Five Years Experience with Zidovudine: A Milestone in the Management of HIV

1. History

In 1984, when HIV as first confirmed as the cause of AIDS, Wellcome was in an ideal position to take up the challenge of discovering an agent which was active against the retrovirus. For more than 30 years, Wellcome has devoted extensive resources to antiviral research and has become an acknowledged leader in this field.

Building on the work of Nobel prize winner, Dr Gertrude Elion, the company developed Zovirax* (acyclovir) the first selective antiviral agent which effectively controls the reproduction of the herpes simplex virus with minimal side effects. Subsequently, Zovirax has become the cornerstone of antiviral treatment of herpes infections including recurrent genital herpes, cold sores and shingles.

From its extensive knowledge of molecular virology, Wellcome began an active screening programme in 1984 which lead to the discovery of the potent anti-HIV activity of zidovudine (Retrovir* or AZT). Clinical trials began the following year and zidovudine received regulatory approval in France, Norway, the USA and the UK in March 1987. It is currently available in more than 70 countries.

2. Clinical experience

Today, zidovudine is the most widely prescribed antiviral agent in the management of HIV infection and since its introduction it has been used in an estimated 200,000 patient years of treatment.

More than 20,000 people have participated in clinical trials of zidovudine and it has been the subject of over 3,000 publications. No other antiretroviral agent has been subjected to such intensive study, and to-date, no other agent has achieved superior efficacy.

Comparative, placebo-controlled and open studies1-11 demonstrate that:

When treatment with zidovudine is initiated at an early stage of HIV infection, for example before any symptoms have appeared, it reduces progression to AIDS and ARC by up to two-thirds.1,2

If treatment is delayed until a more advanced stage of HIV disease, zidovudine can:

- Extend survival1-5
- Reduce the frequency and severity of opportunistic infections1-4
- Reduce the neurological complications of HIV infection6-9
- Maintain or improve quality of life10

These reductions in the severity of HIV disease enable many with advanced HIV disease to remain active members of the community.

Whether treatment is initiated at an early or late stage of infection, zidovudine can maintain CD4 cell counts, thereby helping to maintain the body's natural immune defences.

The extensive experience, both within the controlled conditions of clinical trials and in regular clinical practice, indicates that zidovudine can have significant benefits in both adults and children and regardless of route of HIV transmission, sex or ethnic background.

Results of epidemiological studies in the USA suggest that the use of zidovudine has helped bring about a slowing in the increase in AIDS numbers - a phenomenon which first became evident in 1987, the year in which zidovudine was first licensed.11
The potential benefits of zidovudine are still the subject of an active research programme which, it is hoped, will continue to define the optimum use of the drug, particularly in early HIV infection.

3. Statement from the International Coordinating Committee

Wellcome study H56-020; Zidovudine in "low-risk" HIV-positive asymptomatic individuals (CD4 greater than 400/mm³)

The International Coordinating Committee (ICC) for this study has recommended termination of the placebo-controlled phase following the interim analysis that has recently been completed. Since disease progression was significantly reduced in the zidovudine group (p=0.001) the ICC believe that participants in the study should now be offered treatment with zidovudine. The first volunteers were entered into the study more than three years ago.

Study H56-020 is a randomised, blinded, placebo-controlled trial to determine the efficacy of zidovudine in reducing disease progression among individuals with asymptomatic HIV infection and CD4 cell counts above 400/mm³. Treatment consisted of either 500mg zidovudine twice daily or matching placebo for up to three years. The study began in December 1988 and has enrolled nearly 1,000 volunteers in Australia, Spain, Belgium, Denmark, Germany, Norway, Austria, Luxembourg, Finland and Iceland. Participants showing evidence of disease progression as specified in the protocol (development of AIDS, ARC or other CDC group IV defining conditions in two CD4 cell counts of less than 350/mm³) and those completing three years have to-date been offered open zidovudine therapy.

