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Effects of Political Conflict Induced Treatment Interruptions on HIV Drug Resistance

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Abstract

34 million people worldwide were living with the Human Immunodeficiency Virus (HIV) by the end of 2010. Despite significant advances in antiretroviral therapy (ART), drug resistance remains a major deterrent to successful, enduring treatment. Unplanned interruptions in ART have negative effects on HIV treatment outcomes including increased morbidity and mortality, as well as development of drug resistance. Treatment interruptions due to political conflicts, not infrequent in resource-limited settings, result in disruptions in health care, infrastructure, or treatment facilities and patient displacement. Such circumstances are ideal bases for ART resistance development, however there is limited awareness of and data available on the association between political conflicts and the development of HIV drug resistance. In this review we identify and discuss this association and review how varying ART half-lives, genetic barriers, different HIV subtypes, and archived resistance can lead to lack of medication effectiveness upon post-conflict resumption of care. Optimized ART stopping strategies as well as infrastructural concerns and stable HIV treatment systems to ensure continuity of care and rapid resumption of care must be addressed in order to mitigate risks of HIV drug resistance development during and after political conflicts. Increased awareness of such associations by clinicians as well as politicians and stakeholders is essential.

Keywords

Treatment Interruption; Unplanned; Resistance; Political Crises; NNRTI Tail

Introduction

HIV affects 34 million people worldwide of whom over 68% live in Sub-Saharan Africa[1]. Advances in treatment for HIV, specifically the implementation of highly active antiretroviral therapy (HAART), have significantly decreased HIV-associated morbidity and mortality[2]. Evolution of ART resistance remains a major concern in the management of HIV-infected patients around the world, resulting in treatment failure and limited subsequent therapy options[3].

HIV care in developing countries is intertwined with and negatively affected by infrastructural concerns such as lack of electricity, food insecurity, limited housing availability, and unsafe drinking water[4]. Situations leading to these concerns can be related to uncontrollable conditions including nature-based weather disasters, fires, or earthquakes; but also to modifiable, human-caused situations such as wars and political

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conflicts. Many such conflicts have occurred in the developing world, including over 300 with at least 100 casualties just between 1995 and 2009[5]. Some examples of major conflicts include the Ugandan war in the 1980's[6], the El Salvadorian civil war in 1980–92[7], the Rwandan refugee crisis in the mid-1990s[8], and the Kenyan post-election crisis in 2007–8[9]. Reports of the consequences of these conflicts on the people they affect have focused primarily on loss of life due to violence, loss of property, and the political ramifications[10]. Comprehensive understanding of the specific implications on health in general and HIV-infected individuals in particular is lacking.

Negative outcomes of political conflicts may have significant effects on HIV patient care. In addition to mental health outcomes that may disrupt pill-taking routines, HIV-infected patients may experience interruption of ART due to loss of or inability to adequately store medications, inability to attend clinics and pharmacy stock-outs[11–13]. A resulting treatment interruption, whether planned[14,15] or unplanned, is a significant problem in HIV therapy and is not recommended[16].

In this review we make the linkage between unplanned ART interruptions induced by political conflicts and their effect on HIV-infected patients. We discuss conflicts and their effects on treatment interruption; why interruptions are not favorable in HIV care and how they can result in development of ART resistance; the mechanisms of resistance pathways during and after treatment interruption; and recommendations to prevent them. Ultimately, the combined effects of consistently available HIV treatment systems, infrastructure stabilization and optimized ART cessation strategies (if needed), together with increased political insight, will minimize the harmful effects of political conflicts on HIV patient care. Though uncontrollable by patients, such conflicts are programmatically modifiable.

Political Conflicts, Treatment Interruption, and Health Care Impact

Conflicts Occur in Resource Limited Settings

Political conflicts occur all too frequently in resource limited settings, unfortunately producing almost unavoidable turmoil resulting in violence and negative health consequences[10]. Conflicts often have a basis in economics and inequality, destabilizing communities by slowing economic development and increasing insecurity, and therefore have a profound effect in the developing world[17]. These factors tend to be weak in developing countries even during unconflicted times, and conflict thus has an exacerbating effect[17]. In developing countries conflicts tend to include such tactics as disruption of agricultural production, systematic destruction of service infrastructure, sabotage of water and electrical supplies, poisoning of wells, killing of livestock, burning of harvests, elimination of markets, and confiscation of property, tactics which are less often used in developed world conflicts[17]. All of these aspects combine to create a destructive cycle of poverty, conflict, under-development, and lack of economic growth.

