3TC/FTC Monotherapy vs. Continuing Failing cART as a Bridging ART Strategy in Persistently Non-adherent HIV-infected Youth with M184V Resistance: Results of IMPAACT P1094

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Virologic Failure in Perinatally HIV-Infected Youth

- 30-40% of perinatally HIV-infected youth have virologic failure (VF) with persistent viremia >400 copies/mL while on cART
- Similar proportion in non-perinatally HIV-infected youth
- VF leads to antiretroviral drug resistance, immunologic failure , and limits antiretroviral treatment options.
- No consensus on optimal management of HIV-infected youth with virologic failure from non-adherence

Agwu et al. JPIDS 2013; Van Dyke et al. JAIDS 2011; Flynn et al. JID 2004

Clinical Scenario of Persistent Non-adherence and VF

- 17 y/o perinatally HIV-infected adolescent
  - CD4 330 cells/mm^3, HIV RNA 6,000 copies/ml on cART (atazanavir/ritonavir + tenofovir/FTC)
- 12 months later
  - CD4 declines to 280 cells/mm^3
  - Genotype: M184V
- Assessment of barriers: No structural barriers
  - Virologic failure due to non-adherence
- What is the optimal management?
  - Continue failing regimen
  - Discontinue cART
  - Switch
  - Bridging regimen

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3TC/FTC Monotherapy as a "Bridging Regimen"

- M184V
  - Confers high level resistance to 3TC/FTC
  - Reduces viral fitness by 10-20% relative to wild type
- 3TC or FTC monotherapy despite pre-existing M184V HIV variants
  - Ongoing exposure needed to maintain M184V mutants in circulation
  - Does not lead to further accumulation of ARV drug resistance mutations
  - Adherence advantages over standard multi-pill combinations
  - Well tolerated
  - May preserve immunologic status (vs. discontinuing cART)
  - Strategy is employed in settings where treatment options are limited

We hypothesized that 3TC/FTC monotherapy would prevent immunologic deterioration compared with continuing failing cART.

Devereux et al. J Med Virol 2001; Castagna et al. AIDS 2006; Abadi et al JAIDS 2006. Deeks et al. JID 2005 Lazarus EM et al. J AIDs Clin Res. 2013, 4(10); Fairlie L et al. CROI and IAS 2013

Primary Objective of IMPAACT P1094

To compare immunologic deterioration during a 28 week "bridging" ART strategy of 3TC or FTC monotherapy vs. continuing failing cART in HIV-infected children, adolescents, and young adults with virologic failure and documented M184V resistance who are likely to be non-adherent to an optimized cART regimen due to problems related to adherence, tolerability, or toxicity

