Case Examinations of Difficult HIV Diagnoses

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Case #1

- **“Do I Have HIV or Not? Lack of RNA Detection and the Case for Sensitive DNA Testing”**

Sandra A. Springer, Silvina Masciotra, Jeffrey A. Johnson, and Sheldon Campbell. *Open Forum Infectious Diseases 2020*

A 20-year-old male who had ambiguous HIV test results after entering new provider care

› The individual reported at the visit that he had been diagnosed with **HIV-1 (RT+)** during routine military academy admission testing in **July 2018**, discharged from the military academy, and referred to a nearby academic ID clinic 1 month later.

› He reported that he received an **HIV-negative test result the year before entrance** into the military academy at a local walk-in clinic; he also reported that he had not been taking pre-exposure prophylaxis (PrEP) at that time.

› One month after this initial HIV-1 antibody diagnosis and **3 days before his follow-up ID visit, HIV-1 RNA viral load (VL) testing** was performed, but the VL results were not yet available at the time of the ID visit; did have a result of **HIV-1 pos by Ab diff**.

› At the ID visit, the individual reported to the provider that he had recently become sexually active and had engaged in receptive condomless anal intercourse with male partners of unknown HIV status that year, including **~1 month before the test result** on his admission to the military academy.

Case # 1

Table 1. Summary of HIV Test Results Performed in 2018–2019 in the Investigation of Infection Status of a 20-Year-Old Male

Sample Date	Procedure	Method	Result
Before VA Presentation: July 2018–March 2019			
July 31, 2018	HIV Ab serum test	Unknown at military academy	HIV-1 Ab positive
September 4	HIV supplemental assay	Geenius	HIV-1 Ab positive
	HIV-1 RNA quantitative	Roche Cobas at ID clinic	28 copies/mL (test done 9/4 but results reported after 9/7/18)
September 7	Treatment initiation	Dolutegravir + tenofovir/emtricitabine	
October 8	HIV-1 RNA quantitative	Roche Cobas at ID clinic	Not detected
December 8	Treatment change	Bictegravir/TAF/emtricitabine	
January 2019	HIV-1 RNA quantitative	Roche Cobas at ID clinic	Not detected
March 2019	HIV-1 RNA quantitative	Roche Cobas at ID clinic	Not detected
Start of VA Presentation: August 2019			
August 19	HIV screening assay	Architect at VACHS	Repeatedly reactive S/CO 2.63
	HIV supplemental assay	Geenius at VACHS	HIV-1 indeterminate
	HIV-1 RNA quantitative	Roche Cobas at VACHS	Not detected
	HIV screening assay	HIV combo Ag/Ab EIA at CT DPH laboratory	Repeatedly reactive
	HIV supplemental assay	HIV Ab differentiation assay at CT DPH laboratory	HIV-1 indeterminate
	HIV-1 RNA quantitative	Roche Cobas at CT DPH	Not detected
August 30	HIV screening assay	Architect at VACHS	Reactive S/CO 2.27
	HIV supplemental assay	Geenius at VACHS	HIV-1 positive
	HIV-1 DNA qualitative	Lab-developed test at Quest	Not detected
	HIV-1 RNA quantitative	Roche Cobas at VACHS	Not detected
	HIV-1 coreceptor tropism, ultradeep sequencing	Lab-developed test at Quest	Test not performed, unable to amplify viral nucleic acid for sequence analysis due to low viral load or viral sequence heterogeneity
	T-cell subsets	Flow cytometry	CD3 + 4+# 811 CD3 + 4+% 50 CD4/CD8 ratio 2.20
September 2	HIV-RNA quantitative	Roche Cobas at VACHS	Not detected
	HIV-1 DNA qualitative	Lab-developed test at Quest	Not detected
September 6	Treatment stopped		
October 2	HIV screening assay	Architect at VACHS	Reactive S/CO 57.77
	HIV supplemental assay	Geenius at VACHS	HIV-1 positive
	HIV-RNA quantitative	Roche Cobas at VACHS	Not detected
October 25	Treatment restarted	Bictegravir/TAF/emtricitabine	
r 15	HIV screening assay	Architect at VACHS	Reactive S/CO 51.63
	HIV supplemental assay	Geenius at VACHS	HIV-1 positive
	HIV-RNA quantitative	Roche Cobas at VACHS	Not detected
	T-cell subsets	Flow cytometry (VACHS)	CD3 + 4+# 774 CD3 + 4+% 51 CD4/CD8 ratio 0.61
	HIV-1 drug resistance proviral DNA, deep sequencing	Lab-developed test at Quest	HIV proviral DNA: Detected HIV subtype: B (no ART-related mutations detected)
November 22	HIV screening assay	Architect	Reactive S/CO 44.15
	HIV-RNA quantitative	Roche Cobas	Not detected
	HIV screening assay	Bio-Rad GS HIV combo Ag/Ab EIA at CDC	Repeated reactive
	HIV supplemental assay	Geenius at CDC	HIV-1 positive
	HIV-1 RNA qualitative	Aptima HIV-1 RNA qualitative assay at CDC	Not detected

