AIDS

DOI: 10.1097/QAD.0000000000001144

Associations between HIV-RNA-based indicators and virological and clinical outcomes

Running head: HIV-RNA-based indicators and outcomes

Authors: Kamilla LAUT[1], Leah C SHEPHERD[2], Court PEDERSEN[3], Jürgen K ROCKSTROH[4], Helen SAMBATAKOU[5], Dimitry PADUTA[6], Raimonda MATULIONYTE[7], Tomasz SMIATACZ[8], Fiona MULCAHY[9], Jens D LUNDGREN[1], Amanda MOCROFT[2], Ole KIRK[1], on behalf of EuroSIDA in EuroCoord

Affiliations: [1]CHIP, Centre for Health & Infectious Diseases Research, Department of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. [2]HIV Epidemiology and Biostatistics Unit, Dept Infection and Population Health, University College London, London, United Kingdom. [3]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark. [4]Immunologische Ambulanz, University Hospital Bonn, Bonn, Germany. [5]2nd dept of Internal Medicine, Hippokration General Hospital, University of Athens, Athens, Greece. [6]Epidemiology and Health Care, Gomel Regional Centre for Hygiene, Gomel, Belarus. [7]Department of Infectious, Chest diseases, Dermatovenerology and Allergology, Vilnius University; Centre of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania. [8]Tomasz Smiatacz Dept of Infectious Diseases, Medical University Gdansk, Gdansk, Poland. [9]The Guide Clinic, St James' Hospital, Dublin, Ireland.

Total word count: 3,499 words

Abstract word count: 250 words

Corresponding author: Kamilla Grønborg Laut.

Rigshospitalet, University of Copenhagen, CHIP, Department of Infectious Diseases, Section 2100, Finsencentret, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark

Email: kamilla.groenborg.laut.01@regionh.dk

Abstract:

Objectives: To evaluate and compare the performance of six HIV-RNA-based quality of care indicators for predicting short-term and long-term outcomes.

Design: Multinational cohort study.

Methods: We included EuroSIDA patients on antiretroviral therapy (ART) with ≥3 viral load (VL) measurements after baseline (the latest of 01/01/2001 or entry into EuroSIDA). Using multivariate Poisson regression we modelled the association between short-term (resistance, triple-class failure) and long-term (all-cause mortality, any AIDS/non-AIDS clinical event) outcomes and the indicators: *(i)* viraemia copy years (VCY), *(ii)* Consecutive months with VL ≥50copies/mL, *(iii)* percentage of time on ART spent fully suppressed (%FS), *(iv)* stable on ART, *(v)* 48 weeks snapshot, and *(vi)* current VL. Indicators were compared using area under the ROC curve (AUC) and different measures of model fit.

Results: Adjusted incidence rate ratios for all outcomes tended to increase with increasing VCY, number of consecutive months with VL ≥50copies/mL, current VL and with lower %FS, but the gradient of increased risk was weak across strata. None of the indicators reliably identified those at risk of long-term outcomes (AUC 0.54-0.58), but performed consistently better with short-term outcomes (triple class failure [AUC 0.67-0.76]) and resistance [AUC 0.64-0.79]). Goodness of fit varied with the outcome evaluated, but differences between indicators were small.

Conclusions: Differences between quality of care indicators were small and no indicator performed consistently better than current VL. Given the simplicity in assessing and interpreting this indicator, we propose to use current VL when HIV-RNA-based indicators are used to evaluate the efficacy of ART programs.

Keywords/MeSH terms: quality indicators, benchmarking, HIV, viral load, AIDS, outcome assessment (health care)

Introduction

Evaluating and comparing the quality of antiretroviral (ART) care is essential to ensure that effective ART is provided to individuals with HIV. How best to monitor the quality of care has received growing interest in recent years, within [1–4] as well as beyond the HIV field [5–8], and using indicators has become a common approach to measuring quality of care, in that they allow for some quantification of program performance, allow for comparisons between different programs, and may help to identify gaps in care[8]. Clinicians have long sought to find an indicator that assesses the quality of ART care in a simple and uniform way, and have proposed several HIV-RNA-based indicators to distinguish those at high risk of HIV progression from those at low risk. Because of the well-known benefits of a suppressed HIV viral load (VL) in reducing mortality and morbidity [3,9–11], VL has long been used as an indicator to monitor the efficacy of ART in clinical trials as well as in clinical care. Thus, VL suppression at 12 months after ART initiation is a WHO-recommended indicator of quality of ART care [3], whereas recent studies suggest that cumulative measurements, such as viraemia copy years (VCY) and percentage of follow-up time

spent with suppressed VL are also associated with AIDS-related malignancies [12,13], non-AIDS defining malignancies [14] and death [15–17].

There is a need to consider whether indicators currently used capture those at highest risk of disease progression, and thus which can best be used to evaluate the efficacy of ART programs. While some have compared the performance of cross-sectional and cumulative VL-measures at predicting various outcomes [12,14,15,17,18], none have evaluated both short-term and long-term outcomes comparing a wide range of HIV-RNA-based indicators. An indicator that reliably predicts outcome may be used to establish a benchmark level of achievable viral suppression at a population level, which allows for comparing ART programs across clinics, countries, and regions [3,7,8]. We compared the performance of existing quality of care indicators for a range of short-term (resistance and triple class failure) and long-term (all-cause mortality and any AIDS/non-AIDS clinical event) outcomes. The aim was to identify the indicator that most reliably can evaluate care in different populations.

Patients and methods:

Patients: EuroSIDA is an observational cohort study of 20,852 HIV-1 positive individuals (as of December 2015) followed in 105 clinics in 35 countries across Europe, Israel, and Argentina. Details about the study have been published elsewhere [19]. In brief, demographic and clinical data, including all CD4-cell counts and HIV-RNA measurements, are collected at enrolment in the study and every 6 months thereafter. Data about ongoing ART and reasons for stopping or switching ART are collected, as are data on resistance testing, including resistance test results, if available. The date of diagnosis of all AIDS-defining illnesses are collected, using the 1993 Centers for Disease Control and Prevention definitions, as well as dates of any non-AIDS defining illness. Detailed

information about the cause of death is collected using the Coding of Death in HIV (CoDe) system [20]. An extensive quality assurance program has been implemented and includes site visits with source verification of all major clinical events and monitoring data from a random selection of patients followed at each site.

