

**A retrospective review of strong opioid use in
the last 6 days of life of patients with
HIV/AIDS or cancer at the In-patient Unit of St.
Francis Hospice.**

Dr. Renée Els

M.B.Ch.B

Radiation-oncology department,

Port Elizabeth Provincial Hospital, South Africa.

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Masters of Palliative Medicine

Supervisor: Dr. HM Power

BSc (Hons), M.B. B.Ch., M.D., DCH

Sowerby Centre for Health Informatics, University of Newcastle upon Tyne, UK

Department of Public Health

Division: Family Medicine

University of Cape Town

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Abstract

Background: The study was prompted by nursing concern at St Francis Hospice that, in HIV-positive patients, the use of opioids for symptom-control may shorten life, while I felt that pain was not recognized and therefore analgesia was withheld until the HIV-positive patients were close to their natural death.

Objective: To compare pain control and sedation practices for terminally ill patients with HIV or cancer.

Methods: This was a retrospective case-control study. Cases were consecutive deaths related to AIDS in St. Francis Hospice, Port Elizabeth, South Africa from August 1998 to December 2001. Controls were cancer patients matched for race and socio-economic circumstances.

Main Findings:

Five days before their day of death, 3 of the 29 (10%) AIDS patients were given morphine for pain control compared with 20 of 29 (69%) cancer patients. On the day of their death 17 (59%) AIDS patients were given morphine compared with 25 (86%) cancer patients ($p < 0.5$).

Eleven (65%) of the 17 AIDS patients who were given morphine died within 48 hours of its commencement. The maximum daily dose was 50 mg per os, which is within the recommended starting dose range for opioid naïve-patients.

In the last 24 hours of life sedation was administered to 7 of the 17 (41%) AIDS patients on morphine and 2 of the 25 (8%) cancer patients on morphine ($p=0.01$). The dosages administered were within the lower therapeutic range.

Twenty AIDS patients had pain recorded on admission with only 11 (i.e. 55% of those with pain) receiving morphine. This compares to 12 patients with cancer who had pain on admission, with 100% of these receiving morphine.

Interpretation: There are statistically significant and clinically important differences in morphine administration between AIDS and cancer patients. Care for cancer patients was similar to accepted best practice where between 70 and 89% of cancer patients near end-of-life receive morphine. AIDS patients are probably receiving inadequate pain control: in services offering "best practice" palliative care about 80% are treated with morphine in the last few days before death.

The doses of morphine and sedatives given to the AIDS patients are too small to have contributed to their death. A possible explanation is that pain as a symptom was not recognized and therefore not treated timeously in the majority of AIDS patients.

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Summary

Background: Reports in the literature abound that pain is under-recognized and under-treated in AIDS patients, whether ambulatory, hospitalized or terminal. This study was prompted by local nursing concern that in HIV-positive patients, the administration of opioids for symptom-control may shorten life: "They die within 2 days of you starting him/her on morphine." I felt that pain as a symptom was not recognized, and in consequence analgesia was being withheld until HIV-positive patients were close to their natural death, thus denying them adequate pain control. This is out of keeping with palliative care values as defined world-wide.

Objectives: To compare pain control and sedation practices for terminally ill patients with HIV and patients with cancer.

Setting: The 6 bed in-patient unit of St. Francis Hospice, Port Elizabeth, South Africa.

Methods: This was a retrospective case-control study. Cases were consecutive deaths related to AIDS from August 1998 to December 2001. Controls were cancer patients matched for race and socio-economic circumstances. There were 29 people in each group. All 39 patients who died in the in-patient unit with AIDS or complications related to AIDS were identified. Ten people were excluded from further analysis: 7 had both AIDS and cancer, 1 died from causes unrelated to AIDS (gunshot), and records were unavailable for 2. For the remaining 29 AIDS cases, 29 cancer controls were selected by identifying the first HIV negative patient to die in the in-patient unit from cancer who was of the same race, had similar socio-economic status, and had complete records.

Clinical history, progress, mode of deaths, and use of opiates and sedatives were extracted from the charts of study subjects.

Hypotheses:

1. For some AIDS patients death is possibly induced or hastened by administering opioids.
2. Some AIDS patients die without adequate analgesia as too little is administered too late.

Main Outcome measures:

1. **Total numbers on morphine:** Five days before their day of death (D-5), 3 of the 29 (10%) AIDS patients were given morphine for pain control, receiving on average 120 mg per 24

- Symptom prevalence on admission to the in-patient unit in patients who were not given morphine

The doses of morphine and sedatives given to AIDS patients were within the normal therapeutic range and thus were unlikely to have contributed to their deaths.

Morphine use in “best practice” palliative care services is reported to be between 70 and 89% for cancer patients near end-of-life and up to 82% for AIDS patients near death. During the time of the study pain was not treated timeously in AIDS patients in the St Francis in-patient unit. By the end of the study, morphine was being administered substantially more frequently than at the start, but there were still AIDS patients who had significant unrelieved pain and distress during the last 6 days of life. Sedatives were predominantly used in a subgroup of AIDS patients who received morphine for less than 24 hours preceding death. And this suggests that inadequate symptom-control led to the inappropriate use of sedatives.

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University of Cape Town

Table of Contents

<i>Abstract</i>	<i>ii</i>
<i>Summary</i>	<i>iv</i>
<i>Acknowledgments</i>	<i>vii</i>
<i>List of Tables</i>	<i>xiv</i>
<i>List of Figures and Graphs</i>	<i>xv</i>
<i>Chapter 1 Introduction</i>	<i>16</i>
<i>Chapter 2 Theoretical Framework</i>	<i>20</i>
<i>Chapter 3 Ethics</i>	<i>40</i>
<i>Chapter 4 Hypothesis</i>	<i>42</i>
<i>Chapter 5 Methods</i>	<i>44</i>
<i>Chapter 6 Results and Analysis of Data</i>	<i>57</i>
<i>Chapter 7 Discussion and Interpretation</i>	<i>82</i>
<i>Chapter 8 Recommendations for further studies</i>	<i>99</i>
<i>Chapter 9 Conclusion</i>	<i>100</i>
<i>References</i>	<i>101</i>
<i>Appendixes</i>	<i>109</i>

Detailed Table of Contents

<i>Abstract</i>	<i>ii</i>
<i>Summary</i>	<i>iv</i>
<i>Acknowledgments</i>	<i>vii</i>
<i>List of Tables</i>	<i>xiv</i>
<i>List of Figures and Graphs</i>	<i>xv</i>
Chapter 1 Introduction	16
1.1 Developing an idea and motivation for the present study	16
1.2 Research statement/ question	18
1.2.1 Purpose.....	18
1.3 Abbreviations used	18
1.4 Research design and methodology	19
1.5 Outline	19
Chapter 2 Theoretical Framework	20
2.1 Introduction: demarcating the literature covered	20
2.2 Setting and context	21
2.3 Definitions of concepts	22
2.3.1 Palliative care.....	22
2.3.2 Total suffering.....	23
2.3.3 Goals of care.....	23
2.3.4 Pain control.....	24
2.3.4.1 Basic principles of effective pain control.....	24
2.3.4.2 Assessment of pain.....	24
2.3.4.3 4 steps of cancer pain assessment:.....	25
2.3.4.4 Analgesic use.....	27
2.3.4.5 Escalation steps for morphine.....	28
2.3.5 Common adverse effects of opioids.....	28
2.3.5.1 Sedation.....	29
2.3.5.2 Respiratory depression.....	29
2.3.6 Using sedatives during opioid therapy.....	29
2.3.6.1 Relationship between sedatives and hastened death.....	30
2.3.7 Hastening of death.....	31
2.3.8 Advanced Acquired Immunodeficiency Syndrome.....	32
2.3.8.1 Staging Criteria for HIV patients.....	32
2.3.8.2 WHO Staging System for HIV Infection and Disease.....	33
2.3.8.3 Distinctive Features of Palliative Care in AIDS.....	34
2.3.9 Other differences between AIDS and cancer patients at St. Francis Hospice.....	34
2.3.9.1 Criteria for initiating Palliative Care in AIDS.....	35
2.3.10 Prevalence of pain in people with AIDS.....	36
2.3.11 Under-treatment of pain.....	37
2.3.12 Impact of pain on quality of life.....	37
2.3.13 Barriers to managing pain in terminal AIDS patients.....	38

2.3.13.1	Patient	38
2.3.13.2	Clinician.....	38
2.3.13.3	Socio-economic.....	39
2.4	Summary of central concepts.....	39
Chapter 3	<i>Ethics</i>.....	40
Chapter 4	<i>Hypothesis</i>.....	42
4.1	Informal observation and speculation.....	42
4.2	Substantive and statistical hypothesis	43
Chapter 5	<i>Methods</i>	44
5.1	Study design	44
5.2	Issues of measurement.....	44
5.2.1	Variables	44
5.2.2	Selection and exclusion criteria for AIDS patients	46
5.2.3	Sample size.....	46
5.2.4	Measurement tools and data collection	47
5.2.5	Type of death.....	49
5.3	Data collection.....	49
5.3.1	Identify sources and gain access	49
5.3.2	Field notes	50
5.3.3	Data capture.....	50
5.3.3.1	Patient details	50
5.3.3.2	Core data	50
5.3.3.3	Relevant supporting data.....	51
5.3.4	Data quality assurance.....	52
5.3.5	Data analysis and synthesis.....	52
5.4	Pilot study.....	52
5.5	Data capturing and data analysis.....	53
5.6	Statistical analysis	53
5.7	Shortcomings and sources of error.....	54
5.7.1	Access to data	54
5.7.1.1	Inaccessible data	54
5.7.1.2	Incomplete records and missing data.....	54
5.7.2	Errors in using existing data collection instruments.....	54
5.7.3	Errors in scale construction.....	55
5.7.4	Errors in data collection and documentation	55
5.7.5	Errors in data-capturing.....	55
5.7.6	Errors in analysis and interpretation.....	56
Chapter 6	<i>Results and Analysis of Data</i>.....	57
6.1	Sample profiles	57
6.2	Main findings of single factors	58
6.2.1	Total number of patients on morphine	58
6.2.1.1	Five days before their day of death	58
6.2.1.2	On the day of their death:	58
6.2.1.3	Increase in number of patients on morphine.....	58

6.2.1.4	Number of patients who died within 48 hours after starting morphine.....	60
6.2.1.5	Morphine dosages.....	60
6.2.2	Average number of days morphine was administered.....	61
6.2.3	Sedative administration.....	62
6.2.3.1	Types of sedatives administered.....	62
6.2.3.2	Incidence of sedative administration.....	62
6.2.3.3	Dosage of sedatives administered.....	62
6.2.4	Type of death.....	63
6.2.5	Length of stay.....	64
6.2.6	Trend of morphine administration in the in-patient unit over time.....	65
6.3	Findings when factors are combined for relevance.....	66
6.3.1	Doses of subcutaneous morphine, sedatives used and type of death.....	66
6.3.1.1	AIDS patients.....	67
6.3.1.2	Cancer patients.....	70
6.3.2	Combinations with the focus on sedatives used.....	71
6.3.3	Combinations with the focus on the type of death.....	72
6.3.3.1	Type of death: separated into groups according to morphine usage.....	72
6.3.3.2	Type of death: looking at sedation and morphine combined.....	73
6.3.4	Last 48 hours.....	74
6.3.5	Length of stay and morphine administration.....	75
6.3.5.1	AIDS patients: doses of subcutaneous morphine (or equivalent).....	75
6.3.5.2	Cancer patients: doses of subcutaneous morphine (or equivalent).....	76
6.3.5.3	Morphine started during home care versus in-patient unit care.....	77
6.3.6	Symptoms present on admission to the in-patient unit.....	78
6.3.6.1	Patients on morphine.....	78
6.3.6.2	Patients who did not receive morphine.....	78
Chapter 7	Discussion and Interpretation.....	82
7.1	Sample profiles.....	83
7.2	Main findings.....	84
7.2.1	The number of patients on morphine for pain relief.....	86
7.2.2	Increase in numbers of patients on morphine during the last 5 days.....	88
7.2.3	Morphine dosages.....	89
7.2.3.1	Last 48 hours.....	89
7.2.3.2	5 days or more before death.....	89
7.2.4	Duration of morphine therapy.....	90
7.2.5	Morphine usage in context of the total hospice service.....	90
7.2.6	Sedative administration.....	91
7.2.6.1	Combination of morphine and sedative administration.....	92
7.2.7	Type of death.....	93
7.2.7.1	Combination of morphine, sedative and type of death.....	93
7.2.8	Change of trend over time of morphine administration in the in-patient unit.....	94
7.2.9	Pain control in home care unit.....	94
7.2.10	Symptoms present on admission to the in-patient unit.....	94
7.3	Concluding interpretations.....	96
7.3.1	Under-treatment of pain.....	96
7.3.2	Findings viewed within a wider perspective.....	97
7.3.3	The role of objective evidence in bringing to awareness unrecognized issues.....	98
7.3.4	Questions that arise.....	98
Chapter 8	Recommendations for further studies.....	99

Chapter 9 Conclusion..... 100
References..... 101
Appendixes..... 109

University of Cape Town

List of Tables

Table 1: Patient numbers cared for at St. Francis Hospice	22
Table 2: WHO Analgesic ladder	28
Table 3: Morphine escalation.....	28
Table 4: Common adverse effects of opioids.....	28
Table 5: WHO Staging System for HIV Infection and Disease.	33
Table 6: Cultural Context.....	41
Table 7: General statistics at St. Francis Hospice for 2000.....	53
Table 8: Patient characteristics	57
Table 9: Number of patients on morphine the last six days.....	58
Table 10: Number of patients on morphine on the day of their death	58
Table 11: Number of patients who died within 48 hours of starting morphine.....	60
Table 12: Number of patients to whom sedation was administered in the last 24 hours	62
Table 13: Dosage of sedatives of patients (milligram per 24 hours)	62
Table 14: Type of death	63
Table 15: Patients who died a painful death.	63
Table 16: Length of stay and morphine administration.....	64
Table 17: Morphine administration and place of care (home care or in-patient unit).....	64
Table 18: Number of patients using morphine per year.....	65
Table 19: AIDS patients: Subcutaneous morphine doses, sedatives and type of death.	67
Table 20: Cancer patients: Subcutaneous morphine doses, sedatives and type of death.....	70
Table 21: Administration of morphine and sedatives during the last 24 hours.....	71
Table 22: Indications for sedatives and symptoms on admission	71
Table 23: Type of death and morphine administration: 5 days before death	72
Table 24: Type of death and morphine administration: day of death	72
Table 25: Differences of sedative and morphine use in patients who died a painful death.	73
Table 26: Length of stay of AIDS patients associated with morphine administration.	75
Table 27: Length of stay of cancer patients associated with morphine administration.....	76
Table 28: Morphine started during home care versus in-patient unit care.....	77
Table 29: Pain present on admission to the in-patient unit.....	78
Table 30: Symptoms present on admission to the in-patient unit for AIDS and cancer patients NOT on morphine	79
Table 31: Symptoms present on admission to the in-patient unit for AIDS patients on morphine...	80
Table 32: Symptoms present on admission to the in-patient unit for cancer patients on morphine.	81
Table 33: AIDS deaths in in-patient unit expressed as a percentage of AIDS patients cared for.....	83

List of Figures and Graphs

Figure 1: The Statement of Service offered by St. Francis Hospice	21
Figure 2: Total suffering.....	23
Figure 3: Medical admissions sheet presently used St Francis hospice for all patients	26
Figure 4: WHO analgesic ladder.....	27
Figure 5: Extract from nursing notes.	49
Figure 6: Section of Symptom sheet completed on admission.	51
Figure 9: Average number of days morphine was administered before death (bars indicate 95% confidence intervals).....	61
Figure 10: Morphine administration distributed through the years in the two groups.....	65
Figure 11: Venn diagram of AIDS patients using morphine for less than 48 hours and the intersection with painful type of death and sedatives administered during the last 24 hours..	68
Figure 12: For comparison: a diagrammatic illustration of the cancer group.	69
Figure 13: Mission statement of St. Francis Hospice.....	97

Chapter 1 Introduction

Death is a constant ingredient of the human condition. We may try to prevent, delay or cheat it, but it eventually overcomes every one of us. Pain is another persistent ingredient of our human condition and death is often associated with pain. Pain may be the oldest symptom facing humanity. From the primitive medicine-man or shaman at the dawn of health care there has been sufficient time for pain as a symptom to be conquered. In 1990 the WHO declared war on the pain associated with cancer. Yet, today pain associated with AIDS and other terminal conditions remain a major public-health problem even though its causes are clear, its pathophysiology somewhat understood, the way it thrives in poverty and disadvantaged groups is known, and the public can be educated about it.

1.1 Developing an idea and motivation for the present study

What prompted the idea for the study were informal remarks made by some of our nursing staff that strong opioid usage accelerates death in the HIV patients managed at St. Francis Hospice. "They die within 2 days of your starting them on morphine" was a comment frequently reiterated by some nursing staff.

This opinion is questionable. There are several articles in the literature that specifically address the general fear of hastening death by prescribing pain medication.^{26, 69, 73} A number of studies provide evidence that pain is under-treated in AIDS patients in general.^{10, 43, 46, 47} Several articles discuss barriers to pain relief.^{6, 28, 37, 78} In South Africa a common attitude towards caring for AIDS patients is that "nothing can be done": few investigations are requested as resources are scarce, laboratory tests costly³³, and little treatment is available in the public health sector.³¹ The Integrated Community-based Home Care Project in Port Elizabeth²⁸ makes little provision for direct patient management by a medical doctor. It is essentially a nurse driven initiative, utilizing and supervising informally trained volunteer community workers, which supplies a much-needed service, but is unable to provide significant diagnostic and medical symptom management or physician input. During this study, doctors were available for consultation with the managing nursing sister in a remote consulting capacity but personally they did not see and assess significant numbers of patients in the Community-based Home Care Project.

Another difficulty is how to decide when AIDS patients are terminally ill. With prompt diagnosis and treatment of an easily reversible opportunistic infection, the clinical picture of an AIDS patient can change dramatically.^{41, 52}

This combination of factors could put AIDS patients at a disadvantage compared to cancer patients with respect to appropriate care and symptom-control, including adequate analgesia and sedation.

Although the nursing staff may suspect that AIDS patients die because of the opioids that were given, an opposing opinion is that analgesia was withheld until they were close to their natural death! St Francis hospice's logo is "No end to care" and they subscribe to the general principles of reducing suffering as defined in their mission statement.

Neither outcome described above is in keeping with palliative care values as defined world-wide.²⁰

⁸⁰ On the one extreme, death will have been hastened (although unintentional if it did occur as a result) by giving opioids. Towards the other end of the spectrum, relief from pain was not provided, defeating the goals and principles of palliative care.

The central issue is management of pain. The 2 opinions are wide apart on the spectrum of approaches to pain management. They are so wide apart that they can be seen as opposing views. No records are available that reflect the actual situation. This leaves a wide area open for investigation and a need for objective evidence that will as accurately as possible provide clarity.

My aim is to analyze retrospectively clinical records to determine the patterns of strong-opioid administration during last few days of life by HIV/AIDS and cancer patients cared for by St. Francis Hospice. From this analysis I hope to obtain objective evidence to encourage an effective palliative care attitude towards dying patients by recognizing and overcoming barriers that may exist.

1.2 Research statement/ question

Does opioid administration during the last 6 days of life differ for HIV/AIDS patients in comparison with oncology patients in the in-patient unit of St Francis Hospice?

