
David Back
University of Liverpool
August 2014
Overview

1. Some general principles
2. Why drug interactions occur
3. There are more risky ARVs and more risky co-meds for DDIs
4. DDIs are not going away with an Aging Population.
5. DDIs: we need management strategies.
6. What is on the horizon?
Durable suppression of HIV-1 replication requires delivery of drug to target cells at concentrations that exceed the susceptibility of the virus strain(s) infecting the patient.
*In vitro* susceptibility and target trough concentrations

Drug [C] corresponding to IC\(_{50}\) or IC\(_{90}\)

Measured trough Concentration in patient
Pharmacological profile of a QD drug

- Drug concentrations in plasma over a dosing interval at steady state.
- All drug levels are well above the in-vitro PA-IC\textsubscript{90}

Personal communication/data from Professor D Back
RELATIONSHIP BETWEEN DTG TROUGH CONCENTRATION & VIRAL LOAD REDUCTION

Phase IIa, dose-ranging, placebo-controlled, 10-day monotherapy study

DTG is associated with a well characterised exposure-response relationship

Subjects with HIV-1 RNA <50 c/mL are represented by orange-bordered circles
Open circles with lines denote mean standard deviation

Model fit: $E_{\text{max}} = -2.6, IC_{50} = 0.036 \mu g/mL$

Day 11 log_{10} viral load change from baseline

$C_\tau (\mu g/mL)$

c/mL, copies/mL; $E_{\text{max}}$, maximum effect

Adapted from Min S, et al. AIDS 2011; 25:1737–45
Whether you give a drug once or twice/three times a day is largely governed by the **Half Life**: this parameter is the key to Forgiveness.
PK of HIV Drugs With Different Half-lives

Adapted from Taylor S et al AIDS 2007; 21: 1673-1682
Antiretroviral drug half-lives

Why Drug-Drug Interactions (DDIs) occur
3 Distinct mechanisms
- Chelation with cations
- Change in gastric pH
- Altered enzymes or transporters in enterocyte
Chelation with Cations: Integrase Inhibitor and Antacids (polyvalent cations)

Dolutegravir should be taken 2 hours before or 6 hours after taking antacids containing polyvalent cations\(^{1,2}\)

Values shown are GLS mean ratio (90% CI)

*DTG given as 50 mg QD in study

Change in Gastric pH: Rilpivirine & Proton Pump Inhibitors

Dissolution is pH dependent

Small Intestine

Co-meds affecting pH

- Co-administration of Omeprazole 20 mg reduced rilpivirine exposure by 40%
- Combination of rilpivirine with PPIs is contraindicated

Altered Enzyme Activity: CYP3A4 inhibition

(A) Intestine – drug metabolized

(B) Intestine – inhibition

Simeprevir is a mild inhibitor of CYP3A4 in intestine but not in the liver.

So Simeprevir increases the exposure (AUC) of Oral Midazolam by 45%.
Mechanisms of DDIs: Hepatic Clearance

- Enzyme & transporter induction or inhibition

  **Inducers:**
  - rifampicin, rifabutin, efavirenz, nevirapine, phenytoin, carbamazepine, SJW, dexamethasone,

- Inhibitors:
  - ritonavir, cobicistat, macrolide antibiotics, cimetidine, omeprazole, ketoconazole, GFJ, verapamil, sertraline, fluoxetine, cyclosporine, telaprevir, boceprevir.

Questions?
- Impact of Liver disease on a DDI (*Healthy subjects v patients with HCV*)
- Impact of Pharmacogenetics on a DDI

CYP=cytochrome P450;
The Importance of Hepatic Enzymes & Transporters

Proportion of drugs that are substrates for major CYP enzymes

CYP 3A isozymes are the most abundant in the liver

Mechanisms of DDIs: Renal Clearance

Active Tubular Secretion of Creatinine and Tenofovir

- A small percentage of creatinine is secreted via the proximal tubule.
- Some TFV is secreted via proximal tubule.

