Top 10 HIV Advances

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Consultant: EMD Serono; Theratechnologies

Thanks to Roger Bedimo, MD and Marilyn Shi

Advance #1: More Than Half of People With HIV Are on ART

July 20, 2017

PRESS RELEASE

THE SCALES HAVE TIPPED—UNAIDS ANNOUNCES 19.5 MILLION PEOPLE ON LIFE-SAVING TREATMENT AND AIDS-RELATED DEATHS HALVED SINCE 2005

http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2017/july/20170720_PR_Global_AIDS_Update_2017

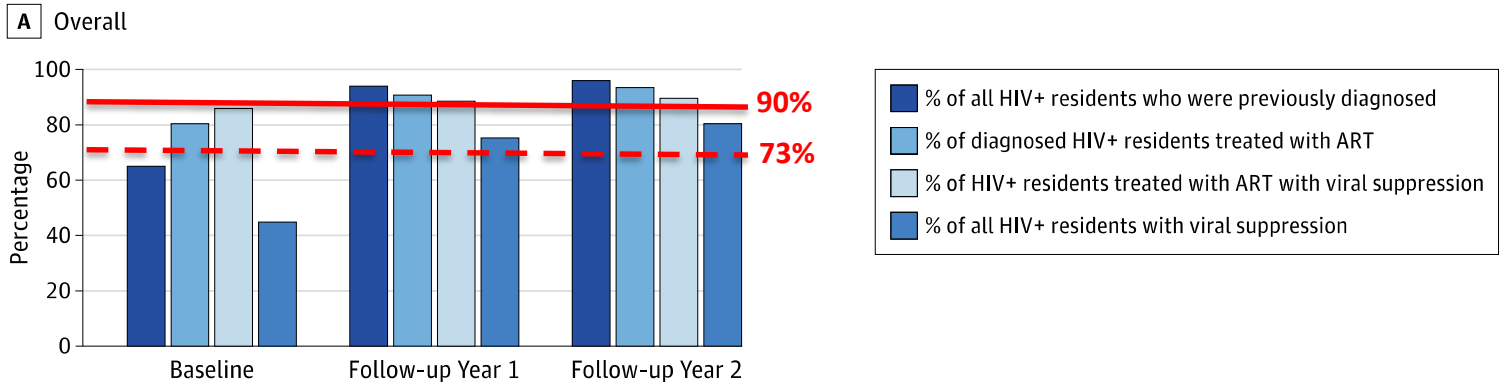
Community-Based Universal HIV Testing and Treatment

JAMA | Original Investigation

Association of Implementation of a Universal Testing and Treatment Intervention With HIV Diagnosis, Receipt of Antiretroviral Therapy, and Viral Suppression in East Africa

Maya Petersen, MD, PhD; Laura Balzer, PhD; Dalsone Kwarsiima, MBChB, MPH; Norton Sang, MA; Gabriel Chamie, MD, MPH; James Ayieko, MBChB, MPH; Jane Kabami, MPH; Asiphas Owaraganise, MBChB; Teri Liegler, PhD; Florence Mwangwa, MBChB; Kevin Kadede, MA; Vivek Jain, MD, MAS; Albert Plenty, MS; Lillian Brown, MD, PhD; Geoff Lavoy; Joshua Schwab, MS; Douglas Black, BA; Mark van der Laan, PhD; Elizabeth A. Bukusi, MBChB, PhD; Craig R. Cohen, MD, MPH; Tamara D. Clark, MHS; Edwin Charlebois, MPH, PhD; Moses Kamya, MMed; Diane Havlir, MD

- Cluster randomized trial of universal test-and-treat in East Africa (SEARCH)
- In two years, virologic suppression increased from 45% to 80%
- 90:90:90 targets met/exceeded



No. of residents/total No. of residents[a]			
Previously diagnosed/all HIV+	5028/7745	6744/7182	6780/7068
Received ART/previously diagnosed	4038/5028	6110/6744	6334/6780
Viral suppression/received ART	3464/4038	5399/6110	5666/6334
Viral suppression/all HIV+	3464/7745	5399/7182	5666/7068

Petersen M et al. JAMA 2017 Jun 6; 317:2196

Efficacy of Community-Based Universal HIV Testing and Treatment

- Community-based test and treat can achieve 90-90-90
  - Community HIV testing campaigns/home visits for non-attendees
  - Facilitated linkage to care:
    - Immediate clinic appointments/Personal introductions to clinic staff/clinician phone number
    - Transport vouchers
    - Tracking of individuals who did not link to care
  - Streamlined ART delivery:
    - 3 month follow-up schedule for stable patients/flexible hours
    - Text or telephone based appointment reminders
    - HIV RNA results discussed with patient
- Focus on “second 90” (linkage); and on men & young people

Advance # 2: Same Day Initiation of ART

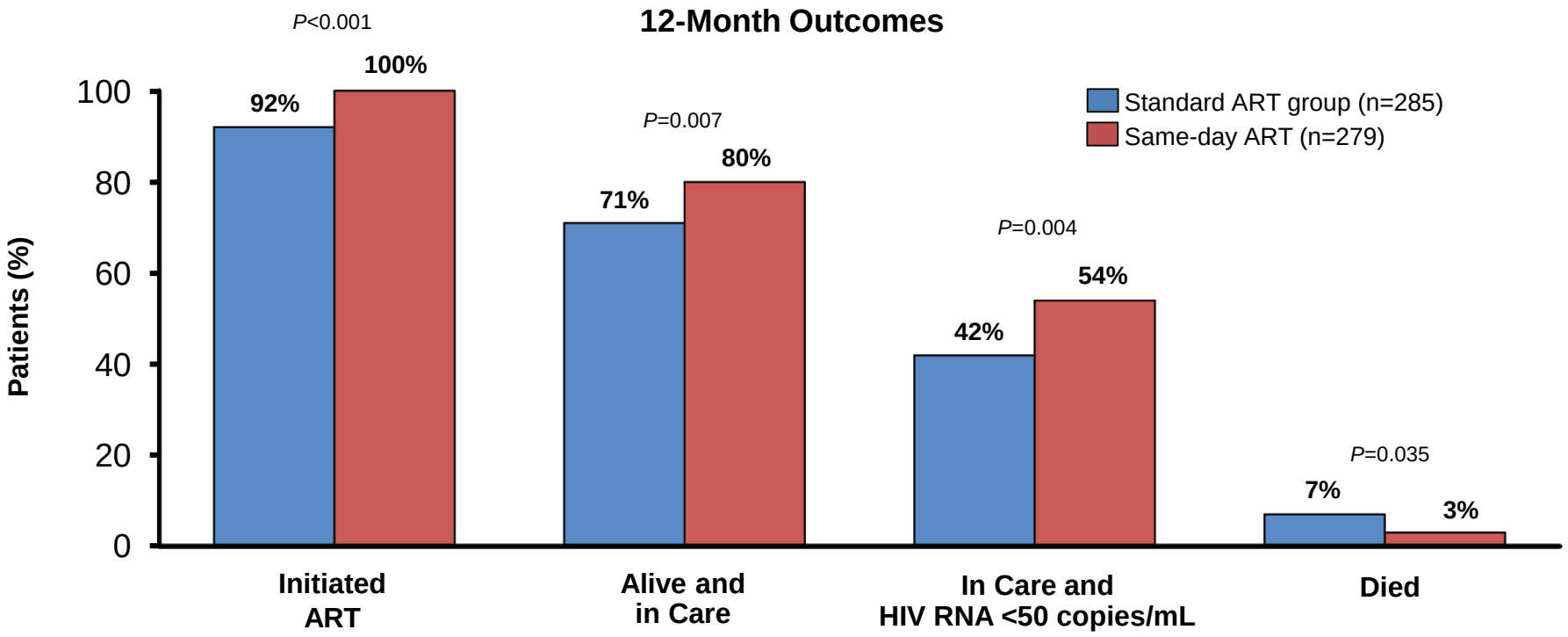
- **Problem:** Delays in initiating ART may lead to clinical progression, disengagement from care, sub-optimal outcomes
- Does initiating ART on the same day as HIV diagnosis improve outcomes?
- Data supporting "Same Day" ART initiation:
  - San Francisco (Pilcher CD et al, JAIDS 2016)
  - South Africa (Rosen S et al, PLoS Medicine, 2016)

Same Day Initiation: Haiti

- ART-naïve adults, CD4 <500, no evidence for TB
- Standard group
  - Days 7, 14, and 21: Physician/social worker visits
  - **Day 21: ART initiation**
  - Week 5: Physician/social worker visit
- Same-day ART group
  - **Day 1: Counseling and ART initiation**
  - Days 3, 10, and 17: Physician/social worker visits
  - Day 24: Physician visit
- Trial stopped early: better outcomes in same-day group

Koenig S, International AIDS Conf., July 2016, WEA0202; PLoS Medicine, 2017

Same Day Initiation: Haiti



Only 4% of same-day patients required regimen adjustment because of abnormal renal function on baseline testing.

Koenig S, International AIDS Conf., July 2016, WEA0202

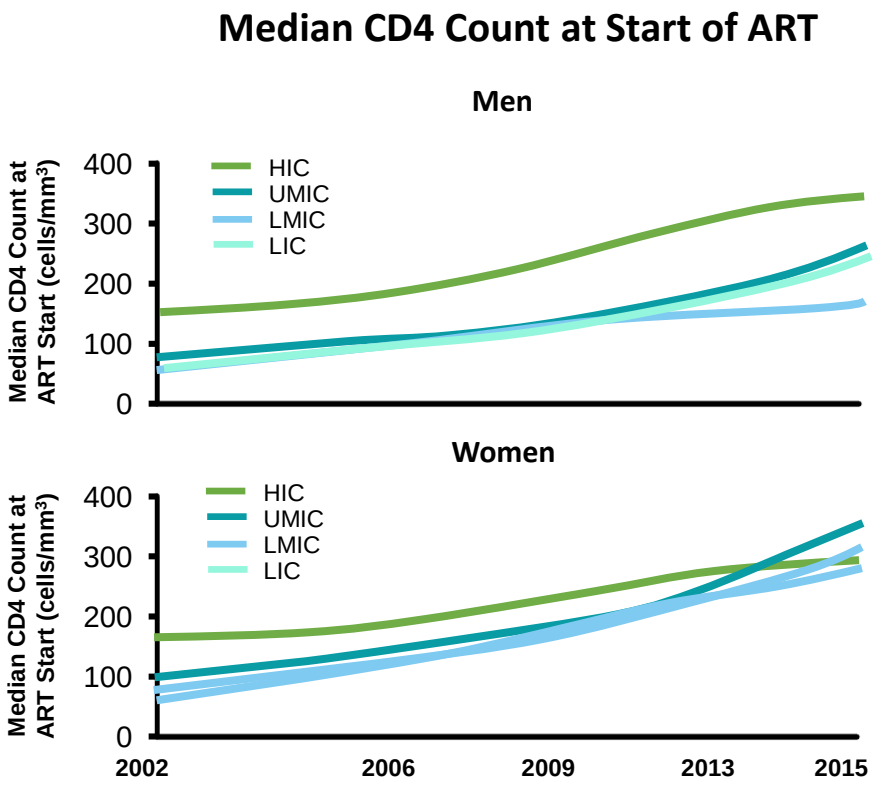
Progress but more work to be done . . . .

