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**Unplanned ART treatment
interruptions in Southern Africa:
a literature review**

Nina Veenstra
Alan Whiteside
David Lalloo
Andrew Gibbs

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The Administrative Officer
Centre for Social Science Research
University of Cape Town
Private Bag
Rondebosch, 7701
Tel: (021) 650 4656
Fax: (021) 650 4657
Email: Kathleen.Forbes@uct.ac.za

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Nina Veenstra is a Research Associate with the Health Economics and HIV/AIDS Research Division at the University of KwaZulu-Natal.

Alan Whiteside is a Professor and the Director of the Health Economics and HIV/AIDS Research Division at the University of KwaZulu-Natal.

David Lalloo is a Reader in Tropical Medicine and Director of the Wellcome Trust Tropical Centre at the Liverpool School of Tropical Medicine.

Andrew Gibbs is a Researcher with the Health Economics and HIV/AIDS Research Division at the University of KwaZulu-Natal.

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Unplanned ART treatment interruptions in southern Africa: a literature review

Adherence to antiretroviral therapy is important to optimise treatment outcomes and prevent the development of drug resistance. It is however compromised under a number of situations in the countries most heavily affected by HIV/AIDS. The question we are concerned with is: ‘How to keep people on treatment?’ The answer lies in an understanding of why adherence is important; what levels of adherence are needed to ensure that treatment remains effective; how different types of crisis affect people’s access to treatment; and how patients and service providers respond to such difficulties.

This paper considers the longer term impact of unplanned ART treatment interruptions and makes suggestions as to how they might be avoided and managed in future, based on a series of case studies. More specifically, it looks at problems with health system functioning and ART delivery during: 1) the 2007 public sector strike in South Africa, 2) the ongoing political and economic crisis in Zimbabwe, and 3) the 2008 floods in Mozambique. As the paper is a literature review, potential strategies identified in the final section of the review are limited in the sense that they are based on reports rather than original data. Nonetheless, we have not yet others taking a similar approach and our hope is that this synthesis will aid further research.

The paper consists of five sections:

1. A closer look at the various undesirable outcomes of sub-optimal adherence and the critical levels of adherence required to avoid these.
2. A review of studies that have focussed on the effects of treatment interruptions specifically, whether purposefully implemented or unintended.
3. A brief investigation into what levels of adherence we might expect from patients on treatment in sub-Saharan Africa (sSA) and the factors hindering such adherence.
4. A review of three specific crises in southern Africa (see above) and the effect that these have had on ART delivery in particular.
5. A brief attempt at identifying potential strategies for keeping patients adherent on ART during a crisis situation, given what we know about patient and provider responses to the three crises studied.

1. Adherence to ART: why is it important?

Much attention is paid to the importance of adherence, indeed in southern Africa patients are often not started on treatment if the necessary support structures are not in place. This caution is well founded, since poor adherence has undesirable consequences for both the individual concerned and the wider population.

At the individual level, failure to realise adequate levels of adherence are reflected in the effect of treatment on:

1. The virus itself (defined by viral load and ability to maintain viral suppression);
2. The patient's immune system (measured by CD4 counts); and
3. Clinical prognosis (measured by clinical disease progression and death)

These are termed virologic, immunologic and clinical outcomes respectively.

In most cases, there is a clear relationship between virologic, immunologic and clinical outcomes. Once on treatment, HIV becomes suppressed and an individual's CD4 count slowly increases. Improved immune functioning means that the risks of morbidity and mortality are reduced. However, in some cases this relationship is not so straightforward. 'Virologic non-responders' are those who experience an increasing CD4 count in the absence of viral suppression, while 'immunologic non-responders' have viral suppression but fail to demonstrate CD4 cell count increases. Discordant responses are reported more commonly in patients with poor adherence and have been found to carry higher risks of mortality (Moore et al. 2005; Aiuti et al. 2006).

Drug resistance - essentially resistance of HIV to certain drug classes - is also associated with adherence levels, and it is a concern that operates at both the individual and population levels. At the individual level, it means that patients are less likely to maintain viral suppression, although in many cases can still derive significant clinical benefit from treatment (Lucas 2005). Drug resistance becomes a public health issue when drug resistant viral strains are transmitted to an increasing proportion of people in a specified population. The evolution of drug resistance in a population takes a longer time to unfold and so remains more elusive than at the individual level. However, it is the reason why some people have argued for withholding therapy in contexts where adherence support mechanisms are lacking (Bangsberg et al. 2004). Ultimately, the prospect of ART becoming more expensive (as is the case for second-line regimens, which become necessary when drug resistance develops) and less effective over time may be more frightening for governments and health agencies than that of non-adherent individuals dying.

1.1 ART adherence and viral suppression

The first group of studies on the association between ART adherence and viral load or viral suppression (HIV RNA level less than 400 copies/mL) were undertaken in the late 1990s (see Bangsberg et al. 2000; Paterson et al. 2000; Arnsten et al. 2001; Gross et al. 2001; Mannheimer et al. 2002). They measured adherence using one or more methods including electronic monitoring, pill counts and self reports, and in all cases demonstrated an inverse relationship between adherence and viral load. The study by Paterson et al (2000) has been most frequently cited and established a benchmark of 95% for the minimum adherence level necessary to maintain viral suppression. In this study, virologic failure (HIV RNA levels greater than 400 copies/mL) was 22% for patients with adherence levels of 95% and above, 61% in patients where adherence levels between 80% and 94.9%, and 80% for patients with adherence levels of less than 80%.

Early estimates of the levels of adherence required to maintain viral suppression have been re-evaluated over time, because they were derived from data on treatment-experienced patients receiving unboosted protease inhibitor (PI) regimens which are less potent than non-nucleoside reverse-transcriptase inhibitor (NNRTI) regimens (Bangsberg et al. 2006)¹. Aside from focusing on NNRTI regimens, more recent studies (see Maggiolo et al. 2005; Tuboi et al. 2005; Gross et al. 2006; Liu et al. 2006; Nachega et al. 2007; Robbins et al. 2007; Shah et al. 2007) have followed patients for a longer period of time and often used pharmacy refill claims to measure adherence. Some have tried to obtain a more nuanced understanding of adherence, for example by evaluating the effect of dose-timing errors in addition to percentage adherence (Liu et al. 2006).

Studies published in the last few years on the relationship between ART adherence and viral load focusing on NNRTI-regimens have shown that viral suppression is still possible in a significant proportion of patients at levels of adherence less than 80%. The study by Nachega et al (2007) in South Africa demonstrated a linear dose-response improvement in virologic outcomes as

¹ NNRTI-regimens are recommended for resource limited settings in WHO guidelines because of their lower cost, greater accessibility, efficacy and low toxicity. A review of ART studies in Africa in 2005 showed that this was indeed the regimen of choice in the vast majority of cases (Akileswaran, C., Lurie, M. N., Flanigan, T. P. and Mayer, K. H. (2005). Lessons learned from use of highly active antiretroviral therapy in Africa. *Clinical Infectious Diseases*, **41**(3): 376-385). See also the following review: Egger, M. (2008). Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. *Tropical Medicine and International Health*, **13**(7): 870-9.

adherence to NNRTI-based regimens increases beyond 50%. A quarter (25%) of all patients achieved viral suppression having filled between 50-60% of pharmacy claims, with this rising to 73% for those that filled between 90-100%. So while NNRTI-regimens are more forgiving than unboosted PI-regimens when it comes to adherence (see also Maggiolo et al. 2005; Bangsberg et al. 2006), any level of adherence less than 100% is less than ideal.

