HIV TREATMENT

HIV/AIDS Department

WHO Updates from CROI 2016

Treatment and Care

Meg Doherty,
Treatment and Care Coordinator
WHO HQ

World Health Organization

Thanks for Slides:

Lynne Mofenson
Martina Penazzato
George Siberry
Silvia Bertagnolio
Andrew Hill
CCO CROI2016 Review

Outline

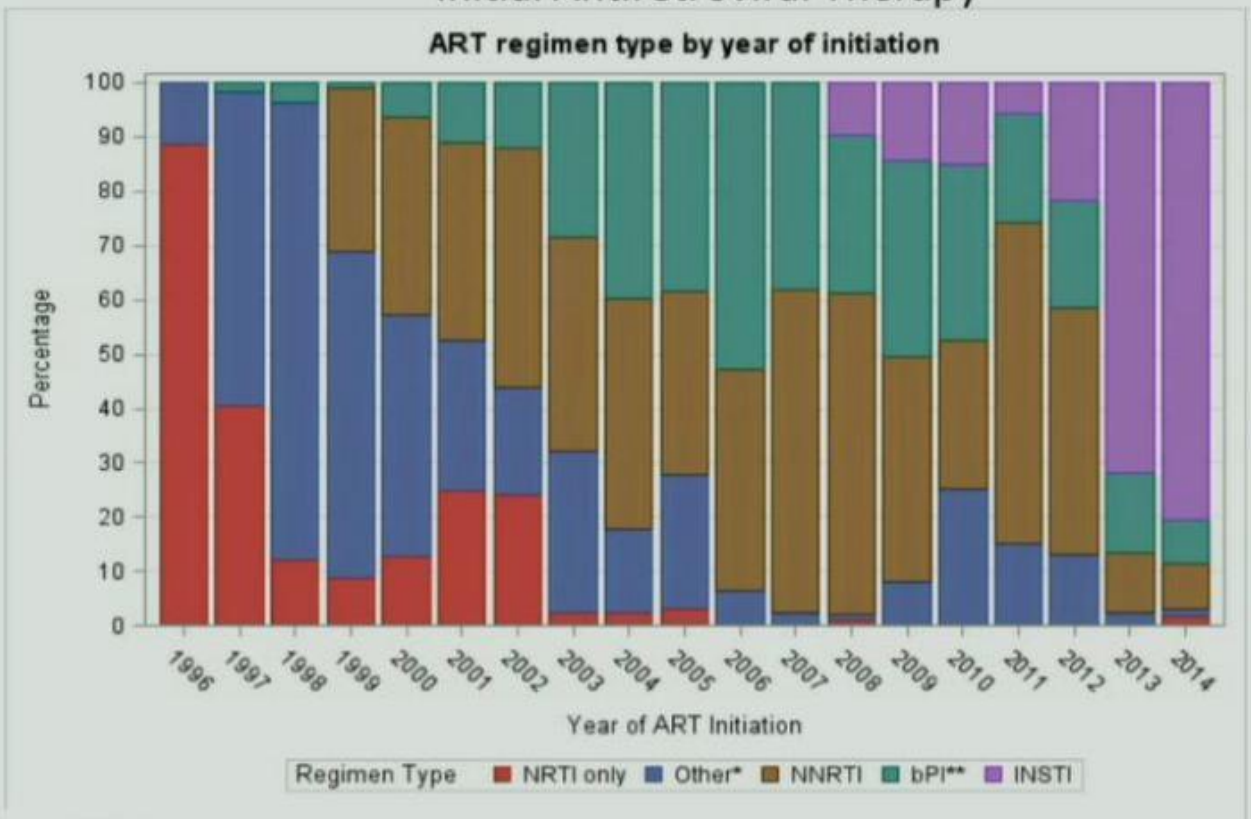
- **New ARV drug trials**
  - **INSTI, ecfTAF, LA-ARVs for treatment, monoclonal Abs**
- **Peadiatrics & pregnant women**
  - **DTG safety in pregnancy & fetus**
- Earlier Treatment and Acute infection
- Cascades – how close are we to 90/90/90?
- HIV Drug resistance
  - First PrEP failure due to resistance

Benefits of INSTI

UCHCC: UNC CFAR
HIV Clinical Cohort

Shift To Integrase Inhibitor-based Therapy

Initial Antiretroviral Therapy



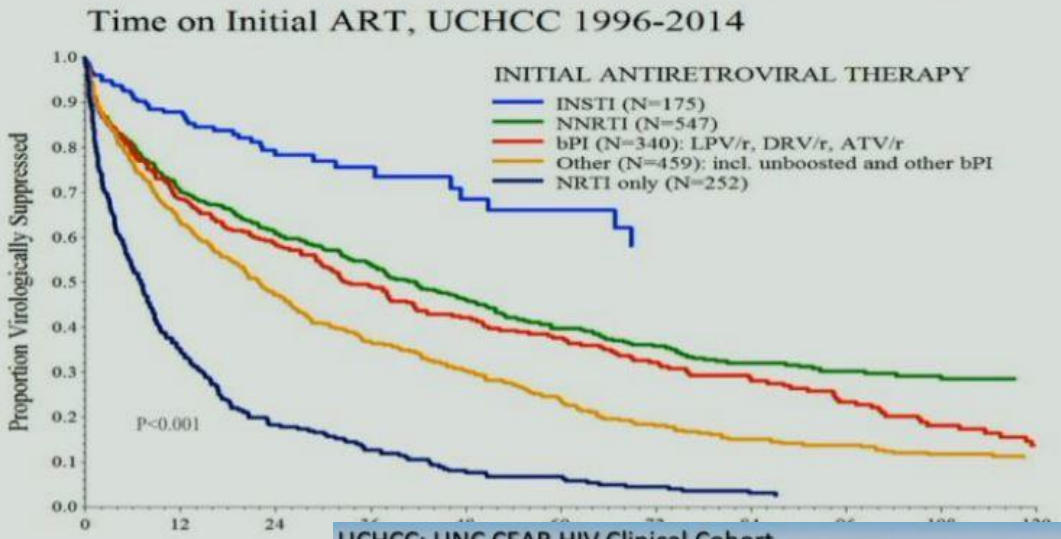
1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Eron, CROI 2016

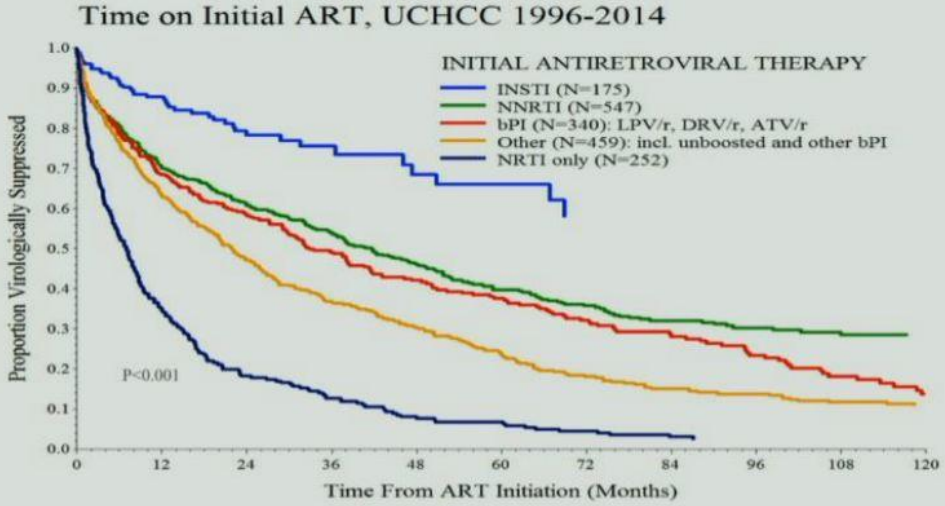
Persistence of Initial ART



- 1,773 patients initiating ART between
- Persistence defined as no switch in an

UCHCC: UNC CFAR HIV Clinical Cohort

Persistence of Initial ART

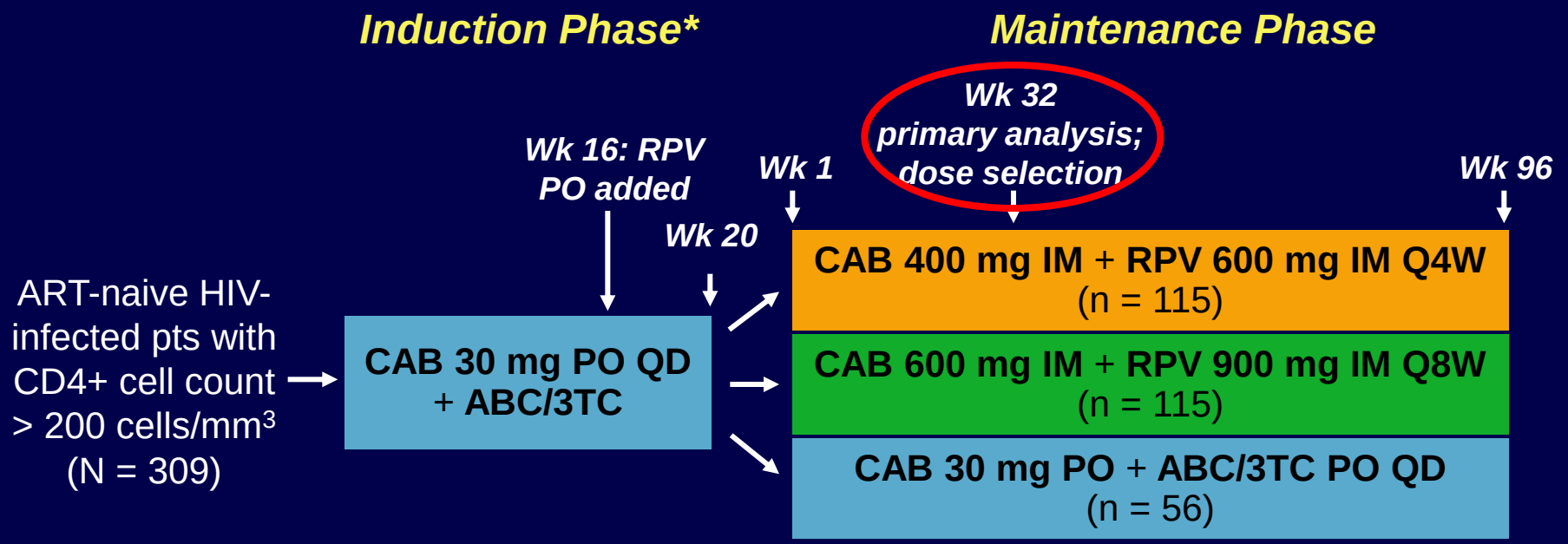


- In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression
- in multivariate analysis see poster 1034 Simoni et al

Eron, CROI 2016

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label phase IIb study
  - Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32

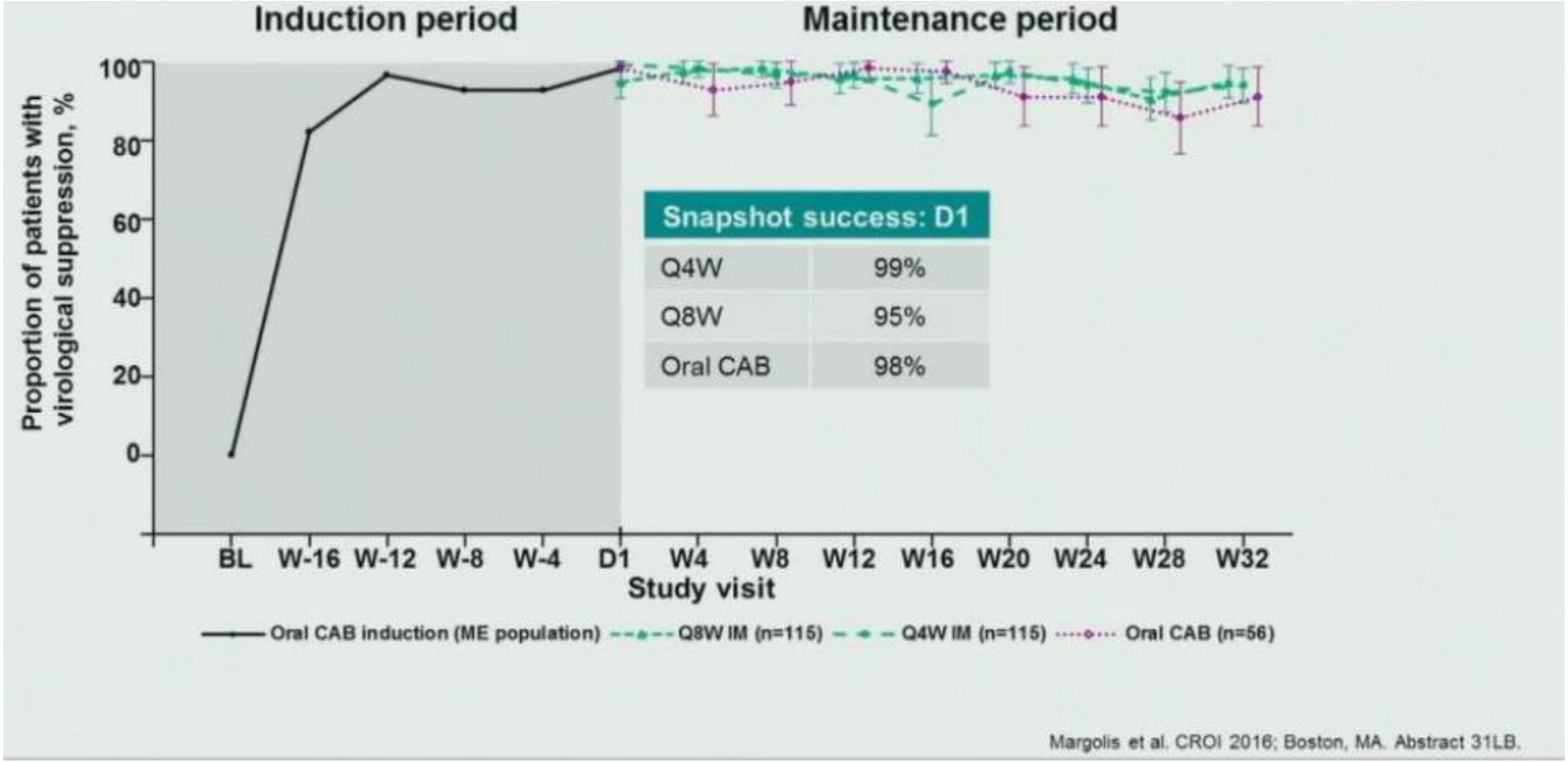


*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. 6 pts discontinued for AEs or death in induction analysis.

Margolis DA, et al. CROI 2016. Abstract 31LB.

