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1 **A new era of HIV care for age-associated multimorbidity**

2

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20 Abstract

21 **Purpose of review:** The management of people with HIV has shifted focus from acute
22 AIDS-defining illness towards improving detection of chronic disease and reducing impact of
23 multimorbidity. In this review we explore this shifting paradigm of HIV care and the evidence
24 for alternative models proposed to provide integrated holistic services for people living with
25 HIV (PLWH) with multimorbidity.

26 **Recent findings:** Despite 25 years of the ART era an increased incidence of NCD and
27 multimorbidity in PLWH persists. As the world moves closer to universal ART coverage this
28 phenomenon is now reported in low- and middle-income settings. Multimorbidity affects
29 PLWH disproportionately compared to the general population and results in reduced health
30 related quality of life (HRQoL), greater hospitalisation and higher mortality. There is
31 evidence that NCD care provision and outcomes may be inferior for PLWH than their HIV
32 negative counterparts. Various models of integrated multimorbidity care have developed and
33 are grouped into four categories; HIV specialist clinics incorporating NCD care, primary care
34 services incorporating HIV care, community NCD clinics offering integrated HIV care, and
35 multidisciplinary care integrated with HIV in secondary care. Evidence is limited as to the
36 best way to provide multimorbidity care for PLWH.

37 **Summary:** A new era of HIV care for an ageing population with multimorbidity brings
38 challenges for health providers who need to develop holistic patient focused services which
39 span a range of coexisting conditions.

40 **Key words;** HIV, multimorbidity, primary care, primary prevention, chronic non-
41 communicable disease, general practice.

42

43 Introduction

44 People living with HIV (PLWH) are living longer due to the success of antiretroviral treatment
45 (ART)(1). This has shifted the management of human immunodeficiency virus (HIV) from
46 responding to AIDS-associated illness to maintaining long-term health through the primary
47 prevention and treatment of chronic non-communicable diseases. Routine monitoring of
48 patients for such comorbidities has become commonplace in many HIV clinics, but it remains
49 unclear how this interfaces with the preventative primary care model. An international
50 consensus statement published in 2021 designated multimorbidity as one of three key
51 health-related challenges for PLWH along with, health-related quality of life (HRQoL) and
52 stigma/discrimination (2). In this review we focus on the challenges of primary prevention
53 and management of multimorbidity in PLWH and present evidence for existing models of
54 care.

55 Multimorbidity

56 One of the challenges of exploring this subject area within HIV care is the variety of
57 language used to describe secondary, non-AIDS-related diseases. The literature is replete
58 with terms such as multimorbidity, comorbidities, age-associated comorbidities, ageing
59 related non-AIDS comorbidities, accelerated ageing process, ageing-associated
60 noncommunicable disease, and chronic non-communicable disease, among other others.
61 Here, we use the term non-communicable disease (NCD) to define the non-AIDS associated
62 diseases which can occur in PLWH as they age. Thus, this definition includes chronic liver
63 disease, but not the viral hepatitis *per se*. We use the WHO definition of multimorbidity as
64 the coexistence of two or more chronic diseases in one individual (3), thus a PLWH with a
65 single NCD has multimorbidity. There is a comprehensive body of evidence explaining the
66 mechanisms and aetiology of specific NCDs in PLWH in isolation, e.g., cardiovascular
67 disease (CVD) and HIV. Here, our focus is on the complexity of multiple conditions and the
68 implications for service delivery.

69 Burden of multimorbidity

70 The higher rates of NCDs and, consequentially, multimorbidity in ART treated PLWH
71 became apparent in longitudinal cohorts as the ART era became established (4–6).
72 Recently published studies that extend over the second decade of the 21st century
73 demonstrate that this increased incidence of NCD and multimorbidity in PLWH persists when
74 compared to matched general population controls (7–9), and the gap may be widening(10).
75 Importantly, this is not a phenomenon restricted to high income countries as studies from

76 low- and middle-income settings as diverse as Kenya (11), South Africa (12)(13) and Latin
77 America (14) all attest.

78 While NCD and multimorbidity accumulate with older age among PLWH (12,15), this doesn't
79 appear to be a legacy effect from pre-ART era AIDS related disease as risk is not associated
80 with the calendar period of HIV diagnosis (12). Indeed, NCDs may be accruing early in life
81 as the differences compared to HIV negative individuals are more pronounced in younger
82 PLWH; in the WHIS cohort, women <25 years old had the greatest NCD incidence rate ratio
83 (7) and in the UK hazard ratios for hypertension (HTN), chronic kidney disease (CKD) and
84 ischaemic heart disease (IHD) are higher in PLWH under, rather than over, 40 years old (9).
85 Thus, with projections estimating the majority of ART-users will be over 50, and one fifth
86 over 65 years old by 2030 (16,17), PLWH will continue to live with greater multimorbidity for
87 the foreseeable future.

