Adherence in the HIV setting: from the simplified ART regimen to novel metrics








XII Course on HIV Infection and Viral Hepatitis
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The problem of adherence in HIV

- Adherence to HIV treatment and PrEP not ideal
  - Prevalence of low level viremia in large (60K) S. Africa cohort/then outright failure 23%/22% (Hermans Lancet ID 2017)
  - Increasing rate of global resistance (Beyer. NEJM 2017)
  - Up to 25% rate of non-adherence/viremia in postpartum women in SSA (Meyer. CID 2017)

What are ways to both measure and intervene?

NEJM THIS WEEK

HIV Drug Resistance — An Emerging Threat to Epidemic Control

Chris Beyrer, M.D., M.P.H., and Anton Pozniak, M.D.

UNAIDS

Fast-Track Targets

by 2020

90-90-90

HIV treatment

500 000

New HIV infections or fewer

ZERO

Discrimination

by 2030

95-95-95

HIV treatment

200 000

New HIV infections or fewer

ZERO

Discrimination

If goal of 90:90:90 is 73% virologic suppression, where are we today?

1. 44%
2. 55%
3. 66%
4. 73%
5. 84%
6. 100% - the world is right and just

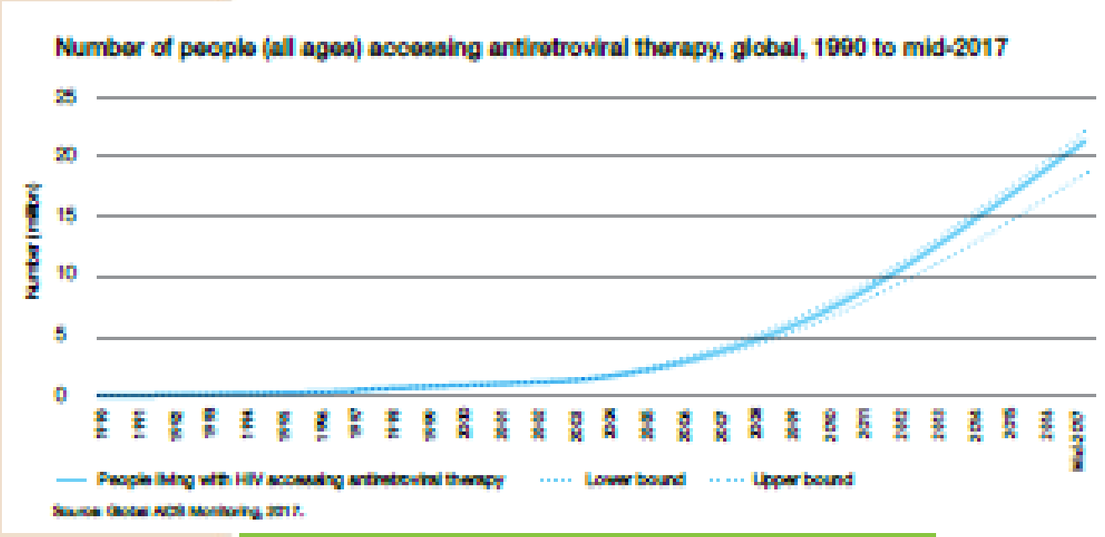
ARS: If goal of 90:90:90 is 73% virologic suppression, where are we on WAD 12/1/17?

1. **44%**
2. 55%
3. 66%
4. 73%
5. 84%
6. 100% - the world is right and just

RIGHT TO HEALTH

MY HEALTH, MY RIGHT.

CLAIMING THE RIGHT TO HIV TREATMENT



20.9
MILLION PEOPLE ON TREATMENT

WORLD AIDS DAY
1 DECEMBER 2017

P. 06
THE RIGHT TO HEALTH

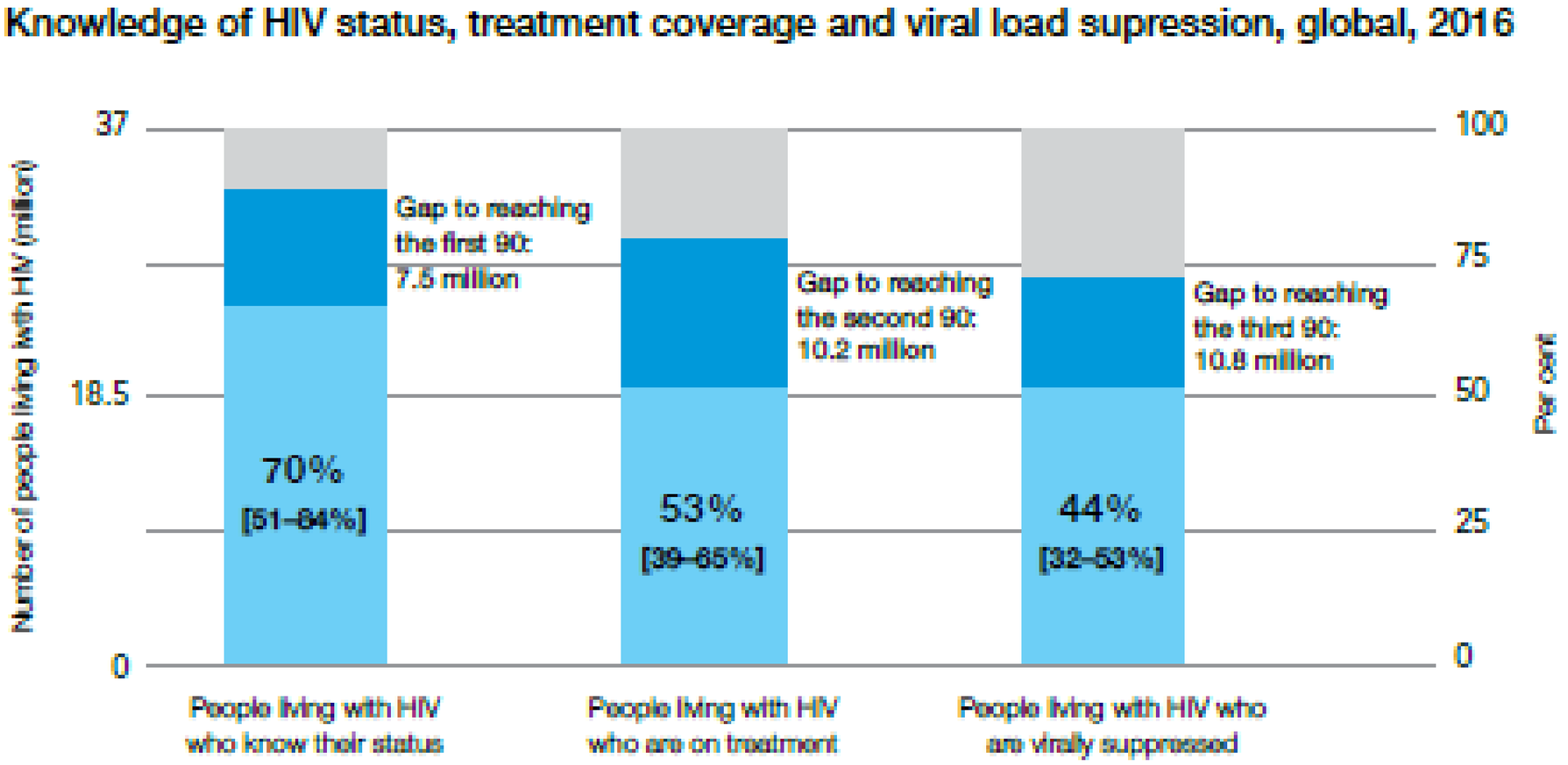
P. 92
INVESTING FOR HEALTH

P. 46
CLAIMING THE RIGHT TO HIV TREATMENT

P. 120
MAKING THE LAW WORK FOR HEALTH

UNAIDS

Current UNAIDS targets



Right to Health 12/1/17

UNAIDS

We are not the only ones

The World Health Organization has decl
that more people wo
would benefit from *ej*
improve medication adherence than from
development of new
treatments

"Drugs don't work in patients who don't take them"

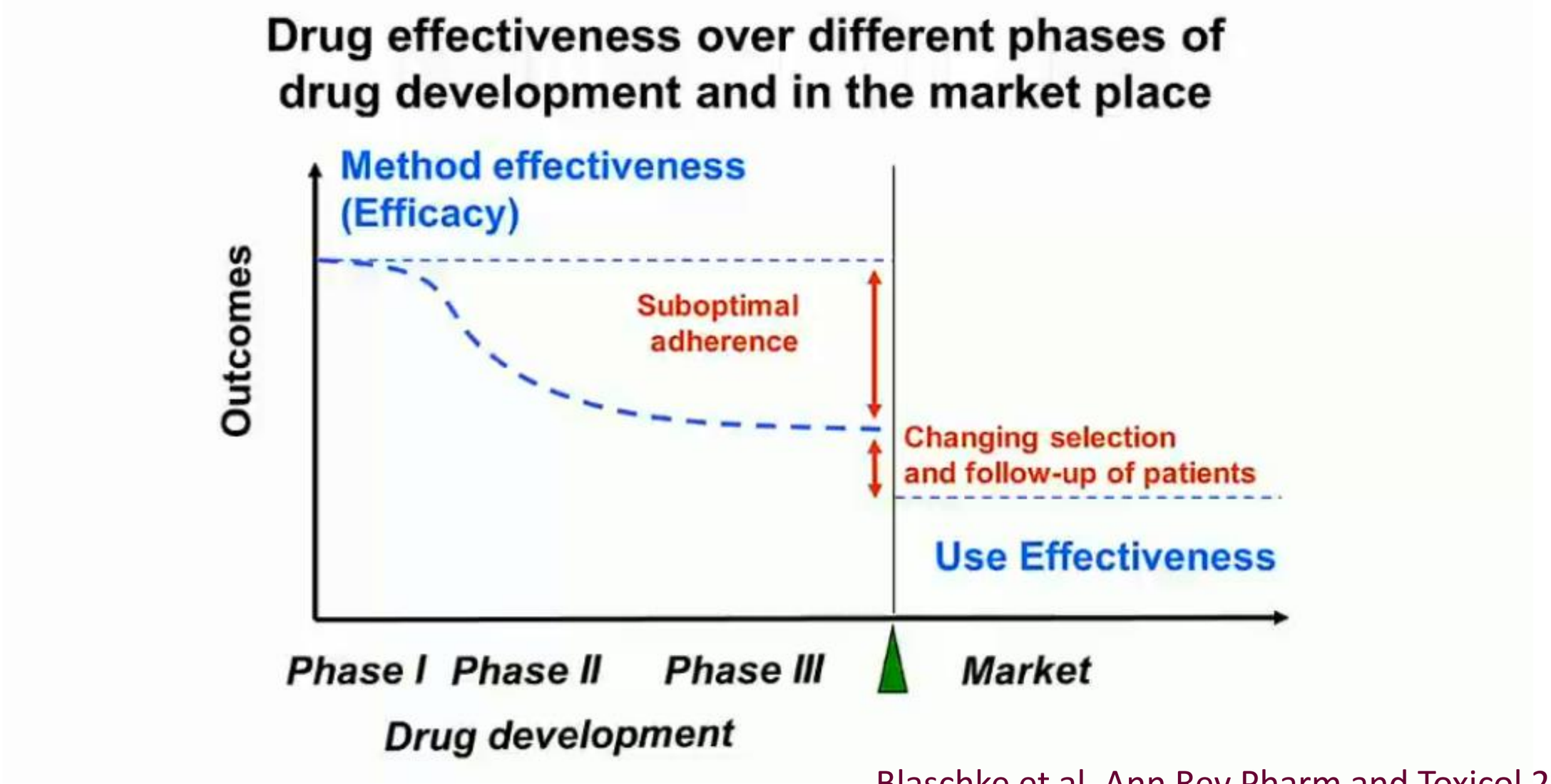
C. Everett Koop

patients
ns within
ment

ociety $290 billion
cancer treatment)

World Health Organization. Adherence to Long-Term Therapy. Evidence to Action. 2003; National Council on Patient Information and Education. Enhancing Prescription Medication Adherence: A National Action Plan 2007. Chobanian AV. JAMA 2003; Cohen JD. J Clinical Lipid 2012; Osterberg & Blaschke. NEJM 2005; Blaschke. Ann Rev Pharm Tox '12

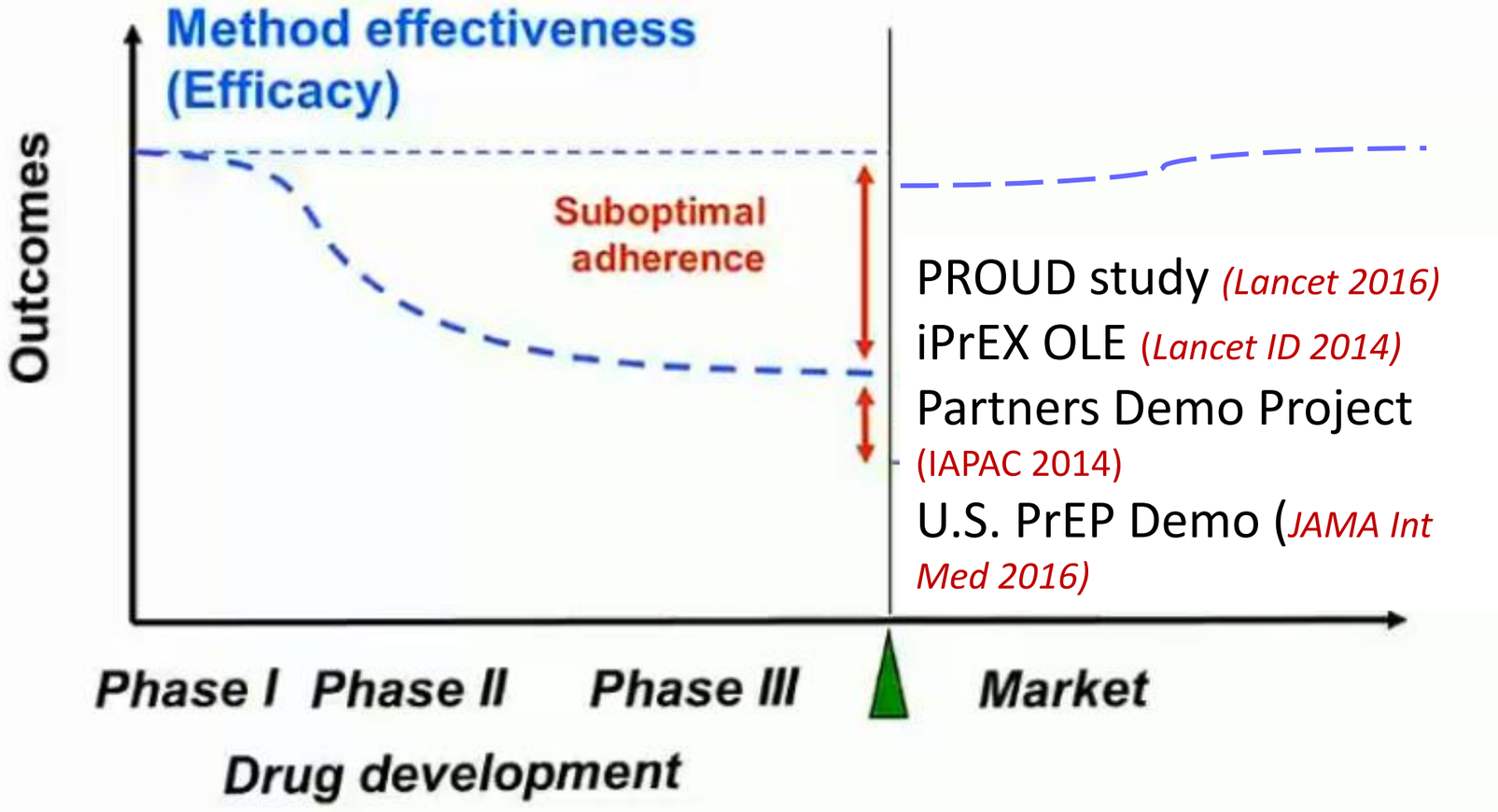
Classic model: Adherence issues start in phase 3 and worsen post-marketing



