The pathogenesis of AIDS

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Faculty of Medicine
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London

22 February 2013

Six core concepts to cover

1) A new disease in 1981 & the AIDS epidemic in 2001 (i.e. 20 years).

2) The clinical spectrum of the disease.

3) How did the virus evolve to infect & spread in man so rapidly?

4) The pathogenesis of HIV infection & development of AIDS.

5) Using the science to develop the patient treatment strategies.

6)What does the future hold for HIV-1+ people?

Turning a terminal disease into
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June 1981

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June 5, 1981 / 30(21);1-3

Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

July 1985 – Nature paper

A molecular clone of HTLV-III with biological activity

Amanda G. Fisher, Enrico Collalti, Lee Ratner, Robert C. Gallo & Flossie Wong-Staal

Laboratory of Tumor Cell Biology, Developmental Therapeutics Programme, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland 20205, USA

Acquired immune deficiency syndrome (AIDS) is an epidemic immunosuppressive disease characteristically associated with a depletion of T lymphocytes of the helper/inducer phenotype[1]. Numerous converging lines of research have implicated a human T-cell lymphotropic retrovirus, HTLV-III, in the pathogenesis of AIDS[2–5]. Recently, several distinct forms of the HTLV-III genome were molecularly cloned in phage and extensively characterized[6,7]. In the present study, a clone containing full-length HTLV-III proviral DNA[7] was inserted into a plasmid and used to transfect cord blood T cells from normal newborn humans. We demonstrate that this molecular clone is infectious *in vitro* and causes marked cytopathic effects on T-cell cultures. This is the first direct evidence that the HTLV-III genome, rather than a minor component of the virus complex, is cytopathic for T cells. Using this biologically competent clone and mutants derived from it, it should now be possible to localize the subgenomic regions that contribute to the biological effects of HTLV-III.

July 1987 & New England J Medicine

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ORIGINAL ARTICLES

Chimps in Africa

1999

Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

Feng Gao*, Elizabeth Bailes†, David L. Robertson‡, Yalu Chen*, Cynthia M. Rodenburg*, Scott F. Michael*§, Larry B. Cummins‖, Larry O. Arthur¶, Martine Peeters#, George M. Shaw*☆, Paul M. Sharp† & Beatrice H. Hahn*

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† *Institute of Genetics, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK*
‡ *Laboratory of Structural and Genetic Information, CNRS, Marseilles 13402, France*
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§ Present address: Department of Tropical Medicine, Tulane University, New Orleans, Louisiana 70112, USA.

Year 1999

Figure 1 Worldwide numbers of adults and children estimated to be living with HIV/AIDS at the end of 2000. (Source: ref. 2.)

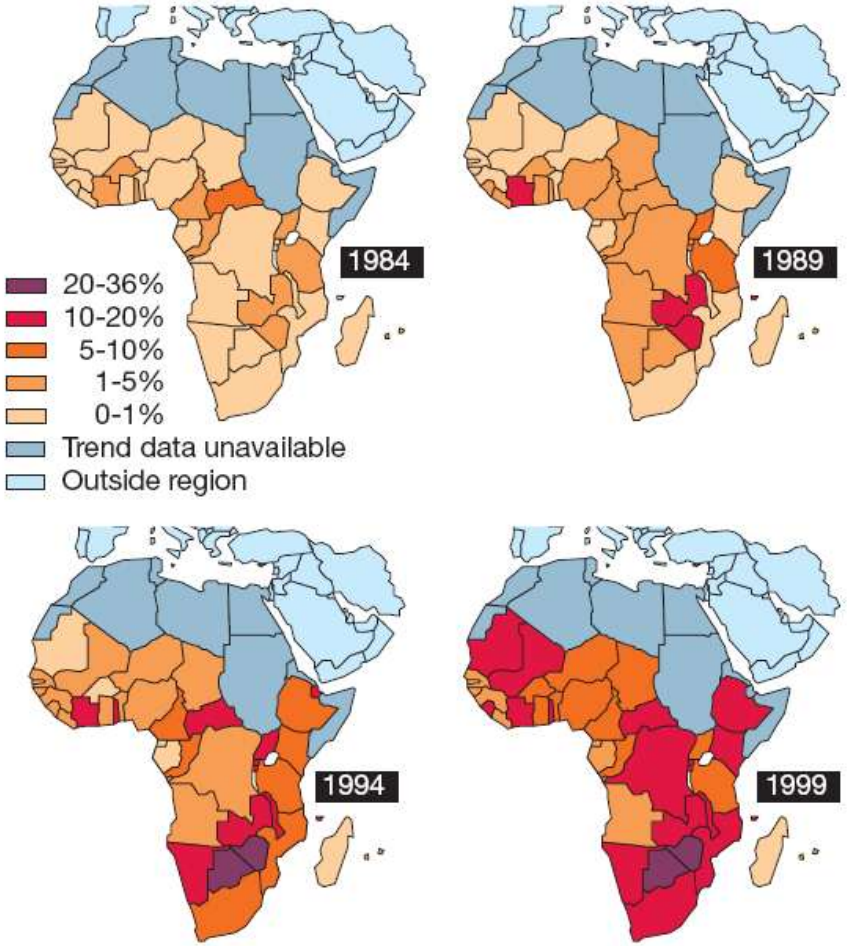
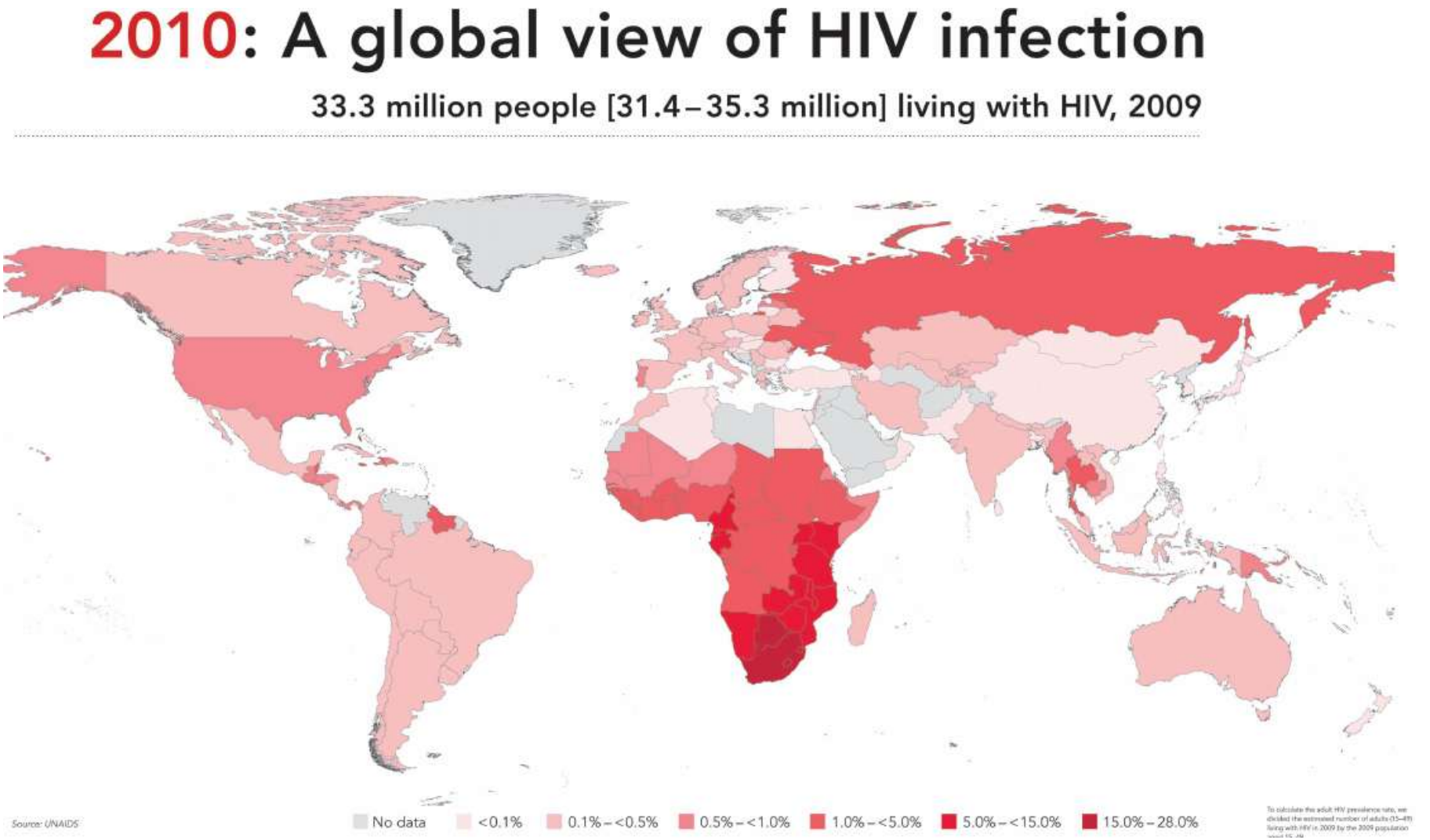


Figure 3 Spread of HIV in Africa, 1984–1999. Estimated HIV prevalence rate in 15–49 year olds in sub-Saharan countries in 1984, 1989, 1994 and 1999.

HIV worldwide in 2010



Deaths worldwide (2010)

World Health Organization

Media centre

The top 10 causes of death

Fact sheet N°310
Updated June 2011

The 10 leading causes of death by broad income group (2008)

Low-income countries	Deaths in millions	% of deaths
Lower respiratory infections	1.05	11.3%
Diarrhoeal diseases	0.76	8.2%
HIV/AIDS	0.72	7.8%
Ischaemic heart disease	0.57	6.1%
Malaria	0.48	5.2%
Stroke and other cerebrovascular disease	0.45	4.9%
Tuberculosis	0.40	4.3%
Prematurity and low birth weight	0.30	3.2%
Birth asphyxia and birth trauma	0.27	2.9%
Neonatal infections	0.24	2.6%

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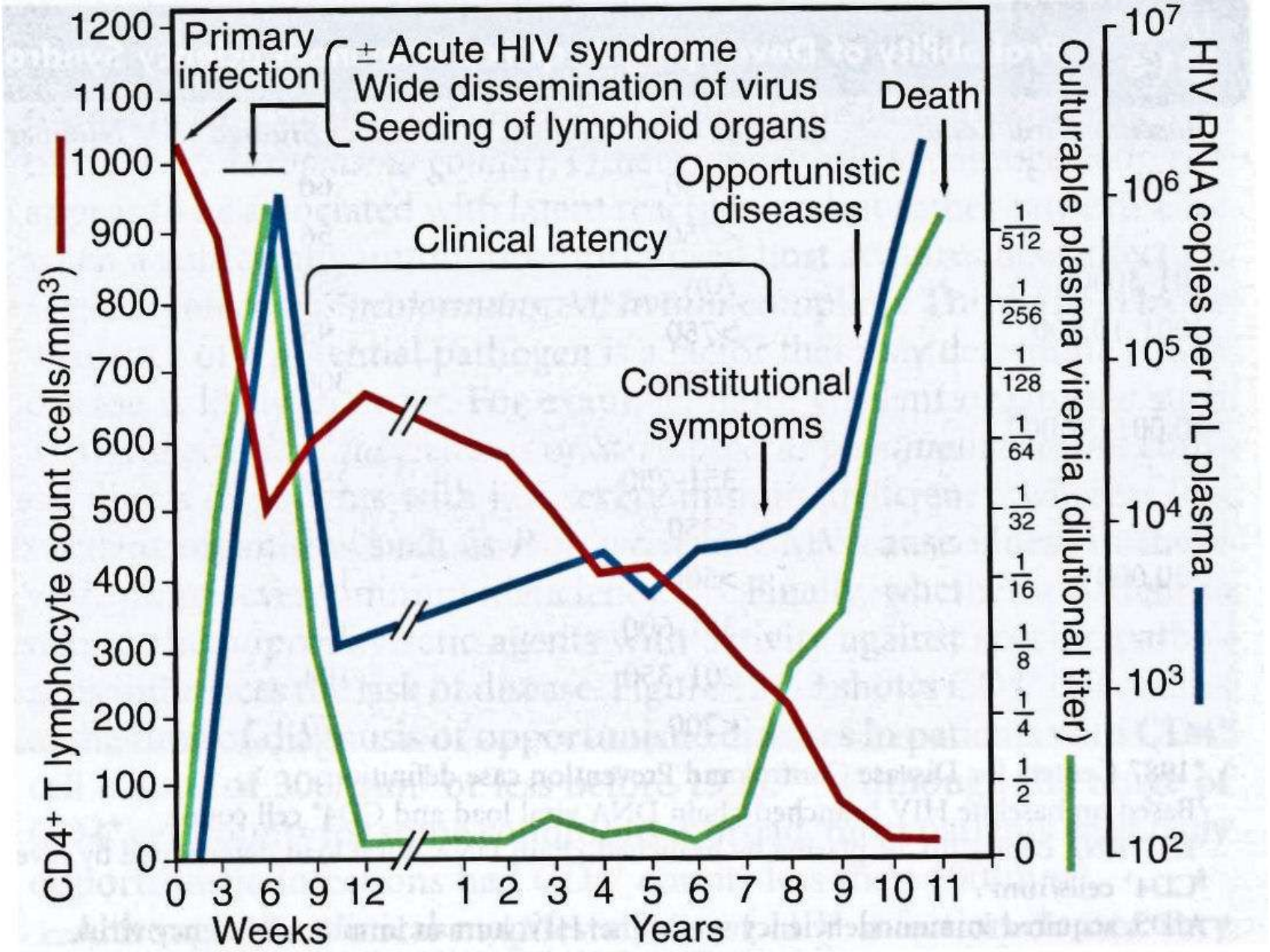
Clinical spectrum of the disease

	Asymptomatic	Symptomatic	AIDS	
Direct effects of HIV	Lymphadenopathy Neuropathies Skin disease Aseptic meningitis	Early dementia Hairy leukoplakia Wasting Thrombocytopenia Fever AIDS-related enteropathy	Kaposi's sarcoma Lymphoma Dementia Myelopathy Ataxia Dyspnea	
CD4+ cells/μL	>400	200-400	<200	<50
Years after infection	0-7	1-9	>>5	

	Asymptomatic	Symptomatic	AIDS	Late stage AIDS
Direct effects of HIV	Lymphadenopathy Neuropathies Skin disease Aseptic meningitis	Early dementia Hairy leukoplakia Wasting Thrombocytopenia Fever AIDS-related enteropathy	Kaposi's sarcoma Lymphoma Dementia Myelopathy Ataxia Dyspnea	
CD4+ cells/µL	>400	200-400	<200	<50
Years after infection	0-7	1-9	>>5	
Infections	Oral candida Herpes simplex virus Varicella zoster virus (dermatomal)	Epstein-Barr virus *Treponema pallidum* Cryptosporidia Isospora Microsporidia	*P. Carinii* Histoplasma Coccidioides tuberculosis Salmonella VZV (disseminated) Leishmania *Toxoplasma gondii* Cryptococcus encapsulated bacteria *M. avium* complex	*Toxoplasma gondii* *M. avium* complex CMV PML


Primary infection
± Acute HIV syndrome
Wide dissemination of virus
Seeding of lymphoid organs
Death
Opportunistic diseases
Clinical latency
Constitutional symptoms
CD4+ T lymphocyte count (cells/mm3)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0 3 6 9 12
Weeks
1 2 3 4 5 6 7 8 9 10 11
Years
1/512
1/256
1/128
1/64
1/32
1/16
1/8
1/4
1/2
0
Culturable plasma viremia (dilutional titer)
HIV RNA copies per mL plasma
10^7
10^6
10^5
10^4
10^3
10^2

