THE IMPACT OF CLINICAL PHARMACOLOGY IN HIV CURE RESEARCH

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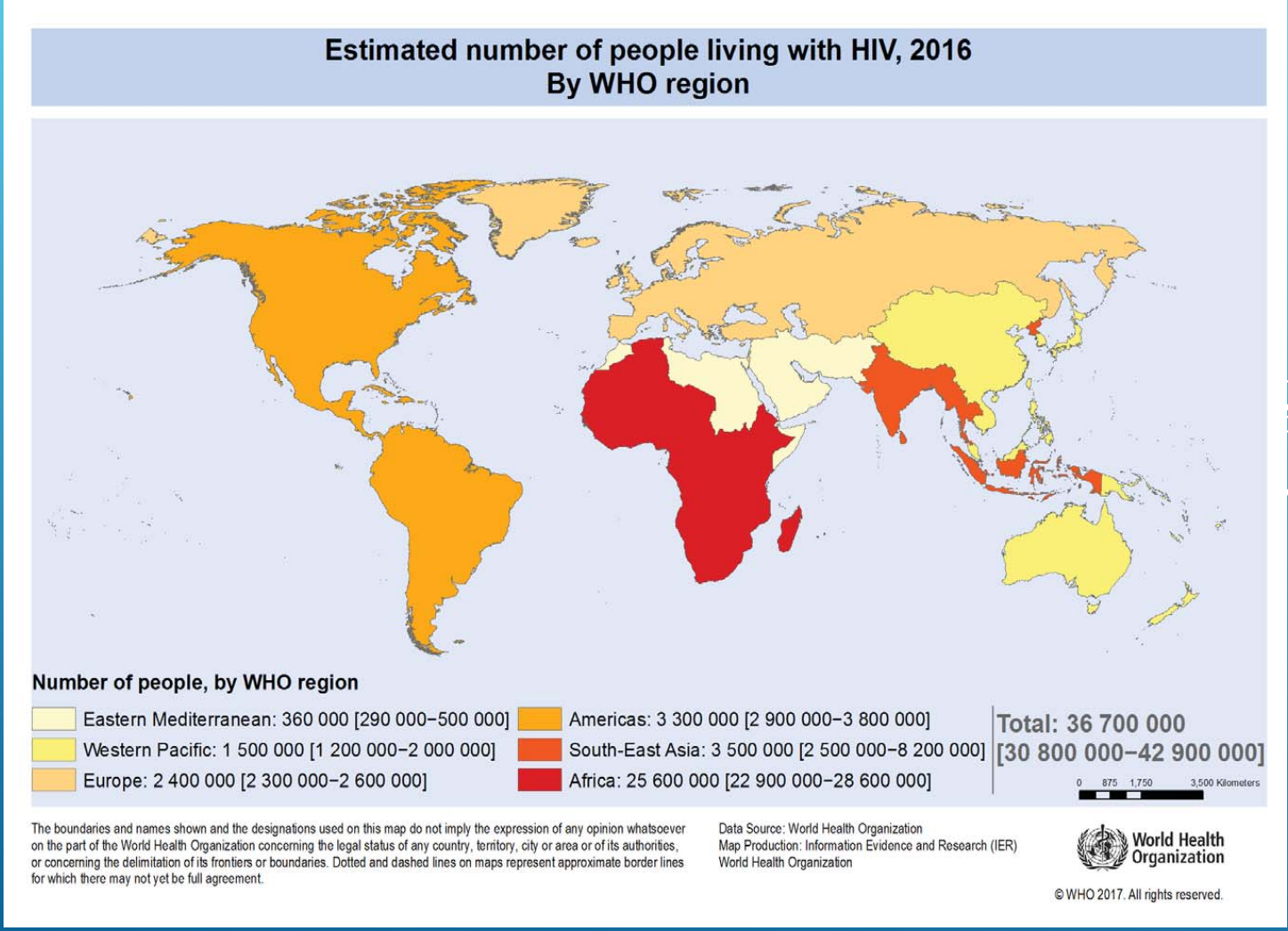
QUESTIONS

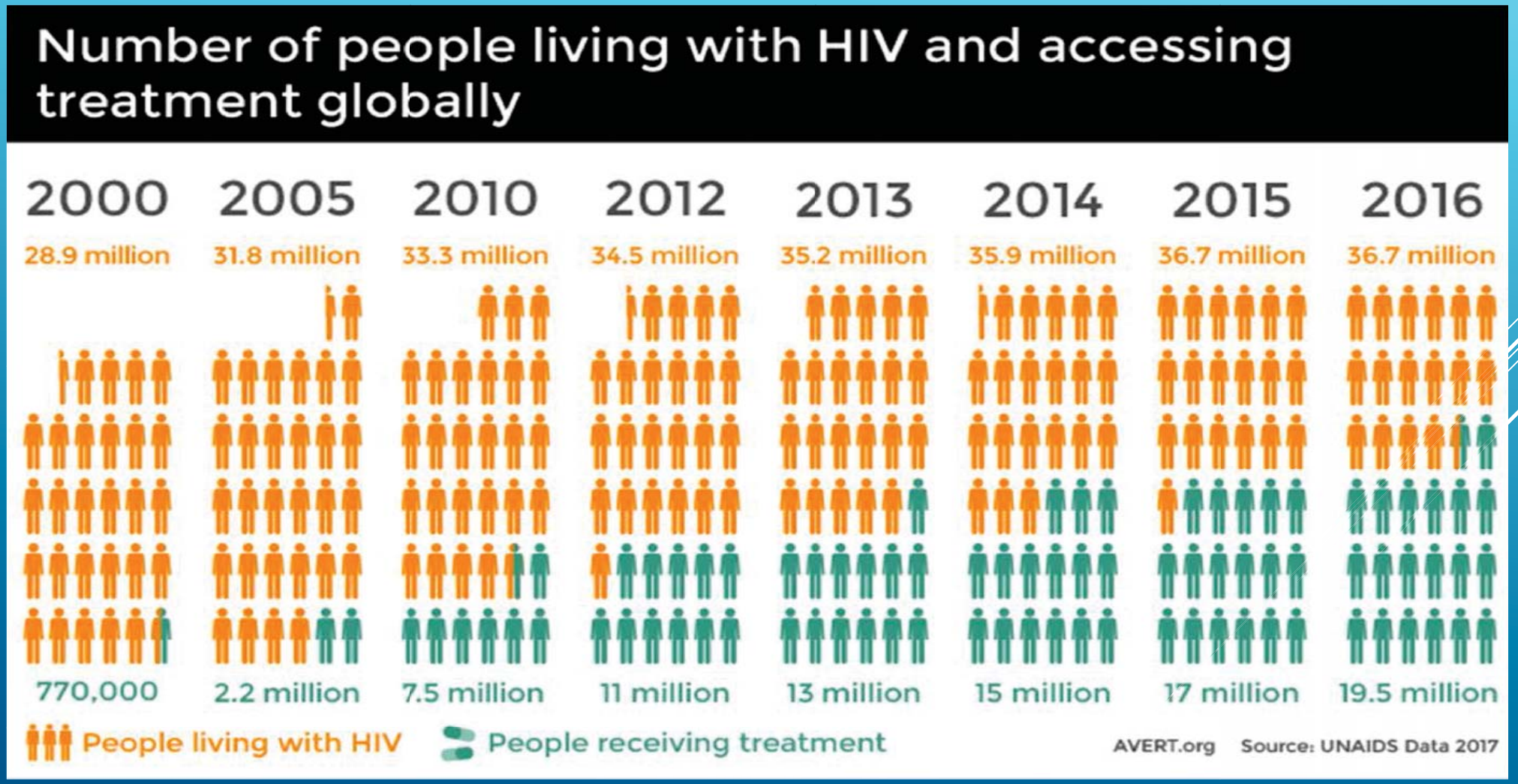
- Why do we need a cure for HIV?
- Why don't we already have a cure?
- What are current strategies for cure?
- What challenges need pharmacology insights?

ONE REASON WE NEED A CURE: GLOBAL HIV BURDEN 2016

People living with HIV	36.7 million
New HIV infections	1.8 million
AIDS-related deaths	1.0 million
5,000 new infections per day	
64% sub-Saharan Africa	
43% female adults	



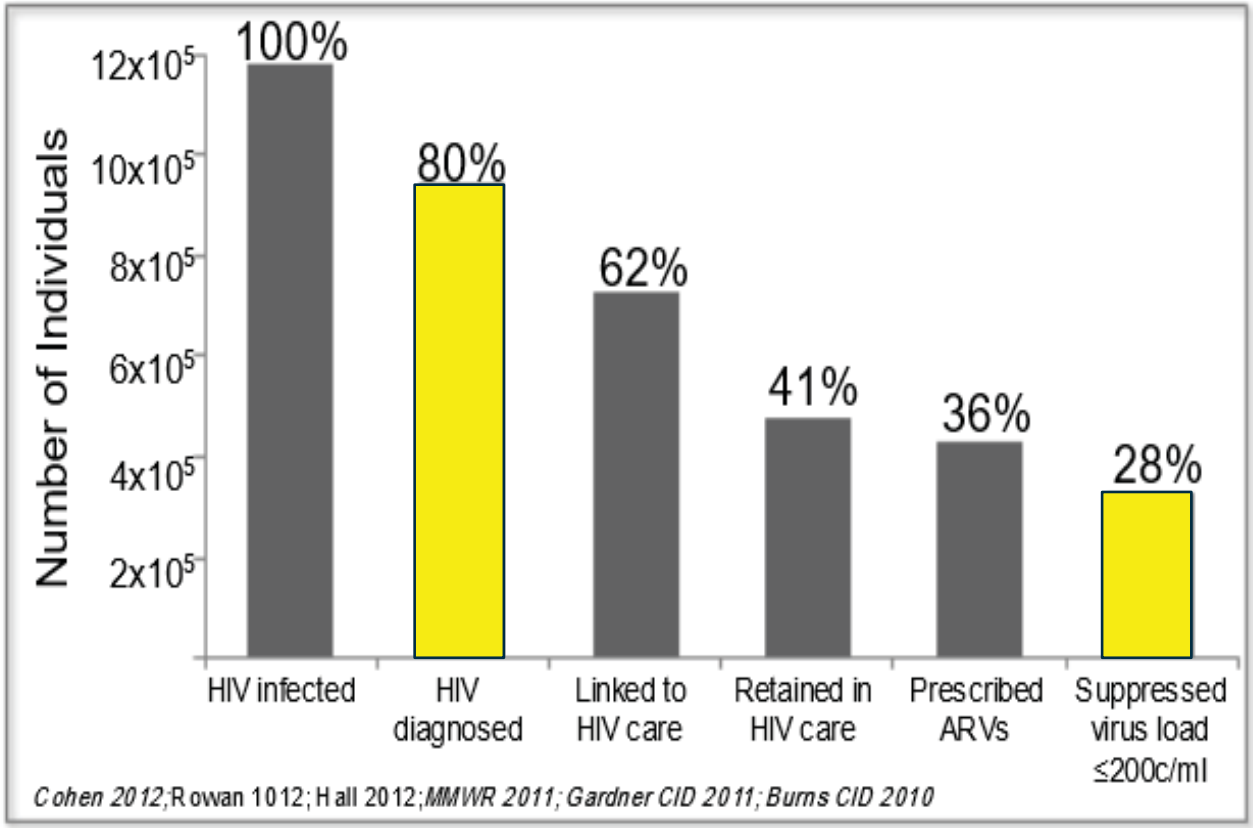
INCREASING ACCESS TO TREATMENT



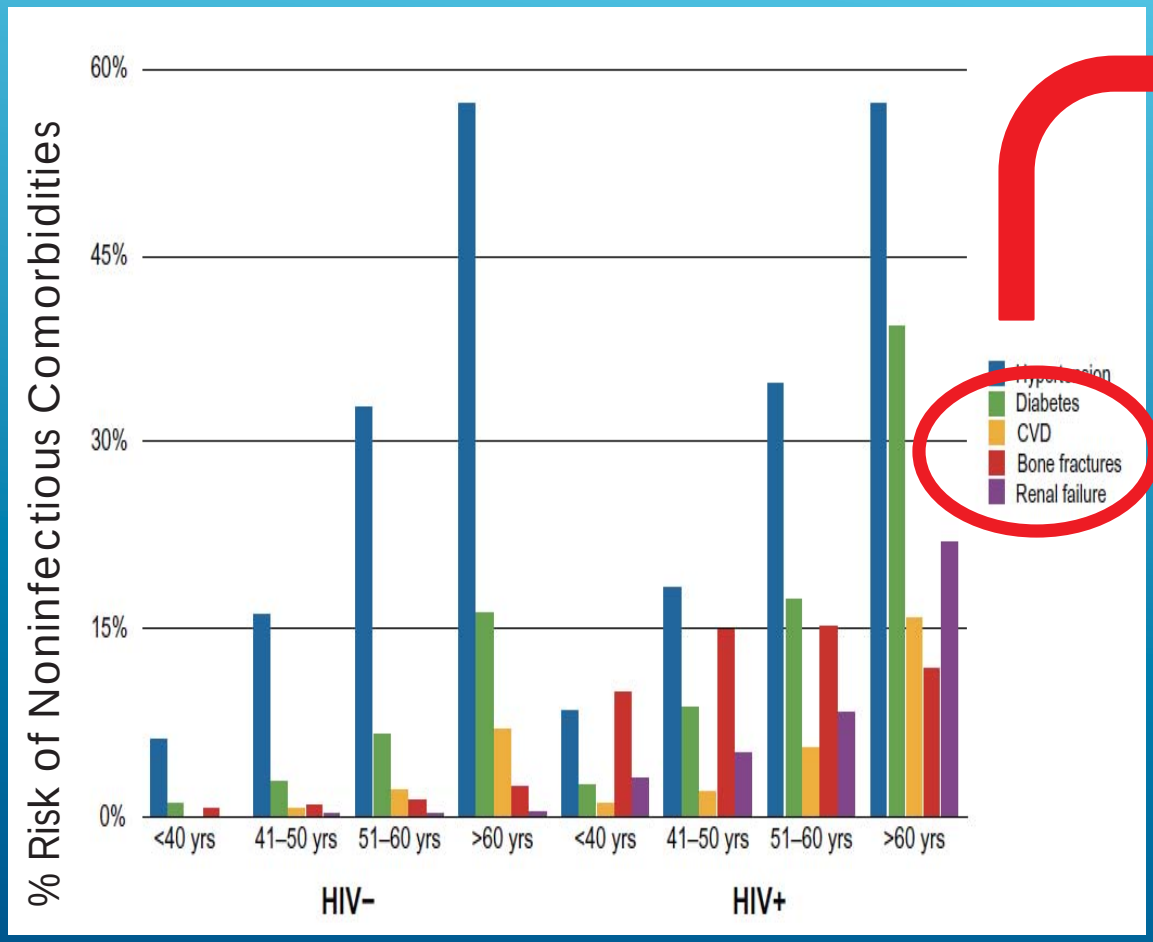
ANOTHER REASON WE NEED A CURE:

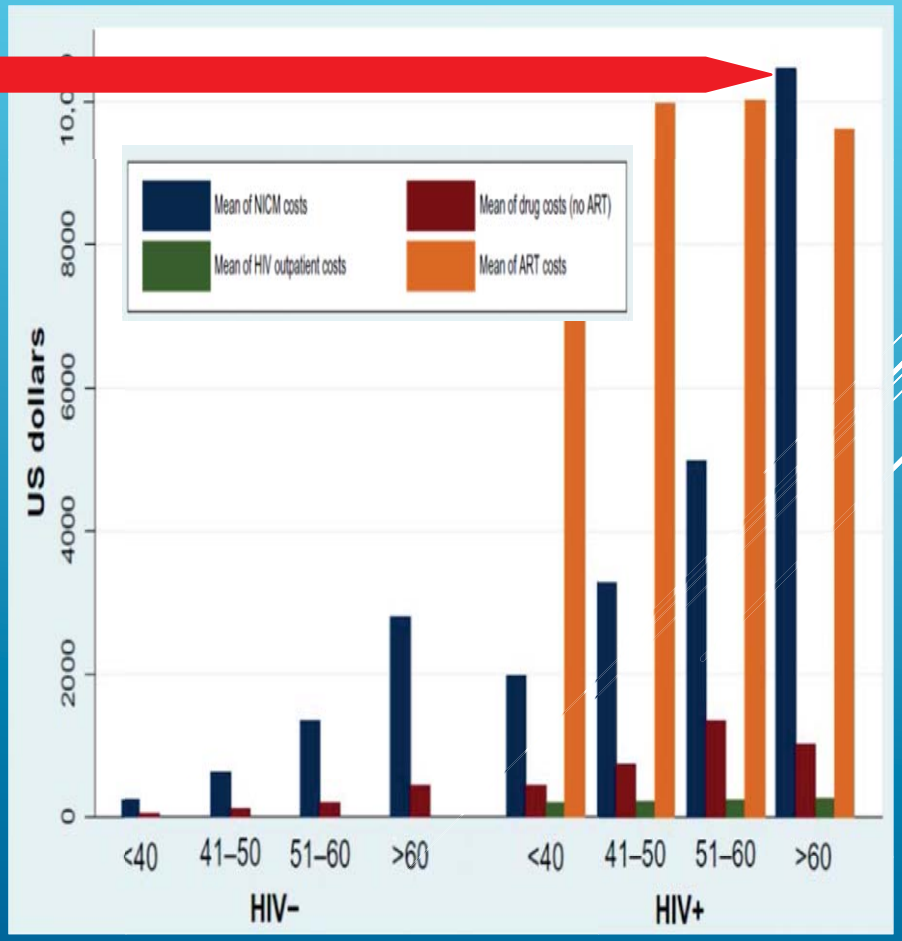
THE TREATMENT CASCADE

Number and percentage of HIV-infected persons engaged in selected stages of the continuum of HIV care in the United States



ANOTHER REASON WE NEED A CURE:
INCREASED COMORBIDITIES (ARVS AND INFLAMMATION)



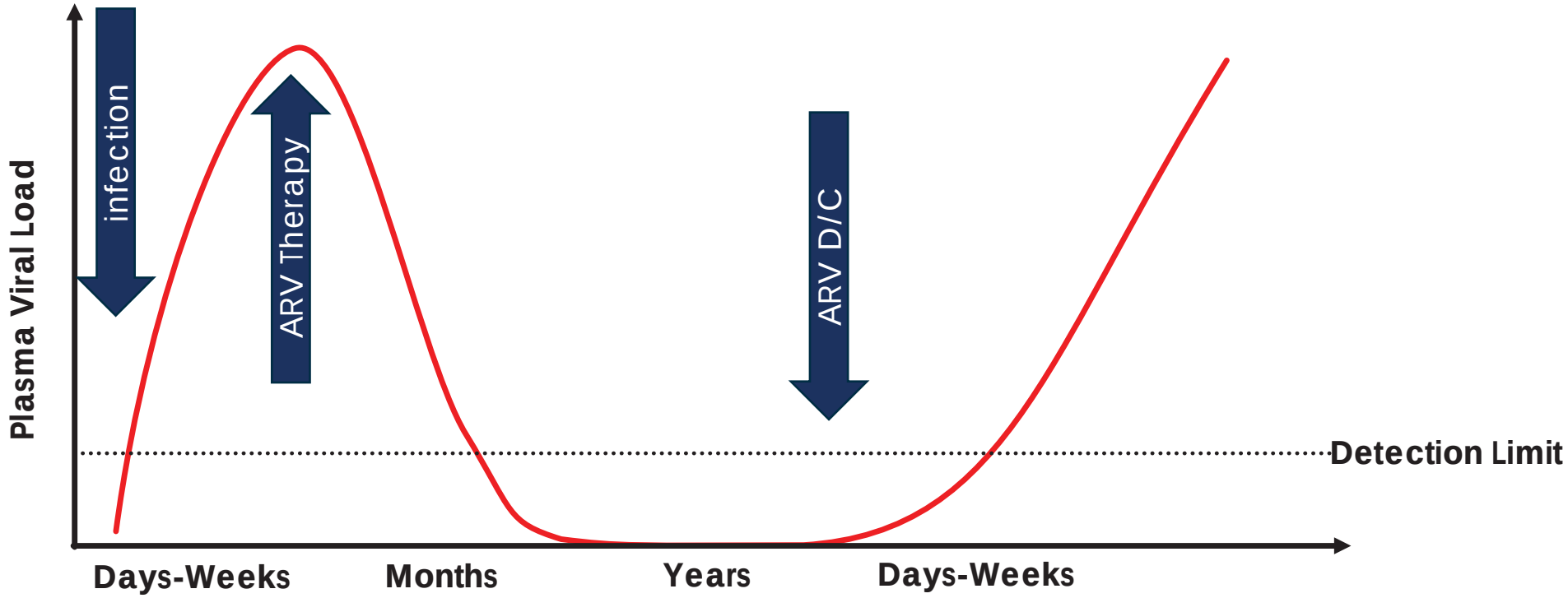


Guaraldi et al. Clinicalecon Out Res. 2013

WHY DON'T WE HAVE A CURE?

HIV PERSISTENCE ON TREATMENT

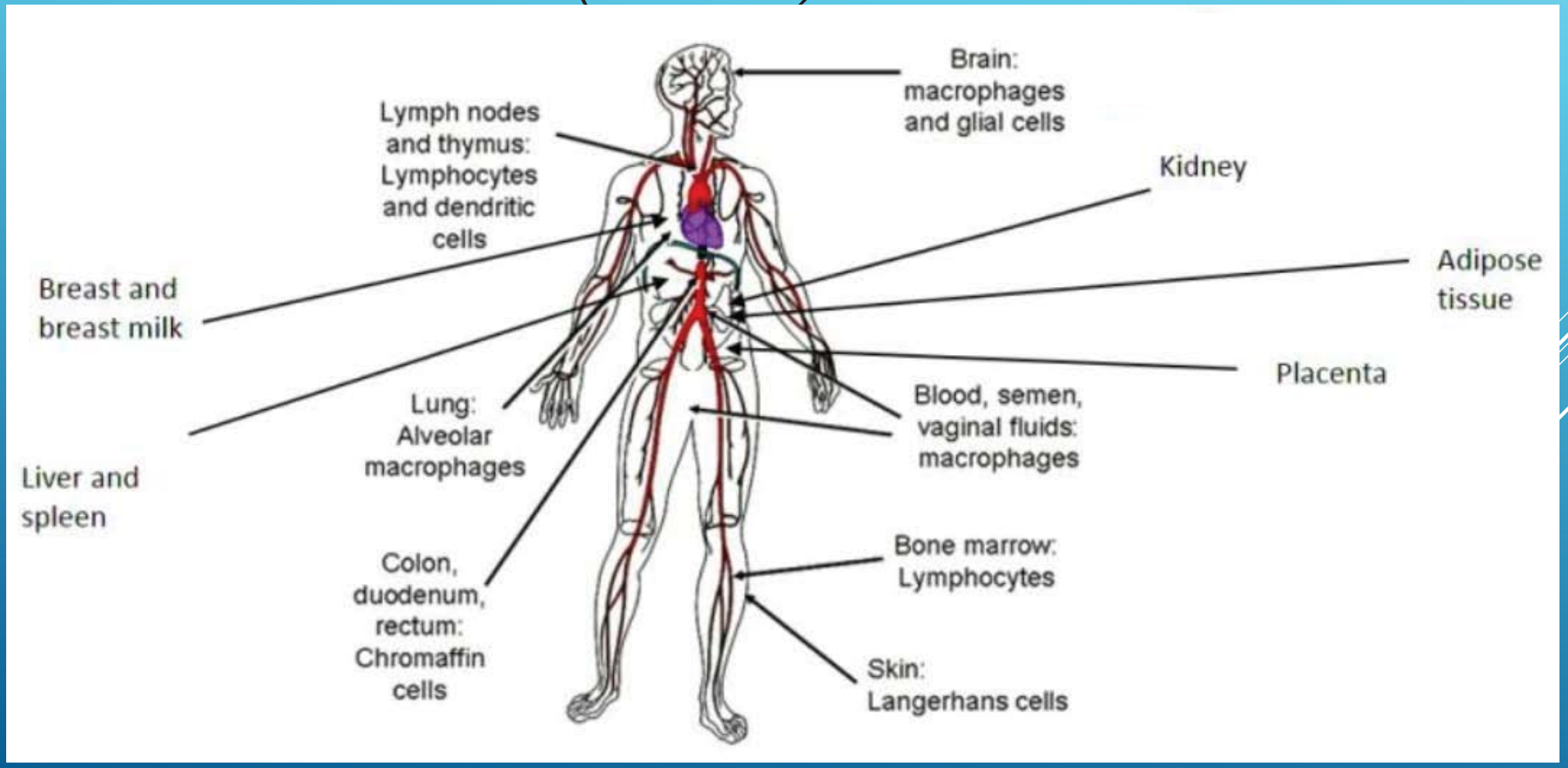
- Removal of ART results in rebound viremia within 3 weeks
- Occurs even in the setting of long-term viral suppression



Modified from Thompson C 2017

WHY DOES REBOUND OCCUR?

