Meccanismi patogenetici alla base delle comorbidità nel soggetto con infezione da HIV

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Comorbidity … a big problem since 1995

The increase in the life expectancy due to effective antiretroviral therapy

means that

the HIV-infected population are exposed to the age-related diseases as the general population

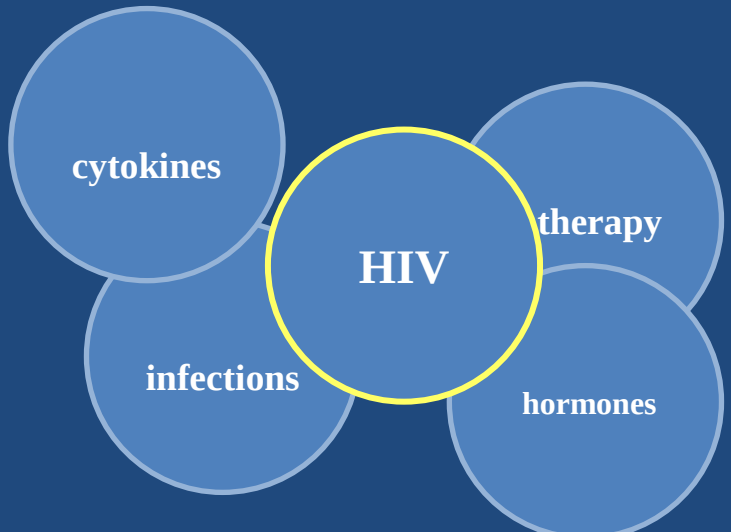
The prevalence of cardiovascular disease, bone, kidney, liver, central nervous system alterations and so on…is higher in comparison to *general* population

The onset is earlier in the HIV population, probably due to the complex interplay between HIV infection, co-infection(s) and ART.

First problem….

one of the uncountable problems

Bone



Bone alterations: a pivotal clinical problem in the management of HIV patients

The major bone lesions are related to bone demineralization

Osteopenia

bone mineral density reduction

Osteoporosis

bone strength reduction with increased fracture risk

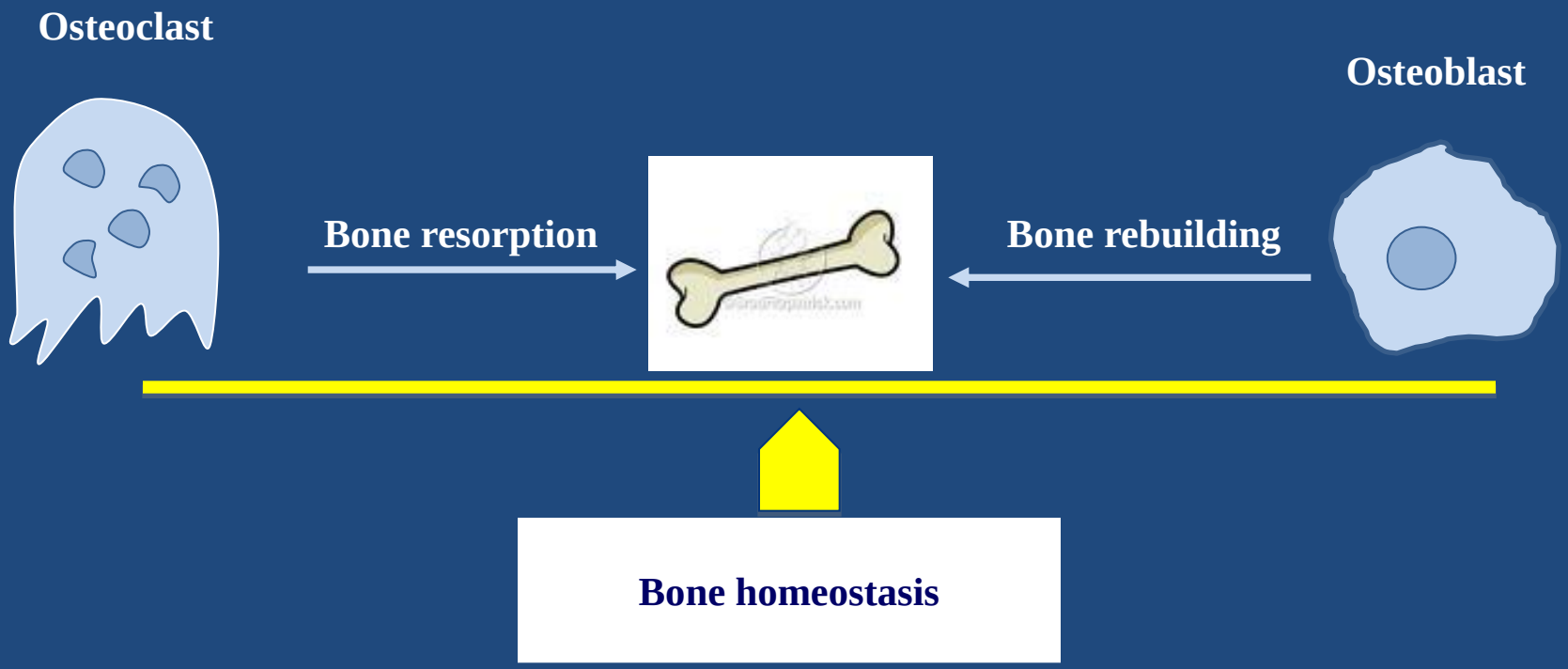
Osteomalacia

softening of the bone (defective mineralization)

Osteonecrosis

bone death (poor blood supply)