Progress:

- 19.5 million people on therapy; AIDS related deaths halved since 2005
- 7 countries have reached the 90-90-90 target, including Botswana, Sweden, UK
- Many other countries striving to reach that goal
- Universal test and treat and early initiation of ART are important advances
- But:
  - **Still a long way off from ideal world where we identify, treat, link and retain all people with HIV before they develop immunodefiency**

IeDEA and COHERE Cohorts: Immunodeficiency and the Start of ART

- Temporal trends in adults starting ART 2002-2015 (n=951,857)
- Aggregation by country income
  - Low (LIC; n=16), lower middle (LMIC; n=11), upper middle (UMIC; n=9), and high (HIC; n=19) income countries
- CD4 count at start of ART increased between 2002 and 2015.
- However at start of ART in 2015:
  - Median CD4 still <350
  - >25% had severe immunodeficiency
- Additional efforts needed to increase testing, linkage, retention in care



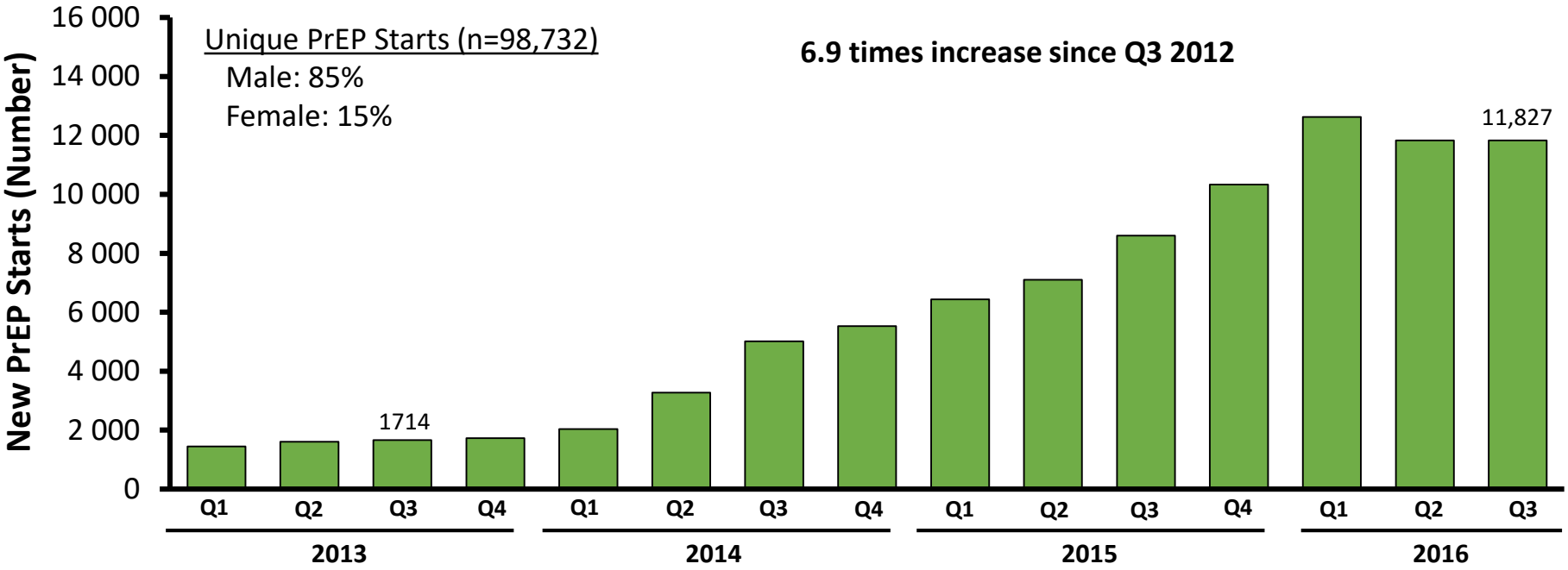
Anderegg N, et al. *J Int AIDS Soc*. 2017;20(suppl 4):6. Abstract MOAB0101.

Prevention

Advance # 3: Expansion of pre-exposure prophylaxis (PrEP)

New PrEP Starts in the US: 2012-Q3 2016

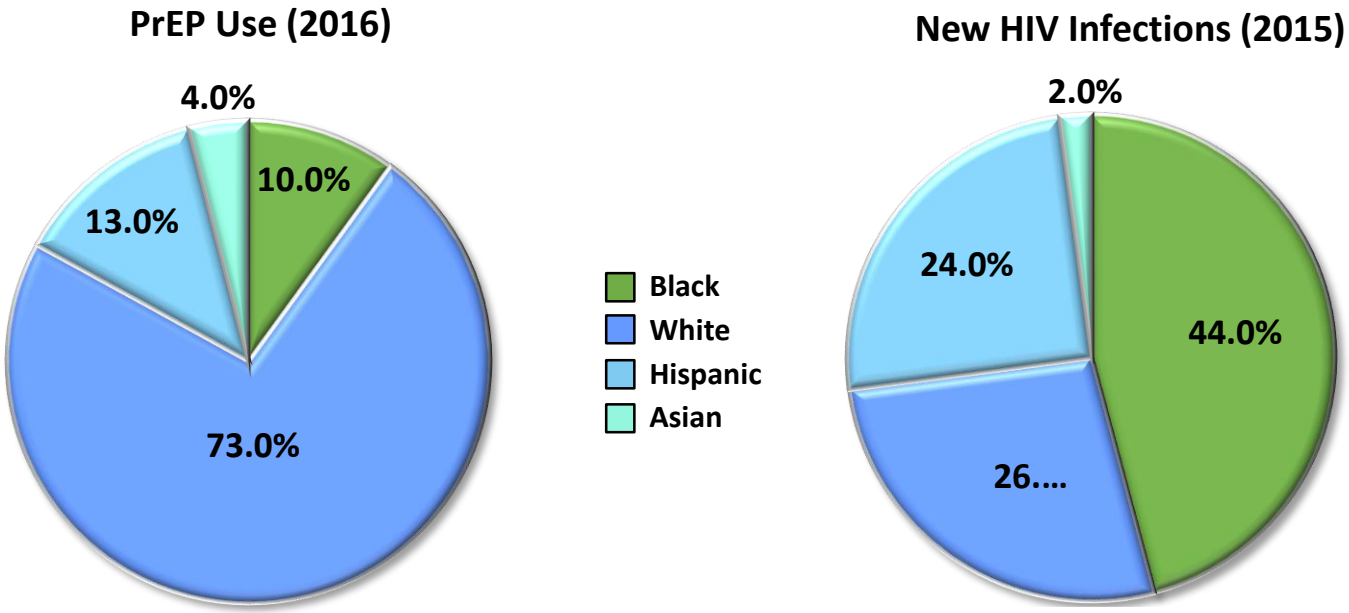
Total Unique PrEP Starts: 98,732



National electronic prescription data collected from 82% of all US retail pharmacies that dispensed emtricitabine/tenofovir DF.
PrEP prescriptions identified by excluding ICD-9 codes for tenofovir DF treatment for HIV infection, HBV, and PEP.

Mera Giler R, et al. *J Int AIDS Soc*. 2017;20(suppl 4). Abstract WEPEC0919.

PrEP Utilization Compared With New HIV Infections



PrEP Use Among Blacks and Hispanics Was Low Relative to the Rate of New HIV Infections

Mera Giler R, et al. *J Int AIDS Soc*. 2017;20(suppl 4). Abstract WEPEC0919.

New PrEP Options Moving Forward

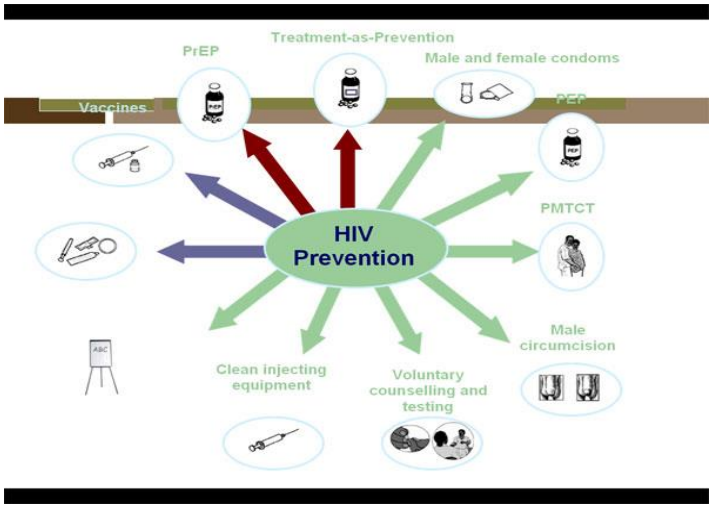
- **Long-acting antiretroviral agents:**
  - Long-acting (LA)-Cabotegravir
    - Injectable integrase inhibitor. Every other month dosing
    - In phase IIb/III clinical trial: HPTN 083 (4500 participants)
  - EFdA: Half-life supports every 6-12 months parenteral dosing
- **Vaginal rings (women-controlled PrEP):**
  - Dapivirine vaginal ring inserted monthly
- **Broadly neutralizing antibodies**
  - Multinational study of VRC01: AMP (n=4500)

Landovitz R et al, Curr Opin HIV AIDS. 2016; http://www.hvtn.org/en/science/HVTN-studies/AMPstudy.html;
Baeten et al, NEJM, 2016. Nel et al, NEJM, 2016; Brown E et al. 21st International AIDS Conference (AIDS 2016). Abstract TUAC0105LB.

HIV Prevention 2017

Where are we now?

- Abstinence
- Condoms
- Male circumcision
- Treatment of infected person prevents transmission to others
- Oral PrEP: TDF/FTC



IAPAC INTERNATIONAL ASSOCIATION OF PROVIDERS OF AIDS CARE

Organización Mundial de la Salud

ONUSIDA

Fast-Track Targets

by 2020	by 2030
90-90-90 Treatment	95-95-95 Treatment
500 000 New infections among adults	200 000 New infections among adults
ZERO Discrimination	ZERO Discrimination

- **Where do we need to be?**
  - Diagnose and treat <u>many</u> more HIV+ people; reduce disparities
  - Make PrEP easy to adhere to, accessible, controlled by those who need it: long-acting formulations
  - Vaccine

Where Are We With a Vaccine?

- New vaccine trial starting in South Africa
  - HVTN 702 (n=5400)
  - ALVAC-HIV + subtype C gp120/MF59 2700
- Promising candidates from animal studies are in human trials
  - Ad26/MVA mosaic + gp140 (APPROACH trial)
- Advances in our understanding of broadly neutralizing antibodies against HIV raising new hope

AFRICA

New HIV Vaccine Trial to Start in South Africa

By THE ASSOCIATED PRESS NOV. 27, 2016, 10:51 A.M. E.S.T.

JOHANNESBURG — A new vaccine against HIV, to be tested in a trial to be launched in South Africa Wednesday, could be "the final nail in the coffin" for the disease if it is successful, scientists say.

The study, called HVTN 702, aims to enroll 5,400 sexually active men and women aged between 18 and 35 at 15 sites across South Africa.

