Poster # 539

# Predictors of Late Virological Failure After Initial Successful Suppression on EFV-based ART

Singini I[1], Campbell T[2], Smeaton L[3], Kumarasamy N[4], Klingman K[5], Taejareonkul S[6], Flanigan T[7], La Rosa A[8], Hakim J[9], Hughes MD[3], for the ACTG A5175/PEARLS Study Team.

[1]Johns Hopkins Research Project, Blantyre, Malawi, [2]University of Colorado Denver, Aurora, CO, [3]Harvard School of Public Health, Boston, MA, [4]YRGCARE Medical Centre, Chennai, INDIA, [5]NIH, NIAID, DAIDS, Bethesda, MD, [6]Chiang Mai University, Chiang Mai, THAILAND, [7]Miriam Hospital, Brown University, Providence, RI, [8]Asociacion Civil Impacta Salud y Educacion, Lima, PERU, [9]University of Zimbabwe College of Health Sciences, Harare, ZIMBABWE

Isaac Singini
Johns Hopkins Research Project
Chipatala Avenue, QECH
P.O. Box 1131
Blantyre, Malawi
+265 877 138 (l), +265 888 204 523 (c)
isingini@jhu.medcol.mw

## ABSTRACT

**Background:** There are practical issues, including high cost, in implementing virologic monitoring of patients on antiretroviral therapy (ART) in resource-limited settings. We evaluated factors that might guide less frequent virologic monitoring after successful virologic suppression on efavirenz (EFV)-based ART in such settings.

**Methods:** HIV-1 RNA was measured every 8 weeks in antiretroviral naive participants with nadir CD4 counts <300/mm$^3$ who were randomized to EFV with lamivudine/zidovudine or emtricitabine/tenofovir in the international ACTG A5175/PEARLS trial, and who achieved HIV-1 RNA <1000 c/mL at 24 weeks without prior virologic failure or new AIDS event. Predictors of late virologic failure (late VF: confirmed HIV-1 RNA ≥1000 c/mL after 24 weeks) were evaluated by multivariate Cox models using stepwise selection from among the following variables: demographic; pre-ART CD4, HIV-1 RNA, AIDS, TB, hepatitis B, laboratory test results and body mass index; ART regimen; occurrence of Grade ≥3 laboratory results and signs/symptoms, ART change, self-reported adherence before week 24; and week 24 CD4 change and HIV-1 RNA (≤400 vs 401-999).

**Results:** 911 of 1045 subjects (87%) had HIV-1 RNA <1000 at 24 weeks. During median follow-up of >3yr after week 24, 82 of the 911 (9%) experienced late VF. VF rate appeared higher between 24 to 48 weeks (2.4%) but was reasonably constant thereafter (~1.25% every 24 weeks). In multivariate analysis, increased late VF risk was significantly associated with lower pre-ART hemoglobin (adjusted hazard ratio [AHR]=1.18 per 1g/dL lower; 95% CI: 1.04, 1.33; p=0.008), and both self-reported imperfect ART adherence (55/516 [10.7%] vs 27/413 [6.8%] for perfect adherence; AHR=1.72; CI: 1.08, 2.72; p=0.022) and absence of Grade ≥3 laboratory results prior to week 24 (77/800 [9.6%] vs 5/111 [4.5%] for those with Grade ≥3 results; AHR=2.53; CI: 1.02, 6.29; p=0.046). Sensitivity analyses restricted to subjects who did not change ART regimen, and to those without Grade ≥3 laboratories, prior to week 24 showed similar results. In time-updated analysis, self-reported imperfect adherence was a significant predictor of increased late VF risk.

**Conclusions:** In this clinical trial setting, the rate of late VF after successful suppression on EFV-containing ART was very low suggesting that virologic monitoring strategies involving infrequent (eg annual) measurements, possibly targeting subjects reporting imperfect adherence and those with lower pre-ART hemoglobin, might be considered; the implications of this for accumulation of resistance mutations needs evaluating. The unexpected finding that subjects without Grade ≥3 laboratory results before 24 weeks had higher risk of late VF needs evaluating further in a larger study.

## BACKGROUND

There are practical issues, including high cost, in implementing virologic monitoring of patients on antiretroviral therapy (ART) in resource-limited settings. We evaluated factors that might guide less frequent virologic monitoring after initial successful virologic suppression on efavirenz (EFV)-based ART in a secondary analysis of data from the ACTG A5175/PEARLS clinical trial.

## OBJECTIVE

To describe the rate of virologic failure over time and predictors of virologic failure among subjects achieving initial suppression of HIV-1 RNA to <1000 copies/mL at 24 weeks after starting EFV-based antiretroviral therapy as initial therapy.

