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SUBSTANTIVE REVIEW

The Role of ARV Associated Adverse Drug Reactions in Influencing Adherence Among HIV-Infected Individuals: A Systematic Review and Qualitative Meta-Synthesis

Haochu Li[1,2] · Gifty Marley[1] · Wei Ma[1] · Chongyi Wei[3] · Mellanye Lackey[2] · Qingyan Ma[2] · Françoise Renaud[4] · Marco Vitoria[4] · Rachel Beanland[4] · Meg Doherty[4] · Joseph D. Tucker[2,5]

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Abstract Poor adherence remains a major barrier to achieving the clinical and public health benefits of antiretroviral drugs (ARVs). A systematic review and qualitative meta-synthesis was conduct to evaluate how ARV adverse drug reactions may influence ARV adherence. Thirty-nine articles were identified, and 33 reported that ARV adverse drug reactions decreased adherence and six studies found no influence. Visually noticeable adverse drug reactions and psychological adverse reactions were reported as more likely to cause non-adherence compared to other adverse drug reactions. Six studies reported a range of adverse reactions associated with EFV-containing regimens contributing to decreased adherence. Informing HIV-infected individuals about ARV adverse drug reactions prior to initiation, counselling about coping mechanisms, and experiencing the effectiveness of ARVs on wellbeing may improve ARV adherence.

Keywords Adverse drug reaction · Adherence · Qualitative meta-synthesis · HIV · Antiretroviral

Introduction

Over 15 million HIV-infected individuals were on antiretroviral therapy (ART) by March 2015 [1]. However, adherence to treatment remains a key challenge for HIV programs to achieve optimal health outcomes and viral suppression [2, 3]. The World Health Organization (WHO) defines treatment adherence as "the extent to which a person's behavior-taking medications, following a diet and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" [4].

ARV adverse drug reactions are an important factor that influences adherence to ARV [5]. WHO defines an adverse drug reaction as "a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for modification of physiological function" [6]. Serious and/or long-term adverse drug reactions can affect adherence to the treatment regimen [7]. There is limited knowledge of how HIV-infected individuals perceive and experience adverse drug reactions to ARVs and how these perceptions and experiences may influence ARV adherence.

Qualitative synthesis focuses on in-depth interpretive explanation of a phenomenon and therefore enables deeper analysis of the complex, multi-faceted experiences of

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✉ Haochu Li
hcli@alumni.cuhk.net; haochuli@med.unc.edu

✉ Joseph D. Tucker
jdtucker@med.unc.edu

1 School of Public Health, Shandong University, Jinan, China

2 UNC Project-China, Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

3 Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA

4 HIV Department, World Health Organization, Geneva, Switzerland

5 UNC Project-China, Guangdong Provincial Skin Diseases and STI Control, Number 2 Lujing Road, Guangzhou 510095, China

adverse drug reactions and its relation to ARV adherence. The aim of this qualitative synthesis was to systematically review and synthesize the qualitative literature examining how perception and experience of ARV adverse drug reactions influence drug adherence among HIV-infected individuals.

Methods

Search Strategy and Selection Criteria

In accordance with guidance from PRISMA checklist [8], ENTREQ [9], and meta-synthesis guidance from the Cochrane group [10], we used a comprehensive search strategy to identify all relevant studies in English (Search strategy available in supplement). The review protocol (CRD42015017265) was registered (www.crd.york.ac.uk/PROSPERO/). The following electronic journal and dissertation/thesis databases were searched from January 1st, 2000 until February 21st 2015 (to limit to recent ARV drug regimens): CENTRAL (Cochrane Central Register of Controlled Trials), EMBASE, LILACS, PsycINFO, PubMed (MEDLINE), Web of Science/Web of Social Science, CINAHL, British Nursing Index and Archive, Social science citation index, AMED (Allied and Complementary Medicine Database), DAI (Dissertation Abstracts International), EPPI-Centre (Evidence for Policy and Practice Information and Coordinating Centre), ESRC (Economic and Social Research Council), Global Health (EBSCO), Anthrosource, and JSTOR. Conference proceedings including the Conferences on Retroviruses and Opportunistic Infections (CROI), International AIDS Conference (IAC), and alternating year International AIDS Society (IAS) clinical meetings were searched from their inception dates (1993, 1985 and 2001, respectively). References of included studies were checked and authors were contacted to provide additional information as required.

