

JULY, 2013

MONDAY

WEEK 30

22

8.7.2020

HIV AND AIDS

this tragedy was facilitated (or even caused,) by human interventions:

Colonization

and probably well-intentioned public health campaigns.

Urbanization

pepin, jacques (2011) . cambridge university press .
the origins of AIDS .

PNEUMOCYSTIS PNEUMONIA - LOS ANGELES (1981)

pneumocystis pneumonia in united states is almost exclusively limited to severely immuno suppressed patients.

all the above observations suggest the possibility of a cellular immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown,

NOTES

^{ES} the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis from previously healthy homosexual males with dyspepsia and pneumonia.

JULY 2013
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 must be
 diagnosis for 6
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 with dyspepsia
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AIDS

- Clusters of PCP and Kaposi's sarcoma observed in other urban centres.
- CDC established case definition of KS or opportunistic infections.
- 1982 disease was called AIDS (formerly GRID)
- found transmitted at birth & heterosexually, blood products.

HIV-1 IS A LENTIVIRUS

- first isolated in 1983 from the lymph node of a patient with lymphadenopathy, in Paris; 2008 nobel to montagnier & barre' osinoussi.
- 1984 blood test developed.
- electron microscopy and sequence analysis revealed HIV-1 to be a lentivirus, known group of retroviruses.

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NOTES

GRID - gay related immunodeficiency

AIDS - acquired immune deficiency syndrome

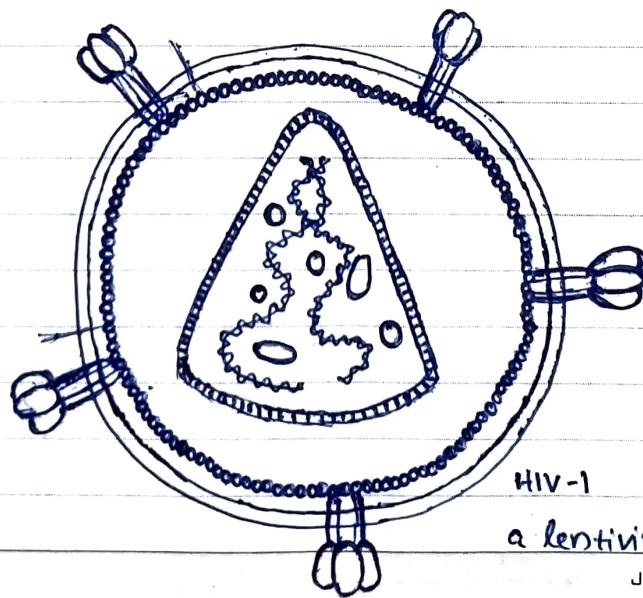
PCP - pneumocystic pneumonia

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RETROVIRIDAE

- Orthoretrovirinae (Subfamily)
 - alpharetrovirus (Avian leukosis virus, ALV
 Rous sarcoma virus) RSV
 - beta retrovirus (Mouse mammary tumor virus)
 - delta retrovirus (Human T cell lymphotropic virus 1, 2, 3)
 - epsilon retrovirus (Walleye dermal sarcoma virus)
 - gammaretrovirus (Moloney murine leukemia virus)
 - lentivirus (Human immunodeficiency virus 1, 2).



HIV-1
a lentivirus

NOTES

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Other retroviruses have a	7	8	9	10	11	12	13
more spherical core and	14	15	16	17	18	19	20
more envelope spikes	21	22	23	24	25	26	27
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Other retroviruses have a
more spherical core and
more envelope spikes

algorithm
explanation + code + pictures

27 SATURDAY
WEEK 30

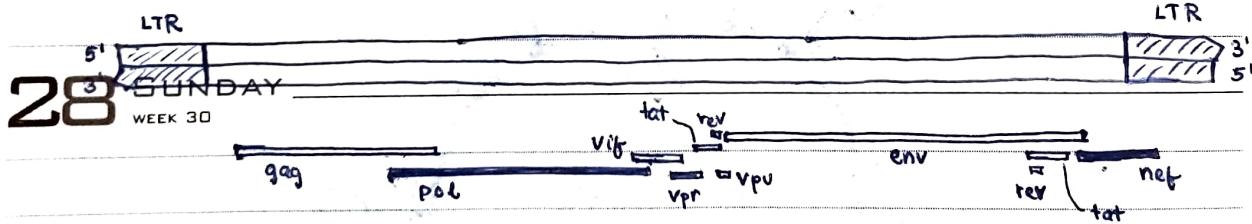
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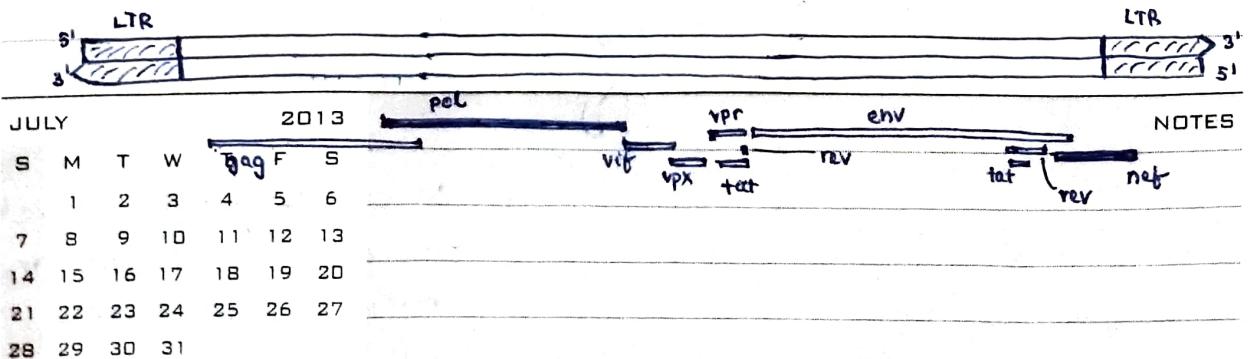
TWO EVOLUTIONARY DISTINCT GROUP OF HUMAN RETROVIRUSES

- the lymphotropic viruses: HTLV 1, 2, 3, 4.
- the immunodeficiency viruses: HIV-1, 2.
 - lentiviruses, not new or unique to humans.
 - equine infectious anemia virus, causes fatal immunodeficiency of horses, isolated early 1900s.
- - bovine, feline, caprine immunodeficiency viruses.

A. HIV-1



B. HIV-2



HIV AND AIDS : ACQUIRED IMMUNO DEFICIENCY SYNDROME

- syndrome: the occurrence together of a characteristic group or pattern of symptoms.
- HIV-1 is the etiological agent of epidemic AIDS.
- AIDS denialists: the hypothesis that HIV-1 causes AIDS has been tested by inadvertent infection of people with HIV-1 contaminated blood.

HIV / AIDS PANDEMIC IN THE US

- in the US, HIV-1 has killed over 800,000, exceeding all US combat-related deaths in all wars fought in the 20th century.
- 1,140,000 people in the US are living with HIV-1; 1 in 7 don't know it.
- 37,832 new infections in 2018;
 - 69% MSM men who have sex with men
 - 24% HHS heterosexuals
 - 7% IVDU intra venous drug users

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SARS-CoV-2 & COVID-19

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GLOBAL SUMMARY OF HIV-1 PANDEMIC (2018)

37.9 million
people living with HIV

UNAIDS / WHO estimates

1.7 million
people newly infected

4,600 New HIV infections
a day,

190 per hour.

