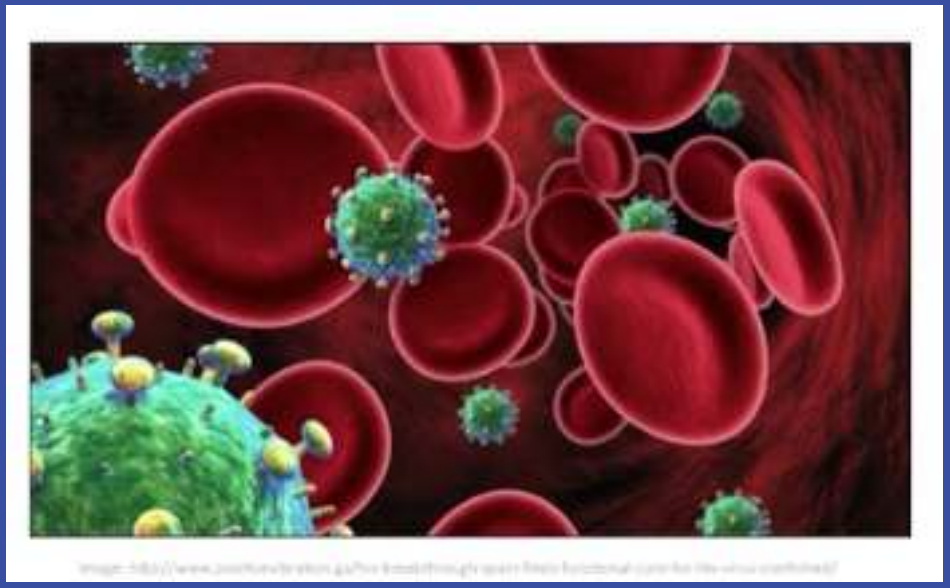
HIV ve KVS Hastalıklar



Dr. Oğuz Karabay

Sunum planı

I. HIV/AIDS ve fizyopatoloji

II. KVS riski nasıl belirlenir ?

III. AIDS ve KVS sorunları

- A. Perikardit
- B. Endokardit
- C. Miyokardit
- D. AIDS ilişkili kanser
- E. Pulmoner HT
- F. HIV Koroner Arter Hastalığı

IV. KVS hastalıktan korunmak için ne yapmalı ?

AJANDA

I. AIDS ve KVS HASTALIKLARDA BAŞLICA FİZYOPATOLOJİ NEDİR ?

II. KVS hastalık riski nasıl belirlenir

III. AIDS ve KVS sorunları

- A. Perikardit
- B. Endokardit
- C. Miyokardit
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IV. KVS hastalıktan korunmak için ne yapmalı

KVS sorunları neden öne çıkıyor ?

- AIDS'li **yaşam süresi uzadı.**
- AIDS'li **yaşlanıyor.**
  - Yaşlanabilen herkesin sorunu
  - Ama AIDS'lide daha sık...

HIV+ hastada yaşla beraber artan hastalıklar

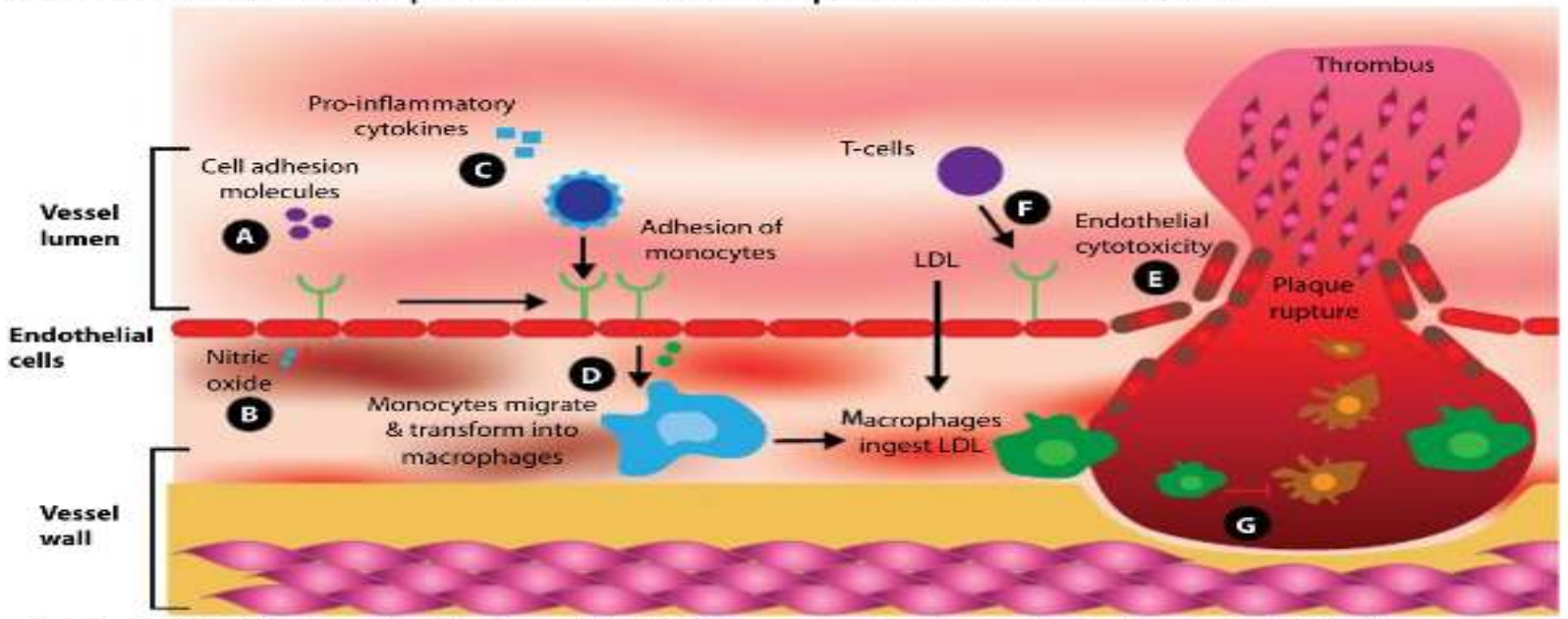
- **KVS hastalıklar**
- Böbrek hastalığı
- KC hastalığı
- Kemik Kaybı
- Bilişsel problemler
- Zayıflama

Current HIV/AIDS Reports February 2017, Volume 14, Issue 1, pp 31–37

Neden KVS hastalığı fazla ?

- HIV + hastada, **İNFLAMASYON** ⬆⬆

Figure 2. Effects of HIV viral proteins on the development of atherosclerosis

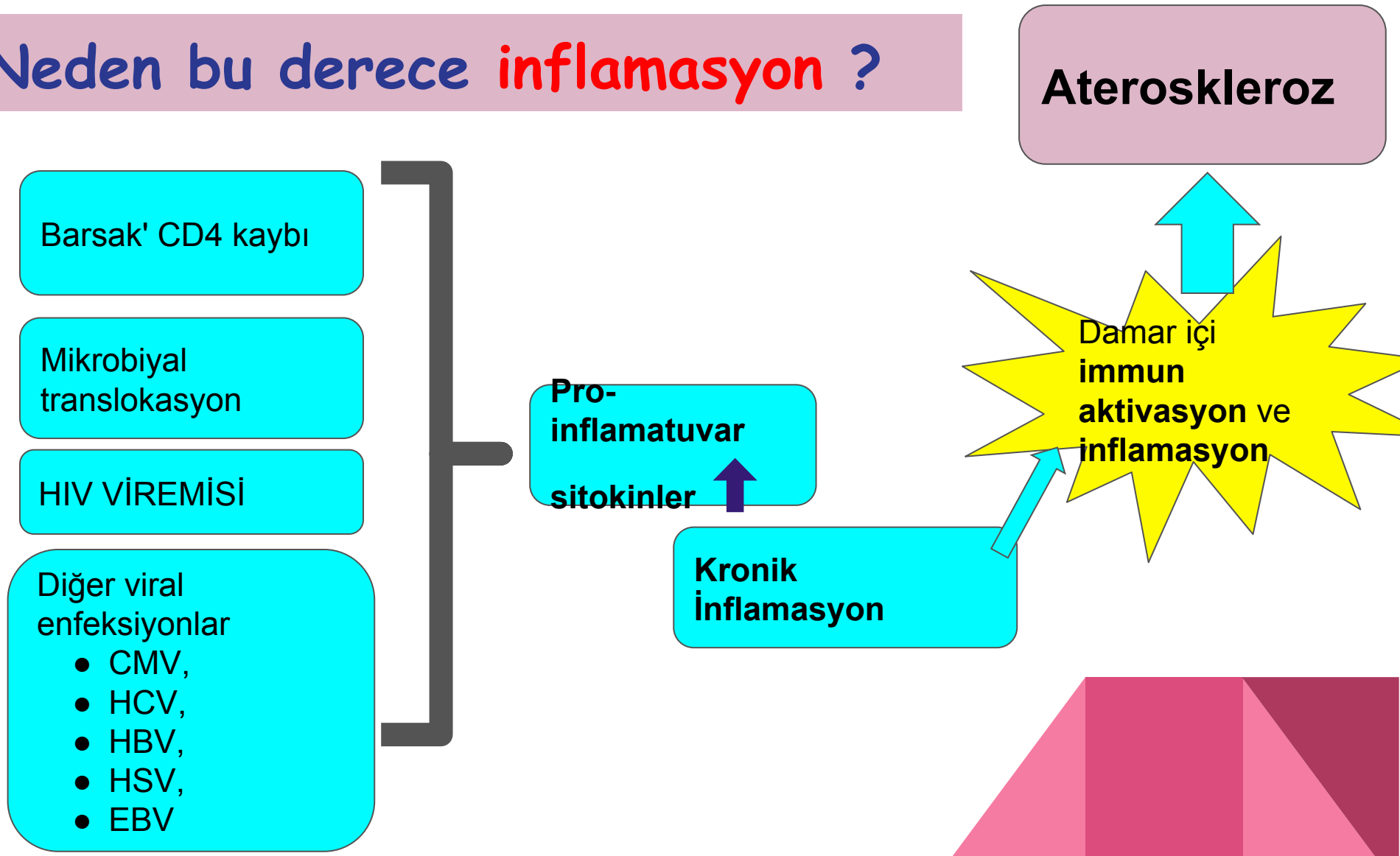


IL=interleukin; LDL=low-density lipoprotein; MCP-1=monocyte chemoattractant protein-1; TNF=tumor necrosis factor. Adapted from Nou et al. *AIDS*. 2016;30:1495-1509.

HIV viral proteins induce:

A. Expression of cell adhesion molecules
B. Nitric oxide production
C. Inflammatory cytokine release (ie, IL-6, TNF-α)
D. Pro-inflammatory monocyte migration protein expression (ie, MCP-1)
E. Endothelial cytotoxicity/apoptosis → fibroatheroma rupture/erosion → acute thrombus
F. Leukocyte adhesion to endothelial walls
G. Reduced cholesterol efflux from macrophages → cholesterol accumulation

Neden bu derece inflamasyon ?



