Bir HIV enfeksiyonu olgusu…

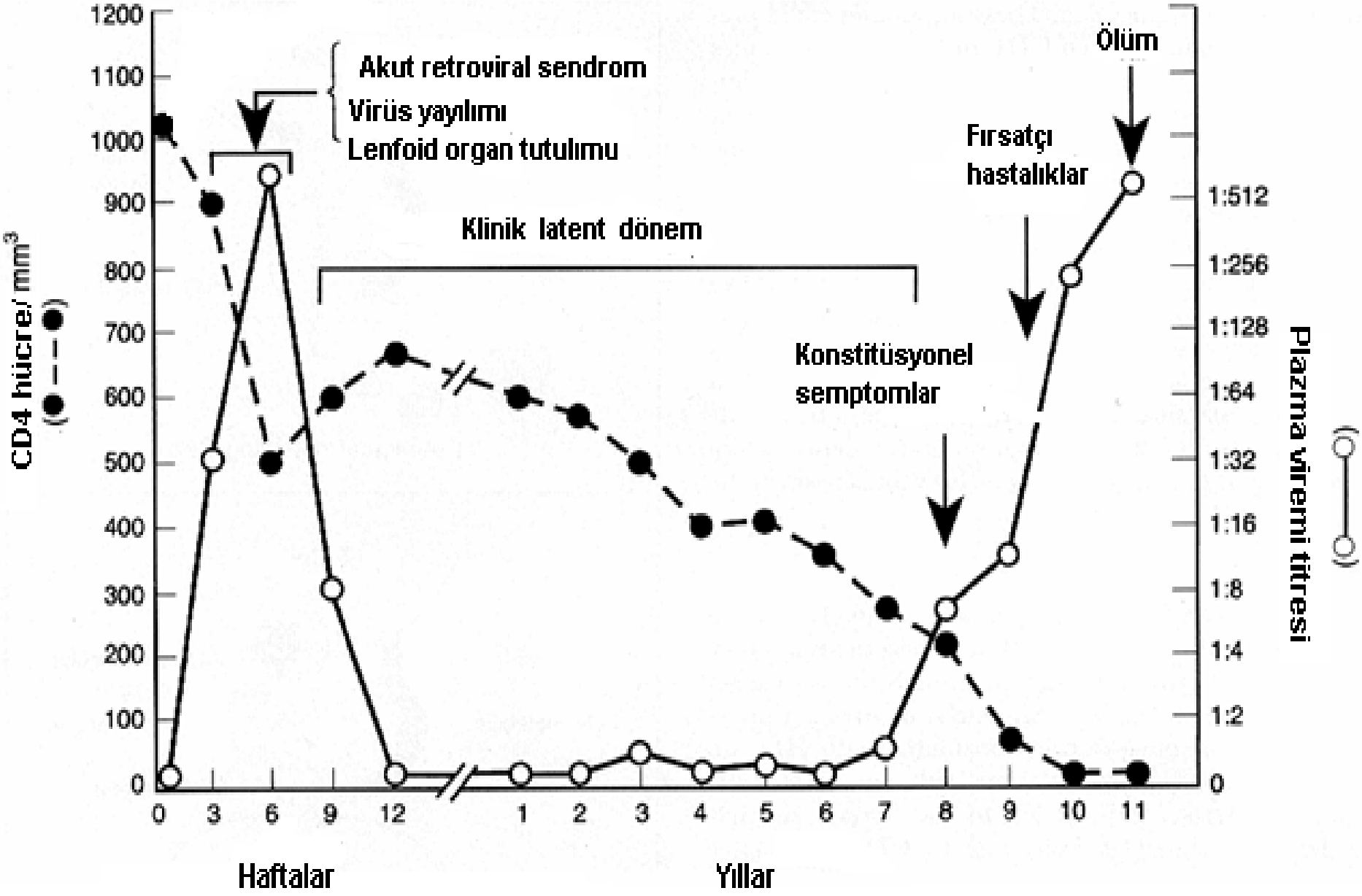
Muzaffer Fincancı

- 35 yaş, E
- Eşi ile birlikte geliyor
- Fiziksel yakınma yok
- Fizik muayene normal
- Anti-HIV testi pozitif
- 18 gün önceki Anti-HIV testi negatif
- Eşi ile 1 hafta önce cinsel ilişki

Nasıl yönetirsiniz?

