Roadmap for today’s talk

• TB in people living with HIV (PLHIV)
  – Risk of LTBI→TB
  – Clinical manifestations
  – TB treatment (ART/TB medication interactions)
  – Immune reconstitution inflammatory syndrome (IRIS)
  – LTBI treatment

• TB and other immunosuppressive states
  – Solid organ (and hematopoietic stem cell) transplant Immunosuppressive/TB medication interactions
  – TB and biologics (TNF alpha inhibitors)
Global HIV/TB

10% new TB cases HIV+

Global TB/HIV epidemiology: over time

~10 % new cases HIV+  ~1/4 TB deaths HIV+

WHO 2018
Latent TB (LTBI) and active TB

HIV- 10% over lifetime

*greatest risk in 1st 2 years*

HIV+ 10% per year

- HIV kills TB-specific CD4 cells
- Impairs macrophage activation
- Fewer lung-homing CD4 cells
- Defective granuloma formation
- Loss of control of infection

Geldmacher, Curr Opin HIV AIDS, 2012
Although ART significantly decreases TB risk, still much higher than among HIV-
Challenges in TB treatment in HIV+

- Adherence
  - polypharmacy
- Side effects
  - overlapping side effects of anti-TB and ART
- Immune reconstitution inflammatory syndrome (IRIS)
- Drug-drug interactions

**What to start, and when to start?**

### TB treatment in HIV+

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>2 months</td>
<td>Daily</td>
<td>Recommended</td>
</tr>
<tr>
<td><strong>Continuation phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF</td>
<td>4 months</td>
<td>Daily</td>
<td>Recommended</td>
</tr>
<tr>
<td>INH/RIF</td>
<td>4 months</td>
<td>3 x week</td>
<td>Alternative</td>
</tr>
<tr>
<td>INH/RIF</td>
<td>4 months</td>
<td>Twice weekly</td>
<td>Not recommended for HIV+</td>
</tr>
<tr>
<td>INH/RPT</td>
<td>4 months</td>
<td>Once weekly</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

*For HIV+ both initial phase and continuous phase are given daily*
TB treatment in HIV+

- **Anti-TB regimen generally the same for non-HIV**
  - Initial phase: INH, RIF, PZA, EMB x 2 months
  - Continuation phase: INH, RIF x 4 months
    - Extended to 7 months if initial CXR + cavitation & Cx + at end of 2 months of initial phase

- **Important exceptions for HIV+:**
  - Initial phase: INH, RIF, PZA, EMB given daily
  - Continuation phase: INH, RIF given daily (or 3 x week)
    - If no ART during TB tx: extend to 7 months
  - Culture-negative pulm TB:
    - 6 months total treatment (vs. 4 months HIV-)

---

Basic Principles in ART and TB treatment

- **Rifamycin-based TB treatment is cornerstone of effective TB treatment**

- **Most drug-drug interactions due to Rifampin**
  - Potent inducer of P450 enzyme 3A
    - Sometimes requires ART dose adjust (typically ↑ dose)
  - **Rifabutin less potent inducer**
    - Sometimes requires rifabutin dose adjust (↑ or ↓ dose)
    - **Important:** if ART dc’d, rifabutin may be subtherapeutic
TB treatment duration in HIV+

- **Culture-negative pulmonary TB**
  - 6 months total treatment (vs. 4 months HIV-)

- **Extra-pulmonary (same as HIV-)**
  - 6-9 months

- **Meningitis (same as HIV-)**
  - 9-12 months

- **Adjunctive corticosteroids***
  - CNS, pericardium involvement
  - *New data to suggest benefit in preventing IRIS

Timing of ART and TB treatment

- **ART is recommended for all HIV+ with TB**

- For ART-naïve
  - CD4 < 50 start ART within 2 weeks
  - CD4 ≥ 50 start by 8-12 weeks

- Exception: TB meningitis
  - start > 8 weeks (to reduce risk of IRIS)

- If already on ART, continue ART
  - May require medication adjustment
**Important ART considerations with TB treatment**

- **Efavirenz preferred ART treatment (still)**
  - RIF decrease EFV levels (**dose adjustment not required**)
- Alternatives: **Integrase inhibitors** (Raltegravir or Dolutegravir)
  - RIF decrease RAL and DTG levels (**in general need to increase INSTI dose**)
- Alternatives: **Protease inhibitors**
  - Rifabutin preferred over rifampin
- Tenofovir disoproxil fumarate (TDF) preferred over tenofovir alafenamide (TAF) (**for now**)

