ASSESSMENT AND CHARACTERIZATION OF HIV CARE CONTINUUM IN MECKLENBURG COUNTY, NORTH CAROLINA 2013-2019

by

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ABSTRACT

Background: The high burden of Human Immunodeficiency Virus (HIV) disease and the increasing rate of new HIV infections among some populations and jurisdictions could reflect failed prevention strategies. Despite progress in controlling the epidemic in the United States, there are deficiencies in the continuum of care at each stage of the clinical care cascade among people diagnosed with the disease. These deficiencies are usually a result of late diagnosis, poor and delayed linkage to care, and disengagement from treatment which could be associated with suboptimal outcomes. To achieve epidemic control at the community level, deficiencies in the continuum of care must be identified, quantified, and addressed. We examined the HIV Care Continuum (HCC) and characterized the cascade of clinical care deficiencies in Mecklenburg County, NC.

Methods: The 2010–2020 National HIV/AIDS Strategy (NHAS) called for research to fill gaps in knowledge along with the HCC and recommended that 90% of the estimated people living with HIV be aware of their HIV status. Of those, the proportion of persons with newly diagnosed HIV linked to care within one month should be increased to 85%. Of those, the proportion of HIV-diagnosed individuals who achieve viral suppression should be increased to 80%. However, currently, there has been no comprehensive evaluation of the HCC in Mecklenburg County. Therefore, we evaluated elements of the HCC in Mecklenburg. HIV incidence cohort data for Mecklenburg County residents from January 2013 to December 2019 were used for the analyses.

Results: 1,521 people living with HIV in Mecklenburg County over 13 years old were newly diagnosed and linked to care (LtC) from 2013–2019. Of those, only 64% were linked to care

within 30 days (LtC30), falling short of the second NHAS goal of 85% of patients aware of their status. We found that Blacks and Hispanics have lower odds of LtC30 compared to Whites. Among 1,134 persons linked to care and available viral load data, 939 (82.8%) achieved viral suppression (VS) within 12 months. Time to the achievement of VS was shorter among those who linked within 30 days (median, 85 days) when compared to those who linked after 30 days (median, 90 days). We found that of those who achieved the initial VS, 86% remained suppressed while about 13% lost viral suppression. The odds of viral rebound were three times higher for young adults, 13–24 year-olds, compared with patients over 45 years old (OR, 3.06; 95% CI, 1.77–5.30) and 2.5 times higher among Blacks compared to Whites (OR, 2.49; 95% CI, 1.27–4.91).

Conclusion: We found race and sex associated with LtC30; baseline VL and LtC30 were associated with time to achievement of VS; and, young age and race were associated with loss of viral suppression and other poor outcomes for people living with HIV in Mecklenburg County, NC. To achieve the NHAS strategic objectives, Mecklenburg County and similar local health departments need to design locally targeted interventions to close cascade gaps.

DEDICATION

I want to dedicate this dissertation to God, who strengthened me when I was weak by His special grace. He lifted me when I was down, provided for me when I needed resources, sent helpers to me when I needed one, and helped me achieve one of my lifetime ambitions. I will forever love and worship him in the beauty of His holiness! Thank you, Lord!

Mark 10:27: Jesus looked at them and said, 'with man it is impossible, but not with God. For all things are possible with God.'

Philippians 4:13: I can do all things through him who strengthens me.

Psalm 107:1: Give thanks to the LORD for He is good: His love endures forever.

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LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
HCC	HIV Care Continuum
PLWH	People Living With HIV
ART	Antiretroviral Therapy
ARV	Antiretroviral
U=U	Undetectable = Untransmittable
TasP	Treatment as Prevention
CDC	Centers for Disease Control and Prevention
LtC	Linkage to Care
ARV	Antiretroviral
ART	Antiretroviral Therapy
CD4	Cluster of Differentiation
Plasma RNA	Plasma Ribonucleic Acid
VL	Viral Load
VS	Viral Suppression
AIDS	Acquired Immune Deficiency Syndrome
MSM	Men who have Sex with Men
IDU	Injection Drug User
NIR	No Identified Risk
NRR	No Risk Reported
HCF	Health Care Facility
HR	Hazard Ratio
OR	Odds Ratio

AOR	Adjusted Odds Ratio
IQR	Interquartile Range
LR	Logistic Regression
A2C	Access to Care
LTFU	Lost to Follow up
NHAS	National HIV/AIDS Strategy
ZCTA	Zip Code Tabulation Areas
eHARS	enhanced HIV/AIDS Reporting System
NCDPH	North Carolina Department of Public Health
MCHD	Mecklenburg County Health Department
GIS	Geographic Information System
IRB	Institutional Review Board
NCEDSS	North Carolina Electronic Disease Surveillance System
EHE	Ending the HIV Epidemic

GLOSSARY OF DEFINITIONS

- Human Immunodeficiency Virus (HIV): HIV is an infectious virus that progressively causes Acquired Immune Deficiency Syndrome (AIDS). HIV is a virus that is primarily a sexually transmitted infection but could be transmitted through other means like injection drug use or perinatal from mother to child in-utero or through breastfeeding. The virus attacks the immune systems in the body, particularly the CD4+ cells (T-helper cells).
- Linkage to care (LtC): is a process that requires a medical visit of a client to a provider after an HIV diagnosis for preliminary assessment and evaluation of the patient's clinical status. Based on national clinical guidelines, the reported laboratory investigation of CD4 cell count, CD8 cell count, or viral load are "biomarkers" but used in the context of this study as surrogates for the date/time of the first linkage to care.
- Viral load (VL): The amount of HIV in a blood sample and is reported as the number of HIV ribonucleic acid (RNA) copies per milliliter of blood.
- Viral suppression (VS: defined as having at least one viral load measure of <200c/mL). It is a measure of treatment effectiveness.
- Loss of viral suppression: People who initially achieved a VL of <200 c/mL who later had a subsequent VL >200 c/mL. Patients with two consecutive VL measures of >200 c/mL).
- U=U "undetectable equals Untransmittable": "Undetectable" describes when a person's plasma viral load (VL) is so low that a lab test cannot measure it. "Untransmittable" means that a person with such undetectable viral load has virtually no chance of transmitting HIV to a susceptible person through sexual contact.

- Treatment as prevention (TasP): Uses antiretroviral treatment (ART) to decrease the risk of HIV transmission to susceptible partners. TasP means that plasma viral load has been suppressed to a level that could be detected by a laboratory test (detection threshold). Therefore the risk of transmission to an uninfected partner is negligible.
- People Living With HIV (PLWH): Residents in Mecklenburg who were diagnosed as HIV-positive at various health care facilities (HCF) are the source population.
- Healthcare Facility: Health care facility where PLWH were diagnosed
- Sex: Describes the sex at the time of birth and registered in the vital records. This does not include transgender.
- HIV Continuum of Care (HCC): a measure of access to care, is a sequence of stages from diagnosis to achieving and maintaining viral suppression.
- Community viral suppression: is an aggregate level viral load concentration in the geographic area or population.
- Getting to Zero Mecklenburg (GZM): is a county-initiated community plan to get to zero new infections.
- Individual factors: demographic characteristics (age, sex, Race/Ethnicity, etc.), clinical characteristics (viral load, CD4 cell count, etc.), transmission risk
- Healthcare delivery systems factors: Diagnostic healthcare facility, provider characteristics (care visits)
- Incidence Cohort: individuals first diagnosed with HIV infection between January 1, 2013, and December 31, 2019, in Mecklenburg County.
- Lost to follow up: Patients who attrition out of the clinical care program. However, it is unclear if these patients have transferred their care services elsewhere.

CHAPTER 1: INTRODUCTION

Assessment and Characterization of HIV Care Continuum in Mecklenburg County, North Carolina 2013-2019

INTRODUCTION

Background

The burden of HIV disease has reduced due to increasing access to antiretroviral treatment (ART).(1-3) However, despite the availability of this life-saving treatment for people living with HIV (PLWH), weaknesses in the healthcare delivery systems lead to delayed diagnosis, delayed linkage to care and treatment, and poor retention in care.(4-9) These deficiencies at each stage of the care continuum are associated with suboptimal clinical outcomes. HIV care continuum (HCC) is a process that requires continuous access to appropriate health services at the proper time. The patient moving through the continuum steps to improve their health status.(10) Prompt linkage to care improves individual treatment outcomes and has implications for population health prevention.(11, 12) Additionally, early diagnosis, prompt linkage to care, and treatment are critical to the survival of PLWH.(13)

Previous studies have revealed that with good adherence for at least six months of treatment, PLWH usually will achieve viral suppression.(14, 15) HIV viral suppression (VS) is associated with superior individual health outcomes and reduced transmission risk to uninfected populations. The HIV Prevention and Trial Network (HPTN 052) study found that ART reduces the transmission risk to a susceptible partner by about 96%.(1) This and other studies underpin the undetectable = untransmittable (U=U) messaging, which essentially means that people with undetectable viral load (VL) cannot transmit HIV. The risk of transmission to an uninfected partner is negligible.(16) As such, it is imperative to achieve community-level (e.g., in Mecklenburg County) viral suppression to control HIV. Achieving VS will become critical to ending the HIV epidemic in the United States. According to Frieden et al. (17), prior published studies estimated that 69% of new infections are transmitted by those diagnosed but not in care. Additionally, most new infections have been reported among young black and Hispanic men.(18,

19) Ensuring that HIV-positive individuals promptly receive care and are retained in treatment is critical to increasing the proportion of those with a suppressed VL and realizing the benefits of treatment to reduce HIV transmission in the United States.(20) However, patient-level factors (e.g., gender, age group, race/ethnicity, geographic locations) and healthcare delivery system-level factors (e.g., access to diagnostic services, diagnostic facility type, and location) operate at all stages of the HCC, LtC30 and threaten the achievement of these outcomes. This lack of access to health services in general and HIV care will invariably lead to poor health outcomes, including progression to an advanced stage of the disease or Acquired Immune Deficiency Syndrome (AIDS), and more importantly, deter achievement of epidemic control. Thus, it is important to assess these deficiencies in the continuum of care and determine factors associated with poor health outcomes to implement more targeted interventions. The continuously evolving landscape of the HIV/AIDS epidemic will require ongoing research on health services delivery and utilization, the timeliness of appropriate care, and continuity of care.(21)

The burden of HIV in Mecklenburg County

The southeastern United States has a disproportionate burden of new HIV diagnoses.(22-24). Mecklenburg County is emblematic of other southern cities/jurisdictions experiencing the "southern" HIV epidemic. Mecklenburg County was identified as one of the priority counties/jurisdictional areas for Ending the HIV Epidemic (EHE) in the United States, where >50% of HIV diagnoses occurred in 2016 and 2017.(25) The overarching goal of EHE is to avert new infections through a multifaceted approach. Examining HCC, the milestone events starting with diagnosis, linkage to care, initiation of treatment, and achieving VS will help understand individual and health system factors that constituted barriers to epidemic control.

In Mecklenburg County, an estimated 6,665 people are living with HIV as of 2019.(26) Of those, 270 people were newly diagnosed. In 2019, Mecklenburg County ranked second in the rate of new HIV diagnosis and had the highest number of new cases of any county in North Carolina.(27) The burden of HIV and the high rate of new infections require enhancement to the prevention strategy. Therefore, examining and describing factors associated with deficiencies in the cascade of clinical care among different subgroups of the HIV population may identify more effective interventions to achieve viral suppression and reduce the rate of new infections. This evaluation and secondary data analysis aimed to identify factors associated with health services delivery in the care continuum. Routine evaluation of the epidemic through surveillance data and using it for programmatic decision-making will be critical to epidemic control efforts.

Examining the HIV continuum of care

HIV continuum of care (HCC) as a measure of access to care has been widely used in several studies to examine and identify weaknesses in the system of healthcare delivery for different diseases, including tuberculosis care continuum,(28) chronic obstructive pulmonary disease,(29) hypertension and diabetes,(4) and maternal, newborn and child health.(30) HCC could be useful as a method to assess care outcomes at individual and population levels, in particular, to analyze the proportion of people in each stage of the cascade and determine where services are deficient. HCC is an uninterrupted sequence of care processes in the management of HIV patients. PLWH faces many challenges regarding access to needed health services due to multiple steps they must complete to achieve ultimate viral suppression. This sequence of events begins with a diagnosis. PLWH should know their status as HIV positive. Next in the sequence of care is linkage to a provider for an initial medical assessment of illness, including determination of Cluster of Differentiation 4 (CD4) cell count and VL. Linkage to care is the

transition from diagnoses to medical care within 30 days and the CD4 cell count or VL measured. The next sequence is that HIV patients must begin treatment immediately to optimize the benefits of life-saving treatment to suppress VL as soon as possible, minimizing the risk of further transmission.(1) Next, their VL should be measured at regular intervals to determine the efficacy of treatment and ensure VS, which is the ultimate health outcome given the lack of cure for HIV infection. Achieving VS means that plasma RNA <200 copies/mL at the most recent measurement. There can be delays at each point of the cascade. Even when all are completed, patients have to be adherent and retained in care to achieve and sustain VS. As a result, some patients who previously achieved VS may lose the suppression due to multiple factors, including poor adherence to medication, among other reasons. Additionally, such patient continues to constitute a risk for transmission to susceptible people. Figure 1.1 illustrates the cascade of milestone events from diagnosis to viral suppression, loss of viral suppression, and the corresponding "objectives" of the investigation into the HIV care continuum in Mecklenburg County. Examining the HCC may identify steps in the sequence of care where there are gaps in care that may otherwise lead to poor individual health outcomes and, by extension, lack of epidemic control.

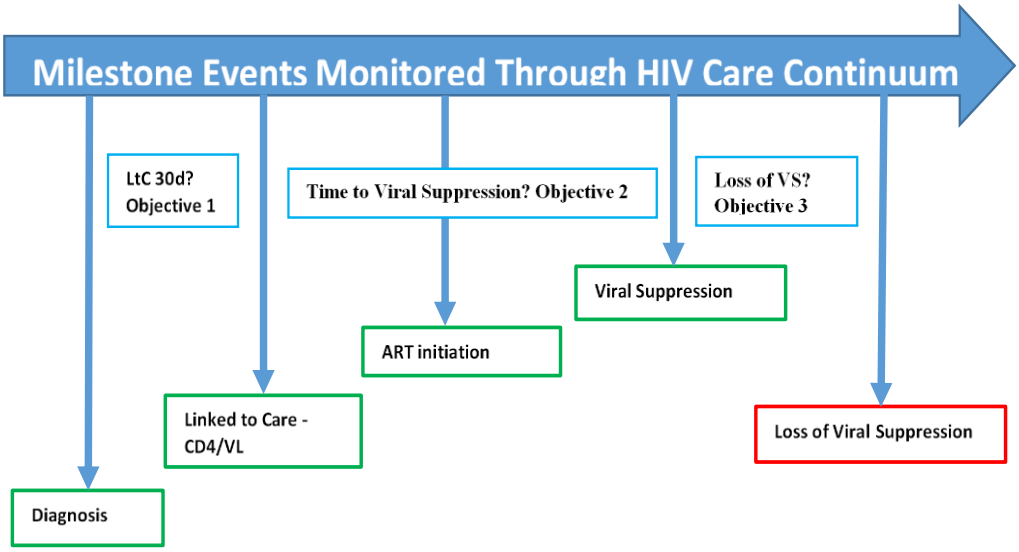

Figure 1.1: HIV Clinical Care Milestone Events (Continuum of Care Cascade). Abbreviations :(LtC30=Linkage to care within 30days; VL=Viral Load; ART=Antiretroviral Therapy; CD4=Cluster of Differentiation 4; VS=Viral Suppression)

Despite progress in controlling the overall epidemic, there are challenges in maintaining and progressing patients in care along each stage of the continuum. National surveillance data showed that not all HIV patients are getting appropriate and timely care. Of the estimated 1.1 million living with HIV in 2016 in the United States, 86% were diagnosed. Of those, only 64% were linked to care, 49% were retained in care, and 53% achieved viral suppression.(31) There is a need for further studies to determine the proportion of people not getting the appropriate care they need at the community level. National clinical guidelines recommended that persons diagnosed as HIV positive should be linked to care within 30 days (i.e., LtC<30d), but this is not always the case for many reasons. Therefore, examining HCC and identifying where the cascade of appropriate and timely clinical care is deficient, population subgroups most impacted will be critical to epidemic control efforts. In addition, examining factors associated with access to care would help to improve continuity of care and the most impactful interventions to improve

treatment outcomes. We aimed to identify factors associated with deficiencies in the HCC and, by extension, the control of the HIV epidemic in Mecklenburg County.

