Yaşlı Hastalarda Antiretroviral Tedavi

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HIV/AIDS Timeline


RARE CANCER SEEN IN 41 HOMOSEXUALS

Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

1981 The New York Times reports a mysterious illness

1982 The name "AIDS" – Acquired Immune Deficiency Syndrome – is created


1984 Françoise Barré-Sinoussi and Luc Montagnier discover HIV as the cause of AIDS and later win the Nobel Prize

1985 A test for screening blood donations is developed through chimpanzee research



1987 AZT, developed in mice, becomes the first drug approved for treating AIDS

1990 8 million people have HIV



1994 Infant HIV infections begin to fall due to AZT treatment

1996 Combination treatment of antiretrovirals developed



1997 AIDS-related deaths fall in developed countries due to combination treatments

2007 33 million people have HIV



2010 After tests in mice and macaques, Truvada is shown to reduce the risk of HIV infection

2011 Antiretrovirals are shown to reduce the risk of transmitting HIV by 96%


2012 The majority of people worldwide eligible for antiretrovirals are now receiving them

Image credits: Inovaire, Gates Foundation, [illegible], Harvell

Understanding ANIMAL RESEARCH

- HIV Enfeksiyonu genç bir hastalık..
- AIDS ilişkili durumlar azaldı
- Yaşlı popülasyondaki prevalans artmakta
  - Hastaların yaşlanması
  - Yeni vakalar

- HAART ile hastaların yaşam süresi uzadı
- Yaşlı hasta sayısı arttı ve artacak
- 2013 te Amerika'da hastaların % 42'si 50, %6'sı 65 yaş üzeriydi
- 2030 yılında hastaların %73'ünün 50 yaş üzeri olacağı tahmin ediliyor

Smith M, et al. Lancet 2015.

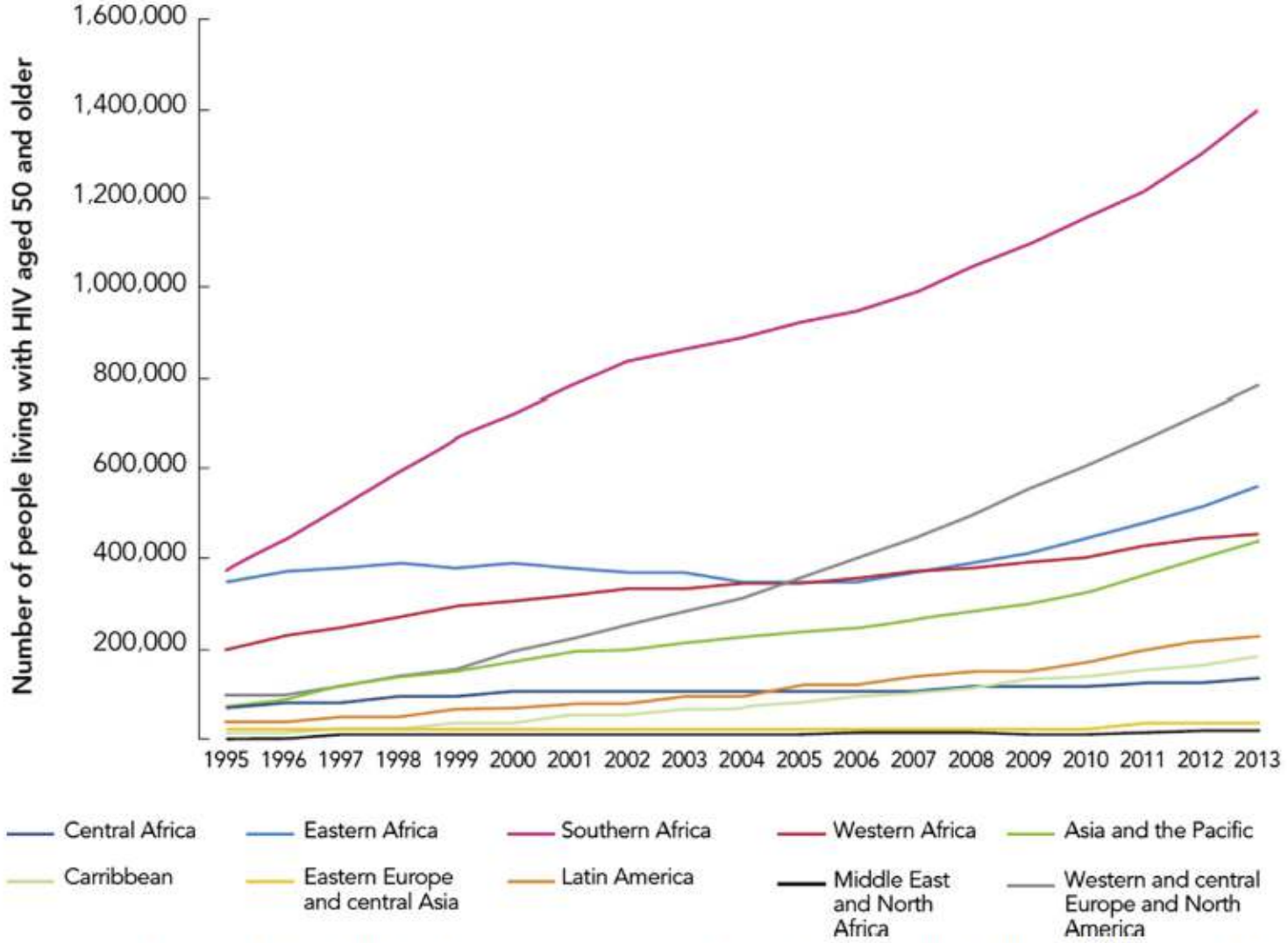
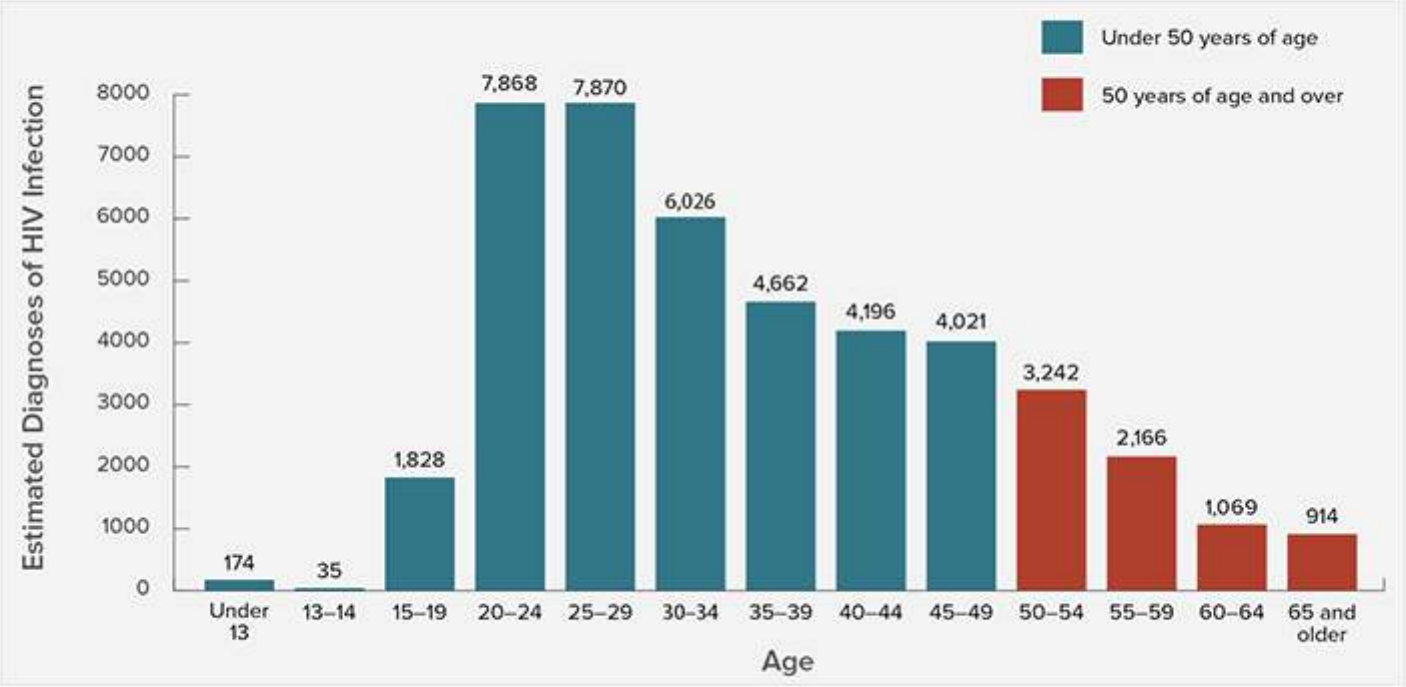


Fig. 1. Estimated number of people living with HIV aged 50 and older by region, 1995 to 2013. (*From* UNAIDS: UNAIDS 2014. The Gap Report. Available at: http://www.unaids.org/node/42898. Accessed October 24, 2015.)