1.2 ART adherence and CD4 count

A decrease in viral load generally goes hand in hand with an increase in CD4 count. However, over the shorter term the impact of adherence on viral load is more apparent than a change in CD4 count, largely because of the time delay between the two responses (Gross et al. 2001; Press et al. 2002). Falling CD4 counts are usually a result of virologic failure. This sequence of events was appreciated in recent research which suggested that pharmacy refill adherence can accurately predict patient's response to treatment (in particular virologic failure) and allow time for intervention, when compared to the use of CD4 counts which the WHO recommends in resource-limited settings to monitor treatment success (Bisson et al. 2008).

Only a few studies have chosen to evaluate immunologic outcomes of adherence specifically (see Wood et al. 2004; Safren et al. 2005), probably because of the concerns highlighted above. However, there are many studies that have assessed both virologic and immunologic outcomes (see Haubrich et al. 1999; Paterson et al. 2000; Gross et al. 2001; Mannheimer et al. 2002; Kitahata et al. 2004). Not surprisingly, these found adherence to be the most significant factor influencing the increase in CD4 count. The study by Wood et al (2004) in particular put an end to concerns that late initiation on ART (after CD4 count drops below 350 cells/ μ L) might cause irreparable damage to the immune system, so precluding a CD4 response to ART. It found that substantial CD4 count gains are possible in patients with advanced stage infection, provided they are adherent to treatment. Among those with a CD4 count of less than 50 cells/ μ L, absolute CD4 counts in adherent patients rose to 200 cells/ μ L during the fifth 15-week period of treatment, compared to 60 cells/ μ L in non-adherent patients. As with viral load, any adherence level less than 100% was associated with a less-than-optimal CD4 count response.

1.3 ART adherence and clinical outcomes

While virologic and immunologic outcomes are of immediate concern to health workers, clinical outcomes carry more meaning to patients on ART. A number of such outcomes have been examined in relation to adherence, including the number of days in hospital, the development of opportunistic illnesses or AIDS, the loss of QALYs, and mortality rates (see Paterson et al. 2000; Bangsberg et al. 2001; Garcia de Olalla et al. 2002; Hogg et al. 2002; van Sighem et al. 2003; Wood et al. 2003; Kitahata et al. 2004; Munakata et al. 2006; Nachega et al. 2006; Stringer et al. 2006; Fielden et al. 2008). Most of the early studies concerned themselves with mortality and two in particular used pharmacy refill data to measure adherence. They determined hazard ratios of 2.90 for less than 75% adherence (Hogg et al. 2002) and 3.87 for less than 90% adherence (Garcia de Olalla et al. 2002). In other words, the most forgiving study by Hogg et al (2002) found that patients were almost 3 times more likely to die when taking 75% or less of their treatment over the course of a year.

As ART became more widely available (in sSA in particular) during the course of the decade, more data on adherence and clinical outcomes emerged from larger studies in high prevalence areas (see Nachega et al. 2006; Stringer et al. 2006). Nachega et al (2006) also used pharmacy refill claims as a measure of adherence in South Africa and found a hazard ratio comparable with the earlier studies outlined above. Out of a total of 6288 ART patients, those claiming less than 80% of their prescription refills were more than 3 times more likely to die than those claiming more than 80%. Unfortunately many patients in the region start treatment with low CD4 counts and this study served to highlight how poor adherence under these conditions greatly heightens the risk of death, when compared to patients with more intact immune functioning. Late access to care and poor adherence are therefore a dangerous combination for patients starting treatment.

1.4 ART adherence and the development of drug resistance

While the relationship between ART adherence and viral suppression is linear, theories emerged in the late 1990s proposing that that the relationship between ART adherence and the development of drug resistance would take on a different form. Friedland and Williams (1999) commented how resistance would be least likely to develop at both extremely high levels of adherence and very

low levels of adherence. At high adherence levels viral replication is maximally suppressed, while at low adherence levels the virus has limited exposure to antiretroviral drugs. In between there is a zone where sufficient viral replication occurs with exposure to drugs, where resistance is most likely to develop. Many early studies on ART adherence and drug resistance set out to determine whether: 1) the relationship was indeed ‘bell-shaped’ as proposed, and 2) which adherence levels were associated with the greatest number of drug resistant mutations (see Gallego et al. 2001; Walsh et al. 2002; Bangsberg et al. 2003; Sethi et al. 2003). Both Bangsberg et al (2003) and Sethi et al (2003) looked at resistance across the full spectrum of adherence and found that it was greatest in those with higher levels of adherence, generally in the region of 70-90%. However, even with adherence levels over 90%, development of resistance was significant.

As with adherence studies looking at other outcomes, those focussing on drug resistance evolved to incorporate different regimens and a consideration for their potency (see Roge et al. 2004; Harrigan et al. 2005; King et al. 2005; Bangsberg et al. 2006; Maggiolo et al. 2007; Lima et al. 2008). The consolidation of knowledge emerging from this next generation of studies led to the conclusion that PI resistance is most likely to develop at high adherence levels (just less than those required for complete viral suppression), while NNRTI resistance is highest at low adherence levels. Therefore the best way to avoid NNRTI resistance is to ensure adherence levels high enough to achieve viral suppression (Bangsberg et al. 2004; Bangsberg et al. 2006). The different adherence-resistance relationships between these two drug classes has been explained by their differing half lives, which in turn impacts on the ability of drug-resistant vs wild-type variants to replicate while exposed to the type of drug levels used in clinical practice (Bangsberg et al. 2006).

‘Acquired’ drug resistance, meaning that which develops within an individual on treatment, impacts on the effectiveness of treatment. Resistance can also become a public health problem when resistant strains arising in individuals are passed on to other individuals through sexual intercourse, vertical transmission, or intravenously (Wainberg et al. 1998; Vella et al. 2005). This is termed ‘primary’ or ‘transmitted’ resistance and depends on a number of factors influencing transmission, including the viral subtype, the types of drugs used, the duration of therapy, the presence of co-infections, the ratio of wild-type vs drug-resistant variants, and the extent to which individuals infected with resistant virus engage in risky sexual behaviour (Vella et al. 2005). The last point in particular has been cause for concern, since less adherent individuals on ART may be those least likely to ensure safe sexual interactions (Flaks et al.

2003; Remien et al. 2007).

Several factors are important when trying to understand the burden of drug resistance at the population level. These include the failure rate for ART, the resistance pattern associated with treatment failure, and how transmissible the resistant viruses are (Wainberg et al. 1998; Vella et al. 2005). Because these factors are not yet well understood, it is difficult to know how population-level resistance will evolve. However, surveillance efforts have indicated that currently, transmitted resistance is more common in the developed world because of geographic trends in the use of ART (Shekelle et al. 2007). In other words, ARV resistance in treatment naïve patients remains most prevalent (over 10%) in North America and Europe where treatment coverage has been high and many patients started out receiving mono- or dual- therapy prior to the advent of Highly Active Antiretroviral Therapy (HAART). The World Health Organization (WHO) has however developed methods of surveillance to monitor transmitted HIV drug resistance in countries currently scaling up ART programmes. These methods suggest that the level of transmitted resistance is still less than five percent at sites in sSA, indicating little cause for concern at this stage (Bennett et al. 2008).

