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Consequences of Low-level Viremia Among Women with HIV
in the United States from 2003-2020

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Consequences of Low-level Viremia Among Women with HIV in the United States from 2003-2020

By

Amalia Aldredge
M.D., University of Washington, 2017
B.Sc., McGill University, 2010

Advisor: Anandi Sheth, MD, MSc

An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research
2024

Abstract

Consequences of Low-level Viremia Among Women with HIV
in the United States from 2003-2020

By Amalia Aldredge, MD

Background
The prevalence and associated sequelae of low-level viremia (LLV) are poorly characterized among women, despite sex differences in potential LLV consequences such as virologic failure, drug resistance, and non-AIDS comorbidities (NACM).

Methods
We included Women's Interagency HIV Study participants from 2003-2020 who reported antiretroviral therapy use ≥1 year followed by ≥2 consecutive HIV-1 viral loads (VL) <200 c/mL. Four consecutive VL measurements were then used to categorize women at baseline as having: virologic suppression (VIROLOGIC SUPPRESSION; all VL undetectable), intermittent LLV (intermittent LLV; non-consecutive VL up to 199 c/mL), persistent LLV (persistent LLV; ≥2 consecutive VL up to 199 c/mL), or virologic failure (VIROLOGIC FAILURE; any VL ≥200 c/mL). Adjusted Cox proportional hazards models estimated the association of virologic category with time to incident a) virologic failure and b) multimorbidity (≥2 of 5 NACM) over 5-year follow-up.

Results
Of 1,598 women, median age was 47 years, 64% were Black, 21% were Hispanic, and median CD4 was 652 cells/μL. After median virologic categorization period of 18 months, we excluded 275 women with VIROLOGIC FAILURE; VIROLOGIC SUPPRESSION, intermittent LLV, and persistent LLV occurred in 58%, 19%, and 6%, respectively. Compared to women with VIROLOGIC SUPPRESSION, the adjusted hazard ratio (aHR) for incident virologic failure was 1.89 (95% CI 1.45-2.47) and 2.31 (1.53-3.47) for women with intermittent LLV and persistent LLV, respectively. After excluding 543 women with baseline multimorbidity, the aHR for incident multimorbidity was 0.84 (0.56-1.26) and 1.61 (0.93-2.82) for women with intermittent LLV and persistent LLV, respectively, compared with women who had VIROLOGIC SUPPRESSION.

Conclusions
One-quarter of women experienced LLV. Women with intermittent LLV and persistent LLV had an increased risk of virologic failure; persistent LLV was associated with increased multimorbidity risk, though the association was attenuated after covariate adjustment.

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Data Availability

Access to individual-level data from the MACS/WIHS Combined Cohort Study Data (MWCCS) may be obtained upon review and approval of a MWCCS concept sheet. Links and instructions for online concept sheet submission are on **the study website**.

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Introduction/Background

The treatment goal for people with HIV (PWH) is to durably suppress plasma HIV-1 RNA, such that the HIV viral load (VL) is below the limit of detection. Achieving and maintaining HIV suppression restores and preserves immunologic function, reduces morbidity and mortality, and prevents HIV transmission, thus having significant individual and public health implications[1]. However, despite adherence to potent antiretroviral therapy (ART), a significant proportion of PWH experience low-level viremia (LLV), defined as an HIV VL that is between the limit of routine assay detection and virologic failure, though exact parameters of VL vary by guidelines[1–4]. Data from large U.S. cohort studies suggest that up to 34% of PWH on ART may experience intermittent LLV, often referred to as a "blip," and nearly 25% of PWH have persistent LLV[5–9], generally defined as sustained episodes of LLV without meeting criteria for virologic failure. For many years, intermittent LLV was thought to be random error of test assay and was not thought to have clinical consequences, whereas persistent LLV was thought to have potential long-term implications.

Recent literature has been more conclusive that there are adverse clinical consequences of LLV, and that these are likely present for both intermittent LLV and persistent LLV. Initially controversial, with robust analyses, it has become clear that LLV, including both intermittent LLV and persistent LLV, is associated with an increased risk of virologic failure[5,10–26]. Persistent LLV has also been associated with development of drug resistance mutations[23,27–34], although a recent study using a lower VL cutoff did not find this association[35]. However, these data are derived from studies of predominantly male cohorts, and also do not necessarily evaluate other

potential consequences of LLV such as risk of non-AIDS comorbidities (NACM), which may differ by sex and gender.

Despite representing 53% of PWH globally[36], women have traditionally been underrepresented in HIV research[37–39]. An evolving body of literature describing sex differences in HIV pathogenesis, treatment response and ART toxicity, and aging considerations including comorbidity development, makes the case to urgently improve this[40]. Due to the association of LLV with markers of inflammation[23,41–46], of great concern is the potential contribution of LLV to the development of individual NACM, such as diabetes and hypertension, as well as multimorbidity, given that PWH have a higher prevalence and overall burden of NACM, which is more pronounced in women versus men[47–54]. Of the few studies that have evaluated the relationship between NACM and LLV, there have been mixed results of whether there is an association[12,55].

Clinical guidance is lacking on how to evaluate and manage PWH who experience LLV, which may be in part due to the etiology and risk factors of LLV being poorly characterized. Some studies have found lower ART adherence or inadequate drug concentration levels to be associated with LLV[56–62], whereas others have not[63,64]. There is speculation that a high pre-ART VL might impact the development of LLV[65,66]. The optimal clinical management strategies of LLV remain unknown. Some studies have shown that switching ART in people with LLV has led to more virologic suppression[67,68], whereas others have not found any difference[35,69,70]. There have been limited LLV studies in the era of modern ART, particularly with the use of first-line

high-potency integrase strand transfer inhibitors (INSTIs)[1]; studies of LLV that have included a large proportion of PWH prescribed INSTIs have been mixed regarding their impact[11,13,18,71–74].

We leveraged longitudinal data from the longest and largest prospectively enrolled cohort of U.S. women with HIV to evaluate the prevalence of LLV despite ART use and downstream clinical consequences including time to (a) incident virologic failure and (b) incident multimorbidity.

