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Systematic Review

Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review

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Summary

OBJECTIVE To characterize the frequency, reasons, risk factors, and consequences of unstructured anti-retroviral treatment interruptions.

METHOD Systematic review.

RESULTS Seventy studies were included. The median proportion of patients interrupting treatment was 23% for a median duration of 150 days. The most frequently reported reasons for interruptions were drug toxicity, adverse events, and side-effects; studies from developing countries additionally cited treatment costs and pharmacy stock-outs as concerns. Younger age and injecting drug use was a frequently reported risk factor. Other risk factors included CD4 count, socioeconomic variables, and pharmacy stock outs. Treatment interruptions increased the risk of death, opportunistic infections, virologic failure, resistance development, and poor immunological recovery. Proposed interventions to minimize interruptions included counseling, mental health services, services for women, men, and ethnic minorities. One intervention study found that the use of short message service reminders decrease the prevalence of treatment interruption from 19% to 10%. Finally, several studies from Africa stressed the importance of reliable and free access to medication.

CONCLUSION Treatment interruptions are common and contribute to worsening patient outcomes. HIV/AIDS programmes should consider assessing their causes and frequency as part of routine monitoring. Future research should focus on evaluating interventions to address the most frequently reported reasons for interruptions.

keywords HIV, unstructured treatment interruption, antiretroviral therapy

Introduction

Antiretroviral therapy (ART) has dramatically reduced HIV-associated mortality and morbidity in high- and low-income countries (Palella *et al.* 1998; Egger *et al.* 2002; Jahn *et al.* 2008; Floyd *et al.* 2010; Mahy *et al.* 2010). Treatment outcomes reported from cohort studies and clinical trials have improved over time as a result of improved drug efficacy, reduced toxicity, and simplified treatment through reduced pill burden and dosing intervals (Boyd 2009). Despite these improvements, consistent adherence and uninterrupted treatment remain major challenges (Lazo *et al.* 2007; Byakika-Tusiime *et al.* 2009; Lima *et al.* 2009; Glass *et al.* 2010; Bastard *et al.* 2011).

Ensuring high levels of adherence is desirable for the treatment of any chronic conditions (Jackevicius *et al.* 2002; Kopjar *et al.* 2003; Cramer 2004; Osterberg & Blaschke 2005) but is particularly important for treatment of HIV in resource-limited settings, where less robust regimens are used and an extremely high level of adherence (>95%) is required to prevent the development of drug resistance (Bangsberg *et al.* 2006). There are many challenges to maintaining such high levels of adherence (Mills *et al.* 2006; Nachega *et al.* 2010). Among these, treatment interruptions are an inconsistently reported yet common phenomenon in clinical practice, often occurring as a result of treatment fatigue or in an attempt to minimize side-effects. Common toxicities such as lipodystrophy and metabolic side-effects related to prolonged use of ART may improve when treatment is stopped (Tuldra *et al.* 2001; Mocroft *et al.* 2005; Mussini *et al.* 2005; Calmy *et al.* 2007). However, the majority of individuals who discontinue treatment only do so temporarily, as they experience a rapid decline in CD4 count and increase in viral load

following discontinuation of therapy (Poulton *et al.* 2003; Skiest *et al.* 2004; El-Sadr *et al.* 2006; Sungkanuparph *et al.* 2007).

The potential for provider-directed, structured treatment interruptions as a way to limit antiretroviral exposure (and therefore both toxicities and costs) was abandoned after randomized trials and cohort studies found an increased risk of opportunistic infection and death (El-Sadr *et al.* 2006; Mugyenyi *et al.* 2008; Seminari *et al.* 2008). Nevertheless, patient-initiated unstructured treatment interruptions are a reality of routine clinical care and have been reported in both developed (Holkmann Olsen *et al.* 2007) and developing country settings (Kranzer *et al.* 2010).

To better characterize the frequency, reasons, risk factors, and consequences of unstructured treatment interruptions in routine clinical practice, we conducted a systematic review of available studies reporting on unstructured treatment interruptions.

Methods

Criteria for selection of studies

We aimed to identify studies reporting on unstructured ART treatment interruptions in clinical practice. Unstructured treatment interruption was defined as discontinuation of all ART drugs for any period of time, after which treatment was resumed. We considered that any interruption was undesirable, and thus did not limit our search to specific causes or durations. We excluded studies reporting on structured treatment interruptions, defined as physician-initiated, cyclical interruptions guided by CD4 count or viral load. We also excluded studies only reporting on patients experiencing virologic failure. We included both cross-sectional and cohort studies, but excluded editorials, case studies, case reports, and reviews.

Search strategy

We searched three electronic databases for primary studies: Medline, Embase, and Global Health using the compound search strategy summarized in Table S1 and searched the bibliographies of retrieved articles for additional studies. Our search was limited to studies published and conducted from 1996 (the time when highly active ART became available) until the end of the search period (March 2011). We also searched for conference abstracts from all conferences of the International AIDS Society (April, 1985–July, 2010), and all Conference on Retroviruses and Opportunitistic Infections (January, 1997–February, 2010) and the PEPFAR implementers meeting 2007–2009. No language restriction was applied.

