When and How to Treat HIV-Infection in 2014

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Disclosures of Interest

Advisory boards: Gilead, Merck, BMS, Janssen, Tobira, ViiV

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HIV/AIDS Epidemic
2013 UNAIDS Report

- Number of people living with HIV/AIDS
  - 2001: 28,6 Millions
  - 2012: 35,2 Millions
- Deaths due to HIV/AIDS
  - 2001: 1,8 Millions
  - 2012: 1,6 Millions
- New HIV infections
  - 2001: 3,4 Millions
  - 2012: 2,3 Millions (33% decrease)

HIV/AIDS Epidemic
2013 UNAIDS Report

- Number of people receiving treatment
  - 2012: 9,7 Millions (61% of those eligible)
- The three UNAIDS objectives
  - No new infection
  - No discrimination
  - No death

World Health Organization

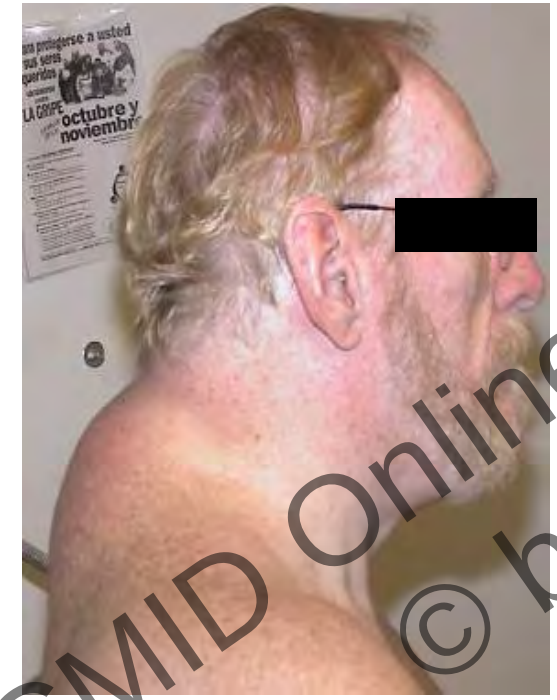
UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
UNHCR UNICEF WFP UNDP UNFPA UNODC ILO UNESCO WHO WORLD BANK

Should We Treat Everyone with HIV?

1. Yes
2. No
3. Maybe

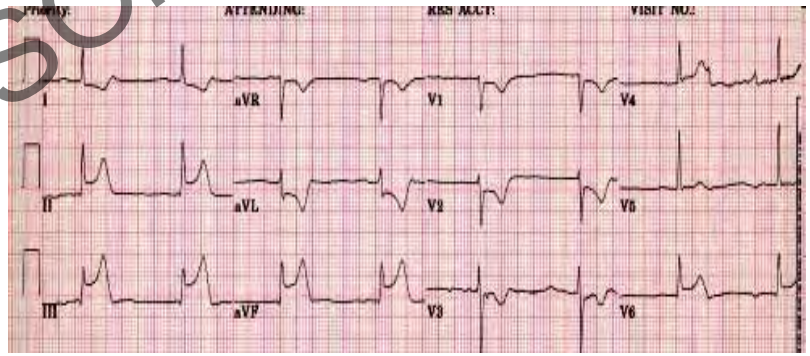
The Historical Reasons for Deferring Therapy

Body shape changes



High pill burden

High cost



Metabolic abnormalities/↑CV risk

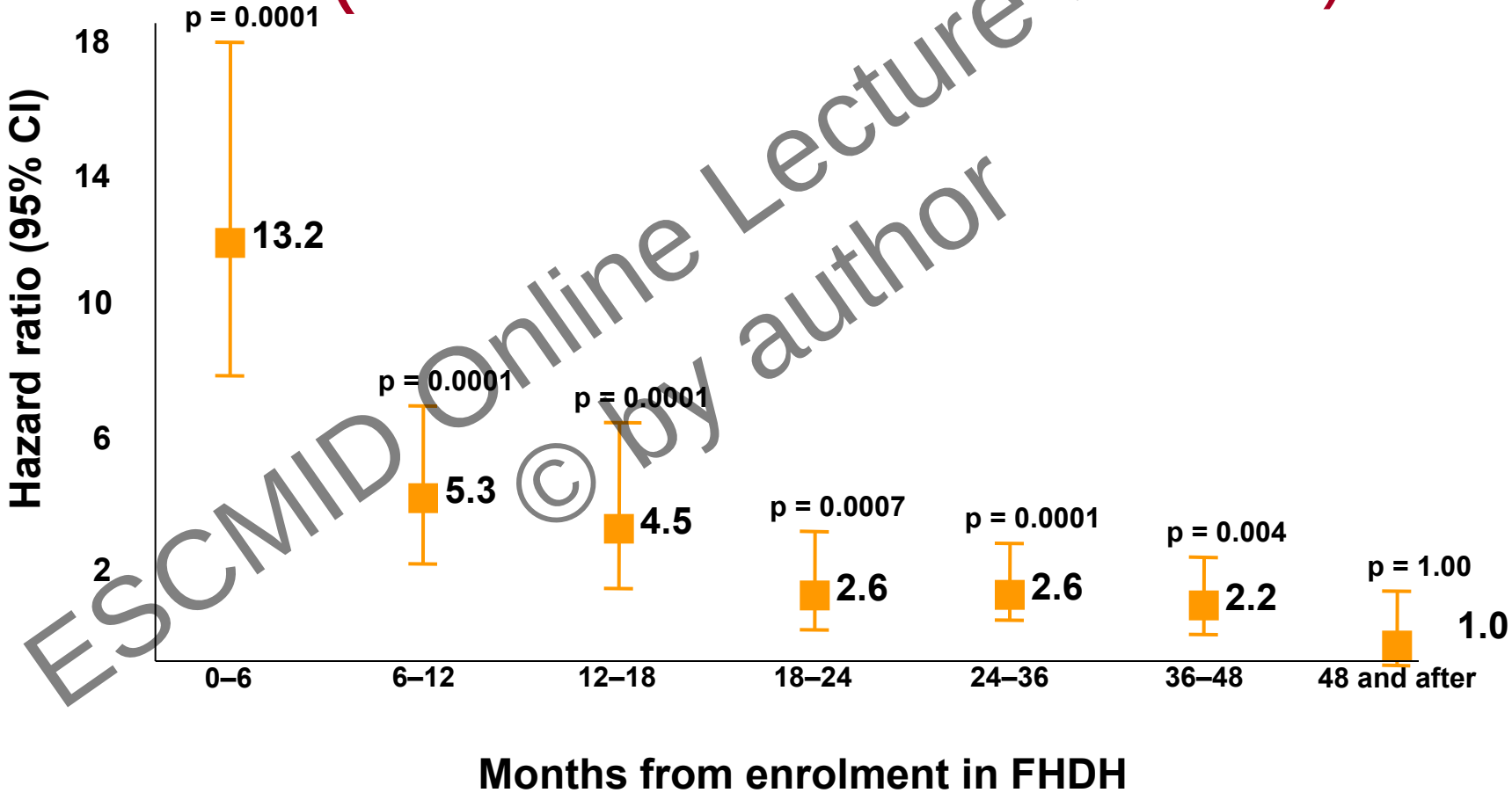
SUMMARY REPORT

			FOLD CHANGE [1]	CUT-OFF [2]	RESISTANCE ANALYSIS [3]	CLINICAL NOTES
NRTI/NtRTI	NRTI / NtRTI mutations: 41L, 44D, 67N, 75M, 118I, 184V, 208Y, 210W, 211wt/K, 214F, 215Y, 218E, 219N					
	Retrovir®	Zidovudine	12.6	1.2	9.6	MINIMAL RESPONSE
	Epivir®	Lamivudine	46.0	1.0	3.4	MINIMAL RESPONSE
	Videx®	Didanosine	2.1	0.9	2.6	REDUCED RESPONSE
	Zerit®	Stavudine	1.9	0.9	2.0	REDUCED RESPONSE
	Ziagen®	Abacavir	4.9	0.8	1.9	MINIMAL RESPONSE
	Emtriva®	Emtricitabine	43.1	3.5		RESISTANT
	Viread®	Tenofovir DF	2.3	0.9	2.1	MINIMAL RESPONSE
NNRTI	NNRTI mutations: 98S, 103N					
	Viramune®	Nevirapine	53.3	5.5		RESISTANT
	Sustiva® , Stocrin®	Efavirenz	11.8	3.4		RESISTANT
PI	PI mutations: 10I, 15V, 20R, 35D, 36I, 37D, 46L, 53L, 54V, 55R, 58E, 62V, 63P, 71V, 73T, 82A, 90M					
	Crixivan®	Indinavir	119.8	0.9	4.5	MINIMAL RESPONSE
	Crixivan ®; boosted	Indinavir/r	119.8	10.6	40.1	MINIMAL RESPONSE
	Viracept®	Nelfinavir	55.1	1.3	7.3	MINIMAL RESPONSE
	Invirase®; boosted	Saquinavir/r	138.8	7.1	26.5	MINIMAL RESPONSE
	Lexiva®,Telzir®; boosted	Fosamprenavir/r	9.3	1.3	11.4	REDUCED RESPONSE
	Kaletra®	Lopinavir/r	105.0	9.7	56.1	MINIMAL RESPONSE
	Reyataz®; boosted	Atazanavir/r	103.6	2.7	32.9	MINIMAL RESPONSE
	Aptivus®; boosted	Tipranavir/r	2.6	1.2	5.4	REDUCED RESPONSE Note 1
	Prezista™; boosted	Darunavir/r	2.4	3.4	96.9	MAXIMAL RESPONSE Note 2

Resistance

Mortality and Delayed Access to Care in France

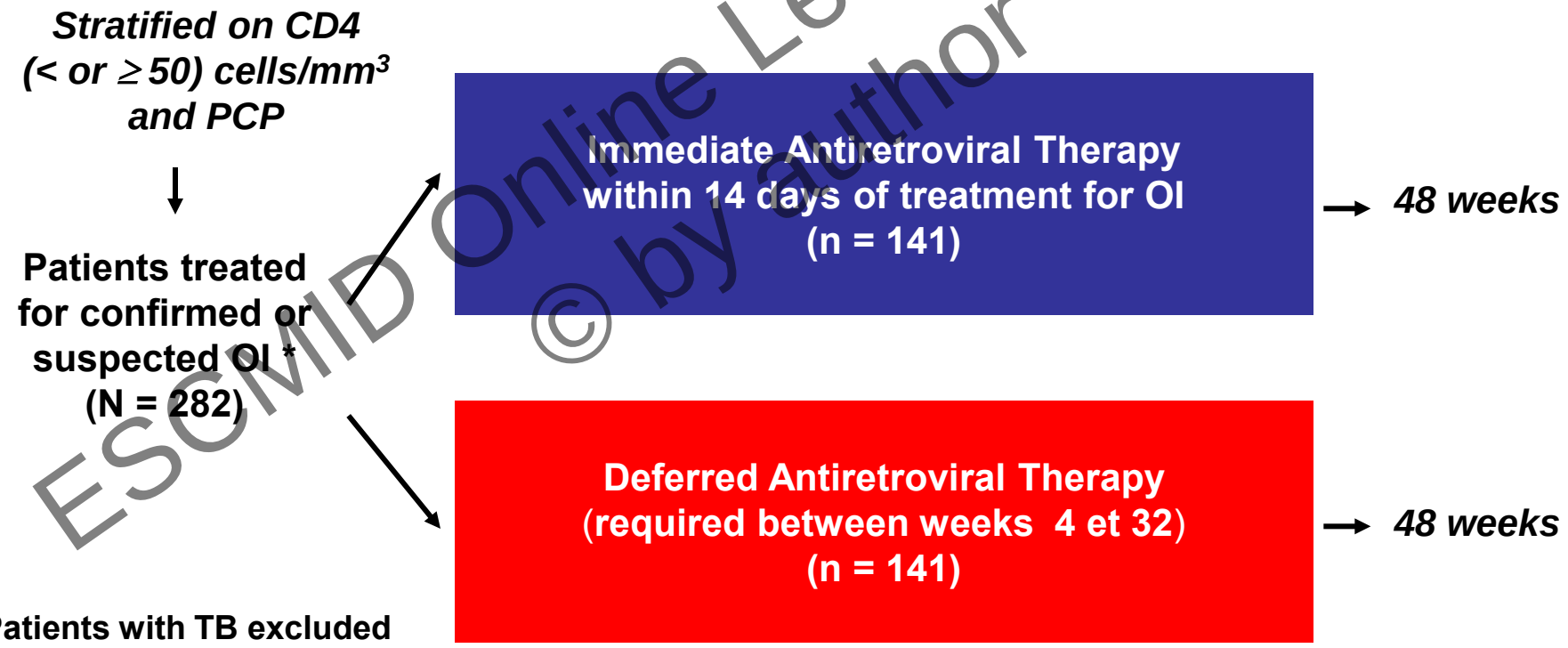
(AIDS and/or CD4 < 200 cells/mm^3)



Lanoy et al. Antiviral Therapy 2007;12:89

When should cART be Initiated in Patients with an AIDS-defining Opportunistic Infection ?

