New-Onset Seizures in Children with HIV

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Presenting for the CHASE Study team
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Outline

- **Overview of neurologic complications of HIV**
- **Brief review of published literature on seizures and HIV**
- **Results from the Cohort of HIV-Associated Seizures and Epilepsy in Zambia (CHASE) Study**

Why talk about seizures and HIV?

Seizures are common in children with HIV in resource-limited settings

Seizures in children with HIV are potentially preventable and treatable

36.7 MILLION

people worldwide are currently living with HIV/AIDS.

2.1 MILLION CHILDREN

worldwide are living with HIV. Most of these children were infected by their HIV-positive mothers during pregnancy, childbirth or breastfeeding.

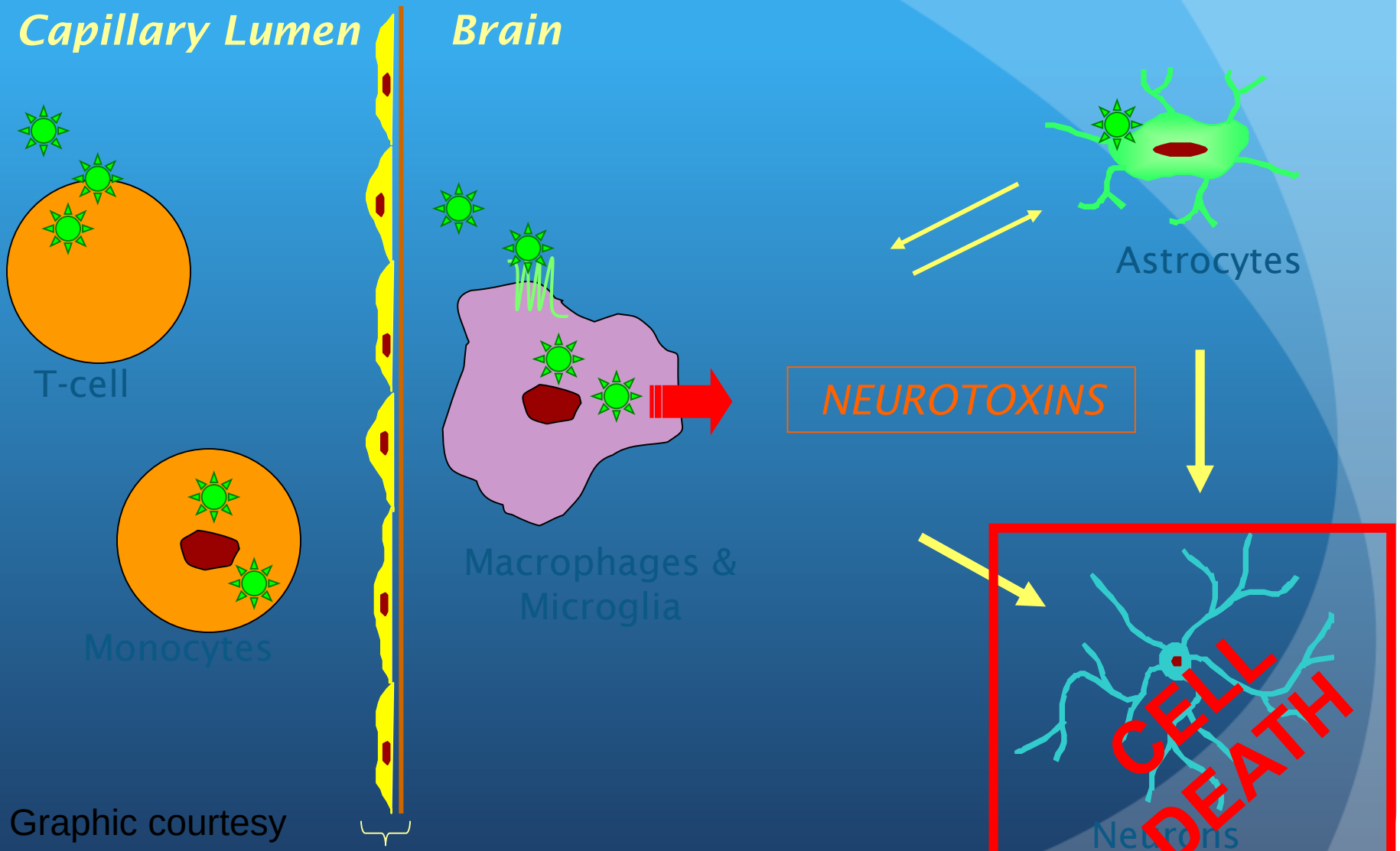
How does HIV affect the brain?

- Direct effects
  - HIV-associated Neurocognitive Disorders
  - HIV-associated cerebrovascular disease
  - Primarily mediated through immune activation and inflammation

How does HIV affect the brain?

- Direct effects
  - HIV-associated Neurocognitive Disorders
  - HIV-associated cerebrovascular disease
  - Primarily mediated through immune activation and inflammation
- Indirect Effects
  - Opportunistic Infections
  - CNS Malignancies
  - Primarily mediated through immune suppression

HIV neuropathogenesis



Graphic courtesy
of Dennis Kolson

Background

- New-onset seizures relatively common among children with HIV in resource-limited settings
- 5-17% of adults with HIV developed epilepsy in pre-cART era
- Minimal published data in children

Birbeck et al 2012; Kellinghaus et al 2008

Prior Studies in Adults	Most common etiologies for seizures	Other causes	Prevalence	% on ART
Bartolomei (France, 85-90)	Toxoplasmosis	PML HAND Drugs	Not reported	0
Wong (NYU, 1984-88)	Toxoplasmosis	Lymphoma Electrolytes Cryptococcus	11%	0
Pascual-Sedano (Spain, 1999)	Toxoplasmosis Drug toxicity or withdrawal	HAND PML	3%	Not reported
Kellinghaus (Germany, 1992-2004)	Toxoplasmosis PML	TBM Cryptococcus Drug withdrawal	6.1%	90%
Chanda (India, 2000)	Toxoplasmosis	Crypto; TB; PML; HAND	5%	Not reported
Millogo (Burkina Faso 2000-2004)	Toxoplasmosis	TBM Crypto	Not reported	Not reported