The interim analysis revealed overall that the estimated probability of disease progression at two years for placebo versus zidovudine was 28 per cent versus 14 per cent. For individuals with baseline CD4 cell counts of between 400 and 500/mm³, the values were 38 percent versus 20 per cent and for those with baseline CD4 cell counts of between 500 and 750/mm³ were 18 per cent versus 9 per cent. Too few events had occurred in individuals with CD4 cell counts above 750/mm³ to determine treatment differences.

Overall, the dosage of zidovudine employed in the study appeared to be generally well tolerated although dose adjustments were necessary in some participants. There were no differences in the incidence of severe haematological toxicity or serious adverse experiences reported for individuals receiving either zidovudine or placebo.

We believe that it is appropriate to provide this preliminary information to HIV treaters, persons infected with HIV and HIV-AIDS Community Organisations since it may be relevant to their considerations of the treatment options available to them. We will endeavour to expedite final analysis of the study so that complete results can be provided at the earliest opportunity.

We would like to take this opportunity to thank the volunteers and all their carers for their contributions to the study over the past three years.

Professor DA Cooper (Chairman) for the International Coordinating Committee of H56-020

31 January, 1992

ICC Membership

Prof DA Cooper, Australia
Dr JM Gatell, Spain
Dr JM Gonzalez-Lahoz, Spain
Prof N Clumeck, Belgium
Dr S Kroon, Denmark
Prof F-D Goebel, Germany
Prof JN Bruun, Norway
Prof G Stingl, Austria

4. Benefits of early intervention with zidovudine now well established says US expert

The benefits of early zidovudine (AZT) treatment of people with HIV who are asymptomatic are now well established, according to a leading US expert on the management of the infection.

In an interview, Dr Marcus Conant, who is Professor of Dermatology at the University of San Francisco, described his experience with zidovudine in his practice which includes about 3,000 HIV-positive individuals.

Dr Conant said that recent evidence supports early intervention with antiretroviral therapy and, particularly, zidovudine.

"The results of the US AIDS Clinical Trials Group (ACTG) studies 019 and 016 have demonstrated the significant benefits of early zidovudine treatment. If HIV-positive individuals are given zidovudine when their CD4 count falls below 500/mm³, the rate of progression of symptoms and the rate of progression to AIDS can be slowed and the lives of these people..."
potentially prolonged," he said.

Additionally, effective therapy empowers patients by giving them an active role in their own treatment. "These highly motivated individuals are not content to be passive recipients of health care. Intervention gives them the opportunity to participate in their own healthcare early in the course of their disease and to take positive action to slow its progress," Dr Conant said.

Other benefits of early treatment with zidovudine include:
- Fewer side effects than treatment given later in the course of the disease; and,
- Emergence of zidovudine resistance occurs more slowly when treatment is started in individuals with a CD4 count of 500/mm³ compared with those with a count of 100/mm³.

5. Additional theoretical benefits of early treatment

In addition to these benefits, which have been established in clinical trials and day-to-day practice, Dr Conant said there are additional theoretical benefits which have yet to be proven (Table 1). These include:
- Improved survival rates which may increase life-expectancy;
- Increased efficacy of combination therapy; and,
- Improved cost effectiveness of intervention.

Discussing the potential for improvement in survival rates, Dr Conant said early treatment with zidovudine may arrest the decline in CD4 cell count for extended periods, i.e. from three to four years.

The enhanced value of combination therapy with zidovudine has been suggested by the results of Study 106 undertaken by the ACTG. This showed that a combination of zidovudine with dideoxycytidine (ddC) produces greater increases in CD4 cell count than monotherapy.

Meanwhile, cost effectiveness may be improved if treatment begins in asymptomatic individuals. "It is likely that because most HIV infected individuals are young, by delaying the development of symptoms early treatment will prolong the productive working lives of many people," Dr Conant said.

But when asked if physicians should consider these theoretical benefits before they are proven in studies, Dr Conant replied: "Although as yet unproven, it is appropriate to consider these benefits because physicians have a responsibility to do everything possible to limit the carnage inflicted by HIV.

"Waiting until the theoretical benefits of early treatment are proved or disproved before recommending such treatment may only lead to the premature death of thousands of people."

