

# HIV, Aging, and Comorbidities Research in Clinical Cohorts: 3 Lessons Learned Using Examples From the CNICS Cohort

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**Background:** Owing to ongoing improvements in antiretroviral therapy, people with HIV (PWH) are achieving near-normal life-spans with many surviving into middle and old age. Despite this success, PWH have a higher than expected risk of developing non-AIDS comorbidities, multimorbidity, and functional decline at ages younger than those without HIV.

**Methods:** As part of the Inter-CFAR (Center for AIDS Research) Symposium, HIV and Aging in the era of Antiretroviral Therapy and COVID-19, we presented a research update from HIV clinical cohorts and specifically described 3 lessons learned from the Centers for AIDS Research Network of Integrated Clinical Systems cohort that are important for HIV and aging research moving forward.

**Results:** Adjudicated outcomes are particularly beneficial for less common comorbidities such as myocardial infarction. Multiple ascertainment approaches increase sensitivity over using diagnoses alone (89% vs. 44%). Adjudication eliminates false-positive events and allows myocardial infarction types to be identified. Comorbidity research has often relied on composite outcomes, such as all cardiovascular diseases, often to increase power. Mechanistic differences across outcomes demonstrate the importance of moving away from many composite outcomes. Timely data are needed to ensure findings are relevant to improve care or outcomes for the population of PWH who are currently aging.

**Conclusions:** A better understanding of the causes, mechanisms, prevention and treatment of functional decline, comorbidities, and multimorbidities is a crucial research focus as PWH are aging. Clinical cohorts with timely, comprehensive harmonized clinical data and carefully adjudicated outcomes are ideally positioned to improve understanding of these questions.

**Key Words:** HIV, people with HIV, aging, comorbidity, antiretroviral therapy

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## INTRODUCTION

Effective antiretroviral therapy (ART) for people with HIV (PWH) has dramatically reduced mortality<sup>1–3</sup> resulting in many surviving into middle and old age. Despite this success, PWH experience high rates of comorbidities, multimorbidity (>1 major chronic illness), and functional decline at ages 10–15 years younger than uninfected controls. Comorbidities that occur at higher rates among PWH include cardiovascular disease (CVD), diabetes, renal and liver disease, certain malignancies, and cognitive decline.<sup>4–8</sup> A better understanding of the causes, mechanisms, prevention and treatment of functional decline, comorbidities, and multimorbidities is a crucial research focus in the current clinical era because people are aging with HIV. Clinical cohorts with timely, rich comprehensive harmonized clinical data, ideally including functional assessments, and carefully adjudicated outcomes are well positioned to improve understanding of these important questions. As the field moves forward to address these important questions, 3 lessons learned regarding conducting research in clinical cohorts to address questions related to HIV, aging, and comorbidities are described using examples from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.

CNICS is a dynamic cohort of PWH in care at 8 sites across the United States.<sup>9</sup> CNICS data encompass the entire ART treatment era (1995–present) and include >37,000 PWH of whom half are alive and currently in care. CNICS is racially and geographically diverse and has included an increasing proportion of older PWH over time (Fig. 1). Additional strengths of CNICS include the comprehensive clinical data; the CNICS clinical assessment of patient-reported outcomes including such measures as substance use, adherence, social determinants of health, frailty phenotype components such as fatigue and mobility issues, and other domains completed as part of routine clinical care visits (~95,000 CNICS clinical assessments completed by PWH to date); and the extensive specimen repository (>800,000 aliquots) with biological specimens linked to comprehensive patient data to support basic and translational research. CNICS data will be used to provide examples for the take-home points described below related to using HIV clinical cohorts to better understand HIV, aging, and comorbidities.

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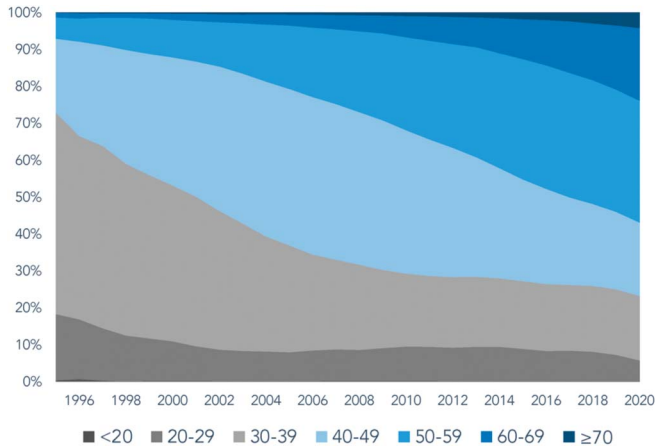
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**FIGURE 1.** Age distribution by year of the CNICS cohort (57% are 50 years of old in 2020).