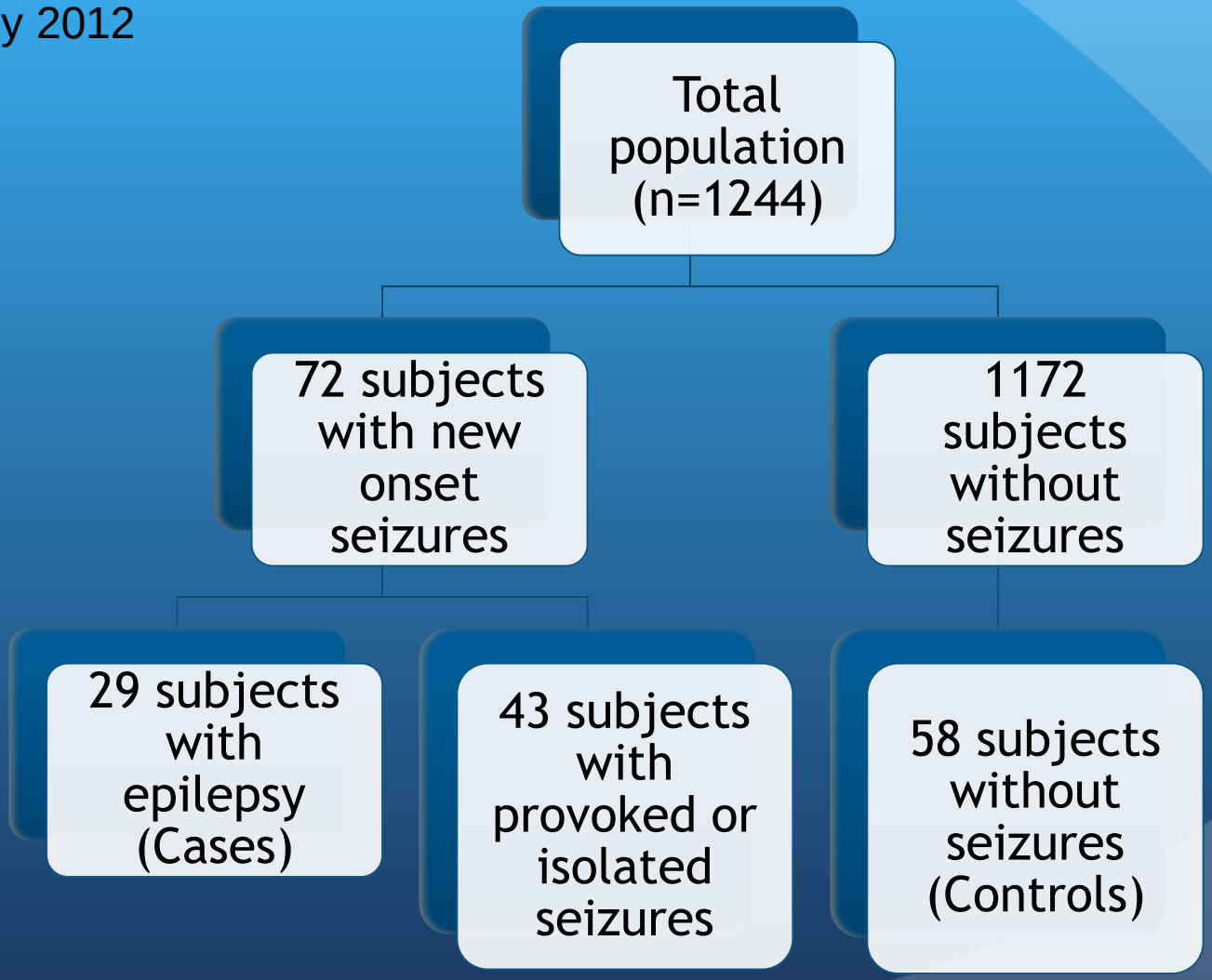
Prior Studies in Children	Most common etiologies for seizures	Other causes	Prevalence	% on ART
Tellechea-Rotta 2003 (Brazil 2003)	CNS Infections	HIVE	6%	Unknown
Samia 2012 (South Africa)	Unknown	TBM Cryptococcus	7.6%	100%
Bearden 2015 (Botswana 2003-2012)	CNS Infections	HIVE	6%	100%
Burman 2019 (South Africa)	Unknown	TBM Other meningitis	23% *	98%

Background: The Epilepsy in Children with HIV in Botswana Study

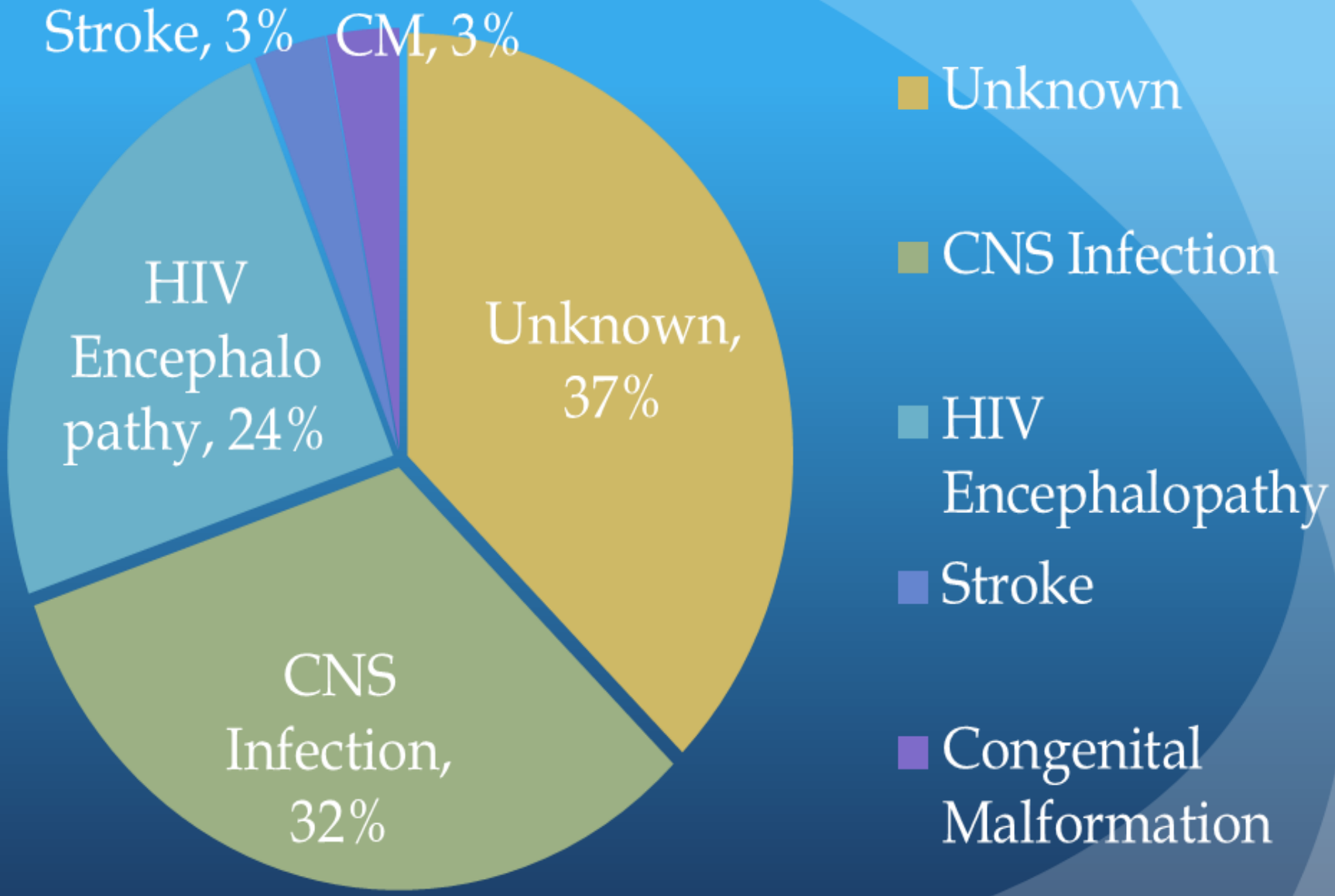
Methods	Retrospective cohort with nested case control component
Sample	All patients with HIV <18 years old and on ART followed at Princess Marina Hospital Pediatric Center of Excellence in Gaborone, Botswana
Sampling procedure	Electronic and manual search of medical records with prospective verification
Imaging	MRI and/or CT performed in 70% of subjects
Laboratory Testing	Standard Clinical testing. Lumbar puncture was performed in 51% of subjects; available tests included cryptococcal antigen, TB culture, VZV and HSV PCR.

