Update on HIV Infection

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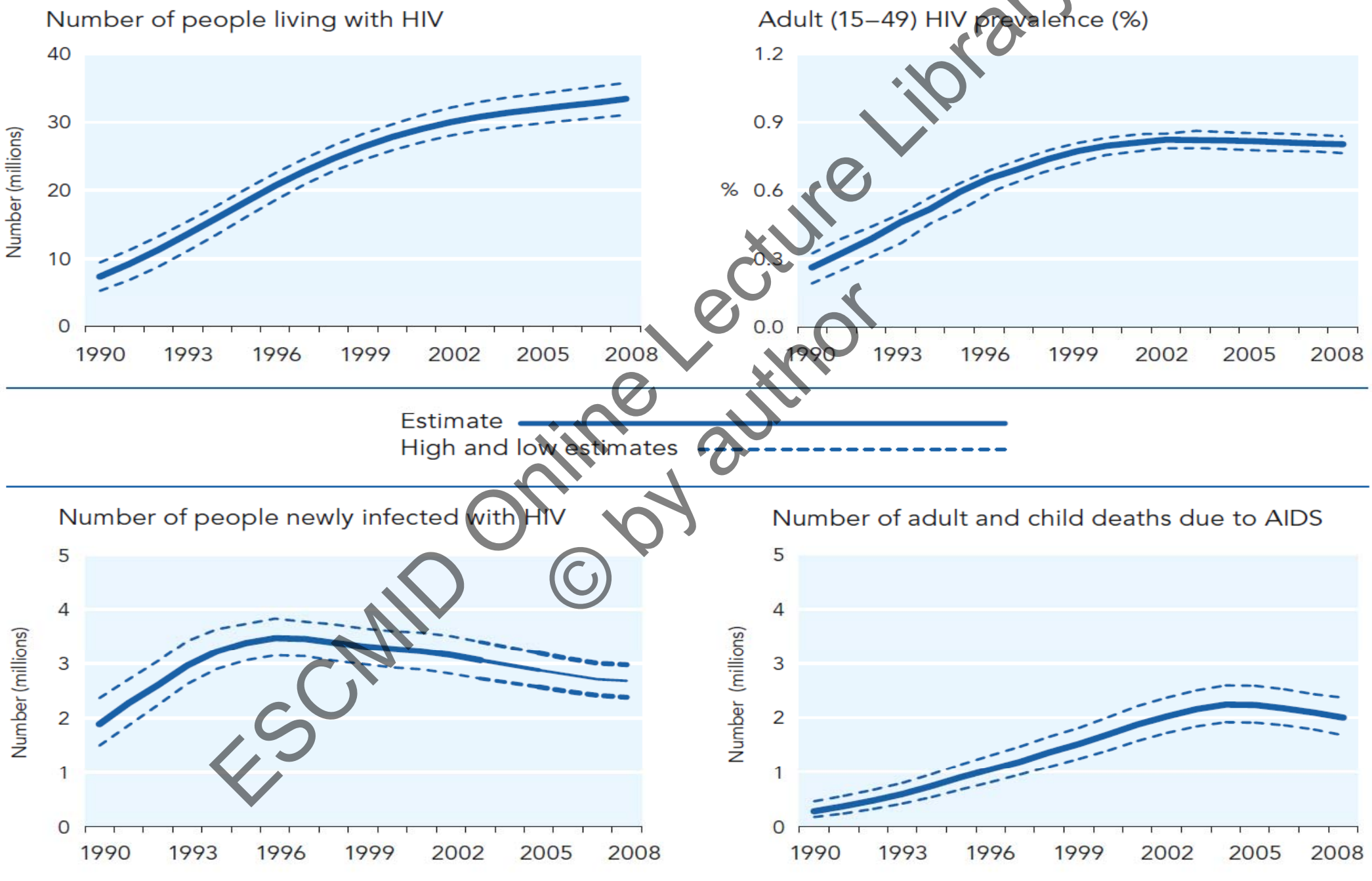
Global estimates 1990–2008



Update on HIV infection

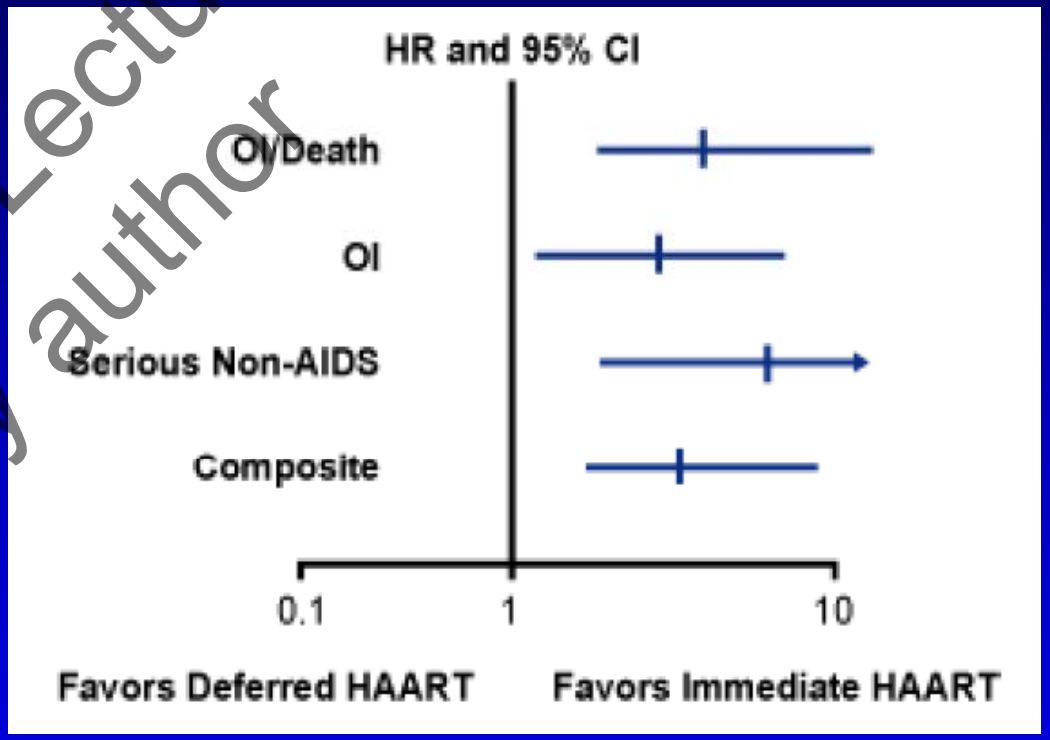
- Start ART earlier
- Integrase inhibitors – firstline,
- Preferred drugs - guideline changes
- Pharmacoenhacers – next generation
- Test & treat strategies, global HIV treatment
- HIV vaccine

Start ART earlier

Studies That Informed Guidelines on When to Start (1)

SMART trial[1]

- Reduced risk of both opportunistic disease and serious non-AIDS events observed in patients who initiated and remained on antiretroviral therapy at CD4+ cell counts > 350 cells/mm^3



1.Emery S, et al. J Infect Dis. 2008;197:1133-1144.

Studies That Informed Guidelines on When to Start (2)

- ART-CC[2]
  - Smaller absolute risk of AIDS or death seen for patients starting ART at CD4+ cell counts > 350 cells/mm^3 vs ≤ 350 cells/mm^3
- NA-ACCORD[3]
  - Survival benefit with earlier vs deferred ART
    - Risk of death 69% higher for patients deferring ART until CD4+ cell count ≤ 350 cells/mm^3 vs 351-500 cells/mm^3
    - Risk of death 94% higher for patients deferring ART until CD4+ cell count ≤ 500 cells/mm^3 vs > 500 cells/mm^3

2. When to Start Consortium. Lancet. 2009;373:1352-1363.
3. Kitahata MM, et al. N Engl J Med. 2009;360:1815-1826

New Studies Supporting Earlier Antiretroviral Therapy

- Low CD4+ nadir associated with
  - Increased rates of HIV-associated neurocognitive disorders[1]
  - Arterial stiffness contributing to CV risk[2]
  - Increased risk of fracture[3]
- Patients with acute OI
  - 2-fold higher risk of clinical progression in patients who deferred HAART vs those started immediately[4]
  - Improved immunologic outcomes in patients starting early vs deferred HAART during acute OI[5]

1. Ellis R, et al. CROI 2010. Abstract 429. 2. Ho J, et al. CROI 2010. Abstract 707. 3. Dao C, et al. CROI 2010. Abstract 128. 4. Miro J, et al. CROI 2010. Abstract 529. 5. Sanchez A, et al. CROI 2010. Abstract 509.

