

NNRTI's in the era of DTG

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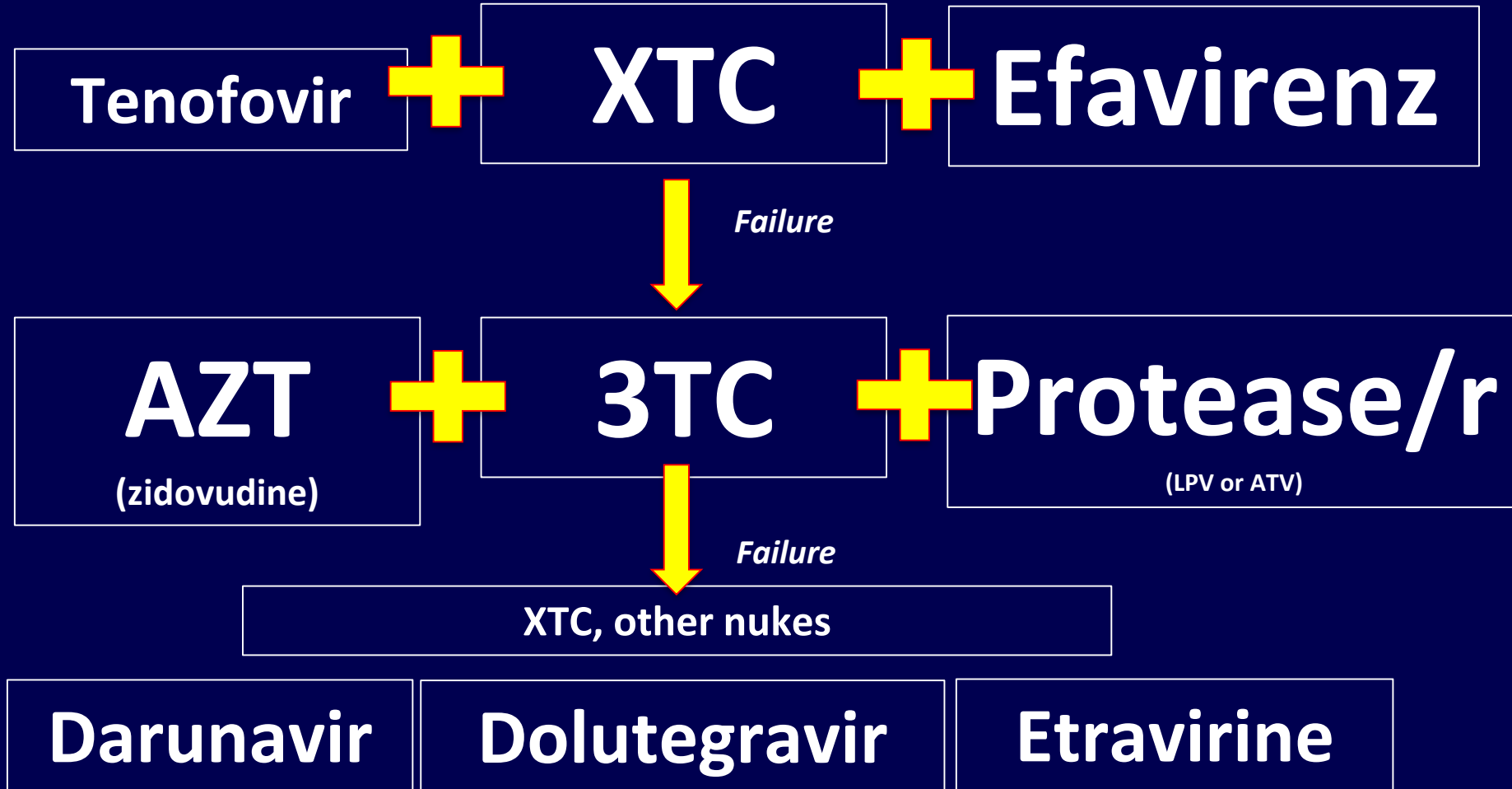
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UKZN

Key Principles

- Choice of first-line determined by:
 - Potency
 - Tolerability
 - PDR
 - Co-morbidities
 - Pregnancy
 - Availability, cost
- Preferred combo: 2 NRTIs (TDF / XTC) + 1 active drug- NNRTI/PI/ INSTI

Current ART in SA



The following drug is main driver of toxicity.