There are many examples of political conflicts in the developing world, some more studied than others [6–9,13,18,19]. Such conflicts led to fatalities, displacement of health professionals and the affected populations; discontinuation of health services and treatments; decrease in the health budgets, life expectancy and immunization rates; disease outbreaks from a lack of sanitary food and water sources; significant increases in childhood malnutrition, morbidity, and morality; and shortages in basic supplies and medications.

Conflicts can Lead to Treatment Interruptions

Episodes of political insecurity in developing countries can quickly destabilize ART programs and lead to treatment interruptions[20]. Conflicts can limit drug availability due to supply chain interruptions and personnel displacement[21]. At any time lack of available

and affordable transport can be a major deterrent to access to care[22]. Thus during times of conflict, exacerbated lack of infrastructure and unsafe travel environments can further deter patient visits to medical clinics, limiting access to prescribed drugs. Treatment may also be interrupted due to displacement of patients owing to destruction of homes, violent environments, or lack of necessities[13]. Furthermore, some patients may experience depression or hopelessness following a conflict and its consequences, de-motivating them from seeking or continuing care[13]. Data on HIV treatment interruption following political crises are limited. In Nairobi, Kenya, researchers found that treatment interruption was 71% higher during the 2007–8 political conflict compared to unconflicted times[12]. We suspect these odds were even higher in Eldoret and surrounding Kenyan rural areas, where the violence was more severe. Despite a lack of HIV-specific data, the detrimental health consequences of conflicts, particularly in the developing world, have been established.

Treatment Interruption and HIV Drug Resistance

Treatment Interruptions are not Favorable in HIV Infection

Treatment interruptions decrease the success of HIV therapy, resulting in increased mortality and morbidities such as opportunistic infections [14,15]. The effects of *structured*, or planned, treatment interruptions have been prospectively and retrospectively studied as potentially beneficial treatment strategies, mainly by (i) a timed-cycle strategy in which ART is stopped for a fixed time period; or (ii) a CD4-guided strategy in which treatment is stopped at a predetermined high CD4 count and restarted at a predetermined low CD4 count [14,15]. A systematic review of structured interruptions demonstrated lack of benefit in people with unsuppressed HIV infection and evidence of possible harm in suppressed patients [14,15].

Table 1 demonstrates major studies of the effects of structured ART interruptions on the immune system (CD4-cell counts), HIV viral load, and treatment outcome. The majority of studies show negative effects on treatment outcome. Though some conflicting data exist, plausible explanations for this discordance include usage of CD4 count as outcome, which may not be directly applicable to treatment outcome in interruption circumstances[23,24]; cessation of treatment arms before study endpoint due to large numbers of failures, which may have left only more moderate groups for analysis and conclusions[23–26]; and minimal follow-up times, which may not have captured the majority of failures[27].

Unstructured treatment interruptions (Table 2) consistently have unfavorable outcomes and should be avoided whenever possible, though studies thus far have focused on interruption during the normal course of treatment as opposed to during conflicts. In such times, more detrimental outcomes are expected, concerning abruptness, length, totality and associated circumstances and stress. Notably, no major cohort studies on unstructured ART interruption have been completed in the developing world.

Treatment interruptions are currently not recommended in HIV patient management [28,29]. Some studies have stated that interruptions can be considered favorable to a treatment plan by relieving negative side effects of medications, alleviating some cost of treatment, or allowing resistant virus to revert to wild type form [25,30]. However, any advantages do not outweigh the risks of resistance development, limitation in subsequent regimens and disease progression, and therefore treatment interruption is not part of recommended HIV-care [31].