DHHS 2017
ATS, CDC, IDSA CID 2016

See additional slides for specific ART regimens and TB treatment issues

---

**Immune Reconstitution Inflammatory Syndrome: IRIS**

- IRIS: collection of inflammatory disorders
  - Paradoxical worsening of preexisting infectious processes
  - Assoc w/ immune recovery following ART initiation
  - Risk Factors: ↓ CD4 and ↑ VL pre- ART, short time between TB tx and ART initiation, **but TB IRIS can occur at CD4 >200**
Immune Reconstitution Inflammatory Syndrome: IRIS

- IRIS: collection of inflammatory disorders
  - Paradoxical worsening of preexisting infectious processes
  - Assoc w/ immune recovery following ART initiation
  - Risk Factors: ↓ CD4 and ↑ VL pre- ART, short time between TB tx and ART initiation, but TB IRIS can occur at CD4 >200

TB IRIS: Clinical manifestations

- **Pulmonary TB**
  - Sx: fever, malaise, weight loss, and worsening resp sx
  - Worsening CXR: new parenchymal opacities and progressive ↑ intrathoracic lymph node

- **Extrapulmonary TB**
  - Worsening lymphadenitis, new pleural effusions, ↑ intracranial tuberculomas, worsening of meningitis or radiculomyelopathy
  - “cold” abscesses
TB IRIS: Treatment

**Continue ART unless life-threatening**

- **Steroids**
  - RCT 4 wks prednisone vs. placebo for TB IRIS tx
  - ↓ symptoms, improved CXR, ↓ hospitalization

- **NSAIDS**

---

TB IRIS: Prevention?

- **PredART**: Empiric prednisone during 1st 4 wks of ART ↓ risk of paradoxical TB-IRIS

---

**A** Cumulative incidence of TB-Associated IRIS at 12 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Prednisone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with TB-Associated IRIS (%)</td>
<td>18/120 (15.0%)</td>
<td>50/130 (46.7%)</td>
</tr>
</tbody>
</table>

Relative risk: 0.37 (95% CI: 0.31 - 0.46)

P=0.00 by chi-square test

---

**B** Cumulative incidence of TB-Associated IRIS over 54 Days

<table>
<thead>
<tr>
<th></th>
<th>Prednisone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>119</td>
<td>87</td>
</tr>
<tr>
<td>Prednisone</td>
<td>119</td>
<td>87</td>
</tr>
<tr>
<td>Placebo</td>
<td>119</td>
<td>87</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.61 (95% CI: 0.41 - 0.92)

P=0.02
## LTBI treatment in HIV+

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>Isoniazid + Rifapentine</td>
<td>3 months</td>
<td><strong>OK if NO ART</strong> or EFV or RAL-based ART. <strong>Drug interactions with TAF</strong></td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td><strong>Drug interactions</strong>&lt;br&gt;May required dose adjustment</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>4 months</td>
<td><strong>Drug interactions</strong>&lt;br&gt;May required dose adjustment</td>
</tr>
<tr>
<td>Rifampin + Pyrazinamide</td>
<td>2 months</td>
<td><strong>Contraindicated</strong></td>
</tr>
</tbody>
</table>

**Recent trials:**
- 1 INH/RPT: not inferior to 9 INH *Swindells NEJM 2019*
- INH pregnancy vs. postpartum: similar maternal safety, higher risk of fetal and pregnancy outcomes *Gupta CROI 2018 IMPAACT 1078*

---

## Shifting gears

[https://www.bicycling.com/training/a20004201/how-to-shift/](https://www.bicycling.com/training/a20004201/how-to-shift/)
TB and Solid Organ Transplant (SOT)

- TB risk 20-74 x higher than general pop
- Incidence in low prevalence regions 0.3-6.5%

Higher mortality 6-22% (vs <5% for TB in general US)

TB and SOT: things to consider

- Reactivation of LTBI in setting of immunosuppression
  - Recurrence of previously treated TB
- Drug-drug interactions
- Baseline organ dysfunction
- Donor derived infections
  - Unrecognized active TB
  - Reactivation of LTBI in the graft
TB and SOT: risk factors

