

New Frontiers for Treatment Strategies for HIV Care

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Disclosures:

- Research support from Abbott, GSK, Merck, Pfizer, ViiV, Gilead
- Consultant/Advisor for BMS, Gilead, ViiV, Merck
- Member of the DHHS Guidelines Panel for the use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (volunteer position)

Overview

- How to thrive with HIV
- Finding the right provider
- What to know about antiretrovirals
 - When start
 - What start
 - Stopping therapy
 - Changing therapy
- Evolving issues in the management of HIV infection
- HIV transmission while on antiretroviral therapy

How to thrive with HIV

- It is all about you
- Take care of yourself
 - Emotional health
 - Physical health
- Seek out the support you need
 - Friends and family
 - Healthcare providers
- Establish a functional relationship with a provider

Finding the right provider

- Ideally via referral from someone you trust or through AIDS Services organization
- Characteristics of the provider
 - Personable
 - At least several years of experience treating HIV (ask him/her)
 - Currently managing at least 20 patients with HIV and has substantial portion of their practice dedicated to this patient population
 - Someone you feel comfortable talking to and that you feel is listening

What you need to address with your provider

- Health maintenance
 - Psychiatric issues
 - Social issues
 - Cardiovascular risk factors
 - Drugs and alcohol
 - Tobacco
 - Exercise
 - Vaccines
 - Cancer screening
- Antiretroviral therapy

What you need to know about medication options

- Starting antiretrovirals is usually life-time commitment
- Key to success is good adherence which means medications should be easy to take and well tolerated
- You and your provider are a team
- Selecting from amongst the options
 - What do guidelines recommend?
 - What is your providers preferences and why?
 - Dosing frequency
 - Drug and food interactions
 - Anticipated side effect: what, how often and how quickly
- Share with your provider ideas you get from friends and other sources, e.g. internet (not all information is good)

What you need to know once you get started

- Exactly how the medications should be taken
- What to do if you miss a dose
- That the first regimen will not necessarily be your last and can be changed for various reasons
 - Poor tolerance (lots of options)
 - Lifestyle change
 - Emerging options
- Goal is to get to undetectable viral load and stay there
 - Intermittent increases in viral load occur and are nothing to panic about
 - CD4 cells bounce around

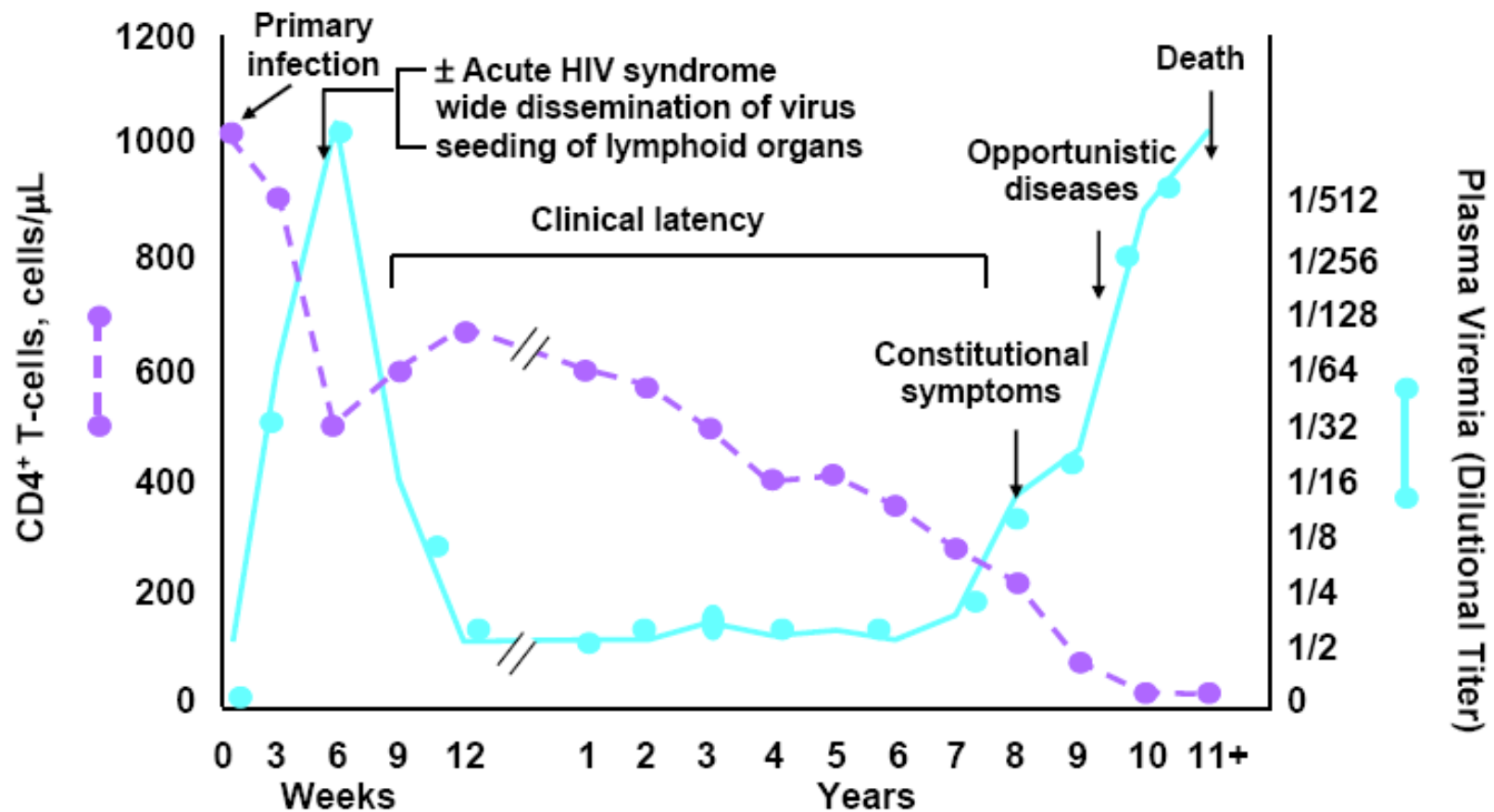
Antiretroviral therapy: When to start therapy

- When you are ready
 - Your life situation is such that you can make a commitment to treatment
 - You have a provider you feel comfortable with
 - The timing is right for you
 - Data driven
 - Personal

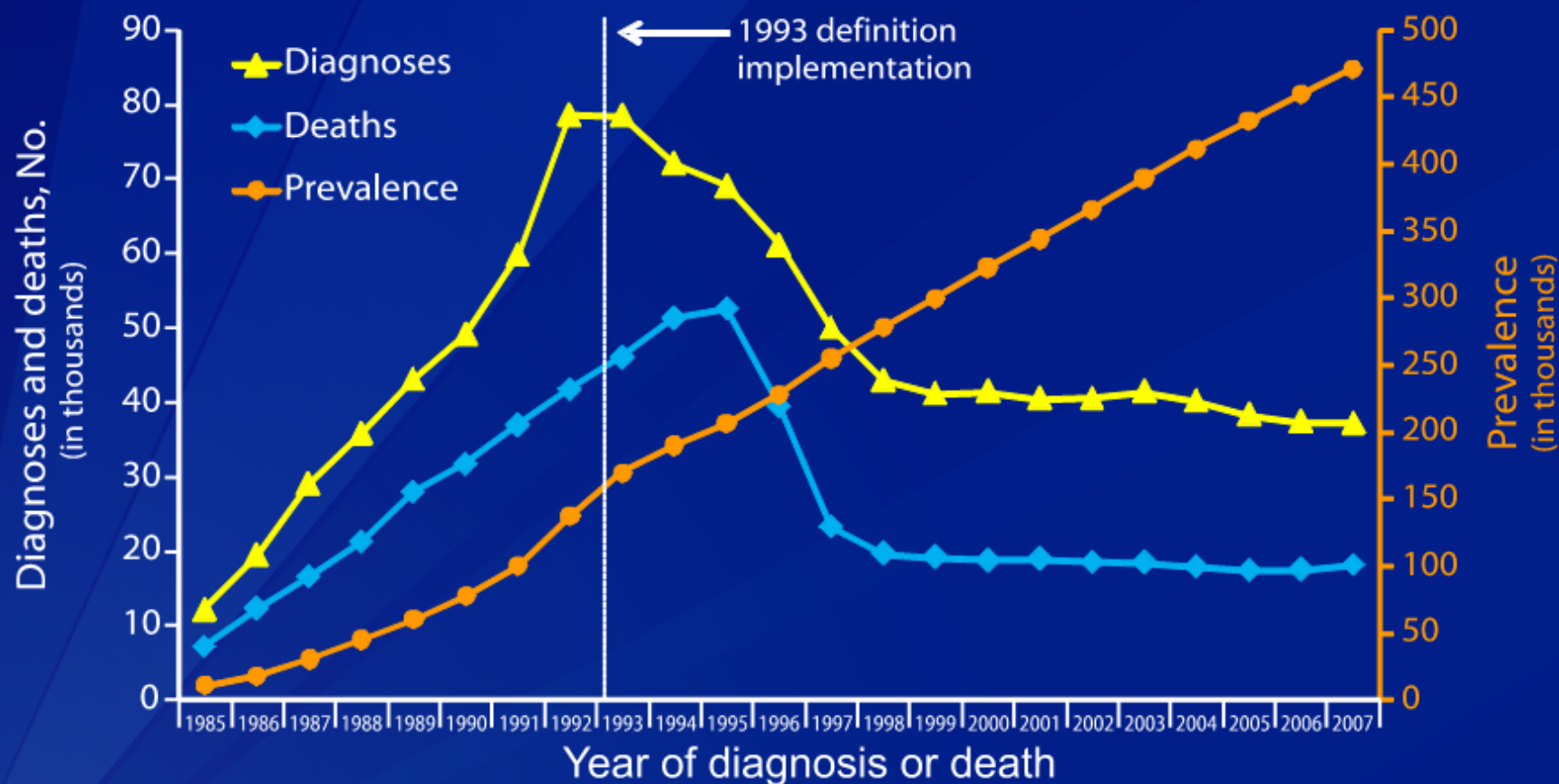
Traditional case made for delaying therapy

- Not ready to commit to treatment
- Short-term and long-term toxicity
- Need for life long therapy
- Risk of virologic failure, resistance and cross-resistance
- Limited evidence for earlier therapy being associated with better outcomes than delayed therapy

