Pharmacy Updates

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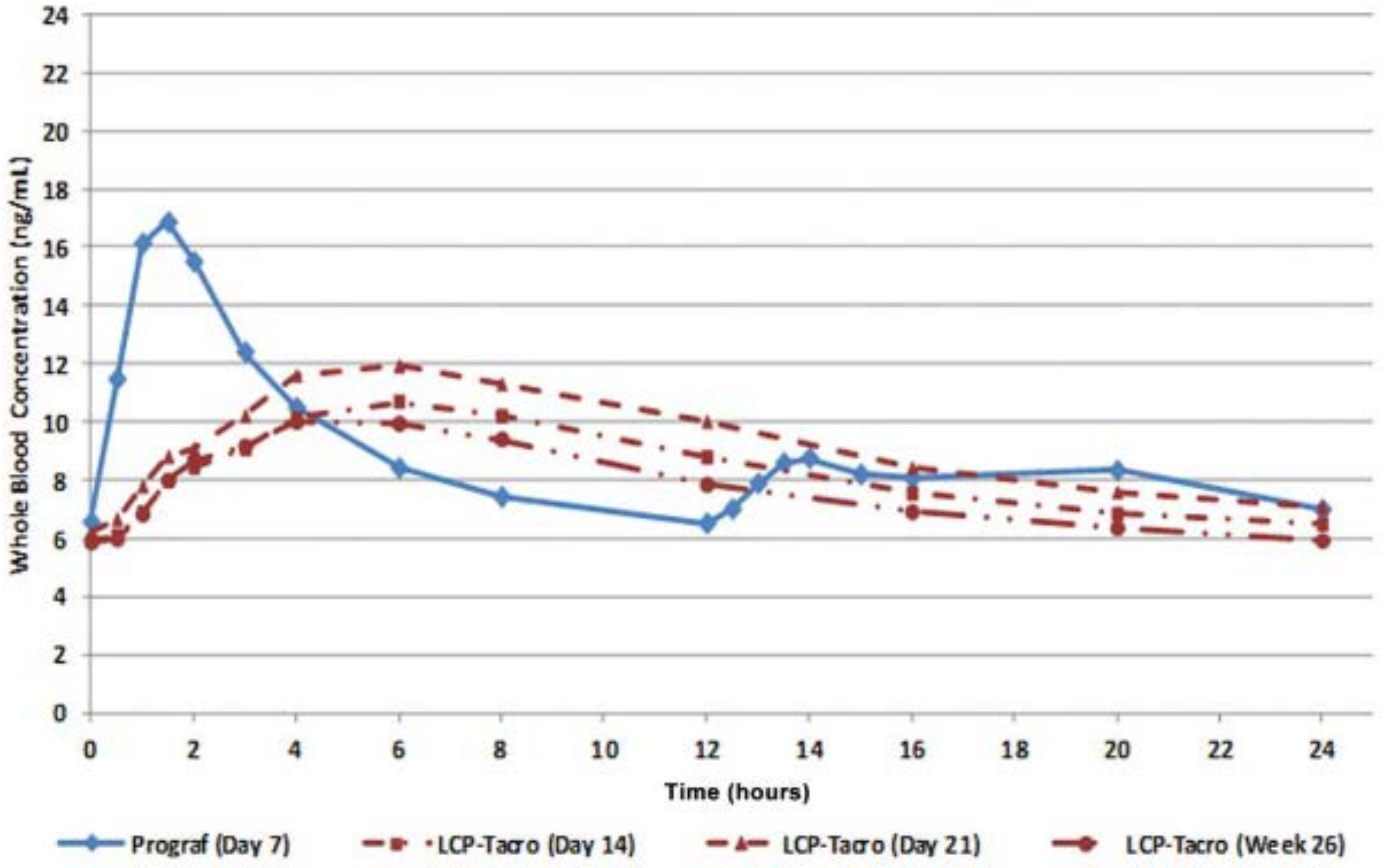
What the FK should I do?

