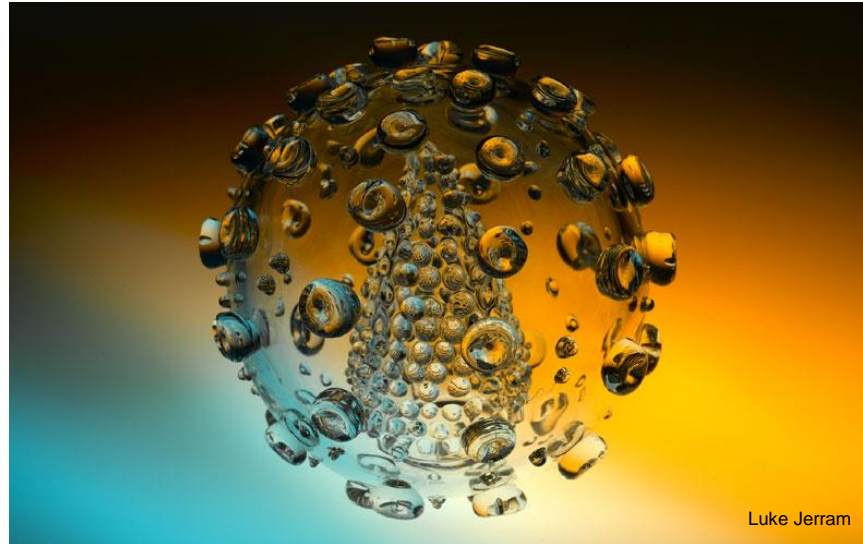


Starting and Switching ART: 2016



Rajesh T. Gandhi, M.D.
Massachusetts General Hospital
Harvard Medical School

Disclosures: grant support from EBSCO, Gilead, Merck, Viiv

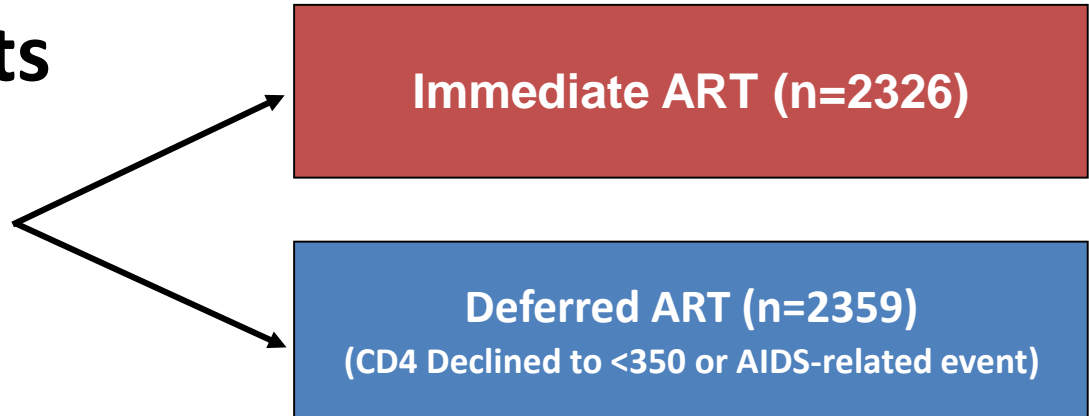
Thanks to Henry Sunpath, Roger Bedimo, Marilyn Shi for assistance with slides

HIV: Starting/Switching 2016

- When to Start
- What to Start?
 - Treatment Guidelines: US and SA
- What's on the Horizon
- Switching ART

When to START?

