Deneyimli Hastada Tedavi Değişim Stratejileri

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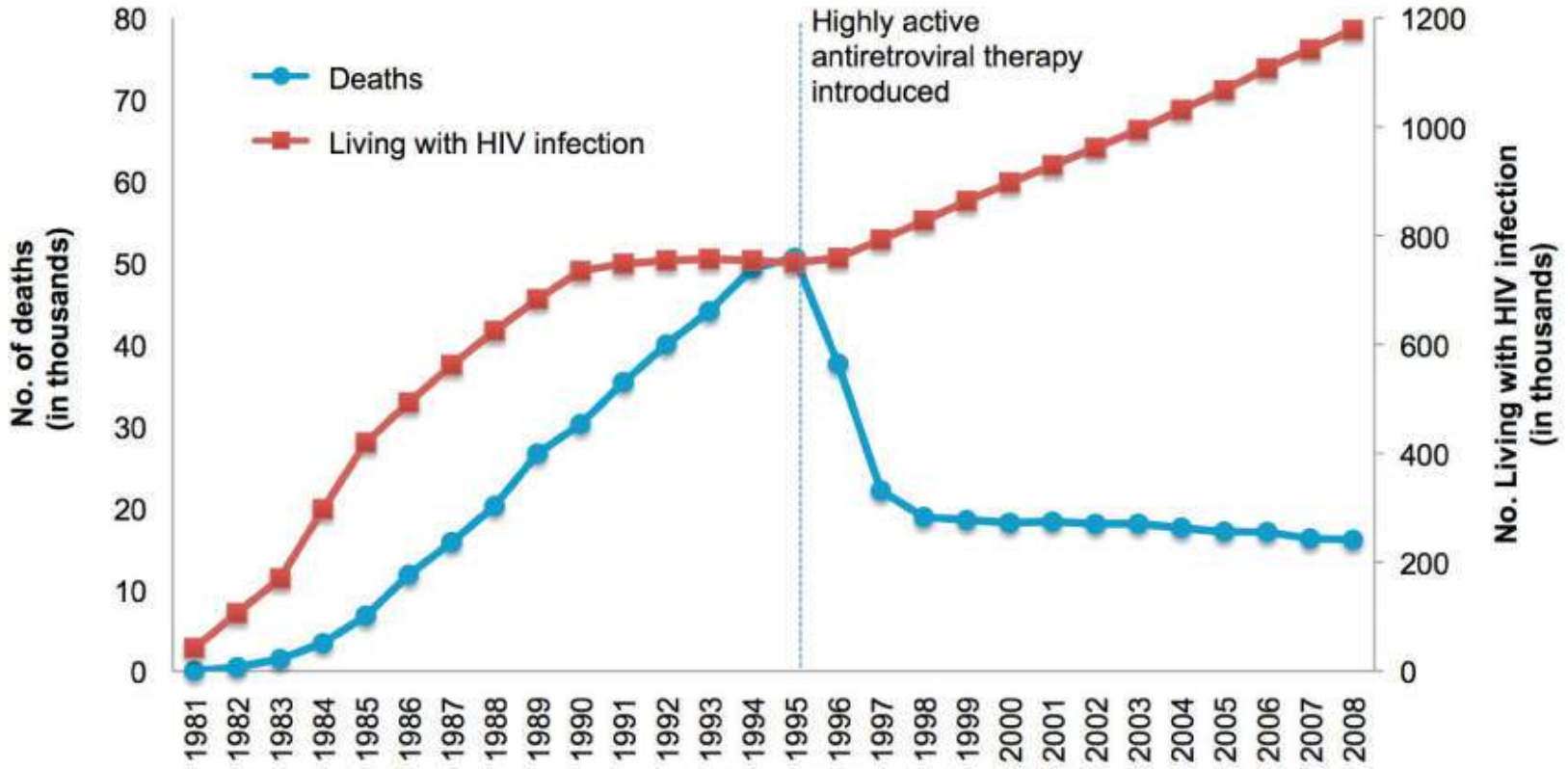
ART ve Mortalite



HIV: Bir başarının öyküsü

- Viral yükün süpresyonu: hastaların > %90
- İmmün restorasyon
- Daha iyi antiretroviral ilaçlar
- Tedavinin basitleştirilmesi
- Sağ kalım oranlarının artması
- Bulaşın azalması

Yeni tanı koyulmuş, 20 yaşındaki bir kişide yaşam beklentisi

1980'ler
Tedavi Yok

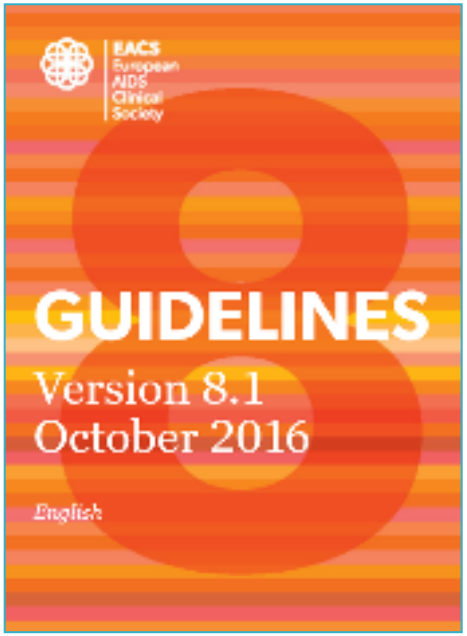
≈12 yıl

Bugün
Tedavi var

≈53 yıl

JL Marcus et al.JAIDS 2016

Rehberler eşliğinde tedavi değişimi



British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update)

AIDSinfo

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2016 Recommendations of the International Antiviral Society–USA Panel

Tedavi değiştirilme nedenleri

İki ana kategori:

1. HIV RNA düzeyinin baskılanmış olduğu hastalar

2. Virolojik Başarısızlık

ART Değişim Endikasyonları (Baskılanmış hastalarda)

Virolojik baskılanma: En az 6 ay süreyle viral yük <50 kopya/ml

- Değişim Endikasyonları:
  - Kanıtlanmış toksisite
  - Uzun dönem toksisitesinin önlenmesi
  - İlaç-ilaç etkileşimlerinden kaçınma
  - Planlanmış gebelik
  - Yaşlanma ve/veya komorbiditeler
  - Basitleştirme
  - Kişisel istek
  - Maliyeti azaltmak

İsviçre kohortu : ART değiştirilme nedenleri (2005-2008)

ART başlanan hastalar:
N=1318

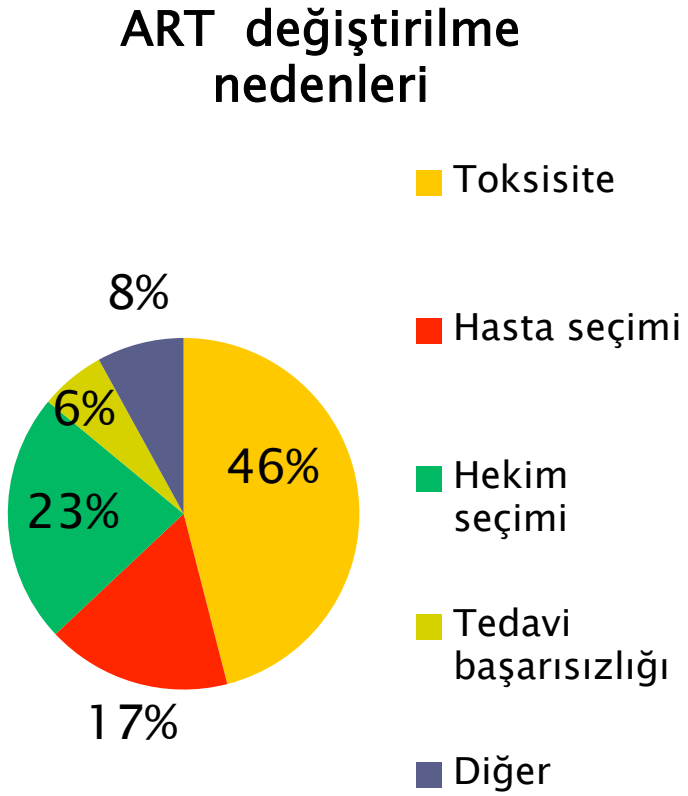
Bir yıl içinde tedavi değişikliği:
n=391 (%30)

Değişiklik:
n=297
(%76.0)

Tedavinin kesilmesi ≥4 hafta:
n=94
(%24.0)

En sık görülen toksisiteler:

- Gastrointestinal (%29)
- Hipersensitivite (%19)
- SSS yan etkileri (%17)
- Hepatotoksisite (%12)