- Transplant-related immunosuppression
- Standard TB risk factors
- Underlying medical condition

| Risk factor | Immunosuppressive therapy
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OKT3 or anti-T lymphocyte antibodies (III)</td>
</tr>
<tr>
<td>Intensification of immunosuppression associated with graft rejection (III)</td>
</tr>
<tr>
<td>Cyclosporine A vs. azathioprine plus prednisone (II)</td>
</tr>
<tr>
<td>Mycophenolate mofetil and tacrolimus vs. azathioprine, cyclosporine, and prednisone (III)</td>
</tr>
<tr>
<td>History of exposure to Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Positive PPD test result (III)</td>
</tr>
<tr>
<td>Radiological evidence of previous untreated TB (III)</td>
</tr>
<tr>
<td>Clinical condition</td>
</tr>
<tr>
<td>Chronic renal insufficiency or hemodialysis (kidney transplantation; II)</td>
</tr>
<tr>
<td>Diabetes mellitus (III)</td>
</tr>
<tr>
<td>Hepatitis C virus infection (kidney transplantation; III)</td>
</tr>
<tr>
<td>Chronic liver disease (III)</td>
</tr>
<tr>
<td>Other coexisting infections: profound mycoses, cytomegalovirus, or Pneumocystis jiroveci or Nocardia pneumonia (III)</td>
</tr>
</tbody>
</table>

TB and SOT: clinical manifestations

- Atypical presentations
  - Non specific sx (fever, weight loss, night sweats)
  - Extrapulmonary/disseminated more common
  - Classic upper lobe infiltrate / cavities less likely

- Diagnostic delays
TB and SOT: screening

- **Recipient prior to transplant**
  - TST or IGRA
    - However many SOT recipients who develop TB had neg TST/IGRA prior to transplant
  - Chest imaging (CXR, +/-CT)
  - Epidemiologic risk assessment

- **Donors**
  - Living donors - LTBI screening (and treatment)
  - Deceased donors - Moderate to high TB risk: imaging (consider CT) + AFB smear (+NAAT/Culture)
  - donor with untreated LTBI, recent exposure, radiographic evidence of untreated TB -> LTBI treatment for recipient

---

LTBI and SOT: treatment

- **Timing: pre- or post-transplant?**

---

Table 3. Factors Affecting Timing of Latent Tuberculosis Treatment Among Solid Organ Transplant Candidates and Recipients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Timing</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretransplant</td>
<td>Posttransplant</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibility higher efficacy in absence of concurrent immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fewer drug-drug interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower medication/pill burden with corresponding better anticipated adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generally well tolerated, even in liver transplant candidates</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentially insufficient calendar time to complete therapy due to unpredictable timing of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulties in differentiating drug toxicity from signs/symptoms of underlying organ disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-induced liver injury could be fatal with preexisting advanced liver disease in liver transplant candidates</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentially lower efficacy in setting of concurrent immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional pill burden to an already complex medication regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentially severe drug interactions with immunosuppressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher reported rate of drug-induced liver injury and discontinuation in liver graft recipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any elevation in liver function tests creates need for extensive evaluation including invasive procedures (eg, liver biopsy to rule out rejection)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---
### LTBI and SOT: treatment

**• Choice of regimen**

<table>
<thead>
<tr>
<th>INH</th>
<th>Best studied well tolerated pre-liver txp</th>
<th>Longer duration ↑ Hepatotoxicity post-txp</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>Shorter duration</td>
<td>↑ P450 inducer ↓ immunosuppressive agents; rejection allograft loss</td>
</tr>
<tr>
<td>INH/RPT</td>
<td>Shorter duration</td>
<td>Doesn’t avoid INH adverse effects / rifamycin drug interactions</td>
</tr>
</tbody>
</table>

**• Need for further study:** RBT, FLQ

---

### LTBI/TB treatment and SOT: important drug interactions

- **Rifampicin reduces levels of many immunosuppressive agents**
  - Corticosteroids
  - Calcineurin inhibitors: tacrolimus, cyclosporine
  - mTORs (mammalian target of rapamycins): rapamycin (sirolimus), everolimus

- **Reduced levels immunosuppressant levels increase risk of graft rejection**

- **Need to increase dose of calcineurin inhibitors 3-5x, closely monitor levels**
TB and Hematopoietic Stem Cell Transplant (HSCT)

- TB risk 10-40x higher than general population
  - ~ 10X less common than among SOT (due to transient immunosuppression)
- Highest risk among allogenic transplants
  - Primarily due to LTBI reactivation
- Donor-derived infections appear insignificant
- Treatment for LTBI prior to conditioning therapy preferred
- Recommendations for screening and treatment of LTBI similar to SOT
TB and Biologics

| TNF alpha inhibitors | Etanercept (soluble p75 receptor)  
|                      | Infliximab, adalimumab, golimumab, certolizumab (monoclonal antibodies) |
| II-1 inhibitors      | Anakinra |
| B-cell depletion     | Rituximab  
|                      | Anti-CD20 |
| T-cell co-stimulation blockade | Abatacept |