Studies were selected that used qualitative research designs, including but not limited to ethnographic research, case studies, process evaluations, and mixed methods research. Studies also had to include qualitative data collection techniques (e.g., participant observation, in-depth interview, or focus group) and a qualitative data analysis approach (e.g., framework analysis, or thematic analysis). The review included studies that provided description and interpretation of the impact of adverse drug reactions on adherence for all HIV-infected individuals. We excluded studies that only used quantitative methods to investigate the same phenomenon.

Data Extraction

A health sciences librarian conducted the electronic searches and excluded duplicates. All titles were reviewed to examine relevance to the meta-synthesis topic. Two authors (HL & GM) independently reviewed abstracts and made a list of categories for exclusion, and then independently reviewed full text manuscripts and noted reasons for exclusion. Discordance between the two authors was resolved by a discussion with a third author (QM). Studies were reviewed for relevance based on adverse drug reaction's impact on adherence, study design, main findings and interpretations of findings. (Fig. 1).

A data extraction form was designed specifically for this review. The characteristics extracted from each study included authors, year published, study design, location/orientation of study, key populations and subgroups, age range, main findings, ARV drug regimen, and adverse drug reactions described.

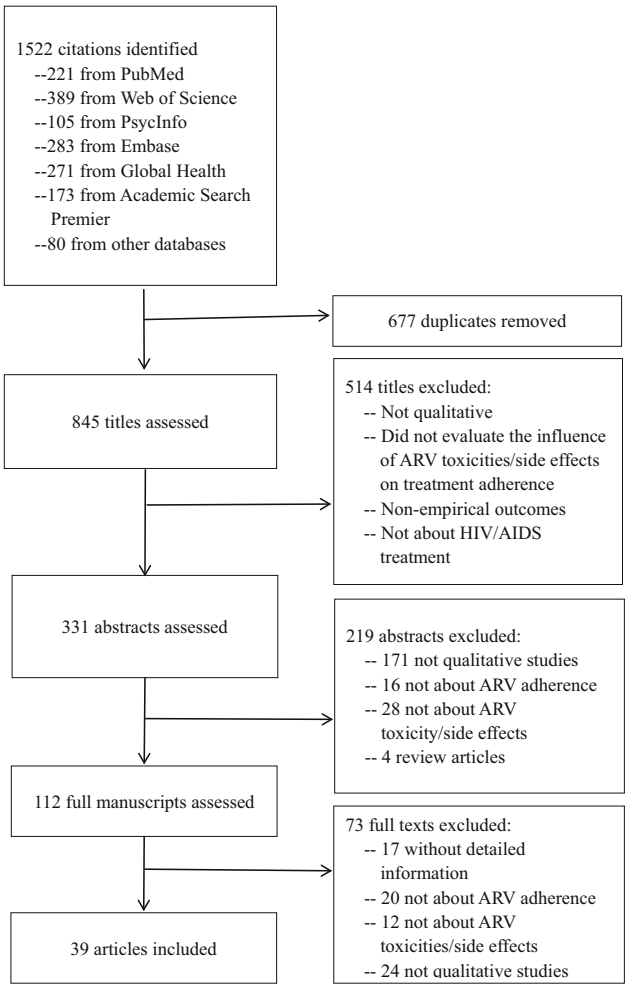

Fig. 1 Prisma Flowchart

Data Analysis

Prior to conducting the synthesis, each paper's quality was assessed by both HL and GM using a seven scale criteria tool adapted from the critical appraisal skills programme (CASP) [11], which has been used in other reviews [12]. The CERQual approach was used to evaluate the certainty of the review finding [13]. This approach includes an assessment of methodological limitations, coherence, relevance, and adequacy (see the supplement for details), based on a guidance document from the Cochrane Collaboration Qualitative Methods Group [10, 13]. Thematic synthesis was adopted in the data analysis. A line-by-line coding of the findings of primary studies was conducted by HL and GM prior to organizing into related areas to construct descriptive themes. Analytical themes were developed based on the descriptive themes [14]. Pre-defined subgroup analyses were conducted among specific groups of adults, children and adolescents, and pregnant women. EFV was specifically chosen in the analysis because it has known adverse drug reactions and yet remains first-line therapy in WHO ARV guidelines.

