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Antiretroviral Concentrations In Hair As A Tool For Monitoring Antiretroviral Therapy Adherence: Systematic Review And Meta-Analysis

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Abstract: ***Backgraound: Antiretroviral therapy (ART) is a therapeutic and preventive cornerstone of comprehensive efforts to reduce HIV morbidity, mortality, and transmission. Close adherence to antiretroviral regimen is crucial to strenghten ART, maximize viral suppression and minimize the risk of resistance. Adherence to ART remains the cornerstone of undetectable viremia. Adherence should be currently maintained and monitored. Therefore, different methods of monitoring ART adhrence lack accuracy. Clinical, immunological and virological failure are less effective in judging ART adherence. Many study have shown the antiretroviral hair concentrations are the strongest independent predictor of patients' adherence. Analyzing antiretroviral levels in hair may be a promising approach to objectively quantify short and long term ART adherence.***

Objectives: To assess the effectiveness of antiretroviral hair concentrations in monitoring patients' adherence. -To provide an accurate cut off between virological failure and success.

Methods: We searched eligible studies from January 2017 to July 2017. The following databases were assessed: PubMed; CENTRAL; CINAHL; LILACS; Scopus. We also identified additional published, unpublished and ongoing studies. JLT and JLT independently assessed eligible studies and the results were reported in data extraction form.

Main results: Twenty two of 4217 articles were selected and assessed for inclusion and exclusion criteria. Among them, 12 articles assessing hair concentrations in adults and children HIV infected were included in meta-analysis. ART hair concentrations mean differences (MDs) were reduced in almost all virological failure groups. Lopinavir (ng/mg) was -3.43 (95%CI -5.85 to -1.02, 5 studies, 674 participants, P < 0.00001), atazanavir(ng/mg)(MD) -2.24 (95%CI -2.93 to -1.54, 2 studies, 196 participants, p=0.01) , indinavir (mg/g)(MD) -8.60(95%CI -11.74 to – 5.46, 3 studies, 162 participants, P < 0.00001), ritonavir (ng/mg)(MD) -0.41 (95% CI -0.81, -0.02, 2 studies, 265 participants, p=0.04), efavirenz (ng/mg)(MD) -3.37(95%CI -4.43 to -2.31, 2 studies, 394 participants, P < 0.00001) and lamivudine (ng/g)(MD) -630.90 (95%CI -994.58 to – 267.22, 1 studies, 217 participants, P = 0.0007). The overall evidence was graded as moderate.

Conclusions: based on the main results, this review has illustrated that antiretroviral hair concentrations were lower in virological failure group than in virological success group. Antiretroviral hair concentrations could play a turnover in monitoring antiretroviral adherence and specify the cutoff between virological failure and success.

Keywords: Hair concentrations; Adherence; Antiretroviral therapy

I. BACKGROUND

Antiretroviral therapy (ART) is a therapeutic and preventive cornerstone of comprehensive efforts to reduce HIV morbidity, mortality, and transmission [1]. Treatment success with ART requires a high level of therapeutic adherence [2]. Meaning then, close adherence to antiretroviral regimen is crucial to maximize viral suppression and minimize the risk of resistance [3]. In fact, numerous studies have demonstrated that suppression of HIV viremia predicts

