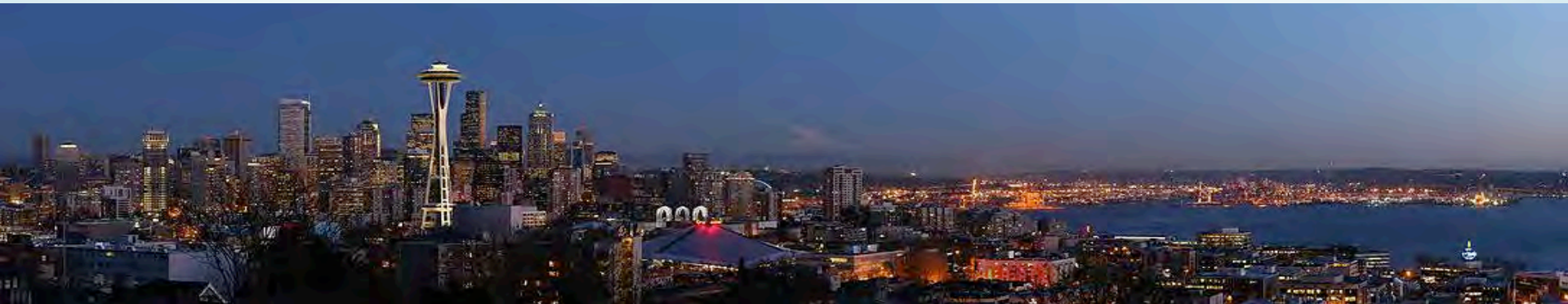
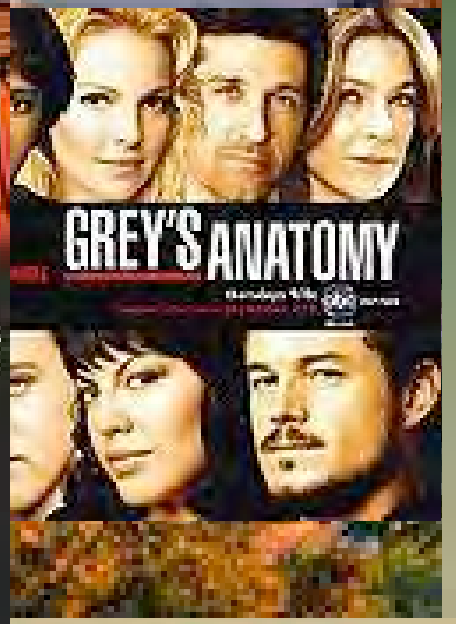
CROI 2012 – New Frontiers

TM Rossouw

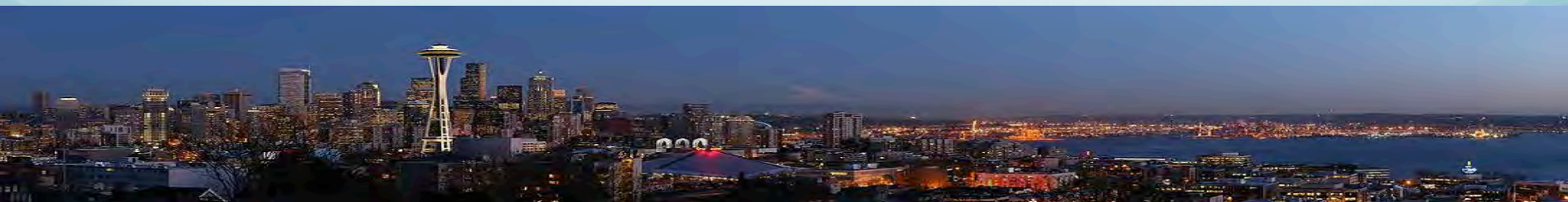




arch 5-8, 2012
vention Center
eattle, WA, US

Outline

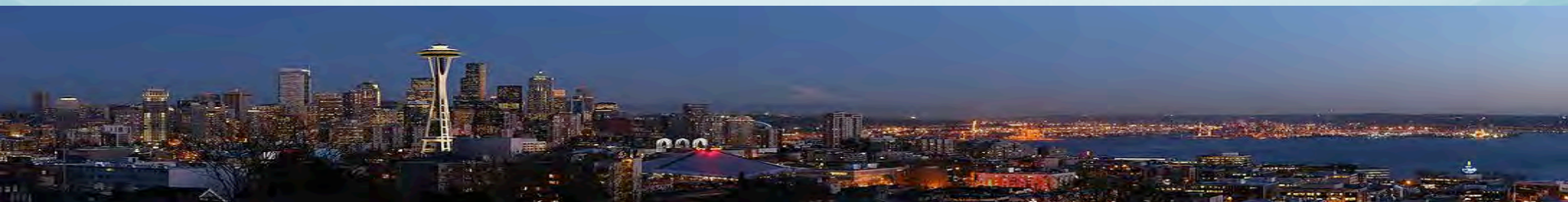
- When to start?
- What to start with?
- Any new drugs?
- Long-term complications
- Prevention
- Basic science



When to Start?

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

Delayed ART



NA-ACCORD: Early vs Deferred ART

Risk of Death With Deferral of ART*

CD4+ Cell Count	Relative Risk (95% CI)	*P* Value
351-500	1.69 (1.26-2.26)	< .001
>500	1.94 (1.37-2.79)	< .001

- Study controlled for sex, age, and BL CD4+ cell counts
- HIV-1 RNA response similar in early vs deferred arms
- Results similar when IDUs excluded
- Limitations: observational study with potential for unmeasured confounding

*Without inclusion of HIV-1 RNA data.

Kitahata MM, et al. N Engl J Med. 2009;360:1815-1826.

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; infected partner CD4+ cell count of 350-550

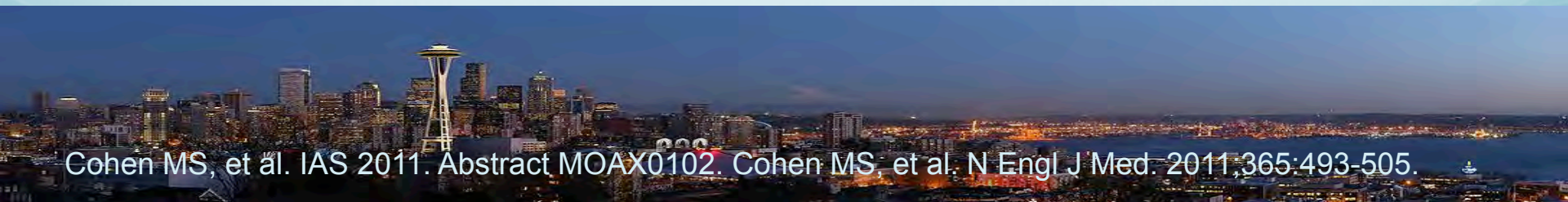
(N = 1763 couples)

Immediate ART
Initiate ART at CD4+ cell count 350-550
(n = 886 couples)

Delayed ART
Initiate ART at CD4+ cell count ≤ 250*
(n = 877 couples)

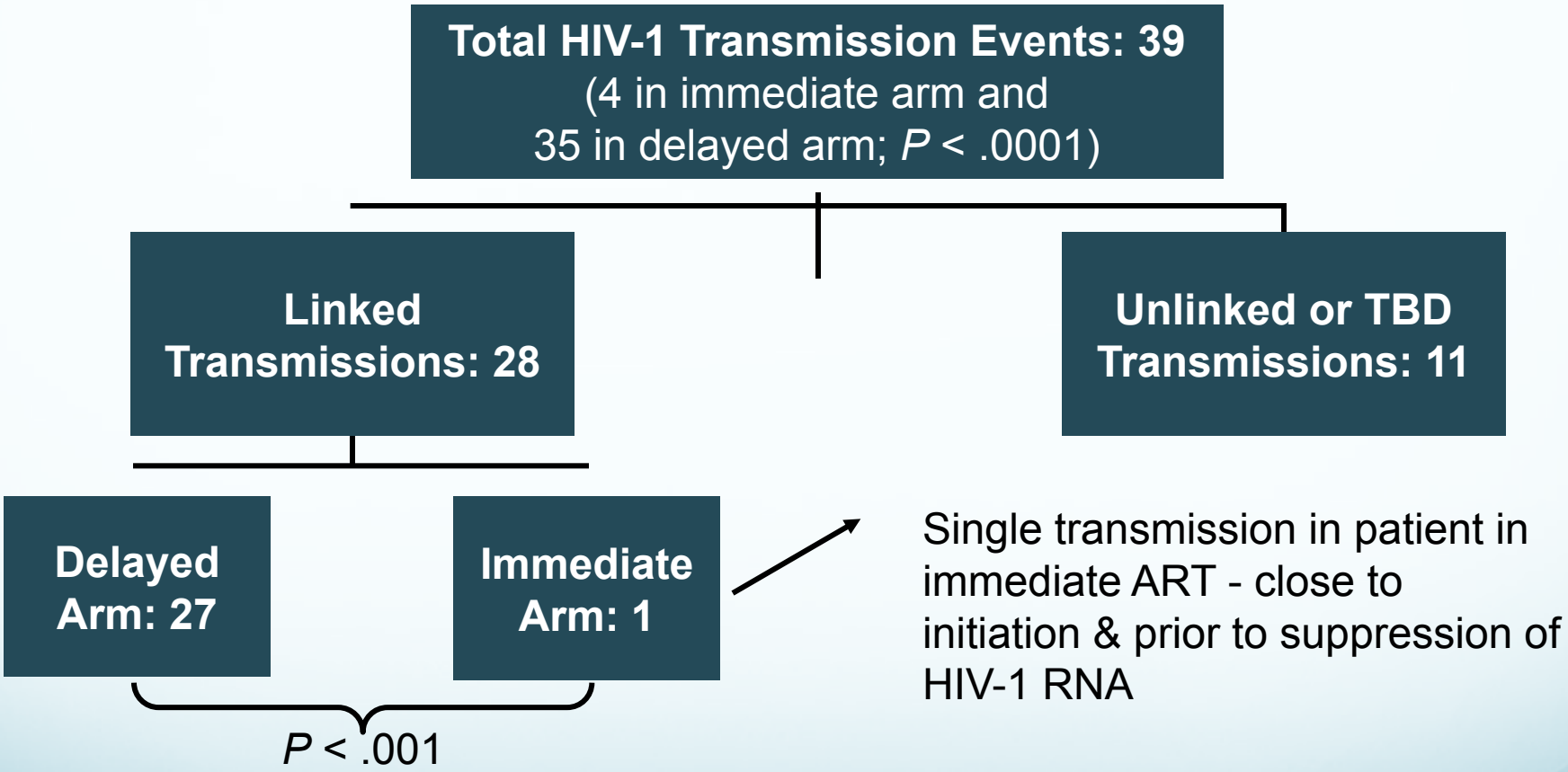
- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection, and/or death
- Couples received intensive counseling on risk reduction and use of condoms

*Based on 2 consecutive values of ≤ 250 cells/mm^3



Cohen MS, et al. IAS 2011. Abstract MOAX0102. Cohen MS, et al. N Engl J Med. 2011;365:493-505.

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

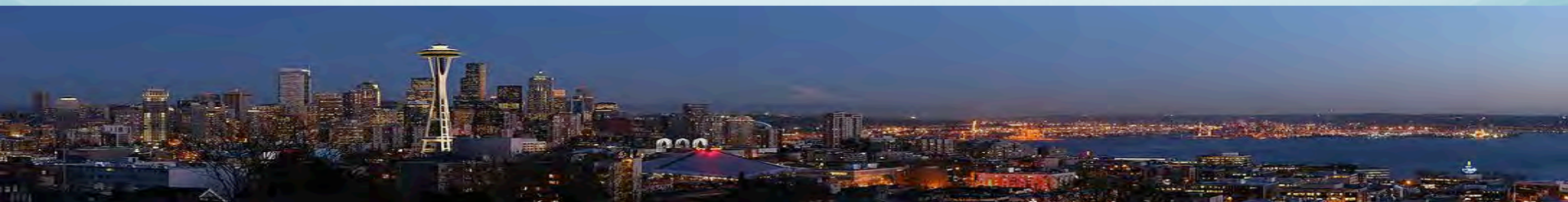


DSMB recommended release of results as soon as possible following 4/28/11 review; follow-up continues but all HIV-positive partners offered ART after release of results.

Cohen MS, et al. IAS 2011. Abstract MOAX0102. Cohen MS, et al. N Engl J Med. 2011;365:493-505.

Benefit To The Individual?

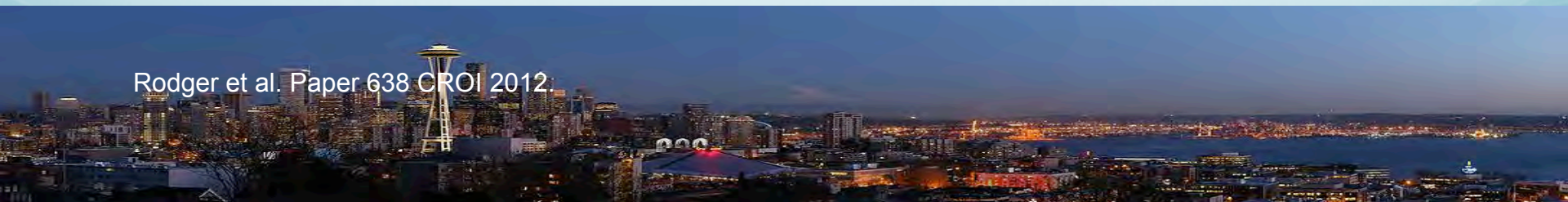
- No direct evidence
  - Waiting for data from START trial (initiate ART at CD4 350 vs. >500)
- Indirect evidence mounting
  - SMART and ESPRIT control groups
    - SMART CD4>350
    - ESPRIT CD4>300
    - Main results: Mortality rate among virologically suppressed ART-treated subjects with CD4 > 350



SMART & ESPRIT

	Overall	Most recent eligible CD4 count (cells/uL)	
		350-499	**>500**
Person-years of follow-up (proportion)	12357 (100%)	3729 (30%)	8628 (70%)
Observed deaths	62	28	34
Expected deaths	49.82	15.86	33.96
SMR	1.24 (0.95-1.59)	1.77 (1.17-2.55)	1.00 (0.69-1.40)

Mortality rate standardised by age, sex and country

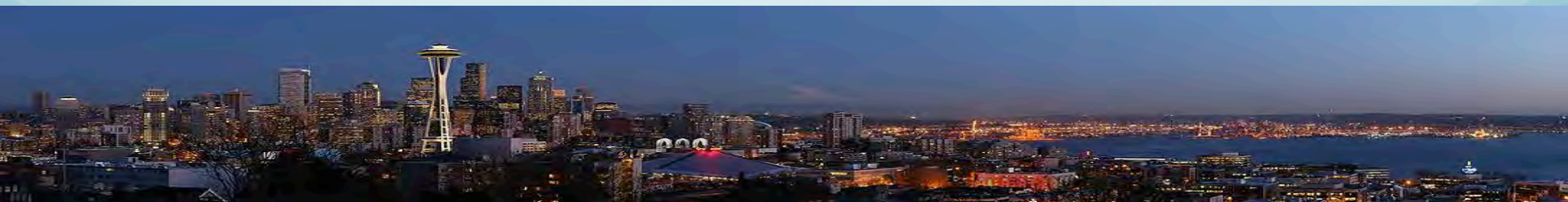


Rodger et al. Paper 638 CROI 2012.

Association Between Current CD4+ Cell Count and Non-AIDS Complications

Study	Non-AIDS Cancer/Death	Renal Disease/Death	CVD Events/Death	Liver Disease/ Death
FIRST	Yes	Yes	Trend	No
D:A:D	Yes	Yes	Trend	Yes
CASCADE	Yes	NA	Yes	Yes
SMART	Trend	Trend	Trend	Yes

Phillips A, et al. AIDS 2008;22:2409-2418.



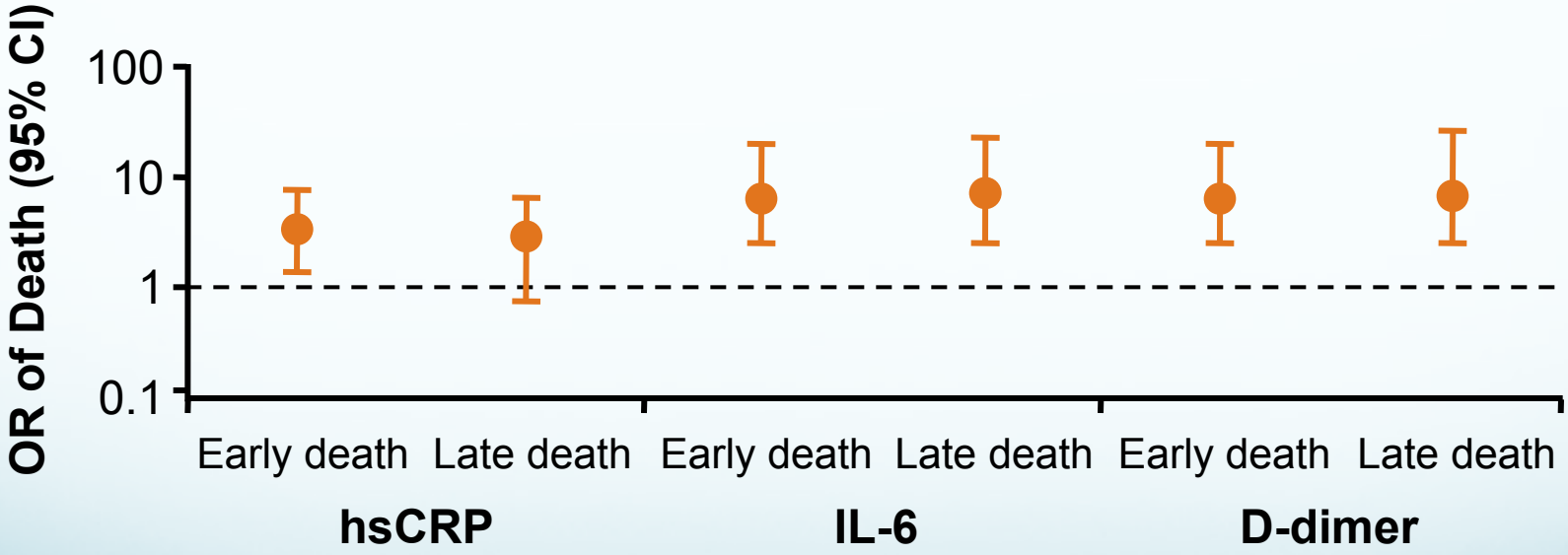
Association of CD4+ Cell Count Nadir With Clinical Outcomes

- Low CD4+ count nadir associated with
  - Increased rates of HIV-associated neurocognitive disorders[1]
  - Arterial stiffness contributing to CV risk[2]
  - Coronary heart disease [3]
  - Increased risk of fracture[4]

1. Ellis R, et al. AIDS. 2011;25:1747-1751. 2. Ho J, et al. AIDS. 2010 ;24:1897-1905
3. Klein D, et al. CROI 2011. Abstract 810. 4. Young B, et al. Clin Infect Dis. 2011;52:1061-1068.