Results

From Bearden et al
Neurology 2012



Epilepsy Etiology



Risk Factors for Epilepsy: Univariate analysis

	Odds ratio (with 95% CI)	P-value
CD4 count<200	2.6	0.05
WHO Stage 4	2.8	0.02
Developmental Delay	16.5	<0.001
History of HIVE	20.5	0.004

Risk factors for epilepsy: Multivariable model

- In the multivariable model, only HIVE and history of CD4 count<200 remained significant.
- Since these tend to be late complications of HIV infection, this would suggest that early treatment with ARVs might be helpful in preventing neurologic complications of HIV.

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Early Antiretroviral Therapy is Protective against Epilepsy in Children with Human Immunodeficiency Virus Infection in Botswana

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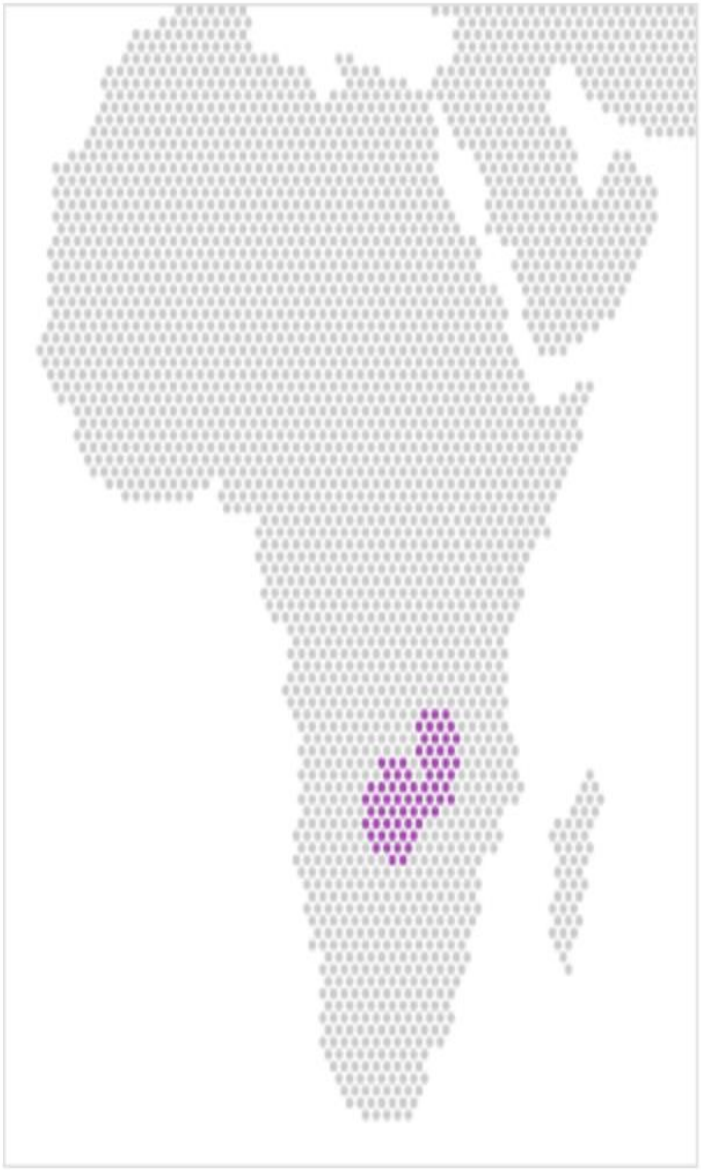
Limitations of Prior Studies

- Old, largely pre-cART era studies
- Primarily retrospective
- Determination of etiology not standardized
- Minimal testing/imaging
- Mortality not able to be assessed

CHASE

- The Cohort of HIV-associated Seizures (CHASE) is a prospective cohort study examining etiology and outcomes in children with HIV presenting with new onset seizures

HIV AND AIDS IN ZAMBIA



Zambia (2016)

