AETC Pacific HIV LEARNING NETWORK
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Didactic Series

Switching Regimens in the Setting of Virologic Suppression

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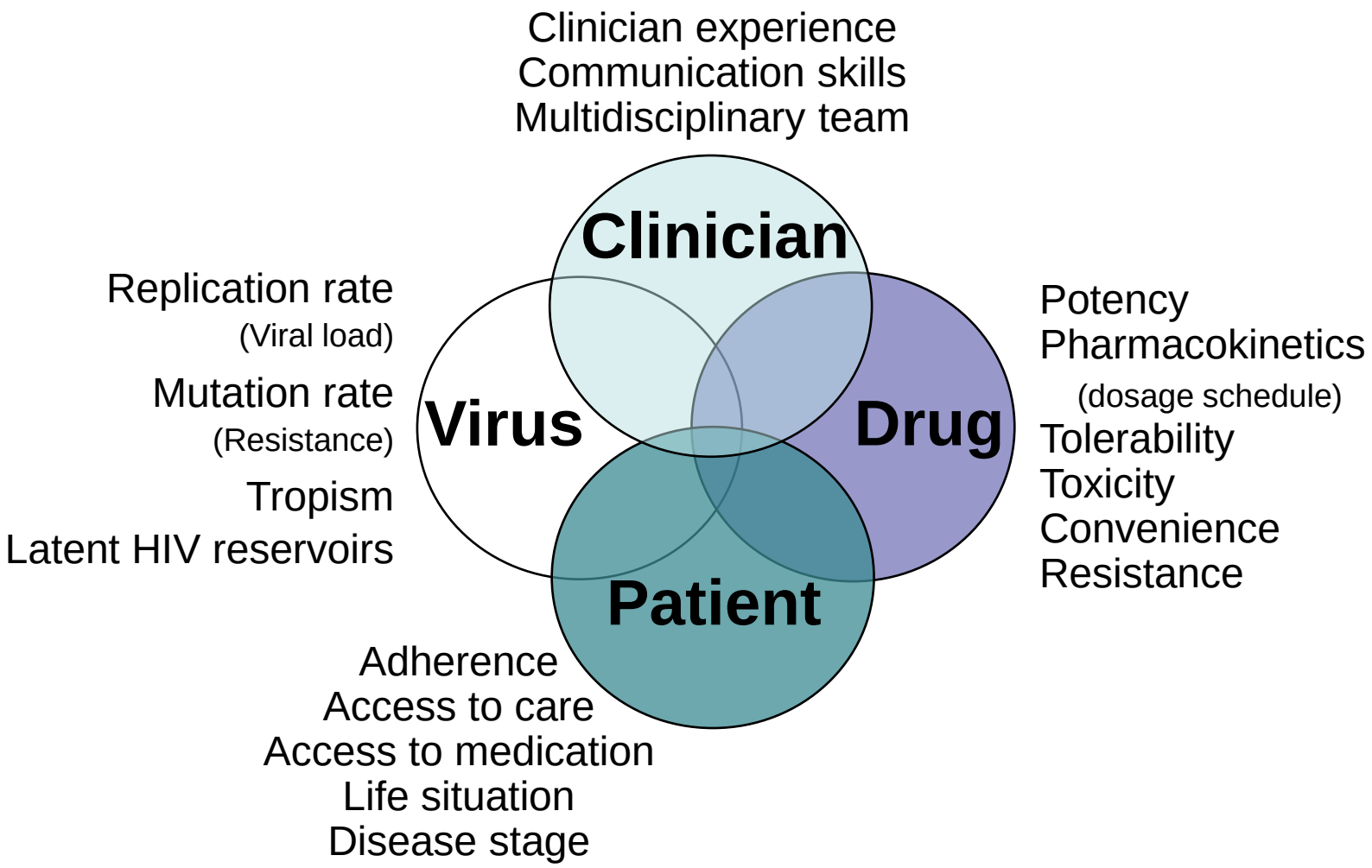
Learning Objectives

1) Describe DHHS guidelines on when and how to switch combination antiretroviral therapy in virally suppressed patients
2) Identify best switch options available to patients based on individual and disease characteristics
3) Recognize the important steps in monitoring patients after switching therapy

Determinants of Successful ART



Current Antiretroviral Agents (FDA Year of Licensure)

(*available in combination tablets**)

Entry Inhibitors (Fusion, R5, other)

- enfuvirtide (T-20) (2003)
- maraviroc (mvc) (2007)
- ibalizumab (2018)

