How can we optimize adherence to products before, during and after phase III trials?

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Overview:

1. Definitions & conceptualization of adherence and acceptability
2. Adherence BEFORE Phase III
   Preferences, choice and acceptability studies
3. Adherence DURING Phase III
4. Adherence AFTER Phase III
5. Summary and Conclusion
Dimensions of adherence

- **Initiation (1)**
  Time point for 1\textsuperscript{st} dose

- **Execution (2)**
  Actual = Instructed dosing

- **Discontinuation (3)**
  Time point for last dose

- **Persistence (P)**
  Period between initiation and discontinuation

Adherence parameters in ~17K ppts; 95 studies

Sources: IOM report 2008; Blaschke et al., Ann.Rev.PT 2012; van der Straten et al., CHAR 2012
VOICE-D: Typology of non-adherence:

Non-initiation
- Temporary
- Permanent

Discontinuation
- Visit-driven use
- Variable taking
- Modified dosing
- Modified regimen

Mis-execution or implementation

Adherence

\[ \times = \text{Undistinguishable with plasma PK} \]

van der Straten et al., AIDS 2015
PrEP/microbicide Acceptability Framework

Influencing factors

Social and structural context
- Organizations
  - Partner
    - Individual characteristics

Product acceptability
- Product-associated norms
  - Partner’s attitude
    - Effects of product use on sex
      - Use attributes
        - Product characteristics
          - Delivery mechanism
          - Efficacy (if known)
          - Dosing regimen

Preference/choice
- Product alternatives
  - Nothing

Acceptability: product related attributes, perceptions and experiences that potentially influence adherence


Adherence
- Initiation
- Execution
- Discontinuation
2. Before phase III trials
(Hypothetical) end-user product preferences:

Preferred attributes:
- Efficacy/safety
  - Safe/no side effects
  - Reliable
  - Reversible; retrievable
- Product:
  - Long(er)-acting
  - Dosing: easy/painless
  - Non-invasive
- Use:
  - Familiar
  - Discreet
  - Female-controlled
- Sex:
  - Non-interference

VOICE-D (N=68)

ASPIRE (N=71)

\[ \geq 50\% \quad , \quad \geq 25\% \quad , \quad < 25\% \]
End-users preference and acceptability studies

- **With placebo products**
  - **TRIO** (SA & Kenya): 3 potential MPT delivery forms
  - **QU4TRO** (SA & Zimbabwe): 4 potential HIV PrEP delivery forms

- **Focus on:**
  - Relative preference
  - **Change over time:** how does presentation, education and experience change relative preference?
  - **Attributes** that are favorable and unfavorable overall and in subgroups (e.g., age; geographical location)
  - **Various users/stakeholders:** women 18-30; male partners, providers
Trio: Three MPT Placebo Products

TRIO = Tablet, Ring, and Injectable as Options for women.

- Monthly silicone ring
- 2x2ml saline injection
- Daily oral tablet
Quatro: Four Vaginal Placebo Products

- Monthly PU ring
- Pre-coital film
- Pre-coital insert
- Precoital gel
Key Study Outcomes

- **Stated preference**
  - Ranking across study products and condoms
  - Satisfaction ratings

- **Choice**
  - Participants asked to choose one of the study products to use after trying all products for one month each

- **Use- adherence**
  - **Trio**: Wisepill electronic monitoring, visual ring inspection, and directly observed dosing in the clinic
  - **Quatro**: objective biomarkers through self-collected vaginal swabs, unused product counts, and directly observed dosing.

- **Most and least preferred product attributes**
  - Detailed questionnaires about product features following use
  - Discrete choice experiment
Discrete-Choice Experiment: What is it?

- Respondents choose between hypothetical products in a series of 8-10 questions.
  - Each defined by attributes with varying levels
  - Profiles do not necessarily characterize existing products; they are combinations of attributes
  - Profiles are determined by an experimental design
- Respondents’ choices depend on the relative importance of attribute levels.
- Statistical analysis estimates the decision weights consistent with observed patterns of choices.
Follow-up questions:
1) Allow respondent to choose “neither”.
2) Ask about likelihood of actually using chosen product.
3. DURING Phase III Trials

- Measurement and accountability
- Need for monitoring: adherence will vary by site/setting, product and population
- Adherence support interventions
The key to understanding adherence (and intervene), is to accurately measure it…

I think if the results of the blood tests came out immediately, then it can also be immediately established whether you were using the product or not. Then, they should tell you, your blood test results. This approach will make you feel more compelled to use the products properly. (VOICE-D participant, Zimbabwe, low PK, gel)
Important variations across regions but also within regions (across sites)

