HIV Güncelleme 2010

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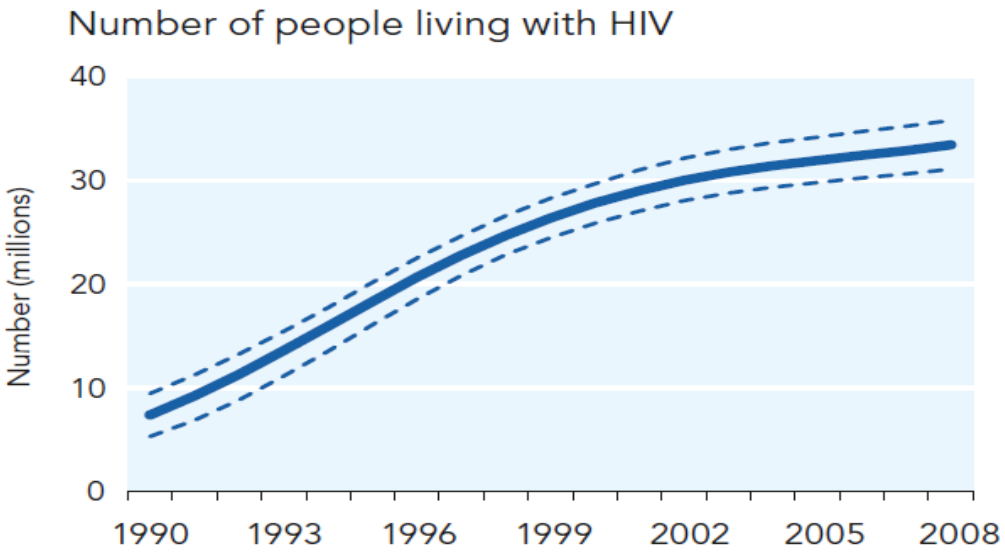
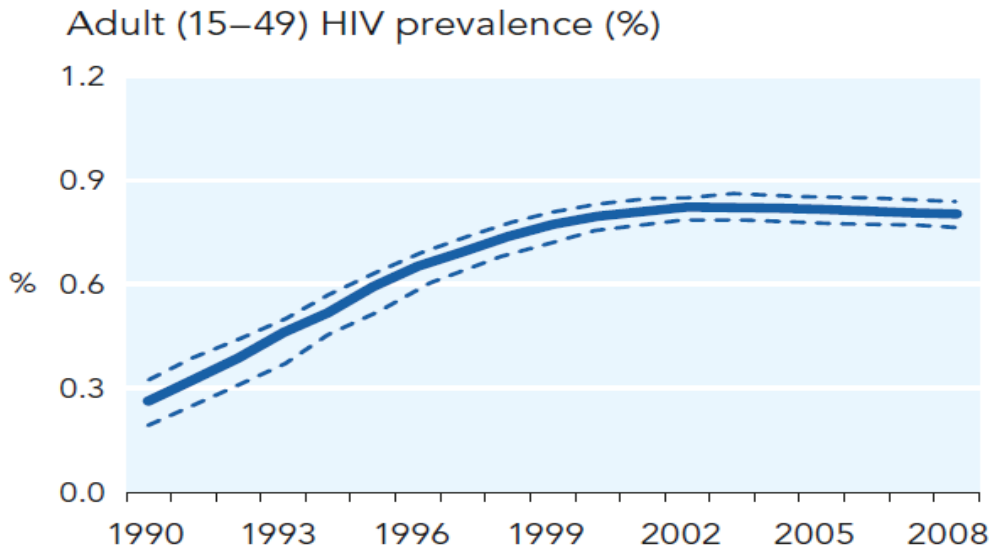
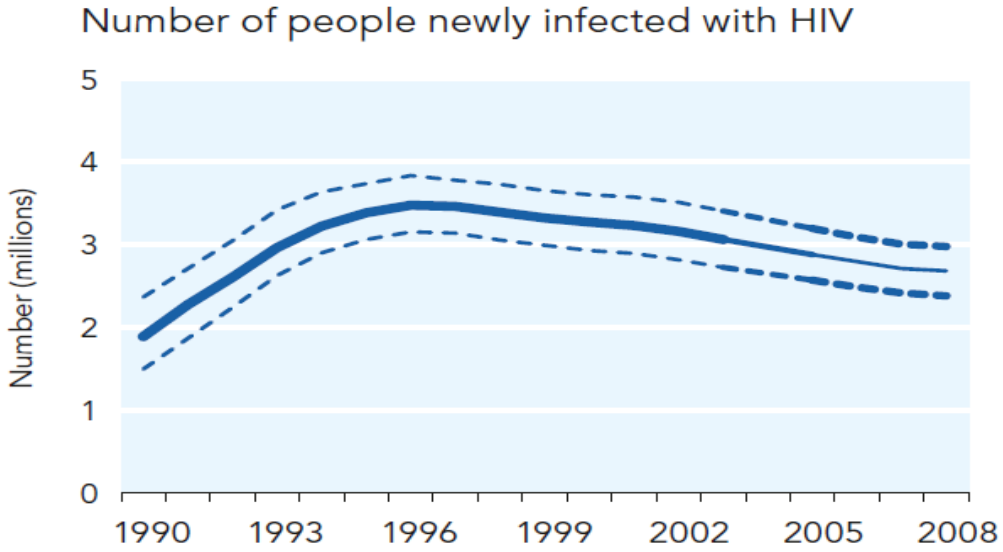
Istanbul

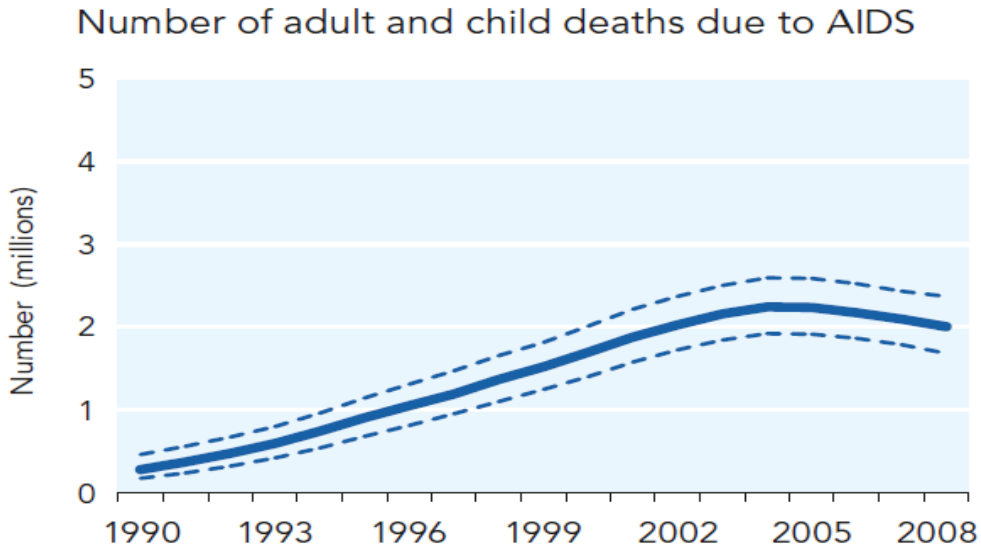
Global estimates 1990–2008





Estimate
High and low estimates





HIV klinik güncelleme

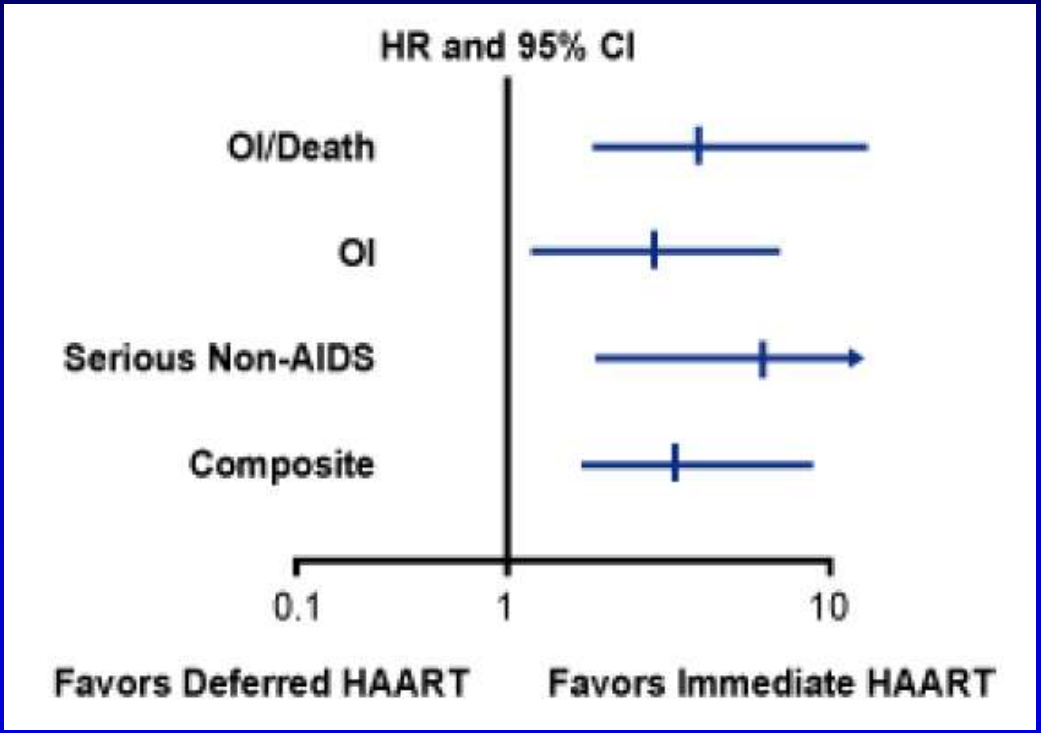
- ART'nin daha erken başlanması
- Integraz inhibitörleri – başlangıç tedavisinde
- Tedavi rehberlerinde tercih edilen ilaçlarda değişiklikler
- Farmakolojik güçlendiriciler – yeni jenerasyon
- Test ve tedavi et stratejileri - küresel HIV tedavisi
- HIV aşıları
- Yaşam beklentisi

Erken ART başlama

Ne zaman başlamalı kararını etkileyen çalışmalar (1)

SMART çalışması[1]

- CD4+ > 350/mm^3 düzeyinde ART başlayan ve bu düzeyde kalanlarda, hem fırsatçı hastalık hem de ciddi AIDS dışı olaylarda risk azalması



1.Emery S, et al. J Infect Dis. 2008;197:1133-1144.