Methods

Study population

The Women's Interagency HIV Study (WIHS, now part of the MACS/WIHS Combined Cohort Study, MWCCS), established in 1993, is the largest and longest observational cohort of women with or at risk of HIV in the United States[75,76]. Women were enrolled in four waves across eleven sites (Atlanta, Georgia; Birmingham, Alabama; Bronx, New York; Brooklyn, New York; Chapel Hill, North Carolina; Chicago, Illinois; Washington, District of Columbia (D.C.); Jackson, Mississippi; Los Angeles, California; Miami, Florida; and San Francisco, California) as previously described in detail[76]. WIHS participants completed study visits semiannually, which involved structured interviews on medical and behavioral health history, comprehensive physical exams, and biospecimen banking (including plasma for HIV-1 VL measurement and laboratory assessment of comorbidities as applicable). Data collection information for the WIHS can be found here (https://drive.google.com/drive/folders/1uHBtp3eLXGpGV3RC_frWt5FR7YkInHIq). The

study protocols were approved by each site's institutional review board; all participants provided written informed consent.

Study Design

We performed a longitudinal analysis of prospectively collected data among WIHS participants to ascertain the prevalence and type of LLV and evaluate the association of type of LLV with incident virologic failure and multimorbidity in women. We included women with HIV who had at least one study visit after January 2003 and utilized data through the end of study observation (March 2020) to focus on a time period of contemporary ART use while maximizing follow-up. Inclusion criteria were: women with HIV who reported ART use for at least one year, at least two consecutive VL <200 copies/mL, followed by at least two subsequently measured VL (for a total of four VL), including at least 2 consecutive study visits with viral load measured, to allow for adequate categorization of LLV (virologic categorization period; Figure 1). ART use was self-reported and defined as any three-drug regimen, of which at least one antiretroviral was an INSTI, boosted protease inhibitor (PI), or non-nucleoside reverse transcriptase inhibitor (NNRTI). There are recommended fully active two-drug ART regimens[1], but these were not widely in use during this time period.

LLV Categorization

At the visit associated with the fourth VL measurement during virologic categorization period, women were categorized as having: sustained virologic suppression (all VL undetectable), intermittent LLV (non-consecutive detectable VL up to 199 copies/mL), persistent LLV (≥2 consecutive detectable VL up to 199 copies/mL), or virologic failure (any VL ≥200 copies/mL).

The lower limit of detection of VL assays varied throughout the study period from 20-400 copies/ml but was <80 copies/ml for all person-visits included in this analysis.

Covariates

We summarized baseline self-reported sociodemographic and clinical characteristics at end of virologic categorization period, including age, race/ethnicity (self-identified Black, Hispanic, White, and Other), annual household income, education, employment, insurance status, smoking status, alcohol use, marijuana use, cocaine use, intravenous drug use, depressive symptoms (using the Center for Epidemiologic Studies Depression Scale, CES-D), obesity (BMI ≥30 kg/m^2), pre-ART VL, pre-ART CD4 cell count, CD4 count, self-reported ART adherence, ART regimen, WIHS enrollment wave, and WIHS enrollment site. If a participant reported simultaneous use of ≥2 anchor drug classes in a single ART regimen, then the ART regimen was hierarchically categorized as: INSTI > PI >NNRTI.

Statistical Analyses

Participant sociodemographic and clinical characteristics are reported overall and by LLV category. Characteristics are described using count and percentages for categorical characteristics and median and interquartile range (IQR) for continuous characteristics.

We used polytomous logistic regression with a baseline referent group (virologic suppression) to examine associations between baseline sociodemographic characteristics and virologic categories (virologic suppression, intermittent LLV, persistent LLV, virologic failure). Odds ratios and 95% confidence intervals are reported for univariable and multivariable models adjusting for age,

race, adherence, crack/cocaine use, ART anchor drug, and WIHS site. Ordinal logistic regression was not used as proportional odds assumption was not met by Score test. Covariates were chosen based on a combination of differences between LLV types at baseline and those that have been previously associated with development of LLV.

Time to Event Outcomes

To assess the relationship between LLV and incident virologic failure and multimorbidity, we performed two separate time-to-event analyses. After excluding women with virologic failure during virologic categorization period, women were followed until time of (a) incident virologic failure or (b) incident multimorbidity (for each respective analysis), or until censorship due to death, end of observation, or lost to follow-up, whichever occurred sooner. Women with multimorbidity during virologic categorization period were excluded from that analysis. 5 years follow-up time was chosen to ensure adequate follow-up data while ensuring inclusion of modern ART regimens. Virologic failure was defined as any VL ≥200 copies/mL. Multimorbidity was defined as ≥2 of 5 total NACM assessed: hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, or chronic kidney disease, using a combination of data sources as previously described (Table 1)[51,52]. These NACM were chosen given their high frequency in the general population and among PWH, and shared risk factors (e.g., smoking, elevated body mass index, etc.) and pathogenesis, including association with persistent inflammation and immune activation, previously shown to be related to cumulative HIV-1 viral exposure in women[54]. After assessing for violations of proportional hazards assumption of LLV and covariates using Supremum tests, adjusted Cox proportional hazards models were used to determine hazard ratios and 95% confidence intervals for type of LLV (intermittent, persistent)

on time to incident virologic failure and time to development of incident multimorbidity as compared to referent virologic suppression. The model for virologic failure was adjusted for age (≥50 years, <50 years), race (non-Hispanic Black, else), CD4 count (<350, ≥350), adherence, and ART anchor drug based on clinical relevance. After excluding women with multimorbidity at baseline, the model for multimorbidity was adjusted for age (≥50 years, <50 years), race (non-Hispanic Black, else), CD4 count (<350, ≥350), adherence, INSTI use, obesity, and smoking status based on clinical relevance. Individuals with missing data were excluded from survival analyses.

Sensitivity analyses were done using a viral load cutoff for virologic failure of 500 copies/mL for virologic characterization given multiple prior studies used this cutoff for LLV. We also performed survival analyses using Cox proportional hazards models to evaluate the association of LLV type and the incidence of each of the 5 individual NACM, adjusting for the same covariates as the model used for multimorbidity. All analyses were conducted using SAS, version 9.4 (SAS Institute).

Results

LLV Prevalence and Risk Factors

Of 3677 women followed in WIHS with HIV, 1598 were included in this analysis (Figure 2). Baseline characteristics included median age 47 years (IQR 41-53), 64% non-Hispanic Black, 47% were obese, 64% ever used cigarettes, median CD4 621 cells/μL (IQR 453-820), 87% self-reported ≥95% adherence, and 28% reported INSTI use, with additional baseline characteristics shown in Table 2.

