ORIGINAL RESEARCH ARTICLE

Factors associated with HIV-1 virological failure in an outpatient clinic for HIV-infected people in Haiphong, Vietnam

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Summary: The objective of our study was to investigate factors associated with virological failure in 100 consecutive HIV-1 infected Vietnamese adults who initiated antiretroviral therapy (ART) from June 2007 to June 2008. Data were collected from medical records, and a structured questionnaire was used in individual interviews to investigate factors associated with adherence to ART. Plasma HIV viral load was measured at the time of the interview. The median age was 35 years, 35% were women and heterosexual intercourse was the most common mode of HIV transmission (61%). After a median of 14 months since starting ART, 23% had detectable HIV-1 viral load ($\geq$400 copies/mL). Patients who had developed a World Health Organization (WHO) clinical stage 4 condition at the time of initiation of ART were more likely to experience virological failure than those in stages 1–3, odds ratio (OR): 5.20 (95% confidence interval [CI] 1.34–20.11), $P = 0.017$. Patients who reported that their health status was evaluated by a physician at each visit were less likely to experience virological failure, OR: 0.02 (95% CI 0.00–0.24), $P = 0.002$.

Keywords: HIV, antiretroviral therapy, virological failure, Vietnam

INTRODUCTION

Recent years have witnessed a substantial increase in the number of HIV-infected people in low- and middle-income countries (LMICs) receiving antiretroviral therapy (ART). In Vietnam, where an estimated 290,000 people are infected with HIV-1, an increasing number of patients have been put on effective ART. In 2009, 53.7% of those in need of ART in Vietnam received treatment. The target for 2010 is coverage of 60%.[1]

In high-income countries, measurement of HIV viral load is used routinely to assess the response to ART and guide clinicians on when to change a failing ART regimen. However, in Vietnam, like in many other LMICs, HIV viral load measurements are not performed routinely in most patients receiving ART. Monitoring of patients on ART and decisions whether to change therapy are therefore typically based on a combination of clinical and immunological criteria according to World Health Organization (WHO) guidelines.[2] Analysis of 10 treatment programmes in Africa and South America has documented that the positive predictive value of these criteria for virological failure is poor.[3] Hence, patients are at risk of switching unnecessarily to more expensive second-line ART regimens or continue receiving failing ART with accumulation of resistance mutations. Studies that investigate risk factors for virological failure and optimal switch strategies in LMICs are therefore urgently needed. While factors associated with virological failure have been well studied in high-income countries there is still a paucity of studies from LMICs, where risk factors for virological failure might depend on other and local factors.

The objective of our study was to investigate factors associated with risk of virological failure in HIV-1-infected patients initiating ART in a large outpatient clinic in Haiphong, Vietnam.

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METHODS

Study design and data collection

We conducted a cross-sectional study at the Viet Tiep Outpatient Clinic (OPC) of the Viet Tiep hospital in Haiphong in north east Vietnam. The study population consisted of 100 HIV-1 infected patients initiating ART in the period from June 2007 to June 2008. Patients were required to be over 16 years of age, to be under active follow-up on the date of the interview, to have available medical records and to have signed an informed consent form. Eligible patients were accessed consecutively in the period from 14 April 2009 to 14 May 2009 when they had their routine monthly appointment in the clinic. A structured questionnaire, based on similar questionnaires used in studies in LMICs,[4,5] was used in individual interviews during this time to investigate factors associated with adherence to ART. The questionnaire included questions on perception and knowledge of ART, self-reported adherence to ART, relation to the health-care service and socioeconomic, behavioural and psychological factors. Use of antiretroviral drugs (ARVs), clinical data and CD4 cell counts were collected from the medical records of all patients who initiated ART from June 2007 to June 2008.

Viral load testing and definition of virological failure

All patients had plasma samples collected at the time of the interview. Plasma was transported on dry ice and stored at −70°C. HIV-1 viral loads were quantified for all samples by use of a commercially available real-time reverse transcriptase polymerase chain reaction (PCR) assay (Generic HIV Charge Virale; Biocentric, Bandol, France) at the Department of Virology of the Saint Paul Hospital, Hanoi, Vietnam. Virological failure was defined as a viral load above the limit of detection, 400 copies/mL.

