British HIV Association
BHIVA

Professor Jeffery Lennox

Emory University School of Medicine
Atlanta, Georgia, USA

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Professor Jeffery Lennox	Dr. Lennox acts in a Consultancy capacity for Merck Inc, BMS and Gilead. He has also received a grant for research from Gilead and ViiV.
Date	**October 2014**

The AIDS Clinical Trials Group (ACTG) and the impact on the treatment of HIV: past, present (A5257) and for the future

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Atlanta, Georgia USA

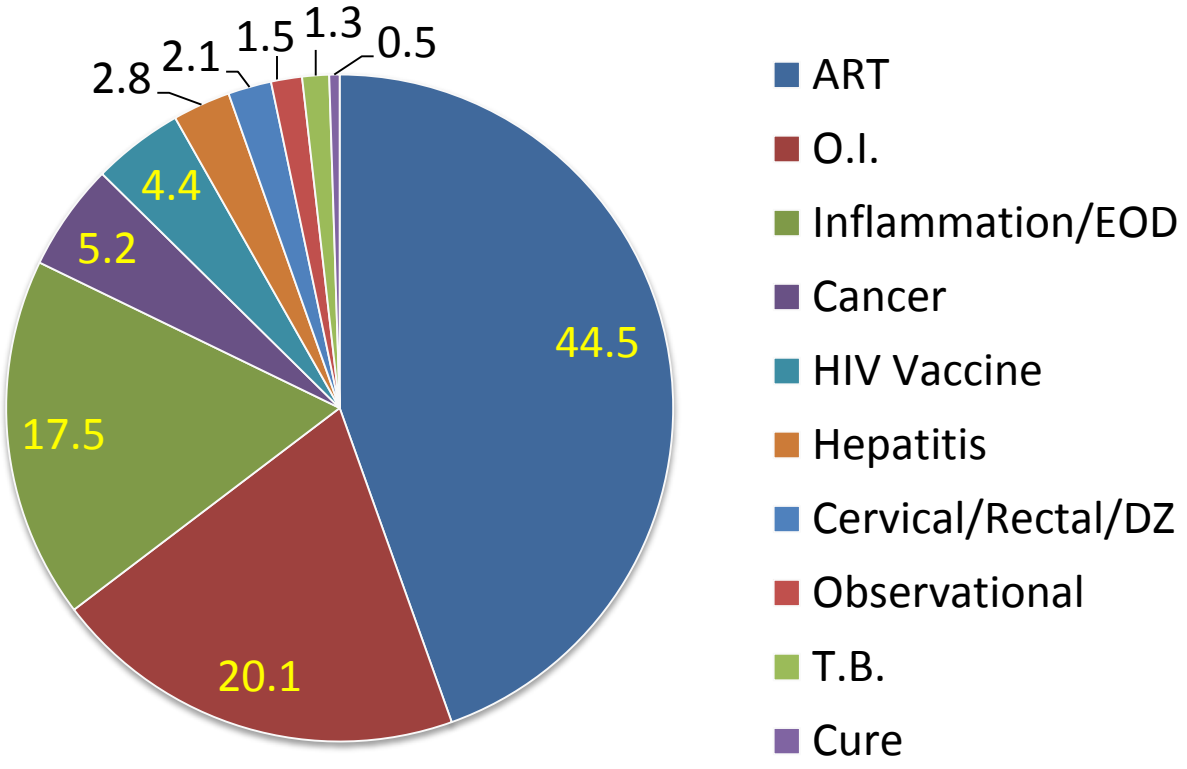
ACTG-Brief History

- Founded 1986 through funding from US NIH
- Initially did both adult and pediatric trials, but pediatrics segregated since 1995
- International Sites were added in 2002
- ACTG re-funded in 2013

  Chair Daniel Kuritzkes, Vice Chairs Judy Currier and Ian Sanne

  Sites in the U.S., Puerto Rico, South Africa, Botswana, Kenya, Malawi, Uganda, Zimbawbe, India, Thailand, Brazil, Peru, Haiti

Categorization of 388 ACTG Studies A0002 – A5257*



*Main studies only, enrolled patients

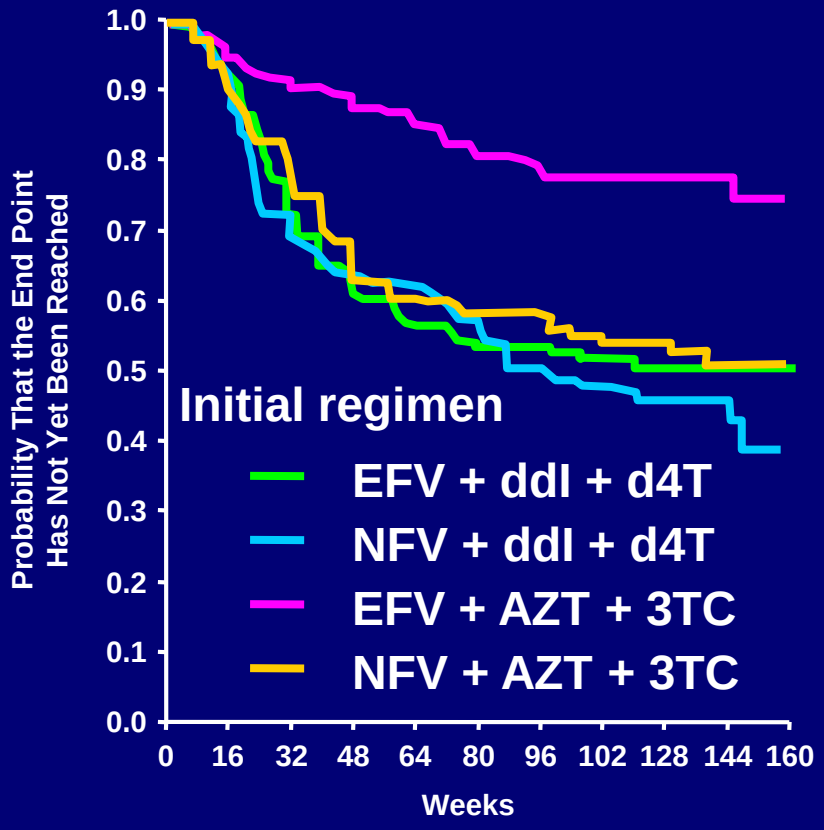
Highlights of Notable ACTG Antiretroviral Studies

1987 - 2012

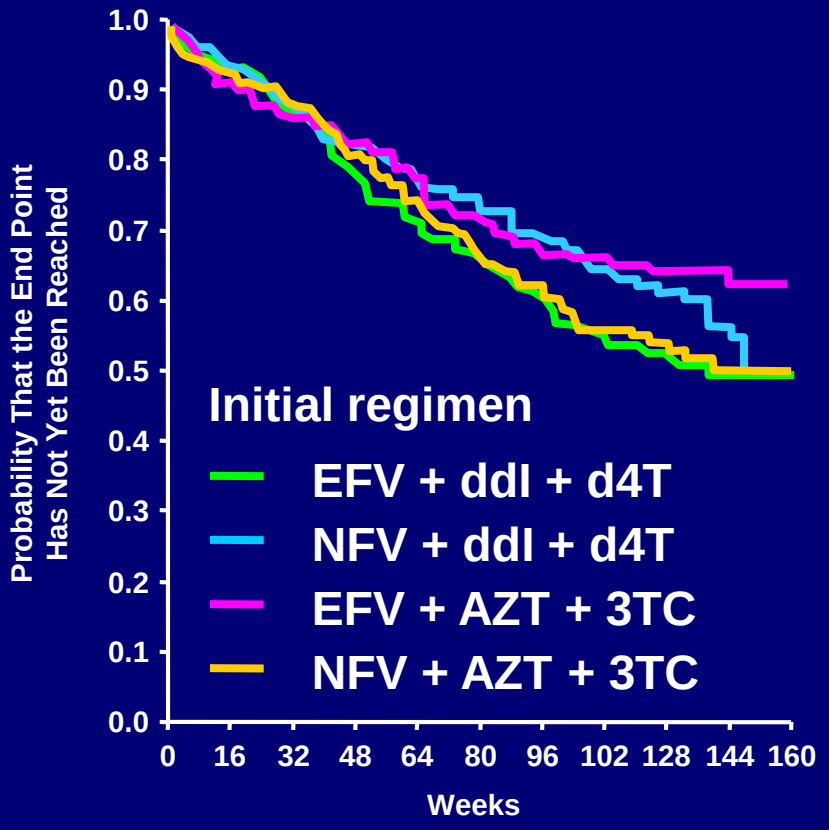
Study	Population	Brief Design	Main Conclusion
002	Naïve after 1st PCP	ZDV vs low dose ZDV	**ZDV 600mg/d = 1500mg/d**
019	Asymptomatic HIV	ZDV vs Placebo	**ZDV superior for CD4 cell**
076	Women & Infants	ZDV vs Placebo	**ZDV prevented transmission**
175	CD4 200-500, naïve & experience	ZDV vs ddI vs ZDV+ddc vs ZDV+ ddI	**ZDV+ddI, ZDV+ddc superior to ZDV (viral load reductions also superior)**
229	CD4 50-200, experienced	ZDV+ddc vs ZDV +SQV vs ZDV+ ddc +SQV	**ZDV+ddc+SQV superior**
244	ZDV therapy, CD4 300-600	ZDV+ddI vs ZDV+ddI+NVP	**ZDV resistance mutation predicted poor response**
364	NRTI experienced	2NRTI+EFV or NFV or EFV+NFV	**≥ 2 active drugs superior to < 2 drugs**
384	Treatment naïve	ZDV/3TC vs D4T/ddI; NNRTI vs PI vs NNRTI+PI	**ZDV/3TC+EFV superior; DTT/ddI toxic, 4 drugs not superior to 3 drugs**

