Management of polypharmacy in the HIV ageing patient

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Model projections: aging of HIV population and comorbidities

Age distribution and number of comorbidities in HIV infected patients in USA (insured patients)

26.9% pts >65 y by 2035

Age distribution and number of comorbidities in HIV infected patients in Italy (ICONA Cohort)

29.3% pts >65 y by 2035

Predicted co-morbidities profiles in 2035
Comorbidity burden driven by moderate CVD (HT, dyslipidemia), moderate CVD + diabetes, moderate CVD + malignancy

44% pts with > 3 comorbidities by 2035

29% pts with > 3 comorbidities by 2035

Smit M et al. PLoS One 2017
Use of non-HIV drugs among individuals with and without HIV

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
Consequences of polypharmacy

Polypharmacy > 5 medications

Drug-drug interactions
- No comedication
- 1 comedication
- 2 comedication
- 3 comedication
- 4 or more comedication
- n = 5761
- n = 2233
- n = 450

Adverse drug reactions
Most common drug classes associated with ADR in elderly:
- Cardiovascular drugs
- Diuretics
- Anticoagulants
- NSAIDs
- Antidiabetics

Geriatric syndromes
- Falls
- Cognitive decline
- Orthostatic hypotension

Nonadherence
Possible causes:
- Side effects
- High pill burden
- Complex dosing regimens
- Depression
- Neurocognitive impairment
- Size of tablets
- Limited health literacy (misunderstanding of instructions)
- Health beliefs (being unconvinced about necessity of medication)


older individuals receive more comedication and thus are at higher risk for DDIs
Adherence and beliefs about chronic co-treatments vs ART

SHCS study using the **Beliefs about Medicine Questionnaire** to evaluate the perceptions of 150 patients about their ART and co-medications

- Median age **56 years**
- **83%** patients adherent to ART and **71%** patients adherent to co-treatments
- Patients had higher necessity and lower concerns scores for ART compared to co-treatments

**Prevalence of co-medications**
- Cardiovascular drugs: 75%
- Antidepressants: 42%
- Anxiolytics: 30%
- Anti-osteoporosis drugs: 28%
- Antidiabetics drugs: 15%

**Co-treatments patients would be most likely to forget or not take**
- Cardiovascular drugs: 13%
- Antidepressants/anxiolytics: 8%
- Anti-osteoporosis drugs: 4%
- Antidiabetics drugs: 1%
- Morning doses of co-meds: 11%
- Noon-time doses of co-meds: 5%
- Evening doses of co-meds: 16%

Kamal S et al. HIV Med 2018
Aging & comorbidities pose additional therapeutic challenges

- **Drug-disease interactions**: prescription of medications aggravating an existing disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug</th>
<th>Potential adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>corticosteroids</td>
<td>increase in blood glucose level</td>
</tr>
<tr>
<td>Parkinson</td>
<td>antipsychotics</td>
<td>aggravation of movement disorder</td>
</tr>
<tr>
<td>Renal failure</td>
<td>NSAIDs</td>
<td>decrease of glomerular filtration rate</td>
</tr>
</tbody>
</table>

- **Age associated changes in pharmacokinetics**

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Altered physiology with aging</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>↑ gastric pH</td>
<td>modification of drug absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>↓ albumin&lt;br&gt;↑ body fat&lt;br&gt;↓ lean muscle and total body water</td>
<td>↑ free fraction of drugs&lt;br&gt;↑ Vd of lipophilic drugs&lt;br&gt;↑ plasma concentration of hydrophilic drugs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>↓ hepatic mass&lt;br&gt;↓ hepatic blood flow</td>
<td>↓ reduced hepatic clearance</td>
</tr>
<tr>
<td>Elimination</td>
<td>↓ kidney mass&lt;br&gt;↓ glomerular filtration rate&lt;br&gt;↓ renal blood flow</td>
<td>↓ reduced renal clearance</td>
</tr>
</tbody>
</table>

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

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

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

- 2000: HIV infection
- 2000-2008: lamivudine + zidovudine + efavirenz
  
  *ARV changed to avoid DDI with treatment for Hodgkin’s lymphoma*

- since 2008: FTC + TDF + raltegravir
- VL: < 20 copies/ml; CD4: 457 cells/mm³
- other co-morbidities: depression, hypertension, atrial fibrillation (prior stroke), hyperlipidemia, urinary incontinence, constipation