Blaschke et al. Ann Rev Pharm and Toxicol 2012

In PrEP, pattern reversed

In the prevention field, adherence increases in post-marketing phase



PROUD study *(Lancet 2016)*
iPrEX OLE *(Lancet ID 2014)*
Partners Demo Project (IAPAC 2014)
U.S. PrEP Demo (*JAMA Int Med 2016)*

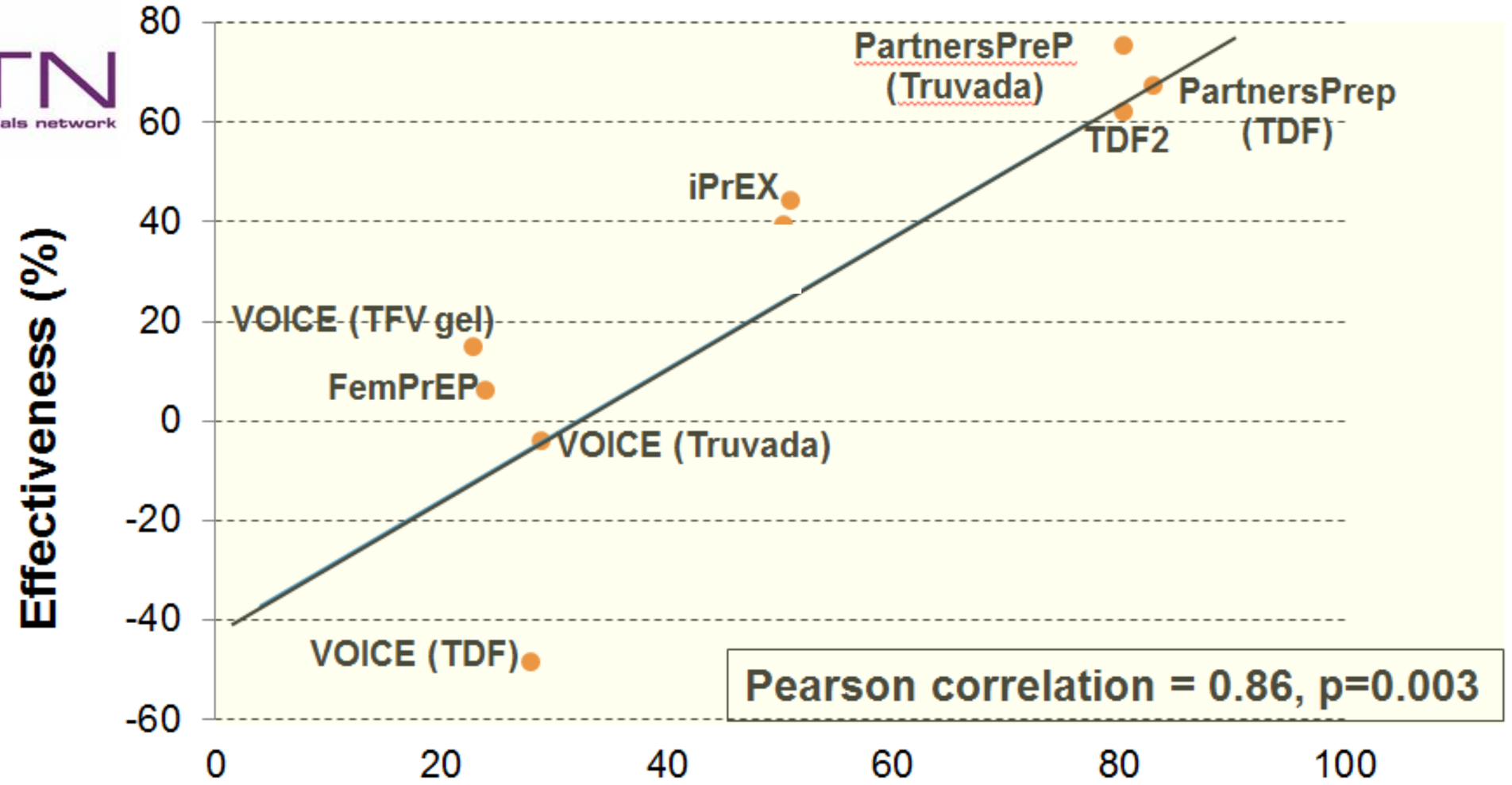
Baeten J. JID 2016

Trials of TDF/FTC-based PrEP and adherence

Trial	Population, Location	Reduction in HIV infections (95% CI)	
		Men, transwomen	Cisgender women
iPrEx[1]	MSM, transwomen Americas, South Africa, Thailand	44% (15-63)	-
Partners PrEP[2]	Mutually disclosed serodiscordant heterosexual couples; Kenya, Uganda	84% (54-94)	66% (28-84)
TDF2[3]	Heterosexual men, women Botswana	80% (25-97)	49% (-22-81)
FEM-PrEP[4]	Women Kenya, South Africa, Tanzania	-	6% (-52-41)
VOICE[5]	Women Uganda, South Africa, Zimbabwe	-	-4% (-49-27)
PROUD[6]	MSM (open-label) UK	86% (58-96)	-

1. Grant et al. NEJM 2010. 2. Baeten et al. NEJM 2012. 3. Thigpen et al. NEJM 2012. 4. Van Damme et al. NEJM 2012. 5. Marrazzo et al. NEJM 2015. 6. McCormack et al. Lancet 2015. 7. Molina et al. NEJM 2015; Thomson. Curr Op HIV/AiDS. Jan 2016

Phase 3 PrEP trials: Adherence correlates with efficacy



SS Abdool Karim IAS 2014

Adherence (%) adjudicated by drug levels

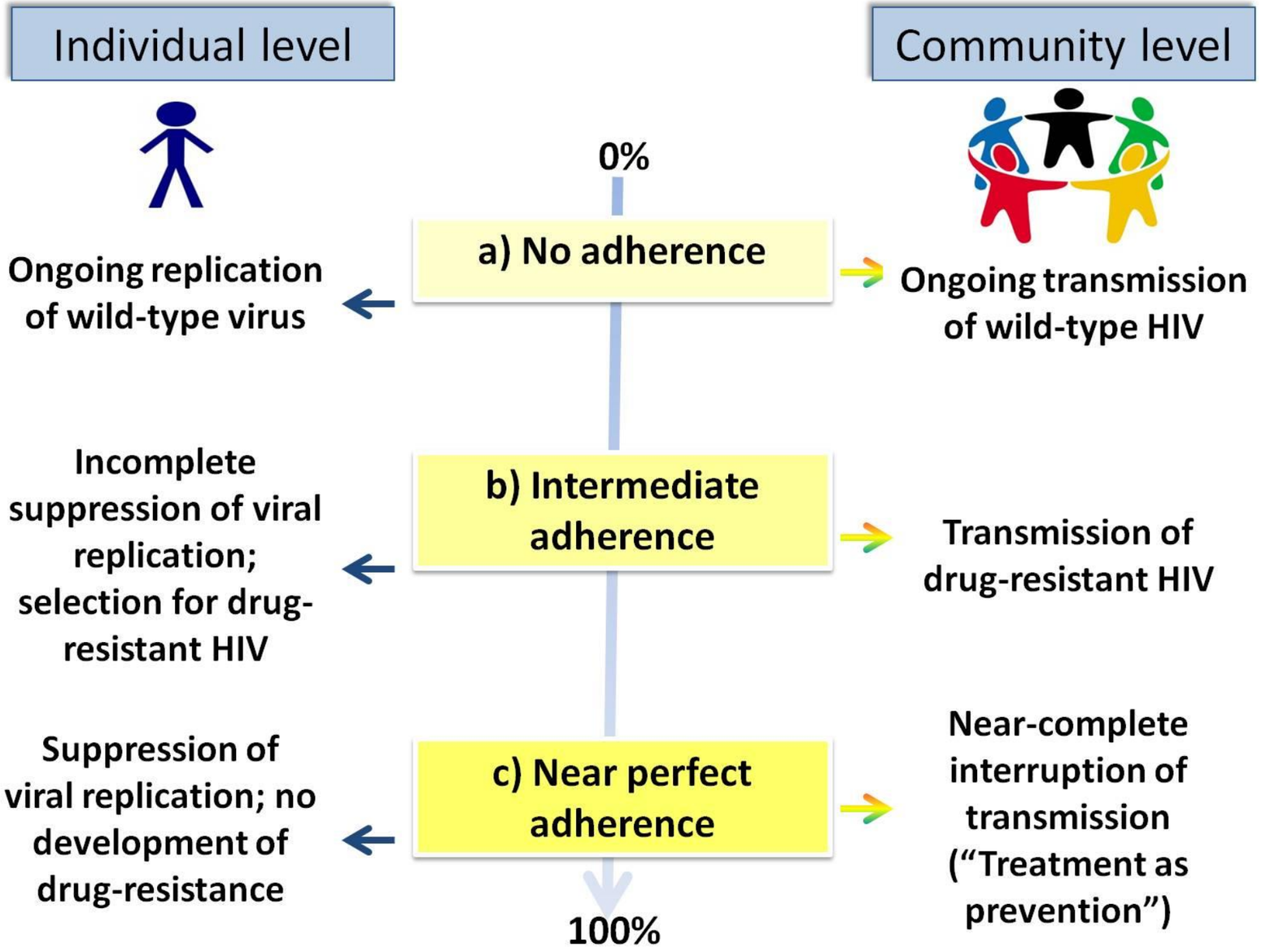
Case

- 52 yo man in San Francisco with HIV CD4 257, viral load 17,000 copies/mL, marginally housed (often shelters), depression, and polysubstance use. Presents to our hospital with pneumonia. Pt originally diagnosed w/ HIV in ‘08 and has had trouble adhering to ARVs in past. After treatment for pneumonia, HIV Consult Service called for ARV recommendations. Virus W.T., HLA-B5701 negative, Cr 1.0, LFTs WNL; team concerned about adherence

Case (continued)

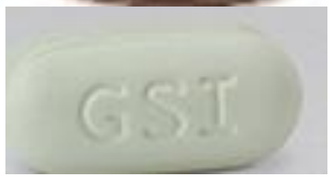
- The patient was prescribed multi-pill ART 2 months ago but hasn't taken regularly, because "taking out lots of pills in my tent or the shelter just announces to the world that I have AIDS". Pt states he would take medications regularly if he could just take "one pill once a day". Not on concomitant meds, but has h/o HTN and pt says he wants one pill "so they will think this is for my blood pressure"

Adherence in HIV has individual and community level effects



Gandhi M and Gandhi RT. NEJM 2014

Currently available SPCs

SPC	Drugs in SPC	Approval date	Food effects
	TDF/FTC/efavirenz (**Atripla®**)	2006	Food ↑ levels
	TDF/FTC/rilpivirine (**Complera®**)	2011	Take with solid meal (390kcal)
	TDF/FTC/elvitegravir/ cobicistat (**Stribild®**)	2012	Take with food (373kcal)
	ABC/3TC/dolutegravir (**Triumeq®**)	2014	Food ↑ levels
	TAF/FTC/elvitegravir/ cobicistat (**Genvoya®**)	2015	Take with food (373kcal)
	TAF/FTC/rilpivirine (**Odefsey®**)	2016	Take with solid meal (390kcal)
	Dolutegravir/rilpivirine (Juluca)	2017	Solid meal

Single pill combinations coming

Bictegravir/TAF/FTC
Next integrase inhibitor; Studied to date only in patients without history of much failure

Darunavir/cobicistat/TAF/FTC:
First PI-based SPC, works with lots of prior resistance

Doravirine/TDF/3TC:
Next NNRTI; works against K103N and Y181C containing viruses

How do we measure adherence?

More Objective Measures

Therapeutic drug monitoring

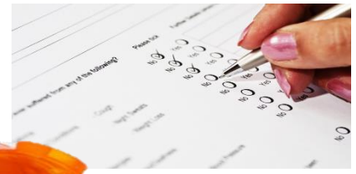
Pharmacy refill data

Automatic compilation of dosing history data

Sensor devices (ingested)

