Bioavailability of Co-Encapsulated Antiretrovirals with Ingestible Sensor for Measuring Adherence

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12th International Conference on HIV Treatment and Prevention Adherence

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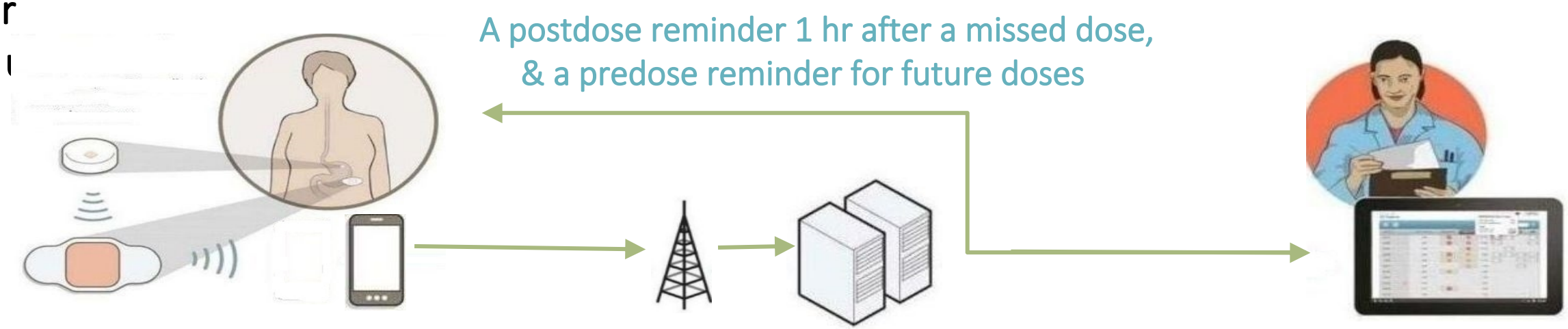
Adherence Measure Overview

♦ Pill ingestion sensor based adherence (Proteus Digital Health Feedback Device [PDHFD]) for



♦ Capabilities/innovations

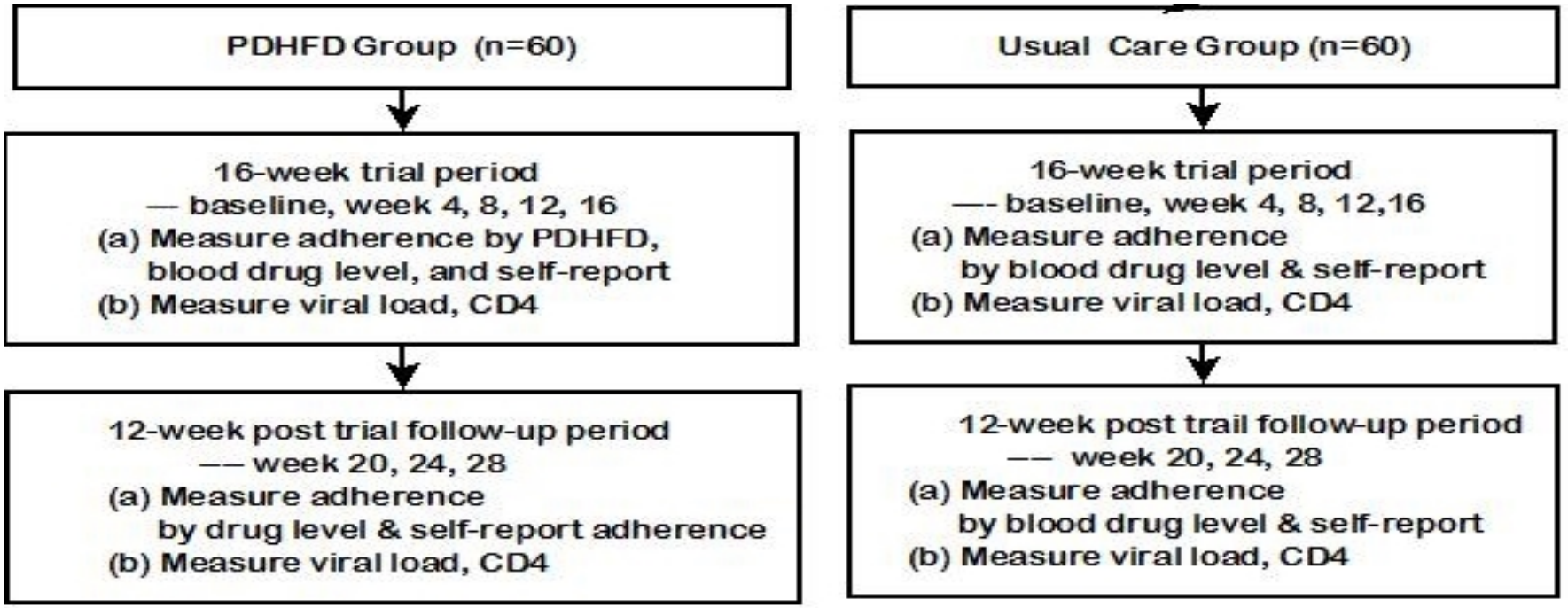
1. Early study using a pill ingestible sensor system to measure adherence to ART in people infected with HIV.
2. Using ingestion sensor-based system to measure, monitor and facilitate patients' adherence by providing real-time messaging for missed doses & conditional prior dose reminders.
3. Evaluate and confirm bioequivalence of co-encapsulated ARVs with sensors used in treating HIV.