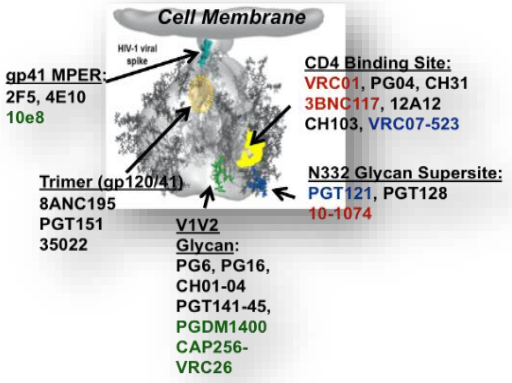
It will be the largest and most advanced HIV vaccine clinical trial to take place in South Africa, where more than 1,000 people a day are infected with HIV.

Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys

Dan H. Barouch, Kathryn E. Stephenson, Erica N. Borducchi, Kaitlin Smith, Kelly Stanley, Anna G. McNally, Jinyan Liu, Peter Abbink, Lori F. Maxfield, Michael S. Seaman, Anne-Sophie Dugast, Galit Alter, Melissa Ferguson, Wenjun Li, Patricia L. Earl, Bernard Moss, Elena E. Giorgi, James J. Szinger, Leigh Anne Eller, Erik A. Billings, Mangala Rao, Sodsai Tovanabutra, Eric Sanders-Buell, Mo Weijtens, Maria G. Pau, Hanneke Schuitemaker, Merlin L. Robb, Jerome H. Kim, Bette T. Korber, and Nelson L. Michael

Cell, 2013

Broadly Neutralizing Antibodies



APPROACH Trial: Phase 1/2a Study of Prophylactic Mosaic-Based Vaccine

- Mosaic vaccines: designed to induce immune responses against wide variety of HIV subtypes
- Proof-of-concept study: ≈400 healthy HIV uninfected volunteers
  - Mosaic Ad26 and MVA vectors combined with Env protein
- HIV antibody responses induced in 100% of volunteers
- Larger studies being considered

Criteria	Endpoint	Target (LL of 95% CI)	Results Post 3rd APPROACH	Results Post 4th APPROACH
Humoral	IgG binding responses on Clade C Env	≥90% (≥77%)	100% (93%)	100% (92%)
	ADCP responses to Clade C Env	≥56% (≥40%)	72% (57%)	80% (65%)
Cellular	Elispot responses to at least one ENV peptide pool	≥50% (≥35%)	77% (62%)	83% (68%)
Env boost	IgG to clade C Env of Ad/Ad+Env over Ad/Ad	≥1.5 fold	5.5 fold (3.5)	6.9 fold (4.5)

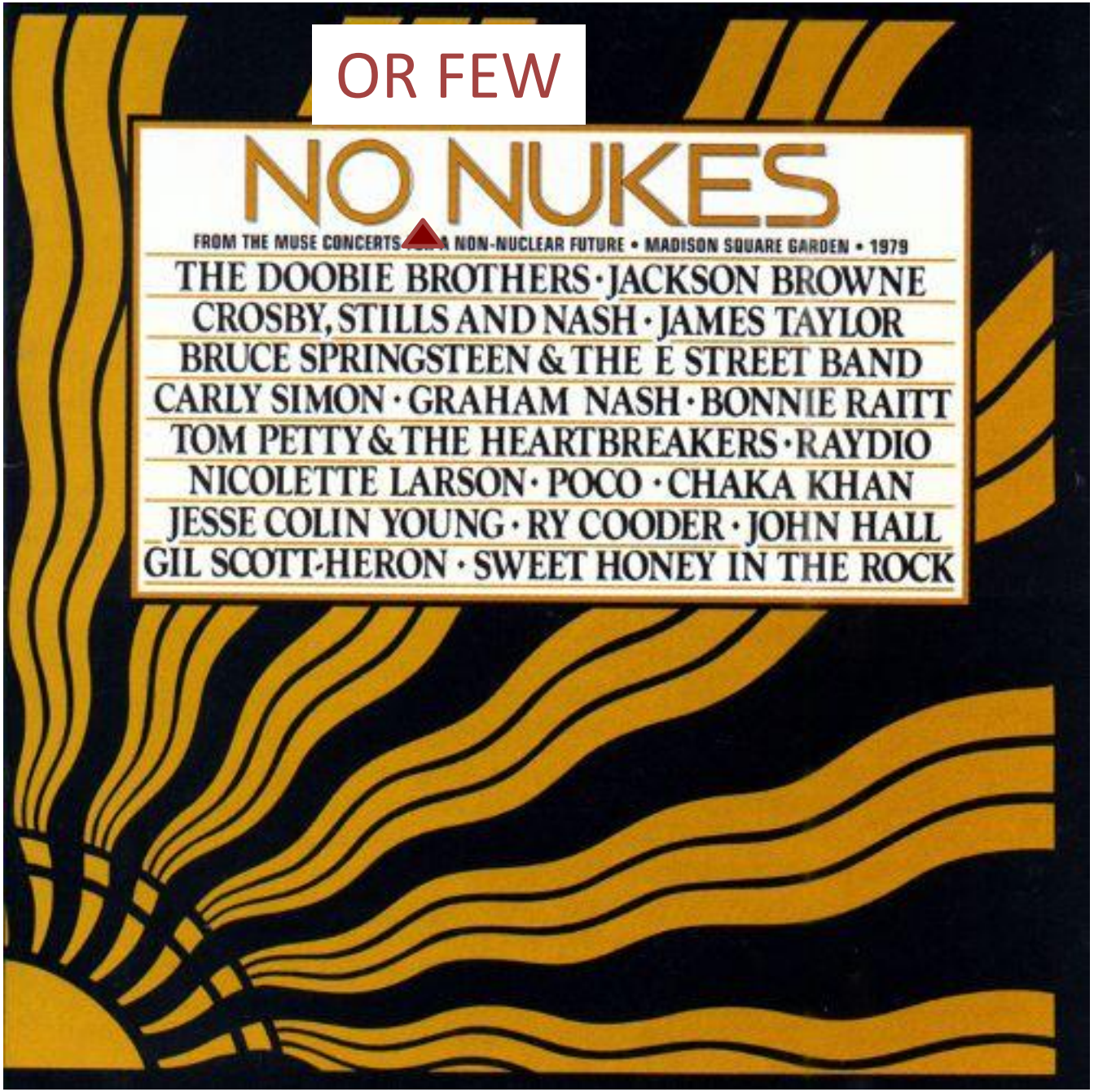
Shuitemaker H. *J Int AIDS Soc*. 2017;20(suppl 4). Abstract MOSY0403.

Treatment

Advance #4:
Promising Data with Two-drug ART

- DRV/r + 3TC
- DTG + 3TC
- DTG + RPV (for people already virologically suppressed)

Modern ART


OR FEW
NO NUKES
FROM THE MUSE CONCERTS FOR A NON-NUCLEAR FUTURE • MADISON SQUARE GARDEN • 1979
THE DOOBIE BROTHERS · JACKSON BROWNE
CROSBY, STILLS AND NASH · JAMES TAYLOR
BRUCE SPRINGSTEEN & THE E STREET BAND
CARLY SIMON · GRAHAM NASH · BONNIE RAITT
TOM PETTY & THE HEARTBREAKERS · RAYDIO
NICOLETTE LARSON · POCO · CHAKA KHAN
JESSE COLIN YOUNG · RY COODER · JOHN HALL
GIL SCOTT-HERON · SWEET HONEY IN THE ROCK

Current NRTI-limiting Regimens for Initial Therapy

- **LPV/r + 3TC (GARDEL)[1]**
  - Non-inferior to LPV/r + 2 NRTI
  - Disadvantages: high pill burden, toxicities
- **DRV/r + RAL (NEAT001)[2,3]**
  - Non-inferior to DRV/r + TDF/FTC
  - CD4 <200: DRV/r + RAL inferior to DRV/r + 2 NRTI
  - VL >100 K: more failures with DRV/r + RAL

[1]Cahn P et al, Lancet ID 2014; [2]Raffi F et al, Lancet, 2014; [3]Lambert-Niclot S et al, J Antimicrob Chemother, 2016; [4]Figueroa MI et al, 15th EACS, 2015

ANDES Study: Darunavir/r + Lamivudine in Treatment-Naïve Patients

Phase 4 study (Argentina)

Treatment-naïve

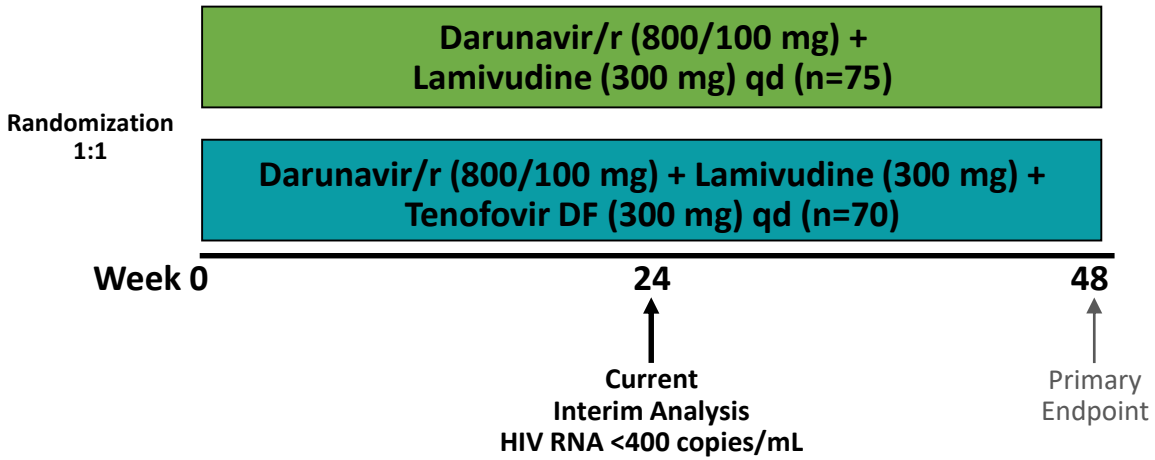
Open-label, non-inferiority

HIV RNA >1000 copies/mL

No major IAS-USA resistance mutations

No HBV

Stratified by baseline HIV RNA <100K, ≥100K copies/mL



Primary endpoint: proportion of patients with HIV RNA <50 copies/mL at week 48.

