ACTHIV 2018: A State-of-the-Science Conference for Frontline Health Professionals

Initial Therapy for Antiretroviral Naïve HIV Infected Patients

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Disclosures

Scientific Advisory Board
Gilead Sciences

There will be no off-label/investigational uses discussed in this presentation.

Learning Objectives

1. Describe the IAS-USA and DHHS guidelines for initial treatment of HIV infected patient

2. Discuss recommendations for treatment in special populations and co-morbidities

3. Review recommendations for lab monitoring post initiation of antiretroviral treatment

Initial Evaluation of the Patient with HIV

4 Steps

Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection prophylaxis (if indicated)

Step 3: Antiretroviral therapy: when and what to start; how to monitor

Step 4: Preventive care

Patient care recommendations are drawn from the US Department of Health and Human Services (DHHS) guidelines unless otherwise noted.

Panel on anti-retroviral guidelines for adults and adolescents. Guidelines for the use of anti-retroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Available at HTTP://aidsinfo.nih.gov/contentfiles/1vguidelines/adultandadolescentGL.pdf

Lab Evaluation: HIV-specific Tests

- HIV confirmation test

  do if HIV not clearly documented
- CD4 cell count and percent
- HIV RNA viral load or VL
- HIV drug resistance test (genotype)
- HLA-B5701: if considering abacavir containing regimen
- Tropism test (phenotypic or genotypic): if considering CCR5 inhibitor

E Phillips, CID, 2006; Aberg, J et al CID 2014

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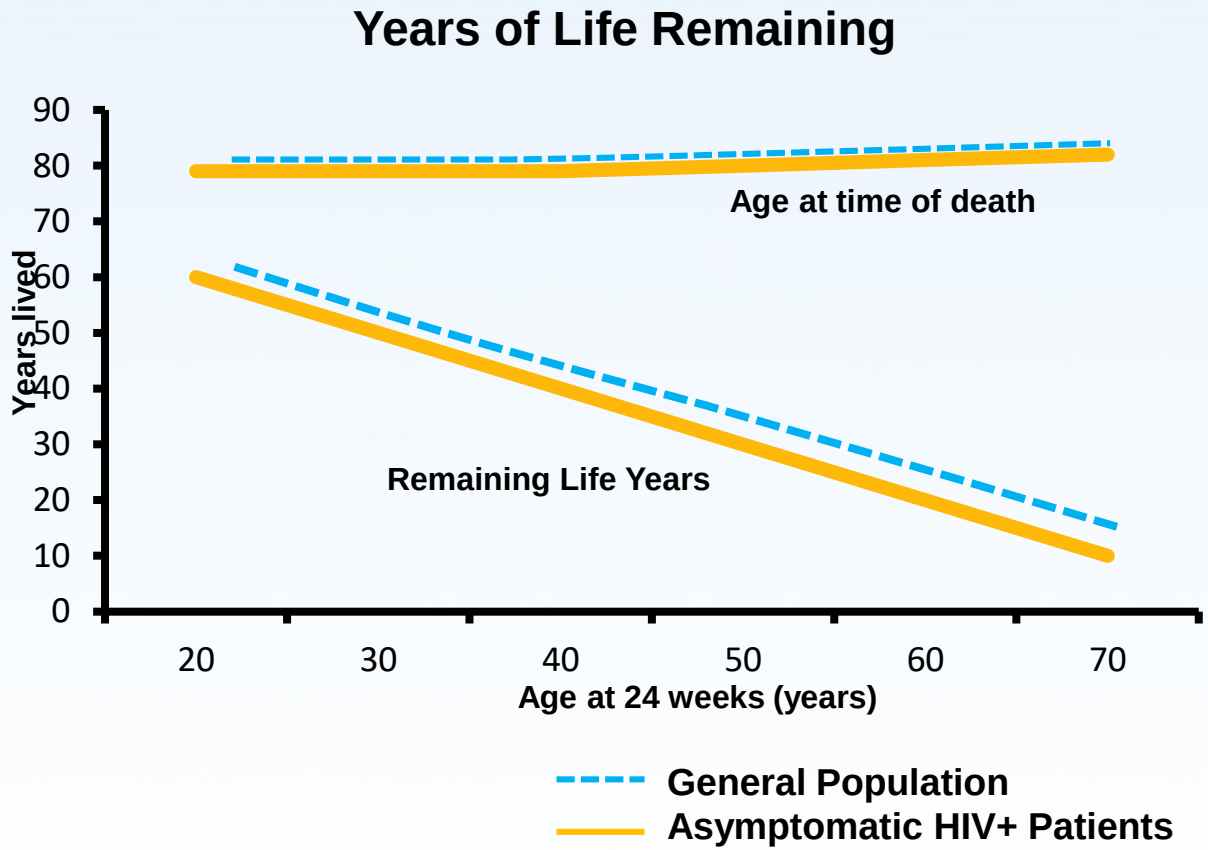
Resistance Testing

- Genotypic testing for reverse transcriptase and protease resistance mutations is recommended prior to treatment initiation

- Routine screening for integrase resistance is ***currently NOT recommended*** prior to treatment initiation unless the source virus is suspected to have been from someone in whom treatment containing an integrase strand transfer inhibitor failed

Life Expectancy of HIV-Infected Patients

- Comparison of life expectancy of Athena cohort patients to general population (n=4174)
- Expected life years remaining at age 25 was 53.1 (44.9-59.5) for general population and 52.7 for asymptomatic HIV+ patients
- The modeled life expectancy of patient presenting at an older age and women were slightly lower that general population



van Sighem A, *AIDS*, 2010

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General Principles

The goal is start and maintain treatment to prevent disease, maintain quality of life, and prevent transmission of HIV to others

“ The sooner, the better.” – reduces size of the reservoir, decreased inflammation, can consider starting before all test results are available

Ideally we want to start a regimen that patients can comply with for a long period of time.