Ne zaman başlamalı kararını etkileyen çalışmalar (2)

- ART-CC[2]
  - ART başlangıcı CD4+ > 350 h/mm^3 olanlarda ≤ 350 h/mm^3' e göre daha az AIDS ve ölüm riski
- NA-ACCORD[3]
  - Erken ART başlayanlarda Geç'e göre sağkalım yararı
    - Ölüm riski % 69 fazla (CD4 ≤ 350 h/mm^3 vs 351-500 h/mm^3)
    - Ölüm riski % 94 fazla (CD4 ≤ 500 h/mm^3 vs > 500 h/mm^3)

2. When to Start Consortium. Lancet. 2009;373:1352-1363.
3. Kitahata MM, et al. N Engl J Med. 2009;360:1815-1826

Erken Antiretroviral Tedaviyi Destekleyen Yeni Çalışmalar

- Düşük CD4+ seviyesi ile birlikte
  - HIV ile ilişkili nörokognitif bozukluk oranlarında artma[1]
  - Kardiyovasküler risk'e katkıda bulunan arteriyal sertlik[2]
  - Artmış kırık riski[3]
- Akut OI'lu hastalar
  - 2-misli yüksek klinik ilerleme riski (geç tedavi başlayanlarda derhal tedavi başlayanlara göre)[4]
  - Akut OI esnasında derhal HAART başlayanlarda geç başlayanlara göre daha iyi immunolojik sonuçlar[5]

1. Ellis R, et al. CROI 2010. Abstract 429. 2. Ho J, et al. CROI 2010. Abstract 707. 3. Dao C, et al. CROI 2010. Abstract 128. 4. Miro J, et al. CROI 2010. Abstract 529. 5. Sanchez A, et al. CROI 2010. Abstract 509.

ARV başlayan serolojileri farklı heteroseksüel çiftlerde HIV bulaş riski

- Afrikalı serolojileri farklı çiftlerde, HIV ile infekte partner ARV alıyor ise % 92 düşük HIV bulaş riski
  - 3381 çift
  - 103 yeni infeksiyonlu kişide gelişen infeksiyon genetik olarak primer partnerle ilişkili,
  - 103 vakanın 102'si, HIV ile infekte partner ARV almıyor ise oluşmuş durumda

Donnell D, et al. CROI 2010. Abstract 136.

Ne zaman başlamalı: 2009 DHHS Rehberi

CD4+ Hücre Sayısı	Öneriler
▪ CD4+ hücre sayısı < 350 h/mm³	▪ ART başla
▪ CD4+ hücre sayısı 350-500 h/mm³	▪ ART başla (55% güçlü öneriyor - 45% orta düzeyde öneriyor)
▪ CD4+ hücre sayısı > 500 h/mm³	▪ Panel bölünmüş durumda (50% tedavi başlama yanlısı)
CD4+ Hücre Sayısına Bakılmaksızın Tedavi Başlanması Ağır Basan Klinik Durumlar	
▪ AIDS-belirleyici hastalık öyküsü ▪ Bazı akut fırsatçı infeksiyonlar ▪ Gebelik ▪ HIVAN ▪ HBV koinfeksiyonu (HBV tedavi endikasyonu varsa) ▪ CD4+ hücre azalması > 100 h/mm³ / yıl ▪ HIV-1 RNA > 100,000 kopya/mL	

DHHS: http://aidsinfo.nih.gov/Guidelines.

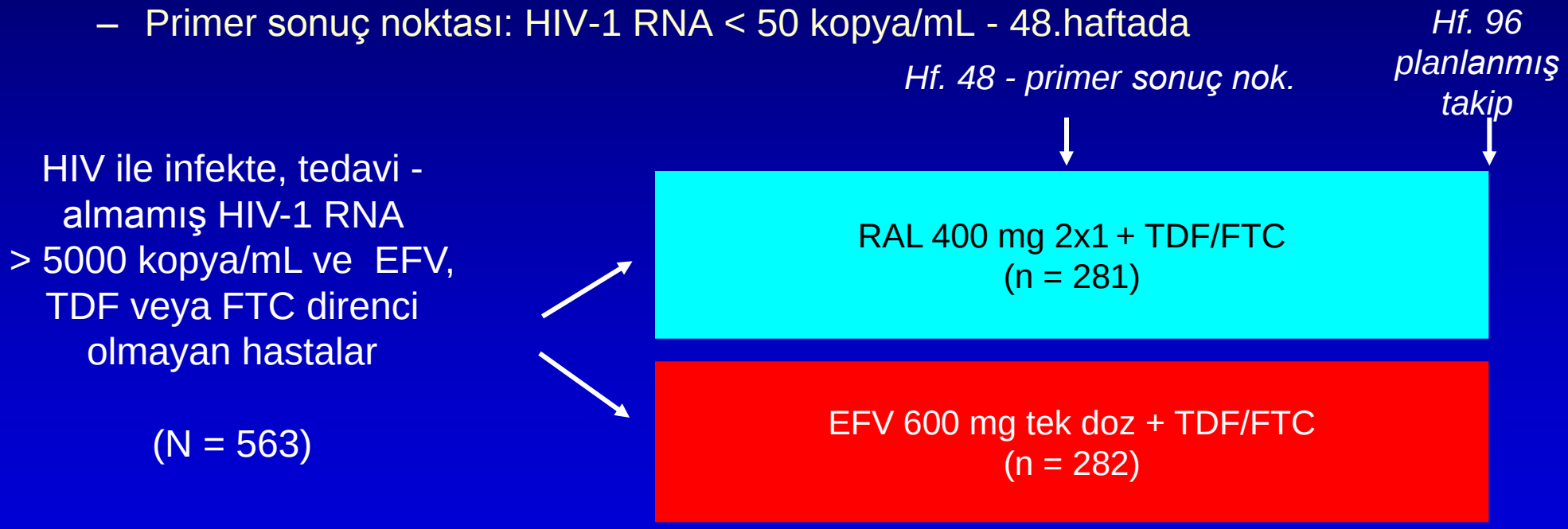
EACS

SYMPTOMATIC	• CDC stage B and C: treatment recommended • If OI, initiate as soon as possible*
ASYMPTOMATIC	• CD4 < 200: Treatment recommended, without delay. • CD4 201-350: treatment recommended. • CD4 350-500: - Treatment recommended if hepatitis C co-infection, hepatitis B co-infection requiring therapy, HIV-associated nephropathy or other specific organ deficiency; - Treatment should be considered if VL>10^5 c/ml and/or CD4 decline >50-100/mm^3/year or age >50 or, pregnancy, high cardiovascular risk, malignancy. • CD4 > 500: - Treatment should generally be deferred, independently of plasma HIV RNA; closer follow-up of CD4 if VL > 10^5 c/ml. - Treatment can be offered if presence of ≥ 1 of the above co-morbid conditions (CD4 350-500). • Whatever CD4 and Plasma HIV RNA, treatment can be offered on an individual basis, especially if patient is seeking and ready for ARV therapy

Integraz inhibitörleri – ilk tedavide

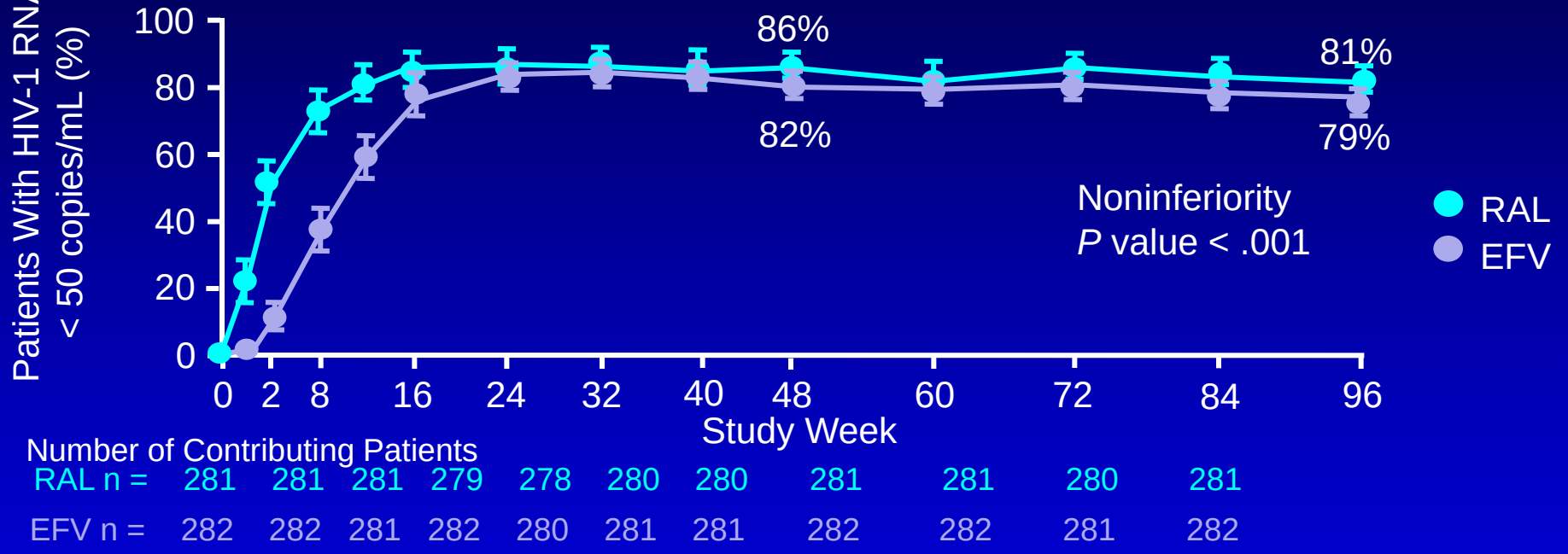
STARTMRK Faz III: RAL x EFV Tedavi-Almamış Hastalarda

- Randomize, plasebo-kontrollü çalışma
  - Primer sonuç noktası: HIV-1 RNA < 50 kopya/mL - 48.haftada



- Başlangıçta hastaların % 53'ünde HIV-1 RNA > 10^5 kopya/mL; % 47'sinde CD4+ < 200 h/mm^3

STARTMRK: 96. haftada virolojik ve immunolojik etkinlik



- Significantly shorter time to virologic response with RAL vs EFV (*P* = .001)
- Similar CD4+ cell count increases with RAL vs EFV
  - +240 vs +225 hücre/mm^3; Δ: 15 cells/mm^3 (95% CI: -13-42)