In addition to the lower levels of ART treatment coverage in the developing world, many patients in these regions have also commenced therapy on HAART (rather than on mono- or dual-therapy). This should theoretically, if adherence is maintained, afford patients some level of protection against them developing drug resistance and passing this resistance on to others. However, Prevention of Mother to Child Transmission (PMTCT) programmes have until recently consisted of only Single Dose Nevirapine (SD-NVP) for the delivering mother and neonate, putting such programmes in the spotlight as a potential source of both acquired and primary resistance. A meta-analysis published in 2007 conservatively estimated that NVP resistance mutations occurred in about one third of women receiving SD-NVP, if measured between four and eight weeks postpartum. They also occurred in half of all children who became infected with HIV despite being on the PMTCT programme (Arrive et al. 2007). Although this resistance may wane over time and ultimately not affect short term treatment outcomes (Arrive et al. 2007; Chi et al. 2007; Shekelle et al. 2007), current World Health Organization PMTCT guidelines (World Health Organization 2006) acknowledge that it is safer to simply prevent the development of resistance through the use of multiple drugs.

As ART and PMTCT programmes have become more sophisticated, they have also evolved to tackle the issue of ARV drug resistance. However, with

improving levels of ART coverage resistance will also inevitably arise, since more of the virus pool will be exposed to drug pressure. The cornerstone of preventing such resistance therefore still rests on patients being adherent to treatment.

2. What we know about treatment interruption

It is unclear how patients respond in instances where they are unable to access ART. If they foresee this coming, do they reduce the number of doses to make the drugs last longer? Do they stop altogether until their access to drugs is again secured? Do they resume treatment immediately the disruption is over, or is their faith in the medical system damaged to the extent that they resort to other modes of treatment temporarily or even permanently? These are questions we don't have answers to. Measurement of 'adherence' as outlined in the section above, captures a range of scenarios. It obviously doesn't address those who discontinue treatment, but does capture those who either miss doses or interrupt treatment for shorter periods of time. In such cases patients will have a lower number of pharmacy claim refills, a popular measure of adherence used in resource-limited settings (see for example Bisson et al. 2008).

Assuming that some patients facing problems with accessing ART will respond by interrupting treatment temporarily, it is useful to understand the outcomes of treatment interruption more specifically. There are two broad categories of literature in this area: 1) that which looks at structured treatment interruptions, and 2) that which looks at unstructured treatment interruptions. While the former might seem somewhat irrelevant (because treatment is interrupted in a very controlled manner), it does give us clues as to how different groups of patients respond when taken off drugs for a period of time. The latter is unfortunately difficult to consolidate due to the different definitions of 'treatment interruption'.

2.1 Structured treatment interruptions

Studies on the effect of structured treatment interruptions started to emerge post 1999, when the first case study was reported on 'the Berlin patient' (as he was known) who interrupted treatment because of complications on ART and subsequently developed a strong HIV antiviral immune response (Liszewicz et al. 1999; Pai et al. 2005). Combined results of many of the earlier studies have been summarised in two Cochrane reviews (Pai et al. 2005; Pai et al. 2006).

These reviews adopted a convenient classification of the literature, according to the three HIV patient populations studied: 1) acute HIV infection (ie those newly infected), 2) chronic HIV infection with viral suppression, and 3) chronic HIV infection without viral suppression.

The Cochrane reviews (Pai et al. 2005; Pai et al. 2006) on chronic infection found that there was insufficient evidence to support structured treatment interruptions for any patient, irrespective of whether viral suppression had been achieved. In fact, for patients without viral suppression but with advanced HIV disease, such an intervention could be dangerous because of its effect on CD4 count and disease progression (Pai et al. 2006). For chronically infected patients with viral suppression, the review (Pai et al. 2005) considered the evolution of studies; from those looking at a fixed period off ART (termed ‘time-cycled STI’), to those looking at a variable period off ART guided by CD4 count decline (termed ‘CD4-guided STI’). It commented that the ‘time-cycle STI’ in particular fell out of favour because many studies reported the development of drug resistance. Studies on ‘CD4-guided STI’ were at this time (in 2005) limited because of their focus on short-term outcomes.

More recently, two large studies on the longer-term outcomes of ‘CD4-guided STI’ found that this strategy put patients at significantly higher risk of severe clinical events and death, when compared to those on continuous treatment (Danel et al. 2006; El-Sadr et al. 2006). It is important to consider the context when interpreting these results, since study sites in Africa have demonstrated unique risks, in particular relating to invasive bacterial infections (Meintjes 2006). Both studies were prematurely stopped on the basis of their findings. Furthermore, there are risks of drug resistance if all drugs are stopped simultaneously when interrupting a NNRTI based regimen in particular, leading to suggestions that any drug with a long half-life or low genetic barrier should not be included in treatment interruption regimens (Ruiz et al. 2007).

A recent review of the current evidence has confirmed that structured ART treatment interruption for both acute and chronic HIV infection is associated with a variable degree of net harm (Paton 2008). Given this observation and the discontinuation of two big trials, it is unlikely that there will be any further studies of this strategy.

2.2 Unstructured treatment interruptions

Studies on unstructured treatment interruptions have captured a wide range of patients and circumstances. Most importantly perhaps, there are those studies that have looked at a patient population with a significant degree of treatment experience (and often on a PI regimen), and those that have focussed on patients in resource-constrained settings. We need to consider that these two groups of patients may interrupt treatment for different reasons (see the next section) and could also respond differently to such disruptions.

European studies have demonstrated that unstructured treatment interruptions are common, but have not all agreed on their consequences. However, studies are not necessarily comparable, because of the different time periods used to define a 'treatment interruption'. Interruptions of less than 3 months in a cohort of Swiss patients commencing treatment in the late 1990's were not associated with significantly higher rates of morbidity or mortality. The authors of this study concluded that such interruptions were not risky, particularly in patients with high CD4 counts and low viral loads (Taffe et al. 2002). Similarly, data pooled from 22 cohorts in Europe demonstrated that treatment interruptions of more than 14 days (median duration 189 days) did not significantly increase the risk of disease progression, but were associated with a CD4 count decline (particularly in those with a low CD4 count) (Touloumi et al. 2006). In contrast, three studies concluded that treatment interruptions did put patients at higher risk of disease progression; one study defined an 'interruption' as two months or more (Poulton et al. 2003) and the other two as three months or more (d'Arminio Monforte et al. 2005; Holkmann Olsen et al. 2007). Those with low CD4 counts, higher viral loads and more advanced disease were more at risk (Poulton et al. 2003; Holkmann Olsen et al. 2007).

Studies from resource-poor settings, in particular Uganda, have highlighted the way in which unplanned treatment interruptions in patients on NNRTI-regimens can lead to virologic failure and drug resistance (Spacek et al. 2006; Oyugi et al. 2007). The study by Spacek et al (2006) showed that interrupting treatment for four days or more was associated with virologic failure. Oyugi et al (2007) demonstrated that treatment interruptions of more than 48 hours were associated with the development of drug resistance. These studies, along with that of Parienti et al (2004) in France, all describe how the long half-life of NNRTIs relative to that of NRTIs essentially results in patients being on monotherapy when all drugs are stopped simultaneously. Treatment interruptions in patients on a NNRTI regimen are therefore particularly problematic and generally more of a concern than single missed doses.