Study selection and data extraction

Studies were entered into an electronic database (EndNote X1) to screen potentially eligible studies by title and abstract according to our pre-defined inclusion and exclusion criteria. Full-length articles of all studies considered eligible upon initial screening were obtained and reviewed for eligibility; conference abstracts were screened first by title, then by full abstract. All reviews were carried out independently, in duplicate. After agreeing on eligibility, we abstracted the following information using a standardized extraction form: definitions of treatment interruption, frequency and duration of interruption, reasons, risk factors, consequences of treatment interruption, and proposed interventions. Whenever required, we attempted to contact study authors for clarification by email.

Finally, we assessed full articles for determinants of methodological quality using a pre-defined assessment framework. The following factors were assessed: definition and objectivity of treatment interruption provided, appropriateness of the statistical analysis. Studies investigating consequences or treatment failure (e.g. mortality or viral rebound) were assessed for adjustment for potential confounding and use of objective outcome measures.

Results

Characteristics of included studies

The study selection process is summarized in Figure 1. Our initial search yielded 813 potentially relevant publication and 577 potentially relevant conference abstracts, from which 47 publications and 23 abstracts were considered eligible for inclusion. Three studies considered potentially eligible were excluded because it was unclear whether patients restarted treatment (i.e. interruption) or not (i.e. discontinuation); authors were contacted but did not provide clarification (Berenguer *et al.* 2004; Braitstein *et al.* 2007; Ayuo *et al.* 2008). Sixteen studies were from Africa, 14 from North America, two from Australia, one from South America, two from Eastern Europe, three from Asia, and 32 from Europe. The majority of studies (63) reported results of treatment interruptions in adults from the general population; of the remainder, two studies were among children, one was among adolescents, one was among injecting drug users, one was among men who have sex with men, one was among recurrent prisoners, and one was among women. We judged the methodological quality of studies included as full-length articles to be moderate: a third of studies (15/47) provided a definition and objectivity of treatment interruption; almost all (46/47) used an appropriate statistical analysis approach, and where

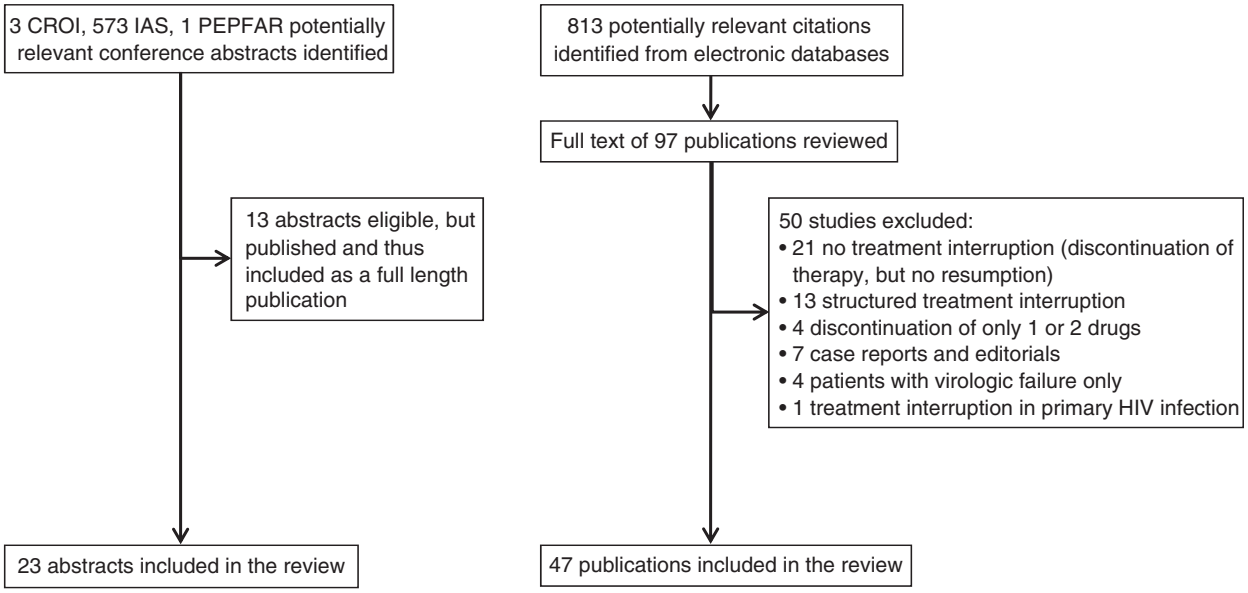

Figure 1 Study selection process.

appropriate the majority (23/25) adjusted for confounders and used an objective outcome measure (29/30).

Definition of treatment interruption and measurement

We found substantial variation and uncertainty in the definition of treatment interruption applied by the individual studies. Twenty-eight did not define the duration of treatment interruption, while of the 42 studies that did specify a definition, duration ranged from 24 h to 1 year (Figure 2). Two cross-sectional studies investigating self-reported treatment interruptions defined interruption as discontinuation of all drugs for more than 24–48 h in the 4 weeks preceding the survey (Glass *et al.* 2006; Marcellin *et al.* 2008). Two studies investigating short interruptions defined a maximum duration of treatment discontinuation of 1 month (Oyugi *et al.* 2007) and 3 months (Taffe *et al.* 2002).

