TUESDAY AM HIV DISCUSSION SERIES

8/25/2015

Management of Treatment-Naïve Patients

Ellen Kitchell, M.D.

HAART Initiation/HIV Treatment for Antiretroviral-Naïve Patients

Ellen Kitchell, M.D.

The Art of HAART…

Annoying Socratic Question #1

- Your patient is a 60 year-old obese long-haul truck driver. He has hypertension. Which of the following agents would be *least* likely to be effective in durably managing his blood pressure?
  - **A. Lisinopril**
  - **B. Hydrochlorothiazide**
  - **C. Amlodipine**
  - **D. Olmesartan**

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  - **D. Olmesartan**

Common Sense Precaution

- Highly-Active Antiretroviral Therapy is extremely effective in suppressing HIV viremia and prolonging life in patients infected with the HIV virus…
- …if the patients in question actually swallow the pills.

Goals of Therapy

- Durably suppress HIV viral load to <48 copies/mL
- Provide regimen that is compatible with patient's lifestyle, in order to ensure **maximal adherence**
- Preserve future therapeutic options
- Restore/preserve immune function
- **Minimize toxicity**

A very good place to start…

- Department of Health and Human Services Guidelines

  http://www.aidsinfo.nih.gov/guidelines/
- International AIDS Society-USA (IAS-USA)

  https://www.iasusa.org/content/antiretroviral-treatment-adult-hiv-infection-0

STARTING HAART: OPTIMAL TIMING

The shifting pendulum…

- In the mid-1990s, recommendations were to start everyone on HAART regardless of CD4 count
- …then people started developing disabling side effects and resistance to antiretrovirals, so CD4 cut-offs were developed, which changed over time
- More recent medications considered to have fewer long-term side effects, so recent guidelines have focused on early treatment

START

- Randomized, controlled clinical trial of patients with CD4 count >500 cells/uL
- Randomized to either immediate initiation of therapy versus deferred until CD4 <350 cells/uL or clinician's judgement
- Various regimens chosen (most popular regimen was Atripla)

START Results

- 4600 patients followed for average 3 years
- Median entry CD4 of 650 cells/uL
- Evaluated “serious-AIDS related events,” serious non-AIDS related events and death
- Serious non-AIDS related events included: CV event such as heart attack, stroke, and stents; ESRD, decompensated liver disease, non-AIDS defining cancer (except skin cancer)

START Results

- Events occurred in 96 patients in the deferred-initiation arm (4.1%) versus 42 in the immediate-initiation arm
- Most common events were CV disease, non-AIDS defining cancer, and TB
- Most events occurred in patients with CD4>500 cells/uL
- 72% relative reduction in serious AIDS-related events in immediate-initiation group, related to decreases in rates of TB, KS and lymphoma
- 39% relative reduction in non-AIDS defining events, mostly related to cancer

TEMPRANO ARNS 12136

- Enrolled >2000 patients in Cote d'Ivoire
- Patients with CD4 <800 cells/uL randomized to immediate versus deferred therapy
- Also involved +/- use of isoniazid
- Evaluated all cause mortality, AIDS diagnoses, non-AIDS malignancies, and invasive bacterial infection
- Lower risk of primary events in early ART group (0.56 HR)

- Temprano ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. Jul 20 2015.

HPTN 052: Immediate vs Delayed ART for HIV Prevention in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm^3

(N = 1763 couples)

Immediate HAART*
Initiate HAART at CD4+ cell count 350-550 cells/mm^3
(n = 886 couples)

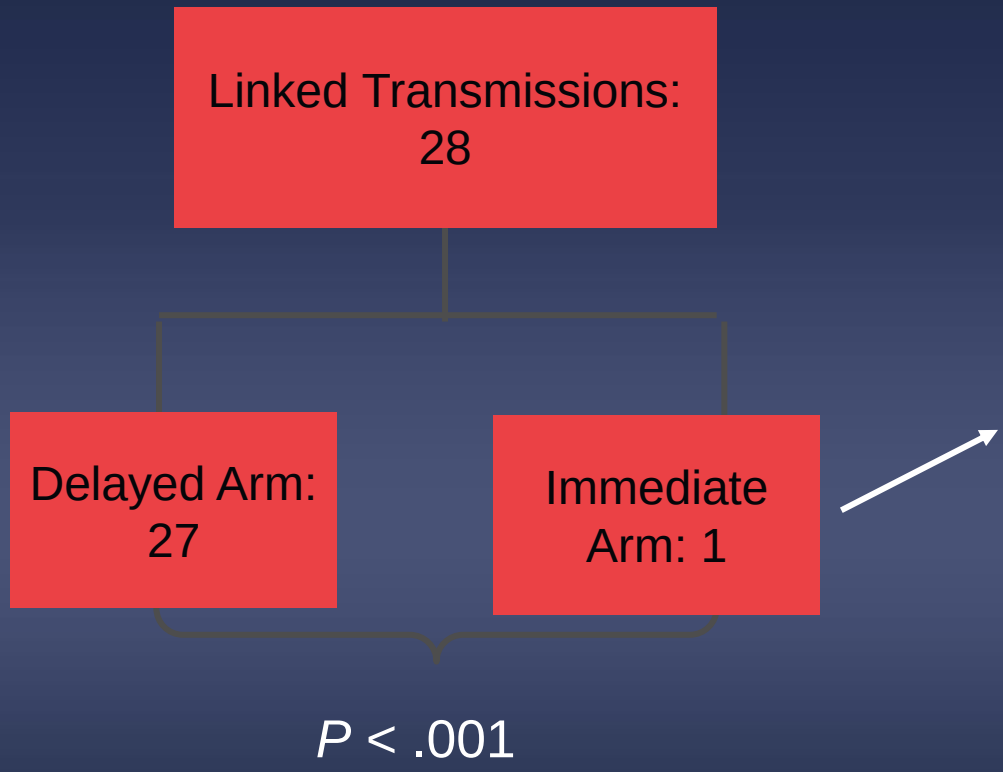
Delayed HAART
Initiate HAART at CD4+ cell count ≤ 250 cells/mm^3†
(n = 877 couples)

*72% of pts received ZDV/3TC + EFV
†Based on 2 consecutive values ≤ 250 cells/mm^3.

- Primary efficacy endpoint: HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

Cohen MS, et al. N Engl J Med. 2011;365:493-505.

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples



Cohen MS, et al. N Engl J Med. 2011;365:493-505.

HPTN 052: Partner Infections With Early vs Delayed ART

- No linked HIV transmissions observed when index participant stably suppressed on ART

Partner Infections, n (rate/100 PY)	April 2005 - May 2011		May 2011 - May 2015		Overall (April 2005 - May 2015)	
	Early (1751 PY F/U)	Delayed (1731 PY F/U)	Early (2563 PY F/U)	Delayed (2449 PY F/U)	Early (4314 PY F/U)	Delayed (4180 PY F/U)
All	4 (0.23)	42 (2.43)	15 (0.59)	17 (0.69)	19 (0.44)	59 (1.41)
Linked	1 (0.06)	36 (2.08)	2 (0.08)	7 (0.29)	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %						
All infections	91	--	14	--	69	--
Linked infections	97	--	72	--	93	--

- 8 linked HIV infections diagnosed after seropositive pt started ART
  - **4 infections likely occurred before, or soon after, ART initiation, and 4 infections occurred after ART failure in seropositive pt**
- Unlinked partner infection rates similar between study arms

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

PARTNER Study

- 1110 sero-discordant couples
- 40% homosexual
- Inclusion criteria of having sexual contact without condoms at least some of the time
- HIV+ partner on ARVs, VL <200 copies/mL
- So far NO transmission within couples where HIV+ partner had undetectable viral load

Rodger A et al. *HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER study.* 21st Conference on Retroviruses and Opportunistic Infections, Boston, abstract 153LB, 2014.

Potential Benefits of Antiretroviral Therapy Initiation at High CD4 Counts

Benefits:

- Mortality benefit
- Prevention of cancer, heart disease
- Possible prevention of neurocognitive decline
- Possible prevention of comorbidities
- Prevention of transmission

Potential Risks of Antiretroviral Therapy Initiation at High CD4 Counts

- Toxicities (including long-term toxicities, which may not be known)
- Development of resistance
- Adherence concerns
- Cost, in resource-limited settings

Guidelines for Timing of Antiretroviral Therapy 2015: DHHS

- **Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression (AI)**.
- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV. The strength of and evidence for this recommendation vary by transmission risks: perinatal transmission **(AI)**; heterosexual transmission **(AI)**; other transmission risk groups **(AIII)**

- “Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence. Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.”

Guidelines for Timing of Antiretroviral Therapy: IAS-USA

- Treatment is recommended for all adults with HIV infection

Guidelines for Antiretroviral Initiation: World Health Organization

- For patients with:
  - **CD4 <500 cells/uL**
  - **History of AIDS-defining illness**
  - **Pregnancy**
  - **Serodiscordant couples**

HAART IN THE TRENCHES: INITIATING IN THE SETTING OF OPPORTUNISTIC INFECTION

ACTG 5164: “Immediate” versus Deferred Antiretroviral Therapy in the Setting of Opportunistic Infection

- Randomized patients with OIs to starting ART within 14 days versus deferring on average for 45 days
- AIDS progression/death in 14% of “early HAART” versus 24% in deferred arm (not statistically significant)
- However, fewer AIDS progression/deaths and longer time to AIDS progression/death

HAART-Immediate Opportunistic Infections

- Symptomatic HIV infection
- Cryptosporidium/Microsporidium
- Kaposi’s Sarcoma
- Lymphoma (especially PCNSL)
- PML
- HIV dementia

Defer HAART in:

- Cryptococcal meningitis
- CNS mass lesion
- TB with higher CD4 count

WHAT TO START

Considering HAART Options

- Baseline genotype
- Consider comorbidities
- Evaluate lifestyle concerns, work, habits
- Plans for pregnancy
- Review concomitant medications/drug interactions
- Potential side effects
- Baseline labs (renal, hepatic function)
- Know HBV/HCV status
- Dosing frequency/pill burden
- Cost/insurance issues

Preferred Regimens: DHHS Guidelines April 2015

- 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) + 3rd active drug
  - Protease inhibitor (PI) boosted with ritonavir
  - Integrase inhibitor (INSTI)
- 3 active medications seems to be the magic number (for now…)
  - Currently 2 and 4+ drug regimens are not as popular
  - Combination products may make <3 pills!

Protease-Inhibitor Based Regimens

- Darunavir (PREZISTA) + ritonavir (NORVIR) + tenofovir/emtricitabine (TRUVADA)

Integrase-Inhibitor Based Regimens

- Dolutegravir (TIVICAY) + tenofovir/emtricitabine (TRUVADA) OR abacavir/lamivudine (EPZICOM)
  - **TRIUMEQ (dolutegravir + abacavir + lamivudine)**
- Elvitegravir/cobicistat/tenofovir/emtricitabine (STRIBILD)
- Raltegravir (ISENTRESS) + tenofovir/emtricitabine (TRUVADA)

Changes Since Last Revision of DHHS Guidelines

- 4 integrase-inhibitor based regimens, one PI-based regimen
- Previously recommended regimens for baseline CD4, VL cutoffs now in “Alternative” category
- Atazanavir and efavirenz have fallen out of the “recommended” category due to tolerability concerns

