SAHIVSOC NEW ADULT GUIDELINES: 2017

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SA HIV Clinician Society
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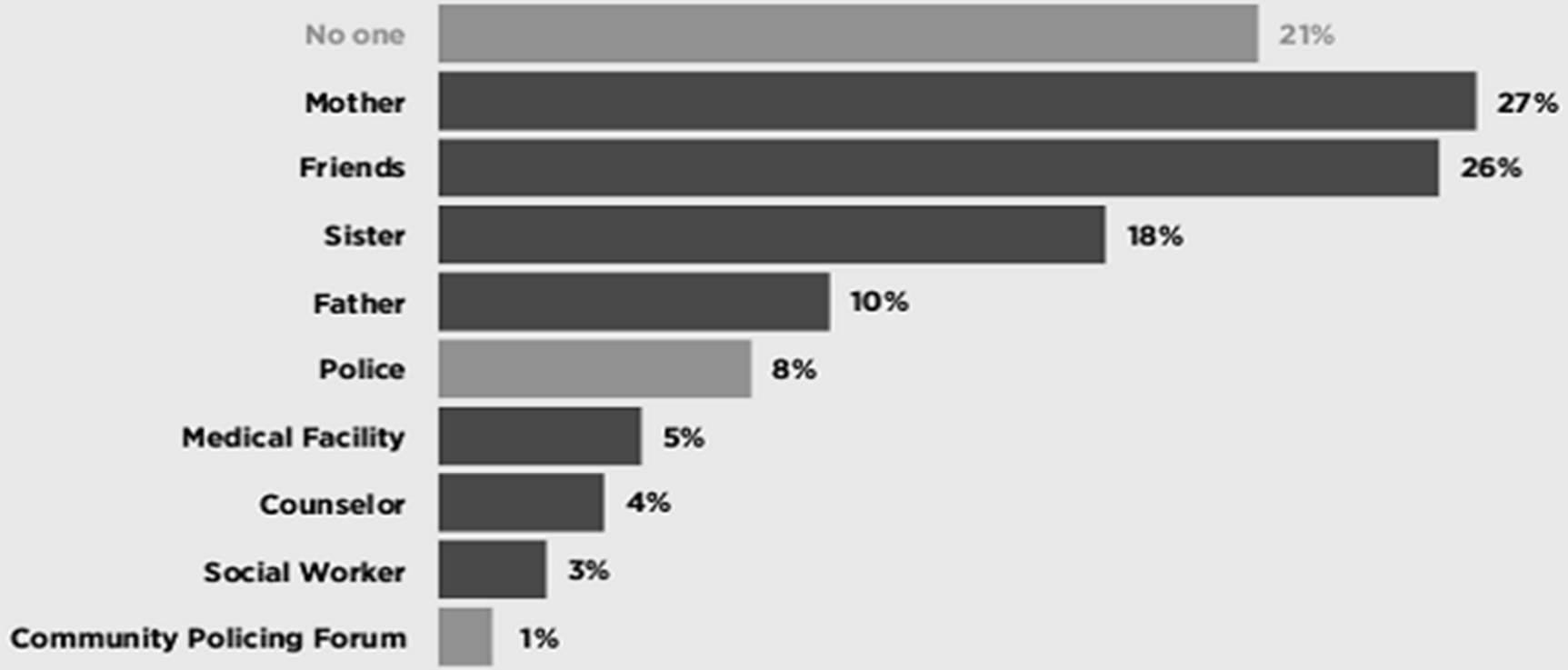
'Nothing will ever be attempted if all possible objections must first be overcome' – Samuel Johnson (1709-1784)