At the end of the virologic categorization period (baseline), which occurred over a median of 18 months, 933 (58%) women had virologic suppression, 295 (19%) had intermittent LLV, 95 (6%) had persistent LLV, and 275 (17%) had virologic failure. Compared to virologic suppression, LLV was associated with identifying as Black (adjusted odds ratio (aOR) 1.69 (1.08, 2.64) for intermittent LLV and 2.32 (1.08, 5.01) for persistent LLV) or other race (aOR 2.81 (1.16, 6.81) for intermittent LLV and 3.48 (0.83, 14.62) for persistent LLV) and reporting use of cocaine (aOR for current cocaine use 2.32 (1.23, 4.36) for intermittent LLV and for former cocaine use 1.78 (1.07, 2.94) for persistent LLV). There was a protective association between LLV and women on an NNRTI as anchor ART (aOR 0.56 (0.39, 0.81) for intermittent LLV and 0.33 (0.18, 0.61) for persistent LLV, Table 3).

Time to Virologic Failure

Of 1323 included in the analysis of time to virologic failure, 266 (20%) developed incident virologic failure, including 148 (16%) of those with virologic suppression, 88 (30%) of those with intermittent LLV, and 30 (32%) of those with persistent LLV. Unadjusted hazard ratio for intermittent LLV was 2.08 (95% CI 1.60, 2.71) and persistent LLV 2.52 (1.70, 3.74). After adjustment, the hazard ratio for women with intermittent LLV was 1.89 (1.45, 2.47) and with persistent LLV was 2.31 (1.53, 3.47) as compared to those with virologic suppression (Figure 3, Table 4). Of those who developed virologic failure at any time during follow-up, 88% developed it before the 5-year cutoff. Sensitivity analysis using a VL cutoff of 500 copies/mL for LLV categorization produced similar results (Tables 5, 6).

Time to Development of Multimorbidity

543 women with multimorbidity by the first visit after virologic categorization period were excluded, comprising 231 (43%) with diabetes, 510 (94%) with HTN, 365 (67%) with dyslipidemia, 145 (27%) with chronic kidney disease, and 179 (33%) with cardiovascular disease (not mutually exclusive). During 5-year follow-up, 154 (20%) of women developed multimorbidity, including 107 (20%) of those with virologic suppression, 32 (18%) of those with intermittent LLV, and 15 (27%) of those with persistent LLV. Among 780 remaining women without multimorbidity, unadjusted hazard ratio for intermittent LLV was 0.94 (95% CI 0.63, 1.40) and persistent LLV 1.74 (1.01, 2.98). After adjustment, the hazard ratio for women with intermittent LLV was 0.84 (95% CI 0.56, 1.26) and with persistent LLV was 1.61 (0.93, 2.82) as compared to those with virologic suppression (Figure 4, Table 4). Sensitivity analysis using a VL cutoff of 500 copies/mL for virologic categorization produced similar results (Table 6).

In adjusted models evaluating the association of LLV and each individual NACM, there was a trend towards increased risk of each NACM for persistent LLV, though not statistically significant; there were insufficient numbers of women with CVD to perform this analysis (Tables 7 and 8, Figure 5).

Discussion

In this cohort of women with HIV on ART, one-quarter of participants had LLV when assessed over an 18-month period. During five years of follow-up, both intermittent and persistent LLV were associated with an increased risk of incident virologic failure. However, persistent LLV, but not intermittent LLV, was associated with an increased risk of incident multimorbidity,

although this finding was attenuated in adjusted models. Our evaluation of LLV in a diverse cohort of women with HIV, with a median time of 14 years from diagnosis of HIV and on combination ART for 8.5 years, highlights that low-level viremia is common and, given the associated downstream clinical consequences, should be prioritized in future studies of risk-assessment and intervention in this population.

Despite sex-differential HIV pathogenesis, treatment response, and outcomes, women have been underrepresented in prior LLV studies[40,53,77,78]. To our knowledge, this is the first study to evaluate LLV in women with HIV as compared to prior studies in majority-male or all-male cohorts. The frequency of LLV varies widely in the setting of lack of standardized definition, but have generally been estimated from 20-30%[6–8,10,14,15,19,24,57,62]; our study shows a similar prevalence in women. Most prior studies of LLV have found an association between persistent LLV and subsequent virologic failure and recent studies have noted this association is also seen with intermittent LLV[5,7,9,14,15,19,20,23–26]. Three recent studies of cohorts comprising >70% men in Australia, Europe and the United States found that women with LLV were up to two times more likely to develop virologic failure than men using adjusted Cox proportional hazard models[14,16,79] although another large Cohort in Uganda found a slightly lower risk of virologic failure in women as compared to men[21]. This could suggest underlying biologic and sociobehavioral differences by sex and gender that impact the development and consequences of LLV, such as ART metabolism and interactions, hormonal changes, and behavioral differences that might affect men and women differently.

Importantly, our analysis showed a trend toward association between persistent LLV and multimorbidity in a cohort of women with HIV. Prior work, including from our group[80], has shown a higher burden of aging-related comorbidities in women versus men, especially among women with HIV. In addition, we previously showed that cumulative viremia was associated with risk of individual comorbidities and multimorbidity among women with HIV[54], though the contribution of LLV to this finding was not known. The current analysis suggests that LLV may contribute to multimorbidity risk among individuals with HIV. There have been limited prior studies of LLV and aging-related comorbidities. One recently performed using data from the US Military HIV Natural History Study found that individuals with LLV and women had higher numbers of NACM, including cardiac disease, vascular disease, CKD, cirrhosis, and cancer[79], with the strongest association between LLV and CKD. Two other recent studies, including 20-37% women, did not find an association between LLV and NACM, which included non-AIDS-related malignancies, cardiovascular, renal, liver, psychiatric, bone, and metabolic events[12,55]. Given the relationship between ongoing viral stimulation, including LLV as well as latent reservoirs, and increased levels of inflammation[43,55,61], which may be more pronounced in women[40,53], we hypothesize that chronic inflammation driven by LLV leads to increased NACM and ultimately development of multimorbidity. This relationship needs to be further explored in future studies, with a focus on exploring differences by sex and gender.

Recent studies suggest that LLV prevalence has not significantly decreased over time as ART has become more potent, tolerable, and simplified, but this may be related to changing definitions of LLV over time along with increased sensitivity of HIV VL diagnostic tests. However, few LLV studies have occurred in the era of modern ART regimens, particularly

INSTIs. Our analysis showed that NNRTI use was associated with lower LLV prevalence compared to use of INSTIs or PIs in a cohort of women followed in the INSTI era. This finding is consistent with other studies[6,56,59,81] and is likely due to selection of INSTI or PI ART over NNRTI ART for individuals who may be at higher risk for virologic failure due to HIV resistance or other factors. The effect of the use of modern INSTIs on LLV remains unclear as even recent studies have included limited data on INSTI-based regimens[14]. Furthermore, despite risk of virologic failure, management of LLV in the INSTI era also remains unclear; a recent study in Taiwan evaluated the impact of a switch from a PI-based regimen to an INSTI-based regimen on LLV and found that there was no difference in LLV between groups[72]. Interestingly, early investigations show intermittent LLV and persistent LLV remain common in people with HIV receiving injectable ART with cabotegravir and rilpivirine[73].

