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Antiretroviral Therapy Outcomes Among HIV Infected Clients in Gweru City, Zimbabwe 2006-2011: A Cohort Analysis

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African Case Studies in Public Health

Participants' Guide

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Antiretroviral Therapy Outcomes Among HIV Infected Clients in Gweru City, Zimbabwe 2006-2011: A Cohort Analysis

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Abstract

The government of Zimbabwe began providing antiretroviral therapy (ART) to People Living with HIV/AIDS (PLHIV) in public institutions in 2004. In Midlands province two clinics constituted the most active HIV care service points, with patients being followed up through a comprehensive patient monitoring and tracking system which captured specific patient variables and outcomes over time. The data from 2006 to 2011 were subjected to analysis to answer specific research questions and this case study is based on that analysis.

The goal of this case study is to build participants' capacity to undertake secondary data analysis and interpretation using a dataset for HIV antiretroviral therapy in Zimbabwe and to draw conclusions which inform recommendations. Case studies in applied epidemiology allow students to practice applying epidemiologic skills in the classroom to address real-world public health problems. Case studies as a vital component of an applied epidemiology curriculum are instrumental in reinforcing principles and skills covered in lectures or in background reading. The target audience includes Field Epidemiology and Laboratory Training Programs (FELTPs), university students, district health executives, and health information officers.

How to Use the Case Study

General instructions: Case studies in applied epidemiology allow students to practice applying epidemiologic skills in the classroom to address real-world public health problems. Case studies are used as a vital component of an applied epidemiology curriculum, rather than as stand-alone tools. They are well suited to reinforcing principles and skills already covered in a lecture or in background reading. Ideally, 1-2 instructors facilitate the case study for 8 to 20 students in a classroom or conference room. Traditionally, the instructor directs a participant to read aloud a paragraph or two, going around the room and giving each participant a chance to read. When the participant reads a question, the instructor directs all participants to perform calculations, construct graphs, or engage in a discussion of the answer. Sometimes, the instructor can split the class to play different roles or take different sides in answering the question. As a result, participants learn from each other, not just from the instructors.

Audience: Residents in Field Epidemiology Training Programs (FETPs), Field Epidemiology and Laboratory Training Programs (FELTPs), university students, district health executives, health information officers from the public health sector, and other partner organizations at national and

regional level. Participants will have basic graduate qualification in health-related field, e.g. medical degree, nursing, environmental health, social science.

Prerequisites: Before using this case study, case study participants should have received lectures or other instruction in basic epidemiology, statistics, and secondary data analysis.

Materials needed: White board or flip chart and markers, graph paper, computers with MS Excel (optional)

Level of training and associated public health activity: Advanced – epidemiology and public health research

Time required: Approximately 3 hours

Language: English

Participant's Guide

Goal of Case Study: To review and simulate the process for secondary data analysis and interpretation using a dataset for HIV antiretroviral therapy in Zimbabwe and draw conclusions to inform recommendations

Learning Objectives - After completion of this case study, the participants should be able to:

1. Define secondary data analysis
2. Identify different sources of secondary data of public health importance and highlight pros and cons
3. Describe the dataset in relation to the research question
4. Outline a data analysis plan including methods of data cleaning and transformation to address the research question
5. Interpret data analysis results in logical sequence
6. Draw conclusions and make recommendations based on the results of the secondary analysis

Introduction

Zimbabwe, a country in Sub-Saharan Africa with a total population of 13.3 million (2012 Census), has an adult human immunodeficiency virus (HIV) prevalence of almost 15%, contributing 6% to the HIV burden in the Sub-Sahara Africa epidemic. Overall, from 2005 to 2013 new HIV infections declined by over 50% among children and adults and HIV-related deaths reduced by 57% [1]. As part of its response to the HIV/AIDS epidemic, the government of Zimbabwe began providing antiretroviral therapy (ART) to People Living with HIV/AIDS (PLHIV) in public institutions in 2004.

Adult ART coverage gradually increased since the program started in 2004. By 2013, approximately 800,000 (76.8%) people were on ART. Around 8000 people were being initiated on ART per month. However, coverage for the pediatric age groups under the age of 15 years remained low at 35% [2].

In 2011, ART program managers in Midlands province became interested in exploring research questions pertaining to ART adherence and general outcomes among PLHIV on ART. The information was required to inform programmatic decisions and possible recommendations regarding the ART program. The researchers started with a literature review around trends of ART outcomes in Zimbabwe and in the region and the factors associated with attrition to ART. Owing to prohibitive costs and time constraints, the program managers proposed to use an existing dataset to answer the research questions. See Appendix 1 for ART dataset variables.

ART Clinics A and B constituted the most active HIV care service points in Midlands Province of Zimbabwe. These clinics were established in 2006 and were actively tracking a cohort of almost 8000 adults and children on ART by the end of 2010. These patients were followed up through a comprehensive patient monitoring and tracking system which captured specific patient variables and outcomes over time. Key variables in the dataset included survival status, loss to follow up, treatment interruption, CD4 count, weight and adverse events. The researchers observed that there were considerations to be made on the suitability of the dataset to yield the required answers regarding data quality issues.