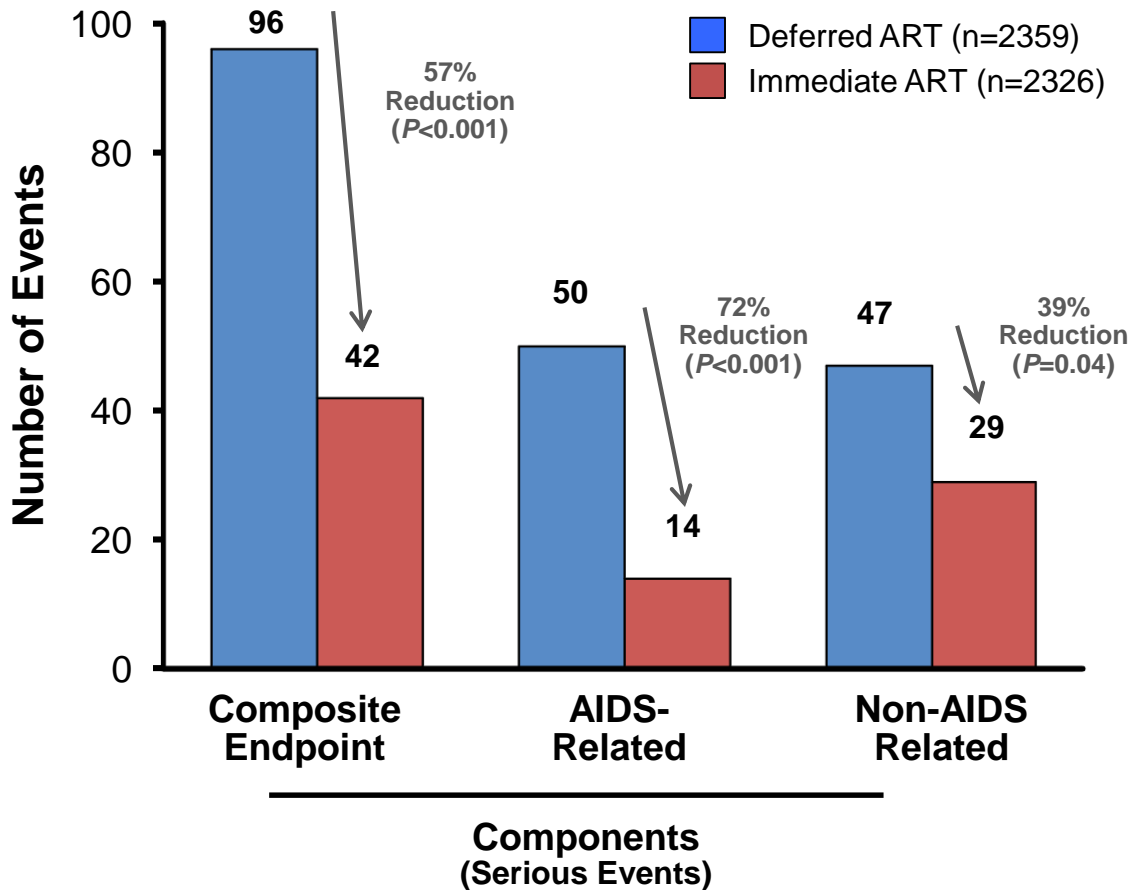
HIV-infected adults
CD4 count >500
N=4685



- Primary endpoint: serious AIDS-related event, serious non-AIDS-related event, or death
- May 2015: DSMB recommended offering ART to all participants
- Median baseline CD4 count 651. Deferred group: median CD4 count at ART initiation, 408
- Median HIV RNA: $\approx 13,000$ (IQR $\approx 3,000, 43,000$)

Immediate ART Prevents AIDS- and Non-AIDS Related Events

Number of Serious Events



- TB, KS, lymphoma — most common AIDS-related events — all less frequent in immediate-ART group¹
- Cancer rates (combining AIDS/non-AIDS) lower in immediate-ART group²
- Greatest benefit: age >50, VL >50,000, CD4:CD8 <0.5, Framingham score >10%³

ART recommended for all HIV+ individuals, regardless of CD4 cell count

CD4 Cell Count	Recommendation
≤ 350	AI
350-500	AI
>500	AI

AI: strong recommendation, data from randomized clinical trials



WHO on Sept 30, 2015: “Treat-all”

Earlier and earlier

Data Supporting **“Same Day” ART Initiation:**

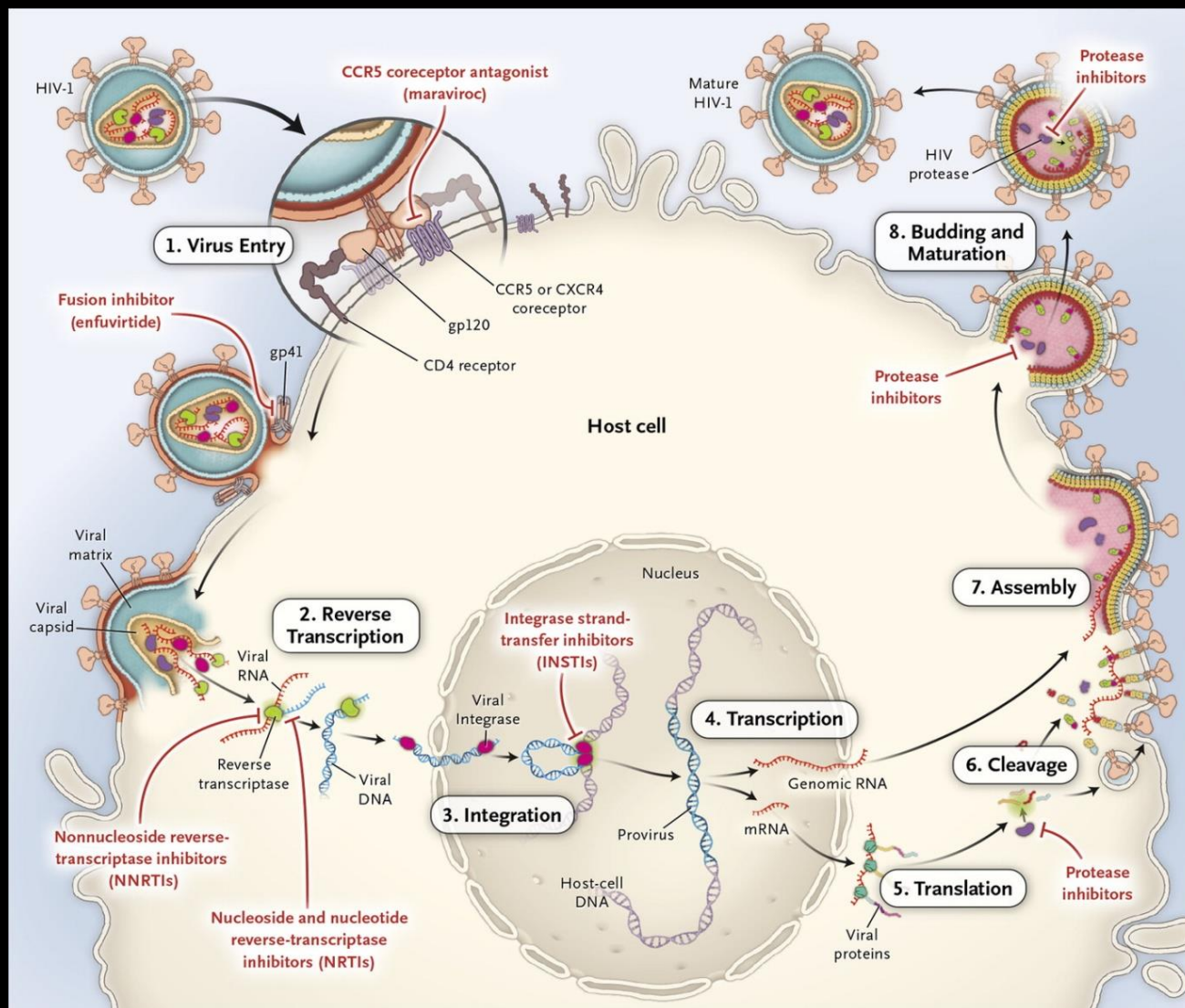
San Francisco (Pilcher CD, JAIDS 2016);