Slide credit: clinicaloptions.com

Latte2 Results



Snapshot success: D1	
Q4W	99%
Q8W	95%
Oral CAB	98%

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

Latte2 Results

Summary of Injection Site Reactions (ISRs)

	Q8W IM (n=115)	Q4W IM (n=115)	IM subtotal (N=230)
Number of injections	1623	2663	4286
Number of ISRs (events/injection)	1054 (0.65)	1228 (0.46)	2282 (0.53)
Grades			
Grade 1	839 (80%)	1021 (83%)	1860 (82%)
Grade 2	202 (19%)	197 (16%)	399 (17%)
Grade 3	12 (1%)	10 (<1%)	22 (<1%)
Grade 4	0	0	0
Duration, days			
≤7	943 (89%)	1121 (91%)	2064 (90%)
Median	3.0	3.0	3.0

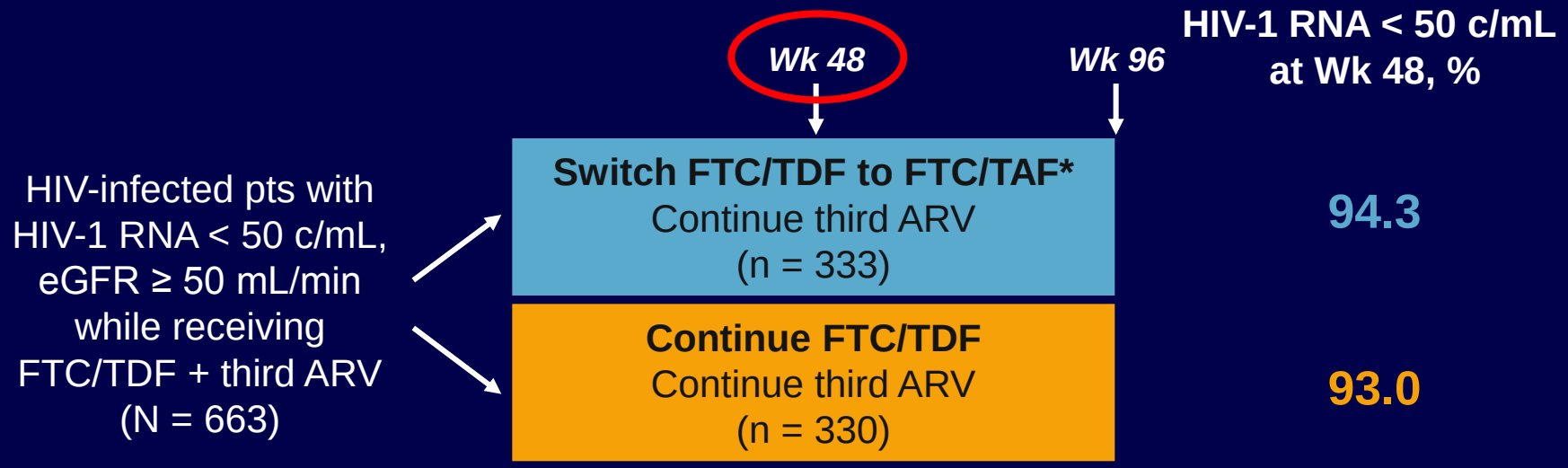
- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)[a]
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)

[a]Represents percent of subjects with a Week 32 visit (n=220).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

GS-1089: Switch From Suppressive TDF- to TAF-Containing ART: Wk 48 Efficacy

- Randomized, double-blind, active-controlled phase III trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48 by ITT FDA snapshot; noninferiority margin 10%



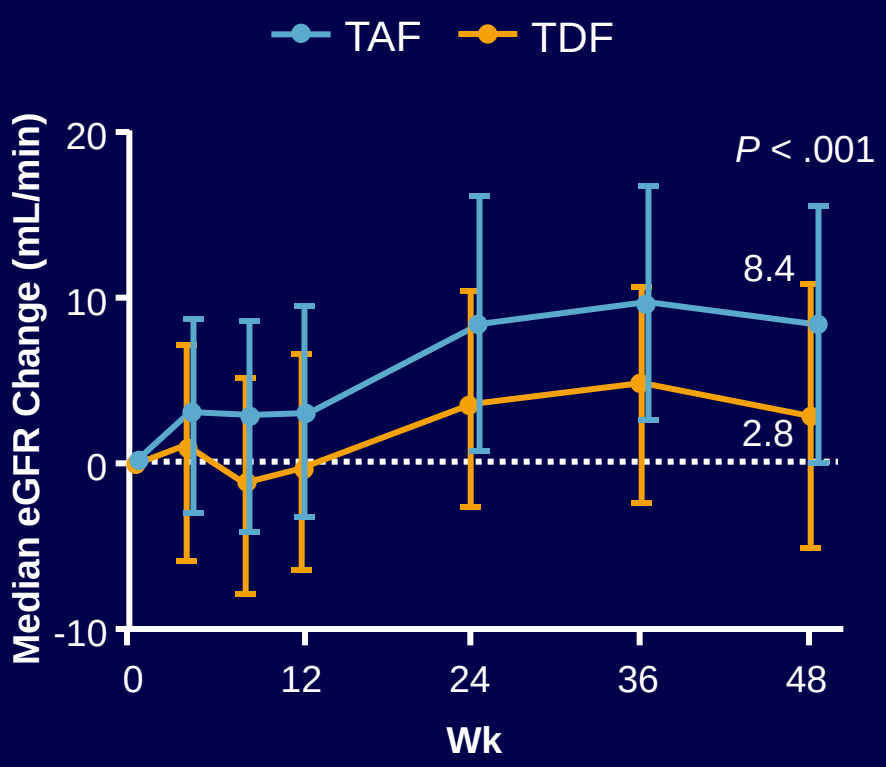
*FTC/TAF dosing: 200/10 mg with boosted PIs; 200/25 mg with unboosted third drug.

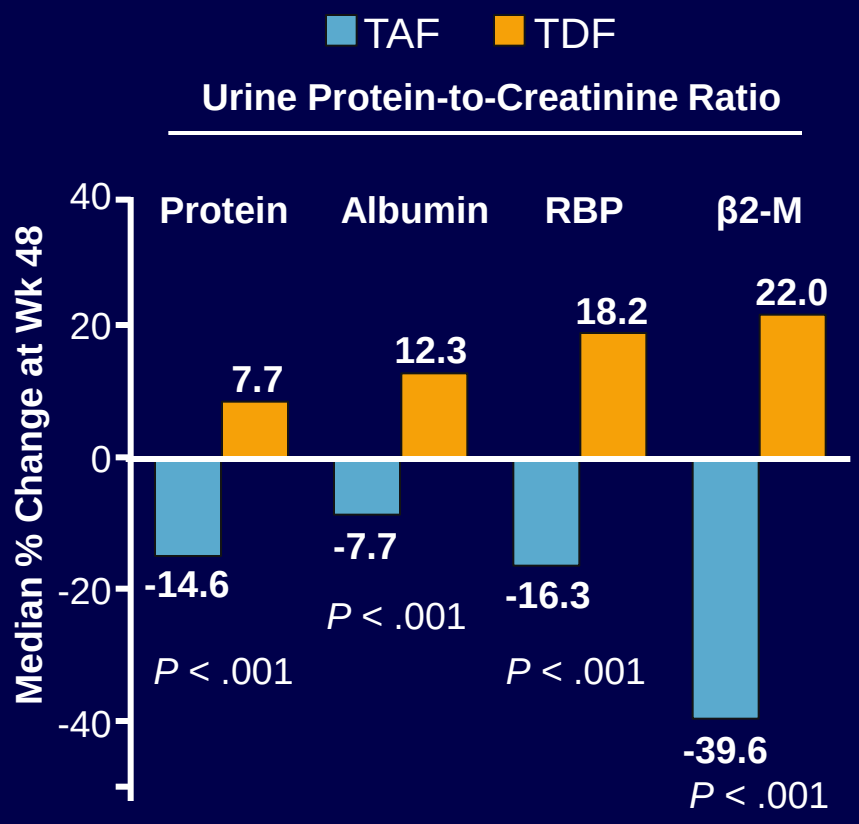
Gallant JE, et al. CROI 2016. Abstract 29.

Slide credit: clinicaloptions.com

GS-1089: Renal Outcomes With Switch From TDF- to TAF-Containing ART

- No proximal renal tubulopathy or Fanconi syndrome in either arm

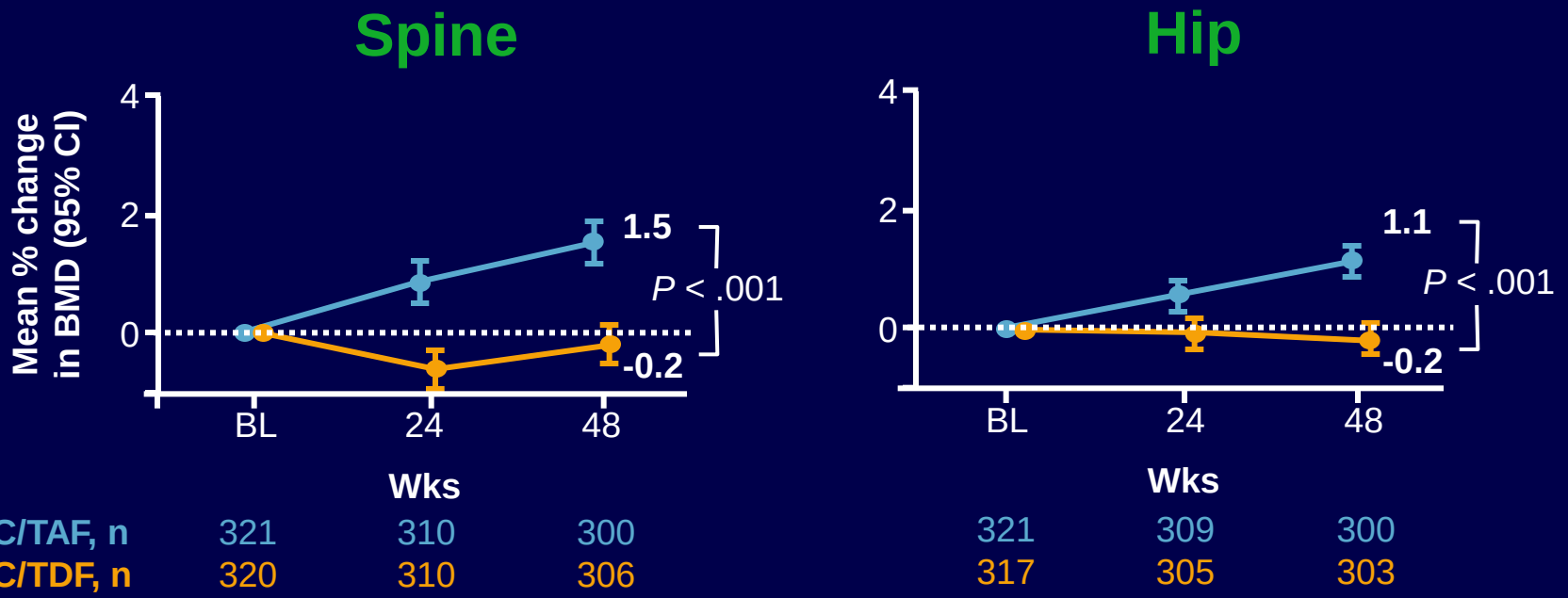




Gallant JE, et al. CROI 2016. Abstract 29. Reproduced with permission.

Slide credit: clinicaloptions.com

GS-1089: BMD Changes With Switch From TDF- to TAF-Containing ART



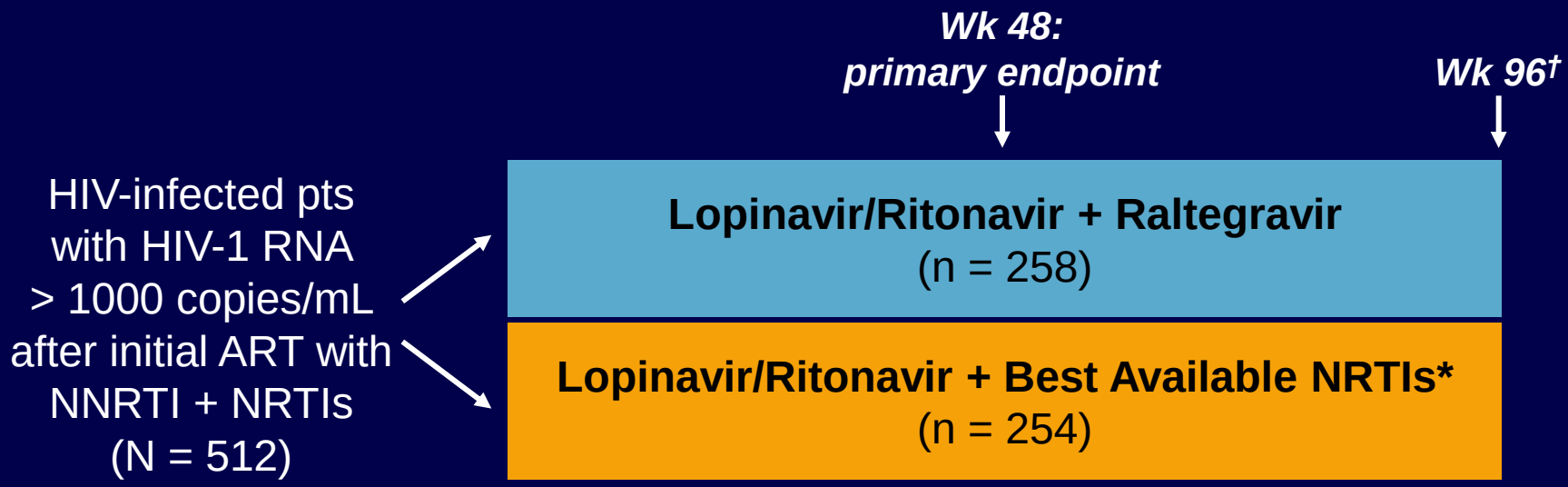
≥ 3% BMD Increase at Wk 48, %	FTC/TAF	FTC/TDF	*P* Value
Spine	30	14	< .001
Hip	17	9	.003

Gallant JE, et al. CROI 2016. Abstract 29. Reproduced with permission.

Slide credit: clinicaloptions.com

ACTG 5273: Second-line LPV/RTV + NRTIs vs LPV/RTV + RAL in African Settings

- Open-label, noninferiority phase III study
  - Primary endpoint: time to VF (confirmed HIV-1 RNA > 400 c/mL at or after 24 wks)



*NRTIs selected according to algorithm, including substitution of zidovudine for tenofovir DF and vice versa. †Shortened to 52 wks after last enrollment.

La Rosa AM, et al. CROI 2016. Abstract 30.

Slide credit: clinicaloptions.com

ACTG 5273: Virologic Failure and Toxicity

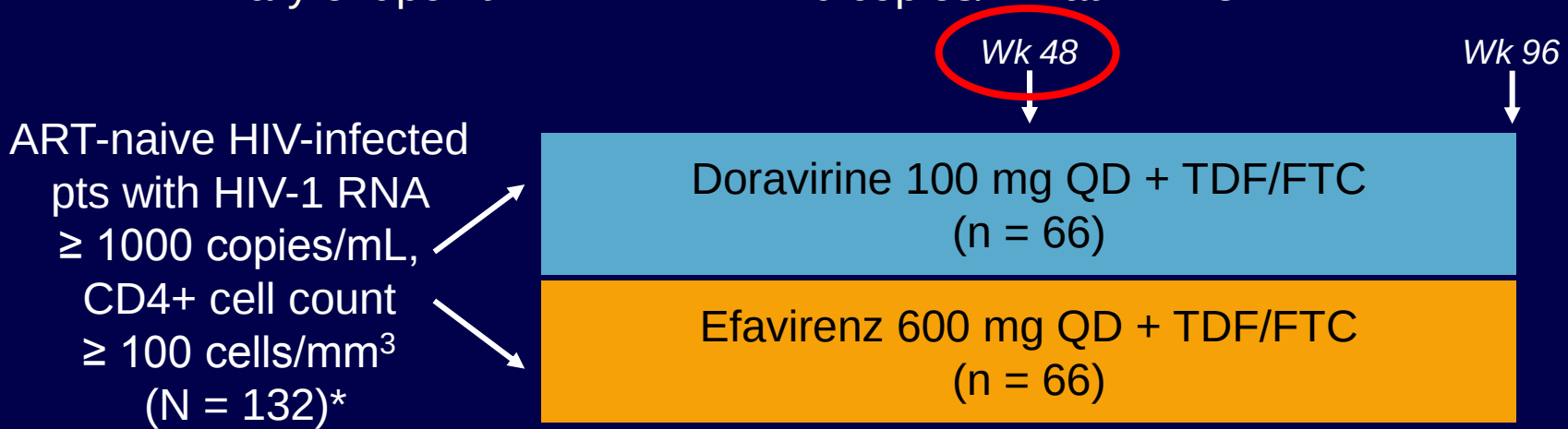
- No differences in number of AIDS events, serious non-AIDS events, or deaths between arms
- Difference in VF through Wk 48:
  - RAL – NRTIs: -3.4% (95% CI: -8.4% to 2.5%)
  - Upper bound of CI < 10%: RAL noninferior
  - Upper bound of CI > 0: RAL not superior
- Cumulative probability of grade ≥ 3 toxicity event higher with LPV/RTV + NRTIs vs LPV/RTV + RAL
  - Stratified log-rank *P* = .040
- Greater increases in total, LDL-, and non-HDL cholesterol and triglycerides with RAL vs NRTIs

La Rosa AM, et al. CROI 2016. Abstract 30.