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The WHO was a funding source for this study. The authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The content of the article is solely the responsibility of the authors and does not necessarily represent the official views of WHO or the National Institutes of Health.

Results

Thirty-nine studies published after 2000 were included in the review. In the CASP assessment, most of the studies reached good quality with the highest score of 7 (17 studies) or 6 (14 studies), while some studies had medium score of 5 (4 studies) and low score of 4 or less (4 studies). Thirty-three out of 39 studies reported that perceived adverse ARV reactions decreased adherence [12, 15–46], whilst six studies [47–52] described no apparent relationship. Nineteen studies [12, 15–27, 29, 32, 36, 44, 47] were conducted in high-income countries, eight [30, 31, 33, 34, 41, 42, 46, 49] in middle-income countries, and twelve [28, 35, 37–40, 43, 45, 48, 50–52] in low-income countries. (Countries—see Tables 1, 2).

The majority of the studies (34/39) sought the perspectives of HIV-infected adults. Two studies considered the views and experiences of children (aged 3–12) and their caregivers [24, 46] and one study of adolescents [45]. Two studies focused on pregnant women [16, 36]. Three studies explored experiences of coping mechanisms for adverse drug reactions as a way of improving adherence [31, 38, 45]. Study characteristics have been summarized in Tables 1 and 2. Eight themes emerged in the thematic synthesis, which included three barriers (i.e., visually noticeable adverse drug reactions, psychological suffering, and Efavirenz (EFV)-containing regimens), three facilitators (i.e., prior knowledge of adverse ARV reactions, coping strategies, and self- perceived effectiveness of ARV), and subgroup analyses among populations of children, adolescents, and pregnant women.

Barriers

Visible Adverse Drug Reactions

Visible adverse drug reactions (e.g., body changes, a buffalo hump, excess sweating, darkening of the skin, body odor, hair loss, weight loss/gain, and skin rash) increased the risk of unintentional HIV disclosure and disturbed HIV-infected individuals' daily routines. It led to low self-esteem and self-stigmatization among some HIV-infected individuals, and was felt to contribute to poor ARV adherence [15, 19, 21, 23, 25, 28, 29, 32, 35, 38–40, 42, 45, 49, 50]. In several persistent cases, ARV adverse drug reactions caused HIV-infected individuals to undertake long treatment free vacations or quit treatment completely [15, 21, 23, 32, 49]. This finding has a CERQual high level of confidence.

For many participants on ARVs, adverse drug reactions were perceived to be detrimental to adherence [29]. Primary data from the reviewed articles include the following: "I have asked my doctor not to put me on any medication that would make me look like a freak. I would simply not take the drug if I developed a buffalo hump on my back" [23]. "I then had a skin rash to a point where I was so uncomfortable and sick that I stopped taking the medication" [21].

Psychological Suffering

Psychological suffering associated with adverse drug reactions (e.g., being reminded of being sick, delusional, a feeling of being killed by taking the drugs, and getting mad) were occasionally considered to be severe enough to contribute to poor adherence [17, 19, 20, 37, 40, 47, 49]. This finding has a CERQual high level of confidence.

