Polypharmacy and Drug-Drug Interactions

David Back

November 2016

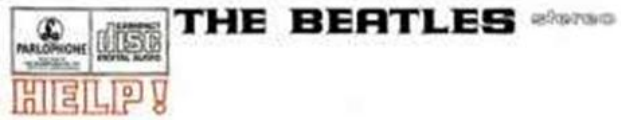
Disclosures

- Honoraria received for advisory boards and lectures from AbbVie, BMS, Gilead, Merck, ViiV, Janssen, Teva
- Educational grants for www.hep-druginteractions.org and www.hiv-druginteractions.org from AbbVie, BMS, Gilead, Janssen, Merck, ViiV

Polypharmacy

More patients on tx

Ageing



Increased OTC

Different prescribers

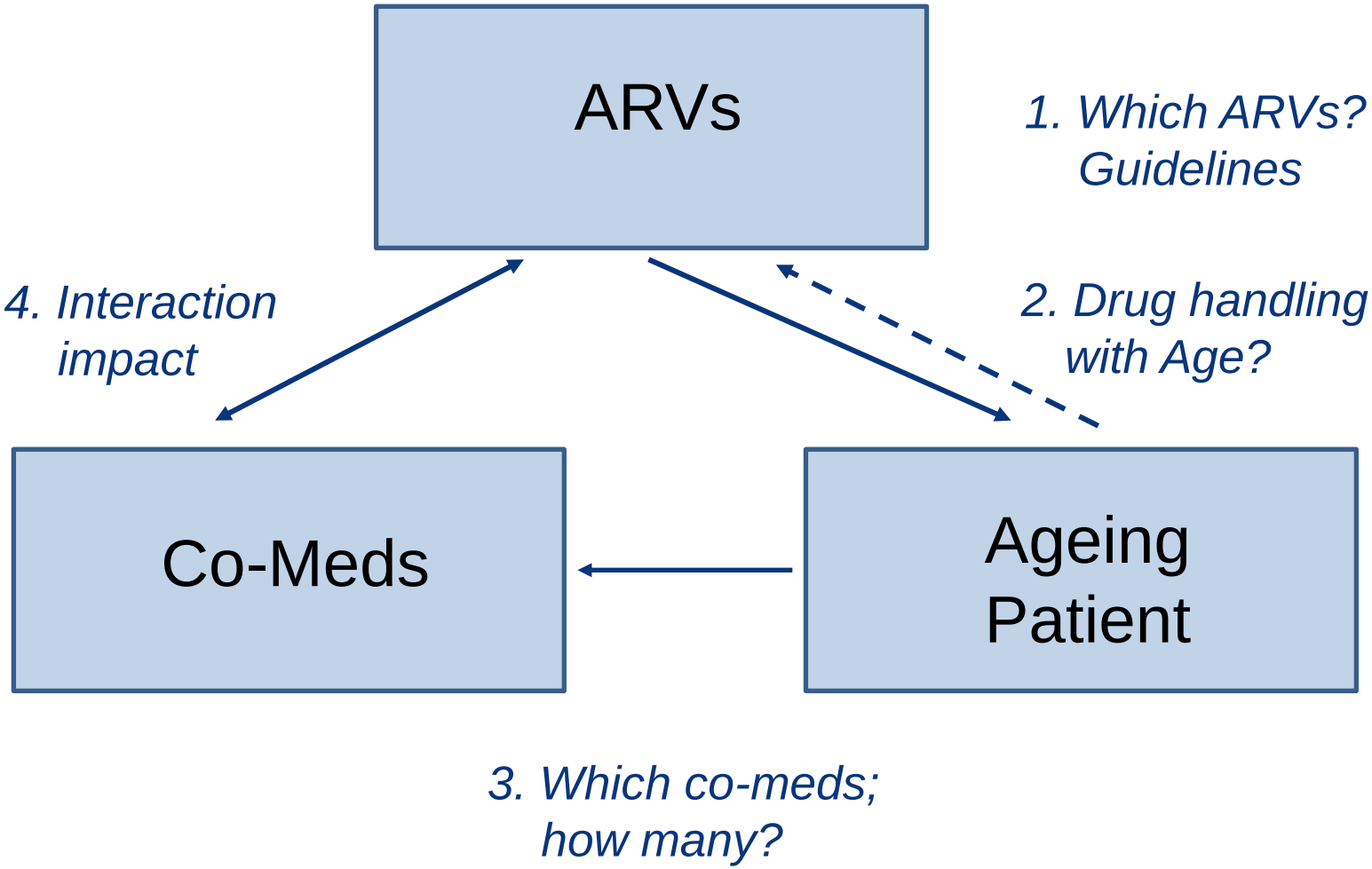
Recreational drugs

Online access drugs

Less Clinic visits?

Adapted from Okoli C - with permission

ARVs, Older Patients and Co-meds



Overview

1. Which ARVs; Guidelines
2.
3.
4.

Recommended Regimens: International Guidelines

Guidelines	Year	NNRTI	INSTI	PI/r
WHO	2016	TDF/FTC (or 3TC) + EFV	TDF/FTC (or 3TC) + **DTG**	NA
EACS (v8.1)¥	2016	TAF/FTC/RPV or TDF/FTC+RPV*	TAF/FTC or TDF/FTC with **EVG/c Or RAL or DTG** ABC+3TC with **DTG**	TAF/FTC or TDF/FTC+DRV/r or DRV/cobi
IAS-USA	2016	TAF/FTC+RPV* (or EFV) if INSTI not appropriate	TAF/FTC with **EVG/c Or RAL or DTG** ABC+3TC with **DTG**	TAF/FTC+DRV/r (if INSTI not appropriate)
DHHS	2016		TDF/FTC with **EVG/c Or RAL or DTG** TAF/FTC with **EVG/c or RAL or DTG** ABC+3TC with **DTG**	TDF/FTC+DRV/r TAF/FTC+DRV/r

* In viral loads <100K copies/mL
¥ Guideline update Oct 2016

TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; FTC, Emtricitabine; 3TC, Lamivudine; ABC, Abacavir; DRV/r, Darunavir/ritonavir, RPV, rilpivirine; EFV, efavirenz; EVG/c, elvitegravir/cobicistat; RAL, raltegravir; DTG, dolutegravir; NNRT, non-nucleoside reverse transcriptase inhibitor; PI/r, boosted protease inhibitor; INST, integrase inhibitor

WHO 2016: http://www.who.int/entity/hiv/pub/arv/arv-2016/en/index.html
EACS v8: http://www.eacsociety.org/files/guidelines_8.0-english-revised_20160610.pdf
IAS-USA 2016: http://jama.jamanetwork.com/article.aspx?articleid=2533073
DHHS 2016: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

EACS Guidelines (v8.1) Oct 2016: Initial Combination Regimens (Recommended and Alternative) for ART-naïve Adult HIV-positive persons

Class	EACS Recommended Regimen	Alternative Regimens
INSTI	▪ TAF/FTC or TDF/FTC + RAL ▪ TAF/FTC/EVG/c or TDF/FTC/EVG/c ▪ ABC/3TC/DTG ▪ TAF/FTC/DTG or TDF/FTC/DTG	▪ ABC/3TC + RAL
Boosted PI	▪ TAF/FTC or TDF/FTC + DRV/c or DRV/r	▪ ABC/3TC + ATV/c or ATV/r ▪ TAF/FTC or TDF/FTC + ATV/c or ATV/r ▪ ABC/3TC + DRV/c or DRV/r ▪ TAF/FTC or TDF/FTC + LPV/r
NNRTI	▪ TAF/FTC/RPV or TDF/FTC/RPV	▪ ABC/3TC + EFV ▪ TDF/FTC/EFV

16 of the 26 regimens have boosters

Also listed are 3TC + LPV/r and RAL + DRV/c or DRV/rFor specific details and cautions please go to the Guidelines