Prior published study estimated that approximately 80% of new HIV transmissions are from persons who are either unaware of their status, not linked to, or not engaged in care.(32) This situation poses a continuing challenge to epidemic control efforts and warrants further studies. HCC was established as a national policy through an executive order in 2013 as part of the National HIV/AIDS Strategy (NHAS) and was intended to improve prevention and access to care. NHAS 2020 called for research to fill gaps in knowledge along the care continuum.(33) Furthermore, the national strategy objectives recommended that 90% of the estimated people living with HIV be aware of their status. Of those, the proportion of persons with newly diagnosed HIV linked to care within one month should be increased to 85%. And, of those, the proportion of HIV-diagnosed individuals who achieved VS should be increased to 80%.(38) However, there was no comprehensive evaluation of the HCC in Mecklenburg County. As a result, the county initiated a community plan to zero new infections (34, 35) "Getting to Zero Mecklenburg" (G2Z-Meck). Additionally, the initiation of the G2Z plan was based on the perceived need to address the HIV epidemic. The studies in this dissertation evaluated the HCC in Mecklenburg County in support of community-based intervention strategies. Knowledge generated from this study will help Mecklenburg County evaluate its G2Z-Meck plan. We hypothesized that contextual factors (individual, health systems) would be significantly associated with deficiencies in the continuum of care among newly diagnosed HIV patients. Our study examined factors related to deficiencies and strengths in the HIV care continuum, populations at risk for delayed linkage to care, time to viral suppression, and investigated factors associated with loss of viral suppression that will engender policy initiatives for epidemic control

in Mecklenburg County. To put things into perspective, we investigated weaknesses and strengths in the HCC, which are essential to reduce the risk of transmission, improve treatment outcomes and survival of HIV patients.

Study Goal and Objectives

Goal: The overarching goal was to assess the weaknesses and strengths in the HCC and characterize the milestone events (e.g., diagnosis, linkage to care, viral suppression, and loss of viral suppression) by demographic characteristics (e.g., age, sex, race/ethnicity), clinical characteristics, geographic clusters of delayed LtC30, and other factors associated with these events to inform strategic interventions for epidemic response by Mecklenburg County health department.

Objectives: To describe the deficiencies or weaknesses of the HCC from diagnosis to VS and their impact on population subgroups.

Primary Objectives

1. To evaluate linkage to care within 30 days (LtC30) among patients newly diagnosed with HIV (Figure 1.1, step 1)
2. To determine time from LtC to Viral Suppression (VS) among patients in care (Figure 1.1, step 2)
3. To assess loss of VS among patients who initially achieved VS (Figure 1.1, step 4)

Secondary Objectives

1) Examine factors associated with early linkage (LtC30) and map the geographic distribution of clusters of suboptimal linkage to care
2) Examine factors associated with VS

3) Examine factors associated with loss of VS or viral suppression rebound

Operational Definitions

HIV Care Continuum (HCC): is a process through the various stages of HIV care in which newly diagnosed HIV patients are linked to care, initiated into treatment, retained in care until they achieve viral suppression.

Diagnosis: is the laboratory investigation and confirmation of HIV infection for an infected individual (i.e., people who have a positive test for HIV and received confirmed positive status of HIV infection) usually by a confirmatory laboratory test.

Linkage to care (LtC): The time between HIV diagnosis (positive test) and initiation of care or antiretroviral therapy. Assessed as the time (days) between the date of HIV diagnosis and first CD4 or viral load (VL) test. Linkage was defined as "early" if the first CD4 or VL assay was done within 30 days after diagnosis (LtC30), "delayed (LtC>30 days)" if the first CD4 or VL assay was conducted after 30 days, or "non-linkage (LtC0)" if there was no documented CD4 or VL. 30-days is recommended for linkage to care.

Treatment initiation: treatment is the process of prescribing antiretroviral therapeutic drugs to a person to control and prevent the multiplication of the virus. Thus, the treatment achieves a two-prong objective –antiretroviral therapy (ART) to suppress viral load and avoid transmitting HIV to an uninfected partner(s).

Retention in care: is defined as an engagement in care and uptake of appropriate health services PLWH. HIV-infected persons are expected to be retained in care once they are enrolled.

Plasma Viral Suppression: Viral suppression is achieved when HIV-1 plasma RNA <200 copies/mL (Not suppressed: HIV-1 RNA >200 copies/mL).

CD4+ T-helper cells: Cluster of differentiation 4: is a marker glycoprotein found on the surface of immune cells such as T helper cells. A type of lymphocyte, CD4+ cells, helps coordinate the immune response by stimulating other immune cells, such as macrophages, B lymphocytes, and CD8 T lymphocytes, to fight infection. HIV weakens the immune system by destroying CD4+ cells. CD4 cell count measures immune injury in HIV infection and reflect the clinical risk of acquiring secondary infections. It is used as an indicator of "advanced" HIV infection. A CD4+ cell count of <200 cell/mm3 is used as one definition of AIDS.

Plasma Viral Load: measures how many copies of HIV are present in a milliliter plasma sample. It is used to assess the level of active viral replication and response to antiretroviral therapy (ART).

ANALYTIC FRAMEWORK

To measure the relevant aspects of access to healthcare, we used the system and population descriptors as process indicators and utilization as outcome indicators in a theoretical access model. The variables being examined define demographic and disease state characteristics that are associated with the satisfactory or unsatisfactory achievement of target goals in the HCC.(36)

Study Design: A retrospective cohort study of the incident and prevalent cases from surveillance data collected for Mecklenburg County. We extracted a retrospective cohort analysis with incident cases from the North Carolina Electronic Disease Surveillance System (NCEDSS).

Data Sources: The HCC investigation utilized data collected routinely through the NCEDSS, which was reviewed, cleaned and reconciled, on a state level and incorporated into the enhanced HIV/AIDS Reporting System (eHARS). We reconciled the eHARS data against the State and national basis. eHARS is a document-based reporting system developed by CDC to

facilitate reporting by health departments (37). Data collection and aggregation are facilitated through importation by electronic case report forms, which are paper-based forms used to collect patients' data at the point of service delivery. eHARS consist of different tables that store specific clients' data uniquely identified in the relational database management system using a unique identifier. Information such as laboratory reports, clients' addresses, vital registration records (including birth and death certificates), among others, are stored for each case/person. eHARS captures individual-level data on people diagnosed and living with HIV. Data deduplication within and across jurisdictions (e.g., states) is done manually. Table 1.1 is a summary of some of the relevant variables in the dataset.

Table 1.1: Possible Risk factors in the surveillance dataset extracted for Mecklenburg County from the enhanced HIV/AIDS reporting system.

Risk factors	Description	Categories
Demographic Factors	Age at Diagnosis Gender Race/Ethnicity ZipCode of residence at time of diagnosis	13–65+ Male/Female White; Black; Hispanic; Others 28262; 28210; 28212; etc
Healthcare Delivery System Factors	Diagnosis facility type In-/Outpatient status County of Diagnosis Health Facility City	Hospital; Office Clinic; Health Dept; Correctional Facility; Inpatient; outpatient Mecklenburg County Charlotte; Huntersville; Mathews; etc.
Epidemiologic Factors	CD4 cell count Viral load value Mode of Transmission	Cell/µL Copies/mL Heterosexual; MSM; PWID; NIR/NRR

MSM=Men who have sex with Men; IDU=Injection Drug User; NIR/NRR=No Identified Risk/No Risk Reported.

Source Population and Sample Selection: Mecklenburg residents (aged 13 and above) diagnosed as HIV-positive at various health care facilities were considered the source

population. We used the Incidence Cohort of individuals first diagnosed with HIV infection from January 1, 2013, to December 31, 2019, with residence in Mecklenburg County.

Incidence cohort: We included all patients with new HIV diagnoses resident in Mecklenburg County at the time of diagnosis from 2013 to 2019. We included those who were deceased or had left Mecklenburg County, provided they were residents in the country at the time of their diagnosis. We excluded children less than 13 years old because their pediatric population's epidemiological context differs from adults.

Statistical Analysis Plan

Incidence cohort data HIV of Mecklenburg County residents from January 2013 to December 2019 was used for the analyses. For exploratory data analysis, we used frequencies distributions and proportions to summarize categorical data. The chi-square test of independence was used to explore and determine whether there was a statistically significant difference between the expected frequencies and the observed frequencies in one or more categories. We used a statistical summary for continuous variables to describe the data distribution (e.g., mean, median). A logistic regression model was used for inferential analysis to determine the association's strength and obtain 95% confidence intervals. In addition, Cox proportional hazard was used for time-to-event analysis as applicable. All statistical analyses were conducted using SAS version 9.4. All tests were performed assuming a two-tailed test of significance and alpha level set a priori at 0.05. Demographic and clinical characteristics for the cohorts were displayed using counts and percentages for categorical variables and measures of central tendency (mean, median, standard deviation) for continuous variables. The total sample tabulated baseline characteristics.

Outcome measures

1. Linkage to care within 30 days (LtC30)

   We measured time from the first diagnosis of HIV (date of first positive HIV dx test) until linkage into care (CD4 cell count visit or date of first VL). Also, we mapped LtC30 by zip code to identify potential "clusters" of delayed linkage to care (LtC>30). Below are the specifics of the measures.

   a. CD4/CD8/VL date – (date of HIV DX test) = days to enter care
   b. Calculated the proportion of those who linked to care within 30days (LtC30), did not link to care within 30 days (LtC>30), and those who were never linked to care (LtC0).
   c. The dependent variable of persons linked to care within 30 days versus over 30 days was tested against the independent variables of demography and epidemiologic and clinical characteristics.
   d. LtC30 and independent risk factors
      i. Examine the association between clients greater or less than 35 years of age and LtC30
      ii. Examine the association between LtC30 and mode of transmission
      iii. Examine the association between LtC30 and type of patient visit at the time of diagnosis (inpatient or outpatient visit)
      iv. Examine the association between LtC30 and type of diagnostic facility
      v. Examine the association between LtC30 and race/ethnicity

vi. Other subgroups were explored based on the statistical analysis construct for each research topic.

2. Evaluation of viral suppression (VS):
    a. Time from entry into care to ^{first} viral suppression
        i. Time to 1VL suppression <200c/mL (based on first VL values <200c/mL and date of entry into care).
        ii. The proportion of patients in care with 1VL <200 c/mL = twelve months after linkage to care
        iii. Factors associated with VS
3. Evaluation of loss of viral suppression:
        i. The proportion of patients with loss of VS after having had VL suppression (i.e., 1st of 2 consecutive >200 c/mL values).
        ii. Factors associated with loss of viral suppression

Findings from this study will contribute to the body of scientific knowledge, and recommendations were made to Mecklenburg County Health Department on data-driven decision-making for programmatic improvement. Finally, this is an opportunity to use data to inform program planning and implementation.

Ethical Considerations

The University of North Carolina, Charlotte (UNCC) Institutional Review Board (IRB) reviewed the study protocol. It determined that the study did not constitute human subjects, and according to federal regulations [45 CFR 46.102 (f)], did not require IRB approval (IRB letter of 4 Jan 2018, ref #17-0418).

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CHAPTER 2: PAPER 1

Evaluation of Linkage to Care Among Newly Diagnosed People Living with HIV in Mecklenburg County, North Carolina, United States 2013-2019

ABSTRACT

Background: Early linkage to HIV care is essential to optimize the benefits of antiretroviral therapy (ART). However, delayed linkage to care continues among newly diagnosed people living with HIV (PLWH). Our study examined and described individual, and healthcare system-level factors associated with linkage to care among newly diagnosed PLWH in Mecklenburg County.

Methods: Surveillance data extracted from the enhanced HIV/AIDS reporting system for Mecklenburg County, North Carolina, was used for this retrospective observational study of newly diagnosed HIV patients (aged ≥ 13 years) and enrolled into care. Linkage to care (LtC) was assessed as the time (days) between the date of HIV diagnosis and the first CD4 or viral load test. Linkage was determined to be early if within 30 days after diagnosis (LtC30), delayed (LtC>30) if it occurred beyond 30 days, or non-linkage (LtC0) if there was no documented CD4 or VL. Logistic regression was used to determine factors associated with LtC30 or LtC>30. In addition, we used logical descriptive analyses and accumulation curves demonstrating time to LtC30 for the subpopulations in outpatient HCF.

Results: Between January 2013 and December 2019, 1,521 persons (≥ 13 years) were newly diagnosed. Of the 1,521 persons, 1,214 (80%) were male. The median age at diagnosis was 31 years (IQR 25-43). 64% of newly diagnosed people were LtC within 30 days, meaning that 36% had delayed or non-LtC. On univariate analysis, age group, gender, race/ethnicity, diagnostic facility type were associated with suboptimal linkage to care. In multivariate analysis after adjusting for other factors, older adults (>35 years) had 1.5 times the odds of LtC30 when compared with young adults (>13–34 years) (AOR = 1.54; 95% CI = 1.17, 2.03). The probability of LtC30 was 40% lower for males when compared with females (AOR = 0.61; 95% CI = 0.41,

0.93); Blacks, Hispanics, and other races had a 50% lower probability of LtC30 as compared to White. Persons diagnosed (not necessarily treated) in outpatient settings had a significantly lower odds of LtC30 (AOR = 0.08; 95%CI 0.04, 0.18) than those diagnosed in hospital facilities. Of those diagnosed in outpatient settings, those diagnosed in infectious disease clinics had higher odds of LtC30 when compared with those diagnosed from other diagnostic health facilities. The mode of acquisition was not associated with the risk of suboptimal linkage.

Conclusion: These findings confirm the role of individual and healthcare delivery system factors in linkage to care. Further studies may be needed to ascertain why these population groups are disproportionately affected by suboptimal LtC30 and the systemic changes necessary to address the healthcare delivery system-level factors that continue to hinder linkage.

Keywords: HIV; Newly Diagnosed; Linkage to Care; Disparities; Mecklenburg County

INTRODUCTION

Background

Linkage to care (LtC) is the referral process and preliminary medical evaluation of people newly diagnosed with HIV infection. Immediate linkage to care after HIV diagnosis is critical to achieve optimal treatment outcomes and prevent ongoing transmission.(1-4) Conversely, delayed linkage to care has been associated with delayed initiation of antiretroviral therapy (ART), which may lead to suboptimal viral suppression.(5) Approximately 80% of people living with HIV (PLWH) in the United States are linked to care; of those, only 40% are retained in care.(6) Review from studies shows that timely linkage to HIV care and treatment has improved individual and population-level benefits. However, about 25%-31% of newly diagnosed people with HIV are not linked to care.(7) Viral suppression (VS) is imperative for people diagnosed with HIV infection to improve their quality of life, improve survival, and necessary to prevent ongoing transmission.

Early linkage to care is an essential measure of how well the healthcare delivery system is functional and can support people diagnosed with HIV in need of appropriate and timely medical care. Linkage to care is an important step in the HIV cascade as it is the precursor to ART initiation, retention in care, and viral suppression.(8, 9) Successful LtC will ensure timely ART initiation and ultimately the achievement of viral suppression. Delayed LtC, on the other hand, effectively limits the ability of PLWH to initiate ART. For HIV epidemic control, LtC is a critical gap that needs to be closed. Evidence from a large study involving 28 U.S. jurisdictions concluded that people who are linked to care within 30 days have better outcomes, in particular viral load suppression.(10) Additionally, the U.S. HIV National Strategic Plan 2021-25 sets ambitious targets aimed at ending the HIV epidemic in the United States by 2030.(11, 12) The

plan has set a target of persons with newly diagnosed HIV linked to care within one month to 95%. This goal is critical to achieving the upstream goal of achieving 95% suppression among PLHIV in the same time frame. Thus, achieving these targets requires optimal linkage to care and, importantly, identifying individual and health delivery system-level factors impeding timely linkage to care among newly diagnosed individuals. Such health system challenges affect critical steps in the entire "cascade of care" — from diagnosis, laboratory evaluation, treatment initiation, and engagement in HIV care to achieving VS. Cascade losses have been extensively studied and reported.(13) Progress towards these objectives varies widely by localities and jurisdictional areas. A study by Dorward et al. in South Africa found that only 54% of PLWH were linked to care within one year of diagnosis.(14)

The updated 2020 NHAS recommended a one-month time frame for prompt LtC as a strategy to achieve the national objective of 85% of persons diagnosed with HIV are linked to care. LtC is also critical to the achievement of prevention targets. A review of the literature shows that linkage to care is necessary to reduce the incidence of HIV.(15, 16) However, there are challenges in the health care delivery system that prevents timely linkage to care after diagnosis. We, therefore, aimed to investigate the individual and system-level factors impacting LtC and how the Mecklenburg County health department could address them. For Mecklenburg County, we sought to answer several specific questions: were all individuals diagnosed with HIV linked to care appropriately? Which population subgroups had suboptimal linkage to care? We hypothesized that individual and health system delivery factors would be associated with suboptimal linkage to care. To the best of our knowledge, this evaluation would be the first large-scale inquiry that assessed and characterized the linkage process at the health delivery system and individual level.

METHODS

Study Population and Sample Selection

Mecklenburg residents (aged 13 and above) diagnosed as HIV-positive at various health care facilities (HCF) are considered the source population. Therefore, we established an Incidence Cohort of all patients with new HIV diagnoses who were residents of the county at the time of diagnosis from 2013 – 2019. Our study examined adults and adolescents older than 13 years whose first HIV-positive diagnostic test was recorded between January 1, 2013, and December 31, 2019. They lived in Mecklenburg County at the time of their diagnosis, regardless of whether they linked to care or received care elsewhere subsequently.

Outcome Measures

U.S. clinical guidelines and the National HIV/AIDS Strategy (NHAS) recommended completing a visit to a medical provider within 30 days of HIV diagnosis as the established metric for LtC. This LtC metric is predicated on laboratory assessment of Cluster of Differentiation 4 (CD4) cell count or HIV Ribonucleic Acid (RNA) test results. These tests are not always available at the point of diagnosis and frequently require referral to care. Thus, any visit over 30 days or one month after diagnosis is regarded as a "suboptimal linkage." This study defined the time of linkage to care as the time between HIV diagnosis and first CD4 cell count or viral load test date. National guidelines recommended LtC within one month of diagnosis. As such, we examined linkage to care within 30 days and the associated demographic and epidemiological correlates. We classified potential correlates of suboptimal linkage into individual-level factors and health system-level factors. We included the individual-level factors known to influence linkages collected during routine HIV testing (e.g., age, gender, race/ethnicity, sexual orientation, mode of acquisition, and CD4 cell count) status at diagnosis.