2014, 40% of people aged 55 and older were diagnosed with AIDS at the time of HIV diagnosis (i.e., diagnosed late in the course of the infection).

Estimated Diagnoses of HIV Infection by Age, 2014, United States



Source: CDC. Diagnoses of HIV infection in the United States and dependent areas, 2014 . HIV Surveillance Report 2015;26.

The Aging of the HIV Epidemic in the US

CDC Surveillance Data

TÜRKİYE'DE BİLDİRİLEN HIV/AIDS VAKALARININ CİNSİYETE GÖRE DAĞILIMI

01 EKİM 1985 – 30 HAZİRAN 2016*

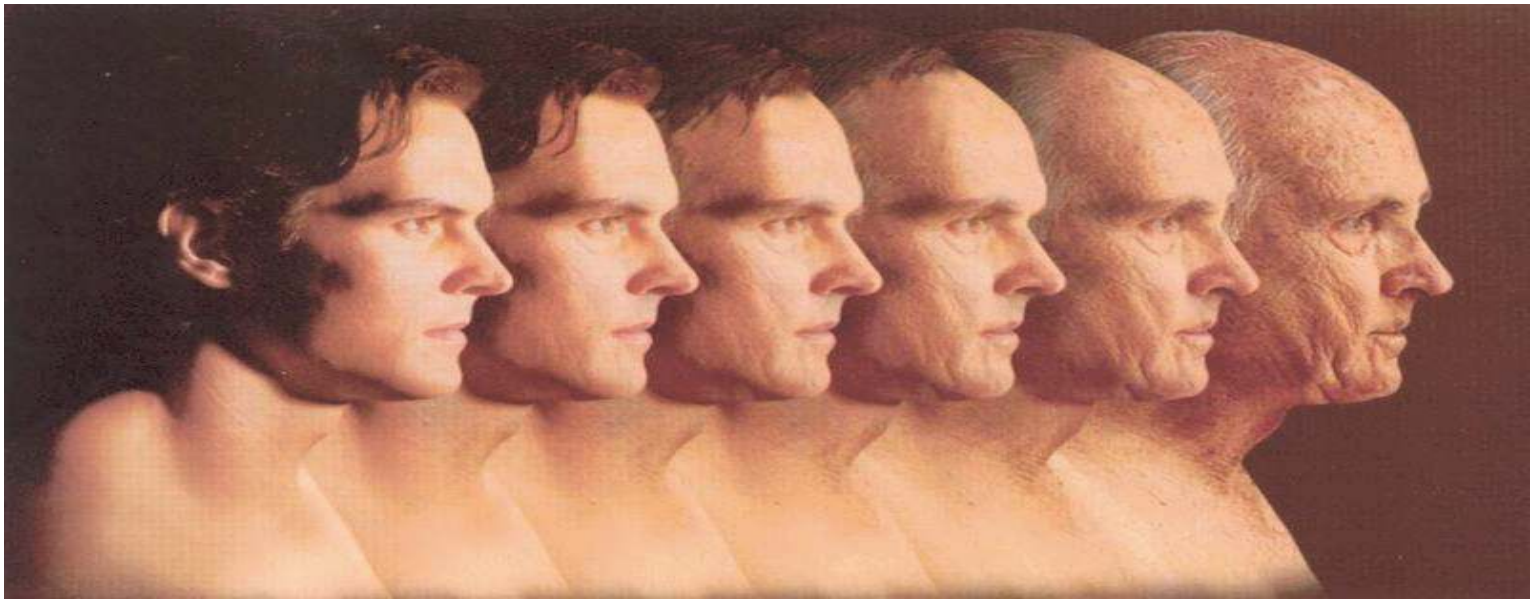
Türkiye Halk Sağlığı Kurumu,
Bulaşıcı Hastalıklar Daire Başkanlığı,
Zührevi Hastalıklar Birimi

YAŞ GRUBU	ERKEK	KADIN	TOPLAM VAKA
0	42	25	67
1-4	30	30	60
5-9	17	9	26
10-14	16	11	27
15-19	181	61	242
20-24	1089	409	1498
25-29	1705	556	2261
30-34	1774	534	2308
35-39	1518	388	1906
40-44	1151	269	1420
45-49	935	187	1122
50-54	635	156	791
55-59	463	126	589
60-64	262	63	325
65 yaş ve üstü	266	59	325
Bilinmeyen	149	65	211
TOPLAM	10 213	2 968	13 181

* İlk 6 aylık verilerdir.

Yaşlı Hastada HIV Enfeksiyonunun Güçlükleri

- Tanıda
- Tedavide
- İzlemde



Yaşlı Hastada Tanı

- Yaşlı hastalarda tanı daha geç dönemde
- Risk faktörleri sorgulanmıyor
- Koruyucu önlemler ihmal ediliyor

Yaşlı Hastada HIV Enfeksiyonu

- Risk faktörlerini konusunda farkındalık az
- “HIV gençlerin hastalığı” yanılgısı
- Güvenli cinsellik daha az
- Rutin takipte HIV taraması yok
- Kondom kullanımı az
- Kadınlarda menopozal değişiklikler geçiş riskini artırmakta..

"HIV/AIDS and Older Adults Henry Pacheco, M.D. Medicine & Public Health Director National Hispanic Council on Aging (NHCOA) Washington, DC NATIONAL HISPANIC."

