Treatment Interruption Strategies for NNRTI-Based Regimens: Does the NRTI Matter?

501

Alice Pau[1], Jacqueline Nordwall[2], Edward Gardner[3], Anna Maria Geretti[4], Kimberly Scarsi[5], John Baxter[6], Virginia Kan[7], Nnakelu Eriobu[8], Vidar Ormaasen[9], Sarah Pett[10], H Clifford Lane[1], Andrew Phillips[10], James Neaton[2] for the INSIGHT SMART Study Group

[1]National Institutes of Health, Bethesda, MD, USA; [2]U of Minnesota, Minneapolis, MN, USA; [3]Denver Public Health, Denver, CO, USA; [4]U of Liverpool, Liverpool, UK; [5]U of Nebraska Medical Center, Omaha, NE, USA; [6]Cooper Medical School of Rowan University, Camden, NJ, USA; [7]George Washington U, Washington DC, USA; [8]Institute of Human Virology, Abuja, Nigeria; [9]Oslo University Hospital, Oslo, Norway; [10]University College London, London, UK

BACKGROUND

- In the SMART study, participants on an EFV or NVP-based regimen who stopped all drugs simultaneously **(Simultaneous** strategy**)** had a lower rate of viral resuppression at 4-8 months after ART restart, and were at higher risk of emergence of resistance mutations, compared to those who either stopped the NNRTI first, followed by the NRTIs in 7-21 days **(Staggered** strategy**),** or replaced the NNRTI with a boosted PI for a minimum of 3 weeks before stopping all ARV drugs **(Switched** strategy**).**[1]
- EFV and NVP have relatively long plasma half-lives ($T_{1/2}$) compared to NRTIs (Table 1) and have a low barrier to resistance. Due to differences in ARV $T_{1/2}$, simultaneous stopping of an NNRTI + NRTI regimen may result in NNRTI monotherapy.
- In a previous analysis of the SMART Study, Geretti et al[3] reported that at 4 weeks after treatment interruption, NVP and EFV drug concentrations were still measurable in 61.3% and 87.2% of the participants, respectively.

Table 1. Plasma $T_{1/2}$ of NNRTIs & NRTIs and Intracellular $T_{1/2}$ of NRTIs[2]

NNRTIs		NRTIs		
ARV	**Serum $T_{1/2}$ (hrs)**	**ARV**	**Serum $T_{1/2}$ (hrs)**	**Intracellular $T_{1/2}$(hrs)**
Efavirenz (EFV)	**40-55**	**Zidovudine (ZDV)**	**1.1**	**7.0**
Nevirapine (NVP)	**25-30**	**Stavudine (d4T)**	**1**	**7.5**
Doravirine (DOR)	15	**Didanosine (ddI)**	**1.5**	**>20**
Etravirine (ETR)	41	**Tenofovir DF (TDF)**	**17**	**>60**
Rilpivirine (RPV)	50	Tenofovir AF (TAF)	0.5	150-180
		Lamivudine (3TC)	5-7	18-22
		Emtricitabine (FTC)	10	>20
		Abacavir (ABC)	1.5	12-26

- The SMART study was conducted from 2002 to 2006, when the most commonly used NRTIs were ZDV, d4T, or ddI.
- Both TDF and TAF have longer intracellular $T_{1/2}$ than older NRTIs (Table 1)

Study Hypothesis: We hypothesized that because TDF has a longer intracellular $T_{1/2}$ than older NRTIs, the resuppression rate after stopping an NNRTI regimen containing TDF would be similar, regardless of whether a Simultaneous, Staggered or Switched strategy was used.

METHODS

SMART Study Design: The SMART Study randomized persons with HIV (PWH) with suppressed HIV RNA and CD4 count > 350 cells/μL to either CD4 guided ART interruption (Drug Conservation or DC arm) or continuous therapy (Viral Suppression or VS arm).[4]

Current Analysis: We reanalyzed the data[1] for participants who interrupted NNRTI-based ART and later restarted an NNRTI regimen.

Inclusion Criteria: Participants from the DC arm on an NNRTI-regimen who had HIV-RNA ≤400 copies/mL at ART discontinuation, restarted an NNRTI-containing regimen, and had an HIV-RNA level drawn 4-8 months after restart.

Genotypic Resistance Testing: NNRTI or NRTI DRMs were assessed by genotypic testing (TRUGENE) for those with HIV RNA >1000 copies/mL within 2 months after ART interruption.

Statistical Analysis: Percentages and medians (IQRs) were used to summarize participants taking TDF and non-TDF by method of interrupting ART. For those interrupting ART simultaneously, the proportion with HIV RNA ≤ 400 copies/mL after restart for participants taking a TDF versus a non-TDF regimen was compared using a chi-square test. Logistic regression was used to consider the interaction of method of stopping and use of TDF in the NNRTI-based regimen. Two-sided p-values are cited.