The methods used to determine treatment interruptions varied: self-report (21/70), electronic medication monitoring (4/70) data, prospectively collected by clinicians (7/70), information extracted from clinical records (7/70), pharmacy prescriptions in combination with clinical records (3/70), pharmacy prescriptions only (2/70),

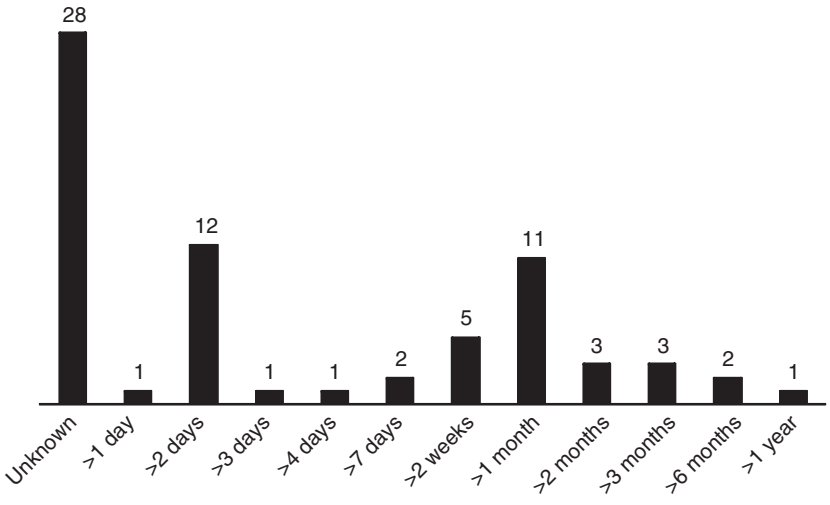

Figure 2 Definition of treatment interruption and their frequencies.

combination of data collected by clinicians and/or self-report and/or prescriptions (4/70). Twenty-two studies did not describe the method used to identify treatment interruptions.

Frequency and duration of treatment interruption

Forty-two studies reported frequencies of treatment interruptions, either as proportions (35), rates (1), or proportions and rates (3) of interruption, or as rates or proportions of discontinuation and resumption (3) (Table 1). The proportion of treatment interruptions ranged from 5.8% [adults in Switzerland (Glass *et al.* 2006)] to 83.1% [recurrent prisoners in the USA (Pai *et al.* 2009)]; the median proportion of patients interrupting treatment was 23.1% (IQR 15.0–48.0). Rates of treatment interruptions ranged from 2.0 per 100 person-years in the United Kingdom (Bansi *et al.* 2008), to 6.0 in the EuroSIDA study (Holkmann Olsen *et al.* 2007). Eleven studies reported on the mean or median duration of treatment interruptions, with durations ranging from 11.5 days (Oyugi *et al.* 2007) to 18 months (Holkmann Olsen *et al.* 2007) (median 150 days). Treatment interruptions were frequently reported as recurrent events, with up to three interruptions per person reported in South Africa (Kranzer *et al.* 2010) and Senegal (Uhagaze *et al.* 2006), five in Switzerland (Taffe *et al.* 2002), six in the EuroSIDA study (Holkmann Olsen *et al.* 2007), and an average of two in Uganda (Oyugi *et al.* 2007).

Reasons for treatment interruption

Twenty-two studies, 18 from developed countries and four from Africa, investigated reasons for treatment interruptions (Table 2). Toxicity, adverse events, and side effects were the most frequently reported reasons, with between 6% (Saitoh *et al.* 2008) and 80% of patients reporting these reasons (Chen *et al.* 2002). Other reasons included pill burden (Moore *et al.* 2009), intercurrent illness (Wolf *et al.* 2005), patient's decision (Krentz *et al.* 2003; Sommet *et al.* 2003; Gibb *et al.* 2004; Pavie *et al.* 2005; Saitoh *et al.* 2008; Moore *et al.* 2009), treatment fatigue (Saitoh *et al.* 2008), social and psychiatric issues (Uhagaze *et al.* 2006; Saitoh *et al.* 2008), perceived lack of benefits (Tarwater *et al.* 2003; Gibb *et al.* 2004) and physician's decision (Wolf *et al.* 2005) because of drug interactions, surgery, or other reasons. A study from Australia found that 38% of patients interrupted treatment for solely clinical reasons and 29% for solely lifestyle reasons (Grierson *et al.* 2004). Costs were the main reason for treatment interruptions (>60%) in two studies from Nigeria (Adeyemi & Olaogun 2006; Wenkel *et al.* 2006). Pharmacy stock outs and poor access to drugs were reported in three of the four studies from developing countries (Adeyemi & Olaogun 2006; Wenkel *et al.* 2006; Pasquet *et al.* 2010).

Risk factors for treatment interruption

Sixteen studies (12 from developed countries) reported on risk factors for treatment interruption. The most commonly reported risk factors were younger age (Mocroft *et al.* 2001; Gandhi *et al.* 2004; Li *et al.* 2005; Nacher *et al.* 2006; Holkmann Olsen *et al.* 2007; Moore *et al.* 2009; Kranzer *et al.*2010) and injecting drug use (Taffe *et al.* 2002; Compostella *et al.* 2005; Touloumi *et al.* 2006; Kavasery *et al.* 2009; Moore *et al.* 2009) (Table 3). The effect of gender and CD4 count on treatment interruption was inconsistent across studies: a high CD4 count (baseline or current) was associated with interruptions in some studies (Taffe *et al.* 2002; Touloumi *et al.* 2006; Holkmann Olsen *et al.* 2007; Moore *et al.* 2009; Kranzer *et al.* 2010) while others reported an association between low CD4 count and treatment interruptions (Li *et al.* 2005; Touloumi *et al.* 2006; Kavasery *et al.* 2009). Socioeconomic variables such as employment, income, education, and being homeless were also identified as risk factors for interruption in some studies (Taffe *et al.* 2002; Oyugi *et al.* 2007; Marcellin *et al.* 2008; Das-Douglas *et al.* 2009; Kavasery *et al.* 2009). One study reported that the odds of treatment interruption among homeless and marginally housed patients was six times higher if their health care plan included consumer cost-sharing (Das-Douglas *et al.* 2009). Finally, a study from Cameroon reported that pharmacy stock shortages were identified as a major risk factor for treatment interruption (Marcellin *et al.* 2008).

