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Contribution of behavioral health factors to non-AIDS-related comorbidities: An updated review

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Abstract

Purpose of review: We summarize recent literature on the contribution of substance use and depression to non-AIDS-related comorbidities. Discussion of recent randomized clinical trials and implementation research to curtail risk attributed to each behavioral health issue is provided.

Recent Findings: Smoking, unhealthy alcohol use, opioid use, and depression are common among PWH and individually contribute to increased risk for non-AIDS-related comorbidities. The concurrence of these conditions is notable, yet understudied, and provides opportunity for linked-screening and potential treatment of more than one behavioral health factor. Current results from randomized clinical trials are inconsistent. Investigating interventions to reduce the impact of these behavioral health conditions with a focus on implementation into clinical care is important.

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Summary: Non-AIDS-defining cancers, cardiovascular disease, liver disease and diabetes are leading causes of morbidity in people with HIV. Behavioral health factors including substance use and mental health issues, often co-occurring, likely contribute to the excess risk of non-AIDS-related comorbidities.

Keywords

HIV; alcohol; smoking; opioid; depression; comorbidity

Introduction

Non-AIDS-defining cancers (NADC), cardiovascular disease (CVD), liver disease, and diabetes are now the leading causes of morbidity and mortality among people with HIV (PWH) [1–3]. The mechanisms underlying this excess risk of non-AIDS-related comorbidities are likely multifactorial and include immunosuppression, immune activation, and inflammation [4, 5], as well as the high prevalence of traditional and non-traditional risk factors (e.g., hepatitis c virus [HCV]) and behavioral health factors (e.g., substance use and depression). In this review, we summarize the recent literature on the contribution of substance use (i.e., smoking, unhealthy alcohol use, and opioid use) and depression to the most common non-AIDS-related comorbidities [1]. Findings reported in this review focus on papers published in the past three years.

Non-AIDS-Related Comorbidities

Non-AIDS-Defining Cancer

Among PWH, NADCs account for 7-20% of deaths [2, 6, 7]. Compared to uninfected populations, PWH have a 21-53% increased risk for non-virus-NADCs, regardless of HIV viral load [8, 9], and 3 to over 5-fold increased risk of virus-related NADCs (i.e., human papillomavirus and HCV-related cancers), variable based on HIV viremia [8, 9]. The most common NADCs are lung cancer (20%), Hodgkin lymphoma (13%), breast cancer (7%), prostate cancer (6%), colorectal cancer (6%) and liver cancer (3%) [6, 10]. Importantly, some cancers including lung, anal, oral cavity/pharynx, kidney, and myeloma may be diagnosed at a younger age among PWH than uninfected populations [4].

Cardiovascular Disease

After adjustment for HIV and CVD-related confounders, PWH experience a 44-79% increased risk of acute myocardial infarction (AMI) [11–13], 81-94% for heart failure [14], 40-156% for ischemic stroke [13, 15, 16], 90% for any coronary heart disease [17], and 19% for peripheral artery disease [18], compared to uninfected populations. Increased risk for AMI persists even with sustained HIV viral suppression [11]. Further, 20% of all non-AIDS deaths are attributed to CVD, with a 70% higher standardized mortality ratio than the general population, matched on age and sex (95% confidence interval [CI] 1.50-1.90) [2].

Liver Disease

Liver disease accounts for 12-14% of all deaths among PWH [1, 2, 19]. The age and sex standardized mortality ratio of death due to liver disease is 3.7 times higher (95% CI 3.3-4.2)

in PWH compared to the general population [1, 2]. PWH carry a disproportionate burden of fatty liver disease (FLD): global prevalence of non-alcoholic fatty liver disease (NAFLD) and virus-associated liver disease (VAFLD) was measured at 25% [20] and 35% [21], respectively. PWH with VAFLD are more likely to develop steatohepatitis and hepatic fibrosis than uninfected populations with NAFLD [22, 23], further increasing disease burden [24]. The prevalence of NAFLD in PWH is estimated to be between 15-72%, and predominantly depends on HCV [25]. It is estimated that 30% of PWH are co-infected with HCV, and this co-occurrence accelerates liver disease risk compared to infection with either virus alone [26, 27].

Diabetes Mellitus

Diabetes is common among PWH [28–30], with incidence rates ranging from 3.1 to 14 cases per 1000 person years [29, 31–34]. The incidence of prediabetes is even higher, with an estimated 125 cases/1000 person years in a recent meta-analysis [35]. Evidence suggests that PWH have greater risk for diabetes compared to uninfected populations, with some excess risk being attributed to older ART regimens [36].

Behavioral Health Factors

Smoking

Smoking prevalence is two-fold higher among PWH than uninfected populations [37], with over 50% of PWH reporting current smoking in the United States, regardless of gender [38]. Death attributed to smoking far exceeds that due to treated HIV infection [39]. The adverse effects of cigarette smoking on nearly all organs is well established and attributed to chronic exposure to over 7,000 chemical compounds from different classes (e.g., N-nitrosamines, polycyclic aromatic hydrocarbons, heavy metals) that cause and accelerate cancer, cardiovascular disease, and myriad other health conditions [40]. The deleterious effects of smoking on immune function are particularly relevant in PWH and may increase viral replication in macrophages, microglia, and T cells, ultimately leading to immune exhaustion and impaired cell function [41].