South Africa (Rosen S, PLoS Medicine, 2016);

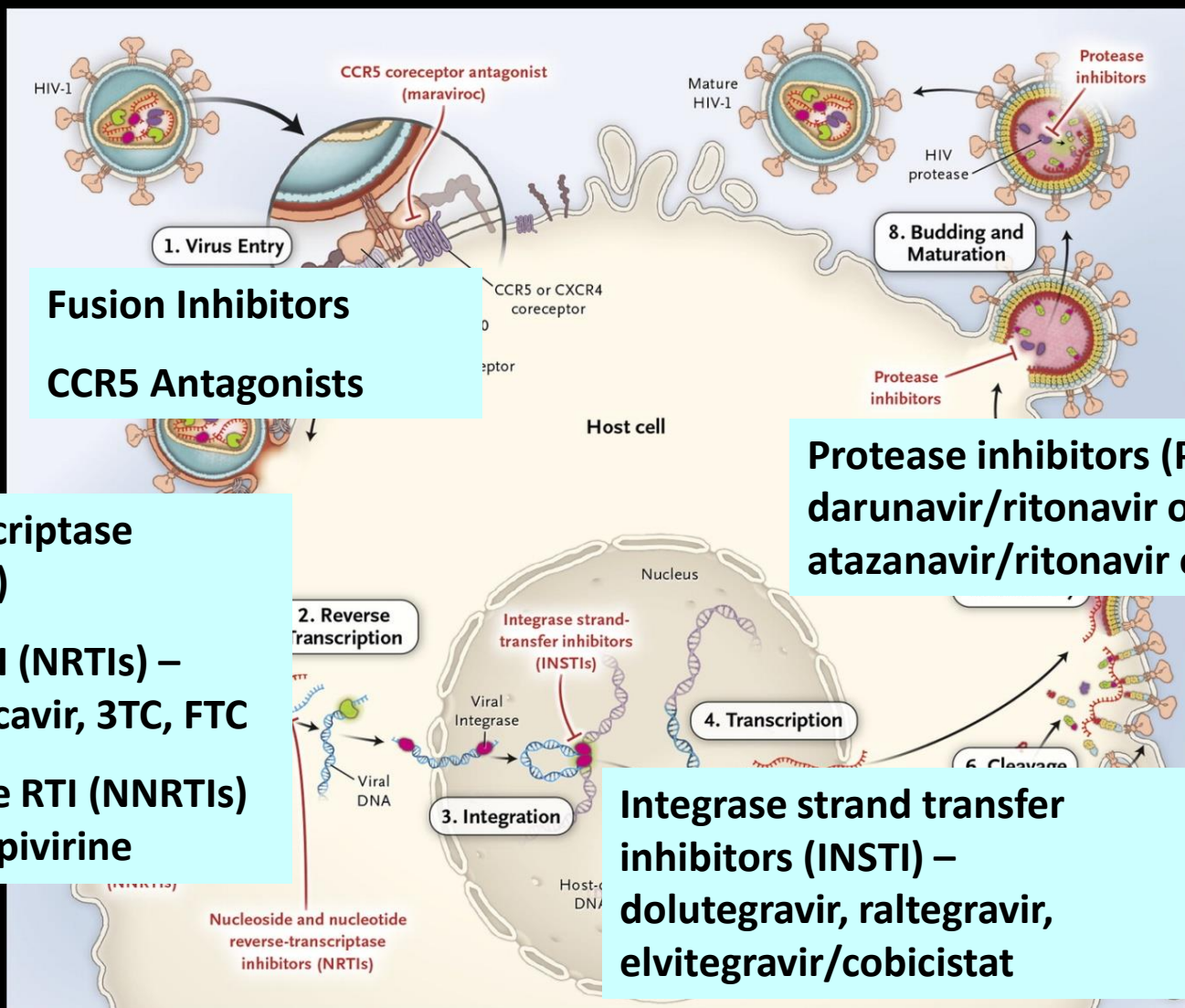
Haiti (Koenig S, International AIDS Conf., July 2016, WEA0202)

