

ORAL ABSTRACT: OL-12
Wednesday, March 11, 2020

DIAGNOSTIC AND THERAPEUTIC CHALLENGES ARISE WITH EARLY HIV INFECTION ON PrEP

Michael J Peluso
*University of California San Francisco
San Francisco, CA, USA*

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Disclosures:

To self, paid to my institution: Research grant/grant pending
Gilead Sciences, Inc

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Diagnostic and therapeutic challenges arise with early HIV infection on PrEP

Michael Peluso, MD

Division of HIV, Infectious Diseases, and Global Medicine
University of California, San Francisco

Study Team: Michael J. Peluso, Monica Gandhi, Susa Coffey, Hiroyu Hatano, Heather Hartig, Susan Buchbinder, Michael Busch, Christopher D. Pilcher, Hyman Scott, Stephanie E. Cohen, Darpun Sachdev, Pierre Crouch, Diane Havlir, Steven G. Deeks, Timothy J. Henrich, Sulggi A. Lee

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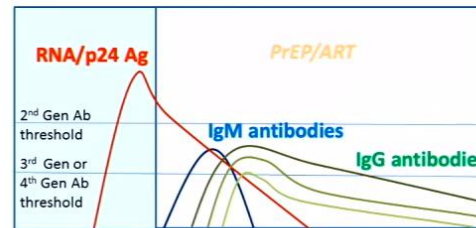
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Background

- PrEP use: **3 million** worldwide may benefit
- PrEP is **99% effective if adherent**
 - Daily
 - On Demand (2-1-1)
- PrEP failure with documented good adherence is **rare**
 - Only 7 published cases worldwide
- PrEP use in setting of undiagnosed HIV infection may reduce/delay:
 - Detection of viral antigens
 - Host antibody responses

HIV/PrEP Overlap



CDC Clinical Practice Guidelines 2014; Grant et al Lancet ID 2014; Smith et al MMWR 2015; Keating et al CID 2016; Cohen et al Lancet HIV 2018; Lowery et al CROI 2020 Abs 1003

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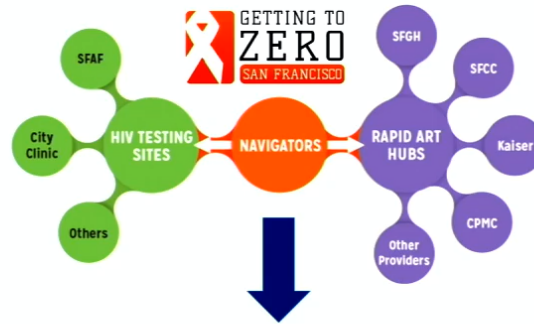
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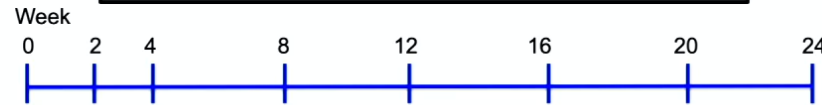
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Sulggi Lee, MD PhD
Principal Investigator
sulggi.lee@ucsf.edu

UCSF Treat Acute HIV Study



- New HIV diagnosis → immediate ART initiation
- Blood sampling monthly x 6+ months (PBMCs, plasma)
- Optional leukapheresis, tissue sampling at 12 months+ (lymph node, GALT)

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UCSF Treat Acute HIV Study

N=58

- Male (87% MSM)
- Median age 30 years
- Median time to diagnosis 29 days

**Never PrEP
N=34**

**Prior PrEP
(>10 days)
N=13**

**HIV/PrEP Overlap
<10 days
N=11**

**PrEP initiated, but
found to be HIV+
N=5**

**HIV Acquired on PrEP
N=6**

- Median VL 2.8 log₁₀ copies
- Discordant test results 67%

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PrEP and Acute HIV: Case Dilemmas

```
graph TD; A[HIV/PrEP Overlap N=11] --> B[Case 1 Emerging Resistance?]; A --> C[Case 2 PrEP Overwhelmed?]; A --> D[Case 3 Aborted Infection?];
```