Liu JAIDS 2014
• Interventions during RCT have yielded mixed results
  – **iPrEX (NSC); VOICE (VASP), FemPrEP:**
    - No evidence of intervention effect
    - No experimental design;
    - implemented late during trials;
    - Didn’t address possible source of non-adherence (mistrust, stigma, RCT setting: placebos and unproven active).
  – **CAPRISA 004, Partners PrEP:** evidence of ↑ adherence
    - CAP004 (N=889): Median adherence 54% pre- vs 66% post-intervention (p<0.01).
    - Partners PrEP (N=1147): Mean (MEMS) adherence 76% pre- vs 84% post-intervention (p<0.001)
  – **ASPIRE/MTN-020:** site level drug feedback and participants engagement activities- Effect TBD.

Timing may be key: VOICE VASP intervention

- **VOICE starts** 9/2009
- **VASP implemented** 5/2011
- **Oral TDF futility results** 9/2011
- **Vaginal TFV futility results** 11/2011
- **VOICE ends** 8/2012

Amico et al., AIBE 2014; van der Straten, AIBE 2015
AFTER Phase III trials: efficacy known!

- Open-Label Trials (ADAPT, MTN-017; MTN-034, HPTN-082)
- OLE (iPrEX OLE; Partners OLE, HOPE/DREAM)
- Demo projects
- Implementation research
- Real World roll out
Does preference influence adherence?

- Open-label trials with active products:

  **REACH MTN-034**: active tablets & ring crossover trial in adolescent and YW (upcoming) in SA and Kenya

- Biological adherence monitoring and feedback
- Preference measured by choice and persistence with product
Does dosing regimen influence adherence?

- **ADAPT/HPTN-067** open-label Truvada Trial: 179 ♀ in CPT, 30 week dosages (daily, time & event-driven)
- Ongoing **Wisepill monitoring**, weekly SMS/phone feedback
- 60 Qualitative participants (IDI, FGD)

### Adherence barriers
- Pill attributes (size, taste)
- Side effects
- ARV stigma
- Non-disclosure/privacy

### Adherence facilitators
- Efficacy beliefs
- Concrete: reminder sys.
- Need protection/Risk
- Social support
- Understands regimen

### Participation challenges
- Safety concerns
- Community mistrust of PrEP or research
- Negative clinic experiences

### Participation facilitators
- Personal experience w/HIV
- Package of care
- Financial/ reimbursement
- Connection with team
- Commitment/alignment

*Bekker, CROI 2015; Amico AIBE 2016*
ADAPT mutuality framework: congruence with VOICE-D adherence typology

Framework identifies 4 unique dynamics & proposes different adherence interventions based on these

Amico et al., AIBE 2016
Summary and conclusions
<table>
<thead>
<tr>
<th>Source/Issue</th>
<th>Focus strategies on:</th>
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<tr>
<td><strong>Distrust; Disinterest or Uncertainty</strong></td>
<td>Adherence pattern: ![Image]</td>
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| Medical or research mistrust | • Community engagement, dispel rumors, ↑ transparency & quality of staff services  
                                    ↑ social ties with staff; ↓ hierarchy  
                                    • Personalize risk/needs; incentivize adherence. |
| Low saliency or intrinsic motivation | |
| **Alignment** | Adherence pattern: ![Image] |
| Lack of accountability  
Forgotten/ regimen burden  
Non-disclosure; low social support | • Real time adherence monitoring and feedback.  
                                  • Reminder systems; alternative formulations.  
                                  • Peer support (PrEP buddies). |
| **Mutuality** | Adherence pattern: ![Image] |
| Sustain high adherence | • Social rewards, PrEP mentoring/champions. |
What is needed to optimize adherence

- **ALWAYS**: have **accurate measurement** and ongoing monitoring.
- **BEFORE** phase III:
  - Identify most/least preferred attributes; optimize delivery form to maximize user and provider “convenience” (minimize burden).
  - Identify barriers and facilitators: individual, social, structural level
- **DURING** phase III:
  - Real-time **objective feedback** to participants for ↑ accountability.
  - Work to better align participants and researchers objectives (engage & educate participants)
  - Provide early, tailored adherence support intervention based on source of non-adherence
- **AFTER** phase III
  - Assess diverse preferences through **choice** and use of PrEP/MPT formulations → one size most likely will not fit all.
  - Foster **trust** between participants & staff to facilitate mutual engagement & supportive partnerships.
  - **Evaluate** adherence support interventions w/ experimental designs. → Assess **scalability** of these interventions.
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Questions? Thank you!