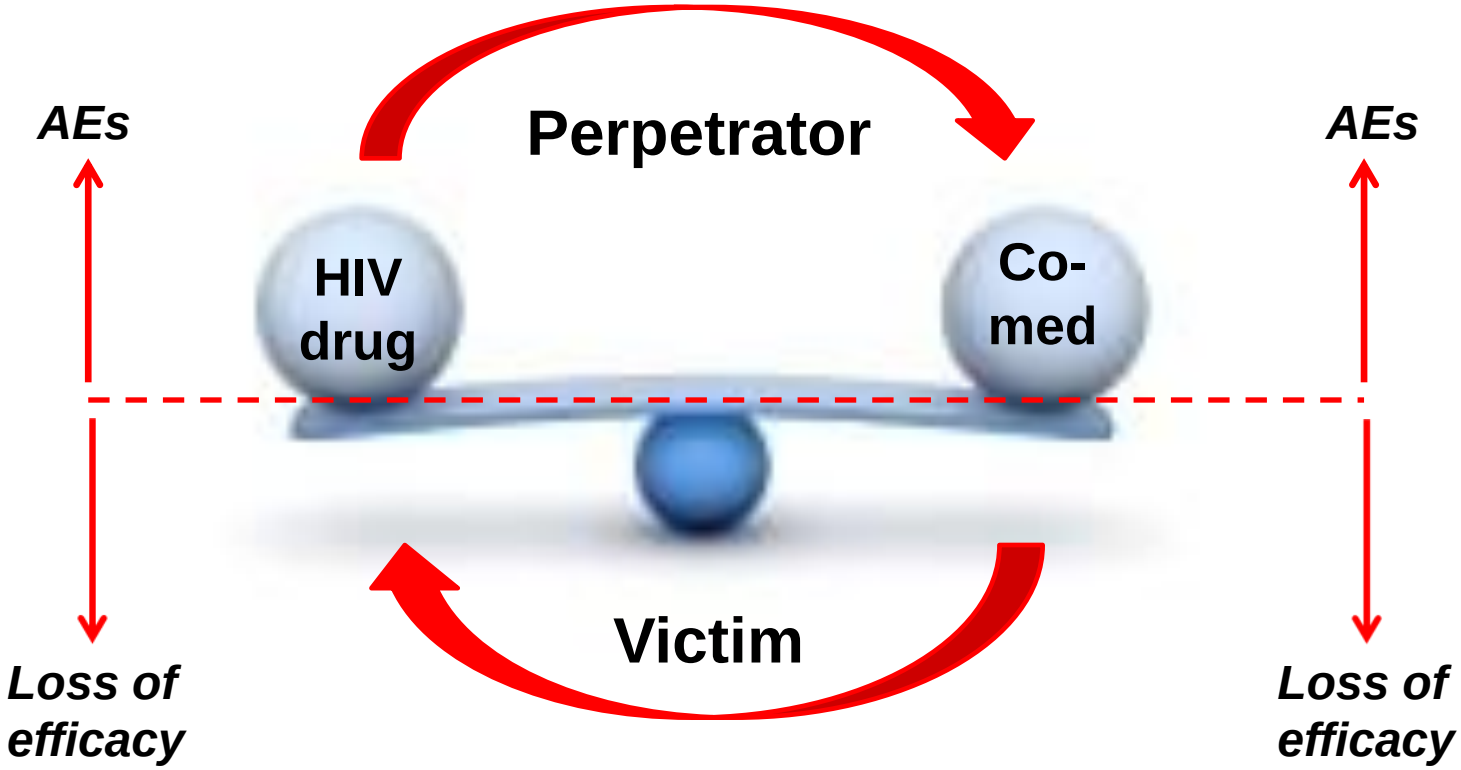
www.eacsociety.org/guidelines

Interaction Potential of ARVs

Higher potential	Moderate Potential	Lower Potential
Boosted PIs **Perpetrators** – enzyme and transporter Inhibition **Victim** - absorption (ATV); induction	**Rilpivirine** **Victim** of enzyme inhibition and induction. Also absorption.	**Raltegravir** **Victim** of few induction and absorption interactions
EVG/cobi **Perpetrator** – enzyme and transporter inhibition **Victim** - absorption; induction	***(Maraviroc)*** **Victim** of enzyme inhibition and induction.	**Most NRTIs** **Victim** of transporter mediated interactions. ← **TDF & TAF**
Efavirenz, *(Nevirapine, Etravirine)* **Perpetrators** – enzyme and transporter induction		**Dolutegravir** **Victim** of enzyme induction and absorption interactions **Perpetrator** of renal interaction

Based on www.hiv-druginteractions.org

Drug- Drug Interactions

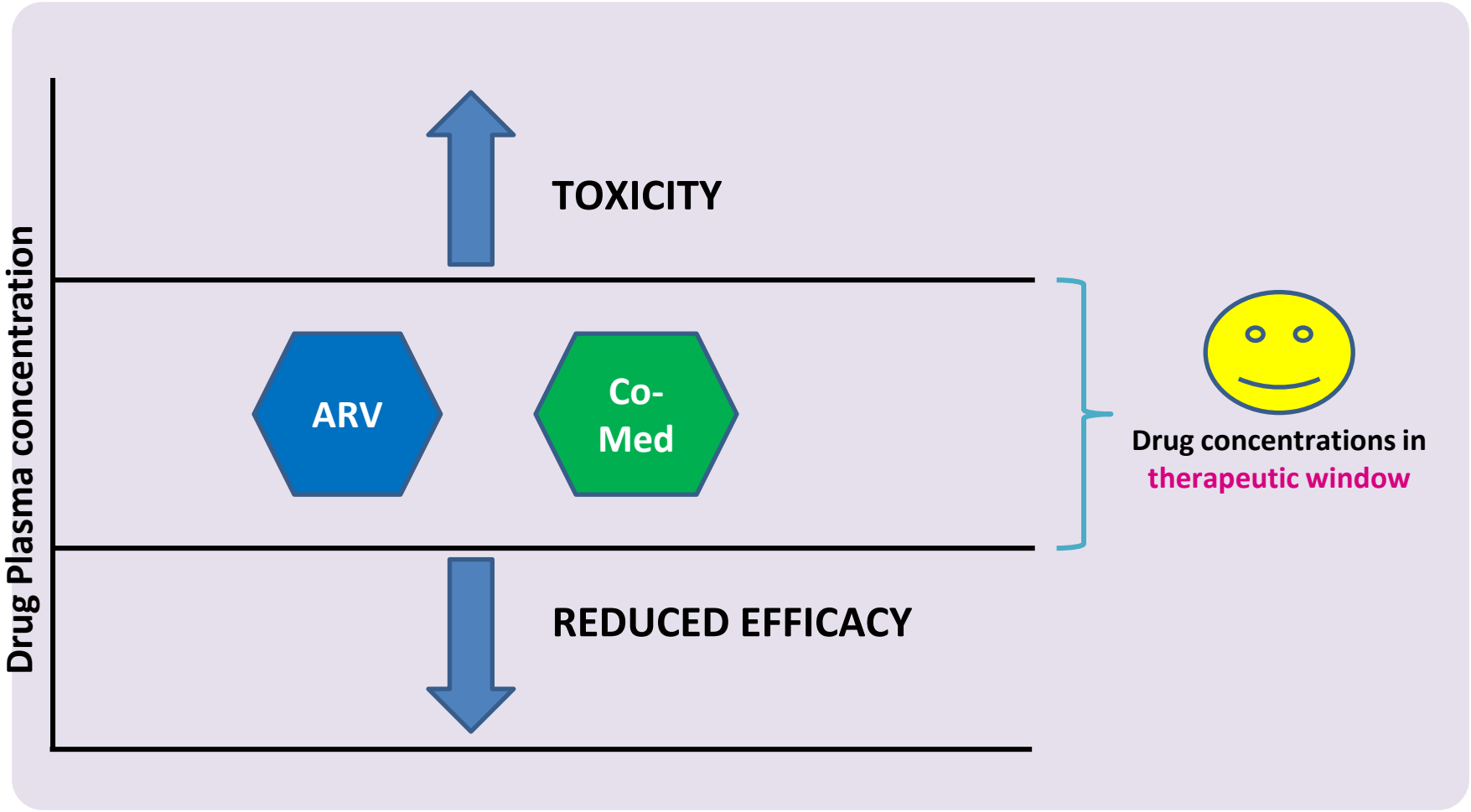


Need to understand:

- The disposition or handling of each drug
- The therapeutic window of each drug

Personal Communication: Professor D J Back

Therapeutic Window



Narrow Therapeutic Window Drugs including:
Anticoagulants, Antiarrhythmics, Anticonvulsants, Steroids, Statins, Immunosuppressants

Overview

1. Which ARVs; Guidelines
2. Drug Handling with Age
3.
4.

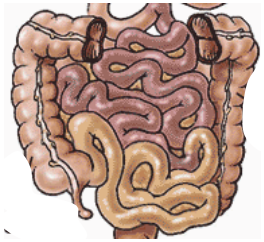
SPC Statements re Elderly

ARV	Statement in SPCs (accessed 20/11/16)
TDF	PK studies have not been performed in > 65 years of age
FTC	PK studies have not been performed in > 65 years of age
ABC	No PK data available in patients > 65 years
3TC	No PK data available in subjects > 65 years
EFV	PK Studies have not been performed in the elderly
RPV	Pop PK shows RPV exposure not different over age range 18-78 but only 3 patients > 65.
ATV/r	No clinically important PK differences based on age.
DRV/r	Limited PK data in patients > 65 (n=12). Caution
RAL	No effect of age on RAL PK over age 19-71 (n = 8 in > 65)
DTG*	Pop PK shows no clinically relevant effect of age, but data in > 65 is limited.
EVG	PK of EVG have not been fully evaluated in age >65.

SmPCs Accessed through the Electronics Medicines Compendium (EMC): www.medicines.org.uk/emc/ Nov 20th 2016

Should we be concerned about age and drug pharmacokinetics?

Absorption

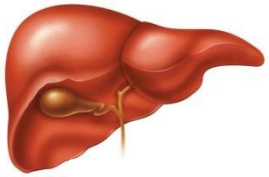


Increased gastric pH and decreased small bowel surface area may lead to a ***higher inter individual variability in drug exposure***. [1]

Distribution

Increase in body fat with older age increases Vd of some drugs and may increase the t1/2. ***Greater drug accumulation and increased risk of toxicity*** are possible.

Metabolism



Reduced liver volume and blood flow with reduced enzyme activity can give ***decreased drug clearance***. Also altered transporters.