Viet Tiep Outpatient Clinic

The Viet Tiep Outpatient Clinic (OPC) is the biggest clinic providing ART for HIV infected people in Haiphong. The number of patients receiving ART at the clinic has increased from 65 patients in 2005 to 605 patients in 2009. Treatment programmes in the OPC are funded by the US Centers for Disease Control and Prevention (CDC) and LIFE GAP, which is an HIV/AIDS prevention and care programme under the Vietnamese Ministry of Health.

In Vietnam, HIV infected people are recommended to start ART when the CD4 T-cell count is less than 200 cells/μL or in the case of severe HIV disease (defined as either WHO stage 3 with a CD4 count of less than 350 cells/μL or WHO stage 4). Before initiation of ART, all patients are required to attend group counselling lasting from two to three days where they are provided with general information on HIV/AIDS, ARVs and their correct use and harmful consequences of treatment interruption. Available first-line regimens consist of stavudine *or* zidovudine *plus* lamivudine *plus* nevirapine *or* efavirenz. There are three available second-line regimens. Among them, the most frequently used regimen is a combination of tenofovir *plus* lamivudine *plus* lopinavir/ritonavir. The other two regimens include didanosine/abacavir *or* tenofovir/abacavir *plus* lopinavir/ritonavir. For the first month after initiation of ART, patients go to the OPC once weekly to get ARVs. After that, most patients have monthly visits to the OPC for their ARVs. Patients who live or work far from the OPC might be provided with ARVs for two months. In the study period, the OPC had no interruptions in the supply of ARVs.

Baseline blood tests include alanine aminotransferase, haemoglobin, anti-hepatitis virus C (HCV) IgG, hepatitis B surface antigen (HBsAg) and CD4 cell count, but not HIV viral load. The CD4 cell count is repeated every three months while it remains lower than 500 cells/μL. Above this value, the interval is increased to six months.

STATISTICAL METHODS

Patient characteristics were described at the time of initiation of ART (baseline), for 100 consecutively included patients in the analysis who took part in the adherence interview and had a viral load measured at the time of the interview. Among all patients who started ART in the period June 2007–June 2008, characteristics were compared between those included in the analysis, those still under follow-up in the clinic but not included in the analysis and those lost to follow-up or who died prior to April 2009, using chi-square and Fisher's exact tests for categorical data and Kruskal–Wallis tests for continuous data. Patients with HIV-RNA $<$ and $\geq$400 copies/mL were also compared. Univariable logistic regression models were then used to identify all variables that were significantly associated with virological failure ($\geq$ 400 copies/mL). The variables that were tested included those relating to demographics, use of ART, clinical data, laboratory values, self-reported adherence to ART, psychology and support. A multivariable model was developed including all variables that were significant in univariable analyses ($P < 0.1$) and a stepwise selection method was used to check that all important variables were included.

All tests were two sided and a P value of <0.05 was considered statistically significant. SAS software version 9.1 (SAS Institute, Cary, NC, USA, 2002–2003) was used for all analyses.

RESULTS

Patients

A total of 151 patients initiated ART in the period from June 2007 to June 2008. At the time of follow-up in April 2009, 19 (13%) patients had died and nine (6%) were lost to follow-up. From the 123 patients still under follow-up, 100 patients were consecutively included for interview and HIV viral load measurement.

Table 1 shows the patient characteristics at the initiation of ART. The median age of the 100 included patients was 32 years and 35% were women. The most common mode of HIV transmission was heterosexual intercourse (61%) and 51% had a CD4 count at the time of starting ART of less than 100 cells/μL (median 97 cells/μL). The prevalence of HBsAg and anti-HCV positivity were 80% and 60%, respectively. Ninety-eight percent were still on a first-line regimen and only 7% had ever changed regimen, most of them being due to adverse effects.

Similar characteristics were observed in the patients who were not included and in the group who were lost to follow-up/died; however, in the latter group there was a higher proportion of patients with a WHO clinical stage 4 condition at the time of initiation of ART compared with those still under active follow-up: 61% compared with 33% of the patients included in the project and 26% of those not included ($P = 0.014$).