What to Start?

Reproductive Cycle of HIV and Sites of Action of Major Classes of Antiretroviral Medications



Reproductive Cycle of HIV and Sites of Action of Major Classes of Antiretroviral Medications



Fusion Inhibitors

CCR5 Antagonists

Reverse Transcriptase Inhibitors (RTI)

Nucleoside RTI (NRTIs) –
tenofovir, abacavir, 3TC, FTC

Nonnucleoside RTI (NNRTIs)
– efavirenz, rilpivirine

Protease inhibitors (PI) –
darunavir/ritonavir or cobi;
atazanavir/ritonavir or cobi

Integrase strand transfer inhibitors (INSTI) –
dolutegravir, raltegravir,
elvitegravir/cobicistat

Antiretroviral Therapy 2016: >25 Options in US

● Nucleoside and nucleotide RTIs (NRTI)

- Zidovudine, AZT
- Abacavir, ABC
- Lamivudine, 3TC
- Didanosine, ddI
- Stavudine, d4T
- Tenofovir, TDF
- Emtricitabine, FTC
- AZT/3TC
- AZT/3TC/ABC
- ABC/3TC
- TDF/FTC
- TAF/FTC

● CCR5 receptor blocker

- Maraviroc

● Integrase inhibitor (INSTI)

- Raltegravir, RAL
- Elvitegravir, EVG
- Dolutegravir, DTG

● Non nucleoside NRTIs: (NNRTI)

- Delavirdine (DLV)
- Nevirapine, NVP
- Efavirenz, EFV
- Etravirine
- Rilpivirine

● Fusion inhibitors:

- Enfuvirtide, ENF or T20

● Protease inhibitors (PIs):

- Indinavir, IDV
- Saquinavir, SQV
- Nelfinavir, NFV
- Amprenavir, APV
- Atazanavir, ATV
- Fosamprenavir, FPV
- Lopinavir/ritonavir
- Tipranavir
- Darunavir
- Darunavir/cobicistat
- Atazanavir/cobicistat

Red – combination agents

Single pill regimens

- EFV/FTC/TDF
- RPV/FTC/TDF
- EVG/cobi/FTC/TDF
- DTG/ABC/3TC
- EVG/cobi/FTC/TAF
- Rilpivirine/FTC/TAF

US Guidelines

Updated July 14, 2016

Guidelines for the Use of Antiretroviral Agents
in HIV-1-Infected Adults and Adolescents



Developed by the HHS Panel on Antiretroviral Guidelines for
Adults and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

Recommended Regimens

Integrase inhibitor + 2 Nucleoside RTI	Dolutegravir/abacavir/3TC Dolutegravir+TDF/FTC or TAF/FTC Elvitegravir/cobi/TDF (or TAF)/FTC Raltegravir +TDF/FTC or TAF/FTC
Protease inhibitor + 2 Nucleoside RTI	Darunavir/r +TDF/FTC or TAF/FTC

SA: First line regimens

Who?	What?	Comments
<ul style="list-style-type: none"> • Adults • Pregnant and breastfeeding women • TB co-infection • HBV co-infection • HIV-positive partner in serodiscordant couple • Adolescents >15 years and weighing >40kg 	<p style="text-align: center;">TDF + FTC (or 3TC) + EFV (FDC preferred)</p>	<p>Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. . Remember CD4 count restrictions for NVP</p> <p>Evidence supports the efficacy and safety equivalence of 3TC and FTC</p>

What's on the Horizon?

What to Start: On the Horizon

- Integrase strand transfer inhibitors (INSTI)
- Tenofovir alafenamide
- Customizing ART based on specific comorbidities and conditions
- Regimens for patients who cannot take TDF or abacavir

