Yıllar İçerisinde Başlangıç Tedavisinin Değişimi

Dr. Figen Kaptan Aydoğmuş
İKÇÜ İzmir Atatürk EAH

1960… Çoğu kanser çevresel retrovirüsler tarafından oluşturulur.

The Nobel Prize in Physiology or Medicine 1975

David Baltimore
Prize share: 1/3

Renato Dulbecco
Prize share: 1/3

Howard Martin Temin
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1975 was awarded jointly to David Baltimore, Renato Dulbecco and Howard Martin Temin *"for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell"*.

The Nobel Prize in Physiology or Medicine 1988

Sir James W. Black
Prize share: 1/3

Gertrude B. Elion
Prize share: 1/3

George H. Hitchings
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1988 was awarded jointly to Sir James W. Black, Gertrude B. Elion and George H. Hitchings *"for their discoveries of important principles for drug treatment"*.

Kuşlardaki kanserlerin hemen hepsi kuş retrovirüsleri tarafından oluşturulur.

İnsan retrovirüsleri?

Nükleik asid sentezini bloke eden bileşikler:
antibakteriyel, antiviral ve antikanser özellik taşır: 6-merkaptopürin

Jerome P. Horwitz developed AZT as a cure for cancer.
Courtesy of Walter P. Reuther Library, Wayne State University

Jerome Horwitz

Barbara Ann Karmanos Cancer Institute

Wayne State University School of Medicine

US National Institudes of Health (NIH): bağış

1964: AZT sentezi

Dr. Horwitz told interviewers that when AZT (short for azidothymidine) had failed as a cancer drug, he literally put it away on a shelf in disappointment and moved on to explore other ideas, never bothering to patent it.

To console himself, he half-kiddingly told colleagues at Wayne State University's cancer research center in Detroit that AZT and several similar drugs he had developed were "a very interesting set of compounds that were waiting for the right disease."

AZT: Azidotimidin

1974, Wofram Ostertag

Max Planck Institute (Göttingen)

AZT, hücre kültüründe

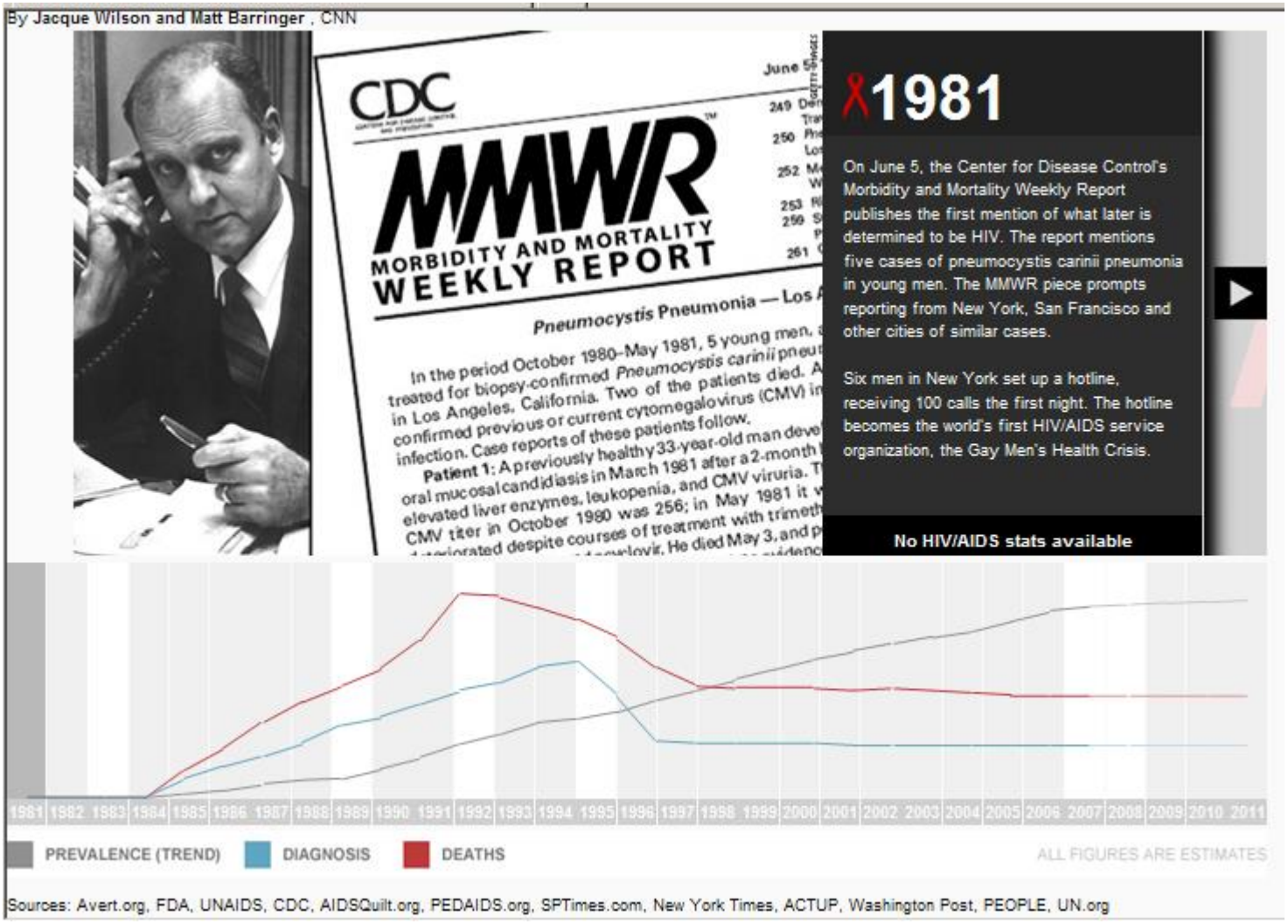
Friend leukemia virüs replikasyonunu inhibe ediyor.

O yılarda insan hastalığı bilinmediği için dikkati çekmemiş.

Gen tedavisi: öncü isimlerinden….

AZT: Azidotimidin

Haziran 1981: ABD, 5 AIDS olgusu.
HIV epidemisinin başlaması.



1983: Institut Pasteur: HIV identifikasyonu

Françoise Barré-Sinoussi
2008: Nobel Ödülü

Samuel Oder, Hiroaki Mitsuya, Robert Yarchoan

US National Cancer Institute: HIV/AIDS tedavi programı

CD4+ hücre dizilerine ilacın etkisinin izlenmesi

- Anti-HIV etkinlik
- T hücreleri üzerine toksik etki

1985: AZT ile Faz I klinik çalışma

Güvenilir, CD4 ↑, kilo artışı,

Yaşam süresinde uzama

Yayınlanma numarası	EP0509019 B1
Yayın türü	Onay
Başvuru numarası	EP19910902028
PCT numarası	PCT/US1991/000005
Yayın tarihi	15 Tem 1998
Dosya kabul tarihi	3 Oca 1991
Rüçhan tarihi ⓘ	3 Oca 1990
Şu şekilde de yayınlandı:	CA2072573A1, Daha Fazla (8) »
Buluş Sahipleri	Samuel Broder, Hiroaki Mitsuya, Robert Yarchoan
Başvuru sahibi	THE UNITED STATES OF AMERICA as represented by the Secretary United States Department of Commerce
Alıntıyı Dışa Aktar	BiBTeX, EndNote, RefMan

Sınıflandırma (10), Yasal Etkinlikler (65)

Dış Bağlantılar: Espacenet, EP Kaydı

20 Mart 1987: azidotimidin FDA onayı aldı.

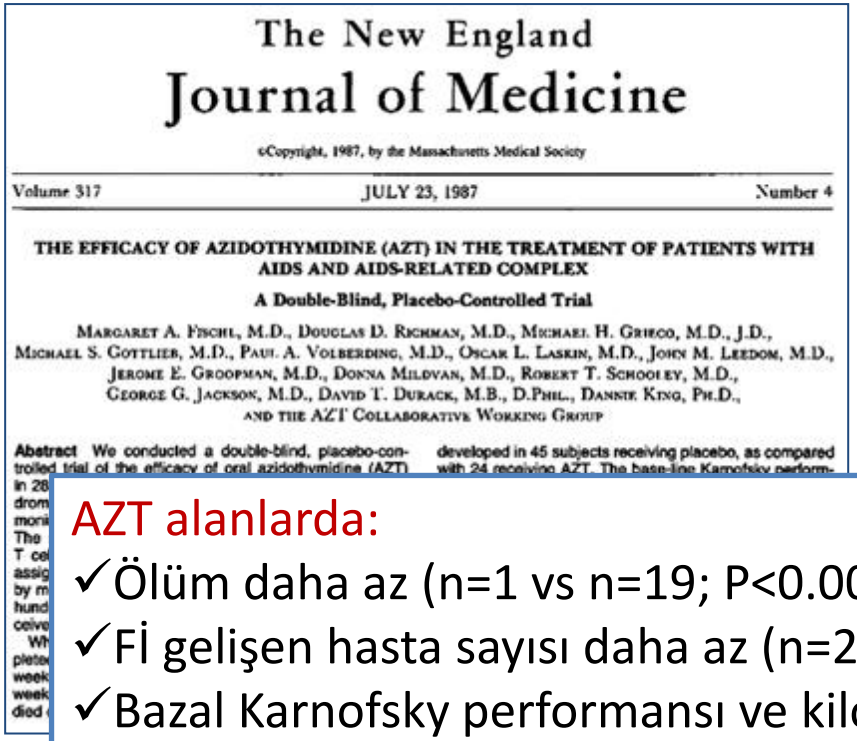
U.S. APPROVES DRUG TO PROLONG LIVES OF AIDS PATIENTS

By IRVIN MOLOTSKY, Special to the New York Times
Published: March 21, 1987

1990: AZT pediatrik hastalar için onaylandı.

1994: US Public Health Service: Gebe kadınlara önerildi.

AZT uygulaması, **AIDS hastalarında** mortaliteyi ve Fİ sıklığını azaltabilir.



The New England
Journal of Medicine

Volume 317 JULY 23, 1987 Number 4

THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

MARGARET A. FISCHL, M.D., DOUGLAS D. RICHMAN, M.D., MICHAEL H. GRIECO, M.D., J.D., MICHAEL S. GOTTLIEB, M.D., PAUL A. VOLBERDING, M.D., OSCAR L. LASKIN, M.D., JOHN M. LEEDOM, M.D., JEROME E. GROOPMAN, M.D., DONNA MILDVAN, M.D., ROBERT T. SCHOOLEY, M.D., GEORGE G. JACKSON, M.D., DAVID T. DURACK, M.B., D.PHIL., DANNIE KING, PH.D., AND THE AZT COLLABORATIVE WORKING GROUP

Abstract We conducted a double-blind, placebo-controlled trial of the efficacy of oral azidothymidine (AZT) ... developed in 45 subjects receiving placebo, as compared with 24 receiving AZT. The base-line Karnofsky perform-

ÇK, **plasebo** kontrollu
N= 282 AIDS hastası
250 mg **AZT** (n=145) veya
plasebo (n=137)
her 4 saatte bir, 24 hafta süreyle

AZT alanlarda:

- ✓Ölüm daha az (n=1 vs n=19; P<0.001)
- ✓Fİ gelişen hasta sayısı daha az (n=24 vs n=45)
- ✓Bazal Karnofsky performansı ve kilo artışı anlamlı olarak yüksek (P<0.001).
- ✓CD4 hücre artışı anlamlı olarak yüksek (P<0.001).
- ✓Anerjik deri testi düzelen hasta sayısı daha yüksek (%29 vs %9; P<0.001).

Fİ: Fırsatçı infeksiyon

CD4 <500 hücre/mm^3 olan **aseptomatik** HIV infeksiyonu hastalarında zidovudin güvenilir ve etkilidir.

N Engl J Med. 1990 Apr 5;322(14):941-9.

Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases.

Volberding PA[1], Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, Balfour HH Jr, Reichman RC, Bartlett JA, Hirsch MS, et al.

Author information

[1]University of California, San Francisco.

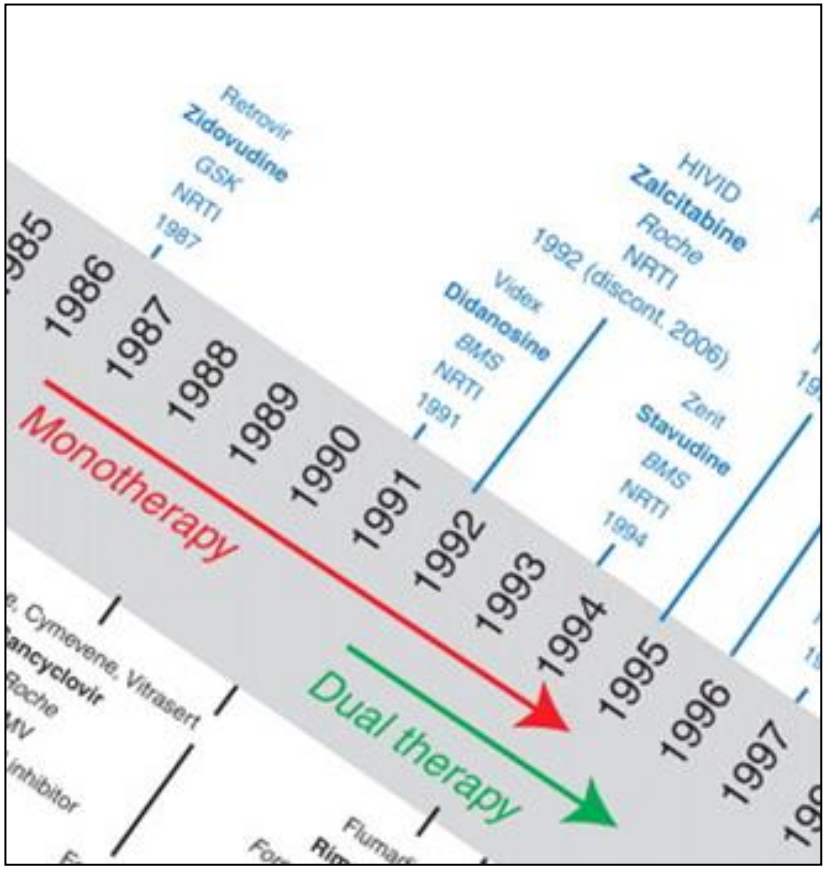
Abstract

Zidovudine (AZT) is a potent inhibitor of the replication of the human immunodeficiency virus (HIV), and it has been shown to improve survival in advanced HIV disease. We conducted a randomized, double-blind trial in adults with asymptomatic HIV infection who had CD4+ cell counts of fewer than 500 per cubic millimeter on entry into the study. The subjects (92 percent male) were randomly assigned to one of three treatment groups: placebo (428 subjects); zidovudine, 500 mg per day (453); or zidovudine, 1500 mg per day (457). After a mean follow-up of 55 weeks (range, 19 to 107), 33 of the subjects assigned to placebo had the acquired immunodeficiency syndrome (AIDS), as compared with 11 of those assigned to receive 500 mg of zidovudine (P = 0.002; relative risk, 2.8; 95 percent confidence interval, 1.4 to 5.6) and 14 of those assigned to receive 1500 mg of zidovudine (P = 0.05; relative risk, 1.9; 95 percent confidence interval, 1.0 to 3.5). In the three treatment groups, the rates of progression (per 100 person-years) to either AIDS or advanced AIDS-related complex were 7.6, 3.6, and 4.3, respectively. As compared with those assigned to placebo, the subjects in the zidovudine groups had significant increases in the number of CD4+ cells and significant declines in p24 antigen levels. In the 1500-mg zidovudine group, severe hematologic toxicity (anemia or neutropenia) was more frequent than in the other groups (P less than 0.0001). In the 500-mg zidovudine group, nausea was the only toxicity that was significantly more frequent (in 3.3 percent) than in the placebo group (P = 0.001). We conclude that zidovudine is safe and effective in persons with asymptomatic HIV infection and fewer than 500 CD4+ cells per cubic millimeter. Additional study will be required to determine whether such treatment will ultimately improve survival for persons infected with HIV.