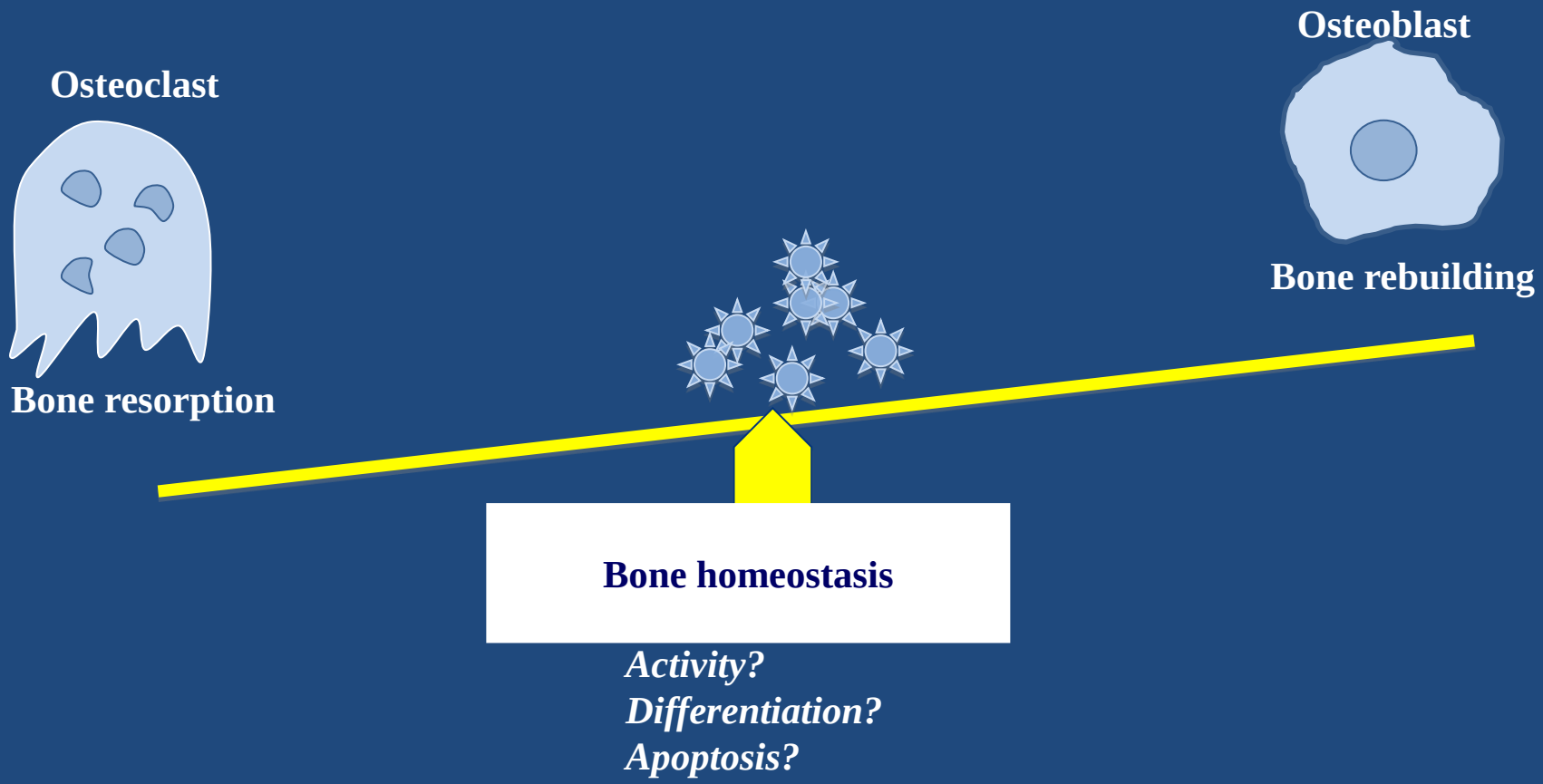
Bone homeostasis



functionally connected and regulated by mediators such as hormones, vitamins and cytokines that strongly affect the skeletal biology throughout life

Bone homeostasis might be altered

Infection, hormonal, immunological and metabolic disorders could impair both bone mass and structure impairment resulting in increased bone fragility and fracture risk.



HIV …..which role?

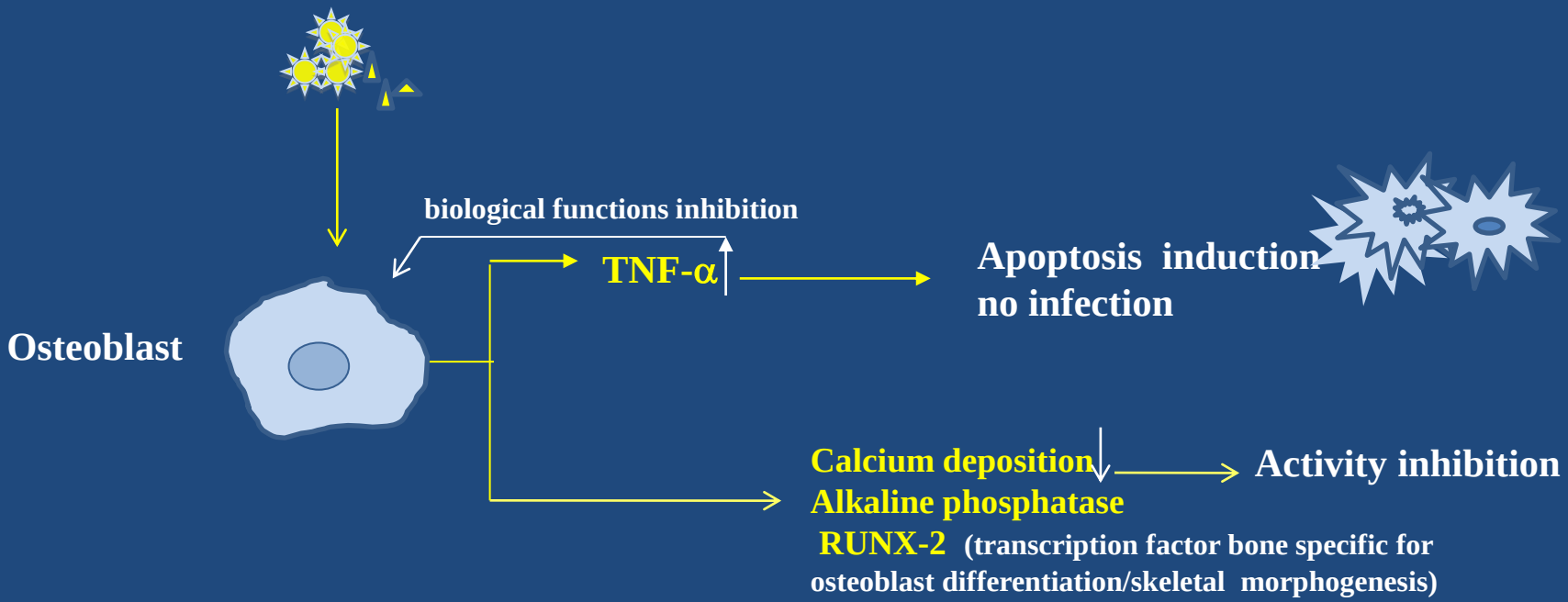
- **Hypothesis 1: human osteoblast may be a permissive target for HIV infection decreasing BMD through a direct viral mechanism**

bone might be considered an HIV reservoir [with a limited blood flow and with a particular anatomical structure…(drugs?)]

