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Antiretroviral concentration in hair as a measure for antiretroviral medication adherence: A systematic review of global literature

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Abstract

This review aims to validate hair antiretroviral concentration (HAC) as a measure for antiretroviral medication adherence. This review included 31 studies that analyzed a total of 11 ARV drugs in four different drug classes. The associations between HAC and non-pharmacokinetic measures were generally lower than the association between HAC and other pharmacokinetic measures: the correlation coefficients (r) ranged from −0.20 to 0.38 for self-report or pill counts and 0.20 to 0.85 for electronic drug monitoring; HAC and other pharmacokinetic measures were positively correlated with the correlation coefficients (*r*) ranging from 0.20 to 0.72, 0.34 to 0.86, 0.50 to 0.85 for antiretroviral concentration in plasma, peripheral blood mononuclear cells, and dried blood spots, respectively. HAC was one of the strongest independent predictors of virologic responses. HAC of tenofovir was significantly associated with renal toxicity in large sample studies. This review suggests that HAC is a valid biomarker of antiretroviral medication adherence.

Keywords

Antiretroviral therapy; Adherence; Hair; HIV/AIDS; Pre-exposure prophylaxis

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors because it relies on primary studies.

Informed Consent Not applicable.

Introduction

Antiretroviral (ARV) medication is the primary modality for the treatment and prevention of the HIV infection and can substantially reduce HIV-related morbidity, mortality, and transmission [1, 2]. Adherence to ARV medications is paramount for not only disease treatment among people living with HIV (PLWH) but also prevention of HIV infection as pre-exposure prophylaxis (PrEP) among populations at risk for HIV infection [3, 4]. Optimal adherence to ARV medications is a critical determinant for adequate ARV exposure, which has been vital to viral suppression and improved clinical outcomes among PLWH and HIV prevention among populations at risk for HIV infection. Given the pharmacological relationship between ARV medication adherence and levels of ARV exposure, analysis of ARV drug levels in pharmacokinetic (PK) metrics has been used as an alternative method to assess ARV medication adherence besides the commonly used non-pharmacokinetic (non-PK) assessments of adherence (e.g., self-report) and pharmacodynamic (PD) responses of ARV medication adherence (e.g., viral suppression) [5–8].

Pharmacologic measures of ARV medication adherence often involved measurement of ARV levels in PK metrics, such as plasma[9], peripheral blood mononuclear cells (PBMC) [10], dried blood spots (DBS)[11], and hair[12, 13]. Among those PK metrics, measurement of ARV concentration in plasma has been frequently used to monitor the ARV exposure, but it only represents a short-term window of ARV exposure (hours to days). For example, tenofovir (TFV) and emtricitabine (FTC) in plasma have terminal elimination half-lives of 17 hours and 10 hours, respectively[14], and therefore plasma concentrations of TFV and FTC only represent 17 hours and 10 hours of ARV exposure, respectively. Besides, plasma ARV concentration may be susceptible to “white coat effects” [15], and requires specimen collection using biohazardous precautions and freezer storage. Measurement of ARV concentration in PBMC provides moderate-term windows of ARV exposure (days to weeks). For example, TFV is phosphorylated in cells to FV-diphosphate (TFV-DP). The terminal half-life of TFV-DP in PBMC has been shown to be approximately four days [14]. Thus, PBMC concentration of TFV-DP represents four days of ARV exposure. However, processing PBMC (e.g., PBMC isolation from blood) requires a skilled technician and PBMC also requires freezer storage. Compared with plasma and PBMC, measurement of ARV concentration in DBS provides a longer-term window of cumulative ARV exposure because metabolites of some ARV drugs have longer half-lives in red blood cells than in plasma and PBMCs. DBS also has advantages in ease of collection (e.g., finger prick), storage and processing. However, DBS requires standardization against hemoglobin concentrations and the time window of DBS analysis relies on the half-life of ARV drugs. For example, TFV-DP and FTC-triphosphate (FTC-TP) in DBS have a terminal elimination half-lives of 17 days[16] and 1.5 days[17], respectively, and therefore DBS concentrations of TFV and FTC represent 17 days and 1.5 day of ARV exposure, respectively.

Alternatively, measurement of ARV concentration in hair (hair ARV concentration, or HAC) might overcome the limitations of the other PK metrics (i.e., plasma, PBMC, and DBS) for several reasons. First, HAC provides a long-term window of cumulative ARV exposure (weeks to months). The major pathway for ARV drug delivery into hair has been proposed to be from the bloodstream into the hair follicle and gradually deposited in the growing hair

shaft[5]. Because human hair grows at an average rate of 1 cm per month, ARV concentration in 1cm hair represents a one-month window of ARV exposure[18]. Second, hair can be used to quantify long-term exposure of multiple ARV drugs[12, 13, 19, 20]. Third, hair samples are easy to collect[21] and can be stored at room temperature and shipped by regular mail without biohazardous precautions. All of these advantages make HAC appealing as an ARV medication adherence monitoring measure [14, 22].

While HAC has been increasingly used in the literature as a measure of ARV medication adherence [5, 8, 14, 18, 22], limited effort has synthesized the global literature regarding the validity of HAC as a measure for long-term ARV medication adherence. A critical step in validating the utility of HAC is to establish the empirical evidence that HAC indeed monitors ARV exposure and represents ARV medication adherence over extended periods of time (e.g., weeks or months). A potential approach to prove such a concept is to show that HAC correlates well with non-PK and other PK adherence measures, as well as with pharmacodynamic (PD) responses. Therefore, we conducted a systematic review of existing literature that reported associations of HAC with non-PK adherence measures (e.g., self-report, pill counts, and electronic drug monitoring), other PK adherence measures (e.g., ARV concentration in plasma, PBMC, and DBS), and PD responses (e.g., viral load and toxicity).

This systematic review has the following four objectives: (1) to elucidate the relationship of HAC with non-PK adherence measures; (2) to elucidate the relationship of HAC with ARV concentration in other PK metrics as measures of ARV medication adherence; (3) to elucidate the relationship of HAC with PD responses; and (4) to provide recommendations for further research and practice in using HAC as a biomarker for long-term ARV medication adherence.

Methods

Data source and searching algorithm

A literature search was performed in July 2018 utilizing the following three databases: PubMed, Web of Science, and CINHAL. The keywords used for the search included antiretroviral (antiretroviral therapy, antiretroviral drugs, and antiretroviral treatment) in combination with hair (hair level and hair concentration). References of included studies were also hand-searched for additional papers. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [23].

Inclusion criteria

The following inclusion criteria were used in this review: (1) peer-reviewed empirical studies and published in English-language journals, (2) conducted among humans (e.g., PLWH or populations at risk for HIV infection), (3) reported the associations of HAC with one or more non-PK adherence measures, other PK adherence measures, or PD responses.

Screening and data extraction

The initial search identified 294 articles from the three electronic databases. After removing 62 duplicated records, 232 articles were screened based on their titles and abstracts. Then 132 articles were further excluded by title screening and 58 articles were excluded by abstract screening. An additional six articles were identified through a hand-search of references in relevant articles, which resulted in a total of 48 articles for full-text screening. Seventeen articles were excluded during the full-text screen due to their focus on the chemical analysis of the antiretroviral drugs in hair (n=7), lack of data on other ARV medication adherence measures or PD responses (n=2), lack of data on the association between HAC and other ARV medication adherence measures or PD responses (n=3), and non-empirical studies (n=5). Thirty-one studies were included in the final review (Figure 1).

The following data were extracted from the included articles during the review: (1) study location and year of data collection; (2) sample characteristics including sample size, age and sex distributions; (3) classes of ARV drugs; (4) other ARV medication adherence measures (non-PK and other PK adherence measures) and PD responses; (5) characteristics of non-PK adherence measures, PK adherence measures, and PD responses; (6) characteristics of HAC; (7) statistical method; and (8) associations of HAC with non-PK adherence measures, other PK adherence measures, and PD responses.