Retrospective questionnaire

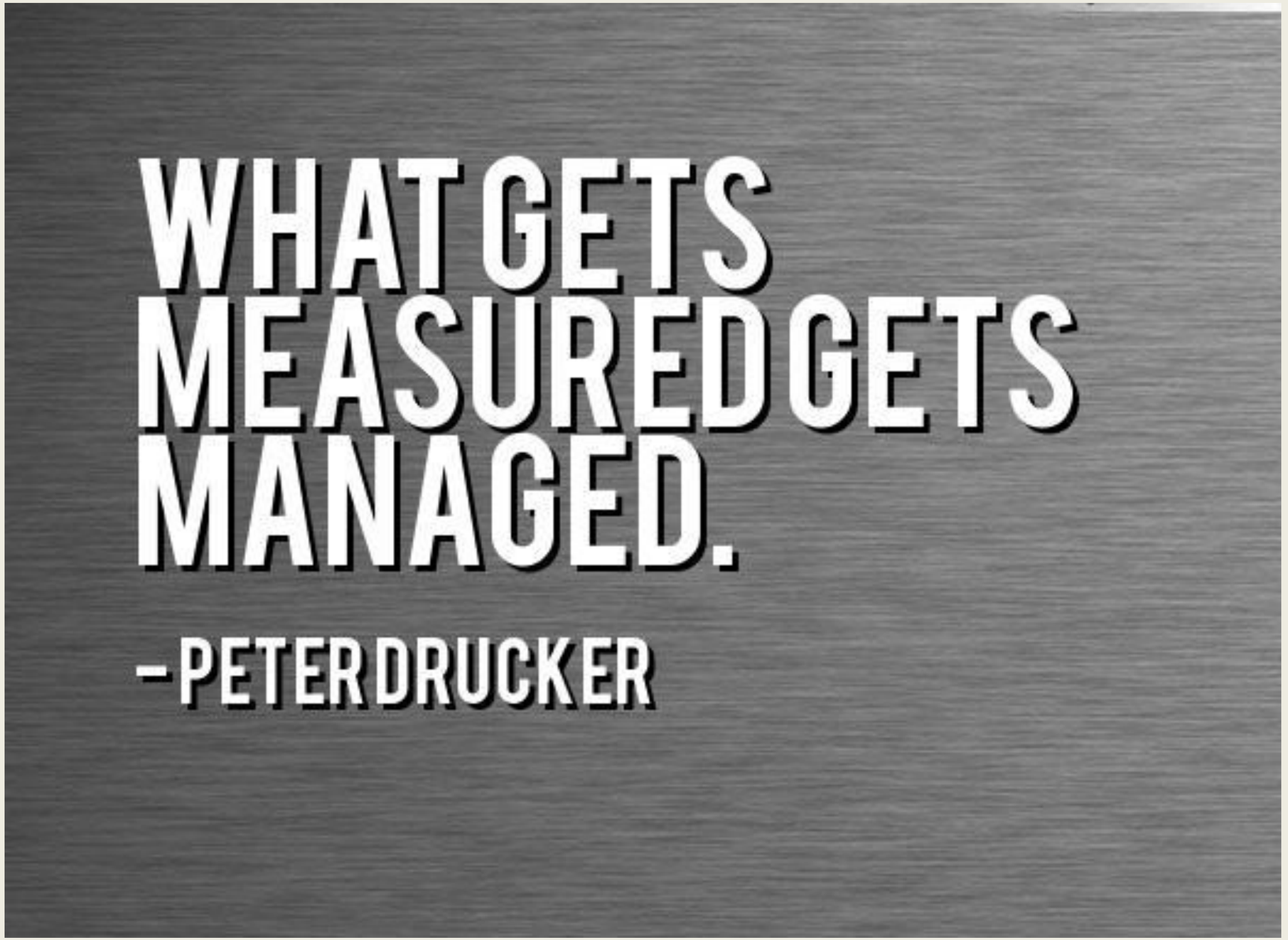
Pill Counts



Patient diaries

More Subjective Measures

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


WHAT GETS
MEASURED GETS
MANAGED.
– PETER DRUCKER

Pros and cons of each measure

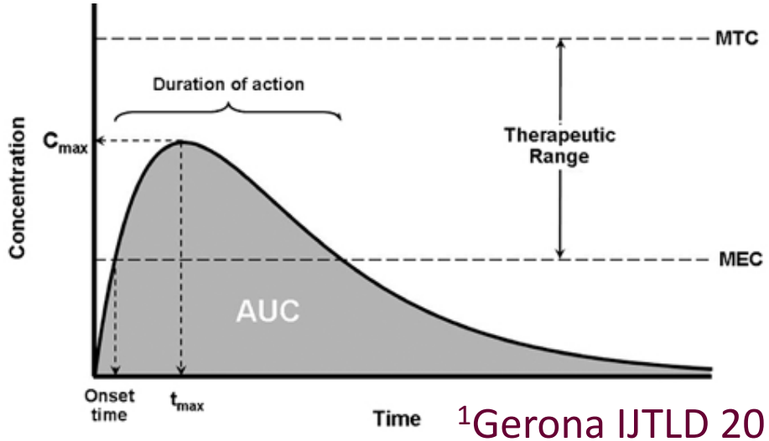
Subjective

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	• Can be expensive • Measure ingestion
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) to assess drug-taking and exposure
- Assess both behavior (adherence) and biology (pharmacokinetics)
- Has proven essential in PrEP
  - Cannot measure HIV viral loads in HIV-negatives
- Good for other prevention strategies employing meds
  - TB infection monitoring (latent or active)[1,2]



[1]Gerona IJTLD 2016; [2]Gandhi PLOS ONE 2016 .

Plasma measures proved critical to the interpretation of various PrEP trials

- Efficacy of TDF/FTC in iPrEx rose from 44% to an estimated 92% (CI 40, 99%) among those with detectable drug levels (plasma or PBMC)
- Efficacy 93% (CI 60, 99%) Partners PrEP with TFV plasma levels c/w daily dosing

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

Grant et al. NEJM 2010; Marrazzo et al. NEJM 2015; Van Damme et al. NEJM 2012; Baeten et al. NEJM 2012; Donnell et al. JAIDS 2014

Plasma measures also helpful to interpretation of microbicide trials with 1% TFV gel

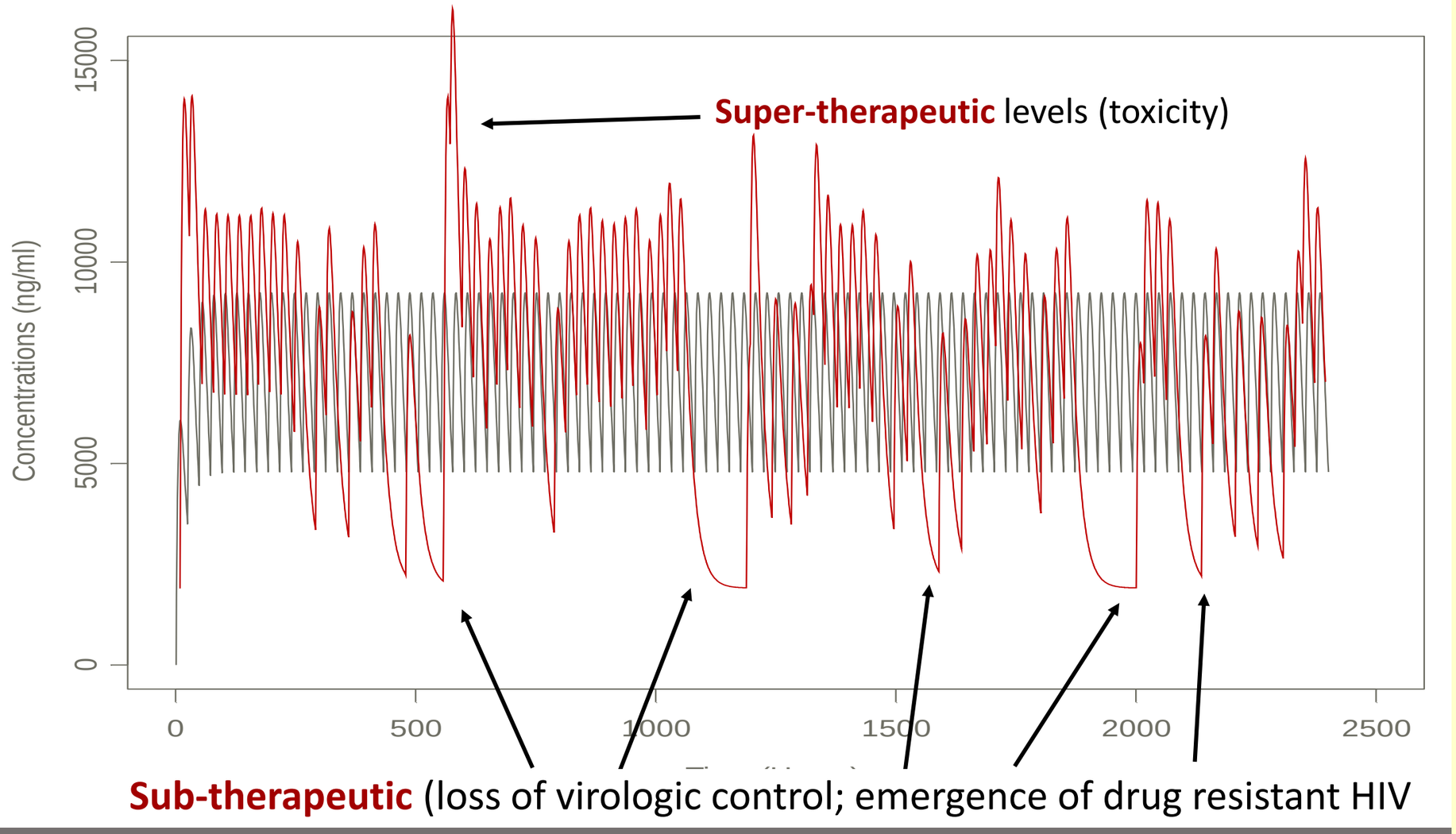
Trial	Reduction in HIV acquisition
CAPRISA 004*	IRR 0.61 (95% CI 0.40-0.94)
FACTS 001*	IRR 1.0 (95% CI 0.70-1.4)
VOICE	HR 0.85 (95% CI 0.61-1.21)

*TFV levels in cervicovaginal lavage measured adherence

- In VOICE, 90% self-reported adherence to 1% gel, 86% returned applicator counts, 23% plasma TFV detection
  - Those with detectable TFV plasma levels had a lower likelihood of HIV acquisition than did those with no TFV detected (HIV incidence per 100 py: 1.9 vs. 6.1, HR 0.34; 95% CI, 0.13 to 0.87; P = 0.02)

QA Karim Science 2010; Marrazzo et al. NEJM 2015. Rees H CROI 2015; Kashuba JAIDS 2015

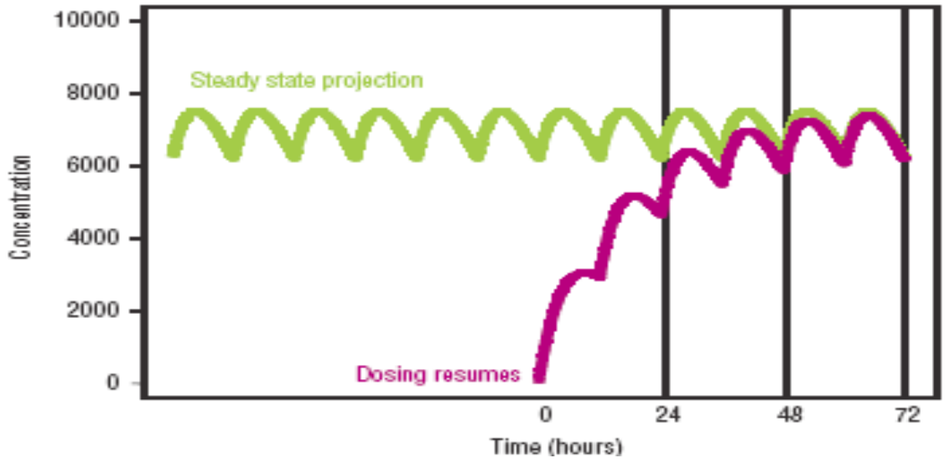
Untimed plasma samples to measure adherence have several limitations

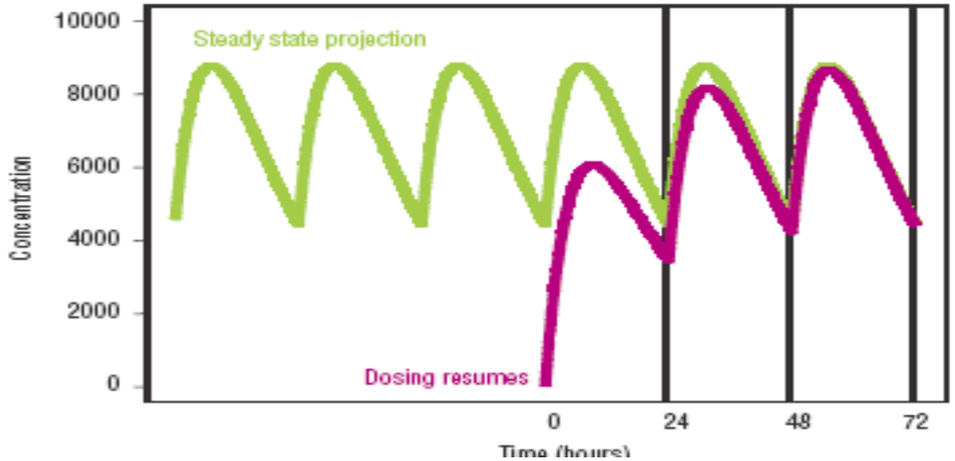


- Short window of exposure (same with urine, saliva)
- Can vary significantly day-to-day (intra-individual variability) so what is “typical” level?
- Interpretation relies on patient report of last dose taken
- Subject to “white coat” adherence

Blaschke T. Ann Rev Pharm Toxicol 2012

“White coat” effect with short-term measures

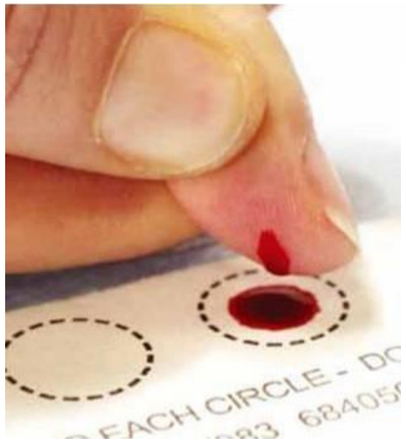


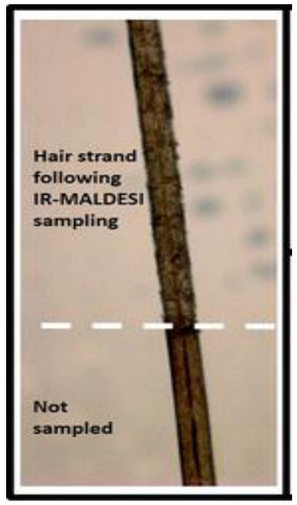


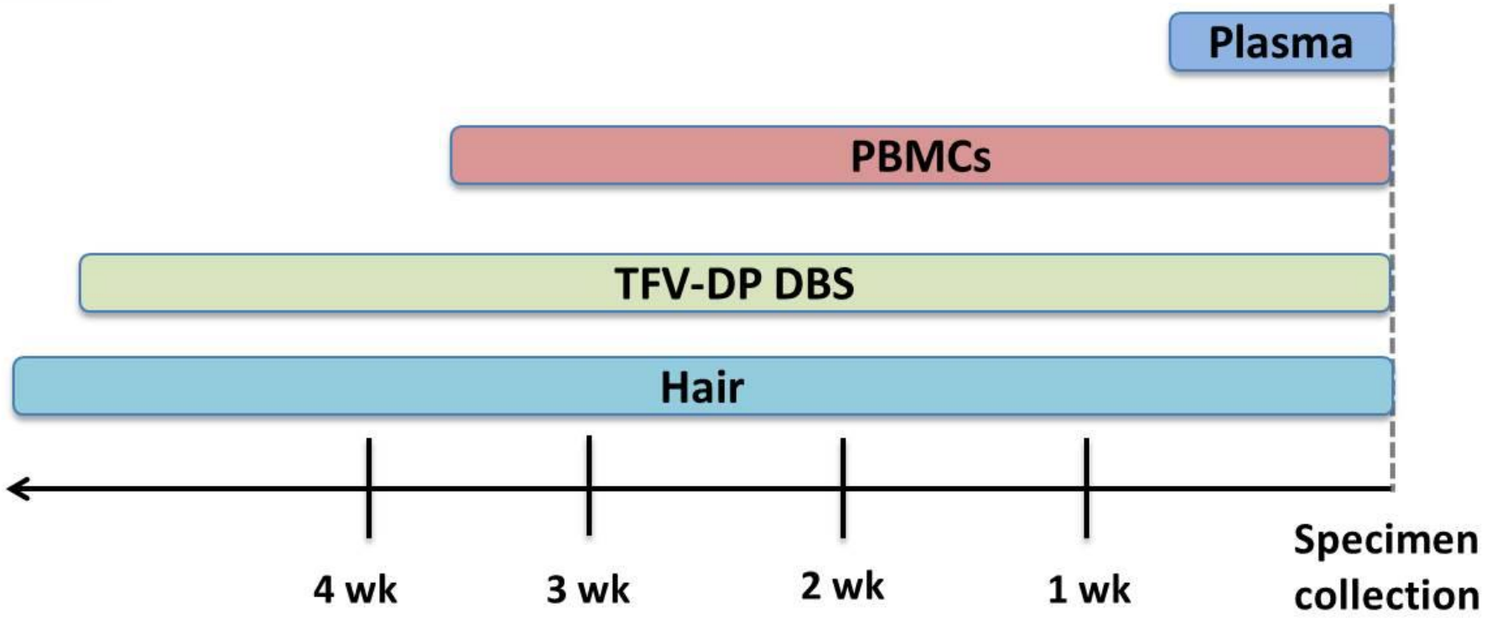
- Adherence 1-3 days prior gives plasma levels close to steady state
- Study used MEMS caps monitoring & TDM to assess adherence
- Improved compliance immediately prior to visits, leading to “enhanced” drug levels (79% of pts with <95% adherence took meds days 3, 2 and 1 before visit)

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

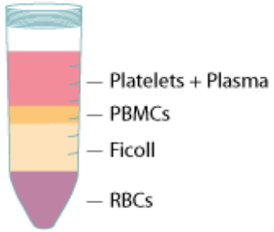
Untimed plasma measures used most commonly, but short-term; what are other novel measures of assessing adherence pharmacologically?







