Novel measures of adherence in PROMISE 1077BF

Adherence Working Group
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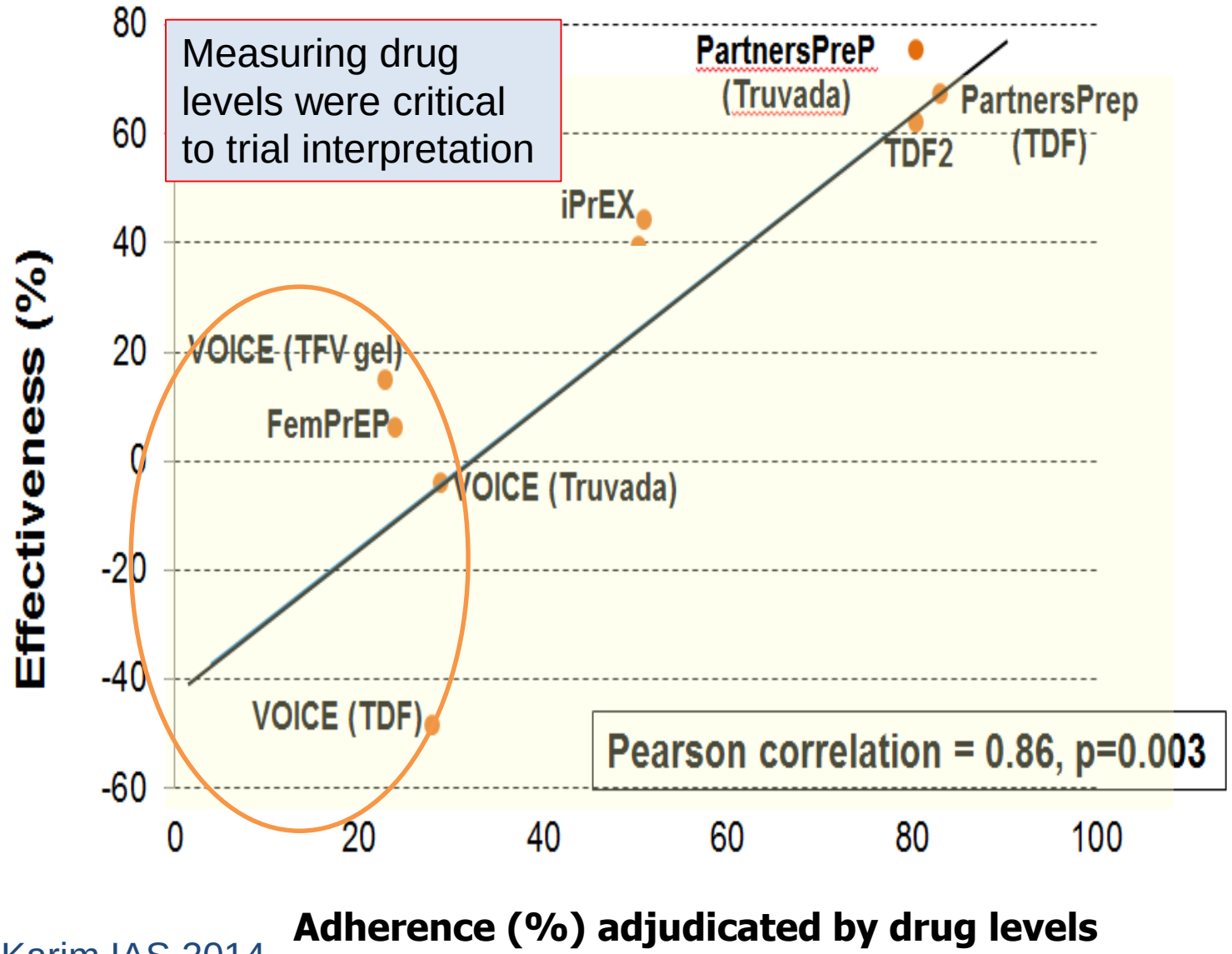
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Outline

- The problem of adherence in PMTCT and other periods
- Novel approaches to adherence measurement
- Hair collection in PROMISE 1077BF
- Proposed analysis of adherence in pregnancy and postpartum in PROMISE
- Other analysis plans and opportunities using hair collected in 1077BF

