

HIV 101: Fundamentals of HIV Infection and Applications of Antiretroviral Therapy

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Financial Relationships With Ineligible Companies (Formally Described as Commercial Interests by ACCME) Within the Last 2 Years:

*Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc., and ViiV Healthcare.
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*Planner/Reviewer 1 has no relevant financial affiliations to disclose.
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*Planner/Reviewer 2 has no relevant financial affiliations to disclose.
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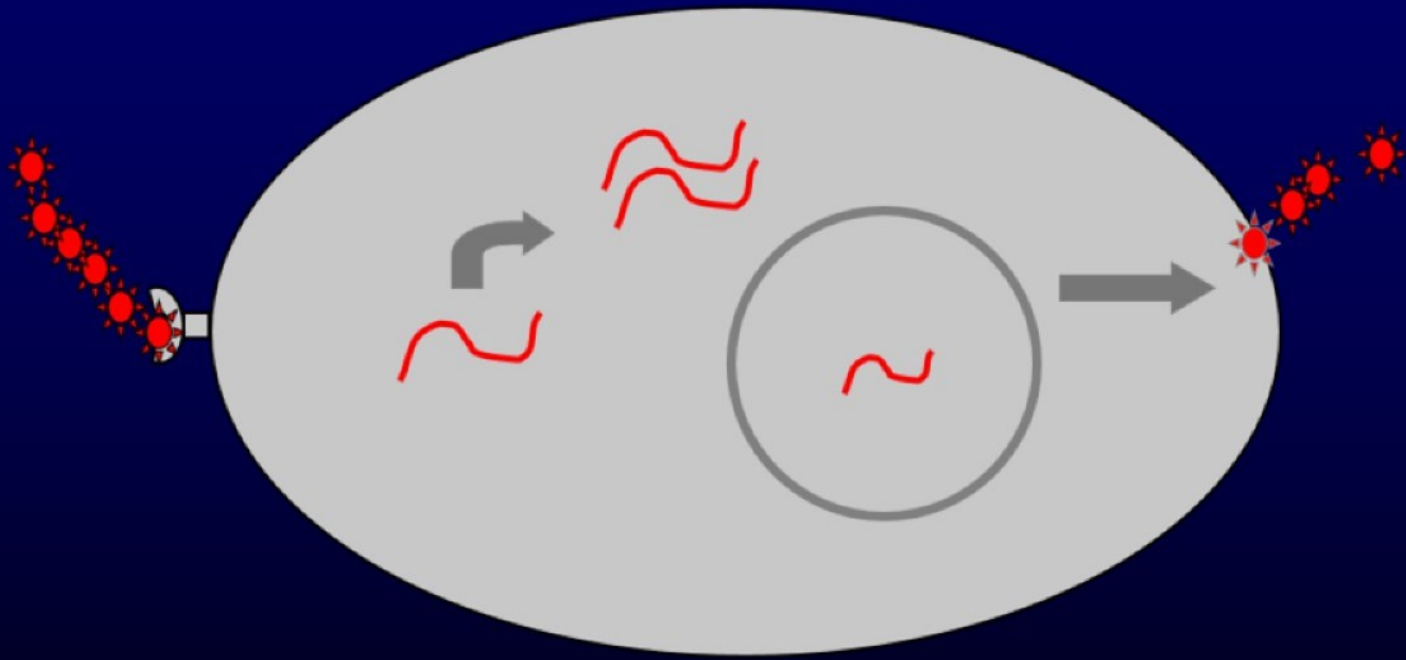
Pretest Question #1

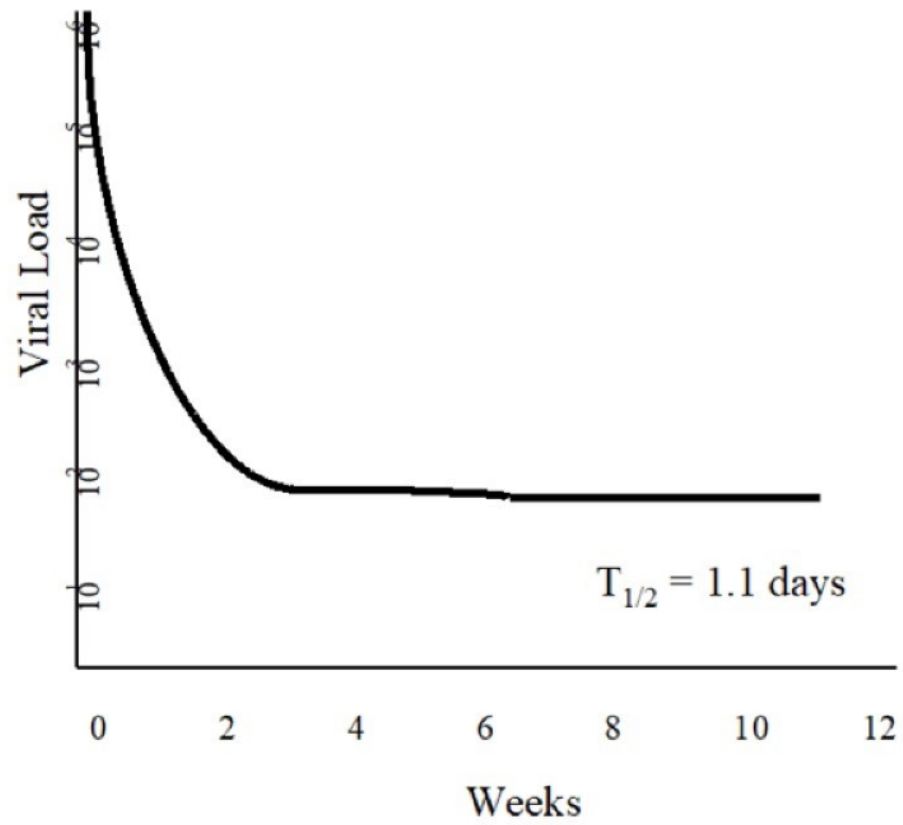
At steady state, when an actively producing cell dies it is replaced by how many newly infected cells?

1. One
2. Twenty five
3. One hundred
4. One thousand
5. It depends on the viral load



BACK TO BASICS





ARS 1

How many HIV virions are produced a day in an infected person?

1. 1
2. ~ 1000
3. 570,342
4. ~ 1 million
5. > 1 billion

Viral dynamics in human immunodeficiency virus type 1 infection

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Emilio A. Emini[‡], Paul Deutsch[§], Jeffrey D. Lifson^{||}, Sebastian Bonhoeffer^{*},
Martin A. Nowak^{*}, Beatrice H. Hahn^{*}, Michael S. Saag[†]
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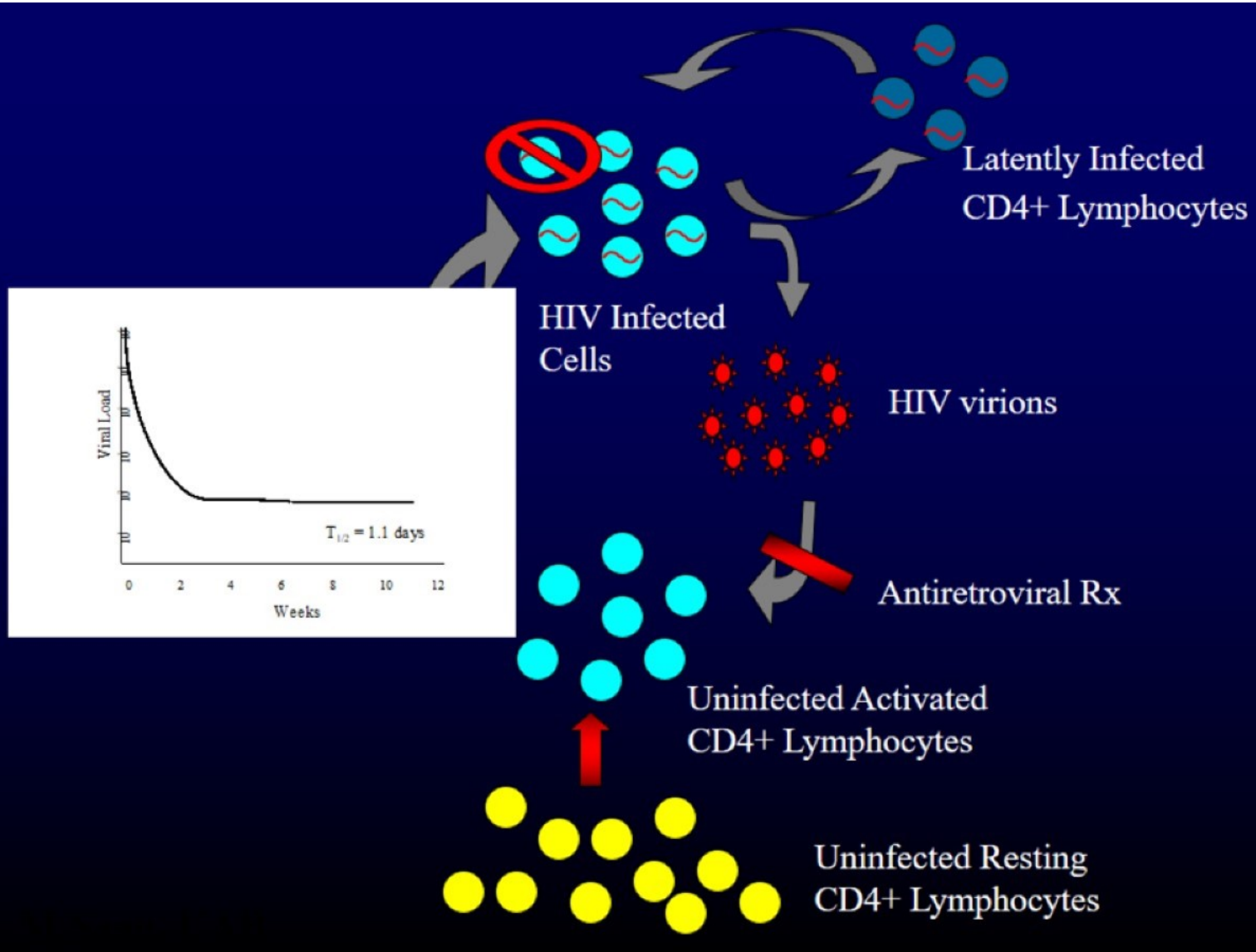
Departments of [‡] Antiviral Research and [§] Clinical Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486, USA

^{||} Division of HIV and Exploratory Research, Genelabs Technologies Inc., Redwood City, California 94063, USA