HIV/AIDS'lide inflamasyon fazla !

- **Yüksek IL-6** seviyesi **KVS** mortalitesi ile beraber.
- Monosit'den artmış **CD16 ve azalan CD14** seviyesi mortalite ilişkili.
- HIV viral yükü ⬆ ise;
  - **Fibrin yıkım ürünleri** (D-Dimer) ⬆⬆
  - **VCAM** ⬆⬆⬆
  - **ICAM-1** ⬆⬆

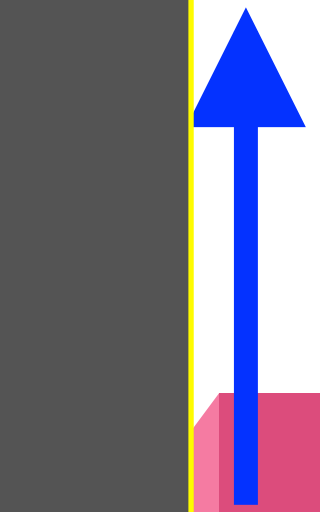
AIDS. 2012 Apr 24;26(7):843-53.

Kronik inflamasyon varsa KVS hastalık sıklığı zaten artar.

- **ÖRNEK**
  - SLE
  - RA
  - AIDS

İnflamasyon varsa ,

- h-CRP
- IL-6
- D-Dimer
- LPS
- LDL
- CD163
- CD14
- CD16
- Soluble VCAM



KVS İÇİN RİSKLİ

- Yüksek viral yük.
- Düşük CD4 (< 200).
- Lipid profil bozukluğu

Bazı ilaçlar : riskli ART (PI ya da **abakavir**).

AJANDA

I. AIDS ve KVS HASTALIKTA MEKANİZMA

II. **Risk nasıl belirlenir ?**

III. AIDS ve KVS sorunları

- A. Perikardit
- B. Endokardit
- C. Miyokardit
- D. AIDS ilişkili kanser
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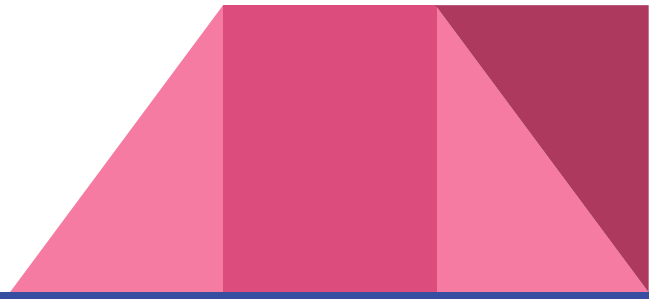
- F. HIV Koroner Arter Hastalığı

IV. KVS hastalıktan korunmak için ne yapmalı



Kardiyovasküler risk nasıl belirlenir ?

- **Skor ile**
  - Halen çok sayıda skorlama sistemi var...
    - **Framingham sistemi** (En eskisi ve en çok kullanılanı)
    - **DAD skorlama *****
    - **SCORE,**
    - **PROCAM, (kadınlarda sorunlu)**
    - **QRISK,**
    - **WHO/ISH,**
    - **Reynolds Risk Score**

http://www.chip.dk/Tools

Ulaşmak çok kolay

- **Framingham Risk Skoru (FRS)** –
  - 10 yıl
    - *Yaş,*
    - *Total kolesterol,*
    - *HDL,*
    - *TA,*
    - *Sigara*
      - Düşük (<10%)
      - Orta (10%-20%)
      - Yüksek (>20%)

Framingham Risk Score Calculator

Framingham Risk Score is the estimation of 10-year cvd (cardiovascular disease) risk of a person. It was developed by the Framingham Heart Study to assess the hard coronary heart disease outcome. It is used to estimate the risk of heart attacks in adults older than 20.

In the below calculator enter your gender, age, cholestrol level, BP and you get the 'Framingham Risk Score' and the risk of developing CHD. Higher the score, higher is the percentage of developing CHD.

CVD (Cardiovascular Disease) Risk Calculator

Gender: Male	Age: 45-49 years
Total Cholesterol (mg/dL): 160-199	HDL Cholesterol (mg/dL): 40-49
Smoker: No	Systolic BP(mmHg): 140-159
On Blood pressure medication(Yes|No): Yes	

Calculate Reset

DAD skoru

- The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) model,
- HIV hastalarında **5-yıl** **CVD riski araştıran skorlama**.

ATP III

ATP III Guidelines At-A-Glance Quick Desk Reference

Step 1

Determine lipoprotein levels—obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

RİSK NE ZAMAN ALARM VERİR !!!

Eğer risk > %20 ise riskli

- İlaç değişikliği
- Yaşam tarz değişikliği öner...

AJANDA

I. AIDS ve KVSHASTALIKTA MEKANİZMA

II. KVS riski nasıl belirlenir

III. **Başlıca KVS sorunları**

- A. Perikardit
- B. Endokardit
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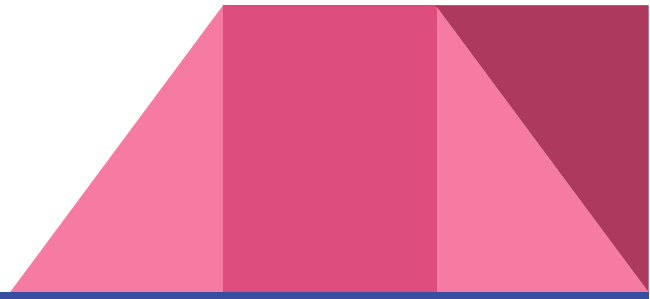
IV. KVS hastalıktan korunmak için ne yapmalı

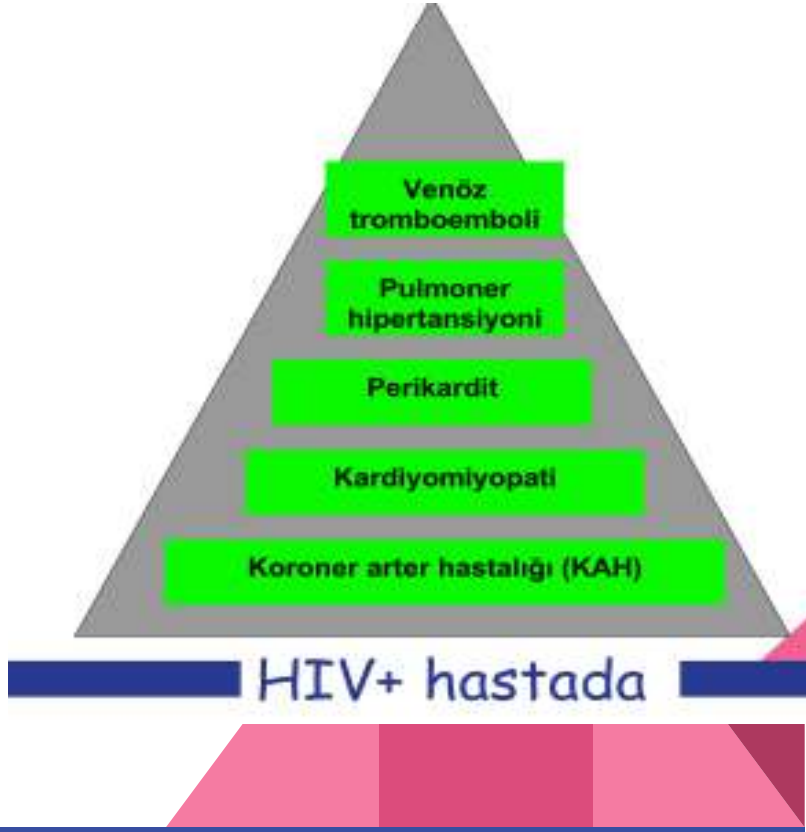


KALP VE AIDS

- HIV ile enfekte hastada **kalp tutulum sıklığı** %25-75

- Tüm ölümlerin **1/10'u KVS kaynaklı**.

Singh A. Int J Clin Med 2012:3:178



1.Perikardit

III.1. Perikardit

- AIDS'in ilk tanımlandığı yıllardan beri biliniyor.
- **Sıklık: %11**
- Asemptomatik // **Kalp tamponadı**

- *ETYOLOJİ*
- Çoğu zaman etiyolojik ajan Ø
  - M.tuberculosis
  - S.aureus
  - C.neoformans
  - HSV
  - Kalp neoplazmı

- **Perikardit gelişlenlerde yaşam süresi daha kısa**

III.2 Endokardit

- Bu grupta **nonbakteriyel trombotik endokardit** ve **enfektif endokardit** saptanabilir.
- Etkenler, normal konaktan farklı olabilir
  - Özellikle de IVDU bu grupta sık.
  - Sağ kalp tutulumu sık.

ETKEN DAĞILIMI

- S.aureus,
- S.pneumoniae, H.influenzae,
- Candida spp., Aspergillus spp.

III.3 Miyokard Tutulumu

- **Dilate kardiyomiyopatinin** önemli nedenlerinden;

- 71 hastalık bir seride olguların
  - **%50'sinde sol dilate miyopati,**
  - **%10'unda biventriküler miyopati.**

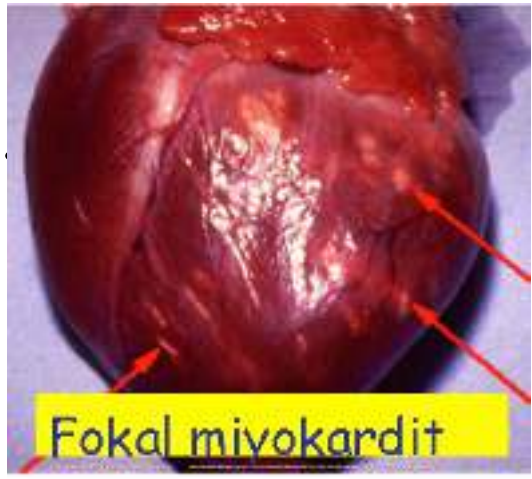
Liphults SE. Circulation 2000;102:1542
Herskowitz A. J Am Coll Cardiol 1994;24:1025
Anderson DW. J Am Coll Cardiol 1998. ;11:792

Kardiyomiyopati hep semptomatik mi ?

- Hayır !!!
  - Kardiyomiyapati **asemptomatik** olabilir
  - Kardiyomiyapati **kalp yetm ile beraber** olabilir.

Fokal miyokardit

- Otopsilerde **fokal miyokardit** saptanabilir.
  - ART öncesi dönemde otopsilerde sıklığı %33 .
  - Tamamında mononükleer hücre infiltrasyonu +
  - Neredeyse %100 asemptomatik



- Lanjewar DN, Katdare GA, Jain PP, Hira SK. Pathology of the heart in acquired immunodeficiency syndrome. Indian Heart J 1998; 50:321.

MİYOKARD HASTALIKLARI

- Erkenden ART ile **kardimiyopati sıklığı ⬇⬇.**

III.3 Miyokard tutululumu ve ilaçlar !