In conclusion, treatment interruptions in patients with more advanced disease and on NNRTI regimens are likely to have more adverse outcomes. Unfortunately these are the circumstances of a large proportion of those on treatment in sSA.

3. ART adherence in sSA

If maintaining adherence to ART is essential for optimal treatment outcomes, then the next logical questions are about: 1) our knowledge of current adherence levels, and 2) the reasons behind either poor adherence or treatment interruptions. Answering these questions will help us to understand how effective ART is likely to be in the region and how we can reduce the risks of poor outcomes at both the individual and population levels.

3.1 What can we expect in terms of adherence?

When patients were first commenced on ART in sSA, one of the biggest concerns was whether they would be able to adhere to treatment, given mixed successes with drug regimen compliance for other common diseases in the region and severe health infrastructure constraints. Some argued that in a situation of ‘antiretroviral anarchy’, potential individual gain in the shorter term would be outweighed by harm at the population level in the longer term (Harries et al. 2001; Stevens et al. 2004). This debate pitched efforts to reduce morbidity and mortality against fears of increasing levels of drug resistance. Its premise was that in sSA, there was a higher likelihood of poor adherence compared to the developed world. Patients would lack the resources to ensure regular attendance at health facilities and the health system itself would not be able to provide a structured enough framework within which to effectively administer ART.

In 2006, concerns about sub-optimal adherence in sSA were allayed by a meta-analysis that concluded that there have been higher levels of adherence to antiretroviral regimes in sSA than in North America (Mills et al. 2006). This meta-analysis included 30 North American studies and 22 African studies and affirmed what some authors had been trying to say since as early as 2003 – that lower socio-economic status does not necessarily result in inadequate adherence and that it should not be a barrier to initiating ART programmes in Africa (see for example Orrell et al. 2003). However, the concern remains that many of the early ART programmes, which were logically the subject of early adherence

studies in sSA, have captured a set of circumstances that will not be the norm once treatment scales up. Getting more people on treatment in the region will increase stresses on fragile health systems, and so we need to remain cognisant of potential breaking points.

3.2 Reasons for poor adherence and treatment interruption

Even though patients in sSA are capable of being as adherent on ART as patients in the developed world, there are still many factors specific to the different contexts that could potentially influence adherence. These are drawn out in a body of literature that has examined the determinants of poor adherence or treatment interruptions.

Nearly all the early studies on factors influencing ART adherence came from the developed world. They found a number of determinants consistently being identified, including side effects, psychological distress, lack of social support and complexity of the drug regimen (Ammassari et al. 2002). Many other variables, such as substance abuse, depressive symptoms and knowledge and beliefs about treatment, gave inconsistent findings. There were further concerns about the comparability of study populations and the fact that cohorts are often studied out of convenience. Nonetheless, the meta-analysis by Mills et al (2006) looked at barriers to adherence in different economic settings and concurred on many of the above concerns. It would seem that social support and the ability to disclose one's status, as well as having a simple regimen with as few pills as possible, are important considerations for treatment adherence irrespective of context (see also Nachega et al. 2004; Hardon et al. 2007).

Studies looking at adherence in resource-limited settings draw out a number of additional and generally more prevalent concerns highlighting the direct and indirect economic burdens borne by patients and their families in accessing treatment. More commonly studies have looked at the direct costs. There is evidence from Uganda, Nigeria, Cameroon, Tanzania, Malawi, Botswana, Senegal and India to say that financial constraints and/or user fees are associated with lower rates of adherence (Laniece et al. 2003; Weiser et al. 2003; Byakika-Tusiime et al. 2005; Iliyasu et al. 2005; Laurent et al. 2005; van Oosterhout et al. 2005; Crane et al. 2006; Kumarasamy et al. 2006; Kiguba et al. 2007; Oyugi et al. 2007; Ramadhani et al. 2007). This is supplemented with similar data from 15 programmes in Africa, Asia and South America (Brinkhof et al. 2008). Important indirect costs potentially incurred in accessing treatment include those

associated with time off work; an inability to care for other members of the family during medical visits; and difficulties with transportation to the nearest medical facility (Castro 2005). The most comprehensive study drawing out how indirect costs adversely affect adherence was done by Hardon et al (2007) in Botswana, Tanzania and Uganda. However, others have specifically highlighted costs and difficulties associated with transport (see Weiser et al. 2003; Pienaar 2008).

In addition to financial constraints, disruptions in drug supply are frequently reported in resource limited settings and are rated as another of the major barriers to adherence in these contexts (Hawkins et al. 2007). Unfortunately, some countries have more frequent problems with drug supply. In Nigeria, for example, a shortage of drugs was found to be the main reason for non-adherence (Iliyasu et al. 2005). Similarly, in Malawi a shortage of drugs combined with personal financial constraints was found to account for the vast majority of non-adherence amongst patients paying for treatment (van Oosterhout et al. 2005). Yet other authors have commented on irregular drug supplies as a cause of treatment interruption (Laurent et al. 2005; Spacek et al. 2006). Concerns about drug access may extend to when patients are away from home, which was found to be a major reason for missed drug doses in Soweto in particular (Nachega et al. 2004).

Unfortunately, in resource constrained settings ART becomes pitched against many other priorities, both for individuals taking treatment and the health services that supply it. One author suggested it is more appropriate in such settings to think of adherence issues as issues of access (Crane et al. 2006).

4. Specific events or circumstances that have influenced patient's ability to maintain adherence in southern Africa

Unfortunately, sSA is a region which is plagued with health system constraints and economic and political crises. These circumstances are not going to change in the foreseeable future and so ART scale-up will continue to suffer set-backs as a result. Those not yet on treatment may not be able to access it when they need it, while those already on treatment may have poor access to drugs. Our focus here is on the latter group and we suggest that understanding the effect of different types of crises and how they are handled might help us to develop strategies to keep patients on treatment under difficult circumstances.

Crises are of different natures, various durations (short term vs long term) and various extents (localised vs widespread). For the purpose of this review we have identified three main types of crisis to consider. The first are 'natural disasters' such as floods or volcanic eruptions. These disrupt the health system and force people to move. They are short to medium term and localised. In this paper we look at the 2008 floods in Mozambique.

The second category is political and/or economic failure as has been seen in Zimbabwe, which is our case study. Sadly this is a feature of many African countries including, most recently, Madagascar. International aid agencies are paying increasing attention to 'failed' states, and the consequences of such failure for people needing secure drug supplies should be considered. This type of crisis is invariably long term and widespread.

The third category is service or system failure, which can manifest in many ways. This paper discusses the 2007 public sector strike in South Africa. However, other types of system failure occur when health services run out of money or drug supplies fail. The former was recently experienced in South Africa's Free State Province when, in November 2008, a moratorium was issued stating that no new patients should be put on ART until the new financial year (1 April 2009). Service or system failures, provided they are not a symptom of broader political and/or economic collapse, tend to be short term and can be localised (as in the case of the Free State Province) or widespread (as in the case of South African public sector strike).