1.2 million people living with HIV

12.4% adult HIV prevalence

59,000 new HIV infections

21,000 AIDS-related deaths

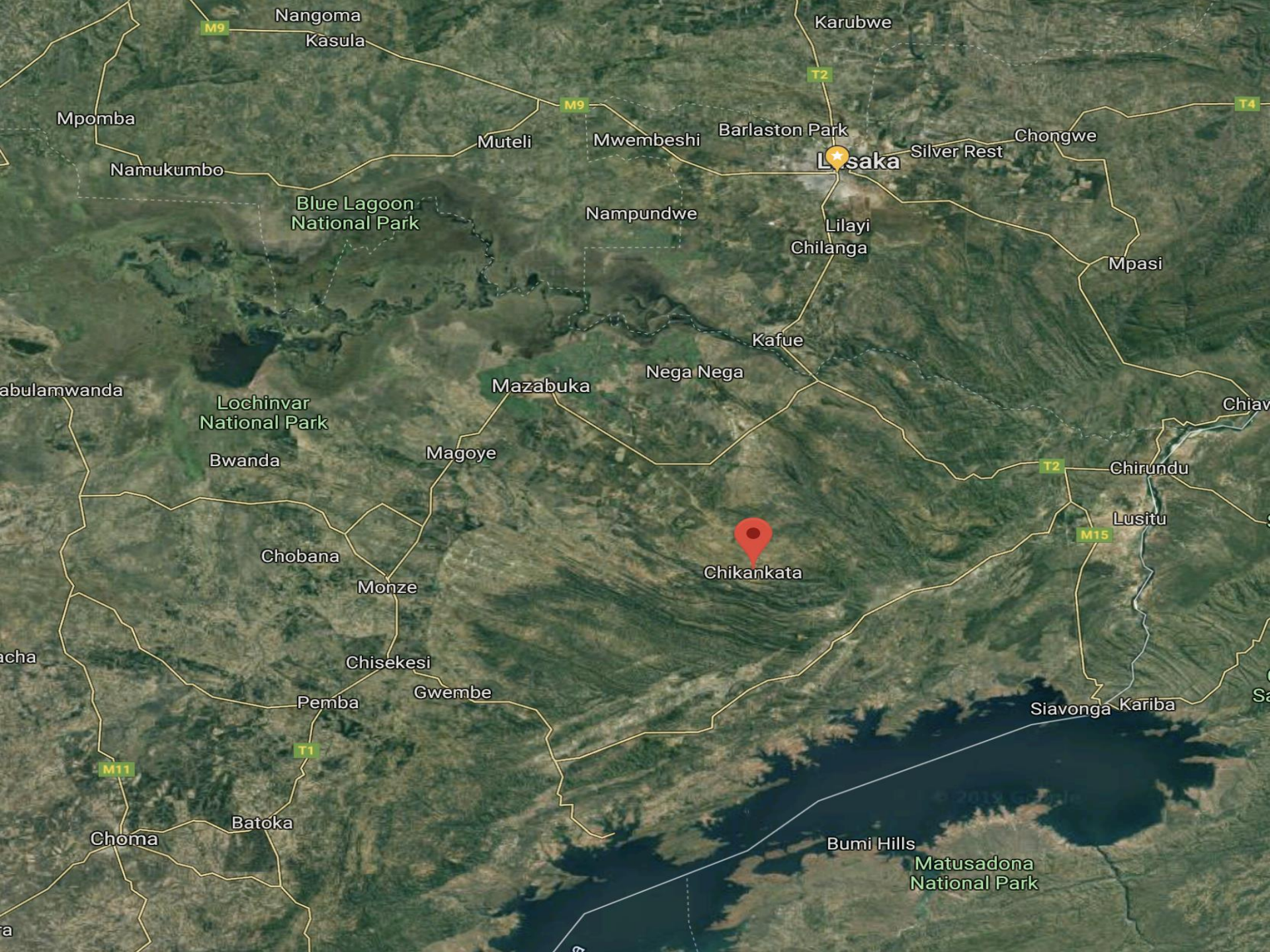
67% adults on antiretroviral treatment

52% children on antiretroviral treatment

Source: UNAIDS Data 2017

Methods

- Study Design: Prospective Cohort with case control component
- Population: All children with HIV presenting with new onset seizures.
- HIV+ Controls with no history of seizures recruited from outpatient clinics
- Additional study sites at two rural sites (Monze and Chikankata) are enrolling both children and adults


Nangoma
M9
Kasula
Karubwe
T2
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Mpomba
Muteli
Mwembeshi
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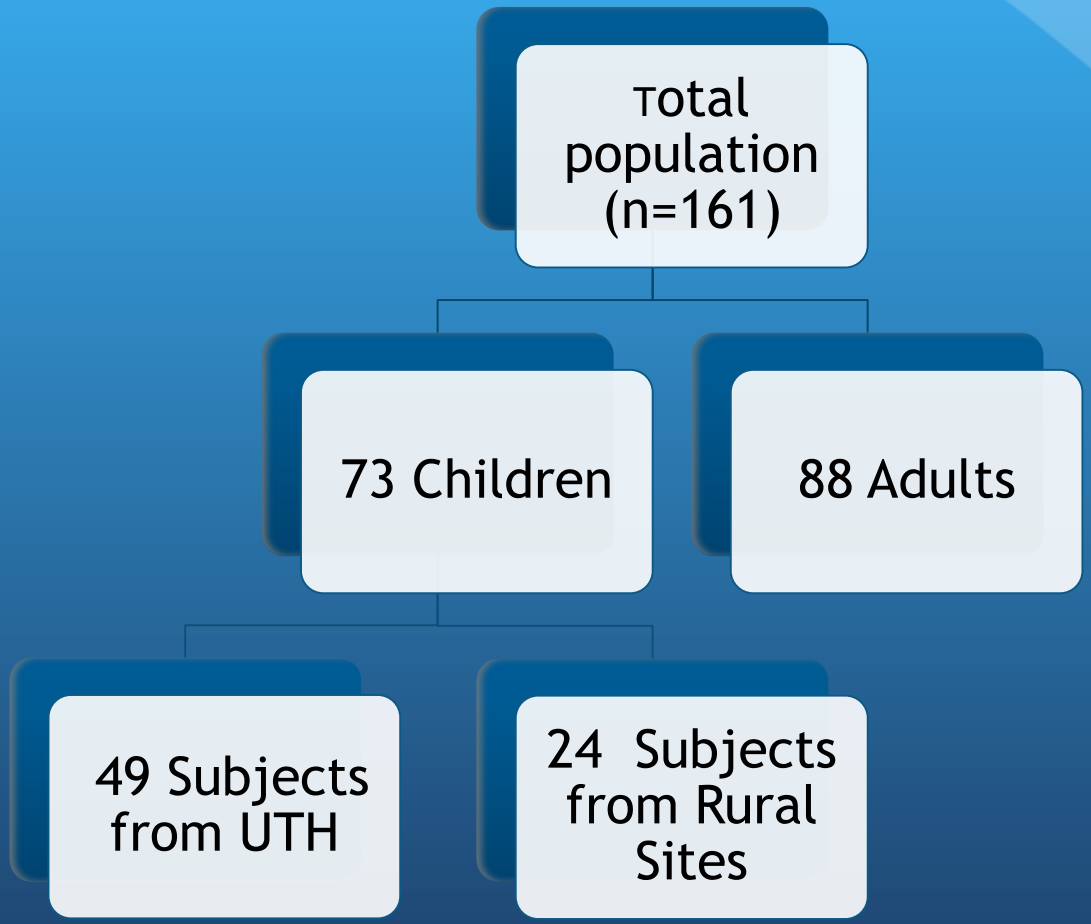
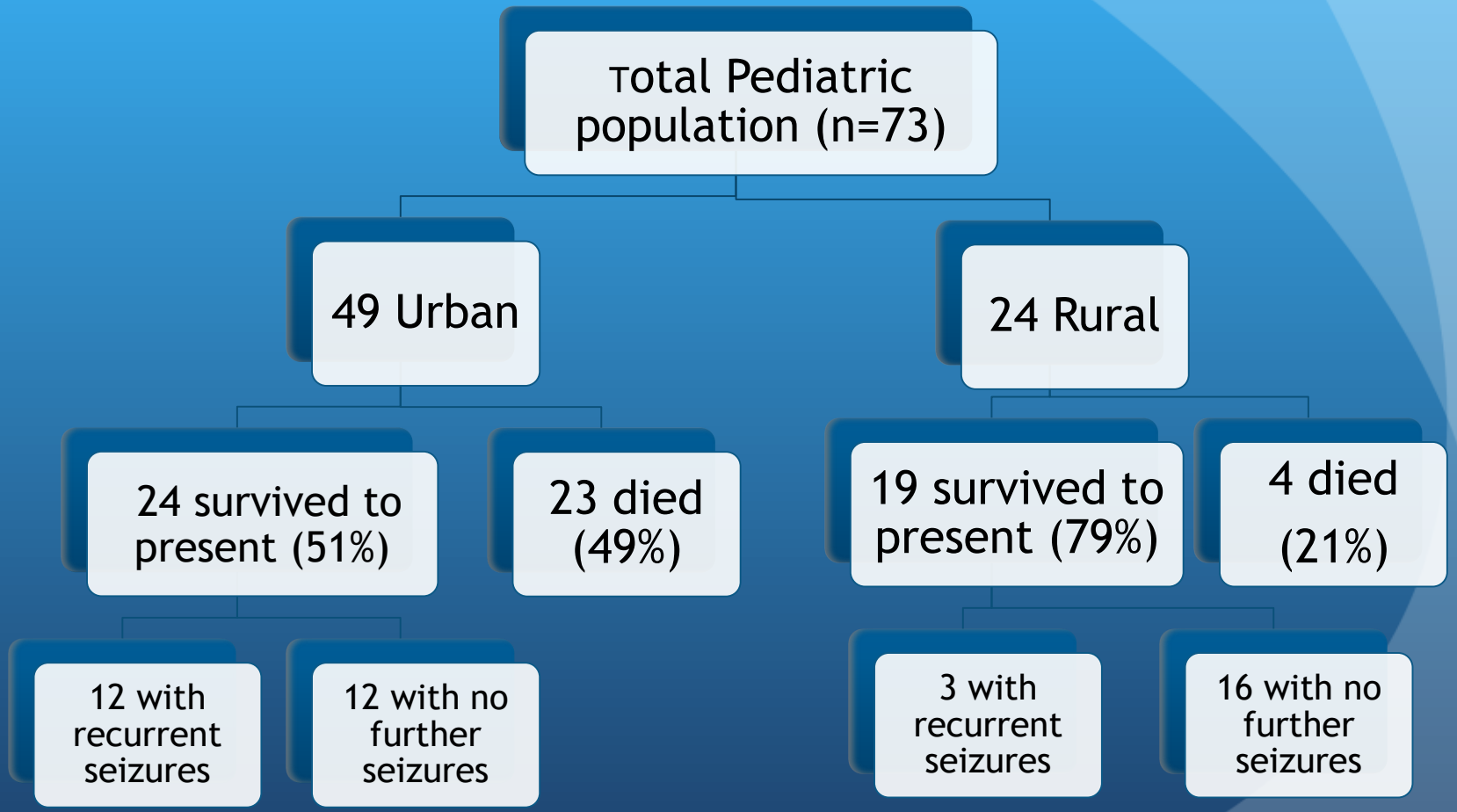
Chongwe
Silver Rest
Namukumbo
Lusaka
Blue Lagoon
National Park
Nampundwe
Lilayi
Chilanga
Mpasi
Kafue
Nega Nega
Mazabuka
Lochinvar
National Park
Bwanda
Magoye
T2
Chirundu
Lusitu
M15
Chobana
Chikankata
Monze
Chisekesi
Gwembe
Pemba
Siavonga
Kariba
T1
M11
Batoka
Choma
Bumi Hills
Matusadona
National Park