Treatment Interruptions Lead to HIV Drug Resistance

HIV is characterized by error prone reverse transcription and high production and turnover rates[32]. The combination of these mechanisms in the presence of recombination leads to numerous mutations that are generated during the viral life cycle, resulting in a large and

diverse viral population of quasispecies[33]. Though as little as a single amino acid substitution can produce high levels of drug resistance[34], HAART reduces the probability of resistance evolution by incorporating several drug classes that are detrimental to HIV via different mechanistic actions, thus ensuring treatment success.

Interruptions in HIV treatment can have varying harmful effects on development of drug resistance with serious implications for future treatment[35]. Upon inadequate ART exposure, such as may occur with non-adherence or during a conflict-related unplanned treatment interruption, viral variants with mutations that confer drug-specific selective advantage may become more prevalent[36]. In such a scenario, upon resumption of care and reinstitution of ART, the now-predominant viral population will be resistant to the HAART regimen and treatment failure will follow[36]. Non-nucleoside reverse transcriptase inhibitor containing regimens, the vast majority of first-line HAART in resource limited settings, are often the drug class most susceptible to the development of drug resistance[37]. Such regimens, which are usually continued upon post-interruption resumption of care, may no longer be effective if resistance has developed, resulting in a higher risk of morbidities and mortality [16]. Although it is necessary to change regimens to second- or third-line regimens for patients who have developed such resistance, such options and the monitoring capacity to make such decisions, are often restricted in resource limited settings.

A window into the potential effects of treatment interruption on the development of drug resistance can be derived from a specific case – the use of single dose nevirapine to prevent mother to child HIV transmission. This mode of therapy, given to mother and baby before and after birth, respectively, has been used in resource limited settings since the HIVNET 012 study demonstrated in 2003 a 41% reduction in HIV vertical transmission [38]. Though the World Health Organization removed single dose nevirapine from their guidelines for prevention of mother-to-child transmission in resource limited settings in 2010, this preventative treatment continues to be used in some developing countries[3]. During the few days after ingestion of single dose nevirapine, HIV is exposed to decreasing blood levels of this medication, during which drug resistance develops, as can occur after treatment interruption. Further mechanistic details are provided below. As a result, the use of single dose nevirapine can produce resistance to nevirapine in as many as 25–75% of women treated with it[39]. The implications of nevirapine resistance can be daunting as it limits use of subsequent non-nucleoside reverse transcriptase inhibitor containing HAART regimens, which are the mainstay of first-line ART in the developing world[40].

Mechanisms of Drug Resistance Following Treatment Interruptions

Various biologic mechanisms may be related to the process of drug resistance development following treatment interruptions. As outlined below, some of them are more understood than others and their integration and occurrence in resource limited settings may be detrimental.

Antiretroviral Drug Levels and Half Lives—Varying half-lives of ARTs significantly affect patient drug levels when therapy is interrupted[41]. When drugs given simultaneously as part of HAART have significantly different plasma half-lives, their metabolism and clearance times differ[42]. As a result, during simultaneous cessation of all drugs, as occurs in unplanned treatment interruptions, drugs with longer half-lives remain detectable for a prolonged period of time, resulting in a functional mono- or dual-therapy[43]. Such circumstances, which are somewhat similar to the single dose nevirapine circumstances discussed above, significantly increase the likelihood of drug resistance development and jeopardize current and subsequent ART. The two main factors that influence the development of resistance in this scenario are[43]: (1) time that a single drug remains

detectable at a concentration sufficient for viral replication; and (2) genetic barrier of the drug.

Time of Drug Detectability

The World Health Organization-recommended first-line ART in resource limited settings includes two nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir or zidovudine and lamivudine or emtricitabine), and one non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine)[3]. In second line recommended ART protease inhibitors (atazanavir/ritonavir or lopinavir/ritonavir) replace the non-nucleoside reverse transcriptase inhibitor[3].