Drug levels in PBMC and DBS

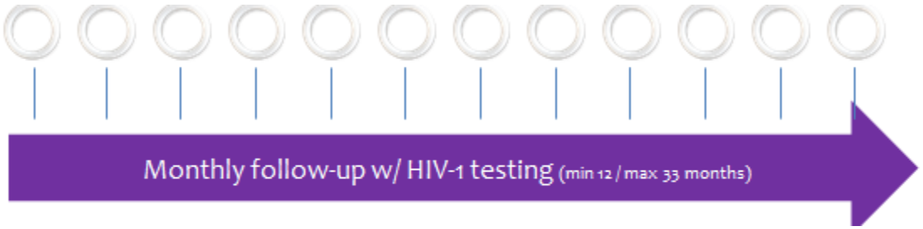


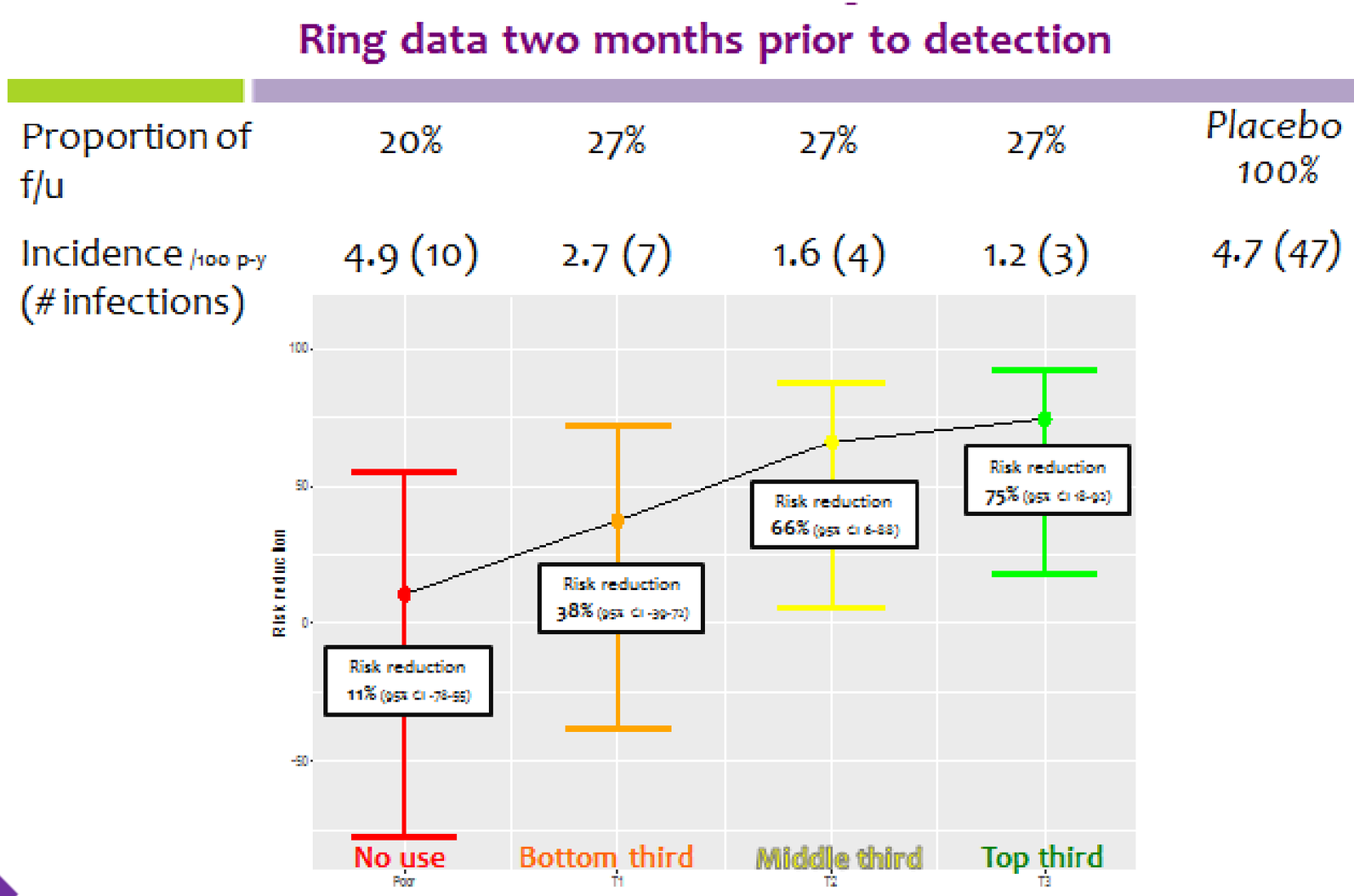
- Drug levels (TFV-DP/ FTC-TP) in PBMC associated with protective efficacy in iPrEx but processing, isolating, counting costly, challenging
- TFV-DP/ FTC-TP in dried blood spots (DBS) –mainly red blood cells- provides longer-term exposure (half-life 17 days) and associated with protective efficacy in iPrEx OLE and PrEP Demo
  - Must be standardized to hemoglobin counts, biohazard, cold chain
  - Only good for meds processed intracellularly

Anderson P. Sci. Trans. Med 2012; Castillo-Mancilla JR. ARHR 2013; Grant Lancet ID 2014; Liu A. JAMA Int Med 2015

Dapivirine vaginal ring (IPM-027, MTN-020/ASPIRE)

- Silicone ring containing 25 mg dapivirine (DPV) given every 4 weeks
- Novel methods of assessing adherence in these trials –residual DPV levels in used rings (short-term plasma levels not as useful)



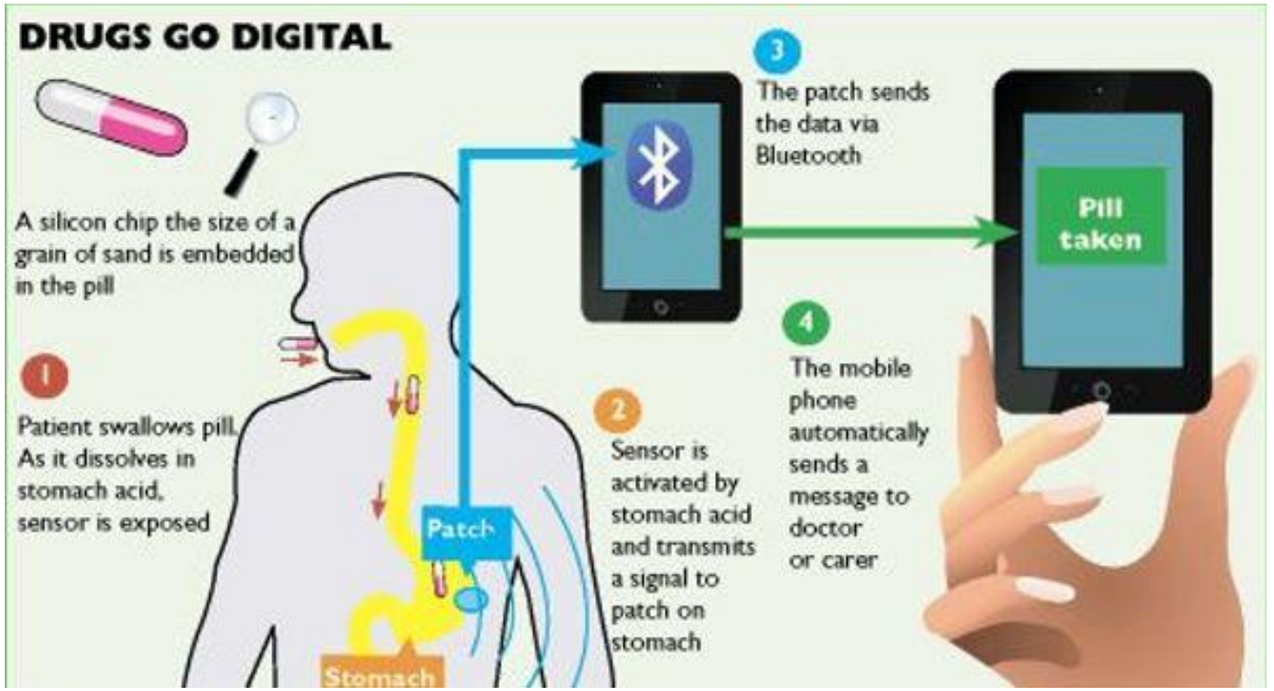


Baeten J. NEJM 2016; Nel A. NEJM 2016; Brown E. IAS 2016

Sensors and taggants novel, interesting

- Taggant: Drugs marked with an inert detectable taggant and adherence then measured through a breath test (ester taggant to vaginal gel; exhaled alcohol and ketone metabolites)

  Sensors: Literally put an electronic sensor in a capsule (along with the pill) and then the ingestion of the pill is sensed by a sensor worn on the skin



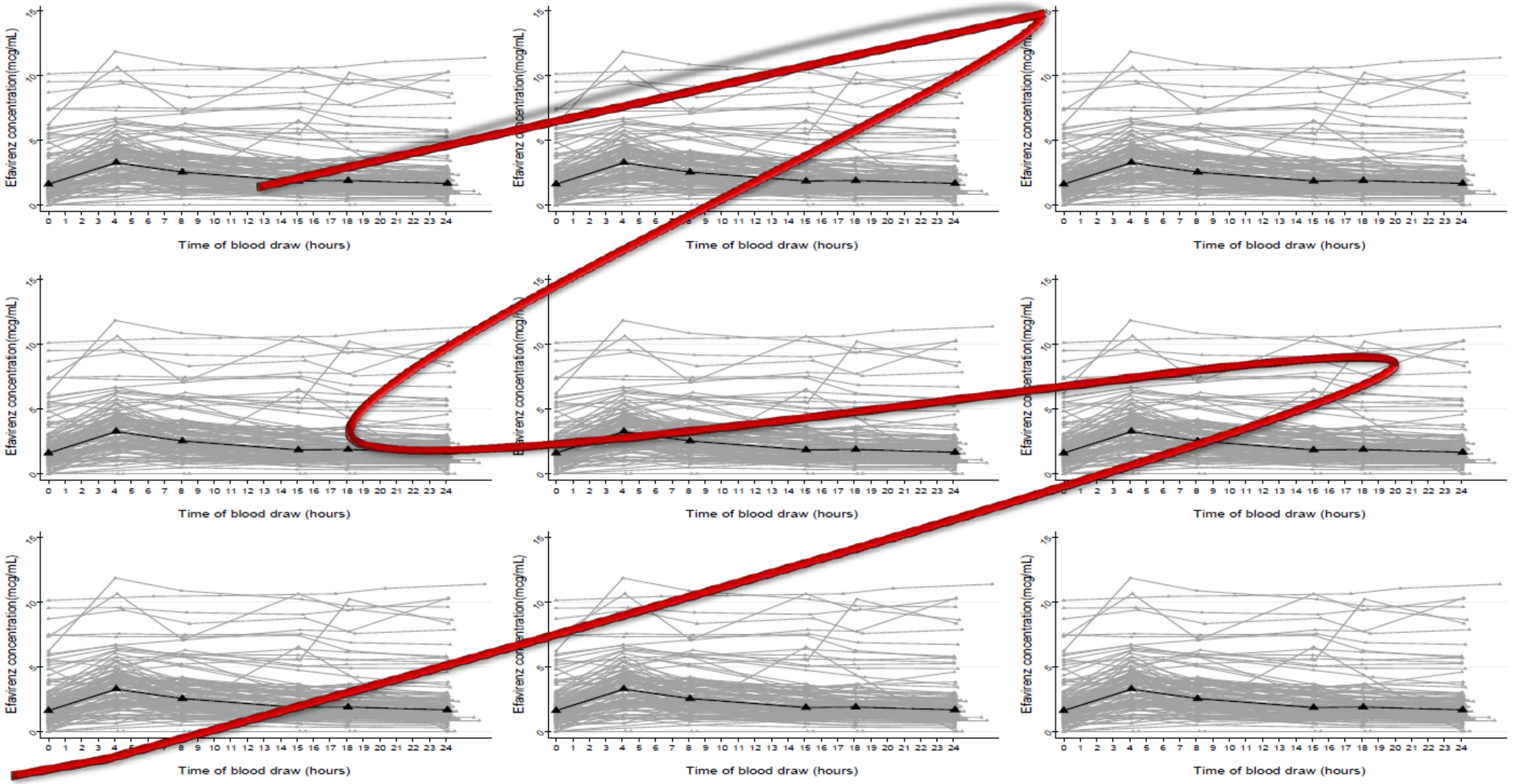
Morey GE. J Clin. Pharm 2013; Moorehead J Am Pharm Assoc 2017.

Real-time feedback devices and biological measures

- Many MEMs devices need downloading centrally
- Some real-time adherence monitoring devices have wireless chip e.g. Wisepill®
- RCT in patients on ART (China[2]) 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
  - A) adherence measure self-referential
  - B) no pharmacologic measure to prove ingestion
  - C) No improvement in viral loads
- Similar finding in Uganda cohort[3]

Sabin LL. JAIDS 2015; [2]Haberer AIDS 2016; [3]Haberer AIDS 2017

Other ways to measure cumulative exposure?



Hair it is!