Diagram:
- Blood vessel connected to Proximal Tubule Cell
  - Cr
  - TFV
  - OCT2
  - OAT1
  - OAT3
  - MRP4
  - MATE1
- Urinary space
  - Creatinine filtered from the glomerulus
  - Cr

References:
- Lepist EI, Ray AS. Expert Opin Drug Metab Toxicol 2012;8:433–48
Drugs interfering with Creatinine tubular transporters

Creatinine → OCT2 (Basolateral) → Renal tubular cell → MATE1 (Apical) → Creatinine → Urine

Inhibition by:
- Rilpivirine
- Dolutegravir

Inhibition by:
- Cimetidine
- Trimethoprim
- Ritonavir
- Cobicistat

Adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724
SPRING 2: Change in serum creatinine levels to 48 weeks

Mean change from baseline in creatinine (µmol/L)

Week 2 4 8 12 16 24 32 40 48
–10 –5 0 5 10 15 20 25 30

Subjects receiving each NRTI background, n (%)

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<tr>
<th>NRTI Background</th>
<th>DTG</th>
<th>RAL</th>
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<tr>
<td>TDF/FTC</td>
<td>242 (59)</td>
<td>247 (60)</td>
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<tr>
<td>ABC/3TC</td>
<td>169 (41)</td>
<td>164 (40)</td>
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</table>

Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282
Drugs interfering with Tenofovir tubular transport

- **Inhibition by:** Ritonavir
- **Inhibition by:** Diclofenac

**Blood** → **OAT1** → **Renal tubular cell** → **MRP4** → **Urine**

**Active Tubular Secretion**

**OAT1** and **MRP4** are transport proteins involved in the secretion of Tenofovir into the urine.

Adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724
Boosted PIs increase tenofovir exposure

**Table 1: effects of protease inhibitors on tenofovir, Geometric mean ratio (90% confidence intervals)**

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<th>Protease Inhibitor</th>
<th>Effect on Cmax</th>
<th>Effect on AUC</th>
<th>Effect on Cmin</th>
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<td>Lopinavir (7)</td>
<td>1.15 (1.07-1.22)</td>
<td>1.32 (1.25-1.38)</td>
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<td>Atazanavir (8)</td>
<td>1.34 (1.20-1.51)</td>
<td>1.37 (1.30-1.45)</td>
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<td>Darunavir (9)</td>
<td>1.24 (1.08-1.42)</td>
<td>1.22 (1.10-1.35)</td>
<td>1.37 (1.19-1.57)</td>
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Should the dose of tenofovir be reduced to 200-250mg/day, when combined with protease inhibitors?

Andrew Hill, Saye Khoo, David Back, Department of Molecular and Clinical Pharmacology, Liverpool University, UK
Anton Pozniak, Marta Boffito, St Stephens Centre, Chelsea and Westminster Hospital, London, UK

International Workshop on HIV Clinical Pharmacology, Washington, USA, May 2014 [poster]
Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration

M Bickel,1 P Khaykin,1 C Stephan,1 K Schmidt,1 M Buettner,2 K Amann,2 T Lutz,3 P Gute,3 A Haberl,1 H Geiger,4 HR Brodt1 and O Jung4

- Retrospective analysis of 89 patients with diclofenac prescriptions
- 68.5% treated with TDF regimen
- 31.5% treated with TDF-sparing regimen
- 13 patients (14.6%) developed AKI after initiating diclofenac. ALL were TDF-treated patients.

NSAID | IC50 MRP4 [uM]
--- | ---
Celecoxib | 35
**Diclofenac** | **0.006**
Ibuprofen | 26.3
Indomethacin | 6.1
Naproxen | 42.3
Piroxicam | 216
HIV/HCV co-infected male patient on ATV/r + TDF/FTC started TVR and within 1 week experienced progressive deterioration in renal function. Note: ATV/r is only PI recommended for use with TVR.

TDF/FTC switched to ABC/3TC and TVR stopped. Abnormal liver function tests.

Mechanisms?

i) TVR inhibition of renal OCT2 - increased serum creatinine
ii) TVR inhibition of tenofovir renal elimination – increased serum tenofovir.
iii) TVR inhibition of ATV clearance – increased atazanavir.
There are more risky ARVs and more risky co-meds for DDIs
## Antiretrovirals and Interaction Potential

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<th>Highest potential</th>
<th>Moderate Potential</th>
<th>Low Potential</th>
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<tr>
<td><strong>Boosted PIs</strong></td>
<td><strong>Rilpivirine</strong></td>
<td><strong>Raltegravir</strong></td>
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<td>Perpetrators – enzyme and transporter inhibition</td>
<td>Victim of enzyme inhibition and induction. Also absorption.</td>
<td>Victim of few induction and absorption interactions</td>
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<td><strong>EVG/cobi</strong></td>
<td><strong>Maraviroc</strong></td>
<td><strong>Most NRTIs</strong></td>
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<td>Perpetrators – enzyme and transporter inhibition</td>
<td>Victim of enzyme inhibition and induction.</td>
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<td><strong>Efavirenz, nevirapine, etravirine</strong></td>
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<td><strong>Dolutegravir</strong></td>
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<td>Perpetrators – enzyme and transporter induction</td>
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<td>Victim of enzyme inhibition and absorption interactions</td>
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[www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
Polypharmacy and Risk of Antiretroviral Drug Interactions Among the Aging HIV-Infected Population