HIV Transmission Risk in Heterosexual Serodiscordant Couples Initiating ARV

- 92% lower risk of HIV transmission in African serodiscordant couples when HIV-infected partner receiving ARV therapy
  - 3381 couples
  - 103 individuals with incident infections that were genetically linked to the primary partner,
  - 102 of 103 cases of confirmed HIV transmission occurred in couples with HIV-infected partner not receiving ARV therapy

Donnell D, et al. CROI 2010. Abstract 136.

When to Start: 2009 DHHS Guidelines

CD4+ Cell Count	Recommendation
▪ CD4+ cell count < 350 cells/mm³	▪ Start ART
▪ CD4+ cell count 350-500 cells/mm³	▪ Start ART (55% strongly recommend and 45% moderately recommend)
▪ CD4+ cell count > 500 cells/mm³	▪ Panel divided (50% favor initiating therapy)
Clinical Conditions Favoring Initiation of Therapy Regardless of CD4+ Cell Count	
▪ History of AIDS-defining illness ▪ Certain acute opportunistic infections ▪ Pregnancy ▪ HIVAN ▪ HBV coinfection when HBV treatment is indicated ▪ CD4+ count decline > 100 cells/mm³ per yr ▪ HIV-1 RNA > 100,000 copies/mL	

DHHS: http://aidsinfo.nih.gov/Guidelines.

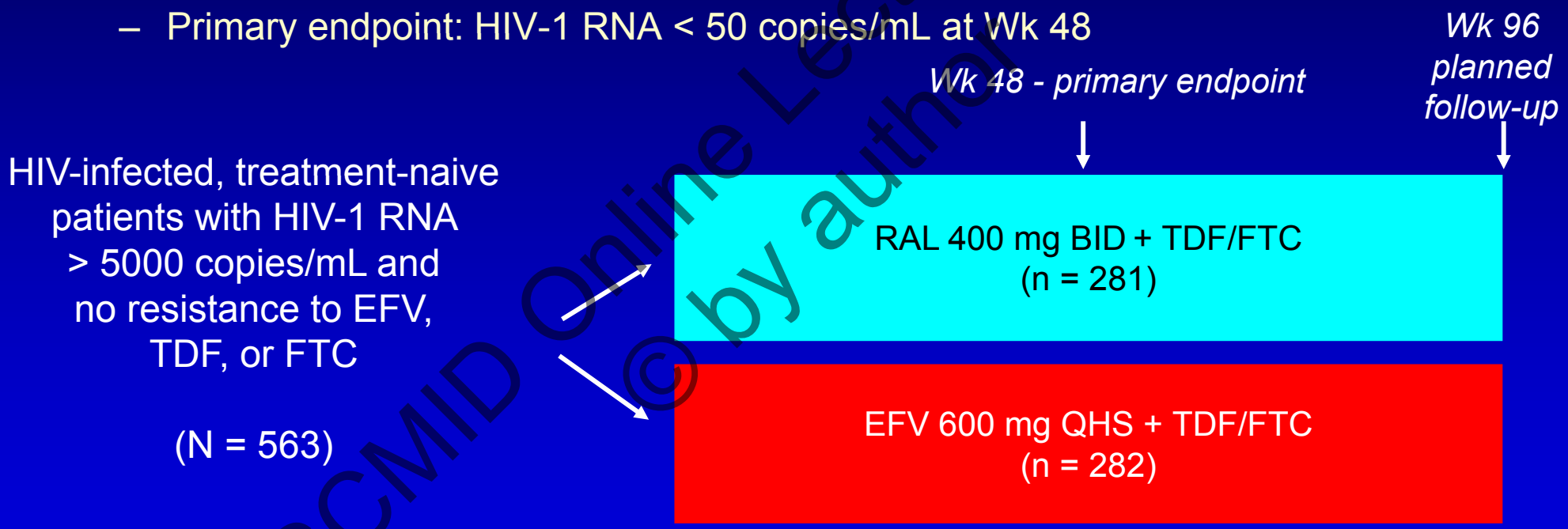
EACS

SYMPTOMATIC	• CDC stage B and C: treatment recommended • If OI, initiate as soon as possible*
ASYMPTOMATIC	• CD4 < 200: Treatment recommended, without delay. • CD4 201-350: treatment recommended. • CD4 350-500: - Treatment recommended if hepatitis C co-infection, hepatitis B co-infection requiring therapy, HIV-associated nephropathy or other specific organ deficiency; - Treatment should be considered if VL>10^5 c/ml and/or CD4 decline >50-100/mm^3/year or age >50 or, pregnancy, high cardiovascular risk, malignancy. • CD4 > 500: - Treatment should generally be deferred, independently of plasma HIV RNA; closer follow-up of CD4 if VL > 10^5 c/ml. - Treatment can be offered if presence of ≧ 1 of the above co-morbid conditions (CD4 350-500). • Whatever CD4 and Plasma HIV RNA, treatment can be offered on an individual basis, especially if patient is seeking and ready for ARV therapy

Integrase inhibitors – firstline

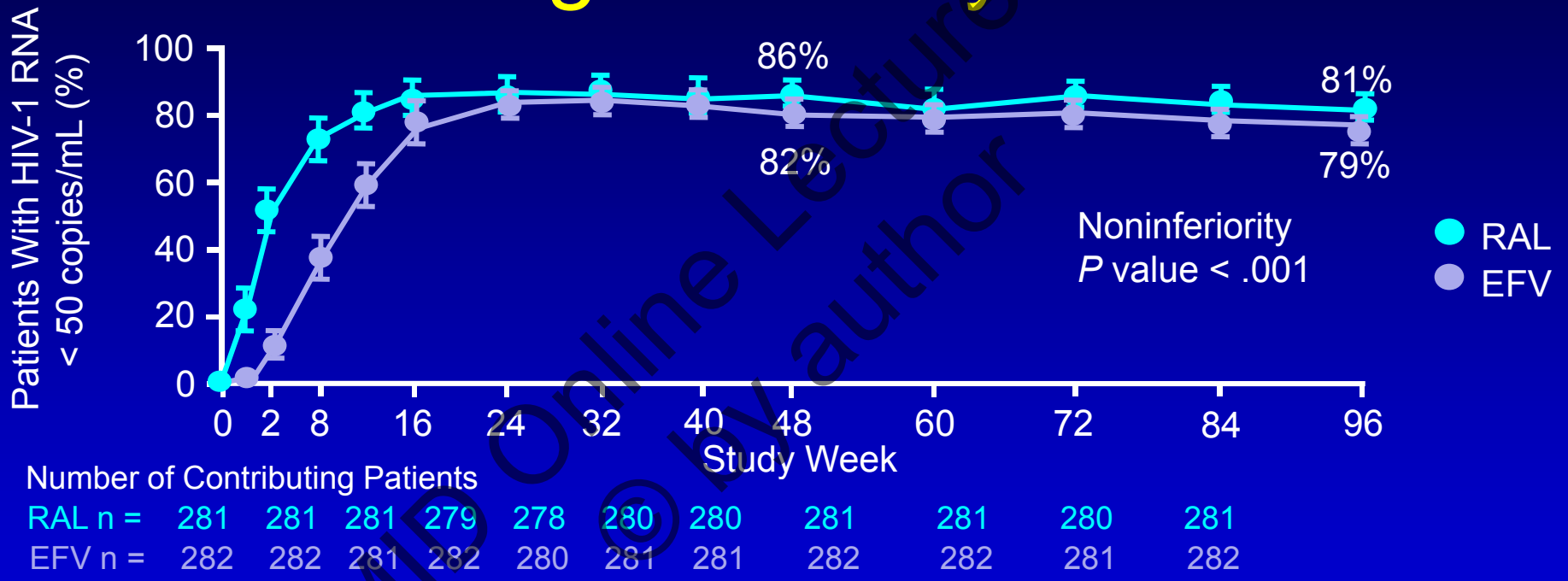
STARTMRK Phase III: RAL vs EFV in Treatment-Naive Patients

- Randomized, placebo-controlled trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



- 53% of patients had HIV-1 RNA > 10^5 copies/mL; 47% of patients had CD4+ cell counts < 200 cells/mm^3 at baseline

STARTMRK: Virologic and Immunologic Efficacy at Wk 96



- Significantly shorter time to virologic response with RAL vs EFV (*P* = .001)
- Similar CD4+ cell count increases with RAL vs EFV
  - +240 vs +225 cells/mm^3; Δ: 15 cells/mm^3 (95% CI: -13-42)