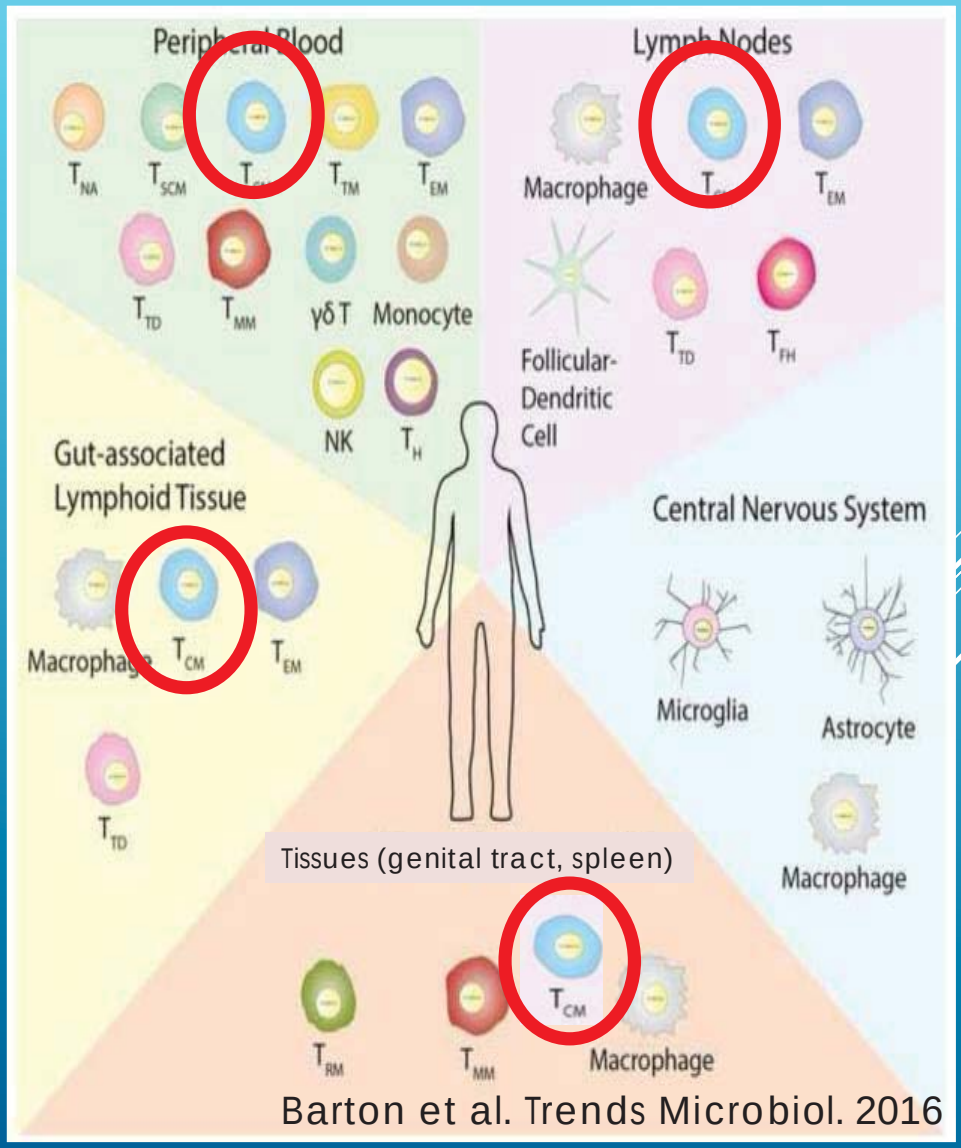
ANATOMICAL SITES OF HIV (DNA/RNA)



Adapted from Wong et al Curr Opin HIV AIDS 2016, Holdrych CROI 2018

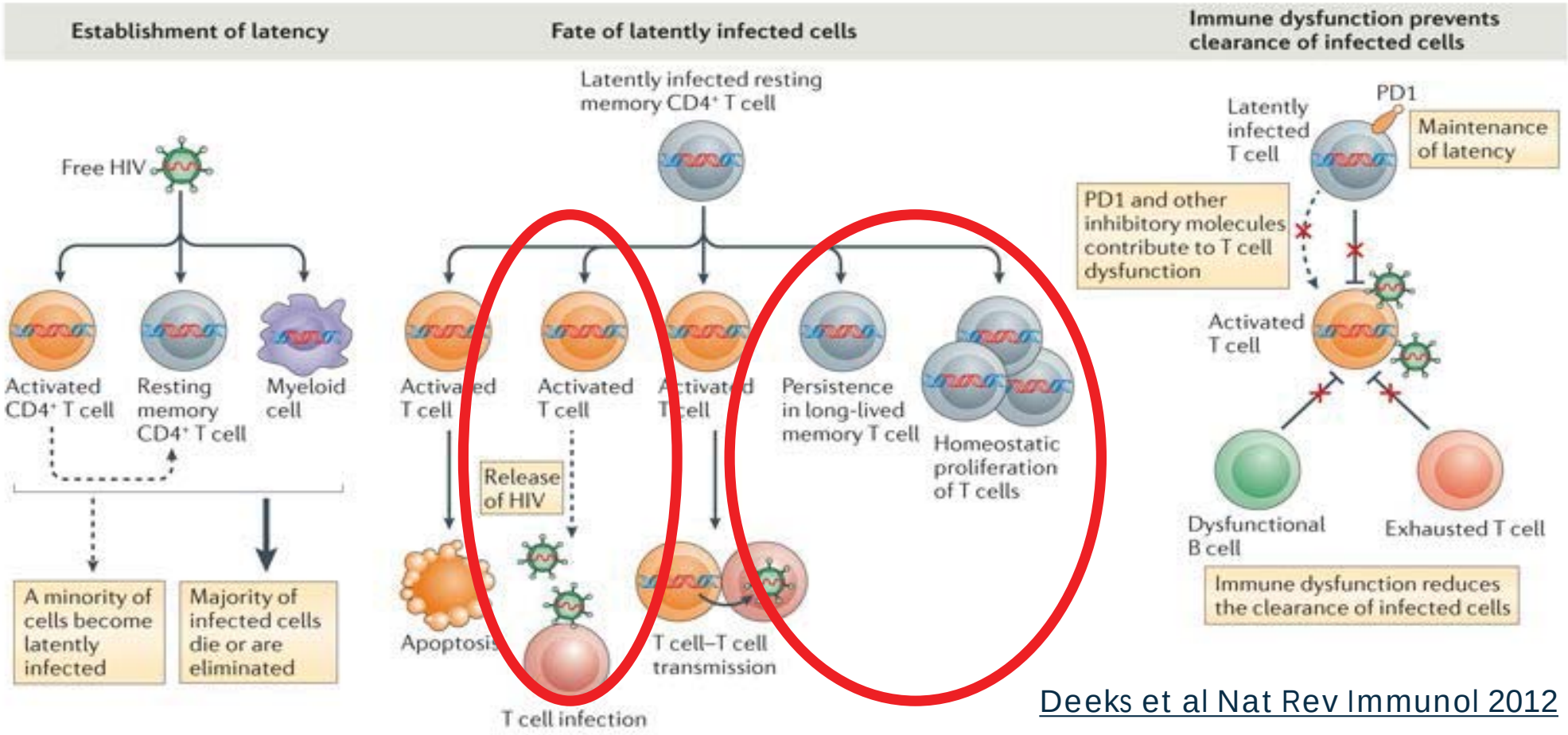
THE VIRAL RESERVOIR:
A CENTRAL PROBLEM TO CURE

- Sequestered anatomic sites
  - Genital tract
  - Central nervous system
- Central memory T cells (T follicular helper cells); quiescent
- Lymphoid organs
  - Lymph nodes
  - Spleen
  - Gastrointestinal tract



Barton et al. Trends Microbiol. 2016

MULTIPLE MECHANISMS OF HIV PERSISTENCE



Deeks et al Nat Rev Immunol 2012

LOW LEVEL REPLICATION OR CLONAL EXPANSION?

LOW LEVEL REPLICATION (ARVs)

- Evidence of viral evolution in anatomic compartments
- ARV intensification with INSTI results in increased 2-LTR circles
- Imaging evidence of active HIV replication in LN under suppressive ARV therapy
- Lower drug concentrations in anatomical sites?

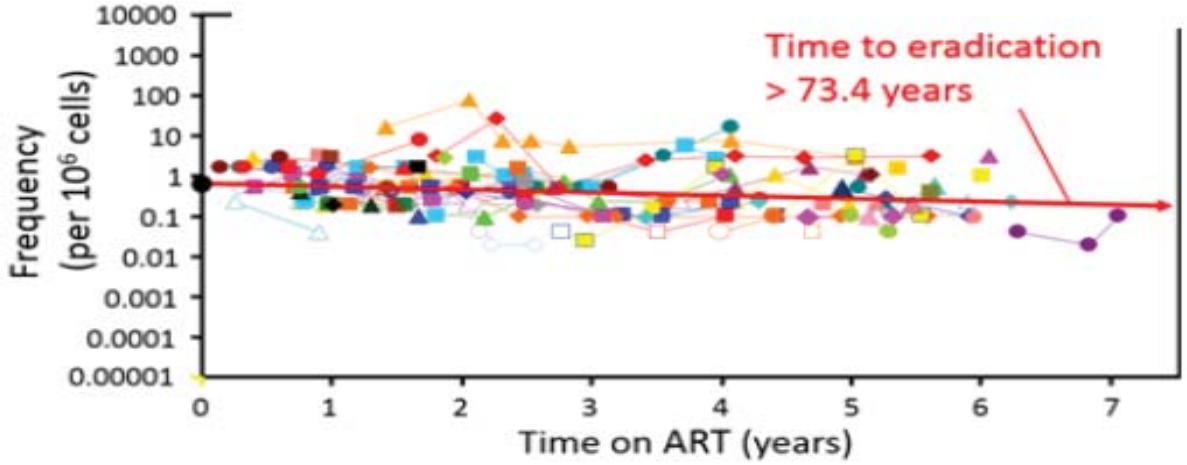
20+ references

CLONAL EXPANSION (IMSs)

- No evidence of viral evolution in anatomic compartments
- ARV intensification does not change the size of the viral reservoir
- Evidence of clonal expansion in lymph node
- Absence of breakthrough resistance at a population level
- Drug concentration targets unknown at a cellular level

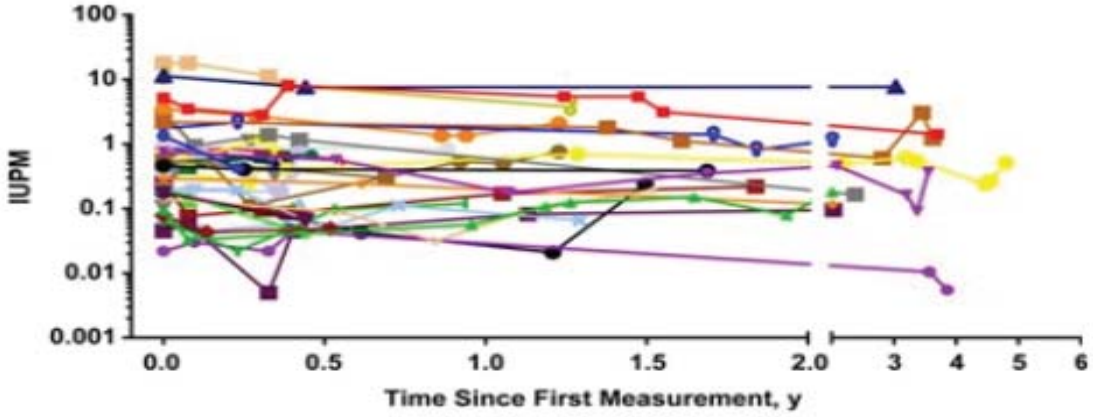
20+ references

WHATEVER IS RESPONSIBLE, THE VIRAL RESERVOIR DECAYS SLOWLY



$t_{1/2}$ = 44 months

Siliciano et al., Nature Med., 2003



$t_{1/2}$ = 43 months

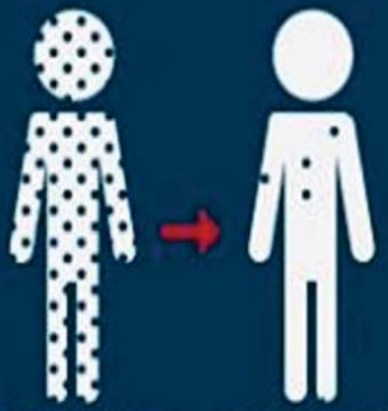
Crook et al, JID 2015

CAN'T USE ARV TX ALONE FOR CURE:

STRATEGIES FOR A CURE

FUNCTIONAL CURE

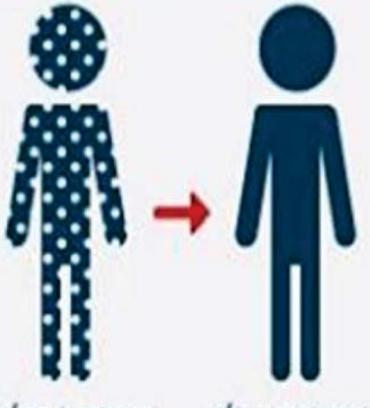
When the level of HIV particles in an infected person's body has been reduced to such an extremely low level that the person can stop treatment and not worry about the disease rebounding and damaging his immune system or body.



STERILIZING CURE

Eradication of HIV

When every last particle of HIV has been destroyed or cleared out from an infected person's body.



Immune-mediated control of HIV infection (eg "Elite Controllers")

Withdraw ARV without rebound (eg remission after cancer therapy)

Increase inflammation/comorbidities?

N=1: Timothy Brown ("Berlin Patient")

SCT with CCR5 Δ32Δ32 + GVH Disease

Must remove virus AND target cells

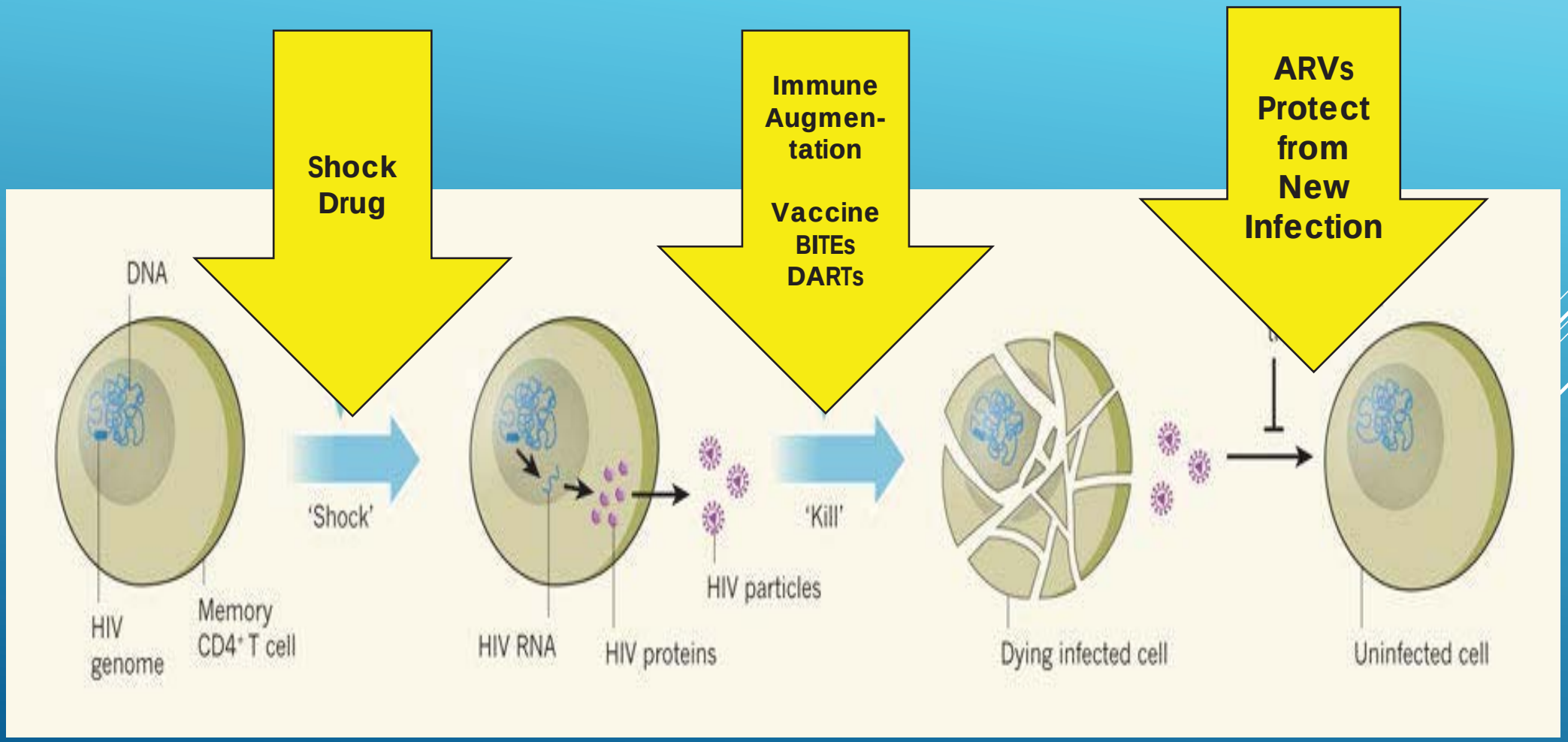
STRATEGIES FOR A CURE

Find and shrink the size of the HIV reservoir

- Reduce seeding of the latent pool with early ARV therapy (eg Febig 1/2)
- Reverse latency (shock and kill)
- Suppress latency (block and lock)
- Increase HIV-specific immune function (vaccines)
- Immune checkpoint blockade (antibodies – eg anti-PD1 Ab)
- Gene therapy targeting for the virus or host (CCR5 knockout/knockdown)
- Stem cell transplant