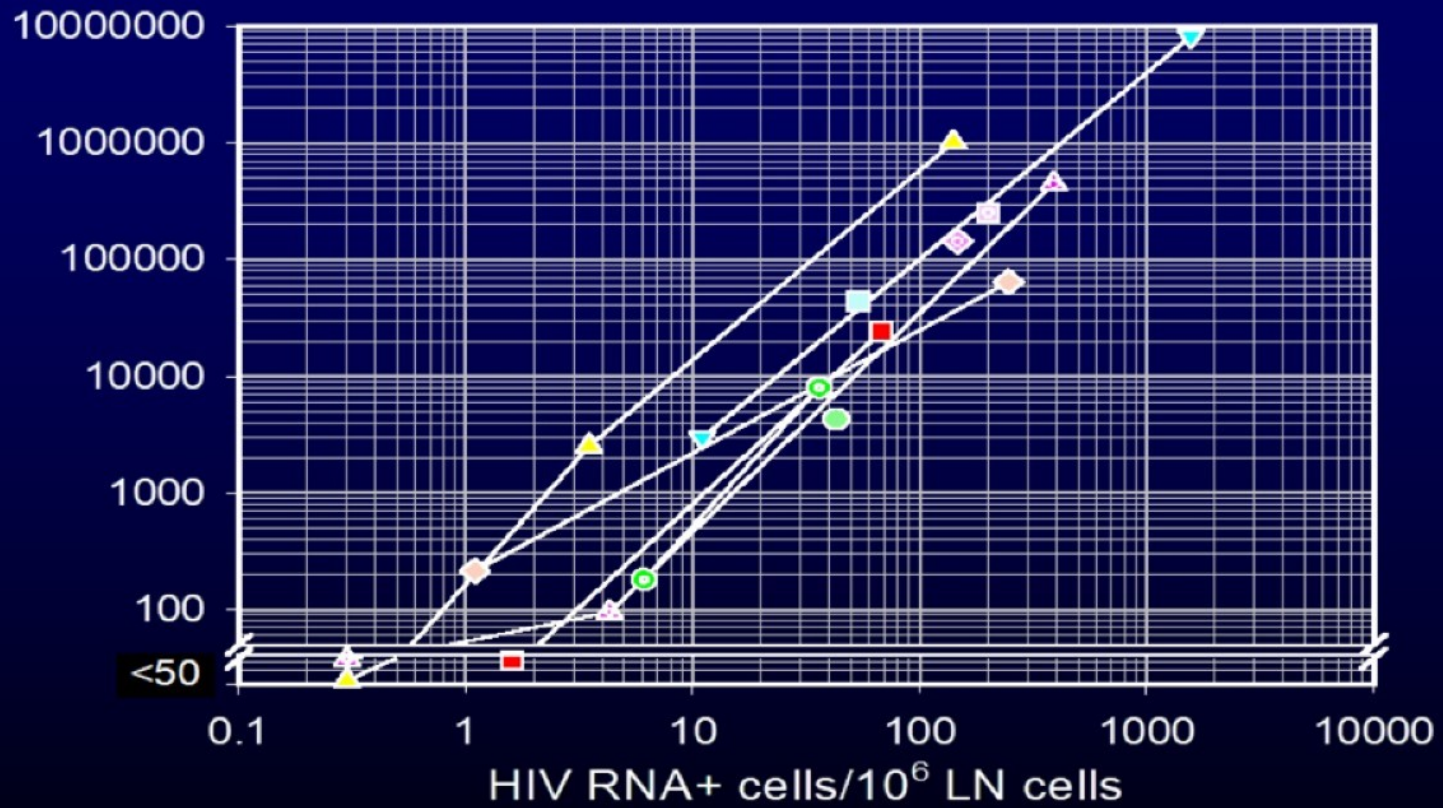
[#] Department of Zoology, University of Oxford, Oxford OX1 3PS, UK

The dynamics of HIV-1 replication *in vivo* are largely unknown yet they are critical to our understanding of disease pathogenesis. Experimental drugs that are potent inhibitors of viral replication can be used to show that the composite lifespan of plasma virus and virus-producing cells is remarkably short (half-life ~2 days). Almost complete replacement of wild-type virus in plasma by drug-resistant variants occurs after fourteen days, indicating that HIV-1 viraemia is sustained primarily by a dynamic process involving continuous rounds of *de novo* virus infection and replication and rapid cell turnover.

NATURE · VOL 373 · 12 JANUARY 1995



RNA+ cells in Lymph node vs RNA in Plasma

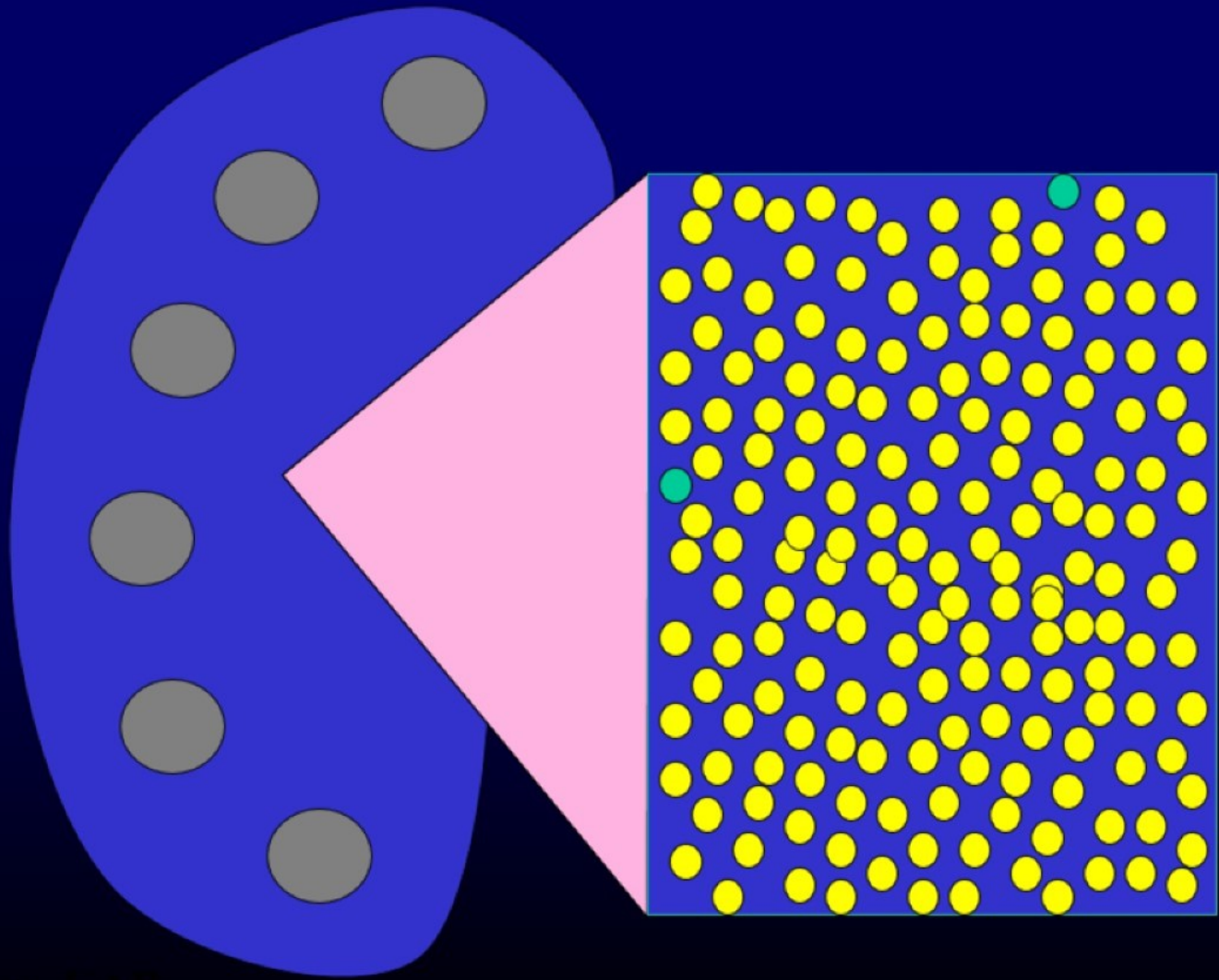


Plasma Viral Load

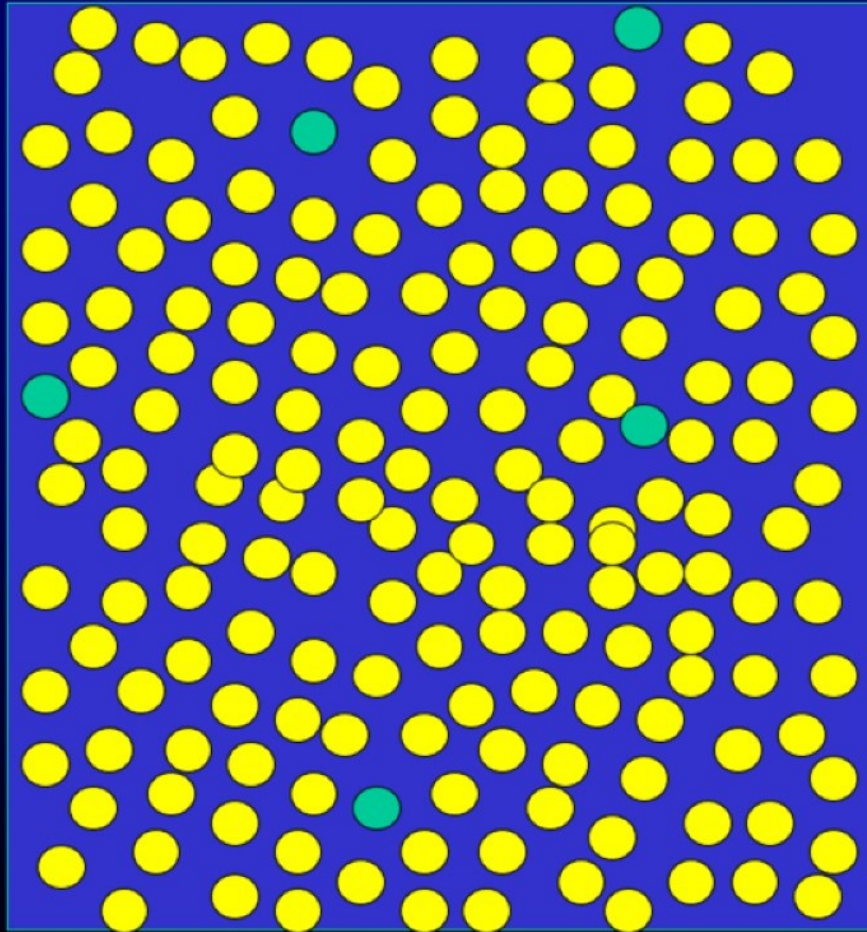
ARS 2

At steady state, when an actively producing cell dies, it is replaced by how many newly infected cells?