Inflammatory Markers in Treatment Interruption Studies

- INSIGHT/SMART study group: nested case-control study of pts who died from any cause classified as early deaths (≤ 2 yrs after randomization, n = 95) or late deaths (> 2 yrs, n = 71)



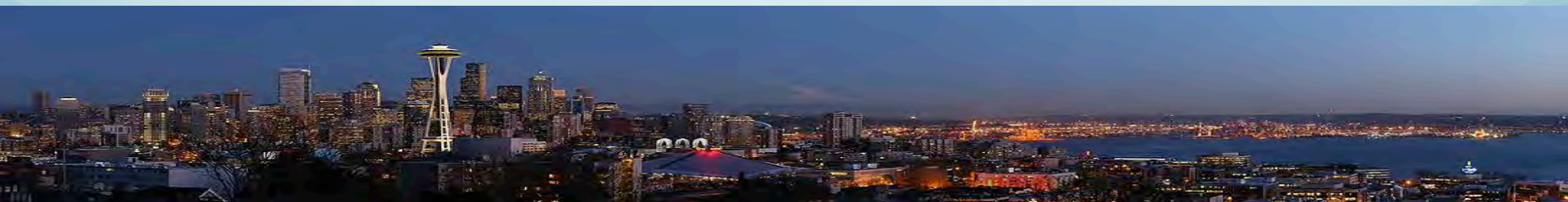
Paton N, et al. IAS 2009. Abstract MOPEA034.

When to Start Therapy: Balance Now Favours Earlier ART

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

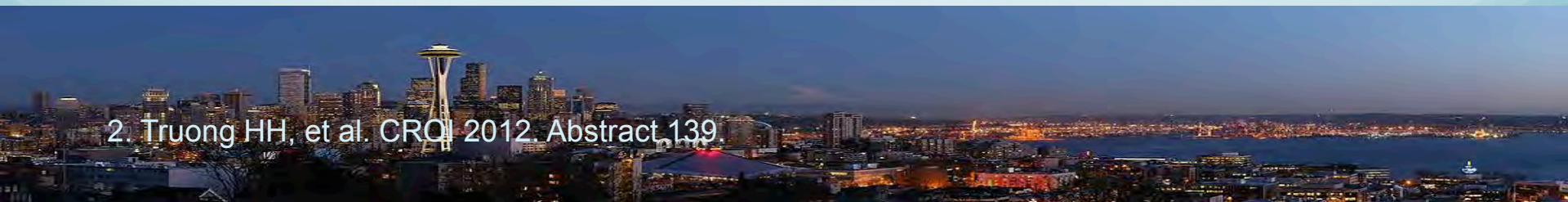
- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia at all CD4+ cell count levels
- ↓ transmission

Delayed ART **Early ART**



When Do We Start?

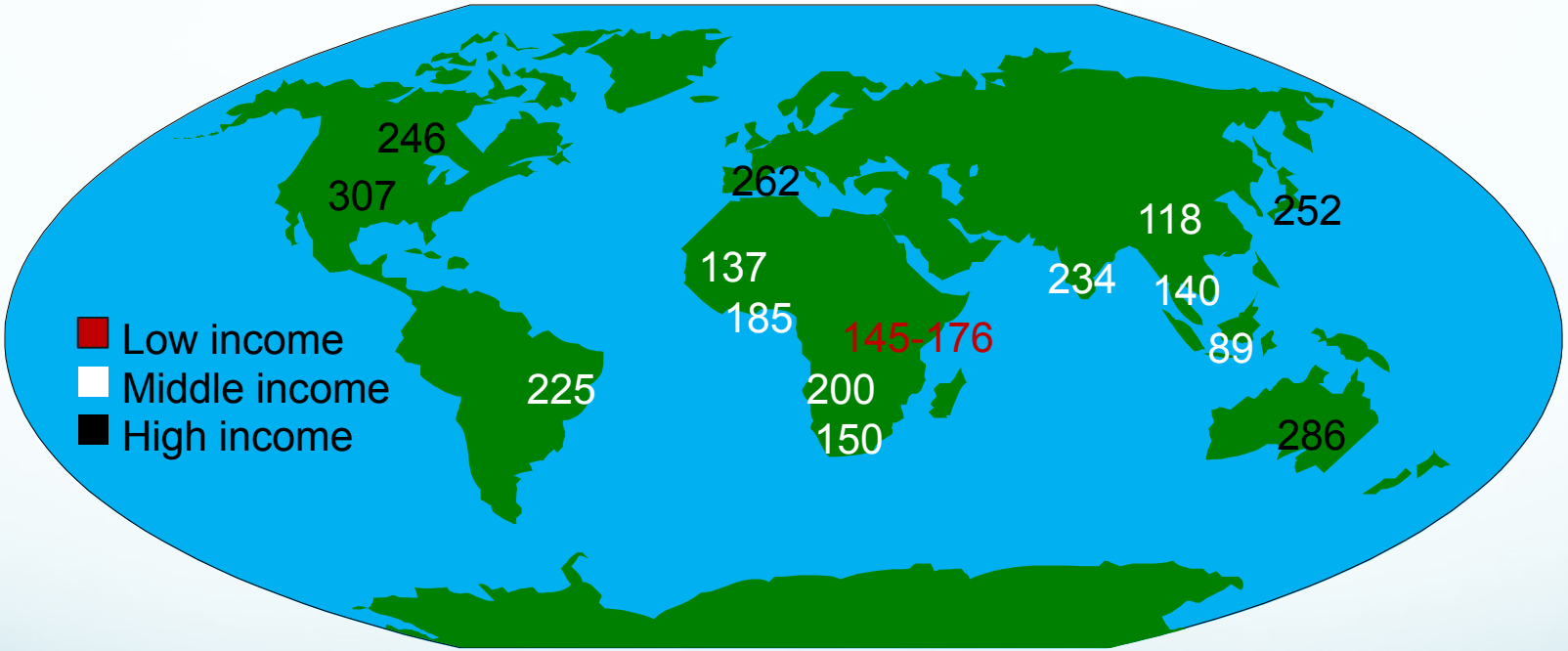
- Starting CD4s have improved dramatically since 2002
- USA only country where average starting CD4 is > 300
- San Francisco policy of recommending ART for all with HIV as a public health measure has substantially raised the CD4 at treatment initiation in that city – model to follow for SA?
  - But pts initiating ART at CD4+ counts > 350 cells/mm^3 significantly more likely to be white, older, MSM, nonpoor, and diagnosed by private provider[2]
- Even so, only 44% of patients diagnosed with HIV in the USA are receiving care



2. Truong HH, et al. CROI 2012. Abstract 139.

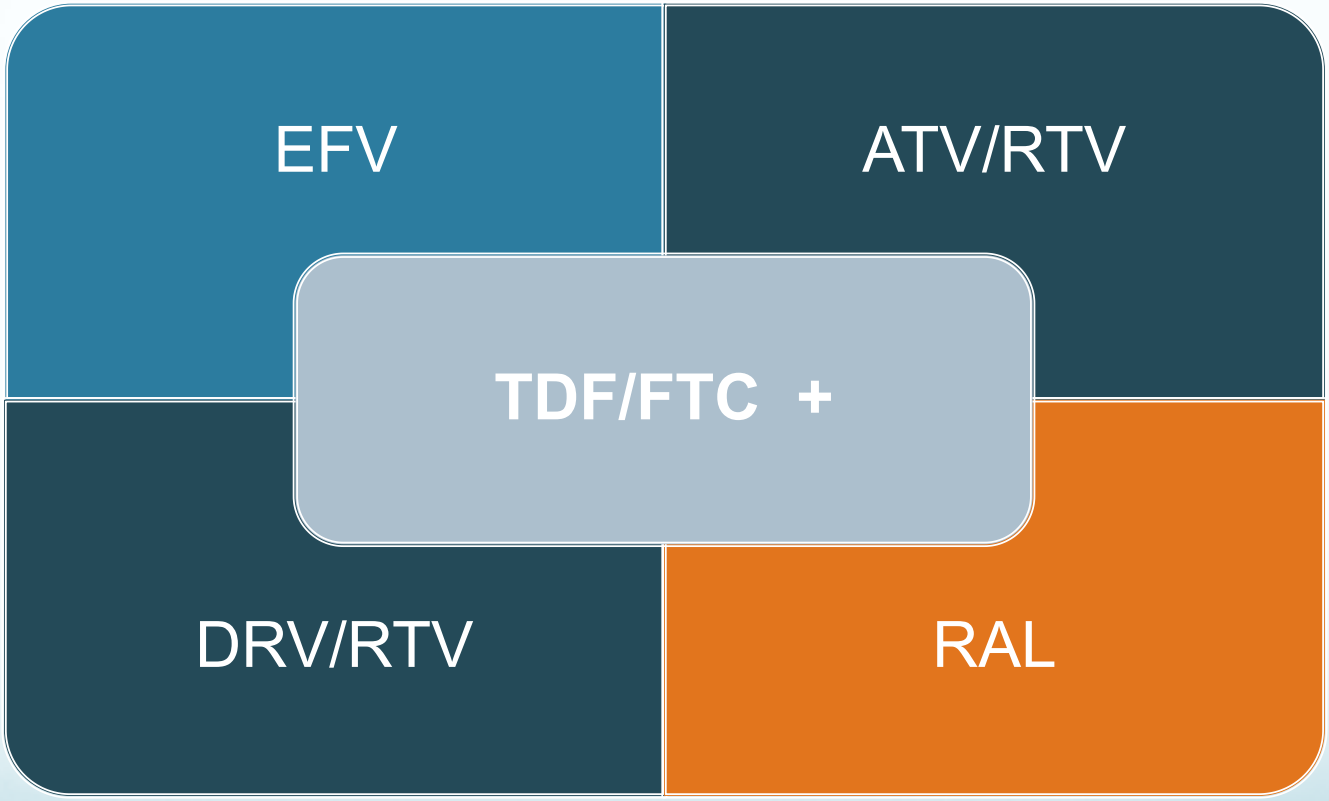
Patients Starting ART at Higher CD4+ Cell Counts Overall, but Disparities Remain

- CD4+ cell count at start of ART (cells/mm^3), 2009[1]



1. Mugglin C, et al. CROI 2012. Abstract 100.

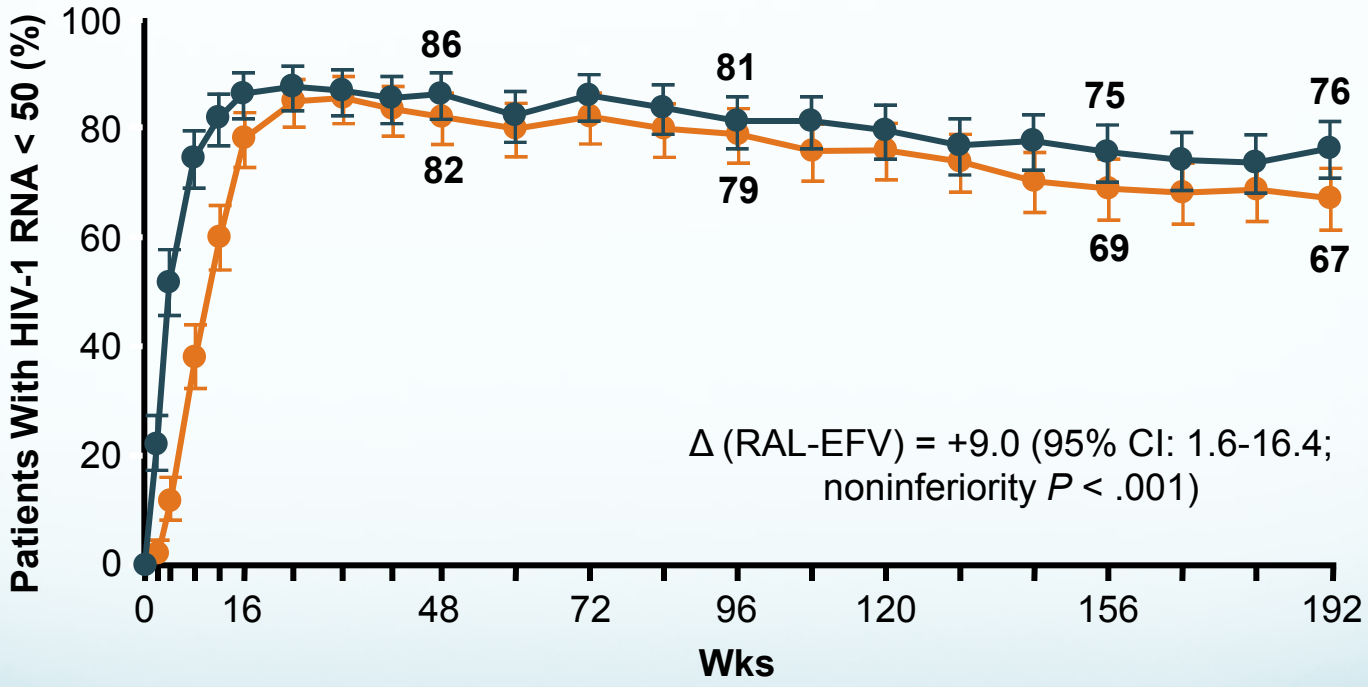
What To Start With?



DHHS Guidelines . October 2011; Thompson MA, et al. JAMA. 2010;304;321-333.

STARTMRK: RAL vs EFV in ART-Naive Patients, 192-Wk Data

- Randomized phase III trial; double-blind through follow-up



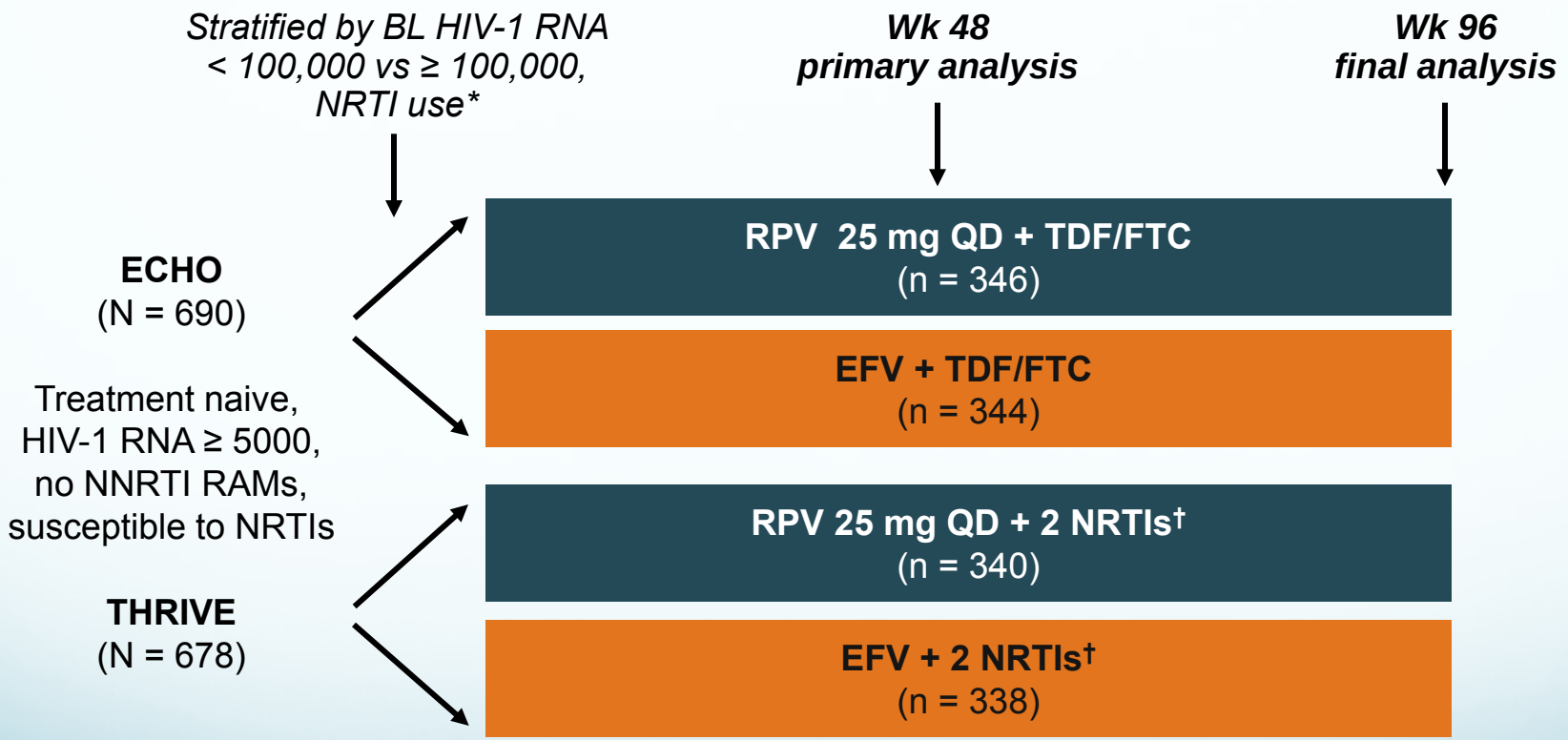
Contributing Patients, n

RAL	281	281	280	281	281	277	281	281
EFV	282	281	281	282	282	281	282	282

Rockstroh J, et al. EACS 2011. Abstract. PS 1/1.