The clinics implemented treatment protocols, drug regimens, and program reporting tools according to Zimbabwe guidelines for antiretroviral therapy. Guidelines recommended close monitoring to assess adherence to treatment, tolerance, side effects and efficacy of treatment. Serial height measurements were important for evaluating children; hence, readings were

obtained every 6 months. An objective assessment was made of adherence to treatment through pill counts and evaluation for emerging serious side effects. The ART treatment guidelines also recommended CD4 count testing every six months [3].

High rates of attrition from treatment programs posed a serious challenge to program implementers and constituted an inefficient use of scarce treatment resources. It was therefore important to assess ART outcomes as part of Early Warning Indicators (EWIs) that are a key component of the World Health Organization (WHO) public health strategy to assess and minimize HIV Drug Resistance in countries scaling up ART.

With substantial emphasis placed on rapid implementation and scale-up of treatment services in Zimbabwe, there was little opportunity to examine longitudinal treatment data, and as of April 2016 not much analysis was being done regarding ART programmatic and clinical outcomes in Midlands province.

Question 1: What kind of patient outcomes would be measured in a system like the one described above? Identify the cohort in this setting and explain why it meets the definition of a cohort.

Question 2: Given this scenario and data set, what are plausible research questions? What hypotheses could be explored in this scenario?

Question 3a: Compare and contrast primary data and secondary data.

Question 3b: In the ART program, what are the possible data sources from the external researcher's point of view? Classify the data sources as primary or secondary.

Question 4: Considering the ART program, under what conditions would you conduct primary data analysis? Secondary data analysis?

Question 5: What are the advantages and disadvantages of secondary data analysis?