Hypothesis 2: human osteoblast is not a permissive target for HIV infection (shortage of CD4 receptor and/or CD4/CXCR4 complexes be not sterically closed to constitute the trimeric complex with gp120 essential)

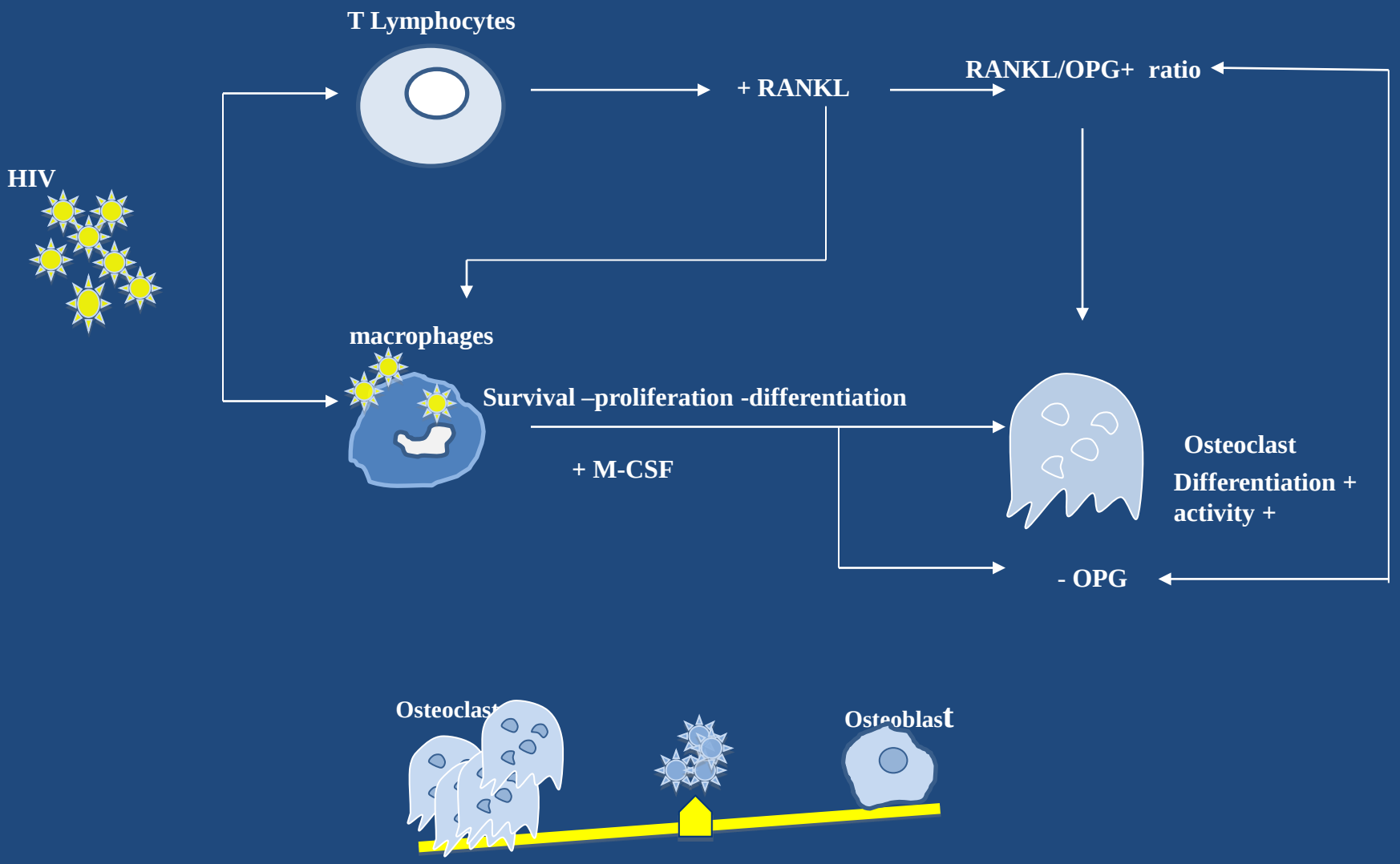
Why the bone derangement?

Problem n°1: osteoblasts
Apoptosis induction and biological functions inhibition



Gibellini et al. J Med Virol 2007; Re et al. Clin Microbiol Infect *2009;* De Crignis et al New Microbiologica 2008; Borderi *et al*. AIDS 2009

Problem n°2: osteoclasts
Increase of differentiation and activity



Bone alterations: HIV or therapy or both?

A significant signs of bone loss have been demonstrated in antiretroviral naive HIV-1 infected patients

but

HAART-treated individuals displayed a more rapid derangement of bone structure related to specific antiretroviral drugs such as

zidovudine and tenofovir able to

increase osteoclastic activity

impair bone mineralization

NRTIs inhibit DNA polymerase γ (replication of mitochondrial DNA) leading to mitochondrial damage and dysfunction

NRTIs induce lactic acidaemia (calcium hydroxyapatite loss) leading to osteopenia

PRIs inhibit

1) osteoblast formation from progenitor cells
2) bone formation and calcium deposition thereby decreasing osteoblast activity

PRIs inhibit osteoclastogenesis by the abrogation of a physiological block to RANKL

PRIs cause vitamin D deficit (determining osteomalacia through the reduction of phosphates available to bone

Osteoclast

Osteoblast

DRUGS and VIRUS

Bone resorption

Bone rebuilding

Bone homeostasis

In addition to the HIV direct effect

HAART-treated individuals displayed a more rapid derangement of bone structure related to specific antiretroviral drugs able to

increase osteoclastic activity

impair bone mineralization

Another problem….