1.2.1 Purpose

- The study will quantitatively describe opioid administration during the last six days of life with the aim of determining whether differences of usage exist between cancer and AIDS patients.
- Critical evaluation of the gathered information will attempt to identify patterns and quantify the differences, if they exist.
- It may suggest ways to further assess, address or explain differences. For example, attitudes may change when made aware of differences or methods used by clinical staff to elicit symptoms may improve.
- It may also contribute to ideas for further studies that may attempt to clarify underlying reasons for the findings.
- Deficiencies in the data in routine patient records, if found, will be documented and suggestions for improving information necessary for patient care, clinical audit and research may evolve.

1.3 Abbreviations used

AIDS – Acquired Immunodeficiency Syndrome

HIV – Human Immunodeficiency Virus

PO – Per os

prn – as required/ needed ("pro re nata")

SC – subcutaneous

WHO – World Health Organization

1.4 Research design and methodology

This was a retrospective, case-control study evaluating opioid administration to terminal AIDS and cancer patients in the 6 bed in-patient unit of St. Francis Hospice, Port Elizabeth, South Africa. Objective evidence was gathered from the two parallel groups of patients to evaluate the situation objectively.

Cases were consecutive deaths related to AIDS from August 1998 to December 2001. Controls were cancer patients matched for race and socio-economic circumstances. There were 29 people in each group. All 39 patients who died in the in-patient unit with AIDS or complications related to AIDS were identified. Ten people were excluded from further analysis: 7 had both AIDS and cancer, 1 died from causes unrelated to AIDS (gunshot), and records were unavailable for 2. For the remaining 29 AIDS cases, 29 cancer controls were selected by identifying the first HIV negative patient to die in the in-patient unit from cancer who was of the same race, had similar socio-economic status, and had complete records.

Study subjects charts were reviewed for clinical history, progress, mode of deaths, and use of opiates and sedatives.

1.5 Outline

A review of the literature was summarized in the context of the problem formulation.

Key concepts are defined in chapter 2 for clarity of interpretation of the findings within the present understanding (framework). General concepts such as palliative care, suffering, pain control, adverse effects of opioids will be discussed as well as more specific concepts such as the definition of advanced AIDS, the decision on when to institute palliative care for AIDS, pain and AIDS.

An overview of the research design and methods applied will be given in chapter 5. The description of the methods will include variables, data-capturing and editing as well as short-comings and sources of error.

The results and analysis of data (chapter 6) will be discussed and displayed in tables and graphs after which main findings will be summarized and discussed (chapter 7) within the broader framework of palliative care before final conclusions will be formed and implications be considered.

Chapter 2 Theoretical Framework

2.1 Introduction: demarcating the literature covered

A literature search was done using MEDLINE and AIDSLINE.* Numerous complete journal articles were available in electronic format thanks to access through a "log in and password system" at the University of Port Elizabeth Library. The search was concentrated on studies pertaining to symptom-control during the last week in life of AIDS and cancer patients. Key words used were combinations of AIDS, pain control, end-of-life, last week, palliative, terminal. Few articles were found, especially about AIDS patients, and the search was broadened to include symptom prevalence and management in the terminal phase that encompasses a period of more than a week.

To put the study in context of a palliative care setting, general palliative care references were consulted as well as a study of home-based care for AIDS patients in which St. Francis Hospice is participating and following defined guidelines for the care of people with AIDS patients.²⁸ During the course of assimilating and writing the dissertation, a number of resources on research methods and statistics were consulted.

* AIDSLINE no longer available on the internet.

2.2 Setting and context

ST. FRANCIS HOSPICE ... A SERVICE OF CARE AND COMPASSION

A Hospice is a specialised centre offering medical and nursing expertise, in an environment of peace and compassion, to help those in the final phase of an incurable illness to achieve a quality of life that is appropriate to them. It also provides support for the family both during the patient's illness and after death. Care is also provided in patients' own homes. The dedicated approach of those who serve enables patients and their families to face one of the greatest crises of their lives.

THE GOALS OF HOSPICE

- * To care humanely for the terminally ill.
- * To provide for the physical, emotional, social and spiritual needs of the patients as well as those of their loved ones.
- * To give to family and friends the opportunity to share actively in the care, comfort and support of the dying person.
- * To make the patient's final days as painless and meaningful as possible.

Figure 1: The Statement of Service offered by St. Francis Hospice

St. Francis Hospice has a 6 bed in-patient unit. Annual totals for in- and out-patients cared for during the study period ranged from 664 to 1080. Yearly admission statistics are available since 2000. The average admission rate is 21.5%; i.e. The admission rate varies, and between 18 and 30% of registered patients are admitted to the in-patient unit during the course of different years. From the admission-book, 22 and 24 AIDS patients were identified that were admitted for AIDS-related problems during 2000 and 2001 respectively. The proportions of admissions for AIDS patients and cancer patients are not available from the recorded data, but it seems that the admission rate for AIDS patients is substantially less than that for cancer patients.

	AIDS patients	Cancer patients	Total Patients	In-patient Unit Admissions	Admission rate (%)
03/1998 to 02/1999	71 (12%)	588	664	n/a	n/a
03/1999 to 02/2000	155 (25%)	616	776	238	30%
03/2000 to 02/2001	221 (32%)	691	912	169	19%
03/2001 to 02/2002	533 (49%)	547	1080	189	18%

Table 1: Patient numbers cared for at St. Francis Hospice

There are no statistics available indicating the proportion of patients who died in the in-patient unit and those who were discharged home.

2.3 Definitions of concepts

2.3.1 Palliative care

The World Health Organization²¹ defines palliative care as: "the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems, is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families."

Palliative care:³⁹

- Affirms life and regards dying as a normal process
- Neither hastens nor postpones death
- Provides relief from pain and other distressing symptoms
- Integrates the psychological and spiritual aspects of care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help patients' families cope during and after the patient's illness

A typical hospice palliative care services in South Africa focuses mainly on home care. It also includes in-patient units in selected hospices according to availability of resources.

The Hospice Association of South Africa claims that hospices are the only facilities in South Africa that provide palliative care as defined according to the WHO.

2.3.2 Total suffering

A focus on quality of life leads inexorably to related issues that are contributing to suffering. This includes consideration of relationships, confidentiality, spirituality, symptoms and their management, rehabilitation, rights and responsibilities, and people's relationship with their God.

Suffering is a complex multifactorial entity.⁸⁰ Contributing causes can be expressed as:

Pain
+ physical symptoms
+ psychological conflicts
+ social difficulties
+ cultural factors
+ spiritual concerns

= Total suffering

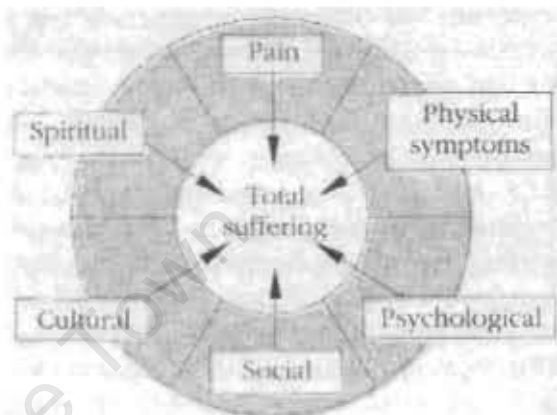


Figure 2: Total suffering

All patients with a terminal illness experience suffering to a greater or lesser degree. The combinations of factors differ between each patient. The multifactorial nature of suffering is the reason why several factors influence the management of pain, and also why a multidisciplinary approach is required.

2.3.3 Goals of care

During palliative care the goals of treatment shifts from prolonging survival to optimizing functions and later to optimizing comfort. As the goals of prolonging life and function become increasingly unachievable, priorities shift. It is important to recognize and respect the priorities of the patient in preference to the care team in enabling the patient to make informed decisions about therapeutic options.

2.3.4 Pain control

2.3.4.1 *Basic principles of effective pain control*

- Pain is a multidimensional construct.
- A disciplined, multidimensional assessment is essential. This includes addressing reversible causes.
- Avoid delay in treating.
- Communicate with the patient, family and other caregivers.
- Follow a stepped approach that depends on severity and cause of pain (This requires early formal assessment, which at present is not incorporated into St. Francis home care project)
- Constant pain requires regular administration of analgesics.
- Always leave instructions for a "breakthrough dose".
- Consider opioids as only one part of the management of total pain.
- Patients with rapidly changing clinical circumstances require ongoing assessments.

2.3.4.2 *Assessment of pain*

Failure to assess pain can lead to less than optimal pain control for the patient.

Assessments should occur:

- At regular intervals after initiation of the treatment.
- At each new report of pain or change in quality/intensity of pain.
- At a suitable interval after pharmacological or non-pharmacological interventions.

The goal of the initial assessment is to characterize the pain by location, intensity and aetiology.

Essential to the initial assessments are:

- A detailed history.
- A physical examination, including neurological.
- A psychosocial assessment.
- A diagnostic evaluation. Disease modifying therapies may contribute to managing pain.

2.3.4.3 4 steps of cancer pain assessment:

Step 1: Assess whether the pain is being produced by direct or indirect tumour involvement, cancer treatment or whether it is unrelated to the tumour and treatment

Step 2: Treatment of the concurrent infections may result in more effective pain relief than general measures alone.¹⁵⁾ [For AIDS patients pain can be caused by damage from HIV infection, co-infections or tumours, treatment (anti-TB or anti-retroviral), or unrelated diseases.]

Step 3: Measure the intensity of pain and other symptoms.

a. Example of a Visual Analogue Scale (0-10 cm)¹⁶⁾

No Pain 0 _____ 10 Worst Possible Pain

b. McGill Pain Questionnaire⁵⁵⁾

c. Wisconsin Brief Pain Inventory¹⁸⁾

Step 4: Assess the multiple dimensions of the expression of pain.

Step 5: Identify poor prognostic factors for pain control.

This is a validated method of pain evaluation. It is not followed at St. Francis hospice.

A nurse at St Francis record the presence of pain on a 4 item scale:

1. Major problem 2. Minor problem 3. Not a problem 4. Not known.

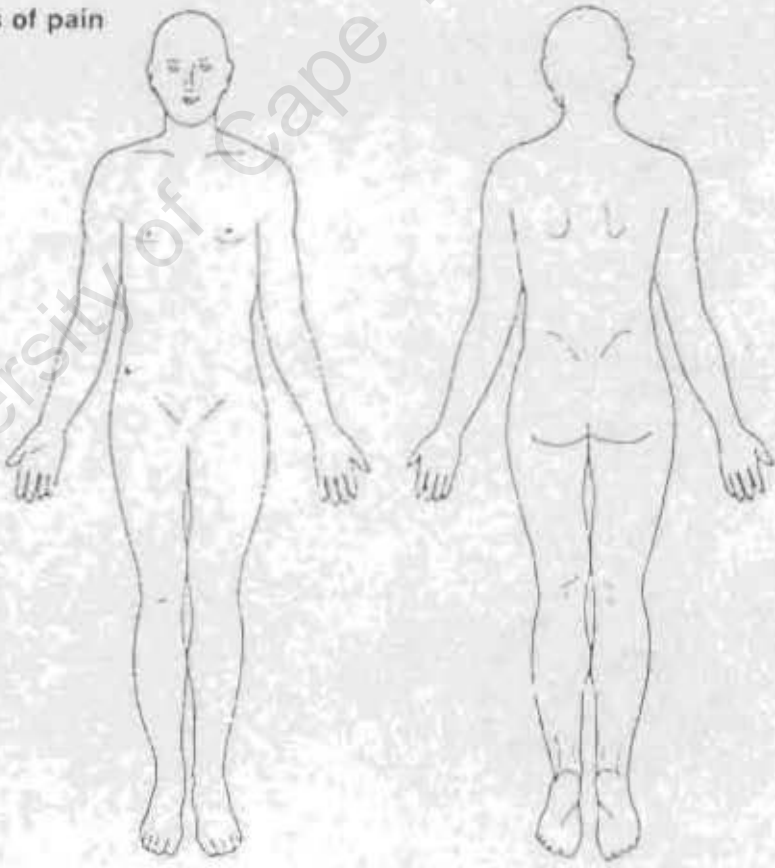
Medical staff use the medical admissions sheet shown in Figure 3

ST FRANCIS HOSPICE ADMISSION SHEET

Name & age Date of admission Date of discharge Problems 1 2 3 4 5	Medication on admission 1. 2. 3. 4. 5. <hr/> Complaints on admission 1. 2. 3. 4. 5.
--	--

A. Pain

A1. Sites and mechanisms of pain



A2. Intensity of pain

- Mild
- Moderate
- Severe
- Incapacitating
- Overwhelming

A3. Duration of pain

- < 2 weeks
- 2-4 weeks
- 1-2 months
- 2-4 months
- > 4 months

B. Sleep

C. Mobility & Activity

D. Relatives views

Figure 3: Medical admissions sheet presently used St Francis hospice for all patients

2.3.4.4 Analgesic use

Pain control is one of the *most important* aspects of end-of-life care.^{41, 73, 80.}

Choice of drug

- select a drug appropriate for the type of pain
- select a drug appropriate for the severity of pain
- use combinations of drugs, not combined preparations
- follow the "analgesic ladder"
- use adjuvant analgesics
- never use a placebo

The analgesic ladder

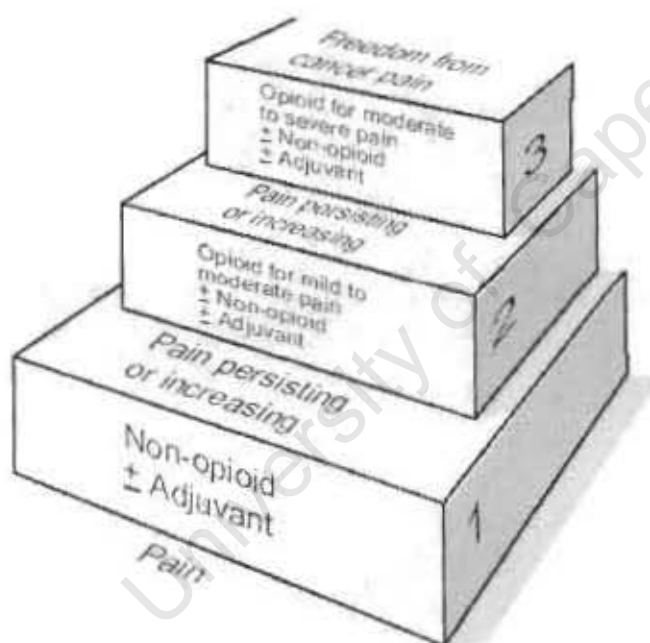


Figure 4: WHO analgesic ladder

- if the prescribed drugs do not produce adequate analgesia, treatment is escalated in an orderly manner
- from non-opioid to weak opioid to strong opioid, as illustrated in the World Health Organization's "Analgesic Ladder"
- non-opioid analgesic should be continued when opioid drugs are commenced, as their action can be complementary and allow lesser doses of opioids to be administered
- adjuvant analgesics should be administered whenever indicated

	Analgesics	Drug of Choice	Alternative
Step 1 Pain	Non-opioid ± adjuvant	paracetamol	NSAID
Step 2 Pain persists or increases	Weak opioid ± non-opioid ± adjuvant	codeine	dextropropoxyphene tramadol
Step 3 Pain persists or increases	Strong opioid ± non-opioid ± adjuvant	morphine	fentanyl buprenorphine

Table 2: WHO Analgesic ladder

2.3.4.5 Escalation steps for morphine

Opioid	Route	Dosage steps in opioid naïve patient (every 4 hours)													
Morphine	PO	5	10	15	20	30	40	60	80	100	130	160	200	250	300
	SC	2.5	5	7.5	10	15	20	30	40	50	65	80	100	125	150

Table 3: Morphine escalation

- Administer a breakthrough medication dose consisting of 50-100% of the 4-hourly dose, up to 1 hour from time of dose prn.
- Progress to the next level of the protocol up to once per 24 hours if pain not controlled.
- Continue other modalities of treatment, including local therapy for regional pains

2.3.5 Common adverse effects of opioids

Central	Sedation, drowsiness, confusion, narcosis, coma Dysphoria, psychomimetic effects Myoclonus Miosis
Gastrointestinal	Nausea and vomiting, delayed gastric emptying, constipation, dry mouth Biliary colic
Respiratory	Respiratory depression Suppression of cough reflex
Cardiovascular	Postural hypotension
Urinary	Urgency, retention
Skin	Flushing, sweating, pruritus

Table 4: Common adverse effects of opioids

Side-effects that may hasten death are: sedation and respiratory depression.

2.3.5.1 Sedation

Sedation usually accompanies the commencement of morphine therapy. It is usually mild and lasts from two to five days whereafter much tolerance emerges. When severe drowsiness occurs, other causes such as metabolic disturbances, infection, cerebral mass lesions and other drugs should be excluded. Patients at risk are:

- Elderly and frail people
- Renal and hepatic impairment
- Other causes of central nervous system depression, including drugs
- Opioid naïve-patients
- Patients with only mild pain
- Patients whose pain has been acutely relieved by a procedure such as a nerve block.

The use of sedatives concomitant to morphine use, may enhance sedation.

2.3.5.2 Respiratory depression

Because respiratory depression is potentially life threatening, it is considered the most serious opioid side effect and is of great concern to doctors and nurses. Opioids can depress both the rate and depth of respiration. Although respiratory arrest is possible, it occurs in combination with mental clouding and somnolence, allowing for a reduction or discontinuation of medication if these symptoms develop. An excessive dose can, of course, cause respiratory depression. Patients in pain also respond differently to opioids than do persons without pain. Pain acts as a natural antagonist to the respiratory depressant effect of opioids. As pain increases, the level of opioid necessary for relief goes up, and so does the tolerance to respiratory side effects. Opioids beneficially overcome the oxygen hunger of patients who experience prolonged shortness of breath.

2.3.6 Using sedatives during opioid therapy

The indications for administration of sedatives in palliative care (and other drugs that have sedative effects) are numerous. During the terminal phase common indications are anxiety, intractable pain, massive haemoptysis, respiratory panic and terminal agitation.

Sedation Goals are: To achieve a peaceful death by:

- decreasing uncontrollable suffering
- decreasing fear
- improving family support
- reducing risk of accidental injury

Ideally one strives for a level of consciousness that allows for meaningful interaction with the family for as long as possible whilst reducing suffering at the same time.

2.3.6.1 Relationship between sedatives and hastened death

Benzodiazepines: In St Francis Hospice midazolam is the most frequently administered drug for sedation near end-of-life. Other alternatives are Diazepam and Lorazepam.

- Significant respiratory depression can occur with benzodiazepines in patients with chronic obstructive pulmonary disease and sleep apnoea – especially with parental midazolam.
- In hypovolemic states, congestive cardiac failure and other conditions that impair cardiovascular function, benzodiazepines may cause cardiovascular depression.
- Concurrent administration of opioids enhances sedation.
- Abnormal liver and renal function frequently jeopardizes the elimination of drugs. Patients are at greater risk for drug toxicity and side effects.

Neuroleptics: Neuroleptics have several uses in palliative care.

Where there is a legitimate concern regarding respiratory depression or compromise, classical neuroleptics are safer than benzodiazepines as anxiolytics. They also have anticholinergic side-effects which may be useful in the terminal phase (aid in secretion control).

2.3.7 Hastening of death

Hastening of death can be divided into two categories according to intent. If the intent is to hasten death, it is called euthanasia. The term "principle of double effect" is used²⁵ to justify the administration of medication with the intention to relieve pain or other symptoms even though it may lead to the unintended, although foreseen, consequence of hastening death by causing respiratory depression or other vital organ depression.