The median duration (interquartile range, IQR) from the time of initiation of ART to viral load measurement was 14 (11–22) months; 23% had detectable HIV-1 viral load ($\geq$400 copies/mL) with a median (IQR) viral load of 3.3 (2.8–3.9) $\log_{10}$ copies/mL. Seven of the 23 patients with virological failure also had immunological failure according to WHO criteria.[6]

Factors associated with virological failure

Compared with patients with viral suppression, patients with detectable viral load were more likely to be infected with HIV through injecting drug use (IDU) (52.2% versus 28.6%), have a body weight $<$50 kg (52.2% versus 32.5%) and to be clinical stage 4 at the initiation of ART (56.5% versus 26.0%). The prevalence of hepatitis co-infection and ART history were similar regardless of virological response to ART (Table 1).

Data on self-reported adherence to ART and other variables collected during patient interviews are described in Table 2. Compared with patients with HIV RNA $<$400 copies/mL, patients with HIV RNA $\geq$ 400 copies/mL were less likely to be married (56.5% versus 79.2%) and employed (16.9% versus 34.8%). All patients reported to have taken all ARVs in the

Table 1 **Patient characteristics at the initiation of antiretroviral therapy**

	Patients with HIV RNA < 400 copies/mL (n = 77)	Patients with HIV RNA ≥ 400 copies/mL (n = 23)	Patients not enrolled (n = 23)	Patients-lost to follow-up/died (n = 28)
Sociodemographics				
Age (median years, IQR)	33	32	28 (27–34)	31 (26–36)
Women (n, %)	28 (36.4)	7 (30.4)	9 (39.1)	6 (21.4)
Weight ≤50 kg (n, %)	25 (32.5)	12 (52.2)	NA	NA
HIV infection				
Mode of infection with HIV (n, %)				
Injecting drug use	22 (28.6)	12 (52.2)	10 (43.5)	9 (32.1)
Heterosexual intercourse	50 (64.9)	11 (47.8)	10 (43.5)	13 (46.4)
Others or unknown	5 (6.5)	0 (0)	3 (13.0)	6 (21.4)
CD4 + cell count ≤ 100 cells/μL (n, %)	37 (48.1)	14 (60.9)	12 (52.2)	18 (64.3)
Clinical stage 4 (WHO) (n, %)	20 (26.0)	13 (56.5)	6 (26.1)	17 (60.7)
Hepatitis				
HBsAg positive (n, %)	63 (81.8)	17 (73.9)	NA	NA
Anti-HCV IgG positive (n, %)	47 (61.0)	13 (56.5)	NA	NA
ART history				
ARV regimen started (n, %)				
First line regimen*	75 (97.4)	23 (100)	20 (87.0)	28 (100)
Second line regimen†	2 (2.6)	0 (0)	3 (13.0)	0 (0)
Ever changed regimen (n, %)	6 (6.8)	1 (4.3)	2 (8.7)	2 (7.1)
Reasons for changing regimen (n, %)				
Treatment failure	2 (2.6)	0 (0)	2 (8.7)	1 (3.6)
Adverse effects	4 (4.2)	1 (4.3)	0 (0)	1 (3.6)
Duration from initiation of ART to viral load test (median months, IQR)	14 (10.5–21.4)	14 (11.1–18.4)	NA	NA

IQR = interquartile range; ART = antiretroviral therapy; ARV = antiretroviral drug; HCV = hepatitis C virus; WHO = World Health Organization
*Stavudine or zidovudine + lamivudine + nevirapine/efavirenz
†Lopinavir/ritonavir together with tenofovir + lamivudine *or* didanosine + abacavir *or* tenofovir + abacavir
P values obtained using chi-squared and Fisher's exact tests for categorical data and Kruskal–Wallis tests for continuous data

past seven days, but the group with virological failure were more likely to have taken ≥1 dose early or late (≥1 hour) in the past seven days (56.5% versus 32.5%). The most common reasons for early/late use of ART were 'simply forgot' and 'too busy'. Patients with virological failure were also less likely to perceive HIV as a deadly disease (21.7% versus 53.2%) and to believe strongly in the efficacy of ART to improve health (39.1% versus 57.1%). Overall, around 56% experienced adverse effects to ART with no difference between the two groups.