Hepatic Impairment.

Renal elimination

GFR may decrease as much as 50% with increasing age, which can affect renal elimination of some drugs. Clinical consequence (***toxicity***) depends on the extent of renal elimination.

Boffito M and Back DJ, Personal communication;

Drugs Aging (2015) 32:999–1008
DOI 10.1007/s40266-015-0318-1

REVIEW ARTICLE

Age-Related Changes in Hepatic Function: An Update on Implications for Drug Therapy

Joseph L. Tan[1] · Jacques G. Eastment[1] · Arjun Poudel[2] · Ruth E. Hubbard[1]

Key Points

Age-related change in hepatic function causes much of the variability in older people's responses to medication.

In the absence of randomised controlled trials supporting titration of doses in older people, an appreciation of the fundamental pharmacokinetic changes related to hepatic drug clearance and protein binding can guide clinicians in their decision making concerning dose adjustment.

A decline in the ability of the liver to inactivate toxins may contribute to a proinflammatory state in which frailty can develop.

Best evidence for age-related changes is from older studies!

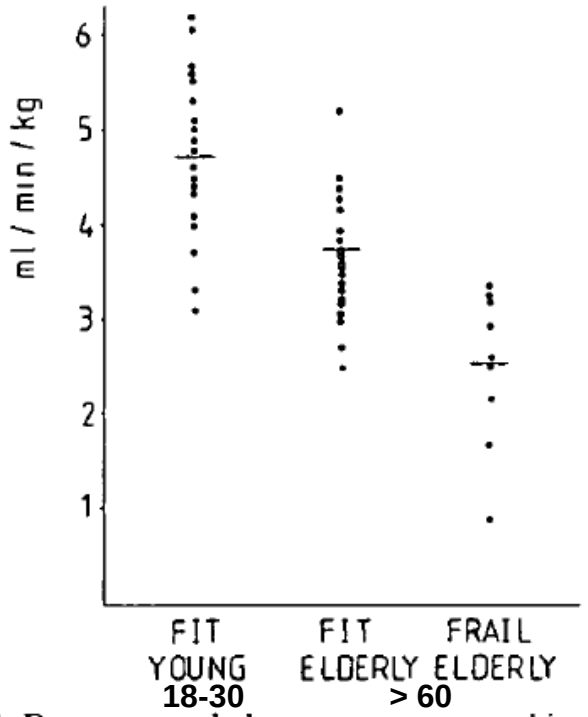


Figure 1. Paracetamol clearance expressed in terms of body weight in the three groups ($p < 0.01$ ANOVA).

- Paracetamol metabolised to form glucuronide and sulphate conjugates
- Clearance declines from 4.8 to 3.8 to 2.7 ml/min/kg.
- Means that drug exposure **increases by 30% (fit elderly) and 80% (frail elderly).**

Wynne HA et al Age & Ageing 1990; 19: 419-424; Wynne HA et al 1993; 22: 354-9

Brief Report

The pharmacokinetic profile of raltegravir-containing antiretroviral therapy in HIV-infected individuals over 60 years of age

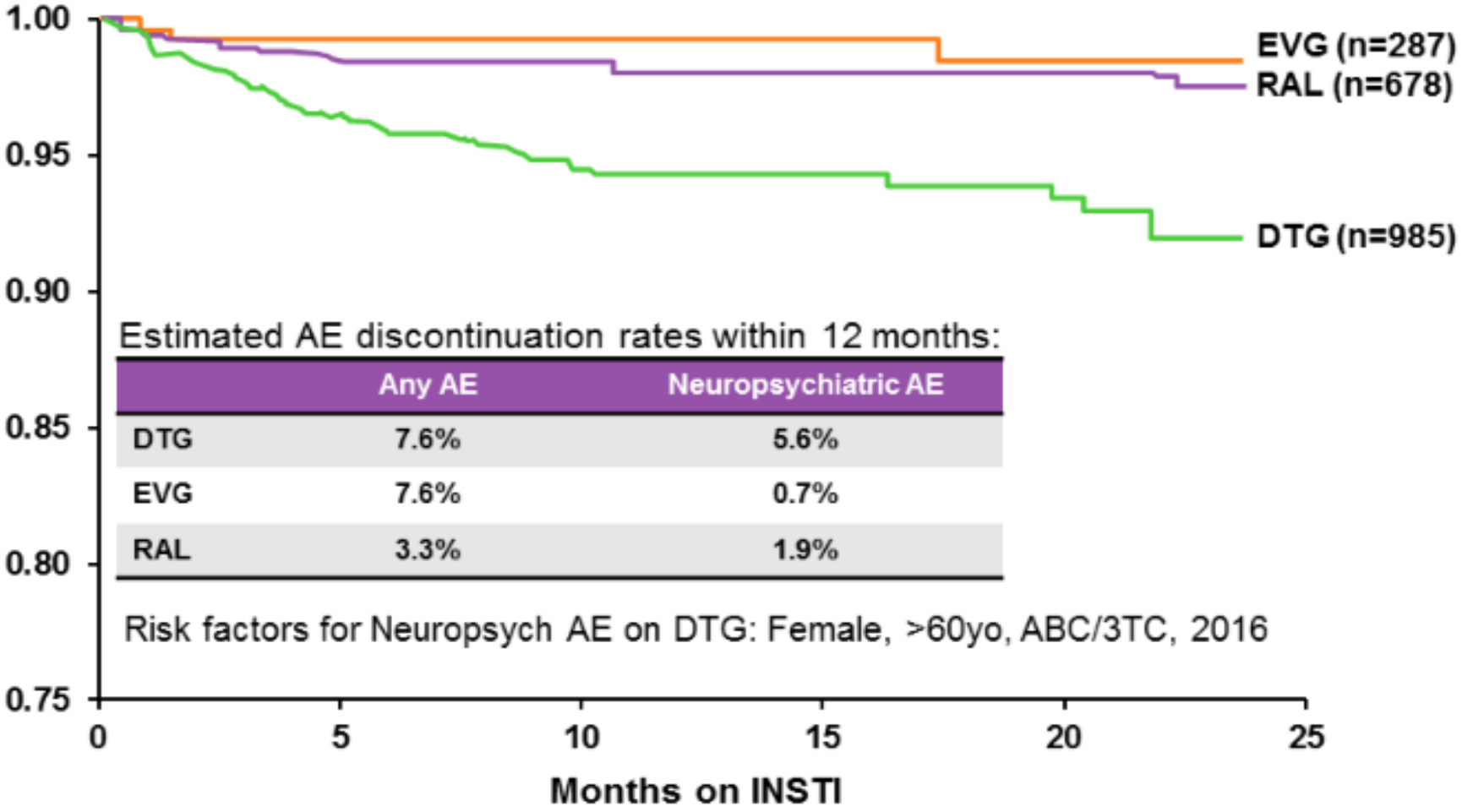
Jaime H. Vera[1], Akil Jackson[2], Laura Dickinson[3], Laura Else[3], Tristan Barber[2], Borja Mora-Peris[1], David Back[3], Marta Boffito[2], Alan Winston[1]

- 19 HIV+ subjects with mean (SD) age of 66 (3.4) switched to RAL containing regimen.
- No difference in RAL apparent oral clearance when compared to 38 younger HIV+ subjects with mean age of 41 (9.2) based on population PK.
  - RAL metabolised by enzyme UGT1A1

HIV Clin Trials 2015; 16: 39-43.

Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients

(All Other Events Censored, Main Events: Insomnia, Headache)



Estimated AE discontinuation rates within 12 months:

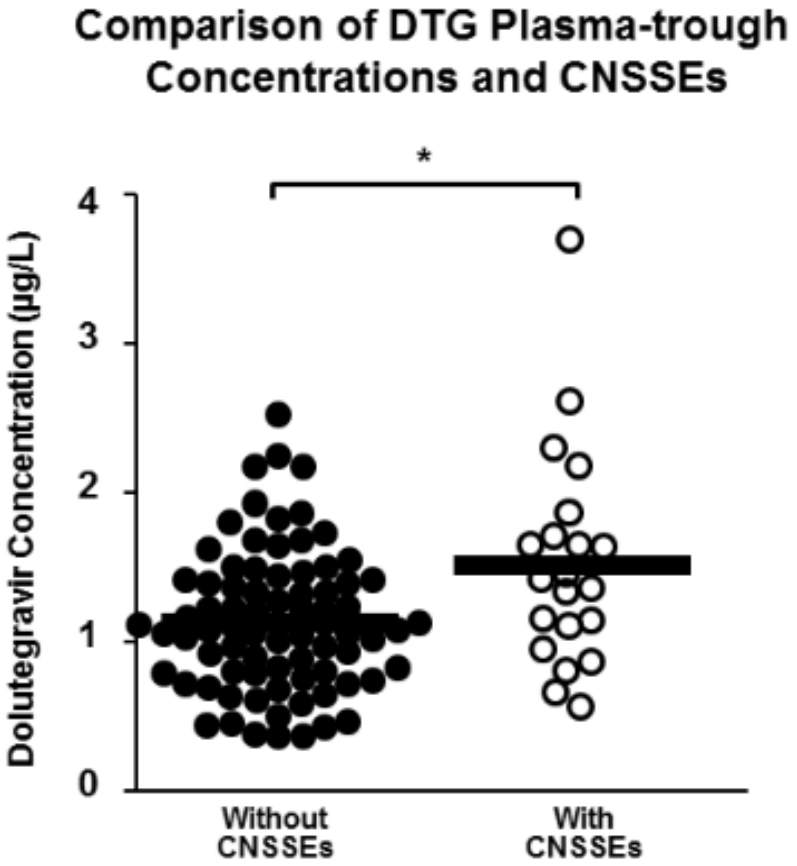
	Any AE	Neuropsychiatric AE
DTG	7.6%	5.6%
EVG	7.6%	0.7%
RAL	3.3%	1.9%

Risk factors for Neuropsych AE on DTG: Female, >60yo, ABC/3TC, 2016

Sabranski M et al HIV Glasgow 2016; Abs O214

Relationship between DTG plasma trough concentration, UGT1A1 polymorphisms and side-effects of the CNS in Japanese HIV-1 infected patients

- N = 101
- UGT1A1 *6 and *28 studied
- Median DTG C_{trough} was significantly higher in patients with CNS side effects
- However, no difference in CNS AEs in terms of genetic polymorphisms



Yagura H et al HIV Glasgow 2016; Abs P312.

