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Efficacy of second-line antiretroviral therapy among people living with HIV/AIDS in Asia: Results from the TREAT Asia HIV Observational Database

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Abstract

Background—Roughly 4% of the 1.25 million patients on antiretroviral therapy (ART) in Asia are using second-line therapy. To maximize patient benefit and regional resources it is important to optimize the timing of second-line ART initiation and use the most effective compounds available.

Methods—HIV positive patients enrolled in the TREAT Asia HIV Observational Database who had used second-line ART for ≥6 months were included. ART use and rates and predictors of second-line treatment failure were evaluated.

Results—There were 302 eligible patients. Most were male (76.5%) and exposed to HIV via heterosexual contact (71.5%). Median age at second-line initiation was 39.2 years, median CD4 cell count was 146 cells/mm^3, and median HIV viral load was 16,224 copies/mL. Patients started second-line ART before 2007 (n=105), 2007-2010 (n=147) and after 2010 (n=50). Ritonavir-boosted lopinavir and atazanavir accounted for the majority of protease inhibitor use after 2006. Median follow-up time on second-line was 2.3 years. The rates of treatment failure and mortality per 100 patient/years were 8.8 (95%CI 7.1 to 10.9) and 1.1 (95%CI 0.6 to 1.9), respectively. Older age, high baseline viral load and use of a protease inhibitor other than lopinavir or atazanavir were associated with a significantly shorter time to second-line failure.

Conclusions—Increased access to viral load monitoring to facilitate early detection of first-line ART failure and subsequent treatment switch is important for maximizing the durability of second-line therapy in Asia. Although second-line ART is highly effective in the region, the reported rate of failure emphasizes the need for third-line ART in a small portion of patients.

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Introduction

For the past decade, substantial effort has been devoted to the rapid scale-up of antiretroviral therapy (ART) access in areas where it is most needed. The UNAIDS report for 2013[1] states that 4.9 million people were living with HIV in the Asia Pacific region in 2012. Of these, 1.25 million where receiving ART. Roughly 4% of patients on ART are on second-line therapy.[2]

The 2013 WHO guidelines recommend initial ART consists of a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs).[3] The rate of virological suppression on first-line ART commonly exceeds 80% at one year on treatment among patients retained in care.[4] After failure on an NNRTI-containing regimen, the WHO advise second-line ART consist of a boosted protease inhibitor (PI) in combination with two NRTIs, at least one of which is new to the patient.[3] In wealthier areas, it is recommended that second-line ART consist of the most active drugs available based on genotypic analysis, treatment and adverse event history, and availability of additional classes of drugs.[5]

PIs, including the current WHO preferred PIs - ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted atazanavir (ATV/r), have been available to varying degrees across Asia for over a decade. In a study of second-line regimens containing LPV/r at a center in Cambodia, 85.7% of the 70 HIV-infected study participants had an undetectable viral load at 24 weeks.[6] However, significant challenges remain. A 2010 Cochrane review concluded that while outcomes of second-line regimens with boosted PIs are generally favorable, there is limited evidence to evaluate second-line ART in patients who fail first-line WHO-recommended treatment.[7] Furthermore, very little of the currently available literature describes second-line ART outcomes in HIV-infected patients in Asia.[6, 8-10]

Identification of treatment failure in Asia is frequently determined by clinical and immune changes, which may occur long before or long after the loss of virological suppression.[11-15] A delay in recognizing treatment failure can result in the accumulation of resistance mutations that jeopardize next-line options and efficacy[11, 16-19], a greater risk of mortality[20], and may increase the transmission of (resistant) HIV. A 2012 study out of India found 24 (53%) of 45 viremic second-line patients genotyped had triple-class resistance to NRTIs, NNRTIs, and PIs.[10] On the other hand, switching to second-line ART before it is indicated unnecessarily increases the use of expensive and less tolerated second-line agents and may result in quicker progression to treatment exhaustion.

The number of patients requiring second-line ART in Asia will increase as the number of patients accessing ART grows. To maximize patient benefit and the use of regional resources, it is important to optimize the timing of second-line ART initiation and use the most effective compounds available. The aims of this analysis are to describe the second-

line ART regimens used in a regional cohort in Asia and evaluate rates and predictors of treatment failure.

Methods

The study population consisted of patients on second-line ART who were enrolled in the TREAT Asia HIV Observational Database (TAHOD) and/or the TREAT Asia Studies to Evaluate Resistance-Monitoring (TASER-M). These cohorts have been described previously.[21, 22] Briefly, TAHOD is an observational study of patients with HIV involving 21 adult treatment centers in 12 countries and territories in Asia, which aims to assess HIV disease natural history in treated and untreated patients in the region. Retrospective and prospective data is collected at each site. Recruitment started in September 2003. TASER-M was a multi-centre, cohort study monitoring development of HIV drug resistance in patients taking ART. Patients eligible for first- or second-line ART initiation were enrolled sequentially. Data on any previous antiretroviral use was collected retrospectively. Patient recruitment commenced in March 2007 and ceased in 2011. Follow-up data continues to be collected as TASER-M was merged with TAHOD in 2012. Currently, each TAHOD site has contributed data from 100-450 patients. Data is transferred to the data management centre at the Kirby Institute, Sydney, Australia twice annually in March and September.