What to Start



Recommended Regimens

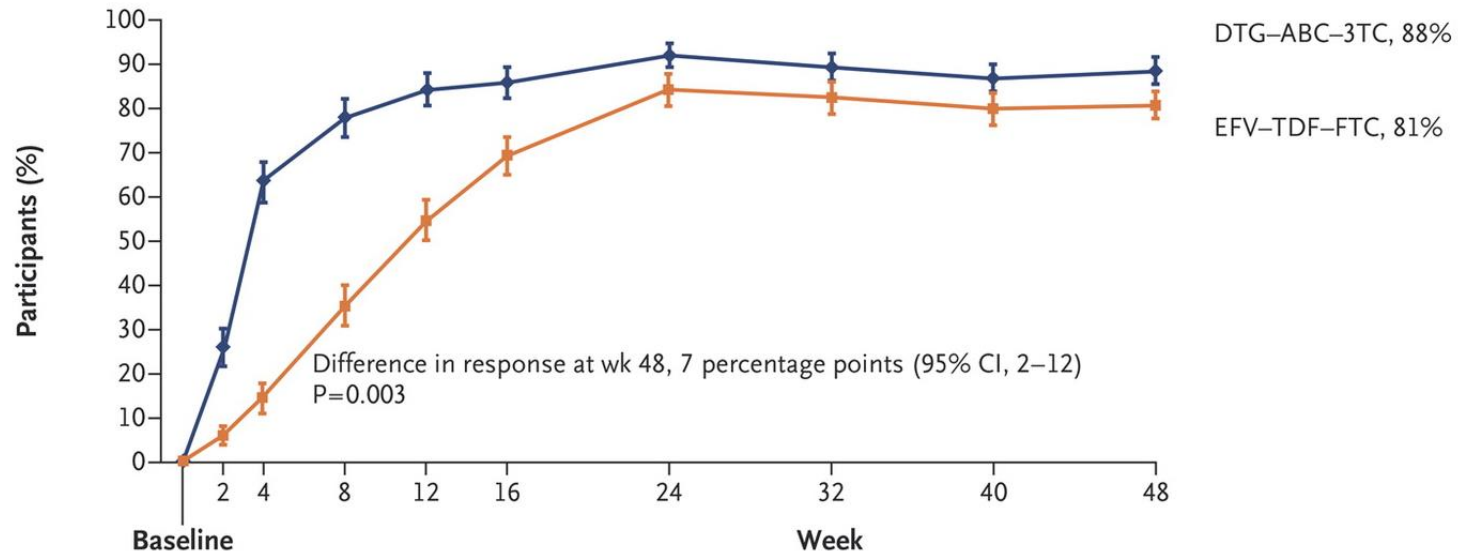
Randomized controlled trials indicate INSTI-based regimens are optimal for most patients with newly-diagnosed HIV

	Raltegravir +TDF/FTC or TAF/FTC
Protease inhibitor + 2 Nucleoside RTI	Darunavir/r +TDF/FTC or TAF/FTC

Randomized controlled trials: INSTI vs. NNRTI

- Dolutegravir + ABC/3TC superior to EFV/TDF/FTC (SINGLE)

A Proportion of Participants with HIV-1 RNA Level <50 Copies/ml



- More discontinuations in EFV group (10% vs. 2%)

INSTI**PROS****CONS****RAL**

- Longest-track record
- Fewest drug interactions

- Twice daily (once daily formulation coming – ONCEMRK trial)
- Not coformulated as part of single-pill regimen

EVG/c

- Available in single-pill regimen with TDF/FTC, TAF/FTC

- Most drug interactions (because of co bi)
- Food requirement

DTG

- Available in single-pill regimen with ABC/3TC
- High genetic barrier to resistance

- Not coformulated with tenofovir
- Largest pill size of single pill regimens
- Drug interaction with metformin