Fewest number of pills

Fewest times needed to be taken in a day

Fewest complaints - best side effect profile

Role of the Multidisciplinary Care Team

- Interventions to improve linkage, retention, and adherence to care are essential.
- Barriers to adherence to ART and appointments should be assessed prior to initiating therapy and thereafter, as needed.
- Multidisciplinary approaches to address adherence issues are often necessary.
  - Collaboration with social work and case management to help mitigate competing priorities (e.g. housing, food insecurity, transportation, employment status, out-of-pocket costs) is recommended
  - Linking patients to counseling to overcome stigma, substance use, or depression improves outcomes.
  - A care team approach to continued education and linkage to resources to overcome barriers is encouraged.

Multidisciplinary Team Members

Social Work

Case Management

Mental Health

Harm Reduction

Nursing

Entitlement Specialist

Peer Educators

Pharmacist

Clinical Providers

Initial Treatment:
When and Who to Start

- Antiretroviral therapy (ART) is recommended for all patients with established HIV infection, a detectable viral load, and regardless of CD4 cell count
- Initiation of ART is recommended as soon as possible in the setting of acute HIV infection
- Initiation of ART is recommended for individuals who have persistent undetectable viral load (*elite controllers*) without ART but have declining CD4 cell counts

Günthard HF *JAMA* 2016; Lundgren JD, *N Engl J Med*. 2015; Danel C, *NEJM*, 2015; Grinsztejn B, *Lancet Inf Dis* 2014

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Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive yesterday.

Pt denies any prior illness. Her labs were only significant for a mildly elevated WBC. Has h/o unprotected sex with 5 male partners in her lifetime and is now in a committed relationship. Denies any recreational drug use or excessive alcohol use. Smokes 1ppd x 19 years.

A CD4 and VL were obtained yesterday. CD4 267 17%, viral load and genotype are pending.

Pt feels weak, but was symptomatically improved at time of discharge. You order additional blood work in your office.

She has no barriers to care, has been educated about HIV, and is eager to start treatment.

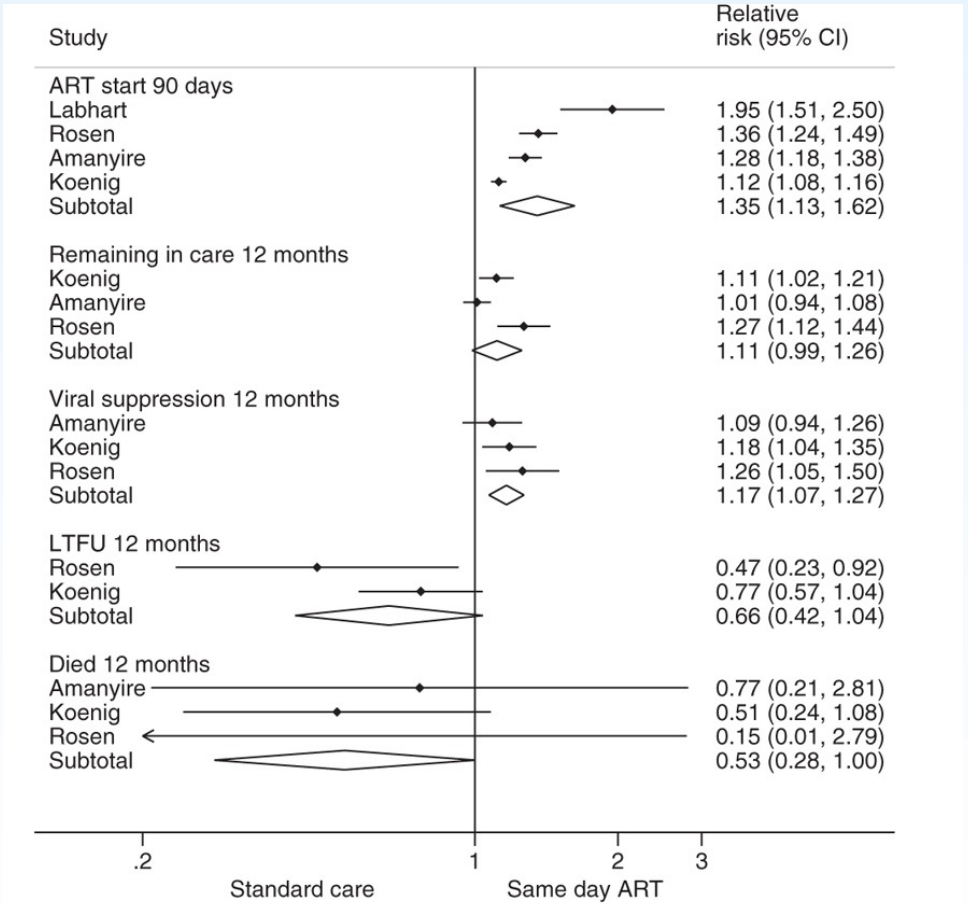
Question 1

1. Make an return appointment in 4 weeks when genotype result will have returned.
2. Make an return appointment in 2 weeks to re-assess her readiness to start, review labs.
3. Start treatment with DTG/ABC/3TC
4. Start treatment with EVG/c/TDF/FTC
5. Start treatment with RPV/TAF/FTC

