HIV Medications as Drugs of Abuse

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Abstract Antiretrovirals (ARVs) have been increasingly reported among medications diverted to the black market, and ARVs have been described as a category of emerging drugs of abuse. We present an overview of media reports, qualitative studies, and quantitative studies that characterize the diversion and recreational use of ARVs, particularly efavirenz, in the United States and South Africa. Theoretical reasons for the misuse of ARVs are explored. Further research is needed to understand the prevalence, patterns, and consequences of ARV diversion and misuse.

Keywords Recreational antiretroviral use · Substance abuse · Whoonga and nyaope · Antiretroviral diversion · ARV · Efavirenz

Introduction

The development of antiretroviral (ARV) medication has dramatically reduced morbidity and mortality associated with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) [1]. Vigorous expansion in the global access to ARV medication, particularly within the past decade, has led to tremendous progress in stemming the HIV/AIDS pandemic [2]. In recent years, however, there have been

emerging reports that ARVs are being diverted and used both as recreational drugs (alone or in combination with other substances) and as unmonitored treatment for HIV infection [3, 4•, 5•, 6•]. Although most epidemiologic surveillance of prescription drug misuse focuses on medications with clearly understood abuse potential, such as opioid analgesics, stimulants, and sedatives [7], many medications affecting neural systems, including ARVs, have been identified as additional culprits for misuse [8].

The emergence of ARV misuse adds complex public health challenges to the existing landscape of HIV/AIDS treatment, addiction medicine, and psychiatry. Here, we present the available evidence of ARV diversion and misuse, explore the motives and consequences of such misuse, and discuss recommendations for further research and intervention.

Antiretroviral (ARV) Diversion Discovered

Diversion of ARV medication came to light in March 2007 when a group of researchers published a report in the journal *Pain Medicine* detailing interview results with drug-using, street-, and club-based populations in Miami [9]. The data confirmed that previously documented avenues, Internet sales, stolen shipments, “doctor-shopping” (patients gathering multiple prescriptions from different doctors), and unscrupulously prescribing physicians, were active channels for prescription drug diversion, but they also uncovered numerous largely unstudied street markets: patients trading (for illicit drugs) or selling legitimate prescriptions; healthy individuals being paid by pill brokers to defraud doctors; pharmacies buying back, then re-selling patients’ medications; and burglaries and thefts at residences and pharmacies [9]. A few years later, fraud charges brought against doctors and pharmacies in New York confirmed that such markets existed in other large metropolitan centers [10–12].

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While these markets alone were surprising, Inciardi et al. noted three particularly novel findings: 1) the development of the HIV-positive patient as a targeted prescription pill source, 2) the black market sale, theft, and trade of ARVs, and 3) the recreational use of ARVs [9]. Previous research had documented HIV-positive individuals supplying others with their own benzodiazepines and opioids, but this team observed trade in *all* HIV-positive patients' drugs, including their ARVs [9]. Further interviews reported pill brokers approaching HIV-positive patients at clinics, pharmacies, and support groups; pharmacists employing "spotters" to find HIV-positive patients with ARVs for resale; HIV-positive patients selling pills, or giving them away to those they felt were in greater need, taking only what remained; and illicit drug-using HIV-positive individuals being specifically targeted as low-price pill suppliers [9]. Inciardi et al. noted that diverted pills were ones patients did not like or ones with the highest value. HIV-positive individuals did not appear to understand the necessity of taking their entire medication cocktail [9].

In such a diversion, the buyer is not necessarily a pill broker. In fact, the HIV-positive informants noted that they more often *purchased* diverted HIV medications than sold, traded, or had them stolen [9]. While some purchases were to make up for selling too many pills when finances were limited, many black market purchases appeared because of a discomfort with serostatus disclosure [9]. Three years later, a South African ethnographic study uncovered a similar trend: interviews revealed off-label therapeutic use of ARV medication because of confidentiality concerns and mistrust of healthcare workers [13]. HIV-positive patients sold pills directly to other patients or to intermediaries who mirrored Miami's pill brokers [13].