TAHOD (and former TASER-M) patients from the March 2013 data transfer were included in this analysis if they experienced treatment failure whilst on first-line ART and subsequently used a regimen for ≥6 months that contained ≥3 antiretroviral drugs and at least one drug class that was new to them. Day one of first-line ART was when the first regimen containing ≥3 antiretrovirals used for >14 days was initiated. Patients that underwent a drug class change on first-line ART without documentation of treatment failure were excluded. Treatment breaks and regimen modifications that did not involve a drug class change were ignored for first- and second-line ART. Since treatment monitoring protocols between TAHOD sites differ substantially and have changed over time, we applied a strict, multifaceted definition of treatment failure based on the current WHO guidelines.[3] The first occurrence of virological, immunological or clinical failure whilst on first- or second-line ART was considered the date of failure. Where multiple failure types were documented on the same day, priority was given to virological, immunological, and then clinical failure. Virological failure was considered a viral load >1,000copies/mL after 6 months of ART, confirmed within 6 months; immunological failure was defined as CD4 cell count <100 cells/mm^3 or less than baseline CD4 cell count after 6 months of ART, confirmed within 6 months and; clinical failure comprised of a new or recurrent WHO stage 3 or 4 illness or death after 6 months of ART. Baseline was considered the first day of second-line ART.

The window period for baseline CD4 cell count and viral load was between 3 months prior to, and 2 weeks after, second-line ART initiation. The measurement taken closest to second-line ART initiation was used. Patients were considered hepatitis B co-infected if they had any record of a positive hepatitis B surface antigen test in the database and hepatitis C co-infected if they had any record of a positive hepatitis C antibody test.

Statistical analysis

Cumulative incidence functions were used to evaluate rates of failure. Other types of failure were considered competing events when individually assessing virological, immunological, clinical and immunovirological failure. Cox regression stratified by study site was used to evaluate predictors of second-line ART failure. Patients with missing data were included but hazard ratios for missing categories are not reported. Follow-up time was measured from second-line ART start or enrollment date (if already on second-line ART at enrollment) until treatment failure or censoring. Censoring occurred at the last recorded clinic visit whilst still on second-line ART or at the time of a drug class change without failure.

Predictors to be used in the multivariate model were selected based on a significance level of ≤0.15 in the univariate analysis. Predictors were retained in the multivariate model if one or more categories exhibited a p-value ≤ 0.05. Multivariate hazard ratios were used to estimate the absolute risk of failure based on the survival probabilities at 12, 24 and 36 months of second-line ART in the reference group.

Stata software version 12.1 was used for all statistical analysis.

Results

Of 7,320 patients that had a history of ≥6 months of first-line ART use, 302 (4.1%) had documented evidence of treatment failure with subsequent use of a second-line regimen for ≥6 months and at least 1 day of prospective follow-up. Baseline data is presented in Table 1. The majority of eligible patients were male (76.5%) and exposed to HIV via heterosexual contact (71.5%). Median age at second-line ART initiation was 39.2 (interquartile range [IQR] 34.1 to 44.5) years, median CD4 cell count was 146 (IQR 58 to 268) cells/mm^3, and median HIV viral load was 16,224 (IQR 2,060 to 84,656) copies/mL. Hepatitis B and C status was positive in 22 (9.3%) of 237 patients tested and 25 (11.4%) of 220 patients tested, respectively. Most patients (n=228, 75.5%) initiated ART with an NNRTI-based regimen and median time on first-line ART was 3.5 (IQR 2.2 to 5.4) years. Median time from confirmation of first-line failure to second-line initiation was 9.9 (IQR 2.0 to 29.4) months. A total of 221 (73.2%) patients were switched to a dual NRTI plus PI regimen, 58 (19.2%) a dual NRTI plus NNRTI regimen, and 23 (7.6%) to an alternative second-line regimen. Alternative regimens included single NRTI plus NNRTI and/or PI (14; 60.9%), triple NRTI (4; 17.4%) and dual NRTI plus raltegravir (5; 21.7%).

Figure 1 shows the initial second-line ART regimens used by year of start. Before 2007 (n=105), dual NRTI plus PI (51.4%) was the most commonly used second-line combination. LPV/r (9.5%) and ATV/r (7.6%) use was outweighed by that of other PIs (34.3%). Other PI use mostly comprised of indinavir (80.6%). In the same period, dual NRTI plus NNRTI was used by 36.2% of patients; efavirenz being used by 23.8% of patients and nevirapine by 12.4%. Alternate second-line regimens were used by 12.4% of patients. Between 2007 and 2010 (n=147), dual NRTI plus PI (83.7%) remained the most commonly used second-line regimen though LPV/r (51.7%) and ATV/r (21.1%) use dominated over other PI (10.9%) use. Indinavir (31.3%) and darunavir (31.3%) made up the majority of other PI use. Dual NRTI plus NNRTI was used by 11.6% of patients and this mostly comprised of efavirenz-

based therapy (10.9%). Other second-line regimens were used by 4.8% of patients. After 2010 (n=50), dual NRTI plus PI (88.0%) regimens comprised LPV/r (50.0%), ATV/r (26.0%) and unboosted ATV or LPV (12.0%). Dual NRTI plus efavirenz was used by 4.0% of patients and dual NRTI plus nevirapine by 2.0%. Other second-line ART was used by 6.0% of patients. Overall, the most commonly used NRTIs for second-line ART were lamivudine/emtricitabine (76.5% of all patients), tenofovir (44.4%), zidovudine (32.1%), stavudine (12.9%), and abacavir (12.3%).