ECHO, THRIVE: Rilpivirine vs EFV in ART-Naive Patients

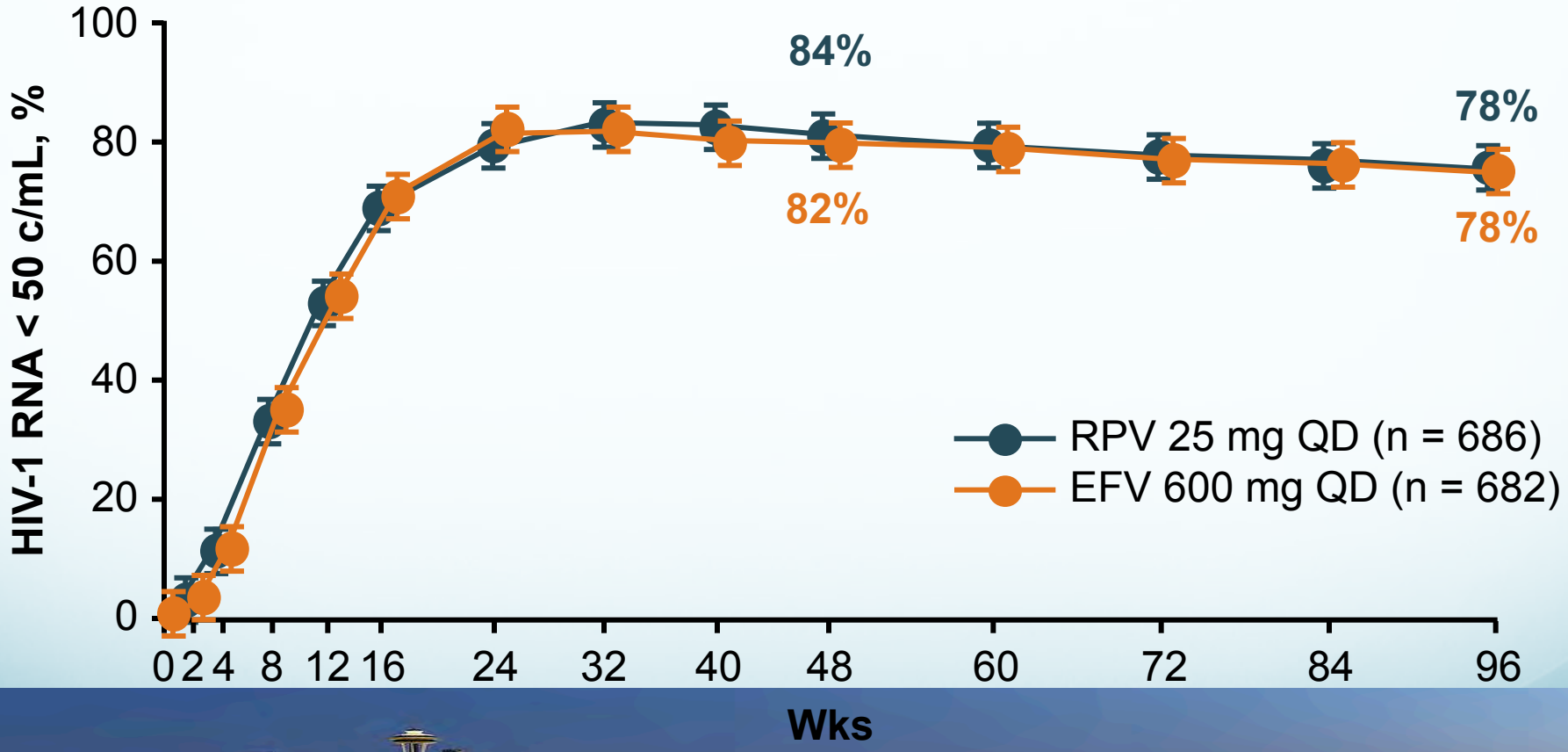
- Randomized, double-blind phase III trials



*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

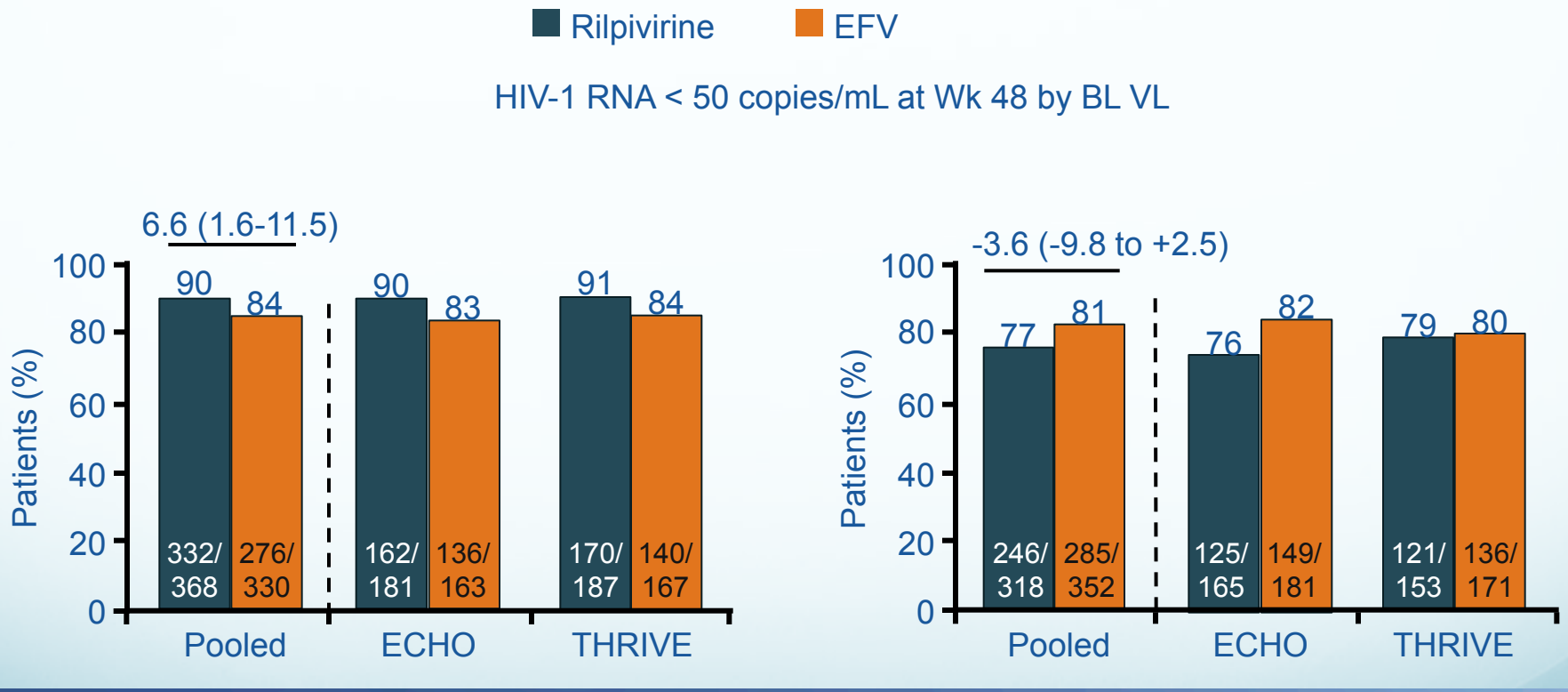
Cohen C, et al. AIDS 2010. Abstract THLBB206.

ECHO/THRIVE: HIV-1 RNA < 50 c/mL at Wk 96



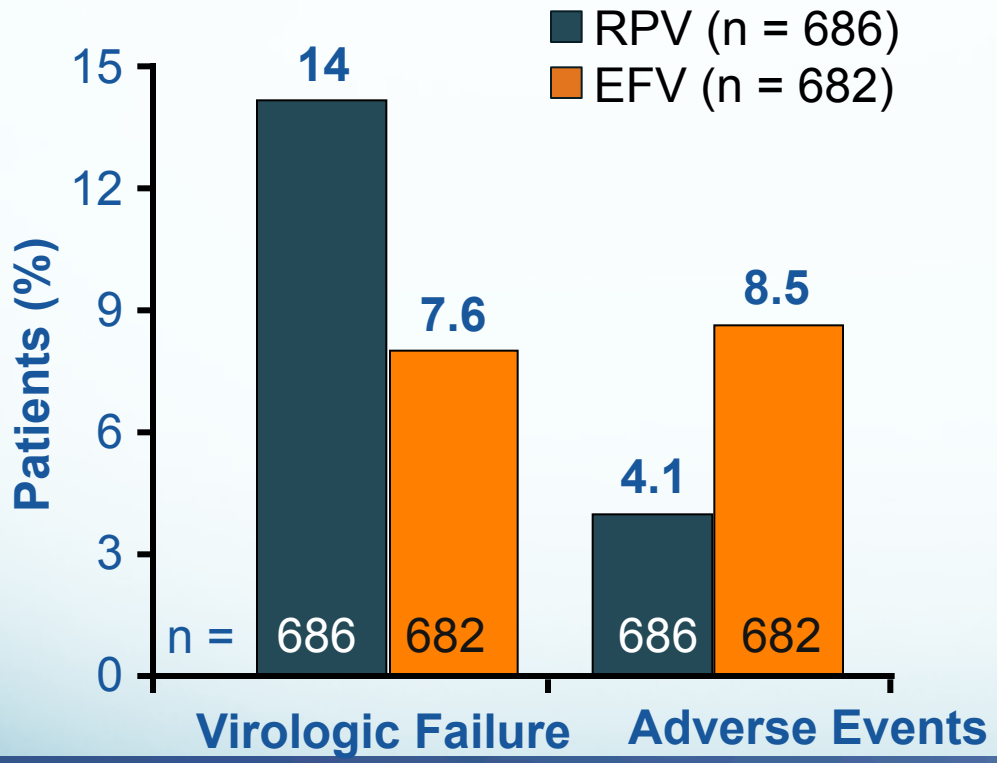
Cohen C, et al. IAS 2011. Abstract TULBPE032. Cohen C, et al. Lancet. 2011; 378: 229-237. Molina J-M, et al. . Lancet. 2011;378:238-246

ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients: Results by VL

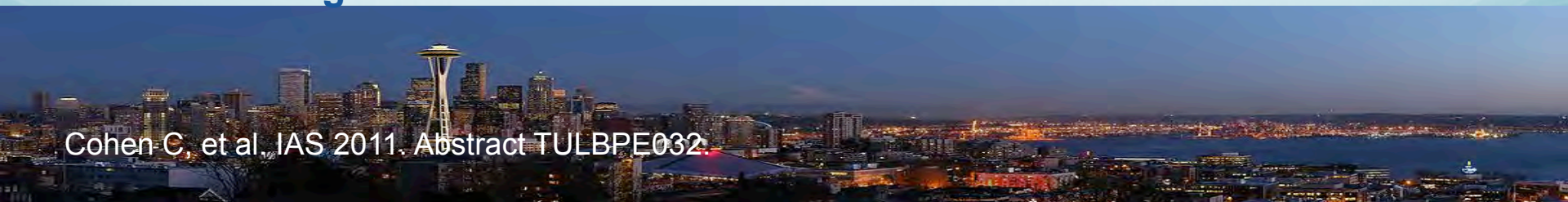


Cohen C, et al. AIDS 2010. Abstract THLBB206. Cohen C, et al. Lancet. 2011;378:229-237. Molina JM, et al. Lancet. 2011;378:238-246.

ECHO and THRIVE: Causes of Failure at Wk 96



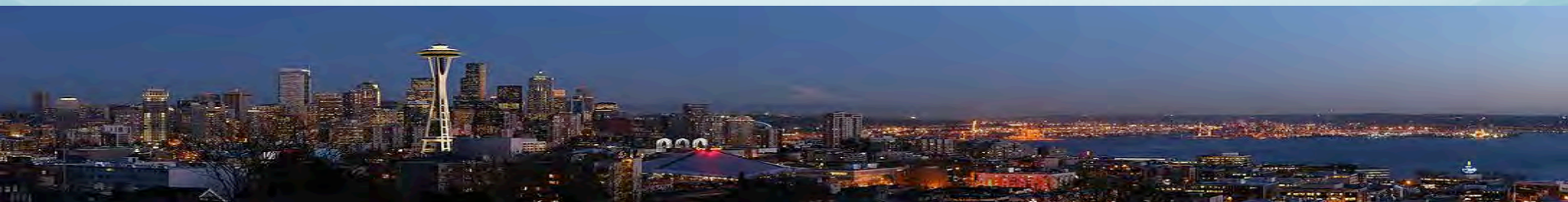
- More virologic failures with RPV vs EFV
  - Difference due to more VF between Wks 0-48 at VL > 100,000; VF similar Wks 48-96
  - NRTI mutations more common with VF on RPV vs EFV
  - Cross-resistance to ETR more common with RPV failures (E138K mutation)
- D/C due to AE more common with EFV vs RPV



Cohen C, et al. IAS 2011. Abstract TULBPE032.

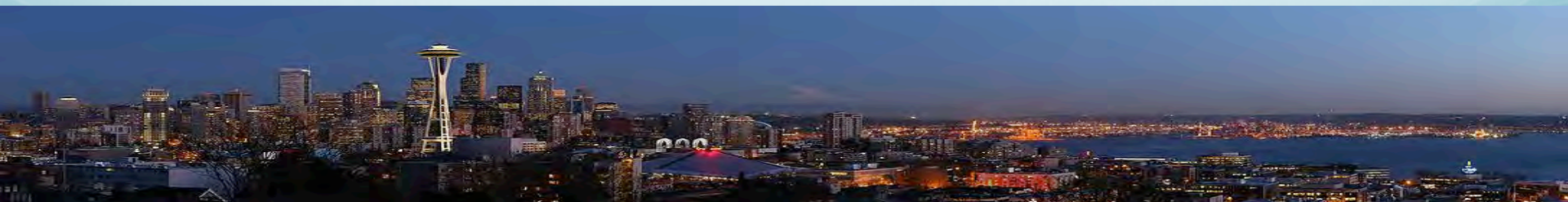
New Drugs?

- Three drugs investigated
  - Quad
    - Co-formulated TDF/FTC/elvitegravir/cobicistat
    - Submitted for FDA review
  - Dolutegravir
    - 96-week coverage of phase II data
    - Phase III data later this year
  - GS-7340
    - New formulation of Tenofovir



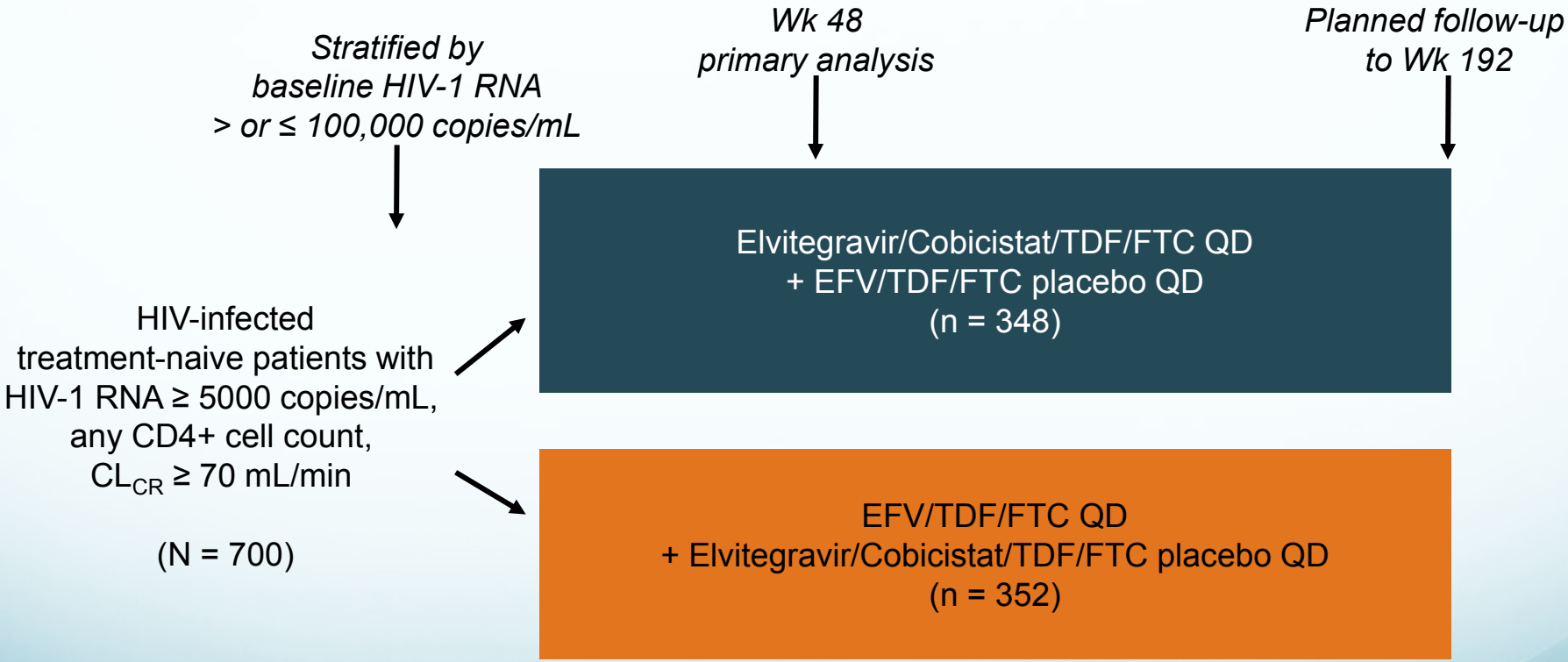
Quad

- One tablet, once daily
- Cobicistat inhibits tubular secretion without changing GFR
- Creatinine increases in first 2 weeks & stabilizes by week 8
- Randomized, double-blind, placebo-controlled
  - Pts: ARV-naive, 90% men, ~62% white, HCV 4%
  - Mean CD4 ~385, VL 4.7 log10, 33% VL>100K



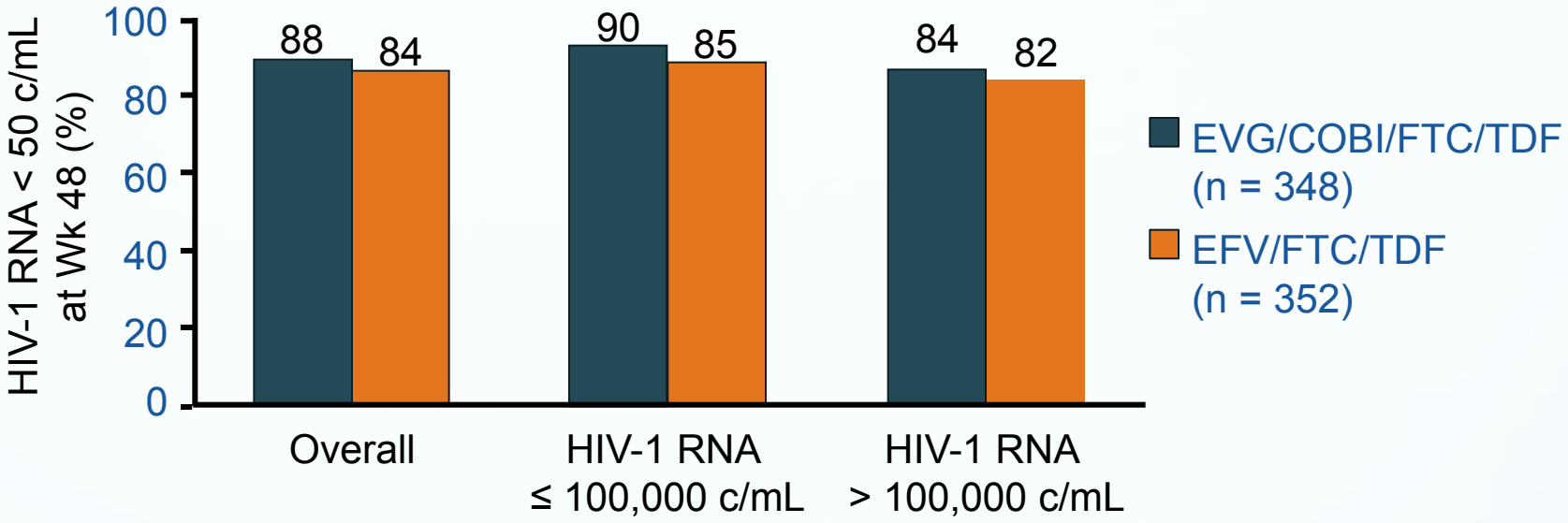
Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC in Treatment-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study

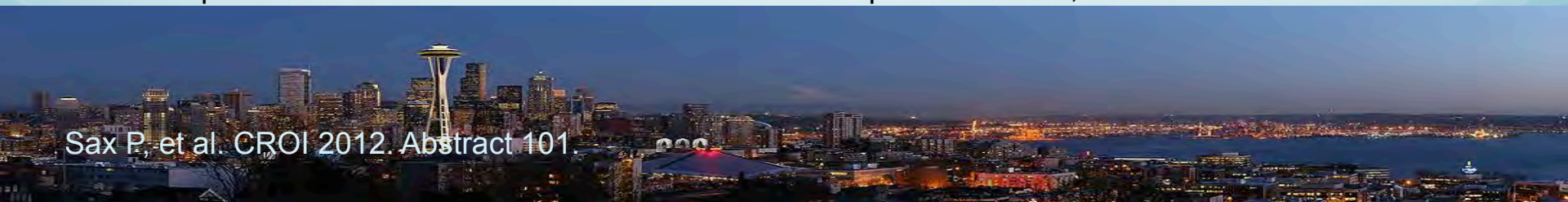


Sax P, et al. CROI 2012. Abstract 101.

