Polypharmacy

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HIV & Aging Workshop 2018
Aging of HIV population: model projections

Age distribution and number of PLWH with ≥ 3 comorbidities

Netherlands

By 2030
39% pts > 60 years old
28% pts > 3 comorbidities

USA

By 2035
27% pts > 65 years old
44% pts > 3 comorbidities

Italy

By 2035
29% pts > 65 years old
29% pts > 3 comorbidities

Comorbidity burden driven by cardiovascular diseases, diabetes and malignancies

Comorbidities & polypharmacy in uninfected versus infected elderly

- **GEPPO Cohort** (prospective multicentric italian cohort including > 65 years old individuals)
- **1258 HIV positive** (65-74 y: 965; > 75 y: 292) and **315 HIV negative** (224 and 91)

Overall, prevalence of comorbidities was comparable among HIV infected/uninfected elderly (64%/59%). After stratification based on HIV infection duration, individual comorbidities dyslipidemia, chronic kidney disease, diabetes were more prevalent in infected compared to uninfected individuals.

Overall, prevalence of polypharmacy was higher among HIV infected/uninfected elderly (37%/24%).
# Prevalence of polypharmacy in PLWH

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

Polypharmacy > 5 medications

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)

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

Drug-drug interactions

older individuals receive more comedications and thus are at higher risk for DDIs

Aging & comorbidities pose additional therapeutic challenges

- **Drug-disease interactions**

  **Examples**

<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, ↑ body fat, ↓ lean muscle and total body water</td>
<td>↑ free fraction of drugs, ↑ Vd of lipophilic drugs, ↑ plasma concentration of hydrophilic drugs</td>
</tr>
<tr>
<td>Metabolism</td>
<td>↓ hepatic mass, ↓ hepatic blood flow</td>
<td>↓ reduced hepatic clearance</td>
</tr>
<tr>
<td>Elimination</td>
<td>↓ kidney mass, ↓ glomerular filtration rate, ↓ renal blood flow</td>
<td>↓ reduced renal clearance</td>
</tr>
</tbody>
</table>

Progressive decline in physiologic parameters important for drug disposition is noted with age. The «pharmacological» age cut-off for elderly is difficult to define because it is not known when these changes affect drug pharmacokinetics significantly. Lack of studies correlating changes in physiologic parameters to drug pharmacokinetics.

Stader F & Marzolini C. Clin Pharmacokinet 2018
Aging & comorbidities pose additional therapeutic challenges

- **Age associated changes in pharmacodynamics:**
  - changes in affinity of some medications to receptor sites or in number of receptors ⇒ affect efficacy or increase sensitivity to certain drugs
  - regulation of some physiologic 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>

**PD effects could be aggravated by inhibition of metabolism by PI/r, cobicistat**

Wooten JM. South Med J 2012
68-year old woman

Admitted in September 2016 to emergency room: lost balance, fell and broke arm. Reports repetitive falls since the summer.

At admission:  
- BP: 102/69 mmHg, heartbeat: normal  
- eGFR: 71 ml/min/1.73m²  
- glucose, electrolytes, liver parameters: normal  
- several recent and old bruises, slight confusion

### Medical history

<table>
<thead>
<tr>
<th>Year</th>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>HIV infection</td>
<td><strong>raltegravir</strong> (400 mg BID) + <strong>FTC</strong> (200 mg QD) + <strong>TDF</strong> (300 mg QD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VL: undetectable, CD4: 467 cells/mm³</td>
</tr>
<tr>
<td>2013</td>
<td>hyperlipidemia</td>
<td><strong>rosuvastatin</strong> (5 mg QD)</td>
</tr>
<tr>
<td>2015</td>
<td>depression</td>
<td><strong>amitriptyline</strong> (50 mg QD)</td>
</tr>
<tr>
<td>Jun 2016</td>
<td>hypertension</td>
<td><strong>amlodipine</strong> (10 mg QD)</td>
</tr>
<tr>
<td>Jul 2016</td>
<td>ankle oedema</td>
<td><strong>furosemide</strong> (20 mg QD)</td>
</tr>
<tr>
<td>Aug 2016</td>
<td>overactive bladder</td>
<td><strong>tolterodine</strong> (4 mg QD)</td>
</tr>
<tr>
<td>Sept 2016</td>
<td>xerostomia, constipation</td>
<td><strong>anetholtrithion</strong> (25 mg TID) and <strong>sterculia</strong> (875 mg BID)</td>
</tr>
</tbody>
</table>

