

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

## **Part 0: Preamble**

University of Cape Town

THESIS TITLE

**Barriers to adherence in patients failing second-line antiretroviral treatment in a township in South Africa: a qualitative research study.**

University of Cape Town

NAME: Whitney Barnett  
STUDENT #: BRNWHI001  
SUPERVISOR(S): Christopher Colvin

THESIS SUBMITTED IN FULFILLMENT OF A  
MASTERS DEGREE IN PUBLIC HEALTH  
AT THE SCHOOL OF PUBLIC HEALTH  
AT THE UNIVERSITY OF CAPE TOWN

July 2012

## DECLARATION

I, Whitney Barnett, hereby declare that this is my original work and has not been presented before for the award of a Masters' Degree in Public Health.

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

University of Cape Town

## **DEDICATION**

I would like to dedicate this thesis to my mother, father and brother for all their support and encouragement.

## THESIS ABSTRACT

**Introduction.** The recent scale-up of ART coverage in resource-limited settings has greatly improved access to treatment. However, literature indicates that patients on ART have high rates of non-adherence (32% to 67%), virological failure (5.2%, to 47%) and resistance to ARVs (5.4% to 80%). These patients are failing first- and second-line ART, leaving no treatment options for successful virus suppression. Yet, literature addressing facilitators and barriers faced by patients on second-line ART is scarce. This study examined factors affecting adherence to second-line ART from the perspective of clinic staff as well as second-line failure patients, assessing both individual and structural barriers. Research was conducted at a large primary-care clinic in Khayelitsha, a peri-urban township in Cape Town, South Africa.

**Methods.** A literature review was conducted to present 1) rates of non-adherence, virological failure and resistance and 2) to present known facilitators & barriers faced by patients on ART, with a specific focus on second-line patients. The literature was found via PubMed and Cochrane Central Register of Controlled Trials (CENTRAL), with a preference for studies in low and middle income countries and those including second-line ART populations. The primary research used participants who were drawn from an MSF-run program to support patients failing second-line treatment. A qualitative research approach was used, combining multiple methodologies including: key informant interviews with staff (n=11), in-depth interviews with patients (n=10) and a Photovoice workshop (n=11).

**Results.** Staff identified drinking, non-disclosure, not using condoms, and pill fatigue as barriers to adherence, whilst patients identified side effects, not using condoms and lack of understanding around medication timing. With respect to service delivery, staff identified a need for continued counseling and educational support following ART initiation as important. Patients were concerned about missing medical records and poor staff attitudes in the broader clinic, citing improved patient/staff relationships and continuity of care within the MSF-run program as significant.

**Conclusions.** These findings identify a need for ongoing counseling and education following ART initiation as well as improved methods to quickly identify and address patient issues around medication adherence.

## **ACKNOWLEDGEMENTS**

I would like to acknowledge the following people for their help and support in completing this thesis.

To my supervisor, Christopher Colvin, thank you for all your feedback during the writing of the thesis as well as all your guidance during data collection and the analysis.

To Gabriela Patten and Ben Kerschberger, thank you for initiating this project and for all of your support.

To Karien Conradie, the dedicated staff at Ubuntu clinic and the participants who were involved in this study; thank you for allowing me into your project.

University of Cape Town

## TABLE OF CONTENTS

|   |          |
|---|----------|
| <b>Part 0: Preamble</b> .....                                   | <b>i</b> |
| Thesis Title .....  | ii       |
| Declaration.....  | 1        |
| Dedication .....  | 2        |
| Thesis Abstract.....  | 3        |
| Acknowledgements.....   | 4        |
| Table of Contents.....  | 5        |
| Figures and Tables .....  | 7        |
| <b>Part A: Protocol</b> .....                                   | <b>1</b> |
| Study Protocol.....   | 2        |
| Principal and co-investigators.....                             | 3        |
| <i>ABBREVIATIONS</i> .....                                      | 3        |
| Background .....  | 4        |
| <i>AIMS AND OBJECTIVES OF THE STUDY</i> .....                   | 4        |
| <i>METHODS</i> .....  | 5        |
| Overview .....  | 5        |
| Literature review.....  | 5        |
| Semi-structured interviews.....                                 | 6        |
| PhotoVoice.....   | 6        |
| Data analysis (semi-structured interviews and PhotoVoice) ..... | 7        |
| OTHER CONSIDERATIONS .....                                      | 8        |
| Informed consent process .....                                  | 8        |
| Data safety and confidentiality .....                           | 8        |
| Potential risks and benefits.....                               | 8        |
| Ethics.....   | 8        |
| Reimbursement for participation.....                            | 9        |
| Communication of the results.....                               | 9        |
| Resources and budget.....                                       | 9        |
| Timeline .....  | 9        |
| PROTOCOL REFERENCES .....                                       | 10       |
| <b>Part B: Structured Literature Review</b> .....               | <b>1</b> |
| Literature Review .....   | 2        |
| <i>OBJECTIVES</i> .....   | 2        |
| <i>SEARCH STRATEGY</i> .....                                    | 2        |
| <i>QUALITY AND RELEVANCE OF STUDIES INCLUDED</i> .....          | 2        |
| <i>SUMMARY OF LITERATURE</i> .....                              | 2        |
| <i>FURTHER RESEARCH</i> .....                                   | 7        |
| LITERATURE REVIEW REFERENCES.....                               | 8        |
| <b>Part C: Journal “Ready” Manuscript</b> .....                 | <b>1</b> |
| Title page.....   | 2        |
| ABSTRACT.....   | 3        |
| INTRODUCTION.....   | 4        |
| <i>METHODS</i> .....  | 5        |
| <i>RESULTS</i> .....  | 5        |
| <i>DISCUSSION</i> .....   | 8        |
| <i>STUDY LIMITATIONS</i> .....                                  | 9        |
| <i>STUDY SIGNIFICANCE</i> .....                                 | 10       |
| <i>FURTHER RESEARCH/RECOMMENDATIONS</i> .....                   | 10       |
| <i>ACKNOWLEDGEMENTS</i> .....                                   | 10       |

|   |           |
|---|-----------|
| ARTICLE REFERENCES.....   | 11        |
| <b>Part D: Appendices.....</b>  | <b>1</b>  |
| Appendix 1: Questionnaire/data capture instrument(s) .....  | 2         |
| <i>Interview guide for individual semi-structured interviews (patients on second-line ART).....</i> | <i>2</i>  |
| <i>Interview guide for key informant semi-structured interviews (health care staff).....</i>        | <i>5</i>  |
| Appendix 2: Consent forms and participant information forms.....                                    | 8         |
| <i>PhotoVoice: Information and Consent form .....</i>   | <i>8</i>  |
| <i>Information and Consent form: Key informant interviews .....</i>                                 | <i>11</i> |
| <i>Information and Consent form: Patient interviews .....</i>                                       | <i>14</i> |
| Appendix 3: Letter of approval from Research Ethics Committee .....                                 | 17        |
| Appendix 4: Instructions for Author of journal whose format has been used .....                     | 18        |

University of Cape Town

## FIGURES AND TABLES

**Table 1: Summary of Barriers by Respondent**

| Patient Cited Barriers       |           | Key Informant Cited Barriers  |           |
|------------------------------|-----------|-------------------------------|-----------|
| Issue                        | Frequency | Issue                         | Frequency |
| Not condomizing              | 3         | Drinking                      | 9         |
| Timing of medication         | 3         | Disclosure                    | 8         |
| Side effects                 | 3         | Not condomizing               | 6         |
| DDI/one hour delay           | 3         | Pill Fatigue                  | 5         |
| Pills too large              | 3         | Forgetting                    | 5         |
| Forgetting                   | 2         | Not honest with clinic staff  | 3         |
| Life stress                  | 2         | Stigma                        | 3         |
| Drinking                     | 1         | Side effects                  | 3         |
| Gave up                      | 1         | Lack of food in home          | 2         |
| Haven't accepted HIV+ status | 1         | Life stress                   | 2         |
| Disclosure                   | 1         | Insufficient support          | 2         |
| Unable to keep appt          | 1         | Treatment partner not working | 1         |
| Pill fatigue                 | 1         | DDI/one hour delay            | 1         |
|                              |           | Denial                        | 1         |
|                              |           | Feeling better                | 1         |
|                              |           | Embarrassed about defaulting  | 1         |
|                              |           | Timing of medication          | 1         |
|                              |           | Staff shouting                | 1         |

**Legend:** The table above lists barriers to ART adherence identified by both patients and key informants, with frequency cited.

**Table 2. Photovoice Themes**

| Main Photo Theme                  | Frequency |
|-----------------------------------|-----------|
| Support of family/friends         | 12        |
| Importance of treatment in lives  | 5         |
| Gratitude toward MSF staff        | 3         |
| Difficulty of treatment           | 3         |
| Religion as source of strength    | 2         |
| Overcome drinking problem         | 2         |
| Poor living environment           | 2         |
| Food insecurity                   | 1         |
| Regret for losing previous wealth | 1         |

**Legend:** The table above lists frequency by main theme of photos shared during the photovoice workshop.

Figure 1. Counselor explaining medication parameters to patient.



Figure 2. This patient struggled with an alcohol abuse problem for over two years; she has since stopped drinking. Here she is shown pouring out the alcohol remaining in her home.



Figure 3. Patient with daughter who assists her in remembering to take her medication.



## Part A: Protocol

This protocol was originally written and submitted by Ben Kershberger and Christopher Colvin as part of a Medecins Sans Frontieres operational research project. It has received minor edits for the purpose of thesis submission.

*N.B. The results reported within this thesis only represent a portion of the original protocol/research project.*

University of Cape Town

## STUDY PROTOCOL

Research proposal for Qualitative Research at Ubuntu clinic, Khayelitsha, Cape Town

**TITLE: Barriers to adherence in patients failing second-line antiretroviral treatment in a township in South Africa: a qualitative research study.**

University of Cape Town

March 2011

Medecins Sans Frontieres  
Khayelitsha, Cape Town, South Africa

School of Public Health and Family Medicine, Faculty of Health Sciences  
University of Cape Town

## PRINCIPAL AND CO-INVESTIGATORS

### Principal investigator:

- Dr Christopher Colvin, PhD, MPH

School of Public Health and Family Medicine, University of Cape Town, South Africa

### Main researchers:

- Dr Bernhard Kerschberger, MD, MPH  
Epidemiologist, MSF Khayelitsha, South Africa
- Dr Karien Conradie, MD  
HIV/TB doctor, MSF Khayelitsha, South Africa

### Co-investigators:

- Dr Daniela Garone, MD  
Medical Deputy Coordinator, MSF, Khayelitsha, South Africa
- Whitney Barnett  
Candidate, Masters in Public Health, University of Cape Town

## ABBREVIATIONS

|       |  |
|-------|--|
| ART   | antiretroviral therapy   |
| ARV   | antiretroviral   |
| LMICs | Low and middle-income countries  |
| MSF   | Médecins Sans Frontières   |
| PLWHA | people living with HIV/AIDS  |
| SLTF  | patients failing second-line antiretroviral therapy (second-line treatment failures) |

## BACKGROUND

In 2000 HIV/AIDS antiretroviral therapy became available on a large scale in resource-limited settings. In 2009 5.2 million people living with HIV/AIDS (PLWHA) in low and middle income countries (LMICs) were receiving antiretroviral therapy (ART) and an estimated 2.4% (outside of the Americas) received a second-line regimen.<sup>1</sup>

Adherence to treatment predicts the level and duration of viral inhibition and immune recovery; whereas sub-optimal adherence leads to drug resistance, increased morbidity and mortality. To achieve good clinical outcomes, 95% adherence to ART is deemed necessary.<sup>2</sup> However, medication adherence behavior is complex and often unpredictable<sup>3-5</sup> and various factors have been identified leading to poor adherence.<sup>4,6-9</sup> Sub-optimal adherence can reduce the efficacy of treatment, leading to treatment failure and a need to switch to a more expensive<sup>1</sup> second-line regimen. In South Africa no third-line treatment options are available in the public sector for patients failing their second-line regimen.

In Khayelitsha, a periurban township of more than 500,000 inhabitants in Cape Town, has reported an increasing number of patients failing ART.<sup>10</sup> Khayelitsha has one of the highest burdens of HIV infection nationally and worldwide and antenatal HIV prevalence was more than 30% in 2009.<sup>10</sup> ARVs have been available since 2001 and more than 16,000 PLWHA accessed ART in 2010.<sup>11</sup> However, after 5 years on ART, an estimated 14% of patients experienced virological failure and 12% were switched to a second-line regimen.<sup>10</sup> Viral genotyping of patients failing a second-line regimen suggested that treatment failure was mainly due to sub-optimal treatment adherence rather than to resistance to second-line ART. Médecins sans Frontières (MSF), an international non-governmental organization, provides medical support at Ubuntu clinic. MSF initiated a program, in coordination with the provincial government, which dedicates staff and resources to provide clinical and counseling support to patients with at least one raised viral load on second-line ART.

The lack of a comprehensive understanding of barriers and facilitators of treatment adherence for patients on second-line ART is currently an obstacle to define a more patient centered model of care. The literature addressing the needs of this patient group in resource constraint settings is scarce. In addition, program data and experiences from health care staff indicate that characteristics of patients failing second-line ART are different from patients failing first-line ART. There is a need to improve understanding of adherence behavior within this patient population in an effort to decrease morbidity and mortality among patients failing second-line ART.

### AIMS AND OBJECTIVES OF THE STUDY

The overall aim of the study is to develop a model of adherence support for people on second-line ART in Khayelitsha. The objective is to identify main factors leading to sub-optimal adherence as well as facilitators that improve adherence to second-line ART. This will help to design an intervention to improve adherence to second-line ART that is feasible and sustainable in Khayelitsha.

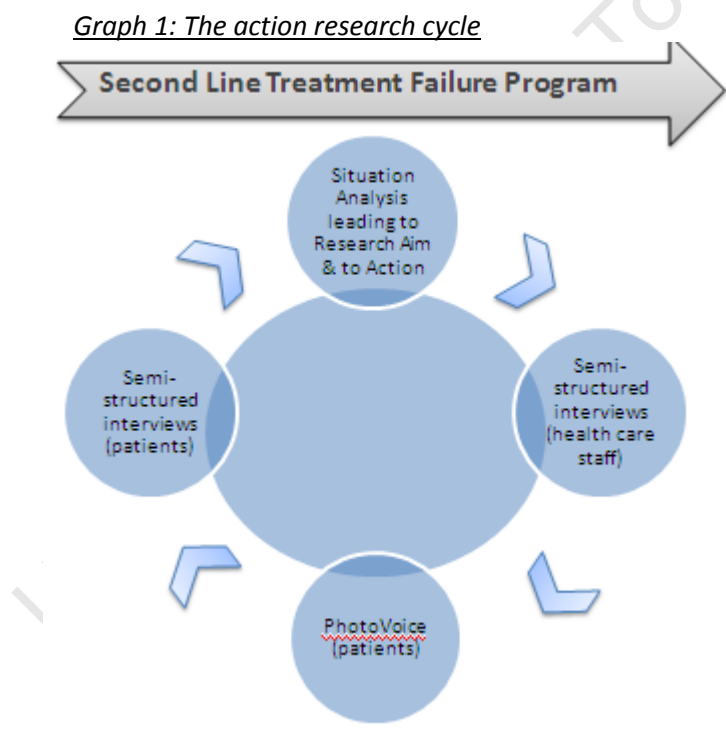
## METHODS

### Overview

Multiple research methodologies will be used for this study. Information collection and analysis methods during the research project will include the following:

- A **literature review**, with a focus on adherence issues related to second-line ART will help to identify factors associated with sub-optimal adherence.
- **Key informant semi-structured interviews** (including physicians, nurses, counselors) addressing second-line treatment adherence.
- **PhotoVoice**, a participatory qualitative research method, based on patients' use of cameras and brief text description of photos taken, will address issues related to the therapy and will give patients a voice.
- **Individual semi-structured interviews** with participants from the PhotoVoice project addressing issues revealed from PhotoVoice.

