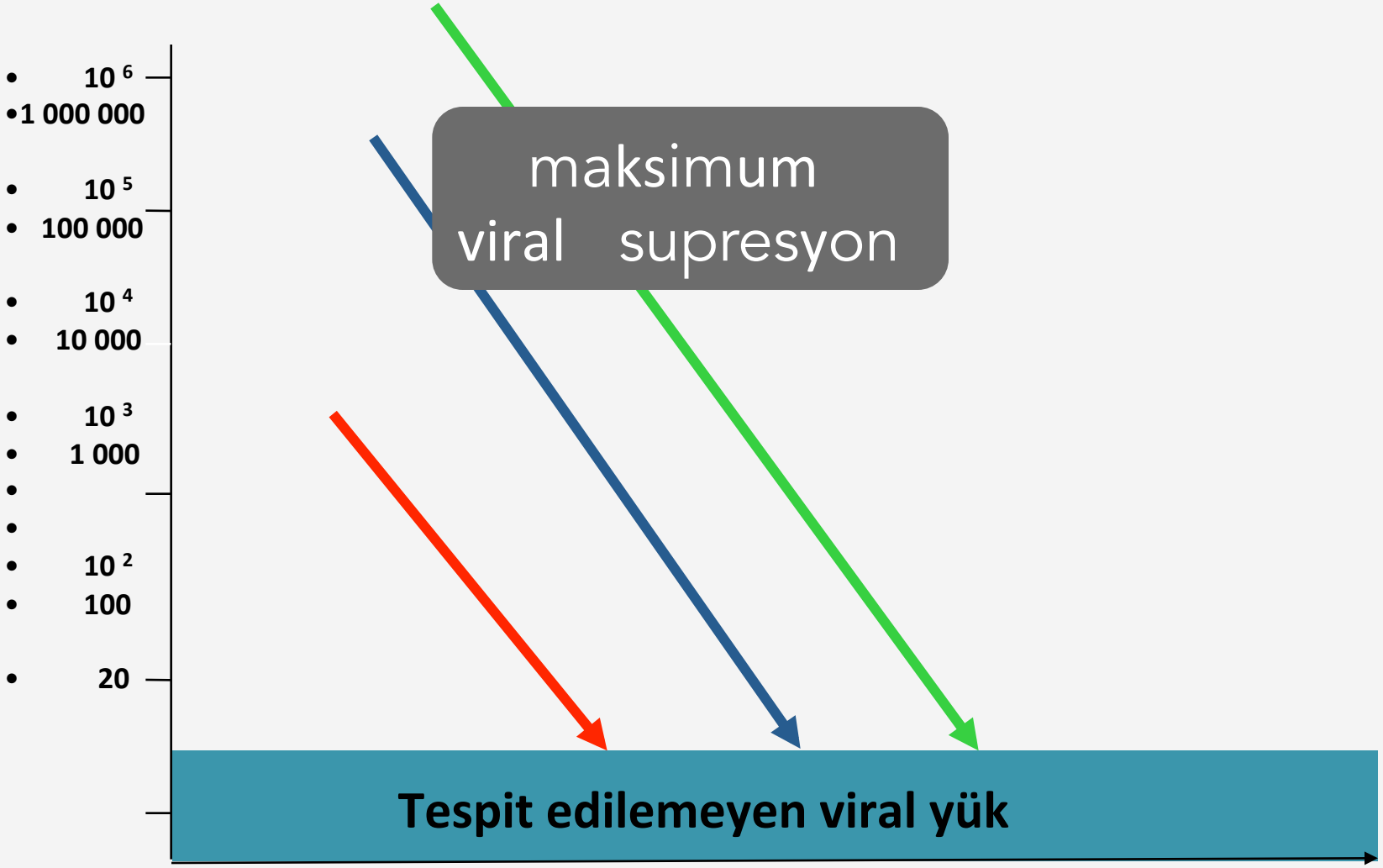
İntegraz İnhibitörleri

Dr Özlem Altuntaş Aydın

11/05/2016

ART hedefi


10 6
1 000 000
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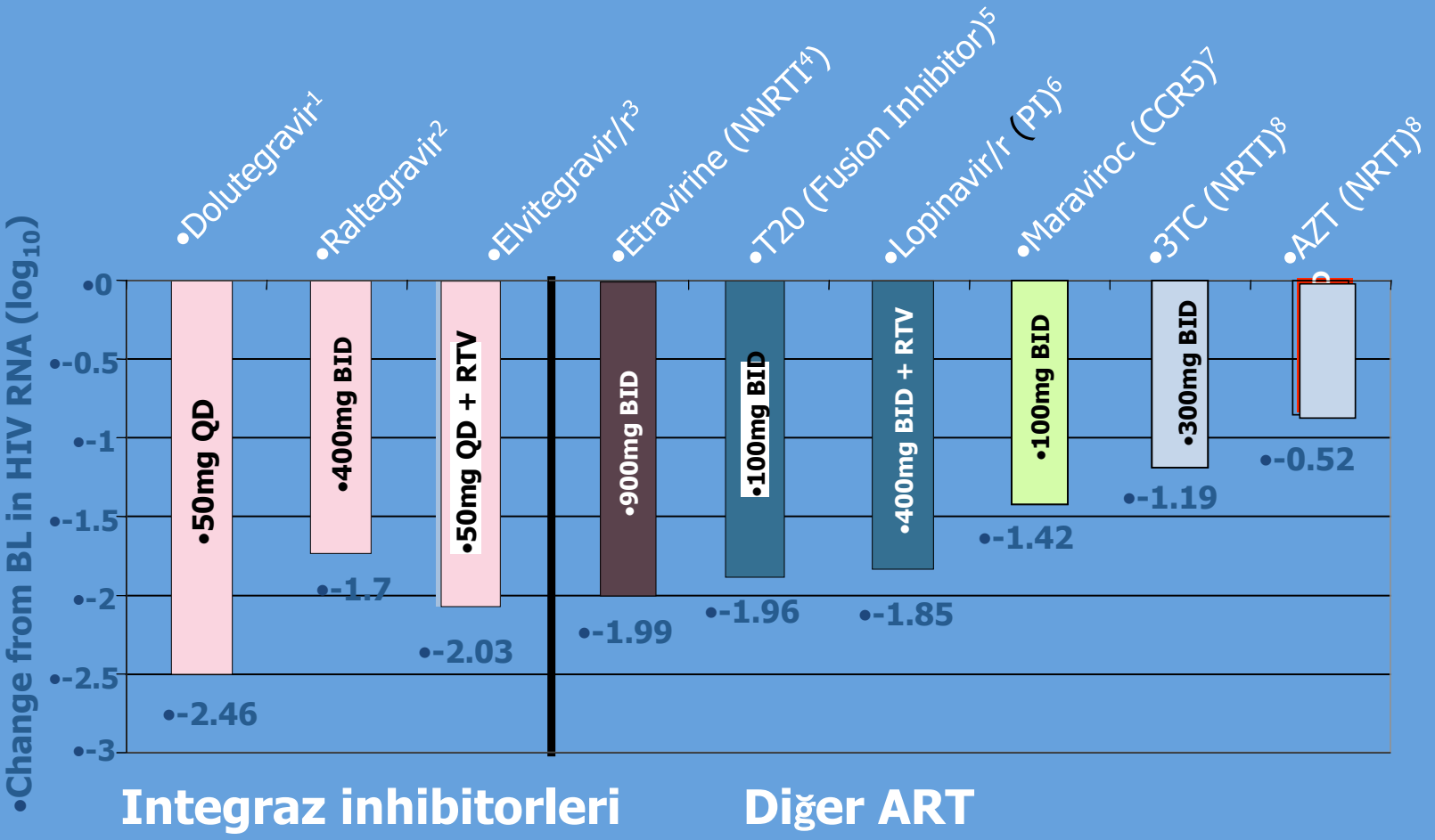
maksimum
viral supresyon
Tespit edilemeyen viral yük



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2. DeJesus E. J Acquir Immune Defic Syndr 2006 ; 43:1-5.
3. Markowitz et al. JAIDS Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. AIDS 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy RL. AIDS 2001;15:F1-F9.
7. Fätkenheuer G et al. Nat Med 2005 Nov; 11:1170-1172.
8. Eron JJ, N Engl J Med 1995, 333:1662-1669.

Recommended Regimen Options

(Drug classes and regimens within each class are arranged in alphabetical order.)

INSTI-Based Regimens:

- DTG/ABC/3TC[a]—**only** for patients who are HLA-B*5701 negative **(AI)**
- DTG plus TDF/FTC[a] **(AI)**
- EVG/c/TAF/FTC—**only** for patients with pre-treatment estimated CrCl ≥30 mL/min **(AI)**
- EVG/c/TDF/FTC—**only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(AI)**
- RAL plus TDF/FTC[a] **(AI)**

PI-Based Regimens:

- DRV/r plus TDF/FTC[a] **(AI)**

Alternative Regimen Options

(Drug classes and regimens within each class are arranged in alphabetical order.)

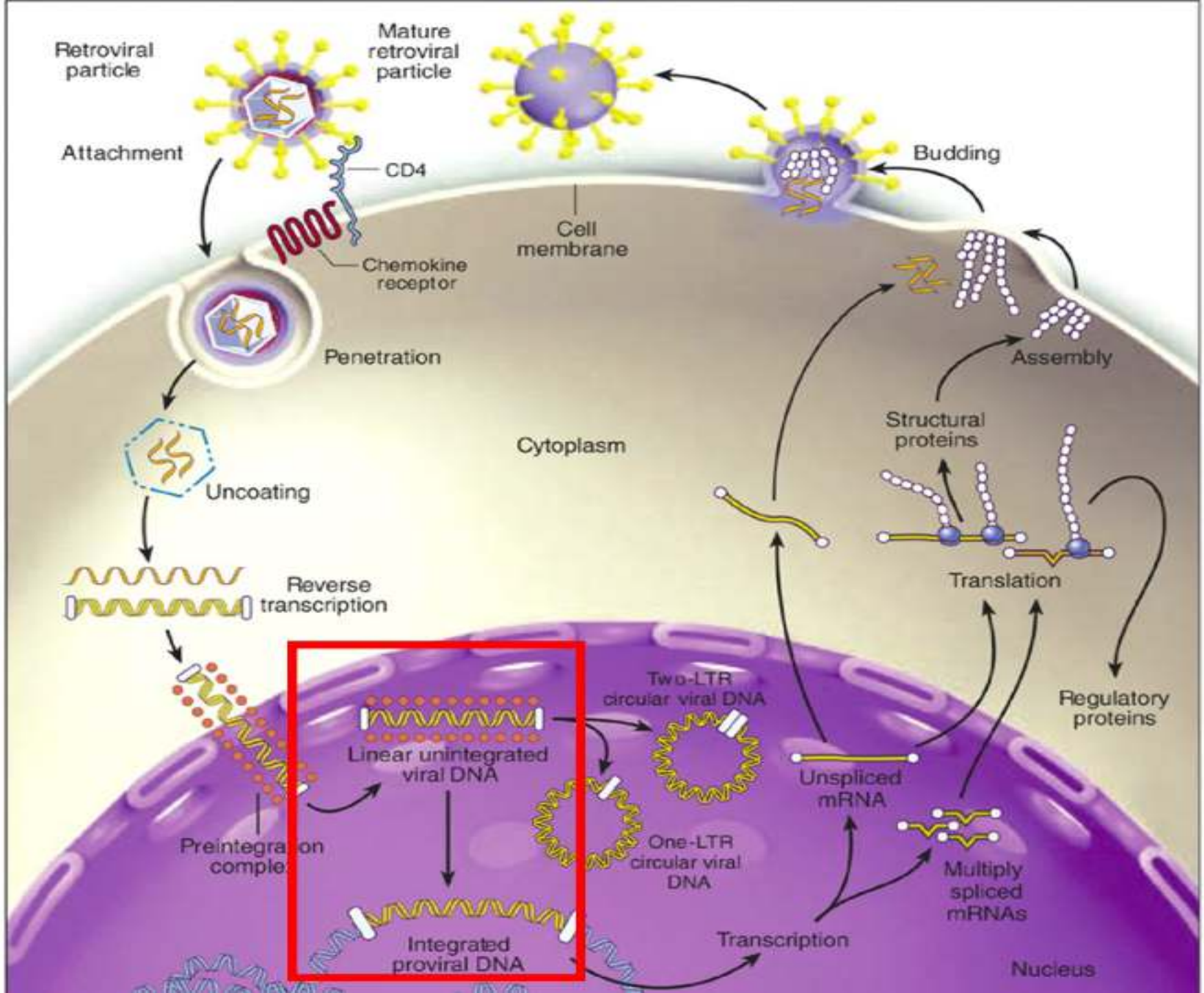
Regimens that are effective and tolerable, but that have potential disadvantages when compared with the recommended regimens listed above, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **An alternative regimen may be the preferred regimen for some patients.**

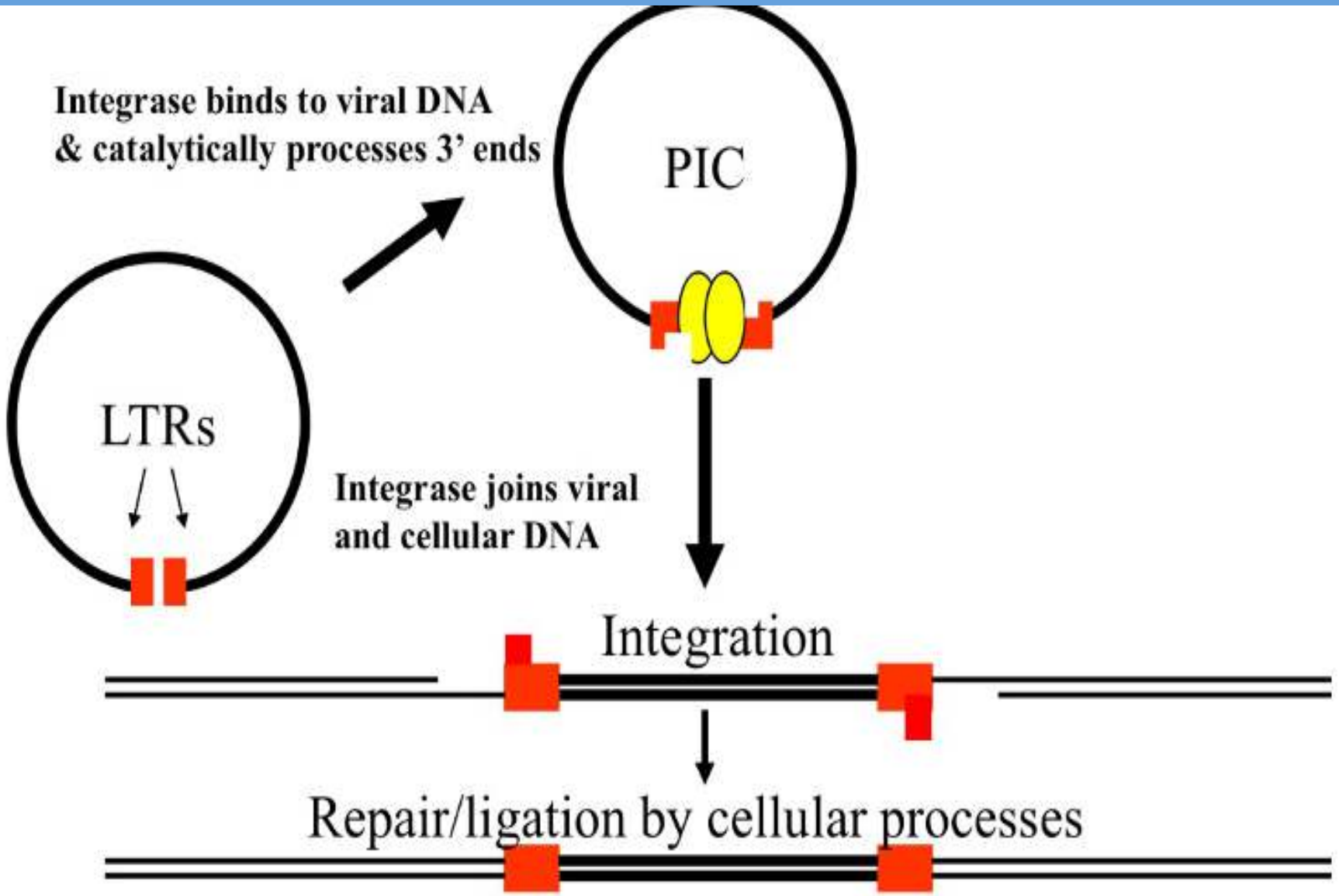
NNRTI-Based Regimens:

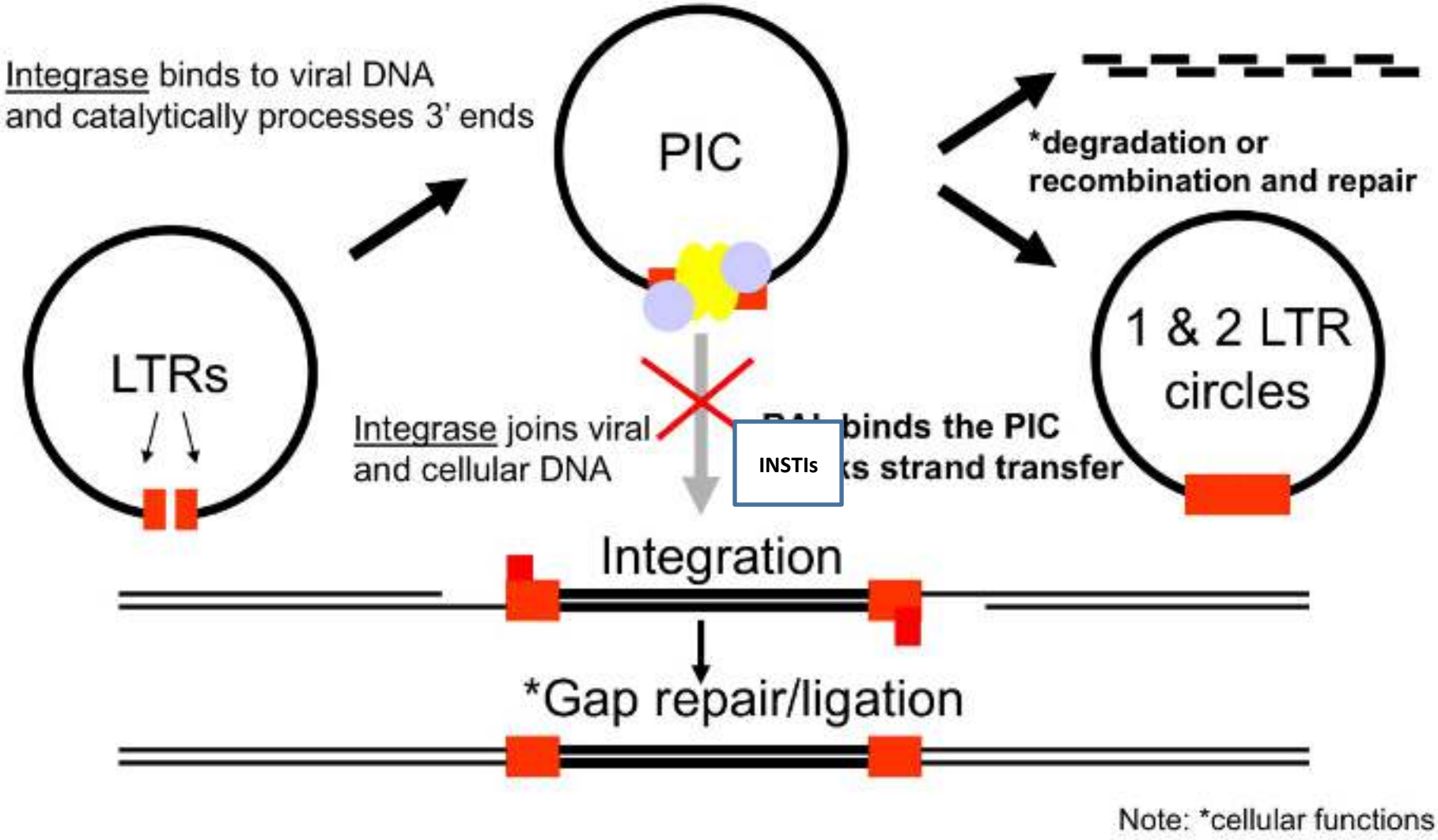
- EFV/TDF/FTC[a] **(BI)**
- RPV/TDF/FTC[a]—**only** for patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3 **(BI)**

PI-Based Regimens:

- ATV/c plus TDF/FTC[a]—**only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(BI)**
- ATV/r plus TDF/FTC[a] **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC[a]—**only** for patients who are HLA-B*5701 negative (**BIII** for DRV/c and **BII** for DRV/r)
- DRV/c plus TDF/FTC[a]—**only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(BII)**

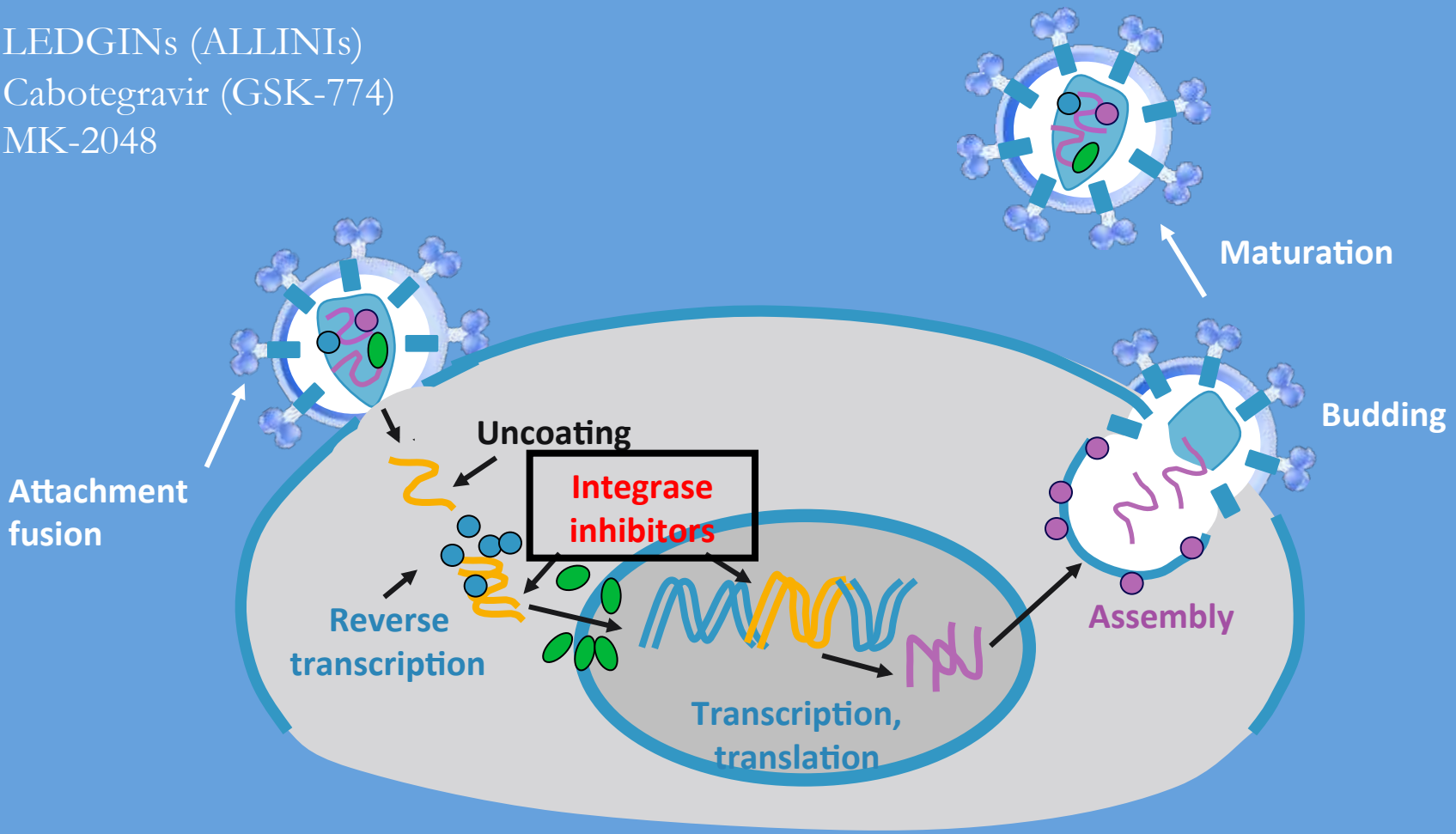

Retroviral particle
Mature retroviral particle
Attachment
CD4
Chemokine receptor
Cell membrane
Budding
Penetration
Assembly
Structural proteins
Cytoplasm
Uncoating
Translation
Reverse transcription
Regulatory proteins
Two-LTR circular viral DNA
Linear unintegrated viral DNA
Unspliced mRNA
Preintegration complex
One-LTR circular viral DNA
Multiply spliced mRNAs
Integrated proviral DNA
Transcription
Nucleus


Integrase binds to viral DNA
& catalytically processes 3' ends
PIC
LTRs
Integrase joins viral
and cellular DNA
Integration
Repair/ligation by cellular processes


Integrase binds to viral DNA
and catalytically processes 3' ends
PIC
*degradation or
recombination and repair
LTRs
1 & 2 LTR
circles
Integrase joins viral
and cellular DNA
INSTIs
Integration
*Gap repair/ligation
Note: *cellular functions

Raltegravir (approved 10/07)
Elvitegravir (approved 8/12)
Dolutegravir (approved 8/13)

LEDGINs (ALLINIs)
Cabotegravir (GSK-774)
MK-2048



Raltegravir (MK-0518)

Kullanıma giren ilk INSTI
R5 ve X4 tropik viruslere ve HIV-2'ye etkin
10 günlük monoterapi ile viral yük 2 log düşmektedir

Hızla absorbe olur ve Cmax'a 1 saatte ulaşır
2 günde kanda kararlı konsantrasyona erişir
Plazma proteinine %83 oranında bağlanır

Pozoloji 2X400 mg (yeni formülasyon 1X1200 mg)
Yiyeceklerle alınma zorunluluğu yoktur

- Sitokrom P450’nin indukleyicisi/inhibitörü değil
- Komedikasyon gereken hastalarda iyi bir seçenek
- Omeprazol ile RAL konsantrasyonu artar, ancak doz ayarlamasına gerek yok
- Child-Pugh A ve B’de doz ayarına gerek yok
- Ciddi renal yetmezlikte bile doz ayarına gerek yok
- Diyalizin raltegravir konsantrasyonuna etkisi net değil. Diyaliz öncesi kulanımı önerilmez

Elvitegravir

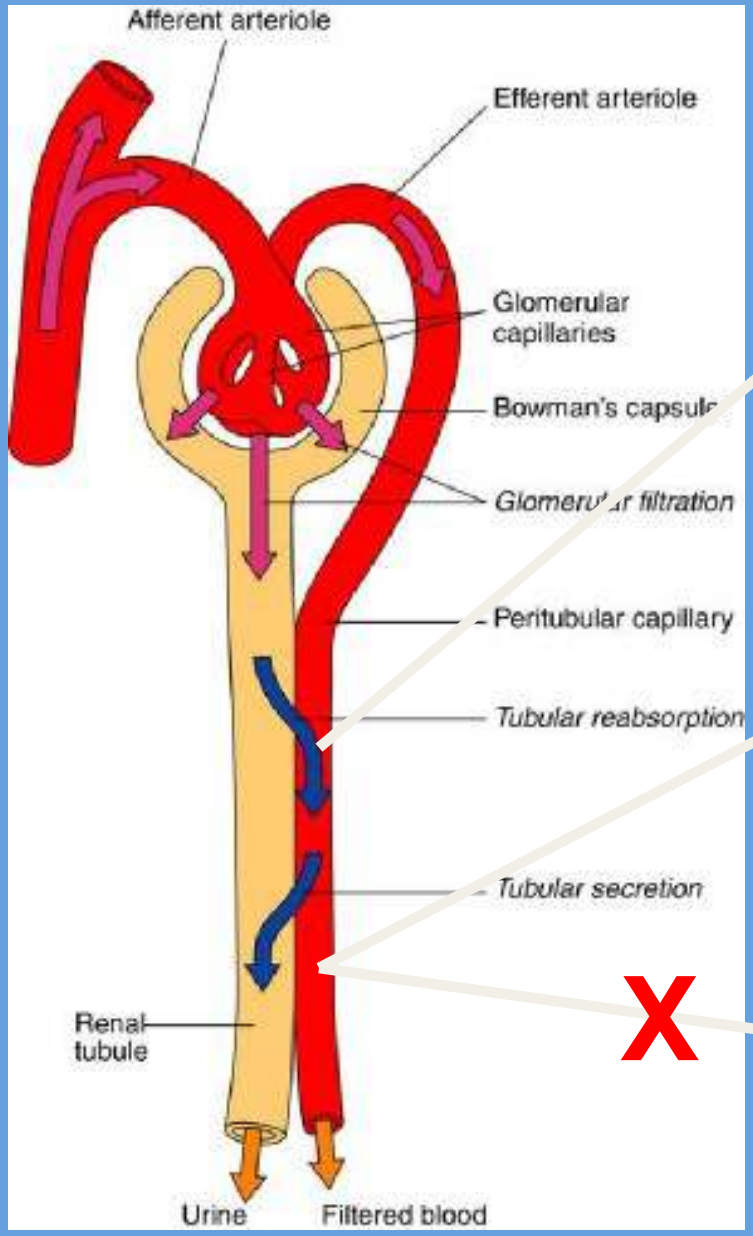
150 mg ETG +150 mg COB (CYP3A ve CYP2D6 inhibisyonu)

Hızla absorbe olup 4 saatte Cmax'a ulaşır

%50'si yağ olan 800 kcal diyet ile alındığında düzeyi %87 artar

85 mg ve 150 mg tabletlerin tek ajan olarak PI/r kullanımı onaylanmıştır

Elvitegravir (EVG) Vitekta Also available as a component of fixed-dose combination.	85 and 150 mg tablets	With Once Daily ATV/r or BID LPV/r: • 85 mg once daily with food With BID DRV/r, FPV/r, or TPV/r: • 150 mg once daily with food Unboosted EVG is not recommended.	CYP3A, UGT1A1/3 substrate	~9 hours	• Nausea • Diarrhea



X

Tubular Reabsorption

Substances reabsorbed back into blood from the renal tubule

Tubular Secretion

Substances secreted from the blood back into renal tubule for elimination

Blocking Tubular Secretion

Cobicistat BLOCKS tubular secretion of creatinine, causing an increase in blood levels of creatinine

- FİX doz tablet kullanımında tenofovirin de nadiren renal hasar yapabilmesi nedeniyle dikkatli olunmalı
- Serum kreatininde ≥0.4 mg/dL artış tek başına COB etkisi değildir, akut renal hasar açısından dikkatli olunmalı
- CrCl <70 mL/dak ise başlanmamalı
- CrCl <50 mL/dak ise kesilmeli

Dolutegravir

2. kuşak INSTI

- genetik bariyeri daha yüksek

10 günlük monoterapide VL 2.5 log azalmıştır

Kc glukuronidasyon ile metabolize olur

Kreatininin tubuler sekresyonunu inhibe eder

GFR'de değişiklik olmadan serum kreatinini artar. Sonra sabit kalır

ART naif olgularda 1X50 mg

Tedavi deneyimli-dirençli olgularda 2X50 mg

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

N/A indicates either that there are no reported cases for the particular side effect or that data for the specific ARV drug class are not available. See Appendix B for additional information listed by drug.