Non-AIDS-defining Cancers.—Six recent epidemiologic studies characterize the risk that smoking poses for NADC among PWH (Table 1). Overall, smoking among PWH is associated with a two-fold (95% CI 1.80, 2.98) increased risk for NADC, attributing 50% of NADC risk (95% CI 39-59%) compared to non-smoking PWH [42] (Table 1). The most common cancers associated with smoking among PWH include lung (incidence rate [IR] 91-175 per 100,000), head and neck (IR 80), esophageal (IR 12-21), anal (IR 76-147), and cervical cancers (IR 21 -506) [43]. Cancer of lung and head and neck, combined, are particularly associated with smoking in PWH, with over 8.5-fold higher risk compared to non-smoking PWH [44]. Excluding lung cancer, ever smoking remains associated with 36% increased risk for NADCs, with an attributable risk of 24% [45]. While data overwhelmingly suggests an increased risk for cancer among smokers, a recent study found lower colorectal cancer screening uptake among current smokers, regardless of HIV status [46]. Lastly, overall cancer risk tends to decline to a level similar to non-smoking PWH after 5 years of cessation, with the exception of lung cancer risk, which was sustained at over 8-fold at 5

years after cessation relative to never smokers [47]. Longer term follow-up was not reported. For context, in a non-HIV sample with over 25 years of follow up, lung cancer risk remained persistently elevated relative to never smokers [48]. Nevertheless, it is important to underscore that cancer risk drops markedly with smoking cessation.

Cardiovascular disease.—In two of the largest prospective observational cohort studies of persons living with and without HIV, PWH who were current smokers had 55-78% greater risk for AMI, compared to non-smokers [11, 45, 49]. Similarly, current smoking among PWH is associated with a 90% (95% CI 1.41-2.56) increased risk for ischemic stroke [50], 42% (95% CI 1.29-1.57) for heart failure [51], and 27% to over 4-fold increased risk for peripheral artery disease [52, 53], compared to never smokers. Likewise, recent studies among PWH have found current smoking to be associated with subclinical atherosclerosis measures (e.g., carotid intima-media thickness and coronary artery calcium) [54, 55].

Diabetes.—Research on the relationship between smoking and diabetes in PWH is sparse [33, 56]. Smoking increases the risk of diabetes in the general population, attributable in part to altered glucose homeostasis in smokers [57–59]. It is unknown if smoking has a greater magnitude of effect in PWH.

Clinical interventions.—A meta-analysis of 12 trials was conducted to determine if tailoring behavioral interventions to PWH was effective relative to non-tailored standard care (i.e., combined pharmacologic and behavior therapy) [60]. Results supported combined interventions for PWH, although the effects of tailoring behavioral interventions were unclear, and authors called for additional research on this question. More recently, in a randomized clinical trial (RCT; Table 2) in PWH of NRT plus either cognitive-behavioral therapy (CBT) or weekly check-in, 7-day abstinence was significantly greater in the CBT group post-treatment and at 6-month follow-up [61]. Another RCT investigating delivery mode (video-call vs. voice call) of an 8-session intervention plus NRT found that video-calls were associated with 10-fold higher odds of 6-month prolonged cessation [62]. Taken together, these two latter trials offer potential methods to optimize treatment in PWH.

Varenicline, a partial agonist of the nicotinic acetylcholine receptor $\alpha 4\beta 2$, is a first-line treatment for nicotine addiction [63], although few RCTs have investigated its use in PWH. A recent double-blind, placebo-controlled RCT in PWH reported nearly 3 times the odds of continuous cessation from weeks 9-48 in the treatment versus placebo groups [64], and a second RCT found that adding text messaging support and adherence-focused behavioral sessions increased cessation relative to varenicline alone [65]. Finally, varenicline may be particularly relevant to smoking treatment among PWH because varenicline is twice as effective as NRT for cessation among smokers who metabolize nicotine faster (as opposed to slower) [66], and PWH tend to be faster metabolizers [67, 68].

Several future RCTs have recently been funded by the National Cancer Institute (R01CA243552; R01CA243800; R01CA243907; R01CA243910; R21CA243911 R01CA243914) to test the incorporation of different aspects of smoking cessation (i.e., comprehensive wellness including stress/mood, nutrition, and other substance use), modes and types of treatment delivery (i.e., phone/text counseling; group-based video-

conferencing; contingency management), and technology-guided decision making (i.e., algorithms that include non-response and relapse; use precision medicine such as leveraging information on nicotine metabolism and other genetically-determined endophenotypes). Results from these trials will further guide smoking cessation treatment among PWH.

Implementation.—Even though smoking cessation treatment relates to better health outcomes in the general population, few studies have tested specific implementation strategies for treatment in PWH. While the 5As (Ask, Advise, Assess, Assist, and Arrange) for smoking cessation have been implemented to a degree into clinical practice, disparities in implementation persist among PWH. In one study of primary care clinics, PWH who smoke (vs. uninfected controls) reported 50% lower odds of being advised to quit and 40% lower odds of being assessed for readiness to quit [69]. Additional support for PWH who smoke may help alleviate such disparities. A recent feasibility study implemented a decisional algorithm for smoking cessation in HIV primary care among non-treatment-seeking smokers and found self-reported smoking reduced by half from baseline to 3-month follow-up [70]. A future trial (R21CA243906) aims to implement a peer navigator model (already used in HIV care) to improve smoking quit attempts, use of existing quit lines, and cessation rates among PWH who smoke.

Unhealthy Alcohol Use

Unhealthy alcohol use ranges from at-risk use (>14 [7] drinks per week for men [women]), binge drinking (>4 [3] standard drinks on one occasion in men [women]) to alcohol use disorder [71]. PWH are nearly twice as likely as uninfected populations to drink heavily (≥5 drinks/day) [72], with detrimental effects on the HIV care continuum [73].

Non-AIDS-defining Cancers.—In the general population, unhealthy alcohol consumption is causally associated with cancers of the liver, mouth, throat, esophagus, breast, colon and rectum [74]. Recent studies (Table 1) of cancer risk factors among PWH [44, 75, 76] were not designed to assess the association between alcohol and cancer. Therefore, important phenomena were not captured including quantity, frequency, and duration of alcohol consumption; nor were potentially sick quitters separated from current abstainers. Mechanisms underlying alcohol-related cancer risk include acetaldehyde toxicity, oxidative stress [77], malnutrition [78, 79]. DNA methylation [80], immune system alterations, estrogen elevation, and gut microbiota dysbiosis [81].

