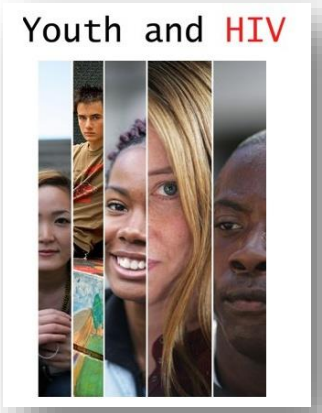
CROI 2019

Selected PMTCT, Pediatric, Adolescent, and Maternal/Adult Abstracts

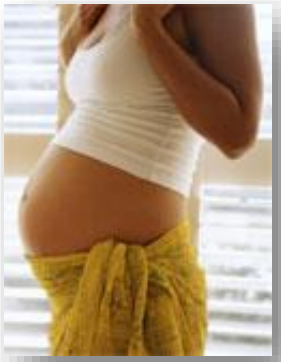
Lynne M. Mofenson MD

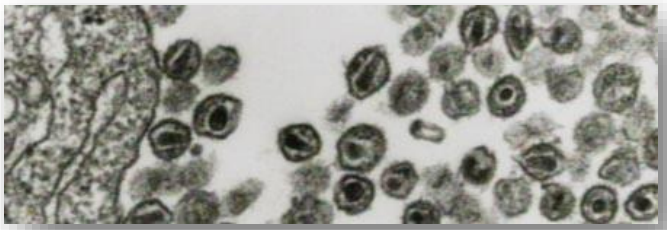
unicef

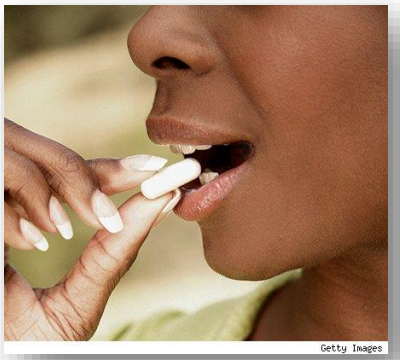
Elizabeth Glaser Pediatric AIDS Foundation
Until no child has AIDS.



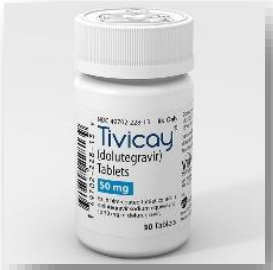
March 21 2019

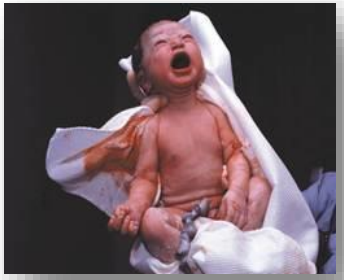


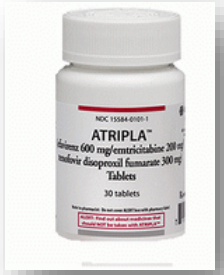




Pregnancy, ARV Drugs, Viral Suppression, Pregnancy Outcome



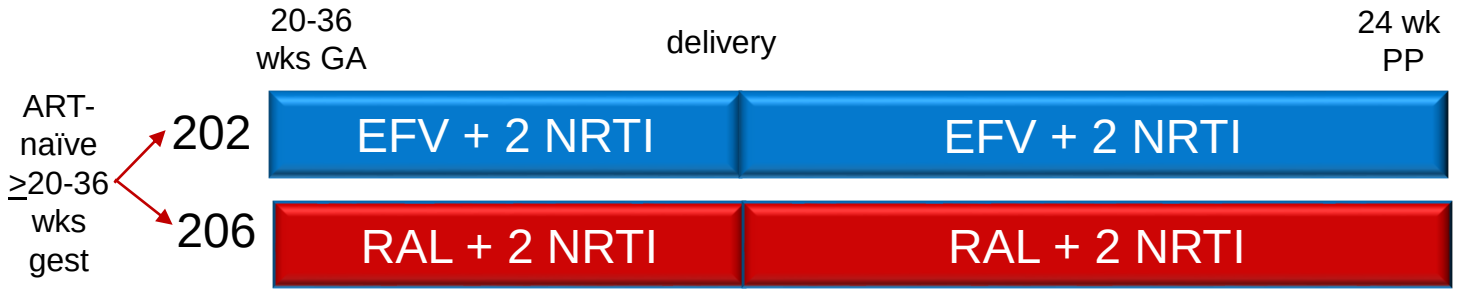




Randomized Trial of RAL vs EFV-Based ART Started in Late Pregnancy: IMPAACT P1081

Mirochnick M et al. CROI, 2019 Seattle Abs. 39LB

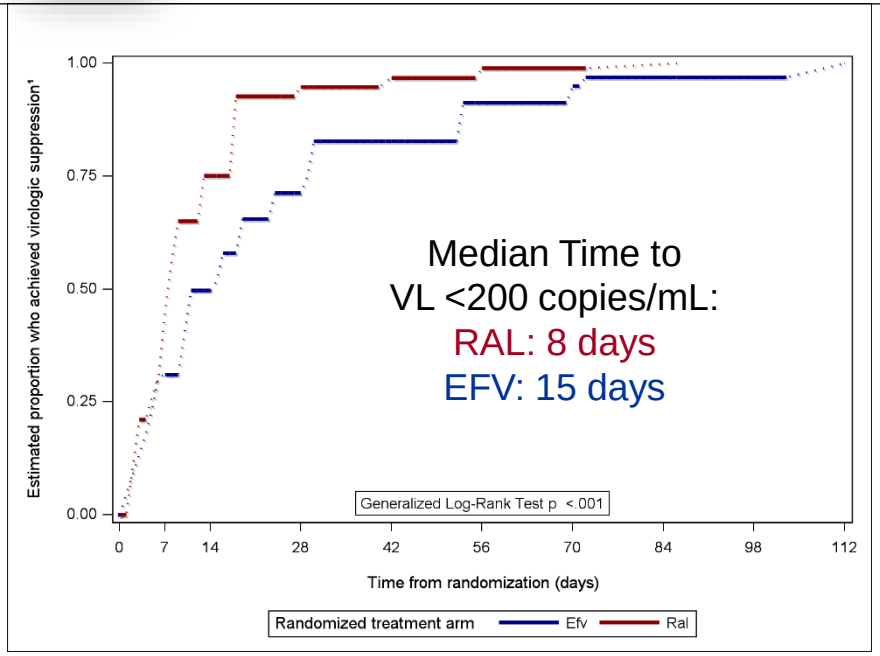
- Randomized trial of RAL+2NRTI vs EFV+2NRTI in 408 pregnant ART-naïve women S America, Africa, Thailand and US presenting to ANC at ≥28-36 weeks (later expanded to ≥ 20 weeks) gestation. Primary endpoint is virologic response (VL <200) at delivery.



Delivery	Efavirenz	Raltegravir	P value
VL <200	84% (151/179)	94% (174/183)	<0.001
Enrolled 20 to <28 wks	97% (87/90)	96% (85/88)	NS
Enrolled 28 to <37 wks	71% (64/89)	93% (89/95)	0.05

More Rapid VL Decline with RAL than EFV

Mirochnick M et al. CROI, 2019 Seattle Abs. 39LB



- VL decline was greater in raltegravir arm than efavirenz arm at study weeks 2, 4 and 6.
- Both regimens well-tolerated; no difference AE, stillbirth, preterm.
- 1 raltegravir and 6 efavirenz infants were infected (p=0.06).

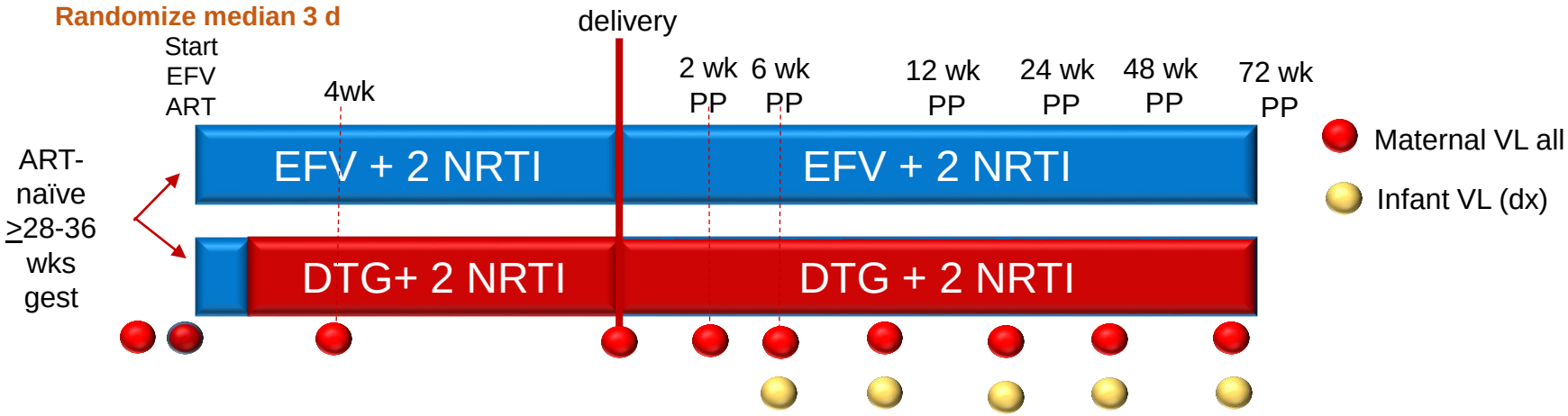
	Efavirenz	Raltegravir	P-value
VL ↓ by wk 2 and sustained to delivery	84/131 (64%)	121/132 (92%)	<0.001
VL ≥2.0 log ↓decline or <200 by wk 2	91/131 (69%)	123/132 (93%)	<0.001
VL <1,000 all time pt after wk 4	117/123 (95%)	115/120 (96%)	NS
Stayed on study drug through delivery	129/131 (98%)	131/132 (99%)	NS

DTG vs EFV When Starting ART in Late Pregnancy

Khoo S et al. CROI 2019 Seattle, WA Abs. 40LB

DolPHIN 2

- Open-label randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naïve women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.
- Primary endpoint is virologic response (VL <50) at delivery.



- Analysis at delivery (ITT): 122 DTG, 115 EFV
- Median gestation age at enrollment, 31 weeks
- No difference in baseline VL (median 4.4 log), CD4 (median 445), prior obstetric history, gestation, BMI

More Rapid VL Decline with Dolutegravir than Efavirenz

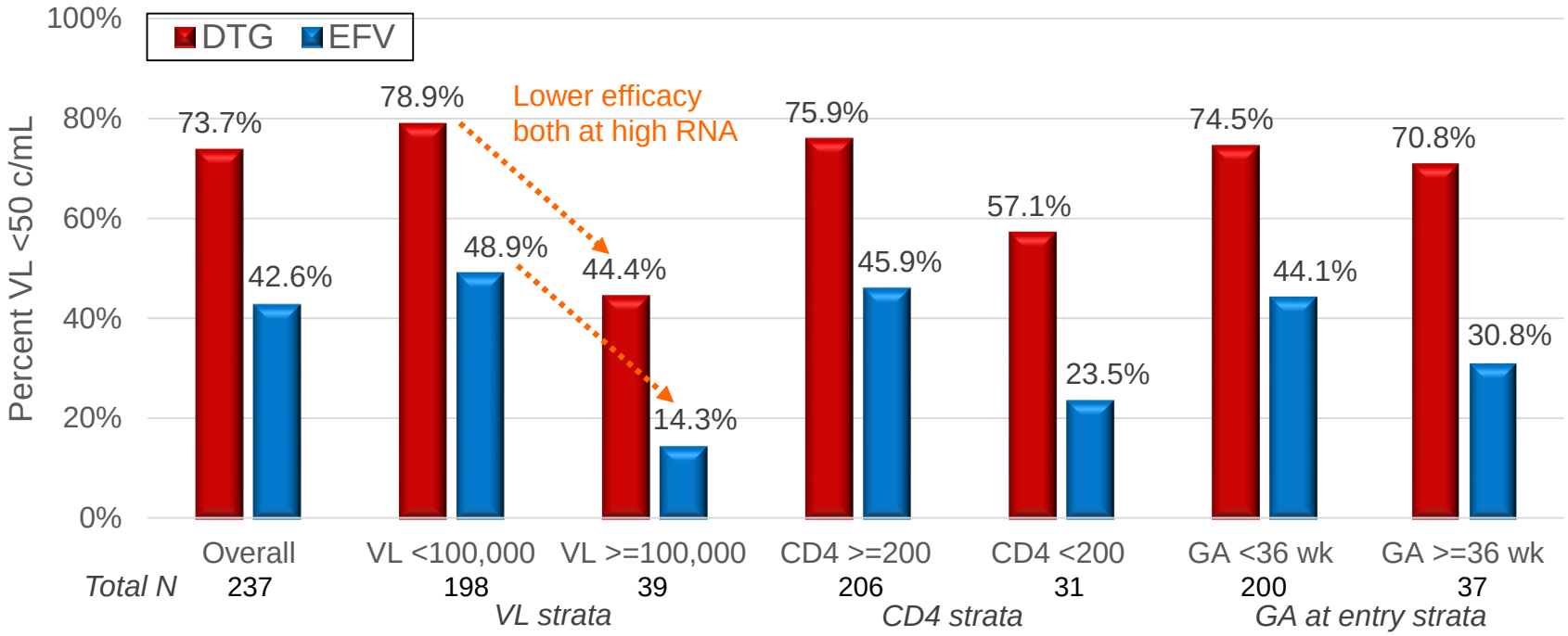
Khoo S et al. CROI 2019 Seattle, WA Abs 40LB

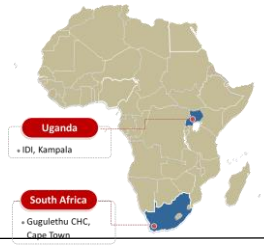
DolPHIN 2

- Primary outcome
  - Time on medication before delivery, median 55 days

Delivery	Dolutegravir	Efavirenz	aRR DTG vs EFV*	P value
VL <50	73.8% (90/122)	42.6% (49/115)	1.66 (1.2, 2.1)	<0.0001
VL <1000	92.6% (113/122)	82.6% (95/115)	1.11 (1.0, 1.2)	0.0513

*Adjusted for age, country, VL (<> 100,000), CD4 (<>200), GA at start ART





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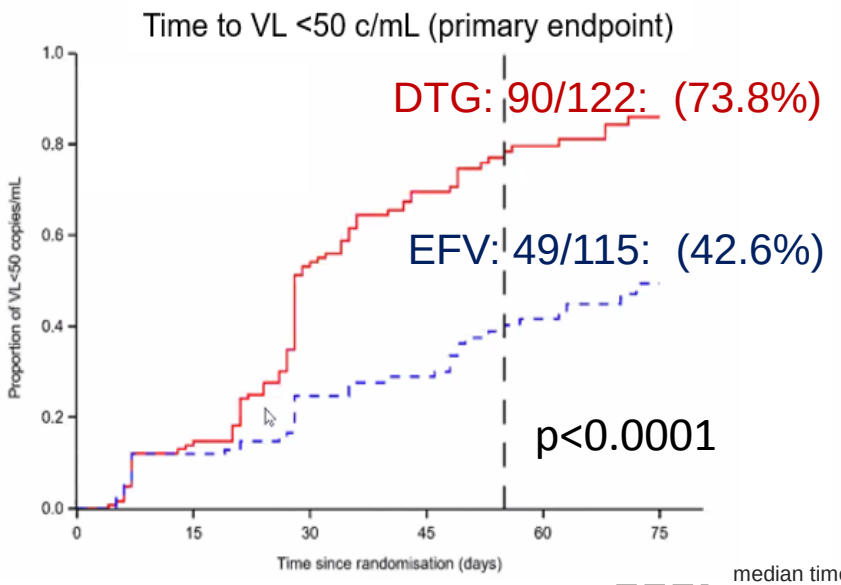
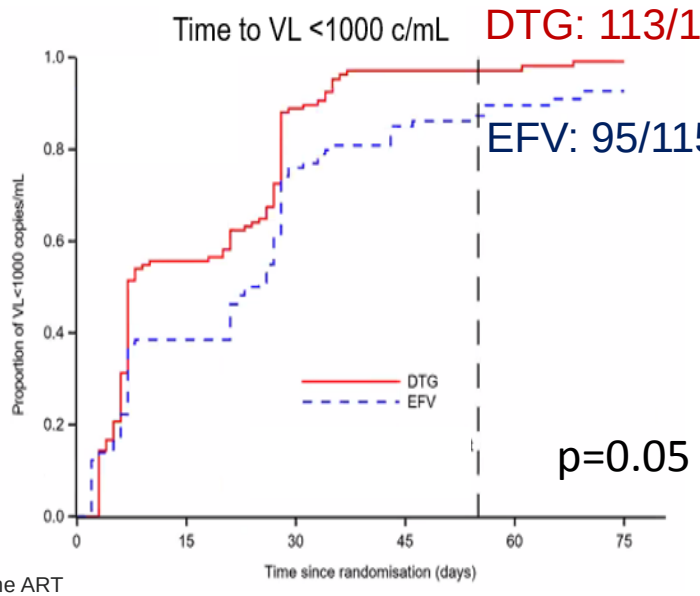
DolPHIN 2





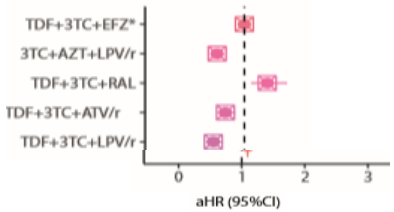
median time ART before delivery (55d)

- Preterm rates similar (17% DTG, 16% EFV, similar to Botswana 18%)
- 4 stillbirths – all DTG arm
- 3 infant infections at birth (thought IU infection) – all DTG arm

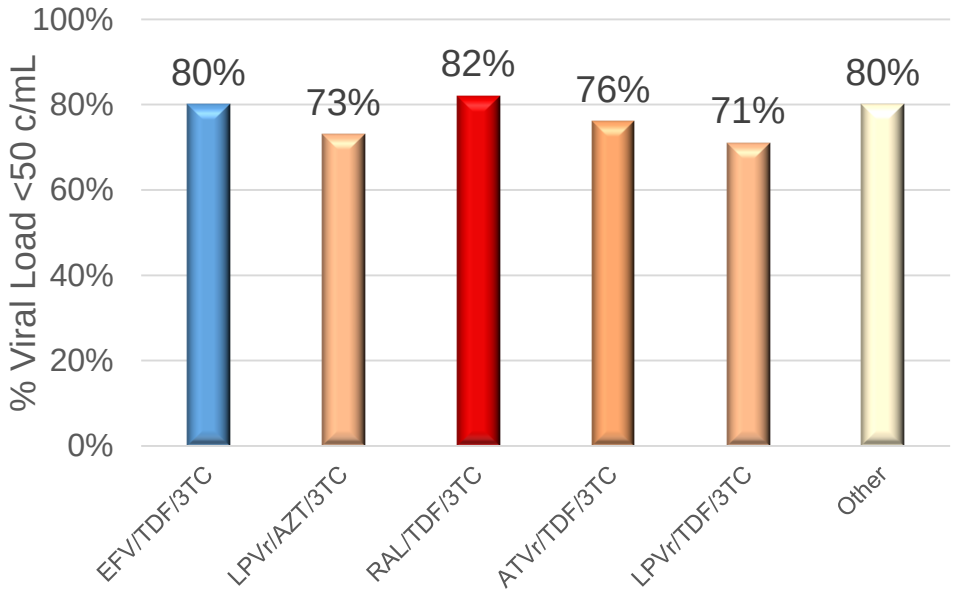
ART Regimen and Viral Suppression in Pregnant Women, Brazil

Pascom ARP et al. CROI 2019 Seattle, WA Abs. 760

- 8,539 pregnant women age >15 years (median 29 years); 38% ART naïve (63% RAL, 49% EFV), 42% ART >2 years.
- VL <50 c/mL 2-6 months after first prescription in pregnancy: overall 77%
  - Multivariate analysis, compared to EFV ART, 36% higher odds of suppression if on RAL (aOR 1.36, 1.1-1.7) and 49% lower odds suppression if using LPV/r (aOR 0.51, 0.4-0.7)



ART Regimen First Dispensed in Pregnancy

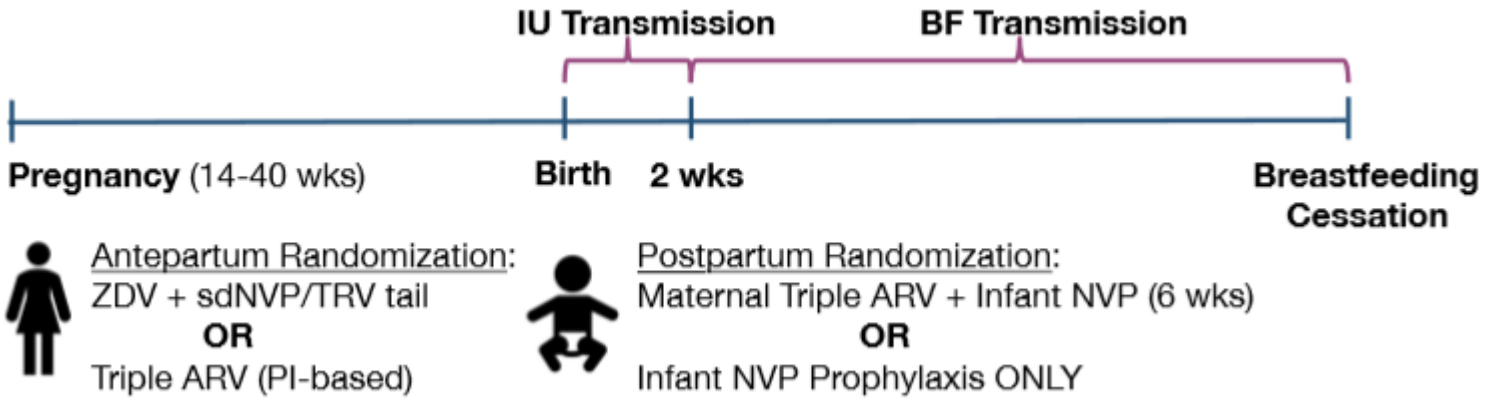


- Other factors associated with suppression:
  - Lower baseline VL
  - Higher baseline CD4
  - Older age
  - Higher education level
  - Lower time on ART

Maternal ARV Resistance and MTCT, PROMISE

Boyce CL et al. CROI 2019 Seattle, WA Abs. 769

PROMISE 1077 BF Antepartum and Postpartum Schema

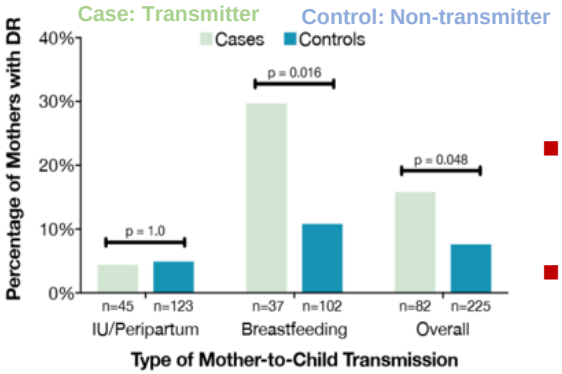


- Nested case-control study (1 transmitting:3 non-transmitting mother-infant pairs) to evaluate maternal/infant drug resistance (DR) and MTCT:
  - Cases: 85 transmitting mothers/infant:
    - 48 in utero/peripartum (IU)
    - 37 breastfeeding (BF)
  - Control: 254 non-transmitting mothers matched by delivery date and site

Maternal ARV Resistance and MTCT, PROMISE

Boyce CL et al. CROI 2019 Seattle, WA Abs. 769

Frequency maternal HIV DR at infant dx

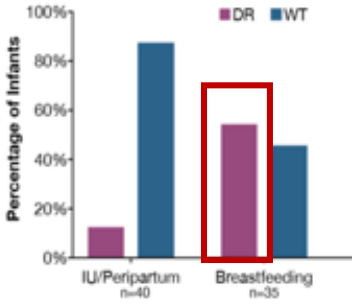


Covariate (Reference)	OR (95% CI)	p-value
Plasma Viral Load (<4log c/mL)	2.40 (1.38-4.22)	0.002
DR Genotype (WT Genotype)	2.35 (1.01-5.37)	0.043
Antepartum Triple ARV (None, Late Presenter)	0.24 (0.09-0.67)	0.006
Antepartum ZDV-monotherapy (None, Late Presenter)	0.48 (0.17-1.31)	0.148

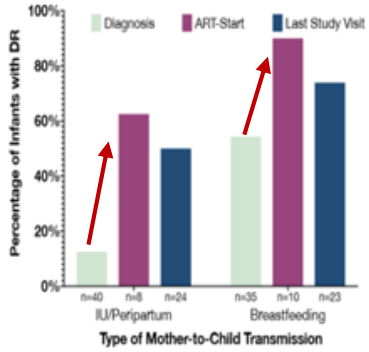
Complete antepartum treatment comparison for PROMISE trial: Fowler *et al.* N Engl J Med 2016;375:1726-37.

- Maternal DR in transmitters at infant dx was associated with MTCT during BF but not IU/peripartum.
- After adjusting for HIV RNA, maternal DR was significantly associated with ↑ MTCT.

Infant DR at diagnosis



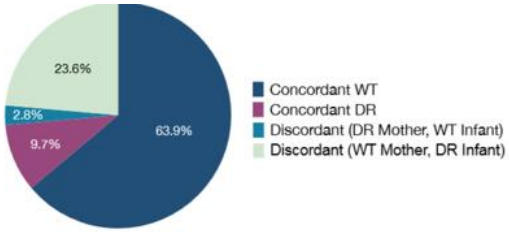
Emergence of Infant DR During BF



Median time dx and ART start
IU/IP: 6 wk (range 5-23)
BF: 10 wk (range 1-24)

Median time dx and last visit
IU/IP: 14 wks (range 1-204)
BF: 48 wks (range 1-92)

Concordance DR in mother and infant at infant dx (N=72)



- DR in infant at diagnosis was higher in infants diagnosed BF vs IU/IP.
- Comparing DR at diagnosis, ART start and last visit, DR emerged over time (exposure of infant to maternal ART via BM *or* infant NVP. prophylaxis *or* ART failure infant?).
- In those with DR, finding WT in mother and DR in infant at infant dx most common (suggesting DR arising de novo in infant).

Maternal HIV RNA After Delivery is Correlated with Infected Infant Pre-Treatment HIV RNA

Sakol-Mosethl M et al. CROI 2019 Seattle, WA Abs.797

- Data from 40 mother-infant pairs from the Early Infant Treatment Study enrolled at <7 days from delivery (median 2 d).
- All infants received sdNVP at birth and AZT BID per MOH protocol until HIV dx, when changed to ART.
- Maternal RNA done at infant enrollment (median 2 d PP); infant RNA at baseline prior to ART.
- Higher maternal RNA correlated with higher pre-treatment infant RNA.
- Lowest infant RNA values in those exposed IU to DTG.

ART exposure *in utero*	Median Duration of in-utero ART exposure (weeks) / [range]	Median Maternal HIV RNA (copies/ml) / [range]	Median Infant HIV RNA (copies/ml) / [range]	Correlation* r-value / p-value
No ART exposure (n=17) 42%	NA	64,072 [547,491512]	31,708 [<40, >10000000]	0.41 / 0.11
EFV-based ART (n=10) 25%	14 [1, 39]	10,259 [67, 144729]	1749 [1005, 1111950]	0.42 / 0.23
DTG-based ART (n=11) 27.5%	11 [1, 29]	56 [<40, 85697]	310[79, 389270]	0.88 / <0.001
LPV/r-based ART (n=2) 5%	NA#	29,085 [23912, 34257]	80,430 [17244, 143616]	NA#
Total (n=40)	2.5 [0, 40]	24,789 [<40, 491512]	11,335 [<40, >10000000]	0.63 / <0.001

* by Spearman's correlation , # not applicable because of small sample size (n=2).

HBV Viremia and Adverse Infant Outcome in Women with HIV/HBV Coinfection

Bhattacharya D et al. CROI 2019 Seatte, WA Abs. 41

- Retrospective testing maternal samples from HPTN 046 (extended infant NVP for prevention postnatal transmission, 2007-2010) for HBV viral load at L/D.
- Of 2016 women, 88 (4.4%) had HBV/HIV coinfection; evaluated association of high HBV VL with infant outcomes.

