An update on drug-drug interaction: New ART and new co-medications

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Declaration of Interests

www.hiv-druginteractions.org & *www.hep-druginteractions.org*
Receives sponsorship from AbbVie, Merck, BMS, Janssen, Gilead, ViiV.
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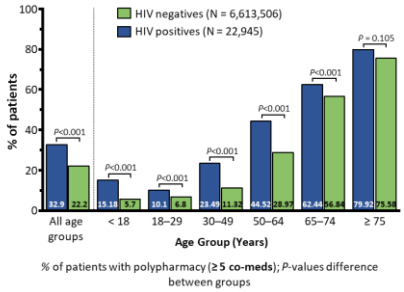
See https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/

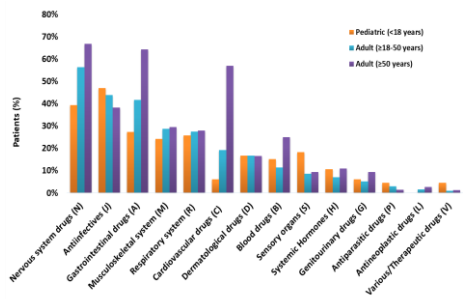
Menu

- **Polypharmacy, Multi-Morbidity**
- **Co-prescribing *vs* de-prescribing**
- **Interaction liability of modern ART regimens**
- **Managing DDIs without fear**
- **DDIs in 2019**
  - **TB co-infection**
  - **RTV vs cobi**
  - **antiplatelet agents**
  - **NOACs**
  - **statins**

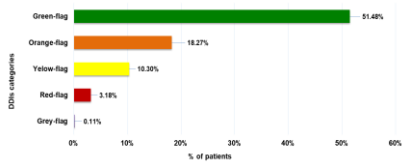
PODIVM Study



% of patients with polypharmacy (≥5 co-meds); *P*-values difference between groups



- **Madrid Health Records - ↑polypharmacy with HIV, across all age groups**
- **Most frequent: CNS, GI, cardiovascular drugs**
- **Of 729 'RED' DDIs, corticosteroids accounted for 375 (51.4%), followed by anti-psychotics (14%), anti-thrombotics (12%) and statins (6%)**

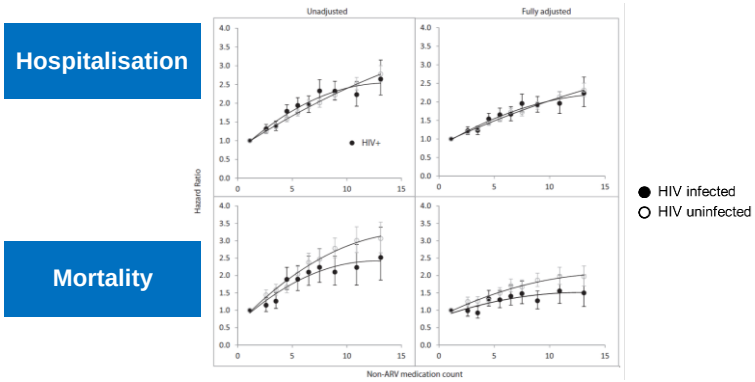


Lopez-Centeno et al. HIV11 Glasgow 2018;

Prevalence of Polypharmacy in PLWH

Reference	Country	N	Age	Nb comeds / person	Polypharmacy
Livio F et al. Int Work Clin Pharm HIV 2018	Switzerland	111	≥ 75	**5** (3-8)	60 %
Guaraldi G et al. BMC Geriatr 2018	Italy	1258	≥ 65	NA	37 %
Justice A et al. AIDS 2018	USA	1311	≥ 65	NA	43 %
Nunez-Nunez M et al. Farm Hosp 2018	Spain	242	≥ 50	NA	48 %
Ssonko M et al. BMC Geriatr 2018	Uganda	411	≥ 50	NA	15 %
Mc Nicholl I et al. Pharmacotherapy 2017	USA	248	≥ 50	**11** (± 6)	94 %
Krentz H et al. AIDS Pat Care STDS 2016	Canada	386	≥ 50	NA	43 %
Greene M et al. J Am Geriatr Soc 2014	USA	89	≥ 60	**8** (4-14)	74 %
Holtzman C et al. J Gen Intern Med 2013	USA	1312	≥ 50	NA	54 %

Polypharmacy and adverse health outcomes



US Veterans Affairs Healthcare system

- HIV+ (N = 9473) and HIV– (N = 39,812)
- **Polypharmacy independently associated with ↑ hospitalisations & mortality**
- VACS score corrects for mortality associated with physiologic measures, frailty, multiple morbidities and burden of co-morbidities

Justice AC. AIDS 2018

Polypharmacy – What we already know

The (*blindingly*) obvious

- **The HIV-infected patient population is ageing**
- **Burden of multiple morbidities, multiple medications**
- **DDIs more likely**

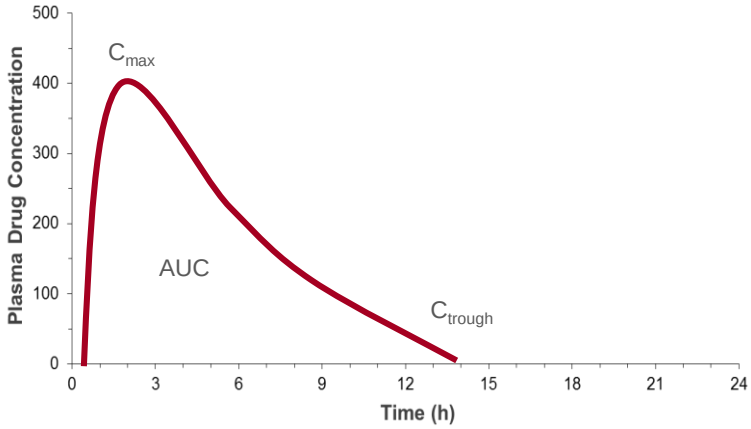
The (*equally*) obvious

- **Comorbidities need to be treated**
- **DDIs - inevitable, unavoidable, and (usually) manageable**
- **DDIs - Not all are harmed, not all harms are recognised**
- **Fragmented care reduces recognition, increases risk of harm from DDIs**
- **Full medicines reconciliation is key – ie health systems**