Primary endpoint: ≥30% decline in absolute CD4

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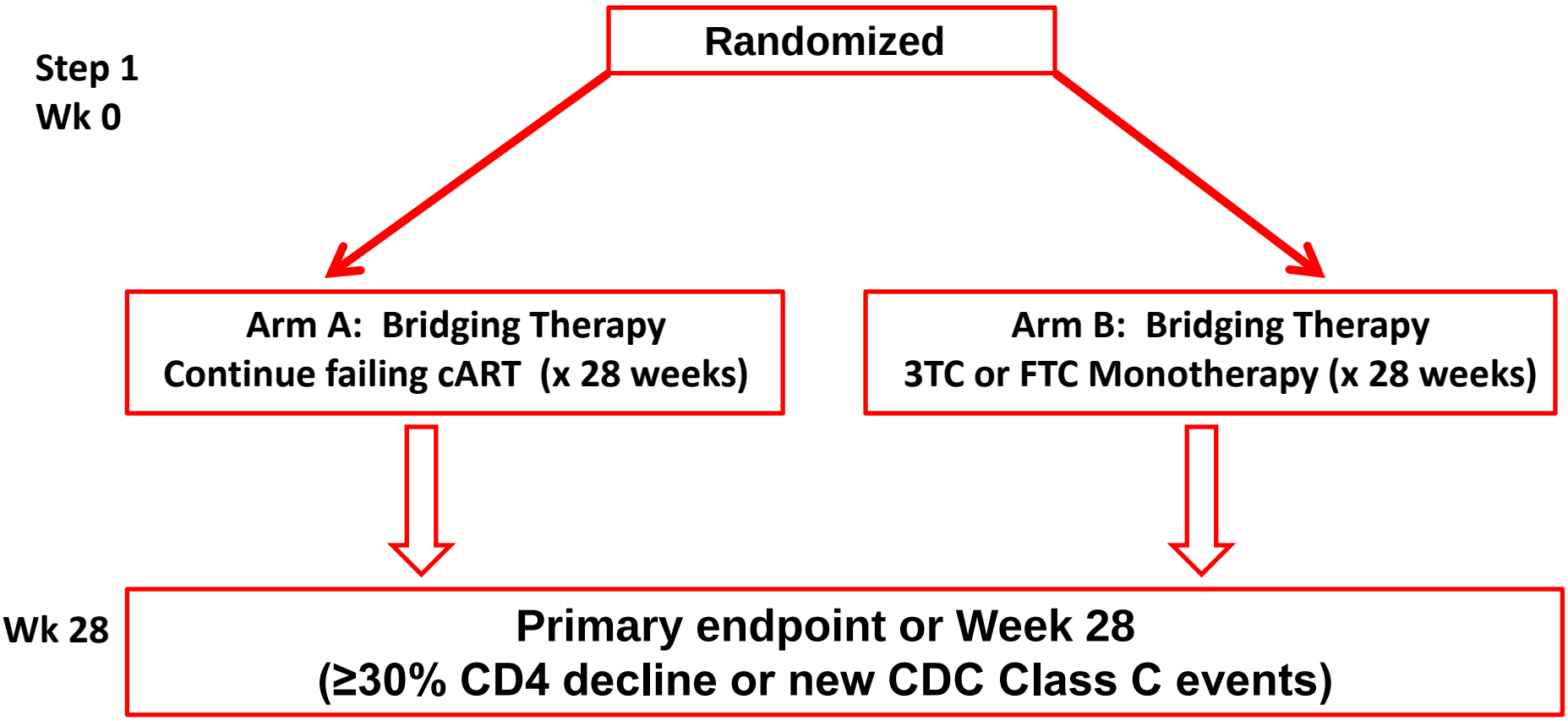
HIV-infected School-Aged Children and Adolescents Failing cART with the M184V Mutation and Unlikely to Adhere to Optimal cART



Step 1 [Wk 0-28]: Patients with virologic failure are randomized to 3TC/FTC Bridging vs. Continuing failing cART for at least 6 months and only switch if they reach endpoints as defined in the protocol.