Figure 1. Data and patient flow systems at clinics A and B, Midlands, Zimbabwe

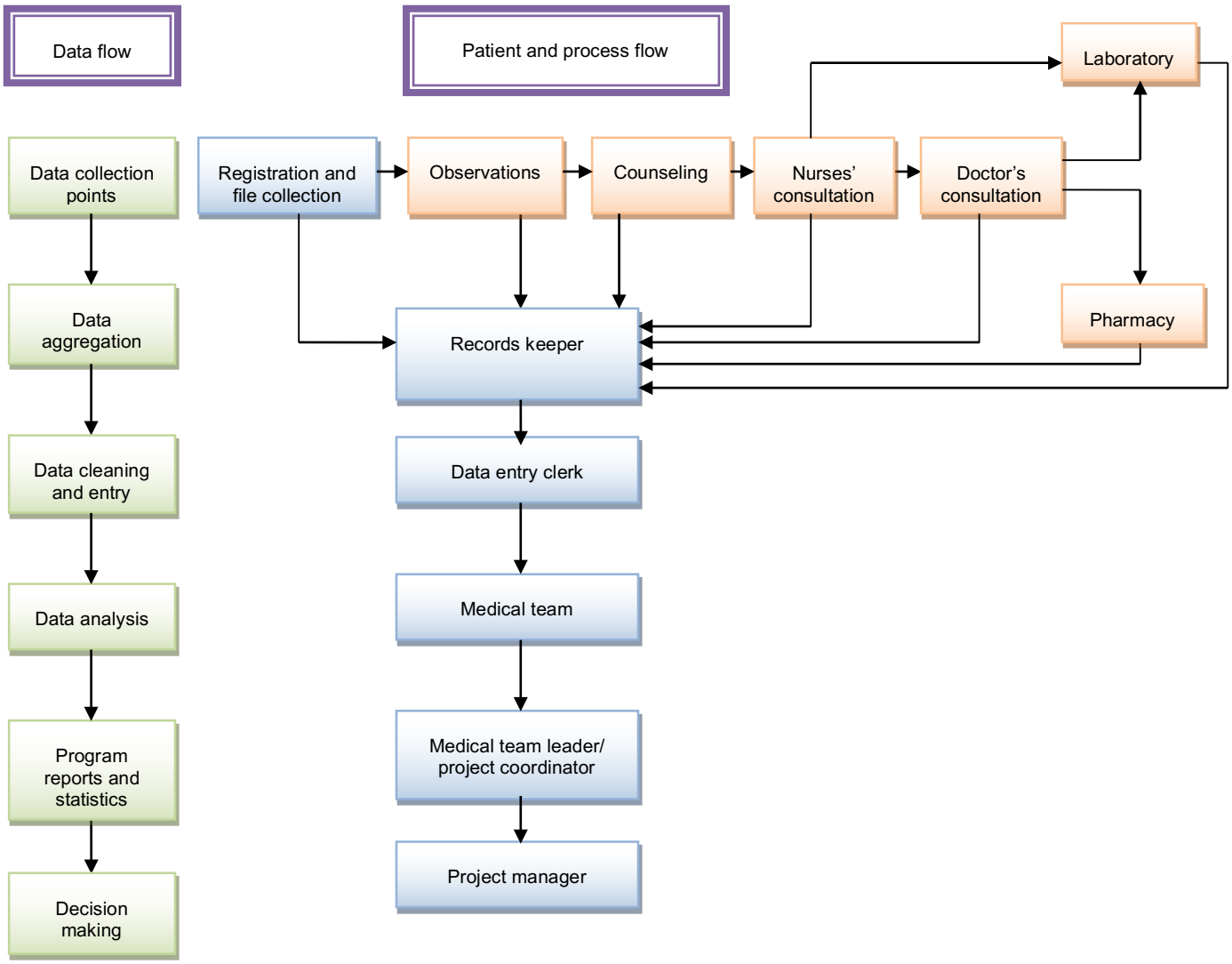

Figure 1 illustrates the flow of patient data at clinics A and B. Data in the system was collected on paper before submission to a central office where it was entered by data entry clerks into an electronic Follow Up and Care for HIV Infection and AIDS (FUCHIA) database, an Excel-based patient record management system which recorded information on each patient and generated summaries per patient or for a given cohort for any specified time period. After consulting stakeholders on feasible sources of data, the researchers also considered other datasets (e.g. census, demographic health survey) for potential merging. They familiarized themselves with data quality issues [1].

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Question 6: Looking at the data flow in the system depicted in Figure 1, describe data validity challenges that may be encountered by the users (Figure 1).

The researchers sought to determine critical outcomes (attrition, retention rates, survival trends and adverse events) of this cohort and identified this database as a readily available source. This database provided a rich source of secondary data to answer programmatic questions. The project coordinator instructed the team to list possible sources of data to answer the proposed research questions [1]:

1. What proportion of ART patients are alive and on treatment 3, 6, 12 and 24 months after initiating therapy?
2. What proportion of patients on ART was started on treatment based on WHO staging and/or CD4 count consistent with the national treatment guidelines?
3. What proportions of patients on ART are still on First line at 3, 6, 12 and 24 months after treatment?
4. What proportion of patients on ART was lost to follow-up within 3, 6, 12 and 24 months after ART initiation?
5. What proportion of patients on ART experienced at least one adverse event (severe rash, neuropathy, liver disease, kidney disease, other) of ART within 3, 6, 12 and 24 months after ART initiation?

Question 7: Given the context of the ART program in Zimbabwe, would you as the program manager recommend new data collection or secondary analysis? Explain your answer.

A decision was made to analyse existing ART data. The researchers organized a two-day meeting to acquaint themselves with the protocol used to collect the ART data, the nature of the variables collected, and any contextual issues around the process of data collection.

Question 8: What are the major phases and steps needed to complete secondary data analysis?

Part 1

The investigators completed a comprehensive review and analysis of the dataset. In addition, they conducted an extensive literature review on outcomes among patients on ART in the region. They found a total of 15,766 records in the database representing a unique patient. Each patient record analyzed had at least 11 observation points spanning from 2006 to 2011. Average completeness was around 80% per record. Investigators anticipated that the analysis would help in comparing achieved proportions to the recommended targets of the early warning indicators of HIV drug resistance. The investigators were requested to provide results concerning key attributes of patients on the database, especially those that initiated ART in 2006 [1].

The existing Microsoft Excel-based data set was cleaned and converted exported into Microsoft Access database.

Table 1. Sample of database extracts of patients on ART, Gweru City, Zimbabwe, 2011 [1]

ID	Gender	Entry Point	Marital Status	Date of Birth	Date of Initiation	Weight (kg)	Height (cm)	Baseline CD4 (cells/µl)	CD4 at 4 Months (cells/µl)	12 Month Survival Status
1	M	PMTCT	S	1/16/2010	1/20/2010	30.2	48	-	421	A
2	M	VCT	M	9/5/1956	4/10/2008	44	153	73	74	A
3	F	VCT	S	5/27/1998	8/20/2008	28	126	-	-	D
4	M	PMTCT	S	7/30/2010	8/4/2010	2.5	49	-	320	A
5	F	VCT	W	3/9/1957	4/10/2008	73	158	1704	200	A
6	F	VCT	M	4/30/1976	4/20/2008	55	152	225	220	A
7	F	PMTCT	S	11/11/1986	8/20/2008	54	158	261	350	D
8	F	VCT	S	5/16/1986	6/19/2008	85	166	373	500	A
9	F	PMTCT	S	6/8/2009	4/10/2008	32	47	-	-	D
10	F	PMTCT	M	6/4/1976	4/20/2008	60	155	696	540	A

Key: S= Single, M= Married, W= Widowed, A=Alive, D= Dead, PMTCT= Prevention of Mother to Child Transmission, VCT= Voluntary Counselling and Testing

NB: Normal CD4 count range from 500 cells/mm3 to 1,200 cells/mm3.