Methods	Longitudinal prospective study
Sample	All patients with HIV presenting to the University Teaching Hospital or one of two rural sites with new-onset seizures.
Sampling procedure	All new admissions to surveyed by study nurse, subjects prospectively enrolled
Instruments	Standardized questionnaire to assess demographics, clinical history, HIV history, nutritional status, and socioeconomic status
Neuropsychological testing	Universal Test of Intelligence-2 Malawi Developmental Inventory
Imaging	MRI and/or CT performed in all surviving subjects at UTH
Laboratory Testing	Serum and CSF Viral load Serum and CSF cryptococcal antigen CSF Gene Xpert, EBV, CMV, JC Virus, HSV, HHV6

Results: Subjects Enrolled



CHASE Outcomes



Results: Demographics and Clinical Characteristics

	Urban Site (n=49)	Rural Sites (n=24)
Sex	57% male	58% male
Age in years	6 (IQR 2-11 years range 3 months-16 years)	6 (IQR 2-9 years; range 3 months-14 years)
On ART	54%	33%
Viral load undetectable	1 (3%)	3 (13%)
WHO Stage 4	75%	45%
CD4 < 200	45%	26%

Etiology of Seizures	N (%) Total n=73
CNS Infection (TBM, Cryptococcal meningitis, PML, bacterial meningitis, viral meningoencephalitis)	26 (35%)
HIVE/severe malnutrition	13 (18%)
Hyponatremia	9 (12%)
Nephropathy with hypertensive encephalopathy	3 (4%)
Severe Malaria	2 (3%)
Neurocysticercosis	2 (3%)
Unknown* (Information limited by lack of LP)	18 (25%)

Key Risk Factors for Death: Univariate analysis

Variable	Odds Ratio	P-Value
Hyponatremia (Serum sodium on admission <130)	14.0	0.02
CD4<200	8.9	<0.001
CNS Infection	4.2	0.006
WHO Stage 4	4.0	0.02
Glasgow Coma Scale < 10	3.3	0.02

Risk Factors for Death: Multivariable Analysis

- Low CD4 count
- WHO Stage 4
- Hyponatremia
- Low Lansky score (rating of pre-hospitalization function)
- Age under 5
- Site
- This model explains 58% of the variance in mortality

Key Risk Factors for Recurrence: Univariate analysis

Variable	Odds Ratio	P-Value
Hyponatremia (Serum sodium on admission <130)	Perfect prediction (no recurrence in hyponatremic group)	n/a
Focality	5.0	0.02
Status epilepticus	3.4	0.07
WHO4	2.3	0.2

Key Risk Factors for Seizures: Univariate analysis

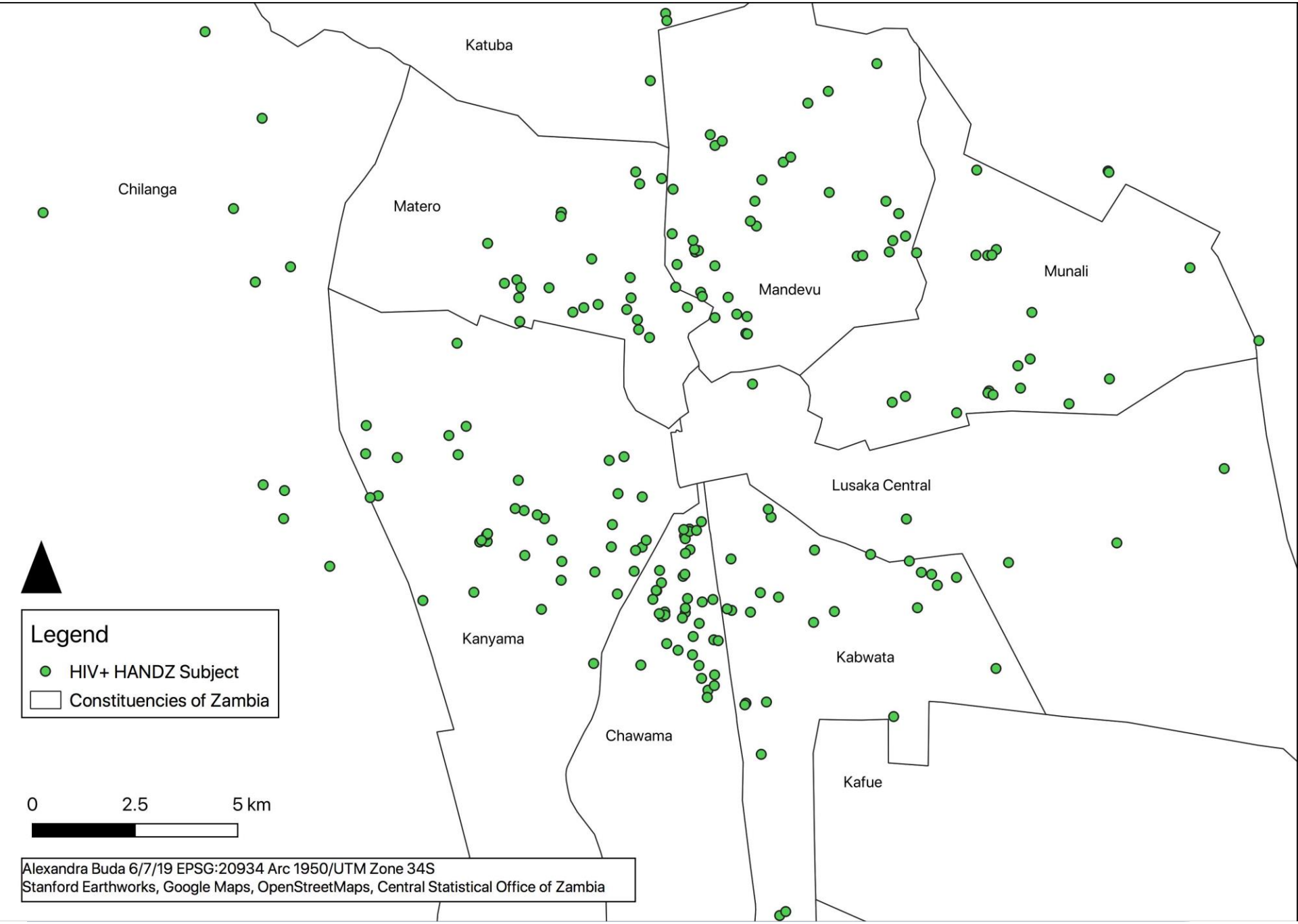
Variable	Odds Ratio	P-Value
Undetectable Viral load	0.02	<0.001
CD4<200	6.3	<0.001
WHO Stage 4	2.2	0.005

Risk Factors for Seizures

- In the multivariable analysis, only undetectable viral load and low CD4 count remained significant.
- This model explained 48% of the variance in seizure outcomes
- What drives differences in ART coverage/effectiveness between groups?

