World Health Organization
REGIONAL OFFICE FOR Europe

Treatment of DR-TB/HIV co-infection: Overview of drug- to- drug interactions and management

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DR-TB/HIV co-infection

5th Webinar of the Virtual Medical Concilium

in the framework of the Operational Study of the Modified Fully Oral RR-TB Shorter Treatment Regimen

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Principles of drug-to-drug interactions

- **Pharmacodynamic**
  - Changes in the pharmacological effects of a drug:
    - additive, synergistic or antagonistic
- **Pharmacokinetic**
  - Changes in the amount of drug in a human body:
    - absorption, distribution, metabolism, excretion

Pharmacodynamic interactions

additive or synergistic toxic effect

- Peripheral neuropathy

  Lnz, Cs, S, H, FQ, Pto/Eto, E, stavudin, didanosin (d4T, ddI)

- Myelosuppression

  Lnz, AZT (zidovudine)

- Prolongation of QT interval

  Cfz, Bdq, Mfx, Dlm, Lfx, NNRTI, enhanced PI, erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole, neuroleptics, antiemetics (ondansetron, granisetron, domperidone), methadone

- Optic nerve damage

  Lzd, E, Eto/Pto, Cfz, rifabutin, H, S, didanosin (ddI)

- Hepatotoxicity

  Lzd, Cfz, Bdq, nevirapine (NVP), cotrimoxazole

- Hypothyroidism

  Eto/Pto, PAS, Lnz, stavidun (d4T)

- Electrolyte disorders

  Am, S, Mfx, Lzd, NRTI

- Nephrotoxicity

  S, Am, TDF

Pharmacokinetic interactions:
absorption

Medicines that reduce the acidity : H^+ inhibitors, H_2 antagonists, antacids

reduce the absorption of drugs, which require the acidity of gastric juice for optimal absorption

atazanavir

Polyvalent cations: antacids, Fe, Al, Ca, Mg

they bind to drugs, reducing their absorption

integrase inhibitors (DTG, RAL)

Inducers/inhibitors of intestinal cytochrome P450 (CYP) 3A4,

P-glycoprotein

Reduce / increase the absorption of substrates:

Inducing P-glycoprotein, **rifabutin** reduces the absorption of **tenofovir alafenamide (TAF)**

Pharmacokinetic interactions:

metabolism of drugs in liver

CYP450

CYP3A4 – most common - oxidation

UGT-1A1

uridine-diphosphate-glucuronosyl-transferase - glucuronidation

II: bictegravir *(BIC) and dolutegravir (DTG) substrates and CYP3A4, and UGT1A1*

Inducers and inhibitors of CYP3A4 and UGT1A1 have an impact on the metabolism of BIC and DTG

