30 Years of HIV:
An Update on Treatment Guidelines and Beyond

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Conflict of Interest Declaration

- Speaker and Spouse are Stockholders: Pfizer, GSK, Merck
- Spouse is an employee of GSK

Any conflicts were resolved through peer review.

Pharmacist Objectives

-Describe recent revisions to the Department of Health and Human Services (DHHS) Guidelines for treatment of HIV-1 infected adults.

-Review first line antiretroviral regimens recommended by DHHS Treatment Guidelines.

-Compare and contrast recently approved antiretrovirals and those in development to first line antiretroviral agents.

-Recognize clinically significant drug interactions specific to antiretroviral therapy.

Pharmacy Technician Objectives

-Identify DHHS Guidelines recommended antiretrovirals by brand and generic name.

-Recognize recommended initial combination regimens for HIV treatment-naïve adults.

-Identify laboratory markers used to initiate and monitor antiretroviral therapy.

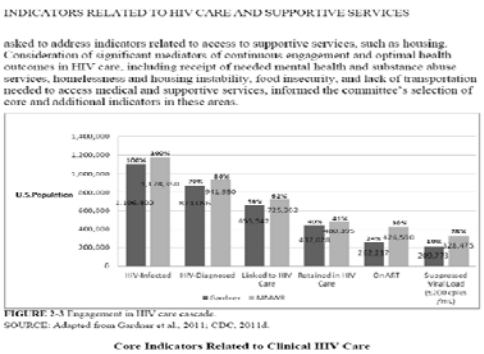
-Recognize side effects of antiretrovirals recommended for HIV treatment-naïve adults.

Epidemiology

In the beginning…

- 1981
  - Ronald Reagan is president
  - Avg pharmacists salary ≈ $35,000/yr
  - June 5th- MMWR describes the unusual occurrence of Pneumocystis carinii pneumonia (PCP) in 5 otherwise healthy, Caucasian MSM.
- 1982
  - CDC coins the term “AIDS”
  - 1600 cases/700 deaths
- 1985
  - HIV confirmed as cause of AIDS

HIV Linkage and Retention in Care


INDICATORS RELATED TO HIV CARE AND SUPPORTIVE SERVICES 43

asked to address indicators related to access to supportive services, such as housing. Consideration of significant mediators of continuous engagement and optimal health outcomes in HIV care, including receipt of needed mental health and substance abuse services, homelessness and housing instability, food insecurity, and lack of transportation needed to access medical and supportive services, informed the committee's selection of core and additional indicators in these areas.

FIGURE 3-3 Engagement in HIV care cascade.
SOURCE: Adapted from Gardner et al., 2011; CDC, 2011d.

Core Indicators Related to Clinical HIV Care

24 FDA Approved Antiretroviral Medications

NRTI
- Abacavir (Ziagen)
- Didanosine (Videx)
- Emtricitabine (Emtriva)
- Lamivudine (Epivir)
- Stavudine (Zerit)
- Tenofovir (Viread)
- Zidovudine (Retrovir)

NNRTI
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)
- Etravirine (Intelence)
- Nevirapine (Viramune)
- Rilpivirine (Edurant)

PI
- Atazanavir (Reyataz)
- Darunavir (Prezista)
- Fosamprenavir (Lexiva)
- Indinavir (Crixivan)
- Lopinavir/r (Kaletra)
- Nelfinavir (Viracept)
- Ritonavir (Norvir)
- Saquinavir (Invirase)
- Tipranavir (Aptivus)

•Fixed Dose Combination
- **Atripla** (TDF/FTC/EFV)
- **Truvada** (TDF/FTC)
- **Epzicom** (ABC/3TC)
- **Combivir** (AZT/3TC)

Integrase Inhibitor
- Raltegravir (Isentress)

Fusion Inhibitor
- Enfuvirtide (Fuzeon)

CCR5 Antagonist
- Maraviroc (Selzentry)

- **Complera** (TDF/FTC/RPV)
- **Trizivir** (ABC/AZT/3TC)
- **Kaletra** (LPV/RTV)

Treatment Guidelines

What's New in the Guidelines?