Follow-up:

We evaluated follow-up time for patients on ART followed in the EuroSIDA study from baseline, defined as the latest of January 1st 2001 or entry into EuroSIDA, and with ≥3 VL-measurements after baseline with detection limit 50copies/mL. The first 4 months after treatment initiation or change due to treatment failure and with HIV VL ≥50copies/mL were censored to allow full suppression to occur [21]. VL-measurements were censored if the lower limit of detection was >50 copies/mL. To model VL between measurements, each measured value was carried forward until the next measurement or for a maximum of 12 months, after which it was censored and restarted at the next VL-measurement. Follow-up was until death or last follow-up, and multiple events were allowed (not for triple class failure or all-cause mortality). ART was defined as receiving any ≥3 antiretrovirals from any class. Virological suppression was defined as VL <50copies/mL. Triple class failure of the three original ART classes was defined as virological failure (at least 4 months continuous use of a drug with VL >500copies/mL) of two nucleoside reverse transcriptase inhibitors (NRTI), one non-nucleoside reverse transcriptase inhibitor (NNRTI) and one protease inhibitor(PI)[22,23]. Resistance was defined as any NRTI, NNRTI, or major PI mutation.

Calculating the six quality of care indicators:

The six quality of care indicators were calculated as illustrated in figure 1. *Current VL* was the value of the most recent HIV-RNA within 12 months of assessment. *Viraemia copy years (VCY)*

[17] was calculated as the area under the curve using the trapezoidal rule. Values below the assay detection limit were set to zero, meaning that an individual would not accumulate VCY if fully virologically suppressed. *Consecutive months with VL ≥50copies/mL* was calculated as a summation of the number of consecutive months with VL ≥50copies/mL. *Percentage of time on ART spent fully suppressed* (%FS) [13,14,24,25] was calculated as the cumulative percentage of time on ART spent with VL <50copies/mL, and was modeled as a categorical value (0-69%, 70-79%, 80-89%, 90-94%, 95-99%, 100%). The *48 weeks snapshot* [3] assesses the virological outcome at 48 weeks (window ±24 weeks) after treatment initiation or change. VL <50copies/mL was characterized as "suppressed", VL ≥50copies/mL or missing was characterized as "not suppressed". *Stable on ART* was defined as being on the same ART regimen for a minimum of the prior 12 months with at least 1 VL <50copies/mL during that time. Those with missing VL were considered "not stable on ART".

Incidence rates:

All events occurring during the follow-up time were recorded and Poisson regression, using generalized estimating equations, was used to model incidence rates (IR) of each endpoint, adjusting for age* (per 10 years older), gender, body mass index, smoking status*, mode of transmission, ethnicity, region of residence, CD4 cell count*, cumulative years on ART*, current PI use*, current NNRTI use*, cumulative number of antiretrovirals used historically*, prior AIDS events*, prior non-AIDS events* (cardiovascular disease, end stage liver disease, end stage renal disease, pancreatitis), prior AIDS/non-AIDS-defining malignancies*, prior hepatitis B*, prior hepatitis C*, diabetes*, and hypertension*. Resistance models were also adjusted for prior resistance*. Time updated variables are indicated by *. Due to low numbers, incidence rates could not be calculated for triple class failure at different levels of current VL.

Comparison of quality of care indicators:

We compared the performance of each quality indicator model with a reference model containing current VL by calculating discrimination and goodness of fit. Logistic regression models were used to assess the Area Under the Receiver Operating Curve (AUC) for each model's ability to identify those at risk of developing each endpoint within a common, fixed follow-up time of 5 years after baseline. Because the 48 weeks snapshot is a time-fixed indicator at 48 weeks, comparisons with this model were performed prospectively up to 5 years after this 48 week mark. We compared the goodness of fit of models containing each indicator only, to models containing any combination of indicator information, and compared global model fit using generalized score tests [27] and QIC statistics (Quasi-likelihood under the Independence model Criterion)[28].

Results:

Of 18,786 patients in the EuroSIDA study at the time of analysis, 11,860 had ≥3 VL measurements available after baseline. The majority of patients were Caucasian (86.8%), male (75.0%) and with median age 41 years (interquartile range [IQR] 35-48). The predominant route of infection was men who have sex with men (44%) followed by heterosexual transmission (31%) and injecting drug use (18%). Median baseline CD4 was 430 cells/mm^3 (IQR 283-609), median baseline HIV-RNA was <50copies/mL (IQR 39-79). Patients contributed with a median of 4.9 (IQR 2.3–8.4) person years of follow-up (PYFU) and 14 (IQR 5-24) VL-measurements with a median time between two consecutive measurements of 10 months (IQR 7.5-12.75). The majority of patients (95%) had at least 1 HIV-RNA <50copies/mL during follow-up, and patients had been on ART for a median of 4.5 (IQR 3.2-5.9) years.

During 64,658 PYFU 561 patients died with non-AIDS related conditions being the main causes of death (n=487, 86.6%). The median time between last VL-measurement and any AIDS/non-AIDS clinical event was 3.0 months (IQR 1.0 -5.0) and until death 3.0 (IQR 2.0-5.9) months. Proportionally more follow-up time was censored in East and Central Eastern Europe compared with other regions (41% versus 28% of total follow-up time censored). The numbers of other events were as follows: triple class failure n=78, resistance n=779, non-fatal AIDS/non-AIDS defining event n=1620 of which 57% were not AIDS-related.

Incidence rates:

Table 1 shows the crude incidence rates per 1000 PYFU of triple class failure, resistance, any AIDS/non-AIDS clinical event and all-cause mortality, separately by each quality of care indicator. The number of events, person years of follow-up and incidence rates for strata of each indicator are shown. There were 1,726 AIDS/non-AIDS clinical events among patients with current VL <50 copies/mL during 55,049 PYFU, giving a crude incidence rate of 31.4 (95% Confidence Interval [CI] 29.9, 32.9) per 1000 PYFU, rising to IR 99.7 (95%CI 85.4, 116.5) per 1000 PYFU at current VL >10,000 copies/mL. Overall, incidence rates of any outcome increased across strata of increasing current VL, increasing VCY, with a higher number of consecutive months with VL ≥50copies/mL, and with decreasing %FS.