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding Events	N/A	N/A	Spontaneous bleeding, hematuria in hemophilia. TPV: Intracranial hemorrhage associated with CNS lesions, trauma, alcohol abuse, hypertension, coagulopathy, anti-coagulant or anti-platelet agents, vitamin E	N/A	N/A
Bone Density Effects	TDF: Associated with greater loss of BMD than other NRTIs. Osteomalacia has been reported in association with proximal renal tubulopathy.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiovascular Disease	ABC and ddI: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	Associated with MI and stroke in some cohorts. SQV/r, ATV/r, and LPV/r: PR prolongation. Risks include pre-existing heart disease, other medications. SQV/r: QT prolongation. Obtain ECG before administering SQV.	N/A	N/A
Cholelithiasis	N/A	N/A	ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months.	N/A	N/A
Diabetes Mellitus/ Insulin Resistance	ZDV, d4T, and ddI	N/A	Reported for some (IDV, LPV/r), but not all PIs	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 2 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Dyslipidemia	d4T > ZDV > ABC: ↑LDL and TG	EFV: ↑TG, ↑LDL, ↑HDL	All RTV-boosted PIs: ↑LDL, ↑TG, ↑HDL LPV/r = FPV/r and LPV/r > DRV/r and ATV/r: ↑TG	EVG/c/TDF/FTC: ↑TG, ↑LDL, ↑HDL	N/A
Gastrointestinal Effects	Nausea and vomiting: ddI and ZDV > other NRTIs Pancreatitis: ddI	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) Diarrhea: Common with LPV/r, more frequent than DRV/r and ATV/r	Nausea and diarrhea: EVG/c/ TDF/FTC	N/A
Hepatic Effects	Reported with most NRTIs. Steatosis most common with ZDV, d4T, or ddI. ddI: Prolonged exposure linked to non-cirrhotic portal hypertension, esophageal varices. Flares: HIV/HBV-co-infected patients may develop severe hepatic flares when TDF, 3TC, and FTC are withdrawn or when HBV resistance develops.	NVP > other NNRTIs NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis, or in patients with hepatic insufficiency (Child-Pugh B or C).	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported; greatest frequency with TPV/r. IDV, ATV: Jaundice due to indirect hyperbilirubinemia TPV/r: **Contraindicated** in patients with hepatic insufficiency (Child-Pugh B or C)	N/A	MVC: Hepatotoxicity with or without rash or HSRs reported

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: **Contraindicated** if HLA-B*5701 positive. Median onset 9 days; 90% of reactions occur within first 6 weeks of treatment. HSR symptoms (in order of descending frequency): fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. Symptoms worsen with continuation of ABC. Patients, regardless of HLA-B*5701 status, should not be re-challenged with ABC if HSR is suspected.	NVP: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 count >250 cells/mm^3 and men with pre-NVP CD4 count >400 cells/mm^3. Overall, risk is higher for women than men. 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL given in combination with other drugs known to cause HSR. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: Reported as part of a syndrome related to hepatotoxicity
Lactic Acidosis	Reported with NRTIs, especially d4T, ZDV, and ddI: Insidious onset with GI prodrome, weight loss, and fatigue. May rapidly progress with tachycardia, tachypnea, jaundice, weakness, mental status changes, pancreatitis, and organ failure. Mortality high if serum lactate >10 mmol/L. Women and obese patients at increased risk.	N/A	N/A	N/A	N/A

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	Lipoatrophy: d4T > ZDV. May be more likely when NRTIs combined with EFV than with an RTV-boosted PI.	Lipohypertophy: Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL: ↑CPK, weakness and rhabdomyolysis	N/A
Nervous System/ Psychiatric Effects	Peripheral neuropathy: d4T > ddI and ddC (can be irreversible). d4T: Associated with rapidly progressive, ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare)	EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, and suicidal ideation. Symptoms usually subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and increased EFV concentrations because of genetic factors or increased absorption with food. An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among younger patients and those with history of mental illness or substance abuse) was found in a retrospective analysis of comparative trials.	N/A	All INSTIs: Insomnia RAL: Depression and suicidal ideation (uncommon)	N/A
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, FPV, LPV/r, TPV	RAL, EVG/c/TDF/ FTC	MVC

Table 14. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effect	NRTIs	NNRTIs	PIs	INSTI	EI
Renal Effects/ Urolithiasis	TDF: ↑SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis Concurrent use with PI appears to increase risk.	N/A	ATV and LPV/r: Increased chronic kidney disease risk in a large cohort study. IDV: ↑SCr, pyuria, renal atrophy or hydronephrosis IDV, ATV: Stone, crystal formation; adequate hydration may reduce risk.	COBI (in EVG/c/ TDF/FTC) and DTG: Inhibits Cr secretion without reducing renal glomerular function.	N/A
Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	ddI, ZDV: Reported cases	NVP > DLV, EFV, ETR, RPV	FPV, DRV, IDV, LPV/r, ATV: Reported cases	RAL	N/A

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BMD = bone mineral density; Cr = creatinine; CrCl = creatinine clearance; CNS = central nervous system; COBI or c = cobicistat; CPK = creatine phosphokinase; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IDV = indinavir; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PT = prothrombin time; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQV = saquinavir; SQV/r = saquinavir/ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

TABLE 128-5 Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy—cont'd

ANTIRETROVIRAL DRUG	FDA PREGNANCY CATEGORY	PK IN PREGNANCY	CONCERNS IN PREGNANCY	RATIONALE FOR RECOMMENDED USE IN PREGNANCY
Integrase Inhibitors				
Insufficient Data to Recommend Use				
Raltegravir (RAL)	C	In third trimester, RAL PK showed wide variability but RAL exposure was similar to postpartum and historical data Variable but high placental transfer to fetus	Insufficient data to assess for teratogenicity in humans. Increased skeletal variants in rats but not in rabbits. Limited experience in human pregnancy.	Safety and PK in pregnancy data are limited; can be considered for use in special circumstances if no other alternatives are available
Elvitegravir/cobicistat (available in the Quad pill formulated with TDF/FTC/EVG/COBI) (brand name: Stribild)[†]	B	In third trimester, AUC lower than postpartum but trough levels adequate Unknown placental transfer to fetus	No evidence of teratogenicity in rats and rabbits with all four components of medications. If hepatitis B coinfection present, possible hepatitis B flare if drug stopped postpartum.	Safety and PK in pregnancy data are insufficient to recommend use during pregnancy
Dolutegravir	B	No PK studies in human pregnancy Unknown placental transfer to fetus	No teratogenicity in rats and rabbits	Safety and PK in pregnancy data are insufficient to recommend use during pregnancy

*Triple NRTI regimens including abacavir are less potent virologically compared with PI-based highly active antiretroviral therapy regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based highly active antiretroviral therapy regimen cannot be used, such as because of significant drug interactions.

[†]Stribild FDA-approved product information. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203100s000lbl.pdf. Accessed March 1, 2013.

ARV, antiretroviral; AUC, area under the concentration-time curve; FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NtRTI, nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetics.

Modified from the U.S. Public Health Service Task Force. Recommendations for the use of antiretroviral drugs in pregnant HIV-infected women for maternal health and

TABLE 127-2 Cerebrospinal Fluid Penetration Effectiveness Score

	4	3	2	1
Nucleoside analogue reverse-transcriptase inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Non-nucleoside analogue reverse-transcriptase inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir-r Atazanavir Fosamprenavir	Nelfinavir Ritonavir Saquinavir-r Saquinavir Tipranavir
Fusion/Entry inhibitors		Maraviroc		Enfuvirtide
Integrase inhibitors		Raltegravir		

*Numerical score of 4 is highest and 1 is lowest by method of Letendre.[62]
-r, ritonavir-boosted.

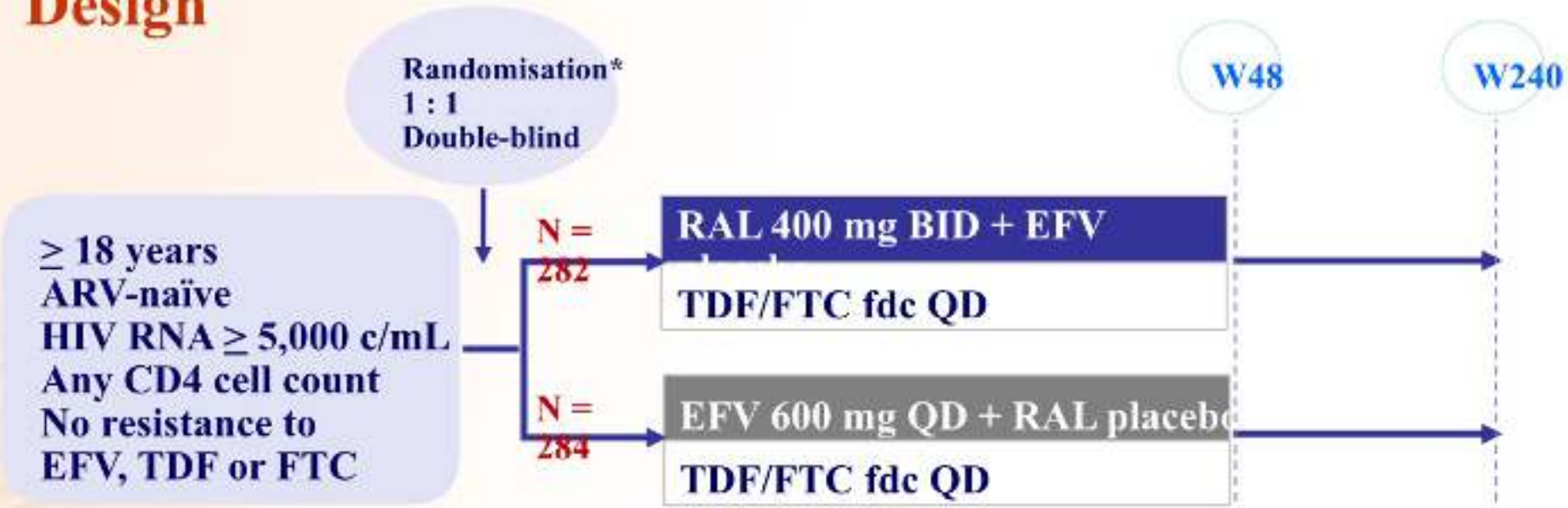
RAL genital sekresyonlara iyi geçer

HIVRNA semende ölçülemeyecek düzeye iner

Tedavi naif hastalarda İntegraz inhibitörleri

STARTMRK Study: raltegravir vs efavirenz, in combination with TDF/FTC

Design



*Randomisation was stratified by baseline HIV RNA (≤ or > 50,000 c/mL) and viral hepatitis co-infection status

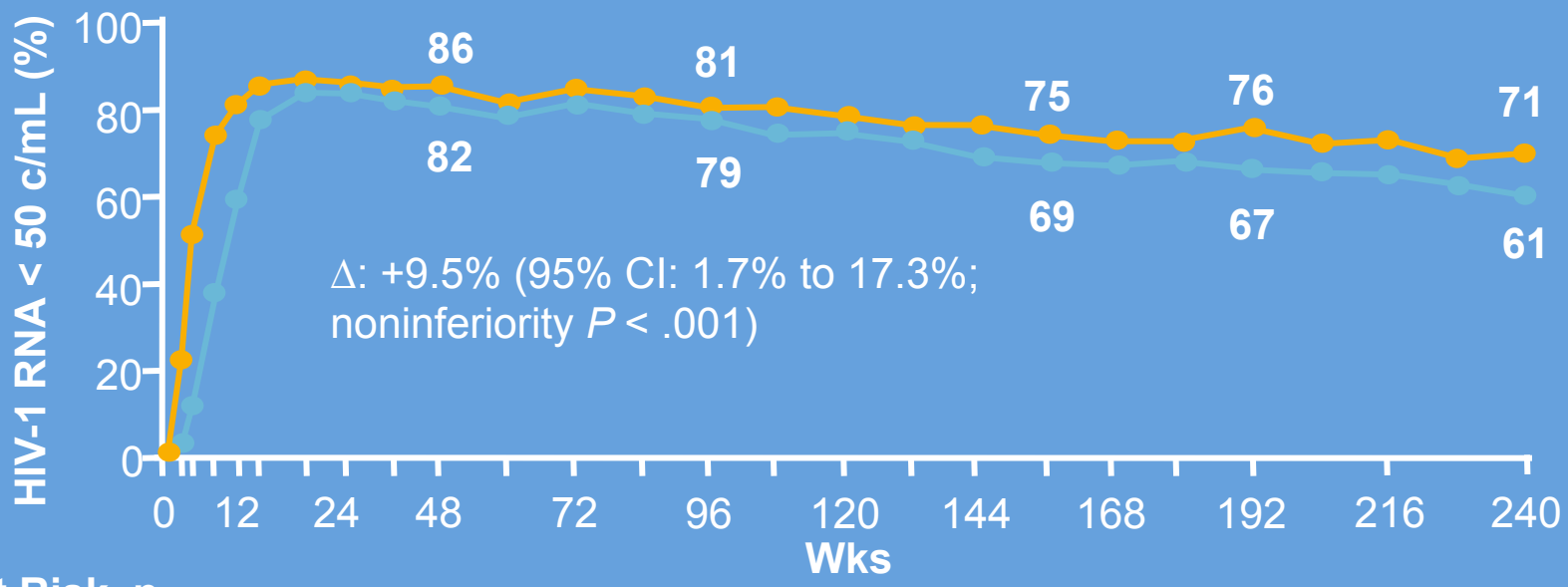
Objective

Non inferiority of RAL vs EFV: % HIV RNA < 50 c/mL by per protocol, non-completer = failure analysis (lower margin of the 2-sided 95% CI for the difference = - 12%, 90% power)

