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Advancements in HIV Diagnosis Using Urine: A Review of Virological Characteristics, Detection Technologies, and Clinical Applications

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ABSTRACT

Early diagnosis and monitoring of HIV infection are crucial for disease management and control. Urine, as a non-invasive and easily collected sample type, offers unique benefits in the field of HIV diagnosis. In recent years, research on using urine to screen for HIV has gradually increased, covering the dynamic characteristics of the virus in urine, relevant virological studies, and detection technologies for HIV-related biomarkers in urine. Additionally, the application of urine in screening for co-infections (such as tuberculosis, CMV, HPV) has attracted widespread attention. This article reviews the promising potential of urine testing in monitoring treatment adherence and organ transplantation, analyzing the sensitivity, specificity, and application prospects of urine HIV testing in different populations by integrating the latest molecular diagnostic technologies and clinical research findings. It also discusses the current challenges and future directions, providing new ideas and methods for the early diagnosis of HIV and promoting the progress of related medical research.

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Key Words: HIV diagnosis; Urine testing; Virological characteristics; Molecular diagnostics; Antiretroviral therapy; Co-infection; Treatment adherence monitoring

Abbreviations: HIV, Human Immunodeficiency Virus; LAM, Lipoarabinomannan; HOPE Act, HIV Organ Policy Equity Act; ART, Antiretroviral Therapy; SGA, Single-gene Amplification; CMV, Cytomegalovirus; PrEP, Pre-exposure Prophylaxis; sIR, soluble Insulin Receptors; LC-MS/MS, Liquid Chromatography-tandem Mass Spectrometry;HPV, Human Papillomavirus; TFV, Tenofovir.

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Introduction[1-6]

The global epidemic status of HIV (human immunodeficiency virus) and the importance of early diagnosis are crucial. According to data from the World Health Organization, approximately 38 million people worldwide are infected with HIV, most of whom live in low- and middle-income countries. The transmission of HIV primarily occurs through unsafe sexual practices, sharing needles, and mother-to-child transmission. Although antiretroviral therapy (ART) has significantly improved the survival rates of those infected, the epidemic worsens because many individuals do not receive timely diagnosis and treatment after infection. Therefore, early diagnosis can help reduce virus transmission, improve treatment outcomes, and enhance the quality of life for patients.

Early diagnosis is key in HIV management. Studies have shown that early diagnosis can significantly reduce the incidence of HIV-related complications and improve the success rate of antiretroviral therapy. However, traditional HIV testing methods mainly rely on blood samples, which have limitations in certain situations. For example, the blood collection process may cause discomfort for some patients, and in resource-limited settings, the transporta--tion and storage of blood samples pose challenges. Therefore, finding alternative samples to improve the convenience and accessibility of HIV testing has become an urgent issue.

Urine, as a potential alternative sample, holds great promise. The urine collection process is non-invasive and easy to perform, making it particularly suitable for high-risk populations and young individuals. Moreover, urine contains various biomarkers associated with HIV infection, which can be used to assess infection status and disease progression. Studies have found that HIV-specific antigens and antibodies can be detected in urine, and the results correlate with blood tests. This finding provides a theoretical basis for the application of urine in the early diagnosis of HIV.

With the continuous development of new detection technologies, the accuracy and sensitivity of urine tests for HIV are continually improving. For example, digital PCR technology can detect extremely low concentrations of HIV in urine samples. Additionally, new rapid testing tools such as urine Lipoarabinomannan (LAM) detection can quickly and effectively screen for HIV infection in clinical practice. These technological advancements make urine testing a feasible method for early HIV diagnosis, especially in resource-limited environments.

In summary, early diagnosis of HIV is of great significance in global public health. As home urine self-testing can cover both HIV-1 and HIV-2 viruses, the application of urine as an alternative to blood samples not only enhances the convenience of testing but also

provides possible solutions for early detection and intervention. With advancements in related technologies, the compliance and low-risk nature of urine self-testing in HIV diagnosis will become increasingly important, providing new momentum and direction for the global fight against the HIV epidemic.

Virological Characteristics and Dynamics of HIV in Urine[1]

1 Differences in Distribution of HIV-1 in Urine, Blood, and Semen

The differences in the distribution of HIV-1 in different bodily fluids are important for understanding its transmission and infection mechanisms. Studies have shown that the detection rate of HIV-1 in urine can be as high as 95%, while the detection rate in semen is about 75%. This difference suggests that the kidneys may serve as a significant viral reservoir, reflecting the dynamic changes of HIV-1 in the body. This high detection rate may be related to the relatively high viral concentration in urine, thus supporting the use of urine as a biomarker for detecting HIV-1.

Furthermore, studies have found a phenomenon of compartmentalization of HIV-1 in different bodily fluids. This means that although HIV-1 may exist in blood, urine, and semen, its specific viral subtypes or variants may differ in distribution among these fluids. Specifically, some studies have indicated that the HIV-1 env gene sequences detected in urine may differ from those found in blood, suggesting that the kidneys may serve as an independent site for viral replication. Notably, in some patients, the persistent HIV-1 env sequences in urine show significant differences from those in blood, indicating that localized viral replication may occur in the kidneys.

Further research has shown that the viral populations in the kidneys remain consistent over time, supporting the phenomenon of localized replication of the virus in this site. This phenomenon is particularly important for understanding the transmission mechanisms of HIV-1 and the effects of antiviral treatment. Additionally, this localized replication of HIV-1 may lead to different responses to antiviral therapy, affecting clinical management and the development of individualized treatment strategies.

Overall, the differences in the distribution of HIV-1 in urine, blood, and semen, as well as the phenomenon of localized replication, provide new insights into the transmission and infection of HIV-1. Future research should further explore the potential of urine in HIV-1 detection and its role in infection control to better understand and utilize this biomarker to reduce the risk of HIV transmission. At the same time, this also provides foundational data support for the development of new HIV detection technologies and treatment strategies.

2.Long-term Isolation and Dynamic Changes of Viral Populations

In HIV-infected individuals, the viral populations in urine persist and show significant differences from those in blood. Studies have shown that the HIV-1 viral population in urine has a certain degree of isolation, meaning that these viruses may replicate locally in the urogenital tract and maintain relatively independent viral population characteristics. Specifically, in an analysis of 19 HIV-1 positive participants, HIV-1 env gene sequences were detected in 100% of blood samples, while 95% were detected in urine samples, indicating that the presence of the virus in urine is relatively stable. This phenomenon of viral isolation is also reflected in the dynamic changes and distribution of the virus in different sample sources (such as urine and semen), with significant differences observed in the HIV-1 env sequences detected in urine and semen in some participants, further supporting the local replication and isolation of viral populations in the urogenital tract.

