Factors Related to Hair Antiretroviral Concentration: A Systematic Review of Global Literature

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Abstract

Assessment of antiretroviral (ARV) concentration in hair (hair antiretroviral concentration [HAC]) is one of the latest non-invasive innovations for measuring long-term ARV adherence. We performed a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines to identify the factors that may affect the validity and reliability of HAC. This review included 25 studies that reported data on the associations of hair concentrations of 10 ARVs with 22 potential factors related to HAC. Notwithstanding scarce data and some inconsistencies, the data from existing studies suggested that (1) HAC was associated with hair types, hair segment position, housing, illegal drugs use, high-risk sexual behaviors, renal function, and genetic factors; (2) HAC was not associated with race/ethnicity, location of sample, ARV side effects, length of ARV treatment, smoking, alcohol use, orange consumption, depression, or anthropometry characteristics; and (3) the relationships of HAC with natural hair color, hair treatment, age, sex, dosing schedule, and liver function need further study. This review of factors related to HAC informed the design, analysis, and interpretation of the future HIV treatment and HIV prevention research utilizing hair concentrations of various ARVs as a biomarker of ARV adherence. (AIDS Rev. 2020;22:25-33)

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Key words

Antiretroviral. Adherence. Hair. Pharmacokinetics. HIV/AIDS.

Introduction

Optimal antiretroviral (ARV) adherence is vital to viral suppression and improved clinic outcomes among people living with HIV (PLWH) and HIV prevention among populations at risk for HIV infection[1-3]. Numerous studies have made attempts to develop valid and reliable measurements for assessing ARV adherence. Compared with the self-report approach, the measurement of ARV concentration in various pharmacokinetic (PK) metrics

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(e.g., plasma, dried blood spots, and hair) could provide relatively objective evidence of adherence without the risk of recall bias and social desirability[4-7]. Among all measurements of ARV concentration in PK metrics, hair ARV concentration (hair antiretroviral concentration [HAC]) shows promise due to its various advantages. Hair collection is noninvasive, and hair specimens do not require sterile equipment or specialized storage conditions[5,7,8]. More important, HAC reflects ARV uptake from the systemic circulation over weeks to months, providing a cumulative record of ARV exposure[8,9]. All of these advantages make HAC appealing as a biomarker of long-term ARV adherence[7,9-11]. Recently, studies demonstrated that HAC is the independent predictor of virologic success[12-14], and HAC has been associated with other adherence measures, such as electronic drug monitoring[15] and ARV concentration in plasma[15,16], peripheral blood mononuclear cells[15], and dried blood spots[17].

However, many factors may affect the validity and reliability of HAC as a measurement of ARV adherence. The principal source of drug levels in hair has been proposed to be through active or passive diffusion from the bloodstream[18,19]. Therefore, various factors related to the process of drug incorporation into hair may also affect the validity and reliability of HAC. For example, existing studies suggested that the factors related to ARV adherence behavior (adherence-related factors, e.g., substance use) and the factors related to ARV absorption, distribution, metabolism, or excretion (e.g., genetic factor) were associated with plasma ARV concentration[20-24]. In addition, hair-related characteristics (e.g., natural hair color) were associated with hair concentration of other drugs such as amphetamine[25], cocaine[26], and ethyl glucuronide[27]. Therefore, these factors may also affect ARV levels in hair, inducing threats to the validity and reliability of the HAC measurement.

While very limited studies have specifically examined the influences of these factors on ARV levels in hair, a majority of HAC studies considered these factors as covariates in statistical analyses. To better understand the HAC measurement and enhance its validity and reliability in ARV adherence, it is worth identifying factors that may provide confounding effects on HAC. Accordingly, we conducted a systematic review of global literature associated with HAC. This systematic review study has multiple aims: (a) to identify factors related to ARV levels in hair, and (b) to identify the knowledge gaps and provide recommendations for further research and practice in using HAC as a biomarker of ARV adherence.

Methods

Data source and searching algorithm

Literature search was performed in March 2019 utilizing the following three databases: PubMed, Web of Science, and CINHAL. The keywords used for the search included: ARV (ARV therapy, ARV drugs, and ARV 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-analyses guidelines[28].

Inclusion criteria

The following inclusion criteria were used in this review: (1) original research articles published in English-language journals before March 2019; (2) studies conducted among humans (e.g., PLWH or populations at risk for HIV infection); and (3) articles reported appropriate statistics (e.g., correlation coefficients and odds ratio) on the associations between HAC and the factors.

