Pharmacy Pearls

Stephanie Hamel, PharmD, BCTXP

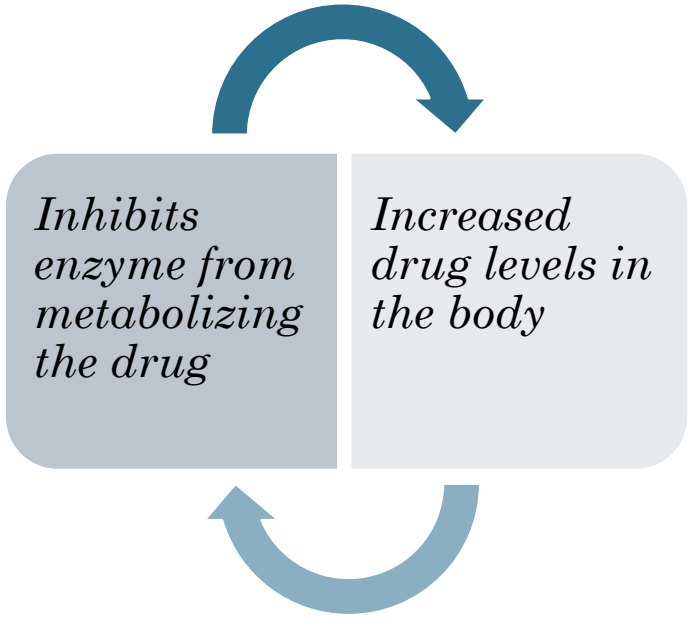
Haley Gutstein, PharmD

What Goes up Must Come Down

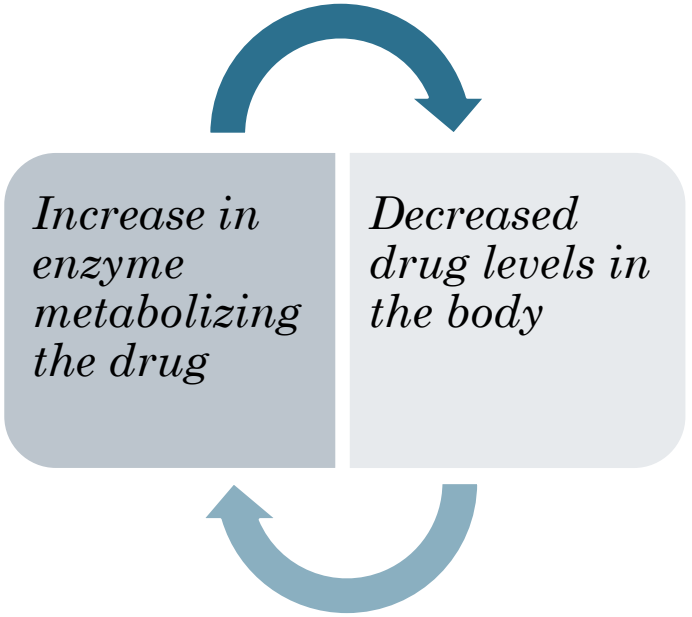
Practical Tips for Managing Immunosuppression Drug Interactions

CYP 3A4/5 Drug Interactions

CYP Inhibitors



CYP Inducers



When Should You See An Interaction?

