**Beyond blood: feasibility of saliva-based assays for antiviral therapeutic drug monitoring**

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**Introduction.** Transplant recipients are highly vulnerable to opportunistic viral infections, necessitating antiviral prophylaxis or treatment post-transplantation. Optimal therapy depends on maintaining appropriate drug exposure to prevent treatment failure or toxicity. Therapeutic drug monitoring (TDM) enables individualised dosing but currently relies on blood samples. Saliva is a non-invasive alternative matrix for antiviral TDM, but its feasibility remains uncertain.

**Aims**. This systematic review aims to assess the feasibility of saliva-based assays for antiviral TDM.

**Methods**. A systematic search of MEDLINE, EMBASE, clinicaltrials.gov, regulatory databases, and conference abstracts identified primary studies reporting both saliva and plasma concentrations of (val)acyclovir, amantadine, baloxavir, brivudine, cidofovir, famciclovir, favipiravir, foscarnet, (val)ganciclovir, letermovir, maribavir, molnupiravir, nirmatrelvir, oseltamivir, peramivir, remdesivir, ribavirin and rimantadine. Physicochemical properties were extracted from PubChem and DrugBank to predict salivary excretion. Feasibility was assessed using clinical data and physicochemical analyses, and classified as: (1) likely, (2) possible, (3) unlikely, (4) unclear but possible, or (5) unclear but unlikely.

**Results.** Nine studies were included in the review. (Val)acyclovir and favipiravir were considered possibly feasible for saliva-based TDM, whereas molnupiravir and oseltamivir were unclear but possible. Nirmatrelvir was deemed unclear but unlikely. For other antivirals, no primary studies were available, yet most physicochemical profiles suggested limited salivary penetration to facilitate antiviral TDM.

**Discussion.** Evidence for saliva-based antiviral TDM was limited. Inconsistencies between physicochemical predictions and clinical data suggest that factors such as drug transporters, saliva flow, pH, and interpatient variability can influence salivary drug penetration. Despite these challenges, preliminary studies demonstrating measurable antiviral concentrations in saliva and detectable correlations with plasma levels indicate promising potential for saliva as a non-invasive alternative to blood. Standardised collection methods, validated assays, and robust pharmacokinetic studies are needed to confirm the clinical feasibility of saliva-based antiviral TDM.