0.8 million
HIV related deaths.

t.	people living with HIV	newly infected in 2018	HIV related deaths 2018
total	37.9 m	1.7 m	770 000
adults	36.2 m	1.6 m	670 000
women	18.8 m		
men	17.4 m		
children	1.7 m	0.16 m	100 000
≤15y			

africa	america	SE asia	europe	east. mediterranean
25.7 m	3.5 m	3.8 m	2.5 m	0.4 m

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NOTES

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1 2 3 4 5 6

West Pacific

7 healthcare systems¹³
14 are not good
21 22 23 24 25 26 27

1.9 m

28 29 30 31
lack of anti-
retrovirals.

kids are getting infected at birth

nobody should die of AIDS

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WEDNESDAY

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DISTRIBUTION OF NEW HIV-1 INFECTIONS BY KEY POPULATION, GLOBAL (2018)

16%. remaining population

18%. clients of sex workers and sex partners of other key populations

17%. gay men & other men who have sex with men.

12%. people who inject drugs

6%. sex workers.

1%. transgender women

CONTROL OF AIDS

triple drug therapy has slowed the pandemic in countries with money.

Anti retroviral (ART) coverage over time

NOTES	2000	2010	2018	JULY	2013					
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2y.		24y.	62y.							
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we have get to 100%.

BUT...

- there is as yet no cure
 - can't clear virus from an infected individual.
- there is no vaccine
 - can't block primary infection.
- can't stop taking antiviral drugs
 - reservoirs: latently infected hematopoietic progenitor cells.
- drug resistant viruses appear
- drugs are expensive.

OUT OF AFRICA

first studies in Africa, in Zaire & Rwanda, showed that AIDS was common in Kinshasa & Kigali, where nearly 90% of sex workers were infected.

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NOTES

looking for viral protein in the blood (test)

you are stuck with triple therapy your whole life.

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FRIDAY
WEEK 31 **02**

AUGUST, 2013

OUT OF AFRICA

- testing of archival samples suggested that HIV-1 was present in the 1960s & 1970s in several locations in central Africa, but not in west or east Africa.
- serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998.
- lymph node sample from DRC adult female (1960).
- DRC60 & ZR59 differed by about 12y.
- no doubt that HIV-1 was present in Leopoldville (Kinshasa today) by 1959-60.

WHAT WAS THE SOURCE OF HIV-1?

- SIV first isolated from chimpanzee in 1989 (SIVcpz).
- analysis of >7000 chimpanzee fecal samples from 90 field sites confirmed natural SIVcpz reservoir.
- only pan troglodytes and P.T. schweinfurthii

NOTES harbor SIVcpz.

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03 SATURDAY
WEEK 31

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SIVCPZ

- transmitted among chimpanzees by sexual intercourse; mother to child; possibly blood-blood during aggression.
- estimated transmission probability per coital act 0.008 - 0.0015, similar to humans (0.0011).
- SIVcpz is pathogenic in natural host, disease similar to AIDS.

A gag (488aa) B pol (927aa) C env/nef (854aa)
0.07 0.05 0.2

- Sequencing the chimp isolates & human isolates clearly show that they have a common ancestor.
- 3 phylogenetic trees, of different regions of the genome.

04 SUNDAY
WEEK 31

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NOTES

HIV-1 is a chimp virus (became human)

SARS-CoV-2 is a bat virus

chimps found dead in the woods, having SIV.

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MONDAY

WEEK 32

05

AUGUST, 2013

HERE IS THE STORY

sykes's monkey

SIV syk

p.t. of central africa

mantled guereza

SIV col

vervet monkey

SIV ver

{ that's where vervet kidney cells come from
used to grow SARS-CoV-2

l'hoest's monkey

SIV lho

mandrill

SIV mnd

western gorilla → human

SIVgor

HIV-1 P&O

red-capped mangabey → chimpanzee → human

SIVrcm

↑ SIVcpz

HIV-1 M&N

mona monkey

SIV mon

SIVgen
mus
mon

RECOMBINANT! (SIVcpz)

infected with both viruses

sooty mangabey → human

SIVsmm

HIV-2 A-H

NOTES
each have their own
kind of SIV

→ SIVmac

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monkeys are OK with their SIV,
evolved with them for ages.

□6 TUESDAY
WEEK 32

8-7-2020
AUGUST 22 2013

WHEN DID SIV INFECT HUMANS

- four separate crossover events
- M,O: 1st 3 decades of 20th century. (1920)
- N,P: more recently but not enough data.
- the cut hunter: bushmeat hunting
- cutaneous and mucous membrane exposure to infected chimpanzee blood, body fluids.
- calculations suggest that in 1921 number of people infected with SIVcpz was <10, but probably only one spread and multiplied.
- such cross-species infections probably have occurred many times previously.
- why this one spread?
} involves human intervention }

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NOTES

people hunt chimps; it's getting harder & harder to do.

SPREAD OF HIV-1

- leopoldville (Kisangani) was the ^{most} dynamic city in the region, attracted large numbers of migrants and traders.
 - the cat hunter might have traveled there, visited a brothel, then a STD clinic.
 - then, amplification by non-sterile syringes, sex (some women had 1000 clients/yr.)
 - haiti & "belgian" congo.
- we want some countries too
still had belgian doctors from haiti.
- european colonization of africa begining end of 19th century.
 - establishment of large population centres, movement of adult males for labor - large scale prostitution.
 - introduction of healthcare - colonial medicine - injections and transmission of viruses.
 - egypt at turn of 20th century - well intentioned treatment for schistosomiasis spread HCV to millions
 - large scale amplification of HIV-1.

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didn't use autoclaved Syringes

08 THURSDAY
WEEK 32

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AUGUST, 2013

EARLY HIV/AIDS IN NORTH AMERICA

HIV-2

- first isolated guinea-bissau, 30-40% identity HIV-1.
 - restricted primarily to populations in west africa.
 - less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother infant spread.
 - crossover from sooty mangabey.
 - 8 distinct lineages, each arose from separate infection

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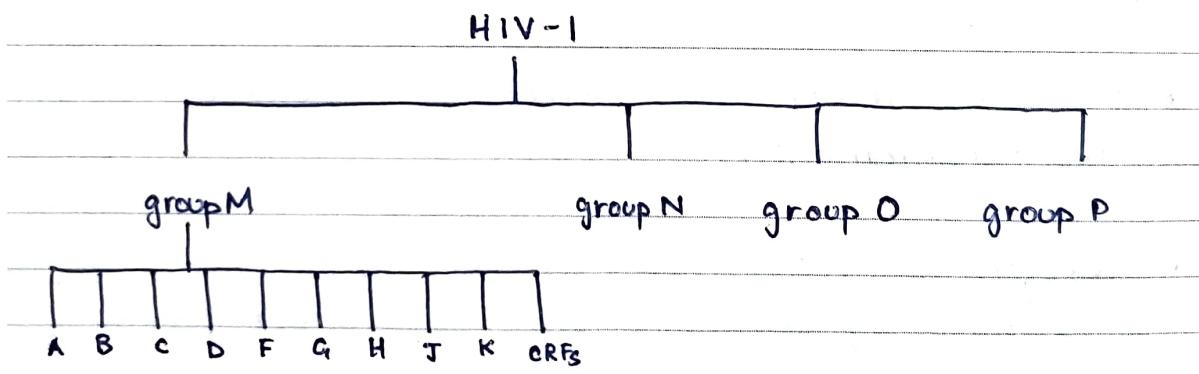
FRIDAY

WEEK 32

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HIV-1 DIVERSITY

- four groups based on sequence alignment
- group M (main): 99% of all HIV-1 infections
- group O (outlier): <1% of infections, limited to cameroon, gabon, neighbouring countries.
- group N: only 13 cases, cameroon
- group P: only 2 cases, cameroon
- each from independent transmission event from SIV to humans.



