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Use of Dried Blood Spots as a Screening Method in STI Testing: A Mini-Review

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Mini Review

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Abstract

There is an increasing interest in using dried blood spots (DBS) for screening communicable and non-communicable diseases in hard-to-reach populations. This method of screening has many advantages over others such as cost-effectiveness, the requirement of minimal infrastructure, effortless storage, transport, and preservation. This short-review provides an overview of the use of DBS in the screening of sexually transmitted infections (STIs). Also included in this review are reports where DBS was determined to not be feasible because of technology limitations.

Keywords: Dried Blood Spot; Syphilis; Dried Blood Spot; Sexually Transmitted Infections (STIs); Human Immunodeficiency Virus (HIV); Hepatitis B (Hep B); Hepatitis C (Hep C); Syphilis

Abbrevations: STIs: Sexually Transmitted Infections; HIV: Human Immunodeficiency Virus; Hep B: Hepatitis B; Hep C: Hepatitis C; DBS: Dried Blood Spots; MSMs: Men having sex with Men, FSWs: Female sex workers; LOD: Limit of Detection; DHS: Demographic and Health Surveys; TPHA: Treponema Pallidum Haemagglutination Assay; TPPA: Treponema Pallidum Particle Agglutination Assay; EIA: Enzyme Immunoassay; RPR: Rapid Plasma Regain; SMS: Short Message Service.

Introduction

The concept of using Dried Blood Spot (DBS), collected on blotting paper, was developed after the Second World War. This technology principally involves a membrane carrier, on which a biomaterial sample is absorbed and transported to laboratories for further testing [1]. The first large-scale DBS-based screening was used for phenylketonuria in the 1960s. Subsequently, this method was implemented to diagnose infectious diseases as well. Later on the utility of DBS was increased for the therapeutic monitoring of HIV infection in the beginning of the 21st century. Currently, this method of screening and diagnosis has been employed in the serological surveillance or diagnosis of trypanosomiasis, hepatic amebiasis, congenital rubella, and hepatitis [2]. The clinical utility of DBS sampling to improve diagnostics and care of HIV and hepatitis B and C infection in hard-to-reach populations, key populations and people living in low-income settings were carried out in the recent past. Literature about the usefulness of DBS specimens in the therapeutic cascade of care – screening, confirmation, quantification of nucleic acids, and resistance genotyping has been widely accepted [3]. The specimen collected through DBS are considered as "universal tube" as a single sample can be used for analyzing an array of biomarkers [4], viruses, nucleic acids [5], RNA [6], antibodies [7] and antigens [8]. According to the WHO guidelines for antiretroviral therapy, the use of DBS is recommended as an alternative option for improving access to viral load monitoring for HIV, HBV and HCV diagnosis [9]. Literature has indicated that results of screening for HIV,

HBV and syphilis through DBS technology are as reliable as the venous blood puncture method [10-13]. Additionally, DBS technology has been an effective tool for the pre-analytic stages of diagnostics [14]. However, the development of associated technical methodologies and standardization of procedures for the pre-analytical diagnostic stage has only occurred over the past five years [15].

Dried Blood Spot (DBS): Types and Working Principle

Current trend reveal that DBS is becoming a convenient tool for qualitative and quantitative diagnostics of biological samples. It is described as an appropriate method for biomaterial sampling as it requires a small volume of biomaterial and does not require special laboratory conditions for sample collection, storage, and transportation. The sample can be delivered to testing laboratories in packages with variable isothermality ranging from +5°C to -35°C [15]. The samples collected through DBS technology show improved stability of analytes and reduced risk of infection resulting from contaminated samples. After drying the sample an array of analytical, immunological or genomic diagnostic methods can be employed for screening [16]. There are two general types of DBS carriers in modern research: fibreglass and pulp and paper. Researchers at the Centers for Disease Control and Prevention compared Whatman 903, Ahlstrom 226, and Munktell-TFN membrane materials for quantifying HIV viral load and genotyping drug resistance. The results showed that samples collected with Munktell-TFN carriers exhibited the highest genotyping efficiency (100%) compared to Whatman 903 and Ahlstrom 226 membrane carriers (91.7 %). Moreover, Munktell-TFN was more sensitive for the identification of HIV drug resistance mutations [14].

The general principle of obtaining biomaterial in dry form consistently involves the impregnation of a membrane carrier fibreglass strip with blood by immersing its tip in the test liquid, or, if it is blood, transferring a drop of blood from the heel, finger, or foot of the patient to pre-printed areas on MC, followed by air drying. Notably, it is not recommended that DBS technology be used for the analysis of volatile substances or contaminated or hemolyzed samples [17].