Nucleoside RT Inhibitors

- zidovudine*(azt) (1987)
- didanosine (ddI) (1991)
- stavudine (d4t) (1994)
- lamivudine* (3tc) (1995)
- abacavir* (abc) (1998)
- emtricitabine* (ftc) (2003)

Nucleotide RT Inhibitors

- tenofovir disoproxil fumarate* (tdf) (2001)
- tenofovir alafenamide* (taf) (2016)

Integrase Inhibitor

- raltegravir (ral)(2007)
- elvitegravir* (evg) (2015)
- dolutegravir* (dtg) (2013)
- bictegravir* (bic) (2018)

Non-nucleoside RTIs

- nevirapine (nvp) (1996)
- delavirdine (dlv) (1997)
- efavirenz* (efv) (1998)
- etravirine (etv) (2008)
- rilpivirine* (rpv) (2011)

Protease Inhibitors

- saquinavir (sqv) (1995)
- ritonavir* (rtv) (1996)
- indinavir (idv) (1996)
- nelfinavir (nfv) (1997)
- amprenavir (apv) (1998)
- lopinavir/rtv (kta) (2000)
- atazanavir* (atv) (2003)
- fosamprenavir (fpv) (2003)
- tipranavir (tpv) (2005)
- darunavir* (drv) (2006)
- atazanavir/cobicistat (2015)
- darunavir/cobicistat* (2015) (2018)

DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

Class	2018 DHHS[1]	IAS-USA[2]* 2016
INSTI	▪ DTG/ABC/3TC ▪ DTG + (TAF or TDF)/FTC ▪ EVG/COBI/(TAF or TDF)/FTC ▪ RAL + (TAF or TDF)/FTC ▪ BIC/TAF/FTC	▪ DTG/ABC/3TC ▪ DTG + TAF/FTC ▪ EVG/COBI/TAF/FTC ▪ RAL + TAF/FTC

*Guidelines have not yet been updated to reflect February 2018 FDA approval of BIC/FTC/TAF.

Recommendations may differ according to renal function, HLA-B*5701 status, HBsAg status, osteoporosis status, other comorbidities

1. DHHS ART Guidelines. March 2018. 2. Günthard HF, et al. JAMA. 2016;316:191-210.

Initial Regimens: Preferred in 2013

NNRTI based	▪ EFV/TDF/FTC[1,2] (AI)
PI based	▪ ATV/r[3] + TDF/FTC[2] (AI) ▪ DRV/r (QD) + TDF/FTC[2] (AI)
II based	▪ RAL + TDF/FTC[2] (AI) ▪ EVG/COBI/TDF/FTC[1,4] (AI) ▪ DTG (QD) + ABC/3TC[2,5] (AI) ▪ DTG (QD) + TDF/FTC[2] (AI)

1. Consider alternative to EFV in women who plan to become pregnant or are not using effective contraception.
2. 3TC can be used in place of FTC and vice versa. TDF: caution if renal insufficiency.
3. ATV/r should not be used in patients who take >20 mg omeprazole per day.
4. EVG/COBI should not be started if CrCl <70 mL/min.
5. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.

Combination Antiretroviral Agents
(FDA Year of Licensure)

Protease Inhibitors (FDC)_
- darunavir/cobicistat (Prezcobix) (2015)
- atazanavir/cobicistat (Evotaz) (2015)
- *darunavir/cobicistat/taf/ftc (??)(2018)

Integrase Inhibitors(FDC) mSTR*
- elvitegravir/cobicistat/tdf/ftc (Stribild) (2012)
- dolutegravir/abacavir/lamivudine (Triumeq) (2014)
- elvitegravir/cobicistat/taf/ftc (Genvoya) (2015)
- dolutegravir/rilpivirine (Juluca) (2017)
- bictegravir/tenofovir alafenamide/ftc (Bictarvy) (2018)

Non-nucleoside RTIs (FDC) mSTR*
- efavirenz/tenofovir/emtricitabine (Atripla) (2006)
- rilpivirine/tenofovir/emtricitabine (Complera) (2011)
- rilpivirine/taf/emtricitabine (Odefsey) 2016

Nucleoside (tide) RT Inhibitors (FDC)
- zidovudine/lamivudine (Combivir) (1997)
- abacavir/lamivudine/zidovudine (Trizivir) (2000)
- abacavir/lamivudine (Epzicom) (2004)
- tenofovir disoproxil fumarate/ emtricitabine (Truvada) (2004)
- tenofovir alafenamide/emtricitabine (Descovy) 2016

* mSTR = multi-class single tablet regimen
FDC = fixed dose combination

Reasons to Consider Regimen Switching in Virologically Suppressed Pts

- **Simplification** (reducing pill burden/dosing frequency)
- **Minimize toxicity** (short or long term toxicity)
- **Improve tolerability or convenience** (enhance adherence, quality of life)
- **Manage drug–drug or drug–food interactions**
- **Pregnancy** (pre-pregnancy or optimize during pregnancy)
- **Cost reduction** (Insurance formulary preference)

DHHS ART Guidelines. March 2018.