Figure 2 shows adjusted incidence rate ratios (aIRR) for each of the four outcomes by quality of care indicator. The figures are ordered horizontally by indicator and vertically by outcome. The adjusted incidence rate ratios increased across strata of increasing current VL, increasing VCY, with higher number of consecutive months with VL ≥50copies/mL and with lower %FS. However, the gradient varied greatly depending on the outcome evaluated. For example, compared to those with current VL<50 copies/mL, the rate of any AIDS/non-AIDS clinical event was similar (aIRR

0.9 [95%CI 0.8, 1.1, p=0.452]) for those with current VL 51-500 copies/mL, increasing to aIRR 1.6 (1.1, 2.3, p=0.007) at 501-1,000 copies/mL, aIRR 0.98 (0.8, 1.3, p=0.900) at 1,001-10,000 copies/mL, and aIRR 1.9 (1.6, 2.3, p<0.0001) for those with current VL >10,000 copies/mL. Thus, although the incidence of any AIDS/non-AIDS clinical event was significantly higher at high (>10,000 copies/mL) compared with low current VL (≤50 copies/mL), the gradient was weak across strata of increasing current VL. Furthermore, those with current VL >10,000 copies/mL had a 32.6 times higher (aIRR 32.6 [95%CI 23.6, 45.1, p<0.0001]) incidence of resistance than those with current VL <50 copies/mL, whereas the adjusted incidence rate ratios for all-cause mortality (aIRR 1.6 [1.1, 2.2, p=0.011]) and for any clinical event (aIRR 1.9 [1.6, 2.3, p<0.0001]) were considerably lower when comparing the same two strata of current VL. All indicators were weakly associated with all-cause mortality and any AIDS/non-AIDS clinical event, but were significantly associated with triple class failure and resistance.

Patients who were not stable on ART had a higher incidence rate of all outcomes than those who were (any clinical event aIRR 1.2 [1.1, 1.4, p=0.003], all-cause mortality aIRR 1.1 [0.9, 1.3, p=0.536], resistance aIRR 12.4 [9.4, 16.3, p<0.0001], triple class failure aIRR 7.30 [IQR 4.3, 12.5, p<0.0001] for not stable on ART compared with stable on ART).

Comparison of quality of care indicators:

As shown in figure 3, the moderate association between any indicator and clinical events was reflected in a poor discriminative ability with AUC-scores between 0.54-0.58 for identifying those at risk of any clinical event or all-cause mortality. For a model containing current VL, AUC was 0.57 (95%CI 0.55,0.59) for predicting any AIDS/non-AIDS clinical event and 0.56 (95%CI 0.53,0.60) for predicting all-cause mortality. The differences in AUC between indicators were 0.03 or less. Two models were significantly different from the reference current VL-model, but neither performed better than current VL at identifying those at risk of any clinical event. Adding VCY to a

model containing current VL contributed with some information at predicting any AIDS/non-AIDS clinical event (AUC 0.58 [95%CI 0.56,0.60]), but did not increase the AUC compared with current VL alone (AUC 0.58 [0.55,0.60], p for comparison =0.02). The indicators were consistently better at identifying those at risk of short-term outcomes (AUC 0.74-0.86 for predicting triple class failure, AUC 0.74-0.82 for predicting resistance). Adding %FS to a model containing current VL increased AUC for predicting resistance from 0.79 (0.75,0.82) to 0.82 (0.79,0.85, p=0.001). The predictive value of all other indicators was equal to or significantly worse than current VL at identifying short-term outcomes. Sensitivity analyses using an assay cut-off <500 copies/mL showed similar results.

Table 2 shows the results of the generalized score tests. Each row shows the χ^2-values and corresponding p-values for a model containing all indicators, and for separate models leaving out each of the indicators one at a time. A higher χ^2, and corresponding lower p-value, indicates that model fit decreases when the indicator is left out. In other words, an indicator that improves model fit will have a higher χ^2 and a lower p-value. Thus, leaving out consecutive months with VL ≥50 copies/mL did not change model fit significantly (χ^2 = 9.36, p=0.096), whereas leaving out current VL did (χ^2 = 30.38, p<0.0001) when modelling the association between indicators and any AIDS/non-AIDS clinical event. Likewise, there was no evidence that leaving out VCY from the model significantly changed model fit (χ^2 = 16.22, p=0.006), whereas current VL seemed to add information to a model of any AIDS/non-AIDS clinical event (χ^2 = 29.68, p<0.0001). Again, the best fitting models depended on the outcome evaluated: including VCY gave the best model fit for triple class failure, current VL for resistance and any clinical event, and including %FS gave the best fit for all-cause mortality. Although cumulative measures contributed with some information,

goodness of fit was not substantially improved when compared to the model containing current VL only.

Using QIC to identify the best fitting models, we again found that the models were ranked differently depending on the outcome evaluated (data not shown).

Discussion:

We compared six indicators of quality of ART care in the EuroSIDA study. We found that the predictive value of each indicator depended on the outcome evaluated, and no indicator was consistently better than the others. Whereas current VL most reliably identified those at risk of developing short-term outcomes such as resistance and triple class failure, cumulative indicators were more informative for long-term outcomes such as the risk of any AIDS/non-AIDS clinical event and all-cause mortality. All indicators generally performed better at predicting short-term outcomes than clinical events. Using a range of statistical methods, we repeatedly found that, although cumulative measures had some prognostic value, only little extra prognostic information could be gained compared to current VL alone. From a clinical viewpoint, using current VL has some obvious advantages, as it is simpler to both understand and calculate than cumulative indicators. Further, a strength of using current VL as a quality of care indicator is that it reflects current care, rather than reflecting previous clinical practices, as do some cumulative HIV-RNA-based indicators.

Our findings are unlike some recent studies that found an association between cumulative HIV measures and varying clinical outcomes [12–17]. An association between higher viraemia copy years and mortality was reported by some [15], while others found an association only if VCY was dichotomized to high compared with low values [16,18]. We, too, found that high VCY was

associated with a higher risk of any of the evaluated outcomes compared with VCY=0, but the gradient was weak across strata of VCY. Further, this pattern was similar for any indicator with evidence of a difference in clinical outcome between high and low values of the indicator, but a weak gradient across strata. However, the gradient of increased risk was consistently higher for short-term outcomes. VCY was originally derived in a cohort of HIV-positive men who did not receive effective ART [17], and it is quite possible that VCY is a reliable indicator in such high-risk patients, but may not perform as well in a population on ART with an abundance of low-risk patients.

Few other studies have investigated the association between quality of care indicators and short-term outcomes. Some have investigated the association with cross-sectional VL measures and development of resistance [29,30] and triple class failure [31], whereas studies of the association with cumulative VL are few. One previous EuroSIDA study found that low VCY was associated with a high rate of resistance development, and hypothesized that a high VCY is a surrogate for low resistance pressure due to poor adherence [32]. Others found some evidence of association between a higher cumulative time on ART with VL >500copies/mL and development of triple class failure following virological failure of an NNRTI [22].

Monitoring and improving HIV care has received much interest in recent years and researchers have attempted to develop new or synthesize existing indicators into a model for assessing care [1,2,4]. A clinical event may be thought of as the result of the comprehensive care provided to a patient. For HIV-positive individuals, however, there is a substantial time-delay between starting ART and developing clinical events, and HIV-RNA serves as a surrogate for health outcomes that could otherwise only be measured after years. As indicated by some, there are limitations to using viral

suppression as a general measure of quality of care, as a range of patient-specific factors may affect the level of suppression [33]. Although the absence of viral suppression is thus not always a marker of poor quality of care, we believe it may help to identify high and poor performing providers, and may serve as a useful benchmark to allow comparisons between programs nationally and internationally.