Elzi, *et al. Arch Intern* 2010;**170**:57–65

Tedavi deneyimli hastalarda virolojik başarısızlık nedenleri

Hastaya Ait Nedenler	Tedaviye Bağlı Nedenler
Yüksek bazal HIV RNA	İlaçların istenmeyen etkileri
Düşük bazal CD4	Yetersiz farmakokinetik özellikler
Eskiden AIDS tanısı almış olmak	İlaç-gıda etkileşimleri
Uyuşturucu, depresyon	İlaç-ilaç etkileşimleri
Dirençli virüs ile enfekte olmak	Güçlü olmayan kombinasyon
Daha önce tedavi başarısızlığı	Yanlış reçeteleme
Yetersiz uyum/takip	

Olgu-1

Kanıtlanmış toksisite nedeniyle ART değişimi

Olgu-1

73 yaşında erkek hasta

Tanı:2009 yılında geçirdiği MI sırasında

Başlangıç değerleri (2010):

- CD4:218/mm3, HIV-RNA:179.000 kopya/ml
- HBsAg (+), Anti-HCV (-)
- HLA B*5701 (-)

Tanıdan itibaren TDF/FTC/EFV

- Tedavinin 6.yılında viral yük<20 kopya/ml, CD4:531
  - Tam Virolojik Yant

Olgu-1

Kullandığı ek ilaçlar:

- Sertralin
- Kandesartan/hidroklortiazid
- Metoprolol
- Tamsulosin
- Ketiapin
- Aspirin

Olgu-1

- Tedavinin 6.yılında ⟹ uykusuzluk ve özkıyım düşüncelerinin olduğu ifade etmektedir

Tedavi değişikliği ???

A. Evet
B. Hayır
C. Bilmiyorum

Hangi tedavi ???

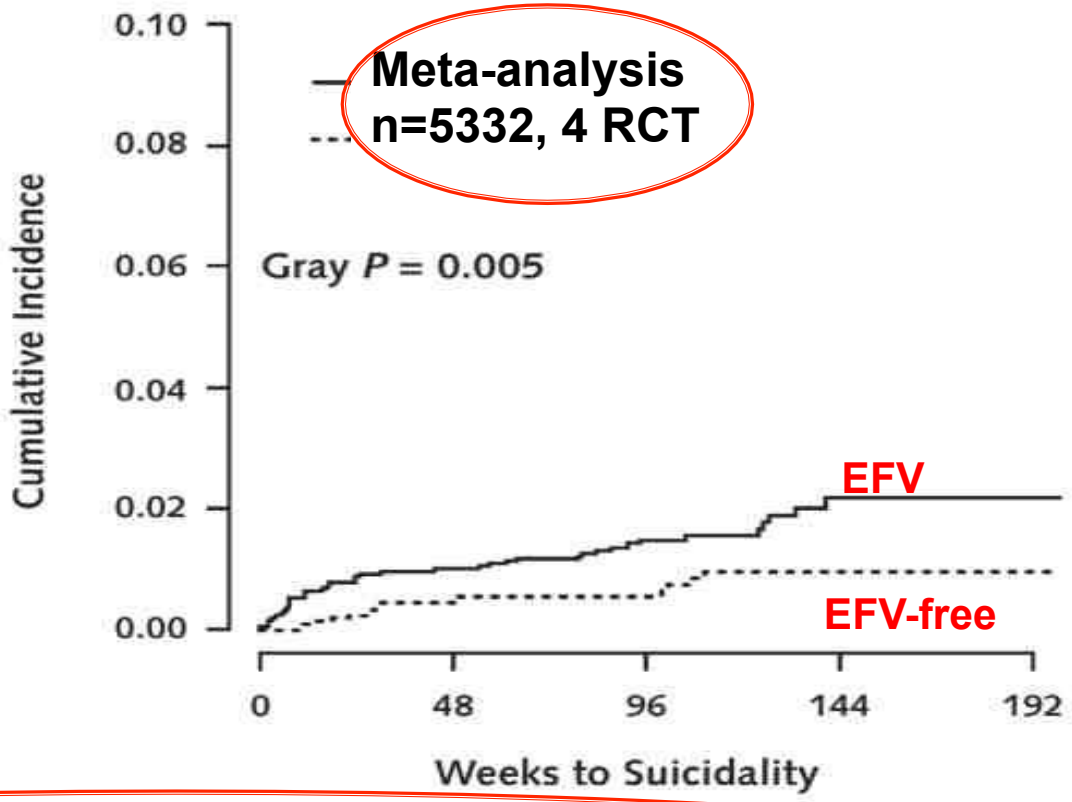
A. DTG/ABC/3TC
B. EVG/COBI/TDF/FTC
C. TDF/FTC + RPV
D. TDF/FTC + RAL
E. LPV/r + RAL
F. Diğer

SSS - Depresyon

- Efavirenz

özkıyım riski 2x

- Rilpivirine
- Elvitegravir/c
- Raltegravir
- Dolutegravir

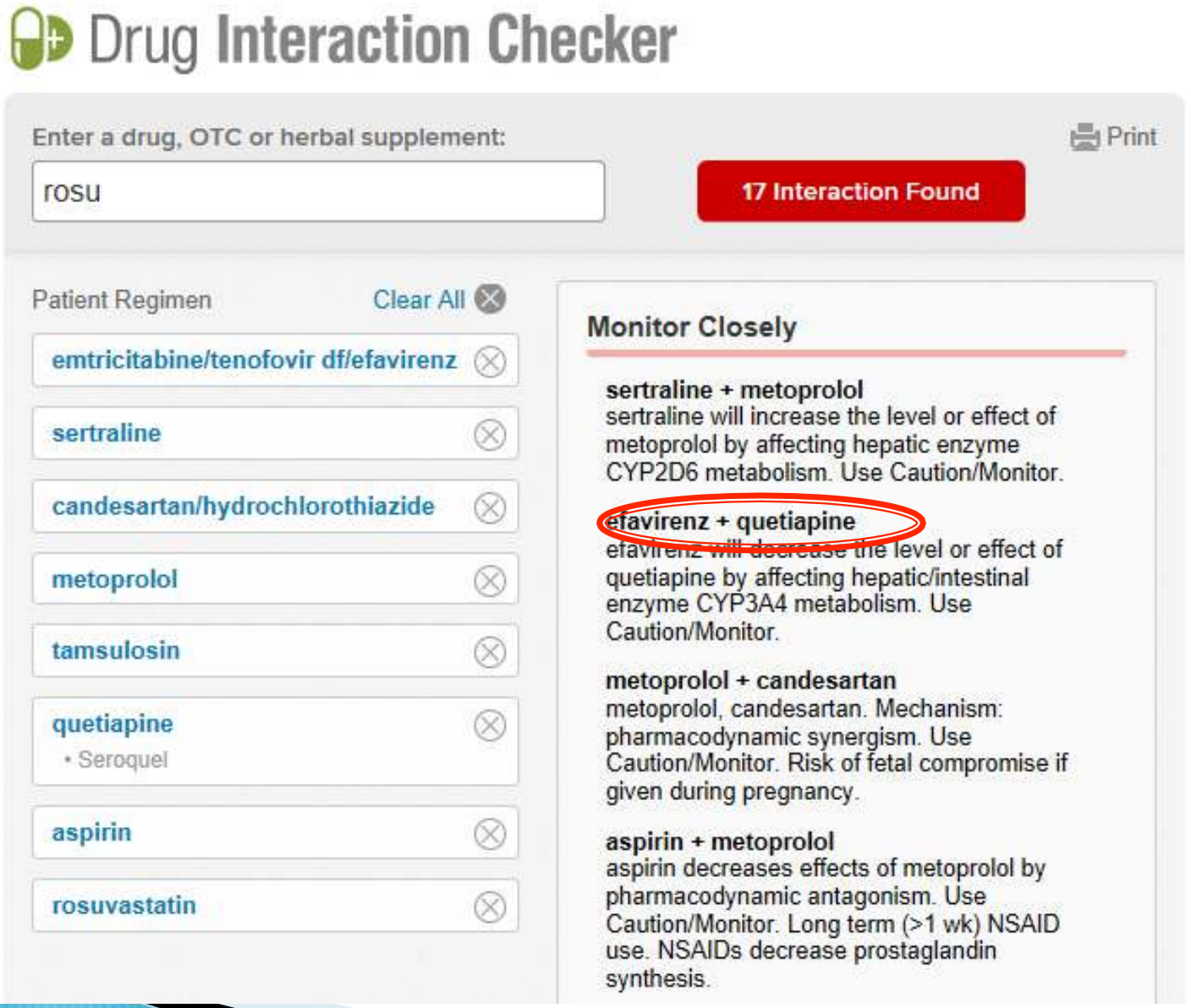


But Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study

C. Smith; L. Ryom; A. d' Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

Cohen et al., Lancet 2011; Mollan et al, Lancet 2011; Elion et al., JAIDS 2013; Mollan et al, Ann Intern Med 2014