1. Tenofovir
2. Efavirenz
3. Emtricitabine

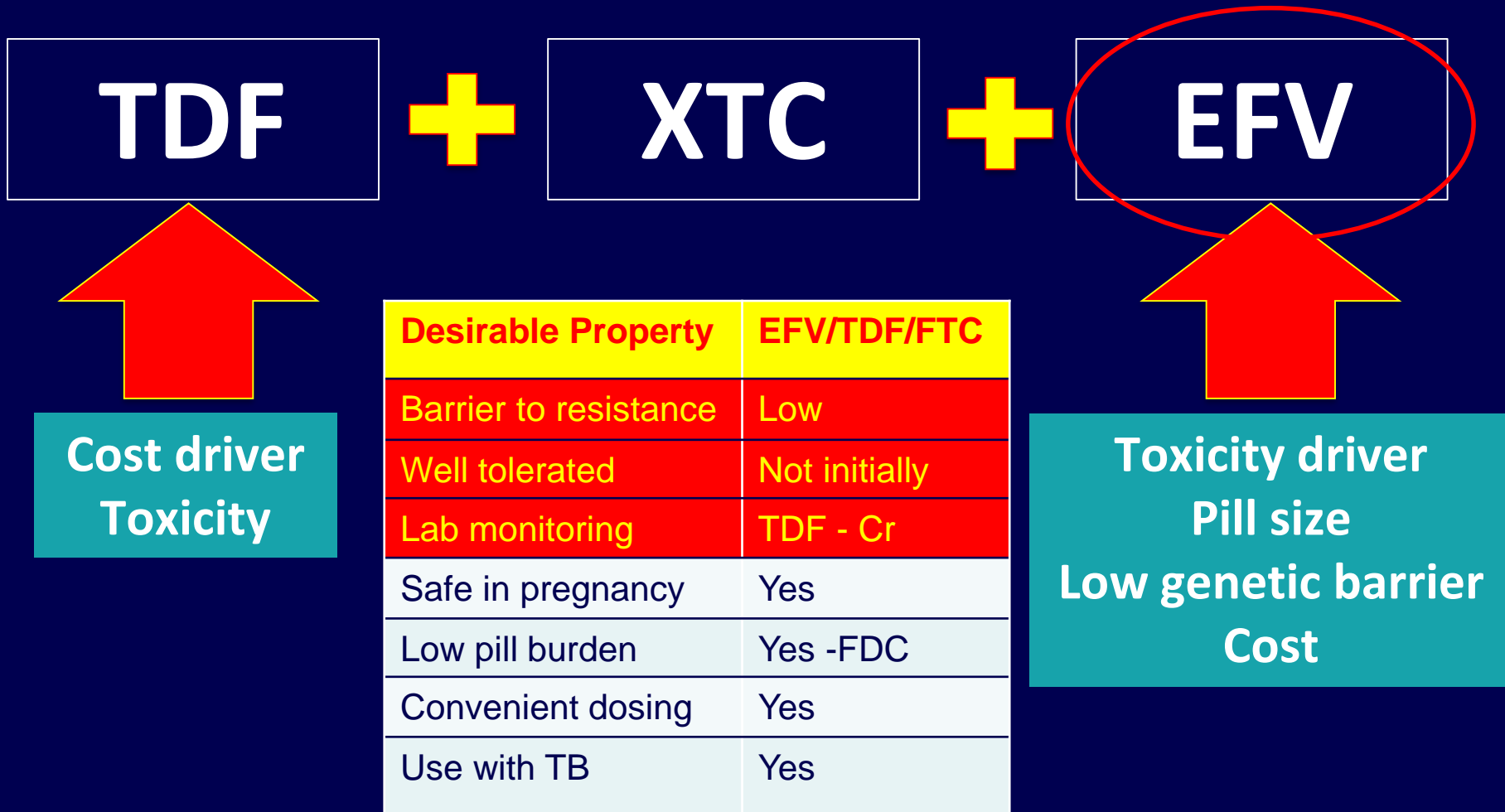


The following drugs is main driver of
Cost.