The plasma half-lives of these drugs, listed in Table 3, demonstrate clear differences[43]. Pharmacokinetically, after one half-life 50% of the drug is eliminated from the body and only 50% remains. Similarly, after two half-lives, 75% remains and after five half-lives just over 3% remains, and as a rule of thumb it has been virtually eliminated from the body[44]. As seen in Table 3, non-nucleoside reverse transcriptase inhibitors have lengthy half-lives therefore remain in the body days to weeks longer than nucleoside reverse transcriptase inhibitors upon abrupt treatment cessation. This functional mono-therapy (or 'tail') exposes the virus to decreasing drug levels, increasing the likelihood of resistance evolution. The longer the 'non-nucleoside reverse transcriptase inhibitor tail', the more significant are the potential effects of the treatment interruption [30], similarly to the effect after single dose nevirapine. Though less studied, differing protease inhibitor and nucleoside reverse transcriptase inhibitor half-lives can potentially have similar consequences.

Drug Genetic Barrier

The genetic barrier of a drug refers to the number of mutations that need to occur in the viral RNA in order to render a drug ineffective, while maintaining viral fitness[45]. Non-nucleoside reverse transcriptase inhibitors such as efavirenz and nevirapine have particularly low genetic barriers, and even one mutation is enough to cause high-level resistance[46]. For example, a single amino acid mutation of lysine (K) to asparagine (N) at the HIV reverse transcriptase position 103 (K103N) leads to high level resistance to both nevirapine and efavirenz[46]. Other ARTs, such as most nucleoside reverse transcriptase inhibitors that are part of first-line regimens, and protease inhibitors that are part of second-line regimens, have higher genetic barriers to resistance. Upon treatment interruption differences in half-lives and genetic barriers of medications of one HAART regimen can result in drug resistance evolution. This most likely will initially be to non-nucleoside reverse transcriptase inhibitors for reasons discussed above, however, due to lack of close virologic monitoring in resource limited settings[47], resistance can subsequently develop to other drugs that are part of the regimen.

The Subtype Variable—Nine group M subtypes, several sub-subtypes, and numerous recombinant forms are responsible for the vast majority of HIV-1 global infections[48]. Subtype B is the most prevalent in the developed world while non-subtype B variants predominate globally [48,49]. The majority of research and development of ART has been in industrialized countries, and therefore knowledge of drug resistance pathways in subtype B is most complete, while data are still being collected for non-B subtypes. Despite significant similarities, there is growing evidence on inter-subtype differences in drug resistance development [50]. This is reasonable as different subtypes and recombinant forms are genetically and phylogenetically distinct throughout their genome, including the *pol* gene from which the majority of the data are derived [51,52]. Differences in the development of drug resistance after exposure to single dose nevirapine have been reported among HIV-1 subtypes, involving increased susceptibility of individuals infected with

subtype C to nevirapine resistance compared to those infected with subtypes B or D[53]. Subtype specific effects on the evolution of drug resistance following treatment interruptions are not known, but the analogy to single dose nevirapine as well as the abundance of viral diversity worldwide is concerning and mandates close follow-up[52].

Archived Resistance—Current ART can suppress but not eradicate HIV[54]. A primary cause for this unfortunate circumstance is the incorporation of replication-competent pro-viral HIV DNA into human DNA in cells such as peripheral blood mononuclear cells. The viral DNA remains dormant at sub-detectable levels even during effective ART[55]. If that archived virus was previously exposed to low drug levels, as occurs immediately following a treatment interruption, it may contain drug resistance mutations. Consequently, that drug resistant variant may be permanently incorporated into human DNA, and re-emerge at later times[56]. In this context, restarting the same HAART regimen upon post conflict resumption of care, as is usually the case in resource limited settings, can provide selective advantage to that viral variant, which can then reemerge and lead to treatment failure.

Guidelines for Stopping ART

Several global and United States based agencies publish guidelines on HIV treatment, prevention, and care, including the World Health Organization[3], the USA Department of Health and Human Services[28] and the International AIDS Society-USA[29]. The recommendations regarding treatment interruptions as incorporated in these and other guidelines are given in Table 4. The World Health Organization as well as the international organization Doctors Without Borders[57] guidelines currently do not contain any recommendations regarding the interruption of ART. The thorough Department of Health and Human Services guidelines recommend against planned interruptions but provide conditional guidelines for short-term interruption (<2–3 days) in regimens with similar half-lives, in line with the above discussion. International AIDS Society-USA has issued brief guidelines for ART stopping procedures, but overall recommend against any treatment interruption. Organizations in Europe such as the British HIV Association[58] and European AIDS Clinical Society[59] have issued similar blanket recommendations against interruption. Finally, the Canadian HIV Trial Network (most recently issued 13 years ago) gives vague recommendations instructing physicians to counsel patients on any interruption[60].