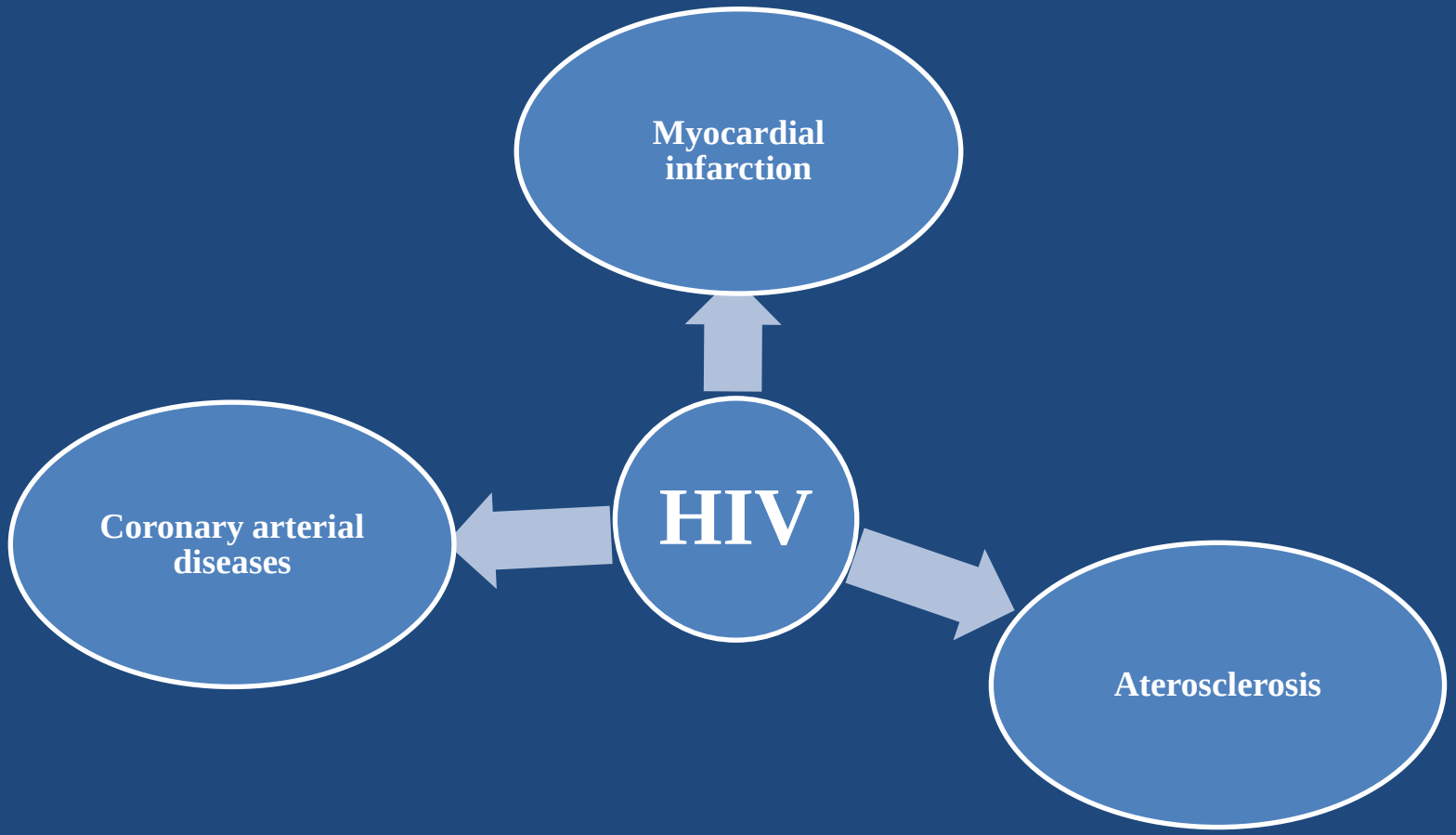
one of the uncountable problems

Cardiovascular disease

CVD had become the leading cause of death and a major factor limiting the increase in life expectancy beyond the age of 45 years.

Increased CVD rates are seen among HIV-infected patients, compared with age-matched non–HIV-infected patients

….The same protagonist and a different pathology….



in HIV positive subjects atherosclerotic lesions have been observed in absence of classical risk factors

HIV infection is an independent risk factor of atherosclerosis and coronary arterial disease

Cardiovascular diseases are mainly related to vessel wall homeostasis impairment

Atherosclerosis

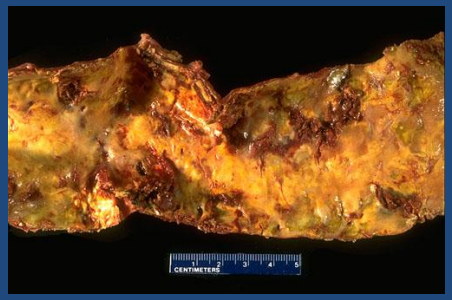
is linked to

severe endothelial dysfunction with arterial wall injury

triggering

a chronic inflammatory response

with subsequent atheromatous plaque formation

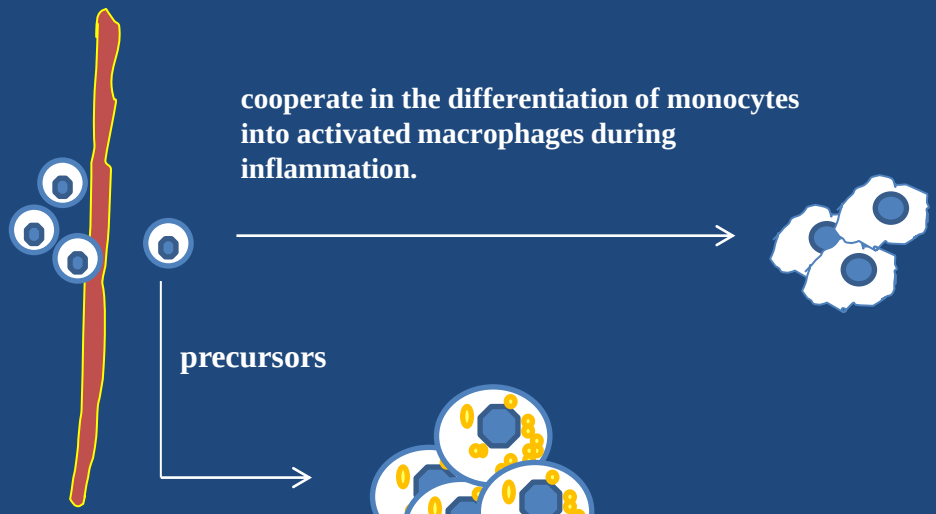


Which mechanisms involved in the genesis of atherosclerosis and cardiovascular damages in HIV patients?

