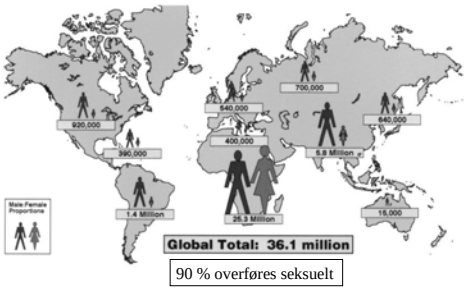
# HIV / AIDS
- infeksjon
- behandling

## HIV / AIDS

- 1981 – første gang anerkjent som distinkt sykdom
- Opprinnelig overført fra sjimpanse
- Viruset kan ha sirkulert fra 1915-1941
- Trolig sirkulert blant populasjoner i Vest-Afrika – klinisk udetektert

- Totalt: over 50 mill HIV-infisert i live
- Mer enn 20 mill allerede døde av AIDS
- 2001: 5 mill individer ble HIV infisert, 3 mill dødsfall

## Global distribuering av HIV-infiserte individer (2000)




90 % overføres seksuelt

## Ekspanderende epidemi

- 40 mill med HIV-infeksjon
- 1/3 av HIV-infiserte: 15-25
- Flere land fra sørlige Afrika
  - 20-30 % i alderen 20-49
  - Botswana: 36 % (!!) av voksne infisert
  - 2000: 20-30% av alle barn under 15 år er blitt foreldreløse i ni land i sørlige Afrika

- *Globalt ekspanderer epidemien fortsatt*
- *Framtidig dramatisk økning dersom ikke effektiv behandling utvikles*

## Global fordeling av HIV subtyper


Tre genetiske hovedgrupper:
- **M** (major = viktigst): **subtype A-J**
- N (new) = sjelden
- O (outlier) = sjelden

Subtype B dominerer i USA og Vest-Europa

Subtypene C og A er vanligst i verden – særlig i Afrika og Asia

Spredning av de ulike subtypene – trolig bestemt av *befolkningsgruppenes genetiske* disposisjoner så vel som *virus egenskaper*

## HIV -AIDS

- HIV-infeksjon forårsaker ikke AIDS straks
- Over tid utvikler de fleste sykdom

*Sentralt:*

- *vekst av virus i CD4+ celler*
- *påfølgende immunrespons*

## Infeksjonsforløp

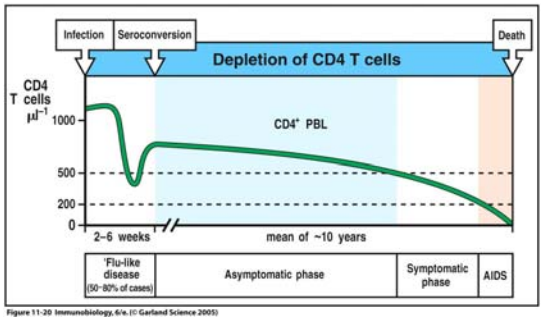


Figure 11-20 Immunobiology, 6/e. (© Garland Science 2005)

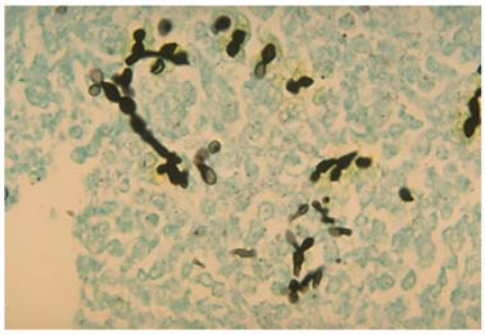
## AIDS definisjon

- 1) Teste positiv for HIV eller HIV antistoff
- 2) Drastisk reduserte mengder CD4+ T-hjelperceller

*eller*

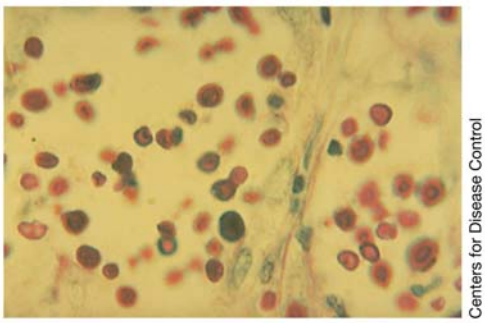
- 3) En eller flere opportunistiske infeksjoner eller atypiske cancere