ACTG 384: Time to First and Second Regimen Failure by Initial Three-Drug Regimen

First Regimen Failure
Secondary End Point



Second Regimen Failure
Primary End Point



Robbins GK, et al. *N Engl J Med* 2003;349:2293-2303.

Highlights of Notable ACTG Antiretroviral Studies
1987 - 2012

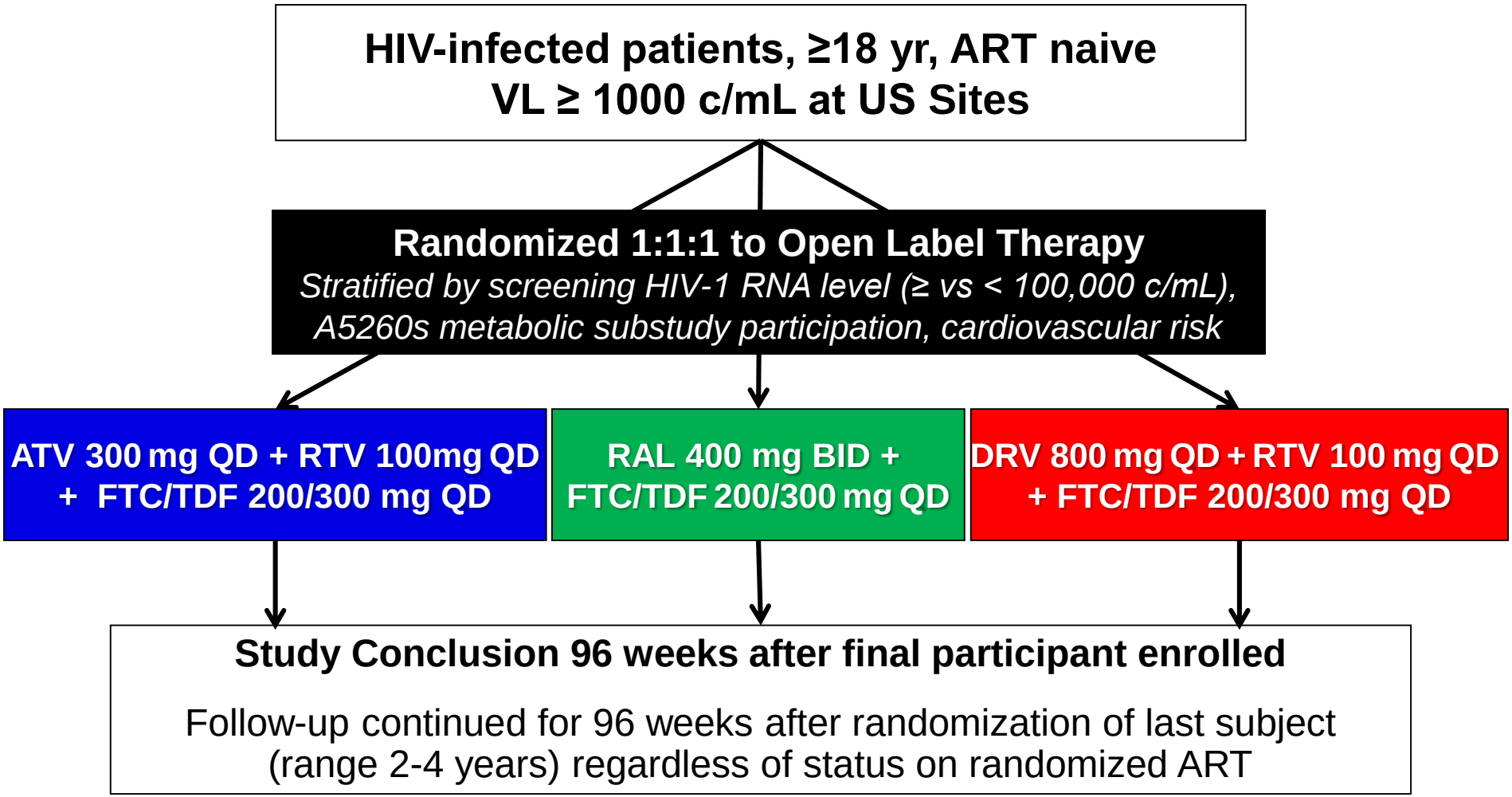
Study	Population	Brief Design	Main Conclusion
5095	Naïve	ZDV/3TC/ABV vs ZDV/3TC +EFV vs ZDV/3TC/ABV+EFV	**ZDV/3TC/ABV inferior; 2NRTI = 3NRTI when both with EFV**
5142	Naïve	LPVr+EFV vs 2NRTI+LPVr or EFV	**EFV superior to LPVr; more NNRTI resistance in NRTI sparing arm**
5164	ART for acute O.I.	Early vs delayed ART for patients with an O.I.	**Early ART reduces AIDS progression**
5175	Naïve, RLS	ZDV/3TC+EFV vs TDF/FTC+ EFV vs ddI+FTC+ATV	**ddI+FTC+ATV inferior; ZDV/3TC toxic compared to TDF/FTC**
5202	Naïve	QD arms of TDF/FTC vs ABC/3TC, plus EFV vs ATV/r	**TDF/FTC superior to ABV/3TC HIV RNA > 100k; ABC/3TC+EFV less tolerable**
5221	Naïve with T.B.	Immediate vs deferred ART	**Immediate ART superior if CD4 < 50**
5241	Experienced, salvage	3 active drugs ± NRTI	**NRTI provided no additional benefit**

Efficacy and Tolerability of Atazanavir, Raltegravir, or Darunavir with FTC/TDF: ACTG A5257

(**ARDENT** Study- **A**tazanavir, **R**altegravir or **D**arunavir with **E**mtricitabine/tenofovir DF for **N**aïve **T**reatment)

Study chairs:
Jeffrey Lennox and Judy Currier
Study Vice Chairs
Raphael Landovitz and Igho Ofotokun
for the A5257 Study Team

A5257 Study Design*



*With the exception of RTV, all ART drugs were provided by the study

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Study Design

- **Hypothesis**
  - FTC/TDF with ATV/r, RAL, or DRV/r will be equivalent in terms of virologic efficacy and tolerability over 96 weeks
- **Primary Endpoints***
  - Time to HIV-1 RNA ≥1000 c/mL wk 16 to before wk 24, or ≥200 c/mL at or after wk 24 (VF)
  - Time to discontinuation of randomized component for toxicity (TF)
- **Pre-planned Composite Endpoint**
  - The earlier occurrence of either VF or TF in a given participant

** Time measured from date of study entry/randomization*

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Key Inclusion Criteria

- No NRTI or PI mutations
- ART-naïve (defined as <10 days of ART at any time prior to entry)

  Prior ART during pregnancy that resulted in virologic suppression and was not complicated either by detectable HIV-1 RNA following suppression or the development of resistance was allowed
- CrCl ≥50mL/min
- Ability to obtain RTV by prescription

