HIV ile yaşayan bireylerde Fırsatçı Hastalıklar ve Epidemiyoloji

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

6 Haziran 2023, Türkiye EKMUD İstanbul Günleri


cystoisosporiasis
cytomegalovirus retinitis
candidiasis
toxoplasmosis
Opportunistic Infections
coccidioidomycosis
TB
cryptosporidiosis
microsporidiosis
tuberculosis
salmonellosis
HSV infection
histoplasmosis
Mycobacterium avium complex
pneumonia

- Değişen HIV epidemiolojisi
- HIV enfeksiyonunun doğal seyri
- Fırsatçı hastalıkların insidansı
- Epidemiolojik veriler

Major milestones in the history of HIV/AIDS

- 1981 - first reports of the appearance of AIDS
- 1983/84 - identification of HIV
- 1985 - HIV test commercially available
- 1986 - WHO global AIDS program started
- 1987 - UN general assembly debates AIDS
- 1987 - AZT treatment
- 1988 - AIDS in Asia
- 1994 - AIDS in South Africa
- 1996 - effective antiretroviral treatment

LAP-associated virus (LAV) by Luc Montagnier et al

Human T-lymphotropic virus type III (HTLV-III) by Robert Gallo et al

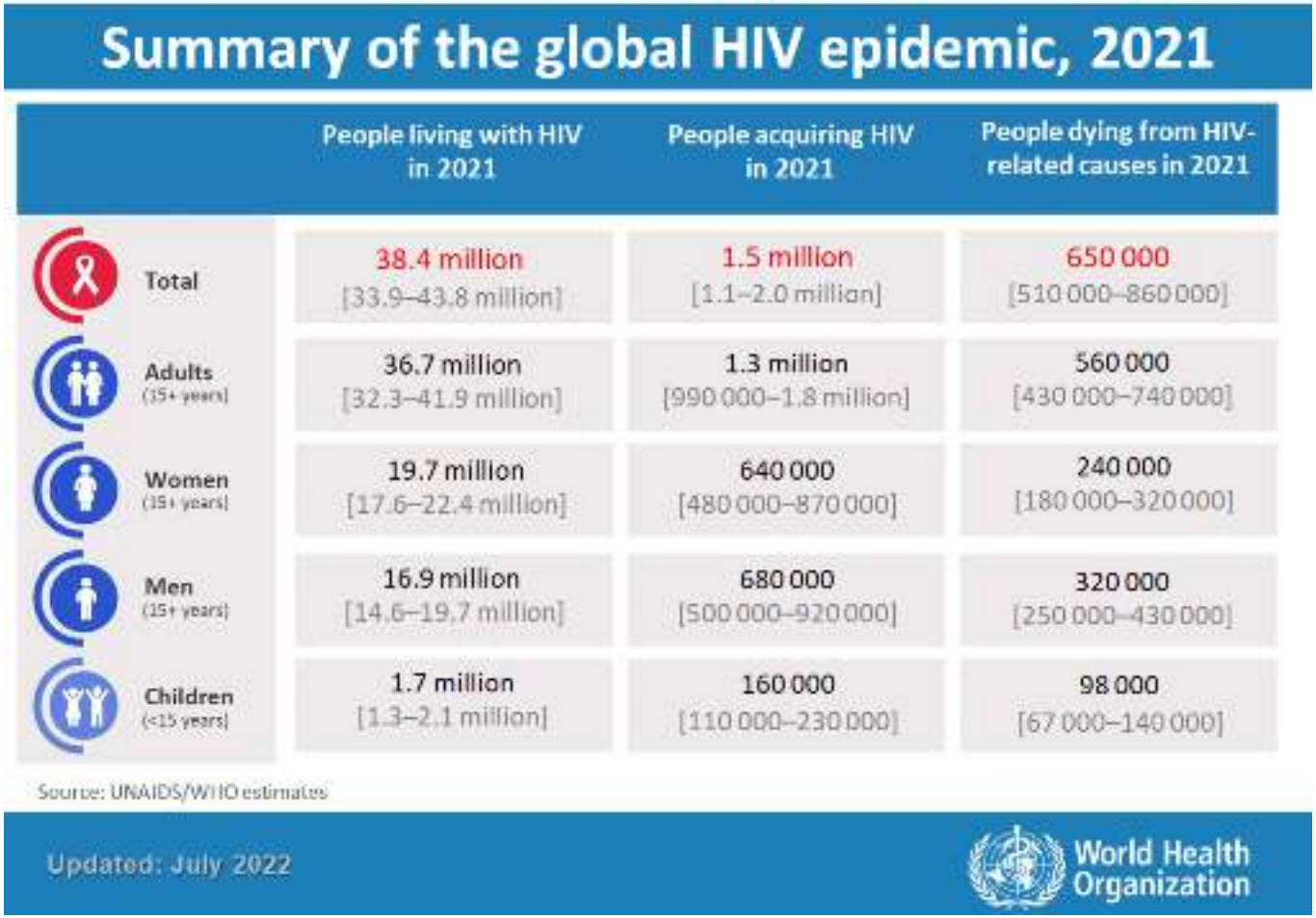
In the 1990s

Up to 20 pills daily, taken at different intervals throughout the day

Today

As little as 1 pill per day, delivering multiple drugs

Long-acting injectable ART



2021 yeni HIV enfeksiyonu insidansı
2001'e göre (3.4 milyon yeni enfeksiyon)
%54 azalma göstermekte

Adults and Children Estimated To Be Living With HIV: 2020

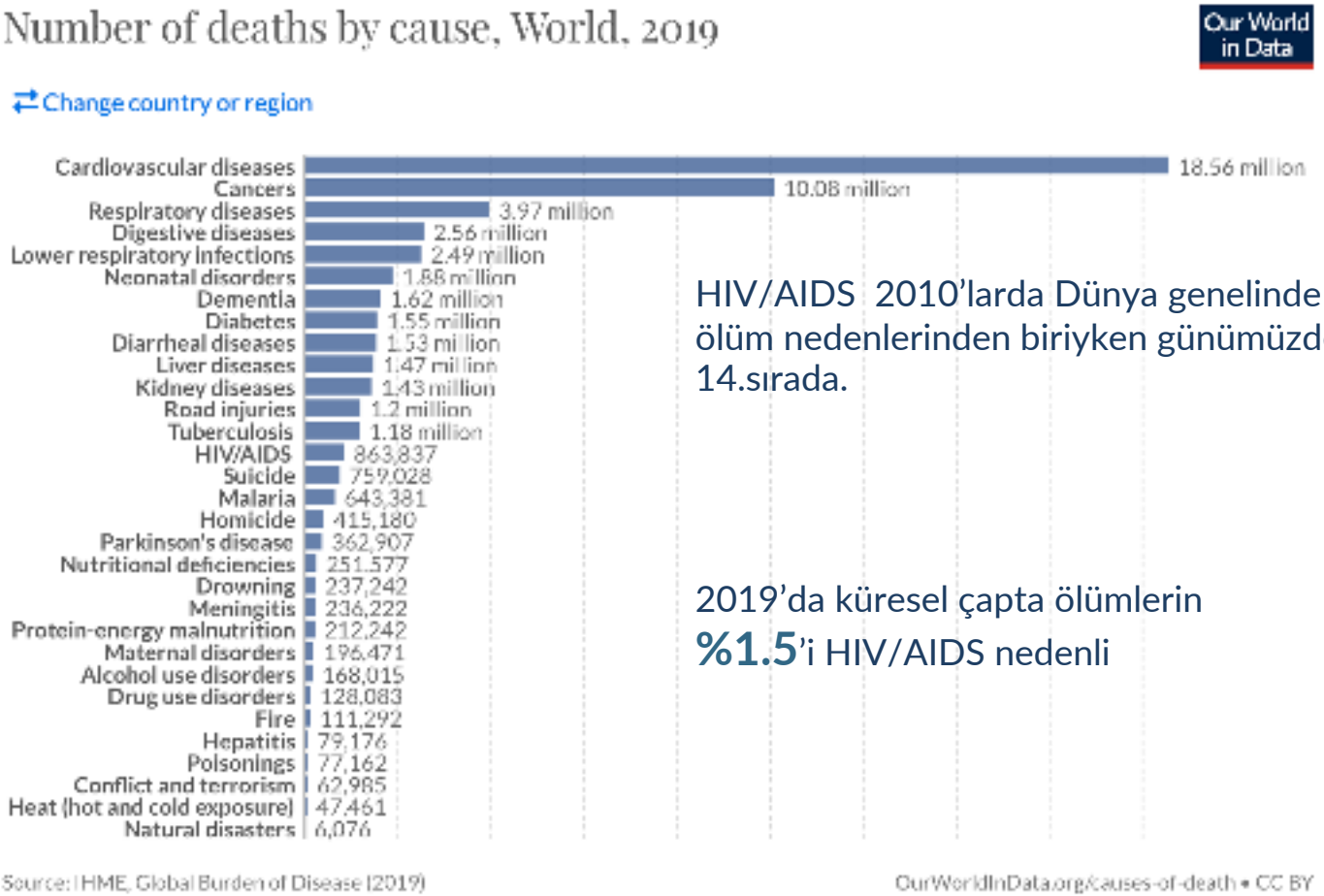
Total: 37.7 million [30.2 million–45.1 million]

Note: Map reprinted from United Nations (UN) source. UN and U.S. representations of international boundaries do not align in all cases. Map is shown for informational purposes only and does not reflect U.S. government policy. Lower and upper bounds of estimates are shown in brackets.
Source: United Nations Programme on HIV and AIDS, 2021.

HIV ile yaşayan Dünya popülasyonun yaklaşık **%60**'ı Sahra altı Afrika'da yaşıyor.

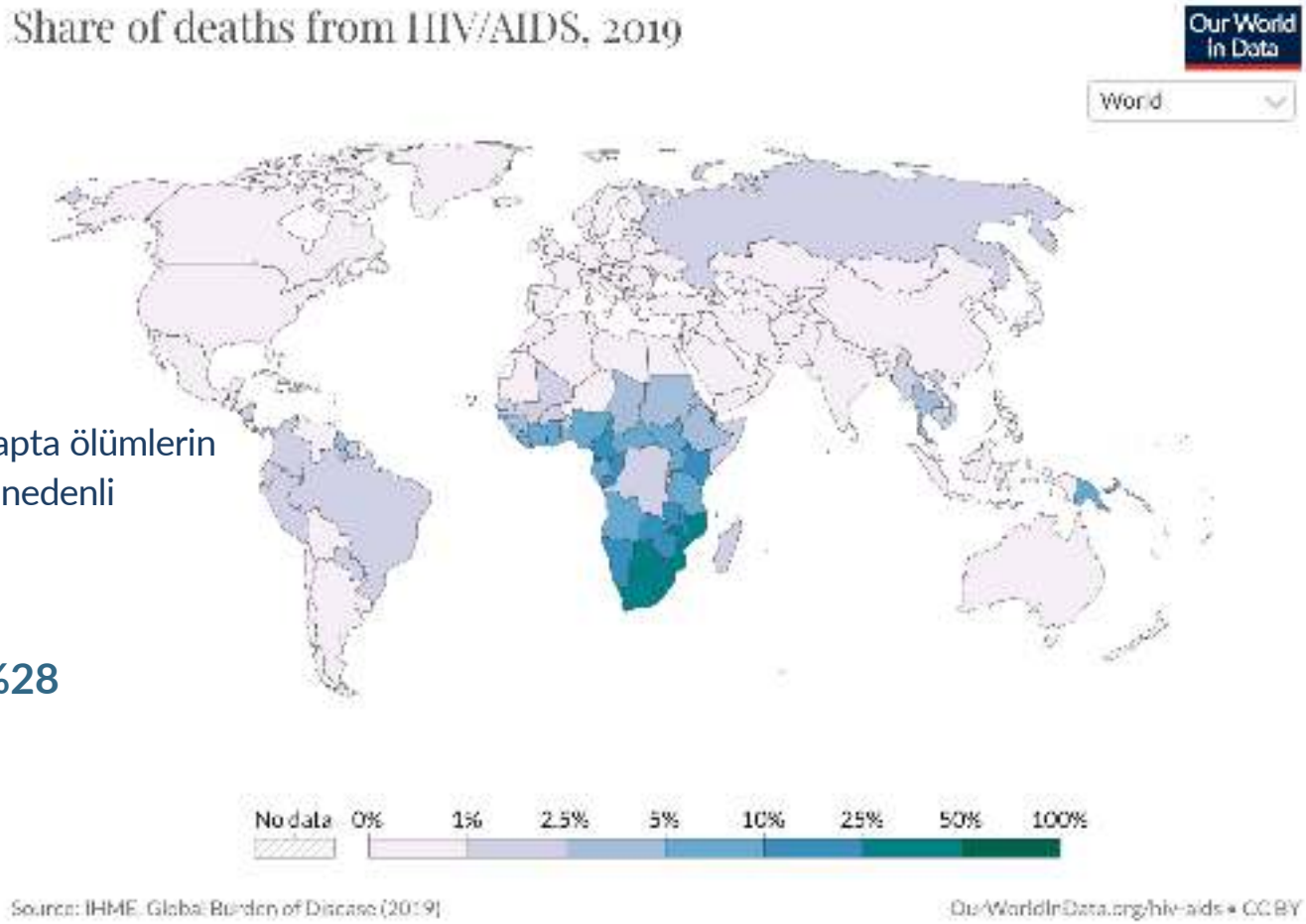
2021'de erişkin HIV prevalansı Orta Doğu ve Kuzey Afrika'da **%0.1**'den Sahra altı Afrika'da **%7**'ye değişmekte.

Bazı Sahra altı ülkelerde **%25**'in üzerinde.



HIV/AIDS 2010'larda Dünya genelinde ilk 10 ölüm nedenlerinden biriyken günümüzde 14.sırada.

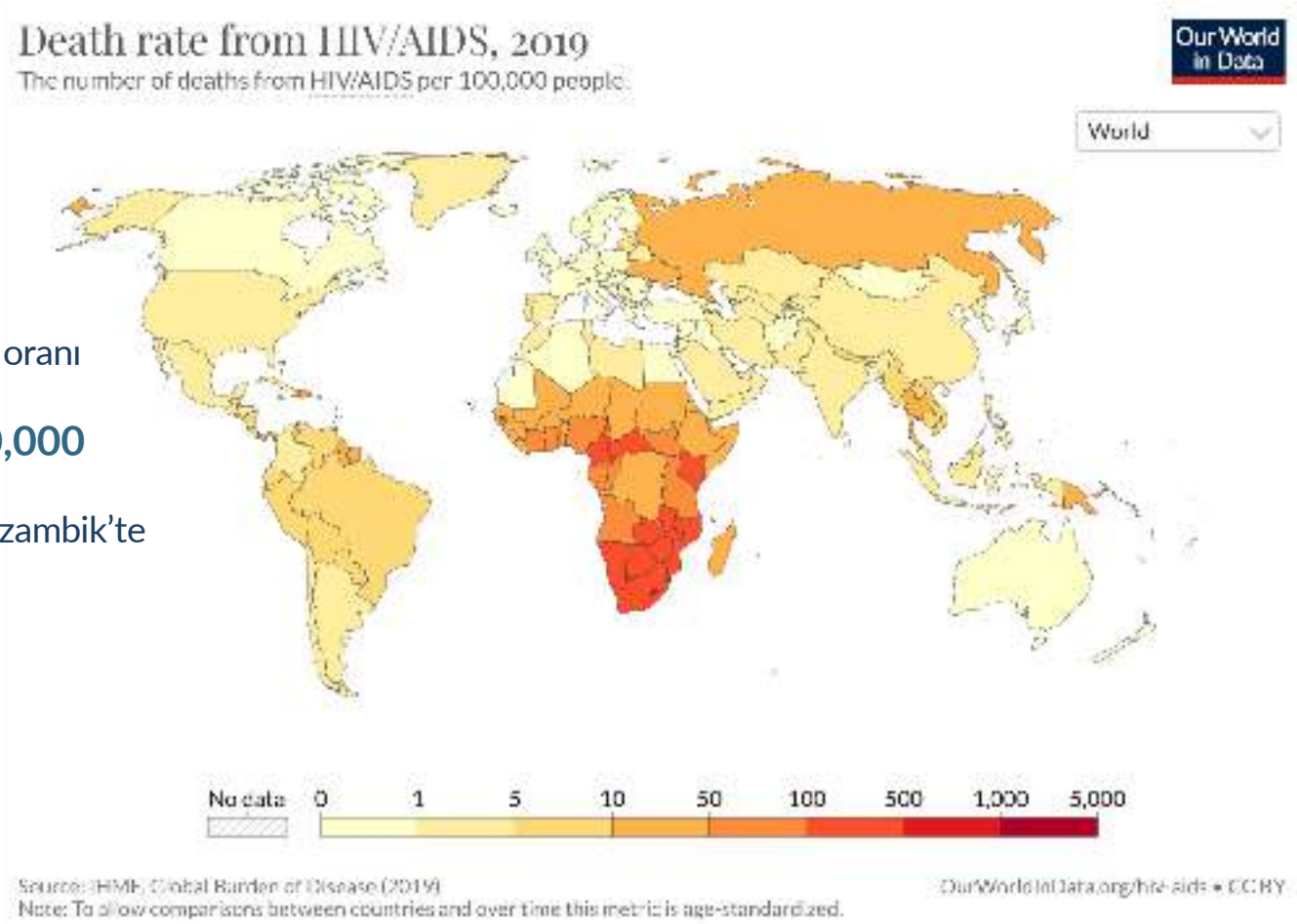
2019'da küresel çapta ölümlerin **%1.5**'i HIV/AIDS nedenli