- medications:
  - raltegravir 400 mg BID
  - emtricitabine 200 mg QD
  - tenofovir 300 mg QD
  - amitriptyline 50 mg QD
  - amlodipine 5 mg QD
  - lisinopril 10 mg QD
  - rivaroxaban 20 mg QD
  - rosuvastatin 5 mg QD
  - tolterodine 4 mg QD
  - sterculia 875 mg BID
  - amitriptyline 50 mg QD
  - amlodipine 5 mg QD
  - lisinopril 10 mg QD
  - rivaroxaban 20 mg QD
  - rosuvastatin 5 mg QD
  - tolterodine 4 mg QD
  - sterculia 875 mg BID
  - dry eye drops (as needed)
Case: 77-year old man

- The patient found by daughter in a state of confusion, agitation
- Clinical examination: BP 130/85 mmHg, ↑heartbeat, skin red, hot and dry, slight bilateral mydriases
- Daughter reports: patient had a cold and took diphenhydramine 25 mg for a couple of days to relieve the nocturnal cough and help with the sleep

The patient presents the signs of an anticholinergic toxicity: what do you suspect?

1) interaction between diphenhydramine and raltegravir
2) diphenhydramine overdosed as some drugs not eliminated as well in elderly
3) interaction between diphenhydramine and the other co-medications
Some answers

- **DDI between diphenhydramine and raltegravir?**
  
  NO: diphenhydramine metabolized by CYP2D6, raltegravir no inhibitory effect on CYP2D6

- **dosage diphenhydramine (25mg) not adapted for elderly individuals?**
  
  NO: usual hypnotic dose: 25-50mg (lower dose to be used in elderly)
  
  no significant effect on diphenhydramine PK in elderly vs young
  
  no different effect on mood, memory, heart rate in elderly for diphenhydramine vs placebo

BUT....


www.hiv-druginteractions.org
Inappropriate drugs in elderly

... the patient is taking several drugs with anticholinergic properties

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

Inappropriate drugs led to prescribing cascade

**Treatment**

- raltegravir
- emtricitabine
- tenofovir
- amitriptyline
- amlodipine
- lisinopril
- rivaroxaban
- rosuvastatin
- toltedrine
- sterculia
- dry eye drops

- escitalopram

**Drug Interactions**

- amitriptyline → interfere with bladder contraction + overflow incontinence was misdiagnosed!
- toltedrine → constipation, dry eyes: side effects of drugs with anticholinergic properties
- sterculia + dry eye drops + diphenhydramine precipitated anticholinergic toxicity

**Diagram**

- Inappropriate medicines
- Polypharmacy
- Prescribing cascades
- Adverse Drug Events
# 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 unnecessary 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
- Check for any missing medicine

Beers criteria
STOPP/START criteria

Beers and STOPP criteria are used to detect inappropriate medicines including for instance:
- medicines which can lead to drug-disease interactions in elderly 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

Polypharmacy and PIM in older HIV positive patients

- prescriptions of 248 patients (mean age: 58 y) from San Francisco General hospital

<table>
<thead>
<tr>
<th>Common potentially inappropriate prescribing based on STOPP criteria</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates without bowel stimulant</td>
<td>51</td>
<td>20.6</td>
</tr>
<tr>
<td>Duplicate drug classes</td>
<td>49</td>
<td>19.8</td>
</tr>
<tr>
<td>First generation antihistamines (diphendydramine, promethazine,…)</td>
<td>21</td>
<td>8.5</td>
</tr>
<tr>
<td>Aspirin dose &gt; 150 mg/day</td>
<td>19</td>
<td>7.7</td>
</tr>
<tr>
<td>Long-acting benzodiazepine (diazepam, flurazepam,…)</td>
<td>15</td>
<td>6.1</td>
</tr>
<tr>
<td>Non selective beta blocker in patients with COPD</td>
<td>14</td>
<td>5.7</td>
</tr>
<tr>
<td>Aspirin use in patients with no coronary artery disease</td>
<td>10</td>
<td>4.0</td>
</tr>
<tr>
<td>Benzodiazepines in patients with history of falls</td>
<td>6</td>
<td>2.4</td>
</tr>
</tbody>
</table>

- 54% patients had PIM
- 8% patients had contra-indicated DDI

McNicholl IA. Pharmacotherapy 2017
PIM 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

<table>
<thead>
<tr>
<th>Proportion patients</th>
<th>HIV positive patients</th>
<th>Uninfected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially inappropriate drugs</td>
<td>52%</td>
<td>29%</td>
</tr>
<tr>
<td>Anticholinergic risk score ≥ 3</td>
<td>17%</td>
<td>4%</td>
</tr>
<tr>
<td>Mean nb non HIV medications</td>
<td>8 medications</td>
<td>6 medications</td>
</tr>
</tbody>
</table>

Reasons medication-related problem were more common in HIV infected patients could include that HIV specialists are less familiar with geriatric prescribing.
Interventions to limit/manage polypharmacy

3) Prioritize medications according to risk and benefit within the context of an individual patient’s care goals, current level of functioning, life expectancy and patient preferences.