Natural History of HIV Infection



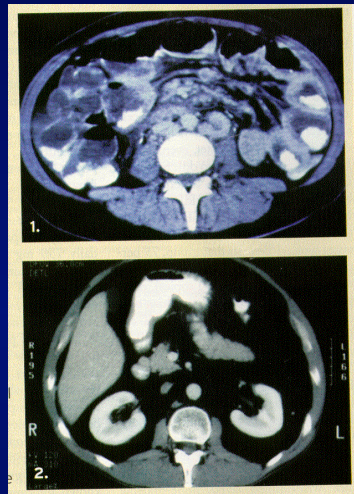
AIDS Diagnoses, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas



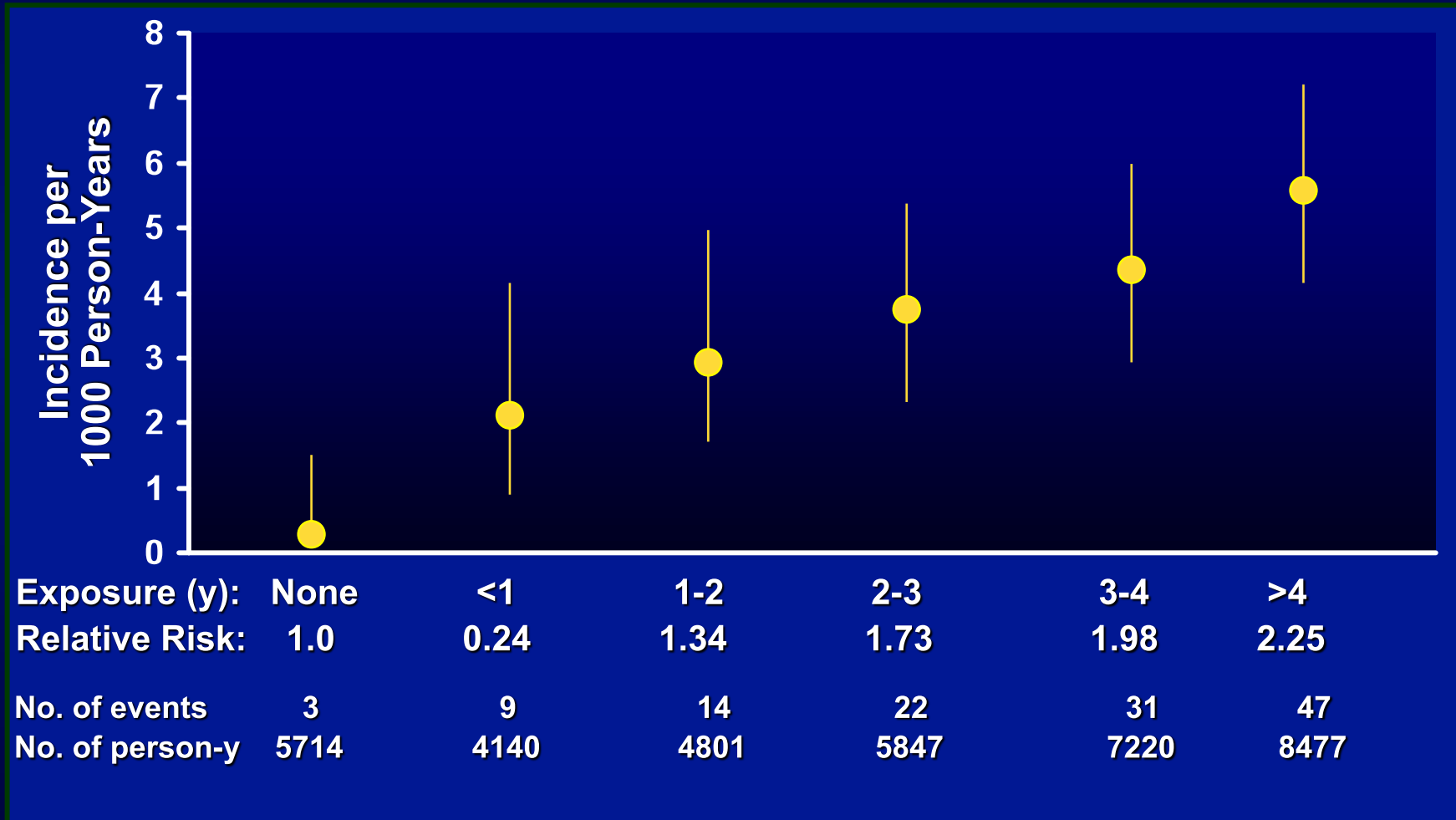
Note. All displayed data have been estimated. Estimated numbers resulted from statistical adjustment that accounted for reporting delays, but not for incomplete reporting.



Physical Manifestations of Fat Redistribution Syndromes

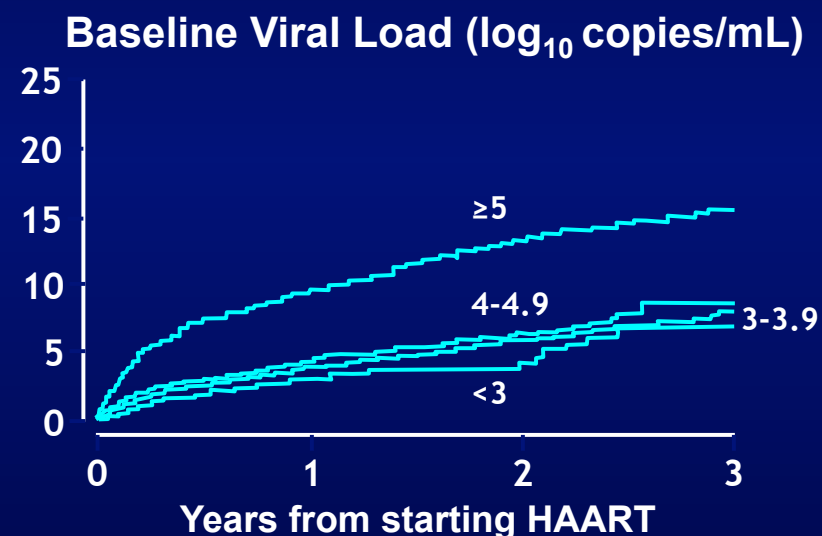
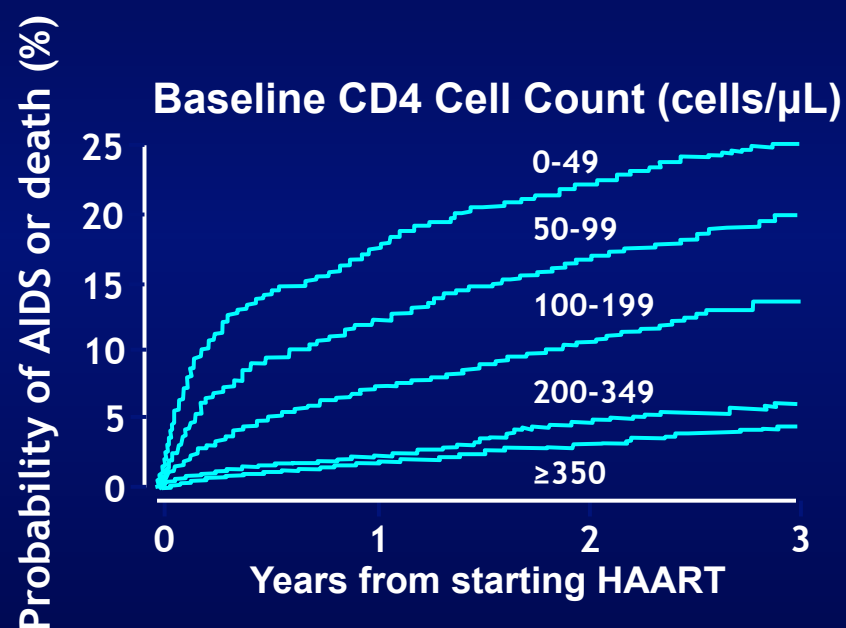


Myocardial Infarction and Duration of Combination ART (D:A:D Study)



Friis-Møller N et al. *N Engl J Med.* 2003;349:1993-2003.

When to Initiate ARV Therapy: Effect of Baseline CD4 and HIV RNA Level

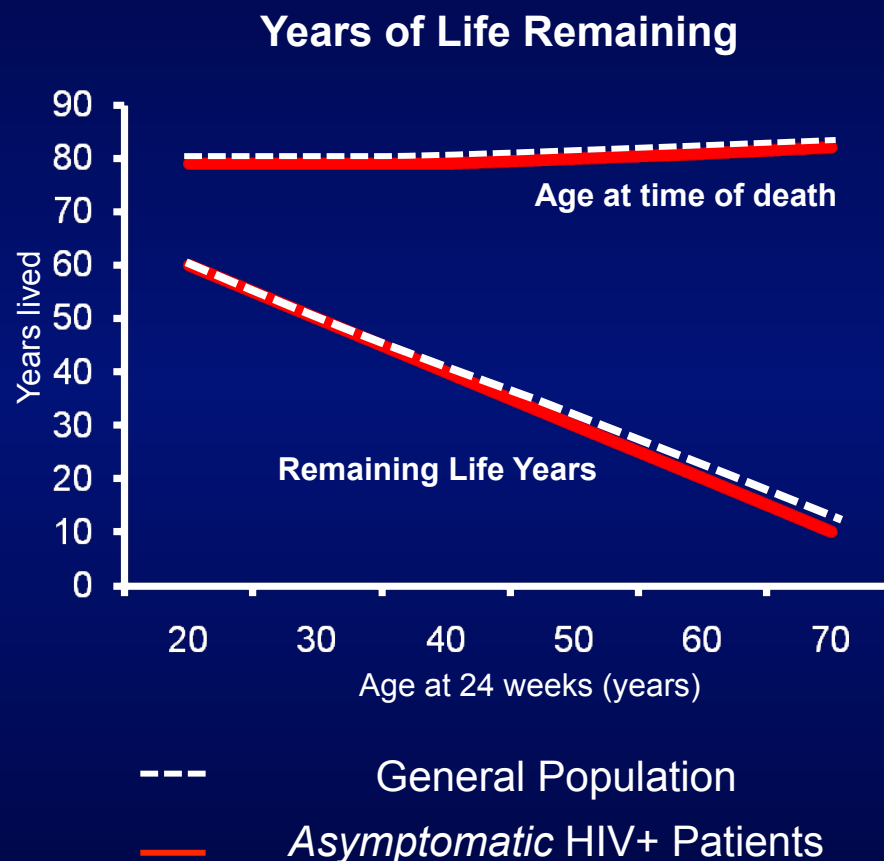


HAART=highly active antiretroviral therapy.

Egger M et al. *Lancet*. 2002;360:119-129.