Our study does have several important limitations. As an observational cohort study, there is an inherent risk for bias, but we performed adjusted analyses to limit confounding, and performed additional sensitivity analyses with higher cut-off viral loads for virologic failure to ensure results were robust. To maximize follow-up time for survival analyses, we limited virologic categorization period to four visits, raising concern for the chance of misclassification. However, the follow-up time for virologic outcome categorization is similar to other LLV studies. We were unable to evaluate the association between pre-ART CD4 or pre-ART viral load on LLV due to missing data that we cannot impute. We also did not account for changes in ART in this analysis which could have affected outcomes. To assess incident multimorbidity, we had to exclude a large proportion of our study population with baseline multimorbidity, limiting the power of our analysis, especially for assessment of certain individual comorbidities. Finally, some NACM

outcomes rely on self-reported data from patients which could be inaccurate, although integration of objective measures were used where possible, any misclassification would be expected to affect each virologic category equally, and these definitions have been previously published. The strengths of this study include the utilization of a multisite cohort, increasing the generalizability of findings to other women with HIV in the United States. With longitudinal robust data collection through WIHS, we were able to have long follow-up time for outcomes assessment.

In the future, we plan to complete a similar analysis including both men and women to better evaluate the effect of sex as a biological variable on both virologic category as well as outcomes of virologic failure and development of multimorbidity. We will also evaluate the association of baseline characteristics on the development of LLV to determine potential areas of intervention to prevent development of negative outcomes associated with LLV.

In conclusion, we found that LLV occurred in a quarter of included WIHS participants. Compared to women with virologic suppression, both intermittent and persistent LLV were associated with increased virologic failure risk, whereas only persistent LLV was associated with increased multimorbidity risk, though the association was attenuated after covariate adjustment. Research is needed to assess the risk factors associated with development of LLV, the effect of sex on LLV prevalence and consequences to inform clinical management of LLV, and evaluation of LLV as it relates to new ART regimens including injectable ART.

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Table 1. Definitions of Non-AIDS Comorbidities (NACM)

NACM	Definition	Source
Hypertension	Receipt of anti-hypertensive medication or elevated blood pressure on any two study visits (systolic ≥140 and/or diastolic ≥90)	Self-report or study measurement
Hyperlipidemia	Receipt of lipid-lowering medication or LDL ≥130 mg/dL and HDL <40 mg/dL	Self-report or laboratory
Diabetes Mellitus, Type 2	Receipt of anti-diabetic medication or FBG ≥126 mg/dL on two study visits or HgbA1c ≥6.5% and FBG above threshold at one study visit	Self-report or laboratory
Cardiovascular Disease	Any one of the following: Myocardial infarction or heart attack, revascularization or angioplasty, transient ischemic attack/stroke, angina or hospitalization for heart condition	Self-report
Chronic Kidney Disease	eGFR M60 mL/min/1.73m2 (determined by the CKD-epi formula) on two or more consecutive study visits	Laboratory

Table 2: Baseline Demographic and Clinical Characteristics of Women with HIV with Viral Suppression on Antiretroviral Therapy Enrolled in the Women's Interagency HIV Study Characterized by Virologic Outcome (2003-2020)

Participant Characteristics, Median (Q1, Q3) or n (%)[a]	Total Women with HIV (n=1598)	Virologic Category			
		Virologic Suppression (n=933)	Intermittent Low-level Viremia (n=295)	Persistent Low-level Viremia (n=95)	Virologic Failure (n=275)
Age, years	47 (41, 53)	47 (41, 53)	47 (41, 54)	50 (44, 55)	47 (40, 53)
Age ≥ 50 years	650 (41)	370 (40)	121 (41)	54 (57)	105 (38)
Race/Ethnicity					
Black, non-Hispanic	1016 (64)	579 (62)	196 (66)	69 (73)	172 (63)
Hispanic	346 (22)	203 (22)	61 (21)	15 (16)	67 (24)
White, non-Hispanic	195 (12)	133 (14)	28 (10)	8 (8)	26 (10)
Other	41 (3)	18 (2)	10 (3)	3 (3)	10 (4)
WIHS Enrollment Wave					
1994/1995	660 (41)	368 (39)	112 (38)	36 (38)	144 (52)
2001/2002	393 (25)	232 (25)	70 (24)	12 (13)	79 (29)
2011/2012	149 (9)	74 (8)	38 (13)	23 (24)	14 (5)
2013-2015	396 (25)	259 (28)	75 (25)	24 (25)	38 (14)
Depression (CES-D Score ≥16)	482 (31)	263 (29)	95 (33)	33 (35)	91 (33)
Annual Household Income					
≤$12,000	801 (51)	433 (47)	167 (58)	51 (55)	150 (56)
$12,001-$24,000	379 (24)	222 (24)	72 (25)	19 (21)	66 (25)
>$24,000	382 (25)	258 (28)	50 (17)	22 (24)	52 (19)
Obese (BMI ≥30 kg/m^2)	738 (47)	429 (47)	146 (51)	45 (48)	118 (43)
Education					
No high school diploma	567 (36)	304 (33)	107 (36)	30 (32)	126 (46)
High school diploma	476 (30)	270 (29)	94 (32)	39 (41)	73 (27)
College or higher	548 (34)	353 (38)	93 (32)	26 (27)	76 (28)
Employed	589 (37)	388 (42)	89 (30)	37 (39)	75 (27)
Cigarette Use					
Never	572 (36)	364 (39)	106 (36)	24 (25)	78 (28)