Cardiovascular disease.—A meta-analysis of 13 cross-sectional studies including alcohol as a potential risk factor for CVD among PWH estimated that unhealthy alcohol use was associated with a 37% increased risk of CVD compared to non-heavy use [82], while a recent study found no association between alcohol consumption and CVD events among PWH [83]. Mechanisms underlying alcohol-related CVD risk overlap with those for alcohol-related cancer and additionally include alcohol-related hypertension, alcoholic cardiomyopathy, altered blood coagulation, endothelial dysfunction, and subclinical atherosclerosis [84–87].

Liver Disease.—Recent studies including PWH highlight associations of unhealthy alcohol use and liver fibrosis and liver-related mortality with some exceptions [88–93]. Some evidence suggests that the association of alcohol and liver fibrosis differs by antiretroviral therapy regimen, with protease inhibitor-based regimens driving higher than expected FIB-4 increases among unhealthy drinkers [94].

Diabetes.—There is a paucity of data on the relationship of alcohol consumption and diabetes risk in PWH. Prior work assessing risk correlates of prevalent or incident diabetes has shown inconsistent associations with alcohol use [95–99]. The largest of these studies from IeDEA Asia-Pacific reported missing alcohol data for 78% of participants and did not find a significant association of alcohol above moderate/low risk drinking and incident diabetes (unadjusted HR (95% CI): 1.15(0.49, 2.73))[99]. Large meta-analyses in the general population have found light alcohol intake may be associated with lower diabetes risk, an effect that may be stronger for women, while heavy alcohol intake was not clearly associated with the diabetes risk [100, 101]. Whether the association between alcohol consumption and diabetes differs by HIV status remains unknown.

Clinical Interventions.—Several recent RCTs have assessed pharmaco-behavioral alcohol interventions in the context of HIV. These recent studies report clinically relevant improvements in alcohol use and HIV-related outcomes with interventions such as injectable naltrexone with counseling, motivational interviewing, and stepped care [102–111] (Table 2). Importantly, these studies demonstrate challenges with recruitment and retention in alcohol-focused studies of nontreatment seeking PWH presenting to HIV clinics.

A 2017 systematic review and meta-analysis summarized data from 21 behavioral alcohol intervention studies among 8,461 PWH [112], from across several countries. Overall, these studies demonstrated significant but modest effects on reducing alcohol consumption among PWH while also increasing condom use, medication adherence, and consequently, reduced HIV viremia. Madhombiro et al. [113] reached somewhat contrasting conclusions in their 2019 systematic review. While both studies agreed on the lack of large intervention effects on alcohol use in HIV, the latter reported no significant intervention effects overall (no metaanalysis was performed). The studies involving interventions primarily targeting unhealthy alcohol use alone had larger effects than those intervening on multiple behaviors concurrently (e.g., substance use and HIV control). Since these reviews, Kahler et al. [107] randomized men who have sex with men to motivational interviewing-based interventions or usual care, finding greater and faster reductions in alcohol consumption in the intervention group.

Implementation.—Recent studies have focused on integrating alcohol treatment with routine HIV care. We found that a stepped care model, where treatment services were intensified as needed to address alcohol use, led more PWH with unhealthy alcohol use to receive evidence-based alcohol-related care with potential translation into alcohol reduction and meaningful clinical improvements (i.e., HIV viral load, liver measures) [102, 103]. However, given observed challenges in recruiting and retaining PWH in alcohol interventions, innovative approaches to engage (e.g., contingency management) and promote

retention in alcohol treatment (e.g., implanted extended release drug formulations), are needed and underway (ClinicalTrials.gov Identifier: NCT03089320).

Opioids

PWH are disproportionately exposed to opioids, including heroin and prescription opioids [114]. About 230,500 people who inject drugs (PWID) have HIV in North America [115]. Until recently, PWH had been prescribed opioids routinely for pain, at higher doses than the general population [116], and with limited monitoring [117].

Beyond overdose (Bosh et al., Conference on Retroviruses and Opportunistic Infections 2019, Abstract #147) and the impact of addiction on health in PWH, emerging data indicate that opioids exert physiologic effects and may promote immunosuppression [118], with resulting increased risk of infectious complications [119]. Opioids may be associated with immune activation by compromising gut integrity, through microbial translocation [120] and injection-related practices and consequences (e.g., abscesses) [121]. Data on whether opioids impact HIV biomarkers and serves as an important, independent risk factor for comorbidities [122], especially among PWH [123], is largely understudied; the below highlights recent articles published specifically on this topic.

Non-AIDS-defining Cancers.—To our knowledge, there are no studies linking opioid use to cancer in PWH. However, the potential contribution of opioids to NADCs is biologically plausible, given that opioids act on mu receptors found on lymphoid cells, potentially affecting their proliferation, inhibiting natural killer cell cytotoxicity, and upregulating the secretion of glucocorticoids acting on lymphoid organs [122]. Opioid use in the general population is associated with an increased risk of cancers of the esophagus, stomach, larynx, lung, and bladder [124].

Cardiovascular Disease.—There are sparse data regarding CVD risk with opioid use in PWH [125]. Prescribed opioid use was associated with an increased risk of CVD in participants of a general veteran population (Hazard Ratio [HR] 1.99; 95% CI1.36-2.92) [126] and with death due to coronary heart disease and CVD in women, but not men [127]. Potential mechanisms of these findings include increased oxidative stress and ischemia through opioid receptors on myocardial cells, increased inflammation, and accelerated atherosclerosis [127].

Injection drug use is a known risk factor for infective endocarditis due to unsafe injection practices (reusing and sharing needles, not using sterile technique)[128] and potentially from opioid immunosuppressive effects [128, 129]. Compared to the general population, infective endocarditis associated with drug use is more common among PWH. One retrospective cohort study found that among patients who were hospitalized for infective endocarditis, HIV was more common among those with drug associated infective endocarditis vs. non-drug associated infective endocarditis, 6% had versus 1.2%, respectively ($p<0.001$) [130].