Randomize, ÇK
Erişkin, asemptomatik, CD4 <500
Plasebo (n=428);
Zidovudin, **500** mg/gün (n=453);
Zidovudin, **1500** mg/gün (n=457).
Ortalama izlem 55 hf (19-107 hf),

AIDS veya AIDS-ilişkili kompleks gelişme hızı:
sırasıyla, **7.6**, **3.6**, ve **4.3** (100 hasta yılı için)
1500-mg zidovudin grubu:
ciddi hematolojik toksisite daha sık (P <0.0001).

Yeni NRTİ'leri



1991: Didanozin

1992: Zalsitabin
(2006 yılında kaldırıldı)

1994: Stavudin

1995: Lamivudin

İki nükleozit ile tedavi, HIV infeksiyonunun ilerlemesini yavaşlatır ve ZDV'den üstündür.

The New England
Journal of Medicine

VOLUME 335 OCTOBER 10, 1996 NUMBER 15

A TRIAL COMPARING NUCLEOSIDE MONOTHERAPY WITH COMBINATION THERAPY IN HIV-INFECTED ADULTS WITH CD4 CELL COUNTS FROM 200 TO 500 PER CUBIC MILLIMETER

SCOTT M. HAMMER, M.D., DAVID A. KATZENSTEIN, M.D., MICHAEL D. HUGHES, PH.D., HOLLY GUNDACKER, M.S., ROBERT T. SCHOOLEY, M.D., RICHARD H. HAUBRICH, M.D., W. KEITH HENRY, M.D., MICHAEL M. LEDERMAN, M.D., JOHN P. PHAIR, M.D., MANETTE NIU, M.D., MARTIN S. HIRSCH, M.D., AND THOMAS C. MERIGAN, M.D., FOR THE AIDS CLINICAL TRIALS GROUP STUDY 175 STUDY TEAM*

ABSTRACT

Background This double-blind study evaluated treatment with either a single nucleoside or two nucleosides in adults infected with human immunodeficiency virus type 1 (HIV-1) whose CD4 cell counts were from 200 to 500 per cubic millimeter.

Methods We randomly assigned 2467 HIV-1–infected patients (43 percent without prior antiretroviral treatment) to one of four daily regimens: 600 mg of zidovudine; 600 mg of zidovudine plus 400 mg of didanosine; 600 mg of zidovudine plus 2.25 mg of zalcitabine; or 400 mg of didanosine. The primary end point was a ≥50 percent decline in the CD4 cell count, development of the acquired immunodeficiency syndrome (AIDS), or death.

Results Progression to the primary end point was more frequent with zidovudine alone (32 percent) than with zidovudine plus didanosine (18 percent; relative hazard ratio, 0.50; $P<0.001$), zidovudine plus zalcitabine (20 percent; relative hazard ratio, 0.54; $P<0.001$), or didanosine alone (22 percent; relative hazard ratio, 0.61; $P<0.001$). The relative hazard ratios for progression to an AIDS-defining event or death were 0.64 ($P=0.005$) for zidovudine plus didanosine, as compared with zidovudine alone, 0.77 ($P=0.085$) for zidovudine plus zalcitabine, and 0.69 ($P=0.019$) for didanosine alone. The relative hazard ratios for death were 0.55 ($P=0.008$), 0.71 ($P=0.10$), and 0.51 ($P=0.003$), respectively. For zidovudine plus zalcitabine, the benefits were limited to those without previous treatment.

Conclusions Treatment with zidovudine plus didanosine, zidovudine plus zalcitabine, or didanosine alone slows the progression of HIV disease and is superior to treatment with zidovudine alone. Antiretroviral therapy can improve survival in patients with 200 to 500 CD4 cells per cubic millimeter. (N Engl J Med 1996;335:1081-90.)

Kombine olarak kullanılan NRTİ'leri klinik olarak yararlı olmakla birlikte, hastalığın AIDS'e ilerlemesini önleyememektedir.

Natural History of Opportunistic Disease in an HIV-Infected Urban Clinical Cohort

Richard D. Moore, MD, MHSc; and Richard E. Chaisson, MD

[+] Article, Author, and Disclosure Information

Ann Intern Med. 1999;124(7):633-642. doi:10.7326/0003-4819-124-7-199604010-00003 Text Size: A A A

Article | Figures | Tables | References | Comments (0)

Objective: To determine the effect of contemporary clinical care on the natural history of opportunistic disease in an urban population infected with the human immunodeficiency virus (HIV).

Setting: Urban university HIV clinic.

Design: Retrospective and prospective observational study.

Patients: 1246 HIV-infected patients with CD4+ counts of 300 cells/mm^3 or less.

Measurements: Incidence rates and Kaplan-Meier estimates of the probability of developing opportunistic disease with time, distribution of the CD4+ counts at which opportunistic disease develops, survival after the development of opportunistic disease, and the association between preventive drug therapies and the occurrence of opportunistic infection.

Results: The most common opportunistic disease was Candida esophagitis, which had an incidence of 13.3 events per 100 person-years and a 3-year Kaplan-Meier probability of 0.30. Pneumocystis carinii pneumonia, Mycobacterium avium complex bacteremia, cytomegalovirus, and the acquired immunodeficiency syndrome dementia complex occurred at rates of 5 to 9 events per 100 person-years and 3-year Kaplan-Meier probabilities of 0.15 to 0.22. Toxoplasmosis, cryptococcal meningitis, herpes zoster, the wasting syndrome, and Kaposi sarcoma occurred at rates of about 2 to 4 events per 100 person-years and with 3-year Kaplan-Meier probabilities of 0.05 to 0.10. Non-Hodgkin lymphoma, M. tuberculosis infection, progressive multifocal leukoencephalopathy, and cryptosporidiosis were the least common disorders, with an incidence of about 1 to 2 events per 100 person-years and a 3-year Kaplan-Meier probability less than 0.05. Only the incidences of cryptococcal meningitis, secondary P. carinii pneumonia, and herpes zoster decreased ($P < 0.05$) between

1246 HIV-infekte, CD4 ≤300

- **Tanı sonrası ortalama yaşam:**

NHL 35 gün; herpes zoster 680 gün

- **1989-1992 ve 1993-1995**

- Kriptokok menenjiti,
- Sekonder PCP ve
- Herpes zoster

insidansında anlamlı azalma ($P < 0.05$)

Olay	Olay/100-hasta yılı; 3-yıllık Kaplan-Meier olasılığı
Candida özofajiti	13.3; 0.30
PCP, MAC bakteremisi, CMV, AIDS demans kompleksi	5 – 9; 0.15 - 0.22
Tokzoplazmoz, kriptokok menenjiti, herpes zoster, wasting sendromu, Kaposi sarkomu	2 – 4; 0.05 - 0.10
NHL, *M. tuberculosis* infeksiyonu, PML, cryptosporidium	1 – 2; <0.05

NRTİ’leri hastalık progresyonunu önlemek açısından zayıf ilaçlardır.

Plazma HIV RNA düzeyinde

- NRTİ monoterapisi ile 0.5 ile 1 log/mL azalma
- İkili NRTİ tedavisi ile 1 ile 1.5 log/mL azalma

N. Clumeck, S. De Wit. Update on highly active antiretroviral therapy: progress and strategies.Biomed & Pharmacother 2000 ; 54 : 7-12. Dossier: 1999-2000 Special AIDS issue.

Kombine antiretroviral tedavi
HAART: Highly active antiretroviral therapy

ARV tedavide yeni bir strateji: HIV replikasyon döngüsünde farklı basamakları inhibe eden ilaçların kombine kullanımı

1995

Sakinavir

1996

Ritonavir

Nevirapin

İndinavir

İlk viral yük testi onay aldı.

Treatment of Human Immunodeficiency Virus Infection with Saquinavir, Zidovudine, and Zalcitabine

Ann C. Collier, M.D., Robert W. Coombs, M.D., Ph.D., David A. Schoenfeld, Ph.D., Roland L. Bassett, M.S., Joseph Timpone, M.D., Alice Baruch, M.D., Ph.D., Michelle Jones, M.Sc., Karen Facey, Ph.D., Caroline Whitacre, Ph.D., Vincent J. McAuliffe, M.D., Harvey M. Friedman, M.D., Thomas C. Merigan, M.D., Richard C. Reichman, M.D., Carol Hooper, M.D., and Lawrence Corey, M.D. for the AIDS Clinical Trials Group

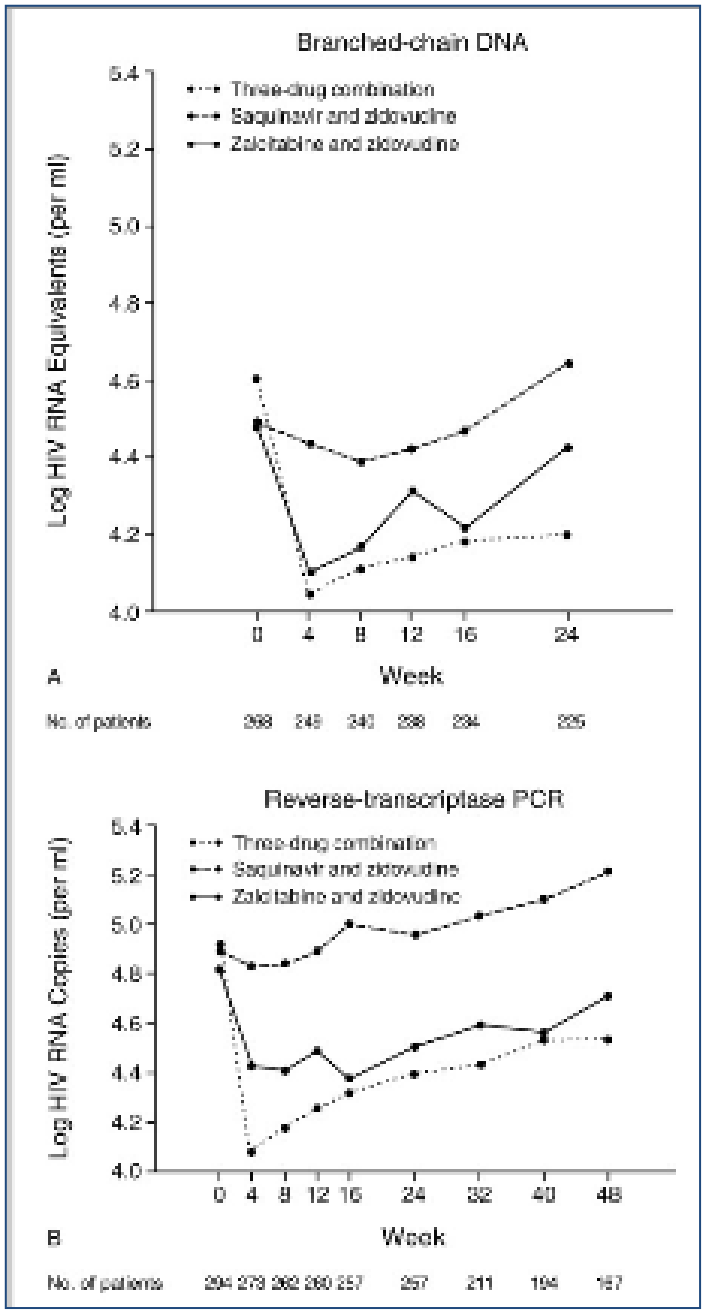
N Engl J Med 1996; 334:1011-1018 | April 18, 1996 | DOI: 10.1056/NEJM199604183341602

İyi tolere edilir.

Sakuinavir Zalsitabin Zidovudin	Zidovudin Sakinavir	Zidovudin Zalsitabin

- ✓HIV-1 daha iyi baskılanır.
- ✓CD4 artışı daha iyi.
- ✓Serum aktivasyon göstergelerindeki düşme daha iyi.

RT-PCR: Alt sınır: 400 kopya/ml



ARV ilaçların kombinasyonu, plazma HIV-1 virüs yükünü saptanabilen düzeyin altına düşürerek immün sistemin rekonstitüsyonunu sağlar.

J Infect Dis. 1998 Jul;178(1):70-9.

Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315.

Lederman MM[1], Connick E, Landay A, Kuritzkes DR, Spritzler J, St Clair M, Kotzin BL, Fox L, Chiozzi MH, Leonard JM, Rousseau F, Wade M, Roe JD, Martinez A, Kessler H.

