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

Michael S. Saag, MD
Professor of Medicine
University of Alabama
at Birmingham

2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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. (Updated 9/28/2021)

Planner/Reviewer Financial Disclosures:

Planner/Reviewer 1 has no relevant financial affiliations to disclose. (Updated 09/22/21)

Planner/Reviewer 2 has no relevant financial affiliations to disclose. (Updated 09/28/21)

Slide 2

Pretest Question #1

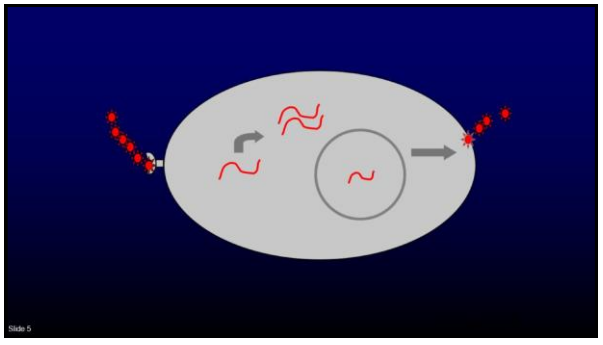
At steady state, when an actively producing cell dies it is replaced by how many newly infected cells?

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

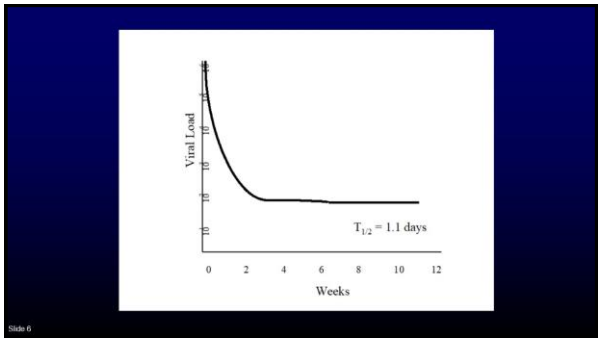
Slide 3

BACK TO BASICS

Slide 4



Slide 5



Slide 6

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

Slide 7

nature

ARTICLES

Viral dynamics in human immunodeficiency virus type 1 infection

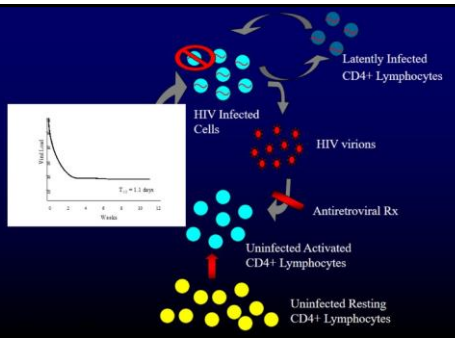
Xiping Wei*, Sajal K. Ghosh†, Maria E. Taylor‡, Victoria A. Johnson‡, Emilio A. Emini‖, Paul Deutsch‖, Jeffrey D. Lifson‖, Sebastian Bonhoeffer‖, Martin A. Nowak‖, Beatrice H. Hahn†, Michael S. Saag‡ & George M. Shaw*,†

* Division of Hematology-Oncology and † Infectious Diseases, University of Alabama at Birmingham, 613 Lyons-Harrison Research Building, 701 South 19th Street, Birmingham, Alabama 35294, USA
‡ 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

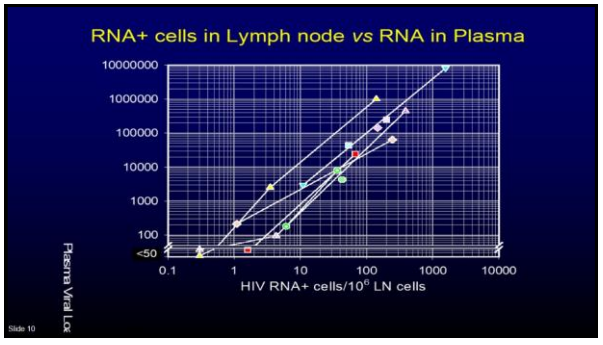
The dynamics of HIV-1 replication *in vivo* are largely unknown yet they are critical to our understanding of disease pathogenesis. Experimental drugs that are potent inhibitors of viral replication can be used to show that the composite lifespan of plasma virus and virus-producing cells is remarkably 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