Health system-level factors included diagnostic facility types (e.g., hospital, infectious disease clinic, health department, blood plasma center) and geographic location based on zip code tabulation areas.

Primary outcome: our primary outcome was linkage to care within 30 days (LtC30). LtC30 was dichotomized with a threshold of ≤30-days and >30 days. People who did not link to care were excluded from this analysis. LtC was calculated as the time from the first diagnosis of HIV (date of first positive HIV test) until linkage into care using the date of the CD4 cell count visit or date of first VL as a proxy to determine LtC.

Secondary outcome: we investigated the geographic distribution of clusters or hotspots of people with poor linkage to care across the county's various zip code tabulation areas.

Excluded from Cohort

Incidence cohort (but not prevalence cohort): HIV diagnosis before January 1, 2013, or after December 31, 2019. For the incidence cohort, those living in another county at the time of diagnosis (even if they move into Mecklenburg County subsequently)

Not excluded from the cohort

Patient who died

Patient not living currently in Mecklenburg County

Data collection

Incident cases from surveillance data reported by health care facilities to the state health department were extracted for Mecklenburg County residents from the Enhanced HIV/AIDS Reporting System (eHARS). eHARS is a document-based reporting system developed by CDC to facilitate reporting by health departments.(17) Data collection and aggregation are facilitated through importation by electronic case report forms, which correspond to paper-based case

report forms. eHARS consisted of tables that store specific patient data, uniquely identified in the relational database management system using a unique identifier. Information such as laboratory reports, patient address, vital registration records (including birth and death certificates), pediatric case reports, among others, are stored for each case/person. eHARS captures individual-level data on people diagnosed and living with HIV. Data was prepared by the North Carolina Department of Public Health, edited to include Mecklenburg County residents at diagnosis, and shared with Mecklenburg County Health Department.

Statistical Methods

We retrospectively analyzed incidence cohort data from January 2013 to December 2019. We used surveillance data from eHARS to determine the time of LtC from diagnosis. Specifically, we sought to know if newly diagnosed PLWH were able to LtC within one month and the factors associated with such. In addition, we also investigated if the location of residents was relevant to the risk assessment using a geographic information system. We mapped different population subgroups who achieved LtC30 and those who did not (late linkers) and compared the difference in clusters. We also used cumulative graphs and forest plots to compare the effect size and differences in time to LtC30 among diagnostic HCF with the hospital facility.

Statistical analysis

We explored the data using univariate methods and used those results to construct a series of multivariate analyses using logistic regression. Chi-square test of association was used to examine patients' demographic and clinical characteristics of the outcome measure. Individuals' backgrounds and clinical characteristics were summarized using proportions. For inferential analysis, logistic regression (LR) modeling was used to determine the strength of association between linkage to care (dichotomized as within 30 days or greater than 30 days) and the

explanatory variables. A manual selection process arrived at a series of LR models, culminating with the final, parsimonious LR.

Chi-square was used to test independence for the risk factors and to explore if LtC30 was statistically significantly associated with the risk factors. We assessed the proportion linked to care within 30-days and determined factors associated with linkage within and over 30 days after diagnosis. Furthermore, we used cumulative distribution curves to assess a subgroup of patients within the hospital and other HCF. And also use this method for other subgroups of interest (e.g., among the various outpatient HCF). Finally, we used a geographic information system (ArcGIS) for mapping geographic variations in LtC30, comparing early linkers with delayed LtC30 to examine if the location was relevant to the risk assessment.

Ethical approval

The UNCC Office of Research Protections and Integrity determined that the study did not constitute human subjects research, and according to federal regulations [45 CFR 46.102 (f)], did not require IRB review (IRB letter of 4 Jan 2018, ref #17-0418).

RESULTS

Baseline Characteristics

One thousand five hundred twenty-one (1,521) adults and adolescent residents of Mecklenburg County were diagnosed with HIV between January 2013 and December 2019. The majority (79.5%) were male. Black or African Americans (70%) were the predominant ethnic/racial group, followed by whites (14.8%) and Hispanics (11%). Male to male sex was the dominant mode of transmission reported, 59%). Most patients were diagnosed in Physician office clinics (38%), followed by health department testing sites (27%) and hospitals (12%). Table 2.1 describes the demographic characteristics of newly diagnosed people living with HIV (PLWH), according to LtC30 status.

Using univariate analyses, we found that younger patients, in particular, 18-24 years olds were less likely to be linked to care within the first month than other age categories. Similarly, Blacks and Hispanics were less likely to compared to be linked Whites. Patients diagnosed in hospitals, physician offices (clinics), and infectious disease clinics were more likely to be linked to care within one month than patients diagnosed in any other type of HCF. Patients with lower CD4 counts were more likely to be linked by day 30 than those with high CD4 counts (Table 2.1).

Table 2.1: Baseline Demographic Characteristics and Proportion (%) of Linkage to Care Among Newly Diagnosed HIV-positive Adults and Adolescents Living in Mecklenburg County at time of diagnosis (n=1,521).

	Linked to care within 30 days after diagnosis					
Characteristic	***Total***	***Never***	***No***	***Yes %***	***(n)***	***P value***
Sex						
Male	1214	72	*382*	*62.60*	*(760)*	*0.0042*
Female	307	15	*64*	*70.36*	*(216)*	
Age at Diagnosis						
75th percentile		*42*	*37*	*46*		
Median		*29*	*28*	*33*		
25th percentile		*25*	*23*	*26*		
Race/Ethnicity						
White	*225*	*8*	*40*	*78.67*	*(177)*	
Black	*1061*	*74*	*339*	*61.07*	*(648)*	
Hispanic	*169*	*5*	*51*	*66.86*	*(113)*	
Other	*66*	*0*	*21*	*68.18*	*(45)*	<0.0016
Transmission mode						
Heterosexual	132	3	40	67.42	(89)	
MSM	875	25	300	62.86	(550)	
MSM-IDU/IDU	47	1	14	68.09	(32)	
NIR-NRR	467	58	97	66.81	(312)	<0.0012

	Linked to care within 30 days after diagnosis					
Characteristic	***Total***	***Never***	***No***	***Yes %***	***(n)***	***P value***
Sex						
Male	1214	72	*382*	*62.60*	*(760)*	*0.0042*
Female	307	15	*64*	*70.36*	*(216)*	
Age at Diagnosis						
75th percentile		*42*	*37*	*46*		
Median		*29*	*28*	*33*		
25th percentile		*25*	*23*	*26*		
Race/Ethnicity						
White	*225*	*8*	*40*	*78.67*	*(177)*	
Black	*1061*	*74*	*339*	*61.07*	*(648)*	
Hispanic	*169*	*5*	*51*	*66.86*	*(113)*	
Other	*66*	*0*	*21*	*68.18*	*(45)*	<0.0016
Health Care Facility						
Agency	27	4	10	48.15	(13)	<.0001
Blood Bank Plasma	85	17	53	17.65	(15)	
Office Clinic	580	11	98	81.21	(471)	
Community Health Center	11	0	3	72.73	(8)	
Correctional Facility	14	2	7	35.71	(5)	
Emergency Department	45	6	14	55.56	(25)	
Family Planning	4	2	0	50.0	(2)	
Health Department Site	417	38	223	37.41	(156)	
Home Health Agency	9	0	7	22.22	(2)	
Hospital	186	3	8	94.09	(175)	
Infectious Disease Clinic	73	0	4	94.52	(69)	
Laboratory Site	1	0	0	100.00	(1)	
Not Specified	38	3	19	42.11	(16)	
O.B. Gynecology Clinic	14	0	0	100.00	(14)	
Other	6	0	1	83.33	(5)	
Urgent Care	11	1	4	54.55	(6)	

Legend: MSM=Men who have Sex with Men; MSM-IDU=Men who have Sex with Men and Injection Drug Users; NIR-NRR= No Identified Risk / No Reported Risk; E.R. = Emergency Room.

Overall, 64% (N=976/1521) of all newly diagnosed Mecklenburg County adults and adolescents linked to care within 30 days. Eighty-seven (87) patients were not linked within our observation

period of one year after diagnosis. When we plotted a cumulative graph of LtC30 over a six-month observation period as the timeline for the standard of care, we found that about 71% achieved LtC30 by 30 days and 94% by 90 days (Figure 2.1a). Using the same parameter and method, we compared and contrasted differences between inpatients and outpatient HCF and outpatient HCF to achieve LtC30. In addition, we found that patients diagnosed in hospitals achieved LtC30 earlier than outpatient diagnostic facilities (98% and 68.8% by 30th day, respectively). Among outpatient facilities, the patients in infections disease clinics were linked earlier than in any other outpatient facility type (97% linked by day 22). In contrast, those diagnosed in blood bank and plasma centers were linked later than other outpatient facilities; only 28.6% of patients were linked to care by 30 days after diagnosis (Figure 2.1b).

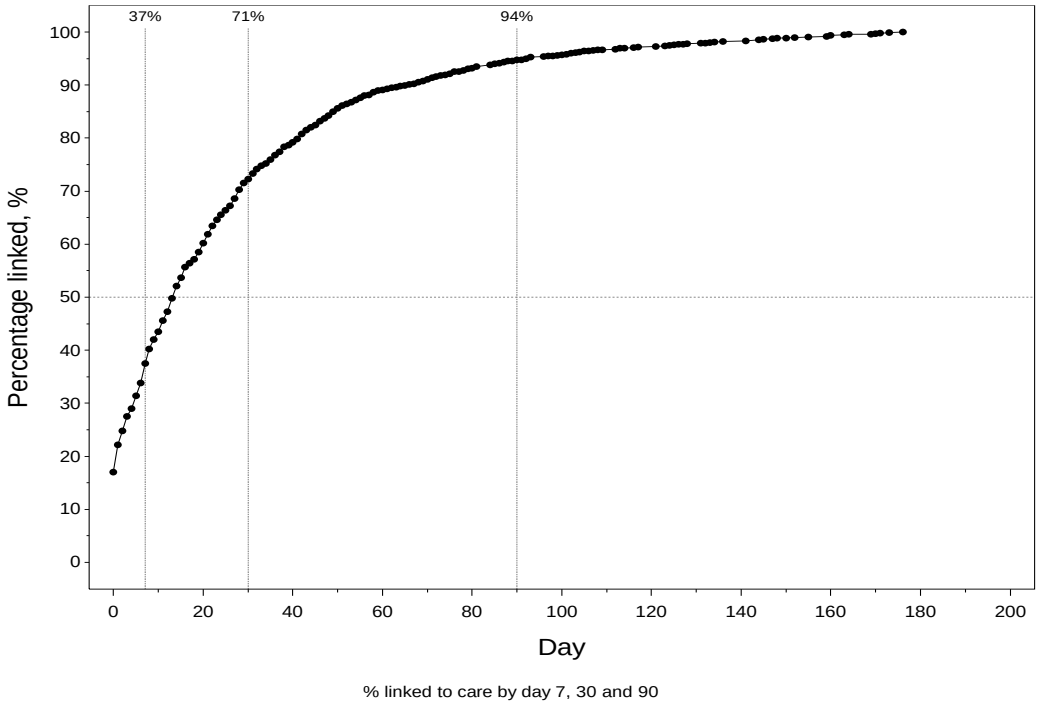

Figure 2.1a: Cumulative proportion of adult and adolescent Mecklenburg County residents linked to care for patients who linked within six months of diagnosis, 2013-2019.

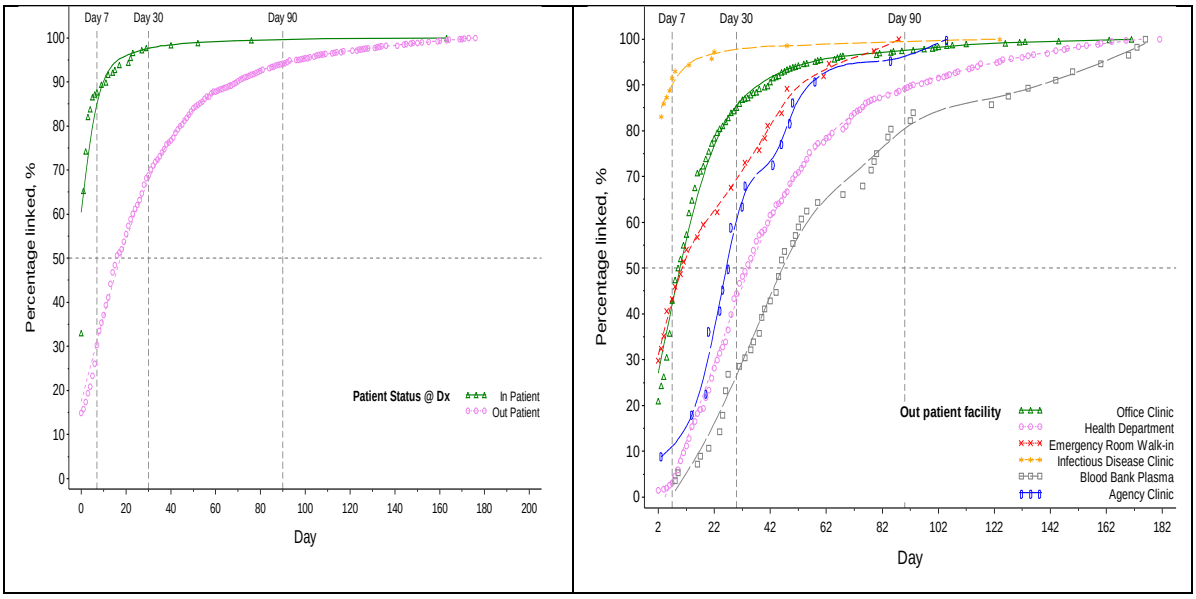

Figure 2.1b. Cumulative proportion of adult and adolescent MeckCo residents linked to care for patients who linked within six months of diagnosis, 2013-2019 according to healthcare facility performing HIV diagnosis.

To determine the structural attributes achieving LtC30 and the diagnostic health care facility, we examined the strength of association between diagnosing HCF and achieving LtC30 as depicted in Figure 2.2. We found that the odds of LtC30 were lower when PLWH were diagnosed at other outpatient HFC compared with Hospital ($p<0.001$) (Figure 2.2).

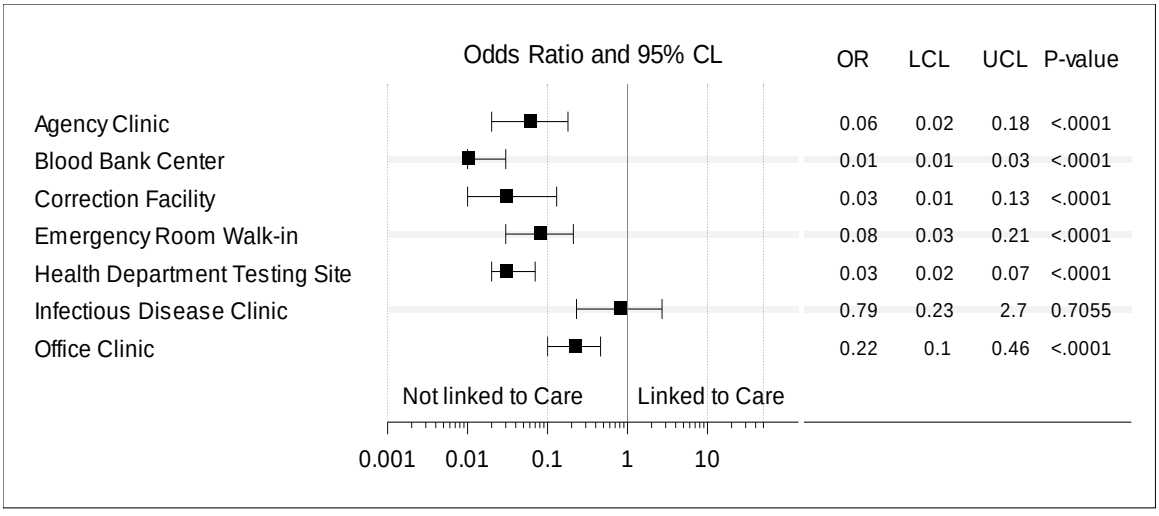

Figure 2.2: Forest plot of unadjusted Odds Ratios of risk factors for linkage to care for facility types compared to hospital

Factors associated with linkage to care

Using univariate logistic regression models, we found potential unadjusted associations of lower proportions of LtC30 occurring among patients first diagnosed in outpatient HCFs, males, patients <35 years of age, persons of color, and persons with higher pre-treatment CD4 cell counts. However, there was no apparent association between transmission risk factors and LtC30 (Table 2.2).

Table 2.2: Univariate logistic regression estimates of odds ratios of being linked to care.