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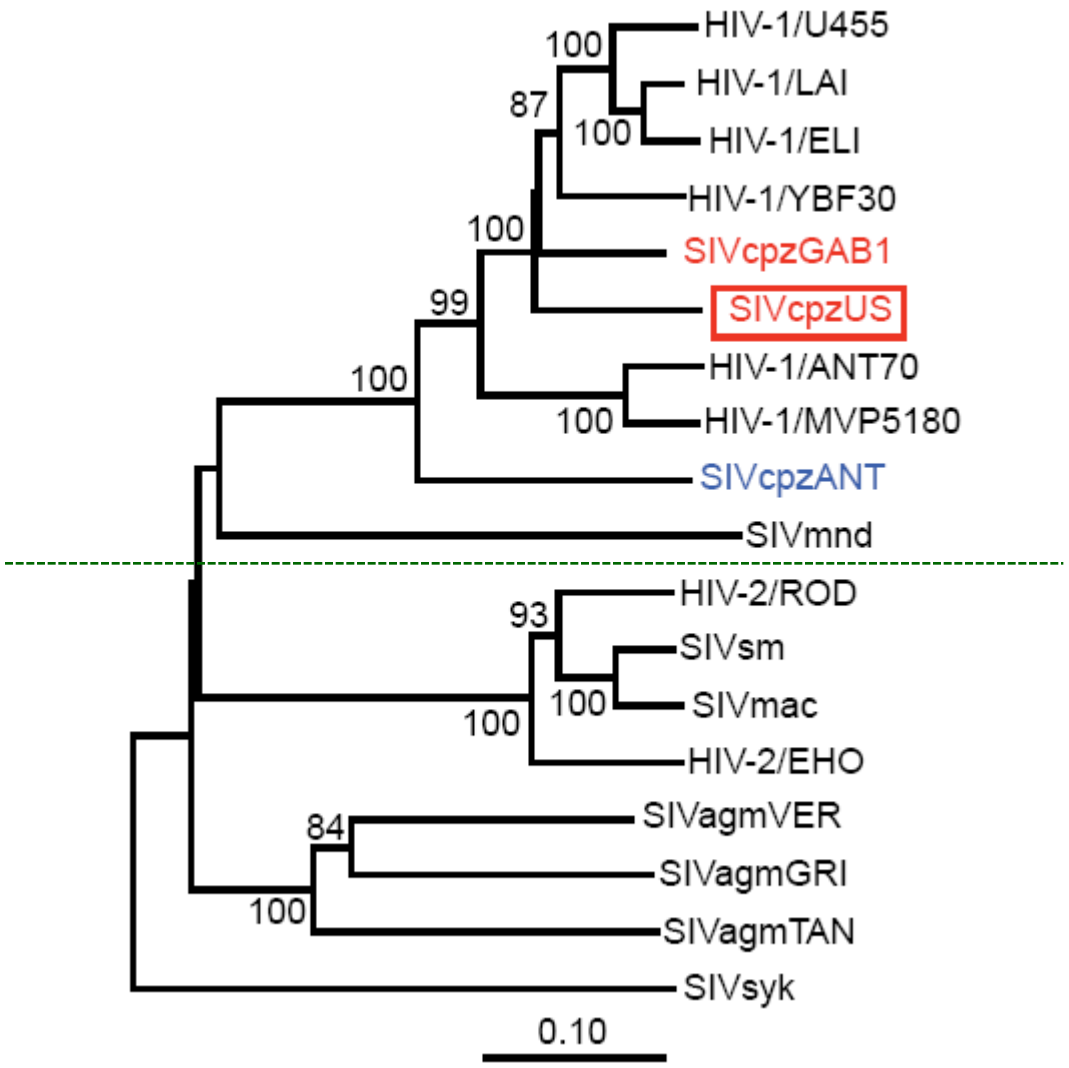
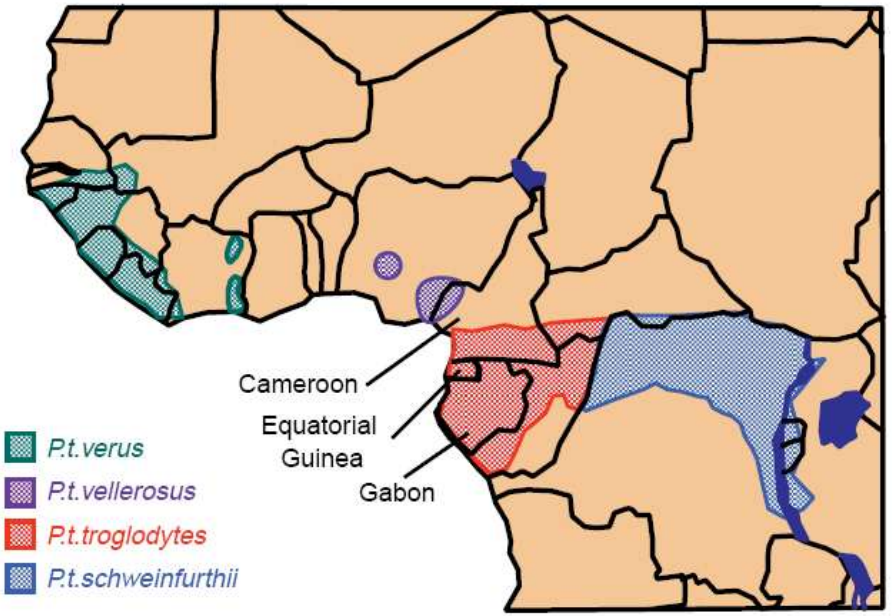
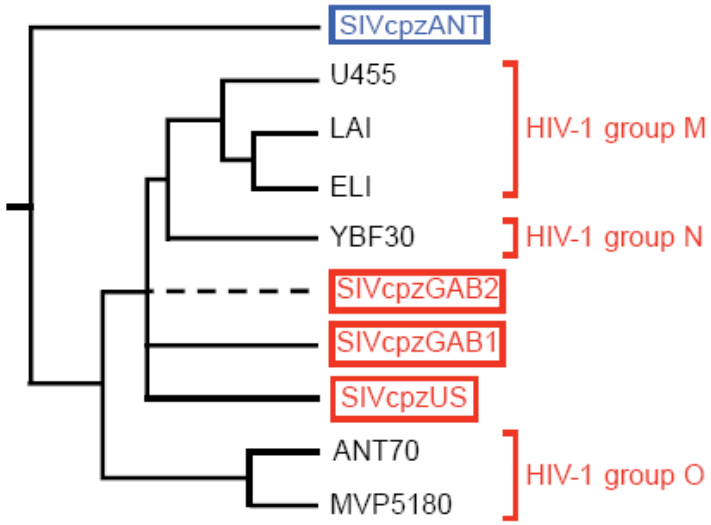
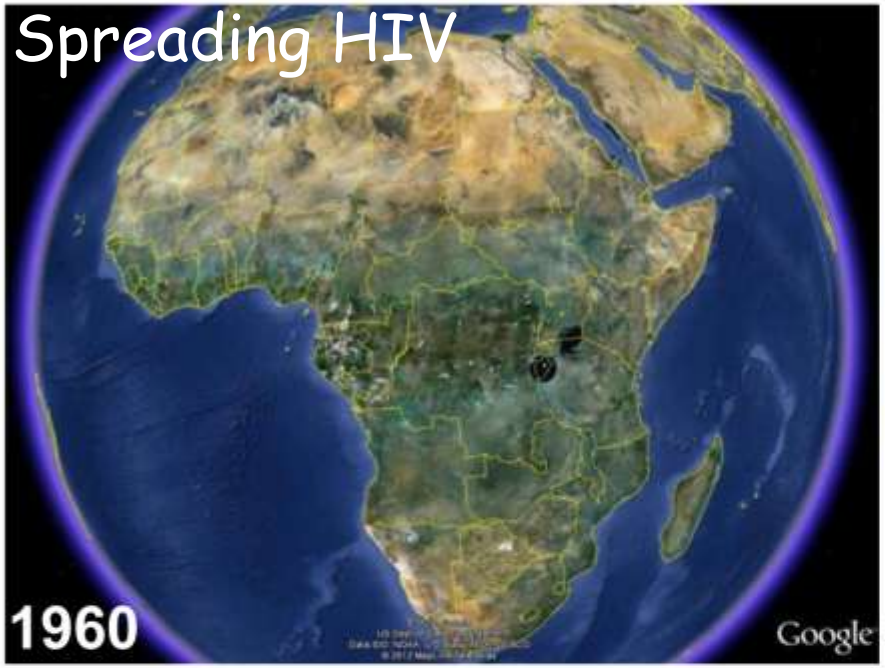
Chimps - 1


HIV-1/U455
HIV-1/LAI
HIV-1/ELI
HIV-1/YBF30
SIVcpzGAB1
SIVcpzUS
HIV-1/ANT70
HIV-1/MVP5180
SIVcpzANT
SIVmnd
HIV-2/ROD
SIVsm
SIVmac
HIV-2/EHO
SIVagmVER
SIVagmGRI
SIVagmTAN
SIVsyk
100
87
100
100
99
100
100
93
100
100
84
100
0.10

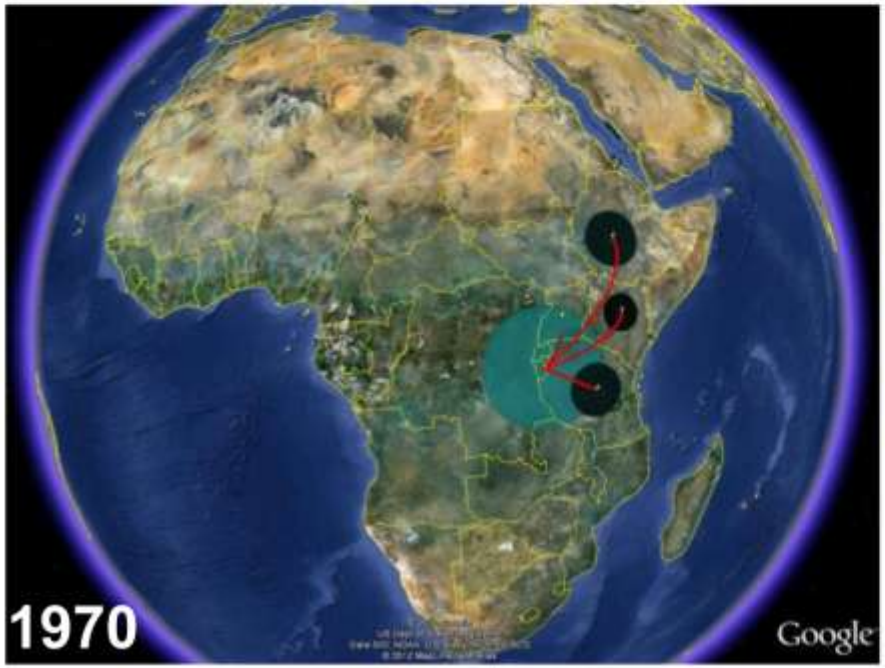
Chimps - 2

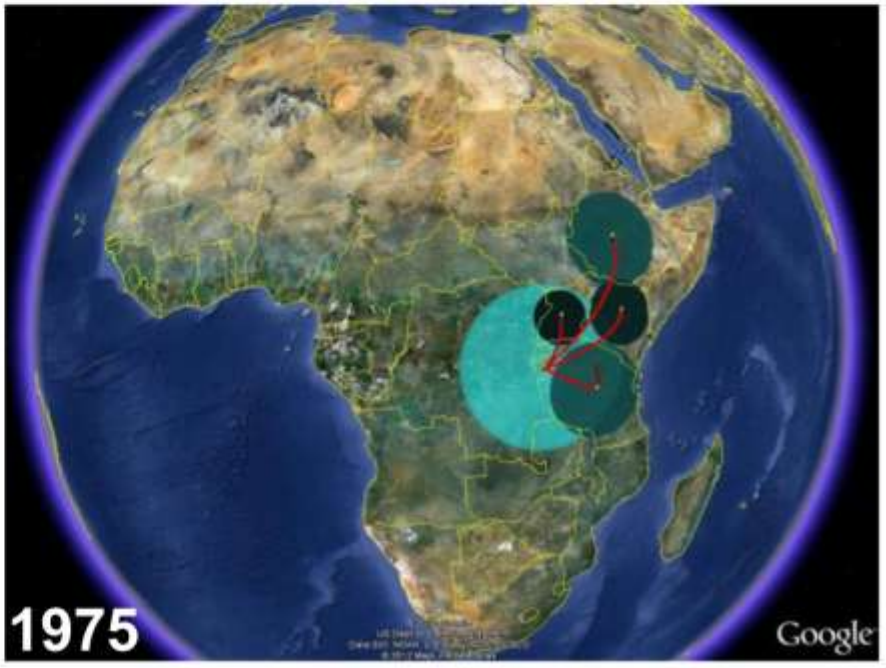

Cameroon
Equatorial Guinea
Gabon
P.t.verus
P.t.vellerosus
P.t.troglodytes
P.t.schweinfurthii


SIVcpzANT
U455
LAI
ELI
YBF30
SIVcpzGAB2
SIVcpzGAB1
SIVcpzUS
ANT70
MVP5180
HIV-1 group M
HIV-1 group N
HIV-1 group O