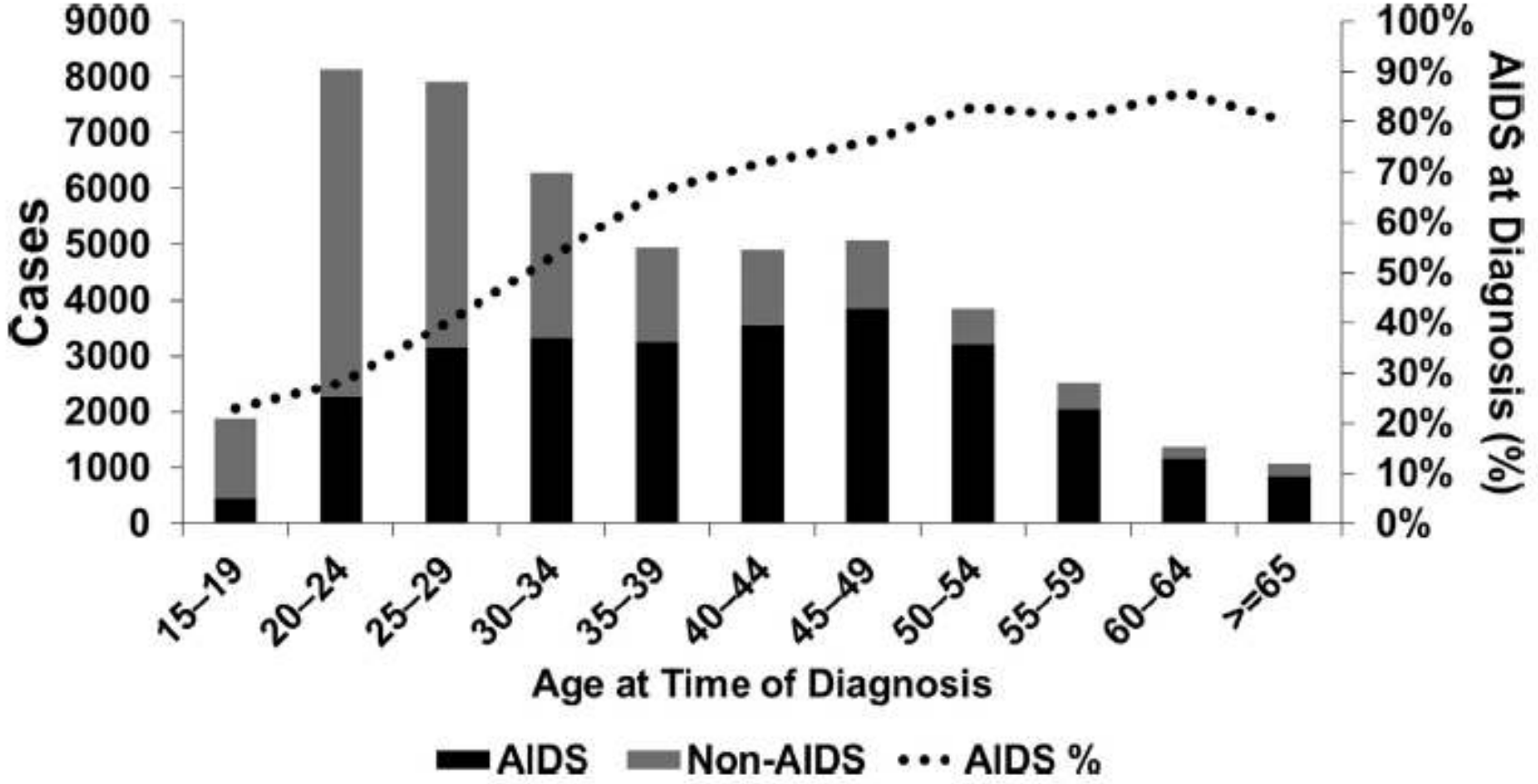


Fig. 2. Clinical status at time of diagnosis USA, 2013. Bars show the number of cases in each age strata who at the time of diagnosis of HIV infection who did (*black bar*) or did not (*gray bar*) have an AIDS-defining diagnosis. The dotted line shows the percentage of patients who had an AIDS-defining diagnosis. (*Data from* Centers for Disease Control and Prevention. HIV Surveillance Report, 2013. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/2013/surveillance_Report_vol_25.html. Accessed August 9, 2015.)

Çoklu ilaç kullanımı

- HIV ile infekte yaşlılarda daha sık
  - Analjezik
  - GİS ilaçları
  - SSS etkili ilaçlar
  - Antiinfektif ilaçlar
  - Solunum yoluna yönelik ilaçlar

Gimeno-Gracia M, et al. Polypharmacy in older adults with human immunodeficiency virus infection compared with the general population. Clinical Interventions in Aging 2016:11.

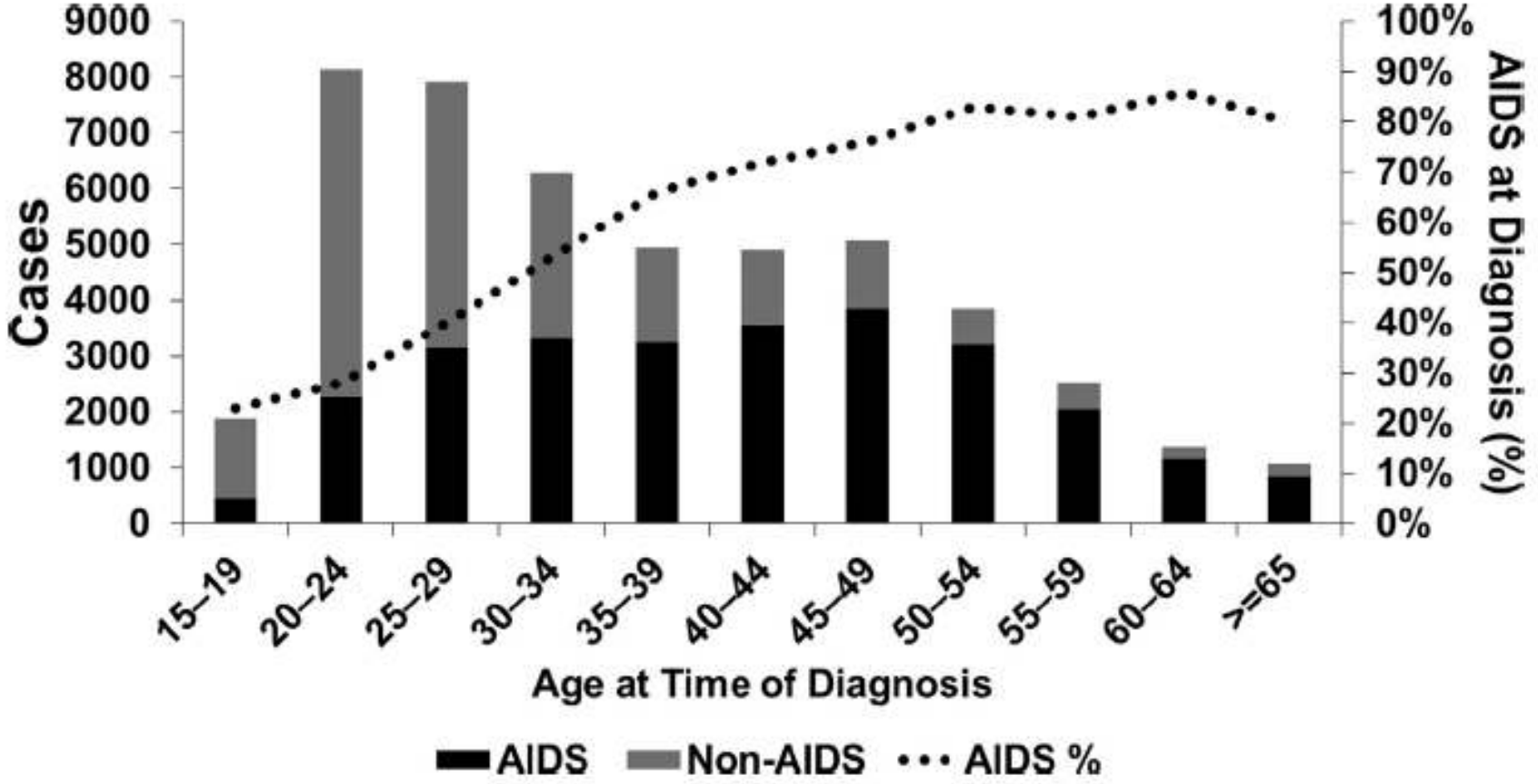

..Well... The GLAXO pill protects my heart from the side effects of the PFIZER pill that prevents potential liver failure due to the MERCK pill that minimizes the risk of stroke posed by the NOVARTIS pill that reduces blood clots caused by the GLAXO pill..
..The devil of it is I can't remember the illness that started all this...
JOHN COE

Yaşlılarda doğal seyir farklı mı?

- Tanı anında CD4 sayısı daha düşük,
  HIV-RNA daha yüksek
- CD4 düşüşü daha hızlı
- AIDS'e ilerleme daha hızlı
- AIDS tanımlayıcı olaylar gençlere göre daha sık

COHERE study group. Response to combination antiretroviral therapy, AIDS 2008.

Scott J, et al. Clin Geriatr Med 2016.



