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Advances in biosensing strategies for HIV-1 detection, diagnosis, and therapeutic monitoring☆

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ABSTRACT

HIV-1 is a major global epidemic that requires sophisticated clinical management. There have been remarkable efforts to develop new strategies for detecting and treating HIV-1, as it has been challenging to translate them into resource-limited settings. Significant research efforts have been recently devoted to developing point-of-care (POC) diagnostics that can monitor HIV-1 viral load with high sensitivity by leveraging micro- and nano-scale technologies. These POC devices can be applied to monitoring of antiretroviral therapy, during mother-to-child transmission, and identification of latent HIV-1 reservoirs. In this review, we discuss current challenges in HIV-1 diagnosis and therapy in resource-limited settings and present emerging technologies that aim to address these challenges using innovative solutions.

Contents

Abbreviations: ART, antiretroviral therapy; RLS, resource-limited settings; POC, point of care.

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1. Introduction

HIV-1 remains a major epidemic despite significant efforts made with early diagnosis, treatment, and prevention of HIV-1. In 2014, there were 36.9 million people living with HIV-1, with 2 million new cases, and 1.2 million deaths worldwide [1]. The overall incidence of HIV-1 has decreased due to various factors including suppressive antiretroviral therapy and needle exchange programs in developed countries [2–4]. Prevalence of HIV-1 increases more slowly each year due to the expanding implementation of (ART), particularly in resource-limited settings [5,6]. As such, there is an increasing need to (i) reduce incidence of HIV-1 infection by strengthening current prevention programs, (ii) detect and diagnose HIV-1 infections as early as possible, and (iii) effectively monitor treatment efficacy, including management of secondary (non-AIDS) HIV-1-related illnesses such as cancer, cardiovascular, liver diseases, and co-infections [7–12]. However, solving these problems is expensive and challenging in resource-limited settings given the large number of HIV-1-infected individuals living in these settings.

In developed countries, nucleic acid testing (NAT)-based viral load and flow cytometry-based CD4 cell counting are routinely used to monitor ART therapy. However, these technologies are complex and costly, making them unsuitable for resource-limited settings, where there is a shortage of laboratory infrastructure and financial support. Although first-line ART drugs may be available for free or inexpensively in resource-limited settings, the expansion and universal access of ART has been significantly thwarted by the lack of appropriate diagnostic tools for detecting HIV-1 infections and initiating and monitoring ART. Creating sensitive diagnostics would allow for early identification of acute HIV-1 infection (AHI), thus helping reduce the transmission rate among high-risk populations. Such tools could also be used to identify HIV-1 infection in pregnant women to reduce the risk of mother-to-child transmission (MTCT) during childbirth; currently a major problem in resource-limited settings [13].

To address this technological gap, researchers have been developing devices for HIV-1-infected individuals in resource-limited settings that are affordable, sensitive, specific, user friendly, robust and rapid, equipment-free, and deliverable (ASSURED) [14]. Microfluidic and nanotechnologies have the potential to fulfill ASSURED criteria, because they require small sample volumes, have short assay turnaround and enable highly sensitive detection. We begin our discussion with recently developed diagnostic devices employing different micro- and nanotechnologies for clinical management of HIV-1 in resource-limited settings. These devices utilize a variety of sensing modalities including electrochemical, optical, and mechanical sensing. We then detail the latest advances in diagnostic tools currently being used for the detection of acute HIV-1 infection, CD4 cell count, viral load measurement, and latent HIV-1 reservoirs. Lastly, we provide future directions on the development of POC devices for improving HIV-1 management in resource-limited settings.

2. Recent advances in biosensors and chemical detection systems for HIV-1 detection

Nanotechnology has had a large impact on the field of biosensing by allowing biomedical scientists and engineers to create tools that can directly monitor biological interactions for diagnosis of diseases, including HIV-1. In this section, we introduce emerging technologies, categorized by their transducing method, which are being used to both qualitatively and quantitatively detect HIV-1 via direct (i.e., capture of intact virus), indirect (i.e., capture of virus by host antibodies), or amplification methods (i.e., polymerase chain reaction).

2.1. Electrochemical-based assays

Electrical sensing technologies are used to report binding and recognition events occurring on a sensing surface, including protein-antibody, nucleic acid hybridization, and enzyme-cofactor coupling [15–17]. The broad class of sensors has several advantages, including short assay times and ease-of-use. However, there are technical challenges when used as point-of-care diagnostics in resource-limited settings, such as increasing the signal-to-noise ratio and eliminating electrical interference from highly ionic biological backgrounds. In the following section, we will provide a brief overview on different electrochemical sensing modalities and their applications in HIV-1 detection.

2.1.1. Electrical sensing-based platforms

Electrical-based sensors monitor electrochemical reactions, such as enzymatic conversion or capture of biological targets, through an electrode interface by monitoring changes in electrical current, resistance, impedance, or voltage signals [18]. There are different strategies to measure electrical properties on a sensor surface, including amperometric, voltammetric, potentiometric, and impedance measurements.

Amperometric/voltammetric biosensors are mainly used to measure an electrochemical reaction, which is triggered by the generation or perturbation of a redox current. Thus, these biosensors simply record current generated by direct oxidation or reduction of target molecules that are immobilized on an electrode surface [18,19]. For affinity-based sensing strategies, antigen molecules are captured by specific antibodies elements (e.g., antibodies aptamers) on an electrode surface and the resulting electrochemical reaction blocks electron transfer, thus reducing output current. The degree of output reduction provides quantitative measurements of the captured target molecules [20]. For instance, an amperometric sandwich immunoassay was developed for HIV-1 protein detection, where the electrode was modified with anti-p24 antibodies to capture HIV-1 p24 protein, followed by labeling with a horseradish peroxidase secondary antibody [20]. Signal was produced by immersing the electrode in a solution containing hydrogen peroxide and hydroquinone, which are directly catalyzed by the HRP-secondary antibody complex. Results showed a linear dynamic range spanning from 0.01 ng/mL to 100 ng/mL of HIV-1 p24 protein and a detection limit of 0.008 ng/mL was observed, which is two orders of magnitude better compared to conventional ELISA methods (~1 ng/mL). Amperometric sensors were also utilized to measure zidovudine (ZDV), a nucleoside analog reverse-transcriptase inhibitor that can be one of many drugs used for ART [21]. The concentrations of ZDV were measured using an amperometric sensor fabricated using silver nanofilm (Ag-NF) and multiwalled carbon nanotubes (MWCNTs) immobilized on glassy carbon electrode (GCE). This amperometric strategy under optimal conditions reported a linear detection range for ZDV concentrations spanning from 0.1 to 400 ppm (0.37 μM–