Life Expectancy of HIV-Infected Patients

- Life expectancy of Athena cohort to general population (n=4,174)
- Expected life years remaining at age 25
 - 53.1 (44.9-59.5) for general population
 - 52.7 for asymptomatic HIV+ patients

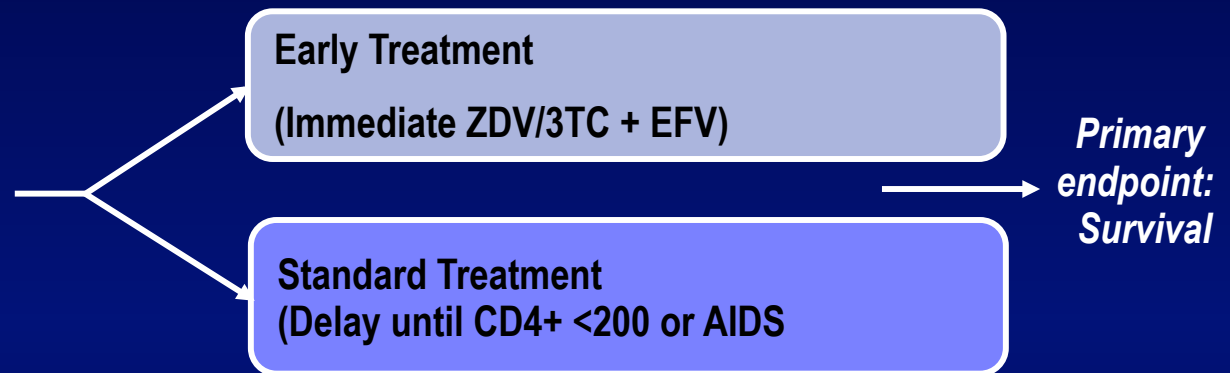


Case for Earlier Therapy

CIPRAHT001: Randomized Trial of When to Start ART in Haiti

Randomized clinical endpoint study of when to start therapy

- Treatment-naïve
- No hx AIDS-defining illness
- CD4 200-350



Baseline Characteristics	Early (n=408)	Standard (n=408)
Median age (years)	40	40
Male (%)	41%	44%
Median CD4+ (cells/mm ³)	280	282
Body Mass Index (kg/m ²)	21.4	21.0

CIPRAHT001: Clinical Endpoints

May 2009: DSMB review stopped study due to excess deaths in Defer Treatment arm

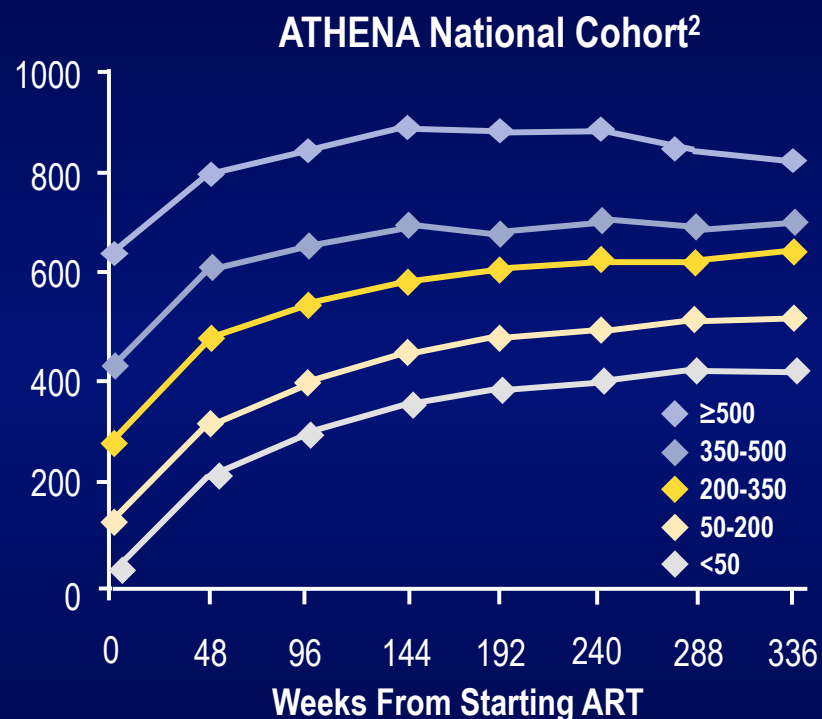
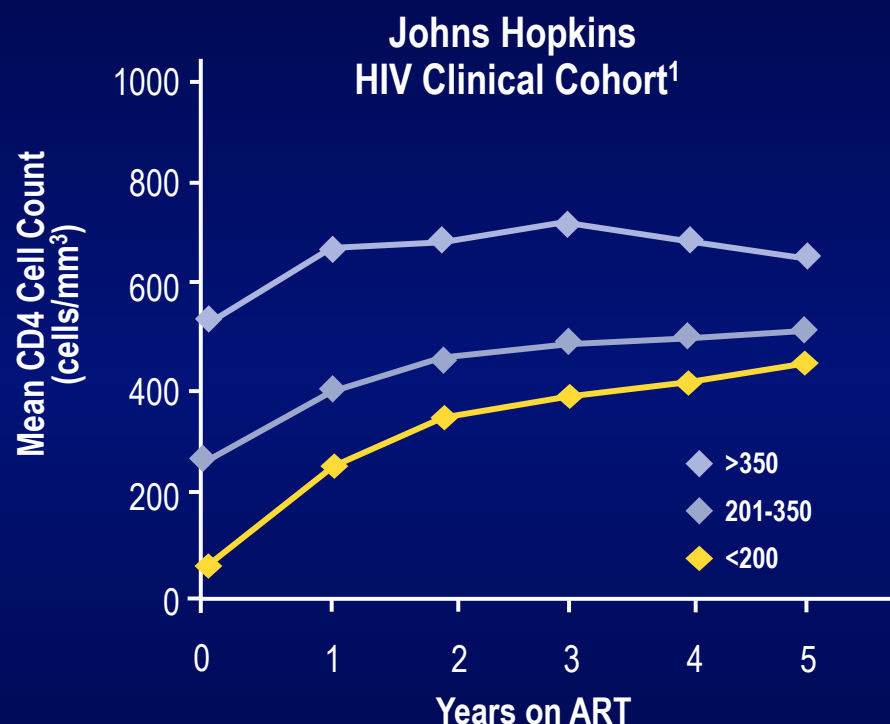
Clinical Endpoints	Early	Standard	Hazards Ratio (p value)
Death	6	23	4.0 (.0011)
Incident Tuberculosis	18	36	2.0 (.0125)

- Infectious causes of death
 - Early: 1 (gastroenteritis)
 - Standard: 17 (7 gastroenteritis, 5 TB, 4 pneumonia, 1 cholangitis/sepsis)
- More toxicity from ART and intensive need for lab f/u for deferred grp
- WHO start guidelines now modified to <350 cells/uL

NA-ACCORD: Risk of Death with ART Deferral

	351-500 CD4+			>500 CD4+		
	RR	95% CI	<i>P</i>	RR	95% CI	<i>P</i>
Deferral of ART	1.7	1.3, 2.3	<0.001	1.9	1.4, 2.8	<0.001
Female Sex	1.2	0.9, 1.6	0.24	1.9	1.3, 2.6	<0.001
Older Age (per 10 years)	1.7	1.5, 1.9	<0.001	1.8	1.6, 2.1	<0.001
Baseline CD4 count (per 100 cells/mm³)	1.1	0.7, 1.8	0.59	0.9	0.9, 1.0	0.03

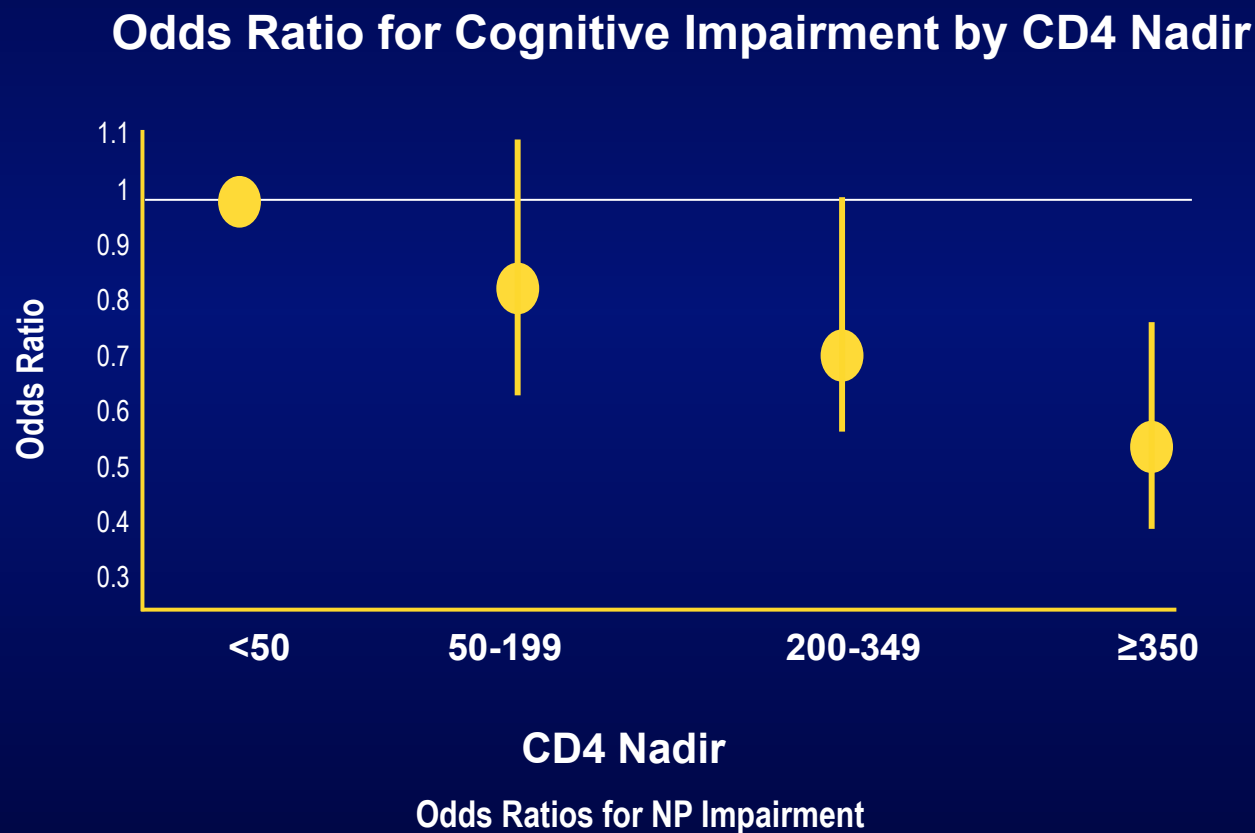
Ultimate CD4 Cell Count Depends on Where You Start



Magnitude of increase in CD4 cell count greatest if therapy started at low CD4 cell counts, but greater likelihood of CD4 cell count normalization with earlier therapy

1. Moore R, et al. Clin Infect Dis. 2007;44(3):441-446; 2. Gras L, et al. J Acquir Immune Defic Syndr. 2007;45(2):183-192.