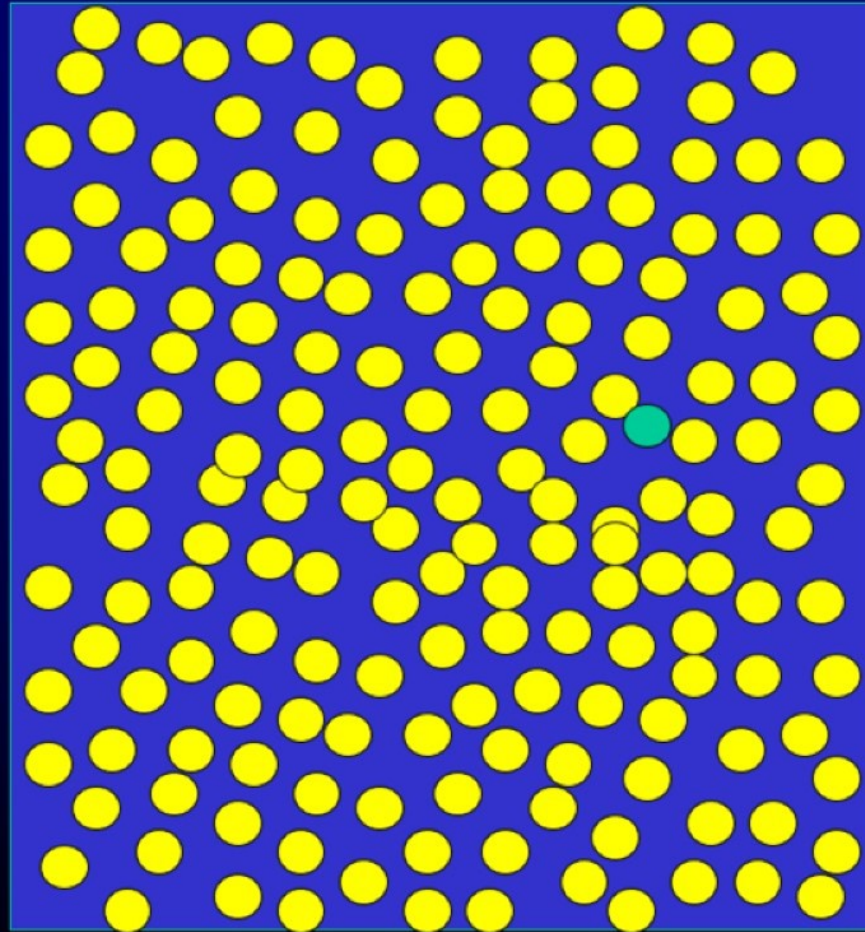
1. One
2. Twenty – Five
3. One Hundred
4. One Thousand
5. It depends on the viral load

