ART in the Era of Polypharmacy

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Declaration of Interests

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See https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/
ART in the Era of Polypharmacy

1. **Ageing** – effect on PK, PD and biological ageing

2. **Multi-morbidity** – and Polypharmacy

3. **DDIs** – in the era of unboosted INSTIs
Is PK Meaningfully Different?

- \textbf{Disentangling chronological age} from GFR, and BMI
  - TFV, FTC, 3TC exposure renally driven
  - Good evidence all NNRTIs / ATV / Ral / DTG unaffected by age
  - No evidence that other bPI / INSTI exposure is affected to any meaningful or actionable degree

- \textbf{Effect on compartments}
  - Sparse data, weak evidence (abstracts)
  - ↑ CSF EFV and TFV >60y [Croteau - abstract]

- \textbf{Effect of menopause}
  - ↑ plasma/genital tract [TFV] in post-menopausal women [abstract- Patterson]
  - (Trend for ↓ Ral in CVF [Cotterell])

- \textbf{Effect of cellular senescence}
  - ↓ TFV-dp & FTC-TP with increasing T cell senescence (p16\textsuperscript{INK4a} expression) [Dumond]
  - Telomere length ↑ with TDF/FTC in NEAT001 [Stella-Ascariz]
  - Mitochondria – confounded by prior AZT/d4T/ddI [Payne]

- \textbf{Considerations with injectables}

- \textbf{Adherence}
POPPY: PK, age and renal function

Regression analysis beta coefficient at 95% CI

- TFV / FTC / 3TC exposures associated with eGFR, after adjusting for age, bPI use, BMI, comeds
Post Menopausal Women

Pharmacokinetic

- Literature inconclusive, examples of clinical relevance hard to come by
- Increased oestrogen and progesterone alter hepatic enzyme activity (↓elimination, ↑exposure)
- Female sex hormones may play a dominant role in gender-based PK differences
- Midazolam clearance does not fluctuate with menstrual cycle
- Plasma trough TFV not different in pre-M (28) vs post-M (22) women
- FGT expression of drug transporters in post-menopausal women
- Vaginal microbiome and TFV?

Pharmacodynamic

- Sex hormones and receptors
- Susceptibility to certain toxicities- eg bone
- HIV acquisition and progression (and prevention ?)

Gervasoni et al. JAC 2013;68:1206
Nichol et al J Clin Pharm 2014;54:574
Cellular Senescence and NRTI phosphorylation

- Chronological age relatively uninformative for NRTI-phosphorylation
- Frailty phenotype and p16\textsuperscript{INK4a} gene expression (N = 91)
- Population PK model developed

- Higher p16\textsuperscript{INK4a} associated with ↑Cl (and ↓ concentrations) of TFV-dp and FTC-tp from PBMCs
- Plasma Cl for TFV / FTC associated with CrCl
- No independent effect of chronological age or frailty

Can ARVs accelerate biological ageing?

**Putative Mechanisms**

- Oxidative Stress
- Telomere shortening with accelerated cellular senescence
- Accumulation of lamin A precursors (a nuclear envelop protein)

*Caution: caveats over ‘premature aging’*

- Telomere length conserved by telomerase (TERT subunit)
- TDF/3TC/FTC/ABC/ZDV/ddI all shown to inhibit TERT activity

Leannsyah et al. JID 2013; 207:115
Torres at al. Lab Invest. 2014; 94(2): 120
NEAT001/ANRS143: telomere length

RCT evidence
- NEAT001 substudy (N = 201)
- TL changes over 96w
- TL significantly increased only in subjects on TDF/FTC arm
- not significantly confounded by age, gender, ethnicity, T since diagnosis, baseline VL/CD4 count, tobacco/alcohol, statins, or hepatitis C
Mitochondria

- ATP synthesis and ROS homeostasis
- NRTIs cause mtDNA mutations which clonally expand
- Myopathy, wasting and premature frailty

N = 37 PLWH
- Molecular analysis of mtDNA defects (single fibres)
- Phosphorous MRS imaging to study in-vivo muscle mitochondrial oxidative function
- Older NRTIs – complex I & IV deficient fibres
- Contemporary NRTIs (TDF, FTC, 3TC, ABC) complex I deficient fibres
- Age effects confounded by duration of NRTI exposure