Phase 3 PrEP trials: Adherence correlates with efficacy



Prior to universal ART/B+ -- 76% adherent in pregnancy and 53% postpartum

Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis

Jean B. Nachega[a,b,c,d], Olalekan A. Uthman[e,f], Jean Anderson[g], Karl Peltzer[h,i], Sarah Wampold[a], Mark F. Cotton[d,j], Edward J. Mills[k], Yuh-Shan Ho[l], Jeffrey S.A. Stringer[m,n], James A. McIntyre[o,p] and Lynne M. Mofenson[q]

- Adequate adherence defined as >80% → 100%
- Primary measures self-report or pill counts
- Viral load not measured

AIDS 2012. 26(16):2039-2052

The problem continues in the B+ era

- **Adherence** in Malawi[1]
  - >=90% based on pharmacy refill in:
  - 73% in pregnancy
  - 66% 0-3 months postpartum, 75% 4-21 months
- **Retention** in Malawi[2]
  - Initiation at CD4 >350 in pregnancy – increased risk LTF
  - 17% lost by 6 months (most within 3m)
- **Viremia** in South Africa[3]
  - Among women initiating ART in pregnancy who achieved suppression
  - 22% - 1+ VL >1000 within 1y postpartum
- **PROMISE 1077HS (non-BF postpartum women, global)**[4]
  - ART initiation in pregnancy, CD4 >=400
  - **23% VL failure** (>1000 2x) & 15% discontinued ART
  - Median 2.3y follow-up

1. Haas AD, CID 2016; 2. Tenthani L, AIDS 2014; Myer L, CID 2017; 4. Currier JS, PLoS One 2017

Novel approaches to measuring adherence in HIV treatment & prevention








How do we measure adherence?

More Objective Measures

Pharmacologic measures

Pharmacy refill data

Automatic compilation of dosing history data

Sensor devices (ingested)

Retrospective questionnaire

Pill Counts

Patient diaries

More Subjective Measures

Modified from Vrijens & Urquhart, 2005 Journal of Antimicrobial Chemotherapy.

Pros and cons of each measure

Subjective

Objective

Measure	Pros	Cons
Self-report, questionnaires	• Easy • Cost-effective • Useful in clinical setting	• Recollection bias • Social desirability bias • Inaccurate in many PrEP trials • Cannot measure ingestion
Pill counts	• Easy • Quantitative	• Easy manipulated by patient • Cannot measure ingestion
Medication event monitoring systems	• Somewhat objective • Some with immediate wireless feedback	• Cannot measure ingestion • Large, cumbersome, expensive, interfere with medi-sets
Pharmacy refills	• More objective	• Expensive • Cannot measure ingestion • “White coat” adherence
Pharmacologic measures	• Objective • Short and long-term • Measures ingestion	• Can be expensive
Directly observed therapy	• The best, only way to know	• Not practical • Hiding pills

Pharmacologic measures of adherence

- Measuring drug in a “biomatrix”
  - plasma, PBMCs, dried blood spots (DBS), hair
- Assess both behavior (adherence) and biology (pharmacokinetics)
- Has proven essential in PrEP
  - Cannot measure viral loads in HIV-negatives
- Good for other prevention strategies employing meds
  - TB (latent or active)[1,2]
  - PMTCT when measuring exposure of ARVs to infants

[1]Gerona IJTLD 2016; [2]Gandhi PLoS ONE 2016

PrEP trials, particularly those in women alone, highlighted the power of pharmacologic measures

Adherence Measure	VOICE	FEM-PrEP
Self-report	91%	95%
Returned pill counts	92%	88%
TFV detection in plasma	**29%**	**24%**

Marrazzo NEJM 2015; Van Damme NEJM 2012

Self-reported adherence higher than pharmacologic measure among pregnant women in South Africa