decreased mortality and morbidity and lowers risk of HIV transmission [4, 5-6]. Knowing that adherence to ART remains the cornerstone of undetectable viremia; thus, adherence should be currently maintained and monitored. Although adherence is described as the "behavioral bridge from efficacy to effectiveness" [5], several behavioral interventions are performed to improve adherence. However, adherence assessment in short term as well as in long term is prone to biases. Meaning, current mechanisms to measure adherence have their limitations. Self-report can be limited by recall bias, poor recollection, or a desire to please the provider ("social desirability bias") [5, 7-8]. Even if pill counts and medication event monitoring systems (MEMS) may improve the accuracy of adherence monitoring, [5-9] neither measure can record exactly actual drug consumption [5, 7-10], nor quantify pharmacokinetic parameters [5]. Then, there is not an accurate gold measure of adherence for antiretroviral therapy. Moreover, the threshold between virological success and failure lacks precision. Clinical, immunological and virological parameters are less effective in judging treatment failure or success. Studies have shown that the prevalence of failure in patients on a second-line regimen has been reported to be as high as 33% in South African patients on LPV/r-based regimens [11]. This could be explained by lack of accurate tool in monitoring patients' adherence. The identification of patients with poor adherence can limit unnecessary genotypic ARV resistance testing (GART), which is costly, enabling GART to be reserved for those who fail despite adequate drug exposure. This selective use of GART could aid in the choice of the next optimal regimen, either through using currently available drugs, or by guiding the choice of third-line regimen agents, once newer ARVs become accessible in resource-limited settings [11]. Pharmacologic measures of exposure, most often involving the measurement of antiretrovirals in a matrix such as plasma, peripheral blood mononuclear cells (PBMCs), dried blood spots, or hair, [12-13] reflect both adherence and pharmacokinetics and then offer excited future of monitoring adherence [5]. Studies have shown that antiretroviral hair concentrations reflect uptake from the systemic circulation over an extended time window (weeks to months) [14, 15-16]. Antiretroviral hair analysis provides an advantage over plasma monitoring in assessing average drug exposure over a longer period of time [16]. By the way, hair concentrations of antiretrovirals (ARVs) are the strongest independent predictor of virological success in HIV-infected patients [15, 16-17]. Hair levels reflect drug uptake from the systemic circulation over weeks to months [18], capturing cumulative exposure to medications. Analyzing antiretroviral levels in hair may be a promising approach to objectively quantify short and long term ART adherence. This systematic review analyzed different study to find out the use of antiretroviral hair concentrations in monitoring patients' adherence.

OBJECTIVES

To assess the effectiveness of antiretroviral hair concentrations in monitoring patients' adherence. -To provide an accurate cut off between virological failure and success.

METHODS

This review was registered on PROSPERO with ID: CRD42016034195. The review protocol is available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016034195.

II. SEARCH STRATEGY AND SELECTION CRITERIA

This review followed PRISMA guidelines. Search terms included MESH or other associated terms for HIV cross-referenced with "hair" AND "Antiretroviral therapy" AND "concentration" AND "level" (see Supplementary files). Databases for peer-reviewed articles included PubMed, Scopus, CINAHL Plus, CENTRAL and Web of Science. Grey literature was obtained from WHO trials (www.who.int/trialsearch); Clinicaltrials (www.clinicaltrials.gov); Current Controlled Trials (www.controlled-trials.com), African annals, International AIDS Conference, and Conference of Retrovirus.

Inclusion criteria included pre- and post-test data, clear descriptions of the intervention and sampling methods, and publication in English. We limited our search to articles published between from January 1990 to July 2017. Studies of any design from any country that listed antiretroviral hair concentrations as a primary or secondary outcome were included. In addition, the term virological failure or success; or responders or non- responders were included. Studies were excluded if none of the intervention components aimed to measure antiretroviral hair concentration.

III. SCREENING AND DATA ABSTRACTION

Article citations were organized uploaded and reviewed using review manager software [19] provided by Cochrane. The title, author, journal and year of publication were then exported to an excel spreadsheet for title and abstract review. Articles were screened by JLT and JLT to determine whether they included relevant information. The same two reviewers screened the abstracts for relevant information. If at least one reviewer deemed the abstract relevant, or if the full text had to be obtained to determine if the abstract was relevant, the full text was reviewed. Discrepancies were discussed with a third senior reviewer (JPM) and consensus was reached as to whether or not to include the article. Data were abstracted using a standardized abstraction.

IV. QUALITY ASSESSMENT

JLT and JLT assessed the quality of quantitative data from studies with randomized controlled trial (RCT) (Annex 1), trials, prospective cohort studies and cross-sectional studies (Annex 2). The risk of bias of each included study was assessed using 8-item Newcastle-Otawa for observational studies and the Cochrane Risk of bias for RCTs [20-21]. The datasets were compared and a third party settled discrepancies.