16 months to resolve HIV status.

- Required coordination with the laboratory testing done at the VACHS, commercial laboratories, and the CDC.

Case #2

Pregnancy: received through national Perinatal HIV Hotline

- Woman 2nd TM ~13wks GA

› Tested non-reactive during prior two pregnancies by patient report, was living in Eastern Europe at the time.

› OB ordered **initial *prenatal* screening labs** – processed at commercial lab: **reactive HIV Ag/Ab, and reactive HIV-1 Ab with non-reactive HIV-2 Ab (S/C ratio was 9.2)**.

› **HIV-1 viral load (assay unknown) resulted as target not detected**. Current partner reports neg home HIV screen, no other known exposures outside of current partner.

› Local Public Health Lab able to test specimens and ran **HIV-1 NAT on two different platforms, both resulted as TND**.

› Patient consented to repeat screening (sample drawn **~1 month after initial reactive screen), again reactive HIV Ag/Ab and reactive HIV-1 Ab with NR HIV-2 Ab**.

› **Follow up WB performed at commercial lab interpreted as positive (bands at p24, gp40, p55, gp160; +/- at gp41, gp120); also ran qualitative DNA which came back not detected**.

- Peds ID elected not to prescribe maternal ART due to suspected controller status. Infant delivered mid-January.

› Infant RNA TND; DNA PCR not performed.

Case #3

Received through national HIV Warmline

› Cis-female wishing to conceive in near future, presented to clinic requesting HIV **screening mid-November 2021**. Clinic performed **POC screen using 2 different HIV assays, and both were reactive**.

› Specimen collected to **send out for differentiation: HIV-1 Ab indeterminate and HIV-2 Ab negative**. **Two HIV VL (quantitative RNA) drawn a few days apart reported as not detected**. Had COVID infection about 2 months prior to these results, no known h/o autoimmune disorders.

- Sexually active with multiple cis-male partners, current partner is PWH with unknown ART use/VL suppression.
- On further patient history/review of chart, provider found notes indicating she had been seen **in ED ~2-3 months prior** for unrelated reason and had a **reactive POC HIV Ag/Ab, with negative HIV-1 Ab and negative HIV-2 Ab** on differentiation assay. **However, qualitative RNA was <u>detected</u>** (this ED visit was a few weeks prior to the COVID diagnosis). No known PrEP or PEP use.
- Combo RT pos, diff neg, RNA pos = = acute. HIV RNA qual reactive then RNA quant NR two months later

Case #4

Received through PrEPline

› Cis-male multiple sex partners (other cis M), one of whom might be PWH.

› **Established PrEP care 9/2020** and subsequently maintained on daily F/TDF reported near 100% adherence. Tested for HIV at ~6mo intervals (travel), **last negative test a year prior (9/2021)**.

› At PrEP f/u visit **2/2022, POC Determine Ag/Ab had "shadowy" reactivity at Ab line (nurse repeated immediately and saw same results).** Blood drawn and sent for instrument-based HIV Ag/Ab which was performed at Public Health Lab.

› **PHL testing results: reactive HIV Ag/Ab, diff reactive HIV-1 Ab and NR HIV-2 Ab. DNA PCR also run by PHL which came back TND**.

› Patient counseled to stop PrEP while status clarified → **quantitative RNA** drawn at local Ryan White clinic **~1 week later** (sent to commercial lab) resulted as **detected, < 20 copies/mL**.

› **A few weeks later**, POC Determine again reactive for Ab and blood drawn/send to Public Health Lab → HIV **Ag/Ab combo again reactive but now indeterminate on HIV-1 Ab and NR HIV-2 Ab . DNA PCR again TND**.

- Pt was informed of having acquired HIV and was prescribed ART.