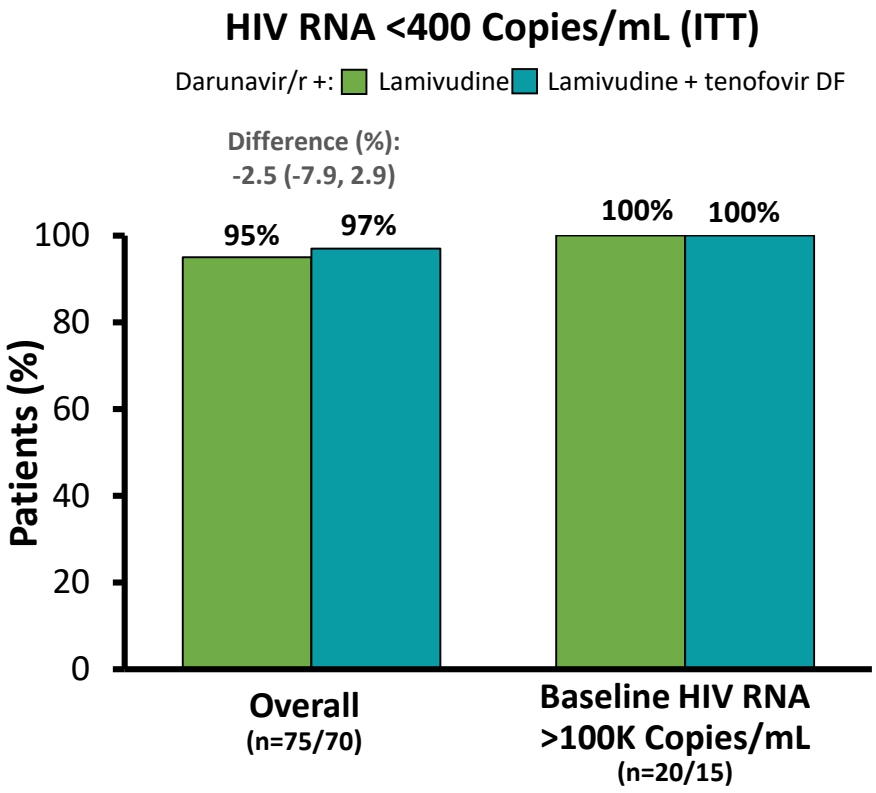
Baseline characteristics:

- Age: 30 years.
- Male: 91%.
- MSM/bisexual: 73%.
- CDC Stage B: 8%.
- HIV RNA: 4.5 $\log_{10}$ copies/mL.
- HIV RNA >100K copies/mL: 24%.
- Median CD4 count: 383 cells/mm^3.

Sued O, et al. *J Int AIDS Soc*. 2017;20(suppl 4):104. Abstract MOAB0106LB.

ANDES: Treatment Outcomes With DRV/r + 3TC in Treatment-Naïve Patients at Week 24

- 145 patients randomized
- HIV RNA <400 at wk 24: 95-97%
  - Baseline VL >100K also had high response rate
- Dual therapy non-inferior to triple therapy at week 24
- Both regimens well tolerated
- Promising results; larger trial ongoing



Sued O, et al. *J Int AIDS Soc*. 2017;20(suppl 4):104. Abstract MOAB0106LB.

ACTG A5353: Pilot Study of Dolutegravir + Lamivudine in Treatment-Naïve Patients

- Phase 2 single-arm study
  - HIV RNA ≥1000 to <500,000; no NRTI, integrase, or PI resistance; no HBV
- 120 patients enrolled
- Week 24, HIV RNA <50 in 90%
  - HIV RNA >100K and ≤100K groups both did well
- Virologic failure (n=3) uncommon; associated with suboptimal adherence
  - 1 person with virologic failure had emergent R263RK and M184V
- GEMINI-1 and -2: phase III trials; will provide data on efficacy and resistance barrier of dolutegravir + lamivudine

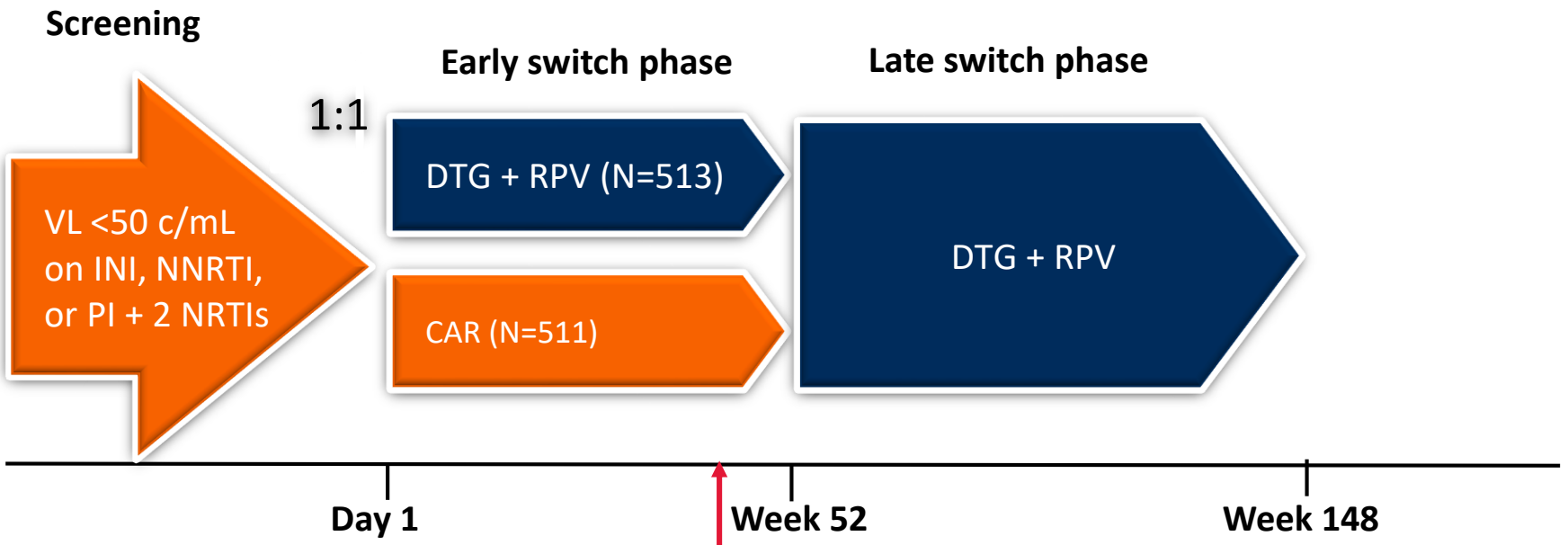
Week 24 Virologic Outcomes

	Baseline HIV RNA (copies/mL)	
	>100K (n=37)	**≤100K (n=83)**
HIV RNA <50 copies/mL (%)	89	90
Virologic non-success (%)	8	0
HIV RNA >50 copies/mL	0	2
Other reasons		

Taiwo BO, et al. *J Int AIDS Soc*. 2017;20(suppl 4). Abstract MOAB0107LB.

Switching to DTG + RPV in Virologically Suppressed Patients: SWORD-1 and -2

Randomized, phase III open-label, non-inferiority studies



Inclusion criteria

- On stable CAR ≥6 mo. before screening
- 1st or 2nd ART; no change in prior regimen due to VF
- Confirmed VK <50 during the 12 mo. before screening
- HBV negative

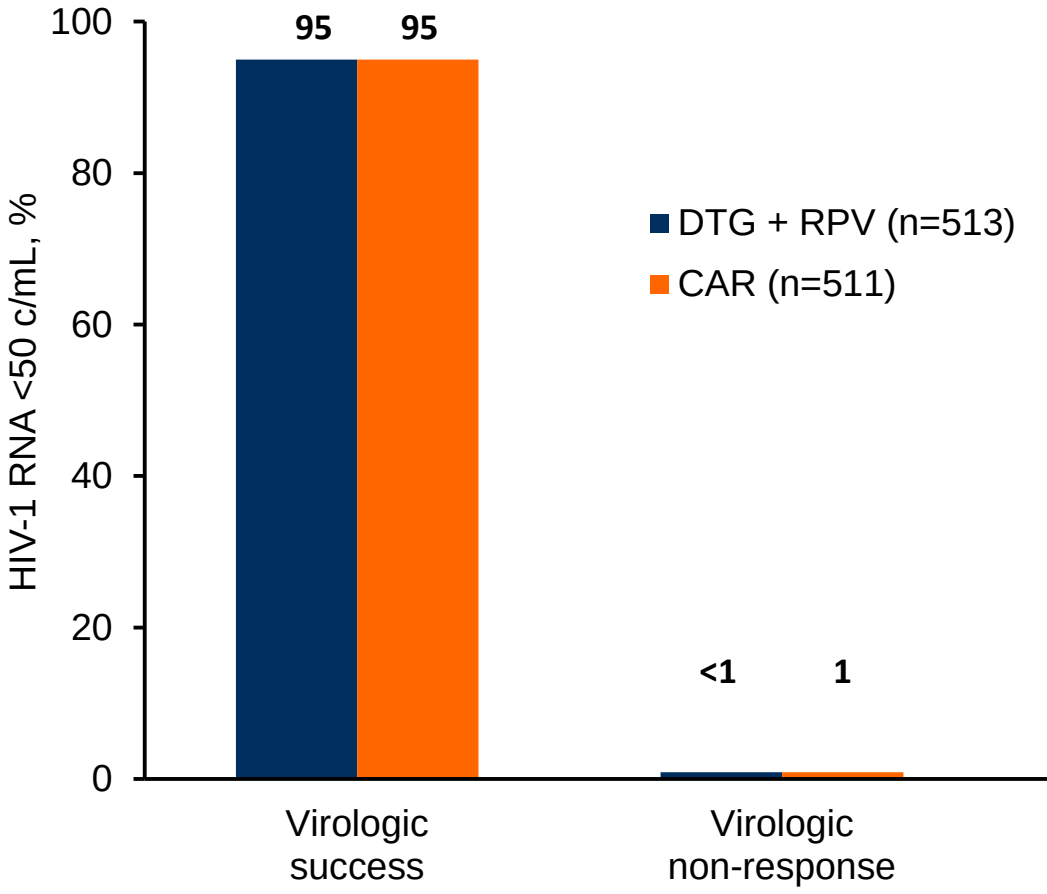
Primary endpoint at 48 wks: VL <50 (ITT-E snapshot)[a]

Duration of ART: ~ 4 y
Baseline TDF use: ~ 70%
Baseline PI ~25%, NNRTI ~50%, INSTI ~20%

Llibre JM et al. CROI 2017; Abstract 44LB.

Switching to DTG + RPV in Virologically Suppressed Patients: SWORD-1 and -2

Virologic outcomes at wk 48



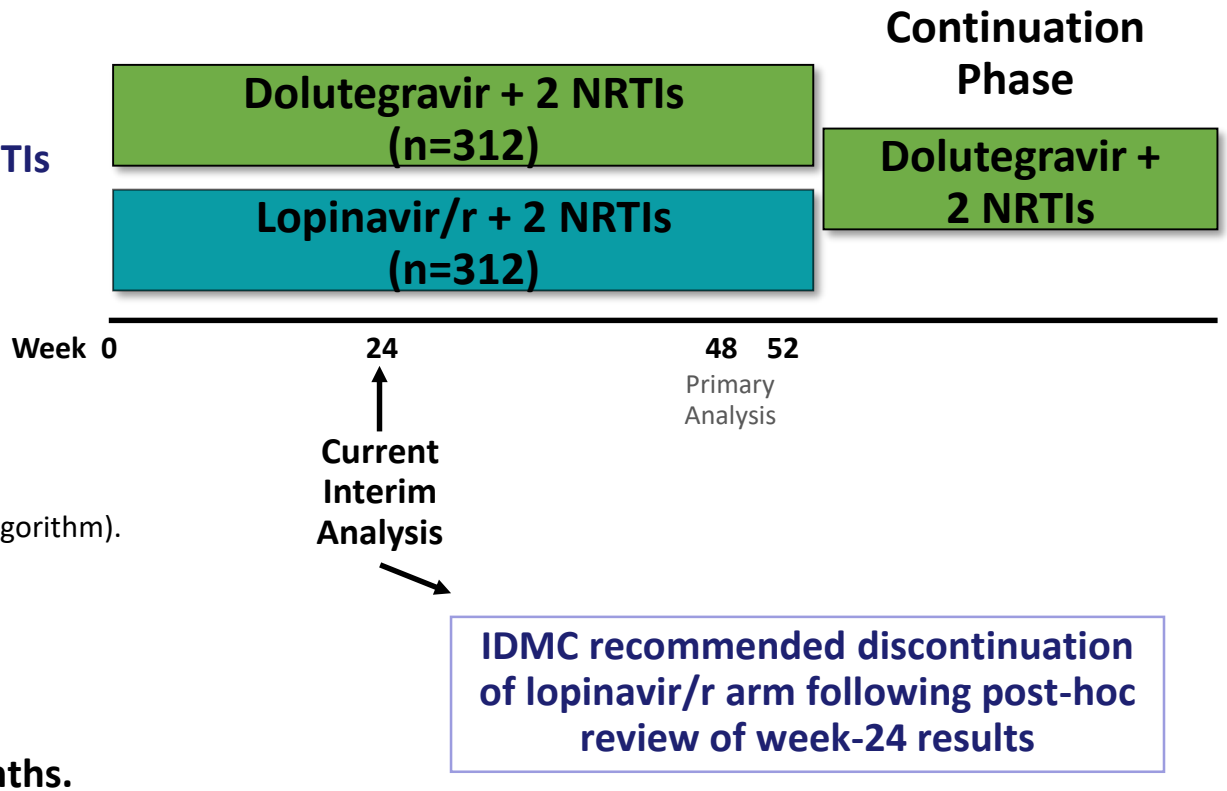
- DTG + RPV **non-inferior** to CAR
- Switch to DTG + RPV: neutral effect on lipids; improvements in BMD and bone turnover markers
- DTG/RPV single tablet regimen submitted for regulatory approval

Llibre JM et al. CROI 2017; Abstract 44LB.