Pathogens associated with AIDS: Candida infection



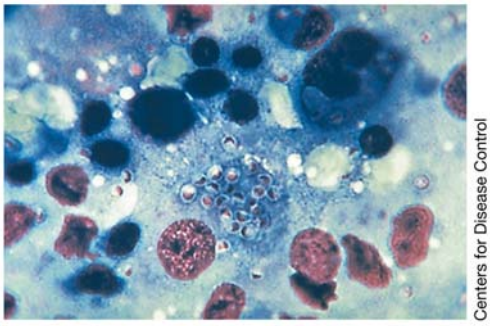
(a)

Pathogens associated with AIDS: Cryptococchus in liver



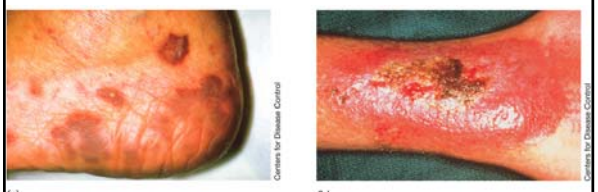
(b)

Pathogens associated with AIDS: Cryptospotidium in intestine

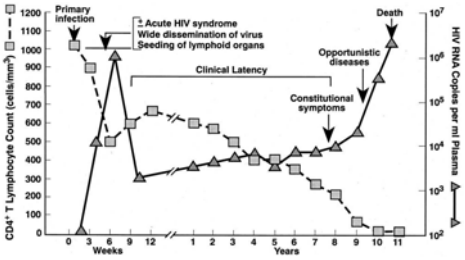


(c)

Cancer associated with AIDS: Kaposi's sarcom


(a) (b)

| Infection | Primary prophylaxis | Secondary prophylaxis |
|---|---|---|
| *Pneumocystis carinii* pneumonia | CD4 cell count > 200 cells per μL for ≥3 months (AI*) | CD4 cell count >200 cells per μL and ≥ 3 months on antiretroviral therapy (BII*) |
| Toxoplasmosis | CD4 cell count > 200 cells per μL for ≥3 months (AI*) | CD4 cell count >200 cells per μL sustained for ≥6 months on antiretroviral therapy plus completed toxoplasmosis therapy and asymptomatic for toxoplasmosis (CII*) |
| *Mycobacterium avium intracellulare* (MAC) | CD4 cell count > 100 cells per μL and ≥3 months on antiretroviral therapy | CD4 cells count 100 cells per μL sustained for ≥6 months on antiretroviral therapy plus completed 12 months of MAC therapy and asymptomatic for MAC (CII*) |
| Cryptococcosis | Not applicable | CD4 cell count >100–200 cells per μL and sustained for ≥6 months on antiretroviral therapy plus completed initial therapy and asymptomatic for cryptococcosis (CII*) |
| Cytomegalovirus retinitis | Not applicable | CD4 cell count >100–150 cells per μL and >6 months on antiretroviral therapy. No evidence for active disease (BII*) |
| Histoplasmosis | Not applicable | No recommendation for stopping prophylaxis |




# HIV / AIDS - risikofaktorer

- Individets genetiske bakgrunn
- Størrelsen og inokulatets infeksiøsitet
- Det lokale miljø der eksponering foregår

# Smitte

- Initiell smitte: overføring av kroppsvæske fra infiserte individer
- Virus bæres i infiserte CD4+
  - T-celler
  - Dendrittiske celler
  - Makrofager
- Fritt virus i
  - Blod
  - Sæd
  - Vaginal væske
  - Morsmelk

# HIV struktur

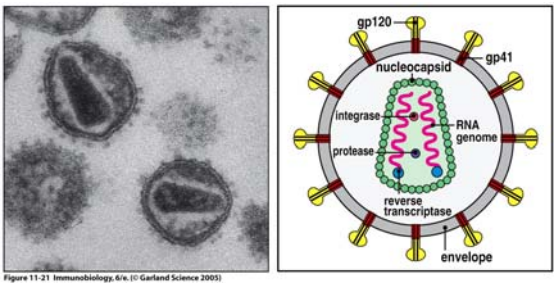
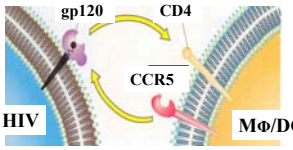



Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

# HIV- reseptorbinding

- Makrofager (CD4+/CCR5+)
- Dendrittiske celler (CD4+/CCR5+)
- T-hjelperceller (CD4+/CXCR4+)




*HIV: infiserer først makrofager/dendrittiske celler:*

**1) MΦ / DC** (APC: lavt **CD4**-uttrykk)

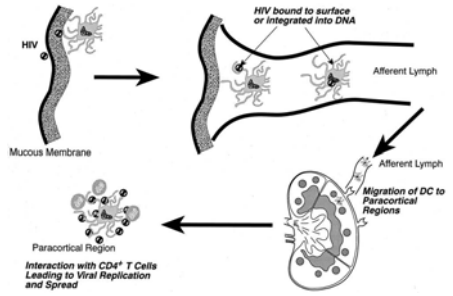
↓ ***gp120 – CD4** binding*

**2) MΦ / DC (CCR5+**; kjemokin-R)

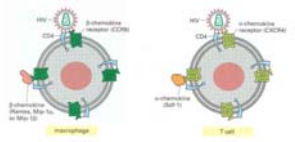
↓ ***CCR5 - CD4** binding*

*Individer som uttykker en variant av CCR5 binder ikke HIV – får ikke AIDS!*

## DC: initiell rolle ved HIV




## HIV reseptorer og ko-reseptorer



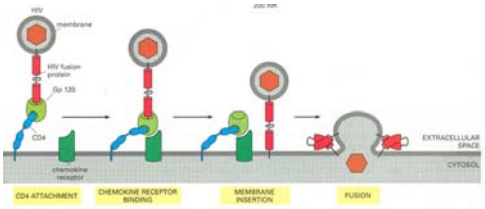
Alle HIV-stammer krever **CD4** som **primær reseptor**

**Tidlig** i infeksjon benytter de fleste virusene **CCR5** som en ko-reseptor – dette tillater at de kan infisere **makrofager** /**dendrittiske celler**

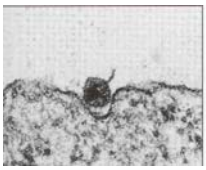
Ettersom infeksjonen fortsetter oppstår *mutante varianter* som benytter **CXCR4** som en ko-reseptor – tillater at de effektivt kan infisere **T-celler**

Invasjon av den ene eller andre ligand kan effektivt blokkeres med naturlig ligand for kjemokin reseptorer (*Sdf-1* for *CXCR4*, *Rantes, Mip-1α* eller *Mip-1β* for *CCR5*)

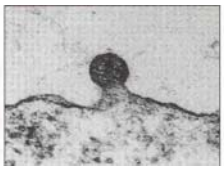
## HIV entry




## HIV entry

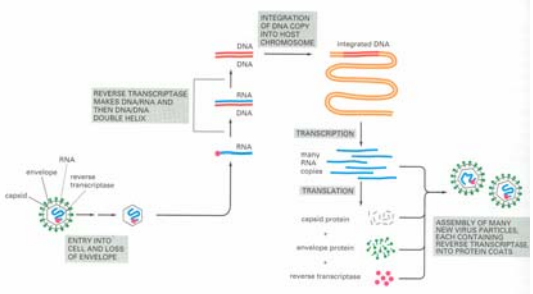


Virus fester seg til cellereseptorer



Virusmembran og cellemembran fuserer

## Retrovirus - livssyklus




## HIV-1 replikasjonssyklus

**1)** Virusinteraksjon med CD4 og kjemokin-R

**2)** Virus entry, fusjon (pH avhengig)

**3)** Delvis uncoating

**4)** RT skjer i virus – mens den er i cytoplasma (medbragt enzym)

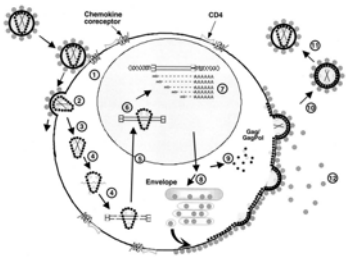
**5)** dsDNA transporteres inn i kjernen