The principle of double effect has its origins in Roman Catholic moral theology. In the paradigm case, although a doctor is not allowed to directly abort a fetus (even to save the life of a woman), a doctor is allowed to remove a diseased and life-threatening uterus containing a fetus. Although the doctor expects the death of the fetus, he does not intend to kill it. Applying the principle of double effect to the use of pain medication, the good effect (pain control) is intended, whereas the bad or secondary effect (hastening death) is foreseen but not intended.

The belief in double effect affects the care of patients and results in under-treatment of physical suffering at the end-of-life. Twycross⁷⁶ found that "*The use of morphine in the relief of cancer pain carries no greater risk than the use of aspirin when used correctly*" [emphasis in the original]. Rather than hastening death, "*the correct use of morphine is more likely to prolong a patient's life because he is more rested and pain-free.*"

In a study at Serei hospice, Japan, Morita⁶⁹ found that a combination of high dose opioids and sedatives used for symptom-control in terminally ill patients in the last days of life are not associated with reduced patient survival. The median midazolam dose was 40 mg per day

2.3.8 Advanced Acquired Immunodeficiency Syndrome

In 1999 South Africa achieved the status of being subjected to the fastest growing HIV epidemic in the world. Educational efforts aimed at reducing the spread of HIV by changing behaviour have failed dismally and health care services, undertakers, family and relatives to name a few are experiencing the result. For every person who dies, many relatives and loved ones are left behind, in mourning. The number of deaths of young people is increasing with its accompanying grief and mourning. Children are being orphaned; elderly parents are left with added burdens of care. To add poor symptom-control to the already heavy burden, increases not only the discomfort of the dying person, it also increases the chance of complicated grief for those left behind.

This is a time that presents opportunities for palliative care teams to significantly contribute to reducing the combined symptom burden and subsequent burden of grief of AIDS patients and their relatives by ensuring that our teams live up to the standards of palliative care as set out by the WHO.

2.3.8.1 Staging Criteria for HIV patients

HIV has become one of the best-measured chronic illnesses of our time in first-world countries. Accurate laboratory tools are available to use as objective measures⁶³, in addition to physical examination and symptomatology, for prognosis and outcomes, as well as for defining decision milestones.

2.3.8.1.1 CD4+ count is useful for

- Staging HIV infection, with resultant guidance for treatment decisions.
- Response to antiretroviral therapy.
- Establishing a differential diagnosis of opportunistic infections in symptomatic patients.

2.3.8.1.2 Viral load is useful for

- Prognosis, determining success or failure of antiretroviral therapy.

Unfortunately CD4+ counts and viral load are beyond the health budget of the public sector and therefore not available to the majority of patients or care teams.³³ A vexing question in a resource-poor country is how to determine the stages of AIDS progression, and for palliative care purposes

the end stage, without laboratory markers. Past history, symptomatology and physical examination are the key to the answer when laboratory markers are unavailable.

When CD4+ count is not available, the WHO Staging System allows stratification of individuals⁶³ into four prognostic categories based on clinical criteria combined with performance status.

2.3.8.2 WHO Staging System for HIV Infection and Disease

Clinical Stage	Associated condition	Performance scale
1	<input type="checkbox"/> Acute retroviral illness <input type="checkbox"/> Asymptomatic <input type="checkbox"/> Persistent general lymphadenopathy	Scale 1 Asymptomatic Normal activity
2	<input type="checkbox"/> Weight loss, < 10% of body weight <input type="checkbox"/> Minor mucocutaneous manifestations <input type="checkbox"/> Herpes zoster within last 5 years <input type="checkbox"/> Recurrent upper respiratory tract infections	And/or scale 2 Symptomatic Normal activity
3	<input type="checkbox"/> Unintentional weight loss (> 10% body weight) <input type="checkbox"/> Diarrhoea or fever > 1 month (Investigated? Results?) <input type="checkbox"/> Oral hairy leukoplakia or oropharyngeal <input type="checkbox"/> Candidiasis <input type="checkbox"/> Vulvovaginal candidiasis > 1 month <input type="checkbox"/> Pulmonary tuberculosis <input type="checkbox"/> Severe bacterial infections	And/or scale 3 Bedridden: < 50% of the day during the last month
4 AIDS- defining conditions	<input type="checkbox"/> HIV wasting syndrome (weight loss plus chronic diarrhoea or fever, what was excluded, and when?) <input type="checkbox"/> HIV encephalopathy (diagnosis by exclusion) <input type="checkbox"/> Malignancies (Lymphoma or Kaposi's sarcoma) Opportunistic infections: <input type="checkbox"/> Extrapulmonary tuberculosis <input type="checkbox"/> Candidiasis of the oesophagus or lower respiratory tract <input type="checkbox"/> Pneumocystis carinii pneumonia <input type="checkbox"/> Herpes simplex (mucocutaneous > 1 month or visceral) (date & lab result) <input type="checkbox"/> Diarrhoea > 1 month due to crypto- or iso-sporiasis <input type="checkbox"/> Extrapulmonary cryptococcosis <input type="checkbox"/> Non-typhoid salmonella bacteraemia <input type="checkbox"/> Cerebral toxoplasmosis <input type="checkbox"/> CMV disease outside the reticulo-endothelial system <input type="checkbox"/> Disseminated non-tuberculous mycobacteria <input type="checkbox"/> Progressive multifocal leukoencephalopathy <input type="checkbox"/> Disseminated endemic mycosis	And/or scale 4 Bedridden: > 50% of the day during the last month

Table 5: WHO Staging System for HIV Infection and Disease.

2.3.8.3 Distinctive Features of Palliative Care in AIDS

AIDS has similarities with cancer in that it is probably, but not necessarily a terminal disease. In both, rapid therapeutic advances are being made.

Differences between AIDS Palliative Care and Traditional Palliative Care⁴¹.

- AIDS affects a younger age group in general.
- Multisystem disorders are more common and more than one disease process may be occurring, a process called "parallel tracking" and "masking". Treatment of the concurrent infections may result in more effective pain relief than general analgesic measures alone.
- Disease patterns are more variable and caregivers must be aware of a range of new presentations of old diseases, e.g. tuberculosis.
- A more variable disease pattern which blurs the distinctions between cure and palliation relatively earlier in AIDS than in cancer and a careful balance between acute treatment and attempts to control chronic symptoms and conditions has to be maintained.
- A more unpredictable terminal phase, with curable components within a progressive and fatal syndrome, resulting in complex decisions about treatment goals. Palliative services need to work closely together with acute sector to manage reversible components of illness. In practice the cooperation is not happening on a general basis.
- Higher incidence of psychosocial problems.
- Associated lifestyle issues and stigmata, which results in reluctance to be identified with the hospice Integrated Community-based Home Care service.

2.3.9 Other differences between AIDS and cancer patients at St. Francis Hospice

Although the same referral form is used, the situation of referral of the cancer patients differs from that of AIDS patients to St. Francis hospice. Cancer patients are referred from a tertiary (or secondary) level to hospice care, which could be categorized as primary care. Cancer patients have all been managed and investigated by an oncologist and disease modifying treatment and options have been fully explored within the relevant health system and economic restraints of a tertiary institution. The referral usually includes an outline of treatment to date as well as recommendations for further management.

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evidence of immune suppression when evaluating patients for inclusion into hospice care. A trial use was proposed. The idea was neither tested nor implemented at St. Francis Hospice.

At present any patient that tests HIV-positive and is referred by a general practitioner is accepted and cared for by care workers and home-care sisters at St. Francis Hospice. With limited medical monitoring, reversible opportunistic infections may not be recognized early. On occasions patients referred for terminal care are diagnosed and treated for opportunistic infections such as pulmonary TB in the in-patient unit, then discharged home with the prospect of living another few months or years. Theoretically, and in selected cases in practice, a patient could die in St. Francis Hospice being HIV-positive, although no WHO stage 4 defined condition was present.

2.3.9.1.3 Clinical state and function of the patient.

Neither the clinical state nor the function (e.g. Karnofsky performance status) of the patient is evaluated upon intake to St. Francis Hospice's Integrated Community-based Home Care Program.

Each element on its own does not contribute enough evidence for "allowing" the patient to die. It is the combination of factors that increases survival prediction.

2.3.10 Prevalence of pain in people with AIDS

Pain in individuals with HIV infection or AIDS is highly prevalent, diverse and varied in syndromal presentation, associated with significant psychological and functional morbidity. Pain of mixed etiology is common.^{4,6,41,47,78} The most common sites for pain are the head, eye, mouth, epigastrium, abdomen and joints. Neuropathic pain presents special problems. Bone pain is very unusual unless associated with malignancy.

Reported prevalence of pain in HIV patients varies between 30% and 90%.^{4,8,43,45,46,89} Breitbart et al 1996^{4,6} reports that the presence and intensity of pain are associated with more advanced HIV disease.

* In South Africa during the time of the study, anti-retroviral medication was not available in the public sector. It was available in the private sector.

2.3.11 Under-treatment of pain

The literature records widespread under-treatment of pain in AIDS patients.^{4,10,43,45,47,53.}

Breitbart, et al 1996⁸ report that less than 8% of ambulatory AIDS patients who reported "severe" pain, were prescribed opioids. Nearly 85% of patients were classified as receiving inadequate analgesia (n= 438 ambulatory patients).

Larue, et al 1997⁴⁵ showed that 62% patients reported pain due to HIV disease severe enough to decrease their quality of life and that over half of them did not receive any analgesic treatment (n= 315, ambulatory care clinics, day hospitals and inpatients).

It is not the aim of this study to determine the reporting of pain or to assess the severity of pain. This study documents opioid administration (types and dosages) in terminally ill AIDS and cancer patients and uses the comparison between the two groups to arrive at conclusions about treatment of pain as a symptom. From the treatment outcomes pain recognition is determined.

2.3.12 Impact of pain on quality of life

In patients with HIV disease, pain has a profound negative impact on physical and psychological functioning, as well as overall quality of life.^{46,65,69} In a study of the impact of pain on psychological functioning and quality of life in ambulatory AIDS patients,⁶⁹ Singer found that HIV-infected patients with pain were more functionally impaired. Functional interference correlated highly with levels of pain intensity and depression.

Larue and colleagues⁴⁵ reported that HIV-infected patients with pain intensities greater than 5 (on a 0–10 numeric rating scale) reported significantly poorer quality of life during the week preceding the survey than patients without pain. Pain intensity had an independent negative impact on HIV patients' quality of life, even after adjustment for treatment setting, stage of disease, fatigue, sadness, and depression. Psychological variables, such as the amount of control people believe they have over pain, emotional associations and memories of pain, fears of death, depression, anxiety, and hopelessness, contribute to the experience of pain in people with AIDS and can increase suffering.

Rosenfeld and colleagues⁹⁵ found that pain had an adverse effect on a broad range of psychosocial functioning. Pain also has an independent, adverse impact on psychological distress, depression and quality of life, *regardless* of number or quality of social supports or potential buffers.

2.3.13 Barriers to managing pain in terminal AIDS patients

Barriers to managing pain in terminally ill AIDS patients are related to the patient, the clinician and social and economic factors.

2.3.13.1 Patient

- Reluctance to report pain
- Limited expectation regarding pain relief
- Fear of addiction and/ or tolerance
- Fear of side-effects such as constipation, confusion, nausea
- Reluctance to take more medication (overwhelmed by quantity of tablets and injections)
- Fear that pain be indicative of greater pathology and disease progression
- Fear of being seen as a "problematic" patient

2.3.13.2 Clinician

- Attention on incurable conditions or opportunistic infections rather than comfort or quality of life
- Focus on social, emotional and spiritual issues and their role in the suffering
- Reluctance to prescribe opioids
- Lack of knowledge about pain management
- Lack of access to pain management experts
- Concern about addiction or misuse of opioids
- Concern that opioids will affect the immune system
- Time constraints
- Fragmented care within the public health system (patients may see a variety of doctors)

2.3.13.3 Socio-economic

- Restrictive regulation of controlled substances
- Access to care, especially in rural areas.
- Costs (financial)

2.4 Summary of central concepts

Good palliative care is essentially to relieving suffering. Pain is one of the most common symptoms requiring control in incurable diseases. The relationship between pain and suffering is multifactorial and complex. Pain influences other factors that contribute to suffering as much, if not more, than they influence pain. HIV/AIDS is no exception: the prevalence of pain and pain syndromes in AIDS is well documented in the literature, as is the pervasive under-treatment of pain in AIDS patients.

Severe pain usually requires strong opioid analgesia. Concerns about hastening death by using strong opioids according to normal guidelines are well documented as well as refuted in the literature. Inappropriate administration of strong opioids however, may hasten death by contributing to respiratory or other problems already present.

This study determines how opioids were used during the last 6 days of life of patients dying in St Francis Hospice.

The objective evidence of opioid-use was used as a measure to evaluate the 2 opposing perceptions within the encompassing framework of pain management.

The management of pain is one facet of symptom-control. Symptom-control is one domain of several others that as a whole comprises patient and family (holistic) care. Pain influences the other domains negatively when present and uncontrolled.

The process of providing care becomes meaningless if the symptoms (and reversible underlying causes) are not timeously recognized and assessed.

Chapter 3 Ethics

Permission from St. Francis Hospice to peruse their records of deceased patients for a certain time period was obtained. Computerized data were kept secure and pseudo-anonymised. Names were stored in one file and connected to a research number. The data were analysed without identifying individual patients.

- **Autonomy:** Protection of persons with impairment or diminished autonomy occurs in the sense that the community of dying patients, especially those dying from HIV/AIDS are vulnerable.
- **Beneficence:** Although the patients in the study are deceased, benefits will pass on to the section of the dying community that will journey through St. Francis Hospice.
- **Justice:** benefits of research will be available to populations being studied indirectly by making the results available to the management of St. Francis Hospice.

Treating HIV-positive patients in a country with limited resources, inadequate infra-structure and a significant level of illiteracy leads to many ethical dilemmas as well as practical stumbling blocks.

Ethical issues are involved in virtually every clinical decision relating to HIV-positive patients.

There are different theoretical frameworks⁷² available to approach ethical decision-making in medicine. From the Hippocratic traditional approach, an approach known as Principlism evolved.

The four cardinal principles³² to apply when facing decisions are:

- do good (beneficence)
- do no harm (non-maleficence)
- respect for patient autonomy
- justice (equitable allocation of available health resources)

What is necessarily the best for society as a whole and seems just, namely restriction of antiretroviral treatment as a trade off for other health care expenses, may be unjust for the individual patient. HIV patients in SA today almost have a duty to die in order to relieve society of undue economical burdens. The dependence on government decisions about availability of resources leaves the patients and their carers with very little autonomy as the people suffering from

the disease and the people supplying medical support have very little influence on the decision process that decided their fates

Different cultures have different values and this affects how they prioritize ethical principles. Cultures can be divided into 2 groups according to the roles that cultural context plays in people's cognition and behaviour.

Cultural Context	
High Context	Low Context
Information drawn from context	Information explicitly communicated
Group	Individual
Interdependence	Independence
Hierarchy	Equality
Traditional ways	Question belief

Table 6: Cultural Context

Western culture, where palliative care originated, is a low context culture. The Xhosa and other indigenous cultures in South Africa are high context cultures, this set of ideals is often referred to as "ubuntu".

Western people hold onto an internal locus of control, and planning for end-of-life follows this system that is based on personal choices. For Low Context cultures, an ethical approach that values the person (Personalism) is strongly advocated in recent times. Personalism asserts that it is the structure of the person that defines the content of our moral duties. "Persona est affirmanda propter se ipsam et propter dignitatem suam" (the person shall be affirmed because of her-/himself and because of her/his dignity.)

How well this fits into a culture where group interest (ubuntu) has higher value than individual interest is questionable. A Utilitarian approach may be more attractive in a High Context culture. Utilitarianism considers whether an act produces the greatest benefit of good for the greatest number of people. The results of an act are what counts, not the act itself or the intentions. Limitations of this approach are that, with our limited knowledge, we seldom foresee all the consequences of our actions.

Chapter 4 Hypothesis

4.1 Informal observation and speculation

At St. Francis Hospice two incompatible policies on the use of strong opioids in people with AIDS were advocated by two different groups on the basis of opposite sets of opinions about the relative importance of indications for, and side-effects of, opioids:

- Death is hastened in some AIDS patients by the use of morphine
- Some AIDS patients die without adequate analgesia (probably because pain is not recognized)

Because neither camp had evidence to support their opinions, the present study was performed in order to produce objective data that would test these two theories.

HYPOTHESIS 1

If opioids were administered in such a way that they hasten death, patient records would show dosages out of the normal range close to the time of death and nursing notes would report changes in conditions such as pin-point pupils, slowing respiration rate, mental clouding and somnolence. Concomitant administration of sedatives could also be responsible for (or aggravate) these signs.

HYPOTHESIS 2

If AIDS patients were to die without adequate analgesia, their records would show that they were distressed when dying, analgesia would not be used or would be started shortly before death, and analgesia would be used in lower doses.

There is general consensus on standards of pain management in terminally ill cancer patients, who therefore form an obvious control group for this study.

4.2 Substantive and statistical hypothesis

The following substantive hypothesis was formed: Group A (AIDS patients) will differ (exceed or fall short) of group B (cancer patients) with respect to Y (morphine administration).

Data for testing (analysis and interpretation) will focus on morphine administration.

Consideration of the above 2 hypotheses gave rise to the following set of questions comparing the group of AIDS patients with the group of patients with cancer:

1. To how many patients in each group was morphine administered for each of the 5 days preceding death?
2. What was the average dosage of morphine administered to each group for each of the 5 days preceding death?
3. Were there differences in the numbers of patients being administered morphine over different calendar years of the study for the two groups?
4. To how many patients in each group was a combination of sedatives and opioid administered?
5. What were the individual and average dosages of sedative administered to each group?

From the clinical notes (nursing and medical)

6. Was the type of death (e.g. painful versus peaceful) different for the two groups?
7. Did symptoms such as reporting of pain, dysphagia, shortness of breath, as reported on admission, differ in the two groups?

Chapter 5 Methods

5.1 Study design

This was a retrospective review of clinical records of two parallel groups of patients to determine whether there were any significant differences in practices of strong opioid administration between oncology and AIDS patients.

Disadvantages of a prospective study in this setting are that it could influence practices in morphine administration, and the small number of AIDS admissions per year would result in an difficult compromise between strength of conclusions (which would require an impractically long study) and feasibility (which requires the data collection to be completed within a year).

5.2 Issues of measurement

5.2.1 Variables

How can one compare opioid administration between the two groups? This will be determined by how morphine administration is evaluated. Review of the medicine charts resulted in 24-hourly summaries of equivalent morphine dosages for 6 consecutive days preceding death.

Do AIDS patients receive opioids for a shorter time? If a significant number of AIDS patients received opioids for less than the last 6 days of life, it can be measured and compared.

The above measures do not give an idea of the cause of death. The patients' notes were read and an opinion formed whether the death could have been opioid related (sudden or unexpected deaths). Together with the opioid dosage escalation one could possibly conclude whether the opioid perhaps contributed to the death or if death was due to disease processes.

An entry for type of death and opioid dosages is therefore necessary.

Discussions were held with staff and documented.

Differences in dosage and dosage escalation: These were calculated and means determined. This serves two purposes: a.) to contribute to the conclusion about cause-of-death of patients who were

initiated on morphine therapy during the 5 days before day of death and b.) to establish comparative dosage figures between the two groups.