6. Many dilemmas and concerns about early treatment are now answered

While the proven and theoretical benefits of early intervention with zidovudine, either as monotherapy or in combination, are widely accepted, the question arises: "At what point should therapy begin?"

Based on currently available data, Dr Conant said: "We should start zidovudine treatment when the HIV-positive person's CD4 cell count reaches 500 cells/mm³. It is also worth considering other predictive markers of the disease progression when deciding whether or not to initiate antiretroviral therapy." For example, levels of neopterin and beta₂ microglobulin provide invaluable markers of an increased risk of disease progression.

The appropriate initial zidovudine dosage has also been discussed and the optimal daily dosage still needs to be established. Dr conant said: "I currently initiate therapy with a dose of 600 mg/day (200mg three times/day). It should be realised, however, that this dose may produce inadequate levels in the central nervous system. If dementia occurs, it is usually appropriate to increase the dose of zidovudine to 800 mg-1g/day."

7. Combination therapy highlights concerns about other agents

Signs of disease progression (Table 2) may point to the need for combination therapy but other antiviral agents lack the extensive knowledge and experience gained during zidovudine studies. "The long-term safety of combinations of zidovudine and other antiretroviral agents is still unknown. Therefore, it is important to consider carefully the merits of adding a second an-

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<th>Table 1 Benefits of early treatment</th>
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<tr>
<td><strong>Known</strong></td>
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<tr>
<td>Reduced rate of progression to symptomatic disease</td>
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<td>Reduced rate of progression to AIDS</td>
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<td>Patient empowerment</td>
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<td>Less drug toxicity</td>
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<td><strong>Theoretical</strong></td>
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<td>Enhanced survival for many years</td>
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<td>Greater efficacy with combination therapy</td>
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<td>Reduced cost to society</td>
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Table 2 Signs of HIV disease progression

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<tr>
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<td>Cough</td>
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<td>Diarrhoea</td>
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<td>Dementia</td>
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<td>Laboratory findings</td>
<td>Decreased CD4 cell count</td>
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<td>Decreased p24 antibody</td>
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<td></td>
<td>Increased neopterin</td>
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ti retroviral agent before doing so," Dr Conant said.

Experience with the addition of a new agent, dideoxyinosine (ddI), has highlighted these concerns. Dr Conant said: "To-date, approximately 150 individuals have been treated with add-on ddI in my practice. Of these, an estimated 20 percent have developed pancreatitis. Some of these individuals have died and many now have chronic recurrent pancreatitis requiring frequent hospitalisation.

"Another 150 have been treated with add-on ddC. By comparison with ddI, ddC appears to cause relatively few cases of pancreatitis, only one case has occurred in my practice so far.

"Thus, although the long-term effects of ddC are not yet known, when a second antiretroviral agent is indicated, ddC appears to offer more promise than ddI, at least with respect to side effects.

"When initiating treatment with a second antiretroviral agent, it is necessary to weight the uncertainties regarding their long-term effects against the possible benefit that such action may produce."

8. Developing a management algorithm

Based on current knowledge and experience with zidovudine, Dr Conant has developed a treatment algorithm for HIV-positive individuals using their CD4 cell count as the main marker (Figure 2). This operates as follows:

HIV-positive individuals with CD4 cell counts above 500/mm² participate in a "wellness" programme which provides health advice tailored to fit the individual's needs and which includes counselling on safe sex:

- When the CD4 count falls below 500/mm², zidovudine treatment begins at a dose of 200 mg three times/day. The person is monitored monthly and haemoglobin and neutrophil status measured;
- When the CD4 count reaches 250/mm³ prophylaxis against Pneumocystis carinii (PCP) is offered and a second antiretroviral agent (usually ddC) is often added to zidovudine; and,
- When the CD4 count falls below 100/mm³ the person is offered prophylactic fluconazole against Cryptococcal meningitis while antiviral therapy and PCP prophylaxis are continued.