Tacrolimus formulations

Type	Brand	Route(s) of administration	Typical Frequency
Immediate release capsules	Prograf	Oral or sublingual	Every 12 hours
Extended-release tablets	Envarsus XR	Oral only	Once daily
Extended-release capsules	Astagraf XL	Oral only	Once daily
Granules	Prograf Granules	Oral only	Every 12 hours
Intravenous	Prograf Injection	IV only	Continuous infusion
Oral suspension*	---	Oral or via feeding tube	Every 12 hours

*typically prepared in-house at most institutions

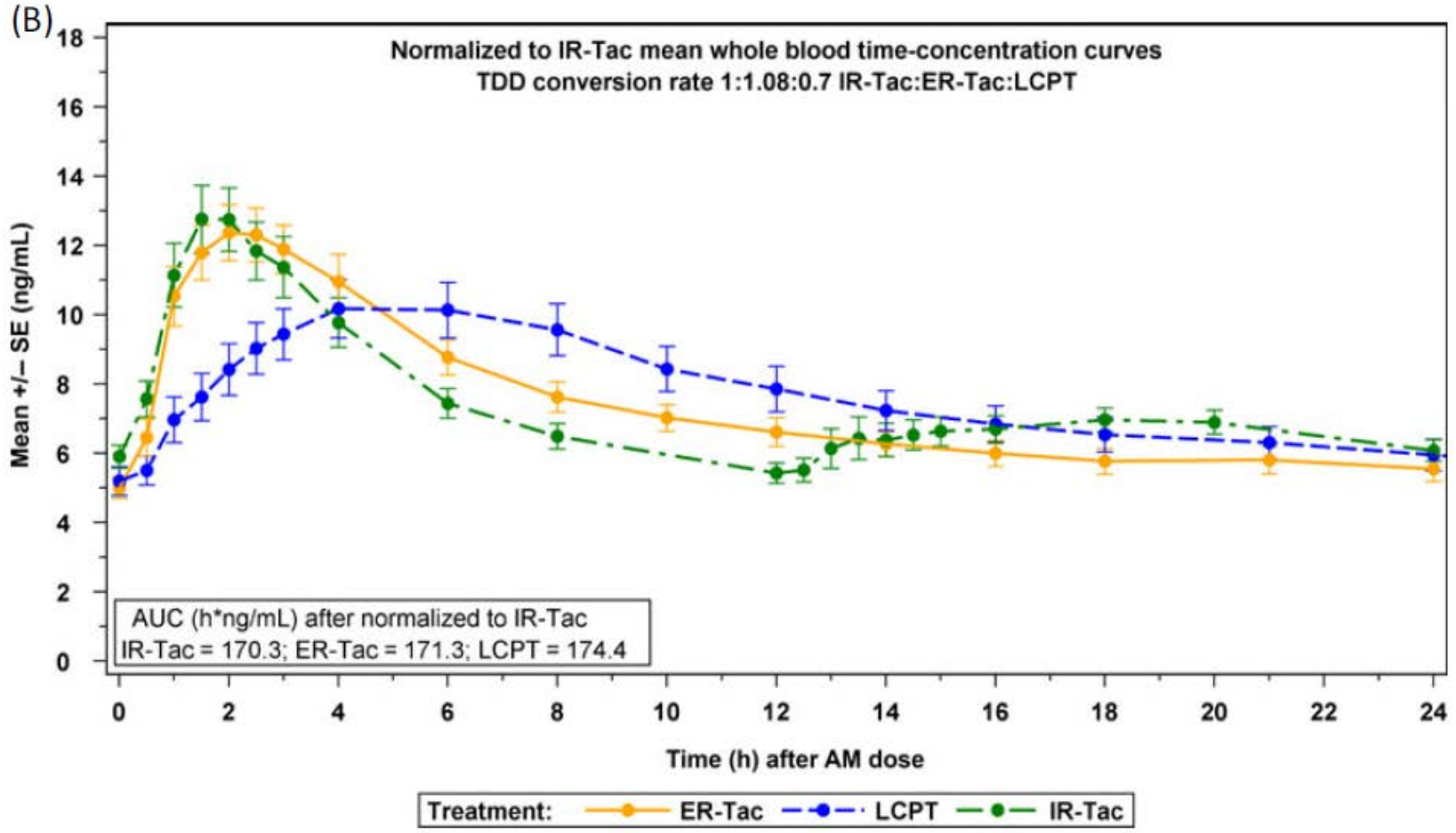
Why does formulation matter?