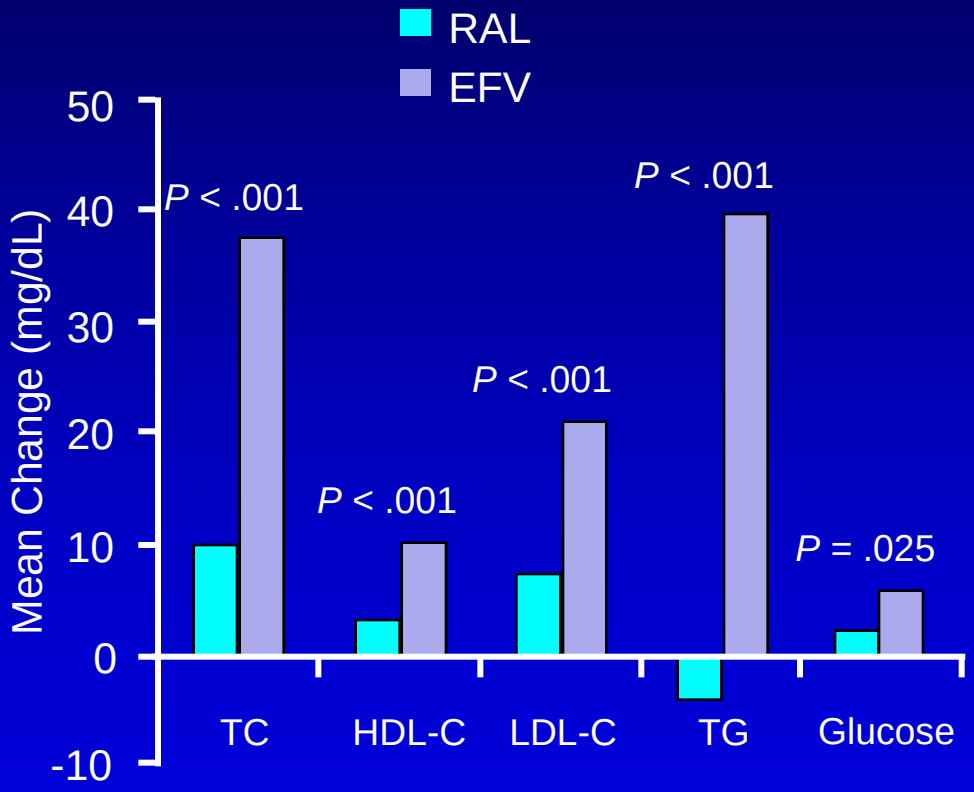
Lennox J, et al. *Lancet 2009; 374: 796–806*

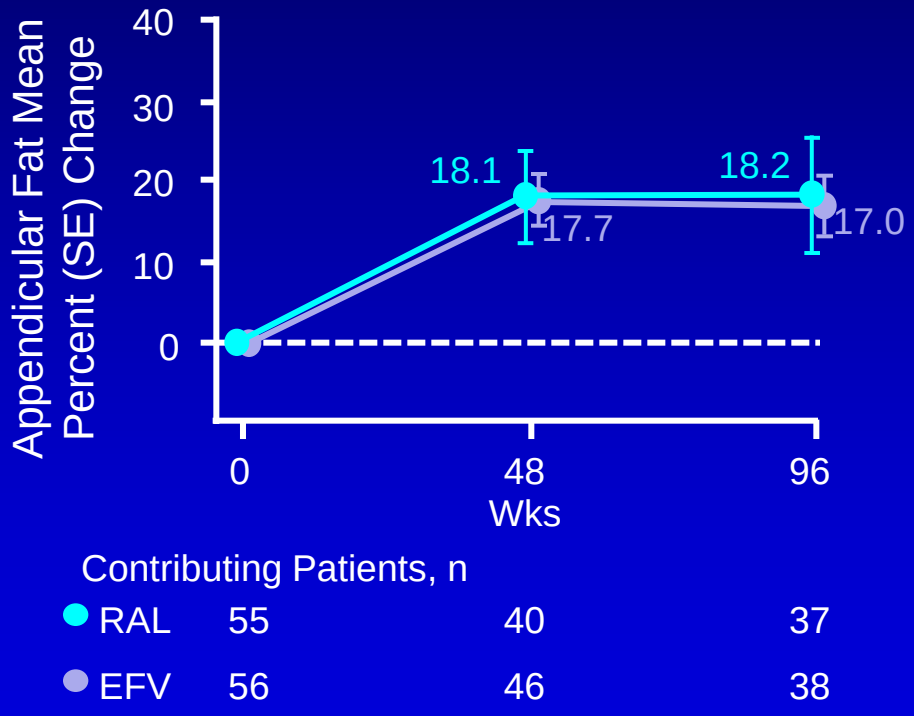
STARTMRK: 96. haftada advers etkiler

- İlaçla ilişkili klinik advers olaylar EFV ile RAL'e göre daha sık (78% - 47%; *P* < .0001)
  - Ciddi klinik advers olay (14% - RAL , 12% - EFV (*P* = .457)
- 8. hf'da RAL ile EFV'e göre daha az SSS etkileri (10.3% vs 17.7%; P = .015)
- Kanser gelişimi (RAL 3 hasta - EFV 11 hasta)
  - Kaposi's sarcoma (n = 7), anal cancer (n = 1), B-cell non-Hodgkin's lymphoma (n = 1), bone cancer (n = 1), lung cancer (n = 1), basal cell cancer (n = 3)

Lennox J, et al. *Lancet 2009; 374: 796–806*

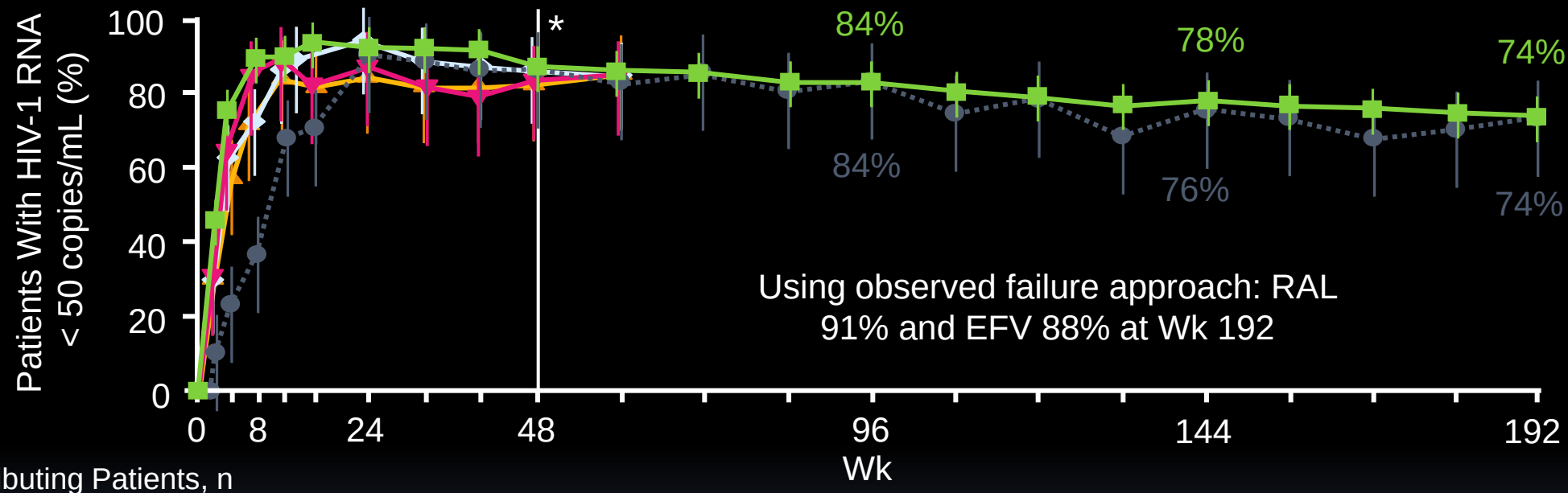
STARTMRK: Metabolik ve Vücut Kompozisyonu Değişiklikleri - RAL vs EFV, 96. hafta





DeJesus E, et al. CROI 2010. Abstract 720.

Protocol 004: 192-Wk Virologic Response to RAL vs EFV in Naive Patients (NC = F)



Contributing Patients, n						
RAL 100 mg BID	39	39	39			
RAL 200 mg BID	40	40	40			
RAL 400 mg BID	41	41	41	159	158	160
RAL 600 mg BID	40	40	40			
EFV 600 mg QD	38	37	38	38	38	38

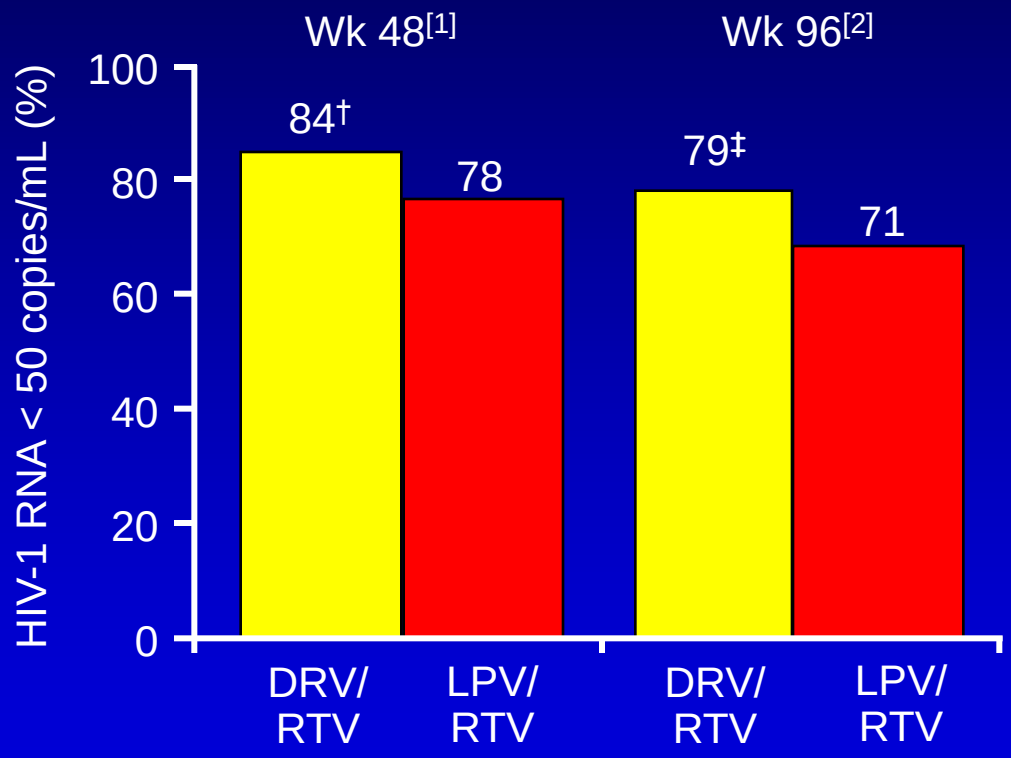
*After Wk 48, patients in all RAL groups continued at 400 mg BID. All patients received TDF+3TC.

Gotuzzo E, et al. CROI 2010. Poster 514.