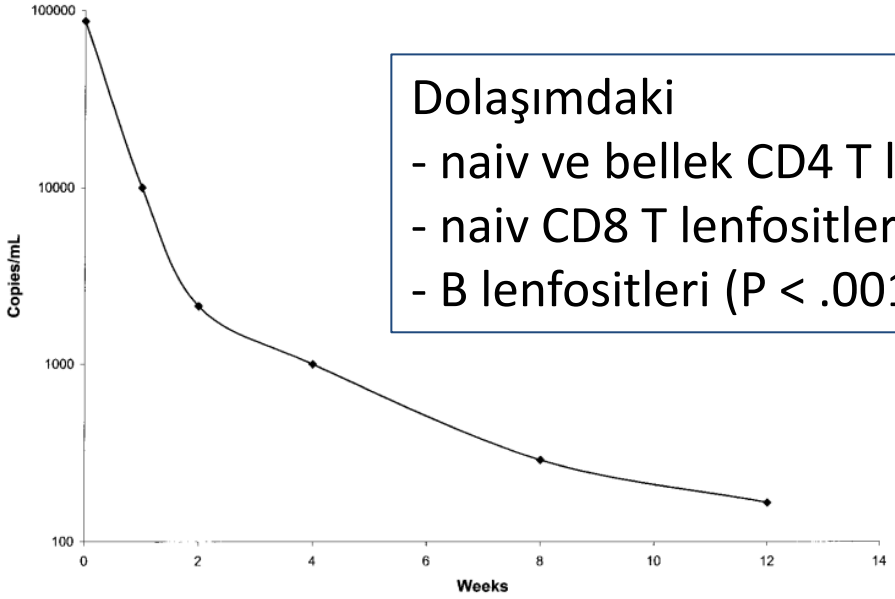
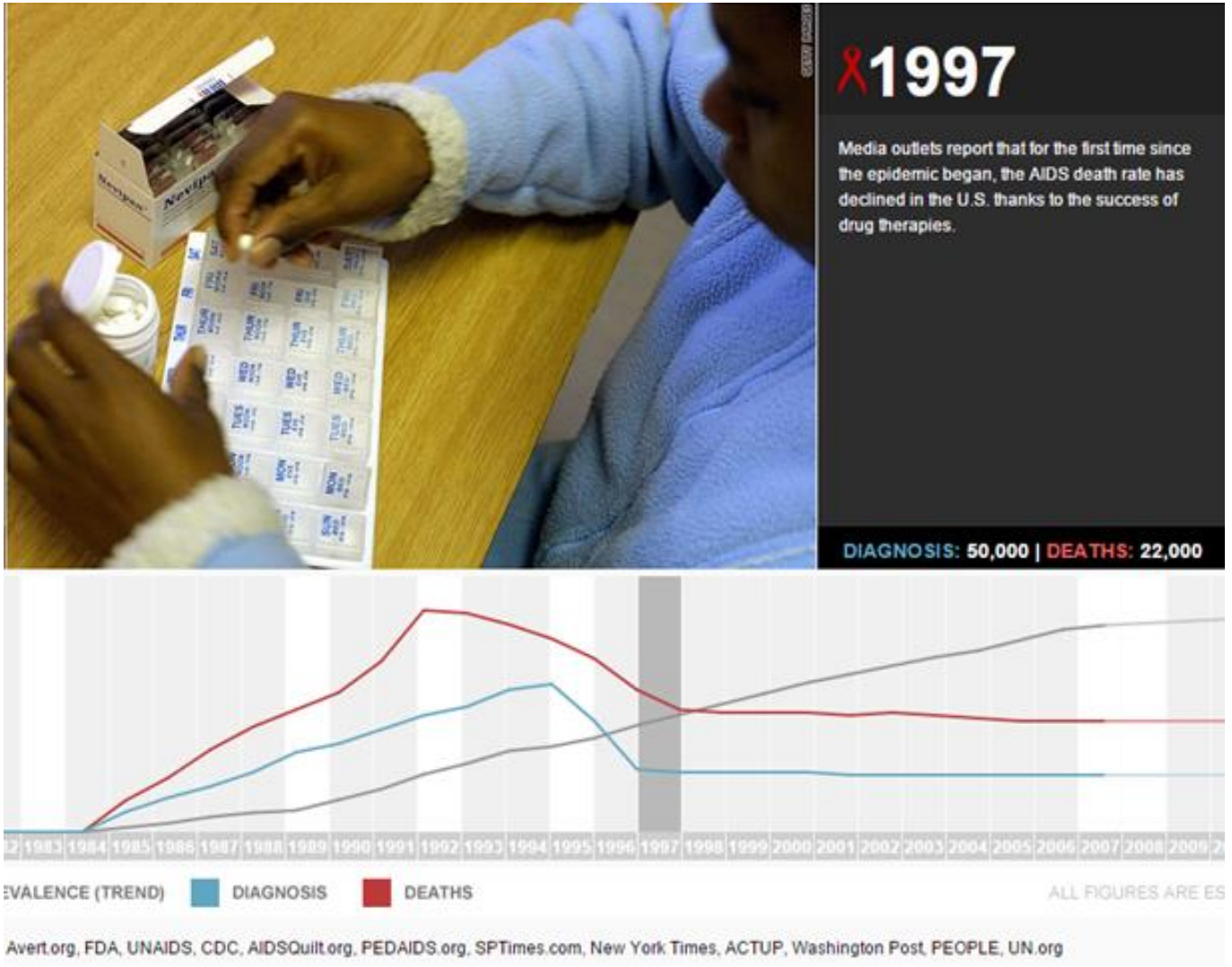


Figure 1. Plasma levels of HIV RNA before initiation of and during highly active antiretroviral therapy. Data represent median levels as measured by nucleic acid sequence-based amplification. Lower limit of detection = 100 copies/mL. Baseline and week 12 values were significantly different, $P < .0001$, Wilcoxon signed rank test.

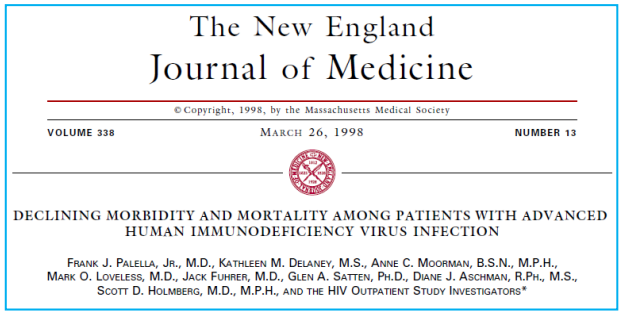
Dolaşımdaki
- naiv ve bellek CD4 T lenfositleri (P < .001) ↑
- naiv CD8 T lenfositleri (P < .004) ↑
- B lenfositleri (P < .001) ↑

Plazma HIV-1 RNA ort. 2.3 log ↓ (P < .0001)

ABD: Epideminin başlangıcından itibaren ilk kez AIDS ölüm oranının, ARV ilaçların başarısıyla azaldığını bildirdi.



AIDS'e bağlı morbidite ve mortalitedeki azalma, daha yoğun antiretroviral tedavilerin kullanımı ile ilişkilidir.



The New England
Journal of Medicine

VOLUME 338 MARCH 26, 1998 NUMBER 13

DECLINING MORBIDITY AND MORTALITY AMONG PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

FRANK J. PALELLA, JR., M.D., KATHLEEN M. DELANEY, M.S., ANNE C. MOORMAN, B.S.N., M.P.H., MARK O. LOVELESS, M.D., JACK FUHRER, M.D., GLEN A. SATTEN, PH.D., DIANE J. ASCHMAN, R.PH., M.S., SCOTT D. HOLMBERG, M.D., M.P.H., AND THE HIV OUTPATIENT STUDY INVESTIGATORS*

Olay*	1995	1997 / II. yarısı
Mortalite	29.4	8.8
PCP MAC CMV retiniti	21.9	3.7

*100 hasta-yılı

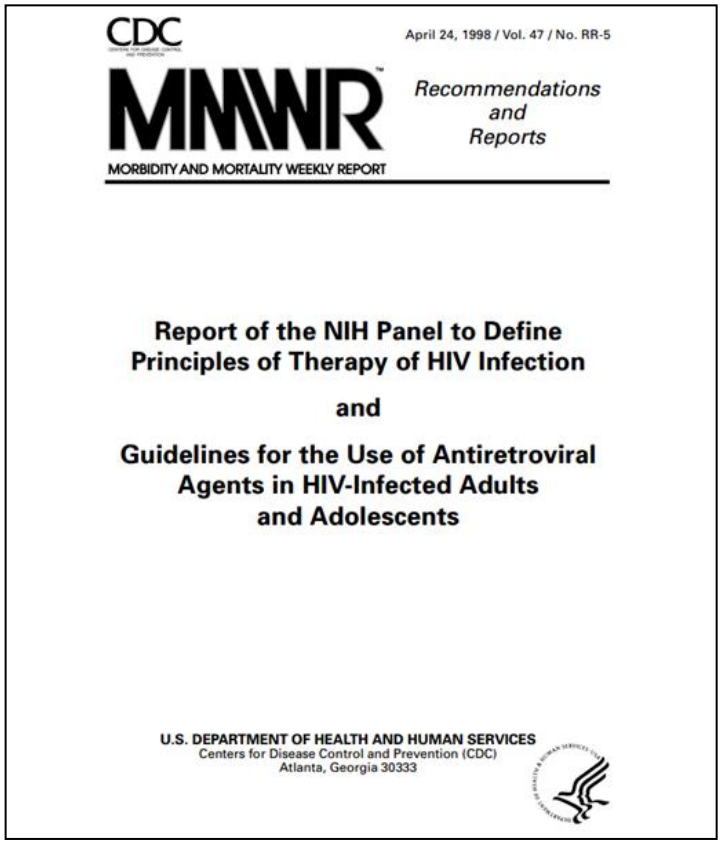
AIDS'e progresyon başlangıç CD4 sayısı ve plazma HIV-RNA düzeyine göre öngörülebilir.

Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma. Mellors JW, *Science 24 May **1996:** Vol. 272 no. 5265 pp. 1167-1170*

Plasma Viral Load and CD4+ Lymphocytes as Prognostic Markers of HIV-1 Infection. Mellors JW, *Ann Intern Med.* **1997**;126(12):946-954. doi:10.7326/0003-4819-126-12-199706150-00003

Prognostic Indicators for AIDS and Infectious Disease Death in HIV-Infected Injection Drug Users: Plasma Viral Load and $CD4^+$ Cell Count FREE
David Vlahov, *JAMA.* **1998**;279(1):35-40. doi:10.1001/jama.279.1.35

1998: DHHS:
HIV-1 ile İnfekte Erişkin ve Adölesanlarda Antiretroviral Ajanların Kullanımı



CDC

April 24, 1998 / Vol. 47 / No. RR-5

MMWR

Recommendations and Reports

MORBIDITY AND MORTALITY WEEKLY REPORT

Report of the NIH Panel to Define Principles of Therapy of HIV Infection

and

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

US Department of Health and Human Services

TABLE 5. Indications for the initiation of antiretroviral therapy in the chronically HIV-infected patient

Clinical category	CD4+ T cell count and HIV RNA	Recommendation
Symptomatic (i.e., AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	CD4+ T Cells <500/mm^3 **or** HIV RNA >10,000 (bDNA) or >20,000 (RT-PCR)	Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival as shown in Table 4 and willingness of the patient to accept therapy.*
Asymptomatic	CD4+ T Cells >500/mm^3 **and** HIV RNA <10,000 (bDNA) or <20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

*Some experts would observe patients whose CD4+ T cell counts are between 350–500/mm^3 and HIV RNA levels <10,000 (bDNA) or <20,000 (RT-PCR).

NRTİ:

- ZDV
- ddI
- d4T
- ddC
- 3TC

Pİ:

- IDV
- NFV
- RTV
- SQC
- SQC/r

NNRTİ:

- NVP

TABLE 6. Recommended antiretroviral agents for treatment of established HIV infection

Preferred: Strong evidence of clinical benefit and/or sustained suppression of plasma viral load (*2, 34, 35*)

One choice each from column A and column B. Drugs are listed in random, not priority, order:

Column A	Column B
Indinavir (AI)	ZDV + ddI (AI)
Nelfinavir (AII)	d4T + ddI (AII)
Ritonavir (AI)	ZDV + ddC (AI)
Saquinavir-SGC* (AII)	ZDV + 3TC§ (AI)
Ritonavir + Saquinavir-SGC or HGC† (BII)	d4T + 3TC§ (AII)

Alternative: Less likely to provide sustained virus suppression; (*36–38*)

1 NNRTI (Nevirapine)¶ + 2 NRTIs (Column B, above) (BII)

Saquinavir-HGC + 2 NRTIs (Column B, above) (BI)

Not generally recommended: Strong evidence of clinical benefit, but initial virus suppression is not sustained in most patients (*39,40*)

2 NRTIs (Column B, above) (CI)

Not recommended:** Evidence against use, virologically undesirable, or overlapping toxicities

All monotherapies (DI)

d4T + ZDV (DI)

ddC + ddI†† (DII)

ddC + d4T†† (DII)

ddC + 3TC (DII)

*Virologic data and clinical experience with saquinavir-sgc are limited in comparison with other protease inhibitors.

†Use of ritonavir 400 mg b.i.d. with saquinavir soft-gel formulation (Fortovase™)400 mg b.i.d. results in similar areas under the curve (AUC) of drug and antiretroviral activity as when using 400 mg b.i.d. of Invirase™ in combination with ritonavir. However, this combination with Fortovase™ has not been extensively studied and gastrointestinal toxicity may be greater when using Fortovase™.

§High-level resistance to 3TC develops within 2–4 wks. in partially suppressive regimens; optimal use is in three-drug antiretroviral combinations that reduce viral load to <500 copies/mL.

¶The only combination of 2 NRTIs + 1 NNRTI that has been shown to suppress viremia to undetectable levels in the majority of patients is ZDV+ddI+Nevirapine. This combination was studied in antiretroviral-naive persons (*36*).

**ZDV monotherapy may be considered for prophylactic use in pregnant women who have low viral load and high CD4+ T cell counts to prevent perinatal transmission (see "Considerations for Antiretroviral Therapy in the Pregnant HIV-Infected Woman" on pages 59–62).

††This combination of NRTIs is not recommended based on lack of clinical data using the combination and/or overlapping toxicities.

İki proteaz inhibitörünün birlikte kullanılması ile Pİ'lerinin bazı kısıtlılıkları giderilebilir.

TABLE 6. Recommended antiretroviral agents for treatment of established HIV infection

Preferred: Strong evidence of clinical benefit and/or sustained suppression of plasma viral load (*2, 34, 35*)

One choice each from column A and column B. Drugs are listed in random, not priority, order:

Column A	Column B
Indinavir (AI)	ZDV + ddI (AI)
Nelfinavir (AII)	d4T + ddI (AII)
Ritonavir (AI)	ZDV + ddC (AI)
Saquinavir-SGC* (AII)	ZDV + 3TC§ (AI)
Ritonavir + Saquinavir-SGC or HGC† (BII)	d4T + 3TC§ (AII)

*Ritonavir CYP 450 3A4 enzimini inhibe eder.

''Booster''
*pK güçlendirici

- Kısa yarı ömür
- Oral emilim farklılıkları
- Diyet gereksinimleri
- İlaç-ilaç etkileşimleri
- Yan etkiler
- Uyum problemi ~ tedavi yanıtı
- Maliyet
- Kompleks dozlama, hap sayısı

Yıllar içinde yeni ARV ilaçlar

1987….