The indication for opioid use may differ. Indications are usually pain, dyspnoea or cough. Are the categories of indications similar for AIDS and cancer patients? I tried to form an opinion about indication for opioid use from reviewing the medical notes in each file. As indications for opioid use were seldom directly noted, the idea proved difficult to put into practice and I judged it as not contributing to results.

Role of Pain and discomfort scales in evaluation to establish comparable standards. These are not used at St. Francis Hospice (apart from the symptom list on admission). The merit, usefulness and increased workload versus benefits to the patients were discussed in team meetings. A decision was made against change of the present situation.

Sedation, if administered inappropriately in conjunction with opioids, could hasten death. Database field entries to record sedatives administered were provided for. Although haloperidol is classified as a classical neuroleptic, the main indication for use in St. Francis Hospice is for nausea. The intent of its use as a tranquilizer/ sedative is difficult to evaluate.

Team meetings (hospice team managing our patients) were held and input from the team was evaluated for further criteria to determine differences in patterns of treatment between AIDS and cancer patients. Meetings were useful for the study as well as evaluation and discussion of present practices.

When the patients spent a portion of their last 6 days outside of St. Francis Hospice, no detailed records of opioid use is available. An assumption was made that patients used the opioids at home as prescribed. No rescue dosages, omissions or boosts from the syringe-driver can be taken into account as it was not noted and therefore not known. If a relatively large number spent less than 6 days in the in-patient unit, the quality of the opioid dosage data may be affected. Length of stay was noted and evaluated with this in mind.

5.2.2 Selection and exclusion criteria for AIDS patients

Selection criterion:

Patients dying in the in-patient unit with AIDS or complications related to AIDS (WHO stage 4) between August 1998 and December 2001

Exclusion criteria:

Co-occurrence of AIDS and cancer; death unrelated to AIDS; records not available; patient not evaluated by St. Francis Hospice doctors

Initial collection of files from Jan 2000 to December 2001 identified 27 AIDS-related deaths according to the combination of the Admission- and Undertaker- books. Of the files accessed from the 27, 7 were excluded. The reasons were: 1 died of cancer of oesophagus, 1 of lymphoma, 2 had Kaposi sarcoma, 2 files were not found, 1 died from a gunshot wound with no previous evidence of immune deficiency (high white cell counts indicating adequate immune response).

The elimination process resulted in 20 files being accepted for data input.

I decided to widen the period to August 1998 when the sequential records of deaths in the Undertaker book was commenced. A further 12 patients were identified for which 3 did not meet selection criteria: 2 had lymphoma, 1 had cancer of mouth. This brought the total of AIDS patients who died in the in-patient unit from advanced AIDS to 29.

Data from the files selected for the pilot study were included due to small numbers.

Individual case discussions with the other medical members of the team were held to evaluate in retrospect the validity for including or excluding patients in the study.

5.2.3 Sample size

Standard power calculations were not performed before the study because there were insufficient data. For descriptive studies de Vos recommends a sample size of about 80% of the population when this is between 20–30¹⁹

5.2.4 Measurement tools and data collection

Each step required thought about the kind of evidence it would produce to enable the selection of the most objective or unbiased method of collection. Where measuring instruments had to be applied, a literature search combined with the requirements for the study was used to decide on appropriate items to be included.

1. Dose: Morphine equivalents were calculated for the 5 days (6 x 24 hour periods) preceding death. These calculations formed the basis upon which comparisons of dosage, dosage escalation and length of opioid treatment were determined.
 - a. For oral routes, routine administrations from the drug chart (4 hourly) and prn administrations (time of administration is charted) was entered. Dosages were correlated with nursing notes as additional administrations and omissions are noted there as well.
 - b. For syringe-driver routes, the dosages were calculated at an hourly rate for the time period the syringe-driver was running. Calculation differed for the first driver and re-siting as about 0.5ml remains in the needle and tubing and thus reduces the time over which the driver can run. Boosts are charted and were added to the hour it occurred in. In the event that the time period (including boosts) does not correlate with the prescription, the dosage of morphine would be divided through the number of hours the syringe-driver ran. The SC dosages were converted to oral equivalent dosages by multiplying by 2⁷⁸.
2. Time was charted hourly, allowing half an hour on each side. As charts may reflect half-hourly times, X:30 was charted under X:00 and not (X+1):00 to maintain consistency. The hourly dosages of opioid were entered on an Excel spreadsheet; 24 hour summaries calculated and entered on the Access main database designed for the study.
3. Type and route of strong opioid administered were recorded.
4. Indications for opioid use were classified as: pain, cough, dyspnoea, combinations.
5. Concomitant sedative administration during the last 12 hours: The combination of sedatives and opioids could play a role in hastening death. For this reason concomitant sedative administration was documented and analyzed. Type of sedative and dosage given during the last 24 hours was entered. Two categories were identified. Benzodiazepines were

calculated to midazolam equivalent⁴². The other group comprised neuroleptics. The only neuroleptic drug used in the study groups was haloperidol.

6. Type of death was determined from clinical records and classified as: peaceful, painful, restless/agitated, other, unknown.
7. Speed of death was classified as gradual or sudden. Most patients gradually deteriorate until they die. A sudden death, not explained by other symptoms or incidents could point to possible misuse of opioids.

The following two points (8 and 9) address issues that are difficult to measure accurately in a retrospective study. The questions attempt to estimate if unreported pain is present in AIDS patients.

8. On admission problematic symptoms are routinely noted on a standard symptom list, graded according to subjective patient evaluation of the importance of the problem. Five items were included in the research database namely, pain, dysphagia, dyspnoea, cough and confusion. Presence of symptoms was entered on the admission date, and one would expect that the symptom would have relevance during the last 6 days of life. It contributed to forming a general opinion of whether symptoms that could have been treated with opioids were present.
9. AIDS is a non-specific diagnosis. When patients are referred, the accompanying documentation seldom contains information about specific opportunistic infections present. It would have been useful to note other diagnostic entities related to AIDS, e.g. diarrhoea, oesophagitis, peripheral neuropathy, meningitis, and others. The combination of oesophagitis, pain not recorded on the symptom chart, and not receiving opioids on admission, may be an indication that under-reporting of pain may play a role in non-use of opioids. This idea could not be developed into a measure of the quality-of-care as the records did not contain enough diagnostic information in the majority of AIDS patients.

A question that falls outside the scope of this study is *How effectively do we use opioids in the palliative care of people dying from AIDS?* This could be best addressed by a prospective study.

5.2.5 Type of death

Type of death was determined from a combination of clinical and nursing notes. Categories defined were: peaceful, painful, restless, wet chest & dyspnoea.

Interpretation required some judgement in interpretation as shown in the example below where the patient had a panic attack, moaned loudly and then "died peacefully". The days before were also marked with anxiety

DATE	DOCTORS' ORDERS & NURSING NOTES	SIC
29.10.01	PT had a 'panic attack' at 18:00 on the commode. (Anxiety) very gross subsequently at 18:15 with	
29.10.	^{anxiety} Patient had further case done took medication well. 21:45 turned himself moaning loudly eyes half closed staring up into the ceiling. 22:00 patient died peacefully - family notified by phone. Bereavement forms to be completed	f A/c

Figure 5: Extract from nursing notes.

5.3 Data collection

5.3.1 Identify sources and gain access

The first step was to identify HIV-positive patients dying in the in-patient unit of St. Francis Hospice who could be classified as in an advanced stage of AIDS (WHO stage 4).

No computerized records that could identify these patients were available. An "Admissions Book" is kept where a patient's name, date of admission to the in-patient unit and diagnosis is written. Using this, I compiled a list of the admissions of patients with AIDS to the in-patient unit from August 1998 to December 2001. Not every patient admitted to the in-patient unit dies there. An unknown percentage of the patients are discharged home. To identify AIDS patients who died in the in-patient unit, the "Undertakers Book" was used. This register was started in August 1998 and includes the date of death but not the cause. From the first list of AIDS-patient admissions, a smaller list of AIDS-patients who died in the in-patient unit was selected.

The folders were obtained and data captured and evaluated. A few patients did not meet the selection criteria (see below for details) and their data were discarded.

The control group of cancer patients was created using the final list of AIDS deaths and the 'Undertakers Book' to identify for each AIDS death the first subsequent patient who died from cancer and met the selection criteria (see below for details).

5.3.2 Field notes

Notes were kept of the progress, problems and questions that arose as the research proceeded. From these notes, team meetings, group discussions and peer discussion were initiated.

5.3.3 Data capture

Three data tables were created in an Access database. The data were captured by myself. It consisted of a mixture of numeric and textual data. Numeric data such as morphine usage and dosages lends itself to a structured and relatively simple capture method.

Textual categories were developed to include type of death, speed of death, sedation required. Provision was made for notes to elaborate or elicit particular aspects of importance or relevance.

Nursing notes were evaluated to reach a conclusion about speed and type of death.

5.3.3.1 Patient details

The first selection effort involved obtaining general patient details such as hospice folder number, name, age, gender, ethnic group, socio-economic status (indicated by privately managed prior to admission or management by governmental structures such as local clinics or a provincial hospital). Each patient was allocated a reference number that provided anonymity for further entries. Data was entered from paper records.

5.3.3.2 Core data

The second table contained the data the main analysis was based on. The core data included:

- Hospice folder (link to patient information)
- Place of death, together with date and time of death

- Final diagnosis and accompanying diagnoses
- An indication of opioid administered: none, morphine, other
- Indication for the opioid: pain, dyspnoea, cough, pain and dyspnoea, dyspnoea and cough
- Route of administration: This is required to calculate equianalgesic doses. At St. Francis Hospice we calculate the subcutaneous dose at 50% of the oral dose.^{76,80} The oral equivalent of morphine dosages were used throughout the study (SC dosages were multiplied by 2 in order to be comparable to the oral dosages³⁶)
- Type of death was categorized as: peaceful, painful, restless, unknown, vomiting, wet chest and dyspnoea. This main symptom was elicited from the nursing notes. Peer discussion as well as nursing input was needed for clarification in a few cases.
- Speed of death: Sudden or gradual. From reading the nursing notes, an opinion of speed of death was formed. One patient died suddenly of a large aneurysm that bled. The bleed was anticipated and appropriate palliative measures were taken to accommodate this.
- Sedatives used. Yes, No and type and dosage in last 24 hours.

5.3.3.3 Relevant supporting data

A symptom sheet with 33 symptoms is completed for each admission by the nurse. The format lends itself to easy capture. From this, a third table was designed incorporating key symptoms related to the study such as the presence of pain, dyspnoea, cough, nausea and vomiting (for which haloperidol is often administered as a first-line drug), confusion, fits,

NAME : _____

NURSING OBSERVATIONS AND ASSESSMENTS

	1	2	3	4	COMMENTS
1. PAIN		✓			
2. NAUSEA			✓		
3. VOMITING			✓		
4. CONSTIPATION			✓		
5. DIARRHOEA			✓		
6. INCONTINENCE	✓				
7. FITS		?			
8. MICTURITION	✓				Incontinent
9. CATHETER			✓		Size 14 Foley inserted today
10. STOHA			✓		
11. WAKING	✓				

Figure 6: Section of Symptom sheet completed on admission.

5.3.4 Data quality assurance

Once the data were entered, the tables were evaluated for lack/ absence of data, inconsistencies, and obvious errors. I also discussed unclear impressions with colleagues employed at St. Francis Hospice in an attempt to obtain objective information. With the entering in the Excel subset of morphine dosages, the entries in the existing Access database were reviewed. A few sample folders were selected and handed to a colleague not related to St. Francis Hospice to complete printed data capture forms. The goal of this request was to evaluate my own clinical judgment in evaluating the files. The two sets were compared and no important differences were found.

5.3.5 Data analysis and synthesis

The tables were linked in Access and the relevant queries run.

A list of patients who were using strong opioids was selected. The list was imported into Excel. A spreadsheet was designed to enter morphine doses administered on an hourly basis. Adjustments were made to use the oral equivalent of subcutaneous dosages (SC multiplied by 2) Working back from the time of death, the hourly values of morphine administration were summed in 24 hour intervals for 6 consecutive days, obtaining the daily morphine dosage.

The 24 hourly results were entered into the Access database. Query results were copied to Excel. Graphs were drawn from the query results.

5.4 Pilot study

A small sample of AIDS and cancer patients was obtained to

- discover errors in the data capture design
- evaluate the design of the database for manipulation
- assess the proposed methods for analyzing the data outcome:

The type of opioid administered was significantly different for cancer patients. A number were on Duragesic (fentanyl), buprenorphine or opioids not available in the provincial hospitals. A close look at the geographic data showed that the AIDS group conformed to the general population as far as

socio-economic status (majority not on medical aid*) and racial grouping was concerned. The cancer group showed a majority of Caucasians compared to the other ethnic groups. A significant percentage was on medical aid or was able to afford private medication.

Looking at the available general statistics of St. Francis Hospice, it is noticeable that cancer patients are mainly from the white population group. The slight difference from the grand total of deaths is due to a small number of patients suffering from Motor Neuron Disease and other diseases.

2000	Black	Coloured	White	Total
AIDS	122 (79%)	17 (11%)	16 (10%)	155
Cancer	181 (29%)	111 (18%)	316 (51%)	616

Table 7: General statistics at St. Francis Hospice for 2000

To circumvent bias in the study it was decided that selection criteria of the cancer group should stipulate similar socio-economic background to AIDS patients. A simple way to achieve the newly defined selection criteria was to choose the following death from a similar race group patient with a similar medical aid/ non medical aid history.

5.5 Data capturing and data analysis

The author designed the forms (in Access) and captured the data. Microsoft Access was used to summarize the data. Graphs were drawn in Microsoft Excel.

5.6 Statistical analysis

Tests for statistically significant differences were calculated using the standard functions provided by

- Microsoft® Excel 2002 (Microsoft Corporation, USA): Chi square test and t test and
- Stata 7.0, (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA): Fisher exact test

The t test was used to compare means, the Chi square test was used to compare proportions.

* I.e. medical insurance

5.7 Shortcomings and sources of error

5.7.1 Access to data

5.7.1.1 Inaccessible data

Two files for AIDS patients could not be located and their records were omitted.

One file of a consecutive death of cancer patients (with same socio-economic status) could not be located. The second consecutive death (with same socio-economic status) was identified and selected.

5.7.1.2 Incomplete records and missing data

Not all information required for study purposes was available. For example, seven symptom charts were absent or not completed from cancer patients' folders.

For the AIDS patients, associated conditions were not always noted adequately. A contributing factor seems to be that the referral form does not make provision for such detail.

5.7.2 Errors in using existing data collection instruments

Although morphine dosages are compared across a wide spectrum of patients, blood levels are influenced by several factors. Factors that influenced the pharmacokinetics of opioids cannot be determined retrospectively from clinical charts.

Patients are not weighed. One would expect different responses to 10 mg of morphine in a 32kg and a 70kg adult. There is little information available in the notes to form an opinion about weight. A percentage of bias can be expected towards underweight patients compared to normal or overweight patients.

Absorption, metabolism (including tolerance) and excretion cannot be determined as gastrointestinal stasis, liver and kidney function/ failure, concomitant use of liver enzyme-inducing drugs were not routinely noted. These factors were excluded from the study.

5.7.3 Errors in scale construction

The measurement scales for mode of death, speed of death have not been formally validated as this was beyond the scope of the project. However, they are simple, intuitive and would seem to have face validity.

5.7.4 Errors in data collection and documentation

I collected and documented the data myself. The drawback from this is that I was not "blinded". I was aware of the diagnosis, research question and background of the study. To assess the extent of this possible bias, a colleague that was not connected to St. Francis Hospice, evaluated for each group 10 folders selected by a third party not involved with the study. My colleague was "blinded" as to the group. The discrepancies highlighted the difficulties in remaining unbiased. I erred to the side of caution and for example categorized more "peaceful deaths" than the non-hospice colleague. A meeting was set up between myself and another colleague from St. Francis Hospice and the files were re-evaluated for subjective bias of input. When difficulties occurred in decision making they were discussed with members of the team who were involved with the specific patient.

I may also be prejudiced, being involved in ongoing debates with staff over the policy of using morphine in dying AIDS patients and adverse effects or benefits it could possibly have on the patients.

The Hawthorne effect⁶¹ may have been present as the incidence of morphine use of AIDS patients increased during the study period (see Figure 10 on page 65).

5.7.5 Errors in data-capturing

The dosage of the morphine was straightforward and was double checked for errors in entry.

Sedative administration was not recorded for this study in the same detail as morphine. It was recorded for the last 24 hours. The reason is that it is unlikely that a sedative administered more than 24 hours before death would contribute to it.

Opioids used at home were not charted in the patient record. There were no entries pertaining to compliance, rescue dosages or omitted dosages. For comparison, it was assumed that morphine

was used as prescribed, without taking into account omission or rescue dosages. The number of stay-days was entered to record accurately the number of days the different patients spent in the in-patient unit.

5.7.6 Errors in analysis and interpretation

The use of inappropriate statistical procedures is a possibility. Advice and assistance were obtained from a statistician.

University of Cape Town

Chapter 6 Results and Analysis of Data

6.1 Sample profiles

	Cause of death	
	AIDS	Cancer
Number	29	29
Age: mean [minimum– maximum]	35 [21–60]	56 [27–89]
Sex ratio, F:M	14:15	19:10
Health care funding: State/Private	29/0	29/0
Ethnic group: Black/Coloured/White	20/3/6	20/3/6

Table 8: Patient characteristics

Twenty nine patients with Advanced AIDS were identified who died in the in-patient unit of St. Francis Hospice between August 1998 and December 2001 and met selection criteria. From their death dates, 29 consecutive cancer patients who died with a similar socio-economic background were identified as controls.

Matching criteria were

- (i) ethnicity and
- (ii) funding of health care as public (i.e. state patient) or private (i.e. medical aid patient).

6.2 Main findings of single factors

6.2.1 Total number of patients on morphine

6.2.1.1 Five days before their day of death

Opioid	AIDS	Cancer	
Patients on morphine	3 (10%)	20 (69%)	
Patients on no strong opioid	26 (90%)	9 (31%)	
Total	29	29	p< 0.001, Fisher exact test

Table 9: Number of patients on morphine the last six days

The proportion of people receiving morphine 5 days before dying from AIDS is significantly different from that in patients dying from cancer, $p < 0.001$ (Fisher exact test).

The result contrasts sharply with both the comparison group of cancer patients of which 69% received morphine five days before death, and the literature on palliative care practices elsewhere.

6.2.1.2 On the day of their death:

Opioid	AIDS	Cancer	
Patients on morphine	17 (59%)	25 (86%)	
Patients no strong opioid	12 (41%)	4 (14%)	
Total	29	29	p= 0.038 Fisher exact test

Table 10: Number of patients on morphine on the day of their death

On the day they died, 12 of the 29 AIDS patients in the study (41%) received no opioid. Only 3 (10%) of the 29 AIDS patients were using morphine for more than 5 days before they died.

6.2.1.3 Increase in number of patients on morphine

For AIDS patients this is an increase in numbers of 470% from 5 days before their death, and for cancer patients 25%. Despite this large increase, the proportion of people with AIDS receiving morphine on the day of their death is significantly different from that in patients dying from cancer, 59% cf 86%.

13 cancer patients (45%) received dosages higher than 60 mg/ 24 hours 5 days before their death compared to 1 AIDS patient (3%) ($p < 0.001$, Fisher exact). Three of the 29 cancer patients (10%) received morphine at dosages of more than 300 mg per 24 hours. No AIDS patients in this study received morphine at dosages higher than 300 mg per day.