Tercih edilen ilaçlar – rehber değişiklikleri

ARTEMIS: Daha önce tedavi almamış hastalarda DRV/RTV vs LPV/RTV 96.hafta

- Randomize, açık, 96-hf'lık çalışma
- DRV/RTV 800/100 mg tek doz (n = 343) vs LPV/RTV tb veya kap 400/100 mg 2x1 veya 800/200 mg tek doz* (n = 346)
  - \+ TDF/FTC 300/200 mg tek doz
- DRV/RTV 48. hf'da LPV/RTV'den aşağı değil; 96. haftada üstün
- CD4+ artışı: +171 (DRV/RTV) vs +188 (LPV/RTV), 96. hf



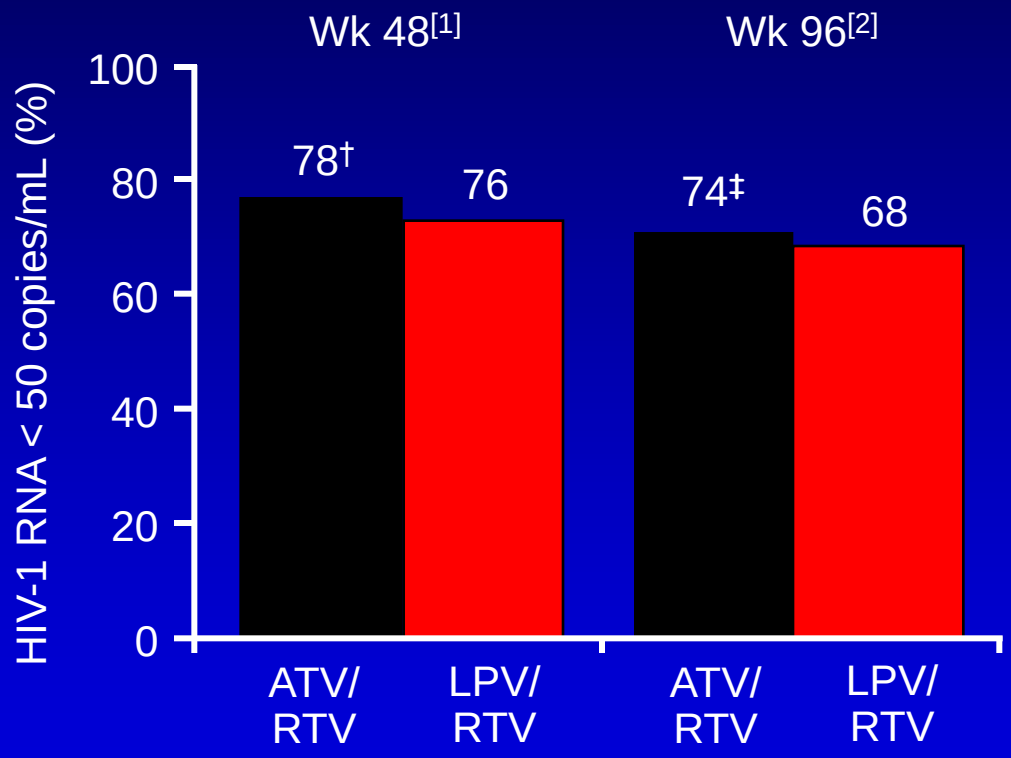
†Noninferiority, P < .001; superiority, P = .062
‡Noninferiority, P < .001; superiority, P < .012

*Depending on availability; switch allowed.

1. Ortiz R, et al. AIDS. 2008;22:1389-1397. 2. Mills A, et al. AIDS. 2009;23:1679-88

CASTLE: Daha önce tedavi almamış hastalarda ATV/RTV vs LPV/RTV 96. hafta

- Randomized, open-label, 96-wk study
- ATV/RTV 300/100 mg QD (n = 440) vs LPV/RTV 800/200 mg QD* (n = 443)
  - Plus TDF/FTC 300/200 mg QD
- ATV/RTV noninferior to LPV/RTV at Wk 48; superior at Wk 96
- CD4+ gain: +268 (ATV/RTV) vs +290 (LPV/RTV) at Wk 96

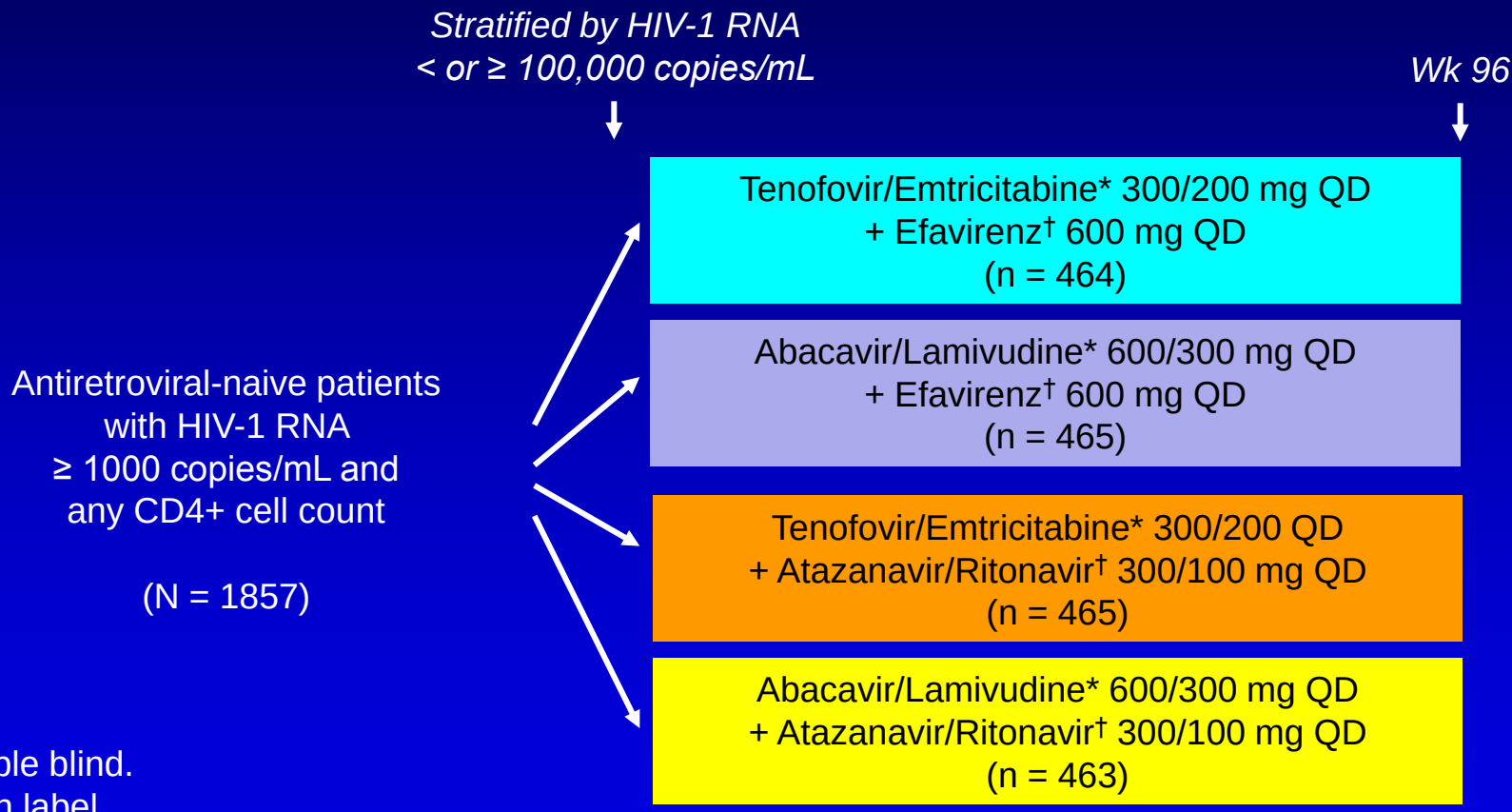


*SGC until Wk 48; tablet formulation after Wk 48.

†Est diff: 1.7% (95% CI: -3.8% to 7.1%; P = NS). ‡Est diff: 6.1% (95% CI: 0.3% to 12.0%; P < .05).

1. Molina JM, et al. Lancet. 2008;372:646-655. 2. Molina JM, et al. ICAAC/IDSA 2008. Abstract 1250d.

ACTG 5202: Başlangıç tedavisi ABC/3TC vs TDF/FTC + EFV vs ATV/RTV



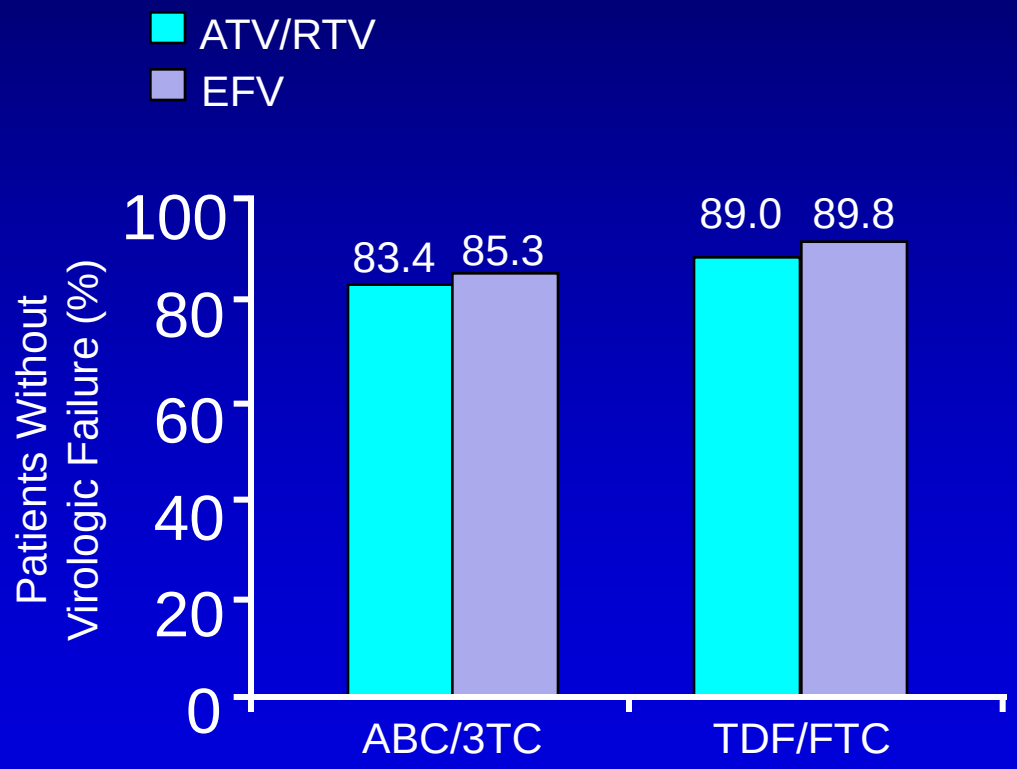
*Double blind.
†Open label.

Daar E, et al. CROI 2010. Abstract 59LB.

ACTG 5202: Virolojik Başarısızlık ATV/RTV vs EFV

- Benzer virolojik başarısızlığa dek geçen zaman, ATV/RTV vs EFV - ABC/3TC veya TDF/FTC ile kombine edildiğinde
  - ABC/3TC, HR: 1.13 (95% CI: 0.82-1.56)
  - TDF/FTC, HR: 1.01 (95% CI: 0.70-1.46)

96. Hf'da virolojik başarısızlık olmaması



Daar E, et al. CROI 2010. Abstract 59LB.