However, good quality HIV care is multifaceted, and our findings underline that understanding and measuring the quality of ART programs goes beyond measuring HIV-RNA. Comparing current levels of viral suppression between countries may thus be the first step to subsequently assess the reasons for the observed differences, and future research should seek to further uncover the linkage between differences in suppression rates and differences in HIV management. Current VL should thus be one indicator in a comprehensive set of core indicators to benchmark HIV care across Europe.

Our study has several strengths. We were able to externally validate and compare a range of different indicators using a variety of outcomes, including key clinical outcomes, in the same large cohort with a high number of person years. Further, our study has the advantage of comparatively longer follow-up times, allowing for a more accurate assessment of the indicators' prognostic value for long-term outcomes. Few other studies have compared the association between cross-sectional and cumulative measures and incidence of clinical outcomes, and none have evaluated both long-term and short-term outcomes using the same dataset.

Our study also has certain limitations. A shortcoming of HIV-RNA-based quality indicators is that they are inherently insensitive to those with missing VL-measurements, but capture only those that are to some extent retained in care. We chose a conservative approach by treating all missing values

as failure, giving a correspondingly conservative estimate of care. However, viral loads may be missing for those on ART but not in care, those refusing VL monitoring, patients with poor adherence and with poor clinic attendance, or those lost to follow-up. Or they may be missing for patients with poor or no access to VL monitoring or may be caused by reporting delays. The implications for these patients may vary greatly, and understanding the relative contributions of the different scenarios is important to determine where effective interventions should be focused.

To avoid censoring a large number of people with ≥6 months between two consecutive VL-measurements, we defined stable on ART as being on the same ART-regimen for a minimum of the prior 12 months with at least *one* fully suppressed VL during that time, rather than two (confirmed failure). Virological "blips" are not uncommon [34], and therefore the number of individuals that were not stable on ART may have been overestimated, leading to an underestimation of the performance of this indicator. Finally, as not all sites have access to assays with a sensitivity of 50copies/mL, proportionally more follow-up time was censured in Eastern Europe compared with other regions, which may also bias our results, although our sensitivity analyses using 500 copies/ml as a lower limit of detection showed similar results.

Conclusion:

We compared six indicators of quality of ART care with the goal of identifying the indicator that most reliably can evaluate and compare the performance of ART programs. Using a range of statistical methods, we found that differences between the indicators were small, and no indicator performed consistently better than current VL. Due to the simplicity in assessing and interpreting this indicator, we propose to use current VL when HIV-RNA-based indicators are used to evaluate the efficacy of ART programs, and we propose that quantifying the level of current VL in a

population on ART allows for comparing and benchmarking the quality of HIV care across populations.

Aknowledgements:

Jens D Lundgren, Ole Kirk, Amanda Mocroft and Kamilla Laut conceived the idea of the study. Leah Shepherd carried out the statistical analysis. Ole Kirk, Amanda Mocroft, Jens D Lundgren, Leah Shepherd and Kamilla Laut contributed to the data analysis and interpretation of the results. Court Pedersen, Jürgen K Rockstroh, Helen Sambatakou, Dimitry Paduta, Raimonda Matulionyte, Tomasz Smiatacz and Fiona Mulcahy contributed with data collection. Kamilla Laut wrote the article with input and review from all authors. All authors have read and approved the final manuscript.

Data have previously been presented at CROI 2015 under the abstract number 561.

The EuroSIDA study group:

(national coordinators in parenthesis)

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

Bulgaria: (K Kostov), Infectious Diseases Hospital, Sofia. **Croatia:** (J Begovac), University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** G Kronborg,T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; NF Møller, C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, U B Dragsted, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. **Estonia:** (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki. **France:** (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; L Cotte, Hôpital de la Croix Rousse, Lyon; C Pradier, E Fontas, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux, C Duvivier, Hôpital Necker-Enfants Malades, Paris. **Germany:** (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. **Georgia:** (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi. **Greece:** (J Kosmidis), P Gargalianos, G Xylomenos, P Lourida, Athens General Hospital; H Sambatakou, Ippokration General Hospital, Athens. **Hungary:** (J Szlávik), Szent Lásló Hospital, Budapest. **Iceland:** (M Gottfredsson), Landspitali University Hospital, Reykjavik. **Ireland:** (F Mulcahy), St. James's Hospital, Dublin. **Israel:** (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem. **Italy:** (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria

Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. **Latvia:** (B Rozentale), Infectology Centre of Latvia, Riga. **Lithuania:** (V Uzdaviniene) Vilnius University Hospital Santariskiu Klinikos, Vilnius; R Matulionyte, Center of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius. **Luxembourg:** (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. **Netherlands:** (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo. **Poland:** (B Knysz), J Gasiorowski, M Inglot, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Bialystok; M Parczewski, M Pynka, K Maciejewska, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz; I Mozer-Lisewska, Poznan University of Medical Sciences, Poznan. **Portugal:** (M Doroana), L Caldeira, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (R Radoi), C Oprea, Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest. **Russia:** (A Rakhmanova) (deceased), Medical Academy Botkin Hospital, St Petersburg; A Rakhmanova, St Petersburg AIDS Centre, St Peterburg; T Trofimora, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute, Nizhny Novogrod. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** A Shunnar, D Staneková, Dérer Hospital, Bratislava. **Slovenia:** (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. **Spain:** (JM Gatell), JM Miró, Hospital Clinic Universitari de Barcelona, Barcelona; S Moreno, J. M. Rodriguez,

Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz. **Sweden:** (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; A Blaxhult, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. **Switzerland:** (B Ledergerber), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen. **Ukraine:** (E Kravchenko), Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, I Baskakov, Luhansk State Medical University, Luhansk; A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv. **United Kingdom:** (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

The following centers have previously contributed data to EuroSIDA: Hôpital de la Pitié-Salpétière, Paris, France. Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany. 1st I.K.A Hospital of Athens, Athens, Greece. Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy. Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy. Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy. Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain. Odessa Region AIDS Center, Odessa, Ukraine.

Funding: Primary funding for EuroSIDA is provided by the European Union's Seventh Framework Programme for research, technological development and demonstration under EuroCoord grant agreement no 260694. Current support also includes unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787). Study supported by grant [grant number DNRF126] from the Danish National Research Foundation.

References:

1 Catumbela E, Certal V, Freitas A, Costa C, Sarmento A, da Costa Pereira A. Definition of a core set of quality indicators for the assessment of HIV/AIDS clinical care: a systematic review. *BMC Health Serv Res* 2013; **13**:236.