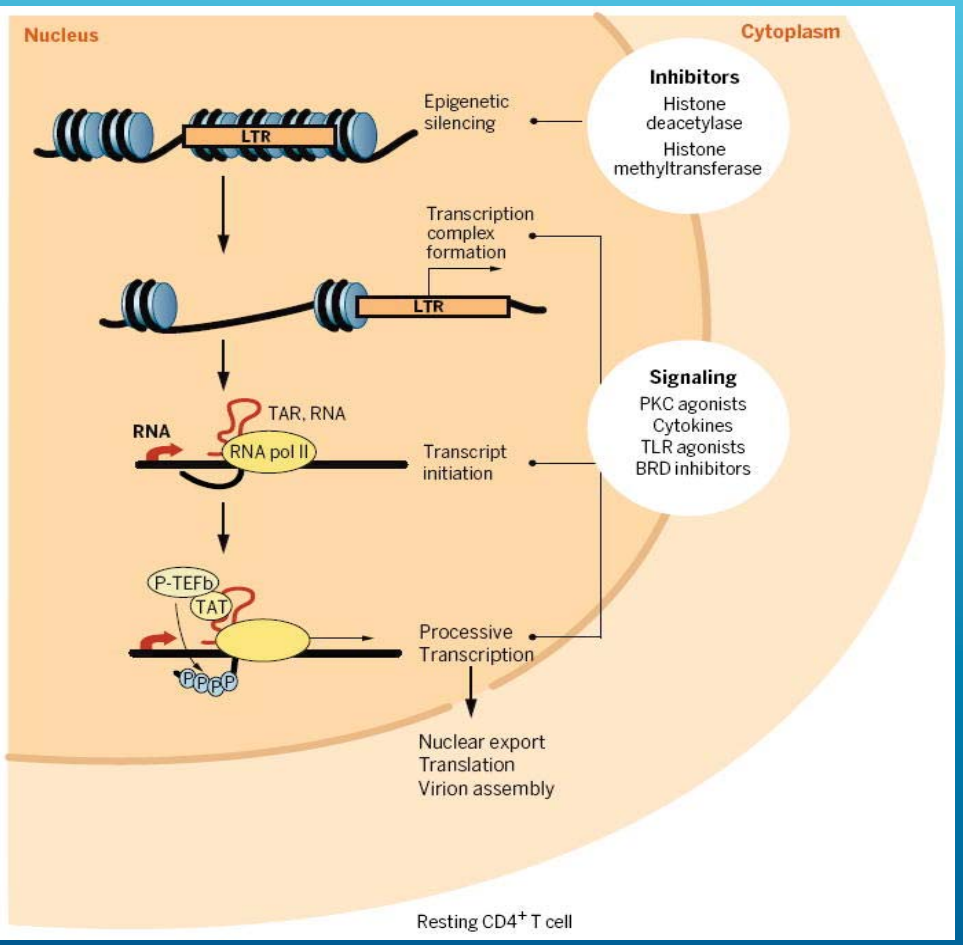
Combination Therapy Will Be Necessary

SHOCK AND KILL STRATEGY

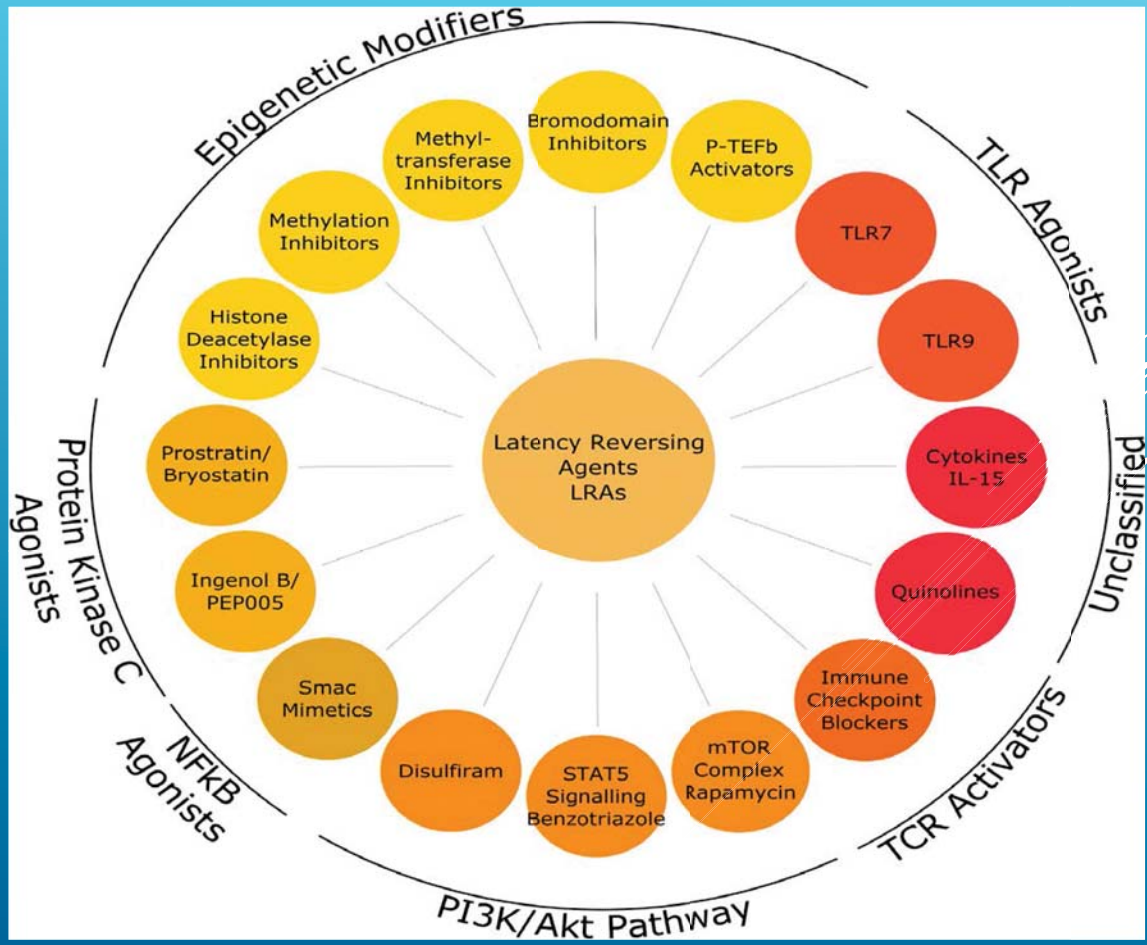


Deeks, Nature Med 2012; D Douek, April 2016, IAS USA

SHOCK APPROACHES

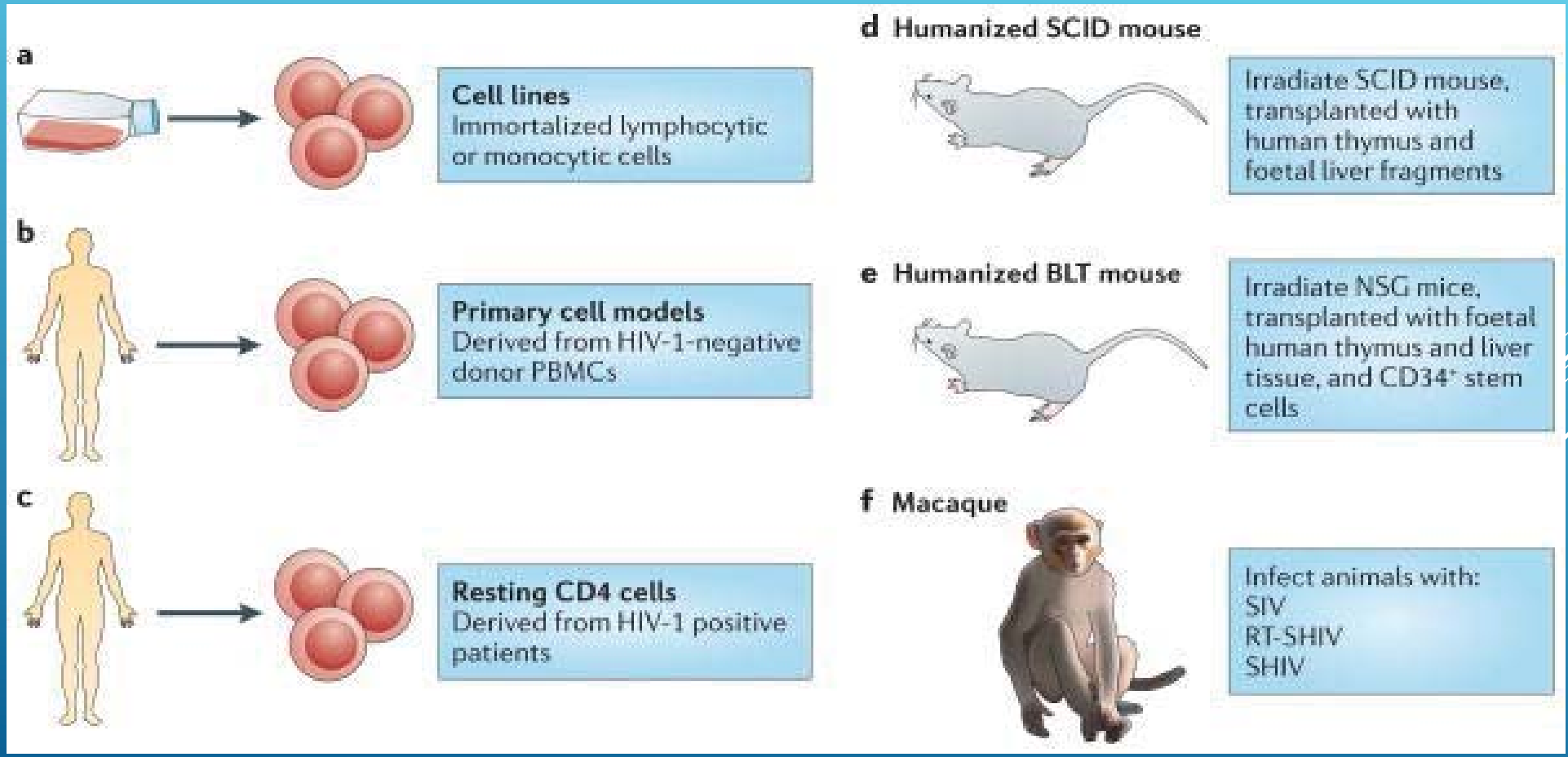


Margolis et al. Science. 2016

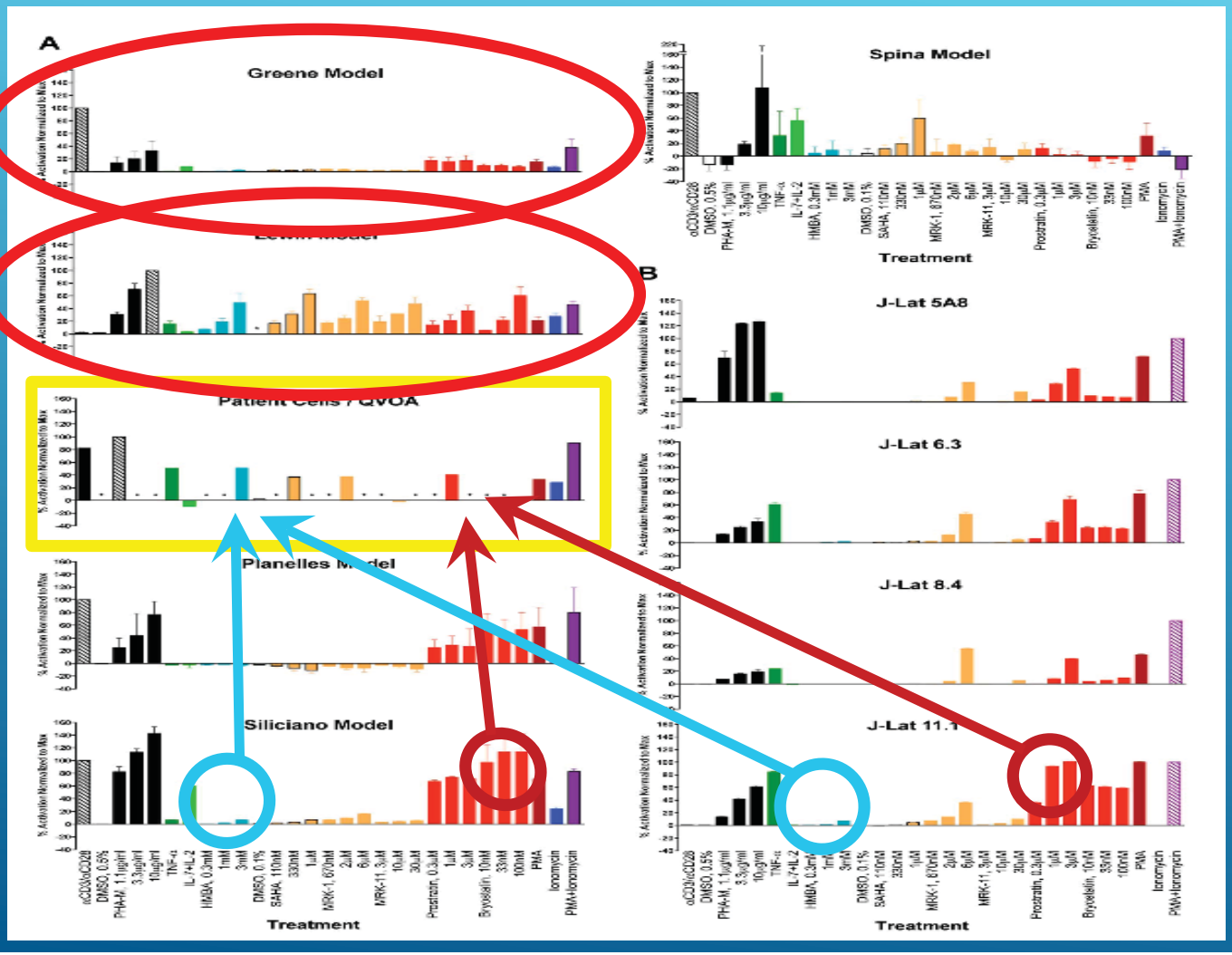


Kim et al. Cell Host and Microbe, 2018

CURRENT SYSTEMS TO STUDY HIV LATENCY



CHALLENGES WITH CELL MODELS



- 5 T cell models
- 4 J-Lat models
- 1 patient cells
- 13 stimuli
- no single model captured patient cell response
- PKC agonists and PHA reactivated HIV across models; drugs in most other classes did not

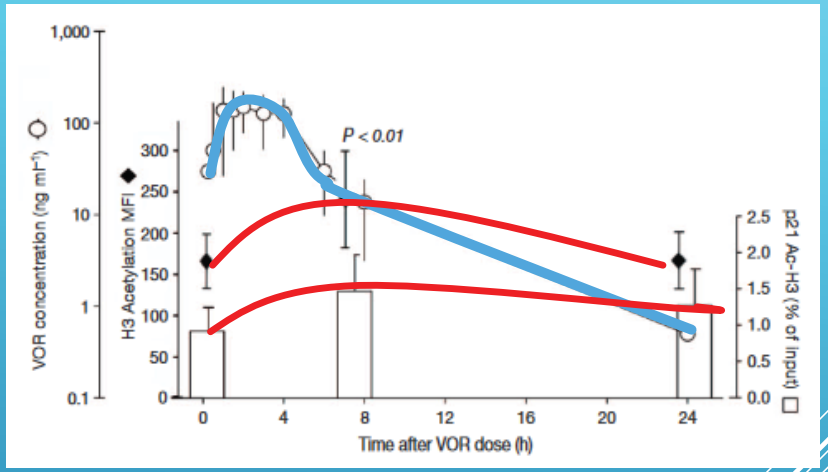
Spina et al. An in-depth comparison of latent HIV-1 reactivation in multiple cell model systems and resting CD4+ T cells from aviremic patients. PLoS Pathog. 2013;9(12):e1003834.

CHALLENGES WITH EXTRAPOLATION TO CLINICAL TRIALS

Nature 2012

Administration of vorinostat disrupts HIV-1 latency in patients on antiretroviral therapy

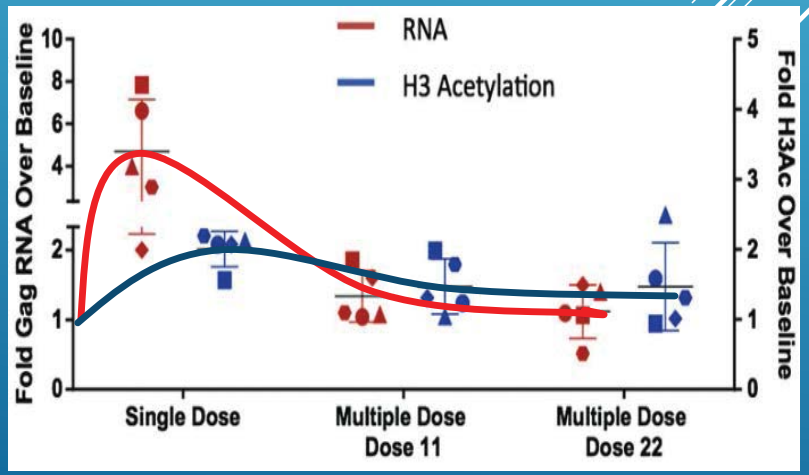
N. M. Archin[1], A. L. Liberty[1], A. D. Kashuba[1], S. K. Choudhary[1], J. D. Kuruc[1], A. M. Crooks[1], D. C. Parker[1], E. M. Anderson[2], M. F. Kearney[2], M. C. Strain[3], D. D. Richman[3], M. G. Hudgens[1], R. J. Bosch[4], J. M. Coffin[2], J. J. Eron[1], D. J. Hazuda[5] & D. M. Margolis[1]



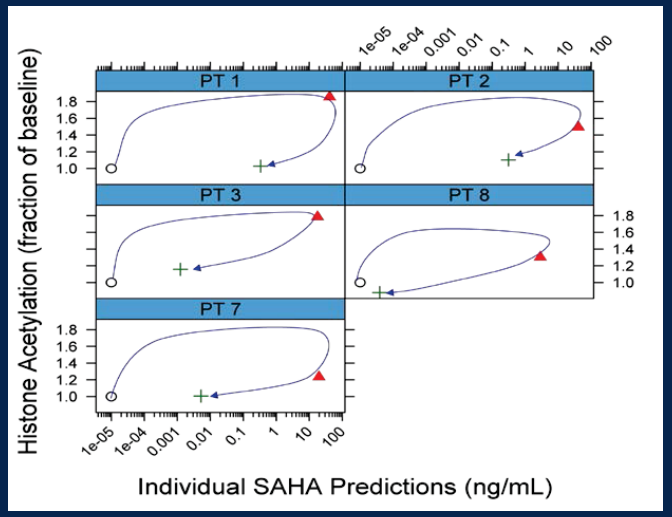
HIV-1 Expression Within Resting CD4$^+$ T Cells After Multiple Doses of Vorinostat

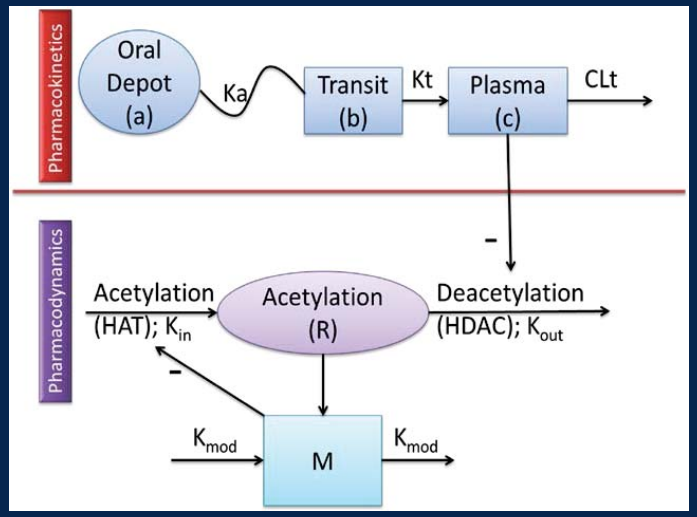
JID 2014

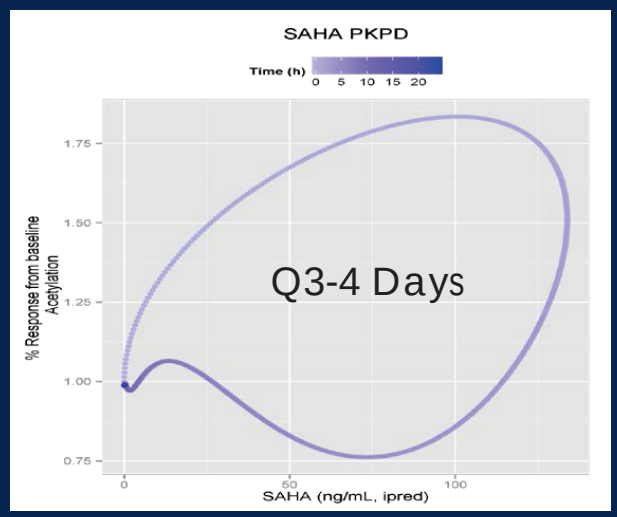
Nancy M. Archin,[1] Rosalie Bateson,[1] Manoj K. Tripathy,[1] Amanda M. Crooks,[1] Kuo-Hsiung Yang,[1] Noelle P. Dahl,[1] Mary F. Kearney,[2] Elizabeth M. Anderson,[2] John M. Coffin,[2,3] Matthew C. Strain,[4] Douglas D. Richman,[4] Kevin R. Robertson,[1] Angela D. Kashuba,[1] Ronald J. Bosch,[5] Daria J. Hazuda,[6] Joann D. Kuruc,[1] Joseph J. Eron,[1] and David M. Margolis[1]



USING PHARMACOMETRICS TO OPTIMIZE DOSING



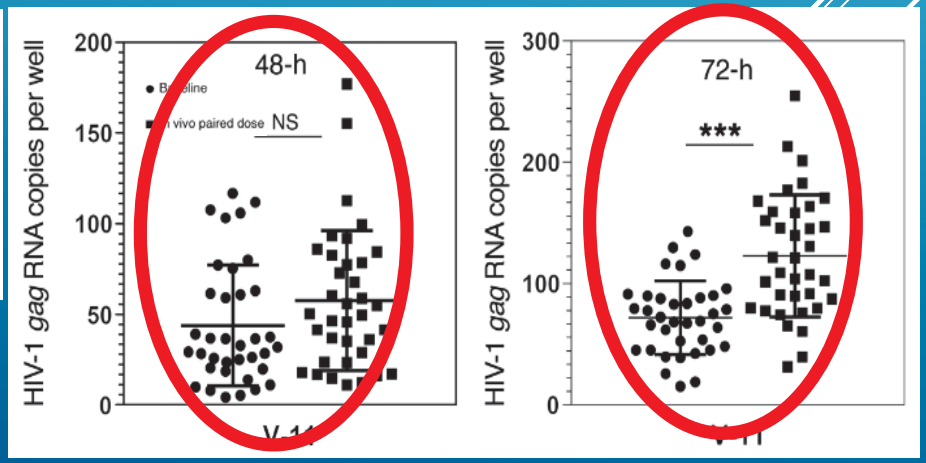




JCI 2017

Interval dosing with the HDAC inhibitor vorinostat effectively reverses HIV latency

Nancie M. Archin,[1,2] Jennifer L. Kirchherr,[1] Julia A.M. Sung,[1,2] Genevieve Clutton,[1,3] Katherine Sholtis,[1] Yinyan Xu,[1] Brigitte Allard,[1] Erin Stuelke,[1] Angela D. Kashuba,[4] Joann D. Kuruc,[1,2] Joseph Eron,[1,2,5] Cynthia L. Gay,[1,2] Nilu Goonetilleke,[1,3] and David M. Margolis[1,2,3,5]



IMPROVING STATIC IN VITRO SYSTEM PREDICTABILITY

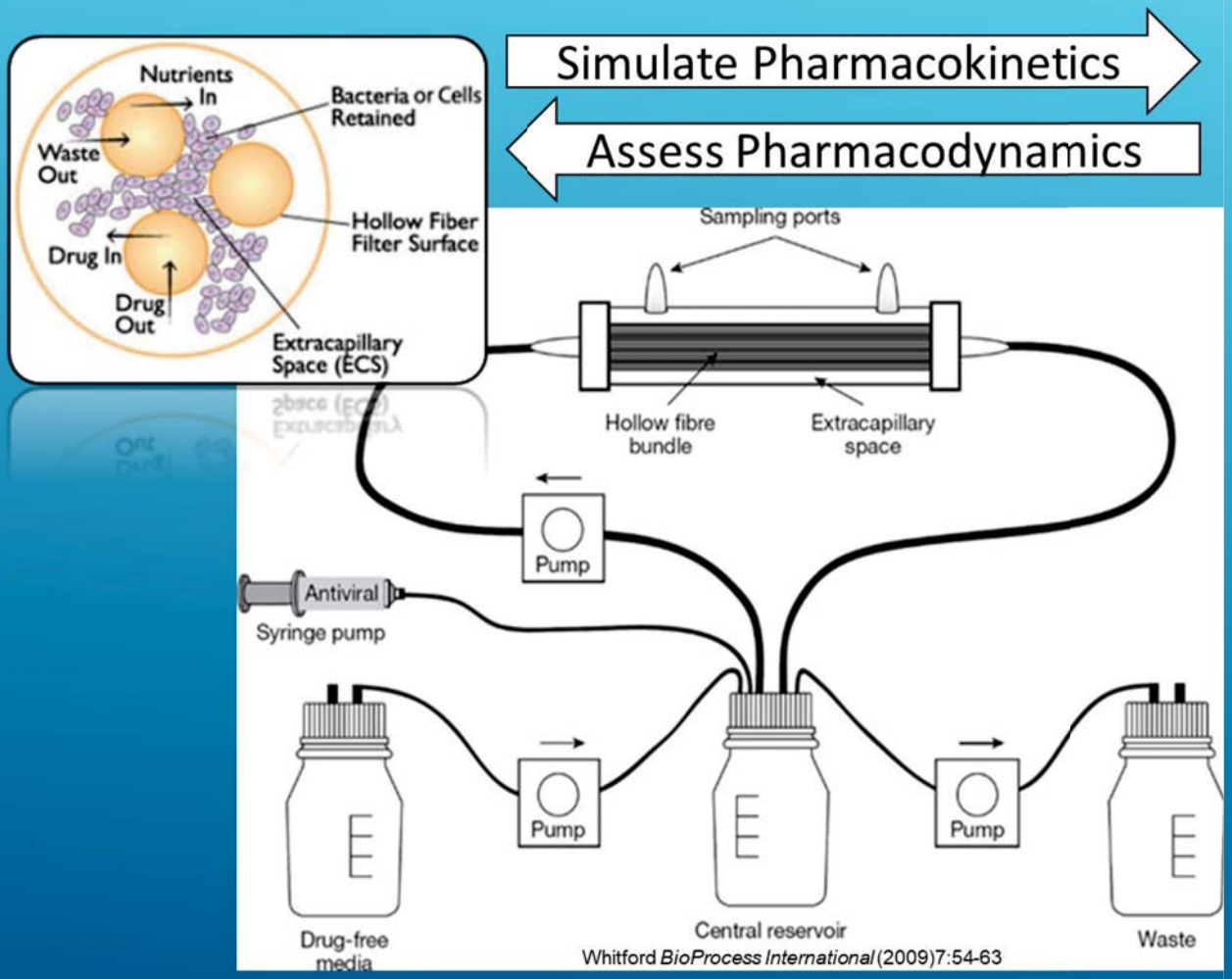


Figure: Graphical Representation of a Hollow Fiber Model (HFM). Whitford *BioProcess International* (2009)7:54-63

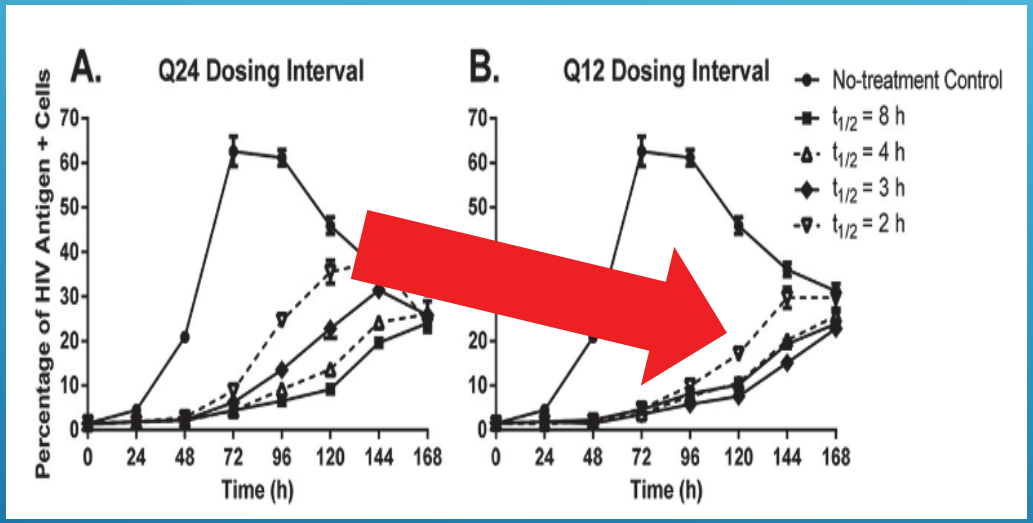
- Central reservoir mimics *in vivo* **circulation**
- Syringe pump infuses drug treated media to mimic *in vivo* drug **absorption**
- Media pumps dilute drug treated media in central reservoir to mimic *in vivo* drug **clearance**