## METHODS

**The ACTG A5175/PEARLS clinical trial:** ACTG A5175/ PEARLS was a randomized trial undertaken in diverse geographic settings that included comparison of two EFV-based antiretroviral therapies (TDF/FTC+EFV and ZDV/3TC+EFV) as initial treatment for HIV infection (Campbell et al., 2012).

During a median follow-up of 184 weeks, for the primary outcome measure of time to virologic failure (confirmed HIV-1 RNA≥1000 copies/mL at/after week 16), new AIDS event or death, the two regimens were similar: 95 (18%) of 526 participants assigned TDF/FTC+EFV versus 98 (19%) of 519 participants assigned ZDV/3TC+EFV (hazard ratio 0.95, 95% CI 0.72–1.27; p = 0.74) [Campbell et al., 2012].

**Study population:** Participants were HIV-infected individuals, age ≥18 years, CD4 count <300 cells/mm$^3$, who had received no more than 7 days of cumulative prior ART (prior use of single-dose NVP or ZDV for any duration for PMTCT). Written informed consent was obtained from all participants. The study was approved by ethics committees at participating institutions.

For this secondary analysis, the study population was restricted to subjects randomized to FTC/TDF+EFV or 3TC/ZDV+EFV who had an HIV-1 RNA measurement at week 24 which was <1000 copies/mL and no virologic failure or new AIDS-defining event identified at or prior to week 24. Changes in one or more drugs at or prior to week 24 were allowed.

**Outcome measure and statistical analysis:** In this secondary analysis, the main outcome measure was time to late virologic failure (VF: confirmed HIV-1 RNA ≥1000 copies/mL after week 24) with time measured from the date of the week 24 HIV-1 RNA measurement. HIV-1 RNA measurements were obtained every 8 weeks. Statistical analysis used proportional hazards models with p<0.10 in univariate analysis required for consideration of a variable in multivariate analysis using stepwise variable selection. Censoring of follow-up was at the last available HIV-1 RNA measurement.

## RESULTS

### Study Population

Of the 1045 subjects randomized to receive TDF/FTC+EFV or ZDV/3TC+EFV, 911 (87%) had HIV-1 RNA <1000 copies/mL at week 24 and were included in our study population.

134 subjects were excluded for the following reasons:

- virologic failure at or prior to week 24 (64 subjects)
- new AIDS defining event prior to week 24 (3 subjects)
- death prior to week 24 (11 subjects)
- HIV-1 RNA >1000 copies at week 24 (18 subjects)
- loss to follow-up at or before week 24 (28 subjects)
- no HIV-1 RNA measurement at week 24 (10 subjects)

**Table 1: Characteristics of the Study Population (n=911)**

| | | |
|---|---|---|
| Sex: % male | | 54% |
| Age, years: median (quartiles) | | 34 (29, 41) |
| Country, %: | India | 17% |
| | Brazil | 16% |
| | S Africa | 13% |
| | USA | 13% |
| | Malawi | 12% |
| | Peru | 9% |
| | Zimbabwe | 7% |
| | Thailand | 7% |
| | Haiti | 6% |
| Pre-treatment HIV-1 RNA, copies/mL: median (quartiles) | | 105000 (38480, 261330) |
| Pre-treatment CD4 count, cells/mm$^3$: median (quartiles) | | 168 (89, 232) |
| Pre-treatment hemoglobin, g/dL: median (quartiles) | | 12.4 (11.2, 13.8) |
| Pre-treatment history of AIDS, % | | 18% |
| Initial ART, % | TDF/FTC+EFV | 50% |
| | ZDV/3TC+EFV | 50% |
| Week 24 HIV-1 RNA, % | ≤400 | 98.4% |
| | 401-<1000 | 1.6% |
| Week 24 CD4 count, cells/mm$^3$: median (quartiles) | | 284 (200, 380) |
| Change in CD4 count from pre-ART to week 24, cells/mm$^3$: median (quartiles) | | 118 (66, 185) |

### Pattern of Virologic Failure After Initial Successful Suppression

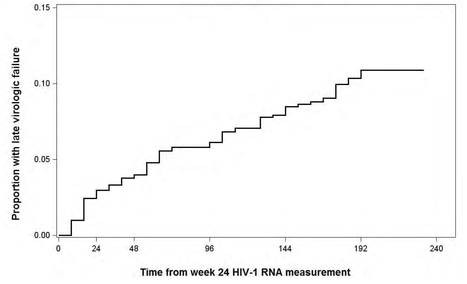
At the time of study closure, subjects had been followed for a median of 160 weeks (3.1 years) from the week 24 visit (equivalently, 184 weeks [3.5 years] from start of initial ART).

During this time, 10% of subjects were lost to follow-up or died without experiencing virologic failure.

Of the 911 subjects, 9% (n=82) subjects experienced late virologic failure.