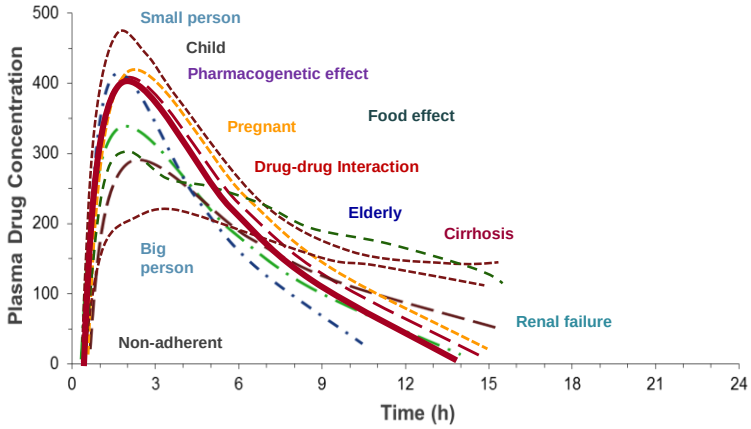
The (*slightly less*) obvious

- **The direction and magnitude of multi-way DDIs not easy to predict**
- **Organ dysfunction - DDIs qualitatively similar, quantitatively different**
- **Guidelines largely do not cater for MM**

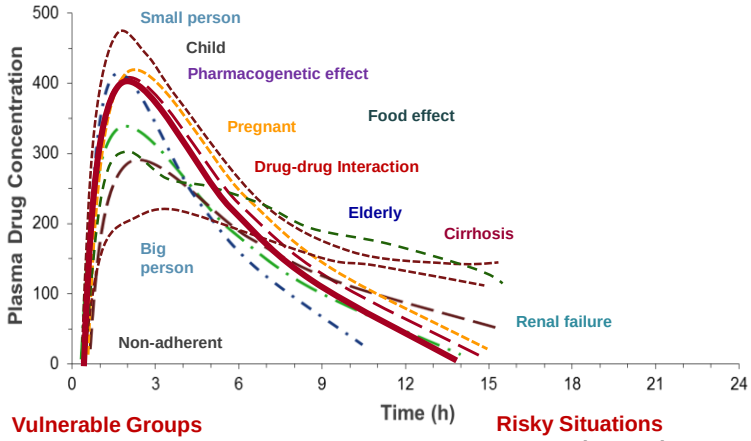
Pharmacokinetics in real life



Pharmacokinetics in real life



Pharmacokinetics in real life

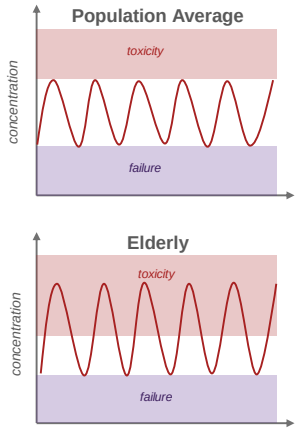


Vulnerable Groups
- Very young children
- Pregnancy and breastfeeding
- Liver / renal impairment
- Pharmacogenetics
- Extremes of body mass
- Effect of age, gender, ethnicity

Risky Situations
- Drug interactions
- Multiple co-morbidities
- Poor adherence
- Food effects

Physiological Factors affecting HIV Drug Disposition

- **Declining eGFR** (~1% per year)
  TFV, FTC, 3TC
- **↓ body weight** (greater dose/kg)
- **Body morphology** (distribution, elimination)
  Sarcopenia
  ↑ fat: ↓plasma volume
- **Gastric pH, absorption**
  achlorhydria, motility, ↓absorption
- **↓ albumin**
- **Liver**
  altered liver blood flow
  ↓CYP2C9, CYP2D6 activity, Phase II↔
- **Post-menopausal women**
- **Compartments**
- **Higher inter-patient variability**



Adapted from Calcagno et al. Infection 2015;43:509

McLachlan et al. J Gerontol A Biol Sci Med Sci. 2012;67:175–80
Rowe, et al. J. Gerontol 1976;31:155–163
Calcagno et al. Infection 2015;43:509

Pharmacokinetics and Ageing: A Summary

NRTI

- TFV, 3TC, FTC exposure mainly renally driven
- ↓ TFV-dp and FTC-TP with increasing T cell senescence
- ↑ Plasma & genital tract [TFV] in post- vs pre-menopausal women [abstract- Patterson]
- ↑ CSF TFV [Croteau - *abstract*]

NNRTI

- ↔ plasma EFV and NVP [Dumond]
- CSF EFV increased >60y [Croteau - *abstract*]
- (↑↔) ETR
- ↔ RPV (N=379, and ECHO/THRIVE)

PIs

- (↑) LPV (ACTG5015) [Crawford]
- (↑↔) DRV [Kakuda, Ahlgren]
- ↔ ATV [Dumond, Chen, von Hentig, Croteau]
- No evidence this is clinically relevant

INSTIs

- ↔ Ral and DTG
- No evidence this is clinically relevant

Kakuda et al. AIDS Res Treatment 2012;Mar21:186987
Ahlgren et al. CROI 2017: Abstr 431
Dumond et al. CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 128
Dumond et al. HIV Med 2013;14(7):401
Patterson et al. 18th CROI 2011;Abstr 32
Calcagno et al. Infection 2015;43:509
Calcagno et al. AAC 2013;57:1840
Tourret et al. J Am Soc Nephrol 2013;24:1519
Poizot-Martin et al. JAIDS 2013;62:375
Croteau et al. CROI 2012: Abstr 592
Dumond et al. CPK 2012;51:809
Kakuda et al. CPT 2010;88:695
Dumond et al. IWCPHT 2015
Crawford et al. AIDS Res Hum Retrov 2010;26:635
Dumond et al. CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 128
Chen et al. Clin Transl Sci 2018;11:226-36
Eliot et al. CID 2018: DOI: 10.1093
Dumond et al. IWCPHT 2015
Neant et al. Eur J Clin Pharmacol. 2018 Apr;74(4):473
Crawels et al HIV10 Glasgow 2010 P186

