Drug-Drug Interactions in TB-Diabetes and HIV-TB

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"Developing a Comprehensive Therapeutic Research Strategy for the Converging Epidemics of TB, T2DM, and HIV" Workshop
NIAID, NIDDK, Office of AIDS Research

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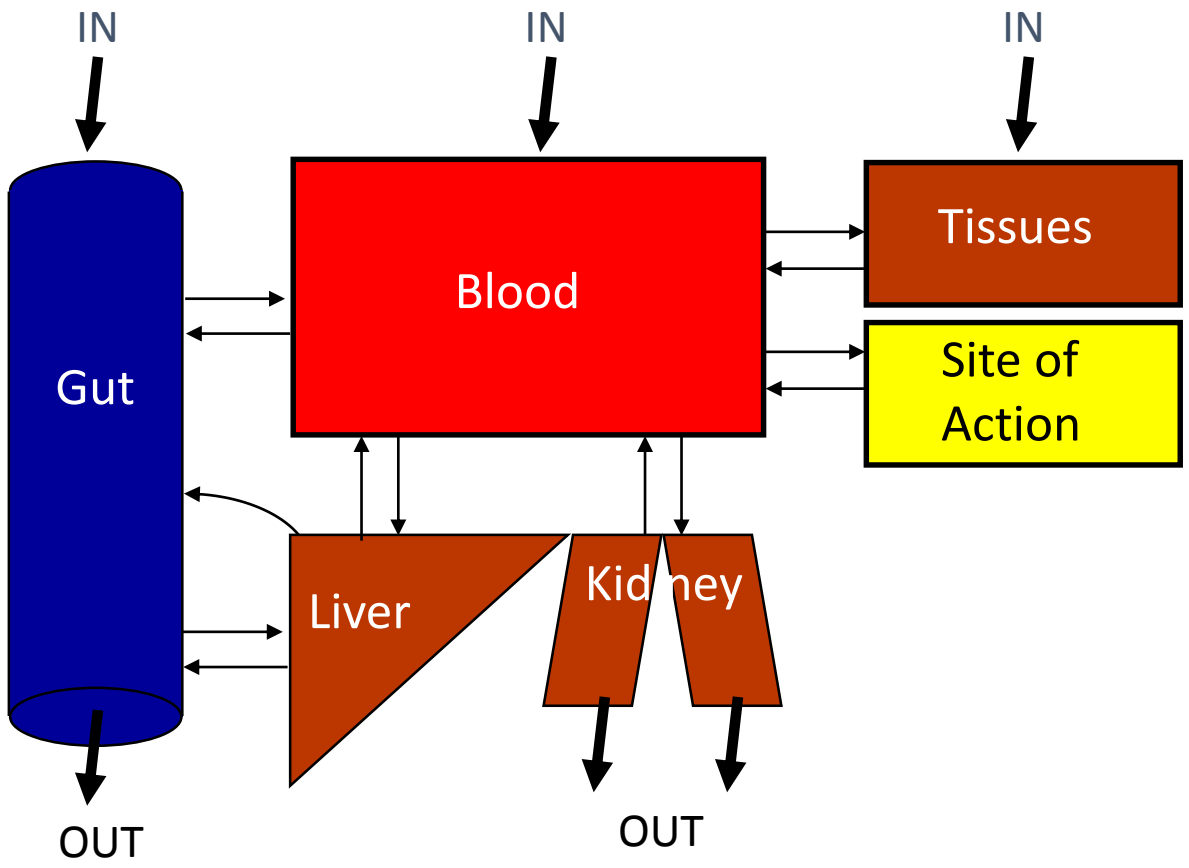
Pharmacology of drug interactions:
DDI can occur with all drug disposition processes



- **Absorption**
  - E.g. chelation, gastric acid, P-gp, gut flora and motility
- **Distribution**
  - E.g. competition for protein binding
- **Metabolism**
  - E.g. CYP450 enzymes
- **Elimination**
  - E.g. inhibition of renal clearance

Drug "interactions"– when to worry?

