

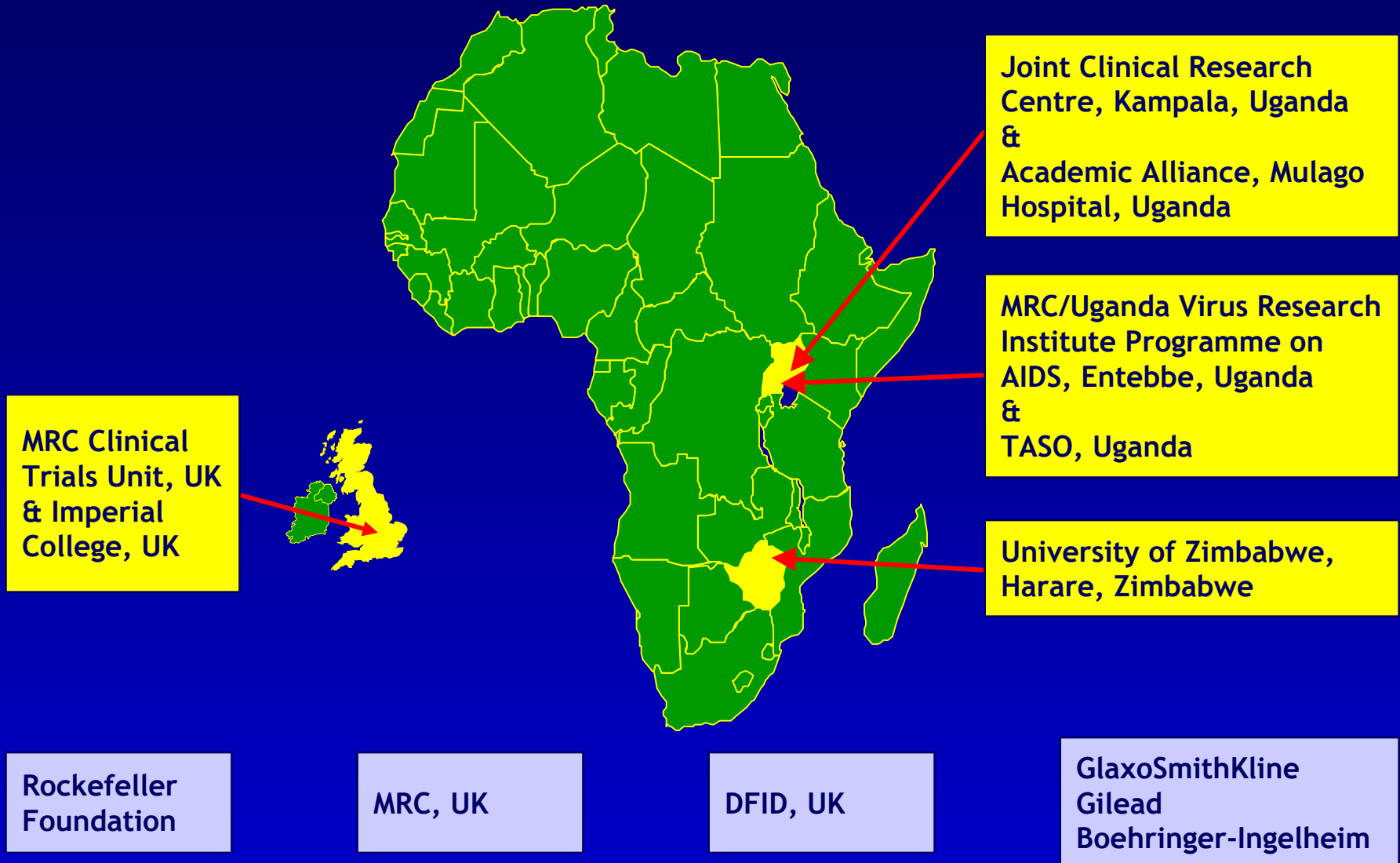


# Short-term Virological Response to a Triple Nucleoside/Nucleotide Analogue Regimen in Adults with HIV Infection in Africa within the DART Trial