Lennox JL. Lancet 2009;374:796-806

STARTMRK: RAL vs EFV in Treatment-Naive Patients: 5-Yr Final Report

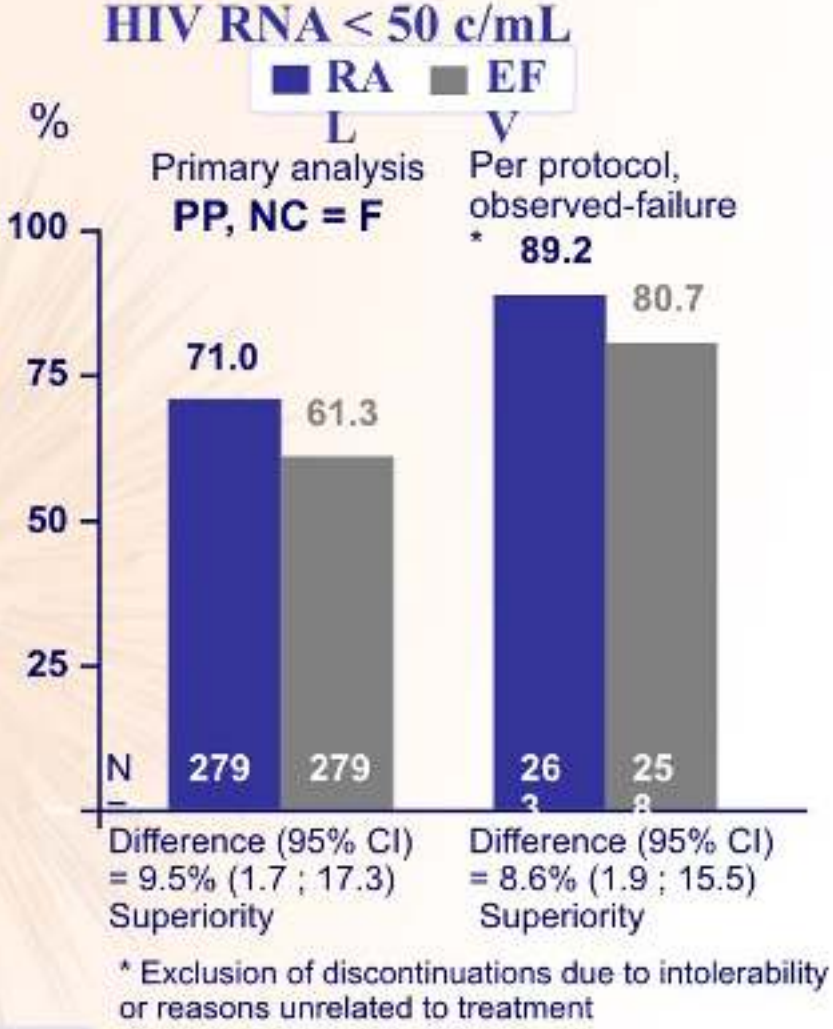
- RAL noninferior to EFV in HIV-1 RNA < 50 c/mL at Wk 48 (primary endpoint; ITT, NC = F analysis); superior from Wk 192



Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;63:77-85.

STARTMRK Study: raltegravir vs efavirenz, in combination with TDF/FTC

Response to treatment at week 240 (5 years)



* Exclusion of discontinuations due to intolerability or reasons unrelated to treatment

HIV RNA < 50 c/mL (observed-failure analysis) by baseline factors

Baseline	RAL	EFV
RNA ≤ 5 log10 c/mL	94%	78%
RNA > 5 log10 c/mL	85%	83%
CD4 > 200/mm3	82.5%	78.7%
CD4 ≤ 200/mm3	88.3%	85.6%
HIV-1 B subtype	90%	79%
Non-B subtype	87%	84%

Increases in fasting serum triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol from baseline were significantly lower at W240 (P < 0.005) in RAL than EFV

Rockstroh JK, JAIDS 2013;63:77-85

STARTMRK Study: raltegravir vs efavirenz, in combination with TDF/FTC

Cumulative summary of genotypicresistance data for patients with RNA > 400 c/mL at the time of virologic failure out to week 240

	RAL N = 281	EFV N = 282
Protocol-defined virologic failure confirmed (HIV RNA > 50 c/mL)	55 (19.6%)	59 (20.9%)
Resistance data available (HIV RNA > 400 c/mL)	23*	20
RAL or EFV resistance alone	1	7
RAL or EFV resistance, and NRTI resistance	3	3
NRTI resistance alone	3	2

* Integrase gene could not be amplified in 5 cases

Emergence of RAL resistance in 4 patients (1.4%)

Sequencing data of the 4 patients with emergence of RAL-associated mutations

Q148H + G140S,
Q148R + G140S,
Y143Y/H + L74L/M + E92Q +T97A,
Y143R

Rockstroh JK, JAIDS 2013;63:77-85

STARTMRK Study: raltegravir vs efavirenz, in combination with TDF/FTC

Summary – Conclusion

At 48 weeks of treatment, RAL was non-inferior to EFV, in combination with TDF/FTC. Virologic non-inferiority of RAL was confirmed through W24. RAL was superior to EFV for virologic outcome at week 240

RAL + TDF/FTC led to more rapid viral load decline (significantly more patients with HIV RNA < 50 c/mL for weeks 2 to 16)

Greater increase in CD4 was observed in the RAL group. It was significant from W156

Upon virologic failure, resistance mutations to RAL was found in few cases

RAL was associated with significantly fewer overall and drug-related clinical adverse events, and CNS-related adverse events than was EFV

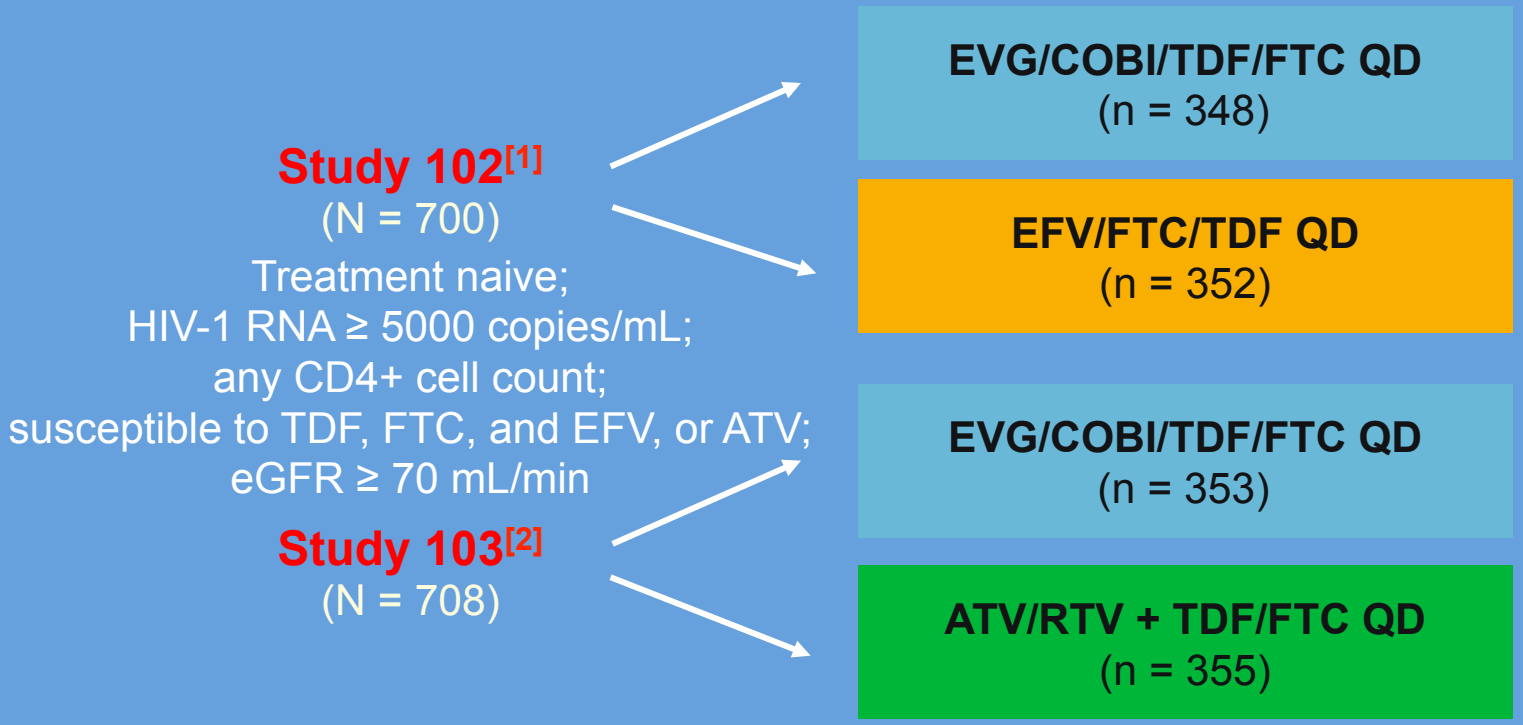
Mean changes in lipid parameters were smaller for RAL than for EFV

RAL + TDF/FTC is an alternative to EFV + TDF/FTC as a first-line combination regimen in treatment-naïve HIV-infected patients

Lennox JL. Lancet 2009;374:796-806; Rockstroh JK, JAIDS 2013;63:77-85

Elvitegravir/Cobicistat vs EFV or ATV/RTV + TDF/FTC in Treatment-Naive Pts

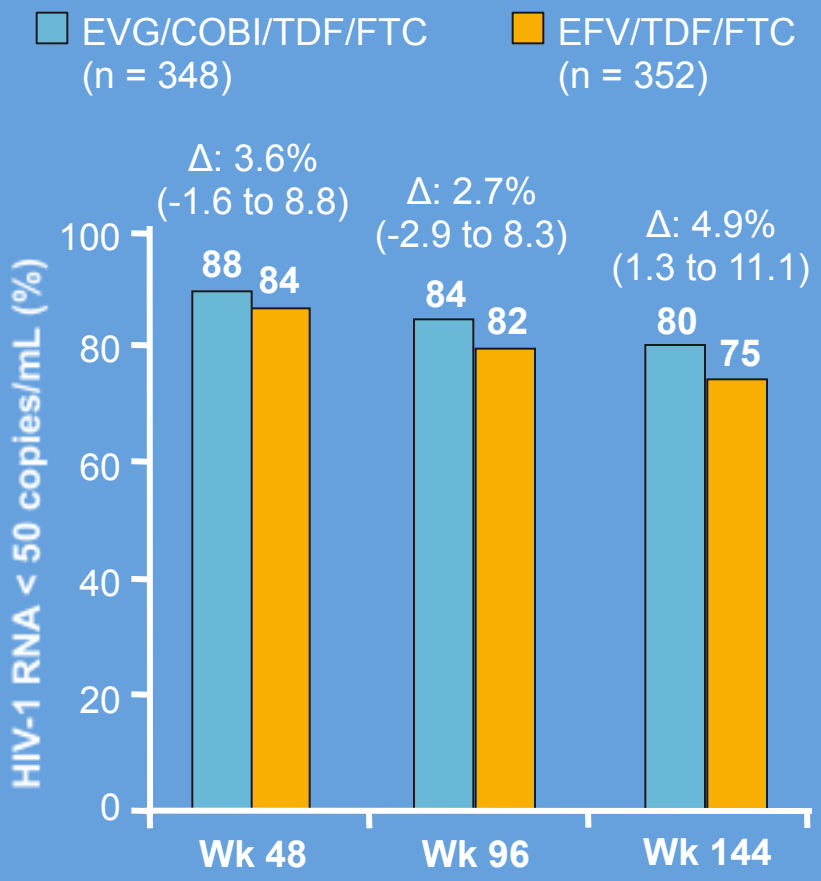
- Randomized, double-blind, active-controlled phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



Sax P, et al. Lancet. 2012;379:2439-2448.

2. DeJesus E, et al. Lancet. 2012;379:2429-2438.

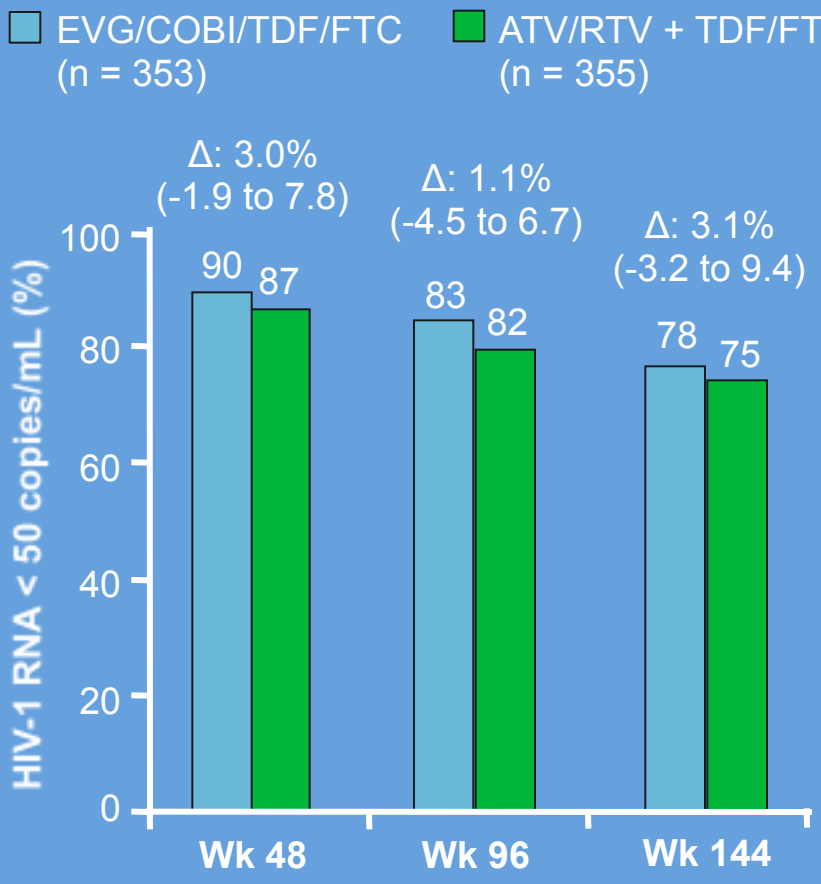
EVG/COBI/TDF/FTC Noninferior to EFV/ TDF/FTC Through Wk 144



- EVG/COBI arm noninferior to EFV arm at Wk 48 primary endpoint[1] and through Wk 144[2,3]
  - Results consistent across subgroups: BL HIV-1 RNA, CD4+ cell count, age, sex, race
    - Treatment-related study d/c: 6% in EVG/COBI arm vs 7% in EFV arm at Wk 144
- VF: 7% in EVG/COBI arm and 10% in EFV arm at Wk 144
- Similar CD4+ cell count increase at Wk 144:
  - +321 cells/mm^3 (EVG/COBI) vs +300 cells/mm^3 (EFV)

1. Sax PE, et al. Lancet. 2012;379:2439-2448.
2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100.
3. Wohl D, et al. ICAAC 2013. Abstract H-672a.