Current	566 (36)	292 (32)	115 (39)	43 (45)	116 (42)
Former	453 (29)	271 (29)	73 (25)	28 (30)	81 (30)
Current Alcohol Use					
None	938 (59)	547 (59)	171 (58)	56 (59)	164 (60)
1-7 drinks/week	538 (34)	322 (35)	99 (34)	31 (33)	86 (32)
> 7 drinks/week	110 (7)	55 (6)	24 (8)	8 (8)	23 (8)
Current Marijuana Use	247 (16)	142 (15)	50 (17)	13 (14)	42 (15)
Crack/Cocaine Use					
Never	1218 (77)	748 (81)	219 (85)	64 (67)	187 (69)
Current	68 (4)	26 (3)	19 (7)	5 (5)	18 (7)
Former	299 (19)	149 (16)	56 (19)	26 (27)	68 (25)
Intravenous Drug Use					
Never	1289 (81)	756 (82)	244 (83)	78 (82)	211 (77)
Current	7 (0.4)	3 (0.3)	1 (0.3)	0 (0.0)	3 (1.1)
Former	288 (18)	163 (18)	49 (17)	17 (18)	59 (22)
Insured	1546 (98)	895 (97)	285 (97)	93 (98)	273 (100)
WIHS Enrollment Site					
Atlanta	115 (7)	80 (9)	16 (5)	7 (7)	12 (4)
Birmingham	60 (4)	31 (3)	14 (5)	8 (8)	7 (3)
Bronx	232 (15)	118 (13)	44 (15)	15 (16)	55 (20)
Brooklyn	228 (14)	103 (11)	55 (19)	9 (10)	61 (22)
Chapel Hill	101 (6)	71 (8)	21 (7)	5 (5)	4 (2)
Chicago	184 (12)	126 (14)	28 (10)	10 (11)	20 (7)
DC	186 (12)	113 (12)	31 (11)	16 (17)	26 (10)
Jackson	64 (4)	44 (5)	10 (3)	2 (2)	8 (3)
LA	199 (13)	124 (13)	26 (9)	6 (6)	43 (16)
Miami	62 (4)	38 (4)	15 (5)	2 (2)	7 (3)
SF	167 (11)	85 (9)	35 (12)	15 (16)	32 (12)
Years Since HIV Diagnosis	14.0 (9.2, 18.2)	13.2 (8.4, 17.1)	14.7 (9.9, 19.6)	16.4 (8.4, 21.4)	15.3 (11.2, 19.0)
Pre-ART VL >100,000 copies/mL	167 (23)	93 (21)	37 (26)	11 (23)	26 (27)
Pre-ART CD4<200 cells/µL	227 (14)	87 (9)	33 (11)	10 (11)	97 (36)
CD4, cells/µL	621 (453, 820)	642 (486, 847)	685 (492, 885)	667 (457, 830)	471 (276, 629)

Adherence ≥95%	1384 (87)	837 (90)	255 (86)	82 (86)	210 (76)
Years since first Combination ART	8.5 (5.4, 11.1)	8.1 (5.2, 10.4)	8.9 (5.5, 12.7)	7.8 (4.9, 14.1)	9.4 (7.1, 12.4)
ART Anchor Drug[b]					
INSTI	454 (28)	258 (28)	93 (32)	37 (39)	66 (24)
PI	587 (37)	293 (31)	115 (39)	38 (40)	141 (51)
NNRTI	516 (32)	357 (38)	80 (27)	19 (20)	60 (22)
Other	41 (3)	25 (3)	7 (2)	1 (1)	8 (3)

Abbreviations: CES-D: Center for Epidemiologic Studies Depression; ART: antiretroviral therapy; VL: viral load; BMI: body mass index; INSTI: integrase strand transfer inhibitor; PI: protease inhibitor: NNRTI: non-nucleotide reverse transcriptase inhibitor.

a. Column percents may not total 100 due to rounding.

b. Categorized hierarchically INSTI>PI>NNRTI, such that a regimen containing an INSTI and PI would be categorized in the INSTI group, for example.

NOTE: Missing data: depression (n=17), annual household income (n=36), BMI (n=38), education (n=7), employment (n=7), cigarette use (n=7), alcohol use (n=12), marijuana use (n=12), crack/cocaine use (n=13), intravenous drug use (n=14), insurance status (n=12), pre-ART VL (n=861), pre-ART CD4 (n=850), adherence (n=1), HIV diagnosis date (n=115)

Table 3: Association Between Baseline Patient-level Characteristics and Virologic Category Among Women with HIV on ART by Crude and Adjusted Polytomous Logistic Regression.

	Intermittent Low-Level Viremia vs. Virologic Suppression		Persistent Low-Level Viremia vs. Virologic Suppression		Virologic Failure vs. Virologic Suppression	
Baseline Characteristic	**Unadjusted OR (95% CI)**	**aOR (95% CI)***	**Unadjusted OR (95% CI)**	**aOR (95% CI)***	**Unadjusted OR (95% CI)**	**aOR (95% CI)***
Age, years	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.04 (1.01, 1.06)	1.03 (1.01, 1.06)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)
Race/Ethnicity						
White, non-Hispanic	REF	REF	REF	REF	REF	REF
Black, non-Hispanic	1.61 (1.04, 2.49)	1.69 (1.08, 2.64)	1.98 (0.93, 4.22)	2.32 (1.08, 5.01)	1.52 (0.97, 2.39)	1.68 (1.05, 2.69)
Hispanic	1.43 (0.87, 2.35)	1.52 (0.91, 2.53)	1.23 (0.51, 2.98)	1.54(0.62, 3.80)	1.69 (1.02, 2.79)	1.57 (0.93, 2.66)
Other	2.64 (1.10, 6.32)	2.81 (1.16, 6.81)	2.77 (0.67, 11.40)	3.48 (0.83, 14.62)	2.84 (1.18, 6.85)	2.78 (1.12, 6.90)
Adherence						
≥95%	REF	REF	REF	REF	REF	REF
<95%	1.38 (0.93, 2.05)	1.23 (0.82, 1.85)	1.40 (0.75, 2.60)	1.28 (0.68, 2.44)	2.73 (1.92, 3.87)	2.20 (1.52, 3.18)
Crack/Cocaine Use						
Never	REF	REF	REF	REF	REF	REF
Current	2.50 (1.36, 4.60)	2.32 (1.23, 4.36)	2.25 (0.84, 6.05)	1.73 (0.62, 4.84)	2.77 (1.49, 5.16)	2.20 (1.13, 4.30)
Former	1.28 (0.91, 1.81)	1.23 (0.86, 1.74)	2.04 (1.25, 3.32)	1.78 (1.07, 2.94)	1.83 (1.31, 2.54)	1.69 (1.20, 2.39)
ART Regimen						
INSTI	REF	REF	REF	REF	REF	REF
PI	1.09 (0.79, 1.50)	0.96 (0.67, 1.38)	0.90 (0.56, 1.47)	0.78 (0.46, 1.37)	1.88 (1.34, 2.64)	1.21 (0.82, 1.77)
NNRTI	0.62 (0.44, 0.87)	0.56 (0.39, 0.81)	0.37 (0.21, 0.66)	0.33 (0.18, 0.61)	0.66 (0.45, 0.97)	0.47 (0.31, 0.72)
Other	0.78 (0.33, 1.86)	0.69 (0.28, 1.69)	0.28 (0.04, 2.12)	0.23 (0.03, 1.82)	1.25 (0.54, 2.90)	0.77 (0.32, 1.86)
Southern Site						
No	REF	REF	REF	REF	REF	REF
Yes	0.88 (0.65, 1.18)	0.79 (0.56, 1.11)	0.86 (0.53, 1.39)	0.64 (0.37, 1.11)	0.41 (0.28, 0.59)	0.42 (0.28, 0.64)

Abbreviations: OR:odds ratio; aOR: adjusted odds ratio; ART: antiretroviral therapy; INSTI: integrase strand transfer inhibitor; PI: protease inhibitor: NNRTI: non-nucleotide reverse transcriptase inhibitor.