Covariate	*Category*	*OR (95%CI)*	*P-value*
Age category	≥35	2.01 (1.59, 2.53)	<.0001
	13-34	Ref	
Race/Ethnicity	Black	0.43 (0.30, 0.62)	<.0001
	Hispanic	0.50 (0.31, 0.81)	0.0044
	Other	0.48 (0.26, 0.90)	0.0222
	White	Ref	
Sex	Male	0.59 (0.43, 0.80)	0.0007
	Female	Ref	
Facility	Office Clinic	0.22 (0.10, 0.46)	<.0001
	Health Department Testing Site	0.03 (0.02, 0.07)	<.0001
	Blood Bank/plasma Center	0.01 (0.01, 0.03)	<.0001
	Agency Clinic	0.06 (0.02, 0.18)	<.0001
	Emergency Room Walk-in	0.08 (0.03, 0.21)	<.0001
	Infectious Disease Clinic	0.79 (0.23, 2.70)	0.7055
	Correction Facility	0.03 (0.01, 0.13)	<.0001
	Hospital	Ref	
Transmission mode	MSM	0.82 (0.55, 1.23)	0.3412
	MSM-IDU/IDU	1.03 (0.49, 2.13)	0.9424

Covariate	*Category*	*OR (95%CI)*	*P-value*
	NIR-NRR/Other	1.45 (0.93, 2.24)	0.0987
	Heterosexual	Ref	
Patient Status @ Dx	Outpatient	0.09 (0.04, 0.18)	<.0001
	Inpatient	Ref	
CD4 category, cell/mm³	≥200	0.68 (0.50, 0.93)	0.0146
	<200	Ref	

We developed a multivariable logistic regression model to calculate adjusted odds ratios (AORs) for factors found in the univariate analyses to be potentially associated with delayed LtC30 (not achieving LtC30). After adjusting for the covariates, age category, race/ethnicity, sex, and patient's diagnosing facility status remained significantly associated with LtC30. After adjusting for the other factors, the probability of LtC30 was reduced by 50% among Blacks, Hispanics, and other race categories compared to White. Similarly, the likelihood of LtC30 was decreased by about 40% for males compared with females after adjusting for other factors (AOR = 0.61; 95% CI = 0.41–0.93). When we dichotomized HCF into inpatient and outpatient for this analysis, the probability of achieving LtC30 was reduced by 92% for those diagnosed in outpatient facilities compared with those diagnosed in the hospital (AOR = 0.08; 95% CI =0.04, 0.18). Point estimates and associated confidence intervals are depicted in Table 2.3.

Table 2.3: Multivariate logistic regression estimates of odds ratios of being linked to care

Covariate	*Category*	*AOR (95%CI)*	*P-value*
Age category	≥35	1.54 (1.17, 2.03)	0.0020
	13-34	Ref	

Covariate	*Category*	*AOR (95%CI)*	*P-value*
Race/Ethnicity	Black	0.42 (0.28, 0.62)	<.0001
	Hispanic	0.50 (0.30, 0.84)	0.0080
	Other	0.51 (0.26, 1.00)	0.0494
	White	Ref	
Sex	Male	0.61 (0.41, 0.93)	0.0216
	Female	Ref	
Transmission mode	MSM	1.43 (0.86, 2.38)	0.1736
	MSM-IDU/IDU	0.86 (0.38, 1.95)	0.7172
	NIR-NRR/Other	1.49 (0.93, 2.39)	0.0975
	Heterosexual	Ref	
Patient Status @ Dx	Out-patient	0.08 (0.04, 0.18)	<.0001
	In-patient	Ref	
CD4 category, cell/mm^3	≥200	0.94 (0.67, 1.33)	0.7349
	<200	Ref	

When we georeferenced LtC30 with zip code of residence, we found patients with delayed linkage clustered in specific zip codes. A review of the zip code tabulation areas shows that the high-risk areas with delayed LtC30 corresponded to communities of color. Charlotte's "arc" and the "wedge" are spatial patterns that identify two geographic regions in Charlotte by social determinants of health. The "arc" described communities of color and concentrated poverty.(18) Fitting our map to describe the arch and the wedge, the areas of high counts of HIV diagnoses and high counts of delayed LtC30 are consistent with the "arc" where households are densely populated (about 48% of the total city population), the average income is below the city average, and constituted about 67% minority population. By contrast, our map's areas of low

HIV diagnoses and low counts of delayed LtC30 corresponded to the "wedge" where the residents are 31% of the total city population, the average income is above the city average and consisted of 63% white. Obviously, social determinants of health played a role in these outcome disparities (Figure 2.3).

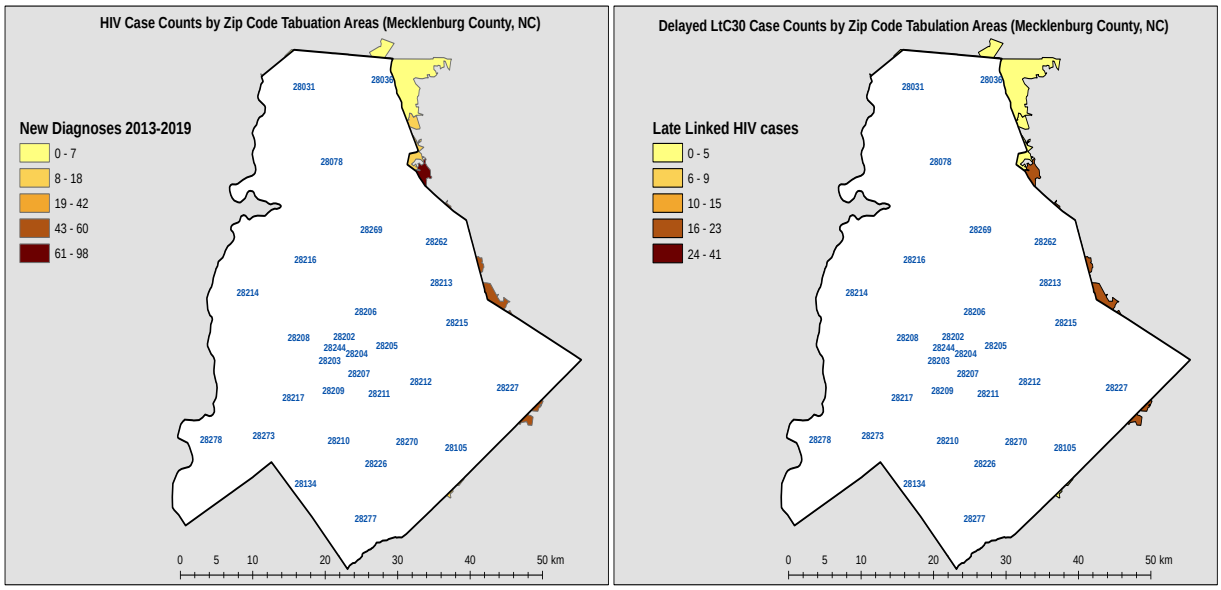

Figure 2.3: Geographic Variations in New HIV Diagnoses and Delayed Linkage to Care.

DISCUSSION

One of the objectives of the NHAS for PLWH is to improve access to care and, as a result, better health outcomes. Access to Care (A2C) was a national HIV linkage to care program aimed to link and retain the most vulnerable PLWH into high-quality HIV care.(19) One approach to achieve this objective is through prompt LtC after diagnosis of HIV, which enables immediate treatment initiation. LtC following an HIV diagnosis remains a critical HIV care continuum milestone, even in the era of "test and treat."(20) To optimize HIV treatment benefits and achieve viral suppression, interventions are needed for timely linkage to care, a critical step in the HIV cascade and a precursor to initiating antiretroviral therapy (ART), retention in care,

and viral suppression.(8) Timely linkage-to-care among the newly infected is important to maximize individual-level and population-level ART benefits.(21) Achieving the NHAS objective of increasing the proportion of persons with newly diagnosed HIV who are linked to care within one month to 90% will require addressing individual and health system-level factors associated with delayed LtC30. This analysis, the first to examine linkage to care at the county level, investigated the individual and healthcare delivery system-level factors impacting LtC30.

Our study found that only 64% of the adults and adolescents diagnosed in Mecklenburg County were linked within the recommended 30 days. We found several individual and healthcare delivery system-level factors of suboptimal linkage. At the individual level, being Black or African Americans, Hispanic, and belonging to other racial minorities was associated with higher odds of delayed LtC30. Young adults, particularly those in the age group 13–34 years, had lower linkage rates. Unsuccessful or delayed linkage to care deprive adolescents living with HIV of the benefits of HIV treatment, risks increased HIV transmission, and increased HIV-related morbidity and mortality.(22, 23) Young adults were more likely not to achieve LtC30, and this finding is consistent with univariate and multivariate analysis results.

However, a 2009 national survey revealed that healthcare providers more often attributed non-engagement in care to structural barriers (finances, transportation, family care, lack of time off from work, and substance use). PLWH often reported psychosocial issues (stigma, concern about medication side effects, and shame) as the most important barriers to care.(24) Additionally, barriers, such as inconvenient location of medical services, long appointment wait times, are likely to contribute to delayed linkage to care. Persons required to test for HIV (e.g., for insurance, employment, or court-ordered purposes) were found to delay linkage after receiving a diagnosis of HIV, compared to those who self-initiate testing or those offered testing

by health care providers through provider-initiated HIV testing.(25) Considering the retrospective nature of this analysis, our findings of disparity in LtC30 require further investigation, including through qualitative studies that include individuals who link, those who link late, and those who never link.

Furthermore, we found that patients with suboptimal linkage clustered in particular zip codes. Our analysis did not include a thorough assessment of the reasons for this clustering and, as such, calls for more detailed inquiry. The clustering of people who did not link could reflect access challenges beyond the scope of our analysis. Disparities in care access by racial and socioeconomic groups have been previously documented by other researchers(26) and call for strengthening the health system(27) to support population subgroups disproportionately impacted by poor access to care.

From a structural perspective, further studies might be needed to assess the impact of health insurance on LtC and other social determinants of health to understand poor LtC in the affected communities better. For the young adults with suboptimal LtC, novel ideas like leveraging mobile health interventions like a mobile phone-enabled application to improve linkage to HIV may be helpful.(28) Overall, epidemic control will require aggressive linkage to care interventions through a concerted effort from individuals, HIV providers, HIV-engaged agencies, and the county government. We also found that the type of HCF of diagnosis affected linkage to care, with outpatient offices being associated with lower linkage. Access to the point of care CD4 and could facilitate timely linkage.

Our study had limitations, including the retrospective nature of our analysis which precludes making causal associations. First, we used routine surveillance data collected at the time of HIV diagnosis. Thus, critical data elements such as health insurance, socioeconomic

status, education, employment status that influence linkage and health care access were not available. In addition, many other person-level factors such as education, privacy concerns, mental health issues, family support, and perhaps knowledge and beliefs about HIV/ AIDS that may impact the time between the diagnosis and the link to care were not available in the dataset.

Moreover, the surveillance data are subject to errors in reporting and missing information. We found missing information for the following data elements, CD4 cell counts, VL results, etc. The use of test sample dates was taken as the epidemiological marker for linkage may overestimate linkage as some individuals may still drop out before actual initiation of ART, especially if results were not available in a reasonable time. The surveillance data used for this analysis represent a specific period and do not account for providers' associations. Despite the limitations of the surveillance dataset, our findings can still generate hypotheses for future studies. For example, a more critical evaluation of reasons for delayed linkage can be answered through an intervention study informed by community engagement (e.g., through a community advisory board that includes racial minorities). Additionally, qualitative studies with subsets of individuals who link, link late, or do not link could help answer the reasons for the gaps we unearthed in our research.

In conclusion, we found suboptimal LtC30, especially among Blacks and Hispanics and young adults 13-34 years. To improve linkage to care and achieve the national strategic plan objective, improvements will be necessary at the healthcare delivery systems level to reach the 36% who linked late and those who did not link at all. This study is primarily descriptive, and further studies may be needed to ascertain why certain population groups are disproportionately affected by suboptimal LtC30 and systemic changes needed to address the healthcare delivery system-level factors that hinder linkage.

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CHAPTER 3: PAPER 2

Evaluation of Factors Influencing Time to Viral Load Suppression Among Newly Diagnosed People Living with HIV in Mecklenburg County, NC 2013 - 2019

ABSTRACT

Background: The potential to reduce the burden of the Human Immunodeficiency Virus (HIV) can only be realized by increased access to highly effective antiretroviral treatment (ART). Viral load suppression (VS) — defined as having less than 200 copies of HIV per milliliter of blood— is one of the most important outcomes and measures of treatment success. Suboptimal VS among people living with HIV (PLWH) is a major challenge that warrants further investigation, particularly at the jurisdictional level. Our study aimed to investigate and evaluate time to VS among persons newly diagnosed with HIV infection and linked to care in Mecklenburg County. We investigated factors associated with VS among a cohort of newly diagnosed HIV patients during the first twelve months in care.

Methods: This retrospective observational study used surveillance data extracted from the enhanced HIV/AIDS reporting system for Mecklenburg County, North Carolina. We examined time from linkage to care (LtC) to VS and determined median time to first VS (<200 c/mL) in the cohort using the Kaplan-Meier estimator. Correlates of VS were determined using Cox proportional hazard models.

Results: Among 1,134 newly diagnosed persons linked to and engaged in care, 939 (82.8%) achieved first VS within 12 months. The median time to VS after LtC was 80 days. Among patients who linked to care within 30 days (LtC≤ 30), the time to achieve VS was shorter when compared to those with LtC>30 days, LtC <=30d vs. >30d (85 vs. 90days). In the multivariate model, the probability of achieving VS was 16% lower for those who linked after 30 days (LtC>30 vs. LtC≤30) even after adjusting for the patient's place of diagnosis and controlling for baseline viral load (adjusted hazard ratio = 0.841, 95% CI 0.727 – 0.973).

Conclusion: We found that only 83% of newly diagnosed individuals achieved VS in 12 months. Persons linked to care within 30 days, those with lower baseline VL, and those diagnosed as outpatients were more likely to achieve VS on time. To optimize outcomes, patients diagnosed in outpatient facilities will require a referral mechanism to promptly link newly diagnosed people to care. In addition, strategies are needed to improve linkage by prioritizing facilities with high volumes of new diagnoses.

Keywords: Evaluation; HIV; Linkage to care; Viral Load Suppression; Disparities; Health Outcome.

INTRODUCTION

Background

Human immunodeficiency virus (HIV) viral load suppression (VS) — defined as having less than 200 copies of HIV per milliliter of blood—is the main outcome and measure of treatment success for individuals in care and treatment.(1) For this to occur, a sequence of clinical care and engagement steps are critical. Persons living with HIV need to be linked to care, initiate and adhere to antiretroviral therapy (ART), and engage in care to achieve and maintain VS. This sequence of events (i.e., clinical care cascade) are needed to prevent the Acquired Immune Deficiency Syndrome (AIDS) progression. The U.S. health resources and multiple studies show that treatment adherence helps achieve VS in people living with HIV.(2-7) Attendance at scheduled clinic visits and the Cluster of Differentiation 4 (CD4) cell count and viral load are measures of continued engagement in care. However, many factors influence linkage to and engagement in care and ultimately the achievement of viral suppression, including access to care.(8, 9) People living with HIV (PLWH) who have limited access to care are less likely to link and are likely to have poor outcomes. Moreover, yet prompt linkage to care and ART initiation has been shown to decrease time to VS.(2, 10) Access to care is recognized as a vital factor for promoting and sustaining health and as a contributor to good health outcomes in HIV patients.(11-13) Research studies have called for achieving VS as a measure for improving health outcomes in a continuum of clinical care for PLWH.(14-17) Assessing treatment coverage is a crucial metric in the HIV care continuum and time to achieve VS can be used to evaluate this metric.

In addition to improved quality of life and overall survival, virally suppressed patients have no risk of transmitting HIV to sexual partners.(5, 18) Given these findings, it is essential to describe how individual and health delivery system factors (2, 9, 19) influence time to VS.

Estimating the time between milestones in the care continuum can be used as priority indicators of gaps in treatment coverage as well as for monitoring the success of any interventions for closing identified gaps.(20, 21) Identifying factors associated with VS can also inform the development of effective, customized strategies for improving access to care and ultimately improve health outcomes among subgroups affected by poor VS and inform public health policy.(22) The National HIV/AIDS strategy recommended that the proportion of PLWH linked to care with VS be increased to 80%.(23) However, there are currently no data describing outcomes such as VS among newly diagnosed HIV patients in Mecklenburg County, North Carolina. Examining individual and healthcare delivery system factors that influence VS at the County level is essential to inform the design of a patient-centered healthcare delivery system that optimizes outcomes. To examine VS among people newly diagnosed with HIV at the county level, it is essential to understand the challenges in the healthcare delivery system and the expected individual-level health outcomes. Access to care for persons newly diagnosed with HIV can be evaluated using proxy measures (e.g., CD4 cell count and viral load levels). The results can be used to determine VS.(24, 25) The evaluation of VS reflects how well the HIV care system is working in the county health jurisdiction. The study aims to investigate the association of VS with the individual and the healthcare delivery system factors and characterize subpopulations impacted by poor VS or at risk of viral load failure after LtC. We hypothesized that individual and healthcare delivery system factors would be significantly associated with time to VS.

Outcome Measures

Primary objectives

The primary endpoint was to determine the time to VS from LtC and within twelve months of receiving care and treatment. We examined factors associated with VS among newly diagnosed HIV persons from January 2013 to December 2019. Patients were followed from the time of linkage to care until VS or until censored. We sought to measure the following outcomes:

- Determine time from entry into care to the first VS (<200 c/mL values) suppression based on the date of viral load measure and entry into care.
- Determine proportions of patients in care with VS (<200 copies/mL) within 12 months after Linkage to Care (LtC) among those diagnosed with new infections.