Given the lack of universally acceptable thresholds in quantifying the strengths of a correlation coefficient (e.g., Pearson's r) which was the most commonly used statistic in assessing the associations between HAC and other adherence measures or PD responses in the included studies, we reported the associations in this review as "weak" if correlation coefficients (r) < 0.30 or significance level of other association measures (p) ≥ 0.05; "moderate" if 0.30 ≤ r < 0.60 or significance level of other association measures (p) <.05 but ≥ 0.001; "strong" if r ≥ 0.60 or significance level of other association measures (p) < 0.001.

Results

Study description

The key characteristics of the study design of the included studies are presented in Table 1. Of the studies included in this review, one was published in 1998, four in the period from 2000 to 2010, and 26 since 2011. In term of the geographic distribution of the studies, 12 studies were conducted in Africa, nine studies were conducted in North America, four in Europe, three in Asia, and three in multiple continents (South America, North America, Asia, and Africa).

The summary statistics of key characteristics of the included studies are presented in Table 2. In terms of the characteristics of ARV drugs, the included studies examined hair concentrations of 11 ARV drugs in four drug classes: nucleoside reverse transcriptase inhibitor (NRTI) including lamivudine (3TC) [24], TFV[25–34], and FTC[26, 28, 32]; non-nucleoside reverse transcriptase inhibitor (NNRTI) including nevirapine (NVP) [35, 36], and efavirenz (EFV) [35, 37–39]; protease inhibitor (PI) including indinavir (IDV) [40–43], atazanavir (ATV) [35, 44–47], lopinavir (LPV) [35, 38, 39, 46, 48–50], ritonavir (RTV) [35, 38, 46, 50], and darunavir (DRV) [47]; and integrase strand transfer inhibitor (INSTI)

including raltegravir (RAL) [47]. The included studies also reported a total of eight adhrences measures that were divided into three main categories including non-PK adherence measures (self-report, pill counts, and EDM), other PK adherence measures (plasma ARV concentration, PBMC ARV concentration, and DBS ARV concentration), and PD responses (viral load, and renal toxicity). Twenty-two studies enrolled PLWH, including children, adolescents, and adults, while other studies were conducted among populations at risk for HIV infection, including seronegative partners of PLWH and seronegative men who have sex with men (MSM). The median sample size in the included studies was 217 (range: 5–1124). The median age of participants was 30.5 years (range: 2–82). Twenty-one studies measured hair concentration of a single ARV drug, while others measured hair concentrations of two or more ARV drugs. Twenty studies reported data on the association between HAC and a single measure of ARV medication adherence or PD response, while others reported data on the associations between HAC and two or more measures of ARV medication adherence and PD responses.

Associaton between HAC and non-PK adherence measures

Self-report—As shown in Table 3, 11 studies reported data on the associations between HAC and four types of self-reported adherence measures (pill taken, percentage of pill taken, visual analog scale, and adherence questionnaire) with varying recall timeframes (ranging from 3 days to 6 months) among PLWH and populations at risk for HIV infection.

Three of the 11 studies reported that HAC was associated with self-reported adherence measures. Gandhi et al. reported that a higher percentage of pill taken was strongly associated with higher HAC of ATV [45]. Koss et al. found that self-reported adherence was weakly correlated with HAC of TFV and HAC of FTC [32]. Baxi et al. found a moderate correlation between self-reported adherence and HAC of TFV at both 8-week and 16-week follow-ups. While self-reported adherence was found to be moderately associated with HAC of FTC at 8-week follow-up and such association became weaker at 16-week follow-up [26].

Seven of the 11 studies reported no or weak associations between HAC and self-reported adherence measures. Three studies found that an increase in self-reported adherence was not associated with an increase in HAC of NVP [51, 52] or HAC of EFV [53]. Four studies found that self-reported adherence was not correlated with HAC of TFV [25, 27, 31] or HAC of EFV, LPV, and RTV [54].

In addition, Chawana et al. found that self-reported adherence was not associated with HAC of ATV at 3-month follow-up. However, among the participants who reported an increase in self-reported adherence from baseline to 3-month follow-up, the self-reported adherence was moderately associated with an increase in HAC of ATV at 3-month follow-up [44].

The existing literature provided some preliminary evidence that the associations between HAC and self-reported adherence measures may vary as a function of the recall timeframe. Four of the 11 studies that used short recall timeframes (e.g., 3 days) all reported non-significant association between HAC and self-reported measures. However, among the seven studies that used longer-term recall timeframes (e.g., 30 days), four reported significant or marginally significant associations between HAC and self-reported measures.

Pill counts—As shown in Table 3, Olds et al. found that pill counts and HAC of NVP were weakly correlated [51]. Baxi et al. found that pill counts and HAC of TFV were moderately correlated [27].

Electronic drug monitoring (EDM)—Five studies reported data on the associations between HAC and EDM adherence measures among PLWH and populations at risk for HIV infection (Table 3). Three of the five studies reported that HAC was associated with EDM adherence measures. Koss et al. found that EDM adherence measures were moderately correlated with HAC of TFV and FTC [32]. Abaasa et al. found that EDM adherence measures and HAC of TFV were strongly correlated among seronegative MSM, but only moderately correlated among seronegative partners of PLWH [25]. Baxi et al. found that EDM adherence measures were moderately correlated with HAC of TFV and FTC at 8-week follow-up, and such associations became stronger at 16-week follow-up [26].

Two of the five studies reported no or weak association between HAC and EDM adherence measures. Baxi et al. found that EDM adherence measures and HAC of TFV were weakly correlated [27]. Both Baxi et al. and Olds et al. found that an increase in EDM adherence measures was not associated with an increase in HAC of TFV [27] or NVP [51].

Associaton between HAC and other PK adherence measures

Plasma—Five studies reported data on the associations between HAC and plasma ARV concentration (Table 4). All studies except one [49] reported that HAC was associated with plasma ARV concentration. Abaasa et al. and Baxi et al. reported weak to moderate correlations between HAC of TFV and plasma TFV concentration [25, 27]. Liu et al. found that an increase in plasma TFV concentration was moderately associated with an increase in HAC of TFV [33]. Baxi et al. a moderate correlation between HAC and plasma ARV concentration for both TFV and FTC at 8-week follow-up, and such associations became stronger at16-week follow-up[26].

Peripheral blood mononuclear cell (PBMC)—Two studies reported data on the associations between HAC and PBMC ARV concentration. Baxi et al. found that HAC of TFV and PBMC concentration of TFV were moderately correlated [27]. Baxi et al. also reported a moderate correlation between HAC and PBMC ARV concentration for both TFV and FTC at 8-week follow-up, and such associations became stronger at 16-week follow-up [26].

Dried blood spots (DBS)—Three studies reported associations between HAC and DBS ARV concentration and all suggested moderate to strong correlations. Bartelink et al. found that HAC of EFV, LPV, and RTV were strongly correlated with the concentration of same ARV drugs in DBS, respectively [54]. Seifert et al. found that HAC of TFV was moderately correlated with DBS concentration of TFV-DP [34]. Gandhi et al. found that HAC of TFV and DBS concentration of TFV-DP were strongly correlated, while HAC of FTC and DBS concentration of FTC-TP were moderately correlated [28].

Association between HAC and PD responses

Viral load (VL)—Seventeen studies reported data on the associations between HAC and virologic response in terms of either VL measure or viral suppression. As shown in Table 5, majority of the studies (16 of 17) reported that HAC was associated with viral suppression, which was defined with a wide range of cutoffs of VL measure from 50 copies/mL, 80 copies/mL, 200 copies/mL, 400 copies/mL, 500 copies/mL, to 1000 copies/ml. Ten of these studies showed that HAC was the strongest independent predictor of virologic success in large prospective cohorts of PLWH [36, 38, 39, 44–46, 48–50] or clinical trials[47]. Additionally, HAC was a stronger predictor of viral suppression than self-reported adherence [36, 39, 45, 46, 48, 49] or plasma ARV concentration[49, 50].

Fifteen of the 17 studies reported data on the associations between hair concentrations of PI drugs and viral suppression. All but two studies consistently showed that HAC was associated with viral suppression. For example, in comparison with PLWH with viral suppression, PLWH with virologic failure had significantly lower HAC, and an increase in HAC was associated with an increase of the odds ratio for viral suppression. However, one study found a significant association of viral suppression with RTV and LPV, but not with ATV [35]. Another study that collected up to 8cm hair specimens from the participants found a significant association between HAC and viral suppression with the first and second 2-cm hair segments, but not with the third and fourth 2-cm hair segments [41].