*Adjusted for age, race, adherence, crack/cocaine use, ART, and site

Table 4: Hazard Ratios of Virologic Category with Time to Virologic Failure and Development of Multimorbidity Using Cox Proportional Hazards Models

	Virologic Failure n=1323		Development of Multimorbidity n=780	
Virologic Outcome	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)***	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)****
Virologic Suppression	REF	REF	REF	REF
Intermittent LLV	2.08 (1.60, 2.71)	1.89 (1.45, 2.47)	0.94 (0.63, 1.40)	0.84 (0.56, 1.26)
Persistent LLV	2.52 (1.70, 3.74)	2.31 (1.53, 3.47)	1.74 (1.01, 2.98)	1.61 (0.93, 2.82)

Abbreviations: HR: hazard ratio

*Adjusted for age, race, CD4 count, adherence, and ART

**Adjusted for age, race, CD4 count, adherence, obesity, smoking status, and INSTI use

Table 5: Proportion of Each Virologic Category Using a Viral Load Cutoff of 500 Copies/mL for Virologic Failure

Virologic Category	Total n = 1598	Proportion
Virologic Suppression	933	58.4
Intermittent Low-Level Viremia	337	21.1
Persistent Low-Level Viremia	130	8.1
Virologic Failure	198	12.4

Table 6. Virologic Outcomes by Virologic Type Using a Viral Load Cutoff of 500 Copies/mL for Virologic Failure

	Virologic Failure		Development of Multimorbidity	
Virologic Type	**Unadjusted HR (95% CI) n=1400**	**Adjusted HR (95% CI)* n=1393**	**Unadjusted HR (95% CI) n=822**	**Adjusted HR (95% CI)** n=800**
Virologic Suppression	REF	REF	REF	REF
Intermittent LLV	2.17 (1.69, 2.79)	1.97 (1.53, 2.54)	0.95 (0.65, 1.38)	0.88 (0.60, 1.29)
Persistent LLV	3.57 (2.62, 4.85)	3.27 (2.38, 4.49)	1.32 (0.80, 2.18)	1.25 (0.75, 2.09)

Abbreviations: HR: hazard ratio

*Adjusted for age, race, CD4 count, adherence, and ART

**Adjusted for age, race, CD4 count, adherence, obesity, and smoking status

Table 7: Risk of Developing Individual Non-AIDS Comorbidities Comparing Intermittent and Persistent Low-Level Viremia to Virologic Suppression

	Hypertension		Hyperlipidemia		Diabetes Mellitus		Chronic Kidney Disease	
Virologic Outcome	HR n=534	aHR* n=520	HR n=864	aHR* n=834	HR n=1071	aHR* n=1033	HR n=1167	aHR* n=1127
Virologic Suppression	REF	REF	REF	REF	REF	REF	REF	REF
Intermittent LLV	0.75 (0.46, 1.23)	0.52 (0.31, 0.87)	0.74 (0.48, 1.14)	0.74 (0.48, 1.14)	1.30 (0.75, 2.25)	1. 19 (0.70, 2.07)	1.05 (0.60, 1.96)	0.96 (0.51, 1.81)
Persistent LLV	1.32 (0.64, 2.71)	1.10 (0.52, 2.31)	1.12 (0.60, 2.09)	1.02 (0.54, 1.92)	1.72 (0.73, 4.03)	1.48 (0.62, 3.53)	1.53 (0.60, 3.89)	1.13 (0.44, 2.91)

Abbreviations: HR: hazard ratio; aHR: adjusted hazard ratio

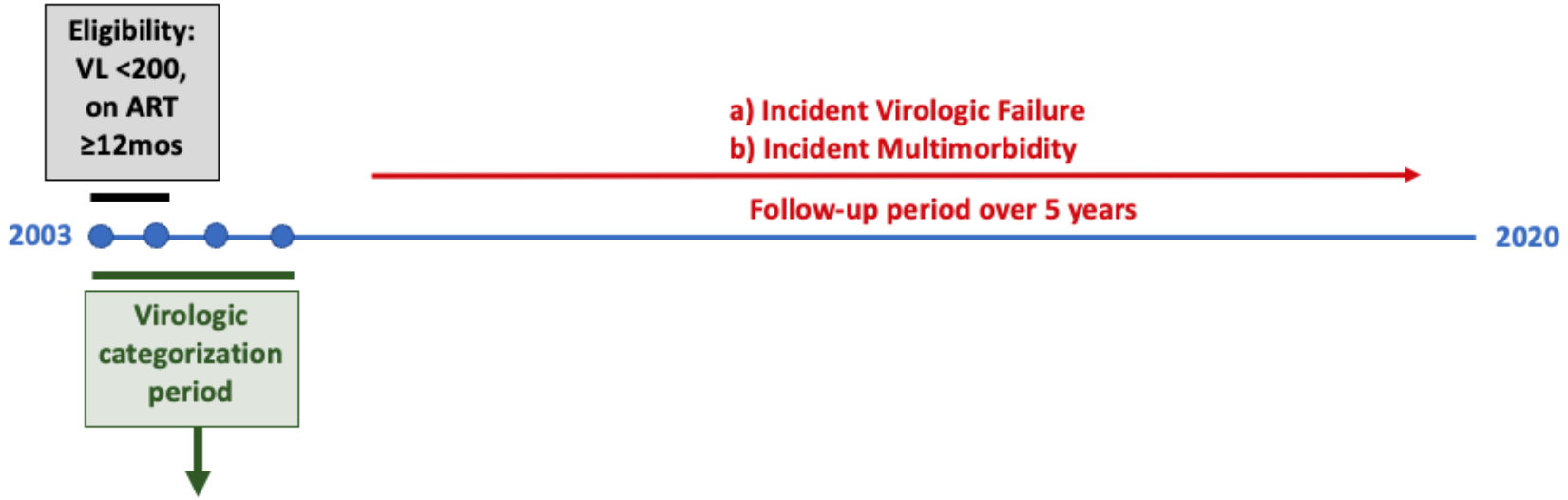
* Adjusted for age, race, CD4 count, adherence, obesity, smoking status, and INSTI use

