TREATMENT
of HIV

The history of HIV infection in the developed world can be divided into 2 eras:

1. **The pre-HAART era** (1981 – 1996)
2. **The HAART era** (since 1996 – so far)

The pre-HAART era

Monotherapy (NRTI)

- results in viral resistance
- should not be used with any available AR drug

Two AR drugs (NRTIs)

- Also result in viral resistance
- Is not recommended

1987

- **the first drug for clinical use**

  NRTI – AZT (later ZDV)

1991-1994

- **next NRTIs (didanosine, zalcitabine, stavudine, lamivudine…)**

Since 1996 the HAART era

- **Has been associated with markedly diminished morbidity and mortality**
- **Three-drug combinations are currently recommended for the initiation of treatment in all patients**

HAART – **H**ighly **A**ctive **A**nti**R**etroviral **T**herapy

cART - **C**ombination **A**nti**R**etroviral **T**herapy

OBT - **O**ptimalising **B**asic **T**reatment

ART - **A**nti**R**etroviral **T**herapy

ART

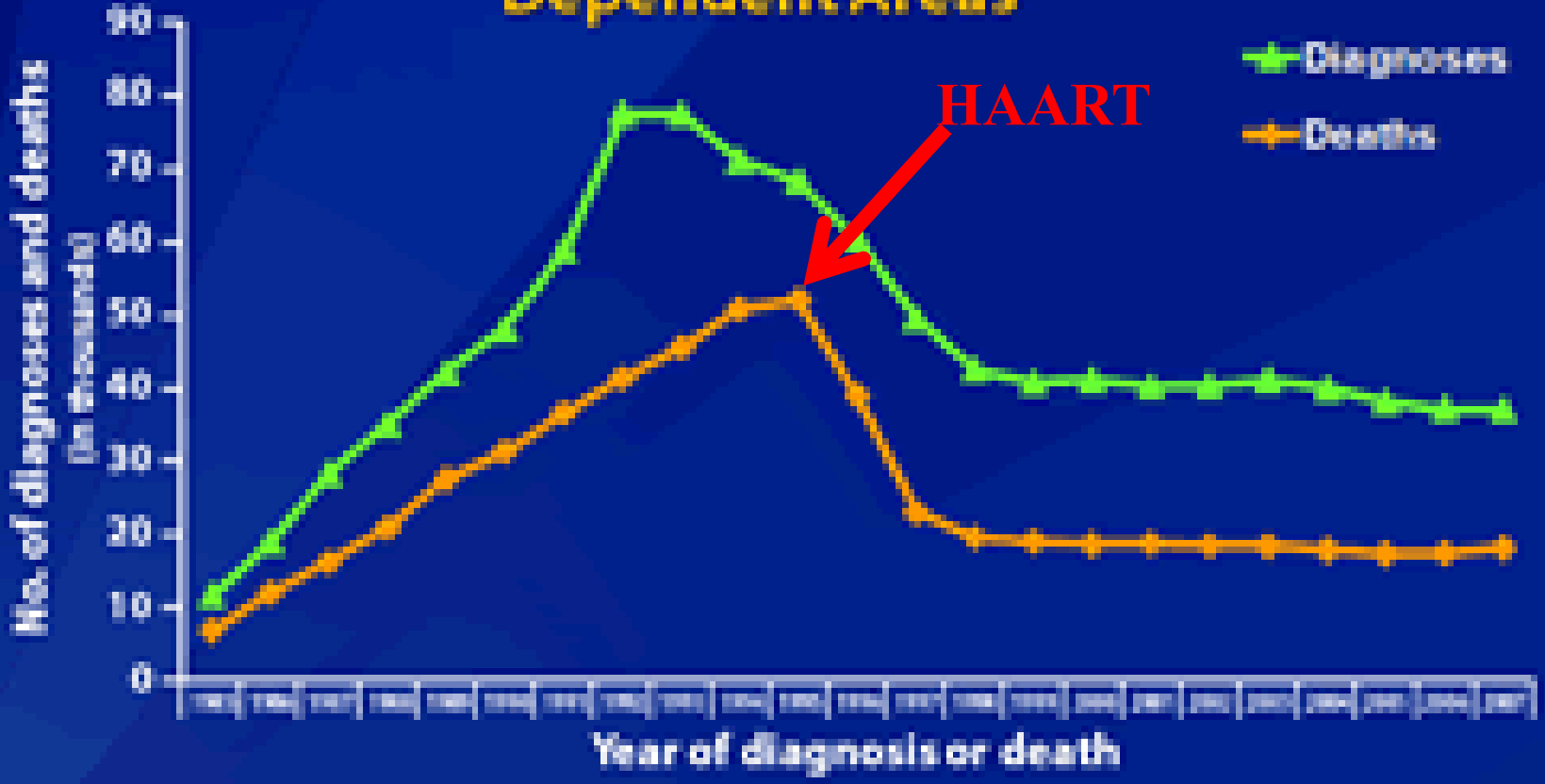
Enormous changes in prognosis of HIV/AIDS disease

- the introduction of triple combination into clinical practice in 1996 represented a significant step forward in the treatment of HIV infection
- the ability of ART regimens has transformed HIV infection into a manageable chronic disease

ART

- Maximally and durable supress VL
- Restores immunological function
- Improves quality of life
- Reduces HIV-related morbidity and mortality

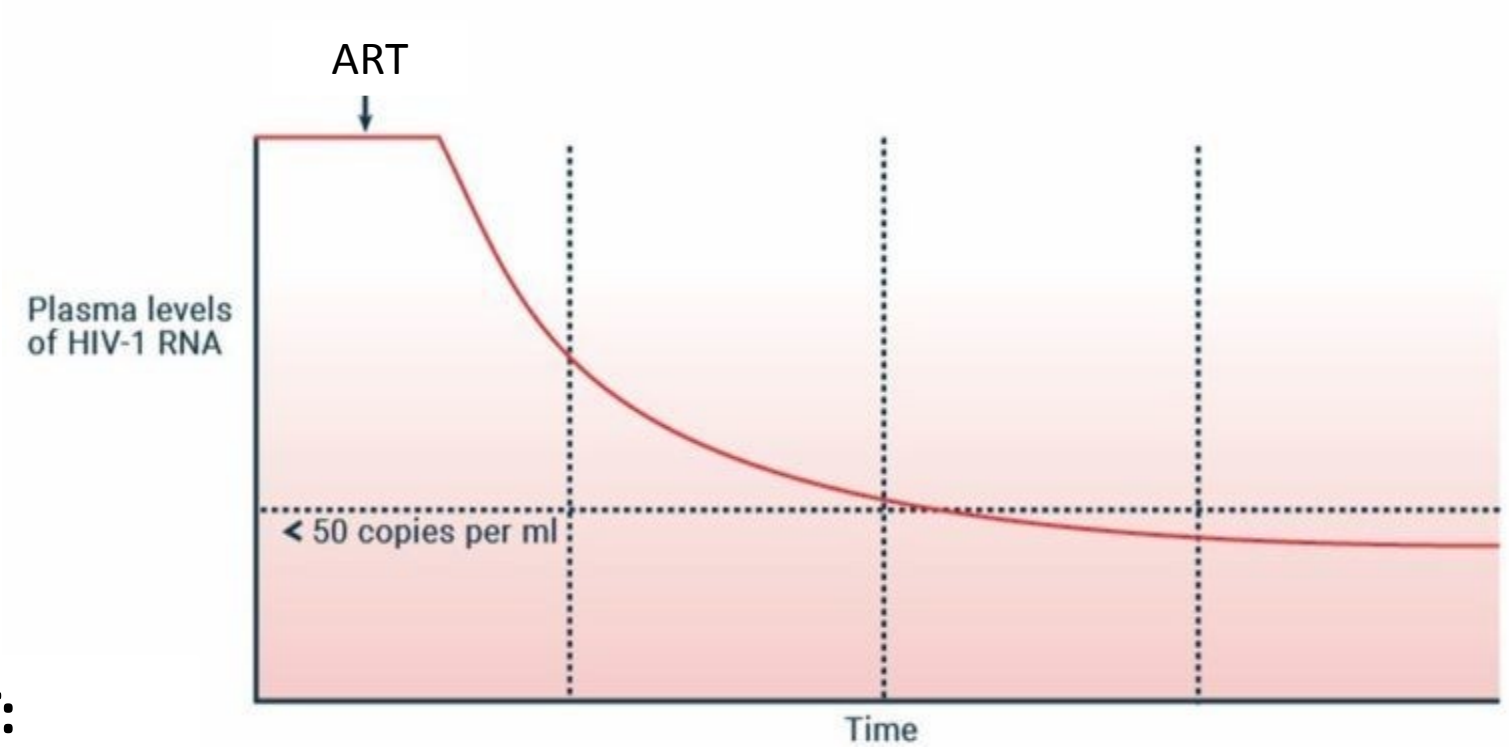
AIDS Diagnoses and Deaths of Adults and Adolescents with AIDS, 1985–2007—United States and Dependent Areas



Note: All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.
Deaths of persons with an AIDS diagnosis may be due to any cause.

Primary goal of ART

↓ morbidity and mortality at all stages of HIV infection



ART:

- Maximal and durable suppression of plasma viremia
  - Restore and preserve immunologic function
  - Preserves or improves CD4 T lymphocyte (CD4) cell numbers
  - Confers substantial clinical benefits
  - Reduce HIV-associated morbidity and mortality