Induction

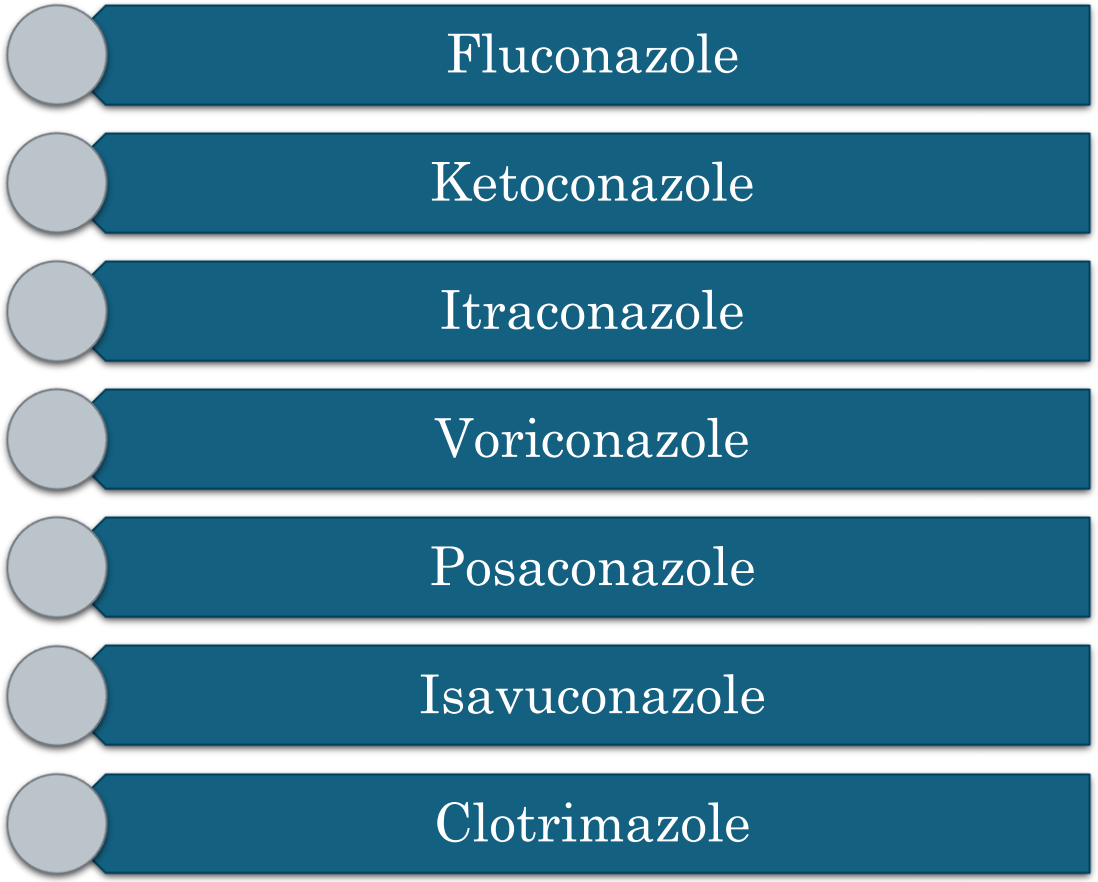
- Requires more time to produce additional enzymes
- Upregulate metabolizing enzymes
- Delay in maximum enzyme induction compared to inhibition

Inhibition

- Consider half-life of inhibitor
- Timing of interaction dependent on when drug reaches steady-state
- Predictable inhibitory effect

Pharm Times. 2011;72:30

Inhibitor Example: Azole Antifungals



Not All Azoles Are the Same!

Variability of interaction

- Itraconazole>ketoconazole >voriconazole/posaconazole > fluconazole
- Isavuconazole and clotrimazole – less interaction

Clinical Pearls

- Fluconazole doses > 200 mg/day clinically significant
- Voriconazole/posaconazole level can be checked ~5-7 days following initiation to assess concentration

Pharmacotherapy. 2006;26(12):1730-44.

Interaction at Steady-State

Ketoconazole	~24-48 hours
Voriconazole	IV loading dose – Day 3 No loading dose – 5-7 days
Itraconazole	Single dose – Day 3 Multiple doses – 5 -7 days
Posaconazole	~3-5 days
Fluconazole	~3-5 days
Isavuconazole	~1-2 weeks

Br J Clin Pharmacol. 2003 Dec;56 Suppl 1:10-6.