Five of the 17 studies reported data on the associations between hair concentrations of NNRTI drugs and viral suppression. Four studies reported a significant association, while one study found nonsignificant association between HAC of EFV and viral suppression among women living with HIV [37].

Two of 17 studies reported data on the associations of viral suppression with hair concentrations of a NRTI drug and an INST drug. Yan et al. reported that PLWH with viral suppression had significantly higher HAC of 3TC than those who had virologic failures with and without HIV drug resistance [24]. Gandhi et al. reported that lower HAC of RAL strongly predicted a higher risk of virologic failure at baseline and 96-week follow-up [47].

Renal toxicity—Six studies reported data on the associations of HAC of TFV and renal toxicity by using creatinine clearance levels as a biomarker of renal toxicity among populations at risk for HIV infection and PLWH. Among six studies, three small PrEP studies (n=23, 47, and 88) reported nonsignificant associations between creatinine clearance and HAC of TFV[26, 27, 33] or FTC[26], while two large PrEP studies (n=220, 280) reported significant associations of creatinine clearance with HAC of TFV [29, 30] and FTC [29]. One small study (n=45) among PLWH found a significant association between creatinine clearance and HAC of TFV [34].

Discussion

Summary of main findings

This systematic review synthesizes existing global literature regarding the associations of HAC with three non-PK adherence measures, three other PK adherence measures, and two

PD responses among PLWH or populations at risk for HIV infection. Hair concentrations of 11 ARV drugs in four different drug classes were assessed for ARV medication adherence in both HIV treatment and PrEP prevention research across various cultural settings. Existing literature has suggested (as expected) inconsistent associations between HAC and non-PK adherence measures (e.g., self-report, pill counts, and EDM) and strong positive associations between HAC and PK adherence measures via other biometrics (e.g., plasma, PMBCs, and DBS). In addition, HAC was significantly associated with PD responses (viral load and toxicity). HAC was one of the strongest independent predictors of virologic responses, supporting the pharmacodynamics relevance of hair assay. HAC of TFV was significantly associated with renal toxicity, especially in studies with large sample sizes. This review suggests that HAC can serve as a valid biomarker that provides an objective measure for long-term ARV medication adherence.

Knowledge gaps

While the existing literature in general supported the utility and validity of HAC as a measure for long-term ARV medication adherence, several knowledge gaps remain in the existing literature.

First, the number of the studies on the validity of HAC as an objective measure for ARV medication adherence are limited. In this review, we were able to identify only 31 empirical studies published between years 1998 and 2018. Even though there has been a growing number of studies in recent years (e.g., 26 of the included studies were published since 2011), there were insufficient number of studies with data on the associations of HAC with some of the other adherence measures. For example, data on the association of pill counts with HAC was only available from two studies which limited our ability to draw a meaningful conclusion. Likewise, data on the associations of HAC with multiple adherence measures were limited. Only seven of the 31 studies reported data on the associations of HAC with two other adherence measures and only four studies reported data on the associations of HAC with three or more other adherence measures [25–27, 51].

Second, there was limited research examining the associations between HAC and some new non-PK or PK adherence measures in this field. These new non-PK (e.g., short message service, or SMS [55]) and PK measures (e.g., ARV concentration in saliva[56, 57] or urine [58, 59]) have shown potential advantages in improving accuracy of the ARV medication adherence measures in HIV-related research. The associations between HAC and new non-PK or PK adherence measures may provide additional insight on the validity of HAC as a measure of long-term ARV medication adherence.

Third, some existing studies might have methodological limitations in terms of study design, sample characteristics, and ARV medication adherence measures. One limitation was that most studies were cross-sectional. Few studies in this review reported longitudinal data on the associations of HAC with other adherence measures[26, 44], virologic responses[47] and renal toxicity[29]. More longitudinal studies are needed to validate the dynamic associations of HAC with other adherence measures and PD responses over the course of treatments or prevention. Another limitation was that some of the existing studies relied on data collected from small samples (e.g., about 30% of the included studies had a sample size of 90 or less),

which might limit the internal and external validity of findings regarding the associations between HAC and other ARV medication adherence measures or PD responses.

In addition, some measurement issues in the existing studies deserve attention. For example, the definition of viral suppression for PD response in the existing studies was based on a wide range of cutoffs from 50 copies/mL to 1000 copies/mL. This variation might have impacted the reported associations between HAC and viral suppression. There might have been some temporal mismatch between the assessment windows of HAC and some other adherence measures. For example, self-report adherence measures typically vary by recall periods (e.g., 4 days, 7day, and 6 months) and ARV concentration in other PK metrics represent hours to weeks of ARV exposure, while HAC represents weeks to months of ARV exposure. Those mismatches might impact the associations of HAC with non-PK adherence measures and ARV concentrations in other PK metrics.

Limitations of the current review

This review is subject to some limitations. First, there were insufficient data in included studies for a meta-analysis on the associations between HAC and other ARV medication adherence measures or PD responses. Second, we cannot draw a conclusive conclusion of the associations between HAC and some other adherence measures (e.g., pill counts) because of limited data in existing studies. Third, empirical studies published in other languages were not included in the current review. This limitation might partly contribute to the lack of studies on Asia and South America in our review.

Implications to future research and practice

Despite these limitations, the findings in the current review suggest HAC as a promising measure of ARV medication adherence in both HIV treatment and PrEP prevention research. The findings have several implications for utilizing HAC in future research and practice of HIV treatment and prevention.

First, more empirical studies examining the associations of HAC of additional ARV drugs with other adherence measures and PD responses are needed to validate HAC as a measure for ARV medication adherence. Besides the four drug classes (NNRTI, NRTI, INSTI and PI) in the current review, inhibitors of virus entry/fusion is another class of ARV drug available for treatment.

Presently, there are more than 25 ARV agents approved for HIV treatment by U.S. Food and Drug Administration (FDA) in both single- and multi-drug formulations (e.g., TDF/FTC) [60, 61] and more than 100 regimens prescribed for the treatment of HIV. Simultaneous determination of multiple ARV drugs in hair is also technically possible [12, 13, 19, 20]. On the other hand, additional ARV medication adherence measures are available in adherence research , such as SMS, pharmacy refill records, ARV concentration in saliva[56, 57] and urine [58, 59], and CD4 lymphocyte count. The associations of available HAC with additional ARV medication adherence measures and PD responses might provide more information regarding the utility and validity of HAC as an objective measure for long-term ARV medication adherence.

Second, future attention should be paid to identifying and controlling for the potential confounders of the associations of HAC with other ARV medication adherence measures and PD responses. There are a number of factors (e.g., demographic, behavior, and biological factors) that might affect HAC, non-PK adherence measures, other PK adherence measures and PD responses [18, 62, 63]. These factors might also have an effect on the associations of HAC with other ARV medication adherence measures and PD responses. Therefore, identifying and controlling for the potential confounders may improve our understanding of these associations as well as the effective use of HAC in HIV treatment and prevention research.

Third, future studies need to pay more attention to methodological issues in study design and data analysis. Studies with large and diverse samples and studies in regions beyond Africa and North America are needed. Longitudinal studies with multiple non-PK, PK measures, and PD responses are needed. It is useful to test HAC not only as a valid biomarker of long terms ARV medication adherence but also examine HAC in its function as a predictor of clinical outcomes (e.g., viral load and CD4 count). The improvement in research methodology will improve the internal and external validity of research on HAC as a valid measure of ARV medication adherence.

Conclusions

This review provides a synthesis of the existing literature about the relationship between HAC and other ARV medication adherence measures and PD responses. This systematic review suggests that HAC could be used as a useful and valid biomarker in objectively monitoring long-term ARV medication adherence in HIV treatment and prevention. Further studies with methodological vigor could strengthen this evidence by controling for potential confounders and examining the associations of various HAC with additional ARV medication adherence measures and PD responses.