Slide 8



Slide 9

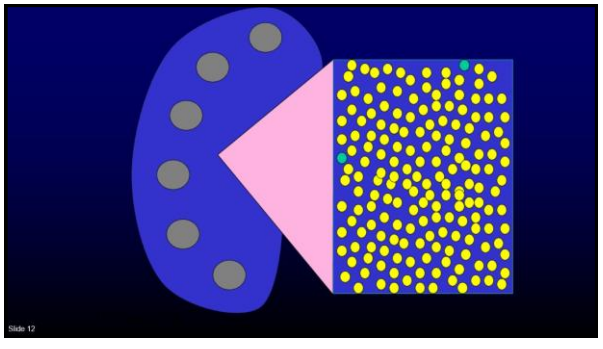


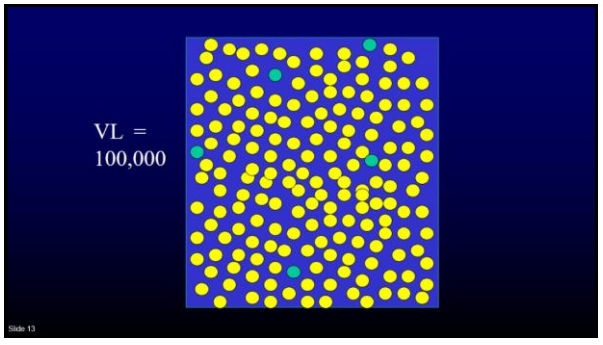
ARS 2

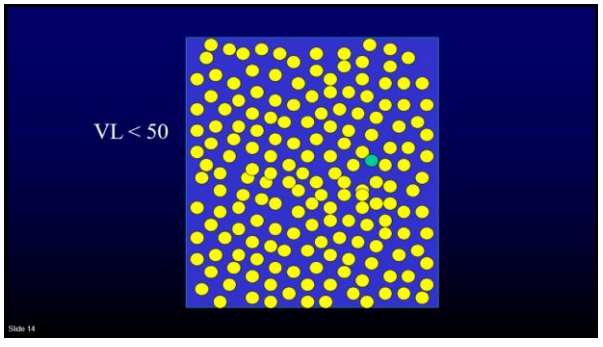
At steady state, when an actively producing cell dies, it is replaced by how many newly infected cells?

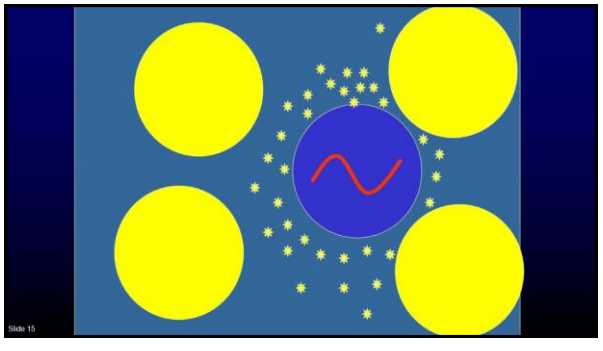
1. One
2. Twenty – Five
3. One Hundred
4. One Thousand
5. It depends on the viral load