Spreading HIV
1960
Google


1965
Google


1970
Google


1975
Google

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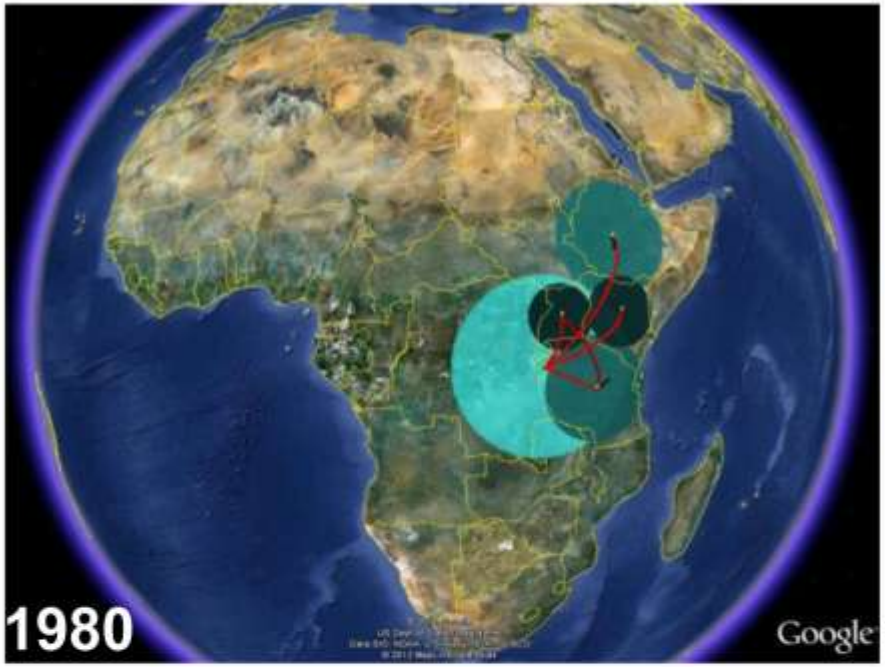
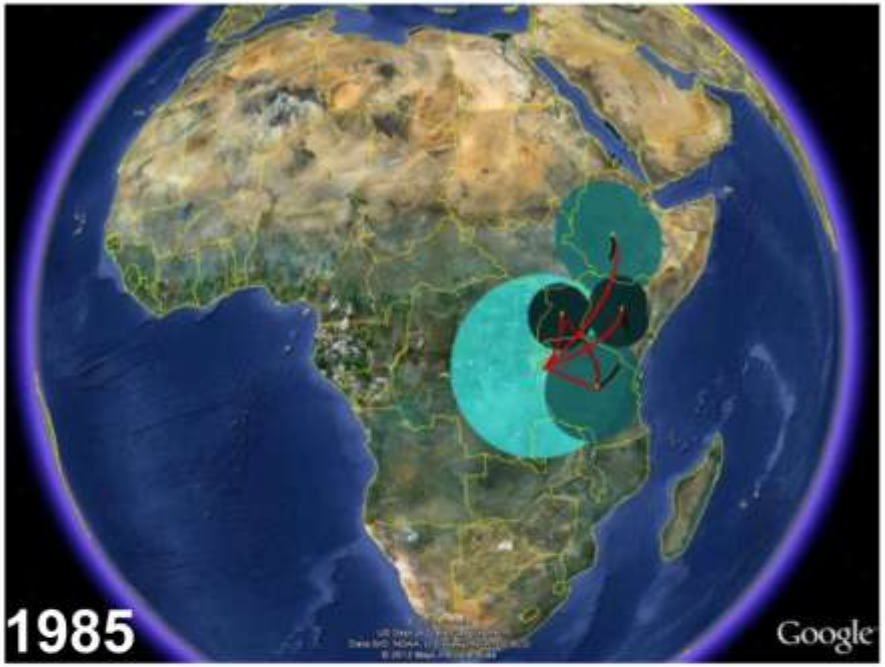
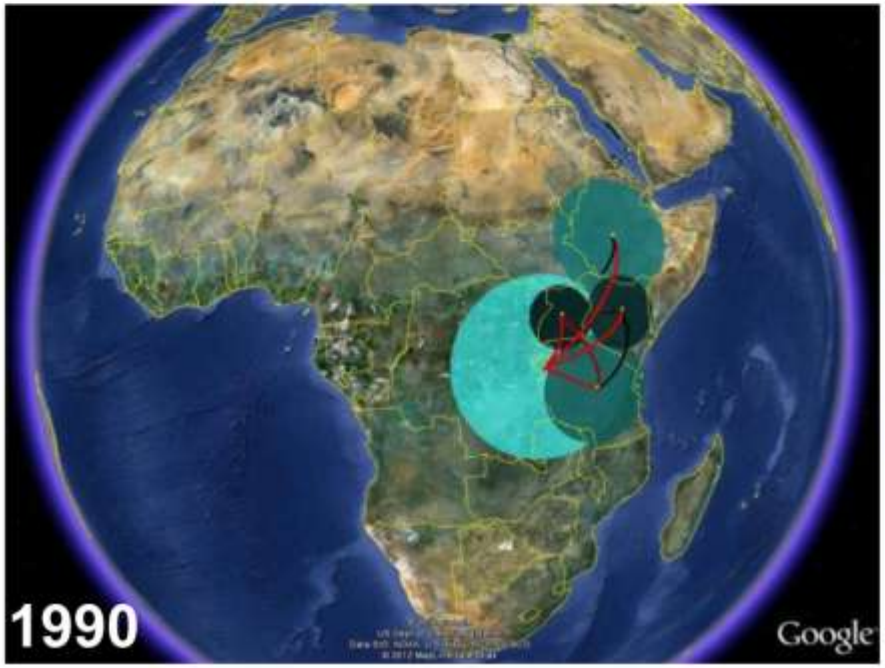
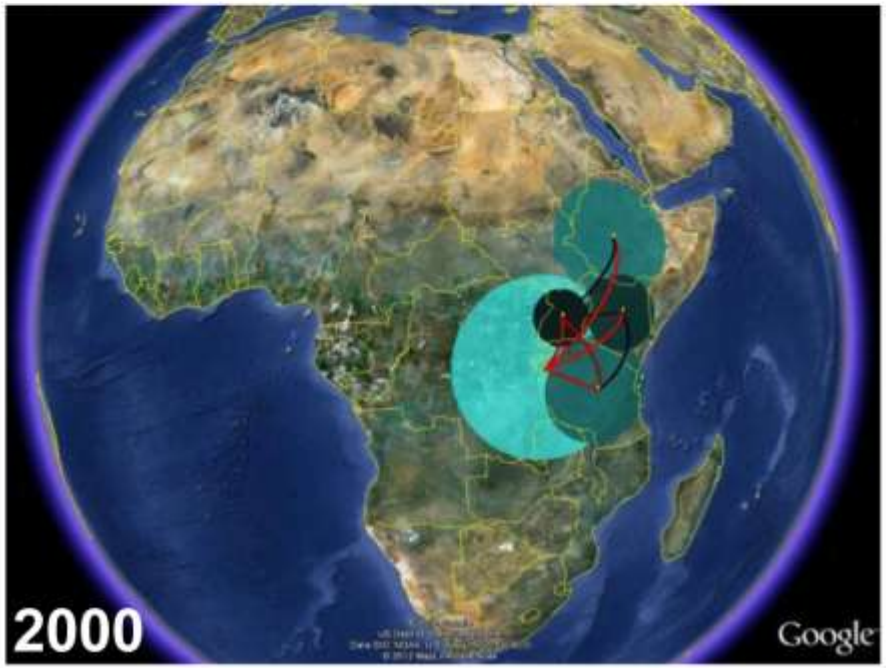

1980
Google


1985
Google


1990
Google


2000
Google

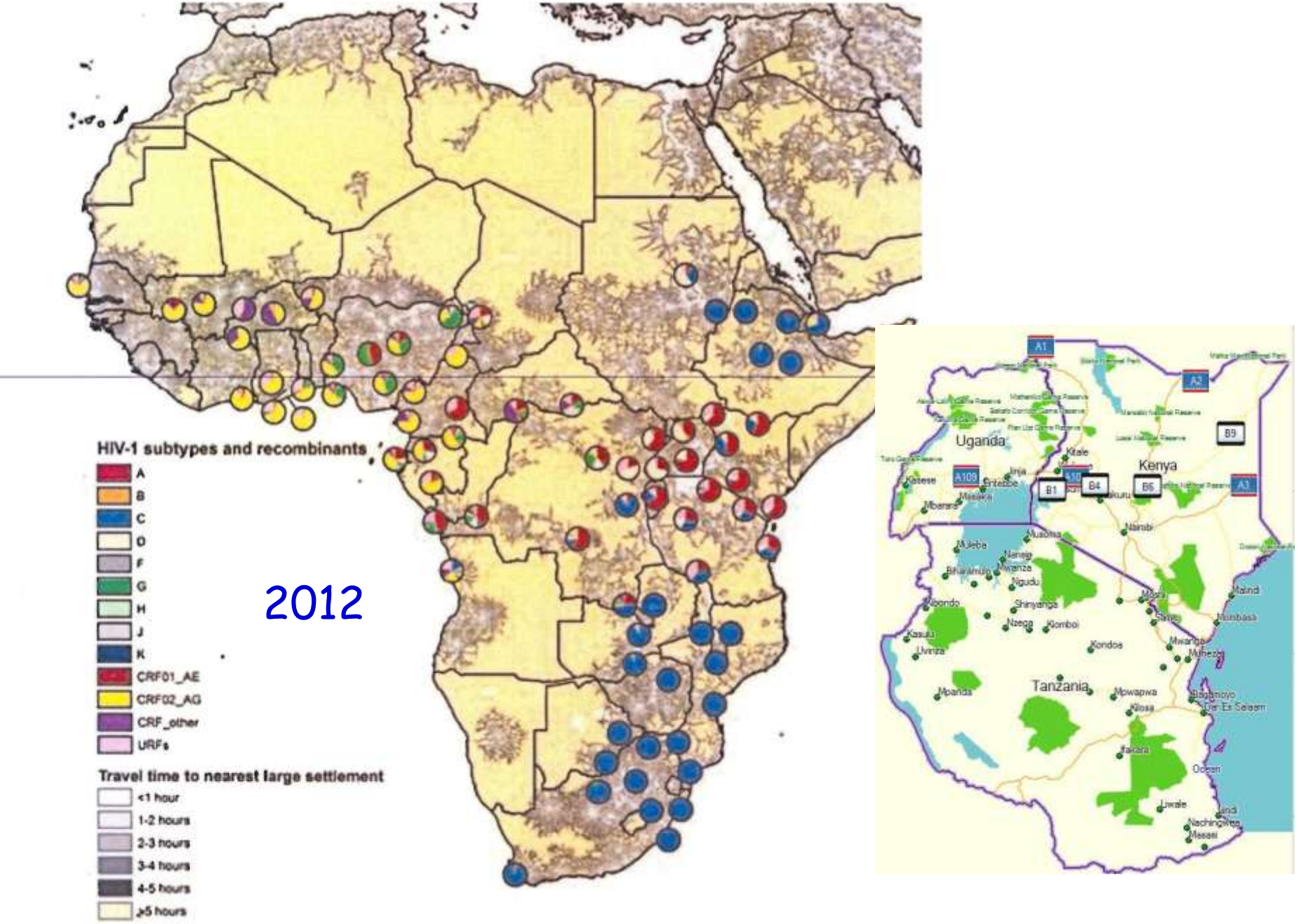


Fig. 1. The spatial distribution of HIV-1 subtype and recombinant samples in mainland sub-Saharan Africa overlaid on a map showing estimated travel times of less than 5 hours to the nearest city of >100,000 population. CRF, Circulating Recombinant Form; URF, Unique Recombinant Form.

Posted on Friday, 07 September 2012 14:26

Long distance truck drivers are spreading HIV Museveni

UGANDA'S PRESIDENT MUSEVENI SAYS THAT TRUCK DIRVERS ARE RESPONSIBLE FOR THE UPSURGE IN HIV INFECTION RATES

Ugandan President Yoweri Museveni has warned women in his country against being involved with long distance truck drivers, saying they are responsible for the spread of HIV.

Museveni's ire was particularly directed at cross border drivers, whom he accuses of having multiple relationships in cities they drive through.

The East African country is experiencing an upsurge in HIV prevalence after years of being the yardstick on how countries could reduce the prevalence of the disease.

Museveni's admonishment of truck drivers follows an outcry by Ugandan children living with HIV and Aids, that they were being stigmatised. Uganda Youth Development Association, an organisation dedicated to fighting for the rights of children and youth, says a number of children living with HIV are stigmatised and is appealing for government intervention to protect the victims.

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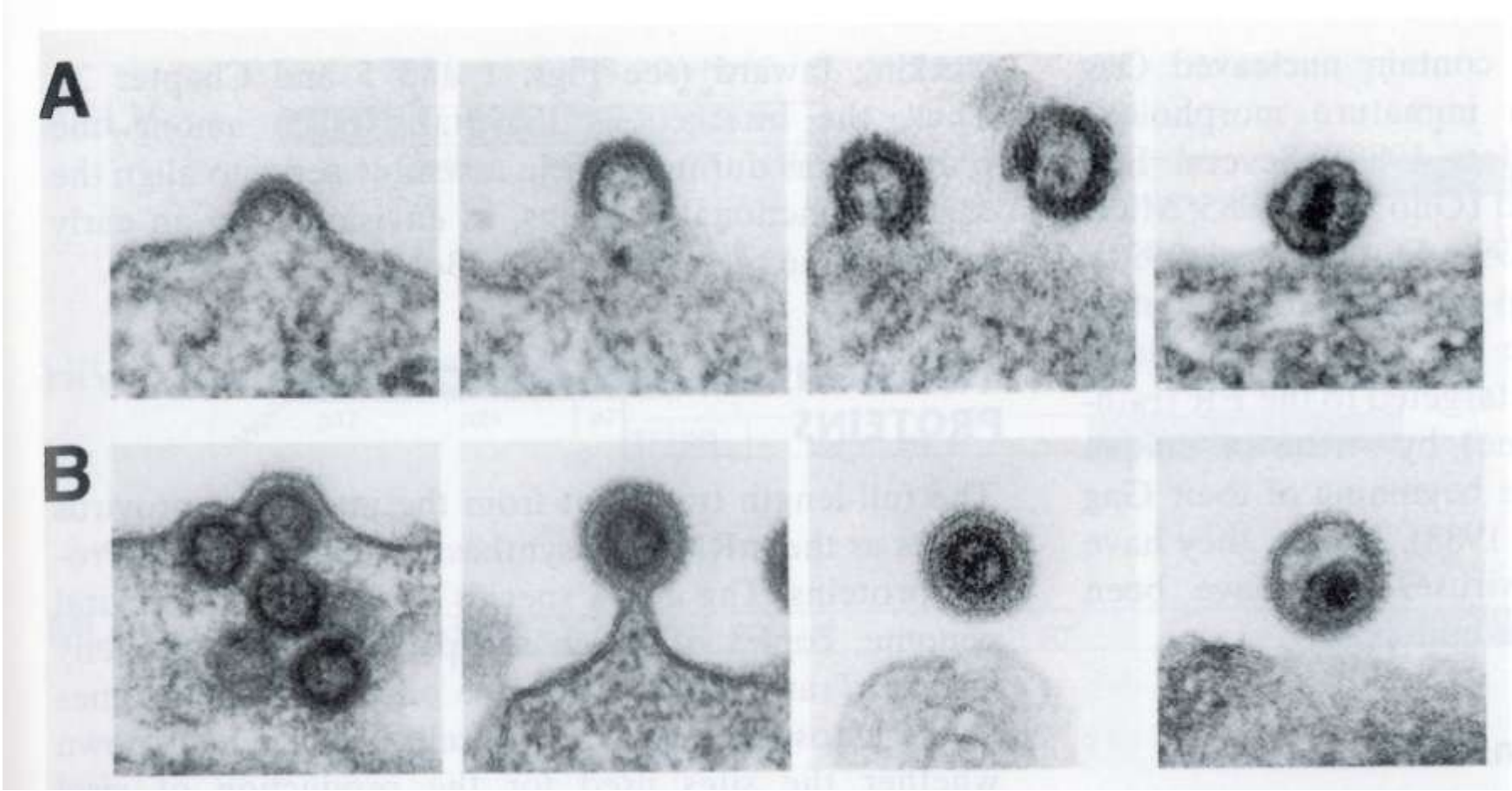
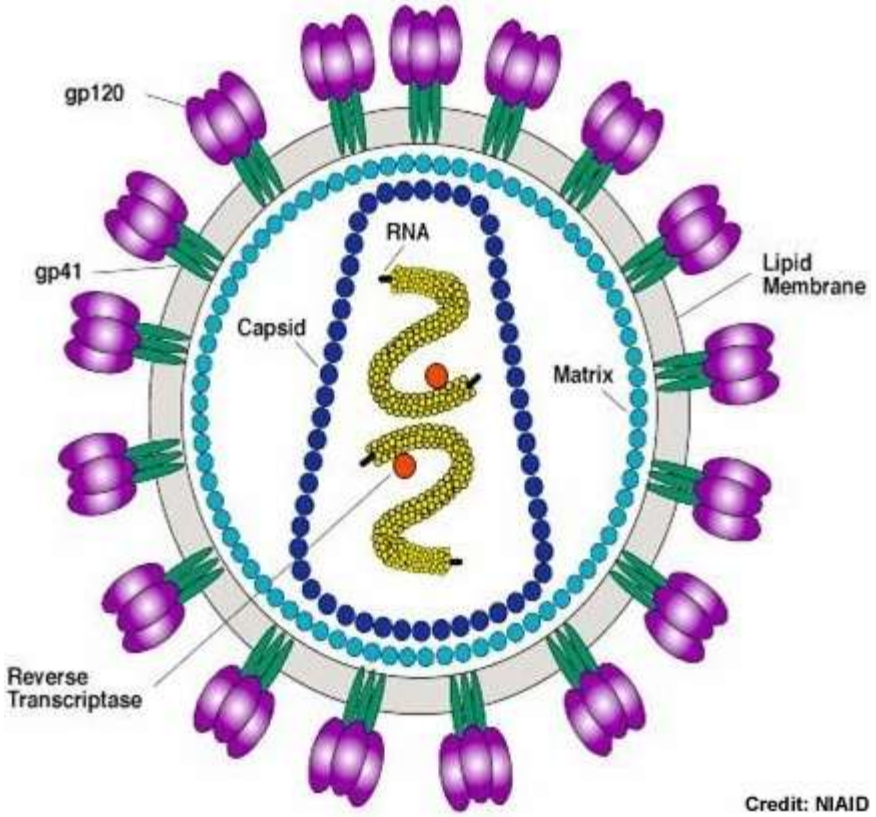
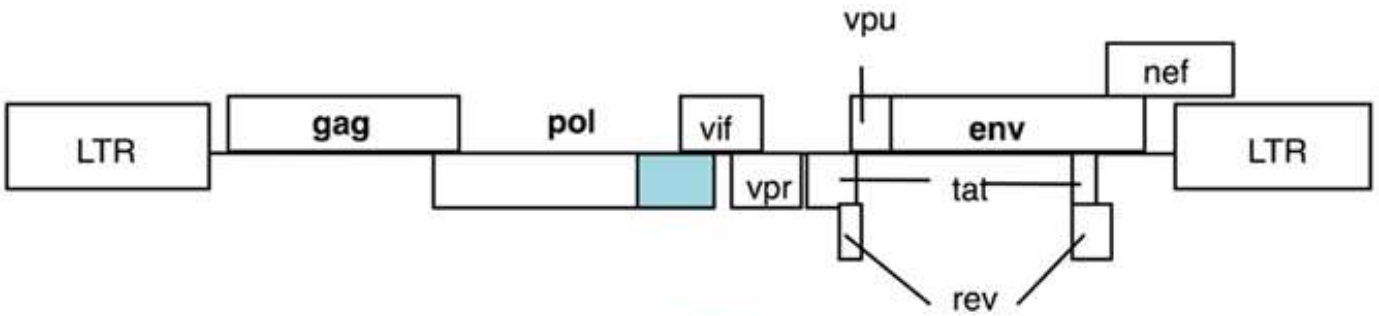
HIV-1 budding from a cell