Drug Safety & Efficacy in Old Age

Pharmacokinetics

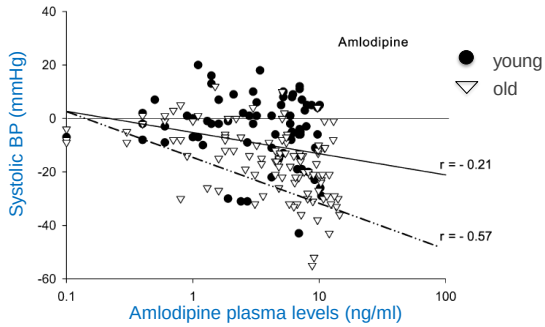
- Beyond renal function (NRTIs) and/or weight/lean mass, no massive effect (over and above PK 'noise')
- Ditto for post-menopausal women

Pharmacodynamics - Safety

- Age effects on pharmacodynamics poorly characterised
- CNS, mitochondrial and QT effects *could* be worse (but not systematically studied)
- Confounding effects of age *vs* duration of infection and exposure to older drugs (d4T, ddI, IDV)

Pharmacodynamic Effects with Age

Effect of age on amlodipine pharmacodynamics

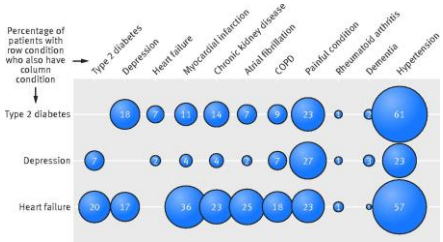


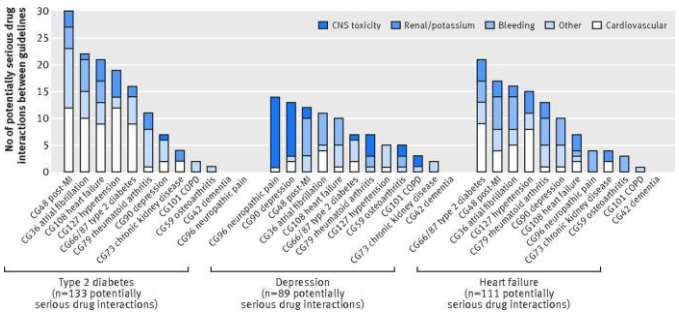
- **Amlodipine pharmacodynamics significantly impacted by age: more pronounced decrease in systolic BP in elderly compared to young.**
- **Age affects regulation of physiologic processes (arterial baroreflex function), elderly are also more prone to thiazide induced orthostatic changes**

Leenen FH et al. J Cardiovasc Pharmacol 2010

Guidelines often do not consider Co-morbidities

- **Survey of NICE Guidelines for T2 Diabetes, Depression, Heart Failure**
- **Compared with recommendations from 12 common co-morbidities**
- **DDI liability assessed**





Dumbreck et al. BMJ 2015;350:bmj.h949

Common Culprits – General

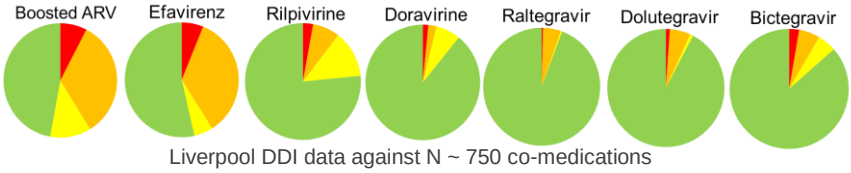
- **Anticholinergics and pyschotropics**
  - association with falls, confusion
  - consider anticholinergic burden of therapy
  - withdrawal of psychotropic drugs significantly reduces falls
- **SSRIs in >50y**
  - decrease bone quality, doubles risk of falls and fractures
  - hyponatremia, serotonin syndrome, ? suicidality risk
- **PPIs**
  - check reason for starting, treatment cascade
- **Benzodiazepines**
  - avoidance reduced hip fractures by 10%
- **If shortened life expectancy**
  - primary prevention – any role ?
  - secondary prevention only if time to benefit > life expectancy

Papaioannou, A et al, Arch Intern Med/Vol 167:188-194
KoKoAung, et al JBI Database System Rev Implement Rep. 2015

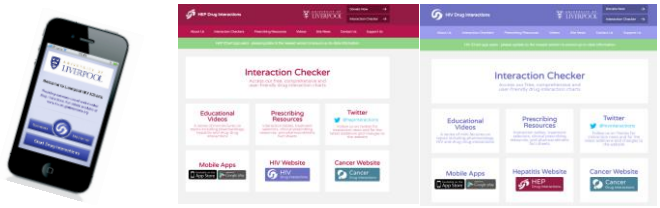
Common Culprits – HIV

- **Steroids and protease inhibitors / cobicistat**
  - drug induced Cushings, AVN of hips
  - can happen very quickly
  - don't forget nasal / inhaled / topical
  - especially don't forget intra-articular triamcinolone
- **NOACs and Antiplatelet agents**
  - clopidogrel vs prasugrel
  - dabigatran and cobi / RTV
- **HIV drugs – tenofovir and protease inhibitors**
  - osteoporosis
- **PPIs**
  - ↓↓ absorption of ATV/RPV
- **Divalent cations (multivitamins, Ca^{++}, Fe^{++}, supplements)**
  - ↓↓ absorption of all integrases