TNF alpha and TB

A: Phagocytosis of bacilli  
B: TNFα release and autocrine stimulation  
C: Cytokine and chemokine release  
- Attraction and stimulation of CD4 and CD8 lymphocytes  
- Increased T-cell adhesion, antigen presentation  
- Proliferation and recruitment of T and B cells  
D: Activated T cells release interferon γ, further activating macrophages  
- Increased antigen presentation  
- Intracellular killing of bacilli  
- Macrophage apoptosis, granuloma formation

TNF alpha blockade increases TB risk

Slide courtesy of Elizabeth Gilliams  
Gardam Lancet Infect Dis. 2003
TB risk and TNF alpha inhibitors

Incident TB
Nelson-Aalen plot

Drug | Registration (entry to study) | 1 year (365 days) | 2 years (730 days) | 3 years (1095 days) | 4 years (1460 days)
--- | --- | --- | --- | --- | ---
DMARD | 3252 | 2652 | 1839 | 742 | 213
ETA | 3913 | 3474 | 3051 | 2363 | 1020
INF | 3295 | 2694 | 1918 | 1392 | 918
ADA | 3504 | 2457 | 1531 | 729 | 247

Slide courtesy of Kevin Winthrop

Winthrop Nature Pract Rheum (in press)
Winthrop Ann Rheum Disease 2013
TB risk and TNF alpha inhibitors: Risks are different by agent

- Infliximab and adalimumab suppress IFNγ production
- Depletion of CD8 cells that aid in killing intracellular TB
- Impaired granuloma formation
  - Antibodies > receptor

LTBI treatment and TNF alpha inhibitors

- **Screen for LTBI prior to anti-TNFα initiation**
  - Ideally receive 1 month LTBI treatment prior to anti-TNFα

- Holding anti-TNFα can be associated with IRIS-like phenomenon
  - Anti-TNFα can be restarted within few months of TB tx initiation
HIV/TB: Take home points

- HIV significantly increase risk of TB
  - ↑ atypical presentations of PTB, EPTB and disseminated TB

- TB treatment similar to non-HIV, but...
  - Daily Initial phase w/ RIPE, at least 3 x week Maintenance w/ IR

- Rifamycin-based anti-TB therapy is key
  - May require ART dose adjustment

- Important to monitor for drug-drug interactions and side effects

- IRIS typically managed w/ NSAIDS, steroids if severe
  - Concerns for TB-IRIS should not delay HAART initiation

TB and other immunosuppressive states: Take home points

- Important to screen for LTBI in SOT/HSCT recipients
  - Ideally before transplant
  - TB risk primarily due to LTBI reactivation, but can be donor derived in SOT

- Rifampicin reduces levels of many immunosuppressant agents used in SOT/HSCT
  - Increases risk of graft rejection
  - Often requires increased dose of immunosuppressants

- TNF alpha inhibitors significantly increase risk of TB
  - Ideally initiate LTBI treatment before anti-TNFα initiation
  - Stopping anti-TNFα assoc with IRIS, can restart within few months of TB tx
Resources
https://www.hiv.uw.edu/go/co-occurring-conditions/latent-tuberculosis/core-concept/all

Acknowledgements
Robert Harrington
David Horne
Masa Narita
Bijan Ghassemieh
Kevin Winthrop
Elizabeth Gilliams
Additional references


## ART and RIF recommended dose adjustments

<table>
<thead>
<tr>
<th>ARV</th>
<th>ARV dose change</th>
<th>RIF dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>None; some ↑800mg if &gt;50kg</td>
<td>No change</td>
<td>Preferred Regimen (still)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↑lead-in dose 200 mg twice daily, continue as maintenance dose</td>
<td>No change</td>
<td>Avoid lead-in 200mg once daily, assoc w/ virologic failure. Consider therapeutic drug monitoring. Rarely used in US</td>
</tr>
<tr>
<td>Rilpivirine Etravirine</td>
<td>Contraindicated</td>
<td></td>
<td>Significant decrease in Rilpivirine</td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate (TDF)</td>
<td>None</td>
<td>None</td>
<td>Preferred</td>
</tr>
<tr>
<td>Tenofovir alafenamide (TAF)</td>
<td>Unknown</td>
<td>TAF concentration decreased in healthy volunteers (but intracellular concentrations still higher than TDF) CROI 2018</td>
<td></td>
</tr>
</tbody>
</table>

