AGING AND HIV

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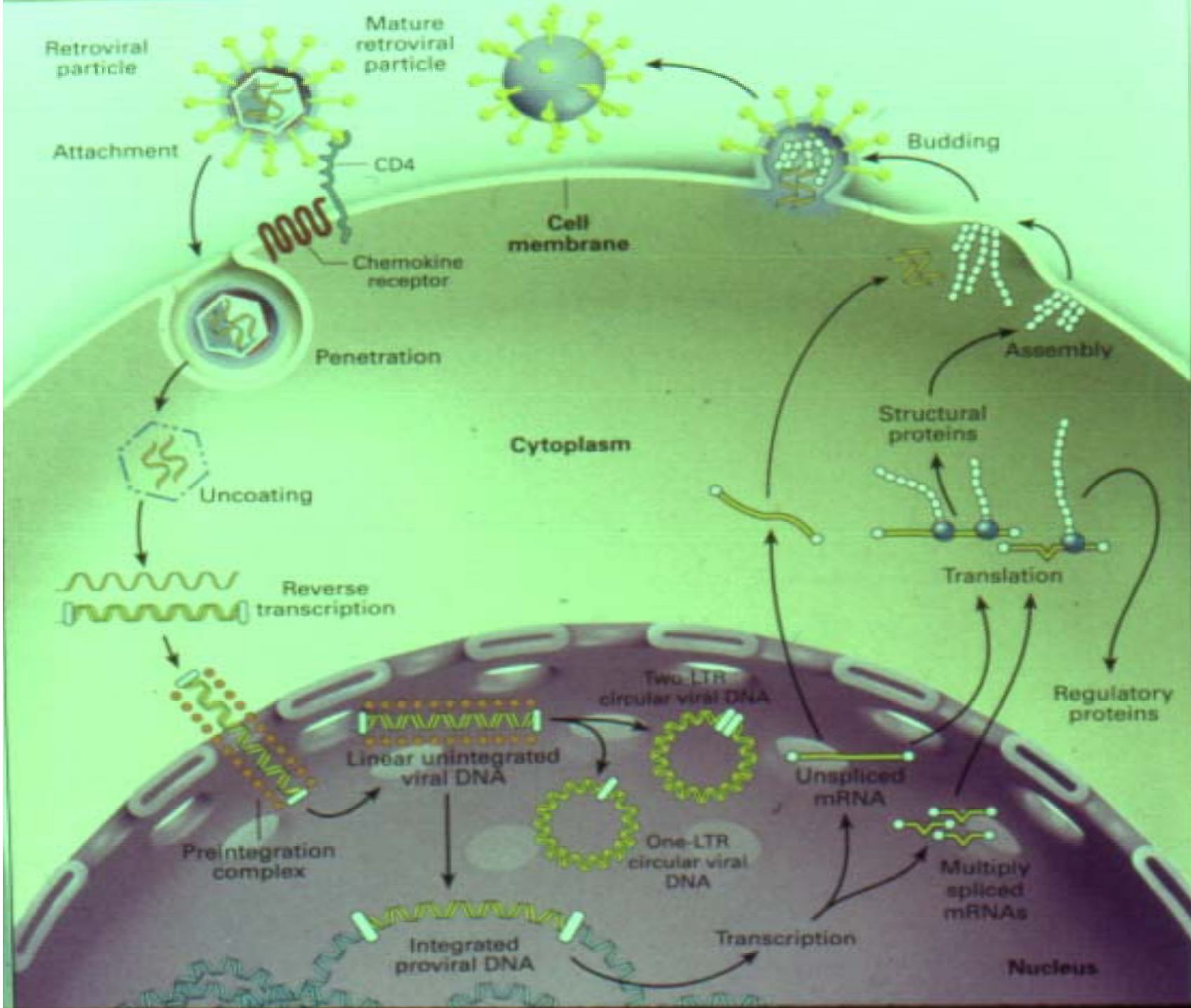
OUTLINE

- HIV PATHOGENESIS
- EPIDEMIOLOGY
- IMMUNOLOGY
- HEPATITIS A VACCINE RESEARCH


Retroviral particle
Mature retroviral particle
Attachment
CD4
Chemokine receptor
Cell membrane
Budding
Penetration
Assembly
Structural proteins
Cytoplasm
Uncoating
Translation
Reverse transcription
Two-LTR circular viral DNA
Regulatory proteins
Linear unintegrated viral DNA
Unspliced mRNA
Preintegration complex
One-LTR circular viral DNA
Multiply spliced mRNAs
Integrated proviral DNA
Transcription
Nucleus

ABBREVIATIONS AND JARGON

- PI PROTEASE INHIBITOR
- NA NUCLEOSIDE ANALOGUE (NUKE)
  - NRTI NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR
- NNRTI NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NON-NUKE)
- HAART HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)
  - TRIPLE OR COMBINATION THERAPY OR COCKTAIL
  - PI + 2 NA OR NNRTI + 2 NA
  - HEART

AGING AND HIV

- BACKGROUND EPIDEMIOLOGY
  - PRIOR TO 1989, BLOOD PRODUCTS WERE MAJOR RISK FACTOR
    - 1% AGE 13-49 YEARS
    - 6% AGE 50-59 YEARS
    - 28% AGE 60-69 YEARS
    - 64% AGE ≥70 YEARS

RECENT EPIDEMIOLOGY

CHARACTERISTIC	50 YEARS	13-49 YEARS
MALE	84%	79%
RACE		
WHITE	39%	38%
BLACK	43%	41%
HISPANIC	17%	19%
RISK FACTOR		
GAY/BISEXUAL	36%	40%
IDU	19%	26%
HETEROSEXUAL	14%	13%
NONE REPORTED	26%	16%
AIDS-DEFINING DX		
HIV ENCEPHALOPATHY	3%	1%
WASTING	7%	4%
OTHER OI	38%	36%
IMMUNOSUPPRESSION	52%	58%