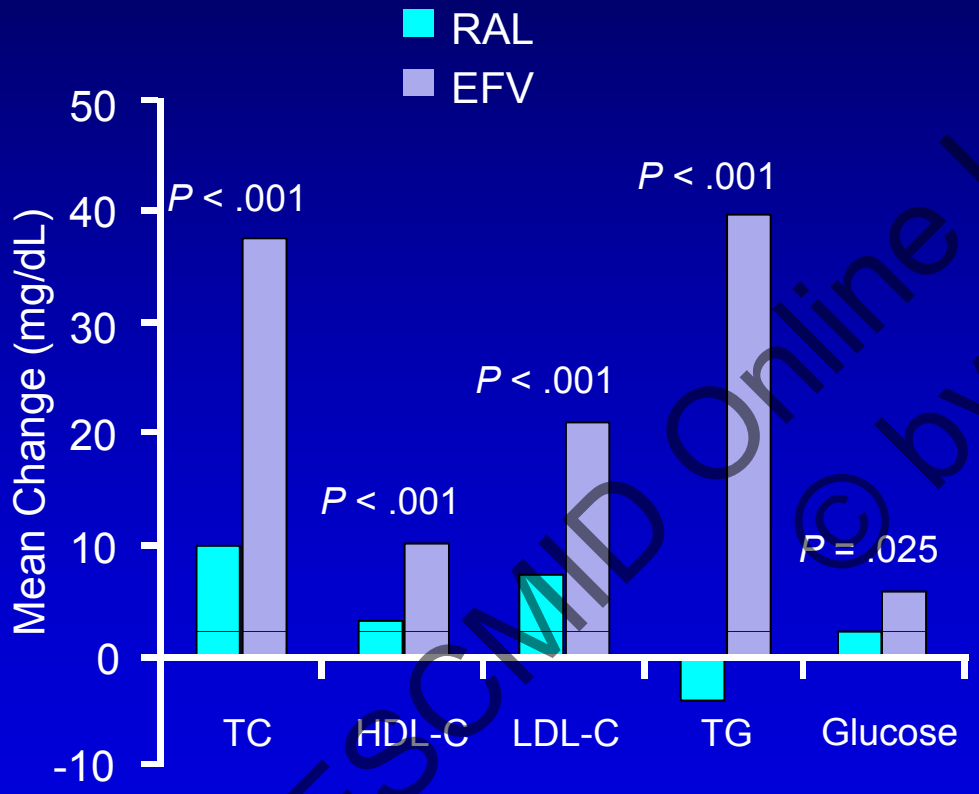
Lennox J, et al. *Lancet 2009; 374: 796–806*

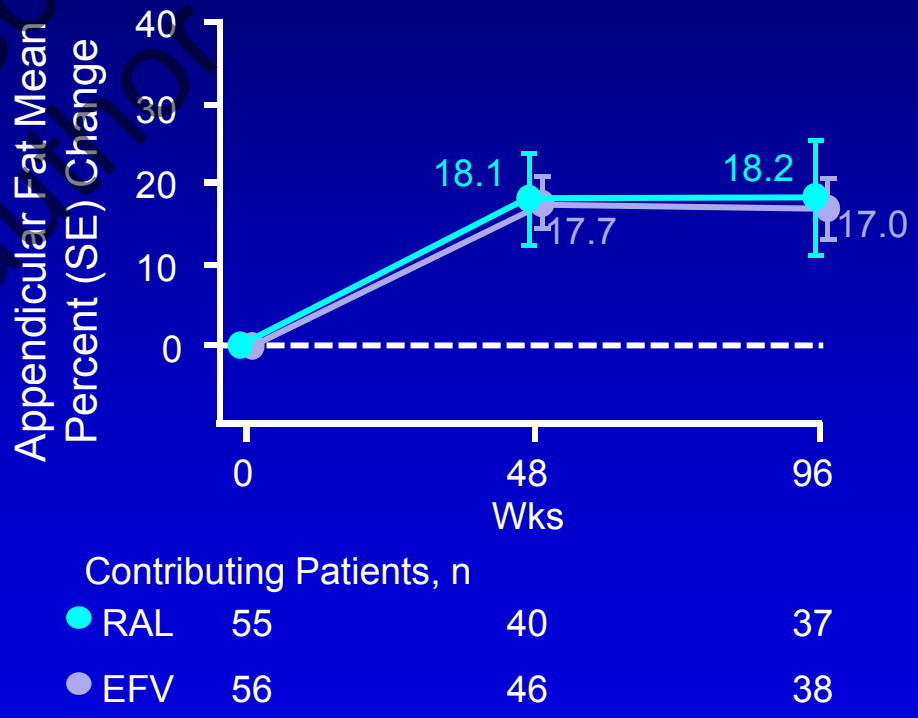
STARTMRK: Adverse Events at Wk 96

- Drug-related clinical adverse events more frequent with EFV vs RAL (78% vs 47%; *P* < .0001)
  - Serious clinical adverse events in 14% of patients in RAL arm and 12% of patients in EFV arm (*P* = .457)
- Fewer patients experienced CNS events by Wk 8 with RAL vs EFV (10.3% vs 17.7%; P = .015)
- Malignancies developed in 3 patients in RAL arm vs 11 patients in EFV arm
  - Kaposi's sarcoma (n = 7), anal cancer (n = 1), B-cell non-Hodgkin's lymphoma (n = 1), bone cancer (n = 1), lung cancer (n = 1), basal cell cancer (n = 3)

Lennox J, et al. *Lancet 2009; 374: 796–806*

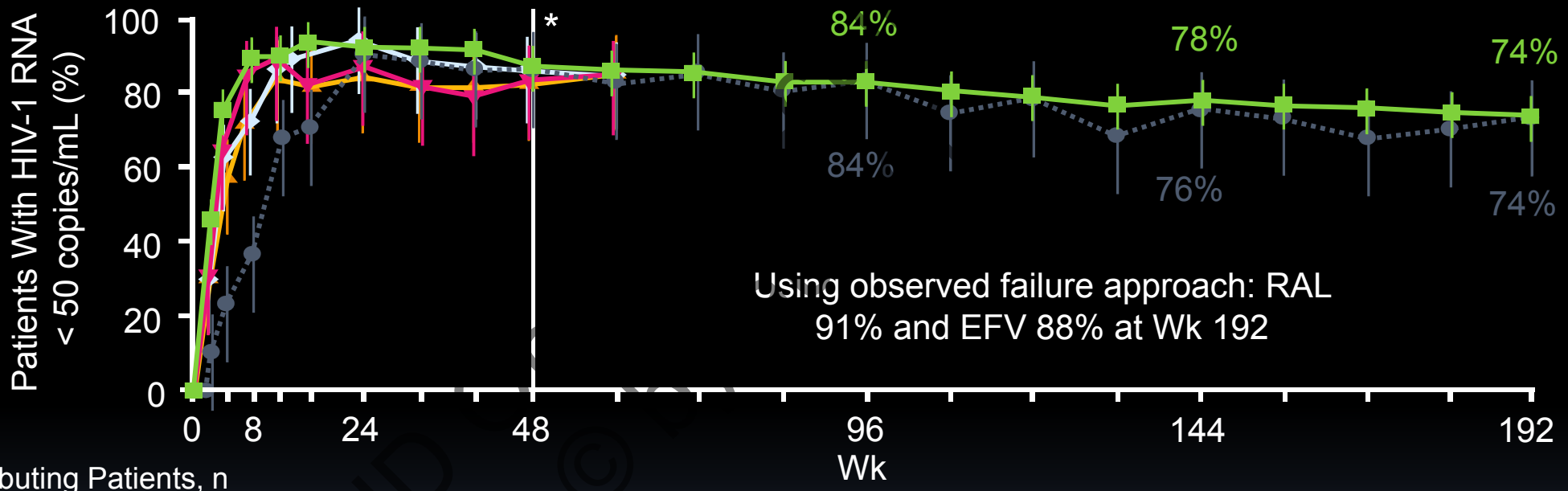
STARTMRK: Metabolic, Body Composition Changes at Wk 96 With RAL vs EFV





DeJesus E, et al. CROI 2010. Abstract 720.