Taken together, treatment interruptions are generally not recommended by guidelines that address them, due to both known and unknown risks and to unclear optimal stopping strategies. Such data are essential and must be provided to policy makers and guideline writing committees. No recommendations have as yet approached the subject of interruption in the context of political conflicts.

Conclusions and Path Forward

Political conflicts occur far too frequently in developing countries and their long-term implications are not always considered a top priority. Regardless of the cause, the association between conflict and health-care consequences in general and HIV in particular, is understudied and is not often considered in real-time decisions during conflicts. The linkage between conflicts and their potential consequences for the HIV pandemic is critical to understand and apply. This review emphasizes this linkage, its circumstances and the importance of understanding potential complications and their implications.

Political conflicts destabilize health care systems, which can lead to disruptions in access to HIV care and interruptions of ART. Whether due to limited drug availability, lack of

infrastructure, unsafe travel conditions, or displacement due to violence or home destruction, the potential results include evolution of drug resistance, increased morbidity, and eventually mortality. Factors discussed in this review, such as ART half-lives, genetic barriers, viral diversity, and archived resistance, can lead to harmful outcomes upon resumption of care after conflict-induced interruption.

Despite confirmed negative effects of treatment interruptions, in circumstances of political conflicts they are often unavoidable. Research is therefore needed to determine optimal ART stopping and restarting strategies for patients who find themselves in situations of unplanned interruptions. Such strategies should take into account the regimen prior to interruption, medication half-life, replacement therapy options, close monitoring, and perhaps, if feasible, resistance testing upon resumption of care prior to re-starting therapy and close monitoring thereafter. An additional strategy should encompass implementation of contingency treatment plans in developing countries addressing factors like consistent drug supplies, improved patient follow-up, and education for health care providers, implementation of viral load monitoring and resistance testing, and availability of multiple treatment regimens. In particular, relief agencies would benefit from an increased focus on identifying HIV positive victims for intensive follow up during times of crisis. Patient concerns for transport and access to clinics including road conditions and transport safety, as well as water and food safety and availability, must also be addressed. Implementing cohort studies on unstructured ART interruption in the developing world is important.

In addition to research, education and patient and provider awareness and preparedness, policy makers and politicians throughout the world can directly impact the lives of HIV-infected patients by avoiding conflicts and their consequences. Perhaps increased awareness of this long-term and often overlooked consequence will provide opportunity for re-consideration in similar future circumstances. Given the severity of the potential effects discussed here, it would be advantageous for political leaders to begin a preemptive discourse on prevention of violence, and for treatment programs a contingency planning for HIV patients before an imminent conflict.