ONE IN FOUR WOMEN LIVING IN RUSTENBURG HAS BEEN RAPED IN HER LIFETIME

Who women told about their experience of rape*

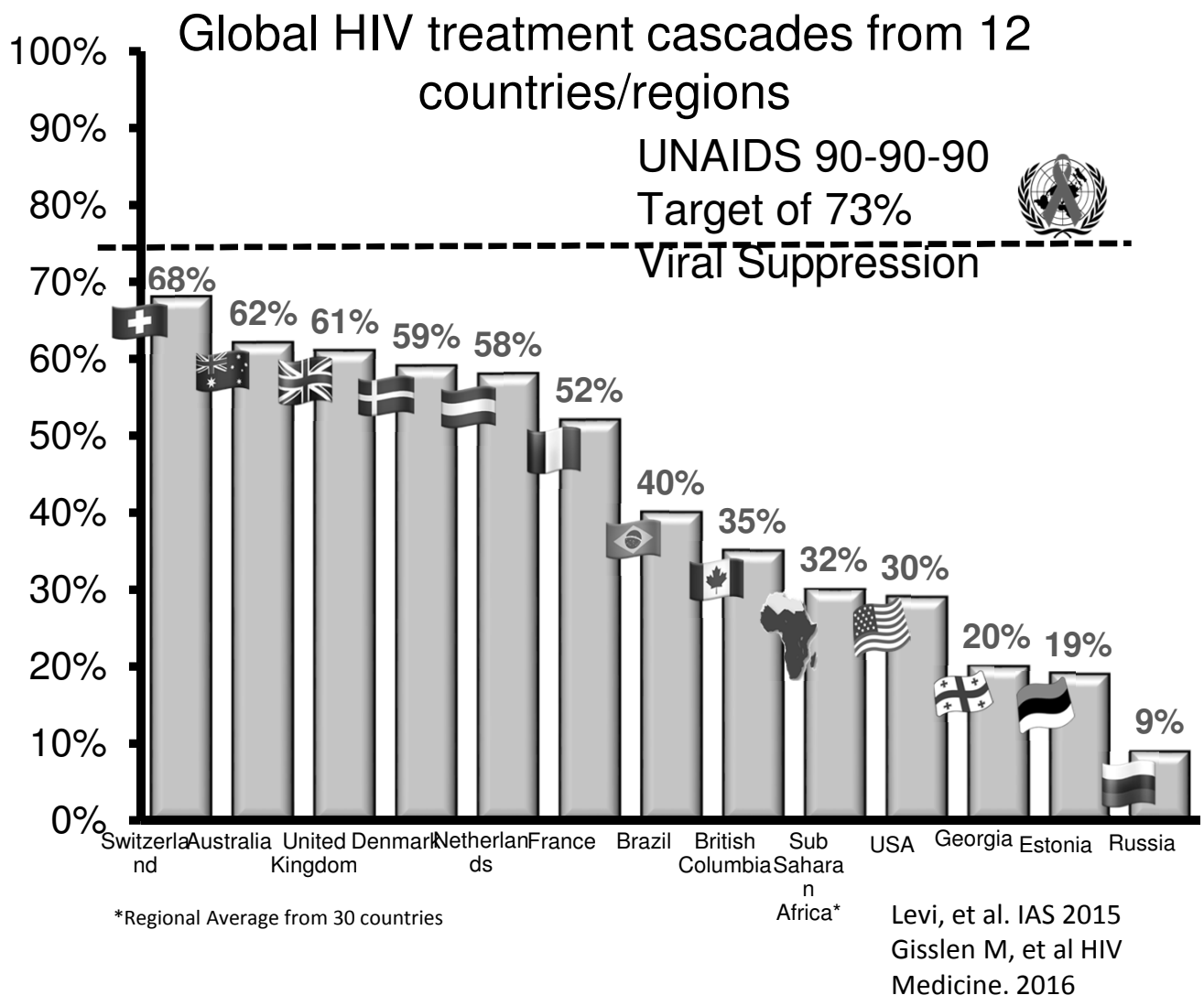


*If women told someone about their experience, options were not mutually exclusive

HIV treatment targets for 2020 with global 2013 estimates

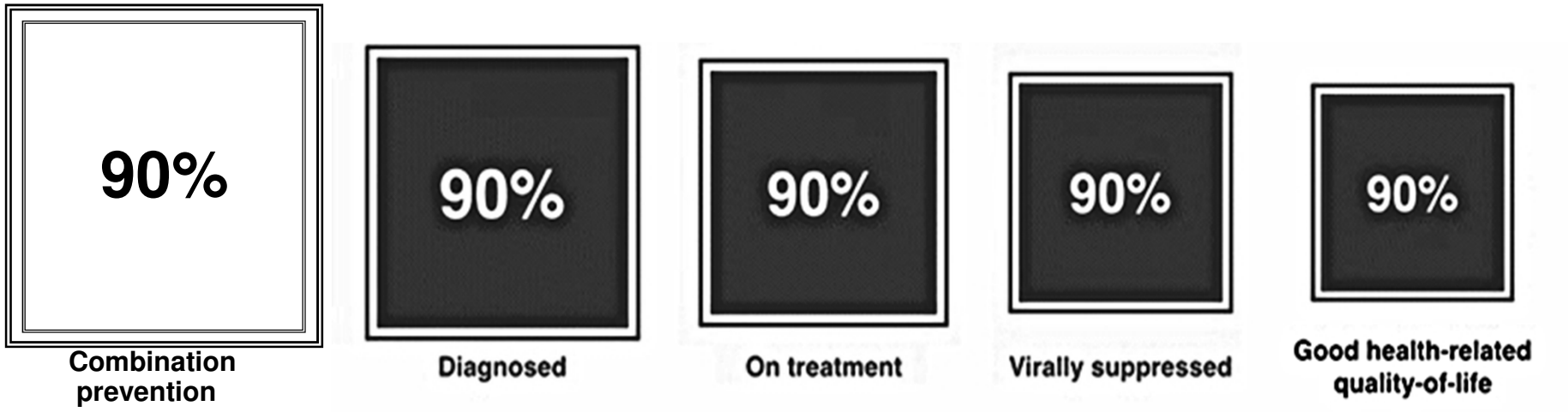
To date, no country or region, with the exception of Sweden, has met the UNAIDS 90-90-90 coverage target of 73% viral suppression