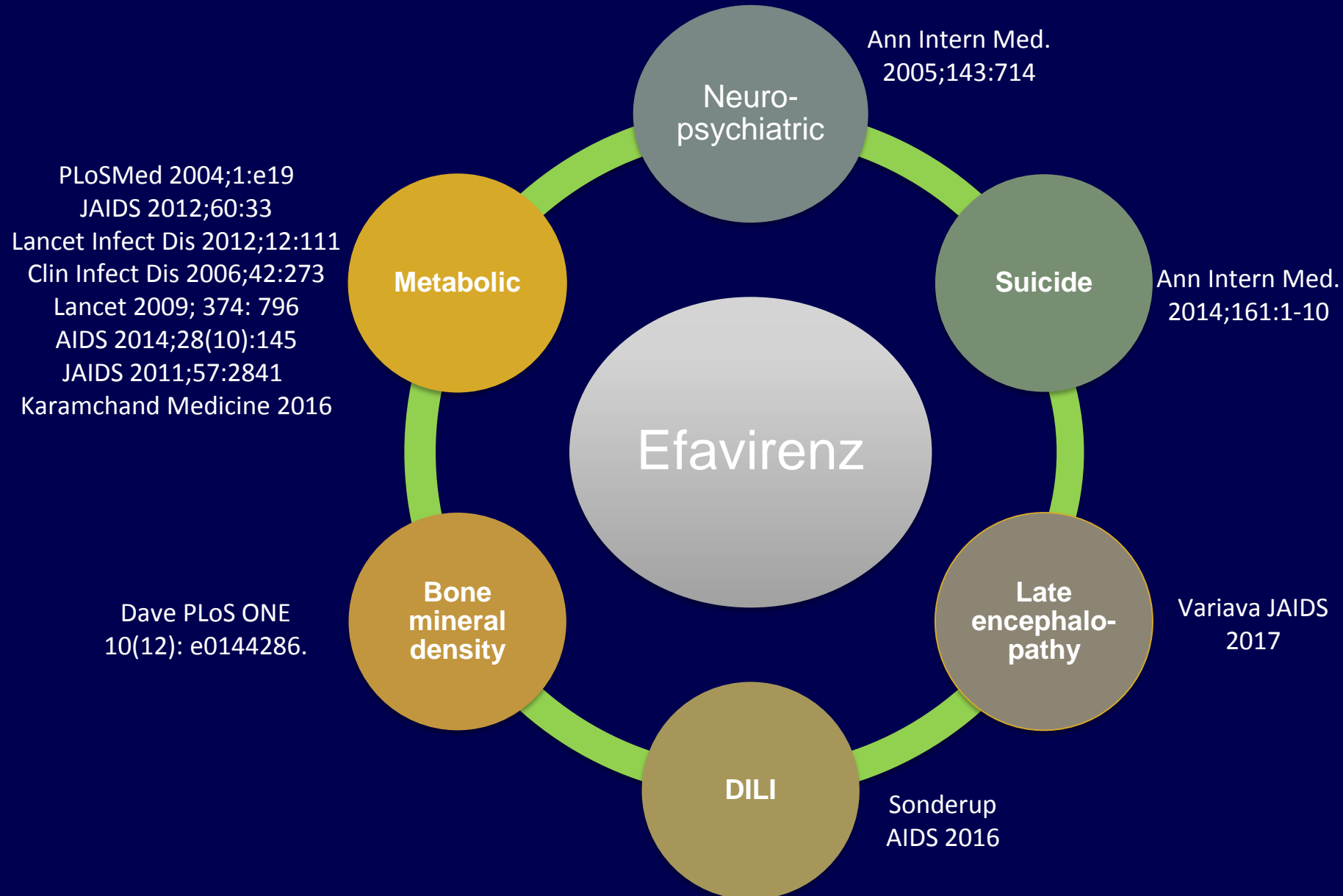
1. Tenofovir
2. Efavirenz
3. Emtricitabine



Issues with current first-line...

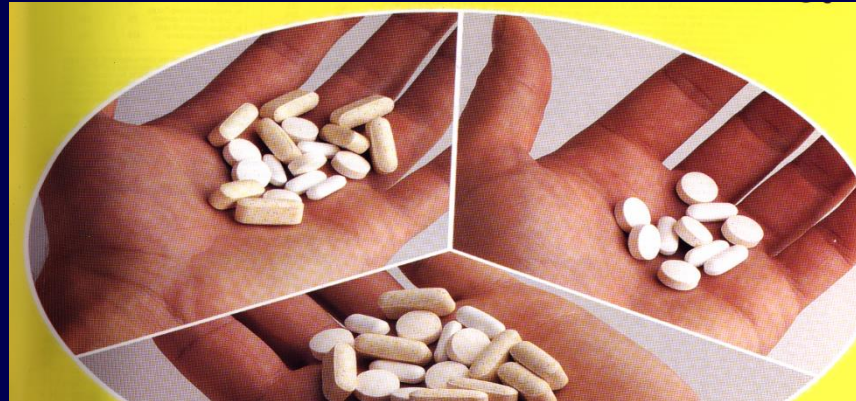


Efavirenz side effects...