Additionally, the dynamic differences of viral populations in different parts of the urogenital tract are also noteworthy. For example, analysis of HIV-1 env gene sequences from the urogenital tract shows temporal stability between urine and blood samples, suggesting that the viral populations in urine may maintain unique genetic characteristics and dynamic changes over time. These results align with the mechanisms of localized viral replication within the urogenital tract, indicating that the analysis of urine samples may provide important clues for understanding the transmission and pathological mechanisms of HIV.

In summary, the long-term isolation and dynamic changes of viral populations in urine reveal the complex biological characteristics of HIV in the urogenital tract, which not only aids in understanding the transmission pathways of the virus but also provides new insights for urine as a biological sample for HIV detection and monitoring. Future research should delve deeper into the genetic characteristics of viral populations in urine and their relationship with clinical outcomes to promote the development of early diagnosis and treatment strategies for HIV.

3.Detection of Virus in Urine of HIV-positive Kidney Transplant Recipients

In HIV-positive kidney transplant recipients, detecting donor virus in urine after surgery is clinically significant. According to a study, the HIV Organ Policy Equity Act (HOPE Act) allows HIV-positive patients to receive organs from HIV-positive donors. While this practice expands the available organ pool, it also raises important virological issues, such as the potential for superinfection in recipients, persistent presence of the virus in the kidneys, and loss of virological control[7].

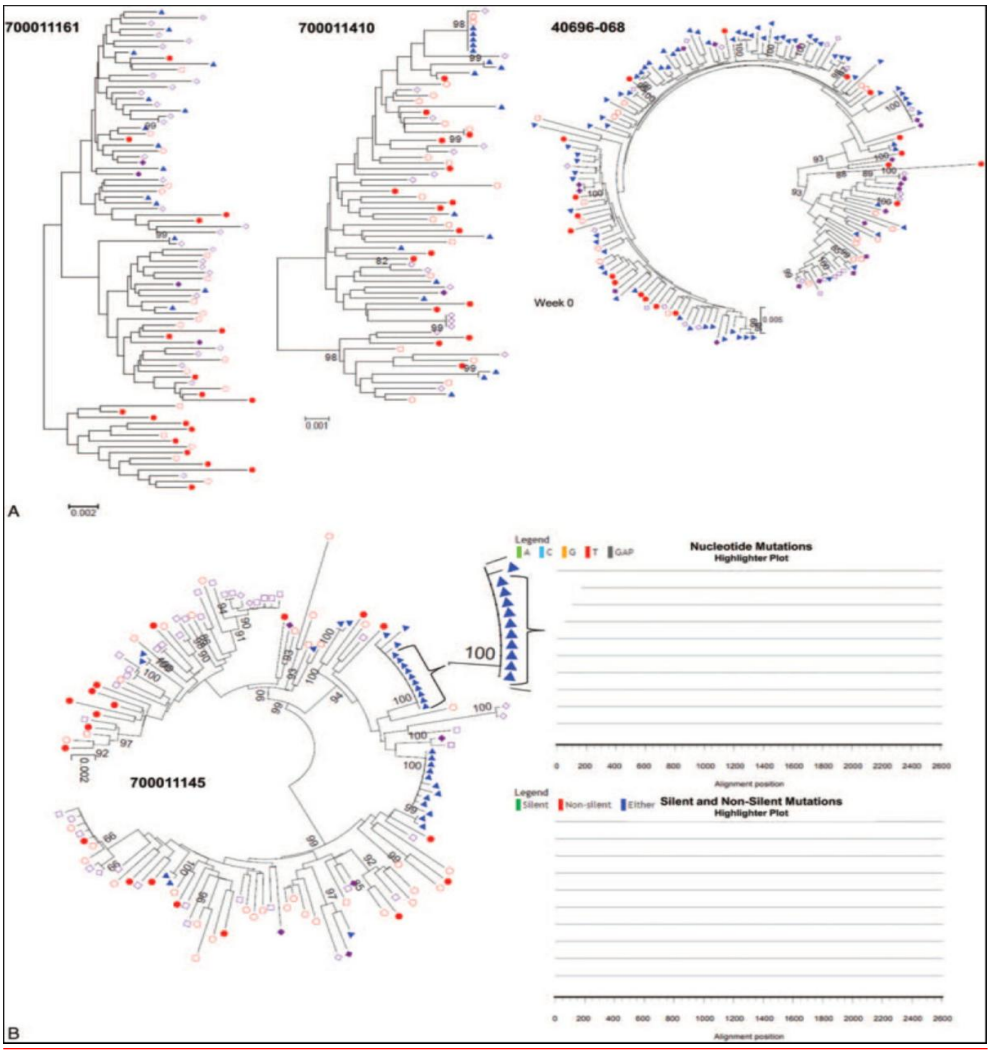

Figure1: Phylogenetic analysis of urine, semen, and blood demonstrates viral equilibrium between urine and semen in some participants and compartmentalization of urine-derived sequences in others[1]. (a) Neighbor-joining phylogenetic tree of full-length env sequences obtained via SGA from urine supernatant, blood plasma, blood PBMCs, semen supernatant, and semen cells from 4 participants. Viral equilibrium between urine and semen was observed in participants 700011161, 700011410, and 40696–068. (b) Compartmentalization of urine-derived viruses was observed in participant 700011145. PBMC SGA-env sequences (full red circles), plasma SGA-env sequences (open red circles), seminal cell SGA-env sequences (full purple diamonds), seminal plasma SGA-env sequences (open purple diamonds), and urine SGA-env sequences (blue triangles). Bootstrap values ⩾80 are shown. Genetic distance is indicated at the bottom of the figure and represents the number of nucleotide substitutions per site.

After kidney transplantation, studies have found that donor HIV-1 env sequences can be amplified and detected in urine, indicating that donor virus is present in the recipient's urine and can be identified shortly after surgery, lasting up to 16 days. This detection can provide important information for clinicians to assess the dynamic changes of the virus post-transplant and the possible clinical consequences.

In one HIV-1 positive kidney transplant recipient, it was demonstrated that the virus in urine was genetically different from the virus found in blood but closely related to renal epithelial cells from urine[7,9], supporting the notion that renal epithelial cells are a source of urine virus. In addition to renal epithelial cells, some urine-derived viruses may originate from interstitial lymphocytes or macrophages within the kidneys. The observed diversity of viruses in urine may also result from ongoing viral transfer between infected lymphocytes and macrophages and renal epithelial cells, as previously demonstrated in vitro[10,11], which may sustain the replication and evolution of HIV-1 in this site.