2019'da küresel çapta ölümlerin **%1.5**'i HIV/AIDS nedenli

Avrupa'da **<%0.1**

Güney Afrika'da **%28**



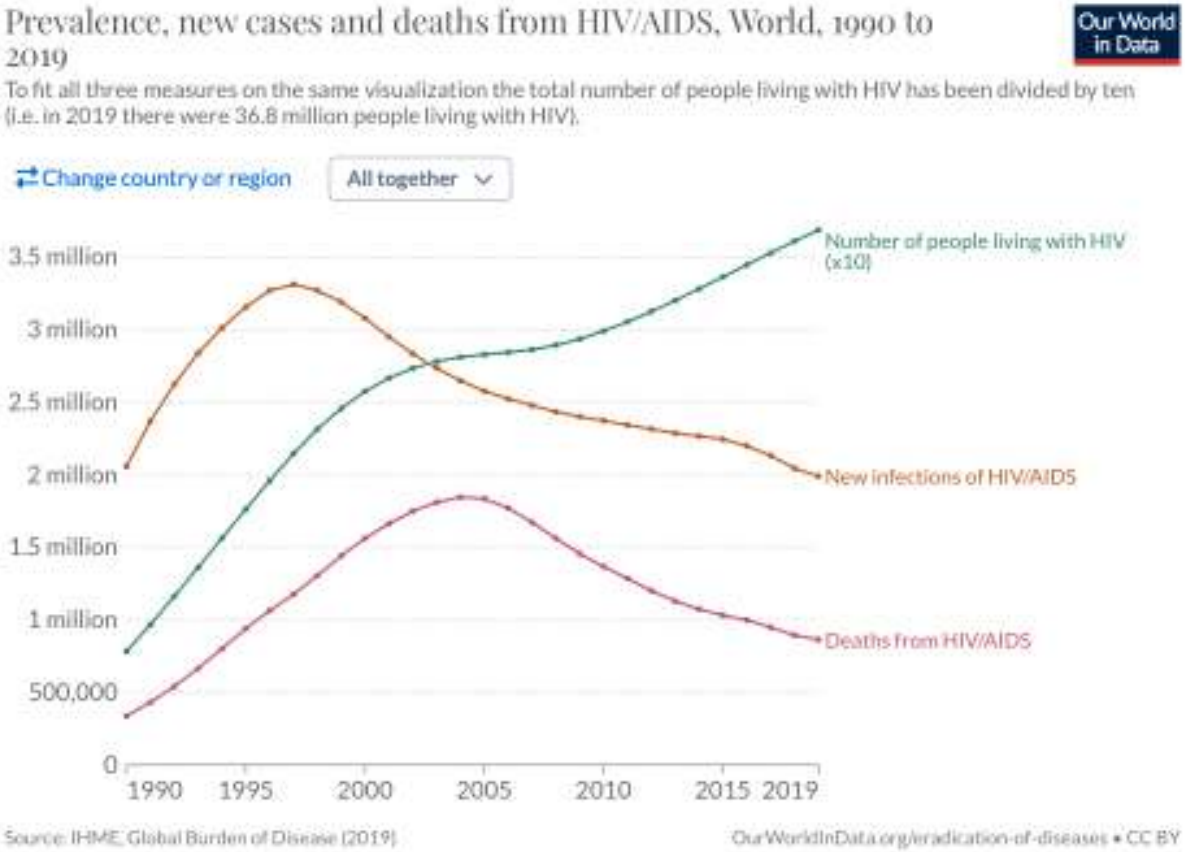
HIV/AIDS'den ölüm oranı

Avrupa'da **< 1/100,000**

Güney Afrika ve Mozambik'te
>200/100,000

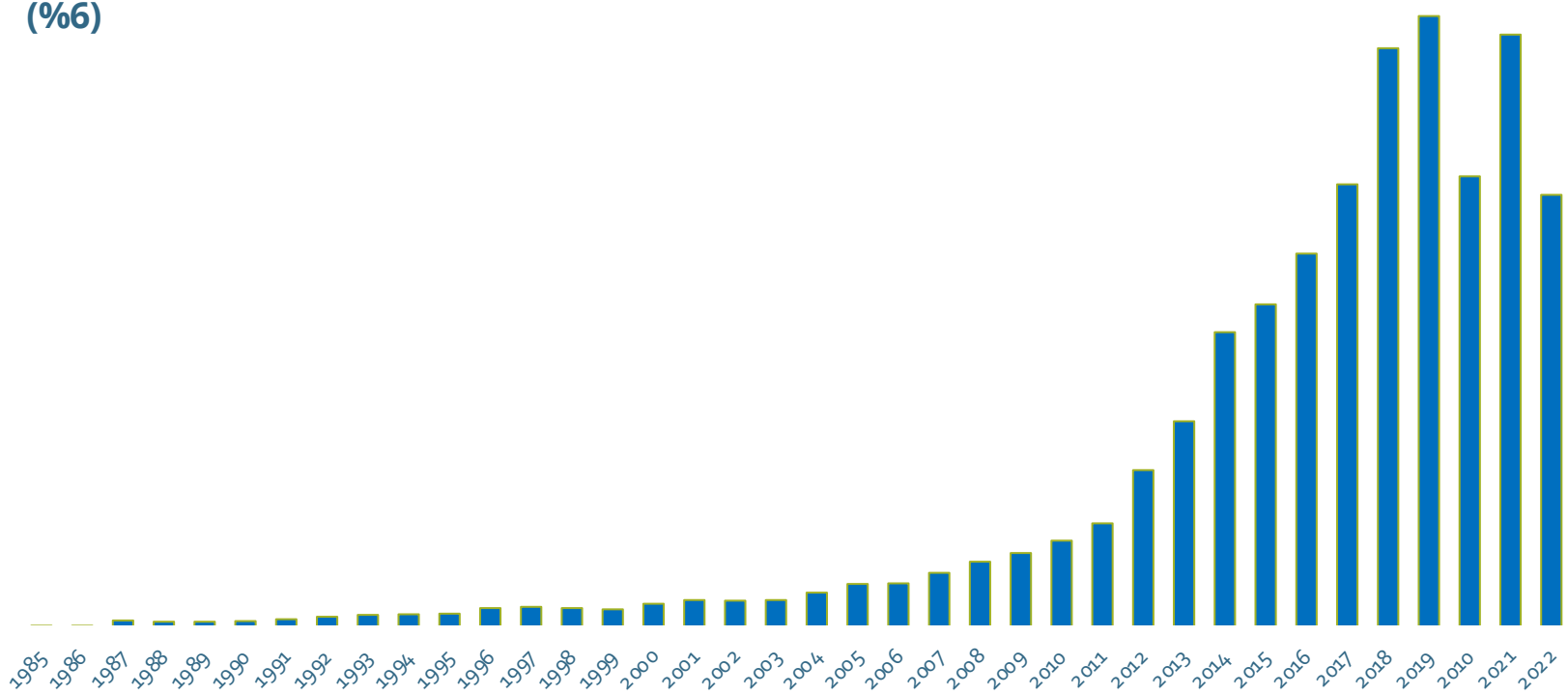
1996 – 2001 arasında her yıl 3 milyondan fazla insan HIV ile enfekte oldu.
Sonrasında yeni enfeksiyonlar azalmaya başladı ve 2019'da 2 milyonun altına indi (1990'dan beri en düşük sayı)

AIDS-ilişkili ölüm sayısı 1990'larda artarak 2004-2005'de pik yaptı (2 milyona yakın ölüm).
Sonrasında azalarak 2016'dan itibaren bir milyonun altına indi.



HIV Pozitif Olgular, Türkiye (15.11.2022, n=34,453)

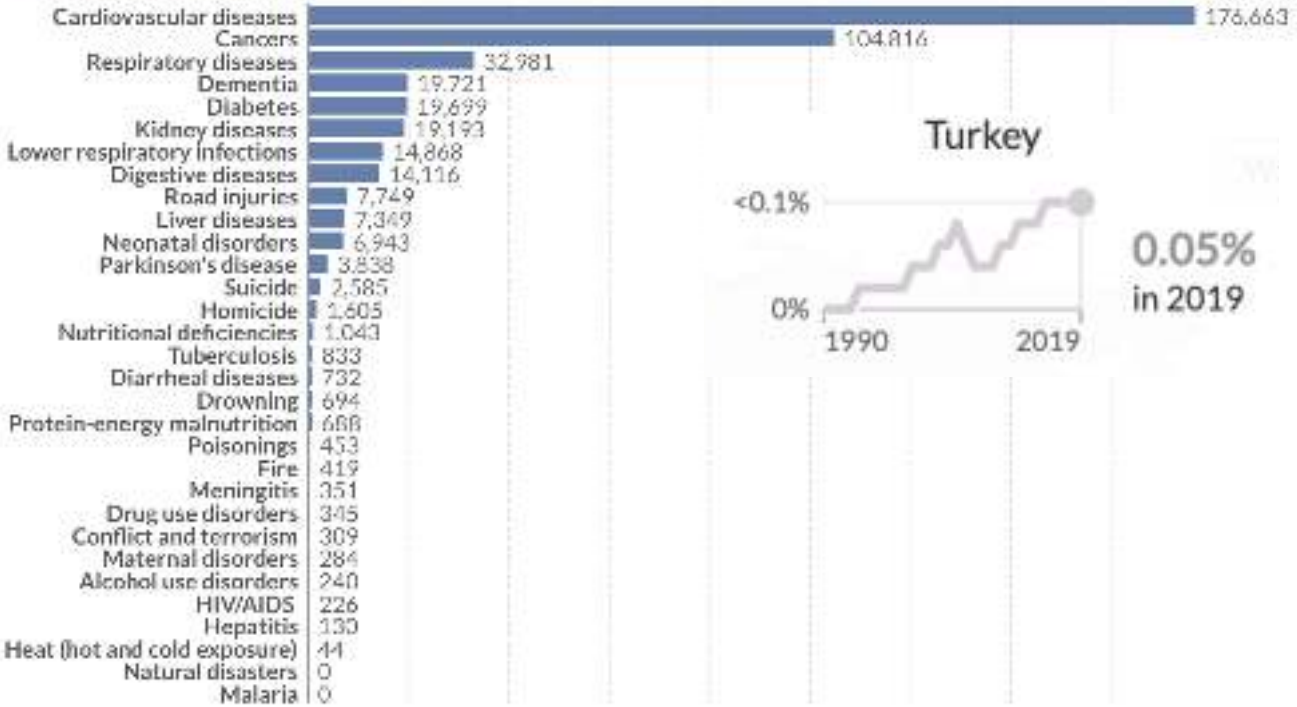
2,177 AIDS vakası
(%6)



Number of deaths by cause, Turkey, 2019

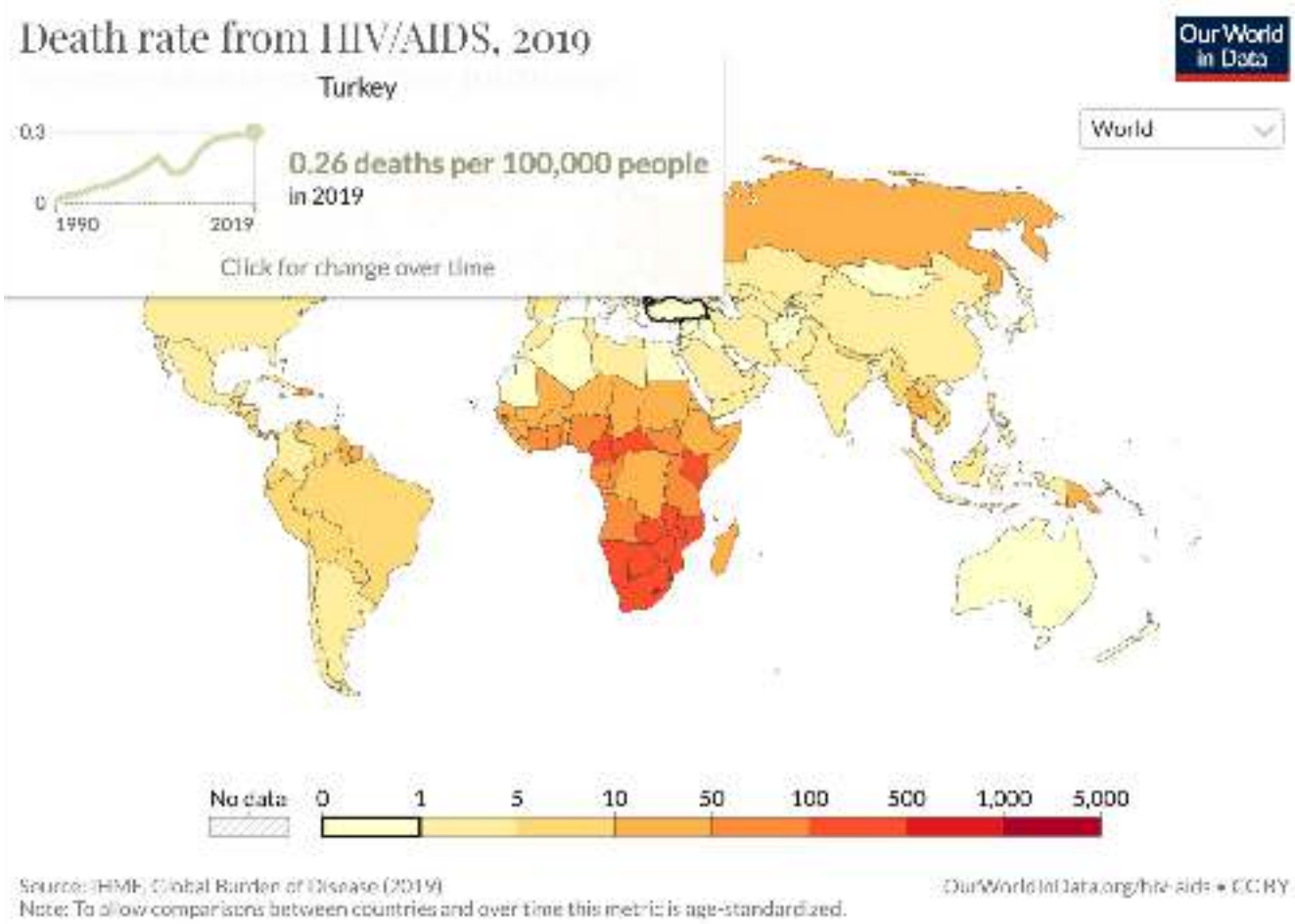
Our World in Data

Change country or region



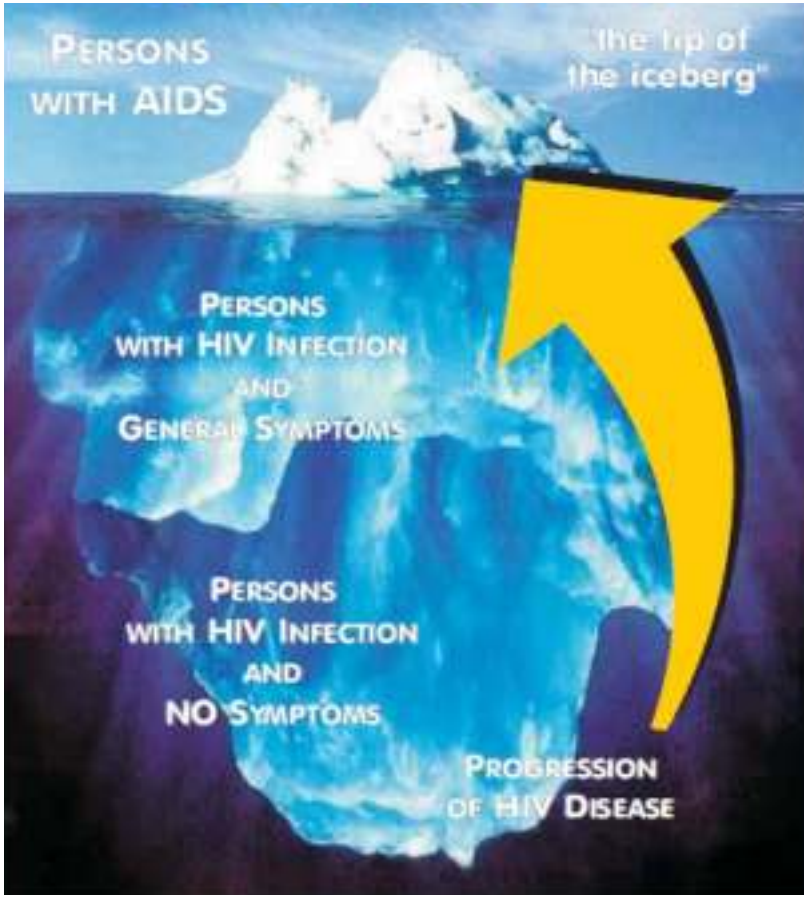
Source: IHME, Global Burden of Disease (2019)