Consequences of treatment interruption

Thirty-eight studies reported on various consequences of treatment interruption, comprising mortality, opportunistic infections, immunological and virologic changes, the development of resistance mutations, neurocognitive impairment, and decreased health-related quality of life.

Consistent with the findings of structured interruption studies, unstructured treatment interruptions were commonly associated with a higher risk of death and opportunistic infection and a lower probability of increased CD4 cell counts (Hogg *et al.* 2002; Taffe *et al.* 2002; Schrooten *et al.* 2004; Holkmann Olsen *et al.* 2007; Pai *et al.* 2009; Zhang *et al.* 2010; Kaufmann *et al.* 2011). Furthermore, a high prevalence of neurocognitive impairment (Munoz-Moreno *et al.*2010) and lower health-related quality of life

Table 1 Frequency of treatment interruptions

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Adeyemi and Olaogun (2006)	Adults	Nigeria	2005	Cross-sectional study	Self-report	–	560	22.0	–	–	–	–
Ahonkhai *et al.* (2011)	Adults	South Africa	2004–2008	Prospective cohort study	Unknown	–	11 397	11.0	–	–	–	–
Ammassari *et al.* (2004)	Adults	Italy	–	Cross-sectional study	Self-report	–	116	15.0	–	–	–	–
Bansi *et al.* (2008)	Adults	UK	1996–2005	Prospective cohort study	Unknown	>2 weeks	12 977	21.7	4.4 months	2.0	–	–
Boileau *et al.* (2008)	Adults	Burkina Faso, Mali	2005	Cross-sectional study	Self-report	–	606	22.3	–	–	–	–
Compostella *et al.* (2005)	Adults	Italy	–	Cross-sectional study	Self-report	–	119	56.3	–	–	–	–
Das-Douglas *et al.* (2009)	Homeless and marginally housed	USA	2006	Cross-sectional study	Self-report	>48 h	125	11.2	–	–	–	–
Ekstrand *et al.* (2010)	Adults	India	–	Prospective cohort study	Self-report	>48 h	552	20.0	–	–	–	–
Ekstrand *et al.* (2008)	Adults	India	–	Prospective cohort	Self-report	>48 h	229	48.0	–	–	–	–
Ekstrand *et al.* (2008)	Adults	India	–	Cross-sectional study	Self-report	>48 h	93	31.0	–	–	–	–
Gandhi *et al.* (2004)	Women	USA	–	Prospective cohort	Self-report	>48 h	120	27.2	–	–	–	–
Glass *et al.* (2006)	Adults	Switzerland	2003	Cross-sectional study	Self-report	>24 h in the 4 weeks pre-survey	3607	5.8	–	–	–	–
Grierson *et al.* (2005)	Adults	Australia	2003	Cross-sectional national survey	Self-report	–	1059	47.0	87 days	–	–	–
Grierson *et al.* (2004)	Adults	Australia	2001/2002	Cross-sectional national survey	Self-report	–	640	71.7	–	–	–	–
Holkmann Olsen *et al.* (2007)	Adults	Europe (EuroSIDA)	Until September 2005	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	>3 months	3811	23.1	18 months	6.0	–	–
Kaptue *et al.* (2002)	Adults	Cameroon	–	Prospective cohort study	Unknown	–	50	30.0	–	–	–	–
Kaufmann *et al.* (2011)	Adults	Switzerland	1996–2008	Prospective cohort study	Recorded by clinician	>1 month	2491	51.0	9 months	–	–	–
Kavasery *et al.* (2009)	Injecting drug users	USA	Until July 2005	Prospective cohort study	Self-report	>6 months	335	77.6	12 months	–	–	–

Table 1 *(Continued)*

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Knobel *et al.* (2009)	Adults	Spain	Until July 2007	Prospective cohort study	Computer assisted pharmacy dispensing system and self-report	>3 days	540	42.8	–	–	–	–
Knobel *et al.* (2002)	Adults	Spain	1998/ 1999	Cross-sectional survey with self-reported TI	Self-report with validation of a subset	>2 days	3004	15.0	–	–	–	–
Kouanfack *et al.* (2008)	Adults	Cameroon	2006/ 2007	Cross-sectional survey	Unknown	–	427	9.6	–	–	–	–
Kranzer *et al.* (2010)	Adults	South Africa	2004– 2009	Prospective cohort study	Pharmacy record and clinical records	>30 days	1154	–	228 days	–	12.8/ 100 PY	21.4/ 100 PY
Lazar *et al.* (2010)	Adolescents	Romania	–	Cross-sectional survey	Self-report	–	96	51.60	–	–	–	–
Li *et al.* (2005)	Homosexual men	USA	Until March 2002	Prospective cohort study	Self-report	–	687	10.5 – 1997 5.2 – 1999 7.7 – 2001	61 days	–	–	–
Marcellin *et al.* (2008)	Adults	Cameroon	2006/ 2007	Cross-sectional national survey	Self-report	>2 days in the 4 weeks pre-study	533	12.8	–	–	–	–
Martsinovskaya *et al.* (2010)	Adults	Ukraiine	2008	Cross-sectional survey	Unknown	–	3133	22.0	–	–	–	–
Mbanya (2003)	Adults, self-paying	Cameroon	–	Prospective cohort study	Unknown	–	50	8.0	–	–	–	–
Mocroft *et al.* (2001)	Adults	UK	Until December 1998	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	–	556	–	7 months	–	26.0%	56.1%
Moore *et al.* (2009)	Adults, outpatients	British Columbia	2000– 2006	Prospective cohort study	Recorded by clinician	>3 months	1707	37.7	–	–	–	–
Murri *et al.* (2002)	Adults	Italy	2001	Cross-sectional survey	Self-report	–	80	26.0	–	–	–	–
Murri *et al.* (2009)	Adults	Italy	2006	Cross-sectional survey	Self-report	–	359	24.7	–	–	–	–