ZDV, ddI, ddC,

d4T, 3TC

SQV, RTV, IDV

NVP

1997

Nelfinavir

ZDV+3TC

Delavirdin

1998

Efavirenz

Abakavir

ART Prensipleri

- Devam eden viral replikasyon, immün sistem hasarına neden olur ve AIDS gelişimine yol açar.
- Viral yük: HIV replikasyonunun boyutunu gösterir. CD4 yıkımı ile ilişkilidir.
- CD4: HIV ilişkili oluşmuş hasarın derecesini gösterir.
- Güçlü ART: HIV replikasyonunu saptanamayan düzeyin altına dek baskılaması hedeftir.

  Amaç: ARV ilaç direnci olan HIV varyantlarının seleksiyonunu önlemek.
- Kombine ARV ilaçlar kullanılır.
  - Tüm ilaçlara aynı anda başlanır.
  - Etkili ilaçlar olmalıdır.
  - Optimal dozda ve zamanında kullanılmalıdır.

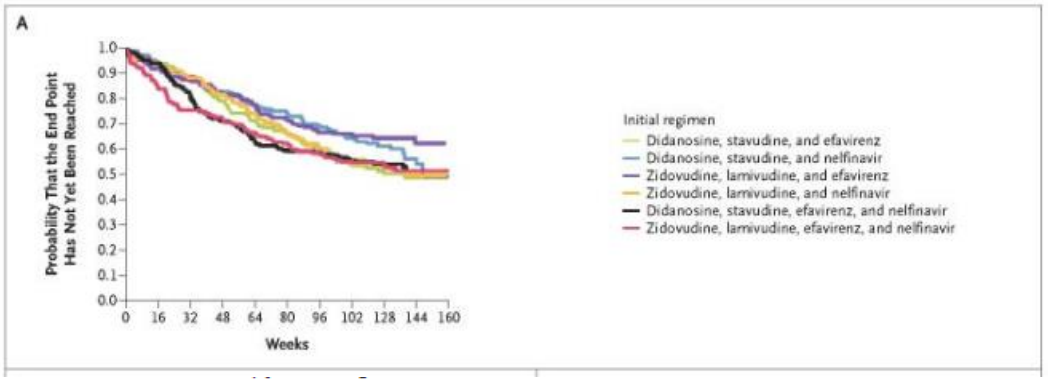
Zidovudin, lamivudin ve efavirenz rejimi, ilk basamak ART için diğerlerinden üstündür.

Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection.

Shafer RW[1], Smeaton LM, Robbins GK, De Gruttola V, Snyder SW, D'Ac
Gripshover BM, Kaul P, Haubrich R, Swingle M, McCarty SD, Vella S, Hi

Author information

[1]Stanford University Medical Center, Stanford, Calif, USA. grobbins



Abstract

BACKGROUND: It is unclear whether therapy for human immunode
-drug or two sequential three-drug regimens.

METHODS: In this multicenter trial we compared initial therapy inv
in combination with either didanosine and stavudine or zidovudine a
-drug regimens the first of which contained either efavirenz or nelfinavir.

RESULTS: A total of 980 subjects were followed for a median of 2.3 years. There was no significant difference in the occurrence of regimen failures between the group that received the four-drug regimen containing didanosine, stavudine, nelfinavir, and efavirenz and the groups that received the three-drug regimens beginning with didanosine, stavudine, and nelfinavir (hazard ratio for regimen failure, 1.24) or didanosine, stavudine, and efavirenz (hazard ratio, 1.01). There was no significant difference between the group that received the four-drug regimen containing zidovudine, lamivudine, nelfinavir, and efavirenz and the groups that received the three-drug regimens beginning with zidovudine, lamivudine, and nelfinavir (hazard ratio, 1.06) or zidovudine, lamivudine, and efavirenz (hazard ratio, 1.45). A four-drug regimen was associated with a longer time to the first regimen failure than the three-drug regimens containing didanosine, stavudine, and nelfinavir (hazard ratio for a first regimen failure, 0.55); didanosine, stavudine, and efavirenz (hazard ratio, 0.63); or zidovudine, lamivudine, and nelfinavir (hazard ratio, 0.49), but not the three-drug regimen containing zidovudine, lamivudine, and efavirenz (hazard ratio, 1.21).

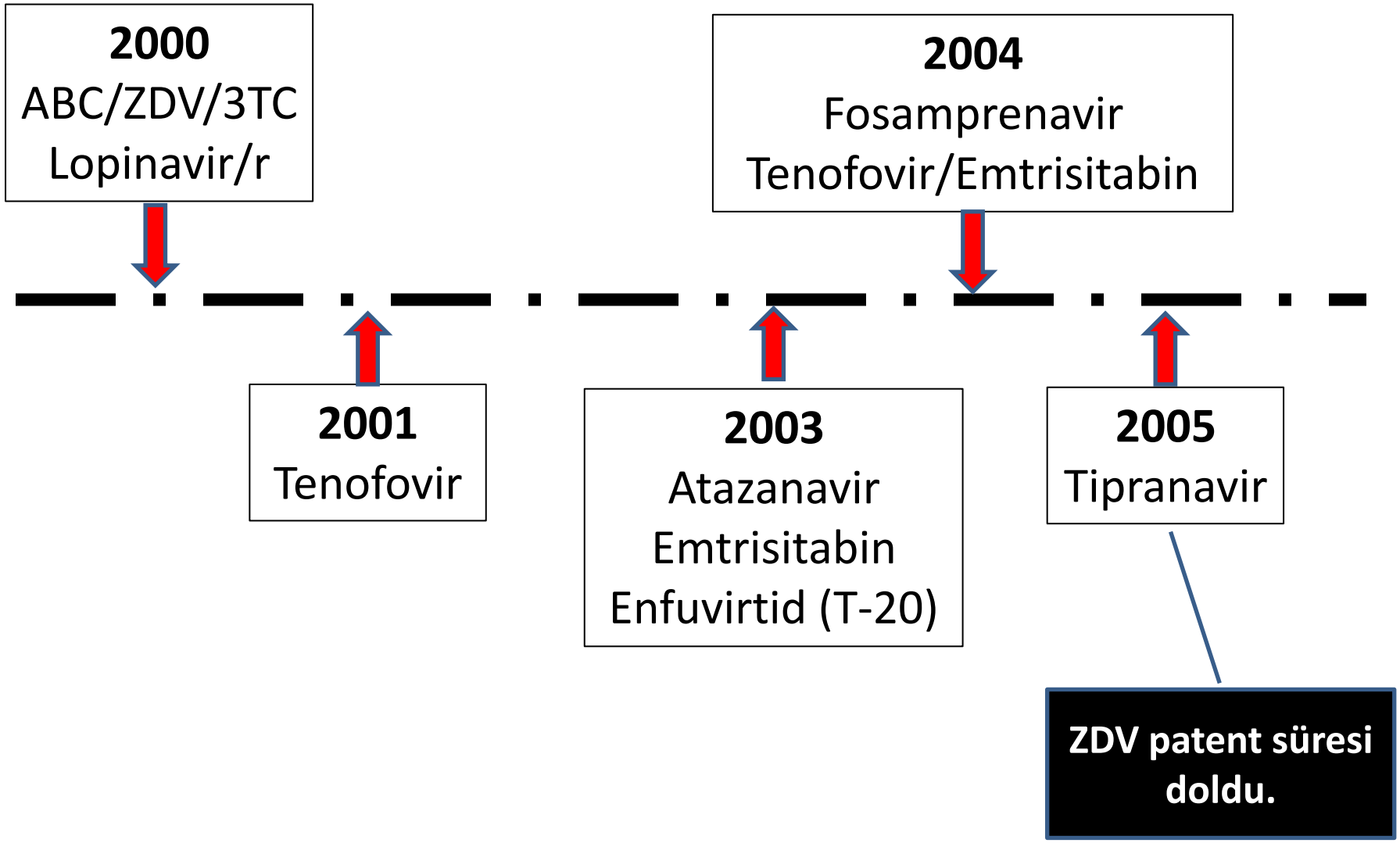
CONCLUSIONS: There was no significant difference in the duration of successful HIV-1 treatment between a single four-drug regimen and two consecutive three-drug regimens. Among these treatment strategies, initiating therapy with the three-drug regimen of zidovudine, lamivudine, and efavirenz is the optimal choice.

NEJM 2003 Dec 11;349(24):2304-15

DHHS 2000

3. İlaç	2NRTI
İndinavir	Stavudin + lamivudin
Nelfinavir	Stavudin + didanozin
Sakinavir/ritonavir	Zidovudine + lamivudin
Efavirenz	Zidovudin + didanozin

Önerilen Rejimler


2000
ABC/ZDV/3TC
Lopinavir/r
2001
Tenofovir
2003
Atazanavir
Emtrisitabin
Enfuvirtid (T-20)
2004
Fosamprenavir
Tenofovir/Emtrisitabin
2005
Tipranavir
ZDV patent süresi doldu.

DHHS 2005

	2 NRTI	
Efavirenz	ZDV veyaTDF	3TC veya FTC
Lopinavir/r	ZDV	3TC veya FTC

Panel's Recommendations

- *Preferred NNRTI-Based*
  - *Efavirenz + (zidovudin*
    or emtricitabine) (excep
    pregnancy or in women w
    (AII)
- *Alternative NNRTI-Base*
  - *Efavirenz + (didanosin*
    + (lamivudine or emtri
    pregnancy, particularly th
    with high pregnancy pote
  - *Nevirapine-based regin*
    alternative in adult fema
    ≤250 cells/mm³ and adult males with CD4⁺ T cell counts ≤400 cells/mm³ (BII).

The Panel does not recommend the following NNRTIs as initial therapy:

- *Delavirdine – due to inferior antiretroviral potency and three times daily dosing (DII)*
- *Nevirapine for adult females with CD4⁺ T cell counts >250 cells/mm³ and adult males with CD4⁺ T cell counts >400 cells/mm³ unless the benefit clearly outweighs the risk (DI)*

** Women with high pregnancy potential are those who are trying to conceive or who are not using effective and consistent contraception.*

emtricitabine

The Panel doe
as initial thera

- *Amprenavir (*
  burden
- *Unboosted in*
  times daily d
  stomach or a
- *Ritonavir as s*
  gastrointestin
- *Unboosted sa*
  due to poor c
  dosing, and l

** ritonavir 100m with atazanavi*
*** ritonavir at da pharmacokine*

Panel's Recommendations:

- ***A 3-NRTI regimen consisting of abacavir + zidovudine + lamivudine should only be used when a preferred or alternative NNRTI-based or PI-based regimen cannot or should not be used as first-line therapy (e.g. for important drug-drug interactions) in the treatment-naïve patient. (CII).***

The Panel DOES NOT RECOMMEND the use of the following 3-NRTI regimens as sole antiretroviral combination at any time:

- ***abacavir + tenofovir + lamivudine (EII)***
- ***didanosine + tenofovir + lamivudine (EII)***

ACTG 5142: 96. hafta sonuçları

Virolojik baskılanma EFV + 2 NRTİ grubunda daha başarılı

CD4 hücre artışı LPV/r + 2 NRTİ grubunda daha iyi

	EFV + 2NRTİ	LPV/r + 2NRTİ	EFV + LPV/r
HIV-RNA <200 k/mL	**%93***	%86*	%92
HIV-RNA <50 k/mL	**%89****	%77**	%83
CD4 hücre artışı/mm^3	273***	**287*****	230

*P= 0.041

**P= 0.003

***P= 0.01

Virolojik başarısızlık LPV/r grubunda daha kısa sürede

Riddler, NEJM 2008

TDF/FTC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

934 Çalışması

Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV

Joel E. Gallant, M.D., M.P.H., Edwin DeJesus, M.D., José R. Arribas, M.D., Anton L. Pozniak, M.D., Brian Gazzard, M.D., Rafael E. Campo, M.D., Biao Lu, Ph.D., Damian McColl, Ph.D., Steven Chuck, M.D., Jeffrey Enejosa, M.D., John J. Toole, M.D., Ph.D., and Andrew K. Cheng, M.D., Ph.D., for the Study 934 Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

ACTG 5202

Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy

Paul E. Sax, M.D., Camlin Tierney, Ph.D., Ann C. Collier, M.D., Margaret A. Fischl, M.D., Katie Mollan, M.S., Lynne Peeples, M.S., Catherine Godfrey, M.D., Nasreen C. Jahed, M.P.H., Laurie Myers, M.S., David Katzenstein, M.D., Awny Farajallah, M.D., James F. Rooney, M.D., Belinda Ha, Ph.D., William C. Woodward, M.D., Susan L. Koletar, M.D., Victoria A. Johnson, M.D., P. Jan Geiseler, M.D., and Eric S. Daar, M.D., for the AIDS Clinical Trials Group Study A5202 Team*