What HIV RNA copy number do you consider as viral suppression?

1. < 20
2. < 50
3. <75
4. < 200
5. All of the above

Principles of Regimen Switching in Virologically Suppressed Pts

Drug Resistance:

- Review ART history for possible VF
- Review all available resistance test results
- If prior resistance uncertain: only consider switch if new regimen likely to maintain suppression of resistant virus
- Caution when switching from boosted PI to another class if full treatment/resistance history not known
- Consult an expert when switching if resistance to ≥ 1 class
- Within class switches usually maintain virologic suppression if no resistance to drugs in that class are present

Safety:

- Review ART history for intolerance
- Must be HLA-B*5701 negative if considering ABC
- Drug–drug interactions with comedications

Comorbidity:

- HBV coinfection
- Cardiovascular disease or risk
- Renal function
- Bone mineral density
- Other coinfections

DHHS ART Guidelines. October 2017.

Slide credit: clinicaloptions.com

DHHS Guidelines: What to Use for ART Switch in Pts With Virologic Suppression

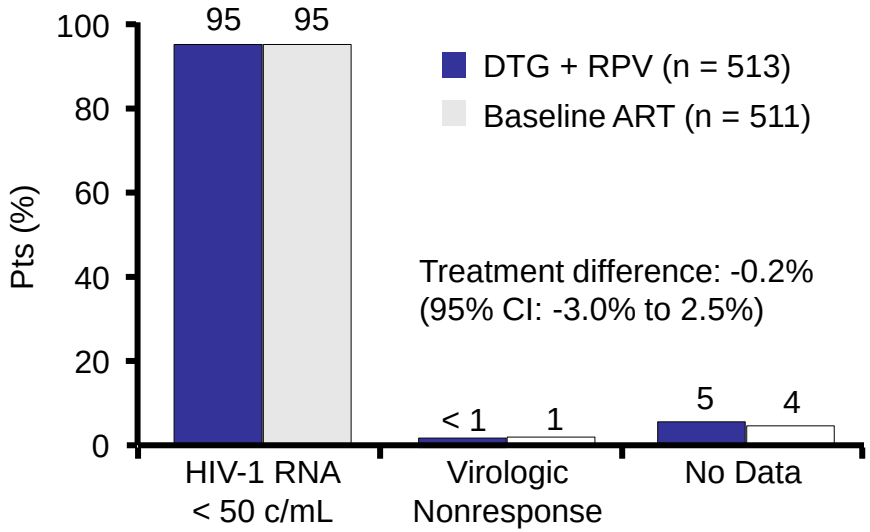
Strategy	Switch to	Considerations
Good Supporting Evidence		
Switching within class	--	▪ Typically maintains virologic suppression if no drug resistance to new ARV present
Switching between classes	--	▪ Generally maintains virologic suppression if no drug resistance to new regimen's components
Switching to 2-drug regimens	RTV-boosted PI + 3TC	▪ Reasonable option where ABC, TAF, or TDF contraindicated or undesirable
	DTG/RPV QD	▪ Reasonable option where NRTI use undesirable and if resistance to DTG or RPV not anticipated
Some Supporting Evidence		
Switching to 2-drug regimens	RTV-boosted DRV + RAL	▪ Efficacy only examined in treatment-naive pts

DHHS ART Guidelines. March 2018.

Slide credit: clinicaloptions.com

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV in Pts With No Previous VF

- Randomized, open-label phase III trials in which virologically suppressed pts with **no previous virologic failure** continued with baseline ART or switched to DTG + RPV (N = 1024; 70% to 73% of pts receiving TDF at baseline)



- 1 pt receiving DTG + RPV with virologic withdrawal at Wk 36 had K101K/E mutation
  - Documented nonadherence at virologic failure; resuppressed with continued DTG + RPV; no INSTI resistance
- Coformulated single-tablet DTG/RPV approved by FDA in November 2017 for use as complete switch regimen in pts with stable viral suppression and no history of resistance or virologic failure

Llibre JM, et al. Lancet. 2018;[Epub ahead of print]. FDA DTG/RPV.