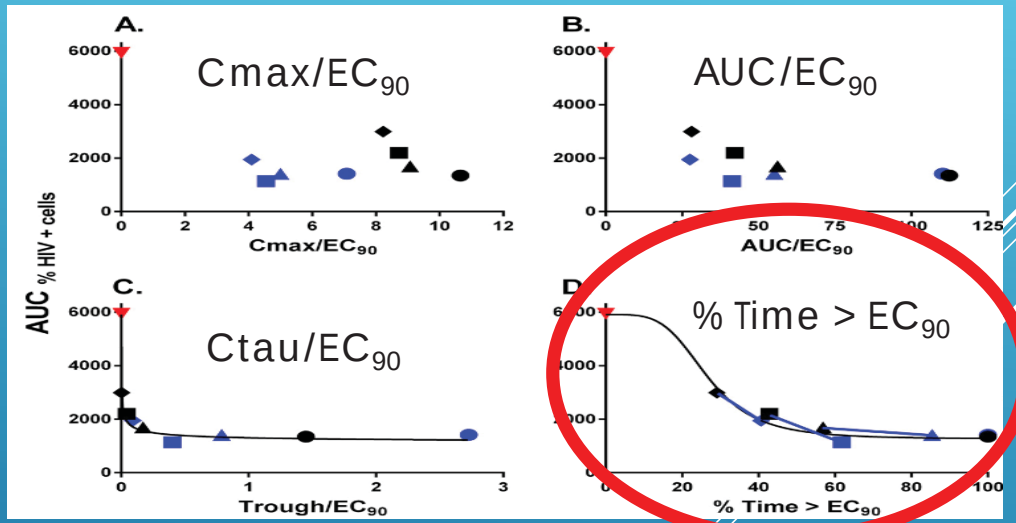
HOLLOW FIBER BIOREACTOR POTENTIAL

Pharmacokinetic Determinants of Virological Response to Raltegravir in the *In Vitro* Pharmacodynamic Hollow-Fiber Infection Model System

Ashley N. Brown, Jonathan R. Adams, Dodge L. Baluya, George L. Drusano

AAC 2015

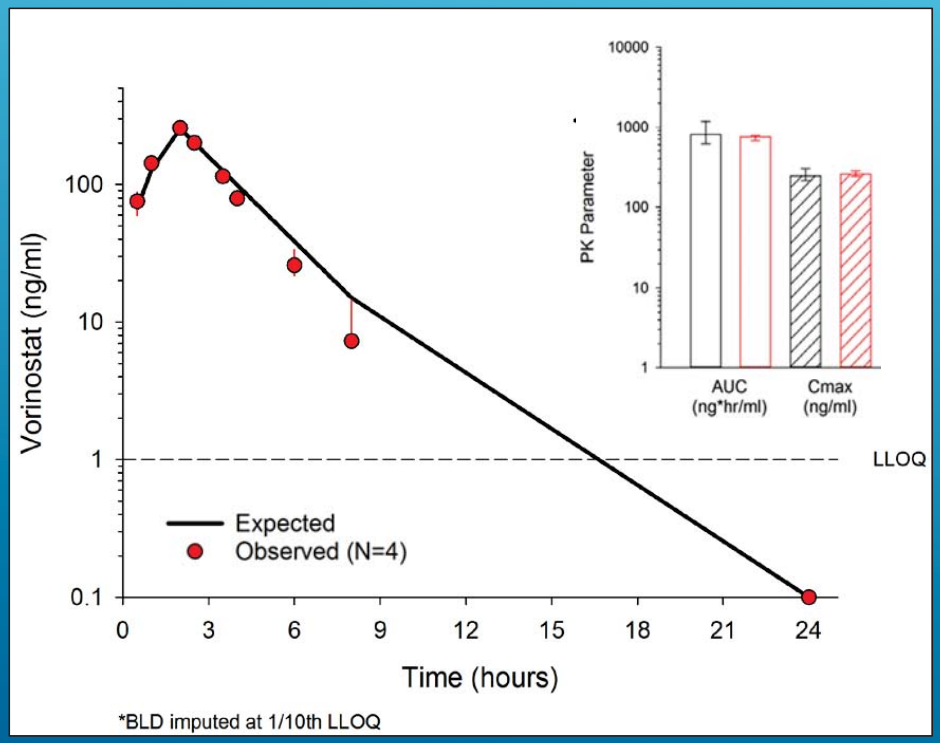


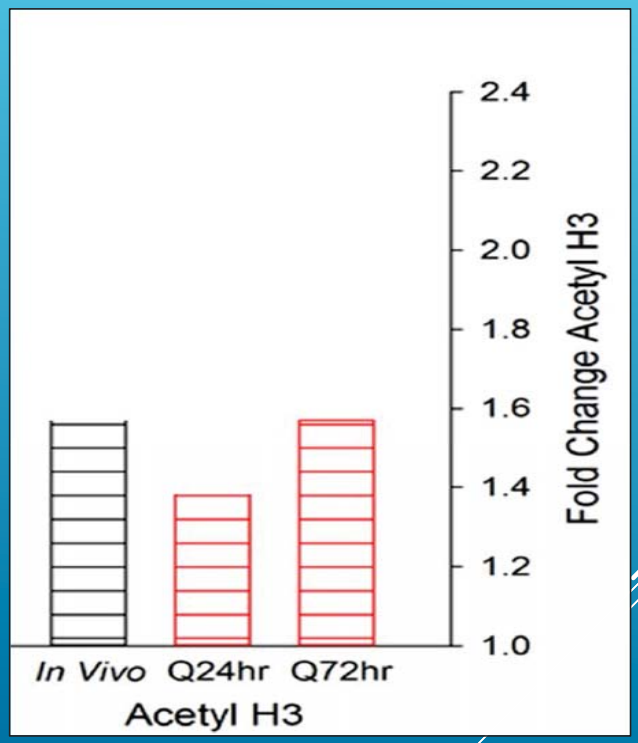


PK/PD Predictions

- Meropenem for Pseudomonas
- Aztreonam+avibactam for MDR Enterobacteriacea
- Oseltamivir for Influenza A
- Amprenavir+ritonavir for HIV

HOLLOW FIBER BIOREACTOR POTENTIAL

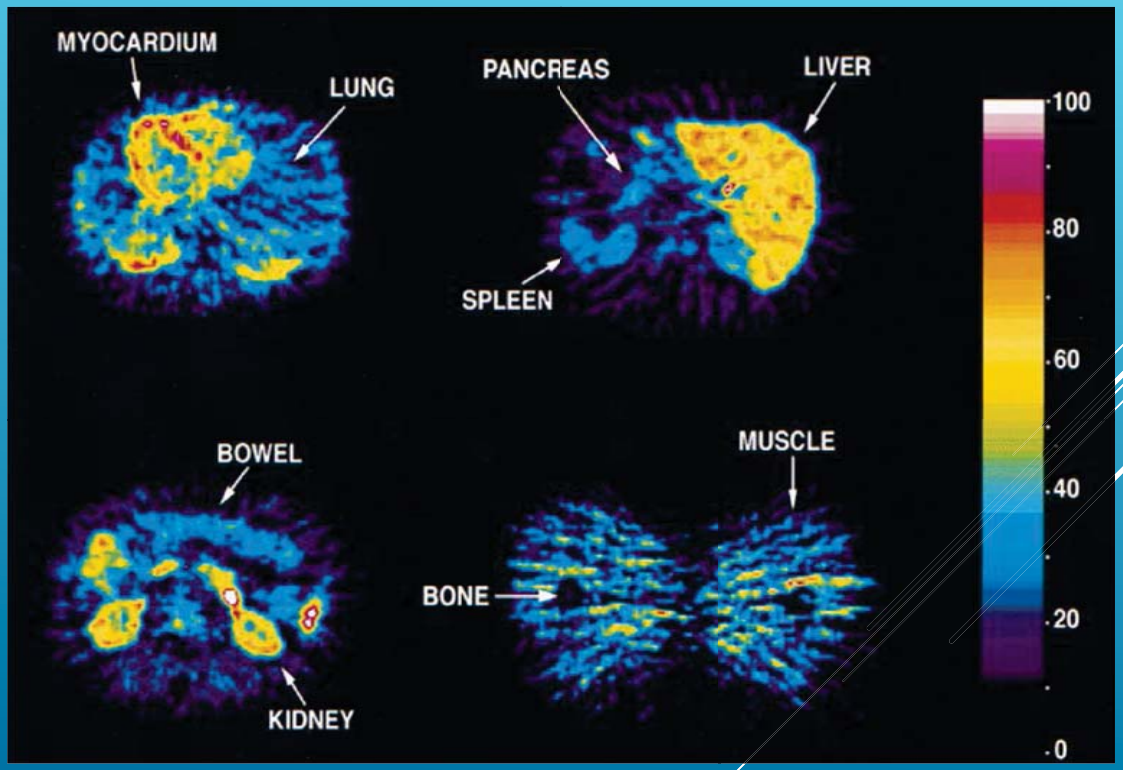




Archin JID 2014
Archin JCI 2017
Cottrell, unpublished 2018

CHALLENGES WITH TISSUE DISTRIBUTION/PHARMACOKINETICS:
LATENCY REVERSING AGENTS AND ANTIRETROVIRALS

- Tissue distribution is heterogeneous
  - Tissue distribution is nonhomogeneous and tissue specific, with high inter-tissue and inter-subject variability
  - target site concentrations may substantially differ from plasma concentrations

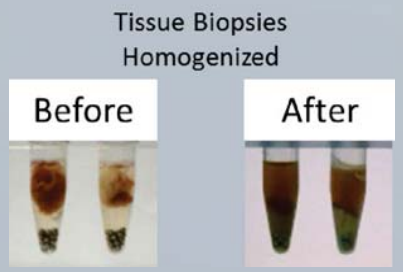


Representative PET images of human subjects following the 18F-trovafloxacin. Muller AAC 2004

MEASURING TISSUE PHARMACOKINETICS FOR LRA AND ARV PK/PD

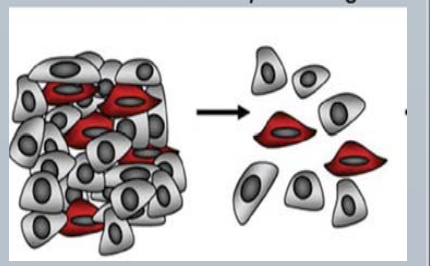
LC-MS methods of quantification

- Extraction of analyte from tissue homogenate
- Useful for providing initial information of averaged concentration
- Lack of spatial resolution
- intracellular+extracellular



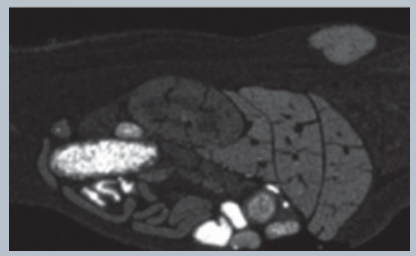
Enzymatic Digestion & Cell Isolation

- Concentrations decline with sample processing
- Lack of spatial resolution



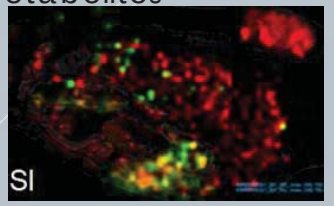
Traditional imaging techniques (QWBA, PET)

- Require radiolabels
- May not distinguish between parent and metabolite
- Challenging to evaluate multi-drug therapies
- Cellular resolution may not be possible



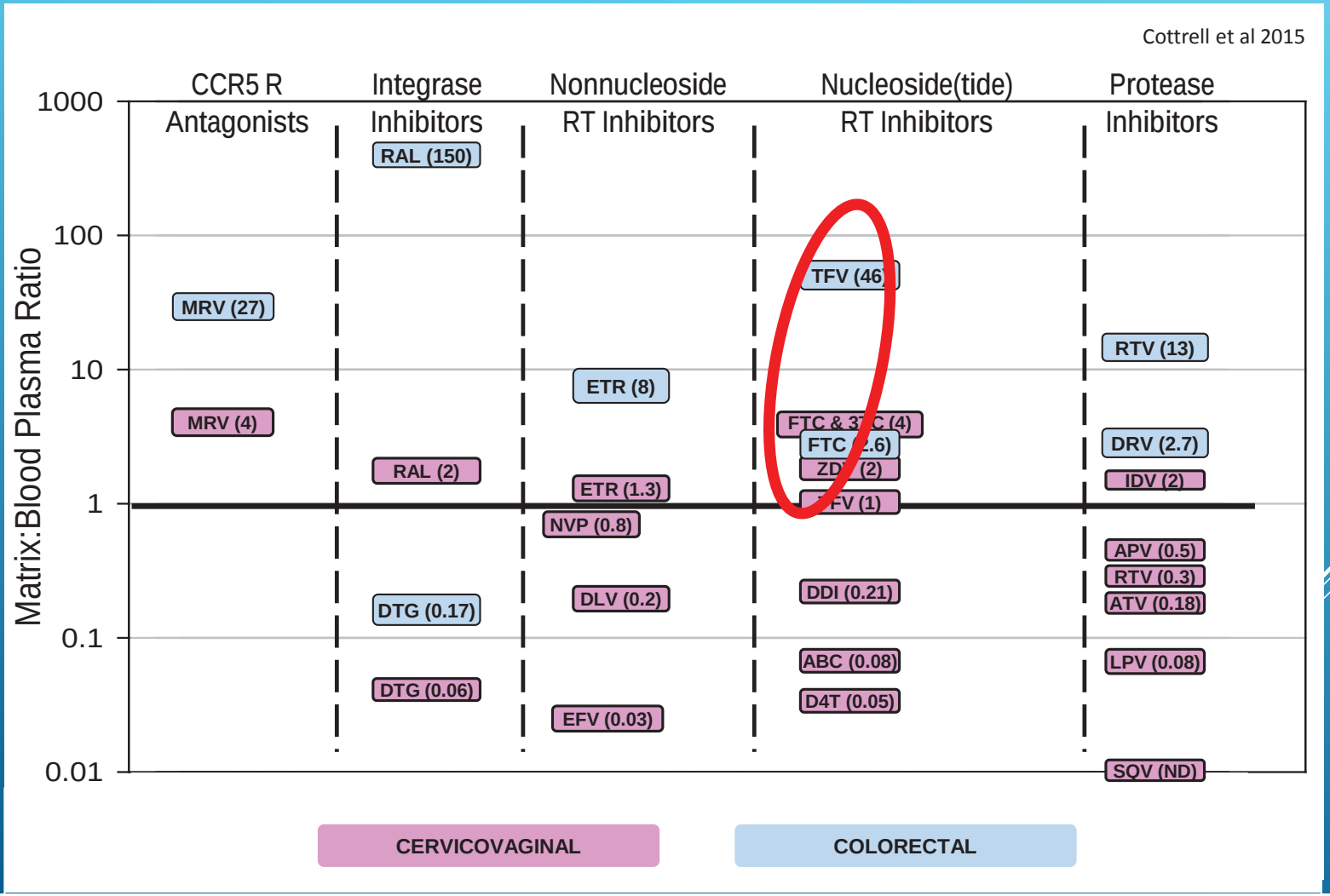
Mass Spectroscopy Imaging

- Only allows ex-vivo measures
- Spatial distribution of compounds
- Distinguishes between parent and metabolite
- Provide additional information on endogenous compounds and metabolites



Solon et al AAPS 2010

UTILITY OF MUCOSAL TISSUE HOMOGENATES IN PREP



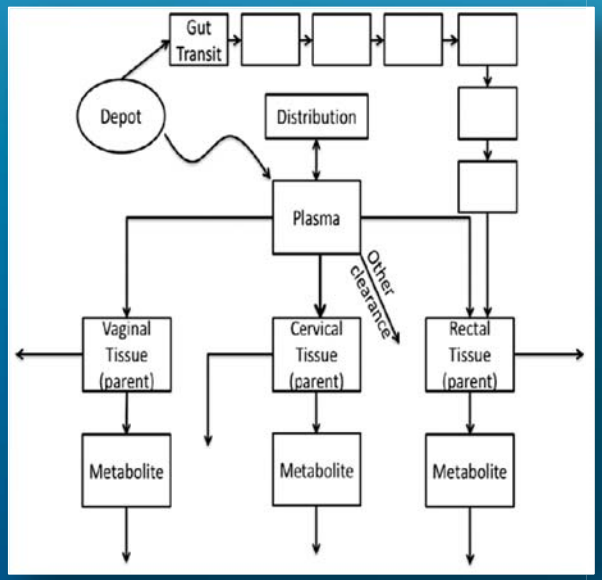
UTILITY OF MUCOSAL TISSUE HOMOGENATES IN PREP

A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine

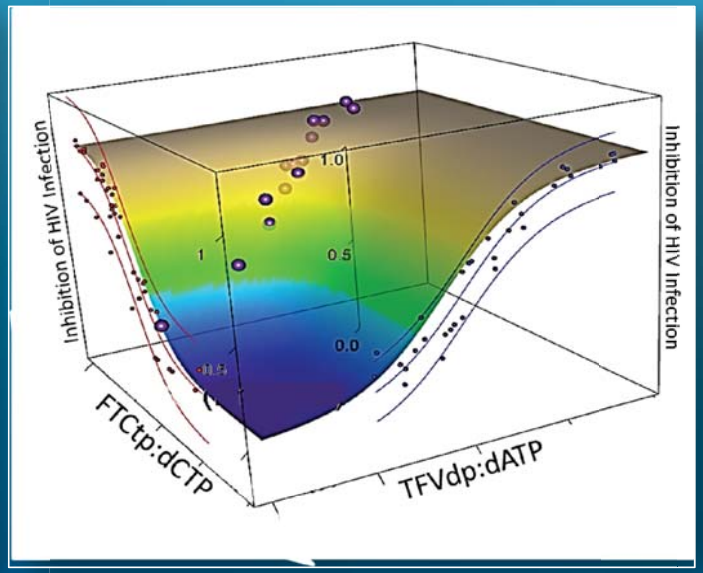
JID 2016

Mackenzie L. Cottrell,[1] Kuo H. Yang,[2] Heather M. A. Prince,[3] Craig Sykes,[1] Nicole White,[1] Stephanie Malone,[1] Evan S. Dellon,[3] Ryan D. Madanick,[3] Nicholas J. Shaheen,[3] Michael G. Hudgens,[4] Jacob Wulff,[4] Kristine B. Patterson,[3] Julie A. E. Nelson,[5] and Angela D. M. Kashuba[1]

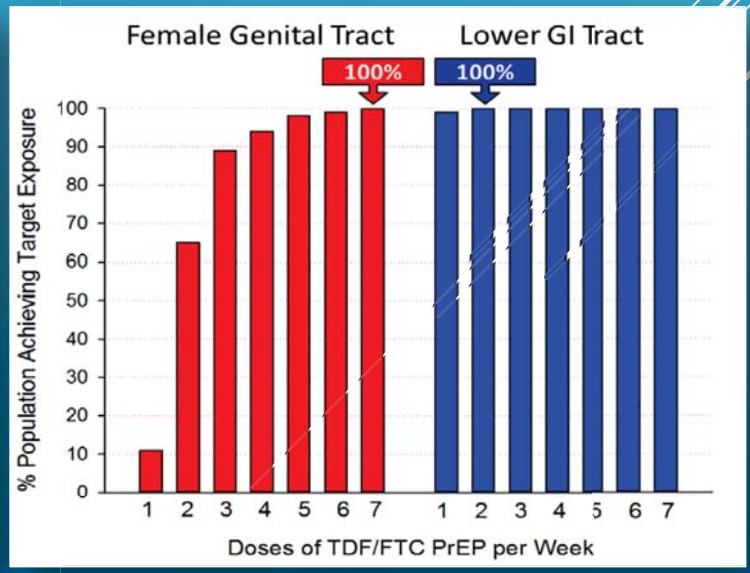
PK Model of TFVdp and FTCtp in Mucosal Tissues



In Vitro Cellular Targets for Efficacy/Synergy



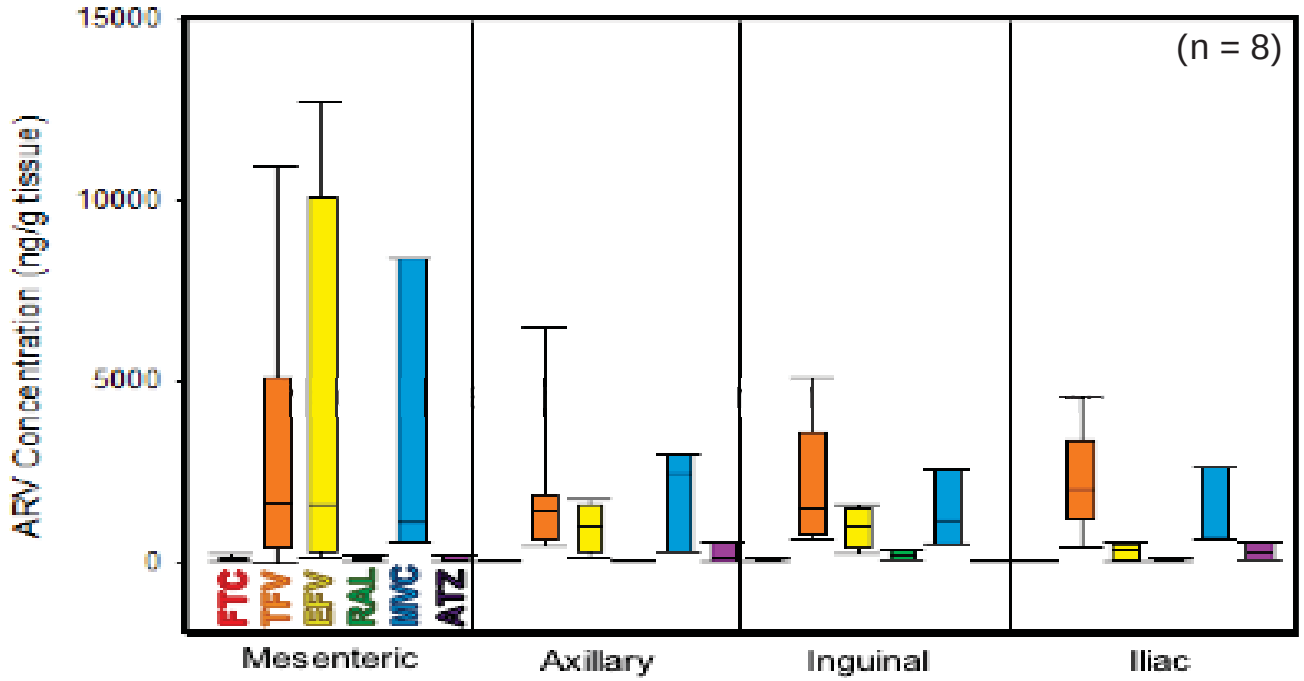
Dose Frequency for HIV Protection



UTILITY OF TISSUE HOMOGENATES LIMITED IN CURE

LN: WHAT CONCENTRATION IS NEEDED FOR EFFICACY?

LC-MS/MS ARV Concentration Analysis in Lymph Nodes



Emtricitabine (FTC)
Tenofovir (TFV)
Efavirenz (EFV)
Raltegravir (RAL)
Maraviroc (MVC)
Atazanavir (ATZ)

Need a better understanding of tissue pk/pd

Burgunder et al. Unpublished data. 2018

ENZYMATIC CELL DIGESTION

Defining total-body AIDS-virus burden with implications for curative strategies

Nature Med 2017

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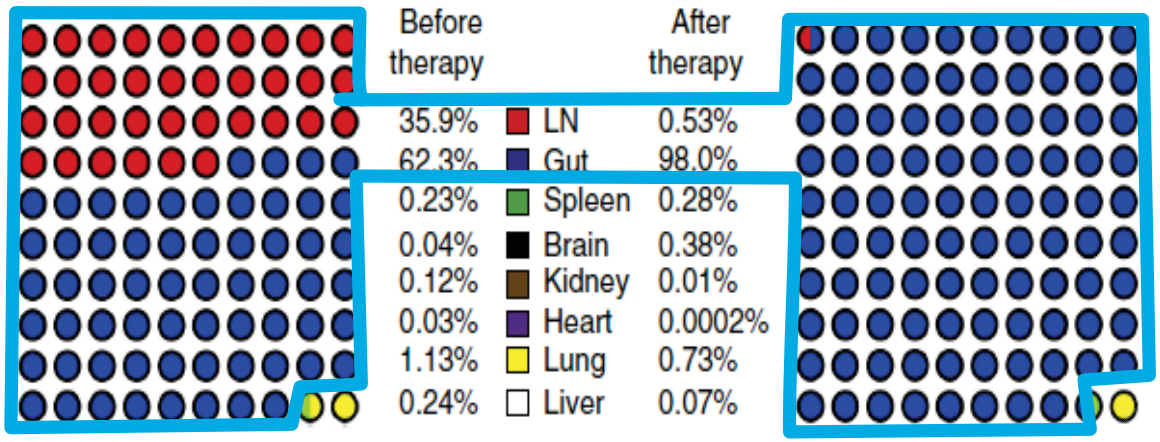


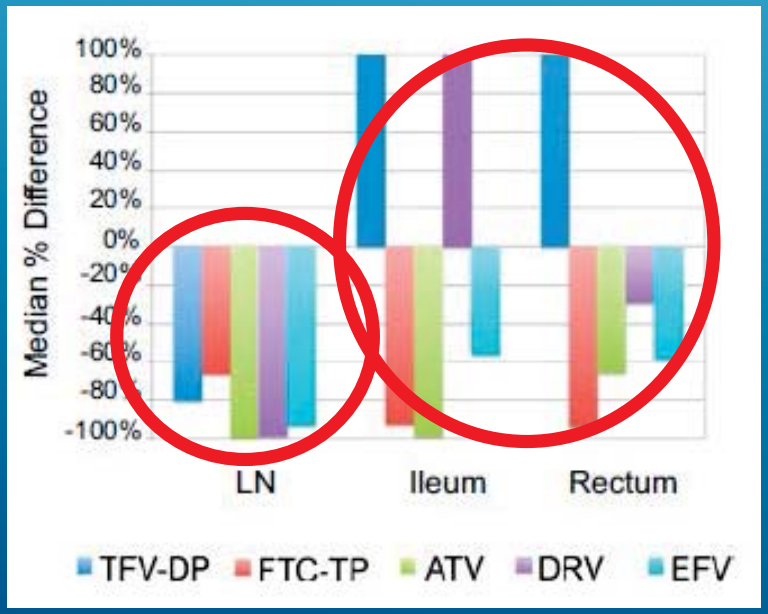
Figure 1 Graphical representation of the proportion of vRNA+ cells in each organ system before and during suppressive ART.