Physiological Factors affecting HIV Drug Disposition

**Young**
- toxicity
- failure

**Elderly**
- toxicity
- failure

### PD – toxicities
- ↑ sensitivity, ↓ tolerance
  - BMI
  - eGFR

### PK – ↑ plasma exposure
- BMI
- eGFR

#### Factors:
- Declining eGFR
  - (~1% per year)
- ↓ body weight
  - (greater dose/kg)
- Body morphology
  - (distribution, elimination)
  - Sarcopenia
  - ↓ fat: ↓ plasma volume
- Gastric pH, absorption
  - achlorhydria, motility, ↓ absorption
- ↓ albumin
  - Unbound fraction
- Liver
  - altered liver blood flow
  - ↓ CYP2D6, CYP2B6 activity, Phase II
- Post-menopausal women
  - CNS
  - Genital tract
- Higher inter-patient variability

*Adapted from Calcagno et al. Infection 2015;43:509*
### Anti-Cholinergic Burden

- Several different anticholinergic burden scoring systems
- Many different toolkits – eg Beers
- Sedation/confusion generally under-recognised

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimuscarinics (bladder)</td>
<td>Avoid (consider mirabegron if required)</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Domperidone, ondanstron preferred</td>
</tr>
<tr>
<td>1st gen antihistamines</td>
<td>Avoid. Prefer lodatidine, fexofenadine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Caution, even with SSRIs</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Caution with tramadol, pethidine</td>
</tr>
<tr>
<td>Sedatives</td>
<td>Caution, prefer newer hypnotics with ↓ hangover</td>
</tr>
<tr>
<td>Anti-psychotics</td>
<td>Hypotension. Start low go slow. Withdraw cautiously</td>
</tr>
<tr>
<td>Anti-Parkinson</td>
<td>Avoid benzotropine, trihexyphenidyl for treating extrapyramidal effects of antipsychotics. Prefer procyclidine</td>
</tr>
<tr>
<td>Anti-spasmidics</td>
<td>Avoid – questionable effectiveness</td>
</tr>
</tbody>
</table>

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De Vreese et al. PLOS ONE 13(10): e0205897
PresQUIPP B140, July 2016
Pharmacodynamic Effects with Age

Effect of age on amlodipine pharmacodynamics

- Amlodipine PD significantly impacted by age: more pronounced ↓ systolic BP in elderly
- Age affects regulation of physiologic processes (arterial baroreflex function)
- Elderly also more prone to thiazide induced orthostatic changes

Leenen FH et al. J Cardiovasc Pharmacol 2010
Clinical Impact of Multi-morbidity and Polypharmacy

**US Veterans Affairs Healthcare system**
- HIV+ (N = 9473) and HIV– (N = 39,812)
- Polypharmacy independently associated with ↑ hospitalisations & mortality
- VACS score corrects for mortality associated with physiologic measures, frailty, multiple morbidities and burden of co-morbidities

**Modena HIV Metabolic Clinic (2006-2015)**
N = 3581; 11,565 PY fu
Frailty Index Tool – 37 variables spanning multiple systems
Frailty can identify those most at risk of harm from polypharmacy
www.hiv-druginteractions.org
Managing DDIs – Considering Individual Risk - Benefits

- **No interaction expected**: no action required
- **Potential weak interaction**: no action required
- **Potential interaction**: Dose adjustment or additional monitoring may be required
- **Contraindicated / should not be co-administered**

This is the problem!
Managing DDIs – Considering Individual Risk - Benefits

This is the problem!

- No interaction expected
- Potential weak interaction: no action required
- Potential interaction: Dose adjustment or additional monitoring may be required
- Contraindicated / should not be co-administered
Case History

59 y male

1 HIV-positive 1999, treatment experienced poor adherence
   NNRTI (K103N) resistance
   suppressed on Truvada + DRVr

2 Chronic Kidney Disease
   multiple strokes – mild cognitive impairment
   Atrial fibrillation (dabigatran)
   Type 2 diabetes – poorly controlled (metformin, gliclazide)
   Hypertension – poorly controlled, BP 150-190/90-115 (amlodipine 10mg)
   Hyperlipidaemia – poorly controlled (pravastatin 40mg)
- TDF + LPVr + Deteriorating eGFR
- Dabigatran + RTV + renal impairment
- Poor BP & glucose control

- Poor BP and lipid control
- Waiting for big stroke!
- Pravastatin + RTV – DDI

- Poor glucose control
- RTV-gliclazide: risk of hypoglycaemia

- Poor adherence, high pill burden
- Risk of multiple DDIs
- Co-morbidities not well managed
Cobicistat vs Ritonavir in 2019

- Guilt by Association
- Important differences
- RTV- mixed inhibitor (CYP3A4, PgP) and inducer (eg UGT)
- Cobi – inhibitor only

Ritonavir induces UGT, whereas cobicistat does not...