Neurocognitive Disorders Associated with Nadir CD4 Counts



Consequences of Stopping ART: SMART Trial

HIV-1-infected
patients with
CD4+ cell count
> 350 cells/mm³

(N = 5472)

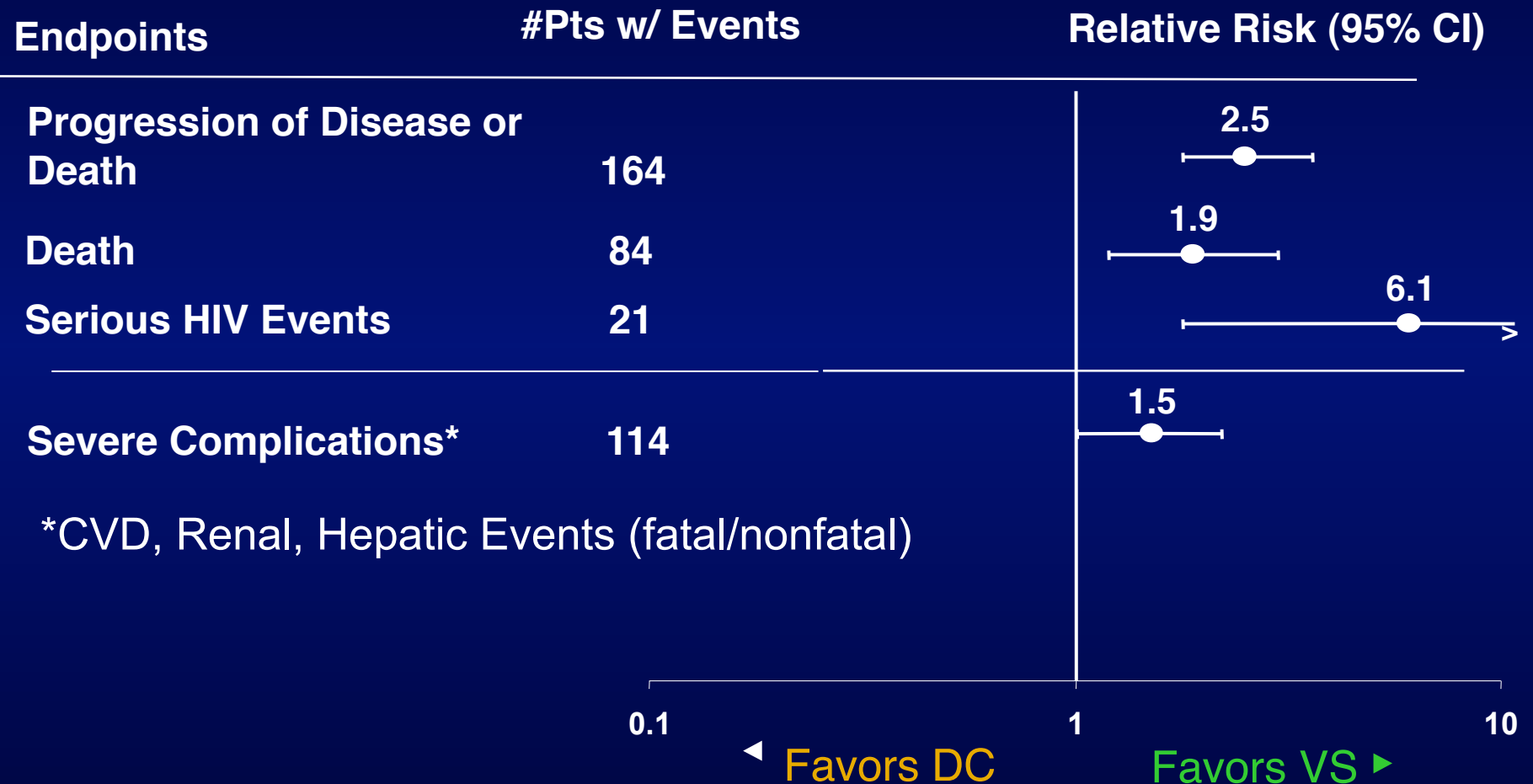
95.4% treatment
experienced



Continuous antiretroviral therapy
throughout follow-up
(n = 2752)

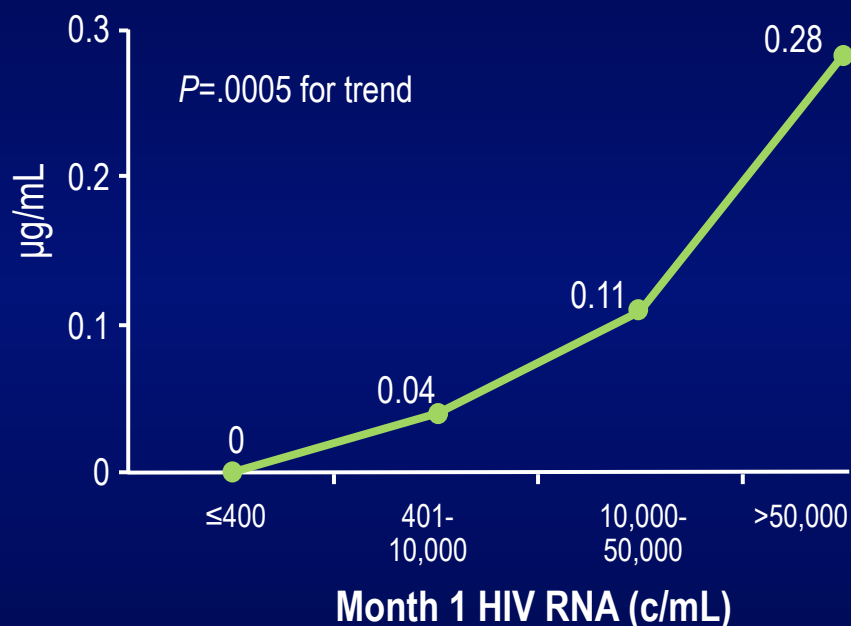
ART stopped/deferred until CD4+
<250 cells/mm³ then started to
increase CD4+ to >350 cells/mm³
(n = 2720)