**6)** Integrering i vertsgenom via viruskodede integraser (åpne sirkler) - del av subviral preintregrasjonskompleks

**7)** Integrert viral DNA tjener som template for DNA-avhengig RNA polymerase (Pol II): prod. av mRNA som translateres til virale proteiner i cytoplasma

**8)** Env og

**9)** Gag plus Gag/Pol polyproteiner transporteres via uavhengige ruter plasmamembran, der avkom viruspartikler knoppskytes fra cellene



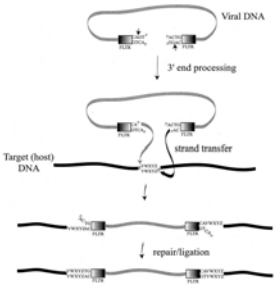

**10)** og frigjøres som umodne viruspartikler

**11)** Påfølgende proteolyse av virion-kodete proteaser danner modne partikler – inneholder en karakteristisk kondensert kjerne

**12)** Ikke-virion-assosiert gp 120 kappe (envelope) protein frigjøres også fra celler

# Integreringsprosessen

Som alle retrovirus har virusgenomet endesekvenser kalt **long terminal repeats (LTR)**, som er involvert i viral integrering i vertsgenomet




# HIV-infeksjon av CD4+ celler

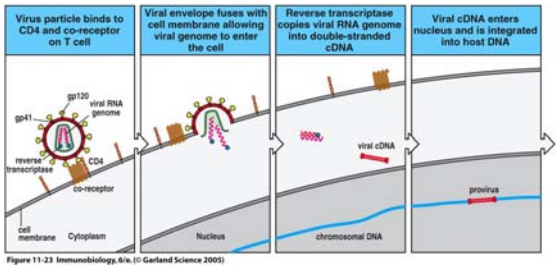



Figure 11-23 Immunobiology, 6/e. (© Garland Science 2005)

# HIV-infeksjon av CD4+ celler

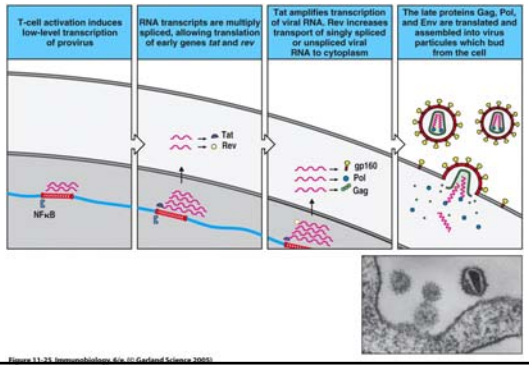
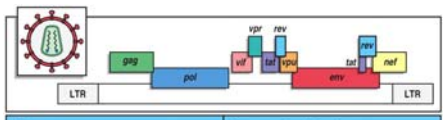



Figure 11-25 Immunobiology, 6/e. (© Garland Science 2005)




**HIV:**

**Gener og gen-produkter**

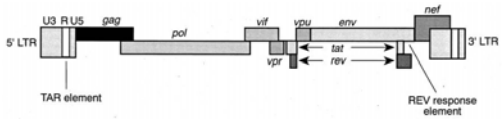
| Gene | Gene product/function |
|---|---|
| *gag* Group-specific antigen | Core proteins and matrix proteins |
| *pol* Polymerase | Reverse transcriptase, protease, and integrase enzymes |
| *env* Envelope | Transmembrane glycoproteins. gp120 binds CD4 and CCR5; gp41 is required for virus fusion and internalization |
| *tat* Transactivator | Positive regulator of transcription |
| *rev* Regulator of viral expression | Allows export of unspliced and partly spliced transcripts from nucleus |
| *vif* Viral infectivity | Affects particle infectivity |
| *vpr* Viral protein R | Transport of DNA to nucleus. Augments virion production. Cell cycle arrest |
| *vpu* Viral protein U | Promotes intracellular degradation of CD4 and enhances release of virus from cell membrane |
| *nef* Negative-regulation factor | Augments viral replication *in vivo* and *in vitro*. Decreases CD4, MHC class I and II expression |

Figure 11-24 Immunobiology, 6/e. (© Garland Science 2005)

Som alle retrovirus har de LTR som er involvert i viral integrering og i regulering av viralt genom

Genomet kan leses i 3 rammer – og flere av de virale genene har overlappende leserammer - tillater