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HIV-1 DIVERSITY

- HIV-1 group M further divided into 9 subtypes.
- high-risk individuals multiply infected, recombinants emerge (CRFs) 48 so far.
- no clear cut difference between subtypes in propensity to cause AIDS, except that those infected with D die faster.
- shedding of subtype C in female genital tract is higher, perhaps higher female to male transmission, extensive spread in Africa.

HIV-1 SUBTYPES

↑ This involves in one direction to numerous subtypes and recombinants.
WEEK 32

- therefore can reconstruct sequence of progress in region or country by examining local distribution of subtypes
- facilitated in 1990s by new tools enabling examination of nucleotide sequences from large number of isolates

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NOTES

- extreme diversity of HIV-1 in central Africa, clearly the origin as had more time to diversify.

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HIV-1 SUBTYPES

- some subtypes associated in specific locations with modes of transmission.
- founder effect: subtype will predominate in at-risk group.
- example: subtype B found in 96% of white ~~hom~~ homosexuals in south africa (imported from us); subtype C accounts for 80% of infections of black heterosexuals.
- Subtype C (50%) of all HIV-1 infections.
B & A
- B & A (10-12%)
- G (6%)

Subtypes F, H, J, K
limited transmission (<1%)

CRF02-AG1 (5%)

CRF01-AE (5%)

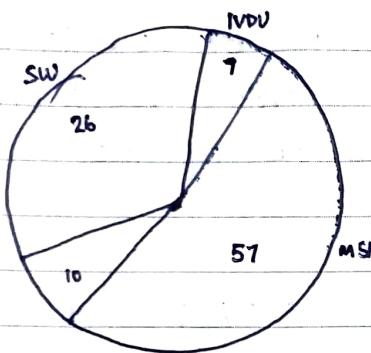
D (2.5%)

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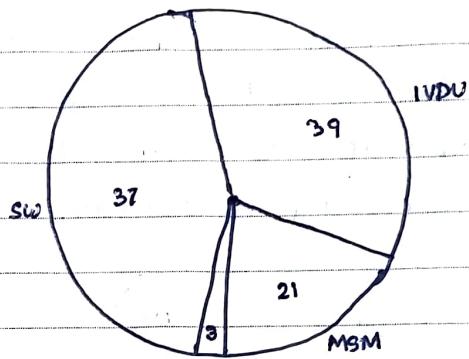
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TRANSMISSION

- transmitted by sex, intravenous drug use, at birth (R_0 2-5)
- Not spread by respiratory, alimentary, or vector routes.



western & central europe
& north america



eastern europe &
central asia

mother to child at birth \approx 5%.

- HIV-1 infectivity reduced by air drying ($99\% / 24 \text{ hr}$)
- by heating ($56^\circ\text{C} / 30 \text{ min}$)
- by 10% bleach or 70% alcohol.

AUGUST ²⁰¹³
by pH extremes (<6 or >10)

S M T W T F S

1 2 3

• 5^{th} / 17^{th} IVDU bypass these!

11 12 13 14 15 16 17

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NOTES

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RISK OF TRANSMISSION OF HIV-1

modeinfection risk per
10,000 exposures

sexual transmission

- receptive anal sex 138
- insertive anal sex 11
- receptive penile-vaginal sex 8
- insertive penile-vaginal sex 4

parenteral

- transfusion of infected blood 9250
- needle sharing 63
- needle stick 23
- needle stick / AZT PEP 1

mother to infant

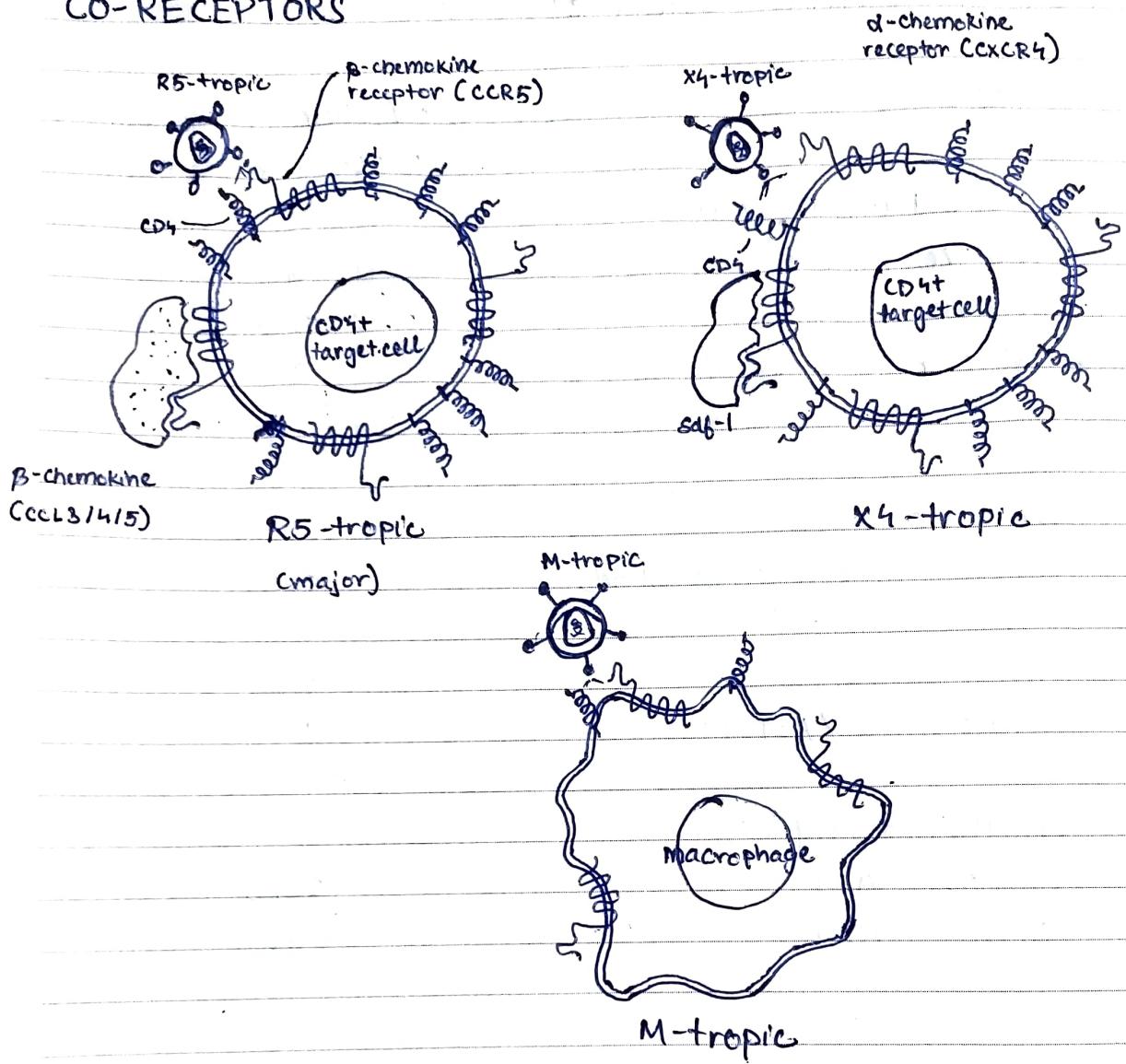
- without AZT 2260
- with AZT <1000

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PEP - post exposure prophylaxis