EVG/COBI/TDF/FTC Noninferior to ATV/RTV + TDF/FTC Through Wk 144



- EVG/COBI arm noninferior to ATV/RTV arm at Wk 48 primary endpoint[1] and through Wk 144[2,3]
  - Results consistent across subgroups: BL HIV-1 RNA, CD4+ count, adherence, age, sex, race
- Treatment-related study d/c: 6% in EVG/COBI arm vs 9% in ATV/RTV arm at Wk 144
- VF: 8% in EVG/COBI arm vs 7% in ATV/RTV arm at Wk 144
- Similar CD4+ cell count increase at Wk 144: +280 cells/mm^3 (EVG/COBI) vs +293 cells/mm^3 (ATV/RTV)

1. *De Jesus E, et al. Lancet. 2012;379:2429-2438.*
2. *Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486*
3. *Clumeck N, et al. EACS 2013. Abstract LBPS7/2.*

EVG/COBI/TDF/FTC Adverse Events Summary

- EVG/COBI vs EFV: fewer CNS, rash events; smaller increase in TC, HDL-C, and LDL-C (but similar increase in TC:HDL ratio), similar TG increase; more nausea[1]
- EVG/COBI vs ATV/RTV: less jaundice; similar increase in TC, HDL-C, and LDL-C; smaller TG increase[2]
- Small, rapid increase in serum creatinine related to inhibition of tubular secretion of creatinine by COBI
  - 0.14 ± 0.13 mg/dL at Wk 48; most change occurs by Wk 2[3]
- 4 pts (0.6% of total) developed tubulopathy, likely from TDF[3]

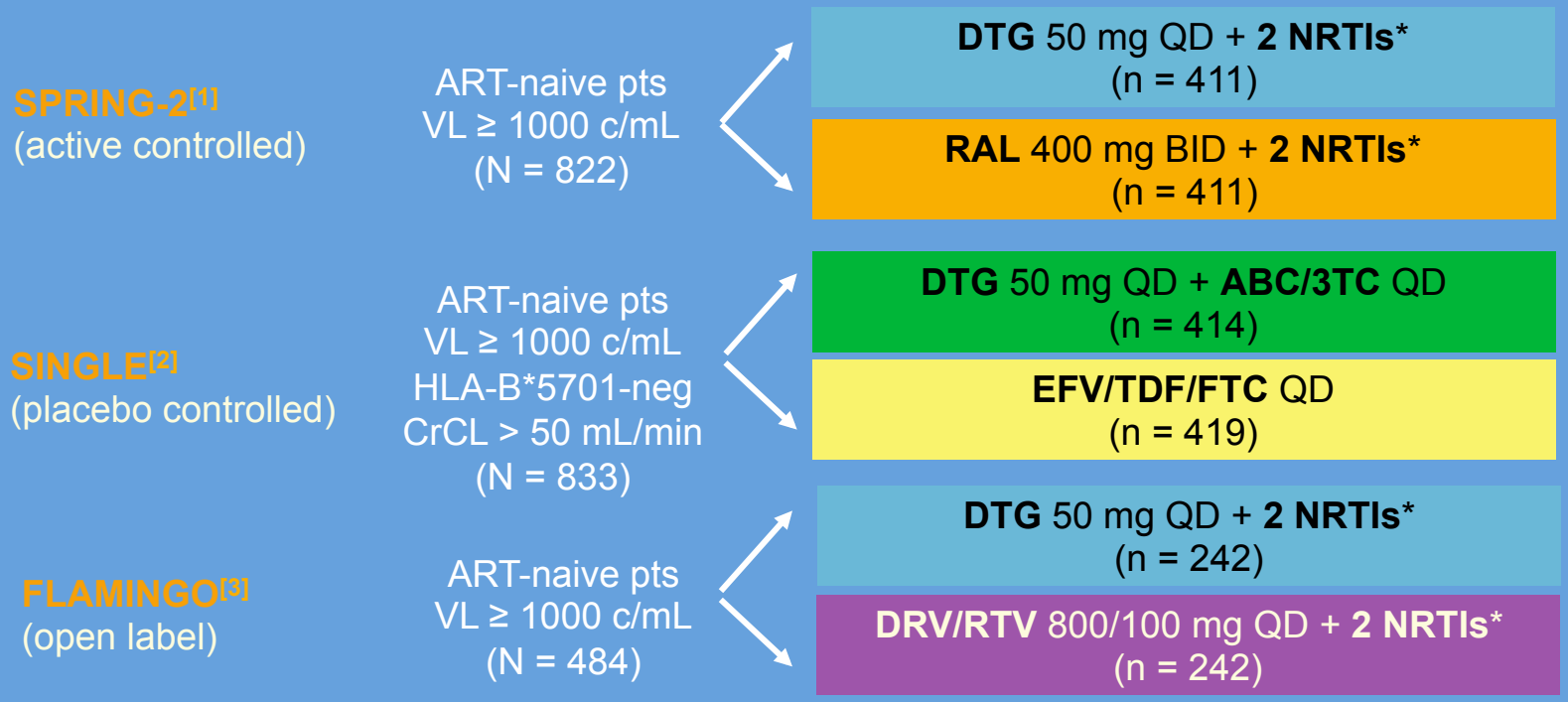
1.Sax P, et al. Lancet. 2012;379:2439-2448.

2. DeJesus E, et al. Lancet. 2012;379:2429-2438.

3. TDF/FTC/EVG/COBI [package insert].

Dolutegravir vs Currently "Preferred" Regimens in Treatment-Naive Pts

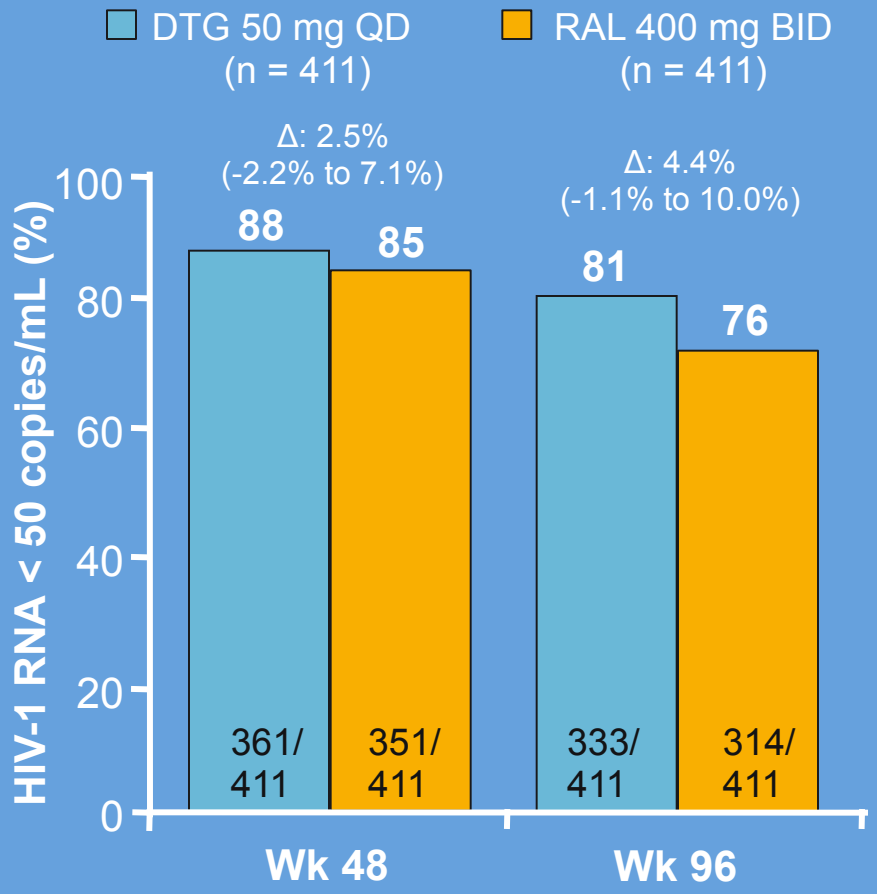
- Randomized, noninferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1.Raffi F, et al. Lancet. 2013;381:735-743.
2. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.
3. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

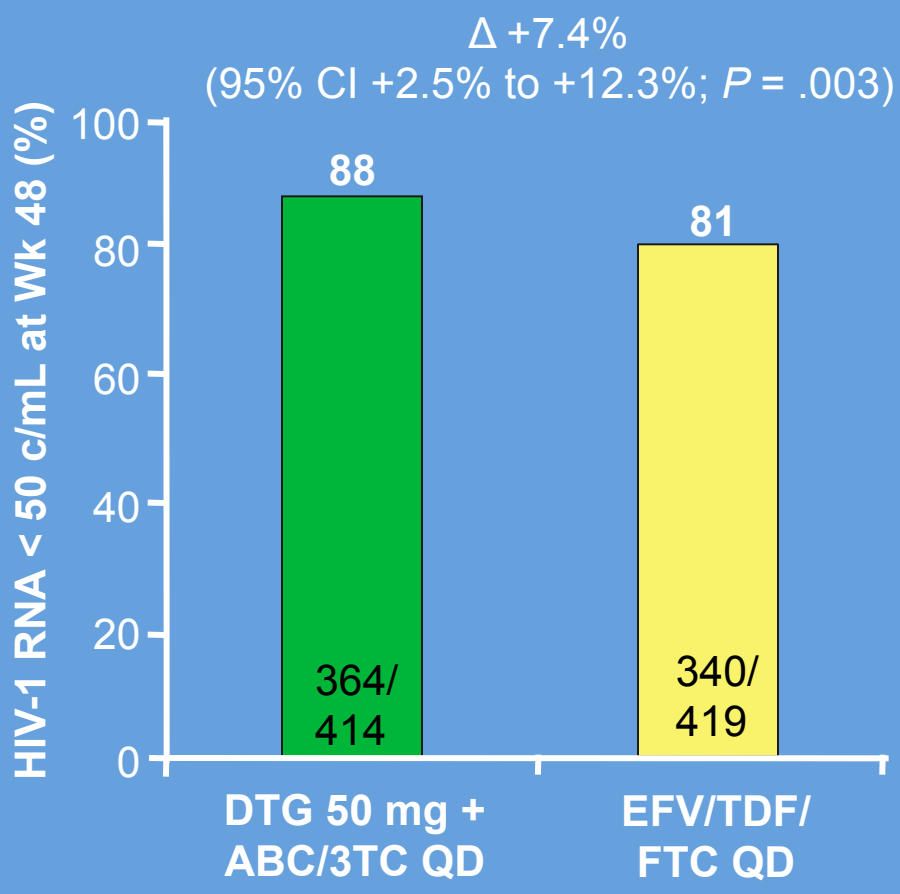
SPRING-2: DTG vs RAL + 2 NRTIs in Naive Patients



- DTG noninferior to RAL at both Wk 48 primary endpoint[1] and Wk 96[2]
- Treatment-related study d/c: 2% in each arm at Wk 96
- VF at Wk 96[2]: 5% (22/411) in DTG arm and 7% (29/411) in RAL arm
- Similar CD4+ cell count increase at Wk 96:
  - +276 cells/mm^3 (DTG) vs +264 cells/mm^3 (RAL)

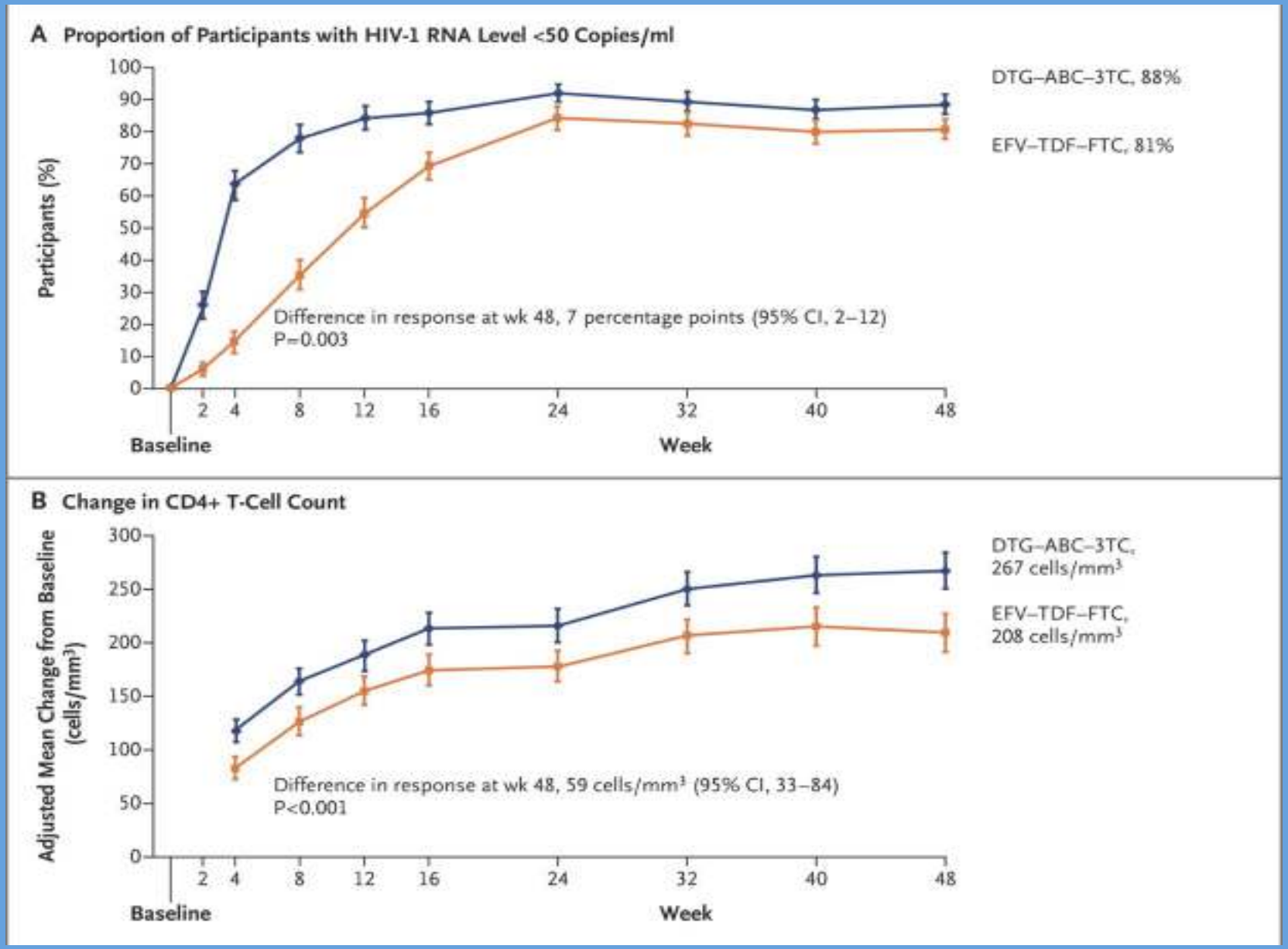
1. Raffi F, et al. Lancet. 2013;381:735-743.
2. Raffi F, et al. IAS 2013. Abstract TULBPE17.