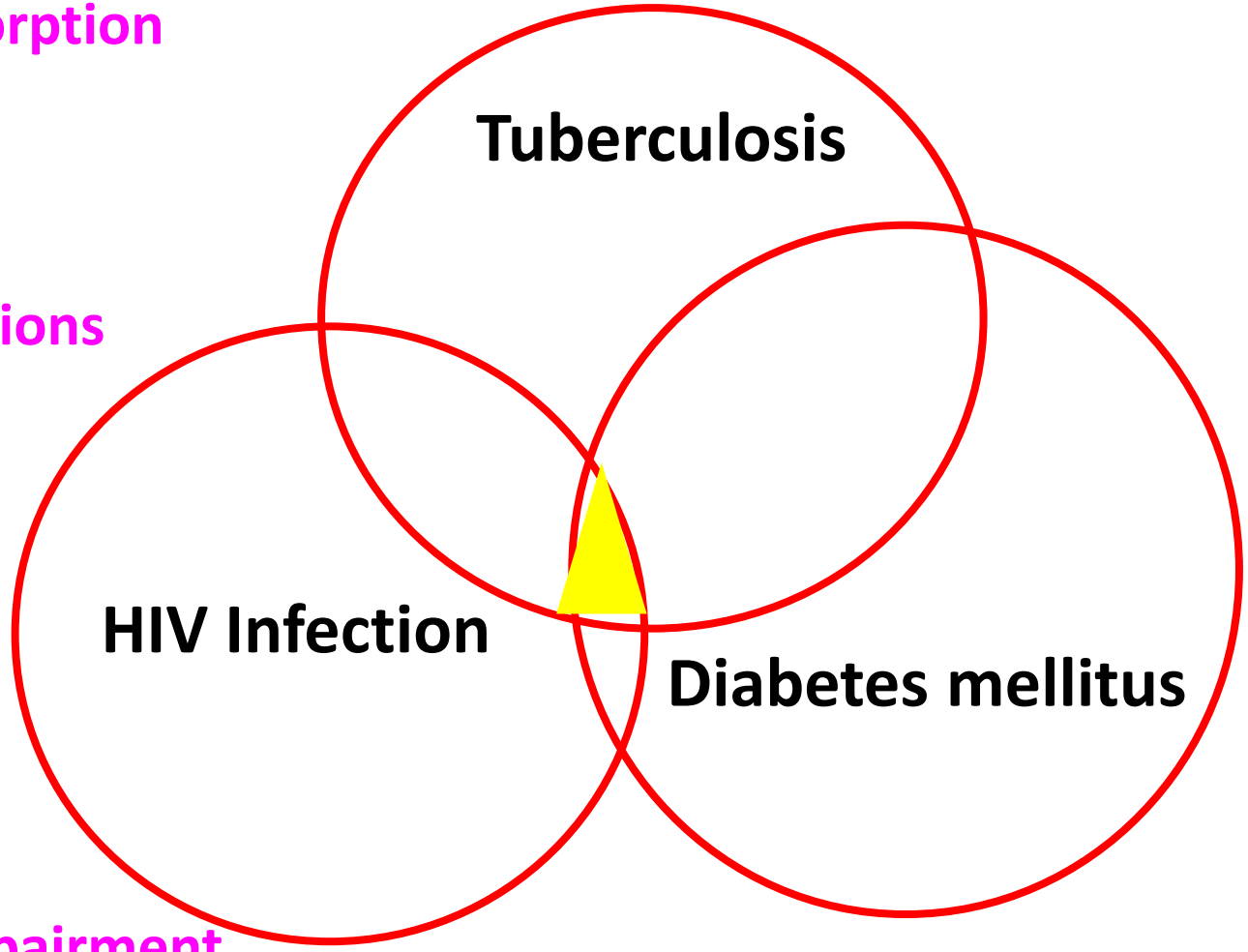
- Drug X is predicted to ***induce* or *inhibit*** the metabolism (or transport or elimination) of Drug Y
- Drug Y has a ***narrow therapeutic index***, and Drug X may affect Drug Y concentrations
- Drug X and Drug Y have ***overlapping toxicities***
- Drug X has ***low or variable bioavailability***
- Drug X used to treat Condition A has ***off-target or unexpected effects*** on Condition B