The median viral load monitoring frequency was 1.5 (IQR 0.3 to 2.3) tests/patient/year. Amongst those with any viral load result during follow-up (n=233, 77.2%), the median viral load monitoring frequency was 1.9 (IQR 1.1 to 2.6) tests/patient/year. One hundred ten (36.4%) patients had <2 viral loads documented whilst on second-line ART. Two hundred eighty nine (95.7%) patients had a follow-up CD4 cell count and the median CD4 monitoring frequency was 2.0 (IQR 1.4 to 2.9) tests/patient/year. During second-line ART, 53 (17.5%) patients had <2 CD4 cell counts documented.

The cumulative incidence of treatment failure and sub-incidences of virological failure, immunological failure and clinical failure are shown in Figure 2. Over a total follow-up time of 924.2 years, 81 patients experienced second-line treatment failure, including 12 deaths. The rate of treatment failure was 8.8 (95% confidence interval [CI] 7.1 to 10.9) per 100 patient/years and the rate of mortality alone was 1.1 (95%CI 0.6 to 1.9) per 100 patient/years. Median follow-up time on second-line was 2.3 (IQR 1.1 to 4.4) years. Median time on second-line regimen without any drug substitutions or treatment breaks was 1.8 (IQR 0.8 to 3.2) years. The rates of virological, immunological and clinical failure per 100 patient/years were 2.1 (95%CI 1.3 to 3.2), 3.3 (95%CI 2.3 to 4.6) and 3.5 (95%CI 2.5 to 4.9) respectively. Immunovirological failure occurred at a rate of 5.3 (95%CI 4.0 to 7.0) per 100 patient/years.

Predictors of second-line treatment failure are outlined in Table 2. In the final multivariate model, age 41-50 years (hazard ratio [HR] 5.50 vs. age <30 years, 95%CI 1.51 to 20.07, p=0.010), age >50 years (HR 7.50 vs. age <30 years, 95%CI 1.93 to 29.19, p=0.004), baseline viral load >10,000 copies/mL (HR 2.90 vs. <1,000 copies/mL, 95%CI 1.17 to 7.18, p=0.021), and an initial dual NRTI plus non-LPV/r, non-ATV/r PI second-line regimen (HR 3.17 vs. LPV/r or ATV/r plus dual NRTI, 95%CI 1.65 to 6.06, p=0.001) were associated with a significantly greater risk of failure. In a sensitivity analysis using only data from patients with baseline viral load available, similar results were observed (data not shown). Patients with <95% adherence during second-line were at greater risk of failure compared to those with ≥95% adherence but this association was not significant (univariate HR 1.61, 95%CI 0.34 to 7.65, p=0.551). Similarly, longer time from first-line failure to second-line ART initiation (univariate HR 0.96, 95%CI 0.56 to 1.67, p=0.896 for >18 months vs. <6 months) and baseline CD4 cell count ≤200 cells/mm^3 (univariate HR 1.33 vs. >200 cells/mm^3, 95%CI 0.78 to 2.29, p=0.296) were not significant predictors of second-line ART failure. Baseline CD4 cell count remained non-significant as a replacement for baseline viral load in the final multivariate model (HR 1.13 vs. >200 cells/mm^3, 95%CI 0.64 to 1.99, p=0.669).

Both linear trends of increasing failure risk with older age and increasing failure risk with rising baseline viral load were significant ($p<0.001$ and $p=0.031$, respectively). The absolute risks of failure for patients with baseline viral load <1,000 copies/mL after 12, 24 and 36 months of second-line ART were 6.3%, 17.1% and 21.3%, respectively (Figure 3). For the same time points, Cox model estimates for absolute risk of failure were 13.4%, 34.1% and 41.2% for those with baseline viral load 1,000-10,000 copies/mL, and 17.1%, 42.0% and 50.0% for those with baseline viral load >10,000 copies/mL.

Discussion

Over 70% of eligible second-line patients used a dual NRTI plus PI regimen. The use of LPV/r or ATV/r was particularly dominant beyond 2006. The rate of mortality was 1.1 deaths per 100 patient/years. Overall rate of second-line treatment failure was 8.8 failures per 100 patient/years however the risk of failure was significantly elevated in older patients, those with a viral load above 10,000 copies/mL at second-line initiation, and those using a PI other than LPV/r or ATV/r.

Compared with other PIs, LPV/r and ATV/r exhibit equivalent or superior efficacy, better safety, a more convenient dosing schedule and a higher genetic barrier to resistance.[23-26] The current WHO guidelines indicate LPV/r or ATV/r are the preferred PIs to be used in combination with two NRTIs after failure on a first-line NNRTI-based regimen.[3] The high proportion of first-line NNRTI use and second-line LPV/r and ATV/r use reported in this study indicates good compliance with these guidelines. A reasonable extension of the WHO advice is that second-line ART should comprise of two NRTIs and an NNRTI where a PI-based regimen was used as first-line. A previous analysis of TAHOD found the common use of PI-based first-line ART in the 90s and early 2000s has been almost entirely displaced by the regional scale up of first-line NNRTI-based therapy.[27] Therefore, it is not surprising that we found a much higher proportion of patients initiated dual NRTI plus NNRTI as second-line before 2007 (36.2%) compared with later time periods (11.6% in 2007-2010, 6.0% after 2010).