ABSTRACT

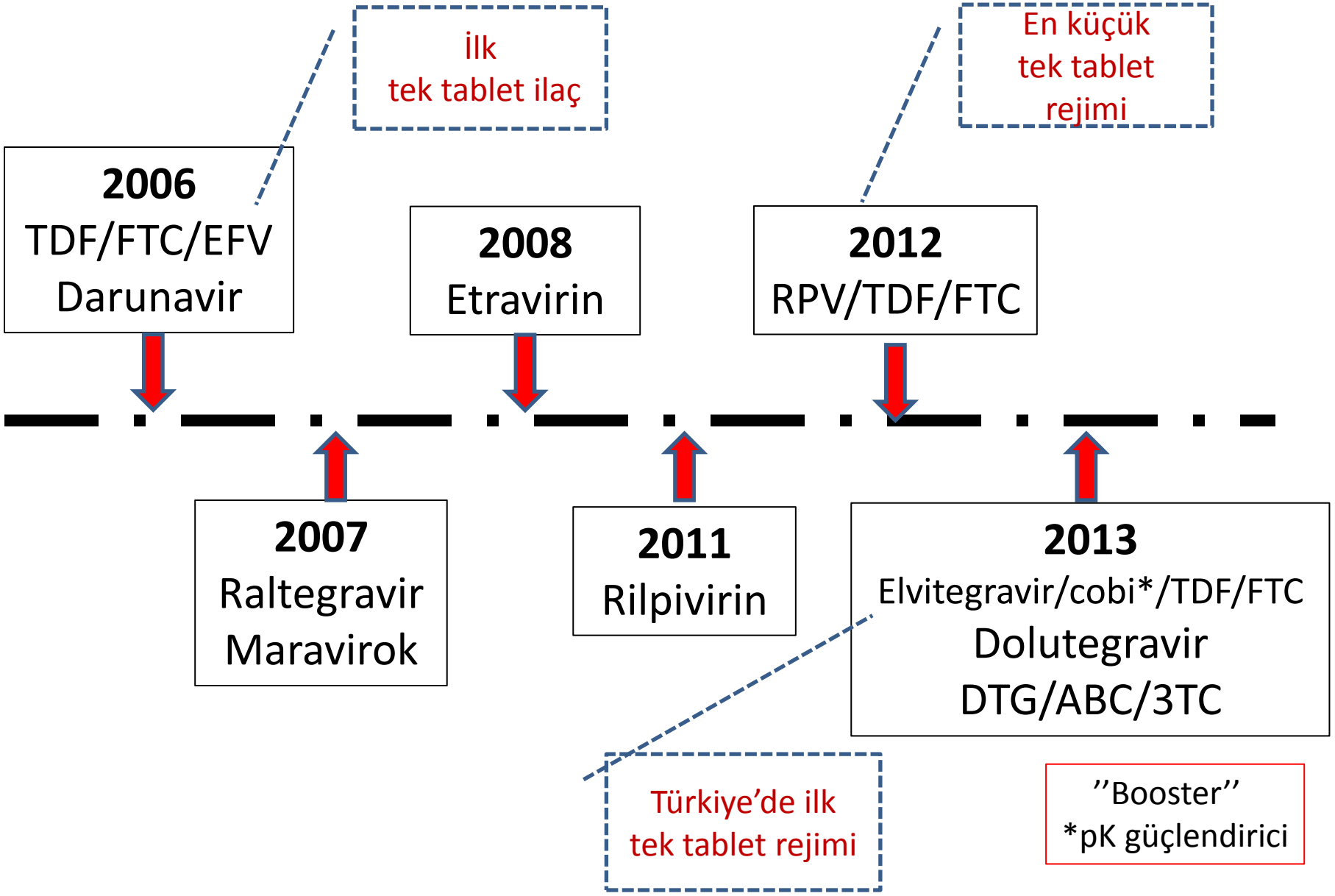
Çalışma	Karşılaştırma	Sonuç
934 N=517 VY >10,000 k/mL	**TDF**/FTC + EFV vs ZDV/3TC + EFV	• 144. hf: <400 k/mL**: %71** vs %58 • CD4 artışı: **+312** vs +217/mm3 • Yan etki nedeniyle **ilacı bırakma**: %5 vs %11 • Ekstremite yağ doku miktarı: 7.9 vs 5.4 kg
ACTG 5202 N=1858 VY >1,000 k/mL	TDF/FTC + EFV TDF/FTC + ATV/r vs **ABC**/3TC + EFV **ABC**/3TC + ATV/r	• 48. hafta <50 k/mL: %80 vs %75 •**VB*: ABC** grubunda daha yüksek ve daha erken (HR=2.08) • Evre 4 **yan etki** ABC grubunda daha yüksek • **Bazal VY** yüksek olan hastalarda ABC dikkatli kullanılmalı

*VB: virolojik başarısızlık

Gallant, NEJM 2006
Arribas JR, JAIDS 2008

Sax PE, NEJM 2009

İlk tek tablet rejimi: EFV/TDF/FTC


İlk
tek tablet ilaç
En küçük
tek tablet
rejimi
2006
TDF/FTC/EFV
Darunavir
2008
Etravirin
2012
RPV/TDF/FTC
2007
Raltegravir
Maravirok
2011
Rilpivirin
2013
Elvitegravir/cobi*/TDF/FTC
Dolutegravir
DTG/ABC/3TC
Türkiye'de ilk
tek tablet rejimi
''Booster''
*pK güçlendirici

Çalışma	Karşılaştırma	Sonuç
ARTEMIS	**DRV/r** + TDF/FTC **LPV/r** + TDF/FTC 96 hf	HIV-RNA <50 k/mL.: VY>10^5 ise DRV/r ile daha iyi p=0.023 CD4 <200 ise DRV/r ile daha iyi p=0.009
STARTMRK	**RAL** + TDF/FTC **EFV** + TDF/FTC 240 hf	RAL ile viral baskılanma ve CD4 artışı anlamlı olarak daha iyi. Nörolojik ve ilaç ilişkili y.e RAL ile daha az.
THRIVE	**RPV**/TDF/FTC **EFV**/TDF/FTC 48 hf	Viral baskılanma benzer. Virolojik başarısızlık RPV ile daha yüksek, çoğu ilk 48 hf içinde ve bazal yüksek VY ve düşük CD4 ile ilişkili. RPV daha iyi tolere edilir.

Çalışma	Karşılaştırma	Sonuç
Study 102	**EVG/Cobi**/FTC/TDF **EFV**/FTC/TDF 144 hf	Noninferior
Study 103	**EVG/Cobi**/FTC/TDF **ATV/r**/FTC/TDF 144 hf	<50 k/mL: %78 vs %75

EVG: Study 102 + 103:
Toplam direnç %2.2

Dolutegravir

Çalışma	Sonuç
SPRING-2 DTG vs RAL ABC/3TC veya TDF/FTC	48. hf: noninferior 96. hf: noninferior
SINGLE DTG + ABC/3TC EFV + TDF/FTC	48. hf: üstün*
Flamingo DTG vs DRV/r ABC/3TC veya TDF/FTC	48. hf: üstün*

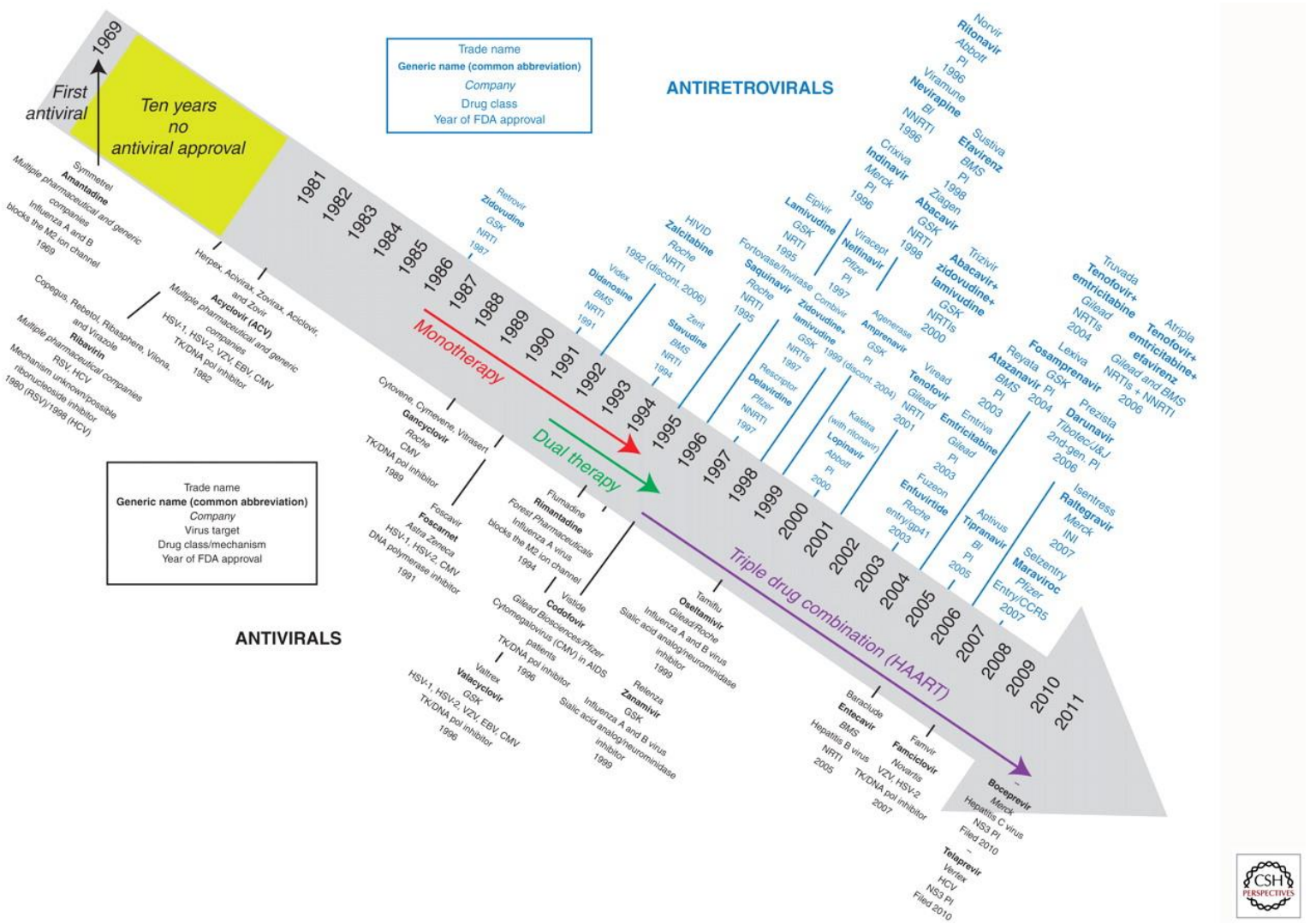
Raffi F, Lancet 2013

Walmsley SL, NEJM 2013

Feinberg J, ICAAC 2013

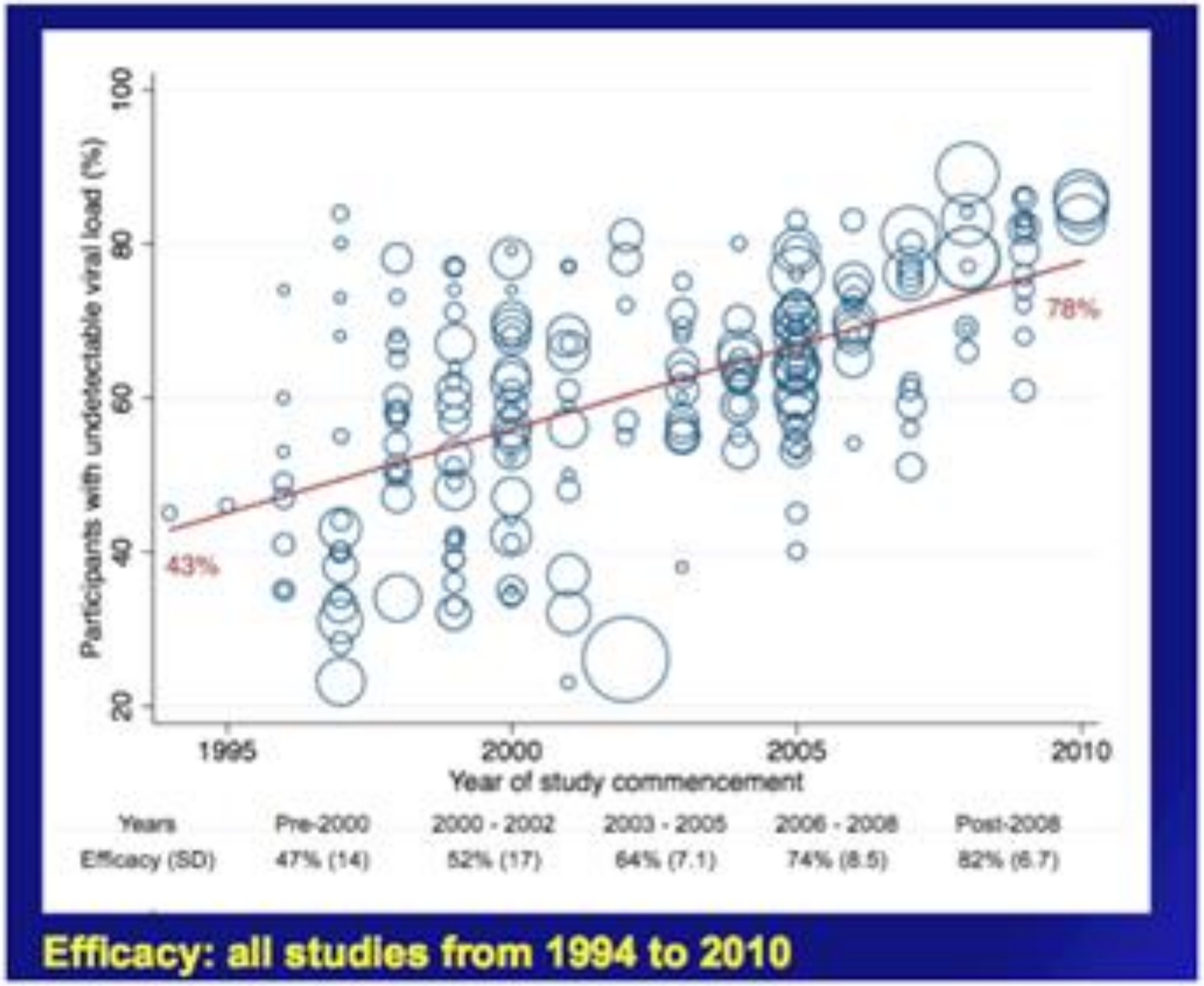
*Yan etki veya diğer nedenlerle ilacı bırakma karşılaştırma gruplarında daha fazla.

Timeline for FDA approval for current antiviral and antiretroviral drugs.