♦ Others adherence measures: plasma drug level adherence and self-report adherence

Overall Study Design

Objectives: Evaluate PDHFD system in measuring, monitoring and facilitating adherence to ART: **(a)** *Feasibility, acceptability & sustainability,* **(b)** *Accuracy, and* **(c)** *Efficacy.*

Approaches: (a) Bio-equivalence of co-encapsulation: 7 ARV with 6 pts each; **(b) Pilot:** 15 pts to pilot-test PDHFD: (i) real-time data collection, (ii) real time automated text feedback, (iii) pts' tolerability of co-encapsulation, and (iv) pts' acceptability with the PDHFD; **(c) Main trial:**



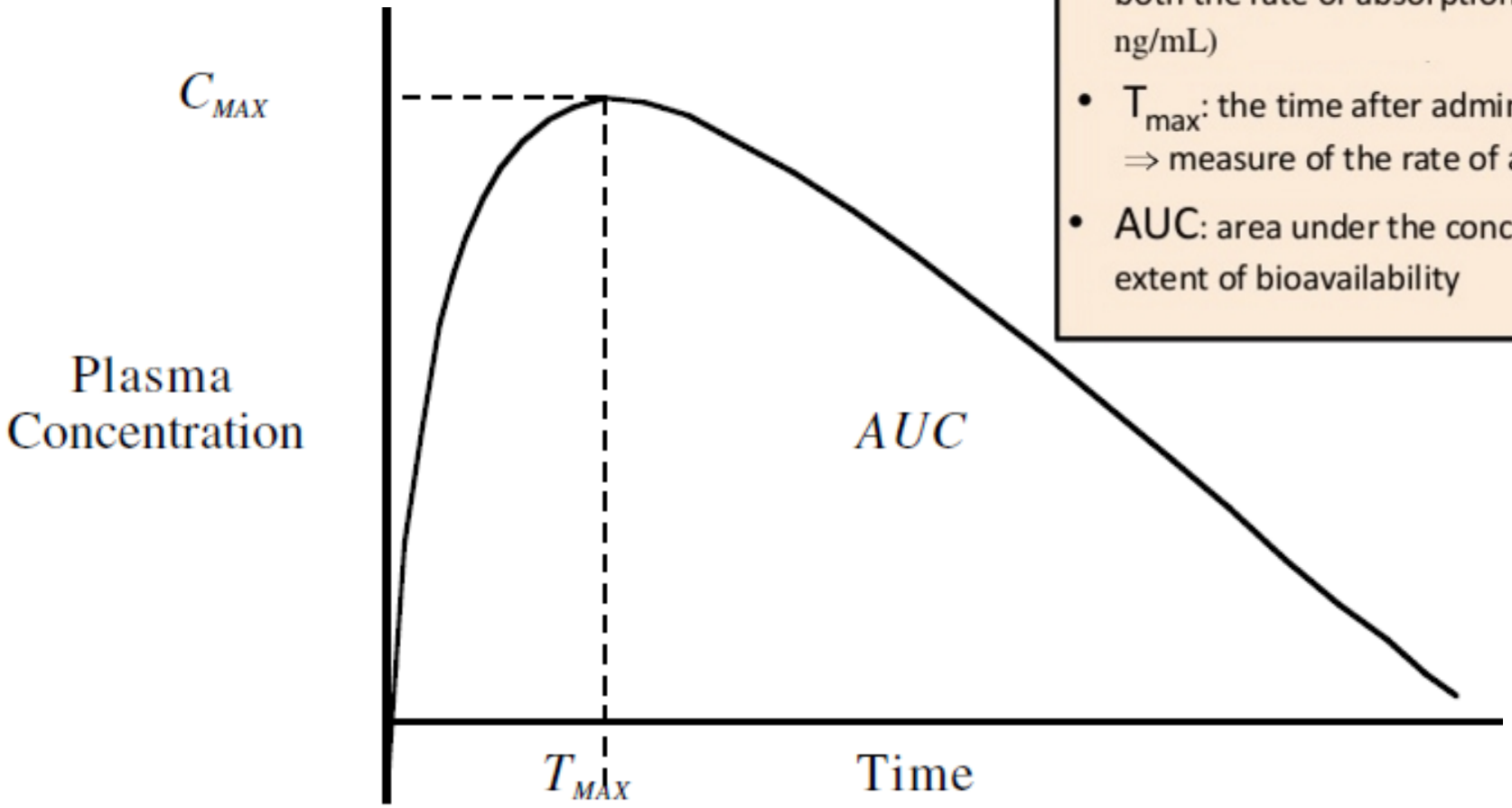
Design for Confirmation of Bioequivalence

- Seven commonly used ARV formulations of **Atripla, Truvada, Descovy, Odefsey, Genvoya, Epzicom, and Triumeq**
- Six patients per formulation (on these regimens for ≥12 weeks and have undetectable viral load)
- Blood draws at pre-dose, and 1, 2, 4 and 6 hours post-dose and PK parameters were measured by LC-MS-MS
- Use historical data as norm and followed by a cross-over test, if can not be confirmed
- Hypothesis: Co-encapsulation should not affect bioavailability.