Regarding the dynamic relationship between donor and recipient viruses, studies have shown that in some cases, donor virus can be detected in urine while only recipient virus is detected in blood. This distribution pattern of the virus may reflect different dynamics in various body compartments. For example, one recipient experienced a viral rebound 3.5 years post-transplant due to interruption of ART, but only the recipient virus sequence was detected in their blood, indicating that the donor virus had not been reactivated in that patient[7]. Understanding this dynamic relationship is crucial for assessing the virological control of the recipient, developing individualized ART regimens, and monitoring potential super--infection risks.

Clinically, monitoring the virus in urine not only helps physicians assess the virological status of patients post-transplant but also provides information about the effectiveness of antiretroviral therapy. By monitoring donor virus in urine, physicians can better understand the patient's immune status and adjust treatment strategies as necessary to improve transplant success rates and patient quality of life. This emerging detection technology demonstrates its potential in clinical practice, providing new ideas and tools for managing HIV-positive kidney transplant recipients.

Advances in Detection Technologies for HIV-related Biomarkers in Urine

1.Detection Technologies for HIV Viral Nucleic Acids

In monitoring and managing HIV infection, viral nucleic acid detection technologies play a crucial role. The application of single-gene amplification (SGA) technology in the analysis of viral populations in urine offers a new approach

for early HIV diagnosis. SGA technology can amplify specific regions of the HIV genome at the single-copy level, allowing for the detection of the virus during early infection. The high sensitivity and specificity of this technology make it an important tool for studying HIV variation and population structure. For example, studies have shown that SGA can effectively monitor the diversity of HIV-1, helping to assess the dynamics of virus transmission and treatment efficacy[4,12].

Additionally, the application of molecular diagnostic technologies such as Xpert MTB/RIF is not limited to detecting HIV itself but extends to detecting HIV-related co-infections. Xpert MTB/RIF is a rapid and sensitive detection technology that can simultaneously detect Mycobacterium tuberculosis and its resistance to rifampicin. This technology has shown high accuracy in detecting co-occurring tuberculosis in HIV-infected individuals, effectively improving early diagnosis capabilities for high-risk populations. This technology is particularly suitable for resource-limited areas, providing test results in a short time and significantly reducing the waiting time for patient treatment[2,8].

Furthermore, urine-based detection methods, such as urine LAM detection, have been proven to have high sensitivity in HIV-infected individuals, helping clinicians better manage the risk of co-infections[6].

As detection technologies continue to advance, the nucleic acid detection technology for HIV in urine is becoming increasingly important, especially in low-resource environments. These emerging technologies not only improve the early diagnosis rate of HIV infection but also provide better monitoring and management tools for patients. Future research can further explore how to optimize these technologies to enhance detection efficiency and accuracy for HIV infection in different populations.

2. Detection of HIV Proteins and Immune Biomarkers

The detection of HIV proteins and immune biomarkers in the urine of HIV-infected individuals provides new perspectives and methods for disease monitoring and management. This section will specifically discuss the detection of soluble insulin receptors (sIR) in urine and its association with neurocognitive impairment, as well as the detection of CMV-DNA in urine and its clinical value in HIV-infected individuals.

First, studies on sIR indicate that elevated sIR levels may be associated with the occurrence of neurocognitive impairment. Research shows that chronic inflammation and immune activation caused by HIV infection are closely related to damage to the central nervous system, thereby affecting cognitive function. As an inflammatory marker, the detection of sIR in urine provides a non-invasive method to assess these changes. Through quantitative analysis

of sIR levels in urine, researchers can find a significant correlation between elevated sIR levels and cognitive decline in HIV-infected individuals. Specifically, some studies have found that in HIV-infected patients, elevated sIR levels are associated with an increased risk of neurocognitive impairment, suggesting that sIR may serve as a potential biomarker for early identification and intervention of cognitive dysfunction[5].

Secondly, detecting CMV-DNA in urine is clinically valuable for managing HIV--infected individuals. Changes in cytokines and viral load can affect the immune status of HIV-infected individuals, and CMV infection often exacerbates this immune suppression. Studies have found that the positivity rate of CMV-DNA in urine is significantly higher in HIV-infected individuals than in healthy controls and is negatively correlated with CD4+ T cell counts and HIV RNA levels.

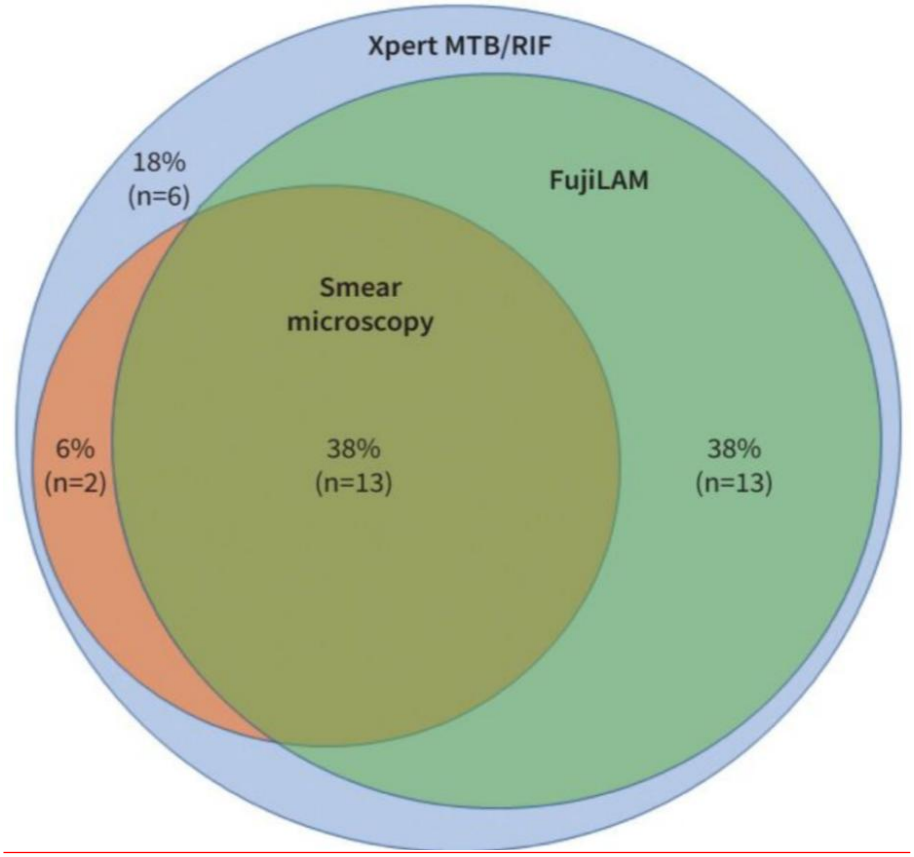

Figure2:Proportional Venn diagram showing the diagnostic sensitivity and number of culture-confirmed tuberculosis cases detected using different assays (n=34 patients)[6]

This indicates that the detection of CMV-DNA in urine can serve as a sensitive indicator of CMV infection in HIV-infected individuals and provide important information about the patient's immune status. By monitoring CMV-DNA, clinicians can better assess the patient's risk and adjust antiviral treatment regimens in a timely manner to improve clinical outcomes[13,14].