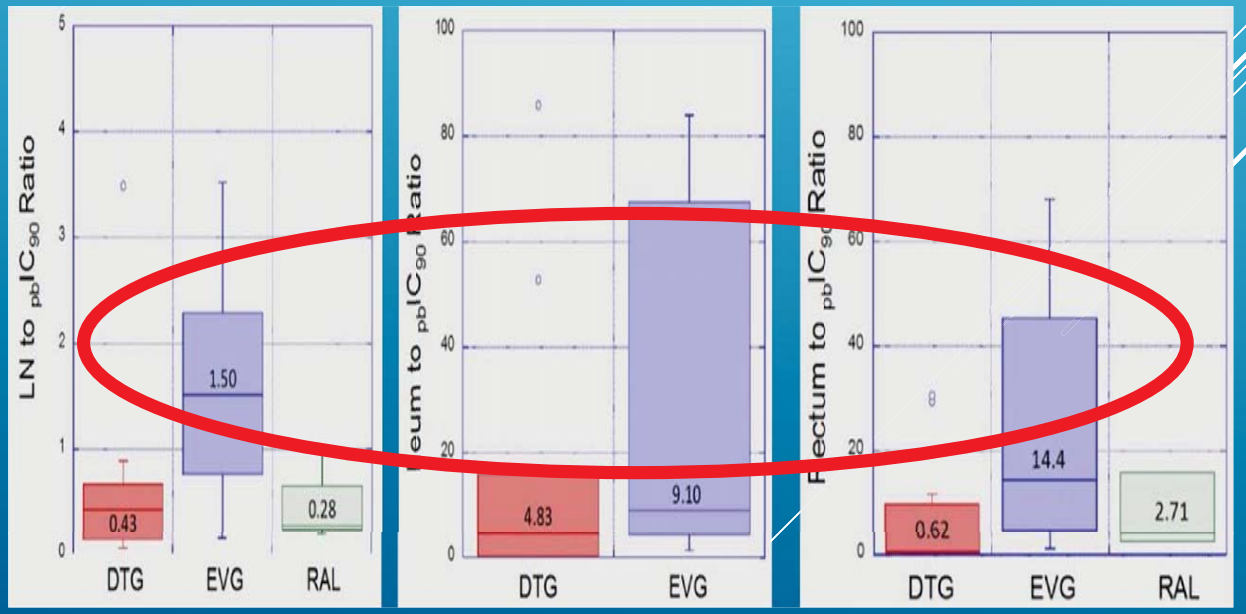
ENZYMATIC CELL DIGESTION

PNAS 2014

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Courtney V. Fletcher[a], Kathryn Staskus[b,1], Stephen W. Wietgrefe[b], Meghan Rothenberger[c], Cavan Reilly[d], Jeffrey G. Chipman[e], Greg J. Beilman[e], Alexander Khoruts[c], Ann Thorkelson[c], Thomas E. Schmidt[c], Jodi Anderson[c], Katherine Perkey[b], Mario Stevenson[f], Alan S. Perelson[g], Daniel C. Douek[h], Ashley T. Haase[b], and Timothy W. Schacker[c,2]

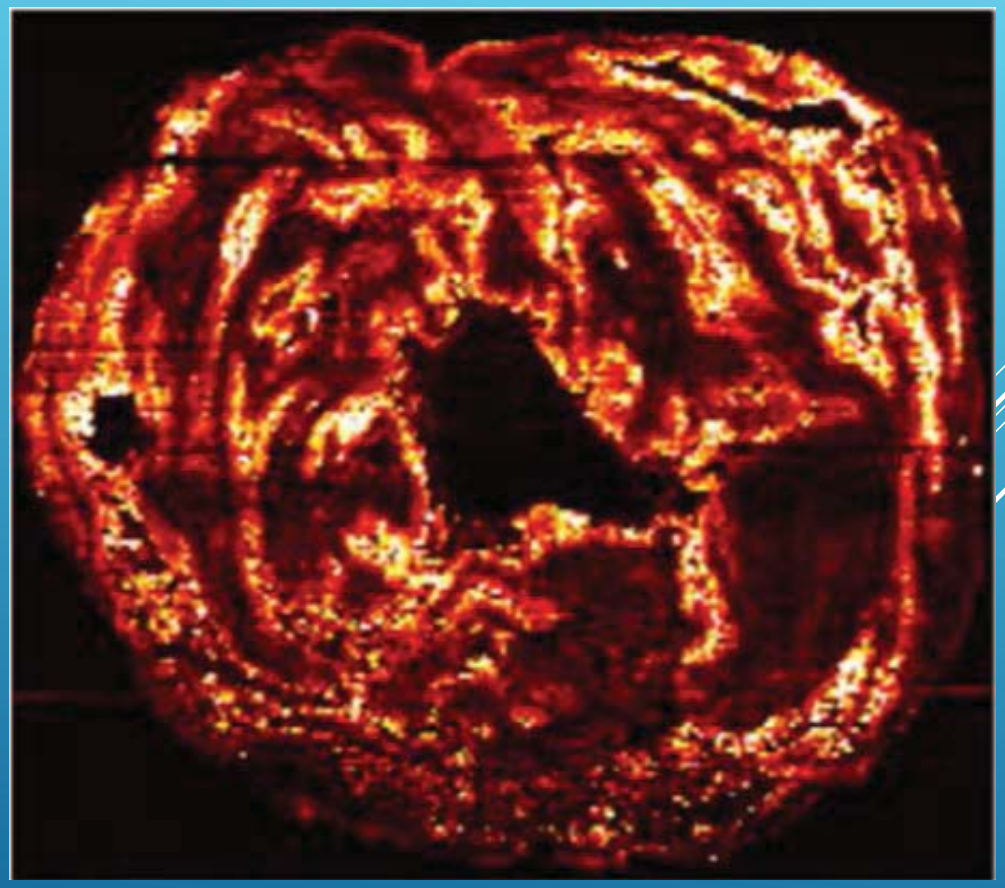




Fletcher et al CROI 2018

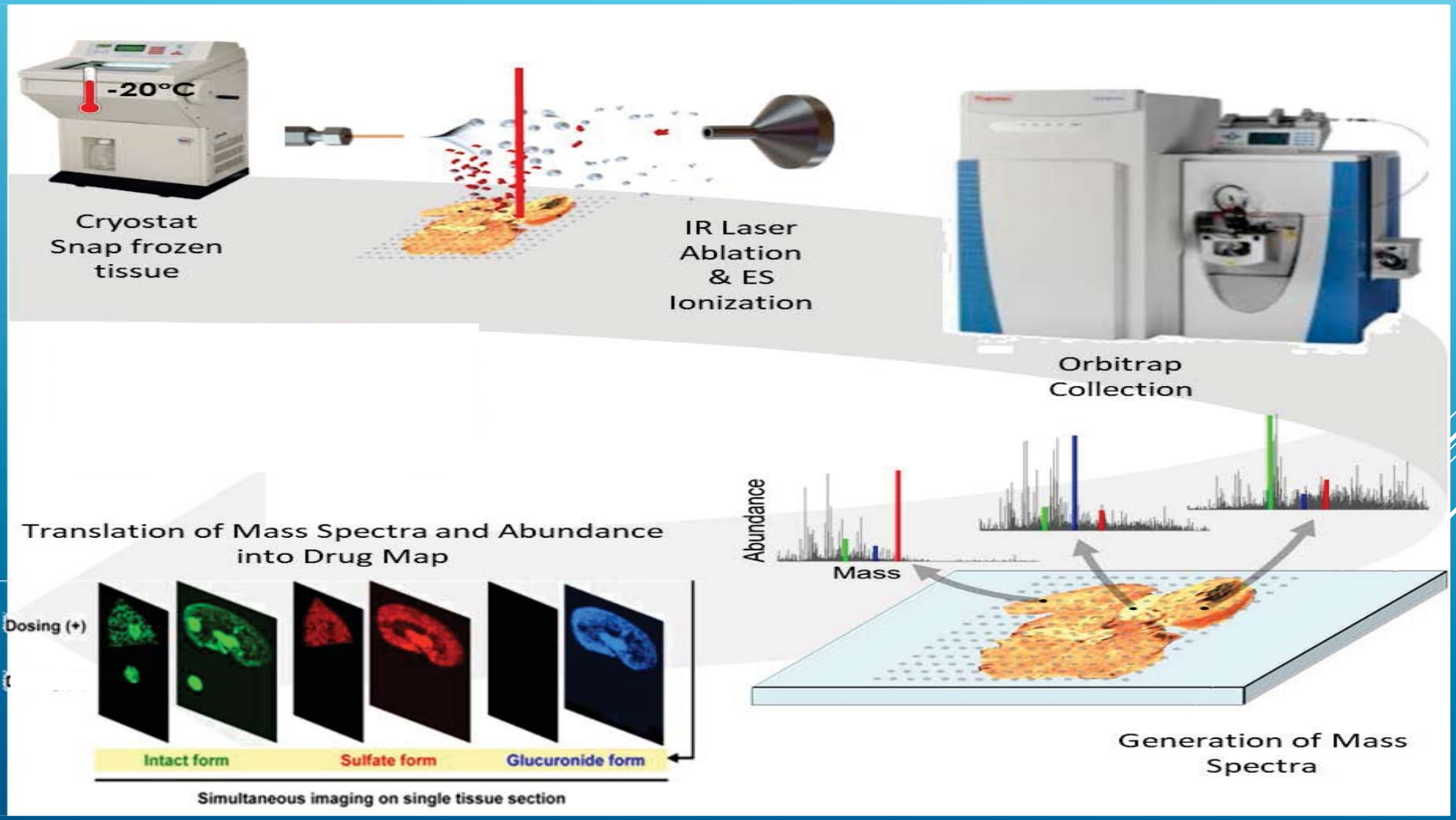
MASS SPECTROSCOPY IMAGING

- Could HIV persistence in reservoirs be due to inadequate ARV distribution?
- Will anti-latency therapies reach all tissue sites ?



Thompson, et al. AAC. 2015, 59(5)

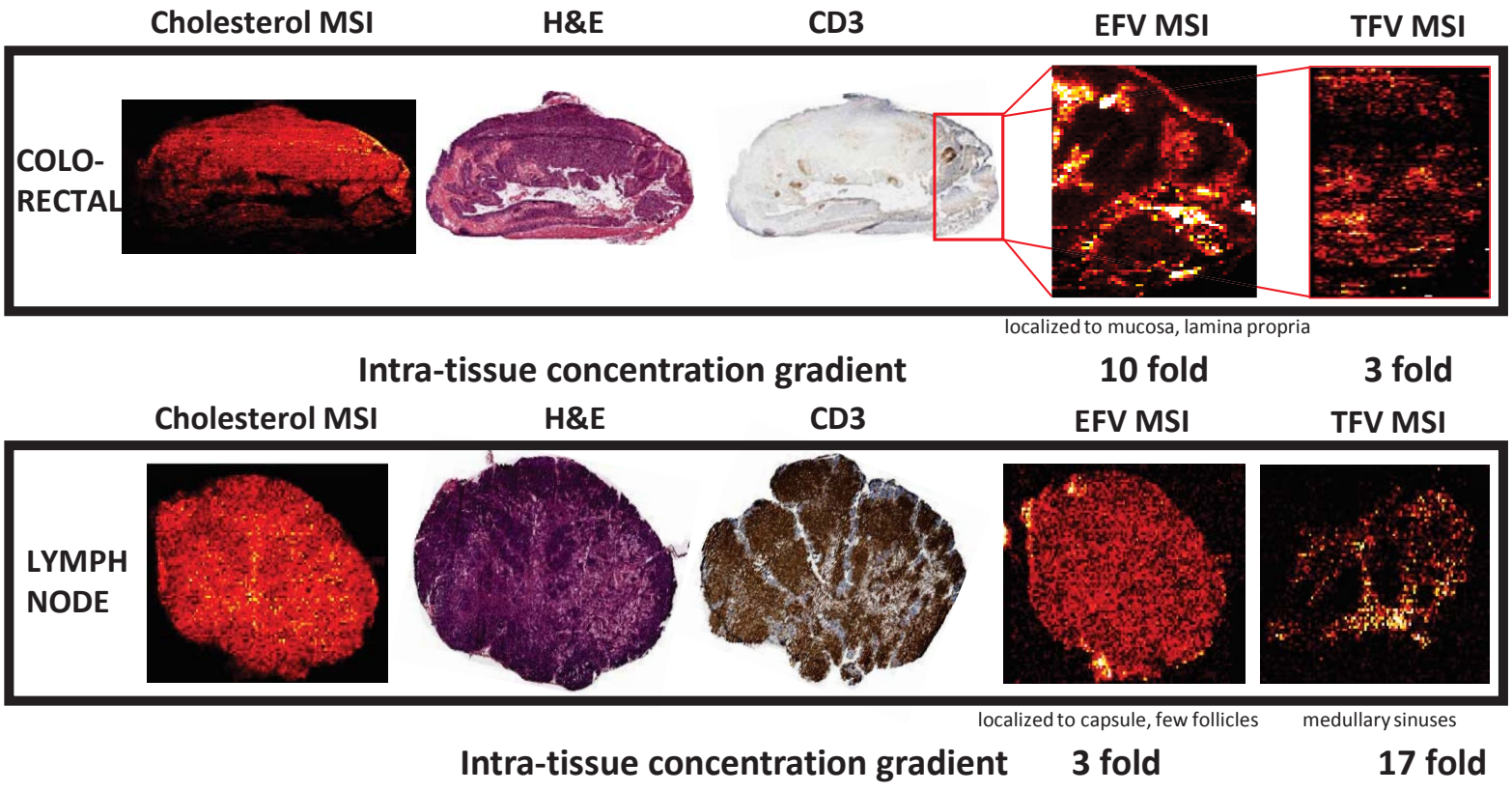
QUANTITATIVE IR MALDESI



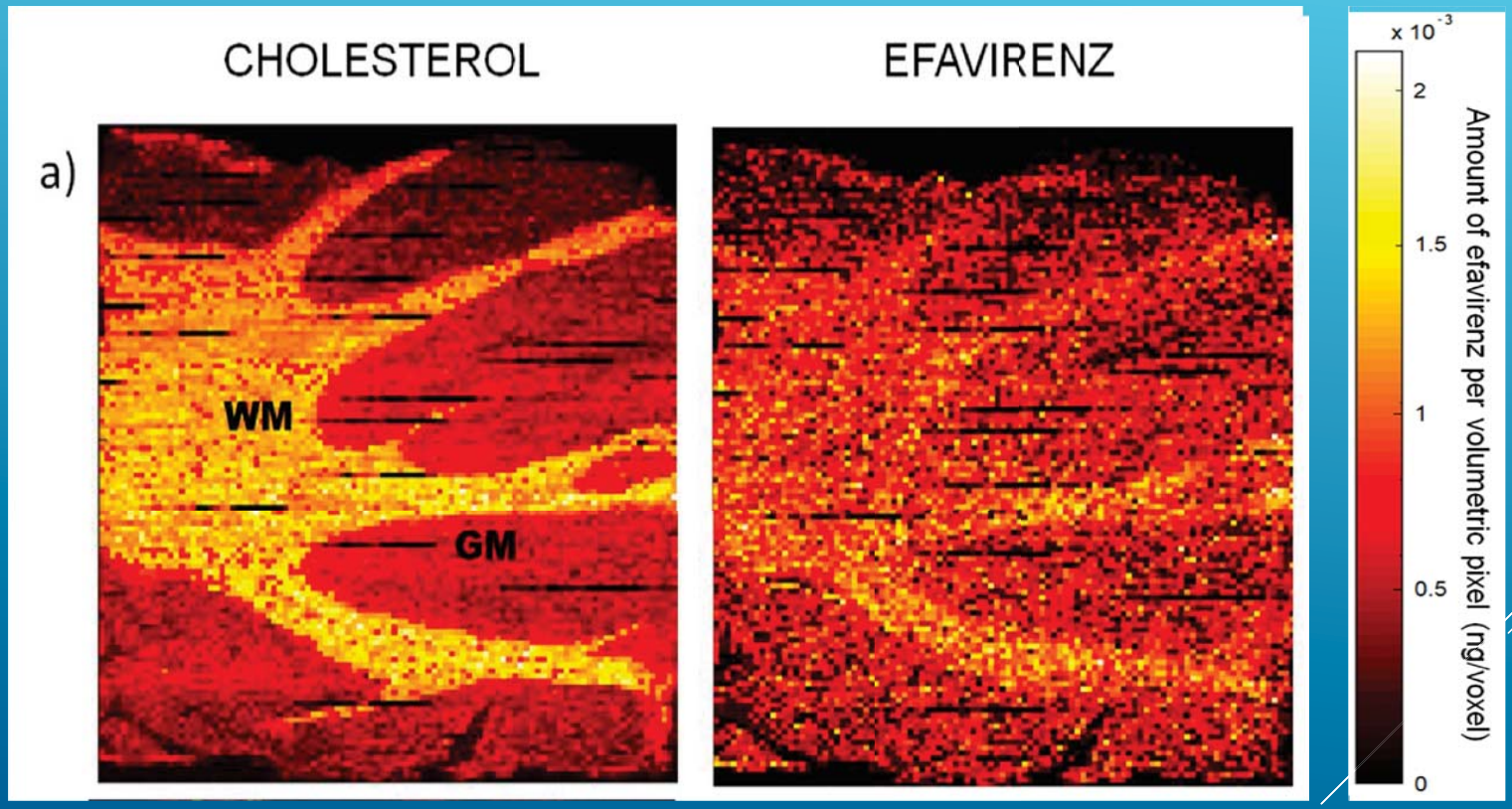
MSI OF ARVS IN TISSUES:
DRUG-SPECIFIC DISTRIBUTION

↑ Conc

↓ Conc



ANATOMIC RESERVOIR MSI:
WHITE VERSUS GREY MATTER



Srinivas et al In review, 2018

PANOBINOSTAT (PANO- HDAC INHIBITOR):

IN VITRO EFFICACY – IN VIVO FAILURE

cells

AAC Journals.ASM.org

Ex Vivo Bioactivity and HIV-1 Latency Reversal by Ingenol Dibenzoate and Panobinostat in Resting CD4$^+$ T Cells from Aviremic Patients

Adam M. Spivak,[a] Alberto Bosque,[b] Alfred H. Balch,[a] David Smyth,[a] Laura Martins,[b] Vicente Planelles[b]
Departments of Medicine[a] and Pathology,[b] University of Utah School of Medicine, Salt Lake City, Utah, USA

humanized mice

Tsai *et al. Retrovirology (2016) 13:36*
DOI 10.1186/s12977-016-0268-7
Retrovirology

In vivo analysis of the effect of panobinostat on cell-associated HIV RNA and DNA levels and latent HIV infection

Perry Tsai[1], Guoxin Wu[2], Caroline E. Baker[1], William O. Thayer[1], Rae Ann Spagnuolo[1], Rosa Sanchez[2], Stephanie Barrett[2], Bonnie Howell[2], David Margolis[1], Daria J. Hazuda[2], Nancie M. Archin[1*] and J. Victor Garcia[1*]

HIV+ Patients

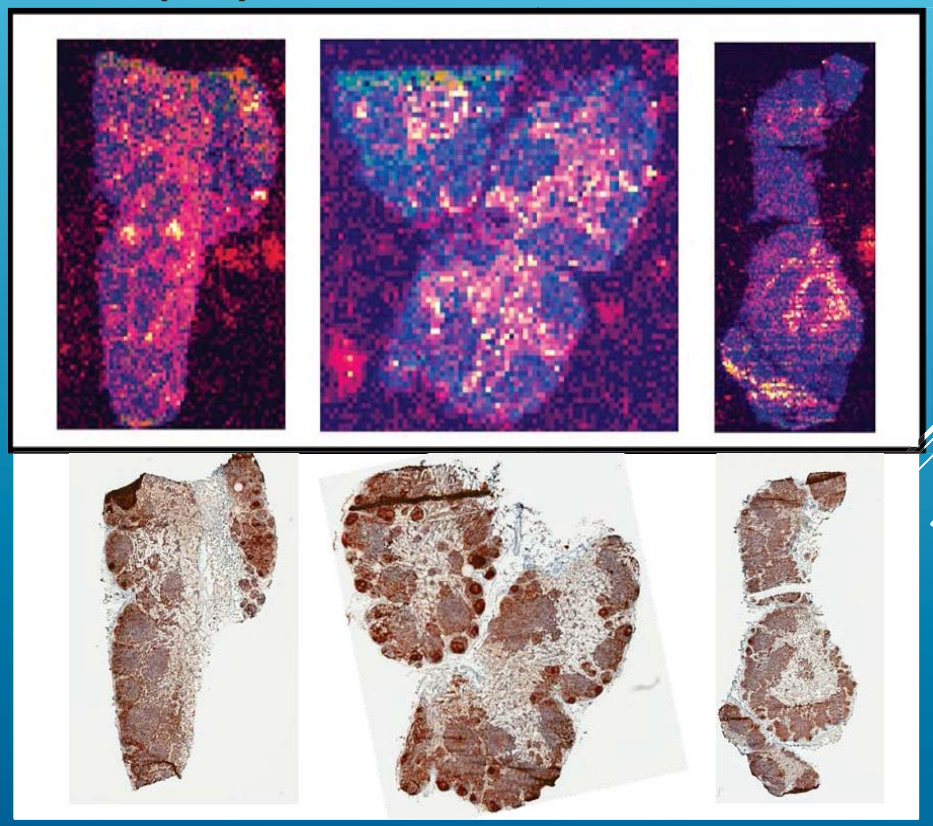
Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial

Thomas A Rasmussen, Martin Tolstrup, Christel R Brinkmann, Rikke Olesen, Christian Erikstrup, Ajantha Solomon, Anni Winckelmann, Sarah Palmer, Charles Dinarello, Maria Buzon, Mathias Lichterfeld, Sharon R Lewin, Lars Østergaard, Ole S Søgaard

Summary
Background Activating the expression of latent virus is an approach that might form part of an HIV cure. We assessed Lancet HIV 2014; 1: e13–21

Is the drug where it needs to be?