“Third drug” Options

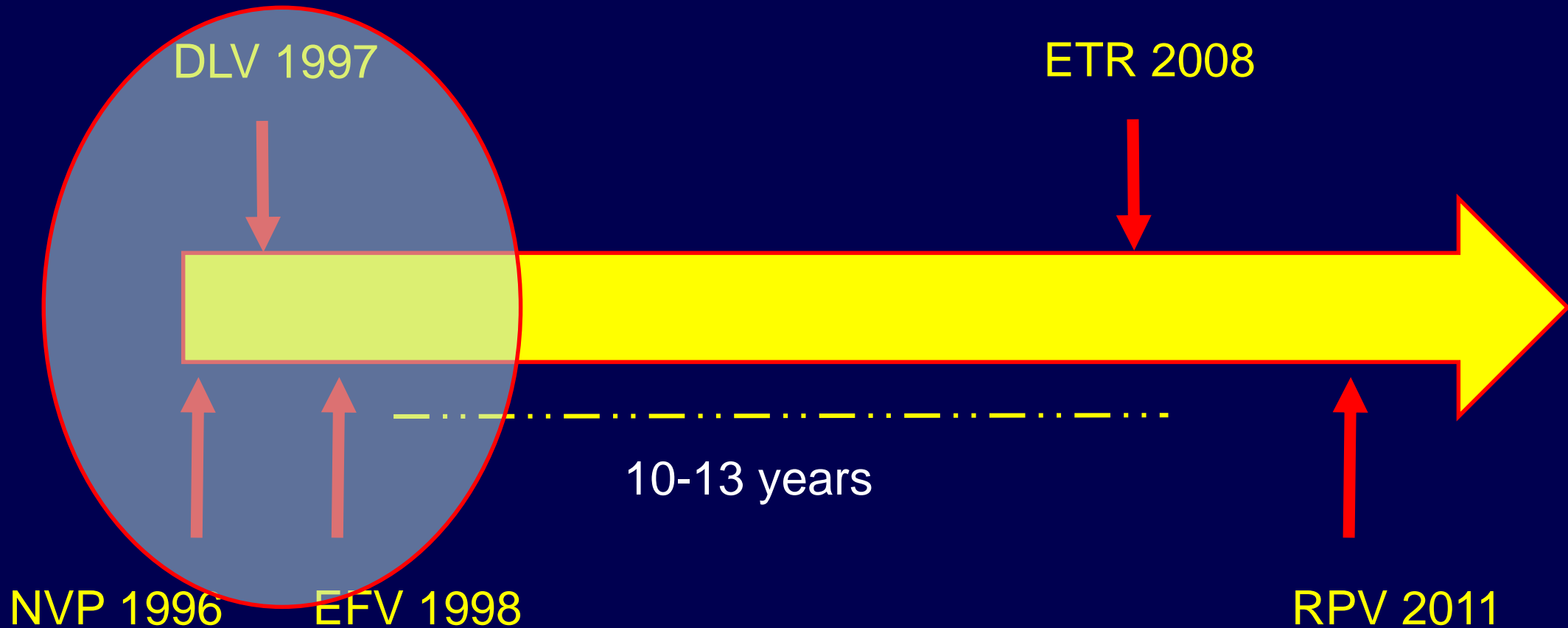
- Protease inhibitors
- Integrase inhibitors
- Non-nucleoside reverse transcriptase inhibitor



NNRTI Development time frame

“First generation” – NVP, DLV, EFV – late 90s

“2nd Generation: RPV, ETR



Rilpivirine: NNRTI

- Formulations:
 - Single (Edurant)
- FDC
 - Complera- RPV/TDF/FTC (not available in ZA)
 - Odefsey- RPV/TAF/FTC (Not available in ZA)
 - Juluca- RVP/DTG (not available in ZA)
- Single available in SA



Following is true about Rilpivirine

1. Administered twice daily
2. Is taken on an empty stomach
3. Double dosed with rifampicin
4. Half life is 6 hours
5. Metabolized by the CYP3A enzyme



Pharmacokinetics

- The solubility and absorption pH dependent
 - Increased bioavailability with food.
 - Fasting decreases AUC by 43%
 - **Affected by drugs that increase gastric pH** (PPI, H2 Antagonists, Antacids)
- Rapidly absorbed - long $t^{1/2}$ of ~50 hrs
- No dose adjustments for mild renal / hepatic impairment
- **Extensively metabolized by CYP3A - caution when administering with inhibitor or inducer** (interactions: Rifampicin, Rifabutin)

The following is true about RPV resistance

1. RPV has a low barrier to resistance
2. There is complete cross resistance between all RPV and EFV
3. Transmitted mutations frequently result in RPV resistance
4. RPV resistance usually requires 2-3 mutations



NNRTI associated Resistance

- Some cross-resistance among NNRTIs
- RPV is spared by some commonly occurring first generation NNRTIs resistance mutations
- Sensitivity to RPV is not affected by most single NNRTI RAM
- Combo of 2 - 3 NNRTI RAM decreases susceptibility to RPV

	100	101	103	106	138	181	188	190	230
<i>Consensus</i>	L	K	K	V	E	Y	Y	G	M
DOR	I	EP		AMI		CIV	LHC	SE	L
EFV	I	EP	NS	AM		CIV	LCH	ASE	L
ETR	I	EP			AGKQ	CIV	L	ASE	L
NVP	I	EP	NS	AM		CIV	LCH	ASE	L
RPV	I	EP			AGKQ	CIV	L	ASE	L

Relevant Randomized Control Trials

ART Naïve: Rilpivirine versus Efavirenz

- Phase III Trials
 - ECHO: Rilpivirine versus Efavirenz
 - THRIVE: Rilpivirine versus Efavirenz

ART Experienced – limited studies

- Switching At Low HIV-1 RNA Into Fixed Dose Combinations (SALIF)
48 weeks results

ECHO: Efficacy Comparison in treatment-naïve HIV infected subjects Of TMC278 and Efavirenz)

- Phase III, randomised, double-blind study
- Treatment naïve patients > 18 with HIV-1
- Viral load ≥ 5000 copies per mL fully sensitive
- 690 Patients: randomly assigned to:
 - Rilpivirine 25 mg daily + TDF/FTC
 - Efavirenz 600 mg daily TDF/FTC