Elvitegravir/Cobicistat Regimen Noninferior to EFV Regimen at Wk 48



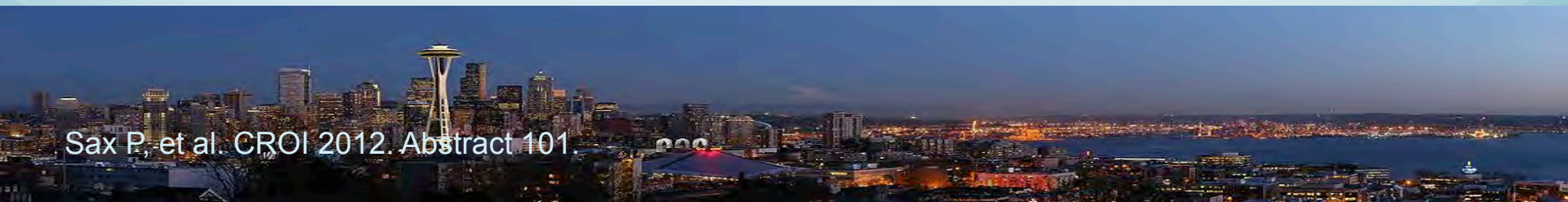
- Greater CD4+ count increase with EVG/COBI vs EFV: 239 vs 206 cells/mm^3 (*P* = .009)
- Virologic failure or rebound: resistance 8/14 in EVG/COBI arm vs 8/17 in EFV arm
  - Primary integrase mutations and primary NNRTI mutations observed in 7 and 8 patients in EVG/COBI and EFV arms
  - All 8 pts in EVG/COBI arm had M184V/I mutation vs 2 pts in EFV arm; 3 and 2 had K65R



Sax P, et al. CROI 2012. Abstract 101.

Safety of Elvitegravir/Cobicistat Regimen vs EFV Regimen

- Significantly greater incidence of nausea with EVG/COBI regimen
- Significantly greater incidence of sleep disturbance, dizziness, rash with EFV regimen
- 1.4% of patients discontinued EVG/COBI regimen due to renal abnormalities vs no patients on EFV regimen
  - Significantly greater increase in median serum creatinine from baseline to Wk 48 in EVG/COBI group: 0.14 vs 0.01 mg/dL ($P < .001$)
  - Majority of increase in serum creatinine clearance occurred within 2 wks of starting treatment and progressed minimally over time
- Significantly greater increases in total, LDL, and HDL cholesterol from baseline to Wk 48 in EFV vs EVG/COBI groups (all $P \leq .001$)



Sax P, et al. CROI 2012. Abstract 101.

Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC in Tx-Naive Patients

- Multicenter, randomized, double-blinded, active-controlled phase III study

Stratified by baseline HIV-1 RNA > or ≤ 100,000 copies/mL

Wk 48 primary analysis

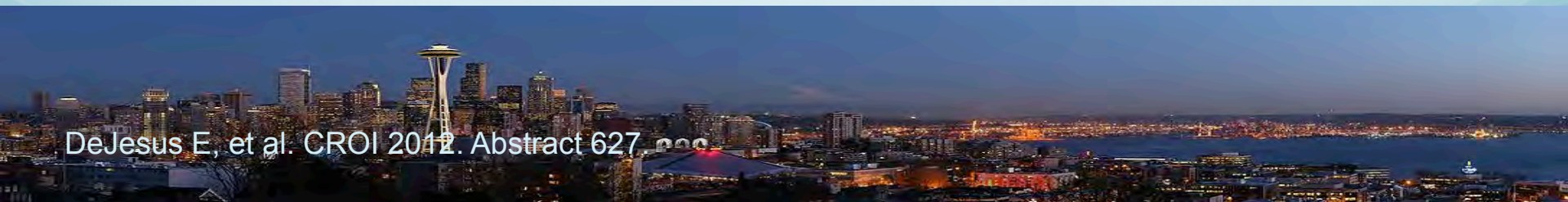
Planned follow-up to Wk 192

HIV-infected treatment-naive patients, HIV-1 RNA ≥ 5000 copies/mL, any CD4+ cell count, CL_{CR} ≥ 70 mL/min

(N = 708)

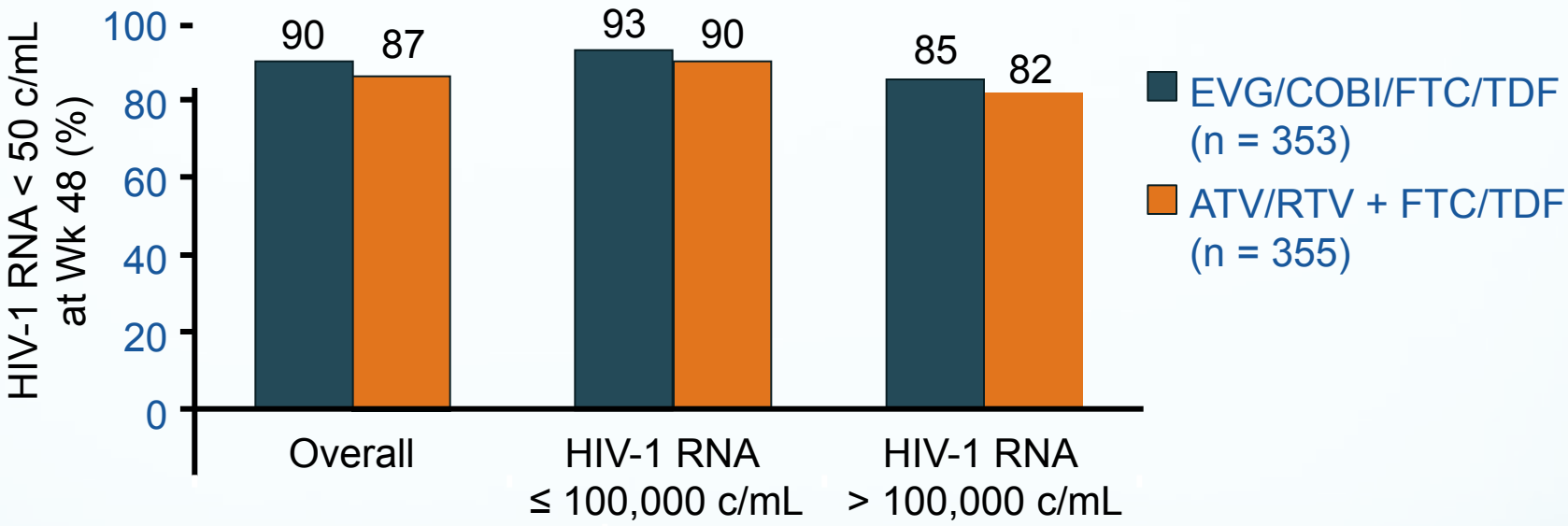
Elvitegravir/Cobicistat/TDF/FTC QD
+ ATV/RTV + FTC/TDF placebo QD
(n = 353)

ATV/RTV + TDF/FTC QD
+ Elvitegravir/Cobicistat/TDF/FTC placebo QD
(n = 355)



DeJesus E, et al. CROI 2012. Abstract 627.

Elvitegravir/Cobicistat Regimen Noninferior to ATV/RTV Regimen at Wk 48

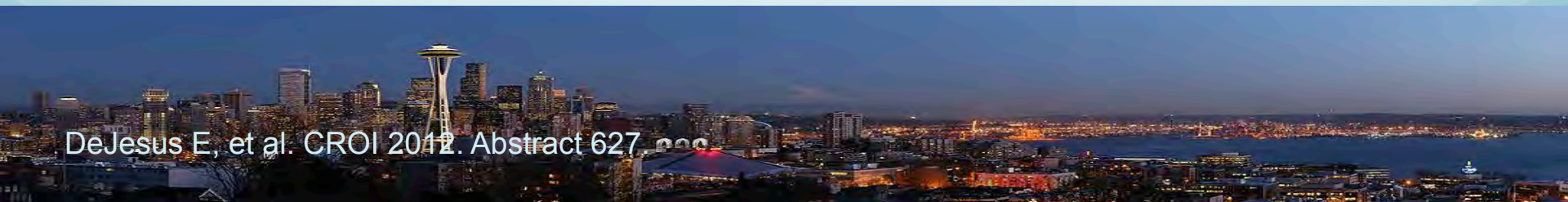


- Similar CD4+ cell count increases in both study arms at Wk 48
- Virologic failure or rebound: resistance 5/12 in EVG/COBI vs 0/8 in ATV/RTV
  - 4/5 pts in EVG/COBI arm had M184V/I mutation; 4 had primary integrase mutations

DeJesus E, et al. CROI 2012. Abstract 627.

Safety of Elvitegravir/Cobicistat Regimen vs ATV/RTV Regimen

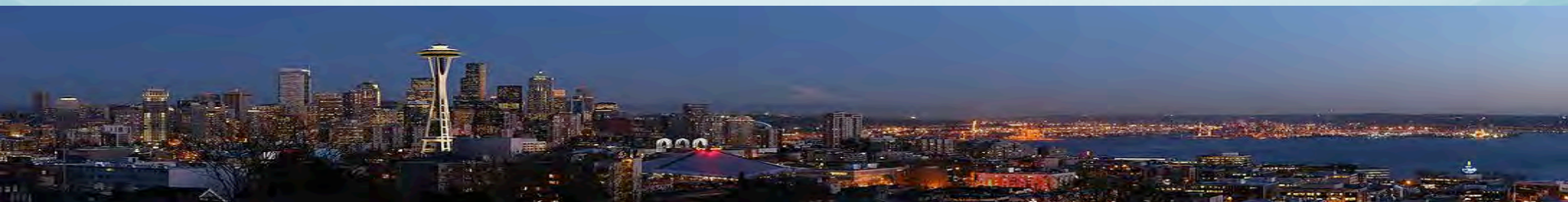
- Similar rates of grade 3/4 adverse events between arms: 13% in EVG/COBI and 14% in ATV/RTV arm
  - Most common adverse events: diarrhea, nausea
- Grade 3/4 hyperbilirubinemia more common in ATV/RTV group: 58% vs 1%
- Significantly greater increase in median serum creatinine from baseline to Wk 48 in EVG/COBI group: 0.12 vs 0.08 mg/dL ($P < .001$)
  - Majority of increase in serum creatinine clearance occurred within 2 wks of starting treatment and progressed minimally over time
- Significantly greater increase in median triglycerides from baseline to Wk 48 in ATV/RTV group: 23 vs 8 mg/dL ($P = .006$); otherwise no difference in lipid values



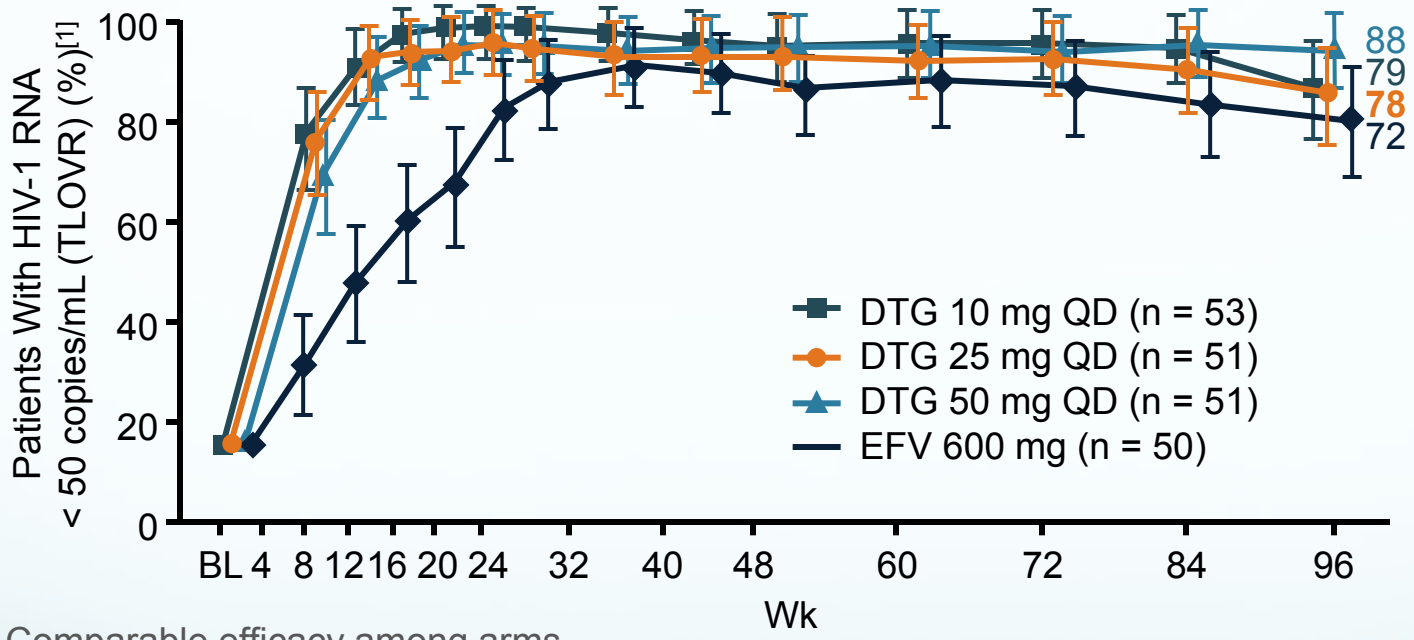
DeJesus E, et al. CROI 2012. Abstract 627.

Dolutegravir

- Once daily integrase inhibitor
- No need for boosting, low PK variability
- DTV metabolized UGT1A1
- No effect on GFR
- Randomized, partially blind, dose-finding study
  - Pts: ARV-naive, 86% men, 80% white
  - mean CD4 324, VL 4.5 log10, 21% VL>100K



SPRING-1: Phase IIb Trial of Dolutegravir vs Efavirenz in Tx-Naive Patients

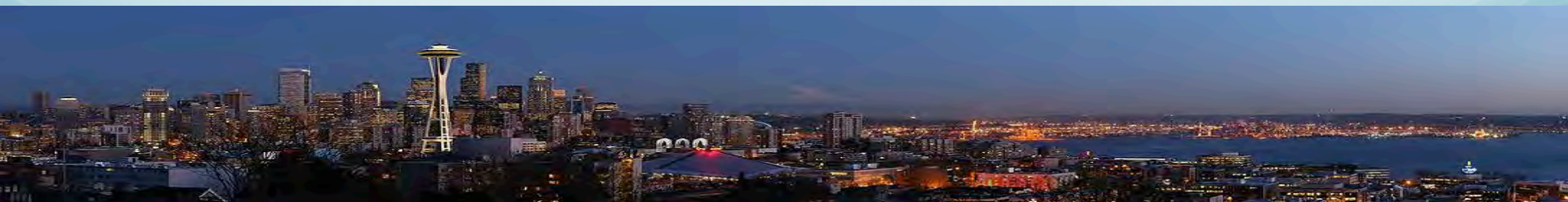


- Comparable efficacy among arms
- No cases of virologic failure in 50-mg arm
- Minimal variations in serum creatinine observed across treatment arms
  - Alterations did not progress over time
  - Previous study showed DTG had no effect on glomerular filtration rate by iohexol clearance[2]

1. Stellbrink HJ, et al. CROI 2012. Abstract 102LB. 2. Koteff J, et al. ICAAC 2011. Abstract A1-1728.

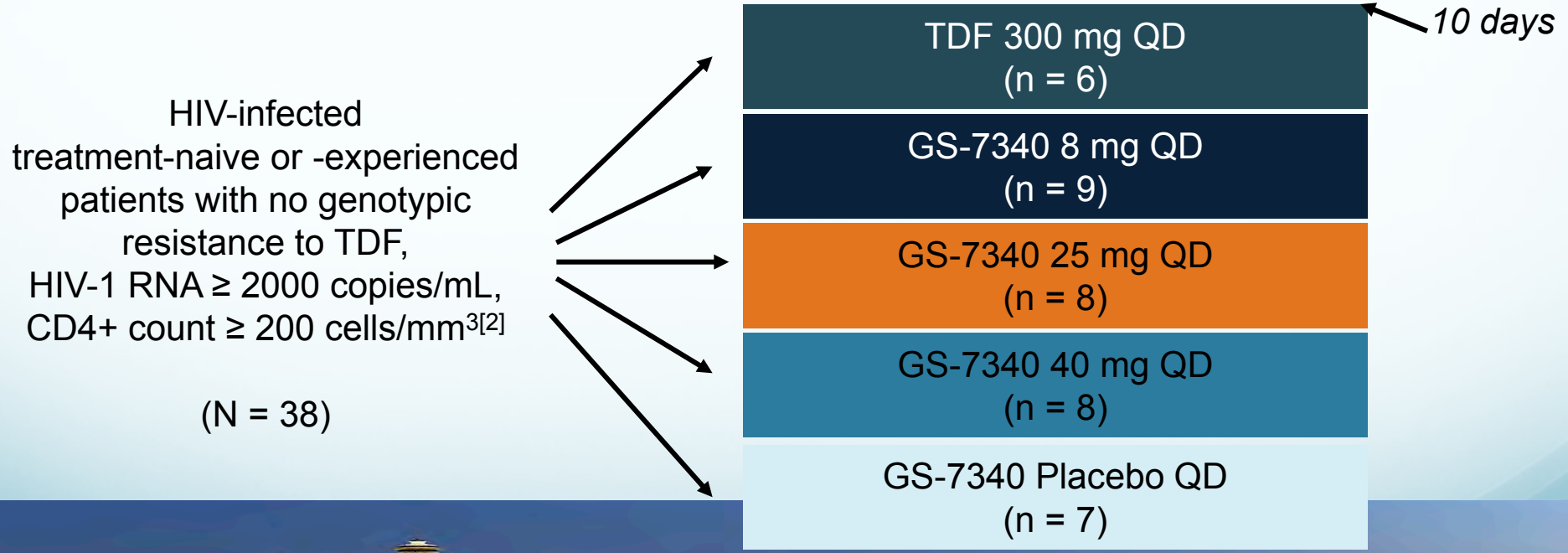
GS-7340

- Novel phenyl monophosphoramidate prodrug of TDF
- Engineered to readily enter PBMCs
- 10 day randomized, placebo-controlled dose finding study in ARV-naïve or pts. off ARVs without GT resistance to TDF
- 38 pts, 90% male, med.CD4 444, VL 4.6 log10



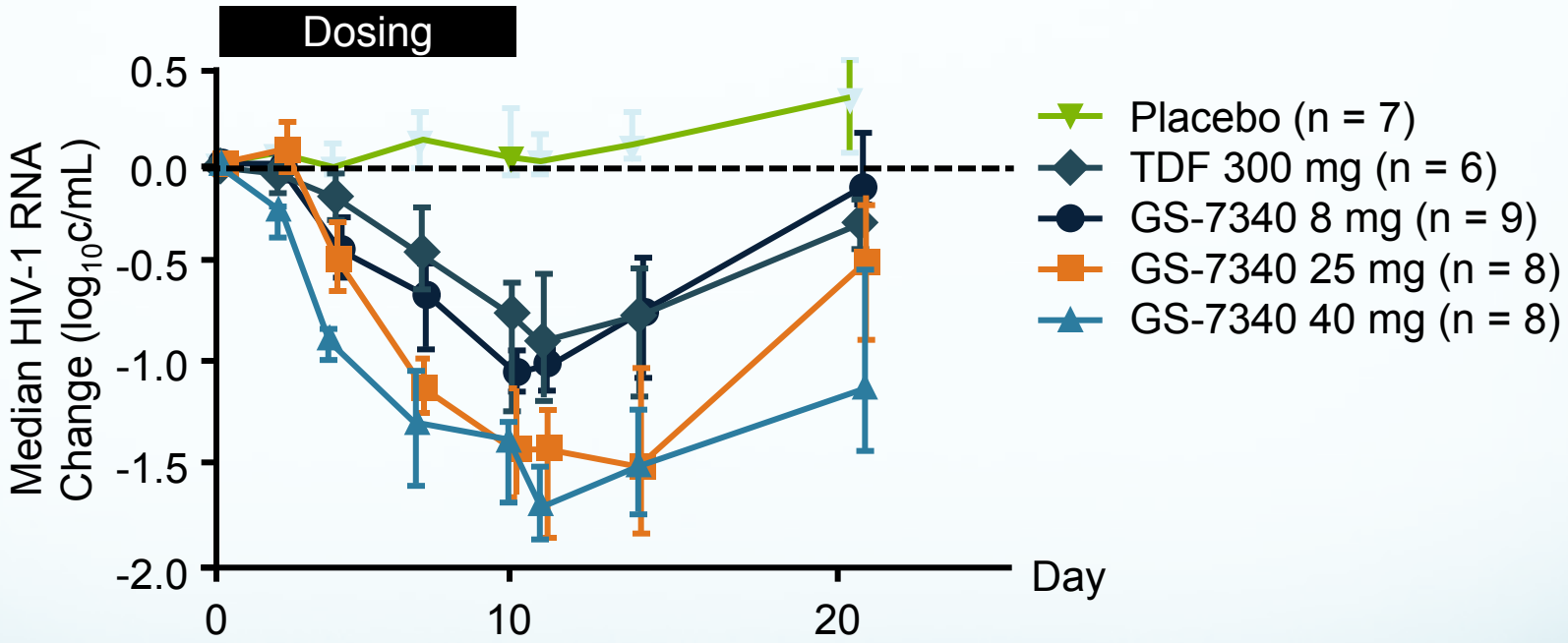
GS-7340

- Lower TDF plasma concentrations, higher intracellular concentrations obtained with GS-7340 vs TDF
  - Hypothesized that this may result in greater efficacy, reduced toxicity
- Previous study evaluated higher doses of GS-7340: 50 mg and 150 mg[1]

