Long-term Adherence Monitoring of Emtricitabine in Hair by Mass Spectrometry Imaging

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BACKGROUND

- Adherence to antiretroviral therapy is critical for effective treatment and prevention of HIV.
- Incorporation of drug in hair creates a long-term record of adherence behavior, and mass spectrometry imaging (MSI) using infrared matrix-assisted laser desorption electrospray ionization (IR-MALDESI) can monitor changes in this record as an objective measure of adherence.
- We benchmarked longitudinal profiles of emtricitabine (FTC) in hair strands using IR-MALDESI MSI following directly observed therapy (DOT).
- Adherence thresholds were identified, and a tool for real-time evaluation of patient adherence in a clinical setting was developed.

METHODS

- As part of the ENLIGHTEN study (*NCT03218592*), healthy volunteers (n=12) were administered Truvada® by DOT in discrete dosing phases that included 28-day periods of daily dosing and differentiated dosing (0, 1, and 3 doses/week; n=4 in each group), separated by up to 7 days.
- Hair (10-20 strands) was collected from the scalp occipital region (regular growth of ~10 mm/month) on days 3, 7, 14, 21, and 28 of each phase. Theoretical disposition of FTC in hair at the end of differentiated dosing is shown in **Figure 1**.

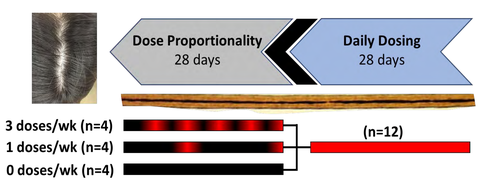


Figure 1. DOT dosing scheme and expected FTC disposition in hair.

- Sample strands (n=4) were mounted to double-sided tape and FTC response was evaluated in the proximal 25 mm by IR-MALDESI MSI. Apparatus and example output are shown in **Figure 2**.

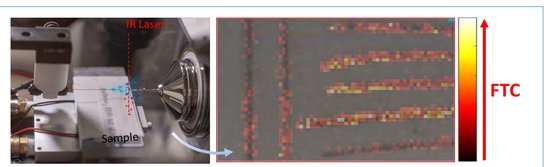
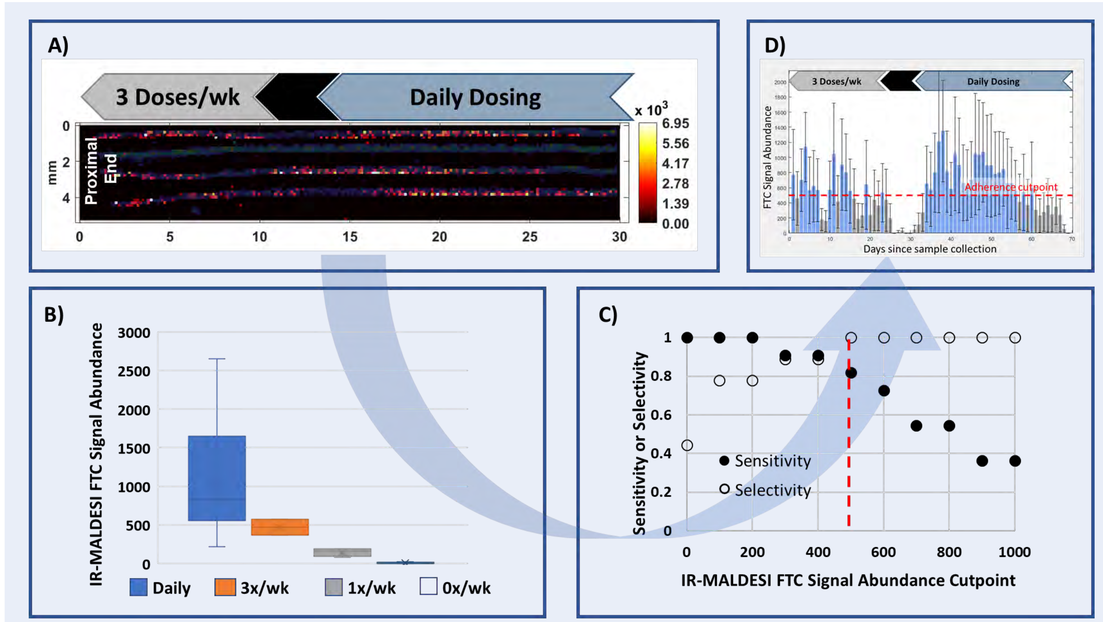


Figure 2. IR-MALDESI MSI analysis of hair strands.