SINGLE: DTG + ABC/3TC vs EFV/TDF/FTC in Naive Patients at Wk 48

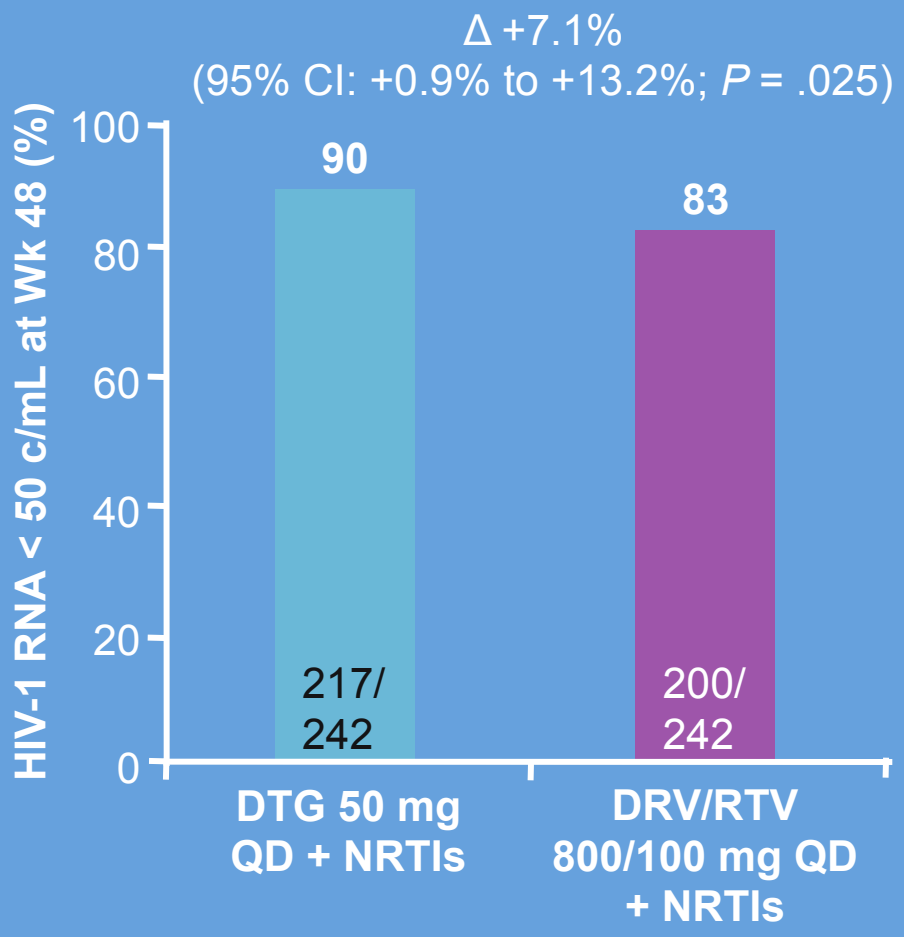


- DTG superior to EFV at Wk 48 primary efficacy endpoint
- Treatment-related study d/c: 2% in DTG arm vs 10% in EFV arm
- VF at Wk 48: 4% (18/414) in DTG arm and 4% (17/419) in EFV arm
- CD4+ cell count increase at Wk 48 greater with DTG:
  - +267 cells/mm^3 (DTG) vs +208 cells/mm^3 (EFV) (P < .001)

Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.


A Proportion of Participants with HIV-1 RNA Level <50 Copies/ml
Participants (%)
100
90
80
70
60
50
40
30
20
10
0
Baseline
2
4
8
12
16
24
32
40
48
Week
DTG–ABC–3TC, 88%
EFV–TDF–FTC, 81%
Difference in response at wk 48, 7 percentage points (95% CI, 2–12)
P=0.003
B Change in CD4+ T-Cell Count
Adjusted Mean Change from Baseline (cells/mm³)
300
250
200
150
100
50
0
Baseline
2
4
8
12
16
24
32
40
48
Week
DTG–ABC–3TC, 267 cells/mm³
EFV–TDF–FTC, 208 cells/mm³
Difference in response at wk 48, 59 cells/mm³ (95% CI, 33–84)
P<0.001

FLAMINGO: DTG vs DRV/RTV + 2 NRTIs in Naive Patients at Wk 48

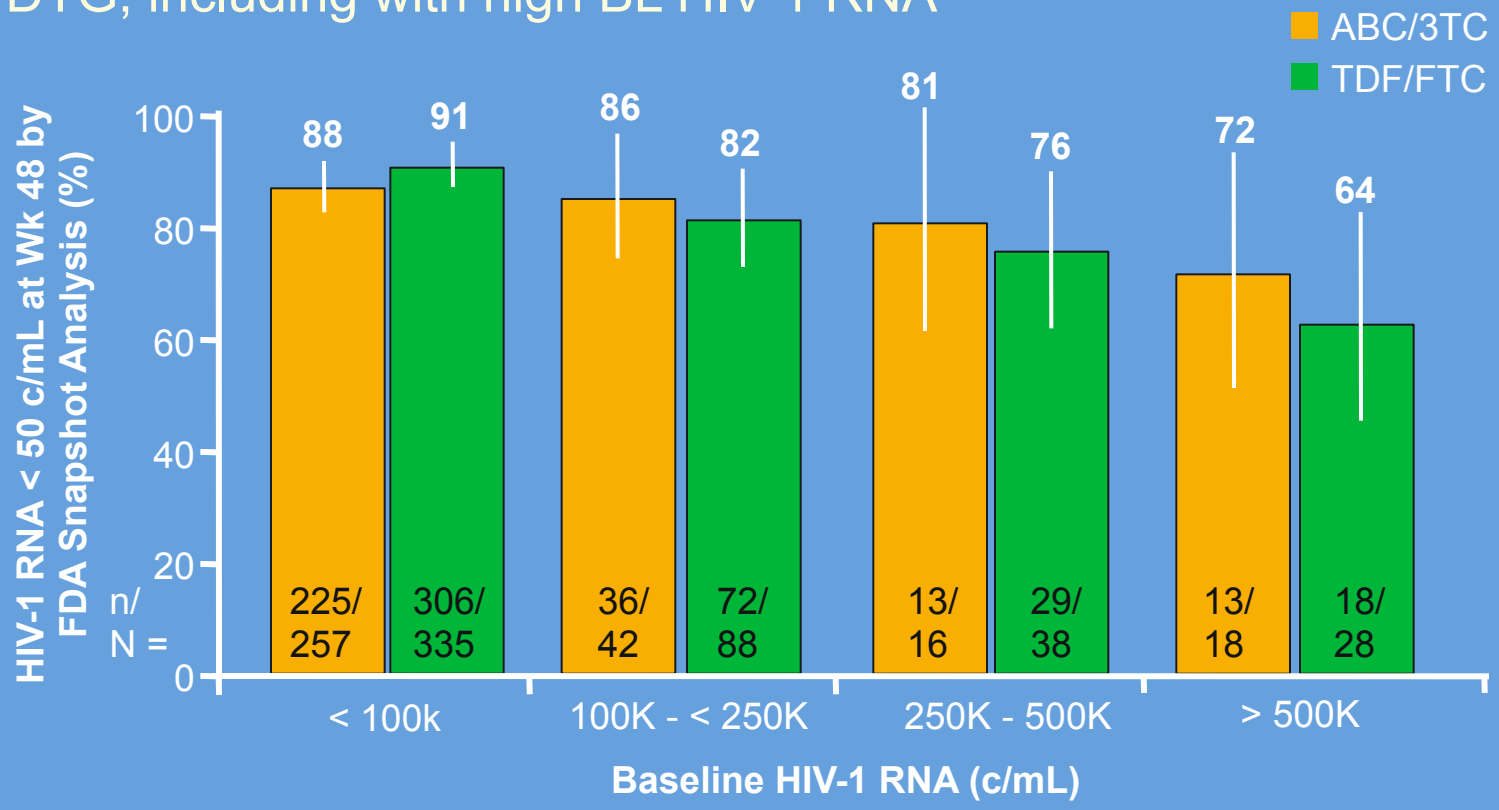


- DTG superior to DRV/RTV at Wk 48 primary efficacy endpoint
  - Treatment-related study d/c: 2% in DTG arm vs 4% in DRV/RTV arm
- VF at Wk 48: < 1% (n = 2) in each arm
- Similar CD4+ cell count increase at Wk 48:
  - +210 cells/mm³ in each arm

Feinberg J, et al. ICAAC 2013. Abstract H1464a.

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even for High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA*



*Pooled data from both INSTIs.

Eron J, et al. Glasgow 2012. Abstract P204.

Integrase Inhibitors for Initial Therapy: Conclusions

- While there are many options for initial therapy, regimens that include an integrase inhibitor have many favorable characteristics
  - All are potent, well tolerated, favorable metabolic profile
  - Rates of transmitted (baseline) drug resistance to INSTIs presumed to be low
  - Few drug–drug interactions (RAL, DTG)
  - Resistance rarely reported with DTG
  - Available as single-pill regimen (EVG)
- Integrase inhibitor–based regimens may be appropriate for many (if not most) treatment-naive patients

İlaç değişiminde integraz inhibitörleri

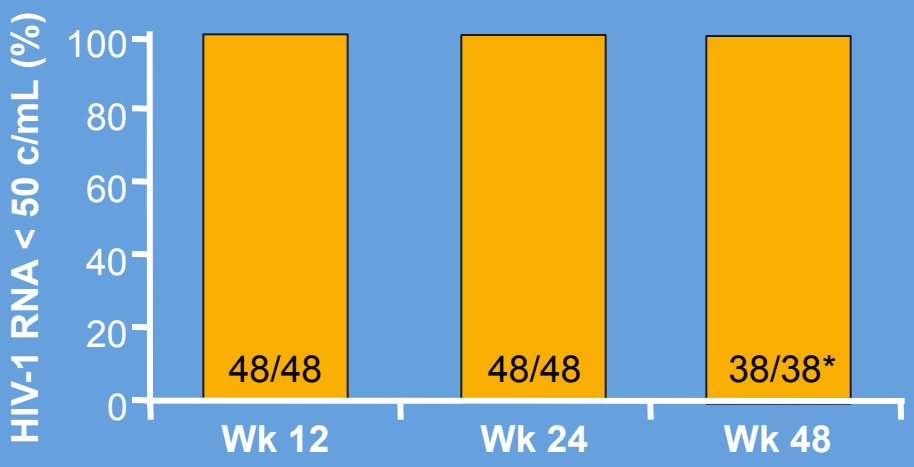
Switching Virologically Suppressed Patients to RAL

- SWITCHMRK-1 and -2[1]
  - Switching to RAL inferior to remaining on LPV/RTV-based regimen in pts with HIV-1 RNA < 50 c/mL for > 3 mos, particularly among those with previous VF
  - TC, non–HDL-C, and TG improved in switch pts
- SPIRAL[2]
  - Switching from to RAL noninferior to remaining on boosted PI-based regimens through Wk 48 in pts with HIV-1 RNA < 50 c/mL for ≥ 6 mos
  - Switching to RAL significantly improved lipids and TC:HDL-C ratio
- EASIER/ANRS 138[3]
  - Switch from ENF to RAL regimens maintained virologic suppression through Wk 48 in patients with multidrug resistance and HIV-1 RNA < 400 c/mL for ≥ 3 mos

1. *Eron J, et al. Lancet. 2010;375:396-407. 2. Martinez E, et al. AIDS. 2010;24:1697-1707. 3. Gallien S, et al. J Antimicrob Chemother. 2011;66:2099-2106.*

Study 123: Switch From RAL + TDF/FTC to EVG/COBI/TDF/FTC

- Open-label, multicenter, 48-wk pilot study of switch from RAL + TDF/FTC to EVG/COBI/TDF/FTC in pts with HIV-1 RNA < 50 c/mL for 6 mos (N = 48)
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 12 postswitch
- Secondary endpoints: Safety and tolerability by Wk 24 and Wk 48
  HIV-1 RNA < 50 c/mL at Wk 24 and Wk 48 postswitch
- All subjects maintained virologic suppression at Wks 12 and 24
  - 38/38 subjects who reached Wk 48 at time of report also suppressed
- TC and LDL-C improved; no renal AEs

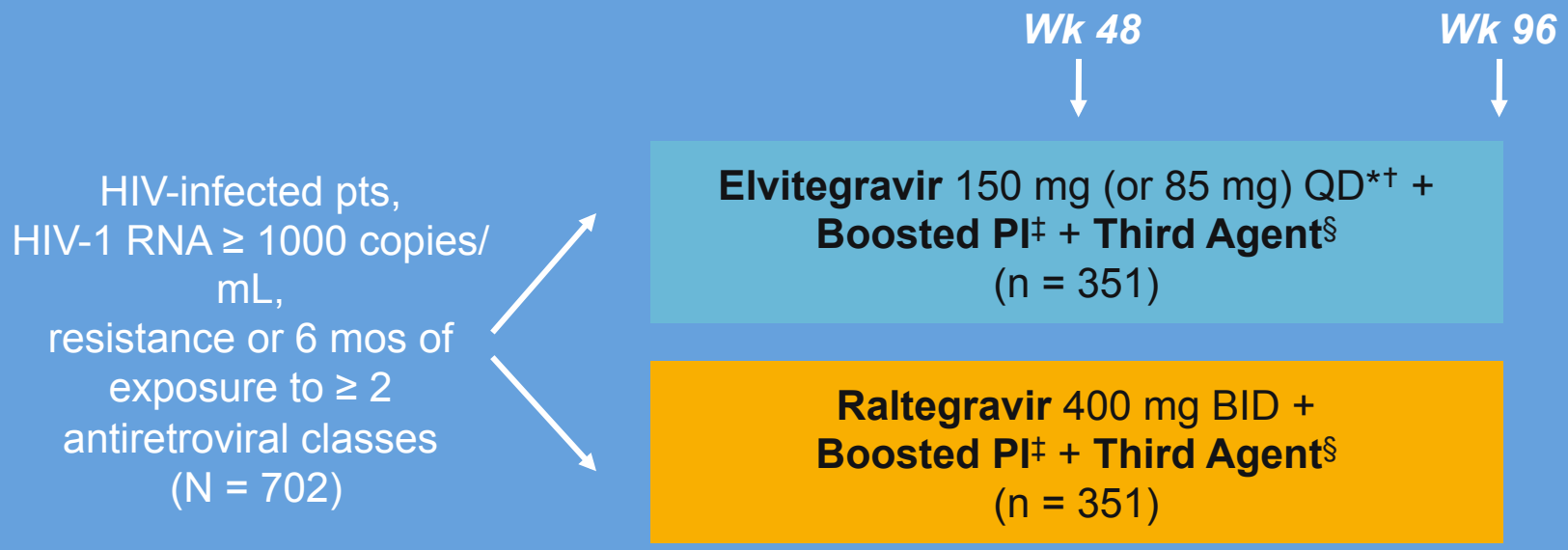


Crofoot G, et al. IAS 2013. Abstract TUPE283.