- **NRTI**
  - **Mitekondriyal miyopati**
    - **Miyokardiyal disfonksiyon**

      - Zalcitabine (ddC) > didanosine > stavudine (d4T) >> lamivudine (3TC) > **tenofovir** > **zidovudine** (AZT) > **Abacavir** (ABC)

Lee H. Biochemistry. 2003 Dec 23;42(50):14711-9.

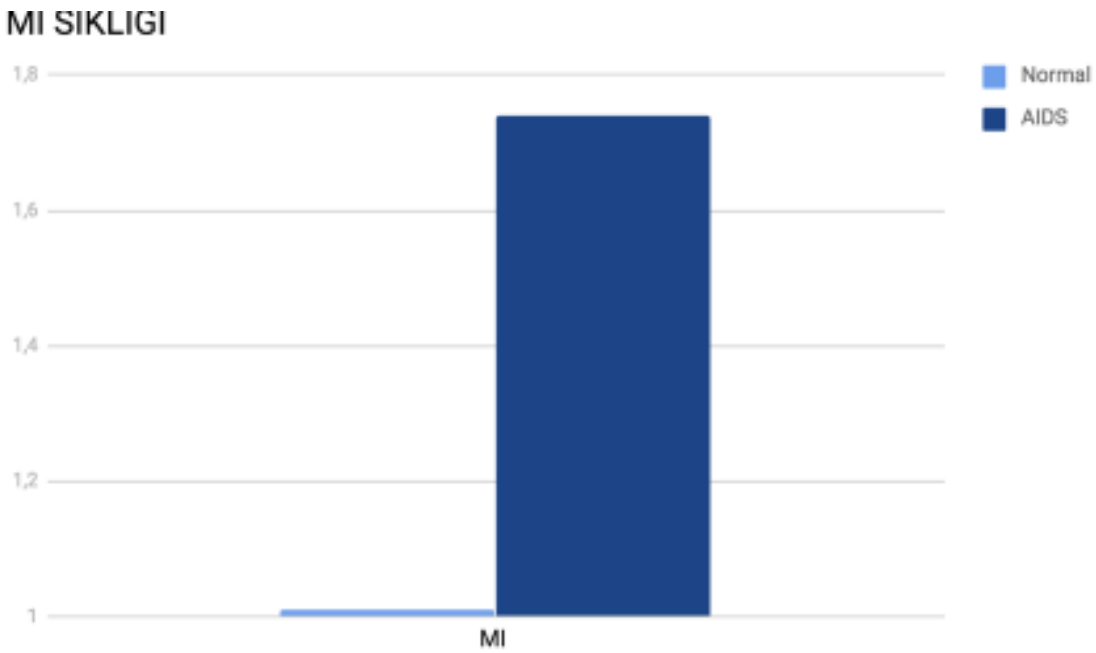
AIDS'de İNFLAMASYON KVS RİSK !

- HIV + bireyde **ATERON PLAĞI** normalden **ÇOK FAZLA**.
  - İnflamasyon plağı, **plak aterosklerozu** tetikler
- HIV + hastalardaki plaklar daha **unstabil**
- Yüksek KVS riskine rağmen **statin verilme oranı %25**.

Zanni MV, Abbara S, Lo J, et al. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. AIDS. 2013;27(8):1263-1272

MI fazla mı ?

- 1.74 kat fazla.



Triant, V.A., Lee, H., Hadigan, C. and Grinspoon, S.K. 2007. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *The Journal of Clinical Endocrinology and Metabolism* 92(7), pp. 2506–2512.

AIDS'li de MI neden fazla ?

- Yaş
- Sigara
- Aile öyküsü
- Dislipidemi ↑ ↑ ↑
- HT ↑ ↑ ↑
- DM ↑ ↑
- Ateroskleroz ↑ ↑
- ART
  - PI kullanımı
  - > 6 ay ABC ya da DDI, Stavudin almak

Triant, V.A., Lee, H., Hadigan, C. and Grinspoon, S.K. 2007. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease.

IV. ART ve KALP

Hangi ilaçlar !

Proteaz inh. (**…..navir**):

- Makrofajdan kolesterol atılımını ⬇ ⬇
- Endotelde NO salımını ⬇
- Lipid profili bozukluğu
- Glikoz met boz.

Endotel hasarı

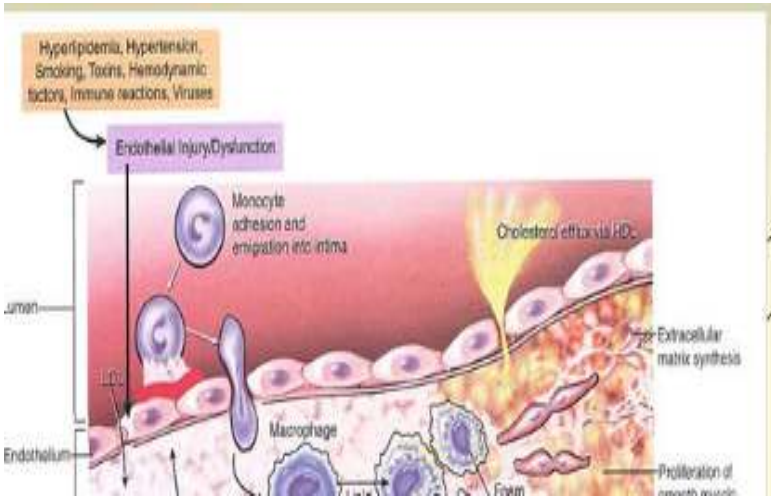
- PI kullananlarda daha **erken** ve **3 kat fazla MI**

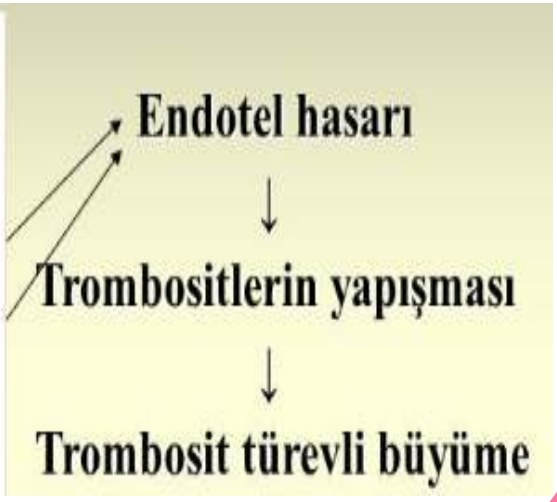
AIDS. 2003 Nov 21;17(17):2479-86.

Hangi İlaçlar

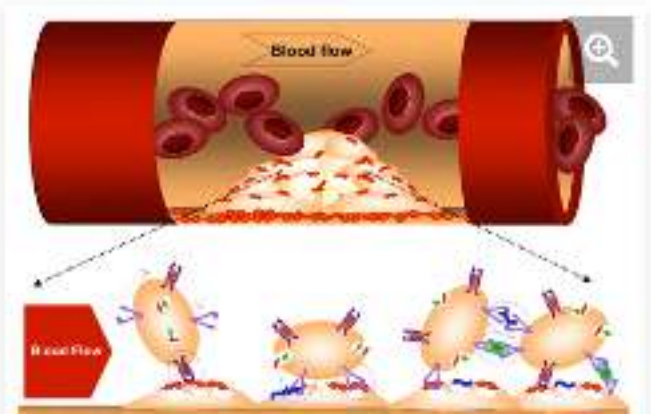
Efavirenz:

- Lökositin endotele tutunmasını arttırır.
- Sonuç: daha fazla inflamasyon





ABAKAVİR



- Trombositlerde kümeleşmeyi ⬆

  - **Abakavir kullanımı MI riskini 2 kat arttırıyor.**

Palella FJ, Althoff KN, Moore R et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD [CROI abstract 749LB]. In Special Issue: Abstracts from the 2015 Conference on Retroviruses and Opportunistic Infections. Top Antivir Med. 2015;23(e-1):335-336.

ABC;

Study	Design	Findings
Positive studies		
SMART/INSIGHT and D:A:D Study Groups 2008	Observational study; n=2,752	• ABC was associated with an approximately doubled CV risk • ABC may cause vascular inflammation, which may precipitate a CVD event
Martin et al. 2009	Randomized, open-label, multicenter, 96-week trial; n= 350	ABC-3TC was associated with more serious non-AIDS events, particularly CV events than TDF-FTC
Lang et al. 2010	Nested case-control study; n=1,173	• Short-term/recent ABC was associated with an increased risk of MI in the overall sample (OR 2.01; 95% CI 1.11, 3.64) • No increased risk with ABC was observed in the subset of patients who did not use cocaine or IV drugs
Obel et al. 2010	Prospective, nationwide cohort study; n=2,952	ABC was associated with an increased risk of MI
Choi et al. 2011	National cohort analysis; n=10,931	Recent ABC exposure was independently associated with increased risk for atherosclerotic CVE
Durand et al. 2011	Cohort and a nested case-control study; n=7,053	• HIV+ individuals were at higher risk of AMI than the general population • Any or current exposure to ABC was associated with increased ORs for AMI • Results should be interpreted with caution in the absence of data on smoking and HIV clinical status

ABC risksiz !

Negative studies		
Brothers et al. 2009	Pooled analysis; n=14,174	• Few MI events were observed • There was no excess risk of MI with ABC
Triant et al. 2010	Retrospective database analysis; n=6,517	Of the ART evaluated, only TDF was associated with acute MI
Bedimo et al. 2011	Retrospective database analysis; n=6,517	• No association was observed between cumulative or current ABC use and acute MI or CVE • ABC was more commonly used than TDF among patients with prior CKD • CKD independently predicted higher rates of acute MI and CVE
Cruciani et al. 2011	Meta-analysis of RCTs; n=7,898 from 20 studies	Compared with controls, ABC did not increase the occurrence of MI (RR 0.73; 95% CI 0.39, 1.35; *P*=0.31), or overall major CV endpoints (RR 0.95; 95% CI 0.62, 1.44; *P*=0.80)
Ribaudo et al. 2011	Cohort analysis of ART-naïve patients randomly assigned ABC in clinical trials; n=5,056	No evidence of increased short- or long-term risk of MI or serious CVD events was found with ABC
Ding et al. 2012	FDA-conducted meta-analysis of RCTs; n=9,868 from 26 studies	No statistically significant difference in MI events was detected between ABC-containing regimens and non-ABC regimens (OR 1.02; 95% CI 0.56, 1.84)

3TC=lamivudine; AMI=acute myocardial infarction; ART=antiretroviral therapy=CI, confidence intervals; CKD=chronic kidney disease; CV=cardiovascular; CVE=cerebrovascular events; FDA=Food and Drug Administration; FTC=emtricitabine; IV=intravenous; OR=odds ratio; RCTs=randomized controlled trials; RR=risk ratio; TDF=tenofovir.