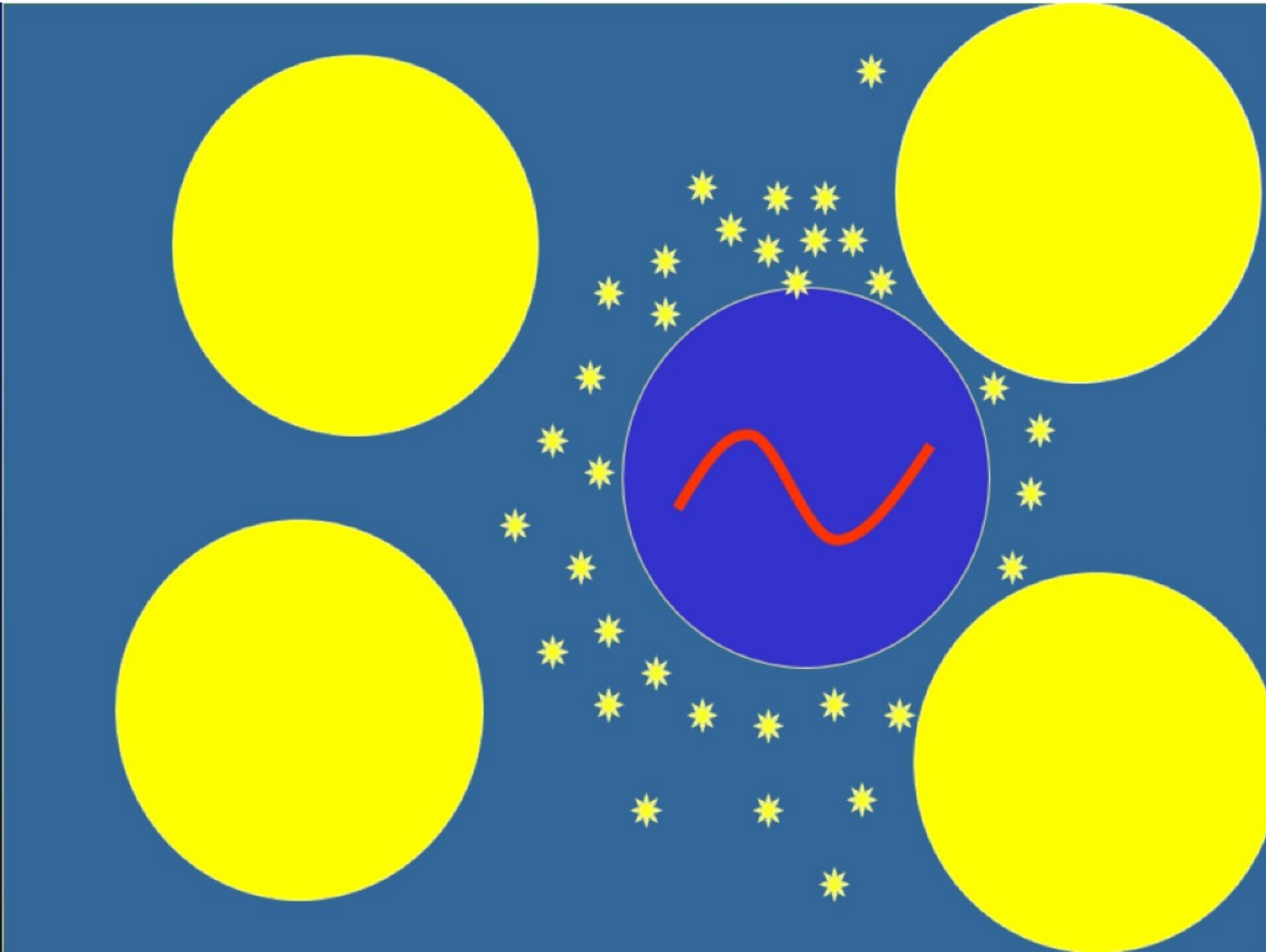


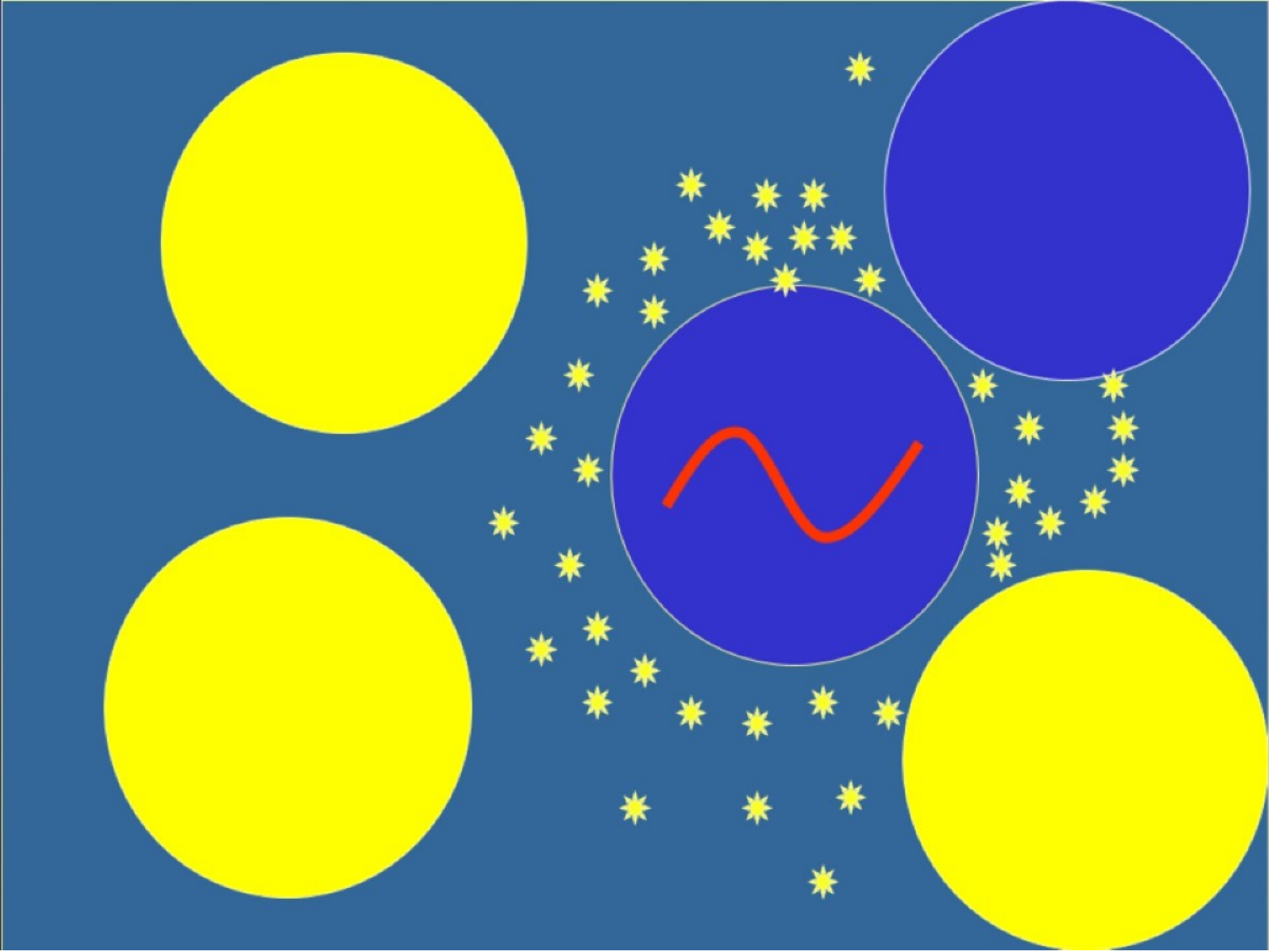
$VL =$
 $100,000$

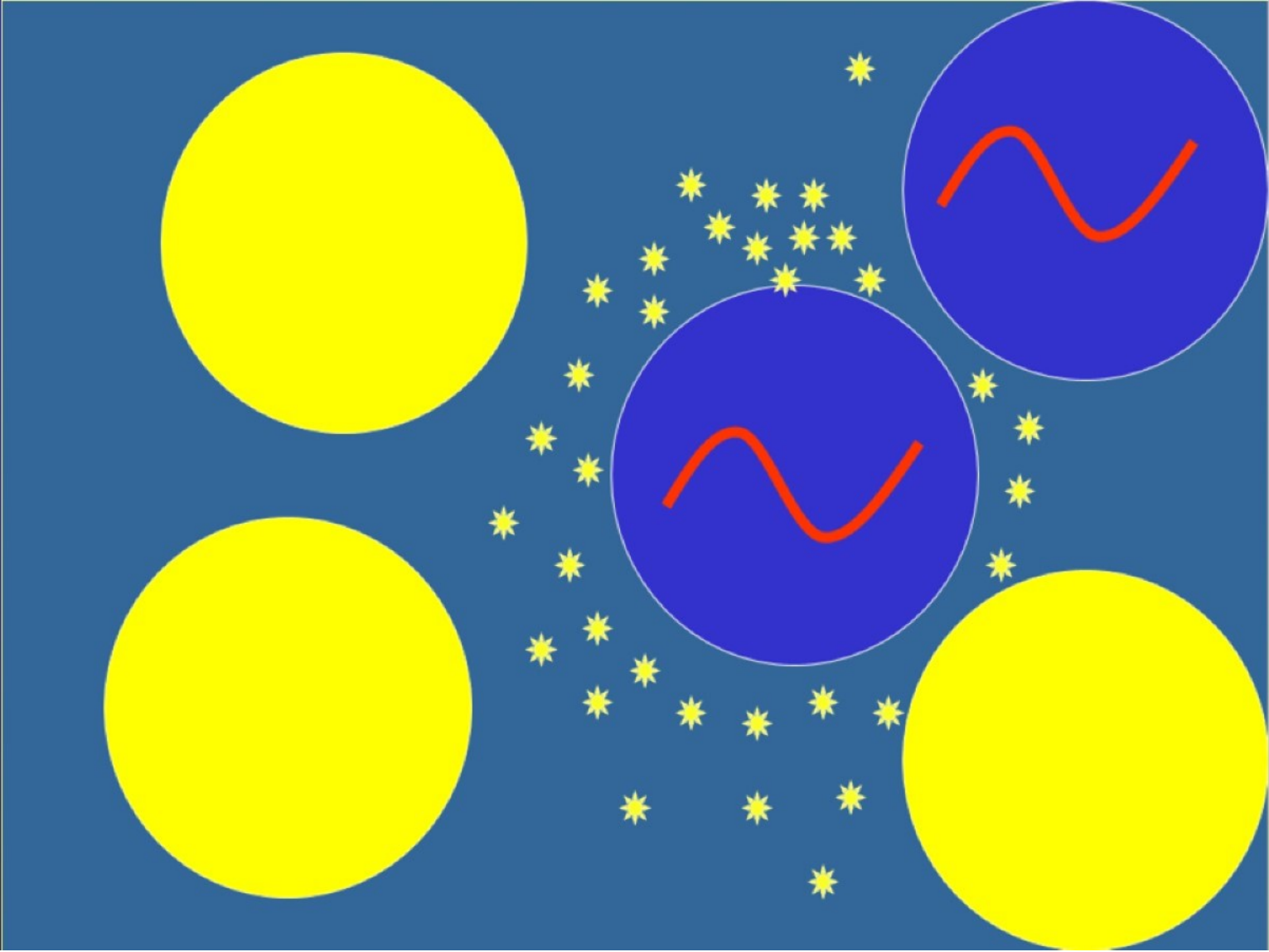


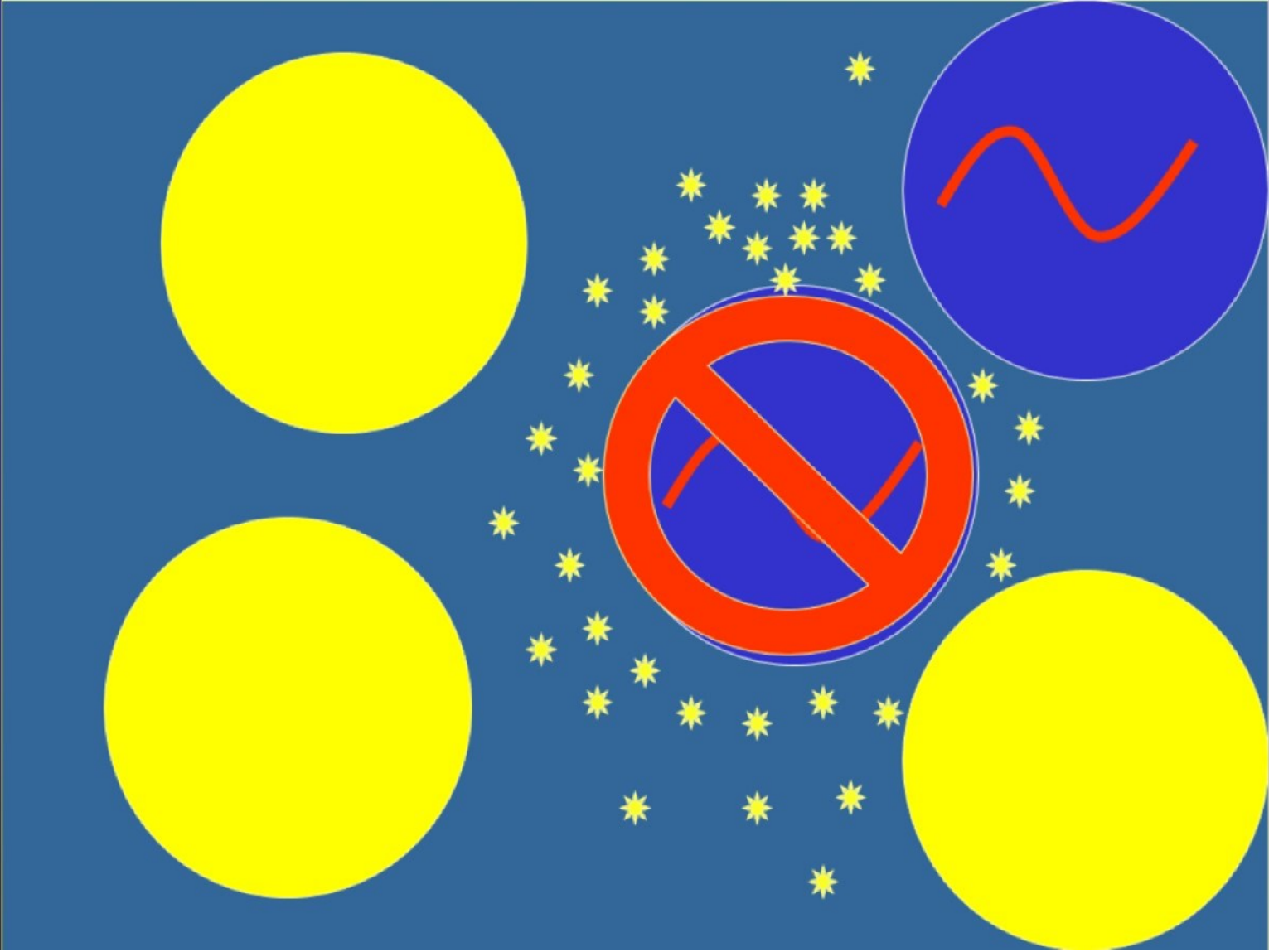
$VL < 50$

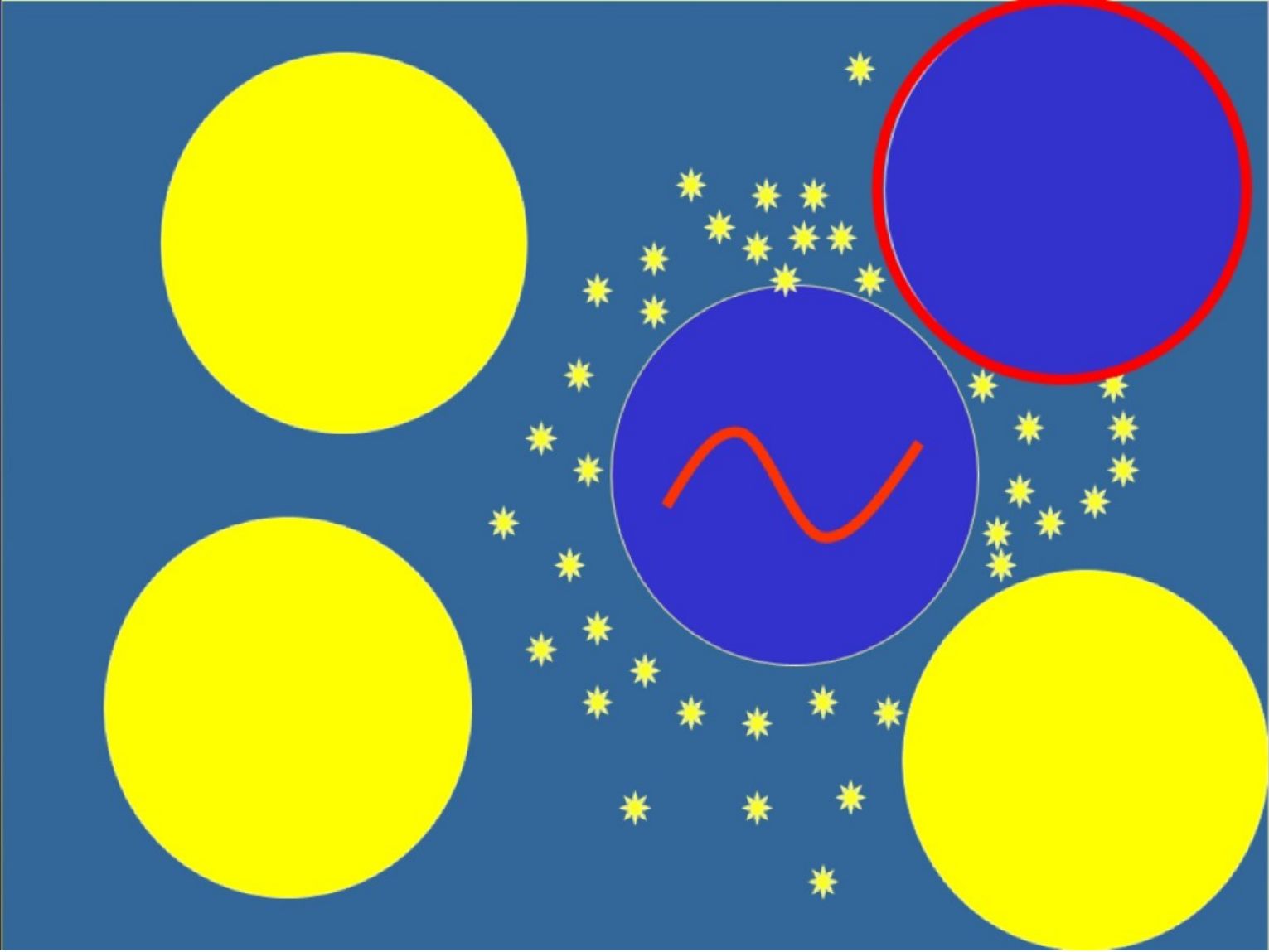


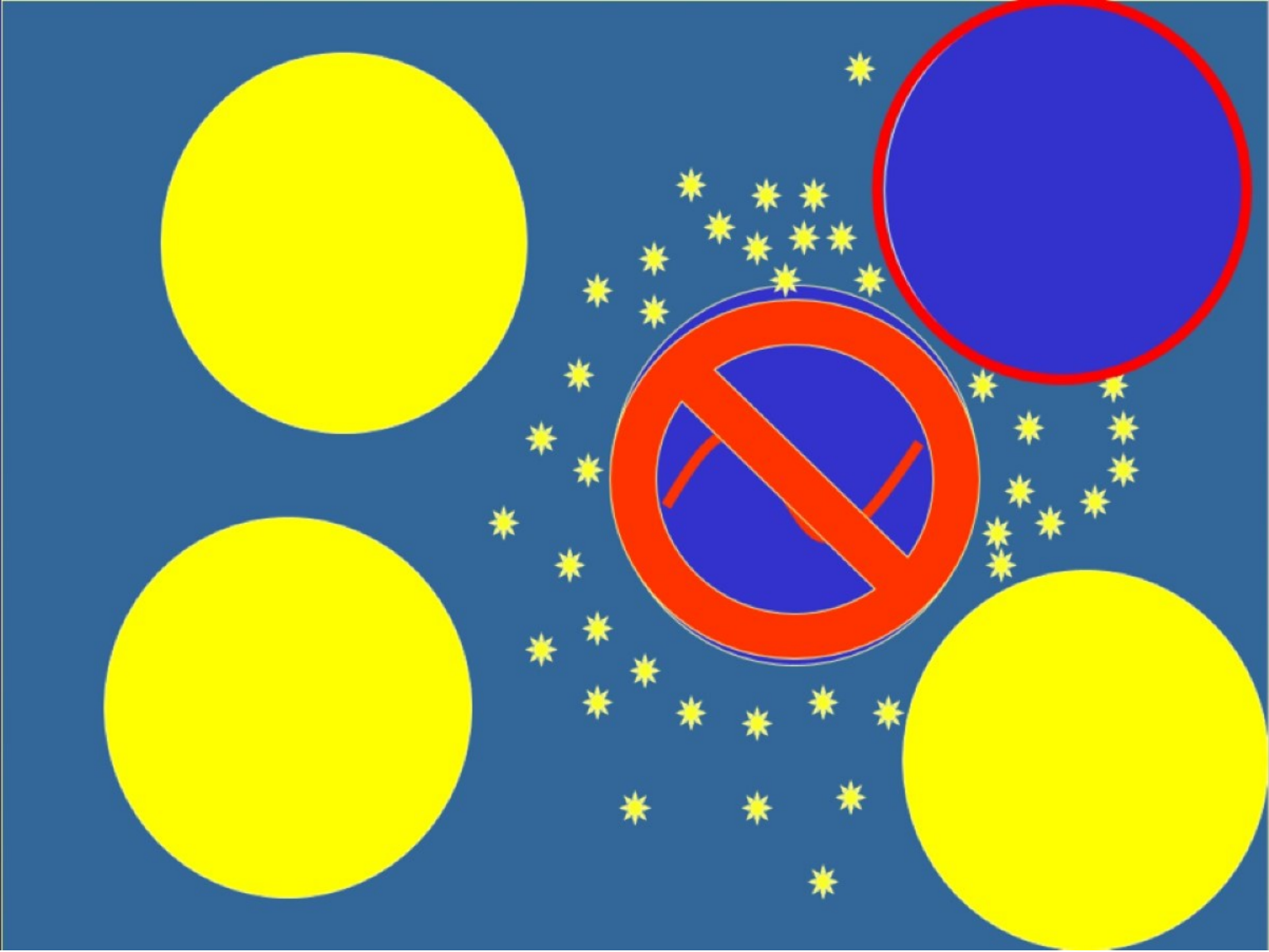


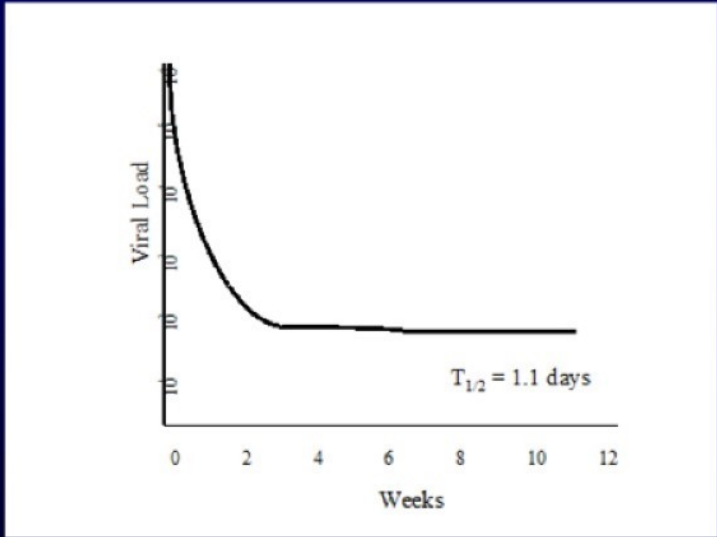


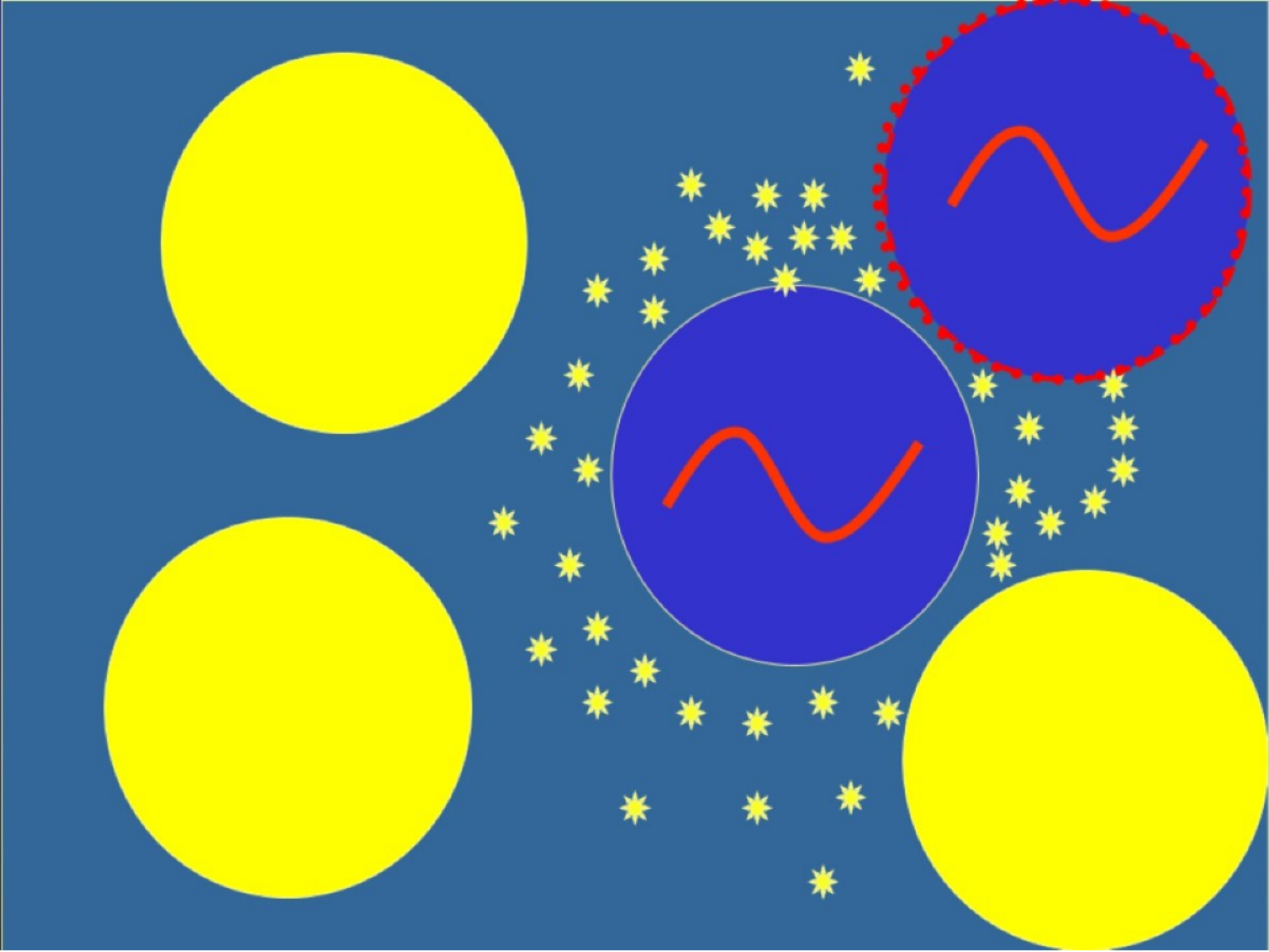


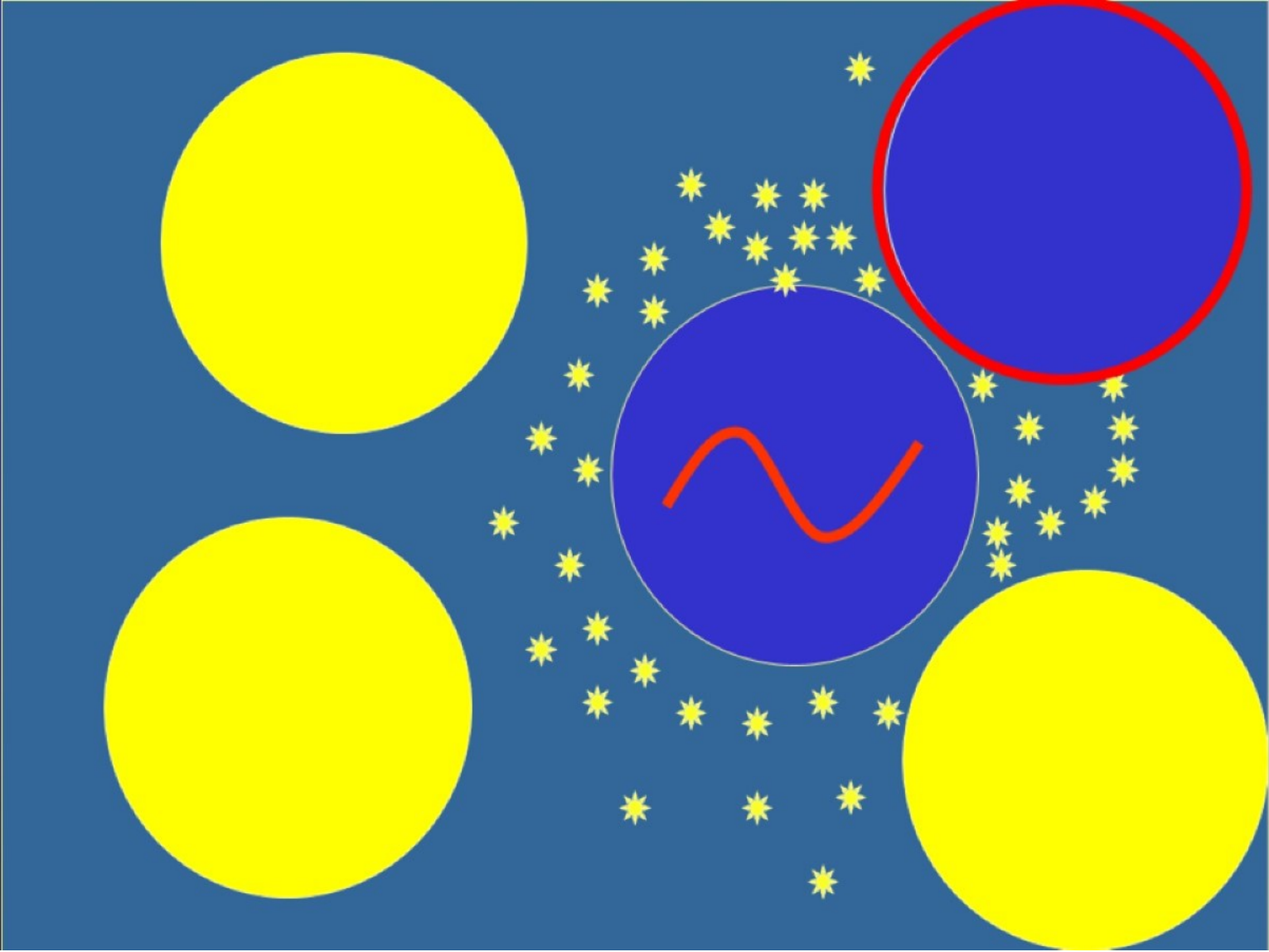












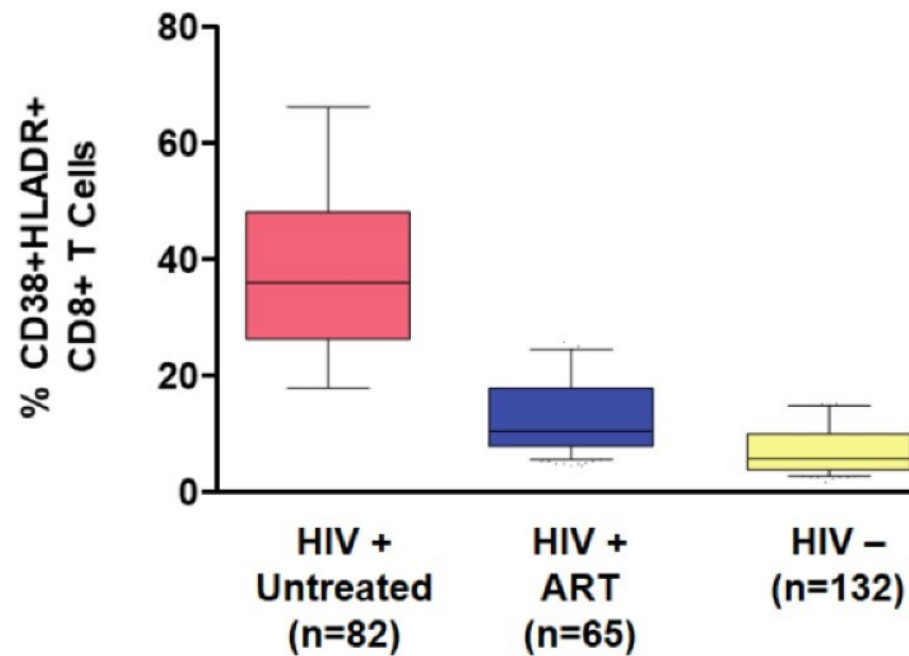
ARS 3

When should antiretroviral therapy be started?

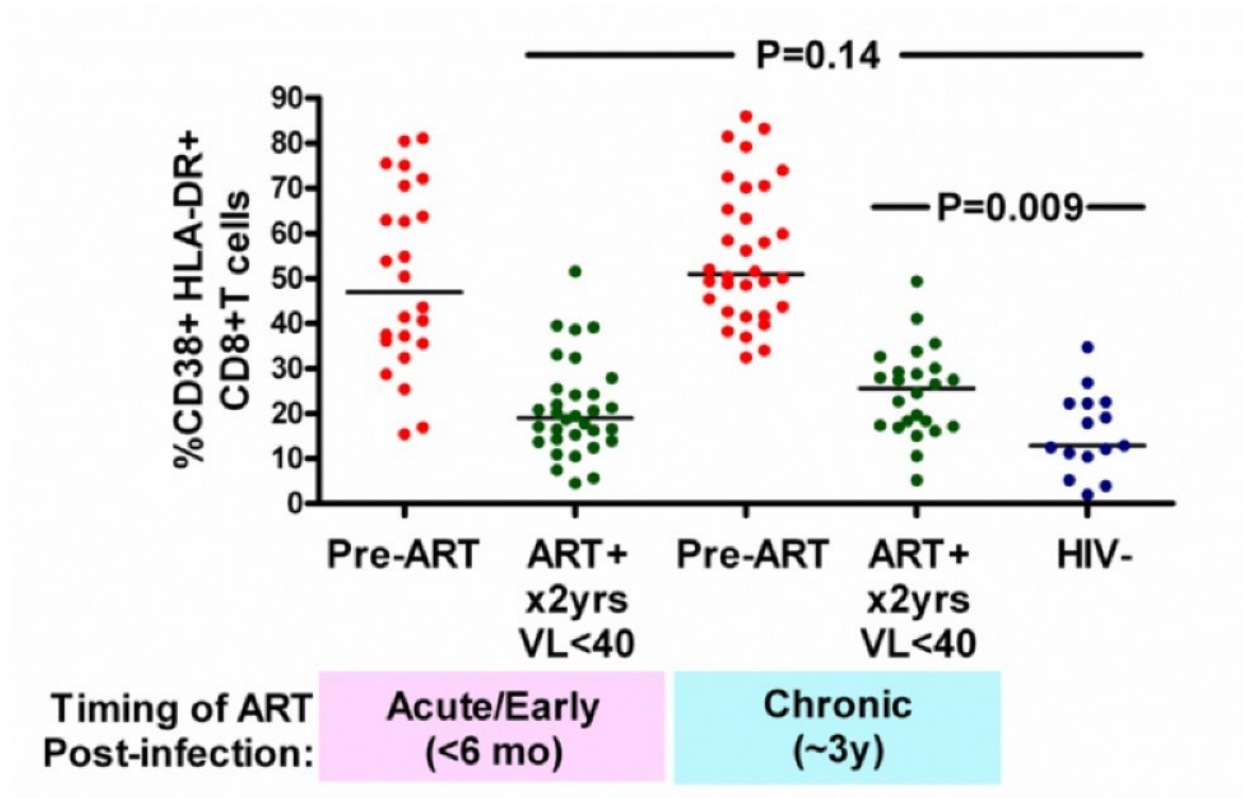
At a CD4 count of:

- A. 200 cells/ul or less