Other mechanisms: transporters

OATP

a polypeptide that transfers organic anions

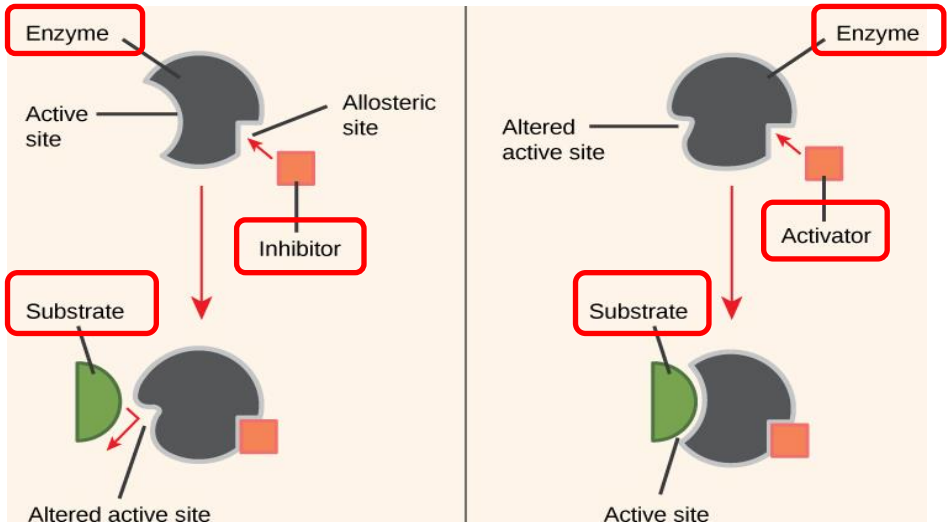
OCT

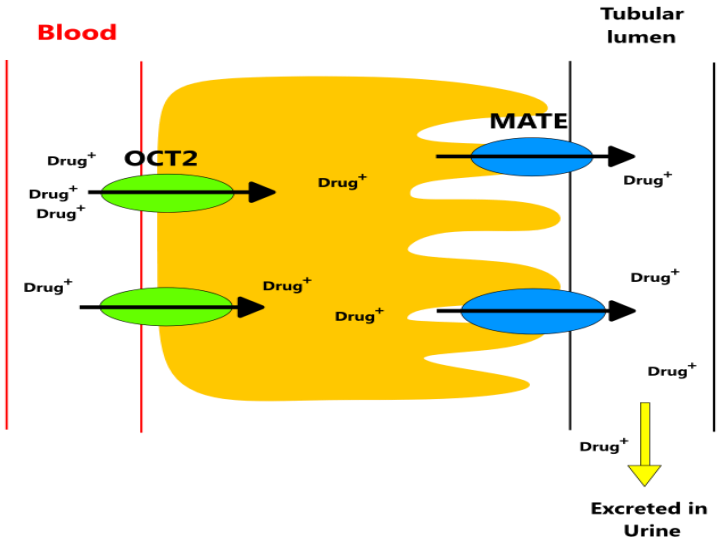
organic cation 2 transporters

MATE

extrusion protein of drugs and toxins

Cinical significance is not fully clear, but is being studied





ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
INSTIs							
BIC	N/A	Concentration decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4	N/A	N/A	Substrate
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate
EVG/c	N/A		Inhibitor	3A4	3A4, 2D6	2C9	Substrate
RAL	N/A		N/A	N/A	N/A	N/A	Substrate
PIs							
ATV	Concentration decreased	N/A	Substrate, Inducer, Inhibitor	3A4	3A4, 2C8	N/A	Inhibitor
ATV/c	Concentration decreased	N/A	Substrate, Inhibitor	3A4	3A4, 2D6, 2C8	N/A	Inhibitor
ATV/r	Concentration decreased	N/A	Substrate, Inhibitor	3A4, 2D6	3A4, 2D6, 2C8	1A2, 2B6, 2C8, 2C9, 2C19	ATV: Inhibitor RTV: Inducer
DRV/c	N/A	N/A	Substrate, effect on P-gp unknown	3A4	3A4, 2D6	N/A	No data
DRV/r	N/A	N/A	Substrate, effect on P-gp unknown	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
LPV/r	N/A	N/A	Substrate	3A4, 2D6	3A4	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
TPV/r	N/A	N/A	Substrate, Inducer	3A4, 2D6	3A4, 2D6	No data	Inducer
NNRTIs							
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A
RPV	Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A
NRTIs							
ABC	N/A	N/A	N/A	N/A	N/A	N/A	Substrate
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
ZDV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CCR5 Antagonist							
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
Fusion Inhibitor							
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

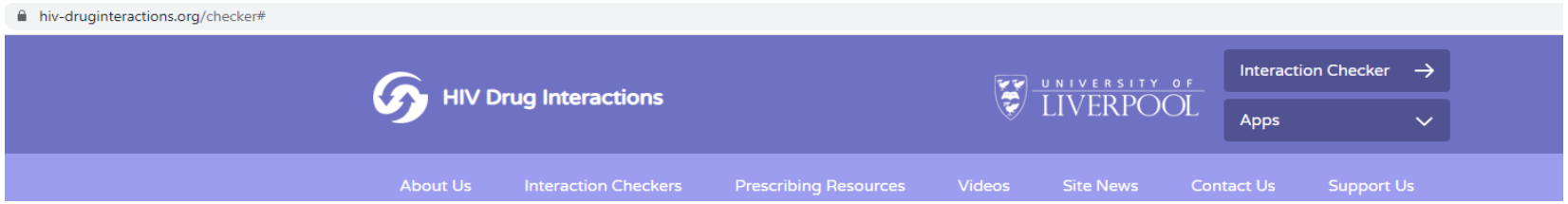
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