CO-RECEPTORS



- these viruses don't affect macrophages very easily (low CD4), but during the course of infection, viruses evolve that can bind to macrophages (typically emerge in CNS, late in disease)

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- in some affected patients, usually late in disease, some viruses appear which can use R4 to get into cells. (X4-tropic) (Why it switches so late?)
- people who have a deletion in CCR5 are resistant to R5 viruses

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FRIDAY ²¹
WEEK 33 16

HOST GENES THAT DETERMINE SUSCEPTIBILITY

- $\text{CCR}5\text{-delta}32$ mutation protects vs HIV-1 infection.
- present in 4-16% of european descent.
- Stem cell therapy cured german and london AIDS patients ~~scared!~~ ^{1/2}
- disrupting CCR5 with crispr/cas9. (Codon genes)

PRIMARY HIV INFECTION

crossing the mucosal barrier

- virus dendritic cell interaction (no activation)
 - infection typically with CCR5 binding strains
 - importance of DC-SIGN (dendritic cell-specific, ^{nonintegrin} _{lamb-3 grabbing})
- delivery of virus to lymph nodes.
- active replication in lymphoid tissue.
- high levels of viremia & dissemination.
- down-regulation of virus replication by immune response.
- viral set-point reached after ~6 months.

NOTES

you can destroy the bone marrow with a radiation, and replace it with a donor who is lacking the CCR5 gene, and that will cure infection S.R5-tropic?

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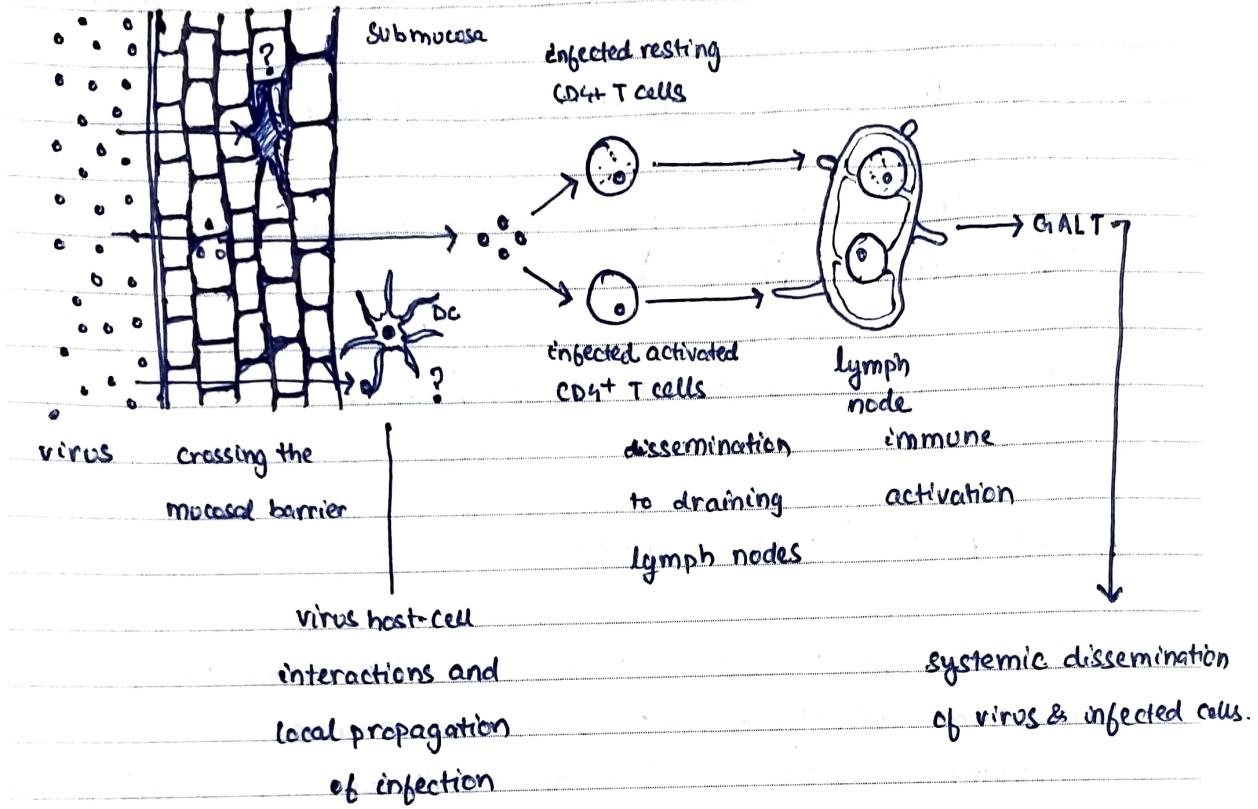
17 SATURDAY
WEEK 33

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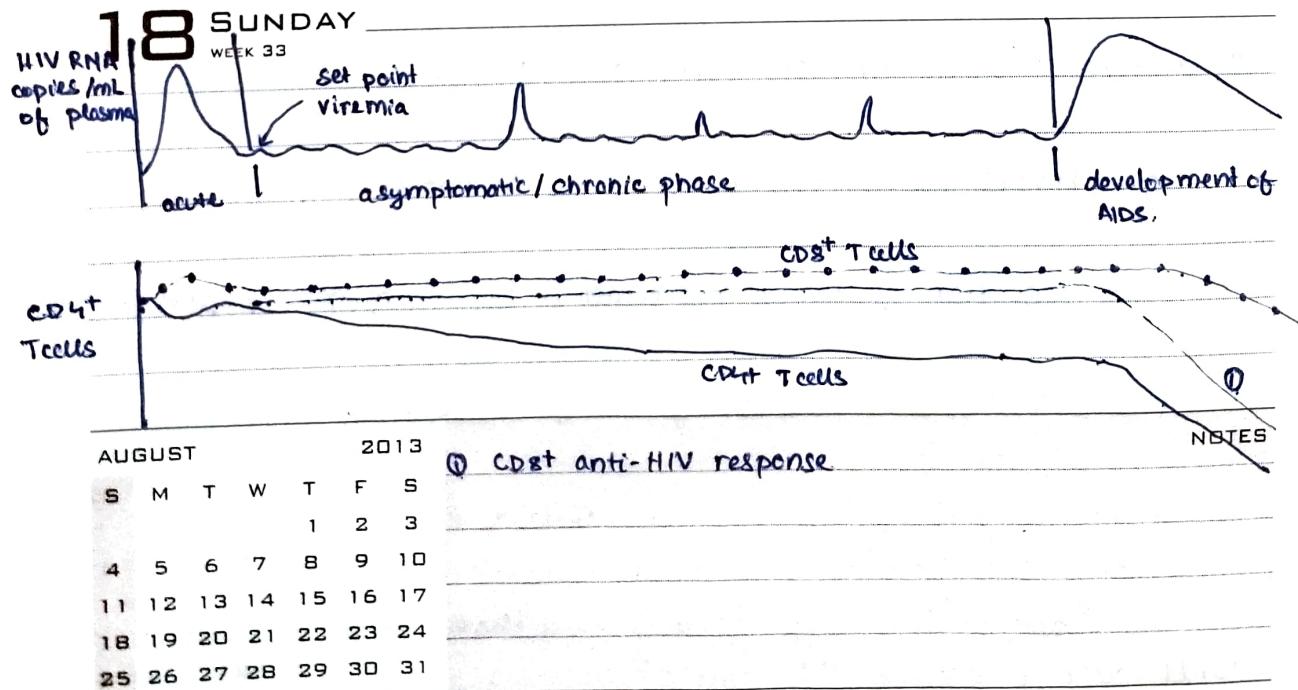
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PRIMARY HIV INFECTION