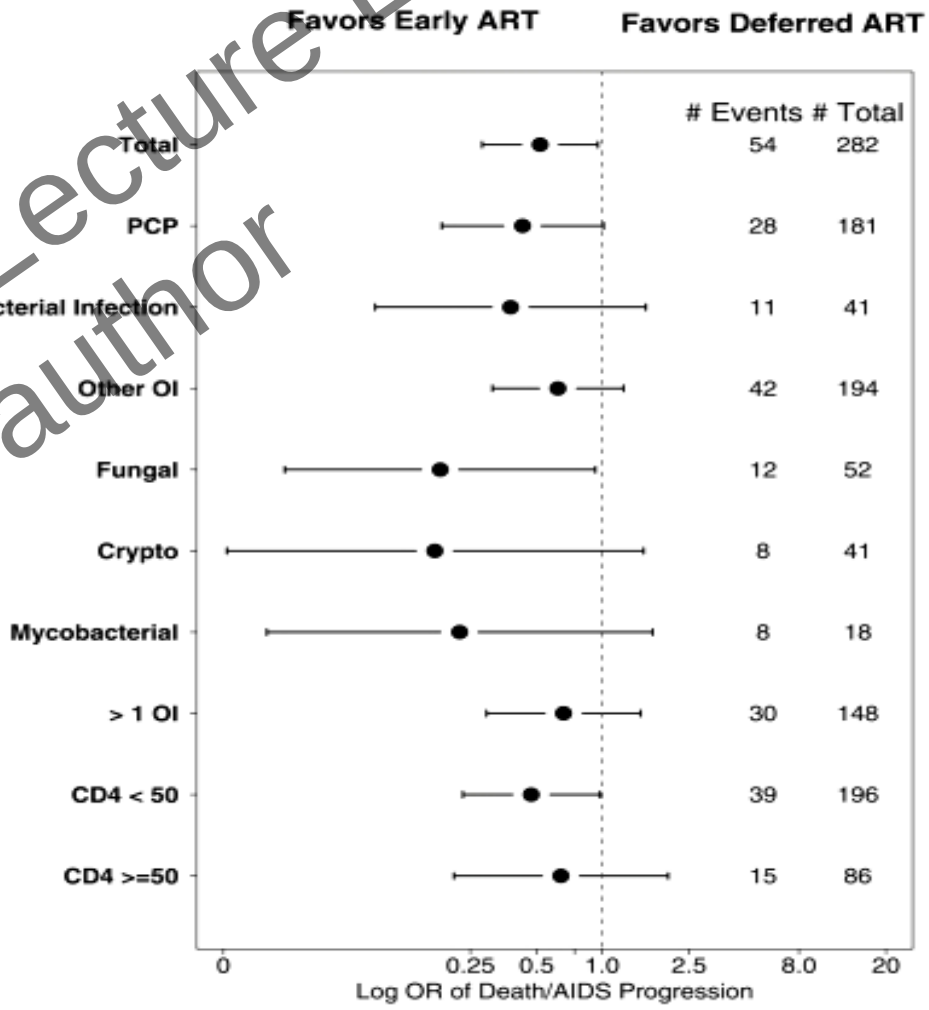
Immediate Treatment of Patients with Opportunistic Infections : ACTG 5164



Zolopa A, et al. PLOSone 2009

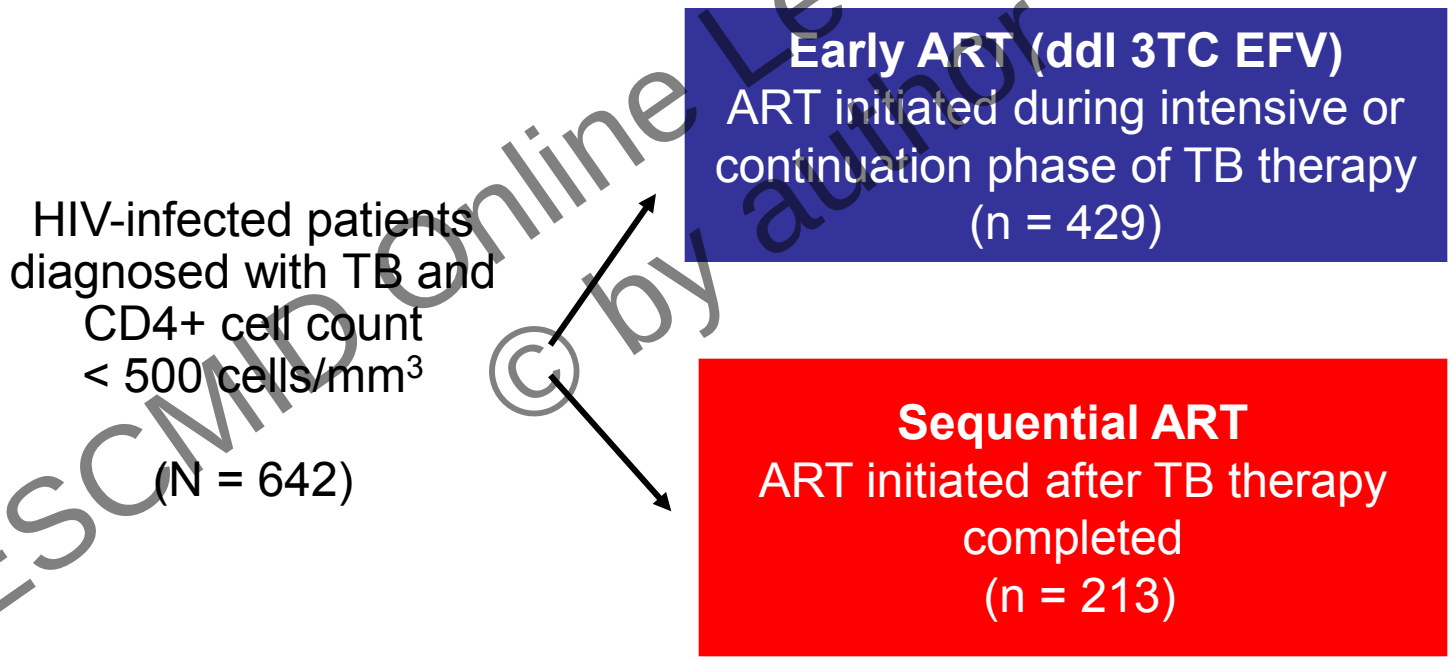
ACTG A5164: Improved Outcomes with Early cART

- Median baseline CD4 count : 29 cells and 63% had PCP
- Median duration between OI treatment and initiation of cART
  - Immediate arm : 12 days
  - Differed arm : 45 days
- Significant reduction of clinical progression (AIDS events and deaths) in the immediate group
  - 20 events (14.2%) vs 34 events (24.1%)
  - HR: 0.53 (95%CI: 0.3-0.9) p=0.023
- Similar antiviral activity in both arms at week 48
- Similar tolerability and IRIS incidence in both arms (role of steroids?)



Zolopa A, et al. PLOs one 2009

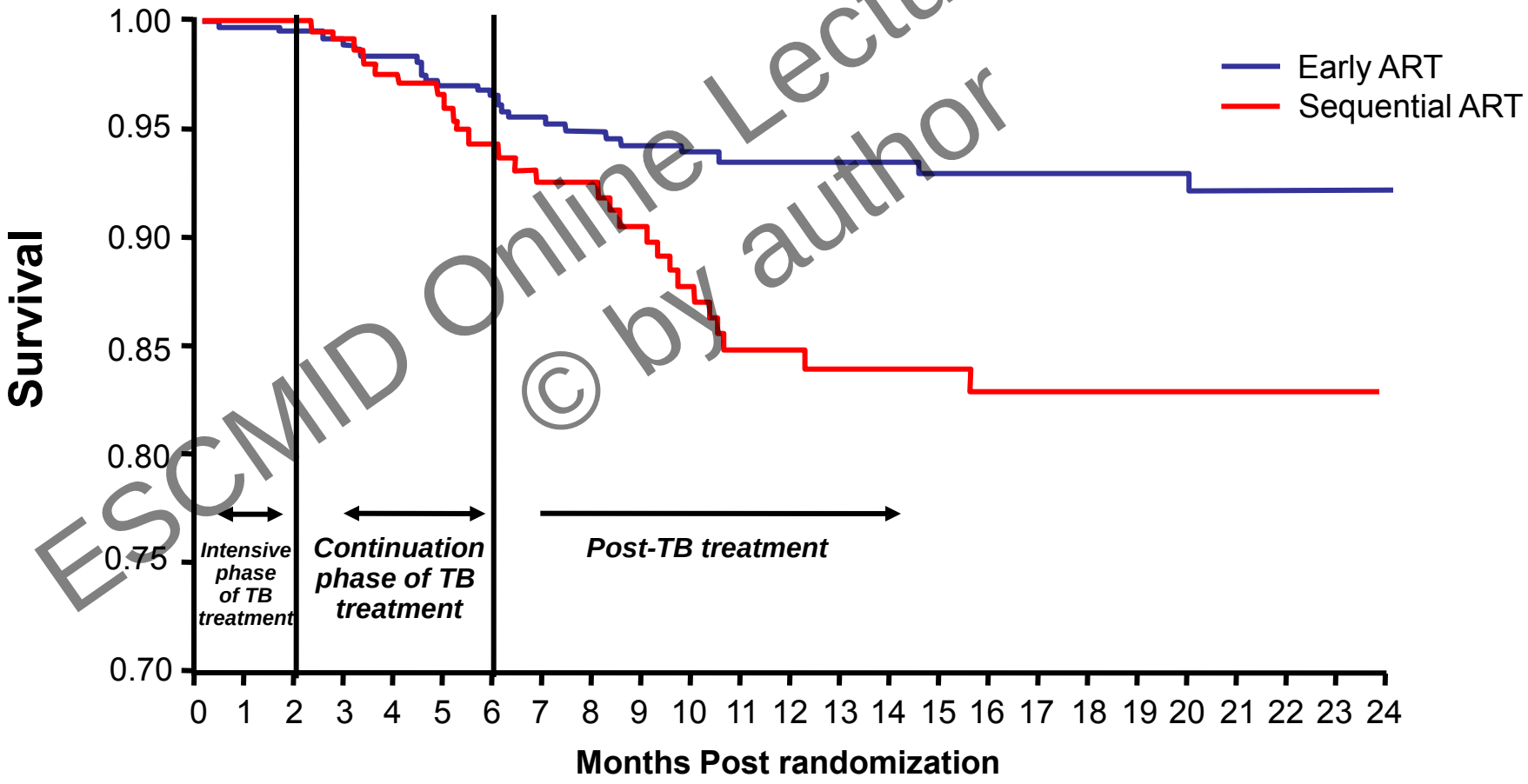
SAPiT: Optimal Time to Initiate ART in HIV/TB-Coinfected Patients