Deprescribing = planned and supervised process of dose reduction or stopping of medications that may be causing harm or no longer provide benefit.

Example: patient with severe dementia is unlikely to benefit from preventive drugs such as biphosphonates.

Also determine patient expectations and preferences – is present day quality of life more important than prolonging life.

Treatment goals need to be adapted. Tight glycemic control can do more harm to elderly as expose patients to more immediate threats of hypoglycemia while may do little to change natural history of disease.

Algorithm for drug discontinuation

1. No benefit
   Significant toxicity OR no indication OR obvious contraindication OR cascade prescribing?
   - Yes
   - No

2. Harm outweighs benefit
   Adverse effects outweigh symptomatic effect or potential future benefits?
   - Yes
   - No

3. Symptom or disease drugs
   Symptoms stable or nonexistent?
   - Yes
   - No

4. Preventive drugs
   Potential benefit unlikely to be realized because of limited life expectancy?
   - Yes
   - No

   Continue drug therapy
   Discontinue drug therapy
   Restart drug therapy

Website for deprescribing of medications: MedStopper: http://medstopper.com
http://deprescribing.org website providing algorithms on deprescribing of PPI, BZD and antidiabetics
STOPPFrail criteria (Lavan HA et al. Age and Ageing 2017)

Scott IA et al. JAMA Intern Med 2015
## Dual ARV regimens as maintenance strategy

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Number of Patients</th>
<th>Undetectable viral load at week 48 (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOL</td>
<td>Tenofovir + efavirenz</td>
<td>71</td>
<td>81.7</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>ATLAS-M</td>
<td>Atazanavir/r + lamivudine</td>
<td>133</td>
<td>89.5</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>SALT</td>
<td>Atazanavir/r + lamivudine</td>
<td>140</td>
<td>78.6</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>OLE</td>
<td>Lopinavir/r + lamivudine</td>
<td>118</td>
<td>91.5</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>DUAL</td>
<td>Darunavir/r + lamivudine</td>
<td>126</td>
<td>89%</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>KITE</td>
<td>Lopinavir/r + raltegravir</td>
<td>39</td>
<td>94.9</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>SPARE</td>
<td>Darunavir/r + raltegravir</td>
<td>28</td>
<td>85.7</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Dat’AIDS</td>
<td>Atazanavir + raltegravir</td>
<td>185</td>
<td>65.4</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>Marinaro et al.</td>
<td>Atazanavir + raltegravir</td>
<td>102</td>
<td>81.4</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>HARNESS</td>
<td>Atazanavir/r + raltegravir</td>
<td>72</td>
<td>69.4</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>PROBE</td>
<td>Darunavir/r + rilpivirine</td>
<td>30</td>
<td>96.7</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>MARCH</td>
<td>Maraviroc + PI/r</td>
<td>157</td>
<td>84.1</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>GUSTA</td>
<td>Maraviroc + darunavir/r</td>
<td>62</td>
<td>72.6</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>Calza et al.</td>
<td>Raltegravir + etravirine</td>
<td>38</td>
<td>81.6</td>
<td>Improved kidney, bone, and lipid parameters</td>
</tr>
<tr>
<td>LATTE</td>
<td>Cabotegravir + rilpivirine</td>
<td>160</td>
<td>76</td>
<td>Non-inferior, improvement in bone markers</td>
</tr>
<tr>
<td>LAMIDOL</td>
<td>Dolasetravir + lamivudine</td>
<td>104</td>
<td>97</td>
<td>Improve in bone biomarkers</td>
</tr>
<tr>
<td>TivEdo</td>
<td>Dolasetravir + rilpivirine</td>
<td>50</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>SWORD 1 &amp; 2</td>
<td>Dolasetravir + rilpivirine</td>
<td>513</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>

**Disadvantage:** unfavorable metabolic endpoint DDIs

**Attractive options**

**Expert opinion:** Some dual antiretroviral regimens are safe and efficacious, particularly as maintenance therapy. At this time, combinations of dolutegravir plus rilpivirine represent the best dual regimen. Longer follow-up and larger study populations are needed before supporting dolutegravir plus lamivudine. In contrast, dual therapy based on maraviroc is less effective. Although dual regimens with boosted protease inhibitors plus either lamivudine or raltegravir may be effective, they are penalized by metabolic side effects and risk for drug interactions.