“Alternative” Regimen Options

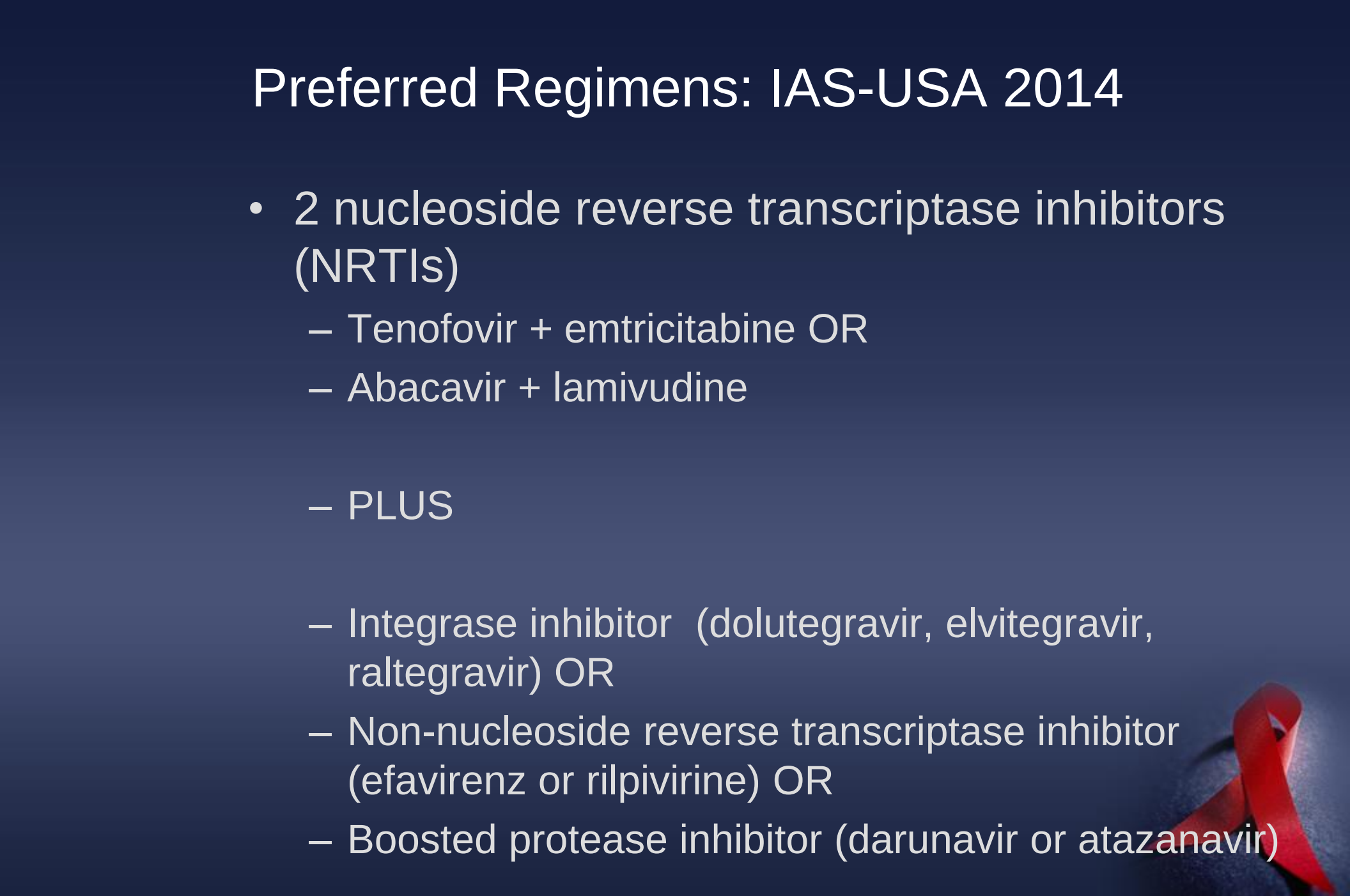
- “Effective and tolerable” but have potential disadvantages when compared with recommended regimens
- “An alternative regimen may be the preferred regimen for [your] patient.”

Alternative Options in DHHS

- Regimens:
  - **Efavirenz/emtricitabine/tenofovir**
  - **Rilpivirine/emtricitabine/tenofovir (only if pretreatment RNA <100k, CD4 >200)**
  - **Atazanavir/ritonavir + tenofovir/emtricitabine**
  - **Atazanavir or darunavir co-formulated with cobicistat**

Preferred Regimens: IAS-USA 2014

- 2 nucleoside reverse transcriptase inhibitors (NRTIs)
  - Tenofovir + emtricitabine OR
  - Abacavir + lamivudine
  - PLUS
  - Integrase inhibitor (dolutegravir, elvitegravir, raltegravir) OR
  - Non-nucleoside reverse transcriptase inhibitor (efavirenz or rilpivirine) OR
  - Boosted protease inhibitor (darunavir or atazanavir)



Preferred Regimen: WHO 2013

- Efavirenz + emtricitabine + tenofovir

Use of Efavirenz in Naïve Patients (SUSTIVA/ATRIPLA)

Efavirenz Is Efficaceous

- Up until recently, efavirenz was non-inferior or superior to other ARVs at suppressing HIV, regardless of baseline viral load or CD4
- Key studies comparing efavirenz to other options:
  - ACTG 5142 efavirenz superior to lopinavir/ritonavir (KALETRA)
  - ACTG 5202: non-inferior to atazanavir/ritonavir
  - ECHO/THRIVE: non-inferior to rilpivirine
  - GS-US-236-0102: non-inferior to elvitegravir

More Recent Efficacy Trials

- In studies of newer integrase-inhibitor regimens (dolutegravir, raltegravir), some regimens have demonstrated superiority to efavirenz (e.g. SINGLE)
- Primarily based on more discontinuations due to adverse effects in efavirenz arm

Adverse Effects of Efavirenz

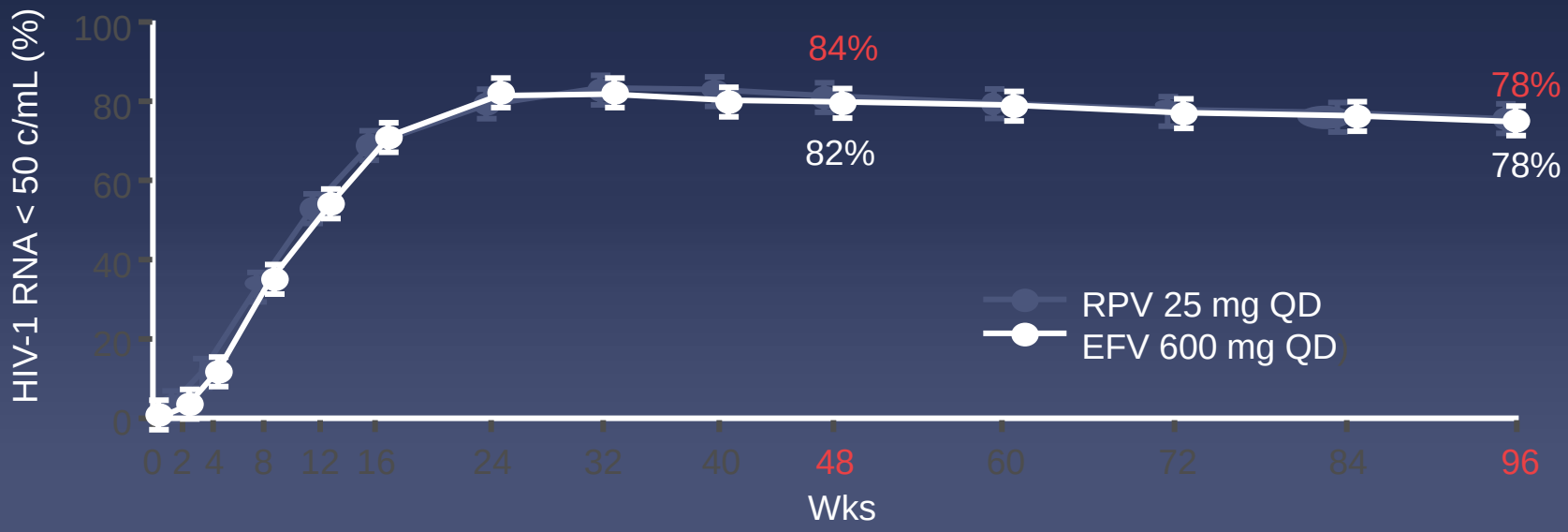
- Neuropsychiatric side effects are common
- Strange/vivid dreams in ~50%
- Dizziness/feeling “drunk”
- Depression, unstable mania
- Increased suicidality
- Potential teratogen – not good choice for child-bearing-age females
- Some drug interactions (substrate of CYP3A4 and inducer of 3A4/2D6)

Risks of Failure with Efavirenz

- Low genetic barrier to resistance—single point mutation
  - Easy to develop resistance to this medication with non-adherence and treatment interruptions
- Higher risk of NRTI resistance with NNRTI failure
  - When you fail the regimen, you can fail with a number of mutations to the accompanying drugs
- It’s easier to adhere to this regimen but the implications of non-adherence can be disastrous!

Why choose rilpivirine (EDURANT/COMPLERA)?

ECHO/THRIVE: Rilpivirine vs Efavirenz in Treatment-Naive Patients



- Discontinuations due to side effects more common with EFV vs RPV: 8.5% vs 4.1%
- More virologic failures with RPV vs EFV: 14% vs 7.6%
  - **Difference due to more VF between Wks 0-48 at HIV-1 RNA > 100,000**
  - **NRTI mutations more common with virologic failure on RPV vs EFV**
  - **Cross-resistance to ETR more common with RPV failure (E138K mutation)**

Lancet 2011; 378(9787): 238-46.

Rilpivirine versus Efavirenz

- Reduced response to rilpivirine vs efavirenz at baseline viral load > 100,000 copies/mL and CD4+ cell counts < 200 cells/mm^3
- Virologic failure in rilpivirine-treated subjects led to higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz

Rilpivirine Usage

- Only approved for relatively “well” patients
- CD4 >200 cells/uL
- Viral load <100,000 copies/mL
- PPI lowers absorption – not a good choice for hospitalized patients

Pros and Cons of Rilpivirine

- PROS
  - **Fewer neuropsychiatric side effects**
  - **Very favorable lipid profile**
  - **Less rash**
  - **Lower discontinuation rate than efavirenz**

- CONS
  - **Increased rates of virologic failure (especially in patients with viral load >100,000 copies/mL)**
  - **Virologic failure leads to resistance to etravirine (2nd generation NNRTI)**
  - **Needs acid absorptions (no PPIs!) and to be taken with food**
  - **Some drug interactions (mostly that interfere with rilpivirine levels)**

Why use a protease inhibitor-based regimen?

Protease Inhibitors

- Very potent class of medications
- Quicker at restoring CD4 count than NNRTI class
- Durable at suppressing virus
- High genetic barrier to resistance
- If patients fail a PI based regimen, rarely develop mutations, and if so, PI mutations are very rare (not true of integrase or NNRTI based regimens)
- Forgiving of non-adherence

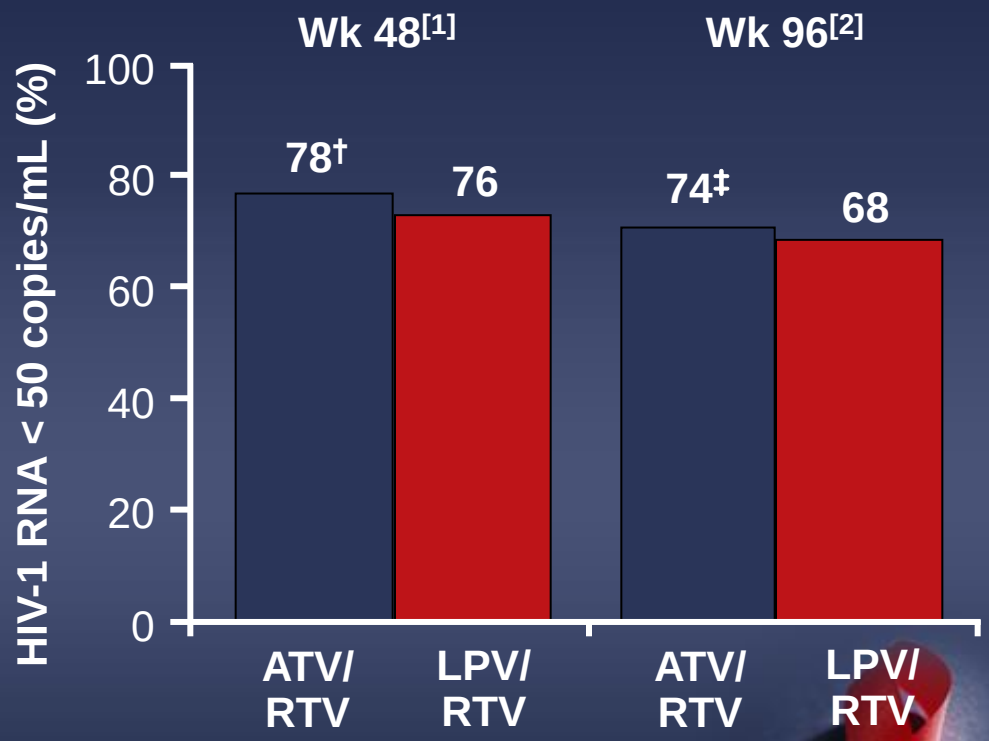
Adverse Effects of the Protease Inhibitor Class