ACTG 5202: Virolojik Başarısızlık ABC/3TC vs TDF/FTC

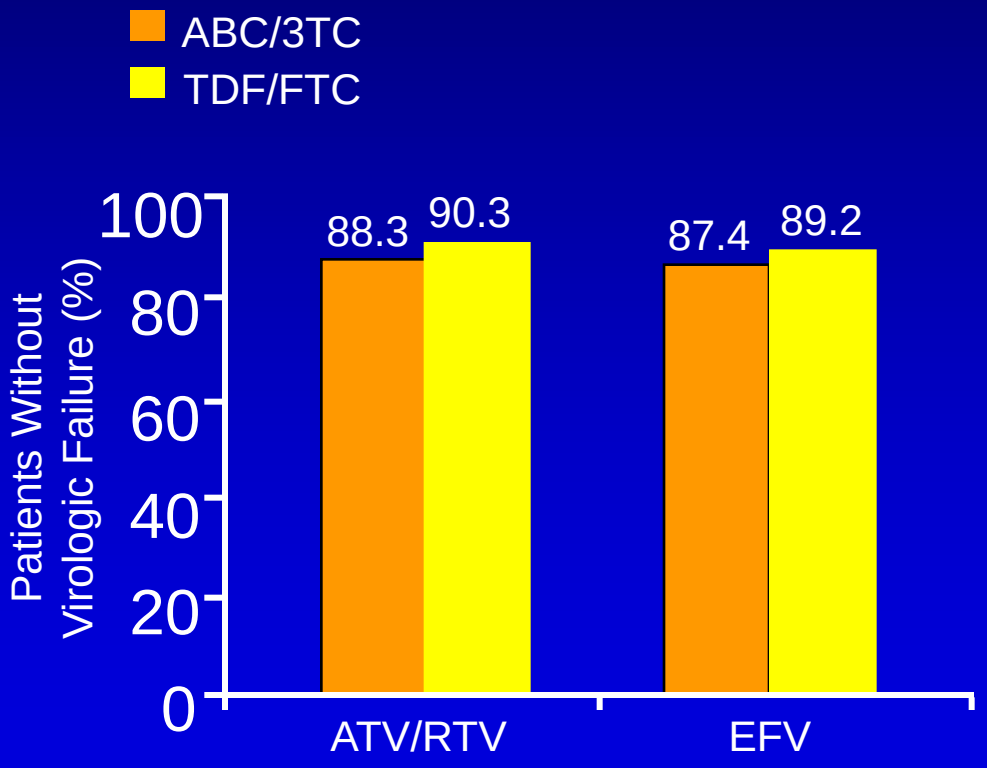
VL < 100,000 k/mL olan hastalar

- Benzer virolojik başarısızlığa dek geçen zaman - ABC/3TC vs TDF/FTC, ATV/RTV veya EFV ile
  - ATV/RTV, HR: 1.26 (0.76-2.05)
  - EFV, HR: 1.23; (0.77-1.96)

VL ≥ 100,000 k/mL hastalar

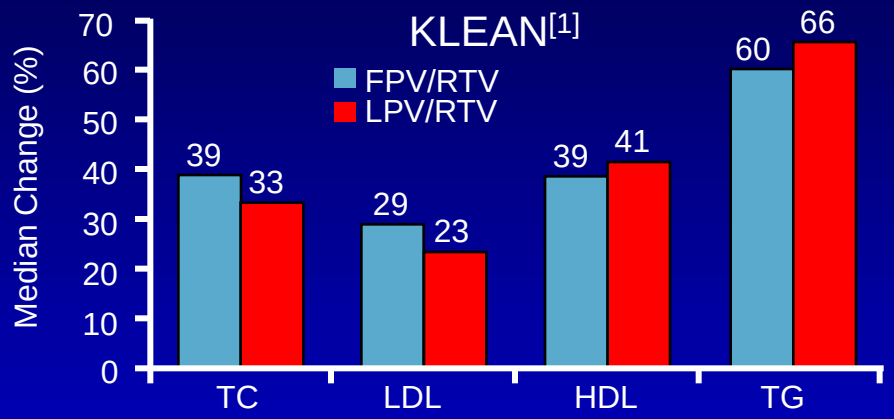
- ABC/3TC ile daha kısa VB'a dek geçen zaman (TDF/FTC'e göre) EFV veya ATV/RTV ile kombine
  - EFV, HR: 2.22 (1.19-4.14)
  - ATV/RTV, HR: 2.46 (1.20-5.05)

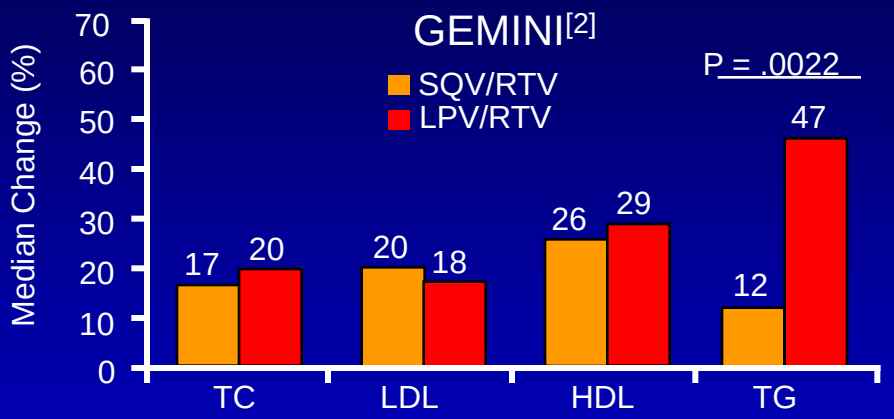
96. Hf'da virolojik başarısızlık olmaması
VL < 100,000 k/mL

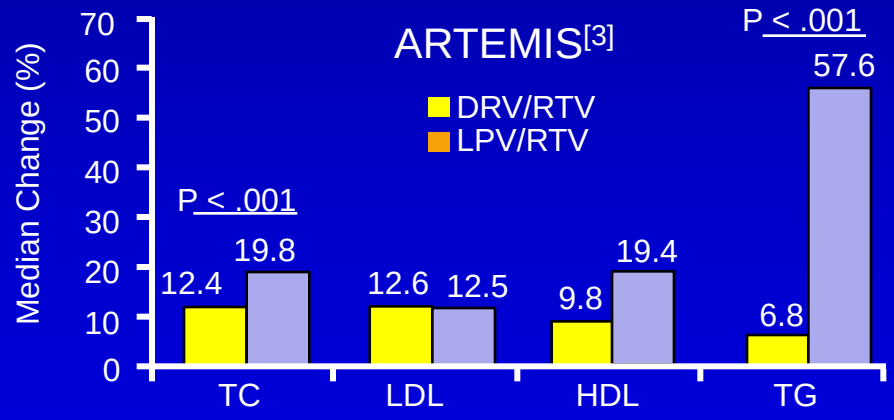


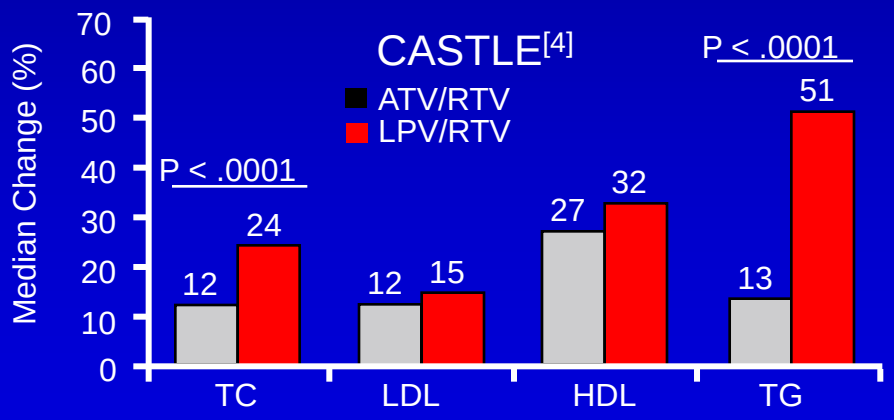
Daar E, et al. CROI 2010. Abstract 59LB.

48. haftada lipid değişiklikleri









This slide is an illustration only and not meant to be a cross-study comparison.

1. Eron J Jr, et al. Lancet. 2006;368:476-482. 2. Walmsley SL, et al. J. Infect Dis. 2009;50:367-374. 3. Nelson M, et al. Inter Congress on Drug Therapy in HIV Infection 2008. Abstract P127. 4. Reprinted from The Lancet, v 372, Molina JM, et al, pp 646-655, Copyright 2008, with permission from Elsevier.

2009 DHHS Rehberi
Başlangıç tedavisi: Tercih edilen

NNRTI temelli	▪EFV/TDF/FTC[1,2]
PI temelli	▪ATV/r + TDF/FTC[2] ▪DRV/r (QD) + TDF/FTC[2]
II temelli	▪RAL + TDF/FTC[2]
Gebeler	▪LPV/r (BID)[3] + ZDV/3TC

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.

December 2009

2009 DHHS Rehberi
Başlangıç tedavisi: Alternatifler

NNRTI temelli	▪EFV[1] + (ABC/3TC) or (ZDV/3TC)[2] ▪NVP[4] + ZDV/3TC
PI temelli	▪ATV/r + (ABC/3TC) or (ZDV/3TC)[2,3] ▪FPV/r (QD or BID) + (ABC/3TC) or (ZDV/3TC) or (TDF/FTC)[2,3] ▪LPV/r (QD or BID) + (ABC/3TC) or (ZDV/3TC) or (TDF/FTC)[2,3] ▪SQV/r + TDF/FTC[2]

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. 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.
4. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.

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2009 DHHS Rehberi
Başlangıç tedavisi: Kabul edilebilir

NNRTI temelli	▪EFV[1] + ddI + (3TC or FTC)
PI temelli	▪ATV + (ABC/3TC) or (ZDV/3TC)[2,3]

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. 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 .

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Başlangıç tedavisi: Kabul edilebilir, fakat daha kesin bilgiye ihtiyaç var

PI temelli	▪DRV/r + (ABC/3TC) or (ZDV/3TC)[1,2] ▪SQV/r + (ABC/3TC) or (ZDV/3TC)[1,2]
CCR5 Antagonist temelli	▪MVC + ZDV/3TC[1,3]
II temelli	▪RAL + (ABC/3TC) or (ZDV/3TC)[1]

1. 3TC can be used in place of FTC and vice versa.
2. 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.
3. Tropism testing required before treatment with MVC; use only if only CCR5-tropic virus is present.