Treatment Strategies

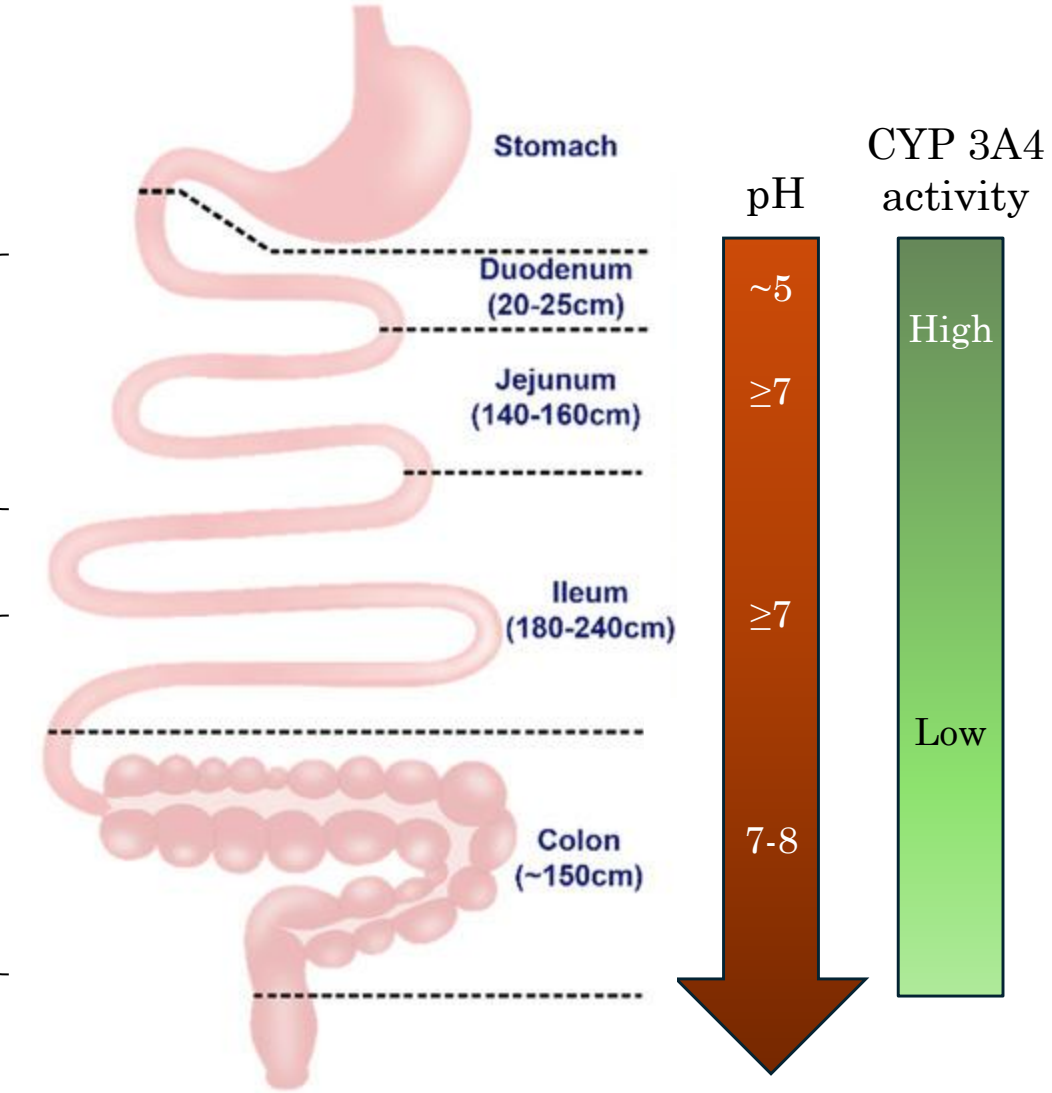
Ketoconazole	Decrease CNI by ~50%
Voriconazole	Decrease CNI by ~50% Decrease mTOR by ~50-75%
Itraconazole	Decrease CNI by ~50%
Posaconazole	Decrease cyclosporine by ~25% Decrease tacrolimus ~50%
Fluconazole	*Dose dependent* Consider dose decrease from 30-50%
Isavuconazole Clotrimazole	Monitor CNI levels

Clin Transplant. 2019; 33:e13510.

Does Formulation Play a Role?

Immediate release (IR) tacrolimus [Prograf] site of absorption

Prolonged release (PR) tacrolimus [Envarsus] site of absorption



Pharmaceutics. 2021;13(8):1261

Clin Pharmacol Ther. 2019;106(6):1290-1298

Does Formulation Play a Role?