Question 9: Classify the variables from Table 1 as categorical or continuous variables.

Question 10a: What are the data quality issues in table 1?

Question 10b: What actions would you take to rectify identified data anomalies?

Prior to conducting the analysis, the investigators sought permission from the Provincial Medical Director of Midlands, Gweru City Health Department, and the Ministry of Health, as well as ethical clearance from the Medical Research Council of Zimbabwe.

Question 11a: What are the ethical issues one would consider for this ART dataset when conducting secondary analysis?

Question 11b: What measures would you take to address the identified ethical issues?

Part 2

The main research question in this analysis was: What were the treatment outcomes and mortality trends of the 2006 ART cohort in Gweru city, Zimbabwe? The researchers were keen to know ART outcomes by sex, WHO staging at initiation and occurrence of side effects. Analysis was done using STATA package. Tables and graphs were used to demonstrate frequencies proportions and trends. The investigators located 15,491 records. However, they only focused on a cohort that initiated on ART in 2006. Out of the 1026 records of patients that were initiated, 237 were discarded [1].

Table 2. ART cohort record analysis, Gweru City, Zimbabwe, 2011

Records	Number
Total number of records found	15491
Total number initiated in 2006	1026
Discarded records	237
Total number of records analyzed	789

Question 12a: What could be possible reasons for discarding 237 records as stated in Table 2?

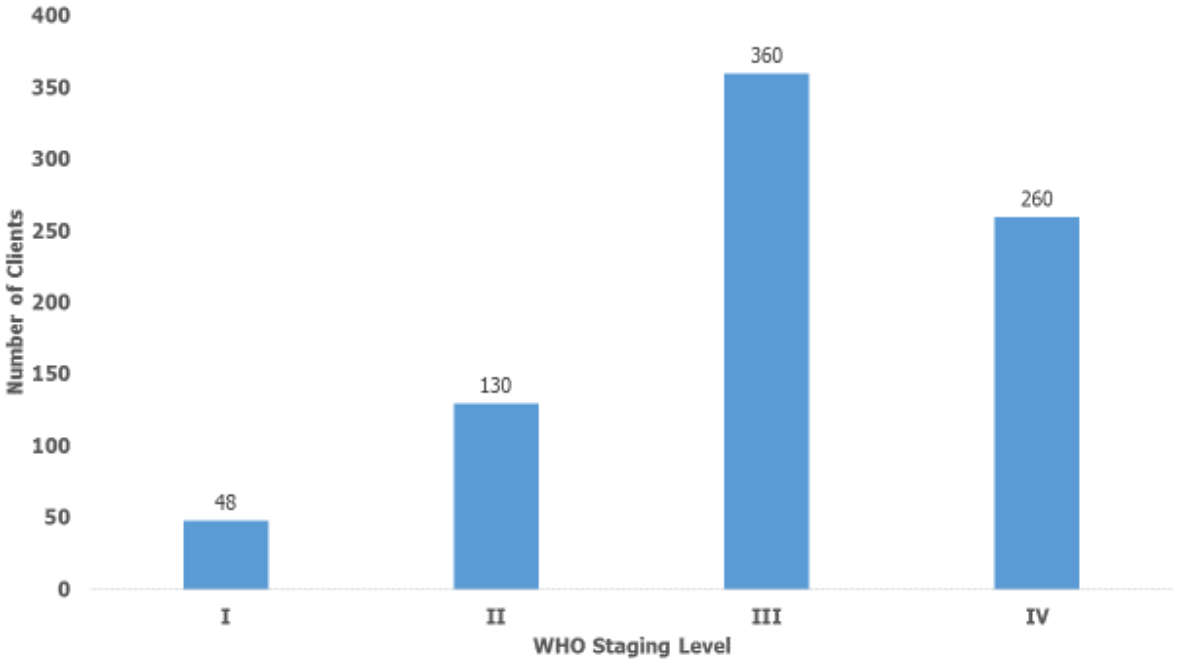
Question 12b: What proportion of the records was included for analysis? What are the implications of this on the final analysis?

Adult HIV progression is classified according to the WHO clinical staging criteria which may be used in clinical decision making to initiate ART and monitor progress to treatment. There are four stages, with stage 1 being the least severe and stage 4 the most severe.

- Stage 1: Asymptomatic persistent generalized lymphadenopathy
- Stage 2: Moderate unexplained weight loss (<10% of presumed or measured body weight. Recurrent upper respiratory tract infections (sinusitis, bronchitis, otitis media, pharyngitis)
- Stage 3: Unexplained severe weight loss, unexplained chronic diarrhea, persistent fever and pulmonary TB
- Stage 4: HIV wasting syndrome, pneumocystis pneumonia, oesophageal candidiasis, EPTB, Kaposi's Sarcoma, HIV encephalopathy, central nervous system toxoplasmosis and invasive cervical carcinoma [4]

To determine the number of clients in each stage of HIV diagnostic classification, the researchers generated Figure 2.