In summary, the detection of sIR and CMV-DNA in the urine of HIV-infected individuals provides new biomarkers for assessing disease progression and immune status. These detection methods offer important information through non-invasive means, aiding in the formulation of personalized treatment plans and improving the quality of life for patients. Future research can further explore the potential applications of these biomarkers in the management of HIV-related diseases to optimize treatment strategies and improve patient health outcomes.

3. Detection of Drug Metabolites

In modern drug monitoring, liquid chromatography-tandem mass spectrometry (LC-MS/MS) is a highly sensitive and specific detection technology widely used for analyzing drug metabolites in urine. Taking tenofovir as an example, studies have shown that LC-MS/MS technology can effectively detect tenofovir concentrations in urine, providing reliable evidence for assessing patient adherence[15]. Tenofovir is a drug used for the prevention and treatment of HIV infection, and its metabolites in urine can reflect the patient's adherence to antiviral therapy. By quantitatively analyzing tenofovir and its main metabolites in urine, clinicians can better understand the patient's medication situation and adjust treatment plans in a timely manner to improve treatment outcomes.

The detection of drug concentrations in urine also plays an important role in monitoring adherence to pre-exposure prophylaxis (PrEP) for HIV prevention. Clinical studies have shown that the detection of tenofovir in urine is closely related to the patient's clinical treatment response. Specifically, detecting tenofovir in urine can help doctors determine whether patients are taking their medication on time, further reducing the risk of HIV infection. This method not only improves the sensitivity and accuracy of monitoring but also makes personalized management of patients possible[16].

Additionally, recent studies have explored the detection of other drugs and their metabolites in urine. For example, the application of LC-MS/MS technology for various types of antibiotics, antiviral drugs, and their metabolites can provide more comprehensive drug monitoring data, helping doctors better assess the safety and effectiveness of medications for patients. The advancements in these detection technologies, especially in the context of precision medicine, provide a solid scientific

basis for clinical treatment.

Overall, the application of LC-MS/MS technology in detecting drug metabolites not only improves the accuracy and sensitivity of drug monitoring but also provides important decision support for clinicians[17]. As this technology continues to advance and improve, its application prospects in drug monitoring, adherence assessment, and personalized treatment will become even broader.

Application of Urine Testing in HIV-related Co-infections

1.Urine Testing in Tuberculosis Diagnosis

In recent years, urine testing has become increasingly important in diagnosing tuberculosis (TB), especially for HIV--infected individuals. The application of urine LAM and Xpert MTB/RIF Ultra combined testing has significantly improved the diagnosis rate of TB. For example, one study indicated that the addition of urine Xpert testing increased the TB diagnosis rate by 58% in newly diagnosed HIV patients[18]. This shows that urine testing can serve not only as a supplementary diagnostic tool for TB but also, in some cases, replace traditional sputum testing, especially in patients where sputum samples are difficult to obtain.

For advanced HIV patients, urine testing has shown great potential in the rapid screening of TB. Studies have shown that the combined use of urine LAM and Xpert Ultra can achieve rapid TB diagnosis within the same day. This method has higher sensitivity and specificity than single testing methods and can initiate treatment promptly, thereby reducing mortality due to TB[21]. Additionally, urine sample collection is relatively simple and non-invasive, making it suitable for large-scale screening in resource-limited environments.

In studies involving HIV-infected individuals, urine LAM sensitivity is especially notable in patients with CD4 counts below 100 cells/ μ L, making urine testing an effective screening tool for these high-risk populations. Research data show that urine LAM demonstrates 100% sensitivity in these patients, enabling timely identification of potential TB infections and facilitating timely treatment[19].

In summary, urine testing, especially the combined use of urine LAM and Xpert MTB/RIF Ultra, provides new possibilities for early screening and timely diagnosis of tuberculosis, particularly in the high-risk group of HIV-infected individuals. With advancements in testing technologies and the expansion of application scenarios, urine testing has the potential to become an important component of TB diagnosis, providing a reliable foundation for public health policy formulation and implementation.

2. Cervical Cancer and HPV Screening

In the prevention and treatment of cervical cancer, HPV (human papillomavirus) screening is a key component. The detection of HPV DNA in urine has gradually gained attention in recent years due to its non-invasive nature, which may increase screening acceptance and coverage. Studies have shown that the detection rate of HPV in urine samples is comparable to that in cervical liquid samples, and in some cases, it may even better reflect the presence of high-risk HPV types. For example, one survey indicated that the HPV positivity rate between urine samples and cervical samples reached 90.4% consistency, demonstrating the effectiveness of urine samples in HPV screening[20]. Furthermore, the sensitivity and specificity of HPV detection in urine show promising prospects, especially in the context of female self-sampling, where urine sampling is widely accepted and provides a convenient and comfortable screening method[21,22].

For HIV-infected women, the feasibility and application prospects of urine HPV testing are particularly important. Studies have shown that the HPV infection rate is higher among HIV-infected women, and they have a significantly increased risk of developing cervical cancer[23]. By detecting HPV in urine samples, an effective screening method can be provided for these high-risk groups, helping to identify potential cervical lesions early. Relevant studies have indicated that the presence of high-risk HPV in urine is significantly associated with the clinical pathological features of cervical cancer, particularly concerning the age and immune status of women, providing theoretical support for the clinical application of urine HPV detection technology[24,25].

In summary, the detection of HPV DNA in urine has significant potential in cervical cancer screening, particularly in improving screening coverage and acceptance. Future research should focus on optimizing the detection process for urine samples to enhance their accuracy and stability, thereby providing more reliable tools for early cervical cancer screening. Additionally, considering the promotion of HPV vaccination, combining urine HPV detection with screening methods can further reduce the incidence and mortality of cervical cancer, promoting public health improvement[26,27].