Results Key

	3TC	ABC	ATV/r	BIC/FTC/TAF	DRV/r	DTG	EFV	FTC	NVP	RAL	TDF
Amoxicillin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Bedaquiline	◆	◆	■	◆	■	◆	■	◆	◆	◆	◆
Clavulanic acid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Clofazimine	◆	◆	■	▲	◆	◆	◆	◆	◆	◆	◆
Cycloserine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Delamanid	◆	◆	■	◆	■	◆	▲	◆	◆	◆	◆
Ethionamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Fluconazole	◆	◆	◆	◆	◆	◆	◆	◆	■	◆	◆
Imipenem/Cilastatin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Isoniazid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Levofloxacin	◆	◆	■	◆	◆	◆	◆	◆	◆	◆	◆
Linezolid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Meropenem	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Moxifloxacin	◆	◆	■	◆	■	◆	■	◆	◆	◆	◆
Pyrazinamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Pyridoxine (Vitamin B6) [alone]	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Rifabutin	◆	◆	■	●	■	◆	■	◆	▲	◆	◆
Rifampicin	◆	▲	●	●	●	■	▲	◆	●	■	◆
Rifapentine	◆	◆	●	●	●	■	▲	◆	●	■	◆
Trimethoprim/Sulfamethoxazole	▲	◆	◆	▲	◆	◆	◆	▲	◆	◆	◆



Bdq

EFV

Not recommended

Management of 33 HIV-infected individuals with Bdq (400 mg/day) and EFV (600 mg/day) reduced AUC Bdq by 18%

Atazanavir/Darunavir/Lopinavir + *ritonavir/cobicistat*

Not recommended

Bdq is being metabolized by CYP3A4 and moderate or strong CYP3A4 inhibitors
Atazanavir/Darunavir/Lopinavir/ ritonavir/cobicistat enhance the effect of Bdq → risk of AE
Bdq prolongs QTcF interval, it is hepatotoxic

If replacement is not possible → QTcF and transaminases monitoring

Dlm

EFV

Psychoneurological monitoring

The total frequency of AE was higher during administration of Dlm + EFV compared to one of the drugs .
Neuropsychic AE (euphoric mood and nightmares) were observed more frequently during treatment with Dlm + EFV compared to one of the drugs

Atazanavir/Darunavir/Lopinavir + *ritonavir/cobicistat*

Not recommended

Dlm is being metabolized by albumin to DM-6705; DM-6705 is metabolized to other metabolites via CYP3A4.
Dlm + strong CYP3A4 inhibitor (atazanavir / darunavir/lopinavir/ritonavir/cobicistat) increased the effect of metabolite DM-6705 by 25-30%. Dlm prolongs QTcF
If replacement is not possible → QTcF monitoring

Clofazimine

Atazanavir/Lopinavir + ***ritonavir***

QTcF monitoring

Pharmacokinetic interaction is unlikely. Cfz is being excreted in faeces and bile unchanged.

And Atazanavir/Lopinavir + ritonavir, and Cfz prolong QTcF

Levofloxacin

Atazanavir/Lopinavir + ***ritonavir***

QTcF monitoring

Pharmacokinetic interaction is unlikely. Lfx is slightly metabolized.

And Atazanavir/Lopinavir + ritonavir, and Lfx prolong QTcF

Moxifloxacin

Efavirenz (EFV)

Clinical response monitoring

UGT1A1 glucuronidation of Mfx. EFV induces UGT1A1 and reduced the level of Mfx

Atazanavir/Darunavir/Lopinavir + ***ritonavir***

Clinical response monitoring

UGT1A1 glucuronidation of Mfx,; its concentration is being reduced due to UGT1A1 induction by ritonavir

Atazanavir/Lopinavir + ***ritonavir***

QTcF monitoring

And Atazanavir/Lopinavir + ritonavir, and Mfx prolong QTcF

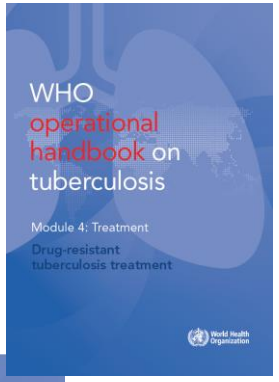
ART: Dolutegravir (DTG) + Tenofovir DF/Emtricitabine (FTC)

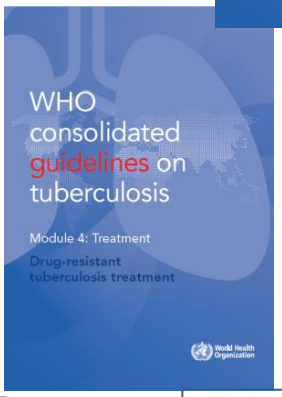
MDR-TB: Lfx, Bdq, Lzd, Cfz, Cs

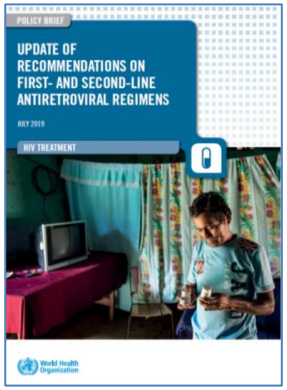
Opportunistic infections: Smx/Tmp, Fluconazole