Prograf = IR tacrolimus, LCP-Tacro = Envarsus XR

Alloway RR, et al. Liver Transplantation 2014. 20:564-575.

The PK of FK



Tremblay S, et al. Am J Transplantation 2017. 17:432-442.

So What?

- Is my patient right for extended-release tacrolimus?
- Will insurance cover extended-release tacrolimus?
- How should I dose extended-release tacrolimus?

Getting into the Weed*(s)*

Marijuana and Herbal Supplement Drug Interactions

CYP P450 Drug Metabolism

Tacrolimus, Cyclosporine
Sirolimus, Everolimus

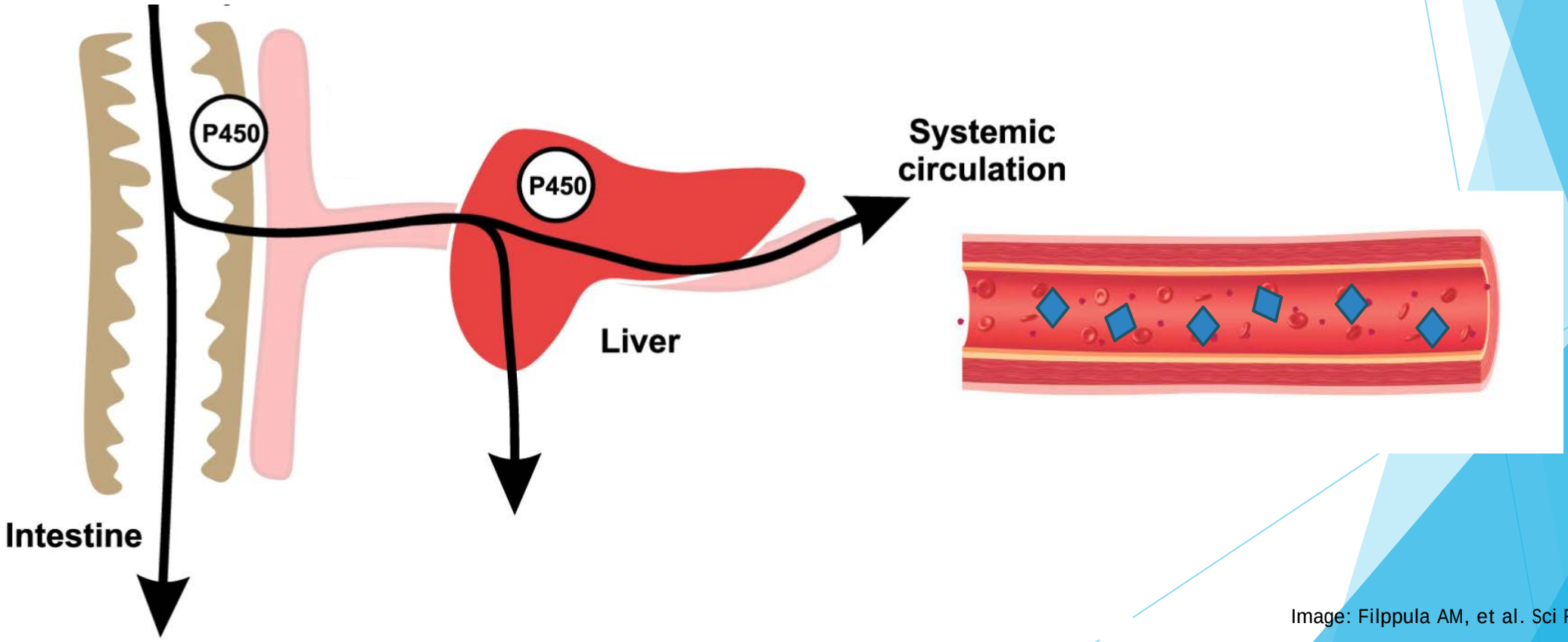


Image: Filppula AM, et al. Sci Rep. 2019; 9(5850)