- Gervasoni, JAC 2017 -
NOACs

- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Anti-Xa or TDM useful?

Dabigatran
NOACs

- Rivaroxaban & Apixaban – CYP3A4 and PgP substrate
- Dabigatran – PgP substrate
- Anti-Xa or TDM useful?

Effect of Renal Impairment

Simulation using PBPK modelling

- dabigatran alone
- dabigatran + verapamil
- dabigatran 2 h before verapamil
- observed clinical data

Dabigatran

Doki K et al. CPT Pharmacometrics Syst Pharmacol 2019, www.hiv-druginteractions.org

Potential Interaction

Daranavi + ritonavir

Dabigatran

Coadministration possible. Caution in case of mild or moderate renal impairment as dabigatran dose might need to be reduced in presence of DRV/r.
PK interaction: clopidogrel versus prasugrel

Study design

12 healthy volunteers treated with antiplatelet agent alone

9 patients treated with boosted ARV + antiplatelet agent

Healthy volunteers

HIV patients with boosted ART

Session 1 or 2

cloridogrel 300mg

prasugrel 60mg

PK:

0, 0.25, 0.5, 1, 1.5, 2, 3, 4h

PO:

0 and 4h

Session 1 or 2

cloridogrel 300mg

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PK:

0, 0.25, 0.5, 1, 1.5, 2, 3, 4h

PO:

0 and 4h

12 healthy volunteers treated with antiplatelet agent alone

9 patients treated with boosted ARV + antiplatelet agent

Itkonen MK et al. Clin Pharmacol Ther 2018

Marsousi N et al. Clin Pharmacokinet 2018

Second independent clinical study:

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

Itkonen MK et al. Clin Pharmacol Ther 2018
PD interaction: clopidogrel versus prasugrel

Marsousi N et al. Clin Pharmacokinet 2018

12 healthy volunteers treated with antiplatelet agent alone

9 patients treated with boosted ARV + antiplatelet agent

Study design

Second independent clinical study:
average inhibition of platelet aggregation:
\( \downarrow 51\% \) (clopidogrel alone) vs \( \downarrow 31\% \) (clopidogrel + RTV)
Itkonen MK et al. Clin Pharmacol Ther 2018

→ prasugrel preferred over clopidogrel with boosted ART

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. Bravo I et al. BJCP 2018
- TDF + bPI + Deteriorating eGFR
- Dabigatran + RTV + renal impairment
- Poor BP & glucose control

- Poor BP and lipid control
- Waiting for big stroke!
- Pravastatin + RTV – DDI

- Poor glucose control
- RTV-gliclazide : risk of hypoglycaemia

**Switch away from TDF – eg Taf/FTC (avoid ABC)**

bPI – simplify to cobicistat + DRV/ATV ? *(beware different effect of RTV vs cobi on Dabigatran)*

bPI – possibility of switching to RAL / DTG / BIC to ↓ DDIs *(think about metformin)*
Outpatient ‘Polytherapy Management Service’ (600 screened, 82 on ARV-psychotropics)

- antidepressants (citalopram, duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine)
- antipsychotics (haloperidol, olanzapine, quetiapine, risperidone and lamotrigine)
- 55% had suboptimal concentrations of psychotropics
- HIV-ve controls – 26% suboptimal

- >50% of patients (n=549) failed to achieve target lipids – evidence of suboptimal dosing of statin due to concern of DDI.