The following graphs show the different patterns of strong opiate use according to dosage in AIDS and cancer patients at St Francis hospice.

Figure 7:
AIDS patients on morphine
(n = 17 of 29)

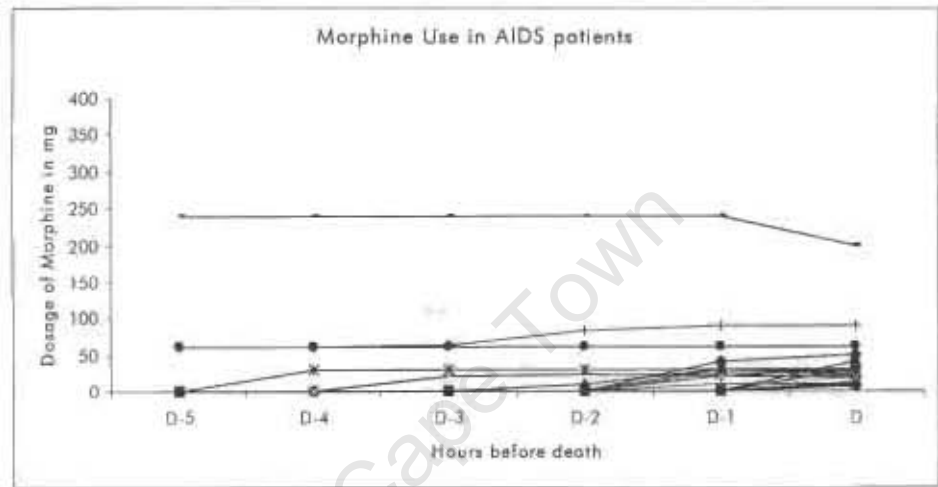
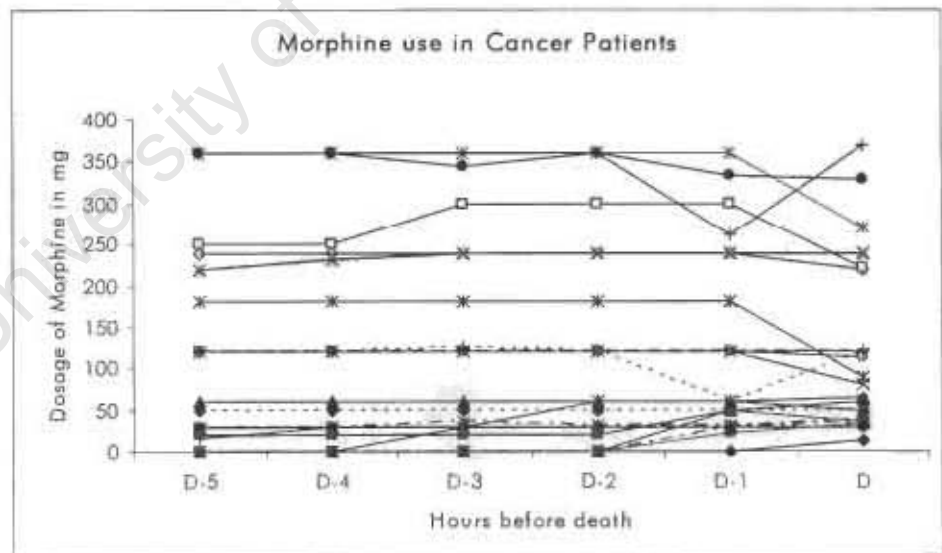


Figure 8:
Cancer patients on morphine
(n = 25 of 29)



The picture of cancer patients on morphine looks vastly different from that of AIDS patients. The morphine dosage of the 3 AIDS patients (10%) who received morphine for 5 days or more before death, compares reasonably well to the morphine dosages of cancer patients receiving morphine for 6 days (or more).

6.2.1.4 Number of patients who died within 48 hours after starting morphine

Opioid < 24 hours	AIDS	Cancer
No morphine	12	4
Morphine < 24 hours	11	4
Morphine > 24 hours	6	21
Total	29	29

Table 11: Number of patients who died within 48 hours of starting morphine

11 of the 29 AIDS patients died within 48 hours of being initiated on morphine (Numbers increased from 6 to 17 patients receiving morphine). Expressed as a percentage of the AIDS patients who were receiving morphine (17 in total), it calculates to 65%.

4 cancer patients (14%) were started on morphine during the last 48 hours of life.

6.2.1.5 Morphine dosages

The maximum dose for AIDS patients who started morphine during the last two days of life was 50 mg per 24 hours. This is within the normal therapeutic range.

There was no excessively large increases in serial morphine dosage noted in either cancer or AIDS patients.

6.2.2 Average number of days morphine was administered

The average number of days that AIDS patients were given morphine was 1.6 and for cancer patients 4.5 (maximum n=6). The average number of days that cancer patients received morphine, is only applicable to this study and is not reflecting the period before the last week.

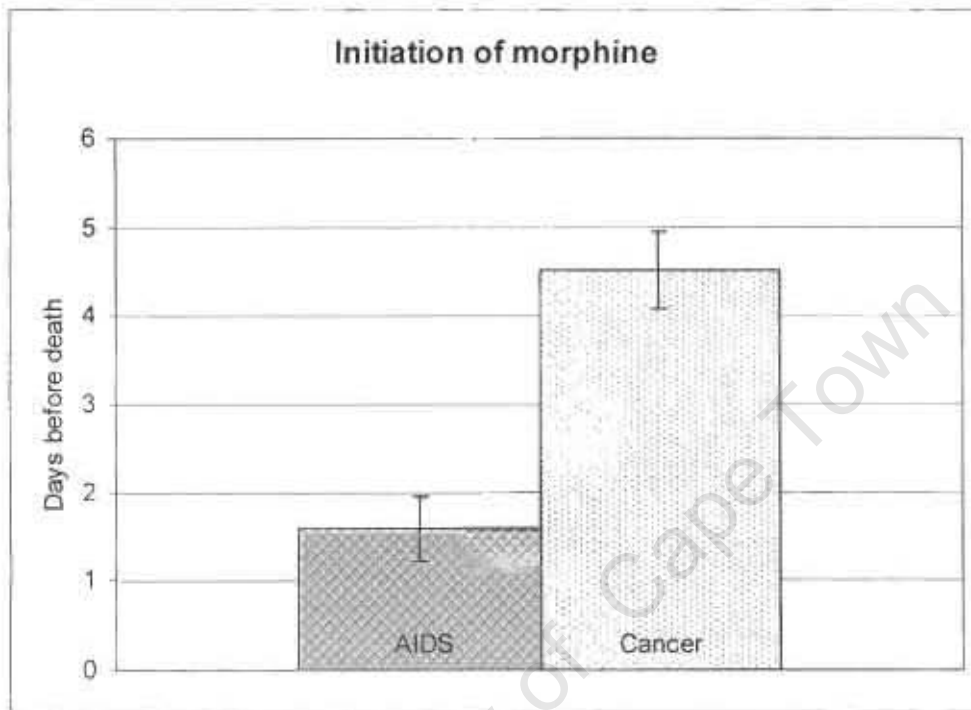


Figure 9: Average number of days morphine was administered before death (bars indicate 95% confidence intervals)

$P < 0.001\%$, from t test

The indication for using morphine in terminally ill patients is usually to palliate pain to ensure a relatively symptom free death.^{20, 80} With refractory symptoms prevailing, sedation is often used to achieve control. The next steps in the analysis examine:

- sedation administered,
- the kind of death that occurred, and
- symptoms noted on admission in the two groups.

6.2.3 Sedative administration

None of the patients in the study receiving sedatives were sedated to a state of unconsciousness.

6.2.3.1 Types of sedatives administered

Two categories of sedative used during the last 24 hours were identified, namely benzodiazepines and neuroleptics. For easy comparison equivalent dosages were calculated. For the benzodiazepine group an equivalent oral midazolam dosage for the 24 hour period was used. Haloperidol was the only neuroleptic administered during the last 24 hours. All patients who received haloperidol were given it by subcutaneous route for nausea and vomiting. No patient in this study selection received haloperidol for sedation. Neuroleptics were therefore excluded from the analysis of sedatives.

6.2.3.2 Incidence of sedative administration

Compared with cancer patients, significantly more of the AIDS patients received sedatives during their last 24 hours: 12 of the 29 AIDS patients; 4 of the 29 cancer patients. $p = 0.038$ (Fisher exact)

6.2.3.2.1 Number of patients receiving sedatives

Sedatives	AIDS	Cancer	
Last 24 hours	12 (41%)	4 (14%)	
None	17 (59%)	25 (86%)	
Total	29	29	$p = 0.038$, Fisher exact test

Table 12: Number of patients to whom sedation was administered in the last 24 hours

6.2.3.3 Dosage of sedatives administered

Midazolam (mg per 24-hr)	Average	Maximum	Minimum
AIDS	7.9	23.75	1.25
Cancer	7.5	7.5	7.5

Table 13: Dosage of sedatives of patients (milligram per 24 hours)

6.2.4 Type of death

Type of death	AIDS	Cancer
Restless	6	3
Painful	5	0
Wet chest and dyspnoea	1	2
Vomiting	0	1
Distressed	12	6
Peaceful	17	23

Table 14: Type of death

5 of the 29 AIDS patients died a painful death compared to 0 cancer patients

Type of death	AIDS	Cancer	
painful	5	0	
not painful	24	29	p= 0.02, Fisher exact

Table 15: Patients who died a painful death.

6.2.5 Length of stay

	AIDS	Cancer
Morphine	5.2	6.3
No morphine	6.1	3.5
All patients	5.5	5.9

Table 16: Length of stay and morphine administration

The average length of stay (5.5 and 5.9 days respectively) is similar for the AIDS and cancer patients in the study.

	AIDS	Cancer	
Morphine commenced in home care	4 (3)*	19	
Morphine commenced in In-patient Unit	13 (14)	6	
No morphine	12	4	P< 0.001, chi test

Table 17: Morphine administration and place of care (home care or in-patient unit).

* Numbers in brackets indicate corrected number of patients.

6.2.6 Trend of morphine administration in the in-patient unit over time

The study period consisted of 3 years and 5 months and commenced in 2001.

		1998	1999	2000	2001
AIDS	Morphine	0	2	3	12
	None	2	5	5	0
	Total	2	7	8	12
Aids M/T%		0%	29%	38%	100%
Cancer	Morphine	1	7	5	12
	None	1	0	3	0
	Total	2	7	8	12
Cancer M/T%		50%	100%	62%	100%

Table 18: Number of patients using morphine per year

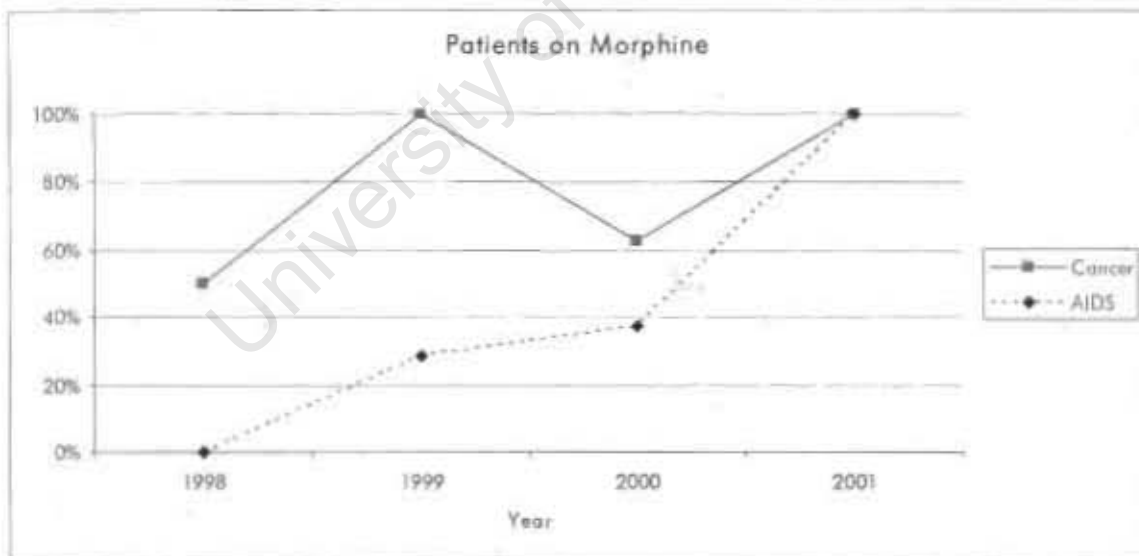


Figure 10: Morphine administration distributed through the years in the two groups

During 2001 a (Table 18 and Figure 10) change in attitude could be seen as evidence in the results. Not only did the incidence of morphine administered to AIDS patients increase dramatically during this year, the number of AIDS patients who died in the in-patient unit from AIDS also increased. Keep in mind that this study excludes the patients who died at home. It is not known if the trend in

morphine administration changed in the home care section. The main reason for admitting patients to the in-patient unit is for uncontrolled symptoms.

6.3 Findings when factors are combined for relevance

There are statistically meaningful differences in the findings shown before. The following section will look at different combinations of key measurements highlighting the intersection and relationship between them.

6.3.1 Doses of subcutaneous morphine, sedatives used and type of death

The following factors and their relationships that are looked at in different combinations:

- Morphine dose (during last 3 days)
- The subgroup who received morphine for less than 48 hours (demarcated)
- Sedative dosages during last 24 hours
- Sedative indication
- Type of death
- Symptoms on admission

6.3.1.1 AIDS patients

AIDS Patient number	Days before death (D= day of death)			Length of stay (days)	Midazolam Equivalent (last 24 hours)	Type of Death
	D-2	D-1	D			
101	0	0	0	4		Peaceful
102	0	0	0	2		Peaceful
104	0	0	0	6		Peaceful
105	0	0	0	8		Peaceful
108	0	0	0	3		Peaceful
103	0	0	0	17		Painful
116	0	0	0	9		Restless
112	0	0	0	12	5	Painful
106	0	0	0	1	7.5	Peaceful
110	0	0	0	3	7.5	Restless
111	0	0	0	6	7.5	Peaceful
117	0	0	0	2	7.5	Restless
109	0	0	6	1	7.5	Restless
115	0	0	10	5		Peaceful
121	0	0	12	1		Peaceful
113	0	0	20	11		Painful
119	0	0	29	2		Peaceful
125	0	0	40	3	7.5	Painful
114	0	10	10	13		Painful
123	0	30	20	3	1.25	Wet chest
124	0	20	29	4	23.75	Peaceful
122	0	25	30	5	7.5	Peaceful
118	0	40	50	5	7.5	Peaceful
107	10	30	20	2		Peaceful
120	23	20	18	5		Peaceful
126	30	30	25	11	5	Peaceful
128	60	60	60	9		Restless
129	83	90	90	3		Restless
127	240	240	200	5		Peaceful
Average	74.3	54.1	39.4	5.5		
Number on morphine	6	11	17			

Table 19: AIDS patients: Subcutaneous morphine doses, sedatives and type of death.

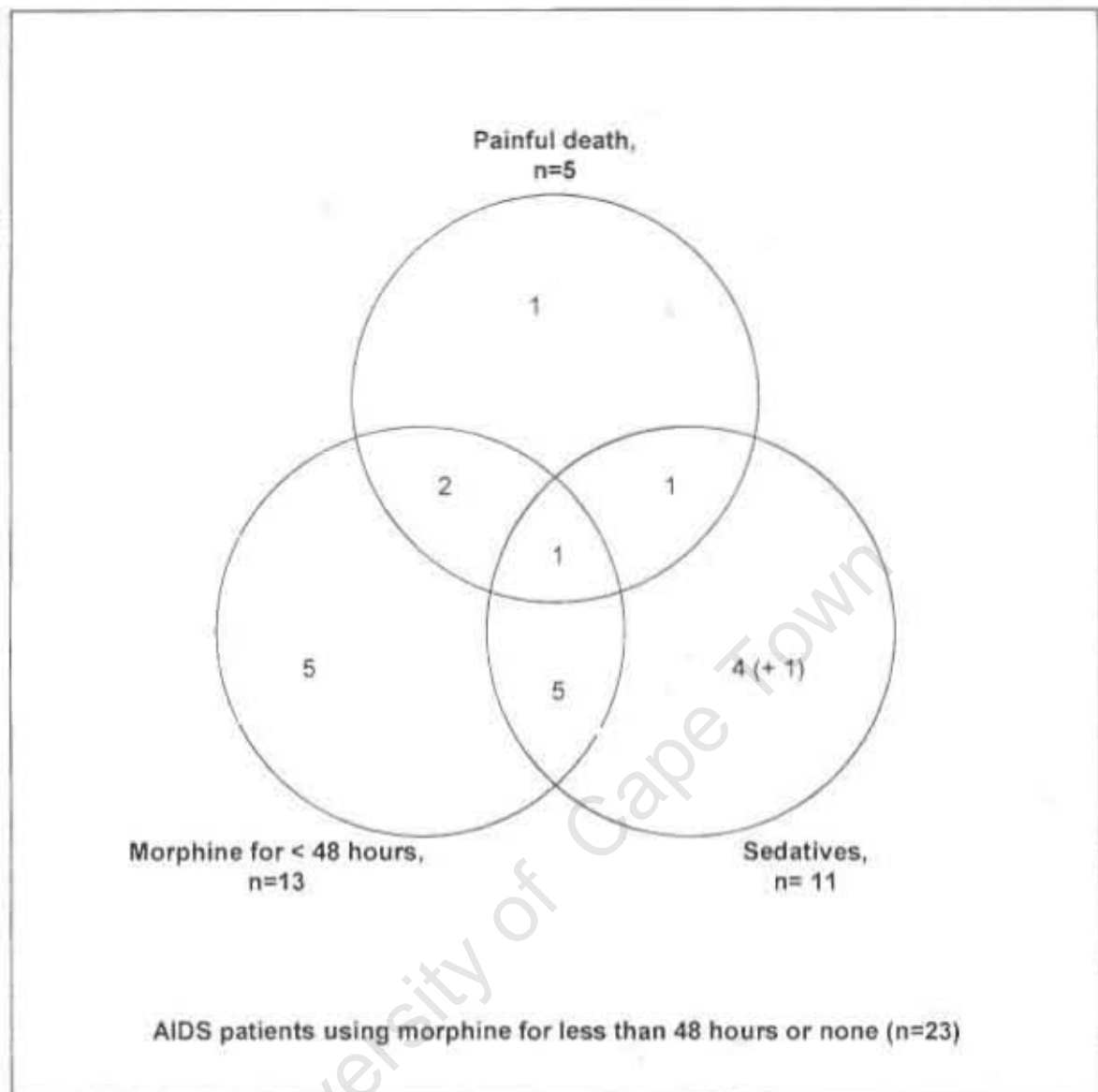


Figure 11: Venn diagram of AIDS patients using morphine for less than 48 hours and the intersection with painful type of death and sedatives administered during the last 24 hours.

The diagrammatic illustration excludes the portion of AIDS patients (6 of the 29) who received morphine for more than 48 hours from the morphine group.

- 1 of the 5 AIDS patients who received a sedative and no morphine, died a painful death – noted with (+1) in the sedative group.
- Of the 7 AIDS patients that received sedation in conjunction with morphine, 6 had been given morphine in the last 48 hours, and 1 in the last 120 hours.

For the comparative illustration for the cancer patients the number that received morphine for more than 48 hours is 21. Although the numbers in each group is different, the point being illustrated is that for the AIDS patients there is an intersection of factors for certain patients which is absent in the control group.

