Managing drug-drug interactions in patients with multiple comedications

Canadian HIV Clinical Forum
Toronto, ON

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Disclosures

• Unrestricted educational grants:
  – Abbvie, Gilead, Merck, Viiv

• Speaker honoraria/consulting:
  – Abbvie, Gilead, Merck

• Advisory board:
  – Viiv
Outline

• Polypharmacy in HIV
• Pharmacology of InSTIs
• Managing DDIs (case-based)
• Resources
Retrospective comparison of 10,318 ageing patients (median age 56) vs 13,302 younger patients (median age 42)

- Patients diagnosed with HIV before 2000 ("experienced ageing") had ≥1 comorbidity (62%) and were receiving at least 1 comedication (71%)
- Most common comedications: CNS agents (44.6%), antilipid agents (44.2%)

InSTIs used in 23% of the population, and were used significantly more often in patients with comorbidities and coprescriptions (p<0.0001)
Prevalence of drug-drug interactions in the era of HIV integrase inhibitors: a retrospective clinical study

- 145 patients started ART between 01/2009-04/2016; median 42 yo, 75% male, CD4 260
  - 42% on InSTI (mostly DTG & EVG), 30% PI, 28% NNRTI
- N=113 (78%) on comedications, median 4 (1-18) per patient
- Polypharmacy in 26%, correlated with age (p=0.024)

- Of 113 taking comedications, 63% had potential DDIs, 1% had contraindicated DDI
- PI-ART risk factor for potential or contraindicated DDI; significantly lower risk with DTG but not EVG

Figure 2. Third agent in ART as independent risk factor for drug-drug interaction

<table>
<thead>
<tr>
<th>Risk Factor for DDI</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-based ART</td>
<td>0.77 (0.32-1.84)</td>
</tr>
<tr>
<td>PI-based ART</td>
<td>2.57 (1.06-6.19)</td>
</tr>
<tr>
<td>DTG-based ART</td>
<td>0.35 (0.15-0.82)</td>
</tr>
<tr>
<td>EVG-based ART</td>
<td>2.51 (0.66-9.58)</td>
</tr>
</tbody>
</table>

Plot of the odds ratios (OR) of third agents in ART as risk factor for potential or contraindicated drug-drug interaction (DDI). Data based on the antiretroviral-treated patients with co-medication (n = 113) with omission of those patients where DDI was solely due to the backbone (n = 3).
## Pharmacology of InSTIs

<table>
<thead>
<tr>
<th></th>
<th>Raltegravir</th>
<th>Elvitegravir</th>
<th>Dolutegravir</th>
<th>Bictegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>400 mg BID or 1200 mg QD</td>
<td>150 mg/150 mg cobicistat</td>
<td>50 mg QD or BID</td>
<td>50 mg QD</td>
</tr>
<tr>
<td><strong>Available as single agent?</strong></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>STR?</strong></td>
<td>no</td>
<td>EVG/c/F/TDF EVG/c/F/TAF</td>
<td>DTG/ABC/3TC DTG/RPV</td>
<td>BIC/F/TAF</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>UGT1A1</td>
<td>CYP3A4</td>
<td>UGT1A1 (major), CYP3A4 (10-15%)</td>
<td>UGT1A1, CYP3A4 (similar)</td>
</tr>
<tr>
<td><strong>Inhibition effects</strong></td>
<td>none</td>
<td><em>Cobicistat:</em> CYP3A4&gt;&gt;2D6, P-gp, BCRP, OATP1B1/3, MATE1</td>
<td>OCT2, MATE1</td>
<td>OCT2, MATE1</td>
</tr>
<tr>
<td><strong>Induction effects</strong></td>
<td>none</td>
<td>2C9 (modest)</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

*Isentress Product Monograph, June 2017; Genvoya Product Monograph, April 2018; Tivicay Product Monograph, May 2018; Biktarvy Prescribing Information (US), February 2018.*
Mr. T

- Hyperlipidemia, hypertension, atrial fibrillation: rosvuastatin 40 mg, diltiazem 360 mg, warfarin 12 mg

- 07/2016: changed to dolutegravir/ABC/3TC. INR 2.35
- 3 weeks later: INR 8.9, ++bruising. Rx vitamin K, hold warfarin
- After 2 weeks, restarted warfarin 7 mg daily, INR 2.33
  - 40% warfarin dose reduction required
Lack of Significant Interactions between Dolutegravir and Comedications
Don’t Forget What Patient Is Discontinuing!

YOU SELECTED:

Lopinavir/Ritonavir & Warfarin

SUMMARY/RECOMMENDATION:

Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing lopinavir/ritonavir therapy.