Primary data showed that some participants stopped taking ARVs because they realized that they were not psychologically prepared to take ARVs. For example, participants described: "Just the fact that I have to take it [medication(s)] and knowing that I'm going to have to take it for the rest of my life is having psychological effects, it's

Table 1 Summary of extracted data from selected full texts

Study	Publication year	Age range (yrs.)	Country	Participants	Data collection	Type of ARV
[15]	2000	24–57	USA	46 HIV positive individuals were purposively recruited	In-depth interview	Not specified
[16]	2001	20–45	USA	51 HIV positive women of reproductive age living in the New York area were purposively recruited	In-depth/ interview	AZT (zidovudine)
[17]	2002	16–24	USA	6 HIV positive adolescents were purposively sampled out of the 12 HIV positive adolescents taking ARVs at the ADAMs clinic at time of the study participated	In-depth interview	Combivir, Sustiva, Hydroxyurea, Crixivan, Epivir, Zerit, Hivid, Prozac, Viramune
[18]	2002	30–50	Netherlands	28 individuals were purposively recruited from the Amsterdam cohort study among HDUs while initiated on HAART and the Drug Department of the Municipal Health Service	In-depth interview	Not specified
[19]	2003	21–47	USA	11 individuals were purposively sampled from a clinic where HIV positive women received care. 6 participants were women with HIV/AIDS who were taking ART while 5 were health care professionals who regularly cared for HIV/AIDS patients	Focus group	Not specified
[20]	2003	NR	USA	24 HIV positive women were purposively selected out of 30 women enrolled in a nurse HIV care manager program for Florida Medicaid enrollees or treated in Florida public health clinics served by these nurse care managers	Focus group	Not specified
[21]	2003	20–56	USA	152 individuals were purposively recruited from selected HIV primary care clinics and community-based service organizations. Sample consisted of 56 HIV-infected/women, 52 MSM, and 44 male IDUs	In-depth interview	Crixivan
[22]	2004	26–61	USA	21 HIV positive individuals were purposively recruited out of over 100 active HIV positive patients enrolled at the comprehensive immunology center of Kansas City	Focus group	Not specified
[23]	2005	NR	USA	15 HIV positive individuals were purposively recruited out of total number of patients receiving their total healthcare at a selected family practice clinic in a Western state	In-depth interview	Not specified
[24]	2005	7–12, 23–63	USA	23 individuals were purposively recruited from HIV/AIDS clinics and community-based organizations located throughout Los Angeles, California. 9 participants were HIV positive young children and 14 were primary guardians of HIV positive children	In-depth interview	Not specified
[25]	2005	20–45	USA	158 individuals were purposively recruited from two samples of women living with HIV/AIDS from different eras of the HIV/AIDS epidemic	In-depth interview	Sustiva, Agenerase, AZT,
[26]	2006	31–54	Canada	15 HIV positive individuals not on ARVs for at least the prior three months were purposively recruited from an outpatient clinic located in the downtown area of a large Canadian city	In-depth interview	Ritonavir,
[27]	2006	25–61	USA	42 HIV positive individuals were purposively recruited from Mount Sinai Medical Center's Jack Martin Fund Clinic (JMFC)	Focus group	Not specified
[28]	2007	NR	Botswana, Tanzania, Uganda	379 HIV positive individuals were purposively recruited from selected health facilities. 183 participants were selected in Botswana, 136 in Tanzania and 60 in Uganda	In-depth interview, focus group	Not specified
[29]	2008	33–73	USA	35 HIV positive individuals were purposively recruited from a selected clinical site	Focus group	Zidovudine, Lamivudine Abacavir
[47]	2008	32–59	USA	24 HIV positive MSM were purposively sampled using the snowball sampling method	Focus group	Efavirenz, indinavir