Medscape Drug İnteractions



sertraline + aspirin
sertraline, aspirin. Either increases toxicity of the other by pharmacodynamic synergism. Use Caution/Monitor. Increased risk of upper GI bleeding. SSRIs inhib. serotonin uptake by platelets.

candesartan + aspirin
candesartan, aspirin. Either increases toxicity of the other by Other (see comment). Use Caution/Monitor. Comment: May result in renal function deterioration, particularly in elderly or volume depleted individuals.

efavirenz + tamsulosin
efavirenz increases levels of tamsulosin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Use Caution/Monitor. Dose reduction may be needed for coadministered drugs that are predominantly metabolized by CYP3A.

aspirin + candesartan
aspirin decreases effects of candesartan by pharmacodynamic antagonism. Modify Therapy/Monitor Closely. NSAIDs decrease synthesis of vasodilating renal prostaglandins, and thus affect fluid homeostasis and may diminish antihypertensive effect.

hydrochlorothiazide + metoprolol
hydrochlorothiazide, metoprolol. Either increases toxicity of the other by Other (see comment). Modify Therapy/Monitor Closely. Comment: May cause idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma, which can lead to permanent vision loss.

candesartan + aspirin
candesartan and aspirin both increase serum potassium. Use Caution/Monitor.

metoprolol + aspirin
metoprolol and aspirin both increase serum potassium. Use Caution/Monitor.

metoprolol + hydrochlorothiazide
metoprolol increases and hydrochlorothiazide decreases serum potassium. Effect of interaction is not clear, use caution. Use Caution/Monitor.

aspirin + hydrochlorothiazide
aspirin increases and hydrochlorothiazide decreases serum potassium. Effect of interaction is not clear, use caution. Use Caution/Monitor.

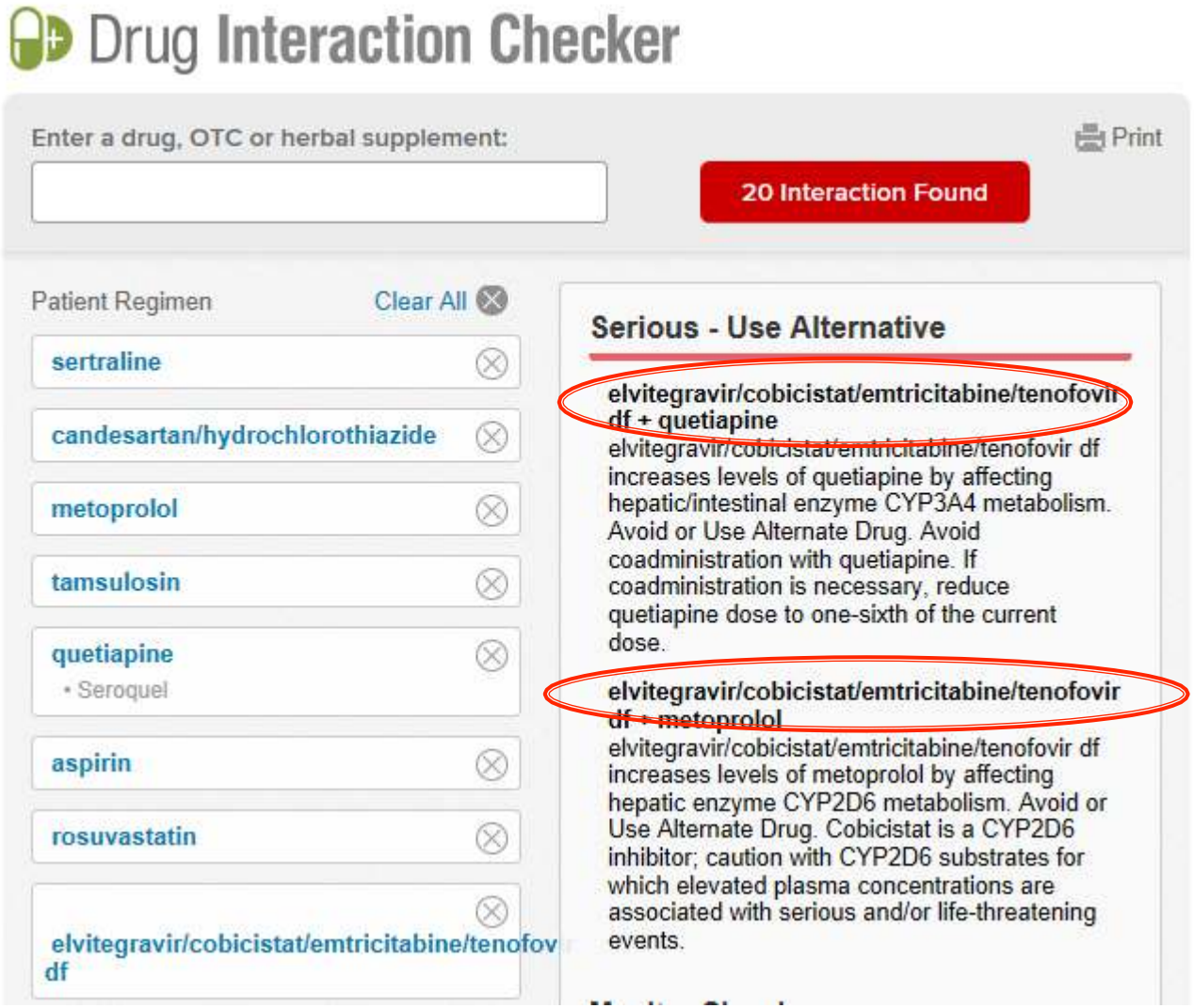
efavirenz + sertraline
efavirenz will decrease the level or effect of sertraline by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Use Caution/Monitor.

sertraline + tamsulosin
sertraline increases levels of tamsulosin by affecting hepatic enzyme CYP2D6 metabolism. Use Caution/Monitor.

Minor

hydrochlorothiazide + aspirin
hydrochlorothiazide will increase the level or effect of aspirin by acidic (anionic) drug competition for renal tubular clearance. Minor/Significance Unknown.

Medscape Drug İnteractions



Monitor Closely

sertraline + metoprolol
sertraline will increase the level or effect of metoprolol by affecting hepatic enzyme CYP2D6 metabolism. Use Caution/Monitor.

metoprolol + candesartan
metoprolol, candesartan. Mechanism: pharmacodynamic synergism. Use Caution/Monitor. Risk of fetal compromise if given during pregnancy.

aspirin + metoprolol
aspirin decreases effects of metoprolol by pharmacodynamic antagonism. Use Caution/Monitor. Long term (>1 wk) NSAID use. NSAIDs decrease prostaglandin synthesis.

sertraline + aspirin
sertraline, aspirin. Either increases toxicity of the other by pharmacodynamic synergism. Use Caution/Monitor. Increased risk of upper GI bleeding. SSRIs inhib. serotonin uptake by platelets.

candesartan + aspirin
candesartan, aspirin. Either increases toxicity of the other by Other (see comment). Use Caution/Monitor. Comment: May result in renal function deterioration, particularly in elderly or volume depleted individuals.

aspirin + candesartan
aspirin decreases effects of candesartan by pharmacodynamic antagonism. Modify Therapy/Monitor Closely. NSAIDs decrease synthesis of vasodilating renal prostaglandins, and thus affect fluid homeostasis and may

elvitegravir/cobicistat/emtricitabine/tenofovir df + tamsulosin
elvitegravir/cobicistat/emtricitabine/tenofovir df increases levels of tamsulosin by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Modify Therapy/Monitor Closely. Cobicistat is a CYP3A4 inhibitor; contraindicated with CYP3A4 substrates for which elevated plasma concentrations are associated with serious and/or life-threatening events.

elvitegravir/cobicistat/emtricitabine/tenofovir df + sertraline
elvitegravir/cobicistat/emtricitabine/tenofovir df increases levels of sertraline by affecting hepatic enzyme CYP2D6 metabolism. Modify Therapy/Monitor Closely. Cobicistat is a CYP2D6 inhibitor; caution with CYP2D6 substrates for which elevated plasma concentrations are associated with serious and/or life-threatening events.

elvitegravir/cobicistat/emtricitabine/tenofovir df + tamsulosin
elvitegravir/cobicistat/emtricitabine/tenofovir df increases levels of tamsulosin by affecting hepatic enzyme CYP2D6 metabolism. Modify Therapy/Monitor Closely. Cobicistat is a CYP2D6 inhibitor; caution with CYP2D6 substrates for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Minor

hydrochlorothiazide + aspirin
hydrochlorothiazide will increase the level or effect of aspirin by acidic (anionic) drug competition for renal tubular clearance. Minor/Significance Unknown.

elvitegravir/cobicistat/emtricitabine/tenofovir df + sertraline
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elvitegravir/cobicistat/emtricitabine/tenofovir df + tamsulosin
elvitegravir/cobicistat/emtricitabine/tenofovir df increases levels of tamsulosin by affecting hepatic enzyme CYP2D6 metabolism. Modify Therapy/Monitor Closely. Cobicistat is a CYP2D6 inhibitor; caution with CYP2D6 substrates for which elevated plasma concentrations are associated with serious and/or life-threatening events.

elvitegravir/cobicistat/emtricitabine/tenofovir df + aspirin
elvitegravir/cobicistat/emtricitabine/tenofovir df, aspirin. Either increases toxicity of the other by decreasing renal clearance. Modify Therapy/Monitor Closely. Toxicity may result from coadministration of emtricitabine and tenofovir with other drugs that are also primarily excreted by glomerular filtration and/or active tubular secretion including high-dose or multiple-dose NSAIDs; alternatives to NSAIDs should be considered.