Table 1 *(Continued)*

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Proportion of TI (%)	Length of TI (median, mean)	TI rate per 100 PY	Rate or proportion of stopping treatment	Rate or proportion of treatment resumption
Nacher *et al.* (2006)	Adults, hospital based cohort	French Guiana	1992–2003	Prospective cohort study	Unknown	>1 year	1213	–	–	4.3	–	–
Oyugi *et al.* (2007)	Adults, self-paying	Uganda	2002–2004	Prospective cohort study	Electronic medication monitor, self-report, pill count	>48 h ≤30 days	97	65.0	11.5 days	–	–	–
Pasquet *et al.* (2010)	Adults	Ivory Coast	2006–2008	Prospective cohort study	Clinical records	>1 month	1554	53.4	–	–	–	–
Pai *et al.* (2009)	Recurrent prisoners	USA	1996–2005	Prospective cohort study	Dispensing pharmacy and community provider	Not taking antiretroviral therapy while outside of jail	467	83.1	–	–	–	–
Protopopescu *et al.* (2010)	Adults	France	–	Prospective cohort study	Clinical records	>60 days	832	11.5	109 days	2.9	–	–
Saitoh *et al.* (2008)	Children	USA	2000–2004	Prospective cohort study	Unknown	>3 months	405	–	16 months	–	17.8%	66.6%
Taffe *et al.* (2002)	Adults	Switzerland	Until May 2001	Prospective cohort study	Self-report	>1 month <3 months	4720	27.5	–	–	–	–
Touloumi *et al.* (2006)	Adults	Europe, Cascade study	Until August 2003	Prospective cohort study	Unknown	>2 weeks	1551	19.3	–	–	–	–
Uhagaze *et al.* (2006)	Adults	Senegal	2004–2005	Cross-sectional survey	Unknown	–	602	7.0	150 days	–	–	–
Wenkel *et al.* (2006)	Adults, user fees	Nigeria	June 2005	Cross-sectional national survey with self-reported TI	Self-report	–	122	72.0	189 days	–	–	–
Zhang *et al.* (2010)	Adult	the Netherlands	Until February 2008	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	Any duration	3321	15.4	3.1 months	–	–	–

Table 2 Reasons for treatment interruption

Author	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Reasons
Adeyemi and Olaogun (2006)	Nigeria	2005	Cross-sectional study	Self-report	–	123	Cost (69%), side effects (22%), missing of clinic days (12%), poor access to drug (urban 52%, rural 87%)
Bedimo *et al.* (2006)	USA	1996–2001	Prospective cohort study	Unknown	>180 days	71	Complete viral suppression (1%), treatment failure (4%), non-adherence and adverse events (94%)
Chen *et al.* (2002)	USA	–	Prospective cohort study	Clinical records	>30 days	75	Side effects (80%), new opportunistic infection (1%), virologic failure (12%), non-adherence (7%), financial (15%)
Gibb *et al.* (2004)*	UK, Ireland	1999–2002	Prospective cohort study	Clinical records	>4 weeks	71	Poor adherence (23%), parent or child request (24%), adverse drug reactions (9%), perceived lack of virologic and immunologic benefits (21%)
Gonzalez *et al.* (2003)	Spain	–	Prospective cohort study	Unknown	–	64	Drug-related adverse events (55%), patient or physician decision (45%),
Grierson *et al.* (2004)	Australia	2001/2002	Cross-sectional national survey	Self-report	–	263	Solely clinical reasons (38%), both/neither lifestyle and clinical reasons (33%), solely lifestyle reason (29%)
Krentz *et al.* (2003)	Canada	1999–2002	Prospective cohort study	Unknown	>2 months	50	Virologic failure and a drug resistance (41%), adverse effects or toxicity (36%), patient decision (14%)
Landman *et al.* (2003)	France	1998–2002	Retrospective cohort study	Unknown	>2 months	80	Patient's request (19%), lipodystrophy (21%), other drug toxicity (23%), pregnancy or post-partum (11%), high CD4 count (20%), early therapy (6%)
Lazar *et al.* (2010)	Romania	–	Cross-sectional survey with self-reported TI	Self-report	–	50	Neglect (59%), boredom (14%), the wish that other do not know that one is ill (10%), lack of medication (10%)
Moore *et al.* (2009)	Canada	2000–2006	Prospective cohort study	Recorded by clinician	>3 months	74	Medication associated adverse event (7%), pill burden (2%), interaction with methadone (0.3%), pregnancy (0.2%), patient-initiated (2%), treatment failure (0.3%), unknown (88%)
Munoz-Moreno *et al.* (2010)	Spain	2006–2008	Cross-sectional study	HIV database, clinical records	>15 days	27	Structured TI (42%), toxicity (22%), individual decision (36.%)
Murri *et al.* (2002)	Italy	2001	Cross-sectional survey	Self-report	–	23	Side effects (43%) – particularly vomiting and gastrointestinal symptoms, other reasons included being bored of therapy and being in holiday
Pasquet *et al.* (2010)	Ivory Coast	2006–2008	Prospective cohort study	Clinical records	–	830	Drug stock outs (9%), travel/funeral/adverse events/ traditional medicine/inability to pay (12%), not recorded (79%)
Pavie *et al.* (2005)	France	1999–2003	Retrospective chart review	Unknown	–	30	Patient initiated (50%), side effects (50%)
Saitoh *et al.* (2008)	USA	2000–2004	Prospective cohort study	Unknown	>3 months	72	Medical fatigue (69%), toxicity (14%), adverse events (6%), social and behavior issues (6%), social issues (11%), behavior issues (7%), psychiatric disease (3%)
Sanchez *et al.* (2007)	Spain	–	Prospective cohort study	Pharmacy prescriptions	>4 weeks	20	Toxicity (65%)