Without a focus on PREVENTION→ targets cannot be met → numbers will continue to rise



Levi, et al. IAS 2015
Gisslen M, et al HIV Medicine. 2016

“UNAIDS”: 90-90-90-90-90



*Adapted from: UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. 2014. Available at http://unaids.org/sites/default/files/media_asset/90-90-90_en_0.pdf. Accessed on 25 April 2016

Clinical Perspective on Treating Diverse HIV Patient Populations

Evolving HIV (Human Immunodeficiency Virus) Treatment Landscape

- Numerous effective regimens
- Fewer toxicities
- Increased lifespan leading to aging population and increased duration on therapies
- Opportunity to individualize treatment

Opportunities to Tailor a Regimen

Medications Factors

- Efficacy
- Safety profile
  - Short- and long-term
- Genetic barrier to resistance
- Rate of transmitted resistance
- Dosing frequency
- Pill size

Individual Factors

- Pretreatment viral load and CD4+ cell count
- Drug resistance results
- HLA-B*5701 status
  - Human leukocyte antigen
- Comorbidities
- Concomitant medications
- Patient preferences

Potential Advantages and Disadvantages of Single-Tablet Regimens

Advantages

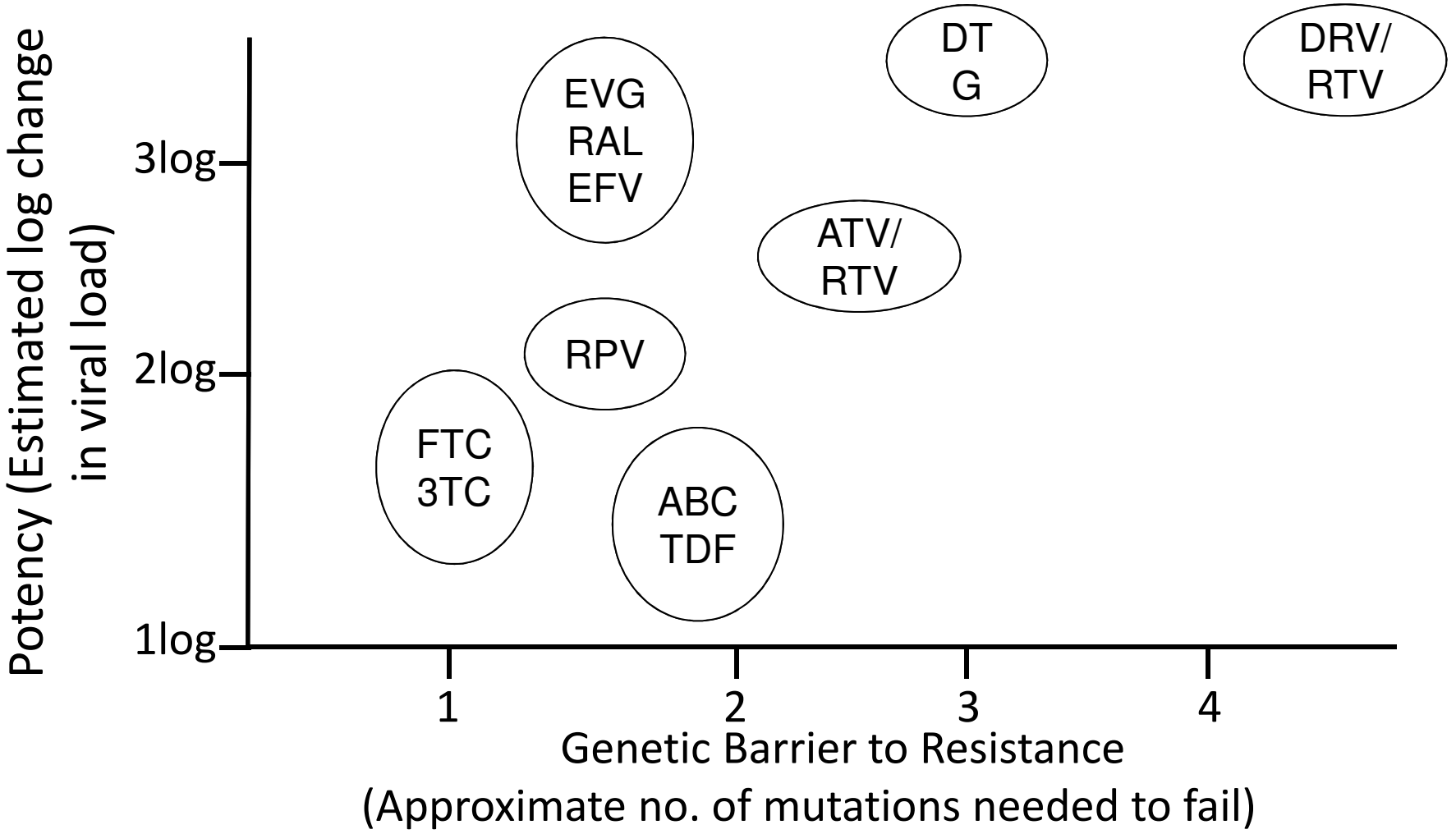
- Simplicity
- Convenience
- Fewer copays
- Reduces selective nonadherence to components of regimen