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

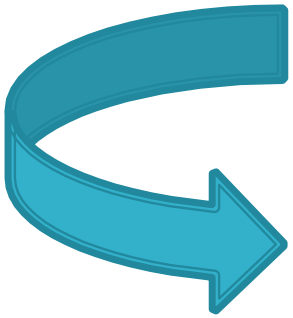
Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Results Key

	Elvitegravir/Cobi/FTC/TDF
Aspirin	
Candesartan	
Hydrochlorothiazide	
Metoprolol	
Quetiapine	
Sertraline	
Tamsulosin	

Olgu-1

- Metoprolol, sertralin ve ketiapin tedavileri kademeli olarak azaltarak kesildi



TDF/FTC+EFV ⇒ EVG/COBI/TDF/FTC

Bir ay sonra depresyon ve uykusuzluk şikayetleri kayboldu

Viral baskılanma devam etti. Stribild tedavisinin 19.ayında sağ MCA infarktı nedeniyle hasta kaybedildi.

Viral yükü baskılanmış hastalarda tedavi değişiklikleri: son çalışmalar

Çalışma	Bazal rejim	Değişiklik	Sonuç
GS-123	TDF/FTC + RAL	EVG/COBI/FTC/TDF	✔
GS-264	TDF/FTC/EFV	RPV/FTC/TDF	✔
Strategy-NNRTI	TDF/FTC + NNRTI	EVG/COBI/FTC/TDF	✔
Strategy-PI	TDF/FTC + PI/r	EVG/COBI/FTC/TDF	✔
SPIRIT	2 NRTI + PI/r	RPV/FTC/TDF	✔
SPIRAL	2 NRTI + PI/r	2 NRTI + RAL	✔
SALT	ATV/r + 2 NRTI	ATV/r + 3TC	✔
OLE	LPV/r + 2 NRTI	LPV/r + 3TC	✔
GS-109	TDF-bazlı ART	EVG/COBI/FTC/TAF	✔
STRIIVING	Baskılayıcı ART	DTG/ABC/3TC	✔
ATLAS-M	ATV/r + 2 NRTI	ATV/r + 3TC	✔
GS-119	“Kurtarma tedavisi”	EVG/COBI/FTC/TAF + DRV	✔
LATTE	CAB or EFV + 2 NRTI	CAB + RPV	✔
GS-1089	TDF/FTC + 3.ajan	TAF/FTC + 3.ajan	✔
SWITHCMRK	2 NRTI + LPV/r (Ted deneyimli)	2 NRTI + RAL	✗

SWITCHMRK: Önceki başarısızlık başarısızlığı öngörür

Inferior efficacy of RAL appeared driven by more failure among pts with previous virologic failure

Outcome	SWITCHMRK1		SWITCHMRK 2	
	RAL (n = 174)	LPV/r (n = 174)	RAL (n = 176)	LPV/r (n = 178)
Patients *without* previous virologic failure				
▪ VL < 50 at Wk 24, %	85.1	85.8	92.5	93.5
▪ Treatment difference, % (95% CI)	-0.7 (-9.9 to 8.6)		-1.0 (-8.5 to 6.3)	
Patients *with* previous virologic failure				
▪ VL < 50 at Wk 24, %	72.3	89.7	79.7	93.8
▪ Treatment difference, % (95% CI)	**-17.3 (-33.0 to -2.5)**		**-14.2 (-26.5 to -2.6)**	

Eron JJ, et al. *Lancet*. 2010;375:396-407.

Olgu-2

Komorbidite nedeniyle viral yükü baskılanmış olan hastada ART değişikliği

Olgu-2 (Kreatinin klirensi azalan olgu)

54 yaşında erkek hasta

5 yıldan beri TDF/FTC + LPV/r

Başlangıç değerleri

- CD4:180/mm3, HIV-RNA:220.000 kopya/ml
- HBsAg (-), Anti-Hbs (+), Anti-HCV (-)
- HLA B*5701 (-)
- Kreatinin:0.91 mg/dl

Tanıdan itibaren TDF/FTC/EFV

- Tedavinin 5.yılında viral yük<20 kopya/ml, CD4:480
  - Tam Virolojik Yant

Olgu-2

Kullandığı ek ilaçlar:

- Rosuvastatin (3 yıl)
- Sertralin
- Aspirin

Son durumu

- Kreatinin:1.8 mg/d,
- Fosfor:2.2 mg/dl
- eGFR: 42 ml/dk
- TİT: 2+ proteinüri
- 24 saatlik idrar: protein 1.2 gr

Kardiyak risk: ASCVD 10 yıllık skoru: %5.8

Tedavi değişikliği ???

A. Evet
B. Hayır
C. Bilmiyorum

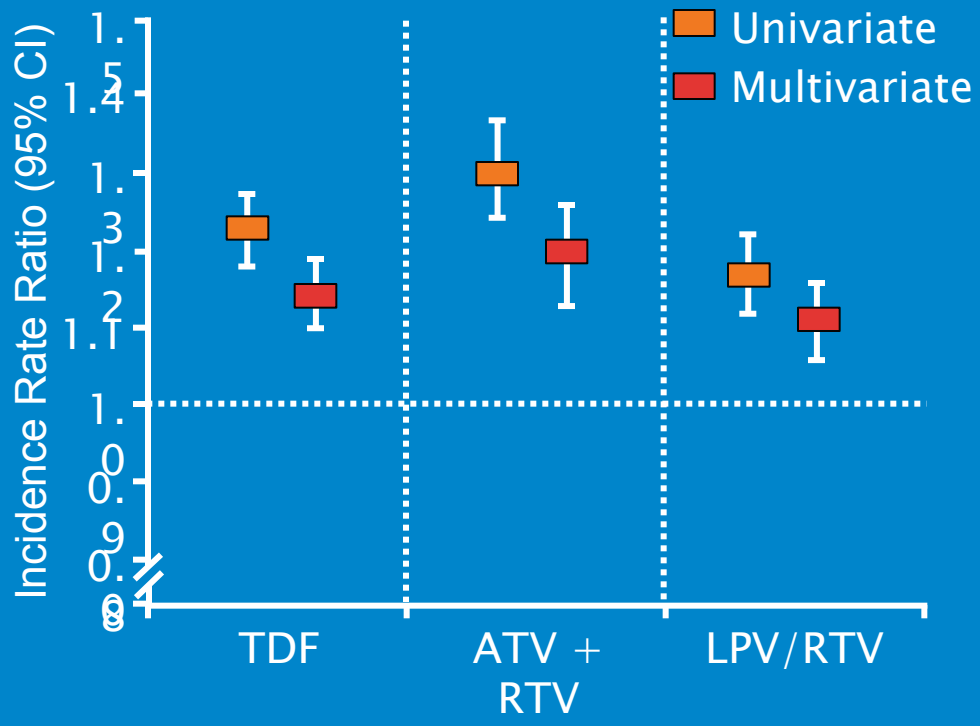
Hangi tedavi ???