Use of the DBS Technique in the Screening/ Detection of Sexually Transmitted Infections (STIs)

Sexually Transmitted Infections (STIs) has become a major public health issue around the globe. Reaching and testing persons at risk of HBV, HCV, and HIV is the main challenge as part of the global effort to eliminate these infections as public health threats by 2030 [9]. Diagnosis of viral hepatitis and HIV follows a sequential strategy initiated by serological screening based on the detection of antibodies or antigens, to which a confirmation step and therapeutic monitoring are performed. Several target-specific interventions have been introduced to increase STI testing even beyond regular STI care, especially in key populations like Men having sex with Men (MSMs), female sex workers (FSWs) etc. The interventions include the usage of web-based outreach strategies along with self-home-collection of samples for screening and testing [18]. It is indicated in studies that self-sampling can prove to be a feasible and effective alternative for key populations which are not keen to visit STI clinics or access other regular health services for care. Self-sampling especially introduced in STI screening programs can be a valuable addition to current STI control [19]. Till now self-based testing interventions mainly focused on chlamydia, trichomoniasis, and *Neisseria gonorrhoeae* testing in heterosexual individuals as these samples are easy to collect, acceptable, and valid compared to samples taken by a health care provider [20]. However, for screening of HIV, HBV and syphilis, a care provider still needs to draw blood intravenously hampering home sampling. Self-taken blood sampling procedures are hardly available in routine STI care settings in industrialized countries. An alternative self-sampling blood test could positively impact the efficiency of STI control (Table 1). Also, in outreach screening and hard-to-reach populations in partner testing or enhanced screening of potentially affected contacts during outbreaks for eg. Syphilis self-sampling may be of added value [21].

Type of STIs	Technique for detection of the infection using DBS	Biomarkers	References
HIV	Real-Time PCR, ELISA	RNA, anti-HIV antibody	[22]
Hep-B	PCR, ELISA	DNA, HBsAg and anti-Hep-C antibodies.	[23]
Hep-C	Real-Time PCR, ELISA	RNA, anti HCV antibodies,	[24]
Syphilis	Agglutination (TPPA), ELISA	Anti-Treponemal antibody.	[25]
HSV-2	ELISA and Western Blot	HSV-2 glycoprotein G antibiodies	[26]

Table 1: Type of confirmatory tests doen for the STI diagnosis based on DBS.

Use of DBS for HIV Screening

DBS may be particularly useful for HIV screening in remote areas, in which unrefrigerated transfer time to a laboratory may take a number of days. However, studies have compared DBS with plasma for viral load testing but lack of standardization in specimen preparation, storage and processing has made the comparison difficult. Additionally, most evaluations have been carried out either on a single or on 2 different assays, limiting the possibility to compare across assays. Thus, there is a need for more reliable, standardized, quality-assured, and validated methods of HIV-1 viral load testing on DBS. Van Loo IHM, et al. [3] highlighted that their study shows that DBS as a method for sampling is a valid alternative for venous blood puncture with high sensitivity (>90%) and specificity (>99%) for HIV ag/Ab and HBsAg. DBS proved to be feasible in routine use since overall, 91% of the DBS was adequately taken to perform the three screening tests. The results of the study on HIV-1 samples in Ghent, Belgium show that DBS viral load for adults performs better than immunological or clinical monitoring [27]. Thus, in settings where DBS is the only viably available option to monitor viral load, it will be more accurate in the assessment of treatment success than immunological or clinical monitoring alone [28].

DBS samples can be used with standard HIV and viral hepatitis immunoassays. The automated immunoassays performed on DBS can be efficient and studies have reported that acute HIV infection was detected earlier on DBS using a fourth-generation HIV test combining detection of total antibody and p24 Ag [13]. DBS can also be used for confirmation of anti-HIV and anti-HCV detection on western blot. The screening test results through western blot yield similar results as in blood in terms of sensitivity and specificity [2,13,29]. Confirmation by genomic detection on DBS is also an effective confirmatory technique for HCV, HBV, and HIV [30]. The nucleic acid tests on DBS are also able to confirm HIV and HCV replication since the RNA level is generally higher than the limit of detection (LOD) in treatment-naive subjects [31], and to detect chronic active HBV infections.

Application of DBS in the Screening of Hepatitis C and Hepatitis B Virus

Hepatitis C virus (Hep C) is a major public health threat around the globe. Most Hep C infections have been acquired by exposure to infected blood or blood products such as sharing of injecting equipment among people who inject drugs [32]. The risk of transmission of Hep C through sexual transmission is reportedly low in heterosexual couples. However, in the mid-2000s, Hep C infection emerged in MSM with men likely due to sexual contact. This contradiction reopened the discussion on studying the aspects of transmission of Hep C through sexual contact. Initially, Hep C was mostly reported among HIV-positive MSM, however recent data show that PrEP using MSM are also at risk of Hep C infection, presumably because there is a shared Hep C transmission network of HIV negative and HIV positive MSM [33].

Home-based testing is an interesting strategy to increase test uptake among high-risk groups. Dried blood spots collected at home are sent to a laboratory for Hep C RNA testing. Technically, Hep C RNA can be detected on DBS with sufficient sensitivity. The use of home collected DBS for this purpose remains to be formally validated in terms of technical performance and acceptance by key populations. Core antigen testing DBS has lower sensitivity and is, therefore, less suitable for diagnosing acute HCV infection [34].