Drug Interactions – CYP 3A4/3A5 Inhibitors

Tacrolimus, Cyclosporine
Sirolimus, Everolimus

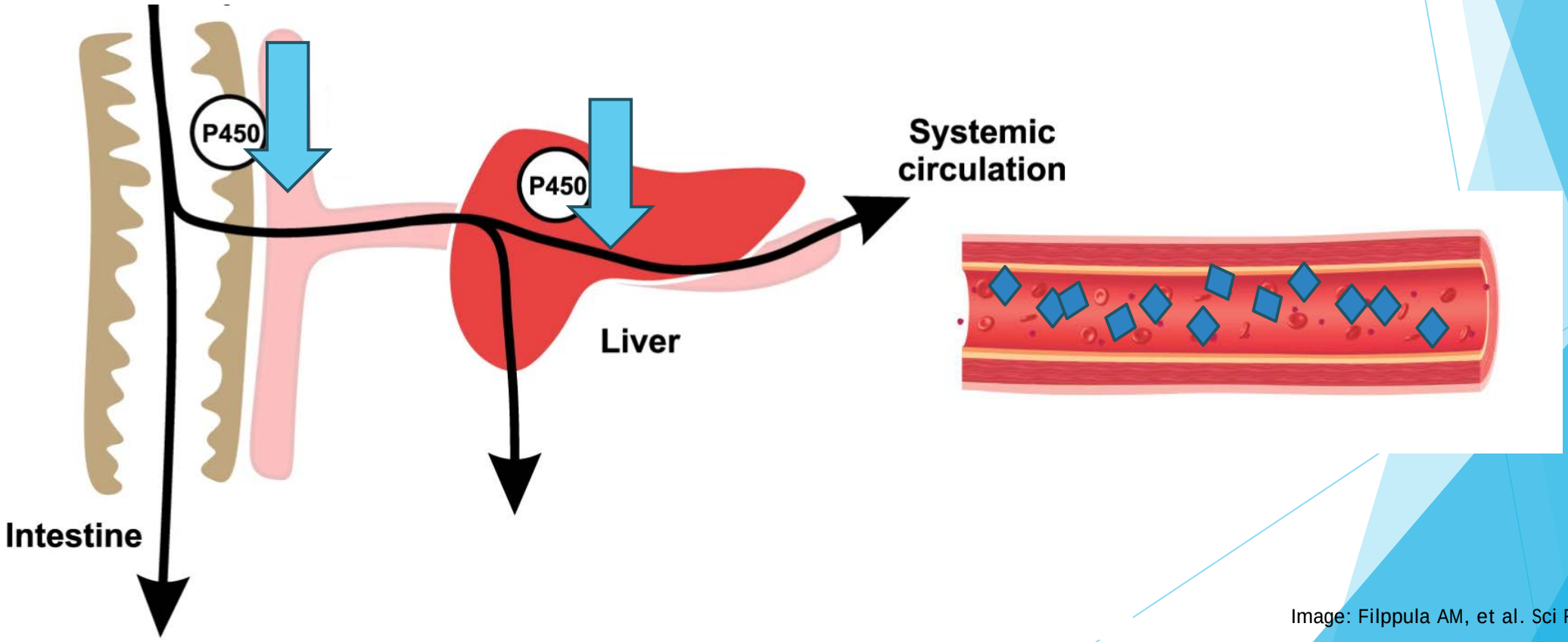


Image: Filppula AM, et al. Sci Rep. 2019; 9(5850)