Advance #5: Dolutegravir + 2 NRTIs for Patients Failing 1st line NNRTI therapy

DAWNING study
Phase 3b (ongoing)

- Open-label, non-inferiority
- Virologic failure of NNRTI + 2 NRTIs (HIV RNA ≥400 for >6 months)
- No primary resistance to PIs or INSTIs
- Investigator-selected NRTIs (≥1 fully active)



Non-inferiority margin: 12% (FDA snapshot algorithm).
Baseline demographics:
- Male: 65%.
- Age: 37 years.
- HIV RNA >100K copies/mL: 21%.
- CD4 <200 cells/mm^3: 50%.
- AIDS: 32%.

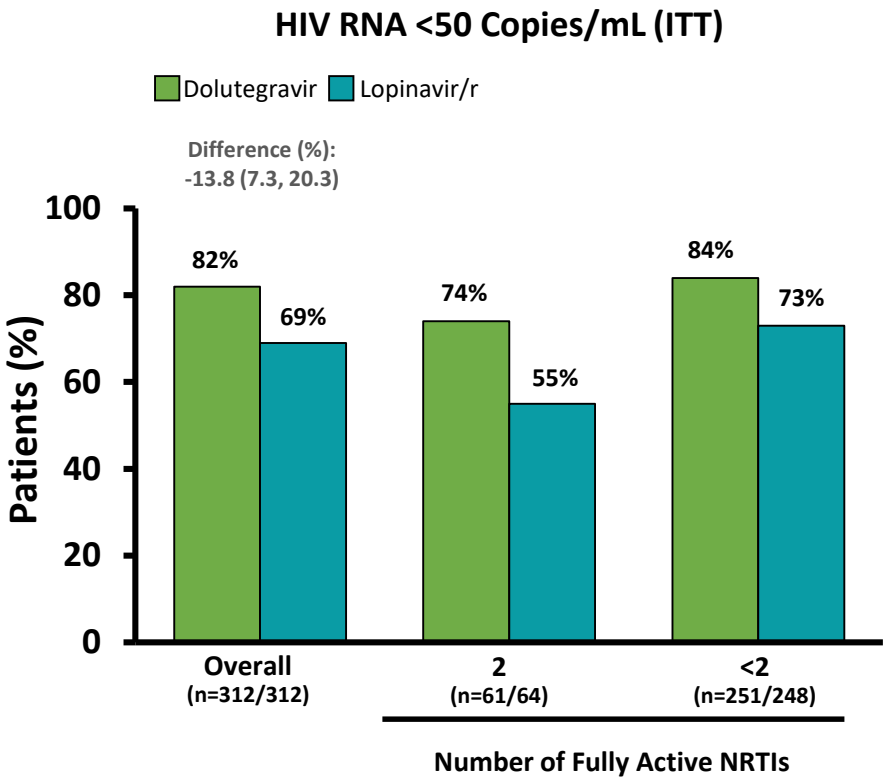
Duration of 1st line ART: 36 months.

Prior therapy agent:
- EFV (78%), TDF (59%), AZT (29%), abacavir (2%).

Aboud M, et al. *J Int AIDS Soc*. 2017;20(suppl 5):111-112. Abstract TUAB0105LB.

DAWNING Study: DTG + 2 NRTI superior to LPV/r + 2 NRTI

- DTG + 2 NRTIs superior to LPV/r + 2 NRTIs for VL <50 at wk 24
  - Similar in subgroups: VL ≤ or >100K, 2 or <2 active NRTIs, and CD4 < or ≥200
- Virologic non-response: DTG versus LPV/r: 12% versus 25%
- No emergent INSTI or NRTI resistance in DTG arm
  - NRTI resistance in LPV/r arm (n=3, 2 with K70R, M184V, 1 with K70R and K219E)
- DTG arm: fewer drug-related adverse events (15% vs 36%); less grade 2-4 diarrhea (<1% vs 7%)



Both arms received 2 NRTIs.

Aboud M, et al. *J Int AIDS Soc*. 2017;20(suppl 5):111-112. Abstract TUAB0105LB.

Advance #6: Safety of Dolutegravir/FTC/TDF in Pregnancy

- **Botswana**
  - In 2016, switched from EFV- to DTG-based regimens for 1st line ART, including for pregnant women
  - Analyzed birth outcomes:
    - EFV/FTC//TDF (8/2014-8/2016; n=4593)
    - DTG/FTC/TDF (11/2016-4/2017; n=845)
- Adverse birth outcomes similar among HIV+ women who initiated DTG or EFV
- More data needed earlier in gestation
  - Pregnancy registries accumulating data

Total and Severe Adverse Birth Outcomes

	Dolutegravir (n=845)	Efavirenz (n=4593)
Any adverse birth outcome (%)	34	35
Severe adverse birth outcome (%)	11	11
Adjusted risk ratio (95% CI)		
Any adverse birth outcome	1.0 (0.9, 1.1)	Reference
Severe birth outcome	1.0 (0.8, 1.2)	Reference

Models adjusted for maternal age, educational attainment, and gravida.

Zash R, et al. *J Int AIDS Soc*. 2017;20(suppl 5):105-106. Abstract MOAX0202LB.

New ART

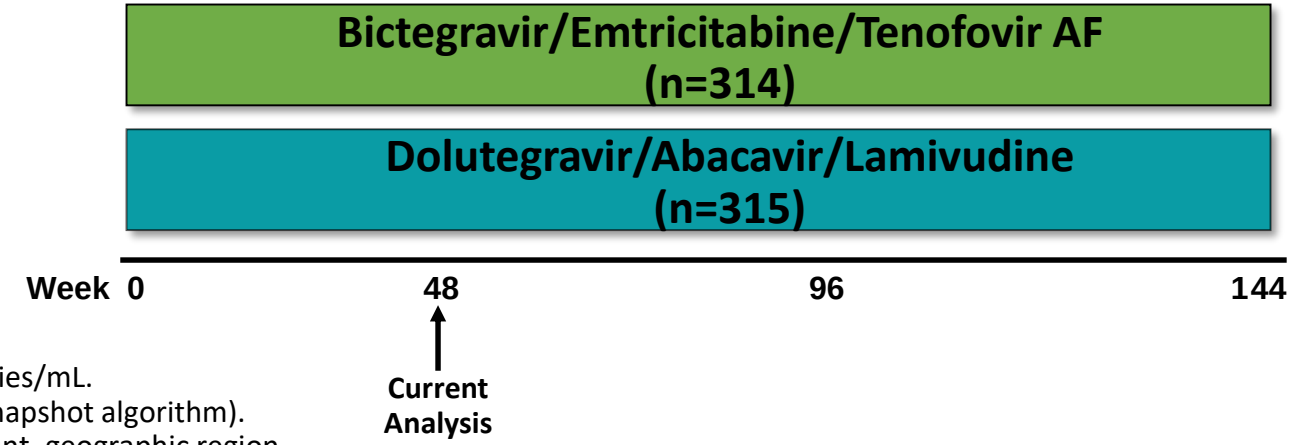
- **Advance # 7:**
  - **Bictegravir: new unboosted INSTI**
- **Advance # 8:**
  - **Long-acting intramuscular cabotegravir + rilpivirine**

Study 1489: Bictegravir/FTC/TAF vs Dolutegravir/ABC/3TC

Bictegravir: unboosted integrase inhibitor; high in vitro genetic barrier to resistance, low potential for drug interactions; being developed in combination with FTC/TAF

Phase 3

Double-blind
Treatment-naïve
HIV RNA ≥500 copies/mL
eGFR: ≥50 mL/min
HLA B*5701 negative
No HBV

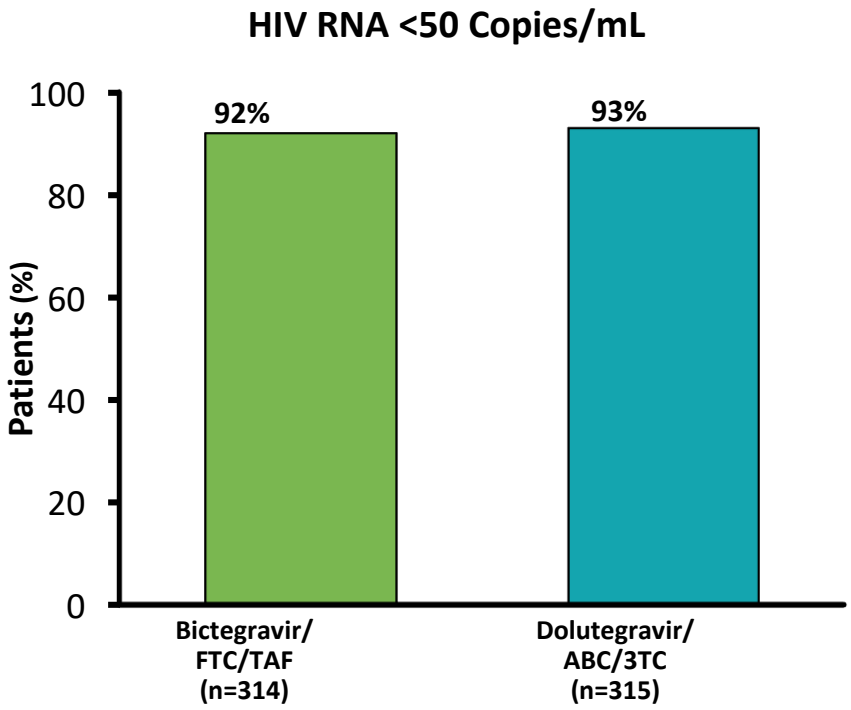


Primary outcome: HIV RNA <50 copies/mL.
Non-inferiority margin: 12% (FDA snapshot algorithm).
Stratified by HIV RNA level, CD4 count, geographic region.
Baseline demographics:
- Male: 91%.
- Age: 31-32 years.
- Black: 36%.
- HCV RNA: 4.4-4.5 log10 copies/mL.
- CD4: 443-450 cells/µL.
- Asymptomatic HIV infection: 91%.
- eGFR: 123-126 mL/min.