- Drug level monitoring in hair – drugs of abuse common application
- Epilepsy literature (carbamazepine, tegretol, phenobarbital, ergotamine)
- TB latent and active treatment (isoniazid -INH)
- Organochlorine pollutants (DDT and biphenyl)
- Forensic analysis
  - Lead poisoning (Beethoven)
  - Arsenic (Napoleon)
  - Thallium, mercury, antimony (Newton)
- Stress – cortisol levels

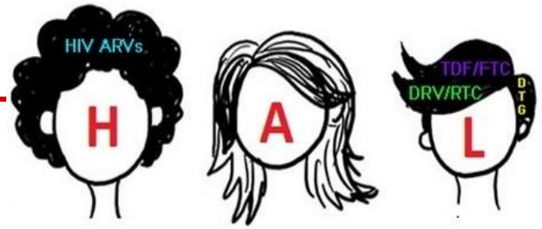
Beumer JH. Int J Clin Practice 2001;Williams J Therap. Drug Monitoring 2001;Covaci A. Chemospheres 2002; Flanagan RJ. Toxicol Rev 2005; Lugli A. Adv Anat Pathol. 2011; Thieme D. Forensic Sci Int. Mar 2007; Schoeman K.TDM 2010; Moller M. TDM 2010; Pelander A. TDM 2008; Karlen J. BMC Clin Pathol. 2011;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

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

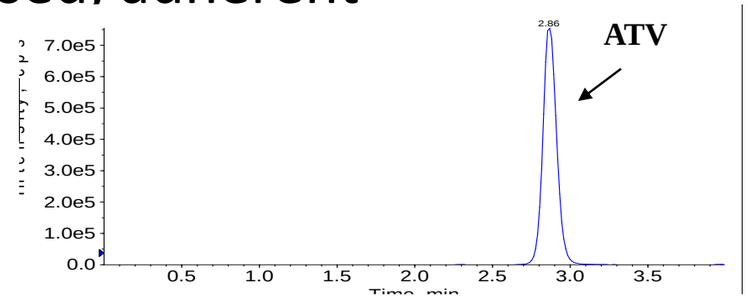
- Hair grows steadily in occiput at rate of ~1cm/month
- Hair shaft therefore becomes a marker of time
- Hair easy and cheap to collect
- No special skills (no phlebotomy)
- Stored at room temperature
- Shipped without biohazard
- Feasible for resource-limited settings
- Not subject to white-coat adherence

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

Development of hair assays



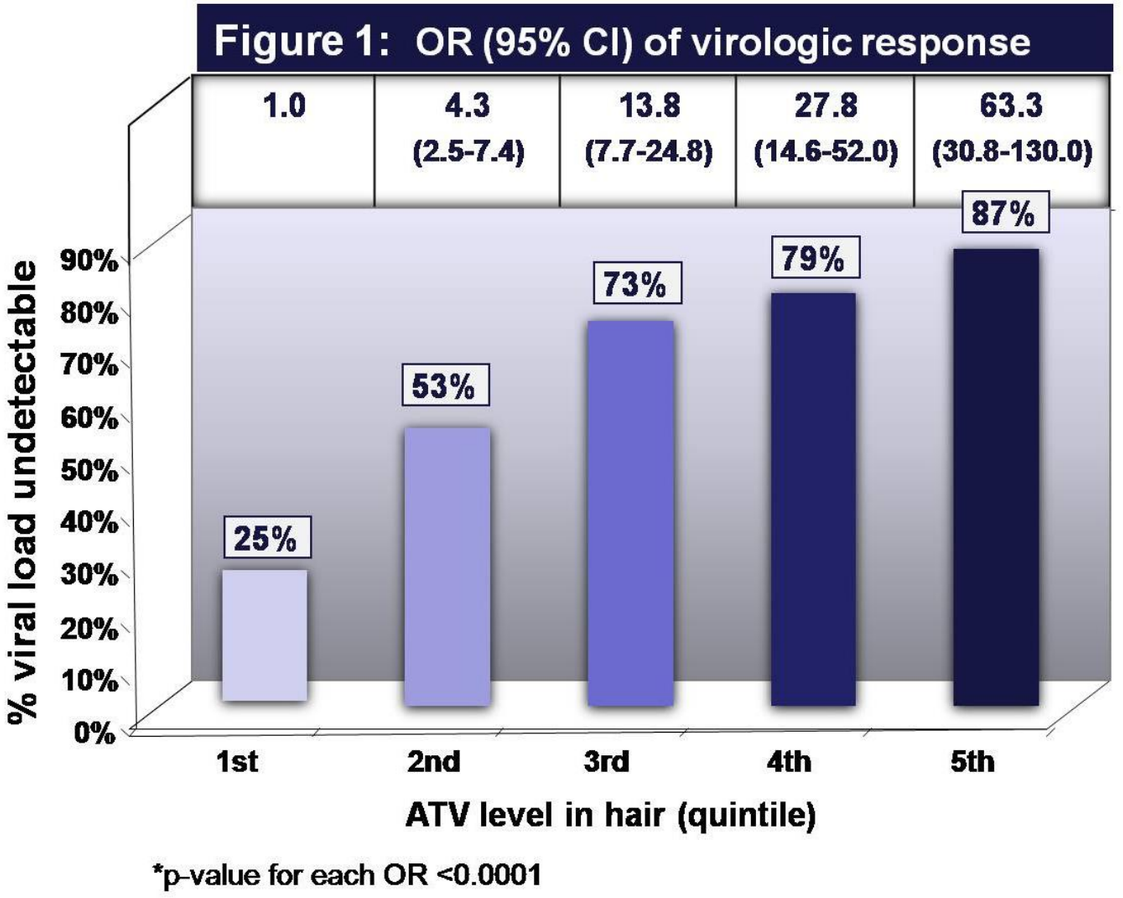
- UCSF Hair Analytical Laboratory (HAL)
- Shaved heads of patients on different antiretrovirals, suppressed. adherent
- Large quantities –assay optimization
  - Finely chop (some labs experimenting with pulverization)
  - Organic solvent and then extraction
  - Injection into liquid chromatography/tandem mass-spectrometry
  - 10-20 strands required for most (50-100 for TFV); only 1 strand for nevirapine
  - Good linearity (R^2>0.99), reproducibility (CV <15%); working with DAIDS-supported Clinical Pharmacology and Quality Assurance (CPQA) program



Give Your Hair for Science

Huang Y. Rapid Comm. Mass Spec 2008; Huang Y. Analytical & Bioanalytical Chemistry 2011

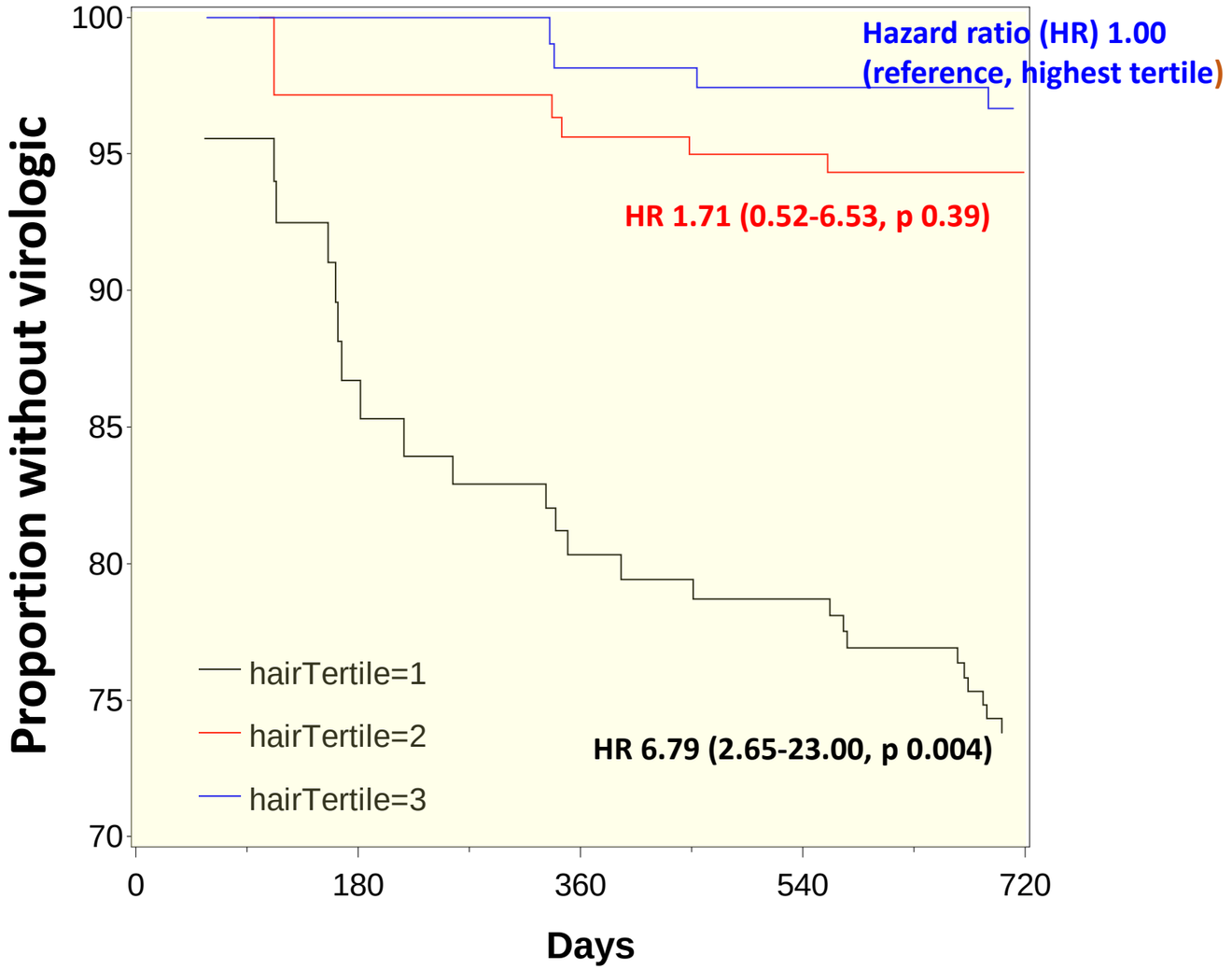
Atazanavir Concentration in Hair Is the Strongest Predictor of Outcomes on Antiretroviral Therapy



- 424 women on atazanavir-based ART (1143 person-visits)[1]
- Longitudinal modeling
- Viral load suppressed in 25% of visits where hair levels of ATV in lowest quintile
- Likelihood of suppression 87% when ATV levels highest quintile
- Increasing odds of response per hair quintile (similar models with NVP)
- Hair strongest independent predictor of virologic response in various cohorts,[2-8] demonstrating pharmacodynamic relevance

[1]Gandhi M. CID 2011; [2]Van Zyl JAIDS 2011; [3]Gandhi M. AIDS 2009; [4]Baxi PLOS One 2015; [5]Koss C. AIDS 2015; [6]Prasitsuebsai ARHR 2015; [7]Pintye JAIDS 2017; [8]Chawana JAIDS 2017

Hair levels predict outcomes in clinical trial



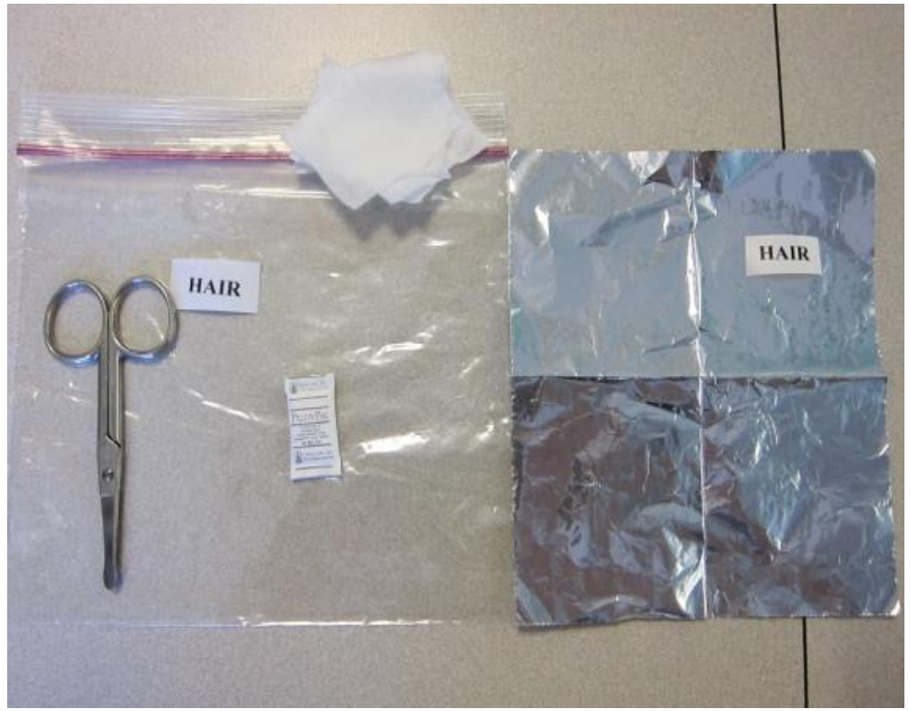
706 person-visits for ATV arm; 776 person-visits for DRV arm; 710 person-visits for RAL arm.

- ACTG A5257 study (ATV/r vs DRV/r vs RAL)[1]
- Hazard of VF with hair ARV levels in the lowest tertile was 6.8 times that with levels in the highest[2]
- Rates of VF by two years were 26%, 6%, and 3% for those with hair levels in the lowest, middle and highest tertiles
- Next step - can doing hair levels early and then adherence intervention avert VF?

[1]Lennox Ann Intern Med 2014; [2]Gandhi CROI 2018

Easy six step process

- Takes about 2 minutes of time
- Tiny snip of hair cut from back of the head, cheap materials
- Painless – no need for blood draw (children)



SHORT HAIR: collect straight into foil; no need to label distal end
(1cm = 1 month growth)

BRAIDED HAIR: collect from short strands between braids.

Place the cut thatch of hair inside the piece of foil with fingers over the distal end.