Protocol 004: 192-Wk Virologic Response to RAL vs EFV in Naive Patients (NC = F)



Contributing Patients, n						
RAL 100 mg BID	39	39	39			
RAL 200 mg BID	40	40	40			
RAL 400 mg BID	41	41	41	159	158	160
RAL 600 mg BID	40	40	40			
EFV 600 mg QD	38	37	38	38	38	38

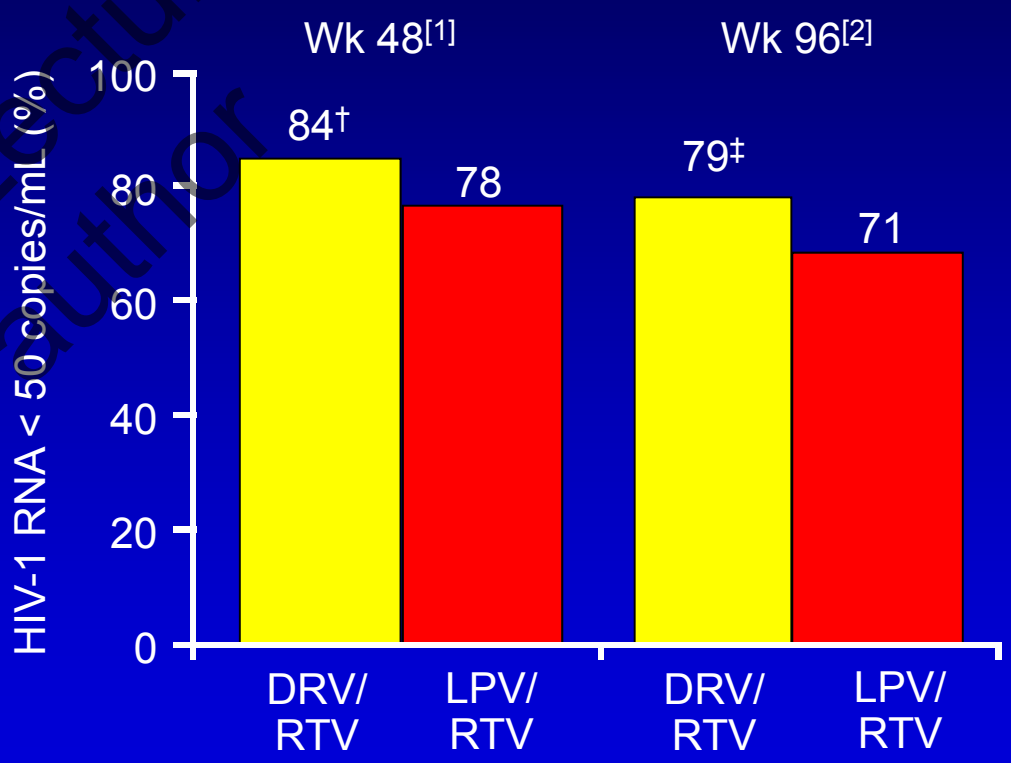
*After Wk 48, patients in all RAL groups continued at 400 mg BID. All patients received TDF+3TC.

Gotuzzo E, et al. CROI 2010. Poster 514.

Preferred drugs - guideline changes

ARTEMIS: Wk 96 Response to DRV/RTV vs LPV/RTV in Naive Pts

- Randomized, open-label, 96-wk study
- DRV/RTV 800/100 mg QD (n = 343) vs LPV/RTV tablet or capsule 400/100 mg BID or 800/200 mg QD* (n = 346)
  - Plus TDF/FTC 300/200 mg QD
- DRV/RTV noninferior to LPV/RTV at Wk 48; superior at Wk 96
- CD4+ gain: +171 (DRV/RTV) vs +188 (LPV/RTV) at Wk 96



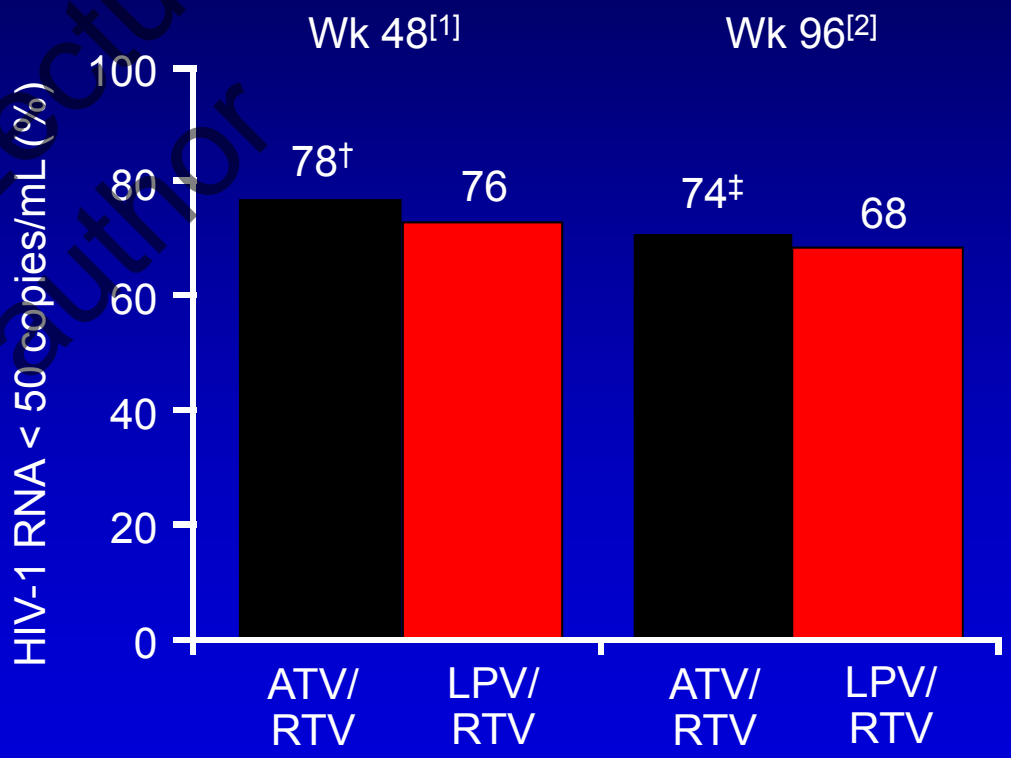
†Noninferiority, P < .001; superiority, P = .062
‡Noninferiority, P < .001; superiority, P < .012

*Depending on availability; switch allowed.

1. Ortiz R, et al. AIDS. 2008;22:1389-1397. 2. Mills A, et al. AIDS. 2009;23:1679-88

CASTLE: Wk 96 Response to ATV/RTV vs LPV/RTV in Naive Pts

- Randomized, open-label, 96-wk study
- ATV/RTV 300/100 mg QD (n = 440) vs LPV/RTV 800/200 mg QD* (n = 443)
  - Plus TDF/FTC 300/200 mg QD
- ATV/RTV noninferior to LPV/RTV at Wk 48; superior at Wk 96
- CD4+ gain: +268 (ATV/RTV) vs +290 (LPV/RTV) at Wk 96