The sequence of this complex and interactive action research can be seen in graph 1.



### Literature review

The literature review will examine the following topics: 1) adherence to HIV/AIDS treatment, 2) HIV/AIDS treatment failure (first-line, and second-line in particular), 3) adherence issues in other chronic diseases, and 4) action research projects addressing adherence to HIV/AIDS treatment and, if not enough data are available, it will be extended to adherence to treatment for chronic diseases in general. Quantitative and qualitative literature will be searched for on a variety of medical and non-medical databases and websites. The search will concentrate on literature from Africa but, if felt necessary, it will be extended to other resource constrained settings.

## **Semi-structured interviews**

First we will interview key informants providing different levels of HIV/AIDS care to patients failing second-line ART at Ubuntu clinic. Second, we will also interview patients who participated in the PhotoVoice project.

### **a.) Semi-structured interviews with health care staff**

We will select participants among medical doctors, nurses and HIV counselors working with second-line treatment failures at Ubuntu clinic; at least three key informants from each health professional group. We expect to interview approximately 10-15 participants. Interviews will be conducted with a preference for staff with the longest work experience related to second-line treatment failures. Additional prospective key informant interviewees may also be identified during the interviews. The following topics will be addressed during the interviews: 1) challenges faced by key informants when providing health care to patients failing second-line antiretroviral therapy (SLTFs), 2) believed critical factors for sub-optimal ART adherence in SLTF and 3) opinion about the current quality of care delivered for SLTF at Ubuntu clinic.

### **b.) Semi-structured interviews with patients from the PhotoVoice project**

All participants from the PhotoVoice project will be asked to participate in the key informant interviews and we expect that about 10 interviews will be done. Interview questions were developed with input from all co-investigators on the project and used to guide participant interviews. We will investigate issues raised but not explored in detail in the Photovoice workshop. In addition, it will give participants the possibilities to discuss topics they did not want to talk about in the PhotoVoice workshop.

All interviews will be done either in English or isiXhosa. If done in isiXhosa, they will be translated back to English. An interview guide will be developed. Interviewers will be trained on key components of the interviewing process. The role of the interviewer will be to facilitate and encourage the interviewee to talk about their views and experiences related to the topic. Interviews will be structured (Appendix 1) and a full record of the interviews will be recorded. Interviews will generally last between 30 and 60 minutes, depending on the willingness of the participant to continue.

## **PhotoVoice**

We will use PhotoVoice as a culturally sensitive participatory method to mobilize PLWHA and failing their second-line ART. PhotoVoice entrusts cameras to people at grassroots level. It is a visual representation technique attempting to motivate and provoke participants to provide their interpretation and meaning to stimuli (e.g.: photos) presented from outside or created by the participants themselves<sup>13</sup> while the researcher acts as a facilitator. Visual representation techniques combined with interactive discussions have the advantage 1) to facilitate finding consensus in different views, 2) to prioritize topics of concern for participants, and 3) to encourage less active participants to actively participate in the discussions. It gives people who do not read or write, who have little money or power and are socially isolated or stigmatized a voice to share their stories and challenges related to treatment. PhotoVoice can reveal the everyday realities and challenges faced by SLTFs. It is not only a method aiming to gather information but also involves participants to investigate and define new ways forward.

Patients failing their second-line ART will be approached by a medical doctor or treatment counselor. The study will be explained to the participants in an appropriate language and the

invitation (Appendix 2), and information/ consent form (in either English or isiXhosa) left with the participant. Prospective participants will then be contacted after 24 hours to establish whether they are willing to participate. This agreement will then be re-affirmed once the participant has met the main researcher. All Participants willing to take part in the study will be invited to an orientation meeting about PhotoVoice. Participants will be briefed on project ground rules, photo-taking stages, calendar of deadlines and ethical considerations. Each participant will receive the following materials: a disposable camera labeled with the participant's name, envelopes, copies of the invitation and consent form (Appendix 2), photo release forms, PhotoVoice ethics and photo reflection sheet. Participants will have 2 weeks to take pictures and to return their cameras and the subject release forms to the researcher or to the MSF office in Khayelitsha. After one week, participants will be reminded of their deadline by phone. Each participant in the study will be expected to take at minimum 10 photographs. When receiving the cameras, the films will be developed and processed on CD and two standard-sized prints of each photo. Both sets of photos will be labeled on the back. The CD and one photo will be kept in a secure place in the MSF office and the second photo will be given back to the participant. Then a full-day workshop will be organized for all participants to come together to learn collectively from the PhotoVoice experience and share their experiences with other participants. The PhotoVoice workshop will promote critical reflection and dialogue by 1) selecting photographs for discussion, 2) contextualizing and sharing stories, and 3) codifying themes of the photographs. The workshop will take place in the MSF office in Khayelitsha. The workshop will be organized by the main researchers and will follow clear, defined steps. The workshop and interviews will either be held in isiXhosa or, if preferred by the participants, in English. The interviewer will be neutral and will rather be an interested listener than somebody valuing the interviewees' performance.

Patients with the following criteria will be eligible to participate: 18 years and older, and currently failing second-line ART (defined as having had at least one detectable viral load), and be enrolled for at least 6 months at Ubuntu clinic. We aim to approach all potentially eligible participants currently failing their second-line regimen, which program data indicate is approximately 15 patients.

### **Data analysis (semi-structured interviews and PhotoVoice)**

The interviews will be audio-recorded digitally, downloaded to a computer and transcribed. A study record will complement the interviews where specific reactions can be recorded that might not be caught on tape. By using an audio recorder, we will achieve a better understanding of the interviews. The transcribed and/or translated interviews will then be analyzed according to the content analysis method. The stories told by the participants will form the basis of the analysis.<sup>14</sup> The story will form the unit of analysis, with meaning units in the form of words, sentences or paragraphs derived from the interview. The use of meaning units aims to shorten the text without losing meaning, and allows for abstraction into themes, categories and codes. The derived categories are the backbone of the content analysis method, allowing for the parts of the material that share a commonality to be grouped. The derived categories will be both exhaustive and mutually exclusive, meaning that no data can be excluded on the basis of a lack of category. Categories can be divided into different sub-categories. The themes focus on the underlying meaning of the unit of analysis, that is the latent content and link the underlying meaning of the condensed meaning units, codes and categories together. A theme answers the question: how? The meaning units, codes and categories can fit into more than one theme as a theme visualizes the underlying meaning of the whole material. A theme can form sub-themes or be formed by sub-themes.<sup>14</sup> Since it will be recorded we will not be able to change what was said.

## **OTHER CONSIDERATIONS**

### **Informed consent process**

Only patients aged 18 years or older will be asked to participate. Participants with mental illness or intellectual disability will not be approached to participate in the study. All eligible participants will be assured that the information they give is confidential and all the information is kept in a fashion to secure this confidentiality. The participants will also be made aware that no names or other identification will be used and that it will not be possible to identify in any material presented or published. The informant will need to sign a written consent form with detailed information about the study (Appendix 2). The consent form will be available in English and also in isiXhosa for the PhotoVoice and patient key informant interviews. If the patient is unable to read the information and sign the consent form, the information will be read aloud and the participant will be able to verify acceptance to participate by using a thumb print or a cross on the signature line. In the case of the participant not being able to sign the consent form, a witness signature will be necessary. Participants will be informed that they can withdraw from the study at any point of the process. The information sheet and consent form (in either English or isiXhosa) will be left with the participant. Prospective participants will then be contacted either by telephone or home visit after 24 hours to establish whether they are willing to participate.

### **Data safety and confidentiality**

An identification code will be assigned to every patient. Thereafter, only the identification code will be used on all forms to safeguard the data. All data will be kept separately from identifying information, and both will be stored in locked files in the MSF office. Only research staff will have access to data. No identifying information will be disclosed in reports, presentations or publications.

### **Potential risks and benefits**

There are no substantial risks to participants through their participation in this study. However, the study process may cause some distress. To deal with this eventuality, all study participants will be followed up by counselors for emotional and psychosocial support.

The participants will develop an increased awareness about health issues related to their treatment which may lead to better drug adherence and clinical outcomes. Findings will also help to adapt trainings for health professionals. There is also the potential that photographs (PhotoVoice) could be displayed in public for advocacy reasons in order to reach policymakers, donors, media, researchers, and others who may be mobilized to create change. Other benefits include better understanding of reasons why patients fail second-line ART in this setting, which may lead to more efficient interventions.

### **Ethics**

Participants will have the option to keep their information confidential at any time during the research process and afterwards. Participants have the right to withdraw from the study at any time and without giving a reason. We will also destroy all potential identification information.

With regards to PhotoVoice, participants have the right not to take photos. Or if they do not wish their photos to be used during the PhotoVoice project or to be displayed publically later on, they can withdraw them at any time. One electronic set of photos will be kept and, if necessary and appropriate, used for advocacy. This electronic set of photos, however, will be destroyed if wished

by the participant. In order to use their photos publically, all participants will have to sign a consent form before. No photos will be displayed publically where other people beside the participant can be recognized. The whole process will be explained in detail to the participants before the study begins.

### **Reimbursement for participation**

Participants will not be remunerated for the time spent on the study. No other expenses are expected to occur to participants.

### **Communication of the results**

Preliminary results will be communicated to all staff working in Ubuntu clinic. Staff will have the opportunity to discuss and review the findings. The results of this study will be written up for publication in an international peer-reviewed journal: all findings will be summarized in an action research report and findings from the individual studies will be written up separately. Results of the study will also be disseminated to district level stakeholders and findings are expected to inform the national scale up of HIV/AIDS health care service in South Africa.

### **Resources and budget**

Costs associated with this project are for translation of written materials, translation of interviews and interview transcripts. For 10-15 interviews, it is estimated that approximately 50 hours will be required, plus an additional 5 hours for written translation. A budget of 7000 Rand has been allocated by MSF for this purpose. In addition, for approximately 10-15 cameras and photo developing costs, a budget of 10,000 Rand will be provided by MSF. All other resources, such as staff time, photocopying and computer access will be provided through the MSF project.

### **Timeline**

Ethical approval obtained April/ May.

|                   |   |
|-------------------|---|
| End of May        | Key Informant Interviews with health care staff; preparation for PhotoVoice |
| Beginning of June | PhotoVoice workshop   |
| July/August       | Individual patient semi-structured interviews                               |

Data analyses will start immediately after having finished data collection. The writing up of findings will start latest in September.

## PROTOCOL REFERENCES

1. *Towards Universal Access, Scaling up priority HIV/AIDS interventions in the health sector, Progress Report 2010*. 2010, World Health Organization: Geneva.
2. Catz, S.L., J.A. Kelly, and L.M. Bogart, *Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease*. *Health Psychol*, 2000. **19**: p. 124.
3. Hill, Z., C. Kendall, and M. Fernandez, *Patterns of adherence to antiretrovirals: why adherence has no simple measure*. *AIDS Patient Care and STDs*, 2003. **17**(10): p. 519-525.
4. Remien, R.H., et al., *Adherence to medication treatment: a qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities*. *AIDS Behav*, 2003. **7**(1): p. 61-72.
5. Reynolds, N., *Adherence to antiretroviral therapies: state of the science*. *Curr HIV Res*, 2004. **2**(3): p. 207-214.
6. Murphy, D., et al., *Barriers to antiretroviral adherence among HIV-infected adults*. *AIDS Patient Care STDs*, 2000. **14**(1): p. 47-58.
7. Heath, K.V., et al., *Intentional Nonadherence Due to Adverse Symptoms Associated With Antiretroviral Therapy*. *JAIDS*, 2002. **31**(2): p. 211-217.
8. Chesney, M., *Adherence to HAART regimens*. *AIDS Patient Care STDs*, 2003. **17**(4): p. 169-177.
9. Gordillo, V., et al., *Sociodemographic and psychological variables influencing adherence to antiretroviral therapy*. *AIDS*, 1999. **10**(13): p. 1763-1769.
10. *Providing HIV/TB Care At The Primary Health Care Level. Khayelitsha Activity Report 2008-2009*. 2010, MSF.
11. *Health information and data*. . 2010, City of Cape Town - Health Services.
12. *Routine health information and data*. 2010, Medecins sans frontieres: Khayelitsha, Cape Town.
13. Görden, R., *Youth Sexual & reproductive health:operational research for baseline and evaluation*, Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ): Eschborn.
14. Granheim, U.H. and B. Lundman, *Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness*. *Nurse Education Today*, 2004. **24**: p. 105-112.
15. O'Brien, R. *An Overview of the Methodological Approach of Action Research*. 1998 [cited 2010 29.04]; Available from: <http://www.web.net/~robrien/papers/arfinal.html>.
16. Hughes, I., et al., *International education for action research: the Bamenda model*, in *Action Research e-Reports*. 2004, The University of Sydney.

## **Part B: Structured Literature Review**

## LITERATURE REVIEW

### OBJECTIVES

This literature review provides context for the adjoining thesis entitled, “Barriers to adherence in patients failing second-line antiretroviral treatment in a township in South Africa: a qualitative research study.” Its objective is to present the current research on barriers to antiretroviral (ART) adherence, both personal and structural, to examine rates of adherence to ART in resource-limited settings and to review the risks associated with poor adherence and treatment failure for patients on ART.

### SEARCH STRATEGY

The search strategy was developed to include literature addressing issues related to both first- and second-line ART; terms included were barriers to adherence, resistance, second-line ART, qualitative and chronic medication adherence. A search of online databases was conducted, including MEDLINE via PubMed and Cochrane Central Register of Controlled Trials (CENTRAL). The search was not limited to a particular time frame, though where articles addressed very similar themes and/or questions, preference was given to the more recent articles.

### QUALITY AND RELEVANCE OF STUDIES INCLUDED

Both quantitative and qualitative studies were included in this literature review. No preference was given to study design; the literature reviewed below includes qualitative interviews and questionnaires, sub-studies within clinical trials, cohort studies, operational research and meta-analyses. The search strategy used yielded a large number of articles. In an effort to focus on those most relevant, the article abstract for each was reviewed and many were excluded. Studies included were selected based on relevance to population, with a preference for studies conducted in resource-limited settings, in particular sub-Saharan Africa. Preference was also given to literature on barriers to adherence as well as rates of non-adherence and resistance in patients on second-line ART rather than first-line. Only published, peer-reviewed studies and studies written in English were included.

