Drug Interactions and Polypharmacy in the Management of HIV: A Case-Based Discussion

Charles W. Flexner, MD
Professor of Medicine, Pharmacology and Molecular Sciences, and International Health
The Johns Hopkins University
Baltimore, Maryland

Financial Relationships With Ineligible Companies*

Dr Flexner has served as a consultant to Gilead Sciences, Merck & Co, Inc, Mylan Pharmaceuticals, and ViiV Healthcare, and served as an expert in a case involving Gilead Sciences, Inc. (Updated 04/13/21)

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*The ACCME recently updated the term from commercial interests to ineligible companies.

Learning Objectives

After completion of this presentation learners will be able to:

- Describe how polypharmacy contributes to morbidity in people with HIV infection, especially older persons.
- Discuss possible strategies for clinical management of polypharmacy.

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Case #1

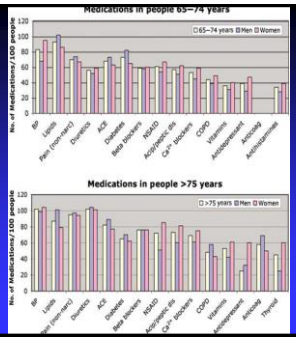
- 59 y.o. male with a long h/o HIV infection, heavily treatment-experienced
- Referred from Urology Clinic for advice about drug regimen for prostatic hypertrophy and urethral obstruction
- Previously healthy except for GERD, H/O depression and H/O STIs
- Current ARV regimen is:
  - Etravirine 400 mg QD
  - Darunavir 800 mg QD
  - Cobcistat 150 mg QD
  - Dolutegravir 50 mg QD
- Also taking:
  - Omeprazole 20 mg QD
  - Maalox 30 cc as needed
  - Sertraline 50 mg QD
  - Trimethoprim/sulfamethoxazole one DS QD

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Aging and Polypharmacy in HIV: How big is the problem?

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Increase in Prescription Meds with Aging



Schwartz JB.
Clin Pharmacol Ther
2007; 82:87

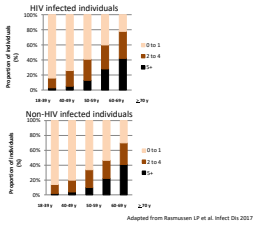
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ARS Question #1

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Fact: HIV-infected individuals are taking more prescription drugs

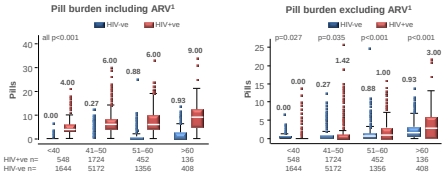
Non-HIV medication use in the Danish HIV Cohort Study (n = 3638) compared to general population (n = 18'190) in 2010



Adapted from Rasmussen LP et al. Infect Dis 2017

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Pill burden increases in HIV population at older ages



- In the general population, 19% of men, 23% of women >65 years of age take ≥5 prescription medications per week[2]
- Polypharmacy is more common in HIV-positive patients with respect to controls; increases with age[1]

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Guaraldi G, et al. 9e Congressio Nazionale SIMIT 2010. 112—P; 2. Kaufman DW, et al. JAMA 2002;287:337–44.

Association of Age With Polypharmacy and Risk of Drug Interactions With Antiretroviral Medications in HIV-Positive Patients

Alice Tseng, PharmD, FCSHP, AAHIVP[1,3], Leah Szadkowski, MSc[1], Sharon Walmsley, MD, MSc, FRCPC[1,2,3], Irving Salit, MD, FRCPC[1,3], and Janet Raboud, PhD[2,3]

Medication	Age < 50 years (n=498)	Age > 50 years (n=416)
Cardiovascular	127 (26%)	271 (65%)
Antidepressants/ Psychotropics	199 (40%)	224(54%)
Gastrointestinal	243 (49%)	276 (66%)
Narcotics/Analgesics	113 (23%)	164 (39%)
Systemic hormonal	49 (10%)	67 (16%)