Drivers of Diversion

While stigma- and privacy-related fears are turning some HIV-positive individuals into black market customers, other factors appear to influence ARV diversion. In the Miami study, diversion-promoting factors included poor HIV-related health education, mistrust of the medical community, poverty, addiction to illicit substances, homelessness, and mental health issues [9]. The importance of such medical, economic, and psychosocial factors was confirmed quantitatively 6 years later. Among 503 HIV-positive individuals in South Florida, significant correlations were found between medication diversion and male gender, depression, anxiety, substance dependence, recent homelessness, and high HIV-related stigma. Non-diversion was associated with higher knowledge of HIV-related treatment, higher health literacy, and 95 % ARV adherence [3]. While most of these correlations are intuitive, the relationship with male gender was not. However, more male participants reported recent homelessness, leading to the

hypothesis that homelessness increased visibility as a target for pill brokers and indirectly increased diversion by male individuals [3]. Broadly speaking, high competing needs, psychosocial vulnerability, and low levels of HIV-related and general health education drive ARV diversion.

Recreational ARV Use

While many diverted medication end users are members of a local HIV-positive community, it is clear that diverted ARVs are also reaching a wider market. Some end users are not HIV positive, and their demand for ARVs is fueling a little-understood corner of the black market trade in HIV medications. Drawing on media reports of HIV medication diversion and confiscation from as early as 1999, Inciardi et al. listed the ARVs lamivudine/zidovudine, ritonavir, efavirenz, lopinavir/ritonavir, and abacavir/lamivudine/zidovudine, and the non-ARV (but commonly prescribed to HIV-positive patients) medications acetaminophen/oxycodone, somatropin, and dronabinol as reported targets, while their own interview data singled out ritonavir and efavirenz as common targets for Miami's pill brokers [9]. Informants in the study reported that ritonavir, a "booster" for other protease inhibitors, was being used to "boost" street drugs, especially methamphetamine and ecstasy, making ritonavir a valuable component in drug cocktails for recreational use [9]. Efavirenz was reportedly desired for its own intoxicating properties [9].

A handful of additional reports supporting claims of ARV misuse have since appeared in the scientific literature. In a South African qualitative study of substance abuse and HIV risk, three (of 22) interviewees spontaneously mentioned ARVs as a component in a recreationally smoked drug cocktail, though none reported personal use [5•]. In another qualitative study, eight (of 43) participants (interviewed about HIV treatment refusal) spontaneously discussed ARV abuse and diversion, though none reported personal use or explicit witnessing of others' use [6•]. To date, only one scientific report explicitly contains a second-hand description of ARV abuse (none contain first-hand, researcher-observed accounts). One of the (over 30) healthcare workers in the South African ethnographic study mentioned above described witnessing her boyfriend steal, crush, and smoke her efavirenz [13]. She reported not understanding his motive, because he had the economic means to buy other drugs [13].

Enter the Media

In 2009, media outlets began running reports of ARVs being crushed and smoked by South African adolescents [14–16]. Little further evidence regarding the manner of use or the ARVs' perceived psychoactive properties was published.

While journalists speculated about the psychoactive and addictive properties of ARVs and the extent of their abuse, insufficient evidence was reported to extrapolate much reliable information from this series of articles.

The media articles, however, generated public fear of the addictive nature and social and health consequences of ARV abuse [13]. The rhetorical power of the recreational abuse of ARVs should not be understated. Nurturing the perception that diverted ARVs feed a rampant abuse trend may further stigmatize HIV treatment, legitimize treatment delays, and even threaten donations of ARV supplies [13].

The Whoonga Controversy

A later series of media reports inflamed public fear of ARV misuse by linking it to a street drug called whoonga, which has an established reputation as highly addictive and destructive in South Africa [17, 18]. Whoonga's contents are a source of disagreement. Media reports variously mention heroin, methamphetamine, rat poison, detergent, talcum powder, milk powder, baking powder, and crushed ARV pills, and informants commonly describe sprinkling the white powder into marijuana (dagga) or tobacco to smoke it [16, 17, 19, 20, 21•, 22, 23]. Thus, whoonga is likely to be a mixture of illicit and non-illicit substances whose precise contents are often unknown to users and may change depending on who is manufacturing the sample [18, 21•, 22]. Such variation stems in part from manufacturers' practice of cutting in cheap and readily available substances as bulking agents, keeping the price of the drug low enough for its target market [18, 22]. With little more than rumor for evidence, media reports articulated growing public fear and indignation, which incited opposing calls for evidence-based and cautious reporting [18, 24]. To this end, eight whoonga samples were chemically analyzed, six by a rehabilitation center director and two by an academic at a local university, and negative results were reported for ARV content [24].