Primary endpoint: all-cause mortality

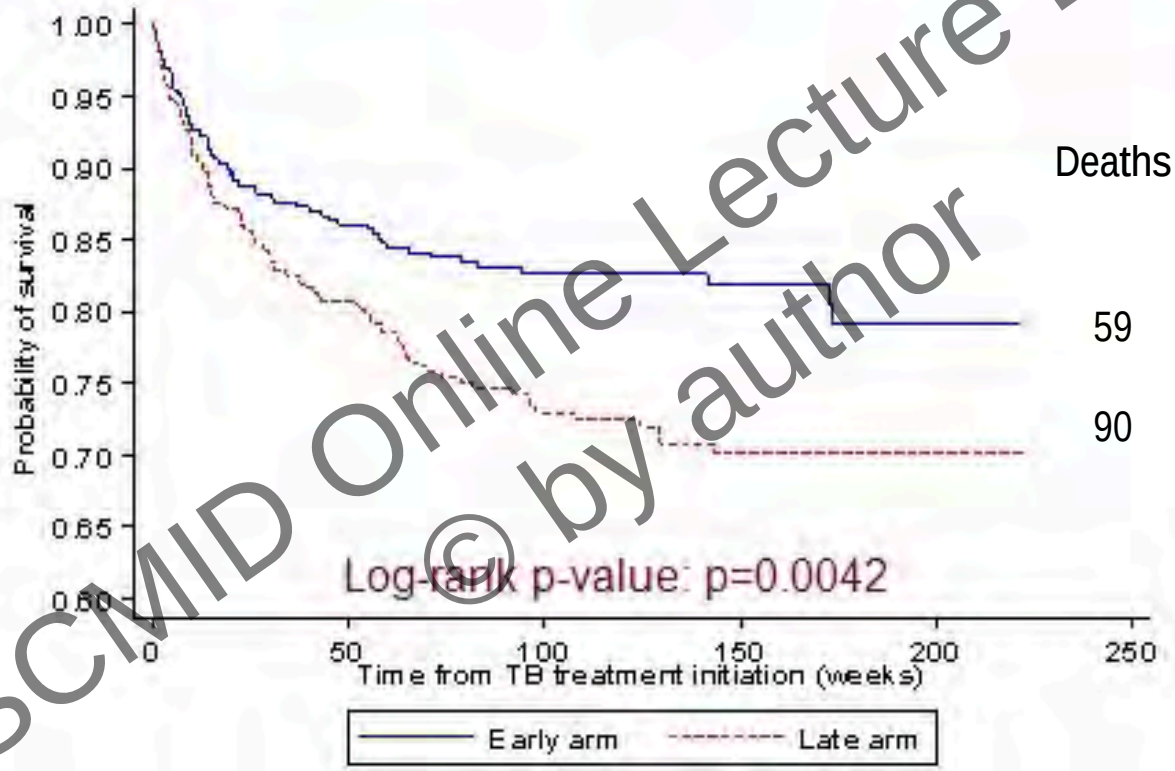
Abdool Karim SS, et al. NEJM 2010

SAPiT: Increased Survival With Concurrent HIV and TB Treatment



Abdool Karim SS, et al. NEJM 2010.

ANRS Camelia
ARVs 2 vs. 8 wks after TB treatment



	Deaths	Mortality rate (95% CI)
	59	8.3 (6.4, 10.7)
	90	13.8 (11.2, 16.9)

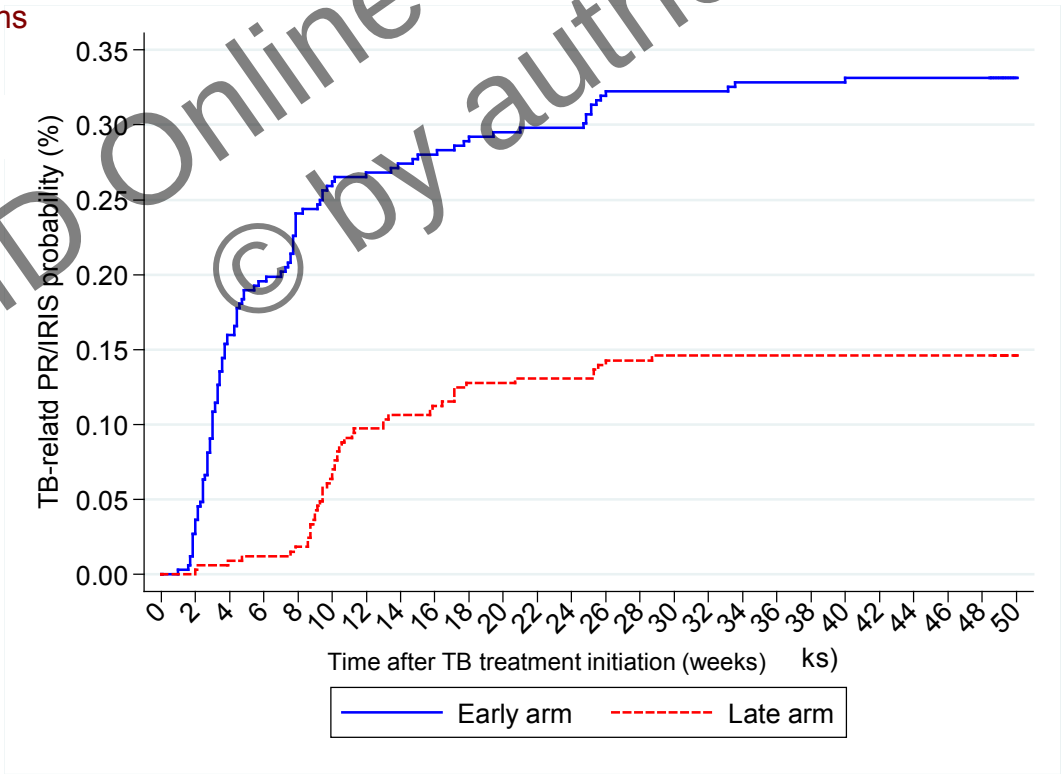
In patients with a median of 25 CD4 cells and TB,
mortality was reduced by 34%
when HAART initiated 2 weeks *vs.* 8 weeks after onset of TB treatment.

Blanc et al. New Engl J Med 2011

IRIS More Frequent in the Early Arm

	N	IRIS	Follow-up time*	Incidence (95% CI)	*p*
Early arm	**332**	**110**	**2 728.5**	**4.03 (3.34 – 4.86)**	<0.0001
Late arm	329	48	3 333.5	1.44 (1.09 – 1.91)	

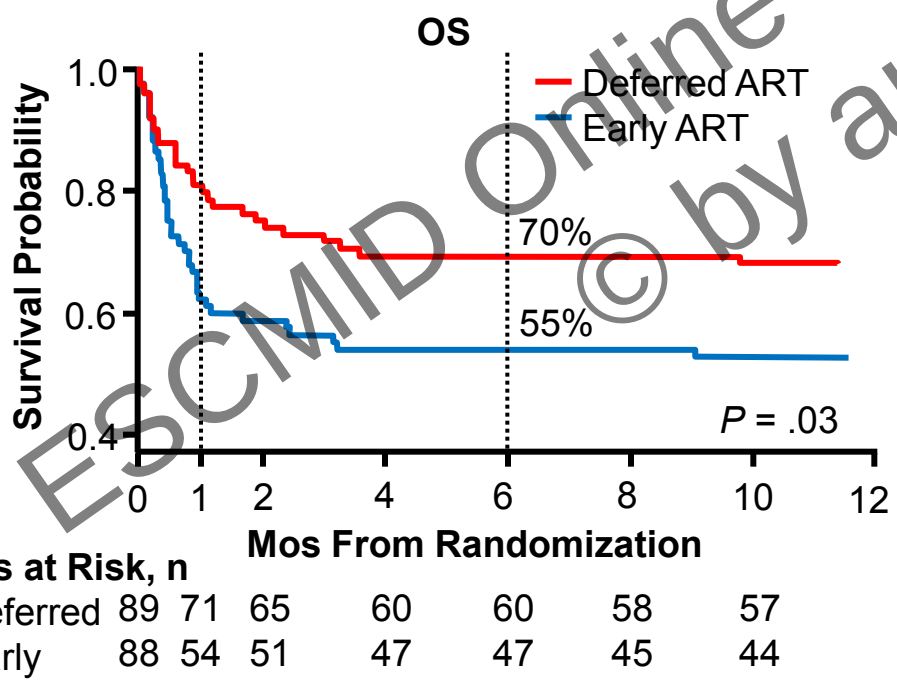
* expressed in person-months
** per 100 person-months



Blanc FX, New England J Med 2011

COAT: Increased Mortality With Early ART During Cryptococcal Meningitis Induction Therapy

- Significantly lower 6-months survival with early (1-2 weeks) vs deferred (5 weeks) ART
  - Enrollment halted early by NIAID Africa DSMB



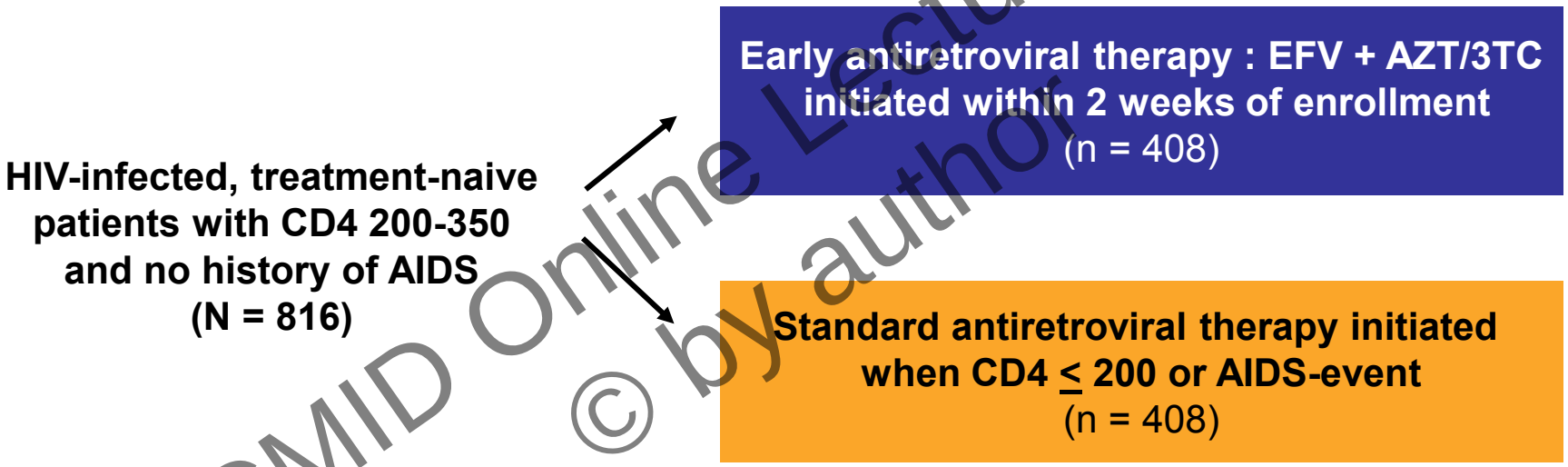
- Mortality : early vs late
  - Patients with CSF WBC counts < 5 cells/mm^3 at randomization (HR: 3.9; P < .01)

- In HIV-infected patients with a recent diagnosis of cryptococcal meningitis
  - ART initiation should be deferred until 5 weeks

Boulware D, et al. New Engl J Med 2014

Is there Evidence that cART should be Initiated in Asymptomatic Patients with CD4 < 350 cells/µL ?