Rapid Initiation of ARV

- Accelerated ART initiation, including starting ART on the same day as HIV diagnosis, can lead to improved clinical outcomes
  - Important for people with very low $CD4^+$ cell counts, for whom the risk of death is high
- ART initiation on the same day as HIV is diagnosed should be offered to those patients who are ready to start
- Genotype and safety labs should be obtained, but do not have to wait for results prior to start
  - ABC containing regimens are not recommended for same day start given need for HLA testing results
  - TAF/FTC containing regimens can be used with CrCl > 30 mL/min

Outcomes from RT of Same day Start vs Standard of Care



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Ford N, *AIDS* , 2018

Available Antiretroviral Agents

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- ~~Stavudine (d4T)~~
- **Lamivudine (3TC)**
- **Abacavir (ABC)**
- **Emtricitabine (FTC)**
- **Tenofovir (TDF)**
- **Tenofovir Alafenamide (TAF)**

CCR5 Antagonist

- Maraviroc (MVC)

* Boosters

- Ritonavir (RTV)
- *Cobicistat (cobi)*

Nonnucleos(t)ide RTIs

- Nevirapine (NVP)
- Delavirdine (DLV)
- Etravirine (ETR)
- **Rilpivirine (RPV)**
- **Efavirenz (EFV)**

Integrase Inhibitors

- **Raltegravir (RAL)**
- **Dolutegravir (DTG)**
- **Elvitegravir (EVG)**
- **Bictegravir (BIC)**

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- **Lopinavir/r (LPV/r)**
- **Darunavir (DRV)**
- **Atazanavir (ATV)**

Fusion Inhibitor

- Enfuvirtide (T-20)

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Initial Treatment

An integrase inhibitor based regimen containing TAF/FTC or ABC/3TC is recommended for initial in treatment naïve individuals

Bictegravir/TAF/emtricitabine

Dolutegravir/abacavir/lamivudine

Elvitegravir/cobicistat/TAF/emtricitabine

Dolutegravir plus TAF/emtricitabine

Raltegravir plus TAF/emtricitabine

* *Bictegravir/TAF/emtricitabine* was added to the DHHS HIV guidelines as a first line recommended regimen on March 27, 2018. It has not yet been added to the IAS-USA guidelines.

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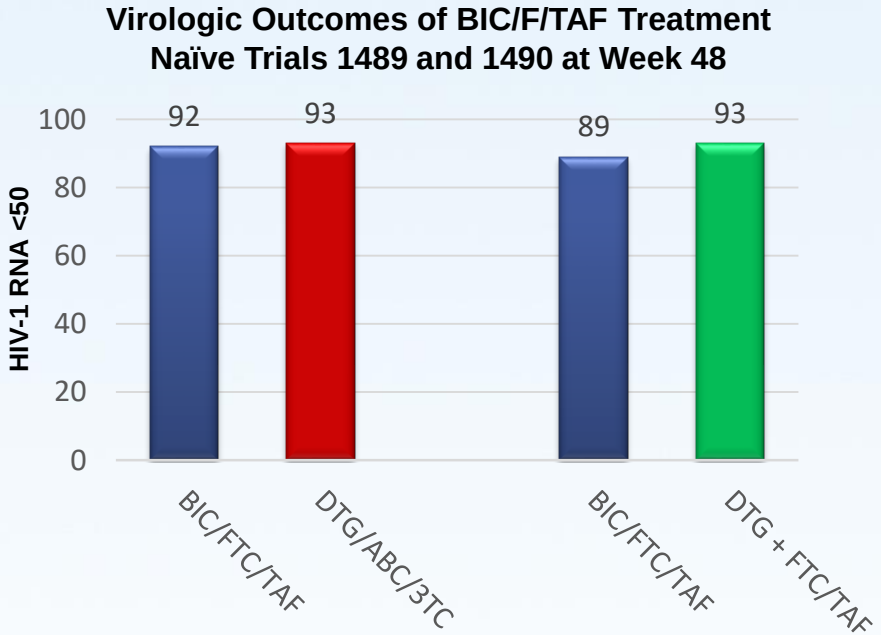
Günthard HF, IAS-USA HIV treatment guidelines JAMA 2016

New Integrase Inhibitor Single Tablet Regimen
Bictegravir/FTC/TAF

- Comparable virologic outcomes to DTG based regimens
- High genetic barrier to resistance
- No need for pretreatment HLA testing
- Does not include a pharmacologic booster, decreasing its potential for drug-drug interactions
- Can be used in patients with a CrCl as low as 30 mL/min
- Co-administration with rifampin is contraindicated due to the effect of rifampin on the BIC component



	Trial 1489		Trial 1490	
	BIC/FTC/TAF (N=314)	DTG/ABC/3TC (N=315)	BIC/FTC/TAF (N=320)	DTG + FTC/TAF (N=325)
HIV-1 RNA > 50	1%	3%	4%	1%
CD4 increase	233	229	180	201
Discontinued due to AE or Death	0	1%	1%	1%
Diarrhea	6%	4%	3%	3%
Nausea	5%	17%	3%	5%
Headache	5%	5%	4%	3%

Bictarvy® PI v2/2018 http://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf?la=en

Pros and Cons

BICTEGRAVIR

- high barrier to resistance
- safe in renally impaired, co-formulated with TAF/FTC
- few drug interactions
- contraindicated with rifamycins
- decreased clinical experience