Tedavi deneyimli hastalarda İntegraz inhibitörleri

Study 145: Elvitegravir vs Raltegravir in Treatment-Experienced Patients

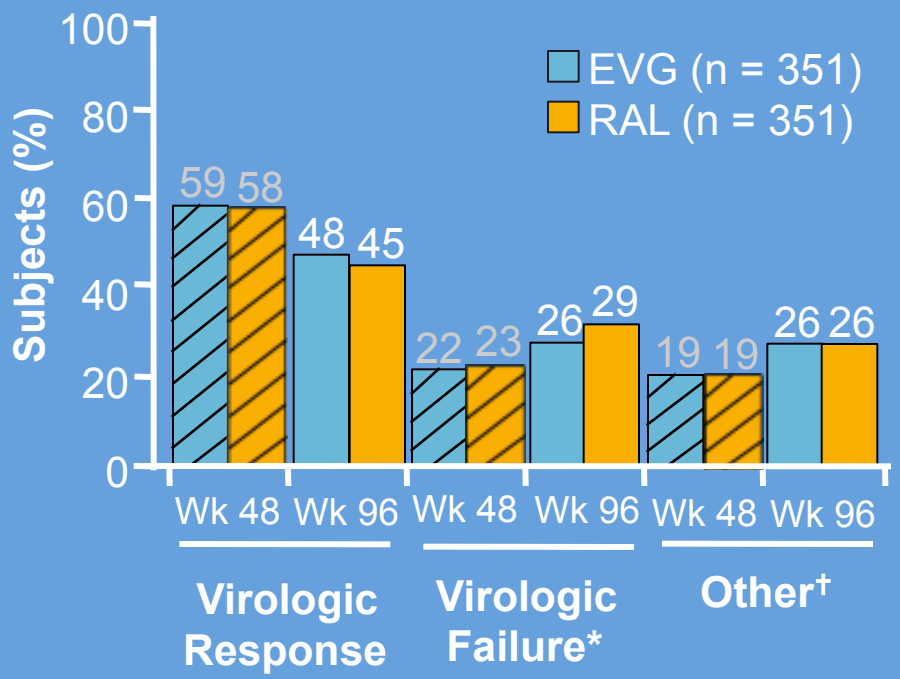
- Randomized, placebo-controlled phase III study



*EVG currently unavailable as single agent.
†EVG dose reduced to 85 mg QD for pts receiving ATV/RTV or LPV/RTV as part of background regimen.
‡Background regimen to include fully active RTV-boosted PI, selected using resistance testing.
§Selected from ENF, ETR, MVC, or NRTI. Option of also adding FTC or 3TC for pts with M184V/I.

Molina J, et al. Lancet Infect Dis. 2012;12:27-35.

Study 145: EVG Noninferior to RAL at Wks 48 and 96



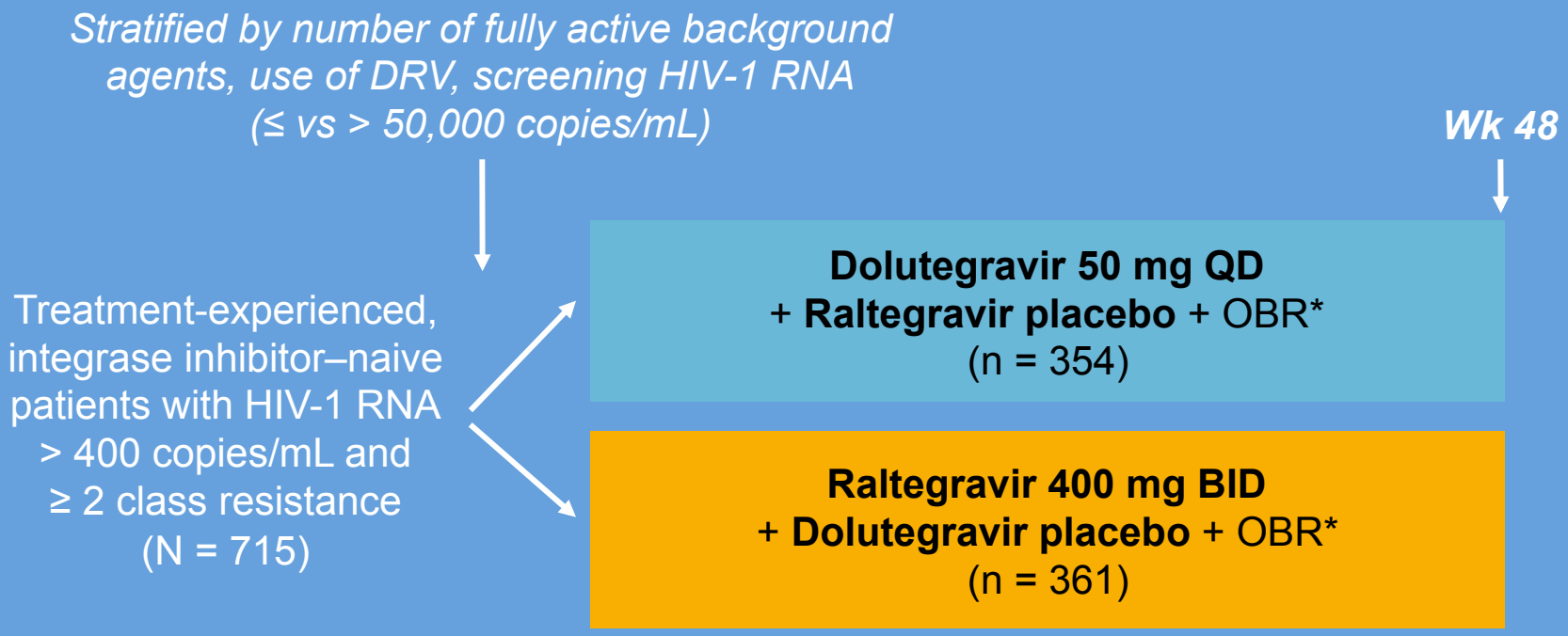
*VF includes never suppressed, rebound, switch of BR, and d/c due to lack of efficacy.
†Others include death, discontinuation due to AE, investigator's discretion, lost to follow-up, pregnancy, protocol violation, subject noncompliance, withdrawal of consent.

- Similar incidence of resistance at VF with EVG vs RAL
  - Integrase resistance: 6.6% vs 7.4%
  - OBR resistance: 7.4% vs 7.1%
- Both regimens well tolerated
  - Higher rates of diarrhea with EVG at Wks 48 and 96
  - Discontinuations: 3% vs 4%

Elion R, et al. J Acquir Immune Defic Syndr. 2013;63:494-497.

SAILING: Dolutegravir vs Raltegravir in ART-Exp'd, Integrase Inhibitor–Naive Pts

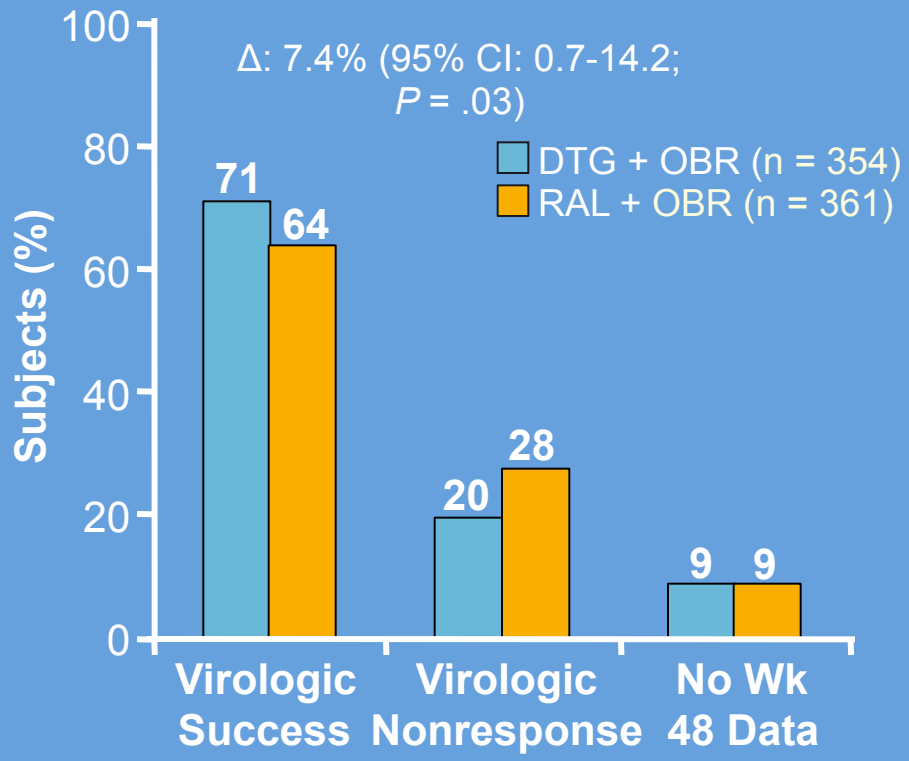
- Randomized, double-blind, noninferiority, phase III study



*OBR comprising at least 1 and no more than 2 active agents.

Cahn P, et al. Lancet. 2013;382:700-708.

SAILING: Superior Rate of Virologic Suppression With DTG vs RAL at Wk 48

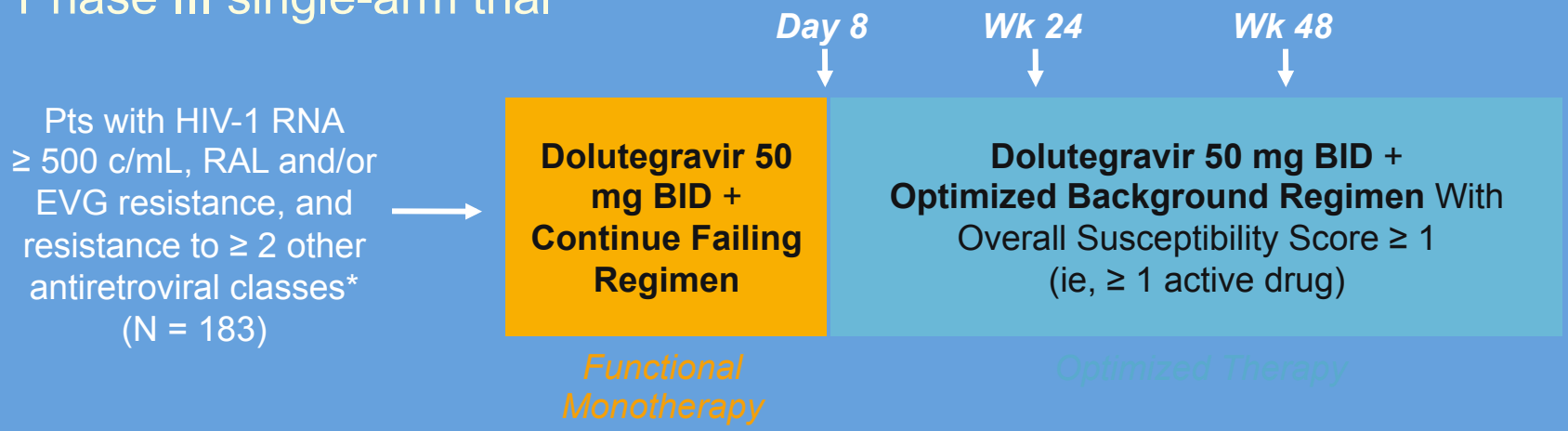


- Lower incidence of resistance at VF with DTG vs RAL
  - Integrase resistance: 1% (4/354) vs 5% (17/361); *P* = .003
  - OBR resistance: 1% (4/354) vs 3% (12/361)
- Both regimens well tolerated with similar AE profiles
  - Grades 2-4: 8% vs 9%
  - Discontinuations: 3% vs 4%
- No difference in outcome between study arms when combined with fully active DRV/RTV

Cahn P, et al. Lancet. 2013;382:700-708.

VIKING-3: Dolutegravir After Failure of Integrase Inhibitor–Based Regimen

- Phase III single-arm trial



- Mean HIV-1 RNA change from baseline to Day 8
  - Overall: -1.4 $\log_{10}$ copies/mL ($P < .001$)
  - No primary integrase resistance mutations at BL: -1.6 $\log_{10}$ copies/mL
  - Q148 + ≤ 1 secondary integrase resistance mutation: -1.1 $\log_{10}$ copies/mL
  - Q148 + ≥ 2 secondary integrase resistance mutations: -1.0 $\log_{10}$ copies/mL

*Detected at screening or based on historical evidence.

Nichols G, et al. Glasgow 2012. Abstract O232.

VIKING-3: Efficacy of DTG in INSTI-Experienced Pts at Wk 48

- 24-wk data on full cohort (N = 183) and 48-wk data on first 114 pts
- Response rates affected by baseline INSTI resistance but not overall susceptibility score of background regimen

Outcome, n (%)	Wk 24 (n = 183)	Wk 48 (n = 114)
HIV-1 RNA < 50 c/mL at Wk 24 (snapshot, ITT-E)	126 (69)	64 (56)
Virologic nonresponse	50 (27)	44 (39)
d/c due to AE or death	5 (3)	5 (4)

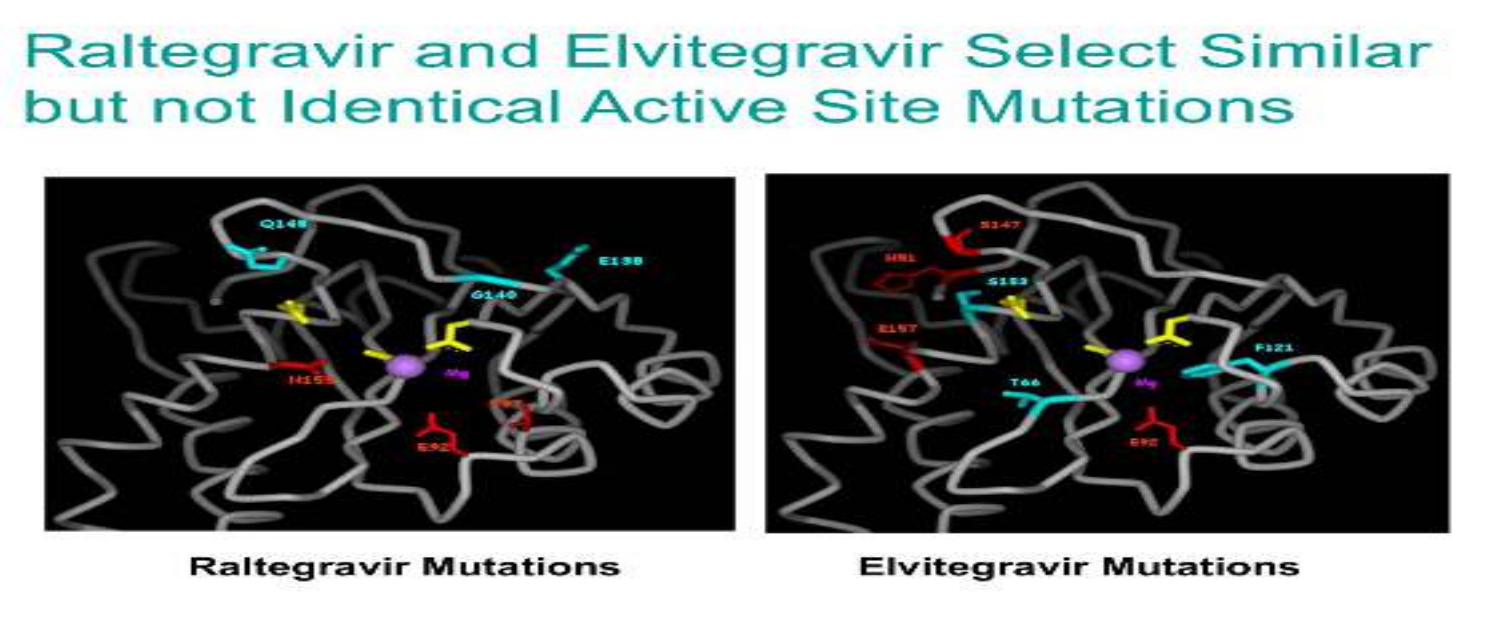
HIV-1 RNA < 50 c/mL at Wk 24 by INSTI Mutation(s), n/N (%)	Overall Susceptibility Score			
	0	1	≥ 2	Total
No Q148	4/4 (100)	35/40 (83)	57/70 (76)	96/114 (79)
Q148 + 1	2/2 (100)	8/12 (67)	10/17 (59)	20/31 (65)
Q148 + ≥ 2	1/2 (50)	2/11 (18)	1/3 (33)	4/16 (25)

Nichols G, et al. IAS 2013. Abstract TULBPE19.