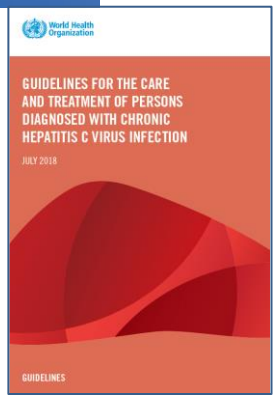
Treatment supplement: Pyridoxine

HCV: Daclatasvir, Sofosbuvir









www.hiv-druginteractions.org

UNIVERSITY OF LIVERPOOL

Interaction Report

Report ID:
Date Produced: 18 June 2019

Antiretroviral Treatment	Co-medications
Dolutegravir	Bedaquiline
Emtricitabine (FTC)	Clofazimine
Tenofovir-DF	Cycloserine
	Daclatasvir
	Fluconazole
	Levofloxacin
	Linezolid
	Pyridoxine (Vitamin B6)
	Sofosbuvir
	Trimethoprim/Sulfamethoxazole

Description of the interactions

Potential weak interaction - additional action/monitoring or dosage adjustment is unlikely to be required (YELLOW)

Emtricitabine (FTC) + Trimethoprim/Sulfamethoxazole
Coadministration has not been studied. Trimethoprim is primarily eliminated by the kidney and in vitro data suggest that it inhibits the renal transporters OCT2 and MATE1, and could therefore potentially decrease emtricitabine renal elimination (via inhibition of MATE1). No a priori dosage adjustment is recommended in patients with normal renal function.

No clinically significant interaction expected (GREEN)

Tenofovir-DF (TDF) + Trimethoprim/Sulfamethoxazole
Emtricitabine (FTC) + Fluconazole
Tenofovir-DF (TDF) + Fluconazole
Emtricitabine (FTC) + Clofazimine
Tenofovir-DF (TDF) + Clofazimine
Emtricitabine (FTC) + Cycloserine
Tenofovir-DF (TDF) + Cycloserine
Dolutegravir (DTG) + Clofazimine
Dolutegravir (DTG) + Cycloserine
Dolutegravir (DTG) + Trimethoprim/Sulfamethoxazole
Dolutegravir (DTG) + Fluconazole
Emtricitabine (FTC) + Sofosbuvir
Tenofovir-DF (TDF) + Bedaquiline
Tenofovir-DF (TDF) + Sofosbuvir
Dolutegravir (DTG) + Bedaquiline
Dolutegravir (DTG) + Sofosbuvir
Emtricitabine (FTC) + Bedaquiline
Dolutegravir (DTG) + Daclatasvir
Emtricitabine (FTC) + Daclatasvir
Tenofovir-DF (TDF) + Daclatasvir
Dolutegravir (DTG) + Levofloxacin
Tenofovir-DF (TDF) + Levofloxacin
Emtricitabine (FTC) + Levofloxacin
Dolutegravir (DTG) + Linezolid
Emtricitabine (FTC) + Linezolid
Tenofovir-DF (TDF) + Linezolid
Emtricitabine (FTC) + Pyridoxine (Vitamin B6) [alone]
Tenofovir-DF (TDF) + Pyridoxine (Vitamin B6) [alone]
Dolutegravir (DTG) + Pyridoxine (Vitamin B6) [alone]

www.hv-druginteractions.org

Interaction Report

Report ID:
Date Produced: 07 March 2021

Antiretroviral Treatment	Co-medications
Efavirenz (EFV)	Bedaquiline
Emtricitabine (FTC)	Clofazimine
Tenofovir-DF (TDF)	Cycloserine
	Daclatasvir
	Fluconazole
	Levofloxacin
	Linezolid
	Pyridoxine (Vitamin B6) [alone]
	Sofosbuvir
	Trimethoprim/Sulfamethoxazole

This report lists the summaries of potential interactions (i.e. "red", "amber" and "yellow" classifications) for the drugs in the table above.

Interactions with a "green" or "grey" classification (i.e. no clinically significant interaction or no clear data) have been checked and are listed at the end of this report, but summaries are not shown.

For full details of all interactions, see www.hiv-druginteractions.org .