### SUMMARY OF LITERATURE

#### *Setting*

By the end of 2010, the WHO estimated that 34 million people were living with HIV/AIDS (PLWHA), of whom more than 30 million live in low and middle-income countries (LMICs). The number of people on antiretroviral treatment (ART) in LMICs had reached 6.65 million people, a more than 16-fold increase in seven years. This represents 47% coverage of those in need of ART, up from 39% at the end of 2009.<sup>1</sup>

As access to ART increases, first- and second-line treatment failure has become more common.<sup>1,2</sup> There is an escalating need to mitigate failure rates and improve the effectiveness of ART within existing public health structures.<sup>3</sup> Treatment failure results in increased morbidity and mortality, larger numbers of PLWHA requiring more expensive second- and third-line treatment, and increased

risk of transmitting HIV, including drug-resistant strains.<sup>2</sup> Patients failing second-line regimens have no further treatment options available in the public sector in sub-Saharan Africa, as third line regimens are too costly.<sup>4</sup> Even second-line drugs are considerably more costly being, on average, six times more expensive than drugs commonly used for first-line regimens.<sup>2</sup>

Patients failing second-line treatment represent a high-risk group and are increasing in number where ART is readily available. However, much of the current literature focuses on barriers identified by patients on first-line ART and fails to explore whether those issues are similar for patients on second-line. It is important to investigate the barriers to adherence patients face on second-line treatment both to assess whether those reasons are similar or not to barriers identified for patients failing first-line and to identify opportunities to decrease the number of patients failing multiple treatment regimens. Furthermore, to our best knowledge, this study is among the first to evaluate facilitators and barriers to patient treatment for patients who have been clinically designated as failing multiple treatment regimens yet have subsequently become re-adherent. This group is of particular interest as they have remained in care following failure, offering an opportunity for the healthcare system to address their adherence-related issues.

This literature review focuses on multiple aspects of treatment failure. The primary research question relates to barriers to treatment adherence as a means of understanding treatment failure. As background, the initial discussion centers around the relationship between adherence, resistance and failure including rates of each within both first- and second-line treatment groups. Following that, literature is presented on both quantitative and qualitative research identifying barriers at the individual and structural level. Lastly, literature addressing facilitators to adherence is reviewed.

#### *Relationship between Adherence, Resistance & Failure*

As treatment failure is central to this study, it is important to define it. There are many routes that can lead to treatment failure in patients. Patients initiated on ART can be designated as treatment failures via clinical indicators, raised viral loads or depressed CD4 counts. A clinical versus laboratory failure differentiates between indicators of HIV disease progression (symptoms, co-morbidity, depressed health) and laboratory confirmed viral loads or CD4 counts. The metric used depends on the setting, resources available and national guidelines. Whether diagnosed clinically or laboratory-confirmed, treatment failure can result from non-adherence or resistance to one or more drugs within an ART regimen.

Non-adherence occurs when a patient does not take their medication as prescribed. It can manifest as a patient taking none of their ART or taking a sub-optimal dose, with adherence rates of less than 90%<sup>5,6</sup> to 95%.<sup>7,8</sup> Resistance is when a patient's particular strain of virus is no longer responsive to one or more drugs in a treatment regimen. It can occur when a patient is non-adherent and their virus develops resistance to a drug or when a patient is primarily or secondarily infected with an already resistant strain of HIV.

#### *ART Adherence, Resistance & Failure Rates*

As detailed below, levels of ART failure and non-adherence have been documented as high as 47% and 68% respectively. These high levels of ART failure and non-adherence highlights the need to identify and address barriers to adherence. In particular, patients who have failed first-line antiretroviral therapy have already displayed insufficient adherence and, once switched to second-line, are likely a higher risk group for virological failure than those patients continuing on first-line. As discussed above, there are two broad measures of ART failure, clinical and laboratory. Clinical failure refers to the assessment by a clinician of treatment failure through clinical symptoms whereas virological failure is laboratory-confirmed high viral loads, in most cases two consecutive measures >1,000 copies/mL.<sup>4</sup>

Table 1 below summarizes the findings of eight studies that were conducted, almost exclusively in sub-Saharan Africa, measuring adherence, failure and resistance rates; six of these deal directly with rates for patients on second-line ART. This overview is to present the scale of the problem of non-effective antiretroviral treatment and thus underscore the need to understand and address issues of adherence in these patient populations.

Table 1. Overview of second-line adherence, failure and resistance rates.

| Author                              | Location                  | Findings   | Study description  |
|-------------------------------------|---------------------------|--|--|
| Rosen <sup>9</sup><br>(2007)        | Sub-Saharan Africa        | 40% discontinuing medication   | Cross sectional study identifying drop out rates for patients on 1 <sup>st</sup> and 2 <sup>nd</sup> line ART.       |
| Hinkin <sup>10</sup><br>(2004)      | US                        | 67% & 32% adherence  | Compared adherence rates over one month period in adults over 50 years and under 50 years, respectively.             |
| Murphy <sup>11</sup><br>(2012)      | South Africa              | 25% failure rate 12 months after initiating 2nd line   | Prospective cohort study assessing adherence and failure rates of patient group switching from 1st to 2nd line ART.  |
| Charpentier <sup>12</sup><br>(2011) | Cameroon                  | 5.2% failed second-line; 80% of those (43) had resistance to one drug.   | Cohort study of 819 1st and 2nd line patients assessing failure and adherence rates                                  |
| El Khatib <sup>13</sup><br>(2010)   | Soweto, South Africa      | 12% of patients on 1st line failed; 33% of patients on 2nd line failed; 78% of those failing 2nd line had drug resistance. | 2008 cross sectional study assessing virological failure for patients taking ART for more than 12 months.            |
| van Zyl <sup>14</sup><br>(2011)     | Khayelitsha, South Africa | 40% of second-line patients failed; 5.4% of those had resistance   | Study of patients on 2nd line ART to assess failure rate and resistance (via genotyping).                            |
| Carpentier <sup>15</sup><br>(2012)  | Central African Republic  | In 15 second- or third-line ART patients, 47% had both virological failure as well as resistance.                          | Study of 242 HIV infected children in the Central African Republic to assess rates of failure and resistance to ART. |
| Ajose <sup>16</sup><br>(2012)       | Multi-country (LMICs)     | Virological failure rates assessed at 6, 12, 24 and 36 months were found to be 22, 23, 27 & 38% respectively.              | Meta-analysis of second-line patients from LMICs, including 19 studies to assess virological failure.                |

The majority of studies above report high rates of non-adherence (40%<sup>9</sup>, 32%<sup>10</sup> and 67%<sup>10</sup>), virological failure (25%<sup>11</sup>, 5.2%<sup>12</sup>, 33%<sup>13</sup>, 40%<sup>14</sup> and 47%<sup>15</sup>) and resistance (80%<sup>12</sup>, 78%<sup>13</sup>, 5.4%<sup>14</sup> and 38%<sup>16</sup>). The study that found a 5.4% resistance rate in second-line ART patients involved a cohort of patients that had been on second-line treatment for a shorter time than the other three studies which reported between 38-80% resistance. Less time on ART likely resulted in fewer mutations creating resistance at the time of the study. The reported rates of non-adherence and failure also involve quite large ranges, which is most likely due to both different settings and the small sample sizes of patients on second-line ART involved in the studies. Overall, this evidence highlights the need to understand what behavior, perceptions or system-level barriers are contributing to patient's high rates of non-adherence and resulting virological failure. Identifying barriers for patients taking second-line ART is a critical step to inform interventions for this group.

### *Individual Barriers to Adherence*

Much of the literature on ART adherence has focused on individual-level barriers such as perceived social support<sup>17</sup>, substance abuse<sup>18</sup> concerns about stigma<sup>19</sup> and depression or psychological stress.<sup>20</sup> Research conducted in Kibera, a slum near Nairobi identified non-disclosure and not having a treatment buddy/low levels of social support as barriers.<sup>21</sup> A cohort study conducted in Johannesburg found that, amongst women, the most common reasons for non-adherence was being away from home, being too busy and forgetting to take their medication.<sup>13</sup> These issues were all identified quantitatively in patient populations on first-line ART.

A number of qualitative studies have been conducted on barriers to adherence, though these have also focused largely on first-line ART; with only two expressly including barriers faced by patients on second-line ART. Studies have shown that women living with children<sup>22</sup> and being unmarried<sup>23</sup> to be associated with lower adherence rates. Therapy-related factors such as complex treatment regimens, a large number of pills, number of daily doses<sup>22,24</sup>, food restrictions and side effects<sup>25,26</sup> are significantly associated with non-adherence. Patient perceptions of chronic medication and not wanting to take lifelong treatment were also factors.<sup>26</sup> Patient-related factors have been found to include low patient self-efficacy, psychological distress and depression<sup>22,24</sup> as well as fear of death and medication adversely affecting existing relationships.<sup>26</sup> Furthermore, inadequate confidence in treatment effectiveness and poor understanding of the relationship between adherence and the development of resistance influenced non-adherence.<sup>22</sup>

Some qualitative studies have focused efforts on uncovering the motivations behind reasons for non-adherence by unpacking issues commonly cited or looking at themes that related to frequently cited barriers. Specifically, issues such as power dynamics between patient and doctor, concepts of missed doses, patient latitude over their medication and religious beliefs' affect on treatment have been addressed.

In a qualitative study on ART adherence in Tanzania Mattes<sup>27</sup> found the asymmetrical power dynamic existing between the patient and doctor to be problematic as patients felt dictated to and powerless over ART in their lives. Additionally, patients felt many of the spheres under discussion that related to their medication such as sexual practices, nutrition, mental health were violating and inherently intrusive. This left many patients feeling violated and powerless with regard to the course of treatment.

A study by Sankar<sup>28</sup> looked at the concept of missed dose and the extent of concordance or discordance between clinicians and patients regarding its definition. Once again, patients felt that there was a powerlessness over medication in their lives, feeling that a missed dose represented a moral failing and that they had done wrong. Additionally, though Mattes<sup>27</sup> found the rigidity of rules around taking medication to be problematic, Sankar<sup>28</sup> found that similarly patients felt powerless but also that where guidelines were vague, they took the strictest interpretation of parameters around medication. This caused many patients not to take medication in situations where a clinician would instruct them to do so (e.g. if the clinician would have instructed a patient to take their medication if 30 minutes late, patients felt unable to make that decision and rather chose not to take a late dose).

A qualitative study in Zambia to assess reasons for discontinuing ART found that some of the lifestyle changes required as part of the parameters of ART such as not drinking, condomizing and eating sufficient food were too difficult to make a permanent part of their lives. Medicines were also thought of as curative, so the idea of chronic medication was difficult for patients to internalize. Lastly, many women found it difficult for their status not to disrupt marriages/relationships and

would rather risk getting sicker than lose these relationships, thus when relationships were threatened, these women would discontinue their medication.<sup>26</sup>

A US study examined the role of religion/spiritual beliefs in adherence behavior. Looking at 79 HIV-positive patients who were offered ART by their physicians, those believing that God/Higher Power controls health were 4.75 times more likely to refuse. Participants believing religion helps them to cope with side effects reported significantly fewer symptoms/side effects and better adherence. Spiritual beliefs therefore operated as both barriers and motivators for treatment adherence in treatment management for those who are HIV-positive.<sup>29</sup>

A meta-analysis of quantitative studies found barriers specific for sub-Saharan Africa to be cost, non-disclosure, fear of being stigmatized, alcohol abuse and difficulty in following complex regimens.<sup>30</sup> A meta-analysis including both quantitative (47) and qualitative (37) studies found issues of access, financial constraints and availability of medication (i.e. stock outs) to be adherence barriers in low-resource settings. Common to both developed and developing countries, were substance abuse, forgetting medication, complicated regimens/number of pills, decreased quality of life and family/work responsibilities. The primary barrier identified in qualitative studies was the lack of trained facilitators/counselors.<sup>31</sup>

Though some of the qualitative studies uncovered barriers similar or the same as those found in the quantitative studies, many delved deeper into underlying psychosocial issues affecting adherence behavior. Rather than depression, forgetting or side effects, cross cutting themes such as patient-doctor power relationships, spiritual beliefs or views on curative rather than chronic medication offer different perspectives to consider when discussing issues of adherence or non-adherence. Though many quantitative and qualitative studies have considered the question of barriers to adherence, there are still areas that are unexplored. Specifically for the population of interest in the adjoining study, issues such as continued engagement with the health care system following failure/discontinuation and successful re-adherence have not been sufficiently explored in the literature.

#### *Structural Barriers to Adherence*

Structural issues affecting adherence rates have also been documented, specifically poverty-related barriers, lack of transportation infrastructure, food insecurity and poor social support. Institutional factors such as difficulty accessing mental health services, overburdened healthcare facilities and staff and poorly trained counselors<sup>32</sup> have been shown to affect adherence. In one study patients were found to have low rates of food security, making it difficult to continue medication due to increased appetites and the need to counteract previous weight loss as well as to feel sufficiently healthy to continue drug regimens.<sup>33</sup> Likely a factor affecting both food security and health, one study found having a low monthly income to be associated with low adherence.<sup>23</sup> Research conducted in Kibera, a slum near Nairobi, demonstrated that low levels of education and poverty were additional structural factors affecting adherence.<sup>21</sup>

Where transportation networks were poor, patients cited inability to make it to clinic appointments, especially to re-fill prescriptions, and the cost of transportation to be prohibitive.<sup>34</sup> This relates to logistical barriers, which beyond transportation, included long queues at clinics, difficulty of taking off time from work and distance from clinics.<sup>35</sup> A lack of trained facilitators/counselors was also the most cited barrier in qualitative studies assessed by meta-analysis.<sup>31</sup> Often lay counselors are employed in an effort to alleviate the burden of existing healthcare professionals, however, insufficient emphasis is often placed on training and ongoing supervision. In one study this was found to result in lay counselors who are only able to disseminate information rather than deal with

patient issues such as emotional stress, alcoholism and substance abuse or appropriate recognition of clinical issues affecting patient behavior.<sup>36</sup>

The myriad of factors identified and the cross cutting nature of many of those factors confirms their complexity<sup>37-40</sup> and the difficulty of addressing these issues, perhaps most especially those issues that are more structural than individual in nature. However, the better barriers to effective treatment are understood, the easier it will be to not only design interventions to address these barriers but also to appropriately allocate resources aimed at reducing those barriers.

#### *Facilitators to Adherence.*

Facilitators to adherence have not featured as prominently in the literature as barriers.

The meta-analysis which included both quantitative (47) and qualitative (37) studies found that none conducted in developing countries discussed facilitators to adherence.<sup>31</sup> However, subsequent studies have investigated facilitators, finding that having a fixed routine, understanding the need for compliance, seeing positive results, treatment knowledge, faith in treatment<sup>25</sup> and social support<sup>24</sup> to be adherence facilitators. Health system-related factors related to adherence include clear instructions regarding medication, better medical follow up, providing adequate knowledge about the relationship between adherence and resistance and support from nurses and pharmacists.<sup>22</sup>

#### **FURTHER RESEARCH**

Much of the current literature focuses on barriers identified by patients on first-line ART and fails to explore whether those issues are similar for patients on second-line. Patients who have failed second-line treatment, have failed multiple drug regimens, whether clinically determined or confirmed via high viral loads. For these patients it is important to understand whether poor adherence behavior fails to be identified or addressed or if issues affecting these patients are deeper, more psychosocial in nature and therefore more difficult to deal with. Focusing on this particular population using qualitative methods will help to illuminate both second-line specific barriers as well as facilitators that have enabled those who became re-adherent to change problematic adherence behaviors.