- Higher pill count
- Gastrointestinal side effects (nausea/vomiting/diarrhea)
- Inhibit cytochrome P450 enzyme system
- Metabolic abnormalities
  - Dyslipidemia
  - Insulin resistance
  - Lipodystrophy, weight gain
  - Older Pis implicated in stroke, MI

CHOOSING AMONG THE RITONAVIR-BOOSTED PIS

CASTLE: Atazanavir/ritonavir vs Lopinavir/ritonavir in Antiretroviral-Naïve Patients

- Atazanavir/ritonavir versus Lopinavir/ritonavir
  - **Plus tenofovir/emtricitabine**
- Atazanavir non-inferior to lopinavir/ritonavir at week 48; superior at week 96 of patients with undetectable HIV viral load
- CD4+ gain similar between groups



1. Molina JM, et al. Lancet. 2008;372:646-655

Other Efficacy Trials for Atazanavir (Reyataz)

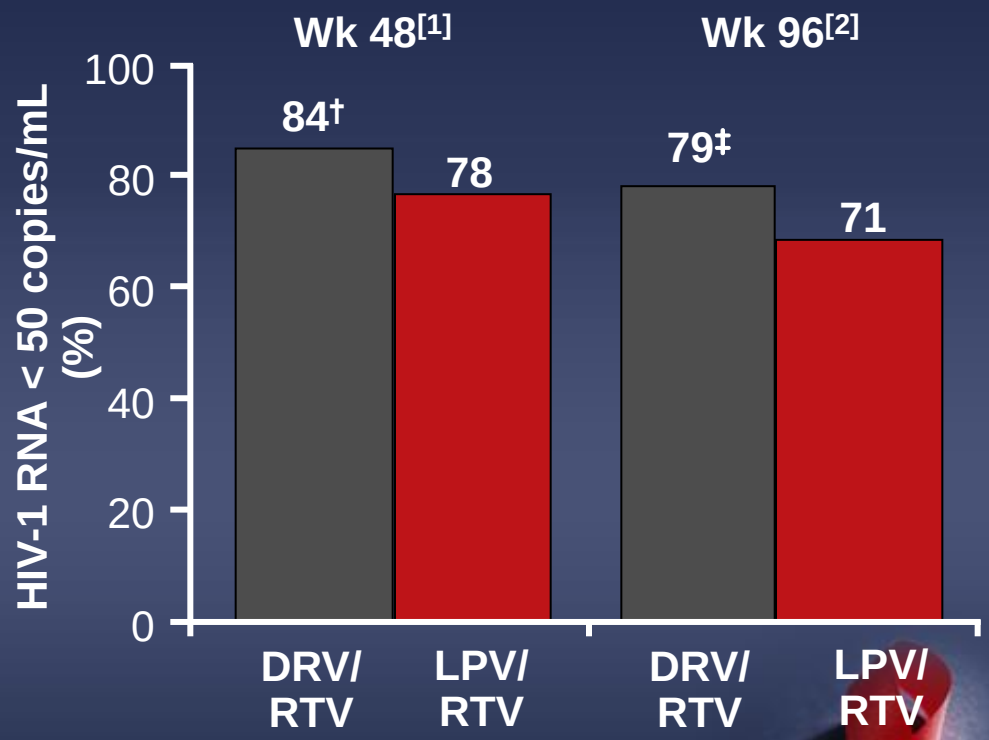
- ACTG 5202 showed similar efficacy between efavirenz + atazanavir
- GS-236-0103 showed similar efficacy between elvitegravir + atazanavir
- ACTG 5257 showed similar virologic efficacy between atazanavir, darunavir and raltegravir
  - **However, more treatment discontinuations in atazanavir group**

Unique Adverse Effects to Atazanavir

- Indirect hyperbilirubinemia
  - Functional Gilbert's syndrome
  - Expected and harmless to patient except for cosmetic appearance
  - Scleral icterus, jaundice
  - Some patients do not like the appearance
  - Is NOT supposed to cause AST/ALT elevation
- Need for acidic gastric pH for absorption
- Nephrolithiasis (rare)

ARTEMIS: Darunavir/ritonavir vs Lopinavir/ritonavir in Antiretroviral-Naive Patients

- Darunavir/ritonavir versus lopinavir/ritonavir
  - **Plus tenofovir/emtricitabine**
- Darunavir/ritonavir noninferior to lopinavir/ritonavir at week 48; superior at week 96 of patients with undetectable HIV viral load
- CD4+ gain similar between groups



1. Ortiz R, et al. AIDS. 2008;22:1389-1397.

Other Efficacy Trials for Darunavir in Naïve Patients

- ACTG 5257 showed similar virologic efficacy to raltegravir
- FLAMINGO study showed darunavir had lower rate of virologic suppression than dolutegravir
  - **Driven by drug discontinuation in darunavir group**

Unique Adverse Effects to Darunavir

- Sulfonamide moiety
  - **Use in caution with patients with severe sulfa allergy; however most patients with h/o sulfa allergy tolerate darunavir well**

Weighing the Options: Choosing Among Preferred Boosted PIs

PI	Daily Pill Burden, Food Requirements	QD?	Other Considerations
ATV/RTV	2, with food	Yes	▪ Absorption impaired with acid-reducing agents ▪ Associated with rise in unconjugated bilirubin and scleral icterus in 4% to 9% of pts
DRV/RTV	2, with food	Yes	▪ Also highly effective against PI-resistant virus in PI-experienced pts ▪ Rash in ~ 3% of pts; use with caution in pts with sulfa allergy

Integrase-Inhibitor Based Regimens

STARTMRK: Raltegravir vs Efavirenz in Treatment-Naive Patients

HIV-infected, treatment-naive pts with HIV-1 RNA > 5000 copies/mL and no resistance to EFV, TDF, or FTC

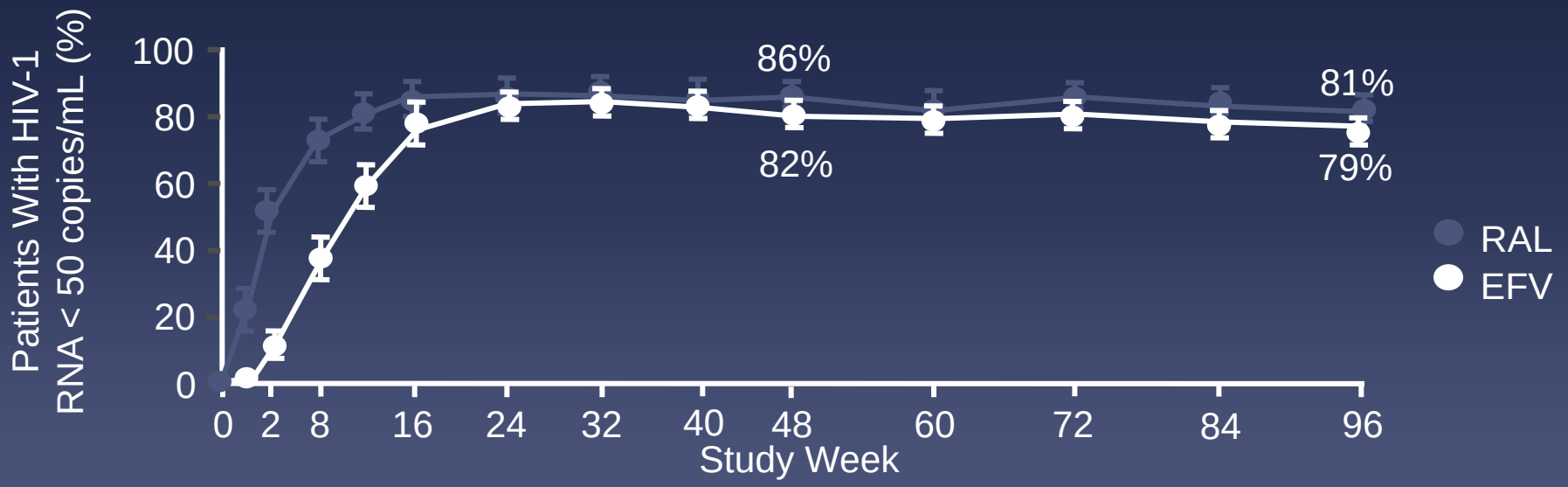
(N = 563)

RAL 400 mg BID + **TDF/FTC**
(n = 281)

EFV 600 mg QHS + **TDF/FTC**
(n = 282)

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.

STARTMRK: Virologic and Immunologic 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; Δ: 15 cells/mm^3 (95% CI: -13-42)

Other Efficacy Studies for Raltegravir

- ACTG 5257 compared atazanavir, darunavir and raltegravir in combination with tenofovir/emtricitabine
- Similar virologic efficacy in all arms
- Fewer discontinuations in darunavir and raltegravir arms (primarily driven by hyperbilirubinemia in atazanavir arm)
- Raltegravir superior to both comparator arms in composite endpoint of time to virologic failure or treatment failure
- Ann Intern Med. 2014 Oct 7;161(7):461-71.

ACTG 5257

- Virologic failure with drug resistance occurred infrequently
- More common in patients assigned to raltegravir arm
- Integrase inhibitor mutations found in all patients who developed virologic failure with drug resistance
- Less bone mineral density loss in integrase inhibitor group

Adverse Effects of Raltegravir

- Very well tolerated
- Rarely causes CPK elevations, rhabdomyolysis, myositis
- Rare rashes
- Minimal drug interactions – great for psych patients and herbal medication takers

Raltegravir Versus Other Options

- Benefits of using raltegravir
  - **Considered least metabolically toxic, both in terms of lipodystrophy and effect on triglycerides**
  - **Lack of drug interactions**
  - **Minimal side effects**
  - **Quick virologic suppression and immunologic recovery**
- Concerns about raltegravir
  - **Only option with BID dosing**
  - **Lower genetic barrier to resistance than PIs (probably higher than NNRTIs)**
  - **Cost**

Why would you use elvitegravir (STRIBILD)?

Elvitegravir/Cobicistat/TDF/FTC vs Efavirenz/TDF/FTC in Treatment-Naive Patients

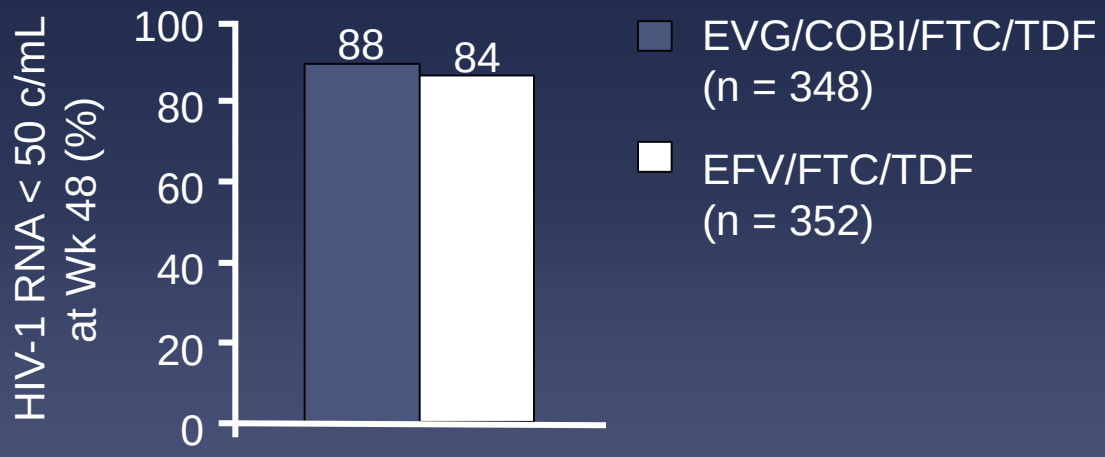
HIV-infected
treatment-naive patients with
HIV-1 RNA ≥ 5000 copies/mL,
any CD4+ cell count,
CrCl ≥ 70 mL/min

(N = 700)

Elvitegravir/Cobicistat/TDF/FTC QD
+ EFV/TDF/FTC placebo QD
(n = 348)