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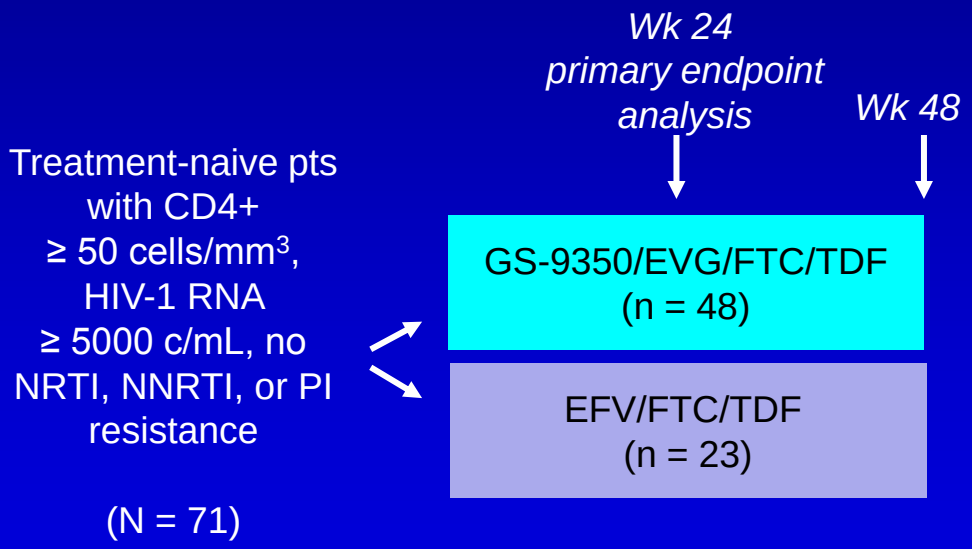
EACS 11/2009

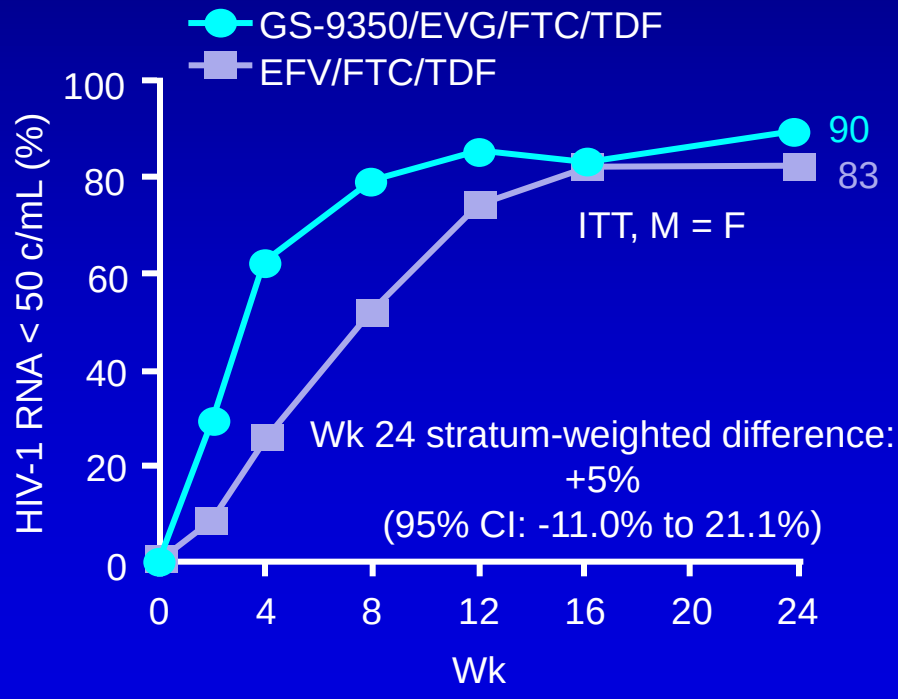
SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B	A	B	REMARKS
Recommended	NNRTI • EFV[1] • NVP[5] or ritonavir-boosted PI • ATV/r[6] • DRV/r[6] • LPV/r[7] • SQV/r	TDF/FTC ABC/3TC[2-3-4]	- TDF/FTC co-formulated - ABC/3TC co-formulated - EFV/TDF/FTC co-formulated - ATV/r: 300/100 mg qd - DRV/r: 800/100 mg qd - LPV/r:400/100 mg bid or 800/200 mg qd - SQV/r:1000/100 mg bid
Alternative	SQV/r FPV/r RAL[9]	• ZDV/3TC[8] • ddI/3TC or FTC[8]	- SQV/r: 2000/100 mg qd - FPV/r:700/100 mg bid or 1400/200 mg qd - RAL: 400 mg bid - ZDV/3TC co-formulated

Farmakolojik güçlendiriciler – yeni jenerasyon

GS-9350 - ile güçlendirilmiş Elvitegravir + FTC/TDF, tedavi almamış hastalarda EFV/FTC/TDF'dan daha az etkin değil

- Cobicistat (GS-9350): deneysel CYP3A inhibitorü
- Elvitegravir: deneysel integrase inhibitorü

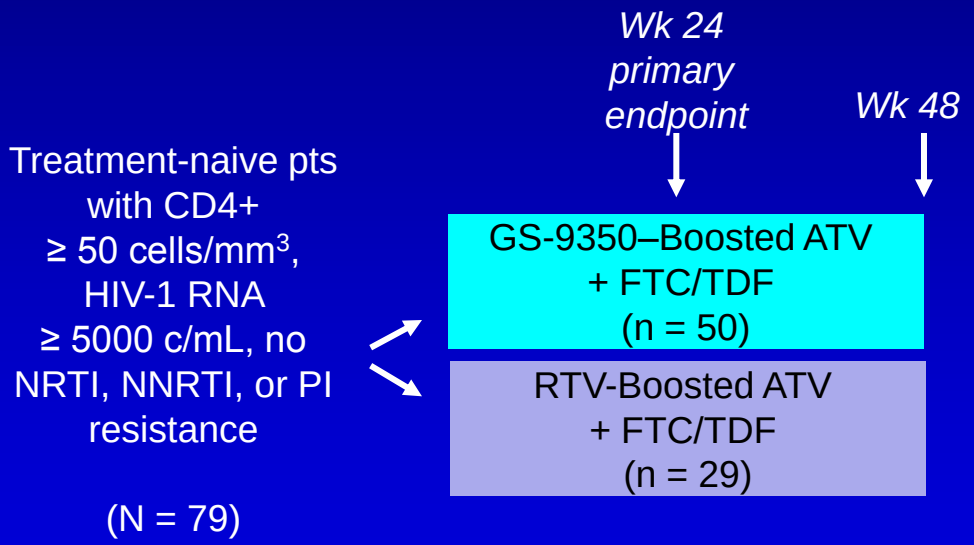


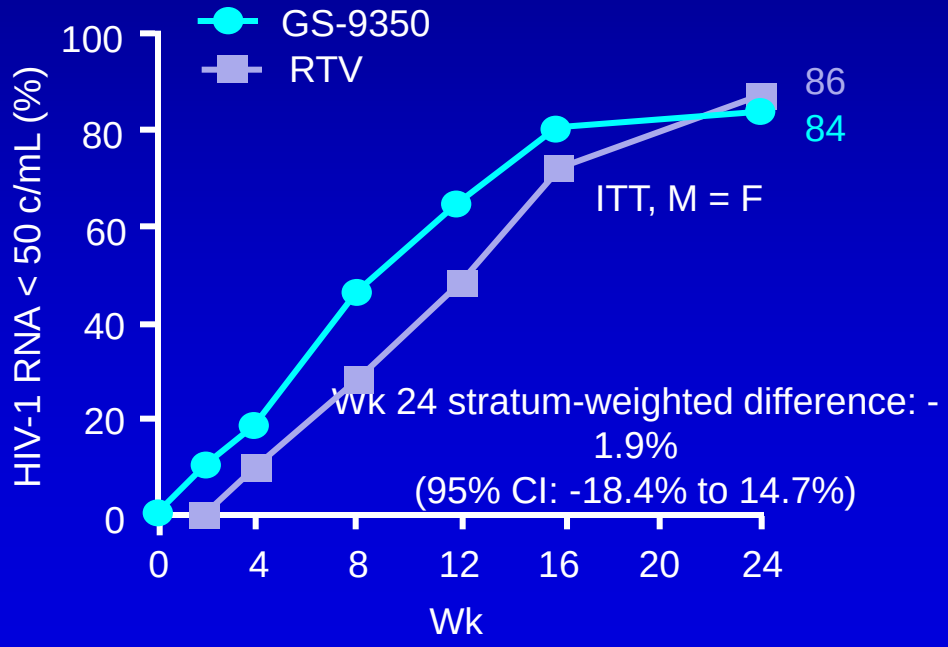


Cohen C, et al. CROI 2010. Abstract 58LB.

GS-9350 - ile güçlendirilmiş ATV: tedavi almamış hastalarda ATV/RTV'e benzer virolojik etkinlik

- Faz II çalışma: atazanavir + güçlendirici olarak cobicistat (GS-9350) ile ritonavir karşılaştırması

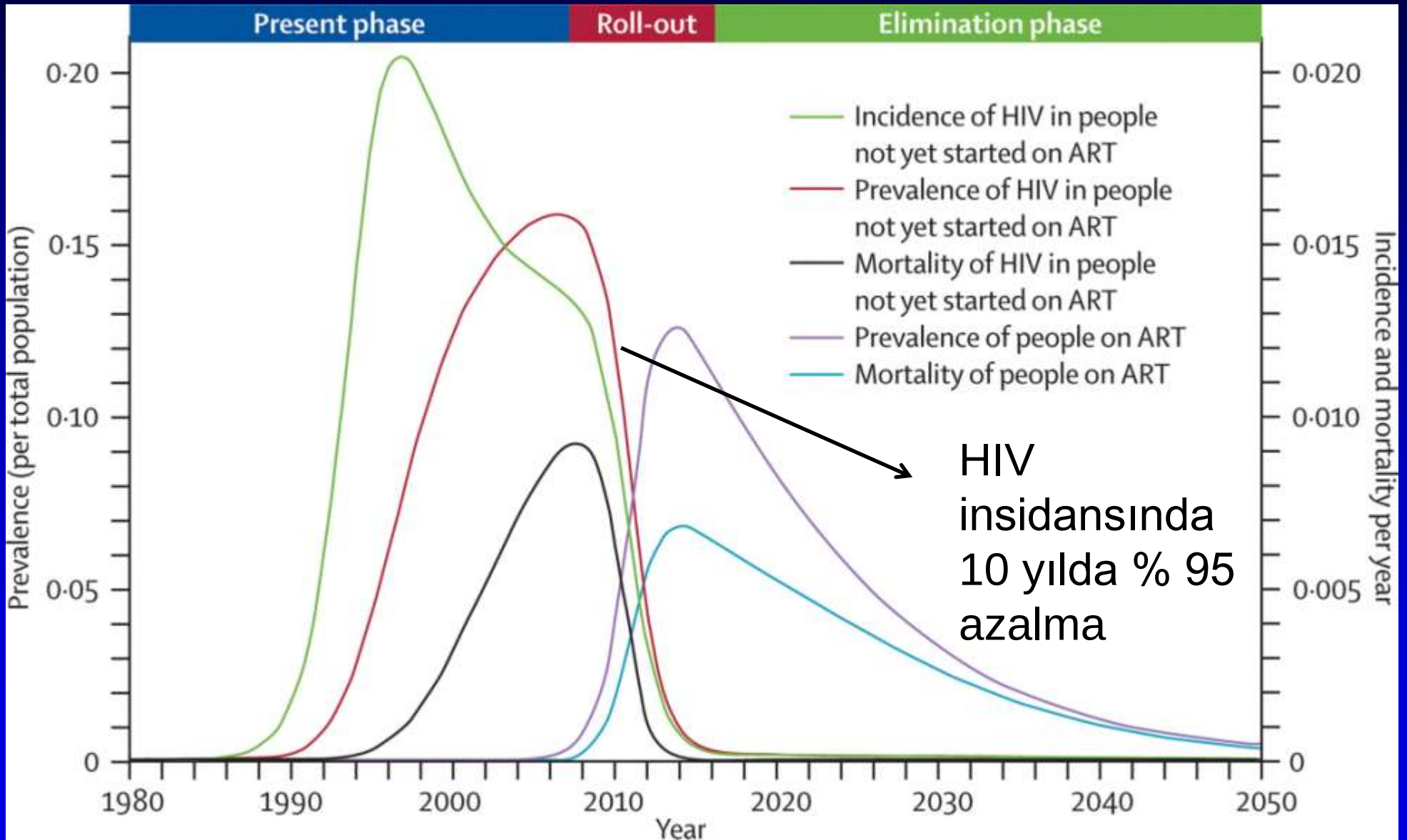




Cohen C, et al. CROI 2010. Abstract 58LB.