-DHHS Treatment Guidelines are updated every 6-12 months (March 2012, 240 page document)
- HIV and the Older Patient
- Treatment as HIV Prevention
- Antiretroviral Drug Cost
- **Initiating ART in Tx-naïve Patients**
- Drug Interactions

HIV and the Older Patient

- Defined > 50 yo
  - Two groups: newly dx and those living with HIV/AIDS on ART
  - 30% of people living with HIV/AIDS > 50
  - Trend will increasingly include care for 60-80 yo
- Areas of concern between aging and HIV
  - Age related co-morbidities complicates HIV tx
  - HIV may effect biology of aging
  - HIV screening remains low in this population

    2008 CDC survey only 35% adults (45-64 years) had ever been tested for HIV despite 2006 CDC recommendation

HIV and the Older Patient
Antiretroviral Therapy

- Initiating ART regardless of CD4 count
  - Older patients have poorer immunological and clinical response to ART than younger patients.
  - Most older HIV+ patients are diagnosed late in disease
  - Choice of ART regimen(s) is not age specific, however can be affected by other co-morbidities and medications.
  - Lack of information on long-term safety, efficacy, changes in pharmacokinetics, and potential drug interactions.
  - Design of specific clinical trials to optimize ART in these patients

Treatment for HIV Prevention

- ART as Prevention
  - Rate of new infections in US has remained stable for past 4 years (~50,000/year)
  - HIV transmission is decreased with lower viral load
    - community viral load
    - HPTN 052 Trial: Marked decrease in transmission in discordant couples
  - PrEP (pre-exposure prophylaxis)
    - Truvada recently FDA approved (July 2012)

ART Cost

Antiretroviral Agent	AWP Cost / month
Atripla	$2,081
Complera	$2,195
Truvada	$1,391
Epzicom	$1,119
Atazanavir (Reyataz)	$1,176
Darunavir (Prezista)	$1,230
Raltegravir (Isentress)	$1,171
Ritonavir (Norvir)	$308 (30 tabs) $617 (60 tabs)

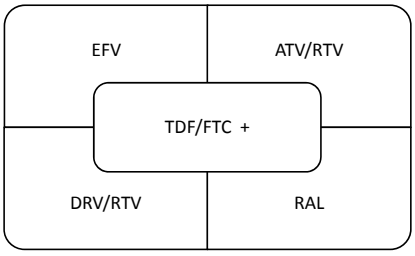
Trade-Offs With Generics

Advantages	Disadvantages
• Clear cost benefit	• May involve change of regimen for patients who are on coformulated or single-tablet regimens • Switch to the same drugs administered separately with generic substitutions • Possible problems with adherence

DHHS Recommended Initial Regimens

Preferred Agents for First-line Therapy	
NRTIs	• Tenofovir/emtricitabine
Plus a third agent	
NNRTI	• Efavirenz
Boosted PI	• Atazanavir/ritonavir
	• Darunavir/ritonavir
INSTI	• Raltegravir

Initial Regimen: Recommended/Preferred Agents



Surrogate Markers

- Efficacy of all antiretroviral clinical trials is based on:

-Clinical endpoints

-CD4+ T-lymphocyte

-HIV viral load (copies/ml)

DHHS Guidelines, March 2012: When to Start

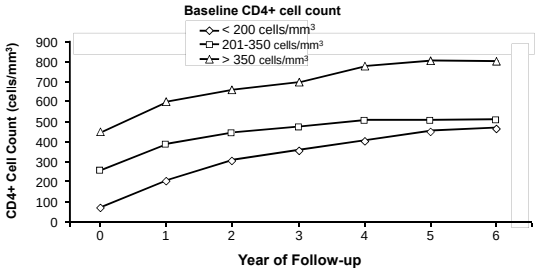
- Antiretroviral therapy recommended for all HIV-infected pts; *strength* of recommendation varies according to CD4+ cell count or condition

CD4+ Cell Count or Clinical Condition

- CD4 + count < 350 cells/mm³ (AI)
- CD4 + count 350-500 cells/mm³ (AII)
- CD4 + count > 500 cells/mm³ (BIII)

- History of AIDS-defining illness (AI)
- Pregnancy (AI)
- HIV-associated nephropathy (AII)
- HBV coinfection (AII)
- Patients at risk of transmitting HIV to sexual partners (AI, heterosexuals; AIII, others)
- HCV coinfection (BII)
- Patients > 50 years of age (BIII)

Full Immune Recovery Is Associated With Higher Baseline CD4+ Count



Moore R, et al. IAC 2006. Abstract THPE0109.