The CIPRA HT-001 Trial in Treatment-Naive Patients in Haiti



- **Primary endpoint: Overall survival**
- **Median baseline CD4 cell count : 280, median age 40y and 42% males**
- **Patients were given cotrimoxazole and INH prophylaxis (when TST positive)**
- **Upon publication NA-accord study, DSMB conducted interim analysis when 29 deaths reported, after a median FU of 21 months**

Severe P, et al. NEJM 2010

The CIPRA HT-001 Trial in Treatment-Naive Patients in Haiti

	Early cART (n=408)	Standard cART (n=408)	Hazard Ratio	P value
Deaths, n	6	23	4.0	0.0011
Gastroenteritis/sepsis	1	7		
Tuberculosis	0	5		
Pneumonia	0	4		
Cholangitis/sepsis	0	1		
Other	5	6		
Incident TB	18	36	2.0	0.0125

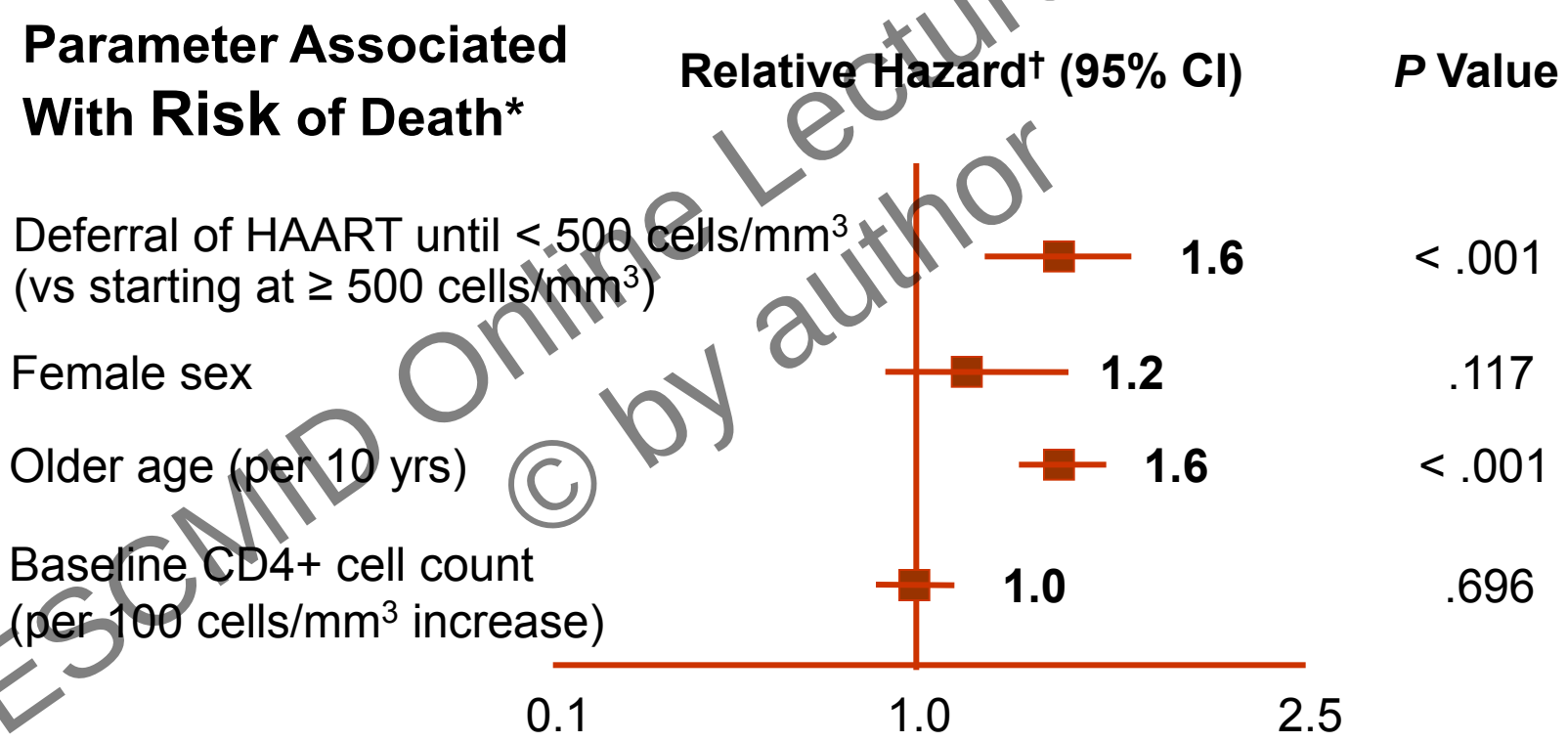
Only 160 of the 408 patients in the deferred arm had received cART at the time of the interim analysis

Mortality was reduced by 75% and incident tuberculosis by 50%

Severe P, Pape J, et al. ICAAC 2009. NEJM 2010

Is there Evidence that cART has a good Benefit:Risk ratio in Asymptomatic Patients with CD4 > 350 cells/µL ?

NA-ACCORD: Survival Benefit of Earlier HAART by Baseline Factor

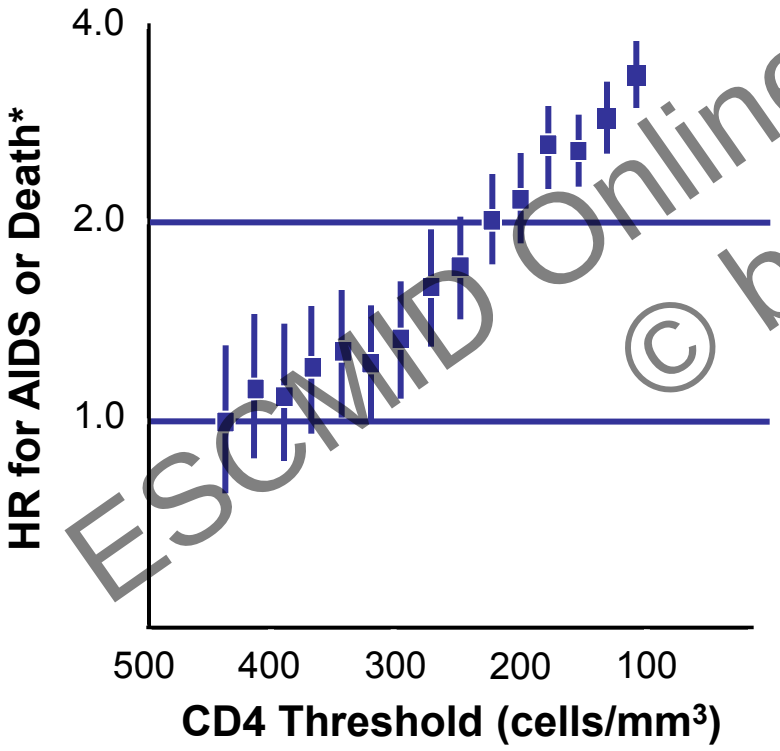


*All causes of death unspecified. †Stratified by cohort and calendar year.

Kitahata et al. NEJM 2009

ART CC: Supports Initiating ART at CD4 Threshold of 350 cells/mm^3

N=24,444 (15 cohorts from US and Europe)



Comparison	HR* (95% CI)
1-100 vs 101-200	3.35 (2.99-3.75)
101-200 vs 201-300	2.21 (1.91-2.56)
201-300 vs 301-400	1.34 (1.12-1.61)
251-350 vs 351-450	1.28 (1.04-1.57)
351-450 vs 451-550	0.99 (0.76-1.29)

*Adjusted for lead-time and unobserved events.