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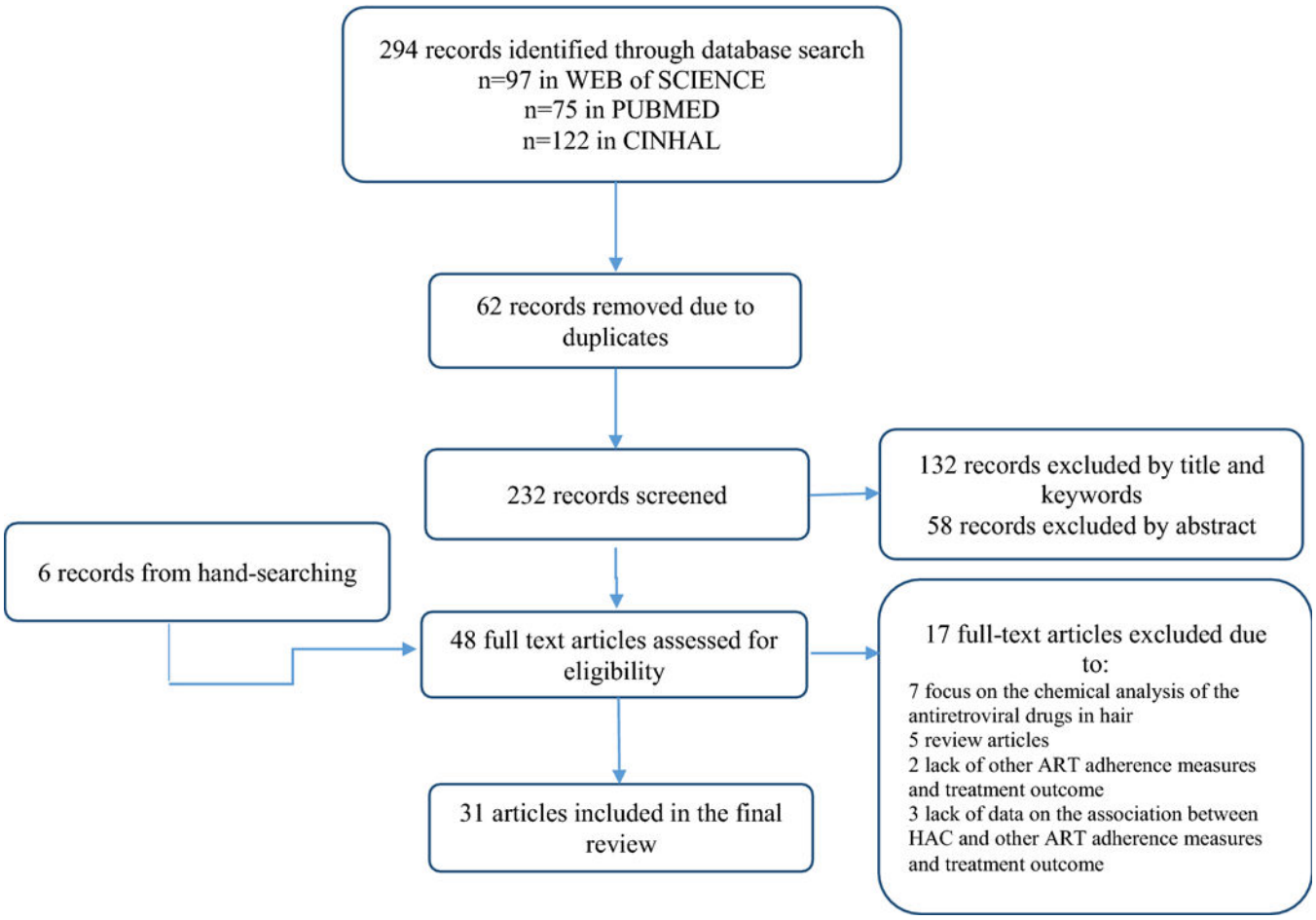

Figure 1.
PRISMA search flowchart for the included studies

Table 1

Characteristics of included studies

study	Country (Year of study)	Sample characteristics	Types of ARV drug				Other adherence measures or PD responses		
			NRTI	NNTRI	PI	INSTI	Non-PK measures	Other PK measures	PD responses
Abaasa et al. (2018)	Uganda and Kenya (2009–2010)	45 PrEP adult, age[*M*±*SD*]: 29.2±6.9y, sex: 66.7% male	TFV	–	–	–	Self-report, EDM	Plasma	–
Bartelink et al.(2014)	Uganda (2009–2012)	221 women living with HIV, age[median (range)]: 30.5 (18–49) y		EFV	LPV RTV	–	Self-report	DBS	–
Baxi et al. (2015)	United States (2003–2008)	271 women living with HIV, age[median(range)]: 39 (20–82)y	–	NVP	–	–	–	–	Viral load
Baxi et al. (2015)	Uganda and Kenya (2009–2010)	88 PrEP adult: 42 in daily PrEP, age[*M*±*SD*]: 29.4±7.0 y, sex: 71.4% male; 46 in intermittent PrEP, age[*M*±*SD*]: 29.6±7.4 y, sex: 73.1% male	TFV FTC	–	–	–	Self-report, EDM	Plasma, PBMC	Renal toxicity
Baxi et al. (2018)	United States (2007–2008)	88 PrEP MSM, age[median (IQR)]: 42 (34–49) y	TFV	–	–	–	Self-report, pill counts, EDM	Plasma, PBMC	Renal toxicity
Bernard et al. (1998)	France (N/R)	30 adult living with HIV, age: N/R, sex: N/R	–	–	IDV	–	–	–	Viralload
Bernard et al. (2002)	France (N/R)	89 adult living with HIV, age: N/R, sex: 73% male	–	–	IDV	–	–	–	Viral load
Chawana et al. (2017)	Zimbabwe (2015–2016)	50 adolescents living with HIV, age[*M*±*SD*]: 15.8±1.8y, sex: 46% male	–	–	ATV	–	Self-report	–	Viral load
Cohan et al. (2015)	Ugandan (2009–2013)	389 women living with HIV: 195 in EFV group age[*M*±*SD*]: 29.5±5.4y; 194 in LPV/RTV group, age[*M*±*SD*]: 29.0±5.4y	–	EFV	LPV RTV	–	–	–	Viral load
Duval et al. (2007)	France (N/R)	43 adult living with HIV, age: N/R, sex: N/R	–	–	IDV	–	–	–	Viral load
Gandhi et al. (2009)	United States (2003–2006)	224 woman living with HIV, age: N/R	–	–	LPV RTV ATV	–	–	–	Viral load
Gandhi et al. (2011)	United States (2003–2008)	424 women living with HIV, age[median(range)]: 43 (21–71)y	–	–	ATV	–	Self-report	–	Viral load
Gandhi et al. (2012)	United States (2003-)	111 women living with HIV, age[median(range)]: 43.1 (20.6–60.4)y	–	EFV	–	–	Self-report	–	
Gandhi et al. (2015)	Brazil, Ecuador, Peru, South Africa, Thailand, and United States (2011–2013)	217 PrEP MSM, age: N/R	TFV FTC	–	–	–	–	DBS	–
Gandhi et al. (2016)	Brazil, Ecuador, Peru, South Africa, Thailand, and United States (2011–2013)	1224 PrEP MSM, age [median (IQR)]: 29 (24–38) y	TFV	–	–	–	–	–	Renal toxicity
Gandhi et al. (2017)	United States (2012–2014)	280 PrEP MSM, age [median (range)]: 34 (19–65) y	TFV	–	–	–	–	–	Renal toxicity
Gandhi et al. (2018)	United States (2009–2013)	599 adult living with HIV. age [median(range)]: 38(18–76)y, sex: 68% male	–	–	ATV, DRV	RAL	–	–	Viral load
Hickey et al. (2014)	Kenya (2011–2012)	373 adult living with HIV, age [median(IQR)]:37 (20–54)y, sex: 36% male	–	NVP	–	–	Self-report	–	–
Koss et al. (2015)	Uganda (2009–2013)	325 women living with HIV, 162 in EFV group age[*M*±*SD*]: 30.3±5.5y; 163 in LPV/RTV group, age[*M*±*SD*]: 29.3±5.3y	–	NVP	LPV	–	–	–	Viral load