Approximately 50,000 of the 1.25 million patients currently on ART in Asia are using a second-line regimen.[1, 2] Applying the rate of second-line treatment failure and mortality reported here, and assuming 53% of failing patients exhibit triple-class drug resistance,[10] an estimated 2,040 patients per year will require third-line ART in the region. Our results differ, however, from earlier work in resource-limited settings. Pujades-Rodriguez *et al* (2010) analyzed data from 632 second-line patients enrolled in Médecins sans Frontiéres (MSF) cohorts in East Africa, Southern Africa, West/Central Africa and Asia (Cambodia, Myanmar, Laos).[9] Treatment failure occurred at a rate of 16.1 per 100 patient/years; almost double what we report here. Thirty-month mortality occurred at a rate of 4.4 deaths per 100 patient/years; four times the rate we report for overall mortality. Importantly, work out of South Africa and Zambia indicates mortality rates on second-line ART may differ substantially between clinical sites (from 0.65 to 4.52 deaths per 100 patient/years in Wanderler *et al* [28]). Rates of immunovirological failure between our cohort and the MSF cohort were the same (5.3 per 100 patient/years), suggesting the difference in treatment failure rates is entirely due to different rates of clinical failure. Unlike us, Pujades-Rodriguez

et al did not include death in their definition of clinical failure thus the rate of WHO stage 3 and 4 events was much higher in their cohort. Since their data was mostly from resource-limited African countries, this may be representative of regional differences in the occurrence of late stage WHO events and our inclusion of data from several high income Asian countries.

Pujades-Rodriguez *et al* (2010) reported that the most important predictors of treatment failure were a nelfinavir-based second-line regimen, low CD4 cell count at second-line initiation, and poor adherence.[9] Concurrently, we found an initial second-line regimen based on a PI other than LPV/r or ATV/r was strongly predictive of treatment failure. Ferradini *et al* (2011) found 85.7% of 70 HIV-infected study participants at a center in Phnom Penh had undetectable viral load after 24 weeks of second-line ART containing LPV/r.[6] Recent evidence from southern Africa also suggests that regimens without tenofovir may impair the durability of second-line ART.[28] Baseline CD4 cell count was not associated with failure in our final model, however, another important measure of HIV disease status, baseline viral load, was. Despite the widely acknowledged importance of good adherence in maintaining ART efficacy, <95% adherence during second-line ART was not significantly associated with treatment failure in our analysis. This was due to the high number of patients with missing adherence data and the very low rate of poor adherence amongst those that had data available.

Madec *et al* (2013) recently published a systematic review that estimated the incidence of switching to second-line ART in sub-Saharan Africa was 2.65 per 100 patient/years.[29] Comparing this against regional estimates of 12 month virological failure rate, which range from 5.0 to 24.5% [30-33], it appears the number of patients switched to second-line is only a fraction of those in need, even taking into account that a portion of patients may achieve virological suppression with improved adherence to a failing regimen.[34] Similarly, in Asia, treatment modification after confirmed failure is frequently subject to delay.[35] In a study of 16,591 patients starting ART in sub-Saharan Africa, cumulative mortality at 1 year was 2.2% in patients on a non-failing first-line regimen, 4.2% in patients who switched from a failing first-line regimen to a second-line regimen, and 11.7% in those who remained on a failing first-line regimen ($p<0.0001$).[20] Although patients that experienced a delay in second-line initiation in our analysis did not fare worse than those switched within 6 months of first-line failure, we did observe a significant association between high viral load at switch and treatment failure. An explanation for this is that, because HIV rapidly acquires resistance mutations when able to replicate in the presence of ART [11, 16-19], a higher viral load at second-line initiation is indicative of added drug resistance. Unfortunately, we did not have sufficient sequencing data to evaluate this further. It is also possible that high viral load at switch was a marker for patients that adhere poorly to ART. Although adherence was not associated with treatment failure in our model, self-report (as is used in TAHOD) is known to overstate adherence[36] and over 40% of patients did not have any adherence data available.

Our results indicate it may be important to switch to second-line ART whilst the virus remains partially suppressed. A 2009 study by the International Epidemiologic Databases to Evaluate AIDS study group found that switching to second-line regimens occurred earlier

and at higher CD4 cell counts in ART programs with viral load monitoring compared to programs without.[37] However, early switching may also lead to quicker exhaustion of treatment options. The WHO recommends appropriate adherence counseling prior to confirmation of virological failure.[3] Supporting this notion, Gupta *et al* (2013) recently reported that 27% of Ugandan patients with virological failure (viral load >1,000 copies/mL) at week 48 of a trial comparing first-line nevirapine or abacavir with zidovudine and lamivudine achieved re-suppression by week 96 without switching.[34] Whilst suitable for a minority, adherent patients experiencing first-line treatment failure require treatment modification. Simplification of the second-line regimen could help ease the cost of treatment, improve adherence, prevent unnecessary adverse effects, reduce the potential for drug interaction and preserve future treatment options. In 2012, Bartlett *et al* reported that LPV/r monotherapy achieved virological suppression in 107 of 123 (87%) patients from Asia and Africa who had started the regimen after virological failure on NNRTI-based first-line.[8] Further work comparing the efficacy of LPV/r monotherapy, and other treatment simplification measures, to currently recommended second-line ART is in progress.[38-42]

Interpretation of the above results and discussion should take into account several limitations. Many patients lacked data on laboratory testing, adherence and drug resistance, and median follow-up time was only 2.3 years. Also, definitions of ART failure and second-line ART are inconsistent in practice and in the literature. This limits the comparability of failure and switch rates between different clinical sites and studies. Indeed, TAHOD and TASER-M are multicenter, observational cohorts and therefore patient characteristics and patient care were heterogeneous even within in our study population. Nevertheless, given the large number of sites involved, and because we have used documented evidence of failure, applied tight criteria to define second-line treatment, and stratified our risk factor analyses by study site, we believe our results are a reasonable reflection of ART use and failure rates in Asia.