3. Detection of Other Viral Infections (e.g., CMV)

In HIV/AIDS patients, the detection of CMV infection has important clinical significance. Studies have shown that HIV infection can lead to uncontrolled replication of CMV, increasing the risk of CMV-related diseases. The detection rates of CMV DNA in various sites (such as the oral cavity, blood, etc.) are generally higher in co-infected patients. For example, in one study, the CMV detection rate in oral samples from HIV-infected individuals

reached 61%, while it was only 16% in non--HIV-infected populations[28]. Additionally, the detection rate of CMV DNA in urine among HIV/AIDS patients was 25.27%, comparable to that in blood, indicating that urine is an effective sample type for screening CMV infection[3].

Common manifestations of CMV infection in HIV/AIDS patients include CMV-related visceral diseases, particularly CMV retinitis and gastrointestinal diseases [29]. Research has shown that the CD4+ T cell count in HIV patients is closely related to the incidence of CMV infection, with patients having CD4+ T cell counts below 200 cells/mm3 being more susceptible to CMV infection[30]. Furthermore, the CMV viral load in HIV-infected individuals is significantly correlated with their immune status and clinical manifestations, with higher CMV viral loads associated with increased rates of pulmonary and cardiovascular visceral diseases[31].

For CMV detection methods, real-time quantitative PCR (qPCR) has high sensitivity and specificity in detecting CMV DNA, effectively identifying the presence of CMV in urine and other biological samples. For instance, one study using qPCR to detect CMV DNA in urine showed good clinical application value[3]. The detection of CMV DNA in urine can serve as an effective tool for screening CMV infection in HIV-infected individuals, especially in the absence of blood testing[28].

Overall, the detection of CMV infection in HIV/AIDS patients not only helps assess the patient's immune status but also provides guidance for clinical management. As understanding of the mechanisms of CMV infection deepens, specific treatment plans targeting CMV may be developed in the future to reduce the clinical risks associated with co-infection.

The Role of Urine HIV Testing in Treatment Adherence and Disease Monitoring

1.Urine Tenofovir Testing and Antiviral Treatment Adherence

Urine tenofovir testing plays an important role in assessing adherence to antiviral treatment. Studies have shown that the sensitivity and specificity of urine testing can effectively reflect the patient's medication usage. For example, in a study involving transgender women, the concentration of tenofovir detected in urine provided real-time feedback on adherence to antiviral treatment. This study found that the levels of tenofovir detected in urine were highly consistent with the patients' self-reported medication behaviors, enhancing confidence in the test results[31].

Additionally, the clinical acceptance of urine testing is relatively high, with patients generally considering this testing method acceptable and beneficial after appropriate counseling.

However, the study also mentioned a phenomenon known as "white coat dosing," where some patients intentionally adjust their medication usage when visiting healthcare providers to avoid being detected as non-adherent. In some cases, patients may restart their antiviral medications before going to the hospital to ensure positive test results, significantly affecting urine testing outcomes[31]. This phenomenon not only impacts the accuracy of urine testing but also reflects the patients' perceptions and psychological burdens regarding their treatment adherence.

In a study involving women, patients tested for tenofovir in urine showed significantly improved adherence to treatment. The study indicated that test results could serve as a basis for adherence counseling, and such strategies may enhance overall treatment effectiveness in clinical practice. Compared to traditional adherence assessment methods, urine tenofovir testing provides a more objective evaluation tool, helping healthcare providers adjust treatment plans in a timely manner to improve patient adherence and treatment outcomes[32].

Overall, urine tenofovir testing has broad application prospects in monitoring adherence to antiviral treatment, but potential patient behaviors affecting test results should also be considered. By ensuring patient education and psychological support, the clinical application effectiveness of urine testing can be effectively improved, providing patients with a better treatment experience.

2. Urine Viral Load Testing and Disease Progress Monitoring

Urine viral load testing, as a non-invasive method, has received increasing attention in HIV virology research in recent years. Studies have shown that the viral load in urine is significantly correlated with plasma viral load, providing a new perspective for clinically monitoring disease progression in HIV-infected patients. According to one study, the detectable levels of tenofovir (TFV) in urine closely correlate with changes in viral load, and in patients receiving antiretroviral therapy (ART), the detectability of urine TFV is consistent with the effects of viral suppression[33,34]. Additionally, urine viral load in HIV-infected individuals is also related to immune function status, with changes in CD4+ T cell counts closely linked to urine TFV levels, suggesting that the viral load in urine may reflect the overall immune status of patients[35,36].

Urine viral load testing not only has potential in monitoring HIV viral load but also shows auxiliary diagnostic value in assessing HIV-related neurocognitive impairment and renal function damage. Multiple studies have confirmed that the incidence of neurocognitive impairment is high among HIV-infected individuals and is associated with elevated plasma viral loads[34,37].

In renal function monitoring, urine biomarkers such as β 2-microglobulin and α 1-microglobulin are widely used to assess tubular damage in HIV-infected patients[38]. The viral load in urine may also positively correlate with changes in renal function, indicating that urine viral load testing can help early identify potential renal damage risks in HIV-infected individuals[34,35].

In summary, urine viral load testing shows good prospects in monitoring disease progression in HIV-infected individuals. Future research should focus on further validating the correlation between urine viral load and plasma viral load, as well as its application potential in other HIV-related diseases (such as neurocognitive impairment and renal function damage). Moreover, urine viral load testing provides a low-cost, non-invasive monitoring method for clinical practice, which may improve the management and treatment outcomes for HIV-infected individuals.