Screening and data extraction

The initial search identified 554 articles from three electronic databases. After removing duplicated records according to the title and abstract review, 52 articles remained for subsequent full-text screening (Fig. 1). Twenty-seven articles were excluded during the full-text screening due to lack of data on the factors related to HAC (n = 11), lack of data on the association between HAC and the factors (n = 8), or non-original research articles (n = 8). Twenty-five studies were included in the final review.

In this review, the following data were extracted from the included articles: (1) study characteristics (e.g., location and year of data collection); (2) sample characteristics including sample size, age, and sex distributions; (3) classes of ARV drugs; (4) factors related to HAC; (5) characteristics of these factors; (6) characteristics of HAC; (7) statistical method; and (8) associations of HAC with these factors.

Results

Study description

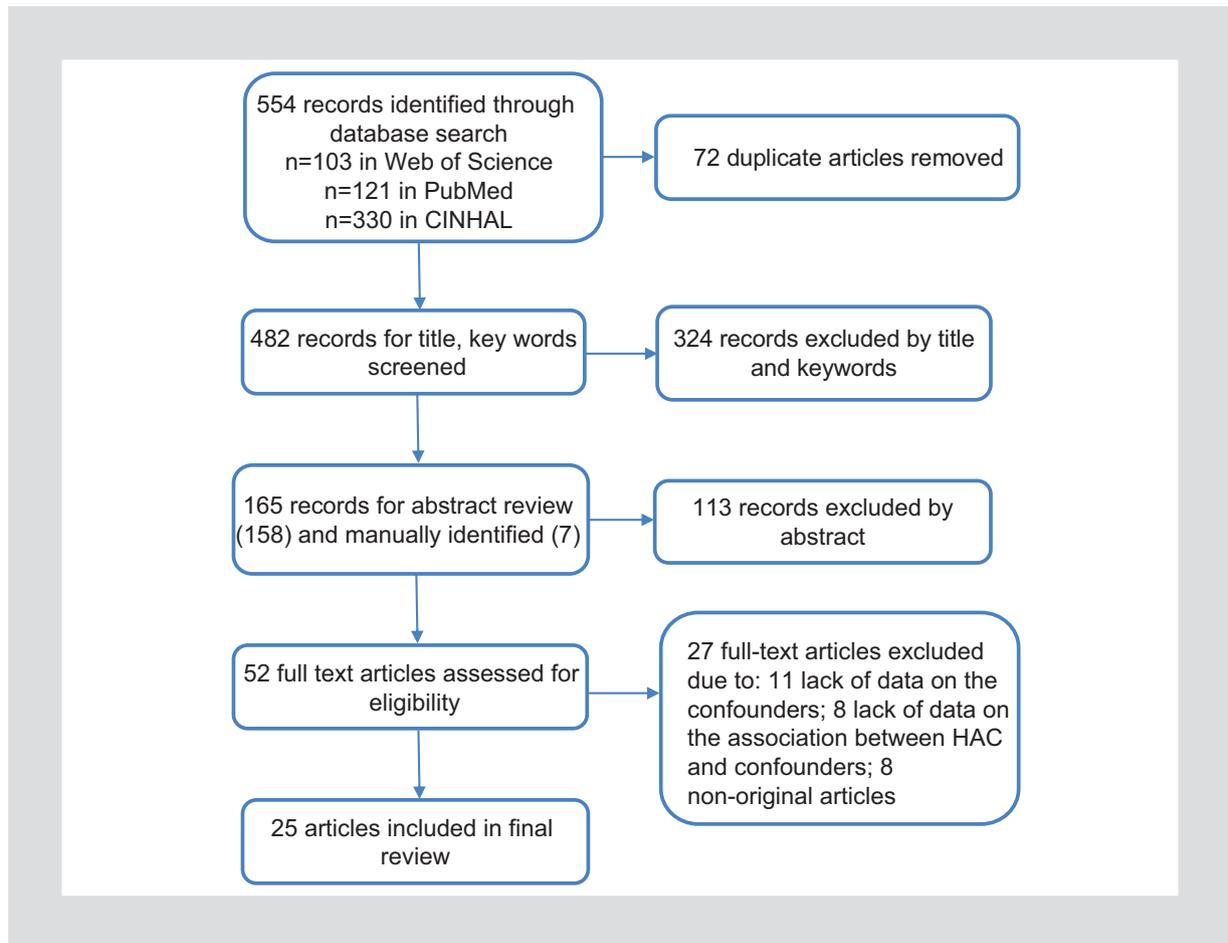The key characteristics of the included studies are presented in supplementary table 1. Of the studies in-