Common clinical conditions – age, low BMI, ritonavir use, mild renal impairment – affect tenofovir pharmacokinetics in a large cohort of HIV-infected women

Sanjiv M. Baxi[a], Ruth M. Greenblatt[a,b,c], Peter Bacchetti[c],

Table 3. Multivariate model showing fold-effects on area under the curve by covariate (renal parameter: Chronic Kidney Disease Epidemiology Collaboration equation, using creatinine prior to visit on tenofovir, $n = 101$).

Parameter	Estimate (95% CI), *P* value
Concomitant RTV use	↑1.33 (1.11–1.59), 0.0020
Per decade of age	↑1.21 (1.08–1.34), 0.0007
Black versus non-black	↑1.04 (0.86–1.25), 0.68
Per 10% increase in BMI	↓0.96 (0.93–0.99), 0.019
eGFRcr <70 ml/min per 1.73 m^2	↑1.31 (0.95–1.81), 0.094

CI, confidence interval; eGFRcr, the CKD-EPI estimate for glomerular filtration rate; RTV, ritonavir.

Mean age 43 (range 22 – 65)

AIDS 2014; 28: 59-66

Prospective Studies

- EFV/TDF/FTC in patients > 55y (n=6)

  ATV/r + TDF/FTC in patients > 55y (n=6)

  Exposure compared to general population.

- ATV/r + 2NRTIs in pts - median age 46y compared to median age 41.9 (n=22).

  Higher ATV conc in older.

- LPV/r + FTC + d4T PK in patients aged 18-30 (n=37) and 45-79 (n=40)

  Older age associated with higher LPC C_{trough} at wk24 but not wk 36 or 90.

1. Dumond JB et al HIV Med 2013; 14: 404-9; 2. Avihingranon A et al AIDS Res Hum Retro 2013; 29: 1541-1546; 3. Crawford K et al AIDS Res Hum Retro 2010; 26: 635-643.

Overview

1. Which ARVs; Guidelines
2. Drug Handling with Age
3. Which co-meds; how many?
4.

FEATURED POSTS

Geriatrics Should Guide Care of HIV Infected Older Adults

Commentary October 14, 2016

Over half of all people infected with HIV in this country are now over the age of 50 and almost one-fifth of new infections occur in this population. Aging with HIV along with the other diseases that occur more commonly in older patients (such as high blood pressure, diabetes, arthritis) is increasingly complex to manage.....
Continue Reading

Older Adults Dominate the USA HIV/AIDS Epidemic

Commentary September 12, 2016 6 Comments

The annual HIV and Aging Awareness Day occurs on Sept. 18th. Older adults are dominating the USA epidemic. In major metro areas more than half of all those living with HIV are age 50 and older. For example, in San Francisco the number of older adults is more than 60% and in NYC the estimate..... Continue Reading

NEW RESOURCE: Staying Healthy with HIV as You Age

CASE STUDIES

UPDATED HIV-Associated Neurocognitive Disorders (HAND)
Updated on September 21, 2016

UPDATED Osteoporosis in HIV and Aging
Updated on August 4, 2016

CLINICAL RECOMMENDATIONS

UPDATED Nutrition in HIV and Aging
Updated on February 27, 2016

UPDATED PrEP and the Older Adult with HIV
Updated on February 23, 2016

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Contents

Future challenges for clinical care of an ageing population infected with HIV: a modelling study

Mikaela Smit, Kees Brinkman, Suzanne Geerlings, Colette Smit, Kalyani Thyagarajan, Ard van Sighem, Frank de Wolf, Timothy B Hallett, on behalf of the ATHENA observational cohort

	ATHENA cohort population (n=10 278)
Sex	
Male	8586 (84%)
Female	1692 (16%)
Age in 2010, years	44·5 (10·4)

Prevalence of NCD	
Diabetes	578 (6%)
Hypertension	2379 (23%)
Hypercholesterolaemia	2502 (24%)
Malignancies*	765 (7%)
Myocardial infarction*	216 (2%)
Osteoporosis	829 (8%)
Chronic kidney disease	1399 (14%)
Stroke*	156 (2%)