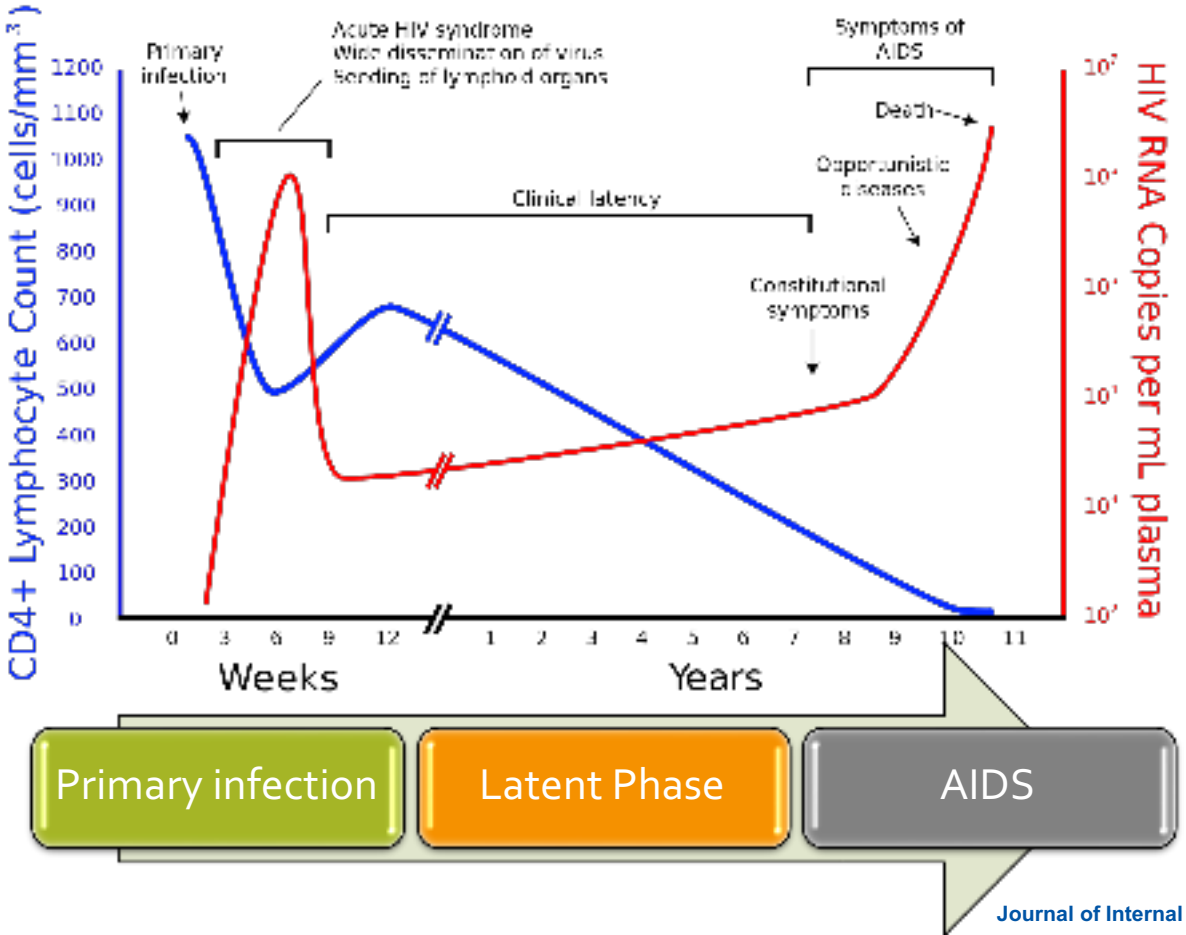
OurWorldInData.org/causes-of-death • CC BY


Death rate from HIV/AIDS, 2019
Our World in Data
Turkey
0.3
0
1990
2019
0.26 deaths per 100,000 people in 2019
Click for change over time
World
No data
0
1
5
10
50
100
500
1,000
5,000
Source: IHME, Global Burden of Disease (2019)
Note: To allow comparisons between countries and over time this metric is age-standardized.
OurWorldInData.org/hiv-aids • CC BY

- HIV azalıyor **??**

- **%10-60** HIV olduğunun farkında değil
  - Bunlar AIDS tanımlayıcı hastalıklardan biri ile prezente olabiliyorlar





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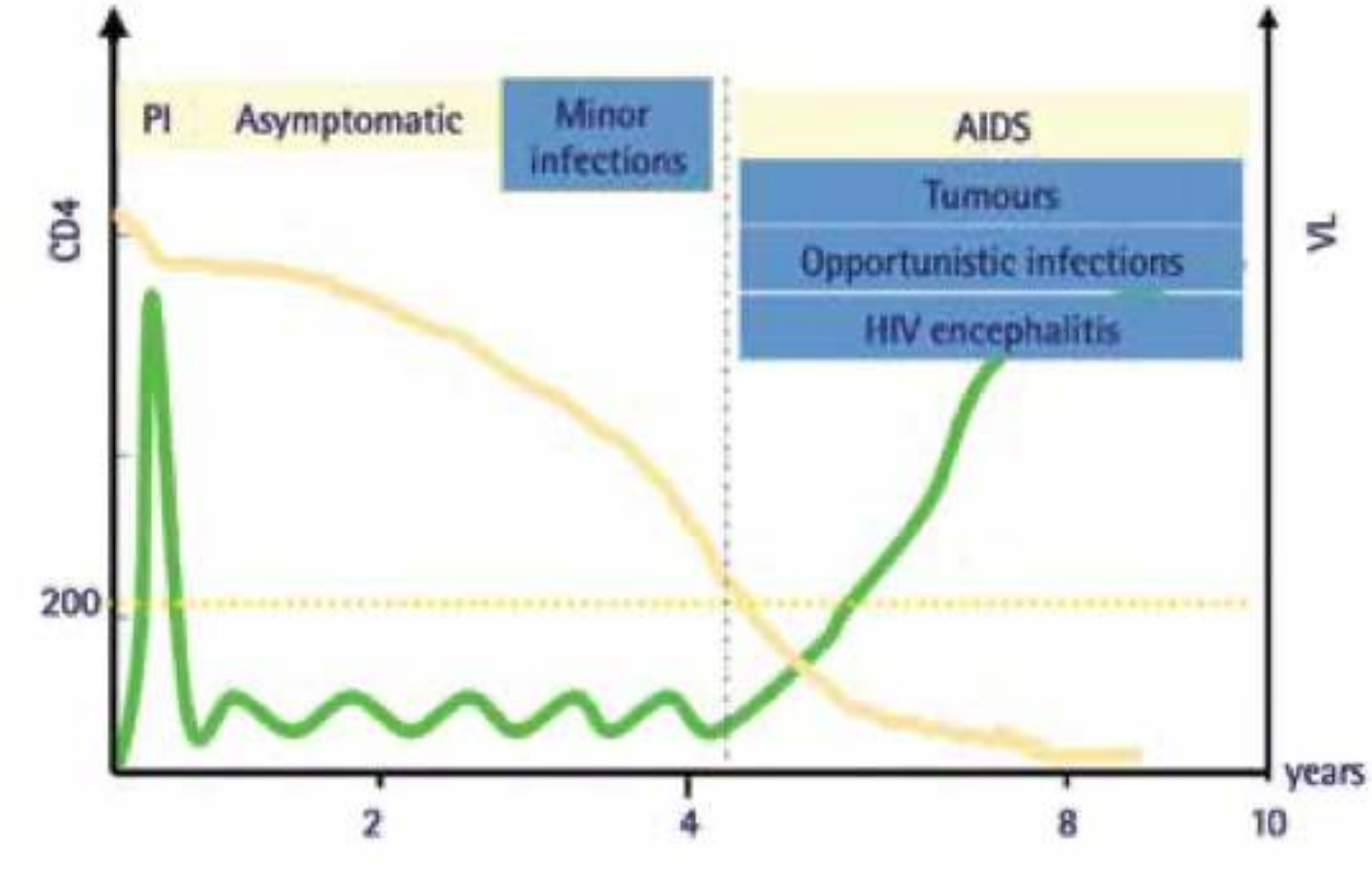
Journal of Internal Medicine 2008; 263 (3): 218-43.


PI
Asymptomatic
Minor infections
AIDS
Tumours
Opportunistic infections
HIV encephalitis
CD4
VL
200
2
4
8
10
years

CDC classification (2014)

2014 CDC Case Definition for HIV Infection Among Adolescents and Adults			
Stage	**CD4 Count**	**CD4 %***	**Clinical Evidence**
Stage 0	Early HIV Infection		
Stage 1	≥500 cells/mm^3	≥26	No AIDS-defining condition
Stage 2	200-499 cells/mm^3	14-25	No AIDS-defining condition
Stage 3	<200 cells/mm^3	<14	*or* Documentation of AIDS-defining condition
Stage unknown	No data	No data	*and* No information on presence of AIDS-defining conditions

*Use CD4 percentage only if no data available for CD4 count

2014 CDC Revised Classification System: Stage 3-Defining Opportunistic Illnesses in HIV Infection

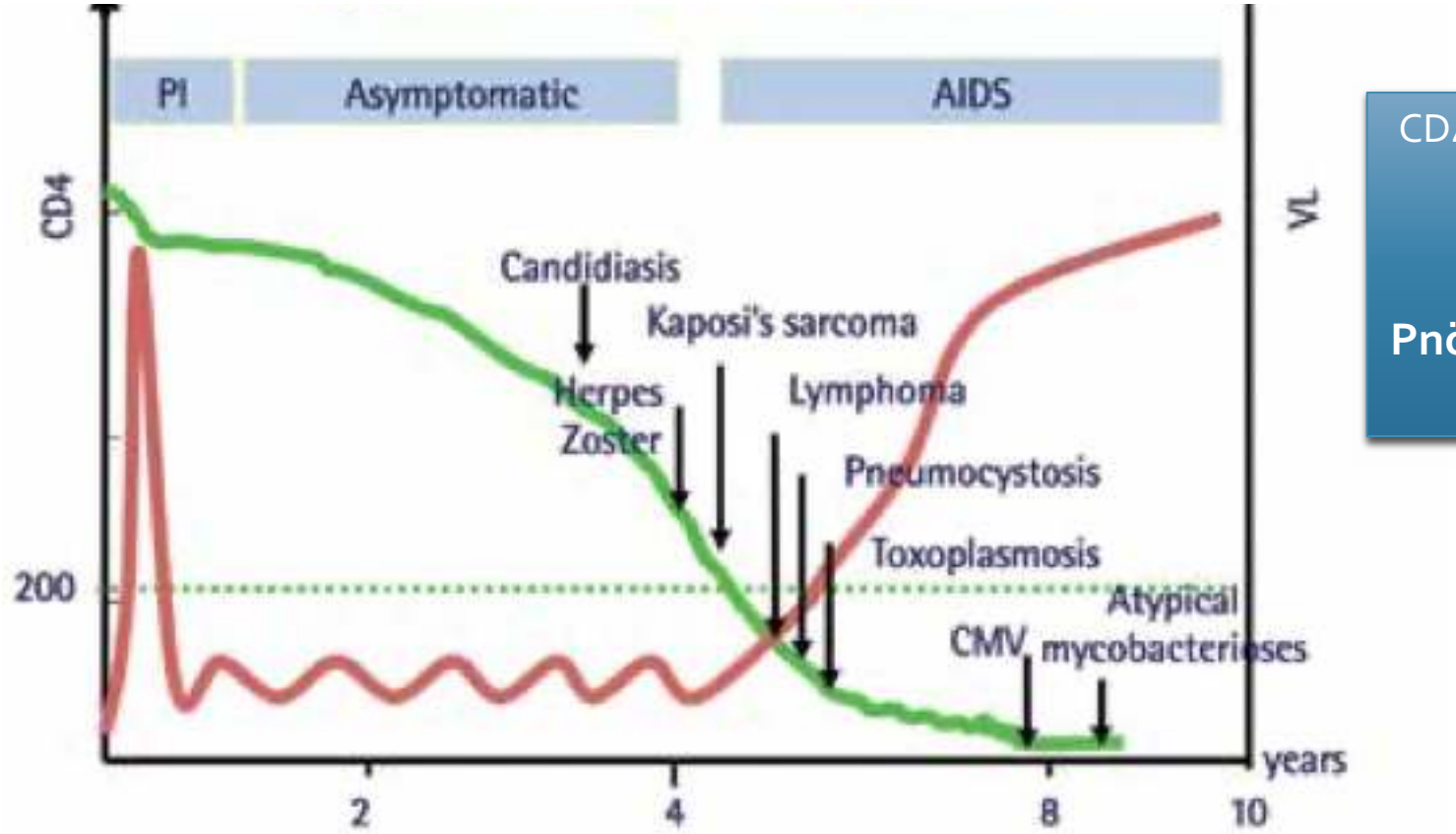
- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchia, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive+
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset age > 1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV^
- Herpes simplex: chronic ulcers (present for >1 month) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary+, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (previously known as "*Pneumocystis carinii*") pneumonia
- Pneumonia, recurrent+
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month
- Wasting syndrome attributed to HIV

*Only among children aged < 6 years
+Only among adults, adolescents, and children aged ≥ 6 years
^Suggested diagnostic criteria for these illnesses are defined in prior surveillance case definitions

Stage 1 Asymptomatic	Stage 2 Mild disease	Stage 3 Moderate disease	Stage 4 Severe disease (AIDS)
No symptoms	Wt. loss>5–10%	Wt. loss>10%	HIV wasting syndrome
	Sore or cracks around the lip	Oral thrush	Esophageal thrush
Or only persistent generalized lymphadenopathy	Seborrhea	Oral hairy	More than 1 month: Herpes simplex ulceration
	Prurigo	Leukoplakia	Lymphoma
	Herpes zoster	More than 1 month	Kaposi sarcoma
	Recurrent URTI	• Diarrhea	Invasive cervicalcancer
	Recurrent mouth ulcer	• Unexplained fever	Pneumocystic pneumonia
		• Severe bacterial infection	Extrapulmonary TB
		• Pneumonia	Cryptococcal meningitis
		• Muscle infection	Toxoplasma brain abscess
		Pulmonary TB	Visceral leishmaniasis
		TB lymphadenopathy	HIV encephalopathy
		Acute necrotizing ulcerative gingivitis	

HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome

The WHO clinical staging of HIV/AIDS cases



CD4 sayısından bağımsız sık görülenler:

TB
Pnömokok pnömonisi
Zona

- AIDS tanımlayıcı hastalıkları olanlarda ART hemen başlanmalı
  - Fırsatçı hastalıkların bir kısmının (kriptosporidiosis ve PML gibi) etkili tedavisi yok ancak ART ile immune fonksiyonun düzeltilmesi hastalık prognozunu iyileştirir
- Ancak erken başlanan ART bazı fırsatçı hastalıklarda (kriptokok menejiti veya TB menenjiti) ciddi IRIS riskini arttırabilir.

WHY DO PEOPLE HOSPITALISED WITH HIV HAVE POOR OUTCOMES?