3 gün sonra…

- CD4 T lenfosit : 358 h/mm³
- HIV-RNA: 531 127 620 kopya/ml
- Hemogram:N, Biyokimya:N,


Akut retroviral sendrom
Virüs yayılımı
Lenfoid organ tutulumu
Klinik latent dönem
Konstitüsyonel semptomlar
Fırsatçı hastalıklar
Ölüm
CD4 hücre/ mm3
Plazma viremi titresi
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1:512
1:256
1:128
1:64
1:32
1:16
1:8
1:4
1:2
0
0 3 6 9 12
1 2 3 4 5 6 7 8 9 10 11
Haftalar
Yıllar

Hasta “Yeni Enfeksiyon” kabul edilerek…

- Primer direnç testi istendi
- Kaletra-Truvada tedavisi başlandı
- Eşine aynı ilaçlar ile proflaksi başlandı

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

- Akut HIV enfeksiyonunun tedavisinin uzun dönemde klinik, immünolojik ve virolojik yarar sağlayıp sağlamadığı bilinmiyor
- Akut HIV enfeksiyonunda tedavi isteğe bağlı (CIII)
- Son 6 ay içinde serokonversiyonu olanlarda tedavi isteğe bağlı (CIII)
- Akut /yeni HIV enf. tüm gebelere mutlaka ART başlanmalı (AI)

Teorik yararlar…

- Akut hastalık daha hafif geçebilir
- Viral “setpoint” değişebilir
- Viral mutasyon olasılığı azalabilir
- Bağışıklık sistemi daha az zarar görebilir
- GIS lenfoid doku kaybı azaltılabilir
- Bulaştırıcılık azaltılabilir

ART başlanması seçilmiş ise

- Primer genotipik direnç testi istenmeli
- Sonuç beklenmeden ampirik ART rejimi ritonavir ile güçlendirilmiş Pİ içermeli
- Tedavi süresi bilinmiyor. Kronik HIV deneyimi ART kesmenin zararlı olabileceğini düşündürüyor

Summary of Studies on the Effects on Virologic Control and/or Disease Progression of Early Antiretroviral Therapy (ART) during Acute or Early Infection with Human Immunodeficiency Virus (HIV) Followed by Treatment Cessation.