Further details of the analyses were not published, but in a radio interview the chemist who analyzed two samples for investigative journalists reported they contained strychnine (rat poison) and opioids. Such content parallels addictive, white-powdered drug mixtures in South Africa commonly smoked with marijuana or tobacco and known by other names, notably the newer "nyaope" and the older "sugars" [18, 21•, 22, 23]. The similarity of these cocktails, and even the interchangeability of their names, lends credence to the hypothesis that "whoonga" may be a rebranded drug, following on the heels of heightened police crackdowns on the sugars trade [22, 23]. The perception that ARVs are a key component of the powerful whoonga cocktail appears to increase its allure, regardless of its actual content [18, 23].

Indications that ARVs provide a powerful high also have the potential to drive ARV misuse independent of whoonga [24].

Intense stomach cramps, joint pain, and headaches have been consistently reported accompanying whoonga use [16, 17, 21•, 22, 23], suggesting that users may be experiencing opioid withdrawal [5••] and opioids may be a common choice of base drug. Bulking agents may also serve a second purpose: the chemist who analyzed the first two whoonga samples hypothesized that the large amount of strychnine was responsible for the acute stomach pains that drive users to smoke whoonga so frequently [22, 23].

A Role for Antiretrovirals in Whoonga?

Complicating the picture, the media (and one scientific report) began conflating the practice of crushing and smoking ARVs (with marijuana or tobacco) with the purchasing and smoking (with marijuana or tobacco) of a manufacturer-created drug cocktail with unknown contents [6••, 16, 25, 26]. The difference is critical for scientists and journalists to maintain while mapping and analyzing emerging ARV abuse. The chemical makeup of whoonga and other such drug mixtures is likely inconsistent. While there is scant evidence that ARVs are currently added to whoonga, manufacturers of illicit drug cocktails in South Africa may find a use for the pills, whether as psychoactive or bulking components [18, 21•].

Possible Mechanisms of Recreational ARV Effects

In a 2013 review of emerging ARV abuse, Davis et al. synthesize the present state of the scientific understanding of the neuropsychiatric effects of ARVs, particularly efavirenz, and propose possible mechanisms of interaction between ARVs and common drugs of abuse [4••]. Tables 1 and 2 summarize their results.

ARV medications have central nervous system (CNS)-stimulating effects, which are thought to be responsible for the neuropsychiatric complications documented in some HIV-positive patients taking ARVs [4••]. In scattered case reports, some ARVs have been associated or suspected to be associated with delusions, hallucinations, and mania (zidovudine); mood changes and hallucinations (abacavir); psychosis and mania (nevirapine); and unspecified neuropsychiatric disorders (ritonavir) [4••]. The majority of neuropsychiatric effects have been associated with efavirenz, reported more frequently in patients with pre-existing psychiatric or substance use conditions [4••]. Clinical trials have associated efavirenz with insomnia, dizziness, vivid dreams, and adverse psychiatric effects, while case and prospective studies have linked it with mania, depression, suicidal thoughts, hallucinations, and psychosis [4••]. It is possible that CNS stimulation is responsible

Table 1 Potential interactions between ARVs and substances of abuse

Substance	Effect of Combination with ARVs
Cannabis	Combination with efavirenz may heighten the euphoria of cannabis by CYP3A4 inhibition
Cocaine	No known effect in combination with ARVs
Heroin	No known effect in combination with ARVs
Oxycodone	Enhanced effect in combination with ritonavir by CYP2D6 inhibition
Methadone	Opiate withdrawal in combination with efavirenz or nevirapine by CYP3A4 induction
MDMA	Enhanced effect of MDMA in combination with ritonavir by CYP2D6 inhibition
Ketamine	Enhanced psychogenic effect of ketamine in combination with efavirenz and ritonavir by CYP2B6 inhibition
PCP	Enhanced psychogenic effect of PCP in combination with efavirenz or ritonavir by CYP3A4 inhibition

Antiretroviral medication: an emerging category of prescription drug misuse. *Am J Addict.* 2013 Sep 17. doi: [10.1111/j.1521-0391.2013.12107.x](https://doi.org/10.1111/j.1521-0391.2013.12107.x). [Epub ahead of print]. Copyright ©2013 American Academy of Addiction Psychiatry. This material is reproduced with permission of John Wiley & Sons, Inc.