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Table 1

*: Major Studies† of Structured HIV Treatment Interruption

Study	Location(s), Year(s)‡	Total (Interruption) No. of Patients	Interruption Criteria	Follow-Up (Years)	Major Results
Major Studies Demonstrating a Disadvantage of Structured HIV Treatment Interruption					
Structured: CD4 Guided§					
SMART[61]	Copenhagen, London, Sydney 2002–2006	5472 (2720)	Stop at CD4>350, restart at CD4<250; repeat throughout study	1.3	OI or Death 3.3 /100 person-years in interruption group; 1.3 in controls (hazard ratio 2.6)
LOTTI[62]	Italy **	329 (165)	Stop; restart at CD4≤350, stop at CD4>700; repeat throughout study	4.2	OI/death/admission 12% in interruption group; 12% in controls (OR 1.05)
TRIVACAN[63]	Ivory Coast, 2002	326 (216)	Stop at CD4>350, restart at CD4<250; repeat	1.7	Severe Morbidity 17.7 /100 person-years in interruption group; 6.7 in controls (p=0.001)
TRIESTAN[64]	Netherlands **	71 (46)	Stop; restart at CD4<300, one cycle	0.9	VL 4.6 log in interruption group; undetectable in controls
Structured: CD4/VL Guided§					
TIBET[65]	Spain, Italy 2001–2002	201 (100)	Stop; restart at VL>100,000 or CD4<350, repeat 2 years	1.8	Median CD4 520 in interruption group; 789 in controls (p<0.001)
Leon et al.[66]	Barcelona, Spain 2002–2005	121 (83)	Stop; restart at VL>50,000 or CD4<350, repeat 2 years	2	Median CD4 count significantly lower than baseline in interruption group (p<0.0001); not lower in controls (p=0.68)
Structured: Timed Cycle§					
DART[67]	Uganda, Zimbabwe 2004–2006	813 (408)	12 weeks off/on therapy throughout study	1	First WHO stage 4 events 6.4/100 person-years in interruption group; 2.4 in controls (p=0.007)
TRIVACAN[31]	Ivory Coast, 2002	422 (315)	2 months off/4 months on therapy, repeat throughout study	2	14.6% CD4<350 in interruption group; 5.6% in controls (LBCI of the difference = 13.9)
Major Studies Inconclusive on Outcomes of Structured HIV Treatment Interruption					
Structured: CD4 Guided§					
BASTA[68]	Italy 2003	69 (46)	Stop; restart at CD4≤400, stop at CD4>800, repeat throughout study	64 Weeks	Proportion with CD4>400 not statistically different
Structured: Timed Cycle§					

Study	Location(s), Year(s)‡	Total (Interruption) No. of Patients	Interruption Criteria	Follow-Up (Years)	Major Results
Major Studies Demonstrating a Disadvantage of Structured HIV Treatment Interruption					
Structured: CD4 Guided§					
Canadian HIV Trials Network 164[27]	Canada 2001–2004	147 (68)	Stop failing regimen for 12 weeks; start salvage regimen; one cycle	3 Months	No increase in proportion with sustained VL<50
Reynolds et al.[26]	Kampala, Uganda 2002–2005	135 (Arm 1: 32; Arm 2: 52)	**Arm 1:** 7 days on/7 days off, repeat throughout study **Arm 2:** 5 days on/2 days off, repeat throughout study	72 Weeks	**Arm 1:** 31% failure, closed **Arm 2:** 12% failure in interruption group; 22% in controls
Structured: CD4 Guided and Timed Cycle§					
Staccato[25]	Thailand, Switzerland, Australia 2003–2005	430 (284)	**Arm 1:** Stop; restart at CD4<350 for ≥12 weeks, stop at CD4>350, repeat throughout study; **Arm 2:** 1 week on, 1 week of; repeat throughout study	1.8 Years	**Arm 1:** 91% reached VL<50 in interruption group; 92% in controls (p=0.90) **Arm 2:** Stopped due to high failure rate
HIV-NAT[23,24]	Thailand 2001–2004	74 (26, 23)	**Arm 1:** Stop; restart for ≥ 12 weeks if CD4<350 or drop >30% from baseline; Stop if CD4>350 or up ≥70% from baseline, repeat for 2 years **Arm 2:** 1 week on/1 week off, repeat for 2 years	108 Weeks	**Arm 1:** 100% CD4 ≥350 in interruption group; 96% in controls, median CD4=489 in interruption; 661 in controls, (p=0.03); **Arm 2:** Discontinued due to high rate of failure

*Table is sorted by descending number of patients within each category. Abbreviations: No.-number, OI- opportunistic infections, OR- odds ratio, VL- viral load, WHO- World Health Organization, LBCI- lower bound of 95% confidence interval.

†Studies included (i) had a control group with no treatment interruption; (ii) had >40 adult participants; (iii) were not limited to patients with multi-drug resistance; and (iv) were completed after 2000.

‡Year(s) listed are dates of conduction of the study.

§See text for additional details.