# HIV – genomisk organisering




Som alle retrovirus har de LTR som er involvert i viral integrering og i regulering av viralt genom

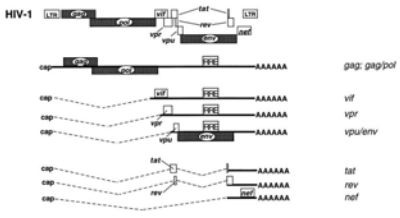
Genomet kan leses i 3 rammer – og flere av de virale genene har overlappende leserammer – tillater

De tre hovedprotein produktene Gag, Pol og Env er tilstede i modne viruspartikler sammen med viralt RNA

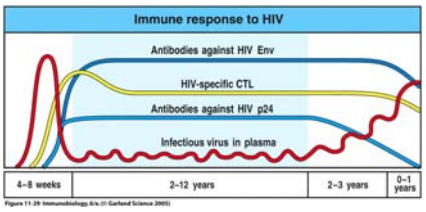
mRNA for Tat, Rev og Nef (regulatoriske proteiner) produseres ved spleising av virale transkripter

De andre genproduktene affiserer virusinfektivitet på ulike måter som ikke er helt forstått enda

# HIV - spleising

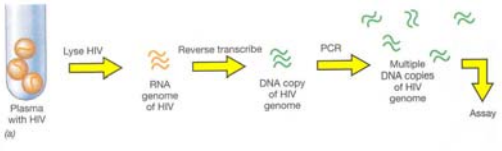


## HIV og immunrespons



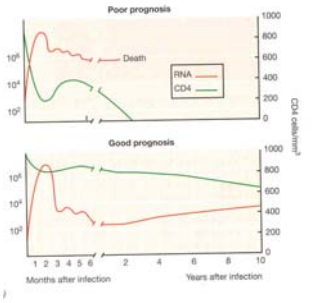

- Infeksiøse virus er tilstede i relativt lave nivåer i perifert blod i løpet av en forlenget, asymptomatisk fase, der virus replikerer persistent i lymfoid vev
- I løpet av denne perioden synker CD4 T-celle tallene gradvis, sel med høye nivåer av CD8+-celler og Ab
- Tilslutt faller også nivåene av disse, og det er en kraftig økning av infeksiøse HIV i perifert blod

## Måling av HIV-mengde




- RT-PCR
- HIV-kopier sammenliknes kvantitativt med DNA-kopier fra kontroll templat som amplifiseres i samme prøve
- HIV-mengde uttrykkes som antall HIV-kopier / ml pasientplasma

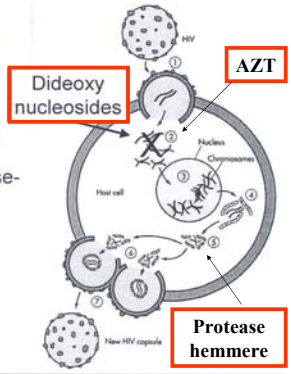
## Tidsforløp av HIV-infeksjon



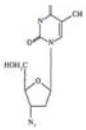

- Infeksjonens progresjon beregnet ut i fra virusmengde ved ulike tidspunkter etter infeksjon
- CD4+ celler målt ved væskestrømscytometri (Flow)
- *Øverst*: virusmengde over $10^4$ kopier / ml korrelerer med unormalt lavt CD4+ celle antall, indikerer dårlig prognose og tidlig død
- *Nederst*: virusmengde under $10^4$ korrelerer med normalt CD4+ celle antall, indikerer god prognose og forlenget overlevelse

## Replication of HIV

1. Virion binding - CD4, chemokines
2. Reverse transcriptase-RNA to DNA
3. Integration of viral DNA
4. Replication of viral RNA
5. Protease



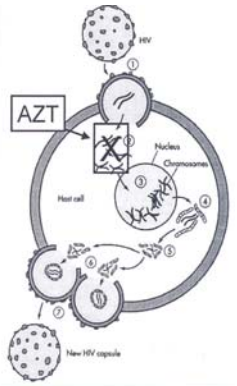

## Zidovudine (Azidothymidine, AZT)



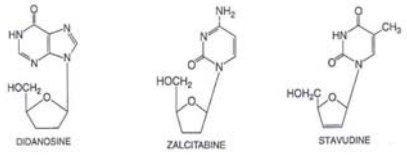
- Triphosphate preferentially inhibits reverse transcriptase
- Clinical efficacy
  - Decreases opportunistic infections
  - Increases survival time
  - Combination therapy is more effective than Zidovudine alone

