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Short Communication

POCT in HIV Diagnosis and Treatment: Addressing Challenges in Seminal Viral Load Testing

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Introduction

Point-of-care Testing (POCT) has transformed HIV care by enabling rapid, decentralized, and widely accessible diagnostics, particularly in resource-limited settings [1]. Currently, blood-based Viral Load (VL) testing remains the cornerstone for monitoring Antiretroviral Therapy (ART) effectiveness. However, expanding POCT to include Seminal Viral Load (SVL) testing is garnering interest due to its implications in sexual transmission, reproductive health, and ART efficacy in male genital compartments.

POCT for SVL could provide real-time insights into transmission risk, especially for serodiscordant couples, ART monitoring, and fertility counseling. Its integration into routine care can enhance clinical decision-making, yet its development faces both biological and technological constraints [2].

Significance of Seminal Viral Load assessment

SVL serves as a crucial biomarker for the potential of HIV transmission, particularly in serodiscordant relationships. Even when ART successfully suppresses the virus in the bloodstream, some individuals may continue to exhibit detectable levels of HIV RNA in their semen, posing a risk of transmission. Incorporating SVL testing into routine POCT could enhance strategies for HIV prevention, inform reproductive planning, and support individualized treatment adaptations [3]. Routine SVL POCT could support safe conception practices, contribute to prevention strategies, and individualize ART regimens by revealing latent HIV reservoirs in the male genital tract.

Key challenges in Seminal Viral Load testing

1. Biological Complexity of Semen

Semen comprises spermatozoa, leukocytes, epithelial cells, and seminal plasma, resulting in significant inter-sample variability. The presence of proteases and RNases complicates RNA extraction and integrity preservation [4].

2. HIV distribution across seminal components

- Cell-free HIV RNA is primarily located in the seminal plasma.
- Cell-associated HIV DNA and RNA reside within leukocytes and possibly spermatozoa [5].
- Viral levels vary across compartments and timepoints, leading to mismatch between blood and SVL measurements.

3. Technical and Methodological Hurdles

- No universal protocol exists for semen handling, leading to inconsistencies in test outcomes.
- Viscosity and cellular debris hinder efficient RNA extraction.
- Pre-treatment methods, such as dithiothreitol application and enzymatic digestion are often required.

4. Proviral HIV in Semen Cells

- HIV provirus integration into seminal leukocyte DNA forms a persistent reservoir.

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- Advanced techniques like digital droplet PCR (ddPCR) and single-cell sequencing are needed for detection in semen-derived leukocytes.
- However, these remain incompatible with field-deployable POCT platforms.

Procedures for SVL testing

Sample collection and processing

- Semen should be collected in sterile containers after 48 hours of sexual abstinence to ensure reliable viral load quantification.
- Immediate sample processing is vital to prevent degradation of RNA.
- Centrifugation is used to separate plasma from cellular content.

A 48-hour sexual abstinence period standardizes semen composition, minimizing variability in seminal plasma volume and leukocyte count, both of which significantly influence RNA yield.

RNA extraction and quantification

- Conventional plasma RNA kits are generally unsuitable due to semen's complexity.
- Techniques like silica column purification and magnetic bead isolation are more effective for extracting RNA.
- Real-time PCR and reverse transcription ddPCR are commonly employed for quantification, offering greater sensitivity.

Both silica column and magnetic bead-based methods are generally preferred over standard plasma extraction kits. A comparison of the two reveals that silica columns are reliable but necessitate centrifugation and careful elution steps to prevent RNA loss, whereas magnetic beads offer scalability and are well-suited for automated workflows [6].

Detection of proviral HIV DNA

- Specialized lysis protocols are essential to access intracellular HIV DNA.
- Nested PCR and next-generation sequencing can help detect integrated viral sequences.Emerging tools like single-cell RNA sequencing may provide detailed insights into viral expression at the cellular level.
  - Requires cell lysis buffers (e.g., SDS + proteinase K) to access nuclear DNA.
  - Nested PCR, qPCR, and Next-generation Sequencing (NGS) are used [7].
  - Recent advances in single-cell RNA-seq and CRISPR diagnostics show promise for detecting integrated provirus.

Future perspectives

Developing POCT tools for SVL

- Lab-on-a-chip and microfluidic platforms may enable rapid SVL detection at the point of care.
- Isothermal amplification techniques such as LAMP could serve as an affordable and efficient alternative to PCR-based methods.
- Microfluidic chips and lab-on-a-chip devices offer rapid, miniaturized SVL quantification [8].
- Isothermal amplification (e.g., LAMP) eliminates the need for thermal cycling and reduces turnaround time [8].

Standardizing testing protocol

- Consensus guidelines for semen processing and RNA extraction are needed to enhance result consistency.
- Automated testing platforms could help minimize procedural variability.
- There is an urgent need for a global consensus on semen collection, pre-treatment, and processing.
- Automation and cartridge-based platforms could enhance procedural reproducibility and operational simplicity.

Utilizing genomic innovations

- Emerging technologies such as nanopore sequencing and CRISPR-based diagnostics may facilitate detection of low-level viral presence.
- AI-based analytics may enhance the accuracy of SVL trend interpretation of viral load changes.
- Nanopore sequencing enables real-time viral genome detection in unamplified RNA.
- CRISPR-based diagnostics (e.g., SHERLOCK) may allow low-cost, rapid identification of HIV nucleic acids. [9].

Clinical relevance for reproduction and prevention

- SVL POCT can empower serodiscordant couples to conceive safely.
- It strengthens public confidence in U=U (Undetectable = Untransmittable) messaging, especially when validated in both blood and seminal samples [10].

Conclusion

SVL testing represents a cutting-edge approach in the evolution of next-generation HIV diagnostics. To enable its effective implementation in Point-of-care Testing (POCT), challenges such as biological variability, technical constraints, and lack of standardization must be addressed. Future progress

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should focus on translating laboratory innovations into practical field solutions, supported by robust clinical validation studies. Expanding the use of SVL POCT has the potential to transform HIV care, especially in reproductive and preventive health contexts [11].

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