HIV infection

systemic inflammation and chronic immune activation

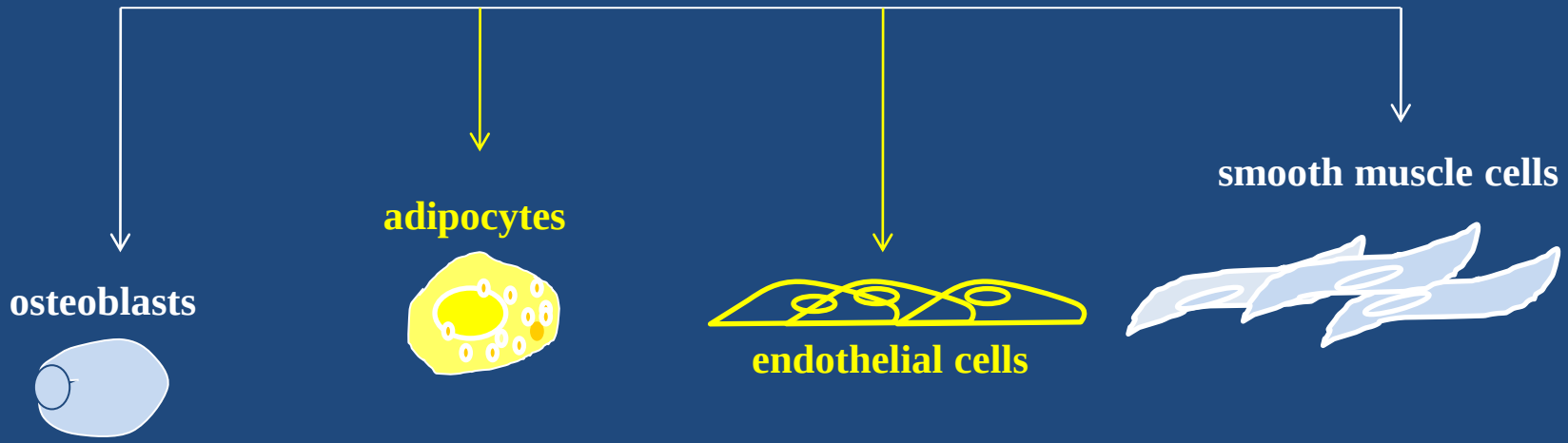
TNF alpha, IL1, IL-6, M-CSF, IL-10 upregulation



MSCs and HIV

MSCs

can be differentiated towards several cell lineages



Retrovirus Lab Experience:
Interaction between HIV-1 and human mesenchymal stem cells (MSCs)

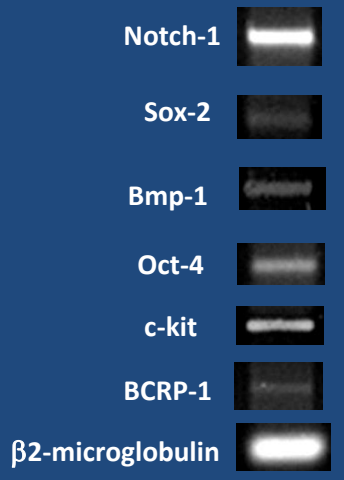
To elucidate a possible additional mechanism in the vessel dysfunctions observed in HIV infected patients.....

MSCs

Obtained from human arterial segments of femoral arteries from three male heart-beating donors

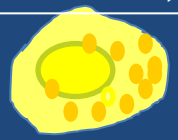
Presence of CD4, CXCR4, CCR5

Treated with HIV-1_{IIIB} or HIV-1_{Ada} gp120



endothelial differentiation
VEGFR-1/2,vWF

adipogenic differentiation
C/EBP b, C/EBP d, adipsin, PPARg, UCP-1, vWF, VEGFR-2)



Retrovirus Lab Experience:
Interaction between HIV-1 and human mesenchymal stem cells (MSCs)

Two main questions

1) **HIV is able to infect MSCs?**

2) **What about differentiation?**

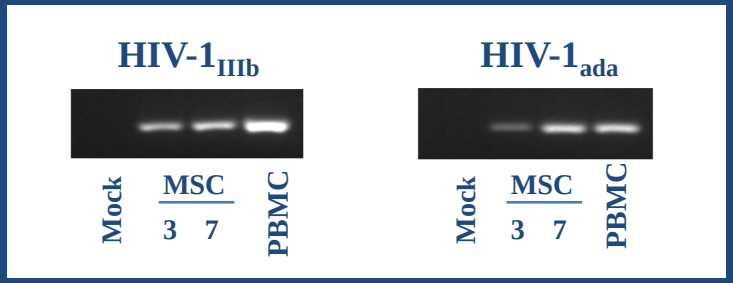
FIRST QUESTION

MSCs may be considered barely permissive to HIV-1 infection

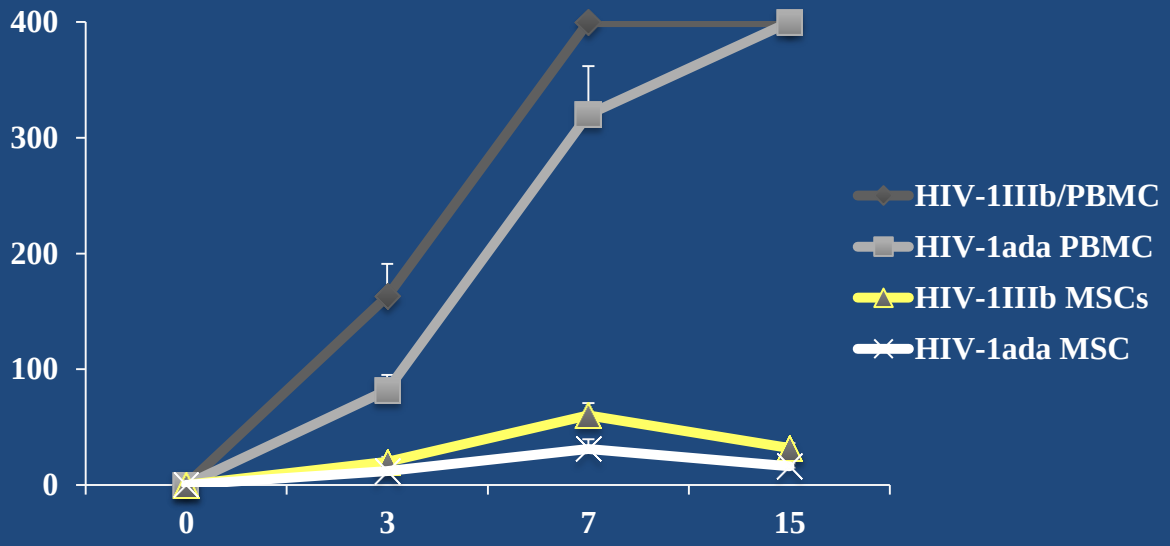
HIV-1 X4 and R5 are able :
to enter
to retrotrascribe
to integrate the proviral DNA in host genome