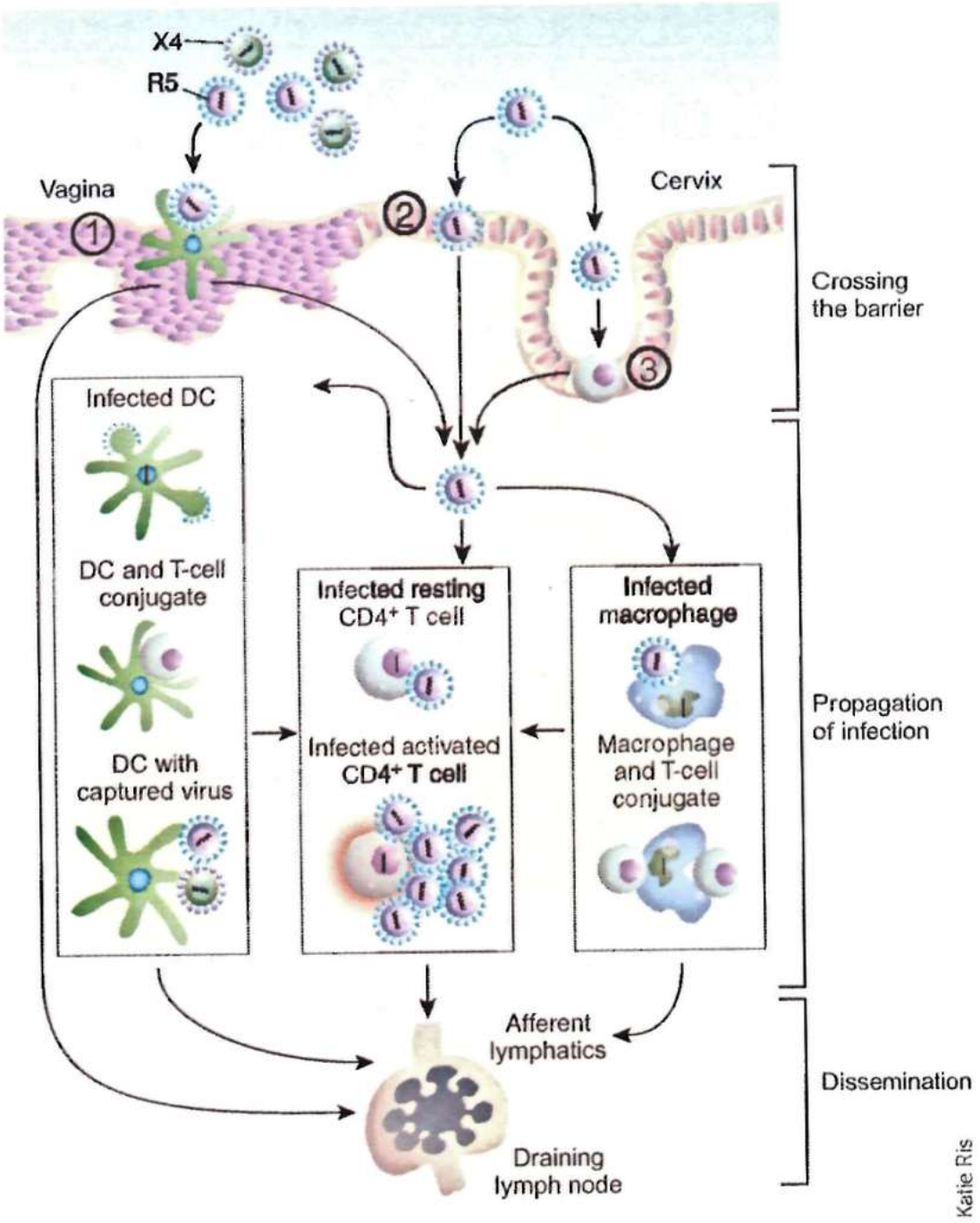


HIV-1 virion

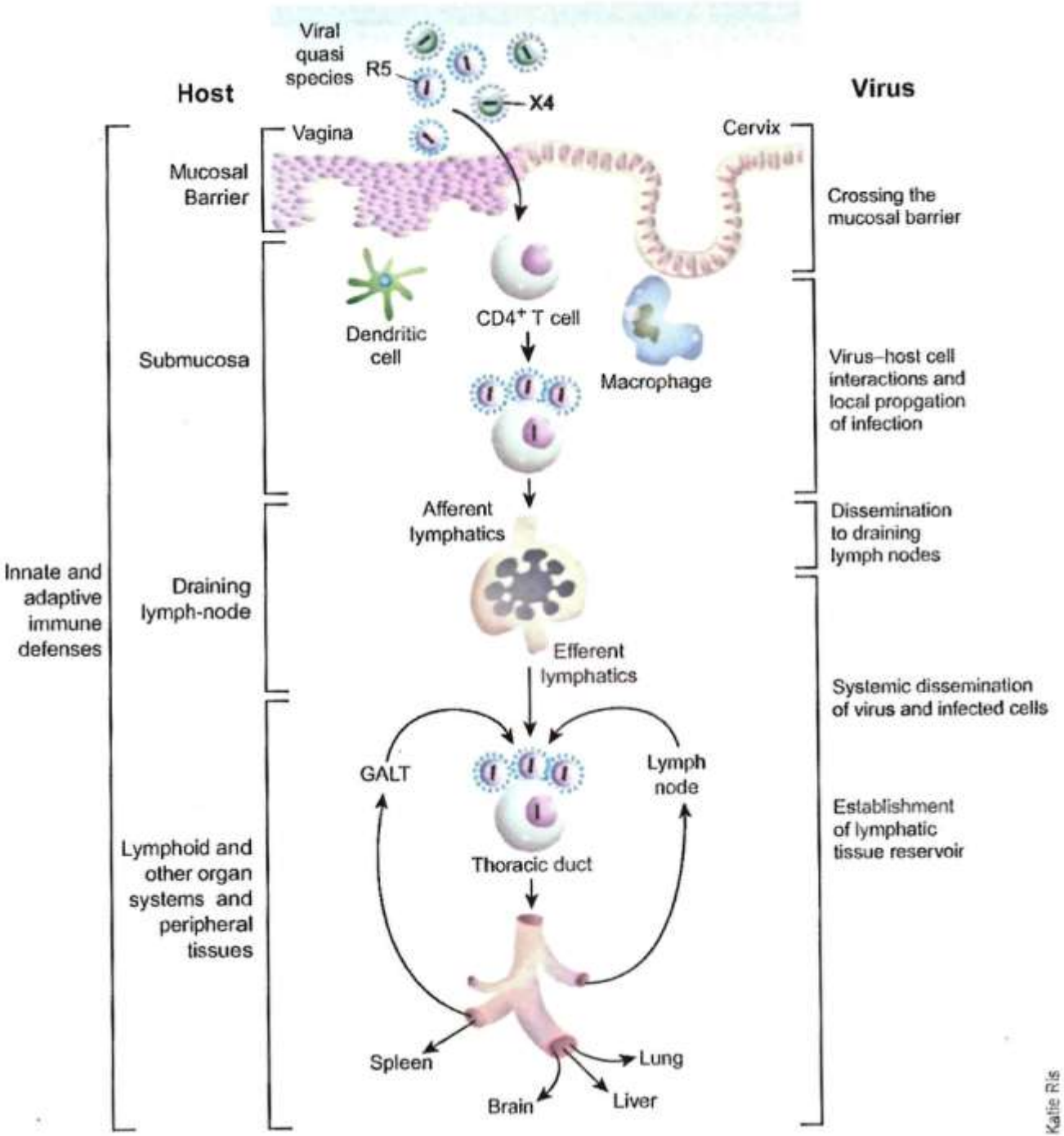

gp120
gp41
RNA
Capsid
Lipid
Membrane
Matrix
Reverse
Transcriptase
Credit: NIAID


vpu
nef
LTR
gag
pol
vif
env
LTR
vpr
tat
rev

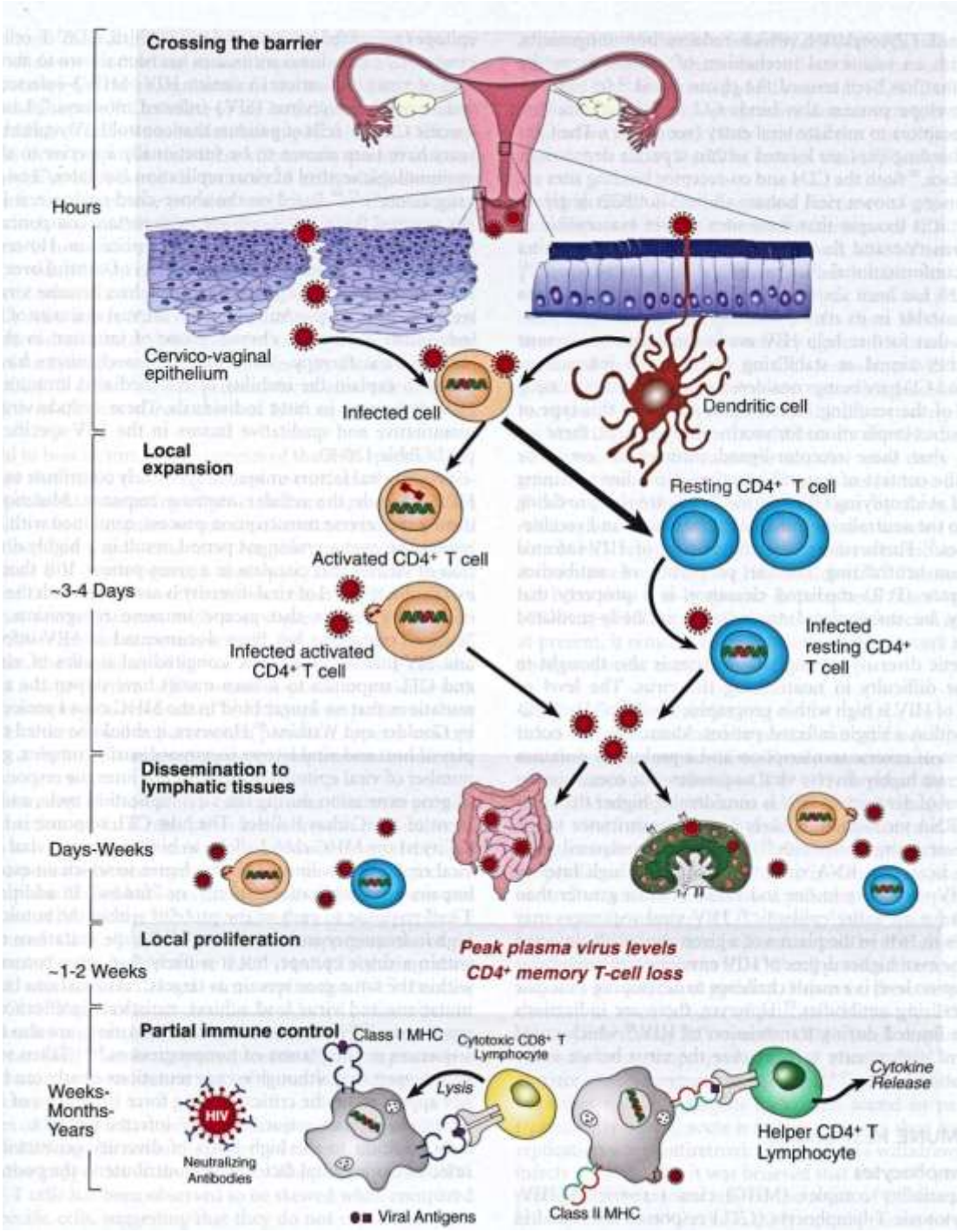
Acute infection



Spread of infection



Days
to
Months
to
Years



Gastrointestinal Tract as a Major Site of CD4$^+$ T Cell Depletion and Viral Replication in SIV Infection

Ronald S. Veazey, MaryAnn DeMaria, Laura V. Chalifoux, Daniel E. Shvetz, Douglas R. Pauley, Heather L. Knight, Michael Rosenzweig, R. Paul Johnson, Ronald C. Desrosiers, Andrew A. Lackner*

Human and simian immunodeficiency virus (HIV and SIV) replicate optimally in activated memory CD4$^+$ T cells, a cell type that is abundant in the intestine. SIV infection of rhesus monkeys resulted in profound and selective depletion of CD4$^+$ T cells in the intestine within days of infection, before any such changes in peripheral lymphoid tissues. The loss of CD4$^+$ T cells in the intestine occurred coincident with productive infection of large numbers of mononuclear cells at this site. The intestine appears to be a major target for SIV replication and the major site of CD4$^+$ T cell loss in early SIV infection.

It is now thought that ongoing HIV replication results in a continual loss of CD4$^+$ T lymphocytes that is nearly balanced by the production of new CD4$^+$ T lymphocytes (*1*). This model explains some of the puzzles of HIV infection, but the events that occur in the initial stage of infection remain largely unexplored. Although it is clear that HIV targets lymphoid tissue, nearly all studies in this area have focused on peripheral blood and lymph nodes. These studies overlook the fact that the gastrointestinal tract contains most of the lymphoid tissue in the body (*2*, *3*). Furthermore, it is likely that the behavior of HIV in the unique immunologic environment of the intestinal mucosa differs from that observed in the periphery.

The gut-associated lymphoid tissue (GALT) consists of organized lymphoid tissue (Peyer's patches and solitary lymphoid follicles) as well as large numbers of activated memory T lymphocytes diffusely dis-