Acceptability of hair collection

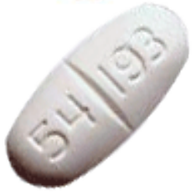
- **Better in Africa, Asia than among MSM**
  - Feasible because room temperature collection and storage
  - Rural Kenya, Asia, Uganda -Acceptability 95% as marker of adherence[1-3]
  - South Africa qualitative study - high acceptability of hair collection pregnant women, different ethnicities[4]
  - ATN 110, 113: >95% in young diverse MSM in U.S.[5]
  - Lower rates in white MSM -ACTG (~55%)[6]; U.S. PrEP Demo project, (58%)[7]

[1]Hickey M. JAIDS 2014; [2]Pintye J. JAIDS 2017; [3]Koss AIDS 2015; [4]Coetzee B. Future Virology 2012; [5]Koss CID 2017; [6]Gandhi CROI 2018; [7]Gandhi AIDS 2017

Antiretroviral assays in hair
UCSF Hair Analytical Laboratory (HAL)

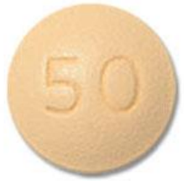
Efavirenz

Atazanavir



Nevirapine

Lopinavir



Dolutegravir

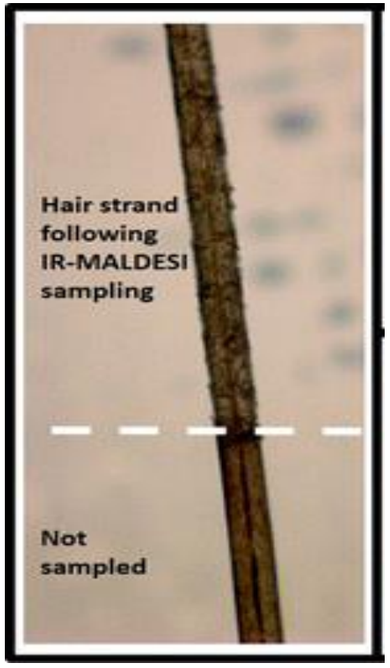
Ritonavir

Darunavir

Raltegravir

20 strands hair

Hair levels in HIV Prevention



3 major lessons of “PrEP 1.0”

1. Adherence key to effectiveness
2. Self-reported adherence unreliable
3. Long-acting methods desirable

“PrEP 2.0”

Adherence and exposure monitoring via pharmacologic measures

Roll-out of oral PrEP in high-incidence settings

Long-acting prevention methods (rings, injectables)

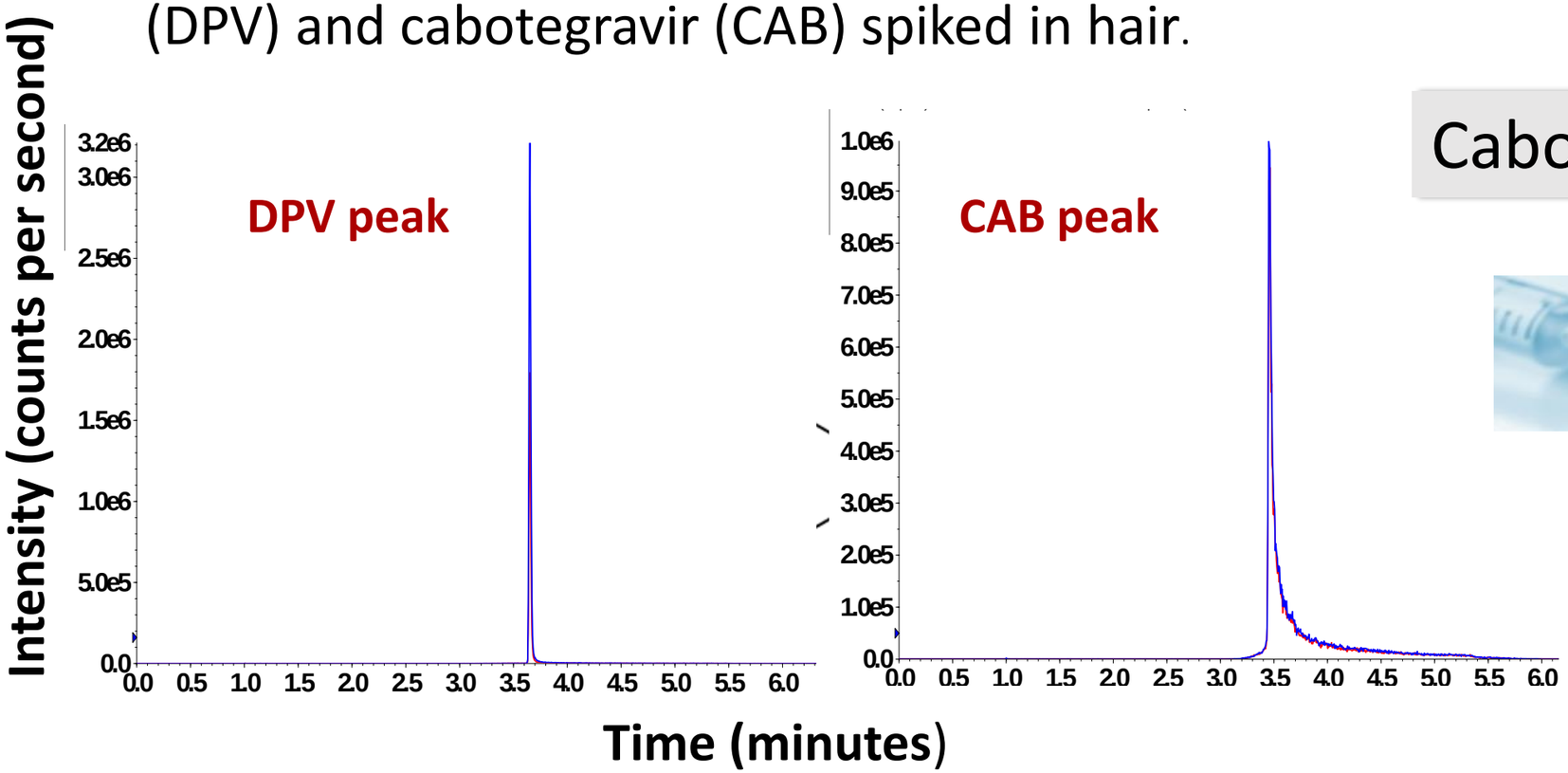
Antiretroviral assays relevant for prevention: UCSF Hair Analytical Laboratory

50-100 strands hair

TDF/FTC and TAF

Representative extracted ion chromatograms for dapivirine (DPV) and cabotegravir (CAB) spiked in hair.

Dapivirine

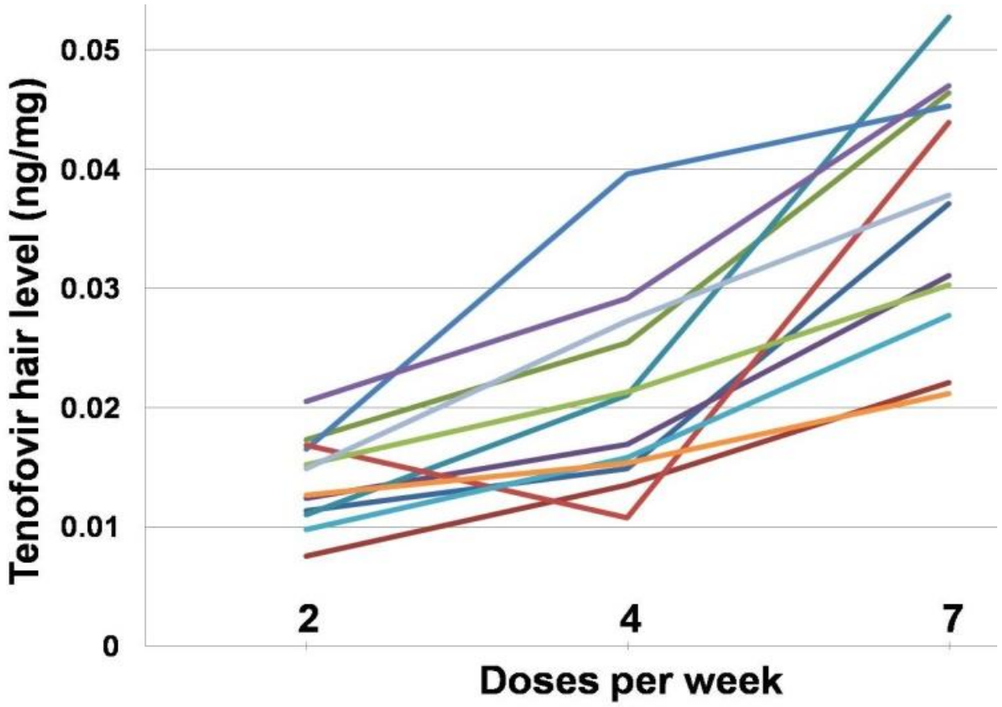


Cabotegravir

Dosing benchmarks for TFV in hair

STRAND study

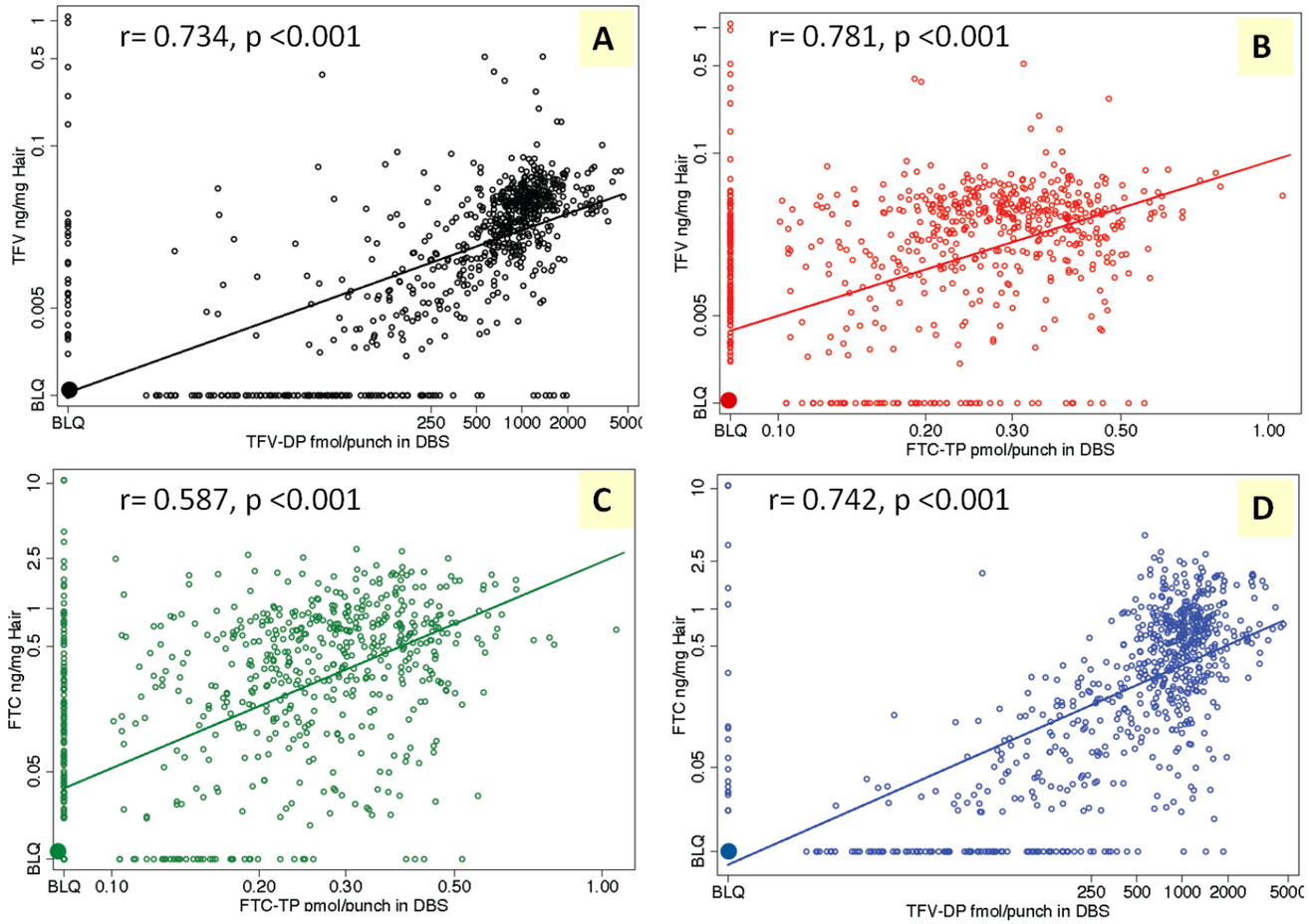
- DOT TFV 300mg to 15 HIV-individuals at 2, 4 and 7 doses/wk x 6 wks (wash-out periods in between)
- TFV hair levels →strong linear relationship with dose
- Establishes adherence "benchmarks" for each dosing strategy
- Hair being analyzed in multiple PrEP studies (including HPTN 067[2])



Dosing strategy	N	Median (range) TFV levels (ng/mg)
2 doses/week	22	0.012 (0.008 to 0.021)
4 doses/week	22	0.023 (0.011 to 0.042)
7 doses/week	21	0.038 (0.021 to 0.053)

[1]Liu A. PLOS ONE 2014; [2]Velozza CROI 2018

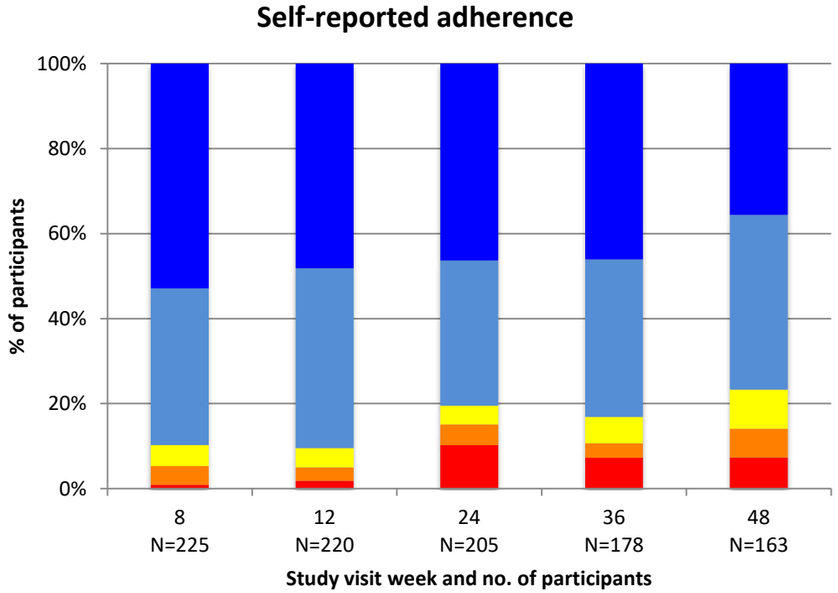
Comparing hair measures to DBS measures (highly correlated)

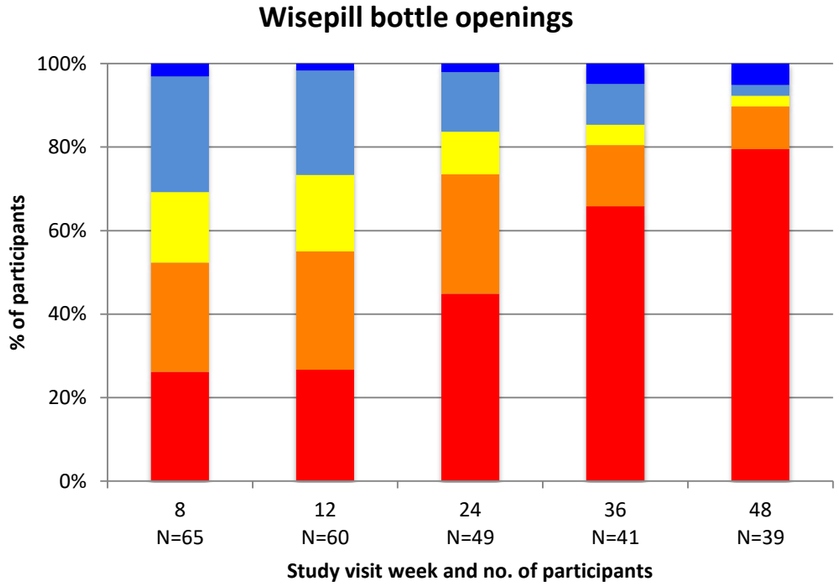


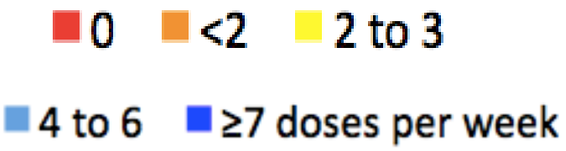
- iPrEx OLE study – Dried blood spot (DBS) measures of TFV-DP predictive of protective efficacy[1]
- TFV/FTC hair levels and associated levels in DBS highly correlated and concordant
- Correlation analysis showed hair level of 0.023ng/mg (corresponding to 4 doses/week) associated with protective efficacy