THRIVE: TMC278 against HIV-infected in a once-daily Regimen Versus Efavirenz)

- Phase III, double-blinded RCT
- Treatment naïve patients > 18 with HIV-1
- Viral load ≥ 5000 copies per mL fully sensitive
- 678 patients randomly assigned to:
 - RPV 25 mg/d + TDF/FTC or AZT/3TC or ABC/3TC
 - EFV 600 mg/d + TDF/FTC or AZT/3TC or ABC/3TC

ITT-TLOVR outcome by Baseline Viral Load, %

VL ≤100,000 copies per milliliter	n = 368	n = 330
Viral load <50 copies per milliliter	90	84
VF _{eff} * (4)	(4)	(3)
Discontinuation due to AE/death	2	6
Discontinuation due to reason other than AE†	4	7
VL >100,000 to ≤500,000 copies per milliliter	n = 249	n = 270
Viral load <50 copies per milliliter	80	83
VF _{eff} * (13)	(13)	(5)
Discontinuation due to AE/death	2	9
Discontinuation due to reason other than AE†	6	4
VL >500,000 copies per milliliter	n = 69	n = 82
Viral load <50 copies per milliliter	70	76
VF _{eff} * (22)	(22)	(11)
Discontinuation due to AE/death	4	7
Discontinuation due to reason other than AE†	4	6

Antiviral Efficacy 48 weeks

	RILPIVIRINE	EFAVIRENZ
Virological response	84%	80%
Virological failure	8%	6%
Mean CD4 increase	224	206

Pooled analysis - 96 weeks for subjects with Baseline VL <100,000

RPV better tolerated than EFV (ECHO and THRIVE)

TABLE 3. Summary of Treatment-Emergent AEs and Laboratory Abnormalities at the Time of the Week-48 Analysis

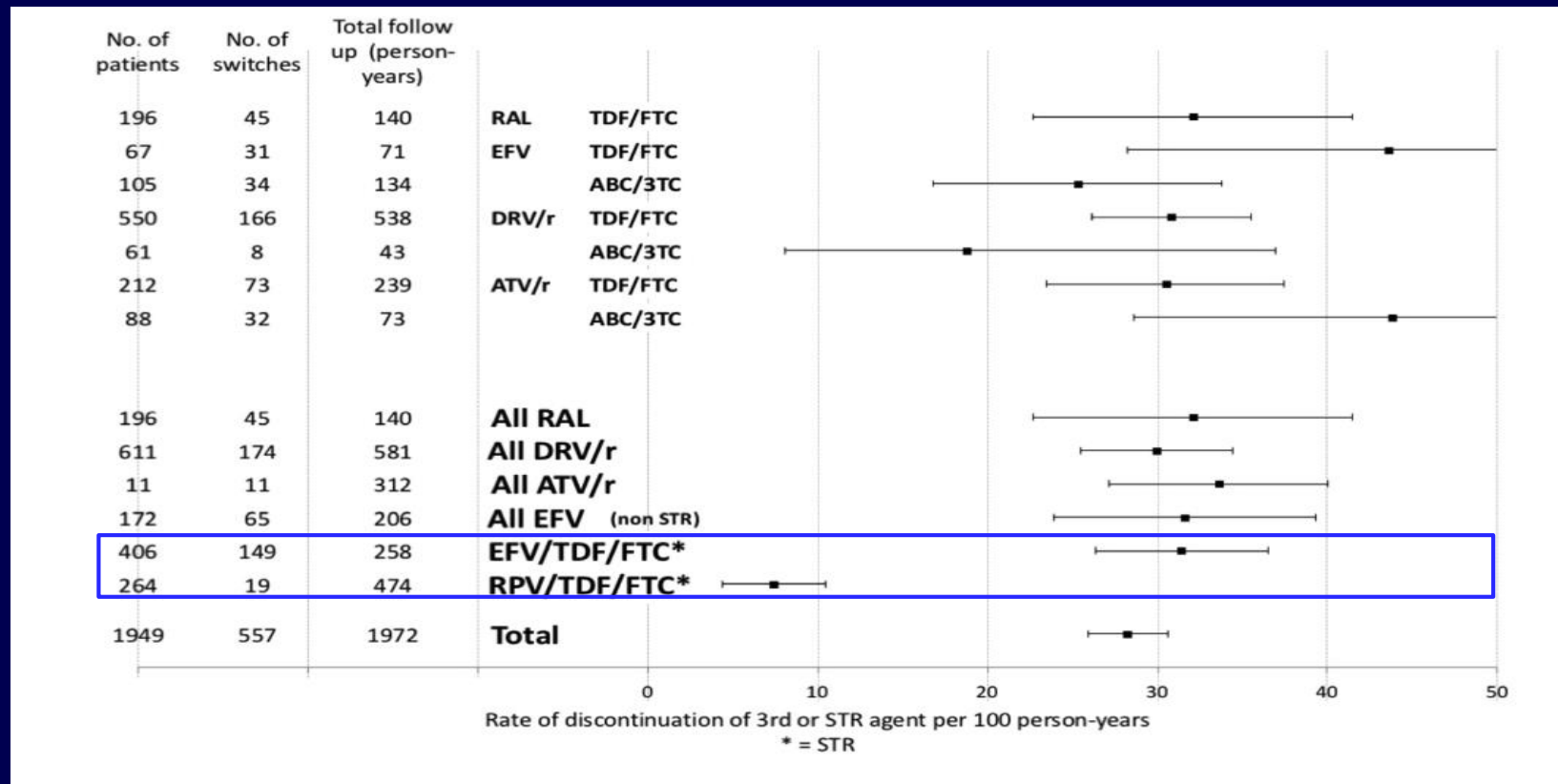
	RPV 25 mg Once Daily, N = 686	EFV 600 mg Once Daily, N = 682
Median (range) treatment duration (wks)	56 (0–87)	56 (0–88)
AE, n (%)		
Any AE	616 (90)	629 (92)
Any treatment-related AE \geq grade 2	109 (16)*	212 (31)
AE leading to permanent discontinuation	23 (3)	52 (8)
Any serious AE (including death)	45 (7)	55 (8)
Death	1 (0.1)	4 (1)
Most common treatment-related AEs \geq grade 2 and occurring in \geq 2% of patients in either group†		
Rash‡	7 (1)*	56 (8)
Dizziness	4 (1)	43 (6)
Abnormal dreams/nightmares	9 (1)	25 (4)
Headache	11 (2)	15 (2)
Insomnia	12 (2)	16 (2)
Nausea	5 (1)	17 (2)
Most common treatment-related AEs of interest (all grades) occurring in \geq 10% of patients in either group†,§		
Any neurologic AE	117 (17)*	258 (38)
Dizziness	55 (8)*	179 (26)
Any psychiatric AE¶	102 (15)#	155 (23)
Abnormal dreams/nightmares	56 (8)**	87 (13)
Rash‡	21 (3)*	93 (14)
Treatment-emergent grade 2–4 laboratory abnormalities occurring in \geq 5% of patients in either group, n (%)		
Any grade 2–4 laboratory abnormality		
Hypophosphatemia	62 (9)	69 (10)
Increased pancreatic amylase	42 (6)	60 (9)
Hyperglycemia (fasted)	37 (5)	30 (4)
Grade 2–3 increased LDL-cholesterol (fasted)††	38 (6)	102 (15)
Grade 2–3 increased total cholesterol (fasted)	34 (5)	122 (18)
Increased aspartate amino transferase	33 (5)	60 (9)
Increased alanine amino transferase	35 (5)	66 (10)