Huppertz et al. 2019

Objective	• Investigate whether prolonged release (PR) tacrolimus [Envarsus] is less affected by the strong CYP3A4 inhibitor voriconazole than immediate release (IR) tacrolimus [Prograf]
Methods	• 18 healthy white males • Four-phase crossover trial • Tacrolimus 3mg (Prograf or Envarsus) x 1 dose; voriconazole 800mg on day 1 then 200mg BID x 3 days
Results	• AUC increased 2.62-fold vs 6.02-fold after PR tacrolimus vs IR tacrolimus, respectively ($p < 0.001$) • Less variability in AUC with PR tacrolimus: AUC increase 1.6 to 4.8-fold with PR tacrolimus vs 1.8 to 19-fold with IR tacrolimus
Conclusion	• Effects of voriconazole on tacrolimus levels were smaller and less variable after a PR tacrolimus formulation was administered

Clin Pharmacol Ther. 2019;106(6):1290-1298

Inducer Example: Rifamycins

Treatment Strategies

- Strong inducers of CYP3A4
- Rifampin: Increase CNI 2-fold and monitor levels weekly
- Rifabutin: Increase CNI by 30-50% and monitor levels weekly

Clinical Pearl: Use rifabutin over rifampin if possible, less interaction

Liver Transpl. 2013 Apr;19(4):457-61.

When the Interaction Goes Away…

CYP Inhibitors

- Increase CNI dose upon discontinuation of inhibitor
- Consider half-life of drug as a guide
- TDM ~3-7 days after discontinuation

CYP Inducers

- Decrease CNI dose upon discontinuation of rifamycin therapy
- Interaction will not go away instantly – takes time for the extra enzymes to degrade
- TDM weekly will be important

TDM = therapeutic drug monitoring

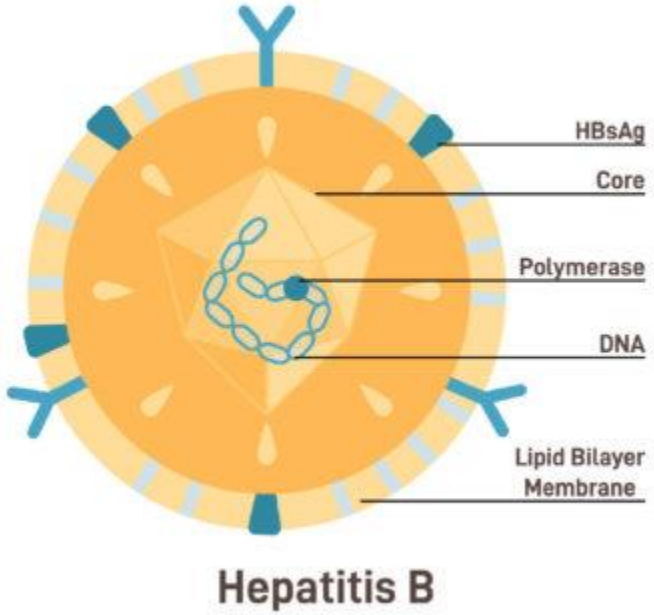
Pharmacotherapy. 2006;26(12):1730-44.

To B or Not to B

Medications for Hepatitis B Virus Prophylaxis & Treatment

Hepatitis B (HBV) Testing

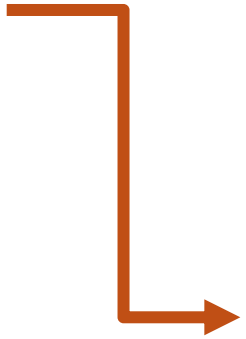
- Hepatitis B surface antigen (**HBsAg**)
  - Detected during acute or chronic hepatitis B infection
  - May be transiently positive after HBV vaccination
- Hepatitis B surface antibody (**HBsAb**)
  - Immunity from hepatitis B infection or immunization
- Hepatitis B core antibody (**HBcAb**)
  - Indicates previous or ongoing hepatitis B infection
  - Persists for life



Smalls DJ, et al. Pharmacotherapy. 2019;39(12):1190-1203.