Factors associated with virological failure were further tested in univariable and multivariable logistic regression models (Figure 1). After adjustment, patients who had developed a WHO clinical stage 4 condition at the time of initiation of ART were five-fold more likely to experience virological failure than those in stages 1–3, odds ratio [OR]: 5.20 (95% confidence interval [CI] 1.34–20.11), $P = 0.017$. Patients who reported that their health status was evaluated by a physician at each visit were less likely to experience virological failure, OR: 0.02 (95% CI 0.00–0.24), $P = 0.002$. There was no difference in the association with virological failure between those receiving stavudine-based regimens versus any other first line regimen, OR: 0.67 (95%CI 0.17–2.57), $P = 0.55$. Self-reported adherence was not significantly associated with odds of virological failure. No patients reported to have ever interrupted their ART. All CIs were quite wide reflecting the relatively low number of patients included in the study.

DISCUSSION

In the present study, we investigated factors associated with virological failure in 100 consecutive HIV-infected persons initiating ART in a large outpatient clinic in Haiphong, Vietnam. Twenty-three percent had detectable HIV viral load after a median of 14 months. This failure rate is similar to what is observed in other cohorts in LMICs,[7–10] but lower than that observed in high-income countries.[11,12] In multivariable analysis, patients who had a WHO clinical stage 4 condition at the time of ART initiation were more likely to experience virological failure, while patients who reported that their health status was evaluated by a physician at each visit were less likely to experience virological failure. Of note, the CIs of these and the other ORs in this study were quite wide due to the limited number of patients included in the present analysis.

For the 23 patients with virological failure, 75% had a viral load <8000 copies/mL. This not only indicates that not taking ARVs at all is uncommon in this population, but also that many patients with virological failure could harbour resistance mutations with risk of onward transmission.[13] Use of HIV viral load tests and resistance tests would be of benefit in specific cases for physicians in their evaluation of patient adherence and resistance development before switching to more expensive second-line regimens, but would require additional funding from the clinic's financial contributors. Transmitted drug resistance is believed to have played a minor role for risk of virological failure in our study, since a study from 2007 of 273 ART naïve HIV-1 patients in Haiphong found that the rate of transmitted resistance mutations was only 2.9%.[14]

Having a WHO clinical stage 4 condition at the time of ART initiation has been found in some,[7,15] but not all,[16–18] studies to be a risk factor for virological failure. Patients with a stage 4 condition generally have low CD4+ cell counts and more advanced immune dysfunction. However, we did not find any association between the CD4+ cell count level and risk of virological failure.

Table 2 **Sociodemographics, self-reported adherence to antiretroviral therapy (ART), psychology and support for patients interviewed**

	Patients with HIV RNA ≥ 400 copies/mL (*n* = 23)	Patients with HIV RNA < 400 copies/mL (*n* = 77)
Sociodemographics		
Currently married	13 (56.5)	61 (79.2)
Living alone	3 (13.0)	6 (7.8)
Have children	15 (65.2)	64 (68.3)
Primary, secondary or high school (Grade 1–12)	22 (95.7)	70 (81.9)
Unemployed	8 (34.8)	13 (16.9)
Income ≤111 US$/ month in the past year	18 (78.3)	58 (75.3)
Use of alcohol in the last 1 month (yes)	9 (39.1)	30 (39.0)
Ever used illicit drugs	9 (39.1)	25 (32.5)
Adherence to ART		
Ever missed ≥1 dose during ART	4 (17.4)	9 (11.7)
Ever early/late use of ≥1 dose for ≥1 hour during ART	18 (78.3)	48 (62.3)
Adherence to ART in the last 1 month (no missed doses or early/late used ARVs in the last 1 month)	5 (21.7)	32 (41.6)
Missed ≥1 dose in the past 7 days	0	0
Early/late use of ≥1 dose for ≥1 hour in the past 7 days	13 (56.5)	25 (32.5)
Experienced adverse effects of ART	13 (56.5)	43 (55.8)
Ever missed their appointment at the OPC	3 (13.0)	15 (19.5)
Someone reminded patient to take ARVs	17 (73.9)	61 (79.2)
Reminder tools to take ARVs at home	19 (82.6)	62 (80.5)
Reasons for early/late use of ARVs		
Simply forgot	12 (52.2)	45 (58.4)
Too busy	12 (52.2)	42 (54.5)
Sleeping	3 (13.0)	9 (11.7)
Stress	0	8 (10.4)
Perception of HIV and ART		
Perception of HIV as a deadly disease	5 (21.7)	41 (53.2)
Stop taking or take less ARVs to alleviate side-effects without consulting doctors	3 (13.0)	5 (6.5)
Interruption affects the efficacy of ART ('no' or 'do not know')	1 (4.3)	9 (11.7)
Believe strongly in efficacy of ART to improve health	9 (39.1)	44 (57.1)
Believe that strictly following ART will improve health significantly	14 (60.9)	55 (71.4)
Psychology		
Afraid to go to the OPC	13 (56.5)	37 (48.1)
Bad or unstable mood in the past 7 days*	14 (60.9)	49 (63.6)
Support from health-care services, society and family		
Used private vehicle to go to the OPC in the past 3 months	16 (69.6)	64 (83.1)
Felt convenient to go to the OPC in the past 3 months (no)	4 (17.4)	10 (13.0)
Expense to go to the OPC in the past 3 months was reasonable, or do not pay	22 (95.7)	71 (92.2)
Physician evaluated health status at each visit	20 (87.0)	75 (97.4)
Do not receive any support from parents, spouses, sexual partner, relatives or friends	0	16 (20.8)
Visitors to support adherence to treatment at home in the last 3 months	9 (39.1)	18 (23.4)
Received support from social organizations in the last 3 months	4 (17.4)	13 (16.9)