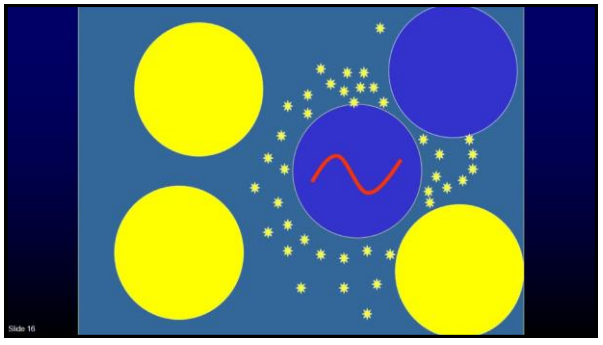
Slide 11

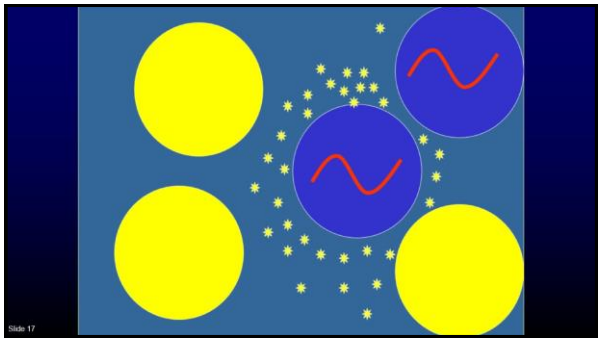


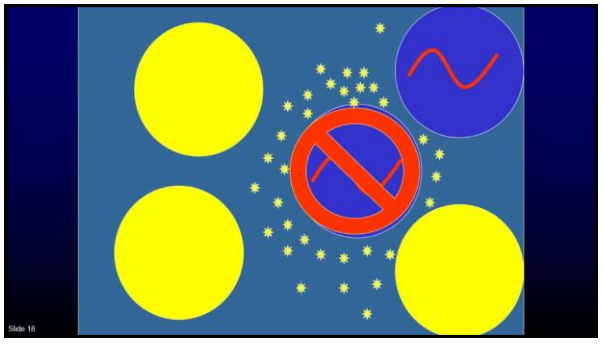

VL =
100,000
Slide 13

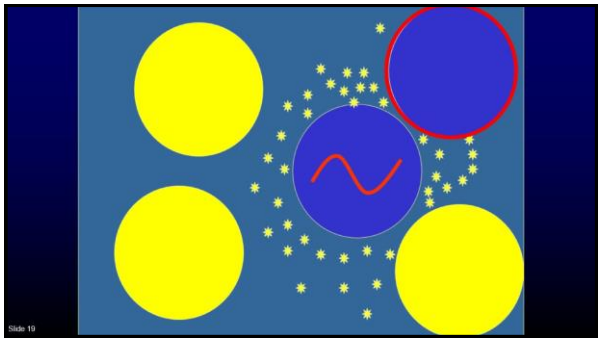

VL < 50
Slide 14

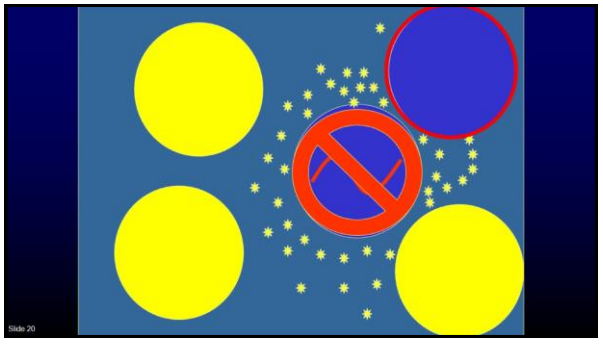

Slide 15

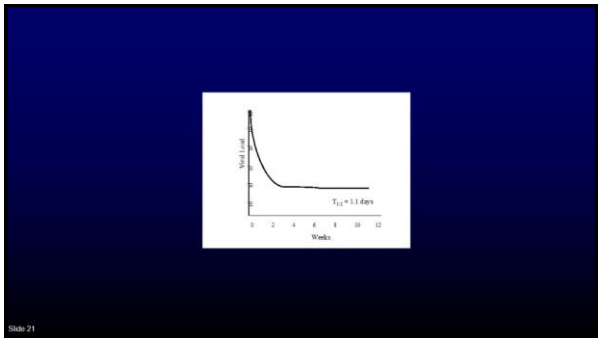

Slide 16

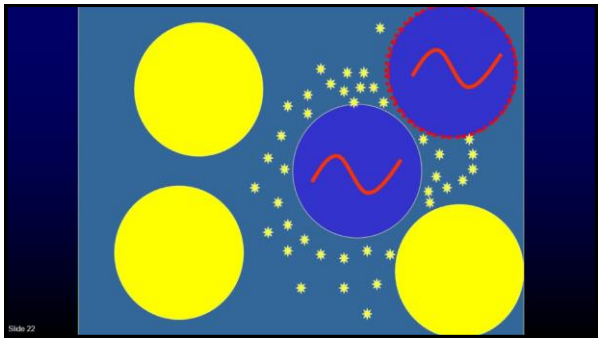

Slide 17

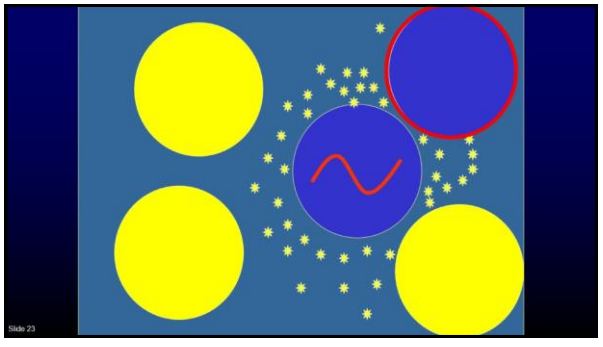

Slide 18


Slide 19


Slide 20


Weeks
Slide 21





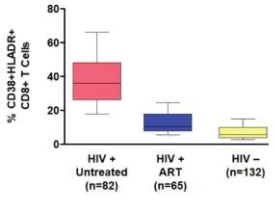
ARS 3

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

Slide 24

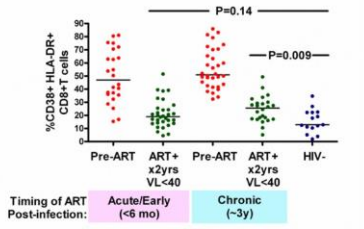
T cell "activation" is lower in treated than untreated adults, but consistently higher than "normal"