Secondary objectives

- Determine demographic, health systems, and epidemiologic factors associated with time to achieve VS

METHODS

We investigated time from LtC to VS among newly diagnosed PLWH in Mecklenburg County. Patients included HIV-infected individuals older than 13 years diagnosed between 2013 and 2019 who resided in the county at the time of diagnosis and were reported to the electronic HIV surveillance system. This study analyzed existing HIV surveillance data collected through the North Carolina public health reporting system. In addition, we established a cohort of those linked to care and analyzed time to achieve VS and their correlations.

Data Sources

The de-identified dataset used for this study was sourced from the enhanced HIV/AIDS Reporting System (eHARS). Data collection and aggregation were facilitated by the importation

of electronic case report forms (CRFs) corresponding to paper-based CRFs used to collect client data at the point of service delivery. HIV cases are typically reported by laboratories and healthcare facilities to local and state health departments, who forward these reports to the Centers for Disease Control (CDC) using the eHARs. The eHARS system referenced for this study contained demographic and clinical information and HIV-related laboratory data (including all CD4 and viral load results) for all persons diagnosed with HIV infection in Mecklenburg County, North Carolina. In addition, since population-based HIV surveillance data are used to assess care based on CD4 cell counts or viral load measures, the surveillance data for Mecklenburg County residents were also extracted. Therefore, our final cohort consisted of incident cases extracted from the North Carolina Department of Public Health eHARS database of PLWH and residing in Mecklenburg County at the time of diagnosis.

Statistical Analysis

We assessed the proportion of those with VS and determined factors associated with VS after LtC. We described the data and determined associations between various risk factors and VS using the Chi-square test of association. The dependent variable, VS, was dichotomized as suppression or non-suppression. An exploratory analysis examined demographics and other clinical characteristics of newly diagnosed adult and adolescent residents (age >13 years) with LtC (defined by clinical visit and CD4 or VL measures). The changes in VL and HIV RNA copies per milliliter of blood (copies/ml) were converted into the more manageable logarithmic scale of log10 and compared across demographic strata using box plots. The inferential analyses examined time from LtC to VS using the Kaplan-Meier model. For the current analysis, we retrospectively observed patients until the earliest time to VS or administrative censoring (right-censoring that occurs when the study observation period ends) due to loss of follow-up, death, or end of observation. The following risk factors were examined for their associations with time to

VS (viral load <200 copies/mL): sex, age group at the time of diagnosis, Race/Ethnicity, time of LtC, diagnostic facilities, patient admission status (in- or outpatient), HIV exposure category, and nadir CD4 lymphocyte count. For time to VS, patients contributed observation time from the date of LtC to date of recorded VS. Patients were censored either at the end of follow-up or death, whichever was earlier. Patients with no viral load test results who either died or were lost to follow-up were also censored at the time of last available value. We used the Kaplan-Meier model to estimate the time to achieve VS in the at-risk population from LtC and generated survival plots for visual representation. Using Cox proportional hazards models, we examined factors associated with viral suppression, including baseline viral load at the time of enrollment into care, LtC within 30 days of diagnosis, and type of diagnostic healthcare facilities, while controlling for demographic, clinical, and transmission risk characteristics. We used Cox proportional hazard regression and log-rank test to evaluate the association between predictive factors and time to VS. We included factors that were statistically significantly associated with the outcome in the univariate analysis. These included: sex, age groups, diagnostic facilities, patient hospital status, exposure category, race/ethnicity, and CD4 count at diagnosis in the multivariate association of time to VS with LtC. The VL variable for which the proportional hazard assumptions were violated in the Cox regression model was used as stratifying variable for the final model. We ran several multivariate models but selected the parsimonious based on the goodness-of-fit criteria. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Ethical consideration

The study protocol was reviewed by the University of North Carolina Charlotte's Office of Research Protection and Integrity. As a result, it was determined by the Institutional Review Board to be exempt from human subject research.

RESULTS

Cohort characteristics

The dataset of newly diagnosed patients (January 2013 through December 2019) extracted from the eHARS database included 2200 unique persons with demographic data merged and integrated with the viral load and CD4 laboratory values data. Of these, 679 patients did not meet demographic data criteria (665 were non-Mecklenburg County residents, and 14 were less than 13 years old), leaving 1,521 patients. When merged with the laboratory data, only 82% (1,245/1,521) had viral load test results for the observation period—the 276 with missing laboratory data and were excluded from further analysis. Of note, we found 91 patients with missing viral load data at initial LtC. After consideration of data collection methods by disease investigation specialists and possible issues with reporting data quality, missing baseline viral load data was imputed if within 15 days of reporting (52/91 successfully imputed). In the final dataset, 9% of the patients (111/1245) had records for baseline VS. The final dataset included 1,134 subjects with baseline viral load included in the subsequent analysis. Figure 3.1 illustrates the numbers and reasons for the exclusion of patients from the final analytical dataset.

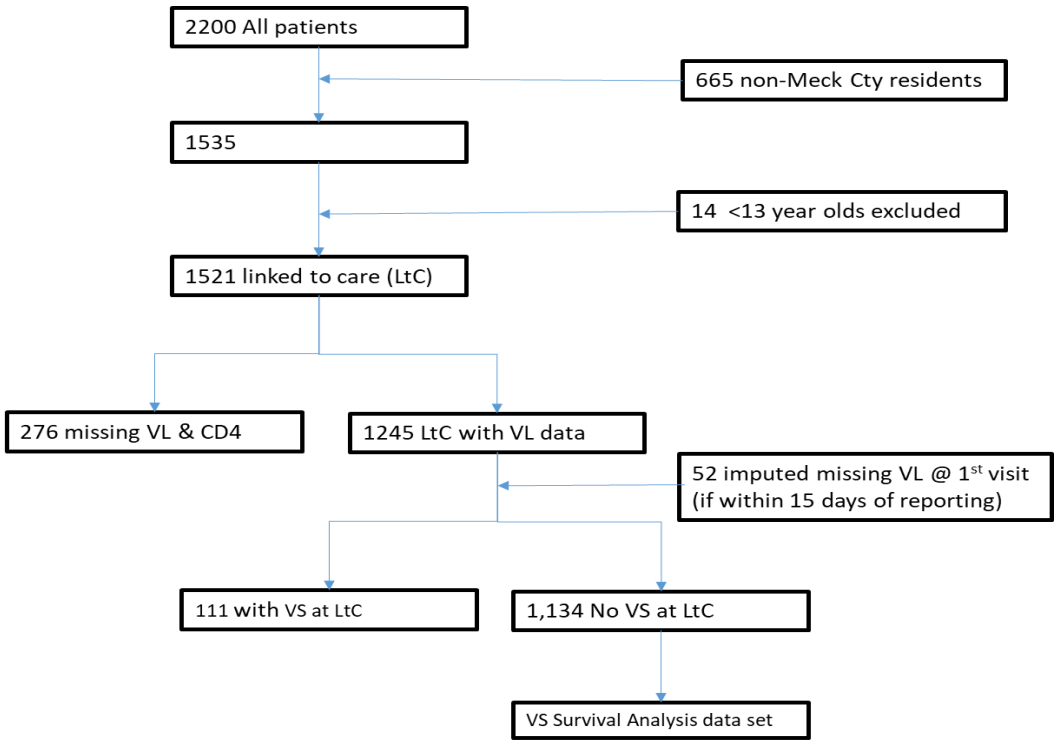

Figure 3.1: Flow diagram showing numbers of patients and inclusion and exclusion criteria in the final dataset used for Kaplan-Meier and Cox Proportional Hazard models.

Patients were predominantly male (81.7%), young adults 18-34 years (57%), African American (70%). The predominant mode of transmission was male to male transmission (59%). A large percentage of the patients (39%) was diagnosed in office clinics, while 11% were diagnosed in hospitals (Table 3.1).

Table 3.1: Demographic characteristics of adolescent and adults newly diagnosed with HIV, linked to care, and achieved VS in Mecklenburg County, NC

Covariate	Category	%(n)	P-value
Age category	13-17	1.5 (19)	<0.0001
	18-24	22.3 (278)	
	25-34	34.9 (434)	
	35-44	19 (236)	
	45-54	12.9 (160)	

Covariate	Category	%(n)	P-value
	55-64	7.5 (93)	
	65+	1.9 (24)	
Race/Ethnicity	White	14.7 (183)	<0.0001
	Black	69.5 (864)	
	Hispanic	11.5 (143)	
	Other	4.3 (54)	
Sex	Female	19.9 (245)	<0.0001
	Male	80.1 (988)	
Diagnostic Facility type	Office Clinic	40 (498)	<0.0001
	Health Department	27.3 (339)	
	Hospital	10.9 (136)	
	Infectious Disease Clinic	5.3 (66)	
	Blood Bank Plasma	4.8 (60)	
	Other	11.7 (145)	
Transmission mode	Heterosexual	9.2 (115)	<0.0001
	MSM	60.1 (748)	
	MSM-IDU/IDU	2.7 (33)	
	NIR-NRR	28 (348)	
Baseline CD4 Counts	>=500	23.6 (294)	<0.0001
	350-<499	15.5 (193)	
	200-<349	14.5 (180)	
	<200	17.3 (216)	
	Unknown	29.1 (362)	

We used box plots to compare viral load (log c/mL) at LtC by demographic characteristics, diagnostic health facility types, and transmission mode. We found no significant differences in median viral load at baseline across the age categories. However, males tended to have a slightly higher baseline viral load when compared with females. In addition, the median baseline viral load among patients diagnosed at infectious disease clinics tended to be slightly lower than that for patients diagnosed at other healthcare

facilities. There were also no differences in median baseline viral load by mode of transmission (Figure 3.2).

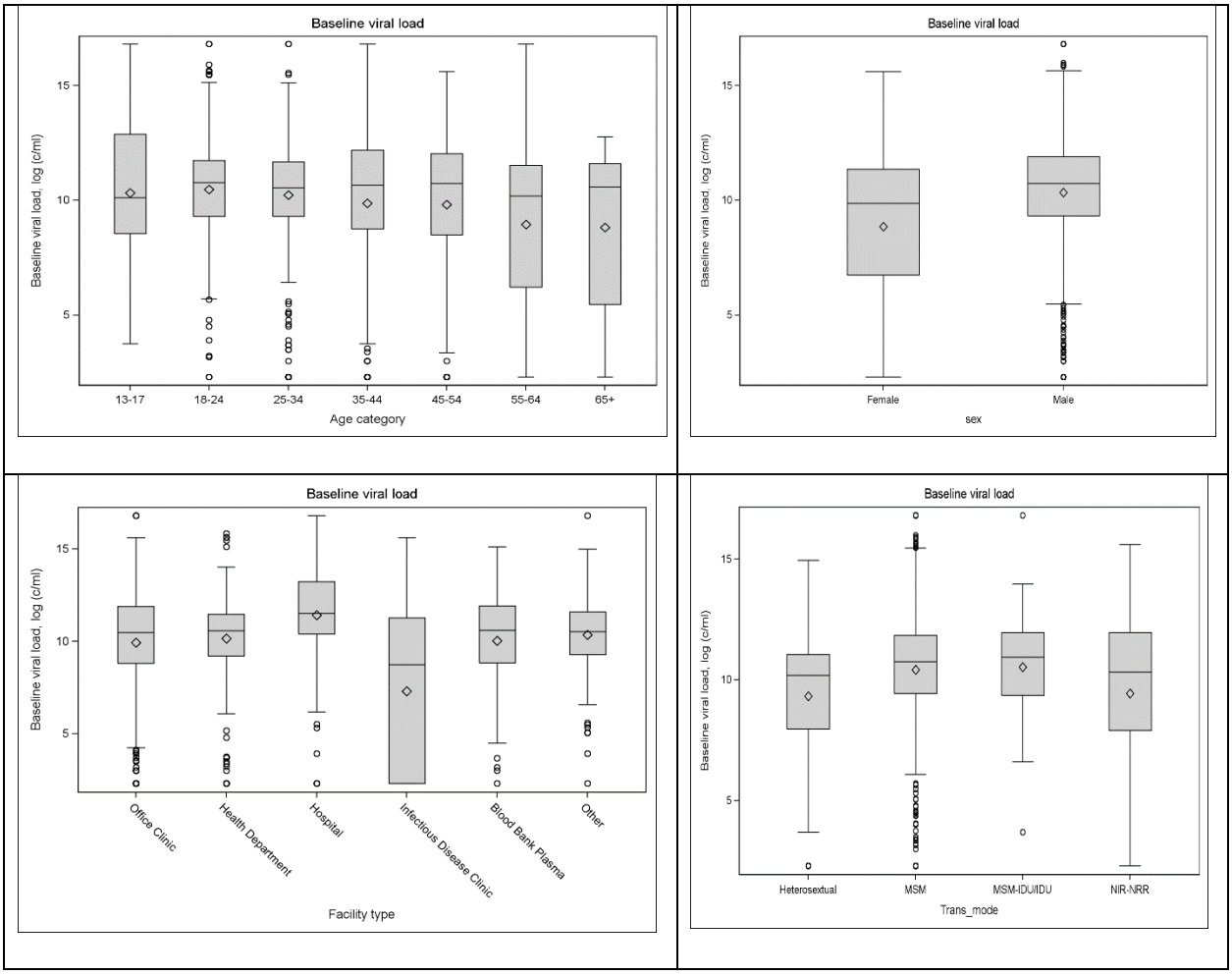

Figure 3.2: A box and whisker plot to visualize the explanatory variables' interquartile range and compare baseline viral load across different factors (the diamond represents the mean; the horizontal represents the median; and the circles represent the outliers).

The proportion of patients and median time to VS

The median time to first VS after LtC was 80 days (25% achieved VS within 51 days and 75% achieved VS within 125 days, interquartile range, IQR 54–152 days). Overall, 83% of patients (939/1134) achieved VS within 12 months of LtC. A higher proportion of White (91%) and Hispanic patients (92%) achieved VS within 12 months of LtC compared with Blacks (79%). The median time to VS was lower

for those who LtC <=30d vs. >30d (85 vs. 90days). The median time to VS was shorter for patients with viral load <=10,000c/mL at LtC (Table 3.2).

Table 3.2: Median Time to VS

	Number in Group	Median time to VS	Interquartile Range	% VS at Month 12
Overall	1,134	80 d	54 d, 152 d	83%
LtC				
<=30d	755	85 d	49 d, 144 d	84%
>30d	378	90 d	61 d, 167 d	80%
Age Group				
13-24	288	94d	56 d, 188 d	77%
25-45	610	83d	54 d, 141 d	84%
45+	236	87d	51 d, 145 d	85%
Race/ethnicity				
White	161	83 d	50 d, 140 d	90%
Black	801	90 d	55 d, 164 d	79%
Hispanic	127	84 d	47 d, 144 d	92%
Other	45	87 d	55 d, 135 d	89%
Gender				
Female	199	92 d	49 d, 172 d	79%
Male	926	85 d	55 d, 147 d	84%
Transmission risk				
Heterosexual	102	91	54 d, 141 d	81%
MSM	707	84	54 d, 145 d	85%
MSM/IDU	33	123	59 d, 262 d	76%
NIR/NRR	292	90	53 d, 162 d	78%
Baseline viral load				
<=10,000c/mL	219	77 d	49 d, 137 d	81%
10,000 – 50,000 c/mL	322	79 d	54 d, 134 d	84%
50,000 – 150,000c/mL	266	84 d	49 d, 155 d	84%
>150,000 c/mL	285	100 d	60 d, 160 d	84%

Survival (VS) Analyses for LtC Cohort

The Kaplan-Meier survival plot shows the proportion of patients and probability of time to VS from initial LtC. There was a significant difference in time to achieve VS in Race/Ethnicity. Median time to VS was lower for White when compared with Blacks (p=0.04). However, Hispanics and other races did not reflect a statistically significant difference in time to achieve VS compared with White. Patients diagnosed as outpatients achieved VS earlier than hospitalized patients.

Further, a comparison among outpatient diagnostic HCFs shows that physician office clinics have a higher proportion of those who achieved VS when compared with others. However, this was not statistically significant (Figure 3.3).