4.1 2008 floods in Mozambique

Flooding and other natural disasters are not uncommon in regions badly affected by HIV/AIDS. Mozambique is a country in southern Africa which has experienced severe flooding in 2000, 2007 and 2008. Although the floods of 2008 were more severe than those of 2000 and 2007, the response of government and aid agencies was better and so the impact was far less harsh. The floods followed a similar pattern to that of previous years, with people coming back to resettle only because of the fertile ground in the affected area. Nonetheless, this paper looks at the 2008 floods, because there were still a large number of people displaced and recall concerning the situation at the time is likely to be better.

The 2008 floods were the result of high levels of rainfall which started in December and fell in Mozambique and in neighbouring countries (Zambia,

Zimbabwe and Malawi). The impact of this rainfall was felt most acutely in the Zambezi River basin, although this was by no means the only area affected. By the 3rd January, flooding was severe enough for the Government of Mozambique to declare a Red Alert, which is the highest level of alert used for natural disasters. Although estimates of the number of people displaced during the floods vary, there is general consensus among reports that it was more than 100 000. The Ministry of Agriculture estimated that 150 923 hectares of agricultural land were washed away, affecting 149 000 people (United Nations Office for the Coordination of Humanitarian Affairs 2008). The World Food Programme predicted that as a result they would have to provide food relief to a substantially larger number of people than initially planned for (World Food Programme 2008). Just as the country was recovering from the floods, cyclone Jokwe came in March, destroying even more houses.

Health problems stemming from natural disasters, such as the floods in Mozambique, are generally caused by the displacement of large numbers of people and damage to health system infrastructure. Of most concern are the sanitary problems and overcrowding in temporary camps. Numerous sources document the risks under such conditions of diarrhoeal diseases, cholera, measles, and in some instances also malaria (Ahern et al. 2005; Inter-Agency Standing Committee 2008; Medecins Sans Frontiers 2008; World Health Organization 2008). Diseases spread by faecal-oral transmission may increase immediately, while the risk of vector borne diseases (such as malaria) tends to increase over the medium term. Poor access to adequate food supplies means that people are more at risk of malnutrition, and poor access to health care can result in worse maternal and child health outcomes and inadequate management of both acute and chronic diseases (World Health Organization 2008).

Cholera was the greatest concern in all assessments of the impact of the 2008 floods in Mozambique. By early March, the Red Cross reported that a flood-related outbreak of cholera had spread to most provinces in the country, with 48 people dead and a total of almost four and a half thousand infected (Schwikowski 2008). Later reports suggested that 72 people died of cholera and an equal number of other waterborne diseases, a number far greater than the dozen or so that died as a result of rising flood waters (Lang 2008). The immediate need to intervene and ensure safe access to clean water meant that any other health problems occurring at the time were eclipsed. Only fleeting mention was made in some reports of the poor access to health facilities in resettlement areas, and the fact that health posts (providing very basic services) in these camps were slow to open due to a lack of drugs (Inter-Agency Standing Committee 2008; United Nations Children's Fund 2008).

Clearly, any situation that results in the temporary or permanent displacement of such large numbers of people will mean that those on ART may not be able to access the medication they require. Unfortunately, emergency responses generally don't take account of the importance to ensure ongoing provision of ART as this has only recently become an issue. Nonetheless, Medecins Sans Frontiers reported in late January that 60 patients in Mutarara (Tete province) on HIV and TB treatment were missing and had not come to the hospital to collect their monthly medication (Medecins Sans Frontiers 2008). In this instance teams were sent out to find them, but public health services don't generally have the capacity to respond in this way.

4.2 Political and economic crisis in Zimbabwe

The current situation in Zimbabwe is an example of a long term crisis with the potential to undermine ART delivery. It has been 10 years since the country first started witnessing high interest rates and inflation, which in turn provoked strikes, riots and increasing support for the opposition Movement for Democratic Change (MDC) headed by Morgan Tsvangirai. The chain of events over the last decade has been widely reported on and is outlined very briefly below (see for example BBC 2008; Reuters 2008).

While economic problems in Zimbabwe started in the last decade, the humanitarian crisis only really escalated after 2000, with the seizure of white-owned farms which was backed by the government. By 2001, foreign reserves were running out and it was clear that there would be serious food shortages in Zimbabwe. In April 2002 the Zanu-PF government declared a state of disaster as the situation worsened. Poor maize harvests in subsequent years left a large number of people in need of food aid. Before the next harvest in April 2009 the FAO/WFP Crop and Food Supply Assessment Mission (CFSAM) believe the number requiring assistance could possibly reach a high of 5.1 million people (World Food Programme 2008).

Political violence and intimidation escalated in 2002. Mugabe won a keenly contested election against Tsvangirai which, according to the Commonwealth Observer Group, was held under conditions that 'did not adequately allow for a free expression of will by the electors' (Commonwealth Observer Group 2002). As a result, Zimbabwe was suspended from the Councils of the Commonwealth for one year (Commonwealth Media Room 2002). In 2003 the suspension was extended indefinitely and Zimbabwe decided to pull out. Meanwhile, the brutality increased after a widely observed strike organised by the opposition.

Tvangirai was arrested and charged with treason, but later acquitted. The climate of violence and intimidation has continued up until today, with numerous accounts of how opposition supporters have been tortured, severely injured, or even killed.

On 19 May 2005 the Zimbabwe Government initiated its 'Operation Murambatsvina' ('Drive out Trash'), in which it drove the urban poor out of cities across the country, leaving an estimated 700 000 people homeless and worsening an already dire humanitarian situation. Two years later only 5 000 new homes had been built to replace the 90 000 destroyed (Kapp 2007). A report by the UN Special Envoy on Human Settlements Issues in Zimbabwe highlighted the widespread effects of this operation which it believes affected a further 2.4 million people in indirect ways (United Nations Special Envoy on Human Settlements Issues in Zimbabwe 2005).

Hyperinflation has been the 'hallmark' of Zimbabwe's economic collapse, pushing people to emigrate and forcing an increasing number of those remaining into poverty. An article by the Cato Institute describes how cumulative inflation was nearly 3.8 billion percent in the ten years between 1997 and 2007, while living standards (as measured by GDP per capita) fell by 38 percent (Hanke 2008). Unfortunately the last official inflation data are from July 2008 and therefore very outdated. However, the Cato Institute estimated Zimbabwe's annual inflation rate to be 89.7 Sextillion (10^{21}) percent as of 14 November 2008 (Hanke 2008). Towards the end of 2008 hyperinflation was fuelled by the dollarization of Zimbabwe's economy as it was gradually legalised (Reuters 2009).

Hyperinflation, dollarization, and a cap on bank withdrawals introduced by the Reserve Bank of Zimbabwe, have all left salaried workers paid in Zimbabwean currency unable to afford basic essentials. A recent report by Physicians for Human Rights has described how a government doctor produced a payslip showing a monthly gross income equivalent to 0.32 US cents (Physicians for Human Rights 2009). Transport costs to get to work are therefore unaffordable for many. While it is difficult to get an accurate idea of exactly how many people have fled Zimbabwe as a result of the crisis, a figure cited last year indicates that it could be in the region of three million (see for example Medecins Sans Frontiers 2008). To add to the situation of economic hardship caused by hyperinflation, a large proportion of the population remain without formal employment. In 2005 this was estimated to be 80%, but a more recent appeal from the United Nations Office for the Coordination of Humanitarian

Affairs cites a figure of just 6% in formal employment at the end of 2008 (Central Intelligence Agency 2008; United Nations 2009).