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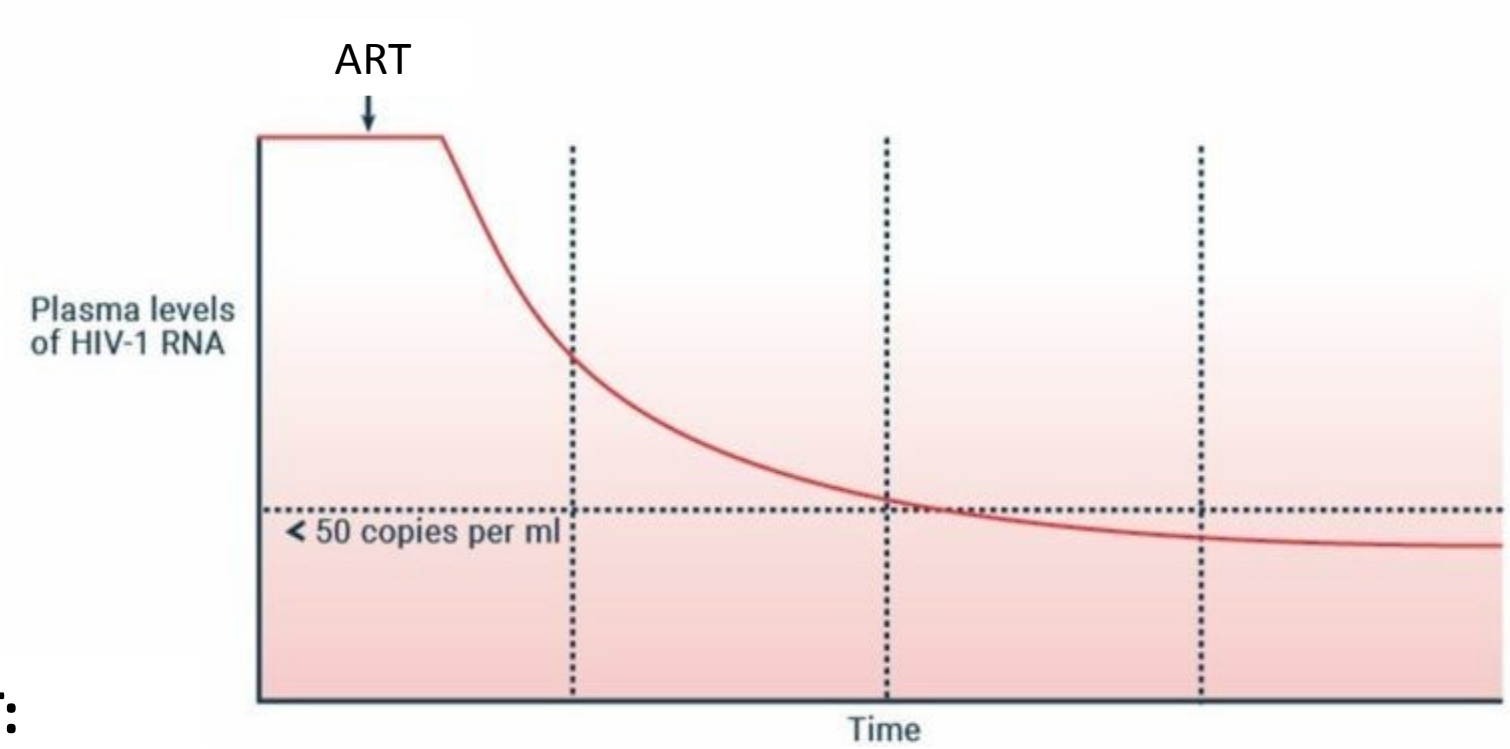
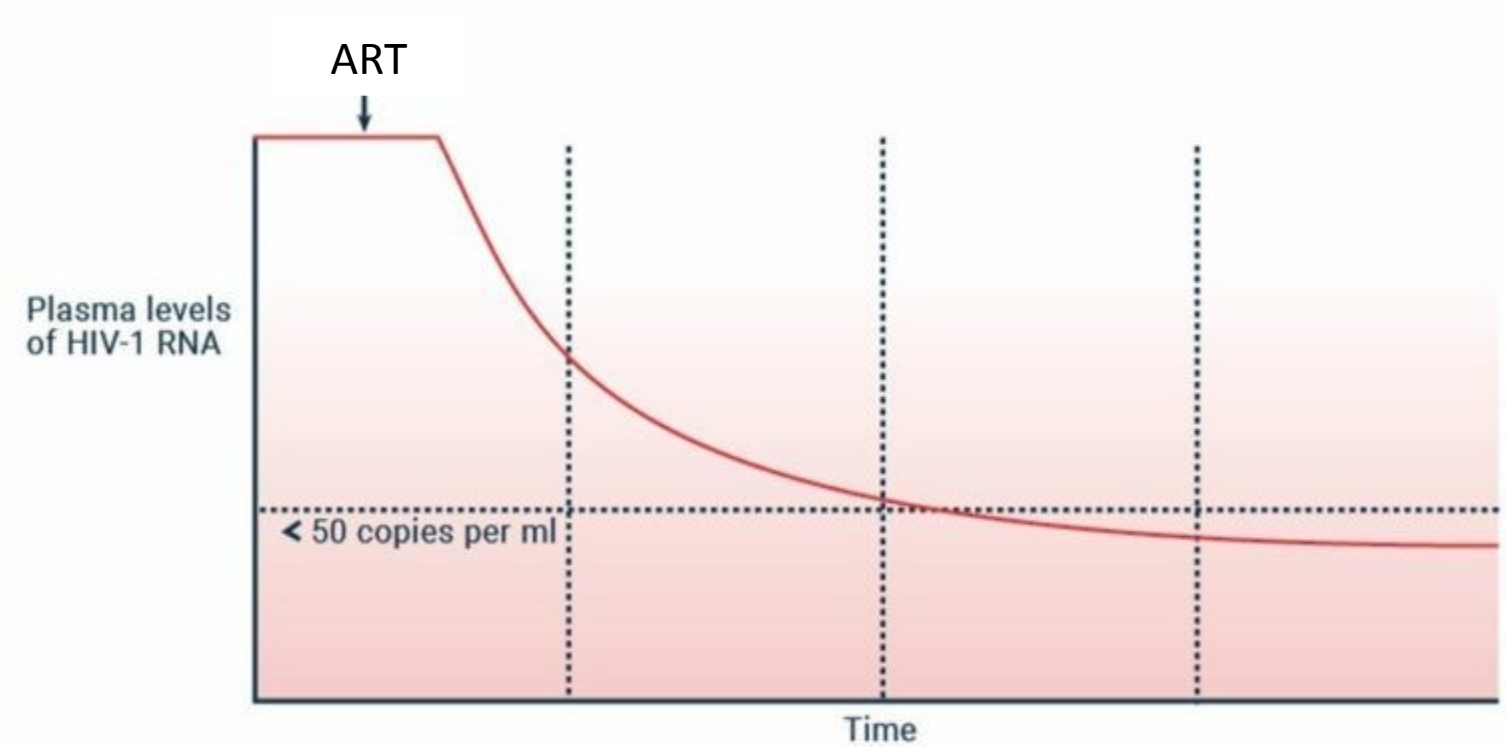


ART:

- Prolong the duration and quality of survival
- Delays or prevents the selection of drug-resistance mutations
- **Decrease inflammation and immune activation** thought to contribute to higher rates of cardiovascular and other end-organ damage reported in cohorts with HIV

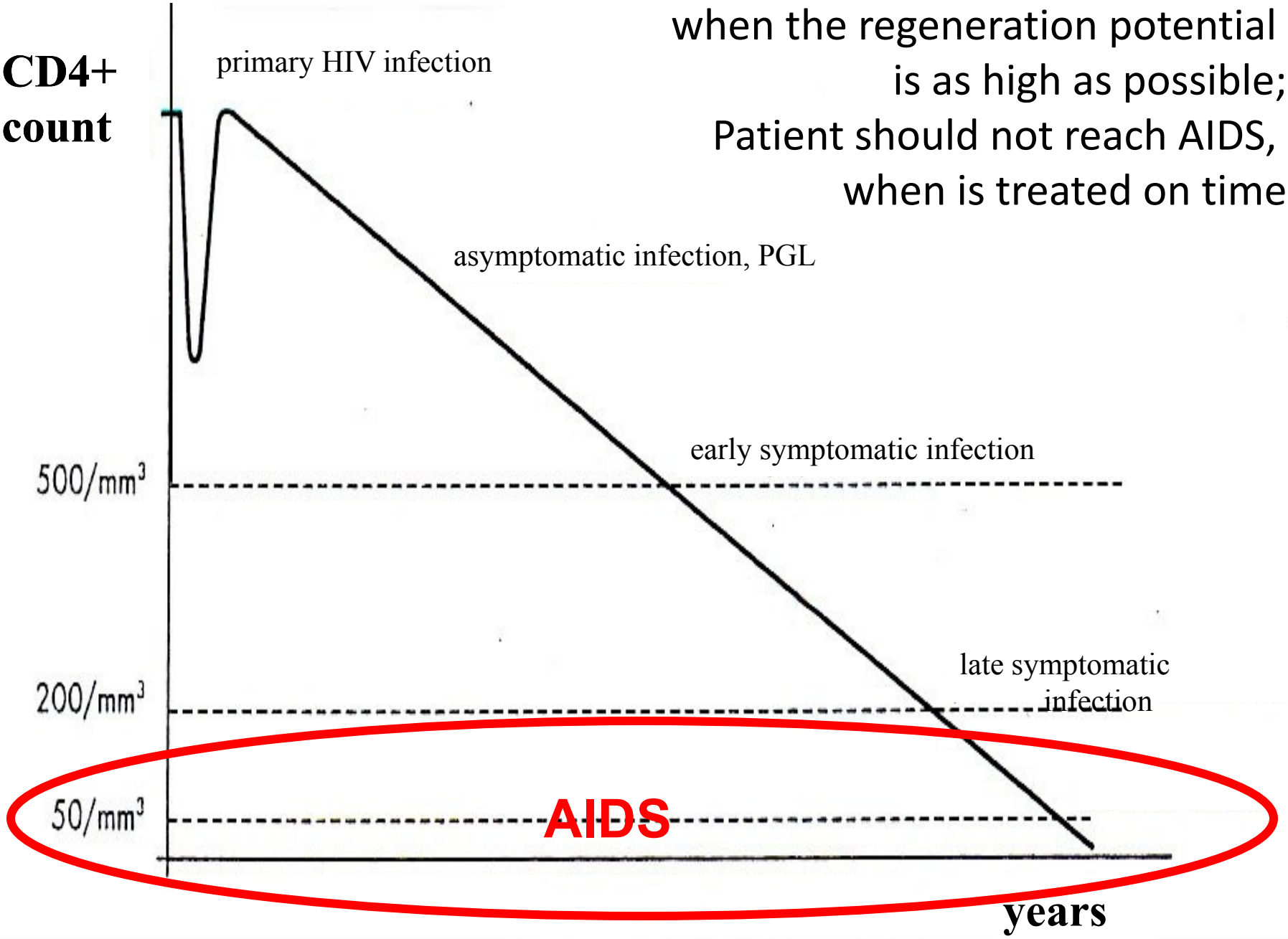
Primary goal of ART

↓ morbidity and mortality at all stages of HIV infection



- ART is recommended for all individuals with HIV,
  regardless of CD4 T lymphocyte cell count
- ART should be initiated **as soon as possible**

ART should be initiated as soon as possible,
when the regeneration potential
is as high as possible;
Patient should not reach AIDS,
when is treated on time



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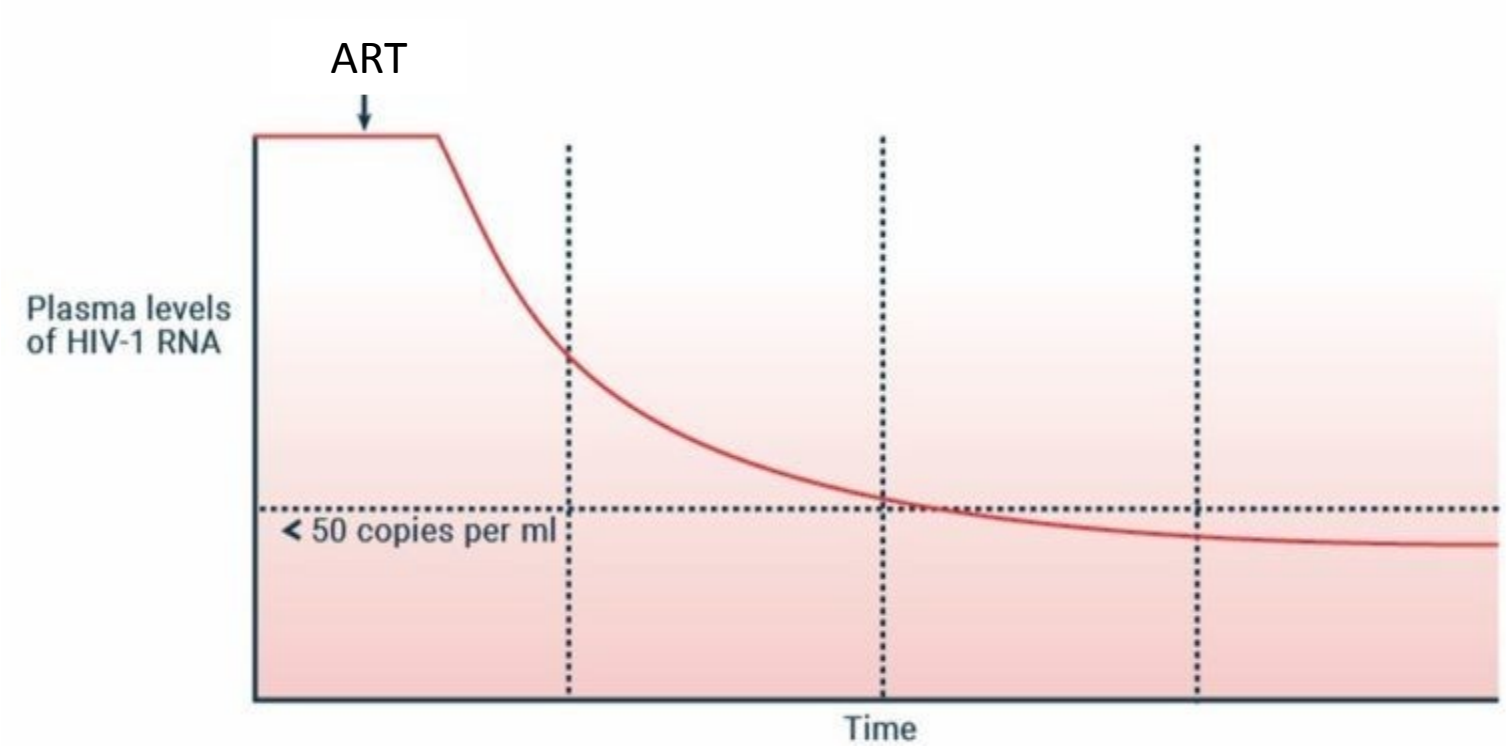
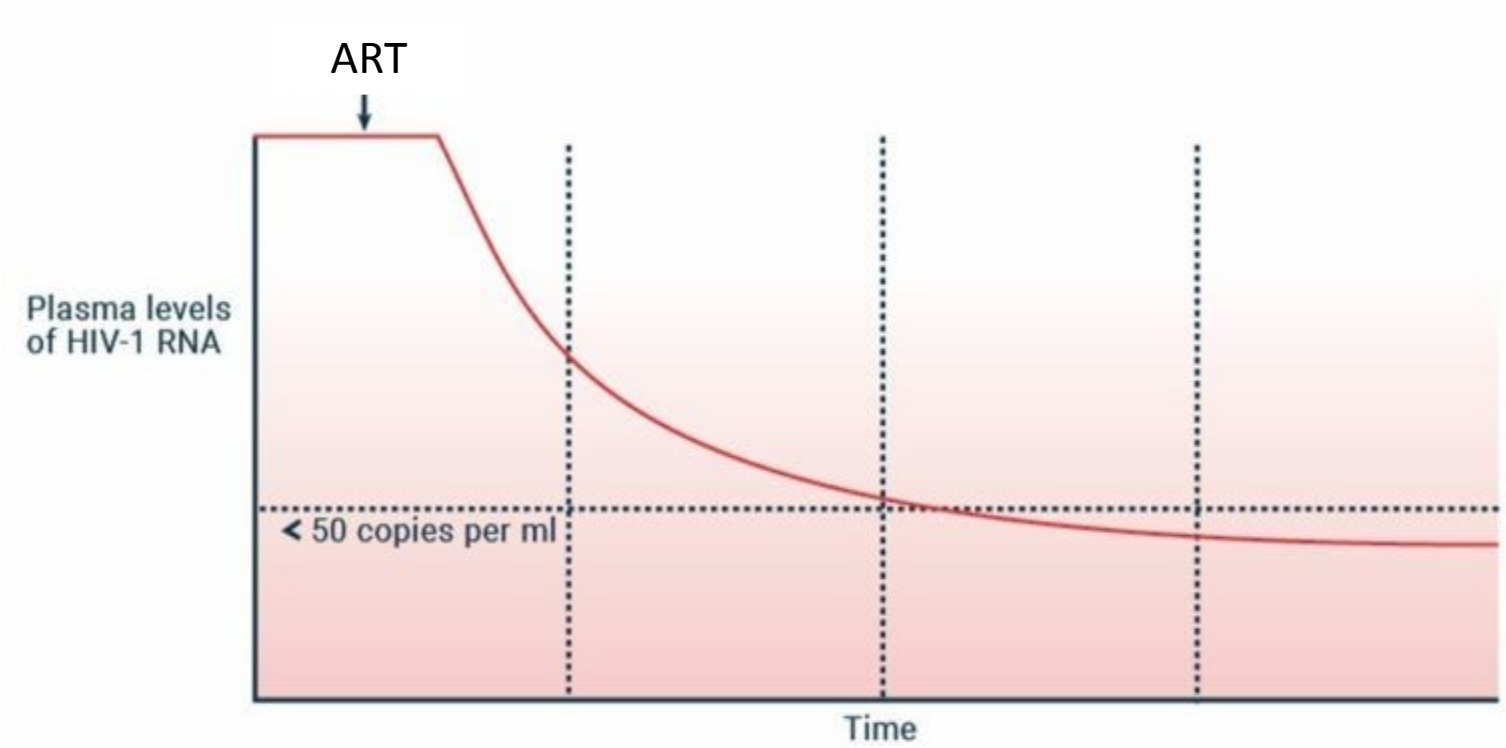