88 The principal NCDs that are more common in PLWH remain consistent, although prevalence
89 and incidence may vary according to each studied cohort's characteristics, and principally
90 include cardiovascular disease (including IHD, stroke, heart failure), HTN, dyslipidaemia,
91 diabetes mellitus (DM), CKD, osteoporotic bone disease, chronic lung disease and
92 psychiatric illness (7,9,10,18–20). Malignancies are also more common in PLWH but will not
93 be explored in this review as their management necessarily involves referral to specialist
94 care rather than in the HIV service or primary care. The consequences of NCD for PLWH
95 are already clear; NCDs adversely impact on health-related quality of life (21) and have all
96 been seen to be increasing (and at a faster rate) in hospitalised PLWH compared to people
97 without HIV (22). Compared to PLWH without NCD, those with 1, 2 and ≥ 3 NCD have 3, 7
98 and 13 fold risk of death respectively (8). With multimorbidity comes polypharmacy (defined
99 as five or more daily medications) which can lead to increased issues with side effects,
100 coherence and interactions (23) and is especially common in PLWH over the age 50, even
101 when antiretroviral medication is discounted(24).

102 The evidence base for how best to deliver services for PLWH with multimorbidity is less
103 conclusive. This should not be a surprise as while chronic disease prevalence in the general
104 population doubled from 1985 to 2005, with a consequent 3-fold jump in the number of
105 individuals with four or more co-existing NCD (25), clinical guidelines and models of care still
106 remain focused on a single disease approach (3). Traditionally, sexual health or infectious
107 diseases specialists have provided HIV care in clinics concentrating on HIV, while NCDs,
108 where they occurred, have been the remit of other specialists or primary care practitioners.
109 The latter group especially being well placed to promote risk factor modification, primary
110 prevention and the timely identification and management of early-stage comorbidities that

111 remain the mainstays of addressing multimorbidity (3). But HIV specialists have found
112 themselves widening their scope of care provision, yet the HIV focused model has rarely
113 changed. For example, a recent cross-sectional analysis from France found a significant
114 increase in use of NCD preventative medication (statins, clopidogrel, aspirin) in PLWH (15).
115 The potential deficiency of the single disease model of HIV care was strikingly illustrated by
116 a 20-year analysis of the Multicenter AIDS Cohort Study cohort that found risk for incident
117 DM in men with pre-diabetes was 40% (95% CI: 0 -80%) higher among PLWH after
118 adjusting for competing risk factors (20). Similarly, in a Spanish study which made
119 comparisons to those in the general population with the same comorbidities, PLWH were 1.5
120 to 3 fold less likely to be receiving treatment for their HTN, DM and dyslipidaemia (19).

121 Moving from a single disease approach to multimorbidity management

122 The transition from a single disease approach to multimorbidity management requires the
123 health system to reorientate the models of care currently in practice. Patients with multiple
124 chronic health conditions are high utilisers of health services, and combining clinic
125 appointments and reviews can positively impact the cost of care(26).
126 As stated, primary care or general practice is usually the provider of holistic and preventative
127 care for NCDs, especially in high-income settings(3). However, a French analysis
128 demonstrated that PLWH with NCDs were less likely to consult a general practitioner
129 compared to controls (76.7% vs. 79.9%; $p = 0.030$)(18). Yet, those PLWH that did manage
130 to get access then had a higher number of consultations (6.2% vs. 5.0%; $p < 0.001$)(18),
131 which suggests that PWH had greater need for general practice even if their access was
132 poorer.

133 Fundamental to providing holistic patient-centred care is understanding that social
134 determinants of health impact health and access to care(27); an unsecured job, poor access
135 to childcare, probation, substance addiction, debt and immigration status influence how
136 people prioritise secondary prevention. Furthermore, multimorbidity and socioeconomic
137 status are strongly linked; people from deprived communities not only die earlier but live with
138 poor health from an earlier age(28). These factors are relevant to many PLWH who often
139 report poor HRQoL and challenges accessing services(29,30). A population-based cohort
140 study that analysed 32 long term conditions including HIV and described patterns of
141 accumulation of comorbidities, found that the speed of transition from no comorbidities to
142 multiple conditions was increased by deprivation and linked to gender and ethnicity(31). The
143 study found consistent links between alcohol and substance misuse as a co-morbidity and
144 HIV, viral hepatitis, and liver disease (31).