A. Güçlendirilmiş PI + 3TC
B. DTG + 3TC
C. DTG veya RAL + Güçlendirilmiş DRV
D. DTG + RPV
E. DTG/ABC/3TC
F. Günaşırı TDF/FTC + üçüncü ajan (örn, güçlendirilmiş DRV, DTG, RAL, or RPV)
G. Diğer

D:A:D: Antiretroviral kümülatif maruziyeti sonucunda ⟹ KBY riski ⇧⇧⇧

CKD Risk by Yrs of ARV Exposure, Incidence Rate Ratio* (95% CI)		
Drug	**1 Yr**	**5 Yrs**
TDF	1.14 (1.10-1.19)	1.94 (1.57-2.39)
ATV + RTV	1.20 (1.13-1.26)	2.44 (1.86-3.21)
LPV/ RTV	1.11 (1.06-1.16)	1.66 (1.32-2.09)

*Multivariate analysis. For each value, $P < .0001$



	TDF	ATV + RTV	LPV/RTV
P value (univariate)	< .0001	< .0001	< .0001
P value (multivariate)	< .0001	< .0001	< .0001

Mocroft A, et al. Lancet HIV. 2016;3:e23–e32.

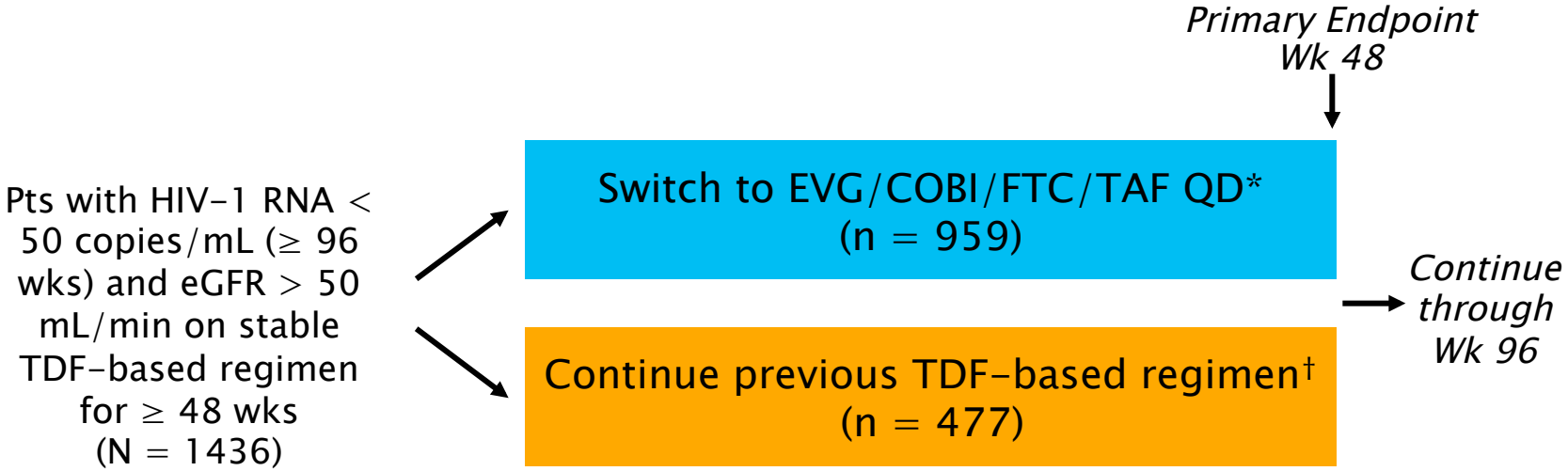
Tedavinin Basitleştirilmesi

Çalışma	N	Tedavi Değişimi	Sonuçlar
ASSURE[1]	296	ATV + ABC/3TC	Benzer etkinlik; idrar β_2-microglobulin/ kreatinin oranında düşüş
OLE[2]	250	LPV/RTV + 3TC or FTC	Benzer etkinlik
NA[3]	48	DRV/RTV + 3TC	Küçük çalışma; umut verici
ATLAS-M[4]	266	ATV/RTV + 3TC	3'lü rejime göre daha etkin
SALT[5]	286	ATV/RTV + 3TC	Benzer etkinlik
KITE[6]	60	LPV/RTV + RAL	Küçük çalışma; umut verici

1. Wohl DA, et al. HIV Med. 2016;17:106-117.
2. Arribas JR, et al. Lancet Infect Dis. 2015;15:785-792.
3. Casado JL, et al. J Antimicrob Chemother. 2015;70:630-632.
4. Di Giambenedetto S, et al. EACS 2015. Abstract 867.
5. Perez-Molina JA, et al. Lancet Infect Dis. 2015;15:775-784.
6. Ofotokun I, et al. AIDS Res Hum Retroviruses. 2012;28:1196-1206.

GS-109: TDF bazlı ➡ E/C/F/TAF

- Randomized, active-controlled, open-label study

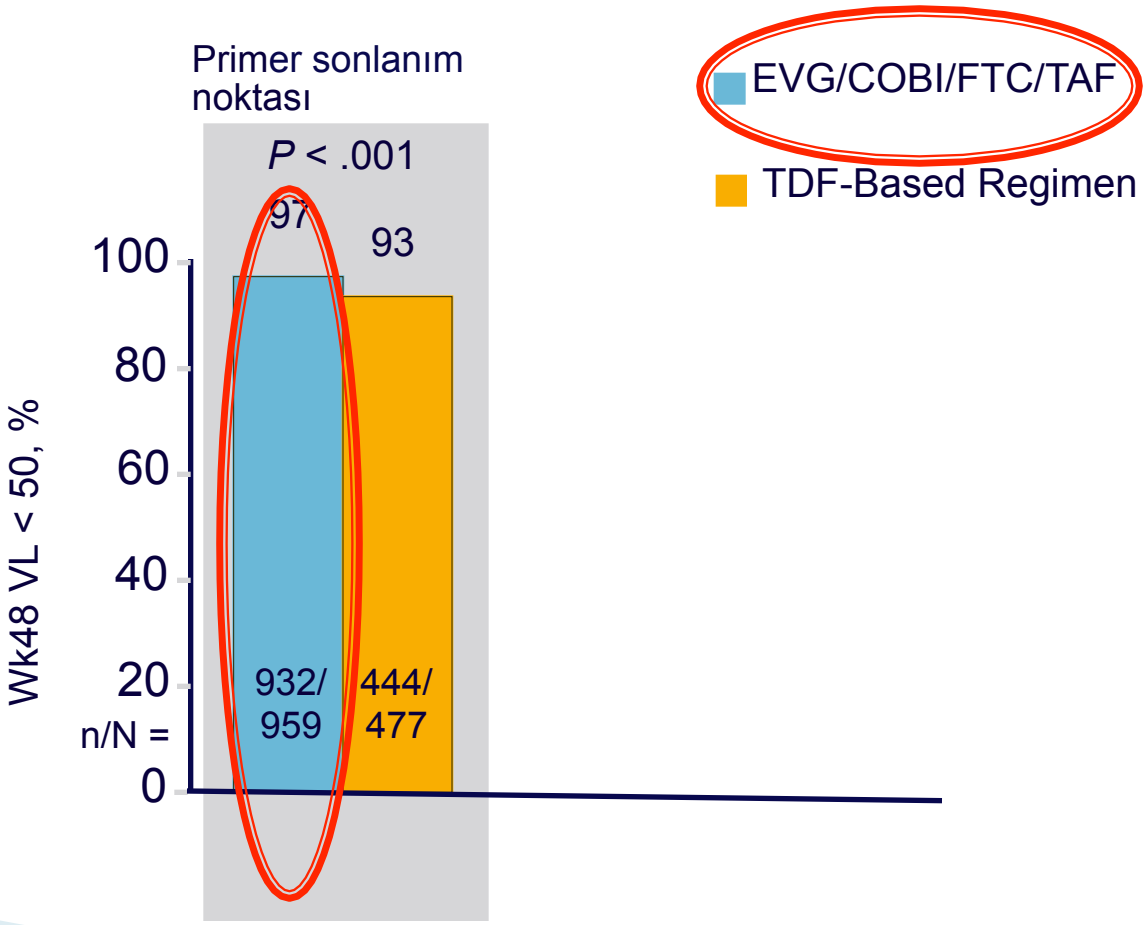


*EVG/COBI/FTC/TAF (150/150/200/10 mg). †Previous TDF-based regimens: EVG/COBI/FTC/TDF (n = 459), EFV/TDF/FTC (n = 376), ATV/(COBI or RTV) + TDF/FTC (n = 601).