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on behalf of the **DART** Trial Team



# Development of AntiRetroviral Therapy In Africa: DART





# DART trial design: main randomisation



3315 previously untreated HIV-infected patients  
stage WHO 2, 3 or 4 and  $CD4 < 200$  cells/mm<sup>3</sup>

randomise to  
initiate triple  
drug ART with

Clinical and  
Laboratory Monitoring  
(12 weekly biochemistry,  
FBC & CD4; no virology)

Clinical Monitoring  
Only  
(biochemistry and/or FBC  
if clinically indicated)

- 2468 (74%) received Combivir (CBV) plus tenofovir DF (TDF) first-line
- 300 patients enrolled into virology substudy (retrospective)



# Rationale for first-line regimen



- Potential advantages of initial regimens containing only nucleoside or nucleotide RTIs
  - avoid drug interactions eg TB therapy
  - class sparing
  - low pill burden
  - good tolerability and toxicity profile
- Concerns
  - suboptimal virological potency (eg ACTG 5095)
  - development of resistance (eg ESS30009)
- Limited data on CBV+TDF as a combination
  - ZDV may reduce emergence of K65R (eg Winston 2004)



# Objectives of virology substudy



- Primary objective
  - determine early virological response to CBV+TDF
- Secondary objectives
  - investigate predictors of virological suppression and failure
  - compare virological response to CBV+TDF with other triple combinations in similar populations with low CD4 counts



# Methods



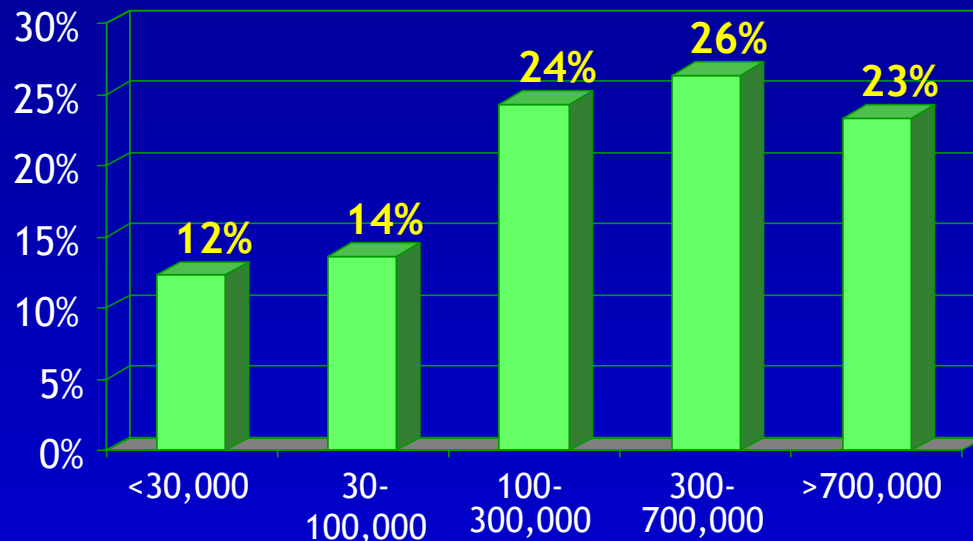
- 300 patients
  - 100 from each of 3 clinical sites in Uganda (2) and Zimbabwe (1)
  - half with baseline CD4 <100 cells/mm<sup>3</sup>
  - consecutive patients enrolled in each CD4 strata after first 2 months of the trial, excluding the first 20 patients in each site
- Plasma HIV-1 RNA assayed on stored specimens at 0, 4, 12 and 24 weeks after initiation of CBV+TDF
  - maximum possible 1200 results
- All assays (**Roche Amplicor 1.5**) performed locally with cross-site QA programme