When to Start Consortium Lancet 2009

International START Trial

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3

Early ART Group

Initiate ART immediately following randomization

N=450 in pilot phase and estimated as N=2,000 for definitive trial

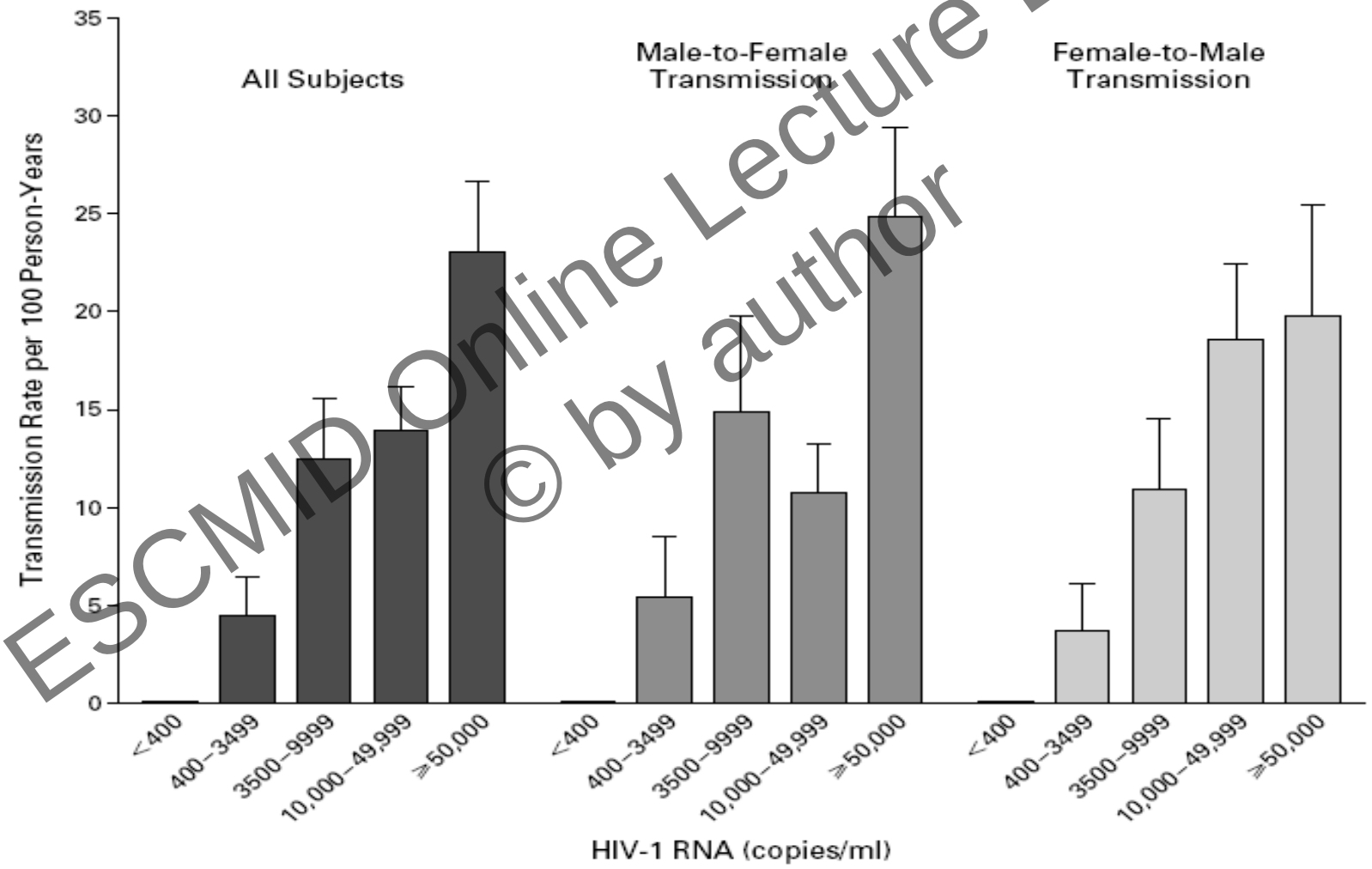
Deferred ART Group

Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

N=450 in pilot phase and estimated as N=2,000 for definitive trial

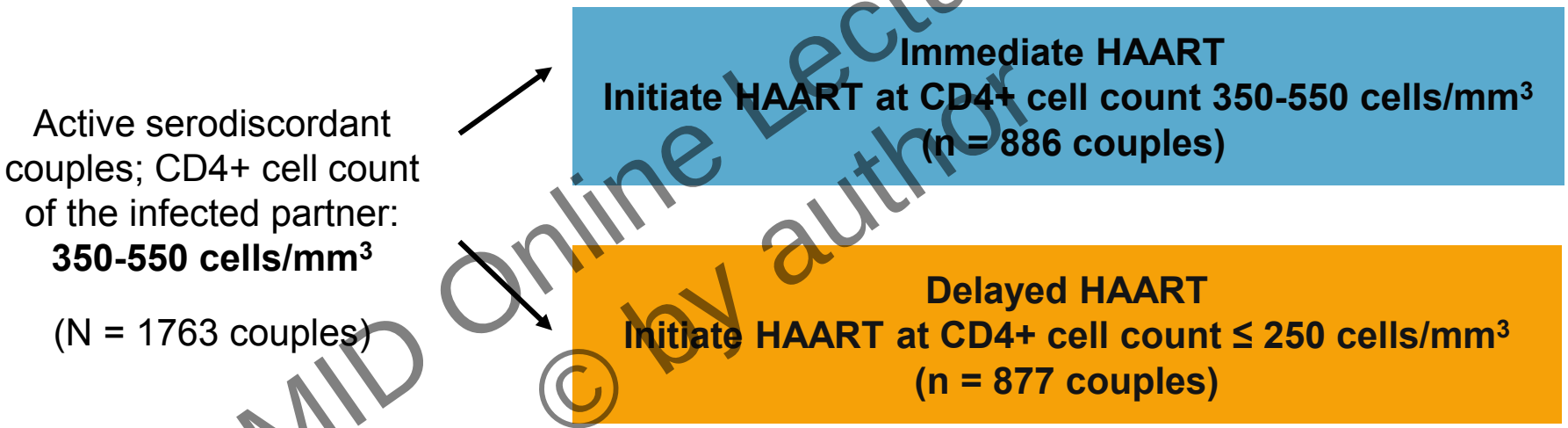
The Role of cART on Prevention
A Reason to Start Early with > 500 CD4 cells ?

HIV Transmission Rate and Plasma HIV RNA levels in the Absence of cART



Quinn et al. N Engl J Med 2000;342:921-9

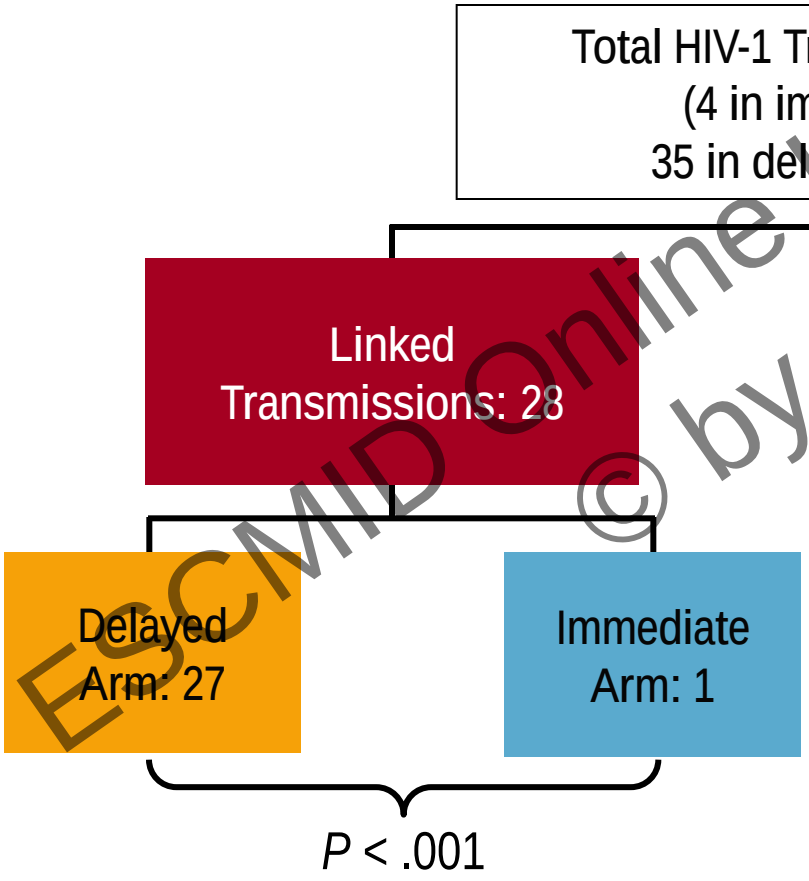
HPTN 052: Immediate vs Delayed ART for HIV Prevention in Serodiscordant Couples



- 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. N Engl J Med. 2011;365:493-505.

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples



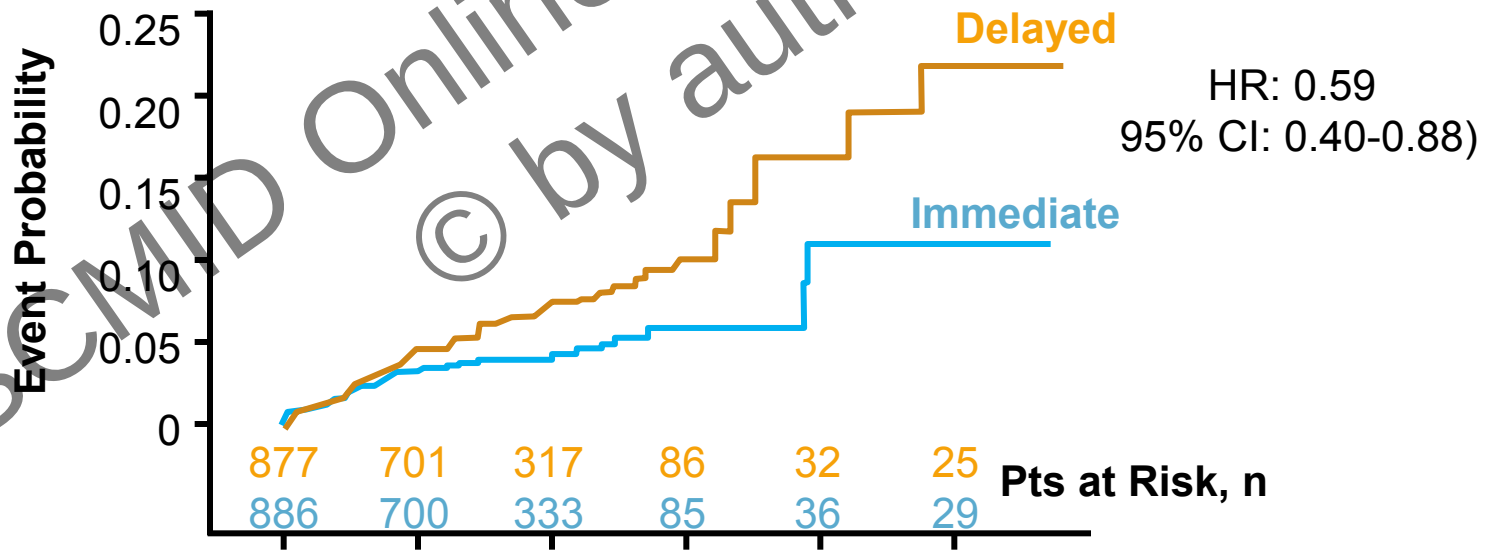
DSMB recommended study discontinuation after a median of 1.7 years of follow-up

☞ **Early ARV reduces heterosexual transmission of HIV by 96%**

Cohen MS, et al. N Engl J Med. 2011;365:493-505

HPTN 052: Analysis of Primary Clinical Events During Follow-up

- 41% reduction in HIV-related clinical events in HIV-infected patients randomized to immediate vs delayed therapy
  - Excess events in delayed arm driven mainly by TB (33 vs 17 cases), particularly extrapulmonary TB (17 vs 3 cases) (*P* = .002)



Cohen MS, et al. N Engl J Med. 2011;365:493-505.

When to start: What guidelines recommend?

Recommendations to reduce the risk of disease progression				
Clinical category	**CD4 cells/mm^3**	**DHHS (2014)**	**EACS (2013)**	**WHO (2013)**
AIDS-defining symptomatic	Any value	Treat (AI)	Treat	Treat (priority)
Asymptomatic	<200-350	Treat (AI)	Treat	Treat (priority)
Asymptomatic	350-500	Treat (AII)	Individual basis†	Treat (A II)
Asymptomatic	>500	Treat (B III)	Individual basis†	Individual basis*

A: Strong B: Moderate I: data from randomized controlled trials, II: observational cohort, III: expert opinion

† considered to reduce HIV transmission, primary HIV infection, and recommended to treat pregancy HCV/HBV coinfection, HIV-AN or neurocognitive deficiency, high CV risk (> 20% at years) or malignancy,

*Active TB, HBV coinfection with liver disease, pregnant women, serodiscordant partnership

DHHS Guidelines. Available www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed May 2014.
EACS Guidelines 2013. Available at http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf
WHO guidelines 2013 Available at http://www.who.int/hiv/pub/guidelines/en/

JD, a 24-Yr-Old Man Who Has Sex With Men and Women

- Recently diagnosed with HIV when evaluated in STI clinic for gonorrhea
  - Also RPR positive, HBsAb positive, HCV Ab negative
- HIV-1 RNA: 57,000 copies/mL; CD4+ cell count: 710 cells/mm^3
  - Repeat labs (8 wks later) : HIV-1 RNA: 53,000 copies/mL; CD4+ cell count: 690 cells/mm^3
- No other medical problems, takes no medications but a multivitamin “when he remembers”
- Several casual and occasional anonymous (Internet) male sex partners with whom he has insertive anal sex
  - Reports ″frequently″ using condoms

Would you Recommend to Start Antiretroviral Therapy?

1. Yes
2. No
3. Only if he has a personal benefit

What to Start With Once the Decision to Treat is Made ?