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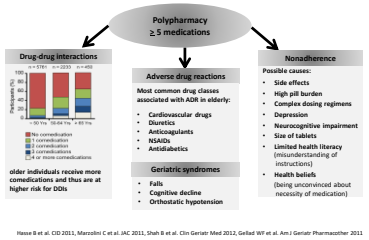
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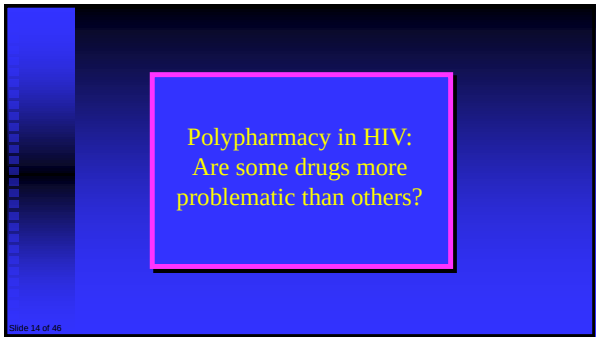
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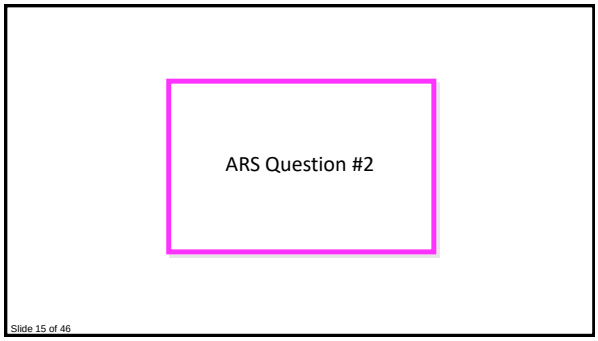
Consequences of polypharmacy

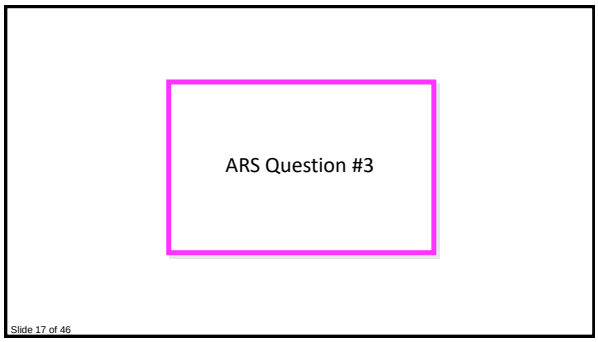


Hasse B et al. CID 2011, Marzolini C et al. JAC 2011, Shah B et al. Clin Geriatr Med 2012, Gellad WF et al. Am J Geriatr Pharmacother 2011

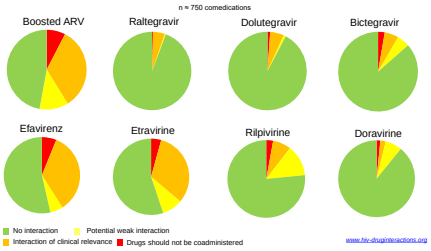
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Polypharmacy in HIV:
Are some drugs more
problematic than others?
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ARS Question #2
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ARS Question #3
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Drug-Drug Interaction Profile of Antiretroviral Drugs



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ARS Question #4

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Potentially Inappropriate Medications (PIMs) more frequent in HIV positive patients

- prescriptions of 94 HIV infected patients (mean age: 64 y) from SF HIV over 60 Cohort
- prescriptions of 28 age and gender matched uninfected patients (mean age: 65 y) from SF aging research center

Proportion patients	HIV positive patients	Uninfected patients
Potentially inappropriate drugs	52%	29%
Anticholinergic risk score ≥ 3	17%	4%
Mean number non HIV medications	8 medications	6 medications

Reasons medication-related problem were more common in HIV infected patients could include that HIV specialists are less familiar with geriatric prescribing.