Disadvantages

- Inability to adjust dosages of components if needed due to drug–drug interactions or tolerability issues, eg, renal insufficiency
- Not available for all ART regimens
- Not available for all NRTI pairings

Slide credit: clinicaloptions.com

Antiviral Drug Potency and Genetic Barrier to Resistance



Initial ART regimens for the previously untreated patient

Recommended Regimens

NNRTI based

- EFV+TDF+FTC (or 3TC)
- RPV+TDF+FTC(or 3TC) (requires HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3)

Recommended Regimens

INSTI based

- DTG + TDF+FTC (or 3TC)

Rilpivrine cannot be used with rifampicin and dolutegravir requires dose adjustment with rifampicin.

*Pt must be HLA-B*5701 negative.

Alternative Regimens

For some patients, an alternative regimen may be the best choice based on individual factors

NNRTI	▪ **EFV+ABC+FTC(or 3TC)** ▪ **RPV+ABC+FTC(or 3TC)** ▪ **EFV+3TC+AZT** ▪ **RPV + 3TC+AZT**

If both TDF and ABC are unavailable or contraindicated, then AZT should be used, provided that the Hb level is >8 g/dL.

What to Start: DHHS Guidelines, July 2016

Recommended Regimens

PI based	▪ DRV/RTV + (TDF/FTC or TAF/FTC)
INSTI based	▪ DTG/ABC/3TC* ▪ DTG + (TDF/FTC or TAF/FTC) ▪ EVG/COBI/TDF/FTC or EVG/c/TAF/FTC ▪ RAL + (TDF/FTC or TAF/FTC)

Alternative Regimens

NNRTI based	▪ EFV/TDF/FTC or EFV + TAF/FTC ▪ RPV/TDF/FTC or RPV/TAF/FTC (requires HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3)
PI based	▪ (ATV/COBI or ATV/RTV) + (TDF/FTC or TAF/FTC) ▪ (DRV/COBI or DRV/RTV) + ABC/3TC* ▪ DRV/COBI + (TDF/FTC or TAF/FTC)

*Pt must be HLA-B*5701 negative.

DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. July 2016.