Patient Demographics by ARVs

ARVs	Male	Female	NH White	NH AA	Hispanic	Asian
TDF/FTC/EFV (Atripla)	6	0	1	2	2	1
FTC/TDF (Truvada)	6	0		2	4	
FTC/TAF (Descovy)	5	1		3	3	
FTC/RPV/TAF (Odefsey)	6	0		2	4	
EVG/COBI/FTC/TAF (Genvoya)	5	1		2	4	
ABC/3TC/ (Epzicom)	5	1	1	4	1	
ABC/3TC/DTG (Triumeq)	5	1	1	2	3	
Summary	38	4	3	17	21	1

Critical Pharmacokinetic Parameters in Assessment of Drug Absorption



- C_{max}: the observed maximum concentration of drug ⇒ measure of both the rate of absorption and the extent of bioavailability (µg/mL or ng/mL)
- T_{max}: the time after administration of drug at which C_{max} is observed ⇒ measure of the rate of absorption (minutes or hours)
- AUC: area under the concentration-time curve ⇒ measure of the extent of bioavailability

Criteria for Bioequivalence (BE)

- 90% confidence interval of the log transformed ratio of test to reference of a PK parameter falls within 80-125% range.
- This acceptance range can be expanded for highly variable drugs to 70-143%.
- Cmax and AUC are the primary parameters for BE.

PK Parameter Estimates

ARVs	Components	Cmax (ng/mL)	Historical Cmax	AUC (ng*hr/mL)	Historical AUC
Atripla	EFV (Efavirenz)	6027.17	3190±915	106812	45500±18051
	FTC (Emtricitabine)	1467.33	1800±720	11025	10000±3120
	TDF (Tenofovir disoproxil fumarate)	299.98	296±90	3134	2287±690
Truvada	FTC	1228.85	1800±720	9286	10000±3120
	TDF	193.97	296±90	2218	2287±690
Descovy	FTC	2239	2100, CV (20.2)	13681	11,700, CV (16.6)
	TAF (Tenofvir alafenamide)	41.1	20 ± 5.2	725.6	290 ± 79.5
Odefsey	TAF	17.11	20 ± 5.2	261.8	290 ± 79.5
	FTC	1890	2100 ± 424	11221	11700 ± 1942
	RPV (Rilpivirine)	145.2	---	2779	2200 ± 838

PK Parameter Estimates

ARVs	Components	Cmax (ng/mL)	Historical Cmax	AUC (ng*hr/mL)	Historical AUC
Genvoya	EVG (Elvitegravir)	1563	2100, CV (33.7)	17217	22,800, CV (34.7)
	COBI (Cobicistat)	1721	1500, CV (28.4)	11174	9500, CV (33.9)
	FTC	1919	2100, CV (20.2)	11977	11,700, CV (16.6)
	TAF	18.67	20 ± 5.2	289.91	290 ± 79.5
Epzicom	ABC (Abacavir)	3973	4260 ± 1190	15174	11950 ± 2510
	3TC (Lamivudine)	1852	2040 ± 540	16092	8870 ± 1830
Triumeq	ABC	3352.83	4260±1190	12363.6	11950±2510
	3TC	1902.67	2040±540	15904.9	8870±1830
	DTG (Dolutegravir)	3650.17	3670±734	50384.94	53600±10720

Summary

- Six co-encapsulated ARV formulations of TDF/FTC/EFV (Atripla), FTC/TAF (Descovy), FTC/TAF/RPV (Odefsey), EVG/COBI/FTC/TAF (Genvoya), ABC/3TC (Epzicom), and ABC/3TC/DRG (Triumeq) appear to be consistent with historical values.

- The Cmax values of TDF and FTC for Truvada are somewhat lower than historical norm and a re-trial with a cross-over design is needed to further confirm its bioequivalence.

Next Steps

- **Complete the Truvada re-trial through cross-over design.**
- **Continue with pilot for patients on regimens of any of these six formulations to test real-time data collection, real time automated text feedback, tolerability of co-encapsulation and acceptability with the PDHFD system.**
- **Will move on to the main trial to formally test the feasibility, acceptability & sustainability, accuracy, and efficacy of the PDHFD system.**

Acknowledgement

We would like to thank all the patients who participated the study.

The study is supported by NIMH/NIH grant R01-MH110056

Thank you for your attention!