2 UNAIDS. Indicator Standards: Operational Guidelines for Selecting Indicators for the HIV Response. 2010. http://www.unaids.org/sites/default/files/sub_landing/files/4_3_MERG_Indicator_Standards.pdf

3 WHO. Consolidated Strategic Information Guidelines for HIV in the Health Sector. 2015.

http://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en/

4 Wilson IB, Landon BE, Marsden P V, Hirschhorn LR, McInnes K, Ding L, *et al.* Correlations among measures of quality in HIV care in the United States: cross sectional study. *BMJ* 2007; **335**:1085.

5 Kelley E, Hurst J. Health Care Quality Indicators Project Conceptual Framework Paper. OECD Health

Working Papers. 2006. http://www.oecd.org/els/health-systems/36262363.pdf

6 International benchmarking of healthcare quality: A review of literature. RAND Eur 2010. http://www.rand.org/content/dam/rand/pubs/technical_reports/2010/RAND_TR738.pdf

7 Mainz J. Developing evidence-based clinical indicators: a state of the art methods primer. *Int J Qual Heal Care* 2003; **15**:5i–11.

8 Mainz J. Defining and classifying clinical indicators for quality improvement. *Int J Qual Heal Care* 2003; **15**:523–530.

9 Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, D'Arminio Monforte A, Hermans P, *et al.* A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. *J Infect Dis* 2002; **185**:178–87.

10 Mellors JW, Muñoz A, Giorgi J V, Margolick JB, Tassoni CJ, Gupta P, *et al.* Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; **126**:946–54.

11 WHO. Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV

Infection. 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/.

12 Zoufaly A, Stellbrink H-J, Heiden MA Der, Kollan C, Hoffmann C, van Lunzen J, *et al.* Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. *J Infect Dis* 2009; **200**:79–87.

13 Chiao EY, Hartman CM, El-Serag HB, Giordano TP. The Impact of HIV Viral Control on the Incidence of HIV-Associated Anal Cancer. *J Acquir Immune Defic Syndr* 2013; **63**:631–638.

14 Kowalkowski MA, Day RS, Du XL, Chan W, Chiao EY. Cumulative HIV viremia and non-AIDS-defining malignancies among a sample of HIV-infected male veterans. *J Acquir Immune Defic Syndr* 2014; **67**:204–11.

15 Mugavero MJ, Napravnik S, Cole SR, Eron JJ, Lau B, Crane HM, *et al.* Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. *Clin Infect Dis* 2011; **53**:927–35.

16 Wright ST, Hoy J, Mulhall B, O'connor CC, Petoumenos K, Read T, *et al.* Determinants of viremia copy-years in people with HIV/AIDS after initiation of antiretroviral therapy. *J Acquir Immune Defic Syndr* 2014; **66**:55–64.

17 Cole SR, Napravnik S, Mugavero MJ, Lau B, Eron JJ, Saag MS. Copy-years viremia as a measure of cumulative human immunodeficiency virus viral burden. *Am J Epidemiol* 2010; **171**:198–205.

18 Chirouze C, Journot V, Moing V Le. Viremia Copy-Years as a Predictive Marker of All-Cause Mortality in HIV-1 – Infected Patients Initiating a Protease Inhibitor – Containing Antiretroviral Treatment. *J Acquir Immune Defic Syndr* 2015; **68**:204–208.

19 Mocroft a, Ledergerber B, Katlama C, Kirk O, Reiss P, Monforte a d'Arminio, *et al.* Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*

2003; **362**:22–29.

20 Kowalska JD, Mocroft A, Ledergerber B, Florence E, Ristola M, Begovac J, *et al.* A Standardized Algorithm for Determining the Underlying Cause of Death in HIV Infection as AIDS or non-AIDS Related: Results from the EuroSIDA Study. *HIV Clin Trials* 2011; **12**:109–117.

21 Reekie J, Mocroft A, Sambatakou H, Machala L, Chiesi A, van Lunzen J, *et al.* Does less frequent routine monitoring of patients on a stable, fully suppressed cART regimen lead to an increased risk of treatment failure? *AIDS* 2008; **22**:2381–2390.

22 Lodwick R, Costagliola D, Reiss P, Torti C, Teira R, Dorrucci M, *et al.* Triple-class virologic failure in HIV-infected patients undergoing antiretroviral therapy for up to 10 years. *Arch Intern Med* 2010; **170**:410–419.

23 Costagliola D, Ledergerber B, Torti C, van Sighem A, Podzamczer D, Mocroft A, *et al.* Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study. *Lancet Infect Dis* 2012; **12**:119–27.

24 Reekie J, Mocroft a, Ledergerber B, Beniowski M, Clotet B, van Lunzen J, *et al.* History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. *HIV Med* 2010; **11**:469–78.

25 Laut K, Shepherd LC, Pedersen C, Rockstroh J, Sambatakou H, Paduta D, *et al.* Evaluating indicators of standard of ART care. CROI 2015. http://www.chip.dk/Portals/0/files/Eurosida/EuroSIDA/CROI15_637_EuroSIDA_DG_final.pdf?timestamp=1425027062265

26 Food and Drug Administration. Guidance for Industry: Human Immunodeficiency Virus-1

Infection:

Developing Antiretroviral Drugs for Treatment. 2013.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm355239.htm

27 Rotnitzky A, Jewell NP. Hypothesis testing of regression parameters in semiparametric generalized linear models for cluster correlated data. *Biometrika* 1990; **77**:485–497.

28 Pan W. Akaike's Information Criterion in Generalized Estimating Equations. *Biometrics* 2004; **57**:120–125.

29 Prosperi MCF, Mackie N, di Giambenedetto S, Zazzi M, Camacho R, Fanti I, *et al.* Detection of drug resistance mutations at low plasma HIV-1 RNA load in a European multicentre cohort study. *J Antimicrob Chemother* 2011; **66**:1886–1896.

30 Mackie NE, Phillips AN, Kaye S, Booth C, Geretti A, Resistance UK. Antiretroviral Drug Resistance in HIV-1-Infected Patients with Low-Level Viremia. 2010; **201**:1303–1308.

31 Mocroft A, Ledergerber B, Viard JP, Staszewski S, Murphy M, Chiesi A, *et al.* Time to virological failure of 3 classes of antiretrovirals after initiation of highly active antiretroviral therapy: results from the EuroSIDA study group. *J Infect Dis* 2004; **190**:1947–56.