Goal is to avoid, manage, measure DDI that may change efficacy or toxicity

Drug interactions can be complex:
interplay of disease states, evolving pharmacodynamics

Absorption

Off target effects



Metabolic
drug interactions

Pharmacodynamics,
changing over time

Inflammation

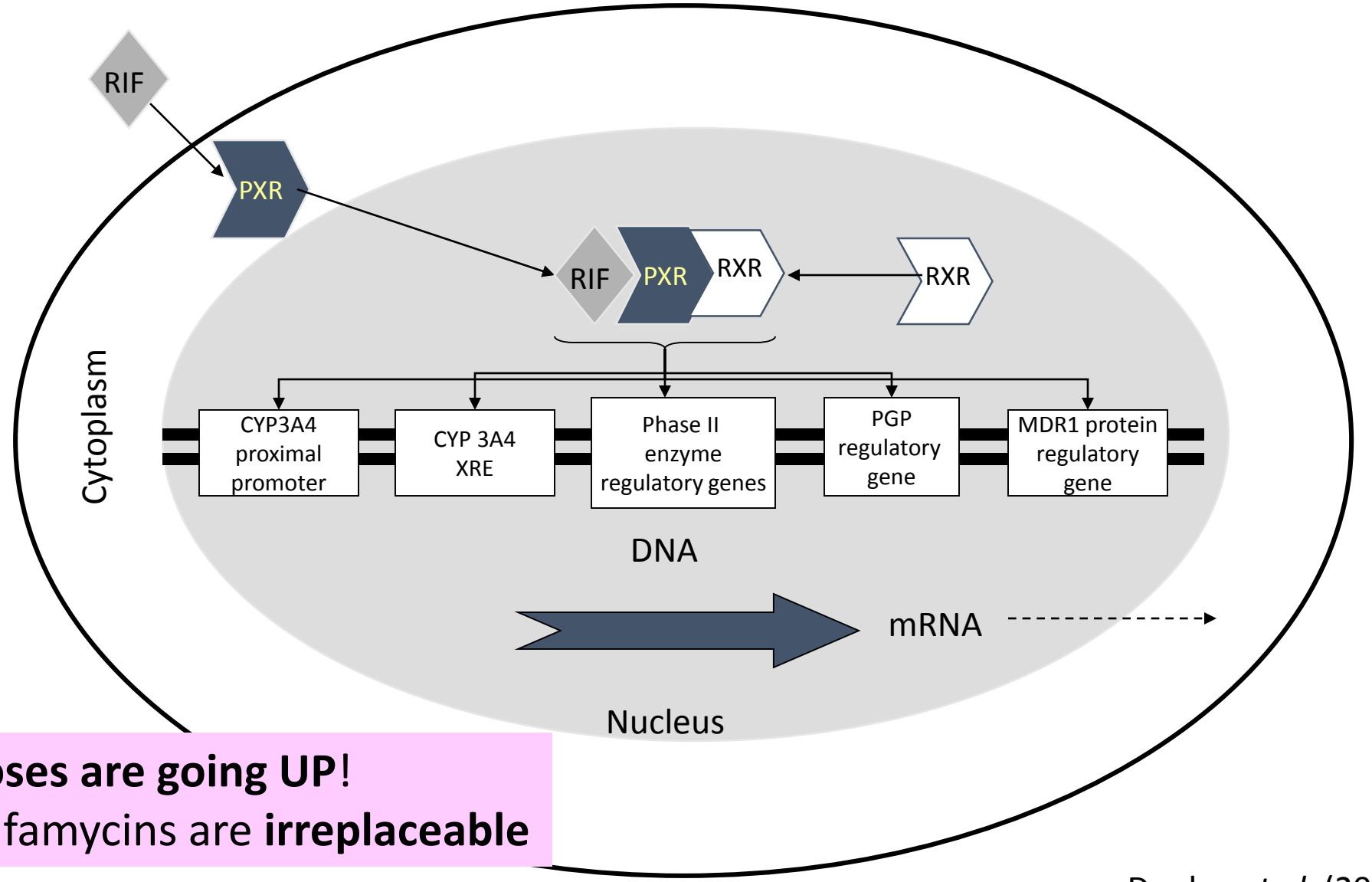
Overlapping toxicities

End organ impairment

The basics– TB/HIV co-treatment

RIFAMPIN: A potent inducer of metabolizing enzymes

This complicates co-treatment of TB and other diseases tremendously



Rifamycin **doses are going UP**!
Up to now, rifamycins are **irreplaceable**

Dooley *et al.* (2008) JID 198: 948.

ARV metabolism

Inhibition

Mixed inhibition/induction

Induction

Substrate

*not determined

Note: NRTI are mostly excreted renally and are not metabolized, so few metabolic drug interactions

Table 1. Metabolic Effects for Antiretrovirals [6,12,18–36].

		Predicted Enzyme Effect						
	Antiretroviral	**3A4**	**2B6**	**2C9**	**2C19**	**2D6**	**1A2**	**UGT**
PIs	Atazanavir	Inhibition, Substrate	–	Inhibition	–[a]	–	Inhibition	Inhibition
	Darunavir/r	Inhibition, Substrate	Induction	Induction	Induction	–[a]	Induction	Induction
	Fosamprenavir	Mixed inhibition/induction	Induction	–	–[a]	–	–	–
	Indinavir	Inhibition	–	–	–	–[a]	–	Inhibition
	Lopinavir/r	Inhibition, Substrate	Induction	Induction	Induction	–[a]	Induction	Induction
	Nelfinavir	Mixed inhibition/induction	–	Induction	Induction	–	Induction	Induction
	Ritonavir	Inhibition[b]	Induction	Induction	Induction	Inhibition	Induction	Induction
	Saquinavir	Inhibition	–	–[a]	–	–	–	–