## Replication of HIV

1. Virion binding - CD4, chemokines
2. Reverse transcriptase-RNA to DNA
3. Integration of viral DNA
4. Replication of viral RNA
5. Protease



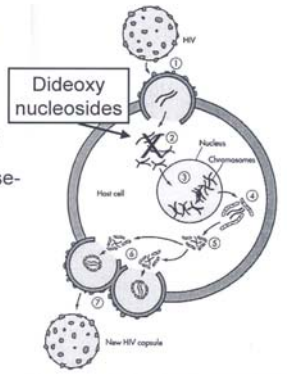
## Dideoxynucleosides



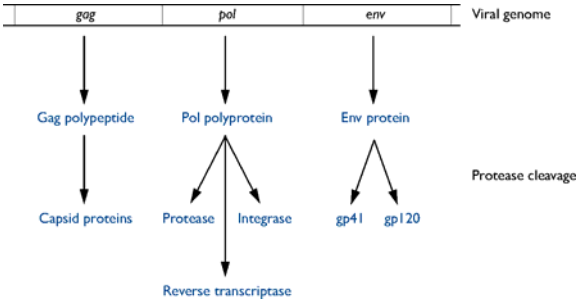

- Metabolized to competitive inhibitors of reverse transcriptase which cause chain termination.
- Useful in treating AZT-resistant HIV
- Combination therapy is standard - combined with AZT and a protease inhibitor

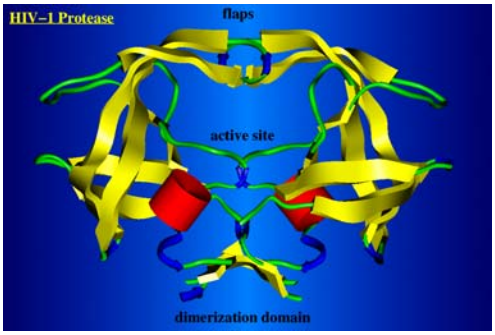
## Replication of HIV

1. Virion binding - CD4, chemokines
2. Reverse transcriptase-RNA to DNA
3. Integration of viral DNA
4. Replication of viral RNA
5. Protease

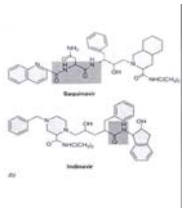



## Kløyving av HIV polyprotein via viral proteaser



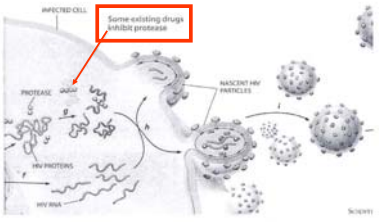




## Proteasehemmere

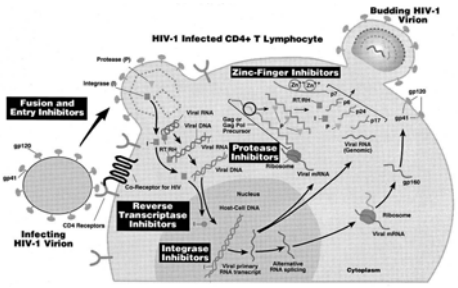


- Blokkerer aspartat protease som bearbeider proteiner nødvendig for HIV replikasjon
- Blokkerer virusmodning
- Brukes i kombinasjonsterapi med AZT