MMWR 1998;47:21

HIV AND AGING: CO-MORBIDITY

- ADVANCING AGE IS RISK FACTOR FOR MANY INFECTIOUS DISEASES
- OLDER HIV-POSITIVE PATIENTS HAVE SHORTER AIDS-FREE INTERVAL AND SHORTER SURVIVAL
- RAPID PROGRESSION MAY BE DUE TO DELAYED DIAGNOSIS OR HIV-RELATED OR NON-HIV-RELATED COMORBIDITY
  - 13% OF ≥50 DIED WITHIN ONE MONTH OF AIDS DX VERSUS 6% of 13-49

IMPACT OF AGING ON HIV PROGRESSION LANCET 1996;347:1573-79

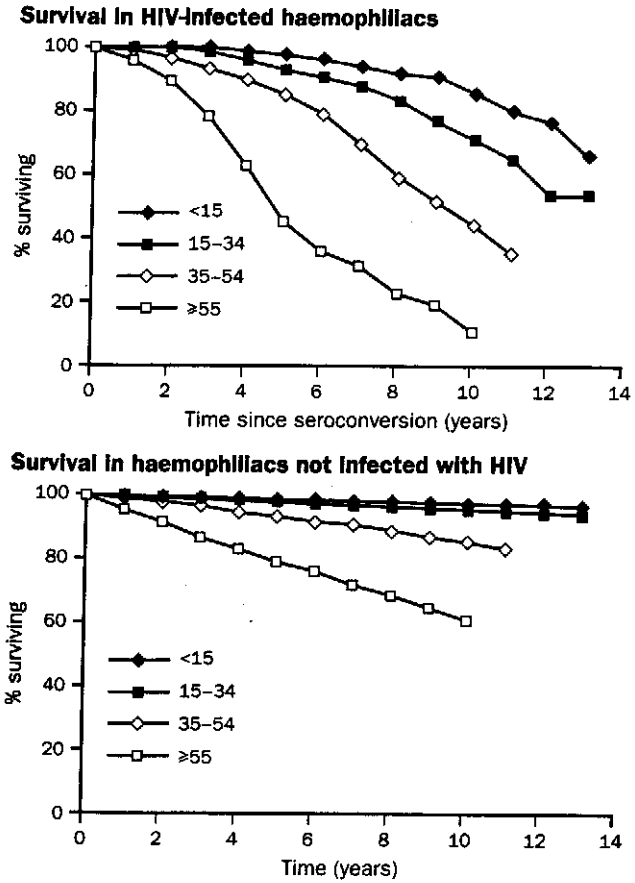


Figure 1: **Survival in HIV-infected seropositive haemophilia patients by age at seroconversion and expected survival based on mortality rates for uninfected patients subdivided by age and severity of haemophilia**
Within each age-at-seroconversion group estimates are censored when fewer than five HIV-seropositive patients remain at risk.

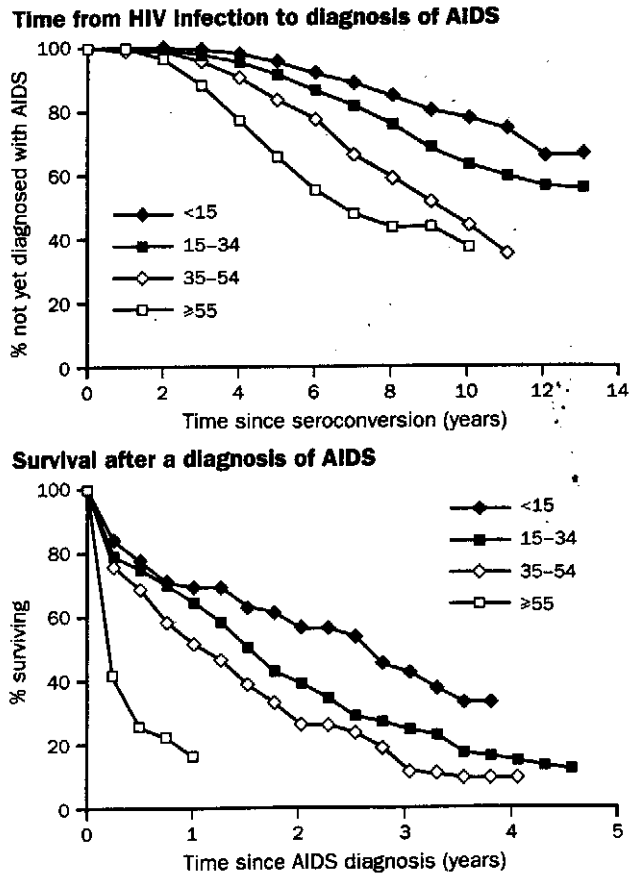
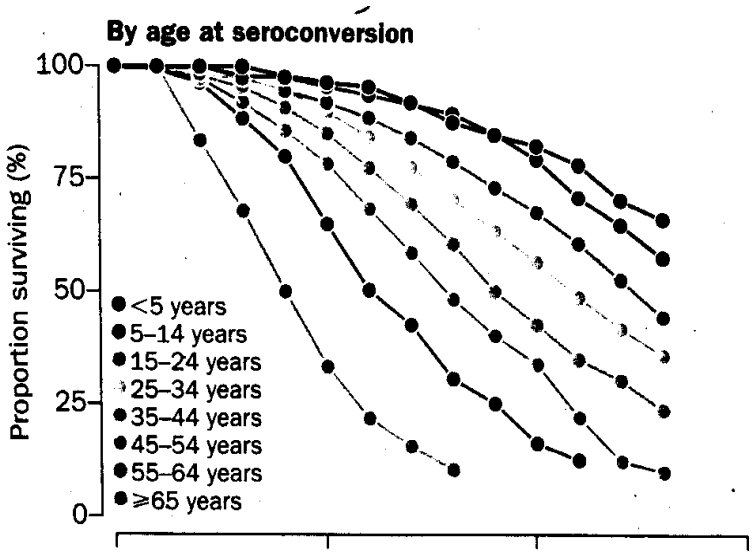
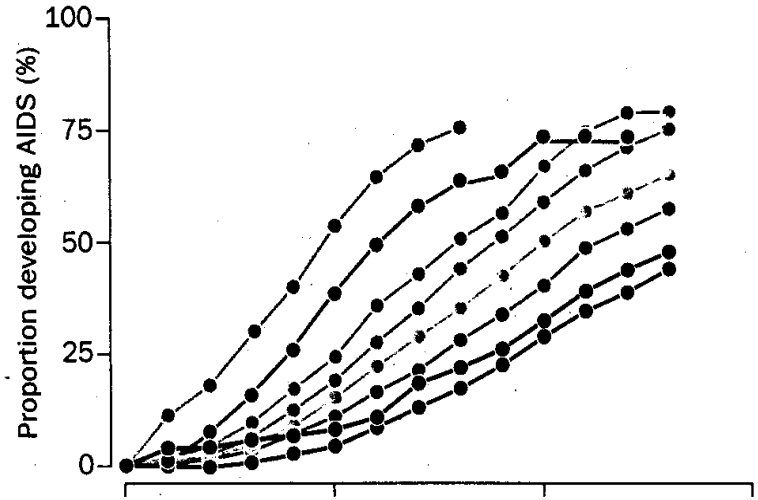