- 55% of patients (n=82) had plasma antidepressant and/or antipsychotic drug levels below target (sub-therapeutic) – due to concern of DDI.
Changing Patterns of ART Use

- **ABC/3TC/DTG** – younger > older
- Patients <50 were taking their (median) third (IQR: 2-4) regimen at time of analysis, while those ≥50 were on their fourth (IQR: 2-6) regimen

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[https://statepiaps7.jhsph.edu/naaccord/](https://statepiaps7.jhsph.edu/naaccord/)

Rebeiro et al. ID Week 2019

Okoli et al. HIV Glasgow Conference 2018; P263
Multi-morbidity Clusters

Study included 1073 PLWH (mean age 52 years) from the POPPY cohort

- Comorbidities co-occur in specific patterns
- Better understanding how comorbidities cluster together would enable the development of targeted interventions and guidelines addressing specifically the needs of PLWH with multiple comorbidities

De Francesco D et al. Open Forum Infect Dis 2018
Co-morbidity clusters – DDI potential

Liverpool DDI Database - % Amber or Red

Boosted ATV, DRV, EVG
47-61%

Boosted ATV, DRV, EVG
37-55%

Boosted ATV, DRV, EVG
28-53%

Interaction Potential (%)
Prevalence of ‘Clinically Significant’ DDIs in HIV Cohorts by Calendar Year

Definitions vary, generally equivalent to Amber / Red in Liverpool tool

% Clinically Significant DDIs

Europe
USA
SS Africa

Europe

Year

% with DDI


Madrid (22,945)
INI use 51%

France (9,076) >65y
INI use 48%

Steroids (29%)
PPI (27%)
Lercanidipine (11%)
Alfuzosin (9%)
Amiodarone (3%)
Simvastatin (3%)
DOAC (3%)

DDIs associated with $2,693 additional cost per year

Barcelona (1,259)
INI use 14.5%

Steroids (51% of Red DDIs)
Quetiapine (14% of Red DDIs)
Clopidogrel (7% of Red DDIs)
Domperidone (7% of Red DDIs)
Simvastatin (6% of Red DDIs)

UK (4,360)
INI use 27%

Sildenafil
Quetiapine
PPIs
OHCs

Swiss (9,034)
INI use 41.7%

Steroids (19.6%)
Quetiapine (19.6%)
PPIs (15.8%)
Clopidogrel 11.4%)

France (9,076) >65y
INI use 48%

Steroids (29%)
PPI (27%)
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DDIs associated with $2,693 additional cost per year

Shah. CROI 2007, Abstr 573
Marzolini. JAC 2011;66:2107–11
Evans Jones. Clin Infect Dis
Seden. JAC 2015;70(12):3017–22
Okoli. HIV Drug Therapy, Glasgow 2018, P263
Demessine. Open Forum Infect Dis. 2019;6(3):otf051
López-Centeno. CID 2019 Aug 20
Deutschmann. EACS conference 2019; Basel. Abst PS13/3
Sangiovanni. AIDS Res Hum Retrovir 2019;35:430-33

GeSIDA 2021
- Madrid Health Records - ↑polypharmacy with HIV, across all age groups
- Most frequent: CNS, GI, cardiovascular drugs
- Of 729 ‘RED’ DDIs, corticosteroids accounted for 375 (51.4%), followed by anti-psychotics (14%), anti-thrombotics (12%) and statins (6%)
ADVANCE: BMI categories over time (obese at BL excluded)
NA-ACCORD (N=24,001) (PI (7,436), NNRTI (11,825), INSTI (4,740))
17 NA-ACCORD cohorts,
Treatment-naïve, starting ART 2007-2016
DTG & RAL > EVGc/bPIs >> NNRTI
- NA-ACCORD (N=21,516) (PI (6.667), NNRTI (10,553), INSTI (4,286))
- Treatment-naïve, starting ART 2007-2016
- Incident DM (HbA1c >6.5%, DM-specific meds, DM diagnosis+DM meds)
- Shorter f-u for INSTIs
- Some INSTI/PI regimens may confer increased risk of DM

Rebeiro et al. IDWeek 2019
ART in the Era of Polypharmacy

Modern ART

• ARVs have potential for interactions
  
  PIs (EVGc) > NNRTIs > MVC > INSTI > NRTIs

• Relative risk for DDIs reduced with unboosted INSTIs

• Absolute risk remains - DDIs still affect ~20-30% patients on ART

• Patients most at risk of harm from DDIs
  
  ≥5 medications
  
  ≥3 comorbidities (≥3)
  
  Frail, neurocognitive impairment, falls
  
  Fragmented care, poor communication

• Physicians only correctly identify a third of clinically significant DDIs

• Need for full medicines reconciliation

• Need for DDI resources

Miller et al Pharmacother 2007;27:1379
Evans-Jones et al. CID 2010;50:1419
Spencer et al Am Heart J 2005;150:838

GeSIDA 2019