### LESSON 1: IMPORTANCE OF ADJUDICATED OUTCOMES

Adjudicated outcomes are particularly beneficial for less common comorbidities such as CVD. For example, CNICS has a state-of-the-art 2-step approach to adjudication for myocardial infarction (MI) and other key outcomes. Step 1 is centralized ascertainment for potential events using not only MI diagnoses but also cardiac biomarkers such as troponin I and T values, as well as related procedures such as coronary artery bypass graft surgery. Sites then assemble deidentified packets of primary data including electrocardiograms (ECGs), notes (inpatient and outpatient), procedure reports, and laboratory values. Key exposures such as ART medications are redacted from the packets so they cannot influence the reviews. Step 2 is adjudication: Packets are

reviewed by 2 expert cardiologists for adjudication followed by a third reviewer if there are discrepancies. Reviewers enter standardized review criteria to define MIs into a web application. This allows multiple operational definitions of MI to be applied. It enables identification of events that are likely false positives and identification of reasons for false-positive events, such as elevated troponin values due to pericarditis or end-stage renal disease rather than an MI. Finally, it allows MIs to be categorized by MI type which requires adjudication.

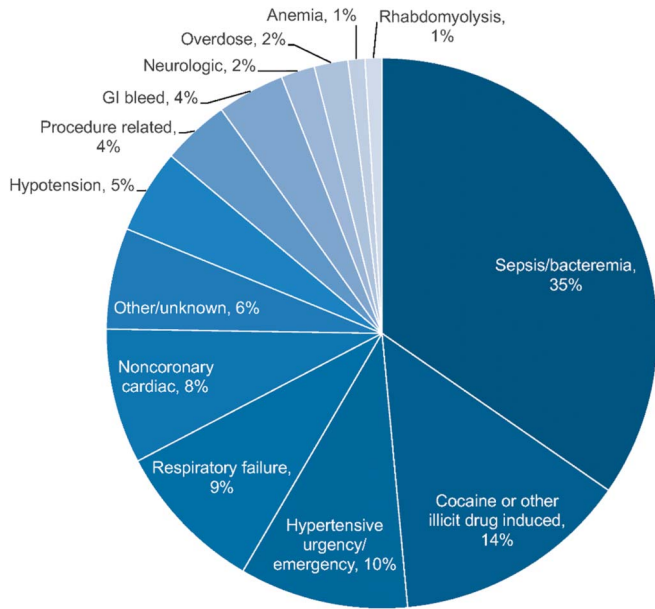
Table 1 from Ref. 10 compares different approaches of identifying possible MIs among PWH with the gold standard which is adjudicated MI outcomes. Historically, studies of MI among PWH have used diagnosis codes to identify MIs. However, Table 1 presents that the sensitivity when using diagnoses alone from multiple HIV clinical care sites across the United States is approximately half of the sensitivity of using cardiac biomarkers for ascertainment (44% vs. 89%). However, although cardiac biomarkers are much more sensitive than diagnosis data for identifying potential MIs, they have a low positive predictive value demonstrating the need to then adjudicate events and exclude the falsely positive events. This suggests studies that rely on diagnoses alone to identify MIs will miss many events. This table also demonstrates that using MI diagnoses identifies PWH who did not have an MI. In fact, 21% of MI diagnosis codes were among PWH who did not have an MI by adjudication. This suggests that diagnosis code-based approaches to identify MIs can result in misclassification and that multiple ascertainment approaches are needed to comprehensively identify all MIs and that once ascertained, a true adjudication is needed to eliminate those that are not MIs.