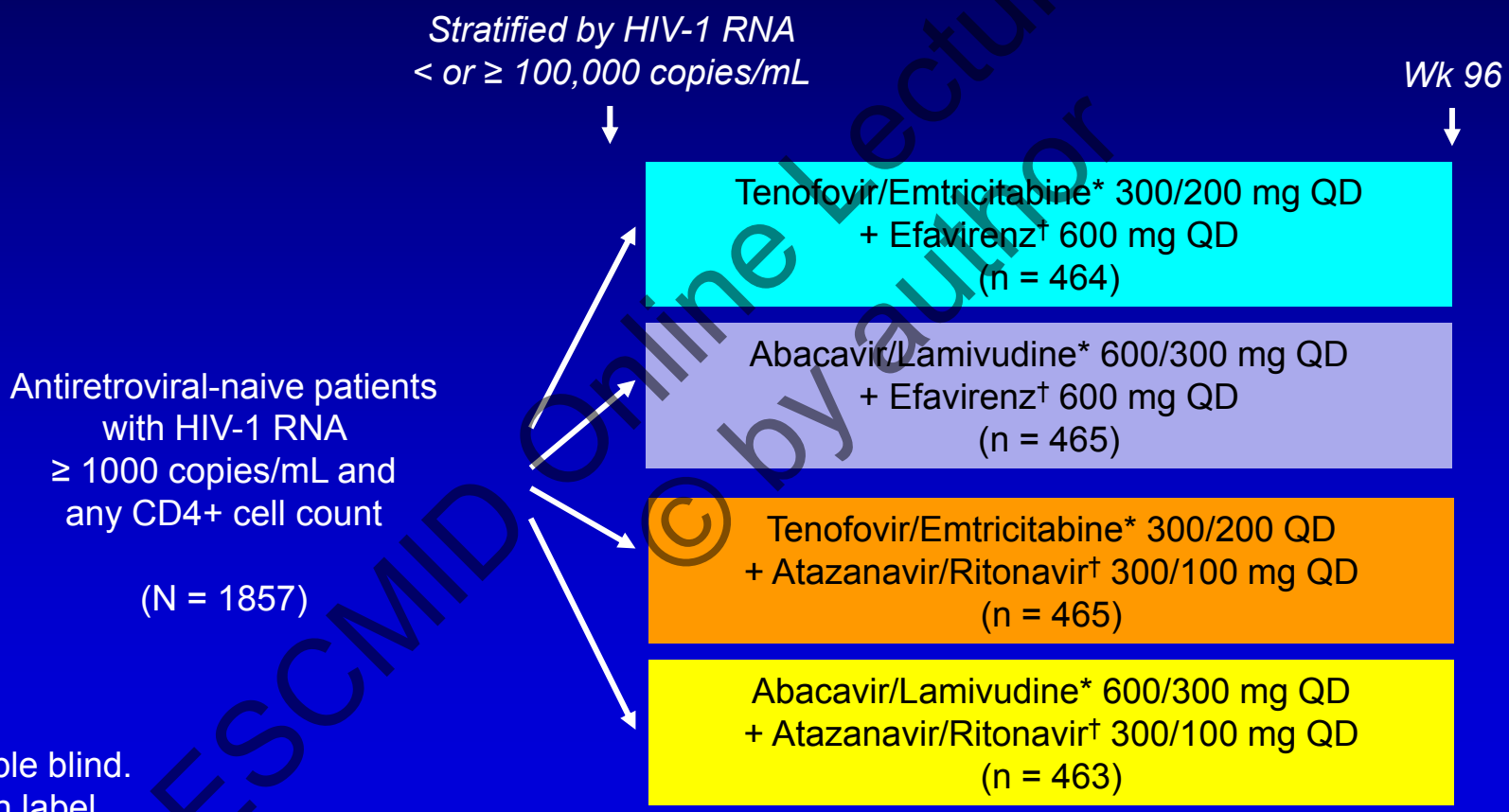


*SGC until Wk 48; tablet formulation after Wk 48.

†Est diff: 1.7% (95% CI: -3.8% to 7.1%; P = NS). ‡Est diff: 6.1% (95% CI: 0.3% to 12.0%; P < .05).

1. Molina JM, et al. Lancet. 2008;372:646-655. 2. Molina JM, et al. ICAAC/IDSA 2008. Abstract 1250d.

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

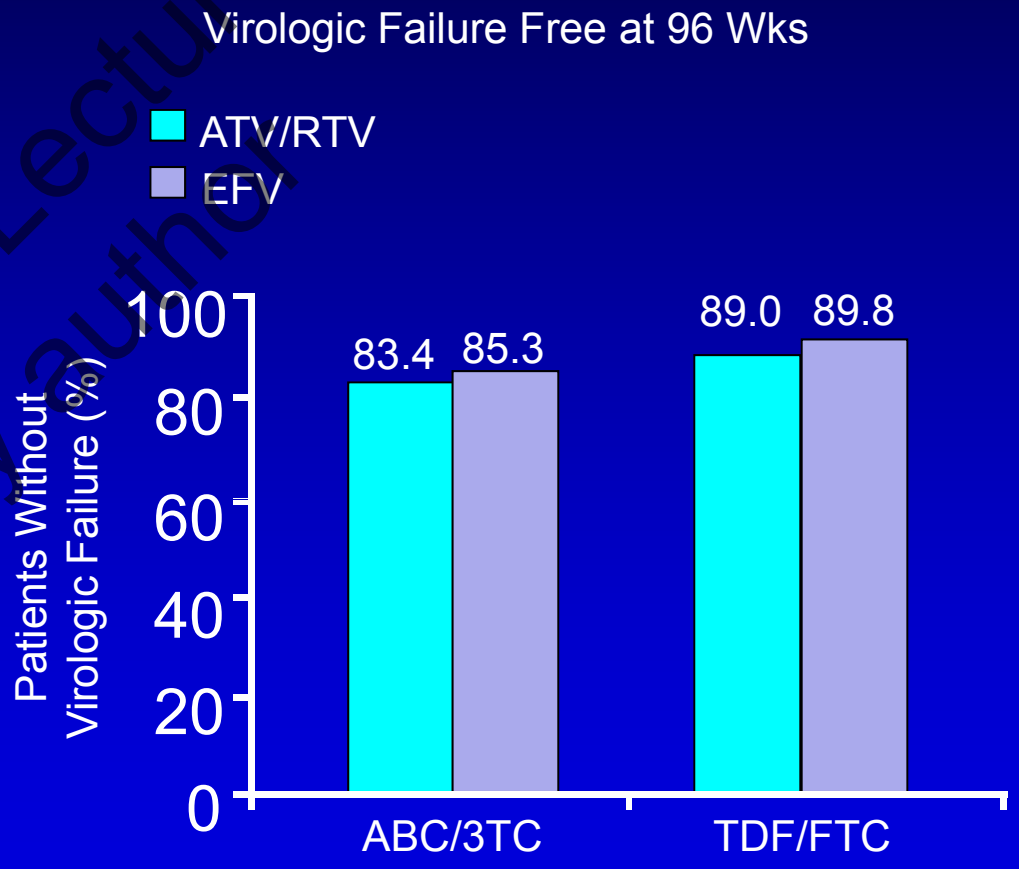


*Double blind.
†Open label.

Daar E, et al. CROI 2010. Abstract 59LB.

ACTG 5202: Virologic Failure With ATV/RTV vs EFV

- Similar time to virologic failure with ATV/RTV vs EFV when combined with either ABC/3TC or TDF/FTC in overall population analysis
  - With ABC/3TC, HR: 1.13 (95% CI: 0.82-1.56)
  - With TDF/FTC, HR: 1.01 (95% CI: 0.70-1.46)



Daar E, et al. CROI 2010. Abstract 59LB.

ACTG 5202: Virologic Failure With ABC/3TC vs TDF/FTC

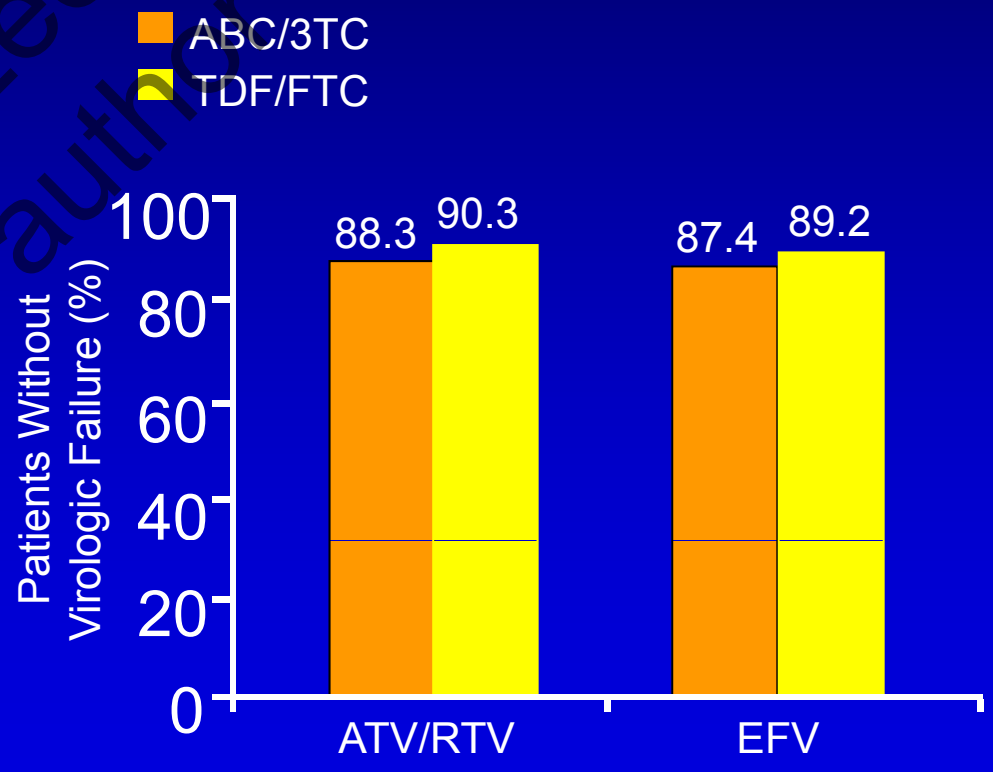
In pts with screening VL < 100,000 c/mL

- Similar time to virologic failure with ABC/3TC vs TDF/FTC regardless of ATV/RTV or EFV
  - With ATV/RTV, HR: 1.26 (0.76-2.05)
  - With EFV, HR: 1.23; (0.77-1.96)