study	Country (Year of study)	Sample characteristics	Types of ARV drug				Other adherence measures or PD responses		
			NRTI	NNTRI	PI	INSTI	Non-PK measures	Other PK measures	PD responses
Koss et al. (2017)	Brazil, Ecuador, Peru, South Africa, Thailand, Uganda, United States and Zimbabwe (2009–2012)	547 PrEP adult: 47 PrEP women, age[median(range)]:27 (19–34) y; 220 PrEP MSM, age[median(range)]:29 (19–70) y; 280 PrEP MSM, age[median(range)]:34 (19–65) y;	TFV	–	–	–	Self-report	–	–
Koss et al. (2018)	United States (N/R)	243 PrEP adolescent and young MSM, age[median(range)]:19 (15–22) y	TFV FTC	–	–	–	Self-report, EDM	–	–
Liu et al. (2014)	United States (2009–2011)	23 PrEP adult, age [M±SD]: 34.2±9.0 y, sex: 48% male	TFV	–	–	–	–	Plasma	Renal toxicity
Olds et al. (2014)	Uganda (2008–2009)	121 children living with HIV, age[median (IQR)]: 4.7 (1.2–8.2) y, sex: 49% male	–	NVP	–	–	Self-report, Pill counts, EDM	–	–
Pintye et al. (2017)	Vietnam, Thailand and Indonesia (2011–2012)	244 children living with HIV, age[median (IQR)]: 10 (7–13) y, sex: 55% male	–	–	LPV	–	–	–	Viral load
Prasitsuebsai et al. (2015)	Vietnam, Thailand and Indonesia (N/R)	149 children living with HIV, age[median (IQR)]: 10.3 (7.9–13.3) y, sex: 53% male	–	–	LPV	–	–	Plasma	Viral load
Röhrich et al. (2016)	South African (2010)	120 women living with HIV, aged 25–69 y	–	EFV	–	–	–	–	Viral load
Seifert et al. (2018)	United States (2015–2016)	45 adult living with HIV: 23 younger adult: age[*M*±*SD*]: 31±3y; 22 older adult: age[*M*±*SD*]: 64±4y, sex: 91% male	TFV	–	–	–	–	DBS	Renal toxicity
Servais et al. (2001)	France (N/R)	5 adult living with HIV, age: N/R, sex: N/R	–	–	IDV	–	–	–	Viralload
Tabb et al. (2018)	Tanzania (2013–2015)	227 youth living with HIV, age[median (IQR)]: 16 (11–24) y, sex: 55% male	–	NVP EFV	LPV ATV RTV	–	–	–	Viral load
van Zyl et al. (2011)	South Africa (N/R)	93 adult living with HIV, age[median (IQR)]: 36 (30–46) y, 36% male	–	–	LPV RTV	–	–	–	Viral load
Yan et al. (2016)	China (2013–2014)	287 adult living with HIV, age[M±SD]: 44.9±10.2y, sex: 52.6% male	3TC	–	–	–	–	–	Viral load

Note. ARV=Antiretroviral; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor; HAC=hair ARV concentration; PK=pharmacokinetic; non-PK=non-pharmacokinetic; PD=pharmacodynamic; N/R=not reported; EDM=Electronic drug monitoring; PBMC=Peripheral blood mononuclear cells; DBS=Dried blood spots; 3TC=Lamivudine; TFV=Tenofovir; FTC=Emtricitabine; EFV=Efavirenz; NVP=Nevirapine; IDV=Indinavir; LPV=Lopinavir; RTV=Ritonavir; ATV=Atazanavir; DRV=Darunavir; RAL=Raltegravir; y=year; PrEP=Pre-exposure prophylaxis; MSM=men who have sex with man; M=mean; SD=standard deviation; IQR=interquartile range

Table 2

Summary of characteristics of included studies (n=31)

Characteristics	Number (%)
Median sample size (range)	**217 (5–1124)**
Median age (range) in years	**30.5 (2–82)**
# of included studies enrolled PLWH	**22 (71%)**
# of included studies enrolled populations at high-risk for HIV infection	**9 (29%)**
# of included studies conducted in Africa, North America, Europe, and multiple continents	**12 (38.7%), 9 (29%), 4 (12.9%), 3 (9.7%), and 3 (9.7%)**
# of included studies employing cross-sectional design	**27 (87.1%)**
Classes of ARV drugs used	**4**
# of included studies reporting NRTI, NNRTI, PI, and INSTI	**11 (35.4%), 9 (29%), 15 (48.4%), and 1 (3.2%)**
# of ARV drugs used	**11**
# of included studies reporting ARV drug	**21 (68%)**
# of included studies reporting multiple ARV drugs	**10 (22%)**
# of included studies reporting single measure of adherence or PD response	**20 (64.5%)**
# of included studies reporting multiple adherence measures or/and PD responses	**11 (35.5%)**
# of non-PK adherence measures used	**3**
# of included studies using self-reported measure	**11 (35.5%)**
# of studies reporting high, medium, or low levels for associations	**1 (9.1%), 1 (9.1%), or 9 (81.8%)**
# of included studies using pill count adherence measure	**2 (6.5%)**
# of studies reporting high, medium, or low levels for associations	**0 (0%), 1 (50%), or 1 (50%)**
# of included studies using EDM adherence measure	**5 (16.1%)**
# of studies reporting high, medium, or low levels for associations	**2(40%), 1 (20%), or 2 (40%)**
# of PK adherence measures used	**4**
# of included studies reporting plasma ARV concentration	**5 (16.1%)**
# of studies reporting high, medium, or low levels for associations	**1(20%), 3(60%), or 1 (20%)**
# of included studies reporting PBMC ARV concentration	**2 (6.5%)**
# of studies reporting high, medium, or low levels for associations	**0(0%), 1(50%), or 1 (50%)**
# of included studies reporting DBS ARV concentration	**3 (9.7%)**
# of studies reporting high, medium, or low levels for associations	**2(66.7%), 1(33.3%), or 0 (0%)**
# of PD response measures used	**2**
# of included studies reporting viral load	**17 (54.8%)**
# of studies reporting high, medium, or low levels for associations	**16(94%), 0(0%), or 1 (6%)**
# of included studies reporting renal toxicity	**6 (19.4%)**
# of studies reporting high, medium, or low levels for associations	**3(50%), 0(0%), or 3(50%)**

Note. ARV=Antiretroviral; PK=pharmacokinetic; non-PK=non-pharmacokinetic; PD=pharmacodynamic; PLWH=People living with HIV; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor; EDM=Electronic drug monitoring; PBMC=Peripheral blood mononuclear cells; DBS=Dried blood spots.