Although this is just 1 example of the need for adjudication based on MIs, CNICS data have similarly

**TABLE 1.** Accuracy of Different Approaches for MI Ascertainment Including Sensitivity and Positive Predictive Value vs. Gold Standard Centrally Adjudicated MIs

Test Criteria	Reference Standard, N (%)			P	Sensitivity		Positive Predictive Value	
	No Event	False-Positive (FP) Event	MI (Probable or Definite)		%	95% CI	%	95% CI
MI diagnosis								
No	549 (79)	121 (95)	166 (56)	<0.001	44	38 to 49	45	39 to 51
Yes	148 (21)	7 (5)	128 (44)					
Elevated CK-MB value								
No	196 (28)	82 (64)	102 (35)	<0.001	65	60 to 71	26	23 to 29
Yes	501 (72)	46 (36)	192 (65)					
Elevated troponin value								
No	639 (92)	15 (12)	65 (22)	<0.001	78	73 to 83	57	52 to 62
Yes	58 (8)	113 (88)	229 (78)					
Any elevated cardiac biomarkers (CK-MB or troponin)								
No	158 (23)	0 (0)	31 (11)	<0.001	89	85 to 93	28	25 to 31
Yes	539 (77)	128 (100)	263 (89)					

Adapted from Ref. 10.



**FIGURE 2.** Causes of type 2 MIs among PWH.

demonstrated that adjudication is needed to accurately identify stroke, venous thromboembolism (VTE), and other key comorbidities in aging PWH populations rather than reliance on diagnosis data or other electronic health record or self-reported data without adjudication.

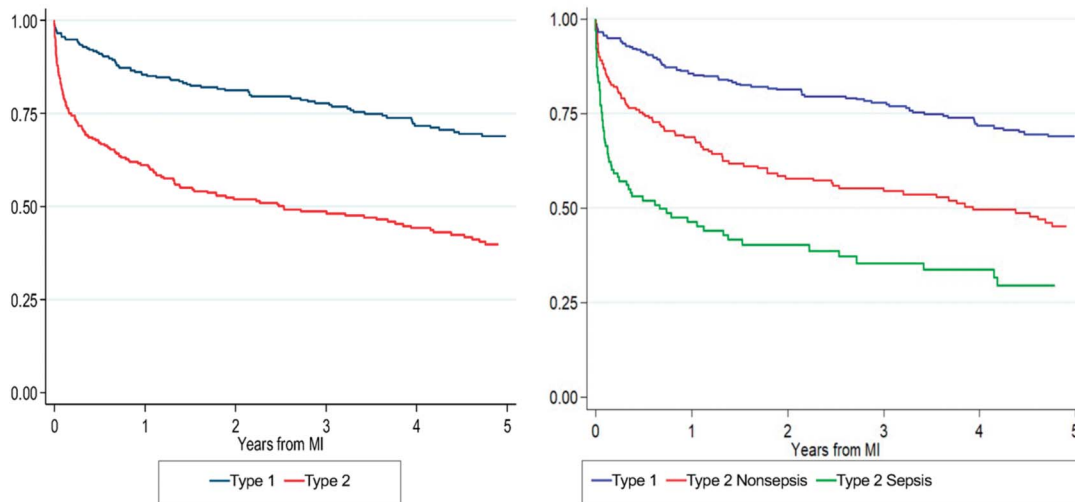
In addition to adjudicating for accuracy, there are other benefits as well. Returning to the MI example, adjudication allows for the type of MI to be identified. The Universal Definition identifies 5 types of MI<sup>11</sup>: type 1 MIs are atherosclerotic often with plaque rupture while type 2 MIs are due to oxygen supply demand mismatch such as that occurs with sepsis or cocaine-induced vasospasm and therefore do not necessarily indicate atherosclerotic disease. Other

types of MIs are rare such as type 3 MI, which has a typical presentation; however, death occurs before cardiac biomarkers are obtained, or type 4 or 5 MIs which occur in the setting of procedures. Among PWH, most MIs are type 1 and type 2 with type 2 MIs making up almost half of all MIs among PWH, a much higher proportion of MIs than seen in the general population.<sup>12</sup>

Figure 2 shows the diverse distribution of causes of type 2 MIs among PWH across the CNICS cohort<sup>13</sup> and demonstrates that sepsis is the most common cause of type 2 MI among PWH followed by cocaine-induced vasospasm. This pattern among PWH is different than type 2 MI causes in the general population.<sup>12</sup> In addition, not only are risk factors and causes of MIs different by MI type but outcomes after an MI also differ by type in PWH.<sup>14</sup> Figure 3 shows overall mortality after a type 1 MI vs. type 2 MI on the left and mortality after type 1 MI, type 2 MI not due to sepsis, and type 2 MI due to sepsis on the right highlighting that outcomes after MIs differ by type. Finally, Table 2 presents rates of MIs by type among PWH by age.<sup>13</sup> Although the rates of both type 1 MIs and type 2 MIs increase with age, at younger ages, PWH are up to 10 times more likely to have a type 2 MI and this difference then disappears by 40 seconds. Only by adjudicating MIs including parsing them by type can these types of patterns be evaluated to better understand mechanisms of these outcomes among aging PWH.