### Treatment

- **raltegravir** (400 mg BID) + **FTC** (200 mg QD) + **TDF** (300 mg QD)
- **rosuvastatin** (5 mg QD)
- **amitriptyline** (50 mg QD)
- **amlodipine** (10 mg QD)
- **furosemide** (20 mg QD)
- **tolterodine** (4 mg QD)
- **anetholtrithion** (25 mg TID) and **sterculia** (875 mg BID)

What is the most probable explanation for the recurrent falls?
Drug-drug interaction with antiretroviral therapy

- **Raltegravir**: UGT1A1 metabolism, no inhibitory effects on CYPs or UGTs
- **Emtricitabine** and **tenofovir**: renal elimination, no inhibitory effects on transporters
- **Furosemide**: renal elimination, weak inhibitor of OAT1
- **Amlodipine**: CYP3A4 metabolism

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### Graphs

**Furosemide**
- No Interaction Expected
- Potential Weak Interaction

**Amlodipine**
- No Interaction Expected

Pharmacodynamic effect in elderly

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

there are some other issues....
Drugs with anticholinergic effects and adverse effects in elderly

... the patient is taking several drugs with anticholinergic properties: amitriptyline and tolterodine

- Anticholinergic drugs are considered as inappropriate 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, cause constipation, xerostomia, dizziness, blurred vision.
• Ankle oedema recognized adverse effect of amlodipine (risk higher in women, older patients)
• Unlike oedema caused by fluid retention, amlodipine induced oedema due to capillary pressure resulting in fluid loss from the capillaries. Does not respond to diuretic treatment.


Treatment
- Raltegravir + 3TC + TDF
- Rosuvastatin
- Amitriptyline ➔ escitalopram
- Amlodipine ➔ lisinopril
- Furosemide
- Tolterodine
- Anetholtrithion
- Sterculia
Interventions to limit/manage polypharmacy

1) Complete medication reconciliation
   • Include over the counter drugs
   • Update at each medical visit

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 ➔ ARV with low DDI potential when possible
   • Check for drug-disease interactions
   • Check for inappropriate drugs in elderly
   • Check for any missing medicine

Beers and STOPP criteria to detect inappropriate prescribing
START criteria to detect prescribing omission

Polypharmacy and inappropriate prescribing in elderly PLWH

- prescriptions of 248 PLWH (mean age: 58 years) from San Francisco General hospital

**Common comorbidities**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>60</td>
</tr>
<tr>
<td>Depression</td>
<td>50</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>40</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>30</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10</td>
</tr>
</tbody>
</table>

**Number of prescribed comedications**

- **Number of prescribed non HIV medications**
  - 0 to 5: 10 patients
  - 6 to 10: 20 patients
  - 11 to 15: 30 patients
  - 16 to 20: 40 patients
  - > 20: 50 patients

**Inappropriate prescribing**

<table>
<thead>
<tr>
<th>Inappropriate prescribing</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 (diphenhydramine, 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>

Inappropriate prescribing in 54% patients
Contra-indicated DDIs in 8% patients

McNicholl IA. Pharmacotherapy 2017
Inappropriate prescribing more frequent in PLWH

- prescriptions of 94 PLWH (mean age: 64 years) from SF HIV over 60 Cohort
- prescriptions of 28 age and gender matched uninfected patients (mean age: 65 years) 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 problems were more common in PLWH could include that HIV specialists are less familiar with geriatric prescribing
Non-HIV comedications count and adverse health outcomes

Analysis of PLWH and uninfected individuals in the US Veterans Affairs Healthcare system showed an association between increased non-HIV medication count and increased risk for hospitalization or mortality for both PLWH and uninfected individuals.
Interventions to limit/manage polypharmacy