Slide credit: clinicaloptions.com

What to Start: IAS–USA Guidelines, July 2016

Recommended Regimens

- DTG/ABC/3TC*
- DTG + FTC/TAF
- EVG/COBI/FTC/TAF
- RAL + FTC/TAF

Regimens When INSTIs Are Not an Option

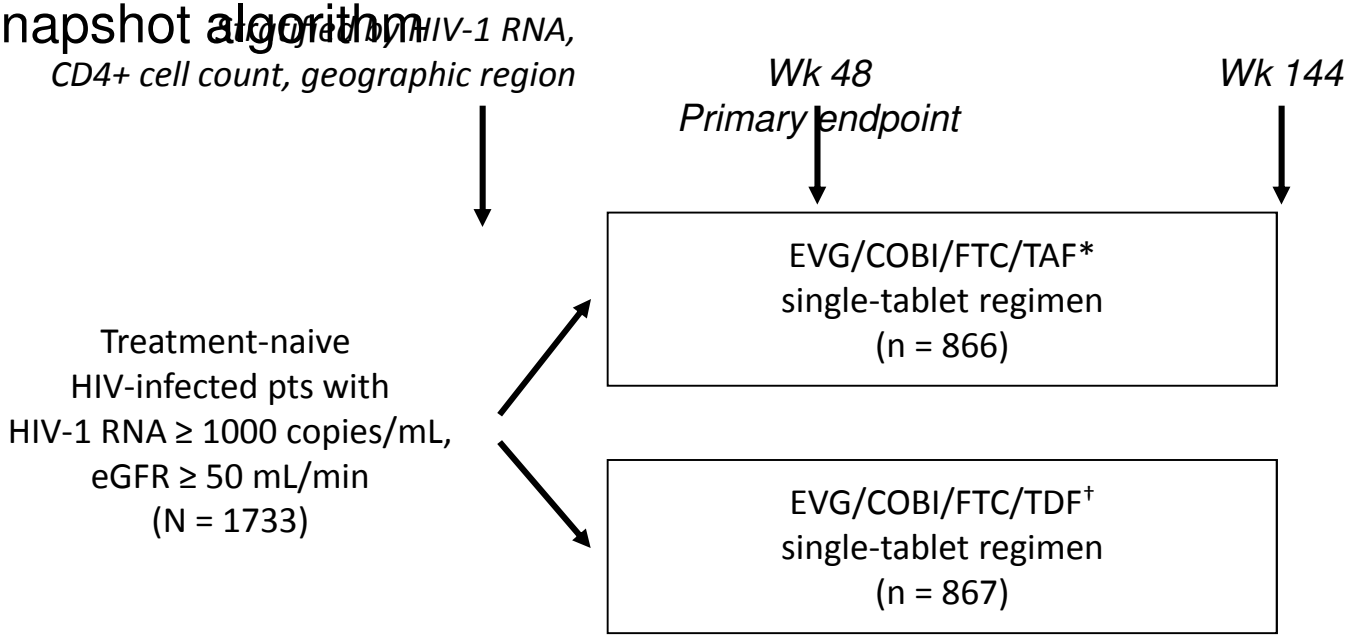
- EFV/FTC/TDF
- RPV/FTC/(TAF or TDF)†
- DRV/COBI or DRV/RTV + (FTC/TAF, FTC/TDF, or ABC/3TC*)

*Pt must be HLA-B*5701 negative.
†If HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3.

Slide credit: clinicaloptions.com

Studies 104/111: Tenofovir Alafenamide Fumarate vs TDF in Treatment-Naive Pts

- Parallel, randomized, double-blind, active-controlled phase III studies
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48, as defined by FDA Snapshot algorithm