DOLUTEGRAVIR

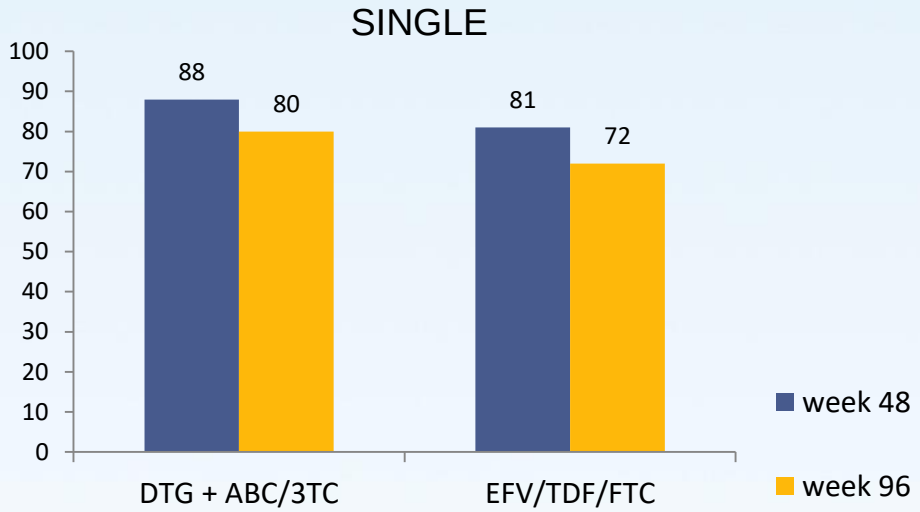
- high barrier to resistance
- superior to EFV and boosted DRV based regimens in clinical trials
- higher rates of insomnia, CNS AE in some studies
- inhibition of tubular secretion of Cr
- largest STR

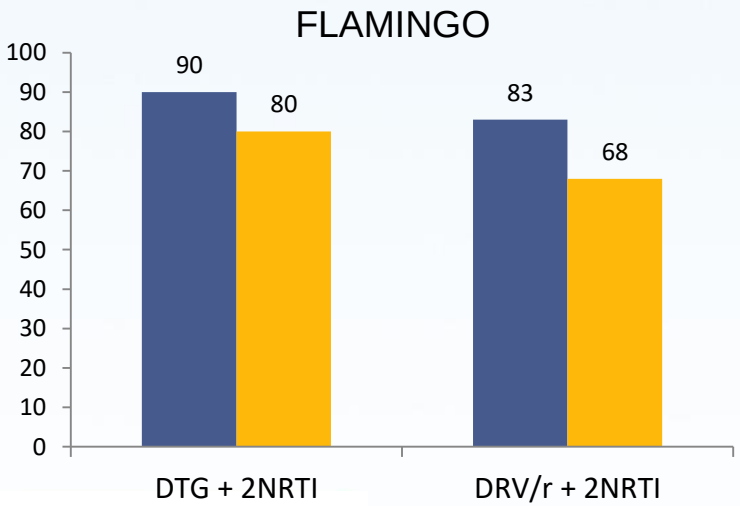
ELVITEGRAVIR

- co-formulated with TAF/FTC
- more drug interactions due to boosting
- cobicistat inhibition of tubular secretion of Cr

RALTEGRAVIR

- twice daily dosing, no co-formulation





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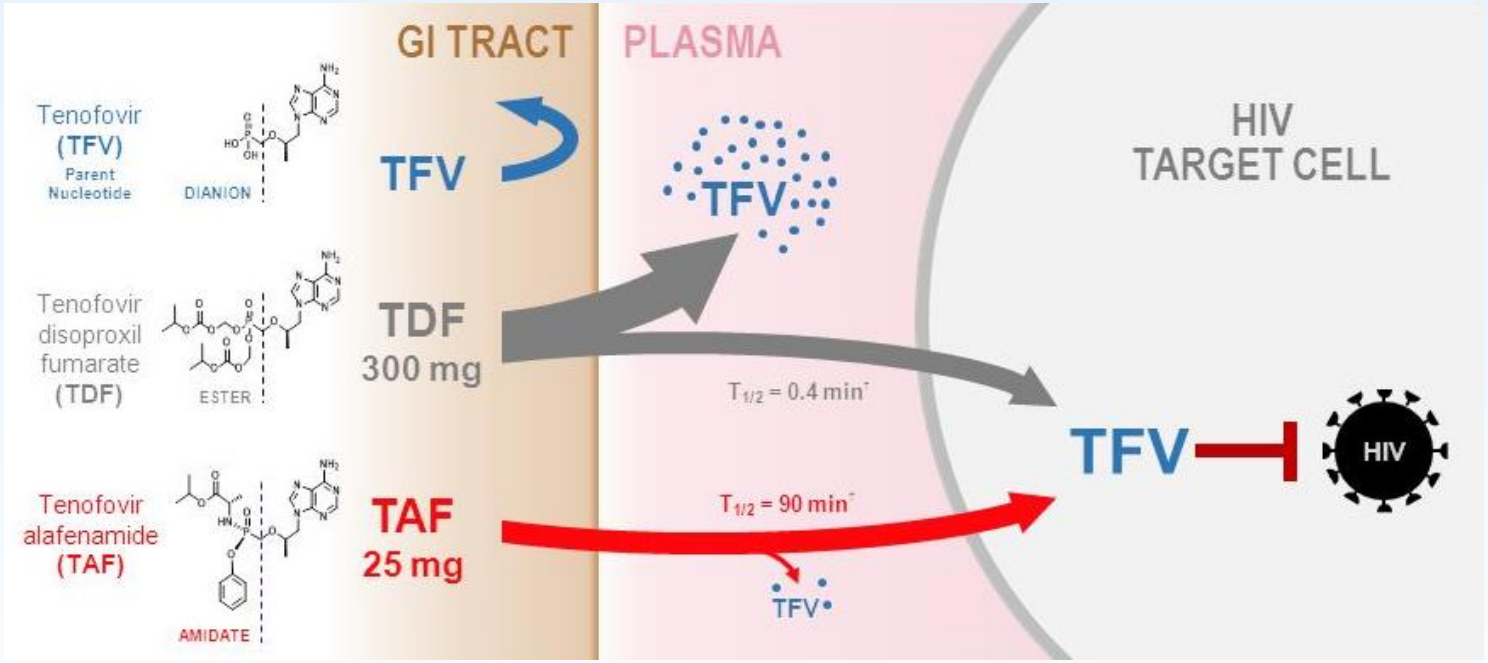
Walmsley, *NEJM*, 2013; Clotet B, *Lancet*, 2014; Molina J, *Lancet*, 2015