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Report of 3 representative cases

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Case 1: Rapid Development of Resistance

Antibody testing
HIV-1/-2 antibody testing
Qualitative plasma RNA
Quantitative plasma RNA
HIV Genotype

The diagram shows a horizontal timeline with three key points: -4 days, 0, and 7 days. A pink vertical bar at -4 days is labeled 'Exposure'. A large light blue arrow points down at 0, labeled 'Starts PrEP'. A yellow shaded area extends from 0 to 7 days. A vertical line at 0 is labeled with a minus sign (-), indicating a negative antibody test. A vertical line at 7 days is labeled with a plus sign (+), indicating a positive antibody test.

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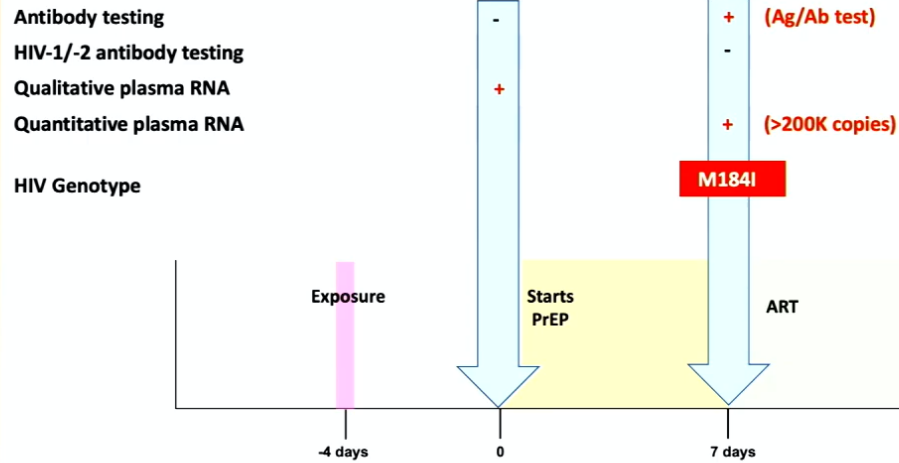
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Rapid Ab test negative initially, TDF/FTC start

Case 1: Rapid Development of Resistance



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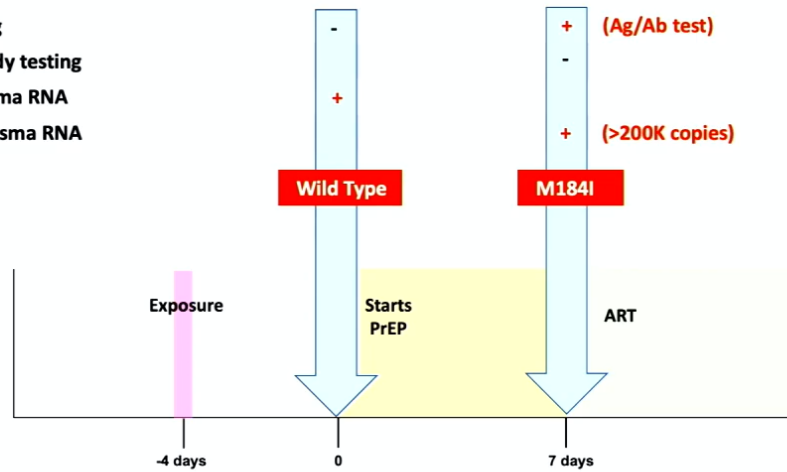
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Case 1: Rapid Development of Resistance

- Antibody testing
- HIV-1/-2 antibody testing
- Qualitative plasma RNA
- Quantitative plasma RNA
- HIV Genotype



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Case 1: Rapid Development of Resistance