RESULTS

Table 2. Study Population, NNRTI and NRTI Usage, and Interruption Strategies

In SMART, randomized to interrupt ART (N)	2,720
Stopped NNRTI-based ART, met inclusion criteria for current analysis(N)	513
NNRTI	
Efavirenz, n (%)	319 (62.2%)
Nevirapine, n (%)	194 (37.8%)
NRTI	
Non-TDF, n (%)	389 (75.8%)
TDF, n (%)	124 (24.2%)
Interruption Strategies	
Simultaneous, n (%)	100 (19.5%)
Staggered, n (%)	302 (58.9%)
Switched, n (%)	111 (21.6%)

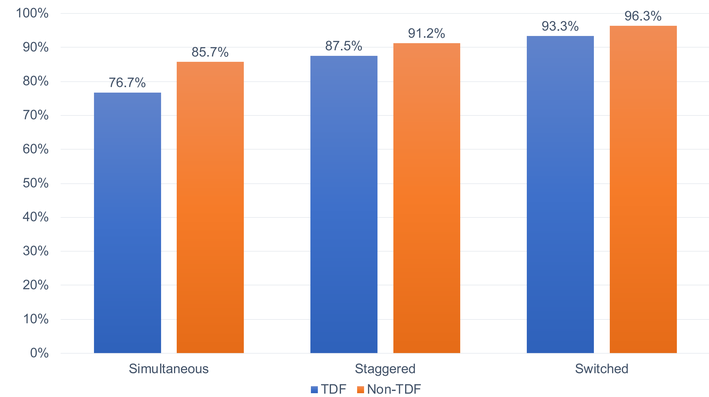
Table 3. Baseline Characteristics & ARV Drugs by NRTI and Interruption Strategies

	Simultaneous		Staggered		Switched	
	TDF	**Non-TDF**	**TDF**	**Non-TDF**	**TDF**	**Non-TDF**
N	30	70	64	238	30	81
Age (median, IQR) years	45 (41 - 50)	44 (37 - 51)	44 (39 - 52)	43 (37 - 50)	45 (39 - 52)	42 (36 - 49)
Gender (% female)	16.7	24.3	25.0	29.4	20.0	23.5
Race (% Black)	20.0	22.9	18.8	18.9	20.0	22.2
CD4 (median, IQR) cells/mm^3	515 (443 - 784)	636 (481 - 852)	626 (491 - 804)	589 (470 - 724)	550 (456 - 759)	613 (478 - 773)
Co-administered NRTIs						
TDF (%)	100.0	0.0	100.0	0.0	100.0	0.0
3TC or FTC (%)	70.0	82.9	73.4	89.9	76.7	90.1
ZDV (%)	0.0	54.3	1.6	63.0	3.3	58.0
d4T (%)	0.0	30.0	0.0	16.8	0.0	22.2
ddI (%)	16.7	12.9	4.7	14.7	6.7	12.3
ABC (%)	13.3	11.4	6.3	13.9	10.0	24.7
Co-Administered NNRTIs						
EFV (%)	43.3	51.4	73.4	66.4	73.3	53.1
NVP (%)	56.7	47.1	26.6	33.6	26.7	48.1

Table 4. Genotypic Resistance Testing Performed within 2 months after ART Interruption Detecting Drug Resistance Mutations (DRM)

	Simultaneous		Staggered		Switched	
	TDF	non-TDF	TDF	non-TDF	TDF	non-TDF
Resistance testing prior to restart, n	20	41	24	32	8	16
N (%) of Participants with NNRTI DRMs	5 (25.0%)	5 (12.2%)	1 (4.2%)	6 (18.8%)	0 (0%)	1 (6.3%)
NNRTI DRM Detected	2-103N, 2-181C/I, 2-188C/H/L	1-108I, 2-181C/I, 1-188C/H/L, 1-190S/A	1-108I	3-103N, 2- 108I, 1-188C/H/L, 1-190S/A	None	1-108I
N (%) of Participants with NRTI DRMs	2 (10.0 %)	7 (17.1%)	5 (20.8%)	6 (18.8%)	1 (12.5%)	2 (12.5%)

Figure 1. Participants (%) with Viral Resuppression (HIV RNA ≤ 400 copies/mL) at 4-8 Months after Restarting NNRTI-Based Regimen – by TDF vs. Non-TDF and by Interruption Strategies



Among those stopping ART simultaneously, the difference in resuppression percentages for TDF vs non-TDF regimens after restart was not significantly different from zero (difference = 9.0%; 95% CI: -26.3% to +8.2%; p=0.27); the p-value for interaction between the method of interrupting ART and TDF in the regimen was 0.94 indicating that differences among methods of interrupting ART did not vary according to use of TDF in the regimen.

DISCUSSION

- Despite the longer intracellular $T_{1/2}$ of TDF (compared to older NRTIs), there was no difference in resuppression rate after stopping all ARV drugs simultaneously. The rate was still lower than using a Staggered or Switched Strategy.
- Limitations of this analysis
  - The SMART trial was conducted over 10 years ago, the ARV regimens used in the trial are different from those currently prescribed in most countries.
  - The interruption strategies were not randomized, there could have been investigator biases in which strategy to use.
  - The participants who were on TDF and those who stopped simultaneously were only a small percentage (5.8%) of the entire cohort.
- It is not known whether the same results for TDF apply to regimens containing TAF.
- The newer NNRTIs – ETR and RPV have similar $T_{1/2}$ as NVP or EFV, thus simultaneous interruption of all ARV drugs in these regimens should be also avoided.
- Doravirine has a shorter $T_{1/2}$, the appropriate strategy is not known.
- Identifying the optimal stopping strategy for the newer ARV regimens is particularly important when designing clinical trials where analytical treatment interruptions are utilized.

References:
1. Fox Z, Phillips A, Cohen C, et al. AIDS 2008; 22: 2279-89.
2. https://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0
3. Geretti AM, Fox Z, Johnson JA, et al. PLOS One 2013; 8 (7): e69266.
4. El-Sadr WM, Lundgren JD, Neaton JD, et al. N Engl J Med 2006; 335: 2283-96.

ADDITIONAL KEY INFORMATION:
Funding Sources for SMART - NIH Grants UM1-AI068641, U01-AI046362, and U01-AI042170
Corresponding Author: Alice K Pau, Pharm.D., NIH Clinical Center, Bldg 10, Rm 11C103, Bethesda, MD 20895. apau@niaid.nih.gov
Acknowledgement: The authors like to thank all the study participants and investigators for their contributions to this research.