EFV/TDF/FTC QD
+ Elvitegravir/Cobicistat/TDF/FTC placebo QD
(n = 352)

Elvitegravir/Cobicistat Regimen Noninferior to Efavirenz Regimen

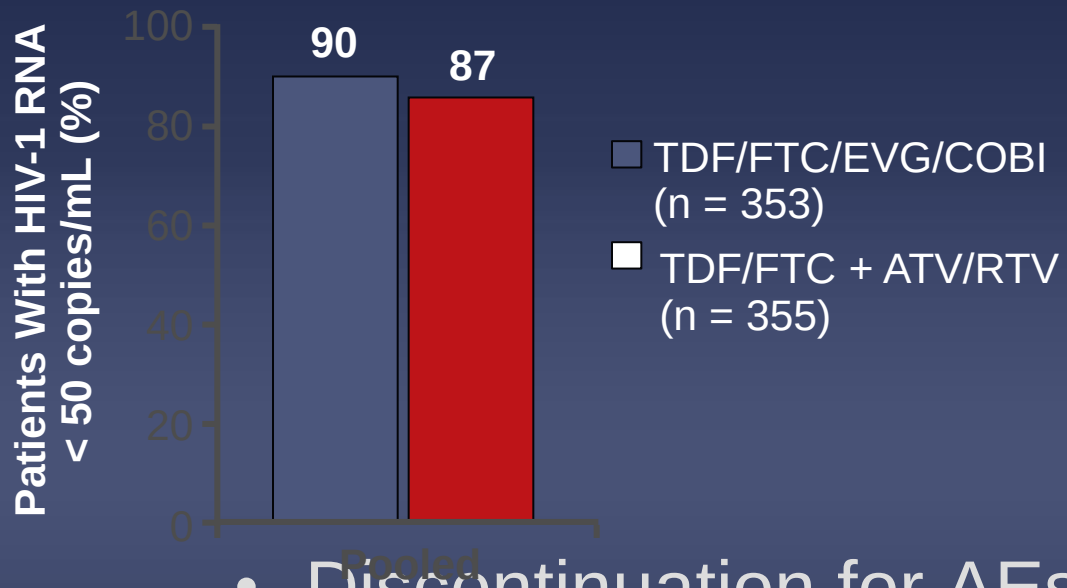


- Greater CD4+ count increase with elvitegravir vs efavirenz: 239 vs 206 cells/mm^3 (*P* = .009)
- Among pts with confirmed virologic failure or rebound, resistance detected in 8/14 pts in EVG/COBI arm vs 8/17 pts in EFV arm
  - **Primary integrase mutations and primary NNRTI mutations observed in 7 and 8 pts in EVG/COBI and EFV arms, respectively**
  - **All 8 pts in EVG/COBI arm had M184V/I mutation vs 2 pts in EFV arm; 3 and 2 had K65R, respectively**

Sax P, et al. CROI 2012. Abstract 101

QUAD vs ATV/RTV + TDF/ FTC: 48-Wk Results

- Phase III trial in treatment-naive patients

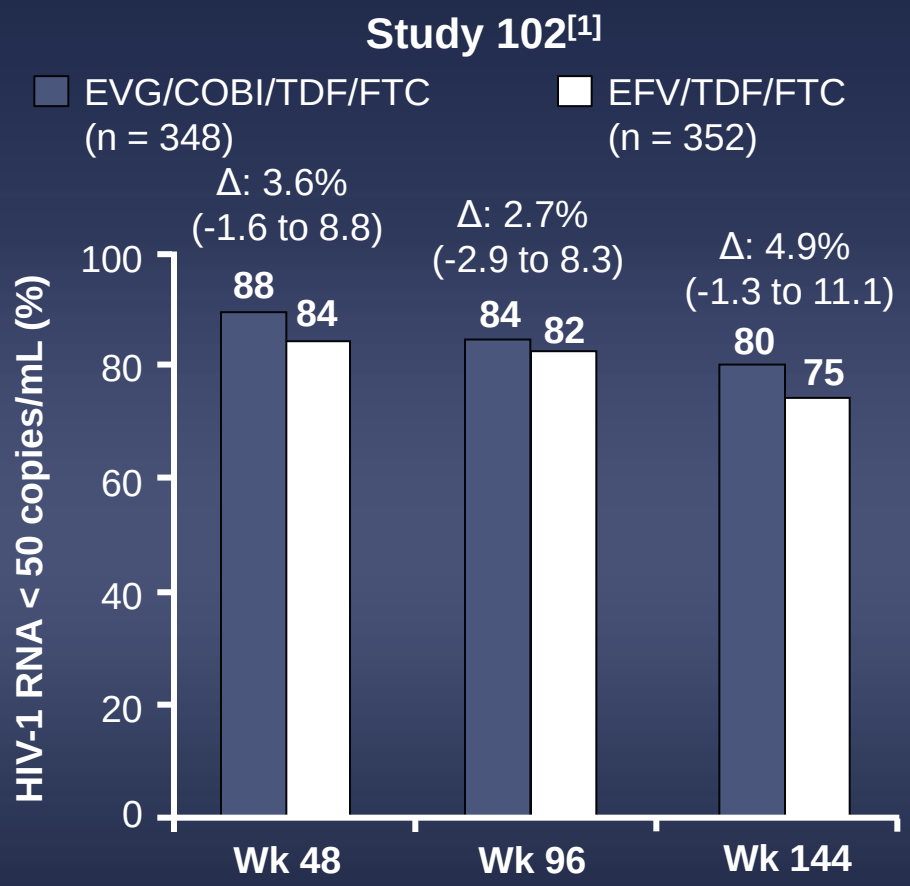


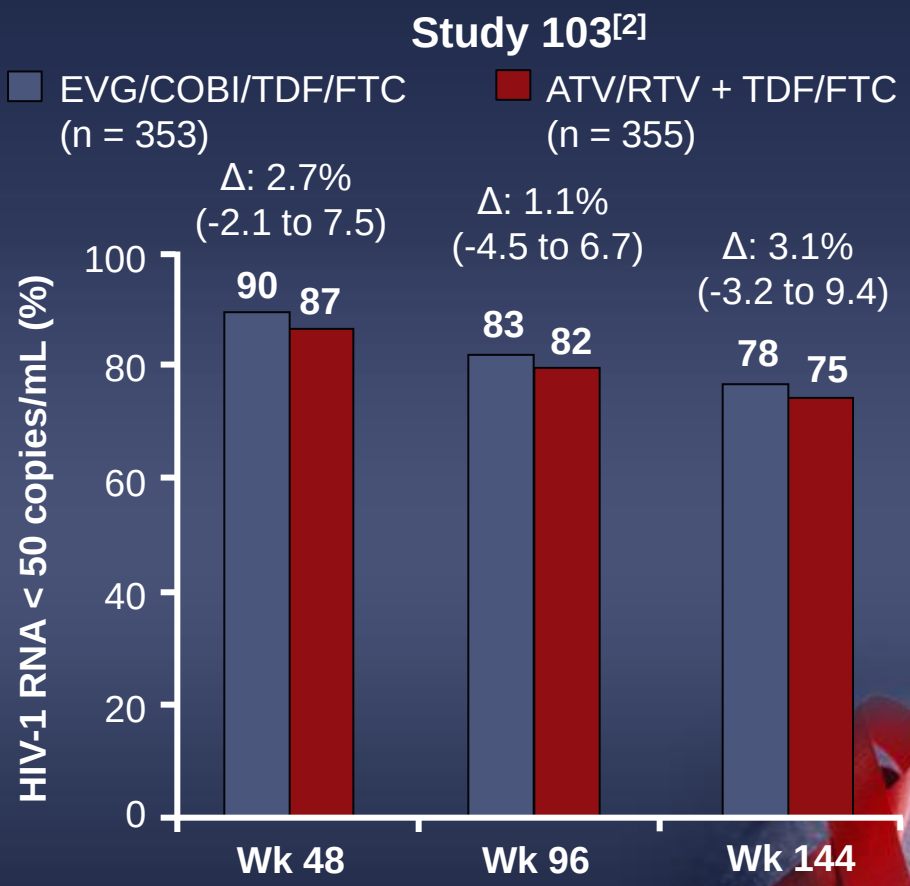
- Discontinuation for AEs higher in ATV/RTV arm (5.1% vs 3.1%), mainly because of hyperbilirubinemia

Results

- Elvitegravir/cobicistat non-inferior to atazanavir/ritonavir regimen at week 48
- Similar CD4 cell count increases in both study arms
- In patients with confirmed virologic failure, resistance detected in 5/12 patients in elvitegravir arm; no resistance in atazanavir arm
  - **4/5 had M184V mutation and 4 had primary integrase mutations**

EVG/COBI Noninferior to EFV and to ATV/RTV, With TDF/FTC, Through Wk 144





1. Wohl DA, et al. J Acquir Immune Defic Syndr. 2014;65:e118-e120.
2. Clumeck N, et al. J Acquir Immune Defic Syndr. 2014;65:e121-e124.

Elvitegravir Adverse Effects

- Elvitegravir very well-tolerated, main side effect was nausea. Headaches also reported.
  - Significantly greater increase in median serum creatinine from baseline : average 0.1 mg/dL
  - Thought to be related to cobicistat inhibition of creatinine secretion in distal tubule
  - Not recommended for patients with estimated creatinine clearance <70 mg/dL

JAIDS 2013; 63(1): 96-100.

Pros and Cons of Stribild

- Pros

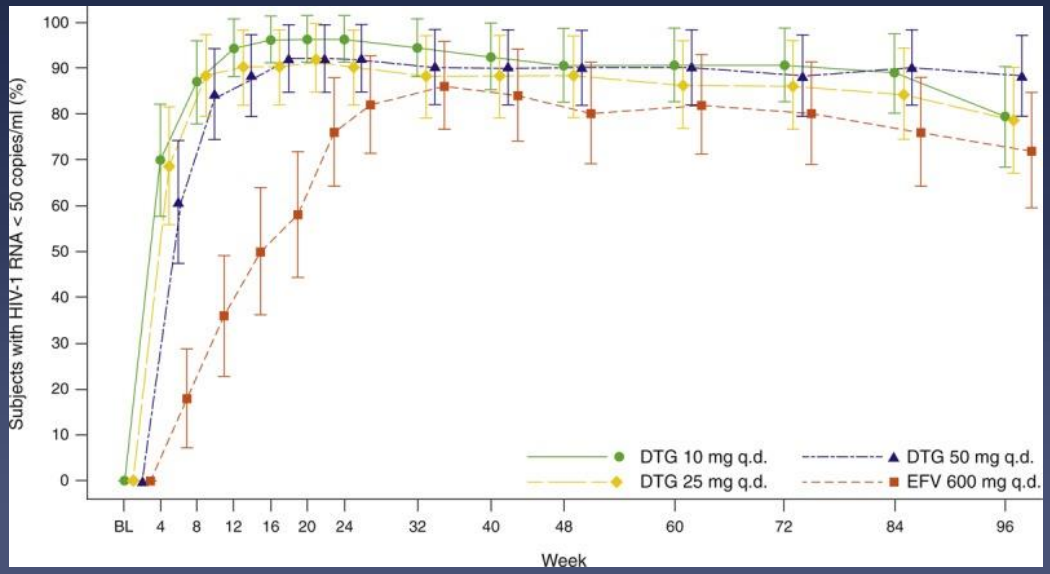
- Low side effect profile
- Highly effective at viral suppression
- Low pill burden

- Cons

- Drug interactions
- Expense
- Monitoring renal function

Why use dolutegravir (TIVICAY/TRIUMEQ)?