- Primary endpoint: proportion of pts with HIV-1 RNA < 50 copies/mL after 48 wks of treatment

Mills A, et al. *Lancet Infect Dis* 2016;16:43-52

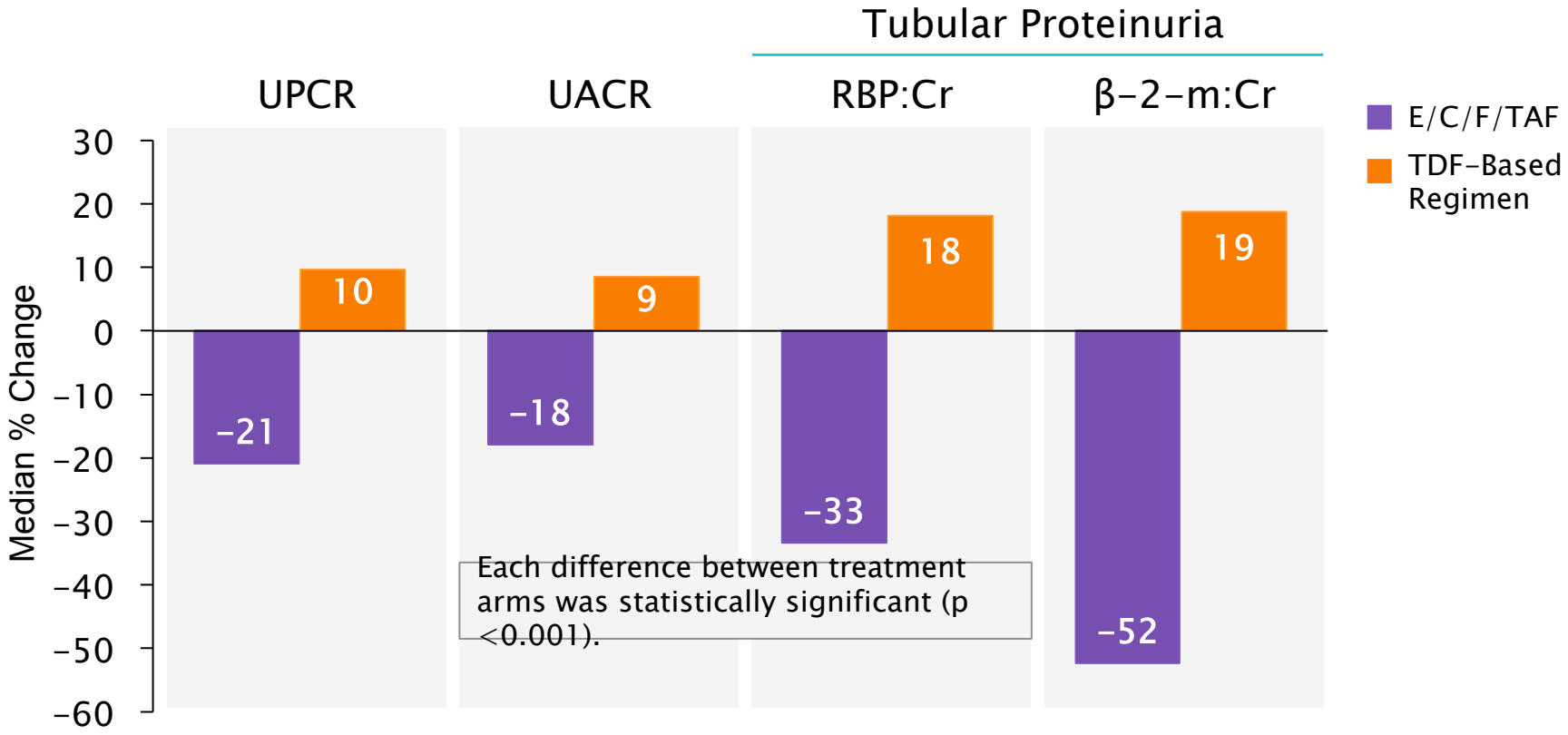
GS-109: TDF bazlı ➡ E/C/F/TAF



Mills A, et al. *Lancet Infect Dis* 2016;16:43-52

GS-109: TDF bazlı ⇒E/C/F/TAF

Böbrek Güvenliği Sonuçları

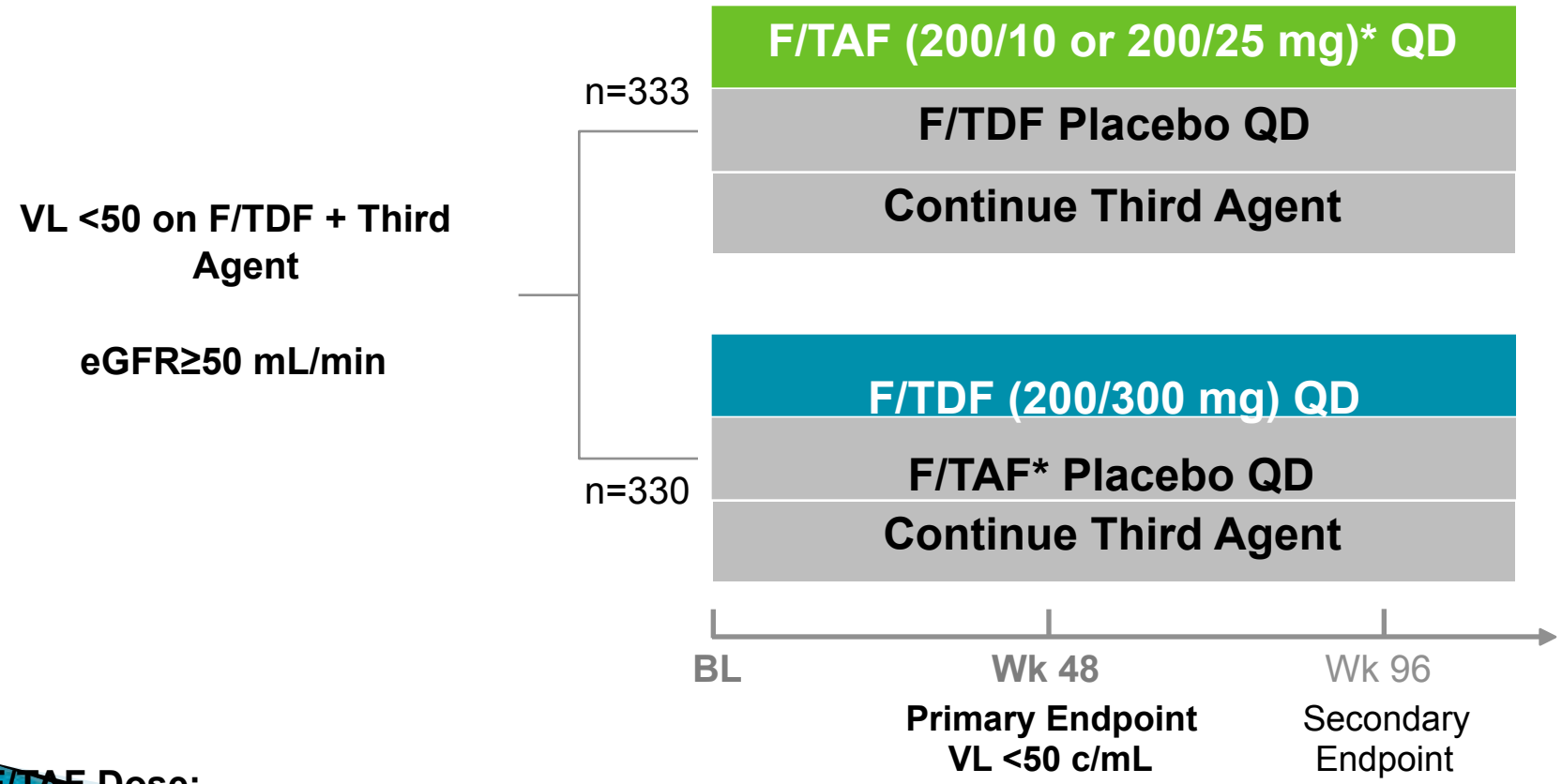


- Statistically significant improvements for participants who switched from either E/C/F/TDF or from boosted ATV + FTC/TDF
  - Serum creatinine (p <0.001); eGFR (p <0.001)
  - Fractional excretion of phosphate, FEPO4 (p=0.05); fractional excretion of uric acid, FEUA (p <0.001)
- Changes began by Week 2 and persisted to Week 48

UPCR; urine protein: creatinine ratio; UACR; urine albumin: creatinine ratio; RBP, retinol-binding protein; β-2-m:Cr , beta-2 microglobulin.