Carol Holtzman, PharmD¹, Carl Armon, PhD², Ellen Tedaldi, MD³, Joan S. Chmiel, PhD⁴, Kate Buchacz, PhD⁵, Kathleen Wood, BSN², John T. Brooks, MD⁵, and the HOPS Investigators

¹Temple University School of Pharmacy, Philadelphia, PA, USA; ²Cerner Corporation, Vienna, VA, USA; ³Temple University School of Medicine, Philadelphia, PA, USA; ⁴Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; ⁵Centers for Disease Control and Prevention, Atlanta, GA, USA.

- N = 3674

- ARV – Non-ARV Interactions identified with the University of Liverpool web site www.hiv-druginteractions.org

- 261 (7%) prescribed at least 1 contraindicated ARV – drug combination
  - Proton pump inhibitors with atazanavir
  - Simvastatin or lovastatin with boosted PI
  - Benzodiazepines and boosted PI

- 1239 (34%) prescribed at least one ARV-drug combination with moderate or high evidence of interaction.
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Colour Legend
- Green: No clinically significant interaction expected
- Red: These drugs should not be co-administered.
- Yellow: Potential interaction which may require a dosage adjustment or close monitoring.
- Orange: Potential interaction predicted to be of week intensity (<2 fold ↑AUC or <50% ↓AUC). No a priori dosage adjustment is recommended.

Text Legend
- ↑: Potential increased exposure of the lipid-lowering drug
- ↓: Potential decreased exposure of the lipid-lowering drug
- ↔: No significant effect
- ↑: Potential increased exposure of HIV drug
- ↓: Potential decreased exposure of HIV drug
## Drug-drug interactions between HIV drugs and non-HIV drugs

### EACS Guidelines 2012

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<tr>
<th>Non-HIV drugs</th>
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<td>pimozide</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>↑D</td>
<td>↑</td>
<td>↑D</td>
<td>↑</td>
<td>↓D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>↓</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>phenytoin</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>↓</td>
<td>↓</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
</tbody>
</table>
Also Tyrosine Kinase Inhibitors (eg: dasatinib, everolimus, imatinib, lapatinib – have complex interaction profile)
Pharmacotherapy in Cancer Patients With HIV/AIDS

JH Beumer¹,², R Venkataramanan²,³ and MA Rudek⁴

Newer antiretrovirals such as raltegravir may become standard of care in patients with multiple comorbidities due to their reduced interaction potential as compared with NNRTIs and PIs.
DDIs are not going away with an aging HIV population.
Considerations in Management of the Older HIV Patient

• Co-morbid conditions
  – eg., cardiovascular, hepatic, metabolic
  – may be exacerbated by effects of HIV or its treatment

• Greater medication use
  – overlapping side effects or potential interactions between ARVs and concomitant medications
# Association of Age With Polypharmacy and Risk of Drug Interactions With Antiretroviral Medications in HIV-Positive Patients

Alice Tseng, PharmD, FCSHP, AAHIVP\textsuperscript{1,3}, Leah Szadkowski, MSc\textsuperscript{2}, Sharon Walmsley, MD, MSc, FRCPC\textsuperscript{1,2,3}, Irving Salit, MD, FRCPC\textsuperscript{1,3}, and Janet Raboud, PhD\textsuperscript{2,3}

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age &lt; 50 years (n=498)</th>
<th>Age &gt; 50 years (n=416)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>127 (26%)</td>
<td>271 (65%)</td>
</tr>
<tr>
<td>Antidepressants/ Psychotropics</td>
<td>199 (40%)</td>
<td>224 (54%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>243 (49%)</td>
<td>276 (66%)</td>
</tr>
<tr>
<td>Narcotics/Analgesics</td>
<td>113 (23%)</td>
<td>164 (39%)</td>
</tr>
<tr>
<td>Systemic hormonal</td>
<td>49 (10%)</td>
<td>67 (16%)</td>
</tr>
</tbody>
</table>
Summary of ARV PK studies in older subjects

- There is an increase in exposure (~20%) of RTV and some **boosted PIs** (DRV, LPV): This could increase the impact of a drug-drug interaction.