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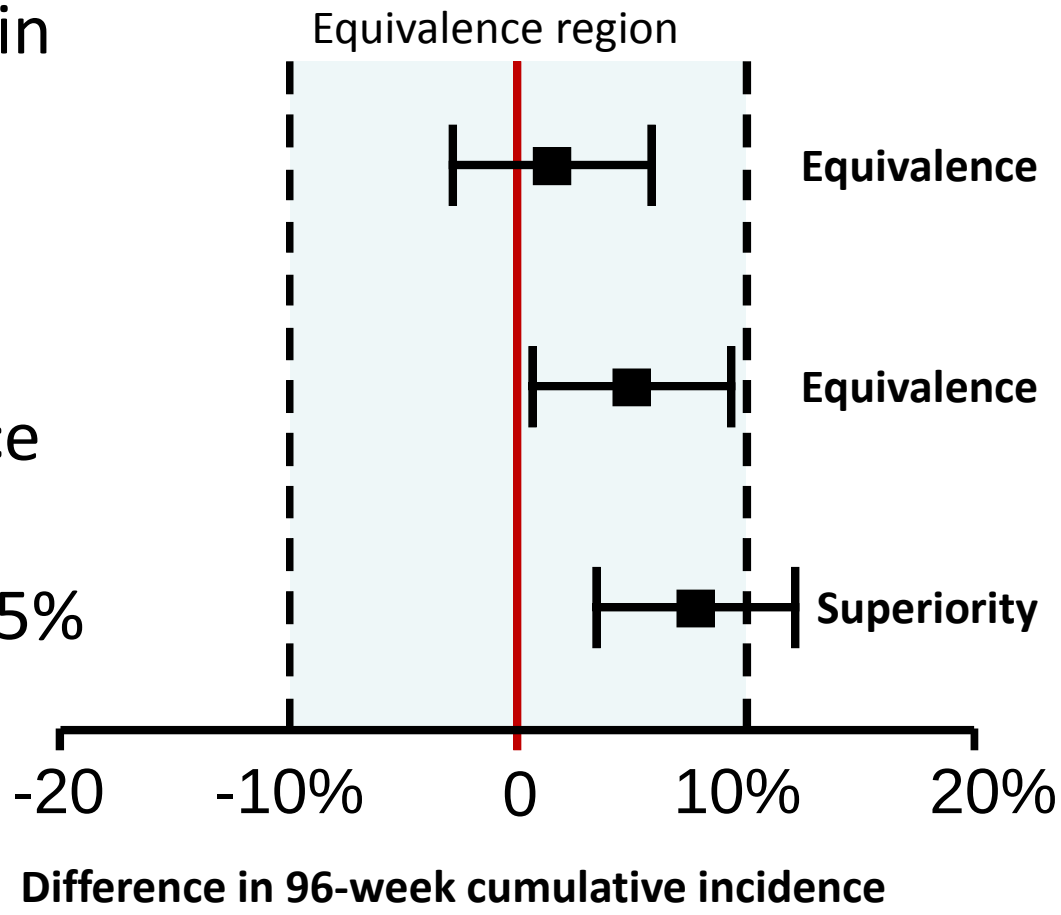
Analysis Considerations

- **Equivalence=** 97.5% CI on the pairwise difference in 96-week cumulative incidence falls entirely within -10% and +10%.
- **Superiority=** equivalence not demonstrated, superiority shown if 97.5% CI excludes zero.



** 97.5% CI controls type I error at 5% for 3 pairwise equivalence comparisons.*

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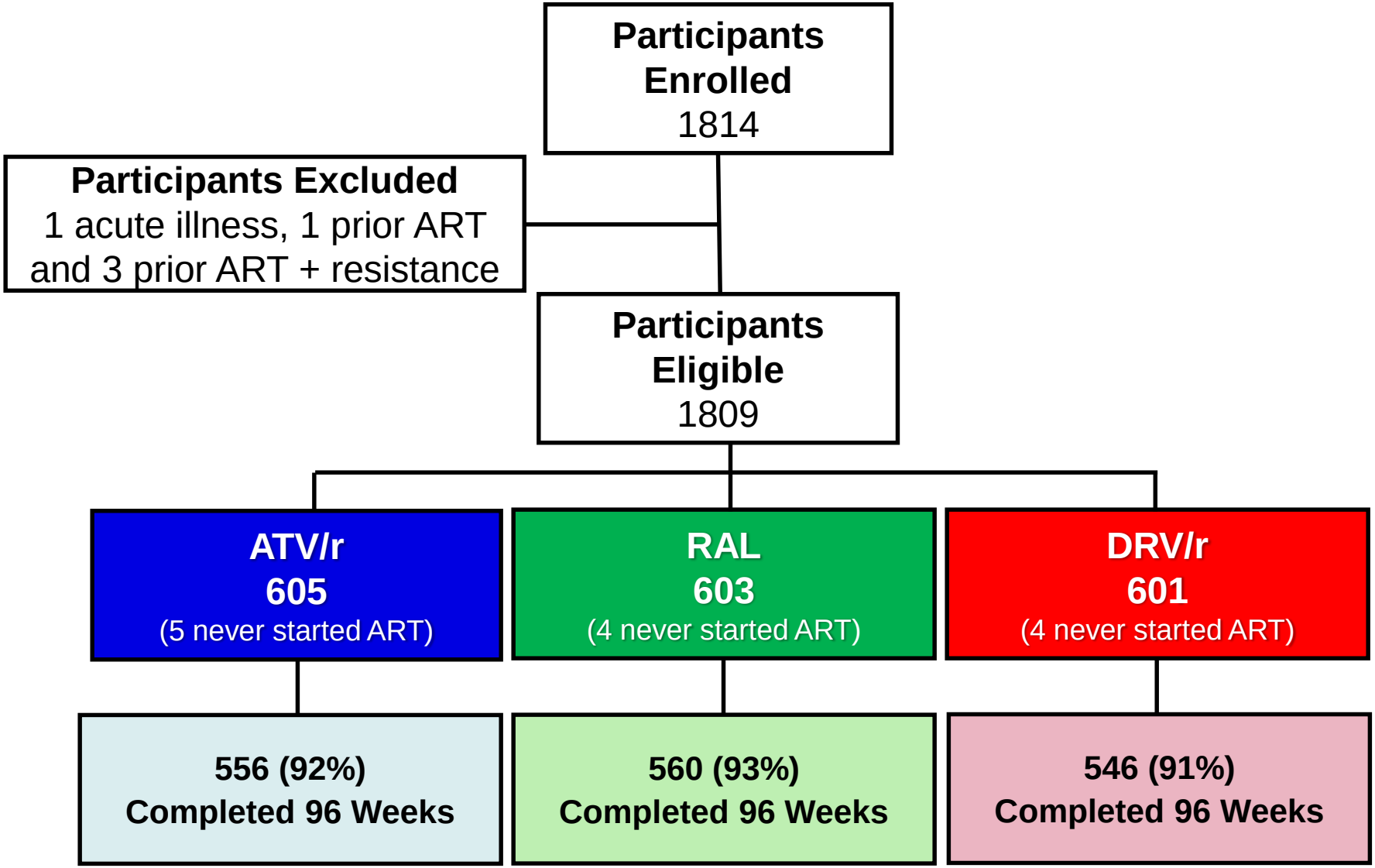

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Baseline Characteristics

Characteristic		Total (N=1809)	Treatment group ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Sex	Female	**435 (24%)**	144 (24%)	148 (25%)	143 (24%)
Age (years)	Mean	**37**	38	37	38
Race/Ethnicity	White Non-His.	**615 (34%)**	212 (35%)	212 (35%)	191 (32%)
	Black Non-His.	**757 (42%)**	252 (42%)	254 (42%)	251 (42%)
	Hispanic	**390 (22%)**	125 (21%)	117 (19%)	148 (25%)
HIV-1 RNA (log_{10} c/ml) (copies/ml)	Median (Q1-Q3)	**4.6 (4.1-5.1)**	4.6 (4.1-5.2)	4.7 (4.1-5.1)	4.6 (4.1-5.1)
	<100,000	**70%**	68%	68%	72%
	100,000-500,000	**23%**	25%	24%	22%
	>500,000	**7%**	7%	8%	6%
CD4+ cells (/mm^3)	Median (Q1-Q3)	**308 (170-425)**	309 (176-422)	304 (158-427)	310 (171-424)
	%<200	**30%**	29%	31%	29%