Seriously ill people living with HIV often suffer from a variety of life-threatening infections

20% of people die in hospital

Tuberculosis, cryptococcal meningitis and severe bacterial infections are the most common causes

19% of people successfully discharged from hospital are re-admitted within a year

Sometimes people are not linked to care following discharge from hospital

14% die within a year of discharge

Patients often suffer with long-term disabilities following discharge and still need care

En mortal fırsatçı enfeksiyonlar

Cryptococcal meningitis	Tuberculosis	Severe bacterial infection
		
• 223,100 cases per year • 81% mortality rate • Represents 15% of AIDS-related deaths worldwide	• 1.2 million cases per year • 33% mortality rate • Represents 33% of AIDS-related deaths worldwide	• Exact statistics in HIV unknown • More than 6 million deaths per year among whole population; people with advanced HIV at higher risk

ART döneminde fırsatçı enfeksiyonların insidansında azalma

1996 ve HAART öncesi

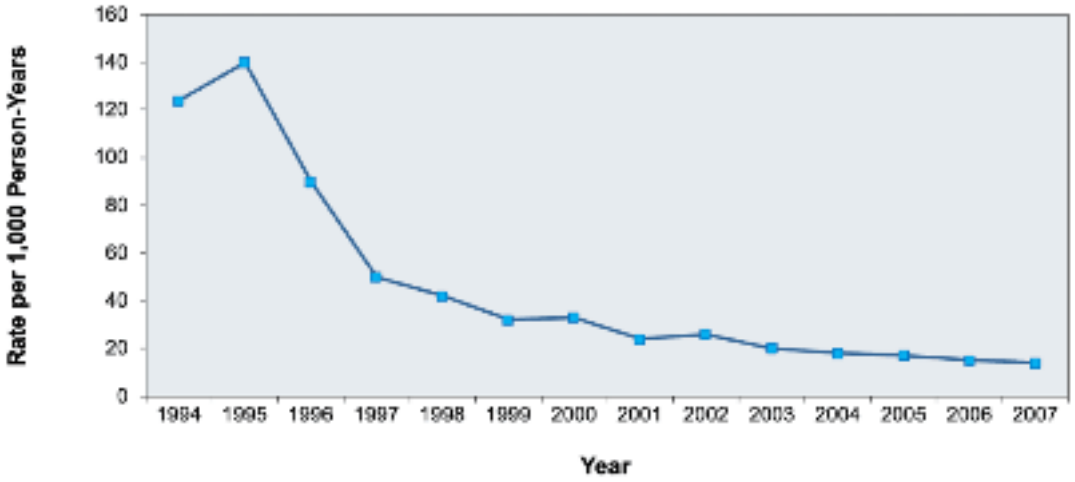
Fırsatçı enfeksiyonların insidansı ve mortalitesi daha yüksek

ART ve primer profilaksi sayesinde

HIV enf.nunun prognozunda ciddi düzelme

Yaşam beklentisinde artma

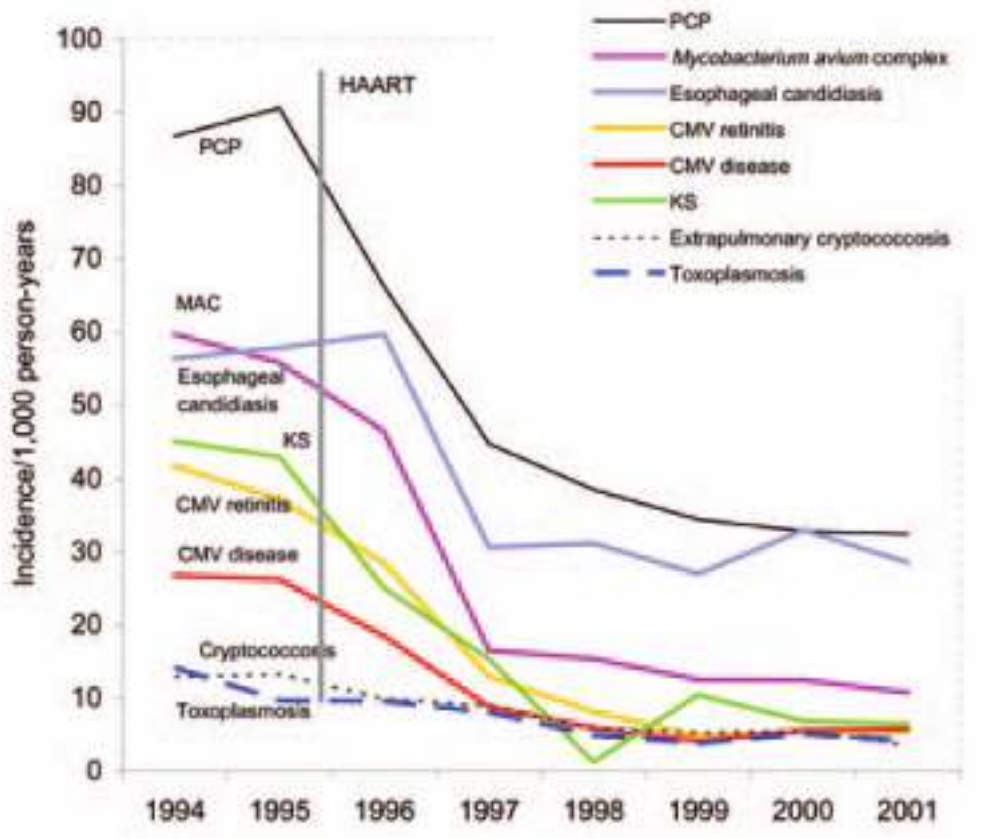
AIDS gelişenlerde,
öz.ART almayanlarda,
mortalite yüksek



Brooks JT, et al. Clin Infect Dis 2009;48:609-11.

1990’larda PCP Avrupa’da en sık FE

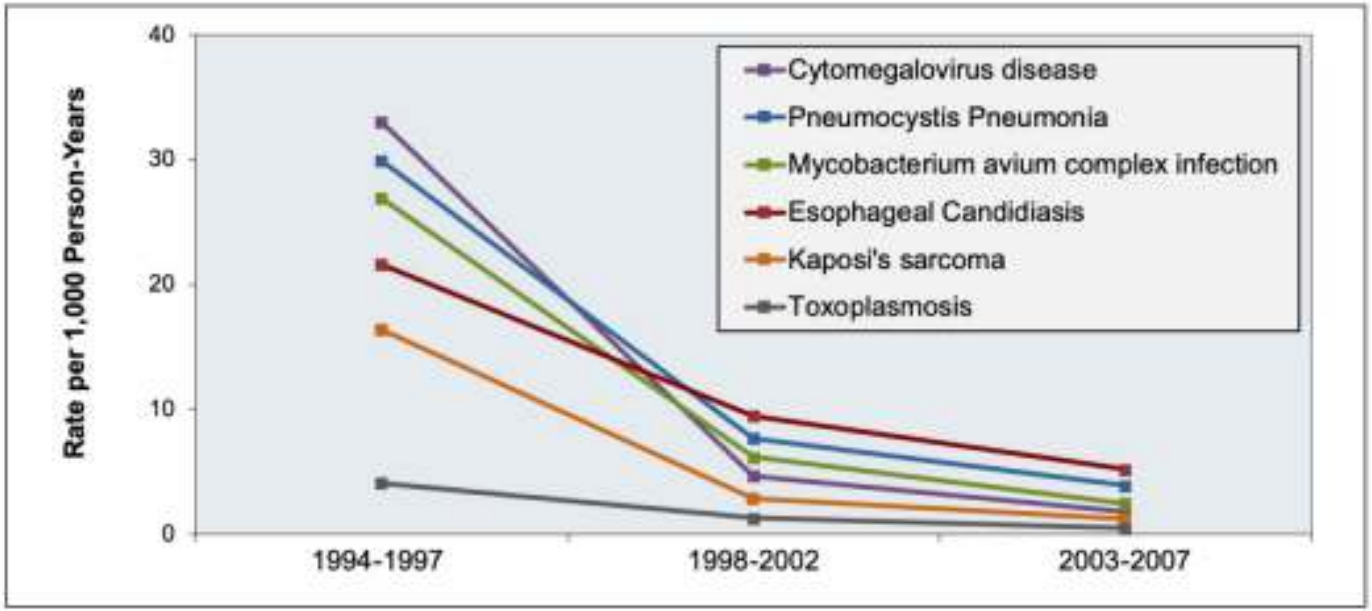
Profilaksi ve HAART ile birlikte bakteriyel pnömoni gelişmiş ülkelerde en sık



Yearly opportunistic infection rates per 1,000 personyears , CDC Adult and Adolescent Spectrum of Disease Project, 1994–2001. CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex; PCP, Pneumocystis pneumonia. Data are standardized to the population

CDC

AIDS-tanımlayıcı fırsatçı hastalıklar (ABD)



Buchacz K, et al. AIDS 2010;24:1549-59.

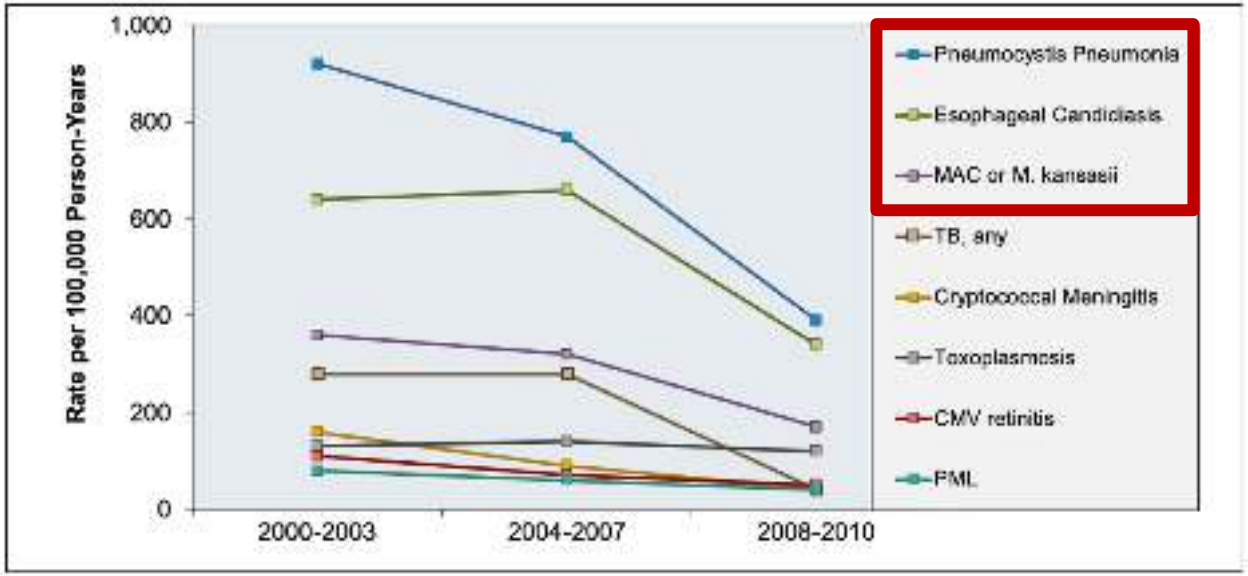
Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000–2010

Kate Buchacz,[1] Bryan Lau,[2] Yuezhou Jing,[2] Ronald Bosch,[3] Alison G. Abraham,[2] M. John Gill,[4] Michael J. Silverberg,[5] James J. Goedert,[6] Timothy R. Sterling,[7] Keri N. Althoff,[2] Jeffrey N. Martin,[8] Greer Burkholder,[9] Neel Gandhi,[10] Hasina Samji,[2,11] Pragna Patel,[1] Anita Rachlis,[12] Jennifer E. Thorne,[7] Sonia Napravnik,[13] Keith Henry,[14] Angel Mayor,[15] Kelly Gebo,[2] Stephen J. Gange,[2] Richard D. Moore,[2] and John T. Brooks[1]; for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA

16 Cohort
63,541 kişi
261,573 kişi-yılı

%9'u en az bir fırsatçı enfeksiyon geliştirmiş.

Üç gözlem döneminde insidans ve mortalite azalmış (p<0.001)



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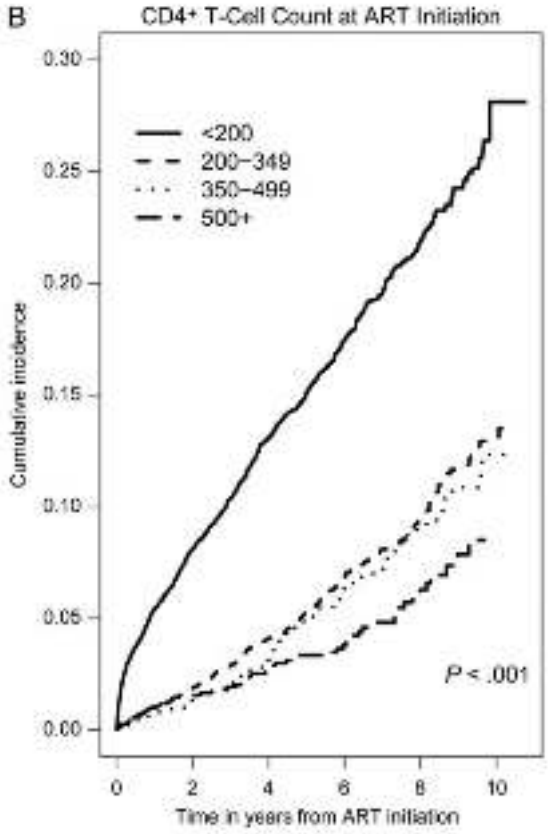
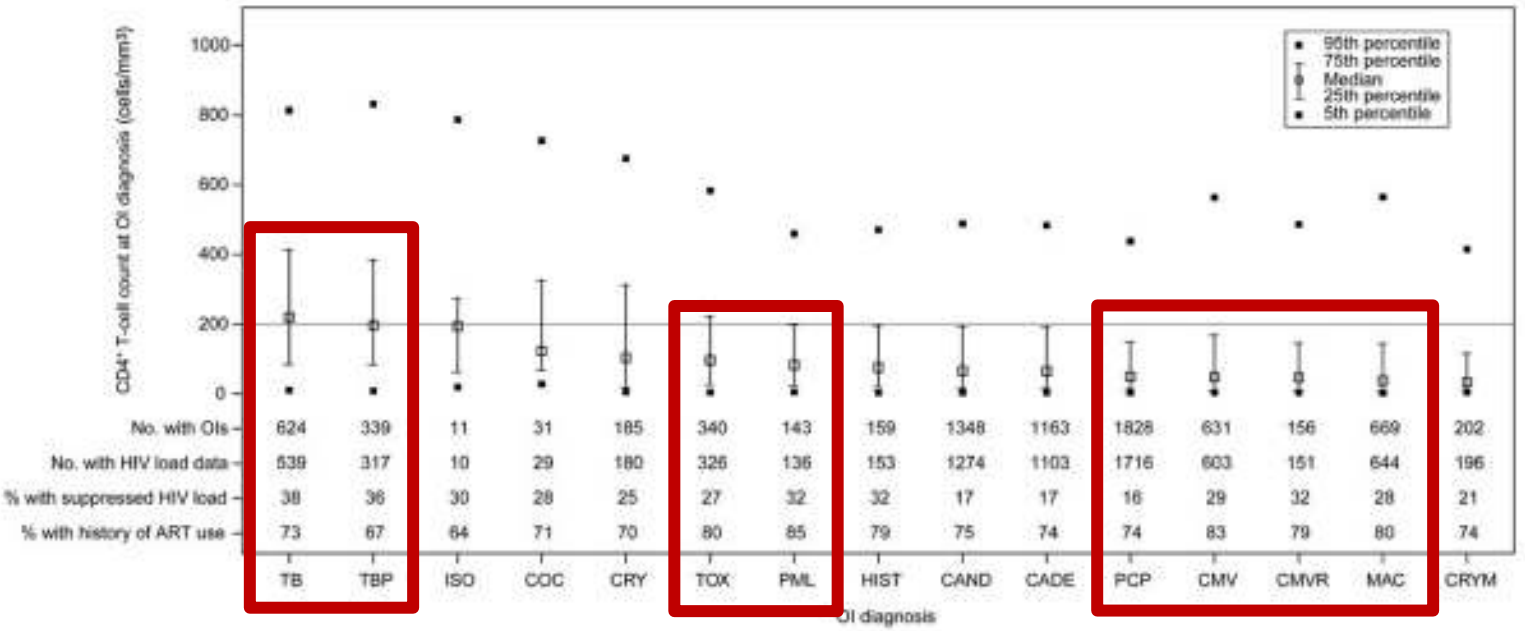
Buchacz K, et al. J Infect Dis 2016;214:862-72.

ART başlangıcında CD4 sayısı ile izlemde FE gelişme riski ters orantılı



Buchacz K, et al. JID 2016;214:862-72.