Figure 2. Distribution of ART clients at clinic A and B in Zimbabwe by WHO starting at initiation, 2011 [1]



Question 13a: Interpret the results from the graph presented in Figure 1.

Question 13b: Why might HIV-infected persons not enroll in ART at an early stage of HIV? Provide answers with regard to barriers at the individual, community, and health system levels.

The investigators assessed treatment outcomes using various parameters including CD4 count of this cohort. Table 3 shows mean CD4 count by month and sex.

Table 3. Monthly mean CD4 county by sex, Gweru, Zimbabwe, 2011 [1]

Month	Mean CD4 Count (cells/µl)	
	Males	Females
Jan	119	134
Feb	109	130
March	265	283
April	256	321
May	273	355
Jun	281	379
July	331	429
August	356	494
Sept	376	511
Oct	381	532
Nov	420	547

Question 14: What other parameters could the investigators select to assess treatment outcomes?

The investigators were requested to assess the difference between mean CD4 count by sex.

Question 15a: Plot a line graph in the space below using data from Table 3.

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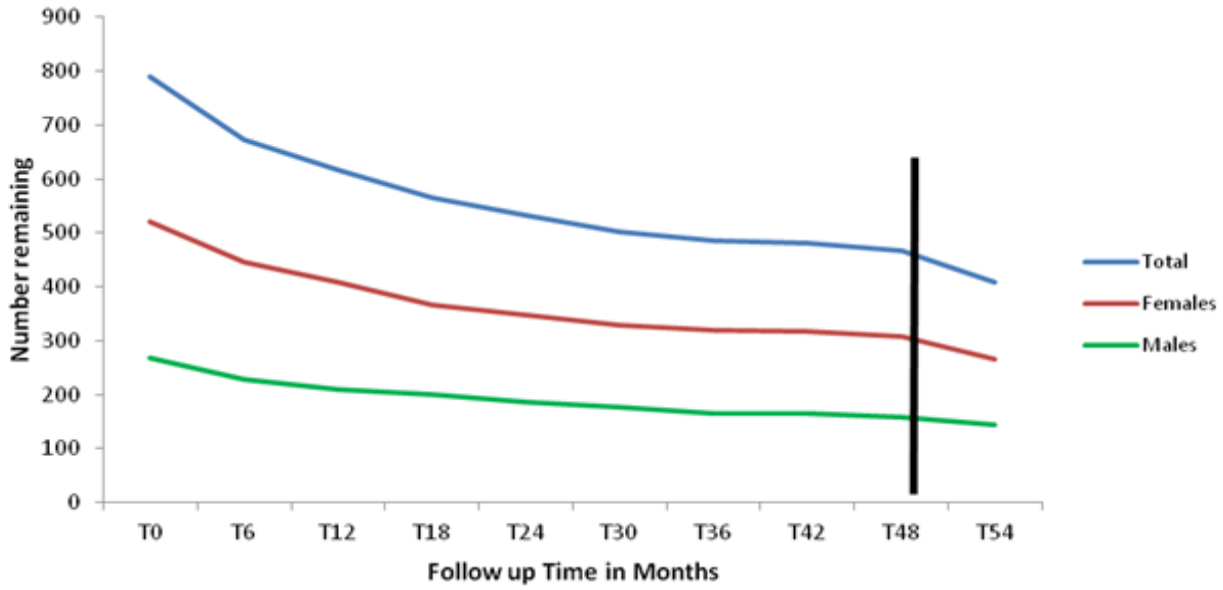
Question 15b: What hypotheses can be generated from the graph developed from table 3?

Question 15c: What is the appropriate statistical test to measure this difference? Why?

Patient retention on ART at 12 months is one of the early warning indicators of HIV drug resistance (WHO). According to Sydney Rosen et al. [1], African ART programs retained about 60% of their patients in the first two years. Based on this information, the investigators decided to analyze the data on patients remaining in care by month and calculate the incidence of adverse events and mortality (Figure 3).

Figure 3. Number of ART Patient Remaining in Care Over 12 Months, Midlands Province, Zimbabwe, 2006-2011 [1]



Question 16: What reasons might have contributed to the decline in the number of patients in care beyond 12 months? What are the implications on the analysis, and how would you address them?

Severe side effects of ART included severe rashes, liver failure, kidney failure and severe neuropathy. Investigators assessed the rate of serious side effects that warranted switching or interruption of treatment, as well as mortality rates among patients.