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Baseline Characteristics

Characteristic		Total (N=1809)	Treatment group ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
IV Drug History	Never	**1,673 (92%)**	558 (92%)	563 (93%)	552 (92%)
	Currently	**4 (0%)**	1 (0%)	0 (0%)	3 (0%)
	Previously	**132 (7%)**	46 (8%)	40 (7%)	46 (8%)
Calculated CrCL (mL/min)	Mean (s.d.)	**125 (39)**	126 (40)	127 (38)	123 (39)
	Min-Max	**50-372**	52-372	50-301	51-327
	Median (Q1-Q3)	**120 (99-145)**	121 (99-146)	122 (101-148)	118 (98-141)
Hepatitis C	Infected	**141 (8%)**	47 (8%)	49 (8%)	45 (7%)
Hepatitis B	SAg +	**49 (3%)**	15 (2%)	16 (3%)	18 (3%)

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Participant and Subject Assessment of whether EFV was appropriate

Characteristic		Total (N=1809)	Treatment group ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
EFV appropriate for participants?	No	**440 (24%)**	153 (25%)	153 (25%)	134 (22%)
Why EFV not appropriate	Women fertility	**91**	28	26	37
	Psychiatric illness	**188**	64	69	55
	Methadone withdrawal	**5**	1	2	2
	NNRTI resistance	**112**	43	45	24
	NNRTI intolerance	**7**	4	1	2
	Other	**37**	13	10	14

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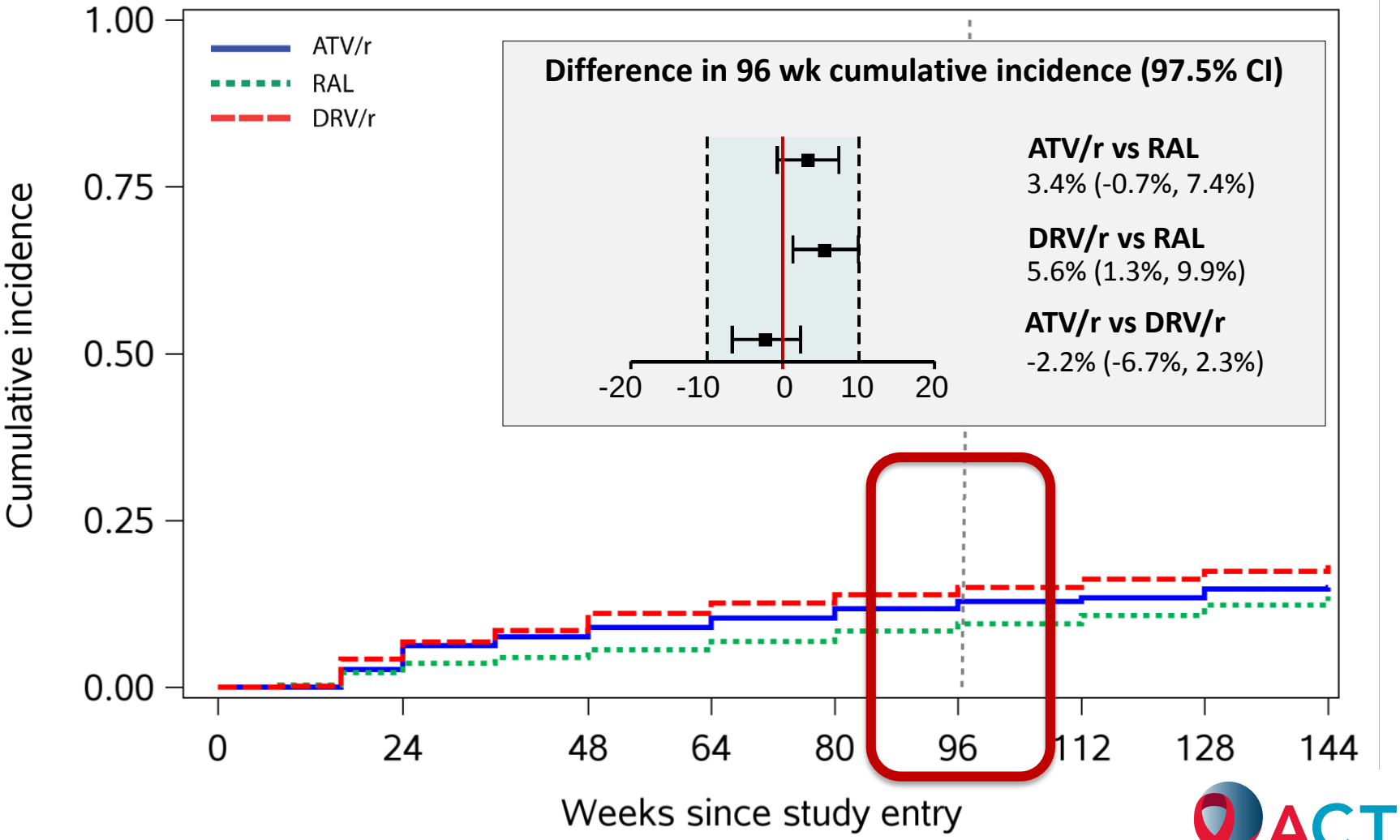
Cumulative Incidence of Virologic Failure



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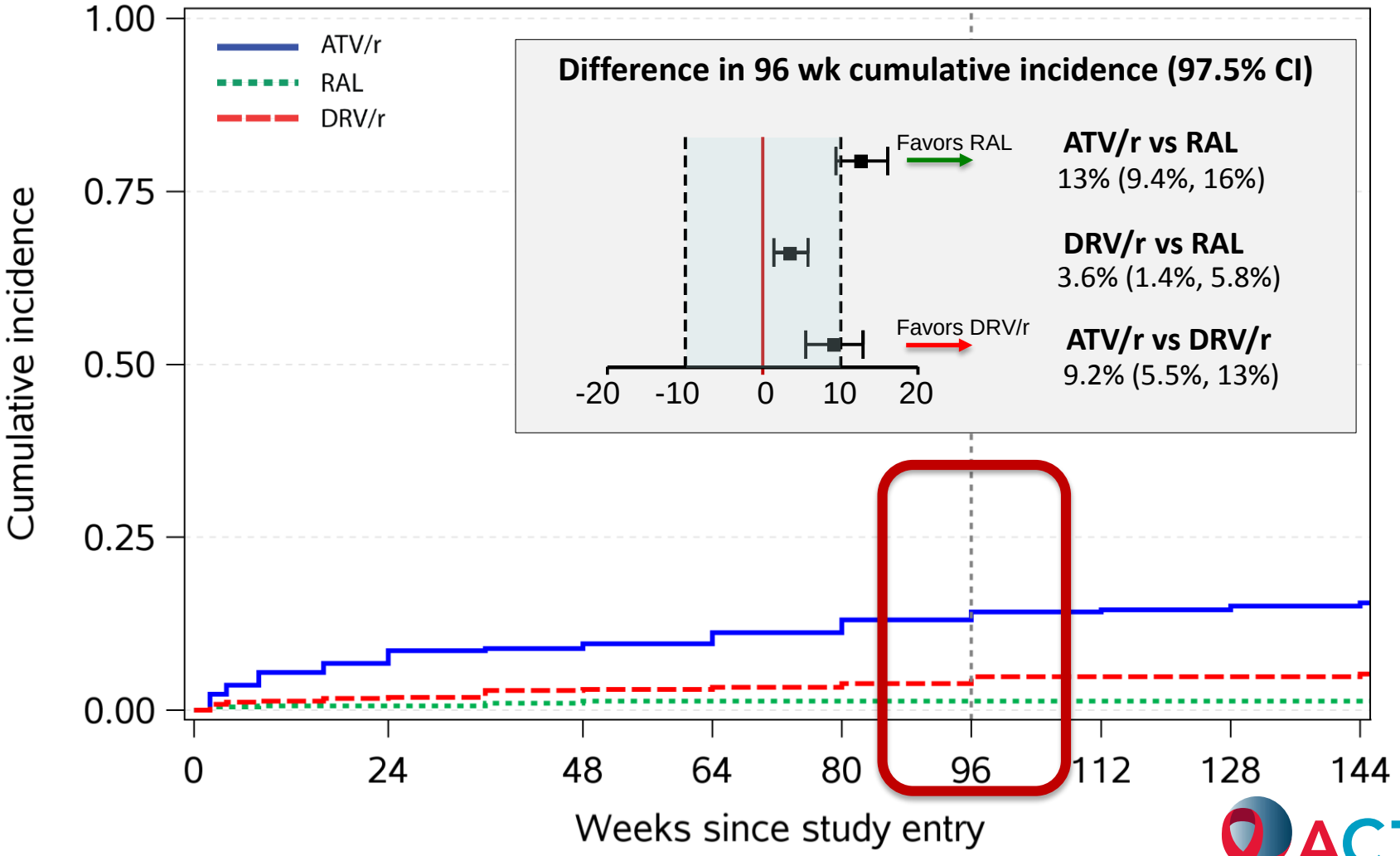
Cumulative Incidence of Tolerability Failure