# Baseline characteristics



- 65% women
- age: median 37.5 years (range 20-62 years)
- CD4: median 100 cells/mm<sup>3</sup>, 29% <50 cells/mm<sup>3</sup>
- WHO stage: 2 (23%), 3 (48%), 4 (29%)
- HIV-1 RNA: median 289,400 c/ml





# Follow-up to week 24



- 1148 (95.7%) results were obtained
  - ITT analysis (based on all available results)
- 52 missing results due to
  - 11 (4%) patients **died before week 24**
    - 4 died before week 4
    - 7 had last HIV-1 RNA <1500 c/ml (4 <50 c/ml)
  - missed visit or sample not taken
  - ITT M=F analysis (missing results due to death, missed visit, or no sample included as “failure”)



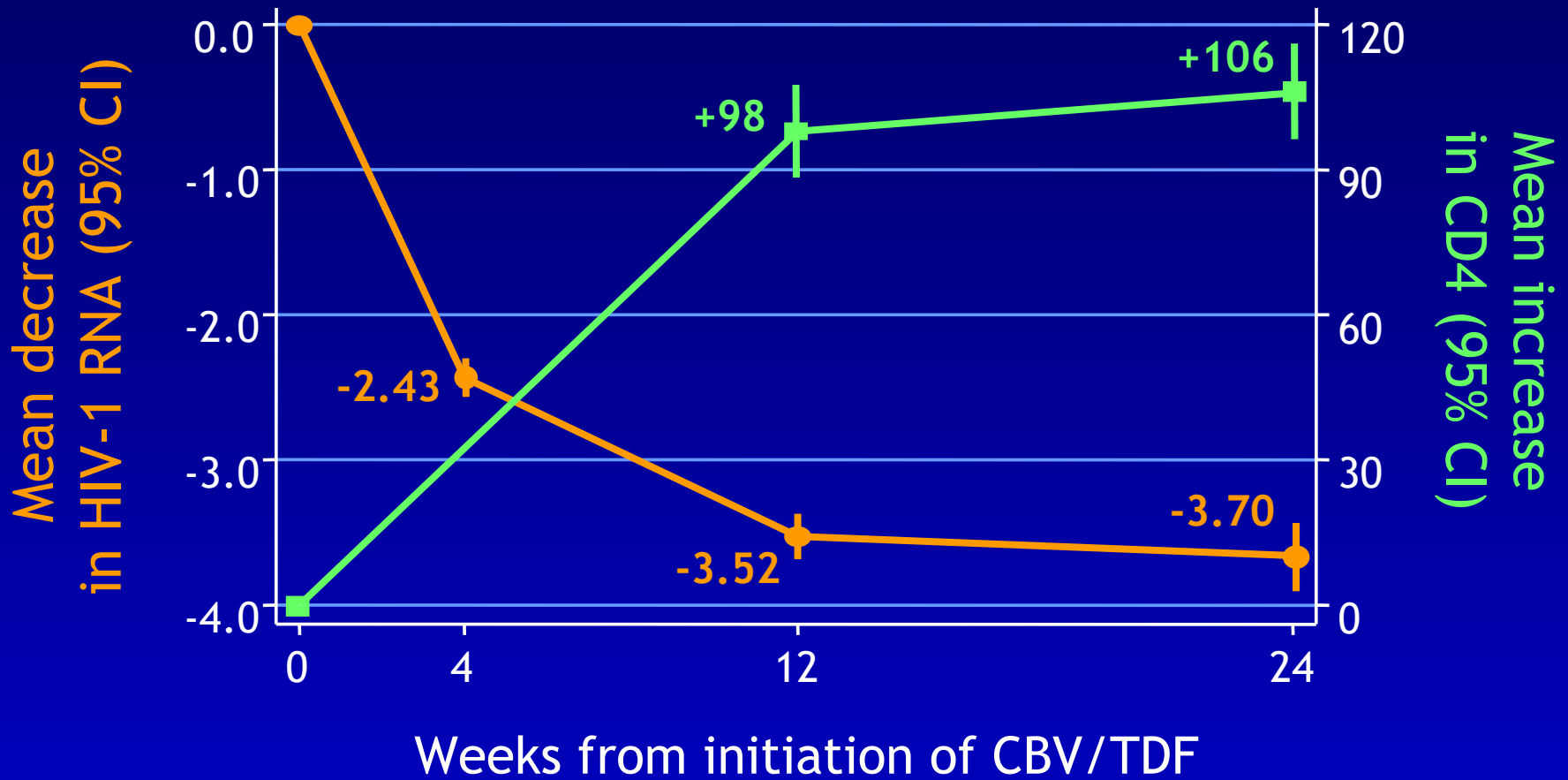
# Follow-up to week 24 (ctd)