- After initiation of effective ART,
  viral load reduction to below limits of assay detection usually occurs within the first 12 to 24 weeks of therapy.
- The objective of ART should be
  to maintain the lowest viral load for as long as possible

Primary goal of ART

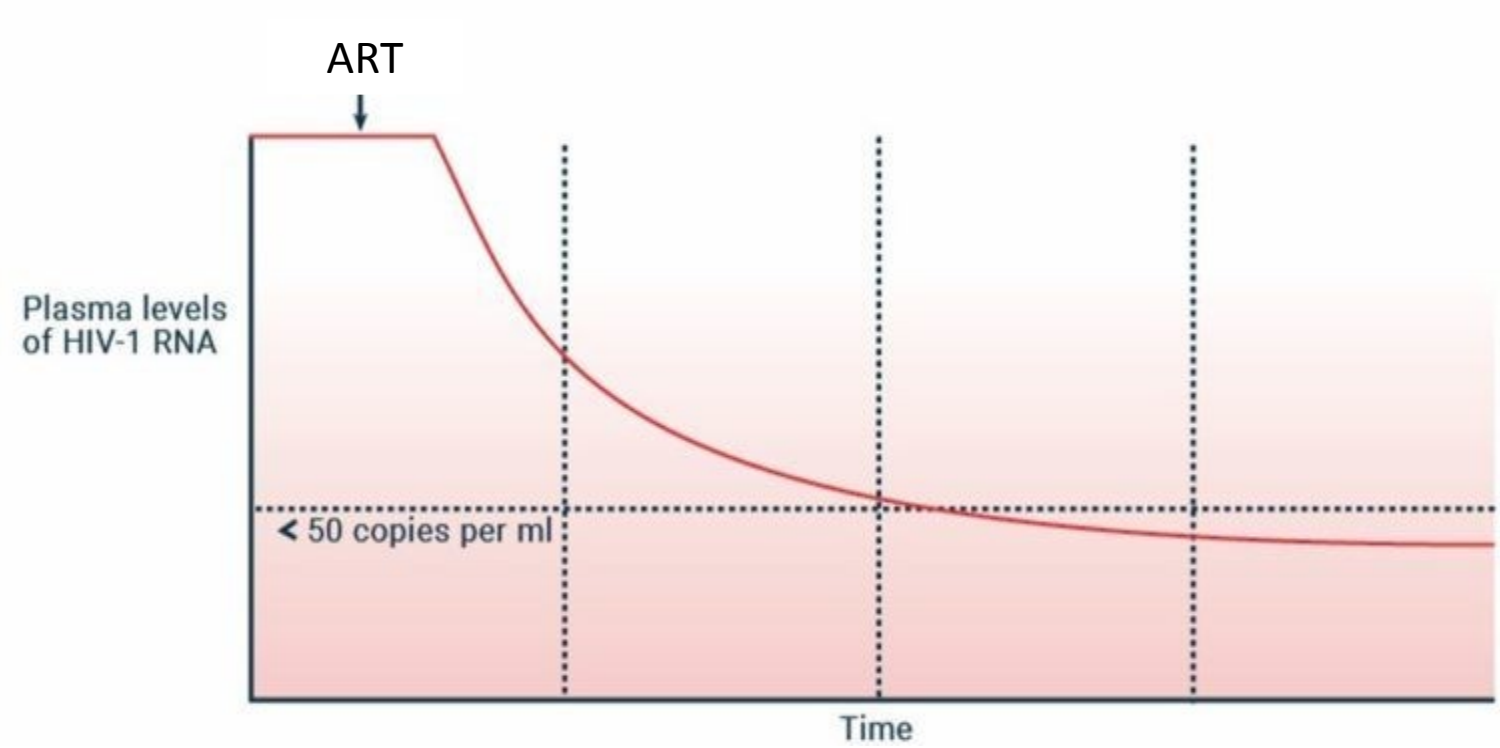
↓ morbidity and mortality at all stages of HIV infection



- Predictors of virologic success include the following:
  - Low baseline viremia;
  - High potency of the ARV regimen; • Tolerability of the regimen;
  - Convenience of the regimen; • **Excellent adherence to the regimen**