Tenofovir Alafenamide (TAF)



- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV
- less effect on renal tubular and overall proteinuria and eGFR than TDF
- little to no effect on bone density

Lee W, *AAC*, 2005; Birkus G, *AAC,* 2007; Babusis D, *Mol Phar*, 2013; Ruane P, *JAIDS*, 2013; Sax P, *JAIDS*, 2014; Sax P, *Lancet*, 2015

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Abacavir

- Requires HLA-B5701 testing prior to start
  - Approximately half of patients positive for the allele experience ABC hypersensitivity reaction
  - 8% of US whites, ~2% of US African-Americans and Hispanics[1]

- The association between abacavir and HIV associated cardiovascular disease remains controversial

- Proposed mechanisms remain unclear
  - ABC is lipid neutral, no change in insulin or limb fat loss
  - leukocyte and platelet–endothelial cell interactions via ATP-2 receptors → increased vascular inflammation response
  - augment adhesion of WBC to the endothelium
  - Increased platelet activation

Cardiovascular Risk with Abacavir

Reference	Study name	Study type	Patients, *n*	MI or (CVD[a]) (*n*)	Abacavir effect?	Exposure risk	Risk (95% CI)
Sabin *et al.* [11][*]	D:A:D Study Group	Prospective observational cohort	33 347	517	Yes	Recent Per year	1.90 (1.47–2.45) 1.89 (1.47–2.45)
Without authors [14][*]	SMART/INSIGHT	Observational analysis Randomized controlled trial	2752	19	Yes	Recent	4.25 (1.39–13)
Martin *et al.* [15]	STEAL	Randomized open-label clinical trial	357	9[d] 4	Yes	–	–
Obel *et al.* [16][*]	DANISH HIV	Prospective observational cohort	2952	67	Yes	Recent	2.00 (1.07–3.76)
Worm *et al.* [12][*]	D:A:D Study Group	Prospective observational cohort	33 308	580	Yes	Recent Per year	1.70 (1.17–2.47) 1.07 (1.00–1.14)
Lang *et al.* [17]	FHDB-ANRS-CO4	Nested case–control study in an observational cohort	74 958	289	Yes No	Recent Recent (adjusted)	1.62 (0.93–2.81) 1.27 (0.64–2.49)
Choi *et al.* [22][b]	VHA CCR HIV	Retrospective observational cohort	10 931	179[d]	Yes No	Recent Per year	1.48 (1.08–2.04) 0.79 (0.93–1.10)
Durand *et al.* [19]	QPHID (Québec's Public Health Insurance Database)	Cohort and nested case–control	7053	125	Yes	Recent	1.72 (1.10–2.71)
Bedimo *et al.* [26][b]	VHA CCR HIV	Retrospective observational cohort	19 424	278	Yes No	Per year Per year (adjusted)	1.18 (0.92–1.50) 1.16 (0.98–1.37)
Rotger *et al.* [18]	MAGNIFICIENT Consortium	Observational case–control	1875	571[d] 273	Yes	Recent	1.56 (1.17–2.07)
Young *et al.* [20]	SWISS	Prospective cohort	4052	195[d]	Yes	Recent Per year	3.69 (2.36–5.75) 1.05 (1.00–1.10)
Desai *et al.* [28][b]	VHA CCR HIV	Prospective cohort	24 510	467	Yes	Current	1.50 (1.26–1.79)
Marcus *et al.* [21]	KAISER PERMANENTE CALIFORNIA	Prospective observational cohort	704	24[d]	Yes	Recent	2.2 (1.4–3.5)
Sabin *et al.* [13][*]	D:A:D Study Group	Observational cohort study	49 717	941	Yes	Recent	1.98 (1.72–2.29)
Palella *et al.* [29]	NA-ACCORD	Retrospective cohort	16 733	301	Yes Yes No	Recent -Without adjustment -Adjustment similar to D:A:D -Adjusted for traditional CVD factors	1.88 (1.35–2.60) 1.71 (1.11–2.64) 1.34 (0.96–1.88)
Brothers *et al.* [23][c]	GSK analysis	Pooled randomized controlled trials	14 174	16	No	Recent	0.81 (0.38–1.75)
Ribaudo *et al.* [24]	ACTG A5001/ALLRT	Observational and retrospective clinical trial cohorts	5056	36	No	Per year	0.7 (0.2–2.4)
Sax *et al.* [25]	ACTG A5202	Observational and retrospective clinical trial cohorts	1857	29[d]	No	–	–
Islam *et al.* [30]	Systematic review and meta-analysis	Meta-analysis (2 clinical trials and 23 observational studies)	–	–	Yes	Recent	1.8 (1.43–2.26)
Bavinger *et al.* [31]	Systematic review and meta-analysis	Meta-analysis (1 clinical trial and 26 observational studies)	–	–	Yes	Recent	1.91 (1.50–2.42)
Cruciani *et al.* [32]	Meta-analysis	Meta-analysis (28 clinical trials)	–	12	No	Recent	0.73 (0.39–1.35)
Ding *et al.* [33][c]	FDA Meta-analysis	Meta-analysis (26 clinical trials)	–	24	No	Per year	1.02 (0.56–1.84)