Figure 1. *PRISMA search flowchart for the reviewed studies.*

cluded in this review, one was published in 1998, two in the period from 2000 to 2010, and 22 since 2011. In terms of the geographic distribution of the studies, seven studies were conducted in Africa, ten studies were conducted in North America, three in Europe, three in Asia, and two in multiple continents (South America, North America, Asia, and Africa). In terms of the sample characteristics of the studies, 19 studies enrolled PLWH, including children, adolescents, and adults, while other studies were conducted among populations at risk for HIV, including seronegative partners of PLWH and seronegative men who have sex with men (MSM). The median sample size in the studies was 152 (range 8-1224). The median age of participants was 30.5 years old (range 11-82).

In terms of characteristics of ARV drugs, the included studies examined hair concentrations of ten ARV drugs in three classes: nucleoside reverse transcriptase inhibitor (NRTI) including zidovudine (AZT), lamivudine (3TC), tenofovir (TFV), and emtricitabine (FTC); non-NRTI including nevirapine (NVP) and efavirenz (EFV); and protease inhibitor (PI) including indinavir (IDV), atazanavir (ATV), lopinavir (LPV), and ritonavir (RTV). The included studies reported a total of 21 factors that were divided into three main categories including hair-related characteristics (e.g., hair types, natural hair color, hair treatment, and hair segment position), adherence-related factors (e.g., socio-demographic factors, medication-related factors, and psychological and behavioral factors), and PK-related factors (e.g., anthropometry characteristics, liver function, renal function, and genetic characteristics).

Hair-related characteristics

As shown in supplementary table 2, eight studies reported data on the associations of HAC with hair-related characteristics, including hair types, natural hair color, hair treatment, and hair segment position.

Hair types

Liu et al. found that scalp hair TFV concentration increased monotonically as the TFV dose increased. However, pubic hair TFV concentration was not mono-

tonically increased when TFV dose increased[29]. Furthermore, Saberi et al. found TFV and FTC concentrations in back scalp hair were highly associated with those concentrations inside scalp hair[30].

Natural hair color

Baxi et al. reported that reddish/blonde hair color (vs. black/brown) was associated with lower HAC of TFV in the unadjusted model, but the association became insignificance in adjusted model[31]. Seifert et al. reported that gray hair color (vs. non-gray) was associated with higher HAC of TFV in unadjusted model, but the association became insignificance in adjusted model[32]. The failure to find an association between natural hair color and HAC of TFV might be because TFV is a hydrophilic drug, which may have a lower binding affinity to melanin. While 3TC is a lipophilic drug that has a greater binding affinity to melanin, Wu et al. reported that PLWH who took the same oral dosage (300 mg) of 3TC and TFV had higher HAC of 3TC than HAC of TFV[33].

Hair treatment

Baxi et al. reported that cosmetic treatment was associated with lower HAC of TFV in the unadjusted model, but the association became insignificance in adjusted model[31]. Huang et al. reported that washed hair showed a lower NVP concentration comparing with unwashed hair, but the difference did not reach a significant level; no difference was found in NVP concentration between ultraviolet light treated hair and untreated hair[34].

Hair segment position

Three studies reported data on the associations of HAC with the position of the hair segment. All three studies found that the highest IDV, 3TC, TFV, or NVP levels were located in the scalp-nearest hair segment, and their levels then decreased with the distance of hair segment away from the scalp[33,35,36]. Bernard et al. reported that the overall mean HAC of IDV decreased about 5 µg/g by every one 2-cm hair segment away from the scalp[36]. Wu et al. reported that HAC of 3TC, TFV, and NVP dropped by 60.4%, 68.5%, and 61.1%, respectively, from the first 1-cm hair segment to the second 1-cm hair segment; and then slowly dropped or kept at low levels[33].

Taken together, the preliminary data suggested that scalp-nearest hair segment is more accurate for measuring ARV adherence than the distance of the hair segment away from the scalp. However, data are still limited or inconclusive on the relationships of HAC of various ARV drugs with hair color and hair treatment.