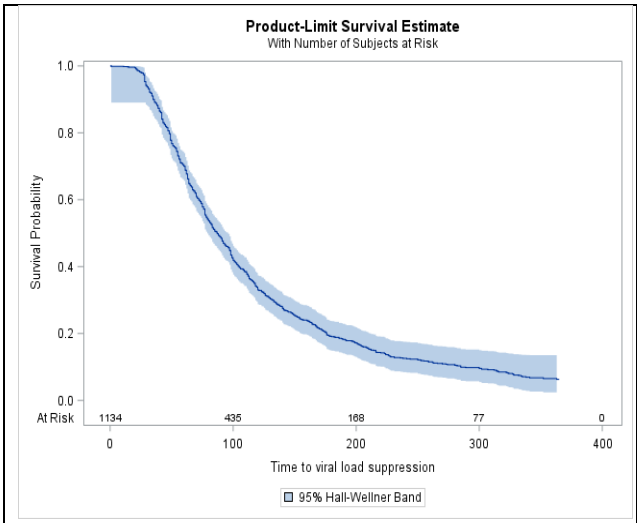

Fig. 3.3a: Overall Time to Viral load suppression (VS)

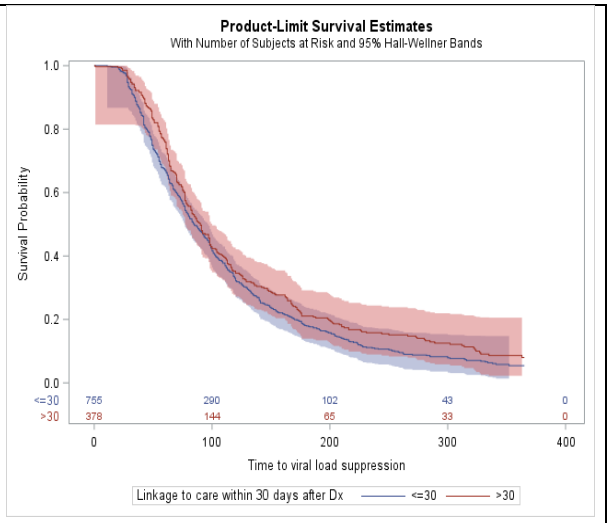

Fig. 3.3b: Time to VS stratified by time of linkage to care

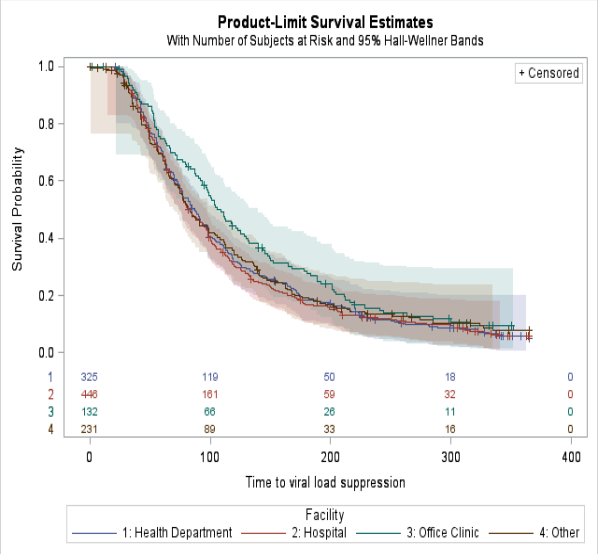

Fig. 3.3c: Time to VS stratified by Healthcare Facilities

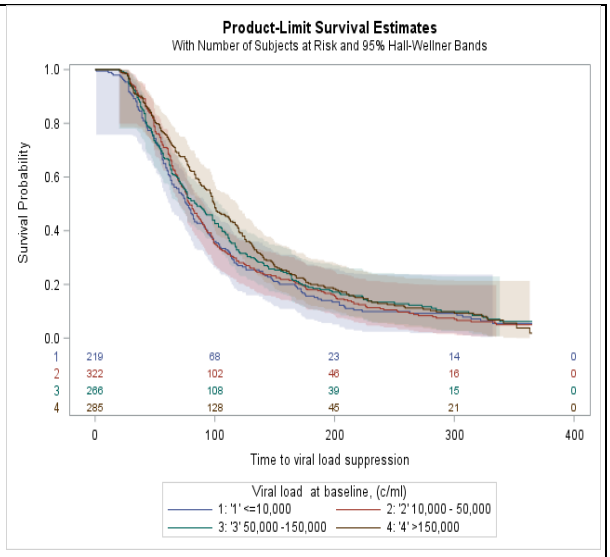

Fig. 3.3d: Time to VS stratified by baseline Viral Load

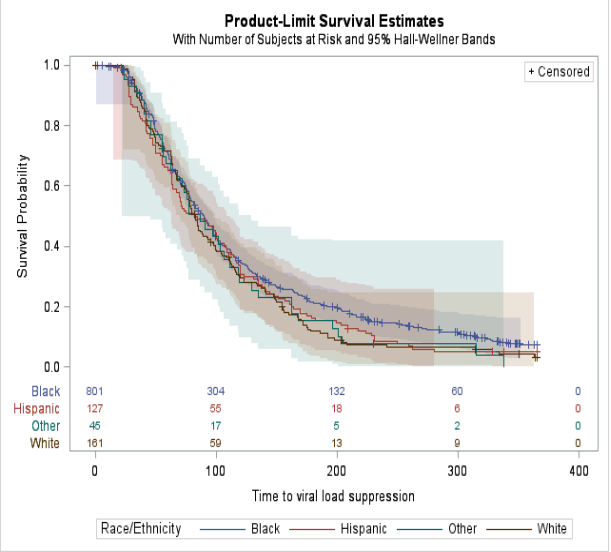

Fig. 3.3e: Time to VS stratified by Race/Ethnicity

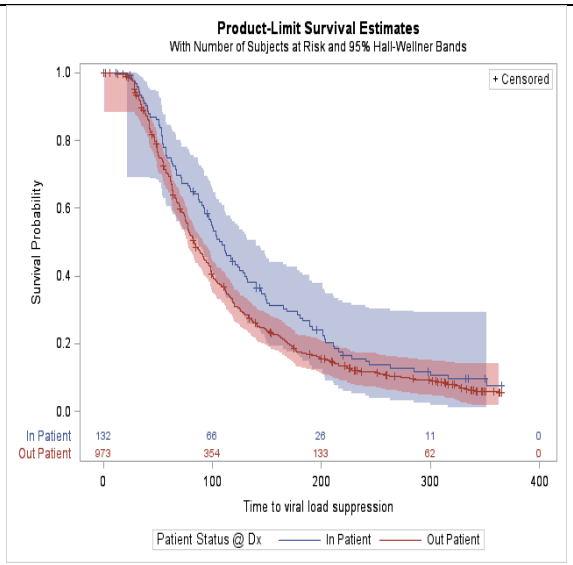

Fig. 3.3f: Time to VS stratified by In/Outpatient

Figure 3.3: Plots of Kaplan-Meier estimates of time to viral load suppression within 12 months of linkage to care: (3a) overall and stratified by: (3b) Linkage to Care; (3c) Healthcare facilities; (3d) VL at baseline; (3e) Race/Ethnicity; and, (3f) Inpatient or Out-patient.

In the univariate model, we found that the hazard (event at risk) of VS was 14% lower among patients with LtC > 30 days as compared with LtC < 30 days (HR=0.87, 95% CI 0.76, 0.99). Similarly, time to VS was longer among Blacks than Whites (H.R. = 0.83, 95% CI 0.69-

0.99 p-value=0.04). In addition, patients diagnosed through outpatient clinics were 27% more likely to achieve VS when compared to inpatients (HR=1.27, 95% CI 1.04, 1.56). Table 3.3 shows a summary of the results of the univariate analyses.

In the multivariate model, the probability of achieving VS was lower by 16% for patients linked to care after one month compared with patients who linked within one month (aHR = 0.841, 95% CI 0.727, 0.973). However, the probability of achieving VS was 37% higher among those diagnosed through outpatients compared to inpatients (aHR=1.375, 95% CI 1.111, 1.702) after adjusting for baseline viral load, time to linkage to care (LtC30), and place of diagnosis. In addition, with one log increase in baseline VL, the probability of achieving VS was reduced by 10% after adjusting for other covariates. Detailed results of the multivariate analyses are shown in Table 3.3.

Table 3.3: Univariate and multivariate Cox proportional hazard of covariates associated with viral load suppression among adolescent and adults newly diagnosed with HIV infection in Mecklenburg County, NC.

Covariates	*Hazard Ratio*	*95% LCL*	*95% UCL*	*P-value*
Linkage to care after Dx				
>30 days	0.866	0.755	0.993	0.0390
<30 days	Ref.			
Sex				
Male	1.071	0.902	1.271	0.4357
Female	Ref.			
Race/Ethnicity				
Black	0.830	0.693	0.994	0.0424
Hispanic	0.969	0.760	1.237	0.8026
Other	1.014	0.714	1.438	0.9397
White	Ref.			

Covariates	*Hazard Ratio*	*95% LCL*	*95% UCL*	*P-value*
Age group				
35+	0.930	0.620	1.394	0.7245
26-35	0.984	0.654	1.481	0.9389
19-25	0.807	0.534	1.218	0.3064
13-18	Ref.			
Facility				
Office Clinic	1.287	1.038	1.596	0.0216
Health Dept.	1.244	0.994	1.556	0.0562
Other	1.209	0.954	1.533	0.1157
Hospital	Ref.			
Patient Status @ Dx				
Out-patient	1.272	1.039	1.556	0.0196
In-patient	Ref.			
Trans mode				
MSM	1.051	0.835	1.322	0.6708
MSM-IDU/IDU	0.665	0.425	1.042	0.0747
NIR-NRR	0.937	0.729	1.205	0.6120
Heterosexual	Ref.			
CD4 @ 1st Visit				
>=500	1.141	0.934	1.395	0.1969
350-499	1.147	0.924	1.424	0.2125
200-349	1.173	0.943	1.460	0.1527
<200	Ref.			
Viral Load at baseline (c/ml)				
10,000 – 50,000	0.949	0.783	1.151	0.5948
50,000 – 150,000	0.903	0.739	1.104	0.3188
>150,000	0.810	0.666	0.986	0.0357
<10,000	Ref.			
Multivariate analysis controlling for Viral Load				
Covariates	*Adj. Hazard Ratio*	*95% LCL*	*95% UCL*	*P-value*
Linkage to care after Dx (>30)	0.841	0.727	0.973	0.0197
Viral Load at baseline log (c/ml)	0.906	0.840	0.977	0.0101
Patient Status @ Dx (outpatient)	1.375	1.111	1.702	0.0034

"Hazard Ratio" means groups with H.R.>1.0 are more likely to achieve VS earlier than the reference group, while those with H.R. <1.0 are less likely to achieve VS earlier than the reference group.

DISCUSSION

The results of this study highlight individual and healthcare delivery system factors that impact the timely achievement of VS. We found that achievement of VS was associated with early LtC30 and place of diagnosis. Patients linked to care within 30days (LtC30) and those diagnosed in outpatient settings were more likely to achieve viral suppression. Individuals who linked late were more likely to be of the Black race and young. We also observed that people diagnosed from physicians' offices were more likely to achieve viral suppression than other outpatient diagnostic facilities. While the respective nature of our analysis precludes making causal inferences, further exploration of these associations through intervention studies could help inform program enhancements that would enable the county to improve the proportion of individuals who link early and achieve suppression.

Studies from elsewhere show that health care facility characteristics influence health outcomes among patients living with HIV. That achievement and maintenance of VS are associated with facilities with higher HIV-positive caseloads.(26) In our case, we neither have information about provider characteristics nor the mechanism for referral, if any, that could facilitate LtC. The lack of information on the types of facilities that provided HIV care to the patients limits our interpretation of these findings. In addition, we also found that patients diagnosed in outpatient clinics achieved VS at a faster rate than patients diagnosed in hospitals (inpatients). This is not surprising as hospitalized patients tend to have opportunistic infections and other comorbidities. Our findings suggest the need for further studies to test novel approaches and interventions to shorten the time to LtC following diagnosis. The finding that high baseline viral load was independently associated with a longer time to VS calls for routinizing viral load monitoring. Therefore, to have good treatment outcomes for PLWH, timely

and effective transitions from diagnosis to LtC should be an important goal. Dombrowski et al. suggested that improving the time to VS from LtC is a shared responsibility of HIV diagnostic facilities, health departments, Ryan White program administrators, HIV clinics, and case management organizations.(27) Given the evidence that undetectable equals untransmittable (or U=U), decreasing the time between patients' linkage to care and VS could be a window of opportunity for decreasing HIV transmission. As such, all stakeholders in Mecklenburg County must work together to address linkage and other cascade gaps. These findings could be more helpful in generating hypotheses for further investigation in prospective studies to understand better the deficiencies in the healthcare delivery system that influences time to VS.

Our study had several limitations. First, we were limited to variables available in the surveillance datasets (demographics, laboratory data). We were, therefore, unable to assess other plausible factors (e.g., adherence to medication, provider characteristics, and social determinants of health that could impact time to VS). Secondly, the unavailability of treatment data meant that we could not control for possible confounders due to the timing of ART, ART regimen type since these data were not collected as part of routine clinical data. As previously noted above, a few patients had achieved VS at the first visit to the provider (LtC). We suspect that these patients might have received treatment elsewhere. They could also be "elite controllers" or "non-progressors." Lastly, the final merged dataset had some missing viral load and CD4 values carried over from the laboratory values dataset.

CONCLUSION

This cross-sectional evaluation described the third metrics in the HIV continuum of care outlined in the National HIV/AIDS strategy for a sample population in Mecklenburg County, North Carolina. We found that only 80% of people who were linked to care and treatment

achieved viral suppression. Given this, a high proportion of individuals did not achieve VS. Among those who achieved VS, early LtC and low VL at LtC were associated with faster VS. A thorough understanding of individual and health delivery system factors associated with community VS in Mecklenburg County is, therefore, necessary to end the HIV epidemic.

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CHAPTER 4: PAPER 3

Evaluation of Loss of Viral Suppression Among People Living with HIV in Mecklenburg County, NC

ABSTRACT

Background: The durability of viral suppression in patients who have achieved suppression has been well documented. However, limited data exist on characteristics associated with a loss of viral suppression or viral rebound in Mecklenburg County to inform HIV program planning.

Methods: A cohort of patients who had achieved initial viral suppression was established for follow-up and examined for possible changes in viral load (VL) status. Patients in the baseline cohort initially achieved viral suppression (VS: defined as having at least one viral load measure of <200c/mL) and then loss of viral suppression (defined as patients with two consecutive VL measures of >200 c/mL). The primary outcome was the loss of VS during the follow-up from 2013 - 2019. We used logistic regression models to examine the relationship between patient-level factors (sex, age, race/ethnicity, HIV risk factors), health system delivery, and the risk of experiencing loss of viral suppression during the follow-up years. In addition, we described patient cohort characteristics and examined factors associated with a loss of viral suppression during the observation period.

Results: Among those in the VS cohort, 155/1159 (13.4%) of patients experienced a loss of viral suppression. 1003/1159 (86.6%) sustained VS during the follow-up period. In the multivariate analysis, after adjusting for other variables, the odds of loss of viral suppression were higher for 13-24 year-olds when compared with patients over 45 years old (OR, 3.06; 95% CI, 1.77 – 5.30); were 2.5 times higher for Black patients as compared with White patients (OR, 2.49; 95% CI, 1.27 – 4.91). However, the probability of loss of viral suppression decreased by 86% with an increase in the average number of monthly care visits (OR, 0.14; 95% CI, 0.04 - 0.46).

Conclusion: We found higher loss of viral suppression rates among adolescents and young adults on ART, particularly young people, and Blacks. While there might have been other

confounding factors (e.g., the social determinants of health that influenced these outcomes), this result may need further investigation to determine causal factors associated with VS loss. Additionally, viral suppression relapse may be mitigated by increasing patients' regular visits to their provider to monitor their viral load routinely.

Keywords: HIV Care Continuum; Loss of viral suppression; Disparities; Health Outcome; Mecklenburg County.

INTRODUCTION

Background

Several research studies have concluded that people living with HIV (PLWH) are unlikely to transmit the virus to a susceptible partner with viral suppression.(1-5) The success of "undetectable = untransmittable" (U = U) to prevent HIV transmission, both at the individual patient and community levels, depends on the maintenance of HIV viral suppression.(6) "Undetectable" describes when a person's plasma viral load (VL) is so low that a laboratory test cannot measure it. "Untransmittable" means that a person with such undetectable viral load has virtually no chance of transmitting HIV to a susceptible person through sexual contact. Furthermore, studies have shown that HIV treatment as prevention (TasP) with VS (<200c/mL) is highly effective in reducing the risk of transmitting the virus. Thus, VL is a vital biomarker to monitor the effectiveness of HIV treatment and the prognosis of patients with HIV.(4) Adherence to antiretroviral therapy (ART) is imperative to sustain viral suppression and prevent sexual transmission of HIV.(7) Virally suppressed individuals are much less likely to transmit the virus and have markedly improved life expectancies.(3, 8-11) However, adherence to ART is critical to achieve VS and prevent sexual transmission of HIV.(7)

Often, due to individual, epidemiologic and clinical factors, some people living with HIV (PLWH) who previously achieved viral suppression may later experience loss of suppression during their HIV care.(12) Loss of viral suppression increases the risk of progression of HIV infection, co-morbidities, and the potential for HIV transmission.(13-15) As such, PLWH must be fully engaged in care and treatment and have achieved sustained viral suppression over time.

In Mecklenburg County, approximately 6,665 people are living with HIV as of 2019.(16) Of those, 270 people were newly diagnosed during the same period. In addition, in 2019, the rate of people living with HIV was 883, and it has the highest number of new cases of any county in

North Carolina.(16) The burden of the disease and the rate of new infections could reflect a failed prevention strategy with HIV positives. We examined viral suppression rebound and its correlates among HIV patients in care in Mecklenburg County who have achieved viral suppression. Identifying factors associated with loss of viral suppression can inform the development of effective, customized strategies to improve health outcomes among the most affected groups.(17) Additionally, despite the widely accepted U=U approach, few studies have examined the risk factors for loss of viral suppression among persons with known viral suppression.(1) It is essential to identify and characterize PLWH with viral suppression, who then rebound for strategic planning and generate hypotheses for further studies.

Several studies have examined the sustainability of viral suppression in HIV clinic populations and analyzed characteristics associated with the loss of viral suppression.(18, 19) However, in Mecklenburg County, no data describes outcomes such as loss of viral suppression in HIV patients in care. To our knowledge, this is the first assessment of factors associated with loss of viral suppression.