Outcome	HIV Alone (N=1953)	HIV/HBV (N=78) HBV $<10^6$ IU/mL	HIV/HBV (N=10) HBV $>10^6$ IU/mL	P value HBV $>10^6$ vs HIV
LBW	194 (10%)	5 (6%)	**3 (30%)**	**0.04**
Birth defect	83 (4%)	2 (3%)	**0**	NS
HIV infection	71 (4%)	0	**2 (20%)**	**0.01**
Infant death	75 (4%)	0	**0**	NS
HIV/LBW	254 (13%)	5 (6%)	**4 (40%)**	**0.02**

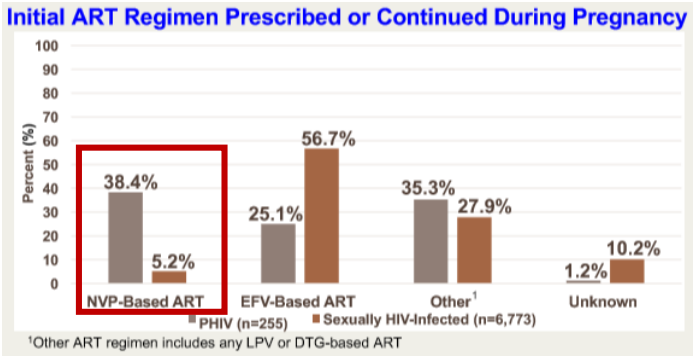
LBW: Covariates maternal age, CD4 at delivery, receipt of cART during pregnancy
Infection/death: Covariates maternal age, CD4 at delivery, receipt of cART during pregnancy, infant NVP assignment

- When compared to women with HIV alone, HIV/HBV coinfected women had association with infant LBW and HIV infection, adjusting for maternal CD4 and maternal cART.
- Reducing HBV VL may have benefit beyond prevention of HBV MTCT.

Adverse Birth Outcome in Women with HIV Acquired Perinatally vs Sexually, Botswana

Fennell C et al. CROI 2019 Seattle, WA Abs. 752

- Compared pregnancy outcome in 255 women with perinatal HIV vs 6,773 women with sexually-acquired HIV in birth surveillance study.
- Perinatal women younger (20 vs 24 years); more likely primagravida (77.6% vs 35.5%); & more likely receiving NVP-based ART in pregnancy.
- Only SGA more frequent with perinatal infection *unadjusted* analysis.
- Multivariate analysis, only NVP-ART associated with adverse outcome.



[1]Other ART regimen includes any LPV or DTG-based ART

	RR (95%CI)	aRR (95%CI)[1]
Preterm Delivery	1.09 (0.87, 1.37)	1.20 (0.93, 1.56)
Stillbirth	0.76 (0.31, 1.83)	0.90 (0.34, 2.34)
Neonatal Death	0.48 (0.12, 1.91)	0.53 (0.12, 2.31)
Congenital Abnormalities	0.83 (0.37, 1.85)	0.91 (0.38, 2.15)
LBW[2]	1.16 (0.90, 1.49)	0.94 (0.71, 1.25)
SGA	**1.33 (1.07, 1.65)**	**1.06 (0.83, 1.35)**

[1]Adjusted for initial ART regimen prescribed or continued during pregnancy, maternal age, gravida, occupation, and education
[2]LBW = Low birth weight (<2500g)

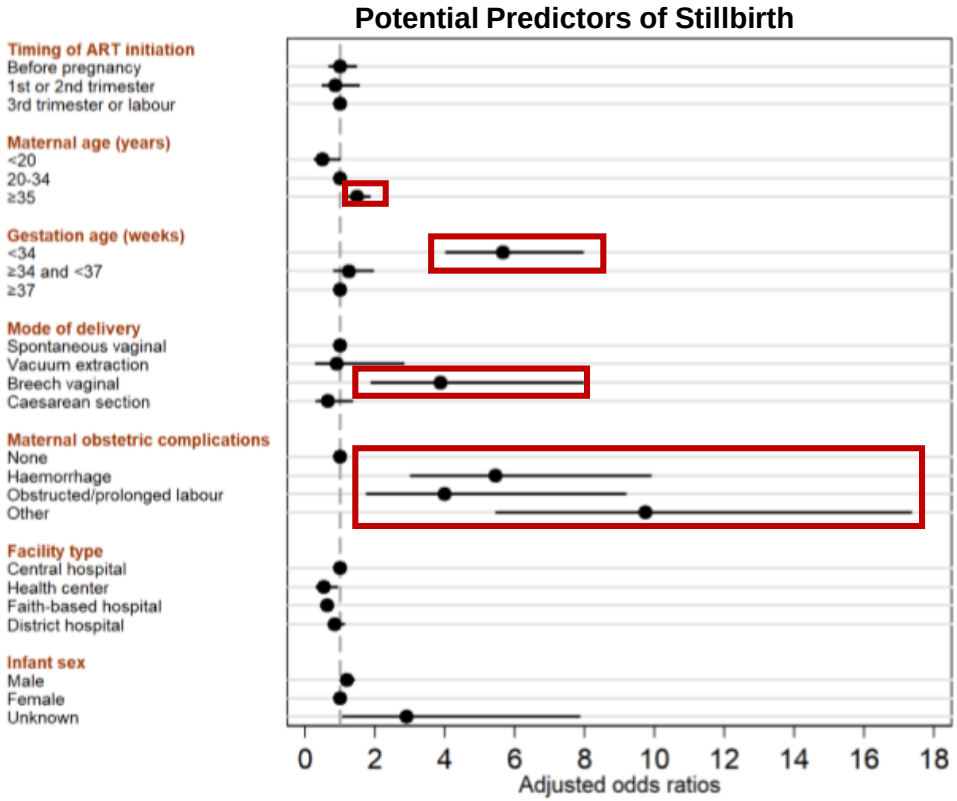
	Any Adverse Outcome[1,4] aRR (95% CI)	Any Severe Adverse Outcome[2,4] aRR (95% CI)
PHIV (n=255)	**1.13 (0.97, 1.32)**	**0.81 (0.57, 1.15)**
Maternal Age	1.00 (0.99, 1.01)	1.01 (0.99,1.05)
Gravida		
≥5	0.95 (0.77, 1.18)	0.77 (0.49, 1.19)
2-4	0.87 (0.80, 0.94)	0.72 (0.61, 0.85)
1	Reference	Reference
Education		
Tertiary/Secondary	0.93 (0.83, 1.05)	0.91 (0.71, 1.17)
Primary/None	Reference	Reference
Occupation		
Salaried	1.10 (0.93, 1.30)	0.85 (0.63, 1.16)
Non-Salaried	1.24 (1.06, 1.44)	1.08 (0.82, 1.43)
Student	Reference	Reference
Initial ART[3]		
NVP-Based ART	**1.33 (1.19, 1.49)**	**1.95 (1.58, 2.39)**
Other	Reference	Reference

[1]Any adverse outcomes include preterm delivery, small for gestational age, neonatal death, and stillbirth
[2]Any severe adverse outcomes include very preterm delivery (<32 weeks), very small for gestational age (<3rd %), neonatal death, and stillbirth
[3]Other ART Regimen includes any LPV, EFV, or DTG-based ART
[4]Adjusted for initial ART regimen prescribed or continued during pregnancy, maternal age, gravida, occupation, and education

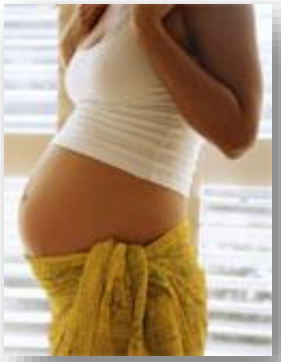
Timing Maternal ART and Stillbirth, Malawi

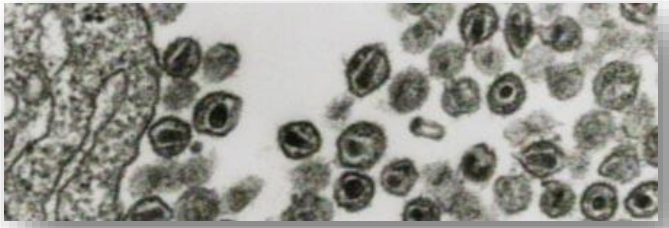
Msukwa MT et al. CROI 2019 Seattle, WA Abs. 754

- Evaluated rate stillbirth among women on ART who delivered singleton live birth or stillbirth at GA ≥28 wks between 2012 and 2015 at 20 clinics; overall rate stillbirth 2.5%. ART initiation stratified by:
  - ART before pregnancy: 5,961 (71%)
  - ART 1st/2nd trimester: 1,128 (14%)
  - ART 3rd trimester or labor: 1,291 (15%)



- Timing of ART initiation was not associated with stillbirth.
- Predictors of stillbirth: older maternal age (>35 years), delivery at <34 weeks gestation, breech vaginal delivery, and any maternal obstetric complication.



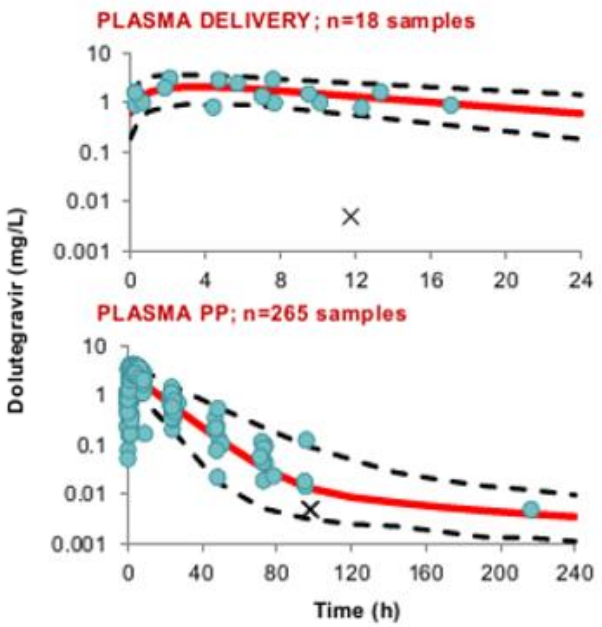


Dolutegravir and Other Integrase Strand Transfer Inhibitors (InSTI) in Pregnancy

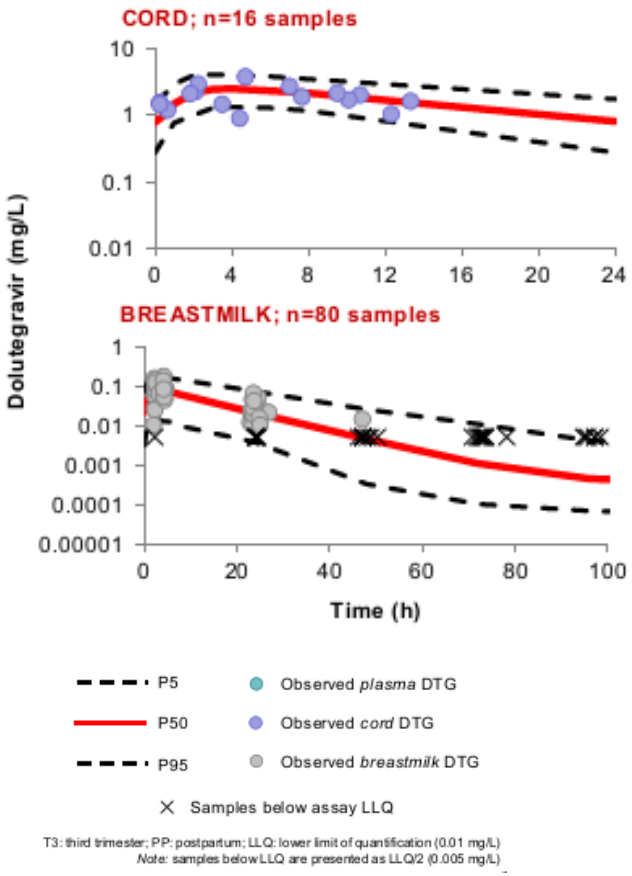
DTG in Breast Milk - DolPHIN

Dickinson L et al. CROI 2019 Seattle, WA Abs. 757

- RCT PK study of DTG vs EFV ART in late pregnancy (>28 weeks).
- Evaluated maternal plasma, cord blood and breast milk DTG levels, used for population PK modeling.



(note: switch to EFV 2wk PP, sampled at 1-3 days post switch)



Median cord AUC_{0-24} was 41.2 mg.h/L - **123%** that of maternal plasma at delivery

Average DTG milk concentration was 0.05 mg/L; median breast milk AUC_{0-24} was 1.2 ng.h/L, **3.3%** maternal plasma at 1-3 d post switch to EFV; average daily infant dose estimated 2.2 ug/kg/day.

Birth Defect Surveillance Uganda – Neural Tube Defects

Barlow-Mosha et al. CROI 2019, Seattle Abs. 743

- 4 hospital defect surveillance: 69,766 births (6,494 to HIV+ women, 80% on TDF-3TC-EFV (**no DTG used in country yet**)

	#	HIV-	HIV+	NTD% births HIV- women	NTD% births HIV+ women
NTD	71	66	5	0.11% (0.08-0.13)	0.07% (0.03-0.17)

Tsepamo NTD prevalence:

HIV- women: 0.09% (95% 0.07-0.12%)

HIV+ EFV preconception: 0.05% (95% CI 0.02-0.15%)

Phenotypes of the 71 NTD:

- Spina Bifida: 41 (58%)
- Anencephaly: 19
- Encephalocele: 12

InSTI Exposure at Conception and NTD French Perinatal Cohort

Sibiude J et al. CROI 2019 Seattle, WA Abs.744

- French Perinatal Cohort: 808 infants InSTI exposure (87% RAL, 7% DTG):
  - G1: exposed conception (301); G2, G3: started pregnancy as 1st or 2nd line (intensification) (183, 324, respectively)
- Within groups, matched 1:1 InSTI unexposed infant matched by other drugs, ethnicity, center, year delivery and GA at ART start

Fig 1 – Selection of study population

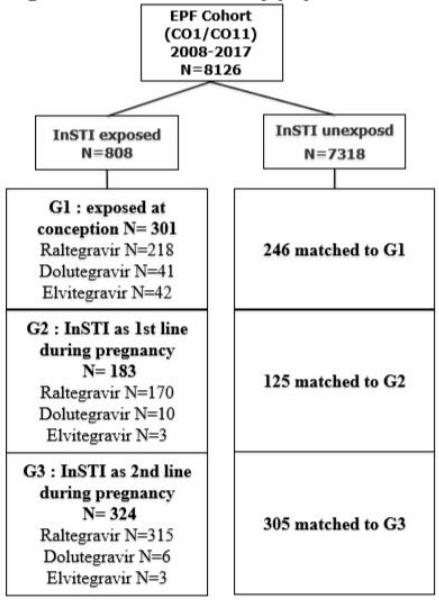


Table 2 – Perinatal outcomes according to exposure group

Perinatal outcomes	Exposed at conception G1 N=301		InSTI as 1st line during pregnancy G2 N=183		InSTI as 2nd line during pregnancy N=324		
	n	%	n	%	n	%	p[a]
Birth defect	18	**5.8**	5	**2.7**	9	**2.7**	0.09
Stillbirths	7	**2.4**	2	**1.1**	1	**0.3**	0.07
Preterm Birth	50	**16.8**	22	**12.1**	47	**14.6**	0.36
Birthweight < 3rd centile	9	**3.0**	6	**3.4**	20	**6.2**	0.13
Length < 3rd centile	12	**4.4**	9	**5.5**	14	**4.5**	0.86
Head circumference <3rd centile	8	**2.9**	8	**4.8**	11	**3.5**	0.56

[a] Chi2 test

- Rate birth defects and stillbirths trend to be ↑ in InSTI conception vs during pregnancy but not significant
- No NTD with InSTI

Table 3– Perinatal outcomes: comparison of InSTI-exposed and matched pregnancies

Perinatal outcomes	InSTI-exposed matched		InSTI-unexposed matched			InSTI-exposed unmatched	
	n	%	n	%	p[a]	n	%
Exposed at conception (G1)							
	N=246		N=246			N=55	
Birth defect	14	**5.7**	7	**2.9**	0.13	4	**7.3**
Stillbirth	6	**2.5**	6	**2.5**	1	1	**1.9**
Preterm birth	41	**16.8**	39	**16.1**	1	9	**17.0**
Unexposed to any ART at conception. InSTI as 1st line during pregnancy (G2)							
	N=125		N=125			N=58	
Birth defect	4	**3.2**	10	**8.0**	0.12	1	**1.7**
Stillbirth	2	**1.6**	1	**0.8**	0.57	0	**0.0**
Preterm birth	16	**12.8**	14	**11.2**	0.70	6	**10.5**
InSTI as 2nd line during pregnancy (G3)							
	N=305		N=305			N=19	
Birth defect	8	**2.6**	14	**4.6**	0.21	1	**5.6**
Stillbirth	0	**0.0**	0	**0.0**	1	1	**5.3**
Preterm birth	45	**14.8**	41	**13.5**	0.65	2	**10.5**

[a] McNemar test for matched data

- In case-control InSTI (any time exposure) vs non-INSTI did not differ in birth defects, stillbirth or PTD.

Merck Review of Raltegravir-Exposed Pregnancies

Shamsuddin HH et al. CROI 2019, Seattle WA Abs. 745

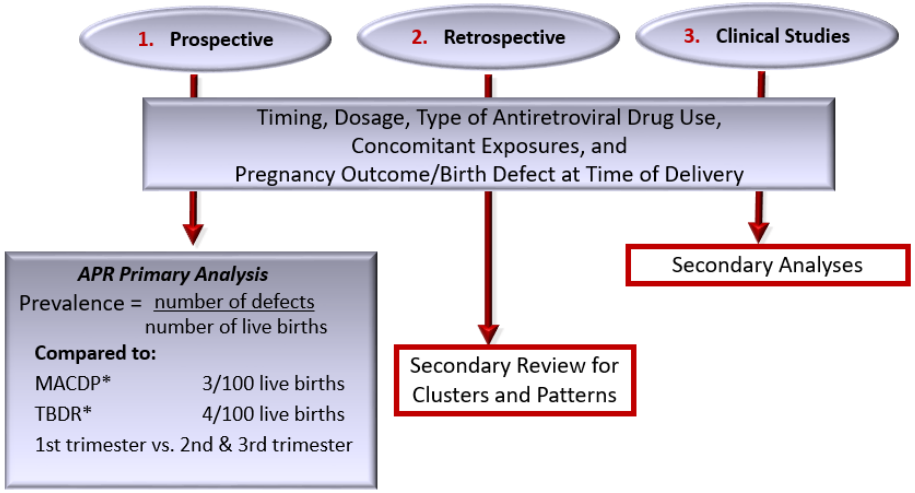
- Merck review of database on 2426 pregnancies with RAL exposure, including data from:
  - Merck safety database, including APR
  - UK/Ireland National Surveillance HIV in Pregnancy and Childbirth (NSHPC)
  - French Perinatal Cohort (includes data from abstract 774)
- Prospective: 1991 cases, with 456 periconception RAL: no NTD
- Retrospective: 435 retrospective reports (no denominator), 4 NTD cases – 1 with periconception exposure; also 1 encephalocele with periconception exposure (APR)
- NSHPC *(Rasi V et al. JAIDS 2018 Nov 20 epub)* also reported on 33 EVG exposures → 26 preconception → no birth defects

Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al. CROI 2019 Seattle, WA Abs. 747

- Evaluation of the prevalence of NTD with InSTI exposure in prospective and retrospective components of the APR (through 31 Jul 2018).

APR Methods



* MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry

- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.
- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).

- Prospective APR=primary analysis: Clinicians register pregnant women (no identifiers) with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data.
- Retrospective APR=secondary review: Reports of exposed pregnancies after pregnancy outcome is known; no denominator.


THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT

Prospective Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al. CROI 2019 Seattle, WA Abs. 747

- 1,193 live births with InSTI exposure at any time in pregnancy; 604 periconceptional exposure, including 174 DTG, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with InSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester).
- There were **no NTD** among **prospective cases** for any InSTI drug.

	Earliest Trimester of Exposure – Prospective Cases		
	Periconception	1st Trimester	2nd/3rd Trimester
	Defects/live birth	Defect/live birth	Defects/live birth
Exposure to any INSTI	16/604 (2.6%)	4/135 (3.0%)	17/452 (3.8%)
Dolutegravir	6/174 (3.4%)	2/55 (3.6%)	4/137 (2.9%)
Elvitegravir	5/186 (2.7%)	0/27 (0%)	0/57 (0%)
Raltegravir	5/244 (2.0%)	4/68 (5.9%)	13/290 (4.5%)

Can be more than one organ system for a defect

No Neural Tube Defects

CNS: 2: 1 (lissencephaly – neural migration disorder) with preconception DTG; 1 (ventriculmegaly) with 2nd/3rd trimester DTG exposure.

Face, ear, face, neck: 2
Cleft lip/palate: 2
Respiratory: 1
Cardiac/circulatory: 11
Lower GI: 1
Renal: 4
Musculoskeletal: 8
Chromosome abnl: 2
Other organ systems: 1
Specified syndromes 1

Retrospective Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al. CROI 2019 Seattle, WA Abs. 747

- There were 7 NTD plus 2 encephalocele cases reported with InSTI exposure in **retrospective reports** to the APR (reported after delivery with defect that has occurred, no denominator, not included in prospective data review).

Summary of Retrospective NTD and Encephalocele Cases with InSTI Drug Exposure through July 2018	
Dolutegravir [timing of exposure, country]	**Raltegravir** [timing of exposure, country]
Anencephaly [P, BW]	Myelomeningocele [P, US]
Iniencephaly [P, BW]	Myelomeningocele [T2, UK]
Myelomeningocele [P, BW]	Myelomeningocele [unk, US]
Meningocele [P, US]	Encephalocele [P, US]
Encephalocele [P, BW]	
P = periconception, T2 = second trimester, unk = unknown; BW = Botswana, PR = Puerto Rico, UK = United Kingdom, US = United States	

Pharmacovigilance Databases and NTD

Hill A et al CROI 2019, Seattle, WA 2019 Abs. 747

- NTDs analysed for 4 INSTI (DTG, RAL, EVG, BIC), 2 PI (DRV, ATV), and 2 NNRTI (NVP, EFV) in 4 PV databases with data available online: FDA Adverse Event Reporting Systems (FAERS); WHO VigiAccess (WHO); European EudraVigilance (EU), UK Medicines Health Regulatory Authority (MHRA)
- Adverse drug reactions in the System Organ Class "Congenital or Familial Disorders" searched for potential NTDs (NTD, spina bifida, meningocele, meningomyelocele, anencephaly, iniencephaly, and encephalocele).

Number of NTD cases

	Database	FDA FAERS	EU Eudra Vigilance	WHO VigiAccess	UK MHRA
InSTI	DTG	6	0	8	0
InSTI	RAL	5	4	17	2
InSTI	EVG	1	0	2	0
InSTI	BIC	0	0	0	0
PI	DRV	3	3	16	3
PI	ATV	6	2	9	0
NNRTI	EFV	13	5	34	0
NNRTI	NVP	14	6	30	3

→As would be expected, NTD seen with multiple ARVs, esp those with more frequent use in population.

→Lack of agreement on #s between databases – and probable duplications

Fetal and Infant Growth Similar Regardless of HIV Exposure or DTG vs EFV ART Exposure

CROI 2019 Seattle, WA Abs. 750 and 751

- *Abs. 750 Masasa et al. Botswana*
  - Ultrasound fetal biometry in 435 pregnant women 16-36 weeks GA
    - 167 HIV-uninfected (mean 26 wk GA)
    - 268 HIV (mean 28 wk GA) (176 DTG 92 EFV ART)
  - No significant differences between uninfected and HIV+ women on ART
  - No significant differences HIV+ women on DTG and EFV ART

HIV+ vs HIV-uninfected mothers

FETUSES	HIV/ARV-exposed	HIV/ARV-unexposed	*p* value
GA at ultrasound, weeks	28 (25, 31)	26 (25, 29)	*0.01*
Head circumference z score	-0.30 (-1.04, 0.28)	-0.26 (-0.97, 0.39)	*0.15*
Biparietal diameter z score	0.09 (-0.63, 0.82)	0.07 (-0.64, 0.68)	*0.22*
Abdominal circumference z score	0.00 (-0.40, 0.82)	0.00 (-0.54, 0.84)	*0.57*
Femur length z score	1.45 (0.67, 2.05)	1.24 (0.45, 2.04)	*0.22*

HIV+ mothers on DTG vs EFV ART

FETUSES	TDF/FTC/DTG (n=176)	TDF/FTC/EFV (n=92)	*p* value
GA at ultrasound, weeks	28 (25, 31)	28 (25, 30)	*0.43*
Head circumference z score	-0.39 (-0.98, 0.30)	-0.62 (-1.11, 0.14)	*0.15*
Biparietal diameter z score	0.14 (-0.60, 0.89)	0.34 (-0.35, 0.71)	*0.27*
Abdominal circumference z score	0.31 (-0.42, 0.74)	0.34 (-0.35, 1.03)	*0.15*
Femur length z score	1.42 (0.56, 1.96)	1.49 (0.82, 2.15)	*0.24*

- *Abs. 751 Kgole S et al. Botswana*
  - Birth anthropometry in 463 infants:
    - 275 HIV-exposed, 158 DTG/117 EFV
    - 188 HIV-unexposed
  - No significant difference in WAZ or LAZ between HEU/HUU or DTG/EFV.

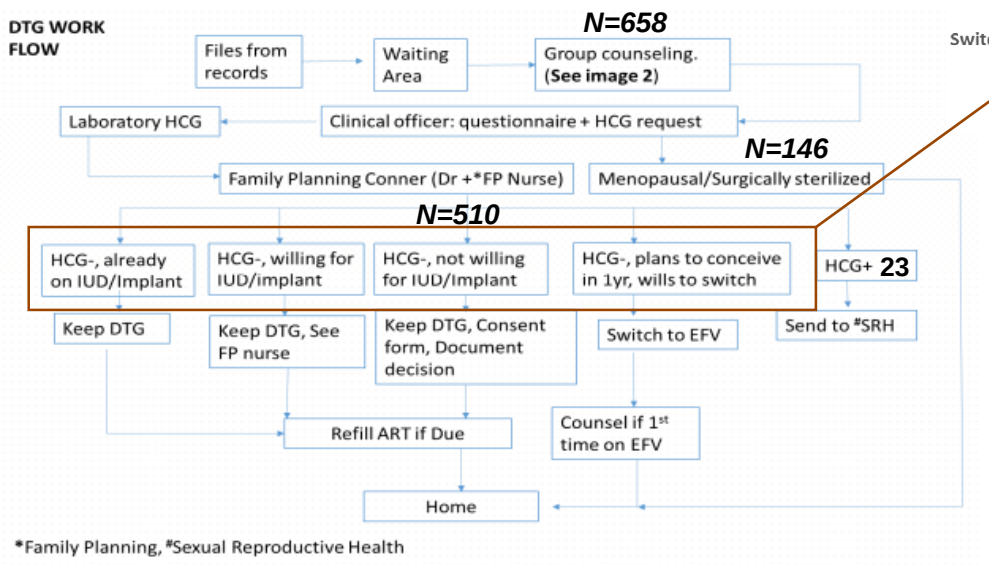
	HEU	HUU	P value
Mean WAZ	-0.13	0.00	0.20
Mean LAZ	+1.07	+1.17	0.51
	DTG	**EFV**	**P value**
Mean WAZ	-0.09	-0.18	0.45
Mean LAZ	+1.16	+0.95	0.28

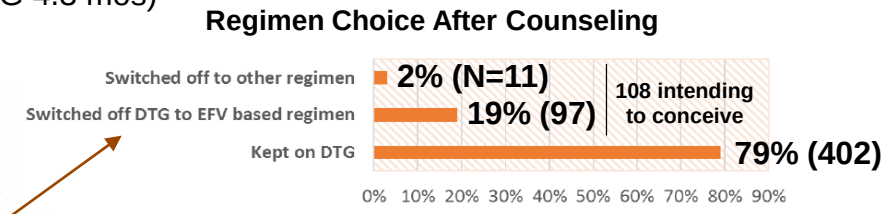
Ugandan Clinic Experience Following Potential NTD Signal with Preconception Dolutegravir

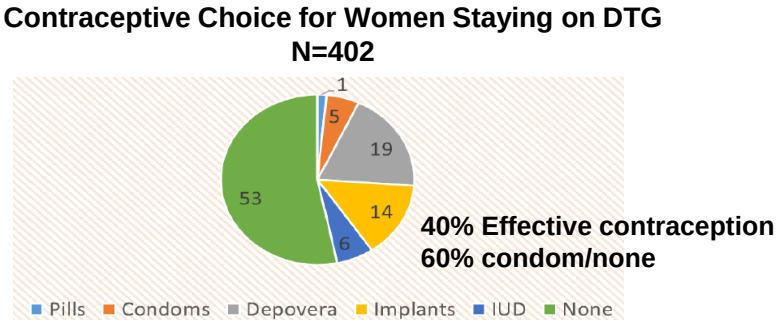
Arnold AS et al. CROI 2019 Seattle, WA Abs. 748

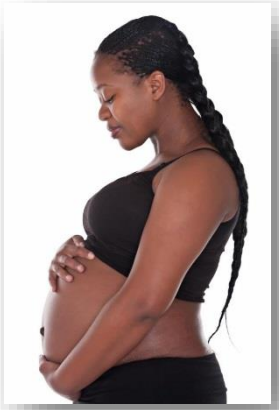
- Following clinical safety alert, clinic response plan developed; all women <55 years on DTG identified and contacted → group counseling session (15/grp)
- Women childbearing potential referred for pregnancy testing, evaluation of pregnancy intention in next 12 mos, and effective FP offerred.
- Women intending to conceive offered EFV-ART; women could choose to remain on DTG without FP signing informed choice declaration.