***Summary Figure*. Development of FTC adherence classification using IR-MALDESI: A) MSI analysis of FTC in DOT hair sample; B) FTC DOT dose-response based on MSI; C) Adherence cut point selection; and, D) Resulting dichotomous daily adherence classification over hair profile.**

RESULTS

Longitudinal Profiling of FTC in Hair Strands

- FTC was measured in strands from 11/12 volunteers (1 reported recent hair salon treatment).
- IR-MALDESI MSI measurements were made every 100 μm along the hair strands (~8 hrs of growth) with distinct and localized bands of FTC measured in each actively growing strand, which were associated with intermittent dosing (proximal) and daily dosing (distal) periods, along with the gap between dosing periods. **Summary Figure A** shows FTC disposition in hair strands from an individual transitioning from daily dosing to 3 doses/week.
- Using custom Matlab scripting[1], composite longitudinal profiles of FTC response in hair strands were calculated based on these images. Example profiles are shown in **Figure 3**.

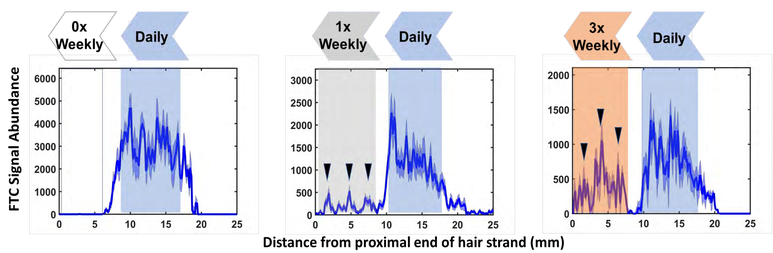


Figure 3. Representative longitudinal profiles of FTC response in hair. Dosing phases within each profile are defined by shaded boxes. Arrows highlight distinct patterns apparent within each differentiated dosing group.

- Average IR-MALDESI FTC signal abundance associated with daily and differentiated dosing phases was calculated for each individual longitudinal profile. A summary of DOT FTC response is shown in **Summary Figure B.**

Adherence Cutpoint Selection

- Interindividual variability in hair accumulation was observed (relative standard deviation $_{\text{daily dosing}}$ = 69%).
- An adherence cutpoint was determined (**Summary Figure C**) for binary classification between full and partial adherence with high sensitivity (81%) and selectivity (100%).

Long-term Adherence Classification

- Based on the adherence cutpoint, the estimated daily response (averaging three adjacent IR-MALDESI MSI FTC measurements) was classified throughout the longitudinal profile, as seen in **Summary Figure D**.
- Adherence reporting based on IR-MALDESI hair analysis of FTC was developed (**Figure 4**) based on feedback from clinicians and patients[2,3], and is now being implemented in a pilot study (*NCT04232540*), assessing feasibility, acceptability and appropriateness of real-time MSI adherence assessment.

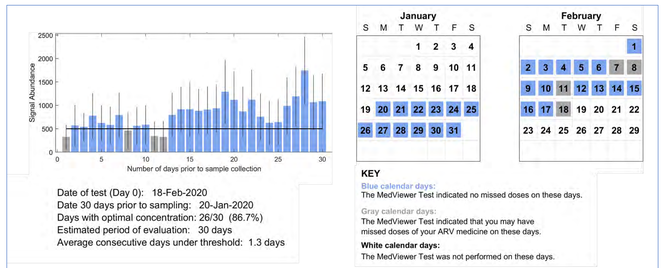


Figure 4. Adherence reporting in profile (clinicians) or calendar (patients) format

CONCLUSIONS

- Longitudinal daily dosing for FTC can be visualized in hair strands by IR-MALDESI MSI. This approach is a non-invasive long-term, daily adherence measure for patients and clinicians, applicable to both treatment and prevention.

References

1. Gilliland et al. (2019). *Analytical Chemistry.* 91(16): 10816-10822.
2. Pack et al. (2019). *Patient Education and Counseling*. 102(6): 1090-1097.
3. Hill et al. (2020). *Journal of the Association of Nurses in AIDS Care.* 31(1):25–34.

Acknowledgements

Funding Sources:
R01AI122319, P30AI050410