ARV = antiretroviral drug; OPC = outpatient clinic

*Less interested and pleasured in activities, depressed, hopeless, more angry, sad, depressed, irritable or anxious than usual

Although 'having ones health status evaluated by a physician' was associated with lower risk of virological failure, 20/23 patients with virological failure were routinely evaluated by a physician, suggesting that this factor did not contribute substantially to poor treatment outcomes. According to the national treatment guidelines in Vietnam, patients are supposed to be evaluated by a skilled provider (usually a doctor) at each visit. To enable scaling up access to ART in LMICs, where lack of physicians trained to treat HIV patients is common, WHO recommends task-shifting of medical care, where, for example, nurses provide monitoring of ART.[19] A recent South African trial showed no difference in virological failure or mortality in patients randomized to ART provided by clinically-trained nurses compared with patients randomized to receiving ART monitored by physicians.[20]

Prior to the initiation of ART, the outpatient clinic requires participation in group counselling on general information about ARVs and the importance of ART adherence. It would be relevant to investigate if an extension of this important initiative to include counselling and support during follow-up would reduce the risk of virological failure. A recent randomized trial from Uganda showed that HIV patients who received clinic- and home-based provision of counselling and support from community-based peer health workers had a lower risk of longer-term (>96 weeks), but not shorter-term, virological failure compared with patients who received standard of care.[21]

We investigated several measures of self-reported adherence, but none of them were associated with risk of virological