Case #5

Received through PrEPline

-Cis-male h/o multiple STIs. Unknown COVID, vaccination history.

› Initiated F/TDF as PrEP 7/2019, **"rapid" HIV Ag/Ab non-reactive** at initial visit. He also **reported recent negative HIV screen 2 weeks prior** at outside clinic/agency.

› **At 3-month follow-up**, pt reported 100% medication adherence; testing: **HIV Ag/Ab reactive, with indeterminate HIV-1 Ab and negative HIV-2 Ab**. **Quantitative NAT reported reactive**, but no exact value provided.

› He was recalled for repeat testing, which was completed **~1 wk later: HIV Ag/Ab again reactive with indeterminate HIV-1 Ab and negative HIV-2 Ab. Another quant RNA drawn, resulted as reactive, 40 copies/mL**.

› Care provider at that point counseled as new diagnosis, started DTG/3TC treatment

› **6 months later**, pt seen in ER for unrelated concern and accepted offer of HIV screening by ER staff (was still prescribed DTG/3TC at that time, reportedly adherent), test **results: HIV-1/2 Ab negative**. Then referred to current care provider who ordered **repeat HIV screen and again HIV-1/2 Ab negative**.

- Pt. went under care by new provider and lost to follow-up regarding additional testing.

Case #6

Received through PrEPline

› Cis M on daily F/TAF since October 2021. Reports sexually active with 1 other cis M partner who is on PrEP.

› PrEP monitoring testing:

- Pt had **non-reactive HIV Ag/Ab on 6/2022 and quantitative VL was TND** from same day (commercial lab).
- On **8/2022, HIV Ag/Ab was non-reactive; viral load was ordered but not performed** for unknown reason. No acute HIV symptoms.
- On **9/2022, HIV Ag/Ab still non-reactive; however, VL drawn same day reported as 186 copies/mL**.

▪ MH only notable for genital HSV and multiple prior STIs

› Repeat testing :

› **10/2022 HIV Ag/Ab and HIV-1 RNA quantitative were both non-reactive** → joint decision to restart PrEP in setting of potential false positive viral load from mid-September

▪ **12/2022 HIV Ag/Ab and HIV-1 RNA quantitative again both non-reactive**

▪ ***Only RNA quant was reactive, then month later NR. No serologic reactivity***

Case #7

Received through PrEPline

› Patient with remote h/o IDU (last use 3 yrs ago); in serodiscordant partnership with PWH with same care provider and on ART with stable virologic suppression.

› **8/2021, negative HIV Ag/Ab screen**, pt was initiated on daily F/TDF as PrEP (reports missing no more than 1-2 doses/week)

› Late **May 2022, VL of 1410** and was subsequently referred to care provider for initial HIV evaluation and *PrEP suspended* – no HIV Ag/Ab done at time of this VL.

› On **6/2022, HIV Ag/Ab was non-reactive, and HIV VL was TND** (had been off F/TDF for about a month at this point).

- After consultation with NCCC, caller reached out to lab which performed **5/2022 VL testing** and they still had stored sample→ sample sent to blood bank which performs HIV screening, and **HIV Ag/Ab was reactive, but differentiation neg for both HIV-1 Ab and HIV-2 Ab. Confirmed prior VL**.

- ***HIV RNA quant reactive one month and NR following month; no Ab diff reactivity***

Recent cases involving pregnancy

Since the last quarter of 2022 CDC has been contacted about **5 separate cases of ambiguous HIV diagnostic results involving pregnant women** in different states

- All have been **Ag/Ab combo screen reactive and result as HIV-1 positive in Ab differentiation** assay
- Four have been **HIV RNA and DNA not detected**, 5th not performed
- Retesting currently underway at our CDC reference laboratory for 3 cases:
  - 3/10/2023 – thus far, two women (NAT NR) are confirmed HIV-1 by Western blot

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HIV/AIDS Warmline **800-933-3413**	HIV treatment, ARV management, complications, and co-morbidities
Perinatal HIV Hotline **888-448-8765**	Pregnancy, breastfeeding and HIV
Hepatitis C Warmline **844-HEP-INFO/** **844-437-4636**	HCV testing, staging, monitoring, treatment
Substance Use Warmline **855-300-3595**	Substance use evaluation and management
PrEPline **855-HIV-PrEP**	HIV Pre-exposure prophylaxis
PEPline **888-448-4911**	Occupational & non-occupational exposure management

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.