ARV antiretroviral, CYP cytochrome P450, MDMA methylenedioxymethamphetamine, PCP phencyclidine

for recreational efavirenz effects, though its frequent coupling with marijuana also suggests an interaction with cannabis.

All of the ARV-illicit drug interactions proposed by Davis et al. result from ARVs' ability to inhibit enzymes involved in the metabolism of other drugs. When the un-metabolized form of the illicit drug is the more potent psychoactive molecule, such inhibition would yield higher concentrations of the un-metabolized substance in the user's bloodstream, increasing the illicit substance's psychoactive effects. Such effects were proposed for interactions between particular ARVs and cannabis, methylenedioxymethamphetamine (MDMA), methamphetamine, gamma-hydroxybutyric acid (GHB), and oxycodone [4••].

Table 2 ARV interactions with substances of abuse

ARV	Potential Interaction with Substances of Abuse
Efavirenz	Enhanced cannabis effect by CYP3A4 inhibition Precipitated methadone withdrawal by CYP3A4 induction
Ritonavir	Enhanced oxycodone effect by CYP2D6 inhibition Enhanced MDMA effect by CYP2D6 inhibition Enhanced GHB effect by CYP inhibition
Nevirapine	Precipitated methadone withdrawal by CYP3A4 induction

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ARV antiretroviral, CYP, cytochrome P450, GHB gamma-hydroxybutyric acid, MDMA methylenedioxymethamphetamine

In the short term, efavirenz inhibits cytochrome P450 (CYP)3A4, which metabolizes marijuana's primary psychoactive components (Δ^8 -THC, Δ^9 -THC, and metabolites), theoretically maintaining higher serum concentrations of these un-metabolized molecules [4••]. (Efavirenz also induces CYP3A4, but the inductive action occurs over the course of days or weeks [4••].) While efavirenz is the ARV featured in reported combinations with marijuana, ritonavir (like all protease inhibitors) also inhibits CYP3A4 [4••], so the proposed metabolic effects of efavirenz on marijuana should be producible by ritonavir or any other protease inhibitor. Efavirenz's additional neuropsychiatric effect may account for its favor. In a manner similar to the interaction with cannabis, inhibition of CYP3A4 may inhibit cocaine metabolism, but because only 10 % of cocaine metabolism involves a CYP3A4 pathway, efavirenz and other protease inhibitors are not expected to have a large enough impact to increase serum concentrations of cocaine [4••].

Ritonavir and saquinavir were hypothesized to use the same pattern of metabolism inhibition to increase serum concentrations of GHB, also through inhibition of the CYP450 system involved in first-pass GHB metabolism [4••]. MDMA and methamphetamine metabolisms involve CYP2D6, which is strongly inhibited by ritonavir, leading to a potentially acute increase in MDMA serum concentrations (and psychoactive effects). This hypothesis is suggested by the abnormally high MDMA serum concentration detected in the autopsy of a 32-year-old, HIV-positive man who took 180 mg of MDMA while on a regimen including ritonavir [4••]. CYP3A4 is also involved in MDMA metabolism, so efavirenz, ritonavir, and other protease inhibitors would also be expected to inhibit MDMA breakdown through this pathway, but it is unclear whether the effects would be pronounced enough to increase serum drug concentrations [4••]. Ritonavir's weak inhibition of CYP2D6 should theoretically increase the serum concentrations of oxycodone [4••].

When the more potent psychoactive molecule is a metabolite of an illicit substance, inhibiting a protein involved in metabolism of a drug would be expected to result in decreased serum concentrations of the more psychoactive molecule. In the case of existing addiction, this might result in a withdrawal effect [4••]. Such withdrawal-inducing interactions have been proposed between ARVs and methadone or hydrocodone. Ritonavir inhibits CYP2D6, which metabolizes hydrocodone to the more potent hydromorphone [4••]. Hydrocodone is also metabolized by CYP3A4, but the dominant effect is expected to decrease serum concentrations of hydromorphone, which may lead to withdrawal in the case of existing opioid addiction [4••]. A parallel induction of opioid withdrawal is expected in the combination of protease inhibitors (efavirenz and nevirapine are mentioned specifically) and methadone, because methadone metabolism is largely conducted by CYP3A4 [4••]. No evidence or plausible interaction mechanisms have

been reported for the combination of ARVs with buprenorphine, heroin, morphine, or codeine.