**RIF decreases NNRTI (and some NRTI) levels**

## ART and RIF recommended dose adjustments (cont.)

<table>
<thead>
<tr>
<th>Integrase inhibitors</th>
<th>ARV dose change</th>
<th>RIF dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>↑ Raltegravir to 800 mg twice daily</td>
<td>No change</td>
<td>Raltegravir trough concentrations still decreased, follow VL carefully</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>↑ Dolutegravir to 50 mg twice daily</td>
<td>No change</td>
<td>follow VL carefully</td>
</tr>
<tr>
<td>Bictegravir</td>
<td>Bictegravir should not be used together</td>
<td>Decrease in Bictegravir even when given BID (Custodia, CROI 2018)</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, TDF or TAF, and emtricitabine (Stribild or Genvoya)</td>
<td>Stribild or Genvoya and rifampin should not be used together</td>
<td>Marked decrease in elvitegravir and cobicistat concentrations predicted based on metabolic pathways of these drugs</td>
<td></td>
</tr>
<tr>
<td><strong>CCR-5 receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>↑ Maraviroc to 600 mg twice-daily</td>
<td>No change</td>
<td>Use with caution, as there is no reported clinical experience with increased dose of maraviroc with rifampin</td>
</tr>
</tbody>
</table>

**RIF decreases INSTI levels**
## ART and RIF recommended dose adjustments (cont.)

<table>
<thead>
<tr>
<th>ARV dose change</th>
<th>RIF dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra™)</td>
<td>Lopinavir 800 mg plus ritonavir 200 mg twice daily</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>(double dose)</td>
<td></td>
</tr>
<tr>
<td>“Super-boosted” lopinavir/ritonavir (Kaletra™)</td>
<td>Lopinavir 400 mg plus ritonavir 400 mg twice daily</td>
<td>No change</td>
</tr>
<tr>
<td>(super boosting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (single agent or ritonavir boosted)</td>
<td>Contraindicated</td>
<td></td>
</tr>
<tr>
<td>Darunavir/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**For PIs RFB preferred**

---

## ART and RFB recommended dose adjustments

<table>
<thead>
<tr>
<th>ARV</th>
<th>ARV dose change</th>
<th>RFB dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>No change</td>
<td>↑ 600 mg (daily or thrice-weekly)</td>
<td>RIF preferred</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No change</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>No change</td>
<td>No change</td>
<td>Conc of both decreased</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Contraindicated</td>
<td></td>
<td>Significant decrease in Rilpivirine</td>
</tr>
</tbody>
</table>

**Protease inhibitors**

<table>
<thead>
<tr>
<th>ARV</th>
<th>ARV dose change</th>
<th>RFB dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (single agent or ritonavir boosted)</td>
<td>No change</td>
<td>↓ 150 mg daily</td>
<td>No pub clinical experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monitor closely for potential rifabutin toxicity – uveitis, hepatotoxicity, and neutropenia</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>No change</td>
<td>↓ 150 mg daily</td>
<td>Monitor closely for potential rifabutin toxicity – uveitis, hepatotoxicity, and neutropenia</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>Saquinavir/r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra™)</td>
<td>No change</td>
<td>↓ 150 mg daily</td>
<td>Hepatotoxicity in healthy volunteers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Better-tolerated among HIV+ already on LPV/r</td>
</tr>
</tbody>
</table>

---

**RFB levels decreased with EFV, increased with PIs**
### ART and RFB recommended dose adjustments (cont.)

<table>
<thead>
<tr>
<th></th>
<th>ARV dose change</th>
<th>RFB dose change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>No change</td>
<td>No change</td>
<td>↑ RAL conc</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>No change</td>
<td>No change</td>
<td>↑ DOL conc</td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, tenofovir, and emtricitabine (Stribild™)</td>
<td>Stribild (or Genwoya) and rifabutin should not be used together</td>
<td>Marked ↓ elvitegravir, cobicistat conc Marked ↑ rifabutin</td>
<td></td>
</tr>
<tr>
<td><strong>CCR-5 receptor antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>No change</td>
<td>No change</td>
<td>No clinical experience; a significant interaction is unlikely, but this has not yet been studied</td>
</tr>
</tbody>
</table>

**INSTI levels increased with RFB**

DHHS 2017  
CDC 2013  
ATS, CDC, IDSA CID 2016