9% (692/7963) were women on DTG, 95% (658) reviewed by 9/2018
510 women of reproductive potential (med age 37 yr, med duration DTG 4.3 mos)
5% (23/510) HCG+, all initial ultrasounds no deformities







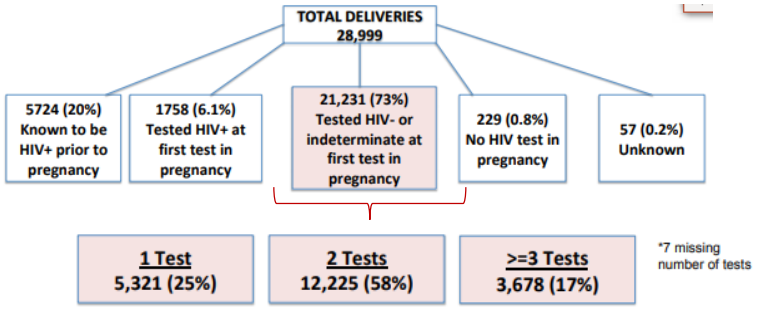


Maternal Health Issues

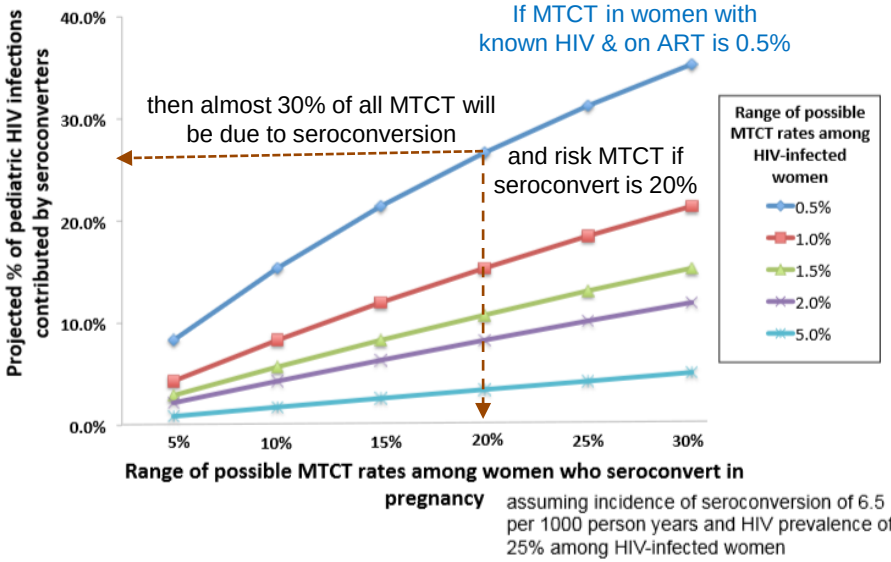
Incident Infection in Pregnancy, Botswana

Mayondi GK et al. CROI 2019 Seattle, WA Abs. 733

- As part of Tsepamo birth surveillance study, HIV status abstracted from all women delivering 8 hospitals Botswana.
- Analyzed women not known to be infected at start of pregnancy for seroconversion.



- 39 seroconversions in 15,490 pregnant women with ≥2 tests = HIV incidence 6.5/1000 person years
- Median GA at seroconversion was 29 weeks; 90% started ART before delivery.
- Among 5,547 women without a 3rd trimester test, estimate 10 seroconversions may have been missed due to lack of testing



- As MTCT rates among women with *known* HIV infection decrease, the proportion of MTCT due to seroconversion during pregnancy will be increasingly important

Prevalence of STI in HIV+ and HIV-Uninfected Pregnant Women, South Africa

Davey DJ et al. CROI 2019 Seattle, WA Abs. 1003

- Cross-sectional study 242 pregnant women attending public ANC in Cape Town (106, 44% HIV+), testing for STI at 1st ANC visit.
- Overall STI prevalence 33%: HIV+ 39%, HIV- 28% (p=0.04)

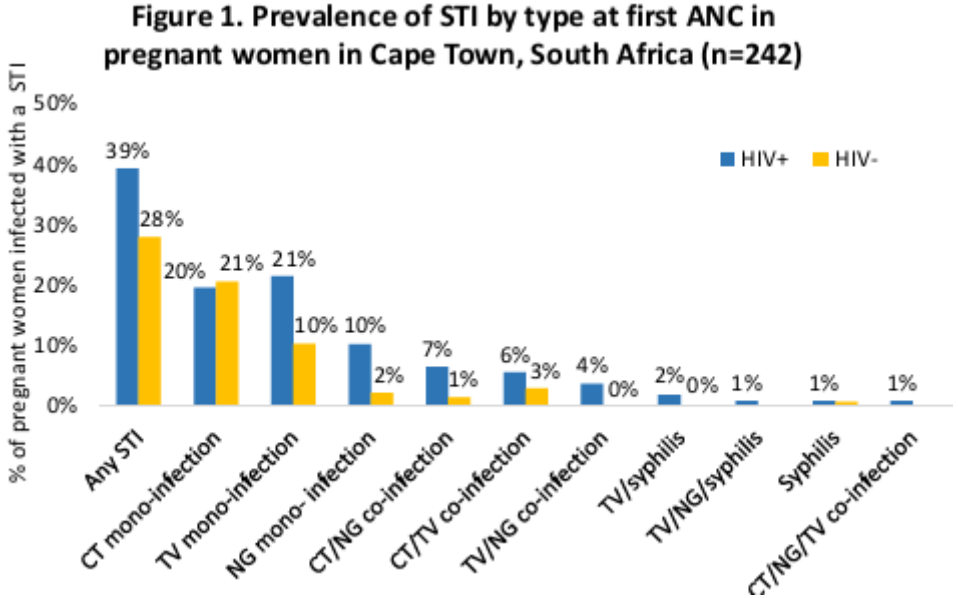


Table 2. Factors associated with sexually transmitted infection diagnosis in pregnant women at first antenatal care visit (n= 242), Cape Town, 2018

	Total, n (%)	Any STI + @ 1st ANC, n (%)	No STI @ 1st ANC, n (%)	OR (95% CI)	Bivariate p-value	Adjusted OR (aOR; 95% CI)
Total	242	80 (33)	162 (67)			
Sociodemographic characteristics						
Age (median, IQR)	29 (24-34)	28 (24-33)	30 (25-35)	**0.95 (0.91 - 1.00)**	**0.05**	**0.95 (0.90 - 1.00)**
Gestational age in weeks (median, IQR)	19 (13-24)	20 (14-24)	18 (13-23)	1.03 (0.98 - 1.07)	0.16	1.03 (0.99 - 1.08)
Relationship with father of child						
Married/Cohabiting	115 (47)	27 (35)	88 (53)	Reference		
Not married/ Non-cohabiting	120 (50)	47 (60)	73 (45)	**2.09 (1.19 - 3.69)**	**0.02**	**2.19 (1.16-4.12)**
No relationship	7 (3)	4 (5)	3 (2)	**4.34 (0.91 - 20.63)**	**0.06**	**3.20 (0.63 - 16.09)**
Clinical characteristics						
HIV Status						
HIV Negative	135 (56)	38 (28)	97 (72)	Reference		
HIV Positive	107 (44)	42 (39)	65 (61)	**1.65 (0.96 - 2.83)**	**0.07**	**1.89 (1.02 - 3.67)**
Any STI symptoms						
No symptoms at all	183 (75)	51 (66)	132 (80)	Reference		
Symptoms a few days ago	16 (7)	11 (14)	5 (3)	**5.50 (1.82 – 16.61)**	**0.002**	**6.60 (2.08 - 20.95)**

* bold is for p-value < 0.10

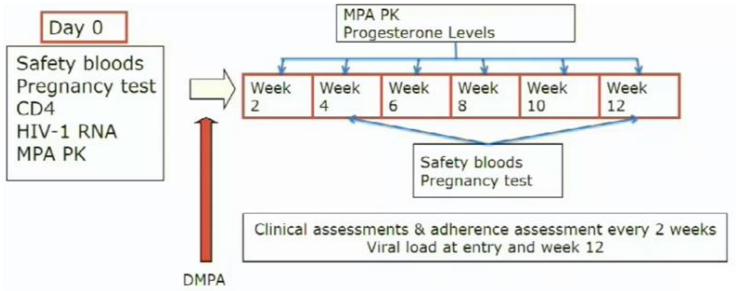
- Factors associated with STI, adjusting for GA and age: unmarried/not cohabiting; HIV infection; recent STI symptoms.

Potential Concern for Timing of DMPA Injection in Women Treated for HIV and TB

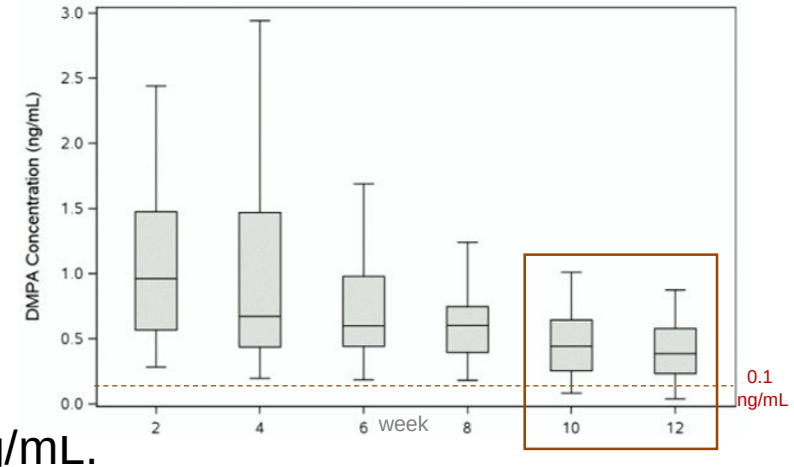
Mngqibisa R et al. CROI 2019 Seattle, WA Abs. 78

- Study to evaluate whether concurrent use of EFV and RIF will decrease clearance of MPA resulting in potential reduced contraceptive efficacy.
- Estimate optimal dosing frequency for DMPA based on target serum MPA level of >0.1 ng/mL.

42 women with HIV/TB, not pregnant, stable on EFV ART >4 weeks , & on continuation phase of TB treatment (INH/RIF)



Median MPA levels weeks 2-12



- MPA levels ≥0.1 ng/mL all through week 8.
- At week 10, 1 woman (2.4%) had level <0.1 ng/mL.
- **At week 12, 5 women (11.9%) level <0.1 ng/mL.**
- However, progesterone stayed low suggesting no ovulation.
- Consider shortening DMPA interval from 12→8-10 week with EFV/RIF coadmin?

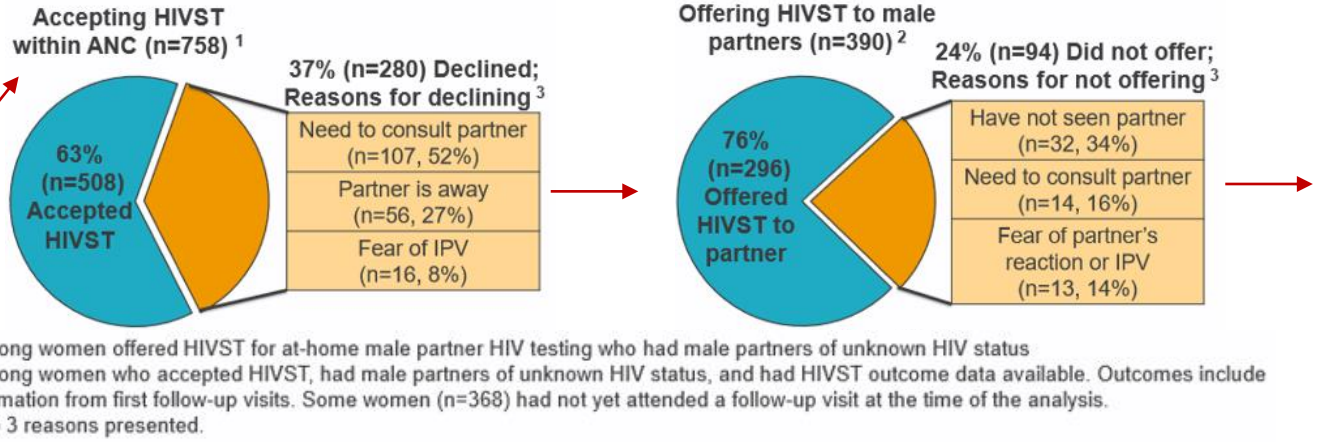
PMTCT Cascade - Male Partner Testing

Self-Tests for At-Home Partner Testing for Women in ANC, Kenya

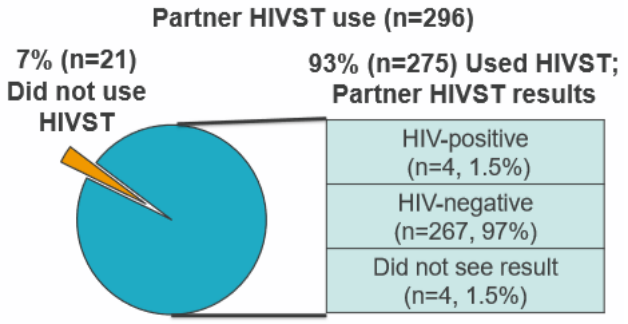
Pintye J et al. CROI 2019 Seatte, WA Abs. 926

- Self-tests for at-home partner self-testing offered to 758 HIV-uninfected women seeking routine ANC at 10 facilities in Kenya.
- Instructed on use and received ≥2 or more oral-fluid tests.
- Data on outcomes assessed at 1 month in person FU visit.

Table 1. Characteristics of pregnant HIV-uninfected women offered HIVST (N=1871)	
	n (%) or Median (IQR)
Male partner HIV status	
HIV-negative	1019 (54%)
Unknown	758 (41%)
HIV-positive	82 (4%)
No partner	12 (1%)
Age, years	24 (20-29)
Gestational age, weeks	24 (20-28)
Education, years	10 (8-12)
Married	1611 (87%)



[1] Among women offered HIVST for at-home male partner HIV testing who had male partners of unknown HIV status
[2] Among women who accepted HIVST, had male partners of unknown HIV status, and had HIVST outcome data available. Outcomes include information from first follow-up visits. Some women (n=368) had not yet attended a follow-up visit at the time of the analysis.
[3] Top 3 reasons presented.



- 63% of women with partner with unknown status accepted HIVST kits; of 390 with FU data, 76% had offered to partner; of 296 with partner data, 93% had tested.

Randomized Trial on Index HIV Self-Testing for Partners of ART Clients, Malawi

Dovel K et al. CROI 2019 Seattle, WA Abs.93

New ART clients ≥15 yrs with partner ≥15 yr, unknown HIV status, no hx IPV, lives in catchment area.

Randomized 1:2.5

Standard of Care (N=135): Passive partner referral slip

Index take slip home to partner; slip asks partner to attend nearest health facility; disclosure counseling

Index HIVST (N=349): Oraquick HIV ST

Index given SOC and HIVST kit; demonstration of HIVST, local tailored HIVST instructions; counseling

Sites: 3 district hospitals
Data Collection: March 2018-January 2019
- ART Client: Baseline and follow-up survey
- Partner (Index HIVST only): follow-up survey
- Medical Chart Review: 6-month follow-up

Outcome Measures

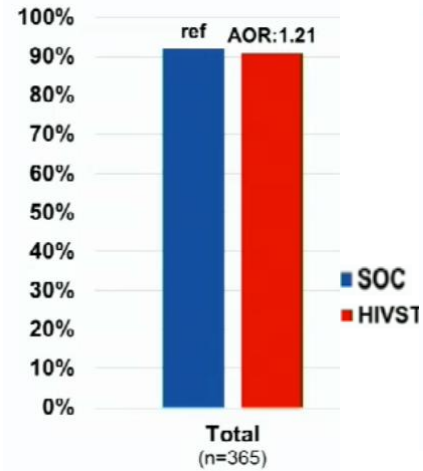
Data Source	Outcome
ART Client: 4-week follow-up survey	HIV testing, positivity rate, adverse events (self-report)
Partner (Index HIVST): 4-week follow-up survey	Usability (self-report)
Medical Chart Review	6-month ART initiation

- 365 ART clients completed FU survey (75% retention)
  - 107 SOC
  - 258 HIVST
- 161 partners completed FU survey (62% response rate)

Partner HIVST Acceptable and Increased Testing and Reached Men and Youth But ART Initiation Suboptimal

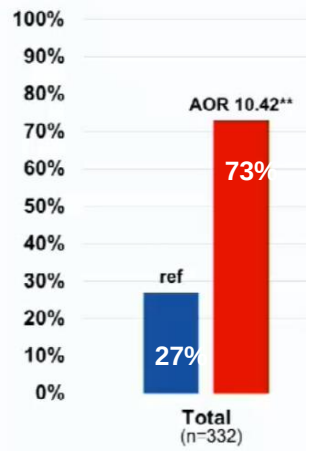
Dovel K et al. CROI 2019 Seattle, WA Abs.93

Distributed to partner



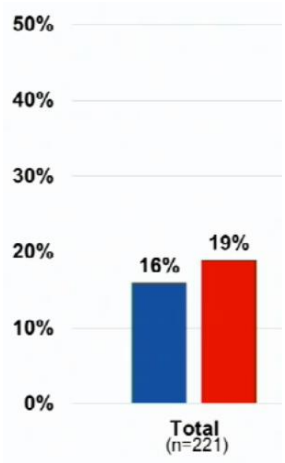
Similar partner distribution

HIV testing in partners



More partners tested

HIV+ partner test



Similar HIV+ prevalence

6-month ART initiation, medical chart review: (n=23 facilities)

Population	SOC	HIVST
Total	3/4 (75%)	7/30 (23%)
Male Partner	3/4 (75%)	6/27 (22%)
Female Partner	0/0 (0%)	0/1 (0%)
Youth (15-24)	0/0 (0%)	1/2 (50%)

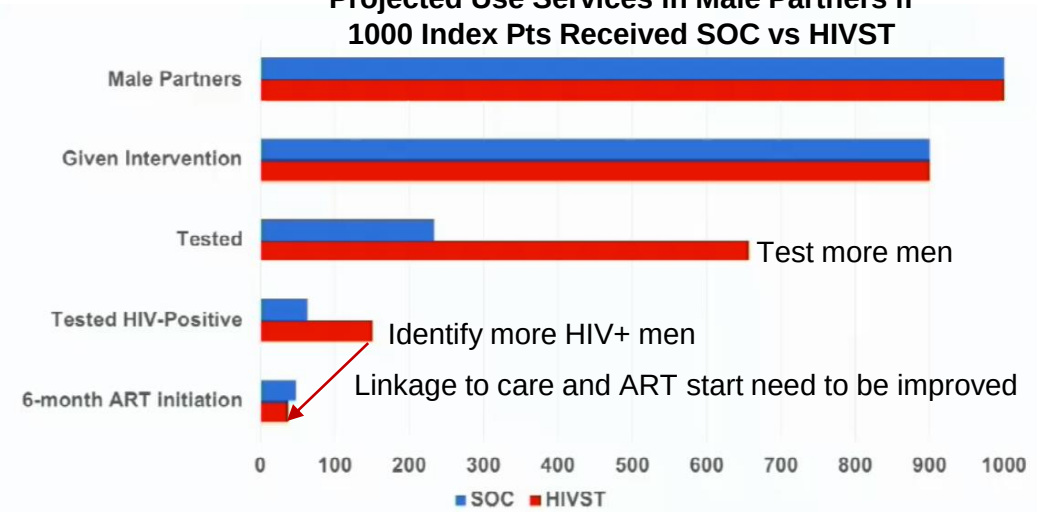
Partner return for ART start poor (23%)

Reported by index partners who used HIVST (n=122)

Variable	Total	Female Partner	Male Partner
ART client helped with HIVST	65% (79/122)	76% (31/41)	59% (48/81)
Unable to interpret result	8% (10/122)	5% (2/41)	10% (8/81)
Difficulty with:			
Understand HIVST instructions	16% (20/122)	22% (9/41)	14% (11/81)
Trusting accuracy of results	7% (8/122)	5% (2/41)	7% (6/81)
Accepting results	8% (10/122)	7% (3/41)	9% (7/81)
Keeping results private	1% (1/122)	2% (1/41)	0% (0/81)

65% partners needed help and 8% couldn't interpret

Projected Use Services in Male Partners if 1000 Index Pts Received SOC vs HIVST



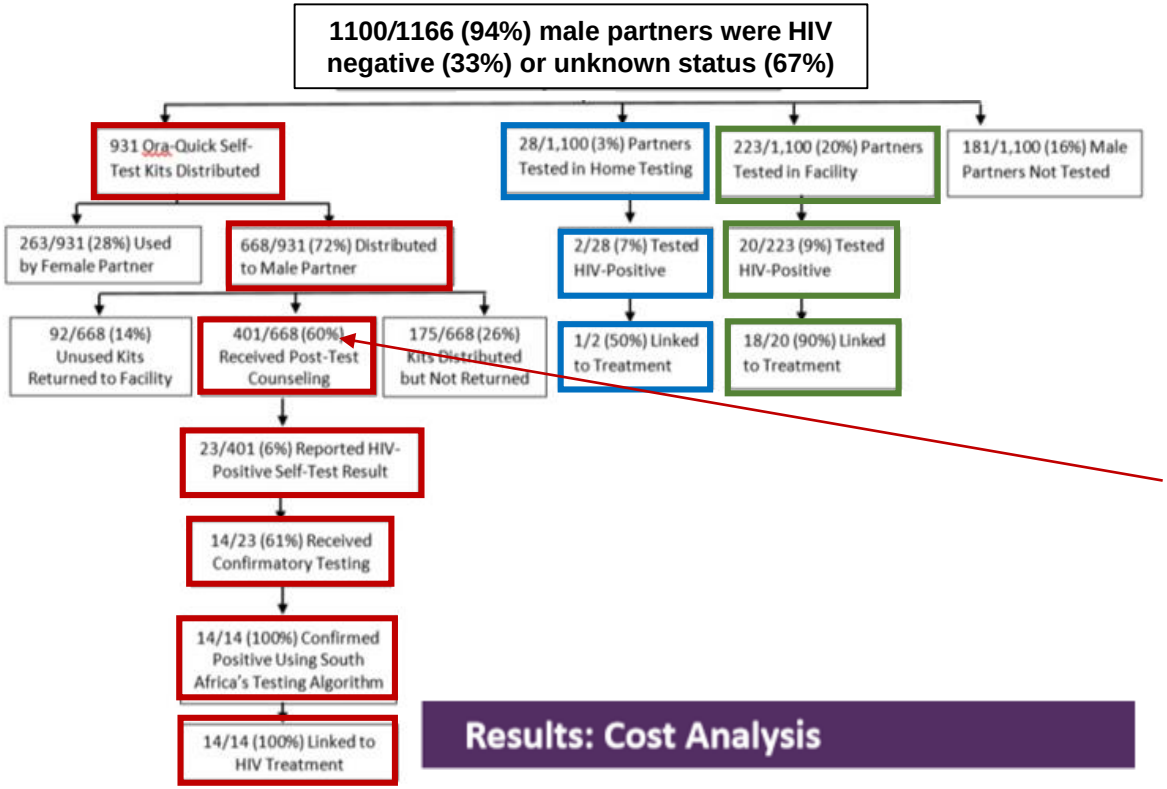
Outcome and Cost of Three Methods to Increase Male Partner Testing, South Africa

Medley A et al. CROI 2019 Seatte, WA Abs. 928

- 1,100 pregnant women seen at large health facility in South Africa with partner HIV- or unknown status offered 3 options for partner testing, Jan 2017-Oct 2017:
  - Facility-based testing through invitation/workplace letters
  - Home-based testing by trained counselor
  - HIV self-testing taking up to 3 Ora-Quick self-test kids for themselves/partners
- Incentives to encourage men to receive post-test counseling:
  - Asked to send free “call me back” text to counselor after self-test → counselor returns call, collects test result and provides counseling ; up to 25 rand (US $2) free airtime vouchers
  - If HIV+, linked to treatment; if HIV-, linked to VMMC

Outcome and Cost of Three Methods to Increase Male Partner Testing, South Africa

Medley A et al. CROI 2019 Seatte, WA Abs. 928



- Women: mean age 28 years, 72% single, 37% 1st pregnancy
- HIV prevalence 21% in women
- Facility: 223 men tested, 20 (9%) HIV+, 18 linked to care
- Home: 28 men tested, 2 (7%) HIV+, 1 linked to care
- Self test: 668 men tested - even with incentives, only 60% received post-test counseling, 23 (6%) self report HIV+, 14 got confirmatory testing, all linked to care

Results: Cost Analysis

Table 1. HIV Testing Costs and Outcome by Method*, US$ 2017

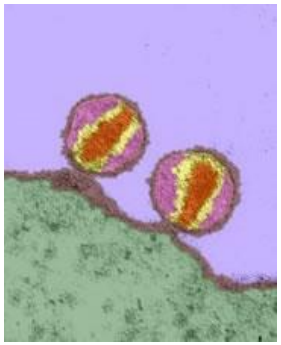
	Facility	Home	HIVST
Cost per New Confirmed diagnosis	$ 355	$ 1038	$ 2350

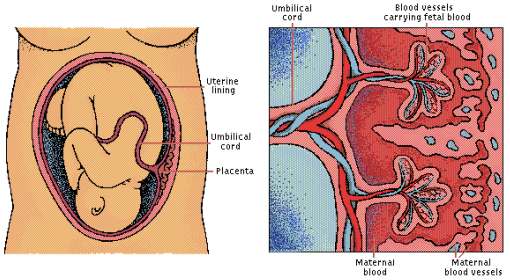
*Time horizon for cost evaluation of facility- and home-based testing methods is Aug. 2015 to Sep. 2016, prior to introduction of HIVST option. Time horizon for HIVST is Jan. to Oct. 2017.

Table 2. Costs across the HIV Self-Testing Cascade, US$ 2017

	Number of...	Cost per...
HIV ST kits distributed	931	$35
HIV ST kits distributed to male partner	668	$49
Partners used ST kit and received post-test counseling	401	$82
Partners self-reporting positive ST	23	$1,431
Partners confirmed positive and linked to treatment	14	$2,350

- While HIV self-testing most popular, also most expensive per HIV dx; need operational research to improve linkage to confirmatory testing and care.





HIV- and ARV-Exposed Uninfected Children

SHINE Trial Presentations

Abs. 42, 784, 790, 791

- SHINE: 2x2 factorial trial community cluster-based RCT compared effect of improved infant feeding, improved hygiene, or both vs SOC on outcomes, including growth and neurodevelopment.
- Women were eligible if they lived permanently in trial clusters (catchment area of 1-4 village health workers) and were confirmed pregnant. Clusters randomized 1:1:1:1 to:

Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial (N=726 HIV-positive women)

Control Standard of Care (SOC)	**IYCF** Infant and Young Child Feeding
WASH Water and Sanitation Hygiene	**IYCF + WASH**

Control: VHW encouraged early ANC, PMTCT uptake and EBF

IYCF: VHW visited with interactive module for improved complementary feeding and 20gm nutri-butter per day between 6-18 mo/o

WASH: ventilated improved pit latrine, handwashing stations, soap, chlorine, play space, hygiene counselling

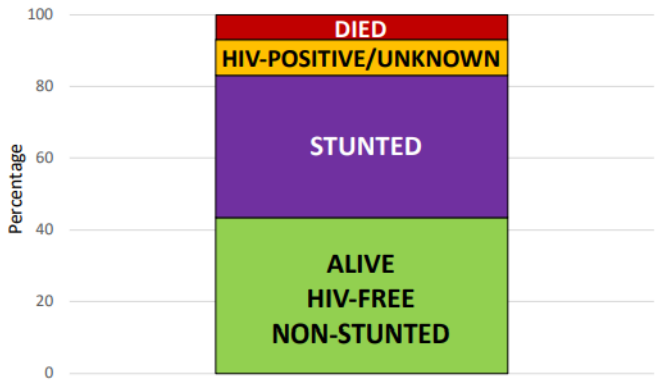
- Included 738 HIV-exposed and 3989 HIV-unexposed infants.