In pts with screening VL ≥ 100,000 c/mL

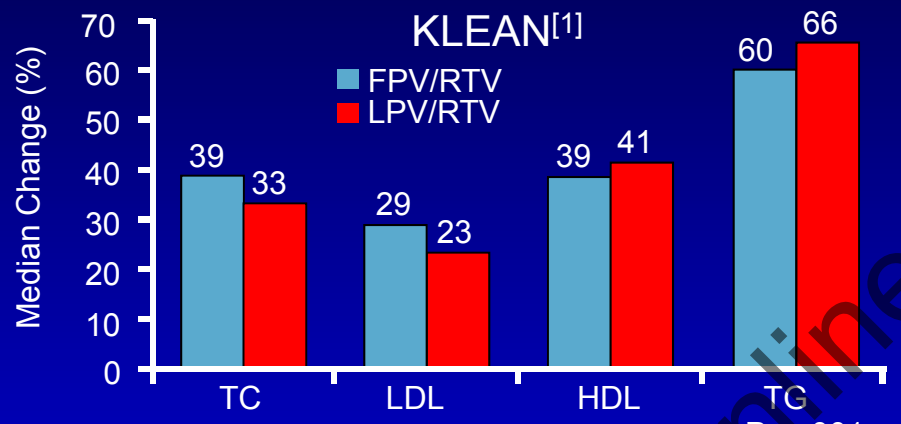
- Shorter time to VF with ABC/3TC vs. TDF/FTC with either EFV or ATV/RTV
  - With EFV, HR: 2.22 (1.19-4.14)
  - With ATV/RTV, HR: 2.46 (1.20-5.05)

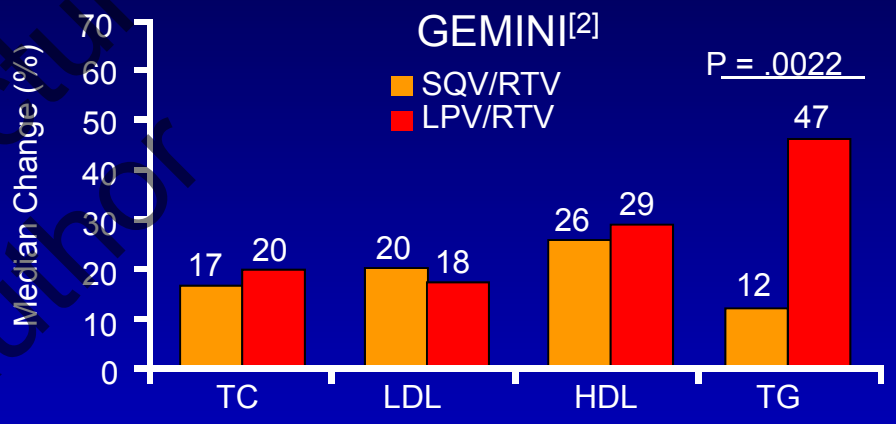
Virologic Failure Free at 96 Wks for Pts With Screening VL < 100,000 copies/mL

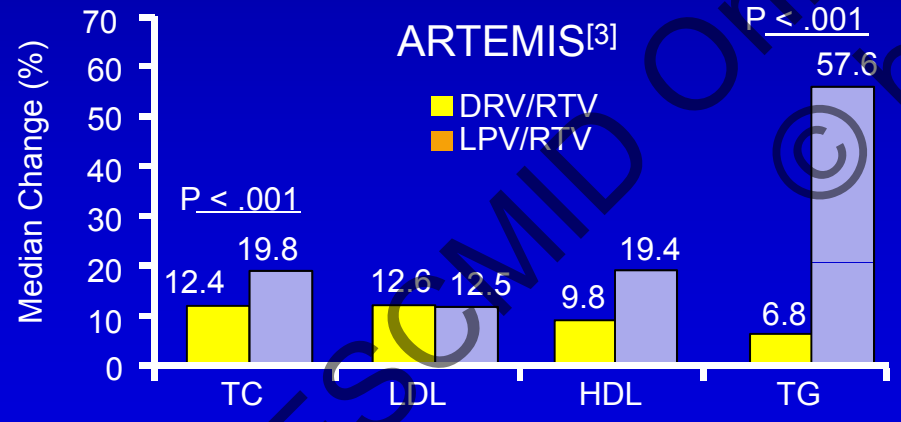


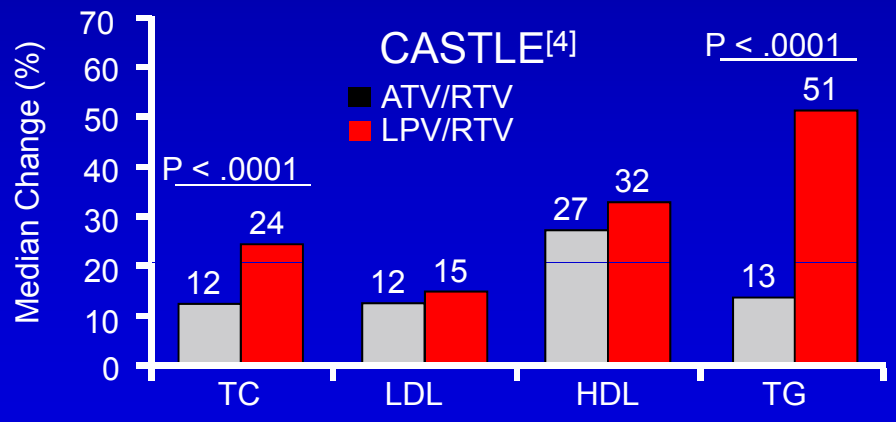
Daar E, et al. CROI 2010. Abstract 59LB.

Lipid Changes From BL to Wk 48









This slide is an illustration only and not meant to be a cross-study comparison.

1. Eron J Jr, et al. Lancet. 2006;368:476-482. 2. Walmsley SL, et al. J. Infect Dis. 2009;50:367-374. 3. Nelson M, et al. Inter Congress on Drug Therapy in HIV Infection 2008. Abstract P127. 4. Reprinted from The Lancet, v 372, Molina JM, et al, pp 646-655, Copyright 2008, with permission from Elsevier.

2009 DHHS Guidelines
Initial Treatment: Preferred

NNRTI based	▪EFV/TDF/FTC[1,2]
PI based	▪ATV/r + TDF/FTC[2] ▪DRV/r (QD) + TDF/FTC[2]
II based	▪RAL + TDF/FTC[2]
Pregnant Women	▪LPV/r (BID)[3] + ZDV/3TC

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.

December 2009

2009 DHHS Guidelines
Initial Treatment: Alternatives

NNRTI based	▪EFV[1] + (ABC/3TC) or (ZDV/3TC)[2] ▪NVP[4] + ZDV/3TC
PI based	▪ATV/r + (ABC/3TC) or (ZDV/3TC)[2,3] ▪FPV/r (QD or BID) + (ABC/3TC) or (ZDV/3TC) or (TDF/FTC)[2,3] ▪LPV/r (QD or BID) + (ABC/3TC) or (ZDV/3TC) or (TDF/FTC)[2,3] ▪SQV/r + TDF/FTC[2]

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. ABC should not be used in patients who test positive for HLA B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.

December 2009

2009 DHHS Guidelines
Initial Treatment: Acceptable

NNRTI based	▪EFV[1] + ddI + (3TC or FTC)
PI based	▪ATV + (ABC/3TC) or (ZDV/3TC)[2,3]

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa.
3. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease .

December 2009

Initial Treatment: May Be Acceptable but More Definitive Data Needed

PI based	▪DRV/r + (ABC/3TC) or (ZDV/3TC)[1,2] ▪SQV/r + (ABC/3TC) or (ZDV/3TC)[1,2]
CCR5 Antagonist based	▪MVC + ZDV/3TC[1,3]
II based	▪RAL + (ABC/3TC) or (ZDV/3TC)[1]

1. 3TC can be used in place of FTC and vice versa.
2. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
3. Tropism testing required before treatment with MVC; use only if only CCR5-tropic virus is present.