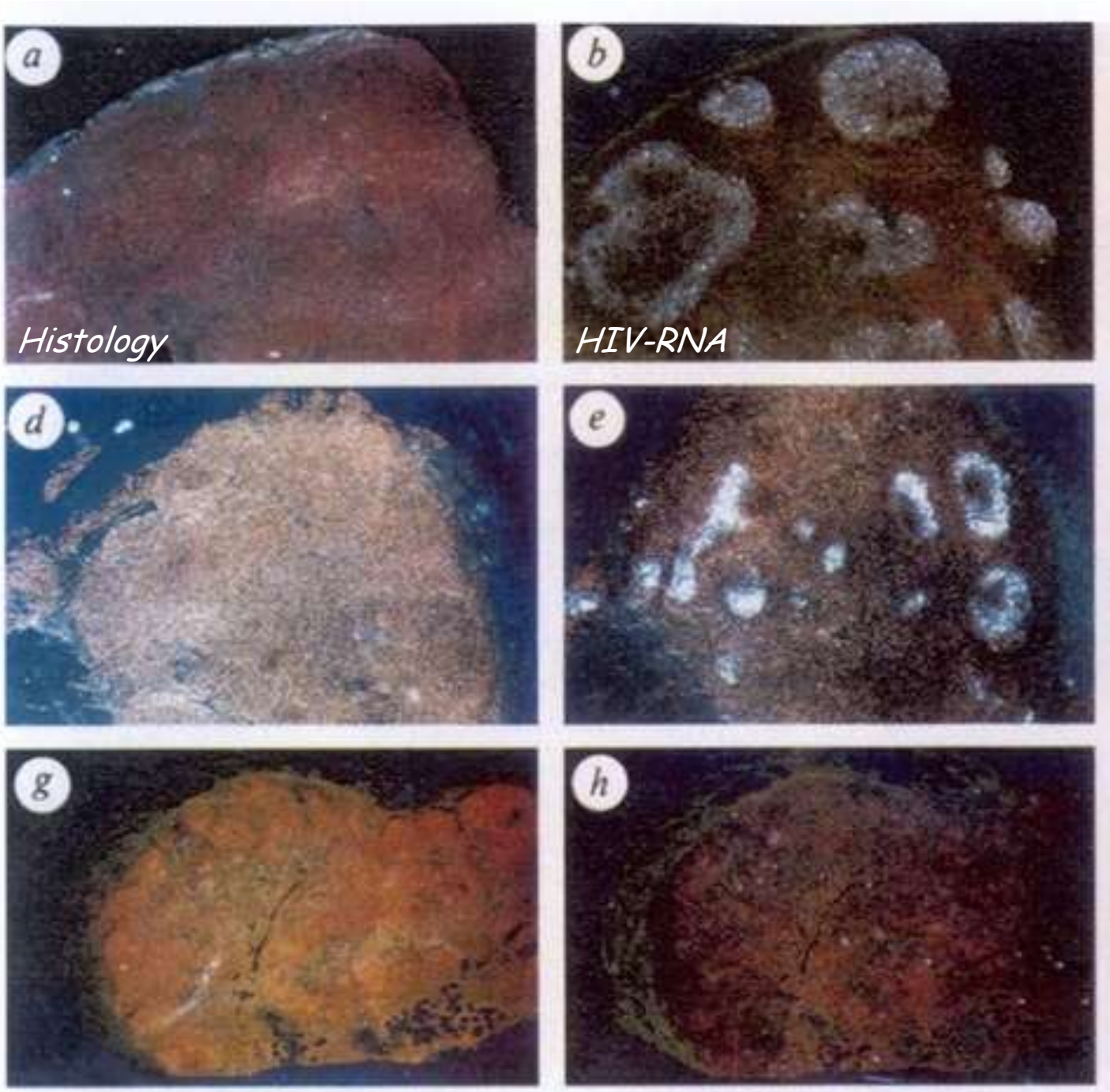
1998

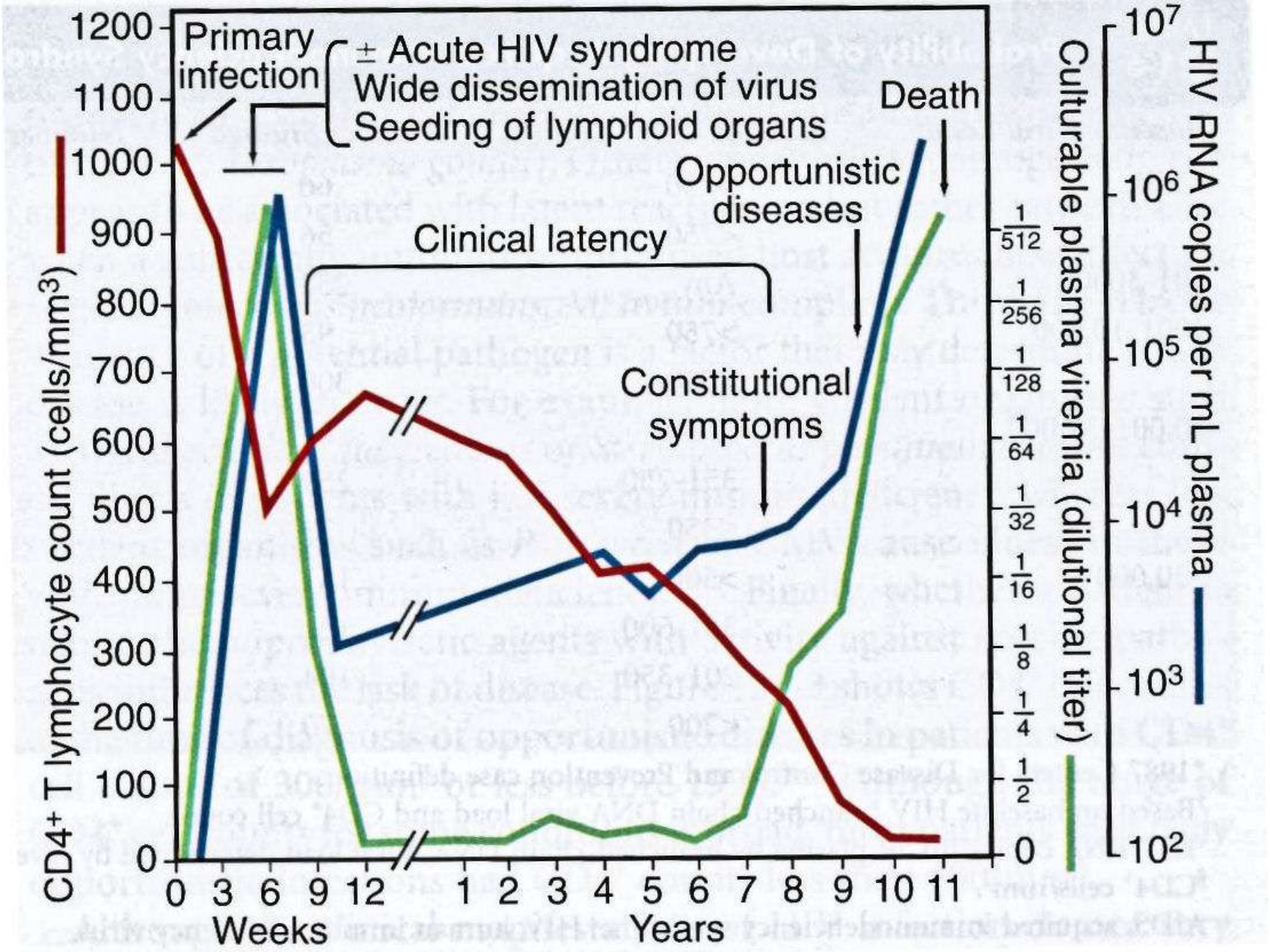
Lymph Node

Early

Mid

Late

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Weeks
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Years
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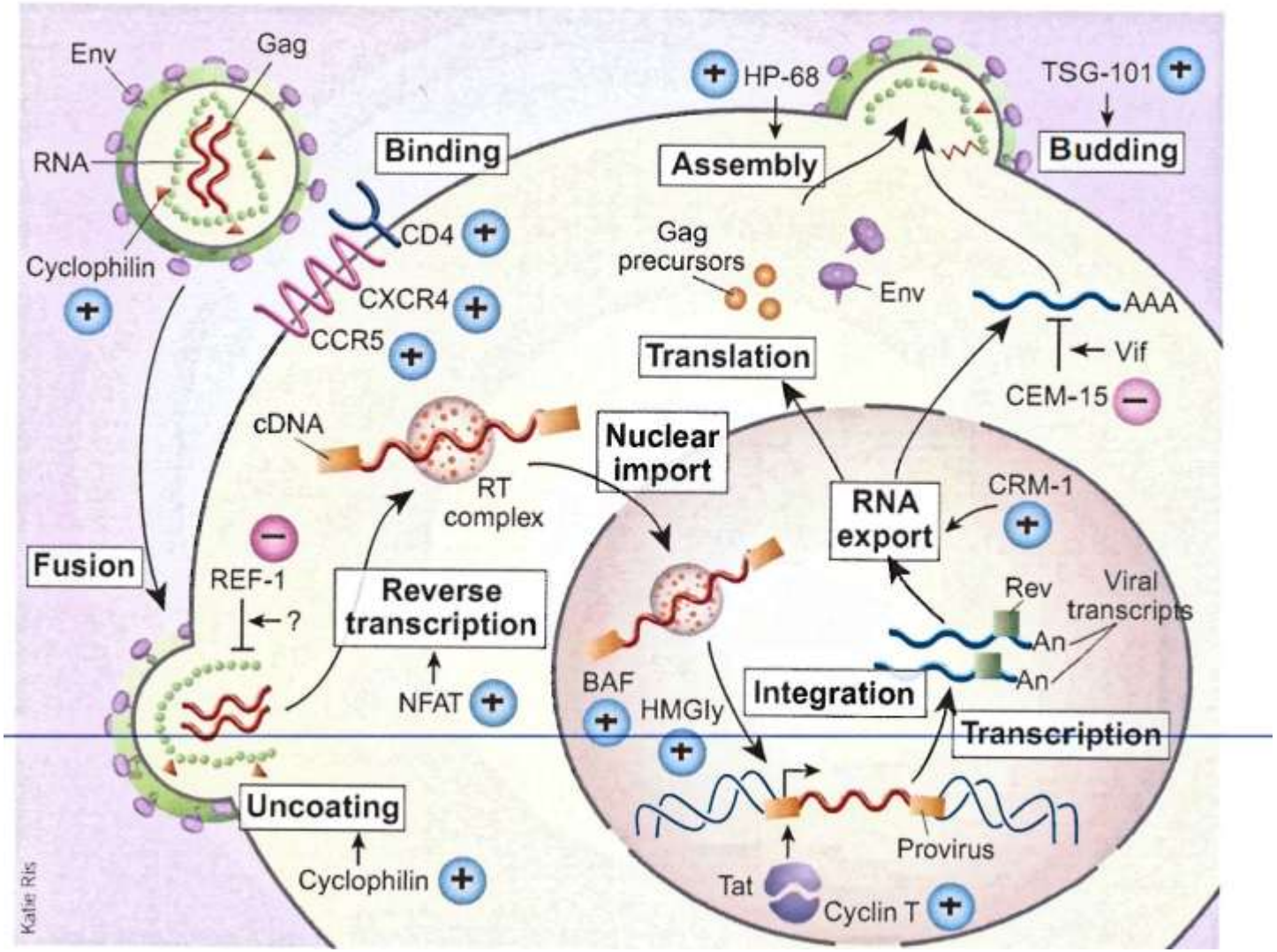
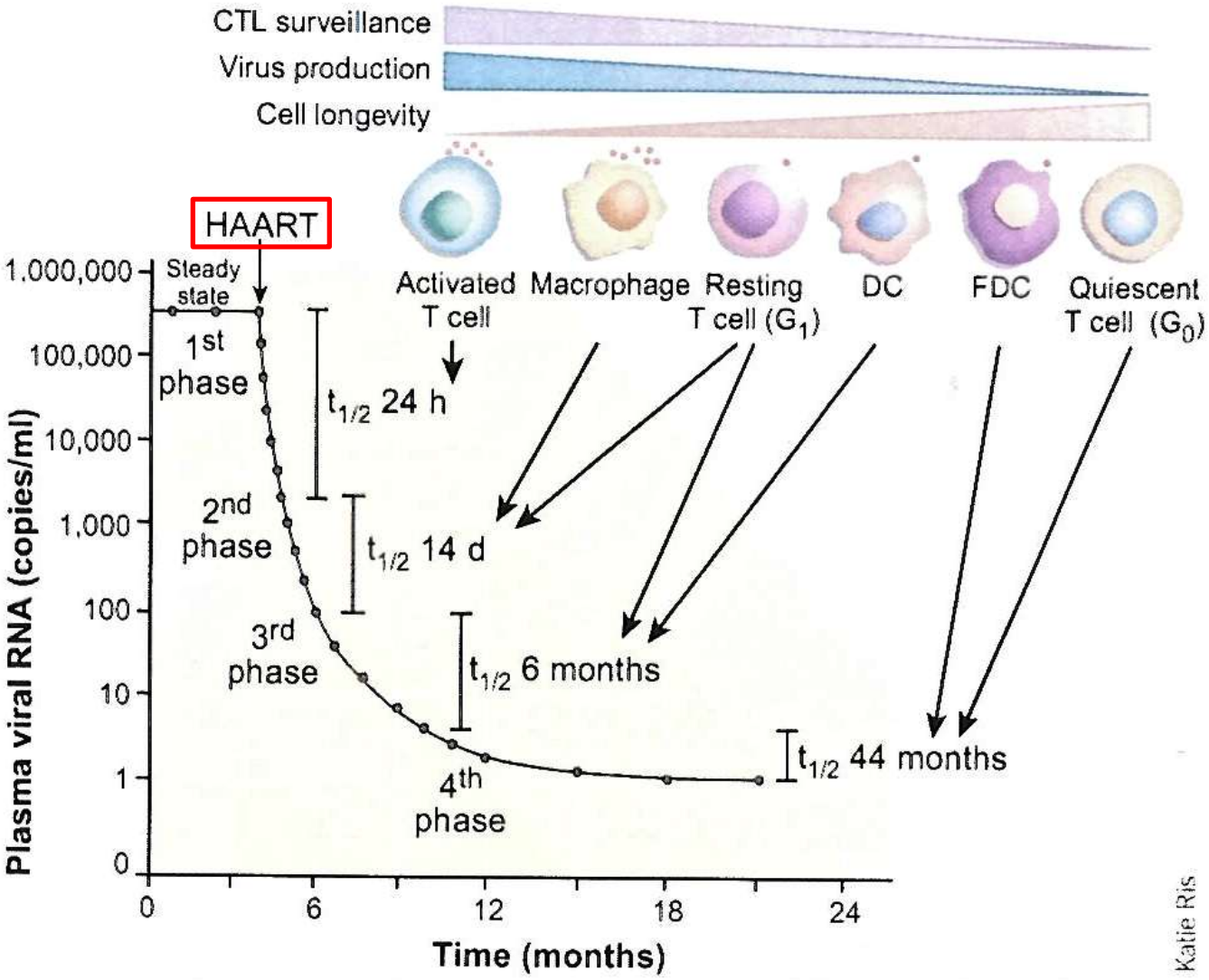
1/256
1/128
1/64
1/32
1/16
1/8
1/4
1/2
0
Culturable plasma viremia (dilutional titer)
HIV RNA copies per mL plasma
10^7
10^6
10^5
10^4
10^3
10^2