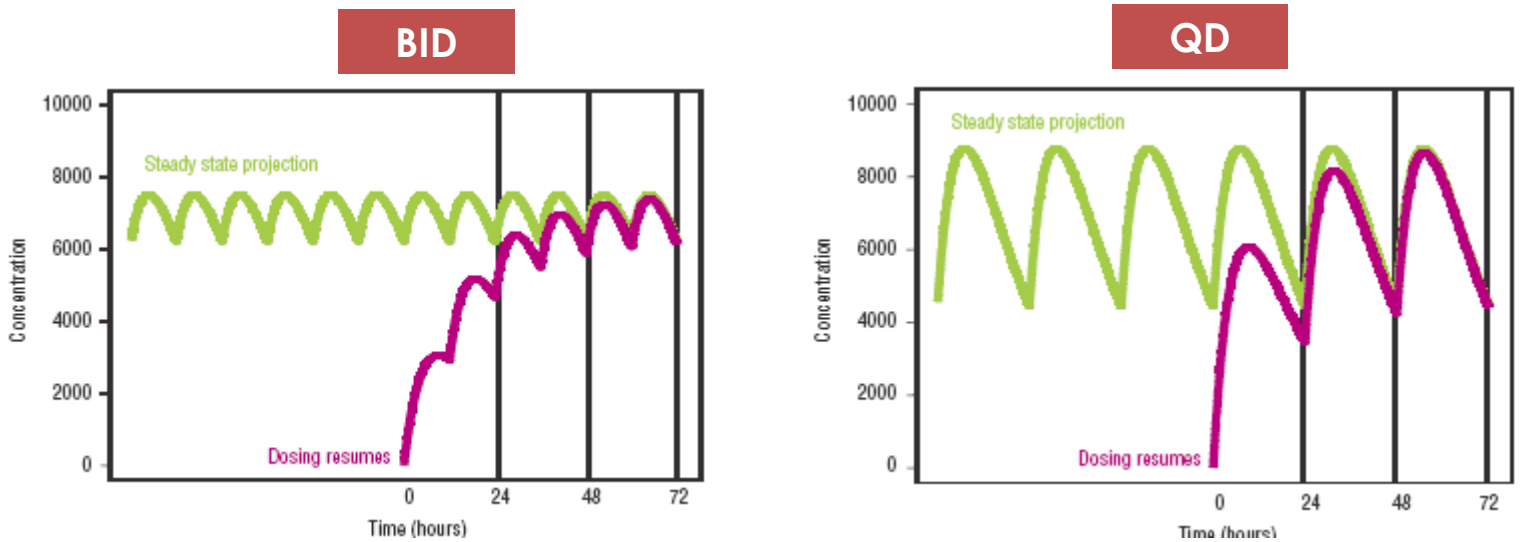
Adherence Measure	% adherent
Visual analog scale (100% past 3 days)	89%
4-day recall scale (100% past 3 days)	80%
DBS (TDF, EFV, 3TC → 2+ drugs detected)	**74%**

Alcaide ML, AIDS Behav 2017

Plasma measures used most commonly, but short-term

- PBMCs and DBS only relevant for drugs processed intracellularly (e.g. tenofovir and emtricitabine for PrEP)

“White coat” effect with short-term measures



- Adherence 1-3 days prior gives plasma levels close to steady state
- Study used MEMS caps monitoring & TDM to assess adherence
- Compliance improved immediately prior to visits, leading to “enhanced” drug levels (79% of pts with <95% adherence took meds days 3, 2 and 1 before visit)

Podsadecki TJ HIV Clin Trials. 2008; 9(4):238

Advantages (long and short of it) of hair levels as adherence/exposure measure

- Reflects long-term adherence
- Not subject to white-coat adherence
- Hair grows steadily in occiput at rate of ~1cm/month
- Hair shaft therefore a marker of time
- Hair easy and cheap to collect
- No special skills (no phlebotomy)
- Stored at room temperature
- Shipped without biohazard
- Feasible for resource-limited settings

Beumer JH. Int J Clin Prac 2001; Gandhi M. Ann Int Med 2002

Hair it is!