1. Often, the earliest we identify individuals who recently acquired HIV infection is during a PrEP initiation visit
2. Transmitted resistance of M184V/I is rare but has been associated with PrEP failure
3. M184 mutation may occur just a few days after initiating PrEP in very early HIV infection
 - Consistent with early in vitro data showing rapid M184 emergence
4. Plasma HIV RNA testing at the time of PrEP or 2-drug PEP initiation may capture additional high-risk individuals with occult acute HIV

Keulen J Virology 1997, Cohen et al Lancet HIV 2018

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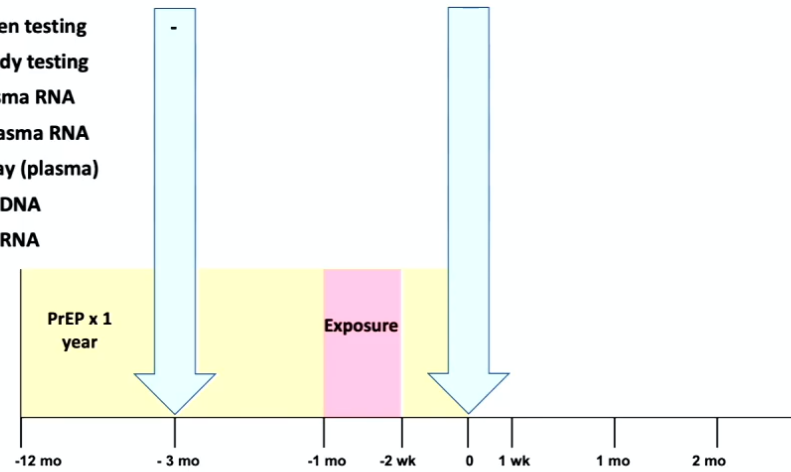
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M184 mutation emerges rapidly: either development of resistance or selection of minor variant (not identified by 1st resistance test)

Case 2: PrEP “Overwhelmed”?

- Antibody/antigen testing
- HIV-1/-2 antibody testing
- Qualitative plasma RNA
- Quantitative plasma RNA
- Single copy assay (plasma)
- Cell-associated DNA
- Cell-associated RNA



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Good adherence was reported by user; 14 days 45 partners anal sex receptive without condom;

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Case 2: PrEP "Overwhelmed"?

The diagram shows a timeline from -12 months to 2 months. A yellow bar from -12 to -3 months is labeled 'PrEP x 1 year'. A pink bar from -1 month to -2 weeks is labeled 'Exposure'. A large cyan arrow points down at -3 months with a '-' sign. Two cyan arrows point down at 0 and 1 week, with a '+' sign and '(Ag/Ab)' next to them. Test results are listed on the left:

Assay	-3 mo	0	1 wk
Antibody/antigen testing	-	+	+
HIV-1/-2 antibody testing	-	-	-
Qualitative plasma RNA	-	+	+
Quantitative plasma RNA	-	+	-
Single copy assay (plasma)	-	-	-
Cell-associated DNA	-	-	-
Cell-associated RNA	-	-	-

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Quantitative plasma RNA test with lower limit of <20 cps/ml was negative

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Case 2: PrEP "Overwhelmed"?

Antibody/antigen testing
 HIV-1/-2 antibody testing
 Qualitative plasma RNA
 Quantitative plasma RNA
 Single copy assay (plasma)
 Cell-associated DNA
 Cell-associated RNA

The diagram shows a timeline from -12 months to 2 months. A yellow bar from -12 to -3 months is labeled 'PrEP x 1 year'. A pink bar from -1 month to -2 weeks is labeled 'Exposure'. A yellow bar from 0 to 1 month is labeled 'ART'. Three blue arrows point to test results at -3 months, 0, 1 week, and 1 month. The results are as follows:

Time Point	Antibody/antigen testing	HIV-1/-2 antibody testing	Qualitative plasma RNA	Quantitative plasma RNA	Single copy assay (plasma)	Cell-associated DNA	Cell-associated RNA
-3 mo	-	-	-	-	-	-	-
0	+	-	+	-	-	-	-
1 wk	+	-	+	-	-	-	-
1 mo	-	-	-	-	-	-	-