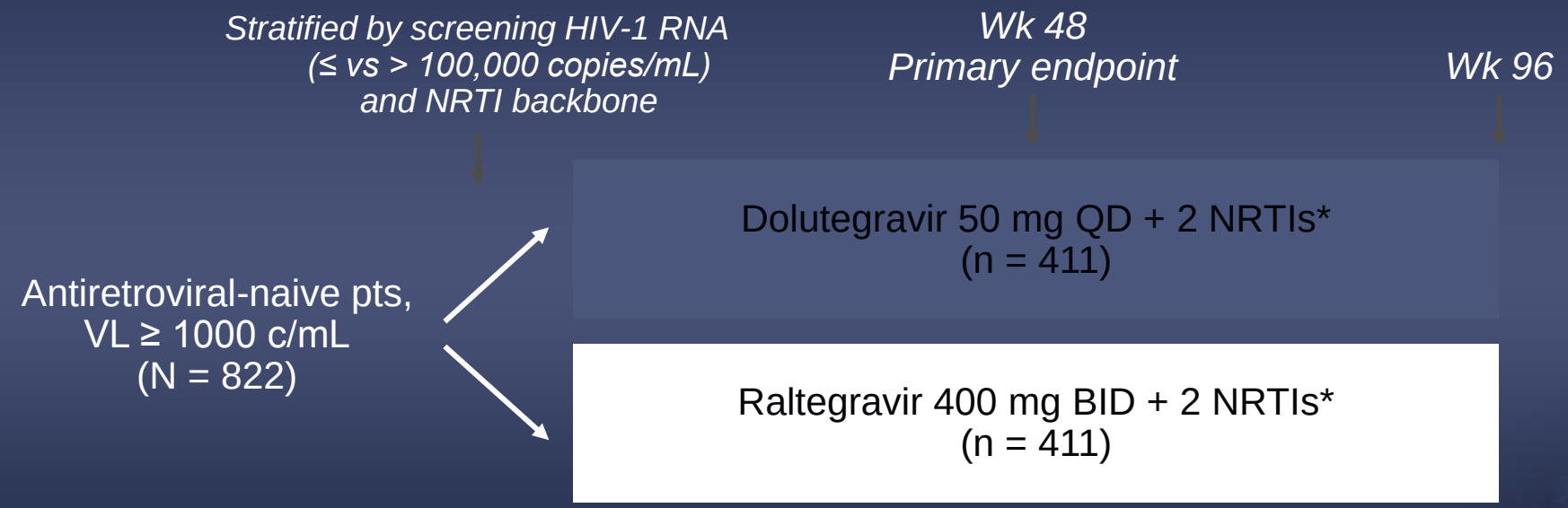
SPRING-1: Phase IIb Dolutegravir vs Efavirenz in ART-Naive Patients—Wk 96 Results



- 88% of patients achieved undetectable viral load as compared to 72% in efavirenz group
- No integrase resistance associated mutations detected in patients failing DTG
- Grade 2-4 AEs numerically higher in EFV arm vs DTG arms
- DTG associated with low-level changes in serum creatinine
  - **Thought to be inhibition of renal transporter rather than true renal toxicity**

SPRING-2: Dolutegravir QD vs Raltegravir BID in Treatment-Naive Pts at 96 Wks

- Randomized, double-blind, placebo-controlled phase III trial
  - **Primary endpoint: VL < 50 c/mL at Wk 48**



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

SPRING-2: Dolutegravir Noninferior to Raltegravir at 96 Wks (81% vs. 76%)

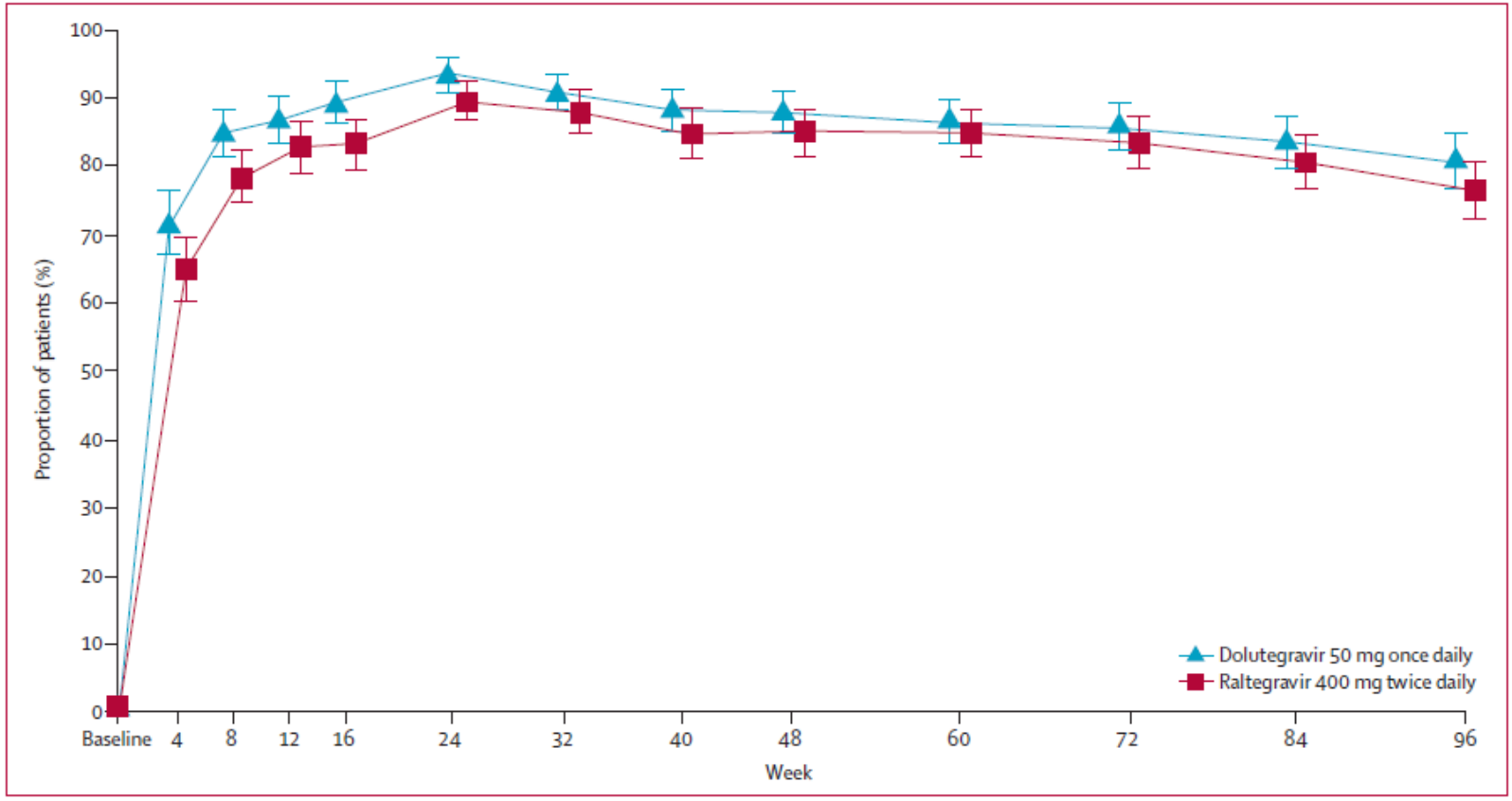


Figure 2: **Proportion of patients with less than 50 copies of HIV-1 RNA per mL, by visit**
Data are % (95% CI). Snapshot (missing, switch, discontinuation=failure) analysis.

SPRING-2 Virologic Failures

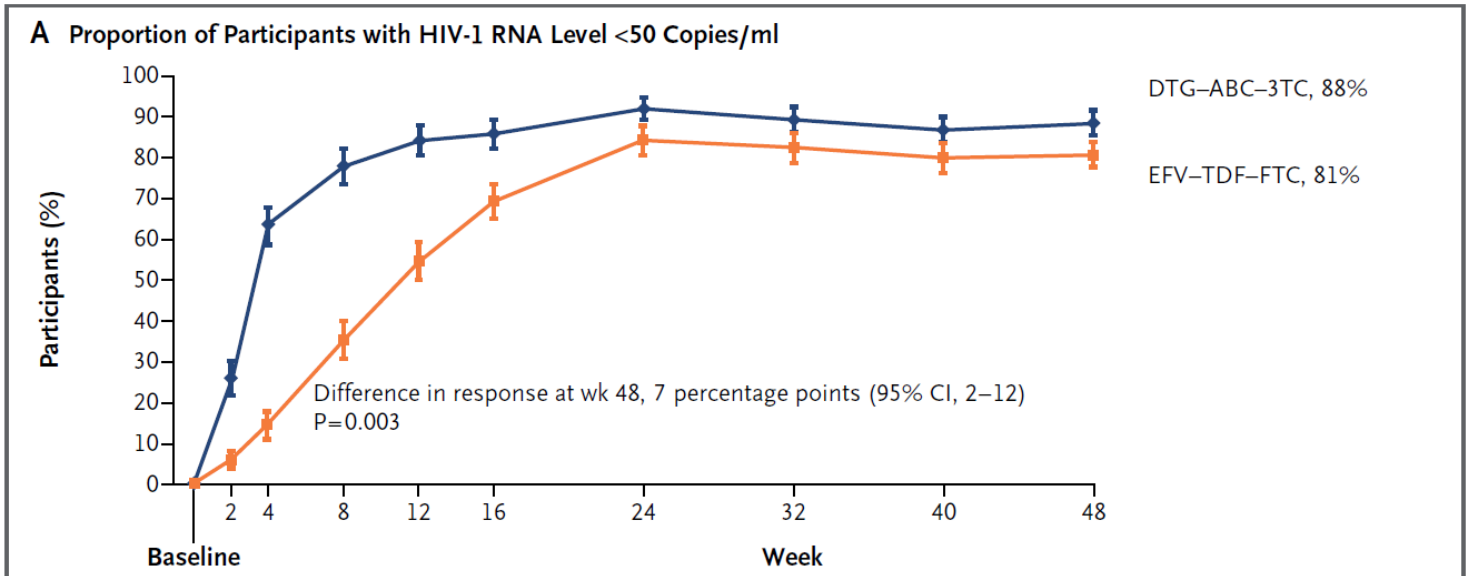
- Virologic failures rare (5% in dolutegravir group, 7% in raltegravir group
- No patients treated with dolutegravir had emergent integrase or NRTI resistance at failure
- In raltegravir arm, 1 patient developed integrase resistance and 4 developed resistance to NRTIs

Raffi F. Lancet 381 (9868): 735-743. 2013;

Adverse Effects of Dolutegravir

- DTG had favorable safety profile, comparable to RAL
  - **Few AEs necessitating treatment discontinuation (2% in each arm)**
  - **Greater increase in creatinine with DTG vs RAL (+0.139 vs +0.053 mg/dL)**
    - DTG increases serum creatinine by inhibiting renal creatinine secretion but does not affect actual glomerular filtration rate
  - **No premature discontinuation for renal events**

Dolutegravir + Abacavir/Lamivudine versus Efavirenz/tenofovir/emtricitabine (SINGLE)