- Drugs of abuse
- Epilepsy medications (carbamazepine, tegretol, phenobarbital, ergotamine)
- TB latent and active treatment (INH)
- Organochlorine pollutants (DDT and biphenyl)
- Forensic analysis
  - Lead poisoning (Beethoven)
  - Arsenic (Napoleon)
  - Thallium, mercury, antimony (Newton)
- Stress – cortisol levels

Beumer JH. Int J Clin Practice 2001;Williams J Therap. Drug Monitoring 2001;Covaci A. Chemospheres 2002; Flanagan RJ. Toxicol Rev 2005; Lugli A. Adv Anat Pathol. 2011; Thieme D. Forensic Sci Int. Mar 2007; Schoeman K.TDM 2010; Moller M. TDM 2010; Pelander A. TDM 2008; Karlen J. BMC Clin Pathol. 2011; Eisenhut M. Tuberc Res Treat. 2012; Gandhi M. Ann Intern Med 2002; Baciu T. Analytica Chimica Acta 2015

Baby Hair

- Drug exposure in utero
  - Scalp hair at birth reflects exposure in 3rd trimester
  - Cord blood, plasma, urine – recent exposure
  - Cord tissue – long term exposure but assays not well studied
  - Meconium – long term exposure, collection/contamination issues
- Infant hair replaces neonatal hair at 3 months of life
- PROMOTE PK study paired mom-baby hair & plasma
  - EFV, LPV, RTV all detectable in mom and baby at birth
  - Only EFV detected in baby plasma at 12 weeks (BF transfer)

Gandhi 2013 JAIDS

Hair collection acceptable to HIV-infected women in South Africa

Published in final edited form as:
Future Virol. 2012 November 1; 7(11): 1135–1142. doi:10.2217/fvl.12.100.

Reactions, beliefs and concerns associated with providing hair specimens for medical research among a South African sample: a qualitative approach

Bronwyne Coetzee[1], **Ashraf Kagee**[1], **Mark Tomlinson**[1], **Louise Warnich**[2,*,‡], and **Ogechi Ikediobi**[3,‡]

- 21 women, Western Cape, South Africa
- Cultural beliefs influence decision to donate hair, but willing when provided enough information by researcher

Hair collection in rural Kenya suggested social desirability bias in self-report

Antiretroviral Concentrations in Small Hair Samples as a Feasible Marker of Adherence in Rural Kenya

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- Age 18-78; 64% women
- Among consented, 95% donated hair
- Self-reported adherence high (IQR 96-100%)
- Wide variation in NVP hair concentrations
  - Suggests over-reporting
  - (No VL measured)

JAIDS 2014 66(3): 311-315

Hair concentrations of EFV & LPV predict viral suppression pregnancy & postpartum

Hair concentrations of antiretrovirals predict viral suppression in HIV-infected pregnant and breastfeeding Ugandan women