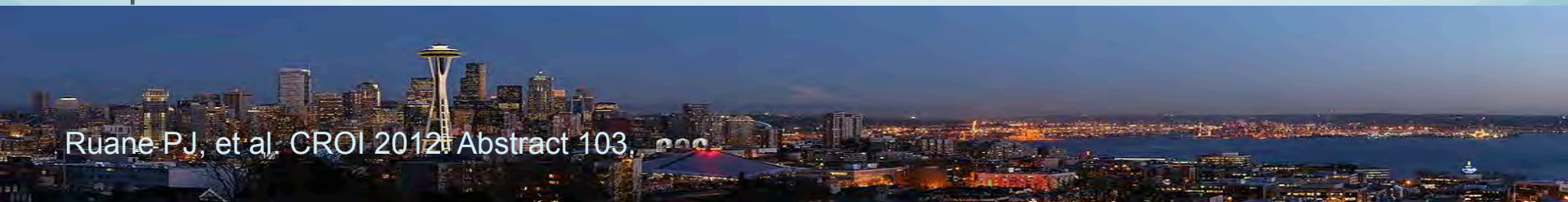


1. Markowitz M, et al. CROI 2011. Abstract 152LB. 2. Ruane PJ, et al. CROI 2012. Abstract 103.

Greater Antiviral Activity of GS-7340 25 mg and 40 mg vs TDF



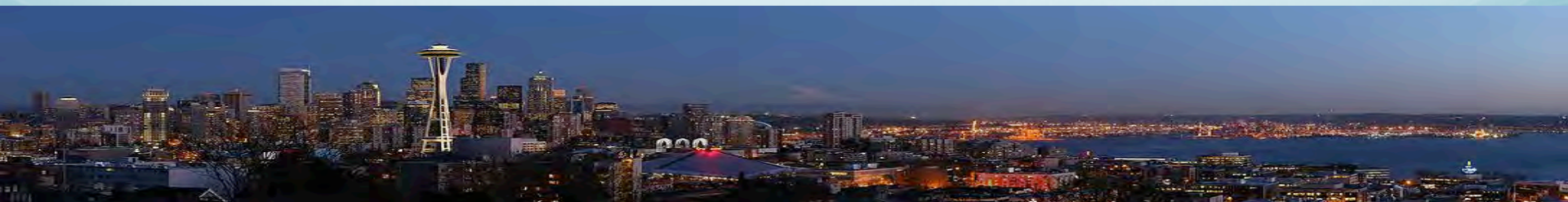
- Higher intracellular tenofovir diphosphate levels and lower circulating plasma tenofovir levels with GS-7340 vs TDF



Ruane PJ, et al. CROI 2012; Abstract 103.

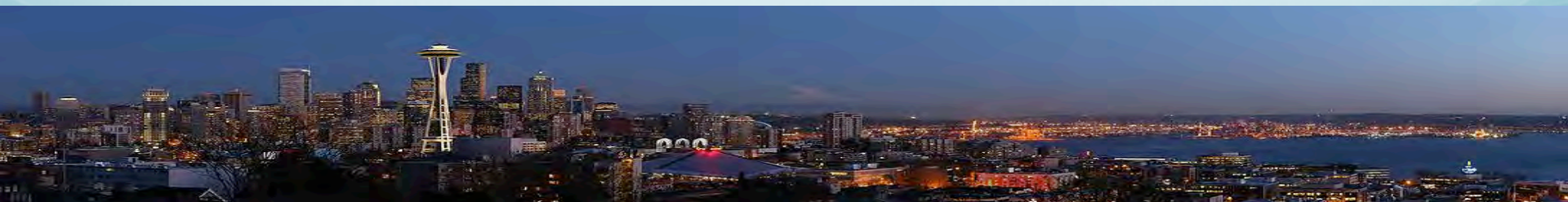
GS-7340

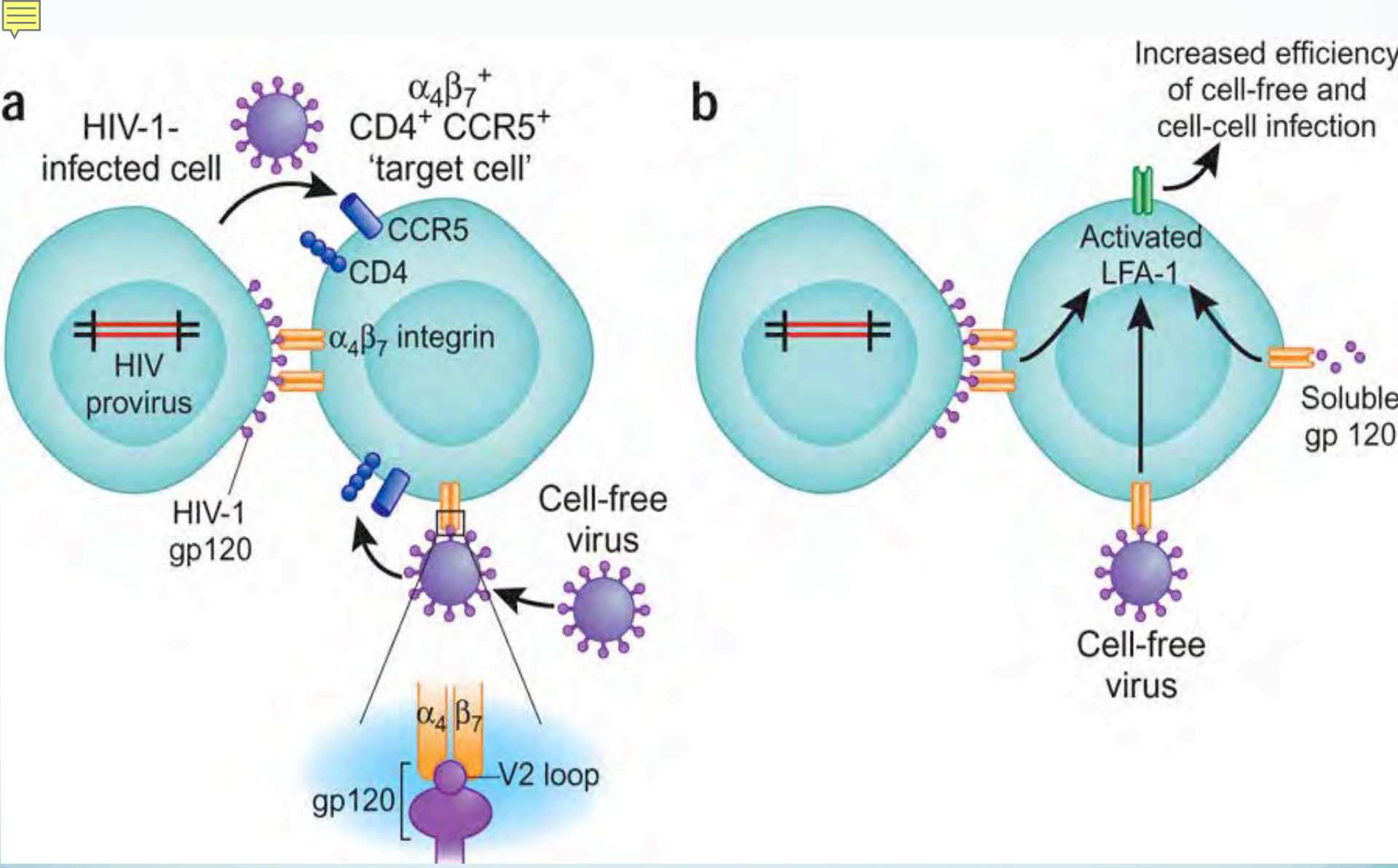
- No premature drug discontinuation
- Most AEs mild-moderate
- Unanswered question: does higher intracellular levels cause more renal toxicity?
- GS-7340: better antiviral activity with 1/10th TDF's mass (potential for single tablet regimens)

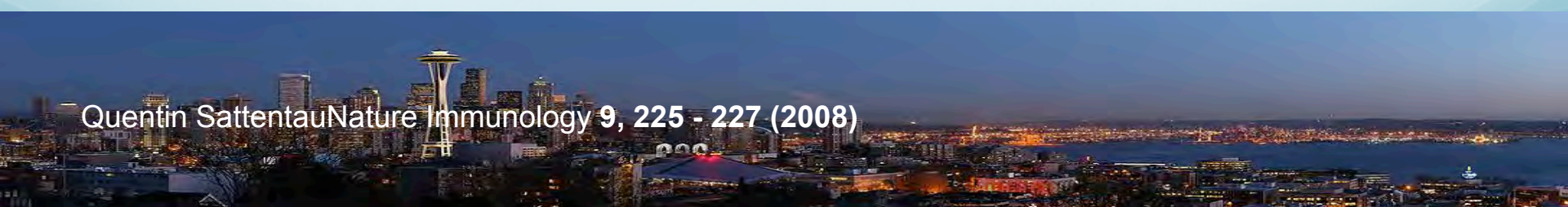


Integrins

- Potential new class – attachment receptor
- Family of large cell-surface proteins - leukocyte surface molecules
- HIV binding to integrin alpha-4 beta-7 initiates a signaling cascade inside the target cell, activating another integrin, alpha-L beta-2, which then binds to another protein on the surface of an infected cell. This establishes a virological synapse, allowing much more effective cell-to-cell transmission of the virus
- No cross resistance to RAL and complementary action
- No single mutation







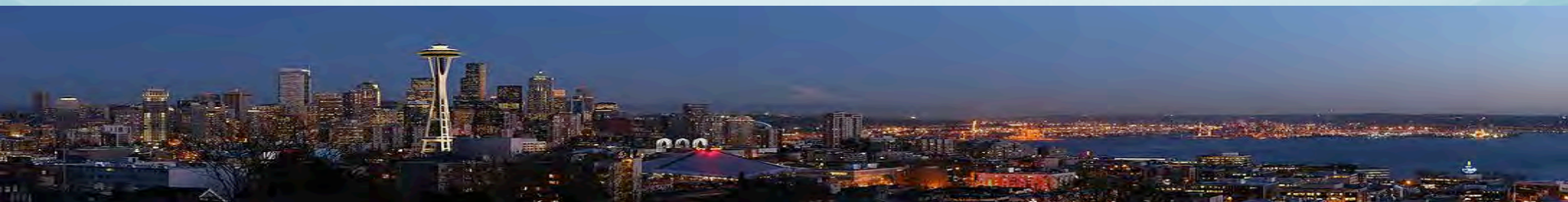
Quentin SattentauNature Immunology **9, 225 - 227 (2008)**

Seattle – New Frontiers

- Industry
  - From a lumbering town to a technological hub – dot-com bo

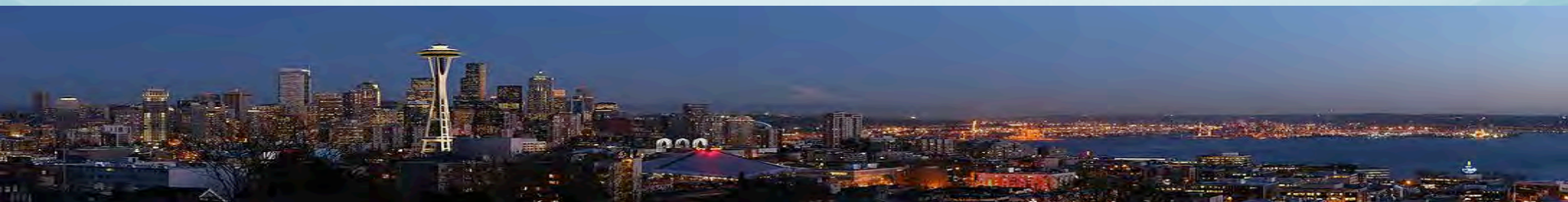
Long-term Complications

- Cardiovascular risk
- HAND
- Bone loss



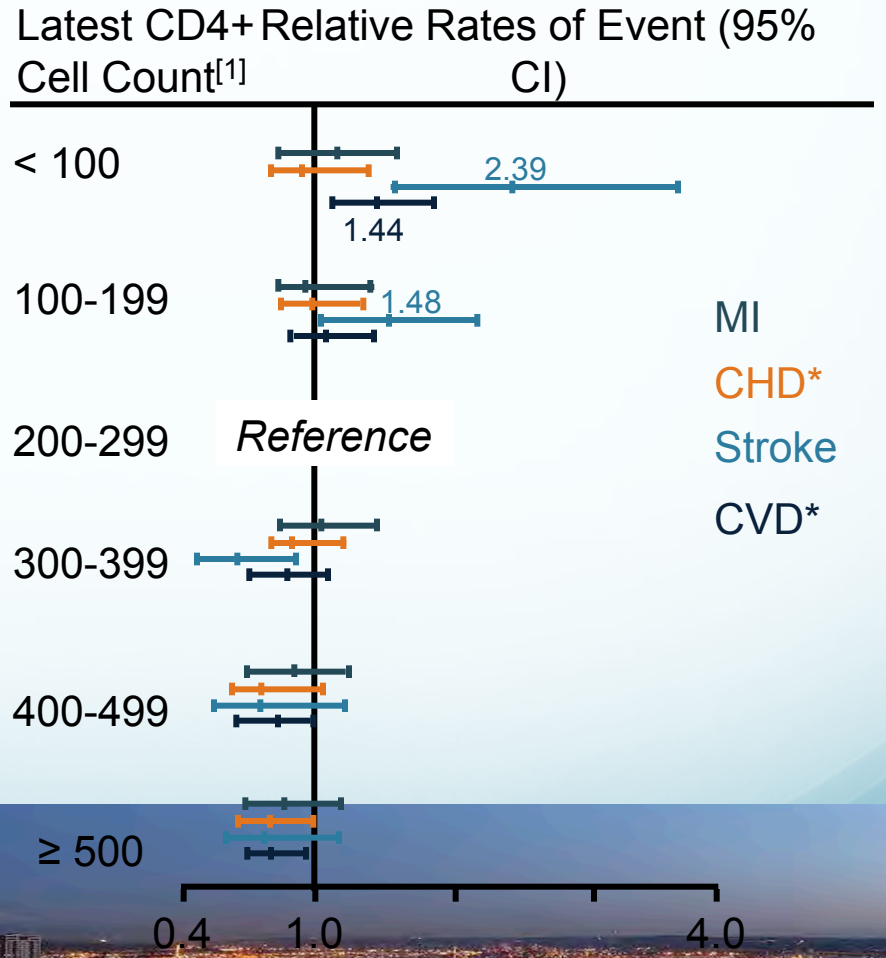
Inflammation

- Late ART era patients still have about a 10 year reduction in life expectancy
- Age-associated morbidity and mortality caused by a combination of lifestyle factors, ART toxicity, persistent inflammation
- Unresolved questions:
  - How much does HIV itself contribute to persistent inflammatory state?
  - To what degree does inflammation drive specific end-organ disease?
  - Are some ART regimens better than others?
  - Which bio markers are the best predictors of clinical effect?



Limited Association of CVD Events With Immune Suppression in D:A:D Study

- D:A:D includes > 49,000 patients with HIV-1 infection from 11 cohorts in Europe, US, and Australia[1]
  - Aim to investigate association of ARVs and risk of CVD and other major disease events
- Previous study showed arterial stiffness, and thus CV risk, associated with CD4+ cell count nadir[2]
- However, current study showed CD4+ cell count nadir not associated with any CVD event[1]

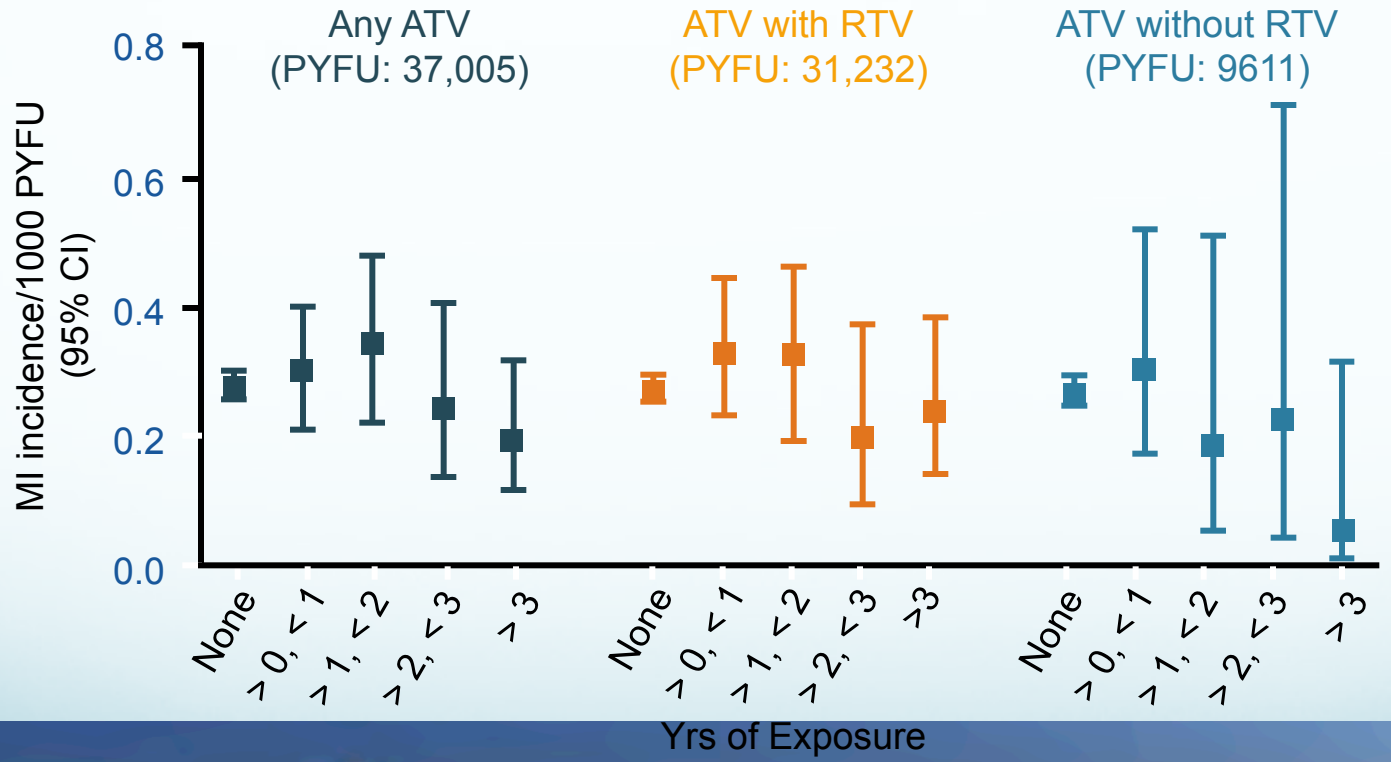


*CHD: MI, sudden cardiac death or invasive coronary procedure; CVD: first CHD or stroke.