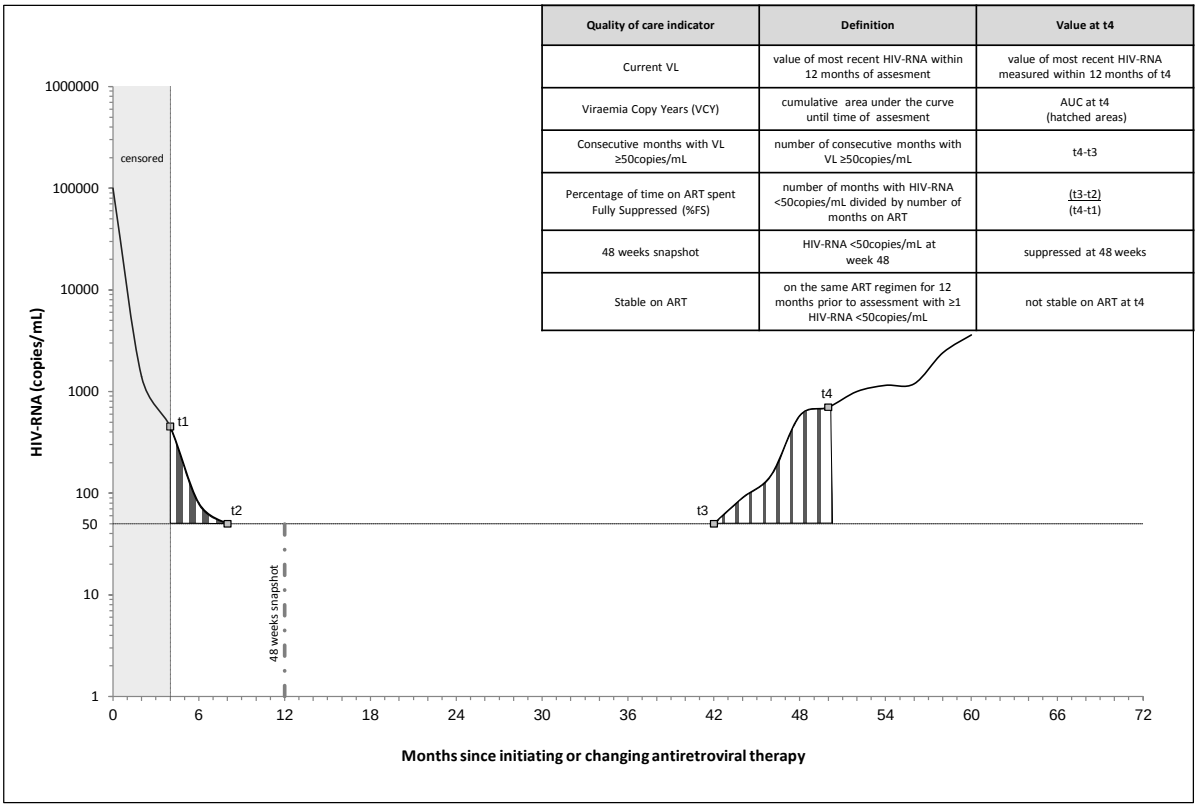
32 Schultze A, Phillips A, Paredes R, Ledergerber B, Laut K, Kirk O, *et al.* Rate of Accumulation of Drug Resistance Mutations during Virological Failure According to Different Measures of Viral Load Exposure. International HIV Drug Resistance Workshop; 2015.

http://www.chip.dk/LinkClick.aspx?fileticket=2a5hfwDMU98%3d&portalid=0&timestamp=1425288685600

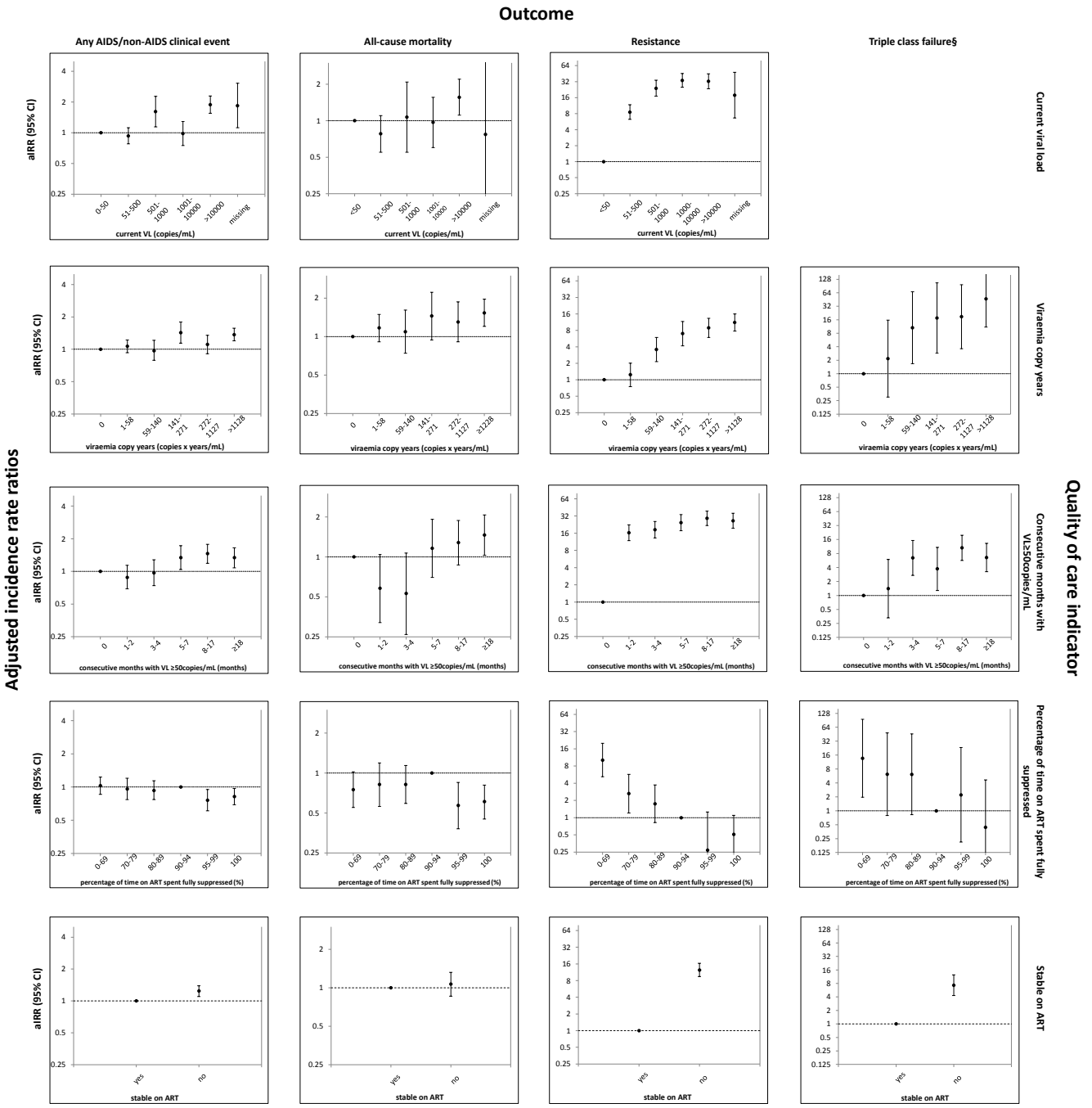
33 Hirschhorn L, Beattie A, Davidson D, Agins B. the Role of Viral Load As a Measure of the