Figure 2: **Development of AIDS in haemophilia patients and survival after a diagnosis of AIDS by age at seroconversion**
Within each group estimates are censored when fewer than five people remain at risk.

IMPACT OF AGING ON HIV PROGRESSION LANCET 2000;355:1131-37





AGE	MEDIAN SURVIVAL	MEDIAN TIME TO AIDS
15-24	12.5 (12.1-12.9)	11.0 (10.7-11.7)
25-34	10.9 (10.6-11.3)	9.8 (9.5-10.1)
35-44	9.1 (8.7-9.5)	8.6 (8.2-9.0)
45-54	7.9 (7.4-8.5)	7.7 (7.1-8.6)
55-64	6.1 (5.5-7.0)	6.3 (5.5-7.2)
≥ 65	4.0 (3.4-4.6)	5.0 (4.0-6.2)

RECONSTITUTION OF T-CELL IMMUNITY

- PROGRESSIVE LOSS OF THYMIC FUNCTION BEGINNING AT AGE SIX YEARS
  - LOSE CD45RA (AND L-SELECTIN)
  - GAIN CD45RO
  - HAART IN CHILDREN (1-16 YEARS)
    - LARGER INCREASE <6 YEARS VS >6 YEARS
- FOLLOWING CHEMOTHERAPY, INVERSE RELATION BETWEEN AGE (1-24YRS) AND CD4+ T-CELL NUMBER
  - CD4+ T-CELL CORRELATED WITH CD4+CD45RA+
- FOLLOWING BURNS, IT TAKES A 40 YEAR OLD TWICE AS LONG AS A 20 YEAR OLD TO REPLACE CD4+ CELLS
- CHEMOTHERAPY FOR BREAST CANCER (33-69)
  - NO RELATION BETWEEN AGE AND CD4 RECOVERY

AGE AND IMMUNE RECONSTITUTION FOLLOWING CHEMOTHERAPY

MACKALL et al, NEJM 1995;332:143

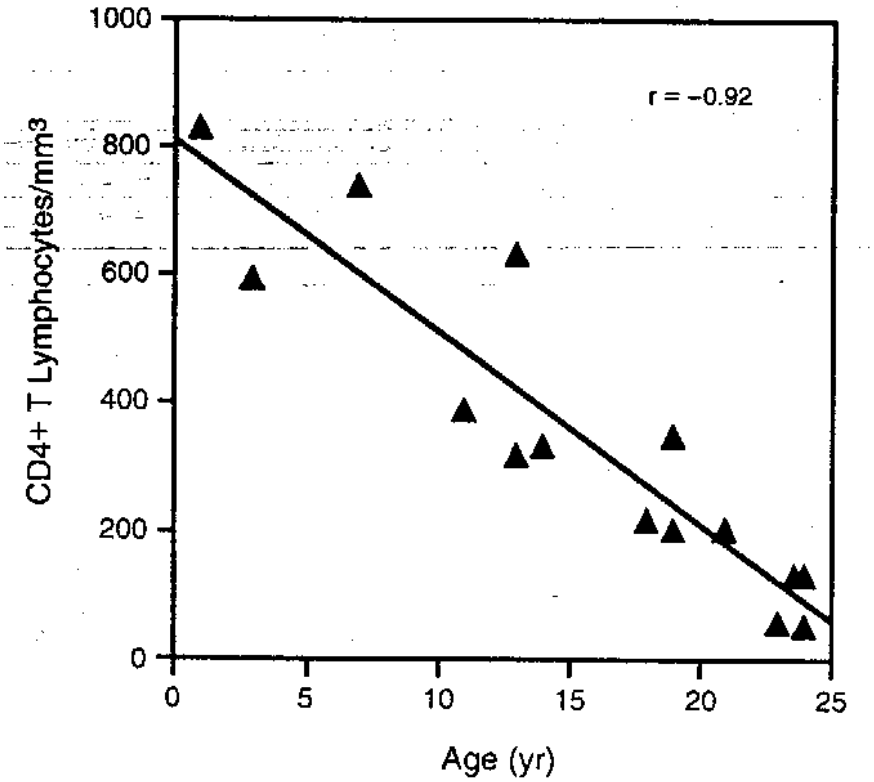


Figure 1. Relation between Age and Reconstitution of CD4+ T Lymphocytes.

Absolute CD4+ T-lymphocyte counts were measured in the peripheral blood of patients approximately six months after the completion of chemotherapy. The correlation coefficient was calculated by the Spearman rank-correlation method.