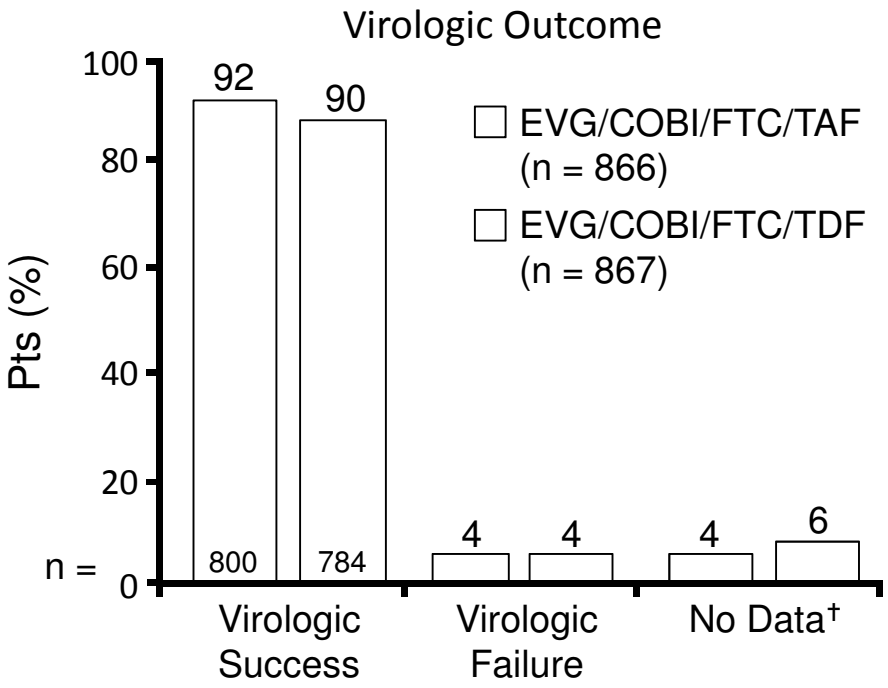


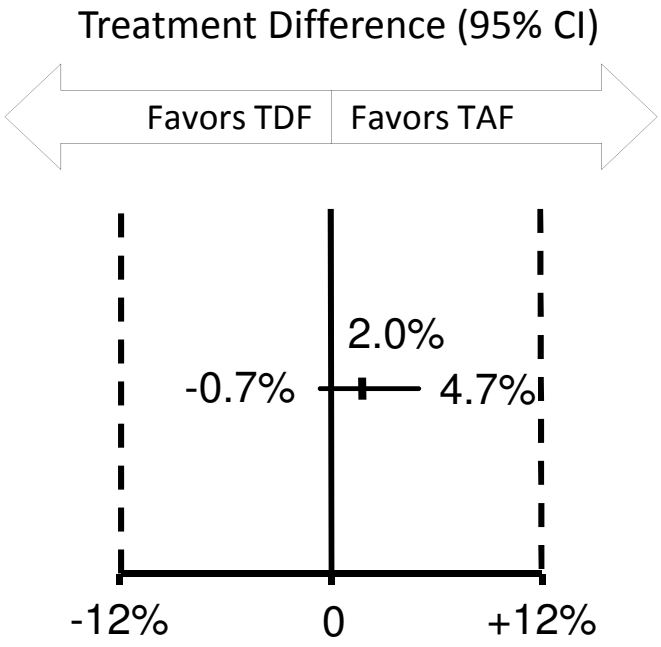
*150/150/200/10 mg once daily.
†150/150/200/300 mg once daily.

Sax PE, et al. Lancet. 2015;385:2606-2615.

Slide credit: clinicaloptions.com

Studies 104/111: TAF Noninferior to TDF at Wk 48





†Discontinued for AE, death, or missing data.

- EVG/COBI/FTC/TAF was noninferior to EVG/COBI/FTC/TDF at Wk 48 in each study: 93% vs 92% (Study 104); 92% vs 89% (Study 111)
  - Race not significant predictor of virologic efficacy in multivariate analysis
- Declines in eGFR and in hip and spine BMD significantly less in TAF arm

1. Sax PE, et al. Lancet. 2015;385:2606-2615.
2. Wohl D, et al. ID Week 2015. Abstract 1073.

Slide credit: clinicaloptions.com

Case 1

- JL arrives to clinic after lost to follow up for 7years.
- She is HIV treatment naive, her HIV genotype is pending, CD4+ cell count is 42 cells/mm^3, HIV viral load 67,000 copies/mL and HLA-B*5701 negative.
- She reports difficulty remembering to take medications everyday and depressed.
- One of her friends has been on efavirenz/emtricitabine/tenofovir DF for years and JS would like to start this medication.
- How would you proceed?

Elvitegravir Efficacy

Phase III Trials	**Study 102**		**Study 103**		**GS-0104/0111**	
Design	Non-inferiority, treatment-naive					
Study Arms	E/C/F/TDF (n = 348)	EFV/F/TDF (n = 352)	E/C/F/TDF (n = 353)	ATV/RTV + F/TDF (n = 355)	E/C/F/TAF (n = 866)	E/C/F/TDF (n = 867)
HIV VL < 50 c/mL*	88%	84%	90%	87%	92%	90%
Overall	E/C/F/TDF non-inferior through Week 144		E/C/F/TDF Non-inferior through Week 144		E/C/F/TAF non-inferior through Week 96	

*At Week 48, primary endpoint.

ATV: atazanavir; C: cobicistat; R: ritonavir; EFV: efavirenz;
E/C/F: elvitegravir/cobicistat/emtricitabine.

Dolutegravir, Raltegravir, Darunavir Studies

Phase III Trials	**SPRING-2**		**SINGLE**		**FLAMINGO**		**ACTG A5257**		
Design	Non-inferiority, treatment-naive						Treatment-naive, open-label, equivalence		
Study Arms	DTG + 2 NRTIs (n = 411)	RAL + 2 NRTIs (n = 411)	DTG + ABC/ 3TC (n = 414)	EFV/ FTC/ TDF (n = 419)	DTG + 2 NRTIs (n = 242)	DRV + RTV + 2 NRTIs (n = 242)	ATV + RTV + FTC/ TDF (n = 605)	RAL + FTC/ TDF (n = 603)	DRV + RTV + FTC/ TDF (n = 601)
HIV VL < 50 c/mL*	88%	85%	88%	81%	90%	83%	-	-	-
VF†	-	-	-	-	-	-	12.6%	9.0%	14.9%
Overall	DTG non-inferior through Week 96		DTG superior through Week 144		DTG superior through Week 96		All 3 regimens equivalent for primary efficacy endpoint.‡		

*At Week 48, primary endpoint for SPRING-2, SINGLE, and FLAMINGO. †Cumulative incidence of virologic failure (VF) over 96 weeks, primary endpoint for ACTG A5257. Defined as confirmed VL > 1000 c/mL at or after 16 weeks and before 24 weeks, or > 200 c/mL at or after 24 weeks. ‡For combined efficacy and tolerability endpoint, RAL superior to both PIs and DRV superior to ATV.