DATA:

Three case reports where INR declined significantly and warfarin dosage was increased 40-140% in order to achieve therapeutic INR following initiation of lopinavir/ritonavir therapy.\(^1\) \(^2\) \(^3\) Mechanism presumed to be 2C9 induction of warfarin metabolism by ritonavir.

Monitor for changes in INR and adjust anticoagulant dose accordingly when starting and discontinuing therapy.
## Using Warfarin with Antiretrovirals: Pay Attention to the Booster and the Partner ARV

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Impact on Warfarin</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir-boosted PIs</td>
<td>↓ warfarin via 2C9, 1A2 induction, often requiring warfarin dose ↑ of 45-100%</td>
<td>51 yo male switched from atazanavir/r to raltegravir: INR ↑ 5.7, required 23% ↓ warfarin</td>
</tr>
<tr>
<td>Cobicistat-boosted PIs</td>
<td>Potential ↑ warfarin via CYP3A4 inhibition</td>
<td>Patient switched from atazanavir/ritonavir to darunavir/cobicistat, required 60% ↓ warfarin</td>
</tr>
<tr>
<td>Elvitegravir-cobicistat</td>
<td>↓ warfarin via 2C9 induction by elvitegravir</td>
<td>42 yo male switched from efavirenz/F/TDF to E/C/F/TDF. On day 20, INR was 1.2, required 60% dose ↑ warfarin</td>
</tr>
</tbody>
</table>

2 patients on the stable levothyroxine for several years developed clinical and biological hyperthyroidism following a switch from ritonavir-boosted PI to dolutegravir ART.

Levothyroxine is metabolised by deiodination and UGT; patients may have required higher doses due to UGT induction by ritonavir.

In both cases, clinical symptoms and decreased TSH values resolved after levothyroxine dose reduction of 40-50%.

Berger et al. Antiviral Ther 2016;10.3851/IMP3107
Mr. T – follow up

- Switch from lopinavir/r (CYP3A4 & transporter inhibitor, 2C9 inducer) to dolutegravir (OCT2 inhibitor)

<table>
<thead>
<tr>
<th></th>
<th>Lopinavir/r impact</th>
<th>After switch to dolutegravir</th>
<th>Time Frame</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (S: 2C9, R: 1A2, 3A4, 2C19)</td>
<td>↓</td>
<td>May need ↓ warfarin dose</td>
<td>2-3 weeks</td>
<td>INR, signs of bleeding</td>
</tr>
<tr>
<td>Diltiazem (3A4 substrate)</td>
<td>↑</td>
<td>May need ↑ diltiazem dose</td>
<td>Few days</td>
<td>Heart rate, blood pressure</td>
</tr>
<tr>
<td>Rosuvastatin (OATP1B1, OATP1B3, BCRP)</td>
<td>↑</td>
<td>May need ↑/↓ rosuvastatin dose</td>
<td>1-2 months</td>
<td>Lipids (removal of LPVr may improve lipids)</td>
</tr>
</tbody>
</table>
Mr. B

- April 2018: diagnosed with type 2 diabetes.
- Started metformin 500 mg BID and sitagliptin 100 mg daily.
GLUCOPHAGE®
Metformin Hydrochloride Tablets
Manufacturer’s standard
500 mg, 850 mg

Oral Antihyperglycemic Agent

Drug-Drug Interactions

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, trandolapril, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such an interaction has been observed between metformin and oral cimetidine in normal healthy volunteers. In both single and multiple-dose metformin-cimetidine drug interaction studies, there was a 60% increase in peak metformin plasma and whole blood concentrations, as well as a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination.

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sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval (Québec) H7V 0A3

Date of revision:
March 2, 2018
The Effect of Dolutegravir on the Pharmacokinetics of Metformin in Healthy Subjects

![Graph A](image)

![Graph B](image)

<table>
<thead>
<tr>
<th></th>
<th>DTG 50 mg OD</th>
<th>DTG 50 mg q12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin</td>
<td>↑ 79%</td>
<td>↑ 145%</td>
</tr>
<tr>
<td>Δ AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metformin</td>
<td>↑ 66%</td>
<td>↑ 111%</td>
</tr>
<tr>
<td>Δ C&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Song et al. JAIDS 2016;72:400-7.
<table>
<thead>
<tr>
<th></th>
<th>Hivclinic.ca</th>
<th>Liverpool</th>
<th>Lexicomp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grading</strong></td>
<td>Yellow</td>
<td>Amber</td>
<td>D – consider therapy modification.</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
<td>Limit MET to 1000 mg/day when starting MET or DTG.</td>
<td>Limit MET to 1000 mg/day when starting MET or DTG.</td>
<td>Limit MET to 1000 mg/day when used with DTG.</td>
</tr>
<tr>
<td><strong>Data</strong></td>
<td>PK study in healthy volunteers (Song et al. 2016); retrospective cohort (Gervasoni et al. 2017)</td>
<td>PK study in healthy volunteers (US prescribing information.)</td>
<td>PK study in healthy volunteers (Song et al. 2016); retrospective cohort (Gervasoni et al. 2017); US prescribing information.</td>
</tr>
</tbody>
</table>
How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life?