OPEN ACCESS Freely available online

PLOS ONE

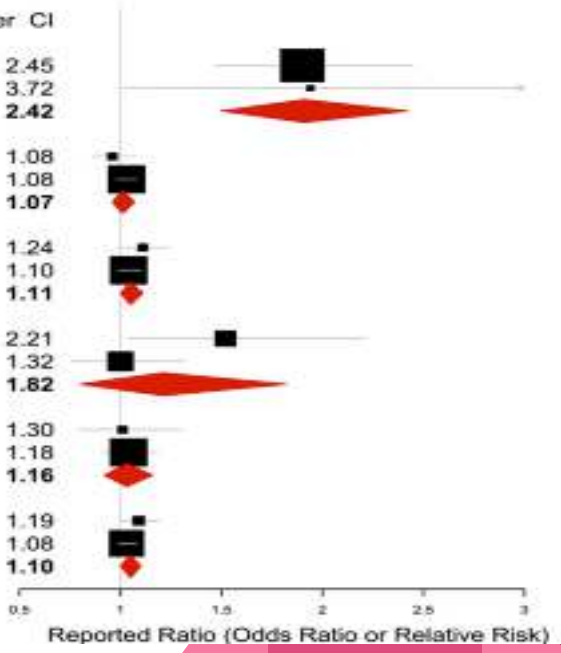
Risk of Cardiovascular Disease from Antiretroviral Therapy for HIV: A Systematic Review

Clay Bavinger[1]*, Eran Bendavid[1,2], Katherine Niehaus[1], Richard A. Olshen[4], Ingram Olkin[5], Vandana Sundaram[1], Nicole Wein[1], Mark Holodniy[3], Nanjiang Hou[1,3], Douglas K. Owens[3,1], Manisha Desai[6]

1 Center for Primary Care and Outcomes Research, and Center for Health Policy, Stanford University, Stanford, California, United States of America, 2 Division of General Internal Medicine, Stanford University Medical Center, Stanford, California, United States of America, 3 Veterans Affairs Palo Alto Health Care System, Palo Alto, California, United States of America, 4 Division of Biostatistics, Stanford University Medical Center, Stanford, California, United States of America, 5 Department of Statistics, Stanford University, Stanford, California, United States of America, 6 Quantitative Sciences Unit, Department of Medicine, Stanford University Medical Center, Stanford, California, United States of America

a.

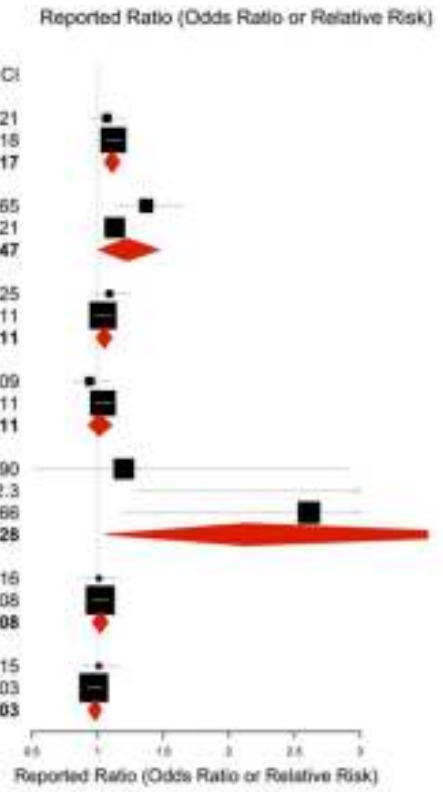
Author	Class	Drug	Exposure Risk	Outcome	Statistic	Lower CI	Point estimate	Upper CI
DAD 2008	NRTI	Abacavir	Recent	MI	RR	1.47	1.90	2.45
Obel	NRTI	Abacavir	Recent	MI	RR	1.01	1.94	3.72
Summary	**NRTI**	**Abacavir**	**Recent**	**MI**		**1.50**	**1.91**	**2.42**
Lang	NRTI	Lamivudine	Per Year	MI	OR	0.86	0.96	1.08
DAD 2008	NRTI	Lamivudine	Per Year	MI	RR	0.98	1.03	1.08
Summary	**NRTI**	**Lamivudine**	**Per Year**	**MI**		**0.96**	**1.01**	**1.07**
Lang	NRTI	Stavudine	Per Year	MI	OR	0.99	1.11	1.24
DAD 2008	NRTI	Stavudine	Per Year	MI	RR	0.99	1.04	1.10
Summary	**NRTI**	**Stavudine**	**Per Year**	**MI**		**1.00**	**1.05**	**1.11**
Durand	NRTI	Stavudine	Recent	MI	OR	1.04	1.52	2.21
DAD 2008	NRTI	Stavudine	Recent	MI	RR	0.76	1.00	1.32
Summary	**NRTI**	**Stavudine**	**Recent**	**MI**		**0.80**	**1.21**	**1.82**
Lang	NRTI	Tenofovir	Per Year	MI	OR	0.79	1.01	1.30
DAD 2010	NRTI	Tenofovir	Per Year	MI	RR	0.91	1.04	1.18
Summary	**NRTI**	**Tenofovir**	**Per Year**	**MI**		**0.92**	**1.03**	**1.16**
Lang	NRTI	Zidovudine	Per Year	MI	OR	1.00	1.09	1.19
DAD 2008	NRTI	Zidovudine	Per Year	MI	RR	0.99	1.03	1.08
Summary	**NRTI**	**Zidovudine**	**Per Year**	**MI**		**1.00**	**1.05**	**1.10**



PI için de Riskli// Risksiz

b.

Author	Class	Drug	Exposure Risk	Outcome	Statistic	Lower CI	Point estimate	Upper CI
Lang	PI	Indinavir	Per Year	MI	OR	0.95	1.07	1.21
DAD 2010	PI	Indinavir	Per Year	MI	RR	1.07	1.12	1.18
Summary	**PI**	**Indinavir**	**Per Year**	**MI**		**1.05**	**1.11**	**1.17**
Lang	PI	Lopinavir	Per Year	MI	OR	1.13	1.37	1.65
DAD 2010	PI	Lopinavir	Per Year	MI	RR	1.05	1.13	1.21
Summary	**PI**	**Lopinavir**	**Per Year**	**MI**		**1.01**	**1.22**	**1.47**
Lang	PI	Nelfinavir	Per Year	MI	OR	0.96	1.09	1.25
DAD 2010	PI	Nelfinavir	Per Year	MI	RR	0.98	1.04	1.11
Summary	**PI**	**Nelfinavir**	**Per Year**	**MI**		**0.99**	**1.05**	**1.11**
Lang	PI	Saquinavir	Per Year	MI	OR	0.81	0.94	1.09
DAD 2010	PI	Saquinavir	Per Year	MI	RR	0.98	1.04	1.11
Summary	**PI**	**Saquinavir**	**Per Year**	**MI**		**0.93**	**1.01**	**1.11**
Daftary	PI	PI	Recent	MI	OR	0.5	1.20	2.90
Holmberg	PI	PI	Recent	MI	OR	1.3	4.92	32.3
Ricketts	PI	PI	Recent	MI	OR	1.19	2.61	5.66
Summary	**PI**	**PI**	**Recent**	**MI**		**1.06**	**2.13**	**4.28**
Lang	NNRTI	Efavirenz	Per Year	MI	OR	0.87	1.01	1.16
DAD 2010	NNRTI	Efavirenz	Per Year	MI	RR	0.96	1.02	1.08
Summary	**NNRTI**	**Efavirenz**	**Per Year**	**MI**		**0.96**	**1.02**	**1.08**
Lang	NNRTI	Nevarapine	Per Year	MI	OR	0.88	1.01	1.15
DAD 2010	NNRTI	Nevarapine	Per Year	MI	RR	0.92	0.97	1.03
Summary	**NNRTI**	**Nevarapine**	**Per Year**	**MI**		**0.93**	**0.98**	**1.03**



Dislipidemi

ART

DAD STUDY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2003 VOL. 349 NO. 21

Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group*

ABSTRACT

23500 hasta.

- Çalışma süresinde **126 tane MI**.
- **ART alanlarda MI riski %26 ⬆**

PI & Dislipidemi

PI kullanalarda

- Dislipidemi
- Hiperinsulinemi
- Bozulmuş glukoz met.

Ritonavir

- Hipertrigliseridemi
- HDL ⬇

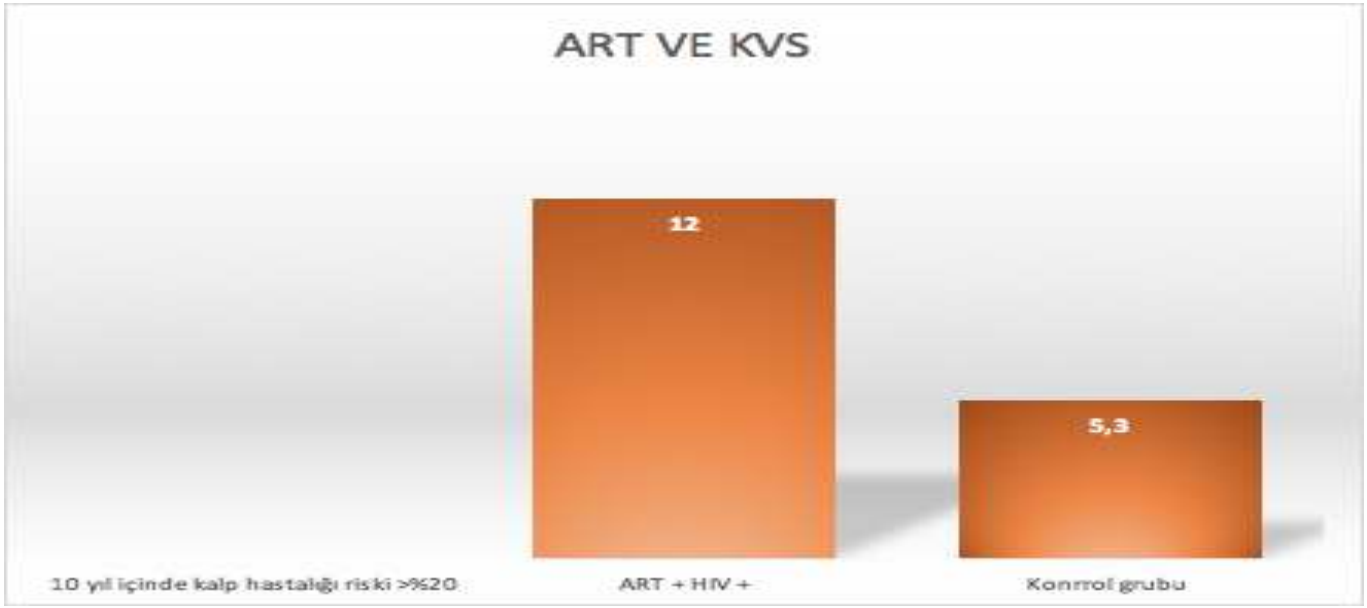
Indinavir

- İnsülin direnci

LPN/RTN

- Hipertrigliseridemi
- İnsülin direnci

>10 yıl içinde kalp hast. riski >%20



Switchmrk: Erken sonlandırılan çalışma ! (24w)

Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials

Joseph J Eron, Benjamin Young, David A Cooper, Michael Youle, Edwin DeJesus, Jaime Andrade-Villanueva, Casey Workman, Roberto Zajdenverg, Gerd Fätkenheuer, Daniel S Berger, Princy N Kumar, Anthony J Rodgers, Melissa A Shaughnessy, Monica L Walker, Richard J O Barnard, Michael D Miller, Mark J DiNubile, Buch-Yen Nguyen, Ranil Leavitt, Xia Xu, Peter Sklar, for the SWITCHMRK 1 and 2 investigators*

Lancet 2010; 375: 396–407
Published Online
January 15, 2010
DOI:10.1016/S0140-6736(09)61913-9
See Comment page 354

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Summary

Background To reduce lipid abnormalities and other side-effects associated with antiretroviral regimens containing lopinavir-ritonavir, patients might want to switch one or more components of their regimen. We compared substitution of raltegravir for lopinavir-ritonavir with continuation of lopinavir-ritonavir in HIV-infected patients with stable viral suppression on lopinavir-ritonavir-based combination therapy.