Assessment of Risk of Bias and Data from Individual Studies. The results of the risk of bias assessments are reported in Table 1 for the included observational studies and Table 2 for the RCT. Overall, all studies had low risk of bias. The resulting data from each included study are presented in Table 4. Among observational studies, 5 were cross-sectional studies. Selection bias was high only in one study. Ascertainment of exposure, confounding, comparability assessment of outcome, follow up long enough and adequacy of follow up were minimized in almost all observational studies. We included observational studies with above 7 score. The review included two RCTs, Blinding of outcome assessment, incomplete outcome data, selective reporting and other bias were well controlled in both studies; therefore, random sequence generation was minimized in Koss 2015 and was unclear in [22]. Allocation concealment was unclear in those RCTs and blinding of participants and personnel was unclear in [22] and high risk of bias in [23].

V. DATA SYNTHESIS

RESULTS

The search criteria identified 1733 potentially relevant articles and reports. After removing 458 duplicates, 1202 peer-reviewed articles and 73 grey literature reports were included in the title review phase (Figure 1). A total of 58 (55 peer-reviewed articles, 3 grey literature reports) met the inclusion criteria and were included for further analysis. 20 studies were excluded with clear reasons[5,6, 15, 16, 24,25,26,27,28,29,30,31,32,33,34,35,36,37,38-39], 18 studies were included in qualitative analysis and 13 studies were used for meta-analysis [11,15,22,23, 36,40,41,42,43,44,45,46-47]. [48-49] were excluded from meta-analysis with reasons.

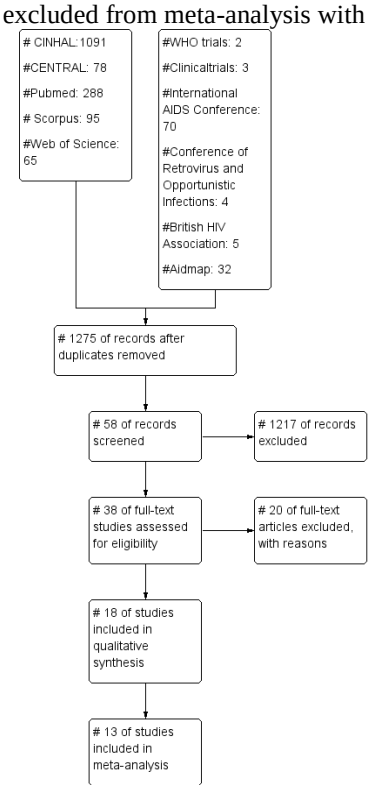

Figure 1: Study flow diagram

VI. STUDY DESIGNS, INTERVENTIONS AND OUTCOMES MEASURES

Only 2 of the 13 studies employed were randomized controlled study design. 5 studies used prospective cohort studies designs. Another 5 studies used repeated cross-sectional. Two studies were conducted in France, three studies were done in Asia (China, Vietnam, Thailand and Indonesia), one study was done United of America and seven studies were conducted in the East and Southern Africa (Uganda, Tanzania, Zimbabwe, and South Africa). HIV-infected adults, pregnant women and children were included in different studies. Interventions typically included different antiretroviral therapy (Atazanavir, lopinavir, indinavir, ritonavir, efavirenz, nevirapine and lamivudine). The antiretroviral hair concentrations measures varied considerably studies. All studies used validated measures (median and range). Knowing that antiretroviral hair concentrations were continuous outcomes, we transformed all median and range to mean and standard deviation respectively. All outcomes were reported in ng/mg, exempt indinavir hair concentration was reported in mg/g.