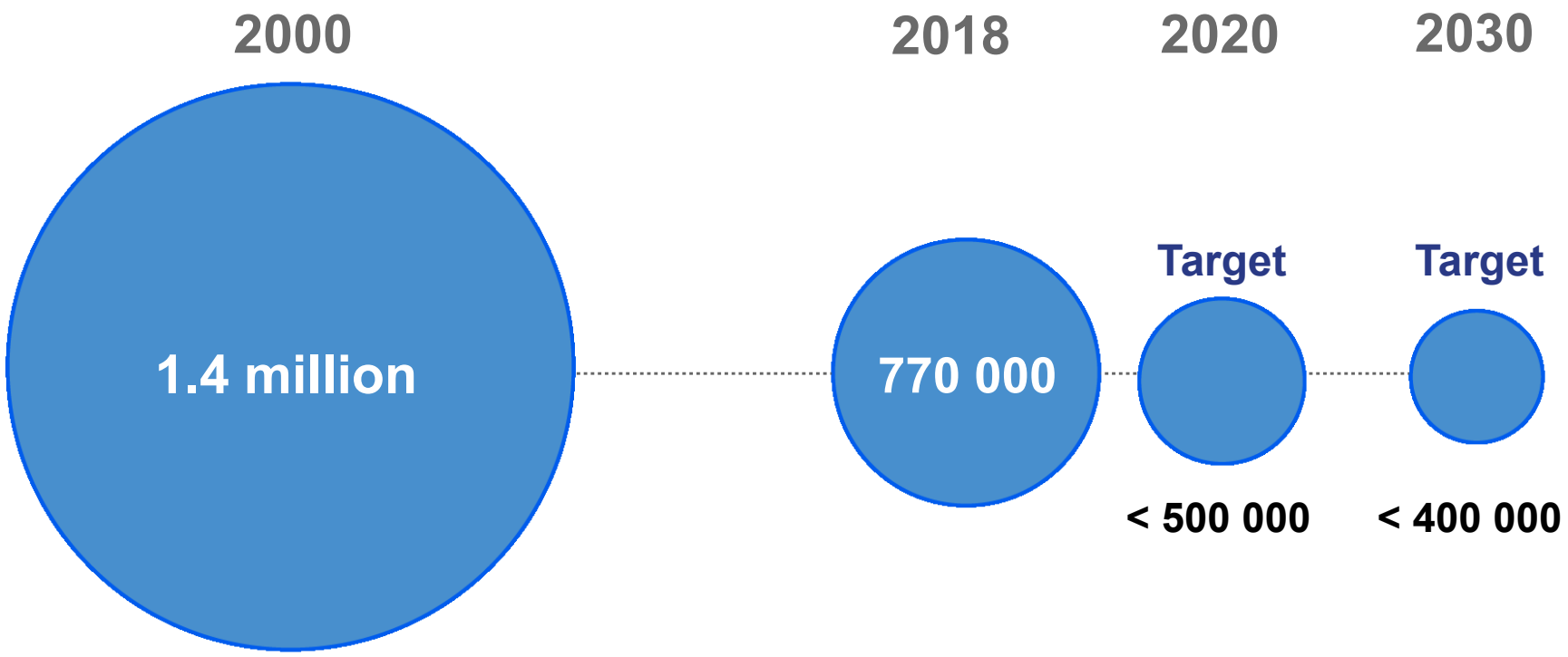
Primary goal of ART

↓ morbidity and mortality at all stages of HIV infection



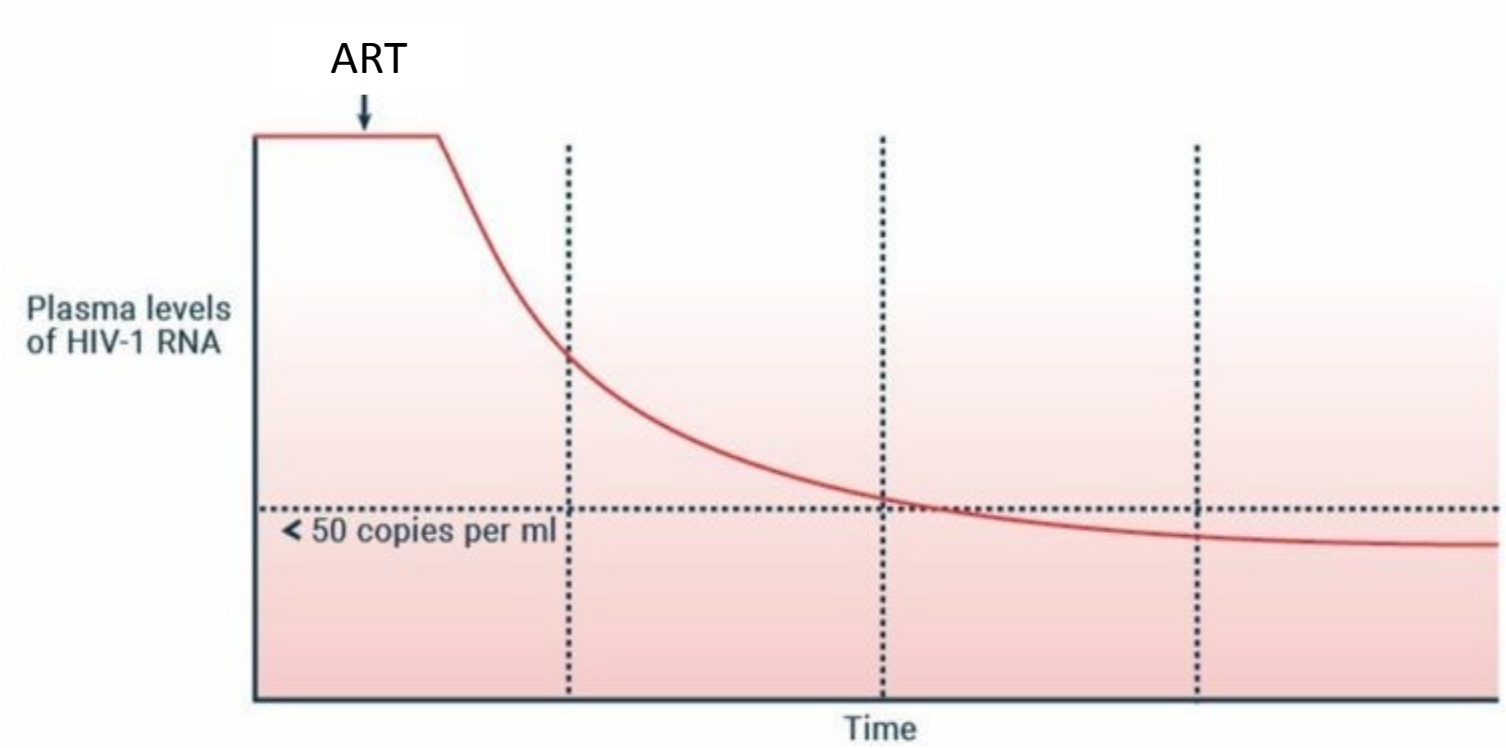
- After initiation, **ART should be continued**
- Treatment interruption has been associated with rebound viremia, worsening of immune function, and increased morbidity and mortality

Global number of HIV-related deaths



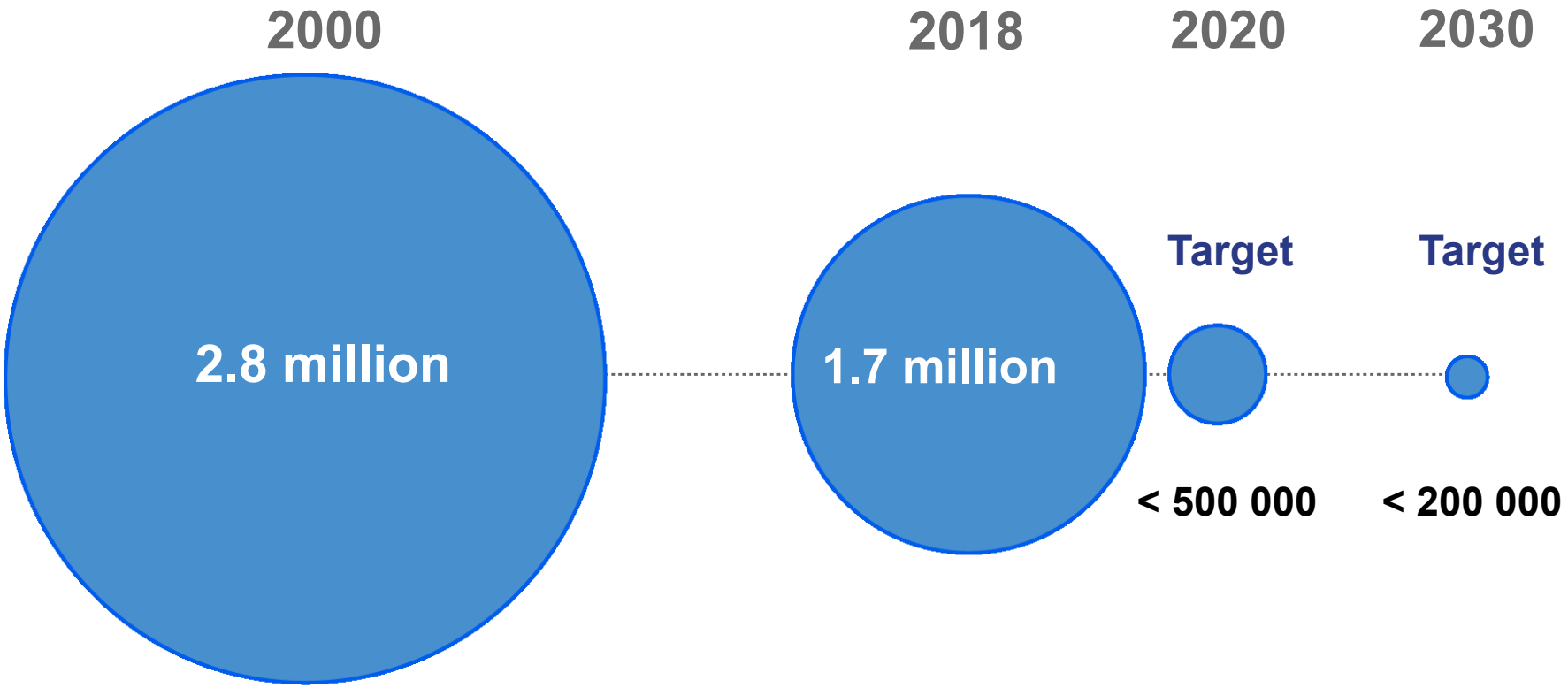
Source: UNAIDS/WHO estimates

Secondary goal of ART
- is to reduce the risk of HIV transmission



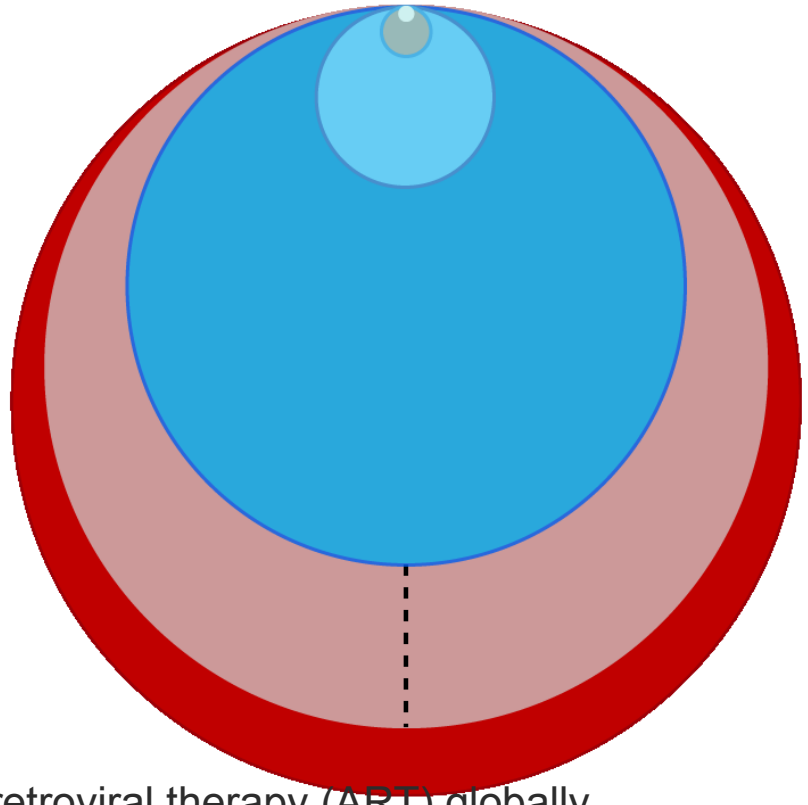
- **High plasma HIV-1 RNA is a major risk factor for HIV transmission**
- When patient is treated
  - And his viral load of HIV is below limit of assay detection in blood by PCR method, transmission of HIV to another subject is improbable

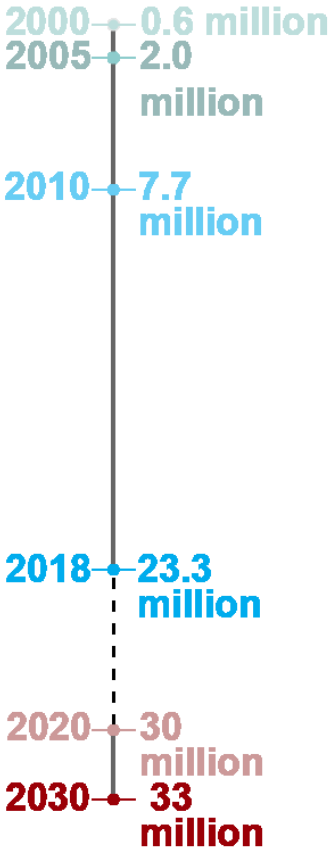
Global number of people newly infected with HIV



Source: UNAIDS/WHO estimates

Global number of people receiving

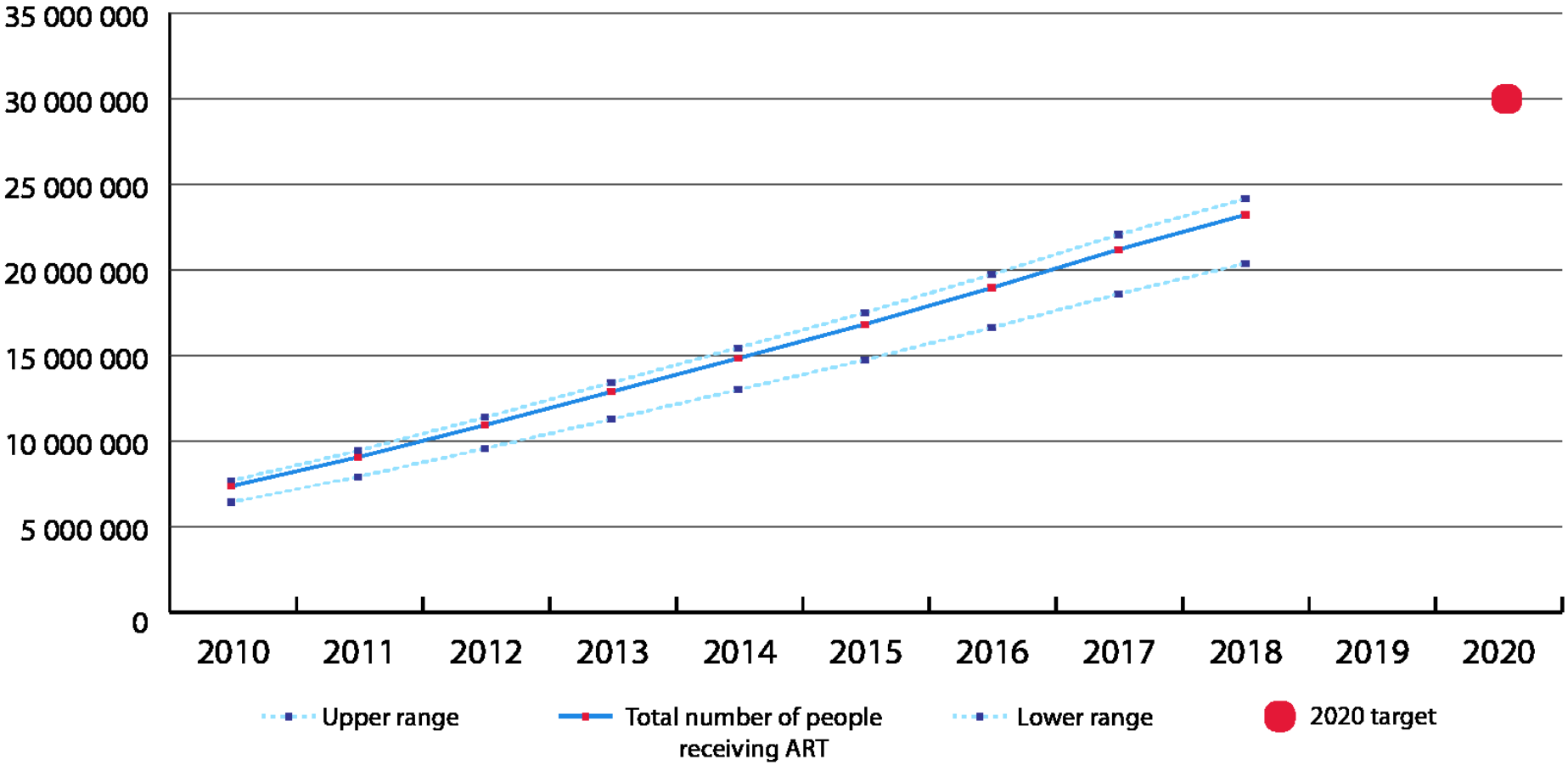




23.3 million people
with HIV (62%)
were accessing antiretroviral therapy (ART) globally,
an increase of 1.6 million since 2017 and up from 8 million in 2010.