Table 1 continued

Study	Publication year	Age range (yrs.)	Country	Participants	Data collection	Type of ARV
[30]	2008	>18	South Africa	12 participants were purposively recruited from ART clinics. The sample consisted of 6 HIV positive patients on ART classified as poor adherers, 5 HIV/AIDs health service providers (including 1 traditional healer), and 1 was a company human resources manager	In-depth interview	Not specified
[48]	2009	22–66	Tanzania	68 HIV positive individuals were purposively selected from a 120-member support group that is associated with the HIV/AIDS clinic in Chake Chake District Hospital in Pemba	Focus group, in-depth interview	Efavirenz,
[31]	2009	23–72	China	29 HIV positive individuals who had received ART for at least 8 weeks were purposively recruited	In-depth interview	Not specified
[32]	2009	27–71	Belgium, Netherlands	30 HIV positive individuals treated with HAART were purposively recruited from three HIV treatment centers, (two in Belgium and one in the Netherlands)	In-depth interview	Triomune, Stavudine, Lamivudine, Nevirapine, Septrin, Zidovudine, Efavirenz, sulfamethoxazole trimethoprim
[33]	2010	≥18	Peru	31 HIV positive individuals were purposively selected for the study	In-depth interview	Nevirapine
[34]	2010	≥18	Ukraine	16 HIV positive individuals on treatment with HAART were purposively recruited from Kiev City AIDS Center	In-depth interview	Not specified
[35]	2010	≥18	Tanzania	207 HIV positive individuals on ARVs for three or more months were purposively recruited from 7 selected facilities	Focus group	Not specified
[36]	2011	25–45	Australia	16 HIV positive women who were engaged in MTCT were purposively recruited out of 34 HIV-positive women who were diagnosed with HIV during their childbearing years	In-depth interview	Not specified
[37]	2012	≥18	Zambia	25 HIV positive individuals were purposively recruited from a group of patients classified as lost-to-follow-up (LTFU) or defaulters by a local public sector clinic for missing their scheduled pharmacy pick up for at least 6 months (180 days)	In-depth interview	Not specified
[38]	2012	19–63	Uganda, Zimbabwe	82 HIV positive individuals were purposively selected from participants in the Development of Antiretroviral Therapy (DART) Trial that investigated whether delivery of ART with or without routine monitoring led to similar health outcomes	Focus group	Bactrim, AZT
[39]	2012	18–62	Nepal	34 individuals were purposively selected from 10 ART sites randomly selected across Nepal. The sample consisted of 17 HIV positive patients on ART, 14 ART service providers and 3 policy-makers	In-depth interview	Not specified
[40]	2012	NR	Nepal	34 individuals were purposively recruited from an ART facility. The sample comprised of 17 HIV positive patients on ARVs, 14 ART service providers, and 3 policy-makers	In-depth interview	Not specified
[41]	2013	13–63	South Africa	12 HIV positive individuals were purposively recruited out of 49 patients participating in the Medicins Sans Frontieres (MSF) second-line failure program	In-depth interview	Not specified
[49]	2013	NR	China	29 HIV positive individuals were purposively recruited from Ditan Hospital's AIDS floor and out-patient clinics	In-depth interview	Not specified

Table 1 continued

Study	Publication year	Age range (yrs.)	Country	Participants	Data collection	Type of ARV
[42]	2013	NR	South Africa	25 HIV positive individuals were purposively recruited from patients who visited the ART center and were on ART from the beginning of the study roll-out and onwards	In-depth interview	Not specified
[50]	2013	26–68	Uganda	34 HIV positive individuals were purposively recruited from participants of the 5-year cluster randomized trial conducted with The AIDS Support Organization (TASO) in Jinja, Uganda between 2005 and 2009	In-depth interview	Didanosine (ddI), Stavudine (d4T), Efavirenz (EFV),
[12]	2013	43–63	USA	35 HIV positive individuals living DM or HTN were purposively recruited from an HIV clinic in Maryland	Focus group	Stavudine
[43]	2013	23–52	Rwanda	47 individuals were purposively recruited from a subset of HIV positive participants who had attended at least 2 follow-up visits under the SEARCH study and from the study clinic healthcare workers	Focus group	Septrin and Efaviren
[51]	2014	≥18	Ethiopia	58 individuals were purposively recruited from Felege-Hiwot hospital and Gondar university hospital in Northwest Ethiopia. Sample consisted of 24 HIV positive patients, 15 nurses and 19 case managers	In-depth interview, focus group	Not specified
[44]	2014	<19–59	Switzerland	17 HIV positive individuals were purposively recruited from patients experiencing or high at risk of sub-optimal adherence to ART who had been referred to a routine ART adherence program at the community pharmacy in the Department of Ambulatory Care and Community Medicine in Lausanne	In–depth interview	Not specified
[45]	2014	9–19	Tanzania	24 individuals were purposively recruited from public, private and secondary schools. Sample consisted of 13 HIV positive children living on ARVs and 11 caretakers of HIV positive children living on ARVs	In-depth interview	TDF/3TC/EFV
[52]	2014	20–41	Sothern Malawi	8 ART clinic healthcare providers were purposively selected from 2 ART clinics located in rural and urban hospitals in southern Malawi	In-depth interview	Not specified
[46]	2015	3–16	Cuba	21 primary caregivers were purposively recruited from caregivers of HIV positive Cuban children and adolescents who were receiving specialized care at Havana's Pedro Kourí Tropical Medicine Institute (IPK)	In-depth interview	Not specified