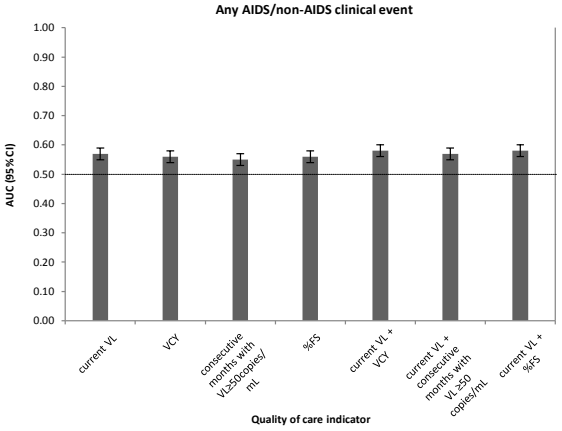
Quality of Care for People With Hiv : the Expert Meeting Report. 2005.

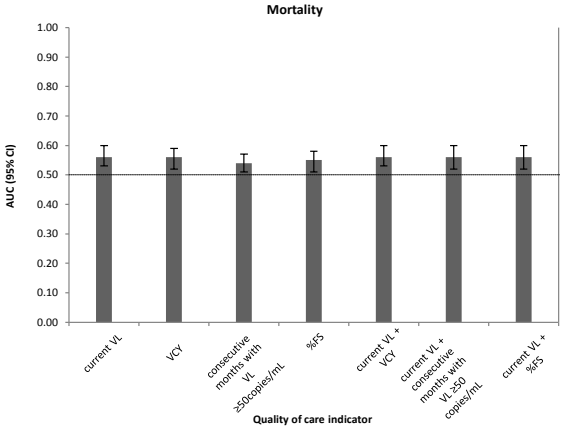
34 Havlir D V., Basset R, Levitan D, Gilbert P, Tebas P, Collier AC, *et al.* Prevalence and Predictive Value of Intermittent Viremia With Combination HIV Therapy. *JAMA* 2001; **286**:171.

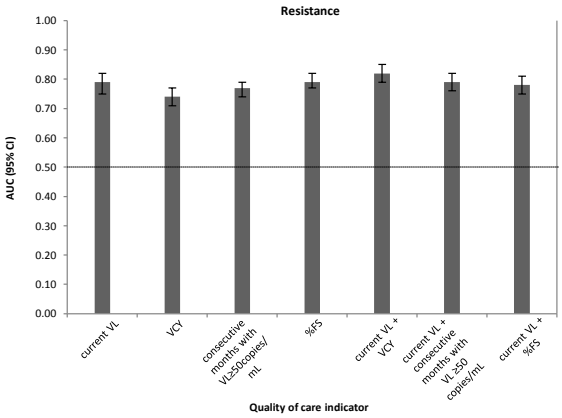


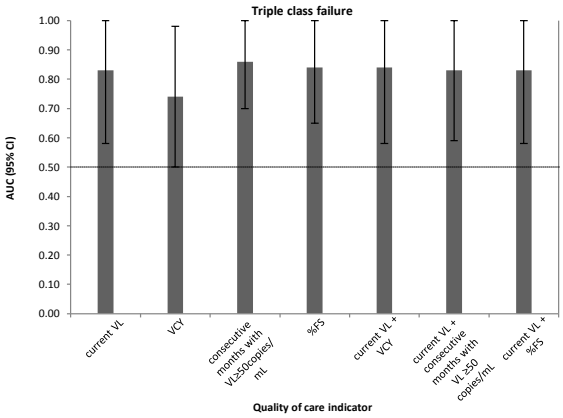
Quality of care indicator	Definition	Value at t4
Current VL	value of most recent HIV-RNA within 12 months of assesment	value of most recent HIV-RNA measured within 12 months of t4
Viraemia Copy Years (VCY)	cumulative area under the curve until time of assesment	AUC at t4 (hatched areas)
Consecutive months with VL ≥50copies/mL	number of consecutive months with VL ≥50copies/mL	t4-t3
Percentage of time on ART spent Fully Suppressed (%FS)	number of months with HIV-RNA <50copies/mL divided by number of months on ART	$\frac{(t3-t2)}{(t4-t1)}$
48 weeks snapshot	HIV-RNA <50copies/mL at week 48	suppressed at 48 weeks
Stable on ART	on the same ART regimen for 12 months prior to assessment with ≥1 HIV-RNA <50copies/mL	not stable on ART at t4