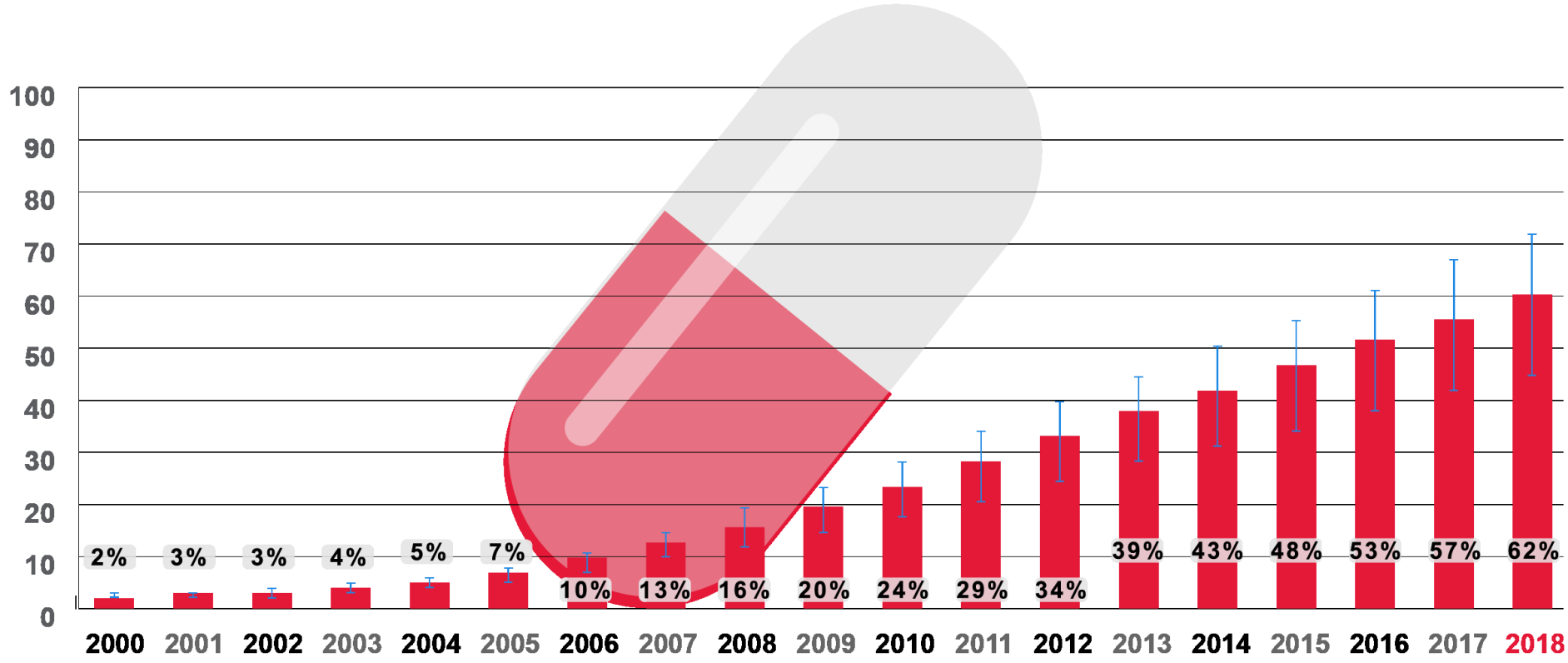
- **HIV treatment access is key to the global effort to end AIDS** as a public health threat.
- People with HIV who are aware of their status**, take ART daily** as prescribed, and get and keep an undetectable viral load can live long, healthy lives and have effectively no risk of sexually transmitting HIV to their HIV-negative partners.

Increase in people receiving ART over time



World Health Organization

Global ART coverage over time



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Secondary goal of ART
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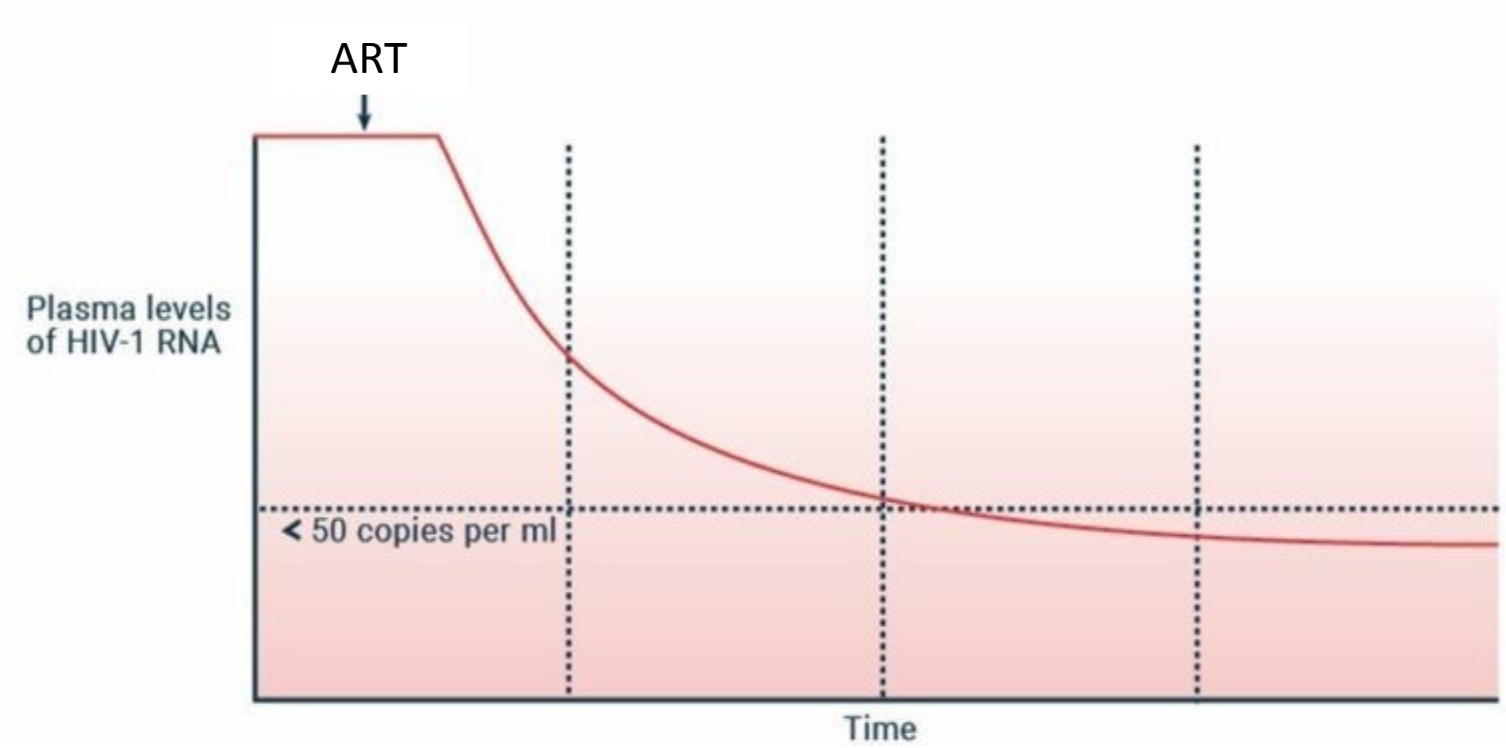

- The objective of ART should be to maintain the lowest viral load for as long as possible
- Eradication of HIV infection cannot be achieved with available antiretrovirals

Triple Combination = standard of care

Advantages:

- Additive or synergistic impact on antiviral activity
- Delay in emerging drug-resistance viruses
- Drugs can reach different cellular and body compartments

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when the regeneration potential
is as high as possible;
Patient should not reach AIDS,
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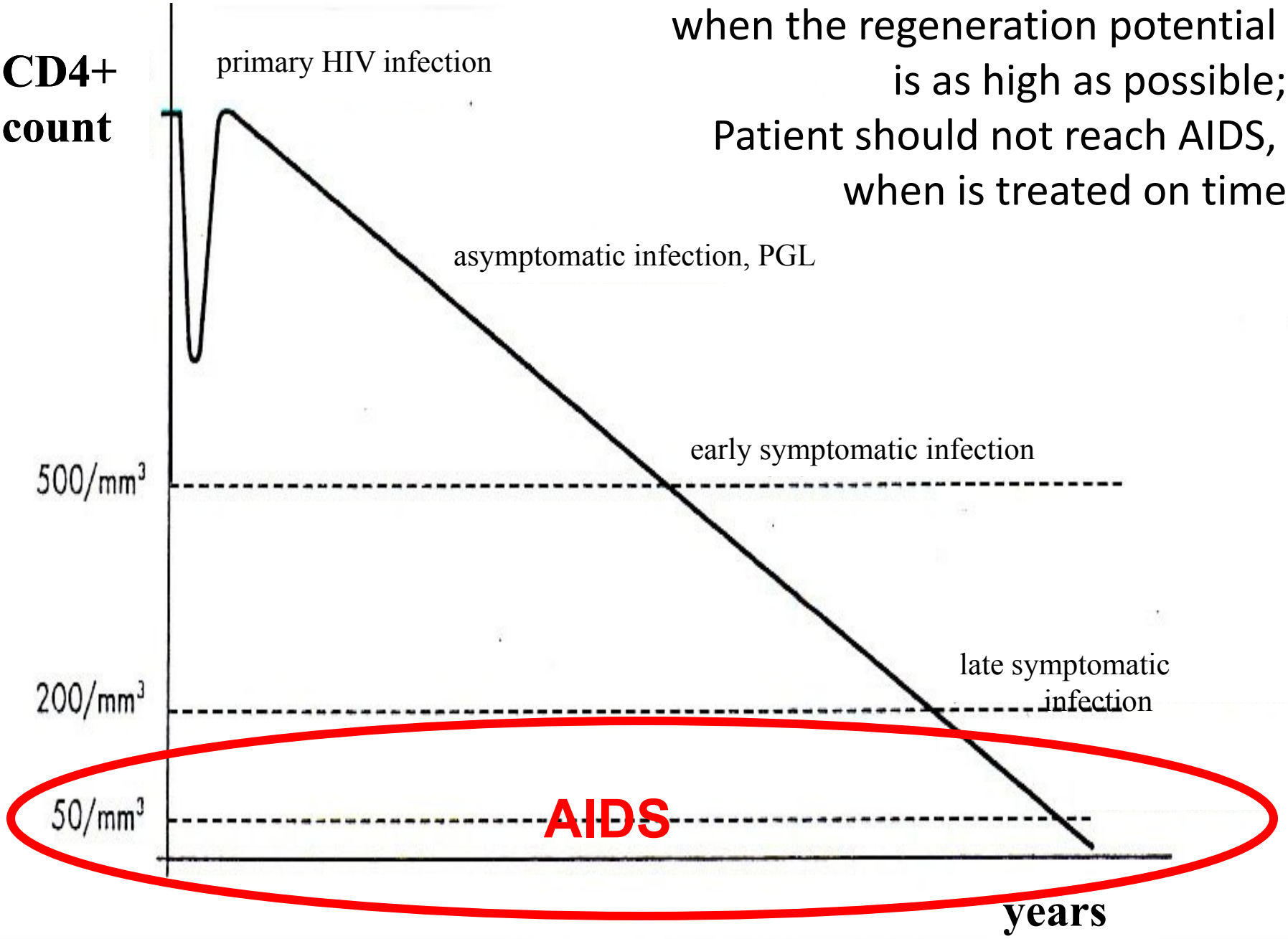