## LITERATURE REVIEW REFERENCES

1. WHO | Antiretroviral therapy. (n.d.).WHO. Retrieved May 26, 2012, from <http://www.who.int/hiv/topics/treatment/en/index.html>
2. WHO | Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. (n.d.).WHO. Retrieved May 26, 2012, from <http://www.who.int/hiv/pub/2010progressreport/en/>
3. WHO | Progress Report 2011: Global HIV/AIDS Response. (n.d.) WHO. Retrieved May 24, 2012 from [http://www.who.int/hiv/pub/progress\\_report2011/en/index.html](http://www.who.int/hiv/pub/progress_report2011/en/index.html).
4. South Africa Department of Health. (2004). National Antiretroviral Treatment Guidelines. Jacana.
5. Sethi, A. K. (2004). Adherence and HIV drug resistance. *HIV clinical trials*, 5(2), 112–115.
6. Arnsten, J. H., Demas, P. A., Farzadegan, H., Grant, R. W., Gourevitch, M. N., Chang, C. J., Buono, D., et al. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 33(8), 1417–1423.
7. Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association*, 19(2), 124–133.
8. Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., Wagener, M. M., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of internal medicine*, 133(1), 21–30.
9. Rosen, S., Fox, M. P., & Gill, C. J. (2007). Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Medicine*, 4(10), e298.
10. Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS (London, England)*, 18(Suppl 1), S19–S25.
11. Murphy, R. A., Sunpath, H., Castilla, C., Ebrahim, S., Court, R., Nguyen, H., Kuritzkes, D., et al. (2012). Second-line antiretroviral therapy: long-term outcomes in South Africa. *Journal of acquired immune deficiency syndromes (1999)*.
12. Charpentier, C., Talla, F., Nguépi, E., Si-Mohamed, A., & Bélec, L. (2011). Virological Failure and HIV Type 1 Drug Resistance Profiles Among Patients Followed-up in Private Sector, Douala, Cameroon. *AIDS Research and Human Retroviruses*, 27(2), 221–230.
13. El-Khatib Z, Ekstrom AM, Ledwaba J, et al. (2010). Viremia and drug resistance among HIV-1 patients on antiretroviral treatment: a cross-sectional study in Soweto, South Africa. *AIDS*, 24(11): 1679–1687.
14. van Zyl, G. U., van Mens, T. E., McIlleron, H., Zeier, M., Nachega, J. B., Decloedt, E., Malavazzi, C., et al. (2011). Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. *Journal of acquired immune deficiency syndromes (1999)*, 56(4), 333–339.
15. Charpentier, C., Gody, J.-C., Mbitikon, O., Moussa, S., Matta, M., Péré, H., Fournier, J., et al. (2012). Virological response and resistance profiles after 18 to 30 months of first- or second-/third-line antiretroviral treatment: a cross-sectional evaluation in HIV type 1-infected children living in the Central African Republic. *AIDS research and human retroviruses*, 28(1), 87–94.

16. Ajose, O., Mookerjee, S., Mills, E. J., Boule, A., & Ford, N. (2012) Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *AIDS*, 26:000–000
17. Holstad, M. K. M., Pace, J. C., De, A. K., & Ura, D. R. (2006). Factors associated with adherence to antiretroviral therapy. *The Journal of the Association of Nurses in AIDS Care: JANAC*, 17(2), 4–15.
18. Tucker, J. S., Orlando, M., Burnam, M. A., Sherbourne, C. D., Kung, F.-Y., & Gifford, A. L. (2004). Psychosocial mediators of antiretroviral nonadherence in HIV-positive adults with substance use and mental health problems. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association*, 23(4), 363–370.
19. Klitzman, R. L., Kirshenbaum, S. B., Dodge, B., Remien, R. H., Ehrhardt, A. A., Johnson, M. O., Kittel, L. E., et al. (2004). Intricacies and inter-relationships between HIV disclosure and HAART: a qualitative study. *AIDS care*, 16(5), 628–640.
20. Kilbourne, A. M., Reynolds, C. F., 3rd, Good, C. B., Sereika, S. M., Justice, A. C., & Fine, M. J. (2005). How does depression influence diabetes medication adherence in older patients? *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*, 13(3), 202–210.
21. Unge, C., Södergård, B., Marrone, G., Thorson, A., Lukhwaro, A., Carter, J., Ilako, F., et al. (2010). Long-Term Adherence to Antiretroviral Treatment and Program Drop-Out in a High-Risk Urban Setting in Sub-Saharan Africa: A Prospective Cohort Study. (G. Maartens, Ed.) *PLoS ONE*, 5(10), e13613.
22. Deschamps AE, Graeve VD, van Wijngaerden E, De Saar V, Vandamme AM, van Vaerenbergh K, et al. Prevalence and correlates of nonadherence to antiretroviral therapy in a population of HIV patients using Medication Event Monitoring System. *AIDS Patient Care STD* 2004; 18:644–657.
23. Byakika-Tusiime, J., Oyugi, J. H., Tumwikirize, W. A., Katabira, E. T., Mugenyi, P. N., & Bangsberg, D. R. (2005). Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. *International journal of STD & AIDS*, 16(1), 38–41.
24. Ammassari A, Trotta MP, Murri R, Castelli F, Narciso P, Noto P, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *J Acquir Immune Defic Syndr* 2002; 31 (Suppl 3):S123–S127.
25. Curioso, W. H., Kepka, D., Cabello, R., Segura, P., & Kurth, A. E. (2010). Understanding the facilitators and barriers of antiretroviral adherence in Peru: A qualitative study. *BMC public health*, 10(1), 13.
26. Murray, L. K., Semrau, K., McCurley, E., Thea, D. M., Scott, N., Mwiya, M., Kankasa, C., et al. (2009). Barriers to acceptance and adherence of antiretroviral therapy in urban Zambian women: a qualitative study. *AIDS care*, 21(1), 78–86.
27. Mattes, D. (2011). “We are just supposed to be quiet”: the production of adherence to antiretroviral treatment in urban Tanzania. *Medical anthropology*, 30(2), 158–182.
28. Sankar, A. P., Nevedal, D. C., Neufeld, S., & Luborsky, M. R. (2007). What is a missed dose? Implications for construct validity and patient adherence. *AIDS care*, 19(6), 775–780.
29. Kremer, H., Ironson, G., & Porr, M. (2009). Spiritual and mind–body beliefs as barriers and motivators to HIV-treatment decision-making and medication adherence? A qualitative study. *AIDS patient care and STDs*, 23(2), 127–134.
30. Mills, E. J., Nachega, J. B., Buchan, I., Orbinski, J., Attaran, A., Singh, S., Rachlis, B., et al. (2006). Adherence to antiretroviral therapy in sub-Saharan Africa and North America. *JAMA: the journal of the American Medical Association*, 296(6), 679–690.
31. Mills, Edward J, Nachega, J. B., Bangsberg, D. R., Singh, S., Rachlis, B., Wu, P., Wilson, K., et al. (2006). Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS medicine*, 3(11), e438.

32. Kagee, A., Remien, R. H., Berkman, A., Hoffman, S., Campos, L., & Swartz, L. (2011). Structural barriers to ART adherence in Southern Africa: Challenges and potential ways forward. *Global Public Health, 6*(1), 83–97.
33. Hardon, A. P., Akurut, D., Comoro, C., Ekezie, C., Irunde, H. F., Gerrits, T., Kglatwane, J., et al. (2007). Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. *AIDS care, 19*(5), 658–665.
34. Kagee, A., Le Roux, M., & Dick, J. (2007). Treatment adherence among primary care patients in a historically disadvantaged community in South Africa: a qualitative study. *Journal of health psychology, 12*(3), 444–460.
35. Breen, A., Swartz, L., Joska, J., Flisher, A. J., & Corrigan, J. (2007). Adherence to treatment in poorer countries: a new research direction? *Psychiatric services (Washington, D.C.), 58*(4), 567–568.
36. Rohleder, P., & Swartz, L. (2005). “What I’ve noticed what they need is the stats”: lay HIV counsellors’ reports of working in a task-orientated health care system. *AIDS care, 17*(3), 397–406.
37. Chesney, M. (2003). Adherence to HAART regimens. *AIDS patient care and STDs, 17*(4), 169–177.
38. Hill, Z., Kendall, C., & Fernandez, M. (2003). Patterns of adherence to antiretrovirals: why adherence has no simple measure. *AIDS patient care and STDs, 17*(10), 519–525.
39. Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: a qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. *AIDS and behavior, 7*(1), 61–72.
40. Reynolds, N. R. (2004). Adherence to antiretroviral therapies: state of the science. *Current HIV research, 2*(3), 207–214.

## **Part C: Journal “Ready” Manuscript**

University of Cape Town

## TITLE PAGE

### **Barriers to adherence in patients failing second-line antiretroviral treatment in a township in South Africa: a qualitative research study.**

Whitney Barnett<sup>1</sup>, Gabriela Patten<sup>2</sup>, Bernhard Kerschberger<sup>3</sup>, Karien Conradie<sup>4</sup>, Daniela Belen Garone<sup>5</sup>, Christopher J. Colvin<sup>6</sup>

**1** MPH, School of Public Health and Family Medicine, UCT, **2** MSc Epidemiology, Médecins sans Frontières, Khayelitsha, Cape Town, South Africa **3** MD, MPH, Médecins sans Frontières, Khayelitsha, Cape Town, South Africa **4** MBChB, DCH(SA), DipHIVMan(SA), Médecins sans Frontières, Khayelitsha, Cape Town, South Africa **5** MD (Infectious Diseases and Clinical Research), Médecins sans Frontières, Khayelitsha, Cape Town, South Africa **6** PhD (Anthropology), MPH, Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, UCT

**Conflicts of Interest and Source of Funding:** There were no conflicts of interest for any of the authors involved in this manuscript. The MSF Operational Centre in Brussels funds all MSF operations in South Africa, including Khayelitsha.

**Conferences:** Data presented at MSF UK Scientific Day, London, 25 May 2012.

**Author for correspondence:**

Gabriela Patten

Fax: +270213617051

Cell: +27 78 135 4333

E-mail: [msfb-khayelitsha-epid@msf.org.za](mailto:msfb-khayelitsha-epid@msf.org.za)

## ABSTRACT

**Introduction.** The recent scale-up of ART coverage in resource-limited settings has greatly improved access to treatment. However, increasing numbers of patients are failing first- and second-line ART. This study examined factors affecting adherence to second-line ART from the perspective of clinic staff as well as second-line failure patients, assessing both individual and structural barriers. Research was conducted at a large primary-care clinic in Khayelitsha, a peri-urban township in Cape Town, South Africa.

**Methods.** Participants were drawn from an MSF-run program to support patients failing second-line treatment. A qualitative research approach was used, combining multiple methodologies including: key informant interviews with staff (n=11), in-depth interviews with patients (n=10) and a Photovoice workshop (n=11).

**Results.** Staff identified drinking, non-disclosure, not using condoms, and pill fatigue as barriers to adherence, whilst patients identified side effects, not using condoms and lack of understanding around medication timing. With respect to service delivery, staff identified a need for continued counseling and educational support following ART initiation as important. Patients were concerned about missing medical records and poor staff attitudes in the broader clinic.

**Conclusions.** These findings identify a need for ongoing counseling and education following ART initiation as well as improved methods to quickly identify and address patient issues around medication adherence.

**Key Words:** second-line ART, second-line ART failure, ART adherence, HIV/AIDS South Africa, ART intervention, qualitative research

## INTRODUCTION

In 2010, the WHO estimated that 34 million people were living with HIV/AIDS (PLWHA), of whom more than 30 million were living in low- and middle-income countries.<sup>1</sup> Around 6.6 million were receiving anti-retroviral treatment (ART), a more than 16-fold increase in seven years.<sup>2</sup> With more people on ART, first- and second-line treatment failure has become more common.<sup>1,3</sup> Treatment failure results in increased morbidity and mortality, larger numbers of PLWHA requiring more expensive second- and third-line treatment, and increased risk of transmitting HIV, including drug-resistant strains.<sup>3</sup> For ART to be effective, adherence rates must be 90%<sup>4,5</sup> to 95%.<sup>6,7</sup> Studies also indicate that many failures are the result of sub-optimal adherence rather than the development of anti-retroviral resistance, suggesting a potential for continued efficacy with improved adherence.<sup>8,9</sup> Patients failing their second-line regimens have no further treatment options available in the public sector in sub-Saharan Africa, as third-line regimens are too costly.<sup>10</sup> With increasing numbers of patients failing first- and second-line treatment, there is an escalating need to mitigate failure rates and improve the effectiveness of ART within existing public health structures.<sup>11</sup>

This study examines the experiences of patients who have failed both first- and second-line ART identified through routine viral load testing. In a study at the same clinic, two interventions were evaluated, a patient centered support group and adherence-focused clinical consultation. It found that of 40 second-line failure patients who remained in care, 45% were able to achieve virological re-suppression at a three month follow up.<sup>12</sup> There is little evidence addressing barriers or facilitators to adherence in patients with multiple episodes of treatment failure and re-adherence. Further study is needed to better understand successful re-suppression of HIV in these patients. This study aims to investigate: 1) major barriers to and facilitators of ART adherence in this population and 2) areas of ART service delivery that shape patient behavior.

### Setting

This study was conducted at Ubuntu Clinic, a public sector HIV/TB clinic in Khayelitsha, a peri-urban township in Cape Town. Khayelitsha, with more than 500,000 residents, has one of the highest burdens of HIV infection nationally and worldwide, and antenatal HIV prevalence was more than 26% in 2010.<sup>13</sup> ARVs have been available since 2001 and more than 20,000 PLWHA were in ART care by 2011.<sup>14</sup> Ubuntu Clinic serves the biggest and oldest cohort of ART patients in Khayelitsha. By the end of 2011, 6296 patients in Khayelitsha were receiving ART, of whom 463 (7.4%) were on second-line treatment. Currently 20 new patients per month are starting second-line ART.<sup>13</sup>

Treatment success is assessed through viral load tests. National guidelines recommend viral loads be done at 4 and 12 months after treatment initiation and on a yearly basis thereafter.<sup>11</sup> After an initial high viral load (defined as >1000 copies/mL), patients attend adherence counseling and a follow-up viral load is taken after 3 months. Two consecutive viral loads >1000 copies/mL confirm laboratory virological failure, following which patients should be switched to a second-line ART regimen. At Ubuntu Clinic, after 5 years on ART, an estimated 14% of patients experienced laboratory virological failure and 12% were switched to a second-line regimen.<sup>15,16</sup> Previous studies have found second-line failure rates in South Africa to be as high as 33%<sup>17</sup> and 40%.<sup>18</sup> The latter study conducted viral genotyping at Ubuntu Clinic and found that 2 of 37 second-line laboratory failure patients had developed drug resistance.<sup>18</sup>

Médecins sans Frontières (MSF) is an international NGO that has worked closely with the public sector during the scale-up of ART coverage in Khayelitsha. In 2010 MSF, in collaboration with Ubuntu staff, developed and implemented a patient-centered model of care for those patients

failing second-line ART. The program provides a dedicated space, individual and group counseling support.

## **METHODS**

*Study Population.* Patients in MSF's second-line failure program (those with at least one viral load > 1000 copies/mL) were approached to take part in this study. Nurses, counselors and doctors were selected from both the MSF program and Ubuntu Clinic staff as key informants; they were purposively sampled to include those with the most exposure to patients on second-line ART.