Methadone is known to prolong the QTc interval, increasing the risk of the potentially fatal arrhythmia torsade de pointes [131]. Given that certain antiretroviral agents (e.g., rilpivirine) may prolong the QTc, this adverse effect may be more worrisome among PWH. One study

found that QTc intervals were longer in PWH compared to uninfected participants. However, while methadone increased the odds for prolonged QTc (OR 4.58, CI 1.41, 14.9), antiretroviral therapy decreased the odds (OR 0.35, CI 0.13, 0.96) [132]. Further, a recent prospective cohort study found that QTc-prolonging medications were associated with an increased risk of mortality in women with HIV (HR 1.15 per drug, 95% CI 1.00-1.33) [133].

Liver Disease.—HCV is a common comorbidity among patients with opioid use disorder (OUD) due to injection related transmission with up to 45% of PWID infected with chronic HCV [134]. While animal and cell models have shown opioids to cause increased transaminases, liver inflammation, fatty accumulation and fibrosis, the results from observational human studies are mixed [135]. A cross-sectional study of HIV/HCV co-infected participants reported that medical and extra-medical opioid use did not increase the risk of liver fibrosis [135]. While HIV and injection drug use were associated with an increased incidence of HCV reinfection, opioid agonist treatment was associated with a lower likelihood of reinfection [136].

Clinical Interventions.—The importance of providing evidence-based harm reduction and treatments, including medications such as buprenorphine, to address OUD among PWH cannot be overstated and have been reviewed elsewhere [137, 138]. Given the potency and high tolerability of direct acting antivirals, recent studies focus on addressing HCV in the context of ongoing injection drug use [139]. Regular telemedicine sessions with healthcare providers for patients with OUD on methadone, over a fifth of whom had HIV, appeared to help with HCV treatment [140]. Being on medications for OUD reduced rates of HCV reinfection and mortality from HCV and HIV in patients with recent extra-medical drug use [141–143].

Implementation.—Integrated care models, where patients are treated in the same location for their OUD, HIV, HCV and other comorbidities, have been increasingly implemented and appear to be cost-saving and improve health [144–146]. Structural changes – such as broad HCV and HIV testing/treatment, substance use screening, medications for OUD, syringe exchange and naloxone programs, supervised injection facilities [147] and increased implementation of HCV treatment, especially to vulnerable areas (i.e., rural locations), will likely be helpful [137, 138] In parallel, efforts to promote more appropriate opioid prescribing in HIV clinical settings with adherence to clinical guidelines are actively needed and underway [116, 148]. The impact of such interventions (e.g., buprenorphine, prescription opioid tapering) specifically on disease comorbidity (e.g., cardiovascular disease), however, remains to be determined.

Depression

Depression, whether defined as a depressive disorder or elevated depressive symptoms, is a common issue in PWH that likely has a more complex etiology than in the general population [149]. The core affective symptoms are depressed mood and loss of interest/pleasure, which are accompanied by various cognitive (e.g., worthlessness and trouble concentrating) and somatic (e.g., sleep and appetite changes) symptoms. For a diagnosis of major depressive disorder, ≥5 of these symptoms must be present nearly every day for 2

weeks, and cause significant distress or functional impairment [150]. Among PWH, the global prevalence of depression is 31% [151], and the incidence of depression is twice that in the general population [152]. While considerable research has examined depression's potential impact on HIV treatment adherence and clinical outcomes [153], an emerging area seeks to determine if depression is associated with leading comorbidities in HIV.

Diabetes.—One prospective study reported a clinically meaningful association between depression and incident diabetes (HR 1.98, 95% CI 1.11-3.54) [154], and arecent cross-sectional study observed an association between depression and prevalent diabetes [155].

Cardiovascular Disease.—The extant epidemiologic literature indicates that depression may indeed be an independent risk factor for CVD in PWH. Most prospective studies have reported clinically meaningful associations between depression and future CVD outcomes (HRs 1.30-4.61), including AMI, incident heart failure, and CVD-related mortality [49, 51, 154, 156]. Importantly, these relationships have persisted after adjustment for traditional CVD risk factors and HIV-specific factors, suggesting that depression independently confers CVD risk. The two prospective studies that did not report depression-incident CVD associations observed trends in the same direction but may have failed to detect relationships due to lower CVD event counts [157, 158].

Although the mechanisms underlying relationships between depression and leading comorbidities in HIV have yet to be elucidated, there are several biological and behavioral candidates [159]. Candidate biological mechanisms include increased immune activation and systemic inflammation. There is mixed but growing evidence that depression is associated with elevated biomarkers of these processes in PWH [160–163]. It is plausible that depression promotes immune activation and inflammation through autonomic dysfunction, hypothalamic-pituitary-adrenal axis dysregulation, and/or increased gut permeability [164–166]. Candidate behavioral mechanisms, which have been associated with depression in PWH, include smoking and unhealthy alcohol use [37, 167], physical inactivity [168], and poor diet quality [169, 170]. Moreover, general population research indicates a link between depression and poor adherence to medical treatments and recommendations [171–173], some of which may help prevent leading comorbidities in HIV.

Clinical interventions.—Evidence-based treatments for depression in the general population, including antidepressant medications and cognitive-behavioral therapy, have been found to be effective in the HIV population [174, 175]. While depression treatment has been investigated as a means to improve HIV outcomes [176, 177], to our knowledge, no published studies have evaluated whether depression treatment reduces risk of non-AIDS-related comorbidities in PWH. Of relevance, our team recently completed a pilot RCT examining the effect of internet cognitive-behavioral therapy for depression on CVD risk markers in PWH and depression receiving antiretroviral therapy (ClinicalTrials.gov Identifier: NCT02309372). This trial is in the analysis phase, and results are forthcoming. In light of the accumulating epidemiologic and mechanistic evidence and dearth of clinical trial evidence, there is a current need for well-powered RCTs to rigorously evaluate the utility of depression treatment as a novel primary prevention strategy for leading comorbidities in HIV.

Implementation.—There are multiple approaches to the implementation of depression care in the HIV population. As previously mentions, integrated care models – which incorporate behavioral health care with general medical care – are becoming increasingly common in specialty medical settings, including HIV clinics, and the available results are promising for depression [178, 179] and cost-effectiveness [180] outcomes. Technology-assisted approaches – such as telephonic and internet interventions – are also becoming more common, likely due to their ability to address barriers to care (e.g., limited time, transportation issues, stigma, and clinician shortages) and their potential cost-effectiveness and scalability [181]. Meta-analytic evidence supports the effectiveness of technology-delivered interventions for depression in PWH [182].