PROGRESSION OF HIV INFECTION



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PROGRESSION OF HIV INFECTION

• acute phase

- swollen lymph nodes (lymphadenopathy)
- CD4⁺ T cells decline temporarily
- fever
- CD8⁺ T cell increase temporarily (homeostasis) & anti-HIV CTLs increase temporarily
- diarrhea
- B cells; anti-HIV-1 antibodies appear

• chronic phase

- usually no symptoms
- CD4⁺ T cells gradually decline
- sporadically: fatigue, mild weight loss, generalized lymphadenopathy, rash, shingles.
- CD8⁺ T cells largely unaffected and CTL responses evolve
- B cells: co-evolution of anti-viral antibodies and viral antigens
- acquisition of macrophage tropism

NOTES

- infection of central nervous system (in some patients)

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PROGRESSION OF HIV INFECTION

- symptomatic phase
- * 200 - 500 CD4⁺ T cells / mL
 - CD4⁺ T cell depletion, loss of helper function
 - oral / skin lesions
 - genital warts
 - development of Kaposi's sarcoma
 - reactivation of latent Mycobacterium tuberculosis
 - B cells: decrease/dysregulation
 - natural killer (NK) cells; impairment of function.
- * < 200 CD4⁺ T cells / mL
 - opportunistic infections by protozoa / bacteria / viruses / fungi
 - weight loss
 - malignancies
 - neurological symptoms.

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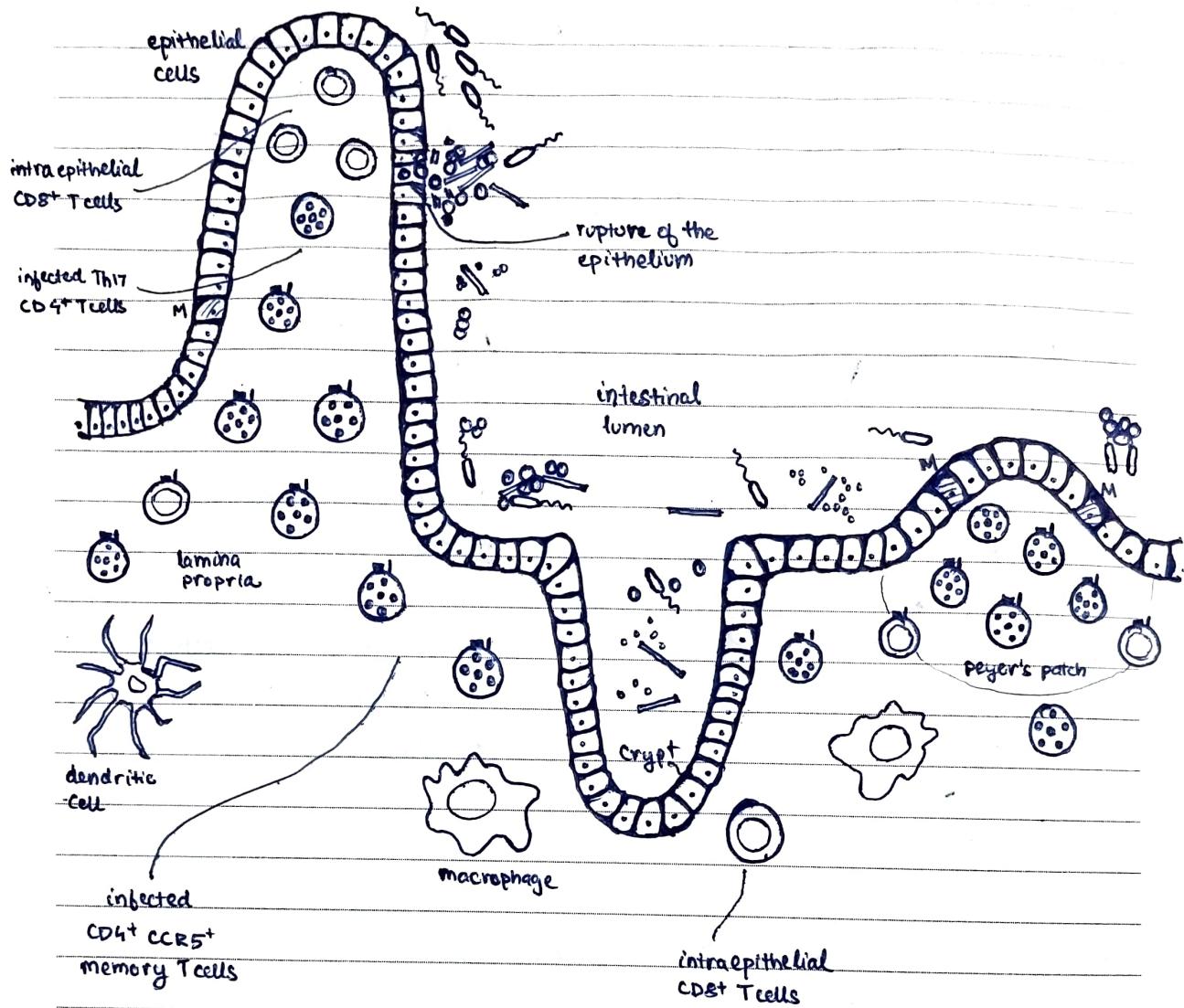
in humans, gut associated lymphoidal tissue has 40% of your lymphocytes.
(major early site of HIV reproduction)

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WEDNESDAY 25
WEEK 34 21

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EFFECTS OF HIV-1 INFECTION ON INTESTINAL MUCOSA



G1 associated lymphoid tissue following acute infection.

- absence of lymphoid cell aggregates in terminal ileum.