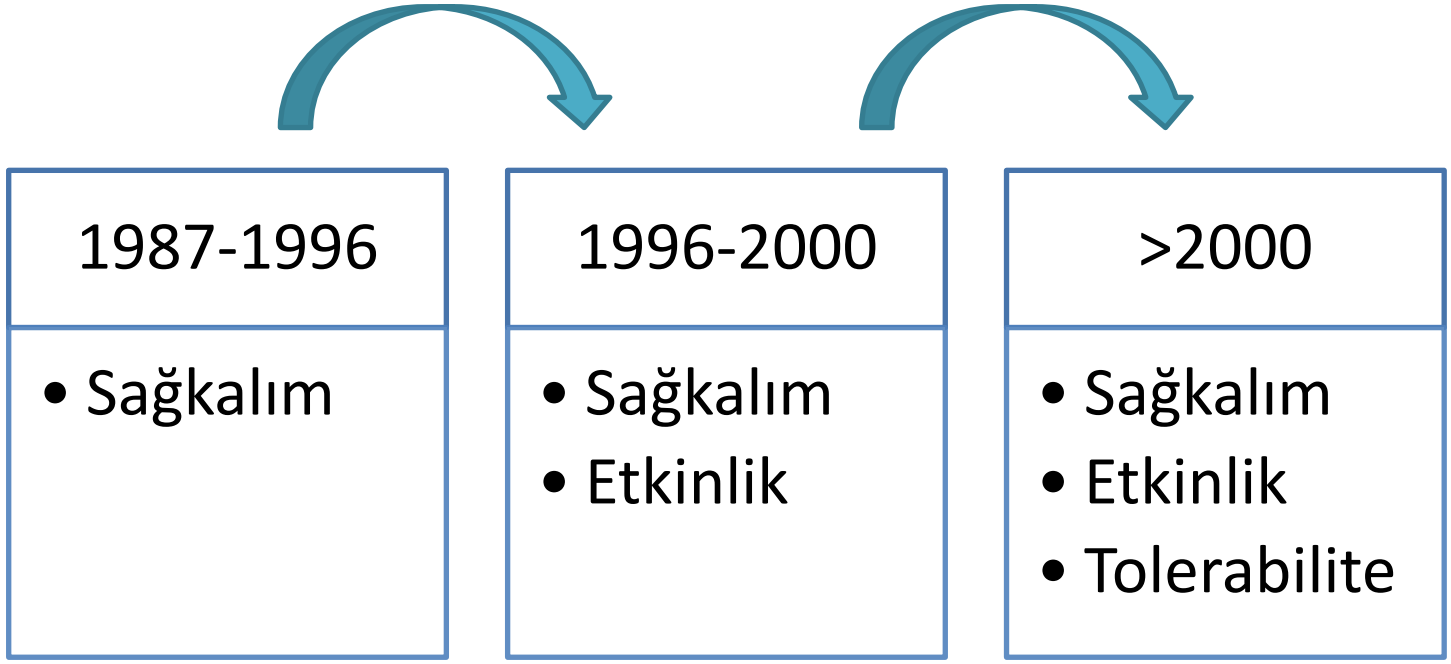


Eric J. Arts, and Daria J. Hazuda Cold Spring Harb Perspect Med 2012;2:a007161

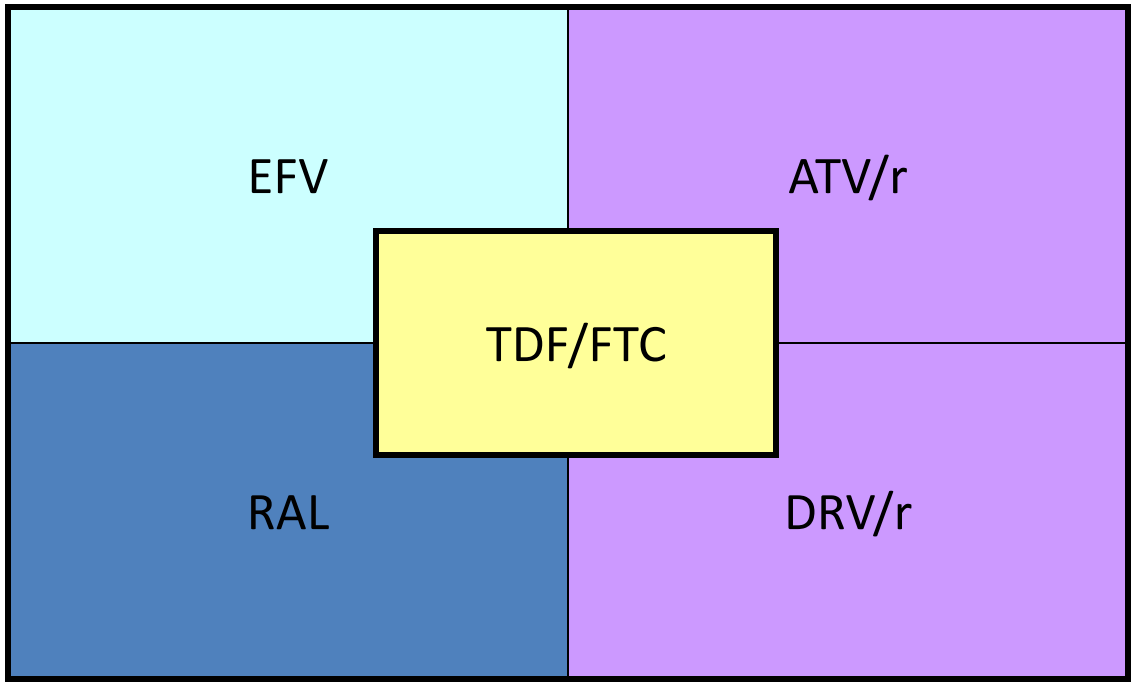
IAS 2013: Efficacy of initial antiretroviral therapy: a meta-analysis of 40,124 adults with up to 144 weeks' follow-up. FJ Lee (Australia)



Antiretroviral Tedavinin Hedefi



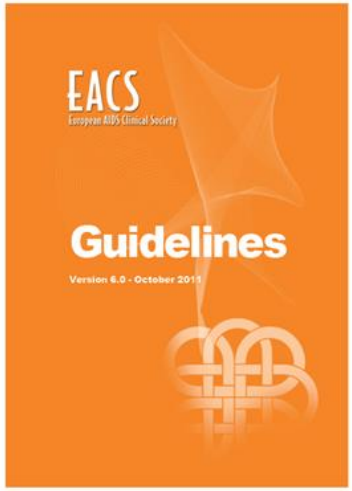
DHHS Ocak 2011



Gebelerde LPV/r günde 2 dozda + ZDV/3TC

Önerilen Rejimler

Etkinliği en üst düzeyde ve kalıcı,
İyi tolere edilen,
Toksisitesi kabul edilebilir,
Kullanımı kolay



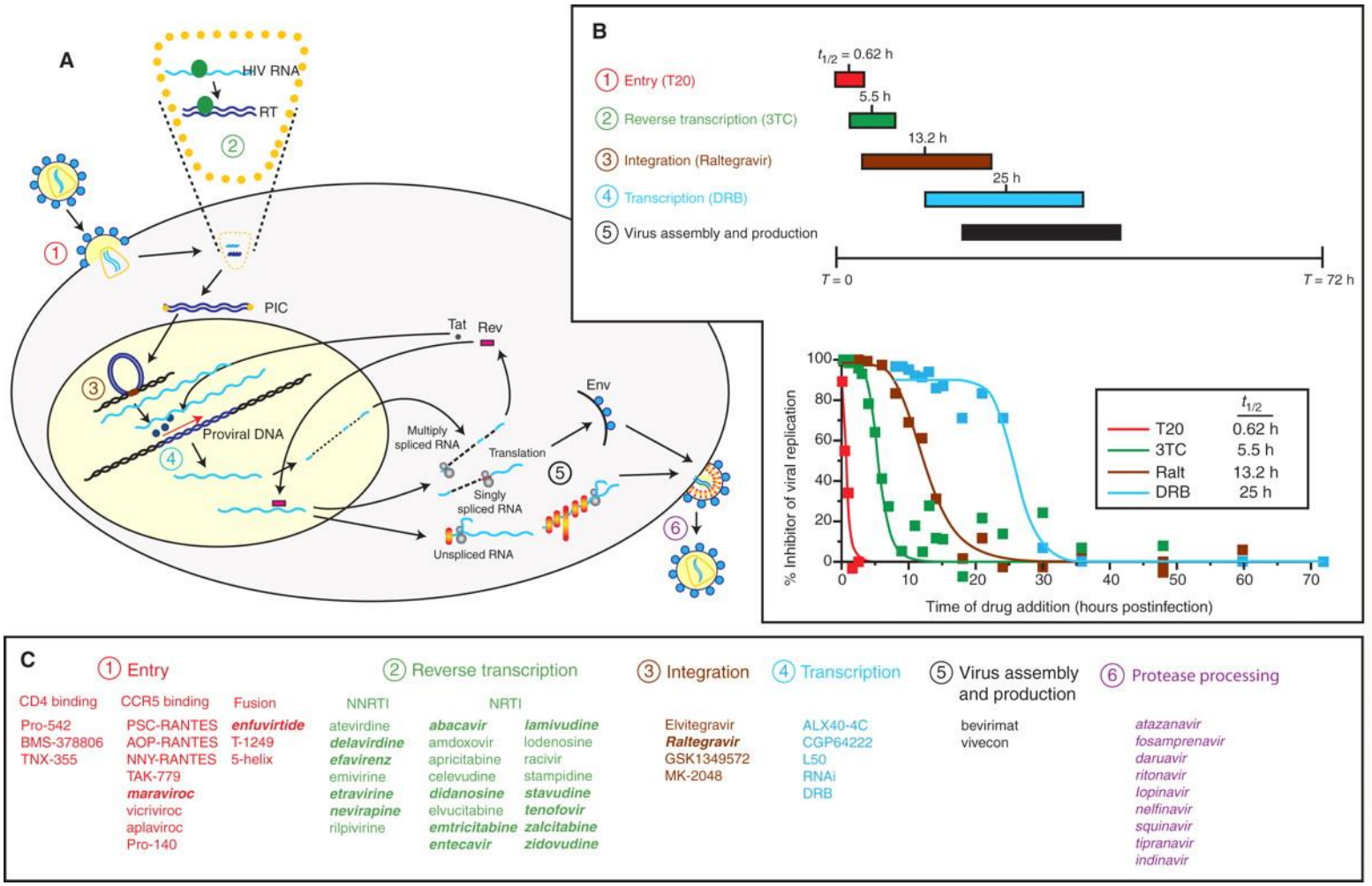
	A	B
Önerilen	**NNRTİ bazlı**	
	EFV	ABC/3TC TDF/FTC
	NVP	TDF/FTC
	Pİ/r bazlı	
	ATV/r	ABC/3TC TDF/FTC
	DRV/r	
	LPV/r	
	İntegraz İnhibitörü bazlı	
	RAL	TDF/FTC
Alternatif	SQV/r FPV/r MVC	ZDV/3TC ddI/3TC veya FTC

A kolonundan 1 ilaç ve B kolonundan 1 NRTİ kombinasyonu seçin

Antiretroviral İlaçlar

NRTI	NNRTI	PI	INSTI	Giriş İnh.
ZDV	NVP	Sakinavir	Raltegravir	Enfuvirtid
ddI	EFV	Ritonavir	Elvitegravir	Maravirok
ddC	Delavirdin	İndinavir	Dolutegravir	
d4T	Etravirin	Nelfinavir		
3TC	Rilpivirin	Lopinavir/r		
ABC		Atazanavir		
TDF		Fos-AMP		
FTC		Tipranavir		
		Darunavir		

Identifying distinct steps in HIV-1 life cycle as potential or current target for antiretroviral drugs.



Eric J. Arts, and Daria J. Hazuda Cold Spring Harb Perspect Med 2012;2:a007161

Table 1. DHHS: Changing Criteria for Initiation of ART

CD4+ Counts, cells/mm^3	1998	2001	2006	2008	2009	2012
> 500	Offer if HIV-1 RNA > 20,000 copies/mL	Offer if HIV-1 RNA > 55,000 copies/mL	Consider if HIV-1 RNA ≥ 100,000 copies/mL	Consider in certain groups*	Consider†	Treat
350-500	Offer if HIV-1 RNA > 20,000 copies/mL	Consider if HIV-1 RNA > 55,000 copies/mL	Consider if HIV-1 RNA ≥ 100,000 copies/mL	Consider in certain groups*	Treat	Treat
200-350	Offer if HIV-1 RNA > 20,000 copies/mL	Offer, but controversy exists	Offer after discussion with patient	Treat	Treat	Treat
< 200 or symptomatic disease	Treat	Treat	Treat	Treat	Treat	Treat

*Includes pregnant women, patients with HIV-associated nephropathy, and patients with hepatitis B virus infection that requires treatment for which there is a definite recommendation to initiate therapy. Other considerations include certain acute opportunistic infections, rapidly declining CD4+ cell counts (> 100 cells/mm^3/year), and higher HIV-1 RNA (> 100,000 copies/mL).

†50% of panel members recommended starting ART at this CD4+ cell count level; the other 50% of members viewed treatment at this level as optional.

Table 2. Current Guidelines for Initiation of ART

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm^3	CD4+ Cell Count 200-350/mm^3	CD4+ Cell Count 350-500/mm^3	CD4+ Cell Count > 500/mm^3
US Department of Health and Human Services[DHHS ART]	Yes	Yes	Yes	Yes	Yes
International Antiviral Society-USA[IAS-USA ART]	Yes	Yes	Yes	Yes	Yes
British HIV Association [BHIVA ART]	Yes	Yes	Yes	Yes	Yes
European AIDS Clinical Society [EACS ART]	Yes	Yes	Yes	Consider	Consider
World Health Organization [WHO 2015]	Yes	Yes	Yes	Yes	Yes

Keywords: Initial Antiretroviral Therapy

START Çalışması: Bazal CD4 sayısından bağımsız olarak ART başlanması, ciddi hastalık ve ölüm riskini, erken tedavi başlanan grupta geç başlanan grupla kıyaslandığında azaltmaktadır.

EACS 2015

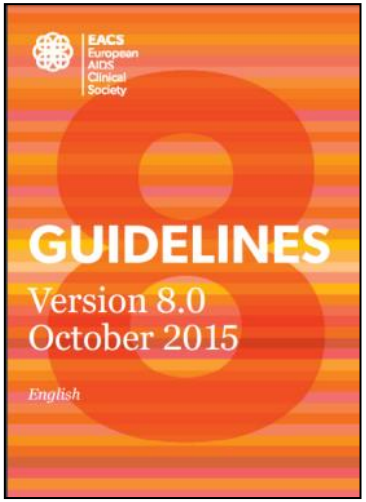
Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure(i)

Recommendations are graded while taking into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

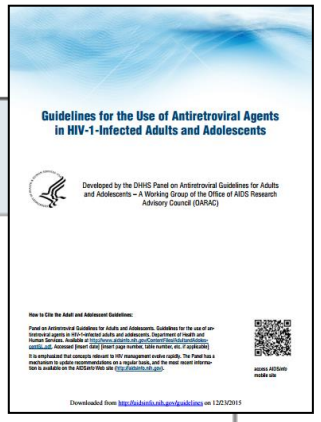
Symptomatic HIV disease (CDC B or C conditions, incl. tuberculosis)	Asymptomatic HIV infection	
Any CD4 count	Current CD4 count	
	< 350	≥ 350
SR	SR	R

SR = Strongly Recommended
R = Recommended

i ART should always be recommended irrespective of the CD4 count with the possible exception of elite controllers with high and stable CD4 count. Time should always be taken to prepare the person, in order to optimise compliance and adherence. Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART. If ART needs to be initiated before genotypic testing results are available, it is recommended to include a PI/r in the first-line regimen. Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response. Moreover, use of ART should also be recommended with any CD4 count in order to reduce sexual transmission, risk of AIDS event and mother-to-child transmission of HIV (before third trimester of pregnancy).