Most patients failing first-line ART in Asia are started on a PI-based second-line regimen, consistent with the current WHO guidelines. Increased access to viral load monitoring across the region to facilitate early detection of first-line ART failure and subsequent treatment switch would lead to earlier switches and maximize the durability of second-line therapy. Although second-line ART is highly effective in Asia, the current rate of failure emphasizes the need for third-line ART in a small portion of patients and the likelihood of increasing numbers of such patients in the future.

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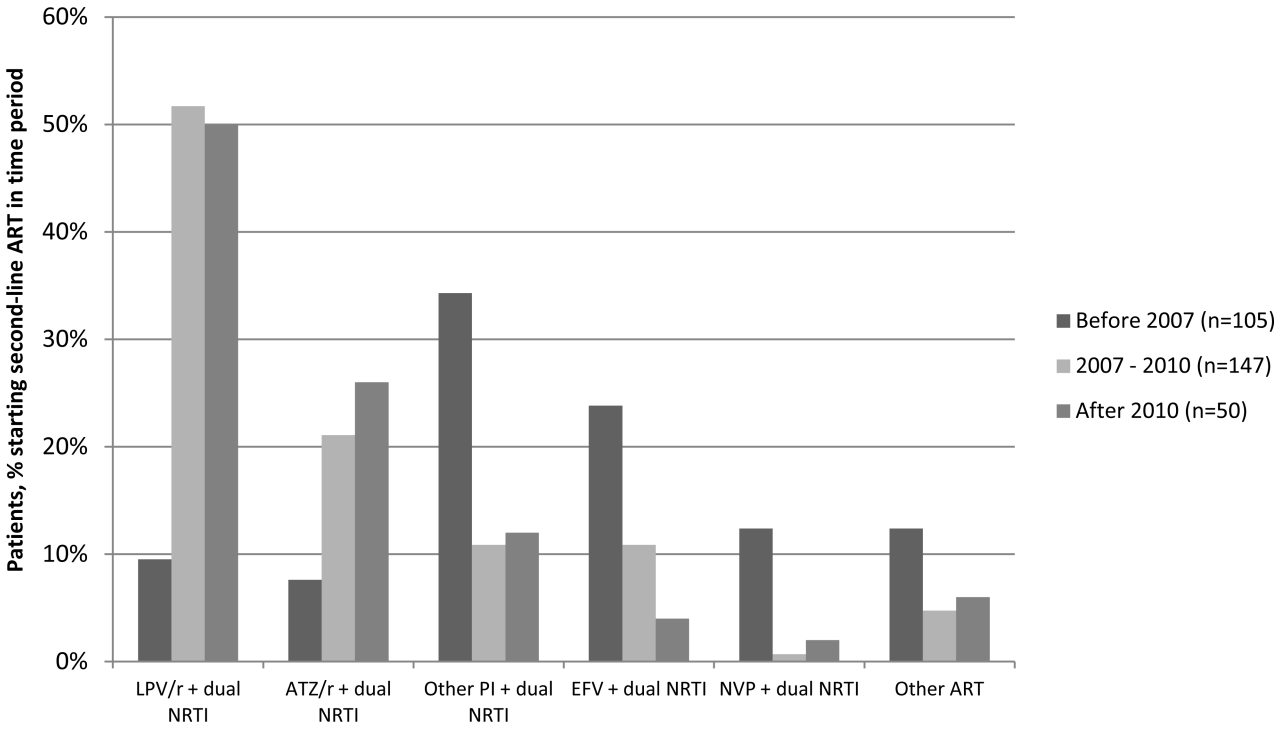