DHHS Guidelines: Switch Strategies NOT Recommended

- As a result of unacceptable efficacy and/or tolerability, including risk of VF and drug resistance in some cases, several switch strategies are specifically NOT RECOMMENDED

Do NOT Switch to:

- Boosted PI or INSTI monotherapy
- DTG monotherapy
- RTV-boosted ATV + RAL
- Maraviroc + boosted PI
- Maraviroc + RAL

DHHS ART Guidelines. March 2018.

Slide credit: clinicaloptions.com

Case 1: RG 58-Yr-old Man Receiving TAF/FTC plus DRV/c since 9/16

- Pt started cART in 9/2010 with TDF/FTC + DRV/r
- Pt is referred for simplification to a single-tablet regimen
- He has been highly adherent through 8 yrs of cART maintained on a boosted PI regimen with viral suppression
- PMH: hypertension, depression
- Other meds: atenolol, losartan, bupropion

Case 1: Summary and Additional Details for RG 58-Yr-Old Man

Characteristic	Finding/Status
Current ART	DRV/c + FTC/TAF (9/8/16 to present); TDF/FTC + DRV/c (3/31/15 to 9/8/16); TDF/FTC + DRV/r (9/7/10 to 3/31/15) Initial regimen
Duration of virologic suppression	8 yrs
Drug resistance	RT: M41L, T215S baseline 8/4/10
CVD	Yes, hypertension controlled; 10yr ASCVD risk score 8.5%
HLA-B*5701	Negative
HBV coinfection	No; vaccinated
Smoking status	None
Renal function	Normal
Requests STR?	Yes

Case 1: RG 58-Yr-old Man: What would be your switch recommendation?

1. DTG/ABC/3TC (Triumeq)
2. BIC/FTC/TAF (Biktarvy)
3. DTG + RPV (Juluca)
4. DTG + FTC/TAF
5. Keep same regimen and wait for FDA approval of DRV/cobi/FTC/TAF
6. Other

Things to consider when switching to a dolutegravir-rilpivirine based regimen

- Patient has food security (Able to take medication consistently with a meal)
- Patient does not need to take a proton pump inhibitor
- Patient knows to separate divalent and polyvalent cation containing supplements/medications from medication (aluminum, magnesium, calcium, iron)
- Patient is consistently adherent
- Know Hep B status
- Confirm medication is covered by insurance

Case 2: JH 48-Yr-old Man Receiving TAF/FTC/EVG/c since 3/2017

- Pt started cART in 1/2008 with TDF/FTC + LPV/r
- Pt is referred for possible switch due to persistent low level viremia
- He has been highly adherent on current regimen by assessment of the Clinical pharmacist team
- PMH: dyslipidemia, family hx ischemic heart disease, gerd
- Other meds: pravastatin, omeprazole, valacyclovir

Case 2: Summary and Additional Details for JH 48-Yr-Old Man

Characteristic	Finding/Status
Current ART	FTC/TAF/EVG/c (03/03/17 to present); TDF/FTC/EVG/c (10/02/14 to 03/02/17); TDF/FTC + LPV/r (01/18/08 to 10/01/14) Initial
Duration of virologic suppression	<20 (3/20/17); 72 (11/6/17); 190 (2/8/18); 85 (3/30/18): CD4 263/17%
Drug resistance	No baseline resistance test; DNA Archive Genotype shows M184V mutation
CVD	Yes, dyslipidemia; Family hx ischemic heart disease
HLA-B*5701	Negative
HBV coinfection	No; vaccinated
Smoking status	None
Renal function	Normal
Requests STR?	No

Case 2: JH 48-Yr-old Man: What would be your switch recommendation?

1. DTG/ABC/3TC (Triumeq)
2. BIC/FTC/TAF (Biktarvy)
3. DTG + RPV (Juluca)
4. DTG + FTC/TAF
5. Keep same regimen and wait for FDA approval of DRV/cobi/FTC/TAF
6. Other

Case 2: JH 48-Yr-old Man: What would be your switch recommendation?