Lancet Infect Dis 2015; 15: 810–18

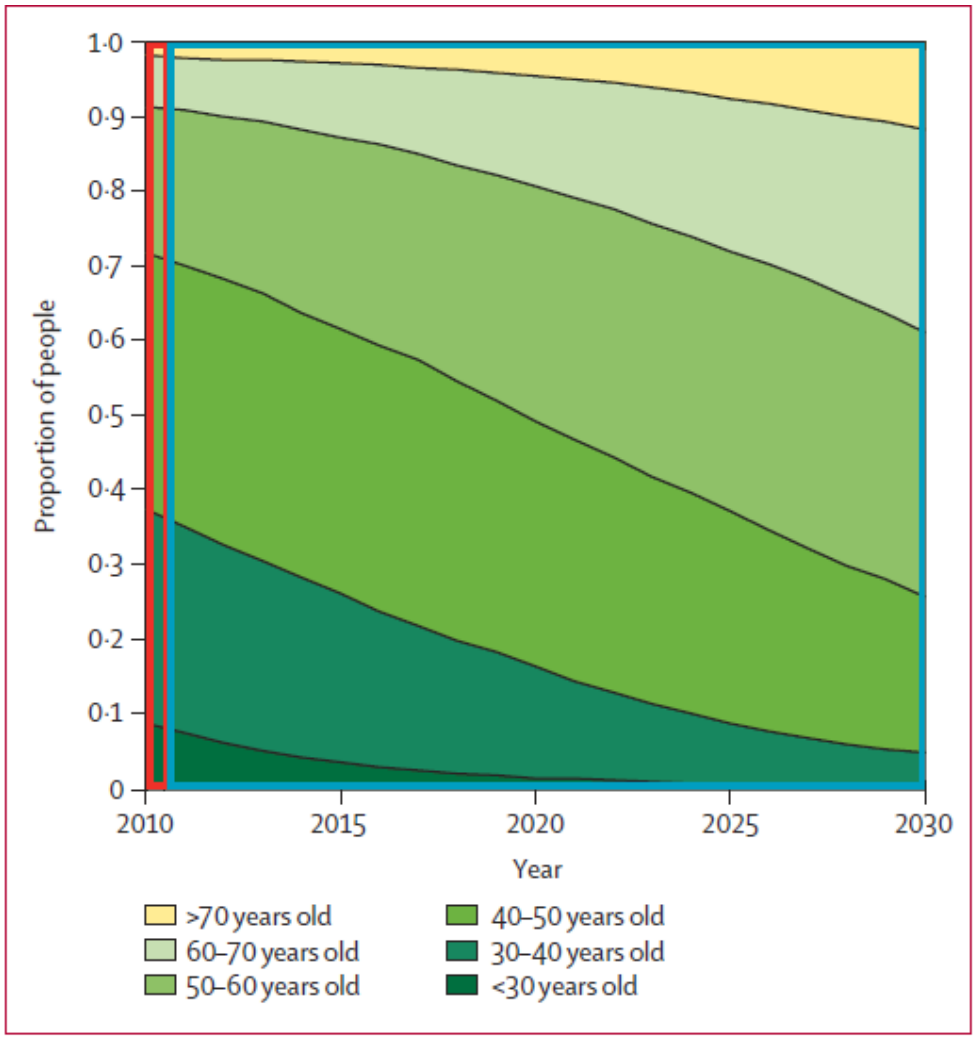
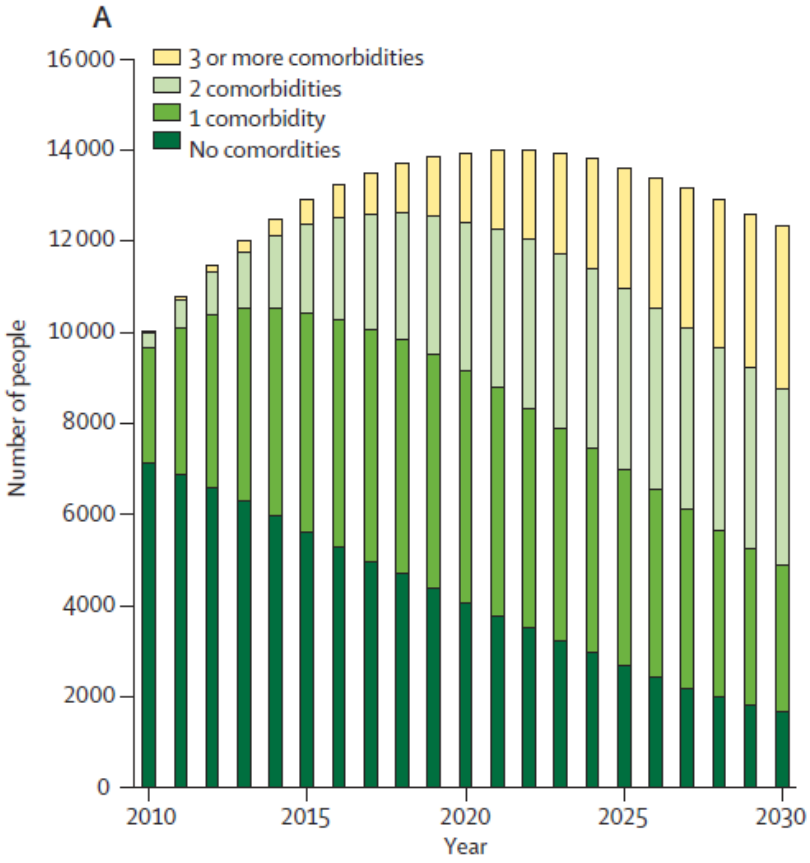
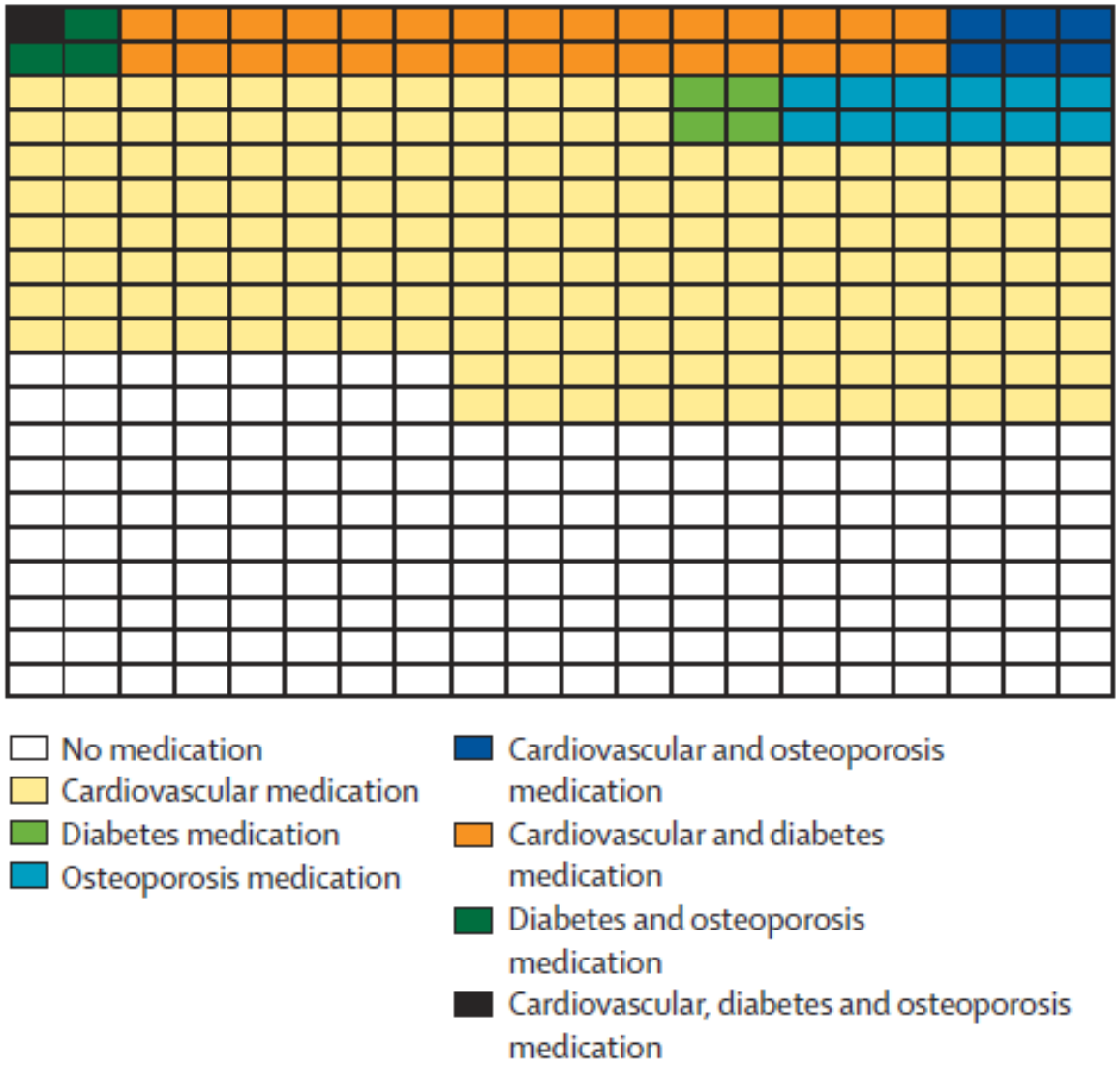


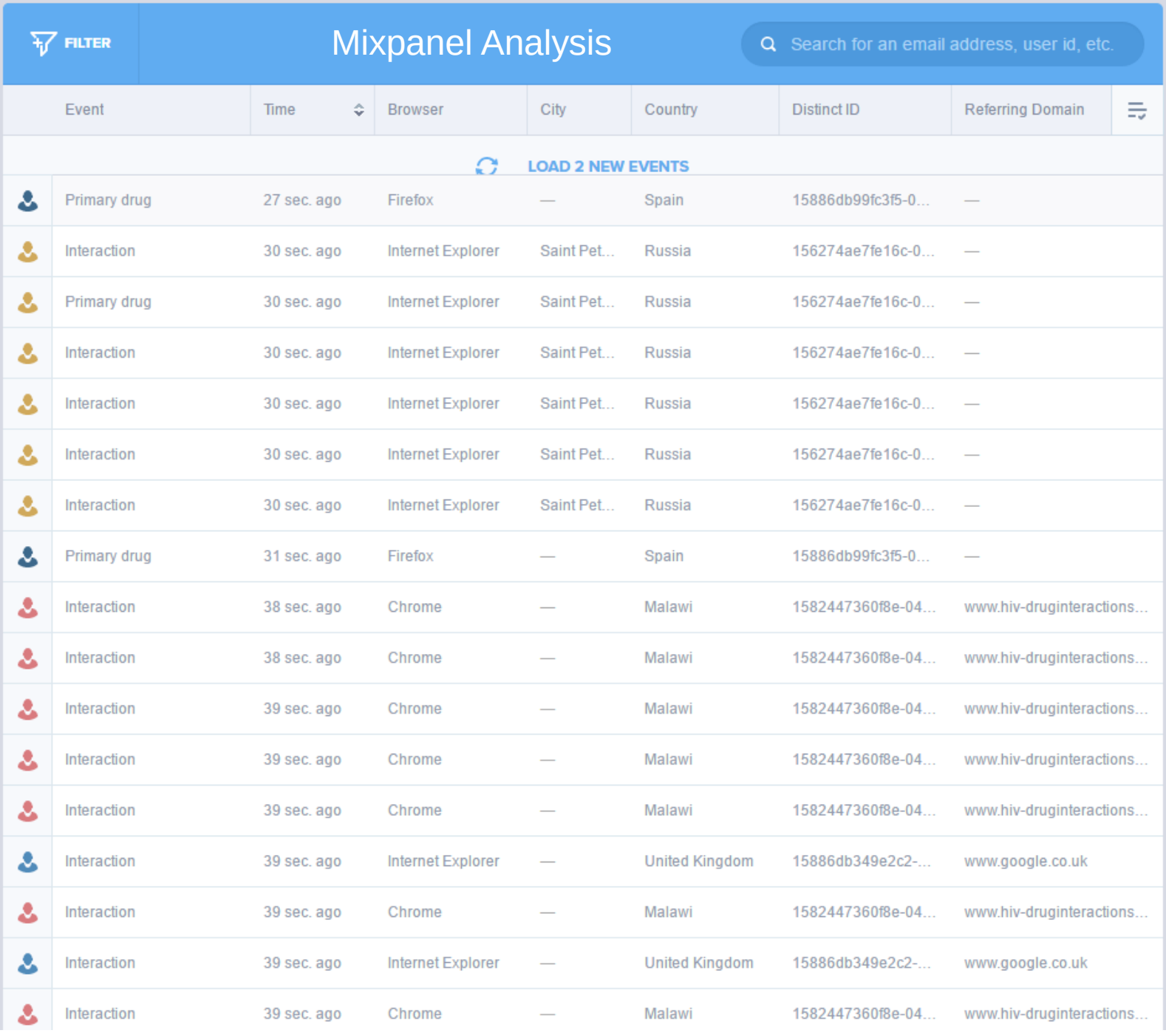
Figure 2: **Projected age distribution of HIV-infected patients**