Real world Cohort data: UK

Low discontinuation rates with RPV compared to other ARVs



Retrospective cohort study from UK (1949 patients on 1st line therapy)

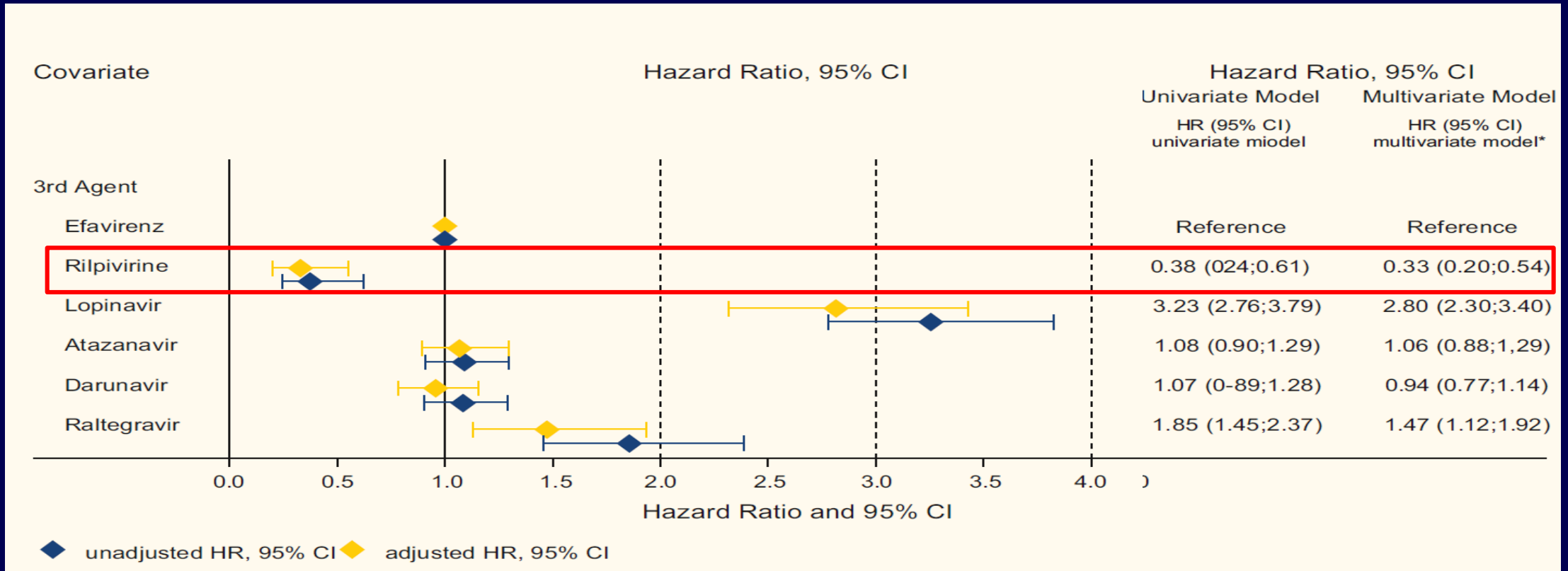


Real world Cohort data: Sweden

Low discontinuation rates with RPV compared to other ARVs



Swedish InfCareHIV database (2541 patients on 1st line therapy)



Which of the following would be reasons to switch treatment in a patient successfully suppressed?

1. Simplify the regimen
2. Drug toxicity
3. Drug/drug interactions
4. Development of comorbidities
5. All of the above