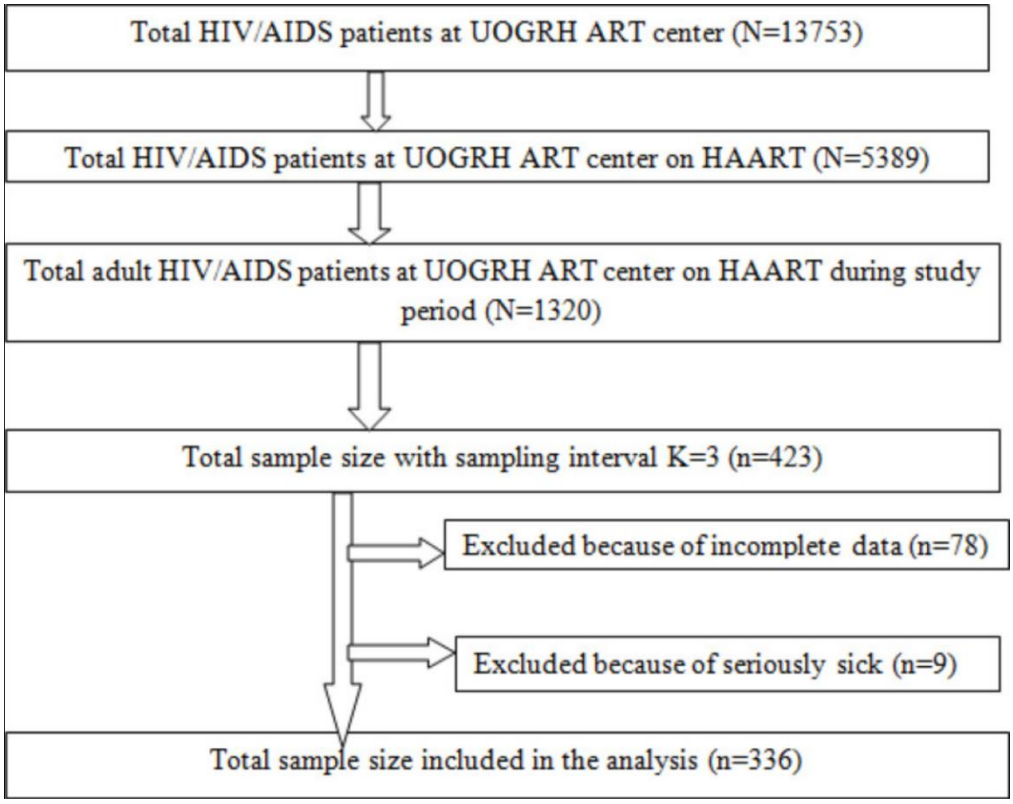

Figure 3: Schematic representation of the sampling procedure adult HIV/AIDS patients on HARRT at University of Gondar Referral Hospital from February to April 2017[35].

Application of Urine HIV Testing in Public Health and Community Screening

1. Urine Rapid Testing Technology in HIV Self-testing

Urine rapid testing technology has shown good accuracy and user preference in HIV self-testing. The advantages of using urine as a sample lie in its non-invasive nature and ease of collection, particularly in resource-limited areas, making HIV testing more convenient and accessible. One study indicated that the accuracy of urine rapid testing is very high, with both sensitivity and specificity exceeding 97%[39].

Notably, the new generation of urine rapid testing technology covers HIV-2, and this testing method is widely accepted by participants, with many expressing a willingness to use urine for HIV self-testing due to its convenience and privacy[39]. The study also found that many individuals who underwent urine testing had positive attitudes toward the feedback on test results, feeling that this method enhanced their sense of control over their health.

Strategies to promote urine testing technology in communities and resource--limited areas need to be adjusted to local cultural and social contexts. Research has shown that community engagement and educational activities can significantly enhance the acceptance of urine testing, especially among high-risk populations. For example, in mobile services conducted on the street, respondents showed high acceptance of on-site testing and immediate treatment, effectively increasing the detection rates of HIV and other sexually transmitted diseases[39]. When promoting urine rapid testing technology, strategies that combine social media and technology platforms can facilitate information dissemination and education, enhancing public awareness and acceptance of HIV testing. Additionally, leveraging the influence of community leaders can further promote the acceptance and use of urine testing.

Despite the promising prospects of urine rapid testing technology in HIV self-testing, potential challenges must be addressed. Studies have indicated that certain populations may experience anxiety regarding test results, particularly the fear of positive results may hinder them from self-testing. Therefore, providing detailed testing information and psychological support during the promotion process is crucial[39].

In conclusion, urine rapid testing technology holds significant application value in HIV self-testing, especially in resource-limited areas. Through effective promotion strategies and community engagement, testing acceptance can be increased, thereby facilitating early detection and treatment of HIV, which is crucial for controlling the spread of HIV.

2. Evaluation of Effects Combining Social Network Interventions with Urine Testing

The importance of social network interventions in enhancing HIV prevention and treatment is becoming increasingly evident. Studies have shown that social networks can significantly influence individuals' health behaviors, including participation in HIV self-testing and treatment. For example, in a study conducted in Kenya, social network interventions increased participants' adherence to PrEP and HIV viral suppression rates[33]. Research indicates that social network interventions can effectively enhance individuals' acceptance and participation in HIV testing and PrEP by strengthening social support and information dissemination.

The core of social network interventions lies in leveraging known social relationships within the network to motivate members to share information and resources, thereby promoting participation in HIV testing and treatment. In a study involving fishermen in Kenya, social network interventions helped enhance awareness and acceptance of HIV self-testing through the role of "promoters." Although no significant statistical differences were observed in PrEP adherence and viral suppression rates, this intervention model demonstrated potential effects, indicating that social network interventions may provide new perspectives and methods for improving HIV-related health behaviors in specific populations[40].

The application of urine testing as an effect monitoring tool in social network interventions also shows potential. Urine testing can provide a more objective assessment of adherence, especially among individuals using PrEP, as urine testing can effectively verify their adherence. For instance, in a study involving fishermen, recent objective adherence was measured via a point-of-care tenofovir urine assay, showing a significant association with self-reported adherence data[41]. This objective biomarker testing can serve as an important tool for evaluating the effectiveness of social network interventions, making monitoring of intervention effects more precise.

However, despite the promising prospects of combining social network interventions with urine testing for effect evaluation, more empirical research is needed to validate its effectiveness and feasibility. Future research should focus on optimizing the design of social network interventions to ensure they can more effectively enhance HIV testing rates, PrEP adherence, and viral suppression rates. Additionally, the application of urine testing should consider its acceptance and feasibility in different sociocultural contexts, which is crucial for enhancing the sustainability and promotion of interventions.

Advantages, Limitations, and Challenges of Urine Testing Technology

1.Non-invasive Sampling and Improved Patient Adherence

Urine, as a non-invasive biological sample, is increasingly valued in various medical tests due to its convenience of collection. For HIV patients, urine sampling provides a more patient-friendly option for diagnosis and monitoring, especially for special populations (such as children, adolescents, and marginalized groups). Studies have shown that urine collection does not require specialized medical personnel or complex equipment, allowing patients to self-collect samples at home, significantly improving patient adherence and satisfaction.

First, urine sampling is particularly suitable for special populations such as children and adolescents. Traditional blood sampling often causes fear and anxiety in young patients, while urine collection is non-invasive and simple, effectively alleviating the psychological burden on patients. For example, in a study involving adolescents, participants indicated that the convenience of urine sampling encouraged them to participate more willingly in HIV testing and follow-up[42]. This non-invasive testing method can reduce anxiety for both parents and children, thereby enhancing the acceptance and adherence to testing.