Description of the interactions

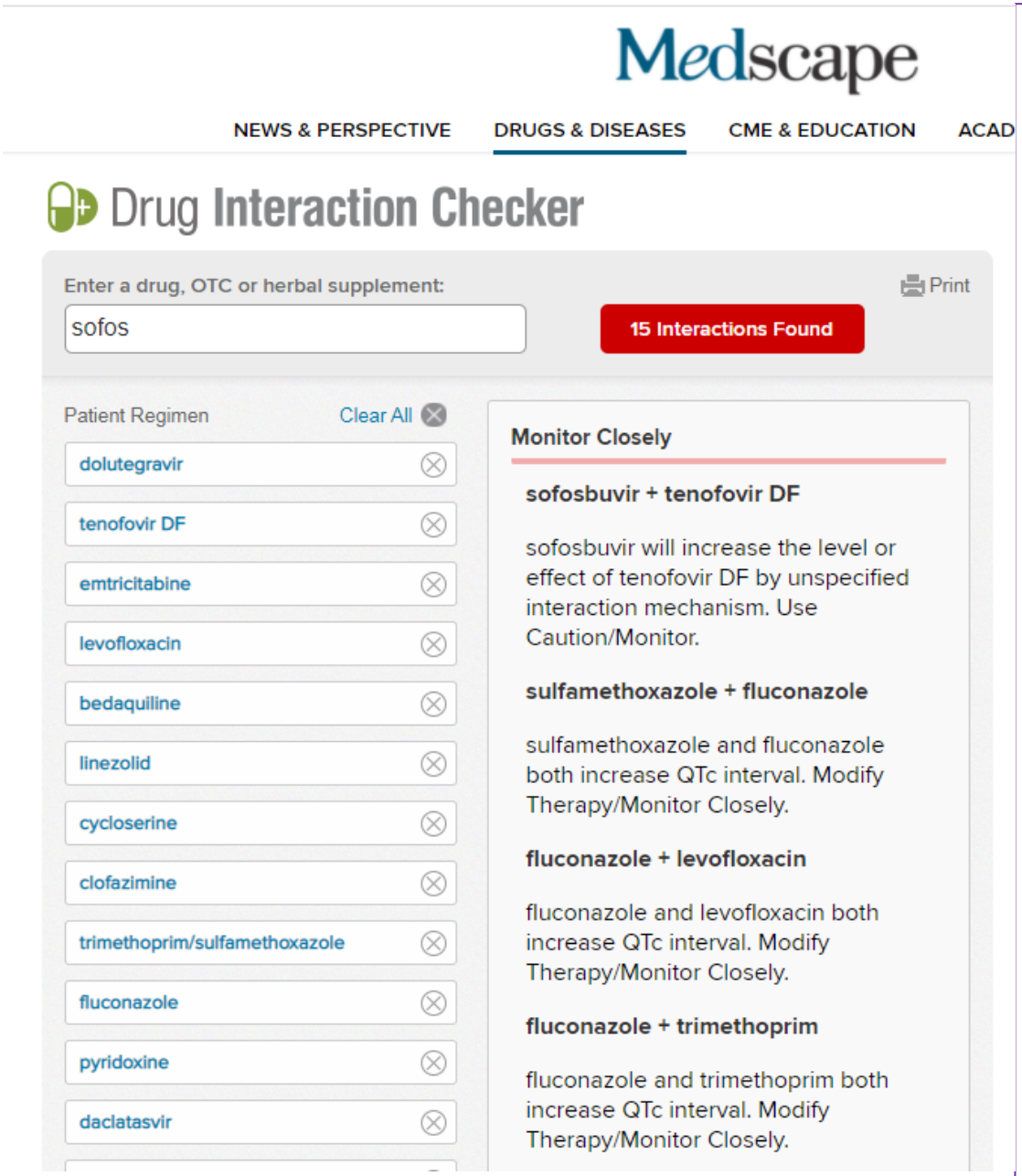
Potential clinically significant interaction - likely to require additional monitoring, alteration of drug dosage or timing of administration (AMBER)

Efavirenz (EFV) + Bedaquiline
Coadministration of bedaquiline (400 mg single dose) and efavirenz (600 mg once daily) to 33 HIV/TB-negative subjects decreased bedaquiline AUC by 18% and had no effect on Cmax. Efavirenz pharmacokinetics were similar to historical data from HIV-infected subjects. A reduction in bedaquiline exposure may result in loss of activity and coadministration is not recommended. There are no clinical data on the safety and efficacy of bedaquiline when co-administered with antiretroviral agents.

Efavirenz (EFV) + Daclatasvir
Coadministration of efavirenz (600 mg once daily) and daclatasvir (60 or 120 mg once daily) decreased daclatasvir AUC, Cmax and Cmin by 32%, 17% and 59%, respectively (results dose-normalised to 60 mg dose). The dose of daclatasvir should be increased to 90 mg once daily when coadministered with efavirenz.