Modern ART



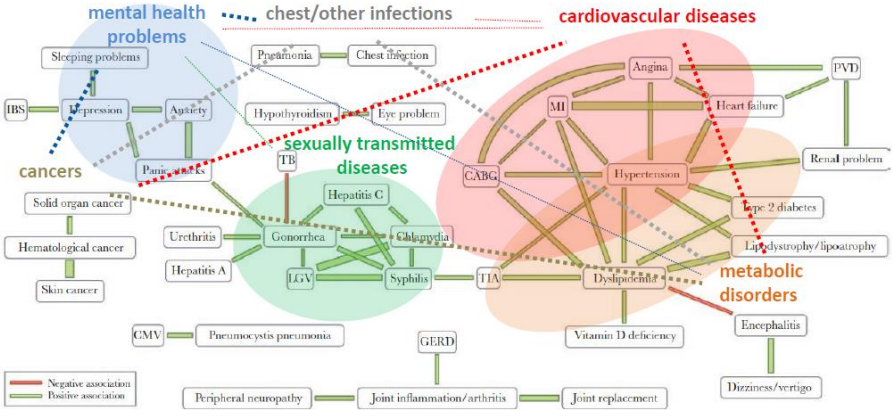
Liverpool DDI data against N ~ 750 co-medications



www.druginteractions.org

Multi-morbidity Clusters

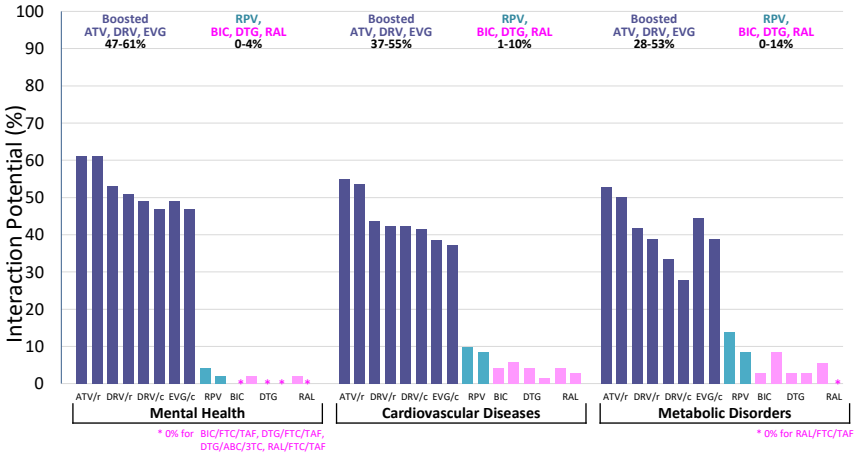
Study included 1073 PLWH (mean age 52 years) from the POPPY cohort



- Comorbidities co-occur in specific patterns
- Better understanding how comorbidities cluster together would enable the development of targeted interventions and guidelines addressing specifically the needs of PLWH with multiple comorbidities

De Francesco D et al. Open Forum Infect Dis 2018

DDI Potential by Co-morbidity Cluster



Gibbons et al. Antiviral PK Workshop Noordwijk, Netherlands 2019 Abstr 19

What can you do about it ?

- **Screen for and manage DDIs**
- **Assess burden of therapy**
- **Adopt a tailored approach to prescribing**

- **Deprescribing**
  - **Beers Criteria**
  - **STOPP-START**
  - **IPET**
  - **Others ….**

"I feel a lot better since I ran out of those pills you gave me."

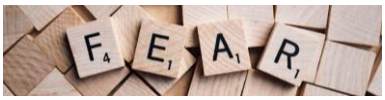
To Prescribe or Not to Prescribe ?

Individualised Benefit – e.g:
- QRISK3
- FRAX
- HASBLED
- NICE database of treatment effects

Aggregate Risks – e.g:
- DDI tools
- QTc liability (CredibleMeds)
- Anticholinergic Burden

Burden of co-morbidity– e.g:
- Charlson Comorbidity Index
- VACS score

Synthesis



Room for manoeuvre when prescribing statins to dyslipidaemic patients on antiretroviral therapy

J Myers, M Rayment, S Somecha, G Moyle and M Boffito
Chelsea and Westminster Hospital NHS Foundation Trust, London, UK

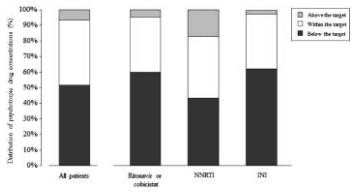
- >50% of patients (n=549) failed to achieve target lipids – evidence of suboptimal dosing of statin due to concern of DDI.

Evaluation of the concentrations of psychotropic drugs in HIV-infected versus HIV-negative patients: Potential implications for clinical practice

Dario Cattaneo[a,b], Sara Baldelli[b], Chiara Resnati[c], Andrea Giacomelli[c], Paola Meraviglia[c], Davide Minisci[c], Noemi Astuti[c], Annalisa Ridolfo[c], Giuseppe V. De Socio[d], Emilio Clementi[b,c], Massimo Galli[c] and Cristina Gervasoni[b,c]

[a]Gestione Ambulatoriale Politerapie (GAP) outpatient clinic, ASST Fatebenefratelli Sacco, Milan, Italy; [b]Unit of Clinical Pharmacology,

- 55% of patients (n=82) had plasma antidepressant and/or antipsychotic drug levels below target (sub-therapeutic) – due to concern of DDI



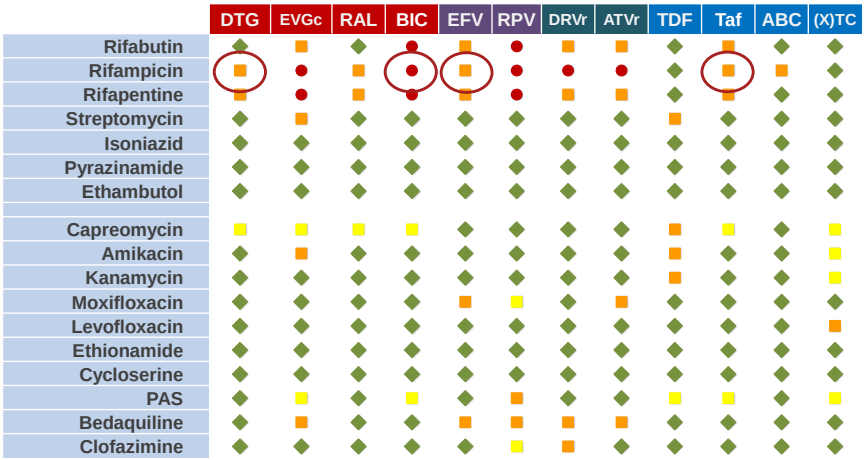
Outpatient 'Polytherapy Management Service' **(600 screened, 82 on ARV-psychotropics)**
- **antidepressants** (citalopram, duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine)
- **antipsychotics** (haloperidol, olanzapine, quetiapine, risperidone and lamotrigine)
- **55% had suboptimal concentrations of psychotropics**
- **HIV-ve controls – 26% suboptimal**