Table 2 *(Continued)*

Author	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Reasons
Sommet *et al.* (2003)	France	1998–2001	Prospective cohort study	Unknown	>30 days	163	Virologic failure (43%), side effects (33%), patient initiated (24%)
Uhagaze *et al.* (2006)	Senegal	2004–2005	Cross-sectional survey	Unknown	–	42	Fear of side effects (72%), having forgotten to take the drugs (26%), the illness (33%), falling asleep (15%), depression (17%)
Tarwater *et al.* (2003)	USA	–	Prospective cohort study	Clinical records, clinician, self-report	–	105	Perceived lack of an indication for therapy on the part of the clinician (44%), drug toxicity (15%), non-adherence (14%), performance of resistance testing (15%), failure (8%)
Van Valkengoed *et al.* (2003)	Europe	–	Prospective cohort study	Unknown	>7 days	201	Toxicity (43%), patient's decision (29%)
Wolf *et al.* (2005)	Germany	1999–2002	Prospective frequency matched cohort study	Recorded by clinician	>2 weeks	133	Toxicity and/or side effects (39%), physician's decision or recommendation (20%), intercurrent illnesses (5%), other reasons (3%)
Wenkel *et al.* (2006)	Nigeria	2006	Cross-sectional survey	Self-report	–	88	Financial constraints (61%), ARVs out of stock (14%), side effects (6%), others (19%)

*Children.

(Krentz *et al.* 2003) were reported in individuals interrupting therapy.

All studies investigating CD4 and viral load response during treatment interruption reported a substantial drop of CD4 count and increase in viral load compared with pre-interruption levels (Gonzalez *et al.* 2003; Sommet *et al.* 2003; Tarwater *et al.* 2003; Gibb *et al.* 2004; Achenbach *et al.* 2005; Burton *et al.* 2005; Giard *et al.* 2005; Pavie *et al.* 2005; Wolf *et al.* 2005; Bedimo *et al.* 2006; Hull *et al.* 2006; Sanchez *et al.* 2007; Saitoh *et al.* 2008; Mussini *et al.* 2009; Sarmati *et al.* 2010). The influence of nadir CD4 counts, CD4 counts, and viral load levels prior to treatment interruption on CD4 decay was inconsistent, with some studies reporting an effect (Gonzalez *et al.* 2003; Wolf *et al.* 2005; Hull *et al.* 2006; Mussini *et al.* 2009) while others reported no effect (Saitoh *et al.* 2008).

CD4 counts rose after resumption of therapy (Chen *et al.* 2002; Sommet *et al.* 2003; Gibb *et al.* 2004; Giard *et al.* 2005; Wolf *et al.* 2005; Sanchez *et al.* 2007; Touloumi *et al.* 2008; Mussini *et al.* 2009). The increase was biphasic with a steeper slope in the first months after re-initiation of therapy (Touloumi *et al.* 2008; Mussini *et al.* 2009). However, CD4 recovery was incomplete: in studies reporting CD4 recovery, the proportion of patients experiencing an increase in CD4 counts to levels before treatment interruption at 24 months ranged from 28% to 69% (Chen *et al.* 2002; Giard *et al.* 2005). One study that investigated the effect of treatment interruption in a prison setting found that patients with continuous ART treatment gained on average 0.67 CD4 cells per months compared with intermittently treated patients who lost cells at an average of 0.93 CD4 cells per month (Pai *et al.* 2009).