Gallant J, et al. *J Int AIDS Soc*. 2017;20(suppl 4):103-104. Abstract MOAB0105LB; Gallant J et al, Lancet 2017.

Study 1489: Bictegravir/FTC/TAF vs Dolutegravir/ABC/3TC

- 629 treatment-naïve adults
- BIC/FTC/TAF non-inferior to DTG/ABC/3TC
- No INSTI or NRTI resistance detected in either treatment arm
- Both regimens well tolerated
  - Nausea more common in DTG/ABC/3TC arm
- Similar changes in eGFR: -11 mL/min
- Similar changes in bone mineral density (BMD) and lipid parameters

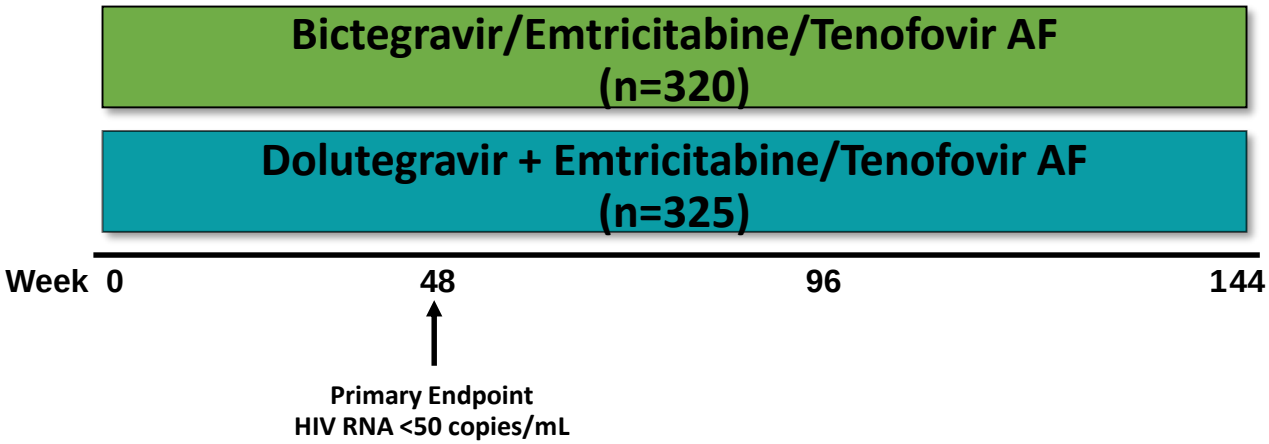


Gallant J, et al. *J Int AIDS Soc.* 2017;20(suppl 4):103-104. Abstract MOAB0105LB; Gallant J et al, Lancet 2017.

Study 1490:
BIC/FTC/TAF Versus DTG + FTC/TAF

Phase 3

Double-blind
Treatment-naïve
HIV RNA ≥500
eGFR: ≥30 mL/min
HBV or HCV allowed

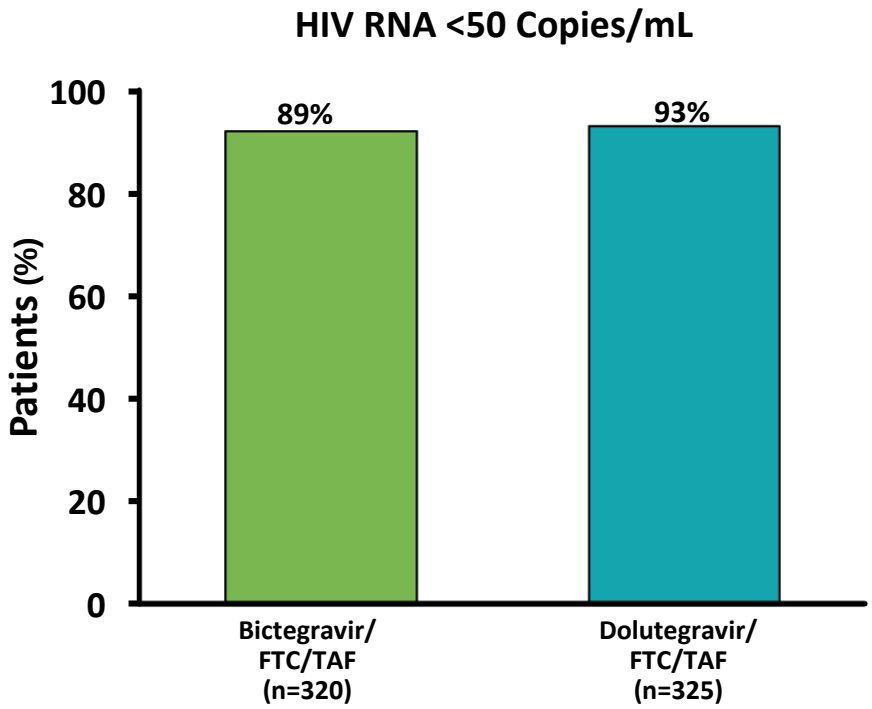


Primary outcome: HIV RNA <50 copies/mL
Non-inferiority margin: 12% (FDA snapshot algorithm).
Stratified by HIV RNA level, CD4 count, geographic region.
Baseline demographics:
- Male: 89%.
- Age: 33-34 years.
- Black: ~31%.
- HCV RNA: ~4.4 $\log_{10}$ copies/mL.
- CD4: ~441 cells/µL.
- HBV/HCV infection: ~2%/2%.
- eGFR: ~120 mL/min.

Sax PE, et al. *J Int AIDS Soc*. 2017;20(suppl 4):121-122. Abstract TUPDB0201LB; Sax PE et al, Lancet 2017

BIC/FTC/TAF Versus DTG + FTC/TAF: Week 48 Results

- BIC/FTC/TAF non-inferior to DTG + FTC/TAF
- No resistance occurred in either group
- No discontinuations due to lack of efficacy
- Overall both treatments well tolerated
  - Rate of nausea similar in both groups
- Smaller decrease in $eGFR_{CG}$ in BIC group
- Similar changes in lipids in both groups
- NDA for BIC/FTC/TAF submitted to FDA

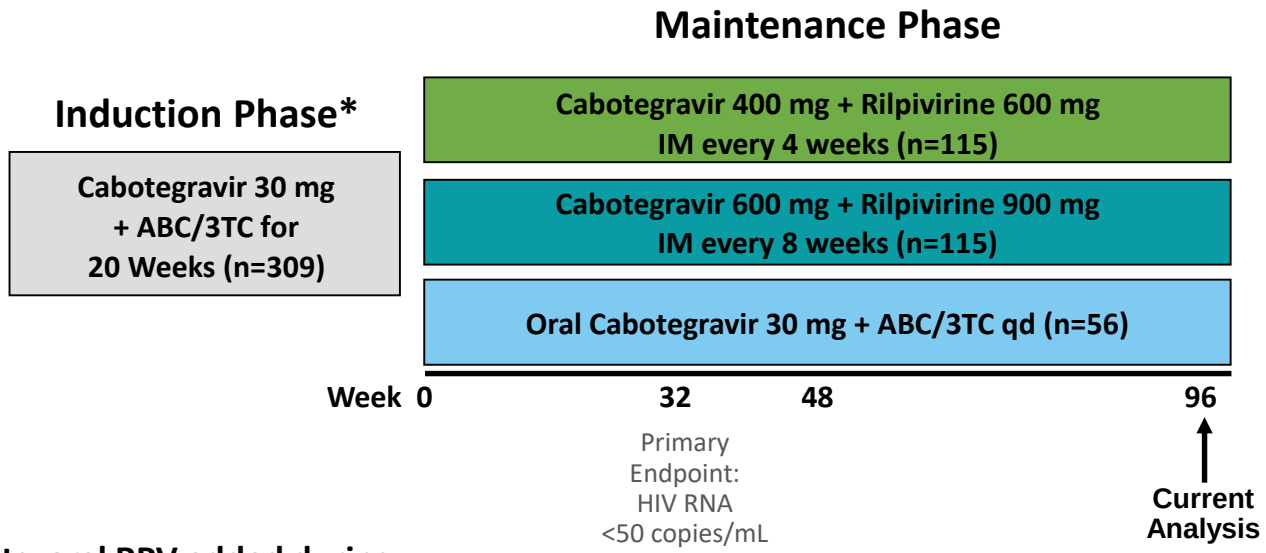


Sax PE, et al. *J Int AIDS Soc*. 2017;20(suppl 4):121-122. Abstract TUPDB0201LB; Sax PE et al, Lancet 2017

LATTE-2: Long-Acting Formulations of Cabotegravir + Rilpivirine as Maintenance Therapy

LATTE-2: Phase 2a

Open-label
≥18 years of age
ART-naïve
CD4 ≥200
Creatinine clearance ≥50
No HBV or ALT ≥5x ULN



***In virologically suppressed patients, oral RPV added during last 4 weeks of induction phase**.

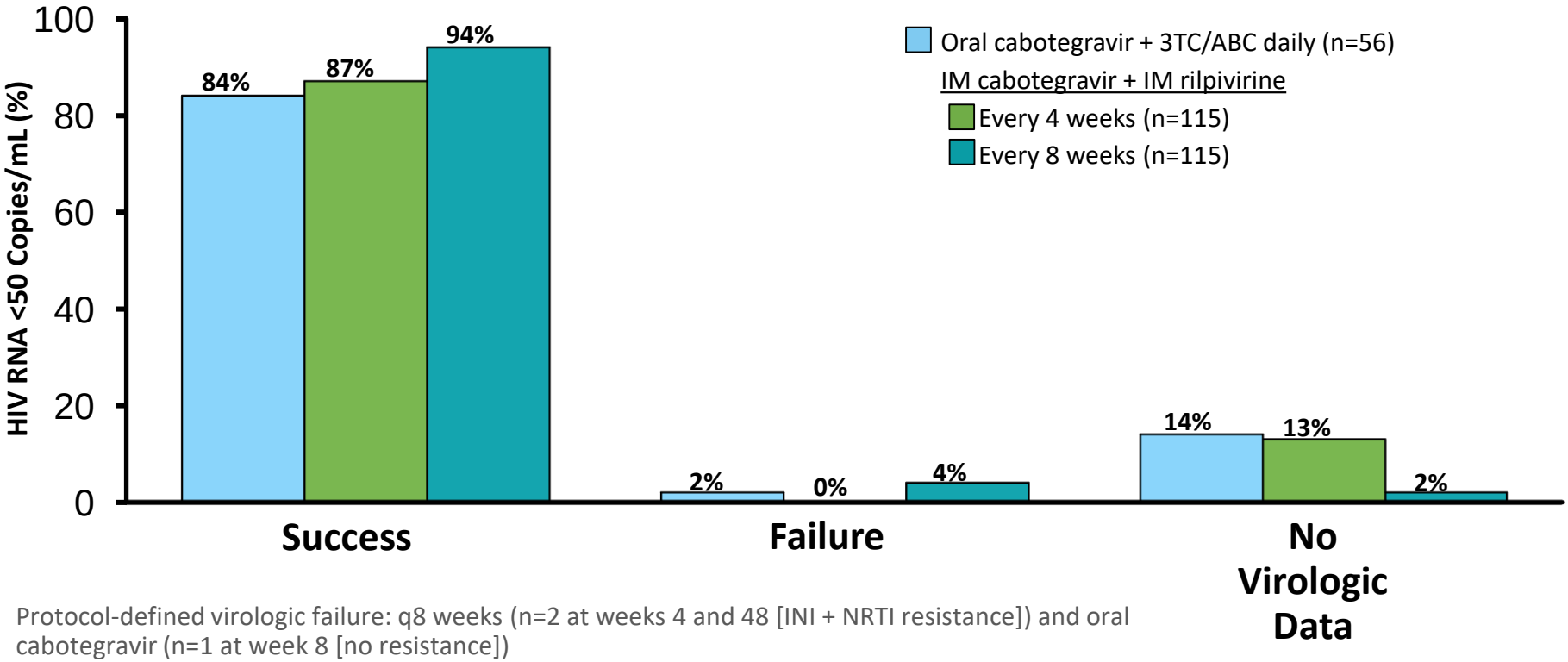
Qualification for maintenance phase: HIV RNA <50 between wk -4 and day 1.