Adherence-related factors

As shown in supplementary table 3, 14 studies reported data on the associations of HAC with adherence-related factors, including socio-demographic factors, medication-related factors, and behavioral and psychological factors.

Socio-demographic factors

HAC studies documented inconsistent findings of the relationship between age and HAC. Eight studies reported the associations of age with HAC. All three PrEP studies reported that age was positively associated with HAC of TFV[15,31,37] or FTC[15] in univariate model, but the association became insignificance in the multivariate model. In five HIV treatment studies, Chawana et al. and Tamraz et al. found that age was not associated with HAC of ATV among a small sample of children with narrow age ranges[38] or a large sample of an adult with broader age ranges[39]. Seifert et al. found that old adults have higher HAC of TFV than young adults, but the association became insignificance in multivariate model[32]. Johnston et al. found that age was not associated with HAC of EFV[16]. However, Hickey et al. found that age was positively associated with HAC of NVP among adults with broader age ranges in both univariate and multivariate model[40].

Seven studies reported data on the associations of sex with HAC. Five studies reported no sex difference in HAC of TFV, FTC, AZT, EFV, or ATV in univariate model[29,41] or multivariate model[15,39,42]. Chawana et al. reported that male adolescent was associated with a higher HAC of ATV at 3-month follow-up[38]. However, Hickey et al. reported that females adults had a significantly higher HAC of NVP than males in both univariate and multivariate model[40].

Three studies reported data on the associations of race/ethnicity with HAC. All three studies reported that race/ethnicity was not associated with HAC of TFV[37], ATV[39], or EFV[43].

Housing may also a socio-demographic factor related to HAC. Gandhi et al. found that, compared to having a stable housing (e.g., renting or owning a house or apartment), having an unstable housing

(e.g., living in a friend or family member's house) was associated with lower HAC of TFV in both unadjusted and adjusted model[37].

Research also revealed a relationship between geographic locations and HAC. Baxi et al. found that subjects from different countries (Uganda vs. Kenya) reported a different level of TFV in hair and plasma in the unadjusted model, but the associations became insignificance in adjusted model[15]. Gandhi et al. found that subjects from different cities (San Francisco vs. Washington DC or Miami) did not differ in hair levels of TFV or FTC in both unadjusted and adjusted model[37].

Medication-related factors

Four studies reported data on the associations of ARV dosing schedule with HAC. Duval et al. found that IDV daily doses (200 mg, 400 mg, or 600 mg BID) were not associated with HAC of IDV or plasma IDV concentration[44]. Baxi et al. found that, compared to intermittent dosing, daily dosing was associated with higher HAC of TFV and FTC than PLWH without daily dosing in unadjusted model, but the association became insignificance in adjusted model[15]. Liu et al. and Koss et al. found that TFV dosing was associated with HAC of TFV[29,45].

Two studies reported data on the associations of ARV side effects with HAC. Both studies found that ARV side effects were not associated with HAC of EFV, LPV, RTV[46], or TFV[29].

Two studies reported data on the associations of the length of ARV treatment with HAC. Both studies reported no association of length of ARV treatment with HAC of ATV[38] or HAC of IDV[36].

Behavioral and psychological factors

Three studies reported data on the associations of HAC with illegal drugs use. Baxi et al. found that the consumption of khat or marijuana was associated with a decrease in HAC of FTC in both unadjusted and adjusted models. However, the consumption of khat or marijuana was not associated with HAC of TFV in either unadjusted or adjusted model[15]. Tamraz et al. found that cocaine use was associated with a decrease in HAC of ATV[39]. Gandhi et al. found that the use of amphetamine was associated with an increase in HAC of TFV in both unadjusted and adjusted model[37].

Tamraz et al. found that neither smoking nor alcohol use was associated with HAC of ATV[39]. Gandhi et al.

found that the presence of depression was not associated with HAC of TFV[37]. However, condomless receptive anal sex was associated with HAC of TFV[37], and orange consumption was associated with plasma EFV concentration, but not associated with HAC of EFV[47].

Overall, the preliminary data suggested that HAC was not associated with most adherence-related factors including race/ethnicity, location of sample, ARV side effects, length of ARV treatment, smoking, alcohol use, orange consumption, and depression, while HAC was associated with illegal drugs use, housing, and condomless receptive anal sex. However, data are still scarce or inconclusive on the relationships of HAC with age, sex, and dosing schedule.