Zimbabwe SHINE Trial: HEU Children Have Worse Overall Mortality and Growth Outcomes Than HUU

Evans C et al. CROI 2019 Seattle, WA Abs.790

- SHINE trial (2012-2015), children followed from birth with longitudinal HIV testing; compared outcomes 738 HEU & 3989 HUU to 18 mos.
- HIV-exposed children: 25/738 (3%) were known HIV-infected by 18 mos, 596 (81%) uninfected, and **117 (16%) unknown HIV status**.
- Overall, HEU had worse outcomes than HUU children, with 39% higher 18-mo mortality and more growth abnormalities.
- Only 43% of HIV-exposed infants were alive, HIV-free and non-stunted at age 18 mos – despite half of children receiving nutritional intervention.

Outcome	HEU (N=738)	HUU (N=3989)	P Value
18-Month Mortality	7%	5%	0.04
Stunting	45.9%	30.7%	<0.001
Underweight	17.4%	9.2%	<0.001
Wasting	4.7%	2.5%	0.001
Microcephaly	9.5%	5.0%	<0.001



Zimbabwe SHINE: HEU have Some Worse Early Childhood Development Outcomes Than HUU

Chandna J et al. CROI 2019 Seattle, WA Abs.784

- SHINE trial (2012-2015), children followed from birth with longitudinal HIV testing; compared early childhood development (ECD) measures in 205 HEU & 1175 HUU at age 24 mos.
- ECD outcomes at age 24 mos in HEU children differed from HUU in some (but not all) measures.
- HEU children had lower total developmental and motor and language scores; no difference in object permanence or self-control.

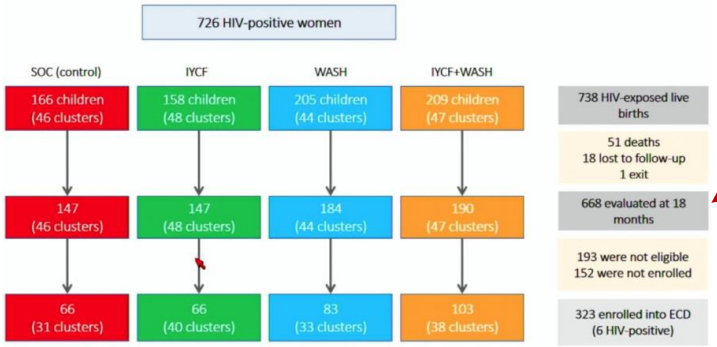
24-month outcomes	HEU N=205	HIV-unexposed N=1175	Comparison	
	Mean (SD)		Difference between means	P
MDAT				
Total score	90.6 (8.7)	92.4 (9.1)	-1.6 (-2.7, -0.5)	0.005
Gross motor	23.0 (2.9)	23.7 (3.1)	-0.6 (-0.9, -0.3)	<0.001
Fine motor	22.8 (2.9)	23.2 (2.5)	-0.4 (-0.8, 0.0)	0.06
Language	20.5 (3.9)	21.4 (4.2)	-0.7 (-1.3, -0.2)	0.007
Social	24.3 (2.3)	24.2 (2.3)	0.1 (-0.2, 0.4)	0.62
MacArthur Bates CDI				
Vocabulary checklist	57.9 (19.2)	61.3 (18.8)	-3.2 (-6.0, -0.4)	0.02
Object permanence	7.8 (1.4)	7.8 (1.4)	0.0 (-0.2, 0.2)	0.88
	Percentage		Relative risk (95%CI)	P
Self-control task				
Hidden	64.5	64.1	1.01 (0.81, 1.21)	0.91
Unhidden	45.5	45.4	0.99 (0.89, 1.13)	0.92
MacArthur Bates CDI				
Uses plurals	18.0	22.6	0.85 (0.65, 1.12)	0.26
Uses imperatives/progressives	71.7	72.3	0.99 (0.91, 1.07)	0.74
Combines words	97.6	98.7	0.99 (0.97, 1.01)	0.27

Malawi Developmental Assessment Tool (MDAT): Gross and fine motor, language, and social components, adapted for rural Zimbabwean households

MacArthur Bates Communicative Development Inventory (CDI): Vocabulary and grammar checklist, translated and validated in Shona

SHINE: Infant and Child Feeding Intervention Improved Stunting in HEU

Chasekwa B et al. CROI 2019 Seatte, WA Abs. 791



This report: Compared length for age z-score and anemia in HEU by study group

- ICYF but not WASH significantly decreased rate of stunting and anemia among HEU.

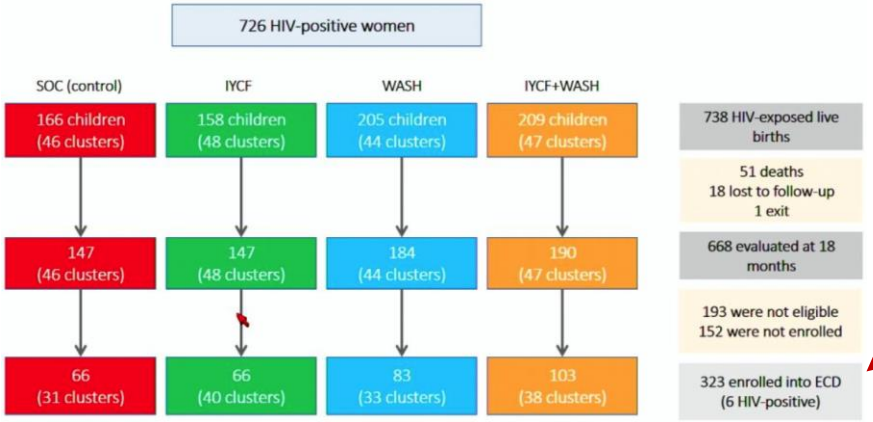
	Main Effects combining arms						
	Treatment group	N		Unadjusted		Adjusted	
			Mean (SD)	Difference (95% CI)	p	Difference (95% CI)	p
Length-for-age Z score	IYCF: no	329	-1.99 (1.13)	0.00 (ref)		0.00 (ref)	
	IYCF: yes	336	-1.73 (1.12)	0.26 (0.09, 0.43)	0.003	0.23 (0.10, 0.37)	0.001
	WASH: no	291	-1.87 (1.16)	0.00 (ref)		0.00 (ref)	
	WASH: yes	374	-1.85 (1.12)	0.01 (-0.16, 0.18)	0.90	0.07 (-0.08, 0.22)	0.37
Hemoglobin (g/L)	IYCF: no	319	116.6 (12.9)	0.0 (ref)		0.00 (ref)	
	IYCF: yes	329	119.5 (11.7)	2.9 (0.90, 4.90)	0.005	2.70 (0.60, 4.80)	0.013
	WASH: no	287	117.6 (11.1)	0.0 (ref)		0.00 (ref)	
	WASH: yes	361	118.4 (13.3)	0.70 (-1.20, 2.70)	0.47	1.10 (-0.90, 3.20)	0.27

- HEU in ICYF group had ↓ stunting compared to non-ICYF groups (40% vs 50%, RR 0.81, 95% CI 0.68-0.97)
- HEU in ICYF group had ↓ prevalence anemia compared to non-ICYF (7% vs 14%, RR 0.52, 95% CI 0.34-0.79)

SHINE: Infant/Child Feeding Plus Sanitation Improved Neurodevelopment in HEU

Ntozini R et al. CROI 2019 Seatte, WA Abs. 42

- Evaluated the effect of the SHINE interventions on early childhood development of HEU children.



This report: Early childhood development study subset – trained nurses administered at age 2 years

- Early child development in HEU significantly improved with the *combined* infant feeding and sanitation intervention (but not individual).

Malawi Developmental Assessment Tool

	Mean (SD)	Unadjusted difference (95% CI)	*P*	Adjusted* difference (95% CI)	*P*
SOC	90.9 (8.2)	0.0 (Reference)		0.0 (Reference)	
IYCF	91.7 (8.8)	0.81 (-1.99, 3.61)	0.57	-0.91 (-3.40, 1.58)	0.48
WASH	89.6 (9.2)	-1.26 (-3.80, 1.28)	0.33	-1.63 (-4.26, 0.99)	0.22
IYCF+WASH	**95.3 (9.0)**	**4.57 (1.91, 7.23)**	**0.001**	**3.05 (0.86, 5.25)**	**0.006**

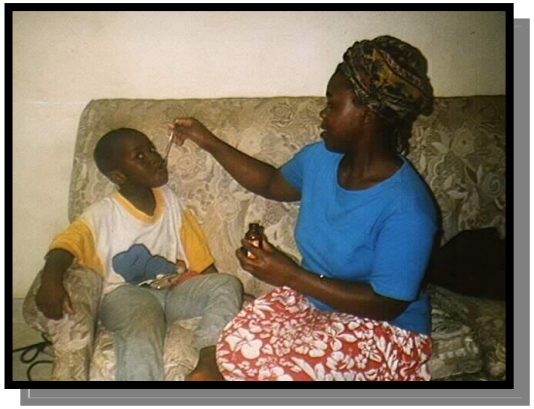
*Adjusted for: maternal baseline mid-upper arm circumference (MUAC), education, employment status, CD4 count, co-trimoxazole prophylaxis and antiretroviral treatment during pregnancy, capabilities (perceived physical health and decision making autonomy), access to improve latrine; Infant variables: low birth-weight, prematurity, gender and infant age at assessment; season of recruitment and nurse who carried out assessment

MacArthur Bates Language Inventory

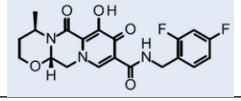
	Mean (SD)	Unadjusted difference (95% CI)	*P*	Adjusted* difference (95% CI)	*P*
SOC	56.6 (18.5)	0.0 (Reference)		0.0 (Reference)	
IYCF	57.6 (21.3)	1.00 (-5.74, 7.55)	0.77	-2.47 (-8.60, 3.67)	0.43
WASH	58.2 (20.1)	1.58 (-4.12, 7.29)	0.59	-2.27 (-8.14, 3.60)	0.45
IYCF+WASH	**65.1 (17.0)**	**8.50 (3.66, 13.33)**	**0.001**	**6.01 (1.14, 10.88)**	**0.015**

*Adjusted for: maternal baseline mid-upper arm circumference (MUAC), education, employment status, CD4 count, co-trimoxazole prophylaxis and antiretroviral treatment during pregnancy, capabilities (perceived physical health and decision making autonomy), access to improve latrine; Infant variables: low birth-weight, prematurity, gender and infant age at assessment; season of recruitment and nurse who carried out assessment

ARV Drugs in Children



Dolutegravir



Dolutegravir in Children

CROI 2019 Seattle, WA

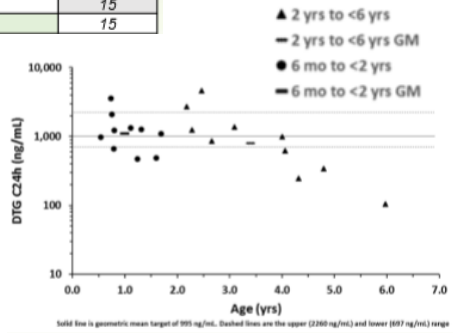
- *Frange P. Abs. 828 (France)*
  - 109 children (92% ART-exp, 11% prior InSTI) 5->18 yrs starting DTG
  - Pre-DTG suppression 58.7%; switch DTG ↑ to 79.8%, similar rates all ages
  - Low rate AE

	Total (n=109)	Age at the time of DTG initiation		
		Group 1 5-12 years (n=33)	Group 2 12-18 years (n=51)	Group 3 ≥18 years (n=25)
Duration of follow-up (months) (median, range)	24 (6-54)	12 (6-36)	24 (6-54)	24 (6-48)
Virological follow-up				
Sustained virological success (n, %)	87 (79.8)	29 (87.9)	37 (72.5)	21 (84.0)
VL <50 copies/mL at the last visit (without ARV change) (n, %)	96 (88.1)	31 (93.9)	43 (84.3)	22 (88.0)
Emergence of RAMs in patients with virological failure (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Safety				
Grade I/II clinical events	7 (6.4)	0 (0.0)	2 (3.9)	5 (20.0)
Grade I/II biological events	30 (27.5)	8 (24.2)	13 (25.5)	9 (36.0)
Grade III/IV biological events	3 (2.8)	0 (0.0)	2 (3.9)	1 (4.0)
Stop for intolerance	1 (0.9)	0 (0.0)	1 (2.0)	0 (0.0)

- *Ruel T. Abs. 829LB (P1093)*
  - Age ≥6 mos-<2 yr and ≥2 yr-<6 yr PK study of higher dosing of dispersible tablet (DT)
  - Increased wt band DTG-DT dosing met pre-specified AUC24 and C24 targets both age groups.

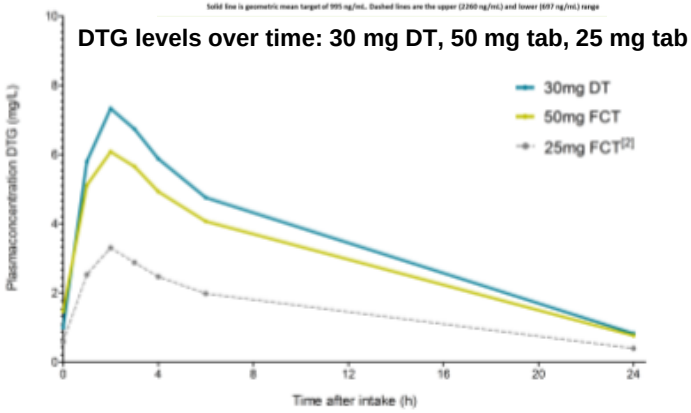
Weight Band (kg)	Revised Dose (mg)	Dose (mg/kg) for Weight Range		Dose previously tested (mg)
		Lower Weight	Upper Weight	
6 - <10	15	2.50	1.50	*10*
10 - <14	20	2.00	1.43	*15*
14 - <20	25	1.79	1.25	*15*

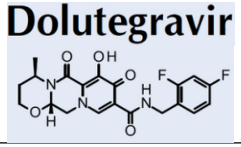
DTG trough by age cohort



- *Bollen P. Abs. 830LB (ODYSSEY)*
  - PK evaluation of 50 mg DTG tab and 30 mg DTG-DT in children 20-<25 kg (EMA rec dose 25 mg tab 20-<30kg).
  - Daily 50 mg DTG and 30 mg DT had similar PK profiles but Cmax (6.07-7.42 mg/L) was slightly higher than adults (5.41 mg/L).

DTG levels over time: 30 mg DT, 50 mg tab, 25 mg tab





Dolutegravir in Children

CROI 2019 Seattle, WA

- *Bunglawala FS. Abs.827*
  - Simulation of DTG dosing for neonates based on PK of RAL (metabolized UGT1A1) and midazolam (CYP3A4) in neonates.
  - Different DTG dosing strategies simulated; target achieve levels ~ to those observed in pediatric (C_{trough} 0.99 mg/L; $AUC2_4$ 50.1 mg.h.L).

DTG PK Parameters in Neonates

	Regimen	Total Dose (mg)	Dose* (mg/kg)	C_{max}[1] (mg/L)	AUC_{av} (mg.h/L)	C_{max}[2] (mg/L)	AUC (mg.h/L)	C_{trough} (mg/L)
Too high→	1	5 QD	1.4 (1.7 - 1.1)	3.99 ± 1.1	66.1 ± 22.9	2.3 ± 1.1	47.8 ± 14.3	1.6 ± 1.1
	2	4 QD	1.1 (1.3 - 0.9)	3.3 ± 0.6	47.0 ± 14.1	1.7 ± 0.6	35.1 ± 10.5	1.1 ± 0.6
	3	3 QD	0.85 (1 - 0.7)	2.4 ± 0.6	35.2 ± 13.4	1.3 ± 0.7	27.3 ± 9.2	0.9 ± 0.7
Too low→	4	2 QD	0.55 (0.7 - 0.4)	1.6 ± 0.3	23.5 ± 6.6	0.8 ± 0.3	18.0 ± 6.4	0.5 ± 0.2
	5	Day 1-7 = 2 QD, Day 8-28 = 3 QD	0.7 (1 – 0.4)	1.8 ± 0.7	30.5 ± 11.7	1.3 ± 0.7	25.9 ± 7.6	0.8 ± 0.7
	6	Day 1-7 = 2 QD, Day 8-28 = 3.5 QD	0.8 (1.2 – 0.4)	2.2 ± 1.4	35.4 ± 17.2	1.6 ± 1.1	28.8 ± 8.4	1.1 ± 1.4

*Median(Range), neonate weight range in the model is 3.0 - 4.5kg. Cmax[1], Maximum plasma concentration over 28 day simulations; Cmax[2], Maximum plasma concentration after final dose has been administered; AUC_{av}, Average area under curve over 28 day simulations; AUC, Area under curve after final dose; C_{trough}, Minimum plasma concentration after final dose.

- Regimens 2, 3, 5 and 6 (>2 to 4 mg QD) result in PK parameters comparable to those in pediatric patients.

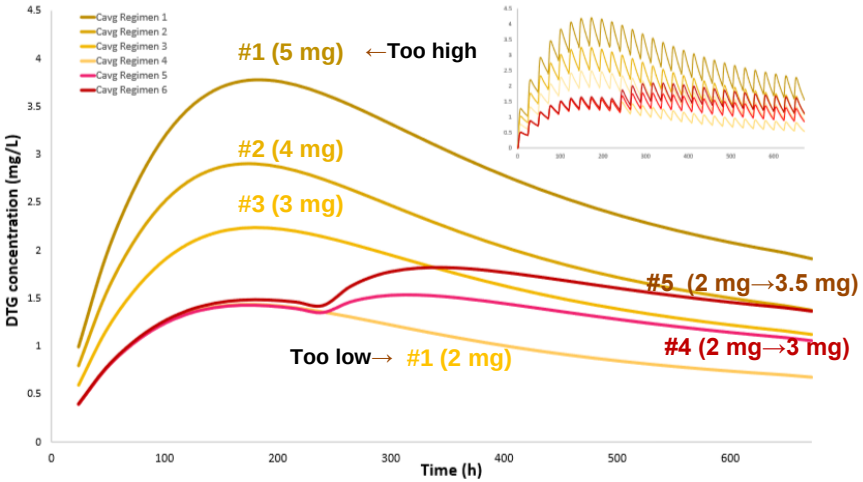
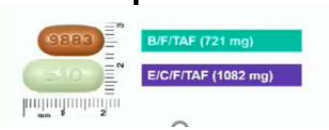


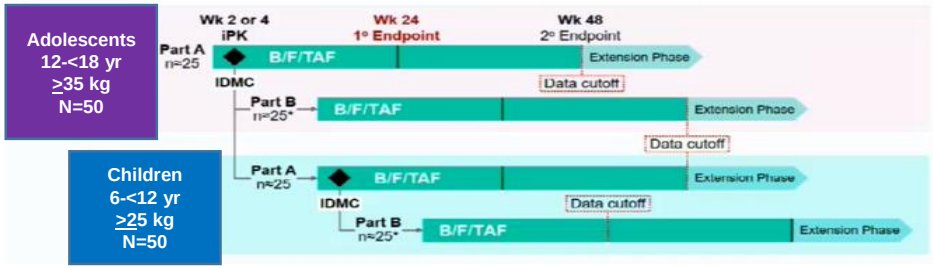
Figure 1 PK profile showing average concentration of DTG (Cavg) from 0-28 days, (inset) DTG PK profile of daily doses.

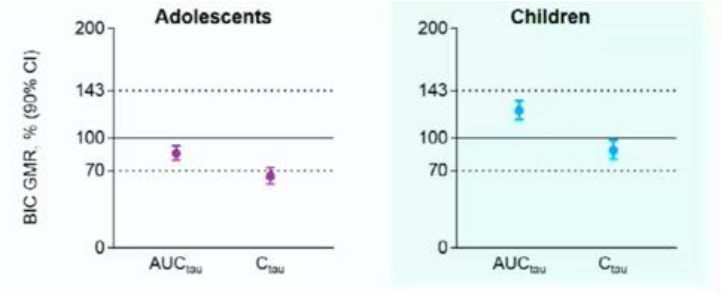
Bictegravir/FTC/TAF Switch Study in Suppressed Pediatric and Adolescent Patients

Gaur A et al. CROI 2019 Seatte, WA Abs.

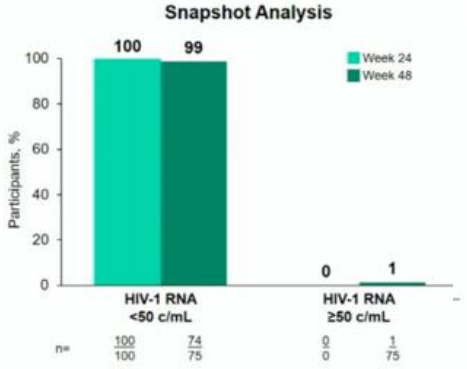
- Wk 48 data from switch study: pt with RNA <50 x6 mos, CD4 ≥200
- PK study to confirm B/F/TAF dosing (50/200/25mg QD), followed by short-term safety study
- Favorable pill size

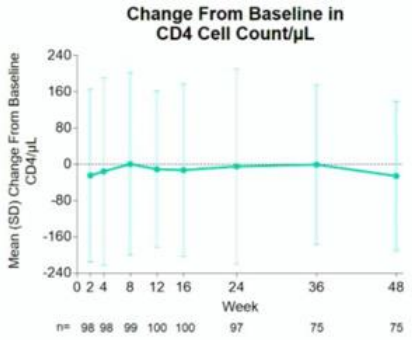






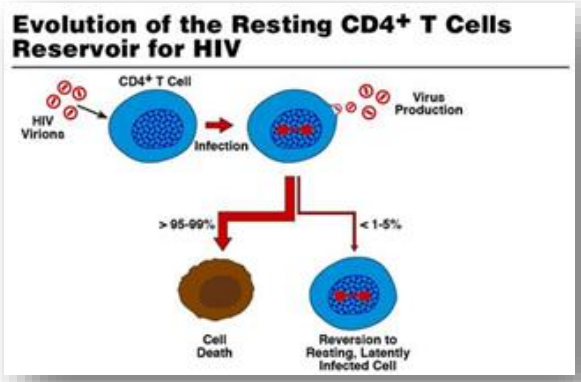
- AUC adolescents/children similar to adults
- C_{trough} children ~same adults; ↓ in adolescents but still >11x > than $_{pa}$IC50
- FTC and TAF exposures similar adults





- Maintained viral suppression and CD4 count post switch

Early Treatment of Infants with HIV



Early Infant Treatment (EIT) Study

Broncano PG et al. CROI 2019 Seatte, WA Abs. 43

- Non-randomized study in Botswana with early infant diagnosis and treatment.
- Screened 10,600 newborns, identified 44 HIV+ infants (0.4%) → 42 enrolled in EIT and start immediate ART (AZT/3TC/NVP then change at 2-5 weeks to AZT/3TC/LPV/r).
- 10 infants have complete testing at 84-96 weeks.

Early ART
ANTEPARTUM group
Test HIV+ within 96 hr after birth and start ART age <7 d

N=9

Early ART
PERIPARTUM group
Test HIV- within 96 hr after birth and HIV+ within 5-42 d birth, start ART <57 d after birth
N=1

Later ART
CONTROL group
Enrolled 24-36 mo/o and started ART at age 30-365 d/o

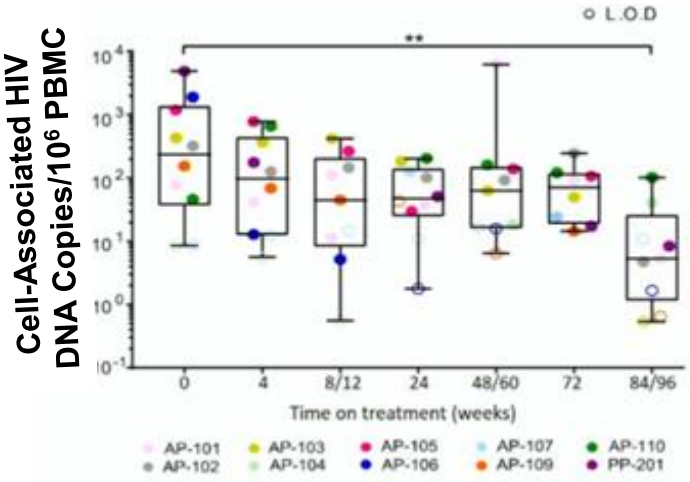
N=10

Decreased HIV Reservoir And Decline in Intact Proviral Sequences with Early ART

Broncano PG et al. CROI 2019 Seatte, WA Abs. 43

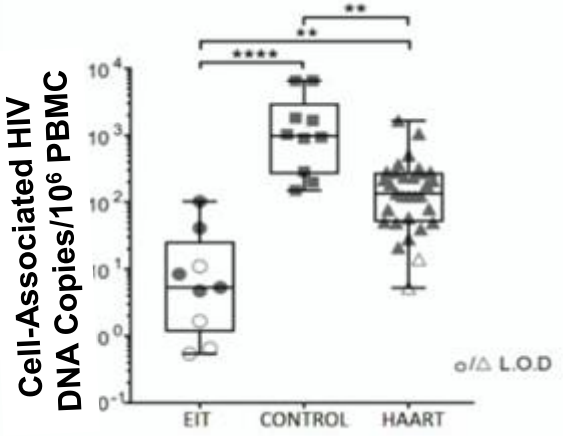
→ Decline cell-associated provirus

Longitudinal Analysis **EIT infants Only**



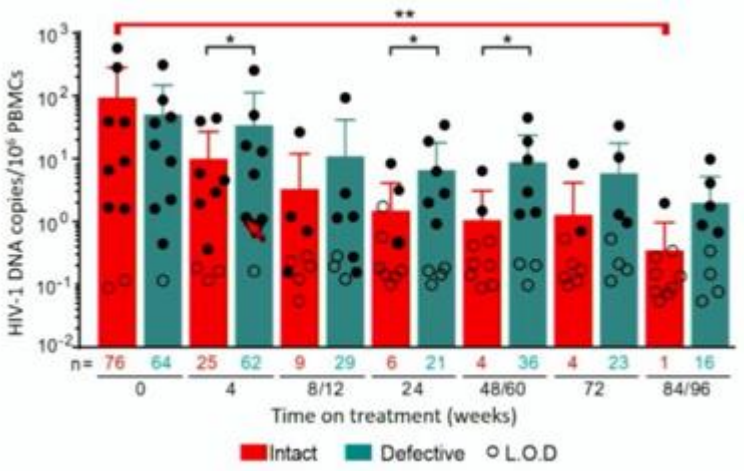
* p<0.05
** p<0.01
*** p<0.001
**** p<0.0001

Cross-Sectional Comparison: **EIT, Control, Adults**

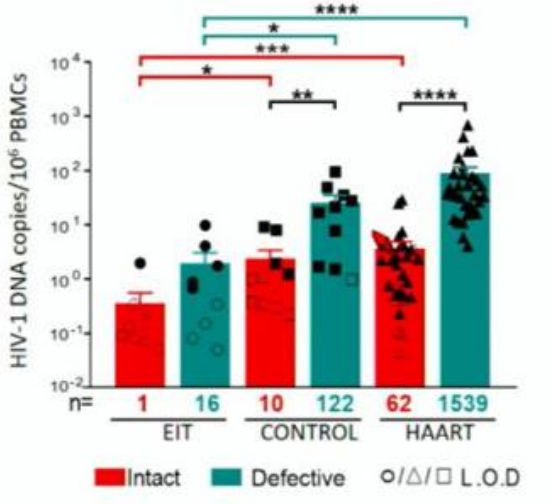


EIT: early ART infants, 84/96 wk on ART
CONTROL: later ART infants, median wk 93 on ART
HAART: adults on ART, median 16 years ART

→ ↓ intact & ↑ defective proviral DNA



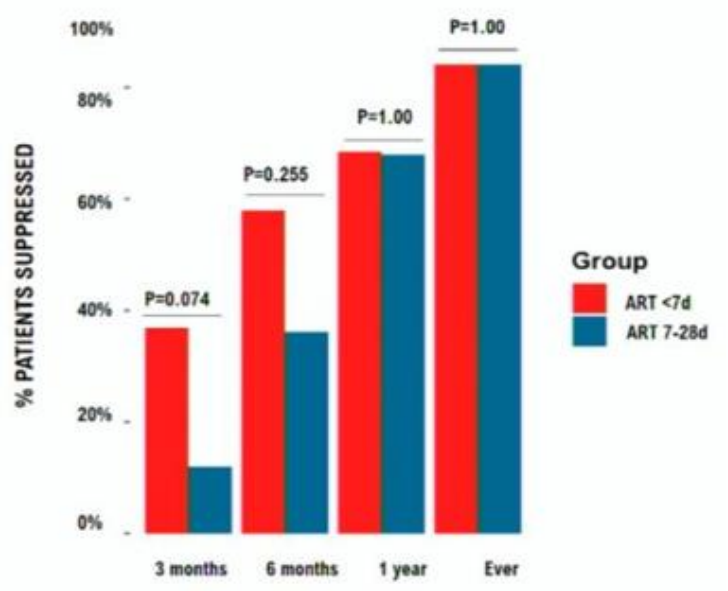
n= number of proviral sequences detected

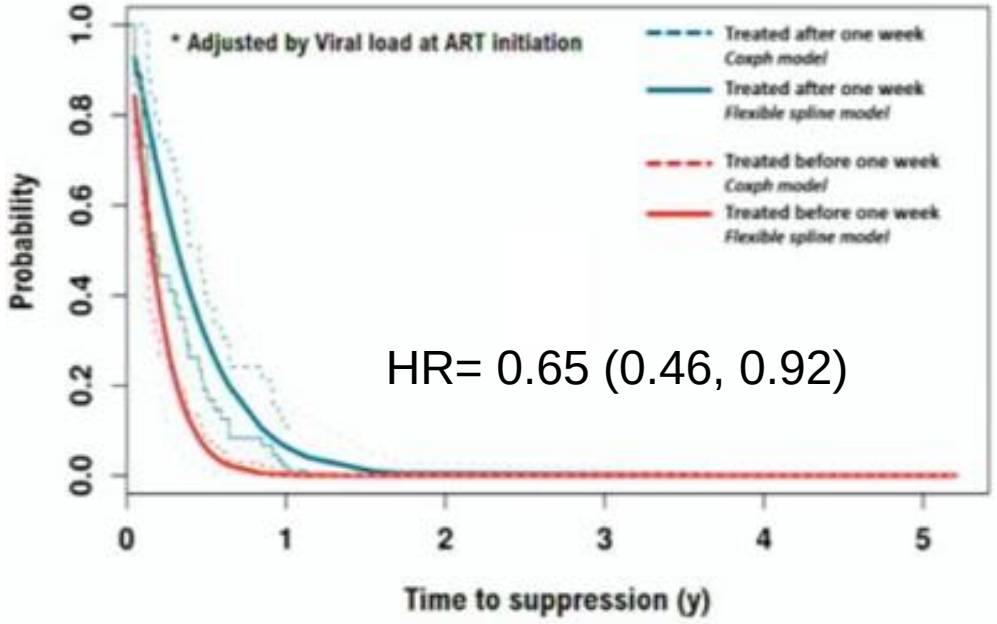


Neonatal ART Started <7 vs 7-28 Days Reduces Time to Viral Suppression

Rodriguez SD et al. CROI 2019 Seatte, WA Abs. 44

- Compared VL decline in 25 infants started at <7 days vs 19 started at 7-28 days of life.
- While overall probability of suppression at 48 weeks similar, the probability **early** suppression (by 3-6 mos) decreased by 35% for each week elapsed prior to starting ART.