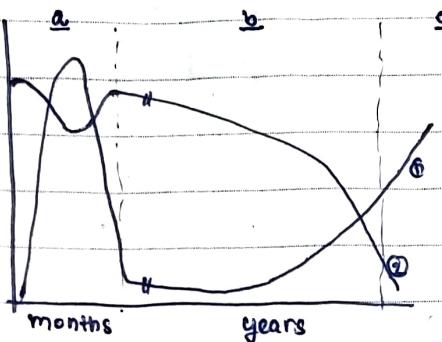
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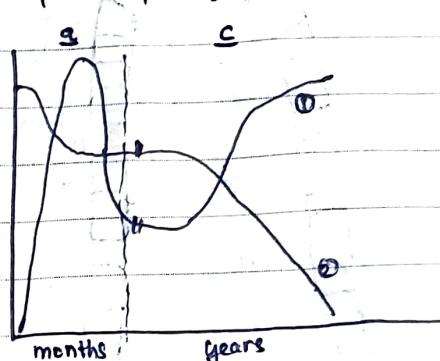
Your gut lumen is full of lipopolysaccharide. This gets into your circulation, & LPS is not good. It disrupts metabolism, digestive function. (Leaky gut)

THE VARIABLE COURSE OF HIV-1 INFECTION

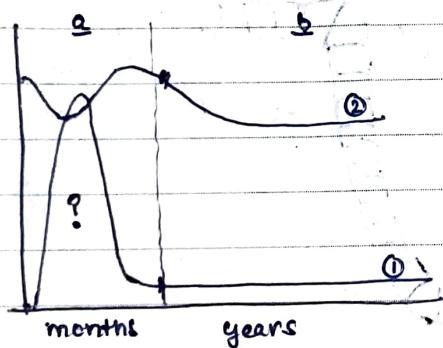
- typical progressor



- rapid progressor



- non progressor



① viral replication

② CD4 level

a primary HIV infection

b clinical latency

c AIDS.

rapid progressor - maybe 1-2 years
correlates with higher set points

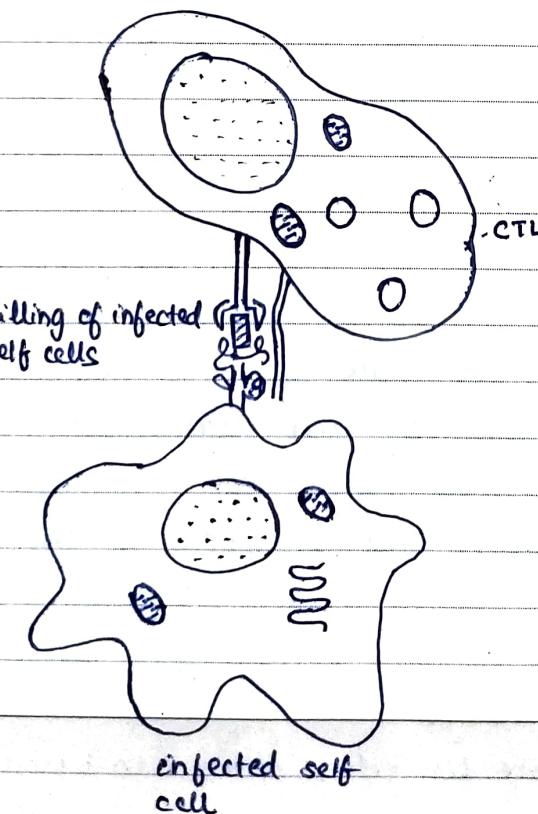
without antiviral therapy, 10% of people go to AIDS in 2-3 yrs
in 10 yrs, over 80% of untreated infected adults have evidence of disease progression,
1/2 of those develop AIDS.

<5% of patients are AIDS free for many years, with elevated

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ELITE HIV CONTROLLERS

- individuals who maintain normal CD4 counts & undetectable viral loads ($1\text{-}30 \text{ copies HIV RNA}/\text{mL}$)
for > 10 years in the absence of antiretroviral therapy.
 - estimated 1/300 people
- 20% are associated with favorable HLA (MHC) types (esp. HLA B57 and B27) and T cell responses (CD4 and CD8) to Gag.
- not associated with attenuated viruses.



NOTES

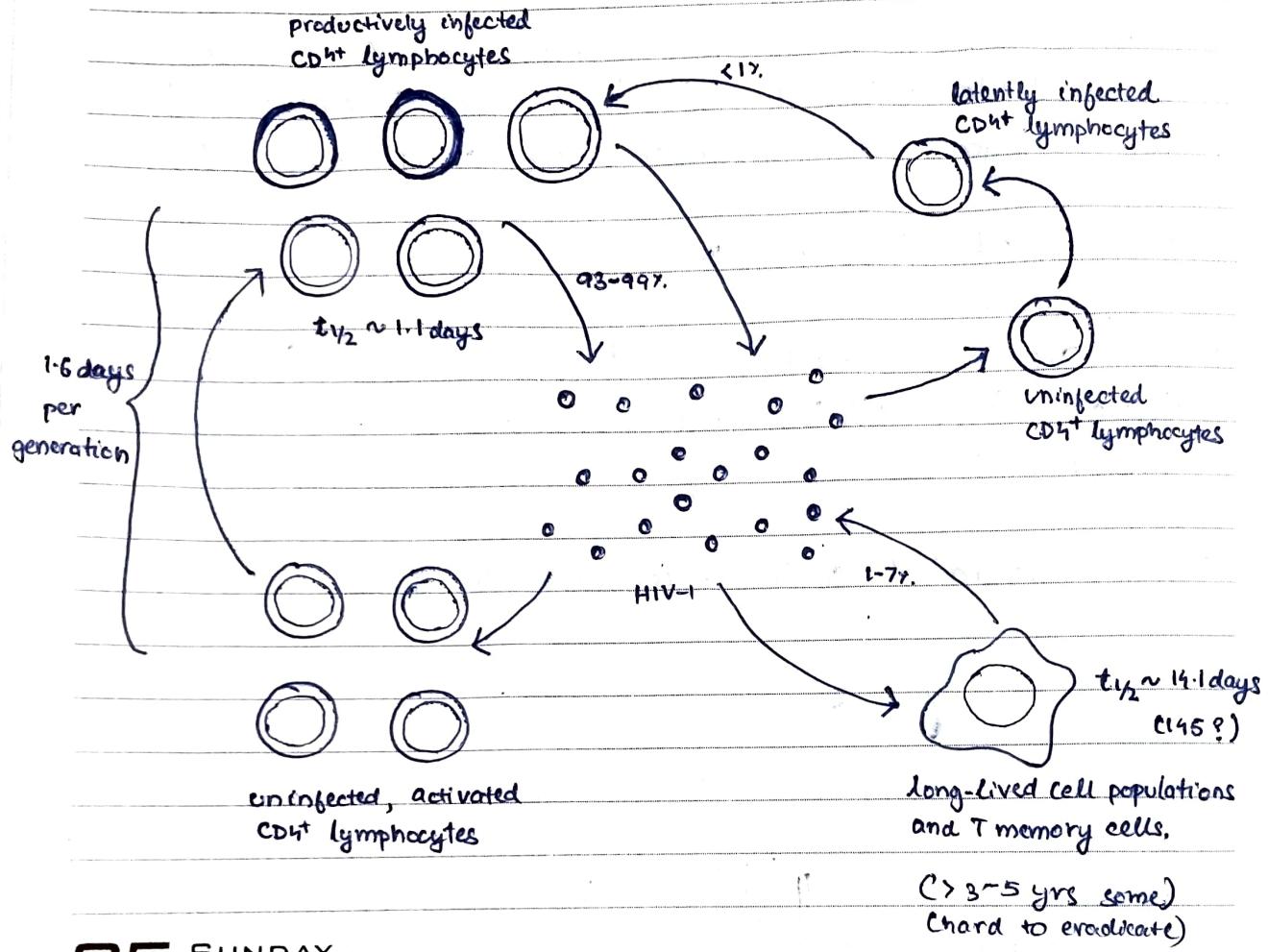
AUGUST 2013					
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4	5	6	7	8	9 10
11	12	13	14	15	16 17
18	19	20	21	22	23 24
25	26	27	28	29	30 31

24 SATURDAY
WEEK 34

9.7.2020
28

AUGUST, 2013

HIV-1 DYNAMICS



25 SUNDAY

WEEK 34

in the absence of drugs, the rate of virus reproduction has to equal the rate of clearance, and mathematical model that have been applied to clinical results can provide estimates of how much HIV appears and disappears in the blood, and other compartments.

results are frankly astonishing.