1. Sabin C, et al. CROI 2012. Abstract 822. 2. Ho JE, et al. AIDS. 2012;24:1897-1905.

D:A:D: No Association Between ATV and Increased Risk of MI or Stroke

- > 49,000 HIV-infected patients from 11 cohorts in Europe, US, and Australia

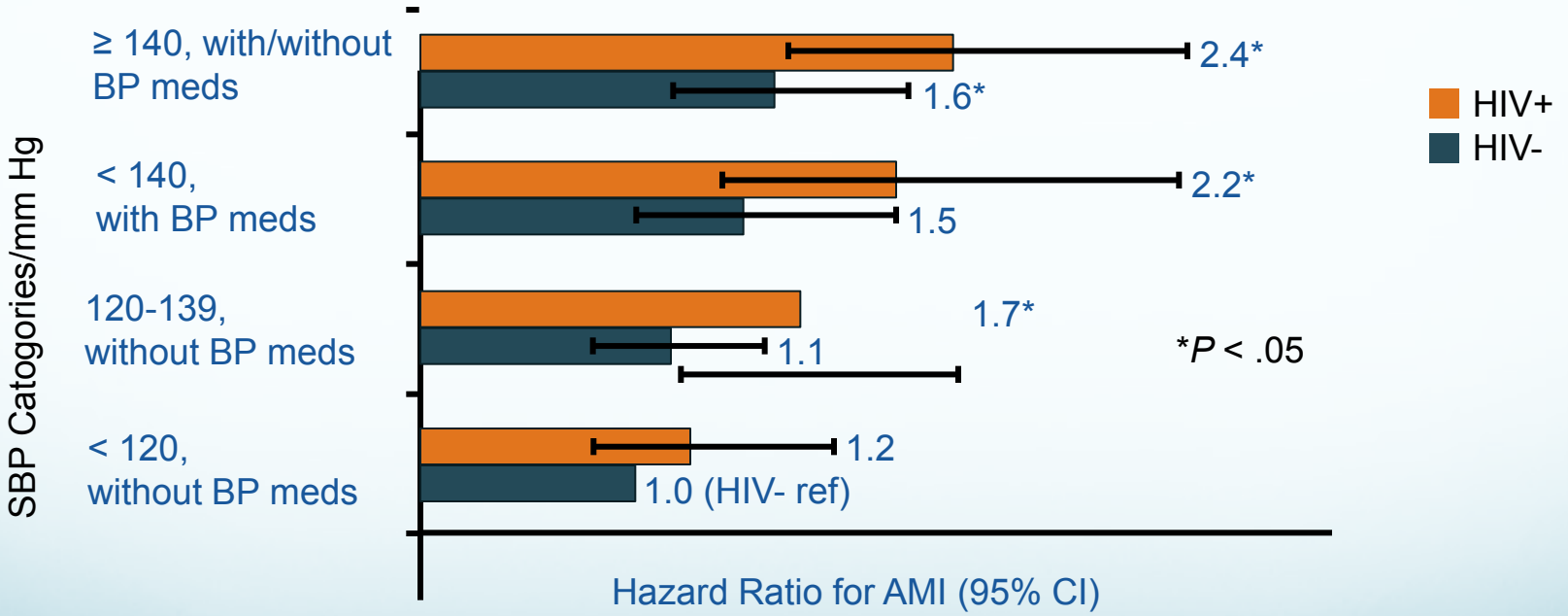


- Similar lack of association observed with ATV use and stroke

Monforte Ad, et al. CROI 2012. Abstract 823.

Hypertension/Pre-hypertension Associated With Higher AMI Risk in HIV+ Veterans

- 27,365 HIV-infected and 55,125 HIV-uninfected persons from Veterans Aging Cohort Study included in analysis
  - 443 AMI events during median 4.6 yrs of follow-up

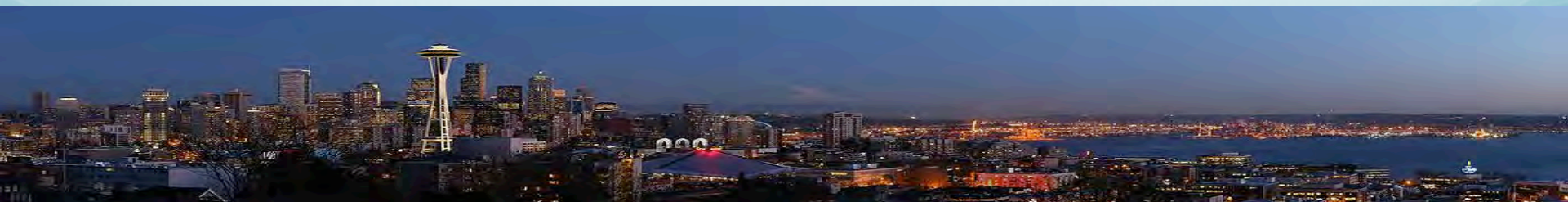


Model adjusted for age, sex, race/ethnicity, diabetes, LDL, HDL, triglycerides, statins, smoking, hepatitis C, BMI, renal disease, cocaine, alcohol use, hemoglobin.

Armah K, et al. CROI 2012. Abstract 120.

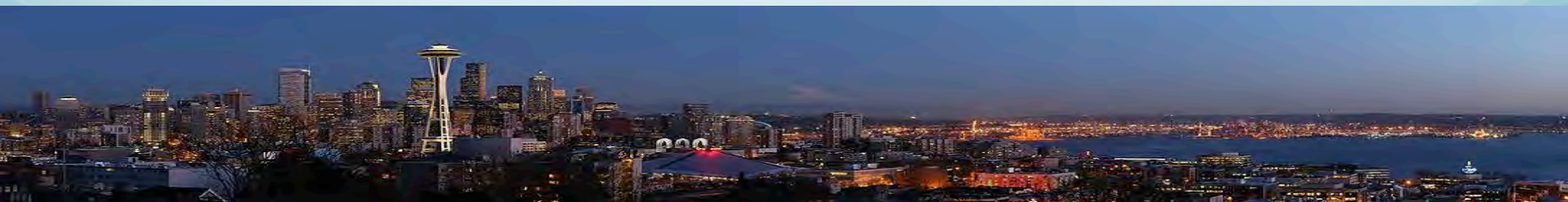
Biomarkers

- CRP
  - Treatment with ABC (or EFV) initially increases CRP
  - Other randomized studies (STEAL & HEAT) found nothing
  - But ACTG 5095 (in which all patients received ABC or EFV or both) showed raised CRP
  - Uncertain clinical significance – linked to ABC cardiovascular risk?
- Markers of inflammation/immune activation/coagulation
  - Swithching PI to RAL improves the biomarkers. Uncertain clinical significance
- Levels of arterial inflammation
  - PET scans in patients with virologic suppression and no CVD
  - HIV+ patients similar inflammation to patients with established atherosclerotic disease. Significantly greater than HIV- controls matched by Framingham risk



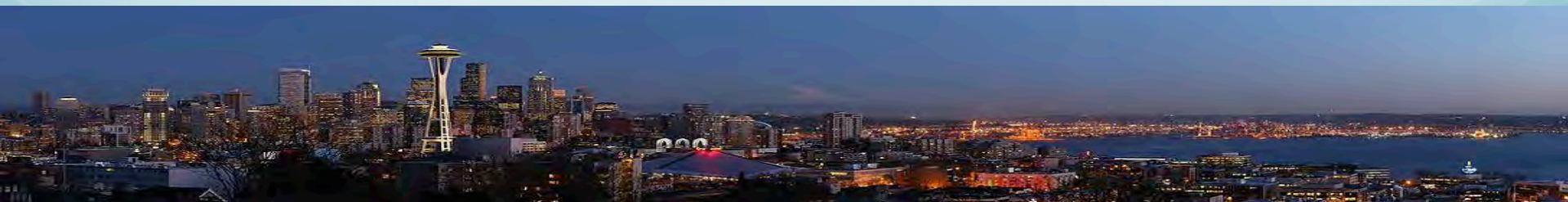
Statins

- Effect of statins on reducing risk of serious non-AIDS defining events and non-accidental death (ACTG/ALLERT)
- N = 3601 patients not on a statin initially
  - 481 started a statin
  - Did not include outcomes that occurred in the first 8 weeks on a statin



ALLERT Baseline Characteristics

Baseline characteristics	N=3601
Median age	39
Gender: M/F	83%/ 17%
Race • Black • White • Hispanic	 30% 47% 21%
Median BMI	25
Current smoker	38%
Median systolic BP	120 mmHg
Median LDL	2.7 mmol/l
CD4 nadir	180 cells/mL
CD4 current	346 cells/mL

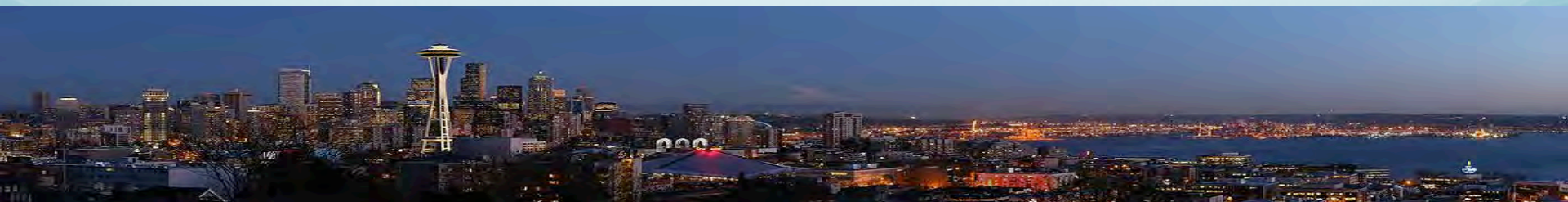


ALLERT Outcomes

Event	No events	Event rate: statin users (per 100py)	Event rate: non-statin users (per 100py)	Crude HR	Baseline adjusted HR	Adjusted and weighted HR
CV event	62	0.5	0.4	1.44	0.82	0.89
Non-CV event	580	4.2	3.8	1.18	0.82	0.85
Bacterial infection	144	0.7	0.9	0.96	0.96	1.25
Incident DM	158	1.3	1.0	1.52	1.02	0.87
Renal events	135	1.4	0.7	1.58	1.00	0.85
Cancer	89	0.5	0.5	1.03	0.71	**0.43**
Death	143	0.5	0.9	0.47	0.41	0.82

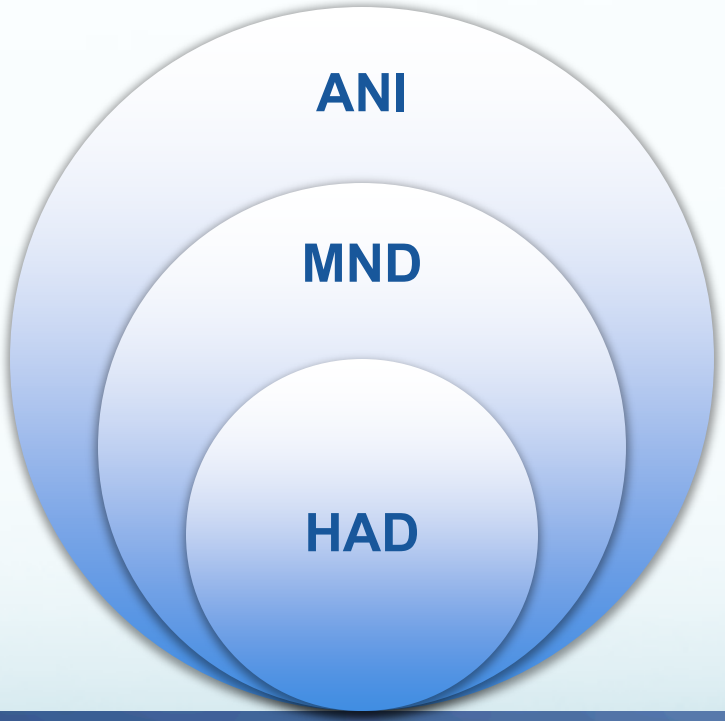
Statins Conclusions

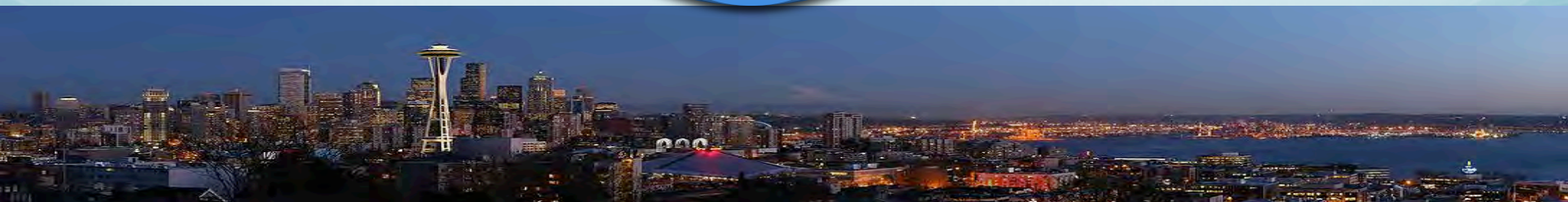
- Non-significant (but maybe clinically meaningful) reduction in non-AIDS events and deaths
  - Consistent with a Hopkins study of 1538 patients: 3 fold reduction in death rate with statin use (More, Plos One 2011)
- Significant reduction in malignancies
  - Consistent with a Kaiser study of 1554 patients: 45% reduction in NHL cases with statin use (Chao, AIDS 2011)
- Benefits of statin use increased with increasing age and higher nadir CD4 count



HAND

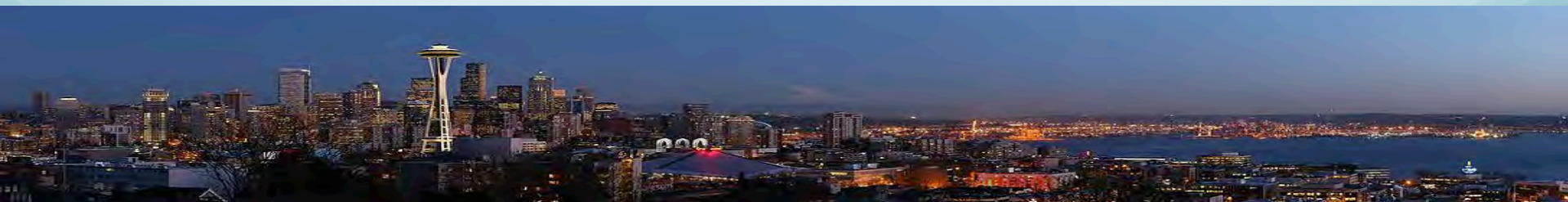
- HAND - HIV Associated Neurocognitive Disorder
- HAND present in 30-50% of patients





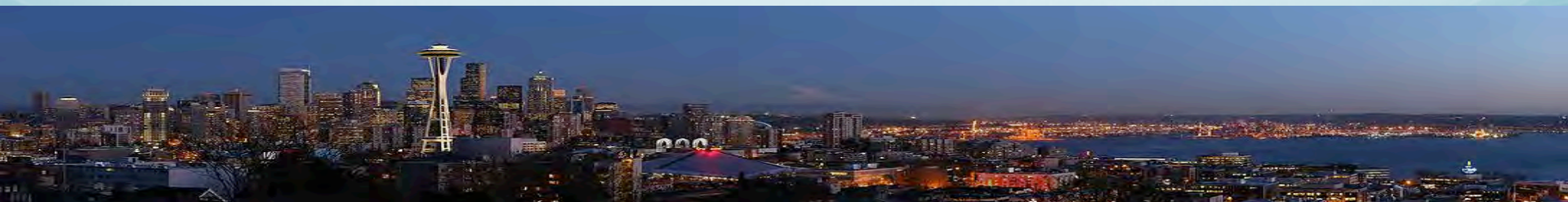
HAND Tests

- Self Reporting (SR)Tests
  - Partial Assessment of Own Functioning Inventory (PAOFI)
  - Activities of Daily Living (ADL)
- Performance Based (PB) Tests
  - Medication Management Test-Revised (MMT-R)
  - Valpar System 3000 Work Samples and Computerized Assessment



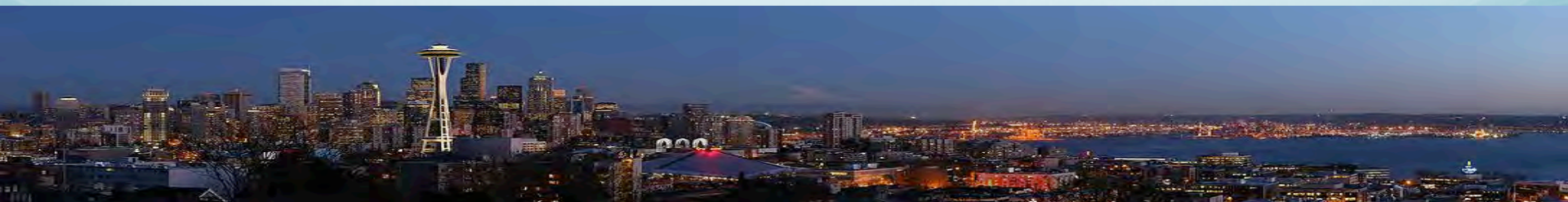
HAND

- Baseline Predictors of Decline in Cognitive Function
- **Yes**: Older age, less education, female sex, substance abuse, co-morbid conditions, AIDS dx, CD4 nadir and HCV infection
- **No**: Ethnicity, ARV treatment, current CD4, estimated duration of HIV infection



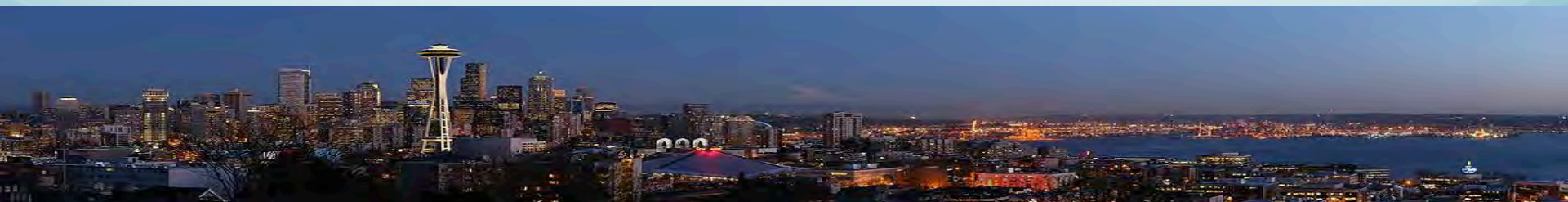
HAND Conclusion

- Asymptomatic mild HAND increases the risk for future symptomatic decline: CHARTER Study
- Patients with ANI have a 3-5 RR of developing symptomatic HAND compared to normal pts even after adjusting for baseline predictors
- Earlier cognitive decline is more common in women, those with substance abuse and other comorbid conditions and those with a lower CD4 nadir, an AIDS Dx, HCV infection and lower follow up CD4 counts