but with very low level of p24 protein

HIV-1_{IIIb} and HIV-1_{Ada} proviral DNA analysis



HIV-1 p24 in cell supernatants

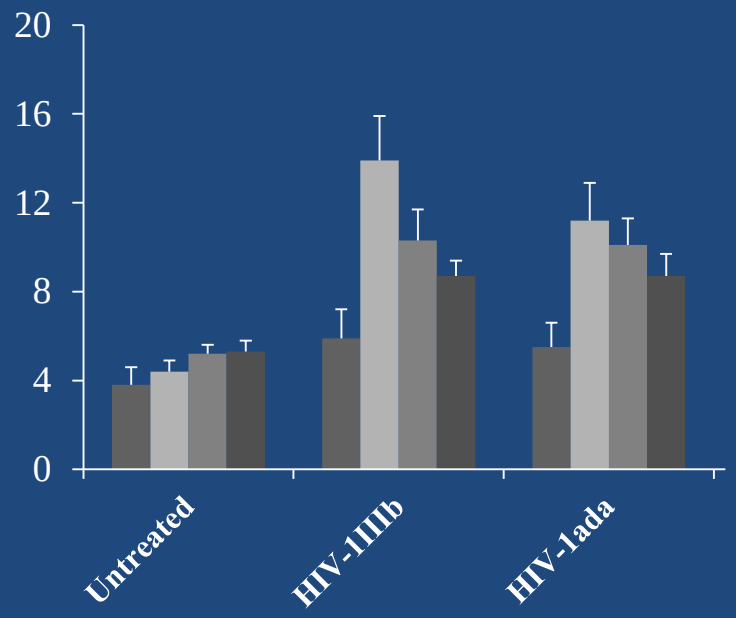


.... a possible role of MSCs as potential infection reservoir.....

FIRST QUESTION

HIV-1strains and recombinant gp120 induce apoptosis in sub-confluent MSCs

Flow cytometry analysis performed at day 1, 3 ,7 and 10 days post-infection showed an increase of apoptotic cells



Apoptosis induction is abolished after pre-treatment of viral strains or gp120 with anti gp120Ab

↓

the interaction between gp120 and cell membrane is pivotal in the activation of programmed cell death.

....a similar situation already demonstrated..... HIV and gp120 are involved in the apoptosis of neuronal and osteoblast cells, respectively, supporting, at least in part, the raising of AIDS dementia complex and the osteopenia/osteoporosis observed in several HIV positive individuals

SECOND QUESTION:

Interaction between HIV-1 and human mesenchymal stem cells (MSCs)

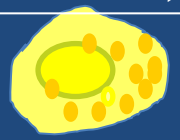
MSCs

Obtained from human arterial segments of femoral arteries from three male heart-beating donors

Treated with HIV-1_{IIIB} or HIV-1_{Ada} gp120

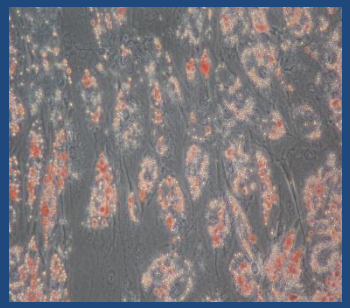
endothelial differentiation
VEGFR-1/2,vWF

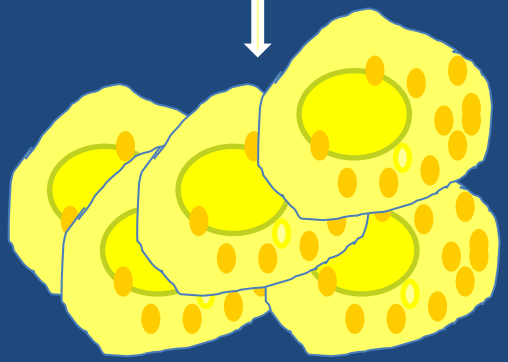
adipogenic differentiation
C/EBP b, C/EBP d, adipsin, PPARg, UCP-1, vWF, VEGFR-2)



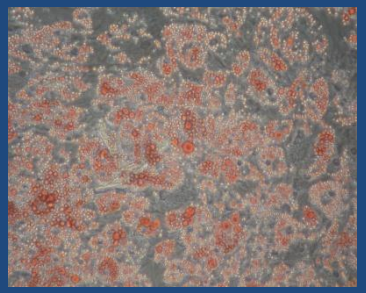
HIV-1 and recombinant gp120 positively modulates the MSCs differentiation to adipogenesis

MSCs





HIV



significant up-regulation of PPAR γ activity
significant up-regulation of C/EBP β
positively modulated the adipsin mRNA expression
UCP-1 is poorly expressed