SMART: Primary Endpoint and Components

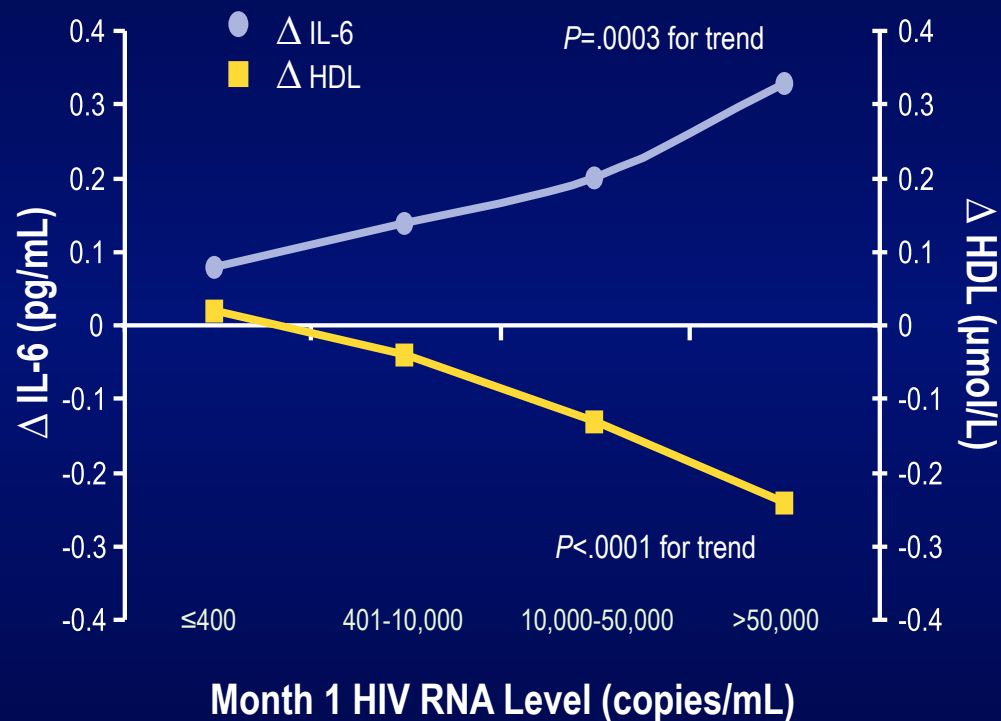


SMART: Changes in D-Dimer and IL-6 Levels

Change in D-Dimer*, BL to 1 Month



Change in Log IL-6 (pg/mL) and HDL (µmol/L) BL to 1 Month^{2*}



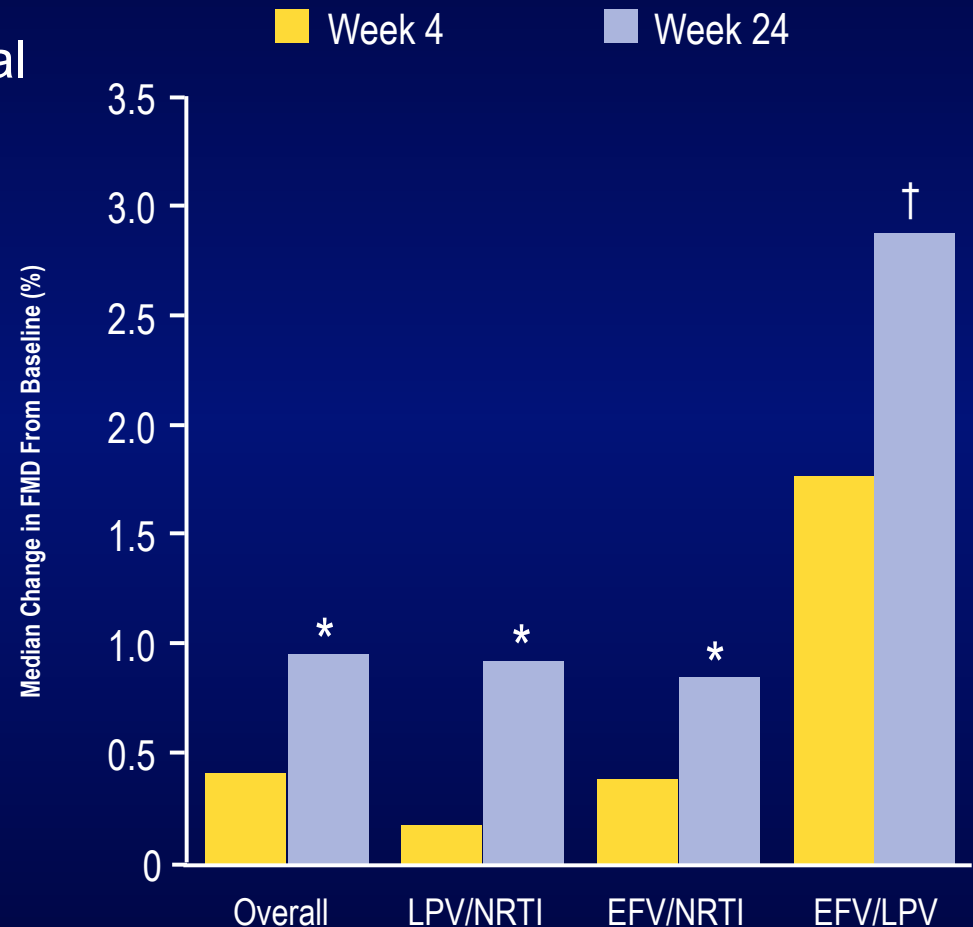
- Suggests HIV viremia effect on endothelium, leading to increased tissue factors and initiation of coagulation cascade

*DC patients on ART at baseline with HIV RNA ≤400 copies/mL

¹Kuller L, et al. PLoS 2008;10:1496-1508. ²SMART/INSIGHT: Duprez et al, CROI, 2009.

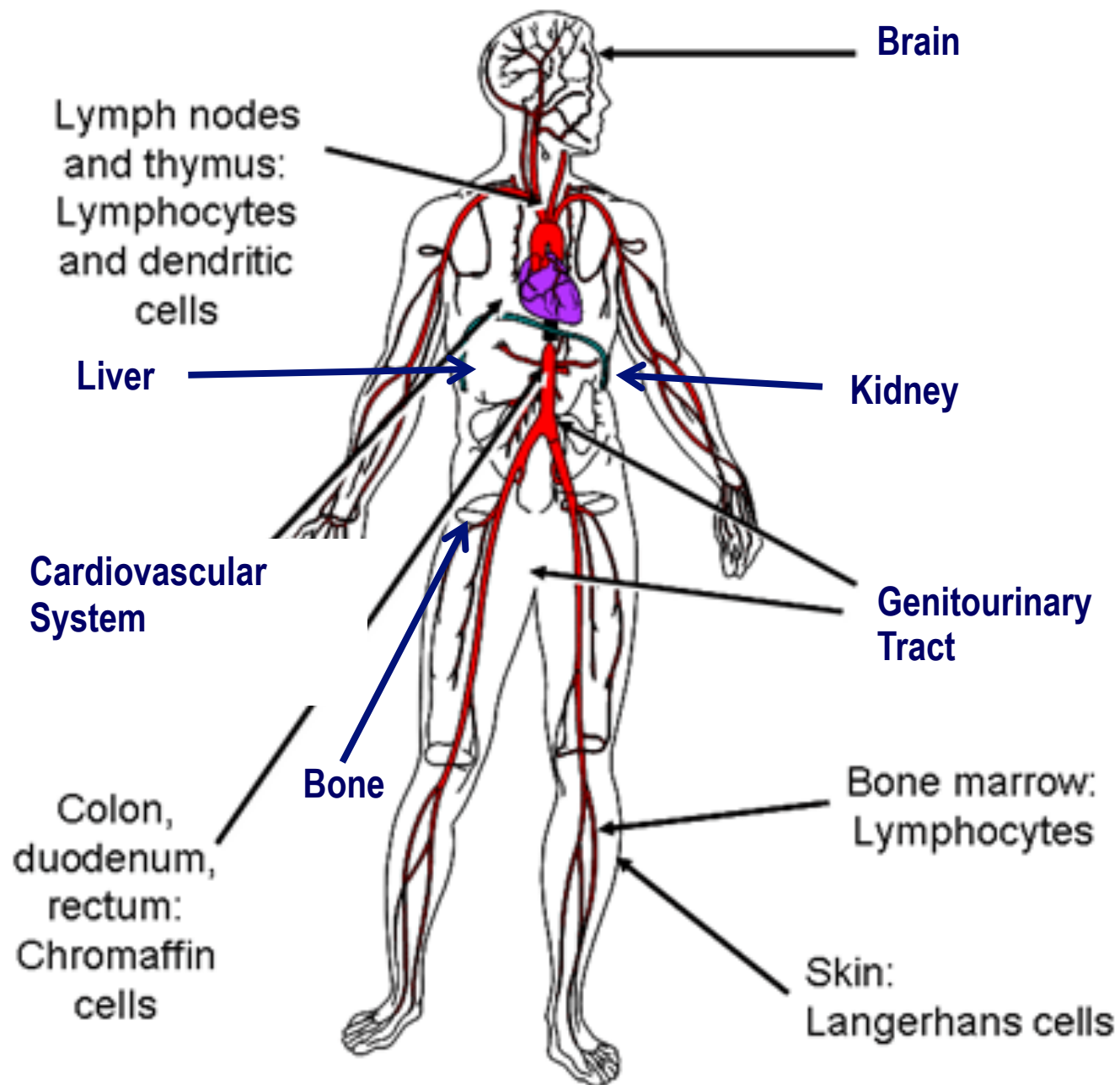
A5152s: VL Decrease Associated With Improved Endothelial Function

- HIV infection affected endothelial function
 - Baseline FMD: 3.7%
- FMD improved during HAART
- No consistent correlations between changes in FMD and changes in any lipids or glycemic parameter
- Improvement in FMD significantly associated with decrease in VL at Week 24
 - No relationship with baseline VL



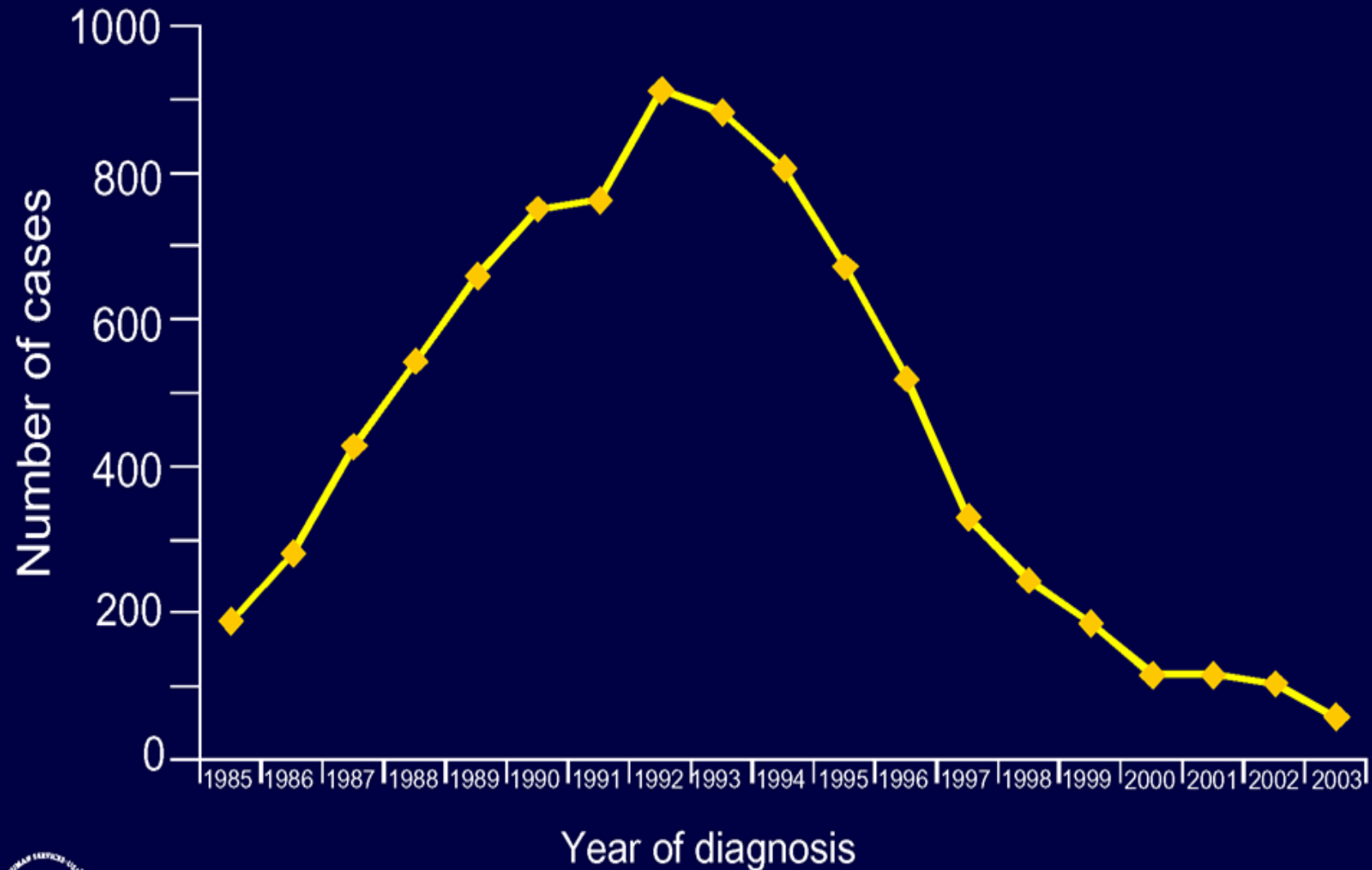
* $P < 0.01$ compared with baseline.

† $P < 0.01$ compared with baseline and within group.