VII. META-ANALYSIS AND HETEROGENEITY ASSESSMENT

As included studies were good in quality, the biases were minimized as well as in RCTs and observational studies; we carry out meta-analysis when studies were similar enough. The first meta-analysis included one RCT, two cross-sectional studies and three prospective cohort studies assessing lopinavir hair concentration between virological failure and success group. The results have illustrated the MD of lopinavir hair concentration (ng/mg) between virological failure and success group was -3.43 (95%CI -5.85 to -1.02, 5 studies, 674 participants). The overall effect Z= 2.78 (P=0.005). Heterogeneity: $Tau^2 = 7.30$; $Chi^2 = 259.91$, df = 4 (P < 0.00001); $I^2 = 98\%$ (Figure 2). The second meta-analysis encompasses three studies (RCT, prospective cohort study and cross-sectional study). We evaluated atazanavir hair concentration in different virological status. The MD of Atazanavir hair concentration (ng/mg) between virological failure and success group was -2.24 (95%CI -2.93 to -1.54, 2 studies, 196 participants). Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 6.38$, df = 1 (P = 0.01); $I^2 = 84\%$. Test for overall effect: Z = 6.29 (P < 0.00001) (Figure 3). The third meta-analysis, the pooled calculated MD in indinavir hair level was decreased in virological failure group compared to virological success group -8.60(95%CI -11.74 to – 5.46, 3 studies, 162 participants). Heterogeneity: $Tau^2 = 4.63$; $Chi^2 = 5.03$, df = 2 (P = 0.08); $I^2 = 60\%$. Test for overall effect: Z = 5.36 (P < 0.00001) (Figure 4). The fourth meta-analysis (RCT, prospective cohort study and cross-sectional study): the pooled summary ritonavir hair concentration (ng/mg) has shown the MD between virological failure and success was -0.41 (95% CI -0.81, -0.02, 2 studies, 265 participants). Test for overall effect: Z = 2.06 (P = 0.04), Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 41.06$, df = 1 (P < 0.00001); $I^2 = 98\%$ (Figure 5). The fifth meta-analysis (RCT, prospective cohort study and cross-

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sectional study): efavirenz hair level (ng/mg), virological failure and success MD was -3.37(95%CI -4.43 to -2.31, 2 studies, 394 participants) Test for overall effect: Z = 6.22 (P < 0.00001. Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%) (Figure 6). The sixth overall results and the seventh overall results demonstrated lamivudine hair level (ng/g) was low in virological failure group compared to virological success group -630.90 (95%CI -994.58 to –267.22, 1 studies, 217 participants). Test for overall effect: Z = 3.40 (P = 0.0007) (Figure 7). In exception of nevirapine hair concentration, all results were statistically (Figure 8).

Clinical and statistical heterogeneities among the studies were identified were high in the first, second and fourth meta-analyses, heterogeneities were low and moderate fourth and fifth meta-analysis. The overall evidence was graded as moderate.

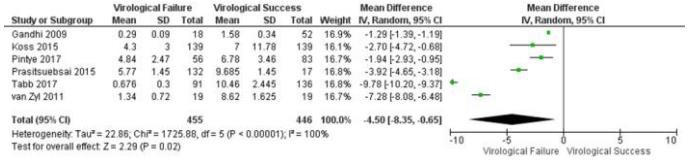

Figure 2: Forest plot of comparison: virological failure versus virological success, outcome: Lopinavir hair concentration (ng/mg)

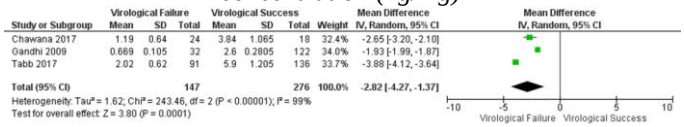

Figure 3: Forest plot of comparison: virological failure versus virological success, outcome: Atazanavir hair concentration (ng/mg)

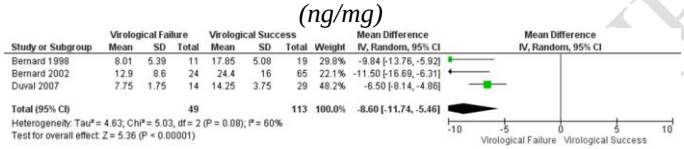

Figure 4: Forest plot of comparison: virological failure versus virological success, outcome: Indinavir hair concentration (ng/mg)

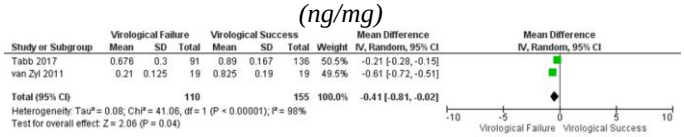

Figure 5: Forest plot of comparison: virological failure versus virological success, outcome: Ritonavir hair concentration (ng/mg)