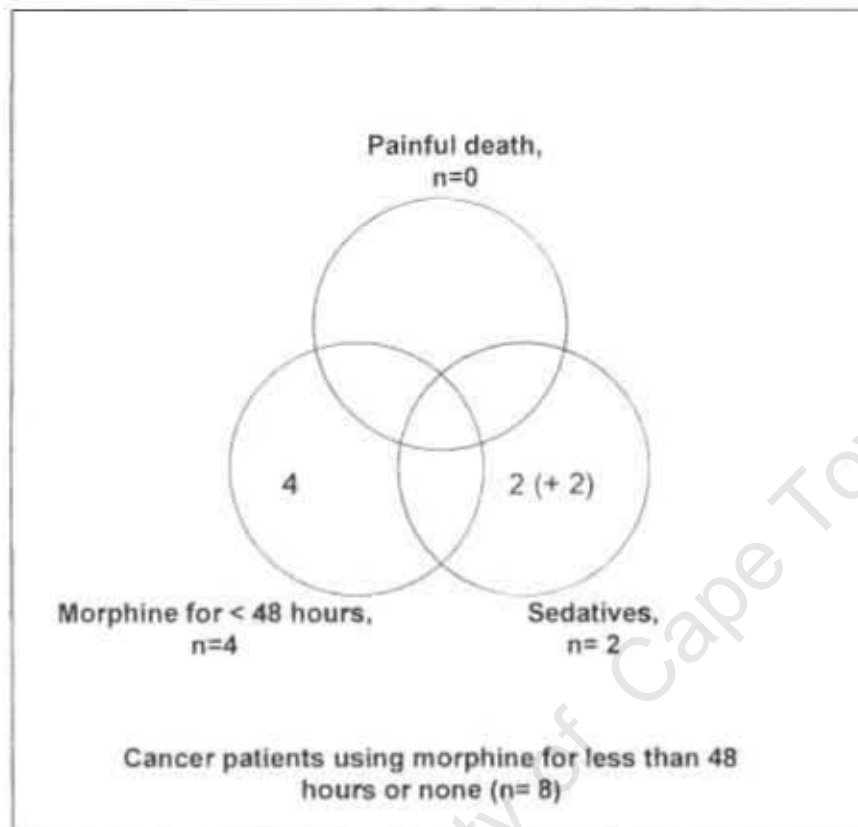


Figure 12: For comparison: a diagrammatic illustration of the cancer group.

Of further note

- 5 out 12 (42%) of AIDS patients who did not receive morphine, received sedatives.
- 2 out 4 (50%) of cancer patients who did not receive morphine, received sedatives.

6.3.1.2 Cancer patients

Cancer	Days before death (D= day of death)			Length of stay (days)	Midazolam Equivalent (last 24 hours)	Type of Death
	D-2	D-1	D			
Patient number	D-2	D-1	D			
201	0	0	0	3	7.5	Peaceful
210	0	0	0	10	7.5	restless
212	0	0	0	0		Peaceful
213	0	0	0	1		Peaceful
220	0	0	13	2		Peaceful
208	0	23	34	2		Peaceful
218	0	50	35	2		Peaceful
203	0	30	40	10		Vomiting
202	60	60	50	4		Restless
207	30	30	30	3		Peaceful
216	28	30	30	14		Peaceful
228	30	30	30	6		Peaceful
217	31	31	34	10		Peaceful
221	50	50	50	11		Peaceful
215	20	50	60	2		Wet chest
211	60	60	65	1		Peaceful
219	120	120	80	4	7.5	Peaceful
227	180	180	90	13		Peaceful
223	120	120	115	0		Peaceful
206	120	60	120	9		Wet chest
226	120	120	120	3		Peaceful
229	120	120	120	8		Peaceful
222	240	240	220	2	7.5	Peaceful
214	300	300	222	7		Peaceful
205	240	240	240	10		restless
224	240	240	240	7		Peaceful
204	360	360	270	0		Peaceful
225	360	332	328	5		Peaceful
209	360	262	368	23		Peaceful
Average	151.9	130.8	120.2	6.3		
Number on morphine	21	24	25			

Table 20: Cancer patients: Subcutaneous morphine doses, sedatives and type of death

6.3.2 Combinations with the focus on sedatives used.

	Sedation		No Sedation	
	Morphine	No Morphine	Morphine	No Morphine
AIDS	7	5	10	7
Cancer	2	2	23	2

Table 21: Administration of morphine and sedatives during the last 24 hours

The patterns of treatment for AIDS and cancer patients differ significantly ($p=0.008$, Fisher exact test).

Patient num	Opioid	Type of death	Sedative	midazolam equivalent	Indication	Symptoms on admission		
						Pain	Dysphagia	Dyspnoea
110	None	restless	Midazolam	7.5	anxiety	1 Major	3 Absent	1 Major
117	None	restless	Lorazepam	7.5	panic attack	1 Major	4 Unknown	1 Major
112	None	painful	Valium	5	Convulsions	2 Minor	3 Absent	3 Absent
106	None	peaceful	Oxazepam	7.5	confusion and restlessness	3 Absent	1 Major	3 Absent
111	None	peaceful	Lorazepam	7.5	restlessness	3 Absent	2 Minor	3 Absent
109	Morphine	restless	Midazolam	7.5	restlessness	1 Major	1 Major	1 Major
118	Morphine	peaceful	Lorazepam	7.5	Anxiety	1 Major	3 Absent	1 Major
126	Morphine	peaceful	Valium	5	Convulsions	1 Major	3 Absent	1 Major
122	Morphine	peaceful	Midazolam	7.5	restlessness	1 Major	3 Absent	4 Unknown
123	Morphine	wet chest dyspnoea	Valium	1.25	noisy respiration, per sister orders	2 Minor	2 Minor	1 Major
114	Morphine	painful	Lorazepam	7.5	pain after rescue dose	2 Minor	3 Absent	1 Major
124	Morphine	peaceful	Midazolam	23.75	restlessness	3 Absent	3 Absent	2 Minor

Table 22: Indications for sedatives and symptoms on admission

2 of the 5 AIDS patients who died a painful death received sedation. One (number 114) received sedation because the rescue dose of morphine did not control pain. In this particular patient, although morphine was prescribed 4 days before death, it was only given "as required" on two occasions before she died. On both days (D and D-1) the dosage was 10 mg per 24 hours. This

consisted of one "rescue dose" of 10 mg morphine on each of the two days. "Rescue dose" in the nursing notes in this case was a misnomer as the actual use in this situation was "as required".

6.3.3 Combinations with the focus on the type of death

6.3.3.1 Type of death: separated into groups according to morphine usage.

Type of death when separated into groups according to morphine usage, 5 days before death and day of death respectively.

Type of death	AIDS	Morphine , 5 days before death (D-5)		Cancer	Morphine , 5 days before death (D-5)	
	Total of AIDS patients	Morphine	No morphine	Total of cancer Patients	Morphine	No morphine
Peaceful	17	1	16	23	20	3
Restless	6	2	4	3	2	1
Painful	5	0	5	0	0	0
wet chest	1	0	1	2	2	0
uncontrolled vomiting	0	0	0	1	0	1
Total:	29	3	26	29	24	5

Table 23: Type of death and morphine administration: 5 days before death

Type of death	AIDS	Morphine , day of death (D)		Cancer	Morphine , day of death (D)	
	Total of AIDS patients	Morphine	No morphine	Total of cancer Patients	Morphine	No morphine
peaceful	17	10 (+9)	7	23	20	3
restless	6	3 (+1)	3	3	2	1
painful	5	3 (+3)	2	0	0	0
wet chest	1	1 (+1)	0	1	2	0
uncontrolled vomiting	0	0	0	2	1 (+1)	0
Total:	29	17	12	29	25	4

(+ n) = increase from D-5 in previous table

Table 24: Type of death and morphine administration: day of death

- For 9 of the 14 AIDS patients who were initiated on morphine during the 5 days before death, a peaceful death was achieved (14 is the total of the numbers in brackets in Table 24)
- Of the 5 AIDS patients who died a painful death, none received morphine five days before their death. Although morphine was initiated close to death for 3 patients, the morphine administration for the short period did not prevent them from dying a painful death. Two patients did not receive any morphine.

6.3.3.2 Type of death: looking at sedation and morphine combined

A more detailed comparison of type of death is shown in the following table.

Type of death	Morphine: Sedation:	AIDS				Cancer			
		yes yes	no yes	yes no	no no	yes yes	no yes	yes no	no no
Peaceful		4	2	6	5	2	1	18	2
Not peaceful		3	3	4	2	0	1	5	0
painful		1	1	2	1	0	0	0	0
restless		1	2	2	1	0	1	2	0
vomiting		0	0	0	0	0	0	1	0
wet chest and dyspnoea		1	0	0	0	0	0	2	0

Table 25: Differences of sedative and morphine use in patients who died a painful death.

- Noticeable is the absence of pain as a symptom in the group of cancer patients who did not die a peaceful death.
- Two AIDS patients died a painful death without the administration of morphine. One of the two received a sedative.
- Three AIDS patients died a restless death without being administered a sedative. Two of the three AIDS patients who died a restless death received morphine.

6.3.4 Last 48 hours

Sedatives were administered on an "as required" basis to 12 out of 29 AIDS patients (41%) and 4 out of 29 cancer patients (14%) in the last 24 hours of life. For AIDS patients 11 of the 12 received either no morphine or morphine for less than 48 hours. (38% of AIDS patients). Of this 11, 6 (21% of all AIDS patients) died a non-peaceful death. The remaining AIDS patient who received a sedative, received morphine for the last 120 hours of life.

2 cancer patients who received sedatives during the last 24 hours also received morphine. Both received morphine for longer than 6 days and average dosages of morphine was 113 mg and 237 mg over the last 6 days of life.

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6.3.5 Length of stay and morphine administration

Length of stay divides the time periods patients received morphine into home care and in-patient unit care.

6.3.5.1 AIDS patients: doses of subcutaneous morphine (or equivalent)

Day before death	D-5	D-4	D-3	D-2	D-1	D	Length of stay (days)
Patient number							
109	0	0	0	0	0	6	1
121	0	0	0	0	0	12	1
119	0	0	0	0	0	29	2
107	0	0	0	10	30	20	2
125	0	0	0	0	0	40	3
123	0	0	0	0	30	20	3
129	60	60	63	83	90	90	3
124	0	0	0	0	20	58	4
115	0	0	0	0	0	10	5
122	0	0	0	0	25	30	5
118	0	0	0	0	40	50	5
120	0	0	19	23	20	18	5
127	240	240	240	240	240	200	5
128	60	60	60	60	60	60	9
113	0	0	0	0	0	20	11
126	0	30	30	30	30	25	11
114	0	0	0	0	10	10	13
Number on morphine	3	4	5	6	11	17	

xx Shaded area denotes days spent in in-patient unit

xx Non shaded area denotes days spent under home care service

Table 26: Length of stay of AIDS patients associated with morphine administration.

The patients who did not receive morphine are excluded from this table.

4 AIDS patients (patient numbers 107, 127, 128, 129) received morphine before admission to the in-patient unit. Patient number 107 does not qualify for this category as morphine was started after the in-patient unit doctor was contacted, reducing the number to 3. The majority (13 + number 107 = 14) was started on morphine therapy during their stay in the in-patient unit. The pattern is different for the cancer patients. For 6 cancer patients morphine therapy was initiated after admission to the in-patient unit whilst the balance (20) received morphine before admission.

6.3.5.2 Cancer patients: doses of subcutaneous morphine (or equivalent)

Day before death	D-5	D-4	D-3	D-2	D-1	D	Length of stay (days)
Patient number							
223	120	120	120	120	120	115	0
204	360	360	360	360	360	270	0
211	60	60	60	60	60	65	1
220	0	0	0	0	0	13	2
208	0	0	0	0	23	34	2
218	0	0	0	0	50	35	2
215	20	20	20	20	50	60	2
222	240	240	240	240	240	220	2
207	30	30	30	30	30	30	3
226	120	120	120	120	120	120	3
202	0	0	30	60	60	50	4
219	120	120	120	120	120	80	4
225	360	360	345	360	332	328	5
228	30	30	29	30	30	30	6
214	250	250	300	300	300	222	7
224	218	232	240	240	240	240	7
229	120	120	120	120	120	120	8
206	120	120	125	120	60	120	9
203	0	0	0	0	30	40	10
217	30	30	35	31	31	34	10
205	220	230	240	240	240	240	10
221	50	50	50	50	50	50	11
227	180	180	180	180	180	90	13
216	16	28	28	28	30	30	14
209	360	360	360	360	262	368	23
Number on morphine	20	20	21	21	24	25	

xx Shaded area denotes days spent in in-patient unit

xx Non shaded area denotes days spent under home care service

Table 27: Length of stay of cancer patients associated with morphine administration.

6.3.5.3 Morphine started during home care versus in-patient unit care

	AIDS	Cancer	Total
Morphine started in Home care	4	19	23
Morphine started in In-patient Unit	13	6	19
No morphine	12	4	16
Total	29	29	58

Table 28: Morphine started during home care versus in-patient unit care

Fisher exact test $p < 0.001^*$

The admission to in-patient unit is associated with a higher incidence of morphine administration.

This is statistically different for AIDS and cancer patients.

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* This was done with Stata 7.0 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA).

6.3.6 Symptoms present on admission to the in-patient unit

6.3.6.1 Patients on morphine

For the AIDS patients, 11 out of 17 (65%) had pain as a major problem, and for the cancer patients, 12 out of 25 (48%) had pain as a major problem.

		AIDS	Cancer
No morphine	pain	9	0
	pain not a problem	3	3
	Absent forms	0	1
morphine	pain	11	12
	pain not a problem	6	7
	Absent forms	0	6

Table 29: Pain present on admission to the in-patient unit

6.3.6.2 Patients who did not receive morphine

Looking at the nursing chart completed for symptoms noted on admission, see Table 31, one notices the following: Of 12 AIDS patients who died without receiving morphine, it was noted that for 6 patients pain was a major problem on admission. For another 3 it was noted that they had dysphagia although not pain, 4 had dyspnoea and for 7 cough was a major problem. Using morphine for dyspnoea requires clinical judgment as it may cause respiratory suppression in patients who are at risk for respiratory failure.

Thus 9 out of 12 AIDS patients who did not receive morphine (75%) had pain reported and noted (including dysphagia) as a **major problem**.

For the 4 cancer patients who did not receive morphine, the symptom chart was not completed for one. Pain was not recorded as a problem for the remaining three.

Table 30: Symptoms present on admission to the in-patient unit for AIDS and cancer patients NOT on morphine

Num	Age	Type	Sedative		Type of death	Pain	Dysphagia	Dyspnoea	Cough	other
			Dose	Indication						
AIDS										
104	51				peaceful	1 major	3 Absent	3 Absent	3 Absent	diabetes, dry cough, terminal, hardly responding.
105	32				peaceful	1 major	1 major	3 Absent	2 minor	ascites, jaundice, large liver, worked until a week ago
108	21				peaceful	1 major	3 Absent	3 Absent	1 major	Abdominal TB
101	59				peaceful	2 minor	3 Absent	3 Absent	3 Absent	
102	26				peaceful	2 minor	1 major	1 major	1 major	
106	32	Oxazepam	7.5	restless	peaceful	3 Absent	1 major	3 Absent	2 minor	
111	29	Lorazepam	7.5	restless	peaceful	3 Absent	2 minor	3 Absent	3 Absent	
103	39				painful	1 major	3 Absent	2 minor	1 major	
112	39	Vallium	5	Panic	painful	2 minor	3 Absent	3 Absent	1 major	fit, ?pneumonia (low air entry RLL), crying in agony & restless
110	37	Midazolam	7.5	anxiety	restless	1 major	3 Absent	1 major	1 major	Pulmonary TB
117	32	Lorazepam	7.5	convulsion	restless	1 major	4 Unknown	1 major	1 major	
116	32				restless	2 minor	1 major	1 major	1 major	
Cancer										
213	48				peaceful					
201	61	Midazolam	7.5	restless	peaceful	2 minor	2 minor	2 minor	3 Absent	
212	89				peaceful	2 minor	3 Absent	3 Absent	3 Absent	
210	40	Midazolam	7.5	restless	restless	3 Absent	3 Absent	2 minor		

Table 31: Symptoms present on admission to the in-patient unit for AIDS patients on morphine

Num	Age	Opioid Indication	Dose		Sedative			Type of death	Pain	Dysphagia	Dyspnoea	Cough	other
			D	D-1	Type	Dose	Indication						
115	33	Pain	10	0				peaceful	1 major	3 Absent	4 unknown	1 major	
121	49	Pain	12	0				peaceful	1 major	4 unknown	1 major	1 major	jaundice
119	35	Pain	29	0				peaceful	1 major	3 Absent	2 minor	2 minor	Pulmonary TB
120	22	Pain	18	20				peaceful	1 major	4 unknown	3 Absent	3 Absent	
122	38	Pain	30	25	Midazolam	7.5	restless	peaceful	1 major	3 Absent	4 unknown	1 major	lymphocyte 0.29
126	23	Pain and Dyspnoea	25	30	Valium	5	convulsion	peaceful	1 major	3 Absent	1 major	1 major	Pulmonary TB
118	29	Pain	50	40	Lorazepam	7.5	anxiety	peaceful	1 major	3 Absent	1 major	1 major	
127	28	Pain	200	240				peaceful	1 major	2 minor	1 major	3 Absent	aneurysm neck & left groin, died of bleed
107	38	Pain	20	30				peaceful	3 Absent	3 Absent	3 Absent	2 minor	hallucinations (visual)
124	60	Pain	58	20	Midazolam	23.75	restless	peaceful	3 Absent	3 Absent	2 minor	2 minor	Deep painful leg ulcers
125	41	Pain	40	0				painful	1 major	2 minor	2 minor	1 major	CD4 of 2
113	40	Pain	20	0				painful	2 minor	3 Absent	3 Absent	3 Absent	abdominal pain +++ and diarrhoea, general body pain, large genital ulcers
114	24	Pain	10	10	Lorazepam	7.5		painful	2 minor	3 Absent	1 major	1 major	Pulmonary TB
109	33	Pain	6	0	Midazolam	7.5	restless	restless	1 major	1 major	1 major	1 major	
128	40	Pain	60	60				restless	1 major	1 major	2 minor	1 major	lymphocyte 0.35
129	33	Pain	90	90				restless	2 minor	3 Absent	3 Absent	2 minor	
123	24	Pain and Dyspnoea	20	30	Valium	1.25	wet chest*	wet chest dyspnoea	2 minor	2 minor	1 major	1 major	

Note: Patients 127, 128 and 129 received morphine during the last 6 or more days and patient 126 received morphine for the last 5 days of life. The rest of the patients received morphine for less than 5 days.

*Valium was ordered by a nursing sister, no doctor was contacted.