HIV-INDUCED IMMUNE PATHOGENESIS

- CHARACTERISTIC LOSS OF HELPER CD4+ T-CELLS
- INFECTION OF PERIPHERAL CD4+ T-CELLS
  - PREFERENTIAL INFECTION OF CD45RO+ CELLS
- DESTRUCTION OF THYMUS
- FUNCTIONAL CONSEQUENCES ARE LOSS OF:
  - NEOANTIGENS
  - ALLOANTIGENS
  - MITOGENS

IMMUNE RECONSTITUTION

- HAART IS HIGHLY EFFECTIVE IN REDUCING VIRAL LOAD AND INCREASING NUMBERS OF CD4+ T-CELLS
- MECHANISMS:
  - MOBILIZATION OF LYMPHOCYTES
  - DECREASED DESTRUCTION
  - INCREASED DIFFERENTIATION FROM THYMIC PRECURSORS

IMMUNE RECONSTITUTION AFTER HAART

- THREE DISTINCT PHASES
  - FIRST 4 WEEKS: INCREASE IN OF CD45RO T-CELLS, CD8 T-CELLS, B-CELLS; THOUGHT TO REPRESENT RECIRCULATION
  - NEXT SEVERAL MONTHS: REDUCTION IN T-CELL ACTIVATION MARKERS, WITH DECLINE IN CD8 T-CELLS
  - 6-12 MONTHS: RISE IN CD45RA T-CELLS, PRESUMABLY THYMIC-DERIVED
- RECOVERY OF FUNCTION?
  - REACTIVITY AGAINST RECALL ANTIGENS
  - INCOMPLETE REGENERATION OF T-CELL RECEPTOR DIVERSITY

EFFECTS OF AGING ON IMMUNE RECONSTITUTION

- MANFREDI, et al AIDS 2000;14:1475
  - 12 mo F/U

AGE	<35	≥55
N	84	21
BASELINE VL	4.5 log	4.7 log
Δ VL	-1.8 log	-1.9 log
BASELINE CD4	231/µl	212/µl
Δ CD4	+114/µl	+72/µl

EFFECTS OF AGING ON IMMUNE RECONSTITUTION

- KAUFMAN, et al AIDS 2002;16:359
  - 95 PERSONS, 48 mo F/U
    - AGE CD4
    - <35 +374
    - 35-44 +318
    - >44 +196
- NEGATIVE PREDICTORS OF CD4 RECOVERY
  - AGE, NADIR CD4

EFFECT OF AGE ON RECOVERY OF CD4 NUMBER VIARD et al,JID 2001;183:1290-4

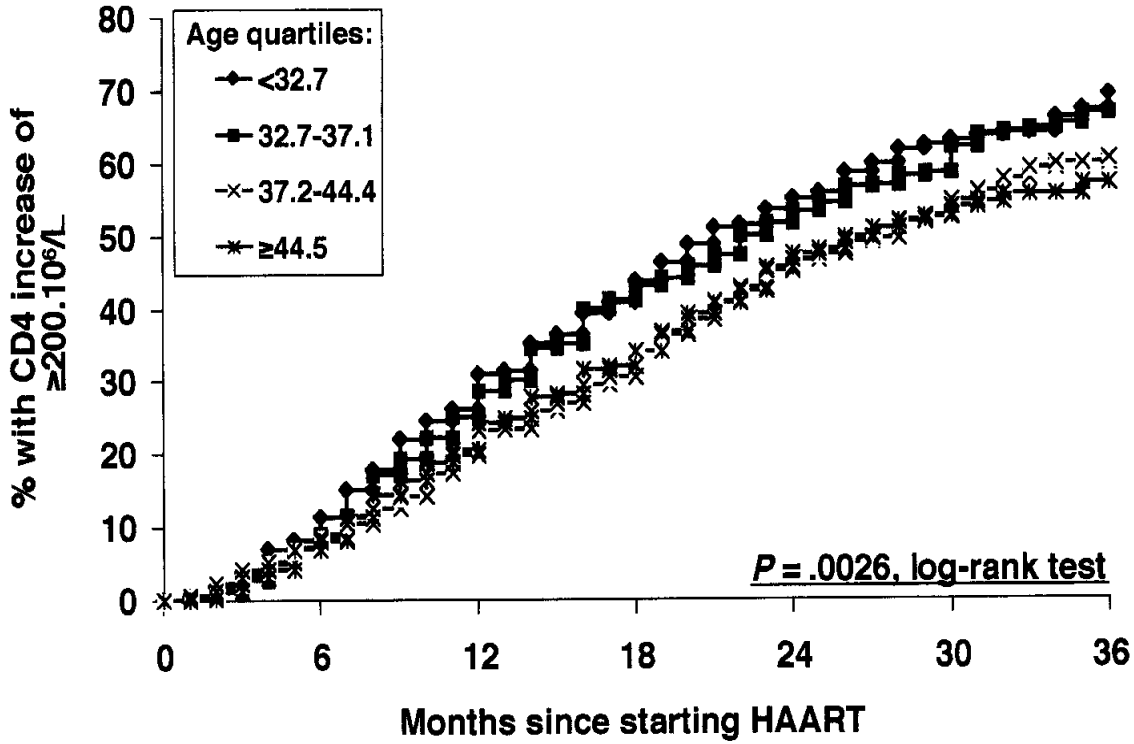
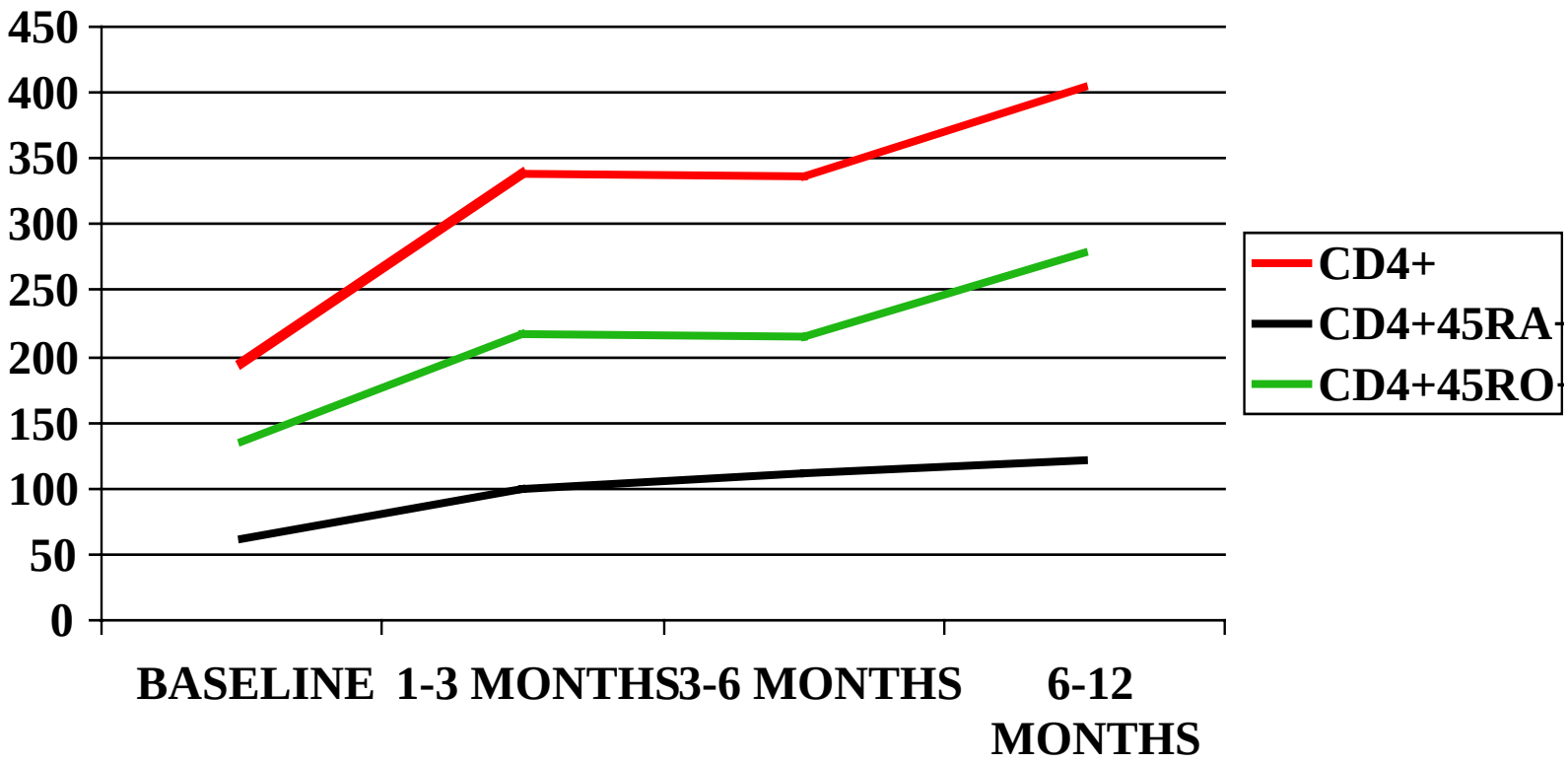