**Dates not available.

Table 2

[††]: Major Studies[‡‡] of Unstructured HIV Treatment Interruption

Study	Location(s), Year(s) [§§]	Total (Interruption) No. of Patients	Interruption Criteria	Follow- Up (Years)	Major Results
EuroSIDA[69]	Europe, Argentina, Israel 1997–2005	3811 (879)	Interruption of ≥3 months	5.5	Incidence of AIDS or Death was 1.14 times more likely in patients who experienced interruption (p=0.37)
I.Co.N.A.[70]	Italy 1997–2004	3142 (721)	Interruption of ≥12 weeks	0.8	Patients who experienced interruption had a 2.75 times higher hazard of HIV clinical progression (p=0.03)
Swiss HIV Cohort[71]	Switzerland 1996–2008	2491 (1271)	Interruption of ≥1 month (2 control groups: Intermittent or constant VL ≥1000)	8	Median CD4=427 in interruption group; 525 or 645 in controls; 63% CD4>350 in interruption group; 76% or 87% in controls, (p<0.001)
Knobel et al.[72]	Barcelona, Spain 1996–2007	540 (231)	Interruption of ≥3 days	8.3	Patients who experienced interruption had a 1.39 times higher hazard of treatment failure (CI 1.04–1.85)
Wolf et al.[73]	Germany [***]	339 (133)	Interruption of ≥2 weeks	2	CD4 no change from baseline in interruption group; significant increase in controls (<0.001)
Ncaca et al. (43)	Cape Town, South Africa 2002–2007	244 (21)	Interruption of ≥27 days	4.4	Odds of failure increase 5.65 times (CI 1.4–22.85)

[††]Table is sorted by descending number of patients within each category. Abbreviations: No.-number, VL- viral load, IRR- incidence rate ratio, CI- 95% confidence interval.

[‡‡]Studies included (i) had a control group with no treatment interruption; (ii) had >40 adult participants; (iii) were not limited to patients with multi-drug resistance; and (iv) were completed after 2000.

[§§]Year(s) listed are dates of conduction of the study.

[***]Dates not available.

Table 3

†††: Plasma Half-Lives of WHO-recommended First and Second-Line Antiretroviral Therapy

Plasma Half-Lives (hours)	
NRTIs	
Lamivudine	5–9
Zidovudine	0.5–3
Emtricitabine	8–10
Tenofovir	12–15
NNRTIs	
Efavirenz	40–100
Nevirapine	25–60
PIs	
Atazanavir	4–24
Lopinavir	5–6
Ritonavir	3–8

†††Abbreviations: NRTIs- nucleoside reverse transcriptase inhibitors, NNRTIs- non-nucleoside reverse transcriptase inhibitors, PIs - Protease Inhibitors.

Table 4

###: Guidelines for Treatment Interruption of ART

Guideline; References	Interruption Category			
	Planned short term	**Planned long term**	**Unplanned§§§**	**Regimen containing EFV/NVP**
United States DHHS [28]	Similar half-lives: Hold all drugs in regimen Varying half-lives: Not recommended	Not recommended	Hold all drugs in regimen	Optimal interval between stopping EFV/NVP and other ART not known (1 to >3 weeks); Alternative strategy: Replace NNRTI with PI before interruption (optimal time not known, up to 4 weeks)
IAS-USA[29]	Not Recommended			Half-lives of all drugs in the regimen should be considered and staggered stopping techniques should be utilized
Canadian HIV Trials Network [60]	Continuous treatment is beneficial, however quality-of-life issues, including drug intolerances or toxic effects, must be considered. Consult with physician before any interruption.			No recommendations
BHIVA[58]	Not Recommended			
EACS[59]	Not Recommended			
WHO[3]	Interruption Not Addressed			
MSF[57]	Interruption Not Addressed			

###Abbreviations: DHHS: Department of Health and Human Services, ASHM- Australian Society for HIV Management, IAS-USA- International AIDS Society USA, BHIVA- British HIV Association, EACS- European AIDS Clinical Society, WHO- World Health Organization, MSF- Médecins Sans Frontières (Doctors Without Borders), EFV- efavirenz, NVP- nevirapine, NNRTI- non-nucleoside reverse transcriptase inhibitor, PI- protease inhibitor.

§§§Due to toxicity or inability to take medications