Methods The SWITCHMRK 1 and 2 studies were multicentre, double-blind, double-dummy, phase 3, randomised controlled trials. HIV-infected patients aged 18 years or older were eligible if they had documented viral RNA (vRNA) concentration below the limit of assay quantification for at least 3 months while on a lopinavir-ritonavir-based regimen. 707 eligible patients were randomly allocated by interactive voice response system in a 1:1 ratio to switch from lopinavir-ritonavir to raltegravir (400 mg twice daily; n=353) or to remain on lopinavir-ritonavir (two 200 mg/50 mg tablets twice daily; n=354), while continuing background therapy consisting of at least two nucleoside or nucleotide reverse transcriptase inhibitors. Primary endpoints were the mean percentage change in serum lipid concentrations from baseline to week 12; the proportion of patients with vRNA concentration less than 50 copies per mL at week 24 (with all treated patients who did not complete the study counted as failures) with a prespecified non-inferiority margin of −12% for each study; and the frequency of adverse events up to 24 weeks. Analyses were done according to protocol. These trials are registered with ClinicalTrials.gov, numbers NCT00443703 and NCT00443729.

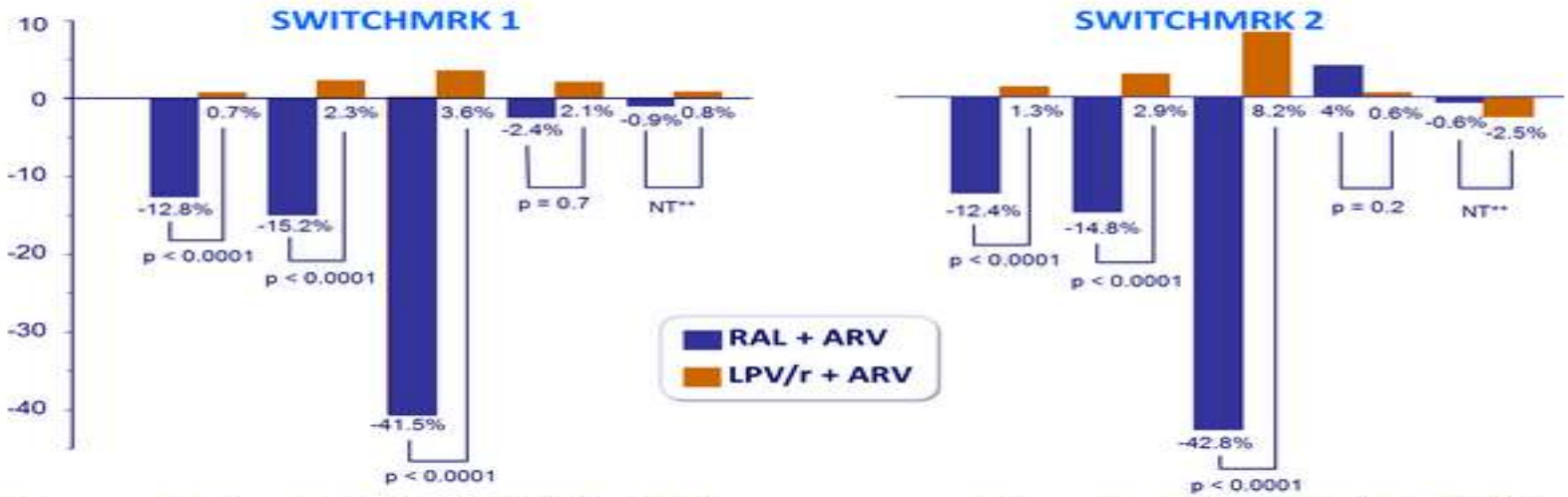
Findings 702 patients received at least one dose of study drug and were included in the efficacy and safety analyses for the combined trials (raltegravir, n=350; lopinavir-ritonavir, n=352). Percentage changes in lipid concentrations from baseline to week 12 were significantly greater (p<0·0001) in the raltegravir group than in the lopinavir-ritonavir group in each study, yielding combined results for total cholesterol −12·6% vs 1·0%, non-HDL cholesterol −15·0% vs 2·6%, and triglycerides −42·2% vs 6·2%. At week 24, 293 (84·4%, 95% CI 80·2–88·1) of 347 patients in the raltegravir group had vRNA concentration less than 50 copies per mL compared with 319 (90·6%, 87·1–93·5) of 352 patients in the lopinavir-ritonavir group (treatment difference −6·2%, −11·2 to −1·3). Clinical and laboratory adverse events occurred at similar frequencies in the treatment groups. There were no serious drug-related adverse events or deaths. The only drug-related clinical adverse event of moderate to severe intensity reported in 1% or more of either treatment group was diarrhoea, which occurred in ten patients in the lopinavir-ritonavir group (3%) and no patients in the raltegravir group. The studies were terminated at week 24 because of lower than expected virological efficacy in the raltegravir group compared with the lopinavir-ritonavir group.

Interpretation Although switching to raltegravir was associated with greater reductions in serum lipid concentrations than was continuation of lopinavir-ritonavir, efficacy results did not establish non-inferiority of raltegravir to lopinavir-ritonavir.

Funding Merck.

Lipid seviyesi ve ilaçlar !

Mean * % changes in fasting lipid concentrations from baseline to W12 :



Mean (mmol/L)	Total cholesterol		Non HDL-C		Triglycerides*		LDL-C		HDL-C	
Baseline	5.6	5.3	4.3	4.1	2.1	1.8	3	2.7	1.3	1.2
W12	4.8	5.3	3.6	4.1	1.3	1.9	2.8	2.7	1.2	1.2

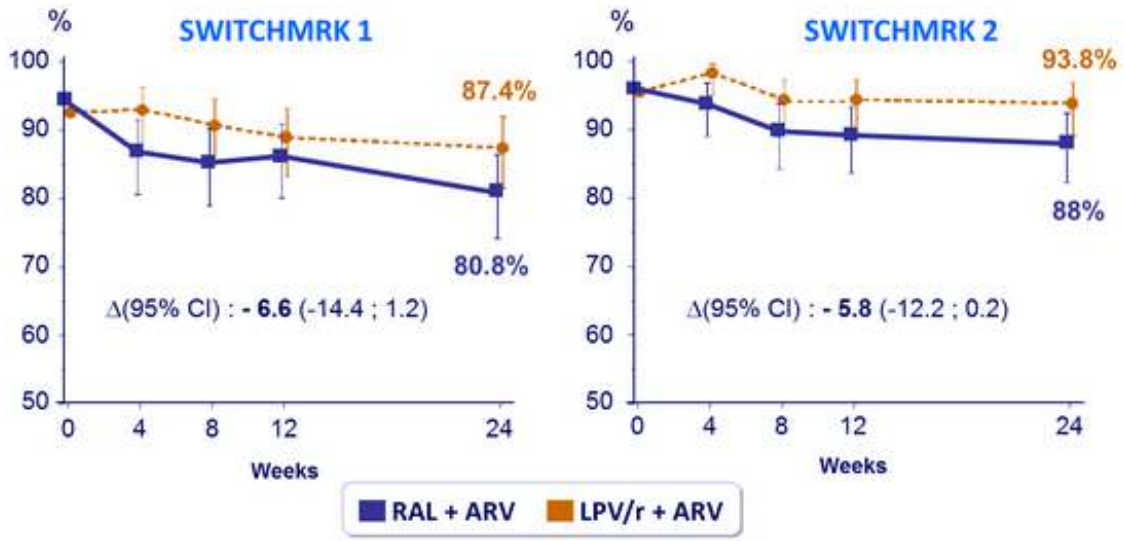
Mean (mmol/L)	Total cholesterol		Non HDL-C		Triglycerides*		LDL-C		HDL-C	
Baseline	5.6	5.5	4.3	4.2	2.4	2.5	2.7	2.7	1.2	1.2
W12	4.7	5.5	3.6	4.3	1.4	2.7	2.7	2.7	1.2	1.2

* median changes for triglycerides
** not tested

Switch to RAL-containing regimen

SWITCHMRK Study: Switch to RAL vs continuation of LPV/r

Proportion of patients with HIV-1 RNA < 50 c/mL :



RAL + ARV	174	166	169	173	172	176	176	176	176	175
LPV/r + ARV	174	171	171	171	174	178	178	177	177	178

GÜVENİLİR ART ?

- İntegraz inh.
- Rilpivirin
- Atazanavir

Dislipidemide hangi ilaç uygun ?

Table 1. Recommendations for High- and Moderate-Intensity Statin Therapy Based on 10-Year Risk for First ASCVD Event[a]

High-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by ≥50% on Average)	Moderate-Intensity Statin Therapy (Daily Dose Lowers LDL-C Level by 30%-50% on Average)
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg Pitavastatin 2-4 mg

Hangisi daha etkili ki?

- **<u>Rosuvastatin</u>** (CRESTOR) (10 mg/day) **daha etkildir**

- Kimden;
  - Atorvastatin (10–20 mg/day),
  - Simvastatin (20–40 mg/day),
  - Pravastatin (20–40 mg/day)

Variable	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
LDL cholesterol reductions (dose range, mg)	38 to 54% (10 to 80)	17 to 33% (20 to 80)	29 to 48% (20 to 80)	31 to 41% (1 to 4)	19 to 40% (10 to 40)	52 to 63% (10 to 40)	28 to 41% (10 to 40)
Elimination half-life, hours	15 to 30	0.5 to 2.3	2.9	12	1.3 to 2.8	19	2 to 3
Bioavailability, percent	12	19 to 29	5	51	18	20	5
Protein binding, percent	80 to 90	>99	>95	99	43 to 55	88	94 to 98
Solubility	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Cytochrome 450 metabolism and isozyme	3A4	2C9	3A4	Limited 2C9, 2C8	-	Limited 2C9	3A4, 3A5
Active metabolites	Yes	No	Yes	Yes	No	No	Yes
Effect of food on absorption of drug	None	Negligible	Increased absorption	Decreases	Decreased absorption	None	None
Optimal time of administration	Anytime	IR: evening (or morning and evening if taken twice daily) XR: anytime	IR: with evening meal (or with morning and evening meal if taken twice daily) XR: anytime	Anytime	Anytime	Anytime	Evening
Renal excretion of absorbed dose, %	2	<6	10	15	20	10	13

Statinler ve Etkileşim !