	Tipranavir/r	Inhibition	Induction	Induction	Induction	Inhibition	Induction	Induction
NNRTIs	Delavirdine	Inhibition	–	Inhibition	Inhibition	–[a]	–	–
	Efavirenz	Induction	Induction	Inhibition	Induction	Inhibition	Inhibition	Induction
	Etravirine	Induction, Substrate	Induction	Inhibition, Substrate	Inhibition, Substrate	–	–	Induction
	Nevirapine	Induction	Induction	Induction	–	–	–	Induction
	Rilpivirine	Induction	Induction	*	Induction	*	Induction	*
INSTI	Raltegravir	–	–	–	–	–	–	Substrate
	Elvitegravir/r	Inhibition	*	*	*	*	*	Induction
	Dolutegravir	Substrate	*	*	*	*	*	Substrate
	Maraviroc	Substrate	–	–	–	–	–	–
	Cobicistat	Inhibition, Substrate				Inhibition		

Rathbun *et al* 2011 Pharmaceutics 3:745.

HIV/TB co-treatment options for adults: **Drug-sensitive TB**

ARV*	Rifamycin	Dose adjustments	Other Issues
Preferred			
Efavirenz	Rifampin	None	Watch for CNS toxicity
Lopinavir/ ritonavir (Darunavir/r)	Rifabutin	Rifabutin 150 mg once daily	Monitor for uveitis; Must coordinate care
Alternative			
Raltegravir	Rifampin	Raltegravir 400 or 800 mg twice daily	Limited clinical experience
Dolutegravir	Rifampin	Dolutegravir 50 mg twice daily	Awaiting results of trial in co-infected patients
Nevirapine	Rifampin	Avoid NVP lead-in	Hepatotoxicity

*All listed antiretroviral drugs should be given together with two NRTI

Overlapping toxicities

Adverse Reaction	TB Drugs	HIV Drugs
Rash	PZA, RIF, INH	NNRTIs, ABC, T/S
Hepatotoxicity	INH, RIF, PZA	PIs, NVP
Nausea	RIF, PZA, INH	RTV, AZT
Cytopenias	RBT, RIF	AZT, T/S
Central nervous system side effects	INH	EFV

Question: Are some toxicities more common in patients with DM, who may be older?