Antiretroviral Drugs Available in 2014 in Europe and USA

Nucleoside RT Inhibitors (NRTIs)

Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Tenofovir (TDF)
Zidovudine (ZDV)
3TC/ABC
3TC/ABC/ZDV
3TC/ZDV
FTC/TDF

Non Nucleosides RT Inhibitors (NNRTIs)

Efavirenz (EFV)
Nevirapine (NVP)
Efavirenz/TDF/FTC*
Etravirine (ETV)
Rilpivirine (RPV)
Rilpivirine/TDF/FTC*

Protease Inhibitors (IPs)

Atazanavir (ATV)
Fosamprenavir (FPV)
Indinavir (IDV)
Lopinavir/ritonavir (LPV/RTV)
Nelfinavir (NFV)
Ritonavir (RTV)
Saquinavir (SQV hgc)
Tipranavir (TPV)
Darunavir (DRV)

Fusion Inhibitors (FIs)

Enfuvirtide (ENF)

Integrase Inhibitors (INSTIs)

Raltegravir (RAL)
Elvitegravir/cobicistat/TDF/FTC*
Dolutegravir

Entry Inhibitors (EIs)

Maraviroc (MVC)

VOLUME 337 SEPTEMBER 11, 1997 NUMBER 11

A CONTROLLED TRIAL OF TWO NUCLEOSIDE ANALOGUES PLUS INDINAVIR IN PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND CD4 CELL COUNTS OF 200 PER CUBIC MILLIMETER OR LESS

SCOTT M. HAMMER, M.D., KATHLEEN E. SQUIRES, M.D., MICHAEL D. HUGHES, PH.D., JANET M. GRIMES, M.S., LISA M. DEMETER, M.D., JUDITH S. CURRIER, M.D., JOSEPH J. ERON, JR., M.D., JUDITH E. FEINBERG, M.D., HENRY H. BALFOUR, JR., M.D., LAWRENCE R. DEYTON, M.D., JEFFREY A. CHODAKEWITZ, M.D., AND MARGARET A. FISCHL, M.D., FOR THE AIDS CLINICAL TRIALS GROUP 320 STUDY TEAM*

Stratified on CD4 < or ≥ 50 cells/mm³

AZT-experienced PI and 3TC naïve HIV-infected adults < 200 CD4 cells (N = 1156)

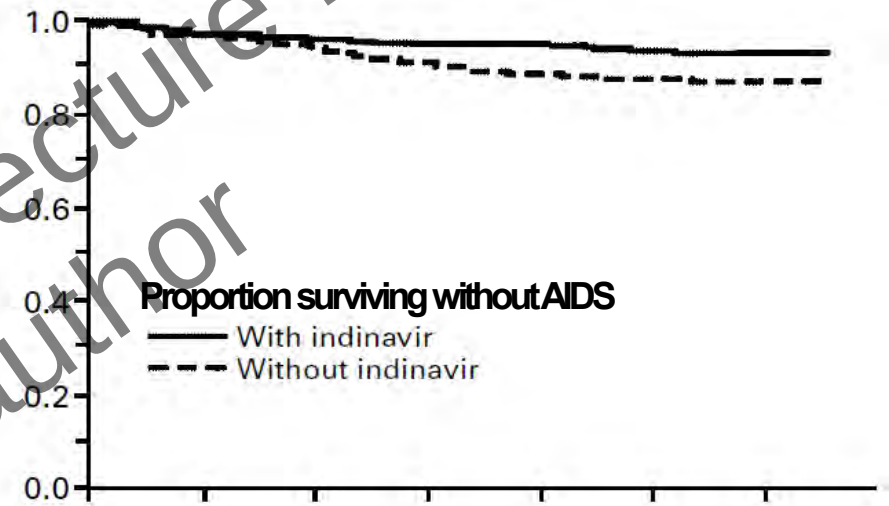
AZT + 3TC + Indinavir placebo → *48 weeks*

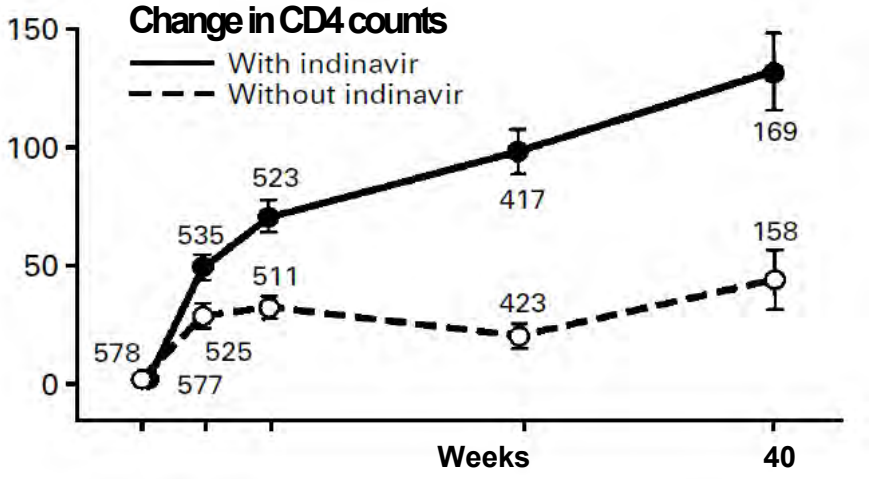
AZT + 3TC + Indinavir → *48 weeks*

Superiority Trial
Primary end-point: development of AIDS or death

Reponses of CD4 cells and Plasma HIV RNA Paralleled Clinical Results

- Clinical Efficacy Results
  - 50% reduction of progression to AIDS and death (6 vs 11%, HR: 0.50, p< 0.001)
  - 57% reduction of mortality 1.4 vs 3.1 %, HR 0.43; p=0.004)
- Change in CD4 counts
  - Mean CD4 cell count at BL : 87 cells
  - Mean increase difference by 82 cells at week 40 in the triple arm vs dual arm
- Changes in plasma HIV RNA levels
  - Mean decrease in VL : 0.6 vs 2.3 log at week 24 (p< 0.001)
  - 60% triple arm vs 9% dual arm had < 500 cp/ml at week 24



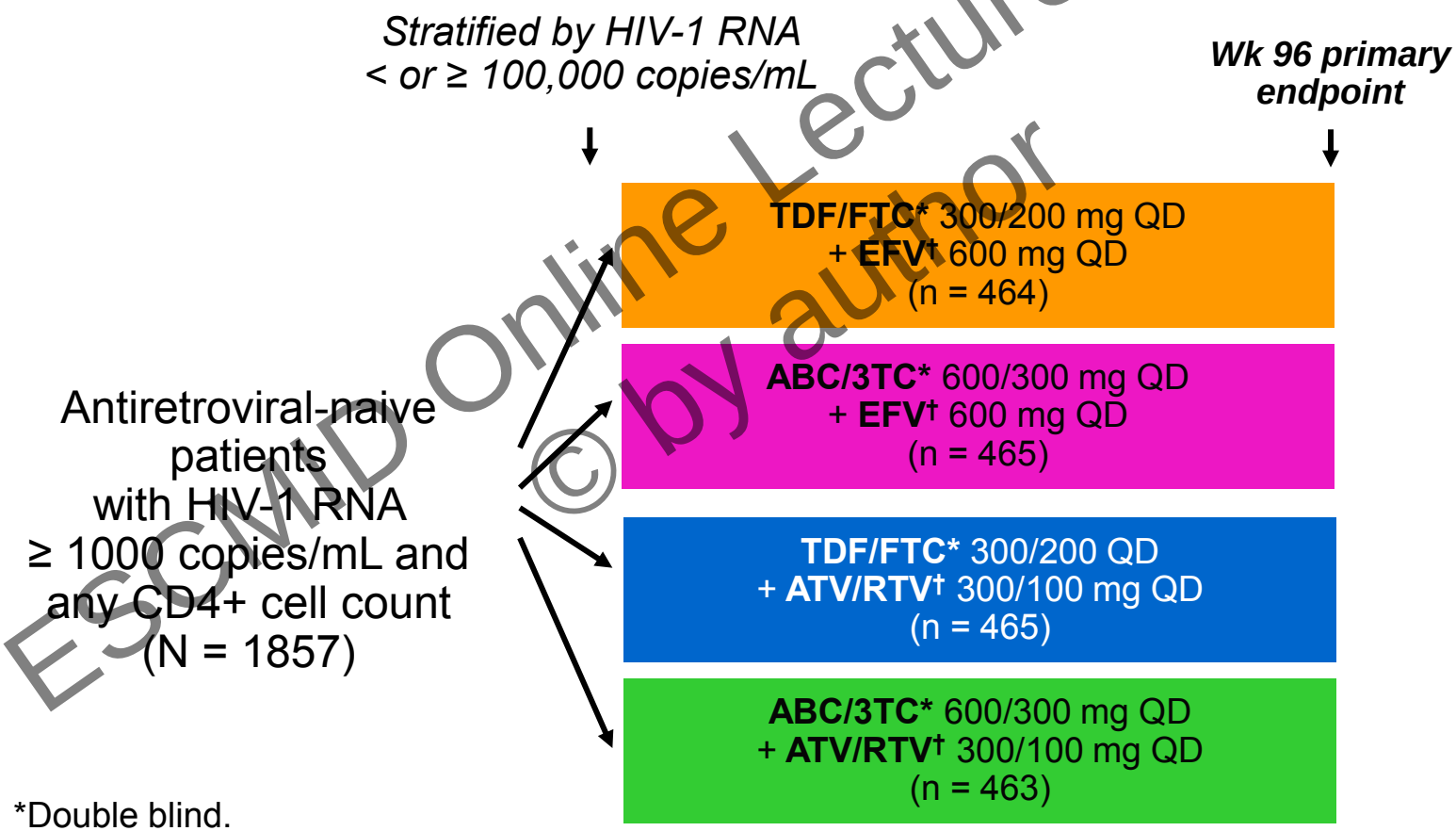


Hammer et al NEJM 1997

2014 US DHHS Guidelines
What to Start with ?

- **3 types of regimens are now recommended <u>regardless of viral load and CD4 counts</u> for treatment naïve patients**
- **All include 2 NRTIs plus either NNRTI, PI/r, or INSTI**
- **NNRTI : EFV + TDF/FTC (664 €/month)**
- **PI/r: ATV/r or DRV/r + TDF/FTC (860 € /month)**
- **INSTI:**
  - **RAL, DTG or EVG (cobi) + TDF/FTC (885 €/month)**
    - **DTG + ABC/3TC**