Original research article

Evaluation of the concurrent use of dolutegravir and metformin in human immunodeficiency virus-infected patients

AIDS 2017, Vol 31 No 15

Dolutegravir and metformin: a case of hyperlactatemia
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Patients</th>
<th>Lab</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gervasoni et al. <em>JAIDS 2017</em></td>
<td>15</td>
<td>Retrospective; all on DTG once daily. Did not specify MET doses used.</td>
<td>No changes in HgbA1c, glycemia; no association between DTG concentrations and DM biomarkers.</td>
<td>Combination well tolerated.</td>
</tr>
<tr>
<td>Masich et al. <em>Int J STD AIDS 2017</em></td>
<td>19</td>
<td>One on DTG BID, rest QD. 7 on MET &gt;1 g/d prior to DTG initiation, 1 pre-emptive dose reduction (from 2 g to 1 g/d).</td>
<td>HgbA1c stable or ↓ at months 3 &amp; 6.</td>
<td>N=3 GI distress and n=3 hypoglycemic Sx leading to MET dose ↓ (n=2) or d/c (n=2). 50% who experienced ADRs were on MET &gt;1 g/day.</td>
</tr>
<tr>
<td>Naccarato et al. <em>AIDS 2017</em></td>
<td>1</td>
<td>77 yo woman on DTG/ABC/3TC and MET/sitagliptin (stable 1 g/50 mg BID x 3 years).</td>
<td>Venous lactate 4.9 mmol/L; held MET, lactate ↓ 1.7. Restarted DTG with RPV, lactate ↑ 2.7.</td>
<td>Severe lipoatrophy, weight loss. Lactate normalized when switched to RAL/RPV.</td>
</tr>
</tbody>
</table>

*normal venous lactate: 0.5-2.3 mmol/L*
Bictegravir is a less potent inhibitor of OCT2 than dolutegravir.

Established and Potentially Significant Drug Interactions: Alteration in Regimen May be Recommended

Mr. O

- 58 year old male, HIV+ 1989, bipolar disorder, hyperlipidemia, GERD, urinary incontinence, drowsiness; 2 falls in last year
- Call from family physician: patient would like to increase his darifenacin dose, but MD concerned re: ++ drugs and potential interactions
Mr. O: medication list

- Dolutegravir/ABC/3TC once daily
- Acyclovir 800mg once daily
- Sertraline 50mg BID
- Haloperidol 5mg QHS
- Risperidone 2mg TID
- Trazodone (50mg) 4 tablets QHS
- Benztropine 2mg QAM
- Clonazepam 2mg BID
- Divalproex 1 g QHS

- Baclofen 20mg QHS
- Darifenacin ER 7.5mg once daily
- Ranitidine 150mg BID
- Rosuvastatin 10mg once daily
- Tylenol #3 (300/30/15mg) 1-2 tablets Q6H PRN
- Salbutamol HFA (100mcg) 2 puffs QID PRN
- Docusate Sodium 100 mg BID PRN

18 medications: 3 antiretrovirals (1 tablet), 15 co-medications
- No significant ART-nonART interactions identified
  - Neither database had all comedication listed
39 drug-drug interactions identified, none involving ART:
- **D** therapy modification (6)
- **C** monitor (30)
- **B** no action needed (3)

2 Duplicate Therapy interactions

Pharmacokinetic interactions (3):
- Darifenacin (2D6 inhibitor)-2D6 substrates

Pharmacodynamic interactions (36):
- Opioid-CNS depressant
- QTc-QTc
- Opioid-anticholinergic
- Opioid-serotonin modulator
- CNS-CNS depressant
- Anticholinergic-anticholinergic

### Drugs in this analysis:
- Acetaminophen and Codeine
- Acyclovir
- Baclofen
- Benzopine
- ClonazePAM
- Darifenacin
- Docusate
- Haloperidol
- RanITidine
- Rosuvastatin
- Salbutamol (INT)
- Sertraline
- TraZODone
- Trumeq
- Valproic Acid and Derivatives