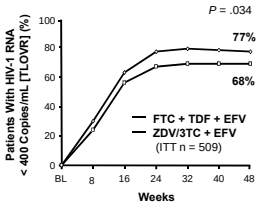
NRTI "Backbone"

Nucleoside Reverse Transcriptase Inhibitors

Truvada > Epzicom > Combivir

GS934: Week-48 Virologic Response

- N = 517 antiretroviral-naive patients randomized to:
  - TDF + FTC + EFV
  - ZDV/3TC + EFV
- Superior efficacy with TDF + FTC
- More discontinuations for AEs with ZDV/3TC



Tenofovir Adverse Effects

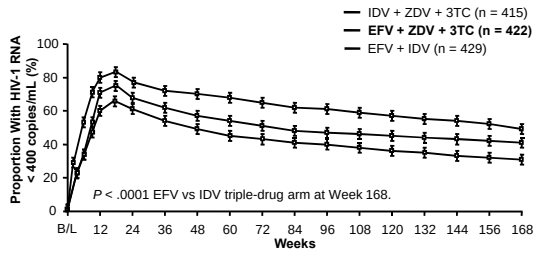
- Nephrotoxicity
  - Vitamin D deficiency, metabolic bone disease
  - Fanconi Syndrome
    - Elevated SCr
    - Proteinuria
    - Glucosuria
    - Hypophosphatemia

NNRTI

Nonnucleoside Reverse Transcriptase Inhibitors

Efavirenz > Rilpivirine > Nevirapine

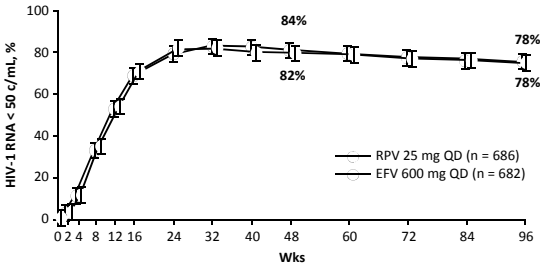
266-006: Sustained Virologic Response With EFV



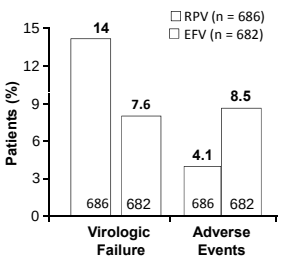
Efavirenz Adverse Effects

- CNS
  dizziness sleep disturbances agitation
  vivid dreams impaired concentration
- Hyperlipidemia (modest)
- Rash
- Drug induced hepatitis (rarely)
- Pregnancy category D
- False + urine toxicology screen for THC
- Drug interactions- CYP3A4 enzyme induction, effect on other CYP enzymes not clear

Rilpivirine vs Efavirenz 96 weeks



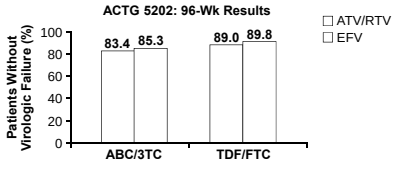
Causes of Failure at Wk 96



- More virologic failures with RPV vs EFV
  - Difference due to more VF between if BL VL > 100,000;
- D/C due to AE more common with EFV vs RPV

Trade-Offs: Efavirenz-Based Regimens

Advantages	Disadvantages
• Long history of use; much clinical trial data • Current gold standard for first-line therapy • As effective or more effective than other regimens in head-to-head comparisons • 1 pill QD coformulation of EFV/TDF/FTC	• Low genetic barrier to resistance—single mutation • CNS adverse effects • Teratogenicity • Potential drug interactions (CYP450)



Trade-Offs: Rilpivirine-Based Regimens

Advantages

- Less CNS side effects, well tolerated
- Pregnancy Category B
- More favorable lipid profile
- Smallest tablet