The majority of studies reported that patients experienced virologic suppression once treatment was restarted (Chen *et al.* 2002; Yozviak *et al.* 2002; Gibb *et al.* 2004; Wolf *et al.* 2005; Touloumi *et al.* 2008; Mussini *et al.* 2009). However, treatment interruptions were associated with an increased risk of rebound and virologic failure in developed and developing countries (Murri *et al.* 2002; Parienti *et al.* 2004, 2008; Spacek *et al.* 2006; Laher *et al.* 2007; Oyugi *et al.* 2007; Bansi *et al.* 2008; Boileau *et al.* 2008; Kouanfack *et al.* 2008; Knobel *et al.* 2009; Datay *et al.* 2010; Ekstrand *et al.* 2010). A study from Spain differentiated treatment interruptions because of patients' choice and adherence difficulties or physician's advice for toxicity, severe side effects, or intercurrent illness. After adjusting for drug regimen and adherence level, the risk of a detectable viral load (>500 copied/ml) or death was 3.62 for the former and 1.36 for the latter, compared with continuous treatment (Knobel *et al.* 2009). A study among adults receiving boosted protease inhibitors (PI) reported

Table 3 Risk factors for treatment interruptions

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Risk factors for TI
Compostella *et al.* (2005)	Adults	Italy	–	Cross-sectional study	Self-report	–	119	Older age Injecting drug use Time lag between HIV diagnosis and treatment initiation Anxiety related to therapy Subjective antiretroviral therapy (ART) intolerance Experience of more than four regimens
Das-Douglas *et al.* (2009)	Homeless and marginally housed	USA	2006	Cross-sectional study	Self-report	>48 h	125	Consumer cost-sharing Emergency department visits in the past year Being homeless Depression
Gandhi *et al.* (2004)	Women	USA	–	Prospective cohort study	Self-report	>48 h	120	Younger age Reduced adherence Alcohol use Higher viral load
Holkmann Olsen *et al.* (2007)	Adults	Europe (EuroSIDA)	Until September 2005	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	>3 months	3811	Higher current log viral load Higher current CD4 count Women Younger age
Kavasery *et al.* (2009)	Injecting drug users	USA	Until July 2005	Prospective cohort study	Self-report	>6 months	335	Younger age Lower CD4 count Higher HIV RNA level Daily injecting drug use Unemployment ART initiation in later calendar years Using crack and alcohol
Kranzer *et al.* (2010)	Adults	South Africa	2004–2009	Prospective cohort study	Pharmacy record and clinical records	0>30 days	1154	Men* Higher baseline CD4 count* Shorter time on ART* ART initiation in later calendar years*
Li *et al.* (2005)	Homosexual men	USA	Until March 2002	Prospective cohort study,	Self-report	–	687	Younger age Black race Lower CD4 count Higher HIV RNA level Shorter time on ART Not taking 3TC
Marcellin *et al.* (2008)	Adults	Cameroon	2006/2007	Cross-sectional national survey	Self-report	>2 days in the 4 weeks preceding the study	533	Men Low educational level Low monthly household income Treatment with 3TC Binge drinking Number of symptoms Pharmacy stock shortages

Table 3 (*Continued*)

Author	Study population	Country	Time period	Study description	Measure of TI	Definition of TI	*N*	Risk factors for TI
Mocroft *et al.* (2001)	Adults	UK	Until end of 1998	Prospective cohort study	Start and Stop date of each ARV recorded by clinician	–	556	Younger age* Men* Higher viral load*
Moore *et al.* (2009)	Adults, outpatients	British Columbia	2000–2006	Prospective cohort study	Recorded by clinician	>3 months	1707	History of IDU Higher baseline CD4 count Hepatitis C pos Women Younger age No AIDS diagnosis at baseline Less experienced physician
Murri *et al.* (2009)	Adults	Italy	2006	Cross-sectional survey	Self-report	–	359	Suboptimal adherence Higher viral load Smokers NNRTIs
Nacher *et al.* (2006)	Adults, hospital based cohort	French Guiana	1992–2003	Prospective cohort study	Unknown	>1 year	1213	Younger age Initial CD4 count >500 cells/μl
Oyugi *et al.* (2007)	Adults, self-paying	Uganda	2002–2004	Prospective cohort study	Electronic medication monitor, self-report, pill count	>48 h ≤30 days	97	Financial difficulties
Protopopescu *et al.* (2010)	Adults	France	–	Prospective cohort study	Clinical records	>60 days	832	Good patient-provide relationship No social support from their main partner No prior history of viral rebound Fewer HIV-related clinical events
Taffe *et al.* (2002)	Adults	Switzerland	Until May 2001	Prospective cohort study	Self-report	>1 month <3 months	4720	High baseline viral load High baseline CD4 count Injecting drug use Low education
Touloumi *et al.* (2006)	Adults	Europe, Cascade study	Until August 2003	Prospective cohort study	Unknown	>2 weeks	1551	Women Injecting drug use High baseline viral load High baseline CD4 count Low current CD4 count

*Associated with discontinuation (not TI).

that average adherence predicted viral suppression, whereas treatment interruption did not in multivariate analysis (Parienti *et al.* 2010).

Four studies investigated the development of resistance mutations (Parienti *et al.* 2004; Spacek *et al.* 2006; Oyugi *et al.* 2007; Sanchez *et al.* 2007). In a study from France, interrupting treatment more than once was significantly associated with the development of resistance to the non-nucleoside-reverse-transcriptase inhibitors (NNRTI) class (hazard ratio 22.5, 95% CI 2.8–180.3) (Parienti *et al.* 2004). Among 19 treatment interrupters in Spain, nine had mutations in the reverse transcriptase gene and 17 had polymorphism in the protease gene, with L63P being the most commonly found (Sanchez *et al.* 2007). In Uganda, none of the patients with continuous treatment had evidence of resistance mutations, but 13% of patients with a history of treatment interruption had resistance mutations: all of them had mutations conferring nevirapine resistance, five had mutations conferring lamivudine resistance, and three had mutations conferring stavudine resistance (Oyugi *et al.* 2007). Another study from Uganda showed resistance to NNRTI class in 26 of 36 patients with detectable viral load with the most common mutation being K103N. Twenty-three of the 36 patients had the M184V/I mutation and three had genotypic resistance to PIs (Spacek *et al.* 2006).