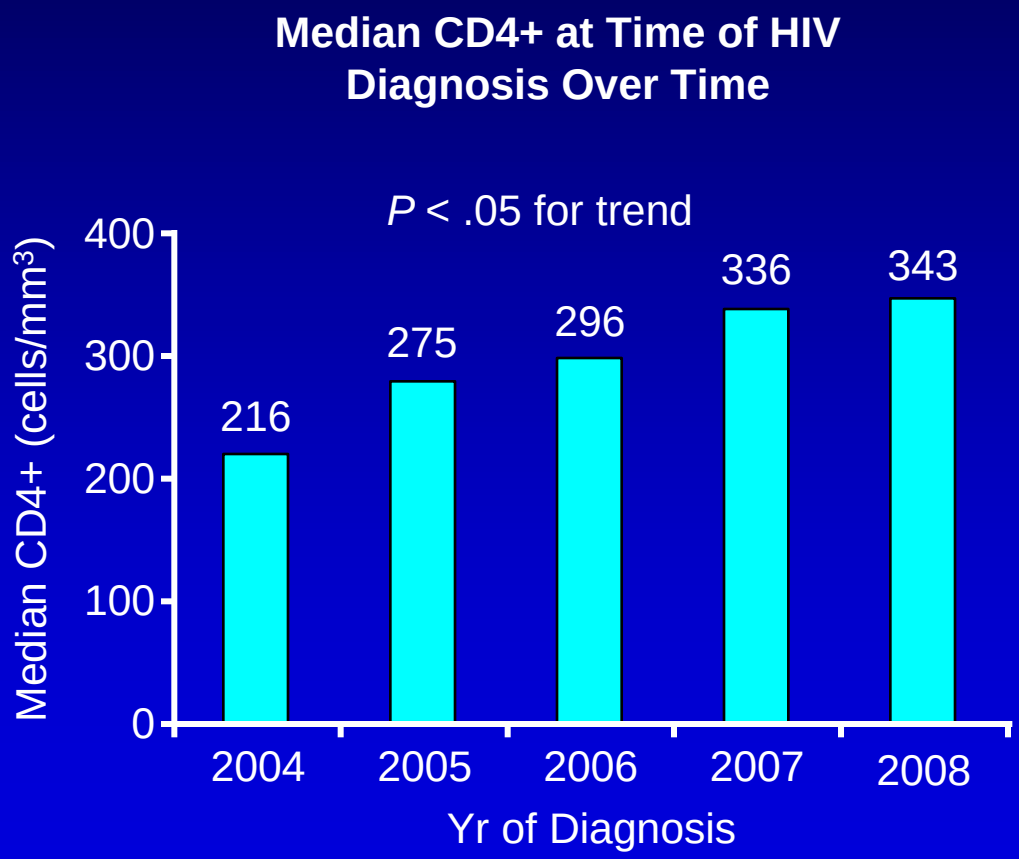
Test ve tedavi et stratejileri, küresel HIV tedavisi

Küresel gönüllü HIV testi ve derhal HAART verilmesi stratejisi *Granich RM, Lancet 2009; 373:48–57*



Genişletilmiş HIV testi stratejisinin sonuçları: Washington, DC

- 3.7-fold increase in number of publicly funded HIV tests performed in Washington, DC, from 2004-2008
  - 2004: 19,766
  - 2008: 72,866
- 17% increase in number of new HIV/AIDS name-based case reports from 2004-2007
- Significant reduction in time to progression to AIDS following HIV diagnosis from 2004-2008 ($P < .0001$)
- Time interval between diagnosis to entry into care significantly improved from 2004-2008



Castel A, et al. CROI 2010. Abstract 34.

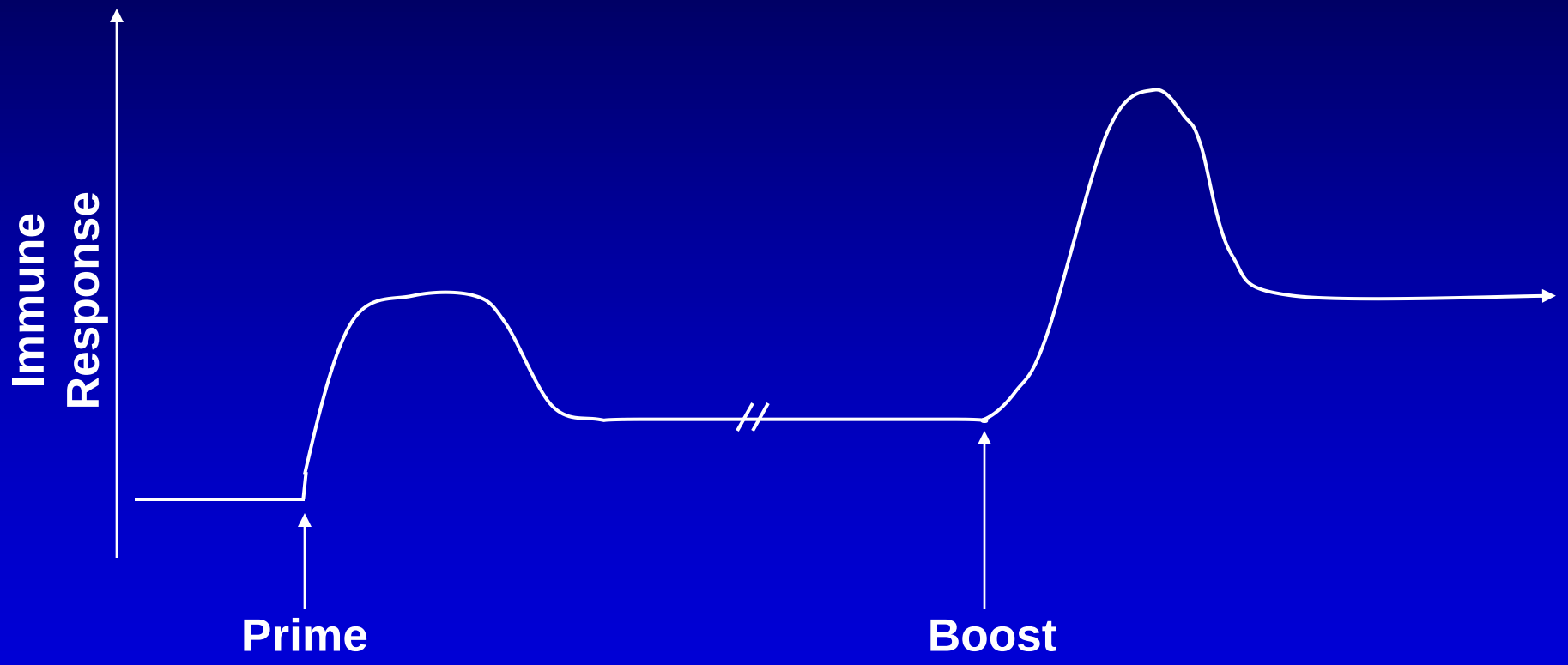
Aşılar

Etkinlik çalışmaları (Faz IIb, III): Aday HIV-1 aşılar - HIV-1-seronegatif gönüllülerde

Vaccine	Start	Sample Size	Location	Target Population	HIV Infection Rate in Vaccine Group (%)	HIV Infection Rate in Placebo Group (%)	Vaccine Approach; HIV-1 Strains	Vaccine Developer
AIDSVAX B/B	1998	5403	North America, Netherlands	MSM	**6.7**	**7.0**	rgp120: MN, GNE8	VaxGen
AIDSVAX B/E	1999	2546	Thailand	IVDU	**8.4**	**8.3**	rgp120: MN, A244	VaxGen
STEP Study	2004	3000	North America, Caribbean, Australia	MSM; sexual exposure	**4.6***	**3.1**	Ad5 gag/pol/nef: clade B gag-CAM-1, pol- IIIB, nef-JR-FL	Merck
Phambili Study	2006	3000†	South Africa	Sexual exposure	**Stopped early**	**Stopped early**	Ad5 gag/pol/nef: clade B gag-CAM-1, pol- IIIB, nef-JR-FL	Merck

Lancet 2008; 372:1881-1893., Lancet 2008; 372:1894-1905.

Hazırlama – iteleme aşı stratejisi



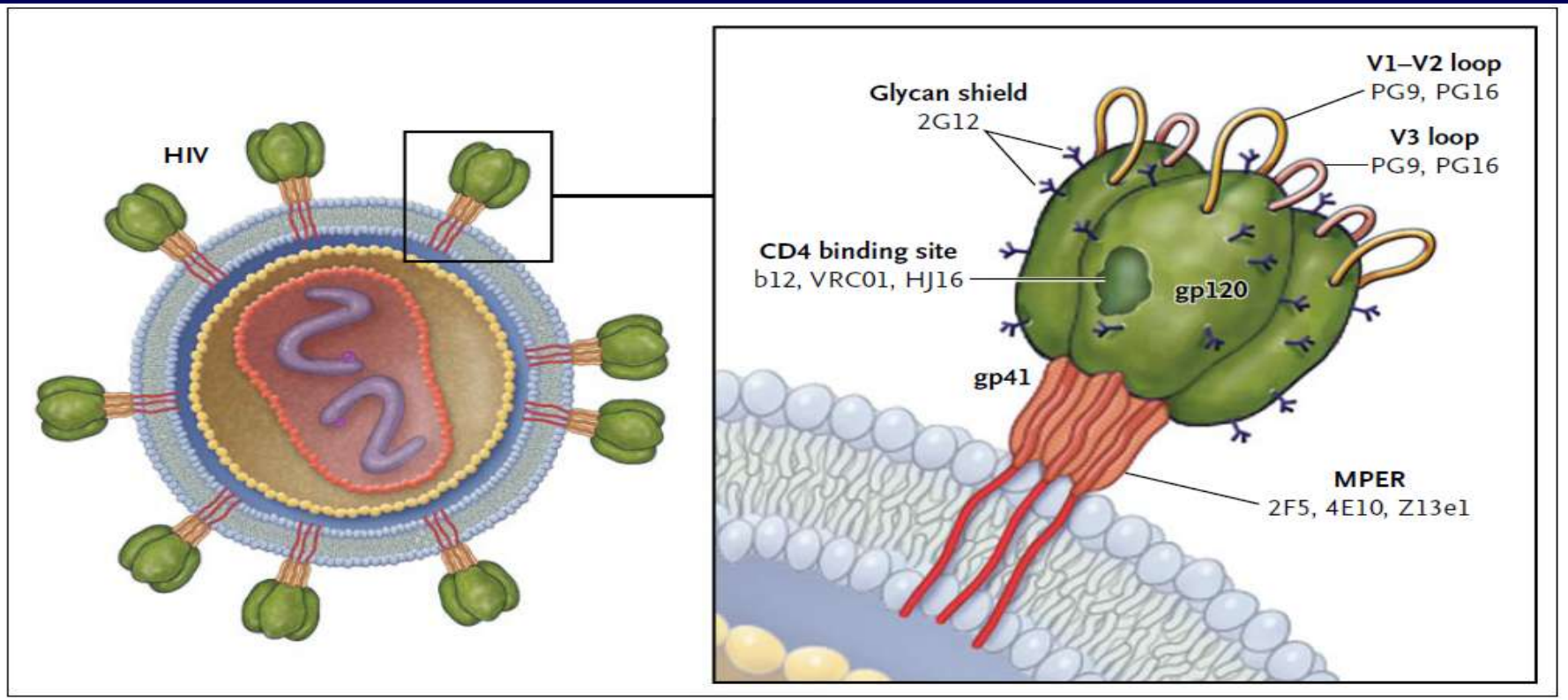
The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