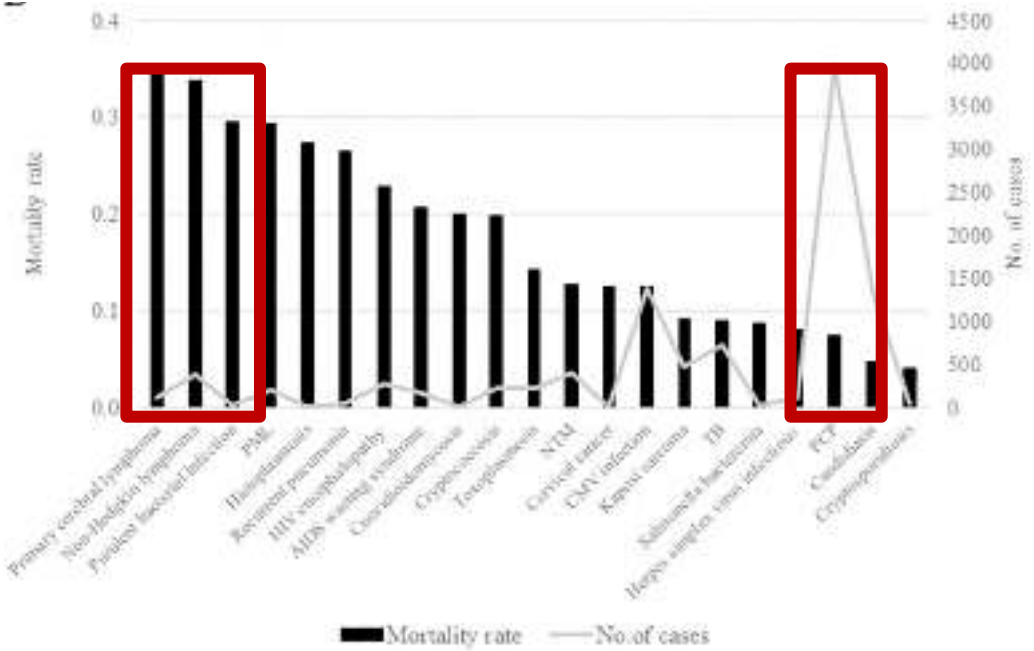


FE tanısı konduğunda CD4 sayıları

Buchacz K, et al. JID 2016;214:862-72.

Nationwide surveillance of AIDS-defining illnesses among HIV patients in Japan from 1995 to 2017

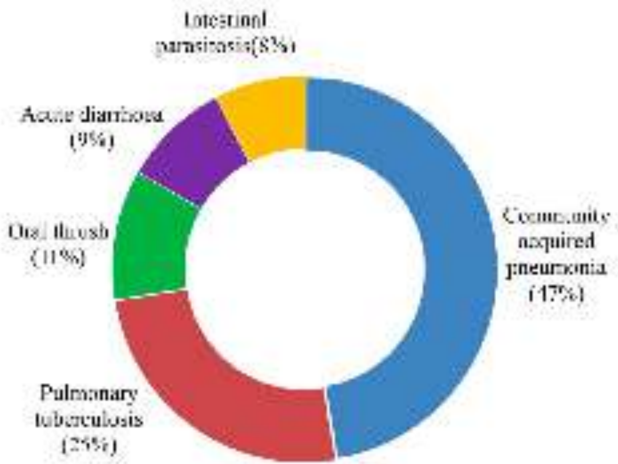
Takeshi Tanaka[1*], Kazuhiro Oshima[2*], Kei Kawano[1], Masato Tashiro[1,3], Akitaka Tanaka[1], Ayumi Fujita[1], Misuzu Tsukamoto[4], Akira Yasuoka[5], Katsuji Teruya[6], Koichi Izumikawa[1,3]



Tanaka T, et al. PLoS ONE 2021;16(8): e0256452.

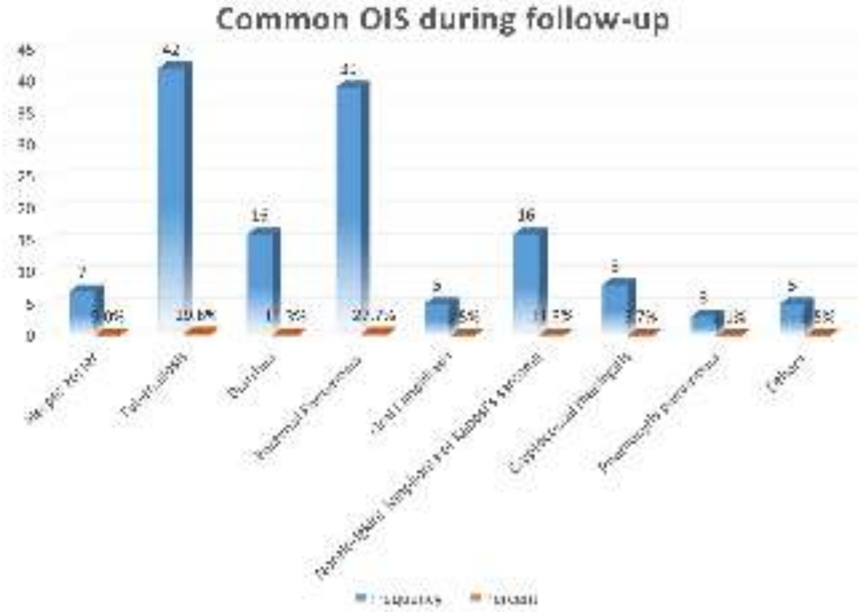
Incidence and predictors of opportunistic infections in adolescents and adults after the initiation of antiretroviral therapy: A 10-year retrospective cohort study in Ethiopia

Beshada Zerfu Woldegeorgis[1*], Chala Wegi Diro[2], Bereket Yohannes[1], Amene Abebe Kerbo[1] and Yordanos Sisay Asgedom[2]



Incidence of common opportunistic infections among HIV-infected children on ART at Debre Markos referral hospital, Northwest Ethiopia: a retrospective cohort study

Mamaru Wubale Melkamu[1], Mulugeta Tesfa Gebeyehu[1], Abebe Dilie Afenigus[1], Yitbarek Tenaw Hibstie[1], Belisty Temesgen[1], Pammla Petrucka[2,4] and Animut Alebel[1,5*]



Woldegeorgis BZ, et al. Front. Public Health 2022;10:1064859.
Melkamu et al. BMC Infectious Diseases 2020; 20:50

Magnitude of Opportunistic Infections and Associated Factors Among HIV-Positive Adults on ART at Selected Public Hospitals in Sidama National Regional State, Southern Ethiopia

Demelash Wachamo[1]
Fisseha Bonga[2]

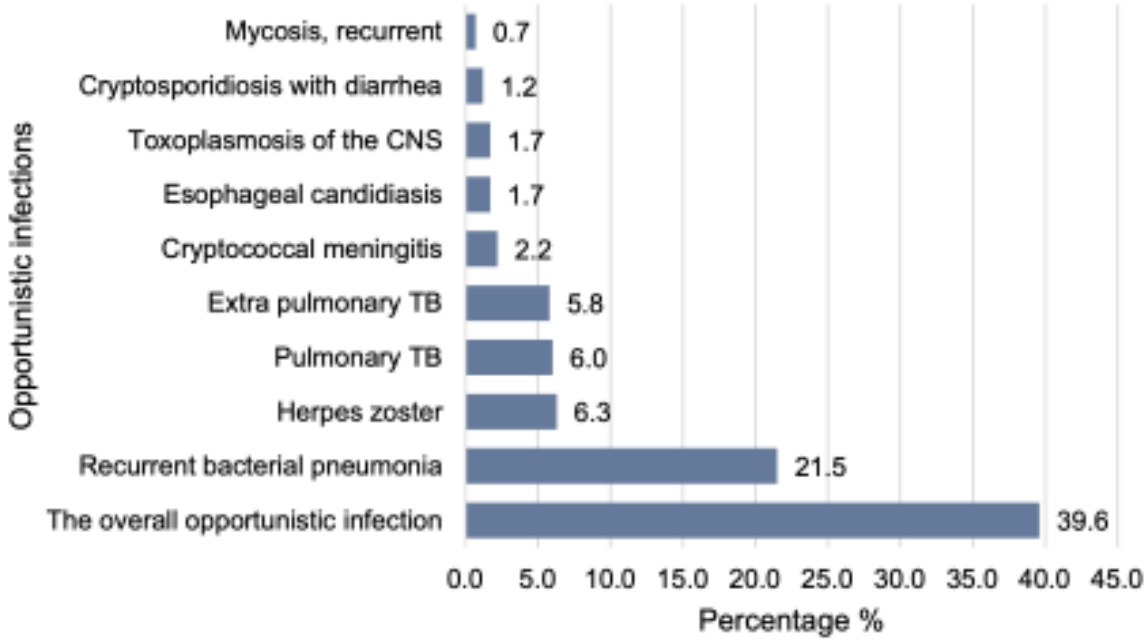


Figure 1 Magnitude of opportunistic infections among HIV/AIDS on ART at selected hospitals in Sidama Regional State, Southern Ethiopia 2019 (n=414).

Wachamo D, et al. HIV/AIDS - Research and Palliative Care 2020:12 479–487

Epidemiology of Opportunistic Infections in HIV Infected Patients on Treatment in Accredited HIV Treatment Centers in Cameroon

Ornella Sybile D. Kouanfack, MD;[1] Charles Kouanfack, MD, PhD;[2,3,4] Serges Clotaire Billong, MD, PhD;[1] Samuel N. Cumber, MPH, PhD;[5,6,7] Claude N. Nkfusai, MSc;[2,3,8] Fala Bede, MD, MPH;[2,3] Emerson Wepngong, MD;[2,3,9] Chombong Hubert, MSc;[2,3] Georges Nguefack-Tsague, PhD;[1] Madeleine N. Singwe, MD[1]

2017-2018
1617 HIV enfekte hasta

%25.9'unda en az bir FE

Zona ve TB en sık

Erkek cinsiyet, ≥50 yaş, CD4<200/mm^3
FE gelişmesi için risk faktörleri

Kouanfack OSD, et al. International Journal of Maternal and Child Health and AIDS 2019; 8 (2): 163-172.

[SS-068]

İstanbul'da Bir Şehir Hastanesinde 503 Takipli İnsan İmmün Yetmezlik Virüsü (HIV) ile Enfekte Hastada Fırsatçı Enfeksiyon-Kanser Prevalansı, Risk Faktörleri ve Mortalite Eğilimleri

Dilara Akmar[1], Ayşe Batırel[2], Serap Gençer[3], Öznur Ak[4], Pınar Öngürü[2], Bülent Kaya[2]

- 2010-2021, **503** HIV enfekte hasta
- Toplam FE: 116 hasta (**%23**)
  - %9 birden fazla FE

Kandidiyazis	40 (8,0)
PCP	36 (7,2)
Zona Zoster	28 (5,5)
CMV	20 (4,0)
Bakteriyel Pnömoni	16 (3,2)
TB	14 (2,8)
HSV 1-2	7 (1,4)
HHV-8	6 (1,2)
Kriptokokoz	4 (0,8)
Toksoplazmoz	3 (0,6)
Aspergilloz	2 (0,4)
PML	2 (0,4)
Beyin Absesi	2 (0,4)

Mediterr J Infect Microb Antimicrob 2023;12:Supplement 1:1-289

- Toplam malignite sayısı: 27 hasta (**%5.4**)

NHL	9 (33,33)
Kaposi	6 (22,22)
Servikal Kanser	2 (7,41)
AC Ca	2 (7,4)
Anal Kanser	2 (7,4)
Hodgkin lenfoma	1 (3,7)
Diğerleri	5 (18,5)

Mediterr J Infect Microb Antimicrob 2023;12:Supplement 1:1-289

Mortalite	Yok	479 (95,2)
	Var	24 (4,8)
Ölüm nedeni FE ve CA olan	**Fırsatçı enfeksiyon**	11 (61,1)
	Aids tanımlayıcı malignite	7 (38,9)
Ölüm Nedeni	Lenfoma	6 (25,0)
	Kriptokokoz	3 (12,5)
	TB	2 (8,3)
	Kaposi	2 (8,3)
	PCP	2 (8,3)
	Bakteriyel Pnömoni	1 (4,2)
	Toksoplazmoz	1 (4,2)
	CMV	1 (4,2)
	Diğer	2 (8,3)
	Bilinmeyen	4 (16,7)

Tüm ölümlerin %75'i

Mediterr J Infect Microb Antimicrob 2023;12:Supplement 1:1-289

Bakteriyel pnömoni

- Gelişmiş ülkelerde bakteriyel pnömoni riski genel popülasyonla çok benzer
- ART öncesi dönemde yıllık bakteriyel pnömoni riski HIV ile enfekte kişilerde daha yüksekdi (%5-29)
- ART kullanımı ile CD4<200 olan hastalarda bakteriyel pnömoni riski (1993-1998 arasında) %45 azalmış
  - Sullivan JH, et al. Am J Respir Crit Care Med. 2000;162(1):64

Decreasing Incidence and Determinants of Bacterial Pneumonia in People With HIV: The Swiss HIV Cohort Study

Suraj Balakrishna,[1,2] Aline Wolfensberger,[1] Viacheslav Kachalov,[1,2] Jan A. Roth,[3,4,5] Katharina Kusejko,[1,2] Alexandra U. Scherrer,[1,2] Hansjakob Furrer,[6] Christoph Hauser,[6] Alexandra Calmy,[7] Matthias Cavassini,[8,9] Patrick Schmid,[6] Enos Bernasconi,[10] Manuel Battegay,[1] Huldrych F. Günthard,[1,2] Roger D. Kouyos[1,2]; the Swiss HIV Cohort Study

2008-2018
12,927 HIV ile yaşayan birey

985 bakteriyel pnömoni gelişmiş

İnsidans 1000 kişi yılında 13.2 vakadan 6.8 vakaya inmiş

J Infect Dis 2022;225:1592–600

- HAART döneminde de bakteriyel pnömoni sık enfeksiyonlardan biri.
  - 16 aylık ortalama izlem süresinde hastaların %2.1'inde gözlendi.
    - Gordin FM, et al. Am J Respir Crit Care Med 2008;178:630–6.
- Mortalite %6-15.
    - Cilloniz C, et al. Expert Rev Anti Infect Ther 2018;16:579–88.
- Bakteriyel pnömoni HIV tanısı koyduran ilk belirti olabilir
- Reküran pnömoni (öz. ≥2 atak/yıl) AIDS-tanımlayıcı durumlardan biri

Pnömoni – risk faktörleri

- İleri yaş
- Düşük eğitim seviyesi
- Düşük CD4 sayısı
- Yüksek viral yük
  - ART kullanmama
- IV ilaç kullanımı
- Sigara kullanımı
  - Bakteriyel pnömoni ve invaziv pnömokokal hastalık riskinde **2-5 kat** artış
- Kaynakları yetersiz ülkelerde yaşama
- Diğerleri: KOAH, alkol, PCP öyküsü, nötropeni, KS tedavisi, ciddi malnutrisyon

Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per µL: secondary outcome results from a randomised controlled trial

Jemma O'Connor, Michael J Vjecha, Andrew N Phillips, Brian Angus, David Cooper, Beatriz Grinsztejn, Gustavo Lopardo, Satyajit Das, Robin Wood, Aimee Wilkin, Hartwig Klinker, Pacharee Kantipong, Karin L Klingman, David Wick, Elbushra Herieka, Eileen Denning, Ibrahim Abubakar, Fred Gordin, Jens D Lundgren, for the INSIGHT START study group

START trial

2009-2013

4685 HIV pozitif kişi

120'sinde ciddi bakteriyel enfeksiyon

Erken ART başlananlarda (CD4>500/mm^3) geç başlananlara (CD4<350/mm^3) göre **%61** daha az pnömoni riski var HR 0.39, 95% CI 0.26-0.57, p<0.0001)

O'Connor J, et al. Lancet HIV 2017;4(3):e105.

- HIV enfeksiyonu reküran pnömokok pnömonisi ve bakteremisi için risk faktörüdür.

- Bakteriyel pnömoninin de HIV enfeksiyonu üzerinde olumsuz etkisi var.
  - Geçici olarak CD4 sayısını azaltabilir.
  - Kalıcı olarak pulmoner fonksiyon azalır.
    - ✓Uzun dönem mortalitede 2-5 kat artış

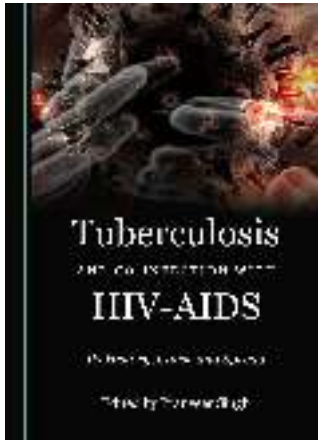
Bakteriyel pnömoni & AC Ca

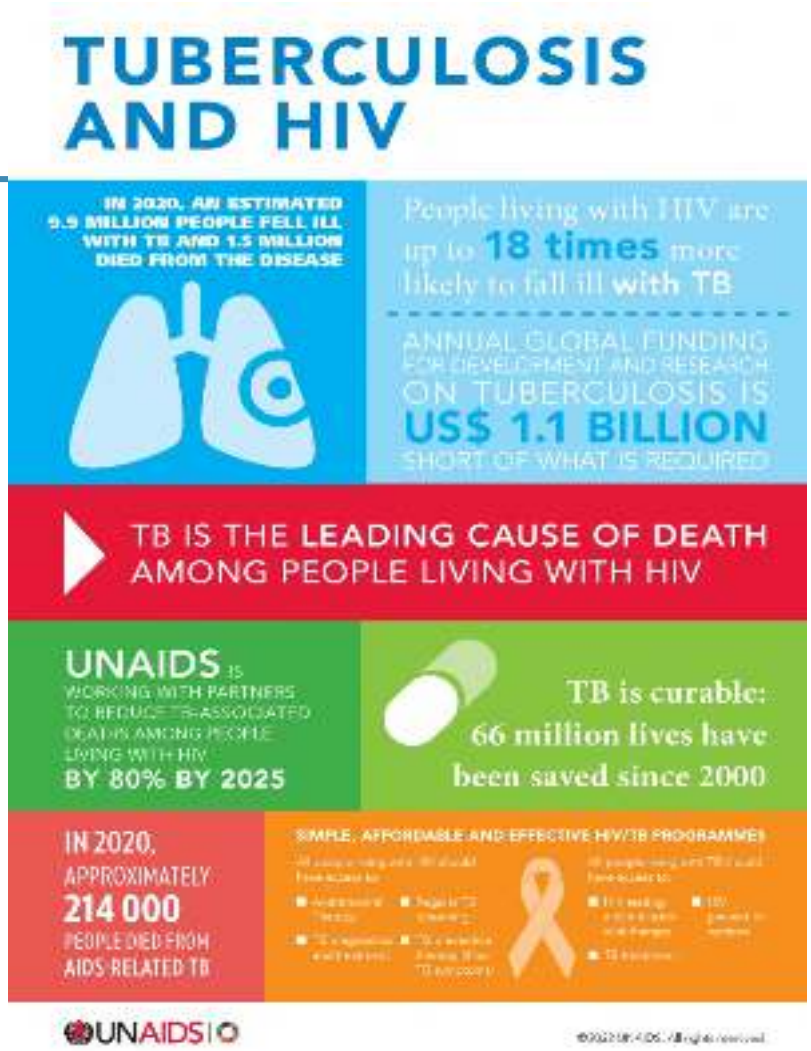
- AC Ca riski de artıyor.
  - Shebl FM, et al. J Acquir Immune Defic Syndr 2010;55:375–9.