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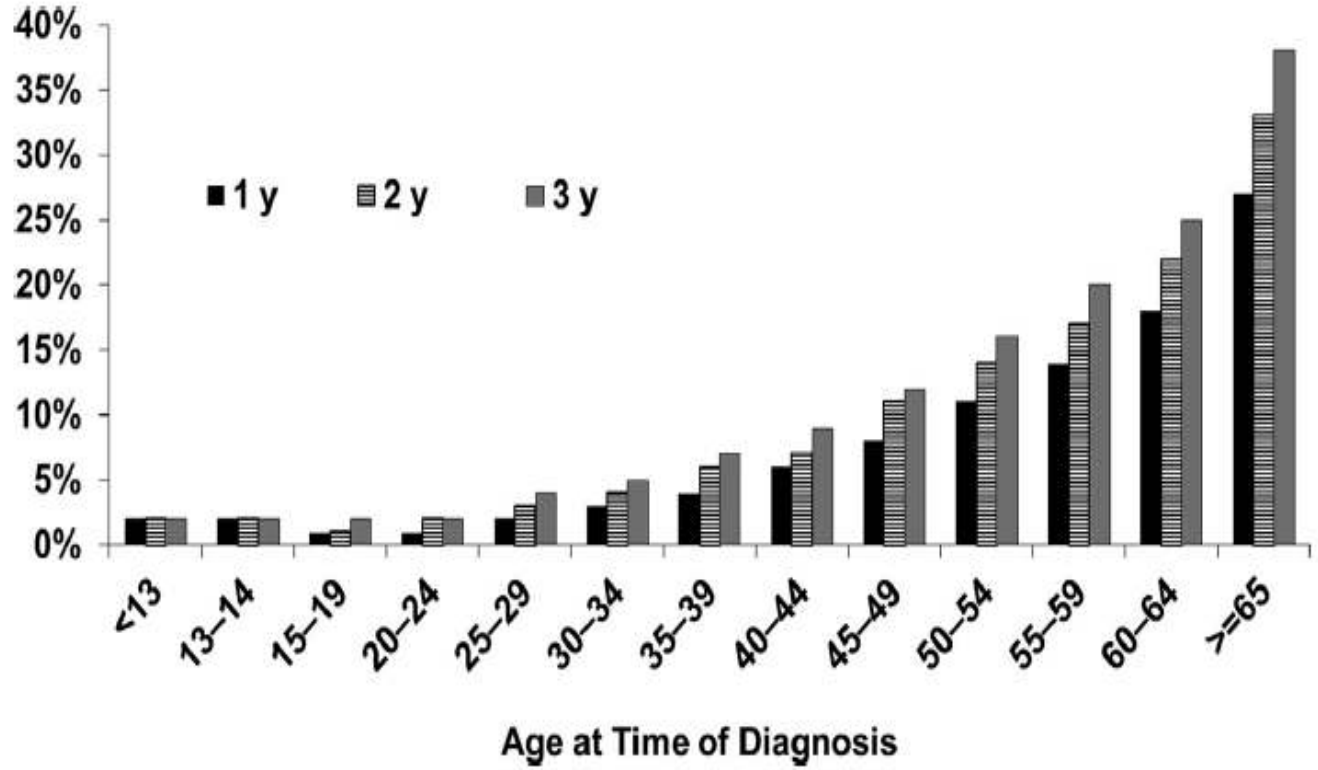


Fig. 3. Mortality after diagnosis of HIV infection in the United States, 2004–2009. Bars show the mortality at 1 (*black bar*), 2 (*horizontal dashes bar*), and 3 (*gray bar*) years after a diagnosis of HIV infection stratified by age. (*Data from* Centers for Disease Control and Prevention. HIV Surveillance Report, 2013. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/2013/surveillance_Report_vol_25.html. Accessed August 9, 2015.)

HIV yaşlandırır mı?

- Yaşlanmadaki biyolojik süreçler daha erken

Brennan-Ing M, DeMarco RF (eds): HIV and Aging. Interdiscipl Top Gerontol Geriatr.Basel, Karger, 2017, vol 42, pp 11-27 (DOI:10.1159/000448539

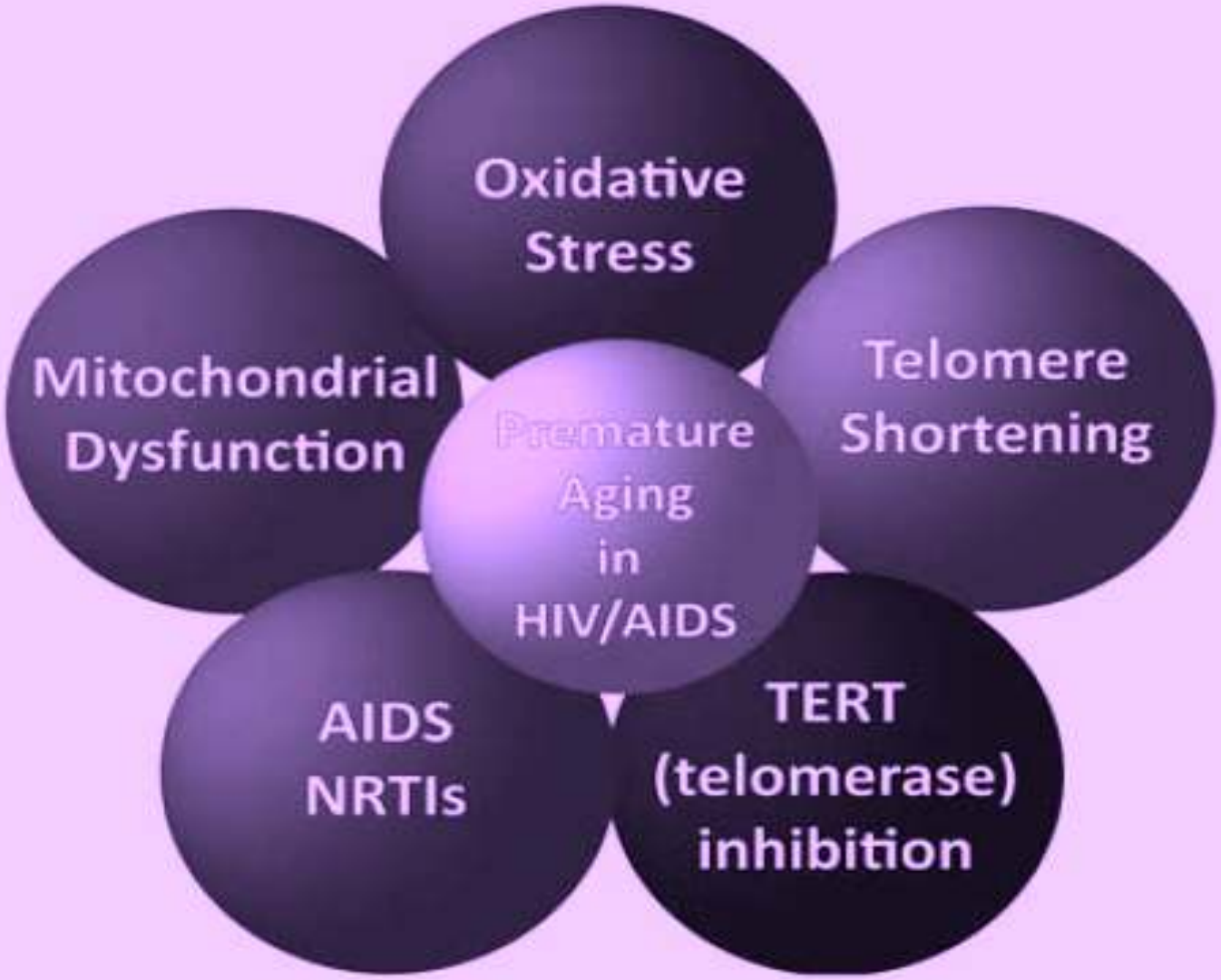
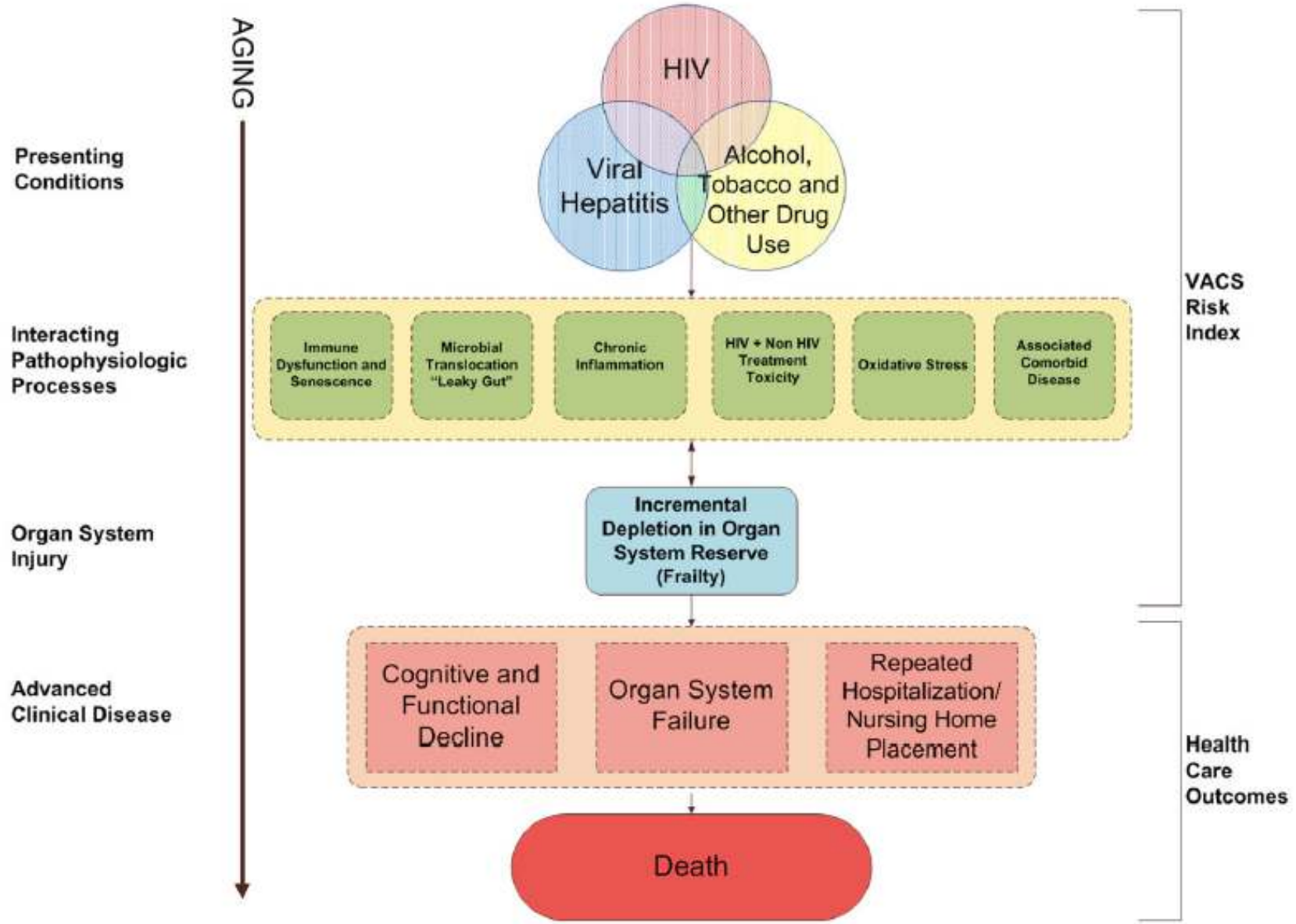