Myers J, *et al. HIV Med* 2018; **13:**190–192.
Cattaneo D et al World Journal of Biological Psychiatry 2019 [Epub ahead of print]

DDIs in 2019

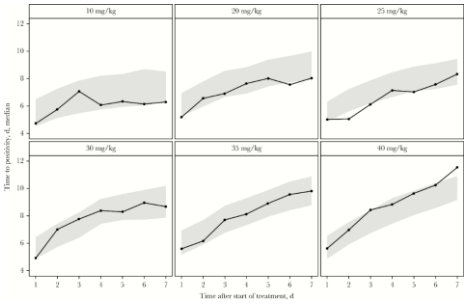
- **New Drugs**
  - Bictegravir/FTC/Taf
  - Doravirine
  - LA CAB / RPV
  - Ibalizumab
  - Albuvirtide
- **Further Insights**
  - TB-HIV co-infection
  - RTV vs Cobi boosting
  - NOACs and antiplatelets

Interactions with TB medications



HIV – TB Drug Interactions: High dose rifampicin

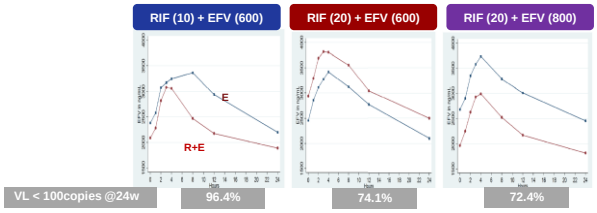
- Initial dose-selection for Rif (~10mg/kg) was empirical
- Greater sterilization/EBA (*in-vitro and in-vivo*) with higher doses
- A number of clinical studies have explored safety and PK-PD, e.g.:
  - HIRIF (20 mg/kg)
  - MAMS-TB01 (35 mg/kg)
- Unclear whether incremental induction will be seen – do DDI studies have to be repeated ?

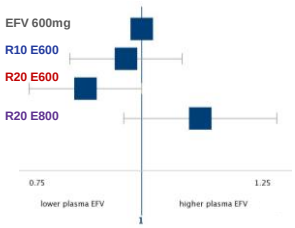


Diacon et al. AAC. 2007 Aug;51(8):2994-6..
Boeree et al. Am J Respir Crit Care Med. 2015 May 1;191(9):1058.
Boeree et al. Lancet Infect Dis. 2017 Jan;17(1):39-49.
Peloquin et al. AAC. 2017 Jul 25;61(8). pii: e00038-17
Svensson et al. JID 2018 Aug 14;218(6):991-999

High dose RIF& EFV (600mg)

ART-naïve, TB-co-infected (N = 33) Rifavirenz

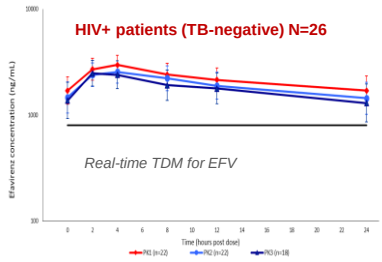




- RIF(20) slightly decreases EFV(600) - ↓13%; compensated with EFV(800)
- RIF(20) with EFV (600 or 800) well-tolerated
- Slight increase in month-2 MGIT culture conversion with high dose R
- Low virological suppression at week 24 with high dose R, although all patients were on standard treatment from week 8

Atwine et al. CROI 2018 456

RIF & EFV (400)



PK parameter	EFV GM (95% CI) EFV 400 day 14 (PK1)	EFV 400 + INH/RIF day 42 (PK2)	EFV 400 + INH/RIF day 98 (PK3)	EFV GMR (90% CI) PK2/PK1	PK3/PK1	
C_{max} (ng/mL)	3257 (2554-4154)	2953 (2293-3804)	2791 (2020-3857)	0.91 (0.83-0.99)	0.95 (0.86-1.05)	0.84 (0.75-0.93)
CV%	83	80	87			
C_{24h} (ng/mL)	1703 (1180-2457)	1441 (948-2191)	1301 (790-2141)	0.85 (0.72-0.99)	0.88 (0.75-1.03)	0.75 (0.62-0.92)
CV%	124	128	133			
AUC_{0-24} (ng*h/mL)	52259 (38284-71335)	47618 (33979-66732)	44004 (29442-65767)	0.91 (0.79-1.05)	0.92 (0.83-1.01)	0.84 (0.72-0.99)
CV%	107	106	113			

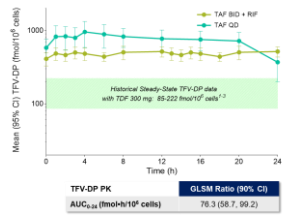
- When EFV400 given with RIF, EFV AUC ↓ 16%, Ctrough ↓ ~25%,
- 2/26 subjects discontinued due to INH/RIF hepatotoxicity
- 4/26 withdrew due to [EFV] < 800 ng/mL in more than 3 consecutive occasions
- EFV400 can be co-administered with RIF/INH (*any caveats re:TDM* ?) and study with co-infected patients in progress

Cerrone et al. CROI 2018 457

RIF & TAF

- TAF (unlike TDF) is substrate for some gut/liver transporters

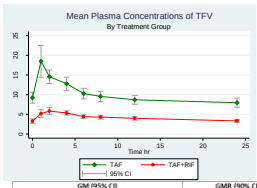
EACS 2017 – TAF twice daily



- Following TAF (bid) plasma TFV ↓ 20%
- ic TFV-dp modestly ↓ 24%, but above historical concentrations seen following conventional TDF dosing