- B. 200 – 350 cells /ul
- C. 350 – 500 cells /ul
- D. 500 – 750 cells/ul
- E. Any CD4 count

T cell “activation” is lower in treated than untreated adults, but consistently higher than “normal”



Early ART Also Appears to Reduce Residual T Cell Activation during ART



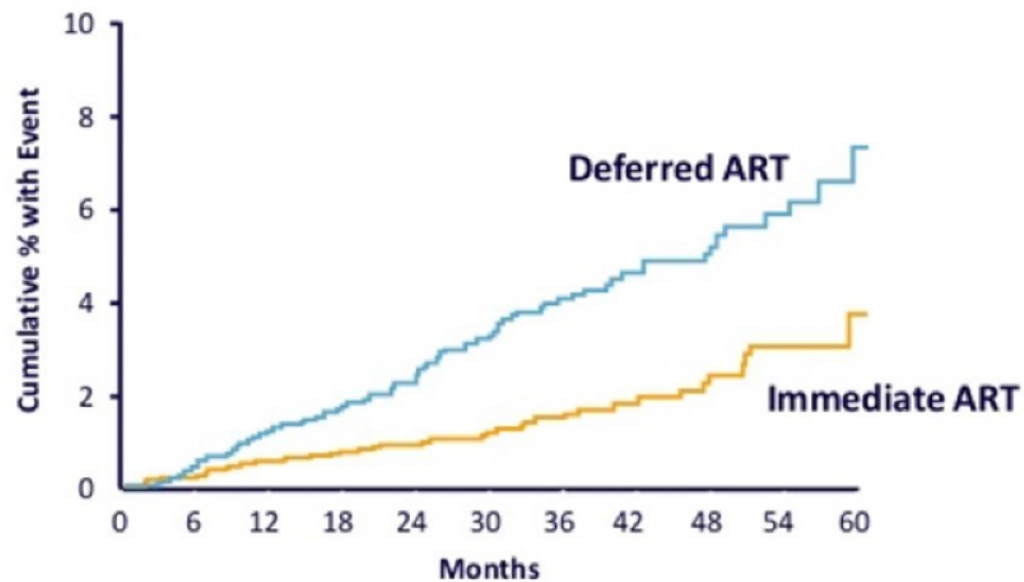
Inverse Probability Weighted Cox Regression Multivariate Analysis

	Relative Hazard (RH)*	95% Confidence Interval	P-value
*Stratified by Cohort and Year			
Deferral of HAART at 351-500	1.7	1.4, 2.1	<0.001
Female Sex	1.1	0.9, 1.5	0.290
Older Age (per 10 years)	1.6	1.5, 1.8	<0.001