Table 3

Summary of statistical findings of HAC with non-PK adherence measures

Study	N	Characteristics of non-PK adherence measure	HAC Characteristics	Statistical method	Result [a]
Self-report					
Abaasa et al., 2018	43	Self-reported pill taking in the last 28 days [median(IQR)]: 7 (7–7) doses per week for Uganda; 7 (6–7) doses per week for Kenya	HAC of TFV [median(IQR)]: 0.07 (0.05–0.11) ng/mg for Uganda; 0.07 (0.03–0.08) ng/mg for Kenya	Pearson correlation	r = −0.01(*NS*) and −0.20 (*NS*) for MSM and seronegative partners of PLWH, respectively
Bartelink et al., (2014)	96	Self-reported the percentage of pill taken was categorized into five categories:<75%, ≥75–85%, ≥85–95%, ≥95–99%, and ≥99%	HAC of LPV, RTV and EFV (range):1.1–13, 0.06–1.35, and 0.4–34 ng/mg	Not specified	Not association (test statistic N/R)
Baxi et al., 2015	88	Self-reported pill taking in the last 28 days: N/R	HAC of TFV and FTC: N/R	Pearson correlation; Regression analysis	r = 0.34 ** and 0.38 *** ! for TFV and FTC at 8 weeks, respectively; r = 0.24 and 0.33 ** for TFV and FTC at 16 weeks, respectively. *OR* 1.04 (95% CI 1.00–1.08), p<0.05 for TFV; *OR* 1.06 (95% CI 1.03–1.09), p<0.05 for TFV
Baxi et al., 2018	47	Self-reported the percentage of pill taken using VAS in the last month [median (IQR)]: 90% (90%−90%)	HAC of TFV [median(range)]: 0.05(0.01–0.21) ng/mg	Spearman correlation; Regression analysis	r = 0.06 (*NS*); *OR* 6% (95%CI −12%−25%), p=0.50; OR_A 5% (95%CI −13%−24%), p=0.59
Chawana et al. 2017	50	Self-reported the percentage of pill taken using VAS was categorized into three categories:<80%, ≥80–94%, and ≥95%; Self-reported closely following dosing schedule in the past 4 days was categorized into two categories: yes or no	HAC of ATV was categorized into two categories: adequate (>2.35ng/mg) and inadequate (≤2.35ng/mg)	Chi-square and Student t tests	p=0. 507 for VAS; p=0.061 for 4-day dosing schedule; p = 0.031 for change in self-reported adherence using VAS.
Gandhi et al., 2011	424	Self-reported the percentage of pill taken using VAS in the past 6 month was categorized into two categories: <95% and ≥95%	HAC of ATV: N/R	Not specified	p< 0.001(test statistic: N/R)
Gandhi et al., 2012	87	Self-reported the percentage of pill taken using VAS in the past 6 month was categorized into three categories: ≤74%, 75–95%, and ≥95%	HAC of EFV [median(range)]: 3.11 (0.05–41.4) pg/mg	regression analysis	ORA 1.00 for ≤74%; ORA 0.94 (95%CI 0.45–1.96), p = 0.88 for 75–95%; ORA 1.11 (95%CI 0.56–2.2), p = 0.77 for≥95%
Hickey et al., 2014	307	Self-reported the percentage of pill taken using the AIDS Clinical Trials Group (ACTG) adherence questionnaire in past 4 days [median (IQR)]: 100% (96%−100%)	HAC of NVP [median(IQR)]: 75.1 (42.1–108.1) pg/mg	regression analysis	OR 1.91 (95%CI 0.42–8.7), p = 0.43; ORA 1.72 (95%CI 0.42–7.1), p = 0.45
Koss et al., 2017	47	Self-reported pill taking in the last 7 days: N/R	HAC of TFV [median(IQR)]: 2.4 (BLQ-16.8) pg/mg	Spearman correlation	r = 0.10 (*NS*)
Koss et al., 2018	243	Self-reported the percentage of pill taken using VAS in the past 30 days [median (IQR)]: 90% (70%−100%)	HAC of TFV and FTC [median(range)]: 0.013(0.002–0.32) ng/mg and 0.16(0.02–2.84) ng/mg	Spearman correlation	r = 0.28 *** and 0.29 *** for TFV and FTC, respectively
Olds et al., 2014	121	Self-reported the percentage of pill taken using caregiver interview in past three days and VAS in the past 30 days [median (IQR)]: 100% (100–100) and 100% (98–102)	HAC of TFV [median(IQR)]: 76.7 (27.7–125.7) ng/mg	Unvariate regression analysis	*OR* 1.10 (95%CI 0.83–1.45) p=0.51 for Three-day caregiver recall; *OR* 1.20 (95%CI 0.97–1.49), p=0.091 for 30-day VAS

Study	N	Characteristics of non-PK adherence measure	HAC Characteristics	Statistical method	Result [a]
Pill counts					
Baxi et al., 2018	47	Announced pill counts in the past 90 days [median (IQR)]: 97.9% (80%−109%)	HAC of TFV median(range): 0.05(0.01–0.21) ng/mg	Spearman correlation Regression analysis	r = 0.38 *; *OR* 12% (95%CI 4% −21%), p=0.003; OR_A 12% (95%CI 4%−20%), p=0.005
Olds et al., 2014	121	Unannounced pill counts [median (IQR)]: 96.1% (87.4–104.8)	HAC of TFV [median(IQR)]: 76.7 (27.7–125.7) ng/mg	Univariate regression analysis	*OR* 0.96 (95%CI 0.90–1.01), p=0.11
Electronic drug monitoring					
Abaasa et al., 2018	43	Pill bottle cap opening in the past 28 days [median (IQR)] openings per week 7 (6–7) for Uganda; 5 (4–7) for kenya	HAC of TFV [median(IQR)]: 0.07 (0.05–0.11) ng/mg for Uganda; 0.07 (0.03–0.08) ng/mg for Kenya	Pearson correlation	r = 0.41 ** and 0.85 ** for seronegative of PLWH partners and MSM, respectively
Baxi et al., 2015	88	Pill bottle cape openings: N/R	HAC of TFV and FTC: N/R	Pearson correlation Regression analysis	r = 0.50 *** and 0.58 *** for TFV and FTC at 8 weeks, respectively. r=0.62 *** and 0.73 *** for TFV and FTC for TFV at 16 weeks, respectively; *OR* 1.08 (95%CI 1.06–1.10) for TFV, *OR* 1.10 (95%CI 1.08–1.12) for FTC, all p<0.05; OR_A 1.08 (95%CI 1.06–1.10) for TFV; OR_A 1.11 (95%CI 1.09–1.13) for FTC, all p<0.05
Baxi et al., 2018	47	Pill bottle cap openings in the past 90 days [median (IQR)]: 87% (77%−93%)	HAC of TFV [median(range)]: 0.05(0.01–0.21) ng/mg	Pearson correlation	r = 0.20 *; *OR* 2% (95% CI −5%−9%), p=0.52; OR_A 2% (95% CI −5%−9%), p=0.50.
Koss et al., 2018	243	Pill bottle cap openings in the past 30 days [median (IQR)]: 3 (IQR, 0–35.5)	HAC of TFV and FTC [median(range)]: .013(0.002–0.32) ng/mg and 0.16(0.02–2.84) ng/mg	Pearson correlation	r = 0.40 *** and 0.36 *** for TFV and FTC, respectively
Olds et al., 2014	121	Pill bottle cap openings [median (IQR)]: 96.1% (87.4–104.8)	HAC of NVP [median(IQR)]: 76.7	Regression analysis	*OR* 1.16 (95% CI 0.93–1.44), p=0.19

Note.

* p<0.05

** p<0.01

*** p<0.001

HAC=hair ARV concentration; non-PK=non-pharmacokinetic; N/R=not reported; EDM=Electronic drug monitoring; VAS=visual analog scale; TFV=Tenofovir; FTC=Emtricitabine; EFV=Efavirenz; NVP=Nevirapine; LPV=Lopinavir; RTV=Ritonavir; ATV=Atazanavir; MSM= men who have sex with man; OR=odds ratios; HR = Hazard ratios; M=mean; SD=standard deviation; IQR=interquartile range.

[a] Odds ratios, hazard ratios, and relative risks are unadjusted unless denoted by subscript “A”.