PI

- Simvastatin ⬆⬆
- Lovastatin ⬆⬆
- PI ile **asla** beraber kullanma (CYP 450 etkileşimi)
- **Rabdomiyoliz riski !**

NNRTI

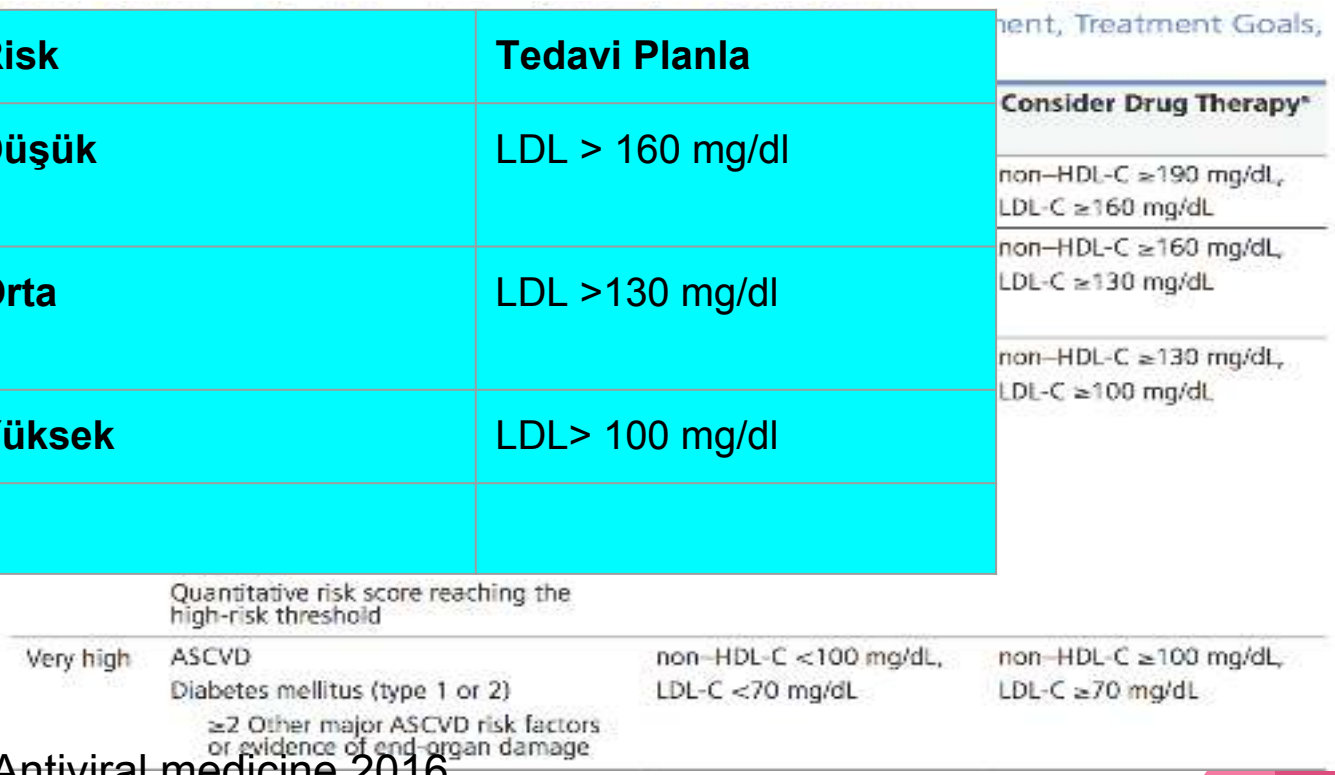
- Efavirenz
  - Simvastatin⬇⬇
  - Lovastatin ⬇⬇
- Rilpivirinde etkileşim yok...

- **INTEGRAZ INH.**
  - Etkileşmez
  - Ama **Cobistat** CYP3A sistemini inh.eder **statin seviyesi artar** ⬆⬆
  - lovastatin and simvastatin kontra endike.

https://www.uptodate.com/contents/lovastatin-drug-information?source=see_link

NE ZAMAN BAŞLAYALIM ?

Risk	Tedavi Planla
Düşük	LDL > 160 mg/dl
Orta	LDL >130 mg/dl
Yüksek	LDL> 100 mg/dl



…nent, Treatment Goals,

			Consider Drug Therapy*
	Quantitative risk score reaching the high-risk threshold		
Very high	ASCVD Diabetes mellitus (type 1 or 2) ≥2 Other major ASCVD risk factors or evidence of end-organ damage	non–HDL-C <100 mg/dL, LDL-C <70 mg/dL	non–HDL-C ≥100 mg/dL, LDL-C ≥70 mg/dL
			non–HDL-C ≥190 mg/dL, LDL-C ≥160 mg/dL
			non–HDL-C ≥160 mg/dL, LDL-C ≥130 mg/dL
			non–HDL-C ≥130 mg/dL, LDL-C ≥100 mg/dL

Topics in Antiviral medicine 2016

SUT izin veriyor mu ?

LDL DEĞERLERİ	EK RİSK FAKTÖRLERİ
190 mg/dL nin üstünde olduğu durumlar	Risk faktörü aranmaz
160 mg/dL nin üstünde olduğu durumlar	2 Risk faktörü aranır
130 mg/dL nin üstünde olduğu durumlar	3 risk faktörü aranır
100 mg/dL nin üstünde olduğu durumlar	Ancak Diabetes mellitus,Akut koroner sendrom,geçirilmiş MI,geçirilmiş inme,Koroner arter hastalığı,Abdominal aort anevrizması veya karotid arter hastalığı olanlarda RİSK FAKTÖRÜNE gerek olmadan başlanır.(Bu durumda sadece 1 tane tetkik yeterlidir.)

SUT ne diyor ?

TEDAVİYE BAŞLAMAYA ESAS OLAN İLK UZMAN HEKİM RAPORUNDA

- Rapor öncesi son **6 ay içinde** 130,160 ve 190 mg/dL değerleri için **en az bir hafta ara ile 2 defa olmak** üzere kan lipid düzeylerinin her ikisinde de yüksek olduğunu gösteren tetkik sonuçları belirtilir. (TETKİK SAYISI İKİYE ÇIKARILMIŞTIR.)
- Rapor süresi boyunca **tetkik sonuçları değerlendirilmeye alınmaz**.
- Raporun **yenilenmesinde** lipid düzeyini gösteren **yeni bir tetkik sonucu istenmez**.
- Bu ilaçlar uzman hekim raporuna dayanılarak **tüm hekimlerce reçete edilir**.

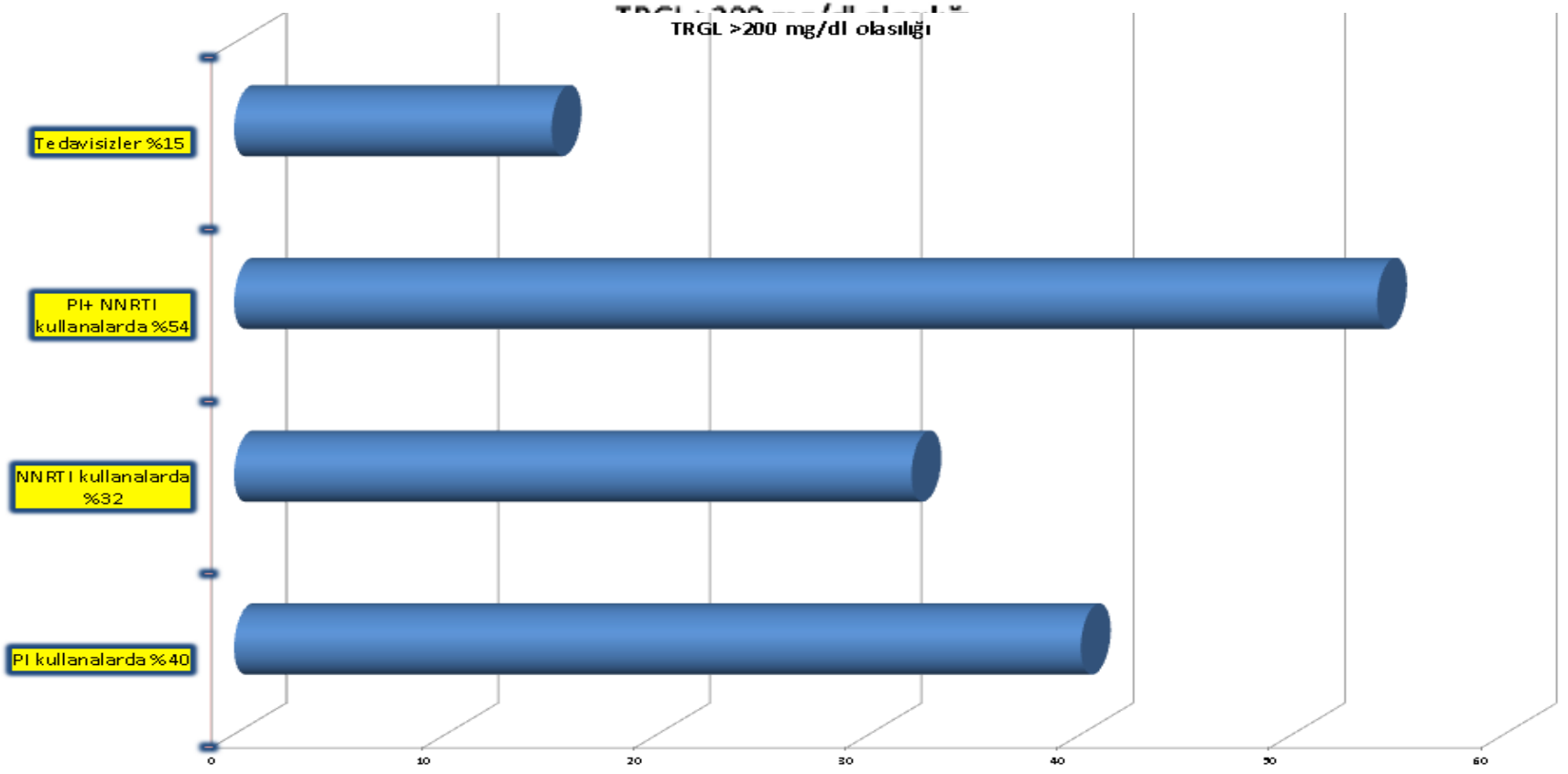
- **ANCAK; Statinlerin 40 mg ve üzeri** etken madde içeren dozları (kombinasyonları dahil) **Kardiyoloji,Kalp ve Damar Cerrahisi ,endokrinoloji** uzman hekimlerince düzenlenecek uzman hekim raporuna dayanılarak **bu hekimlerce reçete edilir.**

Hipertrigliseridemi

- KVS hastalığı için **bağımsız** risk faktörü

- **Pankreatite** yol açabilir.