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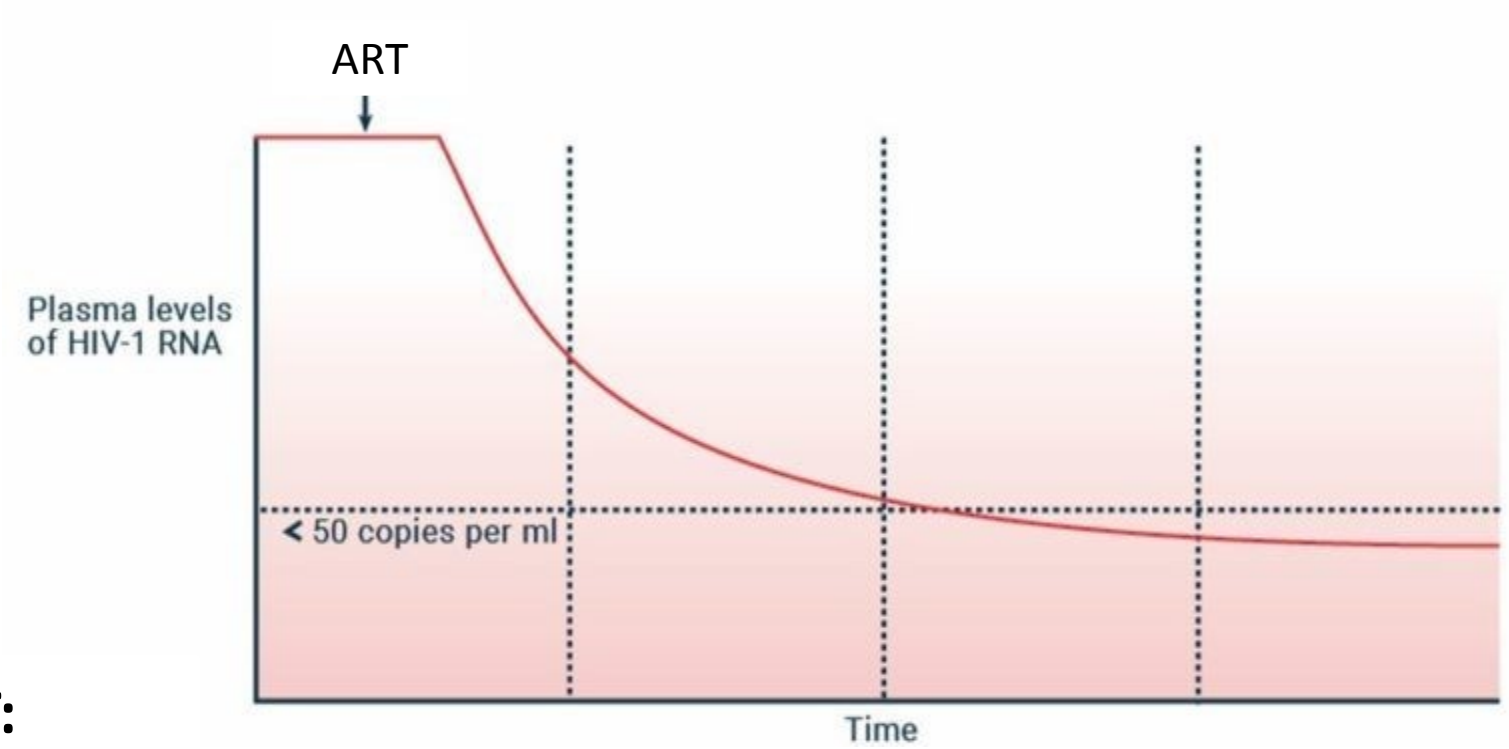

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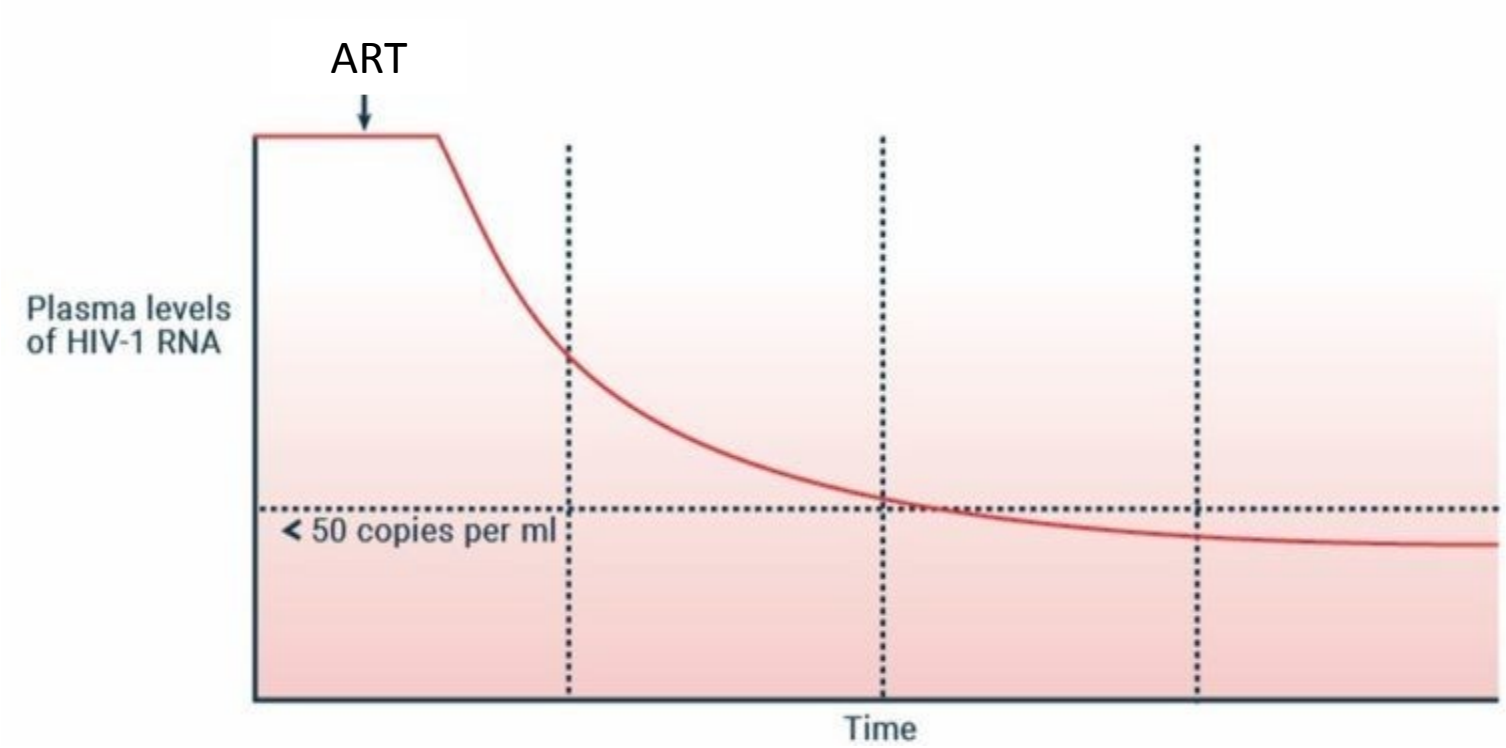

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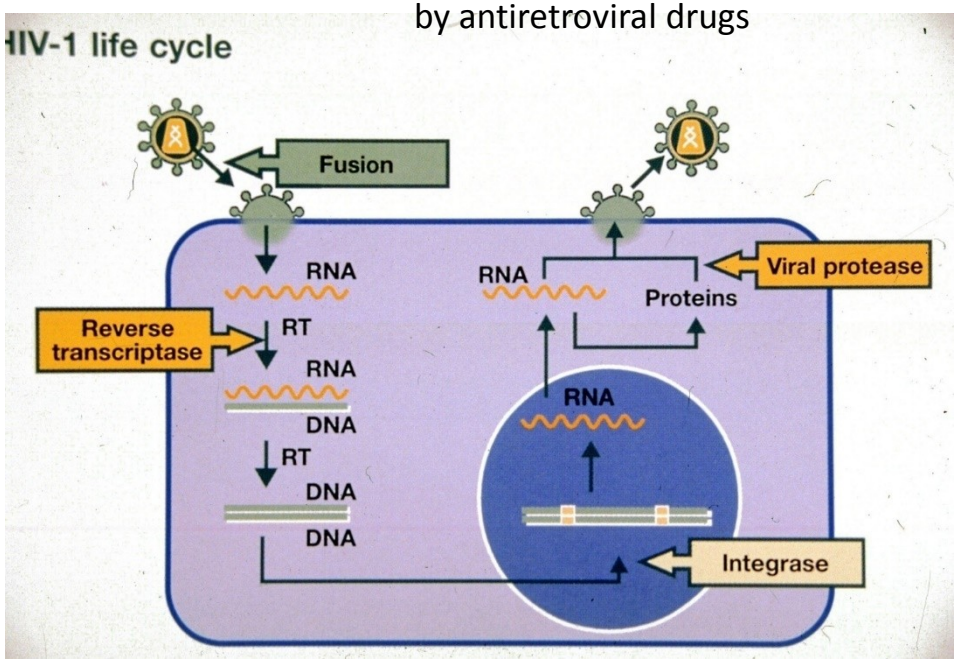
The clasess of AR drugs

1. NRTs – nukleoside reverse transcriptase inhibitors
2. NNRTIs – non-nucleoside reverse transcriptase inhibitors
3. InSTI - integrase inhibitors
4. PIs – protease inhibitors
5. FI – fusion inhibitor
6. CCR5 inhibitor – coreceptor inhibitor

The main enzymes of HIV are blocked by antiretroviral drugs



NRTIs – nucleoside reverse transcriptase inhibitors

(NRTIs block of enzyme reverse trascriprase)

Generic name	Trade made
zidovudine (ZDV), azidothymidine (AZT)	Retrovir, Azitidin
didanosine (ddl)	Videx, Videx EC
zalcitabine (ddC)	Hivid
stavudine (d4T)	Zerit
lamivudine (3TC)	Epivir
abacavir (ABV)	Ziagen
ZDV+3TC	Combivir
ZDV+3TC+ABV	Trizivir
3TC+ABV	Kivexa
emtricitabin (FTC)	Emtriva
tenofovir (TDF)	Viread
FTC+TDF	Truvada

NNRTIs

– non-nucleoside reverse transcriptase inhibitors

(NNRTIs block of enzyme reverse transcriptase)

Genericname	Trade made
nevirapine (NVR)	Viramune
delavirdine (DLV)	Rescriptor
efavirenz (EFV)	Stocrin, Sustiva
rilpivirine (RPV)	Edurant

PIs – protease inhibitors

PIs block of enzyme viral protease

Generic name	Trade made
saquinavir (SQV-hgc)	Invirase
saquinavir (SQV-sgc)	Fortovase
ritonavir (RTV)	Norvir
indinavir (IDV)	Crixivan
nelfinavir (NFV)	Viracept
amprenavir (APV)	Agenerase

PIs – protease inhibitors

Generic name	Trade made
lopinavir/ritonavir (LPV/r)	Kaletra
atazanavir	Reyataz
fosamprenavir	Telzir
tipranavir	Aptivus
darunavir	Prezista