Evaluating neighborhood effects

- Location of all urban subjects residences in each group was mapped using Quantitative Geographic Information Systems (QGIS)
- Clustering of cases and socioeconomic characteristics was evaluated using SATscan.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Chilanga
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Mandevu
Munali
Lusaka Central
Kanyama
Kabwata
Chawama
Kafue
Legend
HIV+ HANDZ Subject
Constituencies of Zambia
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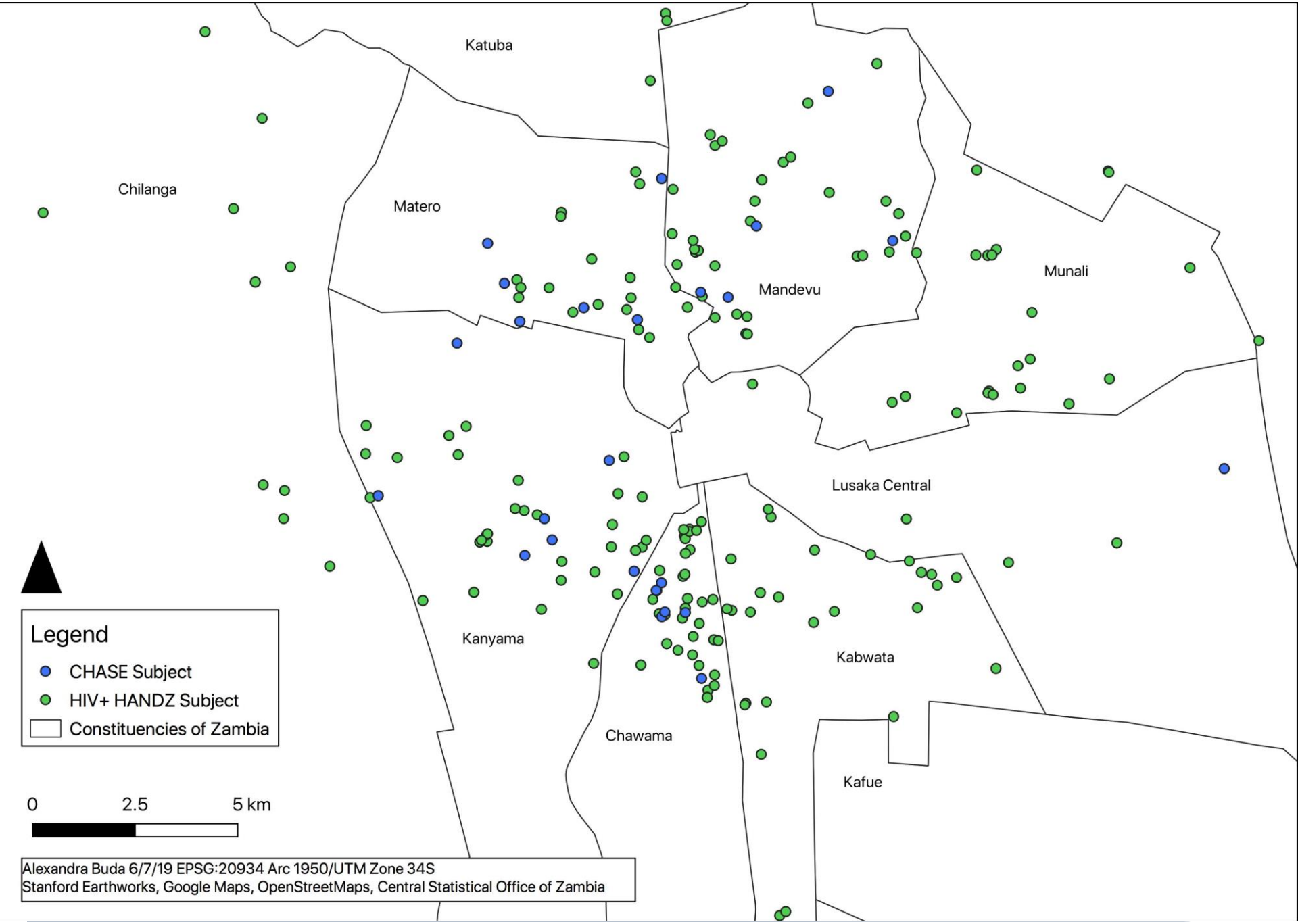
Alexandra Buda 6/7/19 EPSG:20934 Arc 1950/UTM Zone 34S
Stanford Earthworks, Google Maps, OpenStreetMaps, Central Statistical Office of Zambia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CHASE Subject