Figure 1. Kaplan-Meier curves of time to increase in CD4 cell count of $\geq 200 \times 10^6$ cells/L after start of HAART in subjects in 4 age quartiles.

EFFECT OF AGE ON RESPONSE TO HAART

AGE	#	BASELINE		8-12 WEEKS		24-28 WEEKS	
		CD4	VL	CD4	VL	CD4	VL
2-6 yr	20	384	5.4	+144	-2.3	+324	-1.9
6-18 yr	21	176	5.2	+71	-2.0	+105	-1.6
26-39 yr	18	126	4.7	+85	-1.5	+52	-0.8
50-73 yr	19	163	4.5	+77	-1.3	+40	-0.9

IMMUNE RECONSTITUTION IN OLDER HIV+ MEN



EFFECTS OF AGE ON IMMUNE RECONSTITUTION FOLLOWING HAART

- PRIMARY HYPOTHESIS:
  - RETURN OF NAÏVE CD4+ T-CELLS IS THE CRITICAL DETERMINANT OF FUNCTIONAL IMMUNE RECONSTITUTION FOLLOWING HAART
- SECONDARY HYPOTHESIS:
  - THERE ARE INTRINSIC DEFECTS IN NAÏVE CD4+ T-CELLS IN HEALTHY ELDERS

OBJECTIVES

- TEST NAÏVE CD4 T-CELL FUNCTION BY IMMUNIZATION WITH A NEOANTIGEN (HEPATITIS A VACCINE)
- EVALUATE T-CELL RECEPTOR DIVERSITY IN NAÏVE CD4 T-CELLS
- EXAMINE CHANGES IN EXPRESSION OF ADHESION MOLECULES AND CYTOKINE PROFILES

SITES

- GAINESVILLE VA MEDICAL CENTER
- ALACHUA COUNTY PUBLIC HEALTH DEPARTMENT
- UNIVERSITY OF FLORIDA
  - ADULT INFECTIOUS DISEASES CLINIC
  - PEDIATRIC INFECTIOUS DISEASES CLINIC