Disadvantages

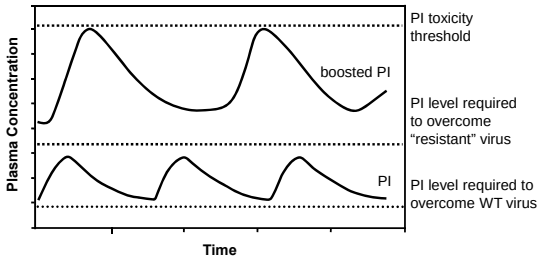
- Cross resistance to other NNRTIs
- Not recommended VL>100,000
- Expensive
- Must be taken with food
- DI with H2 blockers and PPI
- Coformulation not covered on Medicaid

Protease Inhibitors

- Require "boosting" with ritonavir

Darunavir/r = Atazanavir/r > lopinavir/r
All other PIs

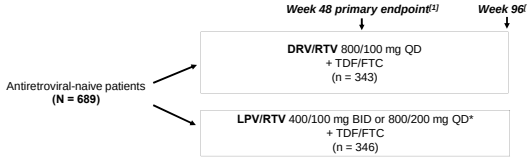
Boosting PI Levels With ritonavir



Moyle G, et al. Drugs. 1996;51:701-712.

ARTEMIS: DRV/RTV vs LPV/RTV in Treatment-Naive Patients

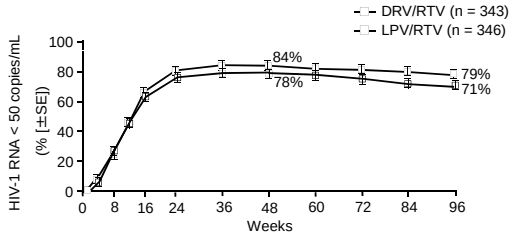
- Randomized, open-label phase III study
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48



*Dosing based on regulatory approval; 77% of patients received BID dosing.

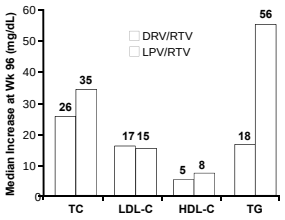
ARTEMIS: Week 48 and 96 Response

48 weeks non-inferior, 96 weeks superior- this is the first head-head PI trial in Tx naïve pts that showed superiority



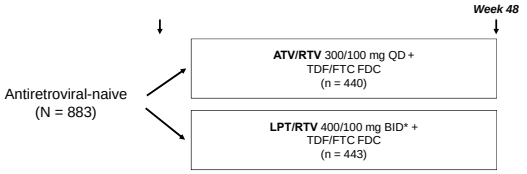
ARTEMIS: Wk 96 Lipid Substudy

- Statistically greater % increases in TC, TG in LPV/RTV arm than DRV/RTV arm ($P < .001$)

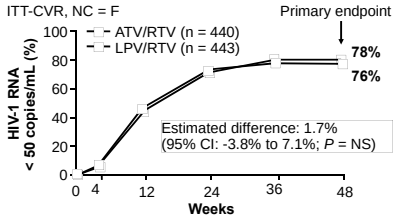


CASTLE: ATV/RTV vs LPV/RTV in Treatment-Naive Patients

- Multicenter, randomized, open-label phase III study
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48



CASTLE: Week 48 Response to ATV/RTV vs LPV/RTV in Naive Patients



- **At 96 weeks**, significantly more patients in the ATV/RTV arm achieved HIV-1 RNA < 50 copies/mL vs patients receiving LPV/RTV: 74% vs 68% ($p < .05$])

CASTLE: Mean Change in Fasting Lipids at Week 48

Lipid Measurement	Mean Change From Baseline to Week 48, %		*P* Value
	ATV + RTV (n = 440)	LPV/RTV (n = 443)	
TC	12	24	< .0001
LDL cholesterol	12	15	NR
HDL cholesterol	27	32	NR
Non-HDL cholesterol	7	21	< .0001
TG	13	51	< .0001

- **Less GI toxicity, higher rate of hyperbilirubinemia**

Protease Inhibitors Adverse Effects

- Gastrointestinal intolerance
- Rash (fosamprenavir = daruanvir > atazanavir)
- Hyperbilirubinemia (Atazanavir)
- Hepatitis (Rarely)
- Dyslipidemia/metabolic syndrome