Potential weak interaction - additional action/monitoring or dosage adjustment is unlikely to be required (YELLOW)

Emtricitabine (FTC) + Trimethoprim/Sulfamethoxazole
Coadministration has not been studied. Trimethoprim is primarily eliminated by the kidney and in vitro data suggest that it inhibits the renal transporters OCT2 and MATE1, and could therefore potentially decrease emtricitabine renal elimination (via inhibition of MATE1). No a priori dosage adjustment is recommended in patients with normal renal function.



Monitor Closely

- ***sofosbuvir + tenofovir DF***

sofosbuvir will increase the level or effect of tenofovir DF by unspecified interaction mechanism.

- ***sulfamethoxazole + fluconazole***

sulfamethoxazole and fluconazole both increase QTc interval.

- ***fluconazole + levofloxacin***

fluconazole and levofloxacin both increase QTc interval.

- ***fluconazole + trimethoprim***

fluconazole and trimethoprim both increase QTc interval.

- ***fluconazole + bedaquiline***

fluconazole and bedaquiline both increase QTc interval.

- ***levofloxacin + bedaquiline***

levofloxacin and bedaquiline both increase QTc interval.

- **sulfamethoxazole + levofloxacin**

sulfamethoxazole and levofloxacin both increase QTc interval.

- ***levofloxacin + trimethoprim***

levofloxacin and trimethoprim both increase QTc interval.

Minor

- ***linezolid + pyridoxine***

linezolid will decrease the level or effect of pyridoxine by altering intestinal flora. Applies only to oral form of both agents.

- ***trimethoprim + pyridoxine***

trimethoprim will decrease the level or effect of pyridoxine by altering intestinal flora. Applies only to oral ***form of both agents.***

- ***levofloxacin + pyridoxine***

levofloxacin will decrease the level or effect of pyridoxine by altering intestinal flora. Applies only to oral form of both agents.

- **sulfamethoxazole + pyridoxine**

sulfamethoxazole will decrease the level or effect of pyridoxine by altering intestinal flora. Applies only to oral form of both agents.

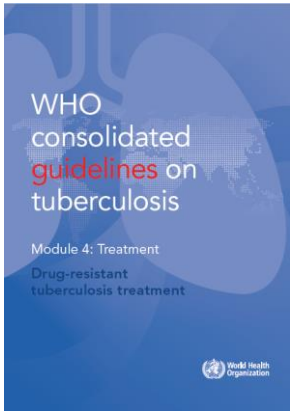
- ***fluconazole + sulfamethoxazole***

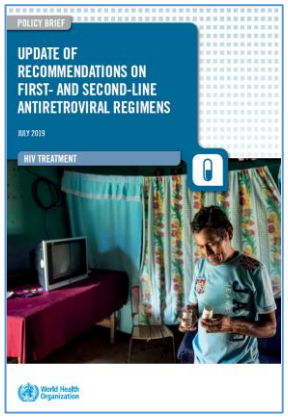
fluconazole will increase the level or effect of sulfamethoxazole by affecting hepatic enzyme CYP2C9/10 metabolism.

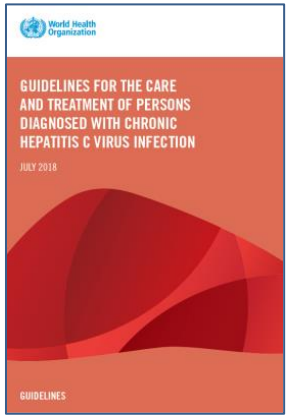
- ***linezolid + sulfamethoxazole***

linezolid increases levels of sulfamethoxazole by unspecified interaction mechanism.