Not to mention pill burden and **coordination of services**…..

HIV/TB co-treatment: **New TB Drugs**

TB Drug	PK challenges	AE Risk	ART DDI
Bedaquiline	CYP3A substrate	Cardiac (QT)	EFV+BDQ-> BDQ ↓ 50% LPV/r+ BDQ → BDQ, M2 ↑ two-fold
Delamanid	Low bioavailability	Cardiac (QT)	No clinically important DDI with EFV or boosted PI
Pretomanid	CYP3A minor metabolic pathway	Liver	EFV+PA-824 → PA824 ↓ 35% LPV/r+PA-824 → PA824 ↓ 17%
Sutezolid	Parent/metabolite contributions to efficacy, toxicity	Undefined: Hematologic Liver Nerves	Unknown

Now add in Diabetes

HIV/TB/DM co-treatment options: **Drug-sensitive TB**

	Metabolism	Effects of Efavirenz	Effects of Ritonavir	Effects of Rifampicin
Metformin	None	None	None	TBD
Insulin	None	None	None	Causes hyperglycemia, hyperinsulinemia
Glipizide	CYP2C9	Inhibits 2C9, Increase [drug]	Induces 2C9, Decrease [drug] (theoretical)	Induces 2C9, Decrease [drug] 22%
Pioglitazone	CYP2C8	Inhibits 2C8, Increase [drug]	Inhibits 2C8, Increase [drug] (theoretical)	Induces 2C8, Decrease [drug] 54%

Consider also that patients with DM often have comorbidities that require medical treatment.
Ritonavir is mixed inhibitor/inducer, risk of DDI with companion drugs is high.

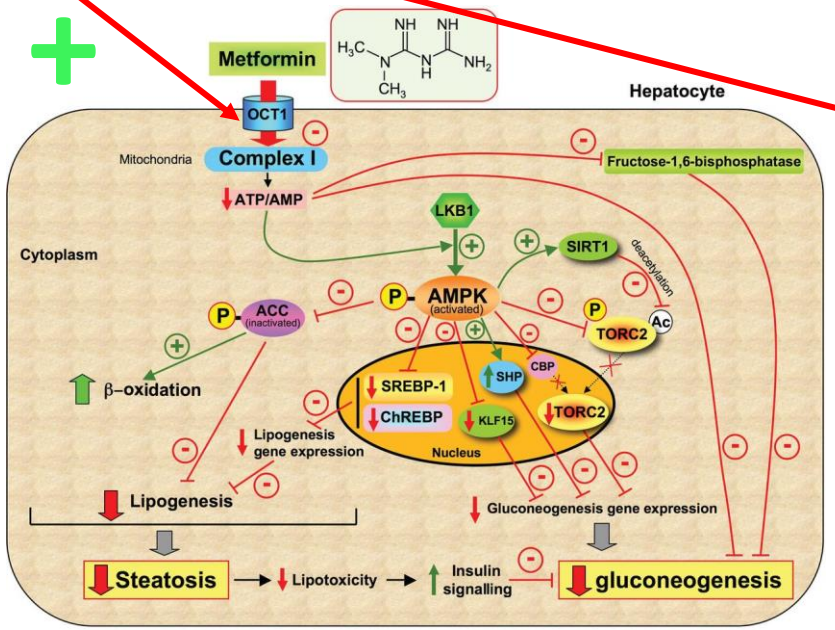
http://www.hiv-druginteractions.org/checker