Figure 1 Aging in AIDS results from the interplay of biological events, toxic events, and therapeutic side effects.

Torres R, et al. Laboratory Investigation (2014)



J Acquir Immune Defic Syndr . 2012 July 1; 60(Suppl 1): S1–18. doi:10.1097/QAI.0b013e31825a3668

İleri yaşta mortalite morbidite nedenleri

- ART alanlarda
  - Kalp hastalığı
  - Kanser
  - Karaciğer hastalığı

Capeau J. Premature Aging and Premature Age-Related Comorbidities in HIV-Infected Patients: Facts and Hypotheses. Clin Infect Dis . Dec 2011

Yaşlı Hastalarda Antiretroviral Tedavi

- CD4 sayısına bakılmaksızın tüm hastalara önerilmekte (AI)
- Yaşlılarda ART daha da önemli
  - AIDS dışı komplikasyonlar daha fazla
  - İmmünolojik cevap daha kötü
- Çoklu ilaç kullanımı daha fazla
- Multidisipliner yönetime ihtiyaç var

http://aidsinfo.nih.gov/guidelines on 1/19/2017

Tedavi seçerken

- Viral yük
- CD4 sayısı
- Direnç testi
- İlacın etkinliği, toksisitesi
- Doz sıklığı, tablet sayısı
- İlaç etkileşimleri
- Eşlik eden hastalıklar

Tedavi Takibi

Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 1 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
HIV Serology	√ If HIV diagnosis has not been confirmed								
CD4 Count	√	√		√ During first 2 years of ART or if viremia develops while patient on ART or CD4 count <300 cells/mm^3		√ After 2 years on ART with Consistently Suppressed Viral Load: *CD4 Count 300–500 cells/mm^3*: • Every 12 months *CD4 Count >500 cells/mm^3*: • CD4 monitoring is optional	√	√	√ Every 3-6 months
HIV Viral Load	√	√	√[d]	√[e]	√[e]		√	√	Repeat testing is optional
Resistance Testing	√	√[f]					√	√	√[f]
HLA-B*5701 Testing		√ If considering ABC							
Tropism Testing		√ If considering a CCR5 antagonist					√ If considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen	√	

Tedavi Takibi

Table 3. Laboratory Testing Schedule for Monitoring HIV-Infected Patients Before and After Initiation of Antiretroviral Therapy[a] (page 2 of 2)

Laboratory Test	Timepoint/Frequency of Testing								
	Entry into Care	ART Initiation[b] or Modification	2 to 8 Weeks After ART Initiation or Modification	Every 3 to 6 Months	Every 6 Months	Every 12 Months	Treatment Failure	Clinically Indicated	If ART Initiation is Delayed[c]
Hepatitis B Serology[g,h]	√	√ May repeat if patient is nonimmune and not chronically infected with HBV[h]				√ May repeat if patient is nonimmune and not chronically infected with HBV[h]		√	
Hepatitis C Antibody Test (if positive, confirm with HCV RNA test)	√	√ May repeat for at-risk patients if negative result at baseline				√ May repeat for at-risk patients if negative result at baseline		√	
Basic Chemistry[i,j]	√	√	√	√				√	√ Every 6-12 months
ALT, AST, T. bilirubin	√	√	√	√				√	√ Every 6-12 months
CBC with Differential	√	√	√ If on ZDV	√ If on ZDV or if CD4 testing is done	√			√	√ Every 3-6 months
Fasting Lipid Profile[k]	√	√			√ If abnormal at last measurement	√ If normal at last measurement		√	√ If normal at baseline, annually
Fasting Glucose or Hemoglobin A1C	√	√		√ If abnormal at last measurement		√ If normal at last measurement		√	√ If normal at baseline, annually
Urinalysis[j]	√	√			√ If on TAF or TDF[l]	√		√	
Pregnancy Test		√ In women with child-bearing potential						√	

Yaşlılarda potansiyel yan etkiler daha sık

- Böbrek
- Karaciğer
- Kardiyovasküler
- Metabolik
- İskelet sistemi etkileri için daha dikkatli olunmalı

http://aidsinfo.nih.gov/guidelines on 1/19/2017

Önerilen Tedavi Rejimleri

INSTI plus 2-NRTI Regimen:

- DTG/ABC/3TC[a] (AI)—if HLA-B*5701 negative
- DTG plus either TDF/FTC[a] (AI) or TAF/FTC[b] (AII)
- EVG/c/TAF/FTC (AI) or EVG/c/TDF/FTC (AI)
- RAL plus either TDF/FTC[a] (AI) or TAF/FTC[b] (AII)

Boosted PI plus 2 NRTIs:

- DRV/r plus either TDF/FTC[a] (AI) or TAF/FTC[b] (AII)

http://aidsinfo.nih.gov/guidelines *2016*

BHIVA 2016

	Önerilen	Alternatif
NRTI	TDF & FTC TAF& FTC	ABC & 3TC[1,2]
3. ajan	ATV/r DRV/r **DTG** EVG/COBI RAL **RPV[3]**	**EFV**