Efavirenz Disadvantages

- Most commonly transmitted mutations are with non-nucleoside reverse transcriptase inhibitors
  - Protease inhibitors and integrase inhibitors have the lowest rate of transmitted mutations
- Low genetic barrier to resistance
- Higher incidence of adverse effects
  - Neurotoxicities: abnormal dreams, depression, dizziness, headaches
  - Suicidality
- Involved in Cytochrome P450 3A4 (CYP3A4) and 2D6

Choosing Among Recommended First-line Regimens

Drug	Advantages	Disadvantages
DTG	▪ Available as STR with QD dosing ▪ High barrier to resistance ▪ No food requirement ▪ Superior to EFV and DRV/RTV ▪ Superior to RAL in tx-exp'd pts ▪ Superior to ATV/RTV in women	▪ Only coformulated with ABC/3TC ▪ Serum Cr increases (inhibits tubular secretion) ▪ Insomnia, headache more frequent in some studies ▪ Largest pill size of STRs
EVG	▪ Available as STR with QD dosing ▪ Superior to ATV/RTV in women	▪ Requires PK boosting (COBI) and food with dosing ▪ Only coformulated with FTC/(TDF or TAF) ▪ High drug-drug interaction potential ▪ Serum Cr increases (from COBI
RAL	▪ Longest safety record of INSTIs ▪ Fewest drug-drug interactions ▪ No food requirement ▪ Superior to ATV/RTV and DRV/RTV ▪ Recommended in pregnancy	▪ Currently BID ▪ Not available as STR
DRV	▪ Long safety record ▪ Highest barrier to resistance ▪ Recommended in pregnancy	▪ DRV not yet available as STR ▪ Requires PK boosting and food with dosing ▪ High drug-drug interaction potential ▪ Higher rate of toxicity discontinuation vs INSTIs

Case 1

- JL arrives to clinic after lost to follow up for 7 years.
- She is HIV treatment naive, her HIV genotype is pending, CD4+ cell count is 42 cells/mm^3, HIV viral load 67,000 copies/mL and HLA-B*5701 negative.
- She reports difficulty remembering to take medications everyday and feeling depressed.
- One of her friends has been on efavirenz/emtricitabine/tenofovir DF for years and JS would like to start this medication. How would you proceed?
- **dolutegravir- based therapies based on safety/efficacy data, potential for non-adherence and starting before genotype is determined**

SECOND-LINE REGIMENS: SAHIVSOC Guidelines, April 2017

Recommended Regimens

PI	▪ ATV/RTV
NRTI	▪ TDF+FTC ▪ AZT+3TC

Alternative Regimens

NRTI	▪ ABC+3TC
PI	▪ LPV/RTV

The EARNEST (Europe-Africa Research Network for Evaluation of Second-line Therapy) and ACTG A5273 trials

*Pt must be HLA-B*5701 negative.

SAHIVSOC: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. April 2017.

Case 2

- EM is a 43 y/o female diagnosed with HIV in 2006 and started CD4=23 VL 472900 .HAART immediately on AZT/3TC+EFV.
- Lost to follow up. Came back 2003 CD4=44 VL=225953
- Restarted treatment on 06/05/2013 on TDF/FTC/EFV.
- Developed resistance in December 2016 CD4=39 VL=76993 and HAART changed to TDF/FTC+ATZ/r.
- Diagnosed with TB 20/02/2017 and HAART changed to TDF/3TC+ LPV/r. Two weeks later presented with severe diarrhoea and dehydration
- **What recommended or alternative regimens are available for her?**

Case 2

Generic Names*	Preferred Initial Regimen?
EFV+FTC+TDF	✗
NVP+FTC+TDF	✗
RPV/FTC/TDF	✗
DTG BID +TDF+FTC	✓
RAL 800mg BD+TDF+FTC	✓

Case 2

- AJ is a 45 y/o male with **CrCl 55 ml/min**, CD4+ cell count 380 cells/mm^3, HIV viral load 200,000 copies/mL, and HLA-B*5701 negative.
- He has no other comorbidities
- He has strong desire for single-tablet once daily regimen.
- What recommended or alternative regimens are available for AJ?