Baseline characteristics:
- Median age: 35 years.
- Male: 92%.
- Black race/ethnicity: 15%.
- CDC class C: 1%.
- Median HIV RNA: 4.4 $\log_{10}$ copies/mL.
- HIV RNA >100K copies/mL: 18%.
- Median CD4: 489 cells/mm^3.

Eron J, et al. *J Int AIDS Soc*. 2017;20(suppl 4):107-108. Abstract MOAX0205LB.
Margolis DA, et al. *Lancet.* 2017Jul 21. [Epub ahead of print].

LATTE-2: Virologic Outcomes With LA Cabotegravir + Rilpivirine as Maintenance Therapy

Week 96 Results



Protocol-defined virologic failure: q8 weeks (n=2 at weeks 4 and 48 [INI + NRTI resistance]) and oral cabotegravir (n=1 at week 8 [no resistance])

Eron J, et al. *J Int AIDS Soc*. 2017;20(suppl 4):107-108. Abstract MOAX0205LB.
Margolis DA, et al. *Lancet.* 2017Jul 21. [Epub ahead of print].

LATTE-2: Safety Outcomes With LA Cabotegravir + Rilpivirine as Maintenance Therapy

- Injection site reactions
  - Mostly mild (84%) or moderate (15%) severity
    - <1% led to discontinuation
  - Most resolved within 7 days after each injection (89%)
- High participant-reported satisfaction
- Ongoing phase 3 trials (FLAIR, ATLAS) evaluating every 4-week dosing
- Every 8-week dosing to be evaluated in a phase 3 trial

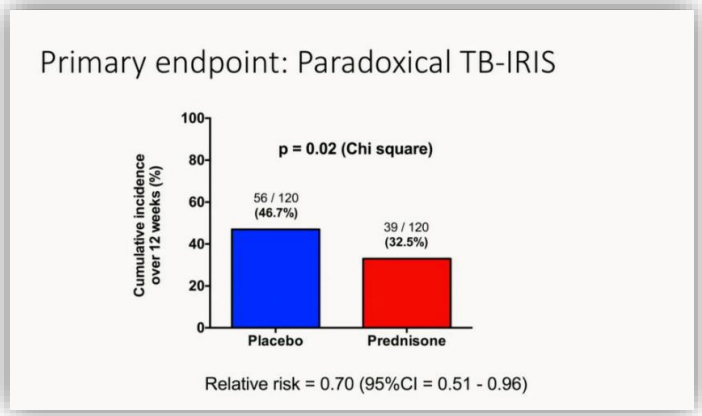
Safety Results for Cabotegravir

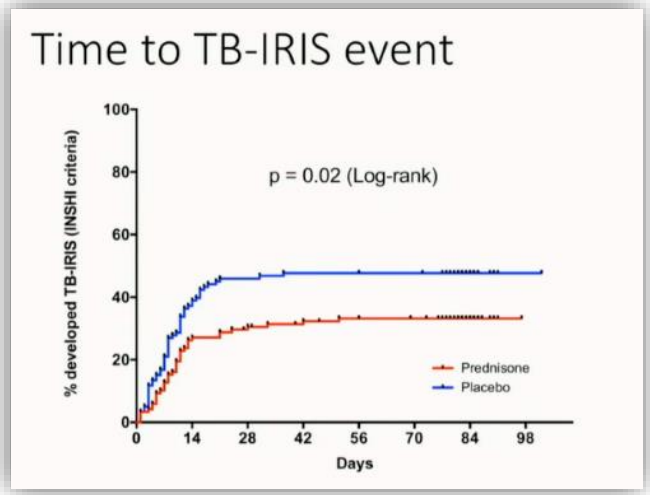
	IM Arms Combined (n=230)	Oral Arm (n=56)
Adverse events leading to withdrawals (%)	4	2
Grade 3/4 adverse events (excluding injection site reactions) (%)	13	7
Most common adverse events (%)		
Pyrexia	5	0
Headache	3	4
Influenza-like illness	3	0
Grade 3/4 laboratory abnormalities (%)	24	21

Eron J, et al. *J Int AIDS Soc*. 2017;20(suppl 4):107-108. Abstract MOAX0205LB.
Margolis DA, et al. *Lancet.* 2017Jul 21. [Epub ahead of print].

Advance #9: Improved treatment of Co-infections

- **RCT of prednisone vs. placebo in TB-HIV patients (PredART trial)**
  - N=240.
  - CD4<100. <30 d of TB treatment initiation
  - Prednisone 40 mg/day for 2 wk; 20 mg/d for 2 wk or placebo, started at time of ART initiation
  - Paradoxical TB IRIS lower in prednisone group: 32.5% vs. 46.7%, RR 0.7.
  - Reduced requirement for steroids to treat TB-IRIS by 53%
  - No evidence for difference in mortality, infections, cancer



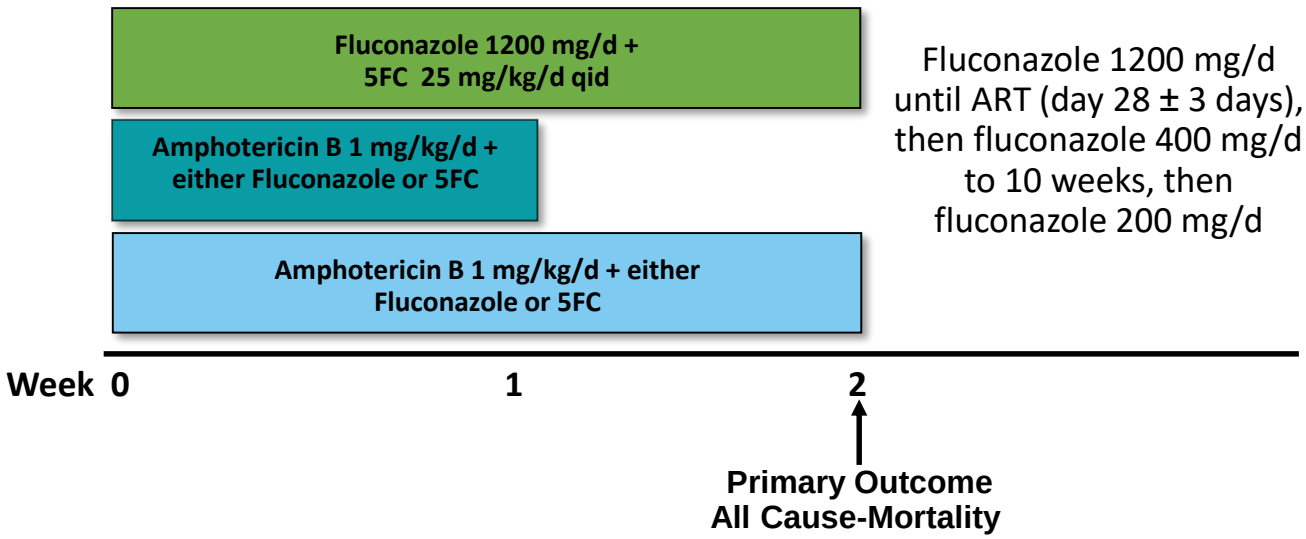


Meintjes G et al, CROI 2017, abstract 81LB

ACTA Trial: Initial Treatment of HIV-Associated Cryptococcal Meningitis in Africa

Phase 3 (n=678)
9 sites in 4 countries in sub-Saharan Africa

Open-label, non-inferiority
HIV positive (≥18 years)
1st episode of cryptococcal meningitis,
CSF positive



Follow-Up Treatment

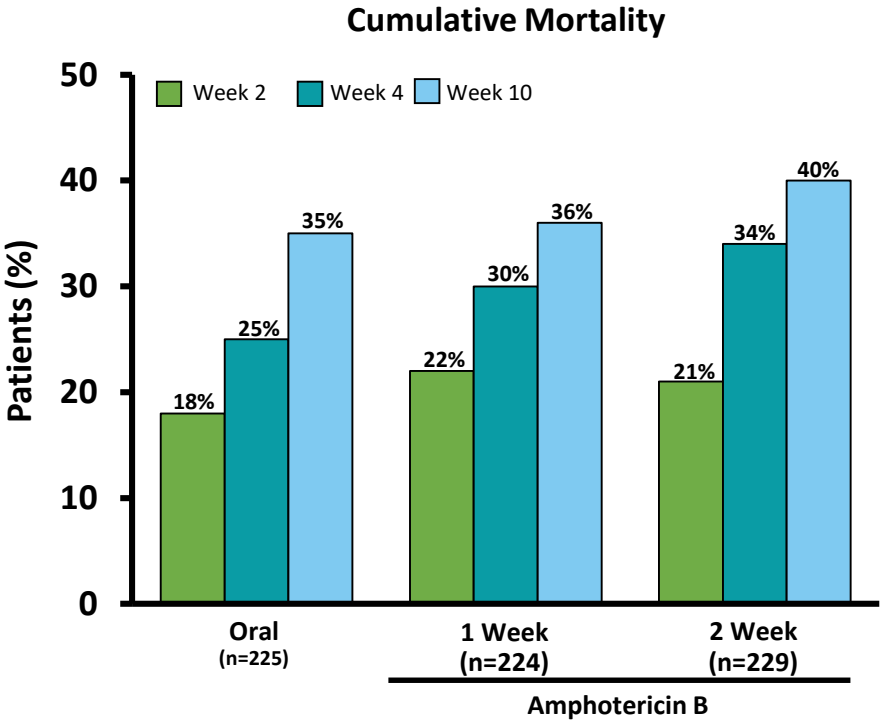
Fluconazole 1200 mg/d until ART (day 28 ± 3 days), then fluconazole 400 mg/d to 10 weeks, then fluconazole 200 mg/d

Non-inferiority margin: 10%.
Baseline demographics:
- Male: 58%.
- Age: 36-39 years.
- On ART: 56%.
- **CD4 count: 25-26 cells/mm^3.**
- Hemoglobin: 10.7-11.0 g/dL.
- CSF fungal count: 5.0 $\log_{10}$ CFU/mL.

Molloy S, et al. *J Int AIDS Soc*. 2017;20(suppl 5):105. Abstract MOAX0201LB.