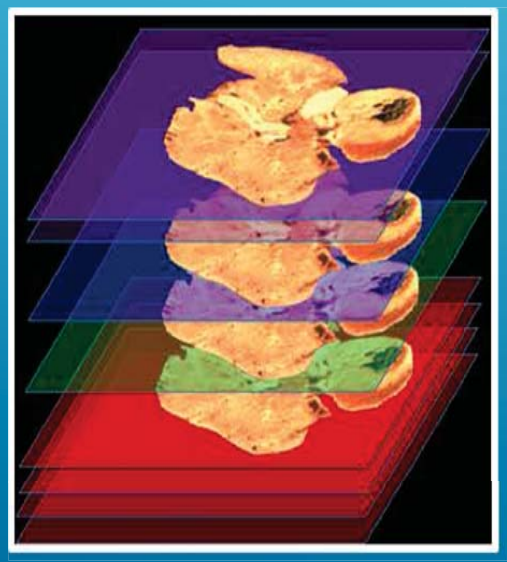
IR MALDESI Visualizes PANO In Vascular Spaces (70%) and Follicles (30%)

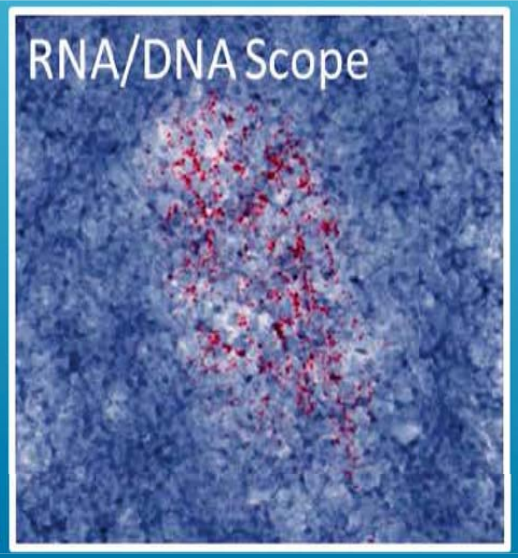


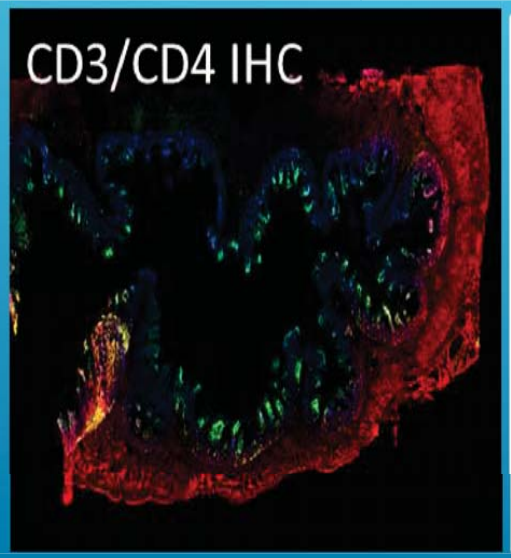
IHC PD1 Staining of NHP Lymph Nodes

Rosen et al IAS 2017

ADDITIONAL INSIGHTS WITH MSI







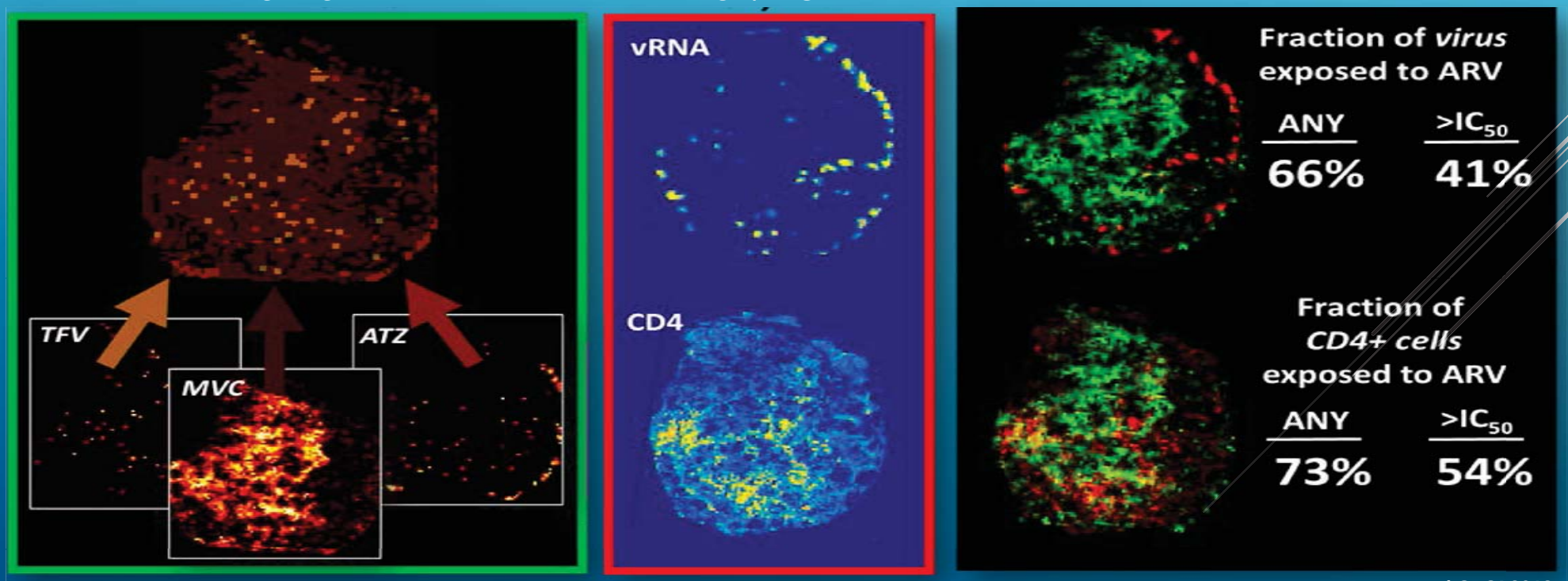
Rosen et al 2017

LYMPHOID TISSUE MSI:
LYMPH NODE OVERLAY FOR PK/PD?

Total ARV Exposure in Lymph Node + Viral Expression or Target Cell Distribution = Image Fusion of ARV and vRNA or CD4+ T Cells

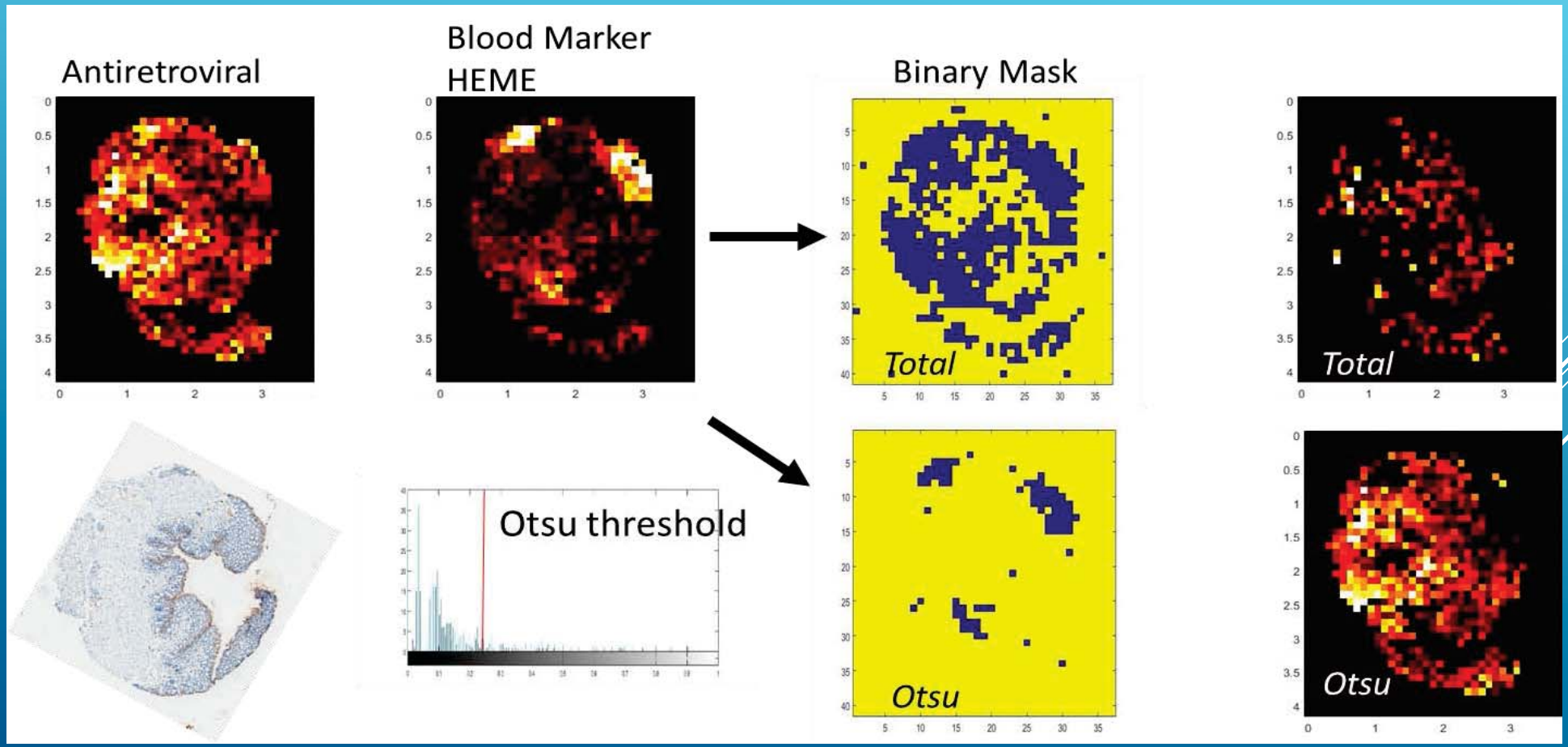
IR-MALDESI MSI

ISH/IHC

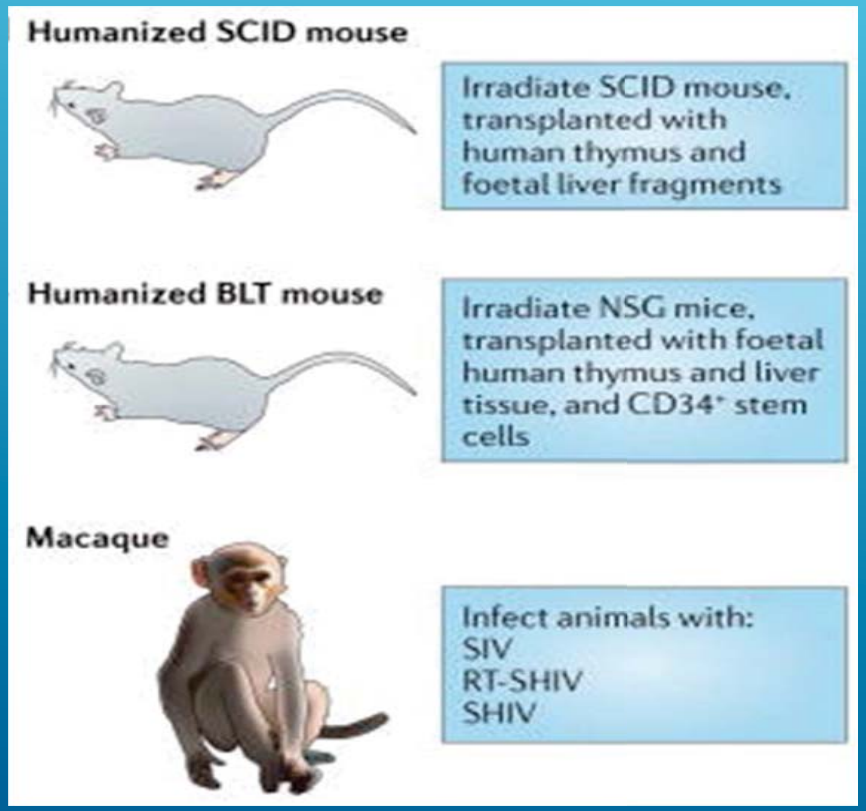


Rosen et al CROI 2018

MSI OF ARVS IN TISSUES:
CORRECTING FOR BLOOD CONTAMINATION



FACTORS AFFECTING DRUG DISTRIBUTION IN ANIMALS

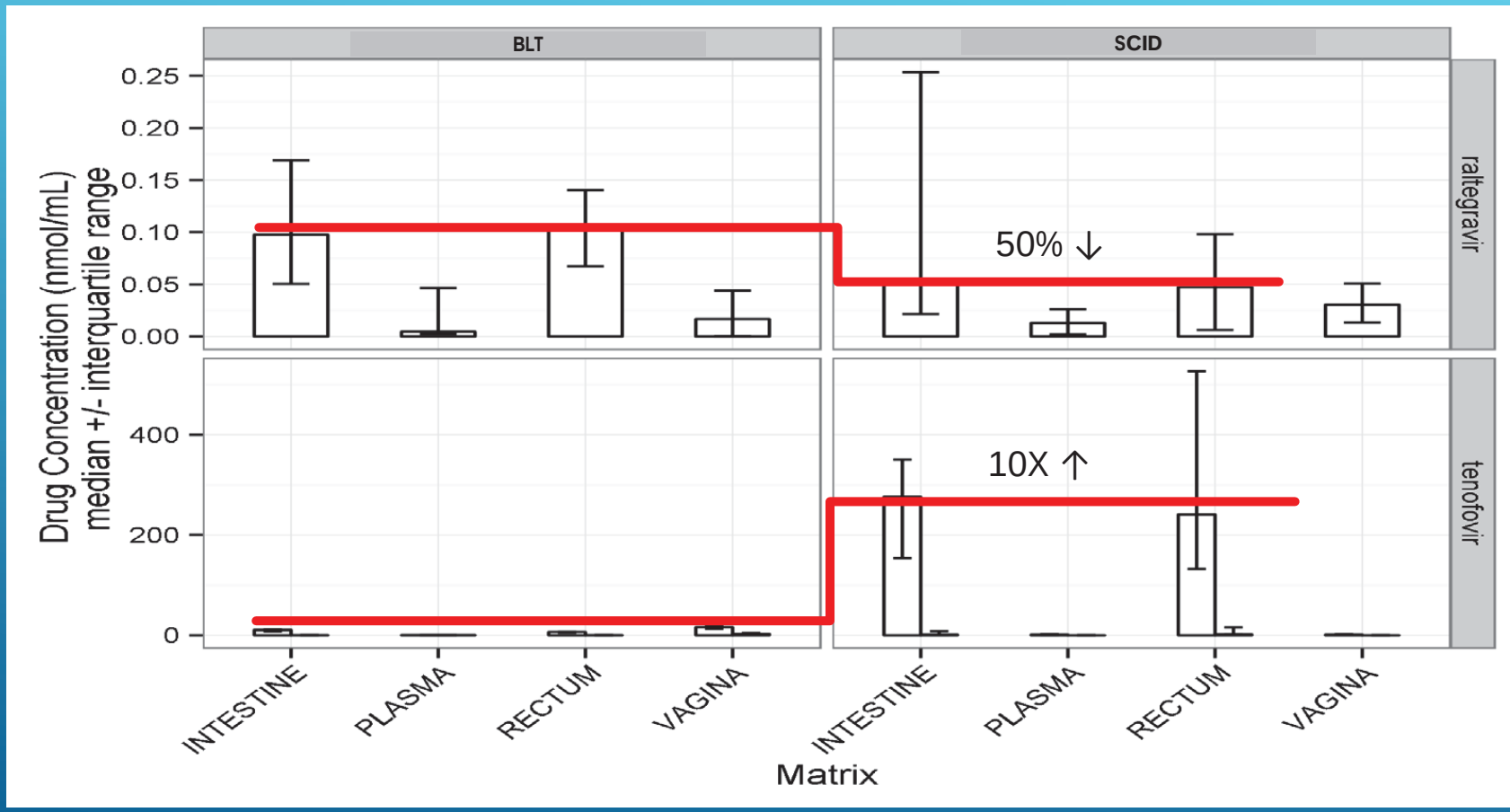


- Drug distribution differences?
  - Drug transporter activity
  - Protein binding
  - Intracellular activation
  - Other local barriers

  …changing the way drug is distributed from one model to the next

ANIMAL ARV TISSUE DISTRIBUTION VARIABLE BETWEEN MODELS

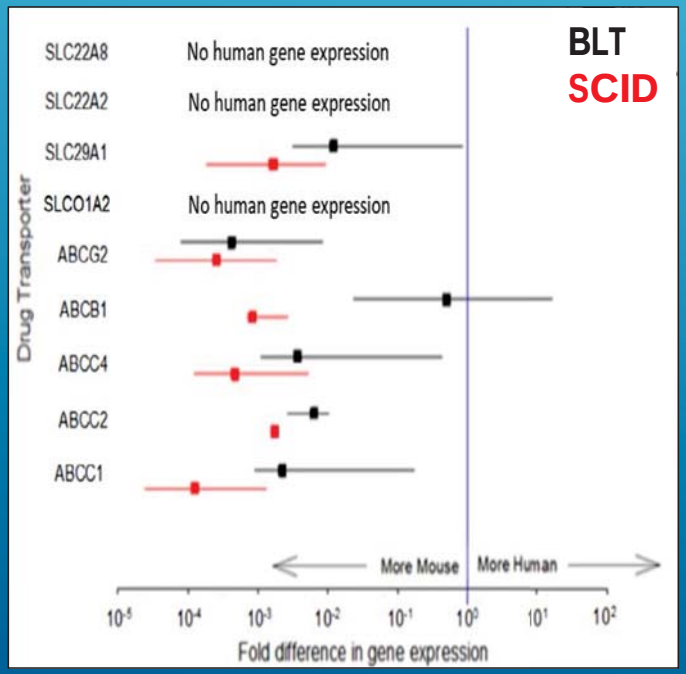
RALTEGRAVIR AND TENOFOVIR IN BLT VS SCID MICE GIVEN THE SAME DOSE



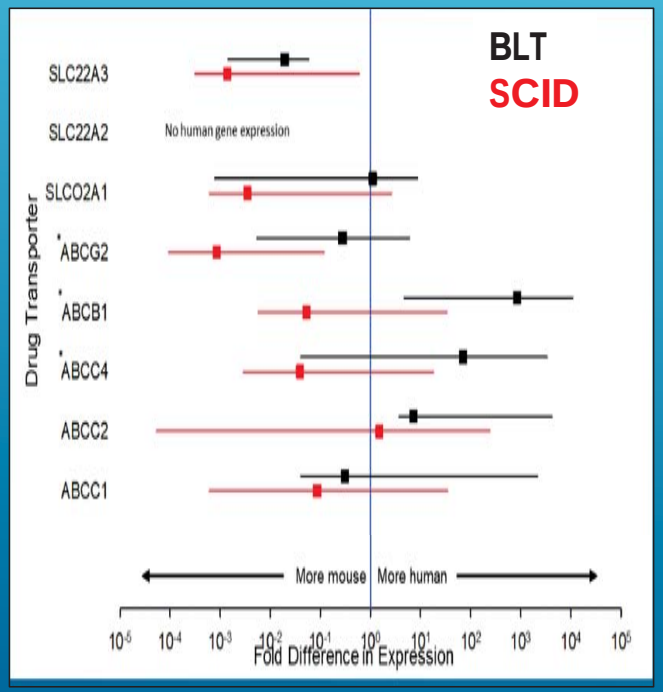
Denton et al. IAS 2013. Plos Pathogens 2013, Akkina et al IAS 2013

HUMANIZED MOUSE DIFFERENCES IN TRANSPORTER GENE EXPRESSION

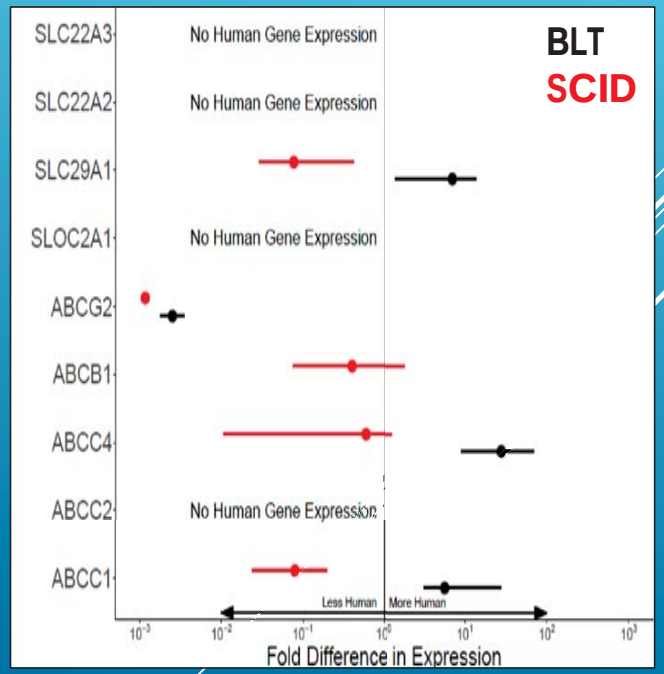
BRAIN



SPLEEN



ILEUM



Srinivas, Burgunder, Devanathan et al. Unpublished data 2018

SUMMARY

- HIV infection still a major cause of morbidity
  - Once ART is stopped, viral rebound inevitably occurs
- Long lived infected cells in privileged anatomic sites cause of slow reservoir decay
  - active viral replication in tissues is controversial, but likely occurs to some extent
- Cure strategies primarily focused on a functional cure
  - a combination of small molecules and immunotherapy (eg shock and kill)
- Unclear which latency reversal model (cells and animals) will be most predictive of efficacy

SUMMARY

- Pharmacologic insights will be critical to streamlining drug development
  - Hollow fiber cell models for PK/PD screening to identify dosing strategies, promising combination therapy, and optimal sequencing of combinations
  - Mass Spec Imaging promising for studying drug distribution and effect in tissues
  - Better prediction of drug penetration in tissue compartments
  - Understanding species differences in tissue PK/PD to develop accurate allometry for cure
    - If we cure a mouse/NHP can we cure a human?