InSTI – integrase inhibitor

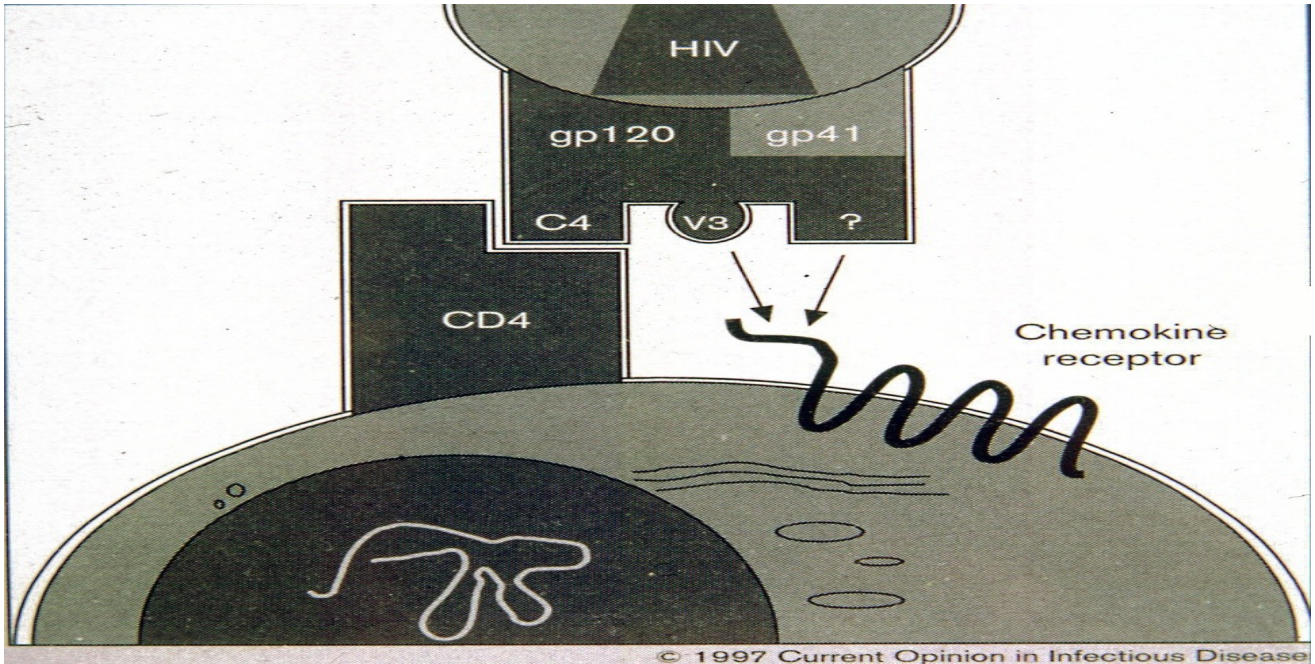
II block of enzyme viral integrase

Generic name	Trade made
raltegravir	Isentress
elvitegravir	Stribild
dolutegravir	Tivicay

FI – fusion inhibitor

FI blocks of receptor CD4 on surface of cell
and block of fusion HIV with CD4 lymphocyte

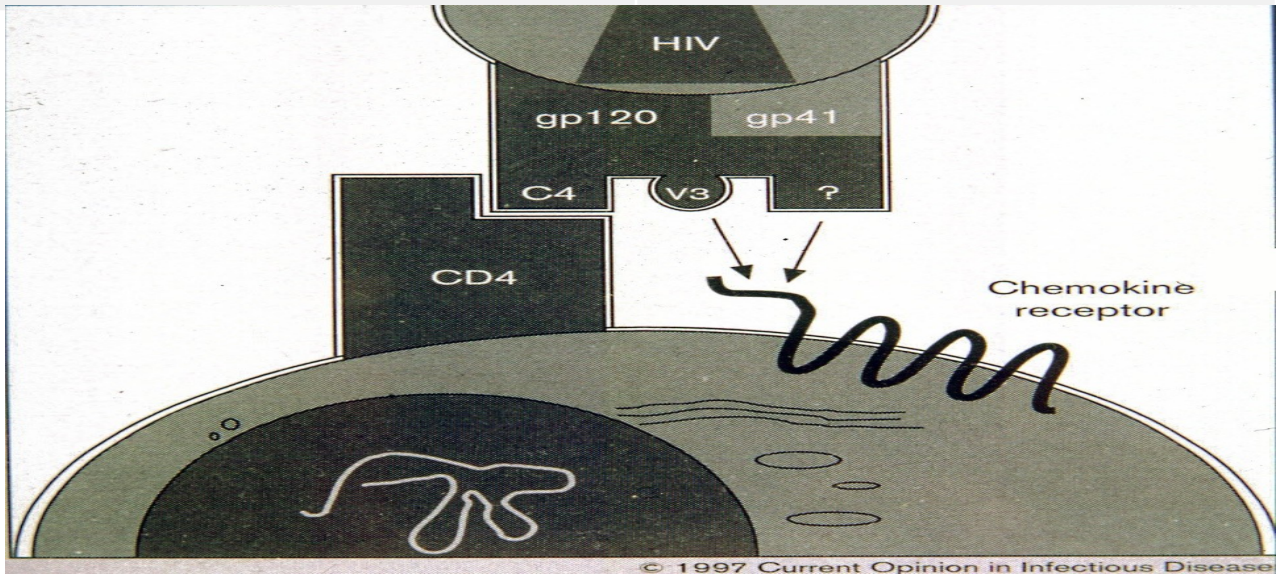
Generic name	Trade made
enfuvirtide	**Fuzeon, T-20**

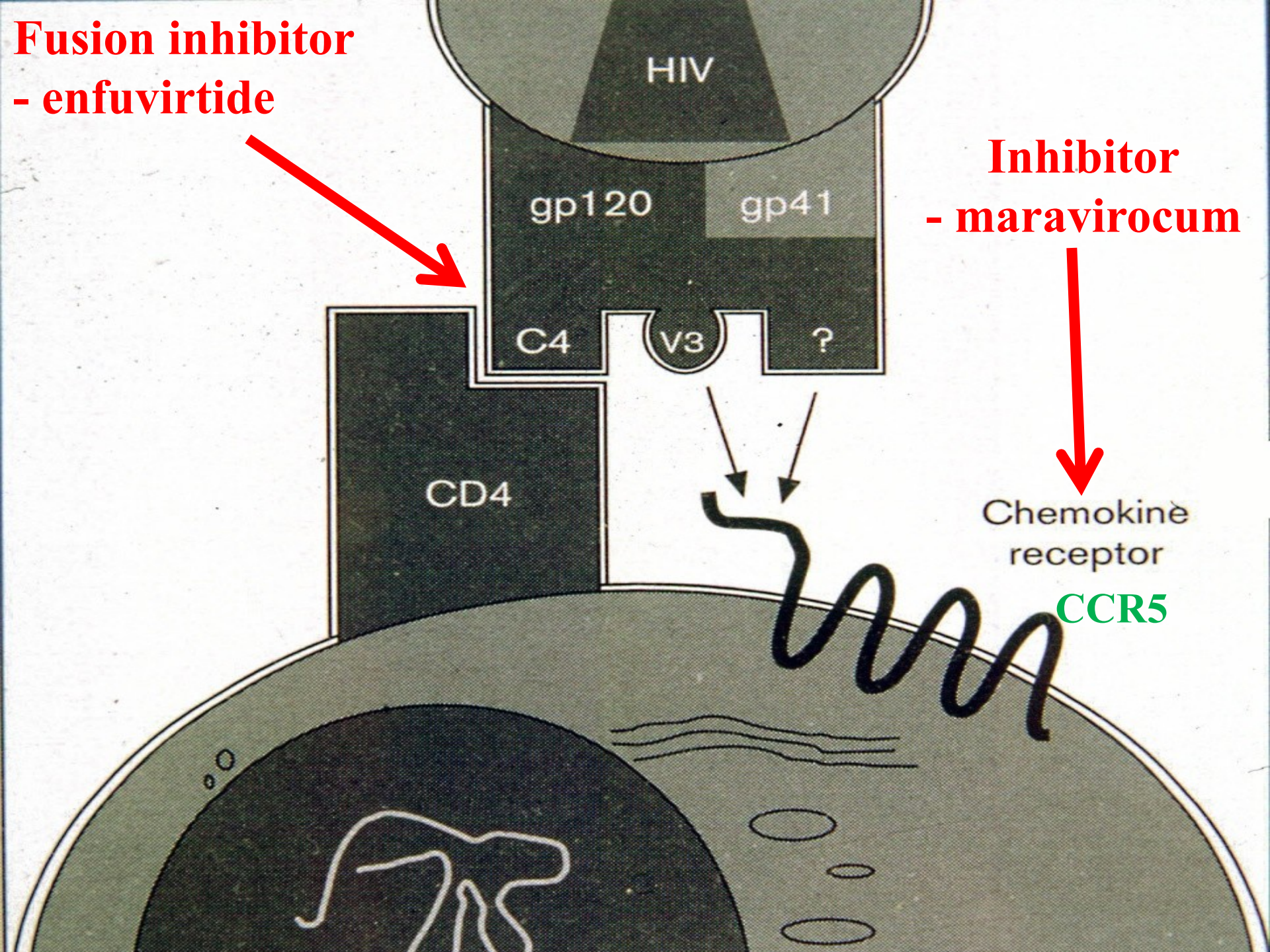


CCR5 inhibitor

CCR5 inhibitor blocks of chemokine receptor on surface of cell and block of fusion HIV with CD4 lymphocyte

Generic name	Trade made
maravirocum	**Celsentri**




Fusion inhibitor
- enfuvirtide
HIV
gp120
gp41
C4
V3
?
CD4
Inhibitor
- maravirocum
Chemokinè
receptor
CCR5

- **Three-drug combinations are currently recommended for the initiation of treatment in all patients**

- **When HIV diagnoses is established regardless on CD4 lymphocyte count**

- **The most widely used combination is**

  two NRTIs with one II, PI or NNRTI

- **Truvada + Stocrin (NNRTI)**
  - **Co-formulation TDF + FTC in one pill**
- **Truvada + Kaletra (PI)**
- **Kivexa + Stocrin**
  - **Co-formulation 3TC + ABC in one pill**
- **Kivexa + Kaletra**

STR – single tablet regimen

- The most advanced way of treatment
- Complete ART for once-daily dosing
  - **in one pill**
- STR co-formulation for once-daily dosing is **the highest level of ART simplification** achieved so far

Co-formulations of drugs for STR

- **Atripla**
  - TDF/FTC/EFV
- **Eviplera**
  - TDF/FTC/RPV
- **Stribild**
  - TDF/FTC/EVG/COBI
- **Triumeq**
  - ABC/3TC/DTV
- **Genvoya**
  - TAF/FTC/EVG/c

STR – single tablet regimen

- Increasing reductions in pill burden and daily dosages
- Significantly **higher comfort for patient**
- Higher adherence
- Higher viral suppression rates
- Lower risk of hospitalization for complications due to disease progression

ART (HAART, OBT) is very potent and has a big benefit

BUT

is unable to completely eradicate the virus from the body !!!

COMPLICATIONS of ART

- Although each of the recommended regiments can result in durable suppression of VL, associated with gradual recovery of immunologic function
- Each regimen has specific advantages and potential toxicities of which the patient must be aware
- Three-drug combinations result in long-term toxicities

Major side-effects and complications

NRTIs

- myelosupression (ZDV)
- GI intolerance
- pancreatitis (d4T, ddI)
- peripheral neuropathy (d4T, ddC, ddI)
- lactic acidosis
- neuropsychiatric manifestations
- hypersensitivity reaction (ABC)
- mitochondrial toxicity

NNRTIs

- GI intolerance
- skin reaction
- neuropsychiatric manifestations (EFV)
  - Nightmares (wild dreams)

PIs

- GI intolerance, diarrhoea
- lipodystrophy
- hypercholesterolaemia
- insulin resistance

ART (combination of drugs)

Is associated with other possible disease sequelae:

- Cardiovascular disease
- Changes in body composition
- Alterations in glucose and lipid metabolism
- Hepatic, renal, bone, neurologic, and oncologic disease complications

- Consequences of which have not yet been fully evaluated.