Slide credit: clinicaloptions.com

MK-1439-007: Doravirine + TDF/FTC vs EFV + TDF/FTC In Treatment-Naive Pts

- Doravirine: investigational NNRTI with potent activity against common NNRTI resistance mutations, QD dosing, no PPI drug–drug interactions, improved CNS safety vs EFV in early studies
- Part 2 of 2-part randomized, double-blind phase II study
  - Primary endpoint: HIV-1 RNA < 40 copies/mL at Wk 48

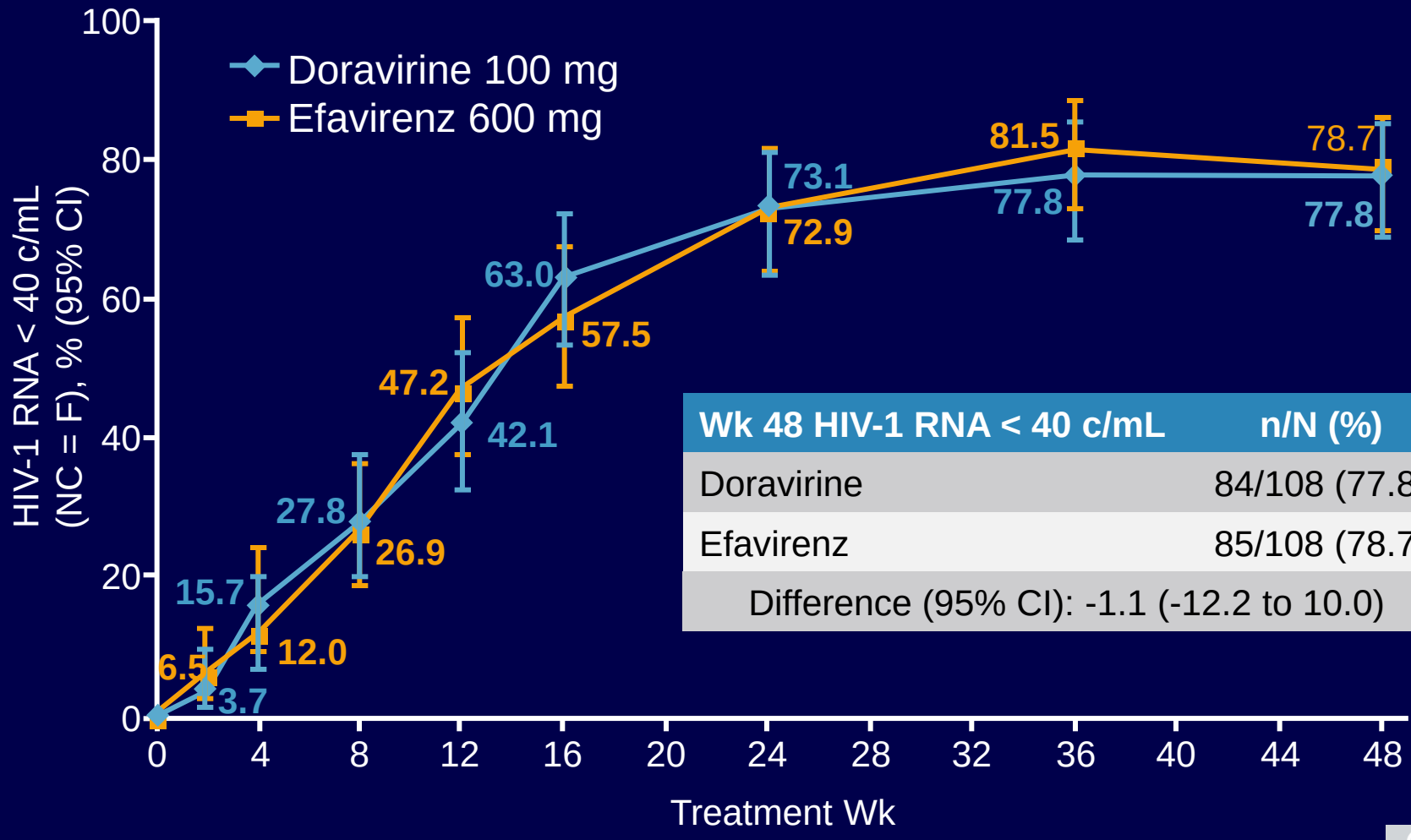


*42 pts receiving doravirine 100 mg QD + TDF/FTC and 43 pts receiving efavirenz 600 mg QD + TDF/FTC in part 1 of this study were included in this analysis.

Gatell JM, et al. CROI 2016. Abstract 470.

Slide credit: clinicaloptions.com

MK-1439-007: Primary Endpoint



Wk 48 HIV-1 RNA < 40 c/mL	n/N (%)
Doravirine	84/108 (77.8)
Efavirenz	85/108 (78.7)
Difference (95% CI): -1.1 (-12.2 to 10.0)	

Gatell JM, et al. CROI 2016. Abstract 470. Reproduced with permission.

Slide credit: clinicaloptions.com

What's new in TO for children and PW

- **No impact of maternal TDF on infant BMD but lower WB BMC** if exposed to LPV-based ART: the PROMISE trial *(Siberry et al. # 36)*

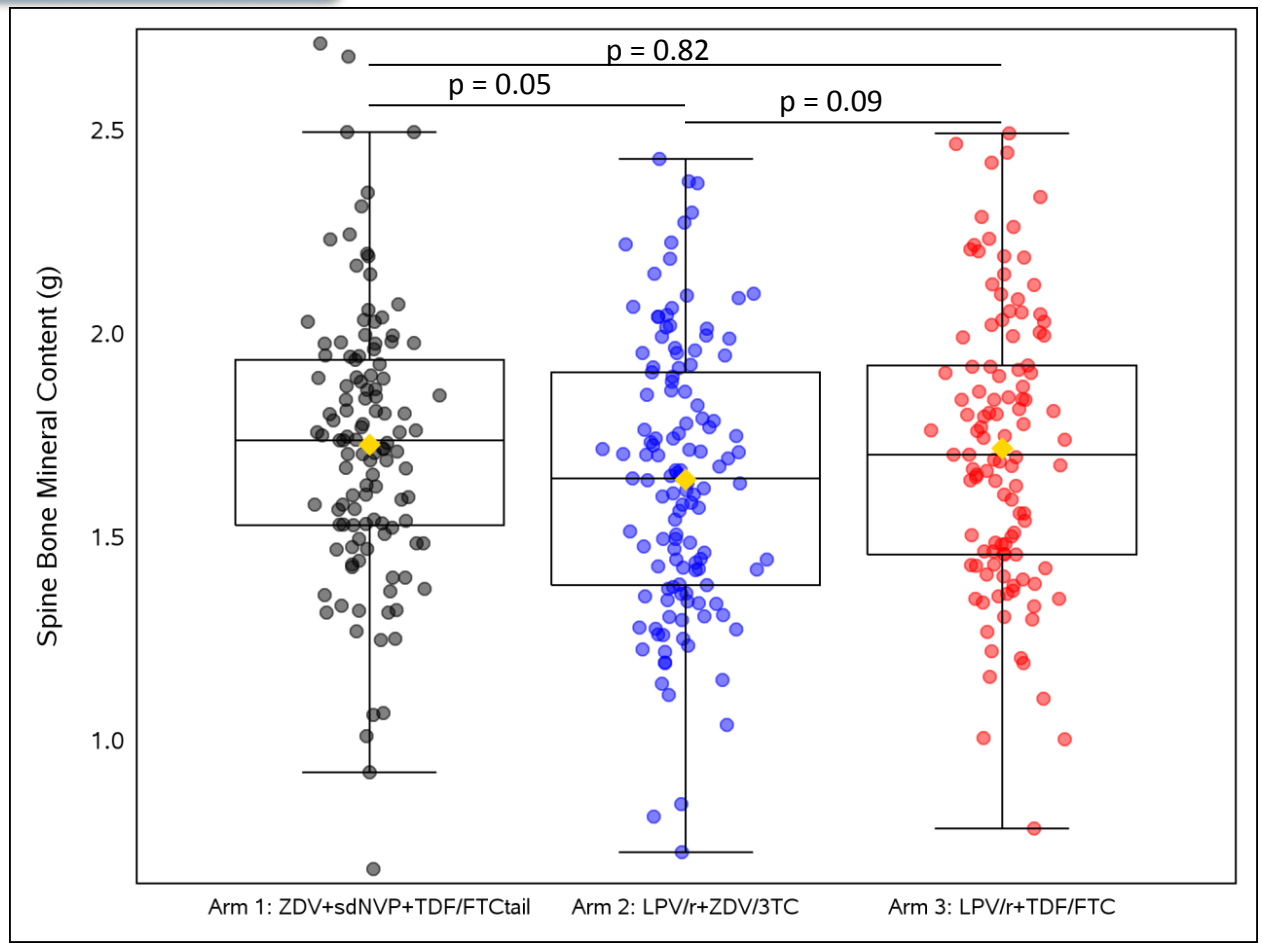
- **DTG PK**: elimination half life twice as high as adults hypoglicemia and congenital abnormalities to be looked at. *(Mulligan et al. #438)*

- **Better PK data to inform dosing of NVP** for use in newborns treatment (*Capparelli et al #815; Mirochnick et al #440*)

- **Maraviroc** dosing for pediatric patients 2-<18 years old supported by safety and efficacy data which were similar to adults (*Giaquinto et al. #1120*)

- **More evidence in support of WHO guidelines**: substituting LPVr with EFV at 3 years showed lower viral rebound, higher CD4%, improved lipid profile and positively impact on bone mineral mass (Arpadi et al. *#40* ; Munarne et al. #39)

No significant difference in Newborn mean Lumbar Spine (LS) BMC between Study Arms (pairwise comparisons)



No impact of maternal TDF on infant BMD but **lower WB BMC if exposed to LPV-based ART: the PROMISE trial** (Siberry et al. # 36)

Comparison	Est'd Mean Difference	95% CI	P
LPVr-ZDV-3TC ***minus*** LPVr+TDF/FTC (primary)	-0.08 g	(-0.16, 0.01)	.09
ZDV(+sdNVP+TDF/FTCtail) ***minus*** LPV/r+TDF/FTC (secondary)	+0.01 g	(-0.08, 0.1)	.82
ZDV+sdNVP+TDF/FTCtail ***minus*** LPV/r+ZDV/3TC (secondary)	+0.09 g	(0, 0.17)	.05

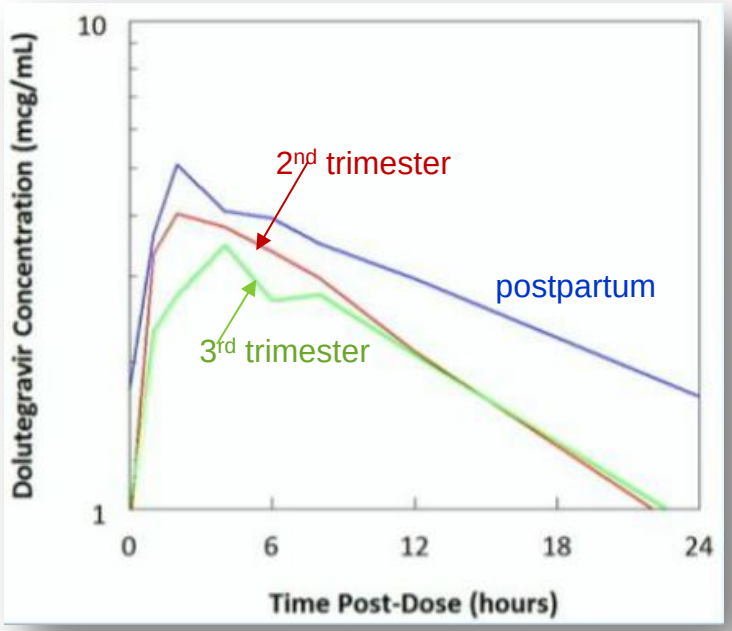
DTG PK in Pregnant and Postpartum Women

Mulligan NA et al. CROI 2016 Boston Abs 438

- DTG levels in pregnancy: AUC 30% lower and C_{24} 40% lower in pregnancy but not significantly different than postpartum (N=4 and N=7 paired comparisons, p<0.10)
- 15/15 (100%) had RNA ≤50 at delivery.
- One possibly treatment-related AE: ↑ LFT
- Two SAEs: pre-eclampsia

Median	2nd tri (N=9)	3rd tri (N=15)	Post (N=9)	Hx control
AUC_{0-24} (ug*hr/mL)	58.4	48.7	71.1	53.6
C_{max} (ug/mL)	4.59	3.92	5.10	3.67
C_{min} (ug/mL)	0.86	0.86	1.70	1.11
$T_{1/2}$ (hr)	10.5	11.2	12.3	14

Median DTG Concentrations

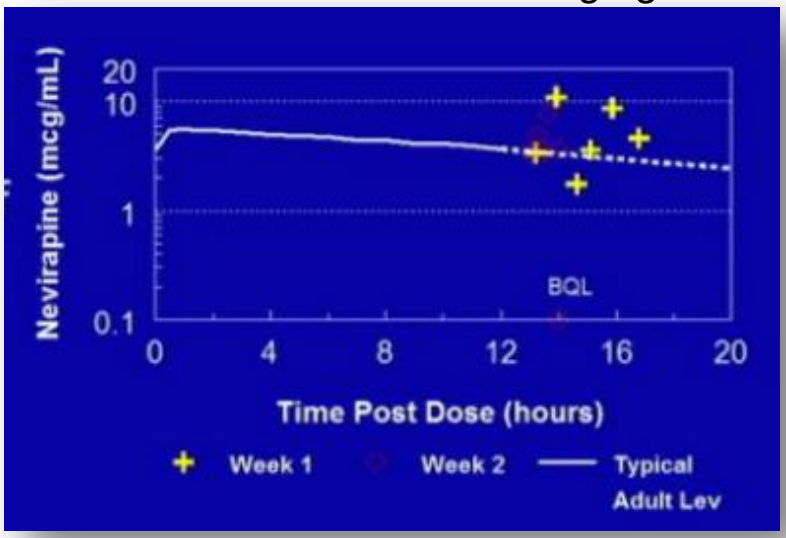


Therapeutic Dosing NVP in Newborns

Capparelli E et al. CROI 2016 Boston Abs 815

- NVP 2 mg/kg QD prophylaxis dosing achieves levels >0.1 ug/mL but not therapeutic target >3 ug/mL. Newborn PK data needed.
- Evaluated PK at 1 & 2 weeks after start ART in 1st 6 infants enrolled in Botswana BPH 075 trial of early ART.
  - Median GA at birth: 37.0 ±1.9 wk
  - Median age ART start: 2.8 ±1.7 d
  - Dose NVP 6 mg/kg BID.