Drug Interactions – CYP 3A4/3A5 Inducers

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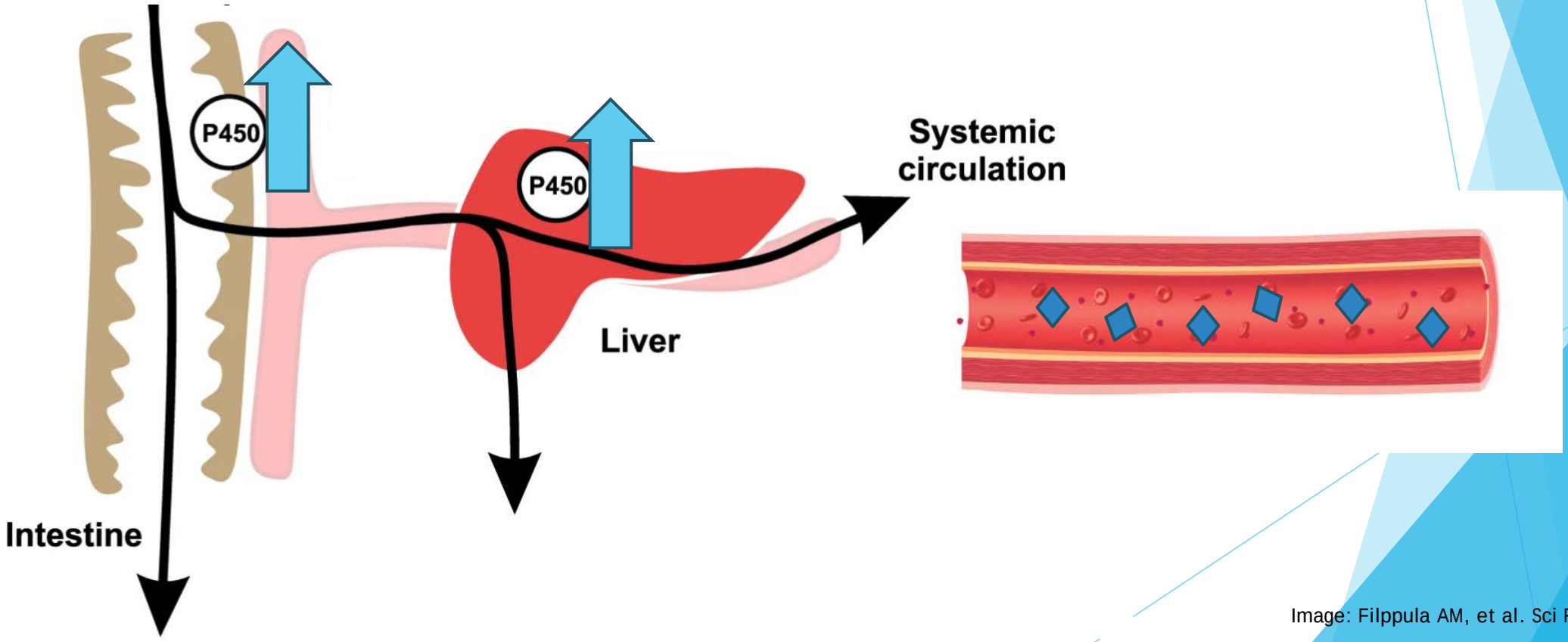
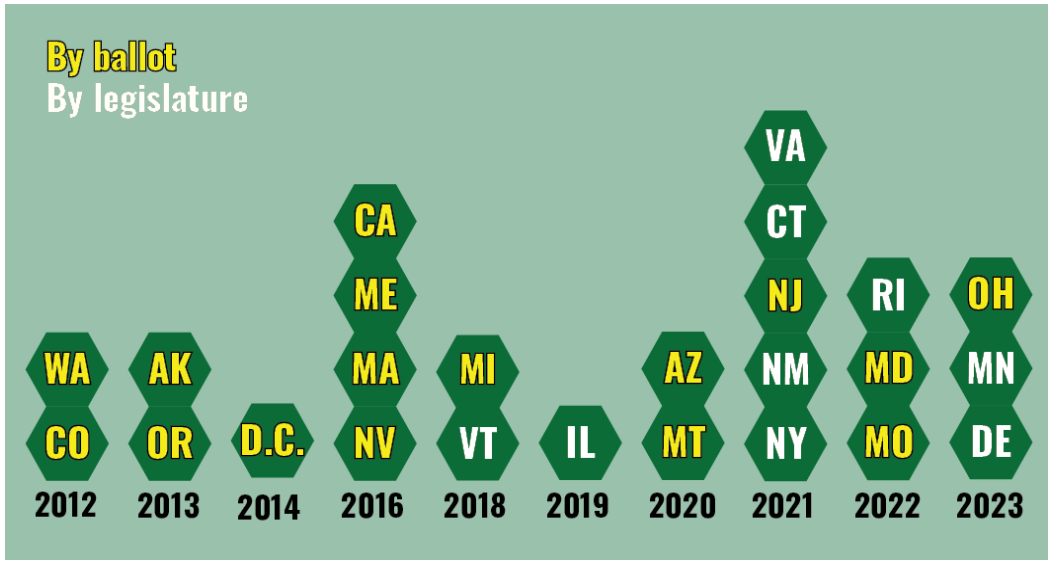
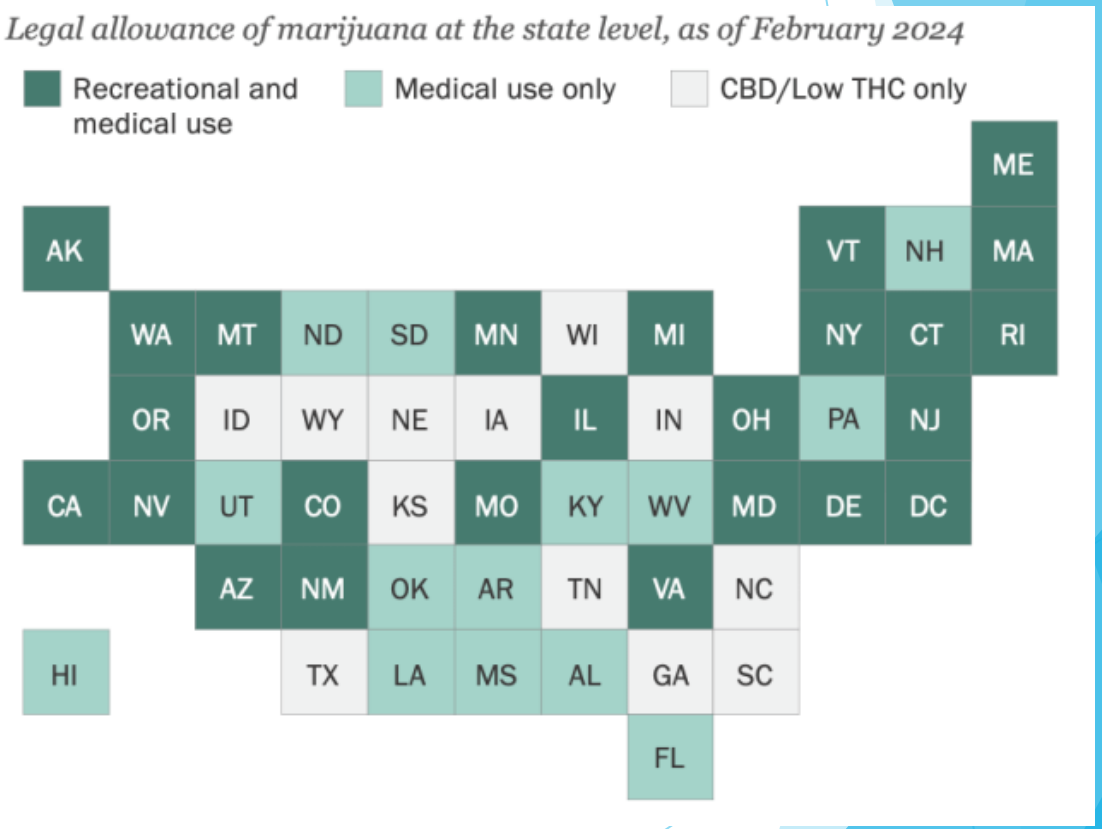