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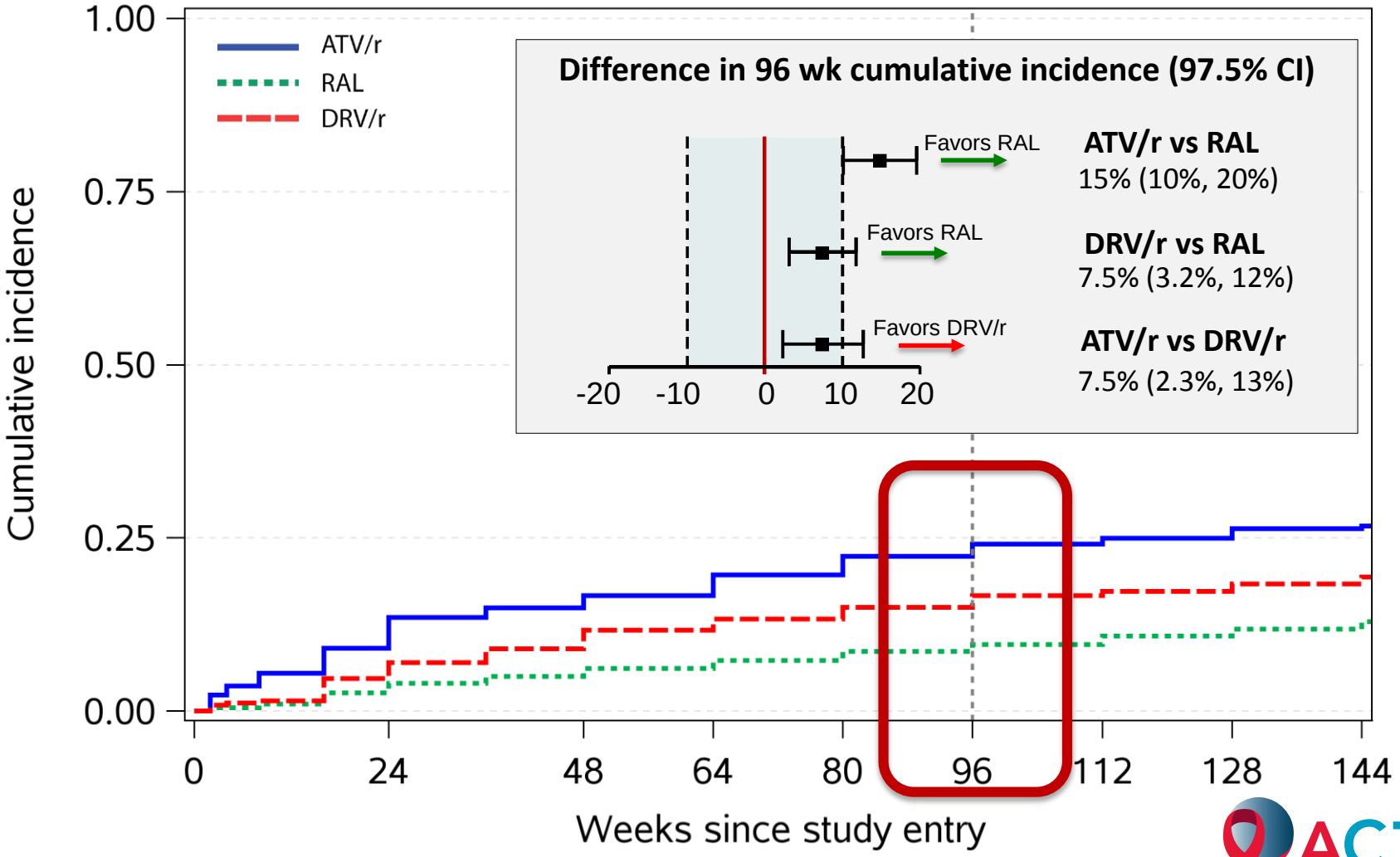
Cumulative Incidence of Virologic or Tolerability Failure



**Consistent results seen with TLOVR at a 200 copies/ml threshold*

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Tolerability Failure

Toxicity Associated Discontinuation of randomized ART

	ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Any toxicity discontinuation	**95 (16%)**	**8 (1%)**	**32 (5%)**
Gastrointestinal toxicity	25	2	14
Jaundice/Hyperbilirubinemia	47	0	0
Other hepatic toxicity	4	1	5
Skin toxicity	7	2	5
Metabolic toxicity	6	0	2
Renal toxicity (all nephrolithiasis)	4	0	0
Abnormal chem/hem (excl. LFTs)	0	0	2
Other toxicity	2	3	4

*Participants allowed to switch therapy for intolerable toxicity

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A Closer Look at ATV/r Hyperbilirubinemia

Maximum Blood Bilirubin	Site-reported Clinical Reason for Discontinuation				Finished on ATV/r N=407
	Hyper-bilirubin N=47	GI toxicity N=25	Other toxicity N=23	Non-toxicity N=98	
Grade 1 (1.1 - 1.5 x ULN)	2%	4%	4%	1%	3%
Grade 2 (1.6 - 2.5 x ULN)	2%	0%	0%	4%	7%
Grade 3 (2.6 - 5.0 x ULN)	43%	24%	22%	28%	40%
Grade 4 (> 5.0 x ULN)	43%	8%	4%	4%	5%

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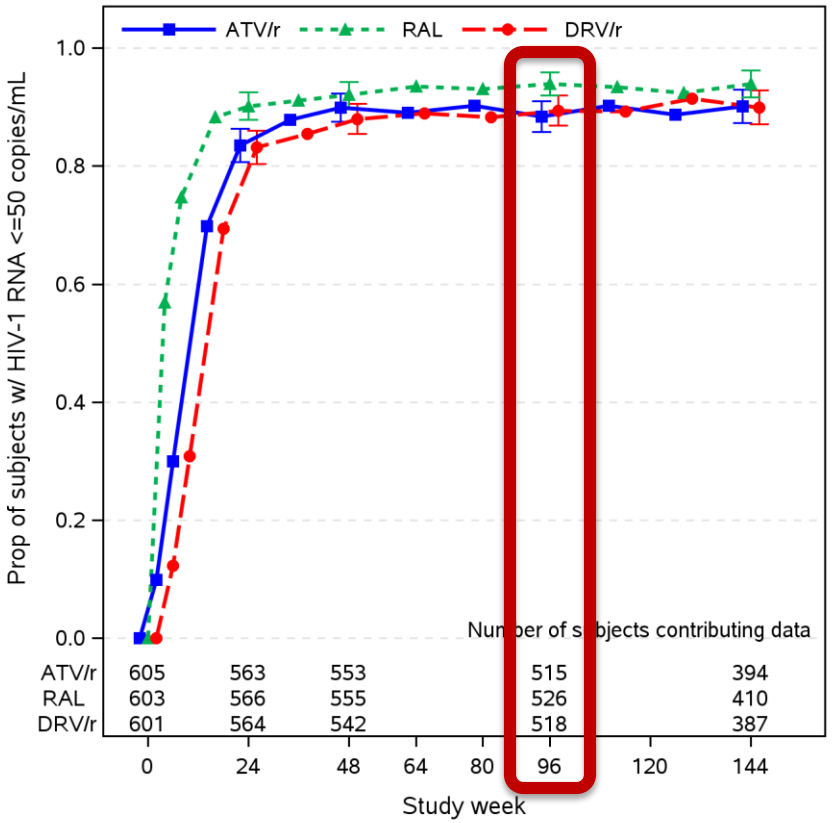
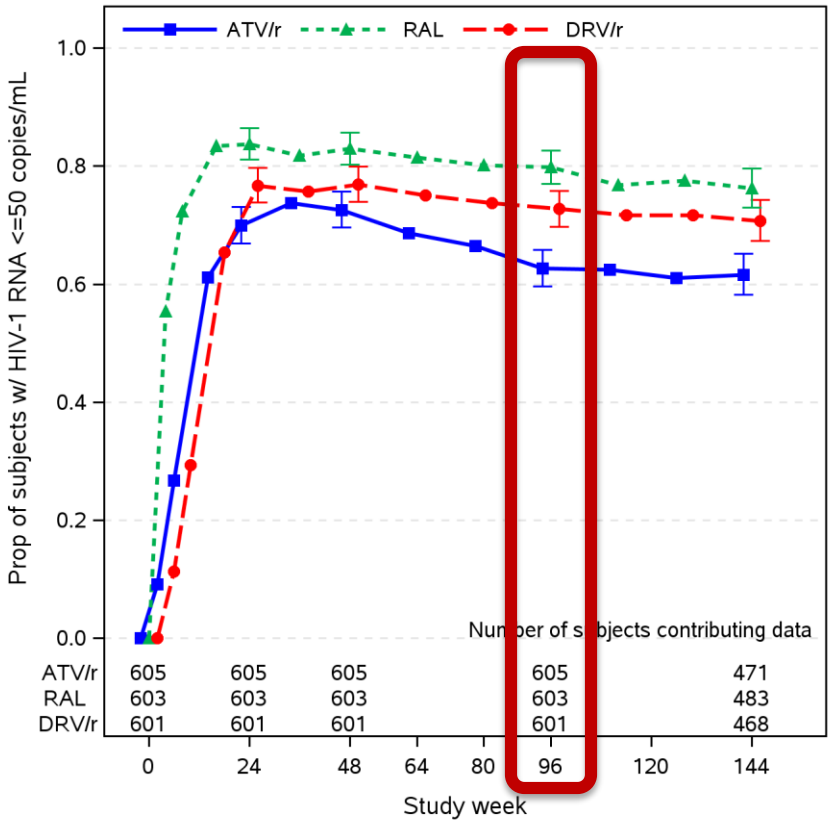
Proportion VL ≤50 copies/mL