Figure 1.
Second-line ART regimens by year of initiation

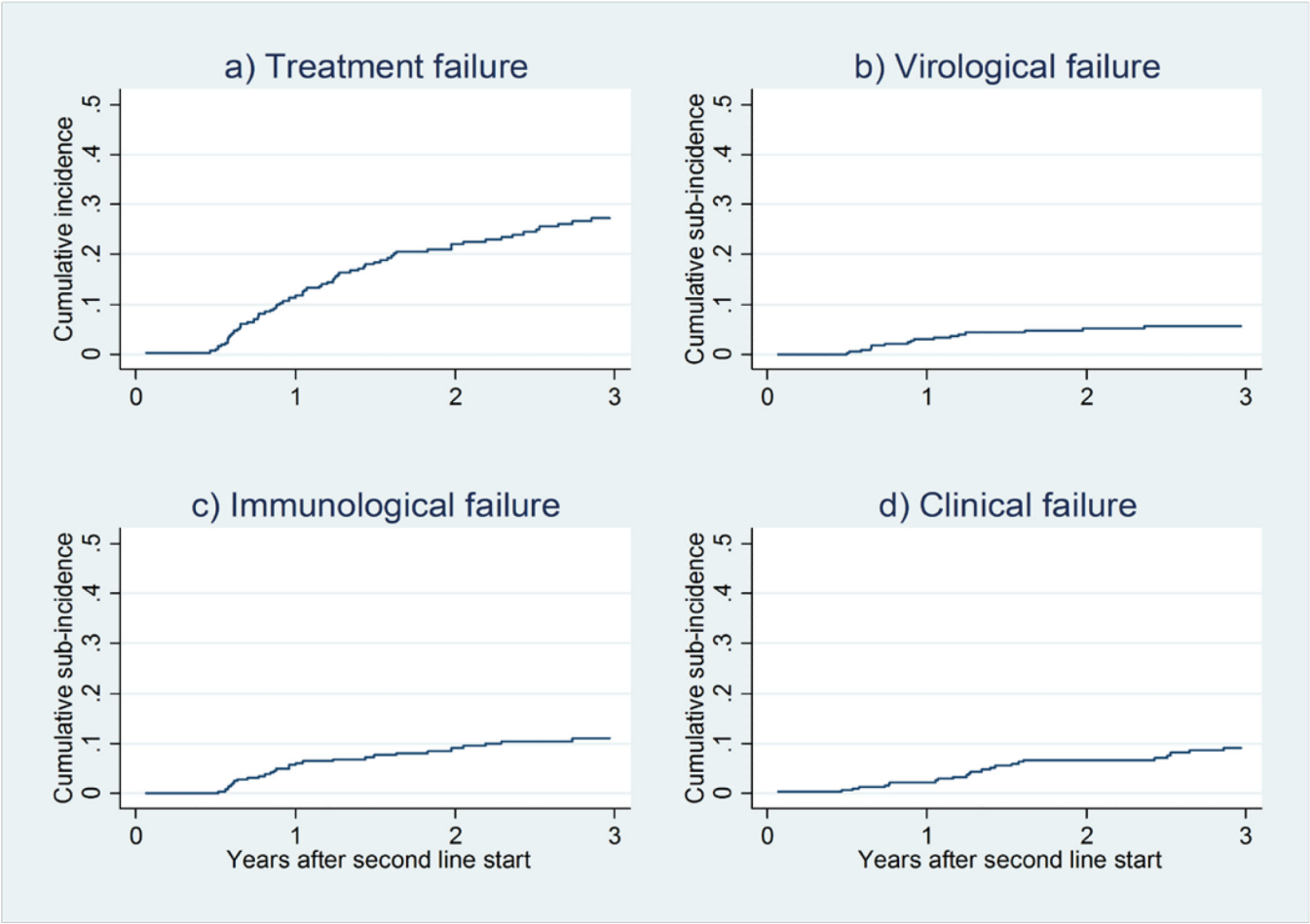

Figure 2a) to d).
Cumulative incidences and sub-incidences of second-line ART failure (n=302)

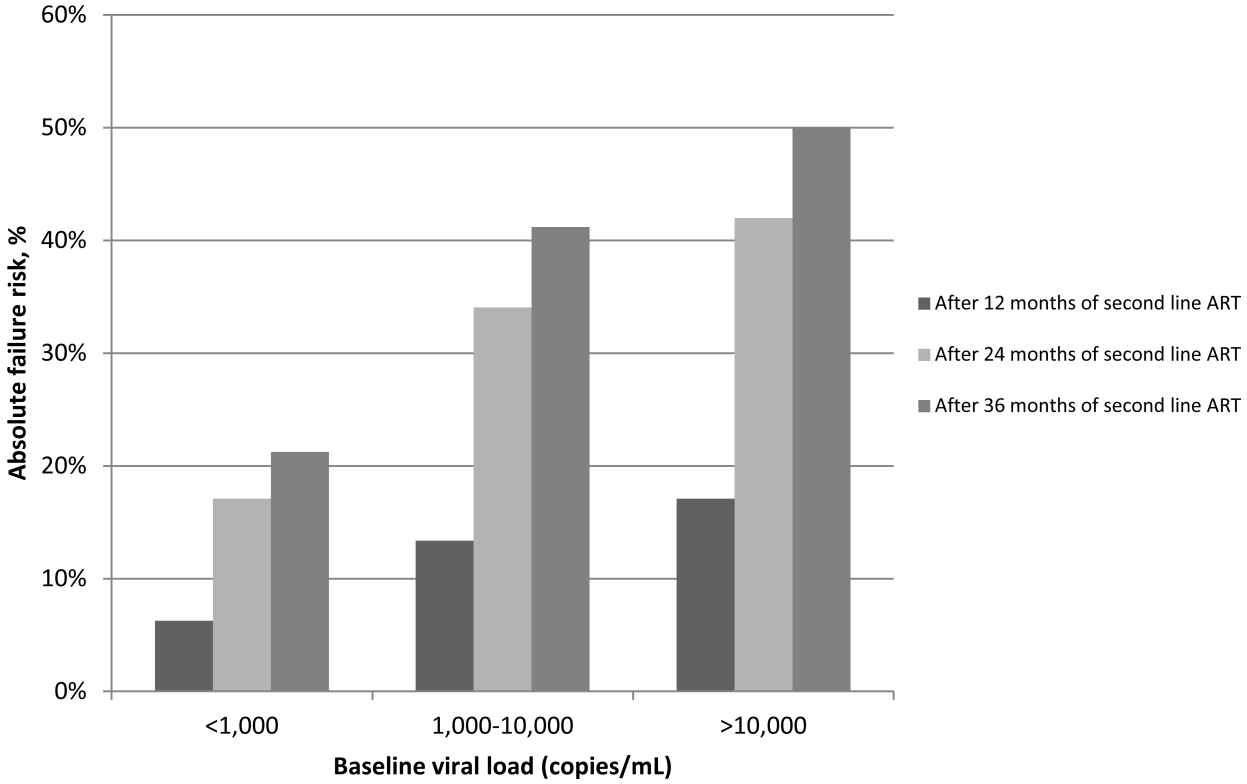

Figure 3.