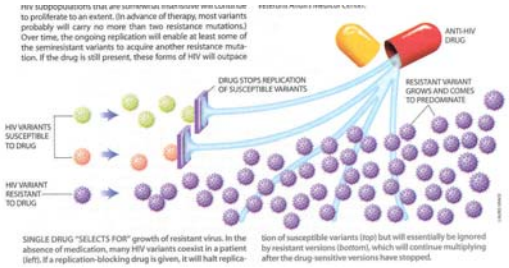
## Protease hemmere



# HIV hemmere - oppsummering




The use of combination therapy increase the efficiency of treatment



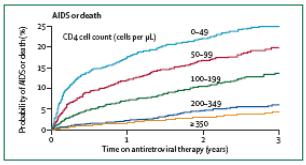




*Figure 1:* Kaplan-Meier plots of the probability of progression to AIDS or death[8]
CD4 cell count at baseline was the strongest prognostic factor for AIDS and death. The group of patients who initiated antiretroviral therapy at or above a CD4 cell count of 350 cells per μL had the lowest risk of progression at all times. In this group, the cumulative risk of progression to AIDS or death at 3 years was below 4% if other risk factors (eg, age) were beneficial as well. The risk increased to 4·7% in patients with CD4 cell counts of 200–349 cells per μL. Patients who started antiretroviral therapy with fewer than 200 cells per μL were at the highest risk of clinical progression. Clinical progression was estimated to increase to 50% in older patients infected through injection-drug use with low CD4 cell counts of less than 50 cells per μL and plasma HIV-1 RNA values of more than 10 000 copies per mL. Reproduced from reference 8 with permission.

Avbrutt behandling

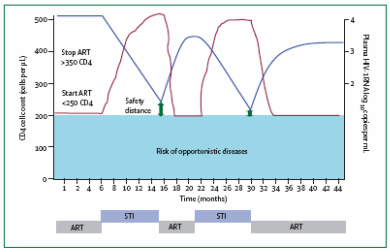
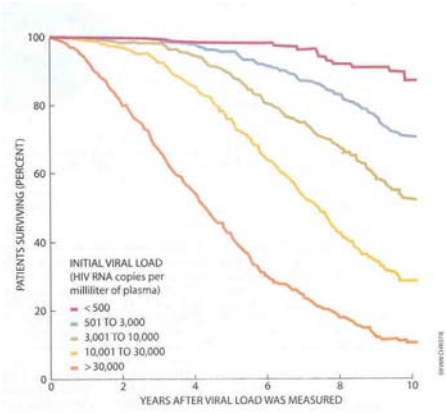
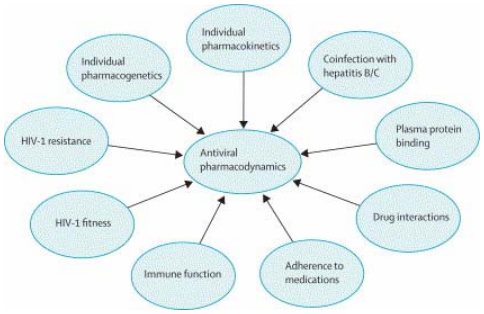



*Figure 4:* Effect of scheduled treatment interruptions on CD4 cell recovery in well-controlled HIV-1 infection
After treatment interruption CD4 cell count (blue line) usually declines. Scheduled treatment interruptions with CD4 guidance takes advantage of CD4 cell thresholds to discontinue (eg, >350 cells per μL) and restart antiretroviral therapy (eg, <250 CD4 per μL). This principle assumes that an HIV-1-infected individual remains at very low risk of opportunistic diseases as long as the CD4 cell count is above a critical threshold. Viral load (red line) mostly increases during antiretroviral therapy interruption. ART=antiretroviral therapy; STI=scheduled treatment interruption.




Faktorer som påvirker HIV-1 protease-inhibitor behandling



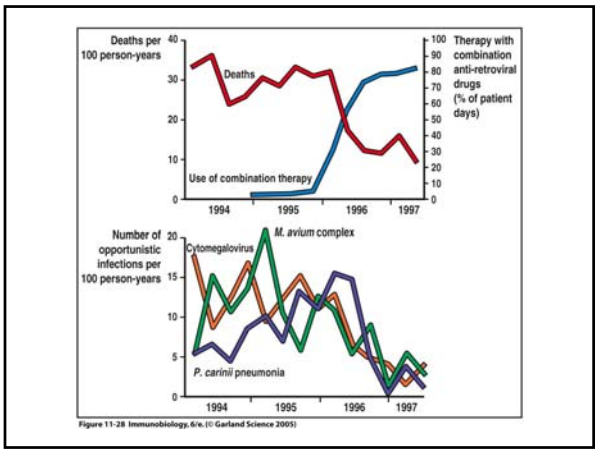


Figure 11-28 Immunobiology, 6/e. (© Garland Science 2005)