ENTRY CRITERIA

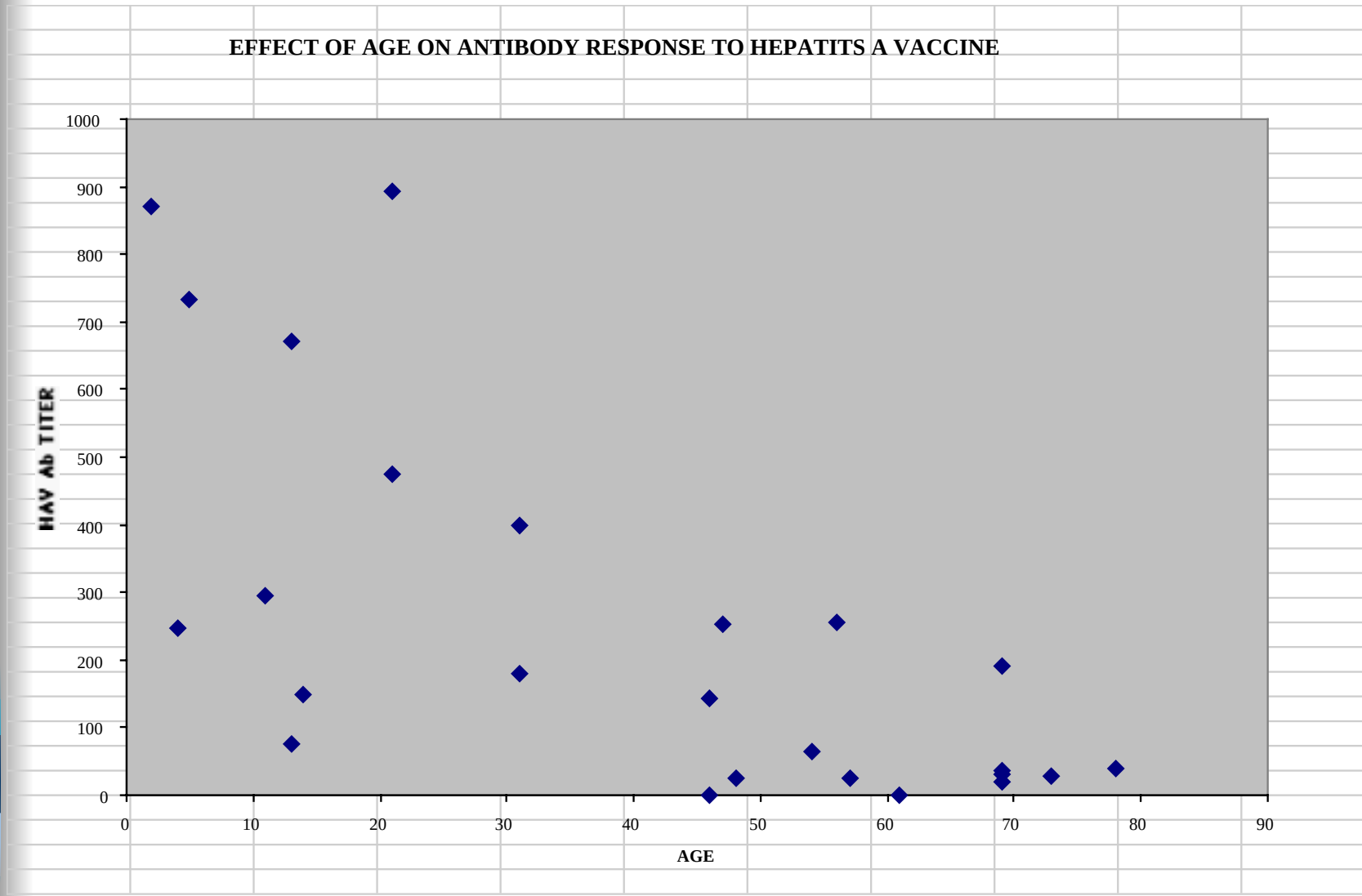
- ALL ANTI-HAV AB SERONEGATIVE AND PREVIOUSLY VACCINATED AGAINST TETANUS
- HEALTHY VOLUNTEERS
  - HIV (-)NO KNOWN IMMUNOLOGICAL PROBLEM
- HIV (+) NAÏVE
  - NEVER ON HAART; DUAL NUCLEOSIDES ALLOWED
- HIV (+) HAART
  - ON PROTEASE INHIBITOR (PI) OR NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) PLUS TWO NUCLEOSIDE ANALOGUES (NA) > 1 YR
  - VL < 50 COPIES/ML OR >1.5 LOG DROP