Effect on Transmission

Estimated perinatally acquired AIDS cases- United States

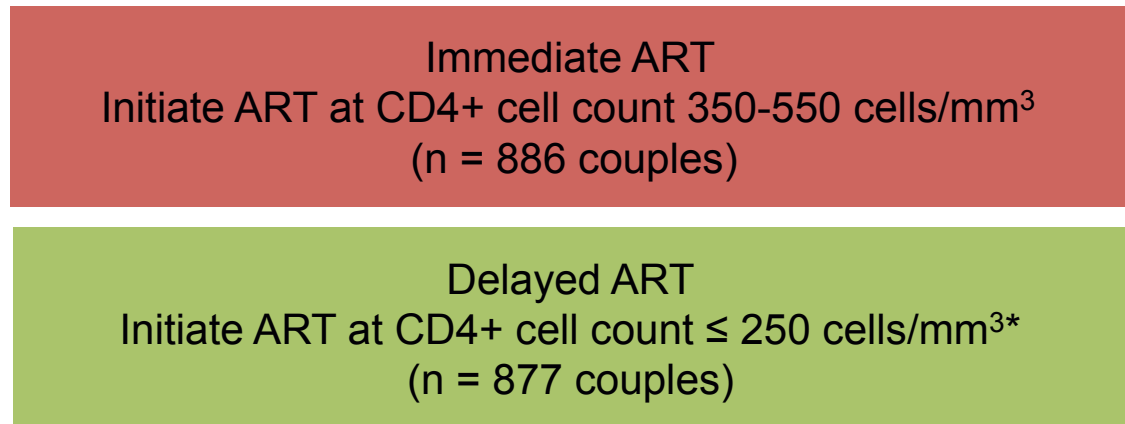


Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases in persons Initially reported without an identified risk factor.



HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm³
(N = 1763 couples)



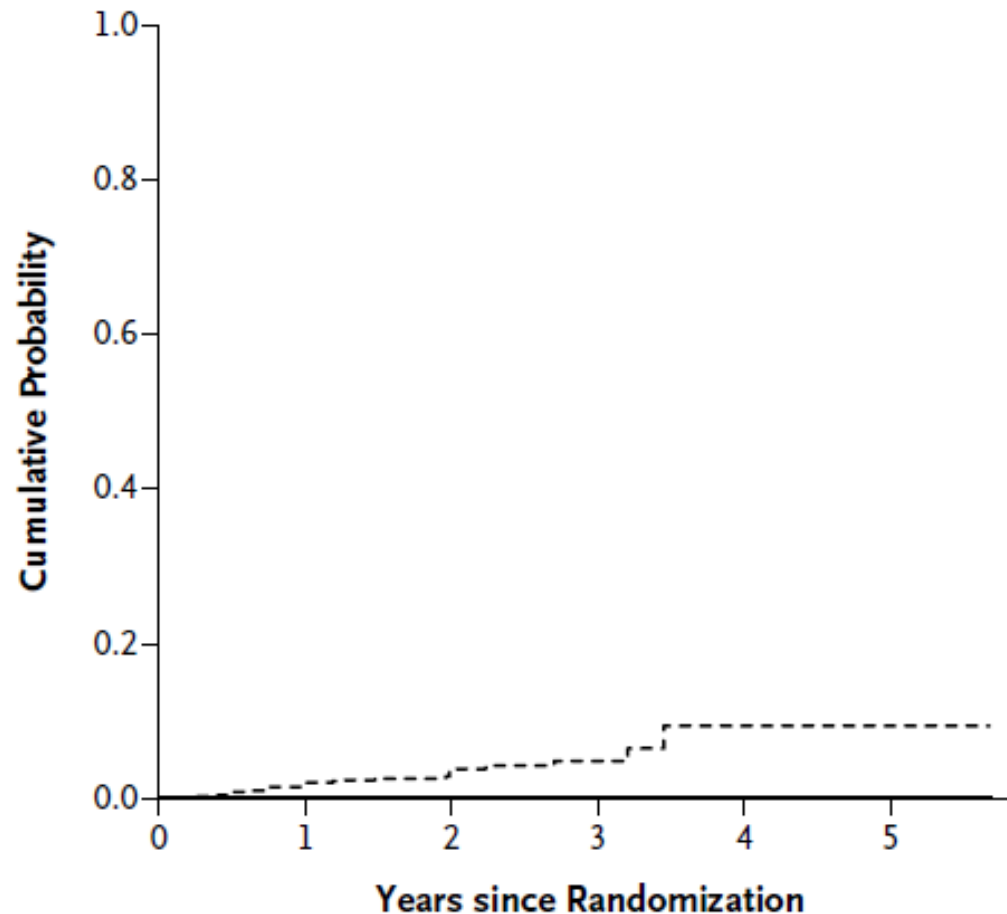
*Based on 2 consecutive values ≤ 250 cells/mm³.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

Cohen MS, et al. IAS 2011. Abstract MOAX0102.

Cohen MS, et al. N Engl J Med. 2011 Jul 18. [Epub ahead of print]

Linked HIV Transmission Events



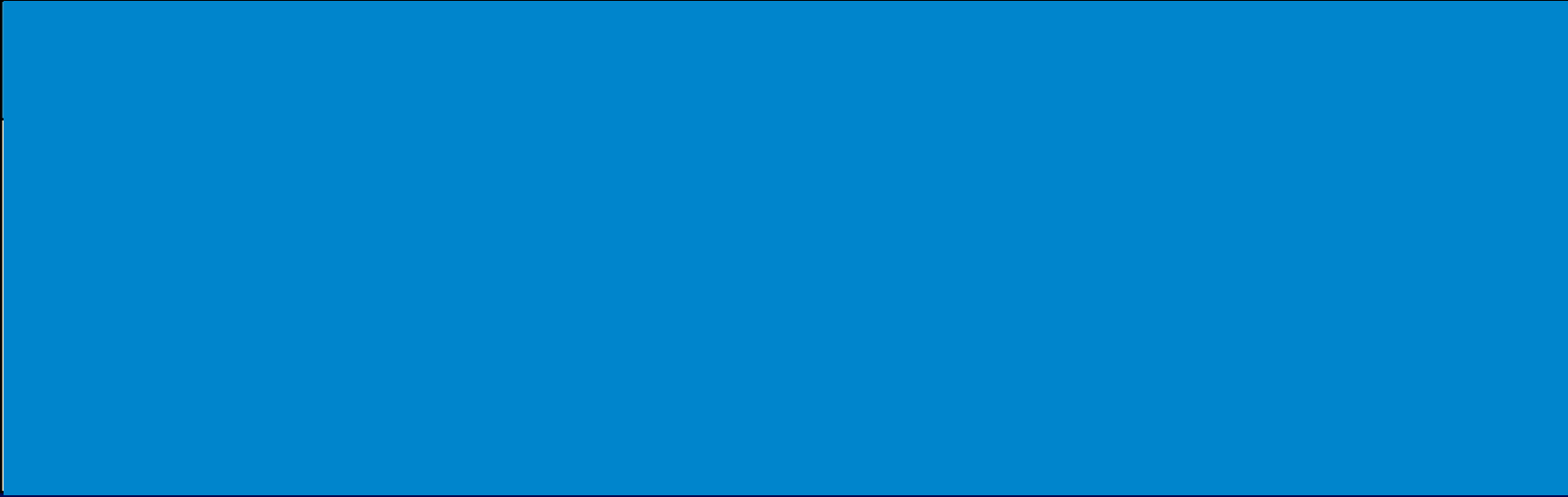
No. at Risk

Early	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

- 61% transmitters had CD4>350 cells/uL at time of Tx with 67% being women
- Tx in early group within 1 month of enrollment
- All Tx in delayed group prior to starting ARVs
- 82% of Tx at African sites

When to Start: 2011 DHHS Guidelines

CD4+ Cell Count	Recommendation
▪ CD4+ cell count < 350 cells/mm ³	▪ Start ART
▪ CD4+ cell count 350-500 cells/mm ³	▪ Start ART*
▪ CD4+ cell count > 500 cells/mm ³	▪ Panel divided†



*Panel divided: 55% strongly recommend and 45% moderately recommend. †50% favor initiating therapy at this stage. 50% view initiating therapy at this stage as optional.

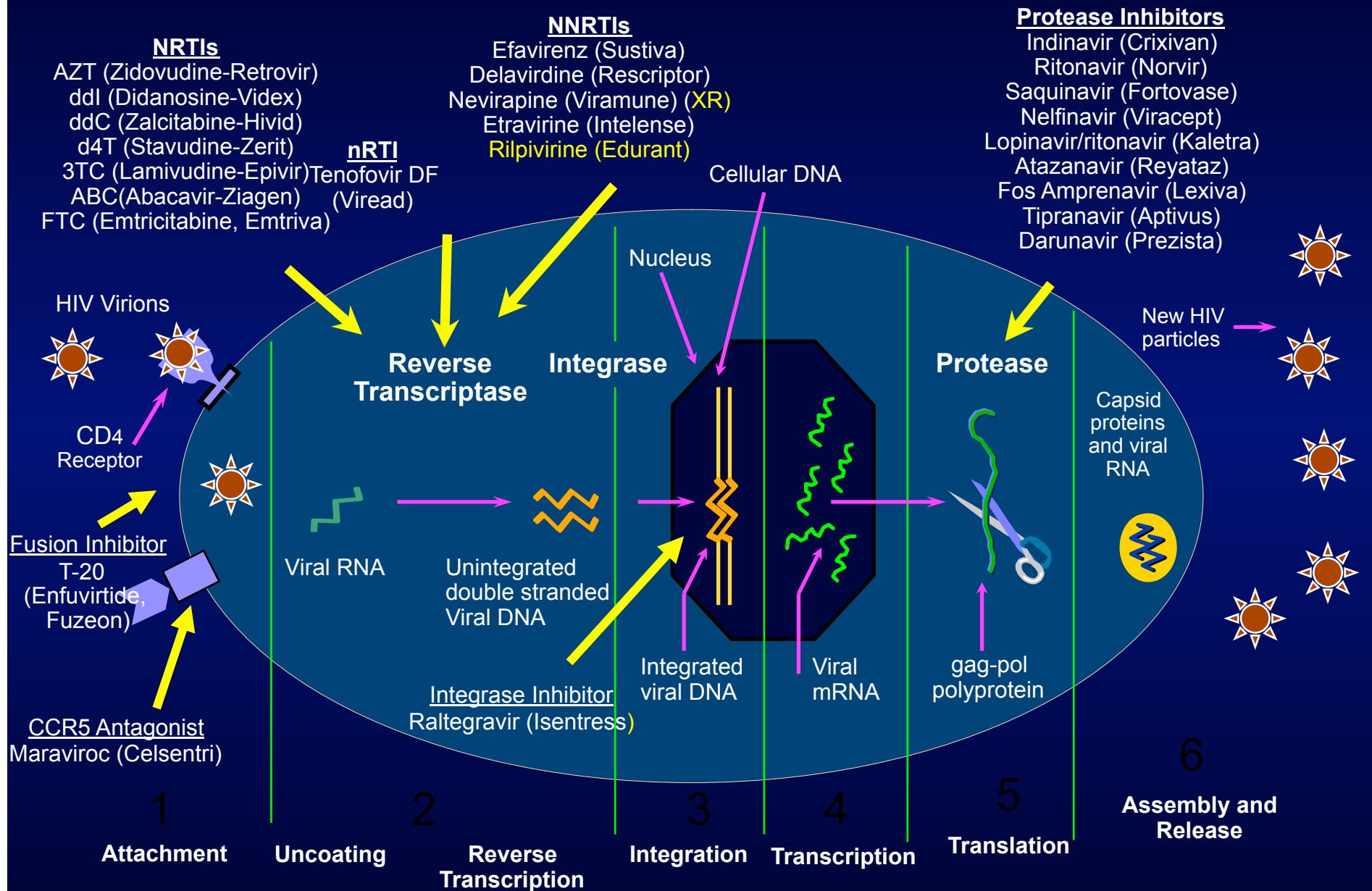
Adapted from US Department of Health and Human Services Guidelines; Revised January 10, 2011.
Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