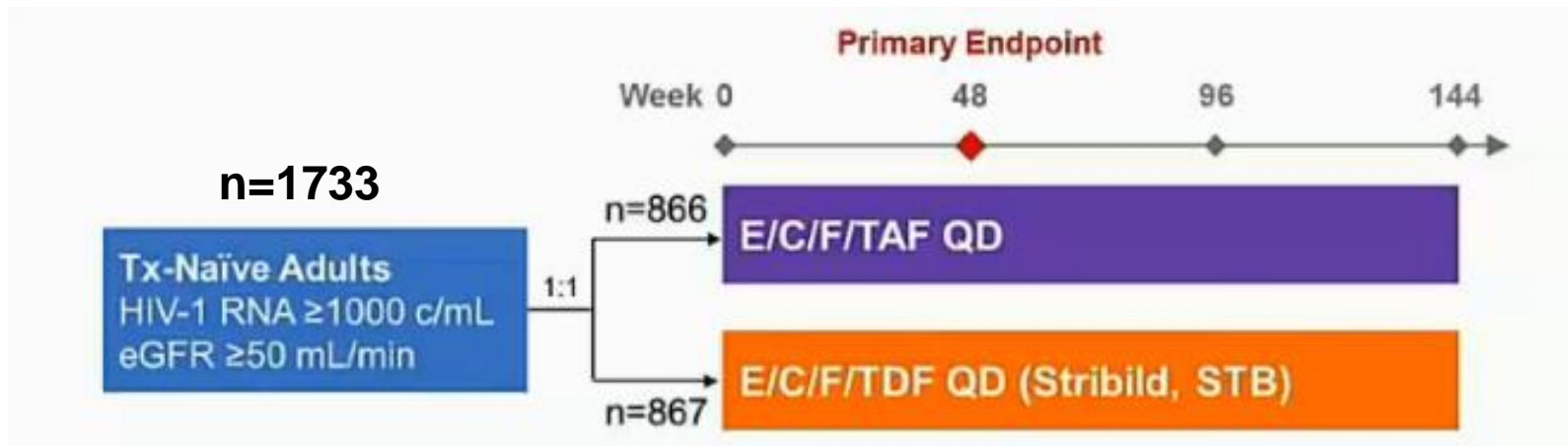
INSTIs: Limitations

- Cations affect INSTI absorption (stagger dosing)
- Adverse events: rhabdo with RAL; insomnia with DTG
- Only INSTI single-pill regimen that contains tenofovir is with EVG/c, which has multiple drug interactions
 - New unboosted INSTI, GS-9883 (bictegravir), being developed for use in TAF/FTC-containing single-pill regimen^{1,2}
- Patient with TB on rifampin-based regimen:
 - Most data with EFV/TDF/FTC
 - Rifampin has less effect on EFV conc. than other ARVs
 - RAL, DTG can also be used (but at increased dose)

¹Tsiang M, ASM Microbe 2016, PW-031; ²Gallant J, ASM Microbe 2016, PW-030

Tenofovir alafenamide (TAF)

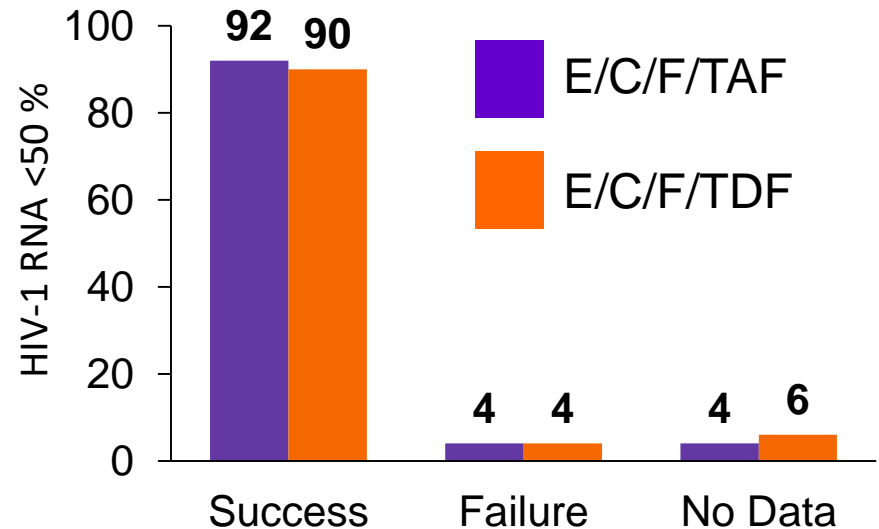
- TAF: pro-drug of tenofovir that concentrates in cells, converted to tenofovir (TFV)
- TAF: 90% lower plasma TFV levels compared to TDF (tenofovir disoproxil fumarate)
- EVG/cobi/FTC/TAF compared to EVG/cobi/FTC/TDF for initial therapy:



Sax P et al, Lancet, 2015

TAF vs. TDF

- Virologic efficacy: E/C/F/TAF non-inferior to E/C/F/TDF¹
- TAF associated with:
 - Smaller decrease in eGFR (-6.4 vs. -11 mL/min)
 - Less proteinuria
 - Smaller decrease in bone mineral density (BMD)
 - But greater increase in cholesterol, LDL, HDL, TGs
 - Δ TC: +29 mg/dL
 - Δ LDL: + 14 mg/dL
 - Δ TC:HDL: same

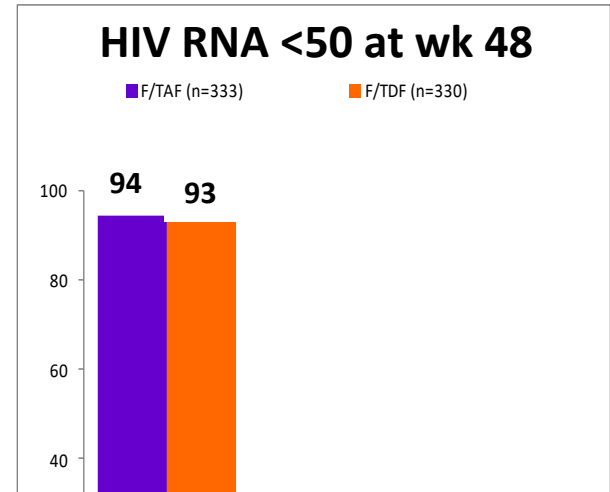


- EVG/c/FTC/TAF approved for patients with CrCL down to 30²

TAF/FTC Switch Study



- 663 patients with virologic suppression on TDF/FTC + 3rd agent randomized to continue TDF/FTC or switch to TAF/FTC (plus 3rd agent)
- TAF non-inferior to TDF in maintaining virologic suppression
- TAF group:
 - increased eGFR (+8.4 vs. 2.8 ml/min)
 - improved proteinuria
 - increased BMD (1.1-1.5%)
 - But: increased cholesterol, LDL, no difference in TC:HDL