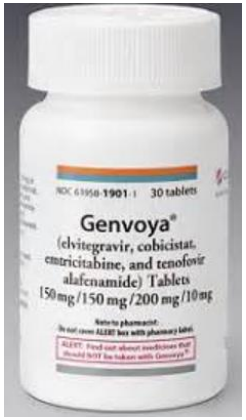
NVP levels at dose 6 mg/kg



- Median NVP trough level: 3.6 mcg/mL (achieved target >3 ug/mL).
- No toxicity observed.

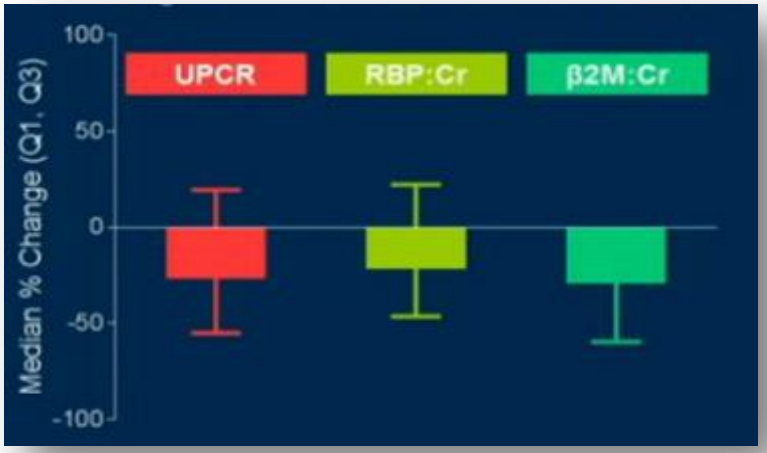
EVG/COBI/FTC/TAF in Adolescents: 48 Week Follow-Up

Gaur A et al. CROI 2016 Boston Abs 817



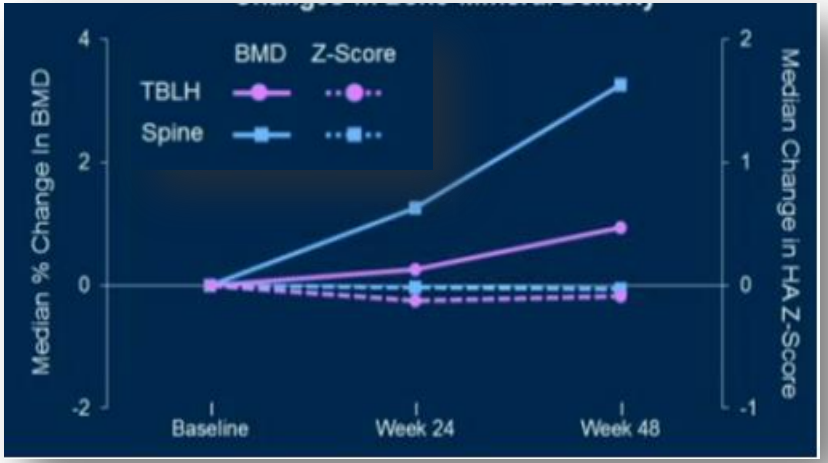
- TAF: enhanced intracellular but lower plasma levels TFV, thus lower toxicity.
- Phase 2/3, single-arm, open-label study of E/C/F/TAF in 50 ART-naïve adolescents.
- RNA <50 c/mL at 48 weeks: **46/50 (92)%**
- Most AE Grade 1/ 2; no AE leading to ART d/c; no cases proximal renal tubulopathy.

Changes in Renal Biomarkers Wk 48



UPCR: urine protein:creatinine ratio; RBP: retinal binding protein; Cr: creatinine; β2M: beta-2 microglobulin

Changes in Bone Mineral Density

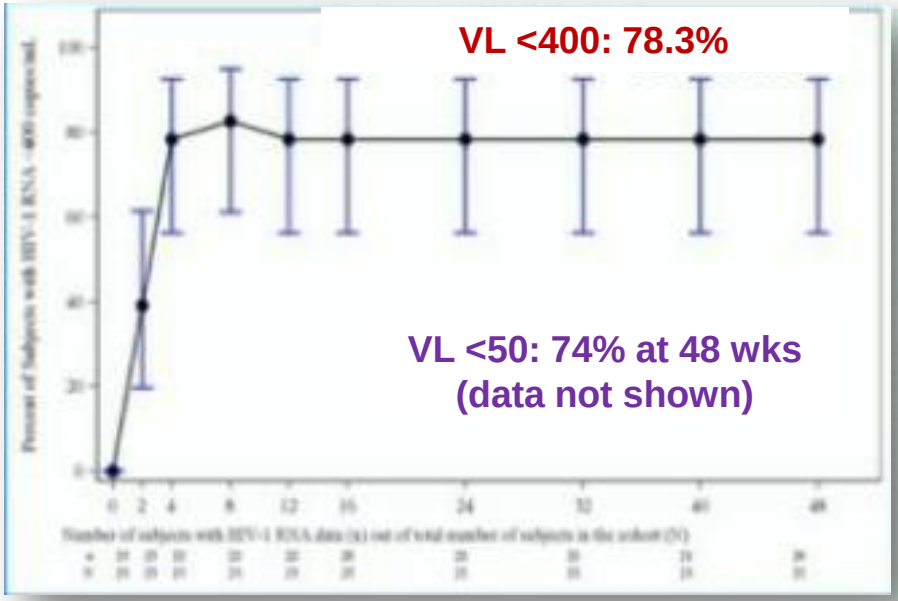


P1093: Dolutegravir (DTG) in 6-12 Year Olds 48 Week Data

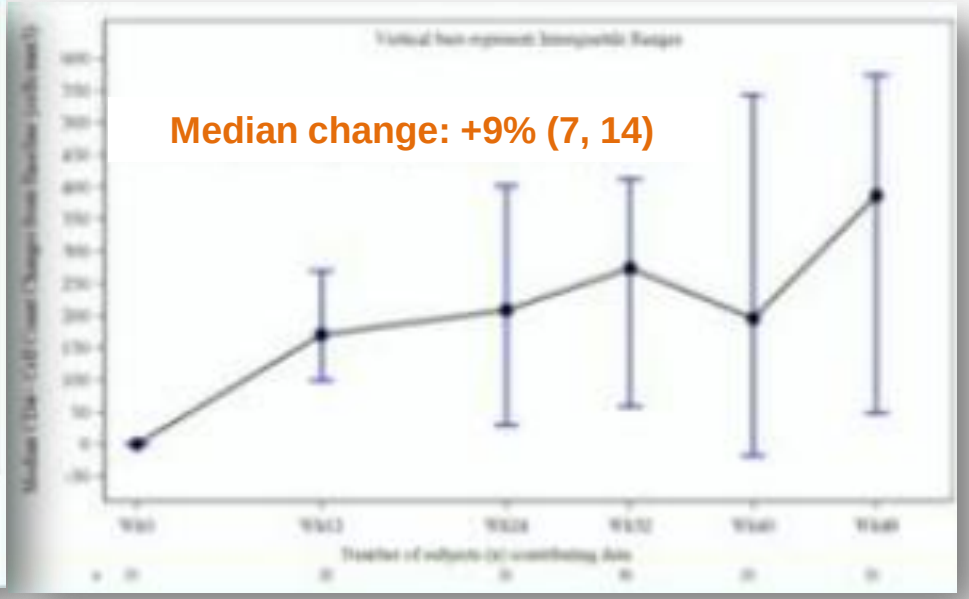
Wiznia A et al. CROI 2016 Boston Abs 816

- Well-tolerated, no treatment-related AE and no d/c for adverse events; good virologic/immunologic efficacy. Now studying younger age cohorts (>4 wks).

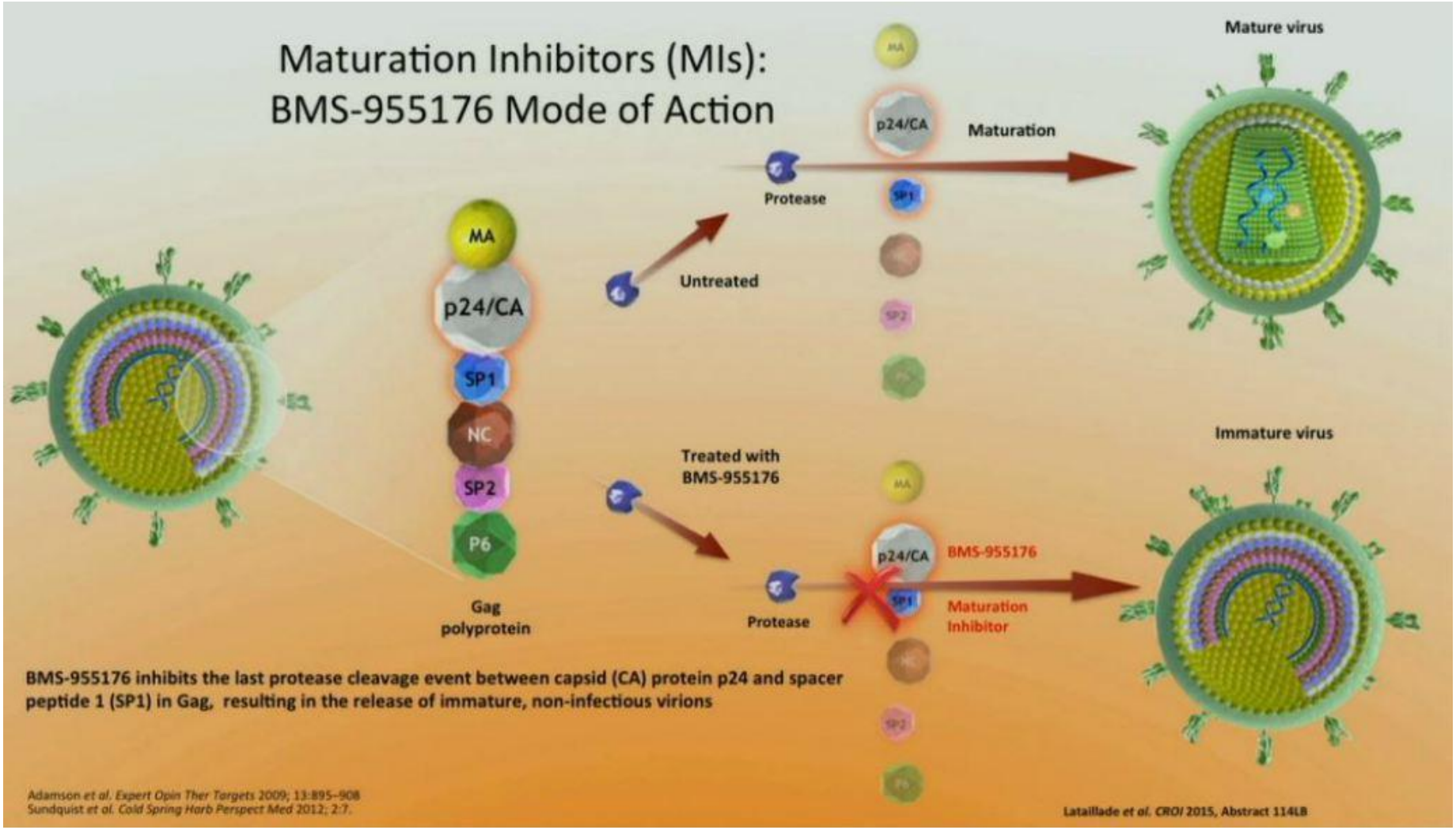
Virologic Efficacy: % VL <400



CD4% Changes

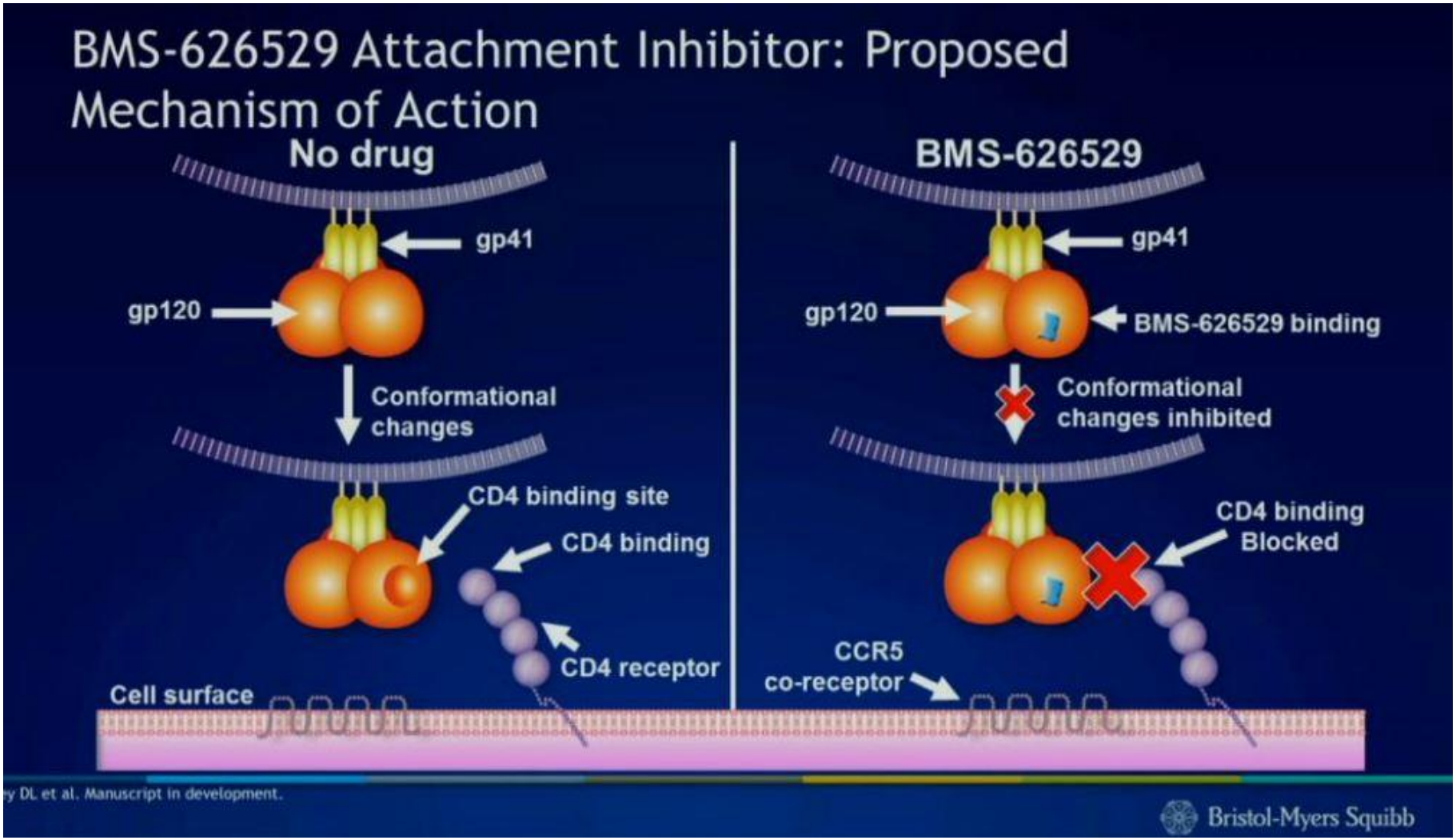


New ARVs: Maturation inhibitors



Eron, CROI 2016

Attachment Inhibitors



Eron, CROI 2016

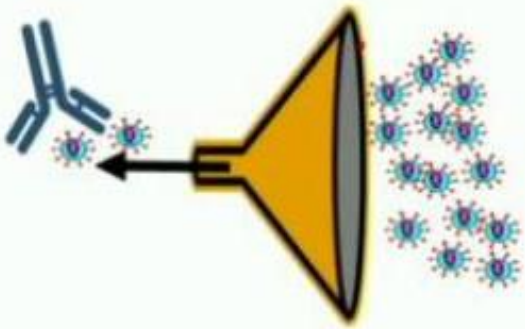
Clinical Use of Antibodies

Prevention and Treatment are Different

Prevention

- Prevent acquisition of infection

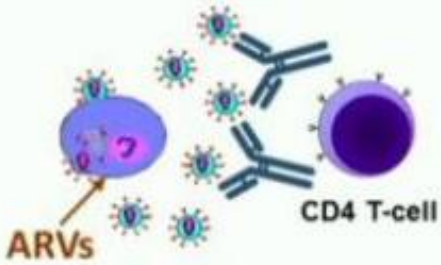
Block
Transmission event



Treatment

- mAbs complementary to ARV drugs
- Different mechanism of action
- Potential to eliminate infected cells
- Impact the cell-associated viral reservoir