Syndemics Framework

Syndemics Research in HIV was identified as a top research priority for NIH HIV/AIDS research at the NIH Workshop on HIV-Associated Comorbidities, Coinfections and Complications (HIV ACTIONS) held in September 2019. A syndemic is the mutually reinforcing interaction of two or more conditions to increase risk for negative health outcomes [183]. The syndemic of smoking, unhealthy alcohol use, and depressive symptoms is common among PWH, with 51% having two and 15% having all three conditions, and is associated with over twice the risk for incident CVD (Chichetto et al., American Heart Association Abstract, 2019) and all-cause mortality [184], compared to having none of the conditions. Among those with the syndemic, PWH had 20% and 36% greater risk for incident CVD (Chichetto et al., American Heart Association Abstract, 2019) and all-cause mortality [184], respectively, compared to uninfected counterparts. Further, the co-occurrence of behavioral health conditions hinders the ability to reduce any one of them. For example, a recent study among PWH receiving care found high smoking relapse among those who quit was significantly associated with concurrent mental health disorders or unhealthy alcohol use [185]. To date, RCTs aimed to reduce concurrent behavioral conditions among PWH are sparse. A recent open-label, randomized pilot study investigating the feasibility and safety of extended-release naltrexone for treatment of concurrent opioid and alcohol use disorders in HIV care found treatment to be acceptable, feasible, and safe for integration into HIV clinics compared to standard care [186]. Further, an ongoing trial among PWH who are current daily smokers and unhealthy drinkers is testing the effectiveness of varenicline and cytisine to reduce alcohol consumption and smoking (ClinicalTrials.gov Identifier: NCT02797587). Results from this and similar studies will guide treatments that target more than one condition at a time.

Conclusions

As the U.S. Department of Health and Human Services has announced an initiative to end the HIV epidemic by 75% over 5 years, and by 90% over 10 years, the substantial burden of comorbidities remains among those who already live with HIV [187]. This lingering challenge calls attention to the special behavioral health needs of PWH who are at significant risk for the chronic comorbidities discussed herein, as well as several not covered in this report such as kidney disease and osteoporosis. In the general population, research supports the combination of behavioral therapy and pharmacotherapy as the most effective treatment for the aforementioned behavioral health risk factors [188–190]. For PWH, there

is an urgent need for increased implementation of these treatments into HIV care settings using integrated models of care.

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Table 1.

Recent (past 3-years) epidemiologic studies of behavioral health factors on HIV comorbidities

Author (Year)	Study Type	N	Cigarette use	N (events)	Age	Outcome	Measure of effect	Effect estimate (95% CI)
Smoking and Non-AIDS-Related Cancers								
Billa (2018)	Prospective France	1391	Current: 69% Former: 18%	60	Median 46 (43-51)	Non-AIDS-defining and Non-HCV-liver related cancers	Hazard Ratio	Current vs Never 0.79 (0.41, 1.51) Former vs Never 1.08 (0.34-3.45)
Altekruse (2018)	Consortium of 22 prospective cohorts North America	52,441	Ever: 79%	2306	18-39: 49% 40-49: 34% 50-59: 14% 60+: 3%	Any cancer Lung-cancer Non-smoking related	Hazard Ratio	Ever vs Never 1.33 (1.18, 1.49) 17.80 (5.60, 56.63) 1.12 (0.98, 1.28)
Rodriguez Arrondo (2018)	Prospective Spain	7,067	Ever: 85%	221	Mean 49.2	Non-AIDS-defining cancers	Odds Ratio	Ever vs Never 8.18 (4.40, 15.21)
Althoff (2019)	Consortium of 22 prospective cohorts North America	72,854	Ever: 60%	1405	18-39: 48% 40-49: 34% 50-59: 14% 60+: 3%	Non-AIDS-defining cancers Non-AIDS-defining (excluding lung)	Hazard Ratio	Ever vs Never 1.61 (1.37, 1.89) 1.36 (1.15, 1.60)
Lam (2019)	Prospective cohort United States	3,177	Current: 12% Former: 48% Unknown: 3%	822	Mean 52.6	Adenoma or Invasive Colorectal Cancer	Prevalence Ratio	Current vs Never: 0.90 (0.67, 1.21) Former vs Never: 1.14 (0.70, 1.85)
Thrift (2019)	Retrospective cohort United States	44,075	Ever: 81%	95	Mean 47.3	Esophageal Stomach	Hazard Ratio	Ever vs Never 7.02 (0.94, 52.4) 2.18 (0.66, 7.22)
Smoking and Cardiovascular Diseases								
Barska (2017)	Cross-sectional, observational Poland	121	Current: 58% mean pack-years: 14		Mean 40	Carotid intima-media thickness	Beta, linear regression	Pack years – Beta 0.004 ($p<.0001$)
Beckman (2018)	Prospective cohort study United States	28,714	Current: 55% Former: 15%	2,609	Mean 47.5	Peripheral Artery Disease	Hazard Ratio	Current vs Never: 1.61 (1.37, 1.89) Former vs Never: 1.23 (0.99, 1.52)
Tarr (2018)	Cross-sectional, observational Switzerland	704 (61% HIV+)	Current HIV+: 35% HIV−: 17%	CAC > 0: n=382 (54.3%) Any Plaque: n=390 (55.4%)	Mean 54	Coronary Artery Calcium (CAC) Score > 1 Any coronary artery plaque	Odds Ratios	Current vs None: 2.01 (1.37-2.93) 1.96 (1.35-2.85)
Knudsen (2018)	Cross-section, observational Denmark	908	Current: 28% Former: 37%	112	Mean 52	Peripheral Artery Disease	Odds Ratio	Current vs Never 4.30 (2.05, 9.04)