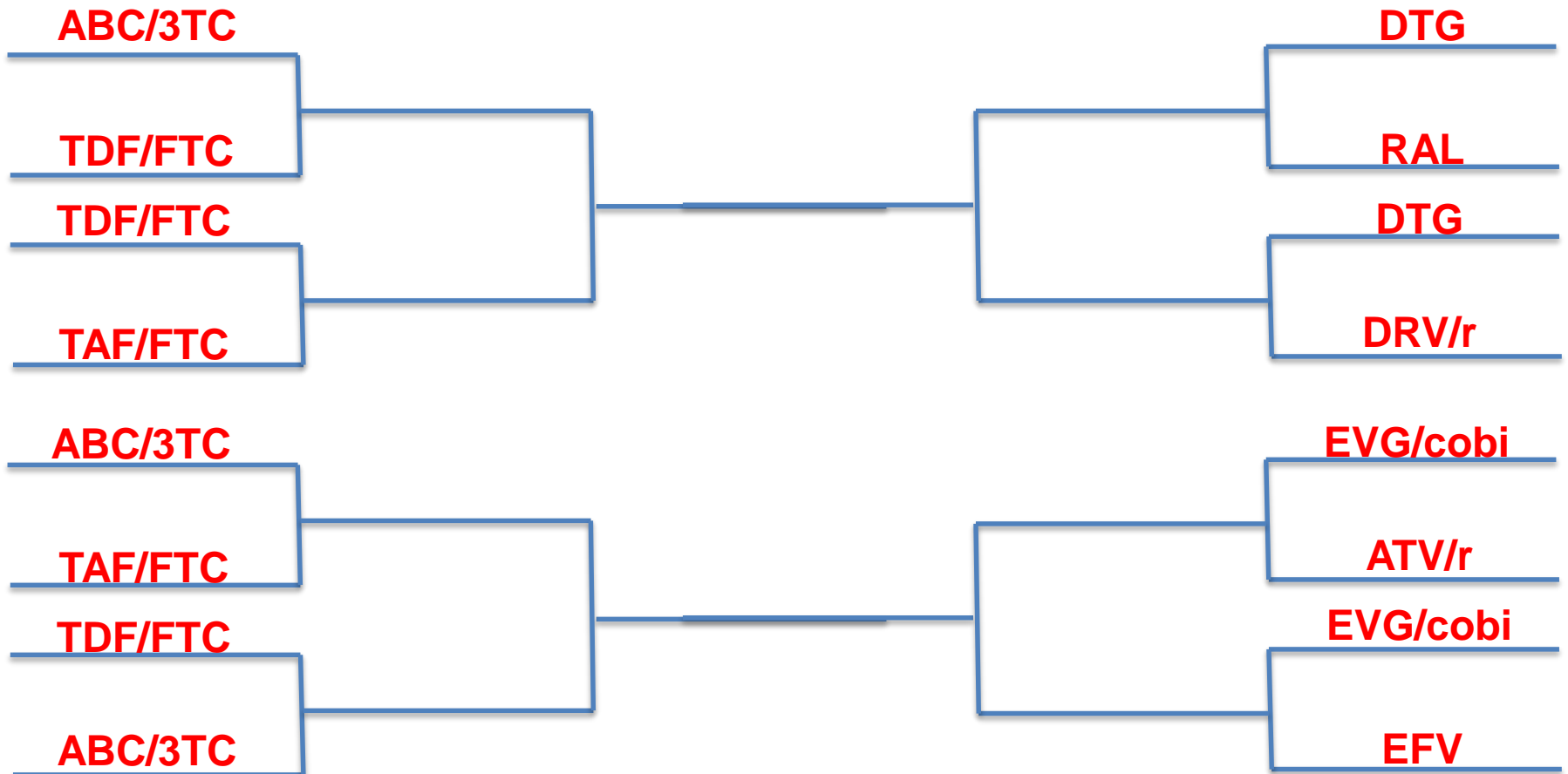


EVG/c/FTC/TAF – Nov. 2015
(initial therapy & switch studies)
RPV/FTC/TAF – Mar. 2016
(bioequivalence study)
FTC/TAF (25 mg) – April 2016
(switch studies)
Darunavir/c/FTC/TAF – phase III

TAF or TDF

- **When is TAF recommended over TDF in the US?**
 - Patient with osteoporosis or osteopenia
 - Patient with renal disease (eGFR >30) or evidence for proximal tubular dysfunction (e.g. proteinuria)
 - Growing proportion of patients: “graying of the epidemic”
- **When is TDF recommended over TAF in the US?**
 - Patient on rifamycin (may decrease TAF levels)
 - Pregnant women
 - For pre-exposure prophylaxis (PrEP)