Table 32: Symptoms present on admission to the in-patient unit for cancer patients on morphine

Num	Age	Opioid		Dose		Sedative			Type of death	Pain	Dysphagia	Dyspnoea	Cough
		Indication	Type	D	D-1	Dose	Indication	Type					
220	59	Pain		13	0				peaceful	1 major	3 Absent	3 Absent	2 minor
217	41	Pain		34	31				peaceful	1 major	1 major	1 major	3 Absent
211	30	Pain		65	60				peaceful	1 major	2 minor	3 Absent	2 minor
229	48	Pain		120	120				peaceful	1 major	3 Absent	1 major	3 Absent
227	75	Pain		90	180				peaceful	1 major	3 Absent	3 Absent	3 Absent
204	59	Pain		240	240				peaceful	1 major	3 Absent	3 Absent	3 Absent
209	41	Pain		368	262				peaceful	1 major	4 unknown	3 Absent	3 Absent
214	55	Pain		222	300				peaceful	1 major	3 Absent	3 Absent	1 major
225	76	Pain		328	332				peaceful	1 major	3 Absent	3 Absent	2 minor
208	60	Pain		34	23				peaceful	2 minor	3 Absent	2 minor	3 Absent
207	72	Pain		30	30				peaceful	2 minor	3 Absent	1 major	1 major
216	66	Pain		30	30				peaceful	2 minor	2 minor	3 Absent	3 Absent
219	65	Pain		80	120	Lorazepam	7.5	Unknown	peaceful	3 Absent	3 Absent	1 major	3 Absent
226	64	Pain		120	120				peaceful	3 Absent	3 Absent	3 Absent	3 Absent
228	74	Pain		30	30				peaceful				
218	59	Pain		35	50				peaceful				
221	60	Pain		50	50				peaceful				
223	27	Pain		115	120				peaceful	4 unknown	2 minor	3 Absent	2 minor
222	30	Pain		220	240	Midazolam	7.5	High pitch cry	peaceful				
224	63	Pain		240	240				peaceful				
202	71	Pain		50	60				restless	1 major	2 minor	3 Absent	3 Absent
205	46	Pain and Dyspnoea		270	360				restless	1 major	3 Absent	1 major	3 Absent
203	42	Pain		40	30				vomiting	4 unknown	1 major	4 unknown	4 unknown
215	51	Pain		60	50				wet chest	1 major	3 Absent	3 Absent	3 Absent
206	61	Pain		120	60				wet chest				2 minor

Chapter 7 Discussion and Interpretation

The results demonstrate that there are measurable and marked differences in morphine administration between AIDS and cancer patients in the in-patient unit of St. Francis Hospice. The differences are noticeable in:

- Proportion of patients being given morphine
- Average dosages of morphine
- Time of initiation on morphine
- Sedatives given in conjunction with morphine
- Annual trends in morphine administration
- Number of patients dying a painful death
- Symptom prevalence on admission to the in-patient unit in patients who were not given morphine

Summary of findings:

- Five days before their day of death (D-5), 3 (10%) of the 29 AIDS patients were given morphine for pain control, receiving on average 120 mg per 24 hours per os. Of the cancer patients, 20 of the 29 (69%) received morphine five days before their day of death, with an average dose of 151 mg per 24 hours per os.
- On the day of their death (D) 17 of the 29 (59%) AIDS patients were given morphine with an average dose of 39 mg per 24 hours per os. For cancer patients on the day of death, 25 of the 29 (86%) were given morphine, with an average dosage of 120 mg per 24 hours per os.
- 11 (65%) of the 17 AIDS patients given morphine died within 48 hours of commencing morphine therapy, the average dose of morphine being 4 mg 4 hourly per os (16 mg per 24 hours). The maximum dose (50 mg per 24 hours) is within the recommended starting dose range for opioid naïve-patients.
- During the last 24 hours sedatives were administered to 12 AIDS patients, 7 received morphine as well and 6 of the 7 AIDS patients received morphine for less than 48 hours. Of the 25 cancer patients given morphine, 2 also received sedatives during the last 24 hours, and 4 of the 25 were given morphine for less than 48 hours.

- Of the 5 AIDS patients (17%) who died a painful death, two did not receive morphine at all, and 3 patients were given morphine a few hours before their death. 1 of the 3 AIDS patients received a sedative as well. No cancer patients died a painful death.
- From 1998 to 2001 there was a marked increase in the proportion of dying AIDS patients being given morphine: from 0% to 100%.

7.1 Sample profiles

The 29 patients who died from AIDS related diseases over a period of 3 years and 5 months in the in-patient unit is a small number of the total patients cared for over the same time period. The average in-patient unit admission rate is about 24% per year (refer Table 1 on page 22) and the average patient load is about 800 patients per year. Some AIDS and cancer patients are discharged home whilst others die in in-patient unit. My impression from working in the in-patient unit was that more than 50% of patients admitted die in the in-patient unit and less than 50% are discharged home. No data are available to substantiate my impression.

AIDS patients	1998	1999	2000	2001	Total
Total number cared for (In-patient Unit and home)	71	155	221	533	980
Number died in In-patient Unit	2 (+1) [#]	7(+2)	8(+3)	12(+4)	39
Number died in In-patient Unit as %	4.2%	5.8%	5%	3%	3.9%

Table 33: AIDS deaths in in-patient unit expressed as a percentage of AIDS patients cared for.

The proportion of AIDS patients dying in the in-patient unit (3.9%) seems very low. However, this is not a conventional death rate: the denominator is the number currently cared for, not the total number of patients dying with AIDS. Although hospice patients with AIDS may live longer than hospice cancer patients, it does raise the suspicion that a disproportionate number of AIDS patients are dying at home.

[#] figure in brackets indicates the number of patients who were excluded from for the study, but died in the IPU during the study period.

The in-patient unit serves the home care populations (both AIDS and cancer) for whom symptom-control becomes challenging and / or family respite is required. The need for family respite is often an indication of symptom exacerbation or entering of the dying stage.

In this study the average AIDS patient was younger than the average cancer patient. This confirms reports that AIDS is a disease that affects young adults, people establishing families and a potentially economically active section of the population.

The ethnic group representation of the AIDS patients in the study is comparable with that of the country: Black 75.2%, White 13.6%, Coloured 8.6%, Indian 2.6%. The pilot study showed bias in the cancer control group towards White "medical aid" patients (i.e. with private medical insurance). The recognition of bias led to a change in selection criteria in order to select a more socio-economic and ethnically matched control group of cancer patients.

7.2 Main findings

The voiced opinion of the nursing staff, that set this study in motion, that the majority of AIDS patients die within 2 days of being started on morphine is valid. The concern about the relation of the deaths to morphine administration is understandable. Such an impression would be harmful to the image of hospice. The questions that arose were: Would these patients have died regardless of the administration of morphine? Or, did the morphine administration influence their time of death? From this, 2 hypotheses in the context of pain control were put forward.

- Pain has to be recognized and assessed before it can be treated e.g. morphine can be administered for pain management. If pain is not recognized, it will not be treated. If there is evidence that a greater proportion of cancer patients (compared to AIDS patients) received morphine and a smaller proportion of cancer patients died a painful or less distressed death, this will support the hypothesis that pain in AIDS patients is under-recognized and under-treated.
- If opioids and/or sedation are administered to HIV-positive patients in such a way that death is hastened, there will be evidence of them receiving dosages above the usual recommended range close to their time of death.

It was important to obtain clarity on the actuality of the situation for the reason of ensuring that patients receive symptom relief without bias or prejudices. It is not hospice policy to hasten death.

Neither is it hospice policy to leave symptoms such as pain (and therefore suffering) untreated. In between these two extremes, lies an uncomfortable compromise as far as *refractory symptoms* are concerned when high dosages of drugs (usually sedatives) are required for relief. The moral conflict between the desire to relieve suffering and the duty to avoid killing is (to some extent) resolved by the doctrine of the double effect.²⁶ The concept of the doctrine of the double effect "allows" for symptom-control (usually by mode of conscious sedation) at the risk of shortening the life of a patient. This concept is controversial and it is not the intent of the study to address this concept directly.

The actual differences noted in morphine use will be discussed and interpreted to show that the underlying reason why the majority of AIDS patients die within 28 hours of being started on morphine is a manifestation of under-treatment of pain in this group of patients. The bulk of the evidence obtained was objective and not influenced by subjective interpretation. The risk of systematic bias in data collection is small. It reflects the situation of pain management by recording the administered drugs according to the medicine charts. Evidence, such as type of death and symptoms on admission, although subjective in nature, also supported the theory of under-treatment of AIDS patients.

There was no objective or subjective evidence to support the idea that death was hastened due to morphine administration.

7.2.1 The number of patients on morphine for pain relief

When AIDS patients are admitted to the in-patient unit from the Home Care Service (see Table 26), 10% were using morphine for pain control. This contrasts sharply with the data for the control group of cancer patients and practices reported in the literature.^{23, 34, 69, 73.} This single piece of evidence is the most significant finding in support of the under-treatment theory. The difference is statistically significant, with a p value of < 0.001.

It is to be expected that towards the end-of-life, an increase in pain and therefore an increasing need for analgesia would occur in both AIDS and cancer patients. The study by Breitbart⁸ confirms this. I would further expect that the increase in pain (and accompanying analgesia required to control it) would be noticeable *before* the last week of life.

There are few studies on the prevalence of pain as a symptom in the last week of life in people with AIDS^{23,43}, and reports of the prevalence of pain in the general AIDS population (ambulatory and hospital) vary between 28% to over 93%.^{10, 12, 23, 27, 29, 43, 45, 47, 50, 53, 80.} It has been reported that pain is more common in advanced disease.⁸ The etiology of pain in AIDS patients can be attributed to:

1. damage from HIV,
2. co-infections or tumours,
3. treatment (of HIV, co-infections and tumours) or
4. unrelated causes.

Neuropathic pain (mainly in the form of a peripheral sensory neuropathy in HIV patients) occurs in 10-20% of patients. Causes are HIV itself or treatment-related (anti-TB and anti-retroviral treatment). Neuropathic pain is only partially responsive to opioids.

Kimball⁴³ reported that of 88% of AIDS patients in Seattle in a hospice setting who experienced pain during the last two weeks of life; 93% received opioid analgesia (0.93 X 0.88 = 82% of total patients in study). No comment was made on serial values of opioid administration. In Rome in an Infectious Disease Hospital wards and day clinic Fantoni²³ reported a 68% prevalence of pain as a symptom during the last week of life of AIDS patients. Opioid analgesics were used in 28.6% of patients in the week before death and in 19% of patients 3 months before death. Fantoni's study covered the 3 months preceding death in AIDS patients and reported equal prevalences of pain as a symptom 3

months before death (60%) and at one week prior to death (58%), although the opioid (and non-opioid) administration increased from 19% to 28% respectively. There was no mention of pain intensity or severity. In a 2 year study in Denmark (Copenhagen) in a Department of Infectious Diseases, Frich²⁹ reported a contrast in incidence of opioid use in AIDS patients of 39% of all patients during the 2 year study period against 69% of patients who died from AIDS in the unit (27 on opioids out of 39 total, died in unit). Not all patients in this study were terminally ill. 20 were alive at the end of the study (n=95).

General AIDS population studies (not terminally ill patients exclusively): Breitbart, in a prospective cross-sectional survey of 438 ambulatory AIDS patients in New York City,⁸ found that 63% of AIDS patients reported frequent or persistent pain of at least 2 weeks' duration at the time of assessment. The prevalence of pain in this sample increased significantly as HIV disease progressed, with 45% of AIDS patients with category A3* disease reporting pain, compared with 55% of those with category B3 disease, and 67% of those with category C1–3 disease. AIDS Patients in this study also were more likely to report pain if they had:

- other concurrent HIV-related symptoms (eg, fatigue, wasting),
- had received treatment for an AIDS-related opportunistic infection, or
- had not been receiving antiretroviral medications.

In a French multicenter study by Larue and colleagues,⁴⁴ 62% of hospitalized patients in France with HIV disease had clinically significant pain. Breitbart and colleagues⁸ reported that ambulatory AIDS patients in their New York City sample reported a mean pain intensity of 5.4 (on the 0–10 numerical rating scale of the Brief Pain Inventory) and a mean "pain at its worst" of 7.4. As with pain prevalence, the intensity of pain experienced by patients with HIV disease increased significantly as disease progressed. AIDS patients with pain, like their counterparts with cancer pain, describe an average of 2.5 to 3 concurrent pains at any given time. Less than 8% of AIDS patients in the Breitbart study⁸ reporting pain in the severe range (8–10 on a numerical rating scale of pain intensity) received a strong opioid, such as morphine, as recommended by published guidelines such as the WHO analgesic ladder. The 8% reflects all categories of patients with AIDS and not exclusively on terminal patients. In addition, 18% of patients with 'severe' pain were prescribed no

* Centers of Disease Control and Prevention, 1993 revision of AIDS Surveillance Case Definition for Adolescents and Adults. This is the classification system used when CD4+ counts are available.

analgesics whatsoever. Utilizing the Pain Management Index (PMI), a measure of the adequacy of analgesic therapy derived from the Brief Pain Inventory's record of pain intensity and strength of analgesia prescribed, Breitbart further examined adequacy of pain treatment. Only 15% of their sample received adequate analgesic therapy based on the PMI. This degree of under-medication of pain in AIDS (85%) far exceeds the 40% under-medication of pain (using the PMI) in cancer populations reported in other studies.¹⁴

One may argue that comparisons are drawn between 1st and 3rd world countries. The similarity of experiences of cancer patients (see following section) to those of 1st world countries would then be discrepant.

7.2.2 Increase in numbers of patients on morphine during the last 5 days

In St. Francis hospice 3 (10%) of terminally ill AIDS patients were using morphine 5 days before they died; 17 (59%) were using morphine on the day they died. This is an increase of 470% over 5 days. The group of cancer patients had a 25% increase in patient numbers using morphine (from 20 to 25) during the last 5 days of life. Despite the large increase in AIDS patients given morphine during the last 5 days, there were still statistically significantly more cancer patients on morphine on the day of their death. This is evidence that under-treatment of pain in the AIDS population under the care of St. Francis hospice was a frequent occurrence during the study.

The data on pain management in cancer patients at St. Francis hospice compares well with studies elsewhere with cancer which report that between 70 and 89% are receiving morphine during the last week of life.^{34, 59, 73}

In London in a hospice setting, Thorns⁷³ reported an increase of morphine administration (from 61% to 89%) for cancer patients during the last week of life. This study shows a similar trend for cancer patients. An increase of morphine administration from 69% to 86% for cancer patients was noted.

Compared to the 10% morphine use 5 days before death, a 59% analgesic use in AIDS patients on the day of death corresponds more favourably with practices reported in the general AIDS pain literature (between 30% and 82%) although it was still statistically significantly different from the experience of cancer patients at St. Francis hospice. By this I do not imply that the prevalence of

pain is necessarily the same for AIDS and cancer patients. It is difficult to validate actual differences in pain prevalence and pain intensity measures between AIDS and cancer patients as the widely reported under-recognition and under-treatment of pain in AIDS patients biases the data for AIDS patients to their disadvantage. Larue⁴⁴ in a French national survey demonstrated that AIDS patients being cared for by a hospice at home had pain prevalence and intensity rates comparable to, and even exceeding those of cancer patients.

7.2.3 Morphine dosages

7.2.3.1 Last 48 hours

Table 11 shows that for the AIDS patients using morphine at time of death, 11 of 17 (65%) were started on it during the last 48 hours. The maximum dose for both groups was 50 mg per day. The average daily dosages of morphine commenced during the last 48 hours were 24 mg and 32 mg per 24 hours for the AIDS and cancer patients respectively. (for AIDS patients the average dosage is $\frac{3}{4}$ of that of cancer patients.) Authoritative textbooks^{36,60} recommend commencing opioid naïve-patients on morphine dosages ranging between 30 to 60 mg per 24 hours per os, divided in five to six dosages. The starting dosages in both the AIDS and cancer groups in this study fell within this therapeutic range. It is unlikely that these dosages could have been the cause of, or a major contributor to deaths in study patients.

7.2.3.2 5 days or more before death

The morphine dosage of the 3 AIDS patients (10%) who received it for 5 days or more before death, compares reasonably well to the morphine dosages of cancer patients receiving morphine for 5 days or more. Average dosages were 120 mg and 151 mg per 24 hours for AIDS and cancer patients respectively.

Three of the 29 cancer patients (10%) received morphine at dosages of more than 300 mg per 24 hours. A survey of hospice care practices in Israel² demonstrated that 12% of the patients required morphine at a dose of more than 300 mg per day. A similar study in Japan⁵⁹ reported a figure of 7%. No AIDS patients in this study received morphine at dosages higher than 300 mg per day. No literature studies for AIDS patients were found on this topic. It takes time to reach stable therapeutic dosages of morphine of over 300 mg per 24 hours. Tolerance needs to develop and this usually

happens over a period of months. I suspect that the different patterns of morphine dosages seen in Table 19 and Table 20 between cancer and AIDS patients may be partially explained by the length of time morphine has been administered. Data to explore this hypothesis were beyond the scope of this study and were not collected.

7.2.4 Duration of morphine therapy

The study results show a shorter duration of morphine administration to the AIDS patients which was to their apparent disadvantage (Figure 9). The average number of days that AIDS patients were given morphine was 1.6. This is significantly different from 4.5 days for cancer patients (maximum n=6). The difference in time that morphine was given was evaluated over a 6 day period only. It raises the question of what the differences are over the whole period of hospice care, including the portion of patients that die without being admitted to the in-patient unit. In contrast, the average length of stay (5.2 and 6.3 days respectively) is similar for the AIDS and cancer patients.

The data confirm the impression that morphine is given too late in the progression of the illness of AIDS patients. It also shows a relative advantage for AIDS patients admitted to the in-patient unit. It is more likely that morphine will be started if AIDS patients are admitted than if they remain under home care exclusively.

7.2.5 Morphine usage in context of the total hospice service

29 of the 39 AIDS patients that died in the in-patient unit were included in this study. 3 of the 29 AIDS patients received morphine before admission to the in-patient unit; another 14 were started on morphine therapy during their stay in the in-patient unit.

The pattern is different for the cancer patients: 23 received morphine before admission and for 6 patients morphine therapy was started after admission to the in-patient unit.

Between 3% and 5.8% of AIDS patients being cared for are admitted, compared to admission figures of between 22% and 30% of the general population cared for by St. Francis hospice. The population of AIDS patients cared for by St. Francis hospice increased from 12% to 49% from 1998 to 2002 – see Table 1. Of the small percentage that died in in-patient unit, only 10% received morphine before admission to the in-patient unit. The question arises about what happens to pain

control in the balance of AIDS patients in the care of St. Francis hospice that die elsewhere (about 96%). It seems plausible to assume that they will have the same or even a lower prevalence of receiving morphine than the population represented by admission to in-patient unit.

7.2.6 Sedative administration

In palliative care sedatives are mainly used to reduce suffering (see 2.3.2 page 23) by lessening awareness of symptoms (refractory to standard treatment) by intentionally clouding consciousness.⁶⁸ Sedatives may contribute significantly to reducing suffering when chosen appropriately for the specific combination of symptoms in conjunction with a multidisciplinary treatment approach to underlying causes of suffering. A statistically significant greater proportion of AIDS patients than cancer patients were given sedatives. A possible explanation for the different prescribing patterns is that sedatives were used to control symptoms for which morphine could have been tried first. AIDS affects a younger age group, more socio-economic problems are present, stigmata and lack of community support are also associated factors.

Clouding of consciousness implies less awareness and function-in-life and it will detract from quality of life if symptoms could be controlled by other means while maintaining a more alert state of consciousness.

For symptoms to be labeled "refractory" and to consider sedation in order to control the "*refractory symptom(s)*", we consider it involves the following:

1. patients are terminally ill with advanced, incurable disease
2. they are "actively" dying (death is expected within hours or days – judged from blood pressure, pulse, respiration, urine output, and level of consciousness)
3. acute or refractory symptoms such as pain, nausea, myoclonus, restlessness, or respiratory distress are present
4. these symptoms have not responded to conventional management
5. the severity of the symptoms and trajectory of the illness requires prompt intervention to relieve distress
6. sedation is chemically induced, using a non-opioid drug.