**Analysis of GEPPPO Cohort (multi-centic italian Cohort including HIV geriatric patients > 65 y)**

In multivariate logistic regression analysis, multimorbidity and polypharmacy were predictive for:
- mono or dual therapy
- NRTI sparing regimens
- TDF sparing regimens

Nozza S et al. JAC 2017
Interaction potential of antiretroviral agents

Inhibition/induction of hepatic CYPs, glucuronidation, or drug transporters
- maraviroc
- rilpivirine
- dolutegravir
- raltegravir

Inhibition/induction intestinal CYPs or drug transporters
- maraviroc
- rilpivirine
- tenofovir prodrugs
- PI/ritonavir
- PI/cobicistat
- EVG/cobicistat

Change gastric pH
- atazanavir
- rilpivirine

Chelation with mineral supplements
- integrase inhibitors

Absorption

Excretion
- tenofovir
dolutegravir
cobicistat
ritonavir

Metabolism

Adapted from Roden DM et al. Nat Rev 2002
Drug-drug interactions studies with ARV often lacking

Amlodipine (Norvasc) product label

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.
Approach to quantify drug-drug interactions with ARVs

Magnitude of drug-drug interaction depends on:

- **Fraction of disposition pathway mediated by the enzyme of interest (DPI)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>DPI&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>triazolam</td>
<td>0.96</td>
<td>almost exclusively metabolized by CYP3A4</td>
</tr>
<tr>
<td>quetiapine</td>
<td>0.68</td>
<td>CYP3A4 contributes to 26% of the overall metabolism</td>
</tr>
<tr>
<td>zolpidem</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

- **Inhibitor (InR) and inducer (IcR) strength**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>InR&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>Strength of InR</th>
<th>Inducer</th>
<th>IcR&lt;sub&gt;CYP3A4&lt;/sub&gt;</th>
<th>Strength of IcR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ritonavir</td>
<td>1.0</td>
<td>strong inhibitor</td>
<td>rifampicin</td>
<td>0.91</td>
<td>strong inducer</td>
</tr>
<tr>
<td>cimetidine</td>
<td>0.22</td>
<td>weak inhibitor</td>
<td>efavirenz</td>
<td>0.58</td>
<td>moderate inducer</td>
</tr>
</tbody>
</table>

- These parameters can be derived from available DDI studies involving similar drug combinations and reporting the magnitude of DDI

- These parameters can then be used to predict the magnitude of DDI for uncharacterized drug combinations involving ARVs to provide guidance on how to adjust dosage

Stader F et al. EACS Conference 2017
All predicted DDI magnitudes were within the 2 fold range of observed clinical data.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>DPI</th>
<th>↑ AUC with RTV (InR = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>0.054</td>
<td>1.1 fold</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>0.078</td>
<td>1.1 fold</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0.205</td>
<td>1.3 fold</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.468</td>
<td>1.9 fold</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>0.507</td>
<td>2.0 fold</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.752</td>
<td>4.0 fold</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.852</td>
<td>7.1 fold</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.915</td>
<td>11.7 fold</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.958</td>
<td>24.0 fold</td>
</tr>
</tbody>
</table>

Stader F et al. EACS Conference 2017
DDI between ritonavir and escitalopram or amlodipine