ITT, regardless of ART change



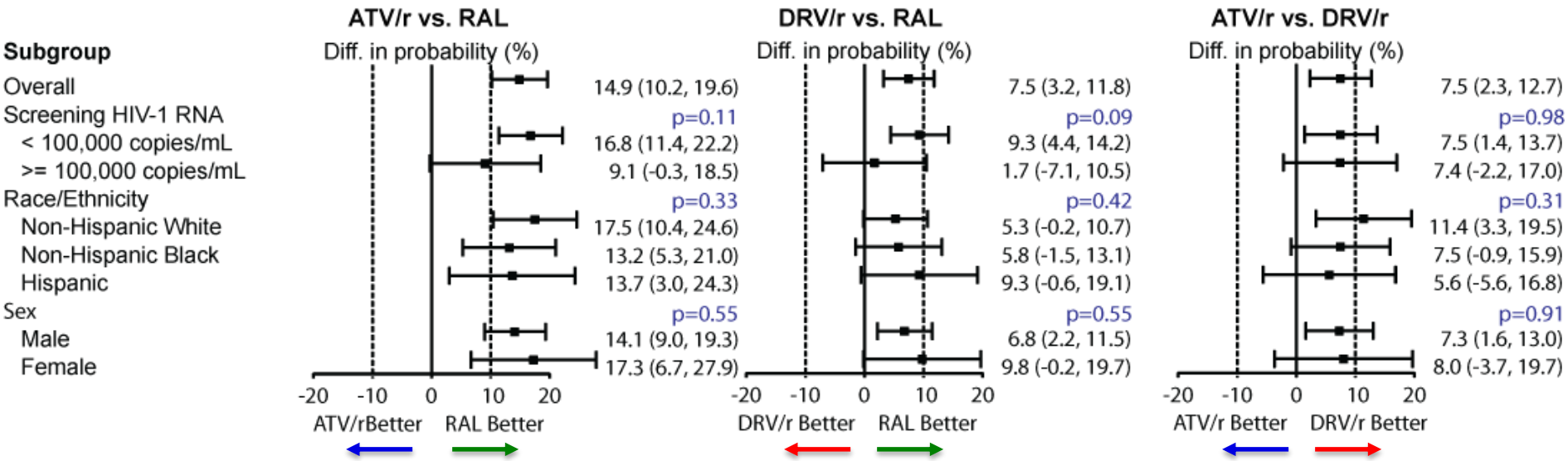
ITT, off-ART=failure (SNAPSHOT)



	24	48	96	144
ATV/r	83%	90%	**88%**	90%
RAL	90%	92%	**94%**	94%
DRV/r	83%	88%	**89%**	90%

	24	48	96	144
ATV/r	70%	73%	**63%**	62%
RAL	84%	83%	**80%**	76%
DRV/r	77%	77%	**73%**	71%

Subgroup Analyses
Virologic or Tolerability Failure



"No differential treatment effects by viral load, race/ethnicity or sex were apparent (P>0.09)"

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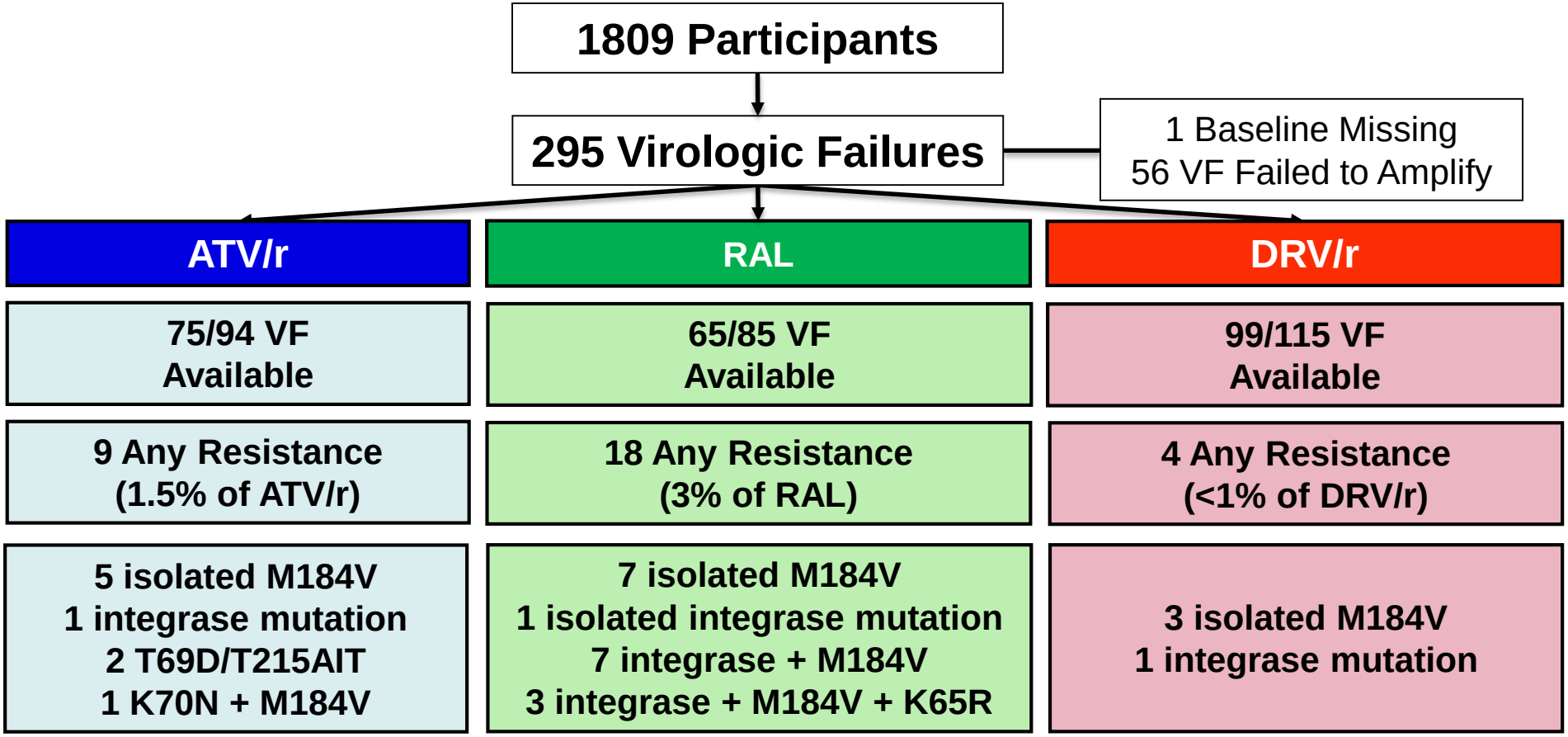
Resistance to Study Agents