Creatinine Clearance Measurements

- 2 mechanisms which falsely ↑ s-creatinine without renal impairment.
- 1. Barbeque or lots of meat: anhydrous creatine
- 2. Egogermic supplements: phosphorus creatine

Creatinine Clearance Measurements

- Two methods of measuring creatinine at the lab
- 1. Jaffey method: cheaper
- -suffers interference (i).glucose
  - (ii) ketones
  - (iii) some drug metabolites
- 2. Enzymatic creatine measurements: expensive
- -doesn’t suffer from interference

Renal Dosing

Antiretroviral Regimens	**Creatinine Clearance Recommendations**
DTG/ABC/3TC	< 50 mL/min: Use not recommended
DTG + FTC/**TDF** or RAL + FTC/**TDF** or DRV + RTV + FTC/**TDF** or ATV + RTV + FTC/**TDF** or EFV/FTC/**TDF** or RPV/FTC/**TDF**	< 50 mL/min: Use not recommended
DRV + RTV or DRV/COBI + FTC/**TAF** or DTG + FTC/**TAF** or EFV + FTC/**TAF** or EVG/COBI/FTC/**TAF** or RAL + FTC/**TAF** or RPV/FTC/**TAF**	< 30 mL/min: Use not recommended

Case 2

- AJ is a 45 y/o male with CrCl 55 ml/min, **CD4+ cell count 380 cells/mm^3, HIV viral load 200,000 copies/mL**, and HLA-B*5701 negative.
- He has no other comorbidities
- He has strong desire for single-tablet once daily regimen.
- What recommended or alternative regimens are available for AJ?

Baseline Considerations

Baseline Characteristic	Recommendations
CD4+ cell count < 200 cells/mm^3	Do NOT use: •Rilpivirine-based therapies
HIV Viral load > 100,000 copies/mL	Do NOT use: •Rilpivirine-based therapies •ABC/3TC with ritonavir-boosted atazanavir •ABC/3TC with efavirenz
HLA-B*5701 Positive	Do NOT use: •Abacavir

Case 2

- AJ is a 45 y/o male with CrCl 55 ml/min, CD4+ cell count 380 cells/mm^3, HIV viral load 200,000 copies/mL, and HLA-B*5701 negative.
- He has no other comorbidities
- He has strong desire for single-tablet once daily regimen.
- What regimen is the best option for AJ?

Case 3: HIV and Pregnancy

- PB is a 31 y/o female newly diagnosed with HIV. Her CD4+ cell count is 650 cells/mm^3, HIV viral load 50,000 copies/mL, and HLA-B*5701 negative.
- **Her workup reveals that she is in her first trimester of pregnancy (~ 7 wks).**
- **She does not have a preference regarding dosing frequency, but when you discuss options she expresses concern about potential jaundice because she works with the public as a sales rep**
- What is the best recommended option for PB?

SAHIVSOC Recommendations: ART Initiation in Pregnant Women

Guideline Status	NRTIs	PIs	Integrase Inhibitors	NNRTIs
Preferred	3TC/ABC FTC/TDF 3TC + TDF	Lopinavir/RTV* Atazanavir/RTV*	Dolutegravir	Efavirenz*
Alternative	3TC/ZDV	Darunavir/RTV*†	Raltegravir* §	Rilpivirine*‡

*In addition to 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if retreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm^3. § If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

DHHS Recommendations: ART Initiation in Pregnant Women

Guideline Status	NRTIs	PIs	Integrase Inhibitors	NNRTIs
Preferred	3TC/ABC FTC/TDF 3TC + TDF	Atazanavir/RTV* Darunavir/RTV*†	Raltegravir* §	
Alternative	3TC/ZDV	Lopinavir/RTV*		Efavirenz* Rilpivirine*‡
Insufficient data to recommend	FTC/TAF	Fosamprenavir	Dolutegravir EVG/COBI EVG/COBI	

*In addition to 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if retreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm^3. § If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

Case 3: HIV and Pregnancy

- **Darunavir + RTV or RAL in combination with ABC/3TC or FTC/TDF are the best options based on patient preference and pregnancy**

No Association Found Between the Components of TDF/FTC and Birth Defects in ART-Treated, HIV+ Women

HIV+ Women on ART	Any FTC-Containing Regimen[1]	Any TDF-Containing Regimen[1]
Pregnancies enrolled, n		
First trimester	1728	2478
Second trimester	525	670
Third trimester	206	351
Defects/live births, n/N (%)		
First trimester exposure	35/1543 (2.3%)	47/2141 (2.2%)
Second/third trimester exposure	15/729 (2.1%)	21/1021 (2.1%)

Among pregnant women in the US reference population, the background rate of birth defects is 2.7%. There was no association between FTC or TDF and overall birth defects observed in the APR[1,2]

1. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2014. Wilmington, NC: Registry Coordinating Center; 2014. http://www.APRegistry.com
2. TRUVADA US Prescribing Information. Gilead Sciences, Inc. 2013.

Save the Date

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