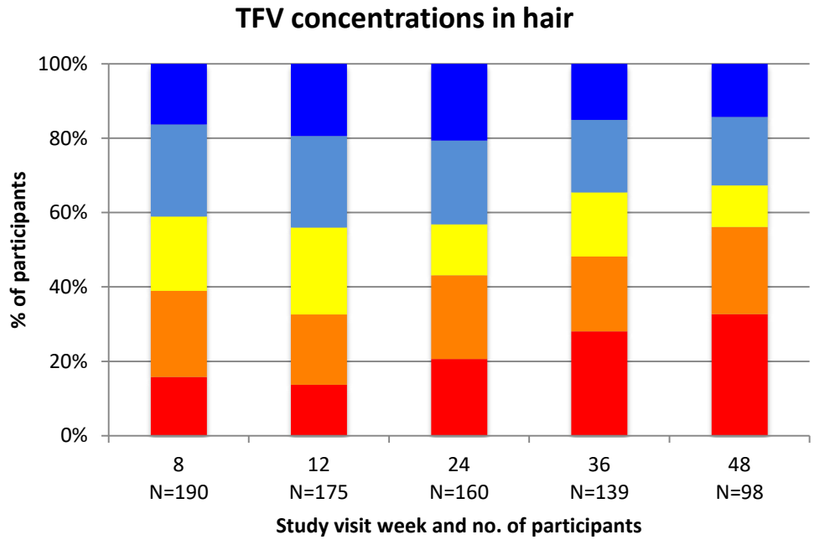
Grant RM. Lancet ID 2014; Gandhi M. JID 2015; Gandhi AIDS 2017; Koss CID 2017

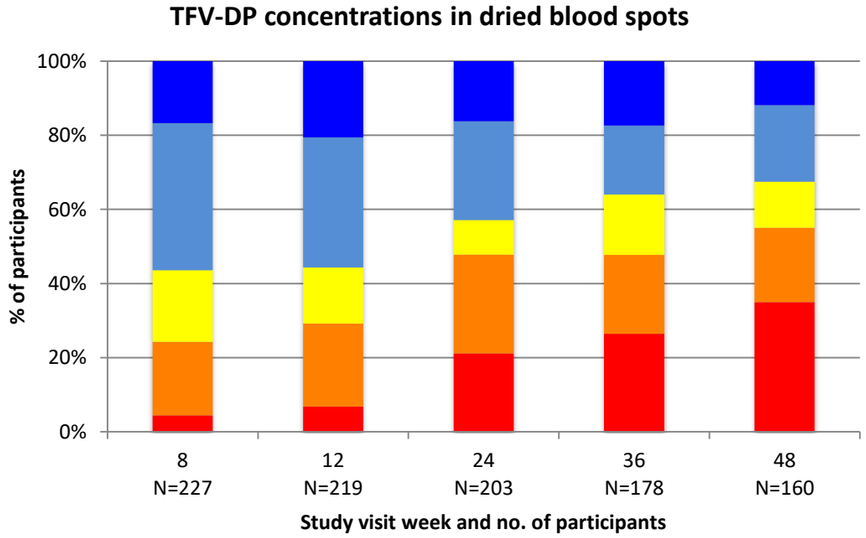
ATN 110, 113: Hair and DBS showed low adherence over time, not by self-report; youth didn't use Wisepill





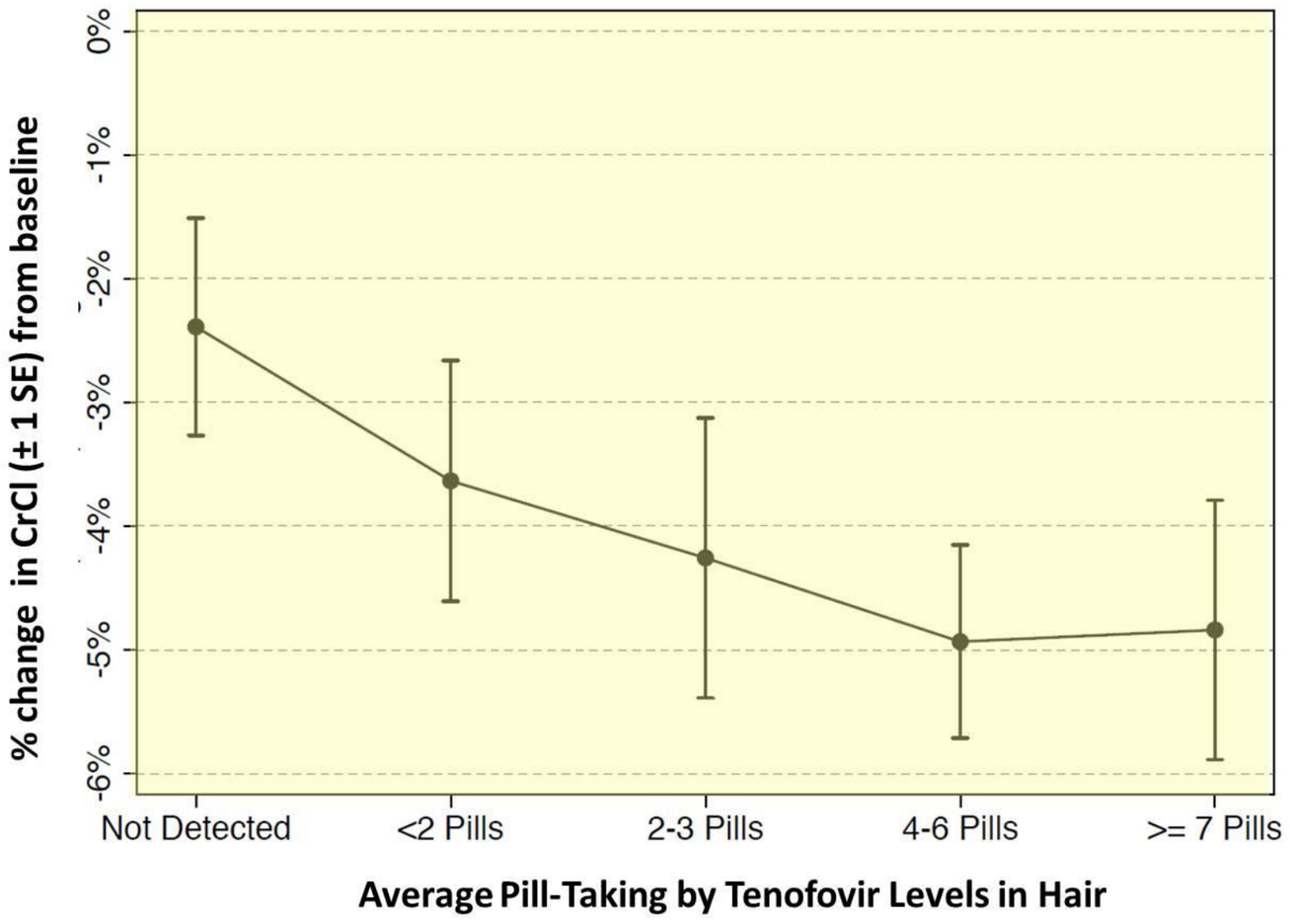






Koss CID 2017

TFV levels in hair (age, starting CrCl) associated with renal toxicities in PrEP

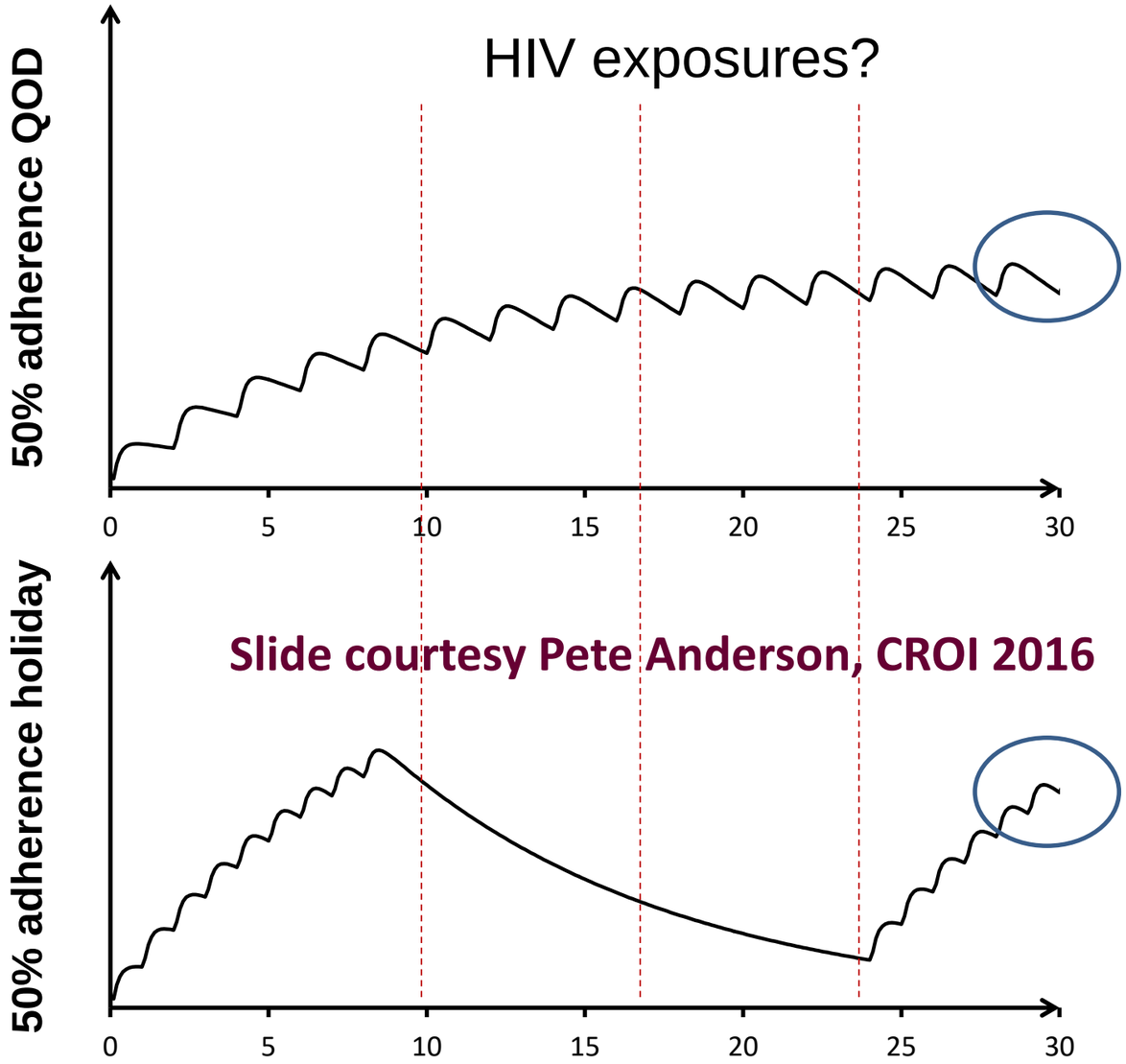


- iPrEx OLE– 1225 MSM and TG
- Renal function decreased moderately over time as in other PrEP studies (2.9% decline 16.8 mo., N=942)
- Hair collected q12 weeks on subset: n=220; 1144 person-visits; median age 29 (19-70)
- Higher hair levels of TFV or FTC associated with greater declines in CrCl (5.6% decline in those with daily dosing)
- Age >40 and baseline CrCl <90ml/min associated with greater declines in CrCl

Gandhi. Lancet HIV 2016; Gandhi AIDS 2017

Limitations of long-half moieties

- Represents averaged adherence, cannot determine dosing patterns
- Need segmental analysis with hair for patterns[1]
- Inter-individual variability leads to overlap in adherence categories (misspecification).

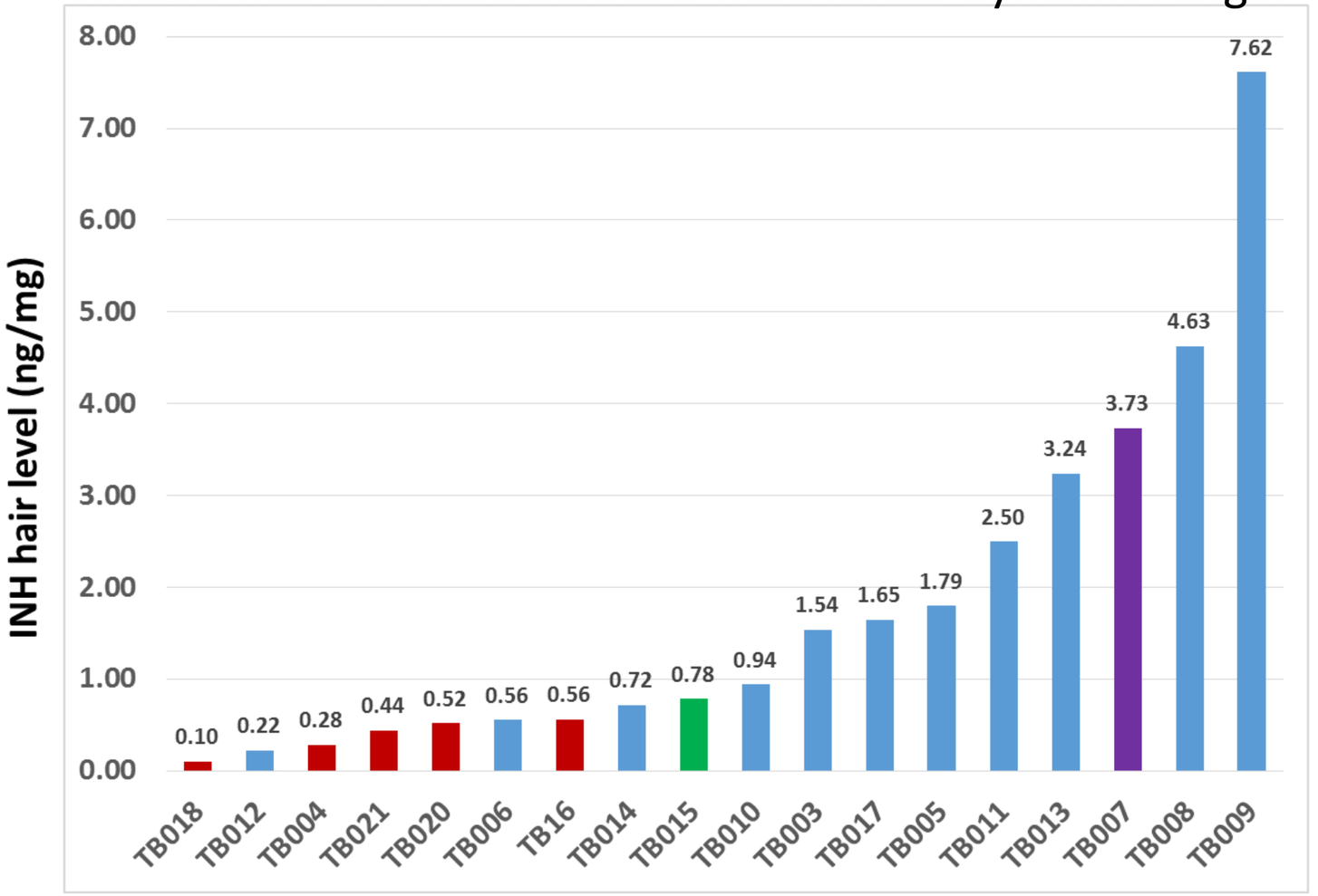


Slide courtesy Pete Anderson, CROI 2016

Thaden CROI 2018

Foray into TB drug monitoring

In 18 patients with latent or active TB on treatment,
isoniazid was detected across a wide linear dynamic range.