  (Kaletra > other PIs)

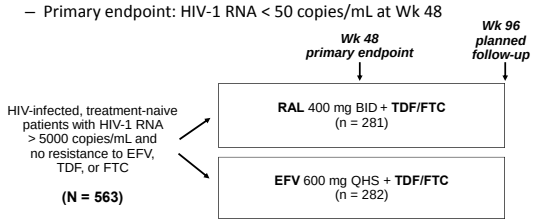
INSTIs

HIV Integrase Strand Transfer Inhibitors

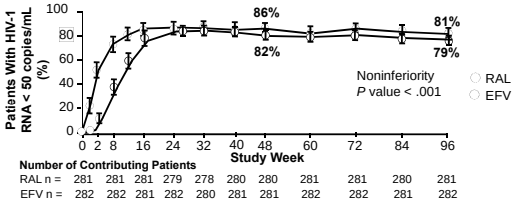
- Raltegravir (Isentress, Merck)
  - FDA approved 2009
  - BENCHMRK, STARTMRK, SWITCHMRK, REALMRK
- Elvitegravir (Gilead)
  - Phase III clinical trials "QUAD Pill"
  - FDA approval 1st quarter 2013?
- Dolutegravir (ViiV)
  - Phase III clinical trials completed

STARTMRK: RAL vs EFV in Treatment-Naive Patients

- Randomized, placebo-controlled trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48

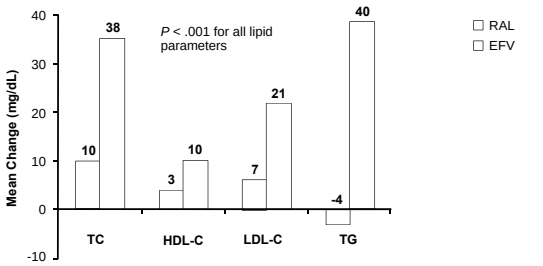


STARTMRK: Virologic Efficacy at Wk 96



- Significantly shorter time to virologic response with RAL vs EFV ($P = .001$)
- Similar CD4+ cell count increases with RAL vs EFV
  - +240 vs +225 cells/mm^3;

STARTMRK: Lipid Changes From Baseline to Week 96



Raltegravir Adverse Events

- Well tolerated – N/V/HA most common AE from clinical trials
  - creatinine kinase
  - myopathy
  - few cases of rhabdomyolysis with/without ARF
- Safe with no dosage change during pregnancy

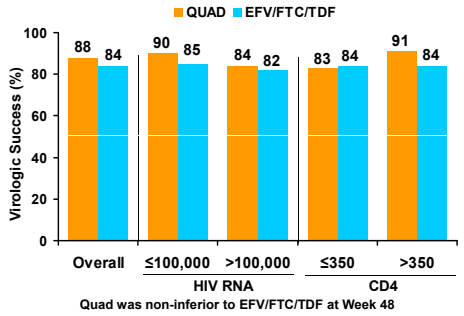
Lennox J, et al. ICAAC 2009. Abstract H-924b.

Elvitegravir
(Gilead)

- Requires boosting
- Ritonavir increases systemic exposure ~ 20 fold and half-life 3 fold allowing for QD dosing
- Potent HIV Integrase Inhibitor
- Led to development of Cobicistat Coformulated "QUAD Pill"

Tenofovir/emtricitabine/cobicistat/elvitegravir
300mg / 200mg / 150mg / 150mg

Quad vs. Atripla
Efficacy by Baseline VL & CD4



Quad was non-inferior to EFV/FTC/TDF at Week 48

Sax P, et al. CROI 2012; Seattle. Oral #101LB

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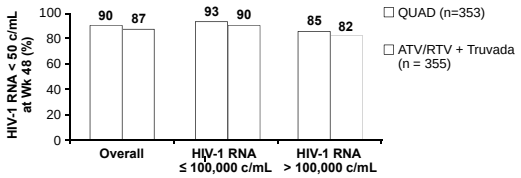
QUAD Regimen Noninferior to ATV/RTV Regimen at Wk 48



- Similar CD4+ cell count increases in both study arms at Wk 48

DeJesus E, et al. CROI 2012. Abstract 627.