AUGUST

2013

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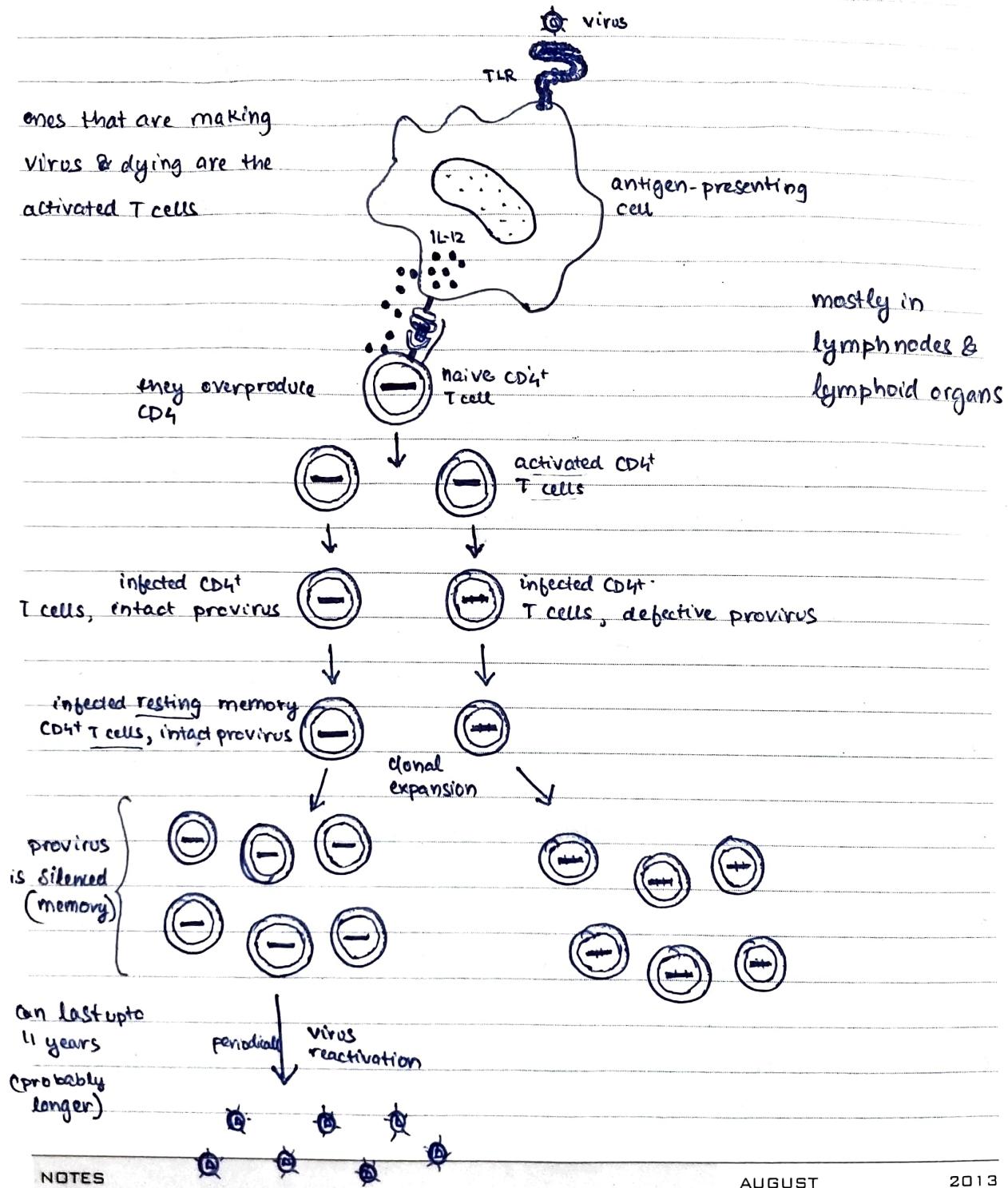
min. rate for release of virus in blood $\sim 10^{10}$ particles / day
(drives pathogenesis, high mutation rates)

every position in the genome is changed multiple times / day.

AUGUST, 2013

HIV-1 LATENCY

ones that are making
virus & dying are the
activated T cells



NOTES

the latent reservoir are the central memory
CD4⁺ T cells, these are important of course in
protection, So they are the reservoir of HIV, how
insidious is that!

AUGUST 2013						
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HIV AND CANCER

- HIV-1 infection leads to increase incidence of malignancy: 40% of infected individuals.
- an indirect effect of dysregulation of the immune system.
 - absence of proper immune surveillance
 - high levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV, HHV8, HPV), angiogenesis.

KAPOSI'S SARCOMA ← cancer? (multifocal cancer)
with many cell types

- described 1872 by hungarian physician (skin spots rarely lethal)
- pre-AIDS: mainly in older mediterranean men.
- occurs in 20% of HIV-1 infected homosexual men, 2% of HTLV-1 infected women, transfusion recipients.
- infection with human herpesvirus 8 is necessary for development of KS.

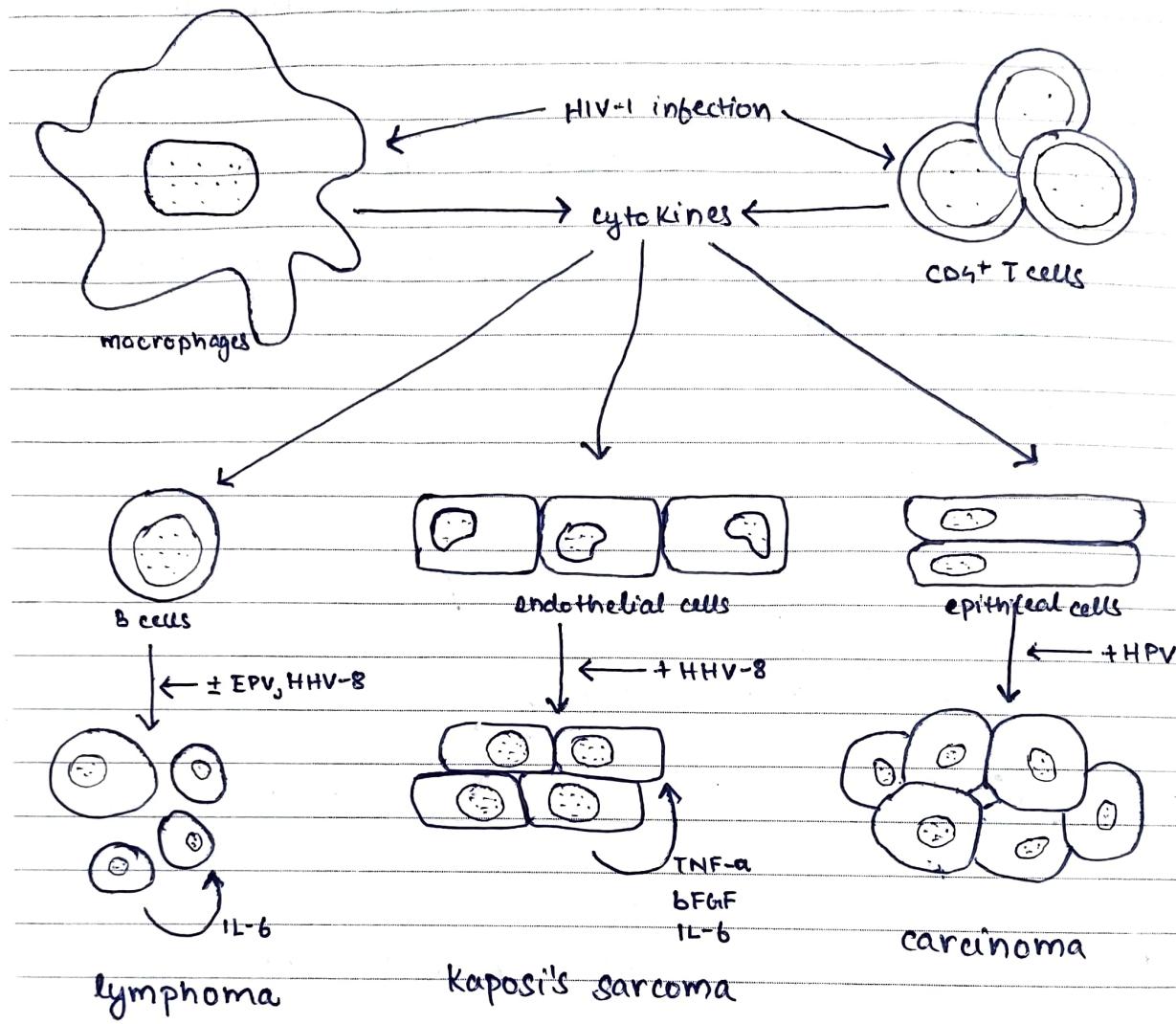
(1981)