### Drug-Drug Interactions

| D | Acetaminophen and Codeine (Opioid Analgesics) – Baclofen (CNS Depressants) |
| D | Acetaminophen and Codeine (Opioid Analgesics) – ClonazePAM (CNS Depressants) |
| D | Acetaminophen and Codeine (Opioid Analgesics) – Haloperidol (CNS Depressants) |
| D | Acetaminophen and Codeine (Opioid Analgesics) – RisperiDONE (CNS Depressants) |
| D | Haloperidol (QTC-Prolonging Agents (Moderate Risk)) – RisperiDONE (QTC-Prolonging Agents (Moderate Risk)) |
| D | Sertraline (Selective Serotonin Reuptake Inhibitors) – TraZODone (Serotonin Reuptake Inhibitor/Antagonists) |
| C | Acetaminophen and Codeine (CNS Depressants) – Sertraline (Selective Serotonin Reuptake Inhibitors) |
| C | Acetaminophen and Codeine (Codeine) – Darifenacin (CYP2D6 Inhibitors (Moderate)) |
| C | Acetaminophen and Codeine (Opioid Analgesics) – Benzopine (Anticholinergic Agents) |
| C | Acetaminophen and Codeine (Opioid Analgesics) – Sertraline (Serotonin Modulators) |
| C | Acetaminophen and Codeine (Opioid Analgesics) – TraZODone (Serotonin Modulators) |
| C | Baclofen (CNS Depressants) – ClonazePAM (CNS Depressants) |
| C | Baclofen (CNS Depressants) – Haloperidol (CNS Depressants) |
| C | Baclofen (CNS Depressants) – RisperiDONE (CNS Depressants) |
| C | Baclofen (CNS Depressants) – Sertraline (Selective Serotonin Reuptake Inhibitors) |
| C | Benzopine (Anticholinergic Agents) – Darifenacin (Anticholinergic Agents) |
| C | Benzopine (Anticholinergic Agents) – Haloperidol (Anticholinergic Agents) |
Mr. O: Assessment

• Potential concern with increasing darifenacin dose:

• Pharmacodynamic:
  – ↑ risk of anticholinergic side effects, incl. constipation and drowsiness
  – Contributing to falls?

• Pharmacokinetic:
  – Darifenacin is a CYP2D6 inhibitor, may ↑ exposures of haloperidol, risperidone; further increase risk of anticholinergic side effects
Ms. N

- 38 year old woman from Zimbabwe, HIV+ 2007
- 2013: diagnosed with CMV retinitis, CD4 46, VL 334,158
  - Rx valganciclovir, TMP/SMX, nystatin
  - Baseline GT: wild type. Started elvitegravir/c/TDF/FTC, VL<40
- Remained suppressed for 7 months, then VL 204.
  - good adherence, no new medications, taking with food
- Two months later: VL 314
  - Upon repeat questioning, has been taking psyllium for last few months to help with diarrhea
Psyllium interaction

- Scientific name: Plantago ovata
  - Also known as blond psyllium, dietary fiber, ispaghula, psyllium husk, etc.
  - Chief ingredient in commonly used bulk laxatives e.g., Metamucil

- Can reduce absorption of medications such as lithium, digoxin, levothyroxine, carbamazepine

A Bulking Agent May Lead to Adrenal Insufficiency Crisis: A Case Report

Salma Ahi¹, Majid Esmaeilzadeh², Elham Kayvanpour², Farbod Sedaghat-Hamedani¹, and Seyed Hossein Samadanifard¹

¹ Department of Internal Medicine, Rasul Akram Hospital, Tehran University of Medical Science, Tehran, Iran
² Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

Received: 17 Jan. 2011; Received in revised form: 21 May 2011; Accepted: 14 Jun. 2011

Abstract- Adrenal insufficiency is a life-threatening disorder which must be treated with glucocorticoid replacement and needs permanent dose adjustment during patient’s different somatic situations. Insufficient glucocorticoid doses result in adrenal crisis and must be treated with intravenous hydrocortisone. The patient was known with Adrenal insufficiency and was treated optimally with fludrocortisone and prednisolone since seven years with no history of adrenal crisis. The patient was admitted with abdominal pain, weakness, fatigue and nausea developed 3-4 days after taking psyllium, a bulking agent, prescribed by a surgeon to diagnose anal fissure. Detailed medical history, physical examinations, laboratory and imaging examinations did not approve any other cause of adrenal crisis. Psyllium may interfere with gastrointestinal absorption of prednisolone and/or fludrocortisone and trigger acute adrenal crisis in patients with adrenal insufficiency.