- BIC/FTC/TAF (Biktarvy) ordered for patient.
- Patient's PPO Health Insurance denied Biktarvy due to not on formulary
- Patient was changed to DTG + FTC/TAF
- Patient HIV pVL < 20 copies/mL one month later
- Continue to monitor

Case 3: JY 29-Yr-old Man Receiving RPV + DTG + DRV + RTV since 7/2016

- Pt started HIV tx in 1989 with ZDV + DDC
- Pt is here at UCSD for initial intake from University of Colorado. Previously followed at UCSD 1999-2004
- Moved back to live with his grandmother where he entered a detox/substance abuse recovery facility
- PMH: heroin addiction, attention deficit disorder, cardiomyopathy
- Other meds: amitriptyline

Case 3: Summary and Additional Details for JY 29-Yr-Old Man

Characteristic	Finding/Status
Current ART	RPV + DTG + DRV + RTV (7/2016 to present) Unknown cART (2003 to 2016) D4T + 3TC + NFV (05/1997 to 2003); ZDV +DDI + NVP (11/1194 to 04/1997); ZDV + DDC (10/1989 to 11/1994) Initial
Duration of virologic suppression	< 20 copies since late 2016
Drug resistance	No baseline resistance test; DNA Archive Genotype (2/2/18) shows RT: M41L, L210W, T215NSY,
CVD	Yes, cardiomyopathy
HLA-B*5701	Negative
HBV coinfection	No; vaccinated
Smoking status	None
Renal function	Normal
Requests STR?	No

Case 3: JY 29-Yr-old Man: What would be your switch recommendation?

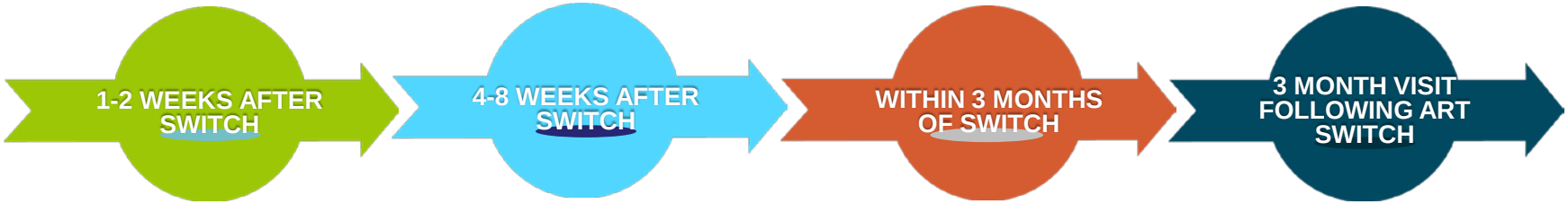
1. FTC/TAF/RPV (Odefsey) + DTG (Tivicay)
2. BIC/FTC/TAF (Biktarvy) + RPV (Edurant)
3. DTG + RPV (Juluca) + DRV/c (Prezcobix)
4. FTC/TAF/EVG/c (Genvoya) + DRV (Prezista) 800 mg
5. Keep same regimen and monitor
6. Other

DHHS Guidelines: HIV/HBV Coinfection

- ART for pts with HIV/HBV coinfection should include (TAF or TDF) plus (3TC or FTC) as NRTI backbone of fully suppressive regimen
- If TDF and TAF cannot be used, alternative is to add entecavir to fully suppressive ART regimen
- Discontinuation of drugs with activity against HBV may cause serious liver damage as result of HBV reactivation

DHHS ART Guidelines. October 2017.

Patients Should Be Closely Monitored After ART Switch



- Clinical visit
- Phone call

- Viral load test to assess rebound viremia

- When applicable, re-assess laboratory abnormalities responsible for the switch in ARV regimen

- Resume clinical and laboratory monitoring on a regularly scheduled basis if:
  - No new complaints
  - No evidence of viral rebound
  - No new laboratory abnormalities

PURPOSE FOR INTENSIVE MONITORING

- Assess patient's understanding of new regimen
- Assess medication tolerance
- Conduct targeted laboratory testing for preexisting laboratory abnormalities
- Potential concerns with the new regimen

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. July 2016.

Conclusions

- There are several highly effective single-tablet or 2-tablet once- daily ART regimens that can be safely used in virologically suppressed pts who require a regimen switch
- The ideal switch regimen should be determined on a case-by-case basis after considering the pt's history of ART, drug resistance, comorbidities, concomitant drugs, and preferences
- The new regimen for pts with HBV coinfection must include HBV-active therapy

Questions and Answers

Knowing is not enough, we must apply.

Willing is not enough, we must do.

Wolfgang von Goethe