METHODS

Study population and setting

PLWH residents in Mecklenburg who were newly diagnosed as HIV-positive at various health care facilities (HCF) are the source population. Our study examined adolescents and adults (aged 13 and above) whose first HIV diagnosis test result date was between January 1, 2013, and December 31, 2019, and who lived in Mecklenburg County at the time of their diagnosis and regardless of whether they linked to care or received care elsewhere subsequently.

Study population and design

We retrospectively evaluated a cohort of PLWH linked to care and who had achieved viral suppression (VL <200c/mL) during the observation period. Surveillance data were extracted from the enhanced HIV/AIDS Reporting System (eHARS) for Mecklenburg County, NC residents. The analysis was limited to HIV-positive adults and adolescents 13 years or older, living in Mecklenburg County and first diagnosed between January 1, 2013, and December 31, 2019. In addition, we identified and analyzed a subset of patients who achieved VS for follow-up and examined for possible loss of suppression. The primary outcome was confirmed loss of VS during the follow-up period. Confirmed loss of VS was defined as having achieved at least one viral load measure of <200c/mL and then rebounding (two consecutive subsequent VL measures of >200 c/mL).

Outcome Measures

Loss of viral suppression was defined as two consecutive plasma HIV RNA measurements above 200 copies/mL, at least 30 days apart. The primary endpoint was a confirmed loss of viral suppression, also referred to as viral rebound. Next, we calculated the proportion of patients with confirmed loss of VS after having achieved VL suppression during the observation period (2VL >200 copies/mL). We considered two VL measurements to avoid including patients with a transient increase above the 200copies/mL threshold referred to as "blips." Finally, we determined the association of individual and health care delivery factors associated with a loss of viral suppression. Patients were followed from the date of initial viral suppression until rebound occurred.

Statistical Analysis

Demographic and clinical characteristics at LtC and first VS (baseline) were summarized using frequencies and proportions for categorical variables and medians, minimum and maximum ranges (Min-Max) for continuous variables. Categorical data were explored using frequency distribution to describe the variables. Chi-square test of independence was used to examine the demographic and clinical characteristics of the outcome measure. To determine the risk factors associated with a loss of viral suppression, we used logistic regression models to examine the relationship between patient factors (sex, age, race/ethnicity, HIV risk factors) and the risk of having a loss of viral suppression during the follow-up period. The following risk factors were examined for possible association with time to viral suppression:

- Sex at birth
- Age at the time of diagnosis
- Race/ethnicity (White, Black, Hispanic, and other)
- Time to linkage to care
- Facility type at which HIV diagnosis was first made, patient in the hospital when first diagnosed
- Potential HIV transmission risk factors (heterosexual exposure, men who have sex with men [MSM], injection drug user [IDU], MSM-IDU, no indicated risk [NIR], or no risk reported [NRR])
- CD4 lymphocyte count.

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). For all analyses, a P-value <.05 was considered statistically significant. In addition, we reported multiplicity-adjusted P-values for multiple comparisons.

Ethical considerations

The UNCC Office of Research Protections and Integrity determined that the study did not constitute human subjects research, and according to federal regulations [45 CFR 46.102 (f)], did not require IRB review (IRB letter of 4 Jan 2018, ref #17-0418).

RESULTS

Study population cohort characteristics

A total of 2,200 patients were extracted from eHARS as newly diagnosed patients for Mecklenburg County. However, upon further review of the data and applying our definition of Mecklenburg County residents and other inclusion and exclusion criteria, 665 patients were determined to be non-County residents, and 14 were children. One thousand five hundred twenty-one patients were linked to care. Of those, 1,159 achieved VS and were included in the final analytical dataset, having met our inclusion criteria, as illustrated by the process's flow diagram. The final dataset was used to describe patients' characteristics and for regression modeling (Figure 4.1).

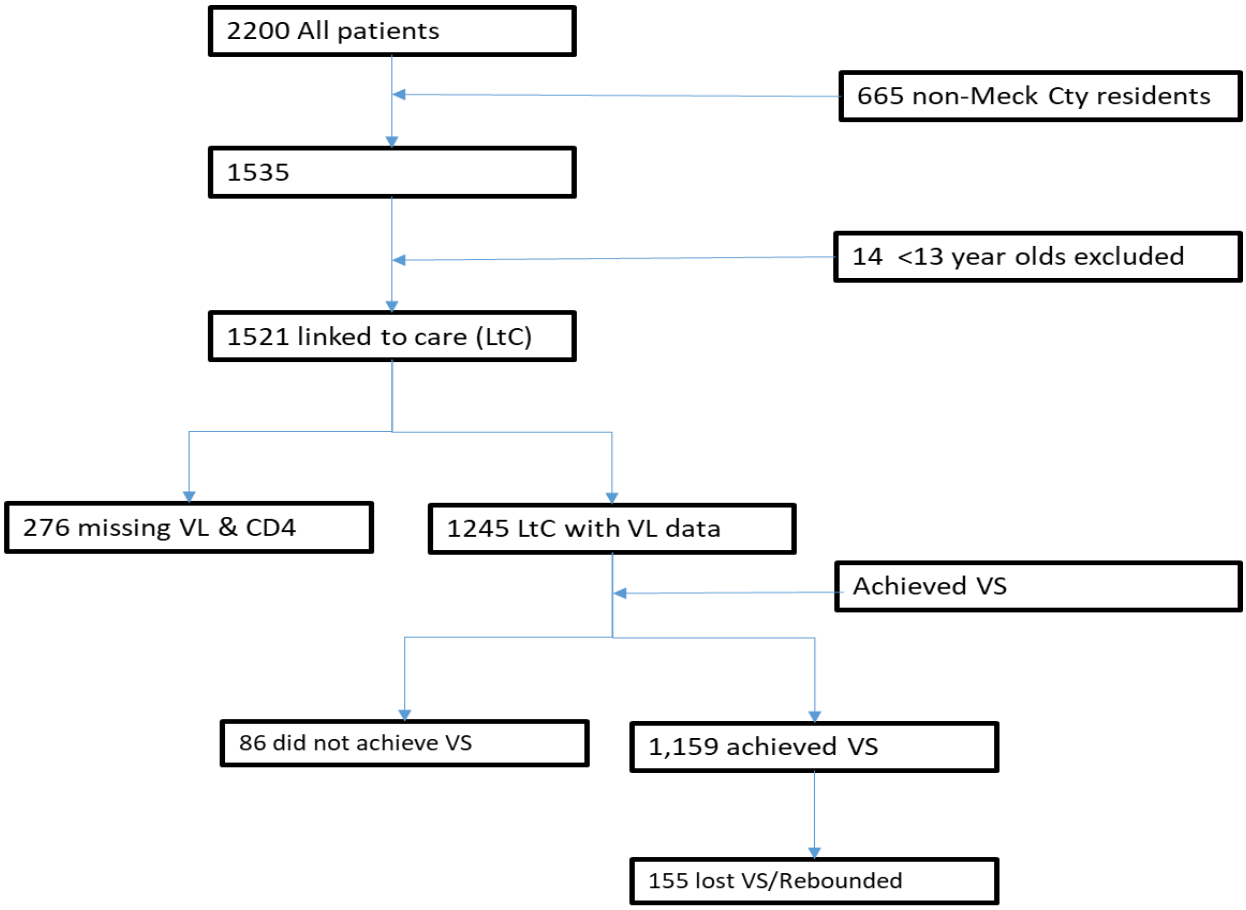

Figure 4.1: Flow diagram showing numbers of patients and inclusion and exclusion criteria in the final dataset used to describe patients' characteristics and regression modeling.

Table 4.1 describes the cohort. The cohort was predominantly male (80%), between 25 and 44 years of age (54.4%), African American (68.5%), and Men who have Sex with Men (MSM) (60.5%). Approximately 89% of the patients were treated as outpatients. Of those, 40% were diagnosed in office clinics. The average number of care visits was 10 (Range: 1-34). The average CD4 count at baseline was 423c/mL (Range: 1-2494), and as of the last visit, the average CD4 was 676 c/mL (Range: 31-2128) (Table 4.1).

155/1159 (13.4%) experienced a loss of viral suppression (two consecutive viral load measures of >200 c/mL) after VS during the follow-up period. Of the remaining 1003, 433 had at least one episode of loss of suppression (one 'blip' of >200 c/mL). Because of our definition of

loss of viral suppression as two consecutive VL measures above 200c/mL, those patients were not included in the analysis or described in this paper in detail.

Table 4.1: Descriptive statistics of patients who achieved VS

Variable	Level	N (%) = 1159
Two successive blips – 1st occasion	No	1003 (86.6)
	Yes	155 (13.4)
	Missing	1
Linkage to care within 30 days after Dx	<=30	786 (67.9)
	>30	372 (32.1)
	Missing	1
Transmission mode	Heterosexual	111 (9.6)
	MSM	701 (60.5)
	MSM-IDU/IDU	30 (2.6)
	NIR-NRR	316 (27.3)
	Missing	1
Age group	13-17	17 (1.5)
	18-24	250 (21.6)
	25-34	406 (35.1)
	35-44	224 (19.3)
	45-54	151 (13.0)
	55-64	89 (7.7)
	65+	21 (1.8)
	Missing	1
Sex at birth	Female	230 (20.0)
	Male	919 (80.0)
	Missing	10

Variable	Level	N (%) = 1159
Race/Ethnicity	White	176 (15.2)
	Black	793 (68.5)
	Hispanic	136 (11.7)
	Other	53 (4.6)
	Missing	1
Patient Status at diagnosis	In-Patient	126 (11.1)
	Out-Patient	1006 (88.9)
	Missing	27
Diagnosis Facility	Office Clinic	464 (40.1)
	Health Department	315 (27.2)
	Hospital	126 (10.9)
	Infectious Disease Clinic	66 (5.7)
	Blood Bank Plasma	56 (4.8)
	Other	131 (11.3)
	Missing	1
CD4 (c/µL)	>=500	275 (23.7)
	350-<499	181 (15.6)
	200-<349	167 (14.4)
	<200	199 (17.2)
	Unknown	336 (29.0)
	Missing	1
Plasma VL (copies/mL)	<=1000 c/mL	148 (12.8)
	>1000 - 10,000 c/mL	157 (13.6)
	>10,000 - 50,000 c/mL	707 (61.1)
	>100,000 c/mL	112 (9.7)
	Unknown	34 (2.9)
	Missing	1

Variable	Level	N (%) = 1159
Total number of visits during the observation period	Mean	10.10
	Median	9.00
	Minimum	1.00
	Maximum	34.00
	Std Dev	5.97
	Missing	0.00
Average # of clinic visits per month	Mean	0.35
	Median	0.29
	Minimum	0.03
	Maximum	2.00
	Std Dev	0.25
	Missing	0.00
Time to link to care (days)	Mean	48.31
	Median	16.00
	Minimum	0.00
	Maximum	1571.00
	Std Dev	134.95
	Missing	1.00
Age at diagnosis	Mean	34.66
	Median	31.00
	Minimum	15.00
	Maximum	87.00
	Std Dev	12.51
	Missing	1.00
Viral load (copies/mL)	Mean	365953.2
	Median	42136.00
	Minimum	10.00
	Maximum	20000000
	Std Dev	1741439
	Missing	35.00

Variable	Level	N (%) = 1159
CD4 at 1st VS	Mean	422.83
	Median	382.00
	Minimum	1.00
	Maximum	2494.00
	Std Dev	305.50
	Missing	332.00
CD4 at last visit	Mean	675.64
	Median	644.00
	Minimum	31.00
	Maximum	2128.00
	Std Dev	310.00
	Missing	594.00

Characteristics associated with loss of viral suppression

Table 4.2 outlines the breakdown and proportion of patients who experienced a loss of viral suppression during the follow-up period. On bivariate analysis, age group (p=<.001), Race/Ethnicity (p=0.011), HCF (p = 0.026), and whether they were first diagnosed as hospitalized or as outpatients (p =0.013) were all associated with loss of viral suppression.

Table 4.2: Univariate association of patients with loss of viral suppression

		First of two consecutive viral load >200 copies per mm³		
Covariate	**Level**	**No N=1003**	**Yes N=155**	**Parametric P-value***
Age group	13-24	205 (20.44)	62 (40)	**<.001**
	25-44	557 (55.53)	73 (47.1)	
	45+	241 (24.03)	20 (12.9)	

Covariate	Level	First of two consecutive viral load >200 copies per mm³		Parametric P-value*
		No N=1003	Yes N=155	
Sex	Female	195 (19.58)	35 (22.88)	0.343
	Male	801 (80.42)	118 (77.12)	
Race/Ethnicity	White	165 (16.45)	11 (7.1)	**0.011**
	Black	673 (67.1)	120 (77.42)	
	Hispanic	121 (12.06)	15 (9.68)	
	Other	44 (4.39)	9 (5.81)	
Transmission mode	Heterosexual	97 (9.67)	14 (9.03)	0.788
	MSM	610 (60.82)	91 (58.71)	
	MSM-IDU/IDU	27 (2.69)	3 (1.94)	
	NIR-NRR	269 (26.82)	47 (30.32)	
Patient Status @ Dx	In-Patient	100 (10.21)	26 (16.99)	**0.013**
	Out-Patient	879 (89.79)	127 (83.01)	
Diagnosis Facility	Office Clinic	411 (40.98)	53 (34.19)	**0.026**
	Health Department	275 (27.42)	40 (25.81)	
	Hospital	100 (9.97)	26 (16.77)	
	Infectious Disease Clinic	62 (6.18)	4 (2.58)	
	Blood Bank Plasma	47 (4.69)	9 (5.81)	
	Other	108 (10.77)	23 (14.84)	
CD4 count (c/µL)	>=500	240 (23.93)	35 (22.58)	0.082
	350-<499	156 (15.55)	25 (16.13)	
	200-<349	145 (14.46)	22 (14.19)	
	<200	161 (16.05)	38 (24.52)	
	Unknown	301 (30.01)	35 (22.58)	
Total number of visits	N	1003	155	**<.001**
	Mean	9.58	13.53	
	Median	8	13	

Risk factors associated with loss of viral suppression

In the univariate logistic regression analysis, the odds of loss of viral suppression were higher for Blacks (OR, 2.67; 95% CI, 1.41-5.07) and other races (OR, 3.07; 95% CI: 1.20-7.87) when compared with Whites. Similarly, the odds of loss of viral suppression were higher for younger age groups 13-24 years (OR, 3.64; 95% CI, 2.13 – 6.24) when compared with those over 45 years old. By contrast, we did not find significant differences in the odds of loss of viral suppression between Hispanic and White.

After adjusting for other factors, the age group 13-24-year-old (OR, 3.06; 95% CI, 1.77 – 5.30). Blacks race (OR, 2.49; 95% CI, 1.27 – 4.91) remained associated with loss of viral suppression. Additionally, the probability of loss of viral suppression decreases by 86% with an increase in the average number of monthly care visits (OR, 0.14; 95% CI, 0.04 - 0.46) (Table 4.3).

Table 4.3: Univariate and Multivariate Logistic Regression of potential associations with loss of VS in patients achieving VS after LtC.

			First of two consecutive viral load >200 copies per mm³		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
Race/Ethnicity	Black	793	2.67 (1.41-5.07)	0.003	0.015
	Hispanic	136	1.86 (0.82-4.19)	0.135	
	Others	53	3.07 (1.20-7.87)	0.020	
	White	176	-	-	

Covariate	Level	N	First of two consecutive viral load >200 copies per mm³ Odds Ratio (95% CI)	OR P-value	Type3 P-value
Age group years	13-24	267	3.64 (2.13-6.24)	<.001	<.001
	25-44	630	1.58 (0.94-2.65)	0.083	
	45+	261	-	-	
HIV stage at 1st VS (cells/cm3)	>=500	275	0.62 (0.37-1.02)	0.059	0.087
	350-<499	181	0.68 (0.39-1.18)	0.168	
	200-<349	167	0.64 (0.36-1.14)	0.129	
	Unknown	336	0.49 (0.30-0.81)	0.005	
	<200	199	-	-	
Transmission mode	MSM[1]	701	1.03 (0.57-1.89)	0.914	0.789
	MSM-IDU/IDU[2]	30	0.77 (0.21-2.88)	0.698	
	NIR-NRR[3]	316	1.21 (0.64-2.30)	0.559	
	Heterosexual	111	-	-	

Multivariate Model

Age group years	13-24 vs. 45+	3.06 (1.77 , 5.30)	<.0001
Age group	25-44 vs. 45+	1.53 (0.91 , 2.59)	0.1099
Ave. # care visits/month	Care Visit /Month	0.14 (0.04 , 0.46)	0.0012
Race/Ethnicity	Black vs. White	2.49 (1.27 , 4.91)	0.0082
Race/Ethnicity	Hispanic vs. White	1.86 (0.80 , 4.36)	0.1510

[1] MSM=Men who have sex with Men;
[2] IDU= Injection Drug Users
[3] NIR=No Incidence Reported NRR=No Risk Reported

DISCUSSION

We found a high rate of loss of VS among patients enrolled in HIV care in Mecklenburg County, North Carolina. A cohort of 1,159 patients who achieved VS and followed up from 2013 to 2019 for possible loss of viral suppression. Of those, 155 (13.4%) experienced the loss of viral suppression. In addition, we found that the odds of loss of viral suppression are higher among those aged 13-24 years and Blacks. Reporting on findings from analysis of 38 jurisdictions in the United States in 2014, Crepaz et al. (2018) noted that Blacks aged 13–24 years had the lowest prevalence of sustained viral suppression, a circumstance that might increase transmission risk potential(11); and that Blacks, in general, had higher rates of loss of viral suppression.(18, 20) Other studies also supported the conclusion that suboptimal VS and transmission risk potential were high for the age group 13-29 years.(21) Barriers such as lack of health insurance, limited access to health services, stigma, health literacy, and lack of trust in providers and the care system might be contributing to these disparities.(11) While our findings were supported by prior published literature, these social determinants of health are potential mediating factors that could potentially influence the results. As a result, further studies are needed to better understand causal factors of loss of viral suppression at the community level.