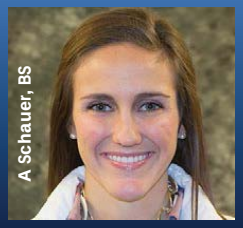
ACKNOWLEDGEMENTS

KASHUBA LAB MEMBERS

Clinical Pharmacology/ Pharmacometrics/ Clinical Trials

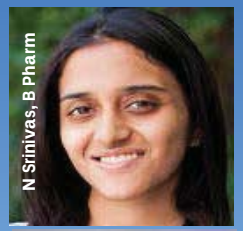
Bioanalytical Chemistry/ Mass Spectroscopy Imaging

M Gilliland, PhD



Laboratory Operations/ QA

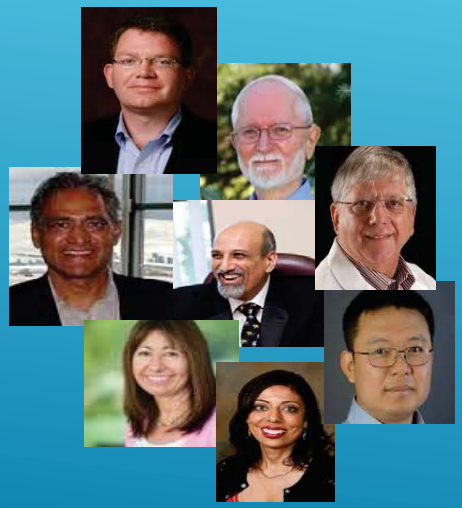
Learners



ACKNOWLEDGEMENTS

UNC Collaborators

External Colleagues/Collaborators



GSK/Viiv
Abbott
Gilead
Tibotec
Merck
Colorado State
UC Davis
FHI360
CAPRISA
FACTS
USAID
CONRAD

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T32 GM086330
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K23 AI077355
U01 AI095031
P30 AI050410
U19
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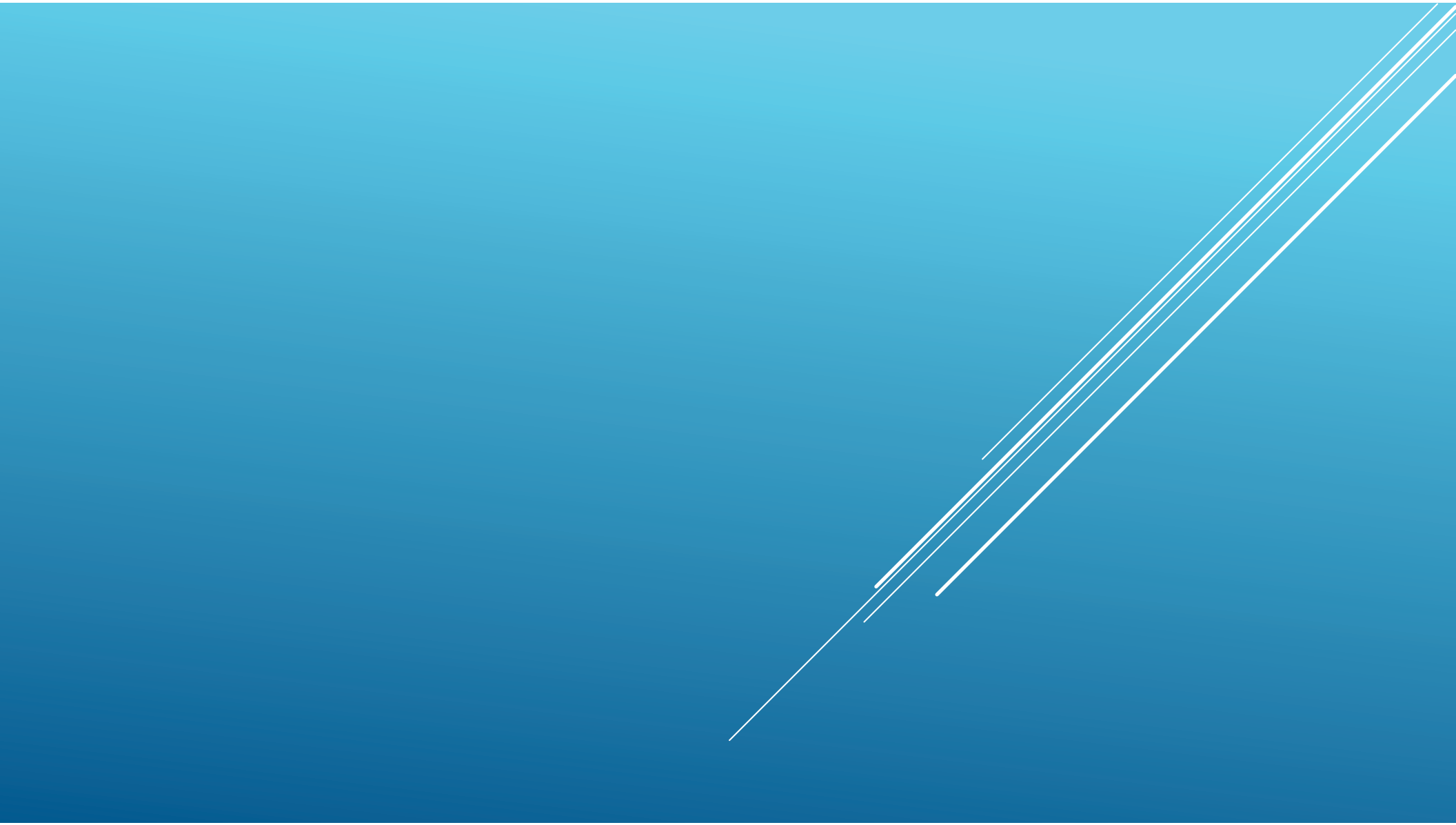
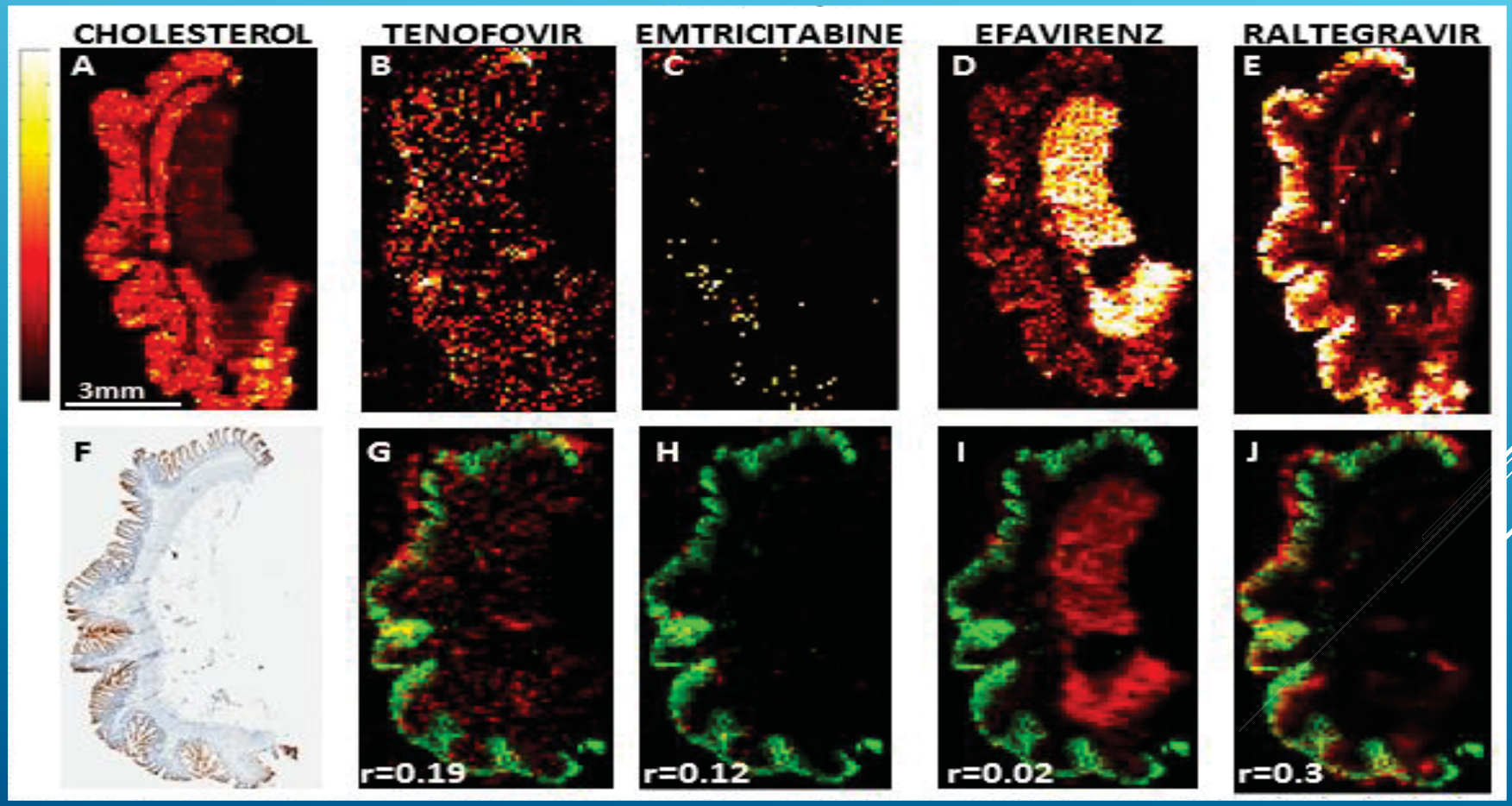
P01
MH094177
R01 AI096138

UNC ESHELMAN SCHOOL OF PHARMACY | UNC SCHOOL OF MEDICINE | HIV CARE Collaboratory of AIDS Researchers for Eradication | University of North Carolina Center for AIDS Research | qura THERAPEUTICS


IT ALWAYS SEEMS
IMPOSSIBLE
UNTIL IT'S DONE.
- NELSON MANDELA
LABORATORY HAZARD INFORMATION
1100 GMRB
cap
ACCREDITED



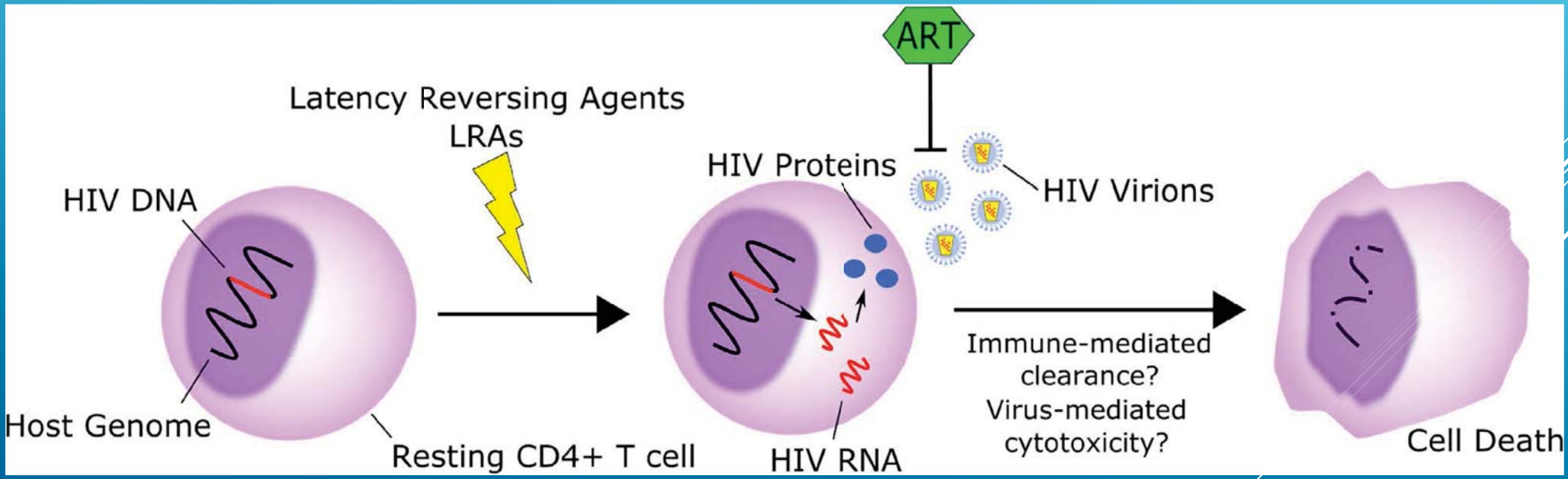
LYMPHOID TISSUE MSI:
INTESTINAL TRANSPORTER OVERLAY



Thompson et al. STM In review 2018

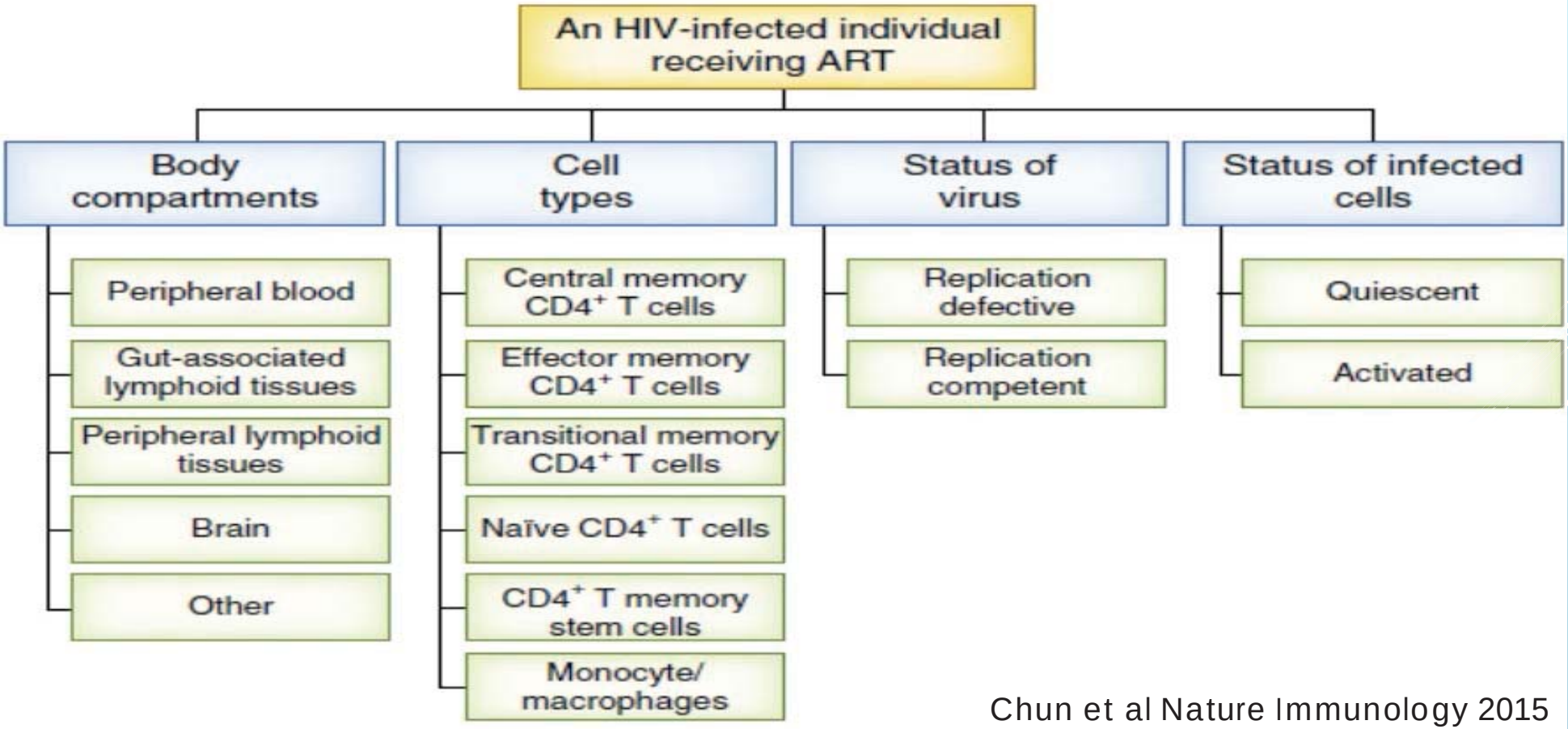
e 1
characteristics of the selected studies.

thor	HDAC inhibitor	Number of Participants	HDAC inhibitor's Regimen	Changes in Resting CD4+ T cells HIV RNA	Other outcomes
chin et al. [28]	Vorinostat	5	Daily Vorinostat Monday through Wednesday for 8 weekly cycles	After dose 11 (second dose of cycle 4) or dose 22 (second dose of cycle 8) increased significantly in only 3 of the 5 participants, and the magnitude of the increase was much reduced compared with that after a single dose	Changes in histone acetylation were blunted. Quantitative viral outgrowth and total cellular HIV DNA were unchanged
chin et al. [25]	Vorinostat	8	A single oral 200 mg dose for assessing tolerability, then 400 mg dose 4 (or more) weeks later	An increase of 1.5- to 10.0-fold (mean 4.8) in expression of unspliced HIV-1 *gag* RNA within resting CD4 + T cells was measured in seven patients	
iott et al. [28]	Vorinostat	20	Vorinostat was administered 400 mg orally once daily for 14 days while maintaining ART	Cell associated unspliced HIV RNA in blood increased significantly in 18/20 patients (90%) with a median fold change from baseline to peak value of 7.4 (IQR 3.4, 9.1).	There were no statistically significant changes in plasma HIV RNA, concentration of HIV DNA, integrated DNA, inducible virus in CD4+ T-cells or markers of T-cell activation.
th et al. [35]	Romidepsin	20	Participants received 6 therapeutic intradermal HIV-1 immunizations with 12 mg/mL Vacc-4 x and 0·6 mg/mL rhuGM-CSF over 12 weeks (at 0 weeks, 1 week, 2 weeks, 3 weeks, 11 weeks, and 12 weeks) before receiving 5 mg/m2 intravenous Romidepsin once a week for 3 weeks.	No major changes in the CD4 T-cell compartment during Romidepsin infusions	Total HIV-1 DNA declined from screening to 6 weeks after Romidepsin treatment (mean reduction 39.7%, 95% CI −59.7 to −11.5; p = .012). The decrease in integrated HIV-1 DNA from baseline to 8 weeks after Romidepsin treatment was not significant between four (24%) and eight (47%) of 17 patients had detectable plasma HIV-1 RNA throughout the course of the study t (19.2%, −38.6 to 6.3; p = .123).
smussen, [32]	Panobinostat	15	Oral Panobinostat 20 mg 3 times/week every other week for 8 weeks while maintaining combination antiretroviral therapy (cART)	Levels of CA-US RNA increased significantly during Panobinostat treatment (p < .0001) with significant increases on time points on-treatment as compared to baseline. The median maximal fold-increase in CA-US RNA was 3.5 (range 2.1–14.4). Levels of CA-US RNA remained elevated 4 weeks post-Panobinostat (fold-increase 1.60; 95% CI: 1.17–2.19; P = .003)	Using a transcription mediated amplification-based semi-quantitative assay (Procleix Ultrio Plus, 59% analytic sensitivity of 3.6 copies/mL), HIV-RNA in plasma was detected more frequently during Panobinostat administration with an odds ratio of 10.5 (95% CI: 2.2–50.3) for a positive test on-treatment compared to baseline
gaard et al. [29]	Romidepsin	6	One 4 h Romidepsin infusion (5 mg/m2) per week for three consecutive weeks and were followed for up to 70 days after the last infusion	HIV-1 transcription quantified as copies of cell-associated un-spliced HIV-1 RNA increased significantly from baseline during treatment (range of fold-increase: 2.4–5.0; p = .03).	Plasma HIV-1 RNA increased from < 20 copies/mL at baseline to readily quantifiable levels at multiple post-infusion time-points in 5 of 6 patients (range 46–103 copies/mL following the second infusion, p = .04).
pia [37]	Romidepsin	20	Six Vacc-4 x (1.2 mg) intradermal immunizations using rhuGM-CSF (60 μg) as adjuvant were followed by 3 weekly intravenous infusions of romidepsin (5 mg/m^2).		Participants with CD8 + T-cell proliferation assay positivity post-vaccination showed reductions in total HIV DNA post-vaccination (p = .006; q = 0.183), post-latency reversal (p = .005; q = 0.183), and CA-RNA reductions post-vaccination (p = .015; q = 0.254). Participants (40%) were defined as proliferation 'Responders' having ≥2-fold increase in assay positivity post-baseline. Robust ELISpot baseline responses were found in 87.5% participants. No significant changes were observed in the proportion of polyfunctional CD8+ T-cells to HIVGag by ICS. There was a trend towards increased viral inhibition from baseline to

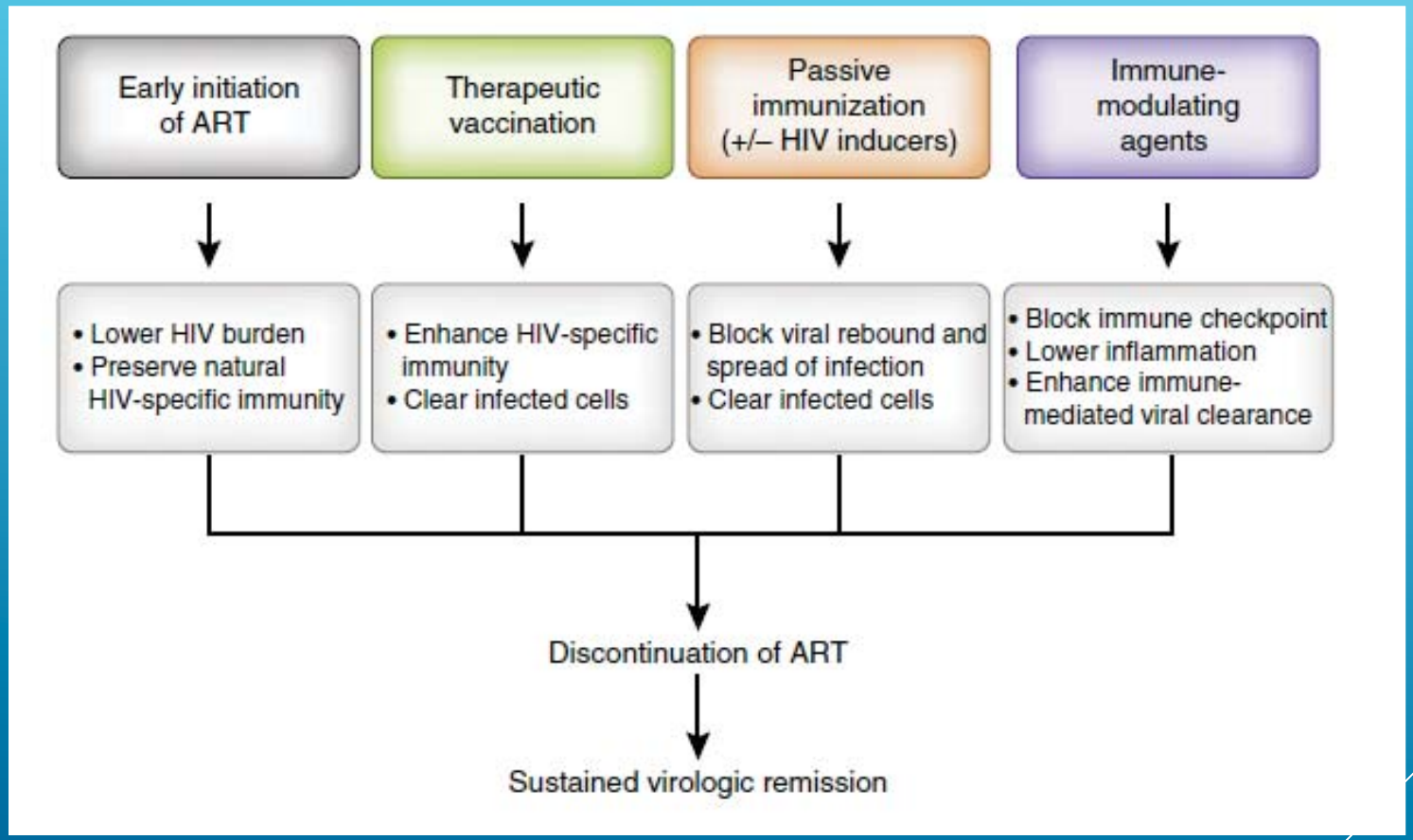


Kim et al. Cell Host and Microbe, 2018

COMPLEX NATURE OF HIV RESERVOIRS



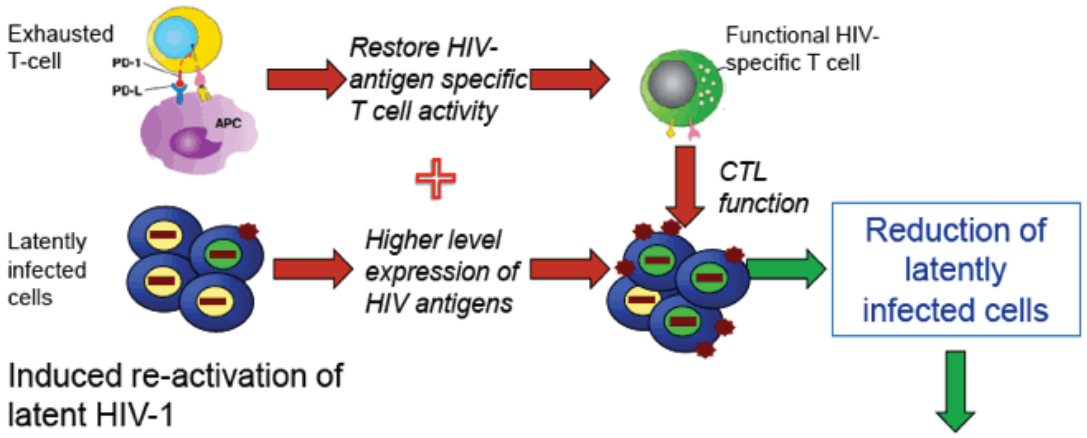
Chun et al Nature Immunology 2015



Chun et al Nature Immunology 2015

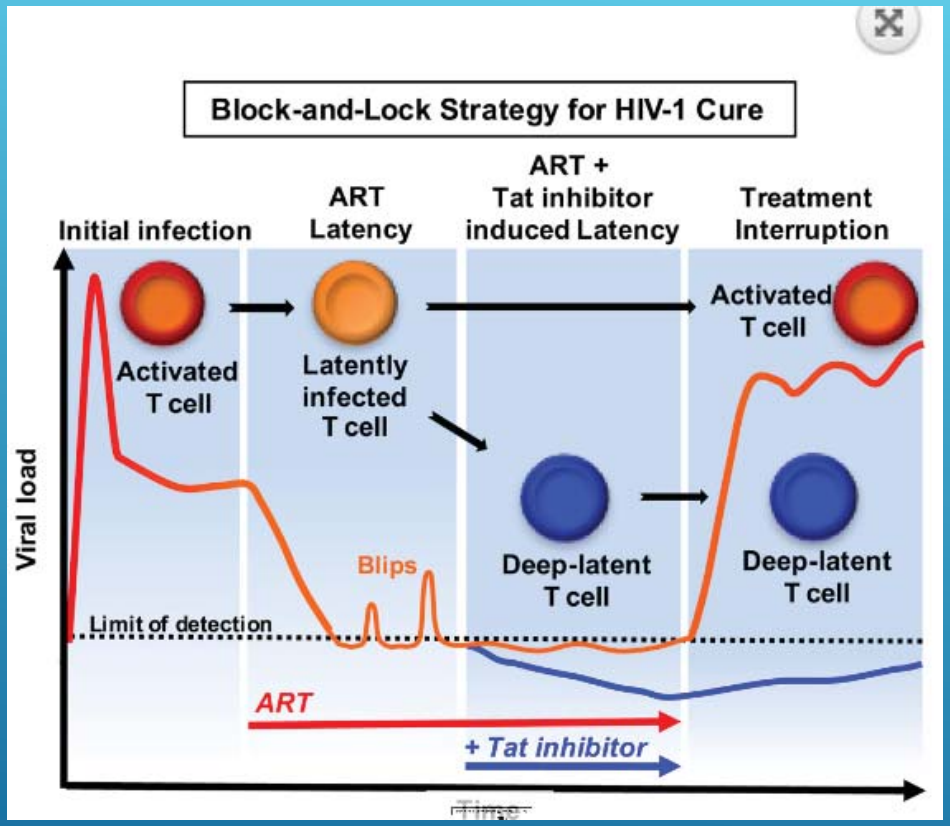
BMS Strategy for HIV-1 Functional Cure:
Dual Approach