Table 4

Summary of statistical findings of HAC with other PK adherence measures

Study	N	Characteristics of other PK adherence measure	HAC characteristics	Statistical method	Result [a]
Plasma					
Abaasa et al., 2018	43	Plasma TFV concentration [median(IQR)]: 70.5 (38.9–94.6) ng/mL for Uganda; 81.0 (40.0–148.2) ng/mL for Kenya	HAC of TFV [median(IQR)]: 0.07 (0.05–0.11) ng/mg for Uganda; 0.07 (0.03–0.08) ng/mg for Kenya	Pearson correlation	$r = 0.29^{*}$ and 0.36^{**} for seronegative partners of PLWH and MSM, respectively
Baxi et al., 2015	88	Plasma TFV and FTC concentration: N/R	HAC of TFV and FTC: N/R	Pearson correlation	$r = 0.41^{***}$ and 0.51^{***} for TFV and FTC at 8 weeks, respectively; $r = 0.61^{***}$ and 0.72^{***} for TFV and FTC at 16 weeks, respectively
Baxi et al., 2018	47	Plasma TFV concentration: [median (range)]: 83 (10–367) ng/mL	HAC of TFV [median (range)]: 0.05 (0.01–0.21) ng/mg	Spearman correlation	$r = 0.36^{*}$
Liu et al., 2014	23	Plasma TFV concentration: N/R N/R	HAC of TFV:N/R	Multivariate regression analysis	*OR* 23%, p=0.035.
Prasitsuebsai et al., 2015	149	Plasma LPV concentration [median(IQR)]: 6.7 (4.1–9.6) mg/L	HAC of LPV [median(IQR)]: 5.43 (3.21–9.01) ng/mg for virologic faire; 9.96 (6.51–12.31) ng/mg for virologic success	Pearson correlation	r=0.20 (*NS*)
PBMCs					
Baxi et al., 2015	88	PBMCs TFV and FTC concentration: N/R	HAC of TFV and FTC: N/R	Pearson correlation	r=0.43*** and 0.50*** for TFV and FTC at 8 weeks, respectively; $r = 0.74^{***}$ and 0.86^{***} for TFV and FTC at 16 weeks, respectively
Baxi et al., 2018	47	PBMCs TFV concentration [median(range)]: 40 (5–102) fmol/million cells	HAC of TFV [median(range)]: 0.05 (0.01–0.21) ng/mg	Spearman correlation	$r = 0.34^{*}$
DBS					
Bartelink et al., 2014	96	DBS LPV, RTV and EFV concentration: N/R	HAC of LPV, RTV and EFV (range):1.1–13, 0.06–1.35, and 0.4–34 ng/mg	Not specified	$r = 0.67^{***}$, 0.85^{***}, and 0.60^{***} for LPV, RTV, and EFV, respectively
Gandhi et al., 2015	217	DBS TFV and FTC concentration: N/R	HAC of TFV and FTC: N/R	Spearman correlation	$r = 0.734^{***}$ and 0.587^{***} for TFV and FTC, respectively
Seifert et al., 2018	31	DBS TFV concentration: N/R	HAC of TFV: N/R	Pearson correlation	$r = 0.50^{***}$

Note.

* p<0.05

** p<0.01

*** p<0.001

HAC=hair ARV concentration; N/R=not reported; PK=pharmacokinetic; PBMC=Peripheral blood mononuclear cells; DBS=Dried blood spots; TFV=Tenofovir; FTC=Emtricitabine; EFV=Efavirenz; LPV=Lopinavir; RTV=Ritonavir; MSM=men who have sex with man; OR=odds ratios; HR=Hazard ratios; M=mean; SD=standard deviation; IQR=interquartile range.

[a]Odds ratios, hazard ratios, and relative risks are unadjusted unless denoted by subscript “A”.

Table 5

Summary of statistical findings of HAC with PD responses

Study	N	Characteristics of PD responses measure	HAC characteristics	Statistical method	Result [a]
VL					
Baxi et al., 2015	271	271 VL[median(range)]: 5300 (80–4800000) copies/ mL VS: VL<80 copies/mL; VF: VL≥80 copies/mL	HAC of NVP was categorized into four quintile: Q1 (0.25–16.28 ng/ mg), Q2 (16.29–32.13 ng/mg), Q3 (32.14–57.33 ng/mg), Q4 (>57.33 ng/mg)	Regression analysis	The OR_A of VS increased with increasing quartile of HAC of NVP. OR_A 2.47, 95% CI (1.09–5.6), p=0.031for Q2, OR_A 3.33, 95% CI (1.33–8.3), p=0.010 for Q3, and OR_A 9.17, 95% CI (3.2–26), p < 0.0001 for Q4
Bernard et al., 1998	30	VS: VL<200 copies/mL, n=19; VF: VL≥200 copies/mL, n=11	HAC of IDV [M±SD]: 17.85±5.08 μg/g for VS and 8.01 ±5.39 μg/g for VF	Mann-Whitney U test	p=0.0001 (test statistic: N/R)
Bernard et al., 2002	89	VS:VL<500 copies/mL, n=65; VF: VL≥500 copies/mL, n=24	HAC of IDV [M±SD]: 24.4 ±16.0 μg/g for VS and 12.9 ±8.6 μg/g for VF	Student t test Mann-Whitney U test	p<0.001 for the first 2-cm hair; p=0.016 for the second 2-cm hair; all $p>0.05$ for the third and fourth 2-cm hair
Chawana et al., 2017	42	VS: VL <1000 copies/mL, n=18; VF : VL≥1000 copies/mL, n=24	HAC of ATV [median(IQR)]: 3.21 (2.35–6.61) ng/mg for VS, 0.94 (0.16–2.73) ng/mg for VF	Chi-square and Student t tests	p <0.0001 (test statistic: N/R)
Cohan et al., 2015	389	VL[median(IQR)]: 4.3 (3.5–4.8) $\log_{10}$ copies/mL for EFV arm, and 4.1 (3.3–4.7) $\log_{10}$ copies/mL for LPV/RTV arm; and 4.1 (3.3–4.7) $\log_{10}$ copies/mL for LPV/RTV arm; VS: VL < 400 copies/mL	HAC of EFV, LPV and RTV: N/R	Not specified	OR 2.25 95% CI (1.53–3.30), p<0.001
Duval et al., 2007	43	VS:VL<50 copies/mL, n=29; VF: VL≥50 copies/mL, n=14	HAC of IDV[median(IQR)]: 15 (6–21) μg/g for VS and 8 (4–11) μg/g for VF	Regression analysis	OR_A= 3.88, 95% CI (1.01–14.94), p=0.04
Gandhi et al., 2009 224	224	VL[median(IQR)]: 4.18 (1.90–6.49) log10 copies/mL for LPV/RTV arm, and 3.96 (1.90–6.10) log10 copies/mL for ATV/RTV arm; VS: VL<80 copies/mL, n=52 and 122 for LPV and ATV; VF: VL>80 copies/mL, n=18 and 32 for LPV and ATV	HAC of LPV and ATV[median]: 1.58 ng/mg for VS and 0.29 ng/mg for VF in LPV arm; 2.60 ng/mg for VS and 0.67 ng/mg for VF in LPV arm; HAC of LPV and ATV was categorized into three tertiles: lowest(≤0.41 for LPV and ≤1.19 for ATV), middle (0.41–1.86 for LPV and 1.19–3.43 for ATV) and highest (>1.86 for LPV and >3.43 for ATV)	Wilcoxon rank test Regression analysis	p =0.0008 for LPV, p <0.0001 for ATV, p <0.0005 for RTV/LPV, p<0.0017 for RTV/ATV (test statistic: N/R) The OR_A of VS increased with increasing tertile of HAC of LPV and ATV. LPV arm: OR_A 2.6, 95% CI (0.59–11.9), p=0.21 for middle tertile, OR_A 39.8, 95% CI (0.59–11.9), p=0.006 for highest tertile; ATV arm: OR_A 2.7, 95% CI (1.00–7.3), p=0.21 for middle tertile, OR_A 7.7, 95% CI (2.0–29.7), p=0.003 for highest tertile
Gandhi et al., 2011	424	VL[median(range)]: 5950 (80–2500000) copies/mL VS: VL<80 copies/mL	HAC of ATV was categorized into five quintile: Q1 (0.05–0.658 ng/ mg), Q2 (>0.658–1.78 ng/mg), Q3 (>1.78–3.13 ng/mg), Q4 (>3.13–5.19 ng/mg), Q5 (>5.19 ng/mg)	Regression analysis	The OR_A of VS increased with increasing tertile of HAC of ATV. OR_A 4.3, 95% CI (2.5–7.4) for Q2, OR_A 12.7, 95% CI (7.1–22.8) for Q3, OR_A 22.9, 95% CI (12.2–43.1) for Q4, OR_A 59.8, 95% CI (29.0–123.2) for Q5, all p <0.001