Predicted burden of NCDs in HIV-infected patients between 2010 and 2030 (model simulation)



Predicted prevelance of comedication use in 2030 as cross section of number of patients on different types of co-meds based on representative 400 patients (each square representing a patient)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Mixpanel Analysis
Search for an email address, user id, etc.
Event
Time
Browser
City
Country
Distinct ID
Referring Domain
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primary_drug_name | A | contains | Darunavir

AND | OR | Country | A | contains | Spain

BY | co_drug_name | A

+ SEGMENT BY ANOTHER DIMENSION

N= ~250 search events

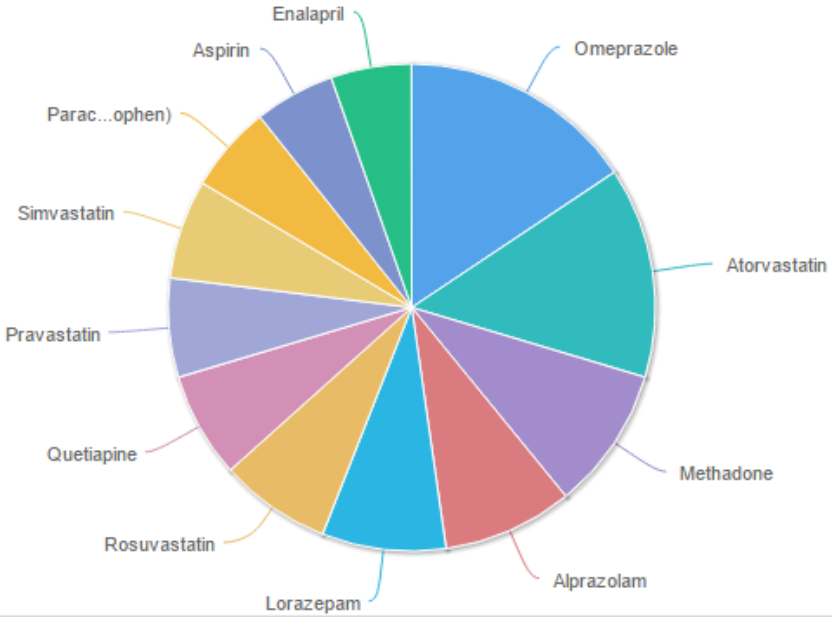
SHOW

Oct 23, 2016 - Nov 21, 2016

Day | Total

Omeprazole | Atorvastatin | Methadone | Alprazolam | Lorazepam | Rosuvastatin

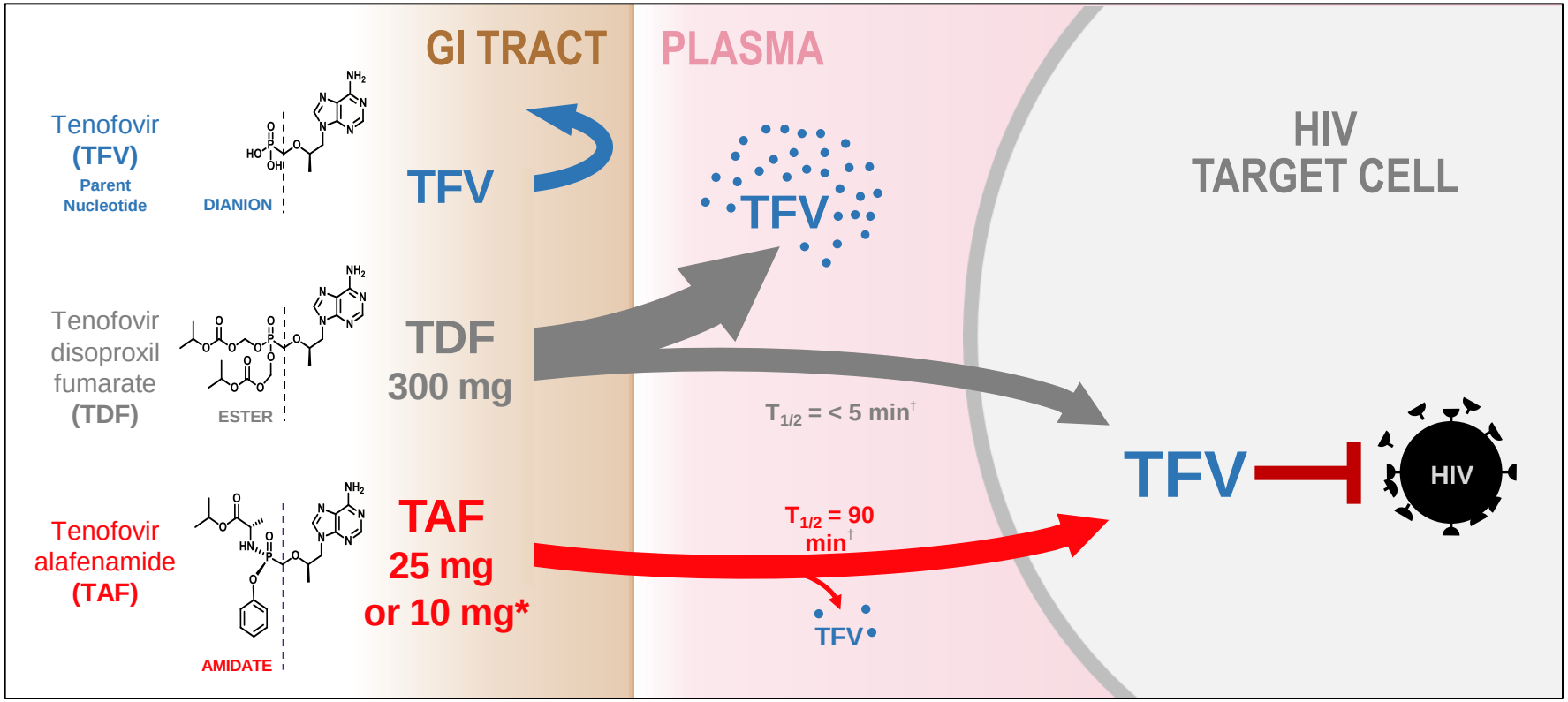
Quetiapine | Pravastatin | Simvastatin | Paracetamol (A... | Aspirin | Enalapril



Overview

1. Which ARVs; Guidelines
2. Drug Handling with Age
3. Which co-meds; how many?
4. Specific DDIs

Absorption of Tenofovir (TFV), Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF)



- 91% lower plasma TFV levels after E/C/F/TAF than E/C/F/TDF administration – TFV AUC is 290 vs 3308 ng.h/ml for Genvoya vs Stribild

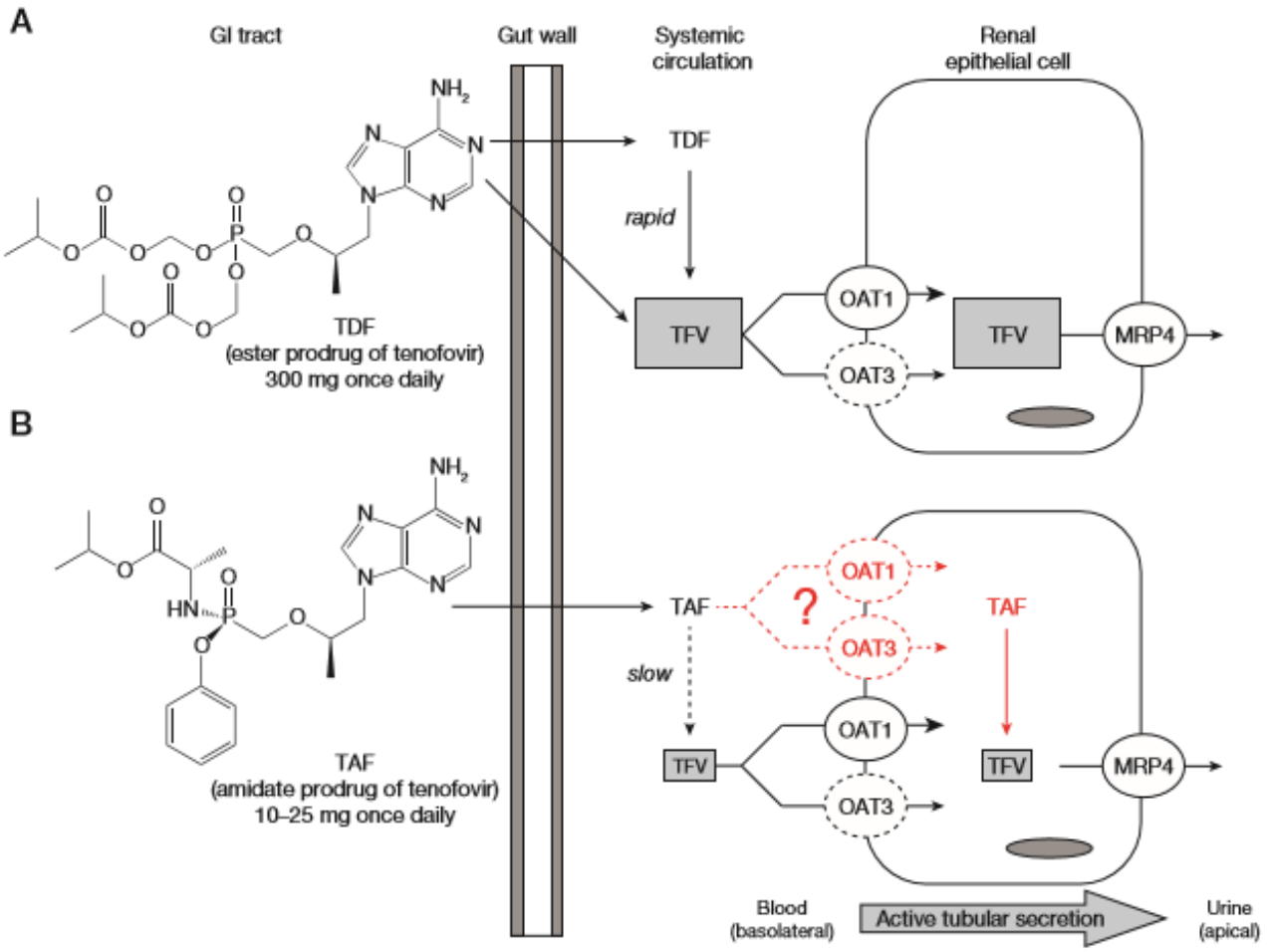
† $T_{1/2}$ based on *in vitro* plasma data.

1. Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. 2. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. 3. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66.
4. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. 5. Sax P, et al. *JAIDS* 2014. 2014;67(1):52-8. 6. Sax P, et al. *Lancet* 2015;385:2606-15.

FDA Center for Drug Evaluation and Research. Clinical Pharmacology & Biopharm Rev 2014 Gupta SK, et al. IAS 2015. Vancouver, CA; #TUAB0103.

Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity

Rujuta A Bam[1], Stephen R Yant[1], Tomas Cihlar[1]*



AVT 2014; 19: 687-692

Differences in the DDI Profile of TDF & TAF

	TDF	TAF	Potential Mechanism
Aspirin			NSAIDS and Renal
Celecoxib			NSAIDS and Renal
Diclofenac			NSAIDS and Renal
Ibuprofen			NSAIDS and Renal
Mefenamic acid			NSAIDS and Renal
Naproxen			NSAIDS and Renal
Nimesulide			NSAIDS and Renal
Acetazolamide			Renal transport
Cefalexin			Renal transport
Dacarbazine			Renal transport
Flucloxacillin			Renal transport
Mycophenolate			Renal transport
Verapamil			P-gp/absorption
Topiramate			Renal toxicity
Oxaliplatin			Renal toxicity
Sirolimus			Renal toxicity
Penicillamine			Renal toxicity
Tacrolimus			Renal dysfunction
Zoledronic acid			Renal dysfunction

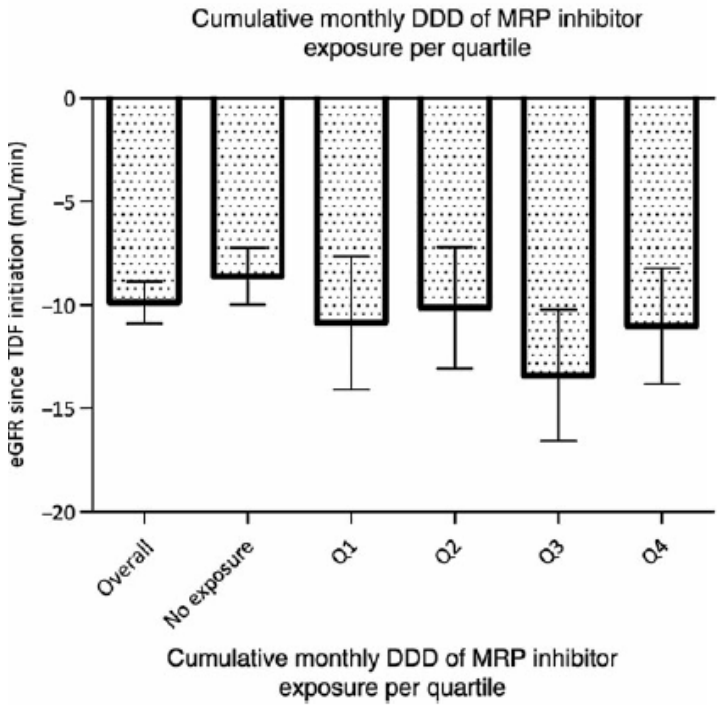
NSAIDS (inhibit MRP4) – important to consider dosing frequency

The Journal of Infectious Diseases
MAJOR ARTICLE

Renal Toxicity of Concomitant Exposure to Tenofovir and Inhibitors of Tenofovir's Renal Efflux Transporters in Patients Infected With HIV Type 1

Casper Rokx,[1] Hanin Alshangi,[1] Annelies Verbon,[1] Robert Zietse,[2] Ewout J. Hoorn,[2] and Bart J. A. Rijnders[1]

- 721 patients with median use of TDF of 54 months
- 321 pts had renal transport inhibitors (NSAIDS; PDE5-I; salicylates) which were categorised as cumulative defined daily doses (DDDs).



JID 2016; 213: 561-568

Differences in the DDI Profile of TDF & TAF

	TDF	TAF	Potential Mechanism
Rifabutin		NR ▲	Induction of P-gp
Rifampicin		NR ▲	Induction of P-gp
Rifapentine		NR ▲	Induction of P-gp
Carbamazepine		NR ▲	Induction of P-gp
Oxcarbazepine		NR ▲	Induction of P-gp
Phenobarbitone		NR ▲	Induction of P-gp
Phenytoin		NR ▲	Induction of P-gp
St John's Wort		NR ▲	Induction of P-gp
Fluconazole		Dose 10 mg TAF	Inhibition of P-gp
Itraconazole		Dose 10 mg TAF	Inhibition of P-gp
Ketoconazole		Dose 10 mg TAF	Inhibition of P-gp
Cyclosporin		Dose 10 mg TAF	Inhibition of P-gp
Boceprevir		NR	Stops intracellular activation
Telaprevir		NR	Stops intracellular activation

Consider dosing of azoles (short course)

NR = Not Recommended ▲ N = Could argue could be red (personal communication, David Back Nov 16)

www/hiv-druginteractions.org

www.hiv-druginteractions.org

UNIVERSITY OF LIVERPOOL

Antiplatelet/ Novel Anticoagulants Treatment Selector

Charts reviewed January 2015. Full information available at ***www.hiv-druginteractions.org*** *and* ***www.hiv-druginteractionslite.org***

		ATV/r	DRV/r/c	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Antiplatelet	Clopidogrel																	
	Prasugrel																	
	Ticagrelor																	
Anticoagulant	Dabigatran																	
	Rivaroxaban																	
	Apixaban																	

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be co administered (contraindicated or not recommended)
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

Note:

Clopidogrel: Prodrug activated by CYP2C19 (major), other CYPs (minor) and CES-1.

Prasugrel: Prodrug activated by CYP3A4 (major) and other CYPs

Ticagrelor: Metabolized by CYP3A4 and transported by P-gp

Dabigatran: Prodrug (the etexilate) is a P-gp substrate

Rivaroxaban: Metabolized by CYP3A4 and transported by P-gp/BCRP.

Apixaban: Metabolized by CYP3A4 and transported by P-gp/BCRP.

Utilizing Phase 3 Clinical Trial Data to Assess AEs Frequency of a Potentially Interacting Medication AMLODIPINE with EVG/COBI

- 9 large CT – onset AEs date within 30 days of drug initiation or discontinuation due to AEs
- List od specific AEs based on: Micromedex, Lexi-Comp, SPC, AHFS Drug Information 2015

Amlodipine Specific Grade 2-4 AEs

Adverse Event	Amlodipine Use (N=153)	No Amlodipine Use (N=4514)	P-value
Any event	14% (22)	5% (237)	<0.001*
Grade 2	12% (19)	4% (194)	<0.001
Grade 3	2% (3)	1% (43)	NS
Palpitations	0.7% (1)	<0.1% (4)	NS
Grade 2	0	<0.1% (4)	NS
Grade 3	0.7% (1)	0	0.033
Peripheral edema	5% (7)	0.4% (16)	<0.001
Grade 2	5% (7)	0.4% (16)	<0.001
Ataxia	0.7% (1)	<0.1% (1)	NS
Grade 2	0.7% (1)	0	0.033
Grade 3	0	<0.1% (1)	NS
Nervous system disorders	3% (4)	0.8% (34)	0.035
Grade 2	2% (3)	0.7% (32)	NS
Grade 3	0.7% (1)	<0.1% (2)	NS

There was a higher discontinuation rate in subject using amlodipine versus not (p=0.031)

* Comparisons done for grade 2-4 events between users and non-users of amlodipine
† includes dizziness (2), convulsion (1), ataxia (1), sedation, lethargy, somnolence
NS=not significant

Podzamczer D, et al. HIV Glasgow; 23-26 October 2016; Glasgow, UK; Abst. P314.