Baseline CD4 count (per 100 cells/mm³)	0.9	0.7, 1.0	0.083

- Results were similar when restricting the analysis to the 77% of participants with baseline HIV RNA data
- Adjusted RH for deferral vs. immediate treatment was also 1.7
95% C.I. 1.4, 2.2; p <0.0001
- HIV RNA was not an independent predictor of mortality

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- Serious AIDS or non-AIDS event or death: 4.1% vs. 1.8% in deferred vs. immediate ART (HR 0.43; 95% CI 0.30-0.62; $P < 0.001$)



INSIGHT START Study Group. *N Engl J Med* 2015

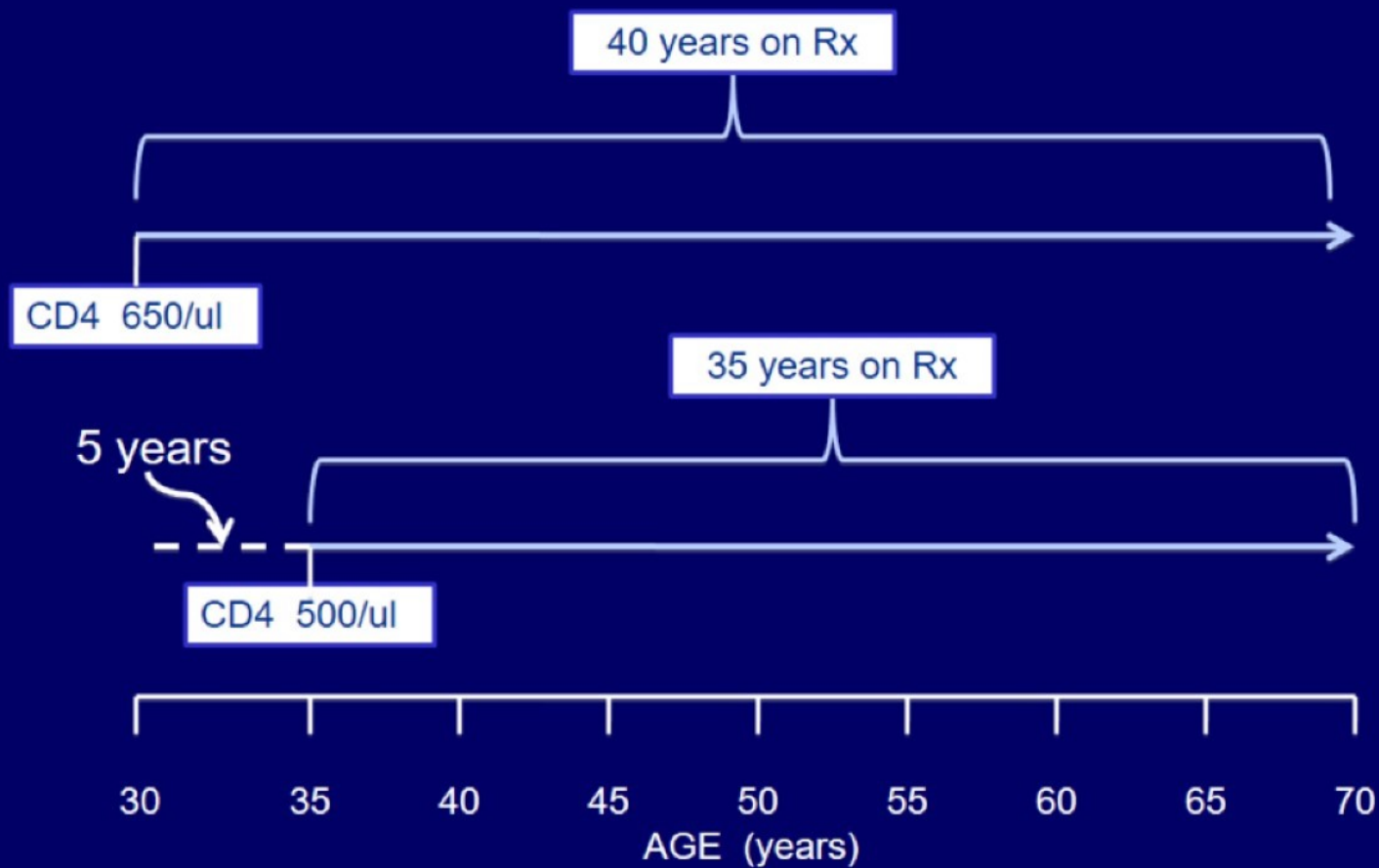
Cost-Effectiveness of Early vs. Deferred ART