DHHS 2015


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

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultAndAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (http://aidsinfo.nih.gov).

access AIDSinfo mobile site

Downloaded from http://aidsinfo.nih.gov/guidelines on 12/23/2015

Recommended Regimen Options

(Drug classes and regimens within each class are arranged in alphabetical order.)

INSTI-Based Regimens:

- DTG/ABC/3TC[a]—**only** for patients who are HLA-B*5701 negative **(AI)**
- DTG plus TDF/FTC[a] **(AI)**
- EVG/c/TDF/FTC—only for patients with pre-treatment estimated CrCl ≥70 mL/min **(AI)**
- RAL plus TDF/FTC[a] **(AI)**

PI-Based Regimens:

- DRV/r plus TDF/FTC[a] **(AI)**

Alternative Regimen Options

(Drug classes and regimens within each class are arranged in alphabetical order.)

Regimens that are effective and tolerable, but that have potential disadvantages when compared with the recommended regimens listed above, have limitations for use in certain patient population, or have less supporting data from randomized clinical trials. **An alternative regimen may be the preferred regimen for some patients.**

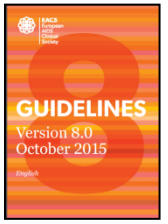
NNRTI-Based Regimens:

- EFV/TDF/FTC[a] **(BI)**
- RPV/TDF/FTC[a]—**only** for patients with pre-treatment HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm^3 **(BI)**

PI-Based Regimens:

- ATV/c plus TDF/FTC[a] —**only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(BI)**
- ATV/r plus TDF/FTC[a] **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC[a] —**only** for patients who are HLA-B*5701 negative (**BIII** for DRV/c and **BII** for DRV/r)
- DRV/c plus TDF/FTC[a] —**only** for patients with pre-treatment estimated CrCl ≥70 mL/min **(BII)**

EACS 2015



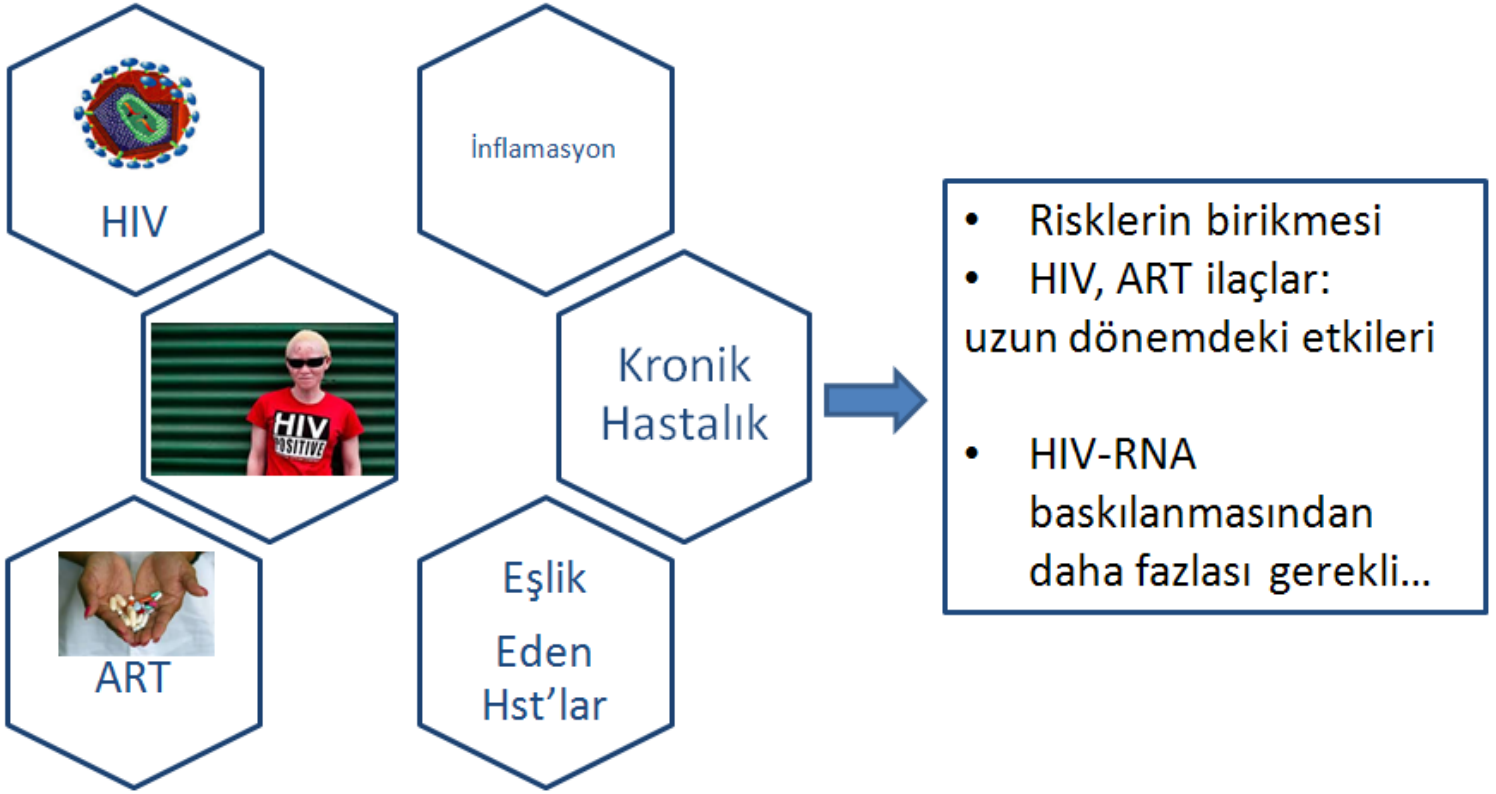
Initial Combination Regimen for ART-naïve Adult HIV-positive Persons

A) Recommended regimens (one of the following to be selected)[*,**]

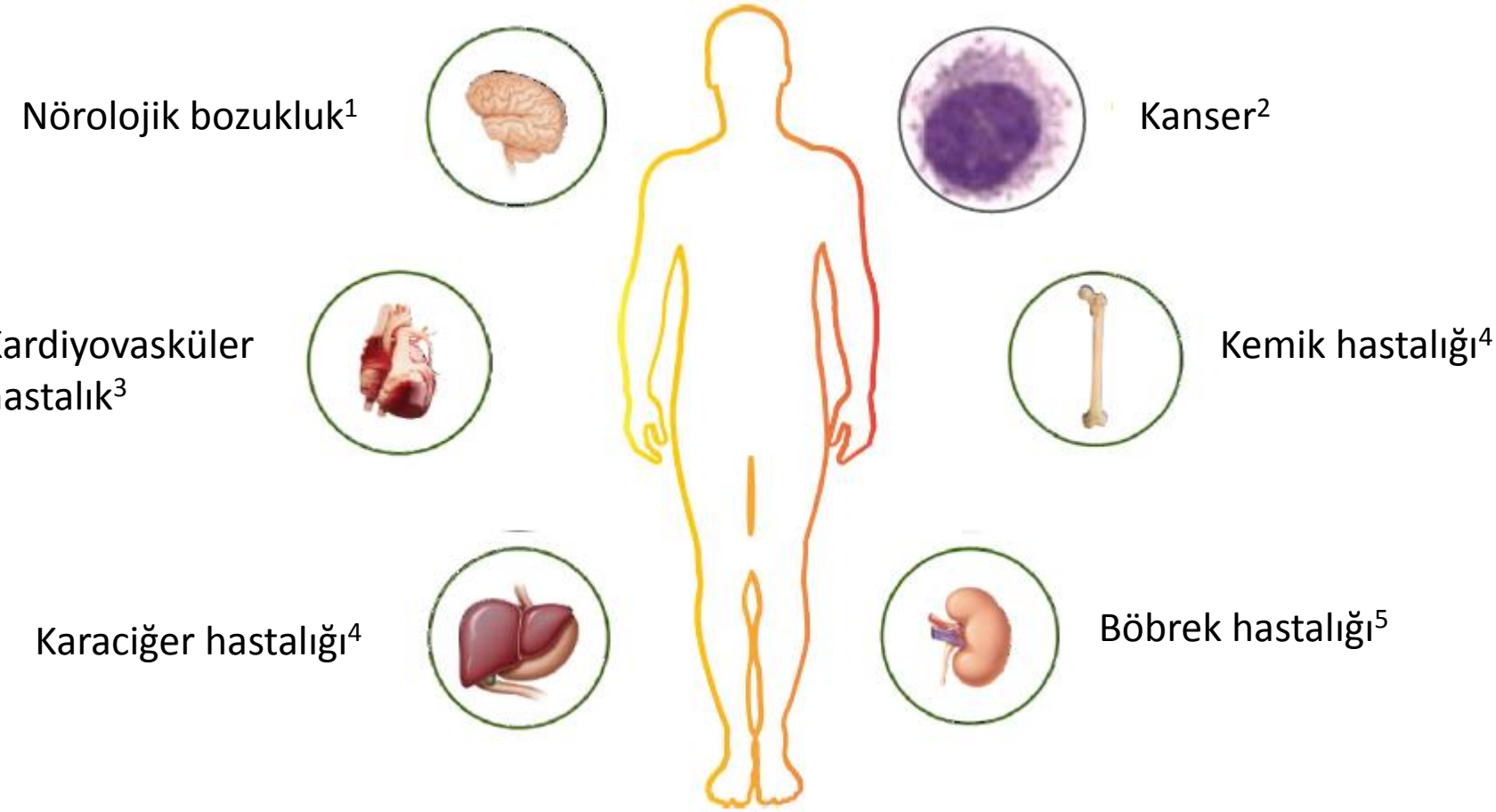
Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG[(i, ii)]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[(iii, iv)] + DTG	TDF/FTC 300[(viii)]/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TDF/FTC/EVG/c[(iii, iv, v)]	TDF/FTC/EVG/c 300[(viii)]/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
TDF/FTC[(iii, iv)] + RAL	TDF/FTC 300[(viii)]/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Al/Ca/Mg-containing antacids should be taken well separated in time (minimum 2h after or 6h before).
2 NRTIs + NNRTI			
TDF/FTC/RPV[(iii)]	TDF/FTC/RPV 300[(viii)]/200/25 mg, 1 tablet qd	With food (min 390 Kcal required)	Only if CD4 count >200 cells/µL and HIV VL <100,000 copies/mL. PPI contraindicated; H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r			
TDF/FTC[(iii, iv)] + DRV/r	TDF/FTC 300[(viii)]/200 mg, 1 tablet qd + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.

Güncel Durum: 2015

- ART'deki gelişmeler sonucu HIV infeksiyonu **kronik bir hastalığa** dönüşmüş ve HIV pozitif hastaların yaşam süresinin uzamasıyla uzun dönemdeki sağlık daha önemli hale gelmiştir.



HIV infeksiyonu ve ART:
Sağlık üzerindeki uzun dönem etkileri



1. McArthur JC et al. Ann Neurol 2010;67:699–714; 2. Nguyen ML et al. 18th IAC. Vienna, Austria 2010. Abstract WEAB0105; 3. Freiberg MS et al. JAMA Intern Med 2013;173:614–622; 4. Brown TT et al. AIDS 2006;20:2165–2174; 5. Towner WJ et al. JAIDS 2012;60:321–327; 6. Lucas GM et al. Clin Infect Dis 2014;59:e96–e138

D:A:D: Increased Risk of Chronic Kidney Disease With Long-term Exposure to Tenofovir DF, Atazanavir/Ritonavir, or Lopinavir/Ritonavir

Over 5 years of exposure, the risk of developing CKD increased > 300-fold with atazanavir/ritonavir, > 200-fold with lopinavir/ritonavir, and 174-fold with tenofovir DF compared with no exposure to each agent.

Source: 2015 Conference on Retroviruses and Opportunistic Infections
Date Posted: 3/2/2015

D:A:D: Current Abacavir Use Remains Associated With Increased Risk of MI in HIV-Infected Patients

The association between abacavir use and risk of MI remained evident through continued follow-up despite decreasing prescription of abacavir to patients with elevated CVD risk.

Source: 2014 Conference on
Date Posted: 3/10/2014

D:A:D: No Associatio
Infarction or Stroke

Lack of association between
and bilirubin level.

Source: 2012 Conference on
Date Posted: 3/13/2012

D:A:D: All-Cause and
Current Era of Antire

Although AIDS-related mortalit
among HIV-infected individual
AIDS deaths in this population

Source: XIX International AID
Date Posted: 7/29/2012

D:A:D Study: Smoking Cessation Reduces Risk of Cardiovascular Disease in HIV-Infected Patients

The risk for cardiovascular disease events among HIV-infected patients in the D:A:D cohort decreased progressively as the length of time since smoking cessation increased.

Source: 2010 Conference on Retroviruses and Opportunistic Infections
Date Posted: 2/20/2010

D:A:D: Short-Term BMI Gain After ART Initiation Associated With Increased Risk of Diabetes Regardless of Pre-ART BMI and Increased CVD Risk in Patients With Normal Pre-ART BMI

In patients with normal BMI before starting ART, weight gain in the first year of ART was significantly associated with increased risk of cardiovascular disease.

Source: 20th International AIDS Conference (AIDS 2014)
Date Posted: 7/25/2014

D:A:D Study Reports Increased Incidence of Myocardial Infarction With Longer Duration of PI Therapy

According to the D:A:D study, the increased risk of myocardial infarctions previously observed with combination antiretroviral therapy is primarily due to exposure to PIs.

Source: 2006 Conference on Retroviruses and Opportunistic Infections
Date Posted: 2/21/2006

J Int AIDS Soc. 2014 Nov 2;17(4 Suppl 3):19745. doi: 10.7448/IAS.17.4.19745. eCollection 2014.

Viral escape in the CNS with multidrug-resistant HIV-1.

Béguelin C[1], Vázquez M[1], Bertschi M[2], Yerly S[3], de Jong D[4], Rauch A[1], Cusini A[1].

Author information

[1]Department of Infectious Diseases, University Hospital and University of Bern, Bern, Switzerland.
[2]Department of Neurology, University Hospital and University of Bern, Bern, Switzerland.
[3]Laboratory of Virology, Geneva University Hospital, Geneva, Switzerland.
[4]Department of Neuropsychology, University Hospital and University of Bern, Bern, Switzerland.