Figure 4. Crude Annualized Incidence of Serious Side Effects Among ART Patients, Midlands Province, Zimbabwe, 2006-2011 [1]

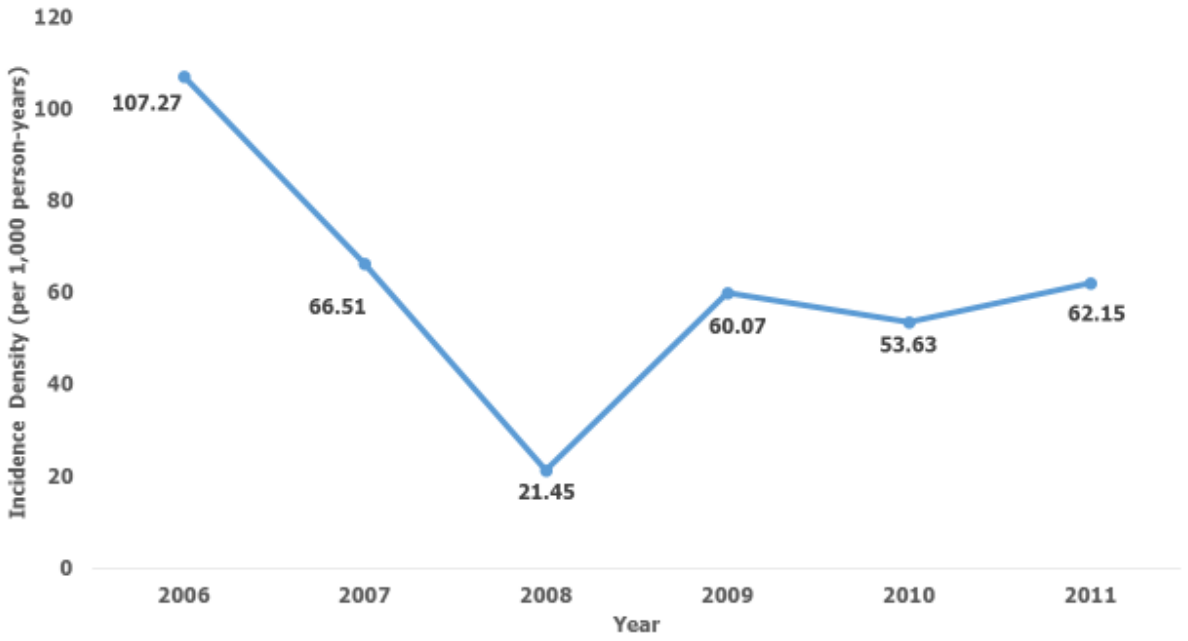


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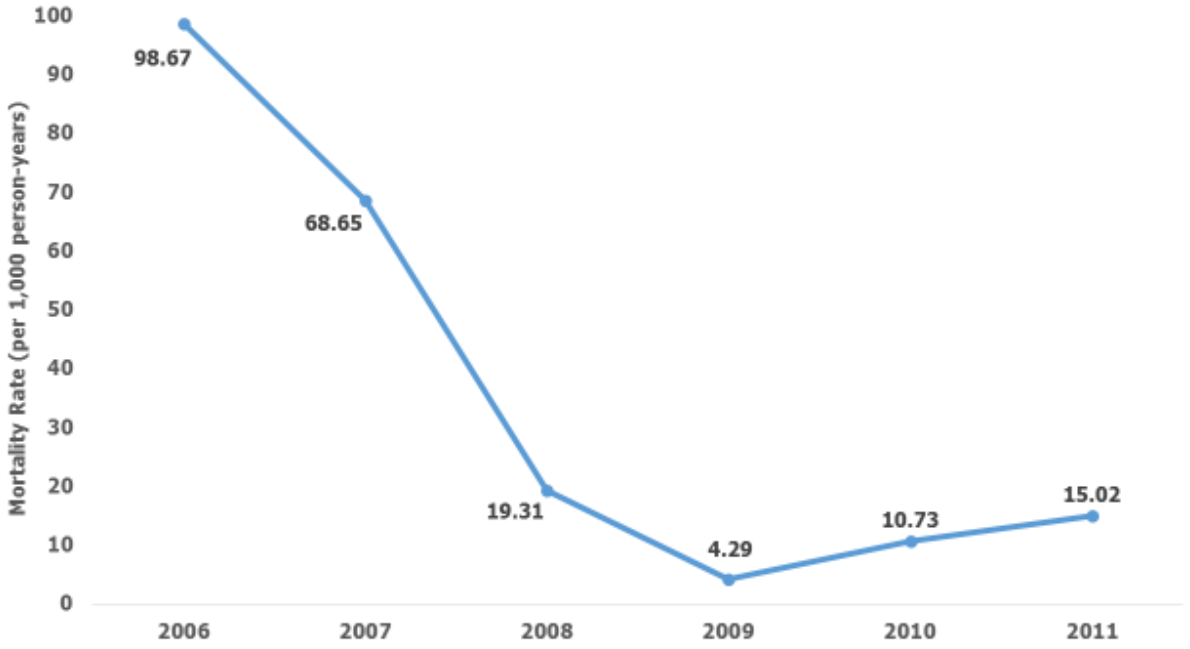
Figure 5. Crude Annualized Mortality Rate Among ART Patients, Midlands Province, Zimbabwe, 2006 – 2011 [1]



Question 17a: What do you observe from Figures 4 and 5?