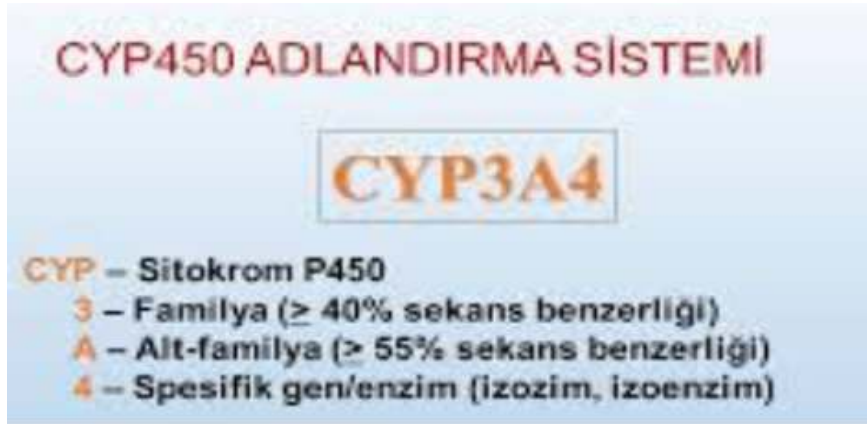
TRGL >200 ma/dl olasılığı



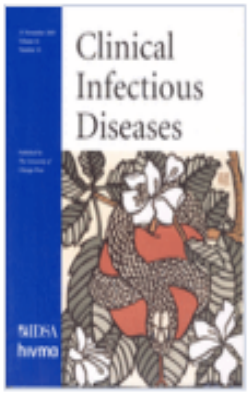
Hipertrigliseridemi (>500 mg)

Lipoprotein lipaz aktivasyonu

- **Fenofibrat** (CYP 4a-ART etkileşmez)
- **Gemfibrozil** CYP 4a-ART etkileşmez)
- Niasin



Balık Yağı Etkin ! (RCT)



Volume 41, Issue 10
15 November 2005

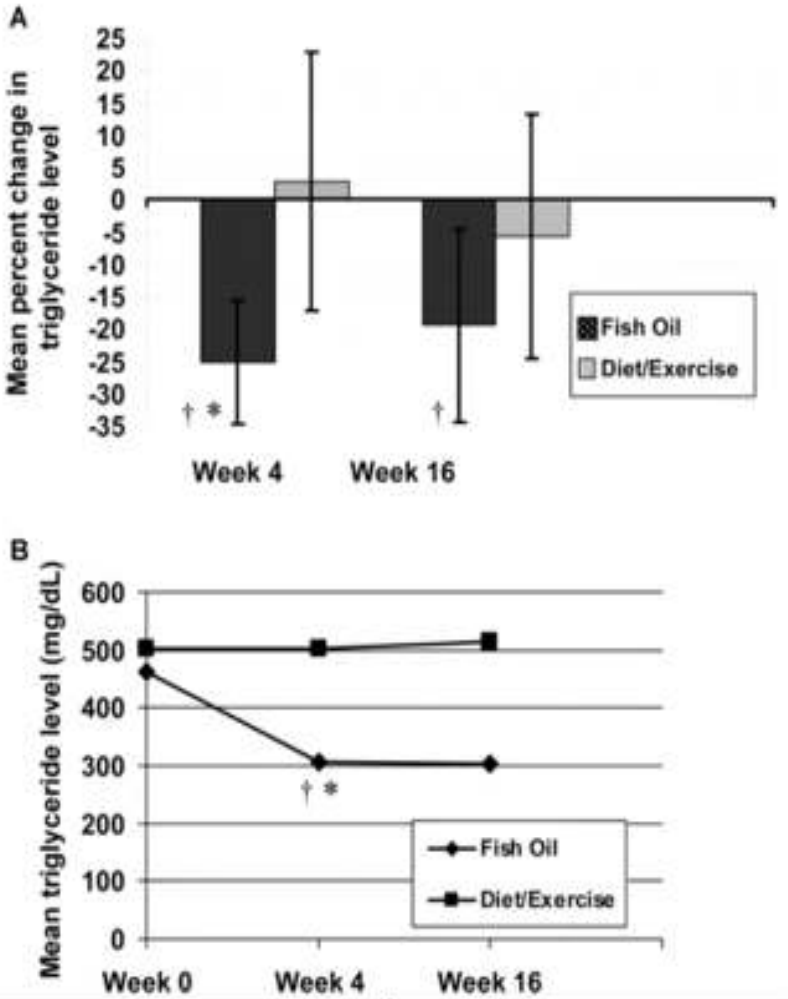
Article Contents

Randomized Study of the Safety and Efficacy of Fish Oil (Omega-3 Fatty Acid) Supplementation with Dietary and Exercise Counseling for the Treatment of Antiretroviral Therapy—Associated Hypertriglyceridemia FREE

David A. Wohl ✉, Hsiao-Chuan Tien, Marjorie Busby, Catherine Cunningham, Beth MacIntosh, Sonia Napravnik, Elisheva Danan, Kimberly Donovan, Mina Hossenipour, Ross J. Simpson

Clinical Infectious Diseases, Volume 41, Issue 10, 15 November 2005, Pages 1498–1504, https://doi.org/10.1086/497273

Published: 15 November 2005 **Article history** ▾



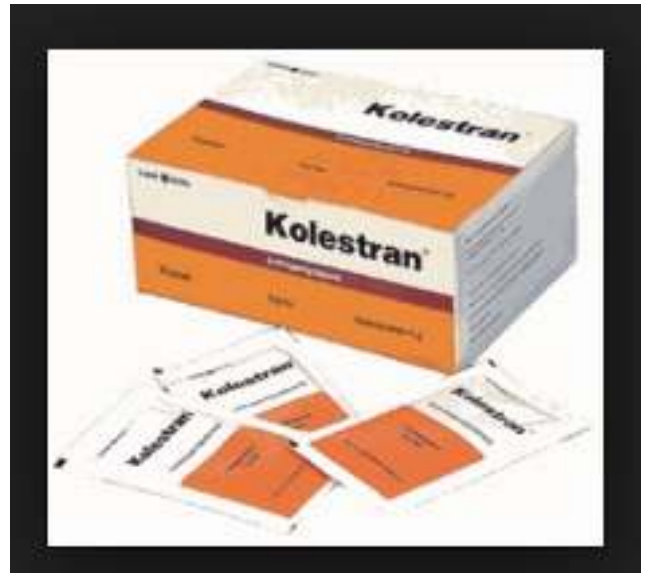
From: Randomized Study of the Safety and Efficacy of Fish Oil (Omega-3 Fatty Acid) Supplementation with Dietary and Exercise Counseling for the Treatment of Antiretroviral Therapy—Associated Hypertriglyceridemia

Clin Infect Dis. 2005;41(10):1498-1504. doi:10.1086/497273

Hiper trigliseridemi (>500 mg)

Kollestirmain :

- Önerilmez !!!
    - **ART emilimini de azaltıyor.**

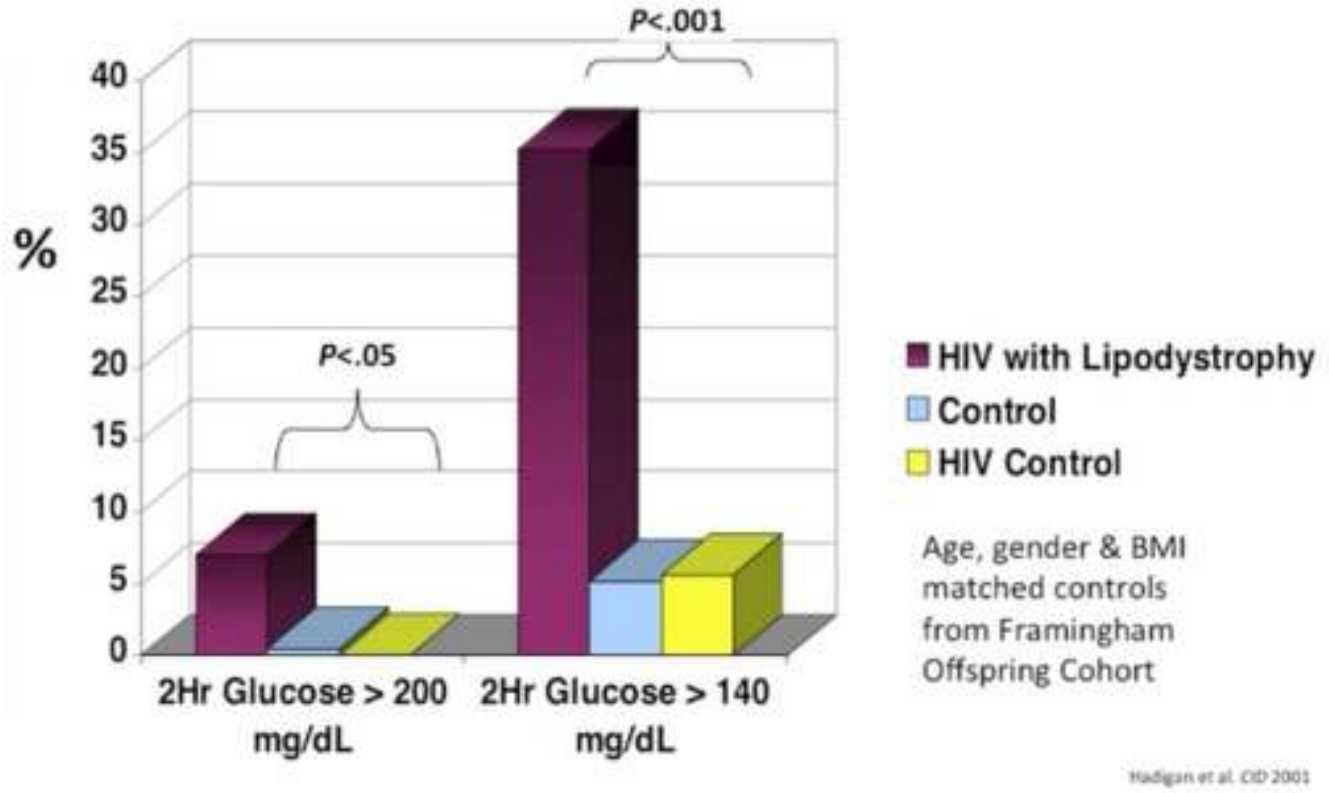


Ezetemib (GIS'den emilim engelliyor)

Ama (AIDS'lilerde) **faydasız** !!!

BMC Infect Dis. 2014; 14: 497.

Lipodistrofiye glukoz met boz. eşlik ediyor. !



Hipertansiyon için FARKLI GÖRÜŞLER

- HIV + grupta HT sıklığı topluma göre **3 kat fazla**
  - Nephrol Dial Transplant. 2004 Sep;19(9):2250-8
  - J Clin Endocrinol Metab. 2007;92(7):2506.
- HIV + grupta **HT sıklığı farksız**.
  - J Hypertens. 2008 Nov;26(11):2126-33.
- İnsülin direnci ve metabolik sendrom varsa HT riski fazla

Sigara bıraktırma >%40 üzerinde etkin

Clin Infect Dis. 2015 May 1;60(9):1415-23. doi: 10.1093/cid/civ013. Epub 2015 Jan 16.