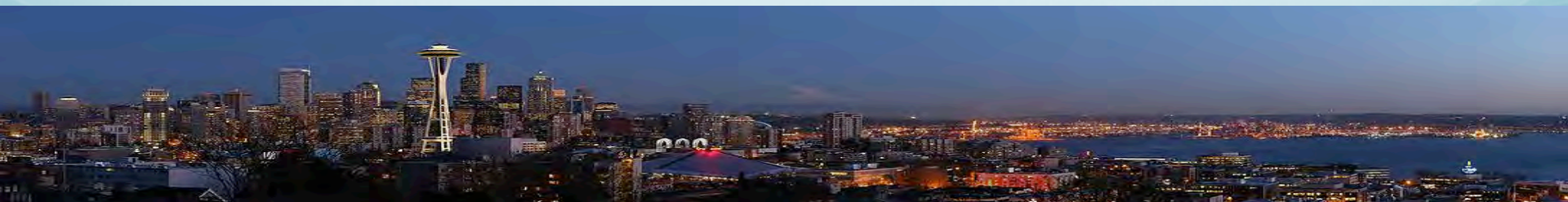
Bone Loss

- Background
  - ART initiation associated with a 2-6% decline in BMD and greater reductions are seen in TDF
  - BMD reductions correlate with increases in biomarkers of bone turnover such as CTX-1 (resorption) and osteocalcin & P1NP (formation)



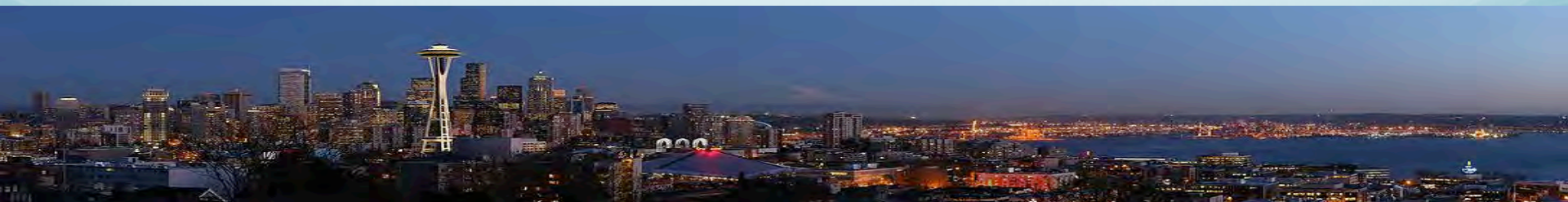
Bone Loss

- Impact of Switching from AZT/3TC to TDF/FTC on BMD and bone metabolism in virologically suppressed patients
- PREPARE sub-study # 125LBA multi-center, randomized, controlled study
  - N = 54 patients, all on AZT/3TC for > 2 years with suppressed viral load
  - Median age 45-47, mostly white males, median CD4 ~ 490



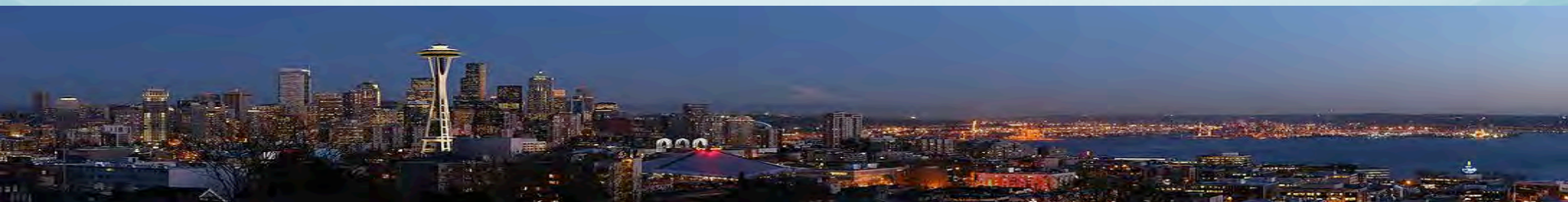
Bone Loss

	Continue AZT/3TC		Switch to TDF/FTC		
	Median change	Within group p-value	Median change	Within group p-value	Between group p-value
Lumbar spine	-0.18	0.91	-2.04	0.01	0.03
Femoral neck	0.14	0.74	-1.52	0.16	0.48



Bone Loss Conclusion

- In virologically suppressed patients on AZT/3TC; switching to TDF/FTC leads to marked increases in bone turnover
- Changes in bone turnover correlate with loss of BMD in the lumbar spine



Seattle – New Frontiers

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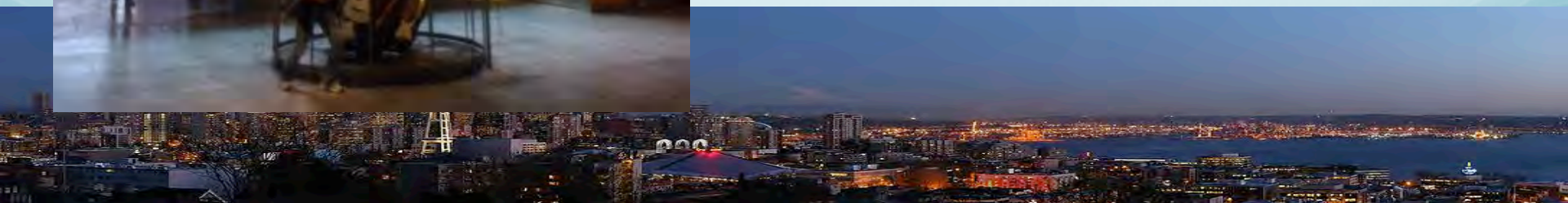
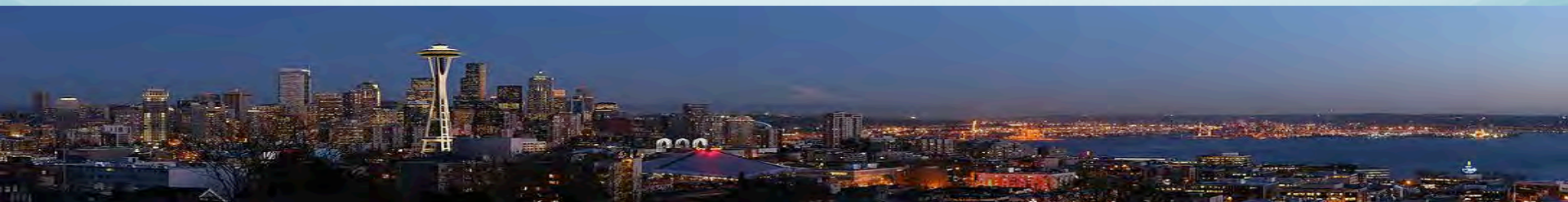


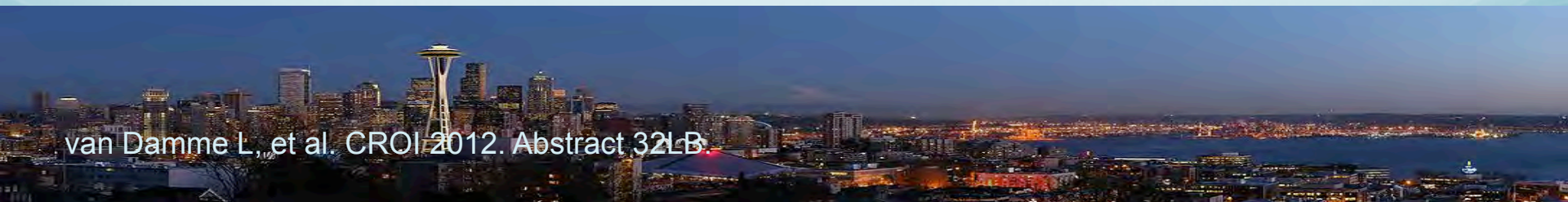
Prevention

- Why did the FEM-PrEP study fail to show protection of TDF/FTC?
- Poor adherence
  - Detectable drug levels in fewer than 50% of infected women assigned to active arm



FEMPrEP: Low Adherence Rates in Oral TDF/FTC Pre-Exposure Prophylaxis Trial

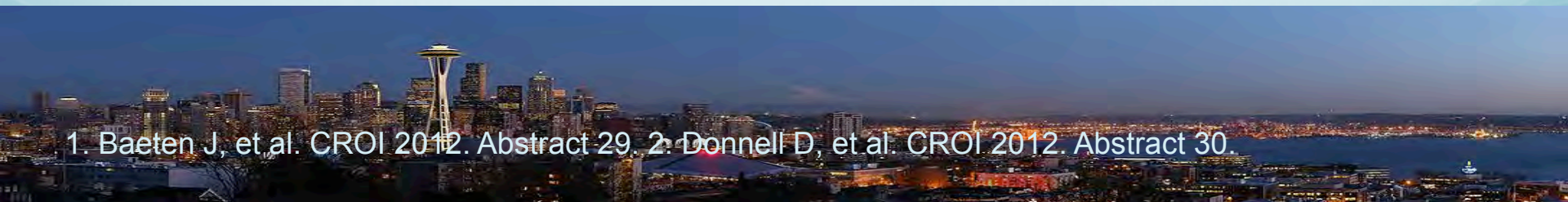
- Phase III study of oral TDF/FTC vs placebo for 52 wks in African women
  - TDF/FTC: 1062 women; placebo: 1058 women
- TDF/FTC associated with 6% estimated reduction in risk of HIV acquisition in primary analysis (HR: 0.94; 95% CI: 0.59-1.52; *P* = .81)
  - Trial stopped for futility in April 2011
- Pregnancy common in both arms; TDF/FTC vs placebo: 11.2% vs 7.5%
- Self-reported adherence overestimated
  - Pts reported 95% adherence; pill counts indicated ~ 86% to 89% adherence
  - However, < 40% of treated women (both infected cases and uninfected controls) had plasma drug levels ≥ 10 ng/mL, indicating pills taken in prior 48 hrs



van Damme L, *et al*. CROI 2012. Abstract 32LB.

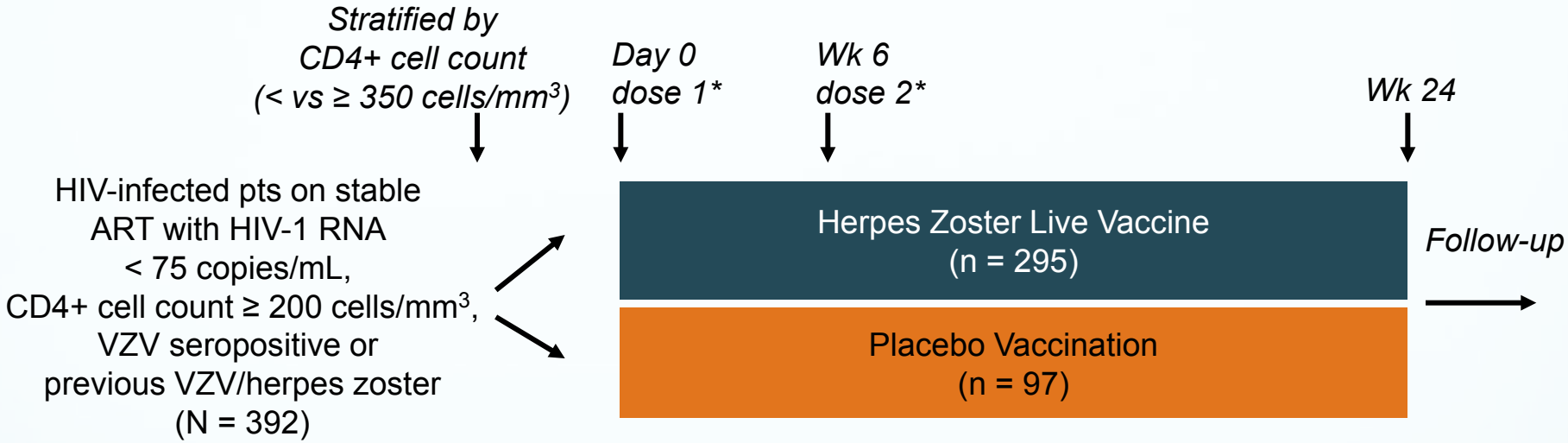
Partners PrEP: TDF and TDF/FTC Significantly Reduce HIV Acquisition

- 4747 HIV-negative partners in HIV-serodiscordant heterosexual couples randomized to receive oral TDF, oral TDF/FTC, or placebo
- Both PrEP strategies associated with significant reduction in HIV transmission vs placebo in both men and women[1]
  - TDF efficacy: 71% in women, 63% in men
  - TDF/FTC efficacy: 66% in women, 84% in men
- In contrast to FEMPrEP, adherence levels high
  - Estimated that 97% of pills were taken based on monthly pill counts[1]
  - TDF detected in plasma at higher rates in uninfected pts vs those who seroconverted, according to case cohort study[2]
    - Infected pts with detectable TDF in TDF and TDF/FTC arms: 31% and 25%
    - Uninfected pts with detectable TDF in TDF and TDF/FTC arms: 83% and 81%



1. Baeten J, et al. CROI 2012. Abstract 29. 2. Donnell D, et al. CROI 2012. Abstract 30.

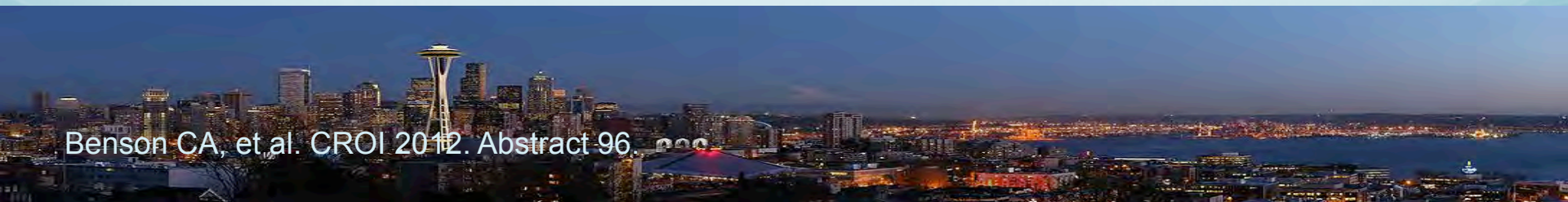
ACTG A5247: Herpes Zoster Live Vaccine in HIV-Infected Patients on Stable ART



*Vaccination delayed in persons with CD4+ cell count < 160 cells/mm^3, HIV-1 RNA > 5000 copies/mL, or contraindication

- Primary endpoint: ICH-defined SAE or NIAID Division of AIDS grade 3/4 signs, symptoms, or AEs within 6 wks of vaccine dose

- Secondary endpoints
  - VZV antibody titer 6 wks after vaccine dose
  - VZV-specific cell-mediated immune response in 40 pts in each CD4+ cell count subgroup



Benson CA, et al. CROI 2012. Abstract 96.

ACTG A5247: Herpes Zoster Live Vaccine Safe in HIV-Infected Pts on Stable ART

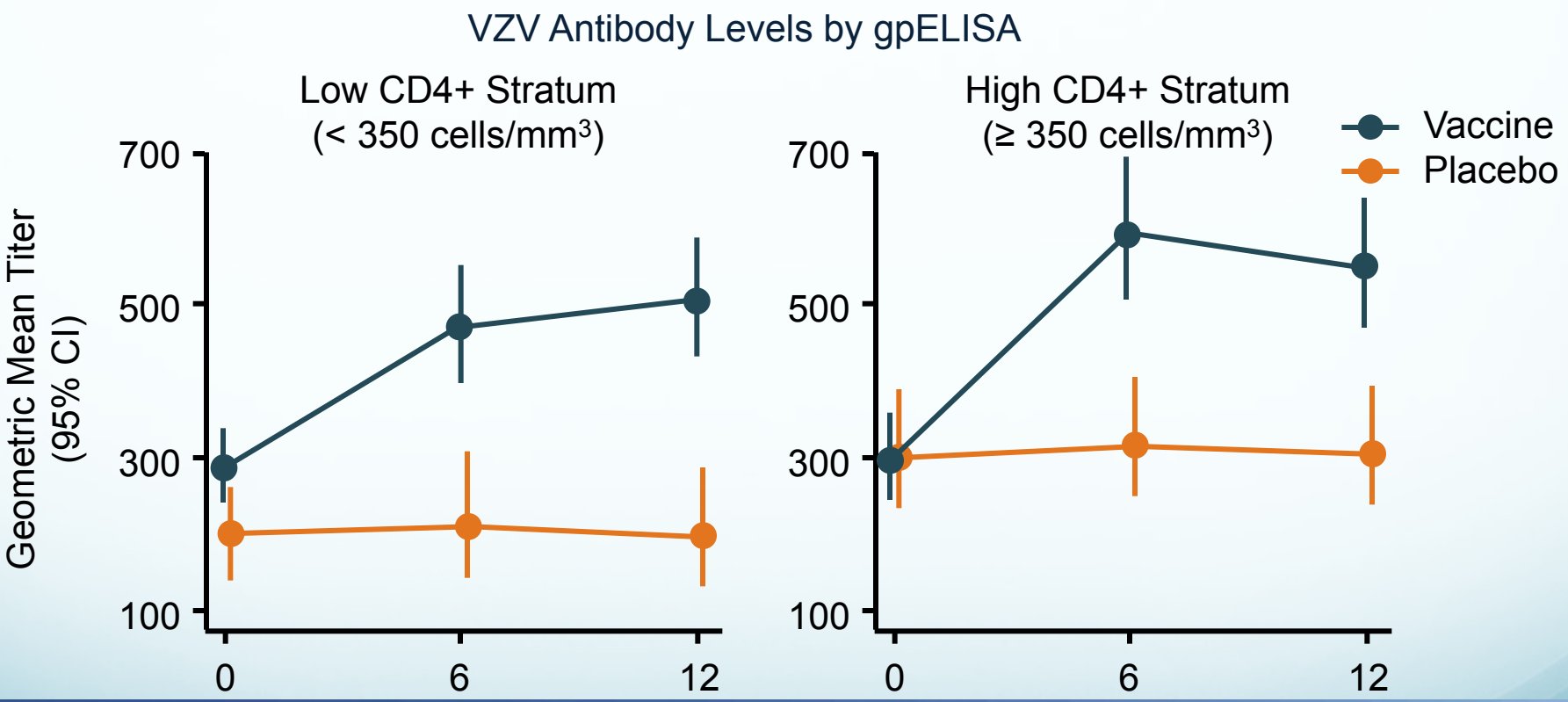
Safety Outcomes, % (95% CI)	Herpes Zoster Live Vaccine (n = 295)	Placebo (n = 97)
Met primary safety endpoint	5.1 (2.9-8.2)	2.1 (0.3-7.3)
Injection-site reaction*	42 (36.3-47.9)	12.4 (6.6-20.6)
Rash	5.1 (2.9-8.2)	4.1 (1.1-10.2)
Fever	4.1 (2.1-7.0)	6.2 (2.3-13.0)

**P* < .001 for difference between arms.

- Clinical VZV or VZV-like rash reported in 3 pts in vaccine arm and 2 pts in placebo arm
  - Wild-type VZV detected in 1 pt in each arm, herpes simplex virus in 1 pt in vaccine arm, whereas rashes in remaining 2 pts negative for VZV
  - No vaccine-strain virus in any of the rashes

Benson CA, et al. CROI 2012. Abstract 96.

