Dried fluid spots for HIV type-1 viral load and resistance genotyping: a systematic review

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CRD summary
This review assessed dried fluid spots (DFS) (whole blood, plasma, or serum) as specimens for HIV-1 viral load and resistance genotyping assays and concluded that DFS were adequate for public health surveillance of pre-treatment populations, but not treatment monitoring. Data were limited to technical characteristics of assays and the authors’ conclusions are subjective judgement, which should be viewed with caution.

Authors' objectives
To assess the usefulness of dried fluid spots (whole blood, plasma or serum) as specimen types for HIV-1 viral load and resistance genotyping assays.

Searching
MEDLINE database, World Health Organisation and Centres for Disease Control and Prevention websites, relevant conferences and bibliographies of retrieved articles were searched for English-language studies published before January 2009. Search terms were reported.

Study selection
Studies that evaluated the performance of dried blood spot (DBS), dried plasma spot (DPS) and/or dried serum spot (DSS) for HIV-1 viral load quantification and/or genotyping were eligible for inclusion. Included studies were required to use liquid plasma assays as the reference standard. Studies that evaluated the performance of dried fluid spots for HIV-1 diagnosis using qualitative molecular methods were excluded.

All studies used the same filter paper (Whatman 903) for collection of dried fluid spot samples. Viral load assays used a variety of commercial kits (reported in paper) and were based on nucleic acid based sequence amplification (NASBA) or reverse transcriptase (RT)-PCR. Specimens were obtained by finger puncture or venipuncture. Where stated, specimen volumes were between 50μL and 200μL.

Two reviewers independently assessed studies for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
The authors did not state that they assessed study validity.

Data extraction
For studies of viral load assays, data were extracted on the lower limits of detection using dried fluid samples. Where possible, correlation coefficients and/or mean differences were extracted for RNA (ribonucleic acid) viral loads in dried fluid samples compared with those in liquid plasma samples.

For genotyping studies, data were extracted on amplification success rates, percentage concordance of nucleotide sequences generated from dried fluid and liquid plasma samples, percentage concordance of drug resistance-associated codons detected from dried fluid and liquid plasma specimens.

Data on the stability of nucleic acid in samples during storage were extracted.

Two reviewers independently extracted data. Disagreements were resolved by discussion.

Methods of synthesis
Studies were summarised using a narrative synthesis and tables.

Results of the review
Viral load quantification:

Twelve studies evaluated DBS (approximately 1,100 specimens, not reported for one study), nine studies evaluated DPS (917 specimens) and no study evaluated DSS. The reported lower limits of detection for DBS at specimen a volume of 100μL ranged from 2.9 to 3.3 log_{10} RNA copies/mL (four studies). Correlation coefficients for DBS compared with liquid plasma specimens ranged from 0.72 to 0.99 (eight studies). Median differences between DBS and liquid plasma specimens were less than 0.5 log_{10} RNA copies/mL (five studies). Reported lower limits of detection for DPS at specimen a volume of 50 μL, ranged from 3 to 3.6 log_{10} RNA copies/mL (three studies); the lower limit of detection was 3 log_{10} RNA copies/mL at a specimen volume of 200 μL (one study). The correlation coefficients for DPS compared with liquid plasma specimens ranged form 0.86 to 0.97 (four studies). Median differences between DPS and liquid plasma specimens were <0.7 log_{10} RNA copies/mL (three studies). Five studies evaluated the correlation between DBS and DPS and significant correlation was found by four studies.

Resistance genotyping:

Nine studies evaluated DBS, two studies evaluated DPS and two studies evaluated DSS. For DBS specimens, amplification success rates ranged from 58% to 95% (eight studies); amplification success rates tended to be higher for higher viral loads (>3 log_{10} RNA copies/mL). Reported concordance between nucleic acid sequences generated from DBS and liquid plasma specimens was between 98.5% and 99.9% (five studies, six data sets) and reported concordance of drug resistance-associated codons detected from DBS and liquid plasma specimens was between 44% and 100% (seven studies, eight data sets). For DPS/DSS genotyping was considered reliable for viral load values above 4 log_{10} RNA copies/mL from 20 μL samples.

Nucleic acid stability:

Adequate nucleic acid stability was reported for a variety of sample storage conditions (full details were reported in the paper).

Authors’ conclusions

Dried fluid specimens offer the advantages of a stable specimen matrix combined with ease of sample collection and transport. Current sensitivity in drug resistance testing was appropriate for public health surveillance in pre-treatment populations, but greater analytical sensitivity was needed for treatment monitoring in individuals who received anti-retroviral therapy, particularly at onset of treatment failure.

CRD commentary

The review addressed a clearly stated objective, which was confined to an assessment of suitability of sample types for two types of genetic assay. Inclusion criteria were defined in terms of sample type under investigation and comparison sample type. The search strategy examined only one bibliographic database and was limited to published English-language studies. It was, therefore, possible that relevant studies were omitted from the review and the review may have been subject to language bias and/or publication bias. Measures were taken to avoid error and/or bias in the review process. No assessment was made of the methodological quality of the included studies, so the reliability of the findings is unclear. The narrative synthesis used was appropriate to the type of data summarised. In general, data reported related to the technical rather than clinical performance of assays in different sample types. Results were derived from few studies with small sample sizes. The authors’ conclusions on clinical applications of assays using dried fluid specimens appeared to be based on subjective judgement and should be viewed with caution.

Implications of the review for practice and research

Research: The authors stated that future studies should focus on optimisation and standardisation of assay protocols, improving sensitivity and precision and nucleic acid stability under extreme storage conditions and eliminating the need for on-site centrifugation to separate plasma.

Practice: The authors did not state any recommendations for practice.

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