Yrs years, *NR* not reported, *ARV* antiretroviral drugs, 'Hard drug users' *intravenous and non-intravenous users of heroin, cocaine, amphetamine, or methadone*, *IDUs* injection drug users, *MSM* men who have sex with men, *HDUs* HIV positive drug users, *DM* diabetes mellitus, *HTN* hypertension

Table 2 Summary of study characteristics

	No. of studies	Percentage (%)
Year of publication		
2000–2004	8	20.5
2005–2009	12	30.8
2010–2015	19	48.7
Study location (countries)		
High income	19	48.7
Middle income	8	20.5
Low income	12	30.8
HIV-infected population		
Children	2	5.1
Adolescents	1	2.6
Pregnant women	2	5.1
Adults	34	87.2
Study quality		
High	31	79.5
Medium	7	17.9
Low	1	2.6
Study method		
Interviews	25	64.1
Focus groups	12	30.8
Mixed methods	2	5.1

causing trauma to my life right now" [19]. Participants generally used adjectives such as depressing, cranky, moody, sad, angry, guilty, irresponsible, nervous, anxious and afraid to describe their negative psychological problems related to ARVs [20].

Adverse Reactions Associated with EFV-Containing Regimens

Some people receiving EFV-containing regimens reported that neuropsychiatric adverse reactions (e.g., intense body heat, delusions, anxiety, intense dizziness, and nightmares) contributed to poor adherence [47–52]. This finding has a CERQual moderate level of confidence.

Participants described their pain and suffering related to EFV-associated adverse drug reactions: "The numbness crept up from my feet and spread out over my body. Just like with an electrical shock, the feet feel it the worst. During the night, my feet are so sore, numb, and swollen that I can hardly sleep. The pain is so constant. I can hardly close my eyes" [49]. "I can't say that they have worked well because as you see now my face it has changed from its normal shape, I don't know whether it is a type of drug or it is because I have spent some time on them" [50].

Facilitators

Prior Knowledge of Adverse ARV Reactions

When people receiving ART had prior knowledge of ARV adverse drug reactions, or had been informed in advance of potential adverse reactions and how to manage them, they felt these reactions were expected, normal and manageable, and therefore reported less non-adherence [35, 38, 48, 50]. This finding has a CERQual moderate level of confidence.

Participants described their experiences: "We were warned that some people would get drug reactions. This helped me not to worry when I fell sick" [38]. "That's normal stuff" [48]. "Those things occur, and after a time they go away" [48]. For those participants who were informed about potential adverse effects of ARVs prior to treatment initiation, the reactions were not reported as reasons for non-adherence [48]. Participants wished they had been pre-informed about the adverse effect profile at the initiation of treatment, so that they know how to manage these effects [35].

Coping Strategies

When people receiving ART developed coping strategies to cope with adverse events (e.g., drinking a lot of fluids and resting to reduce dizziness, or eating a snack or meal before swallowing pills to control nausea), they expressed good levels of adherence [31, 38, 45]. This finding has a CERQual moderate level of confidence.

Participants described how they dealt with adverse drug reactions: "I have abdominal distention. I felt so uncomfortable even if I only ate a little. I felt that the food was stuck there and was not digested. Taking some herb digestion medicine makes me feel better" [31]. A number of strategies were also employed to disguise visible adverse effects. For example, women reported wearing dark nail polish to cover darkened nails and wearing long sleeved clothes, ankle reaching skirts and trousers to cover body sores [38].