Rationale for Recommending Therapy for Those with >350 CD4 cells/uL

- Recent cohort studies (4 for 350-500 cells/uL and 1 for >500 cells/uL)
- HIV replication associated with non-AIDS-defining diseases (e.g. cardiovascular, renal, liver, malignancy)
- Evidence that ARVs may reduce risk of transmission
- ARV more effective, convenient, better tolerated than in the past

Which Antiretrovirals to Start

HIV replication cycle and sites of drug activity



Factors to consider in choosing first-line therapy

- Being willing to commit to therapy
- Baseline resistance
- Efficacy data
- Tolerability
- Convenience
- Consequences of failure (resistance)
- Since the introduction of potent ARV therapy preferred regimens all include NRTIs + third drug

Nucleoside Reverse Transcriptase Inhibitors

- TDF/FTC (Truvada®)
 - At least as effective or better than all comparators
 - No lipoatrophy
 - Minimal short—term toxicity
 - Greatest decline in bone density
 - Greatest association with decreased renal function
- ABC/3TC (Epzicom®)
 - No lipoatrophy
 - Possibly less effective than TDF/FTC in select patients
 - Risk for hypersensitivity (less problem with HLA-B5701 testing)
 - Possible association with cardiovascular events

Third Drug to Combine with NRTIs

Nonnucleoside Reverse Transcriptase Inhibitors

- Efavirenz (Sustiva®)
 - Simple regimen (potentially one-pill once per day)
 - Extensive experience
 - Excellent potency
 - Well-defined limitations: CNS, lipids, rash, resistance
- Nevirapine (Viramune®)
 - Now available once daily (nevirapine XR)
 - Less data than with EFV
 - Only for women CD4<250 and men CD4<400 cells/uL
 - Well-defined limitations: rash, hepatitis, resistance
- Rilpivirine (Edurant®)
 - Simple regimen (potentially one-pill once per day)
 - Better tolerated than EFV (less lipids)
 - Possibly less effective than EFV in select patients
 - Much less experience and can select for resistance

Protease inhibitors

- Darunavir (Prezista[®]) + ritonavir (Norvir[®])
 - Once-daily
 - At least as effective as lopinavir/ritonavir (Kaletra[®])
 - Better tolerated than lopinavir/ritonavir (Kaletra[®])
 - Resistance rare
 - Rash
- Atazanavir (Reyataz[®]) + ritonavir (Norvir[®])
 - Once-daily
 - At least as effective as lopinavir/ritonavir (Kaletra[®])
 - Better tolerated than lopinavir/ritonavir (Kaletra[®])
 - Resistance rare
 - Jaundice
 - Take with caution if using acid reducing agents

Protease inhibitors

- Lopinavir/ritonavir (Kaletra®)
 - Once- or twice-daily
 - Large amount of experience
 - Available as fixed dose combination
 - Resistance rare
 - Preferred PI in pregnancy
 - Not as well tolerated as atazanavir or darunavir
- Fosamprenavir (Lexiva®) + ritonavir (Norvir®)
 - Once- or twice-daily
 - At least as effective as lopinavir/ritonavir (Kaletra®)
 - Similar tolerability as lopinavir/ritonavir (Kaletra®)
 - Resistance rare

Integrase inhibitor and CCR5 antagonist

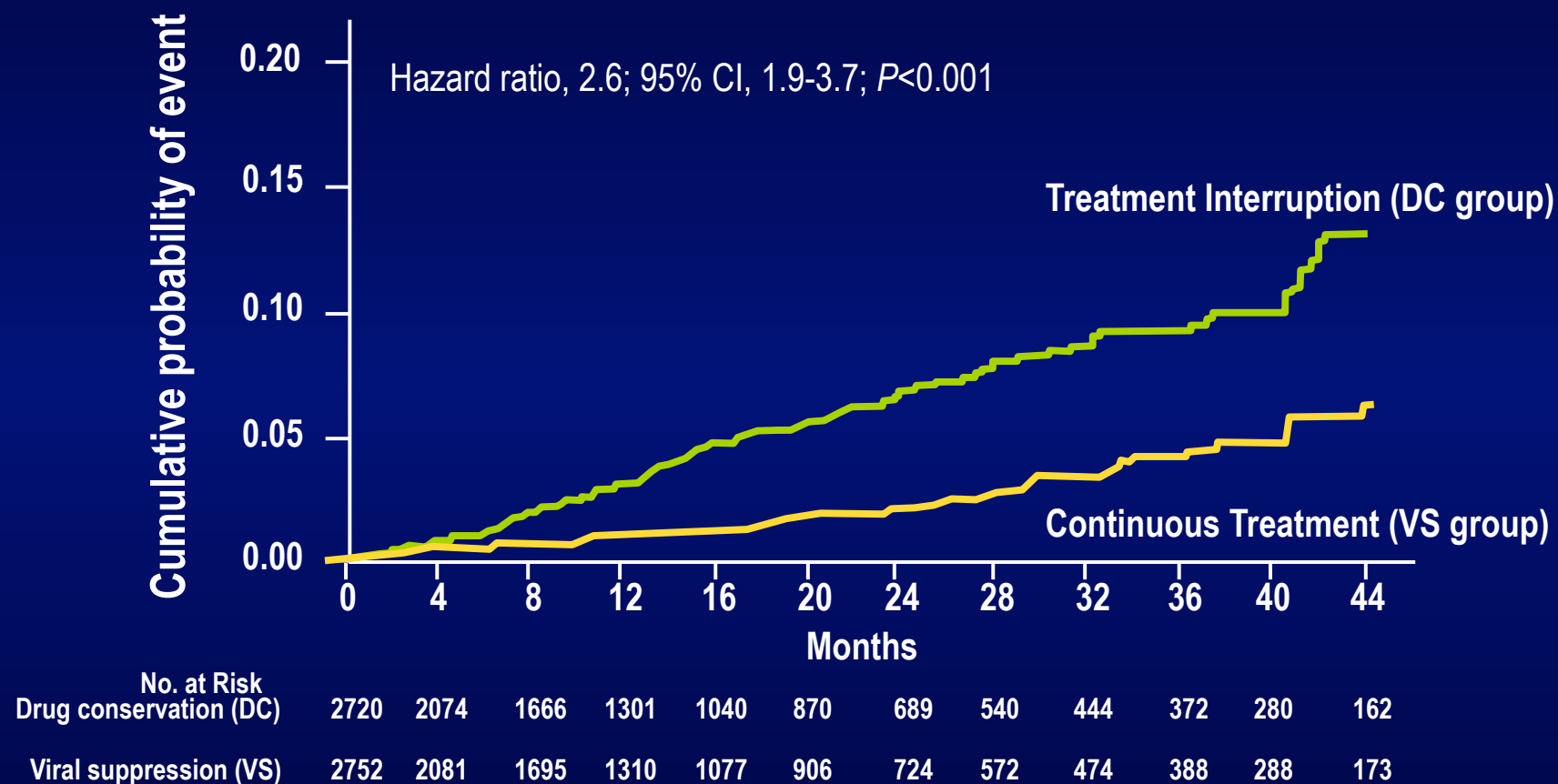
- Raltegravir (Isentress[®])
 - As effective as efavirenz
 - Better tolerated than efavirenz
 - Minimal lipid effect
 - Twice-daily
 - Resistance
- Maraviroc (Selzentry[®])
 - As effective as efavirenz
 - Better tolerated than efavirenz
 - Minimal lipid effect
 - Twice-daily
 - Only for those without detectable CXCR4-using virus

DHHS Jan 2011 Guidelines: Regimens for Treatment-Naïve Patients

Preferred Regimens	• EFV/TDF/FTC • ATV/r + TDF/FTC • DRV/r (once daily) + TDF/FTC • RAL + TDF/FTC [Pregnant Women Only: LPV/r (twice daily) + ZDV/3TC]

Adapted from US Department of Health and Human Services Guidelines; Revised January 10, 2011.
Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