*Data collection.* This study used multiple methods including in-depth patient and key informant interviews and a Photovoice workshop. Semi-structured interviews were developed with input from all co-investigators on the project. Key informant interviews focused on staff perspectives regarding reasons for treatment failure and barriers in health care delivery. Patient interviews focused on individual reasons for treatment failure and perceptions of clinic service delivery.

Patients also engaged in a Photovoice workshop, a participatory qualitative research method where participants are given disposable cameras to take photographs of predetermined themes, and then engage with each other around the meanings and experiences behind these photographs.<sup>19</sup> Participants took part in two day-long workshops. The first introduced Photovoice and, with participants, developed themes to explore the relationship between treatment and the people, places and ideas in their daily lives. Participants were then given two weeks to take photographs and return the cameras to the research team for development. In the second workshop, participants chose three of their photographs to share, and researchers facilitated discussion and identification of themes.

*Data analysis.* Interviews were conducted in both English (3) and isiXhosa (7), depending on participant preference, with the aid of a translator. Interviews and photovoice sessions were tape recorded and transcribed. Interview content and photographs were analyzed to identify recurring themes. A process of coding and categorization of data content assisted in bringing meaning to the responses and photographs.<sup>20,21</sup> Data was transformed into variables and analyzed accordingly.

## **RESULTS**

*Sample characteristics.* Of the 10 patients interviewed, nine were female and one was male. All live in Khayelitsha. On average these patients were on first-line ART for 32 months (range = 13 to 63 months) and on second-line ART for 38 months (range = 10 to 72 months). After being switched to second-line, on average patients experienced their first elevated viral load (>1000 copies/ml) at 12 months (range = 4 to 41 months). Of the 11 key informant interviews, three were nurses, four counselors, and four doctors. Staff had worked an average of 66 months in the clinic (range = 6 to 168 months).

### **Barriers and Enablers to Adherence**

*Patient cited barriers.* No patient responded that a single barrier caused their treatment failure and the majority (6) stated that they had made an active decision to stop taking their medication due to the barriers identified. Top reasons for ART failure (each cited by 3 patients) were side effects, not condomizing, lack of understanding around medication timing, DDI time delay between medication and food intake, and large pill size (Table 1).

*Key informant cited barriers.* The main adherence barriers cited by staff were patient drinking (9), non-disclosure (8), not condomizing (6), and pill fatigue (5), (Table 1).

*Side effects.* One third of patients identified side effects as a reason for treatment failure, citing nausea, vomiting, stomach pains and cramping:

“I have this diarrhea in my stomach and it’s cramping ... it started my viral to go up and up and up because I skip now because I’m scared that maybe I’m going to the church and my stomach maybe want to run.” (P06)

Another patient on second-line stopped because she did not realize her viral load would go up quickly and was surprised when it became detectable. One third of key informants also identified side effects as a barrier.

*Not condomizing.* One third of patients blame their failure on not using condoms:

“I had a boyfriend and didn’t condomize with the boyfriend. After that I...failed and was changed to second-line.” (P04)

Not condomizing also emerged as a central theme in the key informant interviews, with 6 of 11 respondents citing it as a reason for non-adherence. Key informants did appear to understand this risk to treatment success as a consequence of transmission of resistant strains. However, they seemed to inflate the risk of this occurring. One key informant described a tendency of staff to defer to an “easy” explanation for treatment failure.

*Timing of medication.* At ART initiation counselors instruct patients to take pills twice daily at the exact same time in the morning and evening. This is laid out as one of the “rules” of ART adherence and is presented in a concrete format allowing very little scope for the patients when times clashed with their schedules:

“To keep the time is too difficult. I take my pills at 7 but sometimes wake up at 8 and the time has passed.” (P05)

One patient (P04) often missed doses because of her work schedule. Another blamed his counselor for not telling him to take twice daily, e.g. 7am and 7pm. One third of patients indicated that they defaulted on first-line due to such strict parameters:

“Before they said to us, if you used to take your tablets at 8 o’clock in the morning or night you can’t take it at 9 o’clock because it’s too late. But [MSF counselors], said it’s not late, you must take the tablets. If you forget, maybe it’s two hours or one hour, you can take your tablets.” (P02)

Many patients cited this increased latitude around timing as helpful to becoming re-adherent, allowing them more freedom to adjust timing around their schedules. Only one key informant mentioned timing of medication as a barrier to patient adherence.

*DDI time delay.* Until 2009, South Africa guidelines recommended Didanosine (DDI) in its second-line regimen. It required patients to take the medication on an empty stomach, one hour before eating. This time delay was identified by one third of patients as the reason for their failure:

“You must leave [medication] for the hour and then you forget to take other tablets after that. You take it maybe at 6 o’clock; you have to run at 7 o’clock for the train...You think

okay that time is past, so you have to drink at night. That's why your viral load is so grown." (P06)

The DDI time delay was mentioned as a barrier to patient adherence in one of the key informant interviews.

*Pills too large.* One third of patients stated that they had difficulty taking their medication because of the large pill size. Two of these patients discontinued taking their second-line regimen for this reason:

"It was getting so difficult to take second-line. It was a big pill and I decided to stop." (P04)

Pill size was not noted in the key informant interviews as a reason for non-adherence.

*Patient drinking.* One patient identified drinking as a factor in her treatment failure. In the key informant interviews, however, alcohol use emerged as the most cited reason for failure (9). Staff said this affected adherence in two ways. First, patients often forget to take their medication when drinking. Secondly staff reported that, as with the timing of medication, patients understood that they could not drink and take their ARVs literally and stopped treatment altogether:

"[The patient] sees that he is much better and he will start to drink again. Its whereby most of them are failing because when they are drinking, they don't take their medication, they stop their medication." (KI02)

*Non-disclosure.* One patient identified non-disclosure as a barrier, citing the difficulty of maintaining ART without support at home where she felt she had to hide her medication.

Eight of eleven key informants indicated non-disclosure was problematic. Many of their patients felt the need to hide their medication and often would not take it when traveling or if others were present at work or home.

*Pill fatigue.* One patient identified pill fatigue as a reason for defaulting, noting:

"I just getting tired sometimes. To take treatment everyday is not nice." (P03)

Five of eleven key informants identified pill fatigue as a barrier.

### **Service delivery barriers**

*Clinic obstacles identified by patients.* Interviews revealed difficulties with healthcare delivery at Ubuntu, citing missing medical records (6) and clinic staff shouting at patients (6). Few, however, cited these problems in response to questions on defaulting or sub-optimal adherence. Rather, many seemed to view them as an expected part of clinic attendance; two patients stated that clinic problems affected their adherence or their attendance:

"Sometimes they will shout you if you ask something...shouting at the top of their voices. You feel not happy and you go home and feel unhappy. And next time you say I'm not going to this clinic anymore. " (P02)

*Clinic obstacles identified by key informants.* Staff identified a lack of continued counseling support following ART initiation (8) and insufficient education for patients (3) as key obstacles. One counselor noted:

“The point where we are failing is to really find out exactly why [the patient] is failing and try to fix the thing that makes them to fail first-line ... there is no time to focus on the problem, instead we are just providing the medication without support.”

Staff also highlighted the need for increased follow up with patients to catch adherence issues early. One clinician identified counseling as a critical but under-utilized component:

“There is so much pressure for roll out of getting more patients onto ARVs, getting nurses dishing out ARVs...counselors are being overlooked but they are a critical part of the whole process.”

Three of eleven key informants responded that there is no need for improvement and seven did not think the clinic needed more time or resources for patients. These staff felt that patients should engage better with the health care system, that many obstacles faced by patients are difficult for the clinic to solve, or that current resources could be managed better.

*Patient perspectives on MSF program.* Patients cited feeling more comfortable and free to share problems (7), shorter wait times (6), seeing the same staff (4) and support groups (2) as reasons they preferred MSF’s program to the larger clinic.

“I feel free now that on this side of the clinic. I can share everything ... when I come here I feel at home because before when I was taking medicine on that side [larger clinic], I was afraid whether I had done right or done wrong.” (P04)

A more patient centered environment enabled more open discussion of barriers to adherence and facilitated resolution of issues.

### **Photovoice patient perspectives**

The Photovoice component of the study elicited a different patient perspective on treatment compared to interviews. The photographs and the workshop discussion became a platform for sharing successes and sources of strength. Each patient chose three pictures to share (Table 2). Of thirty-three total photographs shared, only nine illustrated negative aspects of patients’ lives such as poor living conditions, difficulty remembering treatment, poor clinic service and not having family support. Yet, when presented by patients, these negative aspects were often treated as barriers overcome or obstacles to get past.

The remaining photographs (24 of 33) showed supportive family and friends (11), importance of treatment (5), gratitude toward the MSF clinic staff (3), religion as a source of strength (2), and overcoming drinking problems (2).

“I believe in tablets, because it’s my life and I will be taking treatment for life. Not for me, but for the kids too.” (P04)

## **DISCUSSION**

South Africa’s *National Strategic Plan on HIV, STIs and TB:2012-2016* calls for 80% of PLWHA to be receiving treatment by 2016,<sup>22</sup> expanding from the 56% of those eligible who were receiving ART in 2009.<sup>23</sup> However, this focus on initiating patients on treatment has largely ignored the rising numbers of failing patients.<sup>11,24</sup> This study aimed to identify barriers and facilitators to long-term ART adherence in the context of second-line treatment failure from the perspective of staff and

patients.

For some patients, ART failure resulted from a lack of understanding around the parameters of their medication. For others, the issues were psychosocial in nature, involving depression, bad living environments or lack of support at home. Yet some patients made an active decision to stop taking medication and became re-adherent when issues such as side effects, pill size or the time delay were addressed. Re-adherence occurred for most patients when a part of the smaller clinic (MSF), likely due to improved access to staff, continuity of staff and more supportive clinic environment, allowing for quicker follow up and more open discussion of issues affecting adherence.

There is currently an information gap between patients experiencing difficulties with treatment and clinic staff addressing those issues. There are personal and structural reasons behind this, stemming from patients not informing staff when experiencing difficulties, not understanding which behaviors will lead to raised viral loads and not feeling comfortable with staff. The most patient-cited clinic obstacle was staff shouting at patients; patients also highlighted the benefit of feeling open and able to share their issues with the MSF program staff. This emphasizes the importance of trust and communication between patients and staff, particularly between patients and counselors; patients' difficulties with treatment remained unresolved until the clinic environment changed, allowing for open discussion and management of those issues.

A tendency toward blaming external factors also emerged in both the patient and staff identified reasons for failure. The top patient identified barriers were side effects, not condomizing, DDI, large pills and not understanding medication, all but condomizing point toward obstacles external to the patient. Whereas staff identified patient drinking, not disclosing, not condomizing and pill fatigue most frequently, all of which focus more on patient behavior.

In the top obstacles identified, the only one common to both patients and staff was not condomizing. Through follow-up interviews staff seemed to understand not condomizing as contributing to the spread of resistant strain within the population. However, given the small numbers of those failing second-line ART, the likelihood of any patients in this sample contracting resistant strain rather than failure resulting from non-adherence is very low. Given the complexities<sup>25-28</sup> involved in identifying behaviors contributing to non-adherence one explanation is that both patients and staff found not condomizing a factor that is easily identifiable and relatively easily addressed, causing both to over-emphasize its role. Patients who do not fully understand their reason for failure would have a significant knowledge gap, which may affect their ability to identify and change the problematic behavior.

Many staff responded that there is no need for improvement in service delivery and that the clinic has sufficient resources to serve its patient population, highlighting a tendency amongst some staff not to be critical of the status quo or look for methods to improve current service delivery. All the indicators of service delivery denote Ubuntu as an exceptionally good public clinic and staff are proud of working there. The present focus on increasing ART coverage and the relatively few patients who are failing treatment has concentrated efforts to increase numbers of patients on ART, leaving little time to focus on the increasing rate of ART failures.

## **STUDY LIMITATIONS**

Interviews conducted in isiXhosa were translated by MSF staff, which may have influenced patient response. The study population was a small group of patients who had a very specific context of care delivery within a program separate from standard government clinical care. Thus their experiences within a better resourced environment than public clinical care is certain to have

affected their perspectives on service delivery as well as their high level of re-adherence. Additionally, because of the relatively low numbers of patients failing second-line, the large bulk of staff experience is with patients on first-line.

### **STUDY SIGNIFICANCE**

This study focused on a patient population that includes among the first patients in South Africa who have experienced virological failure on second-line medication. Yet many of these patients have been able to suppress their viral loads within the MSF-run program. This success highlights the importance of counseling, both to ensure patients are adequately equipped to initiate ART successfully and as the front line for identifying problems as they arise. Many of the patients who became re-adherent, benefitted from open relationships with clinic staff, enabling discussion and management of adherence issues. This offers both a challenge to the current system of ART initiation and continued support as well as an opportunity to improve patient outcomes where these relationships and structures are improved. The largely positive themes elicited by Photovoice illustrates that many multiple failure patients feel positively toward their treatment and lives and with improved support mechanisms this can translate into improved adherence and outcomes. Though some patients did make an active decision to stop taking ART, all continued to attend the clinic and engage with the healthcare system, demonstrating an opportunity for clinic staff to reduce failure rates in a patient population with no treatment option following failure of second-line ART.

### **FURTHER RESEARCH/RECOMMENDATIONS**

The frequency not condomizing was cited as contributing to ART failure should be further examined at the staff and patient level to ensure that messaging is not misleading and that patients address all behaviors affecting adherence. Continued follow-up, especially with regards to easily altered behavior or misunderstood medication parameters (e.g. timing, missed doses, forgetting) should be explored to identify how best to better equip patients for ART. Continuity of care and patient's comfort with staff is another area that could be explored to identify whether, and how, that may have contributed to improved patient outcomes in this group.

### **ACKNOWLEDGEMENTS**

The authors would like to acknowledge the dedicated staff at Ubuntu clinic and the participants who were involved in this study.