- AC Ca genel popülasyona göre 1.7 kat daha sık.
  - Daha agresif ve daha genç yaşta görülüyor
    - Sigel K, et al. AIDS 2012;26:1017-25.
    - Makinson A, et al. AIDS 2016;30:573-82.

Tuberküloz

TB immunyetmezliğin tüm evrelerinde olabilir. Erken dönemde ortaya çıkarsa klinik ve radyolojik bulguları immunkompetan bireylerden farklı değildir.

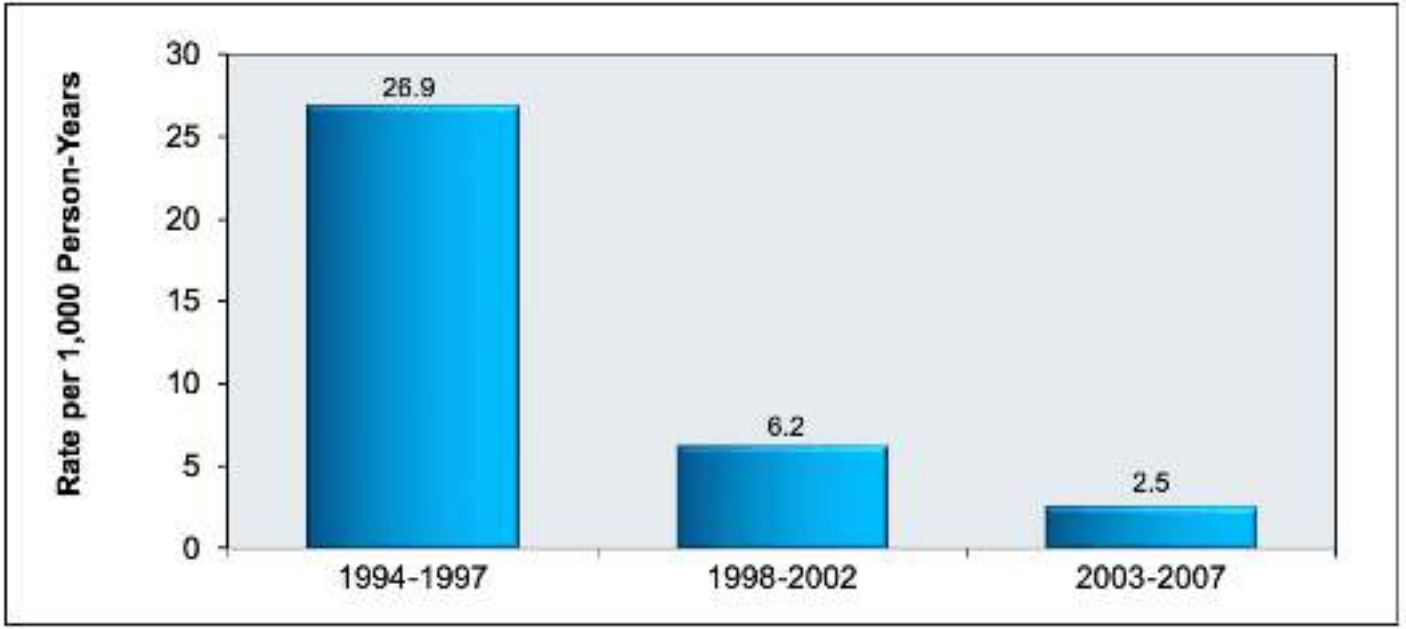




Mycobacterium avium Complex (MAC) Hastalığı

- Çevrede (yiyecek, su) yaygın olarak bulunur.
- İnhalasyon, yutulma, inokülasyon yoluyla bulaşır.
- Insandan insana bulaş olası değildir.
- Tipik olarak **CD4 <50/mm^3** olanlarda görülür.
- Modern HIV çağında dissemine MAC enfeksiyonu çoğunlukla HIV tanısını bilmeyen veya ART almayan, ileri immunsupresyonu olanlarda **%20-40**
  - ART ile belirgin bir şekilde insidans azalıyor

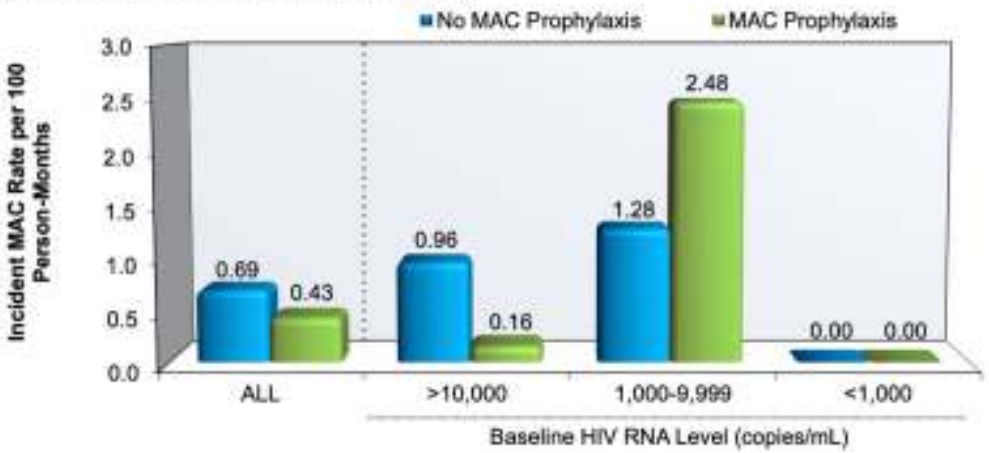
Dissemine MAC enfeksiyonunun insidansı (ABD)



Buchacz K, et al. AIDS 2010;24:1549-59.

Is Primary *Mycobacterium avium* Complex Prophylaxis Necessary in Patients with CD4 <50 Cells/μL Who Are Virologically Suppressed on cART?

Bienvenido G. Yangco, MD, MPH,[1] Kate Buchacz, PhD,[2] Rose Baker, MS,[2] Frank J. Palella, MD,[4] Carl Armon, PhD,[3] John T. Brooks, MD,[2] and the HIV Outpatient Study Investigators



1996-2007
369 HIV pozitif, CD4<50/mm3

HIV RNA < 1000 kopya/mL olan hastalarda görülmemiş.

Yangco BG, et al. AIDS Patient Care and STDs 2014;28(6)

CMV

- CMV genel popülasyonda yaygın – prevalans %45-%100
  - Cannon MJ, et al. Rev Med Virol 2010;20:202–13
- HAART öncesi CMV'ye bağlı erken mortalite yüksek (en tehlikeli FE.lardan biri)
  - Salomon N, et al. AIDS 1997;11:319–24.
- Japonya'da CMV koenfeksiyonu sık ve major AIDS-tanımlayıcı hastalıklar arasında **en yüksek mortalite** oranlarından birine sahip
  - Tanaka T, et al. PLoS One 2021;16:e0256452.

- Vakaların çoğunda **CD4 <50/mm3**
  - Latent virusun reaktivasyonu ile aralıklı veya kalıcı viremi kolonizasyona veya lokalize enfeksiyonlara yol açar.
- En sık retinit
- MSM.lerde CMV antikor pozitiflik oranı **>%90**
- İlave risk faktörleri: önceki FE, yüksek HIV RNA (>100.000 kopya/mL), yüksek CMV viremi seviyesi
  - DHHS, 2023

I. Yust · Z. Fox · M. Burke · A. Johnson · D. Turner · A. Mocroft · C. Katlama · B. Ledergerber · P. Reiss · O. Kirk · EuroSIDA

Retinal and extraocular cytomegalovirus end-organ disease in HIV-infected patients in Europe: a EuroSIDA study, 1994–2001

Her bir takvim yılında CMV hastalık insidansında **%49 azalma** (p<0.0001) (n=8.556).
Mortalite 1994-95'de %79'dan 2000-2001'de **%42**'ye gerileme (p<0.0001).

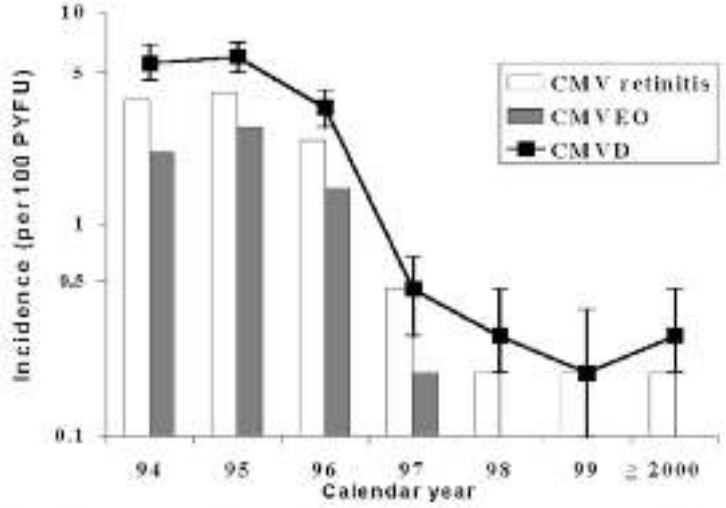


Fig. 1 Incidence of any CMV diagnosis at recruitment. *Y* axis (in

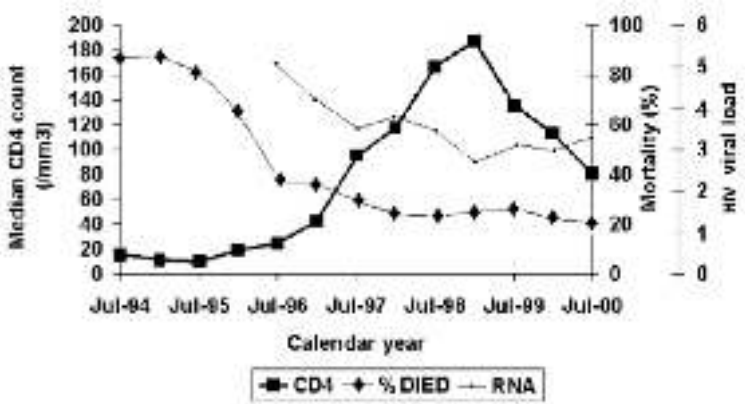


Fig. 4 Mortality, CD4+ count, and HIV viral load in patients with CMVD on maintenance anti-CMV therapy. This analysis uses a

Eur J Clin Microbiol Infect Dis 2004;23:550-9.

IFI

- AIDS-ilişkili ölümlerin **%47**'si IFI.lara ait
  - Denning DW, et al. Philos Trans R Soc B Biol Sci 2016;371:20150468.
- Japonya'da büyük prospektif bir kohort çalışmasında fungal pnömoni mortalitesi **%4**.
  - Nishijima T, et al. AIDS 2020;34:913–21.
- PCP tüm dünyada en sık IFI
  - de Sousa-Neto AL, et al. J Biosci Med 2020;08:15–26
- Diğerleri cryptococcosis, histoplasmosis, IPA
  - Pfavayi LT, et al. Sci Rep 2021;11:13240.

Pneumocystis jirovecii Pnömonisi (PCP)

- Sağlıklı çocukların 2/3'ü 4 yaşına kadar karşılaşıyor.
- Hava yolu ile bulaşır.
- Hastalık yeni enfeksiyon ile veya latent enfeksiyonun reaktivasyonu ile oluşabilir.

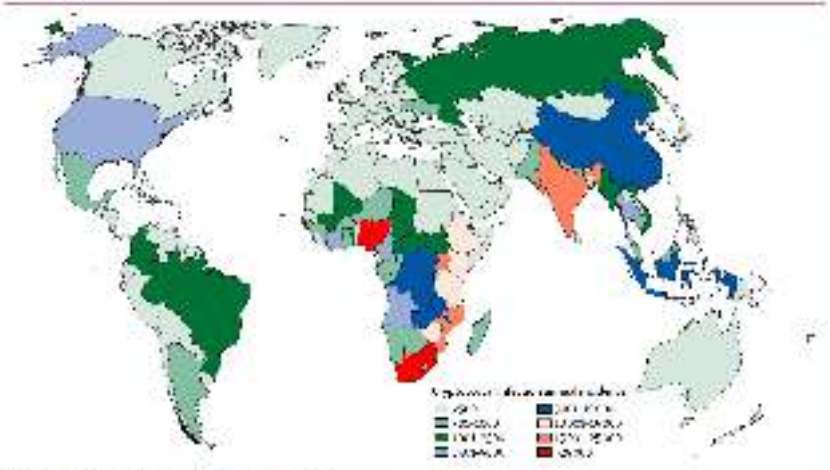
- Etkili ART ve PCP profilaksisi öncesi PCP insidansı **%80**'ne çıkarken ABD ve batı Avrupa'da 100 hasta yılında **%1'in altına** indi.
  - Buchacz K, et al. AIDS. 2010;24:1549-59.
  - Buchacz K, et al. J Infect Dis 2016;214:862-72.
  - Lundberg BE, et al. AIDS 2000;14:2559-66.
- İleri immunsupresyonda PCP riski belirgin artar (%90'ında **CD4 <200/mm^3**).
  - Kaplan JE, et al. J Infect Dis. 1998;178:1126-32.
  - Plair J, et al. N Engl J Med. 1990;322:161-5.
- Her yıl dünya genelinde >400.000 PCP vakası
- Mortalite %10-30
  - Lancet Infect Dis 2017 (http://dx.doi.org/10.1016/S1473-3099(17)30303-1)

PCP – Risk faktörleri

- CD4 <200/mm^3 (%90)
  - CD4 <%14
- Önceden PCP atağı
- Oral kandiyazis
- Reküran bakteriyel pnömoni
- İstemsiz kilo kaybı
- Yüksek HIV RNA yükü

Cryptococcosis

- Cryptococcal menenjit için küresel hastalık yükü yüksek.
  - 2008'de 957,900 vaka/yıl
  - 2014'de 223,100 vaka/yıl
- Hastalarda sıklıkla **CD4<100/mm³**



Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis

Lancet Infect Dis 2017; 17: 873–81

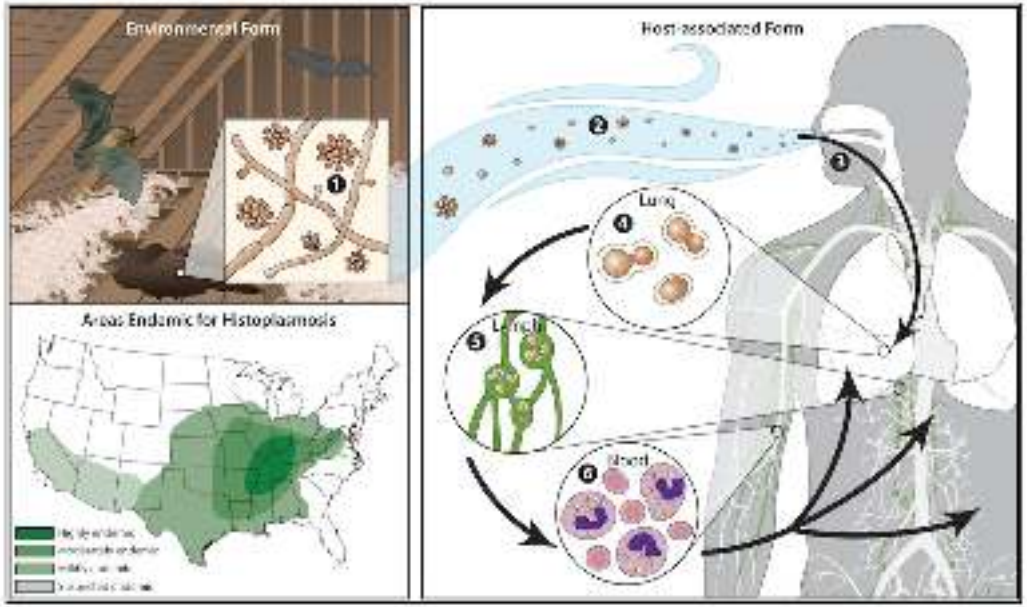
- HIV-ilişkili cryptococ menenjiti yıllık 150.000-200.000 ölümden sorumlu
  - Bu ölümler özellikle Sahra altı Afrika'da (3.ayda mortalite halen **%70**)
    - Lancet Infect Dis 2017 (http://dx.doi.org/10.1016/S1473-3099(17)30303-1)

- *Cryptococcus neoformans*
- *Crytococcus gattii*

Histoplasmosis

In the environment, *Histoplasma capsulatum* exists as a mold (1) with aerial hyphae. The hyphae produce macroconidia and microconidia (2) spores that are aerosolized and dispersed. Microconidia are inhaled into the lungs by a susceptible host (3). The warmer temperature inside the host signals a transformation to an oval, budding yeast (4). The yeast are phagocytized by immune cells and transported to regional lymph nodes (5). From there they travel in the blood to other parts of the body (6).