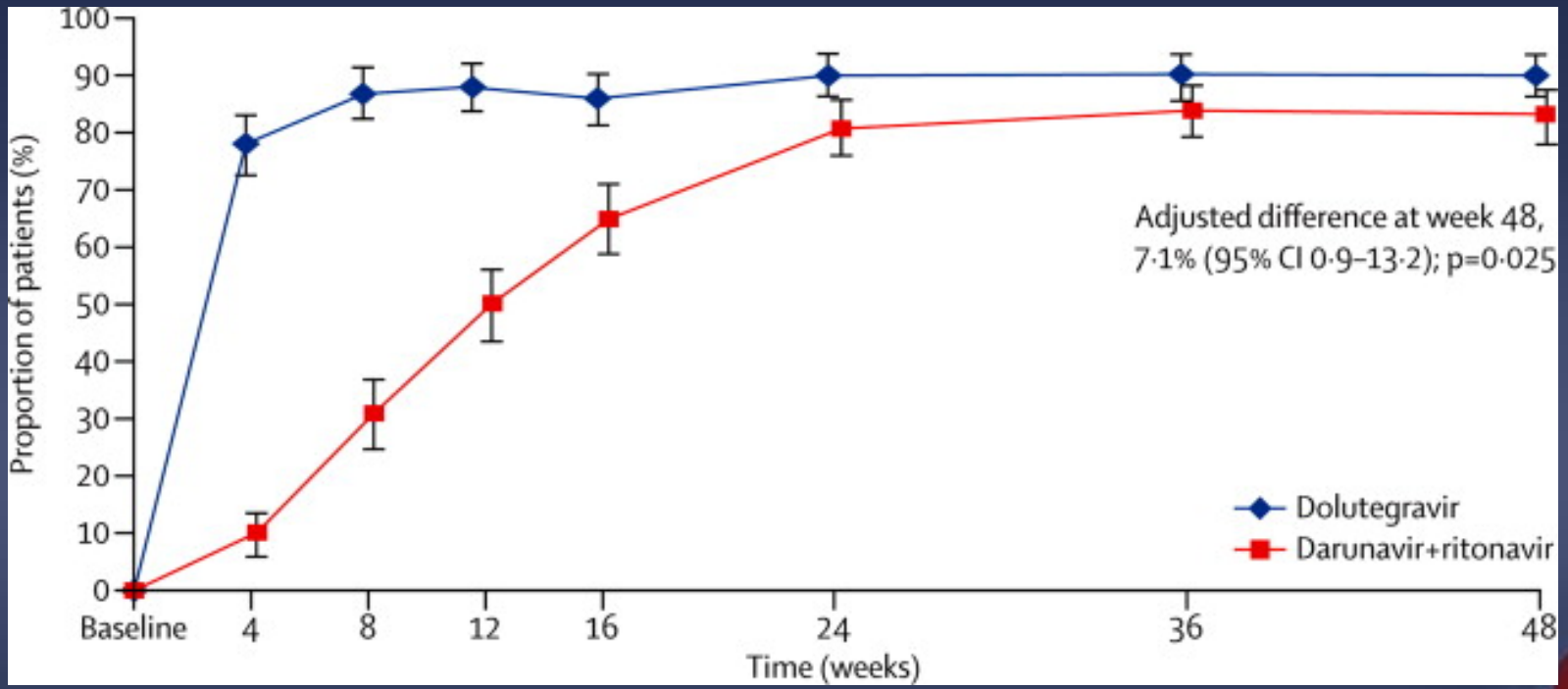
Dolutegravir Versus Atripla

- Dolutegravir was statistically superior at suppressing viral load at 48, 96 and 144 weeks
- Virologic failure 8-9% in both arms
- No integrase or NRTI mutations detected in patients on dolutegravir (multiple mutations in efavirenz arms)
- Dolutegravir had lower rate of CNS and rash
- Fewer discontinuations due to AEs in dolutegravir group (10% in Atripla arm)

FLAMINGO Trial

- Open-label trial comparing dolutegravir to darunavir/ritonavir
- Could use abacavir/lamivudine or tenofovir/emtricitabine

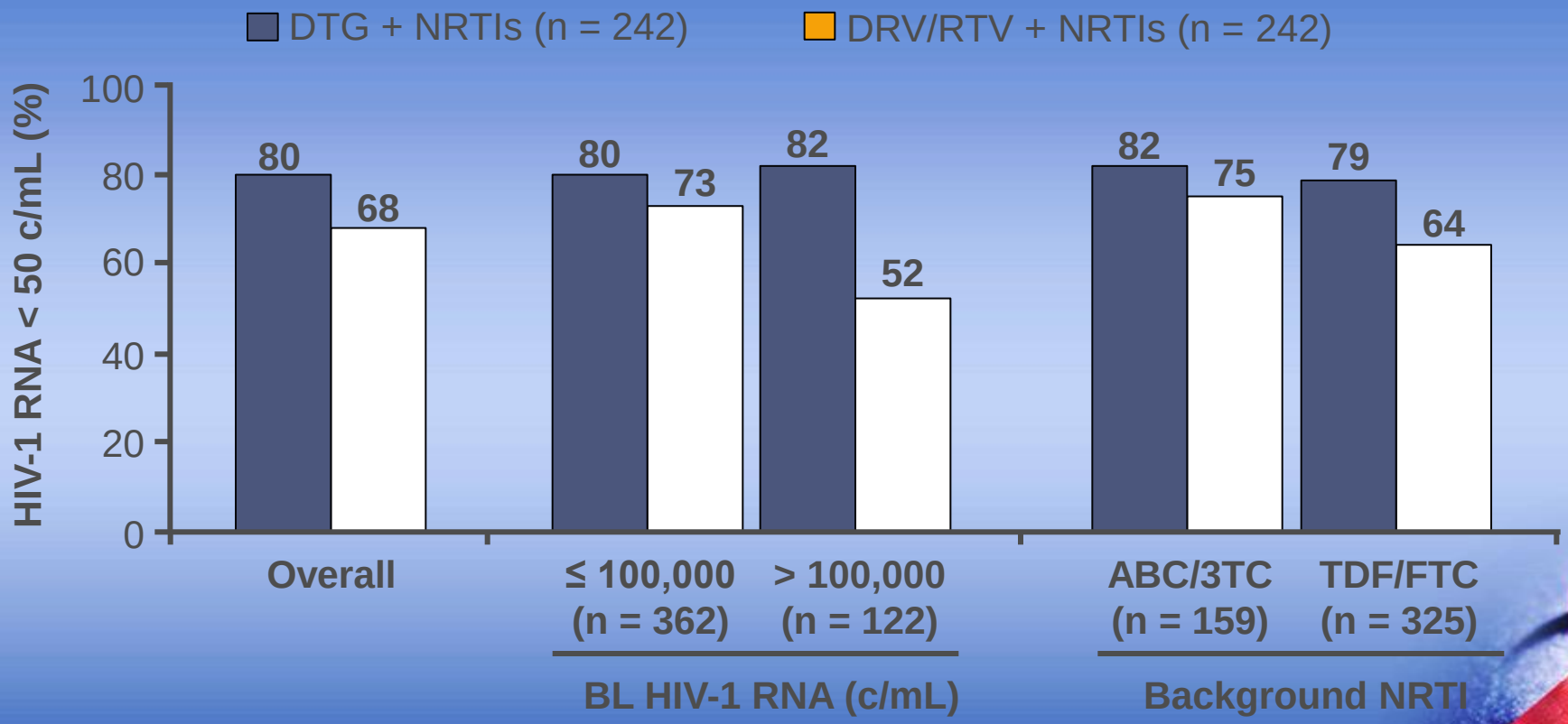
FLAMINGO Results: Dolutegravir Superior to Darunavir in HIV <50 copies/mL (90% vs. 83%)



FLAMINGO Results

- Treatment success driven by higher discontinuation rates for darunavir patients (4% versus 2% in dolutegravir group)
- 2 patients in each group had virologic failure
- No treatment-emergent mutations detected
- Similar results for week 96

FLAMINGO: Wk 96 Subgroup Efficacy Analysis



Molina JM, et al. Glasgow HIV 2014. Abstract O153.

Regimen	Advantages	Disadvantages
Efavirenz	▪ Cost ▪ Single-tablet regimen ▪ Long-term data available	▪ CNS side effects (not good for bipolar) ▪ Teratogenicity ▪ Low genetic barrier to resistance
Rilpivirine	▪ Single-tablet regimen ▪ Well-tolerated	▪ Low genetic barrier to resistance ▪ Higher virologic failures in high viral loads ▪ Need for acid for absorption
Protease-inhibitor based	▪ Most forgiving for non-adherent patients ▪ Safe to use in patients without genotype information	▪ Highest pill burden ▪ Metabolic side effects ▪ Drug interactions ▪ For atazanavir, jaundice and need for acid for absorption
Raltegravir	▪ Minimal adverse effects ▪ Very few drug-drug interactions	▪ Twice-daily dosing ▪ Lower genetic barrier to resistance than protease inhibitors
Elvitegravir	▪ Single tablet regimen ▪ Well-tolerated	▪ Renal effects ▪ Drug interactions ▪ Lower genetic barrier to resistance than protease inhibitors
Dolutegravir	▪ Single tablet regimen available ▪ Few side effects ▪ Likely a high genetic barrier to resistance	▪ Mild renal effects

Cost of Regimens: Average Wholesale Price per Month

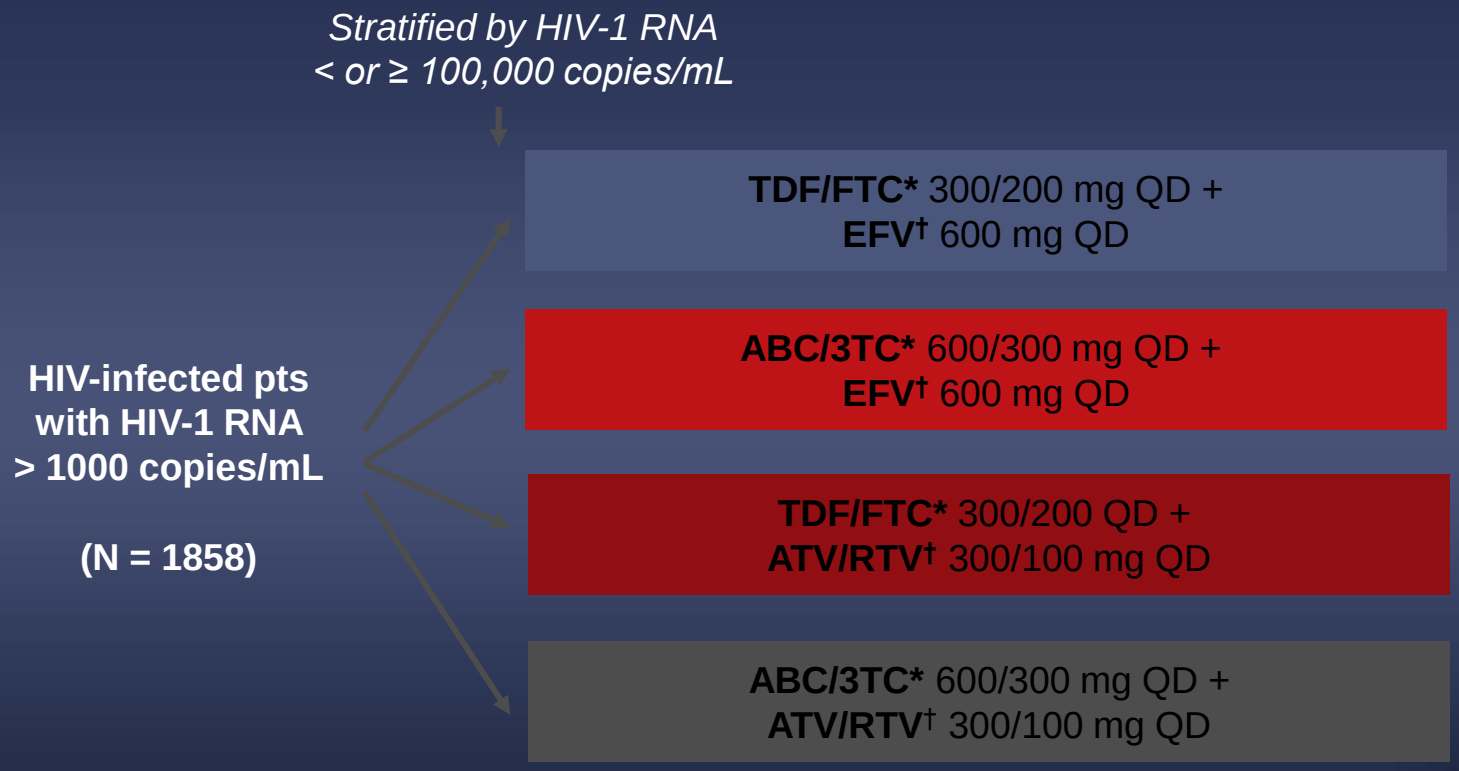
- Atripla (efavirenz/emtricitabine/tenofovir: $725-$2000
- Rilpivirine + tenofovir + emtricitabine: $900-$2400
- Atazanavir + ritonavir + tenofovir + emtricitabine:$1000-$3200
- Darunavir + ritonavir + tenofovir + emtricitabine: $1100-$3200
- Raltegravir + tenofovir + emtricitabine: $1000-$3000
- Dolutegravir + tenofovir + emtricitabine: $1300-$3000
- Dolutegravir + abacavir + lamivudine: $1300-$2600
- Elvitegravir + cobicistat + tenofovir + emtricitabine: $1600-$3000

Choosing Between the NRTIs: Abacavir versus Tenofovir

Abacavir Returns to DHHS (a little)!