## ARTICLE REFERENCES

1. WHO | Antiretroviral therapy. (n.d.). *WHO*. Retrieved May 26, 2012, from <http://www.who.int/hiv/topics/treatment/en/index.html>
2. AIDS, Drug Prices and Generic Drugs. (n.d.). *AVERT*. Retrieved May 26, 2012, from <http://www.avert.org/generic.htm>
3. WHO | Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. (n.d.). *WHO*. Retrieved May 26, 2012, from <http://www.who.int/hiv/pub/2010progressreport/en/>
4. Sethi, A. K. (2004). Adherence and HIV drug resistance. *HIV clinical trials*, 5(2), 112–115.
5. Arnsten, J. H., Demas, P. A., Farzadegan, H., Grant, R. W., Gourevitch, M. N., Chang, C. J., Buono, D., et al. (2001). Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*, 33(8), 1417–1423.
6. Catz, S. L., Kelly, J. A., Bogart, L. M., Benotsch, E. G., & McAuliffe, T. L. (2000). Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health psychology: official journal of the Division of Health Psychology, American Psychological Association*, 19(2), 124–133.
7. Paterson, D. L., Swindells, S., Mohr, J., Brester, M., Vergis, E. N., Squier, C., Wagener, M. M., et al. (2000). Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of internal medicine*, 133(1), 21–30.
8. Levison JH, Orrell C, Gallien S, Kuritzkes DR, Fu N, Losina E, et al. Virologic failure of protease inhibitor-based second-line antiretroviral therapy without resistance in a large HIV treatment program in South Africa. *PLoS ONE*. 2012;7(3):e32144.
9. Ajose, O., Mookerjee, S., Mills, E. J., Boule, A., & Ford, N. (2012) Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. *AIDS*, 26:000–000
10. South Africa Department of Health. (2004). National Antiretroviral Treatment Guidelines. Jacana.
11. WHO | Progress Report 2011: Global HIV/AIDS Response. (n.d.) *WHO*. Retrieved May 24, 2012 from [http://www.who.int/hiv/pub/progress\\_report2011/en/index.html](http://www.who.int/hiv/pub/progress_report2011/en/index.html).
12. Conradie, K., Garone, D., Patten, G. et al. (2012). Intensive adherence counseling of patients on ARV treatment: a model of care for patients failing second-line treatment in Khayelitsha, South Africa. *Unpublished*.
13. 10 years of HIV/TB care at Primary Health Care Level. (2011). *Médecins sans Frontières*.
14. *Health information and data*. 2010, City of Cape Town - Health Services.
15. Boule, A., Van Cutsem, G., Hilderbrand, K., Cragg, C., Abrahams, M., Mathee, S., Ford, N., et al. (2010a). Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. *Aids*, 24(4), 563.
16. MSF report Khayelitsha\_2001-2011. (2011) *Médecins sans Frontières*, Retrieved, Feb 20, 2012 from [http://www.msf.org.za/system/files/publication/documents/MSF\\_report\\_Khayelitsha\\_2001-2011.pdf?download=1](http://www.msf.org.za/system/files/publication/documents/MSF_report_Khayelitsha_2001-2011.pdf?download=1).
17. El-Khatib Z, Ekstrom AM, Ledwaba J, et al. (2010). Viremia and drug resistance among HIV-1 patients on antiretroviral treatment: a cross-sectional study in Soweto, South Africa. *AIDS*, 24(11): 1679–1687.
18. van Zyl, G. U., van Mens, T. E., McIlleron, H., Zeier, M., Nachega, J. B., Decloedt, E., Malavazzi, C., et al. (2011). Low lopinavir plasma or hair concentrations explain second-line

- protease inhibitor failures in a resource-limited setting. *Journal of acquired immune deficiency syndromes* (1999), 56(4), 333–339.
19. Wang, C., Burris, M.A. (1997) Photovoice: Concept, Methodology, and Use for Participatory Needs Assessment. *Health Education & Behavior*, 24 (3), 369–387.
  20. Pope, C., & Mays, N. (1995). Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *Bmj*, 311(6996), 42–45.
  21. Elo, S., & Kyngäs, H. (2008). The qualitative content analysis process. *Journal of Advanced Nursing*, 62(1), 107–115.
  22. National Strategic Plan on HIV, STIs and TB: 2012–2016. (2011) *South African National AIDS Council*. Retrieved June 1, 2012 from <http://www.doh.gov.za/docs/stratdocs/2012/NSPfull.pdf>.
  23. USAID South Africa HIV/AIDS Profile. *USAID*. Retrieved May 20, 2012, from [http://www.usaid.gov/our\\_work/global\\_health/aids/Countries/africa/southafrica\\_profile.pdf](http://www.usaid.gov/our_work/global_health/aids/Countries/africa/southafrica_profile.pdf)
  24. Cornell, M., Grimsrud, A., Fairall, L., Fox, M. P., van Cutsem, G., Giddy, J., Wood, R., et al. (2010). Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007. *AIDS*, 24(14), 2263–2270.
  25. Chesney, M. (2003). Adherence to HAART regimens. *AIDS patient care and STDs*, 17(4), 169–177.
  26. Hill, Z., Kendall, C., & Fernandez, M. (2003). Patterns of adherence to antiretrovirals: why adherence has no simple measure. *AIDS patient care and STDs*, 17(10), 519–525.
  27. Remien, R. H., Hirky, A. E., Johnson, M. O., Weinhardt, L. S., Whittier, D., & Le, G. M. (2003). Adherence to medication treatment: a qualitative study of facilitators and barriers among a diverse sample of HIV+ men and women in four US cities. *AIDS and behavior*, 7(1), 61–72.
  28. Reynolds, N. R. (2004). Adherence to antiretroviral therapies: state of the science. *Current HIV research*, 2(3), 207–214.

## **Part D: Appendices**

University of Cape Town

## APPENDIX 1: QUESTIONNAIRE/DATA CAPTURE INSTRUMENT(S)

### Interview guide for individual semi-structured interviews (patients on second-line ART)

#### Introduction

1. Introduce the interviewer.
2. Explain the reasons for the interview and the aim of the project.
3. Reassure the patient that all information is confidential, that all material will be kept safe and who will have access to the material. Reassure that no material will be used in a way that a person can be identified. Quotes from the interviews will be used in the presentation but without any name or identification linked.
4. Participants will be asked again if they are willing to be interviewed and audio taped.
5. Ask the participant if they have any questions so far.
6. Explain the consent form and ask the patient to sign the form.

#### Intro questions/Photovoice Follow-up

1. Can you tell me where you live? Do you live with your family? Do you have children, how many, boys or girls?
2. Can you tell about when you were diagnosed with HIV?
3. Can you describe your thoughts on the photovoice workshop? Did it make you think in a new way about people or things in your life?
4. How does this relate to your life, the lives of people taking ARVs, or both?
5. What's the real story this photo tells?
6. Why did you choose the pictures you chose? Were the photos you chose of things that give you strength or of challenges?
7. What were the most important ideas you wanted to share through your photographs?
8. What are the most important things in your life?

#### Interview questions

The questions are to be used as a guide. Statements made by the participant can be followed up with questions like: What did you feel about that? How did that make you feel? What did you think about that? How did you understand that? What did you do then? How did you manage that?

#### A: Diagnosis of failing second-line ART

1. Can you please tell me how you were told that second-line treatment was no longer working? What information were you given at this point?
2. How did you feel when you were told that your second-line therapy is not effective anymore?

*Follow up questions to elaborate around:*

- *Fear*
- *Uncertainty*
- *Cause of ineffectiveness of therapy*
- *Social situations*
- *Family support*
- *Stigma*

3. What did you do when you were told that the second-line antiretroviral therapy are not effective?

*Touch on the issues like:*

- Health seeking behavior, going to the clinic, second opinion, traditional medicine etc?
- Social behavior, inclusion/isolation?
- Seeking support, family/friends, health care staff, religious institutions, government institutions (grants etc), other support.
- Disclosing

4. At that time, how did you think failure of second-line medication would change your life?

#### **B: Second-line ART**

1. How did you feel about starting second-line treatment compared to starting first-line treatment?
2. Were there any differences between taking first- and taking second-line treatment? (at the clinic, in your life, how you felt about your medication?)
3. Did your body react differently to second-line treatment compared to first?
4. What is your understanding of your treatment? Do you feel that you have all the knowledge you need to take your medication correctly? Has your understanding changed since starting first-line treatment? If so, how and when?
5. Why do you come to clinic and take your medication?
6. When you do not take your medication, what are the main reasons? What are some of the reasons you have heard from other people who are having trouble (grants, drinking, travel, remembering?)
7. What are your thoughts and feelings concerning the health care staff – specifically counselors, nurses and doctors?
8. Do you feel that the staff are supportive and helpful? Do you feel comfortable with staff?
9. When you started to have raised viral loads and low CD4 counts, how did you feel about going to the counselor? Were they able to help you with taking your medication? What were some of the things you discussed with them?
10. How do you feel about being in the smaller (MSF) group at the clinic? How is this different from your experiences of the clinic before?
11. How do you manage your HIV treatment?
12. What things in your life make it easier to take treatment? What things in your life make it more difficult to take treatment? How have those changed over time?

13. What were the reasons you think your first-line treatment failed? Do you think these are the same reasons your second-line treatment failed?

14. Is there anything you would change about the clinic staff or procedures that could make easier for you to take your treatment?

### **C: Summary**

1. How would you say that second-line HIV treatment has influenced the way you live your life?

2. How do you feel about the future?

3. Do you have any other statement or comment you would like to share?

### Post interview

- Follow up on any need for counseling that was picked up in the interview.
- Follow up with emotional and psychosocial support.
- Ask the participant if they would like to follow up with the interviewer at a later point in time.

University of Cape Town

## **Interview guide for key informant semi-structured interviews (health care staff)**

### **Introduction**

1. Introduce the interviewer.
2. Explain the reasons for the interview and the aim of the project. (Emphasize that the questions are about patients on second-line treatment and not about first-line.)
3. Reassure the interviewee that all information is confidential, that all material will be kept safe and who will have access to the material. Reassure that no material will be used in a way that a person can be identified. Quotes from the interviews will be used in the presentation but without any name or identification linked.
4. Participants will be asked again if they are willing to be interviewed and audio taped.
5. Ask the participant if they have any questions so far.
6. Explain the consent form and ask the participant to sign the form

### **Conversational questions**

1. How long have you been working in this clinic?
2. What is your job in the clinic? Can you explain your responsibilities?
3. Do you come from Khayelitsha? And if not, where do you come from?
4. Have you worked with patients failing second-line ART before?

### **Interview questions**

The questions are to be used as a guide. Statements made by the participant can be followed up with questions like: What did you feel about that? How did that make you feel? What did you think about that? How did you understand that? What did you do then? How did you manage that?

#### **A: Challenges in the delivery of health care to patients failing second-line ART**

5. How do you determine when patients need/are ready to be placed on second-line ART? (nurses/counselors)
6. Can you please tell me more about your responsibilities in the delivery of care to patients on second-line treatment?  
Follow up questions:
  - How are patients informed that they need to take second-line treatment?
  - Are patients informed about the difference between first- and second-line ART? When? How?
7. What do you think about patient's understanding of issues around taking their second-line medication?  
Follow up questions:
  - i.e. Timing of medication, nutrition, drinking alcohol
  - Do patients often have questions about these things?
8. What difficulties do you find when providing care for these patients?  
Follow up questions to elaborate around:
  - Personal emotional difficulties: fear, uncertainty, stigma, peer support, others
  - Lack of Knowledge

- Attitude
  - Practice
9. Do you think that more resources and time should be invested in patients failing second-line treatment?
    - Why is this necessary?
    - In what ways can additional resources and time be invested in patients failing second-line treatment?
  10. Can you explain how you were trained to work with patients failing second-line?
 

Follow up questions:

    - Do you feel prepared to work with these patients?
    - Do you think more training is needed and if yes what kind of training?
  11. Do you enjoy working with second-line patients? Why or why not?
 

Follow up questions:

    - What is the most difficult/worst or easiest/best part?

#### **B: Factors leading to sub-optimal adherence**

1. From your experience, what are the main factors that lead to sub-optimal adherence in patients on second-line?
 

Touch on the issues like:

  - Health seeking behavior, going to the clinic, second opinion, traditional medicine etc?
  - Social behavior, inclusion/isolation?
  - Seeking support, family/friends, health care staff, religious institutions, government institutions (grants etc), other support.
  - Disclosing
  - Health system/ clinic factors
  - Any other factors
2. When you notice that a second-line patient is having trouble maintaining adherence, what steps are taken to address this?
  - Are these steps sufficient
  - What else could be done
3. What explanations are given by second-line patients when their treatment is not working anymore?
 

Follow up question:

  - Can you provide examples of the reasons given?
  - How honest are these patients when talking about their treatment?
4. Do you notice shared characteristics for patients on second-line treatment who have trouble maintaining adherence?
 

Follow up question:

  - Is there a pattern for most patients? Consistently good/bad?
5. Does the patient ever mention factors that help them to take second-line treatment? (Please give examples)

5. How do you feel toward patients who have failed first-line? Follow-up questions:
  - Are these patients challenging for you?
  - Do you see a difference in patients failing first- versus failing second-line?
6. And how do you feel towards patients who fail the second-line treatment?

**C: Quality of care delivered and solutions**

1. Please share with us your opinion about the quality of care delivered to patients on second-line ART and those who are failing their treatment?
  - Enough time available for second-line patient and for patients failing second-line?
  - Behavior of staff
  - Are viral load measurements done often enough to detect treatment failure
2. If you could, what components in the delivery care would you change for these patients and why?  
Follow up questions:
  - Do you think there is anything the health care provider can change that will affect patient's adherence?
  - Do you see problems in the way a patient receives care at the clinic?
  - How can these problems you mentioned be addressed? (Either by the health care provider or patient in order to improve adherence.)
  - Do you have any ideas about how to improve adherence?
3. Do you feel like you need anything to help you do your job? If so, what?
4. Do you have any other statement or comment you would like to share?

## **APPENDIX 2: CONSENT FORMS AND PARTICIPANT INFORMATION FORMS**

### **PhotoVoice: Information and Consent form**

You are being invited to participate in a study about your experiences and challenges that you face when taking anti-retroviral therapy. This information will explain to you about this study, why it is being done, how it is done and what will happen to the result. This information is given to you so it will be easier for you to decide if you would like to take part in the study.

Please take your time and read/listen to it carefully and do not hesitate to ask questions to the researcher. They can be contacted at MSF Office (phone: 021 364 5490). You can also talk to people close to you about taking part in this study. If you decide to participate you will be asked to sign this consent form; you will get one signed copy to keep and the researcher will keep one signed copy.

#### **Information about the study and the researchers**

This study is being done to get a better understanding of the difficulties and challenges of patients who take antiretroviral therapy. By learning about the experiences of people taking antiretroviral therapy hopefully we can improve the way patients receive care and support in the future.

You will be invited to an orientation meeting which gives you an introduction to the study. During this meeting the purpose of the study will be explained.

Then you will receive a disposable camera and you will be asked to make photos about your experiences and challenges related to the treatment. You will have 2 weeks to take the photos. The films will be developed by MSF and you will receive a copy of each photo you made.

Then a full-day workshop will be organized for you and all participants of the study so that you can share your experiences with others. The aim will be to provide an opportunity for discussions and to enable people to record and reflect their strengths and problems related to HIV/AIDS treatment. You will have the opportunity to talk about your photos, how they relate to your life and treatment. The workshop will last for one day. The workshop will be audio taped so that no information is lost. The interviewer will also take some notes during the workshop and it will be conducted in a private location at MSF office and at a time suitable to all participants.

This study is supported by Medecins Sans Frontières (MSF) (Doctors without Borders).

#### **Important information:**

MSF may later use the photos and other documents for presentations to make other people better understand of the challenges faced by people taking second-line antiretroviral treatment. We will only use your photos when you give permission to do so.

There is also the possibility that photographs could be displayed in public to make other patients, health care staff, policymakers, donors, and media, aware about the problems faced by patients taking a second-line HIV treatment. However, it will not be possible to identify you by name or through other background information without your consent.. Therefore, MSF will keep one CD and one copy of your photos. But if requested by you, these copies will be destroyed and not photos will be displayed in the public.

The following people are responsible for this study:

- Dr Christopher Colvin, School of Public Health and Family Medicine, UCT, Cape Town
- Dr Bernhard Kerschberger, MPH, Epidemiologist MSF Khayelitsha
- Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha

You do not have to take part in this study. Your decision to take part in this study or not, will in no way affect your treatment. Information given during the interview will be kept safe and only the persons listed above will have access to it. Your identity will not be revealed in any material published or presented from this study. You can at any time during the PhotoVoice project choose not to participate or withdraw from the study completely without giving a reason.

If you wish to participate in PhotoVoice, you will have to sign the Consent form: PhotoVoice.