SUBJECTS

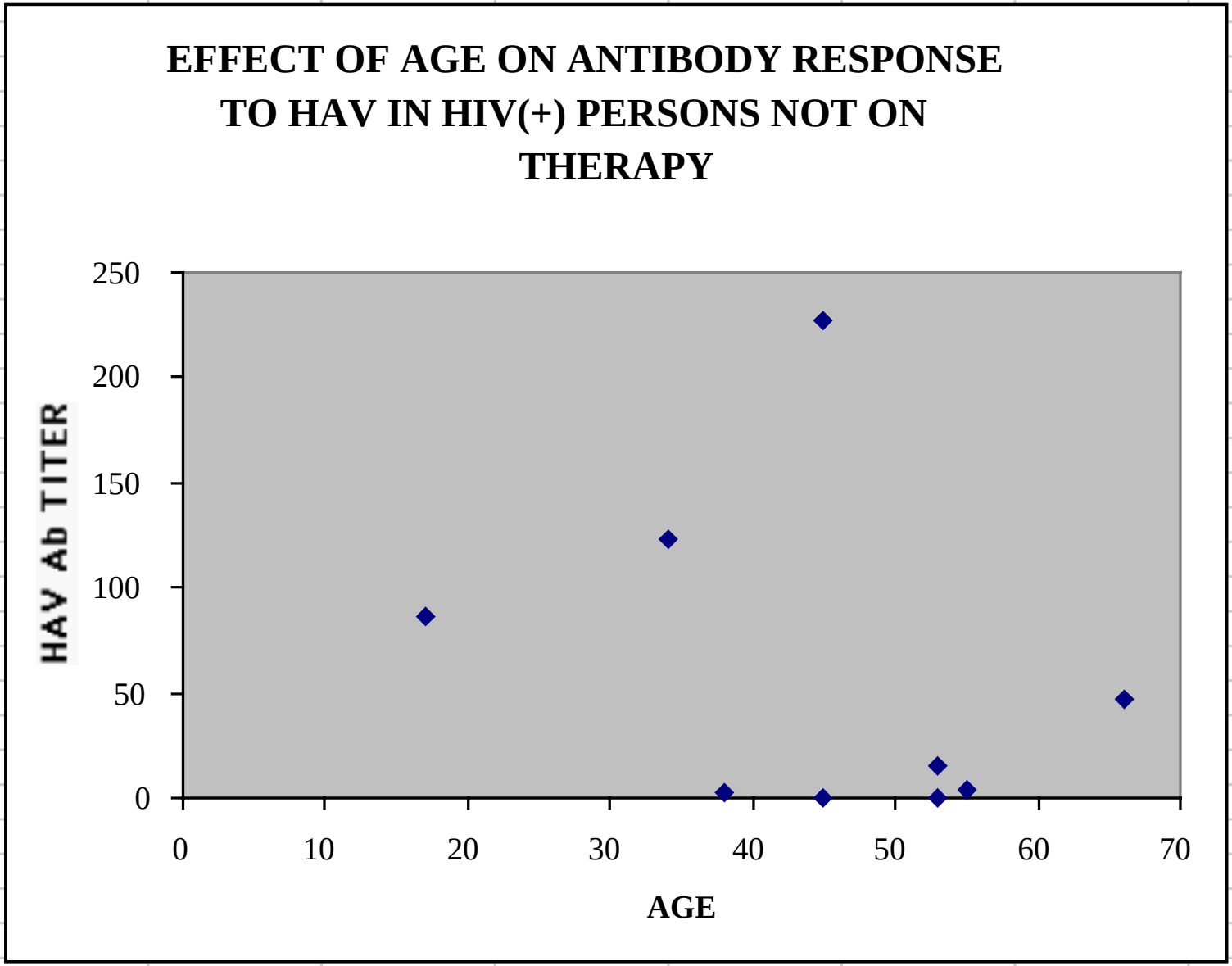
- HEALTHY CONTROLS, N=25
  - HIV (-)
  - AGE 2-78
- HIV (+) NAÏVE, N=9
  - NEVER ON THERAPY OR DUAL NA
  - AGE 17-66
- HIV (+) ON HAART, N=32
  - TRIPLE THERAPY > 1 YEAR
  - AGE 3-62

PROTOCOL

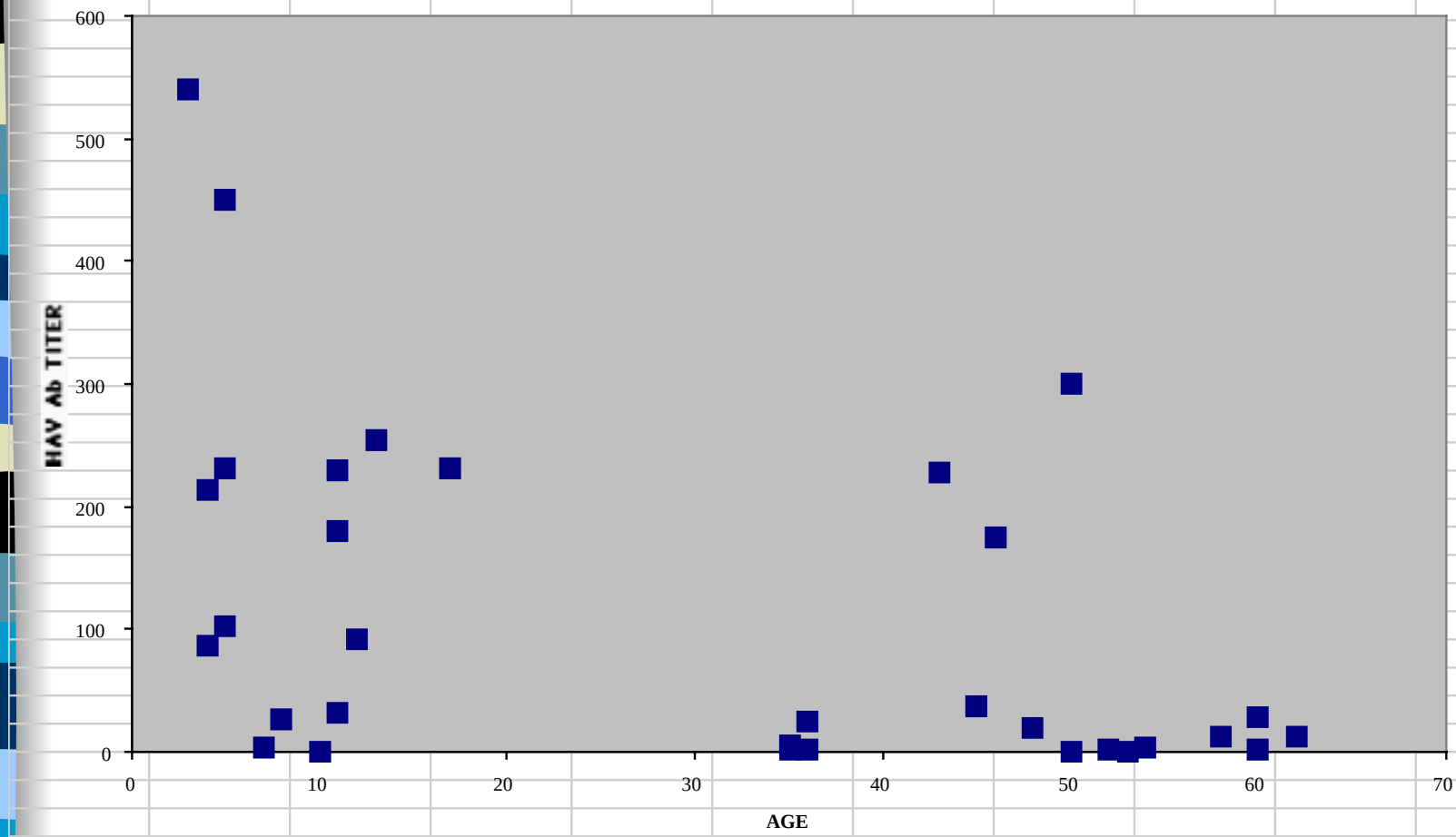
- WEEK 0:
  - VACCINATE WITH HEPATITIS A AND TETANUS
  - BLOOD DRAW
- WEEK 4:
  - RE-VACCINATE WITH HEPATITIS A
  - BLOOD DRAW
- WEEK 8:
  - BLOOD DRAW