[1]E Phillips, CID, 2006, Alverez A, *AIDS*, 2017

Recommendations for Initial Regimen in Certain Clinical Situations

Boosted PI + 2 NRTIs: *In general, boosted DRV is preferred over boosted ATV*

- (DRV/c or DRV/r) + tenofovir /FTC
- (ATV/c or ATV/r) + tenofovir /FTC
- (DRV/c or DRV/r) + ABC/3TC —if HLA-B*5701–negative
- (ATV/c or ATV/r) + ABC/3TC —if HLA-B*5701–negative and HIV RNA 200 cells/mm^3

INSTI + 2 NRTIs:

- RAL + ABC/3TC - if HLA-B*5701–negative and HIV RNA < 100,000 copies/mL

Regimens to Consider when ABC, TAF, and TDF ***Cannot*** be Used

- DRV/r + RAL (BID) - if HIV RNA > 200 cells/mm^3
- LPV/r + 3TC (BID)

*NNRTI regimens are *not recommended* as alternative regimens in the DHHS guidelines

IAS-USA Guideline Recommendations for

When Integrase Inhibitors are not an Option

Darunavir (boosted) plus TAF/emtricitabine or abacavir/lamivudine

Rilpivirine/TAF/emtricitabine

Efavirenz/TDF/emtricitabine

Günthard HF, IAS-USA HIV treatment guidelines JAMA 2016

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Pros and Cons

DARUNAVIR

- low rate of resistance even with poor adherence
- drug interactions with required boosting
- inferior to integrase inhibitor based regimens

RILPIVIRINE

- small size
- not recommended for VL > 100,000 or CD4, 200
- must be taken with meal
- staggered dosing with PPI

EFAVIRENZ

- longest track record
- low genetic barrier to resistance
- CNS side effects

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Special Considerations

Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive.

You write her prescription to start EVG/c/TAF/FTC today.

While she is getting her labs done, your nurse lets you know that her POC urine pregnancy test is reactive.

Question 2

1. You start the same ART, EVG/c/TAF/FTC today as planned.
2. You explain that ART will be started after the 1st trimester to minimize effects to the baby.
3. You decide to start DRV/cobi + TDF/FTC today
4. You decide to start RAL + TDF/FTC
5. You decide to start RPV/TDF/FTC

Pregnancy

- Addressing the fertility desires, preferred method of birth control, and pregnancy testing should be done in women of childbearing potential prior to the initiation of ART
- Goal start treatment as soon as possible is to promote the health of the pregnant woman throughout and to prevent vertical transmission (i.e. maternal VL < 1000 copies)
- ART should be uninterrupted for women who conceive while on treatment or as soon as possible for newly diagnosed unless regimen is contraindicated (ddI, d4t, and *elvitegravir/cobi*)
- NNRTI are no longer considered first line therapy for pregnant women

DHHS Perinatal guidelines, https://aidsinfo.nih.gov/guidelines, accessed 030718

Pregnancy

	RECOMMENDED	ALTERNATIVE
NRTI backbone	TDF/TFC, ABC/3TC, TDF + 3TC	AZT/3TC
NNRTI		EFV, RPV
PI	ATZ/r, DRV/r *	LPV/r
Integrase	RAL	DTG

*DRV/r: must be used twice daily in pregnancy
TAF :Insufficient data on TAF PK and safety in pregnancy
EVG/c: Reports of inadequate drug levels in 2nd and 3rd trimesters with viral breakthroughs

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Hepatitis Co-Infection

Hepatitis B

- regimen should contain two NRTIs with anti-Hep B activity: TDF or TAF, FTC, 3TC
- addition of entectavir recommended if few than two active Hep B NRTIs are not used
- risk of Hep B flare if regimen is changed to an option that doesn't have anti-Hep B activity

Hepatitis C

- goal is to have a regimen that has the fewest drug-drug interactions
- BIC/TAF/FC, DTG/ABC/3TC, and DTG or RAL +TAF/FTC have the best DDI profile in combination with HCV treatments