**If you have any concerns about the conduct of this research project, you can contact:**

Dr. Bernhard Kerschberger, Researcher, MSF Khayelitsha, tel: +27 21 364 5490-23

Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha, tel: +27 21 364 5490

The committee giving ethical approval for this study is the Human Research Ethics Committee, University of Cape Town. If you have any problems with, or questions about this study please contact the Ethics committee directly, telephone number 021 406 6338.

*(This document and the Consent form will be available in the most frequent local languages and will be read by or read to or translated to the participant.)*

**PhotoVoice: Consent Form**

Date: \_\_\_\_\_

**Name of participant:** \_\_\_\_\_

Name of Person taking consent: \_\_\_\_\_

1. I agree to take photos, to participate in the workshop and to be interviewed for this study. The principal researcher is Dr Christopher Colvin.
2. I understand that this study will be about patients on second-line HIV/AIDS treatment. I understand there will be questions about my personal experience when providing care for these patients.
3. I understand that my treatment will not be affected by whether or not I choose to participate in the interview.
4. I understand that I can refuse to participate in the study, refuse to take photos or refuse to attend the workshop or to answer specific questions. I understand that I can leave the study at any time.
5. I understand that during the workshop group and individual interviews will be audio-taped so as not to miss any important information. Transcripts and audiotapes will only be seen by the researchers.

6. I understand that I will not be identified in any of the survey reports or presentations resulting from this research.

7. I understand that the results of this study will be used to improve future treatment of patients receiving second-line antiretroviral treatment in Ubuntu clinic and elsewhere.

8. The facilitators have my permission to access the photos, photo reflections, and other documents that I develop as part of the project.

Yes  No

9. The facilitators have my permission to use photographs that may include me in presentations, as long as they do not identify me by name or through other background information without my consent.

Yes  No

Signature: \_\_\_\_\_  
(participant)

Date: \_\_\_\_\_

Signature: \_\_\_\_\_  
(person taking consent)

Date: \_\_\_\_\_

*If consent form was translated and/or explained to the participant, please enter the name and signature below*

Translators name: \_\_\_\_\_

Date: \_\_\_\_\_

Translators signature: \_\_\_\_\_

*If the participant is unable to give a written consent, please enter the name and signature of person witnessing the consent.*

Witness' name: \_\_\_\_\_

Date: \_\_\_\_\_

Witness' signature: \_\_\_\_\_

## **Information and Consent form: Key informant interviews**

Health care provider's experience of treating patients failing second-line HIV/AIDS treatment

You are being invited to participate in a study about your experiences and challenges faced during the work with people on second-line antiretroviral treatment. This information will explain to you about this study, why it is being done, how it is done and what will happen to the result. This information is given to you so it will be easier to decide if you would like to take part in the study.

Please take your time and read it carefully and do not hesitate to ask questions to the researcher. They can be contacted at MSF Office (Tel: +27 21 364 5490). You can also talk to people close to you about taking part in this study. If you decide to be interviewed you will be asked to sign this consent form, you will get one signed copy to keep and the researcher will keep one signed copy.

### **Information about the study and the researchers**

This study is being done to get a better understanding of the difficulties and challenges faced by health care providers who work with people on second-line antiretroviral therapy. By learning about the experiences of taking HIV/AIDS treatment hopefully we can improve the way patients receive care and support in the future.

You will be asked to participate in an individual interview with the researcher. The interviews will last for about 30 to 45 minutes. The questions will be about your experience when providing health care for people taking second-line antiretroviral therapy. The interview will be audio taped so that no information is lost. The interviewer will also take some notes during the interview. The interview will be conducted in a private location and at a time suitable to you.

This study is supported by Medecins Sans Frontières (MSF) and the University of Cape Town (UCT).

MSF may later use documents for presentations in order to make other people better understand of the challenges faced by health care providers when providing health care for people failing second-line antiretroviral therapy. It will not be possible to identify you by name or through other background information.

The following people are responsible for this study:

Dr Christopher Colvin, School of Public Health and Family Medicine, UCT, Cape Town

Dr Bernhard Kerschberger, MPH, Epidemiologist MSF Khayelitsha

Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha

You do not have to take part in this study. Your decision to take part in this study or not, will in no way affect your work. Information given during the interview will be kept safe and only the persons listed above will have access to it. Your identity will not be revealed in any material published or presented from this study. You can at any time choose not to participate and withdraw from the study completely. You can decide to stop taking part in this study at any time, without giving a reason, and without affecting your work.

Through the interviews we will know more about the challenges faced by you when providing HIV/AIDS care to people on second-line antiretroviral treatment. With this information we hope to improve the care and provide better support to these patients.

If you wish to participate in Key informant interviews, you will have to sign the Consent form: Key informant interviews.

**If you have any concerns about the conduct of this research project, you can contact:**

Dr. Bernhard Kerschberger, Researcher, MSF Khayelitsha, tel: +27 21 364 5490-23

Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha, tel: +27 21 364 5490

The committee giving ethical approval for this study is the Human Research Ethics Committee, University of Cape Town. If you have any problems with, or questions about this study please contact the Ethics committee directly, telephone number 021 406 6338.

**Consent form: Key informant interviews**

Date: \_\_\_\_\_

**Name of participant:** \_\_\_\_\_

Name of Person taking consent: \_\_\_\_\_

10. I agree to be interviewed for this study. The principal researcher is Dr Christopher Colvin.
11. I understand that this study will be about the health care provider's experience providing health care for patients on second-line HIV/AIDS treatment. I understand there will be questions about my personal experience when providing care for these patients.
12. I understand that my work will not be affected by whether or not I choose to participate in the interview.
13. I understand that I can refuse to participate in the study. I understand that I can leave the study at any time and I understand that I can also stop the interview at any time.
14. I understand that the individual interviews will be audio-taped so as not to miss any important information. Transcripts and audiotapes will only be seen by the researchers.
15. I understand that I will not be identified in any of the reports or presentations resulting from this research.
16. I understand that the results of this study will be used to improve future treatment of patients receiving second-line antiretroviral treatment in Ubuntu clinic and elsewhere.
17. The researchers have my permission to interview me.  
 Yes                       No
18. The researchers have my permission to use information given during the interviews, as long as I cannot be identified by name or through other background information without my consent.  
 Yes                       No

Signature: \_\_\_\_\_  
(participant)

Date: \_\_\_\_\_

Signature: \_\_\_\_\_  
(person taking consent)

Date: \_\_\_\_\_

*If consent form was translated and/or explained to the participant, please enter the name and signature below*

Translators name: \_\_\_\_\_

Date: \_\_\_\_\_

Translators signature: \_\_\_\_\_

*If the participant is unable to give a written consent, please enter the name and signature of person witnessing the consent.*

Witness' name: \_\_\_\_\_

Date: \_\_\_\_\_

Witness' signature: \_\_\_\_\_

University of Cape Town

## Information and Consent form: Patient interviews

Patients' experiences of taking second-line antiretroviral therapy

You are being invited to participate in a study about your experiences and challenges faced when taking your second-line antiretroviral therapy. This information will explain to you about this study, why it is being done, how it is done and what will happen to the result. This information is given to you so it will be easier to decide if you would like to take part in the study.

Please take your time and read it carefully and do not hesitate to ask questions to the researcher. They can be contacted at MSF Office (Tel: +27 21 364 5490). You can also talk to people close to you about taking part in this study. If you decide to be interviewed you will be asked to sign this consent form, you will get one signed copy to keep and the researcher will keep one signed copy.

### Information about the study and the researchers

This study is being done to get a better understanding of the difficulties and challenges faced by patients who take second-line antiretroviral therapy and who had two detectable viral loads during the last year. We aim to investigate in more detail the difficulties associated with this therapy and hopefully the findings will help us to improve care and support in the future.

You will be asked to participate in an individual interview with the researcher. The interviews will last for about 30 to 45 minutes. The questions will be related to your antiretroviral therapy. The interview will be audio taped so that no information is lost. The interviewer will also take some notes during the interview. The interview will be conducted in a private location and at a time suitable to you.

This study is supported by Medecins Sans Frontières (MSF) and the University of Cape Town (UCT).

MSF may later use documents for presentations in order to make other people better understand of the challenges faced by you and other patients. It will not be possible to identify you by name or through other background information.

The following people are responsible for this study:

Dr Christopher Colvin, School of Public Health and Family Medicine, UCT, Cape Town

Dr Bernhard Kerschberger, MPH, Epidemiologist MSF Khayelitsha

Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha

You do not have to take part in this study. Your decision to take part in this study or not, will in no way affect your work. Information given during the interview will be kept safe and only the persons listed above will have access to it. Your identity will not be revealed in any material published or presented from this study. You can at any time choose not to participate and withdraw from the study completely. You can decide to stop taking part in this study at any time, without giving a reason, and without affecting your work.

If you wish to participate in Key informant interviews, you will have to sign the Consent form: Patient Key informant interviews.

**If you have any concerns about the conduct of this research project, you can contact:**

Dr. Bernhard Kerschberger, Researcher, MSF Khayelitsha, tel: +27 21 364 5490-23

Dr Karien Conradie, HIV/TB doctor, MSF Khayelitsha, tel: +27 21 364 5490

The committee giving ethical approval for this study is the Human Research Ethics Committee, University of Cape Town. If you have any problems with, or questions about this study please contact the Ethics committee directly, telephone number 021 406 6338.

*(This document and the Consent form will be available in the most frequent local languages and will be read by or read to or translated to the participant.)*

**Consent form: interviews**                      Date: \_\_\_\_\_

**Name of participant:** \_\_\_\_\_

Name of Person taking consent: \_\_\_\_\_

19. I agree to be interviewed for this study. The principal researcher is Dr Christopher Colvin.
20. I understand that this study will be about the health care provider's experience providing health care for patients on second-line HIV/AIDS treatment. I understand there will be questions about my personal experience when providing care for these patients.
21. I understand that my work will not be affected by whether or not I choose to participate in the interview.
22. I understand that I can refuse to participate in the study. I understand that I can leave the study at any time and I understand that I can also stop the interview at any time.
23. I understand that the individual interviews will be audio-taped so as not to miss any important information. Transcripts and audiotapes will only be seen by the researchers.
24. I understand that I will not be identified in any of the reports or presentations resulting from this research.
25. I understand that the results of this study will be used to improve future treatment of patients receiving second-line antiretroviral treatment in Ubuntu clinic and elsewhere.
26. The researchers have my permission to interview me.

Yes                       No

27. The researchers have my permission to use information given during the interviews, as long as I cannot be identified by name or through other background information without my consent.

Yes                       No

Signature: \_\_\_\_\_  
(participant)

Date: \_\_\_\_\_

Signature: \_\_\_\_\_  
(person taking consent)

Date: \_\_\_\_\_

*If consent form was translated and/or explained to the participant, please enter the name and signature below*

Translators name: \_\_\_\_\_ Date: \_\_\_\_\_

Translators signature: \_\_\_\_\_

*If the participant is unable to give a written consent, please enter the name and signature of person witnessing the consent.*

Witness' name: \_\_\_\_\_ Date: \_\_\_\_\_

Witness' signature: \_\_\_\_\_

University of Cape Town

## APPENDIX 3: LETTER OF APPROVAL FROM RESEARCH ETHICS COMMITTEE



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences  
Human Research Ethics Committee  
Room E52-24 Groote Schuur Hospital Old Main Building  
Observatory 7925  
Telephone [021] 406 6626 • Facsimile [021] 406 6411  
e-mail: shuretta.thomas@uct.ac.za

11 April 2011

Sent via Internal mail & Email

HREC REF: 155/2011

**Dr C Colvin,**  
Public Health & Family Medicine  
Falmouth Building, 5.49

Dear Dr Colvin,

**PROJECT TITLE: DEVELOPING A MODEL FOR IMPROVING ADHERENCE IN PATIENTS FAILING SECOND LINE ANTIRETROVIRAL TREATMENT IN A TOWNSHIP IN SOUTH AFRICA: AN ACTION RESEARCH-BASED CASE STUDY.**

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

**Approval is granted until 15 April 2012**

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the HREC. REF in all your correspondence.**

Yours sincerely

**A/PROF MARC BLOCKMAN**  
**CHAIRPERSON, FHS HUMAN ETHICS**

Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

## APPENDIX 4: INSTRUCTIONS FOR AUTHOR OF JOURNAL WHOSE FORMAT HAS BEEN USED

### JAIDS: Journal of Acquired Immune Deficiency Syndromes Instructions for Authors

Accessed at: <http://edmgr.ovid.com/jaids/accounts/ifaauth.htm>

This article will be submitted as an Implementation and Operational Research article under the [Epidemiology and Prevention](#) section.

#### SCOPE

*JAIDS: Journal of Acquired Immune Deficiency Syndromes* is a peer-reviewed, multidisciplinary journal directed to an audience of physicians and researchers. The journal publishes original work in the form of Original Articles, Implementation and Operational Research\*, Rapid Communications, Critical Reviews, Brief Reports, and Letters to the Editor\*. *JAIDS* does not publish case reports. (\*published online only)

#### MANUSCRIPT SUBMISSION

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Lippincott Williams & Wilkins. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the journal, its editors, or the publisher.

All submissions will be rigorously peer-reviewed by members of the Editorial Board and by other specially qualified individuals as well. In the interests of rapid reviewing of contributions, only one of the Editors-in-Chief will, in general, make the final determination as to the acceptability of a submission, after collecting the referee's comments. Contributors may recommend specific names of reviewers from the Editorial Board, as well as other individuals they deem especially well qualified. However, the Editors-in-Chief will not be bound to follow such suggestions.

In general, the instructions for preparation of manuscripts should follow the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals. In case of questions, please feel free to contact the Editorial Office of any one of the Editors-in-Chief.

Authors must submit their manuscripts to the relevant section through the Web-based tracking system:

Basic and Translational Science (<http://jaids-basicscience.edmgr.com>)

Clinical Science (<http://jaids-clinical.edmgr.com>)

Epidemiology and Prevention (<http://jaids-epidemiology.edmgr.com>)

The site contains instructions and advice on how to use the system, guidance on the creation/scanning and saving of electronic art, and supporting documentation. In addition to allowing authors to submit manuscripts on the Web, the site allows authors to follow the progression of their manuscript through the peer review process. Authors should not send hard copies of the manuscript or artwork to the editorial office. Address all inquiries regarding manuscripts not yet accepted or published to the Journal's editorial office. The editorial office will acknowledge receipt of your manuscript via e-mail.

## Editorial Office Addresses

### Basic and Translational Science

David D. Ho, MD  
The Aaron Diamond AIDS  
Research Center  
455 First Avenue  
New York, NY 10016  
917-797-6056  
[tklemt@adarc.org](mailto:tklemt@adarc.org)

### Clinical Science

Paul A. Volberding, MD  
UCSF AIDS Research Institute  
50 Beale St.  
Suite 1300  
PO Box 0886  
San Francisco, CA 94105-0886  
tel: 415.597.4982  
fax: 415.597.8160  
email: [jaids@ucsf.edu](mailto:jaids@ucsf.edu)

### Epidemiology and Prevention

William A. Blattner, MD  
Institute of Human Virology  
725 W. Lombard Street, S419  
Baltimore, MD 21201  
(410) 706-1292  
Fax: (410) 706-1944  
[LZiehm@ihv.umaryland.edu](mailto:LZiehm@ihv.umaryland.edu)

### Authorship

An author is considered to be someone who has made substantive contributions to a published study. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. More specifically, authorship credit requires *a*) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; *b*) drafting the paper or revising it critically for important intellectual content; and *c*) final approval of the version to be published. Contributors must meet conditions for *a*, *b*, and *c*—all 3—to be eligible for authorship. All persons listed as authors must meet the 3 criteria above, and all persons who meet the above criteria must be listed as authors. Please note that acquisition of funding, collection of data, or general supervision of a research group, alone, does not justify authorship.