Absolute risk of treatment failure after 12, 24 and 36 months of second-line ART by baseline viral load

Table 1

Baseline data for eligible patients (n=302)

Gender	
Male	231 (76.5%)
Female	71 (23.5%)
Age (yrs) Median (±IQR) = 39.2 (34.1 - 44.5)	
<30	30 (9.9%)
30-40	136 (45.0%)
41-50	102 (33.8%)
>50	34 (11.3%)
HIV Exposure	
Heterosexual	216 (71.5%)
Homosexual	48 (15.9%)
IDU	23 (7.6%)
Other	15 (5.0%)
CD4 (cells/mm^3) Median (±IQR) = 146 (58 - 268)	
>200	81 (26.8%)
≤200	139 (46.0%)
Missing	82 (27.2%)
Viral Load (copies/ml) Median (±IQR) = 16224 (2060 - 84656)	
<1000	36 (11.9%)
1000-10000	44 (14.6%)
>10000	102 (33.8%)
Unknown	120 (39.7%)
Previous AIDS	
None known	192 (63.6%)
Yes	110 (36.4%)
HBV status	
Negative	215 (71.2%)
Positive	22 (7.3%)
Not tested	65 (21.5%)
HCV status	
Negative	195 (64.6%)
Positive	25 (8.3%)
Not tested	82 (27.2%)
First line regimen	
NNRTI	228 (75.5%)
PI	64 (21.2%)
Other	10 (3.3%)

Initial second line regimen	
LPV/r or ATV/r	163 (54.0%)
Other PI	58 (19.2%)
NNRTI	58 (19.2%)
Other	23 (7.6%)
Time on first ART (yrs) Median (±IQR) = 3.54 (2.16 - 5.37)	
<2	64 (21.2%)
2-4	112 (37.1%)
>4	126 (41.7%)
Time from first failure to second ART (mths) Median (±IQR) = 9.9 (2.0 - 29.4)	
<6	125 (41.4%)
6-18	59 (19.5%)
>18	118 (39.1%)
Year of second ART start	
Before 2007	105 (34.8%)
2007-2010	147 (48.7%)
After 2010	50 (16.6%)
First-line ART failure	
Virological	130 (43.0%)
Immunological	94 (31.1%)
Clinical	78 (25.8%)
Any second line adherence record	
Yes	176 (58.3%)
No	126 (41.7%)

Exposure category ‘Other’ includes those exposed to blood products and unknown exposures. ART = antiretroviral therapy; IDU = intravenous drug use; HBV = hepatitis B; HCV = hepatitis C; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; IQR = interquartile range; LPV/r = ritonavir-boosted lopinavir; ATV/r = ritonavir-boosted atazanavir.

Table 2

Predictors of second-line treatment failure (n=302)

Covariate	Number of failures	Patient years follow up	Rate per 100pt/yrs (95%CI)	Univariate HR (95%CI)	p	p overall	Multivariate[¥] HR (95%CI)	p	p overall
Age (yrs)[¤]									
<30	3	110.48	2.72 (0.88 - 8.42)	1.00			1.00		
30-40	28	448.89	6.24 (4.31 - 9.03)	1.78 (0.52 - 6.08)	0.356		2.36 (0.65 - 8.51)	0.190	
41-50	33	268.18	12.31 (8.75 - 17.31)	3.88 (1.15 - 13.10)	0.029		5.50 (1.51 - 20.07)	**0.010**	
>50	17	96.65	17.59 (10.93 - 28.29)	4.98 (1.39 - 17.89)	0.014	<0.001[†]	7.50 (1.93 - 29.19)	**0.004**	**<0.001**[†]
Baseline viral load (copies/ml)[¤]									
<1,000	7	143.13	4.89 (2.33 - 10.26)	1.00			1.00		
1,000-10,000	12	149.62	8.02 (4.55 - 14.12)	2.30 (0.86 - 6.17)	0.098		2.22 (0.79 - 6.24)	0.130	
>10,000	26	250.23	10.39 (7.07 - 15.26)	2.43 (1.00 - 5.90)	0.050	0.051[†]	2.90 (1.17 - 7.18)	**0.021**	**0.031**[†]
Unknown	36	380.55	9.46 (6.82 - 13.11)	-			-		
Initial second-line regimen									
LPV/r or ATV/r + dual NRTI	29	427.00	6.79 (4.72 - 9.77)	1.00			1.00		
Other PI + dual NRTI	21	188.33	11.15 (7.27 - 17.10)	2.71 (1.40 - 5.25)	0.003		3.17 (1.65 - 6.06)	**0.001**	
NNRTI + dual NRTI	21	232.05	9.05 (5.90 - 13.88)	0.92 (0.48 - 1.76)	0.806		0.96 (0.50 - 1.84)	0.904	
Other	10	76.82	13.02 (7.00 - 24.19)	1.19 (0.54 - 2.62)	0.675	0.018[‡]	1.94 (0.83 - 4.56)	0.128	**0.002**[‡]
Gender									
Male	66	711.59	9.27 (7.29 - 11.81)	1.00			1.00		