- 249 (83%) patients known to be alive at 24 weeks having been prescribed CBV+TDF without interruption
  - on treatment (OT) analysis (based on all available results when patient had been taking CBV+TDF without interruption)
- 15 (5%) patients had substituted d4T for ZDV
- 33 (11%) patients interrupted ART for 3+ days
  - median 12 days (range 3-78 days)



# Change in HIV-1 RNA & CD4 (ITT)



Number

297

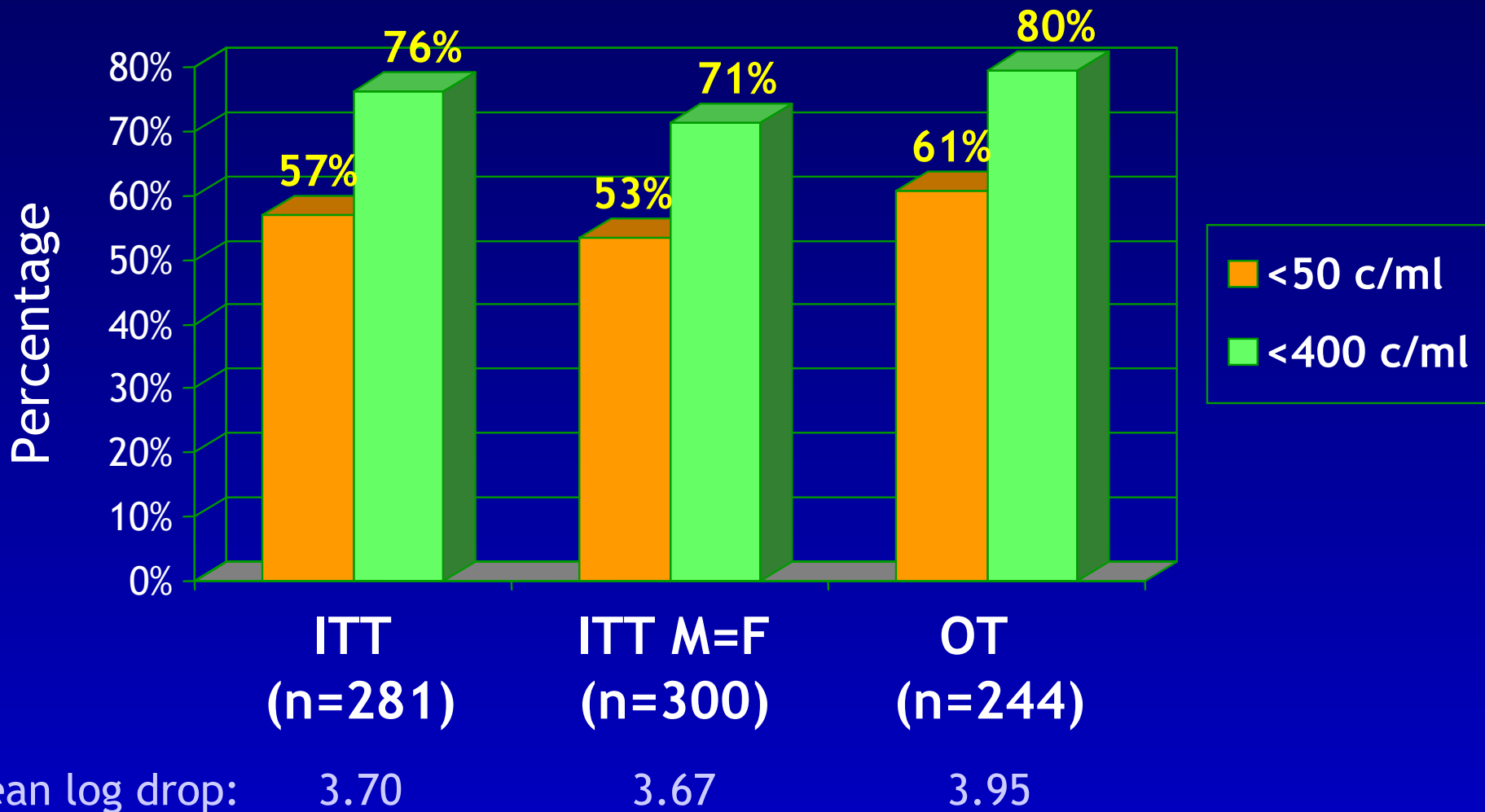
285

282

281



# Viral suppression at week 24



NOTE: 8 values <100 or <400 due to insufficient sample volume are conservatively counted as  $\geq 50$ c/ml (3%)  
CROI 2005



# Predictors of suppression <50 or <400 c/ml at week 24



- Patients who spent more time off ART before 24 weeks were less likely to suppress
  - <400 c/ml: OR = 0.68 per week off ART (p=0.007)
  - <50 c/ml: OR = 0.59 per week off ART (p=0.009)
- No effect of baseline HIV-1 RNA
  - <400 c/ml: OR = 1.01 per 1 log higher (p=0.98)
  - <50 c/ml: OR = 1.00 per 1 log higher (p=0.99)
- Non-significant trends in expected direction for
  - age
  - baseline CD4
  - HIV-1 RNA response at 4 weeks
  - self-reported adherence to prescribed medication



# 12 versus 24 week HIV-1 RNA response



(ITT: n=274)		Week 24			
		<50	50-399	400-1000	>1000
Week 12	<50	32%	7%	3% [8]	5% [15]
	50-399	22%	9%	3%	5% [14]
	400-1000	2% [5]	2%	0.4%	1%
	>1000	2% [5]	2% [5]	1%	4%

- 37 patients had considerably poorer response at 24 weeks