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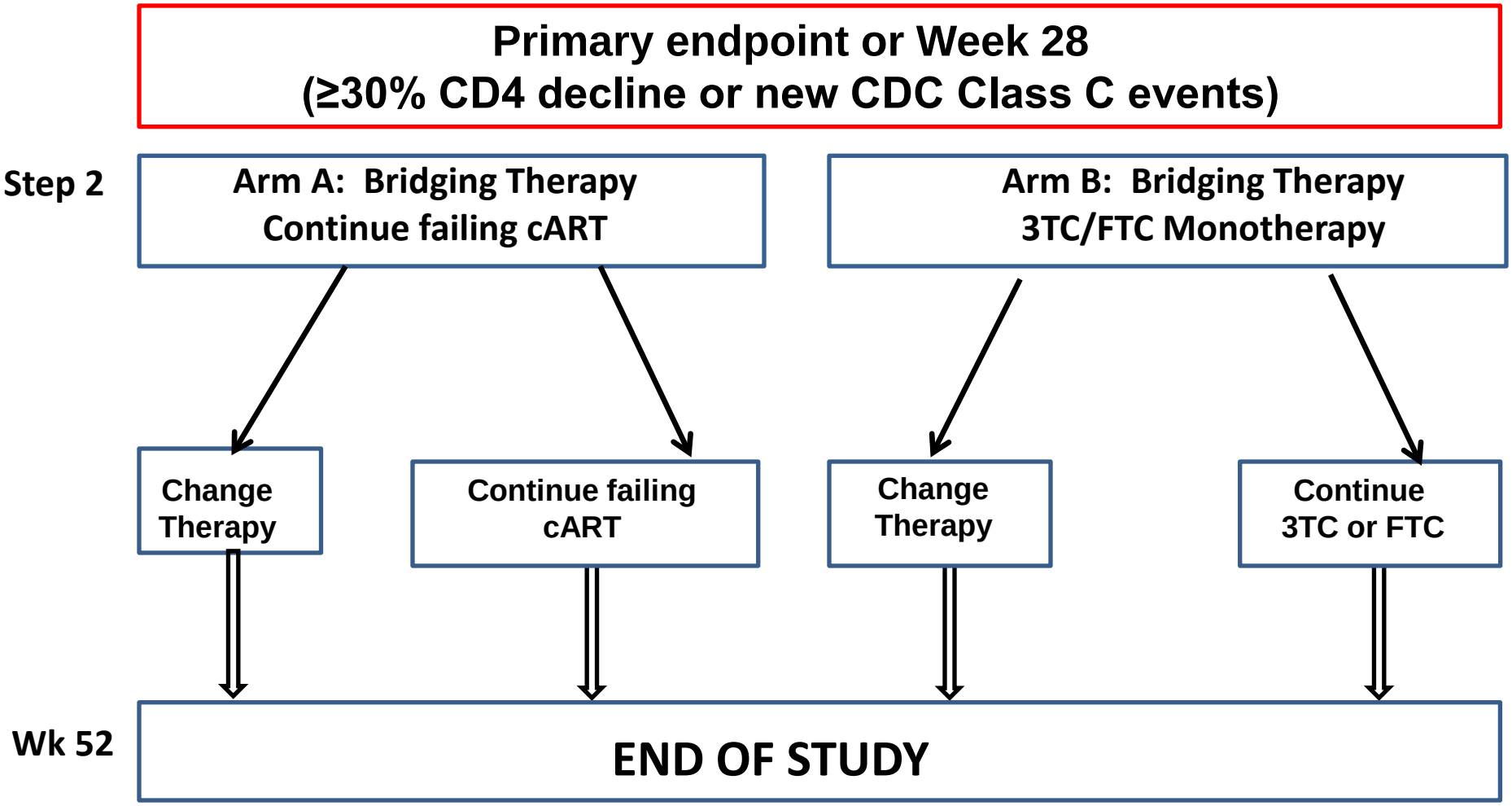

Step 2 [Wk >28 (or time meeting clinical endpoint) to Wk 52]: Subjects may: (a) continue randomized treatment, (b) begin new cART regimen, if adherence is likely or if clinically necessary, or (c) discontinue study treatment. All remain on study follow-up.

Study design

- Randomized controlled trial
- Sites: domestic & international
- Inclusion criteria:
  - Ages 8-24 years
  - cART for a minimum of 6 months
  - Documented non-adherence
  - Persistent VF (HIV-1 plasma RNA ≥400 copies/mL)
  - M184V resistance mutation at or prior to screening
  - CD4≥100 cells/mm^3
  - Attempts to improve adherence unsuccessful

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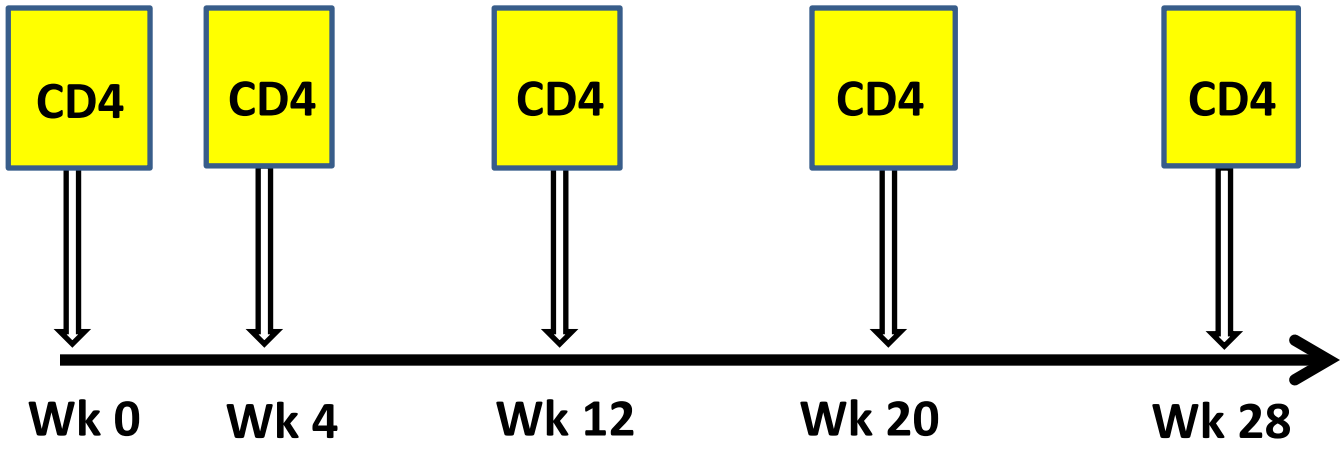
Frequency of CD4 Monitoring during Step 1