PK-related factors

As shown in supplementary table 4, 14 studies reported data on the associations of HAC with PK-related factors, including anthropometry characteristics, liver function, renal function, and genetic factors.

Anthropometry characteristics

Six studies reported data on the associations of HAC with anthropometry measures, including weight, height, and body mass index (BMI). In terms of weight, all three studies found that weight was not associated with HAC of TFV[15,29,31] or FTC[15] in the unadjusted model or adjusted model. In terms of height, Tamraz et al. found that height was not associated with HAC of ATV in adjusted model[39]. Baxi et al. found that height was not associated with HAC of TFV or FTC in unadjusted model, but the association in adjusted model became statistically significant for HAC of FTC[15]. In terms of BMI, all studies found that BMI was not associated with HAC of ATV[38,39] or HAC of LPV, RTV, and EFV[48].

Liver function

Three studies reported data on the associations of HAC of TFV and liver function using alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels as biomarkers of hepatic function. Gandhi et al. reported that ALT level was not associated with HAC of EFV. Baxi et al.[17] found that none of three hepatic function biomarkers was associated with HAC of NVP. Tamraz et al. found that neither ALT nor AST, but GGT was associated with HAC of ATV[39].

Renal function

Seven studies reported data on the associations of HAC of TFV and renal function using creatinine clearance levels as a biomarker of renal function. Among these studies, three small PrEP studies (n = 23, 47, and 88) reported non-significant associations between creatinine clearance and HAC of TFV[15,29,31] and FTC[15], while two large PrEP studies (n = 220, 280) reported significant associations of creatinine clearance with HAC of TFV[37,49] and FTC[49]. Furthermore, two studies (n = 45 and 398) among PLWH found a significant association of creatinine clearance with HAC of TFV[32] and ATV[39].

Genetic factors

Four studies investigated the relationship between genetic factors and HAC. Gandhi et al. reported data on the associations of HAC of EFV with 182 single nucleotide polymorphisms (SNPs) among nine candidate genes. The results showed that, of the SNPs and haplotypes examined, three (CYP2B6 516, CYP2B6 983, and ABCB1) were associated with plasma EFV concentration, but only one (CYP2B6 516) was associated with HAC of TFV[47]. Röhrich et al. reported data on the associations of HAC of EFV with 17 genetic variants in CYP2B6 gene. The results showed that, of the genetic variants examined, CYP2B6*6 and CYP2B6*18 were associated with increased HAC of EFV[43]. Both Röhrich et al. and Johnston et al. reported that HAC of EFV was associated with CYP2B6 metabolizer phenotypes[16,43]. Tamraz et al. conducted a study to identify a candidate gene associated with HAC of ATV by a genome-wide association study. The results showed that, of the 14.1 million SNPs, rs73208473 was associated 46% decrease in HAC of ATV[39]. Two studies investigated the relationship between HAC and drug-resistant genetic mutations by divided PLWH into three groups according to viral load and drug-resistant genetic mutations, including viral suppression, and viral failure with or without drug-resistant genetic mutations. Both studies showed a high level of HAC in viral suppression, intermediate level of HAC in viral failure with mutations, and a low level of HAC in viral failure without mutations[36,50].

Overall, the preliminary data suggested that HAC was associated with genetic factors and renal function, but was not associated with anthropometry characteristics. However, data are still scarce or inconclusive on the relationship between HAC and liver function.

Discussion

Summary of main findings

This systematic review synthesized currently available data regarding the factors related to HAC. Twenty-five studies reported data on the associations of the hair concentrations of 10 ARVs with 22 factors. In general, existing data suggested that (1) HAC was associated with hair types, hair segment position, housing, illegal drugs use, high-risk sexual behaviors, renal function, and genetic factors; (2) HAC was not associated with race/ethnicity, location of sample, ARV side effects, length of ARV treatment, smoking, alcohol use, orange consumption, depression, or anthropometry characteristics; and (3) the relationships of HAC with natural hair color, hair treatment, age, sex, dosing schedule, and liver function need further study.

Knowledge gaps

While existing literature has provided the preliminary data regarding factors related to HAC, the current review identified several knowledge gaps in terms of HAC.