- Previously had fallen off due to concerns about:
  - **Efficacy in comparison with tenofovir**
  - **Cardiovascular toxicity**

ACTG 5202: Abacavir vs Tenofovir + Efavirenz or Atazanavir/ritonavir

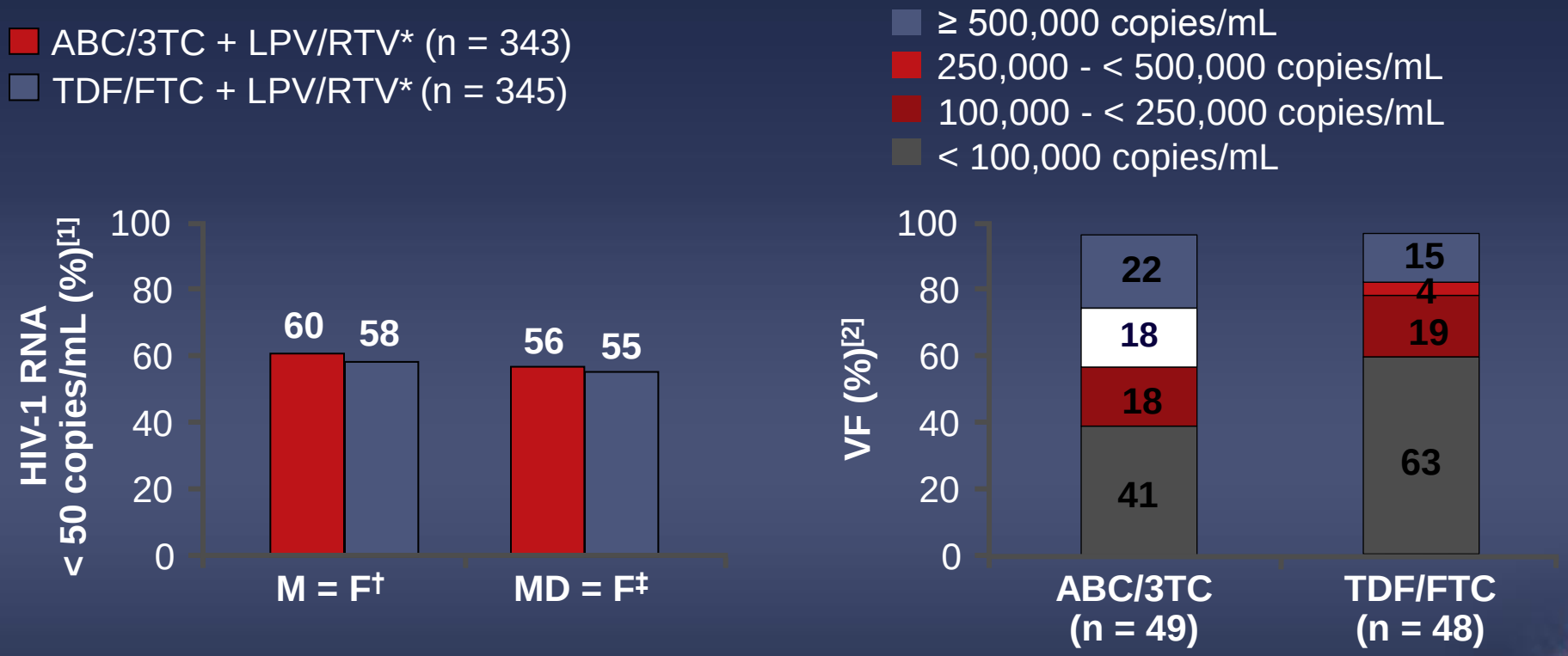


Sax PE. JID 2011 Oct 15; 204(8): 1191-201.

ACTG 5202: Abacavir vs Tenofovir

- Study discontinued early
  - More virologic failure observed with abacavir in patients with HIV RNA >100,000 copies/mL versus in tenofovir

HEAT: Abacavir Noninferior to Tenofovir, even at high HIV viral loads



Smith KY, Patel P, Fine D, et al; HEAT Study Team. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556

Dolutegravir Trials (SINGLE, FLAMINGO)

- No differences between abacavir or tenofovir in virologic efficacy, even at high viral loads (>100k)

Abacavir in DHHS Guidelines

- Recommended in patients taking dolutegravir (extensively tested)
- Use in efavirenz or atazanavir based regimens only if viral load is <100k
- ***Not “recommended” in the guidelines except in use with dolutegravir***

Abacavir and Cardiovascular Risk

- D:A:D cohort study has thousands of patients on multiple regimens
- Found that patients recently started (within 6 months) associated with increased risk of MI, particularly in patients with CV risk factors

Summary of Clinical Trial and Cohort Analyses of ABC Use and CVD Risk

Study	Association	Description
D:A:D[1]	✓	Cohort collaboration (prospective)
Danish HIV Cohort[2]	✓	Cohort (linked with registries)
Montreal study[3]	✓	Nested case-control study
SMART[4]	✓	Post hoc subgroup analysis of RCT (use of ABC not randomized)
STEAL[5]	✓	Preplanned secondary analysis of RCT (use of ABC randomized)
Swiss HIV Cohort[6]	✓	Cohort (retrospective)
FHDH ANRS CO4[7]	?	Nested case-control study
NA-ACCORD[8]	?	Cohort (retrospective)
VA Clinical Case Registry[9]	X	Cohort (retrospective)
Brothers et al. analysis[10]	X	Post hoc meta-analysis of RCTs
ACTG A5001/ALLRT[11]	X	Post hoc meta-analysis of RCTs
FDA meta-analysis[12]	X	Post hoc meta-analysis of RCTs

1. Lundgren JD, et al. CROI 2009. Abstract 44LB. 2. Lang S, et al. CROI 2009. Abstract 43LB. 3. SMART. AIDS. 2008;22:F17-F24. 4. Carr A, et al. CROI 2009. Abstract 576. 5. Cutrell A, et al. IAC 2008. Abstract WEAB0106. 6. Benson C, et al. CROI 2009. Abstract 721. Reiss P. CROI 2009. Abstract 152.

Cardiovascular Risk of Abacavir

- Bedimo et. al (CID 2011 53(1): 84-91) used Veterans Association data to calculate risk of MI and stroke in patients on abacavir and other combinations
  - **Controlled for chronic kidney disease, smoking, lipids etc.**
  - **Observed NO association between abacavir use and MI or CVA once CKD accounted for**

Cardiovascular Risk and Abacavir

- Meta-analysis of randomized, controlled treatment trials and manufacturer data found no evidence that abacavir-containing regimens carry greater risk of MI
  - **Cruciani M. AIDS 2011; 25(6): 1993-2004**

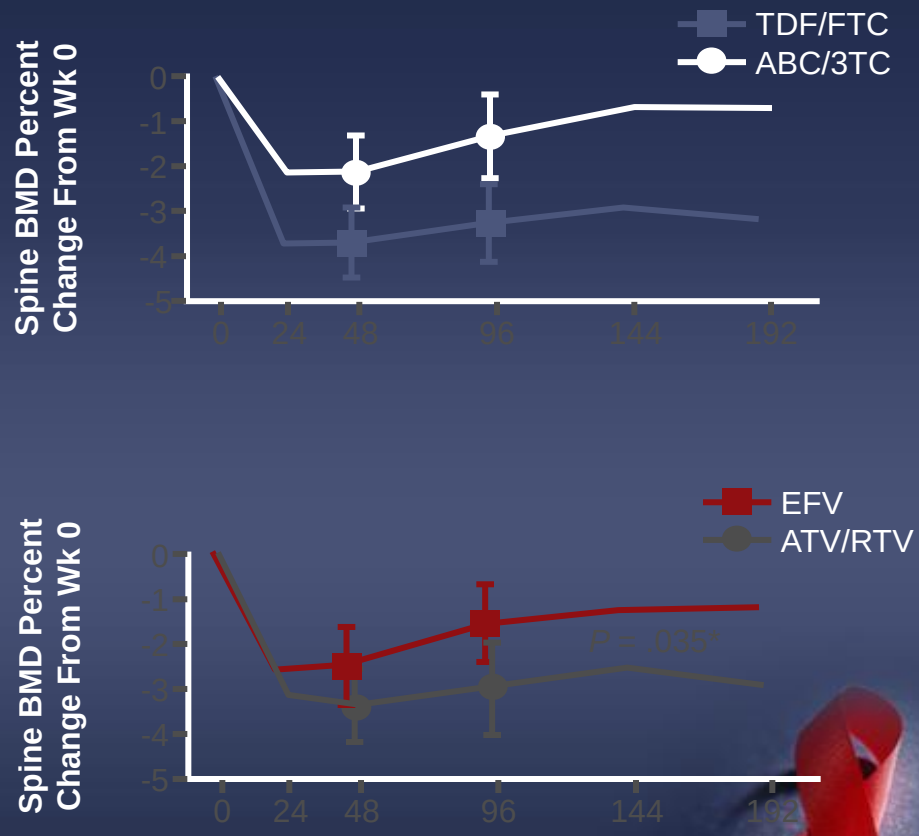
DHHS Guidelines

- “No consensus has been reached on the association between abacavir use and MI risk or the mechanism for such an association.”

Concerns About Tenofovir

ACTG 5224s: Change in Bone Mineral Density

- Substudy of ACTG 5202
  - **Tenofovir versus abacavir and efavirenz vs atazanavir/ritonavir**
- Primary endpoint
  - **Changes in bone mineral density by DXA**
- At week 96, significantly greater losses in BMD with
  - **Tenofovir vs abacavir in both hip and spine**
  - **Atazanavir/ritonavir vs efavirenz in spine**



McComsey GA, et al. J Infect Dis. 2011;203:1791-1801.

Tenofovir: Concerns for Renal Toxicity

- Fanconi's syndrome known potential toxicity of tenofovir
- Multiple case studies and clinical experience of proximal tubular dysfunction and impaired GFR; several observational cohort studies show rates of renal failure with tenofovir use
- Meta-analysis showed "significantly greater decrease" of -3.92 mL/min and increased risk of acute renal failure (0.7%) in patients receiving tenofovir as compared to other regimens

  - Cooper R. CID 2010: 496-505.

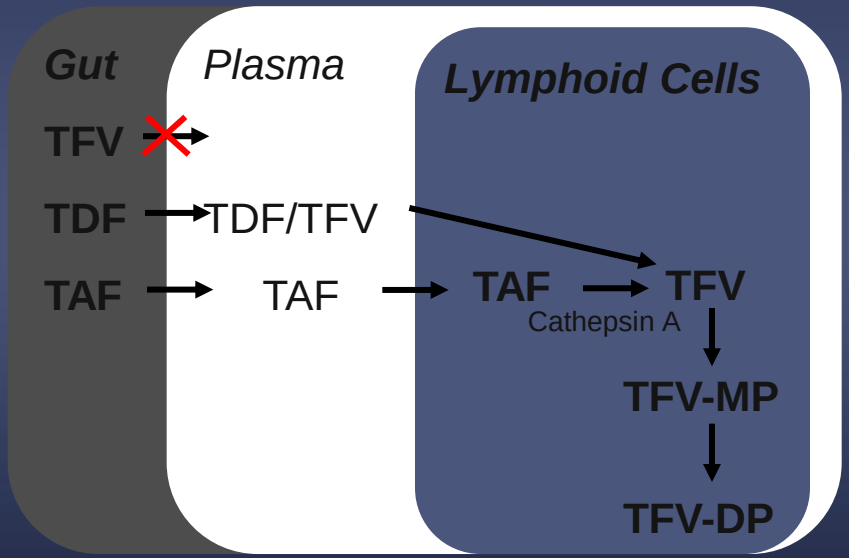
Tenofovir versus Abacavir

Regimen	Advantages	Disadvantages
Abacavir	▪ Similar efficacy to tenofovir in HEAT and dolutegravir trials ▪ Hypersensitivity can be safely avoided with HLA-B*5701 assay	▪ Potential for hypersensitivity reaction ▪ Inferior response high viral load in ACTG 5202 ▪ Association with ↑ risk of myocardial infarction in some studies
Tenofovir	▪ High level of efficacy in clinical trials with efavirenz or boosted Pis	▪ Caution in pts with renal insufficiency ▪ Long-term nephrotoxicity and tubular toxicity not fully understood ▪ Should not be coadministered with other nephrotoxic drugs ▪ Bone toxicity