Primary endpoint: ≥30% decline in absolute CD4

Additional measurements: adherence, viral load, HIV-genotype and phenotype, immune activation markers

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Study Enrollment

- 33 perinatally HIV-infected participants enrolled
  - 16 randomized to continuing failing cART
  - 17 randomized to 3TC/FTC monotherapy
  - US, Brazil, Thailand, Argentina
- Early study closure in February 2013 due to slow accrual at US sites and long regulatory processing times delaying opening at international sites.

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Baseline Demographic and Clinical Characteristics

		Treatment Arm		
		cART (N=16)	3TC/FTC (N=17)	Total (N=33)
Age at Entry (Years)	Median (Q1, Q3) Min, Max	16.5 (14.0,19.5) 11,24	15(13,20) 10,21	15 (14,20) 10,24
Gender	Male	4 (25%)	7 (41%)	11 (33%)
Race	Black White Asian	9(56%) 4(25%) 3(19%)	8 (47%) 6 (35%) 3(18%)	17 (52%) 10(30%) 6 (18%)
Hispanic ethnicity		6 (38%)	8 (47%)	14(42%)
Screening CD4	Median (Q1,Q3) Min, Max CD4<400 CD4≥400	490 (377,615) 262,897 5(31%) 11 (69%)	461 (384,683) 156,1078 5(29%) 12(71%)	472(384,651) 156,1078 10(30%) 23 (70%)
HIV RNA $\log_{10}$ copies/ml	Median (Q1,Q3) Min, Max	4.1(3.3,4.6) 2.2, 5.6	4.0 (3.2,4.1) 2.2,4.9	4.0 (3.2,4.5) 2.2,5.6

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Measures used to Determine Chronic Non-adherence*

		Treatment Arm		
		cART N=16	3TC/FTC N=17	Total N=33
# mechanisms used to determine non-adherence	Median (Q1,Q3) Min, Max	3 (2-3.5) 1,6	2 (2,3) 1,5	3 (2,3) 1,6
Patient admission of non-adherence		13 (81%)	13 (76%)	26 (79%)
Persistent viremia		12 (75%)	11 (65%)	23 (70%)
Pill counts		3 (19%)	4 (24%)	7 (21%))
Pharmacy refill history		8 (50%)	4 (24%)	12 (36%)
Agreement of 2 providers		9 (56%)	11 (65%	20 (61%)
Other		2 (13%)	1 (6%)	3 (9%)

Interventions attempted*: counseling (94%), frequent clinic visits (75%), reminders (56%), DOT (6%), G-tube (6%) , home visits (19%), therapy (56%), peer support (31%), regimen modification/simplification (25%), rewards (31%), ADL triggers (44%)