Hepatitis B (Hep B) causes injuries to the liver which can lead to acute injury (viral hepatitis) and chronic injury (cirrhosis). This virus mostly spreads from one person to another through bodily fluids and rarely through blood transfusions. The World Health Organization estimated that about 290 million people are living with Hep B in 2019. Every year around 1.5 million people acquire the new Hep B infection and sadly, 0.8 million deaths happen around the world [32]. Safe and effective vaccines are available to prevent Hep B infection. As it is not possible to differentiate Hep B from hepatitis caused by other viral agents, therefore, appropriate laboratory testing is mandatory. Hep B is being identified through the serological test by detecting the Hep B surface antigen from the suspects [35]. DBS has been used for serological surveillance and diagnosis of Hep B. DBS specimens collected during Demographic and Health Surveys (DHS) were used for finding the prevalence of Hep B which allows reliable countrywide and regional distribution of the disease [36]. A study carried out by Kenmoe S, et al. [23] showed that the DBS has a sensitivity and specificity of 99% for the detection of HBsAg. Moreover, researchers suggested that DBS is an appropriate tool for the large epidemiological study of Hep B screening.

Use of DBS in the Screening of Syphilis

Syphilis is a common STI across the globe, infecting around 10-12 million people each year. This disease is caused by the bacterium *Treponema pallidum*. While early Syphilis causes significant morbidity, Congenital syphilis remains a major cause of stillbirth, childhood morbidity, and mortality worldwide. Several studies identified Syphilis as a facilitator of HIV transmission. Syphilis is commonly diagnosed using laboratory-based assays such as *Treponema pallidum* haemagglutination assay (TPHA), *Treponema*

pallidum particle agglutination assay (TPPA), rapid plasma reagin (RPR), or enzyme immunoassay (EIA) by collecting serum and plasma from the suspects. DBS samples have been previously used in Syphilis prevalence studies [37]. DBS has been suggested to be a suitable EQA methodology for Syphilis, since they are easily collected, require minimal training, and can be sent at ambient temperature for retesting at a centralized laboratory. DBS samples have been used in prevalence studies for syphilis serology but without prior validation of the methodology. DBS samples have been evaluated with TPPA, TPHA, and an in-house EIA which is not commercially available. The TPHA used in the study by Backhouse is no longer commercially available. Self-collected specimens for syphilis testing are feasible using dried blood from a finger prick and appear to be acceptable among MSM recruited from non-clinical settings in one study [38].

Use of DBS in the screening of HSV-2

Herpes simplex virus type 2 (HSV-2) is a common sexually transmitted virus and the major causative agent for the genital ulcers. Development of better diagnostic tool is not only useful for the HSV-2 detection, also for the diagnosis fo HIV, as HSV-2 infection is a recognized cofactor for sexual transmission and acquisition of HIV [39]. In addition, detection of HSV-2 antibodies used as a biomarker for monitering the sexual activities among adolescent population as the primary mode of HSV-2 trsnsmisison is through sex and viral infection persists for life. Generally, HSV-2 detection is being carried out by cell culture, nucleic acid tests such as PCR and real time PCR and serological techniques like ELISA and Western blot. Commonly, these tests requires serum to diagnose HSV-2 antibodies, however, use of DBS is more advantageous than this mehod such as sample collection is simple and non-invasive, requires small amount of blood, the usage of equipment is less, no need of cold transporation and storage [40]. Currently, detection of HSV-2 glycoprotein G antibodies has become an increasingly common biomarker in HIV/STI prevention studies Various studies have used DBS for the diagnossi of HSV-2 antibody through ELISA and Western Blot, which has the specificity and sensitivity of 99%. However, DBS must be regularly evaluated by the manufacturers using standardized protocols for tool/kit development and regulaortory approvals [26].

Limitations

Standardized protocols are needed for inter-laboratory comparisons, and manufacturers should pursue regulatory approval for in vitro diagnostics using DBS specimens. DBS VL systematically underestimates plasma VL resulting in many false treatment successes in a study on HIV-1 samples in Ghent, Belgium. The performance of HIV RNA testing on DBS to identify a virological failure on antiretroviral therapy is also high but not optimal because of the dilution of dried blood in the elution buffer, reducing the analytical sensitivity, and because of the contamination by intracellular HIV DNA. DBS can be decentralized but it requires a return visit for post-counselling. In this view, the lower rate of retention in care using DBS is a limitation.Most commercially available viral load assays have not been validated for use with DBS and concise locked-down manufacturer protocols for specimen preparation, storage, and processing are often lacking.

Conclusion

Dried blood spot technology is being used in some countries for diagnosis of HIV, HCV, HBV and syphilis among target populations for which accessibility of healthcare services is a challenge. This is emerging as a popular approach among high-risk population groups as a method of self-collection of screening samples. However, its applications are limited to toxicology and laboratory diagnostics in certain countries such as India. Owing to the high risk of STIs in India, barriers of inaccessibility of proper healthcare facilities for STIs in remote areas and the reluctance of people to visit STI/RTI clinics for diagnosis and treatment, this method of self-collection of samples for diagnosis may hold potential in the coming years as a supplementary option with the existing testing technologies. DBS testing may be a useful alternative for screening in remote communities and in situations experiencing delays in collection of samples by healthcare providers and transportation to laboratories due to inaccessible and difficult terrains.

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