1. ABC contra-indicated if HLA-B*5701 positive
2. ABC/3TC not recommended >100k unless with DTG
3. Use only recommended if VL <100,000

BHIVA guidelines for the treatment of HIV-1-positive adults with ART 2015 (2016 interim update)

Alternative Regimen Options

Alternative regimens are effective and tolerable, but have potential disadvantages when compared with the Recommended regimens, have limitations for use in certain patient populations, or have less supporting data from randomized clinical trials. **However, an Alternative regimen may be the preferred regimen for some patients.**

NNRTI plus 2 NRTIs:

- EFV/TDF/FTC[a] **(BI)**
- EFV plus TAF/FTC[b] **(BII)**
- RPV/TDF/FTC[a] **(BI)** or RPV/TAF/FTC[b] **(BII)**—if **HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**

Boosted PI plus 2 NRTIs:

- (ATV/c or ATV/r) plus either TDF/FTC[a] **(BI)** or TAF/FTC[b] **(BII)**
- DRV/c **(BIII)** or DRV/r **(BII)** plus ABC/3TC[a]—if **HLA-B*5701 negative**
- DRV/c plus either TDF/FTC[a] **(BII)** or TAF/FTC[b] **(BII)**

http://aidsinfo.nih.gov/guidelines 2016

Other Regimen Options

When compared with Recommended and Alternative regimens, Other regimens may have reduced virologic activity, limited supporting data from large comparative clinical trials, or other factors such as greater toxicities, higher pill burden, drug interaction potential, or limitations for use in certain patient populations.

If HIV RNA <100,000 copies/mL and HLA-B*5701 Negative:

- ATV/c **(CIII)** or ATV/r **(CI)** plus ABC/3TC
- EFV plus ABC/3TC[a] **(CI)**
- RAL plus ABC/3TC[a] **(CII)**

Other Regimens to Consider when TAF, TDF, or ABC Cannot be Used:

- DRV/r plus RAL (BID) **(CI)—if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm^3**
- LPV/r plus 3TC[a] (BID) **(CI)**

http://aidsinfo.nih.gov/guidelines *2016*

Table 1. Current Antiretroviral Guidelines for Initiation of Treatment

Class	Department of Health and Human Services	International Antiviral Society-USA	European AIDS Clinical Society
Integrase strand transfer inhibitors	DTG/ABC/3TC DTG + TDF/FTC or TAF/FTC EVG/COBI/TDF/FTC EVG/COBI/TAF/TFC RAL + TDF/FTC or TAF/FTC	DTG/ABC/3TC DTG + TAF/FTC EVG/COBI/TAF/FTC RAL + TAF/FTC	DTG/ABC/3TC DTG + TDF/FTC EVG/COBI/TDF/FTC RAL + TDF/FTC
Boosted protease inhibitors	DRV + RTV + TDF/FTC or TAF/FTC		DRV + RTV + TDF/FTC
Nonnucleoside reverse transcriptase inhibitors			RPV/TDF/FTC

DTG = dolutegravir; ABC = abacavir; 3TC = lamivudine; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; TAF = tenofovir alafenamide; EVG = elvitegravir; COBI = cobicistat; RAL = raltegravir; DRV = darunavir; RTV = ritonavir; RPV = rilpivirine.

Kardiyovasküler sistem hastalıkları

- MI, HT, Kalp yetmezliği, ani ölüm, SVO...
- ART ile azalmakta
- Normal popülasyona göre daha sık

Monforte A, etal. Atazanavir is not associated with an increased risk of MI. AIDS 2013.

Obel N, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. Clin Infect Dis. 2007.

HIV ve KVS Hastalığı

- ART yan etkileri
- Kronik inflamasyon
- CD4 <250 – risk artmakta
- Tedaviyi bırakanlarda---tromboza eğilim

Strategies for Management of Antiretroviral Therapy Study Group. N Engl J Med 2006;355:2283–96.

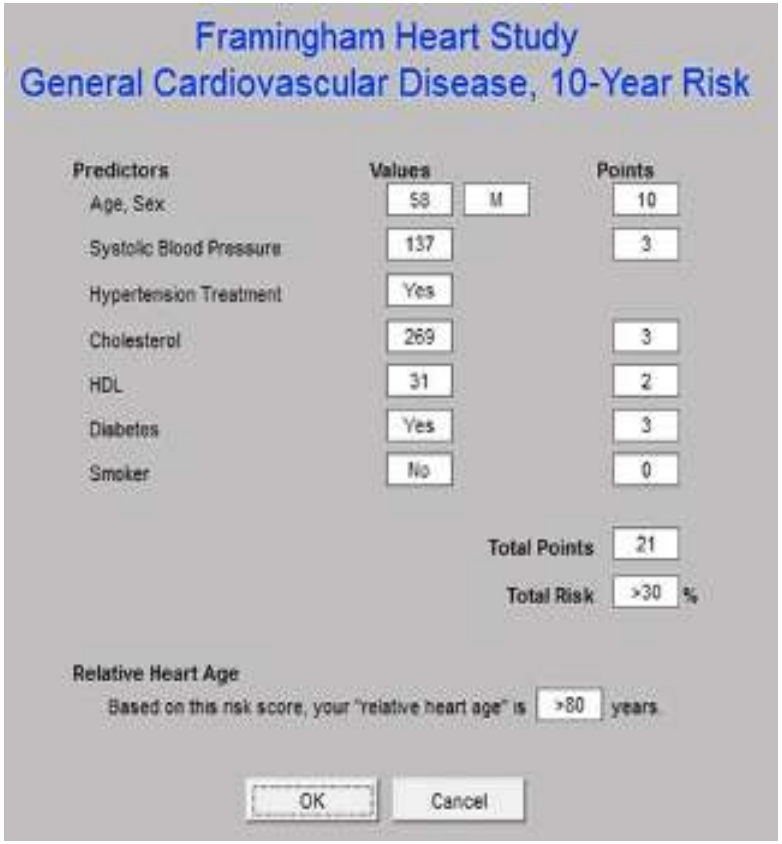
Hemkens L, et al. Eur Heart J 2014;35:1373–81.

Table 3 Main classes of antiretroviral drugs and their impact on lipid and glucose metabolism and coronary artery disease

Drug class	Antiretroviral	Effects on lipids[a]	Effects on glucose[a]	Impact on coronary artery disease
Nucleos(t)ide reverse transcriptase inhibitors	Abacavir	TC⇑ LDL⇑	No effect	Recent exposure associated with increased risk for MI (controversial)
	Azidothymidine	TC⇑ LDL⇑	Insulin resistance+	No association with increased risk for MI
	Emtricitabine	Neutral effect	No effect	No association with increased risk for MI
	Lamivudine	Neutral effect	No effect	No association with increased risk for MI
	Stavudine	Dyslipidaemia+	Insulin resistance+	No association with increased risk for MI
	Tenofovir	TC⇓ LDL⇓	No effect	No association with increased risk for MI
Non-nucleoside reverse transcriptase inhibitors	Efavirenz	TC⇑ LDL⇑	No effect	No association with increased risk for MI
	Etravirine	Neutral effect		No data available (not enough patients exposed)
	Nevirapine	HDL⇑		No association with increased risk for MI
	Rilpivirine	Neutral effect		No data available (not enough patients exposed)
Protease inhibitors	Amprenavir + Ritonavir	Dyslipidaemia++	Insulin resistance+	Cumulative exposure independently increased risk for MI
	Atazanavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Darunavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No data available (not enough patients exposed)
	Indinavir	Dyslipidaemia+	Insulin resistance+++	Controversial results
	Lopinavir + Ritonavir	Dyslipidaemia+++	Insulin resistance+++	Cumulative exposure independently increased risk for MI
	Nelfinavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Saquinavir	Dyslipidaemia+	Insulin resistance+	No association with risk for MI
	Tipranavir + Ritonavir	Dyslipidaemia+	Insulin resistance+	No data available (not enough patients exposed)
Integrase inhibitors	Elvitegravir/cobicistat Raltegravir	Neutral effect	No effect	No data available (not enough patients exposed)
Entry inhibitors	Maraviroc	Neutral effect	No effect	No data available (not enough patients exposed)