Custodio et al. EACS 2017

CROI 2018 – TAF once-daily



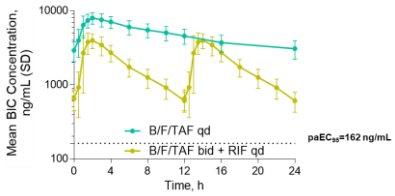
TFV PK parameter	GM (95% CI) TAF/FTC + RIF	TAF/FTC	GMR (90% CI) TAF/FTC+RIF vs TAF	
C_{max} ng/mL	6 (5 - 7)	18 (16 - 22)	0.35 (0.30 - 0.42)	65%
CV	34%	38%		
AUC_{0-24} ng*h/mL	95 (84 - 106)	208 (172 - 251)	0.46 (0.40 - 0.52)	54%
CV	26%	43%		
C_{24h} ng/mL	3 (3 - 4)	7 (6 - 9)	0.45 (0.42 - 0.50)	55%
CV	30%	36%		

- plasma TAF ↓ 55%
- ic TFV-dp ↓ 36%, but still 76% higher than seen with conventional TDF dosing
- FTC (plasma, & ic FTC-tp) unaffected

Cerrone et al. CROI 2018 28LB

RIF & BIC

- **New kid on the block : substrate of CYP and UGT**
- **Likely to be affected by RIF – any possibility of bid dosing of BFTaf ?**

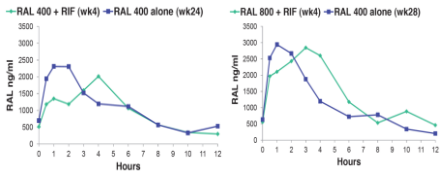


BIC PK Mean (%CV)	B/F/TAF qd n=26 (ref)
AUC_{0-24}, ng•h/mL	115,000 (21)
C_{max}, ng/mL	8530 (16)
C_{trough}, ng/mL	3070 (28)

- Even with bid dosing, BIC AUC ↓ 60%, Ctrough ↓ ~80%,
- A proportion of patients may fall below the $paEC_{95}$ (target)
- (verbally : FTC roughly doubled, no tolerability issues highlighted)
- BFTaf bid with RIF **not recommended**

Custodio et al. CROI 2018 34

RIF + RAL or DTG

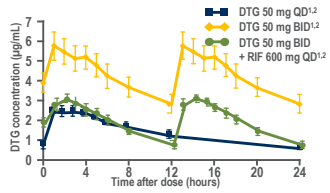


RIF + RAL

REFLATE: HIV/TB coinfected
- **RIF + RAL 400bd – slightly lower exposures(C0 0.46)**
- **RIF + RAL 800bd - overcompensated**

RIFRAL (HIV-) RIF 3x/w + RAL
- **HIV+ Rif (3x/w) Cmin ↓ 60%, restored by 800mg RAL bd**

DOSE at 400 or 800mg bd



RIF + DTG

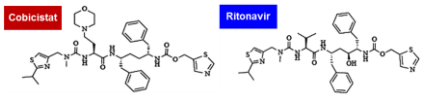
- **HIV- AUC ↓54% Cmin ↓72%**
- **DTG 50 bd + rif comparable Cmin**

INSPIRING (CROI 2018) – 24w outcomes with coinfection

DOSE at 50mg bd

Taburet et al. Clin Infect Dis. 2015 Oct 15;61(8):1328
Dooley et al. J Acquir Immune Defic Syndr 2013; 62:21–7
Reynolds et al. JAC 2015 Feb;70(2):550-4
Dooley et al. CROI 2018

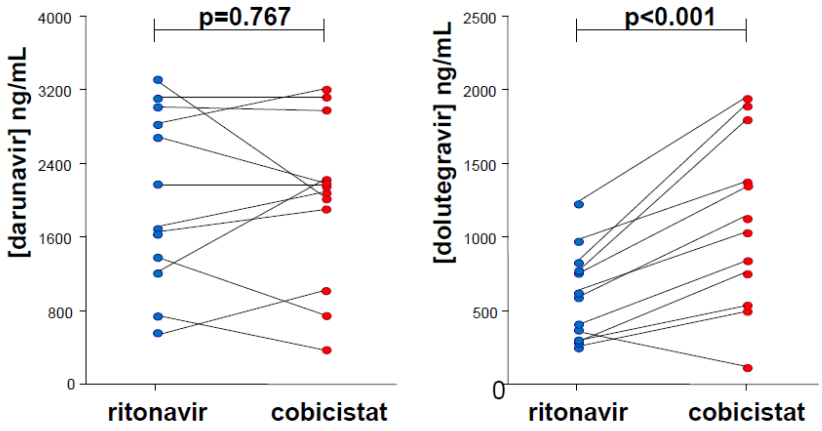
Cobicistat vs Ritonavir in 2019



- Guilt by Association
- Important differences

TARGET	Cobi (compared with RTV)	DDI effect
Cytochrome P450	• Comparable CYP3A4, 2B6 • Less CYP1A • Less CYP2C9 • Less CYP2D6 • No CYP induction	• Similar effects • Potentially less DDI with some cytotoxics, olanzapine • Potentially less DDI with warfarin • Potentially less DDI with SSRIs
UGT	• Does not induce UGT1A1	• Lesser magnitude DDI with opioids, lamotrigine, valproate, some antidiabetics, chemotherapy, etc
Transporters	• Similar PgP inhibition	• Dabigatran DDI is greater (PgP inhibition, no induction)
CYP3A4 inhibition	• Lower $C_{troughs}$ with DRV	• Incremental effects eg with pregnancy

Switch from DRVr to DRVc – impact on DTG



Ritonavir induces UGT, whereas cobicistat does not…

- Gervasoni, JAC 2017 -

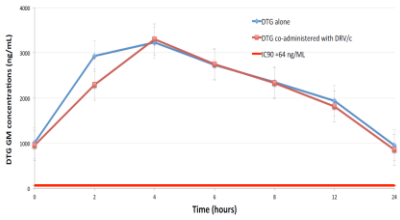
Cobicistat data - DRVc + DTG

Boosted DRV+DTG attractive option

- **Currently being explored in D2EFT**
- **DRVr+DTG (both od) showed adequate PK (DUALIS)**
- **However, UGT induction by RTV could lever DTG AUC (↓22%) and C_{trough} (↓38%)**
- **Previous data: when compared to DRVr (od), DTG levels doubled when switching to DRVc; but ↓38% with DRVr bd**