December 2009

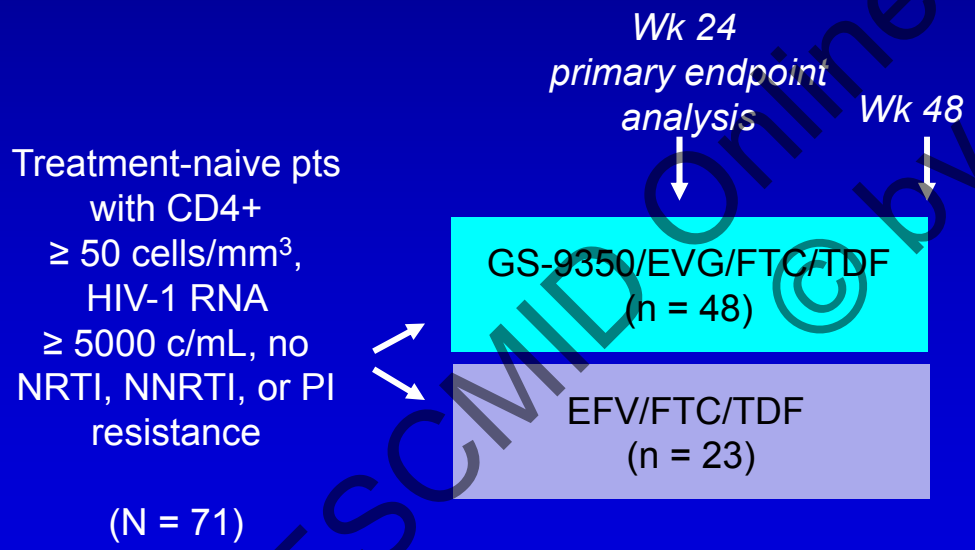
EACS 11/2009

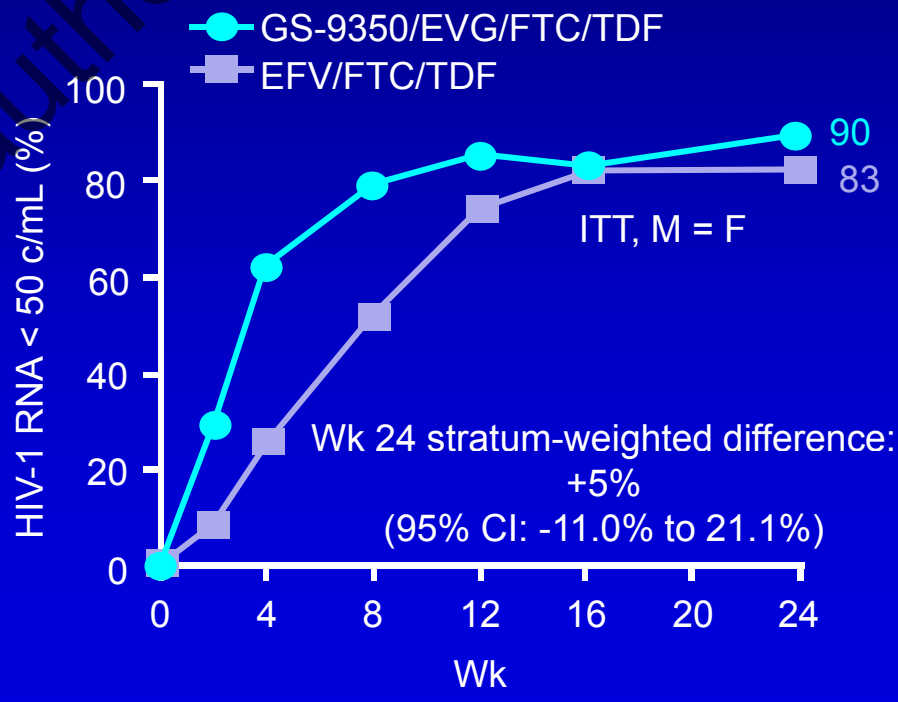
SELECT 1 DRUG IN COLUMN A AND 1 NRTI COMBINATION IN COLUMN B	A	B	REMARKS
Recommended	NNRTI • EFV[1] • NVP[5] or ritonavir-boosted PI • ATV/r[5] • DRV/r[6] • LPV/r[7] • SQV/r	TDF/FTC ABC/3TC[2-3-4]	- TDF/FTC co-formulated - ABC/3TC co-formulated - EFV/TDF/FTC co-formulated - ATV/r: 300/100 mg qd - DRV/r: 800/100 mg qd - LPV/r:400/100 mg bid or 800/200 mg qd - SQV/r:1000/100 mg bid
Alternative	SQV/r FPV/r RAL[9]	• ZDV/3TC[8] • ddI/3TC or FTC[8]	- SQV/r: 2000/100 mg qd - FPV/r:700/100 mg bid or 1400/200 mg qd - RAL: 400 mg bid - ZDV/3TC co-formulated

Pharmacoenhacers – next generation

GS-9350–Boosted Elvitegravir + FTC/TDF Noninferior to EFV/FTC/TDF in Naive Pts

- Cobicistat (GS-9350): investigational CYP3A inhibitor (boosting agent)
- Elvitegravir: investigational integrase inhibitor

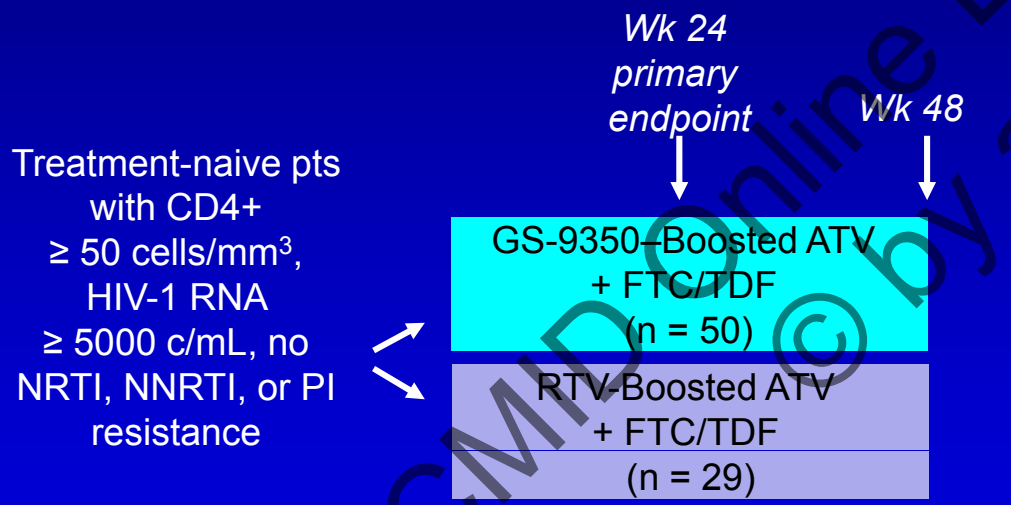


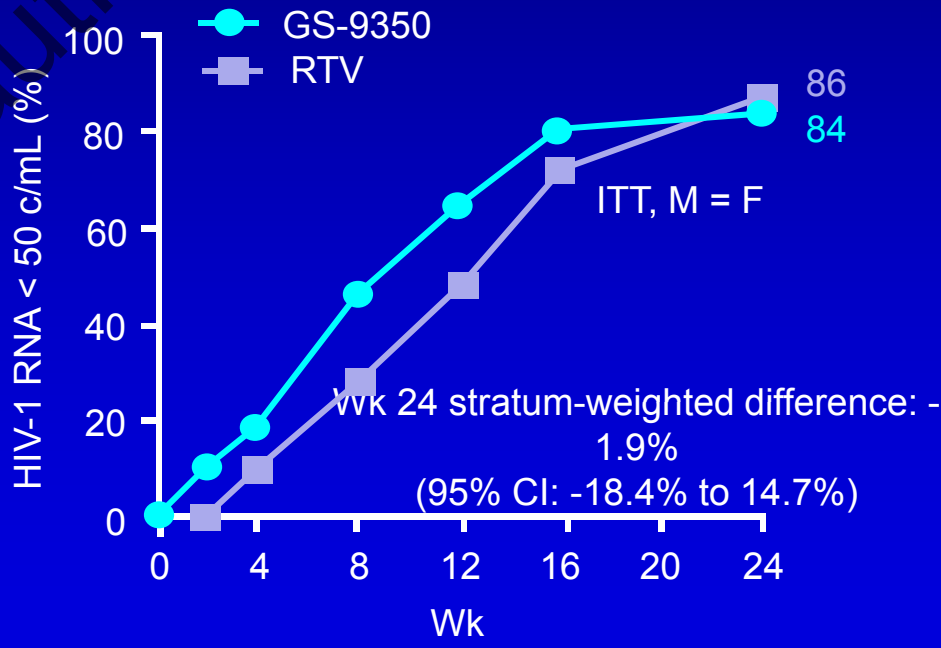


Cohen C, et al. CROI 2010. Abstract 58LB.