EFFECT OF AGE ON ANTIBODY RESPONSE TO HEPATITS A VACCINE
HAV Ab TITER
1000
900
800
700
600
500
400
300
200
100
0
0
10
20
30
40
50
60
70
80
90
AGE

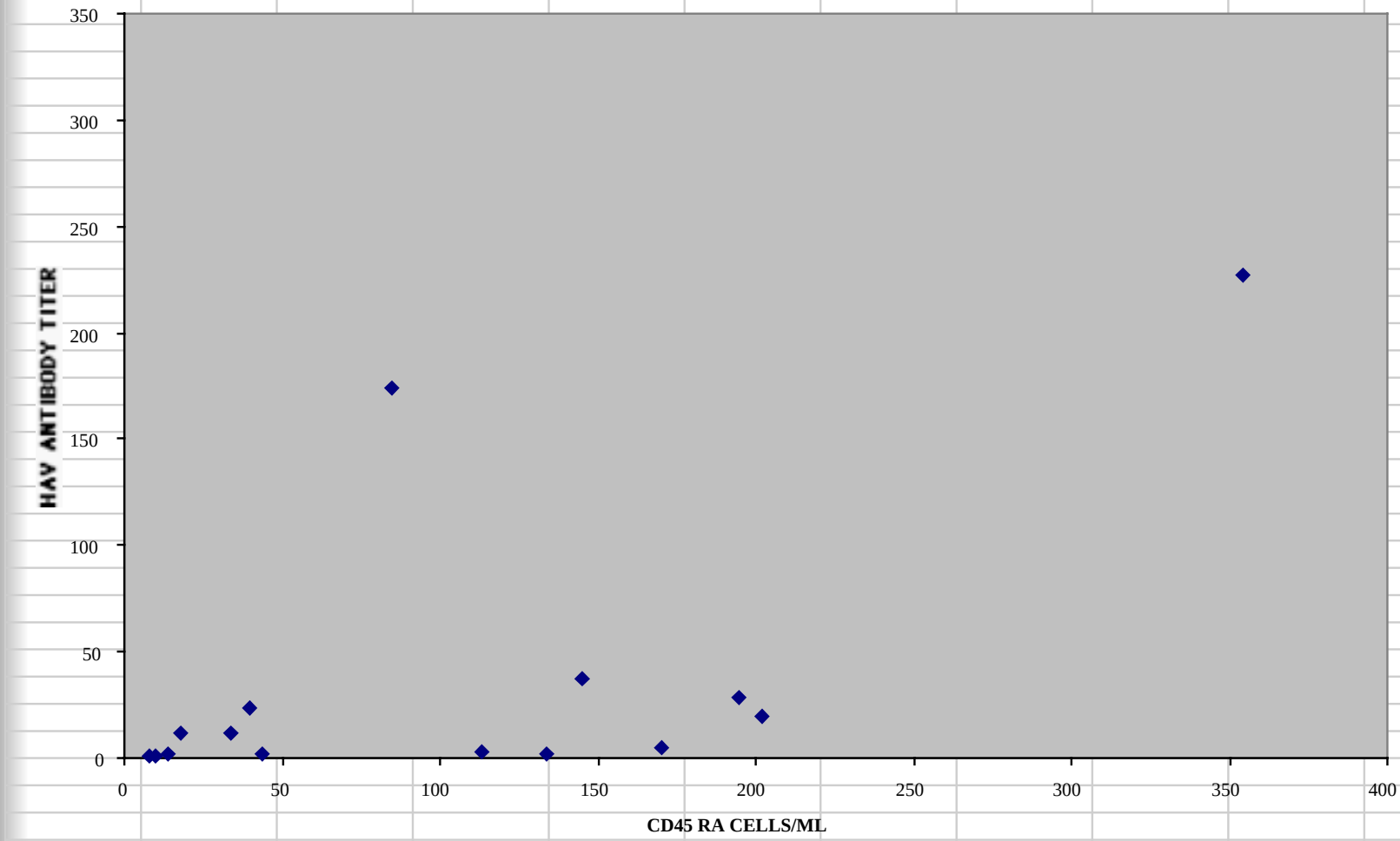
$R^2=0.56$, $p<0.01$


EFFECT OF AGE ON ANTIBODY RESPONSE TO HAV IN HIV(+) PERSONS NOT ON THERAPY
HAV Ab TITER
250
200
150
100
50
0
0
10
20
30
40
50
60
70
AGE

EFFECT OF AGE ON ANTIBODY RESPONSE TO HAV VACCINE IN PATIENTS ON HAART



RECOVERY OF NAIVE CD45 RA CELLS AND HAV ANTIBODY RESPONSE



FURTHER STUDIES

- EXAMINATION OF RESPONSE AFTER 4-5 YEARS OF HAART
- TETANUS ANTIBODY
- SEPARATION OF CD4+45RA+ AND CD4+45RO+ T-CELLS
  - T-CELL RECEPTOR REPERTOIRE DIVERSITY
  - PROLIFERATION TO HEP A, TETANUS, AND PHA

SUMMARY

- THERE IS A SIGNIFICANT AGE-RELATED DECLINE IN SERUM ANTI-HAV Ab RESPONSE
- HIV INFECTION ROBS PERSONS OF THEIR NAÏVE CD4 T-CELL FUNCTION
- MINIMALLY RESTORED BY HAART
  - NO DIFFERENCE IN PI OR NNRTI BASED REGIMENS
  - NOT INFLUENCED BY BASELINE CD4

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