**Stanford University Genotypic Resistance Interpretation Algorithm V 6.3.1*

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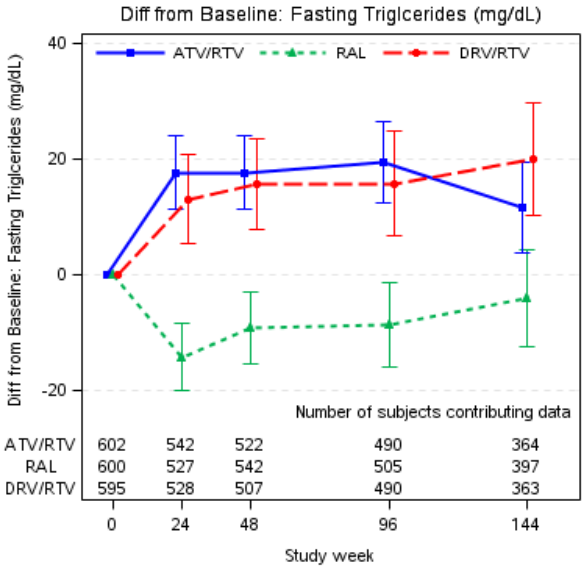
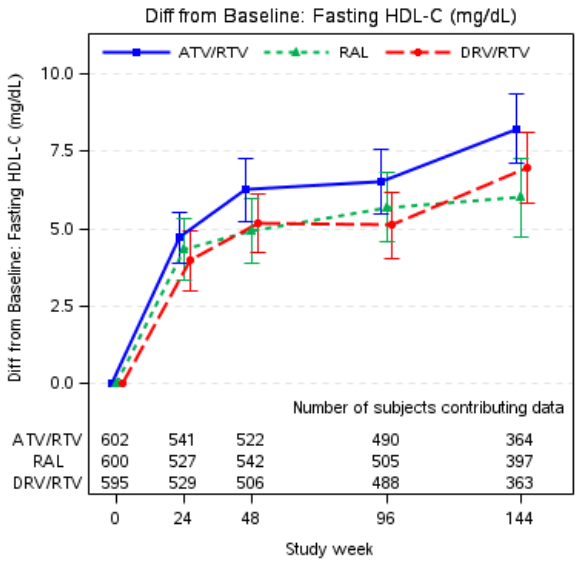
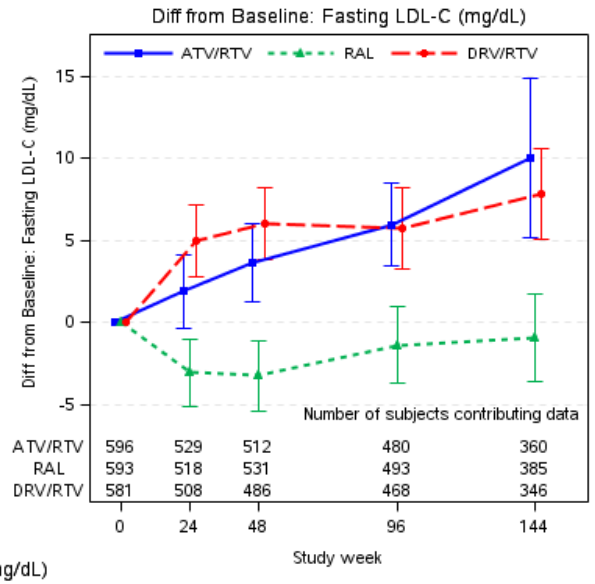
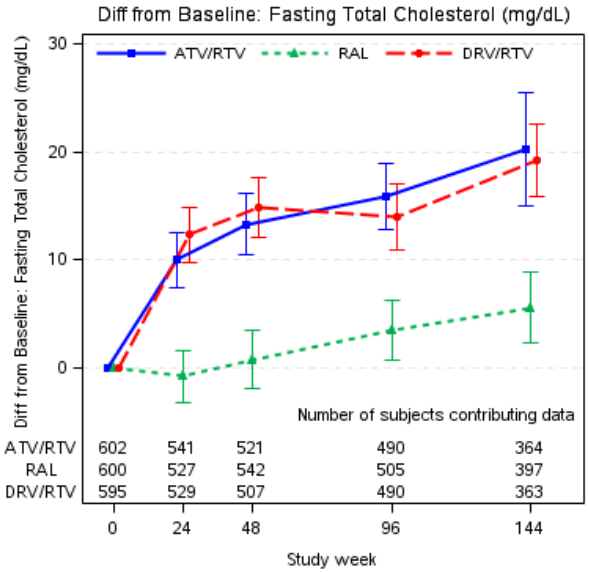
Lipid Changes

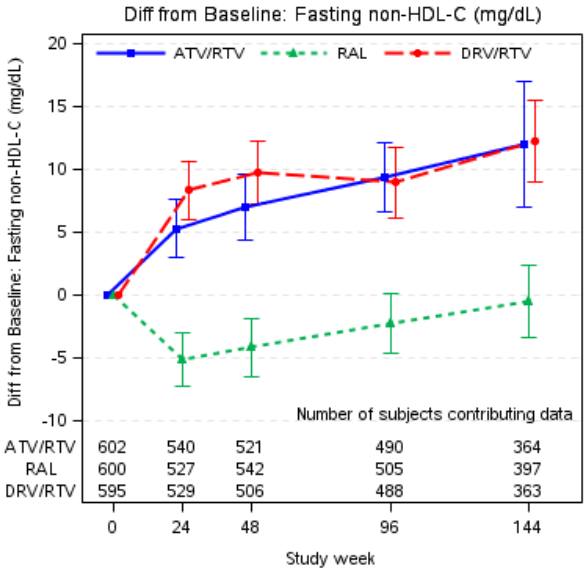
Igho Ofotokun











2014 CROI, Poster 724

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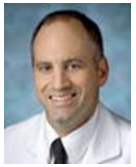
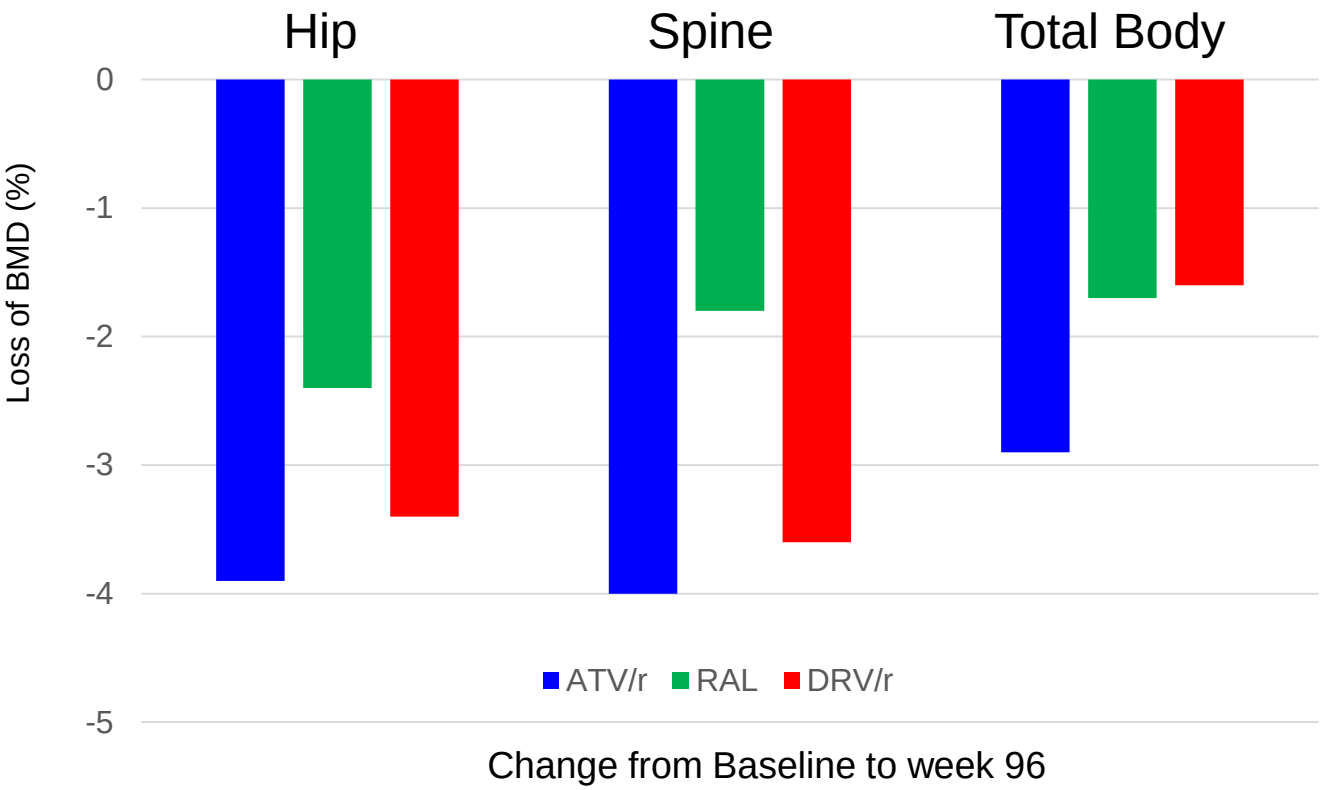
Bone Density Changes- A5260 Substudy