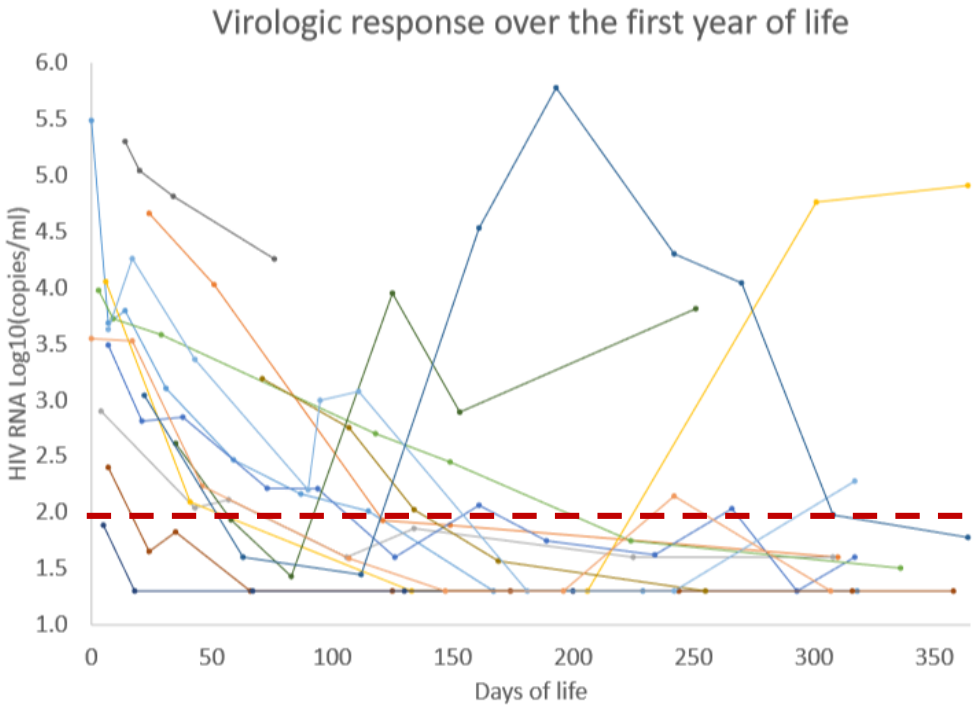




Neonatal Outcome with Rapid HIV Treatment
Treating Infants Early Study (TIES) – United States

Ruel T et al. CROI 2019 Seattle, WA Abs.802

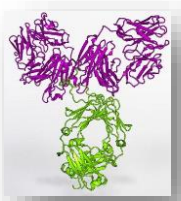
- Observational study of 14 HIV+ infants starting ART age <6 wks
- Median age at diagnosis 4 d (0-17); median age ART start 8.5 d (0-36).
- Viral suppression 11/14 infants (78.6%) after median 143 d ART (13-469).
- Anemia 8 (53%) and neutropenia 5 (33%) but no interruption for toxicity.



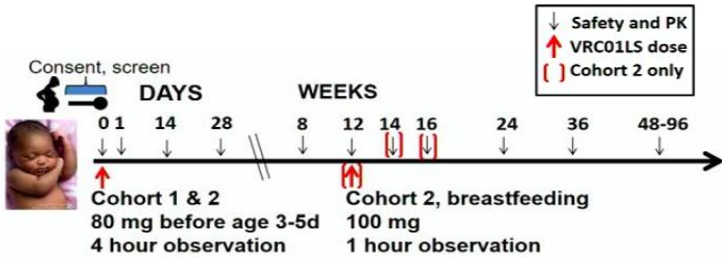
- Heterogeneity in baseline RNA levels
- Viral suppression 11/14 infants (78.6%) after median 143 d ART (range 13-469 d).
- One infant viral rebound >200 c/mL at 295 d; 10 remained suppressed throughout FU.
- One very early and prolonged suppression (66 to 958 d life).

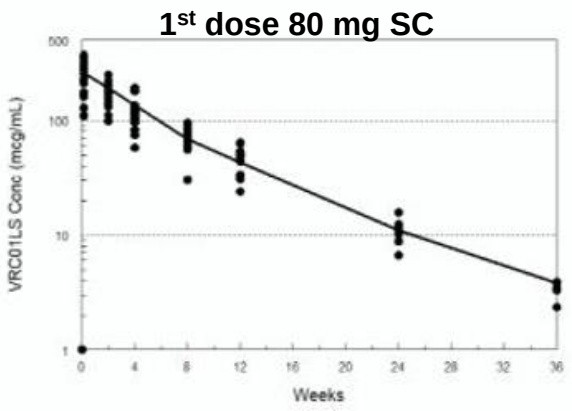
Safety and PK of VRC01-LS Monoclonal Antibody in HIV-Exposed Newborns

McFarland E et al. CROI 2019 Seatte, WA Abs.43



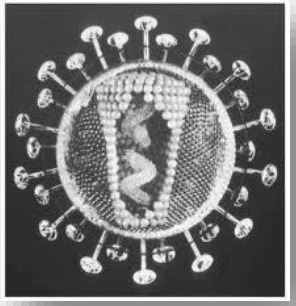
- VRC01-LS is broadly neutralizing anti-CD4 binding site monoclonal antibody with modified affinity for neonatal Fc receptor to increase T½.
- Evaluated PK and safety of single (N=10) and multiple (N=11) subcutaneous dose VRC01-LS in HIV-exposed neonates (all receive ARV prophylaxis).





- T½ : 59±8 days
- Week 12: mean 44.7 mcg/mL (33% >50, 100% >20 mcg/mL)
- Note: IC50 for most clade B, C and A isolates <10 mcg/mL; in NHP models, levels 20 mcg/mL well exceed protective level

- Well tolerated (no Grade 3/4 AE).
- Can be administered at birth and 1-2 time per year to achieve desired levels – additional strategy to prevent postnatal MTCT?



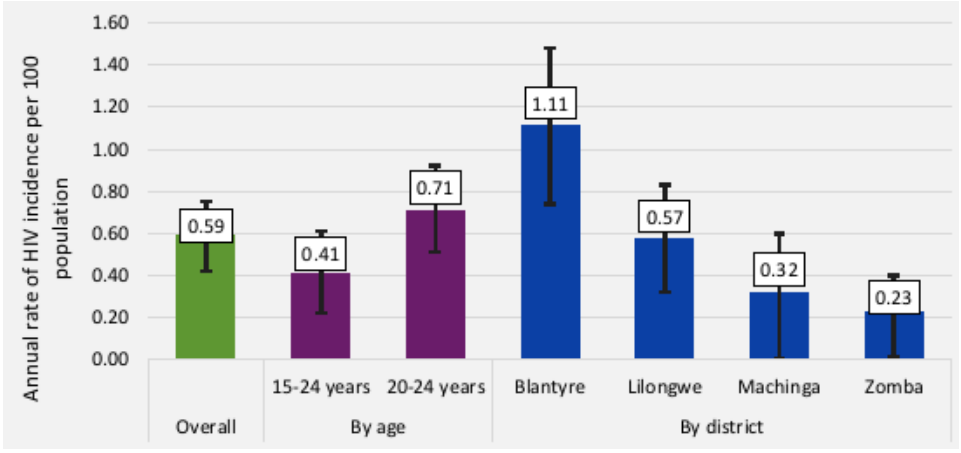
Adolescents and HIV

Recent HIV Infection Adolescent Girls and Young Women, Malawi

Payne D et al. CROI 2019 Seattle, WA Abs. 831

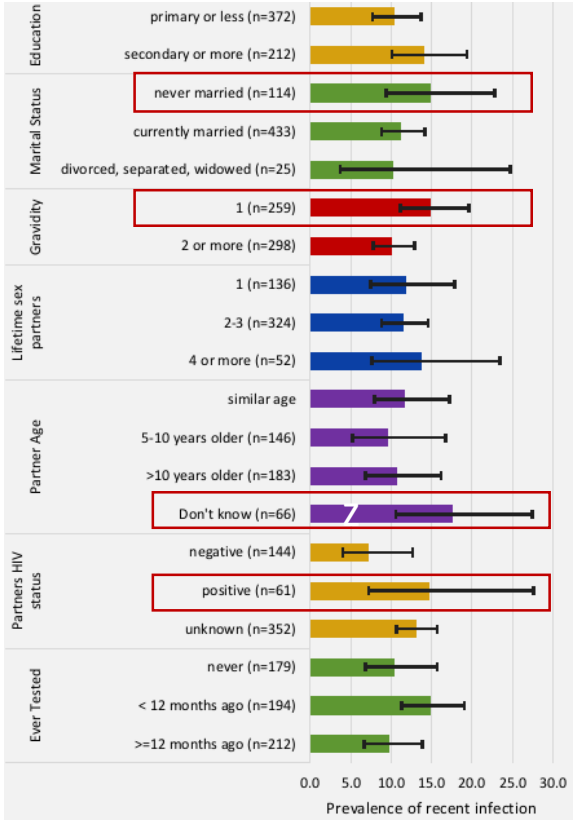
- Nov 2017-July 2018 enrolled pregnant women age 15-24 years newly dx with HIV at 1st ANC visit at 121 facilities; recent infection testing algorithm (RITA) used to define recent infection.
- Among 54,643 attending 1st ANC, HIV prevalence 4.3%; 1,159 had new HIV dx and eligible for study, 589 (50.9%) enrolled in study.

Estimated of HIV incidence in pregnant adolescent girls and young women Malawi 2017-2018



- 11.7% with new dx had recent infection → annualized incidence of 0.59%.
- Incidence higher among those aged 20-24 years (vs 15-19 years); Blantyre residence

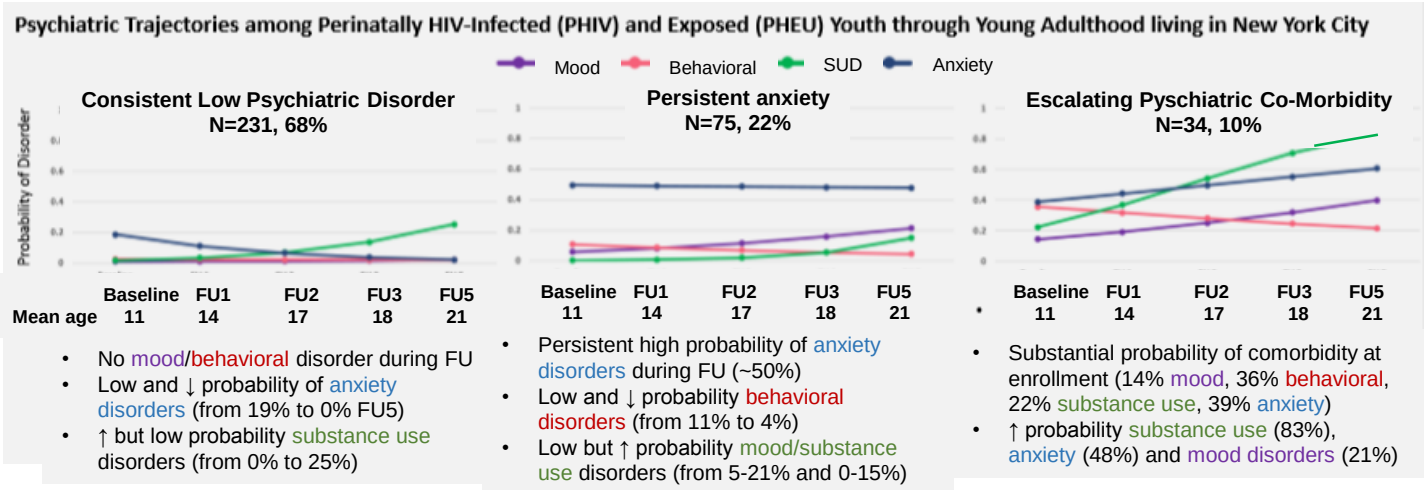
Prevalence recent infection



Youth Psychiatric Trajectories in Perinatal HIV Infection or Exposure Predict Young Adult Viremia

Nguyen N et al. CROI 2019 Seattle, WA Abs. 819

- Child and Adolescent Self-Awareness and Health (CASAH) longitudinal cohort of 340 youth with perinatal HIV exposure (206 PHIV, 134 PHEU) recruited from 4 centers in NYC at age 9-16 yrs; interview q 12-18 mos.
- Analysis focuses on baseline through FU#5 (ages 18-28 yrs); 3 psychiatric trajectories described:



~1/3 of PHIV and PHEU had high burden psychiatric disorder, and nearly 2/3 had a viremic event in young adulthood

Baseline sociodemographic predictors of trajectory type and association with viremic event in last 12 mos of FU#5 ***(62% had at least 1 viremic event [VL >200 c/mL])***

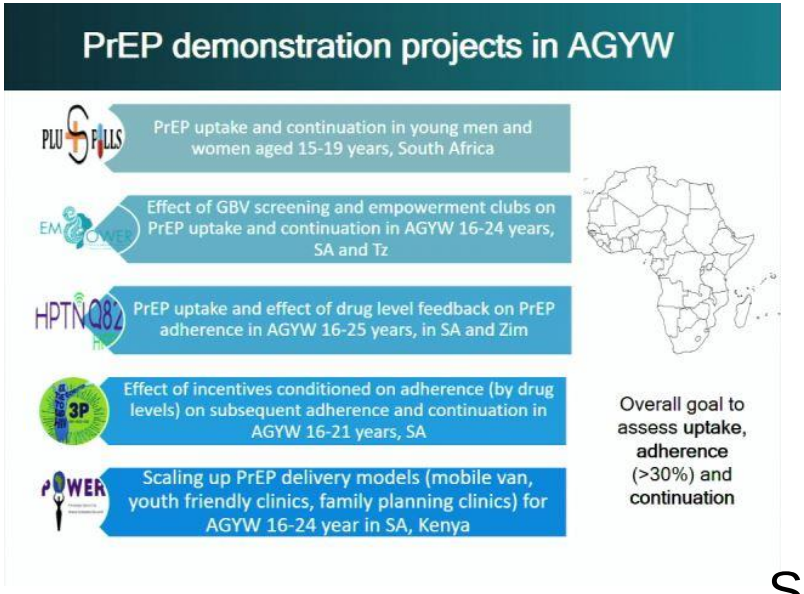
Persistent anxiety	
PHIV status	OR = 0.73 (0.39, 1.36)
Age	OR = 1.02 (0.89, 1.17)
Female	**OR = 2.43 (1.36, 4.34)**
Caregiver HIV+	**OR = 0.45 (0.23, 0.89)**
Poverty	**OR = 2.04 (1.08, 3.85)**
Neighborhood stress	OR = 1.59 (0.83, 3.03)
Viremic event	RR=1.32 (0.98, 1.77)

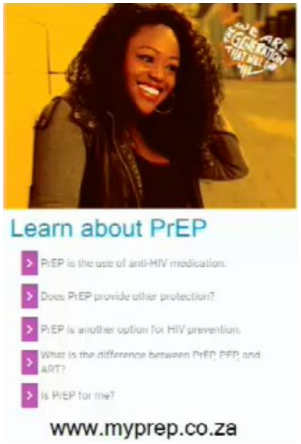
Escalating Psych Co-Morbidity	
PHIV status	OR = 0.58 (0.21, 1.59)
Age	**OR = 1.55 (1.19, 2.01)**
Female	OR = 2.40 (0.92, 6.24)
Caregiver HIV+	OR = 0.39 (0.14, 1.16)
Poverty	OR = 1.00 (0.34, 2.97)
Neighborhood stress	**OR = 4.75 (1.94, 11.60)**
Viremic event	**RR = 1.56 (1.11, 2.18)**

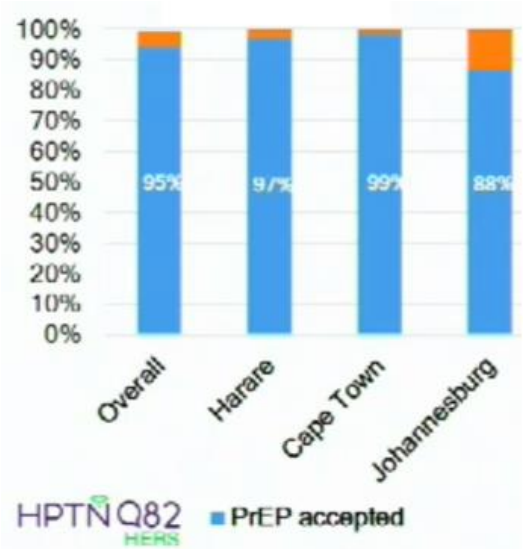
PrEP in Adolescents and Women

Engaging Young Women in Sub-Saharan Africa

Delany-Moretiew S. CROI 2019 Seattle, WA Abs.163







LESSONS LEARNED

Similar findings across all projects:

- PreP interest and uptake is high (>90%) (HPTN 082).
- Risk score high
- STI prevalence ~30%
- IPV in past year 30-50%
- Depressive symptoms 42%
- Limited experience contraceptive pill taking.

Engaging Young Women in Sub-Saharan Africa: Lessons Learned

Delany-Moretiew S. CROI 2019 Seattle, WA Abs.163

- PrEP should be offered as part of comprehensive youth-friendly services
  - Flexible hours, non-judgmental, provide for information needs
- Delivered as a part of a package of sexual and reproductive health services
  - Enhance engagement in care
  - Provide ongoing choice in context of changing risk
  - Refills for PrEP and contraception, Opportunity to add STI testing
  - Platform to introduce new products
- Respond to greatest health needs
  - Screening for violence as part of HCT
  - Referral for mental health services
  - Program benefits, efficiency, cost

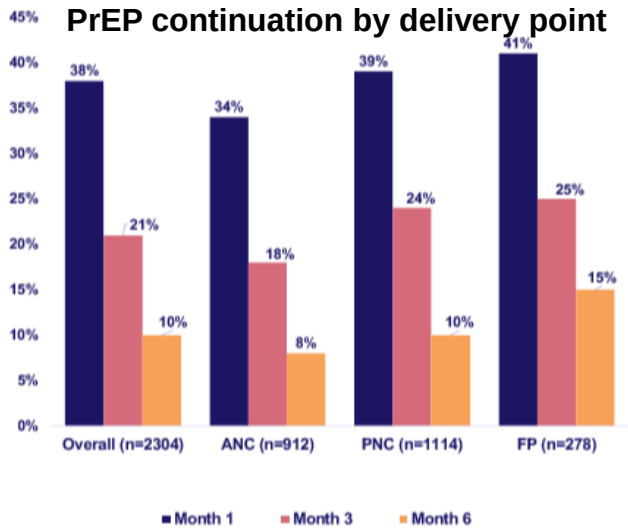
Persistence with PrEP Use in Adolescent and Young Women Initiating PrEP in MCH and FP Clinics

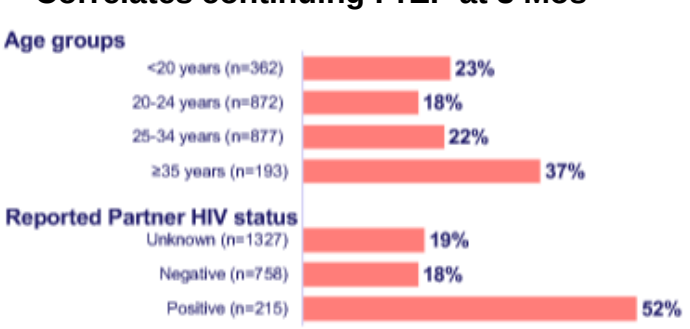
Mugwanya K et al. CROI 2019 Seattle, WA Abs.993

- Women 15-45 years seeking routine ANC, PNC and FP in 16 high volume facilities in Kenya screened for HIV risk and willingness to initiate PrEP; 2304 women initiated on PrEP.
- Median age 24; 58% had partner unknown HIV status, 96% reported recent condomless sex.
- Continuation at 1, 3 and 6 months was 38%, 21% and 10% overall; similar by delivery point.
- Continuation of PrEP use at 3 months was independently higher among women with HIV positive male partners(p<0.01)and older women 35 years and above (p=0.02)(Figure3); only partner HIV status independently associated with continuation at month 6.
- Commonly reported reasons for stopping PrEP included low perceived risk of HIV (23%), experiencing side effects (19%),pill burden (17%),and that partner is HIV negative (17%).

2,304 women on PrEP

	N (%) or median (interquartile range)
Age-Years	24 (21-29)
<24 years	1086 (47%)
≥24 years	1218 (53%)
Marital status	1837 (79%)
Delivery point	
Antenatal care	912 (40%)
Postnatal care	1114 (48%)
Family planning	278 (12%)
Partner HIV status	
Negative	758 (33%)
Positive	215 (9%)
Unknown	1327 (58%)

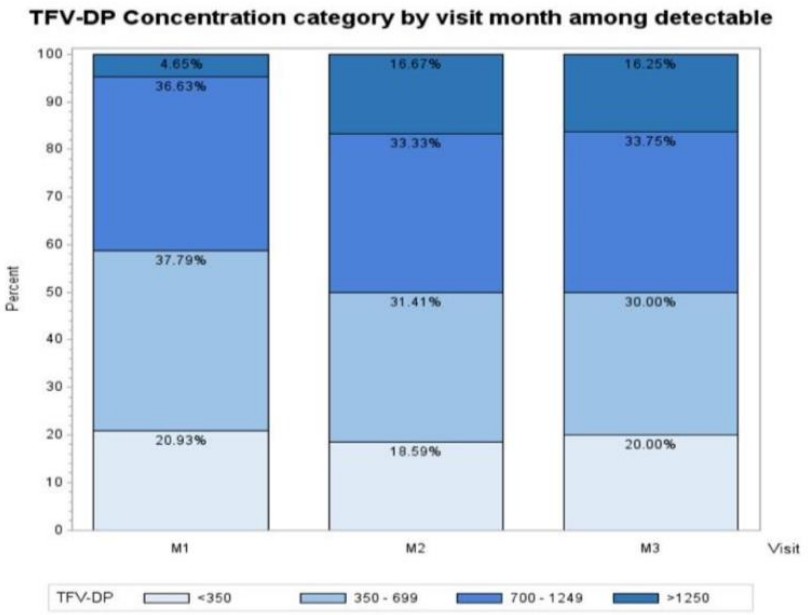




High Adherence in Young Women Cape Town in First 3 Months After PrEP start

Celum CL et al. CROI 2019 Seattle, WA Abs.994

- 3 Ps for Prevention Study (Perception, Partners, Pills) enrolled 200 sexually active women 16-25 years; median age 19 years.
- Adherence at 3 months was assessed by tenofovir-diphosphate (TFV-DP) in dried blood spots. High adherence; TFV-DP >700 fmol/punch (>4 doses/week); Medium adherence 350-700 fmol/punch (2-3 doses/week).

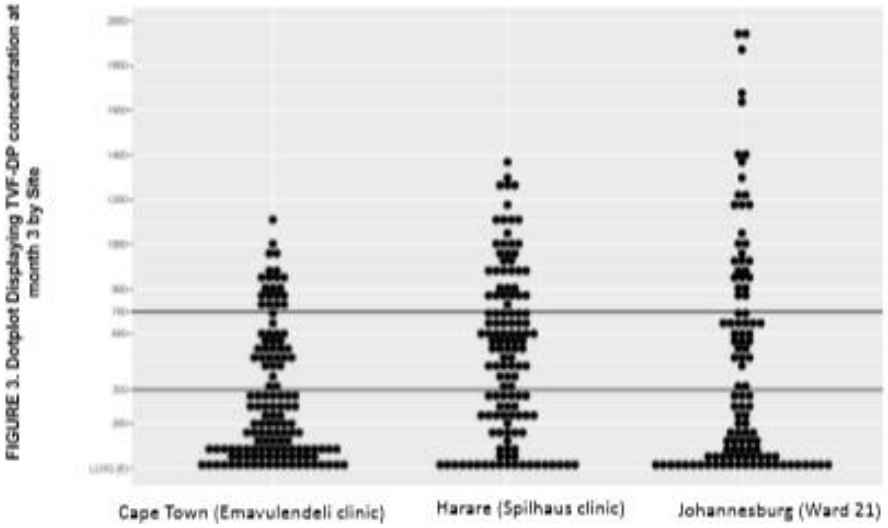


- Retention 89% at 3 mos.
- Median TDF-DP was 622 at 1 mo, 707 at 2 mo; 700 at 3 mo.
  - At 3 months, 50% had high adherence and 80% had medium or greater adherence at 2 and 3 months.
- High adherence associated with: partner unknown or HIV+, disclosure of PrEP use.

Adherence 3 Months After PREP Start, Young Women Cape Town South Africa

Celum CL et al. CROI 2019 Seattle, WA Abs.995

- 451 sexually active HIV-negative women ages 16-25 were enrolled; 427 accepted PrEP (412 at enrollment, 15 after enrollment); median age 21 years (6% <18 years).
- Adherence at 3 months was assessed by tenofovir-diphosphate (TFV-DP) in dried blood spots. High adherence; TFV-DP >700 fmol/punch (>4 doses/week); Medium adherence 350-700 fmol/punch (2-3 doses/week).