Study	N	Characteristics of PD responses measure	HAC characteristics	Statistical method	Result [a]
Gandhi et al. 2018	559	VF: VL>1000 copies/ mL at or after 16 weeks and before 24 weeks, VL>200 copies/ mL at or after 24 weeks	HAC of ATV, DRV, and RAL [median (range)]: 3.52 (0.05–17.3), 2.71 (0.028–21), and 0.54 (0.02–4.2) ng/mg. HAC of ATV, DRV, and RAL was categorized into lowest, middle and highest tertiles: N/R		The HR of VF increased with decreasing tertile of HAC of ATV, DRV, and RAL. HR 2.43 95% CI (1.96–3.13), p <0.001 for baseline HR for highest tertile, HR 1.71 95% CI (0.52–6.53), p = 0.39 for middle tertile, HR 6.79 95% CI (2.65–23.00), p = 0.004 for lowest tertile for follow-up
Koss et al., 2015	325	VS: VL<400 copies/ mL, In EFV arm: 98.0% VS for delivery and 92.5% VS for 24 weeks postpartum In EFV arm: 87.4% VS for delivery and 90.6% VS for 24 weeks postpartum	HAC of EFV and LPV [M (range)]: 5.7 (0.05–36.7) ng/mg and 6.6 (0.05–47.2) ng/mg for delivery; 6.3 (0.05–42) ng/mg and 5.7 (0.05–23.8) ng/mg for postpartum	Regression analysis	OR 1.86, 95% CI (1.14–3.1), p=0.013 and OR_A 1.86, 95% CI (1.14–3.1), p=0.013 for delivery; OR 1.58, 95% CI (1.18–2.1), p=0.002 and OR_A 1.81, 95% CI (1.22–2.7), p=0.003 for postpartum LPV arm: OR 1.62, 95% CI (1.19–2.2), p=0.002 and OR_A 1.90, 95% CI (1.33–2.7), p=0.0004 for delivery; OR=1.51, 95% CI (1.05–2.2), p=0.027 and adjusted OR_A 1.53, 95% CI (1.05–2.2), p=0.026 for postpartum
Pintye et al., 2017	244	VL[median(IQR)]: 5.0 (4.3–5.6) $\log_{10}$ copies/mL VS: VL<400 copies/ mL or VL<1000 copies/ mL, VF: VL>400 copies/mL or VL>1000 copies/mL	HAC of LPV[median(IQR)]: 9.66 (7.00–13.11) ng/mg	Regression analysis	OR 0.56, 95% CI (0.47–0.67), p<0.001 and OR_A 0.41, 95% CI (0.29–0.58), p<0.001 for VL>400 copies/mL; OR 0.54, 95% CI (0.45–0.65), p<0.001 and OR_A 0.46, 95% CI (0.34–0.63), p<0.001 for VL>1000 copies/mL
Prasitsuebsai et al., 2015	149	VS: VL<1000 copies/ mL, n=132 VF: VL>1000 copies/mL, n=17 VS: VL<50 copies/ mL, n=104	HAC of LPV [median(IQR)]: 9.96 (0.51–12.31) ng/mg for VS, 5.43(3.21–9.01) ng/mg for VF; HAC of LPV was categorized into four quintile: Q1 (≤6.11ng/mg), Q2 (6.36–9.56 ng/mg), Q3 (9.75–12.13 ng/mg), Q4 (12.15–22.10 ng/mg) HAC of EFV [median (range)]: Cape Mixed Ancestry: 5.9 (0.9–20.9) ng/mg for VS and 5.5 (1.2–10.2) ng/mg for VF; South African Blank: 5.2 (0.5–27.0) for VS and 8.2 (1.1–9.9) for VF.	Wilcoxon rank test; Regression analysis Regression analysis	p = 0.003 (test statistic: N/R); The OR of VS increased with increasing quartile of HAC of LPV. OR_A 4.05, 95% CI (1.01–16.15) for Q2, OR_A 6.25, 95% CI (1.27–30.88) for Q3 and Q4, p =0.02
Röhrich et al., 2016	120	VF: VL>50 copies/mL, n=16		Regression analysis	Not association (test statistic: N/R; significance N/R)
Servais et al., 2001	5	VL: N/R	HAC of IDV: N/R	Not specified	P < 0.001 (test statistic: N/R)
Tabb et al., 2018	227	VS: VL<400 copies/mL, n=50, 53, 5, 28, and 33 for NVP, EFV, ATV, LPV and RTV, respectively; VF: VL>400 copies/mL, n=28, 33, 8, 22, and 33 for NVP, EFV, ATV, LPV and RTV, respectively	HAC of NVP, EFV, ATV, LPV and RTV [median (IQR)]: 4.85 (3.11–8.47), 54.85 (41.90–75.30), 7.09 (2.30–7.12), 9.72 (6.32–16.10), and 0.84 (0.61–1.27) ng/mg for VS, respectively; 0.98 (0.24–3.65), 34.35 (13.55–59.80), 2.06 (0.75–3.22), 0.53 (0.23–1.42), and 0.14 (0.03–0.51) ng/mg for VF, respectively	Wilcoxon rank test	All p < 0.001 for NVP, EFV, LPV, and RTV; p =0.11 for ATV (test statistic: N/R)

Study	N	Characteristics of PD responses measure	HAC characteristics	Statistical method	Result [a]
van Zyl et al., 2011	93	VS: VL<400 copies/mL, n=19 and 19 for LPV and RTV; VF: VL>400 copies/mL, n=19 and 19 for LPV and RTV	HAC of LPV and RTV [median (IQR)]: 8.36 (5.63–12.13) and 0.81 (0.46–1.22) ng/mg for VS; 0.97 (0.27–3.15) and 0.13 (0.04–0.54) ng/mg for VF	Wilcoxon rank test	p =0.0009 for LPV; p =0.0084 for RTV (test statistic: N/R
Yan et al., 2016	287	VS: VL<1000 copies/mL, n=208; VF: VL>400 copies/mL, n=39 for VF without drug resistance and n=40 for VF with drug resistance	HAC of 3TC[M±SD]: 915.0±670.5 ng/g for VS, 284.1±538.9 ng/g for VF without drug resistance, and 648.4±616.9 ng/g for VF with drug resistance	Wilcoxon rank test	p < 0.001 for compare VS with VF without drug resistance; p=0.0125 for compare VS with VF with drug resistance (test statistic: N/R)
Renal toxicity					
Baxi et al., 2015	88	Creatinine clearance [M±SD]: 111±28.3 mL/min for daily dosing, 107±32.4 mL/min for intermittent dosing	HAC of TFV and FTC: N/R	Regression analysis	*OR* 1.02 95% CI (0.89–1.16) for TFV and *OR* 1.03 95% CI (0.91–1.17) for FTC, all p>0.0
Baxi et al., 2018	47	Creatinine clearance [median (IQR)]: 122 (97–144) mL/min	HAC of TFV: N/R	Regression analysis	*OR* −6% 95% CI (−12% −1%), p= 0.08; OR_A =−6% 95% CI (−12%−1%), p= 0.75
Gandhi et al. 2016	220	Creatinine clearance [median (IQR)]: 112 (99–128) mL/min	HAV of TFV and FTC [M ± SD]: 0.027 ± 0.065 ng/mg and 0.45 ± 0.73 ng/mg	Mix effects models	p=0.008 for TFV; p=0.006 for FTC (test statistic: N/R)
Gandhi et al. 2017	280	Creatinine clearance [median (IQR)]: 129 (109–147) mL/min	HAC of TFV: N/R	Mix effects models	p=0.011 (test statistic: N/R)
Liu et al., 2014	23	Creatinine clearance [M±SD]: 129.4±31.1 mL/min	HAC of TFV: N/R	Regression analysis	p=0.52 (test statistic: N/R)
Seifert et al. 2018	45	Creatinine clearance [M ± SD]: 119±36 mL/min for old adult, 96±32 mL/min for young adult	HAC of TFV: N/R	Regression analysis	*OR* 16.9% 95% CI (9.1% −25.3%), p= 0.0001; OR_A 15.9% 95% CI (7.4% −25.0%), p= 0.0006

Notes.

* p<0.05

** p<0.01

*** p<0.001

HAC=hair ARV concentration; PD=pharmacodynamics; N/R=not reported; VL=viral load; VS=virologic suppression; VF=virologic failure; 3TC=Lamivudine; TFV=Tenofovir; FTC=Emtricitabine; EFV=Efavirenz; NVP=Nevirapine; IDV=Indinavir; LPV=Lopinavir; RTV=Ritonavir; ATV=Atazanavir; DRV=Darunavir; RAL=Raltegravir; OR=odds ratios; HR=Hazard ratios; M=mean; SD=standard deviation; IQR=interquartile range.

[a] Odds ratios, hazard ratios, and relative risks are unadjusted unless denoted by subscript “A”.