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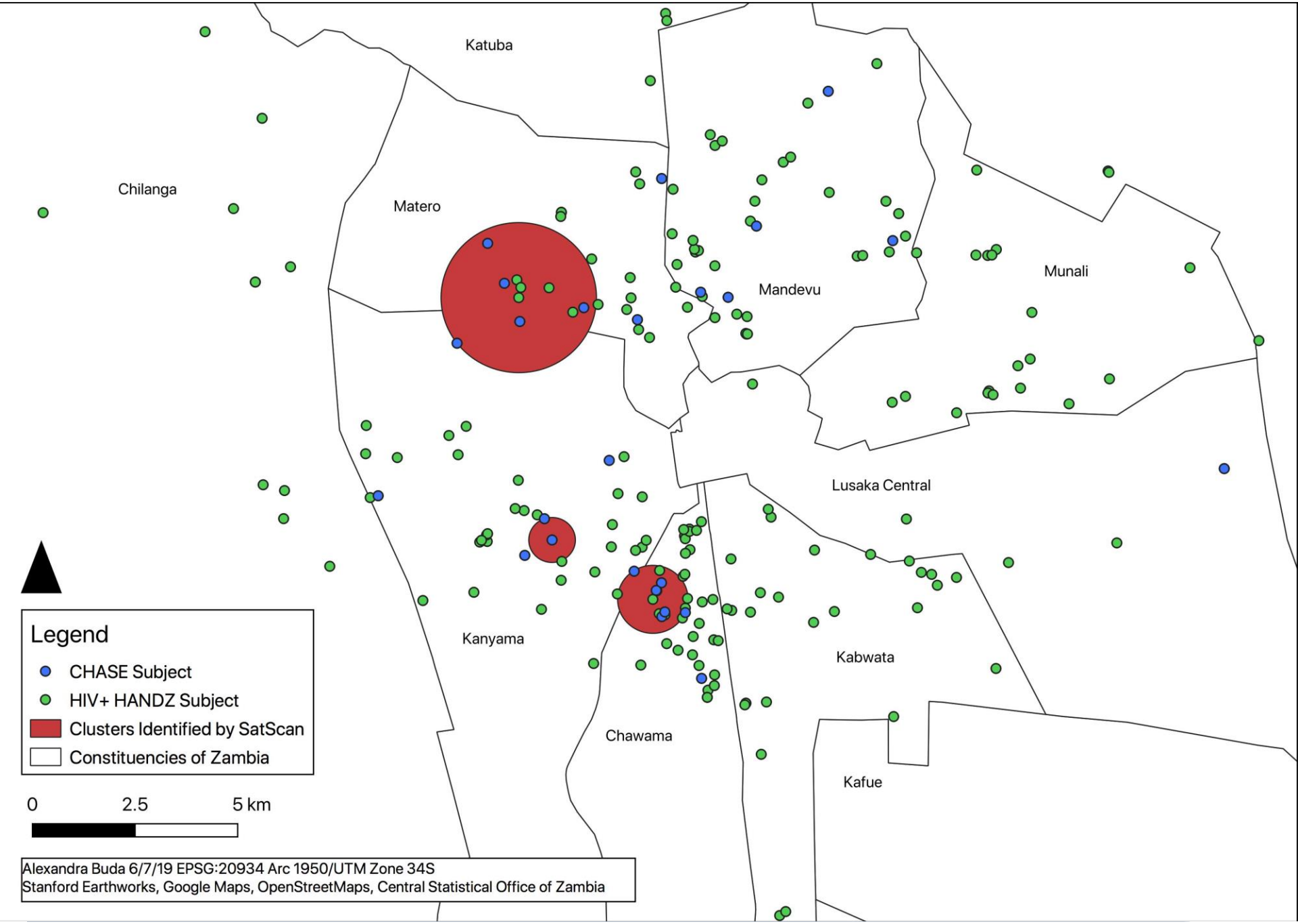
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Lusaka Central
Kanyama
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Chawama
Kafue
Legend
CHASE Subject
HIV+ HANDZ Subject
Clusters Identified by SatScan
Constituencies of Zambia
0
2.5
5 km
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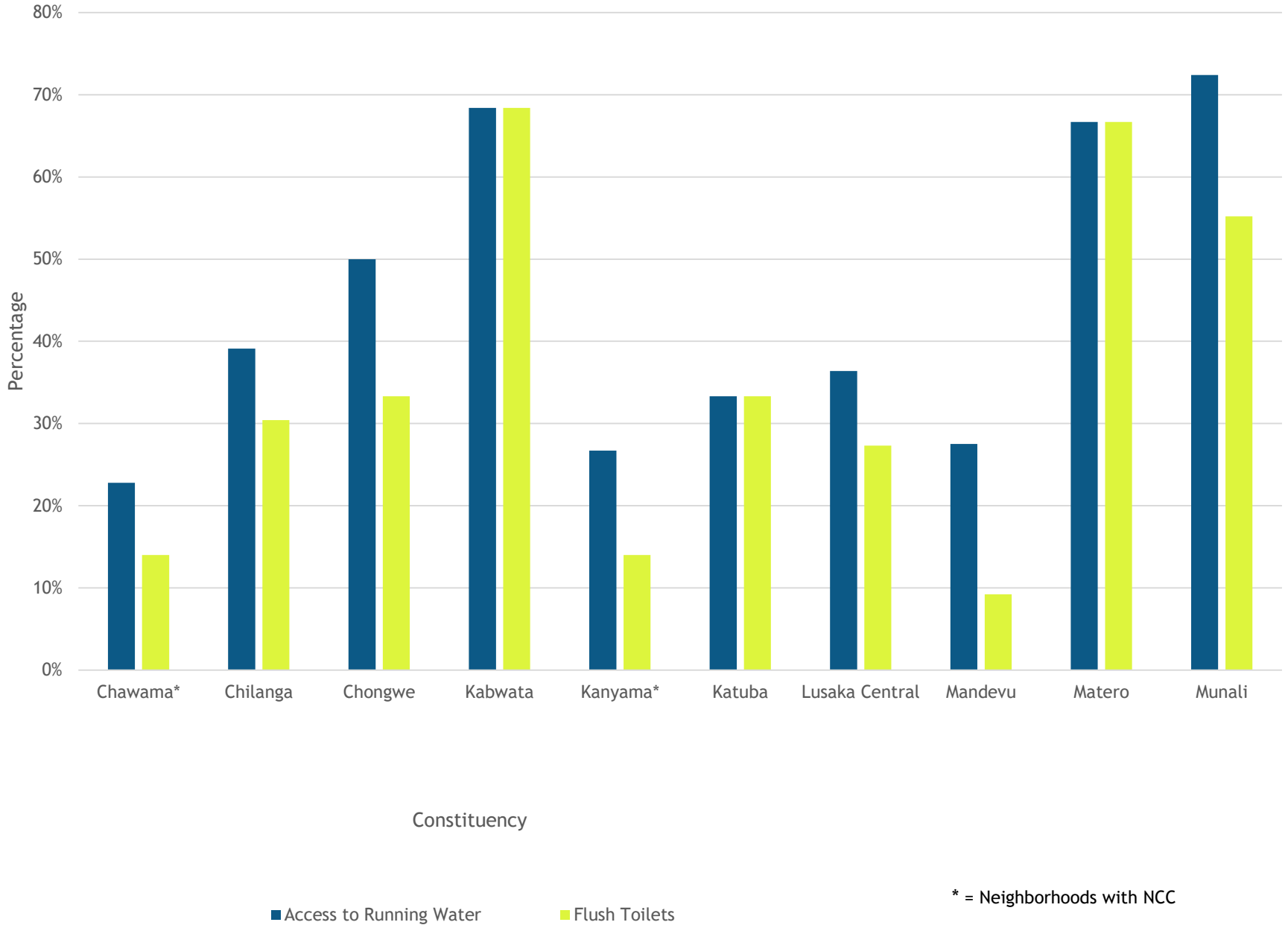
80%
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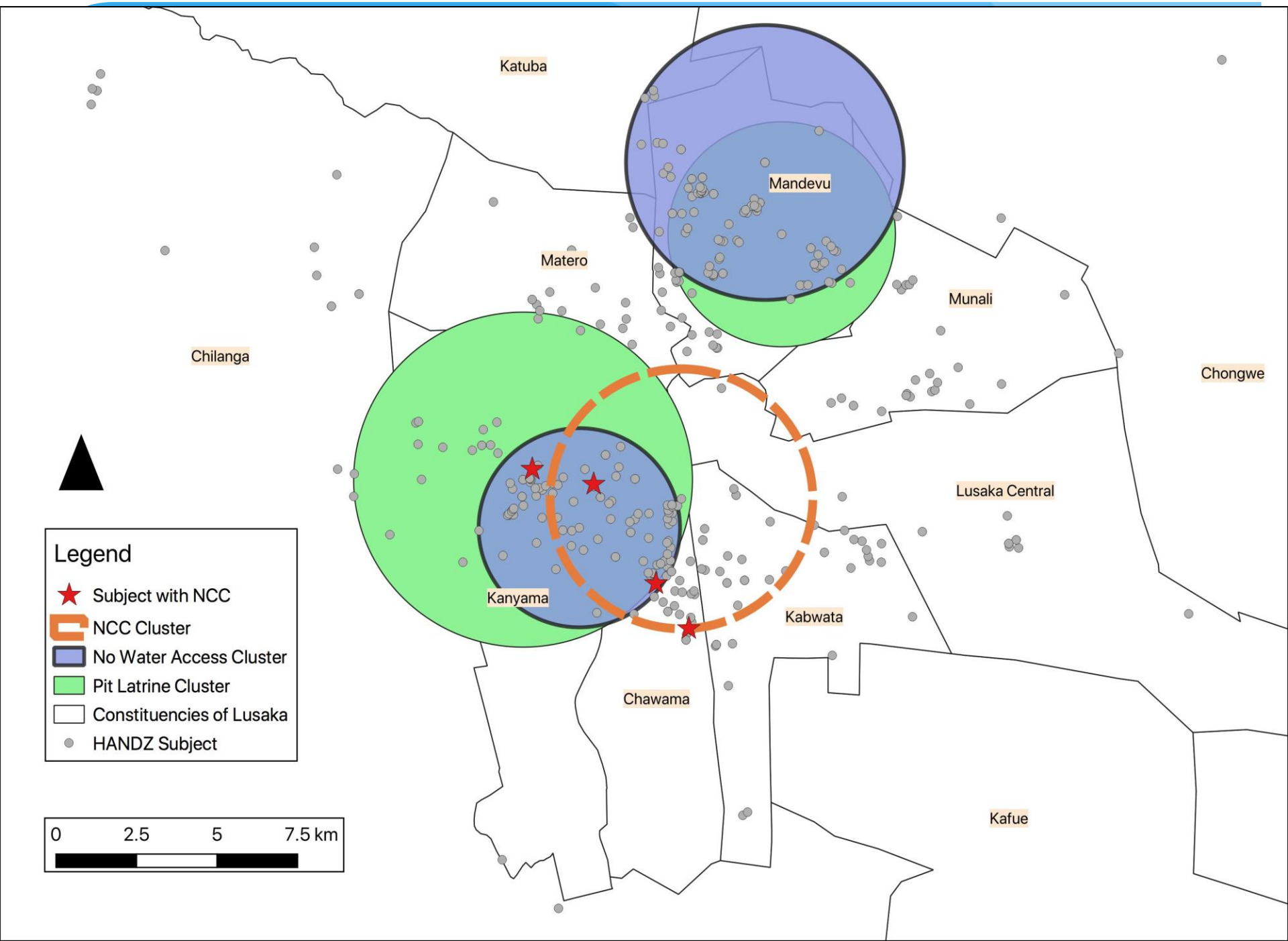
Percentage
Chawama*
Chilanga
Chongwe
Kabwata
Kanyama*
Katuba
Lusaka Central
Mandevu
Matero
Munali
Constituency
Access to Running Water
Flush Toilets
* = Neighborhoods with NCC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Mandevu
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Lusaka Central