9. After five years-A message of hope

Dr Conant concluded: "This treatment regimen appears to be effective. People are being kept alive longer. Five years ago, there were no individuals in this practice who had survived for more than 18 months after a single episode of PCP. Today, there are more than 300 such individuals, most of whom are well enough to continue working.

" Earlier in the epidemic there were no people with less than 50 CD4 cells/mm² who were still alive. There is now good evidence to suggest that such individuals no longer die of opportunistic infections and there are hun-
dreds of individuals in my practice with less than 50 CD4 cells/mm$^3$. Indeed, there are 12 individuals show have no detectable CD4 cells at all."

10. Zidovudine (AZT) halves the likelihood of disease progression in very early HIV infection

A multinational placebo-controlled study, involving almost 1,000 asymptomatic people with HIV infection, has demonstrated that early use of zidovudine (AZT) significantly reduces the progression of the disease.

Initial results of the study were so positive that the International Coordinating Committee of the study recommended that the placebo phase should be terminated (statement enclosed).

These findings strongly support the value of zidovudine in the early treatment of HIV and are expected to be confirmed in a full analysis which will be completed later this year.

The multicentre study (Wellcome study H56-020) began in December 1988. Its objective was to determine the efficacy of zidovudine in reducing disease progression in HIV positive people who are asymptomatic and had little or no impairment of immune function (i.e. CD4 cell counts greater than 400/mm$^3$). They received zidovudine (500mg twice daily) or placebo.

Progression was defined by the development of AIDS, AIDS-related complex (ARC) or a CD4 count of less than 350/mm$^3$ (obtained on at least two occasions a month apart). Participants reaching any of these endpoints were offered open therapy.

Interim results of the study show that zidovudine (Figure 1).

Reduced the probability of progression by about 50 per cent over a two year period

In the placebo group, 28 per cent of the participants showed signs of progression compared with 14 percent of those receiving zidovudine.

11. Effectively reduced the risk of progression irrespective of CD4 count when compared to placebo

In the group with counts of 400-500/mm$^3$, 38 per cent of the placebo group experienced progression compared with 20 per cent of those receiving zidovudine. The ratio of participants with progression was similar in the group with CD4 counts of 500-750/mm$^3$ (placebo = 18 per cent versus zidovudine = 9 per cent). Such results are important as this is the first study to confirm anecdotal reports that early treatment with zidovudine is beneficial in people with HIV or AIDS with CD4 counts greater than 500/mm$^3$.

Zidovudine was generally well tolerated during the study and there were no significant differences in the incidence of severe haematological toxicity or other adverse effects between the zidovudine and placebo groups.

12. Committee acts on interim findings

Based on this initial analysis, the Coordinating Committee decided four weeks ago to terminate the placebo arm of the study and offer open treatment to all participants.

Also, it agreed that the results were important enough to warrant early publication as they confirm that zidovudine significantly slows progression when used early in this course of the infection.

Monotherapy with ddC less effective than zidovudine but combination may have clinical value

Monotherapy with dideoxycytidine (ddC) was shown to be significantly less effective than treatment with zidovudine in a major comparative trial (ACTG 114) which has, therefore, been terminated but initial data from another study suggest that a combination of the two antiviral agents may be clinically valuable. While zidovudine has been widely used in regular medical practice for more than five years, ddC is still an experimental antiviral agent which remains at the clinical trials stage.

The comparative study, which was undertaken by the US AIDS Clinical Trials Group (ACTG), involved 636 people with AIDS or advanced AIDS-related complex (ARC) who had never received zidovudine or not
more than three months of zidovudine therapy. Three hundred and twenty one individuals were randomised to receive zidovudine (100mg every four hours) and 315 were treated with ddC (0.75 mg every eight hours).

The comparative study was terminated when significantly superior survival rates were found in the zidovudine treatment group. After a year, 59 deaths occurred in the ddC group (82 per cent survival) compared with 33 in the zidovudine group (89 per cent survival). The study committee concluded that ddC was significantly less effective than zidovudine in the first year's therapy.