Indicator	Any AIDS/non-AIDS clinical event			All-cause mortality			Resistance			Triple class failure		
	Events	PYFU	IR/1,000PYFU	Events	PYFU	IR/1,000PYFU	Events	PYFU	IR/1,000PYFU	Events	PYFU	IR/1,000PYFU
Current viral load (copies/mL)												
0-49	1726	55049	31.4 (29.9, 32.9)	456	55049	8.3 (7.6, 9.1)	74	8445	8.8 (7.0, 11.0)	32	52910	0.6 (0.4, 0.9)
50-500	163	5084	32.1 (27.5, 37.4)	37	5083	7.3 (5.3, 10.1)	100	1195	83.7 (68.8, 101.8)	28	4686	6.0 (4.1, 8.7)
501-1,000	46	797	57.7 (43.3, 77.1)	9	797	11.3 (5.9, 21.7)	68	261	260.8 (205.6, 330.8)	0	695	0.0 (0.0, 0.0)
1,001-10,000	70	1860	37.6 (29.8, 47.6)	19	1860	10.2 (6.5, 16.0)	287	737	389.5 (347.0, 437.3)	0	1554	0.0 (0.0, 0.0)
>10,000	159	1595	99.7 (85.4, 116.5)	38	1595	23.8 (17.3, 32.8)	246	678	362.7 (320.1, 411.0)	7	1220	5.7 (2.7, 12.0)
missing	17	276	61.7 (38.4, 99.25)	2	276	7.3 (1.8, 29.0)	4	33	123.0 (46.2, 327.8)	11	264	41.7 (23.1, 75.3)
Viraemia copy years (copies x years/mL)												
0	745	27787	26.8 (25.0, 28.8)	176	27787	6.3 (5.5, 7.3)	43	2270	18.9 (14.1, 25.5)	2	27317	0.1 (0.0, 0.3)
1-58	406	13508	30.1 (27.3, 33.1)	105	13508	7.8 (6.4, 9.4)	29	1647	17.6 (12.2, 25.3)	2	13186	0.2 (0.0, 0.6)
59-140	115	3931	29.3 (24.4, 35.1)	31	3931	7.9 (5.6, 11.2)	28	659	42.5 (29.4, 61.6)	3	3815	0.8 (0.3, 2.4)
141-271	99	2290	43.2 (35.5, 52.7)	25	2290	10.9 (7.4, 16.2)	34	415	81.9 (58.5, 114.7)	3	2195	1.4 (0.4, 4.2)
272-1127	148	4407	33.6 (28.6, 39.5)	40	4407	9.1 (6.7, 12.4)	118	1269	93.0 (77.7, 111.4)	6	4075	1.5 (0.7, 3.3)
>1127	668	12737	52.5 (48.6, 56.6)	184	12737	14.5 (12.5, 16.7)	527	5088	103.6 (95.1, 112.8)	62	10740	5.8 (4.5, 7.4)
Consecutive months with VL ≥50 copies/mL (months)												
0	1734	55280	31.4 (29.9, 32.9)	456	55280	8.3 (7.5, 9.0)	74	8440	8.8 (6.9, 11.0)	33	53147	0.6 (0.4, 0.8)
1-2	69	2208	31.3 (24.7, 39.6)	12	2208	5.4 (3.1, 9.6)	97	531	182.7 (149.7, 222.9)	2	2027	1.0 (0.3, 3.9)
3-4	55	1586	34.7 (26.6, 45.2)	8	1586	5.0 (2.5, 10.1)	79	395	200.2 (160.6, 249.6)	7	1441	4.9 (2.3, 10.2)
5-7	70	1421	49.3 (39.0, 62.3)	16	1421	11.3 (6.9, 18.4)	104	385	270.2 (222.9, 327.4)	4	1268	3.2 (1.2, 8.4)
8-17	126	2162	58.3 (49.0, 69.4)	30	2162	13.9 (9.7, 19.9)	224	723	309.8 (271.8, 353.1)	19	1844	10.3 (6.6, 16.2)
>18	127	2000	63.5 (53.4, 75.6)	39	2000	19.5 (14.3, 26.7)	201	875	229.7 (200.0, 263.8)	13	1601	8.1 (4.7, 14.0)
Percentage of time on ART spent fully suppressed (%)												
0-59	591	12268	48.2 (44.4, 52.2)	141	12268	11.5 (9.7, 13.6)	666	4335	153.7 (142.4, 165.8)	53	10363	5.1 (3.9, 6.7)
60-69	119	3269	36.4 (30.4, 43.6)	30	3269	9.2 (6.4, 13.1)	28	842	33.3 (23.0, 48.2)	5	3035	1.7 (0.7, 4.0)
70-79	171	4551	37.6 (32.4, 43.7)	48	4551	10.6 (8.0, 14.0)	29	1076	27.0 (18.7, 38.8)	6	4318	1.4 (0.6, 3.1)
80-89	265	7725	34.3 (30.4, 38.7)	76	7725	9.8 (7.9, 12.3)	26	1403	18.5 (12.6, 27.2)	9	7464	1.2 (0.6, 2.3)
90-94	206	5796	35.5 (31.0, 40.7)	67	5796	11.6 (9.1, 14.7)	9	856	10.5 (5.5, 20.2)	1	5634	0.2 (0.0, 1.3)
95-99	146	5203	28.1 (23.9, 33.0)	37	5203	7.1 (5.2, 9.8)	2	813	2.5 (0.6, 9.8)	2	5077	0.4 (0.1, 1.6)
100	683	25846	26.4 (24.5, 28.5)	162	25846	6.3 (5.4, 7.3)	19	2024	9.4 (6.0, 14.7)	2	25437	0.1 (0.0, 0.3)
Stable on ART												
No	586	12582	46.6 (43.0, 50.5)	140	12582	11.1 (9.4, 13.1)	708	3740	189.3 (175.9, 203.8)	52	11171	4.7 (3.6, 6.1)
Yes	1595	52077	30.6 (29.2, 32.2)	421	52077	8.1 (7.4, 8.9)	71	7609	9.3 (7.4, 11.8)	26	50158	0.5 (0.4, 0.8)
Total												
	2181	64658	33.7 (32.3, 35.2)	561	64658	8.7 (8.0, 9.4)	779	11348	68.7 (64.0, 73.6)	78	61329	1.3 (1.0, 1.6)

Table 1: Crude incidence rates (IR) per 1000 person years of follow-up (PYFU) of four outcomes by quality of care indicator

Indicator	Any AIDS/non-AIDS clinical event				All-cause mortality				Resistance				Triple class failure			
	Effect of dropping indicator		Effect of dropping current VL		Effect of dropping indicator		Effect of dropping current VL		Effect of dropping indicator		Effect of dropping current VL		Effect of dropping indicator		Effect of dropping current VL	
	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value	χ^2	p-value
Viraemia copy years	16.22	0.006	29.68	<0.0001	11.57	0.041	9.03	0.108	24.52	0.0002	156.43	<0.0001	49.26	<0.0001	17.45	0.0016
Consecutive months with VL ≥50 copies/mL	9.36	0.096	30.38	<0.0001	13.66	0.018	5.78	0.328	13.69	0.018	310.55	<0.0001	20.79	0.0009	10.64	0.011
Percentage of time on ART spent fully suppressed	12.95	0.024	33.74	<0.0001	14.65	0.012	9.85	0.08	43.80	<0.0001	315.55	<0.0001	35.81	<0.0001	17.81	0.0001
48 weeks snapshot*	5.41	0.020	26.1	<0.0001	3.52	0.061	8.33	0.140	0.38	0.540	209.08	<0.0001	-	-	-	-
Stable on ART	1.27	0.260	30.59	<0.0001	0.06	0.813	8.42	0.135	16.24	<0.0001	358.76	<0.0001	8.86	<0.0001	15.77	0.0004

Table 2: Contribution of quality of care indicators to prediction of outcomes. The figure gives the values of the generalized score tests for each indicator by outcome, showing the effect on model fit when leaving out each quality of care indicator separately from the model. A higher χ^2, and corresponding lower p-value, indicates that model fit decreases when the indicator is left out of the model. *48 weeks snapshot compared from 48 weeks after treatment initiation or change. Analyses not done for the association between triple class failure and 48 weeks snapshot because of too few events.