Secondly, the advantages of urine sampling are also significant for marginalized groups. Many marginalized populations face barriers to accessing healthcare services due to socioeconomic factors. Urine testing can serve as a convenient screening tool, supporting these groups in receiving HIV testing and treatment earlier. In a study conducted in South Africa, researchers found that urine testing significantly increased the early diagnosis rate of HIV-positive patients, particularly among marginalized populations that traditional testing methods struggle to reach[43]. This method not only lowers the threshold for testing but also encourages more patients to get tested by simplifying the process, making it an effective strategy for improving patient adherence.

Moreover, advancements in modern technology, such as the integration of mobile applications and electronic health records, provide more convenience and flexibility for urine sampling. Patients can submit samples anytime and anywhere via smartphones and receive test results and health advice through applications. This instant feedback mechanism can enhance patients' self--management capabilities and improve adherence to HIV treatment. In a study involving HIV patients, those who used electronic health tools for urine testing and follow-up showed significantly higher treatment adherence than those using traditional methods[44].

In summary, non-invasive urine sampling demonstrates great potential in improving patient adherence. Its convenience and applicability make urine testing an important supplementary method for diagnosing and monitoring HIV patients, particularly among children, adolescents, and marginalized groups, effectively overcoming barriers faced by traditional testing methods and promoting early diagnosis and treatment implementation. In the future, with continuous technological advancements, the application range and influence of urine sampling are expected to expand further, providing strong support for HIV prevention and control strategies.

2. Technical Bottlenecks in Sensitivity and Specificity of Testing

In urine testing for HIV, the sensitivity and specificity of detection are key factors in assessing its effectiveness. First, sensitivity often faces significant challenges in cases of low viral load. Studies have shown that the concentration of HIV in urine can be very low, especially during early infection or late treatment, making it difficult for traditional testing methods to accurately identify the virus. For example, certain urine LAM testing methods have a certain sensitivity in HIV-positive patients, but sensitivity significantly decreases at low viral loads. In one study, the sensitivity of urine LAM was 48%, while in HIV-positive patients with CD4+ cell counts below 200 cells/ μ l, this proportion increased to 50%[45]. This indicates that a decrease in viral load directly impacts the sensitivity of testing, particularly in immunocompromised individuals.

Secondly, inhibitors in urine and sample processing can also significantly affect test results. The way urine samples are processed and stored may lead to the degradation of viral antigens, thereby affecting the final test results. For instance, if there are high concentrations of inhibitors in urine samples, they may interfere with the detection of LAM, resulting in false-negative outcomes. Additionally, the timing of urine collection, sample handling, and analysis methods may all impact the sensitivity and specificity of LAM detection. In a study of urine samples, a new Fuji LAM detection method showed high sensitivity and specificity but was still affected by sample handling and storage conditions, particularly emphasizing that the use of fresh urine samples is critical for ensuring accuracy[6].

In summary, HIV urine testing technology faces multiple technical bottlenecks in terms of sensitivity and specificity. These challenges necessitate the development of more sensitive and specific testing tech-nologies, as well as the optimization of sample handling and storage conditions to improve testing accuracy. Future research should focus on improving testing methods, reducing the impact of sample handling on results, and exploring new detection technologies to better meet patients under different pathological conditions.

3.Lack of Standardization and Clinical Application Guidelines

As a potential non-invasive diagnostic tool, urine HIV testing has shown its effectiveness and feasibility in some studies. However, one of the main issues currently in this field is the lack of unified testing standards and clinical application guidelines. Although some countries and regions have begun to explore the clinical application of urine HIV testing, there are still no established consistent guidelines and standards, leading to inconsistent test results between different medical institutions, which affects the credibility and clinical value of urine HIV testing[1].

In clinical practice, there are significant differences in physicians' awareness and acceptance of urine HIV testing. Some physicians may be reluctant to recommend this testing method in clinical settings due to doubts about its effectiveness and accuracy or a lack of familiarity with the relevant testing technologies for urine samples[18]. Patients may also have doubts about the effectiveness of urine testing, especially when they are accustomed to HIV testing through blood samples. This cognitive disparity poses challenges for the widespread promotion and application of urine testing.

Moreover, while the technological advancements in urine HIV testing are rapid, the corresponding standardization processes lag behind. For instance, although the detection methods for HIV antigens and antibodies in urine have achieved good results in laboratory research, the lack of standardized operational procedures and quality control measures in actual clinical applications raises questions about their reliability[7,17]. Therefore, it is essential to strengthen standardization research on urine HIV testing, establish unified testing processes and quality control standards to ensure consistency and reliability of test results across different institutions.

For clinicians, enhancing awareness of urine HIV testing and understanding its value and potential application scenarios is crucial. Relevant training and educational activities can help physicians better master this testing technology, enabling them to recommend it to patients in appropriate situations. Simultaneously, patients also need more education and information to increase their acceptance and trust in urine testing. Establishing relevant patient education programs and promotional activities will help alleviate patients' concerns and promote the application of urine HIV testing.

In summary, the development of urine HIV testing faces dual challenges of lack of standardization and clinical application guidelines. Only by establishing unified testing standards, strengthening clinical education, and enhancing patient awareness can the widespread application of this emerging testing technology in HIV diagnosis be promoted, thereby better serving patients.

Future Research Directions and Development Trends

1.Development and Optimization of New Molecular Detection Technologies

With the increasing demand for early detection of HIV, the development and optimization of new molecular detection technologies have become a research hotspot. Particularly, innovations in HIV testing technologies using urine samples represent significant progress in the detection field. In recent years, high-throughput, rapid, and portable urine HIV testing platforms are continuously being developed to improve the sensitivity and specificity of testing. These technological advancements provide new options for HIV detection, enabling effective application in resource-limited environments. For example, the application of the CRISPR-Cas system, combined with isothermal amplification technology, can quickly detect HIV RNA without the need for complex equipment[46]. This new detection method not only simplifies operational steps but also significantly increases testing speed, allowing HIV-infected individuals to receive diagnostic results earlier and initiate treatment promptly.

Additionally, the combined application of multiplex detection technologies has also played an important role in enhancing the accuracy of HIV diagnosis. By combining different detection methods, such as simultaneously detecting HIV antibodies and antigens or using molecular markers for rapid diagnosis, researchers can achieve simultaneous monitoring of multiple HIV-related markers on a single testing platform. This approach not only improves sensitivity but also reduces the occurrence of false negatives and false positives, thereby enhancing the early identification of HIV-infected individuals. Studies have shown that systems using multiplex detection technologies can achieve higher accuracy in clinical settings, especially in areas with high HIV prevalence, which is crucial for controlling virus transmission[47,48].