Interventions

We only identified one intervention study. This randomized controlled trial from Kenya showed that short message service reminders either daily or weekly reduced the prevalence of treatment interruptions exceeding 48 h from 19% to 10% ($P = 0.03$) (Pop-Eleches *et al.* 2011).

Six studies investigating risk factors associated with treatment interruptions discussed possible interventions. Studies from developed countries suggested appropriate counseling on the consequences of drug discontinuation, encouragement of optimal adherence, offering of mental health services, addressing addictions, and providing services specifically engaging women and ethnic minorities (Li *et al.* 2005; Moore *et al.* 2009; Murri *et al.* 2009). Studies from Uganda and Cameroon emphasized the importance of steady and reliable access to medication, as well as free access to ART and possibly food supply programs (Oyugi *et al.* 2007; Marcellin *et al.* 2008). A study from South Africa concluded that interventions should be targeted at men and during the first 6 months on ART (Kranzer *et al.* 2010).

When patients were asked to give at least one suggestion how to improve adherence and reduce treatment interruptions: 46% suggested reduction in daily doses, 28% more detailed information about therapy, 27% more attention to side effects, 20% more time dedicated to adherence-related issues, 19% supervised treatment interruptions, and 16% psychological help (Ammassari *et al.* 2004).

Conclusions

Recent research has highlighted the importance of non-adherence to and defaulting from antiretroviral care in contributing to poor program outcomes (Garcia De Olalla *et al.* 2002; Nieuwkerk & Oort 2005; Mills *et al.* 2006; Maggiolo *et al.* 2007; Rosen *et al.* 2007; Brinkhof *et al.* 2009). Our review highlights that unstructured treatment interruptions, while far less frequently reported, are an important phenomenon both in developed and in developing countries and may result in excess mortality and opportunistic infections, increased risk of virologic failure, and poor immunological recovery.

Medication-taking behavior is characterized by adherence which is defined as 'extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen' and persistence defined as 'the duration of time from initiation to discontinuation of treatment' (Cramer *et al.* 2008). Persistence emphasizes the concept of continuous therapy and is influenced by both defaulting from antiretroviral care and treatment interruption' (Bae *et al.* 2011). Adherence and persistence are both important for optimal treatment outcomes, but their impact may vary dependent on the type of regimen prescribed and the duration and frequency of treatment interruptions.

We found that the characterization of treatment interruption in the literature to date is confused by heterogeneous definitions. A quarter of studies provided no definition, while for those that did definitions varied from more than 24 h to more than 1 year of discontinuation of treatment. Only half of studies reported on median duration of interruption. Similar problems with regard to uniformity of definitions have been encountered in studies investigating loss to follow-up where definitions ranged from 1 to 6 months late for a scheduled consultation or medication pick-up (Rosen *et al.* 2007). In addition, the method of determination of treatment interruption varied considerably: over a quarter of studies using self-report, while a similar number did not specify the method used to identify treatment interruptions.

The reported causes of treatment interruption are multidimensional and context-specific. However, research to date has largely assessed risk factors and reasons for treatment interruption, few in developing country settings. Studies from developing countries highlighted pharmacy stock outs and costs as important factors for treatment

interruptions. While several interventions have been proposed, only one has been formally assessed.

Data synthesis is a desirable goal for systematic reviews. However, in view of the substantial degree of heterogeneity between studies with regard to definitions of treatment interruption and methods used to identify treatment interruptions, we decided against providing a data synthesis. In addition, because treatment interruptions depend on duration of ART, incidence would be a more informative measure, but few studies provided incidence estimates. Another limitation of our review, reflecting a limitation of the published evidence, is that only four studies investigated the association between treatment interruption and genotypic resistance. The sample size of these studies was small. One of these studies relied on self-report to identify treatment interruptions. Larger studies using objective measures of treatment interruptions are needed to confirm the association between treatment interruption and genotypic resistance. Finally, although our search strategy was extensive, yielding a high number of studies, we cannot exclude the possibility that our search strategy may not have captured all reports of treatment interruption.

Our study highlights several directions for future research and practice. First, reporting on treatment interruptions should be encouraged, both to improve the quality of program outcome reports, and support better characterization and quantification of the problem. Second, more uniform reporting of treatment interruption should be encouraged to support comparability across studies, as has been proposed for treatment defaulting. The range of proposed interventions in the literature does not reflect the range of causes reported, with a notable absence of attention on some of the most frequently reported drivers of treatment interruption, including drug toxicity, adverse events, and side effects. This suggests that a first step to minimizing treatment interruptions in many settings is simply to provide better care to patients. Finally, intervention studies should be planned to determine the effectiveness of approaches to minimize treatment interruption and encourage treatment resumption.

In conclusion, treatment interruptions are common both in developed and in developing countries and are associated with increased morbidity, mortality, and possibly genotypic resistance. Future research should focus on evaluating interventions to address the most frequently reported reasons for interruptions to support patients in a way that maximizes the chances of continuous and effective treatment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy.

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