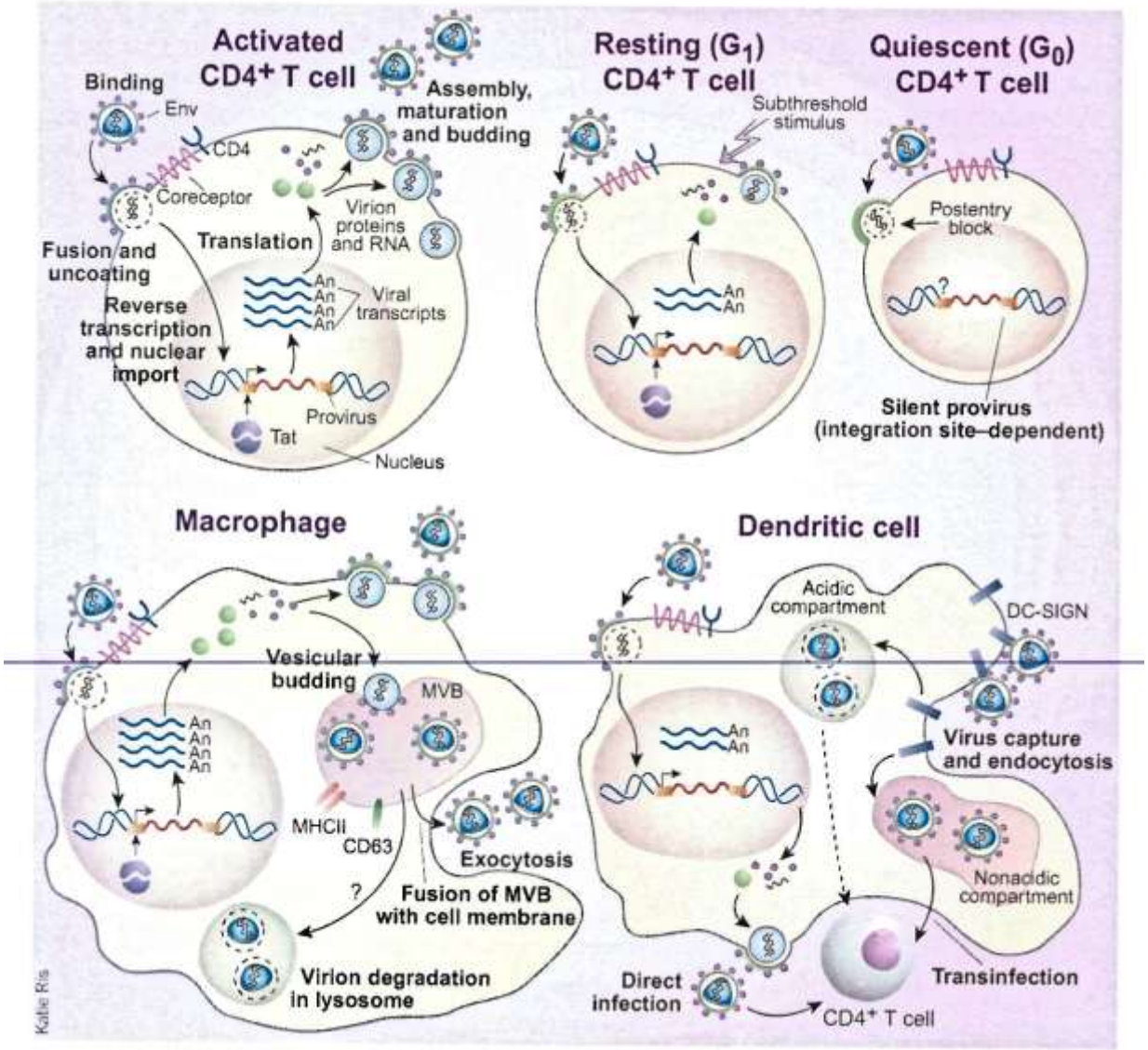
The lifecycle of HIV-1 in the cell



Cell types & their output of virus on anti-HIV drugs



Virus replication in different cell types



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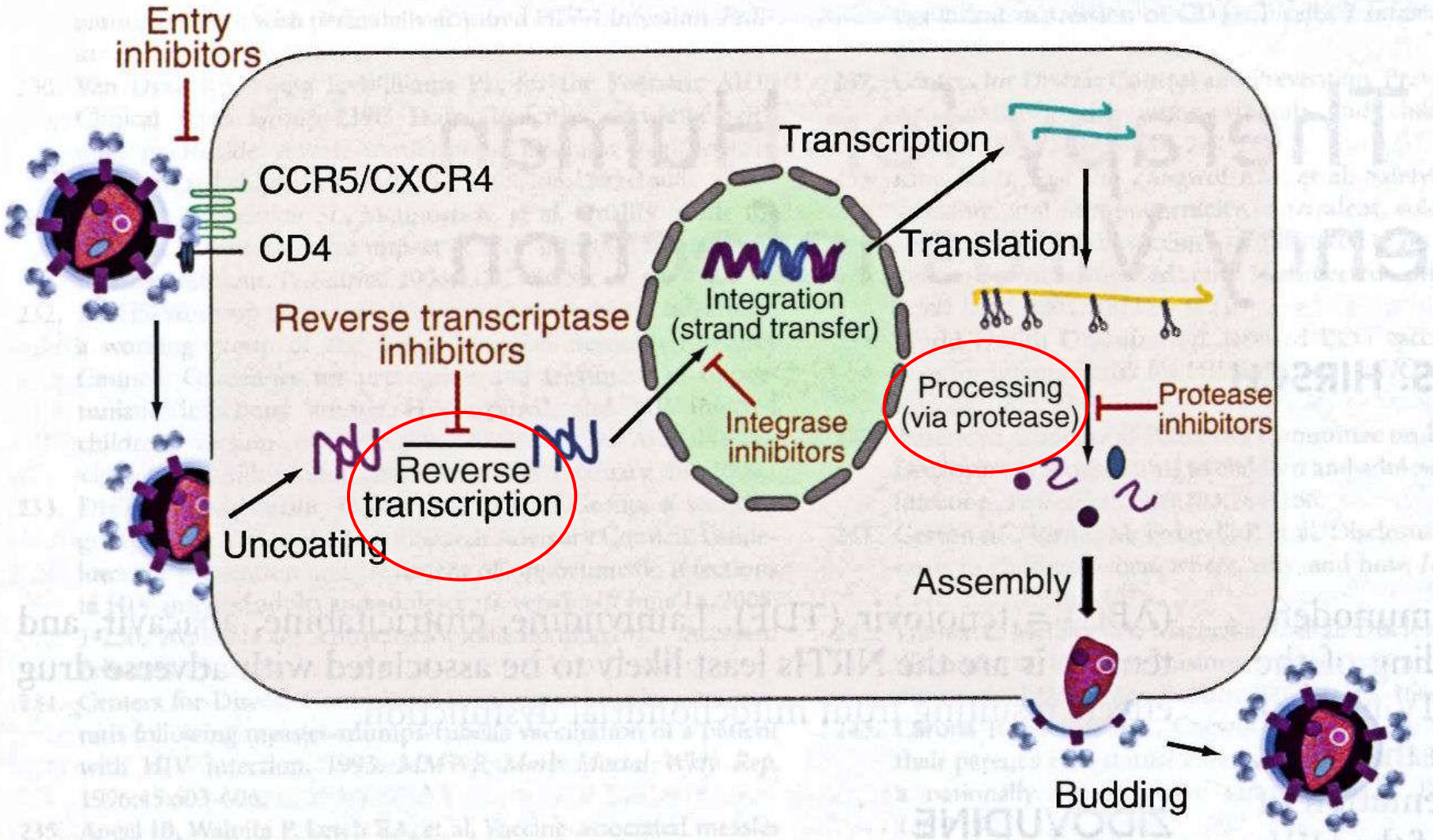
Drug targets - 1



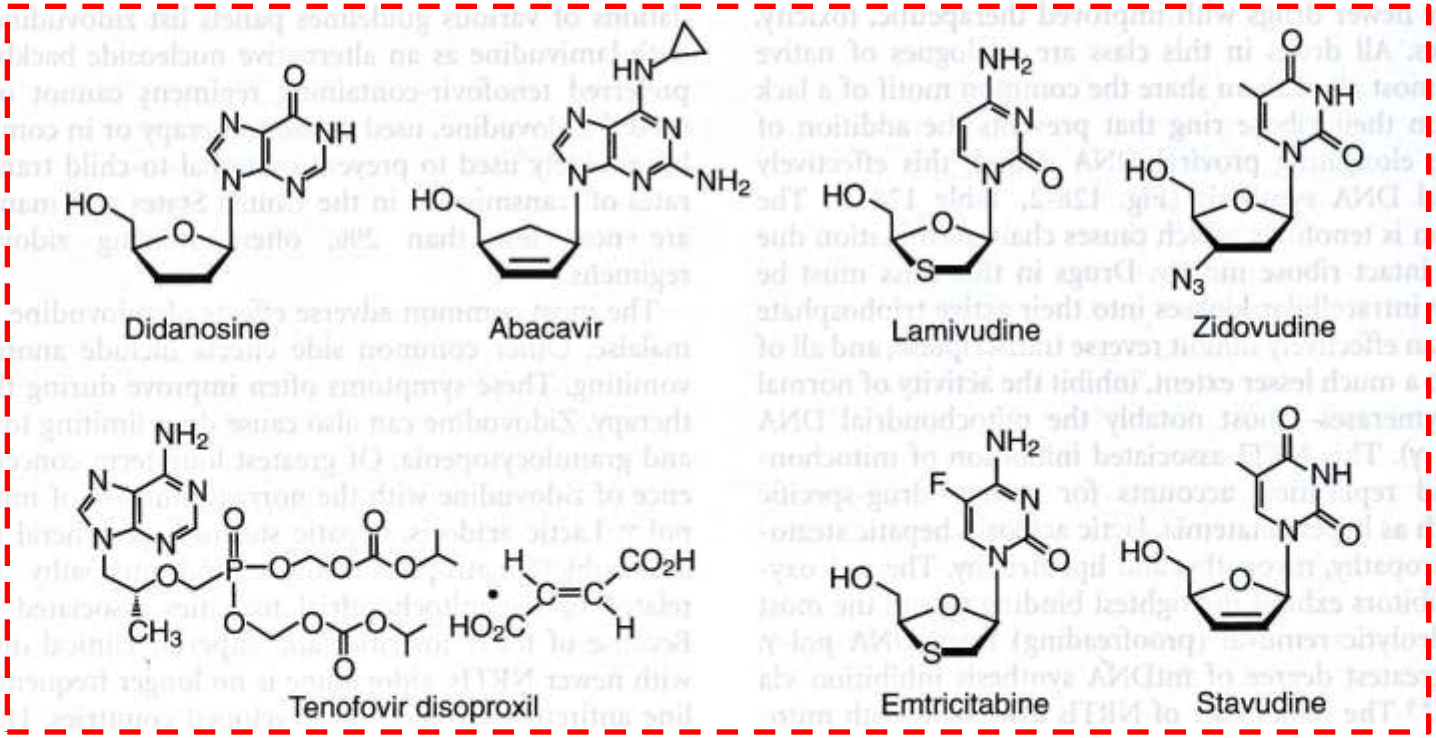


Figure 128-2 Nucleoside and nucleotide analogue reverse transcriptase inhibitors. Shown on top are the naturally occurring nucleosides (adenosine, guanosine, cytosine, and thymidine); below each of them are analogues used in antiretroviral therapy.