First, the number of studies on the factors related to HAC is limited. In this review, we identified only 25 peer-reviewed studies published between the years 1998 and 2019. Even though the number of studies has increased in recent years (e.g., 22 studies since 2011), only a minority of studies have examined the associations between HAC and the factors. For example, data on hair treatment, high-risk sexual behaviors, or depression were only available from one or two studies, which limited our ability to draw a conclusive conclusion from existing literature.

Second, there was limited research specifically examining the associations between HAC and the various potential factors related to HAC. In this review, most of the existing studies focused on the associations of HAC with viral responses or/and adherence behavior, and very few of them were designed to specifically examine the factors related to HAC[42]. Therefore, most of the data in this regard were also available as "secondary data" in these studies, which might limit the validity of our findings. In addition, more studies are needed to identify other factors related to HAC. For example, hair washing frequency is believed to be related to hair concentration of other drugs[51]; however, no study is conducted to assess the relationship of HAC with hair washing frequency.

Third, there are limited studies that have examined the interactive effect of various factors related to HAC. For example, there is evidence that, relative to the younger adults, older adults experienced more decline in physical function, which might cause them to have more chance to develop gray hair[32] and increase the risk of reduced kidney function[49]. These older adults living with HIV or at-risk for HIV infection might be further disadvantaged due to their decreased psychological and social functioning[52]. However, existing literature provides data and discussion of the possible interactive effect of various factors related to HAC.

Fourth, some existing studies might have methodological limitations. One limitation was that most studies were reported cross-sectional data. Therefore, longitudinal data are needed to establish a stable effect of the factors related to HAC. Another limitation was that some of the studies relied on data collected from a small sample, a single gender, and a narrow age range, which might limit the internal and external validity of findings.

Limitations of the current review

This review is subject to some limitations. First, we cannot draw a conclusive conclusion of the associations between HAC and many factors (e.g., hair treatment, or mental health) because of the small number of studies. Second, we only examined direct effects of factors on HAC, but many of these factors were correlated with each other or related to other common underlying factors (e.g., stress and treatment adherence). We were unable to examine the interactions or underlying mechanisms of these factors because of the limited data available. Third, some conference reports, unpublished manuscripts, or empirical studies published in other languages were not included in this review. Those studies may provide valuable information on the factors related to HAC.

Implications to research and practice

Based on the synthesis of empirical evidence, we propose several suggestions for future study on this topic. First, more empirical studies examining the factors related to HAC are needed to improve our understanding of this topic. Variability in HAC occurs due to the influence of various factors such as ARV drug, hair, demographic, behavioral, psychological, social, and biological factors, and their potential interactions[9]. Therefore, future studies would benefit from examining the effect of various factors related to HAC (e.g., hair washing, lifestyle, and social-economic status)[53,54]. In addition, the mixed influences of factors related to HAC might mask the associations of HAC with certain factors related to HAC. Future research could examine the influence of adherence-related and PK-related factors and their joint influences on HAC among PLWH or individuals at risk for HIV infection.

Second, future studies need to pay more attention to methodological issues in study design and data analysis. Studies with large and diverse samples with a wide age range and studies in more regions are valuable. Longitudinal studies are essential to provide a causal inference of the findings in the existing cross-sectional studies or validate other potential factors related to HAC.

Third, future attention should be paid to potential factors influencing ARV concentration in hair. Recent literature has revealed that more than 25 ARV agents were approved for HIV treatment of HIV or PrEP by FDA[55,56], and simultaneous determination hair concentration of multiple ARV drugs is also technically possible[33,41,57,58]. A comparison of the potential factors with hair concentration of various ARVs would give us an opportunity to identify which ARV concentration in hair would be relatively reliable, unlikely influenced by the potential factors. This approach will identify reliable biomarkers of ARV adherence in future research.

Conclusions

This review provides a synthesis of the existing literature about the factors related to HAC. Although the current review produced limited and inconclusive findings, knowledge of these factors-related to HAC is critical given the rapidly developing field. The current findings can be used to inform the design, analysis, and interpretation of HIV treatment or prevention studies that may use HAC as a biomarker of ARV adherence.

Acknowledgments

Supplementary data

Supplementary data is available at AIDS Reviews journal online (http://www.aidsreviews.com). This data

is provided by the author and published online to benefit the reader. The contents of all supplementary data are the sole responsibility of the authors.

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