Author (Year)	Study Type	N	Cigarette use	N (events)	Age	Outcome	Measure of effect	Effect estimate (95% CI)
Althoff (2019)	Consortium of 22 prospective cohorts North America	72,854	Ever: 60%	1405	18-39: 48% 40-49: 34% 50-59: 14% 60+: 3%	Myocardial Infarction	Hazard Ratio	Ever vs Never Among all: 1.82 (1.20, 2.77) Those with BMI data: 1.71 (1.04, 2.81)
Cedarbaum (2019)	Prospective cohort study United States	1,899 (73% HIV +)	Current: 39%	147	Range 49-55	Peripheral Artery Disease	Odds Ratio	Current vs None 1.27 (1.09, 1.48)
Hatleberg (2019)	Prospective cohort study Australia, Europe and United States	43,564	Current: 42% Former: 18%	590 strokes; 296 ischemic, 83 hemorrhagic, 211 unknown	Mean 39	Ischemic stroke Hemorrhagic stroke	Hazard Ratio	Current vs Never: 1.90 (1.41, 2.56) Current vs Never: 1.08 (0.68, 1.71)
Alcohol and Non-AIDS-Related Cancers								
Author (Year)	**Study Type**	**N**	**Alcohol use**	**N (events)**	**Age**	**Outcome**	**Measure of effect**	**Effect estimate (95% CI)**
Thrift (2019)	Retrospective cohort study United States	201,780 (22% HIV +)	Alcohol abuse HIV+: 29.2% HIV−: 13.7%	59 esophageal malignancies, 26 stomach malignancies	Mean (SD) 47 (11)	Esophageal and stomach malignancies	Hazard ratio	Esophageal adenocarcinoma 0.32 (0.07, 1.35; unadjusted) Esophageal squamous cell carcinoma 1.81 (0.88, 3.69) Gastric cardia 1.65 (0.32, 8.65) Gastric noncardia 1.38 (0.53, 3.62; unadjusted)
Billa (2018)	Prospective hospital-based cohort France	1391	Any alcohol use Current: 49% Former: 29%	60	Median 46	Non-AIDS-defining and Non-HCV-liver related cancers	Relative Risk	Current vs. non 0.79 (0.41, 1.51) Former vs. non 0.66 (0.31, 1.40)
Rodríguez Arrondo (2018)	Prospective cohort study Spain	7067	Any alcohol use Cases: 30.6% Controls: 22.9%	221	Mean Cases 49.2 Controls 42.9	Non-AIDS-defining cancers	Odds Ratio	1.42 (0.83–2.46)
Alcohol and Cardiovascular Disease								
Kelso-Chichetto (2017)	Prospective cohort study United States	788	10-year drinking patterns <u>Women</u> Abstinent/Low: 47% Moderate: 43% Heavy: 10% <u>Men</u> Abstinent/Low: 19% Moderate: 72% Heavy: 9%	Women: 57 Men: 52	Mean (SD) Women: 50.6 (45-55) Men: 65.3 (60.7–70.5)	Atherosclerosis (carotid intima media thickness > 1.5mm)	Odds Ratio	Abstinent/Low as Reference Women: Moderate 1.08 (0.58, 2.00) Heavy 1.10 (0.40, 3.02) Men: Moderate 0.07 (0.21, 1.00) Heavy 0.63 (0.43, 4.00)

Author (Year)	Study Type	N	Cigarette use	N (events)	Age	Outcome	Measure of effect	Effect estimate (95% CI)
Chichetto (2019)	Prospective cohort study United States	1551	Women 10-year Abstinence: 35% Low: 30% Moderate: 29% Heavy: 6% Past 6 months Abstinence: 55% Moderate: 38% Heavy: 8% Men 10-year Abstinence: 13% Low: 61% Moderate: 18% Heavy: 8% Past 6 months Abstinence: 58% Moderate: 37% Heavy: 5%	Baseline IMT μm Women 729.8 Men 742.6	Mean (SD) Women 35.2 (7.6) Men 69.6 (5.5)	Carotid Intima Media Thickness progression	Average Change (Beta)	Women 10-year Abstinence as Reference Low 3.39 (−2.36, 9.14) Moderate 3.06 (−2.32, 8.43) Heavy 8.08 (0.35, 15.8) Current Abstinence as Reference Moderate −0.95 (−5.82, 3.93) Heavy −11.4 (−20.2, −2.63) Men 10-year Abstinence as Reference Low 15.3 (6.46, 24.2) Moderate 14.3 (1.36, 27.2) Heavy 21.8 (4.63, 38.9) Current Abstinence as Reference Moderate 0.26 (−9.99, 10.5) Heavy −15.4 (−30.7, −0.13)
Alcohol and Liver Disease								
Canan (2017)	Prospective cohort study United States	1855	Self-report (SR) Heavy: 10% Moderate: 34% None: 56% Provider documented (PD) Heavy within 6-month: 19.1% Never heavy: 64.6% Drinking > 6 months ago: 16.3%	48	Median 44	Liver-related mortality	Hazard Ratio	SR moderate /PD no heavy drinking [Reference group] SR none/ PD no heavy drinking 1.15 (0.40, 3.33) SR none/ drinking>6 months ago [Reference group] SR none/PD heavy drinking 7.28 (2.43, 21.78) SR moderate/PD any>6 months 2.00 (0.38, 10.46) SR moderate/PD heavy drinking 3.52 (1.04, 11.90) SR heavy/All PD 3.00 (0.93, 9.65)
Kim (2017)	Cross-sectional cohort study United States	12849	Alcohol use disorder: 18%	596	Median 47	fibrosis-4 (FIB-4) >3.25	Odds Ratio	1.9 (1.6, 2.3)
Kelly (2017)	Prospective cohort study United States	684	None: 46% Light: 27% Moderate: 7% Heavy: 7% Very heavy: 13%	72	Mean 39.6 (6)	Significant fibrosis (FIB-4>3.25)	Estimated Average Rate of Progression	Light vs. None 0.004 (−0.11, 0.12) Moderate vs. None 0.006 (−0.18, 0.19) Heavy vs. None 0.04 (−0.19, 0.28) Very heavy vs. None 0.25 (0.01, 0.49)
Jaquet (2017)	Cross-sectional, clinic-based cohort	807	AUDIT-C score < 4: 90.6%	43	Median (IQR) 43 (37-50)	Liver stiffness measure ≥7	Odds Ratio	AUDIT -C < 4 as reference AUDIT-C: 4-5