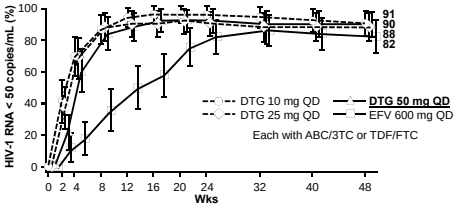
Elvitegravir vs Raltegravir

- Equally efficacious
- QD vs BID
- Both well tolerated
  - Few discontinuations due to adverse effects
- Drug Interactions > ELV
- Cross resistance
- Coformulation
- COST ?
- Will any of this matter once Dolutegravir is available?

Dolutegravir
ViiV

- QD integrase inhibitor without booster
- Lipid neutral
- Well tolerated
- No CYP P450 drug interactions
  - Metabolized via glucuronidation
- Active against RAL/ELV resistant mutations
- Coformulation with Epzicom in the future?

SPRING-1: Dolutegravir vs Efavirenz in ART-Naive Patients—Wk 48 Results



Van Lunzen J, et al. IAS 2011. Abstract TUAB0102.

Drug Interactions

Ritonavir > all other PIs = EFV > Raltegravir

Protease Inhibitor (Norvir) Drug Interactions

- Buprenorphine / Methadone- OK
- Phenytoin- dual DI, decreased PI and phenytoin levels
- Trazodone- 3 fold increase in AUC, use with caution.
- Voriconazole- Can use with low dose RTV (100 mg bid), voriconazole AUC deceased 40%, Cmin 25%
- Warfarin- decrease R-warfarin active metabolite AUC 33%, monitor
- Ca Channel Blockers- increase AUC for all CCB
- Statins- Simvastatin and lovastatin contraindicated, increase AUC for atorvastatin and rosuvastatin.
- Fluticasone- contraindicated
- Erectile Dysfuction- start low go slow: sildenafil 25 mg, vardenafil 2.5 mg in 72 hours

Atazanavir Drug Interactions

- Must use ritonavir boosted ATZ with tenofovir (ATZ AUC ↓25%)
- **Proton Pump Inhibitors**
- **Tx-naïve**: PPI should not exceed dose comparable to omeprazole 20 mg qd (OTC dose) and must be taken 12 hours prior to boosted ATZ.
- **Tx-experienced**: <u>PPI should not be used</u>
- **H2 Antagonists**

  Tx-naïve: ATZ should be given 2 hours before or 10 hours after H2 blocker

  Tx-experienced: ATZ can be given simultaneously or 10 hours after H2 blocker or increase ATZ dose to 400 mg/ritonavir 100 mg if both tenofovir and H2 blocker.

Antiretroviral Drug Interactions

Hepatitis C Protease Inhibitors

Telaprevir (Incivek)	Boceprevir (Victrelis)
• $49,200 for 12 week treatment	• $1,100/week of treatment
• Acceptable HAART regimens: – Atazanavir/ritonavir – Atripla – Raltegravir	• Acceptable HAART regimens: - Raltegravir
• Dose increase with Atripla or EFV to 1125 mg (3 tabs) po q8h	• Do NOT adminster with NNRTIs or boosted PIs

RAL Drug Interactions

- Does not inhibit, induce, nor is RAL a substrate of CYP 450 enzymes: glucuronidation (UGT1A1)
- Rifamycins
  - 40% reduction in RAL AUC; RAL dose increased to 800 mg BID when administered with rifampin
  - No dose adjustment with rifabutin

Efavirenz Drug Interactions

- Hepatic enzyme induction
  - Methadone
  - Calcium channel blockers
  - Statins (atorvastatin, simvastatin, pravastatin)
  - Itraconazole, voriconazole (↑400mg bid, ↓ EFV 300 mg qd)
  - Rifabutin (increase dose to 450 mg qd)
  - Warfarin (monitor INR closely)
  - Erectile Dysfunction drugs (↓ AUC)

References

- Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1-239. Available at: http://www.aidsinfo.nih.gov
- Thompson, MA et al. IAS-USA Guidelines. JAMA 2012;308:387-402.
- http://www.hiv-druginteractions.org