HIV, HCV, alcohol and drug addiction : *ART, DAA, OST*







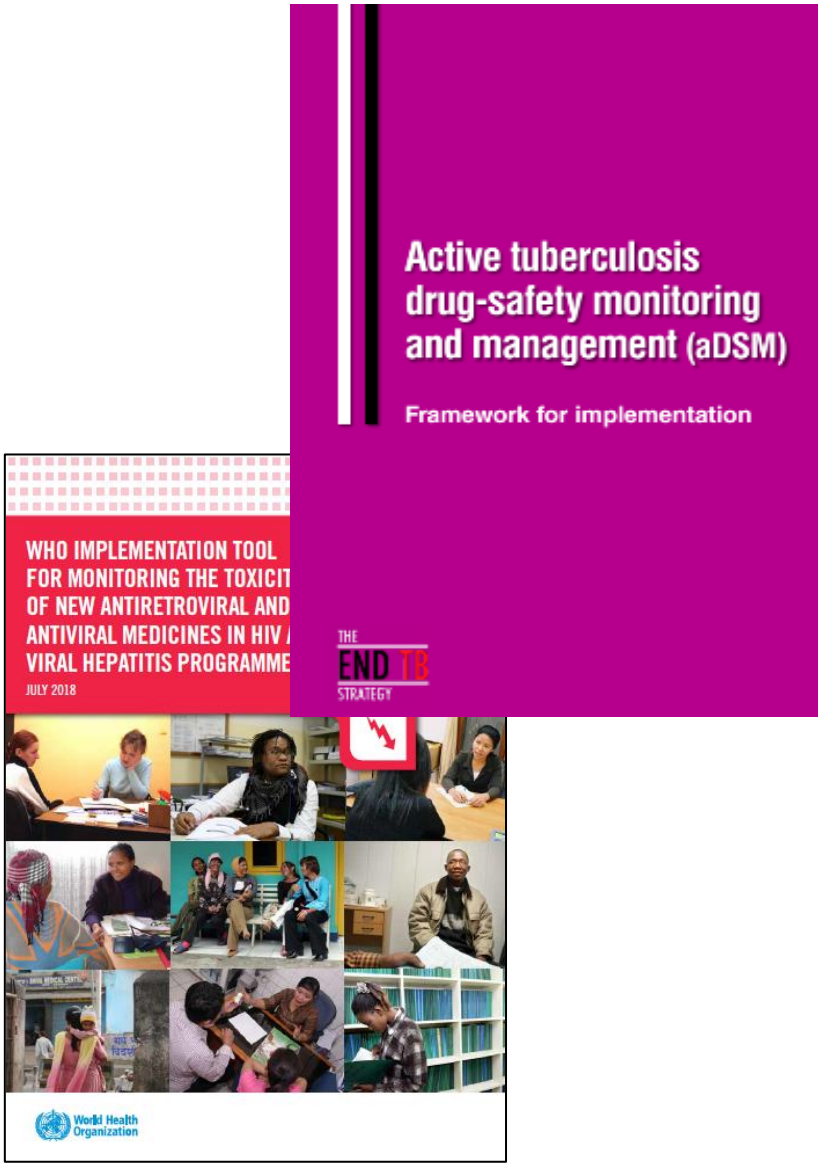
Pregnancy, childhood, concomitant pathology (DM and…)

Main components of aDSM strategy

1. Patients under aDSM are subject to the systematic clinical and laboratory evaluations during treatment that help identify adverse events (AE)