Reference	Year	Study type	Study details	Outcome	Net clinical effect
Rosenberg et al [30]	2000	Prospective observational	8 acutely infected patients who started treatment during acute infection, followed by structured treatment interruptions	Short-term virologic control seen in 5 of 8 patients a median of 6.5 months after cessation of therapy (range, 5–8.7 months)	Virologic control
Desquilbet et al [42]	2004	Comparison of 2 prospective observational cohorts	58 PRIMO cohort subjects who started ART within 3.5 months after acute infection (median time to treatment, 45 days) and continued ART for a median of 17.3 months with sustained virologic suppression, who were then followed for up to 3 years, compared with 116 untreated seroconverters in the SEROCO cohort	Early treatment did not affect the viral set point 12 months after ART cessation, in the treatment group, compared with time-matched assessments in the no-treatment group	No difference in virologic control
Kaufmann et al [43]	2004	Prospective observational	14 acutely infected subjects who started ART during acute infection, followed by structured treatment interruptions	8 (57%) of 14 patients maintained virologic control for 180 days; 6 (43%) of 14 for 360 days, and 3 (21%) of 14 for 720 days. There was no predictable way to determine which subjects would achieve control	Limited virologic control
Streeck et al [44]	2006	Prospective observational	12 acutely infected subjects treated within 25 days for 24 weeks, compared with 8 untreated seroconverters	All treated subjects achieved virologic suppression by 24 weeks (when treatment was stopped), but CD4 cell count and viral load outcomes at 1 year showed no difference between treated and untreated subjects	No difference in virologic control
Hecht et al [45]	2006	Prospective observational	International cohort of subjects with acute infection (n = 13) or early infection (n = 45) who received treatment for ≥12 weeks, compared with a deferred-treatment group (n = 337)	Acute group demonstrated lower viral loads and higher CD4 cell counts 24 weeks after cessation of therapy; early group demonstrated persistent but decreasing CD4 T cell count benefit over time and loss of the viral load benefit by week 72 after discontinuation of ART	Mixed outcomes
Lampe et al [46]	2007	Comparison of 2 prospective observational cohorts	385 subjects in the CASCADE deferred-treatment cohort, compared with 79 treated subjects in the QUEST cohort, who continued therapy for a mean of 2.6 years	Viral load was <1000 copies/mL in 10.1% of CASCADE subjects 3 years after seroconversion and in 17.7% of QUEST subjects 24 weeks after treatment cessation	Virologic control
Fidler et al [47]	2007	Comparison of 2 prospective observational cohorts	89 patients who started treatment within 6 months after acute infection (median time to treatment, 1.5 months) and received highly active ART for a median of 3.3 months, compared with 179 matched untreated controls in the CASCADE cohort	Treated subjects showed a less steep estimated rate of CD4 cell count decline (decrease of 51 cells/mm^3 per year) compared with untreated subjects (decrease of 77 cells/mm^3 per year). There was no significant difference in viral loads between the groups 6 months after ART cessation	Mixed outcomes
Steingrover et al [48]	2008	Comparison of 2 prospective observational cohorts	24 subjects who started ART during primary HIV infection, compared with 46 chronically infected subjects who started ART with a CD4 cell count of <350 cells/mm^3; all subjects underwent a single treatment interruption	Steeper CD4 cell count decline after treatment interruption in the chronic infection group over the first 4 weeks; no difference between groups from 4 to 48 weeks. The median time to viral rebound was shorter in the chronic infection group than in the acute infection group (4 vs 8 weeks). 2 (8.3%) of 24 subjects with acute infection maintained viral loads of <50 copies/mL for up to 48 weeks of follow-up	Mixed outcomes
Pantazis et al [15]	2008	Prospective observational	348 subjects in the CASCADE cohort who started ART within 6 months after infection, compared with 676 subjects identified at seroconversion who had deferred treatment	No difference in viral load set point between the early-treatment and the deferred-treatment groups; significant CD4 cell count benefit 6 months after treatment cessation in the early-treatment group, compared with the deferred-treatment group, but only for subjects who had continued to receive treatment for ≥12 months. The death rate was higher in the deferred-treatment group, largely owing to causes not related to HIV infection	Mixed outcomes
Seng et al [49]	2008	Comparison of 2 prospective observational cohorts	170 treated subjects from the PRIMO cohort, compared with 123 untreated subjects from the SEROCO cohort	Mean CD4 cell count was not significantly different in treated vs untreated subjects at 3 years after treatment cessation	No CD4 cell count benefit
Prazuck et al [50]	2008	Prospective observational	20 subjects enrolled within 10 weeks of seroconversion and started on ART for a median of 2.3 years, compared with 18 subjects deferring treatment	At 144 weeks of follow-up, 25% of the treated group maintained a viral load of <50 copies/mL (vs none in deferred group). The CD4 cell count decline was twice as fast in the untreated group, compared with the treated group, during the period after treatment cessation. Virologic control was maintained for 4–7 years of follow-up	Virologic control and CD4 cell count benefit
Goujard et al [51]	2009	Prospective observational	223 subjects who started treatment within 3 months after seroconversion and continued it for ≥3 months and who stopped treatment for ≥12 months were studied to determine factors associated with virologic control	26 (12%) of 223 subjects maintained viral loads of <500 copies/mL after treatment interruption (median duration of treatment, 19.3 months; median duration of virologic control, 27 months). In 13 (50%) of 26 subjects viral loads were <50 copies/mL for a median of 42 months, and the median CD4 cell count was 946 cells/mm^3	Virologic control
Volberding et al [52]	2009	Prospective observational	121 subjects were enrolled with acute infection (≤14 days after infection) or early infection (14–180 days after infection) and started therapy within 3 days of enrollment; 73 subjects had virologic suppression for 1 year, followed by treatment interruption	40% of 73 treated subjects with acute infection or early infection sustained viral loads of <5000 copies/mL after 24 weeks of treatment interruption	Virologic control
Koegl et al [53]	2009	Comparison of 2 prospective observational cohorts	100 subjects with acute infection who were treated for a median of 9.5 months, compared with 96 subjects with acute infection who had deferred treatment	No difference in median viral load 12 months after ART cessation in the treatment group, compared with the median viral load 12 months after seroconversion in the deferred-treatment group; median time to CD4 cell count <350 cells/mm^3 was 20.7 months after ART cessation in treated group vs 8.3 months after seroconversion in deferred-treatment group	Mixed outcomes
Hogan et al [6]	2010	Randomized controlled trial	130 (of an intended 150) subjects randomized to start ART immediately and continue it for 9 months or to defer therapy	The study was stopped early by DSMB because of more rapid disease progression in the deferred-treatment group; virologic data were inadequate to assess differences between groups in the viral set point	Slower disease progression

NOTE. CD4 cell, CD4 T lymphocyte; DSMB, Data Safety and Monitoring Board; HIV, human immunodeficiency virus.