Author (Year)	Study Type	N	Cigarette use	N (events)	Age	Outcome	Measure of effect	Effect estimate (95% CI)
	West Africa		4-5: 5.4% > 5: 4%					0.5 (0.1-2.5) AUDIT-C: >5 4.3 (1.7-10.8)
Martel-Laferrière (2017)	Prospective cohort study Canada	1238	Alcohol Abuse in previous 6 months: 14%	158	Median (IQR) 44 (38,49)	Significant liver fibrosis (AST-to-Platelet Ratio ≥ 2.0)	Hazard Ratio	1.76 (1.14, 2.72)
Shanyinde (2019)	Prospective cohort study Italy	9542	Abstainers: 36% Moderate: 23% Hazardous: 7% Unknown: 34%	617	Median (IQR) 38 (31,46)	Severe liver disease (FIB4>3.25), clinical diagnosis (ascites, decompensated cirrhosis, hepatocellular carcinoma, hepatic encephalopathy, esophageal varices), liver related death	Hazard Ratio	Moderate as reference Abstainer 1.09 (0.86, 1.38) Hazardous 1.32 (0.94, 1.85) Unknown 1.12 (0.86, 1.46)
Depression and Cardiovascular Disease								
Author (Year)	**Study Type**	**N**	**Depression**	**N (events)**	**Age**	**Outcome**	**Measure of effect**	**Effect estimate (95% CI)**
Vadini (2019)	Prospective cohort Italy	712	22%	54	Mean=46.1	Vascular event	Hazard Ratio	1.37 (0.72-2.58)
Depression and Diabetes								
Tymchuk (2018)	Cross-sectional Canada	265	44.9%	24	Mean=47.5	Diabetes	Mann-Whitney U test	U=1848; p=.012
Opioid use and Cardiovascular Disease								
Author (Year)	**Study Type**	**N**	**% Opioid use**	**N (events)**	**Age**	**Outcome**	**Measure of effect**	**Effect estimate (95% CI)**
Myerson (2019)	Cross-sectional United States	156	Methadone use 8.3%	45	Mean (SD) 52.4 (10.4)	QTc Prolongation	Odds Ratio	4.58 (1.41-14.9)

AST, Aspartate Aminotransferase Test; AUDIT-C, Alcohol Use Disorders Identification Test — C; CAC, Coronary Artery Calcium; FIB-4, fibrosis-4; PD, provider-documented; SR, self-reported;

Table 2.

Summary of Clinical and Implementation Trials for Behavioral Health Conditions in Persons with HIV

Author (Year)	Sex, Age, country	Design, number of participants, and length of cessation intervention	Smoking Cessation Intervention	Outcome	Measure of effect	Effect estimate (95% CI)
Randomized Clinical Trials for Smoking Cessation						
Kim et al. (2018)	Female 100% Mean age (SD), years: 51 (7.7) United States	Parallel RCT Video vs voice call interventions (N=42, n=21 per arm) Two-block randomization Both arms received an HIV-tailored smoking cessation intervention	1) Video-call+NRT 2) Voice-call +NRT	6-month prolonged abstinence	Odds ratio	Video-call vs voice-call 10.0 (1.1, 90.6)
Mercie et al. (2018)	Male 83% Mean age (SD), years: 45 (9) France	Parallel RCT Varenicline (N=123) vs placebo (N=124) Randomization stratified by smoking counselor type (ID specialist or tobacco treatment specialist) and by center had participation in an ancillary study on lung aging. First treatment 12-weeks Weeks 13-24 no treatment; Second treatment in Weeks 25 – 37 for those who resumed smoking	1) Varenicline + smoking cessation counseling 2) Placebo + smoking cessation counseling	Biologically confirmed Continuous abstinence from weeks 9 to 48 Continuous abstinence from weeks 9 to 12	Odds Ratio	2.5 (1.0, 6.1) 3.2 (1.6, 6.4)
O'Cleirigh et al. (2018)	Male 75% Mean age (SD), years: 50.5 (8.2) United States	Parallel RCT Block randomization in blocks of 4 Both arms received a 60-minute psychoeducation session before randomization (session 1). Both groups were provided NRT at week 6 (quit date) Total N = 53 QUIT – nine 60-minutes sessions + NRT (N=26) ETAU – 4 10-minutes sessions + NRT (N=27)	1) QUIT – (CBT + NRT) ETAU – Corresponding to weeks 7-10 of QUIT intervention, control condition received 4 post-quit 10-minute sessions	7-day point-prevalence abstinence Anxiety and depressive symptoms	Beta	At end of treatment 5.60 (2.64, 8.56) At 6-months 7.69 (4.6, 10.8) At end of treatment 0.46 (0.09, 0.84) At 6-months 0.37 (0.05, 0.69)
Implementation Trial for Smoking Cessation						
Cropsey et al (2019)	United States	Single-arm pilot study Integration of smoking cessation decision algorithm within routine clinic visits to engage non-treatment-seeking smokers in smoking cessation therapies	Pre-post – baseline to follow-up smoking behavior	Self-reported smoking behavior (cigarettes per day) Nicotine dependence (Fagerstrom Test for Nicotine Dependence score)	Average frequencies	Baseline vs 3-month follow-up 14.4 vs. 7.1 cigarettes per day 5.6 vs 3.6 nicotine dependence
Randomized Clinical Trials for Unhealthy Alcohol Use						
Edelman (2019)	98% male Mean age, years: 54 (range 23-70 years)	N randomized=128 n = 63 intervention n = 65 usual care	Stepped alcohol treatment with intensification at pre-	Primary: Drinks per week over the past 30-days at week 24	Adjusted mean difference	No difference by treatment group: 10.4 (SD=16.5) vs. 15.6 (SD=17.6)