- 310/374 (84%) had TFV/DP detectable at mo 3
- Median TDF-DP was 485 fmol
  - 25% were 700 (high)
  - 23% 350-699 (medium)
  - 36% detectable <349
  - 16% undetectable
- Predictors high vs low adherence: attend adherence support group, no depression, # sex partners

TAF vs TDF in Women – Pooled Analysis 7 Clinical Trials

Thompson M et al. CROI 2019 Seattle, WA Abs. 519

- Pooled analysis comparative data on efficacy and safety of TAF vs TDF in women (stratified by ART naïve vs virally suppressed).

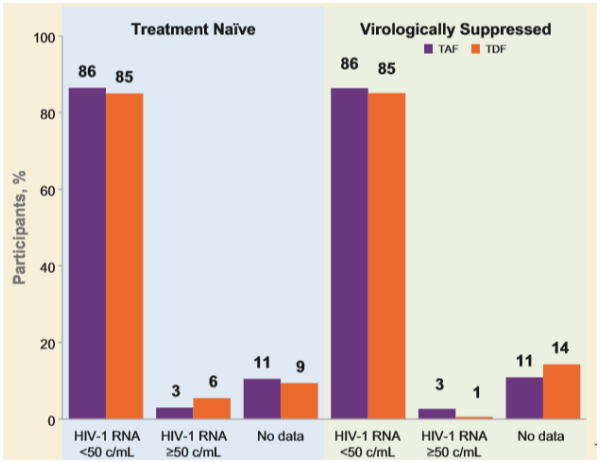
Studies Included in Integrated Analysis

779 women from 7 (5 double-blind, 2 open-label) randomized studies*

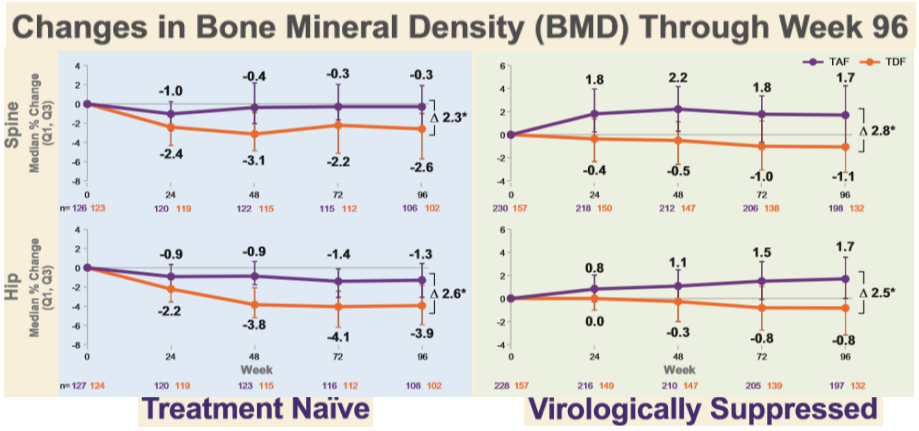
292-0104	N=867	E/C/F/TAF vs E/C/F/TDF
292-0111	N=866	E/C/F/TAF vs E/C/F/TDF
Treatment Naïve (n=2 studies, 260 women)		
380-1878 OL	N=577	B/F/TAF vs boosted PI -regimens
366-1160	N=875	FTC/RPV/TAF vs EFV/FTC/TDF
366-1216	N=630	FTC/RPV/TAF vs FTC/RPV/TDF
311-1089	N=663	F/TAF + 3rd agent vs F/TDF + 3rd agent
292-0109 OL	N=1436	E/C/F/TAF vs TDF -containing regimens
Virologically Suppressed (n=5 studies, 519 women)		

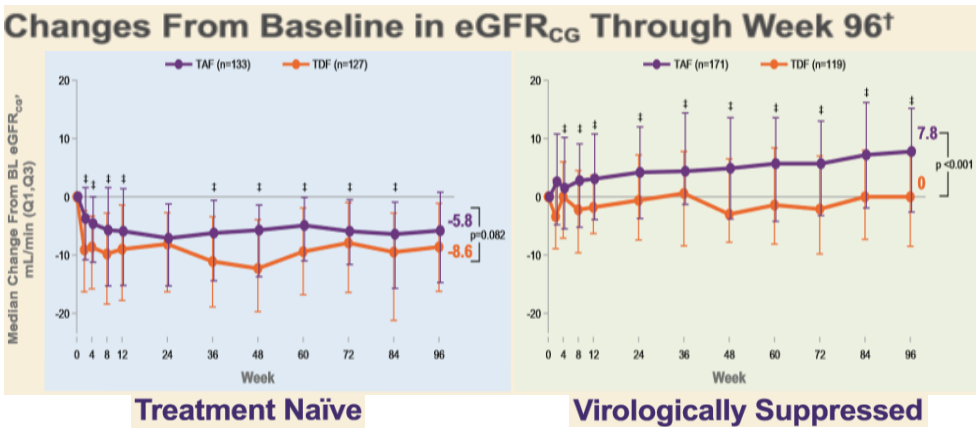
Outcomes

- Efficacy (Snapshot analysis)
- Safety
  - Overall (most common AEs)
  - Renal
    - AEs, AEs leading to discontinuation, cases of proximal renal tubulopathy or Fanconi syndrome
    - eGFR by Cockcroft-Gault (CrCl; mL/min)
    - Glomerular proteinuria (UACR), tubular proteinuria (urine RBP:Cr and β2M:Cr)
  - Bone (BMD)



- Viral response (96 wks) same with TAF but bone and renal toxicity improved compared to TDF.





F/TAF Non-Inferior to F/TDF for PrEP: Discover Study

Hare CB et al. CROI 2019 Seattle, WA Abs. 104LB

5387 high-risk MSM or TGW

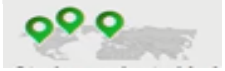
Double-blind Active control

F/TAF 200/25 mg QD N=2694

F/TDF 200/300 mg QD N=2693

96 Weeks

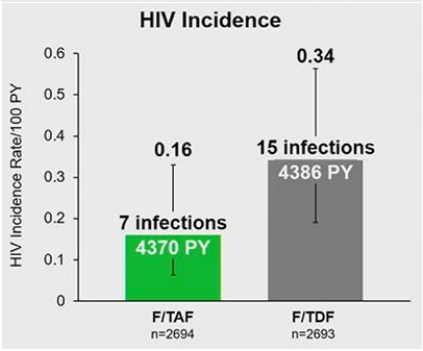
94 sites, 11 countries: NA, EU

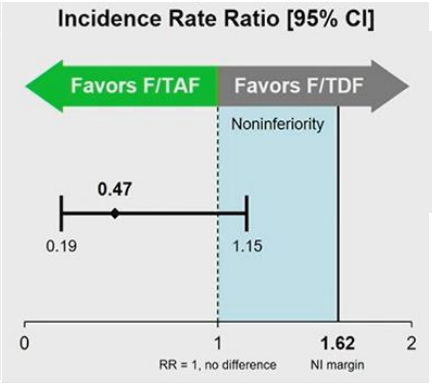


Primary analysis: HIV incidence/100 PY after 100% complete wk 48 and 50% complete wk 96

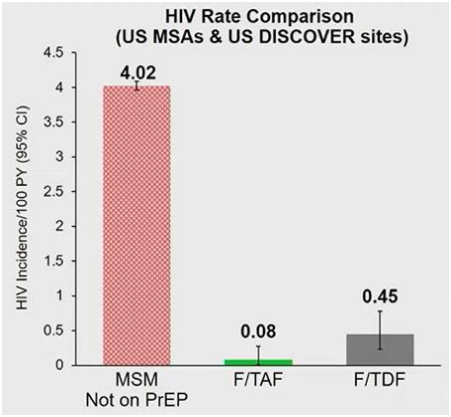
Non-inferiority margin upper 95% CI <1.62
Expected incidence 1.44/100 PY (IPrEx; PROUD; IPERGAY)

22 HIV infections in 8756 PY of follow-up

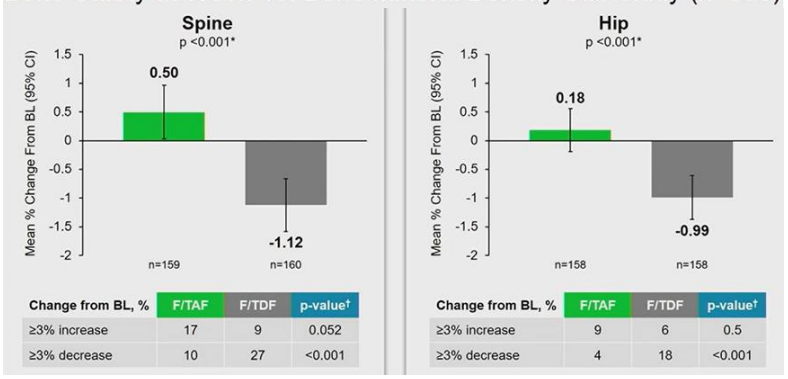


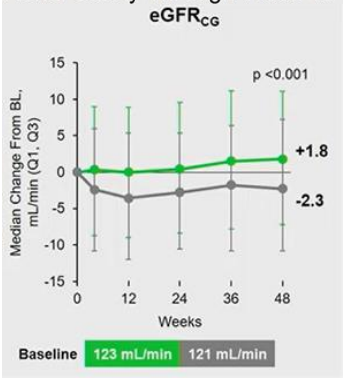


- 7 F/TAF infections: 1 suspected baseline infection, 5 low levels of TFV-DP in DBS,1 medium level
- 15 F/TDF infections: 4 suspected baseline infections, 10 low levels of TFV-DP in DBS, 1 high level
- In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (0.55 [0.20, 1.48])

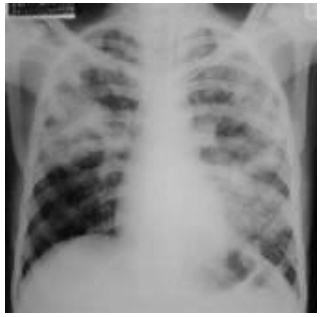


Bone Safety at Week 48: Bone Mineral Density Sub-study (n=383)





- F/TAF non-inferior to F/TDF for prevention HIV infection in MSM/TGQ
- Both well tolerated, low d/c
- F/TAF had better bone and renal outcomes

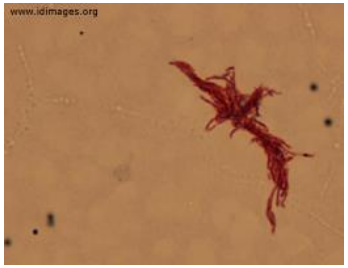


TB and HIV

- Pregnancy

- Pediatrics

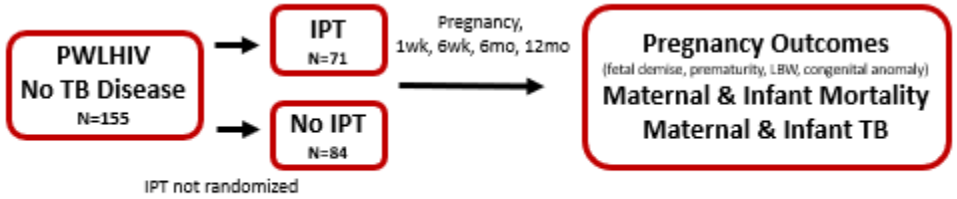
- General



INH Prophylaxis for Latent TB, Pregnancy Tshepiso Cohort, South Africa

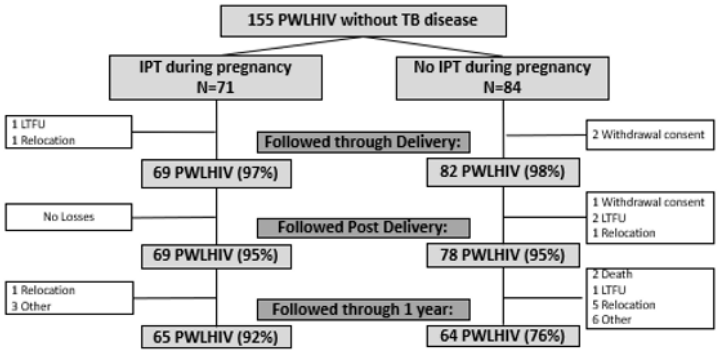
Salazar-Austin N et al. CROI 2019, Seattle, WA Abs. 77

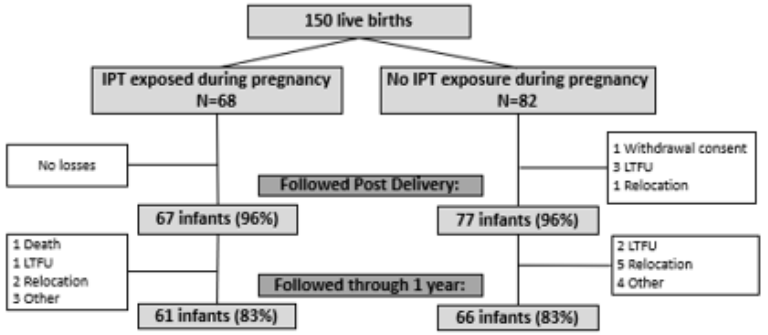
- Prospective cohort pregnant HIV+ women with and without TB disease in Soweto, S Africa, January 2011-July 2014, FU pregnancy to 12 mo PP for MTCT, pregnancy outcomes, maternal/infant mortality and TB.
- Evaluated outcomes by IPT use (non-randomized, self-reported).



Soweto, South Africa

January 2011 – July 2014



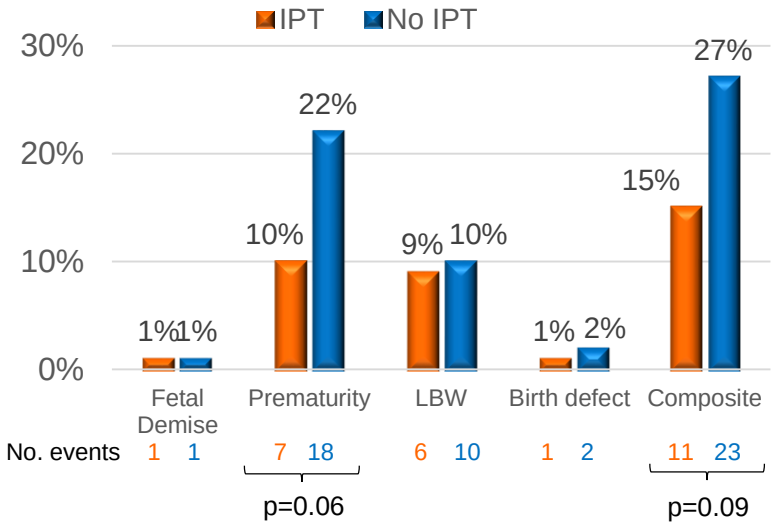


INH Prophylaxis for Latent TB, Pregnancy Tshepiso Cohort, South Africa

Salazar-Austin N et al. CROI 2019, Seattle, WA Abs. 77

- IPT use in 2nd/3rd trimester during pregnancy was *not* associated with a higher rate of poor maternal or infant outcomes in this cohort of 152 women, after controlling for CD4, VL, ART, maternal age, BMI and anemia.

Adverse Pregnancy Outcome by IPT Use



Logistic Regression for having an adverse pregnancy outcome

		Unadjusted OR	95%CI	Adjusted OR	95%CI
IPT	Yes	Ref			
	No	2.02	(0.92, 4.67)	2.79	(1.13, 7.39)
Maternal Age	<35 years	Ref			
	≥35 years	0.40	(0.06, 1.50)	0.62	(0.09, 2.73)
CD4	≥350 cells/mm^3	Ref			
	<350 cells/mm^3	0.36	(0.14, 0.83)	0.24	(0.08, 0.64)
Viral Load	<1000 copies/mL	Ref			
	≥1000 copies/ml	1.40	(0.54, 3.22)	2.16	(0.65, 7.21)
PMTCT Regimen	cART	Ref			
	AZT monotherapy +/- sd NVP or no ART	1.01	(0.44, 2.43)	0.72	(0.22, 2.20)
BMI	BMI ≥ 21.5 kg/m^3	Ref			
	BMI < 21.5 kg/m^3	3.80	(0.67, 21.45)	3.81	(0.62, 23.83)
Anemia	Hgb ≥8.5 g/dL	Ref			
	Hgb < 8.5 g/dL	7.13	(0.66, 156.11)	16.30	(1.24, 421.67)

**Adjusted for CD4, VL, ART type, maternal age, anemia*

→Higher risk adverse pregnancy outcome: no IPT, low CD4, anemia

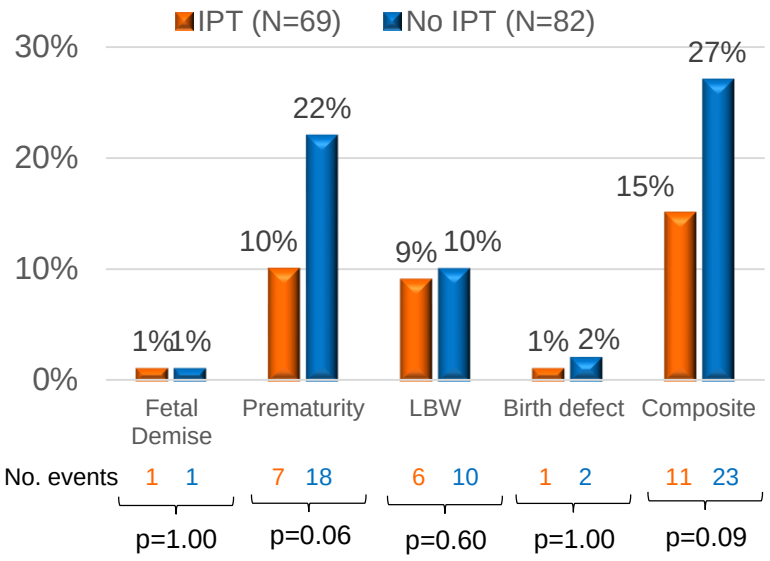
TB disease:
Maternal: 1 case (no IPT)
Infant: No cases

Tshepiso Cohort vs APPRISE RCT Trial

Salazar-Austin N et al. CROI 2019, Seattle, WA Abs. 77

Tshepiso: Observational 2nd/3rd trimester IPT (self-reported); 152 deliveries (69 IPT, 82 no IPT)

Tshepiso
Adverse Pregnancy Outcome by IPT Use

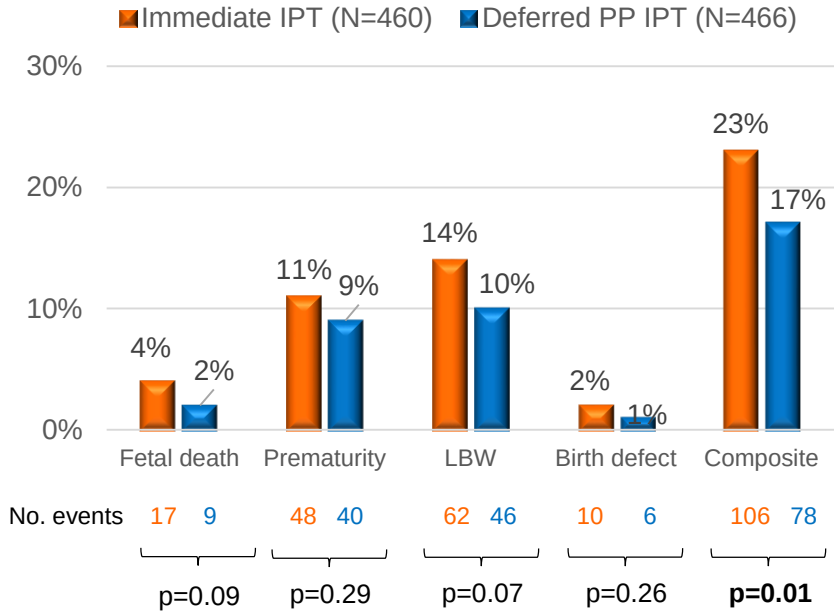


TB disease:
Maternal: 1 case (no IPT)
Infant: No cases
Death:
Maternal: 0 (IPT), 1 (no IPT)
Infant: 1 (IPT), 0 (no IPT)

Gupta A et al. CROI 2018 Boston Abs. 142LB

Apprise: RCT of immediate (2nd/3rd trimester) IPT vs deferred (12 wk postpartum) IPT; 962 deliveries (460 Immediate, 466 Deferred)

APPRISE RCT
Adverse Pregnancy Outcome by Immediate vs Deferred IPT



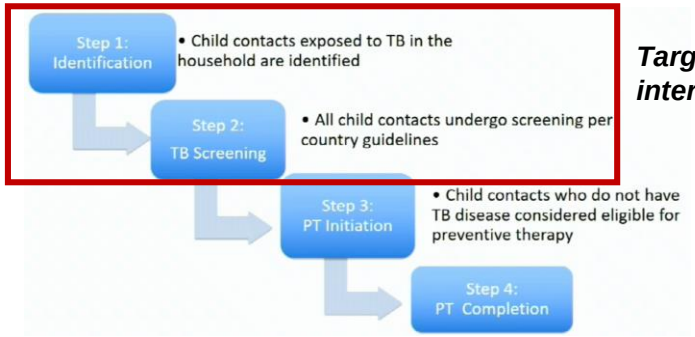
TB disease:
Maternal: 3 (immediate), 3 (deferred)
Infant: 0 (immediate), 1 (deferred)
Death:
Maternal: 2 (immediate), 4 (deferred)
Infant: 11 (immediate), 17 (deferred)

Severe pregnancy outcome composite:
Immediate: 6.3%
Deferred: 4.6%
P=0.27

Improving Child TB Contact Management, Lesotho – PREVENT Study

Hirsch-Moverman Y et al. CROI 2019 Seattle, WA Abs.79

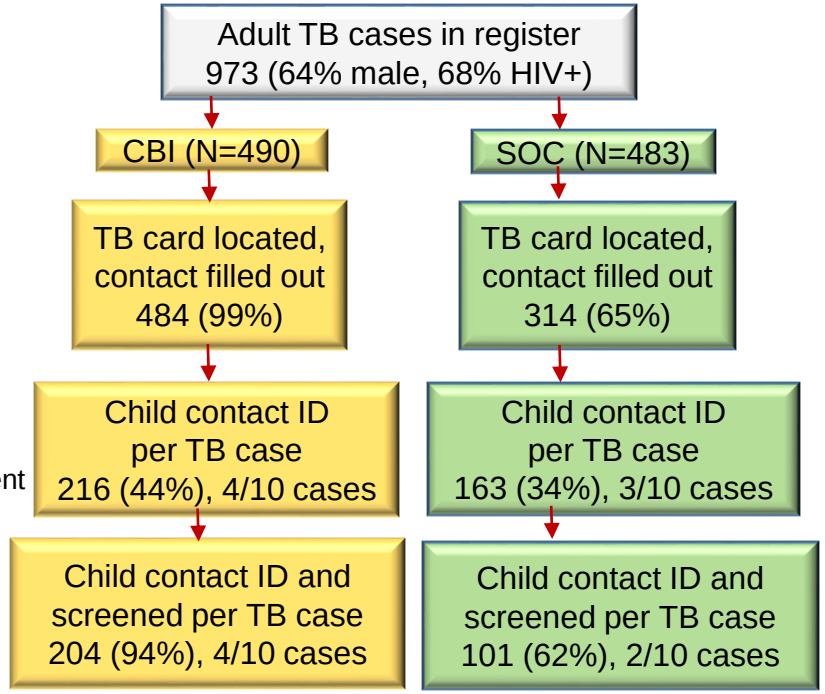
- Cluster-randomized trial of community-based intervention (10 clinics) vs SOC (10 clinics) to improve identification and screening of child contacts.
- All adult TB pt newly registered at clinics Jan 2017-June 2018 and child contacts included, with data collection from medical records.



Target of CBI intervention

Comparison of Study Interventions

	SOC	CBI
Three I's training	X	X
Child contact screening for TB	X	X
PT provision to child contacts	X	X
Child screening and PT provision training according to clinical algorithm		X
Nurse mentorship and monitoring		X
Health education in facilities and community for caregivers using PT literacy curriculum		X
Community-based village health workers (VHW) working with facility-based VHW to link to services		X
Consistent community support via VHW		X



Identification: # child contacts/adult case was low,not significantly different

Screening: More child contacts/adult case screened with CBI but not statistically significant

Yield: Non-significant trend for higher yield at CBI sites

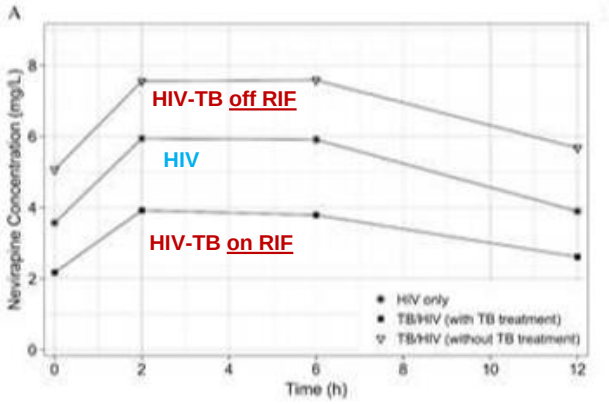
p=0.08

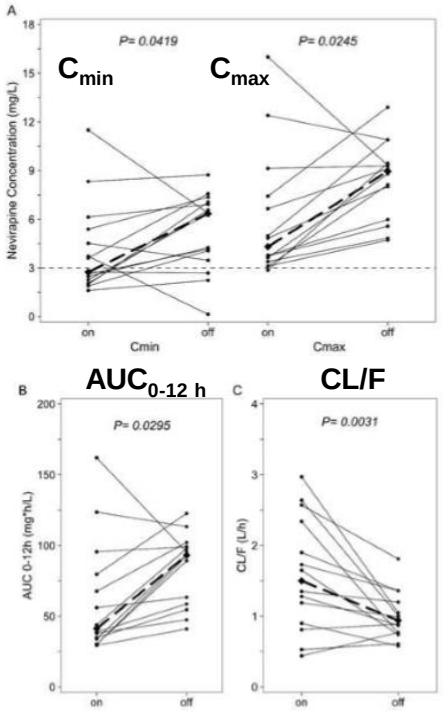
Nevirapine PK is Modified by TB Therapy with Rifampin in Young Children

Kwara A et al. CROI 2019 Seattle, WA Abs.825

- HIV+ children with (N=30) or without TB (N-23) aged 3-35 months or <10kg started on NVP 200 mg/m^2 + 2NRTI with 2-week lead in.
- Proportion of children with NVP C_{min} <3 mg/L was 61% in HIV/TB coinfected children and 31% in HIV only (p=0.03).
- In multivariate analysis, TB coinfection and CYP2B6 516 genotype influenced NVP PK (differences only significant for CYP2B6 516GG and not GT or TT genotypes).

Median NVP Level Post-Dose Over Time
HIV only, HIV/TB on TB rx, HIV/TB off TB rx



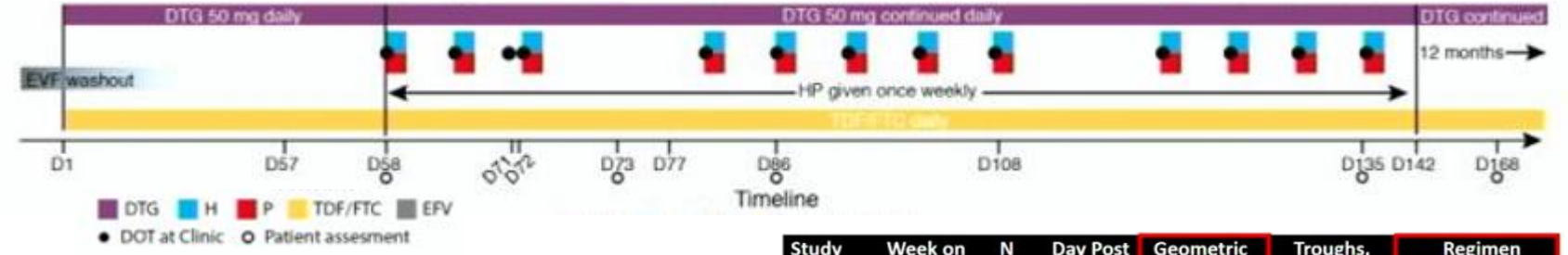


- In 14 HIV/TB children with PK on and off RIF, NVP $AUC_{0\text{-}12h}$ was ↓ by 34% & CL/F ↑ by 45% during coadministration of NVP/RIF.

Safety of Weekly INH/Rifapentine (3HP) in HIV+ Adults on DTG-ART

Dooley KE et al. CROI 2019, Seattle, WA Abs. 80LB

- 61 adults with suppressed VL on EFV-ART with indication for prophylaxis latent TB → switched to DTG (50 mg QD) ART x 8 wks (EFV washout) and then PK safety evaluated with weekly HP x 12 wks.