NB: CVD (n=1096) with too few cases to run survival analysis

Table 8. Incidence of Each Individual Non-AIDS Comorbidity by Low-Level Viremia Category During Follow-Up

Virologic Category	Hypertension n (%)	Hyperlipidemia n (%)	Diabetes Mellitus n (%)	Chronic Kidney Disease n (%)	Cardiovascular Disease n (%)
Virologic Suppression	88 (23%)	103 (17%)	45 (6%)	39 (5%)	44 (6%)
Intermittent LLV	19 (16%)	26 (13%)	18 (8%)	13 (5%)	15 (6%)
Persistent LLV	8 (24%)	11 (17%)	6 (9%)	5 (6%)	6 (7%)

Figure 1. Study Design of Eligible Participants, Including Categorization and Follow-Up of Outcomes



LLV Category	HIV-1 RNA (copies/mL)	Number of Visits
Sustained Virologic Suppression	Below lower limit of detection	All visits
Intermittent Low-Level Viremia (iLLV)	Detectable-199	Non-consecutive visits
Persistent Low-Level Viremia (pLLV)	Detectable-199	Two or more consecutive visits
Virologic Failure (VF)	≥200	Any visit

Abbreviations: VL: viral load; ART: antiretroviral therapy; LLV: low-level viremia

Figure 2: Flow Diagram of Study Participants

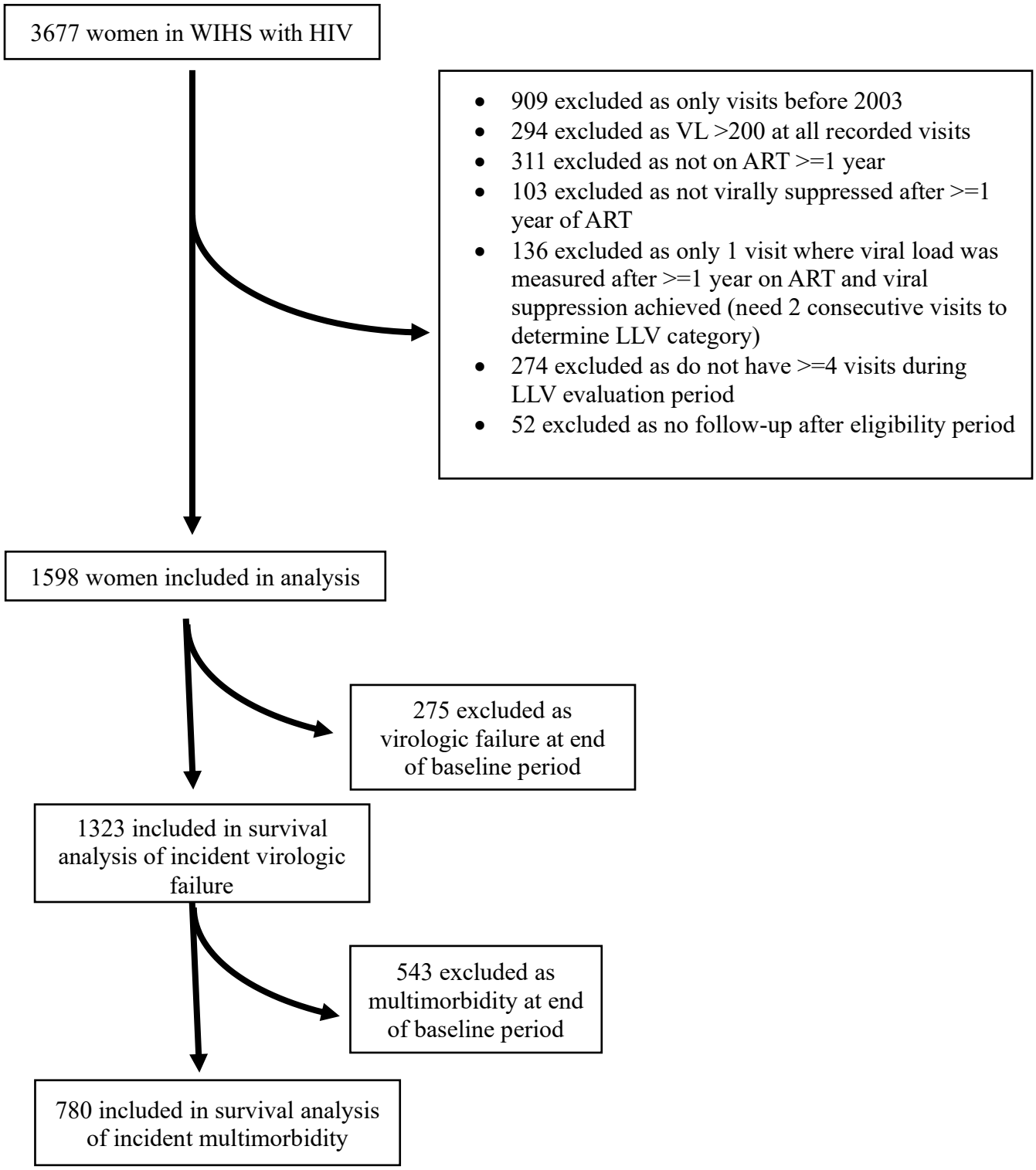


Figure 3: Adjusted Survival Curve for Time to Incident Virologic Failure by Type of Low-Level Viremia