Question 17b: What would you assume from comparing the two graphs?

The investigators assessed the probability of survival of patients initiated on ART over time. The overall hazard ratio was 1.5, 95% CI (1.01-2.4). The investigators hypothesized that there are some significant differences by sex regarding survival. Therefore, the assessed probability of survival of patients initiated on ART by sex was statistically significant (p= 0.04).

Figure 6. Survival Analysis for Those Who Died, Gweru, Zimbabwe, 2011 [1]

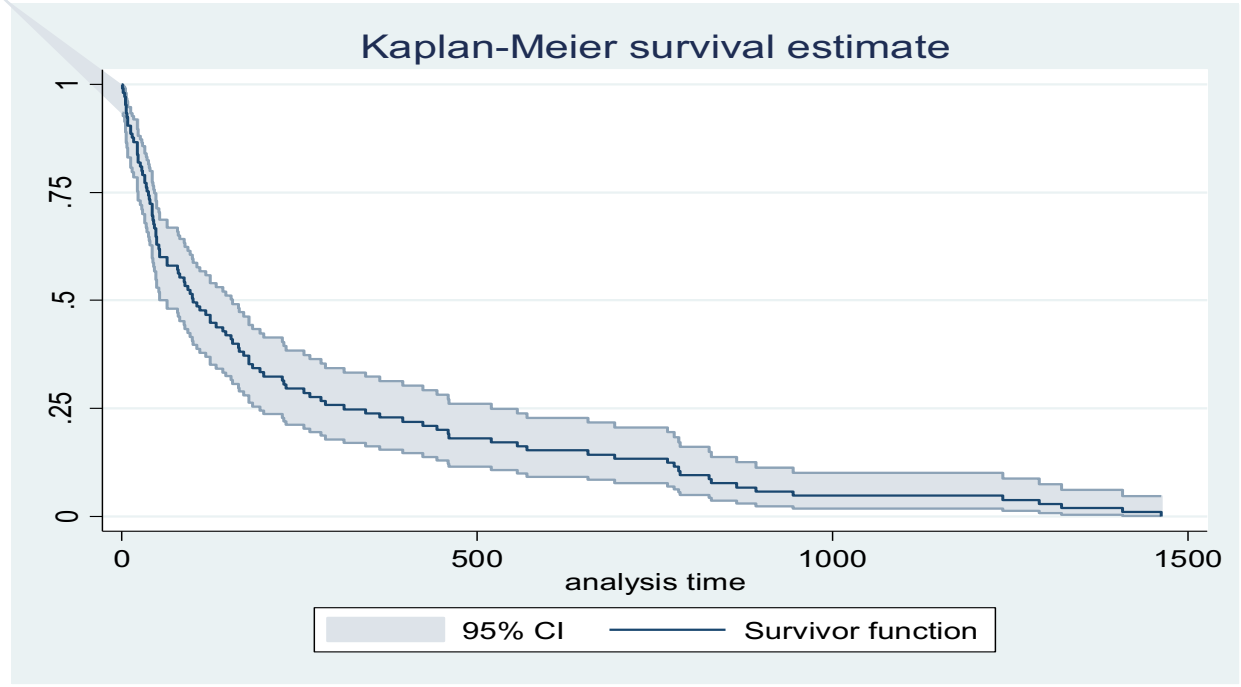


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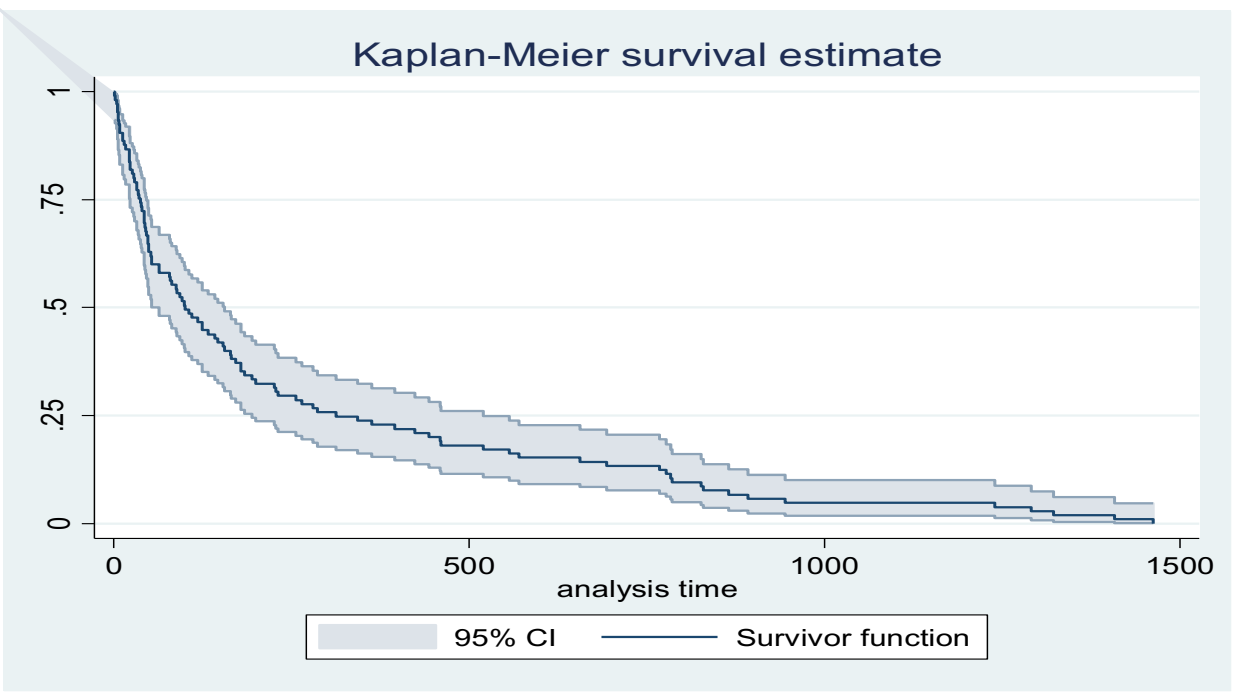
Figure 7. Survival Probability for Those Who Died by Gender, Gweru, Zimbabwe, 2011 [1]