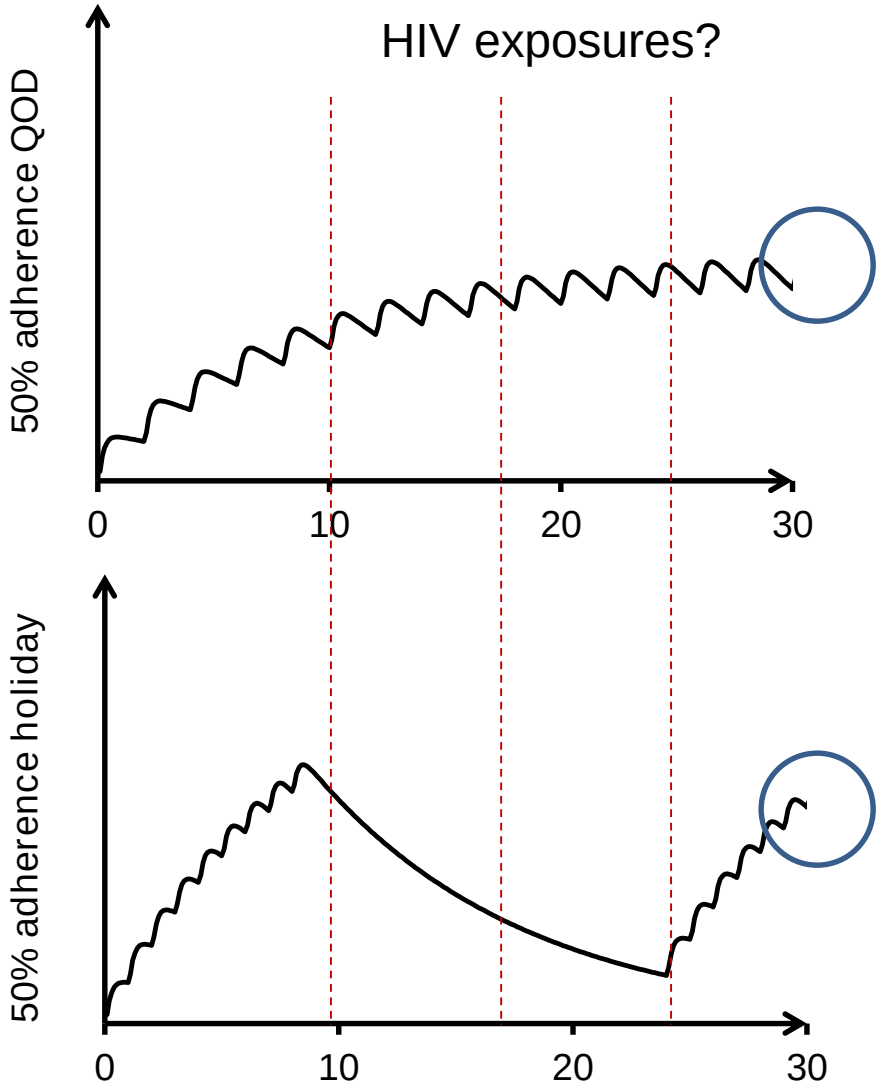
Catherine A. Koss[a,b], Paul Natureeba[b], Julia Mwesigwa[b,c], Deborah Cohan[b,d], Bridget Nzarubara[b], Peter Bacchetti[e], Howard Horng[f], Tamara D. Clark[a,b], Albert Plenty[b,g], Theodore D. Ruel[b,h], Jane Achan[b,c], Edwin D. Charlebois[b,g], Moses R. Kamya[b,i], Diane V. Havlir[a,b] and Monica Gandhi[a,b]

- Hair collected 30–34 weeks gestation & 10–25 weeks postpartum
- Concentrations of EFV and LPV both predicted VL suppression
  - At delivery
  - At 24 weeks postpartum

AIDS 2015 29(7): 825-830

Limitations of long-half moieties

- Represents averaged adherence, cannot determine dosing patterns
- Inter-individual variability leads to overlap in adherence categories (misspecification).



Slide courtesy Pete Anderson
CROI 2016

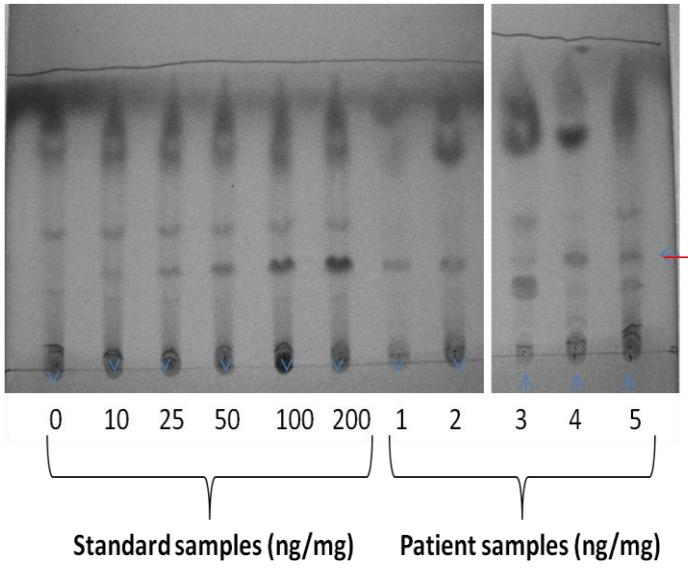
Real-time feedback devices

- Many MEMs devices need downloading centrally
- Some have wireless chip e.g. Wisepill®
- RCT in patients on ART (China[1]) examined real-time reminders if doses >30 min late
  - 87.3% vs 51.8% optimal adherence with intervention (RR 1.7 (1.3-2.2)) BUT adherence measure self-referential, no pharmacologic measure to confirm ingestion, No improvement in viral loads
- Similar finding in Uganda cohort[2]
- Perhaps Wisepill findings best verified by pharmacologic measures