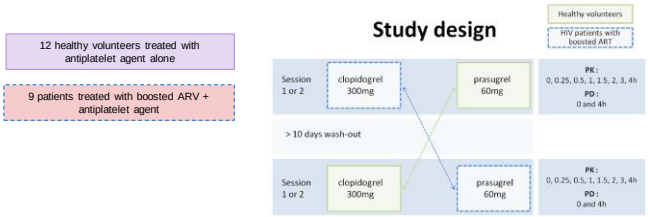
Compared to either drug given alone, co-administration of DRVc + DTG:
- DTG PK: AUC↔ ; Ctrough ↓ 10%
- DRV PK: AUC↔ ; Ctrough ↔ (NS)

DRVc has no clinical impact on DTG; both drugs can be safely combined

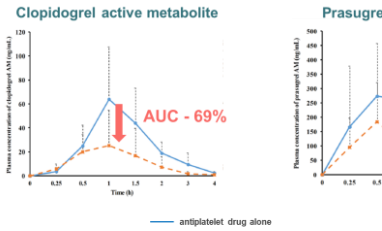


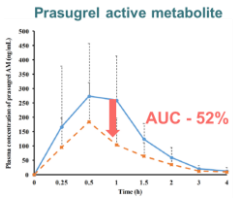
Elliot et al. JAC 2018 Oct 1

PK interaction: clopidogrel versus prasugrel



Marsousi N et al. Clin Pharmacokinet 2018





Second independent clinical study:

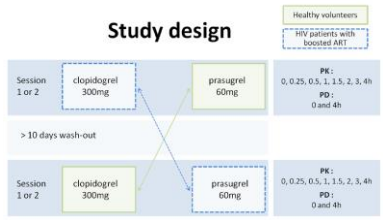
clopidogrel + RTV ➔ clopidogrel active met. **AUC -49%**

Itkonen MK et al. Clin Pharmacol Ther 2018

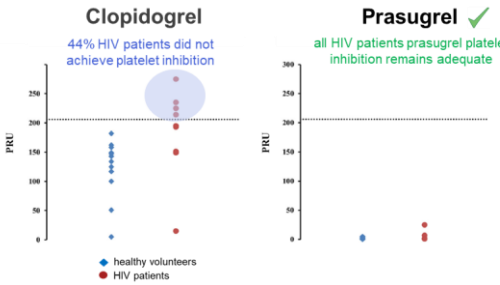
PD interaction: clopidogrel versus prasugrel

12 healthy volunteers treated with antiplatelet agent alone

9 patients treated with boosted ARV + antiplatelet agent



Marsousi N et al. Clin Pharmacokinet 2018



Second independent clinical study:

average inhibition of platelet aggregation: ↓**51%** (clopidogrel alone) vs ↓**31%** (clopidogrel + RTV)

Itkonen MK et al. Clin Pharmacol Ther 2018

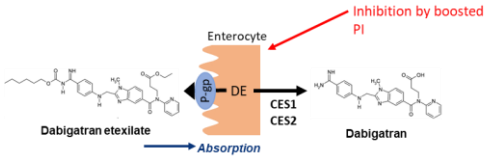
➔ prasugrel preferred over clopidogrel with boosted ART

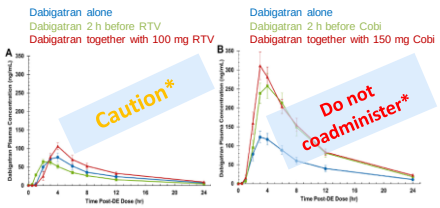
Case report: HIV-infected patient with thrombosis of coronary stent while treated with clopidogrel in presence of DRV/r. No further thrombosis episodes after switching to prasugrel. Bravo I et al. BJCP 2018

NOACs

- **Rivaroxaban & Apixaban – CYP3A4 and PgP substrate**
- **Dabigatran – PgP substrate**
- **Anti-Xa or TDM useful ?**

Dabigatran



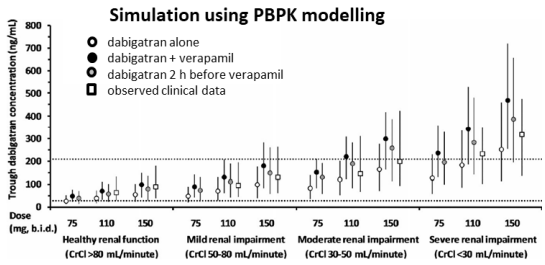


NOACs

- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Anti-Xa or TDM useful ?

Dabigatran

Effect of Renal Impairment



dabigatran + verapamil (multiple doses) : dabigatran AUC + 50%

Potential Interaction
Darunavir + ritonavir
Dabigatran

Coadministration possible. Caution in case of mild or moderate renal impairment as dabigatran dose might need to be reduced in presence of DRV/r.

Doki K et al. CPT Pharmacometrics Syst Pharmacol 2019, www.hiv-druginteractions.org

NOACs

- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Anti-Xa or TDM useful ?

Rivaroxaban

Postoperative Bleeding After Administration of a Single Dose of Rivaroxaban to a Patient Receiving Antiretroviral Therapy

Carmela E. Corallo[1] · Louise Grannell[1] · Huyen Tran[2]

DRV/r + etravirine with rivaroxaban 10 mg — Drug Saf Case Rep 2015

Extensive Bruising and Elevated Rivaroxaban Plasma Concentration in a Patient Receiving Cobicistat-Boosted Elvitegravir

Deborah Yoong, BScPhm, Pharm D , Mark Naccarato, BScPhm , Kevin Gough, MD, FRCPC, MEd

EVG/c with rivaroxaban 10 mg → CI with boosted ARVs — Ann Pharmacother 2017

Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus

Botond Lakatos, Marcel Stoeckle, Luigia Elzi, Manuel Battegay, Catia Marzolini

DRV/r + etravirine with rivaroxaban 10 mg — Swiss Med Wkly 2014

NOACs

- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Anti-Xa or TDM useful ?