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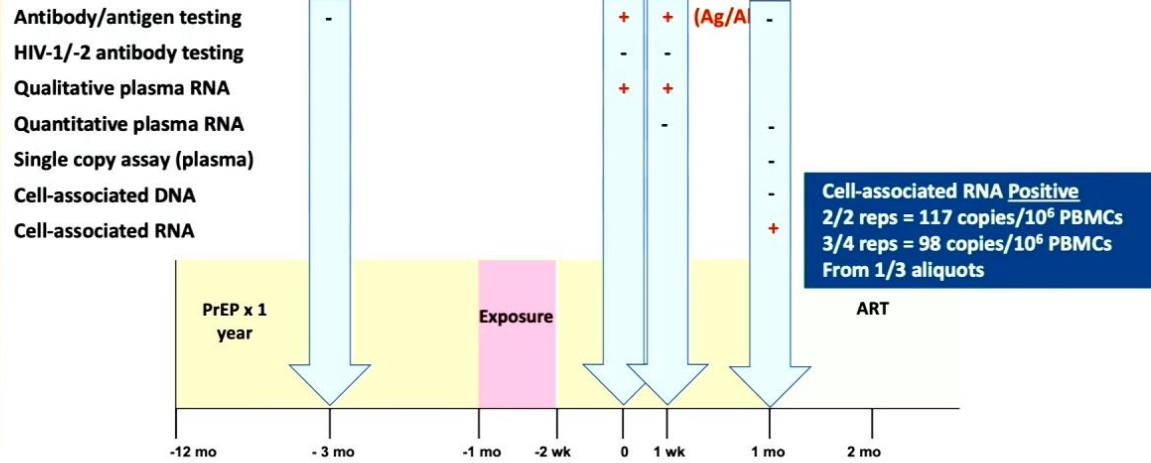
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4drug ART was started

Viral load not detectable with assay with lower limit of <40 cps/ml

Case 2: PrEP “Overwhelmed”?



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Case 2: PrEP “Overwhelmed”? Key Points

1. Objective adherence measures can add clarity to these cases (lack of adherence metric major limitation in this case)
2. Hypothesis-generating case
3. Sero-reversion occurred and research assays needed to confirm diagnosis
4. PrEP might be “overwhelmed” despite reported daily adherence
 - Statistical modeling posits >90 sex acts per month may overwhelm
 - One previously reported case

Desai et al BMJ 2017, CROI 2017 abstract #953

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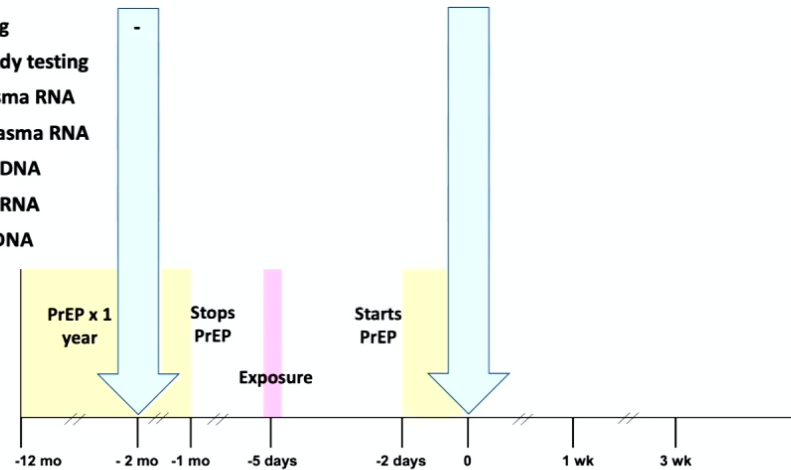
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Case 3: Infection Aborted with PrEP as PEP?