Kanyama
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Kafue
Legend
Subject with NCC
NCC Cluster
No Water Access Cluster
Pit Latrine Cluster
Constituencies of Lusaka
HANDZ Subject
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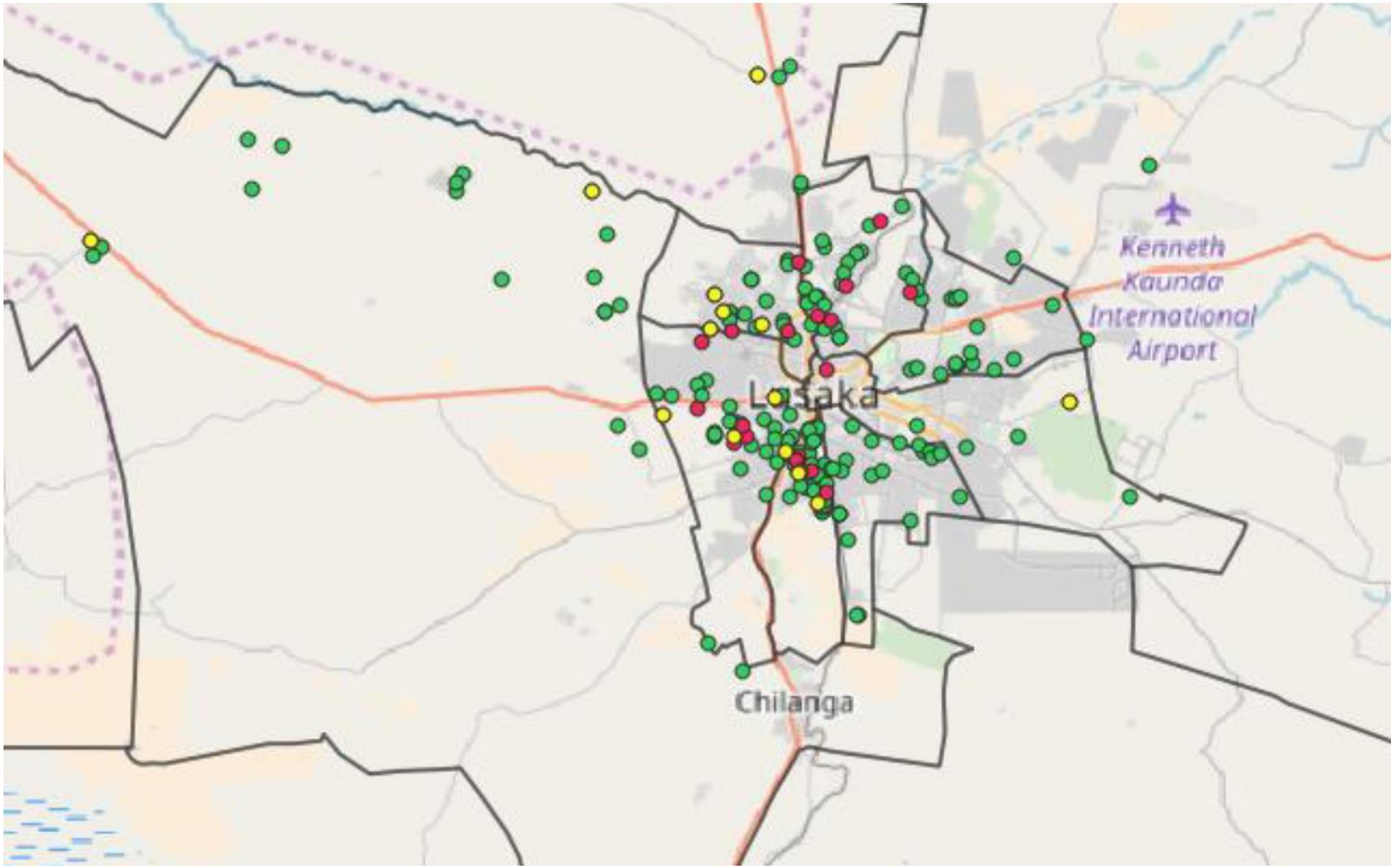
2.5
5
7.5 km

Green – HANDZ Case
Yellow – CHASE participant
Red – Deceased CHASE participant



Conclusions

- Children with HIV and new onset seizures have a high risk of early mortality and seizure recurrence is common.
- Children with HIV presenting with seizures are primarily those who “fall through the cracks” of the HIV treatment cascade
- Early initiation of ART and successful retention in care are likely to reduce incidence of seizures

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