Renal Disease

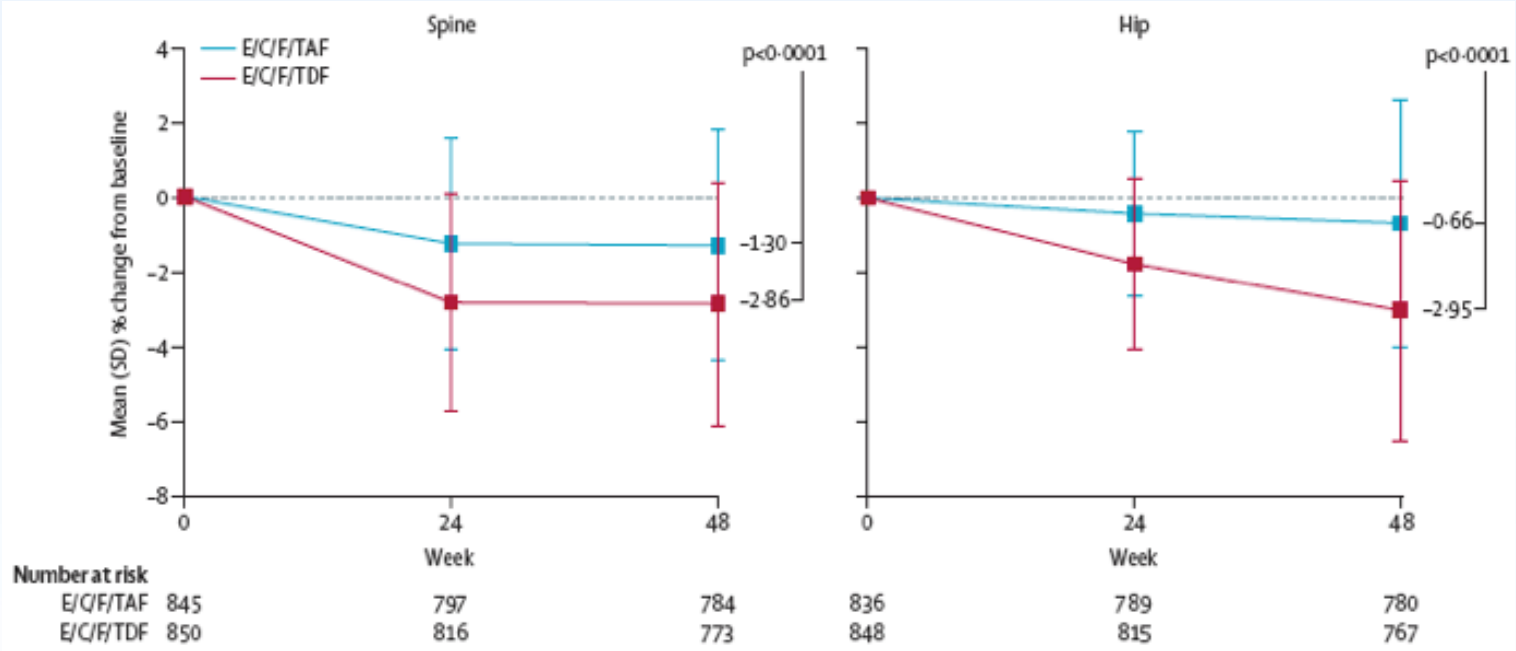
- Urinalysis should be obtained at initiation and at least annually
- TDF (especially with a boosted PI) increased the risk of chronic kidney disease.
- TDF is not recommended for patients with an eGFR below 50 mL/min.
- TAF/FTC can be used for CrCl 30 mL/min or above
- ABC does not require dose adjustment in renal insufficiency

Lucas GM, *CID*, 2014; Mocroft A, *Lancet HIV*, 2016

Bone Density

- Patients may lose 2% to 6% of their bone mineral density at the hip and spine, within the fist 18 – 24 months after the initiation of ARV therapy
- Rates of osteoporosis and fractures are increased HIV infected compared to age / risk factor matched controls
- TAF containing regimens have a more favorable decline in BMD compared to TDF regimens
- Avoid TDF in patients with pre-existing osteopenia / osteoporosis

BMD changes over 48 weeks: E/C/F/TAF vs E/C/F/TDF



Sax P, *Lancet*, 2015

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Clinical Scenario

33 yo AA F presents to clinic after recent hospital admission for pneumonia. During the hospitalization, she accepted HIV testing and her test was confirmed positive.

She insists that she is not pregnant.

Your nurse returns to clarify that there was a lab error and that her repeat pregnancy test is in fact negative.

As you are about to write a prescription for her ART, you get a call from the DOH that her BAL specimen is positive for TB, with no evidence of drug resistant TB