- No clear evidence of an age effect on exposure of **NNRTIs** **but** changes in protein binding could increase unbound concentration (EFV & CNS).

- There is an increase in **FTC** exposure (> 30%) in older patients; some data show altered **TFV** which could be further increased by an interaction at the renal level.

*References*

DDIs: we need management strategies.
Drug Interaction Resources

- hivinsite.ucsf.edu.
  Updated drug interaction database and interactive tool to assess DDIs
- www.aidsinfo.nih.gov
  DHHS guidelines for use of ARVs with updated interaction tables
- www.hivclinic.ca.
  Updated drug interaction tables. Downloadable.
- www.eacsociety.org
  European guidelines including drug interaction tables.
- www.hivmedicationguide.com
  Updated interactive drug interaction database. Apps (iPhone; iPad)
- Micromedex.com.
  Comprehensive database (subscription required)
- www.lexi.com
  Lexi-interact database (subscription required)
- www.hiv-druginteraction.org;
HIV iCharts - we want your opinions

Recent changes to the Apple operating system have caused issues with the update feature of the HIV iCharts app. We are taking this opportunity to investigate alternative options for accessing our drug interaction information on mobile devices and would be grateful if you could take a few minutes to answer a few short questions and to give us any comments.

Click here to take the survey

TREATMENT SELECTOR TABLES

Treatment Selector Tables - now with dolutegravir

We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities.

The tables can be accessed from the Printable Chart & Treatment Selector sub menu on the Interaction Charts menu.

INTERACTION CHARTS FOR YOUR SMART PHONE AND TABLET

HIV iChart - an interaction app for mobile devices

iOS7 - We have recently become aware that the update function on the app may not work properly with iOS7 on some devices. We are currently working to determine the nature and extent of the problem and to rectify this.

Free for Apple and Android devices.
Now optimised for iPads
The UKs most commonly prescribed non-ARV medicines (2010-2012) were identified using the ABPIs ‘top products in the UK’ website.

The potential of a DDI for each non-ARV with selected ARVs were identified and categorised using 3 resources – eBNF, SPCs and www.hiv-druginteractions.org.

DDIs were less likely to be identified by the eBNF or SPCs than the University of Liverpool website.

Clinic letters should recommend clinicians consult www.hiv-druginteractions.org as the preferred source for identifying DDIs.

Table 3: Outcomes against audit standards

<table>
<thead>
<tr>
<th>Audit standard</th>
<th>eBNF 66 (%)</th>
<th>SPC for ARV (%)</th>
<th>SPC for nARV (%)</th>
<th>Liverpool DDI website (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% of potential, clinically significant DDIs will be identified by the medicines resource. (n=20).</td>
<td>60% (12)</td>
<td>75% (15)</td>
<td>70% (14)</td>
<td>100% (20)</td>
<td>0.010</td>
</tr>
<tr>
<td>Each medicines resource gives clear and appropriate advice on 100% of potential, clinically significant DDIs (category A and B from table 3).</td>
<td>20% (4)</td>
<td>60% (12)</td>
<td>65% (13)</td>
<td>100% (20)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
A stepwise approach to DDI management

1. Note all co-medications (prescribed, OTC and herbal products)
2. Consult pharmacist and online resources
3. Consider the nature of any interaction and whether an alternative to an ‘interacting drug’ is possible.
4. Some interactions can be managed by dose adjustment with careful monitoring.
A stepwise approach to DDI management

- Ask key questions

- No clinically significant interaction or interaction not anticipated.

- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.

- Interaction likely – do not co-administer

---

No

- Are drugs necessary?
  - Yes
  - Are there alternatives?
    - Yes
    - Switch
    - No
    - Can DDI be managed?
      - Yes
      - Establish Monitoring Plan
      - No
      - Accept risk, discuss with patient
    - No
  - Stop

---

Yes

Change dose
What is on the horizon?
Long-acting formulations

• Have been used to improve adherence and prevent missed doses/treatment fatigue in several therapeutic areas
  • Contraception: (Depo Provera)
  • Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine, aripiprazole)
  • Hypogonadism: (testosterone undecanoate)
Main focus on prevention but interest also in treatment

2 drugs in clinical trials (PK and PK-PD):

- *Rilpivirine*
- *GSK-1265744 (Cabotegravir)*
Mean rilpivirine plasma concentrations