Question 18: Making reference to Figures 6 and 7, what conclusions can you make on the probability of survival in this cohort? What is a hazard ratio? How do you interpret the ratio given in this scenario?

HIV Drug Resistance (HIVDR) EWIs are a key component of the WHO public health strategy to assess and minimize HIVDR in countries scaling up ART. EWIs specifically assess factors at individual antiretroviral therapy clinics associated with emergence of HIVDR. In addition, the investigators assessed EWI for the last year of this cohort (Table 4). Then they related the outcome of the ART program analysis to the WHO HIVDR EWIs to assess program performance.

Table 4. Early warning indicators (EWI) for HIV drug resistance in a cohort of HIV patients on ART, Midlands, Zimbabwe, 2011

EWI #	Indicator Description	Target (%)	Achieved (%)
1	Percentage of adult patients initiating ART who got an appropriate first-line ART regimen	100	100
2	Percentage of patients lost to follow-up 12 months after ART initiation	20	10
3a	Percentage of adult patients taking an appropriate first-line ART regimen 12 months later	70	100
3b	Percentage of patients whose initial ART regimen was changed during the first 12 months to a regimen that includes a different drug class	0	0.25
4a	Percentage of patients who picked up prescribed antiretroviral (ARV) drugs on time	90	15
5b	Percentage of patients who attended all scheduled or expected clinical consultations on time during the first 12 months of ART	100	72
6a	Percentage of months in a designated year in which there were no ARV drug stock-outs	100	100
6c1	Percentage of patients on ART whose regimen was interrupted due to ARV stock-out in a 12-month period	0	0
6c2	Percentage of patients whose regimen was interrupted due to ARV stock-out during the first 12 months of ART	0	0

Question 19: What conclusions about secondary data analysis of the ART data in Zimbabwe for 2011 would you draw from all of these results? How can these conclusions be applied?

Conclusion

Secondary data can be a valuable source of information for gaining knowledge and insight into a broad range of issues and phenomena.

This cohort analysis demonstrated some of the challenges associated with secondary data analysis, including but not limited to incompleteness and some inaccuracies. However, the secondary analysis generated useful information describing the cohort with respect to stage of ART initiation and probability of survival among those initiated. Researchers also generated summaries on EWIs which could provide some information regarding program performance. Some hypotheses generated from the analysis were used to formulate research questions for the HIV research agenda for the Gweru City Health Department. For example, there was a pressing need to explain why men in this cohort experienced lower mortality than women despite starting ART at an older age or with more advanced disease.

Background Reading

Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med.* 2007; 4(10): e298.
http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2020494

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http://www.nac.org.zw/sites/default/files/2013 Zimbabwe ARV Guidelines Main Document (1).pdf

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We wish to thank the African Field Epidemiology Network (AFENET) for sponsoring the training and the Zimbabwe Program Director, Professor Mufuta Tshimanga for nominating and supporting the training of the two Zimbabwean participants.

We also wish to acknowledge the following for their peer review during the case study workshop: Mahmood Dalhat, Olufunmilayo Ibitola Fawole, Jane Githuku, and Doreen Tuhebwe.

Appendix

ART dataset variables

1. Unique identifier
2. Date of birth
3. Gender
4. Origin, entry (where referred from)
5. Profession
6. Marital status
7. Dates of visits
8. Height
9. Weight
10. WHO stage
11. CD4 count and percentage
12. Haemoglobin
13. ART regimen
14. Date of transfer
15. Date of death
16. Adverse events

References

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4. WHO. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. 2006. Geneva, Switzerland. http://www.who.int/entity/hiv/pub/guidelines/WHO HIV Staging.pdf