HIV ve KVS Değerlendirme

- Risk değerlendirmesi- Framingham skoru
- Tedavi öncesi EKG
- EKO
- Kan basıncı takibi
- Lipid takibi



HIV ve Osteroporoz

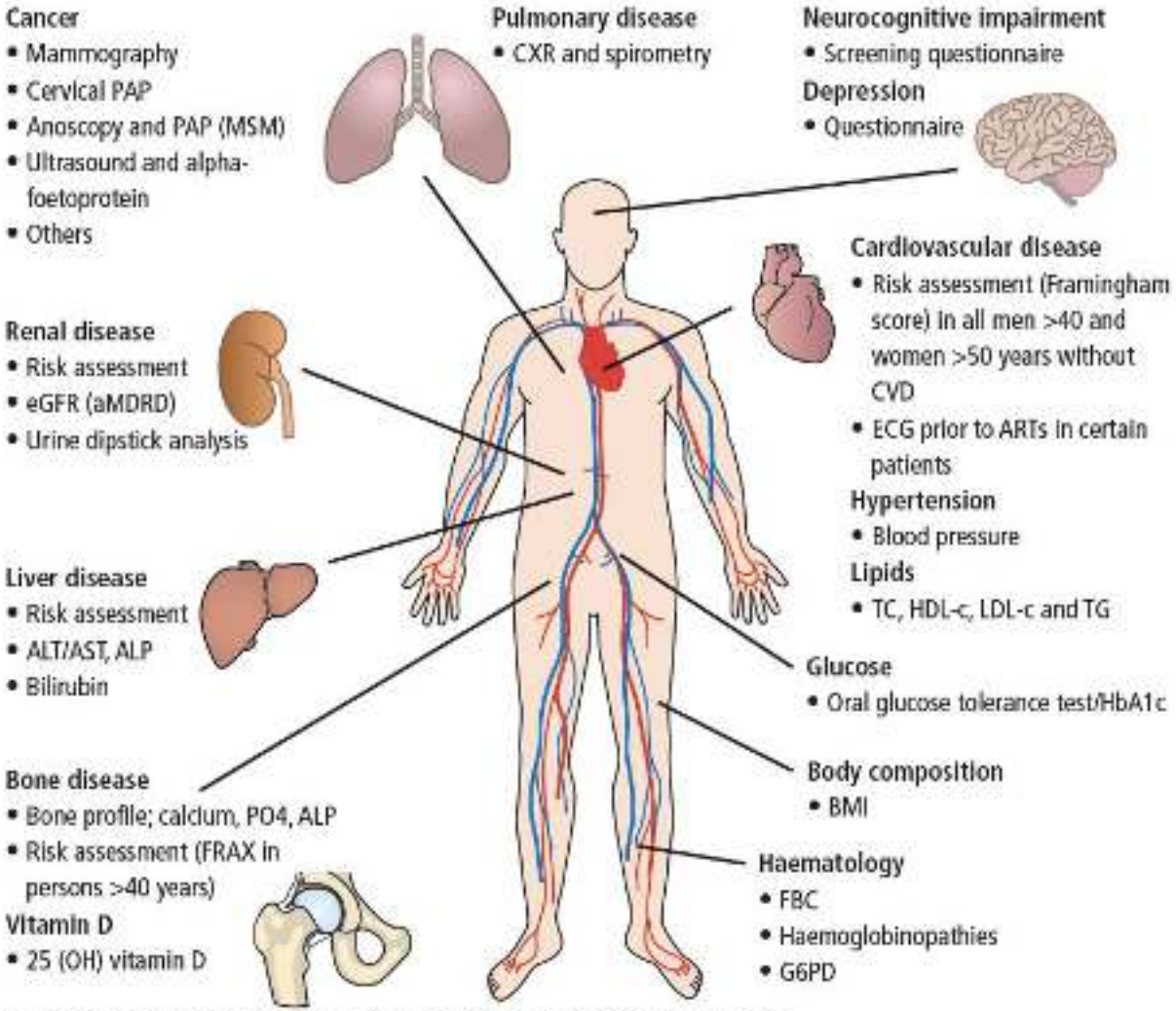
- ART
  - TDF, PI
- Sigara, alkol kullanımı
- HCV koenfeksiyonu
- PPI kullanımı
- İleri yaş
- DM
- Vasküler hastalık....

Yin MT, *et al.* Fracture prediction with modified FRAX in older HIV+ and HIV- men. CROI 2015

HIV ve Osteoporoz

- Ca, PO4 ve ALP
- Kemik dansitometri
- Vitamin D

http://aidsinfo.nih.gov/guidelines



*See guidelines for follow-up frequency, subgroups to be screened and further information

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aMDRD, abbreviated modified diet in renal disease; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; CVD, cardiovascular disease; CXR, chest X-ray; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FBC, full blood count; FRAX, Fracture Risk Assessment Tool; G6PD, glucose-6-phosphate dehydrogenase; HANA, HIV-associated non-AIDS; HbA1c, glycosylated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MSM, men who have sex with men; PAP, Papanicolaou; TC, total cholesterol; TG, triglycerides.

Figure 3: Higher rates of eight HANA comorbidities found among people living with HIV.[22] Comorbidity data taken from Comorbidity distribution, *in Schouten J,* et al. *Comorbidity and ageing in HIV-1 infection: the AGEhIV Cohort Study. XIX International AIDS Conference. July 22–27, 2012. Washington, DC. Abstract No THAB0205*

HIV ve Böbrek Fonksiyon Bozukluğu

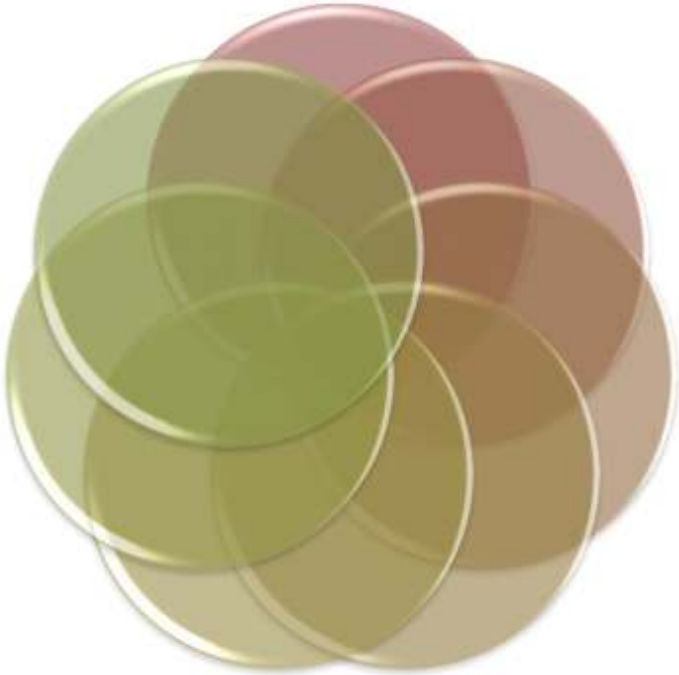
- Hastaların %30'unda
- Mortalite için bağımsız risk faktörü