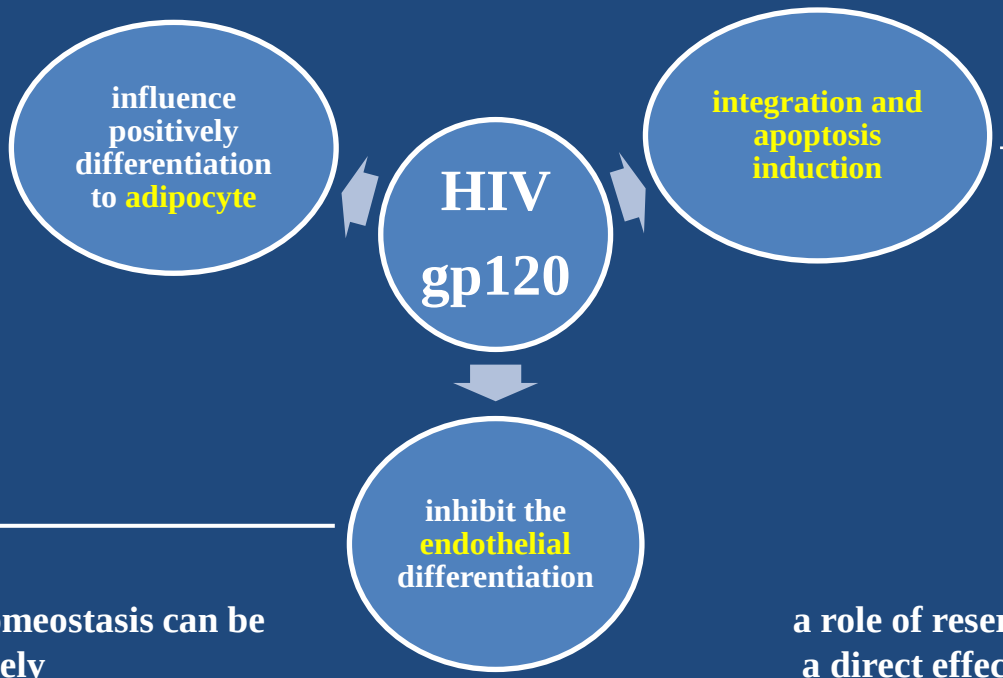
a reliable increase of red oil positive cells in the cell cultures treated with viral agonists at day 7 and 10

HIV and gp120 enhanced a more rapid and massive differentiation of MSC <u>stimulated</u> to adipogenic lineage

HIV-1 and rgp120 inhibit the MSCs endothelial differentiation

HIV:
a clear decrease of all three markers on cell membrane
vWF, VEGF-R1 and VEGF-R2

An additional mechanism in the damage of MSC homeostasis



the endothelial layer homeostasis can be maintained less effectively

the possibility of vascular damage and atherosclerosis lesion evolution can be increased (due to impairment MSC repair control of endothelial structure)

a role of reservoir for HIV infection

a direct effect on primary

Another problem….

one of the uncountable problems

The brain

HIV, dementia and CART

- **Combination antiretroviral therapy (CART) has decreased the incidence of HIV-associated dementia….**

↓ **but**

- **the severest form of HIV-associated neurocognitive disorders (HAND) continue to persist……. and neurocognitive deficits are present even in *acute* HIV infection.**

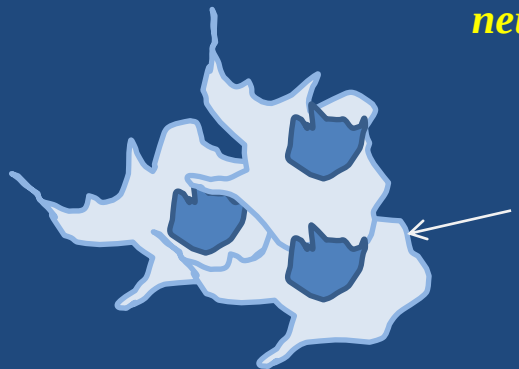
NeuroAIDS: might neurotoxicity be an indirect mechanism responsible for neuropsychiatric complications?

More than 50% of HIV infected patients show signs and symptoms of neuropsychiatric disorders.

These disorders affect *central* nervous system (CNS) and *peripheral* nervous systems (PNS). CNS is one of the most protected organ systems in body which is protected by blood-brain barrier (BBB).

Not only this, most of the cells of CNS are *negative* for receptors and co-receptors for HIV infections.
Neurons have been found to be completely nonpermissive for HIV infection……

These facts suggest that neurotoxicity could be an indirect mechanism responsible for neuropsychiatric complications.



CNS cells are *negative* for receptors and co-receptors

Receptors and Co-Receptors for HIV Infection

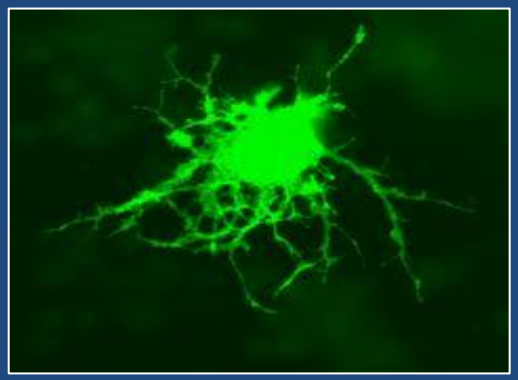
Expression of CD4 receptors on brain cells is from negligible to none.

Oligodendrocytes and neurons

cells producing myelin *(CD4 negative and chemokine receptors positive)*:

↓

A limited HIV infectivity has been reported *in vitro*



the main effector cells for cognitive and motor functions

non-permissive for HIV infection

↓

but

↓

significant neuronal death has been reported in HIV infected brain

↓

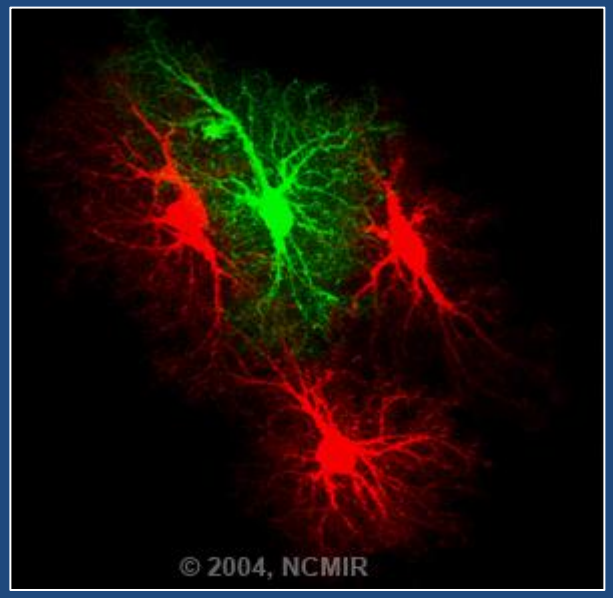
A contribute towards HIV neuropathogenesis. →