Customizing ART based on patients comorbidities and conditions



NRTI	PROS	CONS
ABC/3TC	<ul style="list-style-type: none"> • Not nephrotoxic • Single pill regimen with DTG (unboosted INSTI) 	<ul style="list-style-type: none"> • Must confirm HLA-B5701 negative • Some studies, but not all, show association with cardiac events
TDF/FTC	<ul style="list-style-type: none"> • Single pill regimens with EFV, RPV, EVG/c • Lowers lipids • Active vs. HBV 	<ul style="list-style-type: none"> • Greater nephrotoxicity than ABC and TAF • Larger decline in bone mineral density than with ABC or TAF
TAF/FTC	<ul style="list-style-type: none"> • More favorable effects on renal and bone markers than TDF • Single pill regimens with EVG/c, RPV • Active vs. HBV 	<ul style="list-style-type: none"> • Less long-term data, particularly for initial therapy

Customizing ART

Scenario	Preferred Therapy
Kidney Disease (eGFR < 60)	ABC + 3TC or TAF/FTC (if CrCl >30) (Avoid TDF, ATV/r, LPV/r: associated with kidney disease ¹)
High cardiac risk	Favor TDF or TAF
HBV	TDF/FTC or TAF/FTC (Less data with TAF; HBV indication not yet included in its label)
Pregnancy	ABC/3TC, TDF/FTC or AZT/3TC plus RAL or ATV/r, DRV/r or EFV* <small>*after first 8 wks</small>
Osteoporosis/ osteopenia	Avoid TDF

Customizing ART: Drug Interactions

Scenario	Preferred Therapy
HCV Therapy Anticipated	Often use raltegravir, dolutegravir: fewer drug interactions
Acid-lowering therapy	Avoid or caution with rilpivirine, atazanavir
Cations	Stagger dosing of integrase inhibitors
CYP3A4 metabolized medications	Avoid or caution with PIs, coBI

Useful site: <http://www.hiv-druginteractions.org>

Drug Interactions: Exogenous Steroids

- Injectable steroids: levels increased by PI, coBI
 - 10% of patients on PIs who received steroid injection developed clinical evidence of steroid excess or adrenal insufficiency¹
- Inhaled fluticasone² & budesonide³: systemic levels increased by PI, coBI
 - Beclomethasone is safer alternative⁴

¹Hyle E et al, JAIDS, 2013

²DHHS guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents. <http://AIDSinfo.nih.gov>

³<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSactivities/ucm336367.htm>

⁴Boyd S et al, JAIDS, 2013

What regimens should be used in patients who cannot take TDF or ABC?

Example: HLA-B5701-positive patient with
significant renal disease (estimated
creatinine clearance <30)

NRTI-limiting Regimens for Initial Therapy

- **LPV/r + 3TC (GARDEL)¹**
 - Non-inferior to LPV/r + 2 NRTI
 - Disadvantages: high pill burden, toxicities
- **DRV/r + RAL (NEAT001)²**
 - Non-inferior to DRV/r + TDF/FTC
 - CD4 <200: DRV/r + RAL inferior to DRV/r + 2 NRTI
 - VL >100 K: more failures with DRV/r + RAL
 - Higher rate of resistance in DRV/r + RAL group³
- ***DTG + 3TC – being studied***
 - PADDLE⁴, ACTG A5353 (ongoing)

¹Cahn P et al, Lancet ID 2014; ²Raffi F et al, Lancet, 2014; ³Lambert-Niclot S et al, J Antimicrob Chemother, 2016; ⁴Figueroa MI et al, 15th EACS, 2015

Switching to NRTI-limiting regimens after virologic suppression (maintenance)

- LPV/r + 3TC/FTC (OLE)¹
- ATV/r + 3TC (SALT)²
- DRV/r + RPV (small trial, n=60)³
- *DRV/r + 3TC (DUAL) – being studied*
- *DRV/r + DTG (DUALIS) – being studied*
- *DTG + 3TC (ASPIRE) – being studied*
- *DTG/RPV (SWORD-1 and -2) – being studied*
- *IM Cabotegravir + IM RPV (LATTE-2)⁴ –being studied*

¹Arribas JR et al, Lancet ID, 2015; ²Perez-Molina JA et al, Lancet ID, 2015; ³Maggiolo F, JAIDS, 2016;

⁴Margolis DA et al, CROI 2016, #31LB

Switching ART

Indications for changing ART

- Viral load >1000 \Rightarrow step up adherence interventions
 - Inadequate patient adherence is most common reason for treatment failure
- When viral load is confirmed on a second specimen to be >1000 copies/ml \Rightarrow switch to second-line therapy without undue delay

Second-line Therapy in SA

AZT/3TC + LPV/r

- Anemia → ABC
- Renal failure → ABC
- d4T in failing first line regimen: TDF
- Dyslipidemia or intractable diarrhea from LPV/r
→ATV/r

Summary

HIV: Starting/Switching 2016

- When to Start: Data support starting ART in all patients
- What to Start?
 - US: INSTI-based regimens
 - SA: TDF/XTC/EFV
- What's on the Horizon
 - INSTIs, TAF
- Switching ART: adherence support; if persistent viremia, change before high-level resistance develops