Block viral entry



Cell killing

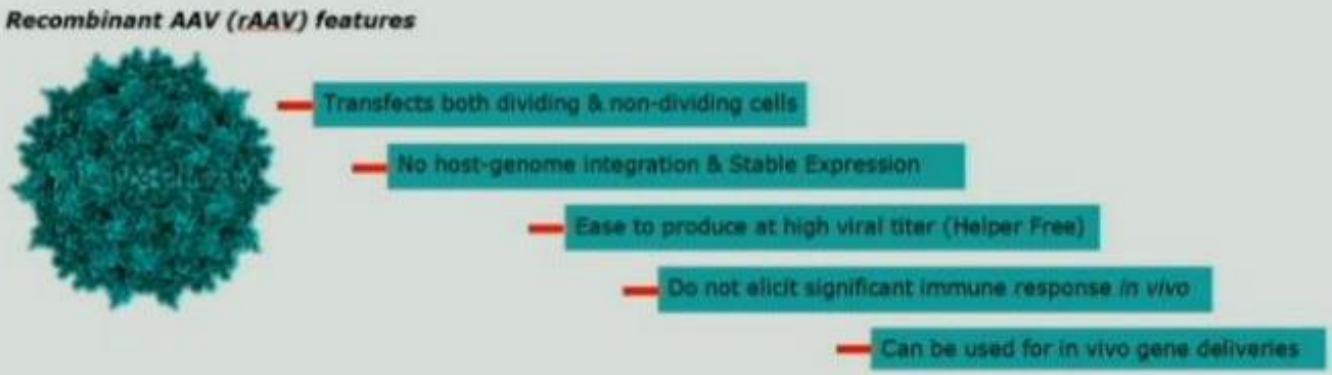
NK cell directed elimination of infected cells

Mascola, CROI 2016

Next Generation Treatment

- Implantable (and removable) combination antiretrovirals

- Vectored delivery of combinations of antibody-based therapy or protein based therapy



Eron, CROI 2016

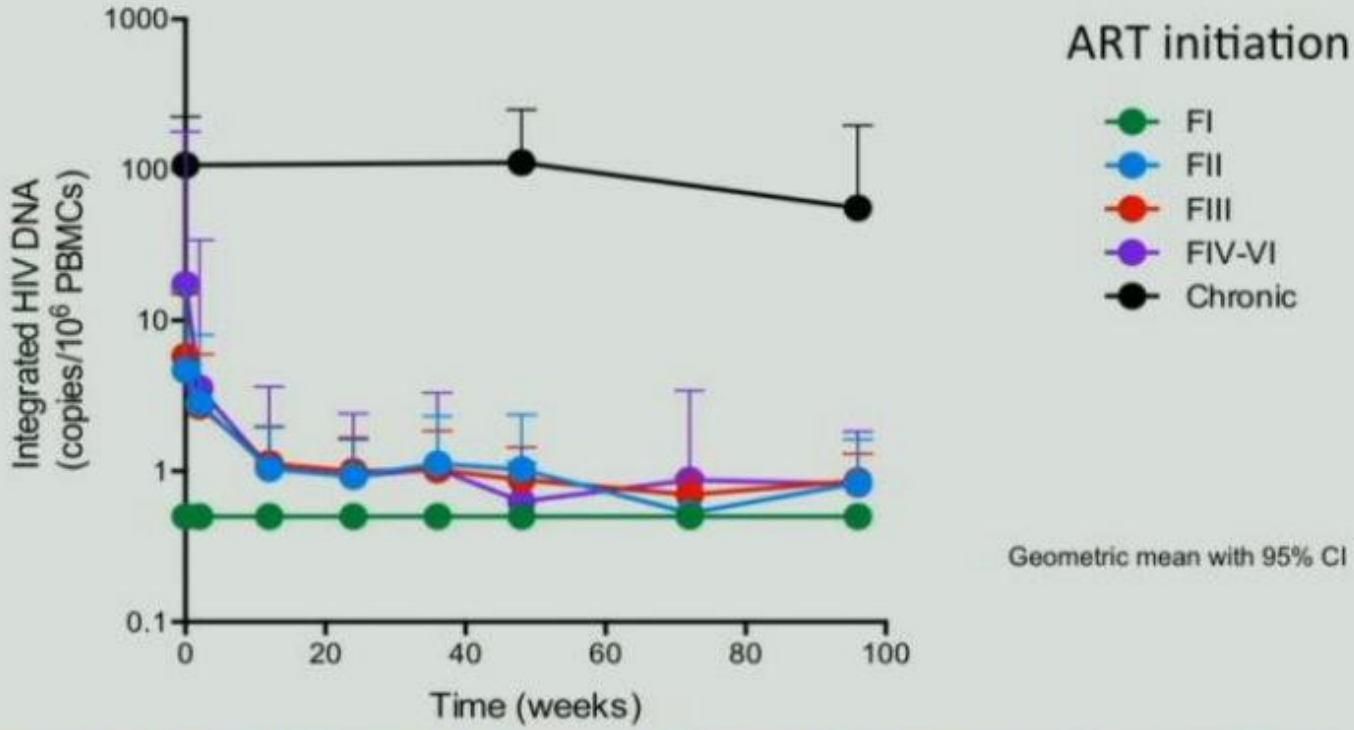
Outline

- New ARV drug trials
  - INSTI, ecfTAF, LA-ARVs for treatment, monoclonal Abs
- Peadiatrics & pregnant women
  - DTG safety in pregnancy & fetus
- **Earlier Treatment and Acute infection**
- **Cascades – how close are we to 90/90/90?**
- **HIV Drug resistance**
  - **First PrEP failure due to resistance**

Very Early Treatment

Very Early Initiation of ART May Limit the HIV Reservoir

Decay of integrated HIV DNA during ART by Fiebig



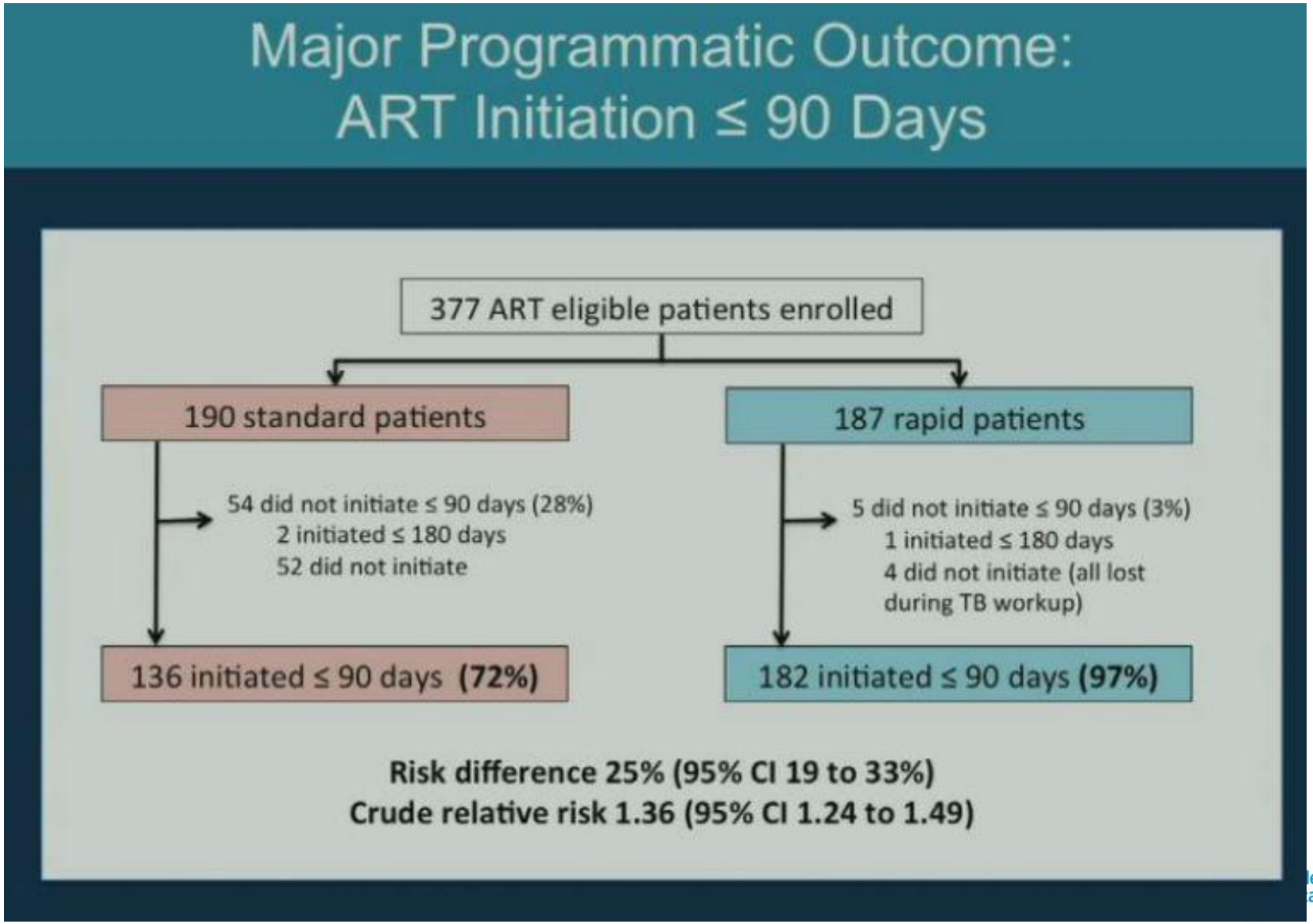
The frequency of PBMCs harbouring integrated HIV DNA decreases rapidly upon ART initiation in FII to FV individuals, whereas no decay is noted in subjects who started ART during chronic infection.

Fiebig I remain below limit of detection.

Courtesy of Ananworanich and Chomont

MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

RAPiT Study


Major Programmatic Outcome:
ART Initiation ≤ 90 Days
377 ART eligible patients enrolled
190 standard patients
187 rapid patients
54 did not initiate ≤ 90 days (28%)
2 initiated ≤ 180 days
52 did not initiate
5 did not initiate ≤ 90 days (3%)
1 initiated ≤ 180 days
4 did not initiate (all lost during TB workup)
136 initiated ≤ 90 days (72%)
182 initiated ≤ 90 days (97%)
Risk difference 25% (95% CI 19 to 33%)
Crude relative risk 1.36 (95% CI 1.24 to 1.49)

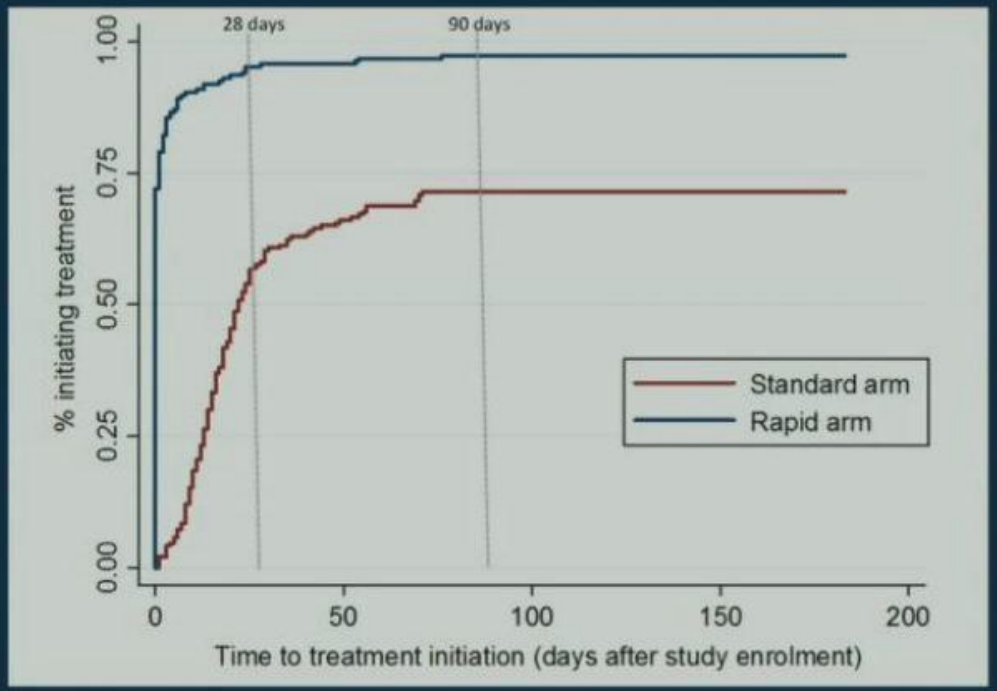
RAPiT Study

Primary Protocol Outcome: Initiated, Retained, and Suppressed ≤ 10 Months

Outcome	Standard arm (n, %) n=190	Rapid arm (n, %) n=187	Crude risk difference [95% CI]	Crude relative risk* [95% CI]
Initiated ≤ 90 days	136 (72%)	182 (97%)	25% (19-33%)	1.36
Initiated ≤ 90 days and retained and suppressed by 10 months	**96 (51%)**			
Of those not initiated ≤ 90 days and suppressed by				
Not initiated	54 (28%)			
Initiated but not suppressed or with no viral load reported	40 (21%)			
Initiated ≤ 90 days and retained at 10 months	121 (64%)			
Of those not initiated ≤ 90 days and retained at 10				
Not initiated	54 (28%)			
Initiated but not retained	15 (8%)			

*Adjusting for sex and baseline CD4 count did not a

How Long Did It Take?