In 2008 Zimbabwe experienced yet another Presidential election marred by violence and intimidation. Tsvangirai won the first round vote held in March but did not manage to secure an absolute majority. He then withdrew from the election run-off after his supporters were attacked. Many parties, including all countries in the European Union (EU) and those not perceived as being friendly towards the Zimbabwe government, were not permitted to send observer missions to witness elections (Electoral Institute of Southern Africa 2008). The African Union called for a government of national unity with equal power sharing between Tsvangirai and Mugabe, a move also supported by the EU (African Union 2008; European Union 2008). Although such a deal was signed in September 2008, it stalled when the two parties failed to agree on who should control key ministries. Most recently, the MDC National Council has again restated its commitment to be part of a Unity Government (Movement for Democratic Change 2009), causing some level of renewed optimism.

While the economic and political crisis in Zimbabwe remains largely unresolved, the humanitarian situation has little hope of improvement. The most recent (2006) estimates of life expectancy at birth from the World Health Organization demonstrate just how dire this is, with females expected to live on average on 43 years and males only 44 years. Contrast this to 65 and 58 years respectively in 1990 (World Health Organization 2008). Meanwhile, the Zimbabwe government made it difficult for humanitarian organisations to assist during election year. The Private Voluntary Organisations Act requires that all Non-Governmental Organisations (NGOs) be registered in order to operate within the country's borders and currently demands that such organisations remain on the 'right' side of the government. On the 4th June 2008 the government suspended the operations of all NGOs and Private Voluntary Organisations for allegedly breaching the terms and conditions of their registration by engaging in political activities (Zimbabwe Ministry of Foreign Affairs 2008). The UN Secretary-General called for these restrictions to be lifted in a statement issued on 14 August 2008 because of the important role these organisations play in improving a very dire humanitarian situation (United Nations 2008). While this ban was subsequently removed, there were still reports of tight controls later in the year (Mail and Guardian 2008).

A protracted crisis that affects all sectors in society, like the one currently experienced in Zimbabwe, has widespread implications for the health system which are a lot harder to manage and control for. As one reporter put it, there are

‘shortages of everything ranging from electricity to sugar to syringes’ and these effects are also felt by the private sector (Kapp 2007). Already in 2003 there were stories of hospitals have to shut their doors because of having no food to feed patients (IRIN news 2003). The lack of basic supplies and equipment at health facilities meant that, even when hospitals were theoretically operating, patient care was seriously limited. Reports suggest that patients were often asked to obtain what was needed for the most vital kinds of assistance, such as child birth. Sadly, few could afford the cost (Baldauf 2008). At the big central hospitals vital machinery, like dialysis machines and incubators, remained largely out of service (Baldauf 2008). Such deficiencies meant that even simple operations could not be undertaken (Meldrum 2008).

Towards the end of 2008, the two largest public hospitals in Harare, Parirenyatwa (the premier teaching and referral hospital) and Harare Central, gradually closed down completely. Details of these closures are outlined in the report by Physicians for Human Rights, which describes how Parirenyatwa was without running water since August 2008 (Physicians for Human Rights 2009). By September surgical services ceased to function and the hospital was officially closed on 17 November. The closures were essentially precipitated by a lack of drugs and medical supplies, and insufficient numbers of health workers on duty. Both of these problems are explored in greater detail below.

Pharmaceutical supplies have, as one would expect, been hard to come by under the harsh economic conditions experienced in Zimbabwe. International sanctions, hyperinflation and a shortage of foreign currency are some of the challenges that saw the pharmaceutical market in 2007 drop 9% on its 2006 value according to the Business Monitor International (2008). This report also highlights accounts in the local media saying that around half of the drugs were out of stock in a number of pharmacies studied. HIV/AIDS drugs are also affected, even though the country has been able to import and manufacture generics under World Trade Organization rules since 2002 when the disease was declared a state of emergency. This is because pharmaceutical companies do not have the foreign currency to import the raw materials required (Salopek 2005; IRIN news 2006). In 2006 there were a number of reports which voiced concerns of how ART drugs were in particularly short supply (IRIN news 2006; Timberg 2006). More recent reports are more encouraging and it may be that foreign aid, in particular the President’s Emergency Plan for AIDS Relief (PEPFAR) which currently provides treatment for 40 000 AIDS patients, has some role to play in keeping the relevant drugs in stock at health facilities (Physicians for Human Rights 2009).

The critical shortage of health care workers is another factor hampering health system functioning, not only in Zimbabwe but throughout sSA, and made worse by the economic and political crisis. An article in *The Lancet* highlighted a number of factors driving health workers out of the country, namely the fact that they: 1) are poorly paid, 2) are overworked, 3) don't have medical supplies to work with, 3) don't have access to reasonable schools for their children , 4) don't have the supplies necessary to protect them from HIV, and 5) are fearful for their personal security, particularly when treating opposition supporters (Meldrum 2008). Although the 2006 World Health Report focussing on human resources for health gave a figure (in 2004) of one doctor for every 6 250 people (World Health Organization 2006) the Zimbabwe Association of Doctors for Human Rights described last year how doctors were leaving 'on a weekly basis', with only 800 doctors still registered in the country – one for every 12 000 people (Meldrum 2008). Official statistics at the time indicated that only 25% of the 425 doctor's posts in the state health system were filled, with the situation being even more critical for specialist posts (Meldrum 2008).

Ongoing industrial action in the public health care system in Zimbabwe is both a reflection of the poor working conditions for health care workers and a further disruption to an already dysfunctional service (Kapp 2007; Gombakomba 2008). Junior hospital doctors, who generally keep the hospitals running, went on strike on a number of occasions in 2007, claiming that they were among the lowest paid professionals in the country (Kapp 2007; Meldrum 2008). Surgeons and anaesthetists at one hospital apparently also staged a protest by refusing to operate, saying that their reputations were at stake when they worked without adequate supplies (Baldauf 2008). The sporadic withdrawal of labour by health care workers finally became a more entrenched problem late in 2008, when many categories of health professionals stopped coming to work altogether or started working very limited hours, due largely to incredibly low salaries (Physicians for Human Rights 2009).

HIV/AIDS care in particular has been heavily reliant on foreign aid in the most heavily affected countries. However, foreign aid in Zimbabwe has declined since the start of the crisis because of the government's mistrust of outside groups. Numerous reports have described how foreign aid assistance (in per capita terms) for HIV/AIDS in Zimbabwe is just a fraction of that of other countries in the region (Salopek 2005; IRIN news 2006; Kapp 2007; Meldrum 2008). Furthermore, such aid relies on basic health system infrastructure to make an impact. For example, the 40 000 AIDS patients whose treatment is currently funded by PEPFAR still need to collect their medication from a functioning health facility and the lack thereof can be a major impediment to the

programme (Physicians for Human Rights 2009). NGO's such as Medecins Sans Frontiers (MSF) have also struggled to maintain their operations because of strict administrative requirements (as described above), as well as the general lack of supplies (Medecins Sans Frontiers 2007). Yet other NGOs, in particular those providing hospice services, are reliant on aid agencies for basics such as food and soap, and so are unable to function properly when this vital assistance does not reach them (Baldauf 2008).

