamycin
  - Etravirine, nevirapine, efavirenz

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Tips for prescribers & pharmacists

2. When swapping to cobicistat from ritonavir:

- Check all other medication with the patient or their GP/pharmacy
- Consider concurrent medication you wish to prescribe
- How has ritonavir been influencing the patient's current medications?
- **How might cobicistat be different?**

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Case of interest

Mr TS, 65yrs, well controlled HIV

- Truvada + atazanavir/ritonavir for many years
- co-morbidities include
  - IHD, AF, T2DM, hypothyroidism, AMI last year
- medication:
  - Warfarin per INR
  - Metoprolol 25mg bd
  - Irbesartan 150mg daily
  - Metformin 1g bd
  - Gliclazide MR 60mg bd
  - Thyroxine 200mcg mane
  - Atrorvastatin 40mg daily
- GP wishes to simplify his ART to reduce pill burden
- Is Genvoya® a good choice?

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Mr TS- regimen simplification?

GP wishes to simplify his ART to reduce pill burden

- Is Genvoya® a safe choice? Would Evotaz® be different?
- Pharmacist review :

	Metabolic pathway	Ritonavir	Cobicistat
Metoprolol	CYP2D6	↑	↑
Irbesartan	Glucuronidation CYP2C9	↓	⟷
Warfarin	CYP2C9>1A2> 3A4>2C19	↓	↑
Metformin	n/a	⟷	⟷
Gliclazide	CYP2C9>2C19	↓	⟷
atorvastatin	CYP3A4	↑	↑
thyroxine	glucuronidation	↓	⟷

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Mr TS- regimen simplification?

- Is Genvoya® a good choice?
- Would Evotaz® be different?

		Ritonavir	Cobicistat	notes
Metoprolol	CYP2D6	↑	↑	Low quality evidence
Irbesartan	Glucuronidation CYP2C9	↓	↔	Very low quality evidence Elvitegravir is 2C9 inducer - ? Impact as part of Genvoya
Warfarin	R: CYP1A2, 3A4 S: (more potent): CYP2C9	↓	↑	Low quality evidence Elvitegravir is 2C9 inducer - case report of decreased warfarin exposure w Stribild
Metformin	n/a	↔	↔	impact of blocking MATE?
Gliclazide	CYP2C9>2C19	↓	↔	Very low quality evidence Elvitegravir is 2C9 inducer - ? Impact as part of Genvoya
atorvastatin	CYP3A4	↑	↑	
thyroxine	glucuronidation	↓	↔	Low quality evidence

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Mr TS- regimen simplification?

Question:
Would Genvoya® or Evotaz® be OK for this gent?

Answer:

- Anything to simplify pill burden is worth consideration
- The interactions may be subtly different between Genvoya® and Evotaz®
  - Genvoya® is fewer pills so maybe 'easier'

- Consider:
  - Close INR monitoring for first few weeks
  - Thyroid function tests and dose adjustment within 2 weeks
  - Monitor BP and drop dose irbesartan if indicated
  - Monitor diabetic control- possible less gliclazide needed

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Tips for prescribers & pharmacists

2. When swapping to cobicistat from ritonavir:

- Check all other medication with the patient or their GP/pharmacy
- Consider concurrent medication you wish to prescribe
- *How has ritonavir been influencing the patient's current medications?*
- ***How might cobicistat be different?***

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Drug interactions and antiretrovirals

Fun, fascinating, AND just plain annoying…..

Ask your pharmacist!

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