Greene M. J Am Geriatr Soc 2014

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Aging & comorbidities pose additional therapeutic challenges

- **Age associated changes in pharmacodynamics:**
  - changes in the affinity of some medications to receptor sites or in the number of receptors
    → affect efficacy or increase sensitivity to certain drugs
  - regulation of some physiological processes (i.e renal hemodynamics) altered with aging

Examples

Drug class	Potential PD issues	Comments
Antihypertensives	orthostatic hypotension	start with lower dose
Benzodiazepines	↑ sensitivity (sedation, confusion…)	use with caution and for short period of time, use lowest dose
Opiods	↑ sensitivity	use with caution, use lowest dose
β-blockers	β-receptors less responsive	may require ↑ β-blocker doses
Diuretics	↑ sensitivity drug effect	monitor blood pressure and electrolytes
Anticholinergic agents	↑ sensitivity (agitation, confusion, decompensation of glaucoma, dry mouth, constipation, urinary retention…)	avoid

Effects could be aggravated by inhibition of metabolism by PI/r, cobicistat

Wooten JM. South Med J 2012

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Question #1:
Is this complex ARV regimen evidence-based?

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Case 1

- Can dolutegravir and etravirine be administered without dose modification?
- Etravirine reduces concentrations of DTG and co-administration is contraindicated EXCEPT in the presence of darunavir/ritonavir (and presumably DRV/COBI).
- Does the double dose of ETV in this case change the potential drug interaction?

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Case 1

- Can darunavir/ritonavir and etravirine be administered without dose modification?
- Etravirine reduces cobicistat concentrations, and hence darunavir concentrations, and co-administration is contraindicated.
- Does the double dose of ETV in this case change the potential drug interaction?

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Case 1

- Should etravirine be administered in treatment-experienced patients at a dose of 400 mg QD?
- Etravirine is only FDA approved for administration as a 200 mg BID regimen.
- The long-half life of ETV (30-40 hours) should support QD dosing.
- The SENSE trial showed that 400 mg ETV QD plus NRTIs was equally efficacious as EFV 600 mg plus NRTIs.
  - M Nelson et al., *AIDS* 2011; Jan 28;25(3):335-40.
  - B Gazzard et al., AIDS 2011; Nov 28;25(18):2249-58.

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Question #2
What about PPIs
and antacids with this
complex ARV regimen?

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ARS Question #5

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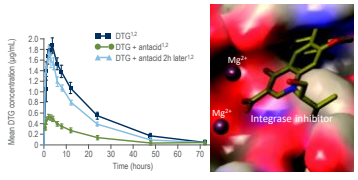
Case 1

- Does omeprazole 20 mg or Maalox® alter the absorption of any of the drugs in this regimen?
- Proton pump inhibitors like omeprazole can reduce the absorption of several ARV's, but would not be expected to affect any of the drugs in this regimen.
- Maalox® contains divalent cations (Mg^{++}) and should only be administered 2 hours before or 6 hours after DTG!

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ISEMINATION

Chelation with Cations: Integrase Inhibitor and Antacids



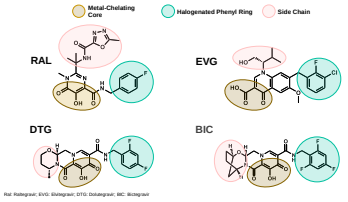
Dolutegravir should be taken 2 hours before or 6 hours after taking antacids containing polyvalent cations[1,2]

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Values shown are GLS mean ratio (90% CI)
*DTG given as 50 mg QD in study

1. Adapted from Patel P, et al. J Antimicrob Chemother 2011;66:1567–72
2. Adapted from Song I, et al. ICAAC 2009; Abstract A1-1305

Integrase Inhibitors



Ral: Raltegravir; EVG: Elvitegravir; DTG: Dolutegravir; BIC: Bictegravir

Metal-Chelating Core: Oxygen atoms chelate a pair of Mg^{2+} ions and bind the integrase catalytic active site
Halogenated Phenyl: Interacts with the integrase pocket that is normally occupied by the terminal 3' base of viral DNA

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Question #3
Drug interaction potential of sertraline?

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Case 1

- What about sertraline (SSRI antidepressant)?