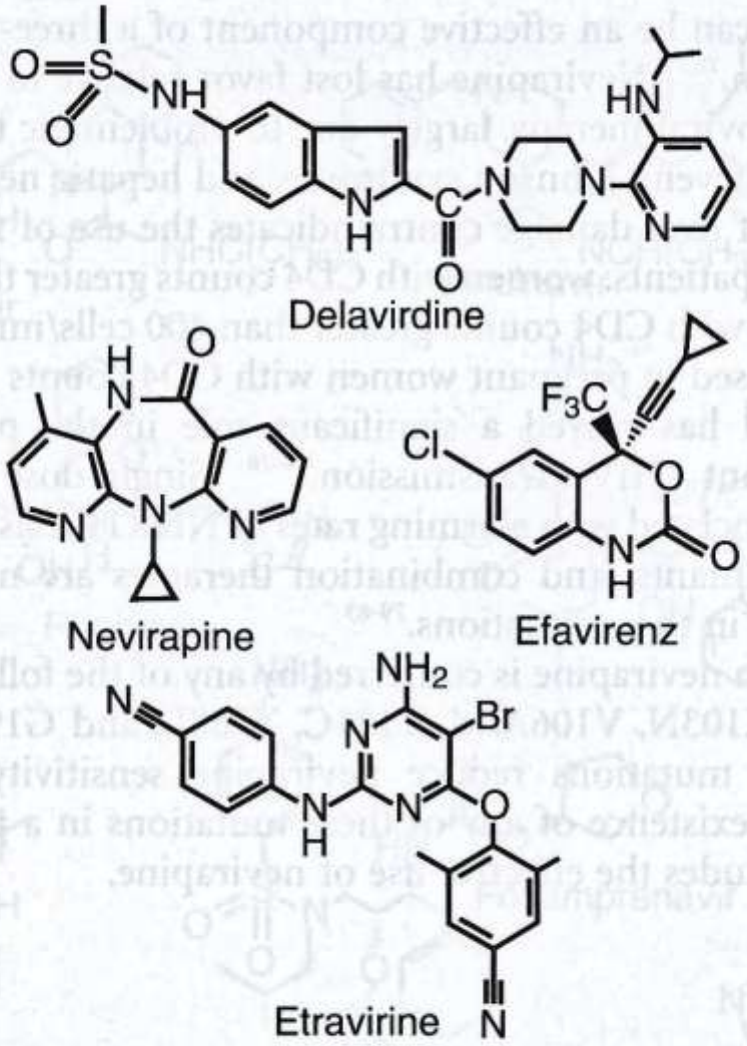


Figure 128-3 **Non-nucleoside reverse transcriptase inhibitors.**

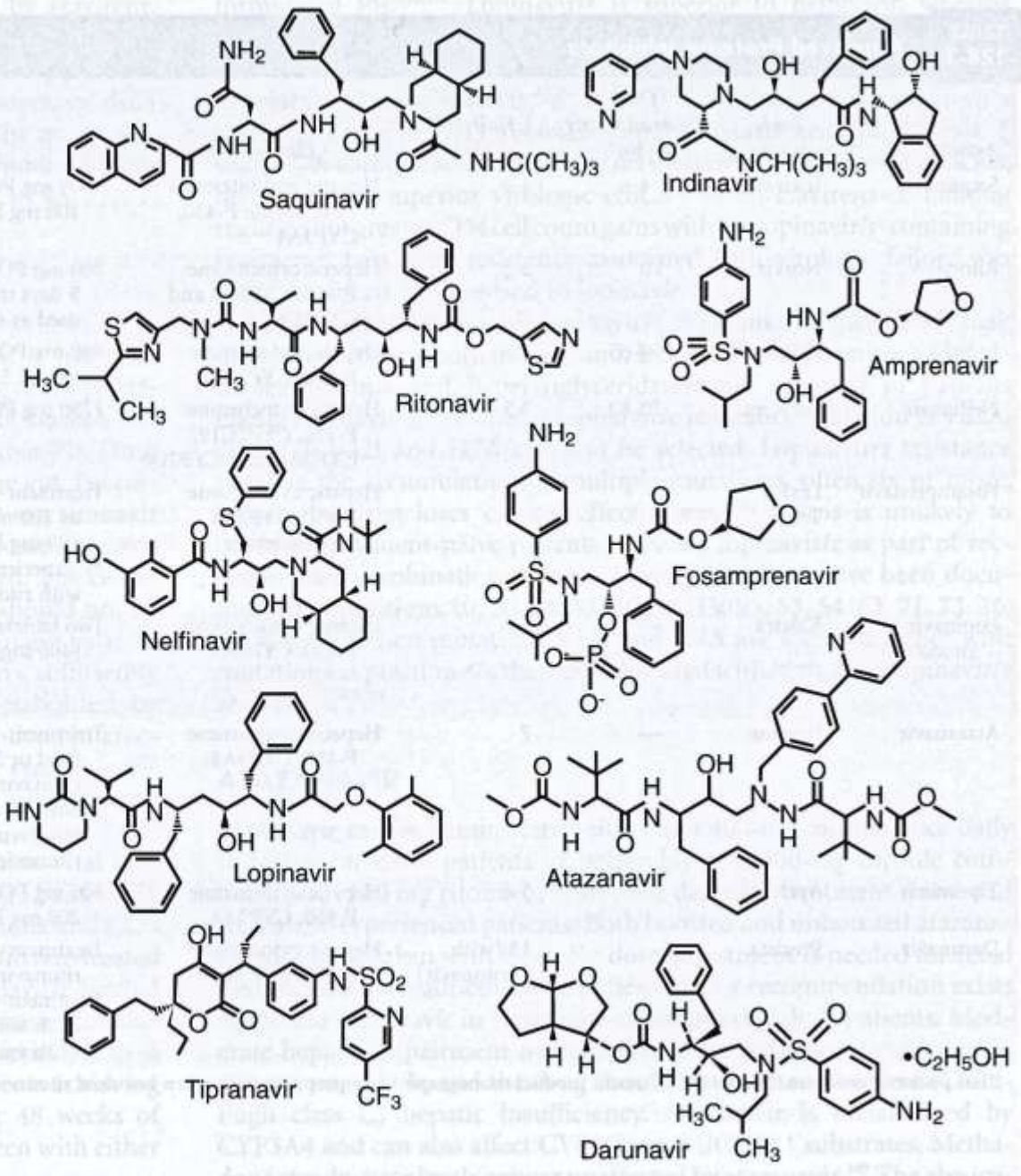
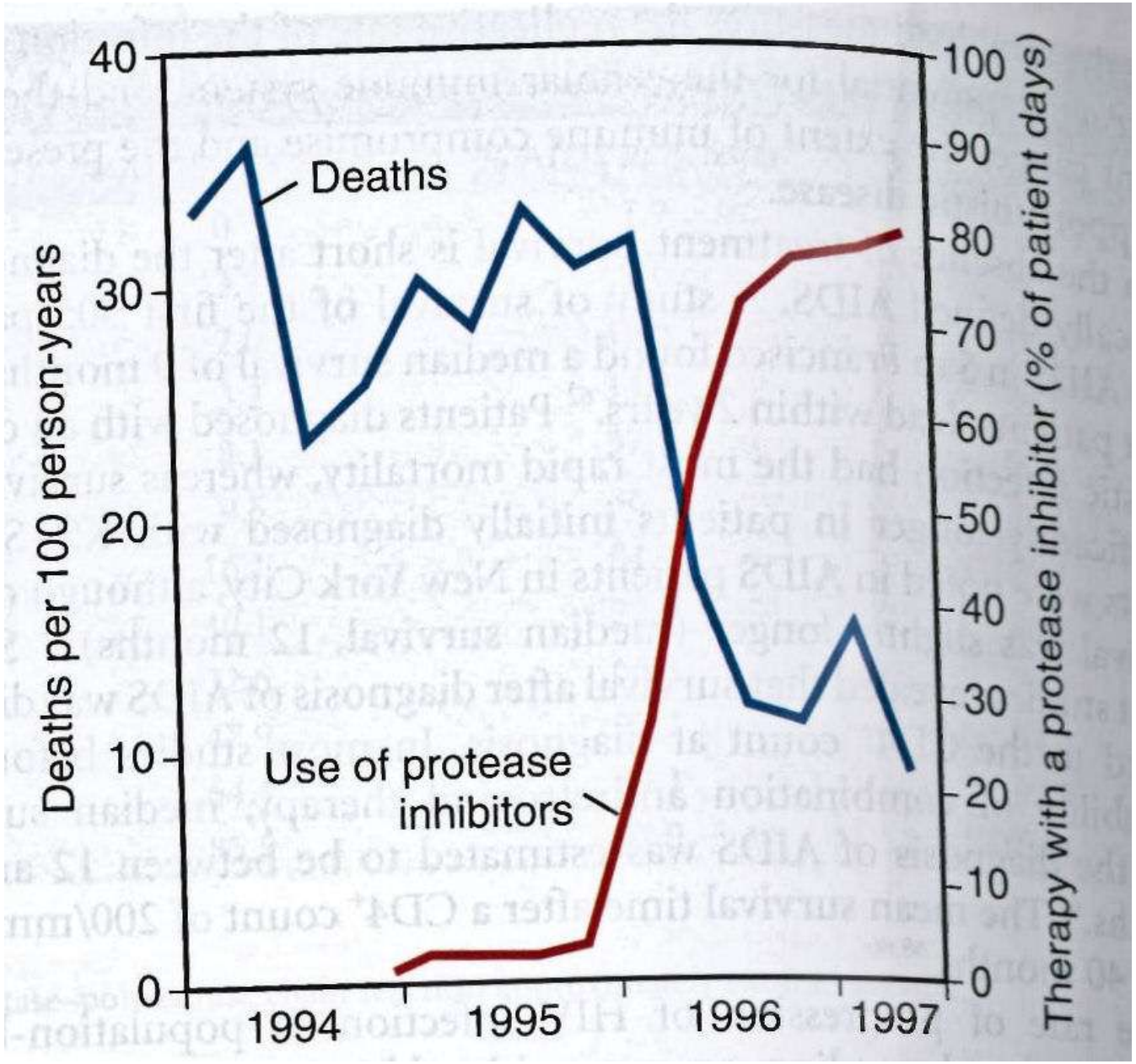
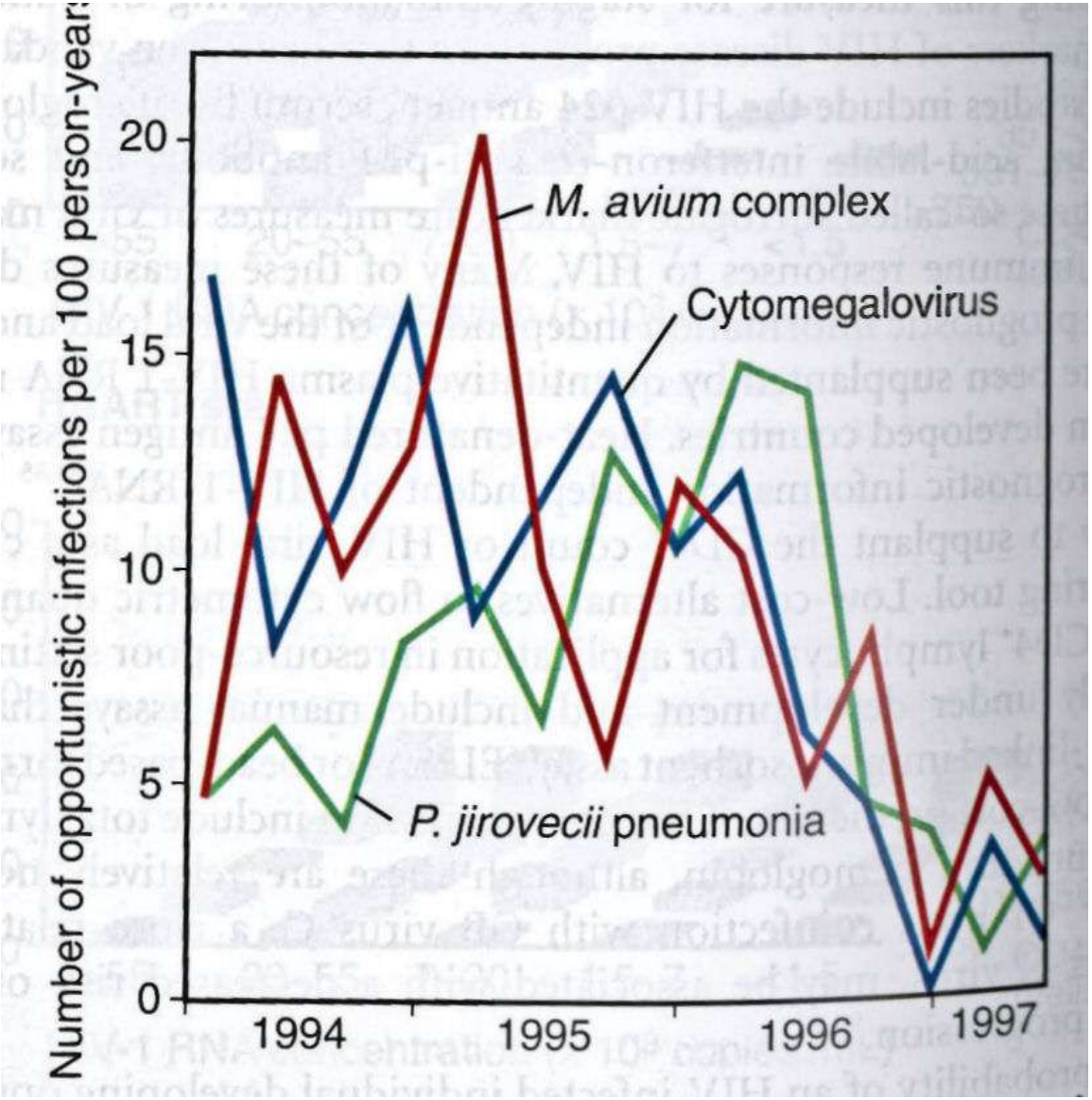


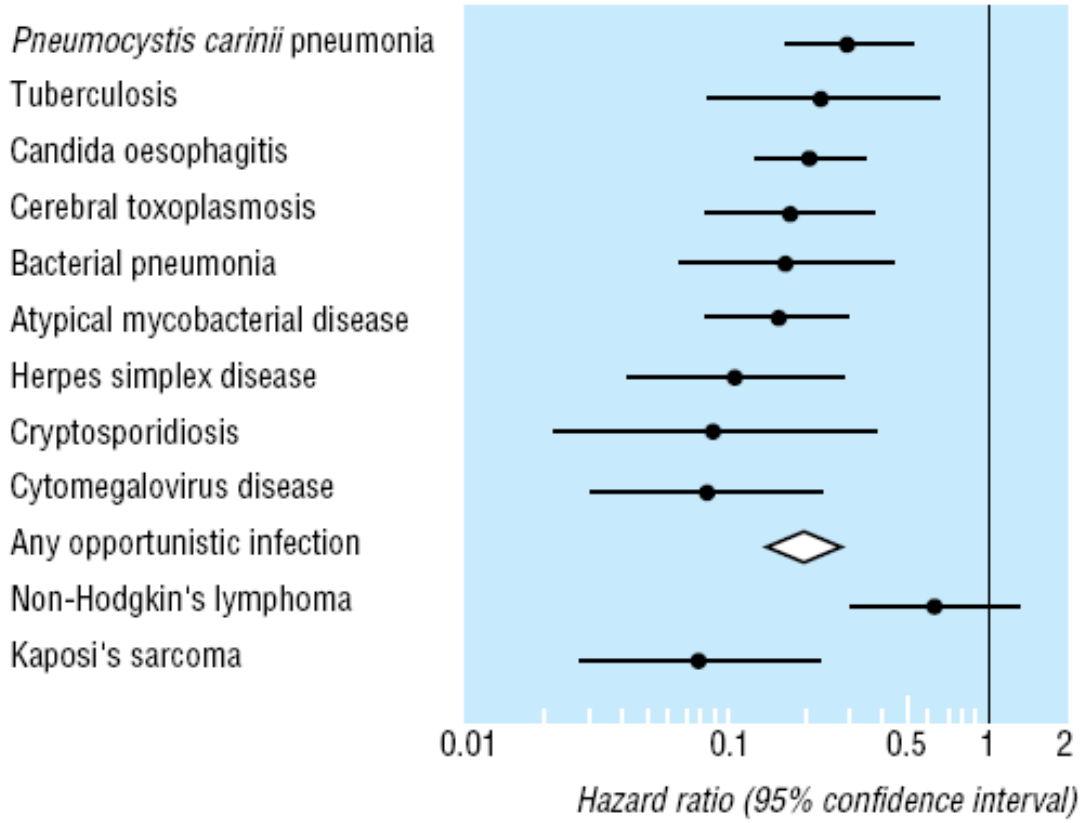
Figure 128-4 **Protease inhibitors.**


Deaths
Use of protease inhibitors
Deaths per 100 person-years
Therapy with a protease inhibitor (% of patient days)
0
10
20
30
40
0
10
20
30
40
50
60
70
80
90
100
1994
1995
1996
1997

The beginning of the end for infections in AIDS

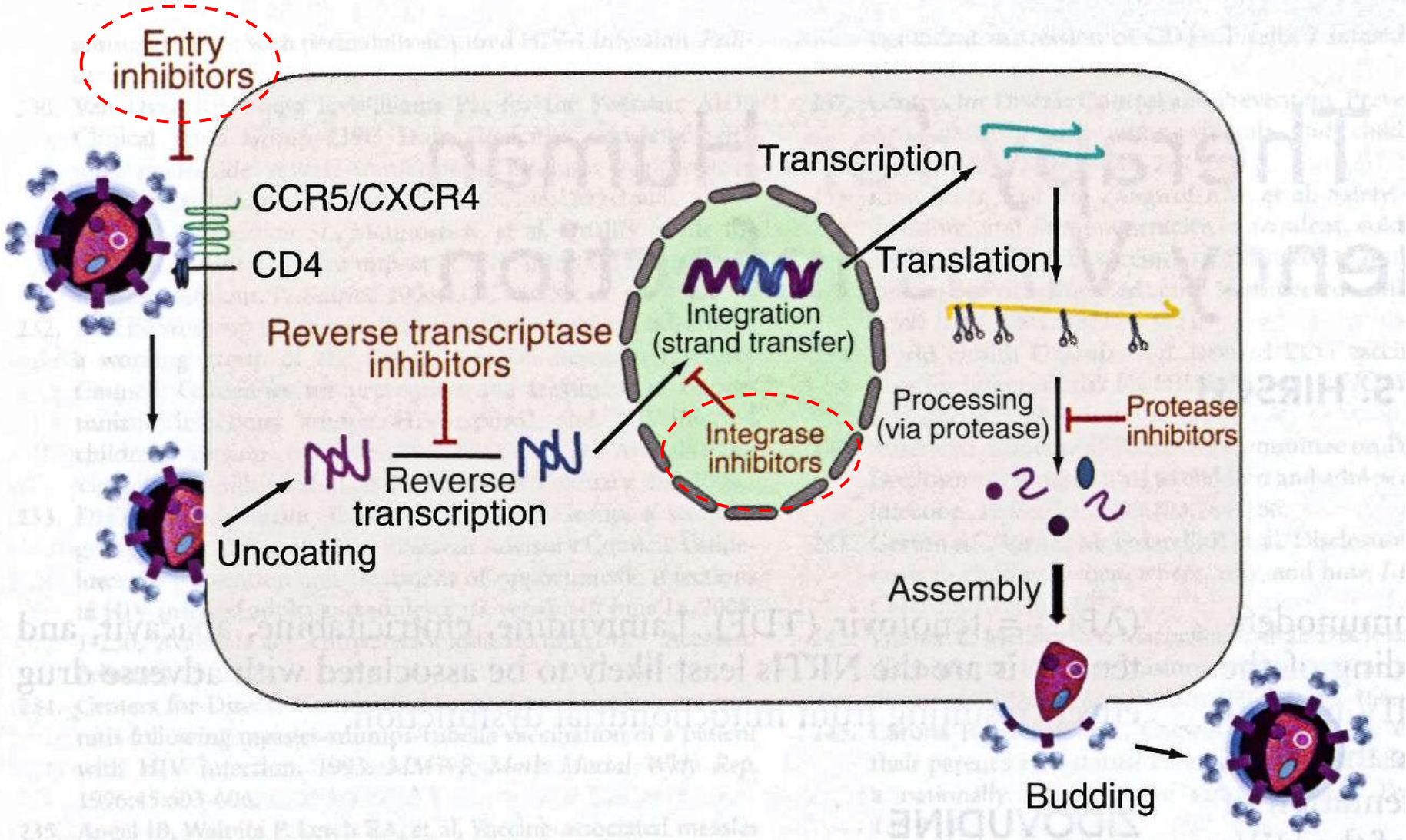


Change in disease pattern with ART drugs in 2000

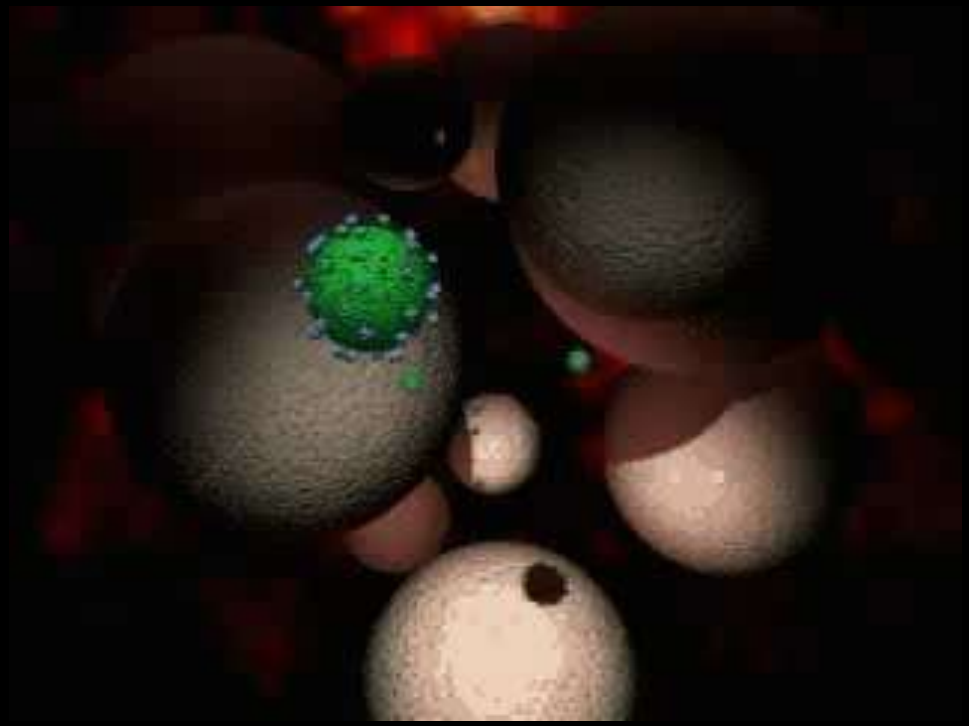


Relative risk (hazard ratio) of AIDS defining opportunistic infections and malignancies, comparing 1992-4 (before introduction of potent antiretroviral combination therapy) with July 1997 to June 1998 (after introduction). Results from Cox regression models adjusted for transmission group, age, and CD4 cell count at baseline