- Rilpivirine plasma concentrations following long-acting injections are comparable to oral 25mg/day in HIV patients
GSK1265744 LA every 4 weeks or 12 weeks
Regimens achieve plasma concentrations >4 x PA-IC90

• Mean GSK1265744 plasma concentration profiles

Spreen W et al. 7th IAS 2013, Kuala Lumpur, Malaysia. Abstract WEAB0103
Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial

ENCORE1 Study Group

<table>
<thead>
<tr>
<th>Strata</th>
<th>Efavirenz 400 mg</th>
<th>Efavirenz 600 mg</th>
<th>Difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified intention-to-treat analysis</td>
<td>N</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>302</td>
<td>94.1% (91.5 to 96.7)%</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Stratified by baseline BMI (kg/m²)</td>
<td>N</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22</td>
<td>104</td>
<td>99 (95.2%)</td>
<td>1% (-2.1 to 5.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>&gt;22-25</td>
<td>113</td>
<td>101 (92.8%)</td>
<td>5.81% (-1.20 to 12.8%)</td>
<td>. . .</td>
</tr>
<tr>
<td>&gt;25</td>
<td>105</td>
<td>99 (94.3%)</td>
<td>-0.95% (-6.98 to 5.07)</td>
<td>0.47</td>
</tr>
<tr>
<td>Stratified by ethnic origin</td>
<td>N</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>118</td>
<td>107 (90.7%)</td>
<td>1.88% (-5.90 to 9.70)</td>
<td>. . .</td>
</tr>
<tr>
<td>Asian</td>
<td>106</td>
<td>103 (97.2%)</td>
<td>0.05% (-3.83 to 5.94)</td>
<td>. . .</td>
</tr>
<tr>
<td>Other</td>
<td>97</td>
<td>92 (94.8%)</td>
<td>2.62% (-4.45 to 9.69)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

BMI=body-mass index. * Data are % (95% CI). Other includes white and Aboriginal and Torres Strait Islander.

Table 2: Primary endpoint stratified by baseline body-mass index and ethnic origin

Figure 3: Mean change in HIV-RNA viral load from baseline to week 48 for the modified intention-to-treat population

Data are presented as mean (SD) log₁₀ copies per mL.
Nanomedicines for HIV therapy

Heterogeneity in response to HIV treatments has been attributed to several causes including variability in pharmacokinetic exposure. Nanomedicine applications have a variety of advantages compared with traditional formulations, such as the potential to increase bioavailability and specifically target the site of action.

Studies ongoing with EFV and LPV
Grateful Thanks
# Tyrosine kinase Inhibitors & antiretrovirals

<table>
<thead>
<tr>
<th>Protein Kinase Inhibitors</th>
<th>Considerations with Antiretrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP3A4 Substrates</strong></td>
<td>PIs may ↑ levels via CYP3A4 inhibition EFV, NVP may ↓ levels via CYP3A4 induction</td>
</tr>
<tr>
<td>eg: dasatinib, everolimus, imatinib, lapatinib</td>
<td></td>
</tr>
<tr>
<td><strong>CYP3A4 Inhibitors</strong></td>
<td>NNRTIs, MVC levels may ↑</td>
</tr>
<tr>
<td>eg: dasatinib, everolimus, imatinib, lapatinib</td>
<td></td>
</tr>
<tr>
<td><strong>UGT1A1 Inhibitors</strong></td>
<td>Potential for ↑ bilirubin levels. RAL levels may ↑(unlikely clinically relevant)</td>
</tr>
<tr>
<td>eg: erlotinib, nilotinib</td>
<td></td>
</tr>
<tr>
<td><strong>QT Interval Prolongation</strong></td>
<td>Increased risk for QT prolongation with PIs, rilpivirine</td>
</tr>
<tr>
<td>eg: dasatinib, lapatinib, nilotinib, sunitinib</td>
<td></td>
</tr>
<tr>
<td><strong>Myelosuppression</strong></td>
<td>Increased risk for myelosuppression with ZDV</td>
</tr>
<tr>
<td>eg: dasatinib, everolimus, imatinib, sunitinib</td>
<td></td>
</tr>
<tr>
<td><strong>Nephrotoxicity</strong></td>
<td>Increased risk for nephrotoxicity with TDF</td>
</tr>
<tr>
<td>eg: sunitinib</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td>Increased risk for hepatotoxicity with some ARVs</td>
</tr>
<tr>
<td>eg: imatinib, lapatinib, sunitinib</td>
<td></td>
</tr>
</tbody>
</table>