Treatment interruption can occur, but only for good reasons

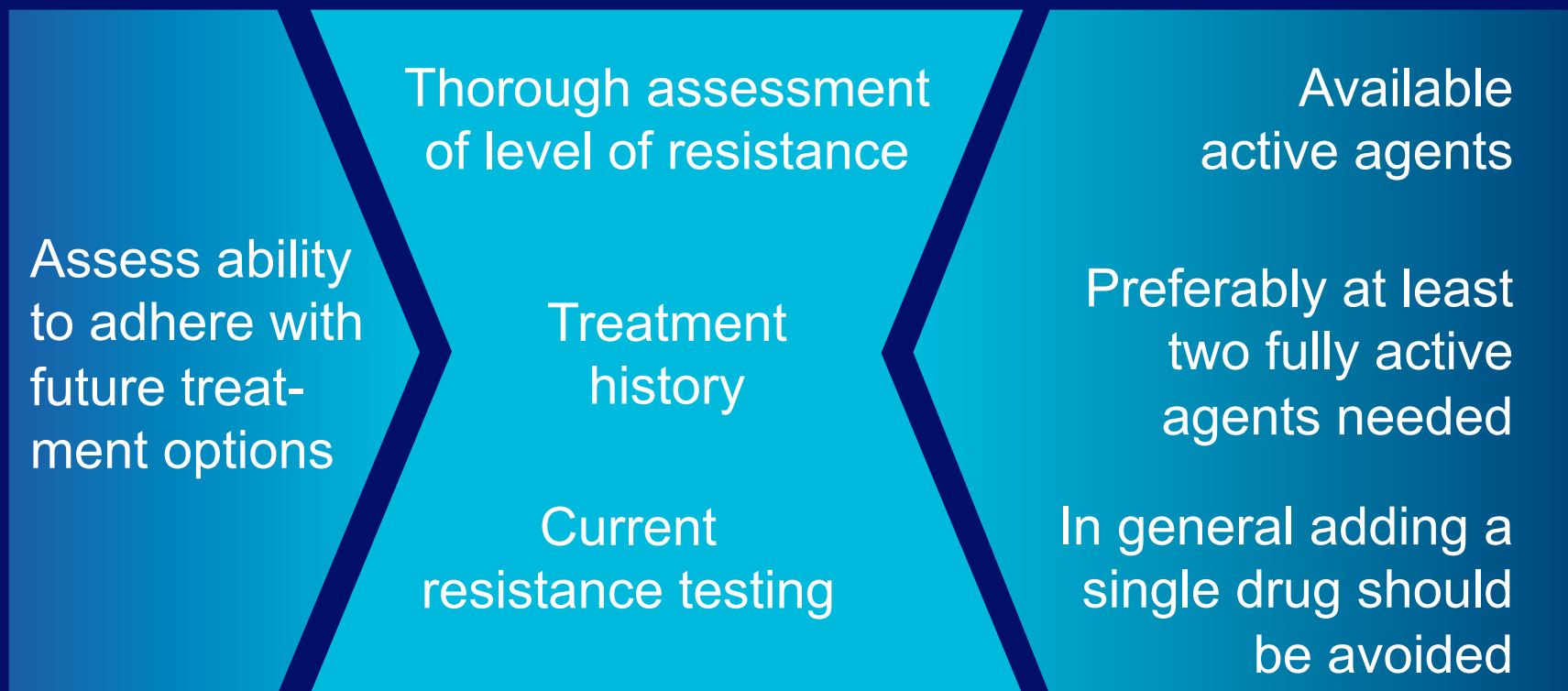


The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. *N Engl J Med.* 2006;355:2283-2296.

When to switch therapy?

- Poor tolerance
- Missing doses because of dosing schedule
- Virologic failure
 - Usually defined as repeatedly detectable viral load (e.g. >200 copies/mL despite excellent adherence)
- Available options

Treatment-Experienced Patients: Full Virologic Suppression is Often Achievable

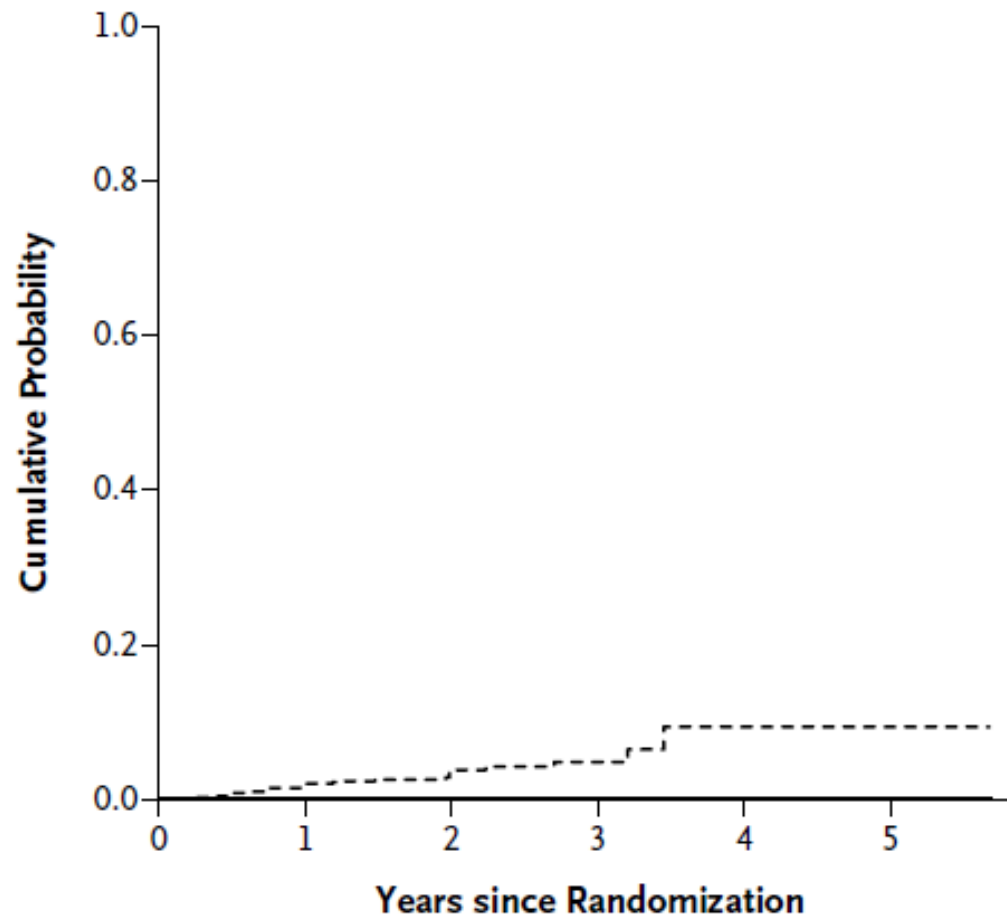


Evolving Issues in Antiretroviral Therapy

- Immune-based therapy
- Eradication (cure): Sterilizing or functional
- HIV and aging
- Different effects of antiretrovirals on different organ systems
 - Brain
 - Liver
 - Kidney
 - Bone
 - Other

HIV Transmission While on Therapy

Protecting others

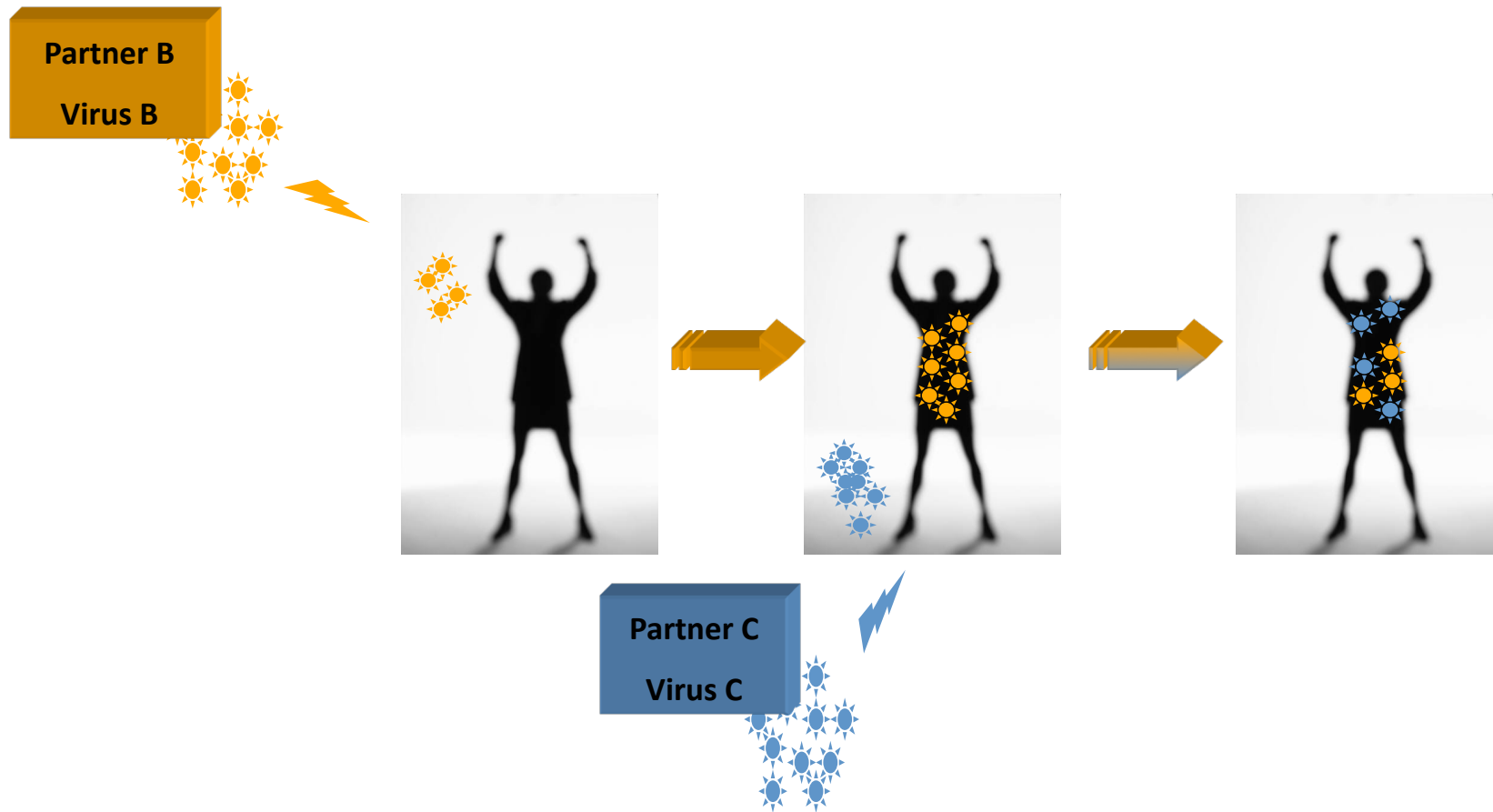


No. at Risk

Early	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

Cohen M, et al. NEJM July 18, 2011.

Protecting yourself



Cases Reported	Time to Superinfection (months)	Subtypes	Risk Factor	Dz Progression*
Ramos (2002)	<3	B after AE	IDU	+
Ramos (2002)	<11	AE after B	IDU	+
Jost (2002)	<28	B after AE	MSM	+
Yerly (2004)	18-24	B after CRF-11	IDU	-
Yerly (2004)	~36	CRF-11 after B	IDU	+
Yerly (2004)	45-55	CRF-11 after B	IDU	+
Fang (2004)	Not specified	C after A	WSM	?
Manigart (2004)	Not specified	G after AG	WSM	+
Manigart (2004)	Not specified	CRF-06 after AG	WSM	+
Altfeld (2002)	<32	B after B	MSM	+
Koelsch (2003)	<4	B after B	MSM	+
Gottlieb (2004)	<15	B after B	MSM	+
Chakraborty (2004)	Not specified	B after B	?	+
Brenner (2004)	10	B after B	MSM	+
Yang (2005)	<5	B after B	MSM	+
Smith (2004)	<14	B after B	MSM	+

*Precision of this estimate varies by case report

Thank You

Questions?