***not mutually exclusive**

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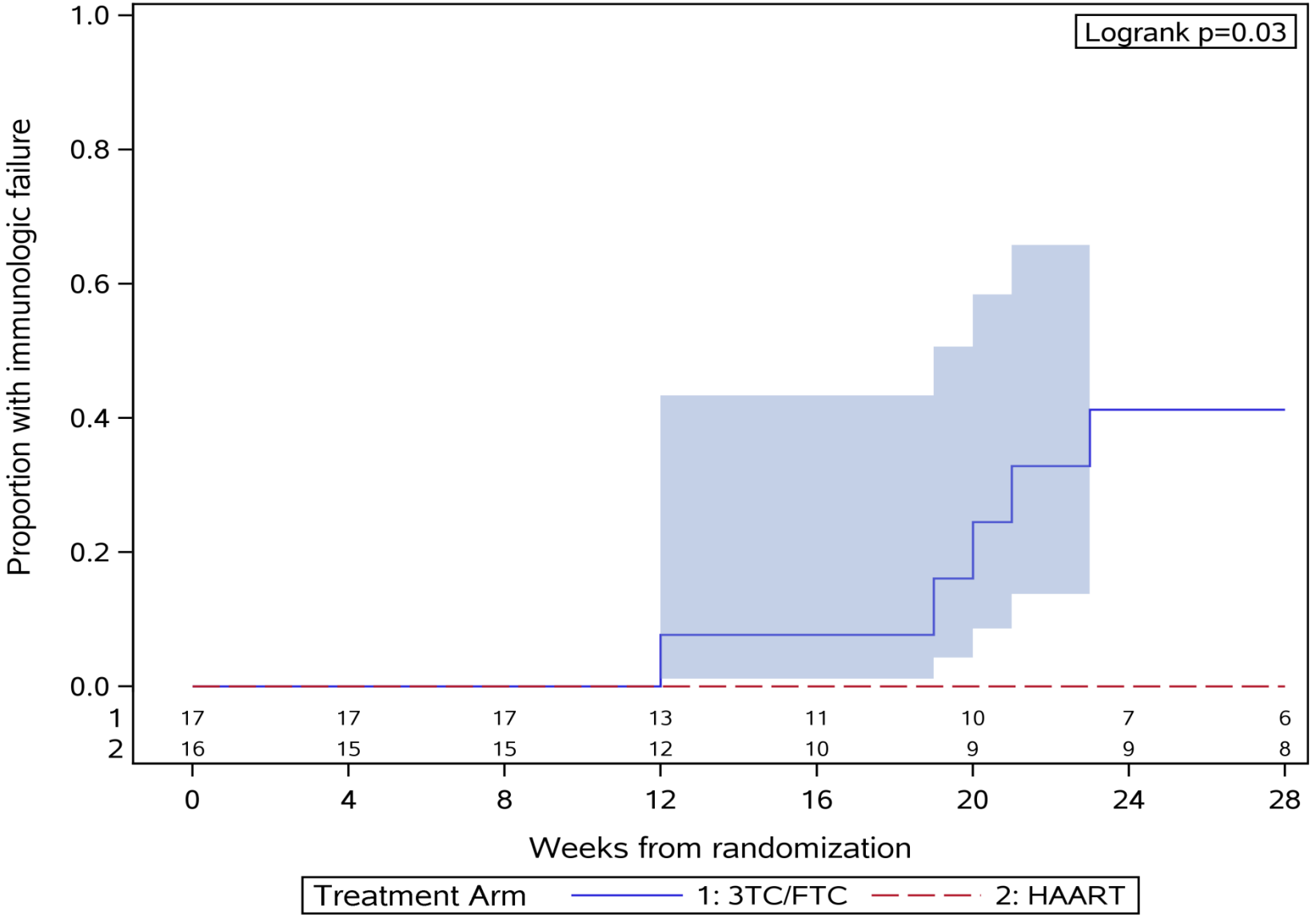
Probability of ≥30% Decline in Absolute CD4 Count



One Grade 3+ adverse event (Grade 4 hyperbilibirubinemia in continuing cART arm).

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Conclusions

- PHIV-infected youth with persistent virologic failure on cART who were randomized to 3TC/FTC monotherapy were significantly more likely to experience ≥30% decline in absolute CD4 count over 28 weeks compared with those maintained on failing cART.

- To our knowledge, this is the first and only RCT of 3TC/FTC monotherapy in this population

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Study Limitations

- Small sample size though findings were highly significant
- Lack of information on actual ARV drug exposure with measurements of drug levels

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Implications

- 3TC/FTC monotherapy is suboptimal as a bridging strategy for PHIV-infected youth compared with continuing a failing cART regimen
- Highlights the need for studies of optimizing current treatment and development of novel agents including long-acting ARVs for youth

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