Bell S K et al. J Infect Dis. 2010;202:S278-S288

The Journal of Infectious Diseases

Tedavinin 1. ayı

- CD_4 T lenfosit: 712 h/ml
- HIV-RNA: 19.989 kopya/ml
- Antiretrovirallere primer direnç yok

Tedavinin devamında…

	Tedavinin 4. ayı	Tedavinin 8. ayı	Tedavinin 11. ayı
CD_4 T hücresi (ml)	407	395	378
HIV –RNA (kop/ml)	1172	Negatif	Negatif
Klinik	Asemptomatik	Asemptomatik	Asemptomatik

NELER OLUYOR?

"DİSKORDAN" YANIT (Virolojik ve İmmünolojik Yanıtlar Arasında Uyumsuzluk

- Viral baskılanma olduğu halde immünolojik iyileşme olmaması (%14-26)

veya

- İmmünolojik iyileşme olduğu halde viral baskılanma olmaması (%10-30)

Diskordan yanıt (yetersiz CD_4 yanıtı): Risk faktörleri

- Yaş (Timus aktivitesinin azalması)
- Tedavi öncesi CD_4 nadir (barsak lenfoid dokusu kaybı)
- CD_4 sayısındaki yavaş düşüş
- Genetik varyasyon (ARV etkileyen P glikoproteninin kodlayan gen (transporter MDRI-3445 TT genotipi)
- T lenfosit apoptosisi ile ilgili genler

Diskordan yanıt (yetersiz CD4 yanıtı): Risk faktörleri

- HIV-2 enfeksiyonu
- İlaç toksisitesi: Tenofovir/ didanosine kombinasyonu: *Her ikisinin de metabolitleri CD4 hücre pürin havuzunun dengesini bozarak sitotoksik etki yapabilir*
- Bazı ko-enfeksiyonlar: Ör: HTLV- 1

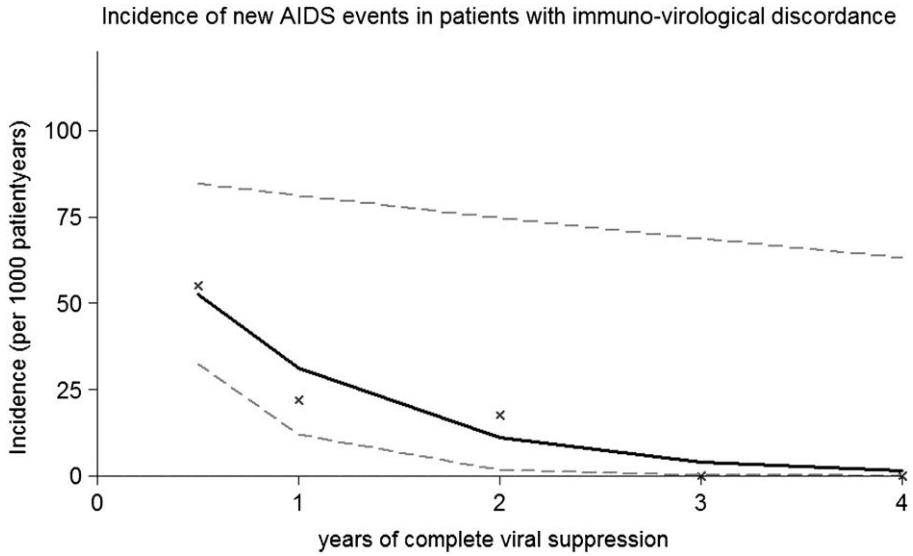
Diskordan yanıt (yetersiz CD4 yanıtı): Klinik Önemi

- *Grabar et al:* 2100 ART alan hasta hasta
  Ortalama 44 ay izlenmiş

Yetersiz immünolojik yanıtlılarda ölüm riski:
1.9 kat fazla

- *Clin Surv Study Group:* 14 000 hasta
  Diskordan yanıtlılarda yeni AİDS ile ilgili olay görülme riski 3 kat fazla

Incidence of new AIDS-defining events in patients with immuno-virological discordance and complete and sustained viral suppression.



Zoufaly A et al. J Infect Dis. 2011;203:364-371

The Journal of Infectious Diseases

Diskordan yanıt (yetersiz CD_4 yanıtı): Ne yapmalı?

- Mevcut rejimin devamı öneriliyor
- Rejimi değiştirmek veya güçlendirmenin etkisi olmamış
- İnsan rekombinan growth hormon vermenin yararını gösteren bir çalışma var
- İmmün modilatör kullanılması önerilmiyor