Author (Year)	Sex, Age, country	Design, number of participants, and length of cessation intervention	Smoking Cessation Intervention	Outcome	Measure of effect	Effect estimate (95% CI)
	United States	24-week treatment; 52-week study Jan 2013-July 2017	defined intervals integrated into HIV care.			Adjusted mean difference −4.2 [−9.4, 0.9; p=0.11] drinks per week in the past 30 days
Edelman (2019)	71% male; Recently released inmates Mean age (SD), years: 51 (8) United States	N randomized=51 n = 25 intervention drug PLUS counseling n = 26 placebo PLUS counseling 24-week treatment April 2011-February 2015	Extended release naltrexone plus counselling	Primary: ≥95% ART adherence;	Adjusted mean difference in proportion	34% vs 23% with ≥95% ART adherence (p=0.4) in naltrexone vs. control group.
Edelman (2019)	99% male Mean age, years: 61 (range 33-87) United States	N randomized=95 n = 49 intervention n = 46 control 24-week treatment; 52-week study January 2013-July 2016	Stepped alcohol treatment with intensification at pre-defined intervals integrated into HIV care.	Primary: past 30-day alcohol abstinence at week 24	Adjusted odds ratio	No difference in self-reported abstinence at 24 weeks (38% vs 23%; AOR 2.6 [0.8, 9.0] p=0.12. All participants increased abstinence over time.
Springer (2018) Springer (2017)	77% male Mean age (SD), years: 45 (8) United States	N randomized=100 n = 67 intervention drug n = 33 placebo 6-month treatment September 2010-February 2016	Extended release naltrexone	Primary (2018): achieve-maintaining HIV viral suppression; Primary (2017): time to first heavy drinking day; number of drinks/ drinking day; percent heavy drinking days; pre vs. post incarceration change in average drinks/drinking day; total number of drinking days	Difference in proportion	Extended release naltrexone associated with improved viral suppression (48 to 64%; p=0.02) from baseline to 6 months vs placebo (64 to 42%; p=0.07) Limited differences by treatment group in alcohol consumption; younger (20-29 years) had longer time to first heavy drinking day in naltrexone vs. placebo arm (24 vs 9.5 days p;<0.001)
Kahler (2018)	100% men who have sex with men Mean age (SD), years: 42 (10) United States	N randomized=180 n = 89 intervention n = 91 control 6-month intervention; 12-month study December 2011-March 2016	60-min, in-person motivational interviewing session with personalized feedback + two brief phone sessions and in-person booster sessions of 10–20 min each at the 3- and 6-month follow-up visits.	Primary: Average number of drinks per week; number of heavy drinking days in the past 30 days	Adjusted Beta (95% CI)	Decline in drinks per week faster in intervention group (50% by 6 months vs. 25% reduction by 12 months). Intervention group had 8.72 fewer drinks at 6 months and 5.98 fewer drinks at 12 months vs control group. Intervention group had fewer heavy drinking days at 6 months (45% lower) and less heavy drinking at 12 months (62% vs. 78%)
Cook (2019)	100% women Mean age (SD), years: 48 (9) United States	N randomized=194 n = 96 intervention n = 98 placebo control 4-month intervention; 7-month study 2013-2016	Naltrexone	Primary: quit drinking or reduction below unhealthy levels (≤7 drinks/week or ≤3 drinks/day in past 30 days)	Odds ratio	No significant difference in odds of reducing/quitting drinking: 1.32 (0.73-2.41; p=0.36). No significant difference between groups on other alcohol outcomes though both groups reduced consumption
Huis in ‘t Veld (2019)	54% men	N randomized = 560 n = 267 intervention	Single delivery of WHO brief intervention package;	Primary: (from 3 to 12 months) reduction in	Odds ratio	No difference by intervention status for primary outcome or

Author (Year)	Sex, Age, country	Design, number of participants, and length of cessation intervention	Smoking Cessation Intervention	Outcome	Measure of effect	Effect estimate (95% CI)
	Medan age, years: 36 years (IQR=31-42) South Africa	n = 293 control 1-day intervention; 12-month study	personalized feedback on AUDIT results; health education leaflet on responsible drinking; advice and brief counseling on excessive drinking	AUDIT score from hazardous/harmful to abstinence or low risk use		secondary AUDIT score outcomes (estimates not provided)
Emenyonu (2017)	55% men Median age, years: 30 years (IQR=25-36) Uganda	N randomized= 373 n = 207 intervention n = 166 control	Quarterly alcohol use and HIV assessments (vs. single, limited assessment at 6 months after initial baseline assessment)	AUDIT-C≥3 (men) ≥4 (women) or PEth≥50ng/ml at 6 months	Odds ratio	No difference in unhealthy alcohol consumption at 6 months aOR:0.95 (0.60, 1.51)
Wandera (2019)	66% men Median age, years: 39 years (IQR=32-46) Uganda	N randomized =337 n = 167 intervention n = 170 control 20-30 minute intervention; 6-month study	Single delivery of brief alcohol counseling (motivational interviewing) plus “positive prevention” information	Primary: mean AUDIT-C score	Mean AUDIT-C change	No differential AUDIT-C reduction by study arm. Mean AUDIT-C change at 6 months = 0.01 (−0.32, 0.34)
Randomized Clinical Trials for Opioid Use Disorder						
Author (Year)	**Sex, Age, country**	**Design, number of participants, and length of cessation intervention**	**Intervention**	**Outcome**	**Measure of effect**	**Effect estimate (95% CI)**
Korthuis (2017)	43% Female Mean age (SD), years:) 46 (10) United States	Open-label, randomized, pilot trial	extended-release naltrexone (XR-NTX) vs treatment as usual (TAU)	Opioid use	Mean difference from baseline to 16-week follow-up	TAU vs XR-NTX Mean days in past month Baseline 17.3 vs 20.3 Follow-up 4.1 vs. 7.7 UDS positive for opioids Baseline 9% vs 9% Follow-up 7% vs 4%