ACTA Trial: Outcomes with Treatment of HIV-Associated Cryptococcal Meningitis in Africa

- 1-wk ampho B-based therapy and oral combination (fluconazole + 5FC) non-inferior to 2-wk ampho B-based therapy
  - Treatment difference:
    - Oral versus 2-week: -3.2 (-9.3, 3.0)
    - 1-week versus 2-week: 0.5 (-5.9, 6.8)
- 5FC as adjunctive therapy with ampho B led to lower mortality compared with fluconazole
- 1-wk ampho B + 5FC was associated with better survival compared with all other arms
- Results may reflect, at least in part, the balance between rate of clearance of infection and tolerability



Molloy S, et al. *J Int AIDS Soc*. 2017;20(suppl 5):105. Abstract MOAX0201LB.

Advance #10: HIV Cure on the Horizon?

Sustained Virologic Control After ART Cessation in a Child With Perinatal HIV Infection

- Infant diagnosed with HIV soon after birth was enrolled in CHER Trial (2005-2011)
  - Deferred versus early limited ART (40 or 96 weeks)
- Initiated LPV/r + ZDV/3TC (HIV RNA 150K) at 8.5 weeks of life
- ART stopped after 40 weeks
- HIV RNA during follow-up remained <20
- Child now 9.5 yr of age, asymptomatic, CD4 >800
  - Small amount of proviral DNA detectable
  - No replication-competent HIV using co-culture methods
- Defining correlates of post-treatment control may yield insights into how to achieve ARV-free remission

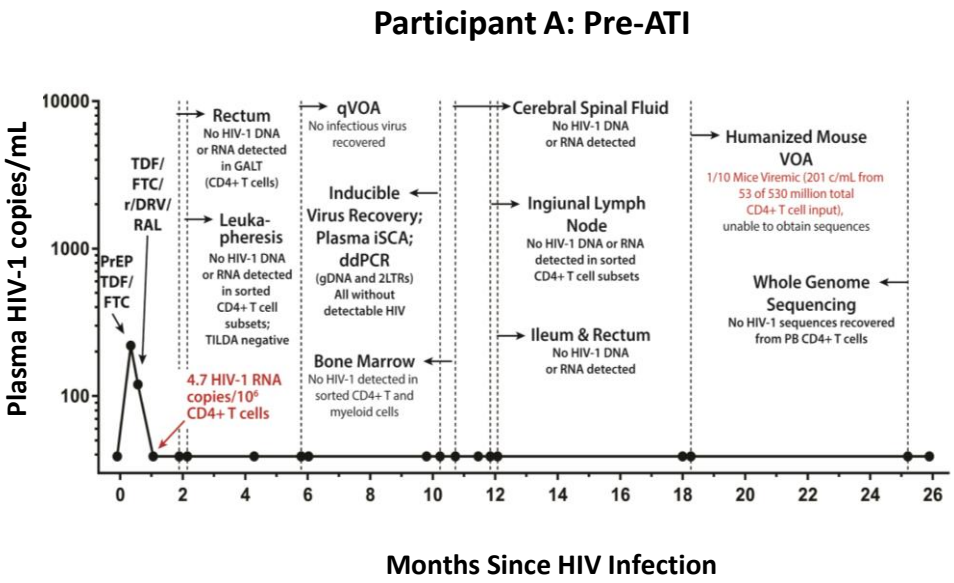
Summary of Key Findings

	Findings
Viral factors Total DNA reservoir	5 copies/10^6 PBMC (similar at ART stop)
Host factors	
Immune activation	Low and similar to uninfected children, but lower than elite controllers
Cell-mediated responses	Weak CD4 response only to Gag; no detectable HIV-specific CD8 responses
HIV-specific Abs	Mostly weak responses; high IgA2 response (mucosal) to gp41
CCR5 expression	Low (surface density) compared to uninfected children and adults; similar to elite controllers
PD-1 expression	High relative to uninfected children/adults/elite controllers (CD4), and uninfected children/ elite controllers (CD8)

Violari A, et al. *J Int AIDS Soc*. 2017;20(suppl 5):124. Abstract TUPDB0106LB.

Prolonged HIV Remission and Viral Rebound in Individual Treated During Hyperacute Infection

- Screening of high-risk individuals in PrEP program for acute HIV infection
- Participant A: PrEP started 10 d after infection
  - 4th generation EIA & rapid HIV-antibody tests negative
  - HIV RNA 220 copies/mL
  - Converted to 4-drug ART 8 days later once HIV RNA level was known (darunavir/r + raltegravir + emtricitabine/tenofovir DF)
  - Continued ART for almost 3 years
  - Multiple tests for persistent HIV were negative

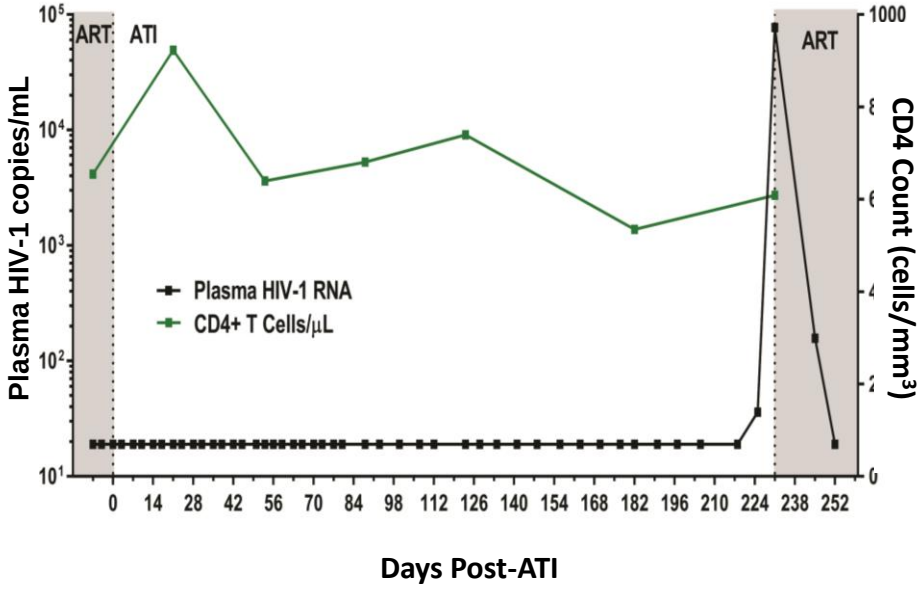


Henrich T, et al. *J Int AIDS Soc*. 2017;20(suppl 5):82-83. Abstract TUPDB0103.

Participant A After 34 Months of Suppressive ART: Results of the Analytical Treatment Interruption

- Prior to treatment interruption
  - Estimates of reservoir size: ~200 cells
- Following treatment interruption, virologic control for almost 8 months
- Viremia eventually led to relapse (identical sequence as during acute infection)
  - Suggests early ART alone will not lead to ART-free remission
- Patients treated early may be optimal candidates for HIV cure trials
  - Small HIV reservoir, limited viral diversity, intact T cell immunity

Participant A: Post-ATI



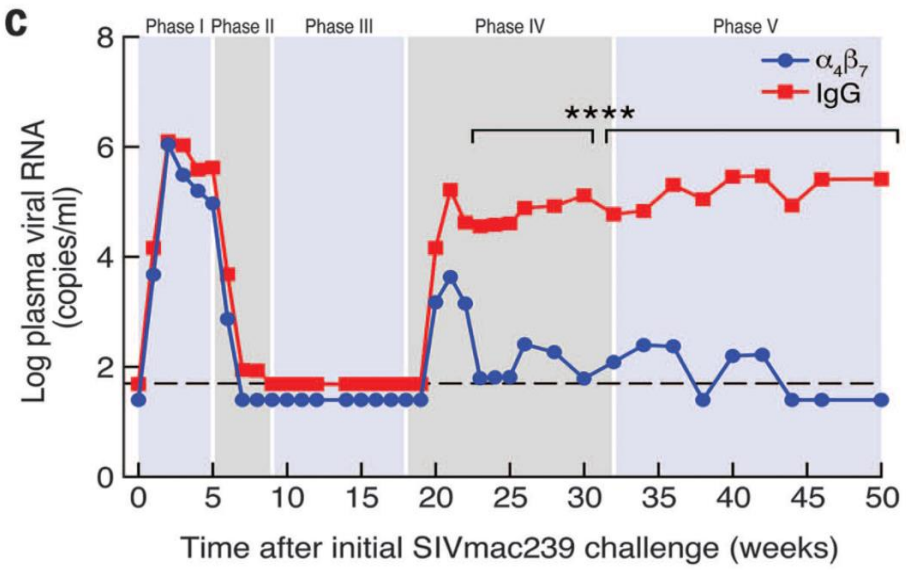
Henrich T, et al. *J Int AIDS Soc*. 2017;20(suppl 5):82-83. Abstract TUPDB0103.

RESEARCH ARTICLE SCIENCE

HIV-1 THERAPY 14 OCTOBER 2016 • VOL 354 ISSUE 6309

Sustained virologic control in SIV$^+$ macaques after antiretroviral and $\alpha_4\beta_7$ antibody therapy

Siddappa N. Byrareddy,[1*†] James Arthos,[2*] Claudia Cicala,[2*] Francois Villinger,[1,3‡] Kristina T. Ortiz,[1] Dawn Little,[1] Neil Sidell,[4] Maureen A. Kane,[5] Jianshi Yu,[5] Jace W. Jones,[5] Philip J. Santangelo,[6] Chiara Zurla,[6] Lyle R. McKinnon,[7§] Kelly B. Arnold,[8] Caroline E. Woody,[8] Lutz Walter,[9] Christian Roos,[9] Angela Noll,[9] Donald Van Ryk,[2] Katija Jelicic,[2] Raffaello Cimbro,[10] Sanjeev Gumber,[3] Michelle D. Reid,[1] Volkan Adsay,[1] Praveen K. Amancha,[3] Ann E. Mayne,[1] Tristram G. Parslow,[1] Anthony S. Fauci,[2] Aftab A. Ansari[1]||



- Most CD4 cells are in GI mucosa
- Alpha-4 Beta-7 (integrin) guides CD4 cells to gut mucosa → infected/depleted by HIV
- Monkeys who received ART during acute SIV were treated with anti-integrin antibody
- After stopping treatment, animals maintained low to undetectable viral loads, normal CD4 counts for >9 months
- Vedolizumab: anti-integrin antibody; FDA approved for inflammatory bowel disease
- Human trials underway

Top 10 HIV Advances

- More than ½ of HIV patients on ART
- Test and treat and early ART should be expanded
- Ongoing roll-out of PrEP; new options being developed
- Dual therapy looks promising; in phase III trials
- Dolutegravir + 2 NRTI for first line NNRTI failures
- Accumulating data on safety of DTG in pregnancy
- New unboosted integrase inhibitor, bictegravir, with TAF/FTC looks promising
- Long-acting injectable cabotegravir + rilpivirine in phase 3
- Advances in preventing TB IRIS and treating cryptococcal meningitis
- Continued efforts to cure HIV

<u>World AIDS Day, 2013:</u>

. . . the United States should be at the forefront of new discoveries into how to put HIV into long-term remission without requiring lifelong therapies -- or, better yet, to eliminate it completely.

Patient: One day I'd love to say, "I used to have HIV."