AUGUST 2013							NOTES
S	M	T	W	T	F	S	
				1	2	3	HPV - human papillomavirus
4	5	6	7	8	9	10	EPV - epstein barr virus
11	12	13	14	15	16	17	so we can't get rid of viruses (one oncogenic)
18	19	20	21	22	23	24	inflammation leads to high cytokines
25	26	27	28	29	30	31	angiogenesis - generation of blood vessels

AUGUST, 2013

9.7.2020
WEDNESDAY 31 WEEK 35 28

INDUCTION OF CANCERS IN HIV-1 INFECTED PATENTS.



NOTES

cytokines can cause proliferation of other cells
B cells, endothelial cells, epithelial cells, that alone can lead to malignancy.

AUGUST 2013						
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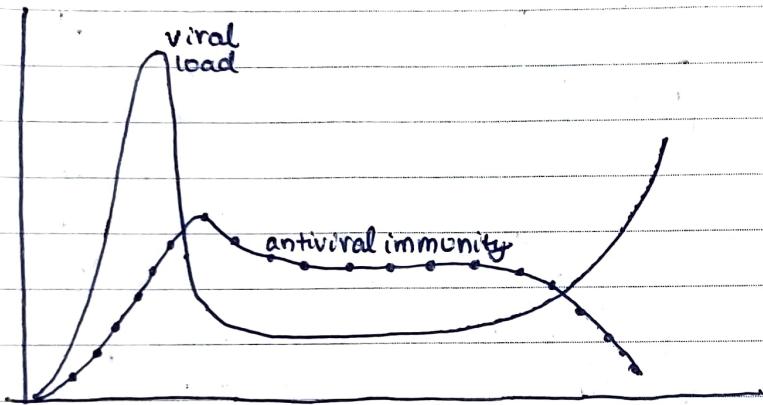
uncontrolled proliferation leads to mutations.

IS AN HIV-1 VACCINE POSSIBLE?

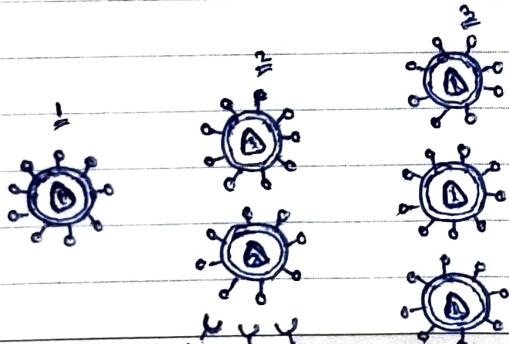
how does HIV-1 persist despite effective anti-viral immunity?

how does it eventually outstrip immune control?

HIV-1 superinfection occurs less frequently than initial infection.



HIV-1 ESCAPE FROM NEUTRALIZING ANTIBODY



virus mutates on the course of infection (many years) and you make antibodies to the initial infecting virus,

AUGUST 2013						
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Y Y Y₂

by the time the antiviruses arise, the virus has changed to another envelope, so it does not react with those antibodies

NOTES

AUGUST, 2013

9.7.2020
33
FRIDAY
WEEK 35 **30**

RV144

- prime-boost: ALVAC-HIV (gag, pol, env in canarypox vector)
AIDS VAX B/E (recombinant gp120 protein)
- 16,000 adult volunteers in Thailand
- 6 prime, 6 boost injections (logistical nightmare, have to track these people)
- lowered rate of HIV-1 infection by 31.2% compared with placebo.
- n = 51 vs n = 74 (marginally worked, but only this trial).

HIV-1 ENVELOPE AND INFLUENZA VIRUS HA DIVERSITY

A. 1996 influenza sequence (n=96) ~ 0.4
hemagglutinin (H3)

B. HIV-1 single individual (n=9) ~ 0.15
subtype B

C. democratic republic of the Congo 1997 (n=193) ~ 1.0

AD CRF01 C K

F1 H J G

NOTES

AUGUST

2013

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31 SATURDAY
WEEK 35

9.7.2020
34
AUGUST/SEPTEMBER, 2013

BROADLY NEUTRALIZING ANTIBODIES

some people produce these, are being studied.

IMMUNOPROPHYLAXIS VS AIDS

the coding genes of these antibodies have been inserted into Adenovirus associated virus vectors, AAV
IgG HC, LC heavy chain, light chain

the mice will produce the antibodies for their lifetime, the viruses remain expressing in them.

when humanized mice (reconstituted with human immune system, so they can be infected with HIV) are challenged every week for 21 weeks with HIV. these AAV carrying the broadly neutralizing antibodies are all protected.

1 SUNDAY
WEEK 35

this is in phase I in people now.

it is unlikely that a single BNAb will be effective because the virus can mutate to escape a single BNAb, nevertheless, if you put a couple in, might help.

SEPTEMBER 2013							NOTES
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29	30						

SEPTEMBER, 2013

9.7.2020

35

MONDAY

WEEK 36

02

CONFRONTING PERSISTENCE AND LATENCY

- eradicating all HIV-1 is challenging due to long-lived latent reservoir.
- intense drug therapy + broadly nAb failed.
- shock and kill: induce provirus expression, treat with antiviral drugs.
- block & lock: complete and irreversible inhibition of genome transcription.

SIV → ~1921: patient zero $\xrightarrow{\text{HIV-1}}$ 75,000,000 infections
32,000,000 deaths

NOTES

IL-2 turns on proliferation of T cells.

SEPTEMBER 2013						
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29	30					