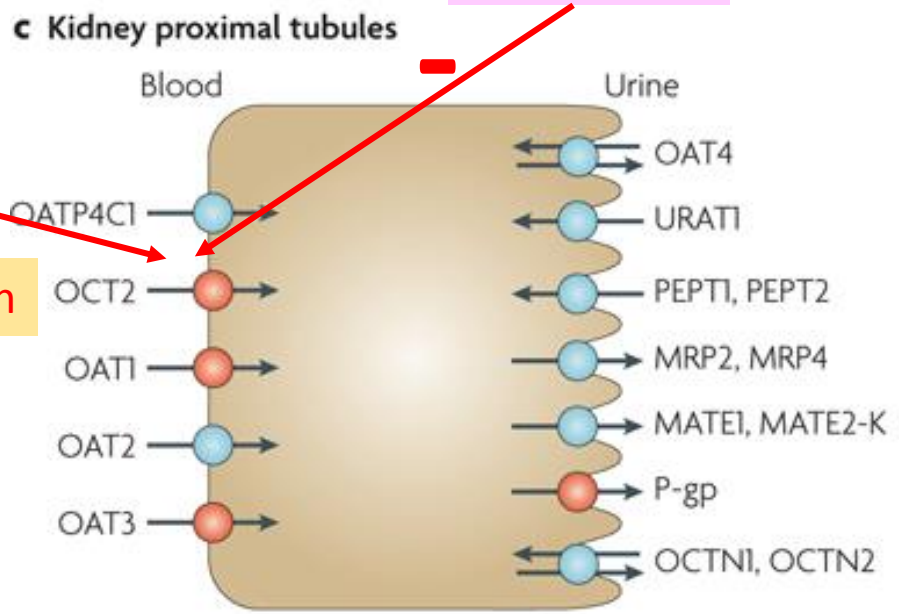
e.g. Metformin, in the TB-HIV co-infected patient

Rifampicin

UGT1

Dolutegravir





Metformin

- **<u>RIF+Metformin</u>**

  RIF induces OCT1, increasing Metformin transport into liver. RIF also induces OCT2, increasing Metformin renal clearance.

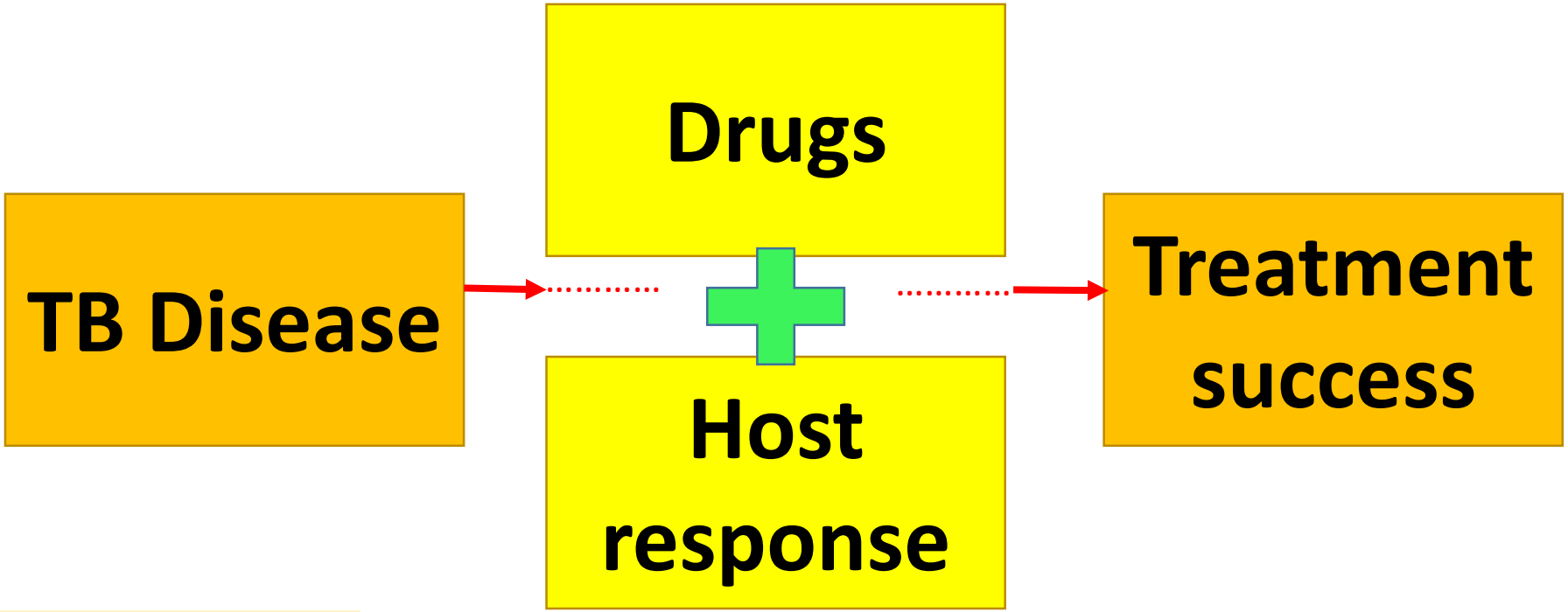
  Is the paradoxic result that diabetes control is improved (increased gluconeogenesis) despite lower serum concentrations**?**