Myocardial infarction among Danish HIV-infected individuals: population-attributable fractions associated with smoking.

Rasmussen LD[1], Helleberg M[2], May MT[3], Afzal S[4], Kronborg G[5], Larsen CS[6], Pedersen C[1], Gerstoft J[2], Nordestgaard BG[4], Obel N[2].

Author information

Abstract

BACKGROUND: Human immunodeficiency virus-infected individuals have increased risk of myocardial infarction (MI); however, the contribution from smoking and potentiating effects of HIV are controversial.

METHODS: From the Danish HIV Cohort Study and the Copenhagen General Population Study, we identified 3251 HIV-infected individuals and 13 004 population controls matched on age and gender. Data on MI were obtained from the National Hospital Registry and the National Registry of Causes of Death. We calculated adjusted incidence rate ratios (aIRR) for risk of MI and population-attributable fractions (PAF) of MI associated with smoking.

RESULTS: In never smokers, HIV was not associated with an increased risk of MI (aIRR, 1.01; 95% confidence interval [CI], .41-2.54). In previous and current smokers, HIV was associated with a substantially increased risk of MI (aIRR, 1.78; 95% CI, .75-4.24 and aIRR, 2.83; 95% CI, 1.71-4.70). The PAF associated with ever smoking (previous or current) was 72% (95% CI, 55%-82%) for HIV-infected individuals and 24% (95% CI, 3%-40%) for population controls. If all current smokers stopped smoking, 42% (95% CI, 21%-57%) and 21% (95% CI, 12%-28%) of all MIs could potentially be avoided in these 2 populations.

CONCLUSIONS: Smoking is associated with a higher risk of MI in the HIV-infected population than in the general population. Approximately 3 of 4 MIs among HIV-infected individuals are associated with ever smoking compared with only 1 of 4 MIs among population controls. Smoking cessation could potentially prevent more than 40% of MIs among HIV-infected individuals, and smoking cessation should be a primary focus in modern HIV care.

Sigaranın bırakılması

Tütün kullanan HIV-pozitif bireyler, sigaranın bırakılmasının sağlık üzerindeki olası yararları konusunda bilinçlendirilmelidir; bunlar, tütünle ilişkili hastalıkların gelişme riskinin azalması, tütünle ilişkili mevcut hastalıkların ilerlemesinde yavaşlama ve yaşam beklentisinin ortalama 10 yıl artması şeklinde sıralanabilir. Aşağıdaki iki soruyu temel alan akış şemasını düzenli olarak değerlendirin

http://www.eacsociety.org/files/guidelines-8.1-turkish.pdf

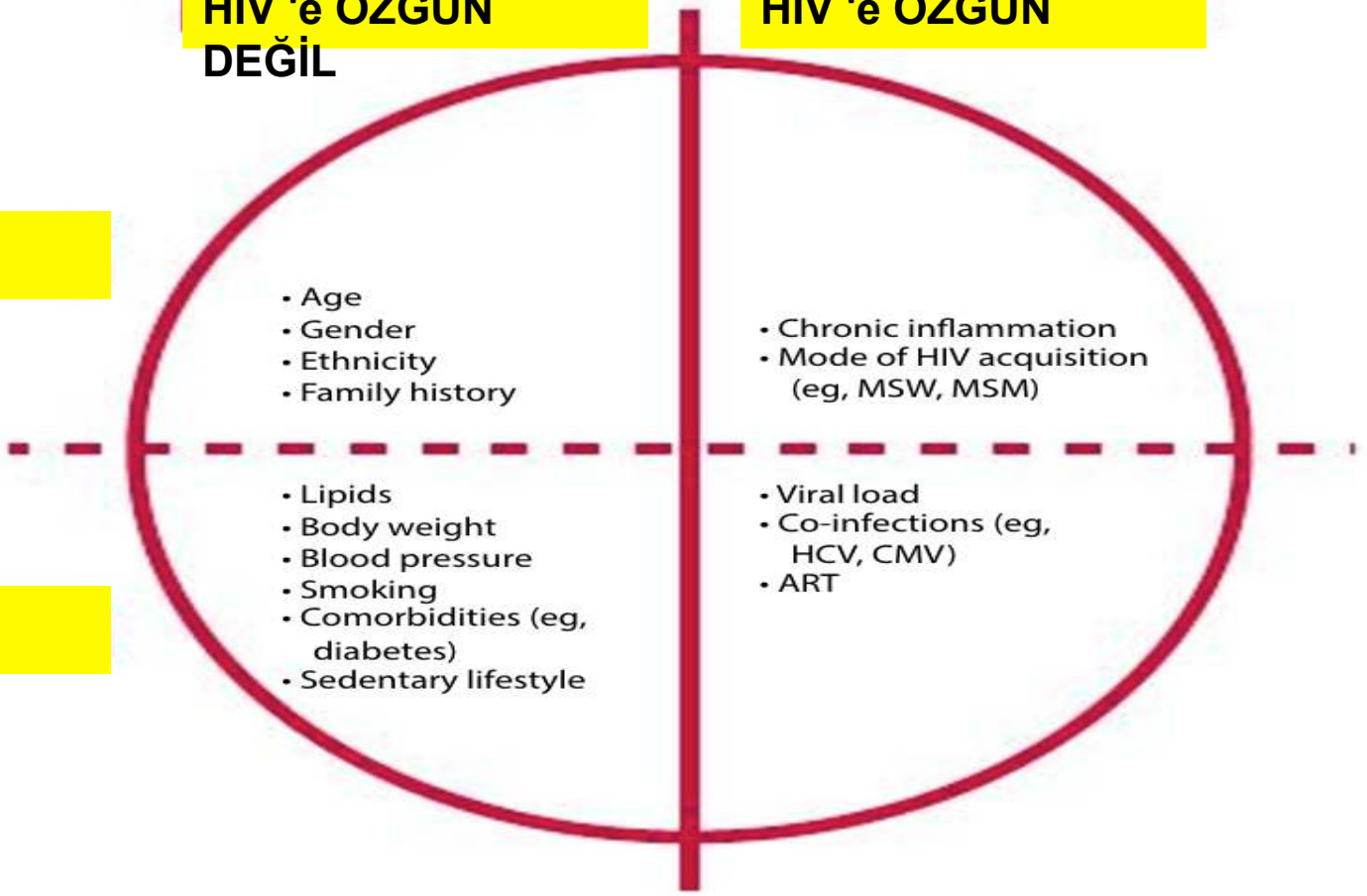
Figure 1. Mechanisms involved in CV risk in HIV population

HIV 'e ÖZGÜN DEĞİL

HIV 'e ÖZGÜN

Değiştirilemez

Değiştirilebilir



ART değişkliği için seçenekler

- **Yıllık KVS riski ≥% 20%ise riskli**
  - PI/r yerine **NNRTI**, **INSTI** veya metabolik etkisi az olan başka bir PI/r kullan.
  - **Stavudin'i değiştir** (Lipoatrofi//Dislipidemi)
  - ZDV // ABC yerine **TDF** kullanmayı dene

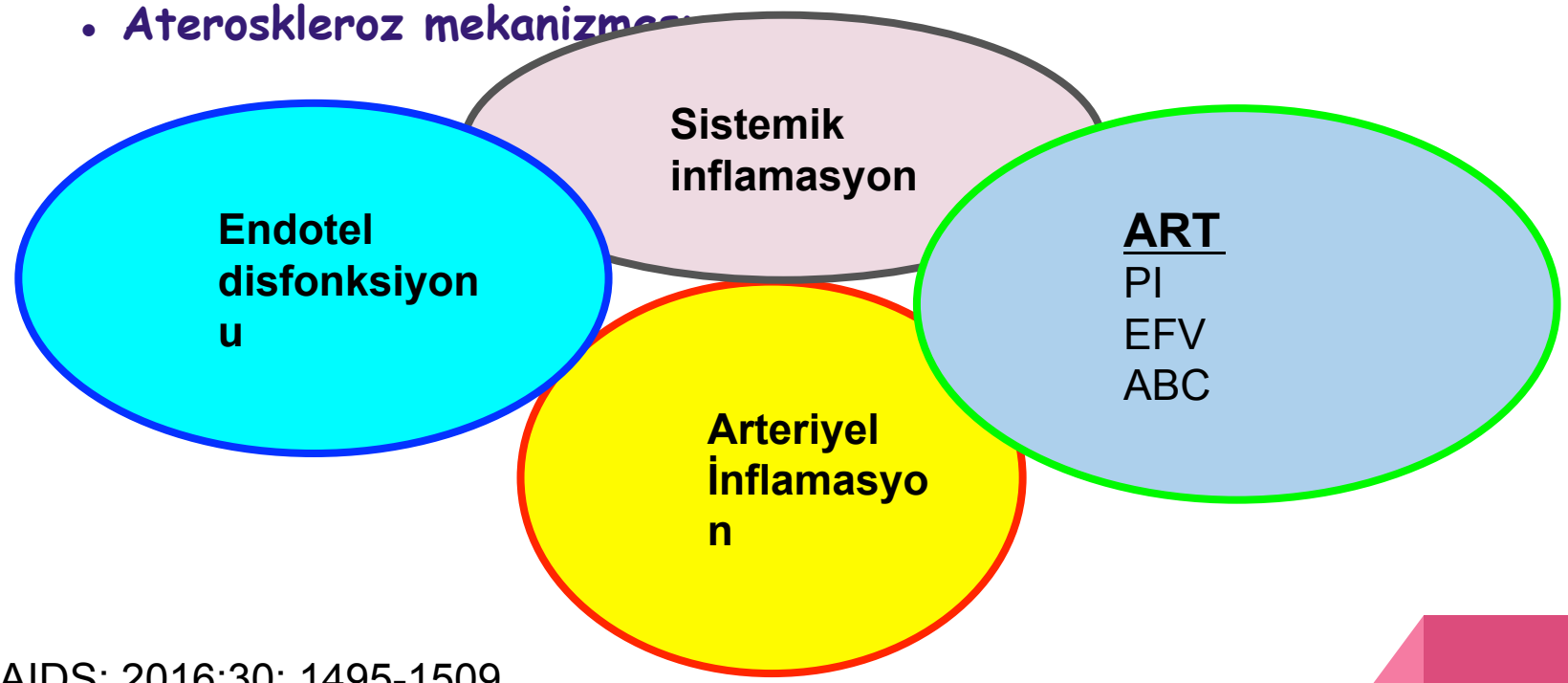
http://www.eacsociety.org/files/guidelines-8.1-turkish.pdf

SONUÇ OLARAK

- HIV + hastada inflamasyon fazla
- Hem HIV viremisi hem de ART KVS riskli...
- Erkenden ART başla
- ART yan etkilerini izle
- Düzenli egzersiz öner... (20 dk/ gün / min)
- Sigarayı bıraktır.
- KVS riski yılda en az bir kez değerlendir.
- Lipidleri düşür.
- Hastaya uygun diyet öner, yağdan kısıtlı diyet öner.

AIDS'li hastada neden KVS hastalığı fazla ?

- Ateroskleroz mekanizmas



AIDS: 2016;30: 1495-1509