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Psyllium (Lexi-Drugs)

**Metabolism/Transport Effects**  None known.

**Drug Interactions**  There are no known significant interactions.

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**Metamucil® Preparations**

psyllium hydrophilic mucilloid

Dietary Fibre Supplement—Bulk-forming Laxative—Cholesterol-lowering Agent

Procter & Gamble

NPN(s): 02174812, 02174790, 02174762, 02174804, 02247034

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**Drug Interactions:**

Limited information available in the literature, including a single letter to the editor on lithium and one pharmacokinetic study with carbamazepine, suggests that psyllium bulk laxatives may interfere with the absorption of other drugs administered concomitantly. The mechanism is unknown, however, it is likely to involve a delay in drug absorption when the drug is mixed in the hydrated viscous psyllium gel matrix in the gastrointestinal tract. Because it is not possible to predict which drugs are of concern, patients are advised not to take Metamucil within 2 hours of taking any other medications.
Interactions with Drugs

CARBAMAZEPINE (Tegretol)
Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = D
Blond psyllium might reduce carbamazepine absorption and serum levels \cite{539,92194}.

DIGOXIN (Lanoxin)
Interaction Rating = Minor Be watchful with this combination.
Severity = Moderate • Occurrence = Unlikely • Level of Evidence = B
Theoretically, psyllium might reduce digoxin absorption. However, some evidence suggests that the effect of psyllium on digoxin absorption is not clinically significant \cite{10098}.

ETHINYL ESTRADIOL
Interaction Rating = Minor Be watchful with this combination.
Severity = Moderate • Occurrence = Unlikely • Level of Evidence = D
 Concurrent use of blond psyllium with ethinyl estradiol results in a slight increase in the extent of ethinyl estradiol absorption and a slower rate of absorption. This is unlikely to be clinically significant \cite{12421}.

LITHIUM
Interaction Rating = Moderate Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = D
There are cases of reduced serum lithium levels associated with psyllium use. This was reversed when psyllium was stopped \cite{540,92194}. The fiber in blond psyllium might decrease the absorption of lithium.
Case report

Significant interaction between activated charcoal and antiretroviral therapy leading to subtherapeutic drug concentrations, virological breakthrough and development of resistance

Alice L Tseng1,2*, Charles La Porte3,4, Irving E Salit1,5

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2Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada
3Ottawa Hospital Research Institute, Ottawa, ON, Canada
4Present address: Janssen-Cilag BV, Tilburg, the Netherlands
5Department of Medicine, University of Toronto, Toronto, ON, Canada

*Corresponding author e-mail: alice.tseng@uhn.ca

A 42-year-old, treatment-experienced woman, virologically suppressed on tenofovir/emtricitabine and boosted atazanavir, experienced virological breakthrough, drop in CD4+ T-cell count and undetectable drug concentrations. Adherence to treatment was confirmed, but repeat testing yielded similar results. After 2 months, the patient stated that she had been taking activated charcoal to manage gastrointestinal symptoms associated with her combination antiretroviral therapy, but she had recently discontinued the charcoal. Atazanavir concentrations were therapeutic but the patient’s viral load rebounded and genotype testing revealed new reverse transcriptase mutations. The patient was changed to zidovudine, lamivudine, and boosted darunavir and achieved viral suppression. At 1 year follow-up, her viral load remained <40 copies/ml. According to the drug interaction probability scale, our patient experienced a probable drug interaction between activated charcoal and atazanavir/ritonavir leading to virological breakthrough and development of resistance.
Summary

- Comorbidities and polypharmacy are common concerns in the aging population
- Identifying and managing drug interactions:
  - Regularly update medication history
  - Encourage patient to use single pharmacy
  - Consider DDI potential whenever starting or stopping medication
  - Utilize >1 drug interaction resource when possible
- Ensure communication with other HCP
- Encourage patients to be pro-active in asking about potential interactions before starting anything new
Obtain a complete (best possible) medication history at each visit

<table>
<thead>
<tr>
<th>Type of Drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs not taken by mouth</td>
<td>Creams, eye drops</td>
</tr>
<tr>
<td>Temporary or once in a while drugs</td>
<td>Puffers for allergy season, antibiotics, antacids, etc.</td>
</tr>
<tr>
<td>You mean <em>those</em> are drugs?</td>
<td>Vitamins, herbal products, supplements, complementary medicine</td>
</tr>
<tr>
<td>“Do I really need to tell you” drugs</td>
<td>Recreational agents, PDE5 inhibitors, steroids</td>
</tr>
</tbody>
</table>

*including new drugs, new dose, drugs stopped

NB: Many of above available without a prescription
KEEP CALM AND LOVE YOUR PHARMACIST