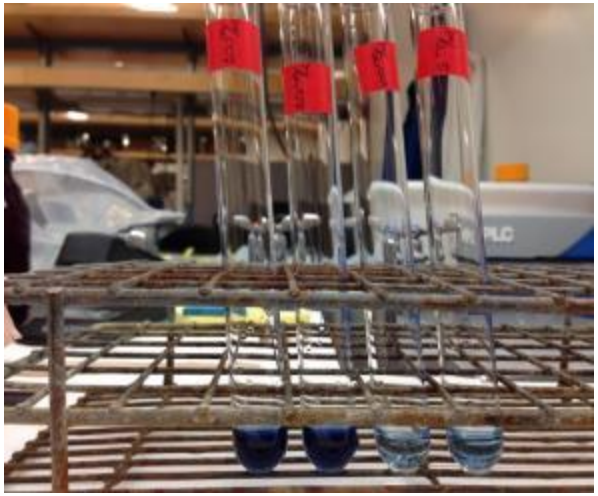
[1]Sabin LL. JAIDS 2015; [2]Haberer AIDS 2016

Low cost point-of-care measures of adherence next frontier

- NVP in hair using thin-layer chromatography (TLC), cheap but **not** real-time



- Colorimetric assays for TFV –cheap but still labor-intensive, competing endogenous compounds



- Immunoassays common for urine/saliva drugs of abuse; Antibodies expensive and can be challenging but hopeful (working with Alere)

Gandhi M. ARHR 2014

Novel measures - Summary

- PrEP efficacy trials dramatically illustrated limitations of self-reported adherence
- PMTCT can be time of flux and social desirability bias
- Plasma most common pharmacologic measure, but only measures recent use
- Hair is easy to collect, measures long term exposure
- Electronic monitoring - detailed dosing history, but does not measure ingestion
- Going forward: Low-cost, point-of-care measures feasible for broad scale-up are needed

PROMISE

IMPAACT 1077

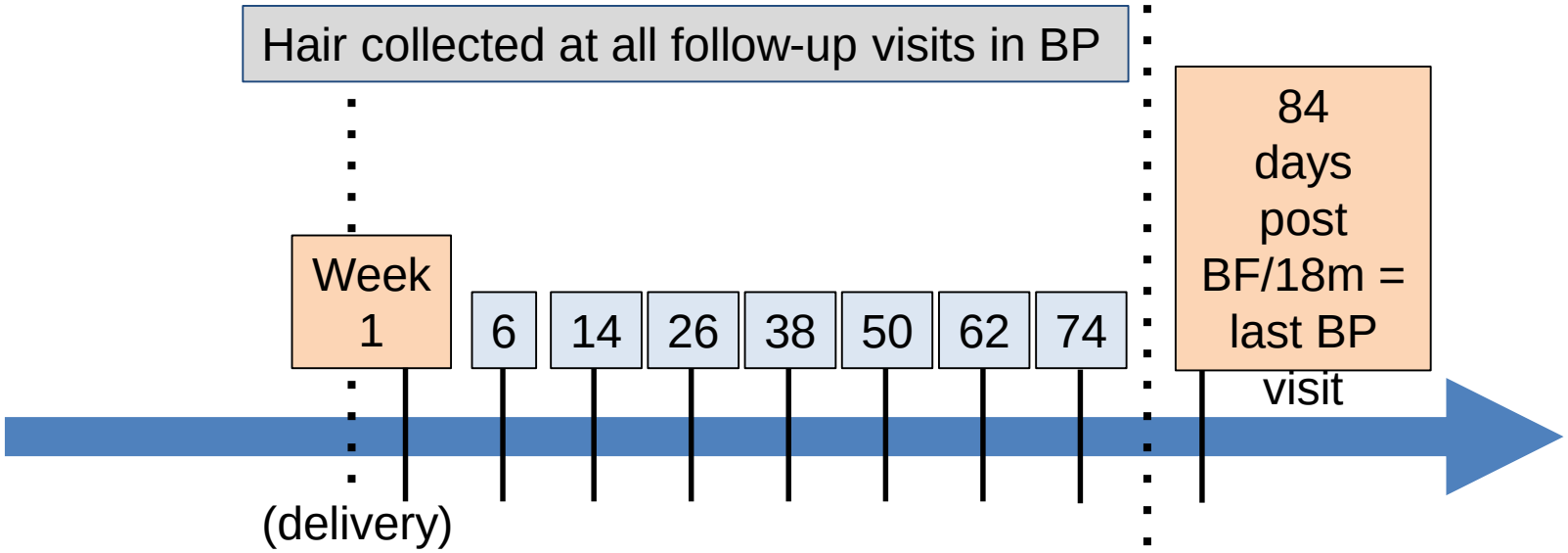
Promoting Maternal and Infant Survival Everywhere