- Markov modeling approach
- Johns Hopkins HIV clinic database

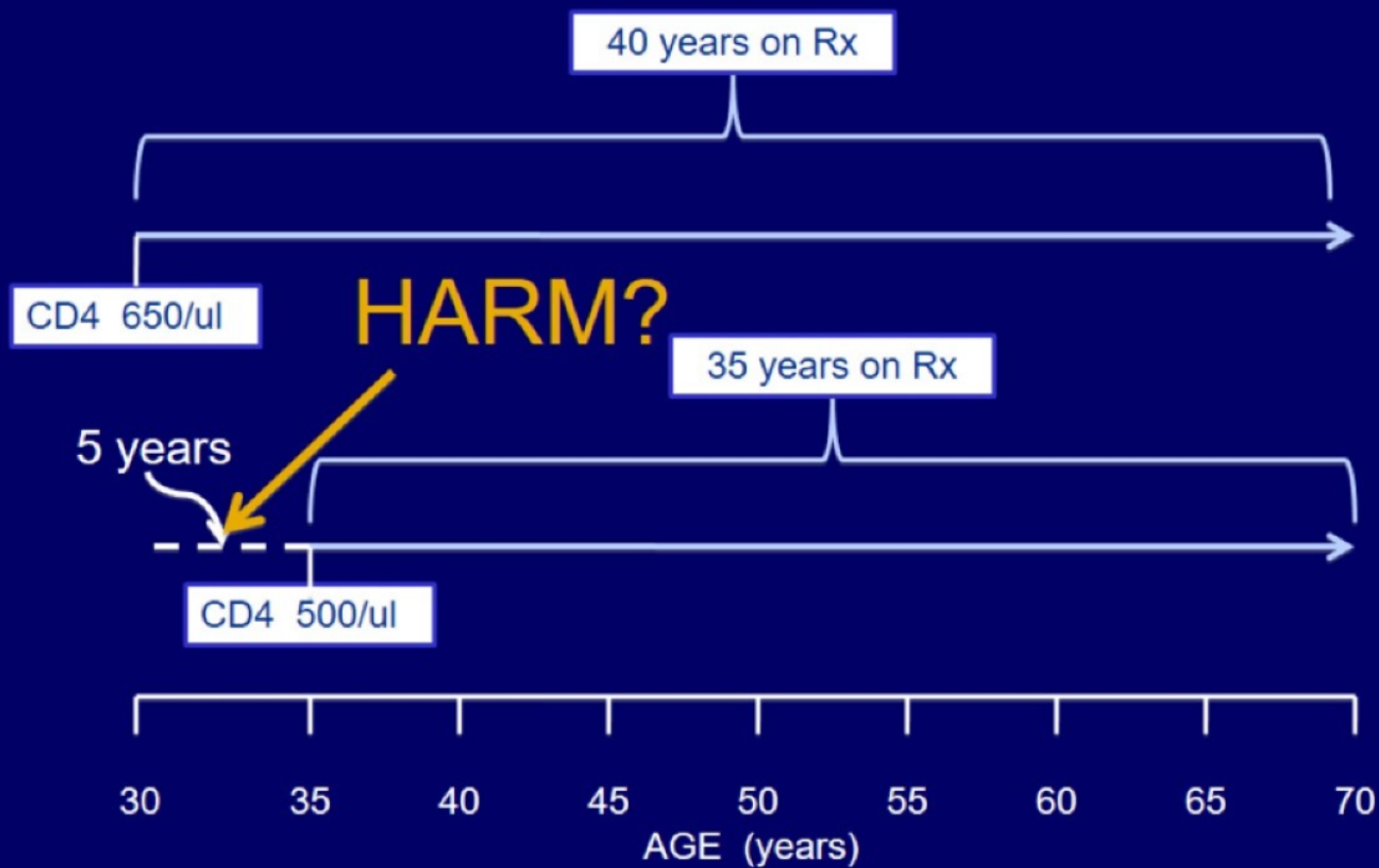
ART Initiation	Incremental Lifetime Costs	Incremental Discounted QALY* Gained	Cost Per Life-Year Gained	Cost Per QALY* Gained
CD4 >350 vs 200-350	\$19,074	0.75 (0.61)	\$25,567	\$31,226

- *“Starting ART earlier ... rather than later ... is a cost-effective strategy (by the generally accepted benchmark in the US).”*

Relative Time on Treatment...

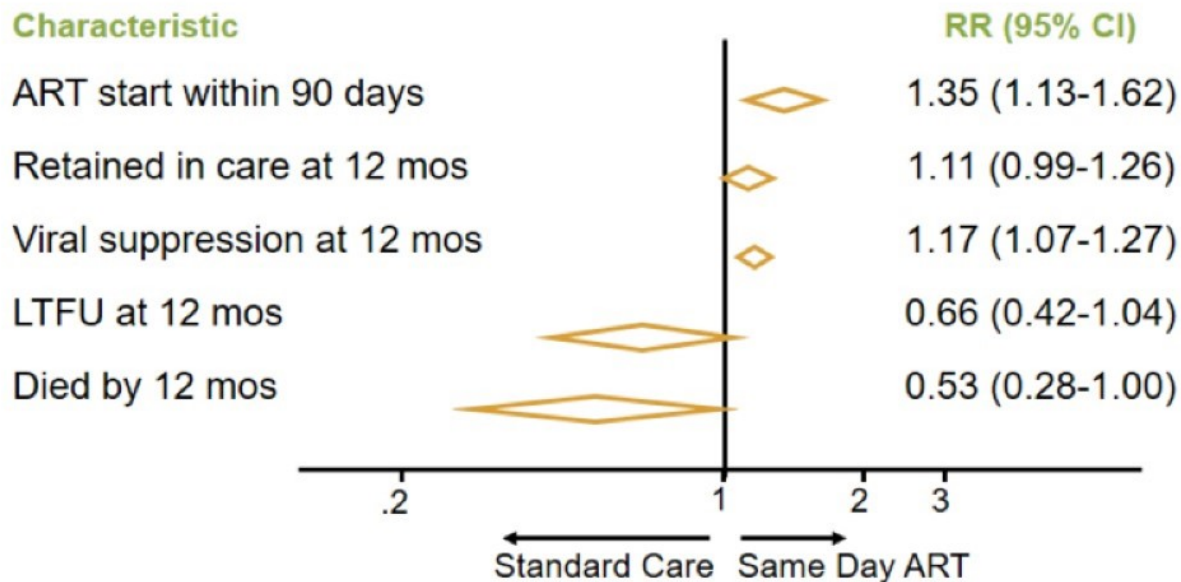


Relative Time on Treatment...



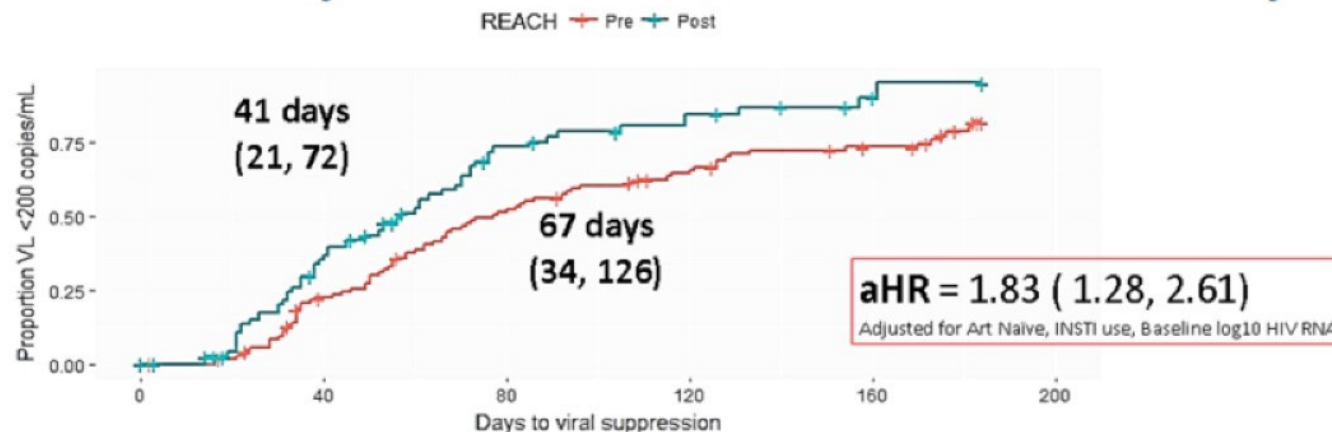
Improved Clinical Outcomes With Rapid ART Initiation

- Universal recommendations for treating all HIV-infected persons
- Systematic review of 22 studies of rapid ART initiation (including 4 RCTs)



Expedited ART– Experience in Atlanta

- Grady reduced barriers, with goal to begin ART within 72hrs
- Pre-intervention days to ART = 22, Post-intervention days to ART= 4.