145

146 Models of integrated care for PLWH with multimorbidity

147 The term integrated care is difficult to define and varies between stakeholder and health
148 system(32). The most commonly used health services definition emphasises services that
149 are “*managed and delivered so that people receive a continuum of health promotion,*
150 *disease prevention, diagnosis, treatment, disease-management... coordinated across the*
151 *different levels and sites of care ...according to their needs throughout the life course.*”(33).
152 In response to the evolving burden of multimorbidity among PLWH, there has been a shift
153 away from single disease services towards integrated care. Duffy and Njuguna describe a
154 framework of four models of HIV/NCD integration, which Gausi et al. have sought to
155 evaluate in a recent scoping review(34–36). We present these models below with further
156 discussion and evidence from additional recent publications (Figure 1).

157 1. HIV specialist clinics incorporating NCD care

158 This model centres on enhancing HIV specialists’ ability to provide NCD or multimorbidity
159 care within their existing service. One example is the use of simplified geriatric principles for
160 non-geriatrics-trained providers(37). There has been limited evaluation of NCD control from
161 this approach to date. Gausi et al found 3 studies focusing on HTN in PLWH, these reported
162 higher rates of control of HIV and comorbid NCDs(36). However, NCD management was
163 often evaluated as a single comorbidity associated with HIV rather than as part of holistic
164 multimorbidity care; the studies simply reported patient outcomes upon integrating NCD
165 screening and treatment services in established HIV programs rather than directly
166 comparing them to outcomes with non-integrated care. While further studies are needed to
167 provide an evidence base for this model, an important discussion is about the capacity of
168 HIV care providers to offer screening and management of multiple NCDs, especially in
169 settings where it is a challenge to adequately provide ART and monitor HIV. Furthermore,
170 the management of NCD needs longitudinal and multidisciplinary services which are more
171 challenging to provide and access in a secondary care setting compared to general
172 practice(3).

173 2.Primary care services incorporating HIV care

174 In this model the management of NCDs is in primary care by primary care providers, general
175 practice or family practice depending on the health system. Also known as shared care or
176 collaborative care, this approach seeks to facilitate primary care to focus on NCD
177 management with support from HIV specialists. Primary care services are better
178 established in high-income settings where this model has most often been described. For
179 example, the British HIV Association outlines how to realise shared care for PLWH(38), the

180 difficulties of PLWH access to primary care services from HIV-related stigma and health
181 discrimination notwithstanding(18,30). A 2015 systematic review of current practice and the
182 clinical, economic and patient satisfaction outcomes of shared care models identified a
183 limited number of studies from Australia, Switzerland, Germany, Canada and UK(39). The
184 overall quality of evidence for these outcomes was poor and the authors postulated that
185 context specific factors might be involved(39). They did note that robust clinical protocols,
186 training and timely communication were key facilitators, and the latter has been
187 demonstrated in the context of prescribing by a 2022 UK intervention called 'Think ARV'(40).
188 This aimed to reduce risk of potential drug-drug interactions (DDI) for people taking ART; a
189 high proportion of general practitioners reported they would like support with prescribing
190 non-ART medications in patients on ART so the initiative provided a dedicated telephone
191 and email service for them staffed by HIV-specialist pharmacists and it led to increased
192 awareness and detection of DDIs among community prescribers(40).

193 3.Community NCD clinics offering integrated HIV care

194 This model involves management of HIV and NCDs concurrently in NCD focused primary
195 care settings. It is most applicable to, and so most often described in, LMIC settings where
196 the driver is to address weak primary healthcare by establishing services for stand-alone
197 NCDs (usually HTN and DM) by integrating them with already successful, better funded
198 vertical HIV programmes(41). In their scoping review Gausi et al. identified 5 studies
199 describing this model(36). Only 1 of the 5 studies, in urban Kenya, compared outcomes
200 against non-integrated care finding some evidence for better control for both HIV and NCDs.
201 Evidence from Ugandan and Tanzanian centres that do cater for PLWH with multimorbidity
202 shows that retention in care is improved(42). Gausi subsequently reported outcomes for
203 integrated ART and NCD clubs in Cape Town(43). This study compared HIV (viral
204 suppressions), HTN (controlled BP) and DM (HBA1C) control in PLWH 12 months before, at
205 entry, and 12 months after joining the integrated care service. High levels of retention in care
206 and good viral suppression were maintained, but not NCD control.