However, a combination of zidovudine and ddC may prove valuable and a study has recently been undertaken by the US National Institute of Allergy and Infectious Diseases (NIAID) in which six dosing regimens were evaluated in 56 people with AIDS or advanced ARC during phases I and II of this open label study (ACTG Study 106). (Table 3)

The combination was generally well tolerated and no adverse effects were reported which had not been previously observed when the agents were given as monotherapy. Severe paraesthesias and pain in the extremities, consistent with ddC-induced neuropathy, were reported in two people and 10 cases of severe haematological toxicity occurred. The frequency of adverse effects was similar in the different treatment groups although sample sizes were small.

Weight gain occurred in all the treatment groups with no significant differences between the dosage regimens.

Initially, the mean CD4 cell count increased in all of the treatment regimens and there were no significant differences between the groups. However, the regimens including the highest dose of 600mg of zidovudine produced increases in CD4 counts which were sustained for longer than those using lower doses. In the groups receiving combinations using zidovudine doses of 300-600 mg daily, there were increases over two consecutive months of 50 CD4 cells/mm³ or more in 69 per cent of people.

Mean levels of p24 antigen decreased after two weeks in each group with the exception of the group using a low dose (150 mg/day) of zidovudine alone. The increases were maintained throughout the study.

**Based on the results, the authors concluded that:**

- Combination therapy with zidovudine and ddC is well tolerated at these doses;
- Low dose zidovudine (150 mg/day) has suboptimal effects on CD4 counts and p24 antigenaemia; and.
- Higher doses of zidovudine combined with ddC produce superior and more persistent efficacy than previously reported in studies of monotherapy.

Therefore, the authors recommended that this combination should be considered in advanced HIV infection and that a large Phase II/III study be started. ACTG 155 has begun recruitment.

This view is supported by Dr Anthony Fauci, the Director of the NIAID. He wrote in an editorial in the *Annals of Internal Medicine* that the combination of zidovudine and ddC increased the size and duration of the CD4 cell counts which were approximately double those reported for either agent alone. Additionally, the combination was generally well tolerated, he wrote.

In his commentary, Dr Fauci emphasised the superior efficacy of zidovudine at a daily dose of 600 mg compared with that of 150 mg. This increased efficacy appears to be achieved without a significant increase in side effects, even when given in combination with ddC. Therefore, he recommended that such low doses of zidovudine should only be used in people who are unable to tolerate higher doses.

Future knowledge will emerge from ACTG 155 which will involve more than 1,000 participants in a comparison of a combination of zidovudine (200mg three times a day) plus ddC (0.01 mg/kg three times a day) with monotherapy with either drug.

**13. The extent of the continuing challenge of AIDS**

Since it was first described in the USA a decade ago, more than 400,000 cases of AIDS have been reported to the World Health Organisation (WHO), although this is recognised as a serious under-estimate.
of the actual number of cases which have occurred. The 
WHO estimates that the total number of AIDS cases is 
actually more than one million. In addition, the spread 
of the virus among children has become a major con­
cern. About 500,000 newborns in Africa have already 
been infected and it is predicted that in 1993 AIDS will 
be one of the five most important causes of infant and 
paediatric mortality in the USA.

WHO projects that some 40 million men, women 
and children may be infected with HIV by the year 2000, 
while the cumulative total of AIDS cases is expected to 
be close to 10 million.

14. Is HIV transmission changing?

There are three main methods of transmission:
- From exposure to blood (or blood products) 
either by transfusion or the use of syringe needles which 
are contaminated with blood containing HIV;
- By sexual intercourse through exposure to se­
men, blood or vaginal and cervical secretions; and,
- From an infected mother to the foetus or neonate 
(so called vertical transmission).

The use of contaminated blood and blood products 
was one of the major routes of transmission in the early 
1980s in many countries including the USA. Efficient 
screening of blood products has since virtually elimi­
nated this route of transmission in many industrialised 
countries. However, this mode of transmission remains 
a major hazard in countries where routine screening is 
not undertaken.

Meanwhile, transmission due to the use of con­
taminated syringes and needles among IV drug users 
appears to be increasing in the USA and much of 
Europe. This is a highly "efficient" means of transmis­sion.