Slide 25

Hunt et al JID 2003, PLoS ONE 2011 and unpublished

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



Slide 26

Jain et al, CROI 2011

Inverse Probability Weighted Cox Regression Multivariate Analysis

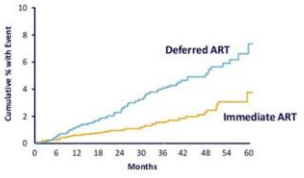
*Stratified by Cohort and Year	Relative Hazard (RH)*	95% Confidence Interval	P-value
Deferral of HAART at 351-500	1.7	1.4, 2.1	<0.001
Female Sex	1.1	0.9, 1.5	0.290
Older Age (per 10 years)	1.6	1.5, 1.8	<0.001
Baseline CD4 count (per 100 cells/mm^3)	0.9	0.7, 1.0	0.083

- 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

Slide 27

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

Slide 28

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

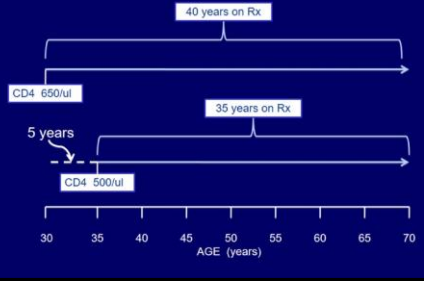
- *"Starting ART earlier … rather than later … is a cost-effective strategy (by the generally accepted benchmark in the US)."*

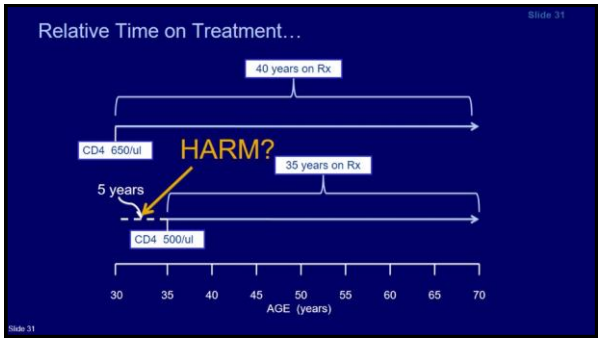
Mauskopf JA, et al. JAIDS 2005;39:562-569.