Covariate	Number of failures	Patient years follow up	Rate per 100pt/yrs (95%CI)	Univariate HR (95%CI)	p	p overall	Multivariate[¥] HR (95%CI)	p	p overall
Female	15	212.60	7.06 (4.25 - 11.70)	0.87 (0.47 - 1.60)	0.647		0.99 (0.51 - 1.90)	0.968	
HIV exposure									
Heterosexual	62	665.32	9.32 (7.27 - 11.95)	1.00			1.00		
Homosexual	12	135.16	8.88 (5.04 - 15.63)	0.74 (0.34 - 1.59)	0.434		1.18 (0.50 - 2.78)	0.710	
IDU	3	80.37	3.73 (1.20 - 11.57)	0.89 (0.23 - 3.36)	0.858		1.04 (0.25 - 4.25)	0.958	
Other	4	43.35	9.23 (3.46 - 24.58)	1.07 (0.37 - 3.09)	0.896	0.871[‡]	0.87 (0.28 - 2.69)	0.816	0.974[‡]
Baseline CD4 (cells/mm^3)									
>200	24	237.00	10.13 (6.79 - 15.11)	1.00			1.00		
≤200	41	409.45	10.01 (7.37 - 13.60)	1.33 (0.78 - 2.29)	0.296		0.96 (0.53 - 1.74)	0.896	
Missing	16	277.75	5.76 (3.53 - 9.40)	-			-		
AIDS prior to second-line ART									
None known	45	583.53	7.71 (5.76 - 10.33)	1.00			1.00		
Yes	36	340.67	10.57 (7.62 - 14.65)	1.28 (0.78 - 2.09)	0.326		1.19 (0.72 - 1.98)	0.505	
HBV status									
Negative	57	700.37	8.14 (6.28 - 10.55)	1.00			1.00		
Positive	6	70.81	8.47 (3.81 - 18.86)	0.85 (0.36 - 2.05)	0.724		1.06 (0.42 - 2.62)	0.907	
Not tested	18	153.02	11.76 (7.41 - 18.67)	-			-		
HCV status									
Negative	57	636.51	8.96 (6.91 - 11.61)	1.00			1.00		
Positive	2	75.00	2.67 (0.67 - 10.66)	0.48 (0.11 - 2.06)	0.323		0.34 (0.08 - 1.51)	0.158	

Covariate	Number of failures	Patient years follow up	Rate per 100pt/yrs (95%CI)	Univariate HR (95%CI)	p	p overall	Multivariate[¥] HR (95%CI)	p	p overall
Not tested	22	212.69	10.34 (6.81 - 15.71)						
First-line regimen									
NNRTI	53	637.85	8.31 (6.35 - 10.88)	1.00			1.00		
PI	23	237.79	9.67 (6.43 - 14.56)	0.89 (0.47 - 1.67)	0.709		1.51 (0.38 - 6.04)	0.561	
Other	5	48.56	10.30 (4.29 - 24.74)	0.48 (0.17 - 1.34)	0.161	0.373[‡]	0.53 (0.13 - 2.19)	0.383	0.243[‡]
Time on first-line ART (yrs)									
<2	34	342.87	9.92 (7.09 - 13.88)	1.00			1.00		
2-4	26	388.40	6.69 (4.56 - 9.83)	0.92 (0.54 - 1.58)	0.770		1.02 (0.58 - 1.81)	0.934	
>4	21	192.93	10.89 (7.10 - 16.69)	1.10 (0.62 - 1.95)	0.747	0.796[†]	1.08 (0.59 - 1.97)	0.797	0.801[†]
Time from failure to second-line ART (mths)									
<6	26	329.73	7.89 (5.37 - 11.58)	1.00			1.00		
6-18	19	223.29	8.51 (5.43 - 13.34)	1.05 (0.56 - 1.98)	0.884		1.19 (0.59 - 2.41)	0.631	
>18	36	371.17	9.70 (7.00 - 13.45)	0.96 (0.56 - 1.67)	0.896	0.879[†]	1.17 (0.64 - 2.12)	0.614	0.641[†]
Year of second-line ART start									
Before 2007	44	466.68	9.43 (7.02 - 12.67)	1.00			1.00		
2007-2010	34	399.67	8.51 (6.08 - 11.91)	1.12 (0.66 - 1.89)	0.669		1.31 (0.73 - 2.37)	0.371	
After 2010	3	57.84	5.19 (1.67 - 16.08)	0.49 (0.15 - 1.67)	0.258	0.591[†]	0.57 (0.15 - 2.12)	0.401	0.953[†]
Adherence during second-line[*]									
>95%	18	554.61	3.25 (2.04 - 5.15)	1.00			1.00		

Covariate	Number of failures	Patient years follow up	Rate per 100pt/yrs (95%CI)	Univariate HR (95%CI)	p	p overall	Multivariate[¥] HR (95%CI)	p	p overall
<95%	2	31.42	6.36 (1.59 - 25.45)	1.61 (0.34 - 7.65)	0.551		1.67 (0.33 - 8.59)	0.537	
Unknown	61	337.50	18.07 (14.06 - 23.23)	-			-		

All models stratified by site.

[¤] Included in final model

[¥] Adjusted for predictors of failure included in the fina model (age, baseline viral load, and initial second-line regimen)

[*] Time updated

[†] p overall for linear trend

[‡] p overall for heterogeneity. ART = antiretroviral therapy; IDU = intravenous drug use; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor based therapy; PI = protease inhibitor based therapy; LPV/r = ritonavir-boosted lopinavir; ATV/r = ritonavir-boosted atazanavir; HBV = Hepatitis B virus; HCV = Hepatitis C virus.