- **<u>HIV+TB+DM</u>**

  HIV infection reduces Rifampicin absorption, TB worsens glycemic control, Rifampicin reduces Dolutegravir concentrations, Dolutegravir blocks metformin elimination, Metformin may have anti-TB activity

figures from Viollet (2012) Clinical Science; Giacomini (2010) Nature Reviews Drug Discovery 9:215.

Scientific question: How does DM impact TB outcomes?



Diabetes:
Rifampicin exposures
Immune response to pathogen

Diabetes treatment:
Metformin HDT effects

You can't sort out this relationship (and know what to recommend) without knowing:

- Rifampicin PK
- Which DM drugs patients are taking
- Metformin PK/PD with RIF
- Longitudinal glycemic control

TB disease:
Worsens glycemic control

TB treatment:
Improves sugars by treating infection
May affect metformin PK/PD
RIF increases hyperglycemia, insulin

Scientific question:

Can we harness drugs with anti-DM and HDT effects for TB/DM co-treatment?

- Sitagliptin as HDT
  - But sitagliptin is renally cleared , partially via transporters induced by rifampicin. Can these drugs be used together?
- Metformin as HDT
  - Will rifampin increase its DM activity by increasing intrahepatic concentrations while at the same time reduce its HDT activity by reducing systemic concentrations?
- Do the drugs get into the sites of disease in adequate concentrations to exert their anti-TB activity at clinically-relevant doses?
- Will dolutegravir give you more bang for your “metformin buck” with TB-DM-HIV?

Research gaps

- High-dose or alternative rifamycins and diabetes drugs/control
- Toxicity profile of TB/HIV drugs in patients with DM, who may be older and/or have co-morbidities (e.g. EFV+INH+DM)
- Effect of DM on TB drug exposures
- Metformin-rifampicin co-administration
  - Effects on metformin pharmacodynamics
  - Metformin as HDT agent
  - Is adding dolutegravir into this mix helpful/harmful?
- Sitagliptin, statins as adjunctive (HDT) TB therapy that may have benefit to patients with DM
  - Rifampicin + sitagliptin PK-PD
  - Which statins can survive rifampicin?

Summary

- Among patients with TB and DM, **treatment of one affects the other in multi-layered and complex ways**
  - Absorption, metabolic drug interactions, overlapping toxicities, inflammation, hyperglycemia, off-target effects, end organ impairment
- **Rifampicin, a potent and promiscuous inducer of metabolizing enzymes and transporters,** is essential
  - It reduces concentrations of many companion drugs, including DM and HIV drugs
  - It also directly increases glucose and insulin levels
- **HIV drugs may induce or inhibit metabolizing enzymes** important in diabetes drug metabolism
- Metformin, sitagliptin, statins are commonly used in DM and hold some promise for **HDT for TB**
  - Rifampicin may affect PK and/or PD of these drugs
  - Do these drugs get into TB lesions?
- **Diabetes may affect TB drug disposition**
  - Effects on gut, kidney, co-morbid fatty liver, etc.
- **Overlapping toxicities** are a concern
  - e.g. peripheral neuropathy or hepatotoxicity with DM and with isoniazid
  - communication between TB and DM providers required
- **Optimal co-treatment of TB, DM, HIV is challenging, complex, and likely dynamic over the course of treatment**

Thank you.