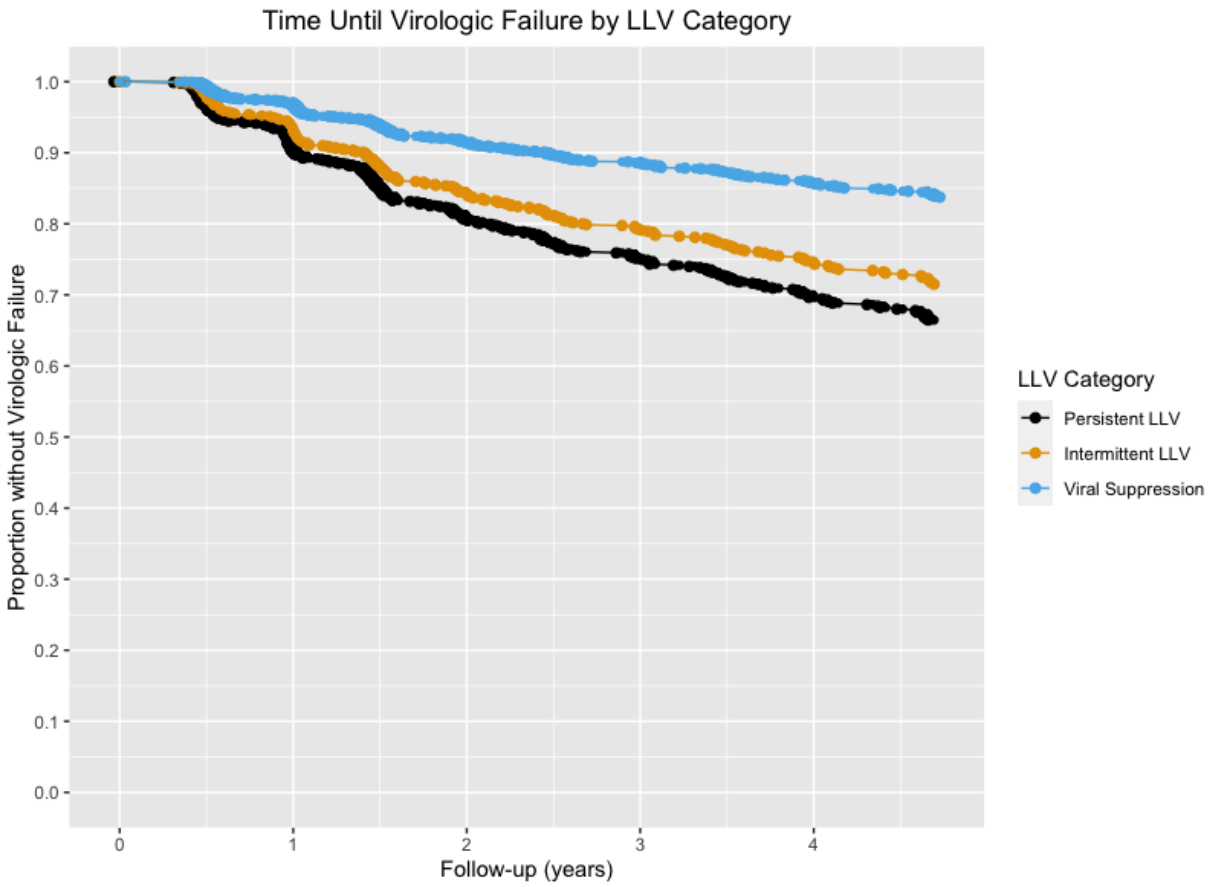


Figure 4: Adjusted Survival Curve for Time to Incident Multimorbidity by Type of Low-Level Viremia

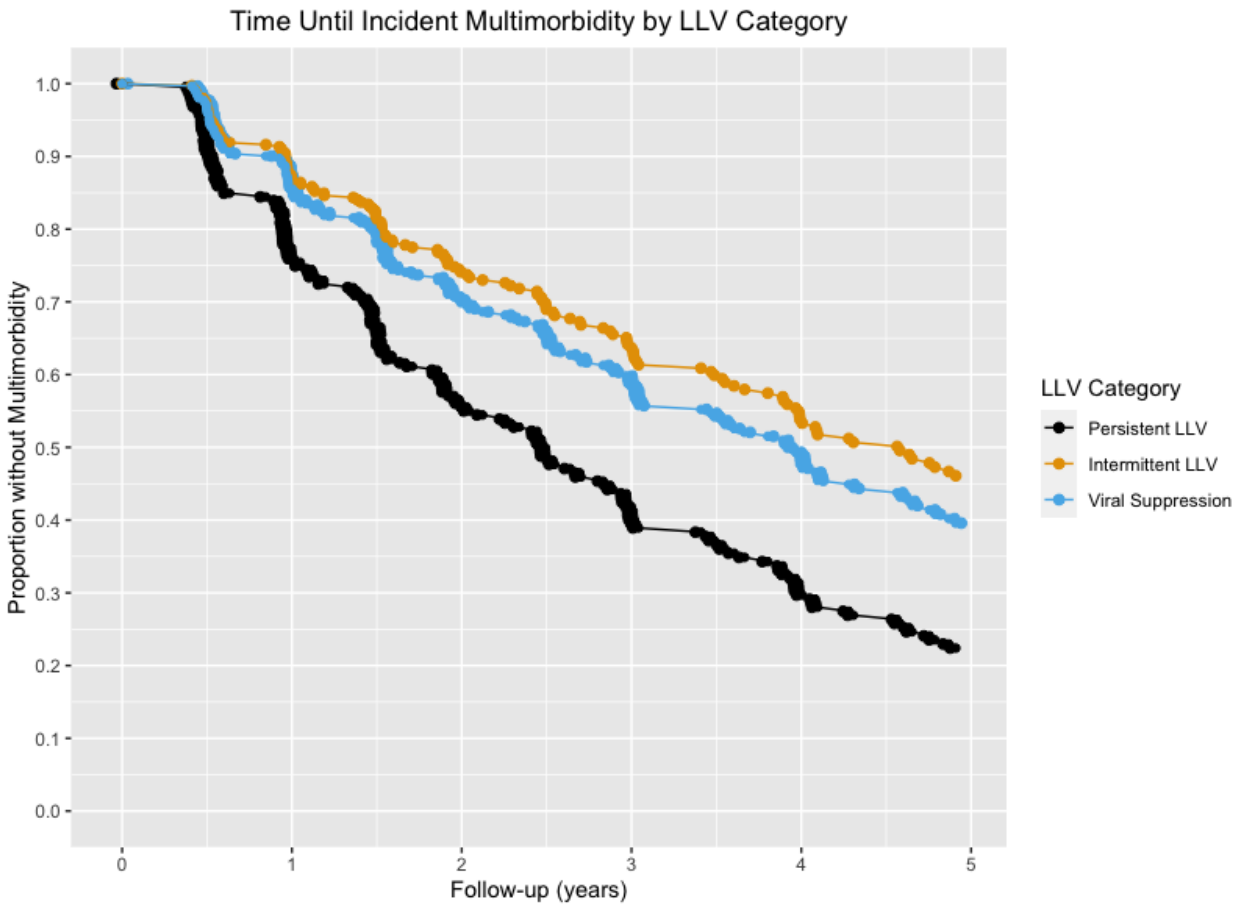


Figure 5: Adjusted Relative Hazards of Development of Individual Non-AIDS Comorbidities by Type of Low-Level Viremia