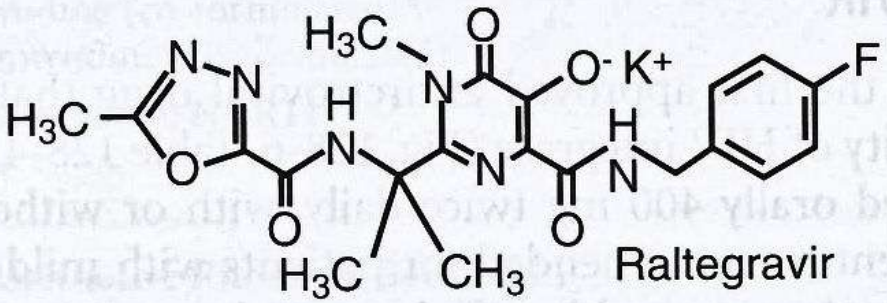
Drug targets - 2



HIV-1 entry into cells



The evolving landscape of new drugs



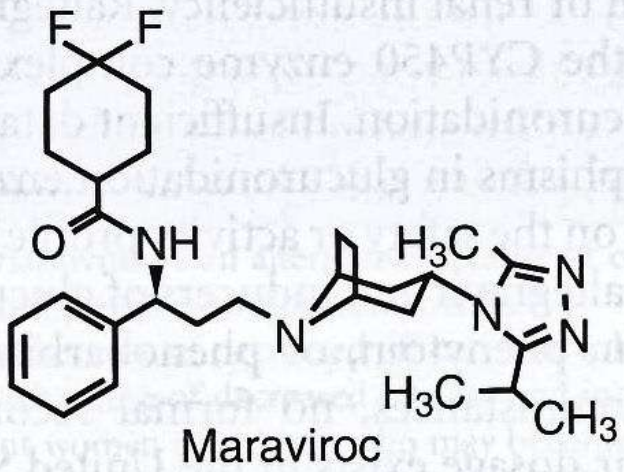
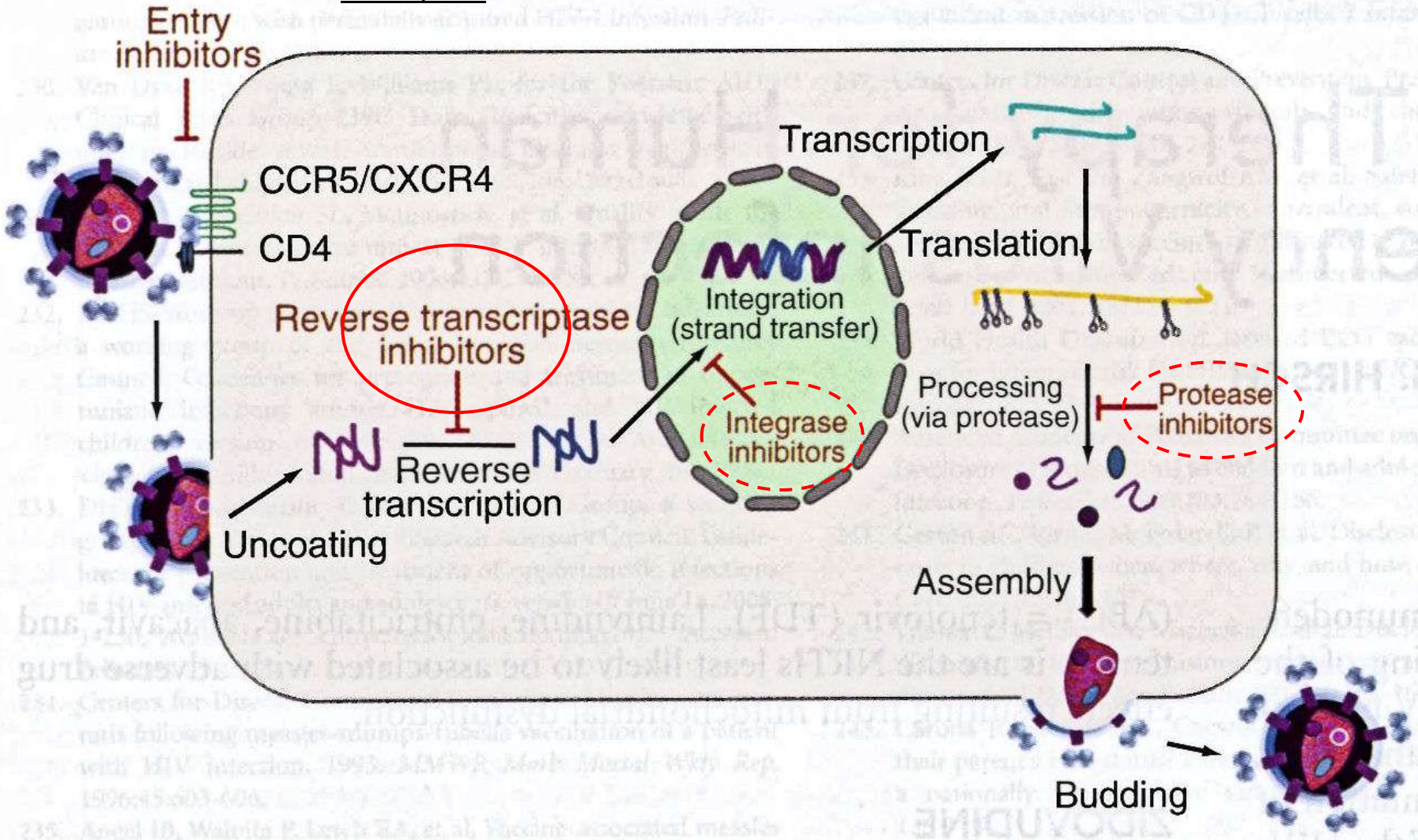


Figure 128-6 Novel antiretrovirals: integrase and fusion inhibitors.

Drug targets - 3

Tenofivir & emtricitabine & one more



Six core concepts to cover

1) A new disease in 1981 & the AIDS epidemic in 2001 (i.e. 20 years).

2) The clinical spectrum of the disease.

3) How did the virus evolve to infect & spread in man so rapidly?

4) The pathogenesis of HIV infection & development of AIDS.

5) Using the science to develop the patient treatment strategies.

6)What does the future hold for HIV-1+ people?

Turning a terminal disease into
a chronic disease like diabetes in 25 years.

Infection related cancers - 1

Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis

Andrew E Grulich, Marina T van Leeuwen, Michael O Falster, Claire M Vajdic

Summary

Background Only a few types of cancer are recognised as being directly related to immune deficiency in people with HIV/AIDS. Large population-based studies in transplant recipients have shown that a wider range of cancers could be associated with immune deficiency. Our aim was to compare cancer incidence in population-based cohort studies of people with HIV/AIDS and people immunosuppressed after solid organ transplantation.

Methods Two investigators independently identified eligible studies through searches of PubMed and reference lists. Random-effects meta-analyses of log standardised incidence ratios (SIRs) were calculated by type of cancer for both immune deficient populations.

Findings Seven studies of people with HIV/AIDS (n=444172) and five of transplant recipients (n=31977) were included. For 20 of the 28 types of cancer examined, there was a significantly increased incidence in both populations. Most of these were cancers with a known infectious cause, including all three types of AIDS-defining cancer, all HPV-related cancers, as well as Hodgkin's lymphoma (HIV/AIDS meta-analysis SIR 11·03, 95% CI 8·43–14·4; transplant 3·89, 2·42–6·26), liver cancer (HIV/AIDS 5·22, 3·32–8·20; transplant 2·13, 1·16–3·91), and stomach cancer (HIV/AIDS 1·90, 1·53–2·36; transplant 2·04, 1·49–2·79). Most common epithelial cancers did not occur at increased rates.

Interpretation The similarity of the pattern of increased risk of cancer in the two populations suggests that it is immune deficiency, rather than other risk factors for cancer, that is responsible for the increased risk. Infection-related cancer will probably become an increasingly important complication of long-term HIV infection.

Infection related cancers - 2

	Cohort	Meta-analysis SIR (95% CI)	Number of studies	Observed number of cancers	Heterogenity p value
EBV-related cancers					
* Hodgkin's lymphoma	HIV/AIDS	11·03 (8·43–14·4)	7	802	0·00
	Transplant	3·89 (2·42–6·26)	4	21	0·65
* Non-Hodgkin lymphoma	HIV/AIDS*	76·67 (39·4–149)	6	5295	0·00
	Transplant	8·07 (6·40–10·2)	4	333	0·02
HHV-8 related cancer					
* Kaposi's sarcoma	HIV/AIDS*	3640·0 (3326–3976)	1	494	
	Transplant	208·0 (114–349)	1	14	-
HBV/HCV-related cancer					
* Liver	HIV/AIDS	5·22 (3·32–8·20)	7	133	0·01
	Transplant	2·13 (1·16–3·91)	3	19	0·25
***Helicobacter pylori*-related cancer**					
Stomach	HIV/AIDS	1·90 (1·53–2·36)	7	89	0·49
	Transplant	2·04 (1·49–2·79)	3	44	0·85

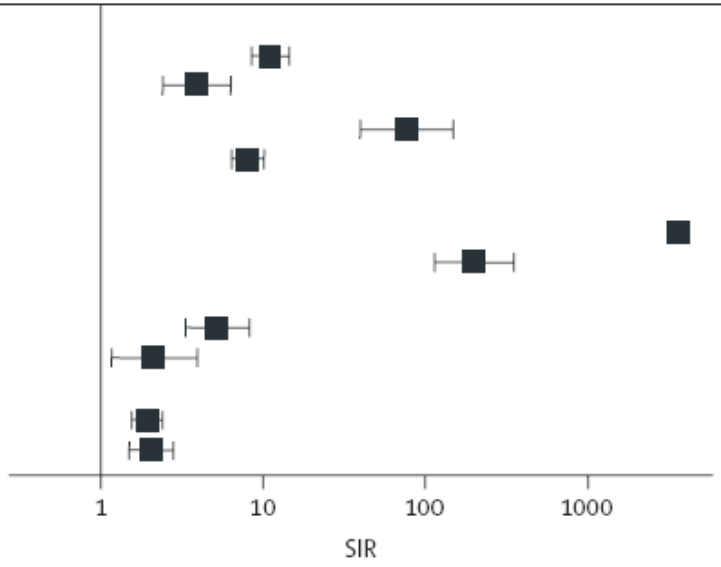


Figure 2: Standardised incidence ratios for cancers related to infection with Epstein-Barr virus, human herpesvirus 8, hepatitis B and C virus, and *Helicobacter pylori* in people with HIV/AIDS and in transplant recipients

Infection related cancers - 3

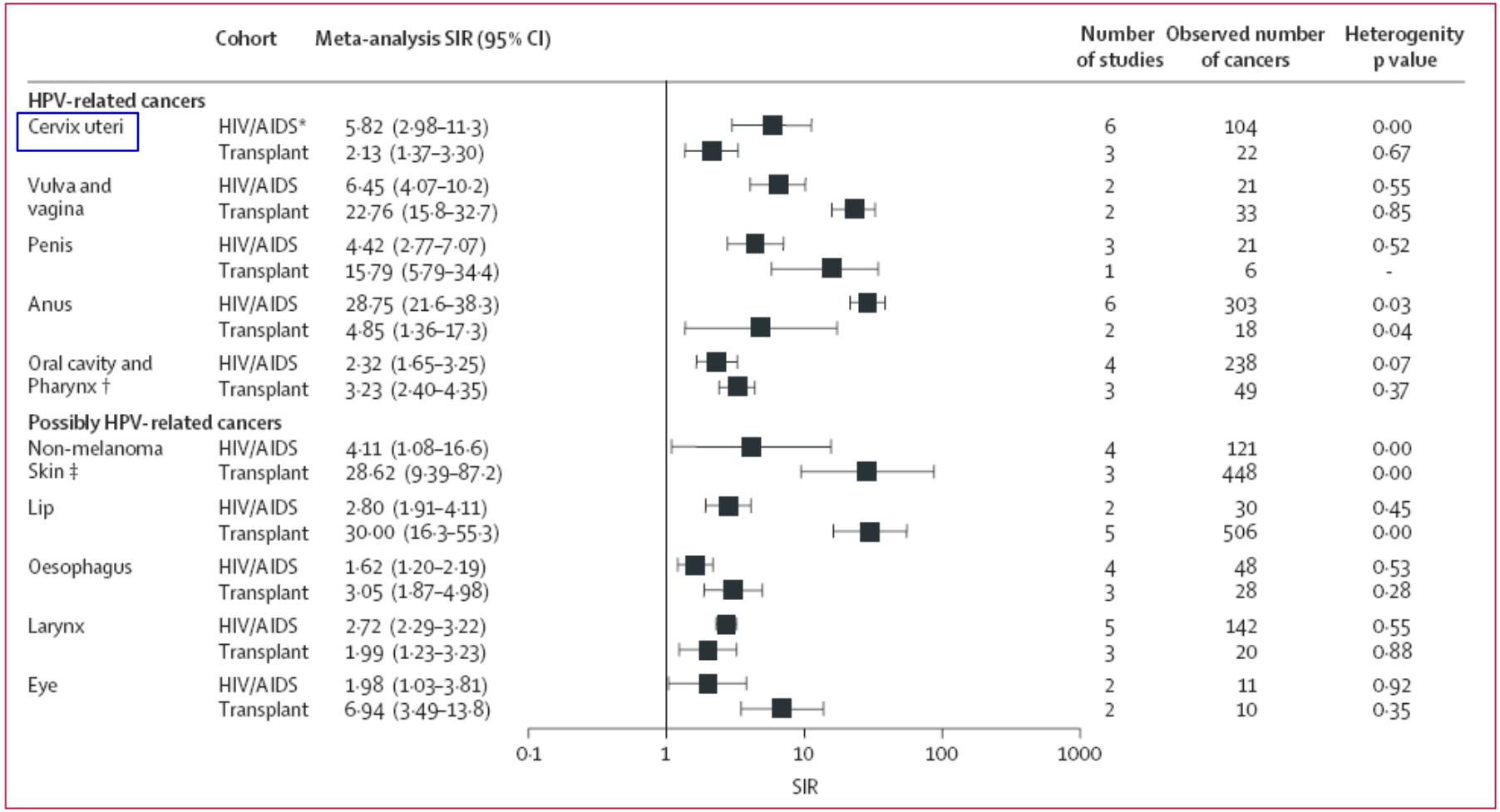


Figure 3: Standardised incidence ratios for cancers related to, or possibly related to, human papillomavirus infection, in people with HIV/AIDS and in transplant recipients

Other cancers

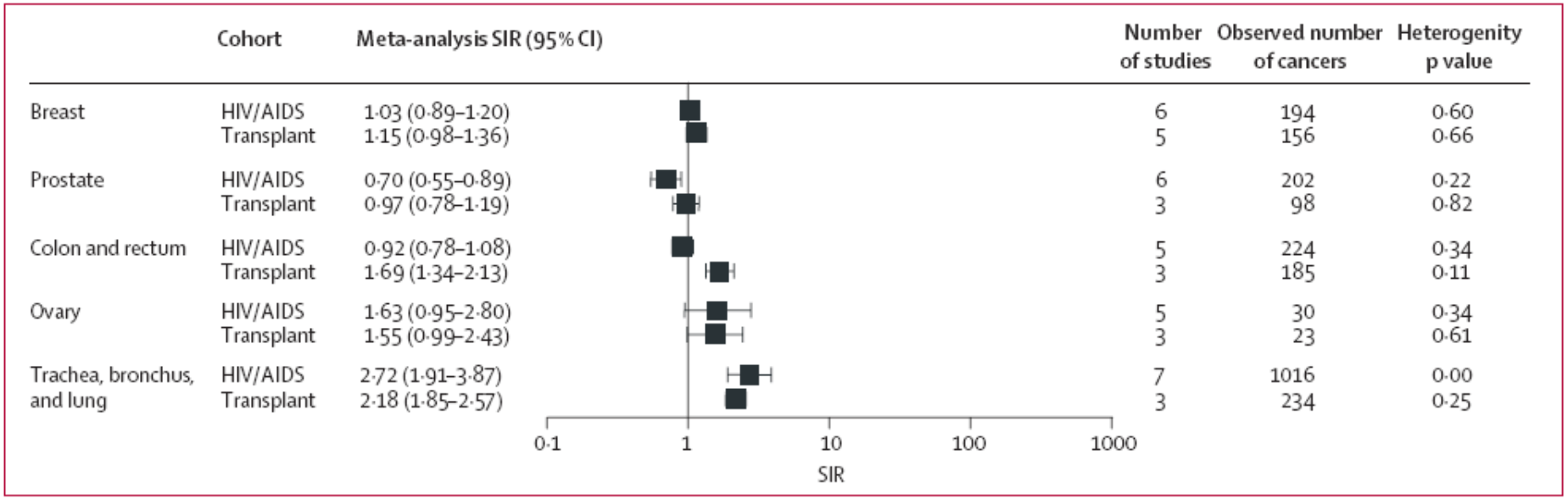


Figure 4: Standardised incidence ratios for common epithelial cancers in people with HIV/AIDS and in transplant recipients

Six core concepts to cover

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End