Hair collection in PROMISE

PROMISE 1077BF components

- BA: Antepartum component (Fowler NEJM 2016)
  - Pregnant women with CD4 >=350
  - ZDV alone vs 3TC/ZDV/LPV/r vs TDF/FTC/LPV/r
- BP: Postpartum
  - From antepartum (any arm) + late presenters where BF is standard
  - Daily infant NVP vs Maternal ART – through BF or 18m
- BM: Maternal Health
  - Mothers on ART -- from BP, and from BA (ineligible for BP) -- randomized to continue or discontinue ART

Hair collected in PROMISE 1077BF



Pregnancy (1077BA)

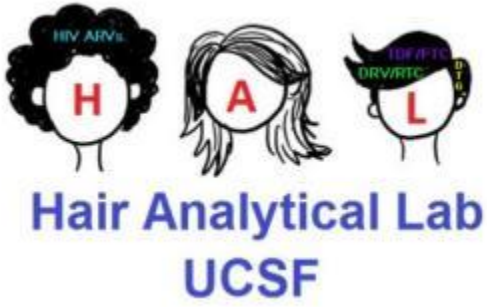
(+Late presenters to care not randomized in BA)

Breastfeeding (1077BP)

Post-breastfeeding (1077BM)

In Zimbabwe, hair collected at **ALL** follow-up visits post-breastfeeding in moms on ART

Mom and baby hair samples in UCSF Hair Analytical Laboratory (HAL)



	N	Median	IQR	Range	Total number of samples
Moms	**786**	5	2-8	1-19	**4251**
Babies	**766**	8	3-10	1-14	**5325**

- All 766 babies in the table above are paired to mothers with hair collected
- An additional 577 babies had hair collected (without paired maternal hair), primarily from the postpartum infant NVP arm

Maternal ART adherence

Proposed analysis in PROMISE 1077BF

Sampling plan for PROMISE analysis

Antepartum arm	Postpartum arm	N moms
Antepartum ART	Maternal ART	361
Late presenter/ ZDV only	Maternal ART	293

- Randomly sample from mothers randomized to ART
- Over-sample key risk factors that may be under-represented

Risk factors for poor adherence measured longitudinally in PROMISE

- Known risk factors from the literature
  - Disclosure to spouse/others in household
  - Food insecurity
  - Alcohol use
  - SES (education, household characteristics, household income sufficient for needs, mother working)
- Detailed breastfeeding history

Detailed mental health/stigma was not systematically evaluated

Summary of hair collection **after** breastfeeding cessation

ART summary	N moms	Months BF Median (IQR)	N moms with 1+ hair post BF
Antepartum & PP	361	15 (12-17)	166
Postpartum only	293	14 (12-16)	138

Adherence analysis plan

- Describe adherence trajectories during
  - Pregnancy
  - Breastfeeding
  - At breastfeeding cessation & post BF
- Assess the impact of time on ART vs. transitions (pregnancy, BF, post BF)
- Evaluate longitudinal risk factors for poor adherence throughout each stage

Other analyses with PROMISE hair

- Baby seroconversions during breastfeeding
- Assess maternal ART transfer to baby with the ratio of maternal hair concentration : baby hair concentration
  - Implications for PMTCT, infant exposure, infant toxicities
- PK study of multiple biomatrices of drug levels in mom and baby hair (n=50)

- **Proposals from IMPAACT investigators are encouraged**
  - ~12K PROMISE hair samples in UCSF Lab
  - A resource for all!

IMPAACT
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- Judy Currier, MD
- Patricia DeMarrais SDAC
- Sean Brummel SDAC

PROMISE study participants for study participation and hair donation

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