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

Patient centered treatment model

Single disease treatment model

79-year old woman

- COPD
- Diabetes
- Osteoporosis
- Hypertension
- Arthrosis

Pharmacological treatments
- 12 drugs
- 5 daily dosing

Non-pharmacological treatments
- 14 non-pharmacological treatments

Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases: Implications for Pay for Performance JAMA 2005

- Evidence based clinical practice guidelines mostly focus on management of single disease
- Following single disease guidelines may result in care that is impractical or harmful
  - adapt treatment goals (examples: tight glycemic control can do harm as expose elderly to hypoglycemia while may not change natural history of disease also preventive medicine become questionable in patients with limited life expectancy)

**Algorithm for drug discontinuation**

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

Website for deprescribing of medications: MedStopper: [http://medstopper.com](http://medstopper.com)

[http://deprescribing.org](http://deprescribing.org) website providing algorithms on deprescribing of PPI, BZD and antidiabetics

NEW: STOPPFrail criteria (Lavan HA et al. Age and Ageing 2017): criteria to help clinicians decide when to stop drugs in frail patients with poor prognosis
Dual antiretroviral regimens as maintenance strategy

Major studies using dual antiretroviral therapy as maintenance

<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>Tenofvir + 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>89.9</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>DatAIDS</td>
<td>Atazanavir + raltegravir</td>
<td>185</td>
<td>65.4</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>Marina 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 + raltegravir</td>
<td>72</td>
<td>69.4</td>
<td>Lower efficacy</td>
</tr>
<tr>
<td>PROBE</td>
<td>Darunavir/r + rilpiviride</td>
<td>30</td>
<td>96.7</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>MARCH</td>
<td>Maraviroc + Plus</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>Non-inferior</td>
</tr>
<tr>
<td>Calza et al.</td>
<td>Raltegravir + etravirider</td>
<td>38</td>
<td>81.6</td>
<td>Improved kidney, bone, and lipid parameters</td>
</tr>
<tr>
<td>LATTE</td>
<td>Cabotegravir + rilpiviride</td>
<td>160</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>LAMIDOL</td>
<td>Dolutegravir + lamivudine</td>
<td>104</td>
<td>97</td>
<td>Improve in bone biomarkers</td>
</tr>
<tr>
<td>TiVedo</td>
<td>Dolutegravir + rilpiviride</td>
<td>50</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>SWORD 1 &amp; 2</td>
<td>Dolutegravir + rilpiviride</td>
<td>513</td>
<td>95</td>
<td>Non-inferior. Improvement in bone markers</td>
</tr>
</tbody>
</table>

Disadvantage:
- unfavorable metabolic endpoint
- DDIs

Attractive options
- minimal metabolic side effects
- lack of kidney/bone effects

Analysis of GEPO Cohort (multi-centric Italian Cohort including HIV geriatric patients > 65 years old)

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
Drug-drug interaction potential of antiretroviral agents

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

PI/ritonavir
PI/cobicistat
EVG/cobicistat
efavirenz
etravirine
nevirapine

Inhibition/induction intestinal CYPs or drug transporters
- maraviroc
- doravirine
- rilpivirine
- bictegravir
- tenofovir prodrugs

Inhibition of renal drug transporters
- tenofovir
- bictegravir
- dolutegravir
- cobicistat
- ritonavir

Change gastric pH
- atazanavir
- rilpivirine

Chelation with mineral supplements
- integrase inhibitors

Adapted from Roden DM et al. Nat Rev 2002
## Selected drug-drug interactions of interest in aging PLWH

<table>
<thead>
<tr>
<th>Drug class</th>
<th>ARV</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPIs, antacids, H2 inhibitors</td>
<td>RIL</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></td>
<td>ATV</td>
<td></td>
</tr>
<tr>
<td>Calcium, mineral supplements, antacids</td>
<td>INSTIs</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</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></td>
<td>PI/c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>PI/r</td>
<td>Avoid tricyclic antidepressants as can cause anticholinergic effects, sedation, delirium and orthostatic hypotension. Side effects reinforced by inhibition of metabolism</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>PI/r</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></td>
<td>PI/c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy drugs</td>
<td>PI/r</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, BIC)</td>
</tr>
<tr>
<td></td>
<td>PI/c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EVG/c</td>
<td></td>
</tr>
</tbody>
</table>