Median time in clinic between study enrollment and ARV dispensing in rapid group:

2.4 hours (IQR 2.1-2.8 hours)

Streamlined Care

1. Patient-centered approach to care

- Welcoming environment
- Fostering trust, connection, and a sense of investment in the patient
- Handling adherence and retention empathetically

2. Efficient Visits for Patients and Staff

- Rapid ART start (same day- a few days ART start)
- Triage by nurse at all follow-up visits
- Minimal wait time, and fast transit through clinic visit
- Clinic visits and ART dispensation every 3 months rather than every 1-2 months

3. Viral Load Counseling

- Structured format for discussion of undetectable and detectable results
- Discussion tailored to patient's ART status (pre-ART vs. early phase vs. stable ART)

4. Clinician Access

- Telephone access for patients
- Easy troubleshooting of questions
- Appointment/scheduling logistics for retention

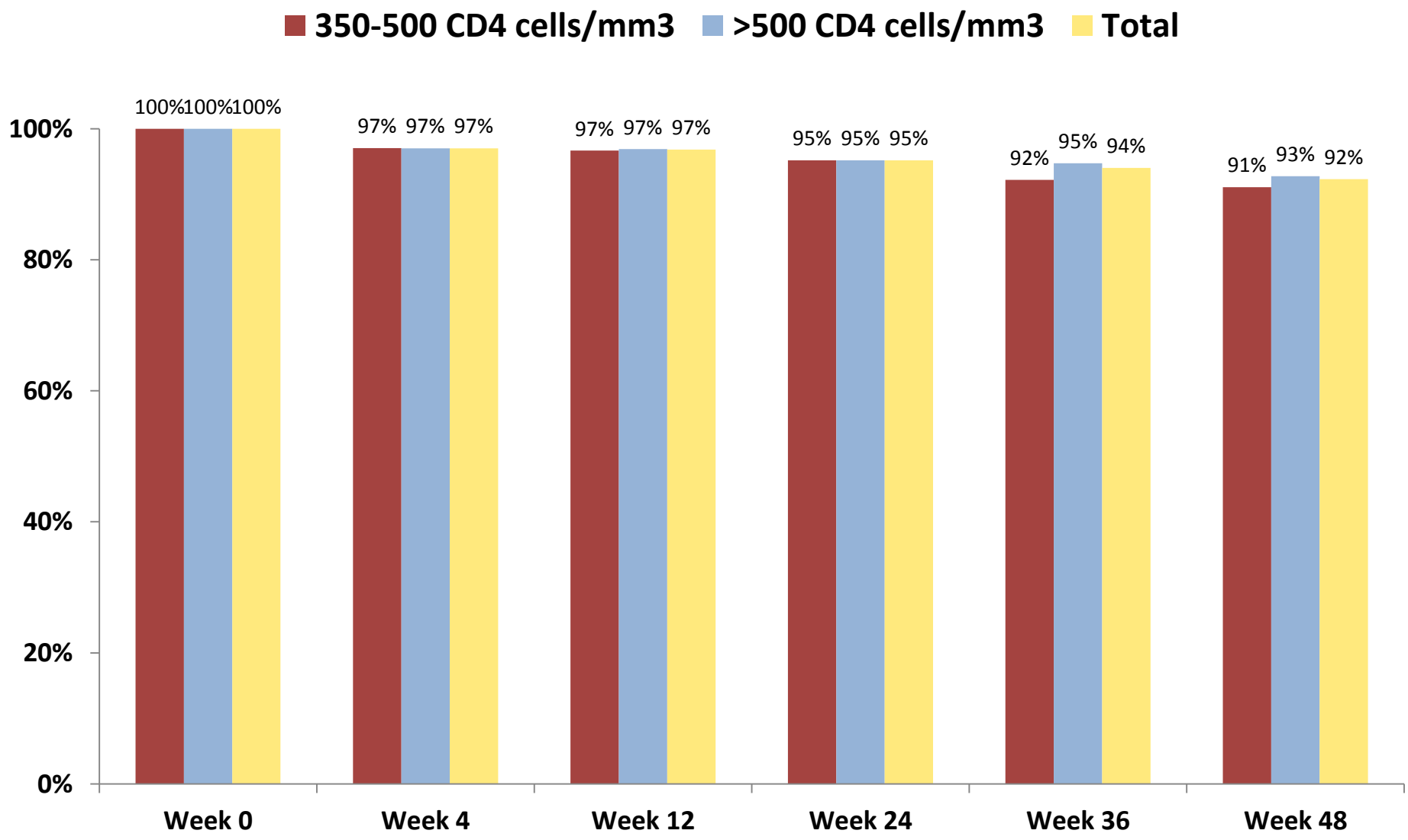
5. Appointment reminders by phone/SMS

- One week to few days in advance
- Retention tool

SEARCH
SUSTAINABLE EAST AFRICA RESEARCH IN COMMUNITY HEALTH

Kwarisiima, CROI 2016

Results: Retention in care (N=972)



How do Botswana's Results Compare to UNAIDS Targets?

HIV-positive who know their status	Currently on ART (among HIV+ who know status)	Virologically suppressed (among persons on ART)	Virologically suppressed (among all HIV-positive)

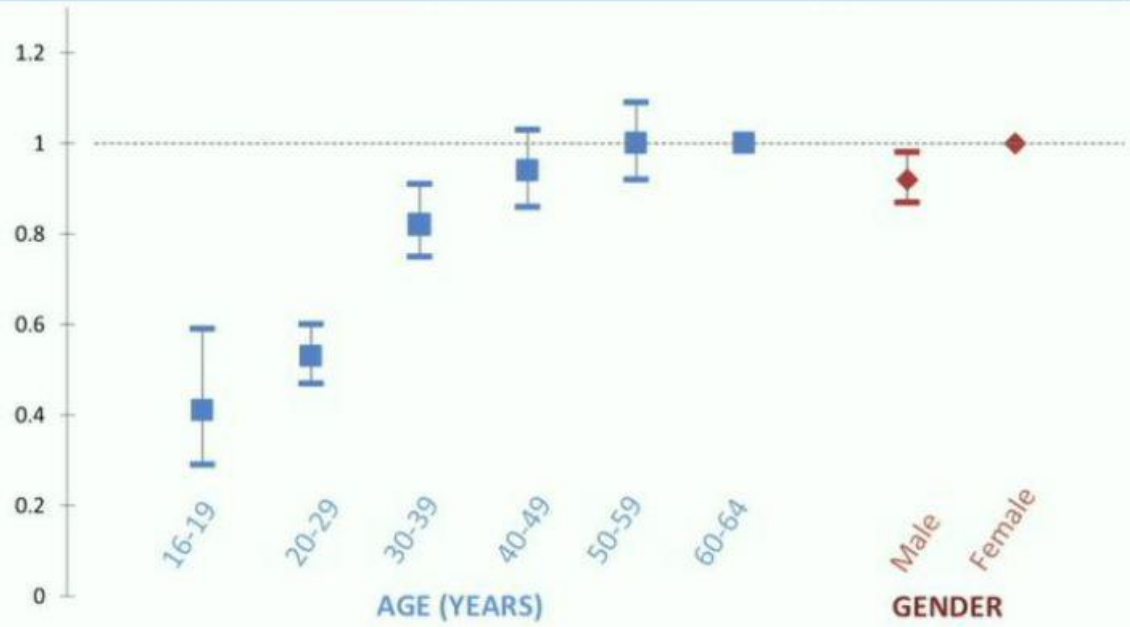
UNAIDS targets:

90% x 90%

Current status in Botsw

83% x 87%

Predictors of Achieving Overall 90-90-90 Target



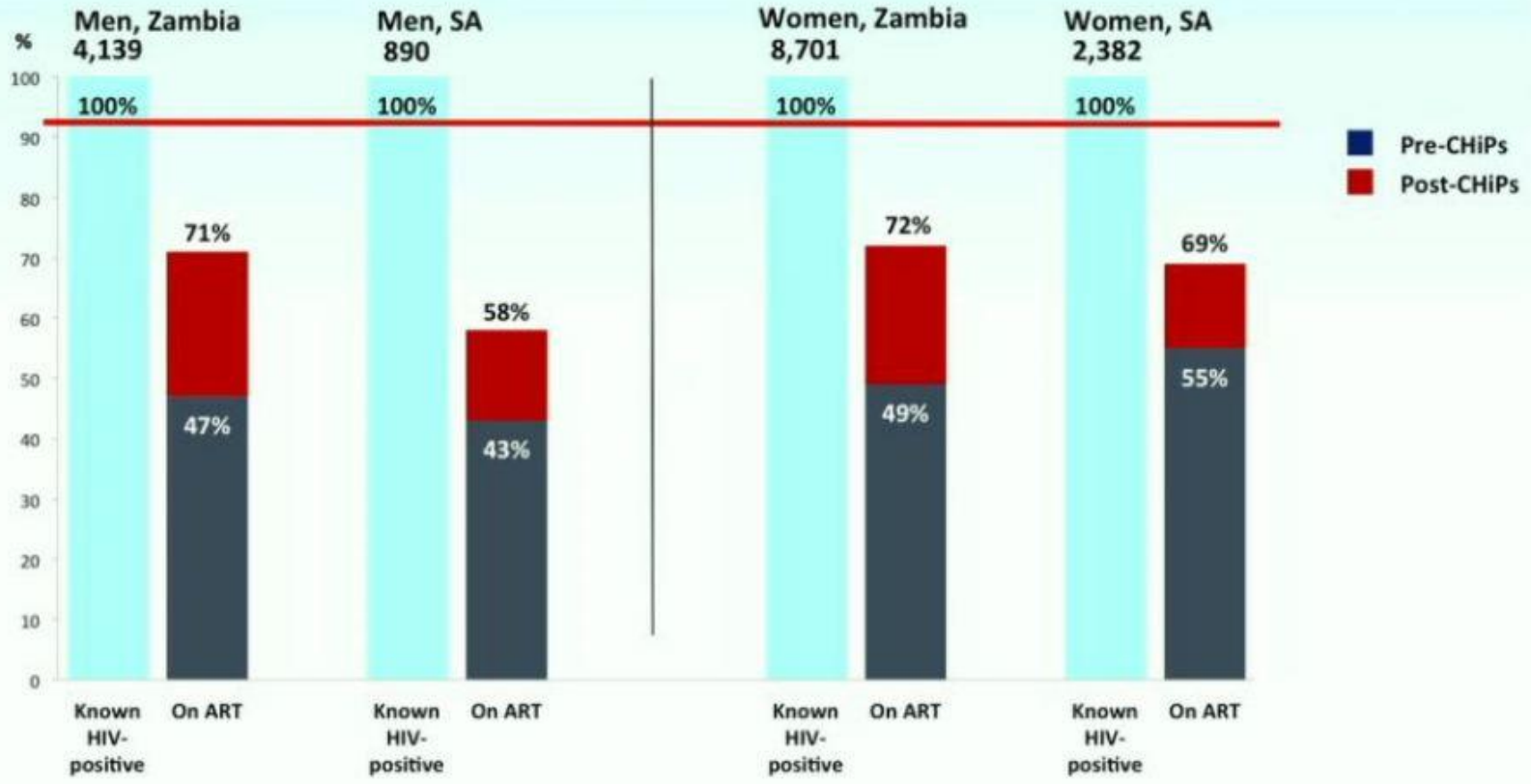
- Younger age was the strongest predictor of being undiagnosed, not on ART and not virologically suppressed.
- Male gender, being single or never married, and higher levels of education were also significantly associated with lower levels of coverage for the overall target

PopART Cascade

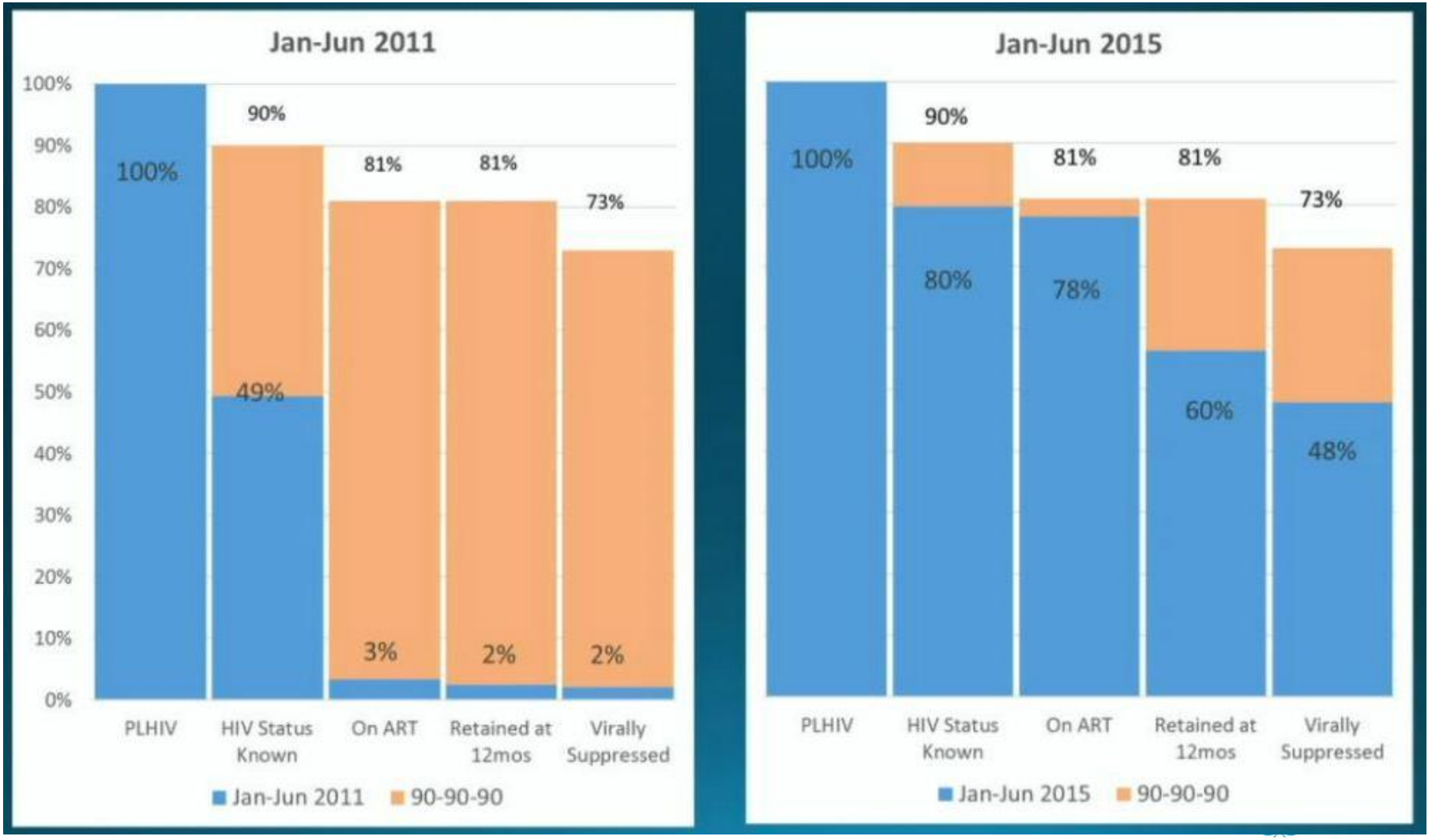
HIV Prevention Trials Network

PopART HPTN 071

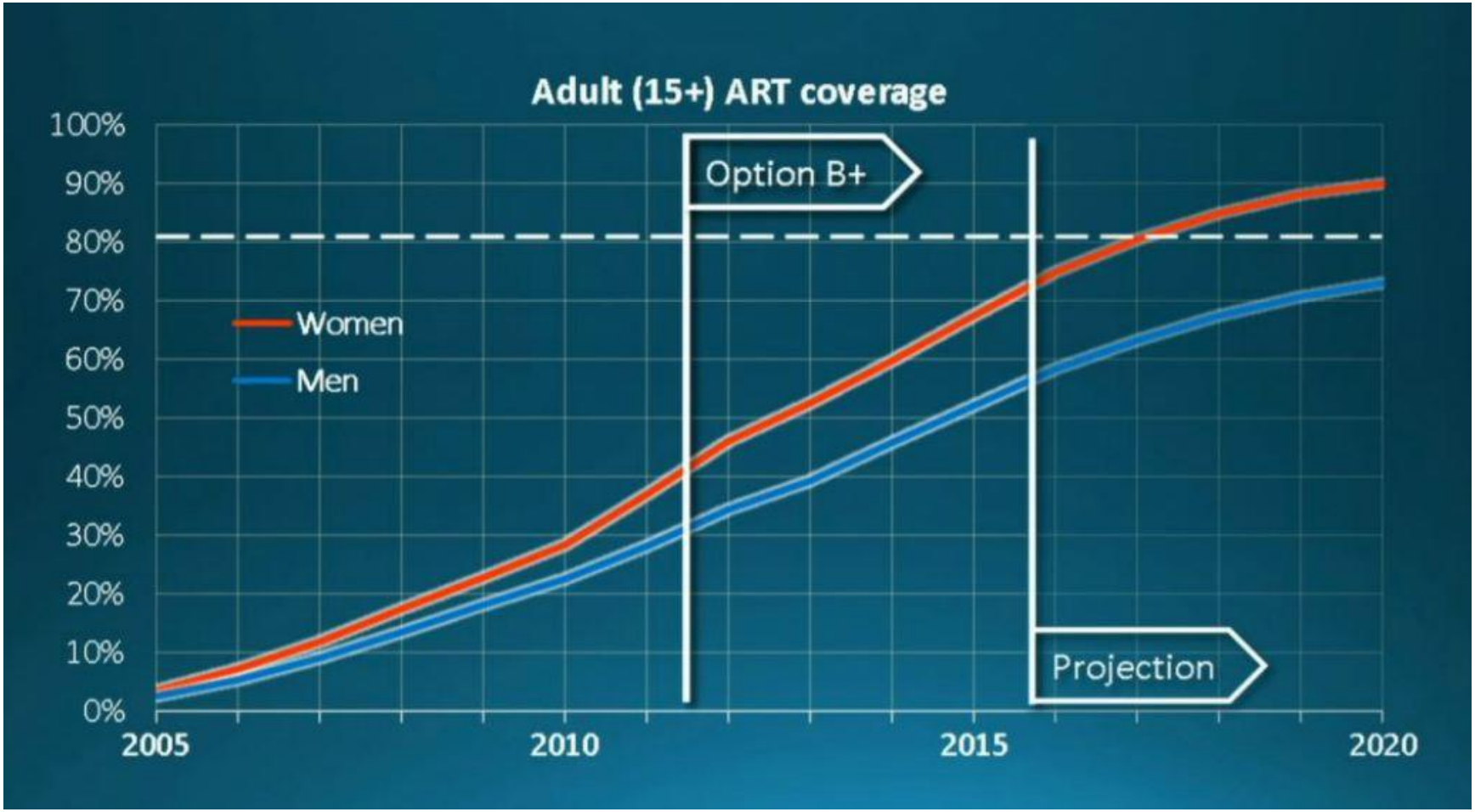
Second 90 Target: ART uptake, among those consenting to intervention