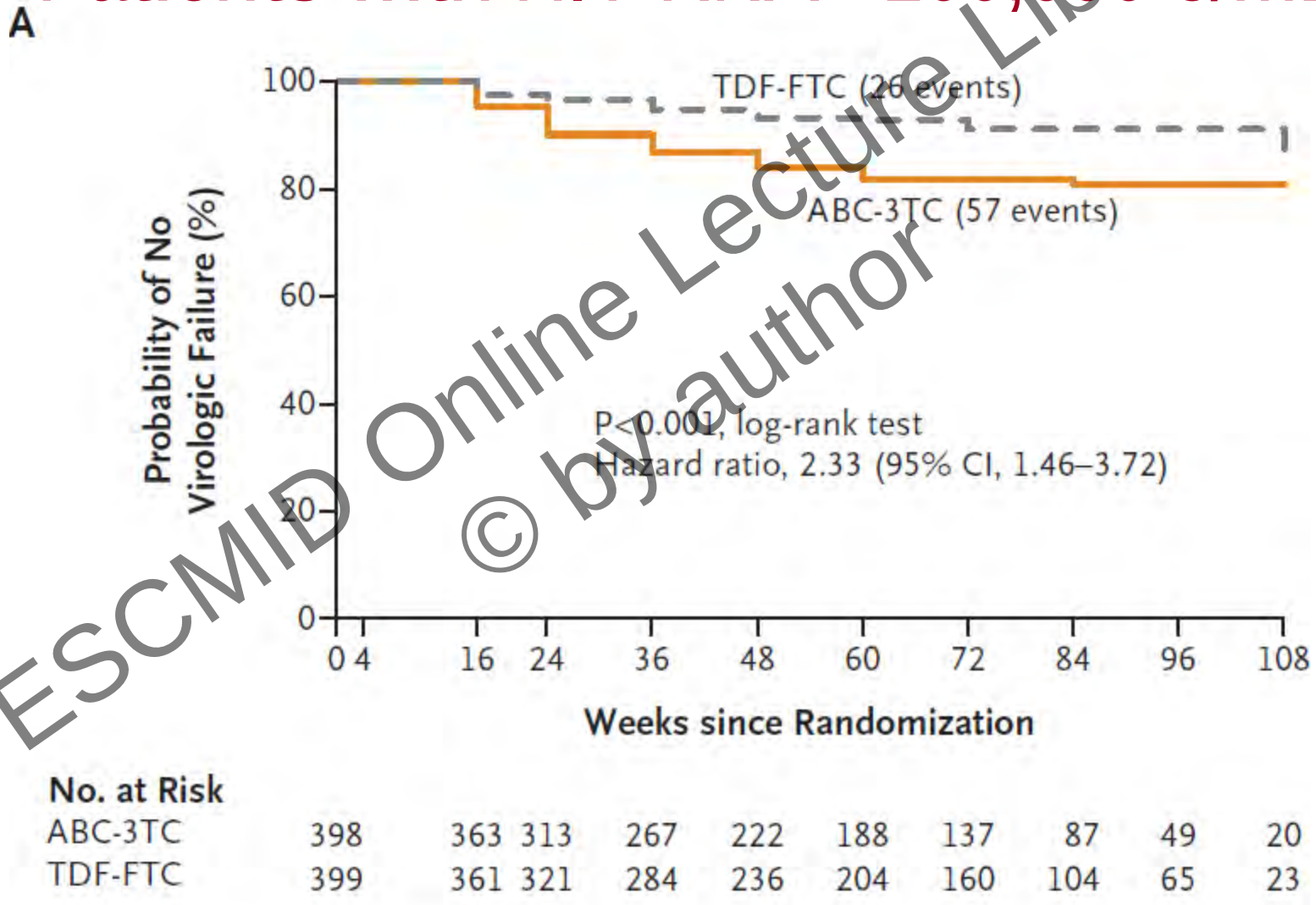
ACTG 5202: First-line Therapy With ABC/3TC vs TDF/FTC + EFV vs ATV/RTV



*Double blind.
†Open label.

Daar E, et al. Ann Inter Med 2011.

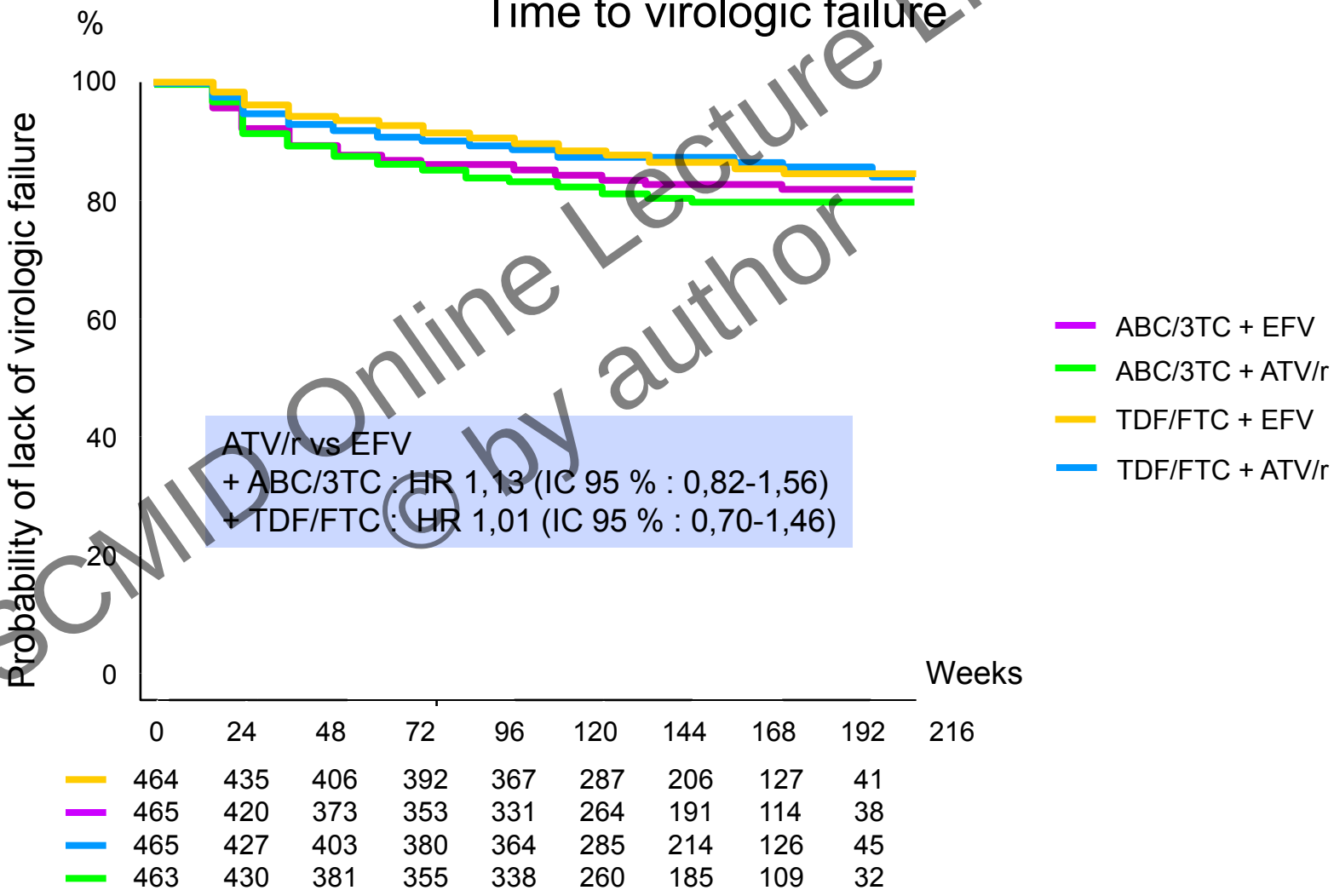
A5202: Time to Virologic Failure in Patients with HIV RNA >100,000 c/mL



Pros and Cons of TDF/FTC vs ABC/3TC

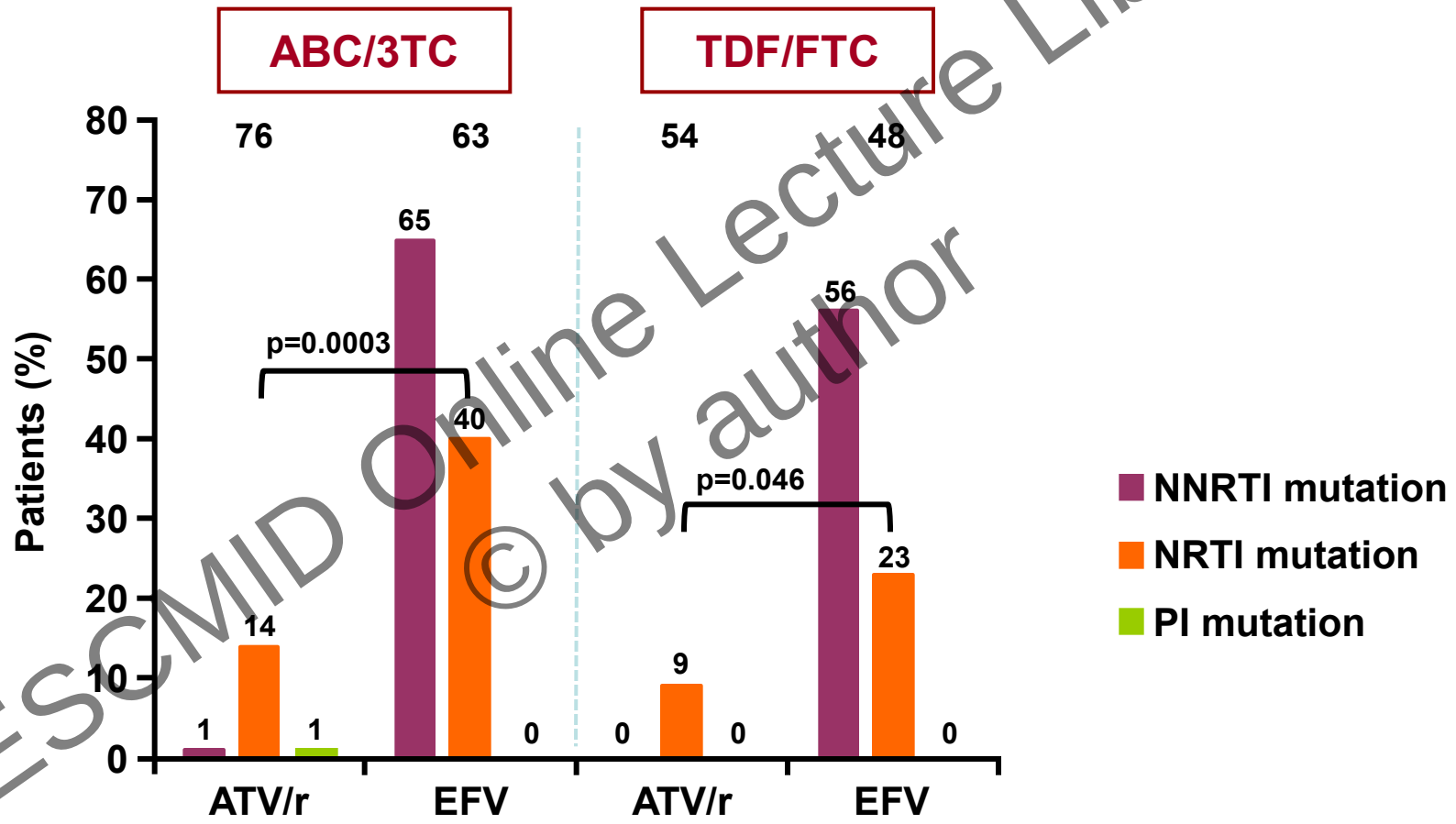
Regimen	Advantages	Disadvantages
ABC/3TC	▪ High level of efficacy in clinical trials with EFV, DTG or boosted PIs in patients with VL < 100,000 c/mL ▪ No renal toxicity ▪ Will be coformulated with dolutegravir	▪ Inferior response in pts with VL > 100,000 c/mL with EFV or boosted PI ▪ Potential for HSR reaction to ABC which can be avoided by with HLA-B*5701 assay ▪ Association with ↑ risk of MI in some studies
TDF/FTC	▪ High level of efficacy in clinical trials with EFV or boosted PIs in patients with VL > 100,000 c/mL ▪ Coformulated with EFV, EVG, and RPV as STR (single tablet regimen) ▪ Better tolerability than ABC/3TC when combined with EFV ▪ Lower increases in lipids than ABC/3TC ▪ No HSR requiring HLA genotyping	▪ Long-term nephrotoxicity and tubular toxicity ▪ Bone toxicity