HIV ve Böbrek Hasarı Çeşitleri

Akut böbrek hasarı

Yaşlanma ilişkili böbrek fonksiyonlarında azalma

İlaçların yan etkileri nedeniyle



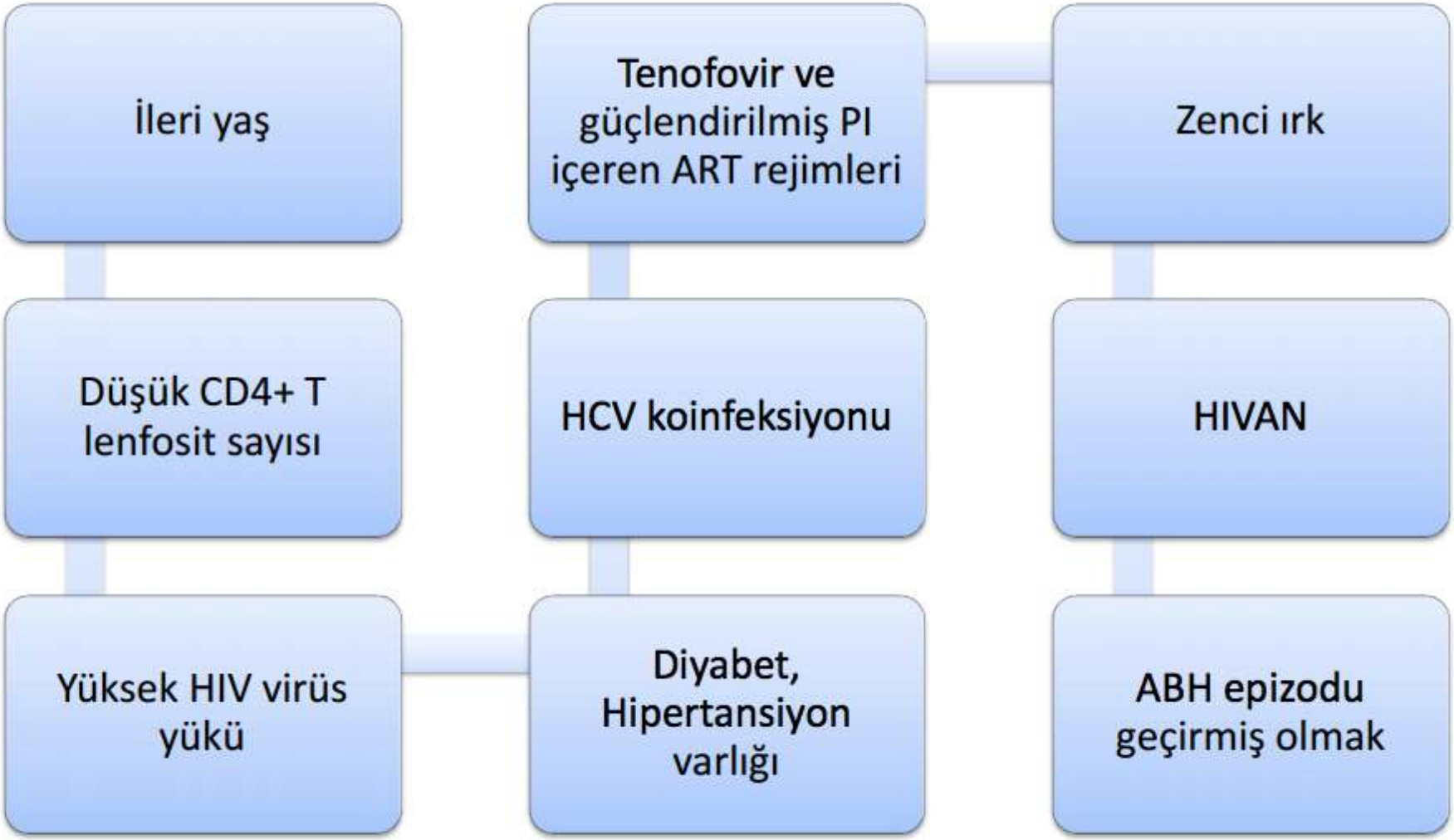
Diyabetik ve hipertansif nefropati

HIV ilişkili trombotik mikroanjiopati

HIV ilişkili nefropati (HIVAN)

Kronik böbrek hastalığı

KBH Risk Faktörleri

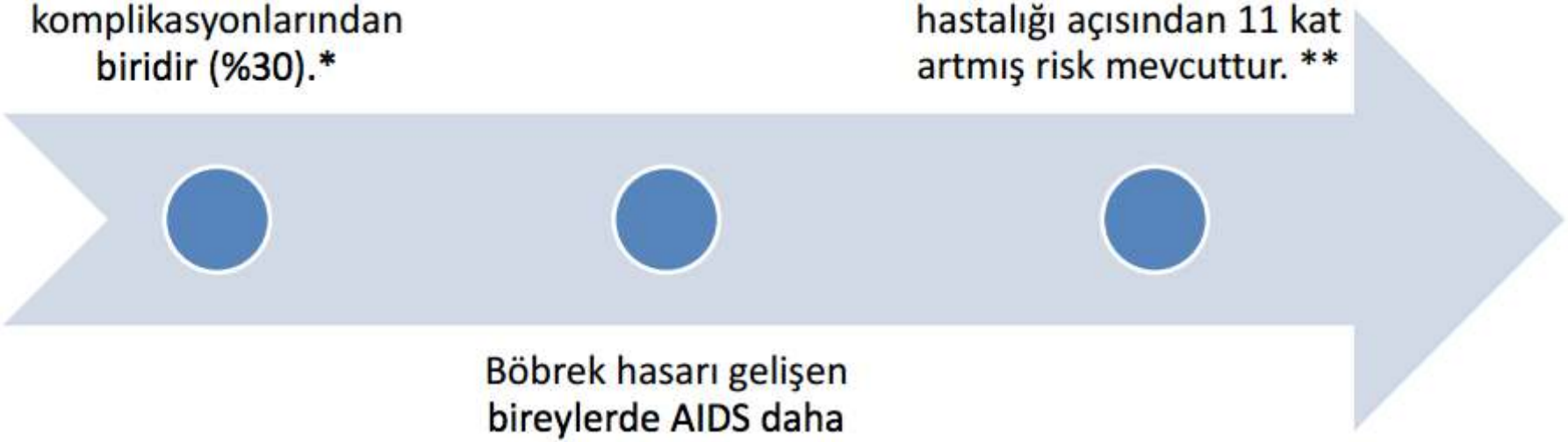


HIV ve Böbrek Hasarı

Böbrek hasarı HIV infeksiyonunun en sık görülen komplikasyonlarından biridir (%30).*

Böbrek hasarı gelişen bireylerde AIDS daha hızlı bir seyir göstermekte ve mortalite nedeni olabilmektedir.*

Zenci bireylerde böbrek hastalığı açısından 11 kat artmış risk mevcuttur. **



* *Szchech LA et el* Clin Infect Dis 2004; 39: 1199-1206.

** *Stehman-breen et al*. J Am Soc Nephrol 2003; 14: 2352-2357

Kronik Böbrek Hastalığı Durumunda Antiretroviral Tedavi

- TDF kullanılmamalı
- ABC ya da TAF tercih edilmeli
- ABC veya TAF kullanılamıyorsa
  - LPV/r + 3TC
  - RAL + DRV/r

http://aidsinfo.nih.gov/guidelines 2016

Table 3. Recommended Immunizations for Individuals with the Human Immunodeficiency Virus Aged 50 and Older

Vaccine	CD4 Count <200 Cells/μL	CD4 Count ≥200 Cells/μL	Comments
IIV	Yes	Yes	According to Centers for Disease Control and Prevention, high-dose equivalent to standard-dose IIV
Tdap and Td	Yes	Yes	Tdap once, then Td every 10 years
Zoster	No	No recommendation	Probably safe if CD4 > 200
Measles, mumps, rubella	No	If indicated	1–2 doses if indicated
Varicella	No	If indicated	2 doses if no evidence of immunity
PCV13 and PPSV23	Yes	Yes	Give PCV13 first, then PPSV23 8 weeks later
Hepatitis A	If indicated	If indicated	2 doses
Hepatitis B	Yes	Yes	3 doses

J Am Geriatr Soc 64:2322–2329, 2016

Yaşlılarda Antiretroviral Tedavi

- Basit olmalı, mümkün olan en az tablet sayısı
- Gereksiz ilaç değerlendirmesi
- Bitkisel tedaviler konusunda dikkat
- Başarısızlığın en büyük nedeni uyumsuzluk
  - Depresyon
  - Nörokognitif bozukluklar

- Yakın takip
- Unutmayı engelleyen uygulamalar (ilaç kutuları vs)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