- Antibody testing
- HIV-1/-2 antibody testing
- Qualitative plasma RNA
- Quantitative plasma RNA
- Cell-associated DNA
- Cell-associated RNA
- Intact proviral DNA



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Partner pos (708000 cps/ml)

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Case 3: Infection Aborted with PrEP as PEP?

Antibody testing
 HIV-1/-2 antibody testing
 Qualitative plasma RNA
 Quantitative plasma RNA
 Cell-associated DNA
 Cell-associated RNA
 Intact proviral DNA

-12 mo -2 mo -1 mo -5 days -2 days 0 1 wk 3 wk

PrEP x 1 year Stops PrEP Exposure Starts PrEP ART

+ (Detected, <20)

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3 drug ART, less than 20 copies/ml but detectable signal

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Case 3: Infection Aborted with PrEP as PEP?

Antibody testing
 HIV-1/-2 antibody testing
 Qualitative plasma RNA
 Quantitative plasma RNA
 Cell-associated DNA
 Cell-associated RNA
 Intact proviral DNA

The diagram shows a timeline from -12 months to 3 weeks. Key events include: PrEP x 1 year (from -12 mo to -2 mo), Stops PrEP (at -1 mo), Exposure (at -5 days), Starts PrEP (at -2 days), ART (at 0), and another ART event (at 1 wk). Testing results are shown as vertical arrows: HIV-1/-2 antibody testing is negative (-) at -2 mo, 0, and 1 wk. Qualitative plasma RNA is negative (-) at -2 mo, 0, and 1 wk. Quantitative plasma RNA is positive (+) at 0 and negative (<20) at 1 wk. Cell-associated DNA, Cell-associated RNA, and Intact proviral DNA are all negative (-) at 0 and 1 wk.

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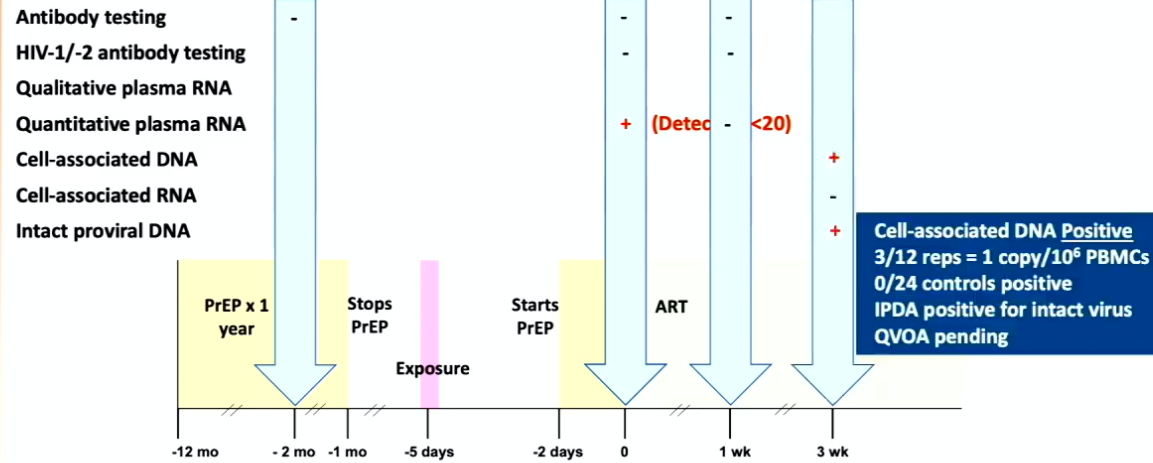
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Not detected with <40 cps/ml

Case 3: Infection Aborted with PrEP as PEP?