Abstract

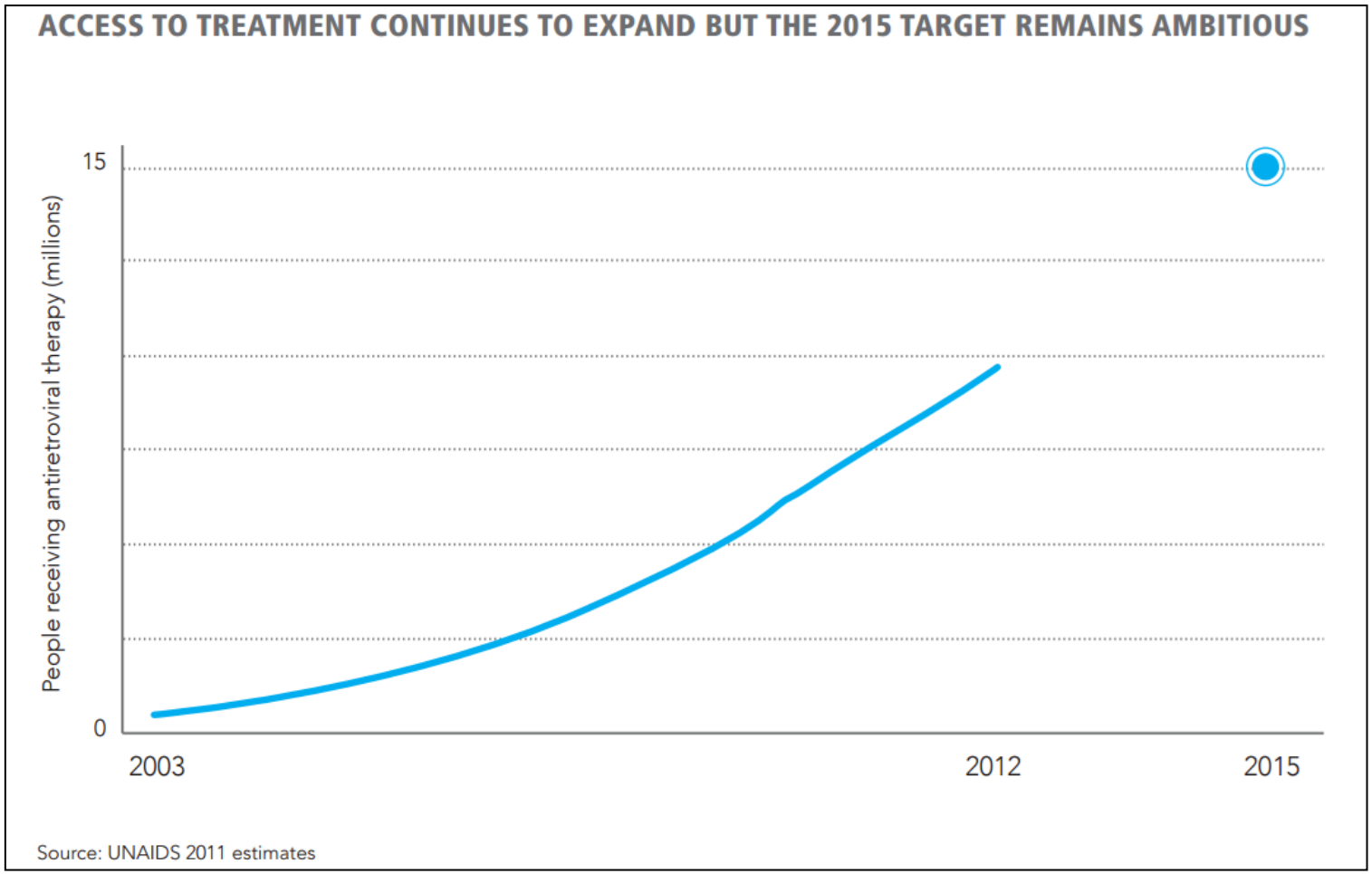
INTRODUCTION: HIV-1 viral escape in the cerebrospinal fluid (CSF) despite viral suppression in plasma is rare [1,2]. We describe the case of a 50-year-old HIV-1 infected patient who was diagnosed with HIV-1 in 1995. Antiretroviral therapy (ART) was started in 1998 with a CD4 T cell count of 71 cells/µL and HIV-viremia of 46,000 copies/mL. ART with zidovudine (AZT), lamivudine (3TC) and efavirenz achieved full viral suppression. After the patient had interrupted ART for two years, treatment was re-introduced with tenofovir (TDF), emtricitabin (FTC) and ritonavir boosted atazanavir (ATVr). This regimen suppressed HIV-1 in plasma for nine years and CD4 cells stabilized around 600 cells/µL. Since July 2013, the patient complained about severe gait ataxia and decreased concentration.

MATERIALS AND METHODS: Additionally to a neurological examination, two lumbar punctures, a cerebral MRI and a neuropsycological test were performed. HIV-1 viral load in plasma and in CSF was quantified using Cobas TaqMan HIV-1 version 2.0 (Cobas Ampliprep, Roche diagnostic, Basel, Switzerland) with a detection limit of 20 copies/mL. Drug resistance mutations in HIV-1 reverse transcriptase and protease were evaluated using bulk sequencing.

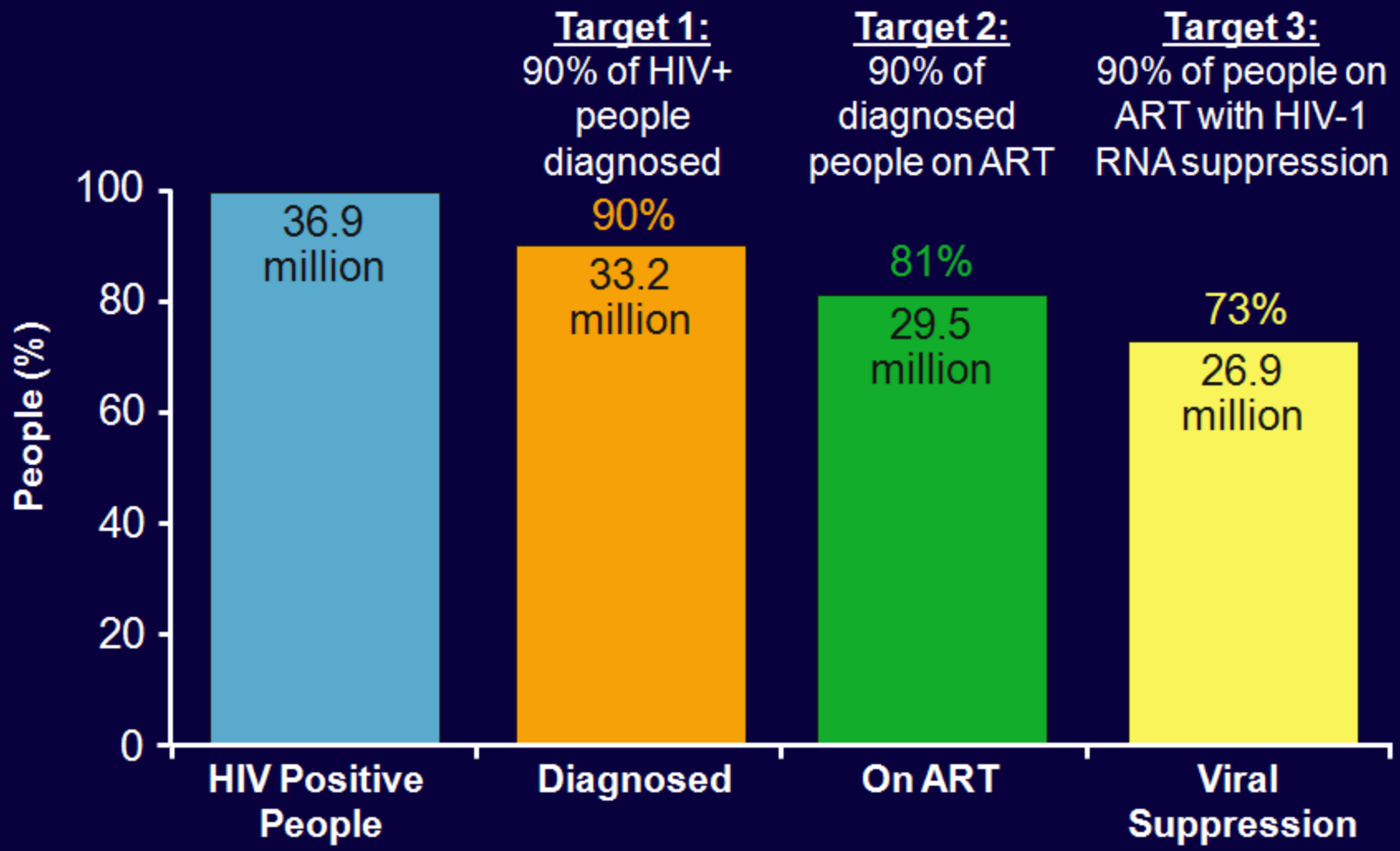
RESULTS: The CSF in January 2014 showed a pleocytosis with 75 cells/µL (100% mononuclear) and 1,184 HIV-1 RNA copies/mL, while HIV-1 in plasma was below 20 copies/mL. The resistance testing of the CSF-HIV-1 RNA showed two NRTI resistance-associated mutations (M184V and K65R) and one NNRTI resistance-associated mutation (K103N). The cerebral MRI showed increased signal on T2-weighted images in the subcortical and periventricular white matter, in the basal ganglia and thalamus. Four months after ART intensification with AZT, 3TC, boosted darunavir and raltegravir, the pleocytosis in CSF cell count normalized to 1 cell/µL and HIV viral load was suppressed. The neurological symptoms improved; however, equilibrium disturbances and impaired memory persisted. The neuro-psychological evaluation confirmed neurocognitive impairments in executive functions, attention, working and nonverbal memory, speed of information processing, visuospatial abilities and motor skills.

CONCLUSIONS: HIV-1 infected patients with neurological complaints prompt further investigations of the CSF including measurement of HIV viral load and genotypic resistance testing since isolated replication of HIV with drug resistant variants can rarely occur despite viral suppression in plasma. Optimizing ART by using drugs with improved CNS penetration may achieve viral suppression in CSF with improvement of neurological symptoms.

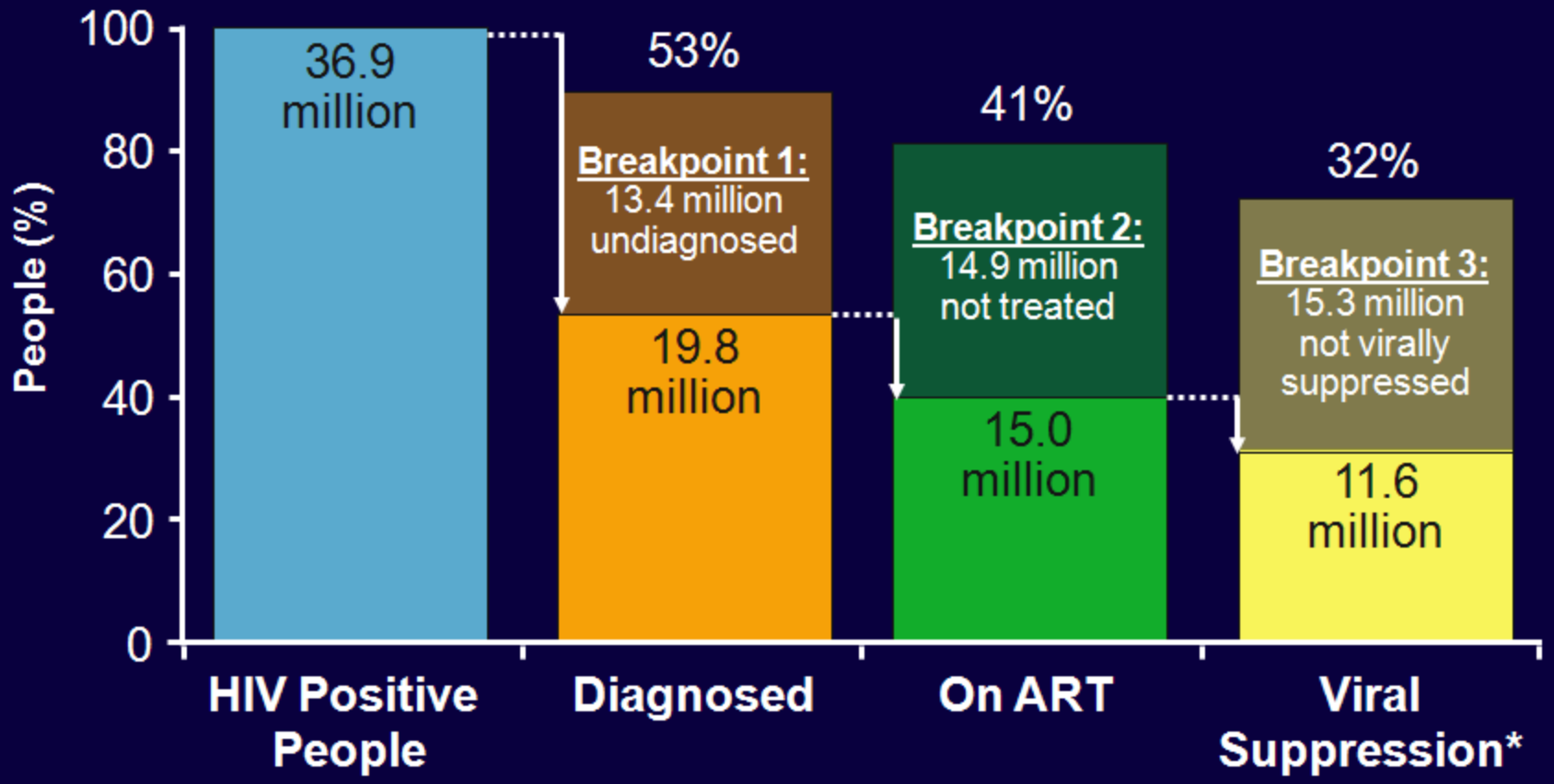
Tedaviye Erişim



UNAIDS: 90-90-90 Treatment Targets



UNAIDS: 90-90-90 Global Estimated Gaps



*HIV-1 RNA < 1000 copies/m

Gelecek Antiretroviral İlaçlar

NRTI	NNRTI	PI	INSTI	Giriş İnh.
TAF	Doravirin	DRV/cobi	RAL tek doz	cenicriviroc
	RPV LA	ATV/cobi	Cabotegravir	Fostemsavir
			GS 9883	
			RAL/3TC	

Sonuç olarak

ART, özellikle ilk kez tedaviye başlayanlar için giderek

- ✓ daha etkili,
- ✓ güvenilir ve
- ✓ daha kolay kullanılabilir olmaktadır.

Ancak hala yeni çalışmalara ihtiyaç bulunmaktadır.

YENİ
YILINIZ
KUTLU
OLSUN