207 4.Multidisciplinary care integrated with HIV in secondary care

208 This fourth model concerns the management of HIV and NCDs by bespoke secondary care
209 teams. This integrated model within a secondary care setting supports multidisciplinary
210 teams that can manage HIV and multimorbidity holistically. Gausi et al. found 3 reports from
211 services using this model all demonstrating high rates of NCD control similar to
212 HIVuninfected populations(36). A recently published example of this multidisciplinary clinic is
213 the Golden Compass Clinical Care Program for Older People with HIV(44). This clinic led by

214 HIV-geriatricians also includes other specialists such as cardiologists, pharmacists and care
215 navigators and offers programmes to patients to improve cognitive and functional ability.
216 Patients reported the value of patient focused, whole-person care. In London a similar
217 over50s clinic has been established to support PLWH and described in a service evaluation,
218 but outcomes have not been compared against existing services(45). The clinic has
219 developed dedicated space for senior doctors, trainee doctors, nurses and pharmacists who
220 can do clinical case review. Patients can also be referred into 'live well' pathways to help with
221 lifestyle modification and well-being services delivered by dedicated dieticians and
222 physiotherapists. Common to all the specialised clinics that offer this model of multimorbidity
223 care for PLWH are entry criteria such as frailty or advanced age, high staff to patient ratios
224 and extended interaction times. Although economic outcome analyses are yet to be reported,
225 it is likely these clinics will be too resource hungry to roll out to a more general population of
226 PLWH with multimorbidity. Furthermore, such comprehensive services are often not available
227 for those living without HIV but who may benefit from integrated care of multimorbidity. A less
228 resource intensive approach, at least for those with geriatric needs, might be to integrate
229 PLWH within existing geriatric services. However, there are barriers to developing HIV care
230 by geriatricians which will need to be overcome, in particular the lack of experience and
231 knowledge about HIV in older adults as it is an evolving area of expertise(46). Thus, although
232 this model provides a fully integrated service for PLWH with multimorbidity, it's unlikely to
233 provide a major part of an integrated health system outside secondary care.

234 Conclusion.

235 There continues to be a disproportionately higher burden of NCD and multimorbidity in
236 PLWH that carries important negative impacts. The traditional specialist HIV service model
237 may not be adequately addressing prevention and management of NCDs which are
238 otherwise in the remit of primary care. New models of more integrated care are evolving
239 which seek to improve care of multimorbidity in PLWH, either by integrating HIV into primary
240 care or by strengthening NCD services within secondary care. Models differ according to the
241 PLWH population and existing healthcare infrastructure; LMIC with high HIV prevalence
242 place more emphasis on community-based approaches whereas higher income setting
243 centres with more elderly PLWH have developed comprehensive services run by
244 multidisciplinary teams in secondary care. As yet there is little evidence evaluating the
245 benefits for NCD or HIV outcomes of integrated models compared with existing approaches.
246 Whatever the model, integrating multimorbidity and HIV care will require generalist care and
247 must be acceptable for the individual and the healthcare providers.

248 **Key points:**

- 249 ● HIV care has shifted focus from acute AIDS-defining illness management towards
250 management of chronic multimorbidity.
- 251 ● The burden of multimorbidity for PLWH continues to be greater than that in the
252 general population with impacts on quality of life and life expectancy.
- 253 ● Evidence suggests that multimorbidity care needs of PLWH are not adequately met by
254 currently configured HIV specialist services.
- 255 ● A range of models of integrated care have developed, but there is only weak or no
256 evidence evaluating their outcomes.
- 257 ● Resource availability and local differences in the multimorbidity burden and existing
258 health service infrastructure dictate which models are being developed but will require
259 collaboration between secondary care HIV expertise and primary care proficiency in
260 chronic disease management.

261

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272 **Annotated references**

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275 of people living with HIV. Nat Commun. 2021 Dec 1;12(1). This is a consensus statement
276 from a global group of experts who identify key issues in moving to deliver integrated,
277 person-centred healthcare for PLWH.

278

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280 noncommunicable diseases and mortality in people living with HIV (PLHIV) in the pre-, early-
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282 population-based Danish medical registry looking at PLWH between 1985 and 2017. This
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300 presents data from Positive Voices, a national cross-sectional probability survey of adults
301 ≥18 years living with HIV. The paper describes HIV-related stigma and discrimination in the
302 UK Health System.

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447 Figure 1 Legend

448

449 Summary of 4 models of integrated care for PLWH with multimorbidity with examples. NCD -
450 non communicable disease; MDT – multidisciplinary team; GP – general practitioner.

451

Models of integrated care for PLWH with multimorbidity