- canarypox ALVAC vektörü (HIV-1 E gp120, B Gag ve proteaz) - 0,1,3 & 6 ay. ve AIDSVAX B/E 3 & 6 ay. iteleme
- n: 16402 (18-30 y, E & K)
- Aşı etkinliği: % 31.2
- Hastaların çoğu - heteroseksüel, yüksek riskli guruplarda değil
- Etkinliğin çoğu ilk yıl içinde görülüyor
- Halk sağlığına yönelik fayda beklenmiyor

Rerks-Ngarm S, NEJM 2009;361: 2209-20.

Geniş nötralizan antikorların keşfi ve ters mühendislikle Ag yapımı



Vulnerable Targets for Potential Vaccines on the Trimeric HIV Envelope Spike Glycoproteins (gp120 and gp41).

Broadly neutralizing monoclonal antibodies have been identified that target the CD4 binding site (b12, VRC01, HJ16) on glycoprotein 120 (gp120), the membrane proximal external region (MPER) (2F5, 4E10, Z13e1) of gp41, the glycan shield (2G12), and epitopes that reside in the variable loops 1, 2, and 3 on gp120 (PG9, PG16).

Koff WC, Berkley SF. NEJM 2010;363(5):e7

Yaşam beklentisi

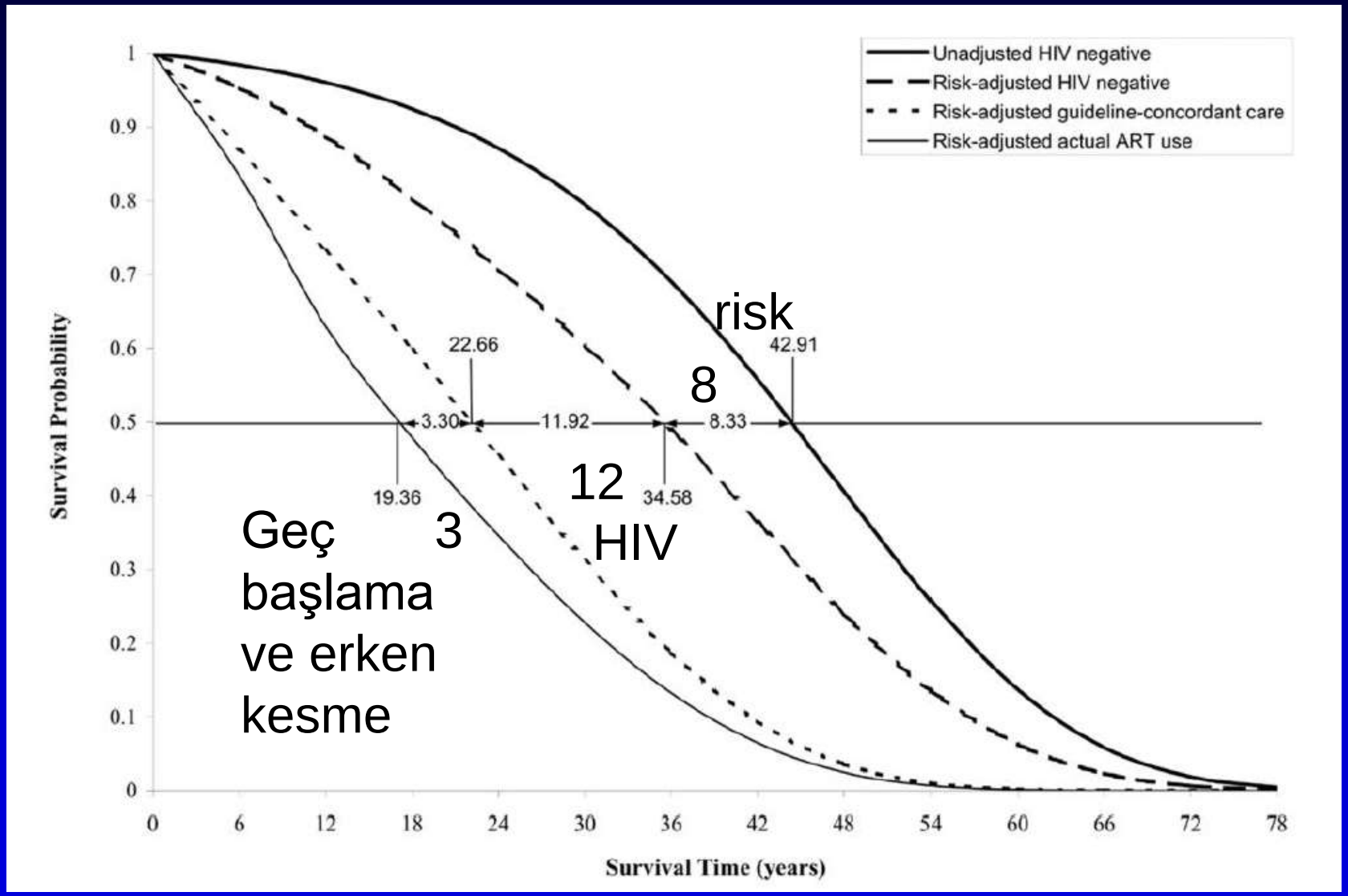
ART-CC
1134 ölüm / 29.935 hasta

- Kaba ölüm oranı 0.95/ 100 hasta yılı
- Kaba SMR: 3.36
- Standardize mortalite oranları:
  - 6.ayda CD4 sayısı düşük ise
  - 6.ayda VL > 500 ise
  - Başlangıçta AIDS var ise
  - DİİB > Homo & hetero

  ise artıyor

International Journal of Epidemiology 2009;38:1624–1633

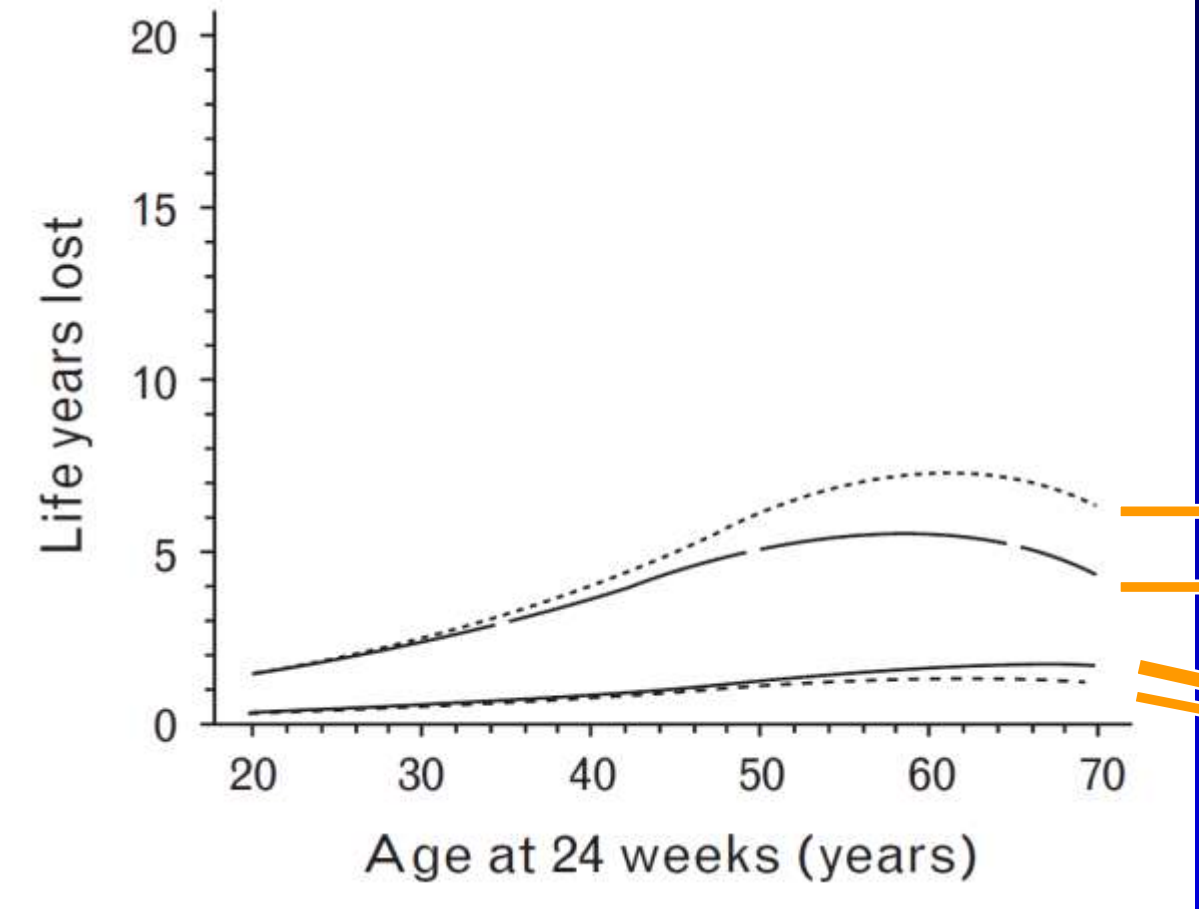
Ortalama serokonversiyon yaşı 33'den itibaren



Losina, CID 2009; 49:1570–8

Hollanda – Athena kohort

Tanıdan 24 hf sonra tedavi almayan ve AIDS olayı olmayan



HIV + Kadın + CDC B

HIV + Erkek + CDC B

HIV + Kadın

HIV + Erkek

van Sighem, AIDS 2010;24:1527-35.