gp120 + to galactosylceramide

↓

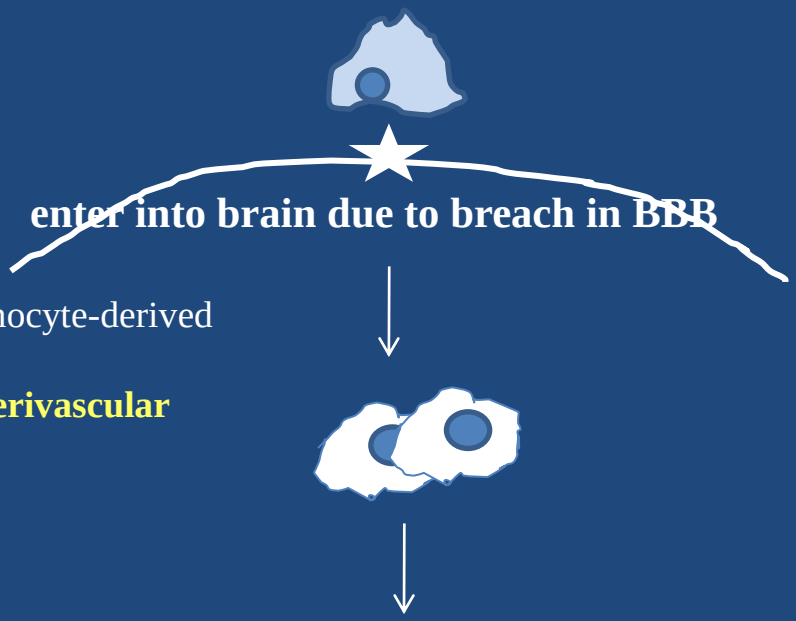
increase in intracellular Ca^{2+} levels and apoptosis

Astrocytes



- Astrocytes maintain homeostasis of CNS and express receptors for various neuroreactive compounds including neurotransmitters.
- Only few astrocytes were found to be positive for HIV antigen.
- The expression of CD4 antigen in astrocytes is subminimal or negligible. Therefore, mechanism for HIV entry into astrocytes is questionable. In HIV patients, astrocytosis has been reported in response to viral proteins or other macrophage products.

Perivascular macrophages the major cell types in perivascular region of brain.



these cells are considered as a possible source for productive HIV infection in brain

Perivascular macrophages get regularly replenished from peripheral monocytes. This replenishment could be considered as side effect of "opening the door" phenomenon. These cells have also shown active viral replication.

Trojan horse hypothesis

Neurocognitive disorders/virus/drugs

we still have

a lot of questions without a secure reply…

Is neurotoxicity an indirect mechanism?

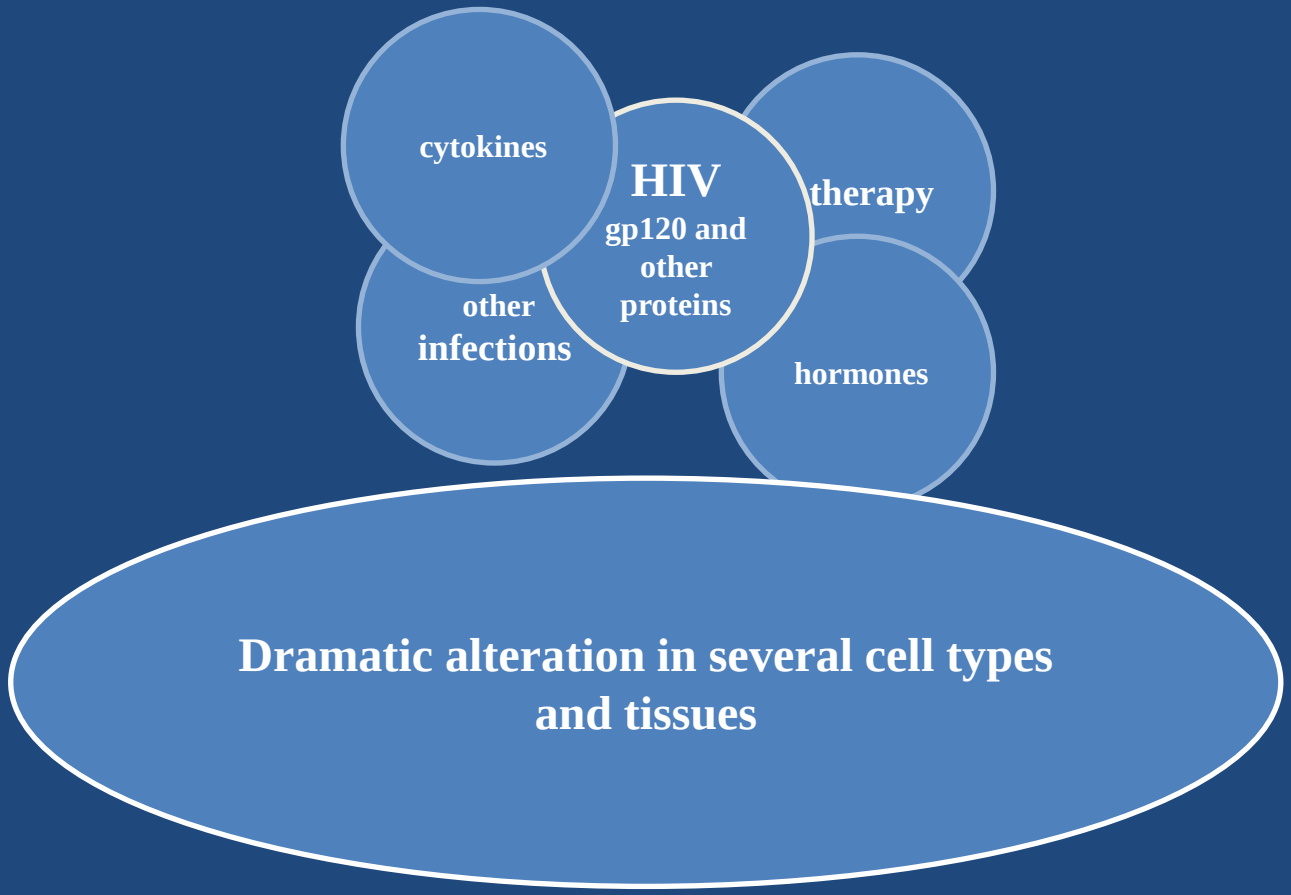
Is Trojan horse hypothesis correct?

Potential neurotoxicity of antiretrovirals

When to start treatment to protect the CNS

The eradication of potential latent reservoirs in the brain

The neurological impact of HIV on the CNS in acute infection



Learning is experience and everything else is just information.
Albert Einstein

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