**LESSON 2: COMPOSITE OUTCOMES**

Research on comorbidities among PWH has frequently relied on composite outcomes, such as all CVD outcomes, often as a way to increase power in cohorts with smaller numbers of outcomes. Table 3 is one of many examples of why there should be a move away from indiscriminate composite outcomes. For example, Table 3 shows that cumulative viral load does not predict type 1 MI<sup>15</sup> or ischemic



\*Adapted from <sup>14</sup>

**FIGURE 3.** Survival after type 1 MI, type 2 MI, and type 2 MI due to sepsis or not due to sepsis.

**TABLE 2.** Rates of Type 1 and Type 2 MI per 1000 Person-Years of Follow-Up Among PWH by Age

Age Category	Rate (CI) Type 1 MI	Rate (CI) Type 2 MI	IRR (CI) Type 2 vs. Type 1 MI, <i>P</i>
<30	0.13 (0.03 to 1.32)	1.31 (0.86 to 2.11)	10.0 (2.43 to 88.24), 0.001
30–39	0.71 (0.50 to 1.03)	1.11 (0.84 to 1.49)	1.57 (0.97 to 2.57), 0.05
40–49	2.33 (1.99 to 2.74)	2.06 (1.74 to 2.45)	0.88 (0.69 to 1.12), 0.3
50–59	3.91 (3.40 to 4.53)	3.04 (2.59 to 3.59)	0.78 (0.62 to 0.97), 0.02
60–69	5.13 (4.07 to 6.56)	3.42 (2.58 to 4.63)	0.67 (0.45 to 0.98), 0.03
≥70	9.32 (6.16 to 14.78)	8.88 (5.80 to 14.26)	0.95 (0.49 to 1.85), 0.9

Adapted from Ref. 13.  
CI, confidence interval; IRR, incidence rate ratio; MI, myocardial infarction.

stroke but is a strong predictor of type 2 MI and VTE. A composite CVD outcome would combine these outcomes together, which would obscure these findings. Another example that demonstrates the importance of avoiding overly inclusive composite outcomes when examining aging comorbidities among PWH is a recent study presented at the Conference on Retroviruses and Opportunistic Infections (CROI). This study examined the associations between 10 different biomarkers with later developing CVD outcomes (type 1 MI, type 2 MI, ischemic stroke, VTE, and mortality) to better understand mechanisms.<sup>16</sup> The differences in patterns for different outcomes further reinforce that examining these outcomes separately rather than combining them as a composite outcome is needed to understand their driving mechanisms among aging PWH.

Of note, although these examples highlight the disadvantages of many if not most composite outcomes, there are well-described composite outcomes that are useful for HIV and aging research. For example, frailty, such as the Fried frailty phenotype,<sup>17</sup> includes exhaustion or severe fatigue, unintentional weight loss/wasting, low mobility, low physical activity, and muscle weakness. Frailty among PWH has value as a composite outcome that has been associated with an increased risk of hospitalizations, falls, mortality, and onset of AIDS across a variety of studies.<sup>18–25</sup> Although composite outcomes focused on comorbidities should almost always be avoided, frailty demonstrates that there are exceptions where composite outcomes can prove useful.

### LESSON 3: TIMELY DATA

We emphasize the importance of using timely, current data to ensure that findings are relevant to current treatment regimens and can improve care or outcomes for the population of PWH who are currently aging. For example, a study recently presented at CROI demonstrated the changes in ART among PWH in the United States over time.<sup>26</sup> It showed the very rapid transition from tenofovir disoproxil fumarate to tenofovir alafenamide fumarate over the past 3 years. Figure 4 demonstrates the rapid change in single-tablet regimens. Although these findings highlight the importance of timely and current data, they do not obviate the need to consider the historical context of treatment trajectories, particularly when considering outcomes among aging PWH. Research to understand aging among PWH will have to

encompass factors, such as changing ART regimens, highlighting the importance of careful consideration of cohort effects and comprehensive ART data, and is a reminder of the benefits of timely data to ensure findings are relevant.