The erosion of the economy and the health system in Zimbabwe has obviously had profound effects on patient care. Those featured more commonly in media reports are outlined below:

- Would-be patients can't physically access services because of transport costs, a problem recently made more acute by a number of hospital closures (Physicians for Human Rights 2009).
- Many patients are choosing not to access care for a whole range of problems, knowing that they can't afford the user fees. Consultation fees and the cost of medicines have risen exponentially to keep pace with hyperinflation (Thornycroft 2006; Timberg 2006; Gombakomba 2008). Laboratory test results have apparently been returned to doctors labelled 'withheld until payment is made' (Timberg 2006). Even in the private sector medical aid societies have been unable to honour payments to medical practitioners (Gombakomba 2008). Premiums and benefits set in advance have been unable to sustain medical insurance due to the rises in medical fees (Business Monitor International 2008).
- When they manage to reach a health facility, patients are often required to purchase basic medical supplies in order for them to receive the necessary care or surgery. These costs are also often beyond the means of most (Baldauf 2008; Meldrum 2008).
- Complications are arising from the lack of basic health services. There have been reports of an increasing number of children with disabilities, in particular cerebral palsy, due to poor obstetric care (Meldrum 2008). The ongoing cholera epidemic, which started in August 2008, reflects both poor access to safe water and sanitation as well as an incompetent public health system (Physicians for Human Rights 2009). An update issued on 27 February 2009 put cumulative cases at 84 818 and deaths at 3 933 (Zimbabwe Ministry of Health and Child Welfare 2009).
- Many HIV/AIDS patients have stopped taking their drugs due to high costs or displacement as a result of 'Operation Murambatsvina' (Salopek 2005; IRIN news 2006; Timberg 2006; Kapp 2007). Reports have described how, a year after the urban eviction campaign, AIDS NGO's were still trying to locate many of their ART patients, fearing that most of those missing had

to discontinue treatment (IRIN news 2006). The UN Special Envoy on Human Settlements Issues in Zimbabwe also highlighted the impact that the campaign had on the HIV/AIDS response, estimating that 79 500 people over the age of 15 living with the virus were displaced (United Nations Special Envoy on Human Settlements Issues in Zimbabwe 2005). Even where drugs are free, patients face obstacles such as high fuel and transport costs (Medecins Sans Frontiers 2007).

- Patients on ART have reported missing doses, sharing drugs, selling their drugs and changing regimens due to inadequate drug supplies and poor economic circumstances, so fuelling concerns that a drug-resistant AIDS epidemic is developing (IRIN news 2006; Bodibe 2009; Physicians for Human Rights 2009).
- The scale up of ART has been slow due to a lack of health workers and drugs, leaving many in need of treatment without access. The most recent UNAIDS report on the global AIDS epidemic indicates that around 98 000 people in Zimbabwe were receiving ART treatment at the end of 2007, with this equating to just 18% of those in need (Joint United Nations Programme on HIV/AIDS 2008). Both MSF and PEPFAR have been providing treatment to a large proportion of these – 16 000 (in 2007) in the case of MSF and 40 000 (in 2008) in the case of PEPFAR (Medecins Sans Frontiers 2008; The President's Emergency Plan for AIDS Relief 2009).

4.3 Public sector strike in South Africa

Starting on the 1st June 2007 and lasting almost a month, South Africa experienced its longest and largest public-sector strike in history. The Department of Public Services and Administration estimated that on the first day of the strike nearly half a million workers downed tools, with 80% of teachers and 22% of national and provincial government workers staying away. The strike action was organised by Congress of South African Trade Unions (COSATU), a labour federation, and supported by 17 unions representing over a million public service workers. It arose following a wage dispute – the government was offering a 6% wage increase and the unions were demanding 12%. They also wanted better housing and medical allowances, and a 30% increase in the minimum annual pay for public servants.

The strike ended on the 28th June 2008 when the public service unions voted to accept the government's 'settlement offer'. This included a 7.5% wage increase, a 10% increase in the monthly housing allowance, a 30% increase in the minimum wage (benefiting 29 000 public servants), and the withdrawal of all

dismissal notices. Although schools, hospitals and public transport were all crippled by the prolonged strike action, schools were reportedly worst hit, prompting the government to put in place an 'education recovery plan'.

The South African public sector strike is classified for the purposes of this analysis as a short-term crisis because it essentially resulted in a temporary disruption to service delivery of no longer than a month. It may, however, reflect more deep-seated and long-term economic problems. An analysis of the 2007 'Winter of discontent' in 'The Nation' (Johnson 2007) suggested that, for the majority, life in socioeconomic terms has worsened. Rising unemployment, growing inequalities, increases in the cost of living, and the degeneration of health and education services have all contributed. This alerts us to the fact that such similar disruptions are likely to occur in future and may be weathered better if given some forethought.

Media reports on the June 2007 strike action documented a number of effects on the health system and its functioning. The shortage of nurses was felt most acutely, even though they were barred from striking on the grounds that they provide essential services when the government refused to accept a 'minimum service agreement'. There was a report from one hospital saying that 5 nurses were on duty to run 33 operating theatres (IRIN news 2007). At a Cape Town hospital, striking workers told the media on the first day of the strike that 25% of staff were assigned to work according to the 'minimum service agreement' and would be the only ones allowed to enter the premises (Independent online 2007). Only a few doctors went on strike, but many health workers allegedly stayed home for fear of intimidation and violence (IRIN news 2007). At a large Durban hospital the intensive care unit had to be shut down when the nurses were physically threatened (Monsters and Critics 2007). Health workers reporting for duty did not dress in white coats or uniforms in order to avoid intimidation (Sidley 2007).

The government's response to the strike in some instances resulted in further disruptions to service delivery; hundreds of health personnel were fired in the Western Cape because of their alleged participation in the strike and disregard for their responsibilities to provide 'essential services'. A news report in the British Medical Journal stated that 600 nurses received dismissal notices (Sidley 2007). The right of health workers to strike became pitched against the right of patients to access health services while the strike was in progress. The Treatment Action Campaign came out strongly in favour of the health workers and, as part of the final settlement, dismissals were withdrawn.

A number of different groups of people were engaged in helping to keep health services operational during the strike. The military (and in particular the Military Health Services) were called on to help with cleaning and nursing duties (Sidley 2007). Patient's relatives helped with basic patient care and there were reports that at one hospital AIDS centre volunteers helped to bathe and feed patients, as well as change linen (Bechtel 2007). The police helped to quell violence and intimidation outside hospitals, so that those wanting to work were able to do so (Sidley 2007).