Consequences of Off-label ARV Use

Black market demand for ARVs may increase the risk of theft of these medications, jeopardizing the safety of patients targeted for their pills [9, 24]. ARV diversion might also alter perceptions of the abuse potential for ARVs, potentially leading to unnecessary regulation of these medications and further restricting access among those who need treatment [13, 24]. Therapeutic end use of diverted ARVs may not follow standard treatment guidelines, resulting in patients with inadequate treatment and less controlled illness [9, 13, 27]. Perhaps the most alarming risk of off-label ARV use, however, is its potential to foster resistant HIV strains. In 2011, researchers investigating ARV treatment resistance in Mwanza, Tanzania discovered dramatically high levels of resistance among 88 self-declared, treatment-naïve patients [27]. Kasang et al. proffered two possible means of developing such resistance: direct sexual transmission of drug-resistant viruses or “selection from the natural pool of quasiespecies in each individual patient following undisclosed antiretroviral drug experience” [27]. While their analyses suggested that most of the mutations were due to transmission, the researchers detected traces of ARVs in the plasma samples of two patients, indicating that these patients had used ARVs within the 1- to 2-week window detectable by the test and had not told the researchers. Kasang et al. concluded that at least some of the treatment resistance was likely due to off-label ARV use, and they hypothesized that self-medication was a likely culprit [27]. Resistance means a diminished effective pharmaceutical armament against HIV, for individuals and for populations [27]. Fewer effective medications, in turn, threaten global efforts to contain this epidemic [27].

Conclusion

There are plausible mechanisms by which ARVs may enhance the effects of illicit drugs [4••]. Enhancing combinations include cannabis with efavirenz and ritonavir with MDMA, methamphetamine, GHB, or oxycodone [4••]. In addition, evidence exists that efavirenz may have independent psychoactive properties [4••]. These actions and interactions mirror the existing evidence of ARV abuse patterns: efavirenz smoked with marijuana in South Africa and desired in Miami for its own psychoactive effects, and ritonavir used as a “booster” for ecstasy (MDMA) and methamphetamine.

Depending on the contents of whoonga, a South African drug cocktail, ARVs may or may not be active if added to the mixture. Because whoonga is reportedly cut into marijuana

and smoked, it is plausible that efavirenz could boost the marijuana high and/or provide its own psychoactive action. Whoonga use in existing reports, however, is described as an intense, opioid-like pain relief and high, followed by symptoms reminiscent of opioid withdrawal [14, 18, 19, 23•, 24, 25]. No interactive mechanisms were uncovered involving ARVs with heroin, morphine, or codeine—opioid components found in two samples of whoonga—or with buprenorphine [4••]. The only opioid-boosting mechanism proposed involved ritonavir (not described in whoonga reports), and oxycodone [4••]. Methamphetamine is a common drug of abuse in South Africa [28], and if a drug cocktail such as whoonga contained it, the addition of ritonavir could conceivably boost the mixture’s effects.

Any off-label ARV use has the potential to create resistant HIV strains, diminishing the effectiveness of currently available drugs [27]. The black market trade in ARVs may also alter public perception of the abuse potential of these drugs, creating supply restrictions and other barriers to treatment [13, 24]. Not all black market trade, however, is abuse driven: significant portions of the market are occupied by off-label therapeutic use [9, 13]. Black market sales of ARVs to areas with little available HIV treatment indicate that a legitimate need for medication coupled with inadequate healthcare fuels ARV diversion [11]. The sale and trade of ARVs in local HIV-positive communities constitutes another significant market component, driven by psychosocial factors including high competing needs, stigma, distrust, and poor health-related education [3, 9, 13].

Further research is needed to demystify the nature and scope of ARV abuse potential. Epidemiologic surveillance is warranted to establish the extent of antiretroviral diversion and misuse and characterize those who are most at risk for misusing these medications. Abuse liability testing in the laboratory is needed to illuminate the euphorogenic effects of ARVs among drug users and further understand the emerging problem of ARV misuse. Psychosocial and health-disparity-related ARV diversion is fueling a significant component of the ARV black market and might be inflating off-label ARV use, contributing to risks of developing resistant HIV strains. Psychosocial factors and health disparities are known enemies in the fight against HIV, and they are amenable to existing interventions. It is recommended that resources be directed toward the most effective of these known interventions to significantly diminish the black market trade in ARVs and stem the serious consequences of off-label ARV use.

Compliance with Ethics Guidelines

Conflict of Interest Kristen Steslow and Glen Davis declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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