COVID-19 is another example that demonstrates the rapidly changing questions and benefits of a cohort that has both timely data and the ability to implement new processes and validation approaches quickly. Cohorts with data uploads occurring only every 1–2 years or that lag a year or 2 are not ideal for addressing timely questions. Instead, the pandemic highlights the benefits of cohorts that are flexible and can rapidly expand or evolve to address emerging questions. For example, CNICS developed an extensive case ascertainment protocol for COVID-19 based on rapidly evolving diagnoses, expanding laboratory criteria, and complemented this with verification both to confirm the cases as well as to validate and better understand different ascertainment criteria and how they varied by site and over time. A recent CROI presentation<sup>27</sup> described the first 198 COVID-19 cases identified among 13,862 PWH and found increased risk among women, PWH who were Black or Hispanic, and those with a body mass index > 30. Among PWH with COVID-19, the relative risk of being hospitalized was 2-fold higher among PWH aged 60 years and older. This demonstrates some of the benefits of nimble cohorts with frequent uploads that are able to institute new validation procedures and address timely and evolving questions that are most likely to be relevant to improving care and outcomes to aging PWH.

### CONCLUSIONS

More research is needed to understand mechanisms of comorbidities and early functional decline among aging

**TABLE 3.** Differences Between Baseline Viral Load, Time-Updated Viral Load, and Cumulative Viral Load for Different CVD Outcomes, Comparing the 75th vs. 25th Percentile of Viral Load

Outcome	Baseline VL	Time-Updated VL	Cumulative VL
Type 1 MI	1.73 (1.26–2.38)	1.41 (1.07–1.95)	1.23 (0.78–1.96)
Type 2 MI	1.51 (1.10–2.08)	2.21 (1.71–2.82)	2.52 (1.74–3.66)
Stroke	1.37 (1.05–1.79)	1.81 (1.39–2.34)	0.91 (0.45–1.87)
VTE/PE	1.21 (1.10–1.34)	1.10 (1.05–1.14)	1.47 (1.21–1.79)

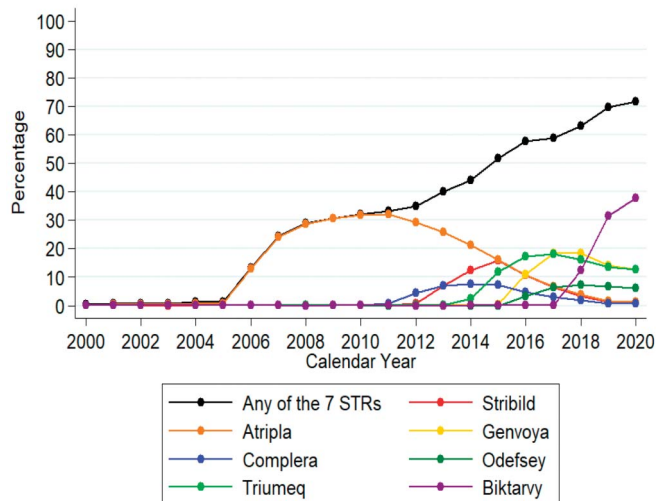
\*Adapted from <sup>26</sup>

FIGURE 4. Change in a single-tablet regimen use over time.

PWH. There are many pending questions related to the extent risks are attributable to age, traditional risk factors, trends in ART, differences in the impact of chronic inflammation, sarcopenia, and other factors. These questions will likely only increase in scope as populations of PWH continue to age. Answering these and many other key questions will require carefully measured/adjudicated outcomes rather than reliance on diagnosis codes, as well as examining comorbidities individually and moving away from composite outcomes for key comorbidities such as CVD. Finally, as questions continue to emerge, whether related to the COVID-19 pandemic, changes in HIV care or regimens, or other factors, clinical cohorts that have the ability to rapidly release data and evolve and expand carefully validated data collection will be much better positioned to address these questions. In particular, clinical cohorts that can expand inclusion of functional assessments and carefully harmonized and validated clinical outcomes and comorbidities will facilitate better understanding of drivers and outcome among aging PWH as well as enable development and testing of prevention approaches and interventions.

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