Todd Brown

328 subjects had BMD measured by DEXA



2014 CROI, Poster 779LB

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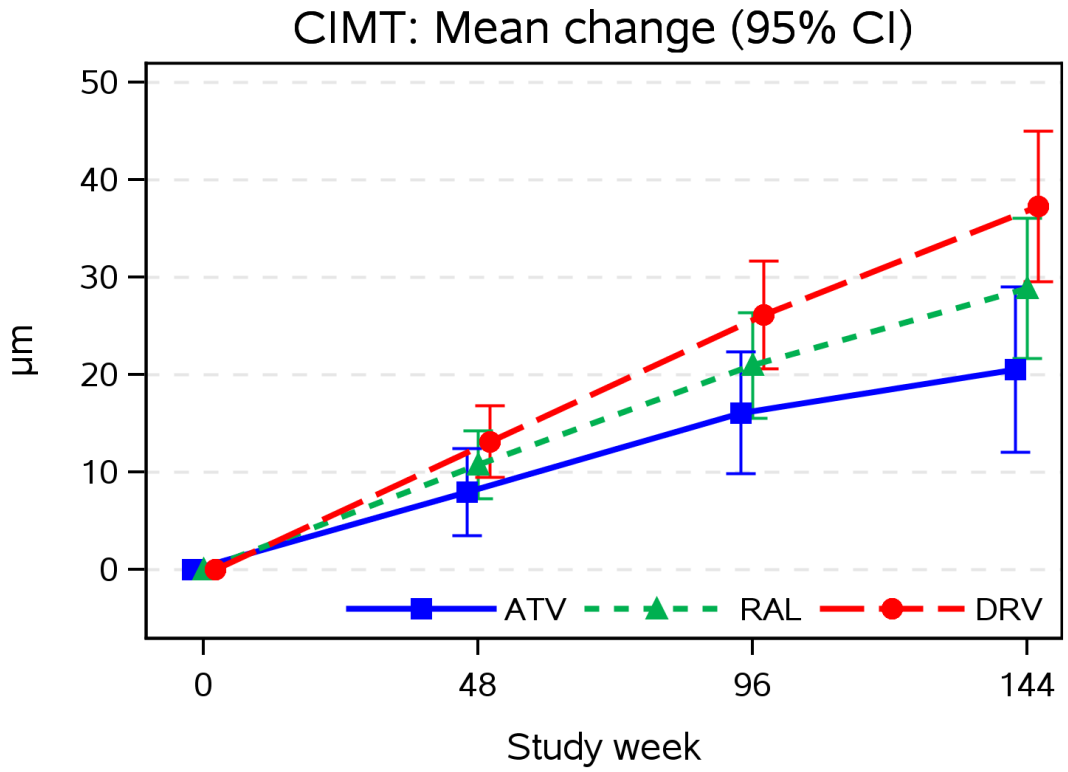
Changes in Carotid Intima-Media Thickness- A5260s

James Stein

326 subjects without diabetes or heart disease had CIMT measured by b mode ultrasonography



J Am Coll Cardiol. 2014;63(12_S):. doi:10.1016/S0735-1097(14)61322-X

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Research Agenda of the ACTG – 2012 and Beyond

- HIV Reservoirs and Viral Eradication
- Inflammation and End Organ Disease
  - Malignancy
  - Neurologic Conditions
- T.B.
- Hepatitis
- HIV Treatment, Pathogenesis and Complications among Women

HIV Reservoirs and Viral Eradication

- Interventions to characterize reservoirs, and methods to detect meaningful changes in reservoirs
- Impact of treatment of acute HIV on reservoir size, and potential for eradication
- Interventions to reduce or eliminate reservoirs

End Organ Disease and Inflammation

- Role of inflammation in viral pathogenesis and persistence
- Interactions of the mucosal immune system, the microbiome and HIV
- Cardiovascular, bone, neurologic and metabolic consequences of HIV, HIV treatment and inflammation
- Modulation of inflammation as a treatment strategy

Tuberculosis

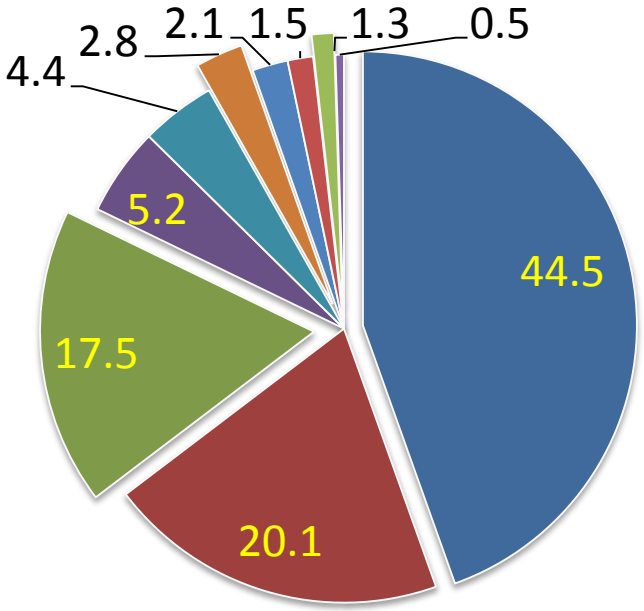
- Methods to improve detection and treatment of latent and active T.B.
- Innovative treatments for MDR & XDR T.B.
- Adjunctive immune modulation for T.B. Treatment
- Shortening the duration of T.B. treatment

Hepatitis

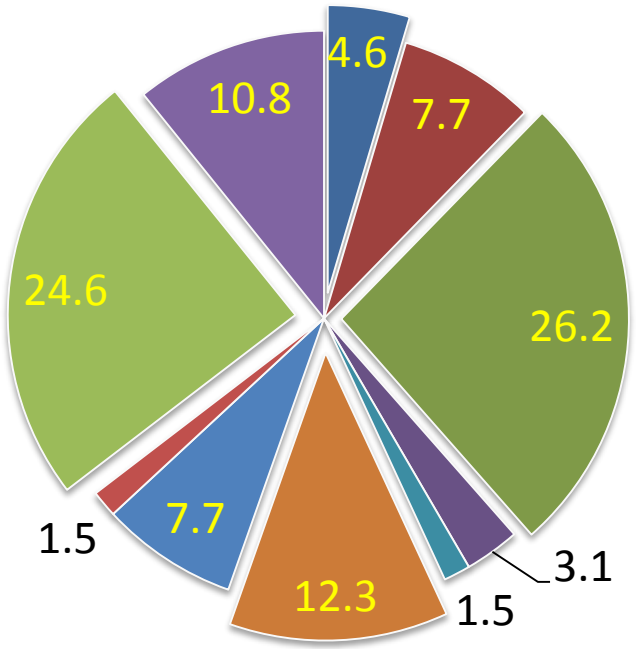
- Treatment of HIV/HCV infection
- Hepatic inflammation, fibrosis and steatosis
- Selected ART and HCV treatment P.K. studies
- New therapeutic strategies for HIV/HBV co-infection

ACTG- Past vs Future Scientific Agenda

Studies Prior to 2012



Studies Since 2012



- ART
- O.I.
- Inflammation/EOD
- Cancer
- HIV Vaccine
- Hepatitis
- Cervical/Rectal Dz
- Observational
- T.B.
- Cure

Conclusion

- The ACTG has played a major role in defining the current paradigm for treating HIV and its associated opportunistic infections, malignancies and end organ diseases.
- ACTG research will contribute to elimination or reduction of the HIV reservoir, and improved treatments for viral hepatitis and TB.
- The ACTG has an extensive bank of human samples and linked data that can be a resource for investigators.