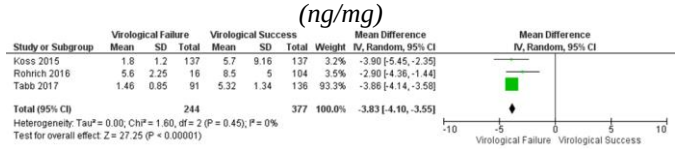

Figure 6: Forest plot of comparison: virological failure versus virological success, outcome: Efavirenz hair concentration (ng/mg)

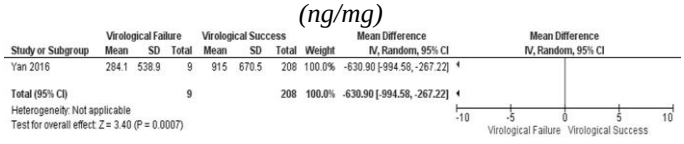

Figure 7: Forest plot of comparison: virological failure versus virological success, outcome: Lamivudine hair concentration (ng/mg)

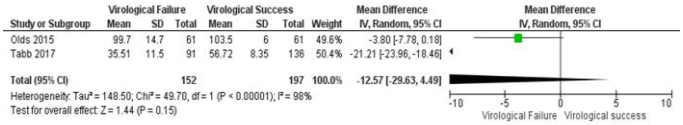

Figure 8: Forest plot of comparison: virological failure versus virological success, outcome: Nevirapine hair concentration (ng/mg)

VIII. DISCUSSION

This systematic review revealed considerable progress in monitoring ART adherence. Until now, critical challenges and gaps were persisting in monitoring ART adherence objectively. ARV hair concentrations could be considered as a useful tool in early diagnostic of virological failure and low adherence.

Our review included a much wider variety of populations, study designs and virological failure and success cutoffs. As results heterogeneity was between studies. ARV hair concentrations between virological failure and success should be considered in a context of precautions. In fact, included studies considered virological failure and success: less or more than 50 RNAc/ml [36-42], 200 RNAc/ml [40-4], 400 RNAc/ml [43-45] 500 RNAc/ ml [11], 1000 RNAc/ml [22-44] and virological not detectable and detectable [15,35,42-46]. This variability could impact sensibly on ARV hair concentrations. More studies with uniform virological cutoffs are needful to specify clinical cutoffs. In addition, the points estimate should be considered as cutoffs between virological failure and virological success in the context moderate grading. In fact, further studies may change the points estimate.

Our review has several clinical implications. Specifically, our findings emphasize that persistent high viral load for several years need clarification whether ART is failing or the adherence is low. This is common issues in low and middle income countries where GARTs are commonly inaccessible and expensive. ARV hair concentrations could constitute an alternative. Given the limited availability of second and third line regimens to treat HIV in the global setting, assessing adherence ART using a pharmacologic biomarker could allow for adherence counseling and closer monitoring to hopefully optimize the duration of first-line cART. Nevirapine hair monitoring was simple and inexpensive assay for the semi-quantitative determination in human hair samples. Further study on cost-effectiveness of other ARVs is needful in resource-limited settings [29]. Then ARV hair monitoring could be implemented by national governments on a larger scale. These findings are encouraging, given other conceptualizations of ART adherence monitoring more accurate than all previous methods.

IX. LIMITATIONS

There are several limitations with the approach used here. We graded the evidence as moderate due to observational studies Included in the review. Meaning then, more RCTs are important to imply the clinical practice. Despite these

challenges, the majority of studies included were assessed as being of high quality. Again, a notable limitation of our review is the lack of data providing tenofovir hair concentration. Nowadays, tenofovir, dolutegravir and lamivudine are the backbone of the ARV first line. We found two excluded studies evaluating tenofovir hair concentration in pre-exposure prophylaxis [5-30]. Only one study assessed lamivudine hair level.

X. CONCLUSIONS

The field has come far in the last decade, though much remains to be done to enable the integration of proven antiretroviral hair monitoring strategies into HIV guidelines. The field of antiretroviral adherence research needs to highlight the importance of antiretroviral hair monitoring. In fact, antiretroviral hair monitoring must become bolder in specifying the threshold between treatment failure and low antiretroviral adherence. This is an accurate method of monitoring adherence. This method could address clearly adherence issues.

In summary, our systematic review contributes to the emerging methods of monitoring ART adherence accurately. Further studies could strengthen this evidence based medicine.

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