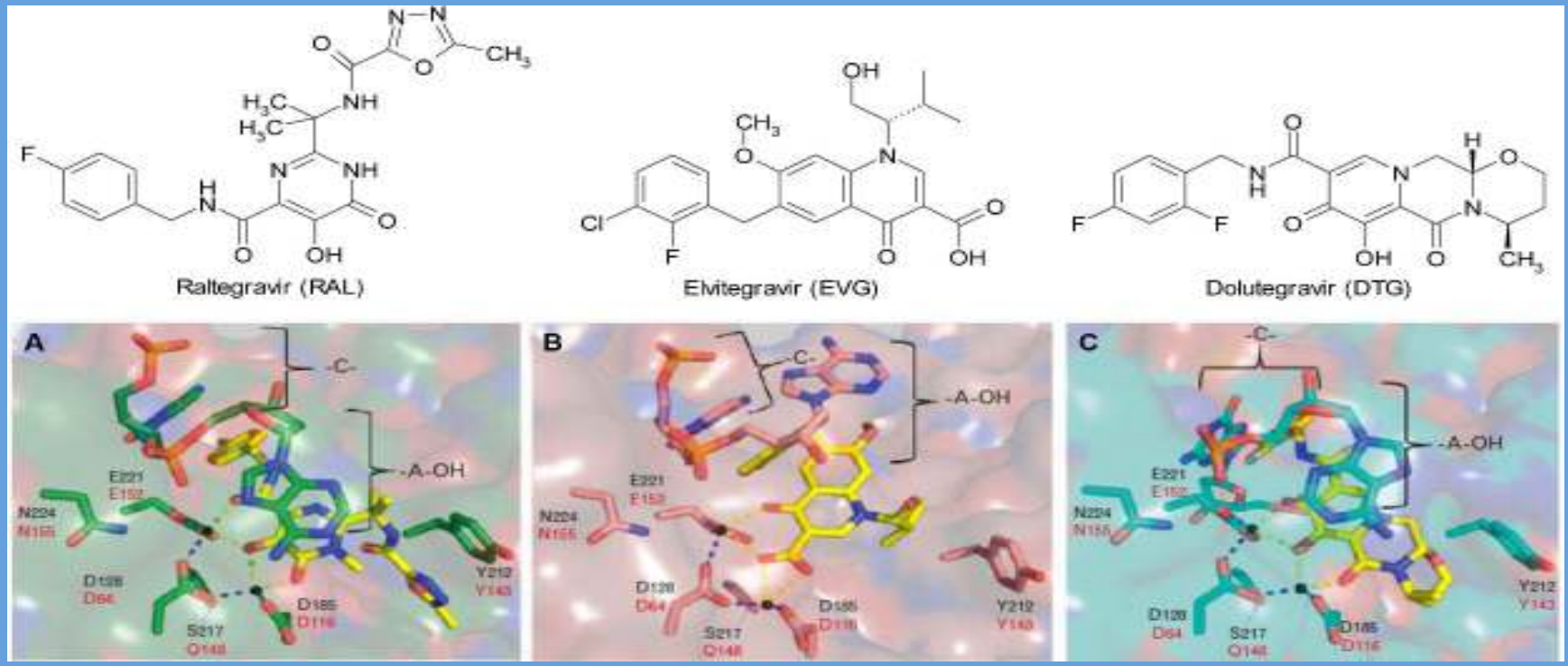
Integrase Inhibitors for Treatment-Experienced Patients: Conclusions

- INSTIs appropriate for many treatment-experienced pts
  - For INSTI-naive pts, all INSTIs should be active
    - DTG superior to RAL, EVG noninferior to RAL
  - For INSTI-experienced pts, DTG superior to RAL
    - Cross-resistance between EVG and RAL
- Difficult to use EVG due to current FDC-only regimen, lack of data combining FDC with other ARVs
- Much clinical experience with RAL as component of new regimens for pts with NRTI, NNRTI, PI experience
- DTG represents a new option for INSTI-experienced pts
  - BID dosing recommended for those with INSTI resistance

- RAL veya ETG kullanıldıktan sonra INSTI mutasyonları seçilmekte ve bu iki ajan arasında çapraz direnç olmaktadır

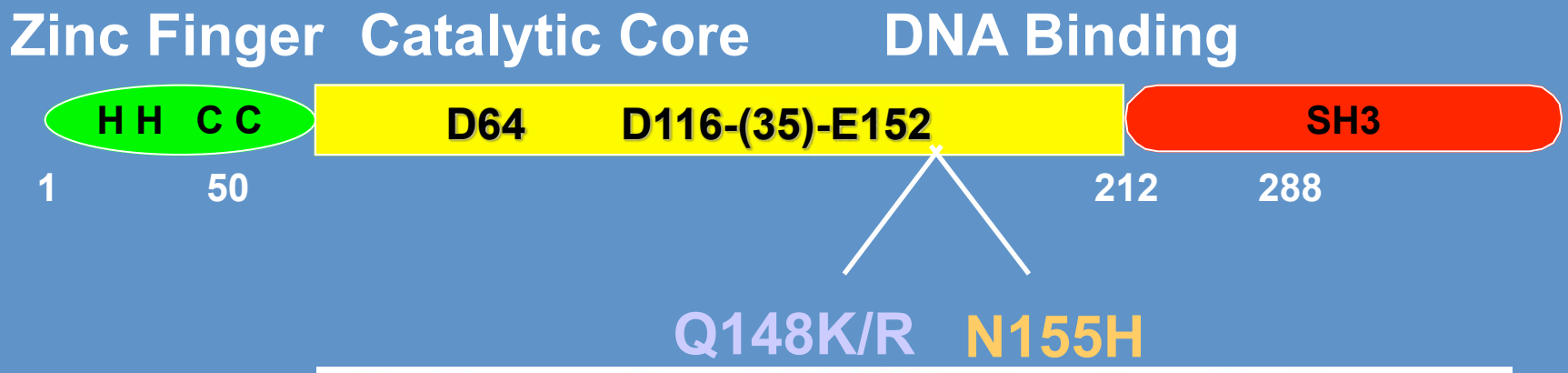


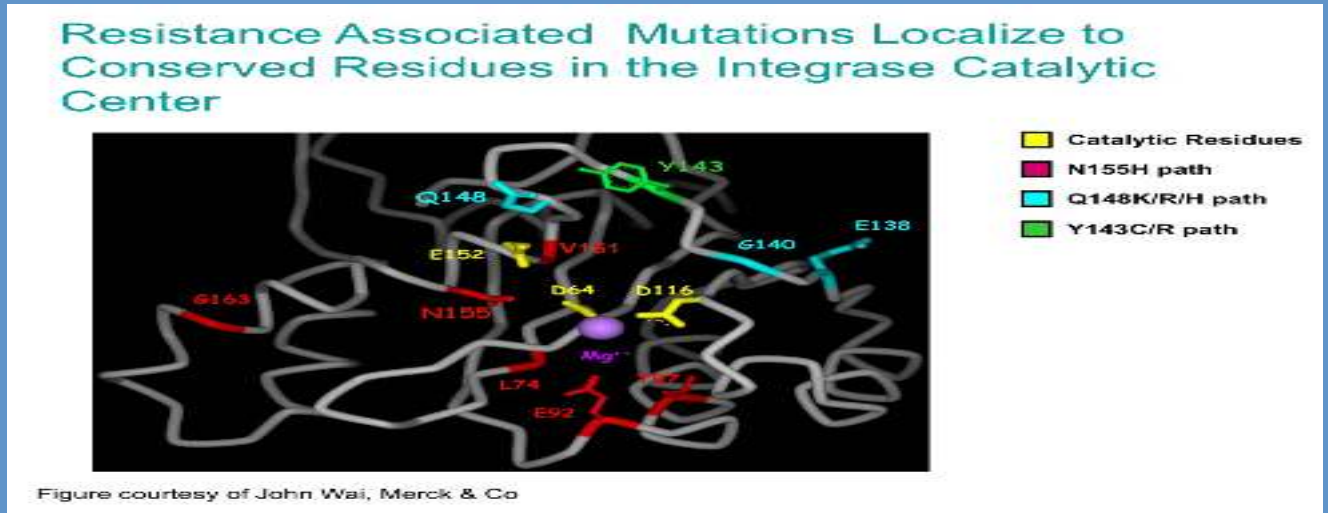
- RAL direnç bariyeri NNRTI'dan yüksek



- İntegraz inhibitörleri arasında çapraz direnç olduğu konusunda kanıtlar mevcut
- INSTI direnç gelişirse ajan stoplanmalı (yeni direnç mutasyonlarını önlemek için)

Resistance maps to the active site





Major Integrase Inhibitor (INI) Resistance Mutations

	66	92	138	140	143	147	148	155
Consensus	T	E	E	G	Y	S	Q	N
Raltegravir (RAL)	A	Q	KA	**SA**	**RCH**		**HRK**	**H**
Elvitegravir (EVG)	**IAK**	**Q**	KA	**SA**		**G**	**HRK**	**H**
Dolutegravir (DTG)		Q	KA	SA			HRK	

The table lists the most common clinically significant INI-resistance mutations. Mutations in bold red are associated with the highest levels of reduced susceptibility or virological response to the indicated INI. Mutations in bold reduce INI susceptibility or virological response. Mutations in plain text contribute to reduced suceptibility in combination with other INI-resistance mutations.

IN VITRO, MOST RAL- AND EVG-RESISTANT SINGLE MUTANTS ARE SUSCEPTIBLE TO DTG

	Mean FC Viruses	
	RAL	EVG	DTG
WT[1,2]	1	1	1
T66A[1,2]	0.26	0.61	4.1
T66I[1,2]	0.26	0.51	8.0
T66K[1,2]	2.3	9.6	84
E92I[1,2]	1.5	2.1	8.0
E92Q[1,2]	1.6	3.5	19
E92V[1,2]	1.3	1.4	8.3
G118S[1,2]	1.1	1.2	4.9
F121Y[1,2]	0.81	6.1	36
T124A[1,2]	0.95	0.82	1.2
E138K[1,2]	0.97	1	0.93
G140S[1,2]	0.86	1.1	2.7
Y143C[1,2]	0.95	3.2	1.5
Y143H[1,2]	0.89	1.8	1.5

	Mean FC Viruses	
	RAL	EVG	DTG
Y143R[1,2]	1.4	16	1.8
P145S[1,2]	0.49	0.87	>350
Q146R[1,2]	1.6	1.2	2.8
Q148H[1,2]	0.97	13	7.3
Q148K[1,2]	1.1	83	>1700
Q148R[1,2]	1.2	47	240
I151L[1,2]	3.6	8.4	29
S153F[1,2]	1.6	1.3	2.8
S153Y[1,2]	2.5	1.3	2.3
M154I[1,2]	0.93	0.82	1.1
N155H[1,2]	1.2	11	25
N155S[1,2]	1.4	6.2	68
N155T[1,2]	1.9	5.2	39
G193E[2]	1.3	1.3	1.3

3 ≤ FC < 5 5 ≤ FC < 10 10 ≤ FC

RAL and EVG-related single mutation SDMs (site directed mutants)

1. Adapted from Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21
2. Adapted from Seki T, et al. CROI 2010. Abstract 555

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI	ABC/3TC	• Co-formulated with DTG as an STR	• Inferior virologic responses in patients with baseline HIV RNA ≥100,000 copies/mL when given with EFV or ATV/r as compared with TDF/FTC in ACTG 5202 study. This difference was not seen when ABC/3TC was used in combination with DTG. • May cause life-threatening hypersensitivity reaction in patients positive for the HLA B*5701 allele. As a result, HLA-B*5701 testing required before use • ABC use has been associated with cardiac events in some but not all observational studies.
	TDF/FTC	• Co-formulated with EFV, EVG/c, and RPV as a STR • Active against HBV; recommended dual-NRTI for HIV/HBV co-infected patients • Better virologic responses than with ABC/3TC in patients with baseline viral load ≥100,000 copies/mL when combined with ATV/r or EFV	• Renal toxicity, including proximal tubulopathy and acute or chronic renal insufficiency • Decreases BMD more than other NRTI combinations
INSTI	DTG	• Once-daily dosing • May have higher barrier to resistance than EVG or RAL • Co-formulated with ABC and 3TC as an STR • No food requirement • No CYP3A4 interactions	• Oral absorption can be reduced by simultaneous administration with products containing polyvalent cations (e.g., Al, Ca, or Mg-containing antacids or supplements, or multivitamin tablets with minerals). See dosing recommendations in Table 19d. • Inhibits renal tubular secretion of Cr and can increase serum Cr, without affecting glomerular function • UGT substrate; potential for drug interactions (see Table 19d)
	EVG/c	• Co-formulated as a STR with TDF/FTC • Once daily dosing • Compared with ATV/r, causes smaller increases in total and LDL cholesterol	• EVG/c/TDF/FTC is only recommended for patients with baseline CrCl ≥70 mL/min; therapy should be discontinued if CrCl decreases to <50 mL/min. • COBI is a potent CYP3A4 inhibitor, which can result in significant interactions with CYP3A substrates. • Oral absorption of EVG can be reduced by simultaneous administration with antacids containing polyvalent cations, such as Al, Ca, or Mg (see dosing recommendations in Table 19d). • COBI inhibits active tubular secretion of Cr and can increase serum Cr, without affecting renal glomerular function. • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Food requirement
	RAL	• Compared to other INSTIs, has longest post marketing experience • No food requirement • No CYP3A4 interactions	• Twice-daily dosing • May have lower genetic barrier to resistance than boosted PI- or DTG-based regimens • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • Rare cases of severe hypersensitivity reactions (including SJS and TEN) have been reported. • Oral absorption of RAL can be significantly impaired by antacids containing Al or Mg; co-administration is not recommended (see dosing recommendations in Table 19d). • UGT substrate; potential for drug interactions (see Table 19d)

Teşekkür ederim