Looking at this present study, the symptoms (of pain, cough and dyspnoea) present in the majority of AIDS patients can not be labelled refractory for the simple reason that enough time has not been available for the trial to demonstrate the failure of conventional management of the relevant symptoms.

Sedation was not used in the in-patient unit as generally understood in hospice care, namely conscious sedation, by the *continuous* administration of sedatives to alleviate symptoms. In a study at Sir Michael Sobell House⁶⁴ it was found that the dosages of SC midazolam for continuous sedation purposes was as follows: Starting dose was between 20 and 30 mg per 24 hours (with 30 mg per 24 hours as the recommended starting dose) and between 30 to 60 mg per 24 hours continuously as the common range for maintaining sedation.

This was not the case at St. Francis hospice.

Sedatives were administered on an "as required" basis to 12 out of 29 AIDS patients and 4 out of 29 cancer patients in the last 24 hours of life. The dosages administered were well within the lower therapeutic range (averages of 7.9 mg and 7.5 mg per 24 hours for AIDS and cancer patients respectively), and below the therapeutic range for "conscious sedation". It is unlikely that the dosages used contributed to death, even in the group of patients who received morphine for a period of less than 48 hours (6 AIDS patients and 0 cancer patients). When morphine is started, one of the side effects is sedation. Apart from this effect of the first few days of morphine treatment, additional sedation was required in a substantial percentage of AIDS patients. This is described in the next section.

7.2.6.1 Combination of morphine and sedative administration

When sedatives given to AIDS patients on morphine are looked at in context of the duration and dosage of morphine administration, another noticeable difference emerges. 6 of the 7 AIDS patients who received both morphine and a sedative, received morphine for less than 48 hours before their death. Another 5 received no morphine. This equates to 38% (6+5 =11 of 29) of all the AIDS patients in the study. Of the 7 AIDS patients on morphine that received sedatives, 4 had been started on morphine in the last 48 -24 hours, 2 in the last 24 hours and 1 in the last 120 hours. The nursing notes did not mention any patients in the study being over-sedated or showing signs of opioid related side-effects. For 2 patients with symptoms of restlessness and 1 with anxiety, a

peaceful death was achieved with the addition of a sedative to morphine (Table 24). For the remaining three (3 of 29 = 10%), the combination did not change the outcome of their death (1 painful, 1 restless, 1 wet chest). For patient number 114 (who died a painful death, received morphine and a sedative) morphine was prescribed for regular use 4 days before death, but only administered in 2 prn dosages, one in each 24 hour period before death. This was incidentally noticed; similar data were not collected for other patients.

The 2 cancer patients who received sedatives (together with morphine) were on higher dosages of morphine for longer periods of time (120 mg and 240 mg per day respectively) than the group of AIDS patients.

It appears that sedatives were used to control symptoms in a group of AIDS patients when there was inadequate time available to control the symptoms by regular titrated administration of morphine. The same scenario is not noted with cancer patients. This supports the impression that pain as a symptom was recognized far too late in the dying process of AIDS patients. By the time it was recognized and treatment started, sufficient time was not available to control symptoms before death occurred, necessitating the use of sedatives.

7.2.7 Type of death

Type of death as a measure is not as objective a measure as morphine dosage. It relies on human subjective interpretation of the clinical notes, which in itself is a subjective perception and interpretation of the actual situation (see Figure 5). This may produce a more distorted reflection of symptom-control in general than morphine dosage which is objective and more symptom-specific.

- 5 AIDS patients and 0 cancer patients died a painful death.
- 6 of the 12 AIDS (and 1 of 4 cancer-) patients who received sedation died a non-peaceful death.

With morphine being prescribed to only 10% of AIDS patients before their death, it is expected to observe pain preceding death and is corroborated in this study.

7.2.7.1 Combination of morphine, sedative and type of death

Of the 5 AIDS patients (17%) who died a painful death, none received morphine for the 5 days preceding their death. Two patients who died a painful death did not receive any morphine at all.

Although morphine was started close to death for 3 patients who died a painful death, this did not prevent them from dying a painful death. All 3 received morphine for less than 48 hours preceding death. 2 of them had been in the in-patient unit for longer than 10 days.

This finding adds weight to the conclusion reached before that pain as a symptom was not recognized and therefore not treated timeously. It appears that morphine therapy was initiated too late during the stage of illness for AIDS patients to improve quality of life significantly.

7.2.8 Change of trend over time of morphine administration in the in-patient unit

A number of discussions about morphine administration and its side-effects in AIDS patients were held with staff since January 2001. Being made aware of the literature seems to have put the issue of inadequate pain control in HIV patients to the fore and changed prescribing and administration habits in the in-patient unit during 2001. Although a larger number of AIDS patients received opioids during the last few days of their lives in 2001, it is unknown if any change occurred in the home care section of the patient population cared for by St. Francis hospice.

I seldom recommend a follow up study to look at current practices of pain management for AIDS patients in the in-patient unit.

7.2.9 Pain control in home care unit

Between 7% and 10% of AIDS patients had been started on morphine before admission to the in-patient unit. See Table 26 on page 22. This is a low proportion in comparison with practices in other similar AIDS palliative services.^{23,43}

I therefore recommend a study to look at the morphine use for AIDS patients in the home care system for a period of 3 - 6 months before their death.

7.2.10 Symptoms present on admission to the in-patient unit:

A symptom form is completed on admission and the quality varies according to the staff members completing the forms. It was noted from entries of cancer patient who were on high doses of morphine, that in some cases, although the pain was controlled, pain was marked on the form as

“4. major problem”. From this it is reasonable to interpret the symptoms on the chart as valid only for patients not receiving morphine on admission to in-patient unit. – symptom-control for the specific symptom not attempted yet.

Twenty AIDS patients had pain recorded on admission with only 11 (i.e. 55% of those with pain) receiving morphine. This compares to 12 patients with cancer who had pain on admission, with 100% of these receiving morphine.

For 12 AIDS patients who received *no morphine* on admission, it was noted that 9 out of 12 (75%) had pain (including dysphagia) reported and noted as a major problem. For 4 patients dyspnoea, and for 7 cough was a major problem. For the 4 cancer patients who did not receive morphine, the symptom chart was not completed for one. None of the remaining three had pain as a major problem.

The high incidence of pain reporting amongst AIDS patients confirms the impression that pain as a symptom is not considered of a similar priority as in cancer patients. The prevalence of symptoms also favours the original idea that pain as a symptom is not given adequate recognition (in preference to the alternative idea that death may have been hastened due to medication).

7.3 Concluding interpretations

7.3.1 Under-treatment of pain

The starting point of the study was to look at pain control and evaluate two statements:

- Death is hastened in some AIDS patients by the use of morphine
- Some AIDS patients die without adequate analgesia (probably because pain is not recognized)

The second view has been validated, namely that of under-treatment of pain in AIDS patients at St. Francis hospice on admission to the in-patient unit.

Clarity was achieved by evaluating the management of pain at St. Francis hospice within a larger context of pain management and of palliative care principles. Cancer patients were used as a control group.

A contrast is shown between pain control in cancer and AIDS patients in the in-patient unit of St. Francis Hospice. The situation of cancer patients correlates with that of 1st world countries and clearly shows the ability of St. Francis hospice staff to manage pain effectively near end-of-life in order to reduce suffering.

Although mechanisms are in place to recognize and treat pain in patients cared for by St Francis hospice, this did not happen in the AIDS population that died in the in-patient unit during 1999, 2000 and 2001. Only 10% received morphine 5 days before they died. This forms a stark contrast to the experience of cancer patients as well as accepted "best practices" in hospice care.

It is unlikely that AIDS patients in the Eastern Cape region are less symptomatic than AIDS patients in the rest of the world. A more likely explanation (for the 10% incidence of opioid usage 5 days before death) is that pain is not recognized and therefore not assessed and treated. The 470% increase of AIDS patients being administered morphine in the in-patient unit during the 5 days preceding death (from 10% to 59%) could be attributed to the fact that pain was identified as a problematic symptom only during the last week of life when an attempt was made to control it. This figure, although showing a marked improvement, is still far from satisfactory.

Under-treatment of pain for AIDS patients is well known from the literature and shown by this study to exist at St. Francis hospice.

7.3.2 Findings viewed within a wider perspective

The actual situation for AIDS patients admitted to the in-patient unit is discrepant with that of:

- cancer patients,
- general literature, as well as
- the mission and vision of St. Francis hospice.

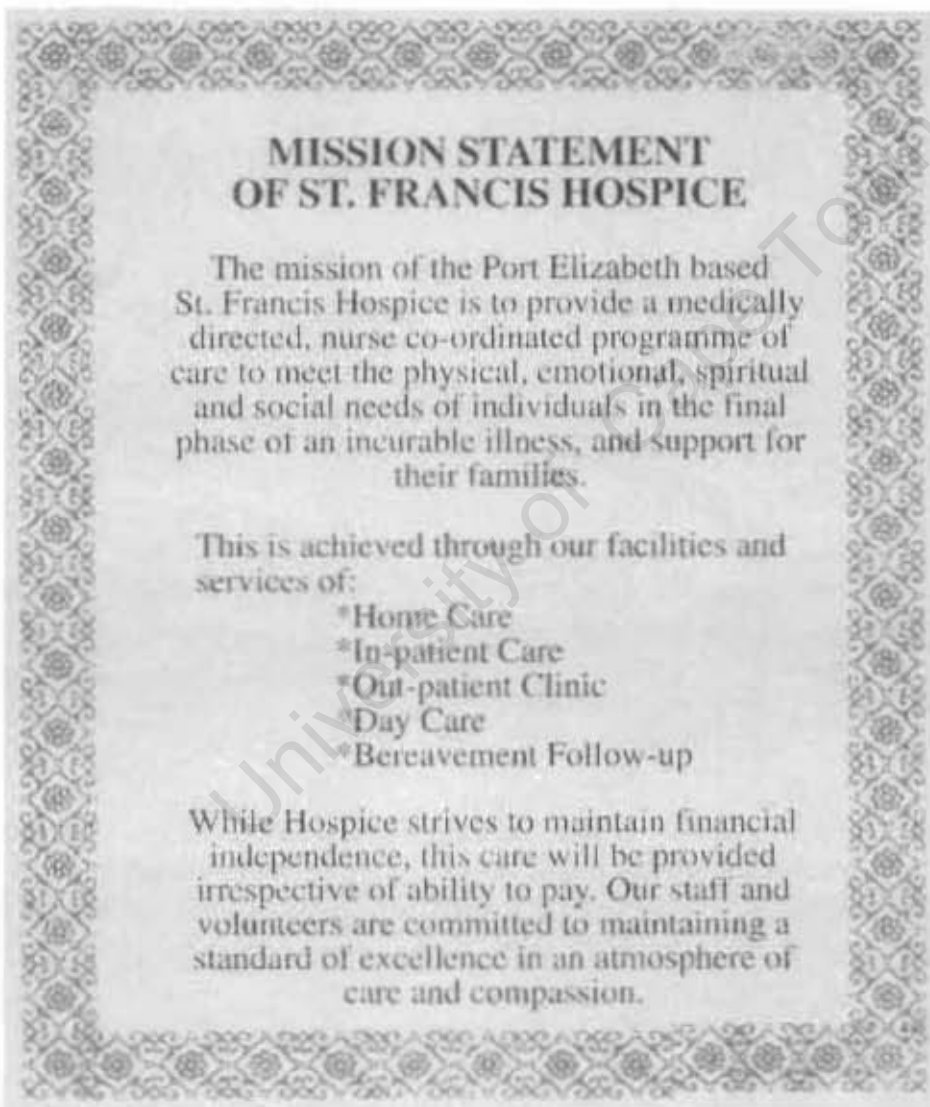


Figure 13: Mission statement of St. Francis Hospice

Good clinical decision making requires ongoing learning & reflection:

- regarding the best interests of the patient
- based on the balance of benefits and burdens weighed up against *available evidence*
- within resource constraints (distributive justice).

7.3.3 The role of objective evidence in bringing to awareness unrecognized issues

- The impression of the connection between death within 48 hours and morphine administration in AIDS patients has been validated.
- The *subjective view*, that death was possibly hastened by the administration of morphine, is not supported by the evidence gathered.
- Objective evidence showed under treatment of pain in AIDS patients at St. Francis hospice.

The unsubstantiated views played a role in the origin and maintenance of the problem. Fortunately the "view taken" was *voiced* by a number of nursing staff. This allowed for the collection of evidence of this study and availed a mechanism to enhance awareness of the actual situation. With objective evidence available, (lack of) treatment of pain can now be recognized and viewed in perspective.

Now that the actual cause of the problem has been identified and clarified, it would be relatively easy to remedy. St. Francis hospice will thus be enabled to *truly* care for patients the way they are known and respected for in our community.

7.3.4 Questions that arise

When the evidence of how morphine was used is looked at from the larger framework of pain control in palliative care, this study clearly shows severe under-treatment of pain in in-patient unit AIDS patients of St. Francis hospice 5 days before they died ($p < 0.001$).

Questions that arise are:

- What is the situation at other hospices in South Africa regarding pain control for terminal AIDS patients in their care?
- How can the hospice system adapt itself to continuously improve the quality of care it provides?

Chapter 8 Recommendations for further studies

The following studies are recommended for further study:

Clinical studies:

- A study to compare the use and non-use of a daily self-assessment of pain/ anguish "faces of pain" scale, and its influence of this daily exercise on pain recognition and management.
- A follow up study to look at current practices of pain management for AIDS patients in the In-patient Unit at St Francis Hospice.
- A study to look at the morphine use for AIDS patients in the home care system for a period of 3 - 6 months before their death.
- Similar studies at other hospices in South Africa regarding pain control for terminal AIDS patients in their care.

Managerial study

- A behavioural study to determine how the hospice system can adapt itself to continuously improve the quality of care it provides.

Chapter 9 Conclusion

The disgruntled dead cannot voice an opinion from their graves. The families of the AIDS patients are in an extremely vulnerable and dependent position. Having very few places to turn to for support, they are not in a position to risk alienating what little support is available by negative statements and complaints.

In a country with limited resources, inadequate infra-structure, a significant level of illiteracy, and a government that is unsure about the cause of AIDS, we find ourselves faced with an epidemic that is causing enormous suffering. Hospital beds and nursing staff have not increased, although increased admissions are required to treat the rising number of patients with TB and other opportunistic infections associated with HIV-positive patients. This produces an increasing burden on a shrinking pool of health care services that deals with disease. The needs of the patient in the process of dying from AIDS is absent from the above scenario.

HIV-positive patients are often denied investigations or treatment when they present with potentially reversible illnesses. On the other hand, inappropriate investigations and futile treatments should be guarded against as it not only wastes valuable resources, but may also detract from quality of life. With prompt recognition of symptoms such as pain and good supportive care, people with AIDS may enjoy a good quality life until they die. This approach has to be *actively* pursued.

Unrecognized and unrelieved pain equates with poor palliative care practices as it does not contribute to quality of life. It contributes to the burden of suffering in an already overburdened section of our population. The good we can do in the AIDS epidemic is adequate palliative care. In South Africa palliative care is at present largely associated with a few hospices. Recognizing and relieving symptoms in the terminal and pre-terminal patient is of utmost importance for a successful palliative care service. Barriers to symptom-control should also be recognized early, and proactively addressed. Unrecognized pain is a formidable barrier to overcome.

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University of Cape Town

Appendixes

Appendix 1: Consent



Dr. Renée Els
PO Box 15827
Emerald Hill
Port Elizabeth, 6011
Tel: (041) 366 2319
Fax: (041) 366 1365

25 July, 2001

Sr. Lesley Lawson & personnel
St. Francis Hospice
PO Box 7793,
Newton Park, 6055
Fax: 360 1279

RE: Research Project: Opioid use in last week of life

Dear Sister Lawson

The topic I would like to do my research on for the Masters degree in Palliative care is: Opioid use in the last week of life. I have designed an applicable database and am ready to enter data.

I would like to start with data for 1 month at first. Could you provide me with:

1. a list of patients who died during May 2001 (in the ward or at home) and
2. their files.

I would appreciate your cooperation and support in this matter.

Thank you for your time and attention.

Yours faithfully

Signed by candidate

Signature Removed

Dr Renée Els.

Informed Consent for research by Dr. R Els at St. Francis Hospice, Port Elizabeth

Preamble

Progress in medicine and in health care is contingent upon the conduct of health and medical research, including retrospective epidemiological studies, which must be based on information concerning the health of individuals, communities, and societies. In many if not most cases, the information required for such studies is of a non-identifying nature.

Title:

A retrospective review of strong opioid use in the last 5 days of life of patients with HIV/AIDS or cancer at St Francis Hospice.

Purpose:

- The study will describe opioid use during the last five days of life with the aim of determining whether differences exist between cancer and AIDS patients.
- This information will attempt to identify and quantify the differences, if they exist.
- It may suggest ways to further assess, address or explain differences. For example, attitudes may change when made aware of differences or methods used by clinical staff to elicit symptoms may improve.
- It may also contribute to ideas for further studies that may attempt to clarify underlying reasons for the findings.
- Deficiencies in the data in routine patient records will be documented and suggestions for improving information necessary for patient care, clinical audit and research will be made

Duration:

Material will be collected for the calendar years of 2000 and 2001. Data for all AIDS patient deaths in the In Patient Unit will be collected as well as the subsequent oncological death. The processing of the data will occur during the calendar year of 2002.

Ethical approval:

Ethical committee approval must be obtained for all research studies

Transparency and openness:

Policies, practices and procedures relating to health information must be transparent so that patients can clearly understand the extent and purpose of health information collection, use, disclosure and access. These must be explicit enough that the patients are adequately informed and able to acquire knowledge germane to their confiding of information, and must also be open to scrutiny and challenge.

This Research Protocol was submitted to the Research Ethics Committee of the University of Cape Town and written approval is awaited. The study has been structured in accordance with the Declaration of Helsinki (last updated: October 2000), which deals with the recommendations guiding doctors in biomedical research involving human subjects, a copy of which may be obtained from the investigator should you wish to review it.

Confidentiality of records:

Computerised data will be kept secure (e.g. pseudo-anonymised, names will be stored in one file, number and personal data in another)

Informed Consent

I hereby confirm that I, as a representative of St. Francis Hospice, have been informed by the study doctor, Dr. Renée Els, about the nature, conduct, benefits and risks of the research about opioid use in the last 5 days of life. I have also received, read and understood the above written information regarding the research.

I am aware that the results of the research, including personal details regarding patient's sex, age, date of birth, and diagnosis will be anonymously processed into a research report.

I may, at any stage, without prejudice, and with reasonable explanation withdraw my consent and participation on behalf of St. Francis hospice of access to patient records at this institution.

I, ALAN CRICHTON, as representative of St. Francis Hospice, Port Elizabeth, have had sufficient opportunity to ask questions and (of my own free will) declare St. Francis Hospice prepared to participate in this research.

Representative of St. Francis Hospice, Port Elizabeth:

A. CRICHTON Signature Removed 8 March 2002
Printed Name Signature Date

I, Dr Renée ELS, herewith confirm that the above person in the capacity as a representative of St. Francis Hospice has been informed fully about the nature, conduct and risks of the above research.

Study Doctor:

Dr. R. ELS Signed by candidate 15 March 2002
Printed Name Signature Signature Removed Date

Witness:

J.M. CALHOUN Signature Removed 15 March 2002
Printed Name Signature Signature Removed Date

Witness:

N. C. SIBERU Signature Removed 15 MARCH 2002
Printed Name Signature Signature Removed Date