Despite this level mobilisation, patient care suffered significantly. Some of the reported effects on patient care were that:

- Patients fearing intimidation chose to stay away from hospitals and clinics. On 13th June only 100 emergencies were admitted at Chris Hani Baragwanath Hospital in Johannesburg, compared to the up to 500 that are received on a normal day. 1000 patients visited the hospital, compared to an average of 2500 on a normal day (IRIN news 2007).
- In some instances patients could not reach hospitals. On the first day of the strike the entrance to a Cape Town hospital was blocked by protesting workers, causing long traffic queues. Police used rubber bullets and stun grenades to disperse the crowd (Independent online 2007).
- Critically ill patients had to be transferred to private facilities for treatment. In consolidating the effects of the strike, the Department of Health reported that between the 1st and the 25th of June 2007, 1136 patients were transferred. Although the private hospital sector charged the government fees substantially lower than those paid by members of medical aid schemes, this still cost R24,9 million (South African Department of Health 2007).
- Some people died as a result of the lack of ambulances or the limited services provided by hospitals during the strike (Sidley 2007). In one case a pregnant woman apparently lost her child at a Durban hospital when no one was available to operate on her (IRIN news 2007).
- Patients with HIV/AIDS and TB could not access their regular treatment because of clinic closures (Alcorn 2007; Sidley 2007). The Southern African HIV Clinicians Society in particular highlighted concerns about treatment interruptions and issued a press statement that appeared on their website and in the Treatment Action Campaign newsletter, advising patients on how they should deal with the situation (see text box).

Press statement by the Southern African HIV Clinicians Society on interrupting antiretrovirals and other HIV-related drugs (reproduced verbatim from the Treatment Action Campaign Electronic Newsletter, 12 June 2007, <http://www.tac.org.za/community/node/2153>)

The South African Public Sector strike has meant that many public sector patients with HIV may or already have had their treatment interrupted. This applies to antiretrovirals, as well as opportunistic illness treatment.

Interruption of treatment should be dealt with in the following manner:

- * Try not to interrupt treatment if at all possible. If the dispensing clinic is not functional, patients should go to their nearest GP or pharmacy with their empty medication bottles, and request a repeat prescription from a private pharmacy. This may be costly, but the strike may be over soon, and a single month of treatment may be sufficient. Generics can be safely used to decrease cost.
- * Should interruption be inevitable, stop all drugs on the same day (if in a controlled environment, nucleoside analogues can be continued for 5 days to cover the efavirenz or nevirapine 'tail'). Ensure that the person is restarted as quickly as possible. Consequences of stopping antiretroviral drugs include continued immune deterioration, so people with low CD4 counts should make every effort to restart immediately once clinics become functional again. Restart medication at prescribed doses as soon as it is available: do not increase or double doses to make up for missed medication.
- * Successful ART requires three drugs. Patients who have run out of one or two of their antiretroviral medicines should NOT continue taking the others, in order to avoid the emergence of drug resistance.
- * If the person can not afford treatment, every effort should be made to attend a functional clinic elsewhere, again with medication bottles so that the clinic staff can confirm doses and formulations.
- * Patients who require initiation of antiretrovirals may find this is delayed. This is obviously not ideal. Clinicians in the public sector will need to weigh starting antiretrovirals without the necessary support systems against continued risk of illness in the face of progressive immunosuppression.
- * Patients should be counselled not to decrease dosages so as to make medication last longer. This will increase the possibility of resistance. Dosing should remain the same, till the tablets run out.
- * Patients and caregivers should stay in telephonic contact with their public sector clinics, if possible. Some HIV clinics are running emergency dispensing services, and patients may be able to get medication in the interim.

5. Potential strategies to improve adherence and general conclusions

As stated previously, this paper aims to ultimately consider different ways to keep ART patients adherent in times of difficulty. Two key messages emerging are that we do need to be planning for and managing various crises impacting on ART delivery and that there are a number of strategies that could be considered.

Many shorter term crises can be anticipated – neither the public sector strike in South Africa nor the floods in Mozambique sprung completely unannounced. This indicates a general need for planning and preparedness. Longer term crises on the other hand, while anticipated, cannot be planned for so easily because of the chronic erosion to the health system and the long time taken to potentially restore services. In these cases, proactive management is needed to alleviate the effects of the crisis on patient treatment, care and support, as well as a carefully designed recovery plan to restore health system functioning as quickly as possible.

Just as shorter term crises will be easier to weather than longer term crisis, so too will localised disruptions when compared to widespread upheaval. Careful management and some reorganisation of existing services may suffice with localised disruptions. Widespread upheaval on the other hand, may benefit most from an increased involvement and co-ordination of health sector partners, be they private, donor, NGO or faith based.

One of the most important requirements for proactive management of crises in health care delivery is access to information. It is striking how little is actually reported on concerning disruptions to the ART programmes in South Africa, Zimbabwe and Mozambique, and most likely this is because the data is not available. Health information systems need to be sensitive enough to alert managers to change (such as when fewer patients start presenting for follow up or drug shortages are imminent) and detailed enough to give a fairly complete picture of what is happening. In situations where large numbers of people are displaced or simply mobile, patient information systems should ideally also facilitate patient's collection of drugs from various locations. There is scope to look at innovative communication mechanisms such as cell phones.

In crisis situations there is always a need to prioritise, however this often results in immediate concerns eclipsing those with longer-term consequences. HIV/AIDS is by nature a long wave disease and failure to maintain treatment

coverage will not immediately result in large numbers of deaths like the spread of many infectious diseases (such as cholera). Unfortunately this does not necessarily mean that the consequences will be less severe – it only means they will play out for many years to come. Responding strategically to the various threats posed by a crisis therefore calls for careful consideration and co-ordination, rather than a knee-jerk response. The comparative advantages of various health sector players need to be utilised to their fullest potential, to ensure that a range of concerns are addressed concurrently.

A number of strategies were considered or employed to keep ART patients on treatment during the strike in South Africa, the protracted political and economic upheaval in Zimbabwe and the floods in Mozambique. Unfortunately many of these efforts may have been ‘too little, too late’ and there has been almost no evaluation as to their effectiveness. Nonetheless, they do point to a number of simple measures that could be taken in the future to prepare for and manage a range of eventualities. Some of the more obvious points are highlighted below:

1. Good patient education is essential. Thorough ART adherence counselling should include some level of discussion on what to do in case of being unable to access drugs. Treatment interruptions are clearly undesirable, but if properly managed may be less likely to result in drug resistance than practices such as sharing drugs, reducing drug doses or taking only one or two types of drugs.
2. Clinicians should be trained in managing treatment interruptions and kept informed about potential disruptions to service delivery. If drugs stock-outs are a problem but patients are still able to access health services, then clinicians can stagger the time at which different drug classes are stopped to avoid the development of NNRTI resistance in particular. If clinicians are aware that services may be temporarily disrupted (such as during flood times), then it may be appropriate for them to dispense drug supplies that can last for more than the usual one-month period.
3. The private health sector, donors and NGOs can all help in various ways to keep ART patients adherent on treatment in times of crisis. If these partners are engaged and prepared prior to the time, then their assistance is more likely to be effective.
4. Support for ART patients may need to be more holistic during widespread crises in particular. In other words, when the socio-economic circumstances of households become compromised, then simply ensuring ongoing service delivery may not be sufficient to maintain ART adherence. In such cases extra support may be required to manage the indirect costs of

seeking care, such as transport costs, and to avoid a situation where people are having to trade-off basic necessities.

In conclusion, ART programmes in sSA will in the foreseeable future always be challenged by a range of different crises. How we plan for and manage these crises could strongly influence treatment outcomes in the years and decades to come. This paper provides some initial insights as to what the longer term effects of crisis-induced treatment interruptions might be and how we might help to alleviate these.

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