In summary, the development and optimization of new molecular detection technologies, particularly innovations in portable and multiplex detection platforms, are reshaping HIV testing methods. These technologies not only enhance the efficiency and accuracy of testing but also provide possibilities for widespread public health interventions, especially in resource-poor areas, effectively reducing the risk of HIV transmission and providing timely treatment options for patients[34]. As these technologies continue to advance and clinical applications are promoted, we look forward to providing more effective tools for controlling the global HIV epidemic.

2.Application of Urine Testing in Individualized Treatment Management

The application of urine testing in individualized treatment management is

gradually gaining attention, primarily reflected in the combination of drug monitoring and virological testing to achieve the goal of precision treatment. By monitoring drug metabolites, such as in patients receiving TFV treatment, the detection of TFV metabolites in urine can reflect patient adherence, which is crucial for assessing treatment efficacy. Studies have shown that using point-of-care (POC) urine TFV tests can effectively predict the viral suppression status of HIV patients, although its specificity is relatively low. The advantage of this urine testing lies in its non-invasive nature and ease of regular monitoring, helping physicians timely adjust treatment plans to improve patient treatment outcomes and quality of life.

Moreover, urine testing is also applied to assess the risks of antiviral treatment failure and drug resistance. Research has found that the HIV-1 env sequences in urine can be used to monitor the dynamic changes of the virus, especially in HIV-positive patients receiving kidney transplants, where urine sample testing can provide evidence of viral reactivation, helping physicians assess the patient's viral load and resistance risks[1]. This dynamic monitoring is crucial for timely adjusting treatment plans and preventing the development of drug resistance.

In the development of urine testing technology, the strategy of combining drug monitoring with viral testing provides new perspectives for individualized treatment management. By regularly testing viral-related indicators in urine, physicians can better understand changes in patients' conditions, thereby implementing personal--ized treatment plans. This approach not only improves treatment precision but also promotes patient adherence and satisfaction. Therefore, in the future, urine testing will play an increasingly important role in the individualized treatment of HIV, becoming a powerful tool to assist clinical decision--making.

3.Large-scale Clinical Validation and Policy Promotion

In the clinical application research of urine HIV testing, large-scale clinical validation and policy promotion play crucial roles. In recent years, with the continuous advancement of HIV testing technologies, the feasibility of using urine as a testing sample has gradually been recognized. This shift requires necessary clinical data support through multi-center clinical trials involving different populations to validate its effectiveness and reliability, as well as policy-level support to incorporate urine testing into national HIV diagnosis and monitoring guidelines.

First, multi-center clinical trials of urine testing involving different populations provide necessary clinical data support for the promotion of urine testing technology. For example, one study comparing urine, blood, and semen samples from 19

HIV-positive participants found differences in HIV-1 env gene sequences between urine and blood, and that the virus in urine may originate from localized replication, demonstrating the potential value of urine as a testing sample[1]. Additionally, another study indicated that urine testing could improve the diagnostic efficiency for tuberculosis, particularly among HIV-positive patients, showing the application potential of urine testing in public health[18].

Second, the promotion of urine testing also needs to consider its feasibility in national HIV diagnosis and monitoring guidelines. For instance, in Ghana, the implementation of national HIV policies has promoted the importance of HIV testing, and by implementing urine testing, more convenient testing options can be provided for those who have not been able to access testing due to social stigma or other barriers[49]. Therefore, policymakers should consider incorporating urine testing into national guidelines to expand testing coverage and reduce undiagnosed cases.

Finally, the key to successfully promoting urine testing technology lies in combining it with different sociocultural backgrounds and healthcare systems. By formulating corresponding policies and promotion strategies based on the HIV epidemic situation in different regions, the acceptance and utilization of urine testing can be effectively increased. For example, in a study conducted in South Africa, combining urine testing with HIV treatment services effectively increased the screening and treatment rates among HIV-positive patients[50]. The success of policy promotion relies not only on the maturity of the technology but also on the collective efforts of all sectors of society to increase public awareness and acceptance of urine testing.

In summary, urine testing has broad application prospects in HIV diagnosis, but large-scale clinical validation and policy promotion still require further efforts and support. Research in this field will provide new ideas for HIV prevention and control, facilitating early diagnosis and timely treatment.

Conclusion

Urine, as a non-invasive sample, is showing increasing potential in the diagnosis and monitoring of HIV, especially in resource-limited areas and specific populations. Through a comprehensive analysis of existing studies, we can identify both the advantages and challenges of urine testing technologies.

Firstly, the technologies for detecting HIV and related markers in urine are continuously advancing. With the deepening of virological research, we are gradually revealing the unique dynamic characteristics of viral populations in urine, offering new perspectives for early detection and monitoring of HIV. The development of this technology can not only improve the

sensitivity of diagnosis but also reduce discomfort caused by sampling to some extent, which is particularly important among young people and women.

Secondly, urine testing plays a crucial supporting role in screening for HIV-related co-infections (such as tuberculosis, CMV, HPV). By combining with traditional testing methods, urine testing can enhance overall diagnostic efficiency, helping clinicians make accurate judgments more quickly. The implementation of this multiplex testing strategy not only improves the utilization of medical resources but also provides patients with a more comprehensive health management plan.

However, there are challenges in the application of urine testing. Although it provides objective evidence in monitoring adherence to PrEP and ART, issues such as the limitations of the detection window and the issue of "white coat adherence" still need to be addressed. These factors may lead to errors in test results, thereby affecting the accuracy of clinical decision-making. To tackle these challenges, standardization of technology, enhancement of sensitivity, and standardizing clinical applications are particularly important.

Looking ahead, the widespread application of urine HIV testing technology requires strengthened multicenter clinical validation to ensure its effectiveness and reliability in different populations and environments. This not only helps promote the clinical translation of this technology but also provides strong support for achieving global HIV prevention and control goals. Through continuous investment in research and technological innovation, we hope that urine testing can play a greater role in the early diagnosis and precise management of HIV.

In summary, urine, as an important sample for HIV testing, holds significant potential for application. With ongoing research and continuous technological advancements, we believe that urine testing will become even more important in HIV management while providing new solutions for HIV prevention and control strategies in resource-limited areas. This all suggests that the future of urine testing looks bright, and we look forward to its widespread application and effectiveness in the field of global public health.

Competing interests

The authors declare all financial and non-financial competing interests.

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