Sexual transmission is now recognised as one of 
the major challenges which has to be overcome as it is 
the primary route of transmission worldwide. There­
fore, many preventative education programmes have 
emphasised the importance of safer sex by encouraging 
the use of condoms and non-penetrative sex.

15. If safer sex is not practised:
- The risk of transmission is comparatively high if 
people engage in unprotected anal intercourse probably 
because cuts or abrasions of the rectal membrane are 
relatively common and offer the virus a route of entry 
into the bloodstream; and,

- Penile-vaginal intercourse carries a substantially 
higher risk of transmission than oral sex. The risk of 
transmission from male to female during vaginal inter­
course is greater than from female to male.

Transmission from mother to foetus or newborn 
infant is an increasingly common problem, with re­
ported transmission rates ranging between 13-62 per 
cent in Europe and Africa.

Overall, there are significant changes in the pattern 
of AIDS reflecting shifts in the significance of different 
routes of transmission.

For example, in the USA, northern Europe and 
Canada, sexual transmission among gay men appears to 
have slowed, possibly as a result of changes in sexual 
habits. However, transmission remains predominantly 
homosexual in a number of Latin American countries, 
e.g. Brazil and Argentina, according to a recent report 
from the Office of Health Economics in the UK, al­
though these trends are also changing.

In areas of the USA and many Southern European 
countries, HIV infection has tended to become a disease 
largely associated with IV drug users. This group now 
accounts for up to 90 per cent of all new cases reported 
in some US cities. Additionally, within the USA, a 
growing number of female partners of IV drug abusers 
have become infected and about 140/100,000 women of 
childbearing age are now believed to be HIV-positive.

In Europe, HIV transmission is increasing most 
rapidly among the heterosexual population. The per­
centage of AIDS cases in Europe attributed to IV drug 
use has risen from two per cent in 1983 to approximately 
50 per cent in 1991. This route of transmission is 
particularly high in Italy and Spain but is also becoming 
iincreasingly important in northern European countries, 
e.g. The Netherlands and Germany.

Within Africa, HIV transmission has primarily 
been heterosexual and until recently has mainly affected 
urban areas. Up to one in 40 adults in Central Africa may 
now be HIV-positive and AIDS is now the leading 
causes of mortality in many cities in sub-Saharan Africa.

16. Are any countries left unaffected?

The reported figures of AIDS cases significantly 
under-estimate the actual number of cases which have 
occurred, according to the World Health Organisation. 
This is particularly true of sub-Saharan Africa, South­
East Asia and the pacific Rim. There is growing evi­
dence that a significant increase in HIV and AIDS cases
can be expected from many countries in these areas, e.g. Thailand and India, with currently low numbers of reported AIDS cases. Indeed, one recent study showed that up to 75 percent of prostitutes tested in Thailand were HIV-positive.

As HIV is predominantly sexually transmitted, it cannot be contained within any country’s borders. HIV is an infection which challenges everyone and, therefore, this challenge must be faced by every nation.

17. Sharing the challenge

By sharing the challenge, people with HIV or AIDS, governments clinicians, researchers and pharmaceutical companies have already made substantial progress in the last decade. For example:

- Major public education campaigns have created a worldwide awareness of HIV and AIDS and have resulted in the adoption of safer behaviours among some sectors of the population;
- A range of self-help groups, community-based organisations and other non-governmental organisations have been developed in many countries which provide invaluable practical and emotional support for people with HIV or AIDS;
- More is being discovered about the virus and this knowledge could lead to the development of additional drugs to delay the progression of HIV infection still further and research may eventually result in a vaccine;
- Already, agents such as zidovudine not only help by prolonging life but help people with HIV infection to have a better quality of life;
- A range of drugs is available which can be used to effectively treat or protect against opportunistic infections. These infections significantly increase the need for hospitalisation and can be life-threatening in individuals with low CD4 counts; and,
- Increasingly sensitive diagnostic tests have allowed for earlier and more reliable identification of HIV infection and, therefore, make it possible to begin medical and psychological support earlier.