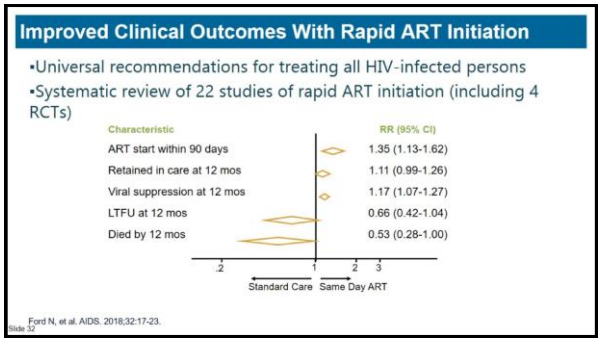
Slide 29

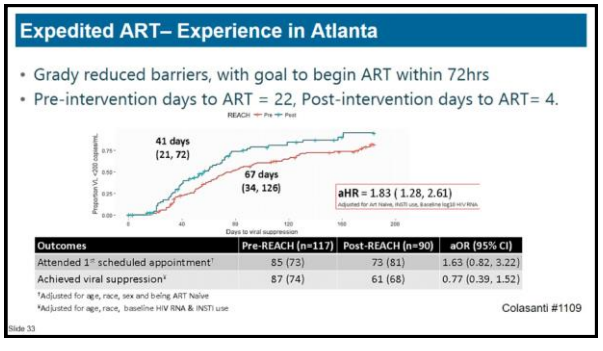
Slide 30

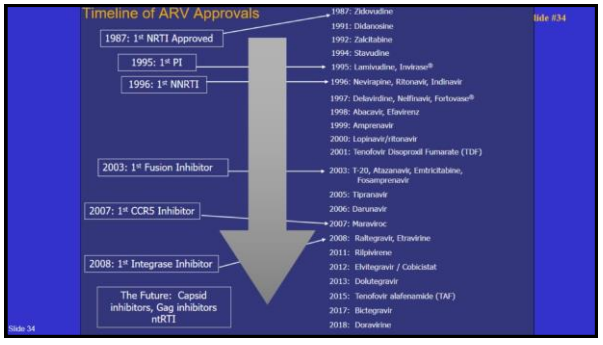
Relative Time on Treatment…

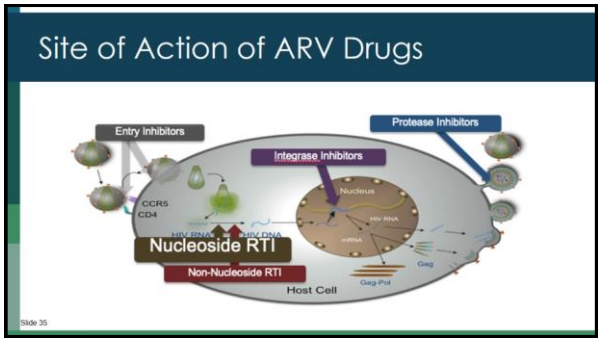


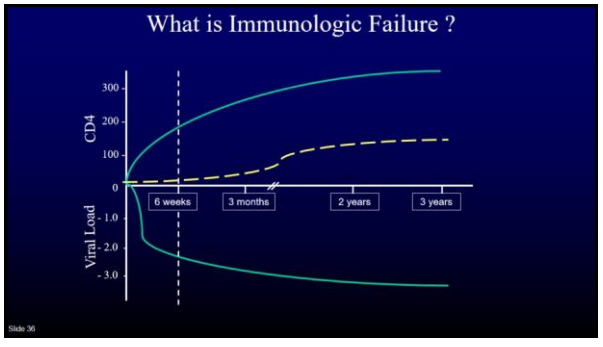

Slide 31
Relative Time on Treatment…
40 years on Rx
CD4 650/ul
HARM?
35 years on Rx
5 years
CD4 500/ul
30 35 40 45 50 55 60 65 70
AGE (years)
Slide 31


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)
Characteristic
RR (95% CI)
ART start within 90 days
1.35 (1.13-1.62)
Retained in care at 12 mos
1.11 (0.99-1.26)
Viral suppression at 12 mos
1.17 (1.07-1.27)
LTFU at 12 mos
0.66 (0.42-1.04)
Died by 12 mos
0.53 (0.28-1.00)
.2
1
2
3
Standard Care
Same Day ART
Ford N, et al. AIDS. 2018;32:17-23.
Slide 32


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.
REACH Pre Post
41 days
(21, 72)
67 days
(34, 126)
aHR = 1.83 (1.28, 2.61)
Outcomes
Pre-REACH (n=117)
Post-REACH (n=90)
aOR (95% CI)
Attended 1st 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 Naïve
‡Adjusted for age, race, baseline HIV RNA & INSTI use
Colasanti #1109
Slide 33


Timeline of ARV Approvals
Slide #34
1987: 1st NRTI Approved
1995: 1st PI
1996: 1st NNRTI
2003: 1st Fusion Inhibitor
2007: 1st CCR5 Inhibitor
2008: 1st Integrase Inhibitor
The Future: Capsid inhibitors, Gag inhibitors mRTI
1987: Zidovudine
1991: Didanosine
1992: Zalcitabine
1994: Stavudine
1995: Lamivudine, Invirase®
1996: Nevirapine, Ritonavir, Indinavir
1997: Delavirdine, Nelfinavir, Fortovase®
1998: Abacavir, Efavirenz
1999: Amprenavir
2000: Lopinavir/ritonavir
2001: Tenofovir Disoproxil Fumarate (TDF)
2003: T-20, Atazanavir, Emtricitabine, Fosamprenavir
2005: Tipranavir
2006: Darunavir
2007: Maraviroc
2008: Raltegravir, Etravirine
2011: Rilpivirene
2012: Elvitegravir / Cobicistat
2013: Dolutegravir
2015: Tenofovir alafenamide (TAF)
2017: Bictegravir
2018: Doravirine
Slide 34


Site of Action of ARV Drugs
Entry Inhibitors
Protease Inhibitors
Integrase Inhibitors
CCR5
CD4
Nucleus
HIV RNA
mRNA
Nucleoside RTI
Non-Nucleoside RTI
Gag
Gag-Pol
Host Cell
Slide 35


What is Immunologic Failure ?
CD4
300
200
100
0
Viral Load
1.0
2.0
3.0
6 weeks
3 months
2 years
3 years
Slide 36

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

Slide 37

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

Slide 38