Apixaban

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Medical history	HIV, T2DM, HCV, NSTEMI	HIV, HTN, COPD, CKD III	HIV, CAD, AF	HIV, HTN, HCV, T2DM	HIV, HTN, prior VTE, PVD	HIV
ARV	**LPV/r** +3TC +ABC	**DRV/r** +3TC +ABC	**DRV/r** +ETV +RAL	**DRV/r** +ETV +RAL	**EVG**c/F/TAF +**DRV**	**ATV/r** +3TC +ABC
DOAC ind.	Acute VTE	Acute VTE	AF	Acute VTE	Acute VTE	Acute VTE
Apixaban dose	10 mg BID x 4 doses then 2.5 mg BID	5 mg BID x 7 days then 2.5 mg BID	2.5 mg BID indefinitely	10 mg BID x 7 days then 2.5 mg BID	5 mg BID x 7 days then 2.5 mg BID	10 mg BID x 7 days then 5 mg BID x 7 days then 2.5 mg BID
Laboratory	Hgb **8.7** g/dL CrCl **35** mL/min	Hgb **11.7** g/dL CrCl 60 mL/min	Hgb 13.3 g/dL CrCl 65 mL/min	Hgb **9.9** g/dL CrCl **< 15** mL/min	Hgb 16.1 g/dL CrCl 65 mL/min	Hgb **11.4** g/dL CrCl 100 mL/min
Adverse events	Surgical bleed while on 10 mg BID. No events on 2.5 mg BID	No adverse events	No adverse events	No adverse events	No adverse events	No adverse events

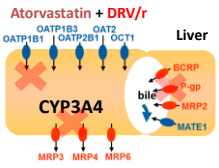
Recommendations: SmPC: **not recommended** with dual strong inhibitors of P-gp and CYP3A4
US PI: **avoid** concomitant use **or** **reduce apixaban dose by 50%** (2.5 mg BID)

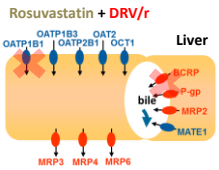
Apixaban product label, Nisly S et al. Int J STD & AIDS 2019

Magnitude drug interaction with atorvastatin

Differences in magnitude of drug-drug interactions with statins explained by different metabolic pathways and affinities to drug transporters.

	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EVG/c
Atorvastatin + (CYP3A4 + transporters)	↑822%	↑	↑290%	↑	↑490%	↑
Rosuvastatin + (transporters)	↑242%	↑213%	↑93%	↑48%	↑107%	↑38%





www.hiv-druginteractions.org

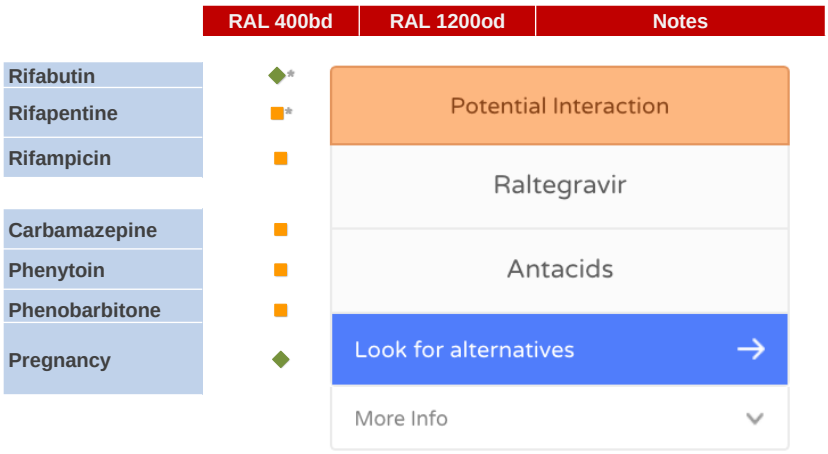
OATP1B1 inhibition: ATV > LPV > DRV > RTV, Cobi

Recommendations

	ATV/c	DRV/c
Atorvastatin	NR/lowest dose Max: 10 mg/d	lowest dose Max: 40 mg/d (US label: 20 mg/d)
Rosuvastatin	lowest dose Max: 10 mg/d	lowest dose Max: 20 mg/d

Start atorvastatin at 10 mg at titrate based on clinical response. Consider maximal daily recommended dose.

Differences between RAL twice and once-daily



HIV DDIs in 2019

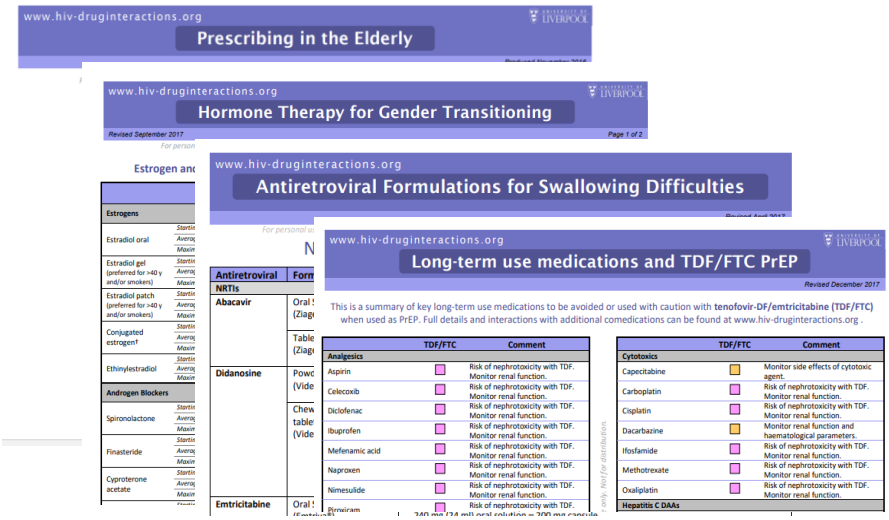
Modern ART

- Trend for ARVs with lower DDI potential – but not obviated
- Multi-morbidity increases absolute risk of harm
- Increasing choice allows shaping of ART around co-meds
- Globally bPIs still have important role

Co-morbidities

- TB-HIV : important data around Taf, EFV400, INSTIs
- Differences between cobicistat and ritonavir
- Differences between clopidogrel and prasugrel
- Differences between NOACs

Additional Material on www.hiv-druginteractions.org



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