Treatment with αPD-L1



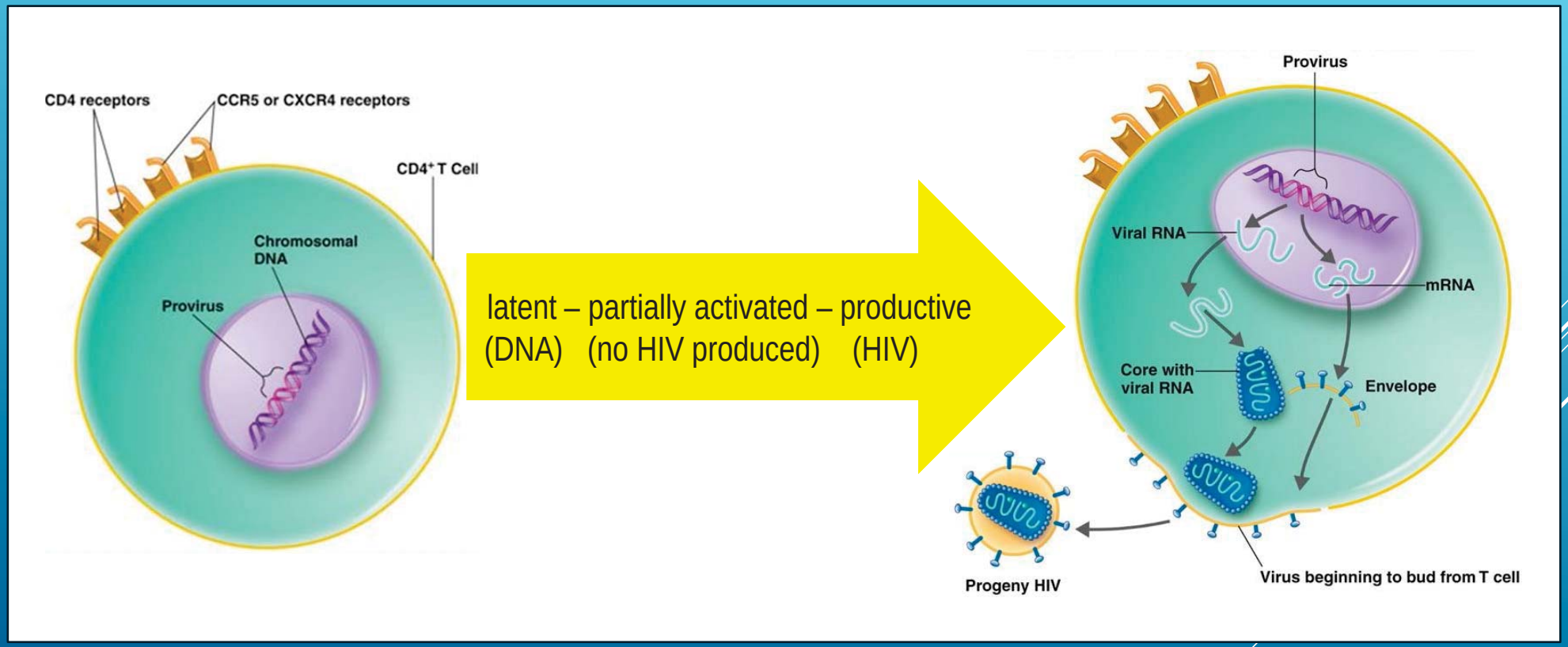
Induced re-activation of latent HIV-1

HIV-1 Functional Cure?



re (Kessing et a1., 2017: doi: 10.1016/j.celrep.2017.09.080)

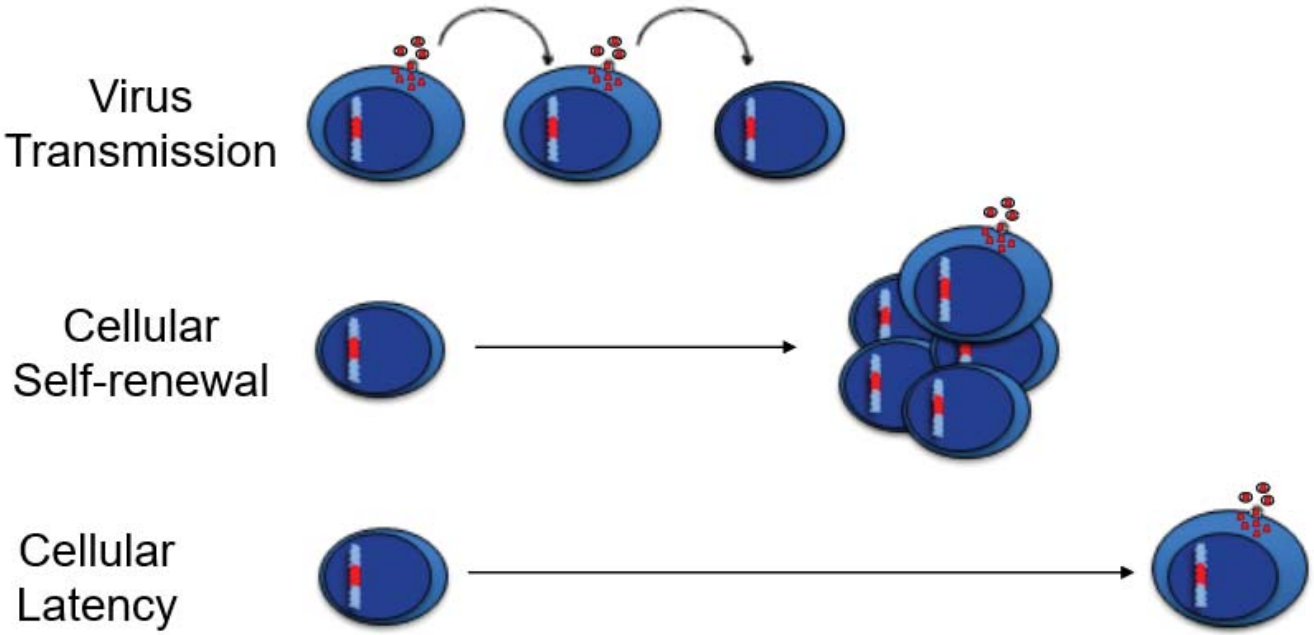
SUBCLASSES OF INFECTED CELLS



Fischer, Retrovirology 2008
Althaus, PLoS Comp Biol, 2015
Yukl, STM, 2018

Adapted from Huldrych, CROI 2018

Three Histories of HIV-infected Cells In Vivo



Multiple mechanisms govern these events

From DC Douek, MD, MRCP, PhD at Atlanta, GA: April 8, 2016, IAS-USA.

Boston Patients: Virus Recrudescence

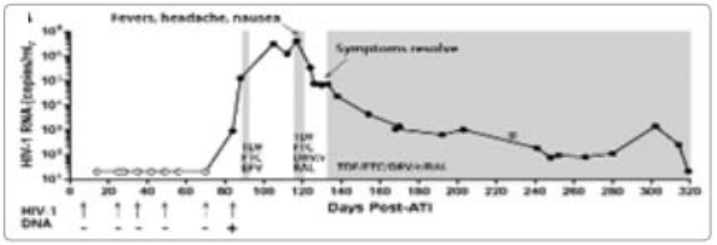
Hematopoietic transplantation with cells susceptible to infection

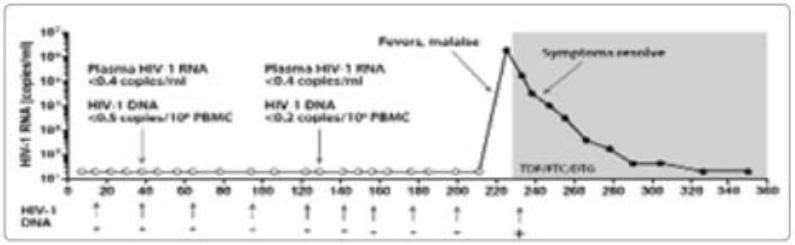
Annals of Internal Medicine | ORIGINAL RESEARCH

Antiretroviral-Free HIV-1 Remission and Viral Rebound After Allogeneic Stem Cell Transplantation

Report of 2 Cases

Timothy J. Henrich, MD; Emily Hanhauser, BS; Francisco M. Marty, MD; Michael N. Sirignano, BS; Sheila Keating, PhD; Tzong-Hae Lee, MD, PhD; Yvonne P. Robles, BA; Benjamin T. Davis, MD; Jonathan Z. Li, MD; Andrea Heisey, BS; Alison L. Hill, PhD; Michael P. Busch, M.D. PhD; Philippe Armand, MD, PhD; Robert J. Soiffer, MD; Marcus Altfeld, MD, PhD; and Daniel R. Kuritzkes, MD





Despite 1000 – 10,000 fold reductions in reservoir size, virus rebounded

Modeling: latent reservoir will have to be depleted > 10^5 fold (Hill, *PNAS* '14)

A single virus accounts for recrudescence

From DC Douek, MD, MRCP, PhD at Atlanta, GA: April 8, 2016, IAS-USA.

STRATEGIES TO A CURE

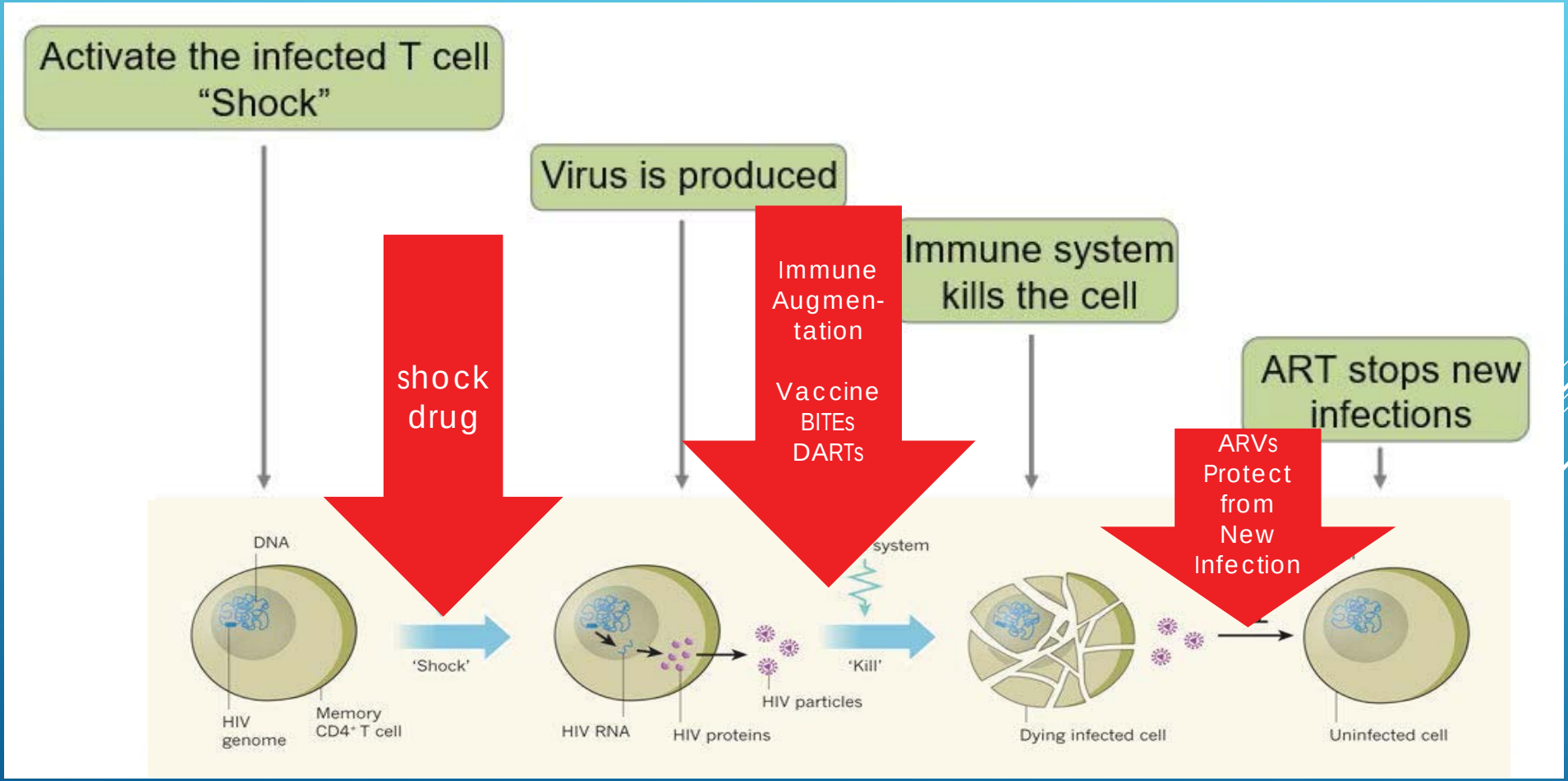
FUNCTIONAL CURE

- Immune mediated control of viral replication
- Eg elite controllers; boosting the immune system
- ART may be withdrawn without subsequent viral rebound (eg "complete remission" after treatment for malignant cancer)
- But these strategies my results in increased inflammation/ comorbidities

STERILIZING CURE

- Elimination of all HIV-infected cells from the body
  - infected cells not visible to host defenses
  - frequency of HIV-specific CD8 T cells typically decreases with ART and often have "exhausted" (or dysfunctional) phenotype
  - Infected cells broadly distributed to sites relatively inaccessible to host defenses or treatment

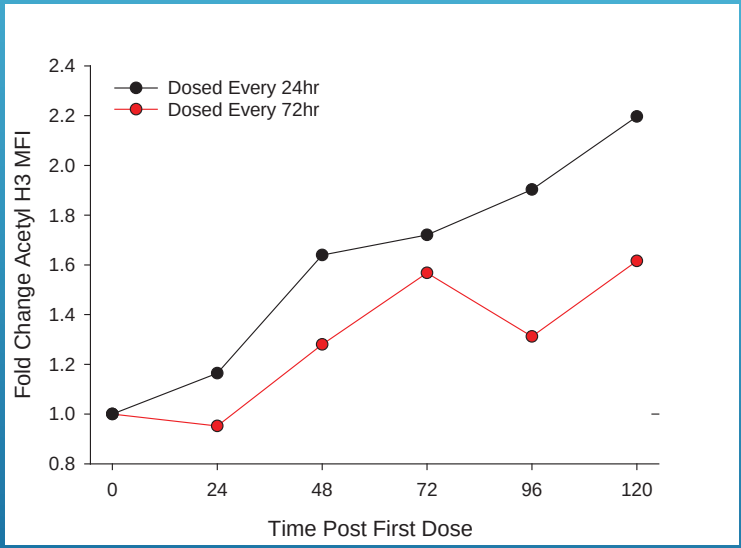
SHOCK AND KILL STRATEGY



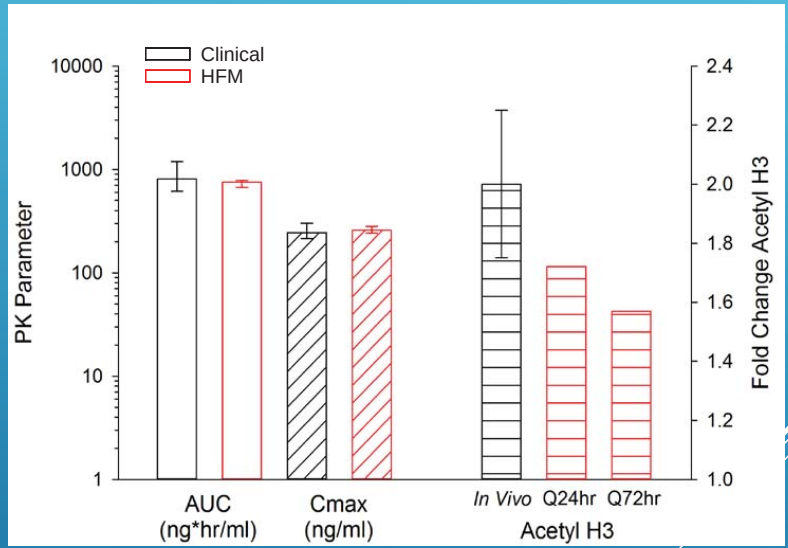
Deeks, Nature Med 2012; D Douek, April 2016, IAS USA

PREDICT PD BY SIMULATING *IN VIVO* PK

PD Measured over Time

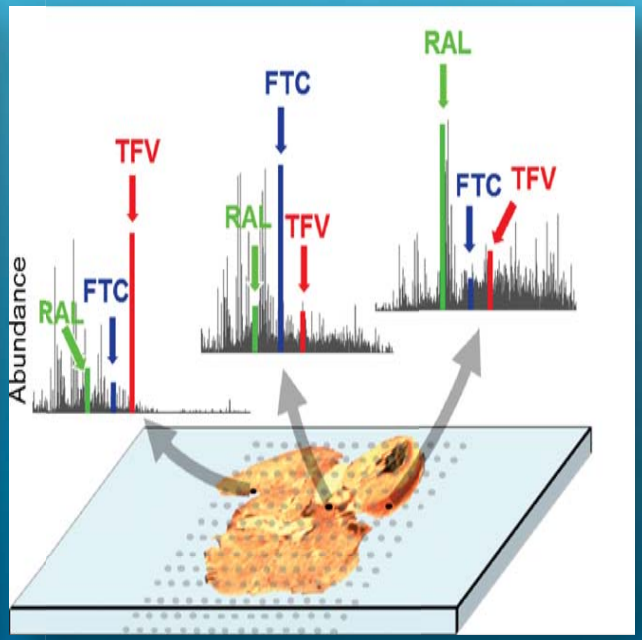


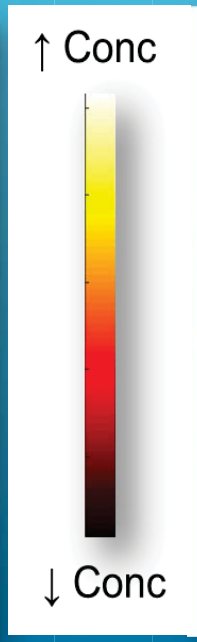
Clinical vs *In Vitro* PK/PD

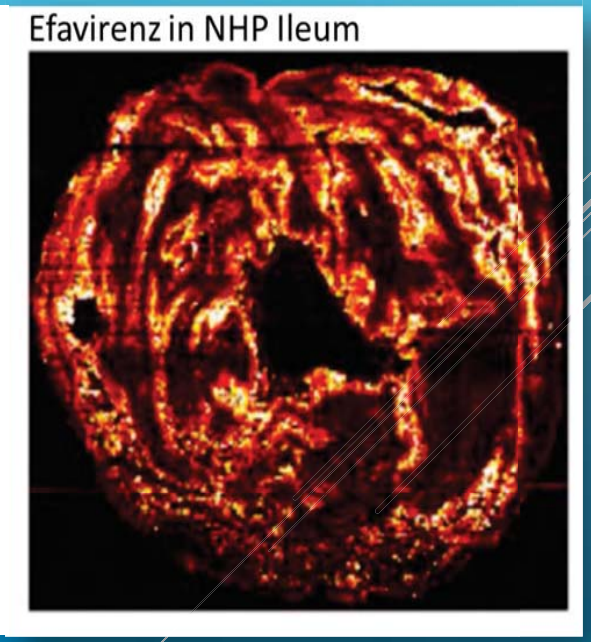


MSI (IR MALDESI)

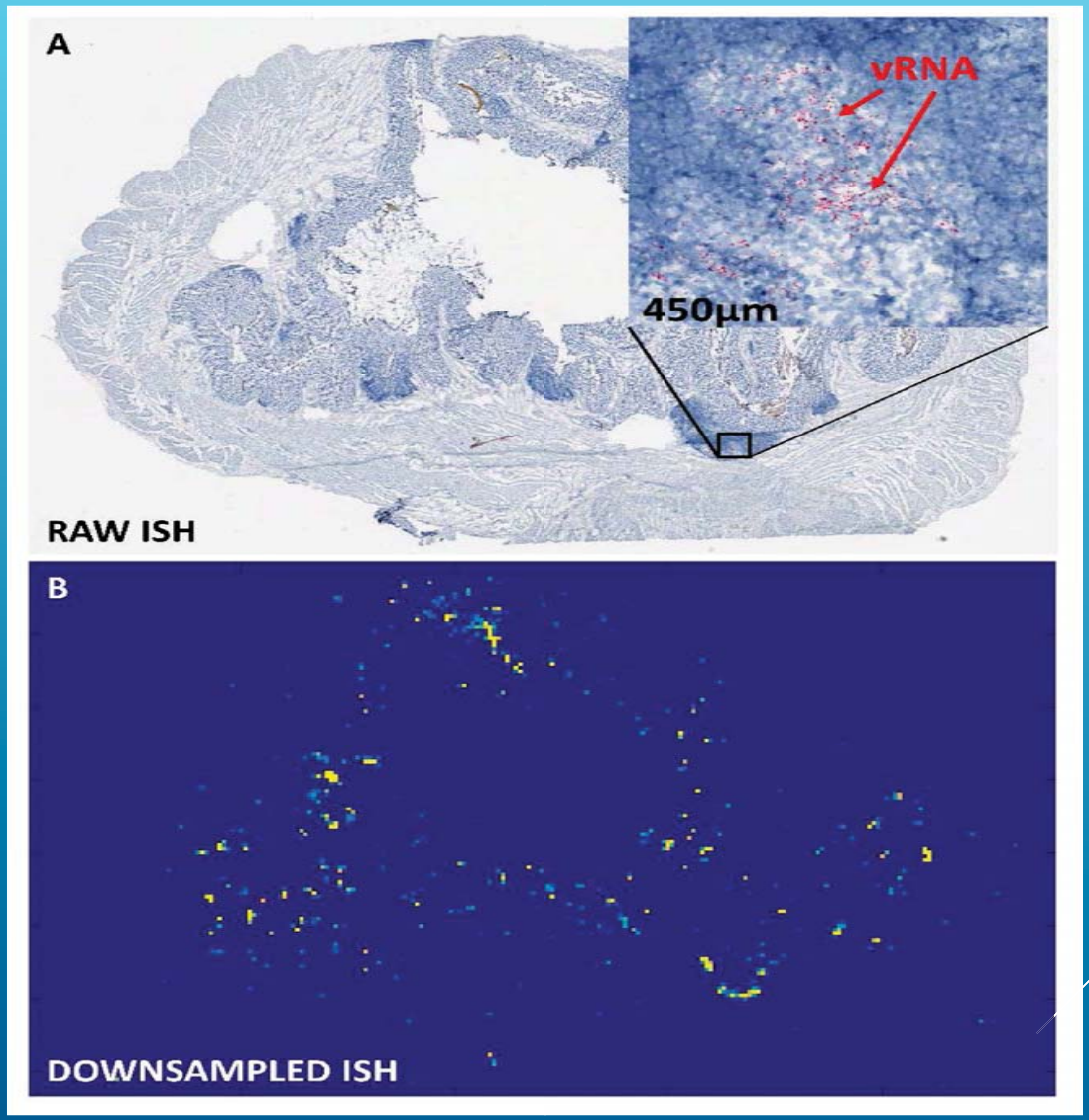
QUANTITATIVE INFRARED MATRIX ASSISTED LASER DESORPTION ELECTROSPRAY IONIZATION







Thompson, et al. Antimicrob. Agents Chemother. 201


A
vRNA
450µm
RAW ISH
B
DOWNSAMPLED ISH