GS 1089: F/TDF ⇒ F/TAF

Randomized, double-blind, double-dummy, active-controlled study

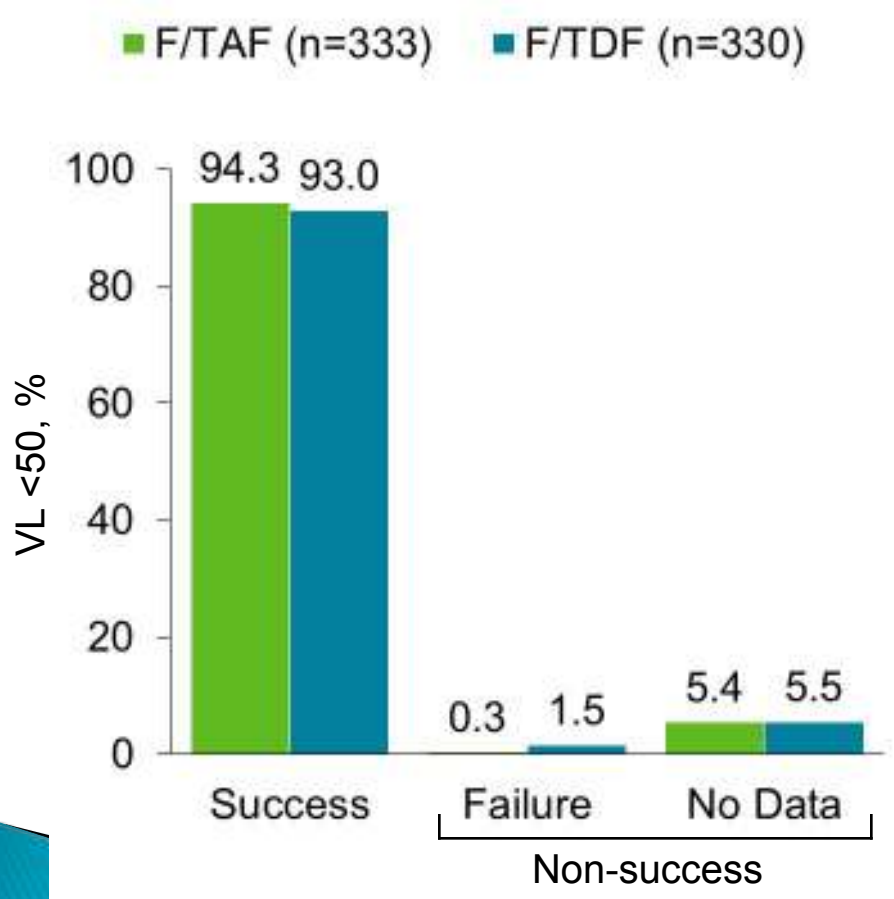


*F/TAF Dose:
- 200/10 mg with boosted PIs
- 200/25 mg with unboosted third agents

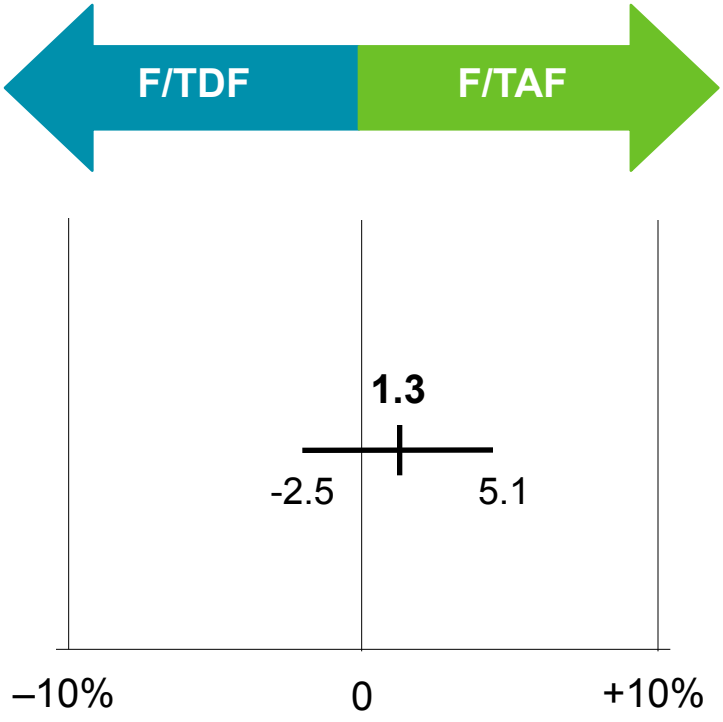
Gallant J, et al. *Lancet HIV* 2016;3:e158-65.

GS 1089: 48. Hafta Etkinliği

Virologic Outcome

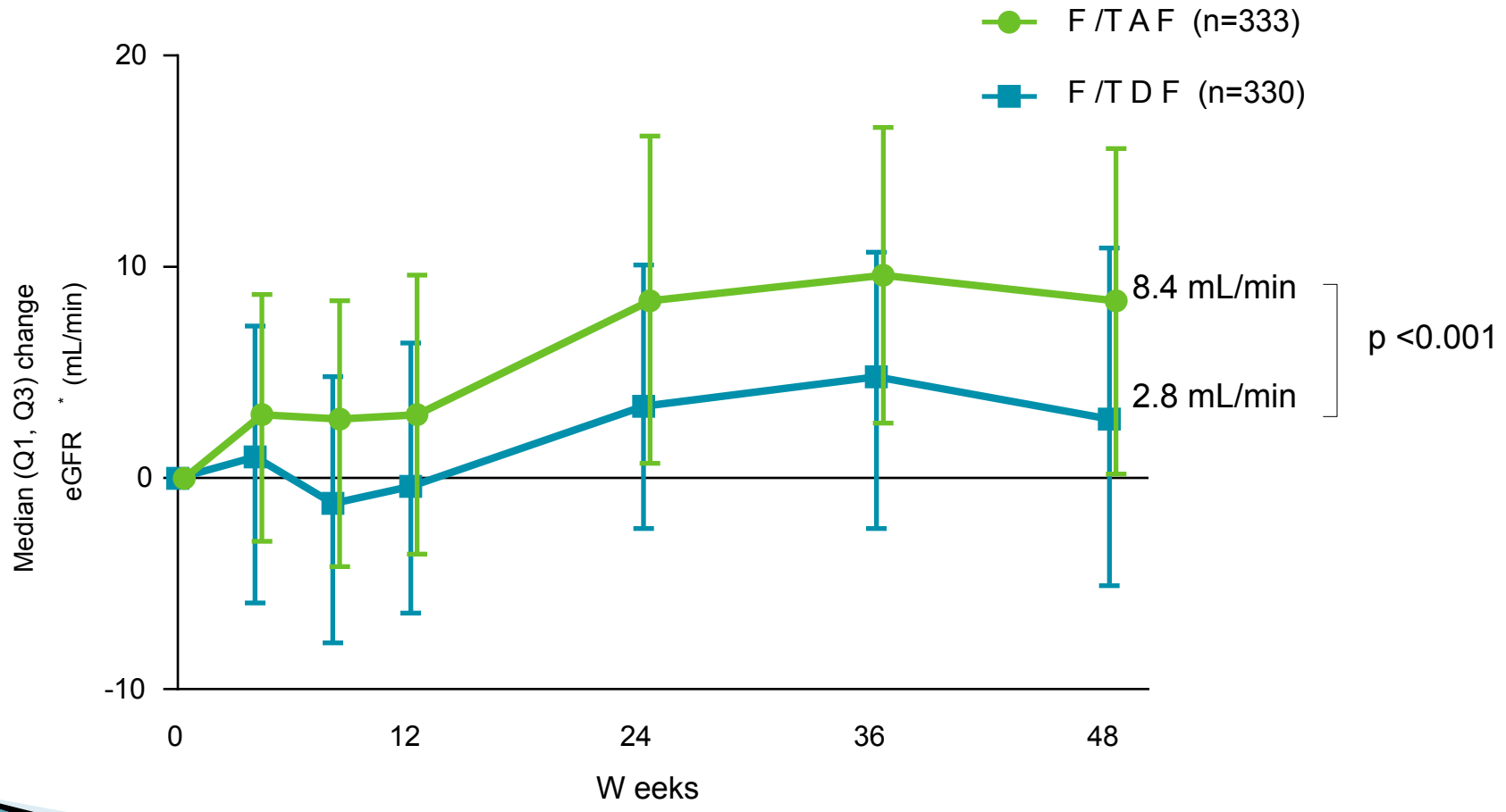


Treatment Difference (95% CI)