To achieve effective implementation of U=U, the individual characteristics and population subgroups at risk of loss of viral suppression should be identified, and measures should be taken to develop specific programmatic interventions to address these at-risk population groups. Some patient characteristics such as young age (18, 22) and Race/Ethnicity (19) have been associated with poor treatment adherence. Our findings align with previous studies that indicate that young adults are more likely than older adults to have suboptimal adherence, poorer retention in care, and a higher risk of loss of viral suppression.(23-26)

Adherence to treatment has been recognized as one the most important causes of loss of viral suppression. Using care visits to the provider as a proxy to assess treatment adherence, results from this analysis reflected poor adherence in this population cohort. Our study showed that numerous care recipients had missed clinical visits, yet more clinical visits were associated with lower odds of loss of viral suppression.

We found that low CD4 at enrollment and follow-up was associated with loss of viral suppression. While the descriptive nature of this analysis limits the strength of our findings, it points to areas for further investigation. This finding can help ensure that patients with low CD4 are better supported when they initiate treatment. According to the WHO treatment guidelines, viral load monitoring is recommended for HIV patients to monitor treatment effectiveness.(27) Routine viral load monitoring may help prevent the development of an accumulation of mutations through early detection of patients failing treatment on first-line regimens.(28, 29) Additionally, the relationship between provider characteristics and health care delivery would need further investigation through a prospective study to understand the dynamics of viral load monitoring and durability of VS. Prospective studies would help determine the specific time to loss of suppression for specific demographic groups and could help pinpoint intervention points. Our study findings should help point researchers in directions that could answer the questions we could not answer through a retrospective cohort. While multiple factors at both individual and health delivery system levels may be associated with loss of viral suppression, the long-term sustainability of viral suppression is invariably dependent on access to care and treatment adherence. Retention in care and treatment is crucial for long-term clinical success and prevention of loss of viral suppression.(30)

Our study does have some limitations. First, we do not have specific ART treatment data to allow examination of the effect or contribution of different ART regimens to rebound. In addition, we do not have data to investigate treatment adherence. Data from clinical settings with larger sets of treatment data may be needed to understand better different factors associated with a loss of viral suppression. Finally, the retrospective nature of this data cannot support drawing causative conclusions, and our findings may not be generalizable due to the small size of study population subgroups and the minimal availability of laboratory and clinical data.

In conclusion, we found high rates of loss of viral suppression among adolescents and young adults in HIV care, particularly young people and Blacks. Findings from this study highlight PLWH subgroups that are at higher risk of VS rebound. While there might have been other confounding factors (e.g., the social determinants of health) that influenced these outcomes, this result may need further investigation to determine causal factors associated with loss of VS. Additionally, viral suppression relapse may be mitigated with an increase in patient's regular visits to their provider to monitor their viral load routinely. Results from this surveillance analysis can be used for future hypothesis generation for future prospective studies.

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CHAPTER 5: OVERALL DISCUSSION

DISCUSSION

Our line of investigation examined HCC among newly diagnosed people living with HIV in Mecklenburg County, one of the highest-burden counties of North Carolina. We identified the risk of delayed and non-linkage to care, suboptimal viral suppression, and loss of viral suppression, in particular, among minority populations. We also found healthcare delivery system factors to be associated with these HIV care continuum milestone events. Specifically, we found that young people and Blacks were at-risk of delayed LtC30. The time to VS was longer for those who linked to care greater than 30 days; and young people and Blacks were at-risk for loss of VS. Additionally, we found that loss of viral suppression may be mitigated by an increase in patient's regular visits to their provider to monitor their viral load routinely.

The Centers for Disease Control and Prevention (CDC) recently estimated that about 80% of new HIV transmissions in the United States are from individuals who are either unaware of their status or are aware but not linked to care and none from virologically suppressed individuals.(1) As such, efforts to improve LtC, initiate treatment, and achieve VS will be pivotal to control the epidemic. Despite the availability of highly effective antiretroviral therapy (ART), some population groups and geographic areas continue to experience a high burden of HIV and are not fully benefiting from ART. In Mecklenburg County, one of the jurisdictions with a high incidence of HIV, achieving the National HIV/AIDS Strategy (NHAS) of goals of 90-85-80 will require comprehensive approaches to address the determinants of suboptimal LtC, virologic non-suppression, and loss of viral suppression.(2-4)

There are several ways of assessing the role of the health system and contextual factors in care cascades. Continuums of care are evolving as a method to evaluate health systems' performance in various settings.(5-11) It provides person-centric monitoring and evaluation of PLWH, particularly health systems performance. The proportions of PLWH who transition from

one stage of the care continuum to the next stage reflect how well the healthcare delivery system is functioning. As a result, longitudinal patient monitoring has evolved as an approach for problem identification and targeted intervention at individual or system levels. These sequential steps or milestones in the care continuum help to assess the progression to epidemic control. This assessment of the care continuum underscores the need to monitor the entire spectrum of care to achieve and sustain the NHAS objective of 90-85-80. The United States CDC suggested that local and state health departments conduct continuum of care assessments and implement locally appropriate interventions to address unmet needs.(12-14)

Our investigation line assessed and characterized the demographic and indicators of how well/poorly patients progressed through the HCC. This investigation will be a marker of the effectiveness of the healthcare delivery system. However, it does not examine the factors (e.g., mechanisms of referral, availability of resources & expertise, the logistics of healthcare delivery and follow-up, etc.). In addition, we quantified the proportion of people diagnosed with HIV, linked to care, and those who achieved VS within one year of initial diagnosis, and among those, the proportion who lost viral suppression. We described and presented our results in three papers.

The first article in this dissertation assessed initial LtC as the first stage of the HCC. We found that only 64% of newly diagnosed HIV-positive individuals were linked to care within 30 days, falling short of the first NHAS goal of 85% of patients who are aware of their status to be initiated on treatment. We also found that Blacks, Hispanics, and other race groups have a 50% probability of delayed LtC30 compared to Whites. LtC30 was 40% lower for males when compared with females. Our analysis points to some gaps but more studies will be needed to identify specific interventions to improve linkage and achieve the HIV strategic plan linkage goals to reach the 85% within one month. These interventions could be aimed at those with high

chances of not linking, such as Blacks, Hispanics, and those identified as males at birth. Our study highlights the inherent constraints and challenges in the healthcare delivery system both at individual and healthcare delivery system levels. At the individual level, Black or African Americans, Hispanics, and other minorities had higher odds of delayed LtC30 than Whites. In addition, young adults seem to have difficulty linking to appropriate health care compared with older adults. Delayed linkage to care deprives youth living with HIV of the benefits of HIV treatment and risks increased HIV transmission.(15) 76% of older adults were linked to care within one month compared to 60% of young adults. This is counter-intuitive because one would expect that young adults are more likely to be educated, gainfully employed with health insurance, have a better understanding of the benefits of life-saving treatment available, and are more physically active to visit healthcare facilities regardless of their proximity. The reality is somewhat different, and from this analysis, the situation might have been compounded by health services available within their geographic confines. One of the questions that will warrant a further investigation is whether a location is relevant to the risk assessment? As we found out, people who did not link or linked late clustered in specific zip codes. The Charlotte "Arc" and the "Wedge" are interesting phenomena to describe the intersection of social determinants of health, access to care, and the resulting health outcomes. This spatial pattern essentially created two geographic regions in Charlotte based on social determinants of health, including the number of households, average income, and the proportion of employed residents to the total workforce, racial groups, and population density. The map shows clear patterns in the distribution of these statistics and disparities and establishes a baseline to understand the inequity results better.(16) The "arc" described communities of color and concentrated poverty. The mapping has been validated with other diseases like COVID. The resulting output is consistent with the arc and the

wedge – the phrase to describe the inequity distribution of resources. Fitting our map to describe the arc and the wedge, the areas of high counts of HIV diagnoses and high counts of delayed LtC30 are consistent with the "arc" where households are densely populated (about 48% of the total city population). The average income is below the city average, and they constituted about 67% minority population. By contrast, our map's areas of low HIV diagnoses and low counts of delayed LtC30 corresponded to the "wedge" where the residents are 31% of the total city population. The average income is above the city average consisted of 63% white. This highlight and reflects disparities in care access racial and socioeconomic groups as previously documented by other researchers(17) and calls for strengthening the health system(18) to support population subgroups disproportionately impacted by poor access to care. From a structural perspective, further studies might be needed to assess the impact of health insurance on LtC and other social determinants of health to understand poor LtC in the affected communities better. For the young adults with suboptimal LtC, novel ideas like leveraging mobile health interventions like a mobile phone-enabled app to improve linkage to HIV may be helpful.(19) Overall, epidemic control will require aggressive linkage to care through a concerted effort from individuals and the county government. Researchers concluded that the average time from HIV infection to linkage-to-care needs to be reduced to ensure that HIV treatment-as-prevention policies are effective.(20)

The second article in this dissertation examined time from linkage to care (LtC) to VS and determined median time to first VS (<200 c/mL). In the assessed cohort of eleven hundred individuals, the median time to VS among those linked was 80 days. Among 1,134 newly diagnosed persons linked to and with reported follow-up VL results, 939 (82.8%) achieved VS within 12 months. Time to VS was shorter among those who linked within 30 days. This is clinically and epidemiologically important in the sense that those patients with delayed LtC and

with no suppressed viral load continue to constitute a risk for transmission of the virus to susceptible partners. Our results might highlight individual and healthcare delivery system factors, but further studies will be required to investigate possible solutions for achieving timely viral suppression. Timely LtC will accelerate ART initiation, which is critical to establish the continuum of care and ultimately VS. Research studies have demonstrated that if a patient receives the standard of care at the appropriate time, VS may be achieved within six months. In addition, studies have established that timely LtC will lead to early VS. Early linkage to medical care is required for the individual and population benefits of treatment to be realized.(21) These results further highlight the importance of linkage in the later part of the cascade. In summary, there was a positive association between baseline viral load, early LtC, type of outpatient facilities at which the diagnosis was established, and time to achieve VS.

The third article in this dissertation describes a study in which we investigated the durability of VS by examining the proportion of VS among adults and adolescent PLWH who were diagnosed, linked to care, and became virally suppressed to <200c/mL and later experienced the loss of viral suppression. We found that of those who achieved the initial VS, 86% achieved durable VS during the follow-up from 2013 to 2019, while about 13% had a loss of viral suppression. The odds of loss of viral suppression were higher for young adults, 13-24-year-olds when compared with patients over 45 years old (OR, 3.06; 95% CI, 1.77 – 5.30). After adjusting for other variables, the odds of loss of viral suppression were 2.5 times higher among Blacks than Whites (OR, 2.49; 95% CI, 1.27 – 4.91). These findings could have important implications but are limited by the retrospective nature of the study.

Nonetheless, Blacks who shared the disproportionate burden of HIV in this study were the same racial demographic group associated with a high risk of loss of viral suppression even

when linked to care. Second, our findings are consistent with other studies that have also found higher rates of suboptimal linkage and suboptimal cascade outcomes among minority populations (e.g., Blacks and Hispanics). Third, loss of viral suppression has prevention implications and could result in ongoing HIV transmission. Patients with viral relapse are more likely to transmit HIV to their sexual partners. Further, results from this study show that the probability of loss of viral suppression decreases with increased monthly care visits (OR, 0.14; 95% CI, 0.04 - 0.46). This could imply that interventions are needed during the first months of ART initiation. We recommend further studies that build on these findings, enabling Mecklenburg County to improve support for specific demographic groups, especially early when they initiated ART.

Multiple factors may have influenced the poor health outcomes found in this line of investigation for young Black people who are disproportionally impacted. First, there is evidence that HIV is more prevalent in low-income communities. The combination of high poverty and disease could result in limited healthcare access by the affected people. Second, the Black race is associated with poverty, having a poverty rate that is twice that of White individuals.(22) They disproportionately reside in the South and are disproportionately affected by HIV.(23) They accounted for 54% of new diagnoses in 2014.(24) Many Black communities affected by HIV in the southern United States are also disproportionately affected by social and structural determinants of health (SDH) that have historical and political roots of injustice, poverty, racism, and unequal opportunities to access education and employment, all of which contribute to HIV-related racial/ethnic disparities.(25) In addition, recent data reflects an increased prevalence of young Black men who have sex with men (BMSM).(26) Our findings of young Blacks being at-

risk for delayed LtC30, suboptimal VS, and loss of VS suggest that these social determinants of health factors could be playing a role in the disparity.

Several social determinants of health (e.g., socioeconomic status, health insurance status, health literacy) contribute to health outcomes.(27) Therefore, there is a need for concerted efforts to develop sustainable interventions to improve the linkage of newly diagnosed HIV-positive individuals promptly, improve access to and engagement in care and treatment, and achieve VS. As a result, a multifaceted strategy may be needed for intervention in this population group.

In 2019, the national initiative Ending the HIV Epidemic (EHE) was announced to focus on select states and counties. Mecklenburg County is one of the jurisdictional areas experiencing the "southern" HIV epidemic and is being prioritized for the Ending the HIV Epidemic (EHE) strategy. The factors contributing to HIV-related disparities in the South are multilayered, and custom solutions will be necessary to address the disparities.(28) In Mecklenburg County, the GZM policy initiative is a great start. This line of investigation, the findings, and the 90-85-80 strategy metrics generated from the studies will be helpful to implement the initiative. The results show that about 64% were LtC which did not meet the national goal of 85%. More work needs to be done by the County to achieve this target. However, about 80% did achieve VS within one year, which meets the national goal. Despite this accomplishment, an estimated 13% experienced a loss of suppression. Again, further studies of a prospective nature are needed to characterize this group to inform the design of interventions that facilitate better access to care.

The next steps with this line of investigation supporting the GZM are to examine the healthcare delivery system's impediments that prevent timely LtC30, VS, and loss of viral suppression among PLWH. Beyrer et al. (2021) suggested that to achieve the EHE initiative in the United States, fundamental barriers and challenges need to be addressed and research efforts

sustained.(29) To achieve EHE in the County, policy initiatives and implementation must be based on scientific findings and data-driven decision-making with surveillance. This line of investigation has produced some data and information that can be used to generate hypotheses. Thus, further work will be needed with hypothesis testing in comparative studies.

The Ryan White HIV/AIDS Program (RWHAP) that supports access to medical care to PLWH will need to be scaled-up and strengthened in the affected communities identified as part of our investigation in the "arc" and the "wedge." RWHAP-funded services have been successful at improving outcomes and reducing disparities for PLWH along the care continuum.(30) With regard to further investigations, due to the scope and limitations in the dataset, we did not look at impediments in the health care delivery system. Given this, looking for specific impediments might be the next step in investigating root causes. Interventions should also be directed at health system impediments to these groups accessing care. In addition, a metric that could be relevant and revealing is the time from diagnosis to VS will be very helpful. While this was not included as part of the line of investigation, it does require an examination to provide a composite view of characteristics associated with VS among PLWH in the County.

Our data and studies did have some limitations. First, we used routine surveillance data collected at the time of HIV diagnosis. Given this, critical data elements such as health insurance, socioeconomic status, education, employment status that influence health care access were not available. In addition, many other person-level factors such as privacy concerns, mental health issues, family support, and perhaps knowledge and beliefs about HIV/AIDS that may impact the time between the diagnosis and the link to care were not available in the dataset. Second, using samples date (when the laboratory samples were collected) as the epidemiological marker for linkage may overestimate linkage as some may still drop out before actual initiation,

especially if results were not available in a reasonable time. In addition, we were limited to the variables available in the surveillance datasets (demographics, laboratory data). We were, therefore, unable to assess other plausible factors (e.g., medication adherence, provider characteristics, and social determinants of health) that could impact time to VS. The unavailability of treatment data meant that we could not control for possible confounders due to the timing of ART and the ART regimen type since these data were not collected as part of routine clinical data. Data from clinical settings with larger sets of treatment data may be needed to understand better different factors associated with a loss of viral suppression. Third, the surveillance data represent a specific period. The studies that looked at data over seven years (2013-19) have not examined whether the metrics of the HCC changed over time. Finally, this is a retrospective analysis. As such, no causal relationship can be inferred, but the findings can generate hypotheses for further studies.

CONCLUSION

Our findings, summarized in three major papers in this dissertation, provided the first primary comprehensive evaluation of the HCC in Mecklenburg County, NC, and could benefit the implementation of "Getting to Zero Mecklenburg" community plan to reduce new cases of HIV in Mecklenburg County. In addition, the research study generated hypotheses for further research studies, including questions and ideas that warranted further scientific inquiries from this investigation. Additionally, we identified weaknesses in HCC. This assessment aimed primarily to identify weaknesses in the HCC and subpopulations disproportionally affected by weaknesses in the healthcare delivery system. This put PLWH at risk of poor access to care and, ultimately, poor health outcomes. In addition, we gained insight into the epidemiologic landscape of HIV, the high-risk subgroups, their disproportionate impact, and their geographic

correlate in the County. Finally, the line of investigation generated data for strategic planning and policy implementation for the G2Z-Meck initiative.

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