To consider when switching suppressed patients to another regimen

- Do not jeopardize virologic suppression
- Consider possible drug-drug interactions
- Consider new adverse effects

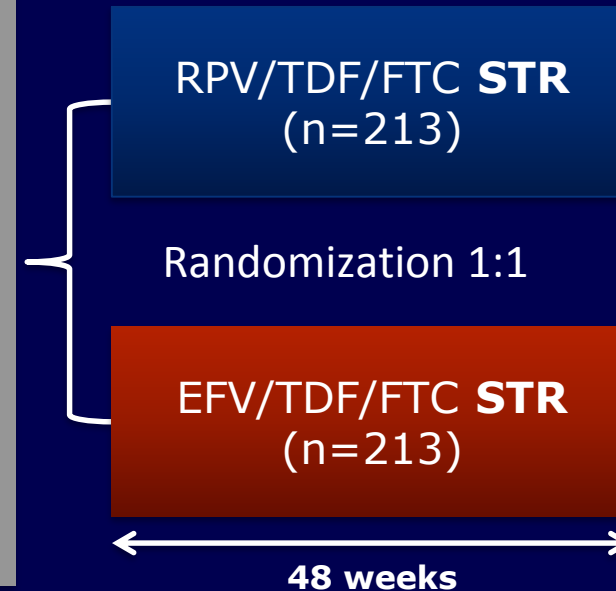
SALIF – Study design

Switching At Low HIV-1 RNA Into Fixed Dose Combinations

A 48-week randomized, open-label study of RPV/TDF/FTC STR as an appropriate “switch” option for virologically suppressed patients in low- & middle income countries on stable NNRTI-based therapies

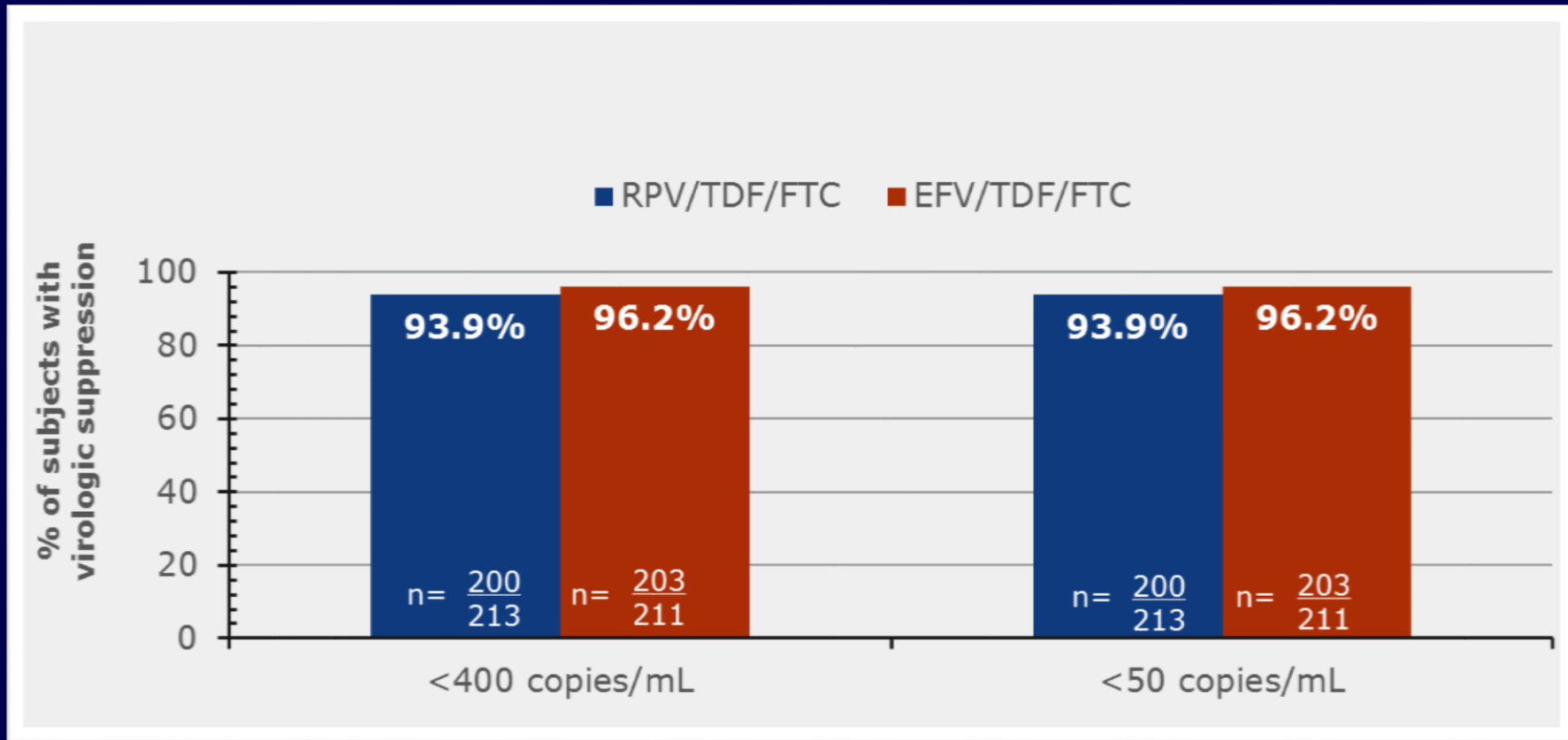
Key entry criteria:

- first-line ART with **EFV** or **NVP** for ≥ 1 yr*
- Plasma VL < 50
- CD4 > 200
- No history of virologic or immunologic failure during ART
- No known primary N[t]RTI or NNRTI mutations



- Randomization stratified by NNRTI at screening (EFV or NVP)
- **Exclusion:** TB requiring rifampicin treatment or CrCl < 50 mL/min

SALIF – Virological suppression



- RPV/TDF/FTC non-inferior to EFV/TDF/FTC
- No ARV resistance observed

SALIF - Safety

Number of Subjects with:	RPV/TDF/FTC (n=213)	EFV/TDF/FTC (n=211)
SAE	16 (7.5%)	11 (5.2%)
At least possibly related	3 (1.4%)	1 (0.5%)
Fatal SAE (MI, unrelated)*	1 (0.5%)	0
AE, grade 3 or 4	40 (18.8%)	56 (26.5%)
At least possibly related	13 (6.1%)	4 (1.9%)
AE of interest (all cause)		
Rash	32 (15.0%)	23 (10.9%)
Neuropsychiatric	60 (28.2%)	63 (29.9%)
Headaches	38 (17.8%)	29 (13.7%)
Dizziness	7 (3.3%)	14 (6.6%)
Insomnia	10 (4.7%)	6 (2.8%)
Nightmare/ abnormal dreams	4 (1.9%)	10 (4.7%)
Potential QT prolongation	3 (1.4%)	3 (1.4%)
AE leading to permanent stop study medication	8 (3.8%)†	1 (0.5%)

Increased toxicity with RPV: d/t effect of switching to a new drug relative to continuing with the “old” EFV-based regimen.

*MI = myocardial infarction; 55 year old, Asian male, with no known risk factors

† Includes 1 virologic failure

SALIF: Summary and Conclusions

- Low virologic failure rates (0.5% per arm)
- No ARV resistance
- Comparable tolerability
- **Comparable adherence:** 412/426 (97%) had >95% adherence overall
- **RPV/TDF/FTC** - alternative option for low- and middle-income countries in virologically suppressed on EFV- or NVP-based ART

Switching from EFV to RPV is safe and effective

Advantages!

- Daily dosing, small pill size
- Higher resistance barrier than first generation NNRTIs
- Pregnancy category B (few exposures in pregnancy registry)
- Very cheap (about half the price of EFV)
- Less toxicity compared to EFV
- Good durability

Restrictions:

- Higher failure if VL >100 000 copies/mL – 2-3x higher risk
- Lack of FDC in SA
- Food restriction
- Cannot be co-administered with rifampicin/rifabutin

RPV in era of DTG

- With increased use of DTG toxicities are/will emerge:
 - Neuropsychiatric: depression, anxiety and suicidal ideation
 - Weight gain
- RPV might best be positioned to fill the gap created DTG intolerance

RPV: Summary

- First line option in healthy person with low VL at baseline
- Option for switch from EFV if EFV not tolerated (off-label, clinical experience)
- Need to individualize depending on:
 - Baseline VL
 - Comorbidities
 - Concomitant medications
 - Commitment to adherence
 - Cost

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