Outcomes	Pre-REACH (n=117)	Post-REACH (n=90)	aOR (95% CI)
Attended 1 st scheduled appointment [†]	85 (73)	73 (81)	1.63 (0.82, 3.22)
Achieved viral suppression [‡]	87 (74)	61 (68)	0.77 (0.39, 1.52)

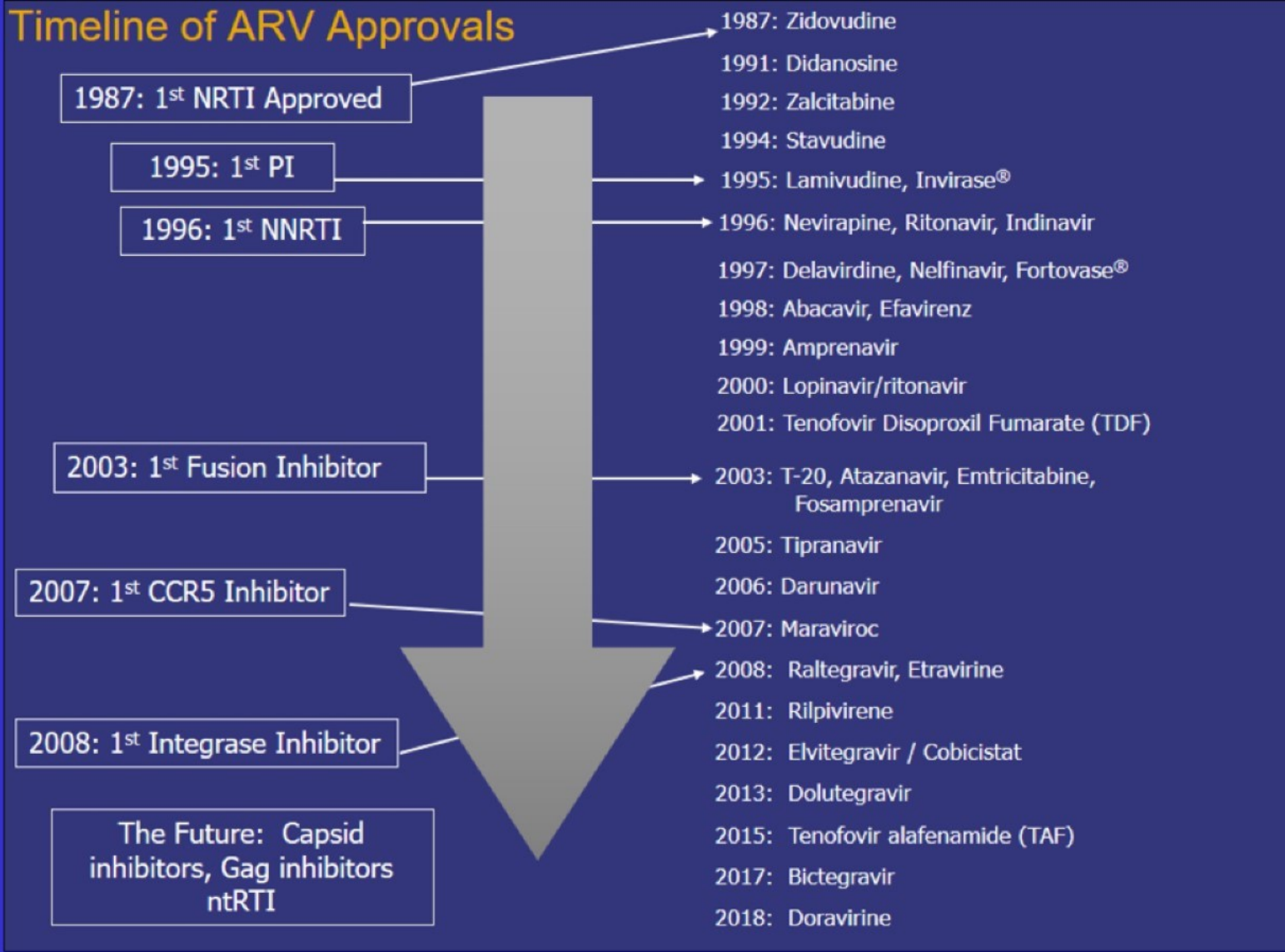
[†]Adjusted for age, race, sex and being ART Naive

[‡]Adjusted for age, race, baseline HIV RNA & INSTI use

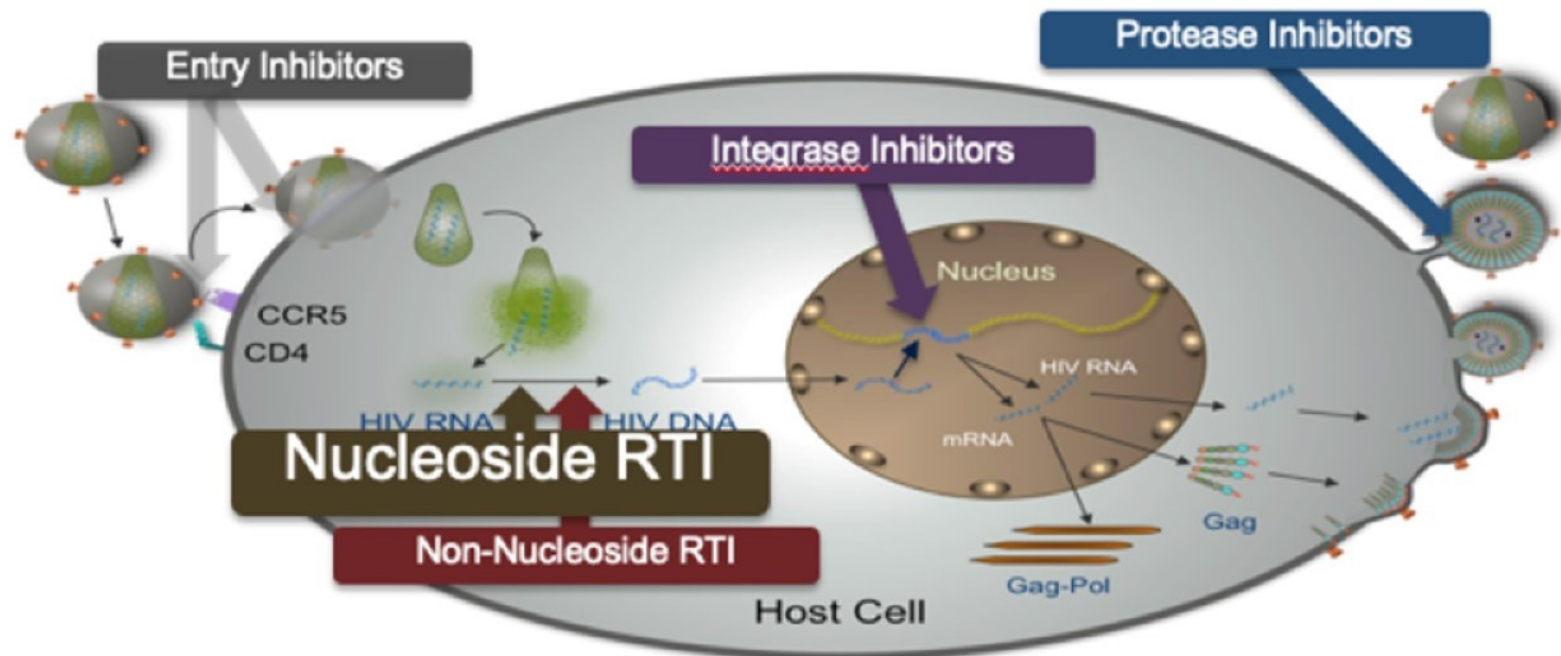
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Timeline of ARV Approvals

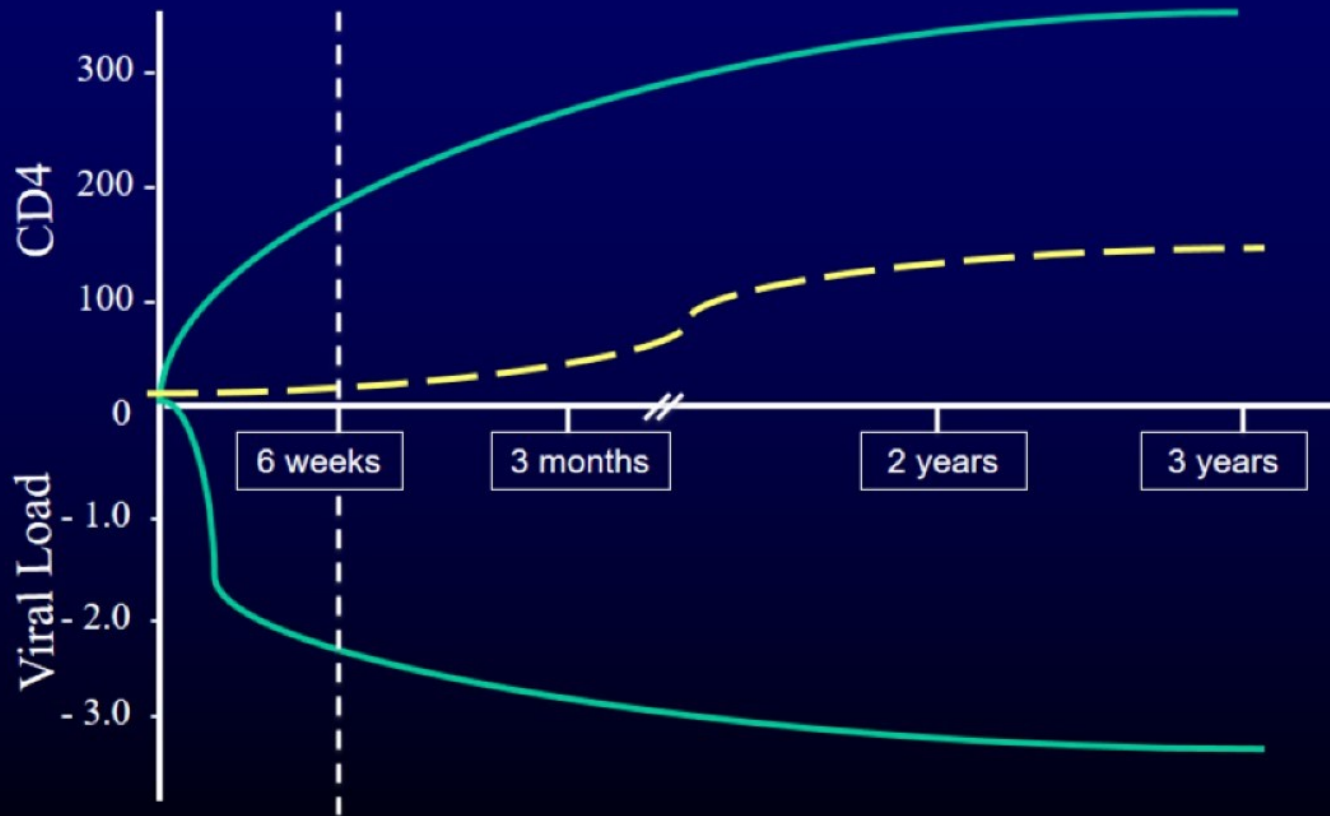
Slide #34



Site of Action of ARV Drugs



What is Immunologic Failure ?



Conclusions

- Understanding HIV viral life-cycle is critical to understanding basis of ARV therapy
- Viral replication is very dynamic (1- 10 billion new viruses produced a day) and is the driving force of HIV pathogenesis
- ARV therapy interrupts HIV replication ~ completely, halting the most of the damage done by HIV
- ARV therapy protects uninfected cells from becoming infected and has no effect on cells already infected
- All ARV drugs target specific sites within the viral life-cycle

Posttest Question #1

At steady state, when an actively producing cell dies it is replaced by how many newly infected cells?

1. One
2. Twenty five
3. One hundred
4. One thousand
5. It depends on the viral load