GS-9350–Boosted ATV Virologic Efficacy Similar to ATV/RTV in Naive Pts

- Phase II study comparing cobicistat (GS-9350) vs ritonavir as boosting agent for atazanavir

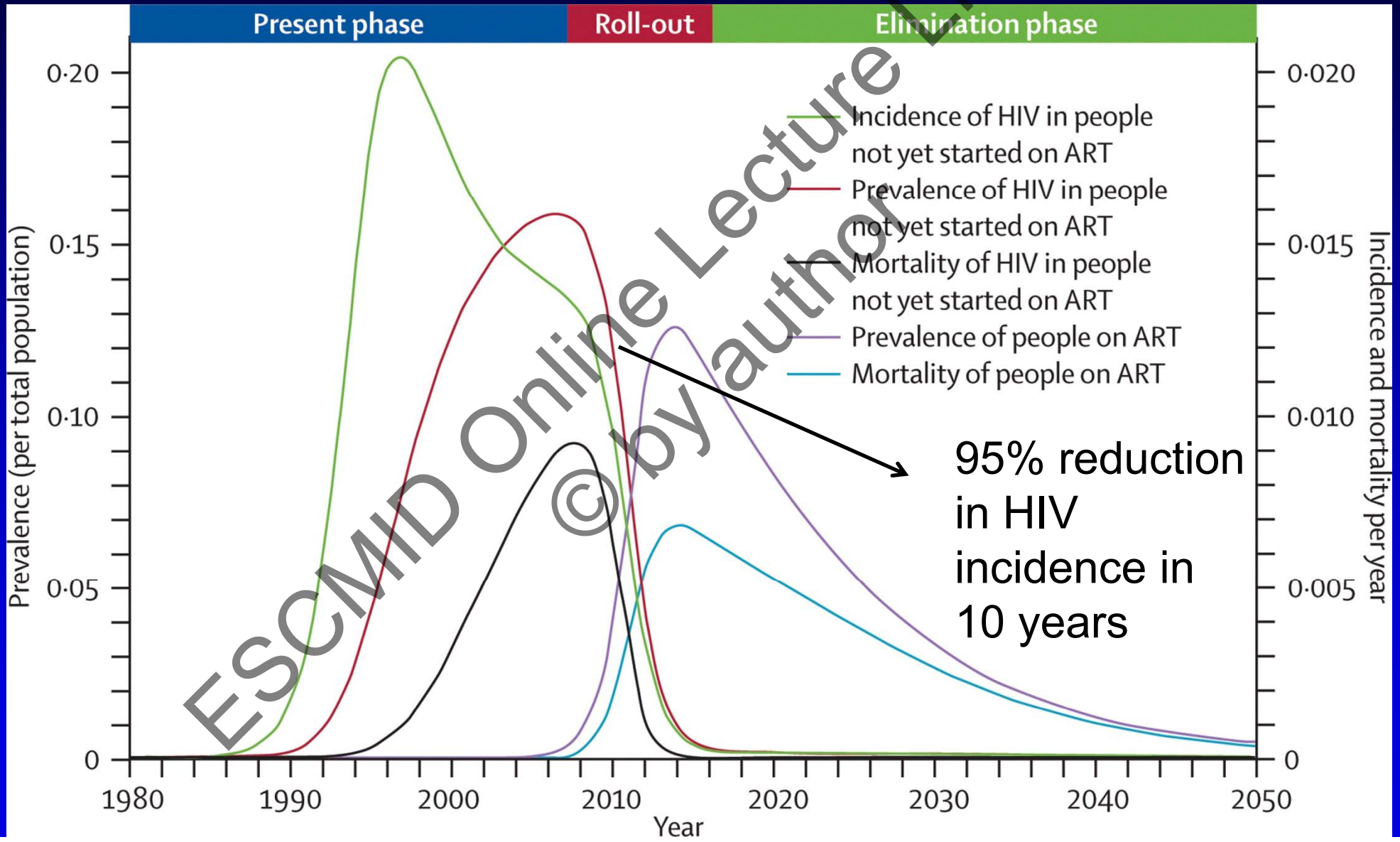




Cohen C, et al. CROI 2010. Abstract 58LB.

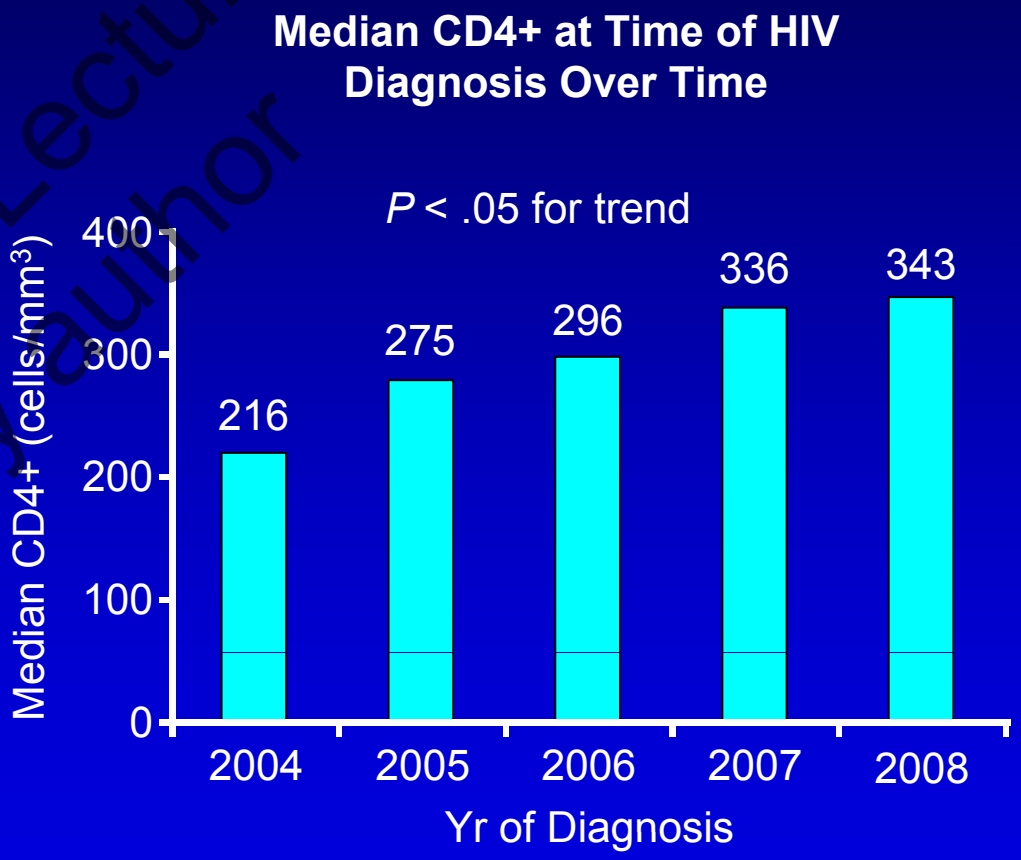
Test & treat strategies, global HIV treatment

Universal voluntary HIV testing and immediate HAART strategy. *Granich RM, Lancet 2009; 373:48–57*



Impact of Expanded HIV Testing in Washington, DC

- 3.7-fold increase in number of publicly funded HIV tests performed in Washington, DC, from 2004-2008
  - 2004: 19,766
  - 2008: 72,866
- 17% increase in number of new HIV/AIDS name-based case reports from 2004-2007
- Significant reduction in time to progression to AIDS following HIV diagnosis from 2004-2008 ($P < .0001$)
- Time interval between diagnosis to entry into care significantly improved from 2004-2008



Castel A, et al. CROI 2010. Abstract 34.

Vaccine

Efficacy Studies (Phase IIb, III) of Candidate HIV-1 Vaccines in HIV-1-Seronegative Volunteers

Vaccine	Start	Sample Size	Location	Target Population	HIV Infection Rate in Vaccine Group (%)	HIV Infection Rate in Placebo Group (%)	Vaccine Approach; HIV-1 Strains	Vaccine Developer
AIDSVAX B/B	1998	5403	North America, Netherlands	MSM	**6.7**	**7.0**	rgp120: MN, GNE8	VaxGen
AIDSVAX B/E	1999	2546	Thailand	IVDU	**8.4**	**8.3**	rgp120: MN, A244	VaxGen
STEP Study	2004	3000	North America, Caribbean, Australia	MSM; sexual exposure	**4.6***	**3.1**	Ad5 gag/pol/nef: clade B gag-CAM-1, pol- IIIB, nef-JR-FL	Merck
Phambili Study	2006	3000‡	South Africa	Sexual exposure	**Stopped early**	**Stopped early**	Ad5 gag/pol/nef: clade B gag-CAM-1, pol- IIIB, nef-JR-FL	Merck

Lancet 2008; 372:1881-1893., Lancet 2008; 372:1894-1905.

Prime – boost strategy

The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

- canarypox ALVAC vector (HIV-1 E gp120, B Gag and protease) - 0,1,3 & 6 mo. and AIDSVAX B/E 3 & 6 mo. boosting
- n: 16402 (18-30 y, M & F)
- Vaccine efficacy 31.2 %
- Most of the pts - heterosexuals, not at the high risk groups
- Efficacy mostly seen in the 1st year
- No expected public health benefit

Rerks-Ngarm S, NEJM 2009;361: 2209-20.