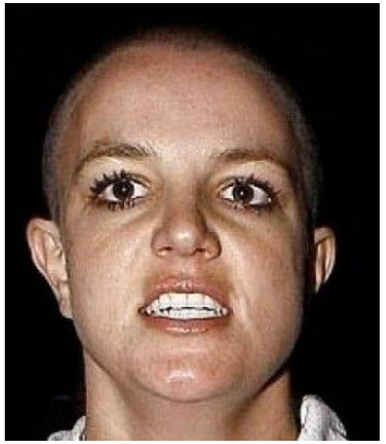


Aims: To develop hair assays for anti-TB drugs, mainly to monitor in “prevention” (LTBI) or MDR TB tx

Gerona IJTLD 2016; Gandhi PLOS ONE 2016; Mave IJTLD 2016; Metcalfe IJTLD 2017 .

Hair testing for substances

- Well described, usually metabolites, tested in neonatal hair to assess maternal exposure
- LC/MS-MS, HPLC, GC-MS methods described
- Alcohol: Ethyl glucuronide[1]
- Cocaine: Norcocaine and cocaethylene[2]
- Marijuana: 11-nor-Δ9-tetrahydrocannabinol-9-carboxylic acid glucuronide[3]
- Metamphetamines: Various metabolites[4]
- Opiates, ecstacy, ketamine, benzos, nicotine, hallucinogens,



[1]Guiterrez. Alcohol 2015; [2]Gambelunghe Drug Test Anal 2015; [3]Pichini. For Sci Int 2015; [4]Han. For Sci Int 2015; Bacui. Anal Chem Acta 2015

CURRENT OPINION

Point-of-care diagnostics: extending the laboratory network to reach the last mile

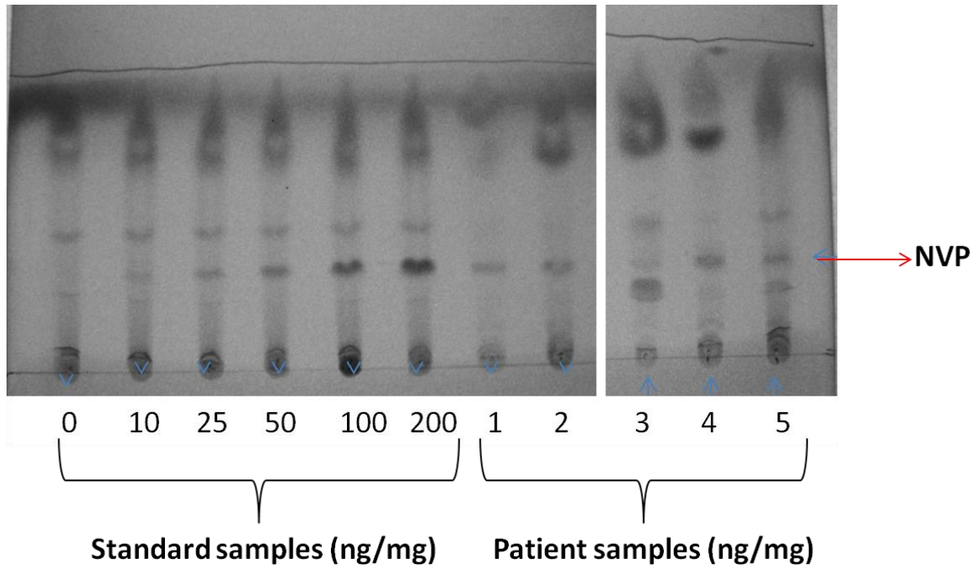
Paul K. Drain[a,b,c,d] *and Christine Rousseau*[a,e]

Purpose of review

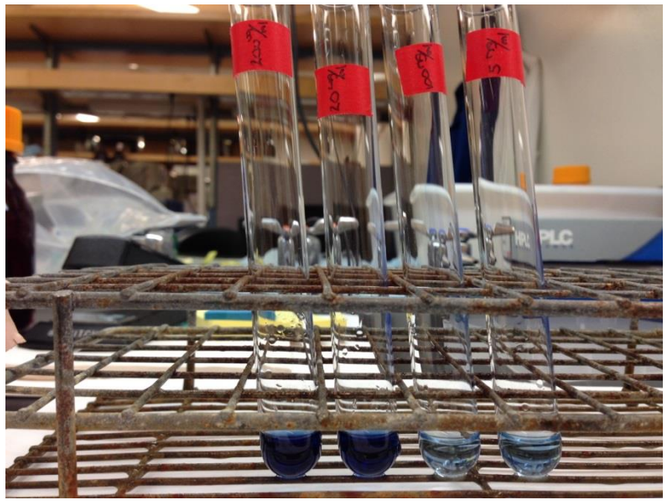
More point-of-care (POC) diagnostic tests are becoming available for HIV diagnosis and treatment in resource-limited settings. These novel technologies have the potential to foster decentralized HIV care and treatment for the benefit of clinical laboratories, HIV clinics, and HIV-infected patients. There continue to be many business, technological, and operational challenges that limit product development and regulatory

Low cost real-time (point-of-care) measures of adherence – possible breakthrough

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



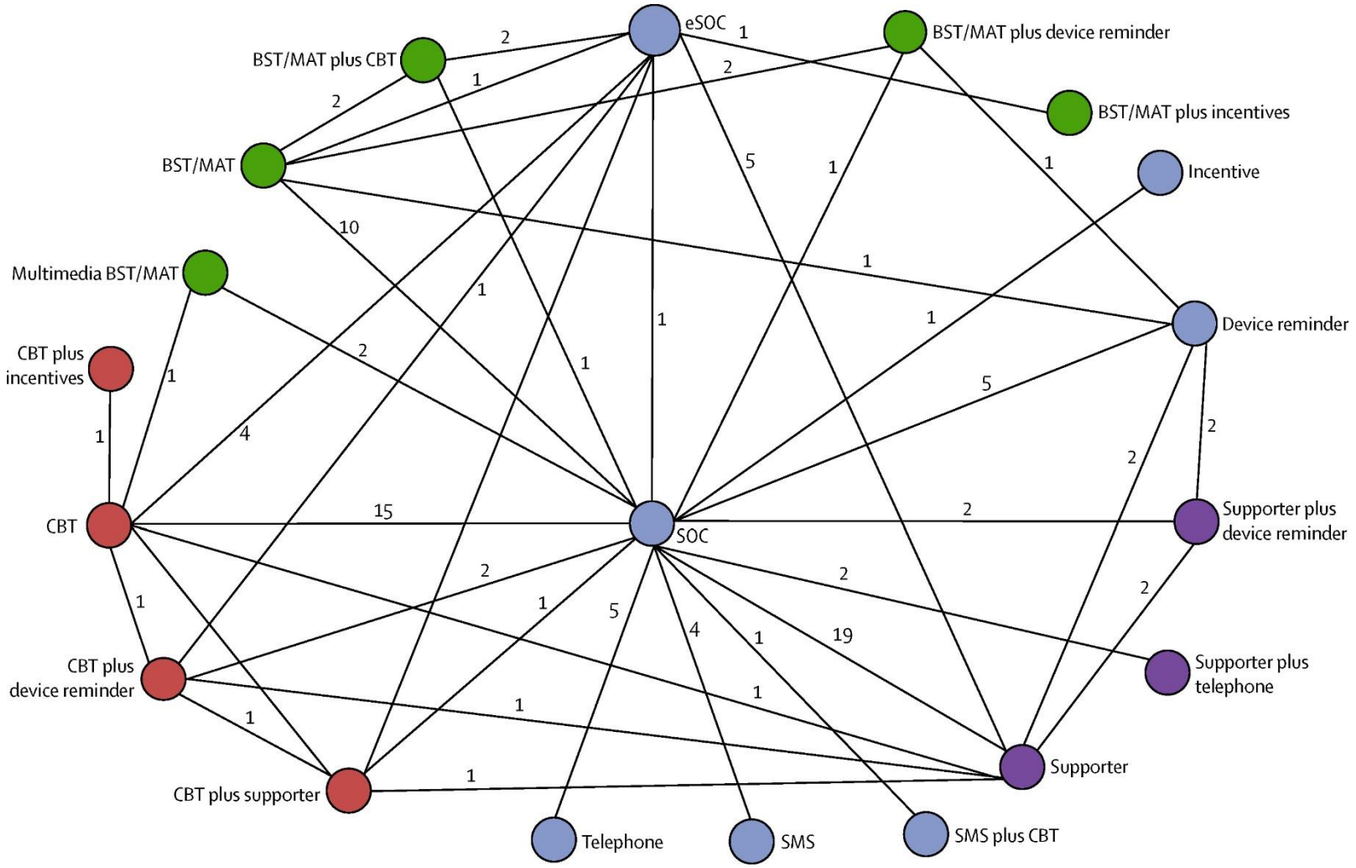
- Colorimetric assays for TFV –cheap but still labor-intensive, competing endogenous compounds



- Immunoassays common for urine/saliva substance use; Antibodies for PrEP close!!

Gandhi M. ARHR 2014

Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis (Kanters et al. Lancet HIV 2017; 4(1): e31-e40



- SMS reminders
- Pill boxes
- Behavioral skills training
- Medication adherence training
- Cognitive behavioral therapy

Summary

- Adherence is a problem in HIV and all chronic diseases
- PrEP efficacy trials dramatically illustrated limitations of self-reported adherence
- Objective biomarkers of adherence needed in PrEP and microbicide research where no surrogate of drug-taking
- Pharmacologic measures involve measuring drug in biomatrix
- Emerging, novel measures of exposure include DBS and hair monitoring; sensors, taggants, antibodies, residual ring levels
- Low-cost, point-of-care, measures for PrEP (and treatment) adherence needed
- Adherence measurement allows adherence intervention

Adherence: the behavioral bridge from efficacy to effectiveness

The UCSF Hair Analytical Lab (HAL)

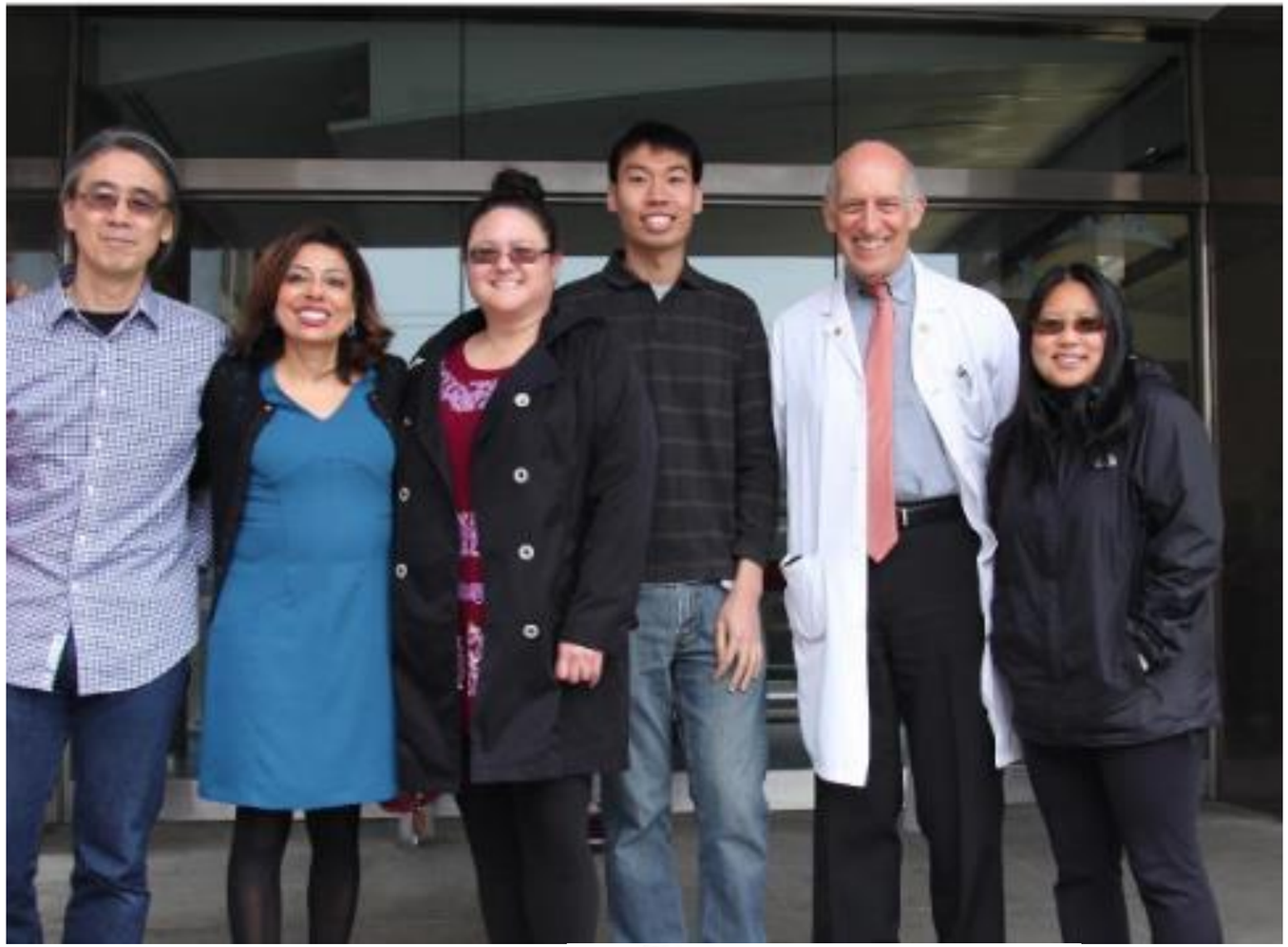
Thanks to

Dr. Luis E. Morano Amado

Dr. Edward Cachay

Diane Havlir MD

The Hair Lab at UCSF



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