Interpreting HBV Serologies

HBsAg	HBsAb	HBcAb
+	—	+



Chronic hepatitis B infection

- Consider Hepatology referral for further evaluation
- Antiviral treatment warranted at transplant (if not already receiving)

Terrault NA, et al. Hepatology. 2018;67(4):1560-1599.

Interpreting HBV Serologies

HBsAg	HBsAb	HBcAb
—	+	+

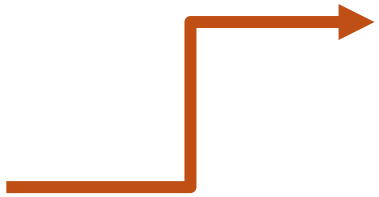
Resolved hepatitis B infection

- Has immunity from natural infection
- HBsAb may wane with time/immunosuppression, putting patient at risk of HBV reactivation

Terrault NA, et al. Hepatology. 2018;67(4):1560-1599.
Smalls DJ, et al. Pharmacotherapy. 2019;39(12):1190-1203.

Interpreting HBV Serologies

HBsAg	HBsAb	HBcAb
—	+	—



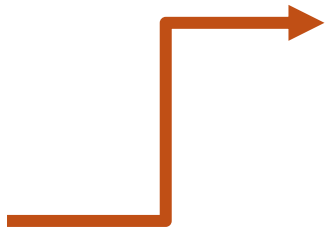
Immune due to vaccination

**HBsAb > 10 IU/mL considered positive after the vaccine series is completed*

Terrault NA, et al. Hepatology. 2018;67(4):1560-1599.

Interpreting HBV Serologies

HBsAg	HBsAb	HBcAb
—	—	—



Susceptible to hepatitis B infection

- Vaccinate prior to transplant

Terrault NA, et al. Hepatology. 2018;67(4):1560-1599.

Tenofovir Products

- Tenofovir disoproxil fumarate (Viread®)
  - Typical dose: 300mg daily
  - Renal dose adjustment required in CrCl<50 mL/min
  - Adverse effects: renal toxicity (including acute renal failure, Fanconi syndrome), decreased bone mineral density
- Tenofovir alafenamide (Vemlidy®)
  - Typical dose: 25mg daily
  - No renal dose adjustment required (not recommended in CrCl<15 mL/min)
  - Administer with food
  - Adverse effects
    - High antiviral activity at lower dose --> reduced renal and bone-related adverse effects
    - Increased LDL cholesterol

Entecavir

- Entecavir (Baraclude®)
  - Typical dose: 0.5mg daily
    - Entecavir 1mg daily recommended in decompensated cirrhosis
  - Renal dose adjustment required in CrCl<50 mL/min
  - **Administer on empty stomach**
  - Adverse effects: lactic acidosis (rare)

Lamivudine

- Lamivudine
  - Typical dose: 100mg daily
  - Renal dose adjustment required in CrCl<50 mL/min
  - Adverse effects: lactic acidosis (rare)
  - Lower barrier to resistance than tenofovir or entecavir, particularly with long-term use (>1 year)
    - Not recommended for initial treatment of chronic hepatitis B infection
    - Reasonable option for hepatitis B *prophylaxis* if no prior exposure to hepatitis B antivirals

Smalls DJ, et al. Pharmacotherapy. 2019;39(12):1190-1203.

Hepatitis B Reactivation

- Patients with previous exposure to hepatitis B (**HBcAb** positive & **HBsAg** positive or negative) have risk of reactivation when receiving certain immunosuppressive medications
  - **Rituximab**
  - Doxorubicin
  - TNF-α inhibitors (etanercept, infliximab, etc.)
  - Tyrosine kinase inhibitors (imatinib, dasatanib, etc.)
- In co-infected patients, hepatitis C treatment with direct acting antivirals (DAAs) may cause hepatitis B reactivation
  - Loss of virally-mediated hepatitis B inhibition
  - Risk highest in **HBsAg** positive patients

Smalls DJ, et al. Pharmacotherapy. 2019;39(12):1190-1203.
Reddy KR, et al. Gastroenterol. 2015;148(1):215-9.

Let's Take Some Questions!