Source: Centers for Disease Control and Prevention (CDC)



- *Histoplasma capsulatum* kuş, tavuk veya yarasa atıkları ile kontamine nitrojenden zengin toprakta çoğalır. Mikrokonidiaların inhalasyonuyla alınır, akciğerlerde maya formuna dönüşür ve enfeksiyon gelişir.
- *Histoplasma capsulatum* ABD'de en sık endemik mikoz.

- Histoplazmoz dünya genelinde sıklıkla ihmal ediliyor, tanınmıyor veya yanlış TB tanısı alıyor.
- Endemik bölgelerde HIV/AIDS hastalarında görülme sıklığı %2-25
- Hastaların **%50-75**'inde ilk AIDS tanımlayıcı enfeksiyonu temsil etmekte
- Mortalite %10-60

Lancet Infect Dis 2017 (http://dx.doi.org/10.1016/S1473-3099(17)30303-1)

- Histoplazmoz vakalarının çoğu CD4 sayısı **<150/mm³** indiğinde latent Histoplazma enfeksiyonunun reaktivasyonuyla gelişir.

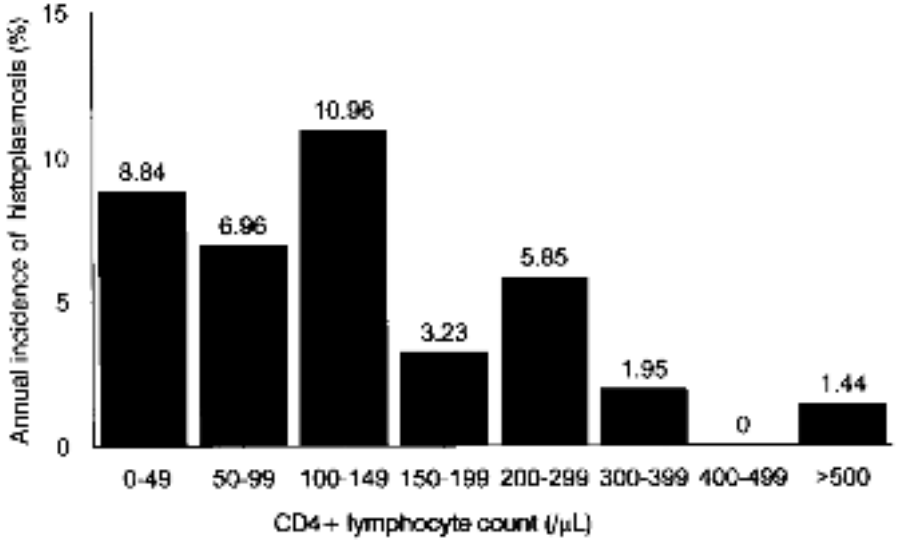
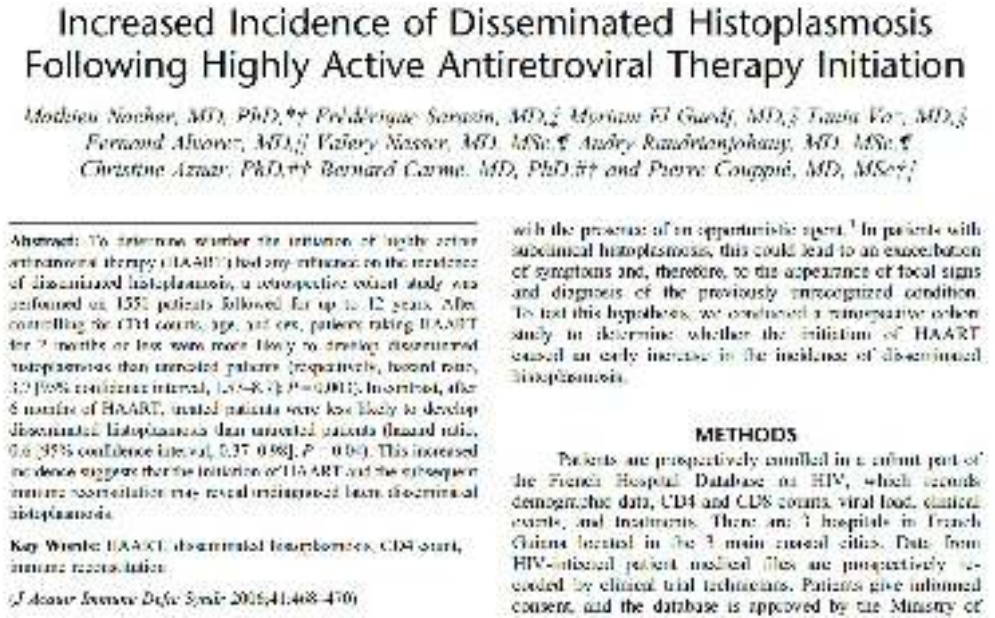


Figure 2. Annual incidence of histoplasmosis in HIV-infected patients; the incidence is stratified by baseline absolute $CD4^+$ lymphocyte counts.

McKinsey DS, et al. CID 1997;24:1195–1203

- Histoplazmoz insidansı da etklili ART ile azalmakta ancak bazen ART başlandıktan sonra immun rekonstitüsyon latent, tanınmamış Histoplasma enfeksiyonunu açığa çıkarabilir.



Increased Incidence of Disseminated Histoplasmosis Following Highly Active Antiretroviral Therapy Initiation

Mathieu Nacher, MD, PhD,† Frédérique Sarrazin, MD,‡ Myriam El Guedj, MD,§ Fanta Ve, MD,§ Fernand Alvarez, MD,|| Valery Nasser, MD, MSc,¶ Audry Randrianjohany, MD, MSc,¶ Christine Azmar, PhD,*† Bernard Carme, MD, PhD,#† and Pierre Couppié, MD, MSc†||*

Abstract: To determine whether the initiation of highly active antiretroviral therapy (HAART) had any influence on the incidence of disseminated histoplasmosis, a retrospective cohort study was performed on 1551 patients followed for up to 12 years. After controlling for CD4 counts, age, sex, etc, patients taking HAART for 3 months or less were more likely to develop disseminated histoplasmosis than untreated patients (respectively, hazard ratio, 3.2 [95% confidence interval, 1.1–8.7]; $P = 0.031$); in contrast, after 6 months of HAART, treated patients were less likely to develop disseminated histoplasmosis than untreated patients (hazard ratio, 0.6 [95% confidence interval, 0.37–0.98]; $P = 0.04$). This increased incidence suggests that the initiation of HAART and the consequent immune reconstitution may reveal unsuspected latent disseminated histoplasmosis.

Key Words: HAART, disseminated histoplasmosis, CD4 count, immune reconstitution

J Acquir Immune Defic Syndr 2005;41:468–470)

with the presence of an opportunistic agent.[1] In patients with subclinical histoplasmosis, this could lead to an exacerbation of symptoms and, therefore, to the appearance of focal signs and diagnosis of the previously unrecognized condition. To test this hypothesis, we conducted a retrospective cohort study to determine whether the initiation of HAART caused an early increase in the incidence of disseminated histoplasmosis.

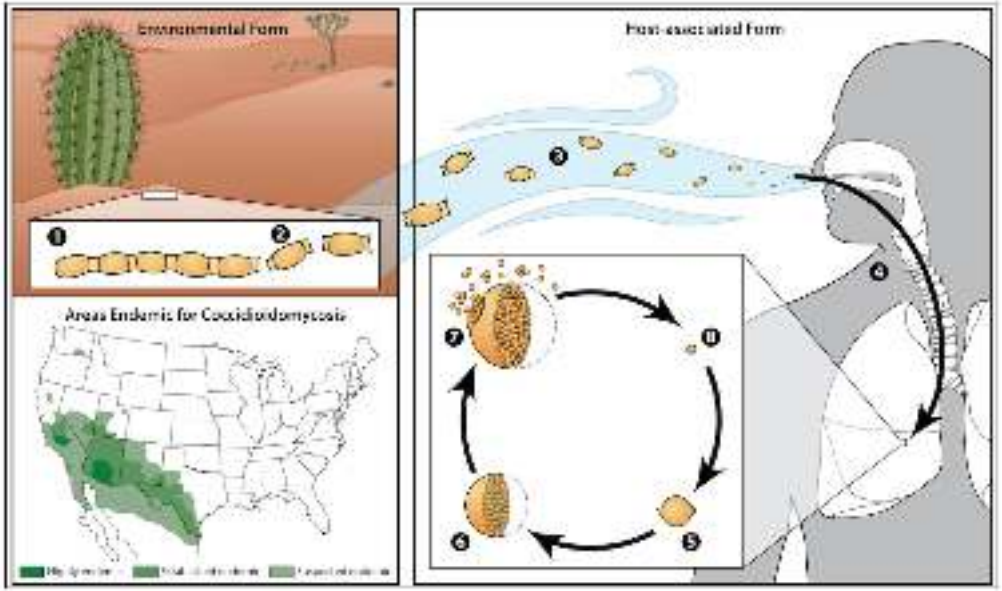
METHODS

Patients are prospectively enrolled in a cohort part of the French Hospital Database on HIV, which records demographic data, CD4 and CD8 counts, viral load, clinical events, and treatments. There are 3 hospitals in French Guiana located in the 3 main coastal cities. Data from HIV-infected patient medical files are prospectively recorded by clinical trial technicians. Patients give informed consent, and the database is approved by the Ministry of

Coccidioidomycosis

In the environment, *Coccidioides* spp. exists as a mold (1) with septate hyphae. The hyphae fragment into arthroconidia (2), which measure only 2-4 µm in diameter and are easily aerosolized when disturbed (3). Arthroconidia are inhaled by a susceptible host (4) and settle into the lungs. The new environment signals a morphologic change, and the arthroconidia become spherules (5). Spherules divide internally until they are filled with endospores (6). When a spherule ruptures (7) the endospores are released and disseminate within surrounding tissue. Endospores are then able to develop into new spherules (8) and repeat the cycle.

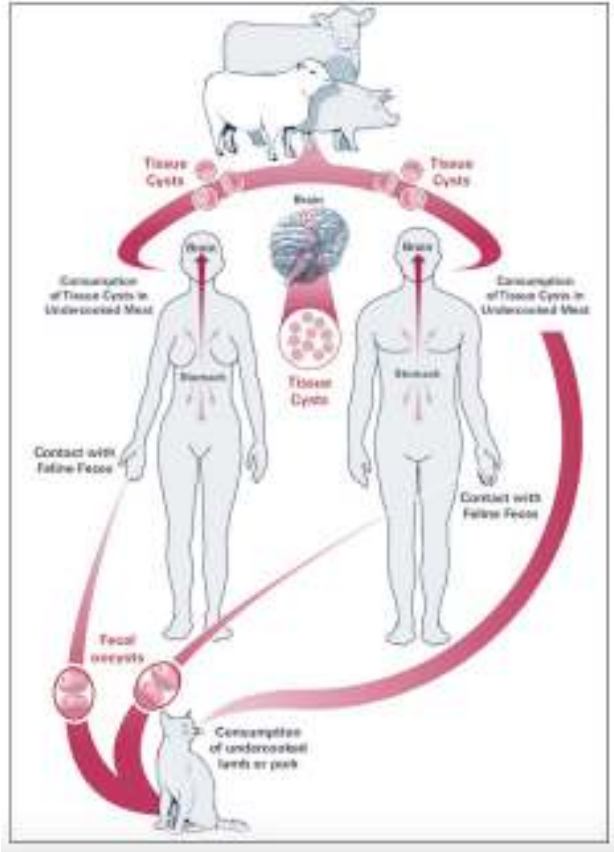
Source: Centers for Disease Control and Prevention (CDC)



- *Coccidioides immitis*
- *C.posadasii*
- Artrokonidiaların inhalasyonu, insanda morfolojik değişikliğe uğrayarak endosporlara dönüşmesi ve organlara yayılması ile enfeksiyon gelişir.
- Semptomatik koksidioidomikoz gelişme riski **CD4<250/mm^3** olan ve endemik bölgelerde yaşayan hastalarda sık

Toxoplasma gondii Ensefaliti (TE)

- Doku kistlerini taşıyan pişmemiş etin yenmesi veya kedi dışkısı ile atılan ve çevrede sporlanan ookistin yutulması ile primer enfeksiyon meydana gelir.
- Latent doku kistlerinin reaktivasyonu ile meydana gelir.
- İnsandan insana bulaşmaz.



- CD4 >200/mm^3 olan hastalarda nadirdir.
- **CD4 <50/mm^3** olan hastalar en yüksek risktedir.
- Toxoplasma seroprevalansı farklı coğrafik bölgelerde değişiklik göstermektedir: ABD'de **%11**, Avrupa, Latin Amerika, Afrika'da **%50-80**.

Herpes zoster

- Herpes zoster HIV ile enfekte bireylerin **%20-30'unda** görülmekte

- Risk faktörü olmayan, genç bir bireyde ortaya çıkması HIV testi için gerekçedir.

Maligniteler

Table 1. Incidence of AIDS- and Non-AIDS-Defining Malignancies in HIV-Positive Individuals and the Influence of ART

	Mean Standardized Incidence Ratios (Range)			Incidence Rate per 100,000 Person-Years	
Cancer Type	Pre-ART Era	Early ART Era	Late ART Era	0–6 Months Post-ART	6 Months–10 Years Post-ART
AIDS-Defining Cancers					
Kaposi sarcoma	1,555.5 (246–2826.5)	440.3 (47.6–840.6)	317.1 (22.6–572)	1,342	164
Non-Hodgkin's lymphoma	537.3 (102–1011.6)	260.4 (26.7–494.4)	107.3 (16.2–212.2)	257	134
Non-Hodgkin's lymphoma (CNS)				160	24
Cervical	69.9 (9.4–148.9)	99.2 (3.7–194.8)	89 (41.5–134.5)	n/a	n/a
Non-AIDS Defining Cancers					
Anal	44.5 (18–87.5)	80.1 (48.3–112.0)	78.4 (44–141.4)	72	69
Hodgkin's lymphoma	16.5 (1.5–34.3)	20.8 (11.1–54.7)	38.4 (20.7–64.4)	144	47
Liver	9.1 (3–19.5)	17.5 (5.9–35.9)	13.7 (5.1–25.4)	18	39
Lung	24.3 (3–51.5)	33.2 (7.8–63.8)	23.5 (7.4–84.9)	54	56
Prostate	5.3 (3–11.7)	13.3 (0–38.0)	9.9 (0–37.5)	22	58
Breast	19.1 (3.6–56.0)	25.5 (1.2–69.9)	32.5 (0.6–98.0)	177	122
Head and neck	9.2 (1.4–28.0)	12.1 (2.2–31)	10.6 (1.5–36.9)	n/a	n/a
Melanoma	4.1 (3–15.6)	8.5 (0–24.8)	10.7 (0.6–37.5)	n/a	n/a
HPV-related cancers				109	102

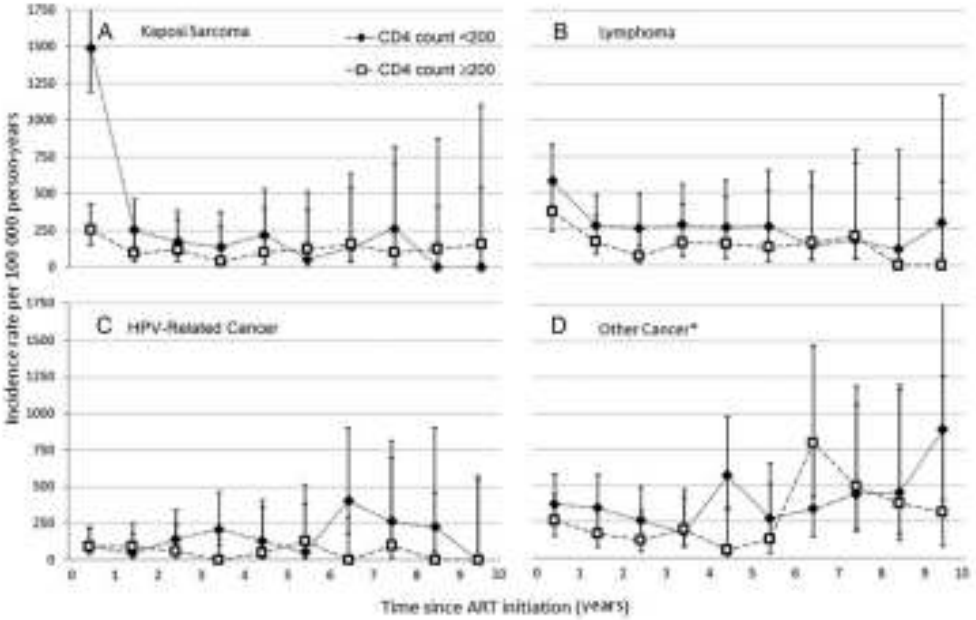
The mean standardized incidence ratios (SIR) were calculated by averaging SIR reported in several studies of cancer risk in persons with HIV (Dal Maso et al., 2009; Franceschi et al., 2010; Patel et al., 2008; Powles et al., 2009). The pre-ART era covers the years prior to 1996, the early ART era covers 1996–2001, and the late ART era covers 2002–2007, though there is some overlap between the studies. The incidence ratios of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL), both AIDS-defining cancers, decrease considerably from the pre-ART era to the late ART era. This is not seen with cervical cancer. In a separate study, administration of ART for >6 months reduced the incidence of both KS and NHL, though no difference in incidence of HPV-related malignancies was noted (Yanik et al., 2013).