ACTG A5247: Immunogenicity of Herpes Zoster Live Vaccine in HIV-Infected Pts

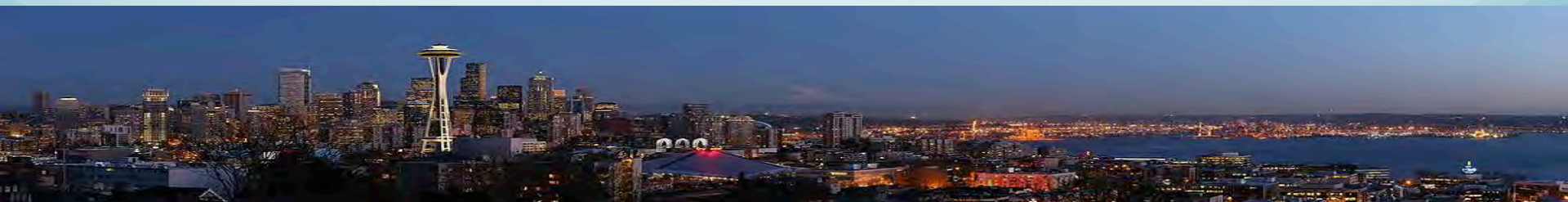


- No apparent benefit to second vaccine dose

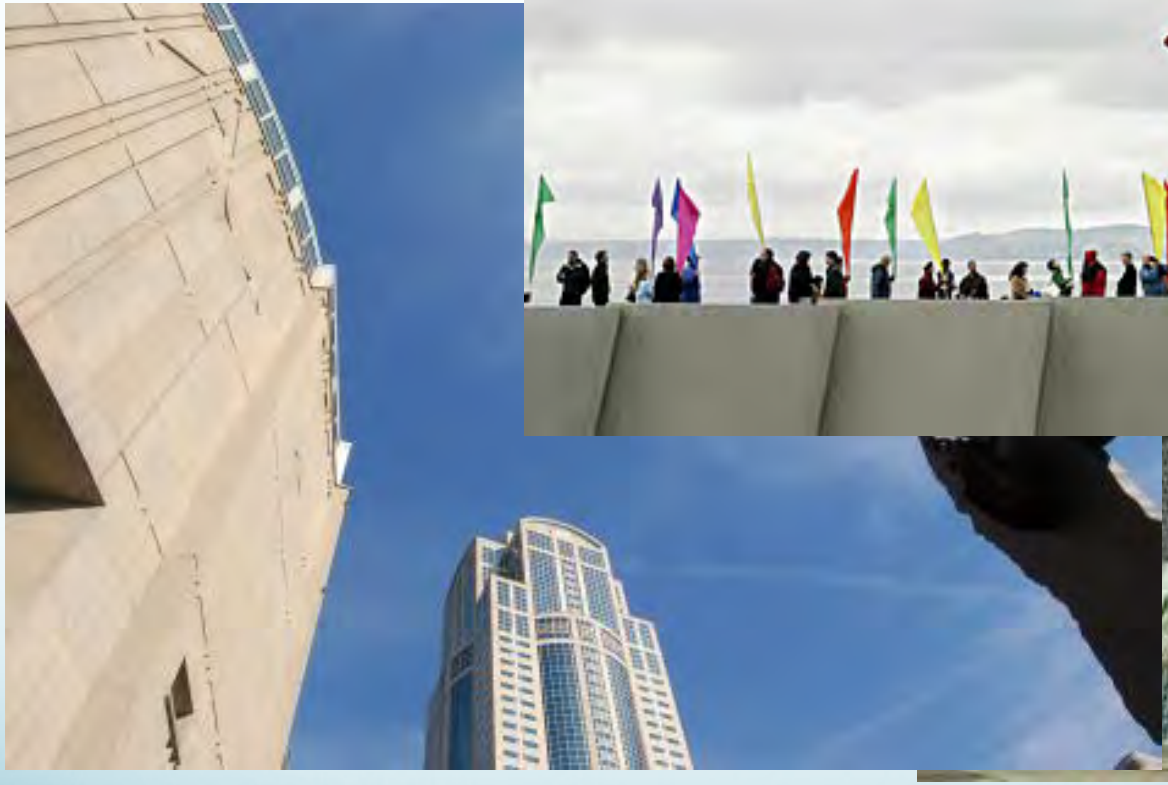
Benson CA, et al. CROI 2012. Abstract 96.

Zoster Vaccine Conclusion

- Safe and immunogenic
- Remaining question
  - Who do we give it to?
    - All with HIV?
    - Just those over 60? Over 50?
    - Those with virologic suppression?
    - Over a certain CD4 threshold?

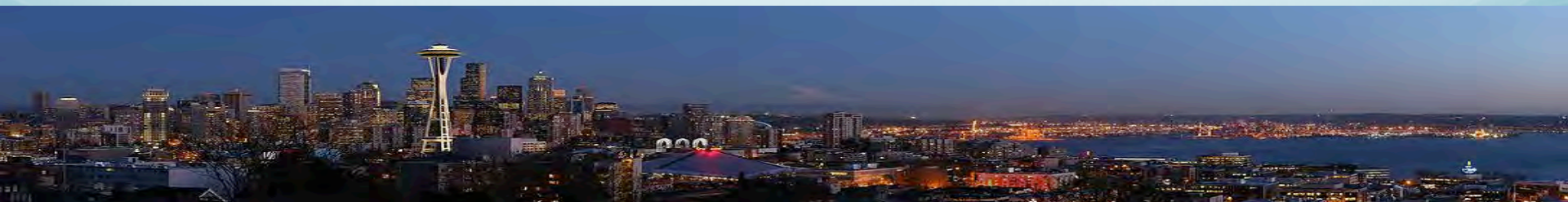


Seattle



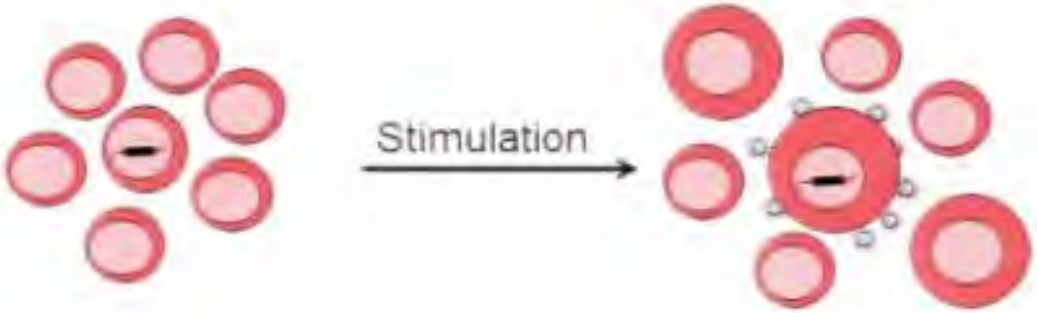
Basic Science

- Latency
- Superinfection

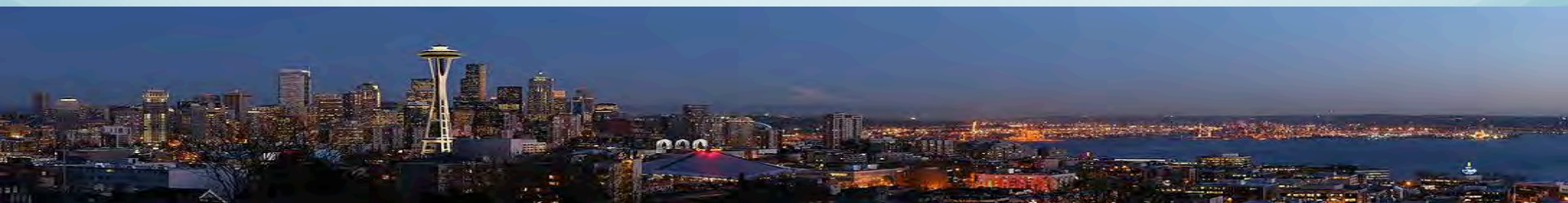


Latency

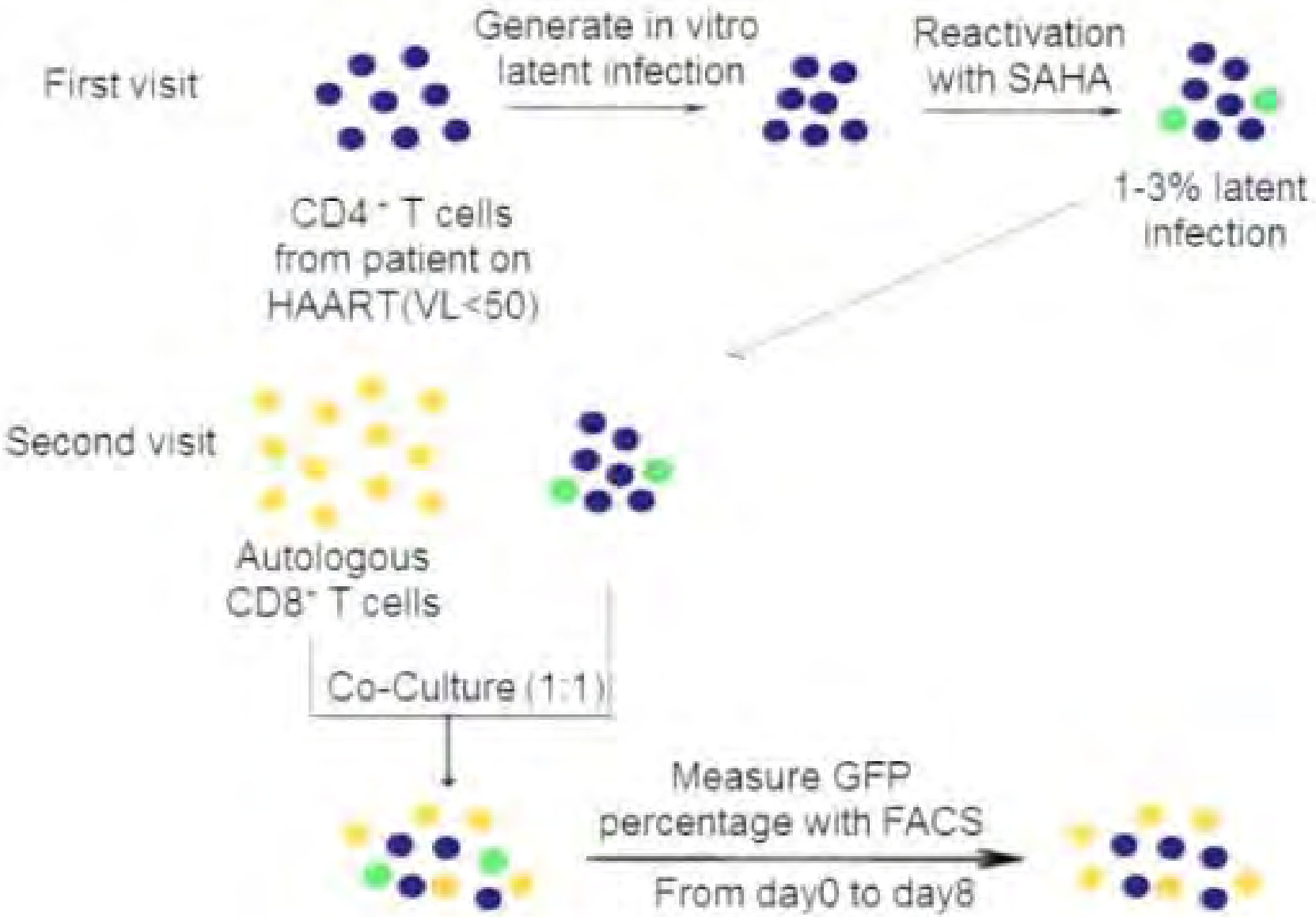
The latent reservoir for HIV-1



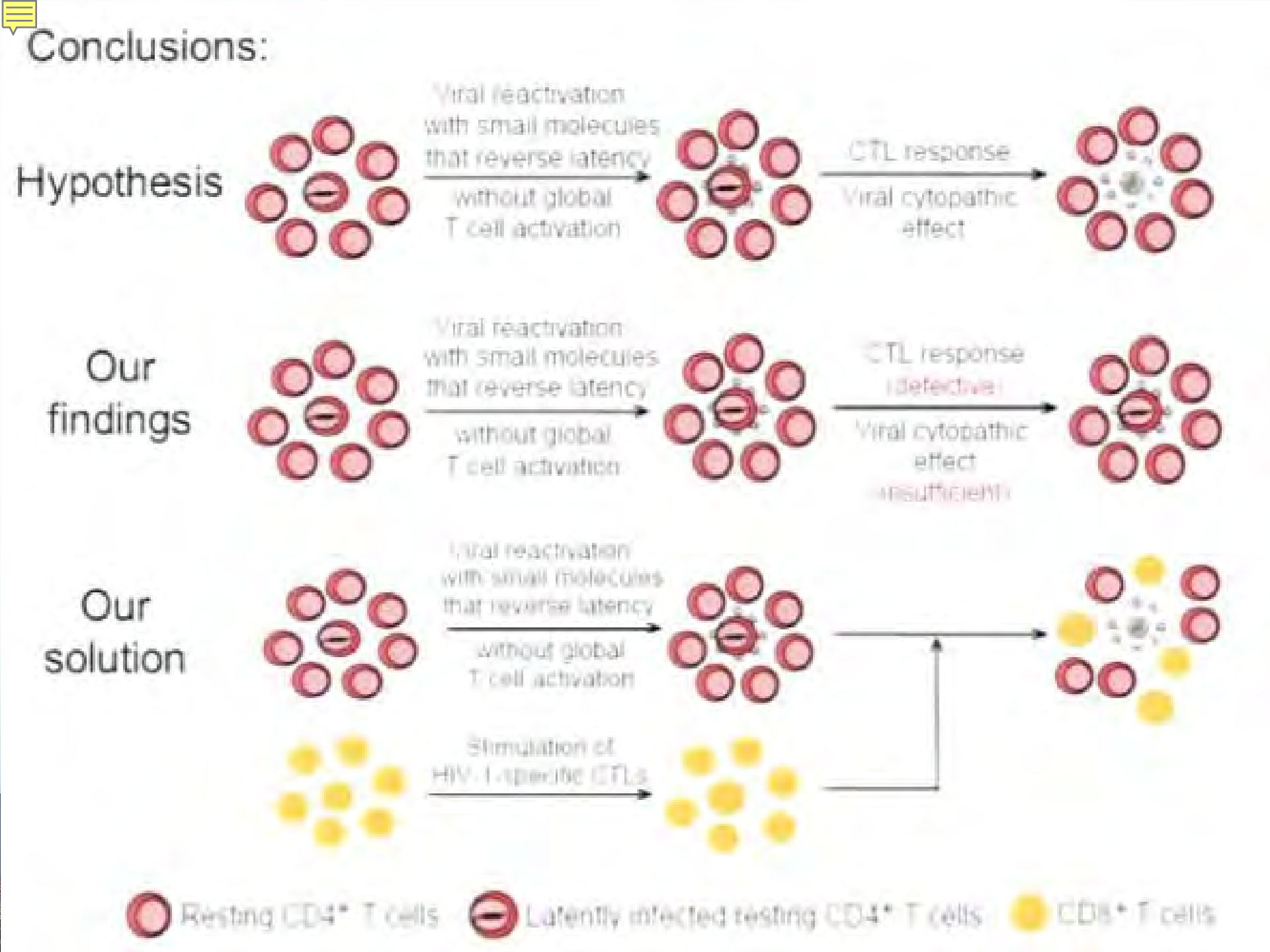
Frequency: around 1 per million
Size: 10^5 to 10^6 cells
Half-life: 44 months
Time to eradicate: around 70 years



Experimental design

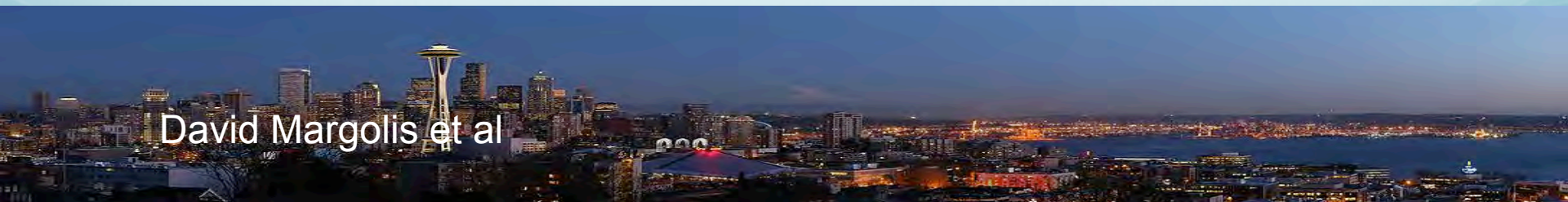


Conclusions:



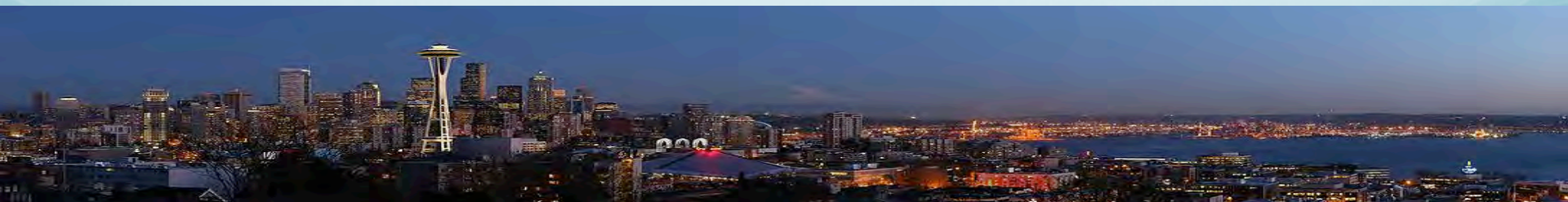
Administration of Vorinostat Disrupts HIV-1 Latency in Patients on ART

- Resting CD4+ T cells primary reservoir of persistent infection
  - Histone deacetylases maintain latency
  - HDAC inhibitor suberoylanilide
- Hydroxamic acid (SAHA – Vorinostat) induces expression of latent HIV from resting CD4+ T cells ex vivo
- Stimulation of HIV-1-specific cytolytic T cells facilitates elimation of latent viral reservoir after virus reactivation



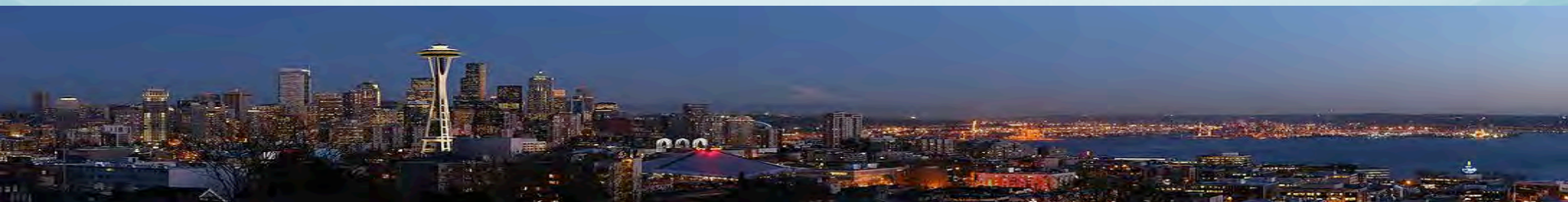
Latency

- First direct measurement of disruption of latent HIV in vivo
- Optimal dosing schedule?
- Can vorinostat deplete latent infection?
- What about mutagenic potential?



Superinfection

- Rakai cohort. SI seems to be similar to the incidence of HIV in the area. 1.3 infections per 100 person-years. 3.6/100py in Mombassa.
- Questions
  - Does this mean that the immune response to HIV does not protect against new infection?
  - Or does it mean that because HIV depletes the immune capacity, it predisposes to super-infection?
- These cases are early cases of superinfection. There are data showing that the immune system takes a few years to give protection



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