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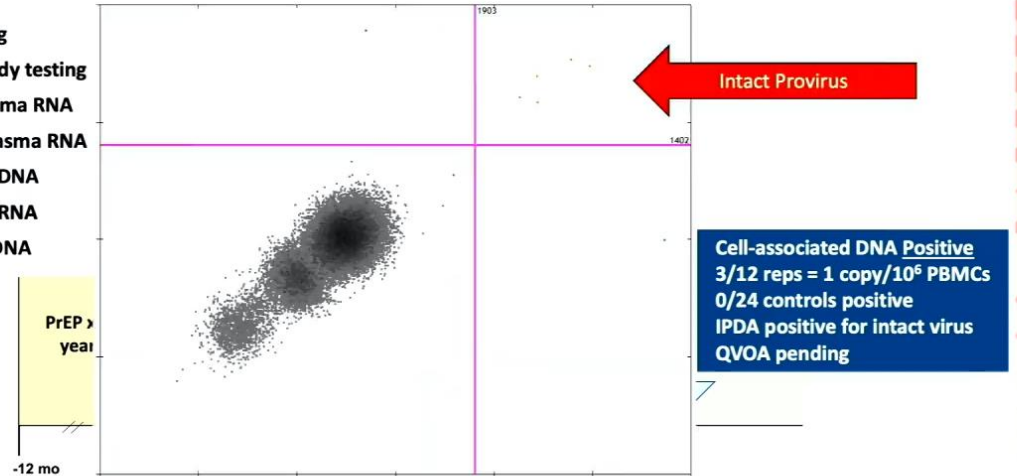
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Case 3: Infection Aborted with PrEP as PEP?

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- Cell-associated RNA
- Intact proviral DNA



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Case 3: Very Early Treatment

1. Initially thought this participant had aborted infection (PrEP at 72 hours, full ART at 5 days)
2. Prior work has reported early diagnosis and initiation of PrEP at 10 and 12 days following HIV acquisition. If confirmed, this might be the earliest documented treatment of HIV infection to date
3. A 72-hour window with 2-drug PEP may be insufficient to prevent establishment of the HIV reservoir
 - NHP model suggested that reservoir is established within 72 hours
4. Further study could reveal important insight into reservoir establishment and immune response at the earliest time points following transmission

Henrich et al PLoS Med 2017, Whitney et al Nature 2014

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Summary/Conclusions

- PrEP confers significant benefit in the vast majority of cases
- HIV/PrEP overlap leads to challenges in diagnosing HIV infection
- In such cases, three factors must be adjudicated:
 - Host responses
 - Virologic factors (e.g., resistance)
 - Objective adherence metrics*

*Mancilla CROI 2020 Abstract 160

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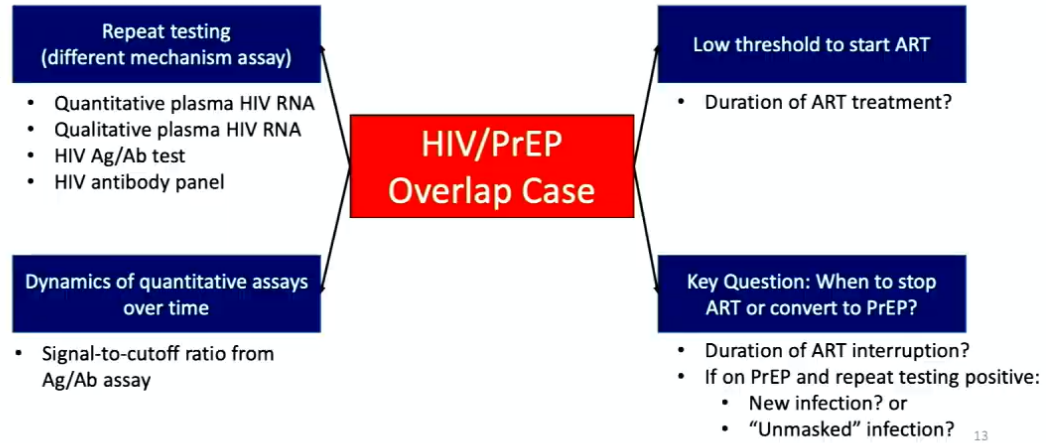
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Challenging Cases: A Suggested Approach



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- amfAR (Deeks)

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