2. All cases of detected AE require immediate response measures and medical assistance for proper AE management

3. There should be a systematic collection of standardized data and reporting on identified adverse events

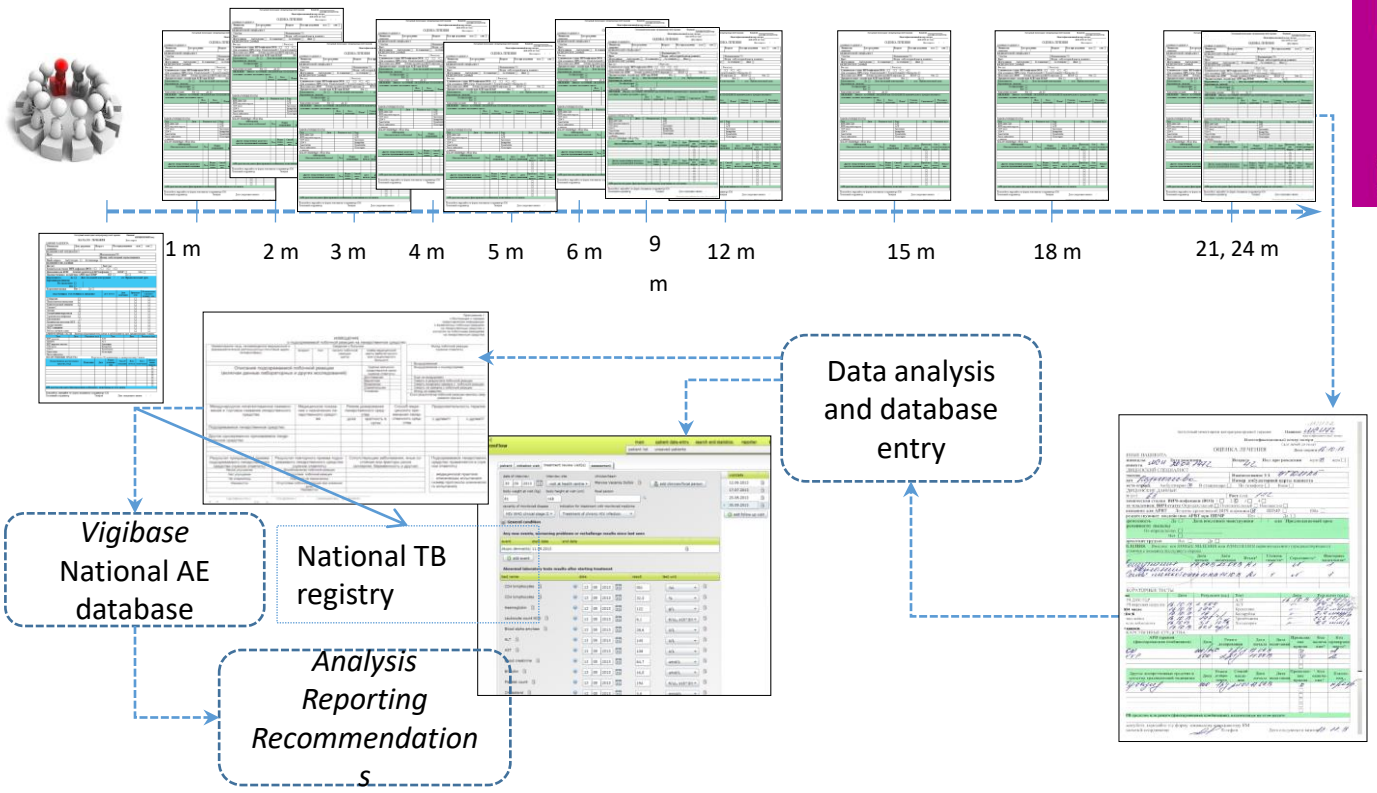


Belarus experience on the use of aDSM

Active tuberculosis drug-safety monitoring and management (aDSM)

Framework for implementation

THE END TB STRATEGY



Monitoring protocol

Тест / исследование	Месяц														
	-10	1	2	3	4	5	6	7	8	9		+6	+12	+18	+24
Мокрота		x	x	x	x	x	x	x	x	x		x	x	x	x
Мазок	x														
X-pert	x														
LPA (1st & 2nd lines)	x				If required										
Посев (BACTEC /L-J)	x	x	x	x	x	x	x	x	x	x	End of treatment	x	x	x	x
ТЛЧ (BACTEC /L-J)	x				If required										
Р-гр / КТ	x			x		x		x		x		x	x	x	x
Беременность	x	Если необходимо													
HIV, HCV, HBV тест	x	При наличии заболевания лечение и коррекция мониторинга										Если необходимо			
Анамнез	x														
Клин осмотр	x	x	x	x	x	x	x	x	x	x		x	x	x	x
ОАК	x	x	x	x	x	x	x	x	x	x		x	x	x	x
Креатинин, клиренс	x	x	x	x	x	x	x	x	x	x			x		x
АЛТ, АСТ	x	x	x	x	x	x	x	x	x	x			x		x
Билирубин	x	x	x	x	x	x	x	x	x	x			x		x
Липаза	x	Если необходимо										Если необходимо			
Амилаза	x	Если необходимо										Если необходимо			
ЭКГ(QTcF)	x	x	x	x	x	x	x	x	x	x		1 раз в 3 м-ца			
K, Mg, Ca, Na	x	x	x	x	x	x	x	x	x	x		Если необходимо			
Albumine	x	x	x	x	x	x	x	x	x	x		Если необходимо			
Гликелиров. Hb (HbA1c)	x	Если необходимо										Если необходимо			
Глюкоза	x	x	x	X	x	x	x	x	x	x		Если необходимо			
ТТГ	x	Если необходимо										Если необходимо			
Офтальмолог	x	x	x	x	x	x	x	x	x	x		Если необходимо			
Невролог (ТВЧ)	x	x	x	x	x	x	x	x	x			Если необходимо			

HIV/RR-TB patients under mSTR

Belarus experience

- 230 RR-TB patients enrolled
  - **13 - with HIV co-infection**
- All 13 on ART
  - with dolutegravir - 7
  - other treatment regimens - 6
- 27-51 y.o.; M - 11, F - 2
- Drug resistance patterns
  - R - 1
  - HR - 1
  - HRE - 2
  - HRZ - 2
  - HRZE - 2
  - HRZE+ any TB drugs except FQ - 5
- Grade 3-4 adverse events (patients):
  - ↑ transaminase - 4
  - anemia - 1
  - hypokalemia - 2
  - QTcF prolongation >60 ms over baseline - 2
- **All 13 patients are cured**

Thank you for your attention!