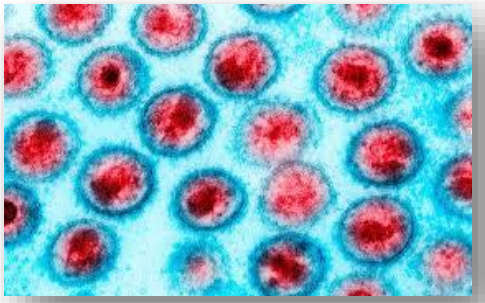
AE	N	Prior to 1st HP dose	After 1st HP dose
Grade 2	2	1[a]	1[b]
Grade 3	3	1[c]	2[d]
Grade 4	0	0	0
Death	0	0	0

[a]GI disturbance; [b]flu-like reaction;
[c]elevated creatinine [d]elevated creatinine, hypertension

Study Day	Week on 3HP	N	Day Post HP Dose	Geometric mean	Troughs, 5th and 95th %	Regimen
57/58		60	0	1003	500 -2080	DTG alone
59	Week 1	30	1	1053	412 - 1834	DTG+HP
72	Week 2	30	7	492	200-1063	DTG+HP
73	Week 3	60	1	657	295-1502	DTG+HP
74	Week 3	60	2	355	134-933	DTG+HP
78	Week 3	30	6	388	140 - 794	DTG+HP
108	Week 8	60	1	703	289 - 1603	DTG+HP
109	Week 8	60	2	394	121 - 1079	DTG+HP

*HP doses were given on Days 58, 65, 72, 79, 86, 93, 100, 107, 114, 121, 128, 135

- Trough DTG levels ↓ ~50% and AUC ↓ ~30% with HP, but median values >300 ng/mL all time points (IC90 64 ng/mL); viral suppression maintained (1 post-HP-treatment rebound 2300, with suppression on 2nd VL). **Concluded <u>no</u> dose increase needed**.

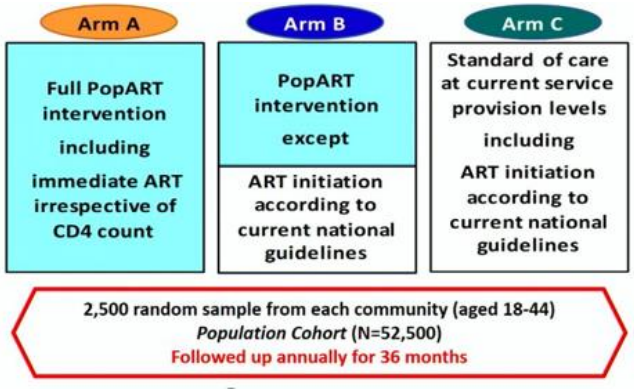


Test and Treat, Viral Load Testing, Viral Suppression

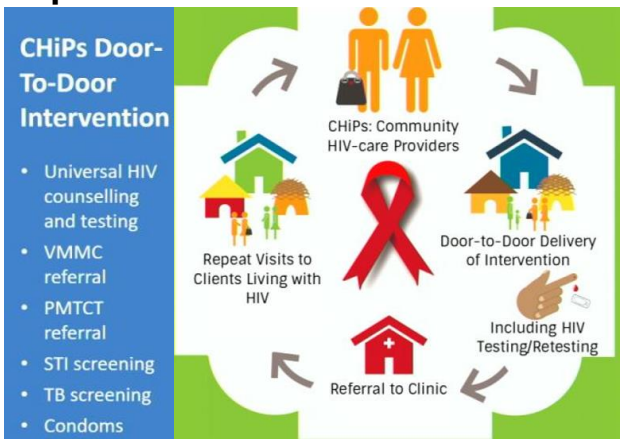
Impact of Universal Testing and Treatment in Zambia and South Africa – HPTN 071

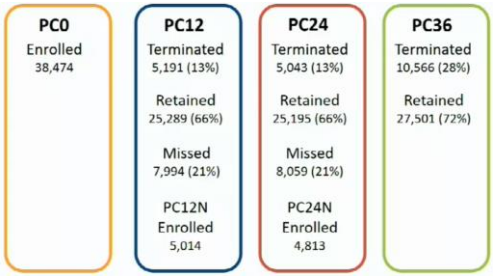
Hayes RJ et al. CROI 2019, Seattle, WA Abs. 92LB

- Universal test and treat – 21 communities randomized to one of 3 arms (7 communities per arm); primary outcome HIV incidence.

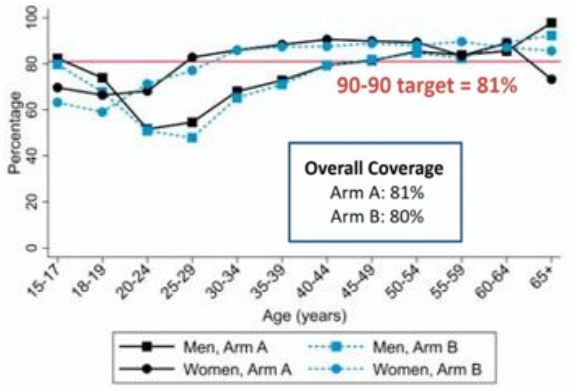


Pop-ART Combination Intervention





ART Coverage in Arm A (Pop-ART universal) & Arm B (Pop-ART national) at End of Trial



Viral Suppression by Arm

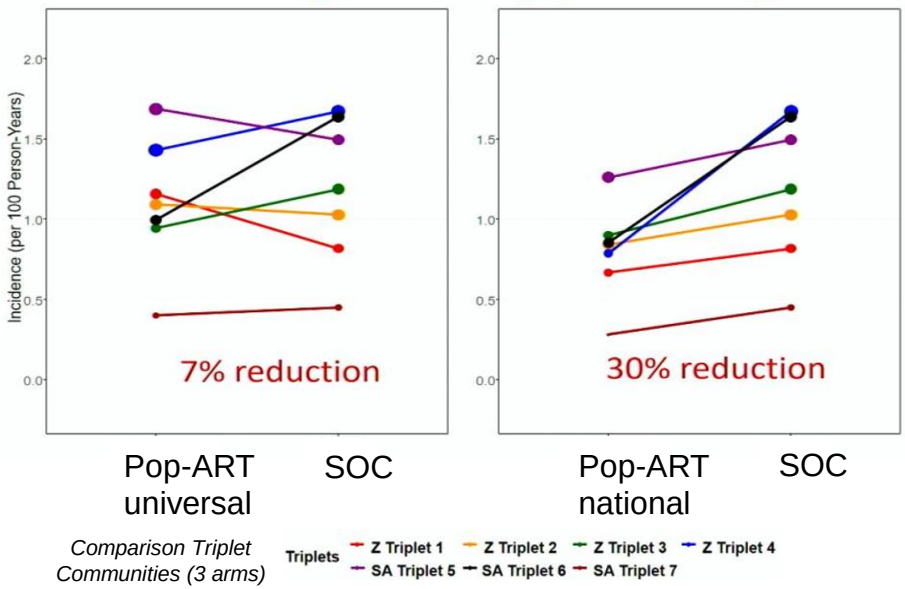
	Pop-ART Immediate	Pop-ART National guide	SOC
Viral suppression	1531/2159 (72%)	1318/1891 (68%)	1480/2183 (60%)
Adjusted prevalence ratio*	1.16 (0.99, 1.36)	1.08 (0.92, 1.27)	1
VS compared to SOC	16% increase	8% increase	
P value	0.07	0.30	

Adjusted for age category, sex

Impact of Universal Testing and Treatment in Zambia and South Africa – HPTN 071

Hayes RJ et al. CROI 2019, Seattle, WA Abs. 92LB

Primary endpoint: Incidence PC12 to PC36 by Community



- PopART achieved first 2 UNAIDS 90-90 targets
- PopART with ART by local guidelines reduced incidence by 30% in these high burden settings
- Community-based services for universal HIV testing and linkage are key component of global combination prevention

Primary endpoint: Incidence in PC12-PC36

	Pop-ART Immediate	Pop-ART National guide	SOC
HIV incidence	198/12,990 (1.45%)	157/14,149 (1.06%)	198/12,563 (1.55%)
Adjusted rate ratio*	0.93 (0.74, 1.18)	0.70 (0.55, 0.88)	1
Incidence compared to SOC	7% reduction	30% reduction	
P value	0.51	0.006	

* Adjusted for age category, sex and baseline community HIV prevalence; reported numbers include imputation for PC12 and PC24 missed visits

Impact of Universal Testing and Treatment Botswana

Wirth K et al. CROI 2019 Seattle, WA Abs.95

- Pair-matched communities randomized trial 30 communities Botswana, October 2013, interventions ended March 2018, FU completed April 2018

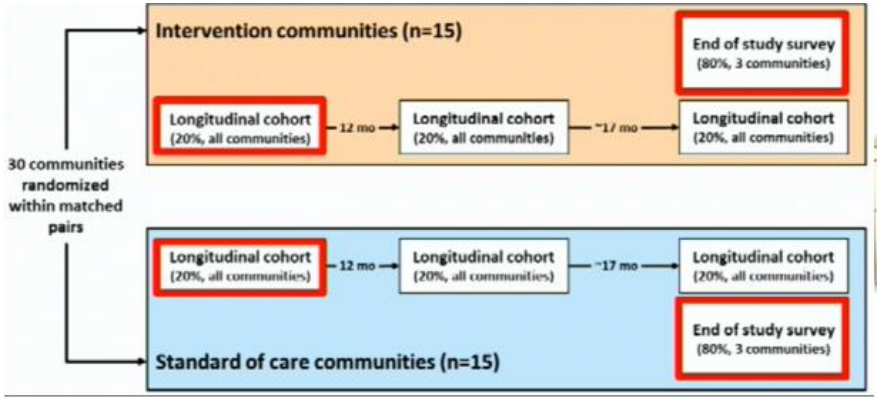
Intervention (15 communities)

- Community mobilization
- Home-based and mobile HIV testing campaigns, targeted testing
- Linkage to care support: scheduled clinic visits, SMS reminder, active tracing is missed apt
- Early ART (universal from June 2016 at 1st visit)
- Strengthened VMMC

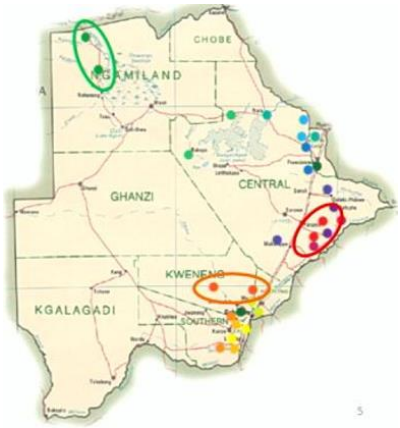
SOC (15 communities)

- ART if CD4 <350 or WHO III/IV or pregnant until June 2016 when moved to universal ART

- Intervention uptake assessed through end-of-study survey in communities not in longitudinal cohort



- Selected 1 pair of communities per region

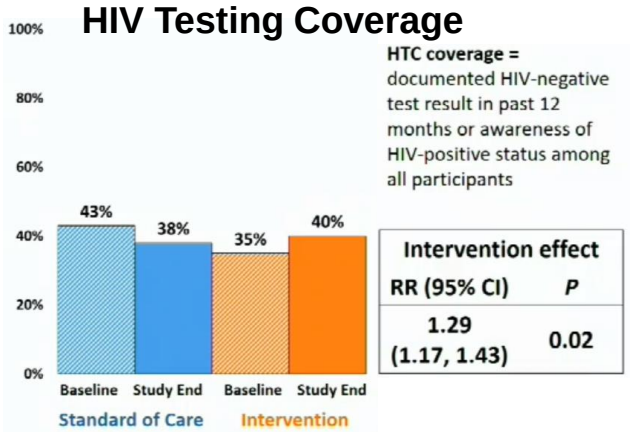


HIV Diagnosis, ART, Suppression and VMMC Increased in Both Arms, with Greater Increase in Intervention

Wirth K et al. CROI 2019 Seattle, WA Abs.95

- Significant increase across cascade with intervention.

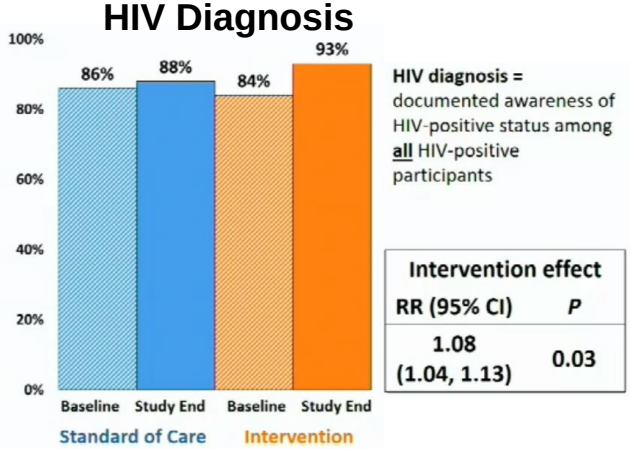
HIV Testing Coverage



HTC coverage = documented HIV-negative test result in past 12 months or awareness of HIV-positive status among all participants

Intervention effect	
RR (95% CI)	*P*
1.29 (1.17, 1.43)	0.02

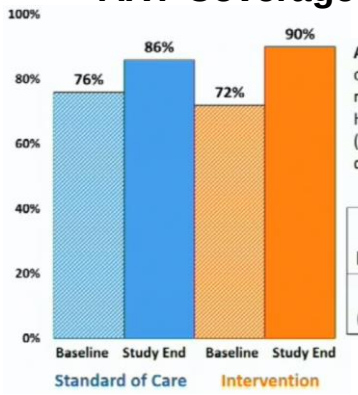
HIV Diagnosis



HIV diagnosis = documented awareness of HIV-positive status among **all** HIV-positive participants

Intervention effect	
RR (95% CI)	*P*
1.08 (1.04, 1.13)	0.03

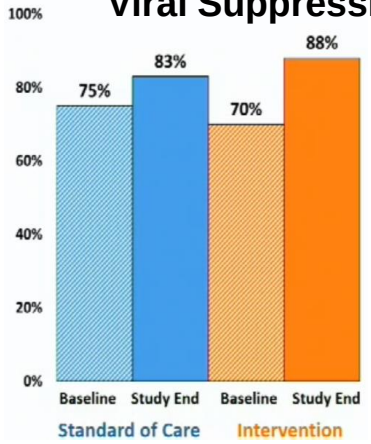
ART Coverage



ART coverage = documented current receipt of ART among **all** HIV-positive participants (regardless of prior diagnosis)

Intervention effect	
RR (95% CI)	*P*
1.11 (1.07, 1.17)	0.02

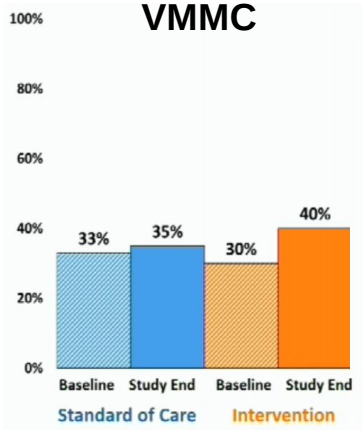
Viral Suppression



Viral suppression = VL <400 copies/mL on ART among **all** HIV-positive participants (regardless of diagnosis/ART status)

Intervention effect	
RR (95% CI)	*P*
1.12 (1.09, 1.16)	0.02

VMMC



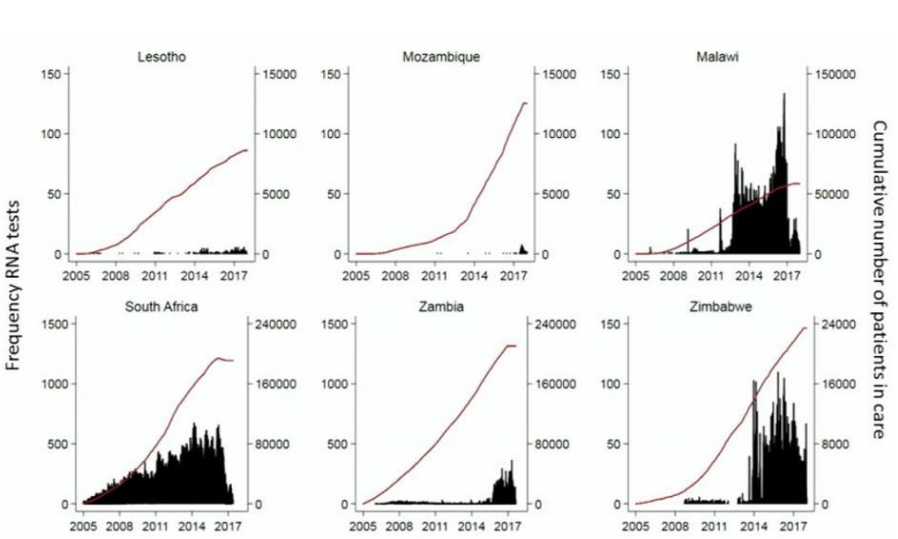
Male circumcision = self-reported receipt of circumcision among HIV-negative men aged 18-49 years

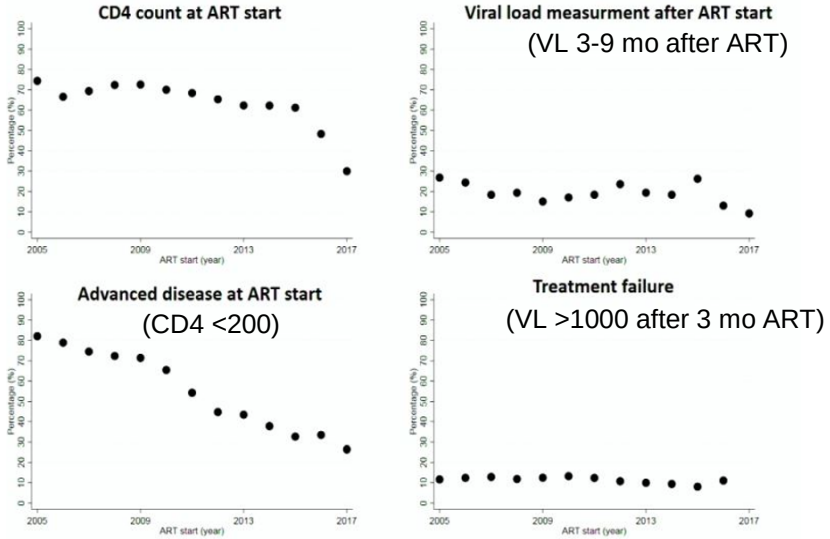
Intervention effect	
RR (95% CI)	*P*
1.26 (1.17, 1.35)	0.03

Trends in CD4 and Viral Load Testing in Southern Africa: Analysis of 6 Countries

Egger M et al. CROI 2019 Seattle, WA Abs.150

- 17 sites in 6 countries in South Africa – evaluated trends 2005-2018 in CD4 and VL testing in adults.
- 542,138 pts, 65% female; median age 34.5 years, median FU 44.9 months; 51% started ART 2009-2013, 30% 2014-2018



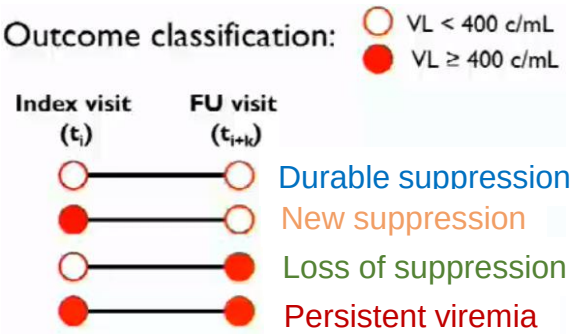


- Scale up VL testing in some but not all countries: 3 countries have scaled up VL testing (black): Malawi, S Africa, Zimbabwe.
- CD4 count at ART start has ↓ (advanced disease may go undetected); VL testing low levels; advanced disease ↓ in 2017 ~20%; failure ~10% without much change.

Factors Associated with Persistent Viremia with Universal Test and Treat, Uganda

Patel EU et al. CROI 2019 Seattle, WA Abs.96

- Rakai Community Cohort Study of adults 15-49 years, 5 surveys Nov 2011 and Feb 2017
- HIV VL measured in all HIV+ persons in 2011, 2015 and 2016



Overall: 1883

- Durable suppression 949 (50%)
- New suppression 571 (30%)
- Loss of suppression 54 (3%)
- Persistent viremia 309 (16%)

- Factors associated with persistent virema included:
  - Being young (<29 years)
  - Being Male
  - Never Marries
  - Recent in-migration

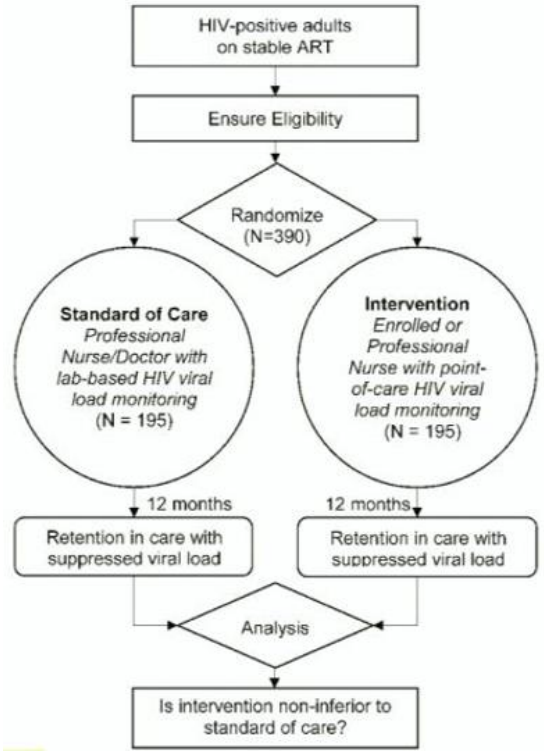
Characteristic	Crude RRR (95% CI)	Adjusted RRR (95% CI)[a]
Age group, years		
15-29	**1.91 (1.28-2.83)***	**1.83 (1.22-2.75)***
30-39	1.46 (0.99-2.16)	**1.55 (1.05-2.29)***
40-49	Ref.	Ref.
Male sex	**2.11 (1.67-2.68)***	**2.22 (1.70-2.90)***
Marital status		
Married	Ref.	Ref.
Previously married	0.82 (0.64-1.05)	0.92 (0.72-1.18)
Never married	**2.38 (1.71-3.31)***	**1.82 (1.30-2.55)***
Educational attainment		
None	Ref.	Ref.
Primary	1.07 (0.75-1.54)	1.00 (0.70-1.43)
Secondary or more	1.38 (0.87-2.18)	1.43 (0.92-2.24)
Migration status		
Permanent resident	Ref.	Ref.
In-migrant (0-2 years)	1.37 (0.98-1.91)	**1.95 (1.36-2.80)***
In-migrant (>2 years)	1.12 (0.75-1.68)	1.45 (0.97-2.17)
Alcohol use (past year)	1.18 (0.93-1.48)	0.99 (0.78-1.26)
No. of sex partners (past year)		
0-1	Ref.	Ref.
2-3	**1.33 (1.05-1.70)***	0.94 (0.73-1.20)
>3	**1.96 (1.46-2.65)***	1.20 (0.88-1.64)

[a] Adjusted for index survey visit, age, sex, marital status, education status, migration status, alcohol use, and number of sexual partners.

Point of Care Viral Load Testing Improves Viral Suppression and Retention in Care

Drain PK et al. CROI 2019 Seatte, WA Abs. 53LB

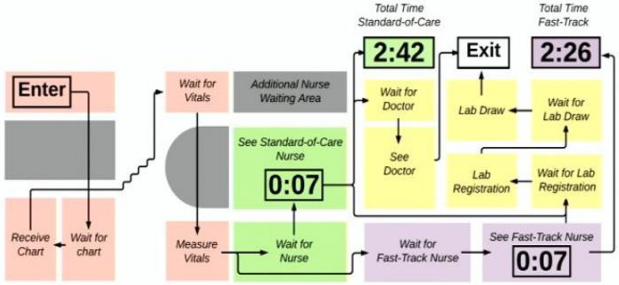
- RCT at public clinic in Durban S Africa in adults >18 years presenting for 6 month post ART start FU visit
  - Intervention: POC viral load testing (Xpert) and same day counseling with task shifting to nurse for stable pt
  - SOC: lab viral load testing and care from nurse)



Primary outcome: 12 mo viral suppression and retention (pick up drugs)

	Intervention Arm	Standard-of-care Arm	Absolute Risk Difference	Non-inferiority (1-side 95% CI) P value	Superiority (2-side 95% CI) P value
Viral suppression (<200 copies/mL) and Retention in care at study clinic	89.7% (175/195)	75.9% (148/195)	**13.9%**	(≥7.6) <0.001	(6.4-21.2) <0.001

After 12 mo clinical FU, the intervention increased viral suppression and retention in care at the study clinic by 13.9% (95% CI 6.4-21.2%)



Total pt visit duration for POC VL testing was 2½ - 3 hours

Point of Care Viral Load Testing Improves Viral Suppression and Retention in Care

Drain PK et al. CROI 2019 Seatte, WA Abs. 53LB

- Secondary outcomes

Viral suppression <50 c/mL and retention

	Intervention Arm (N=195)	Standard-of-Care Arm (N=195)	Absolute Risk Difference	Superiority P value
Viral suppression (<200 copies/ml)	93.3%	83.1%	**10.3%**	0.003
Retention in care at study clinic	92.3%	84.6%	**7.7%**	0.026
Viral suppression ≤50 copies/mL and retention in care	85.6%	71.3%	**14.4%**	<0.001
Viral suppression <200 copies/mL and retention in care at any clinic	90.8%	78.5%	**12.3%**	0.001

Entry VL and Communication of Results

	Intervention Arm	Standard-of-Care Arm	Difference
Entry of viral load result into health information system	100%	100%	**0%**
Median [IQR] days to enter viral load result in health information system	0 [0-0]	2 [1-4]	**2 days**
Communication of viral load result to patient	99.8%	81.5%	**18.3%**
Median [IQR] days to communicate viral load result to patient	0 [0-0]	28 [28-54]	**28 days**

Follow-Up HIV Care and Treatment

	Intervention Arm	Standard-of-Care Arm	Cox Hazard Ratio	Superiority P value
Switch to second-line ART after viral failure (>1,000 copies/ml x2)	6/6 (100%)	4/9 (44%)	--	--
Median [IQR] days to switch to second-line ART after viral failure	1 [0-7]	76 [20-134]	**10.9**	**0.005**
Referral into community-based ART delivery program	116 (60%)	52 (27%)	--	--
Median [IQR] days to referral into community-based ART program	168 [168-175]	261 [231-281]	**3.5**	**<0.001**

Healthcare Utilization

	Intervention Arm	Standard-of-Care Arm	P value
Total clinic visits per patient	5.2 ±1.6	6.1 ±1.5	<0.001
Clinic visits with a Professional Nurse per patient	4.2 ±1.8	5.6 ±1.4	<0.001
Clinic visits with an Enrolled Nurse per patient	0.9 ±0.9	0.4 ±0.7	<0.001
Number of viral load tests per patient	2.0 ±0.3	1.9 ±0.5	0.006

	Point-of-care Test	Centralized Laboratory Test
Cost per HIV viral load test	$21.53	$25.98
Total over 5 years testing per patient	$129.18	$155.88

Dolutegravir Studies in Adults

12 Month Outcomes on DTG ART Botswana: The BEAT Cohort Study

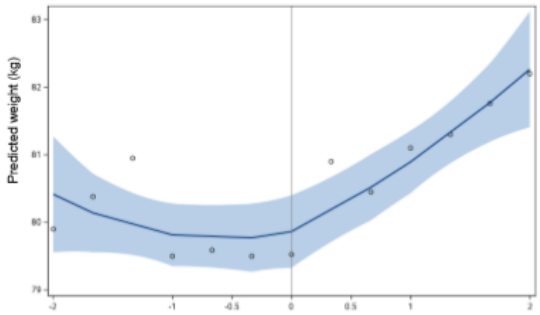
Avalos A et al. CROI 2019 Seattle, WA Abs. 505

- Observational study, with data abstraction electronic national HIV and lab database from 11 urban and semi-rural facilities.
- Data on 2,256 adults: 1,523 ART-naïve, 638 ART-switch, 95 highly ART-experienced.
  - Median age 39 yr (range 32-48), 63% female
  - VL reporting in only 50 % (N=1134)
- 77 women in database pregnant (11 on DTG preconception), no NTD.