Malawi Cascade



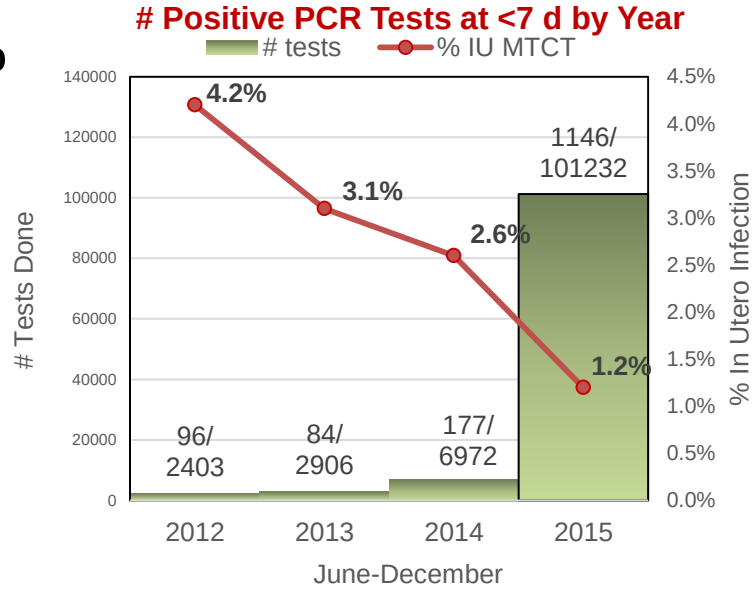
Malawi cascade



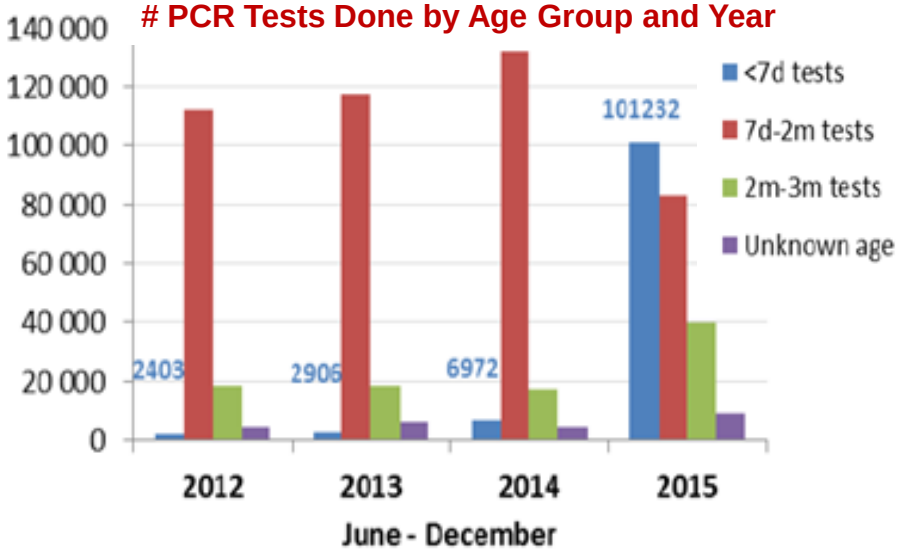
Introduction of Birth Testing, South Africa
Does Birth Testing Decrease 6-10 Wk Testing?

Mazanderani AH et al. CROI 2016 Boston Abs 783

- *In utero* infection rates ↓ from 4.2% to 1.2% in 2015; national 6 wk MTCT in 2014 estimated 1.8%, so high % MTCT may be *in utero* (or reflect move from testing high-risk to low-risk infants)



- While # birth tests ↑, **tests at 7 d-2 mo ↓**, with some ↑ in tests at 2-3 mo, likely reflecting transition from 6 wk to 10 wk testing; 2015 testing coverage for birth testing 79% while **test coverage at 2-3 mo is only 35%.**

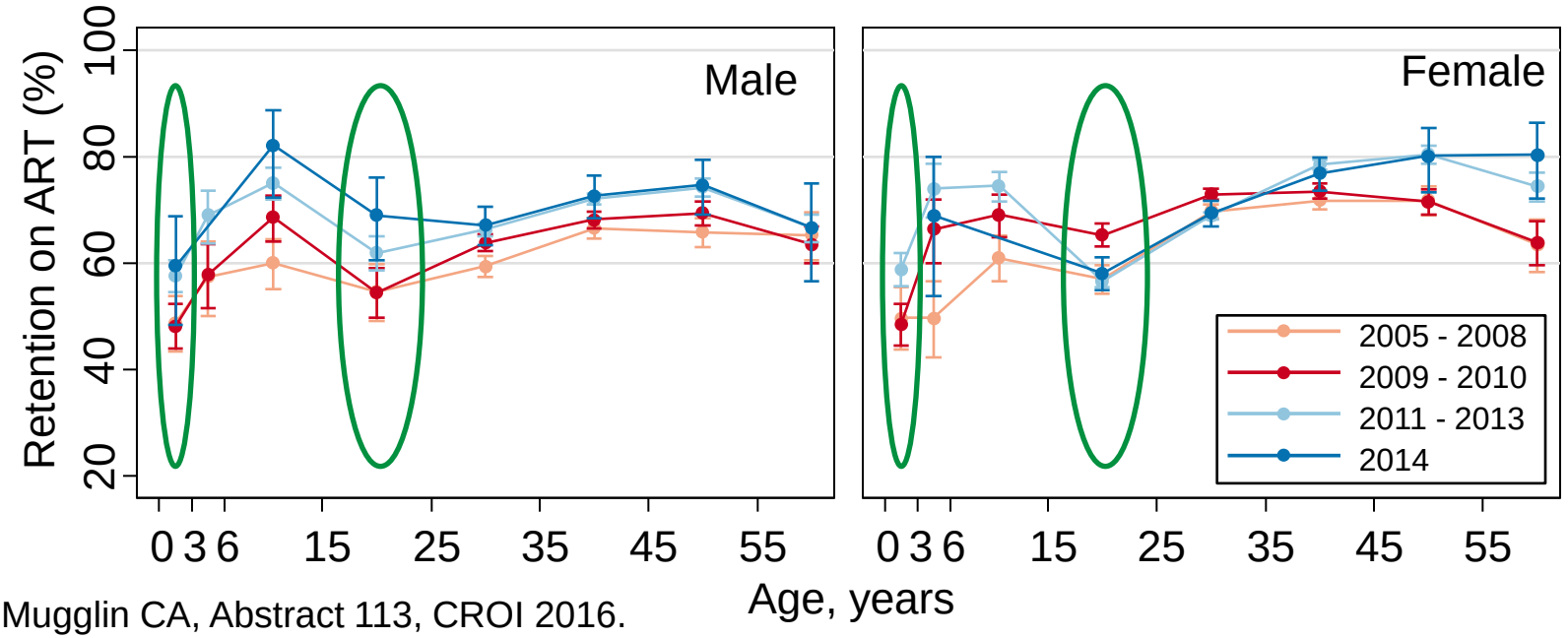


Retention 1 Year After ART Start, Malawi
Poorest Retention in Children and Youth

Sohn A. CROI 2016 Boston Abs 174

1-yr post-ART retention, Malawi, 2004–2014
Impact of Option B+

- N=122,582; 63% female; 13% 15-24 yrs



Mugglin CA, Abstract 113, CROI 2016.

Case Report: Multiclass Resistant HIV Infection Despite High Adherence to PrEP

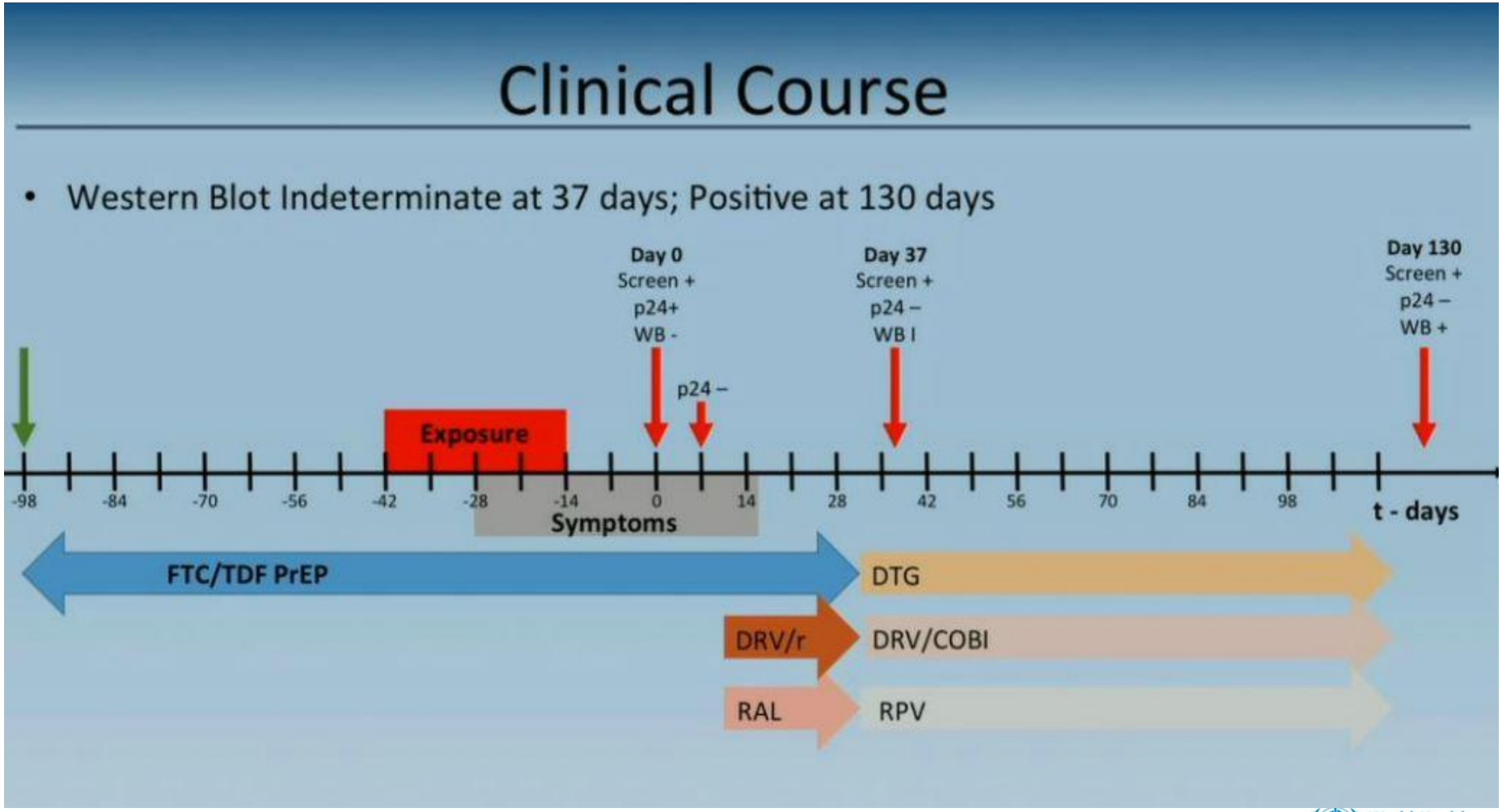
- 43-yr-old MSM acquired multiclass resistant HIV-1 infection following 24 mos of oral once-daily TDF/FTC PrEP
- Pharmacy records, blood concentration analyses, and clinical history support recent and long-term adherence to PrEP
- PrEP failure likely result of exposure to PrEP-resistant, multiclass resistant HIV-1 strain

Drug Class	Mutations Detected on Day 7 Following p24-Positive Test	Estimated Fold-Change in IC_{50} or Change in Response (Drug)
NRTI	41L, 67G, 69D, 70R, 184V, 215E	1.9x (ABC), 61x (3TC), 38x (FTC), 1.3x (TDF)
NNRTI	181C	43x (NVP)
PI	10I	No relevant change
INSTI	51Y, 92Q	Reduced (RAL), resistant (EVG), reduced (DTG)

Knox DC, et al. CROI 2016. Abstract 169aLB.