Image: Filppula AM, et al. Sci Rep. 2019; 9(5850)

Marijuana Legalization





Images: https://no-smoke.org/marijuana-cannabis-our-resources-are-a-beacon-in-the-haze/
Pew Research Center. February 27, 2024.

Marijuana Pharmacology

- Cannabis produces over 100 chemical compounds called cannabinoids
  - Δ-9 tetrahydrocannabinol (**THC**) = main psychoactive substance
  - Cannabidiol (**CBD**) = little psychotropic effect; potential antiseizure, analgesic, antiemetic effects
- THC and CBD distribute widely into adipose tissues and organs (heart, lung, liver, spleen)
  - THC is released slowly from adipose tissue into the blood
- Most cannabinoid metabolism occurs in the liver via CYP P450 enzymes

Abramovici H, et al. Information for health care professionals: Cannabis (marihuana, marijuana) and the cannabinoids. October 2018.
Nasrin S, et al. Drug Metab Dispos. 2021;49(12):1070-1080.

Marijuana Regulation

- FDA regulation of cannabis-derived products is based on *marketed claims*
  - Cannabis products marketed with a claim of therapeutic benefit are considered "drugs"
    - Requires full FDA approval before introduction to interstate commerce
  - THC and CBD products are excluded from the definition of "dietary supplements"
- Product labeling may not reflect actual CBD and THC content
  - Mississippi-based study of hemp oil products found only 3 of 25 products had CBD content within ± 20% of the labeled amount
    - 3 products had THC content exceeding legal limit (0.3%)
  - May impact predictability of drug interactions and clinical effects

FDA Public Hearing: Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds. May 31, 2019.
Gurley BJ, et al. Journal of Dietary Supplements. 2020;17(5):599-607.

Marijuana Drug Interactions in Transplant*

Enzyme	CBD Effect	THC Effect	Interacting Medication	Clinical Implication
CYP 3A4	**Inhibitor**	Inhibitor	Tacrolimus, cyclosporine, sirolimus, everolimus	Increased immunosuppression levels
			Apixaban, rivaroxaban, etc.	Increased anticoagulant concentrations
CYP 3A4	Substrate	Substrate	Fluconazole, voriconazole, etc.	Increased CBD/THC concentrations
CYP 2C9 CYP 2C19 CYP 1A2	**Inhibitor**	Inhibitor	Warfarin	Increased warfarin concentrations
UGT1A9	Inhibitor	---	Mycophenolate	Increased mycophenolic acid (MPA) concentrations

*Not all inclusive

Nasrin S, et al. Drug Metab Dispos. 2021;49(12):1070-1080.
Qian Y, et al. J Clin Psychopharmacol. 2019;39(5):462-471.

Herbal/Dietary Supplement Interactions*

- Detailed clinical data regarding supplement-drug interactions are limited

Supplement	Possible Enzyme Effect(s)
Turmeric	CYP 3A4 inhibitor
Green tea	CYP 3A4 inhibitor
Chamomile	CYP 3A4 inhibitor
Garlic	CYP 3A4 inhibitor
Ginseng	CYP 3A4 inducer (mixed data)
Ginkgo biloba	CYP 3A4 inducer; P-gp inhibitor
St. John's wort	CYP 3A4 Inducer; P-gp inducer

*Not all inclusive

Colombo D, et al. Journal of Toxicol. 2014: 145325.
Cho HJ, et al. Evid Based Compliment Alternat Med. 2015: 736431.

Managing Herbal Drug Interactions

- Discuss center-specific policies/protocols for post-transplant marijuana use with multidisciplinary transplant team
- Marijuana or CBD products should be treated as a medication
  - Add to EMR medication list
  - Maintain consistency of sourcing and product as much as possible
  - Notify transplant team of changes in dose/product
- Closely monitor labs relevant to interacting medications (immunosuppression levels, INR for patients taking warfarin, etc.)
- If immunosuppression levels are unexpectedly fluctuating – ask patient about new/changing use of marijuana, CBD, other supplements