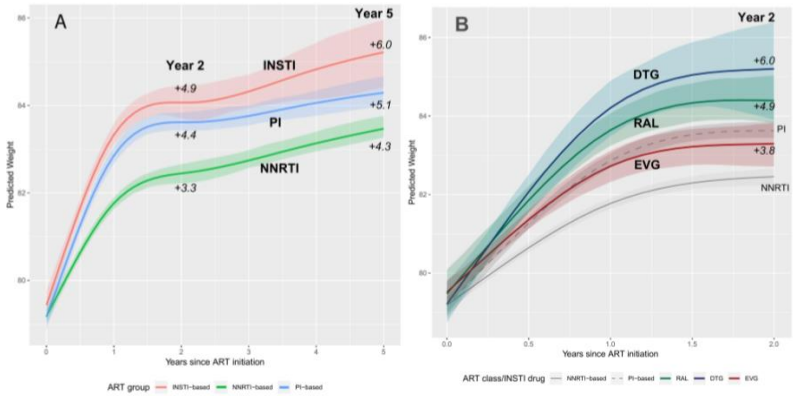
Cohort	% with 12-Month Viral Load Measurements	% VL Suppression <400 copies/mL with (95% CL) Overall and by gender.	Adverse Events % (#) (DAIDS – Grade 3)	LTFU % (#)	Deaths % (#)
Naïve *(n= 1523)*	**41%** *(n=623)*	Overall: **98.6%** *(97.3, 99.3)* Female: **98.8%** Male: **98.2%**	**<1%** *(n=2)*	**6.3%** *(n=33)*	**1.9%** *(n=30)*
Switched *(n=638)*	**70%** *(n=436)*	Overall: **96.9%** *(94.8, 98.1)* Female: **96.3%** Male: **98.3%**	0	0	0
Highly Treatment Experienced *(n=95)*	**79%** *(n=75)*	Overall: **89.1%** *(77.3, 95.1)* Female: **90.1%** Male: **86.4%**	**1%** *(n=1)*	0	0
Total *(n=2256)*	**50%** *(n=1134)*	**Overall: 97.4%** *(96.4, 98.2)*	**<1%** *(n=3)* *Women: 2*	**1.4%** *(n=33)* *Women: 51.6%*	**1.3%** *(n=30)* *Men: 67%*

Dolutegravir and Weight Gain

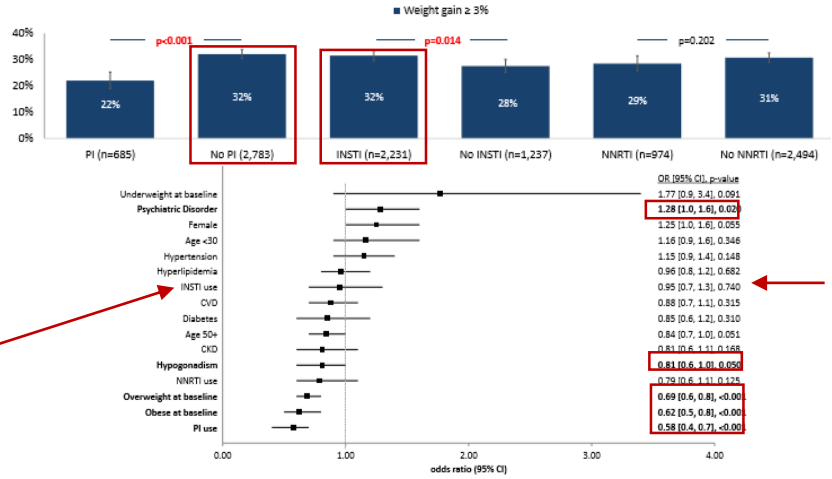
- *Lake J. Abs. 669:*
  - 972 adults switched to InSTI in A5001, A5322; median 7.8 yr prior ART
  - Women, black and age >60 most increase
  - DTG greatest weight gain



- Bourgi K. Abs. 670:
  - 24,001 ART naïve pts starting ART 2007-2016 (NNRTI 11,826; PI 7,436, InSTI 4,440)
  - ART naïve starting InSTI, esp DTG and RAL at risk of weight gain
  - No difference by sex and race

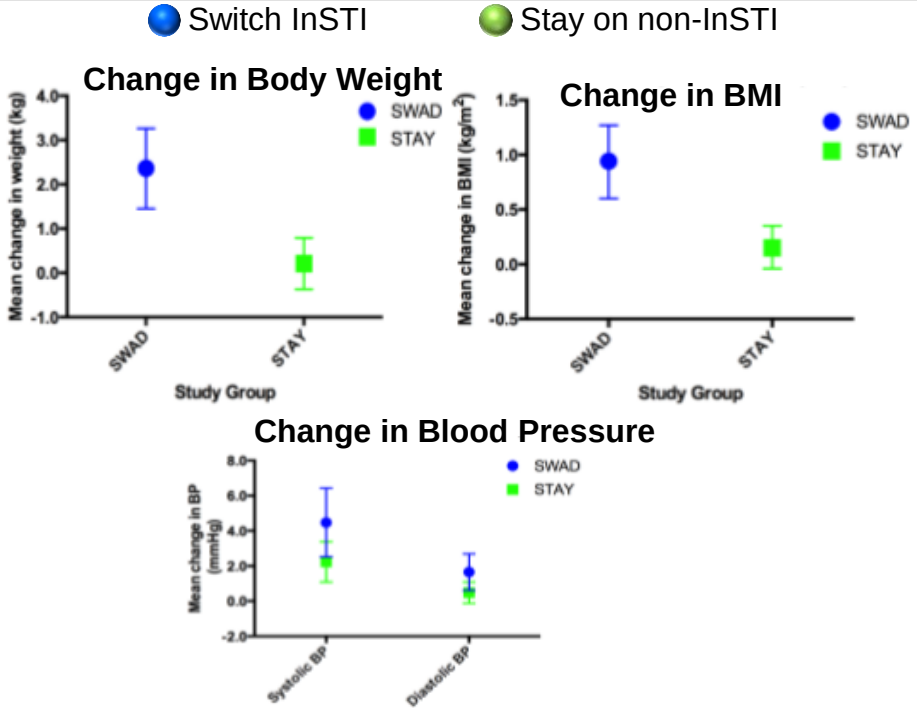


- *McComsey G. Abs. 671*
  - 3,468 pt with viral suppression and BMI measure at start and 1-2 years
  - ≥3% weight gain in 30%
  - Associated with lower/higher BMI baseline, non-PI regimen, psych disorder
  - InSTI *not* associated in multivariate

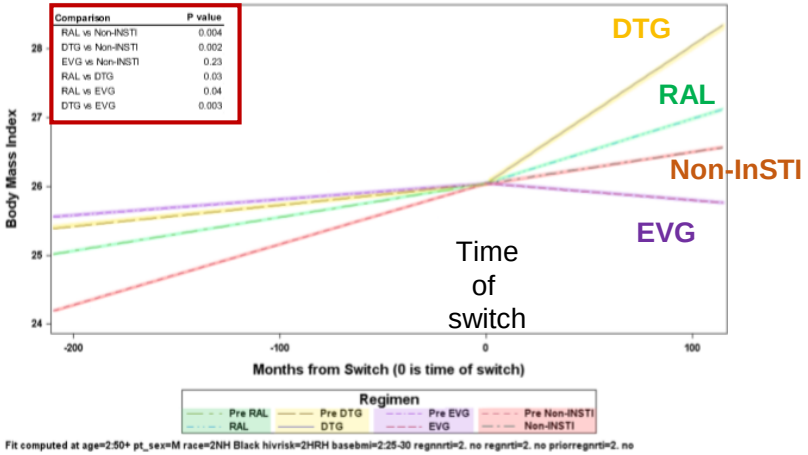


Dolutegravir and Weight Gain

- *Kerchberger AM. Abs. 672*
  - WIHS 2008-2017, evaluated weight in suppressed women who switched to InSTI or stayed on non-InSTI regimen
  - InSTI switch associated with significant ↑ body weight, BMI, total body fat, body circumference measure and blood pressure compared to staying on non-InSTI ART

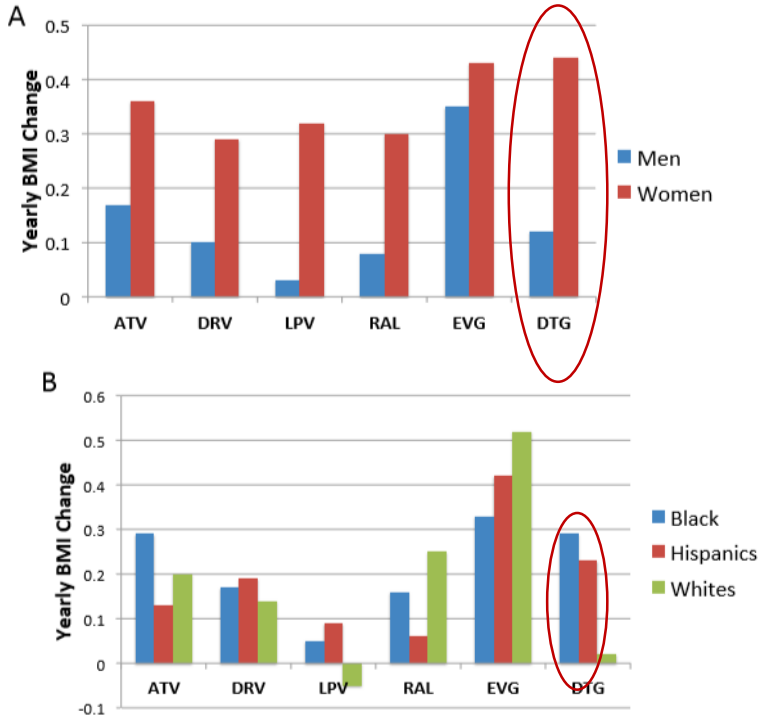


- *Palella FJ. Abs. 674*
  - BMI data from 653 pt from HIV Outpatient Study (HOPS)
    - 368 (56%) switched to InSTI
    - 285 (44%) switched to non-InSTI
  - Weight gain was higher among InSTI switch, and was greatest with DTG (yellow)
  - Associated factors: female, Hispanic ethnicity



Dolutegravir and Weight Gain

- *Bedimo R. Abs. 675*
  - Yearly change in BMI following initiation of PI or InSTI ART
  - Change BMI greatest among women compared to men
  - EVG and DTG had more BMI ↑ than PI
  - Weight gain with EVG had did not vary by sex/ethnicity
  - Weight gain with DTG greatest in women and black/hispanics



DTG vs LPV/r for Second-Line Therapy (DAWNING) Viral Efficacy by Presence Baseline DR Mutations

Brown D et al. CROI 2019 Seattle, WA Abs.144

→ Failing 1st line NNRTI
→ No resistance to PI/ InSTI
→ **At least 1 fully active NRTI (based on resistance testing)**

312 **DTG + 2 NRTI**

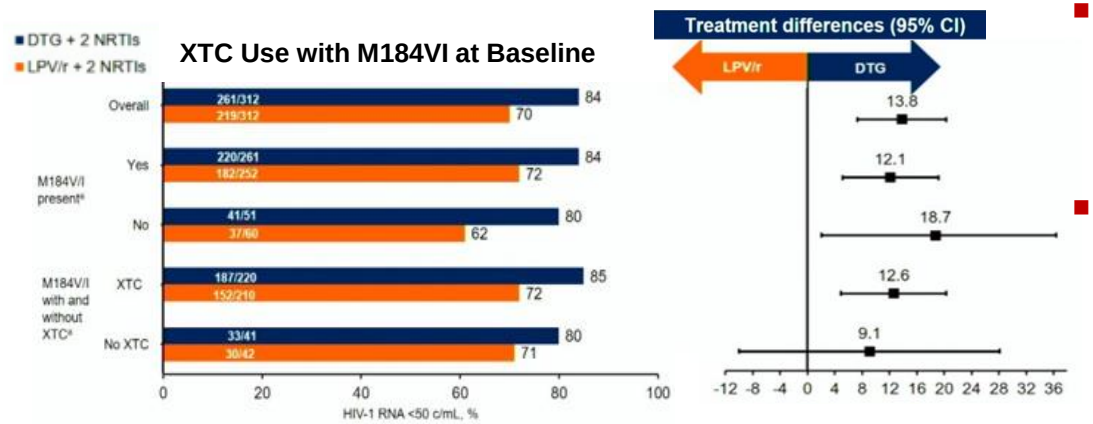
312 **LPVr + 2 NRTI**

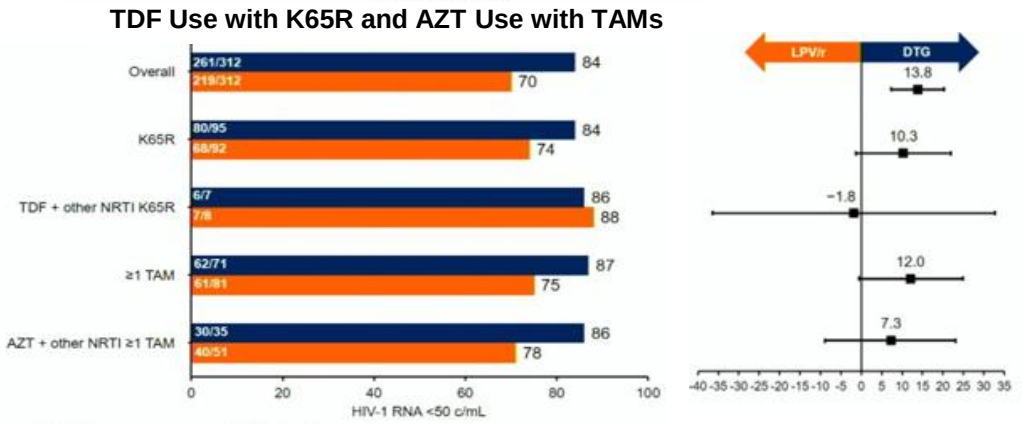
Primary endpoint VL<50 week 48:

Baseline Drug Resistance Mutations

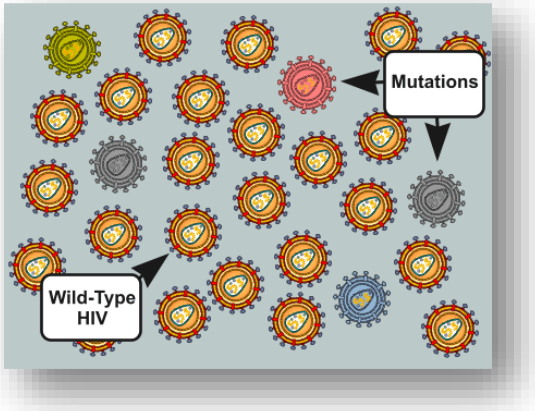
	M184 V/I overall	M184V/I Alone	M184 V/I + ≥1 TAM	K65R	K70E	1 TAM	≥2 TAMs
DTG	84%	25%	59%	30%	11%	17%	6%
LPV/r	81%	27%	54%	29%	12%	20%	6%

Outcomes Overall and by Baseline Resistance Subgroups at Week 48





- Overall results show superior efficacy of DTG over LPV/r for 2nd line ART.
- Consistent with overall results, VL response rates were high regardless of pre-existing resistance to one of the NRTIs in the background regimen, including when XTC used in presence of M184 V/I.
- Rates viral failure lower in DTG arm regardless of baseline NRTI resistance and 2nd line background NRTI.



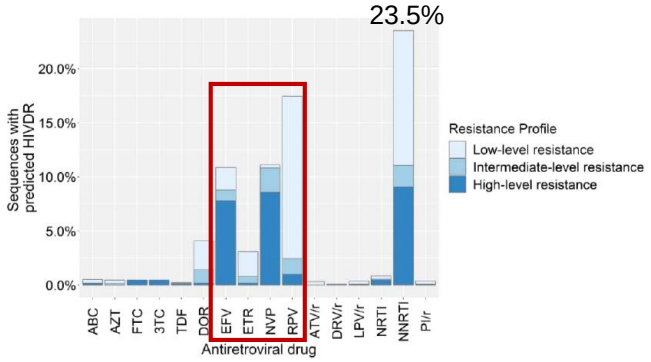
ARV Drug Resistance

Population-Based Monitoring of Pre-ART Drug Resistance, Eswatini

Khan S et al. CROI 2019 Seatte, WA Abs. 537

- Evaluated pre-treatment drug resistance in HIV+ ART-naïve adults enrolling in MaxART trial in Hhohho region Sept 2014-Aug 2017 (N=3485); testing done for 2578 (98%) available samples.
- Resistance seen in 24.1%, primarily driven by NNRTI resistance; 286 (11.1%) had mutations conferring resistance to 1st line NNRTI EFV/NVP.
- Dual class resistance to NNRTI and NRTI drugs was rare (14, 0.5%).

Resistance Level	Drug Class				
	PI	NRTI	NNRTI	NNRTI: EFV or NVP	Any
Low level	0.3%	0.3%	12;5%	0.3%	13.0%
Intermediate	1.0%	0.1%	2.0%	2.2%	2.0%
High	1.0%	0.5%	9.1%	8.6%	9.2%
Overall	0.4%	0.9%	23.5%	11.1%	24.1%



- NNRTI resistance associated with female gender (aOR 1.4, p=0.05) and younger age at ART start (aOR 0.96 per 1 year increment, p<0.01).
- Supports move to DTG as 1st line ART in Eswatini.

HIV Drug Resistance, Population-Based Household Survey, South Africa

Moyo S et al. CROI 2019 Seattle, WA Abs. 152

- Cross-sectional population-based household survey 2017, including HIV testing and DBS resistance testing.
- 2,294 HIV+ → 2,246 VL result → 1,107 unsuppressed → 697 DR testing successful → 200 DR (27%), 497 no DR
- Primarily NNRTI resistance; dual resistance NNRTI/NRTI in 8%; low level resistance to 2nd line.
- Drug resistance in more than half on treatment, 15% naïve; no difference by sex and age.

Resistance	% weighted (95% CI)
Any resistance	27.4% (22.8-32.6)
NNRTI	18.9% (14.8-23.8)
NNRTI + NRTI	7.8% (5.6-10.9)
PI + NNRTI + NRTI	0.5% (0.1-2.1)

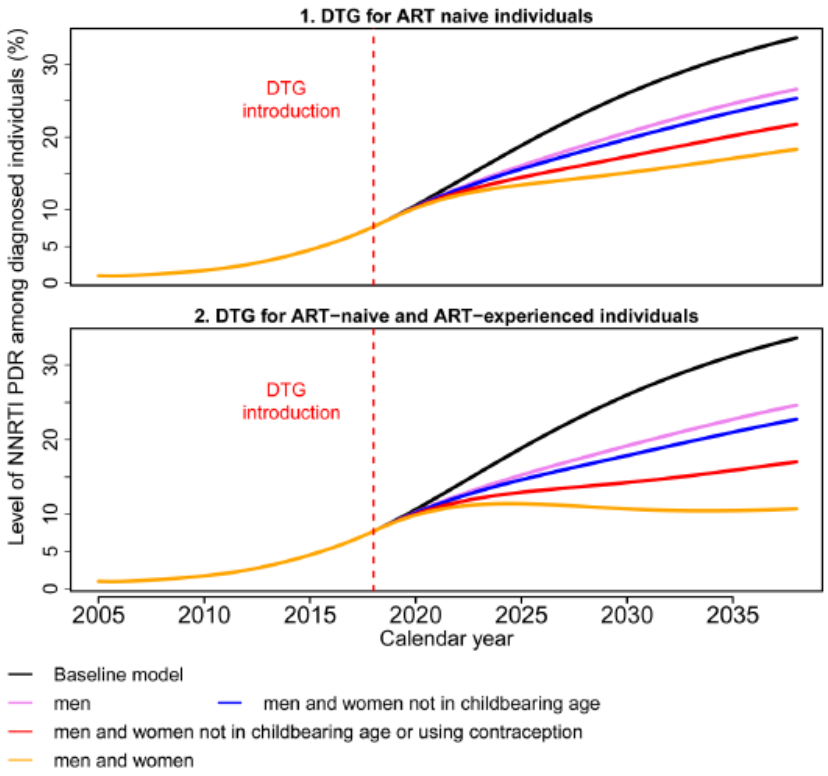
Variable	Any DRM (95% CI)	NNRTI only	NNRTI+NRTI
ARV status:			
On ART	**55.7% (42.6-67.9)**	14.3% (7.5-25.6)	**40.4% (29.6-52.2)**
Defaulters*	75.9% (59.2-87.3)	56.4% (34.4-25.7)	14.3% (2.5-52.1)
ARV-naïve	**15.3% (6.3-32.8)**	15.3% (6.3-32.8)	**0**
Sex:			
Male	29.4% (22.5-37.4)	19.6% (13.5-27.7)	9.7% (5.8-15.7)
Female	25.8% (19.8-32.8)	18.3% (13.2-24.8)	6.3% (4.2-9.5)
Age (years):			
0-14	33.7% (17.6-54.7)	17.7% (7.2-37.4)	14.9% (5.3-35.2)
15-24	30.5% (18.7-45.5)	22.1% (12.6-35.9)	5.7% (1.7-15.9)
25-49	26.6% (21.7-32.2)	18.6% (13.8-24.8)	8.2% (5.4-12.2)
50+	24.1% (14.8-36.7)	17.0% (8.9-30.0)	5.7% (2.5-12.8)

*Defaulter: stated were on ART but negative test ARV

Modeling Impact of DTG Introduction on NNRTI Resistance, South Africa

Hauser A et al. CROI 2019 Seattle, WA Abs. 538

- Epidemiologic modeling to investigate development of pre-ART NNRTI drug resistance (DR) under different scenarios of DTG introduction.
- Assumes DTG efficacy similar to NNRTI and dx and treatment rates constant from 2018.



- DTG to all pt regardless gender and treatment status results in lowest NNRTI resistance, 8.2%, in 2035.
- DTG limited to men (or men+women non-childbearing age) will not prevent increase in NNRTI DR to ~17% in 2035.
- Including men and women using contraception will stabilize resistance at 11.8%.

JAMA Network

“HIV Viral Load & Transmissibility of HIV Infection: “Undetectable Equals Untransmittable”

Robert Eisinger, PhD; Carl Dieffenbach, PhD ; Anthony Fauci, MD
January 10, 2019

The U = U concept bridges the best of biomedical science with current concepts in behavioral and social science by removing the sense of fear and guilt that a person may be harming someone else, as well as the feeling of self-imposed and external stigma that many people with HIV experience

U=U Symposium

THE LANCET

“Providers should discuss U=U with all patients living with HIV”

Sarah Calabrese, Kenneth Mayer
George Washington University, Washington, DC, USA (SC); and Harvard Medical School and The Fenway Institute, Boston, MA, USA
February 13, 2019

With evidence supporting undetectable=untransmittable (U=U) now overwhelming providers should be routinely communicating the message to all of their patients living with HIV.

UNDETECTABLE = UNTRANSMITTABLE

U=U refers to the concept that an individual with an undetectable HIV VL is **incapable** of transmitting their HIV infection to **sexual partners**[1]

Sexual partners

Undetectable VL in this context: **<200-400 c/ml**

"People who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner." The U.S. Centers for Disease Control and Prevention (CDC) (September, 2017)

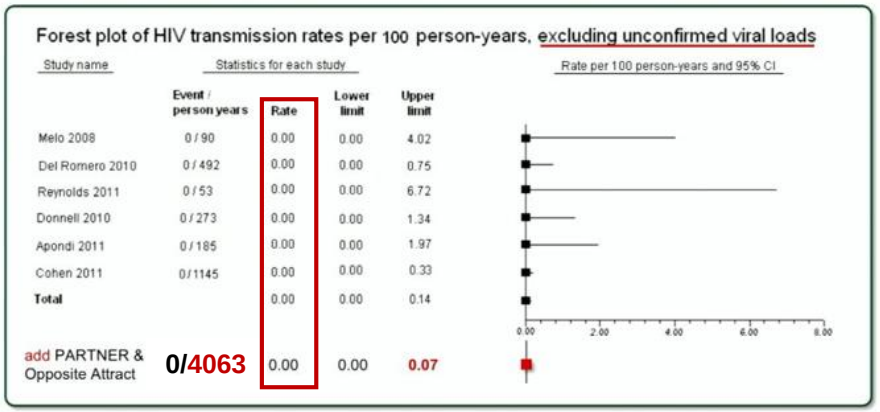
https://www.preventionaccess.org/undetectable

U=U Scientific Underpinning

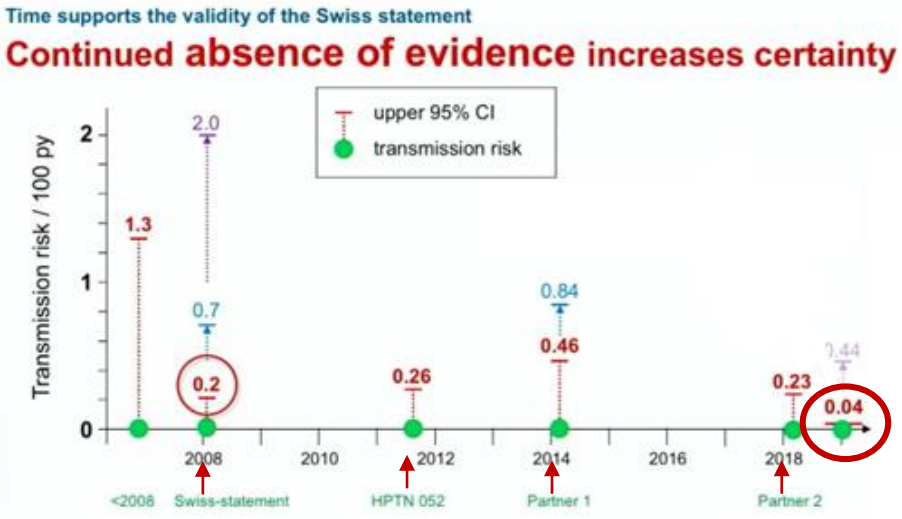
Vernazza PL et al. CROI 2019 Seattle, WA Symposium

- Provided scientific backdrop to U=U (undetectable in the studies defined as <200-400 c/mL).

Zero events, increasing number of observations



Loutfy 2013, PLOS One; Rodger Lancet 2019 in press; Bavinton Lancet HIV, 2018



- So far: **not a single documented case** of transmission during cART
- Continued **absence of evidence** is evidence
- All prospective studies evaluating the risk found **zero risk**!
- Even if risk is not zero, it is **< 1:1000 PY**

U=U Scientific Underpinning

Vernazza PL et al. CROI 2019 Seattle, WA Symposium

Proving the negative

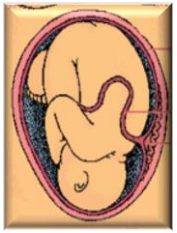
Difficult but not impossible

"In some circumstances it can be safely assumed that if a certain event had happened, evidence of it could be discovered by qualified investigators.

In such circumstances, it is perfectly reasonable to take the absence of proof of its occurrence as positive proof of its non-occurrence"

Copi, Introduction to Logic (1953) pg 95

U=U Scientific Underpinning



Areas of Uncertainty:

MTCT: Transmission seen in women with delivery VL <50 (who weren't <50 when got pregnant)

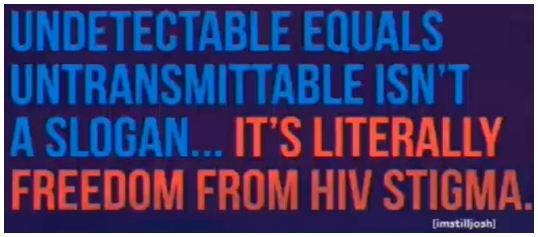
Breastfeeding: PROMISE two postnatal transmissions with undetectable maternal VL

For MTCT/BF, maybe U=U only if:

Undetectable - when get pregnant, throughout pregnancy, at delivery, and throughout breastfeeding

Community Voice on U=U

Foote C. CROI 2019 Seattle, WA Symposium



U=U IS a Game Changer

- Transforms social, sexual, & reproductive lives.
- Dismantles HIV stigma.
- Encourages getting tested and starting and staying on treatment and in care.
- Provides a strong public health argument for eliminating barriers to universal access to care (e.g., the third U = Unequal Access).

Language Matters

*"From a practical standpoint, **the risk is zero**."*
(Dr. Anthony Fauci, NIAID)

Be clear and consistent about risk.

Say:		Don't say:
Can't pass it on		Greatly reduces
Can't transmit		Extremely unlikely
Effectively no risk	VS.	Nearly impossible
No risk		Almost no risk
Zero risk		Close to zero
Prevents HIV		Helps prevent
Eliminates onward transmission		Makes it hard to transmit