Kaposi sarkomu (KS)

- HHV-8 (KSHV) ile ilişkili vasküler tümör
- 4 epidemiyolojik formu var:
  - AIDS-ilişkili veya epidemic KS
    - ✓ART öncesi ABD'de genel popülasyona göre AIDS'li hastalarda 20.000 kat fazla idi
    - ✓Öz.**CD4<200/mm^3** olan hastalarda
  - Endemik veya Afrikan KS
  - Organ transplant-ilişkili KS
  - Klasik KS

Incidence and Timing of Cancer in HIV-Infected Individuals Following Initiation of Combination Antiretroviral Therapy

Elizabeth L. Yanik,[1] Sonia Napravnik,[1,2] Stephen R. Cole,[1] Chad J. Achenbach,[4] Satish Gopal,[2] Andrew Olshan,[1] Dirk P. Dittmer,[3] Mari M. Kitahata,[5] Michael J. Mugavero,[6] Michael Saag,[6] Richard D. Moore,[7] Kenneth Mayer,[8] W. Christopher Mathews,[9] Peter W. Hunt,[10] Benigno Rodriguez,[11] and Joseph J. Eron[2]



KS insidansı özellikle ART'nin başlanmasından sonraki ilk altı ayda yüksektir ve daha sonra tedaviye devam edilmesiyle dramatik olarak düşer.

ART başlangıcından hemen sonraki yüksek insidans, immün rekonstitüsyon inflamatuar sendromu tarafından KS'nun alevlenmesi ve açığa çıkmasıyla ilişkilidir.

Clinical Infectious Diseases 2013;57(5):756–64

Prevalence of Kaposi Sarcoma-Associated Herpesvirus Infection in Homosexual Men at Beginning of and During the HIV Epidemic

Dennis H. Osmond, PhD; Susan Buchbinder, MD; Amber Cheng, MPH; et al

Kaposi sarkomu insidansındaki düşüş, KSHV prevalansını azaltmadı.

HHV-8 enfeksiyonunun yaygınlığı, 1978/1979'dan (yüzde **26,5**) 1984/1985'e (yüzde **29,6**) ve 1995/1996'ya (yüzde **26,4**) kadar San Francisco'daki erkekler arasında yaklaşık olarak sabit kaldı.

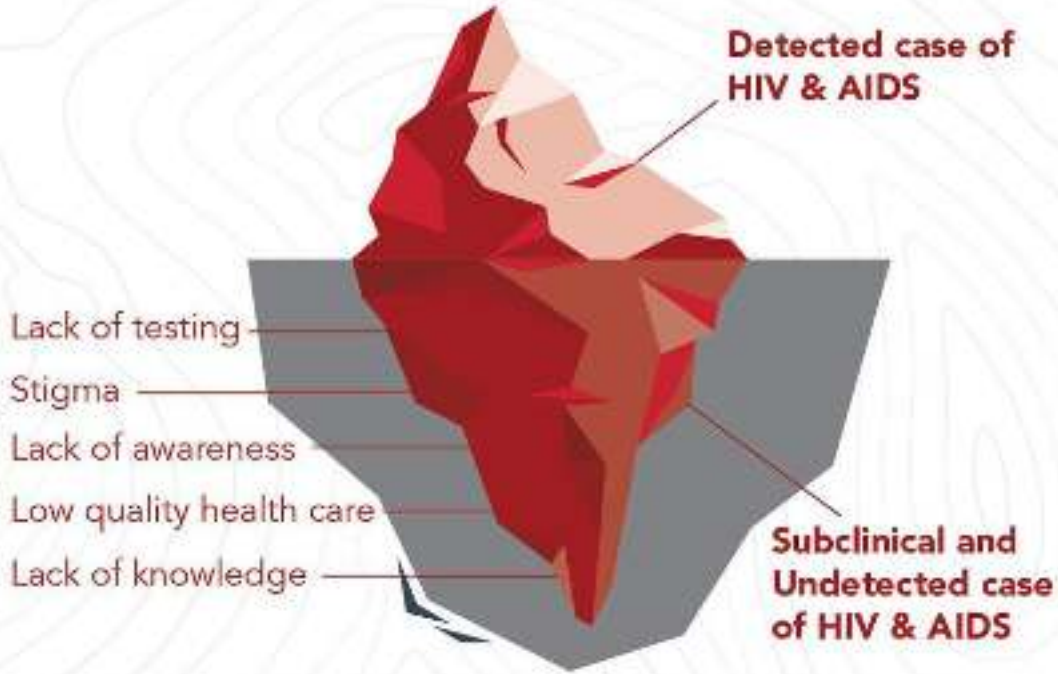
Başlangıçta hem HIV hem de HHV-8 ile enfekte olan HIV ile yaşayan bireyler arasında, 10 yıllık KS geliştirme olasılığı yaklaşık **%50** idi.

Martin JN, et al. N Engl J Med. 1998;338(14):948.

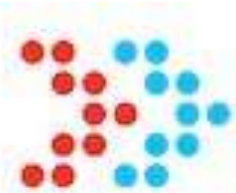
Kortikosteroid kullanımı ve fırsatçı enfeksiyonlar mevcut KS'un alevlenmesi ile ilişkilidir.

JAMA. 2002;287(2):221-225.

ICEBERG PHENOMENON OF HIV & AIDS

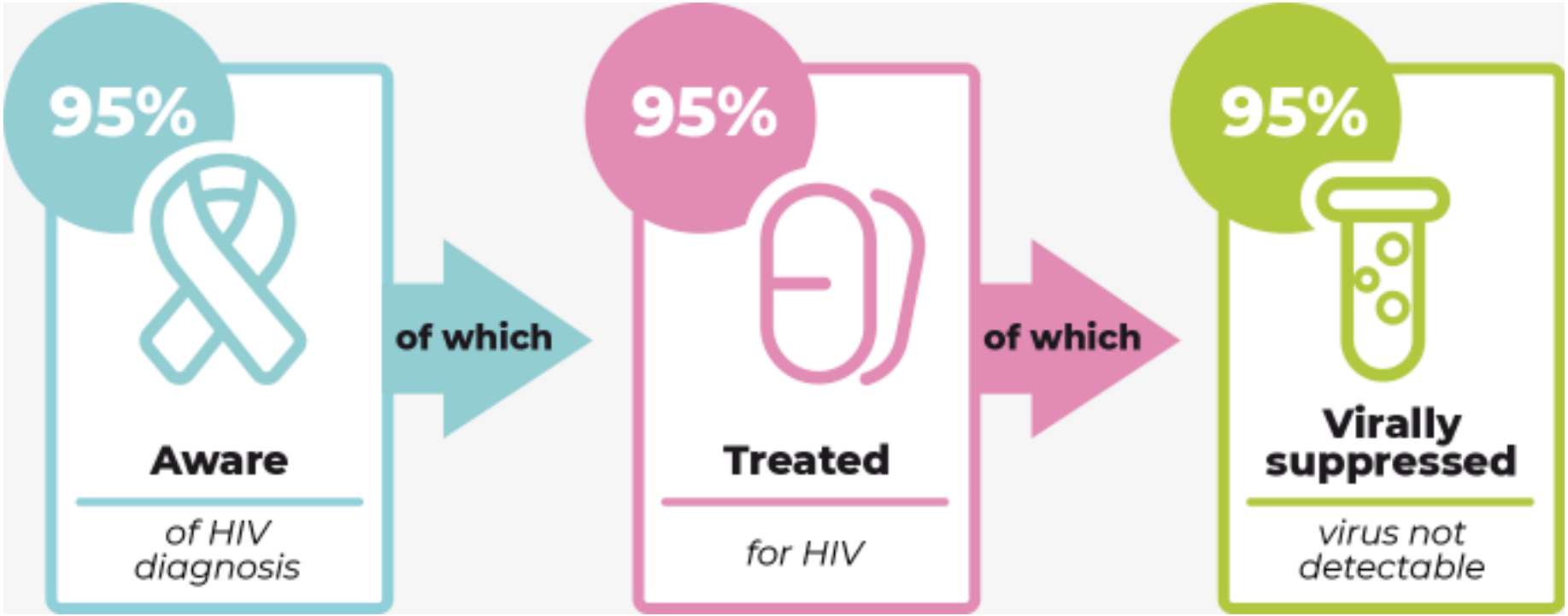



50%
In Europe, every second HIV diagnosis happens at a late stage of infection when the immune system has already started to fail. According to ECDC estimates, it takes on average three years from the time of HIV infection until diagnosis.*
ecdc
To reduce the future number of new HIV infections, Europe needs to focus on three main areas:



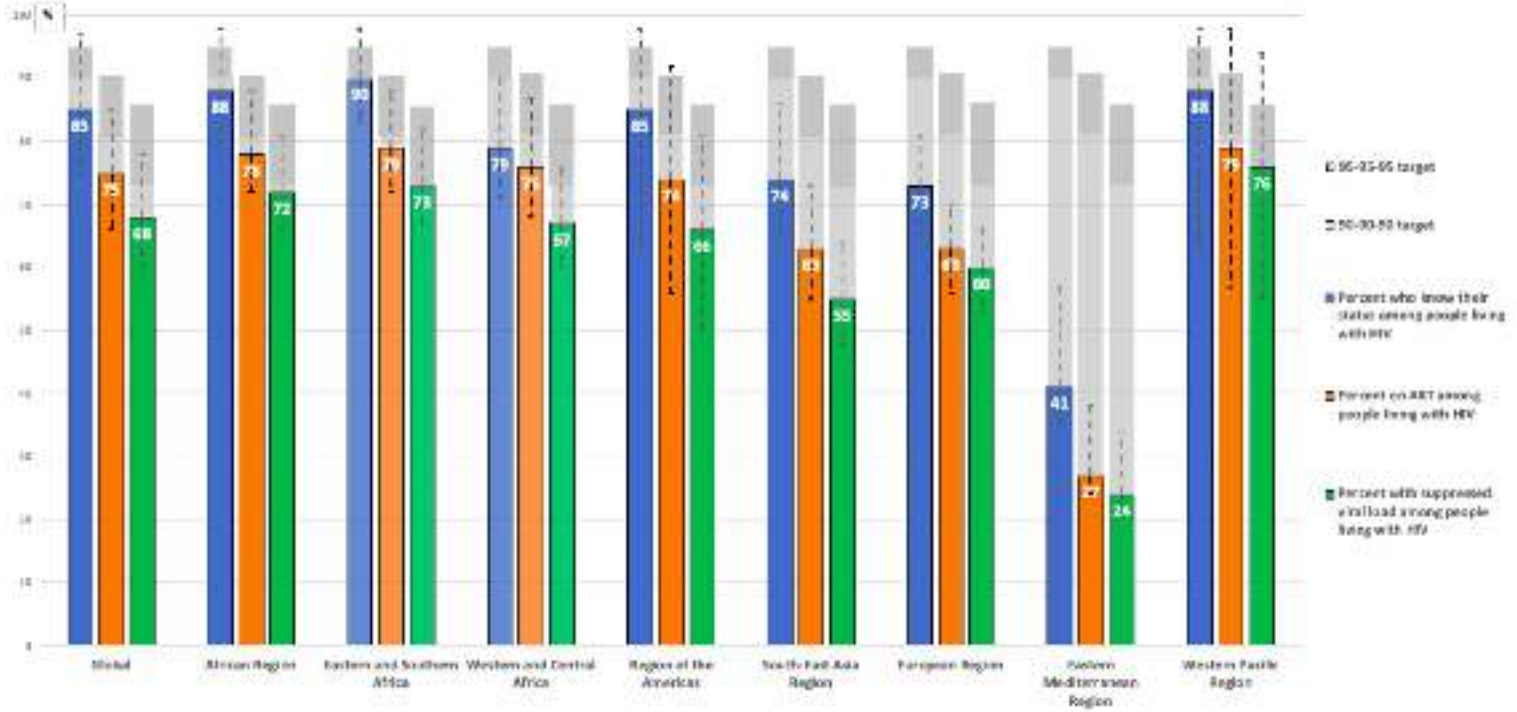
Fast-Track Targets

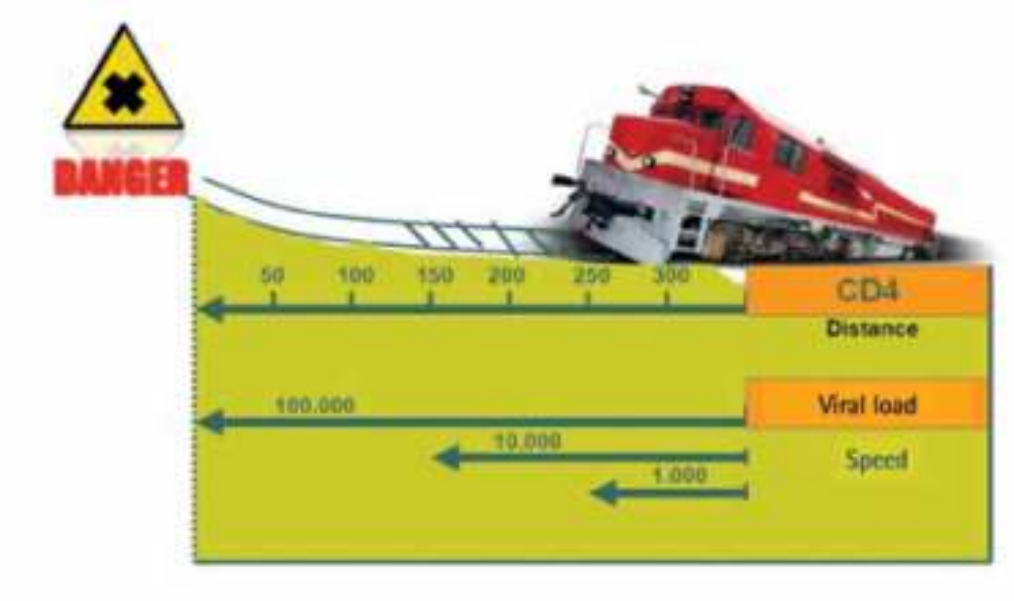
by 2020	by 2030
90-90-90 Treatment	**95-95-95** Treatment
500 000 New infections among adults	**200 000** New infections among adults
ZERO Discrimination	**ZERO** Discrimination


95%
Aware
of HIV diagnosis
of which
95%
Treated
for HIV
of which
95%
Virally suppressed
virus not detectable

World Health Organization

Global and WHO regional 95-95-95 and 90-90-90 cascades, 2021




DANGER
50
100
150
200
250
300
CD4
Distance
100.000
Viral load
10.000
Speed
1.000

The earlier the diagnosis,
the better the prognosis,
the less the opportunistic diseases.