ACTG A5202 : ATV/r vs EFV



Daar E, Ann Intern Med 2011

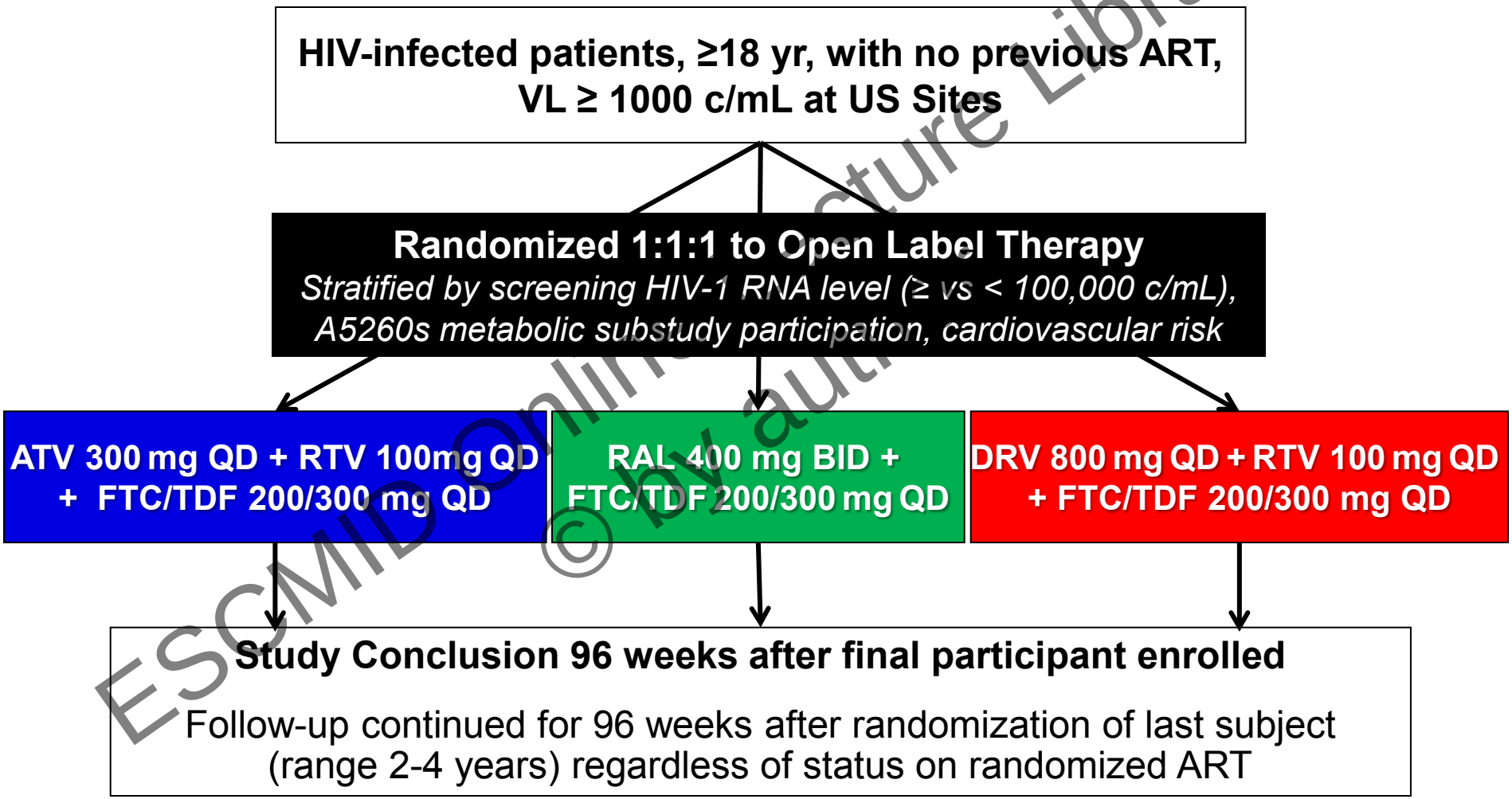
A5202: % of VFs with Emergence of Major Resistance Mutations



p values: ATV/r versus EFV (among failures); *Major mutations defined by IAS-USA (2008) list plus T69D, L74I, G190C/E/Q/T/V for RT and L24I, F53L, I54V/A/T/S and G73C/S/T/A for PR
IAS-USA = International AIDS Society-USA

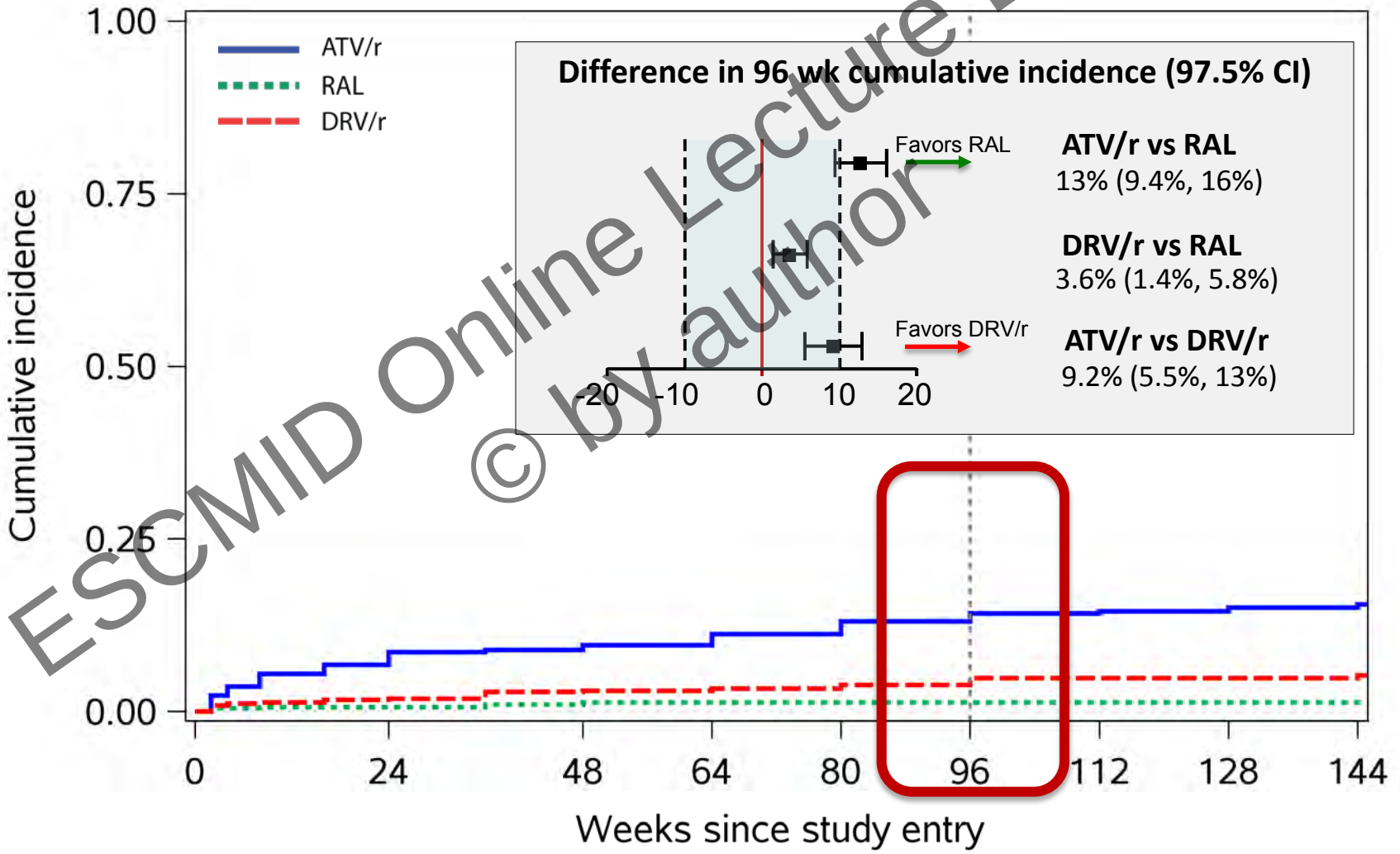
Daar E, et al. Ann Intern Med 2011

A5257 Study Design*



Landovitz et al. CROI 2014 Abstract 85

Cumulative Incidence of Tolerability Failure

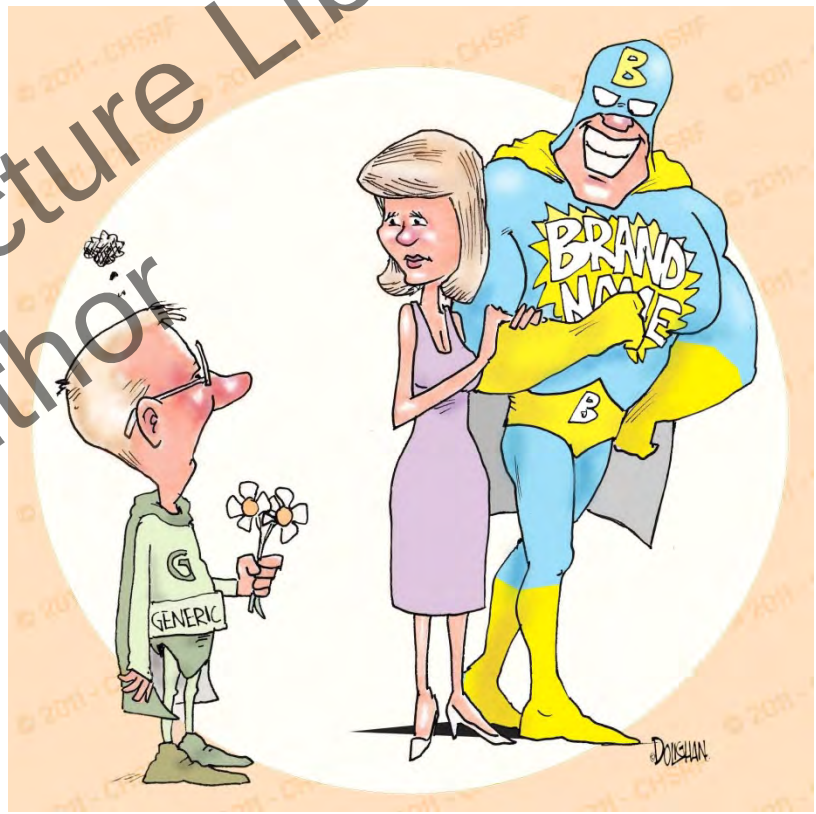


Pros and Cons of NNRTIs vs PIs vs INSTI

Regimen	Advantages	Disadvantages
NNRTIs	▪ Low pill burden (STR) ▪ Low cost	▪ Genotypic resistance test required before treatment ▪ Low genetic barrier to resistance ▪ Tolerability issues with EFV/NVP ▪ Only active against HIV-1
PIs/r	▪ High genetic barrier to resistance ▪ No genotypic resistance test required before starting Rx	▪ Drug-drug interactions ▪ Higher pill burden ▪ Triglyceride elevation ▪ Increase in TDF exposure ▪ Cost
INSTIs	▪ Good tolerability profile ▪ Limited drug drug interaction	▪ Genotypic resistance test required before treatment ▪ Low genetic barrier to resistance ▪ Cost

Generic Drugs for HIV Therapy

- Drugs available (50% discount)
  - NRTIs :
    - AZT
    - 3TC
  - NNRTIs
    - Nevirapine
    - EFV



- Will we break STR to use QD or BID regimens ?

Conclusions

- Antiretroviral therapy has improved and is still improving providing patients more effective and convenient regimens
- More patients are likely to receive treatment not only for their own health, but also to prevent transmission to their partners
- Multiple treatment options are available today, and the choice is mainly driven by
  - Early and long-term tolerability,
  - Convenience of the regimen (fixed combinations)
  - Cost