## Selected drug-drug interactions of interest in aging PLWH

<table>
<thead>
<tr>
<th>Drug class</th>
<th>ARV</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>TDF</td>
<td>Avoid long term use and closely monitor renal function</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>PI/r, PI/c, EVG/c</td>
<td>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.</td>
</tr>
<tr>
<td>Statins</td>
<td>PI/r, PI/c, EVG/c, DTG</td>
<td>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</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>PI/r, PI/c, EVG/c, DTG</td>
<td>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</td>
</tr>
<tr>
<td>Anticoagulants, vitamin K antagonists</td>
<td>PI/r, PI/c, EVG/c</td>
<td>Metabolized by CYP2C9, CYP3A4. Adjust dosage by closely monitoring INR. Dosage adjustment might be needed when switching booster (RTV induces CYP2C9, Cobi: no induction).</td>
</tr>
<tr>
<td>Direct acting anticoagulants</td>
<td>PI/r, PI/c, EVG/c</td>
<td>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.</td>
</tr>
</tbody>
</table>
Switch from ATV/r QD to DRV/c

Cave when switching pharmacokinetic booster

PK/PD study for dabigatran + RTV or Cobi

PK

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

PD

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

Ritonavir and cobicistat:

- Similar inhibition of CYP3A4
- Ritonavir has inducing effects whereas cobicistat does not

Switching from ATV/r QD to DRV/c:

- Reduction of warfarin dose by 60%

Tseng A et al. AIDS 2017; Marzolini C et al. JAC 2016

Kumar P et al. AAC 2017
Although clopidogrel and prasugrel have comparable platelet inhibition potencies, in clinical trials prasugrel has demonstrated greater platelet inhibition and lower rates of recurrent atherothrombotic events compared to clopidogrel. This might be explained by prasugrel more efficient bioactivation and higher concentrations of the active metabolite.
PK interaction: clopidogrel versus prasugrel

**PK effect**

**Study design**

- Session 1 or 2: clopidogrel 300mg
- Prasugrel 60mg
- >10 days wash out

**Clopidogrel active metabolite**

- Plasma concentration of clopidogrel AUMC (ng/mL)
- AUC -69%

**Prasugrel active metabolite**

- Plasma concentration of prasugrel AUMC (ng/mL)
- AUC -52%

Second independent clinical study:

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

- Itkonen MK et al. Clin Pharmacol Ther 2018


12 healthy volunteers treated with antiplatelet agent alone

9 patients treated with boosted ARV + antiplatelet agent

antiplatelet drug alone

antiplatelet drug + RTV/Cobicistat boosted ARV
PD interaction: clopidogrel versus prasugrel

Platelet receptor blockade measured with VerifyNow® (www.accriva.com)

<200 P2Y12 Reaction Units (PRU) suggests P2Y12 inhibition effect

Clopidogrel
44% HIV patients did not achieve platelet inhibition

Prasugrel
all HIV patients prasugrel platelet inhibition remains adequate

➔ prasugrel should be preferred over clopidogrel in presence of boosted regimens

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.

Second independent clinical study:
average inhibition of platelet aggregation decreased:
51% (clopidogrel alone) vs 31% (clopidogrel + RTV)

Itkonen MK et al. Clin Pharmacol Ther 2018

Drug-drug interactions profiles of antiretroviral drugs

n = 700 comediations

- **boosted ARV**
  - Efavirenz
  - Etravirine
- **Raltegravir**
- **Dolutegravir**
- **Bictegravir**
- **Etravirine**
- **Rilpivirine**
- **Doravirine**

Legend:
- Green: no interaction
- Yellow: interaction of weak clinical relevance
- Orange: interaction of clinical relevance
- Red: deleterious interaction

www.hiv-druginteractions.org
HIV drug-drug interactions resources

University of California  arv.ucsf.edu

Toronto General Hospital  app.hivclinic.ca

University of Liverpool  www.hiv-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:
  
  o medication reconciliation
  o 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
  o prioritize medications according to risk and benefit for an individual patient and considering patient preferences
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