Gallant J, et al. *Lancet HIV* 2016;3:e158-65

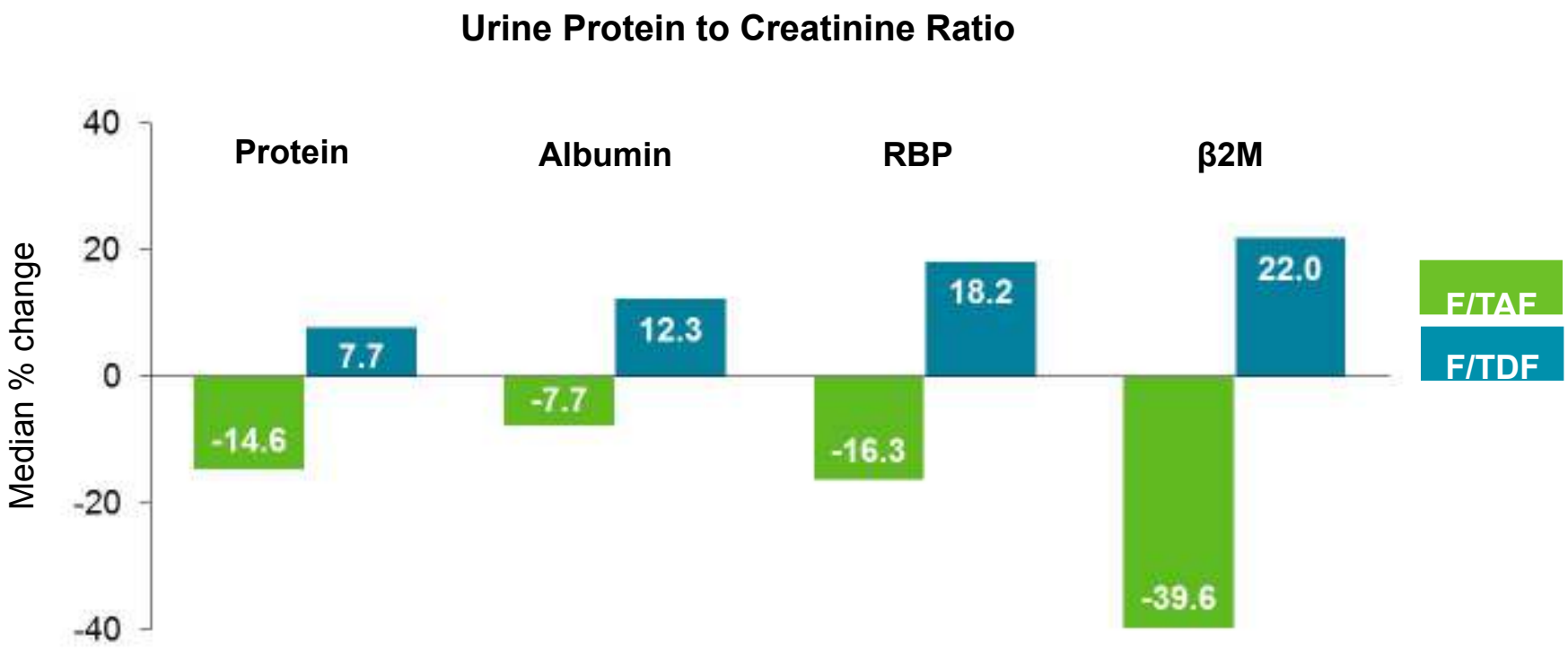
GS 1089: F/TDF ⇒ F/TAF
eGFR değişimi



*eGFR calculated with Cockcroft-Gault equation

Gallant J, et al. *Lancet HIV* 2016;3:e158-65

GS 1089: F/TDF ⇒ F/TAF
48. Hafta Böbrek Biyolojik Belirteç Değişikliği



All differences between treatments statistically significant (p <0.001)

RBP, retinol-binding protein; β2M, β2-microglobulin.

Gallant J, et al. *Lancet HIV* 2016;3:e158-65

Olgu-2

TDF/FTC + LPV/r → ABC/3TC/DTG
tedavi değişikliği yapıldı

- Tedavinin 6.ayında viral baskılanma devam etti

- Rosuvastatin tedavisi kesildi
- Kreatinin:1.02 mg/dl
- LDL-Kol:126 mg/dl

Olgu-3

Virolojik başarısızlık olan hastalarda tedavi değişimi

Olgu-3

32 yaşında transgender, İran uyruklu,mülteci

6 yıldan beri TDF/FTC/EFV (Tek tablet-jenerik)

Bir yıl önce Tahran'da bir hapishanede yaklaşık 3 ay kaldığı ve o sırada ilaçlarını kullanmadığı öğrenildi.

Son 6 ay tedavi rejimine tam uyum

Olgu-3

- Tetkikler
  - CD4:380, HIV RNA: 8.500 kopya/ml
  - Genotipik direnç testi: K103N ve M184V
  - Kreatinin: 1.21 mg/dl
  - eGFR: 59 ml/dk

Tedavi ???

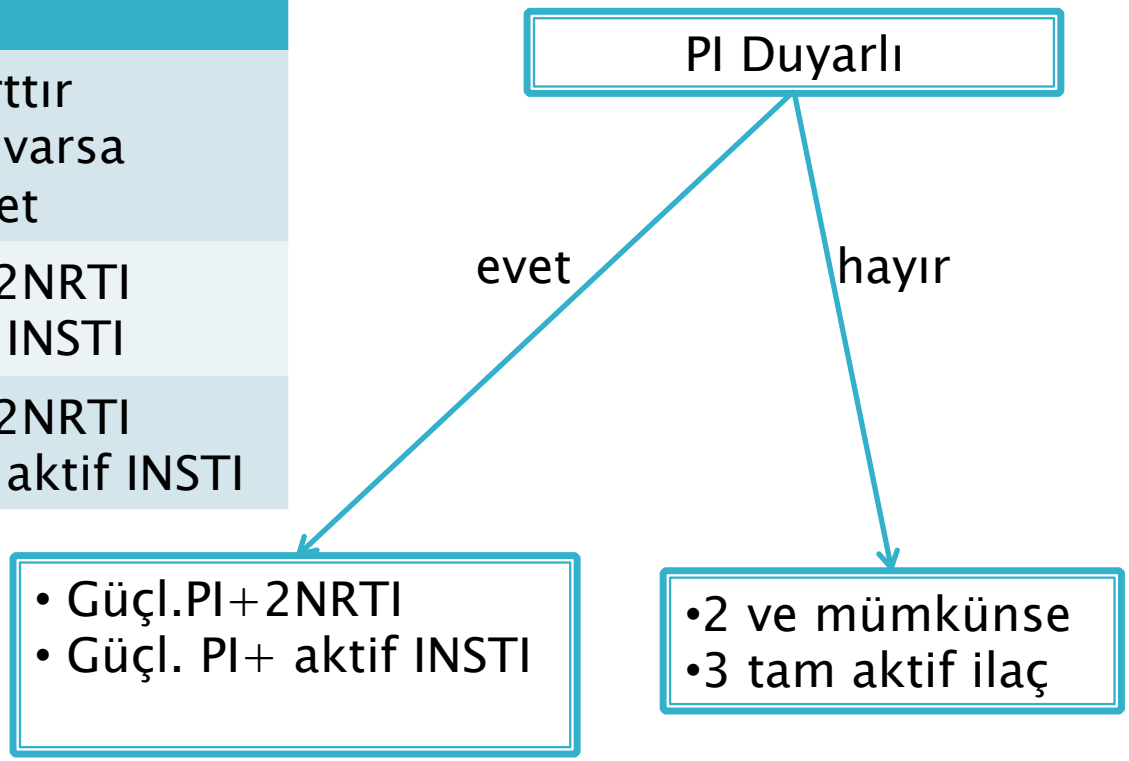
A. PI + 2 NRTI
B. INSTI + 2 NRTI
C. PI + INSTI
D. Diğer

Virolojik başarısızlık:Tedavi stratejileri

Birinci basamak tedavisi

İkinci basamak tedavisi

Başarısız Rejim (+NTRI)	
• Güçlendirilmiş PI	•Uyumu arttır •Toksisite varsa modifiye et
• NNRTI	• Güçl.PI+2NRTI • Güçl PI+ INSTI
• INSTI	• Güçl.PI+2NRTI • Güçl PI+ aktif INSTI



DHHS 2016

Olgu-3

- LPV/r+RAL tedavisi başlandı
- Tedavinin 12.haftasında HIV RNA: <20 kopya/ml
- Tedavinin 24.haftasında HIV RNA: <20 kopya/ml

''Çalışıyorsa, elleme kalsın''

ÖZET

- Tam virolojik yanıtı olan hastalar
  - Hedefler: tedavinin basitleştirilmesi, ilaç toleransının arttırılması, toksisitenin azaltılması, virolojik baskılanmanın sürdürülmesi
  - Kilit noktalar: tedavi hikayesi, direnç testleri, hasta uyumu ve takip
- Virolojik başarısızlığı olan hastalar
  - Uyum araştırılmalı
  - Direnç testi !!! (4 hf'dan fazla ilaç kullanmamış ise sonuç yanlış olabilir)
  - En az **2** tam etkili ilaç, mümkünse **3** (hastaların çoğunda birkaç opsiyon mevcut)
  - Tam virolojik yanıt hedeflenmeli

HCV

HIV

HBV

Teşekkürler....