Slide credit: clinicaloptions.com

First case HIV acquistion during PrEP due to transmitted HIVDR



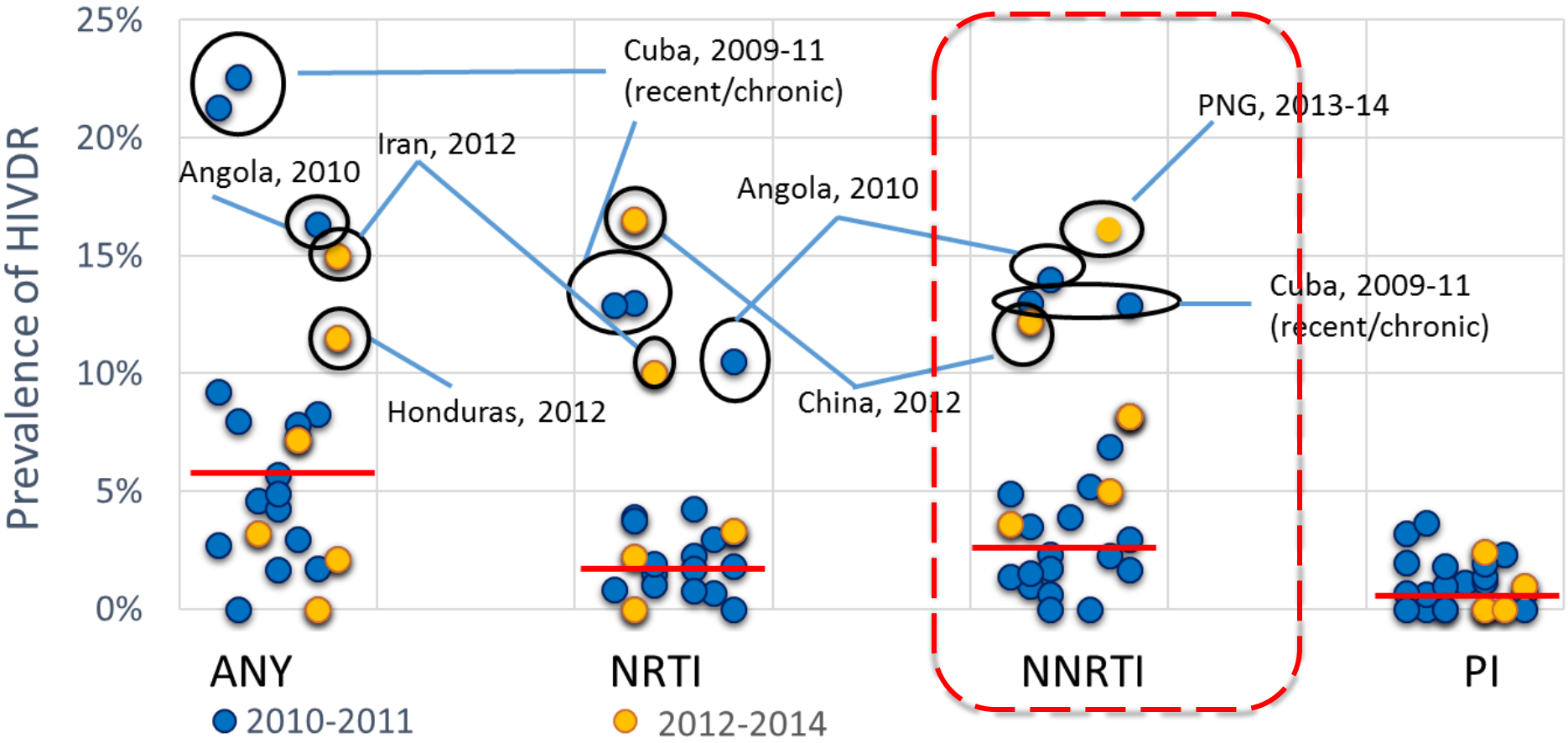
SIDE MEETINGS

HIV DRUG RESISTANCE

HIVDR in ARV-naive in LMIC

HIV/AIDS Department

Literature review update (2010-2014)

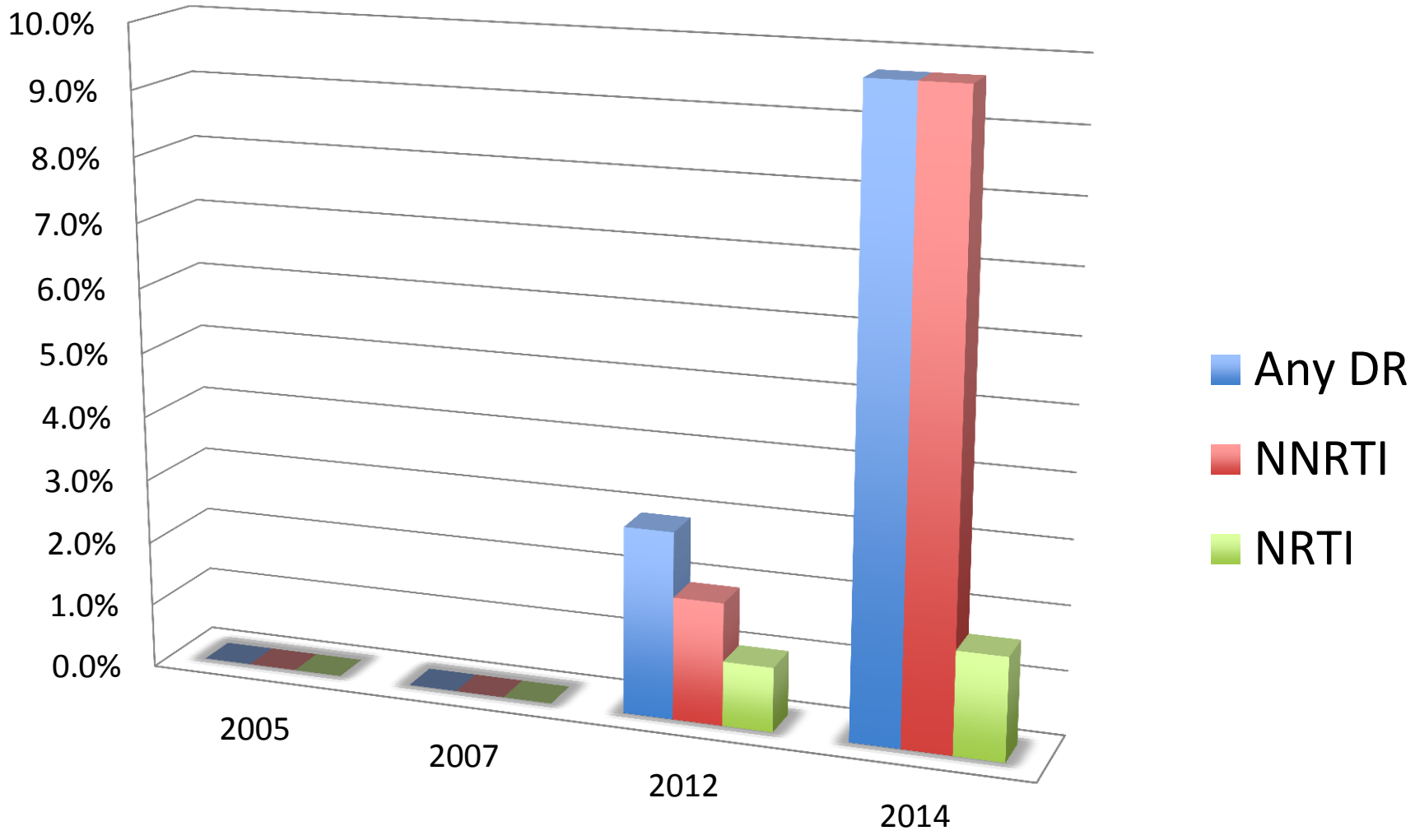


** 3 publications split into cohort years as time period specimens were collected included before & after 2010

*Publication split into recent and chronically infected subjects

World Health Organization

Increasing TDR in **Botswana** (Gaborone) from 2005 to 2014 in recently infected pregnant women

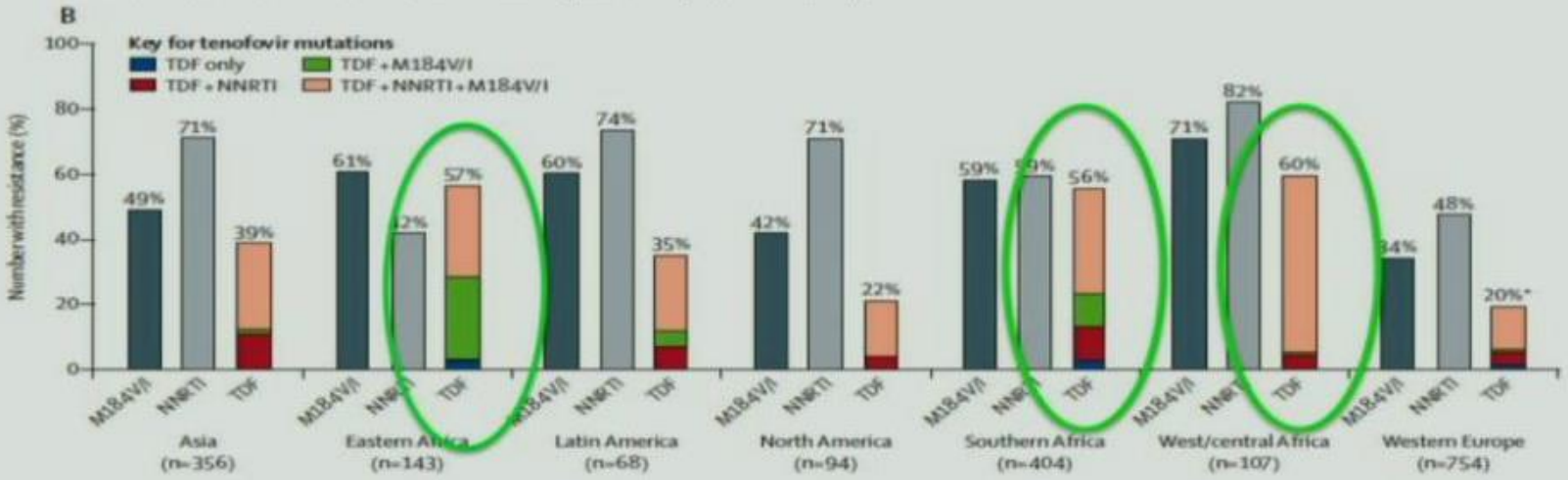


Botswana-Harvard AIDS Institute

Rowley et al. 2016. *in press*

Acquired HIVDR in LMIC

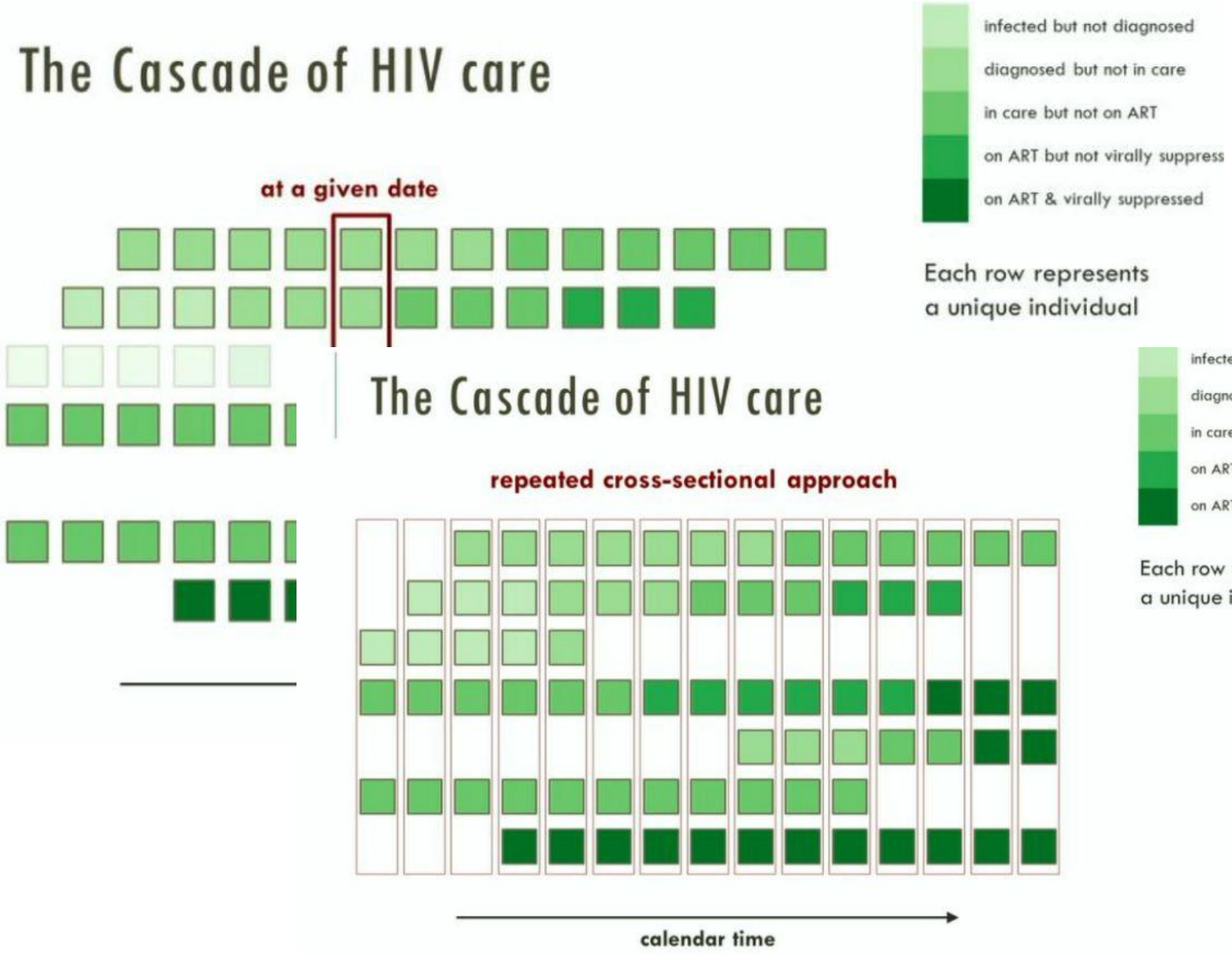
- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples



Boyd, M et al *Lancet* 2013; 381: 2091–99

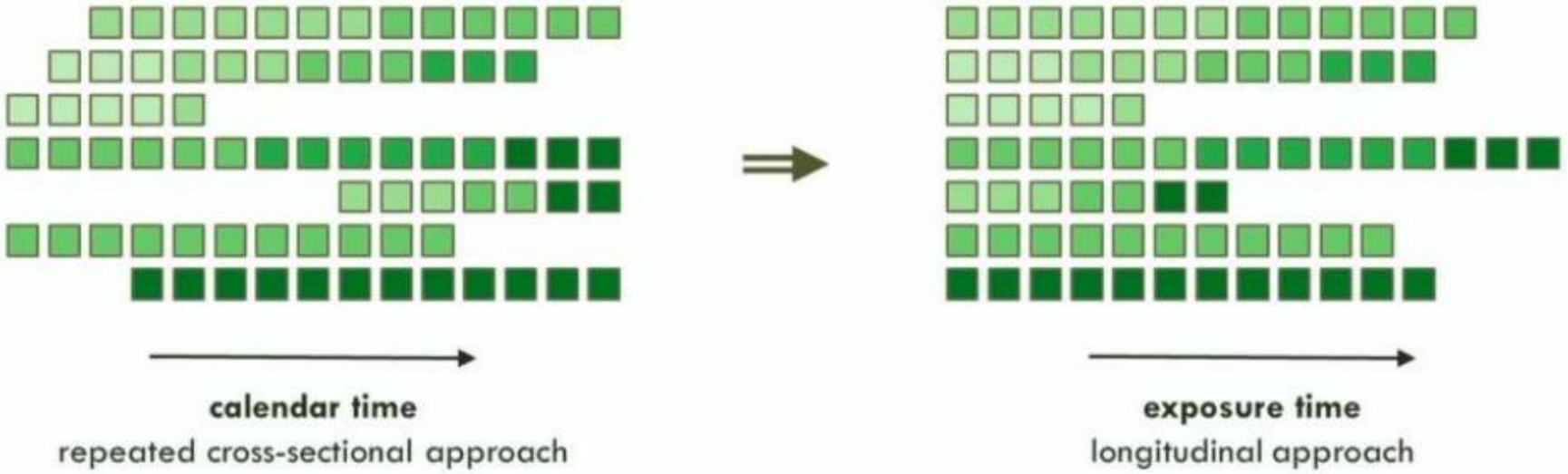
The TenoRes Study Group ***Lancet Infect Dis*** **2016**
Published **Online** January 28, 2015 – **Abstract 503**

KZN TasP Trial Cascade



KZN TasP Trial Cascade

Position within the cascade per exposure time



calendar time
repeated cross-sectional approach

exposure time
longitudinal approach

Exposure time is defined as duration since registration
(or since seroconversion for individuals who seroconverted after trial registration)

KZN TasP Trial Cascade