Drug interactions between antiretrovirals and drugs used to treat benign prostatic hyperplasia/lower urinary tract symptoms

Denise Kreutzwiser[a,b,c] and Alice Tseng[a,c]

	DRV/r	EFV	RAL	DTG	EVG/c	TDF	F/TAF
Doxazocin							
Alfuzosin							
Tamsulosin							
Dutasteride							
Finasteride							

Expert Opinion on Drug Met & Tox 2016; 12: 1211-1224;
www.hiv-druginteractions.org

BHIVA Guidelines 2016

1. We suggest avoiding ritonavir or cobicistat boosted ART in patients who are to receive cytotoxic chemo agents metabolised by CYP450.
2. We suggest switching ARV agents in patients who are to receive cytotoxic chemotherapy to avoid severe and/or overlapping toxicities.

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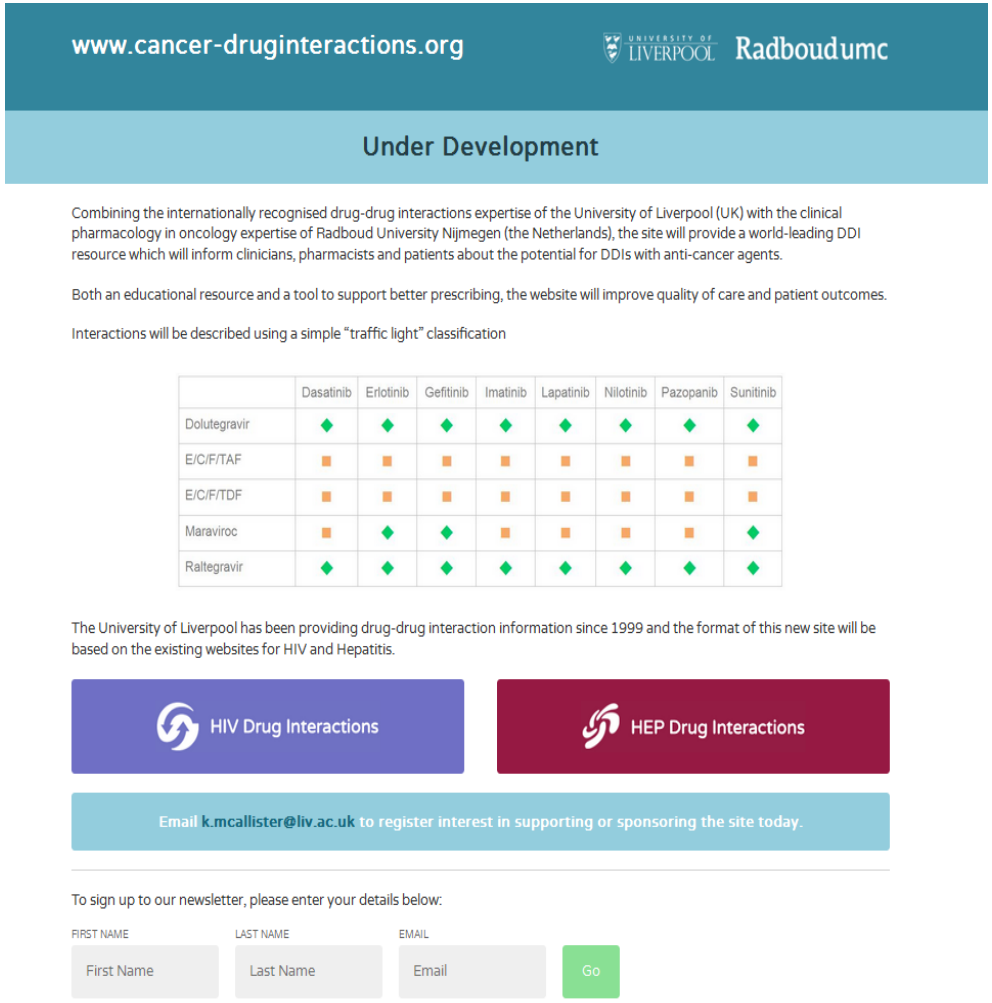
www.cancer-druginteractions.org



Cancer Drug Interactions

ARVs and Herbals

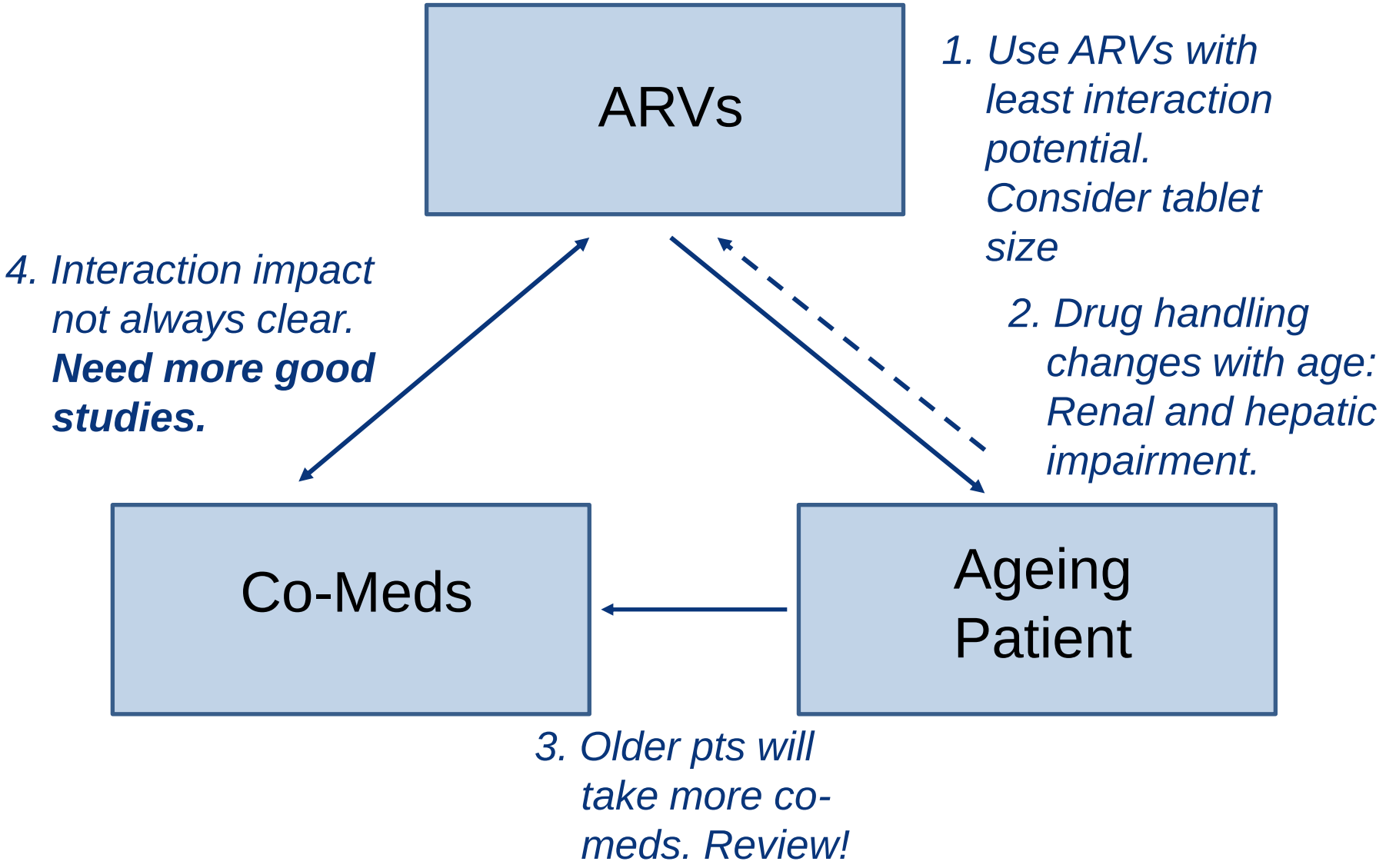
Herbal	Disposition	Interaction Potential
Glycyrrhiza glabra (Liquorice)	Modest inducer of CYP3A4; May induce UGTs; **Inhibitor of P-gp**	Could decrease RPV & MVC; possibly decrease RAL & DTG Increase of TDF & TAF
Zingiber officinale (Ginger)	Moderate inhibition of CYP2C9, 2C19 and 3A4.	Could increase RPV & MVC
Inula racemosa	Moderate inhibition of CYP3A4 in vitro	Could increase RPV & MVC
Piper cubeba	Several constituents strongly inhibit CYP3A4 and **piperine inhibits P-gp**	Potentially increase RPV & MVC (CYP3A4) Could increase TDF and TAF (P-gp)
Menthol	Moderate inhibitory effect on CYP3A4.	Possible effect on RPV and MVC

Liverpool website team - unpublished

Overview

5 Take home points.

ARVs, Older Patients and Co-meds



Thank You

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ART Considerations in Older Pts

- Comorbidities
- Polypharmacy
  - Drug–drug interaction, dosing, adherence challenges
- Renal or hepatic impairment
  - Alterations in pharmacokinetics, potential for drug toxicity
- Challenges with single-tablet regimens
  - Inability to alter single component dosing
  - Difficulty swallowing large tablets

Slide credit: clinicaloptions.com