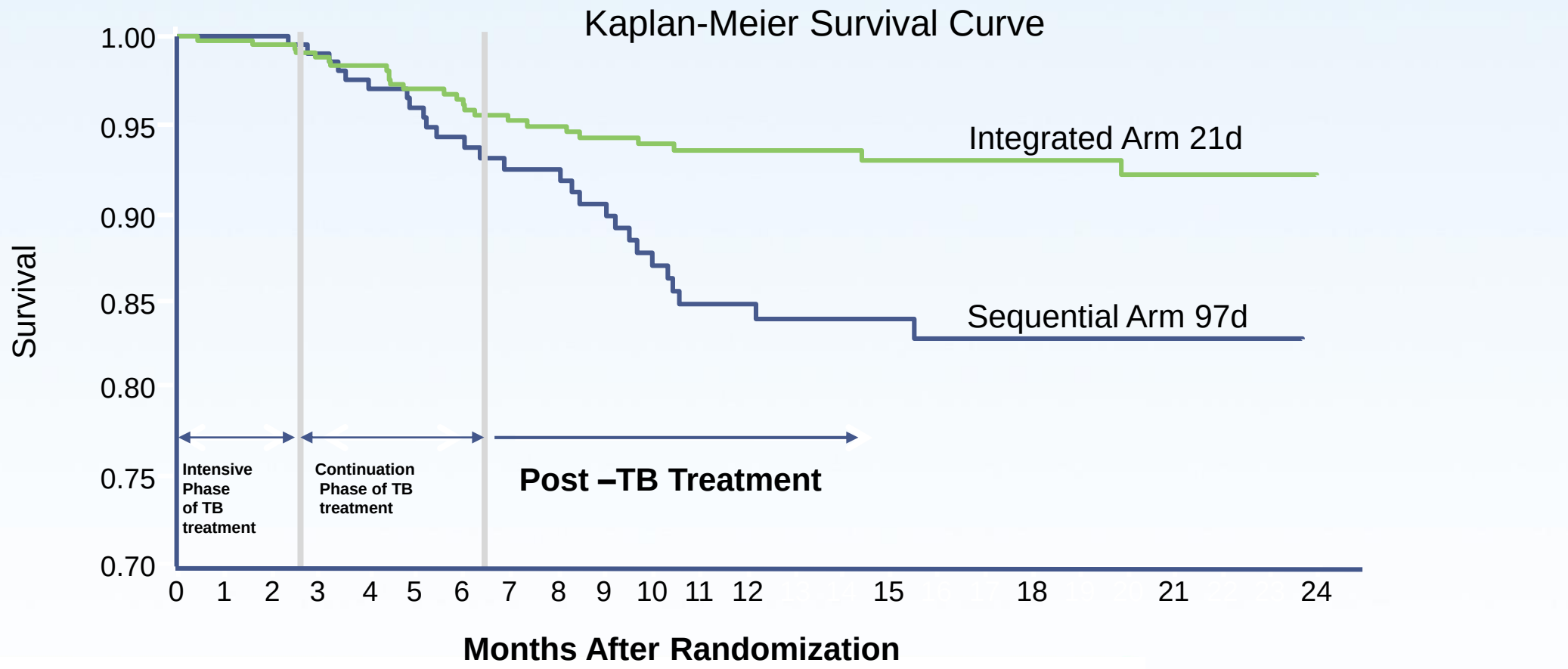
Question 3

1. You hold on starting ART, refer her to pulmonary, and have her return after 2 months of TB treatment.
2. You start the same ART, EVG/c/TAF/FTC, today as planned.
3. You explain that ART will be started 2 weeks after TB treatment.
4. You decide to start DRV/cobi + TDF/FTC today
5. You decide to start DTG + TDF/FTC

Initiating Therapy with an Active OI

- ART should be started within the first 2 weeks after diagnosis for most acute opportunistic infections
  - Drug interactions and tolerability should be considered when choosing a ART regimen
- ART should be started within the first 2 weeks of initiation of tuberculosis treatment for those with CD4 cell counts of 50/μL or less and within the first 2 to 8 weeks for those with CD4 cell counts above 50/μL
- TAF, BIC, and elvitegravir/cobi are *not recommended* with rifamycin drugs
- A boosted protease inhibitor–based regimen should be used only if an integrase strand transfer inhibitor is not an option

SAPiT Trial:
Mortality in Sequential Arm Occurred Late



Abdool Karim S, *N Engl J Med*, 2010

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Delayed ARV Start with Meningitis

Delayed start is recommended in the setting of cryptococcal and TB meningitis

- ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy
  - In resource limited settings, mortality was lower when ART was delayed until 5 weeks after diagnosis
  - In settings where optimized regimens, frequent monitoring, and testing of ICP are available, an earlier start of ARV is recommended
- Early initiation of ART in the setting of TB meningitis may be associated with severe IRIS

Boulware DR, *NEJM*, 2014; Perfect JR, CID, 2010; Mandarzo C, *Expert Rev Anti Infect Ther,* 2015; Ingle SM, 22nd CROI, 2015

Cost Considerations

- Here in the US, approximately 75% of the cost of treating HIV is related to the cost of medications
- It is cost effective to treat HIV even if ARVs are full price.
- As more ART components become generic, cost considerations continue to factor into the debate on resource constraints and best practice on a larger scale
- Guidelines often persuade payors as to which regimens are covered by individual prescription drug plans
- Individual state ADAP formularies and insurance plans may lag or exclude recommended options

Monitoring after Starting ART

HIV RNA

- 4 - 6 weeks after starting ART; then every 4-8 weeks until undetectable
- First 1 year of ART: every 3-4 mo.
- After 1 year of virologic suppression, can extend to every 6 months

CD4 count:

- 3 mo. after initiating ART, until Cd4 > 350
- First 2 years of ART: every 6 months
- After 2 years of virologic suppression, CD4 300-500:every 12 mo.; CD4 >500, optional

Aberg J et al, *CID*, 2014

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Monitoring after Starting ART

Chemistries, BUN/Cr, LFTs: wk 2-8 after starting ART, then every 3-6 mo

CBC/diff: every 3-6 mo

Fasting glucose or HbA1c: every 3-6 mo. If previously abnormal; every 12 mo. If normal

Lipids: if abnormal, every 6 mo; normal: every 12 mo.

U/A annually; every 6 mo. if receiving TDF

DHHS guidelines, http://AIDSinfo.nih.gov; Aberg J et al, CID, 2014

Summary

The overriding principles for initial ART regimen are patient safety, efficacy, tolerability, and options that lead to improved compliance.

Integrase inhibitor based regimens are recommended by guidelines as first line therapy based on data from comparative clinical trials.

Attention should be given to choice and timing of initial ART regimen in special populations at increased risk of adverse events and drug-drug interactions.

Adherence, safety, cost, and access are among the factors to consider when choosing initial therapy. The interplay of cost effectiveness and the availability of lower priced generics is evolving.

"Guidelines are just that . . . *Guidelines*"

- Judith Aberg

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Thank You