VF rate appeared higher between time zero and 24 weeks (equivalent to 24 to 48 weeks after starting ART)(2.4%) but was reasonably constant thereafter (~1.25% every 24 weeks) (Figure 1)

**Figure 1: Proportion of Subject With Late Virologic Failure From Week 24 HIV-1 RNA Measurement**




### Predictors of Virologic Failure After Initial Successful Suppression

The following possible predictors of late virologic failure were evaluated:

- Demographic: sex, age, country
- Pre-ART disease status: CD4 count, HIV-1 RNA, history of AIDS, tuberculosis, hepatitis B infection, body mass index.
- Pre-ART laboratory test results: creatinine clearance, albumin, hemoglobin, and platelet, absolute neutorphil, absolute lymphocyte and white blood cell counts.
- Initial ART regimen (TDF/FTC+EFV or ZDV/3TC+EFV)
- Grade ≥3 laboratory test results or signs/symptoms through to week 24.
- Change in ART regimen through to week 24.
- Self-reported adherence before week 24.
- Change in CD4 count from pre-ART to week 24, and HIV-1 RNA at week 24 (≤400 vs 401-999 copies/mL).

In univariate analysis, lower pre-ART hemoglobin (p=0.025), lower absolute neutrophil count (p=0.044), and higher white blood cell count (p=0.026), as well as imperfect self-reported adherence during the first 24 weeks of ART were significantly associated with higher risk of late VF (p=0.032). There was a trend for lower risk among subjects with a Grade ≥3 laboratory test result during the first 24 weeks of ART (p=0.085).

**Table 2: Summary of Multivariate Analysis**

| Predictor | Category | Number | Number (%) with late virologic failure | Adjusted hazard ratio (AHR) (95% CI) | p-value |
|---|---|---|---|---|---|
| Self-reported ART adherence | Not Perfect | 516 | 55 (10.7) | 1.72 (1.08, 2.72) | 0.022 |
| | Perfect* | 395 | 27 (6.8) | | |
| Lab Grade 3/4 within 24 weeks | Yes | 111 | 5 (4.5) | 0.40 (0.16, 0.98) | 0.046 |
| | No* | 800 | 77 (9.6) | | |
| Pre-ART hemoglobin (per 1 g/dL lower) | | | | 1.18 (1.04, 1.33) | 0.008 |

*Reference category for AHR

Figures 2 to 4 show the cumulative incidence of late VF for the three variables identified in the multivariate analysis (Table 2);. Although hemoglobin was included in the analysis as a continuous variable, for illustration, Figure 2 shows cumulative incidence for subjects with pre-ART hemoglobin below vs above the median of 12.4 g/dL.

Two sensitivity analyses were undertaken: (1) restricted to subjects who did not change ART regimen during the first 24 weeks of treatment, and (2) restricted to subjects without Grade ≥3 laboratory test results during the first 24 weeks of treatment. Both showed similar findings to the main analysis presented in the table above.

**Figure 2: Late Virologic Failure by Self-reported ART Adherence During the First 24 Weeks of ART**

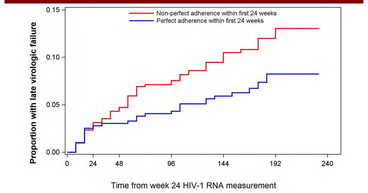



**Figure 3: Late Virologic Failure by Whether or Not a Subject Had a Grade ≥3 Laboratory Test Result During the First 24 Weeks of ART**

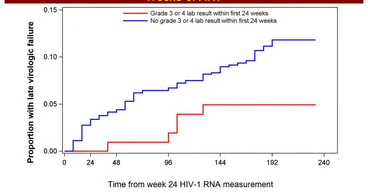
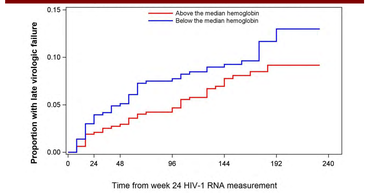



**Figure 4: Late Virologic Failure by Pre-ART Hemoglobin Level**




## CONCLUSIONS

In this clinical trial setting, the rate of late VF after successful suppression on EFV-containing ART was very low suggesting that virologic monitoring strategies involving infrequent (eg annual) measurements, possibly targeting subjects reporting imperfect adherence and those with lower pre-ART hemoglobin, might be considered; the implications of this for accumulation of resistance mutations needs evaluating. The unexpected finding that subjects without Grade ≥3 laboratory results before 24 weeks had higher risk of late VF needs evaluating further in a larger study.

## REFERENCE

Campbell TB, Smeaton LM, KumarasamyN, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. PLOS Medicine 2012. 9(8):e1001290.

## ACKNOWLEDGEMENTS

We thank the study participants, clinical sites and other members of the ACTG A5175/PEARLS study team.