- 15 patients had considerably better response at 24 weeks



# HIV-1 RNA >1000 c/ml at 24 weeks



- 47/281 (17%) patients had HIV-1 RNA >1000 c/ml at 24 weeks
  - 18 (6%) >10000 c/ml
- 12 had never achieved suppression <400 c/ml
- 29 had HIV-1 RNA <400 c/ml at 12 weeks
  - 18/29 had one or more factors in the preceding 12 weeks possibly contributing to rebound
    - off ART for >1 week (n=2)
    - incomplete adherence (n=15)
    - SAE, Grade 3/4 AEs, or other ART-modifying AEs (n=3)
    - malaria (n=6)



# Cohort comparison: UK CHIC



- UK CHIC: 1997 - 2002
  - starting HAART naïve (3+ drugs, 94% PI/NNRTI based)
  - 1971 patients with baseline CD4<200 cells/mm<sup>3</sup>
  - median HIV-1 RNA 161,600 c/ml
  - 24% women, 37% heterosexually infected, 32% Black African
- Suppression rates varied across year of starting HAART

At 24 weeks (ITT)	1998	2000	2002	DART
<400 c/ml	68%	90%	87%	76%
<50 c/ml	[16%]	56%	56%	57%



# Summary and future work



- Good virological response to CBV+TDF at 24 weeks
  - high baseline viral load, co-morbidities
  - tolerability is also good
- Comparable to populations with low CD4 counts initiating PI/NNRTI based regimens
- Genotyping of samples with HIV-1 RNA >1000 c/ml at 24 weeks is currently ongoing
- Extension of viral load testing to 36 and 48 week samples is in progress



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# Viral suppression over time (ITT)