Perceived Effectiveness of ARVs

When people on ART experienced individual benefits of taking ARVs on their health (e.g., regaining physical strength, being more independent, and able to help with domestic work again), they achieved greater adherence independent of the adverse effects [30, 31, 45, 48]. This finding has a CERQual moderate level of confidence.

Participants described benefits of ARVs as a reason to adhere to medication as follows: "I say ARVs are medicine [e.g., effective medicine, not fake]. Because basing it off my health, I had lots of sores all over my body, on my

arms, in my mouth, on my head, on my private parts, you understand? …After being started on the drugs, all those sores went away, my health status started to improve, and I was able to eat well. Until now after coming to test recently I had a CD4 of like 181. So it has risen well. It's these meds [that do it], man" [48]. "I cannot live without these meds. If I did not take them, I might die very soon. The benefit of the meds is they enable me to survive a few more days. As patients, our lives have been shortened by HIV, but ART can extend our lives a little bit longer. Taking meds on time can prolong my life" [31].

Subgroup Analysis

Subgroup Analyses Among HIV-Infected Children and Adolescents

The experience of drug attributed adverse events (e.g., queasy feeling, vomiting, diarrhea, nausea, insatiable hunger, and skin sores) resulted in children's refusal to take ARVs (e.g., coughing, gagging, and throwing it up) [24, 45, 46]. This finding has a CERQual moderate level of confidence.

For example, an adolescent said, "There is this one [pill] at night that makes you feel dizzy, that one bothersome a lot. I keep taking them, and then sometimes they […] provoke these scabs. Those others provoke wounds […], they damage your face. So these ARVs […] and my body don't get along" [45].

Subgroup Analyses Among HIV-Infected Pregnant Women

Pregnant women perceived that the likelihood of their unborn baby suffering from ARV adverse effects was greater than the likelihood of their unborn baby acquiring HIV infection [36]. ARVs also worsened their pregnancy-associated nausea, hence they felt that ARVs did more harm than good [16, 36]. This finding has a CERQual low level of confidence.

For example, a woman described: "When you are pregnant, the thing about taking zidovudine (AZT) is that, it is so strong. Taking AZT is like taking drugs, it's like taking marijuana or smoking crack…it's like the baby is gonna be born with that in his system" [16].

Discussion

This synthesis identified 39 qualitative studies from diverse countries. Most of the studies supported that occurrence of ARV adverse drug reactions are associated with ARV non-adherence. This is consistent with quantitative research demonstrating that adverse drug reactions contribute to poor adherence with treatment interruptions [53–56]. This synthesis formally evaluated the qualitative evidence and extended the literature in three ways: (1) proposing barriers that likely contribute to non-adherence (2) exploring facilitators to improve adherence, and (3) uncovering challenges among specific groups.

This qualitative synthesis explored potential neuropsychological mechanisms of subjective perceptions and experiences influencing ARV adherence. This is consistent with cross-sectional data correlating subjective perceptions of ARVs and adherence [55, 56]. Cross-sectional and cohort studies showed that depression, anxiety, negative cognitive and psychosocial functioning were frequently associated with poorer ARV adherence [57, 58]. This synthesis suggested that the experiences of taking ARVs were associated with significant psychological trauma and emotional suffering in some HIV-infected individuals. In particular, the trauma and constraints were usually related to being on a lifelong therapy associated with HIV infection. Also, visually noticeable adverse drug reactions could disturb daily routines and threaten HIV disclosure and embarrassment in public, which might in turn increase psychological and emotional burden. This suffering may further exacerbate self-stigmatization and further decrease the self-esteem of HIV-infected individuals. When this suffering is not effectively addressed, it may contribute to ARV non-adherence.