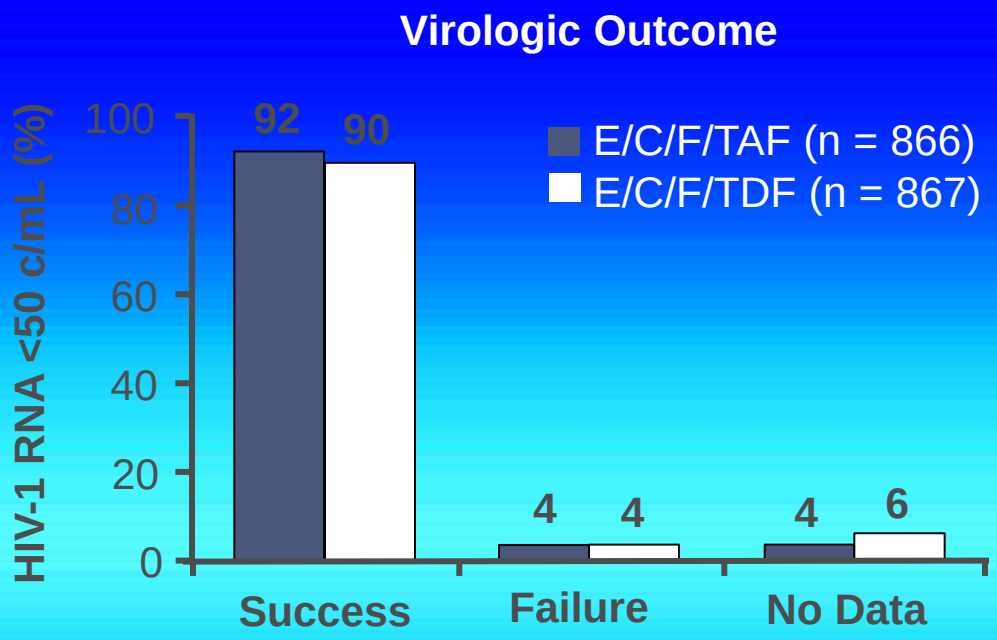
ARV Options in the Near Future

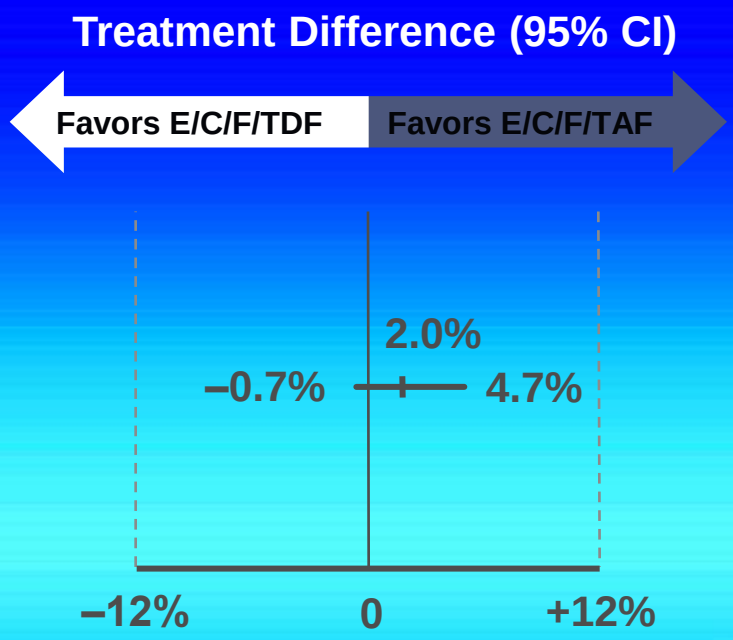
Tenofovir alafenamide (TAF)

- TAF (GS-7340), investigational prodrug of tenofovir with lower tenofovir plasma concentrations, increased delivery to hepatocytes, lymphoid cells



Studies 104 and 111: HIV-1 RNA < 50 c/mL at Wk 48 (Primary Endpoint)





- CD4+ significantly higher for TAF than TDF (*P* = .024)
- D/C for adverse events: TAF 0.9%, TDF 1.5%
- Resistance with failure: TAF 7/866 (0.8%), TDF 5/867 (0.6%)

Wohl D, et al. CROI 2015. Abstract 113LB.

Relative Toxicity of TAF versus TDF

- Patients on TAF had smaller reductions in estimated creatinine clearance (-5.5 vs -10 mL/min)
- Less renal tubular proteinuria (urine protein/creatinine ratio, albuminuria, retinol binding protein, B2 microglobulin)
- Smaller changes in bone mineral density
- Higher lipid levels in TAF group

Tenofovir Alafenamide: Summary and What's Coming

- Development of TAF/FTC and TAF/FTC/DRV/COBI planned

What about if tenofovir or abacavir cannot be used?

- Alternative regimens:
  - **Darunavir/ritonavir + raltegravir (only if HIV VL <100k and CD4 >200 cells/uL)**
  - **Lopinavir/ritonavir + lamivudine**

Darunavir/ritonavir + raltegravir

- NEAT/ANRS 143
  - **Compared darunavir/ritonavir + raltegravir vs. tenofovir/emtricitabine**
  - **At 96 weeks, non-inferior**
  - **More failures seen patients with low CD4 and high viral loads**
  - **Other smaller studies showed similar results (ACTG 5262 and RADAR)**

Lopinavir/ritonavir + lamivudine

- GARDEL
  - **Lopinavir/ritonavir + lamivudine or 2 NRTIs selected by study investigators**
  - **Non-inferior efficacy**
  - **Lopinavir/lamivudine alone was better tolerated**

Lancet Infect Dis. 2014;14(7):572-580

OLE trial: switched stable patients with undetectable viral load off of 2nd NRTI, similar findings

Lancet ID 2015; 15(7): 785-92

The Art of HAART

Know your patient!

- It is imperative to extensively explore factors that may impact adherence prior to HAART initiation:
  - **Lifestyle, work factors**
  - **Concerns about lipodystrophy (avoid protease inhibitors, possibly efavirenz)**
  - **Pregnancy/child-bearing age (efavirenz teratogenicity)**
  - **Works night shifts (efavirenz CNS toxicity)**
  - **Hepatitis B coinfection (need for tenofovir, emtricitabine, lamivudine)**
  - **GERD (avoid atazanavir, rilpivirine)**

Case 1

- 28 year-old Caucasian male, busy professional, concerned about appearance, has very pale skin. Takes Nexium. Viral load 350,000; wild-type genotype. CD4 320 cells/uL. Creatinine normal. HLAB5701 positive. Has private insurance. Wants “one pill, once a day” regimen.

- What would be good options for antiretroviral therapy?

Case 1—Better Options

- Efavirenz-based regimen (Atripla)
  - **One pill daily regimen**
  - **Counsel regarding CNS side effects**
  - **Need for excellent adherence**
  - **Possible lipoatrophy**
- Elvitegravir-based regimen (Stribild)
  - **One pill daily regimen**
  - **Few side effects**
  - **Renal toxicity**

Case 1: Not as Good Options

- Atazanavir-based
  - **Patient has GERD; PPI/H2 blocker will interfere with atazanavir absorption**
  - **Patient may notice scleral icterus**
  - **Metabolic complications**
  - **More than 1 pill**
- Darunavir-based
  - **More than 1 pill**
  - **Metabolic complications**

Case 1: Not as Good Options

- Raltegravir-based regimen
  - **Twice daily but otherwise excellent side effect profile**
- Dolutegravir-based regimen
  - **Once daily but 2 tablets**
- Rilpivirine-based regimen (Complera)
  - **Concern about absorption with GERD**
  - **Concern about efficacy given high viral load**

Nucleotide Regimen

- CANNOT use abacavir due to HLAB5701
- Use tenofovir/emtricitabine
- Monitor creatinine (and maybe bone mineral density)

Case 2

- 31 year-old African-American female, viral load of 70,000 copies/mL; CD4 60 cells. No past medical history, although screening labs show HBsAg positive. Creatinine normal.

Case 2: Treatment Options

- Ask about plans for pregnancy.
- If pregnancy planned in near future, some providers would start preferred regimen for pregnancy: Lopinavir/ritonavir (Kaletra) + zidovudine/lamivudine (Combivir)

Options for Treatment

- Efavirenz-based therapy:
  - **Known teratogen; unless patient willing to use 2+ forms of birth control, don’t use this medication**

- Rilpivirine-based regimen (Complera)
  - **Excellent side effect profile, low pill burden**
  - **Pregnancy category B**
  - **Not recommended for CD4 < 200 cells/uL given higher virologic failure rate**

Treatment Options: Case 2

- Atazanavir-based therapy:
  - **Good option, low pill burden**
  - **Scleral icterus not as noticeable**
  - **Protease-inhibitors will help CD4 increase quickly**
- Darunavir-based therapy:
  - **Higher pill burden but still once daily**
  - **No scleral icterus or GERD concerns**
  - **Durable regimen for non-adherent patients**

Treatment Options: Case 2

- Raltegravir-based regimen
  - **Twice daily but otherwise excellent side effect profile**
  - **Little data in pregnancy**

Treatment Options: Case 2

- Elvitegravir-based regimen
  - **May be good treatment option for this patient**
  - **Minimal side effects, low pill burden**
- Dolutegravir-based regimen
  - **May be good treatment option for this patient**
  - **Minimal side effects, low pill burden**

Nucleoside Options

- Tenofovir-based regimen would be preferable in this patient with active hepatitis B; both tenofovir and emtricitabine are active against HBV

Case 3

- 42 year-old African American female, CD4 2, newly-diagnosed PML, viral load 200k
- When would you start medications, and which medications would you start?

Case 3: Timing

- Immediately, do not pass Go, before leaving the hospital! No other treatment options available for PML

What to Use: Case 3

- Efavirenz-based therapy:
  - **Known teratogen; unless patient willing to use 2+ forms of birth control, don’t use this medication**
  - **Also would expect slower CD4 count rise**
  - **?neurotoxicity**

Treatment Options: Case 3

- Atazanavir-based therapy:
  - **Good option, low pill burden**
  - **Scleral icterus not as noticeable**
  - **Protease-inhibitors will help CD4 increase quickly**
  - **If patient hospitalized, will need to worry about PPI initiation**
- Darunavir-based therapy:
  - **Once daily**
  - **No scleral icterus or GERD concerns**
  - **Durable regimen for non-adherent patients**

Treatment Options: Case 3

- Raltegravir-based regimen
  - **Twice daily but otherwise excellent side effect profile**
- Rilpivirine-based regimen (Complera)
  - **Not recommended in CD4 <200 cells/uL**
  - **Pregnancy category B**

Treatment Options: Case 3

- Elvitegravir-based regimen
  - **May be good treatment option for this patient**
  - **Minimal side effects, low pill burden**
- Dolutegravir-baesd regimen
  - **May be good treatment option for this patient**
  - **Minimal side effects, low pill burden**

Nucleoside Options

- Efficacy concerns about use of abacavir in non-dolutegravir containing regimens given her high viral load (depending on which study you believe)

Case 4

- 48 year-old African American male, CD4 320, viral load 50,000; CKD with baseline creatinine of 2.4, bipolar with psychotic features during manic episodes. On 5 medications for bipolar, seen through Metrocare.

What to Use: Case 4

- Efavirenz-based therapy:
  - **Would be cautious about this therapy given patient's unstable history of bipolar depression**

Treatment Options: Case 4

- Atazanavir-based therapy:
  - **Possibility of drug interactions with psych meds**
  - **Scleral icterus not as noticeable**
- Darunavir-based therapy:
  - **Possibility of drug interactions with psych meds**
  - **Once daily**
  - **No scleral icterus or GERD concerns**
  - **Durable regimen for non-adherent patients**

Treatment Options: Case 4

- Raltegravir-based regimen
  - **Twice daily but otherwise excellent side effect profile; may need to worry about adherence in this patient**
  - **Minimal drug interactions**
- Rilpivirine-based regimen (Complera)
  - **Not as many psychiatric side effects**
  - **Excellent adherence essential, higher virologic failure rate**

Treatment Options: Case 4

- Elvitegravir-based regimen
  - **Stribild not recommended for patients with low creatinine clearance**
  - **Concern about drug interactions with psychiatry medications**

Treatment Options: Case 4

- Dolutegravir-based regimen:
  - **Well-tolerated**
  - **May be forgiving of potential non-adherence**
  - **Low pill burden**
  - **Few drug interactions (watch carbamazepine, phenytoin, St. John's Wort, oxcarbazepine, phenobarbitol)**

Nucleoside Options

- Caution of using tenofovir in patients with chronic kidney disease, needs adjustment if CrCl < 50 mL/min

Questions?