HIV+ Transplants: How to be sure when a patient is positive

Medication Classes

Class	Medications	Major Adverse Effects
Nucleos(t)ide reverse transcriptase inhibitor **(NRTI)**	Abacavir, emtricitabine, lamivudine, tenofovir, zidovudine	Nephrotoxicity, bone toxicity, cardiac concerns (abacavir)
Non-nucleos(t)ide reverse transcriptase inhibitor **(NNRTI)**	Efavirenz, etravirine, nevirapine, rilpivirine, doravirine	Dyslipidemia, rash, fatigue, drug interactions (CYP 3A4, some agents)
Protease inhibitors **(PI)**	Atazanavir, darunavir, fosamprenavir, ritonavir, saquinavir, tipranavir	Dyslipidemia, central fat accumulation, hepatitis, GI upset, drug interactions
Fusion inhibitor **(FI)**	Enfuvirtide	Injection site reactions
Integrase Strand Transfer Inhibitor **(INSTI)**	Dolutegravir, raltegravir, elvitegravir, bictegravir, cabotegravir	Dyslipidemia, pregnancy considerations
Chemokine receptor 5 inhibitor **(CCR5i)**	Maraviroc	Headache, GI upset
Pharmacokinetic Booster	Cobicistat, ritonavir (see above)	Drug interactions, SCr increase

Chawla A, et al. Infect Dis Therapeutics 2018. 7(2):183-195.

Commonly Recommended Regimens

- Bictegravir + tenofovir alafenamide + emtricitabine
  - Single pill (Bikarvy)
- Dolutegravir + tenofovir + emtricitabine or lamivudine
  - Multi-pill regimen(s)
- Dolutegraivr + lamivudine (only in certain patients)
  - Single pill (Dovato)

Gandhi RT, et al. JAMA 2023. 329(1):63-84.

Positively Significant Interactions

- Any protease inhibitor-containing regimen (with a pharmacokinetic booster) will interact STRONGLY with many medications
  - Look for ritonavir or cobicistat (may be hidden in a combination regimen)

Does it really even matter?

YES

- Levels can increase dramatically and rapidly following initiation
- 50yo renal transplant recipient started on cobicistat-containing regimen
  - FK went from therapeutic (goal 4-6 ng/mL) to 111.2 ng/mL in 1 week
- 55yo renal transplant recipient transitioned from a ritonavir- to a cobicistat-containing regimen
  - FK changed from 0.5 mg every 11 days to 0.5 mg every 9 days

Han Z, et al. Pharmacotherapy 2016. 36(6):e50-53.
Erba A, et al. Virology Journal 2023. 20:89.

So What?

- Never change an HIV regimen without discussing with ID or the patient's HIV provider
- If safe, consider switch to a non-boosted regimen
- If changing regimens is not possible, dose any CYP 3A4-metabolized medications VERY conservatively
  - CNIs, mTOR inhibitors, statins, and many more…
- Ask your friendly neighborhood transplant pharmacist for help ☺

To B or not to B

Medications for Hepatitis B Virus Prophylaxis/Treatment

Hepatitis B Testing

- Hepatitis B surface antigen (**HBsAg**): detected during acute or chronic hepatitis B infection
- 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

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)
  - Adverse effects
    - High antiviral activity at lower dose --> reduced renal and bone-related adverse effects
    - Increased LDL cholesterol
  - Administer with food

Entecavir

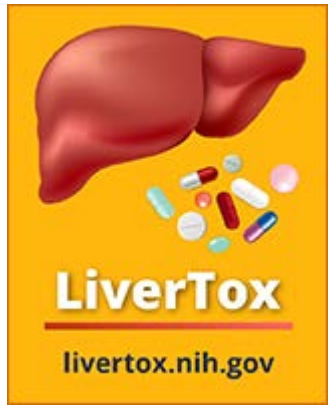
- Entecavir (Baraclude®)
  - Typical dose: 0.5mg daily
    - Entecavir 1mg daily recommended in decompensated cirrhosis
  - Renal dose adjustment required in CrCl<50 mL/min
  - Adverse effects: lactic acidosis (rare)
  - **Administer on empty stomach**

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
    - Not recommended for initial management of chronic hepatitis B infection
    - Reasonable option for hepatitis B prophylaxis

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.