„Lipodystrophy syndrome“ in association with HIV

- was introduced to describe

  a complex medical condition including

  the apparent

  - **abnormal fat redistribution**
  - **and metabolic disturbances**

seen in HIV-patients receiving

a combination regimens of antiretroviral drugs

„Lipodystrophy syndrome“ in association with HIV

- Prevalence has been estimated to be between 30 and 50%
- **Multifactorial pathogenesis**
- Is associated with **many risk factors**

Is complex interactions between

- The effects of chronic HIV infection
- Genetically determined disorders
- The efects of some antiretrovirals
- Lifestyle-induced changes

Lipodystrophy

A historical umbrella term that has included multiple, distinct processes

Dyslipidemia

Hypercholesterolemia

Hypertriglyceridemia

Insulin Resistance

Hyperinsulinemia

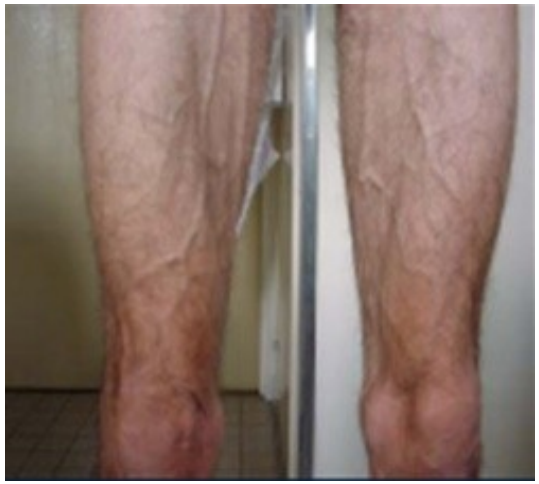
Body-Fat Abnormalities

Lipoatrophy *Subcutaneous Fat Loss*	**Lipohypertrophy** *Visceral Fat Gain*
Limb lipoatrophy	Breast hypertrophy
Facial lipoatrophy	Dorsocervical fat pad
Buttock lipoatrophy	Lipomatosis
Venomegaly	Abdominal fat accumulation

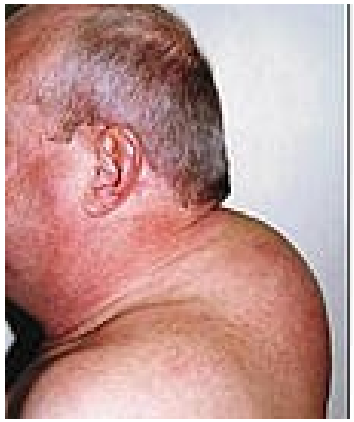
Grinspoon & Carr N Engl J Med 2005; 352:48. Carr A et al. *Lancet 1999*;353:2093-2099. Currier and Havlir. *Top HIV Med* 2004;12:31. Garg A. *N Engl J Med* 2004;350:1220. Montessori et al. *CMAJ* 2004;170:229.

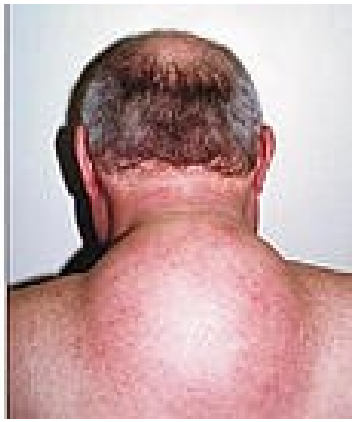
Body-Fat Abnormalities

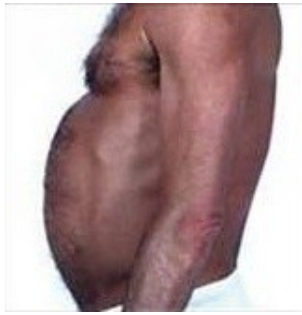
Lipoatrophy



Lipohypertrophy







- **Lipoatrophy and lipohypertrophy may co-present**
- **Some characteristics may be irreversible**

Morse CG et al. JAMA 2006;296:844-854. Parruti & Torro *BMC Infectious Disease* 2005;5:80.

Progression of lipoatrophy over time

Grinspoon & Carr N Engl J Med 2005; 352:48.
James J et al. Dermatol Surg 2002;11:979–986.

Grading

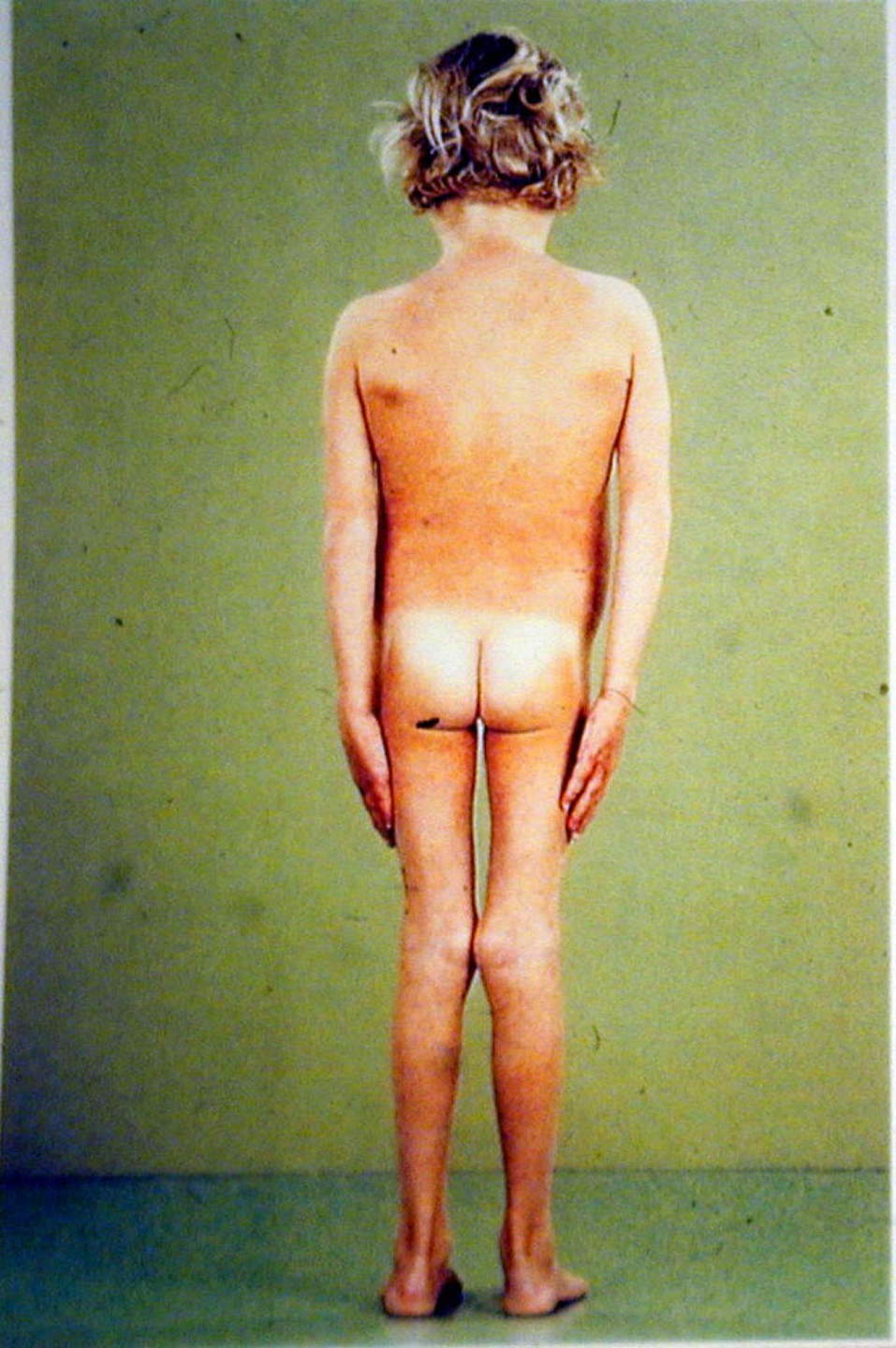
- Definitions based on DEXA or CT scan have not been established in clinical practice
- Qualitative grading scales have been utilized

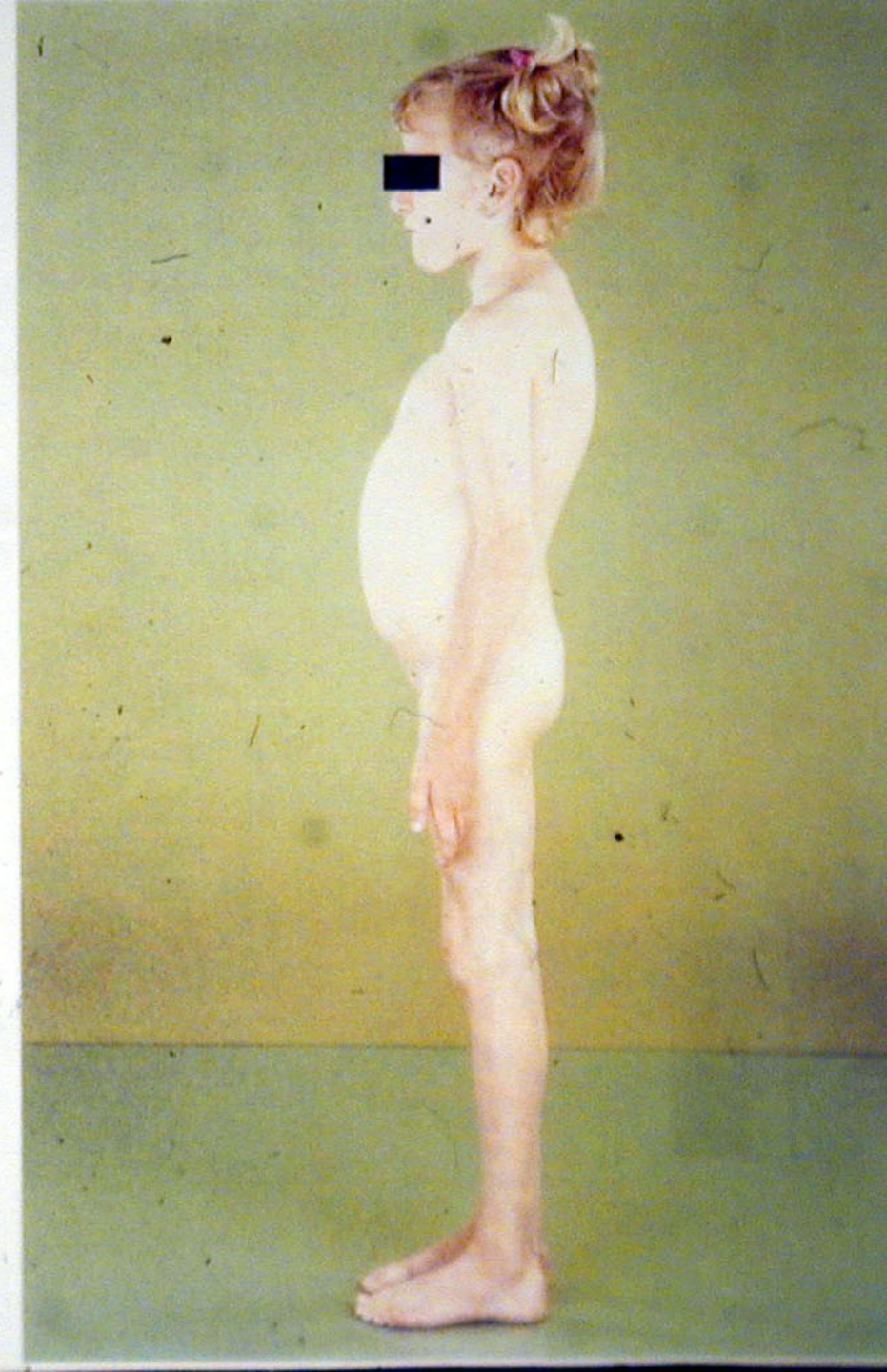
Progression of Lipoatrophy

Facial Lipoatrophy Grading

- Grade 1: Mild/localized. Appearance almost normal
- Grade 2: Deeper, longer central cheek atrophy. Facial muscles (especially zygomaticus major) beginning to show through
- Grade 3: Deeper, wider atrophic area. Muscles clearly showing
- Grade 4: Widespread atrophy. Facial skin lies directly on muscles over a wide area, extending toward the orbital region

Grinspoon & Carr N Engl J Med 2005; 352:48.
James J et al. Dermatol Surg 2002;11:979–986.





- Mechanistic **pathophysiology** of antiretroviral drugs in lipodystrophy syndrome is **very complex** and exactly unknown at present
- Consequences of this disturbances **have not yet been fully evaluated…**

More signs and symptoms

have been described in association with the lipodystrophy syndrome

- dry skin, ingrown toenails
- aseptic hip necrosis
- osteopenia, osteoporosis…
- hepatic, renal, bone, neurologic and other disease complications

We do not know long-term consequences…

It is very likely that the **ongoing inflammation and immune** activation thought to contribute to higher rates of cardiovascular and other end-organ damage

The morphologic and metabolic effects

The fat redistribution and disturbances in fat and glucose metabolism – resemble a clinical situation that is known as

the **„metabolic syndrome“**

in HIV-negative patients

ART is very potent

- Improves quality of life
- Reduces HIV-realted morbidity and mortaliti

BUT

can couse

secondary disorders and complications,

consequences of which

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