For large, multicenter group studies, individuals who accept direct responsibility for the manuscript must be identified. Those individuals will be required to complete the **JAIDS** [Copyright Transfer Agreement](#).

Contributors who do not meet the criteria for authorship should be listed in the acknowledgments section. Persons providing technical help, writing assistance, or a department chair providing general

support are examples of persons who should not be included as authors, but who should be listed in the Acknowledgments section.

### **Conflicts of Interest**

Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included **ON THE TITLE PAGE** of the manuscript with the heading “Conflicts of Interest and Source of Funding”. For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker’s bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

In addition, each author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” ([www.icmje.org/update.html](http://www.icmje.org/update.html)). The form is readily available on the manuscript submission page <http://www.editorialmanager.com/jaids-basicscience/> and can be completed and submitted electronically. Please note that authors may sign the copyright transfer agreement form electronically. For additional information about electronically signing this form, go to <http://links.lww.com/ZUAT/A106>.

### **Copyright**

All authors must complete and sign a copy of the journal's [Copyright Transfer Agreement](#) and submit it when submitting the original manuscript online.

### **Compliance with NIH and Other Research Funding Agency Accessibility Requirements**

A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, LWW will identify to the National Library of Medicine (NLM) articles that require deposit and will transmit the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Wellcome Trust, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The [Copyright Transfer Agreement](#) provides the mechanism.

### **Patient Anonymity and Informed Consent**

It is the author's responsibility to ensure that a patient's anonymity be carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated. Authors should mask patients’ eyes and remove patients’ names from figures unless they obtain written consent from the patients and submit written consent with the manuscript.

### **Protection of Human Subjects and Animals in Research**

When reporting experiments involving human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

For research involving animals, authors should indicate whether the procedures followed were in accordance with the standards set forth in the *Guide for the Care and Use of Laboratory Animals* (published by the National Academy of Science, National Academy Press, Washington, D.C.).

**Permission to photocopy articles:** Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Permission to reproduce copies of articles for non-commercial use may be obtained from the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923; Telephone: 978-750-8400; Fax: 978-750-4470; Web: [www.copyright.com](http://www.copyright.com); E-mail: [customercare@copyright.com](mailto:customercare@copyright.com). For permissions to reuse the material for other purposes: Please go to the Journal website and click the "Permissions" link above the title of the paper in the abstract or html window for the relevant article. Alternatively, send an e-mail to [customercare@copyright.com](mailto:customercare@copyright.com) or e-mail [journalpermissions@lww.com](mailto:journalpermissions@lww.com). Translation Rights & Licensing queries: Please contact Silvia Serra, Translations Rights, Licensing & Permissions Manager, Wolters Kluwer Health (Medical Research) Ltd, 250 Waterloo Road, London SE1 8RD, UK. Phone: +44 (0)207 981 0600; E-mail: [Silvia.Serra@wolterskluwer.com](mailto:Silvia.Serra@wolterskluwer.com). Any permissions fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Lippincott Williams & Wilkins.

#### PREPARATION OF MANUSCRIPT

Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

#### ARTICLE LIMITATIONS – BEGINNING WITH JULY 15, 2010 SUBMISSIONS:

| Article type   | Limitations   | Abstracts               |
|--|---|-------------------------|
| Original Articles  | 3500 words + 5 figures/tables - if more then use Supplemental Digital Content | Structured; 250 words   |
| Implementation and Operational Research ( <i>published online only</i> ) | 3500 words + 5 figures/tables - if more then use Supplemental Digital Content | Structured; 250 words   |
| Rapid Communications   | 2000 words + 2 figures/tables   | Unstructured, 150 words |
| Critical Reviews   | 3000 words + 2 figures/tables   | Unstructured; 150 words |
| Brief Reports  | 2000 words + 2 figures/tables   | Unstructured; 100 words |
| Letter to the Editor ( <i>published online only</i> )                    | 1500 words; 1 figure/table  | none                    |

## ARTICLE TYPES

### Original Articles

The above guidelines apply to the original article format. Articles should be limited to 3500 words + 5 figures/tables. If additional space is needed, then use Supplemental Digital Content options. There should be a structured abstract of 250 words or less.

### Implementation and Operational Research (NEW ARTICLE TYPE)

*JAIDS* is now accepting manuscripts for a new focus area of interest: Implementation and Operational Research. In the context of HIV/AIDS with advances in HIV therapy and care, expansion of global access to treatment, care and prevention Implementation and Operational Research, while having particular relevance to global health is an important domestic focus as well. However the lessons learned through this research discipline are particularly relevant to guiding best practices in low-resource settings as antiretroviral drug access is expanded. Articles that encompass the translation of knowledge, practices, and technologies into clinical care of adult and pediatric patients with HIV/AIDS and their evidence-based effectiveness in “real world settings” are of particular interest.

All manuscripts should be submitted through one of the existing three sections: [Basic and Translational Science](#), [Clinical Science](#), or [Epidemiology and Prevention](#) using the article type Implementation and Operational Research. Structure of article is the same as Original Article.

**If accepted for publication, articles are published ONLINE ONLY with titles appearing in the print and online edition table of contents.**

### Rapid Communications

Articles accepted as Rapid Communications will normally be published within 8 weeks of acceptance. When submitting a paper for consideration as a Rapid Communication, please adhere to the following guidelines:

- Submit your paper to Editorial Manager and designate the article type as "Rapid Communication." Please indicate to the Editor in a cover letter file why the paper merits special attention.
- The paper should not exceed 2000 words and 2 figures/tables.
- The paper should include an unstructured abstract (150 words or less), key words, methods, results, discussion, and reference sections.
- The title page should include the corresponding author's telephone and fax numbers and e-mail address.
- Authors will receive proofs of their article for review by e-mail and will be expected to return corrections by fax within 24 hours of receipt. Changes received after this deadline will not be accepted.

Papers that are not accepted as Rapid Communications may be considered as full-length articles.

### Critical Reviews

Papers reviewing the literature on a particularly timely and interesting topic will be considered for publication in *JAIDS*. Authors are encouraged to keep review articles to less than 3000 words and 2 figures/tables with an unstructured abstract of 150 words or less. In general, review articles written as work-for-hire by industry employees will not be considered for publication. All funding, writing assistance, and other relationships to possibly conflicted sources must be fully disclosed at the time of submission.

### **Brief Reports**

Brief Reports are short versions of clinical studies. They represent observations that are preliminary, speak for themselves, or offer new insight into a recognized condition. Submissions should not exceed 2000 words + 2 figures/tables with an unstructured abstract of 100 words or less.

### **Letters to the Editor**

Letters to the Editor can provide additional comment on an article published in *JAIDS*, or can be a very concise report on study findings. Letters should be no more than 1500 words and 1 figure/table. **Beginning with July 15, 2010 submissions, Letters to the Editor will be published ONLINE ONLY. Title will appear in print and online edition table of contents.**

### **Online Submission**

Manuscript files must be uploaded into the Editorial Manager online interface. Most word-processing file formats are acceptable. Editorial Manager will then create PDF files of the authors' submission, and the author must view and approve the files before they will be submitted to the editorial office. Please be sure that the manuscript file contains complete text for your submission (title page and abstract), as this is the file that will be downloaded by the reviewers and publisher. Please see the sections below for instructions regarding Figure and Table files.

Once the paper has been accepted for publication, and final versions of the manuscript, figures, and table files have been uploaded to the Editorial Manager interface, PDF files will not be used for typesetting. This is important to note for Table and Figure files, which may lose formatting when converted to PDF, but will remain intact in their original file format.

### **Title Page**

A title page must be included in the manuscript file. Include on the title page: *a*) complete manuscript title; *b*) authors' full names, academic degrees, and affiliations; *c*) name and address for correspondence, including fax number, telephone number, and e-mail address; *d*) address for reprints if different from that of corresponding author; *e*) meetings at which parts of the data were presented (including title of conference, city, and date); *f*) sources of support; and *g*) a running head of no more than 40 characters.

The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).

### **Abstract and Key Words**

The abstract should be structured and limited to 250 words depending on article type. It must be factual and comprehensive. Limit the use of abbreviations and acronyms, and avoid general statements (eg, "the significance of the results is discussed"). List 3 to 6 key words or phrases.

### **Text**

Organize the manuscript file into sections with appropriate section headings. The sequence should be as follows: title page, abstract/key word page, introduction, methods, results, discussions, acknowledgments, references, tables, figures and figure captions.

Authors should type, whenever possible, all mathematical and chemical symbols, equations, and formulas, and identify all unusual symbols the first time they are used. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country).

### **Abbreviations**

For a list of standard abbreviations, consult the Council of Biology Editors Style Guide (available from

the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

## References

The authors are responsible for the accuracy of the references. Key the references (double-spaced) at the end of the manuscript. (If using End Note, set the style output to *JAMA*.) Cite references in text in order of appearance. Cite unpublished data, such as papers submitted but not yet accepted for publication, or personal communications, in parentheses in the text. If there are more than 3 authors, list only the first 3 authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names. Sample references are given below:

### Journal Article

1. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr*. 2002;31:257–275.

### Book Chapter

2. Wortmann RL, Bentzel CJ. Renal handling of uric acid. In: Massry SG, Glassock RJ, eds. *Massry and Glassock's Textbook of Nephrology*. Philadelphia: Lippincott Williams & Wilkins, 2001;90–92.

### Entire Book

3. Mandell GL, Mildvan D, eds. *Atlas of AIDS*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

### Software

4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention, 1994.

### Online Journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. *Obstet Gynecol* [serial online]. January 1988;71:22–37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

### Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute, 1996. Updated March 29, 1996.

### World Wide Web

7. Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services and Henry J. Kaiser Foundation, January 28, 2000. Available at: <http://www.hivatis.org/guidelines/AA599.pdf>.

### ***Paper Presented at a Conference***

8. Koenig L, Ellerbrock T, Pratt-Palmire M, et al. Prospective predictors of medication adherence: a study of the first six months of highly active antiretroviral therapy (HAART) using electronic monitoring [WePeB5818]. Presented at: XIV International AIDS Conference; 2002; Barcelona.

### **Figures**

Cite figures consecutively in the text, and number them in the order in which they are discussed. Submit all artwork in camera-ready form through Editorial Manager. Authors must submit figures as separate electronic files. High-quality hard copies may be requested once the manuscript has been accepted for publication. Lettering should be large enough that it will remain legible after figure reduction; typewritten or unprofessional lettering is unacceptable. Figure parts (A, B, C) may be left unlabeled (but clearly marked on back) for professional placement by the journal's printer.

### **Figure Legends**

Legends must be submitted for all figures. They should be included in the manuscript file, should be brief and specific, and should appear on a separate manuscript page after the references. Use scale markers in the image for electron micrographs, and indicate the type of stain used.

### **Color Figures**

The journal accepts for publication color figures that will enhance an article. Authors who submit color figures will receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge.

### **Digital Figures**

Electronic art should be created/scanned and saved and submitted as either a TIFF (tagged image file format), an EPS (encapsulated postscript) file, or a PPT (Power Point) file. Line art must have a resolution of at least 1200 dpi (dots per inch), and electronic photographs—radiographs, CT scans, and so on—and scanned images must have a resolution of at least 300 dpi. If fonts are used in the artwork, they must be converted to paths or outlines or they must be embedded in the files. Color images must be created/scanned and submitted as CMYK files. Files should be submitted electronically through the Editorial Manager interface. Please note that artwork generated from office suite programs such as Corel Draw and MS Word and artwork downloaded from the Internet (JPEG or GIFF files) cannot be used.

### **Supplemental Digital Content (SDC)**

Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are not copy-edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit <http://links.lww.com/A142>.

### **SDC Call-outs**

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it will not appear elsewhere in the article.

Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

### List of Supplemental Digital Content

A listing of Supplemental Digital Content must be submitted at the end of the manuscript file.

Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published.

Example: Supplemental Digital Content 1.wmv

### SDC File Requirements

All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit <http://links.lww.com/A142>. Please do not submit pdfs.

### Tables

Create tables using the table creating and editing feature of your word-processing software (eg, Word, Word-Perfect). Do not use Excel or comparable spreadsheet programs. Group all tables together and upload them in a separate file. Cite tables consecutively in the text, and number them in that order. Key each on a separate sheet, and include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviations used). Do not embed tables within the body of the manuscript. They should be self-explanatory and should supplement, rather than duplicate, the material in the text.

### Style

Pattern manuscript style after the *American Medical Association Manual of Style* (9<sup>th</sup> edition). Stedman's Medical Dictionary (28<sup>th</sup> edition) and Merriam-Webster's Collegiate Dictionary (11<sup>th</sup> edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical names, and do not abbreviate them. Use code numbers only when a generic name is not yet available. In that case, supply the chemical name and a figure giving the chemical structure of the drug. Capitalize the trade names of drugs and place them in parentheses after the generic names. To comply with trademark law, include the name and location (city and state in USA; city and country outside USA) of the manufacturer of any drug, supply, or equipment mentioned in the manuscript. Use the metric system to express units of measure and degrees Celsius to express temperatures, and use SI units rather than conventional units.

### Obligation to Register Clinical Trials

*JAIDS* has adopted the standards of the International Committee of Medical Journal Editors with regard to the registration of clinical trials. As a condition of consideration for publication, data from research projects "prospectively assigning human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome" **must be registered** in a public trials registry. The Protocol Registration System (<http://prsinfo.clinicaltrials.gov/>) offered through the U.S. National Institutes of Health is one such registry.

### GenBank Accession Numbers

When manuscripts include or describe original nucleotide or amino acid sequence data, the sequence must be submitted to the GenBank/EMBL/DDBJ sequence database and an accession number obtained from them. This accession number must be returned to the journal, where it will be placed after the Key Words on the title page in the printed article. URLs for the 3 members of the International Nucleotide Sequence Database Collaboration (GenBank/EMBL/DDBJ) are as follows

(respectively): <http://www.ncbi.nlm.nih.gov/BankIt/>, <http://www.ebi.ac.uk/embl/>,  
<http://www.ddbj.nig.ac.jp/>.

### **Page Proofs and Corrections**

PDF files of the copyedited, typeset pages and support documents (eg, reprint order form) will be sent to the corresponding author via e-mail. Complete instructions will be provided with the e-mail for downloading and printing the files and for faxing the corrected pages to the publisher. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style should be allowed to stand if they do not alter the authors' meaning. Only critical changes improving the accuracy of the content will be made. Changes that are stylistic or are a reworking of previously accepted material will not be allowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer queries. Proofs must be checked carefully and corrections faxed within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

### **Reprints**

Reprint orders should be submitted to the Reprints Department (1-800-341-2258 or [reprintsgroup@LWW.com](mailto:reprintsgroup@LWW.com)). Payment for reprints or a purchase order number must accompany your order form. Orders without these cannot be fulfilled. More information can be obtained at <http://www.lww.com/periodicals/author-reprints/>

University of Cape Town