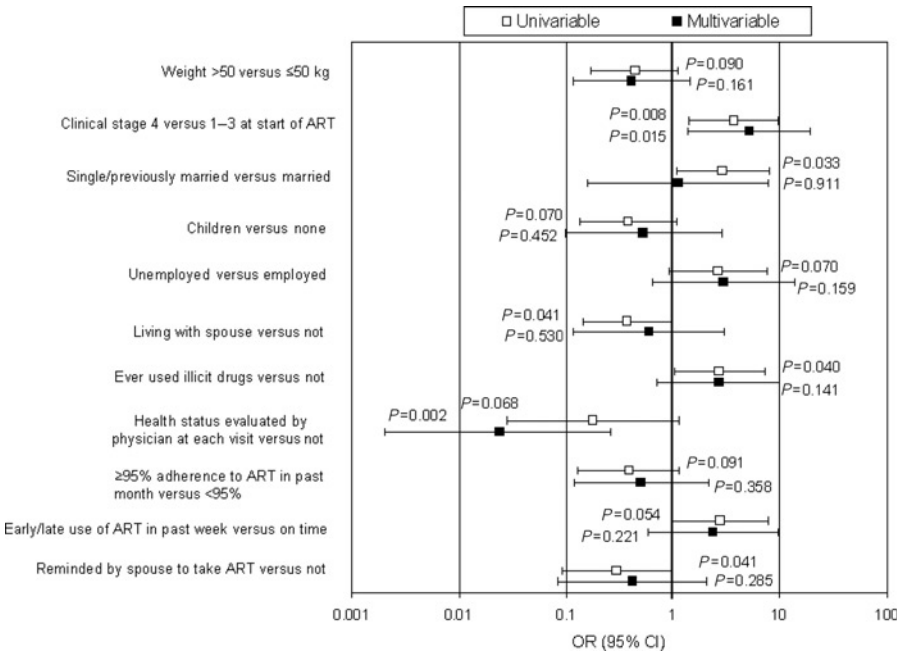

Figure 1 **Univariable and multivariable odds ratios of virological failure in patients who started antiretroviral therapy between June 2007 and June 2008. Virological failure is defined as a viral load ≥400 copies/mL measured between April 2009 and May 2009. *P* values were obtained via logistic regression. Multivariable analyses were adjusted for all variables listed in table. OR = odds ratio; CI = confidence interval; ART = antiretroviral therapy**

failure. Although widely used as a measure of adherence, the validity of self-reported adherence is conflicting and suffers from recall and social desirability biases.[22] Overall, 56% reported adverse effects to ART, which could have influenced adherence to ART and risk of virological failure. However, there was no difference in risk of adverse side-effects between the group with virological failure and the group with response to ART. Our findings are in contrast with a similar study of a cohort of HIV-infected IDUs from Hanoi, Vietnam, where patients with high self-reported adherence (>95% within the last 30 days) were more likely to have viral suppression than patients who were less adherent (29.6% versus 9.6%); both this and our study are limited by the lack of objective surrogate measures of adherence.[10]

Although the OPC recommends initiation of ART when the CD4+ count is below 200 cells/μL (according to WHO guidelines), 51% of patients still under follow-up initiated ART with a CD4+ count <100 cells/μL. Among patients who had died or were lost to follow-up, 18/28 (64%) initiated ART with a CD4+ count <100 cells/μL. Improvements will require not only a broader scale-up of HIV testing, since many HIV patients in Vietnam at the time of HIV diagnosis already are severely immunosuppressed[23] but also a faster scale-up of ART programmes. By April 2009, 1332 HIV patients were on the waiting list to receive ART in the Viet Tiep OPC.

Among patients lost to follow-up, two were receiving care in another clinic while seven were registered as having moved to another place without information whether they were receiving care in another clinic. Considering that most of them had advanced HIV disease at the time of ART initiation, the risk that some of them would have failed therapy or have died is high, thus leading us to underestimate the rate of failure and death.

The prevalences of HBsAg and anti-HCV positivity were 80% and 60%, respectively. Considering that almost two-thirds reported heterosexual intercourse as their risk factor for HIV infection, and only 34% reported IDU, these co-infection rates question whether IDU was under-reported in this study. In a recent study of 1806 Vietnamese HIV-infected patients (45% estimated to be IDUs), 27% were HCV co-infected.[24] In another recent study from Vietnam of 889 HIV patients (80% IDUs) initiating ART, 12.3% and 55.1% were co-infected with hepatitis B virus (HBV) and HCV, respectively.[15] The high prevalence of HBV and HCV in the Vietnamese HIV-infected population is a matter of great concern, given the limited access to tenofovir-based ART and HCV therapy at present. In the present study, patient blood samples are screened by use of a commercialized enzyme-linked immunosorbent assay kit (Standard Diagnostics Inc, Samcheok Si, South Korea) with sensitivity and specificity both above 99%. We are planning additional tests on stored plasma samples from all 100 patients to further characterize the HBV and HCV infections (viral load, genotype, plasma fibrosis markers).

In conclusion, among 100 ART-naïve HIV patients initiating ART in a large outpatient clinic in Vietnam, 23% had virological failure after 14 months of follow-up. The majority of patients initiated ART at much lower CD4+ cell counts than recommended by WHO. Absence of a WHO clinical stage 4 event and 'having one's health status evaluated by a physician at each visit' were both associated with lower risk of virological failure. Further larger, prospective studies of risk factors for virological failure and strategies to reduce it in LMICs are needed.

ACKNOWLEDGEMENTS

We thank professor Jens Lundgren for helpful discussions and support of the present study. The HIV RNA measurements were funded by Copenhagen HIV Programme.

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(Accepted 27 April 2011)