- Sertraline is mainly a CYP2D6 substrate.
- ETV is a weak CYP 2D6 inducer and could modestly decrease concentrations.
- DRV/c is a weak CYP 2D6 inhibitor and is unlikely to increase concentrations.
- Clinical impact unlikely, but monitor for sertraline efficacy and increase dose if needed.
- No interactions expected with DTG.

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Case #1 continued:
The Urology Clinic!

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Case 1

- The Urology Clinic would like to start this patient on a combination of:
- Tamsulosin 0.4 mg QD
- Finasteride 5 mg QD
- Any problem adding these two drugs to this patient's regimen?

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Question #4
Drug interaction potential of meds for prostatic hypertrophy and ARVs?

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Case 1

- Can finasteride be safely administered with DTG, ETV, and DRV/c?

- Finasteride is a CYP3A4 substrate.
- ETV is a CYP inducer and could decrease concentrations, but DRV/c is a CYP inhibitor and could increase concentrations.
- Clinical impact unclear, but monitor for finasteride efficacy and unexpected toxicity.
- No interactions expected with DTG.

Case 1

- Can tamsulosin be safely administered with DTG, ETV, and DRV/c?

- Tamsulosin is a CYP3A4 and CYP 2D6 substrate.
- ETV is a CYP inducer and could decrease concentrations, but DRV/c is a CYP inhibitor and could increase concentrations.
- Tamsulosin has been safely administered with other CYP 3A4 and 2D6 inhibitors, but it is an alpha$_{1A}$ antagonist and could lower blood pressure, esp. in the elderly.
- Clinical impact unclear, but monitor for efficacy and unexpected toxicity, esp. postural hypotension.
- Start with the lowest possible dose (0.4 mg QD).

Question #5:
What are some general approaches to the management of polypharmacy?

Interventions to limit/manage polypharmacy

1) Complete medication reconciliation
- include over the counter drugs
- update at each medical visits

2) Review prescription
- Evaluate indication → discontinue unecessary drugs
- Identify medications that are treating adverse effects of other medications → discontinue drug that is causing side effect if possible
- Simplify dosing regimen
- Ensure appropriate dosing of medications
- Ensure duration of treatment is appropriate
- Check for drug-drug interactions → use ARV with low DDI potential if possible
- Check for drug-disease interactions
- Check for inappropriate drugs in elderly } Beers criteria, STOPP/START criteria
- Check for any missing medicine

Beers and STOPP criteria are used to detect inappropriate medicines including for instance:
- medicines which can lead to drug-disease interactions in eldely persons with certain diseases
- medicines associated with a higher risk of adverse drug reactions in the elderly,
- medicines that predictably increase the risk of falls in the elderly
- medicines to be avoided in case of organ dysfunction.

The START criteria consist of potential prescribing omission in elderly with specific medical conditions

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Shah S et al. Clin Geriatr Med 2012, Edelman E et al. Drugs Aging 2013, O'Mahony D et al. Age and Ageing 2015, American Geriatrics Society. J Am Geriatr Soc 2015

Avoiding inappropriate drugs

… for example, anticholinergic drugs in the elderly

Modified Anticholinergic Risk Scale



Anticholinergics
Tricyclic antidepressants
Urological spasmolytic agents

among top 10 inappropriate drugs for use in elderly

Elderly are more sensitive to adverse anticholinergic effects due to significant decrease in cholinergic receptors in the brain

Drugs with anticholinergic properties can impair cognition → increase risk of falls, negative impact on adherence

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Lemay G et al. Better prescribing in the elderly, Canadian Geriatrics Society 2012

Drug-drug interactions resources: Univ of Liverpool

HIV Drug Interactions
www.hiv-druginteractions.org

HEP Drug Interactions
www.hep-druginteractions.org



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Aging and DDI Summary

- Polypharmacy is a common issue in patients over the age of 59.
- HIV-infected patients tend to be prescribed more medications than age-matched controls.
- Certain classes of medication are more likely to cause clinically significant adverse effects in the elderly, for example drugs with anti-cholinergic side effects.
- Medication review and "de-prescribing" are important interventions to control polypharmacy.

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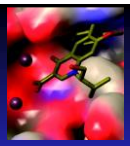
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leap» longactinghiv.org

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Question-and-Answer Session