Even though some ARV drugs (e.g., stavudine) has been recommended to be phased out [59]. This qualitative synthesis highlighted this concern and provided descriptions of adverse drug reactions related to EFV-containing regimens contributing to poor adherence. This is consistent with several quantitative meta-analysis demonstrating the association between EFV use and central nervous system (CNS) toxicity [60] and treatment non-adherence [61]. Shubber and colleagues' systematic review described that around a third of people using EFV experienced CNS adverse reactions (e.g., dizziness, abnormal dreams) with variable degree of severity, which are usually mild and transient [62]. However, Shubber and colleagues' review showed that compared to nevirapine, EFV was associated with a lower frequency of severe adverse reactions, particularly in treatment discontinuation among both adult and children populations [62]. A recent review [63] on comparative safety of EFV and impact of CNS adverse events showed 90 % of patients remaining on EFV (78 weeks). Even though the relative risk of treatment discontinuation due to EFV-related adverse events was higher than that related to other 1st line options (e.g., tenofovir disoproxil fumarate, abacavir, dolutegravir, raltegravir), the absolute differences were low (<5 %) [63]. Although the overall frequency of EFV adverse medication reactions remains rare, our findings suggest that EFV-containing regimens

are perceived by PLWH as related to adverse reactions influencing their lives, appearance, and well-being.

Another important finding of this qualitative synthesis is that the HIV-infected individuals' experience, perception, understanding, and knowledge of adverse drug reactions were related to ARV adherence. When people receiving ART experienced ARVs maintaining their health effectively, had knowledge of adverse ARV reactions, and practiced coping strategies to manage these reactions, they were more likely on adherence. This is consistent with previous quantitative studies that having knowledge about adverse drug reactions, adherence self-efficacy, self-management, and individual strategies for fitting medication into daily routines were associated with ARV adherence [64, 65]. However, researchers also argued that extensive communicating about potential adverse medication reactions may increase the likelihood of a patient developing those reactions [66]. A simplified and structured informing approach about potential adverse drug reactions to ARV is needed.

This qualitative synthesis found very limited studies considering perspectives of children, adolescent, and pregnant women, and the findings were in moderate and low confidence levels respectively. For children and adolescents, refusal of ARVs or doses skipping were related to pediatric adherence barriers, such as feeling sick and needing a break [67], palatability of medication, large medication volumes, and limited treatment options [68, 69]. For pregnant women and women with history of childbirth, some important issues were emerging that they perceived ARVs as medically powerful and full of potential adverse effects, which made these women felt that ARVs did more harm than good. For this specific group of women, ARV adherence became more complicated.

This qualitative synthesis is subject to some limitations. First, some of the reviewed articles are weak in research design or have incomplete reporting. However, we evaluated the quality of individual studies and this quality assessment was reflected in the overall confidence assessment using CERQual. Second, most of the reviewed articles emphasized adults with HIV and few specifically focused on children, adolescents or pregnant women. It is therefore difficult to generalize the findings to other specific sub populations. Third, our qualitative synthesis only provided subjective interpretation of the relationship between patient attributed adverse drug reactions and ARV non-adherence and causal pathways could only be inferred.

Despite these limitations, this synthesis found that visually noticeable drug reactions, emotional and psychological suffering, and EFV-containing regimens may be related to non-adherence for HIV-infected individuals. This synthesis also found that improved knowledge and understanding of adverse ARV reactions, experiencing the health benefits of ARVs, and strategies of coping and self-management were practically important in addressing the problem of ARV non-adherence caused by adverse drug reactions. It's therefore important to provide HIV-infected individuals tailored counselling to enhance knowledge and understanding of adverse ARV reactions and to train and support people receiving ART how to adopt multiple strategies to deal with these reactions. Moreover, this synthesis provided directions for future studies. Vulnerable children, adolescents, and pregnant women are still far under studied in the qualitative literature on their experience and perception related to adherence of ARVs. Future qualitative studies should focus on exploring subjective experiences and perceptions of ARV adverse drug reactions and strategies being used to manage these reactions from the perspective of children, adolescents, and pregnant women.

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Compliance with Ethical Standards

Conflict of Interest RB is an affiliated consultant with the World Health Organization and receives remuneration for work related to the topic of this paper. Other authors declare no conflict of interest.

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

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