Escitalopram is metabolized by CYP3A4, CYP2C19, CYP2D6

- Escitalopram 20 mg alone
- Escitalopram 20 mg + ritonavir 600 mg

Simulation of amlodipine levels +/- ritonavir

Data from clinical DDI studies
- amlodipine + IDV/r BID ≈ 2 fold increase in amlodipine AUC (Glesby M et al. CPT 2005)
<table>
<thead>
<tr>
<th>Drug class</th>
<th>ARV</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI, antacids, H2 inhibitors</td>
<td>RIL, ATV</td>
<td>Decreased absorption of HIV drug can result in treatment failure. Contra-indicated with PPI, antacids, H2 inhibitors: separate drug intake</td>
</tr>
<tr>
<td>Calcium, mineral supplements, antacids</td>
<td>DTG, EVG, RAL</td>
<td>Integrase inhibitors will form a complex with divalent cations at the level of GI and will not be absorbed, risk of treatment failure. Separate drug intake</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>PI/r, PI/c, EVG/c</td>
<td>Increase risk of Cushing syndrome (inhibition of corticosteroids metabolism). If possible avoid PI/r, PI/c, EVG/c. Risk of CS not only limited to oral corticosteroids administration (cave: eye drops, local injection, topical administration...). Triamcinolone, budesonide, fluticasone, mometasone are contra-indicated.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>PI/r, PI/c, EVG/c</td>
<td>Avoid tricyclic antidepressants as can cause anticholinergic effets, sedation, delirium and orthostatic hypotension. Side effects reinforced by inhibition of metabolism</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>PI/r, PI/c, EVG/c</td>
<td>Avoid due to increased sensitivity in elderly (increased risk of cognitive impairment, falls and fractures). Side effects reinforced by inhibition of metabolism. Use at the lowest dose and for a short duration. Midazolam, triazolam are contra-indicated.</td>
</tr>
<tr>
<td>Chemotherapy drugs</td>
<td>PI/r, PI/c, EVG/c</td>
<td>Multiple chemotherapy drugs undergo metabolism via CYP pathways. Increased risk of chemotherapy related toxicities. Favor ARV with a low potential for metabolic DDI (RAL, DTG)</td>
</tr>
</tbody>
</table>
### Selected DDI of interest in aging HIV-infected patients

<table>
<thead>
<tr>
<th>Drug class</th>
<th>ARV</th>
<th>comment</th>
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</table>
| Anticoagulants vitamin K antagonists | PI/r  
PI/c  
EVG/c   | Metabolized by CYP2C9, CYP3A4. Adjust dosage by closely monitoring INR. Dosage adjustment might be needed when switching booster (RTV induces CYP2C9, Cobi: no induction). |
| Direct acting anticoagulants      | PI/r  
PI/c  
EVG/c   | Substrates of CYPs and/or transporters therefore significant DDIs expected. Their effect cannot be measured routinely. Limited data on management of DDIs therefore should be avoided with boosted regimens. |
| Calcium channel blockers          | PI/r  
PI/c  
EVG/c   | Inhibition of metabolism is expected to increase calcium channel inhibitors concentrations and thereby the hypotensive effect. Start at lower dose and titrate based on response to therapy. |
| Statins                           | PI/r  
PI/c  
EVG/c   | Can significantly increase exposure of some statins and thus increase risk of rhabdomylosis. Simvastatin, lovastatin: contra-indicated. Other statins: start with low dose and titrate to effect. Use of standard dose is possible with pitavastatin |
| Antidiabetics                     | PI/r  
PI/c  
EVG/c  
DTG     | Metformin: DTG increases metformin exposure (inhibition OCT2). Dose adjustment should be considered when starting DTG. Saxagliptin: limit to 2.5 mg daily with boosted regimens Exenatide, linagliptin, liraglutide, sitagliptin, vildagliptin: no DDIs with boosted regimens |
| NSAIDs                            | TDF          | Avoid long term use and closely monitor renal function                                                                                                                                                 |
Cave when switching pharmacokinetic booster

Switch from ATV/r QD to DRV/c
→ reduction of warfarin dose by 60%

PK/PD study for dabigatran + RTV or Cobi

- dabigatran alone
  - PK: dabigatran adm 2 h before RTV
  - PK: dabigatran adm together with RTV

- dabigatran alone
  - PK: dabigatran adm 2 h before Cobi
  - PK: dabigatran adm together with Cobi

PK

- dabigatran adm 2 h before RTV: reduction of warfarin dose by 60%
- dabigatran adm together with RTV: no significant effect on PK and PD

PD

- Maximum Thrombin Time (120 sec)
- Inhibitory/inducing effect on P-gp

- 127% AUC
- AUC TT

- Only inhibitory effect on P-gp

ritonavir and cobicistat: similar inhibition of CYP3A4
BUT
ritonavir has inducing effects whereas cobicistat does not

Tseng A et al. AIDS 2017

Kumar P et al. AAC 2017
Drug-drug interactions resources

HIV Drug Interactions
www.hiv-druginteractions.org

HEP Drug Interactions
www.hep-druginteractions.org
Summary

- Polypharmacy ↑ risk of DDIs, drug related side effects and medications errors
- Elderly particularly at risk due to ↑ age related co-morbidities and age related physiological changes which impact the risk-benefit ratio of many drugs
- For an appropriate management of polypharmacy:
  - medication reconciliation
  - review prescriptions
    - indication ==> stop unnecessary treatments
    - dose (e.g. adapt to renal function)
    - duration of treatment
    - drug-drug and drug-diseases interactions
    - inappropriate drugs
    - missing medication
  - prioritize medications according to risk and benefit for an individual patient and considering patient preferences
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Thank you for your attention