Il ruolo della viremia nel management del paziente HIV

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18 giugno 2014

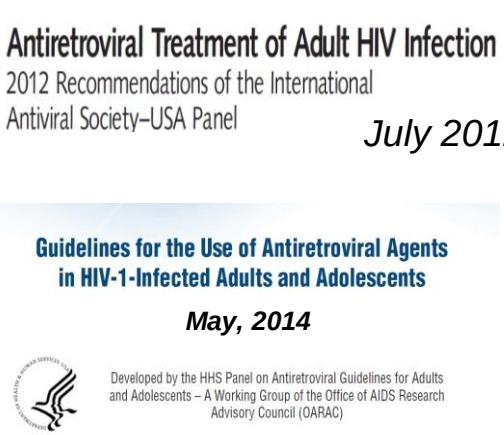
All the current guidelines agree that

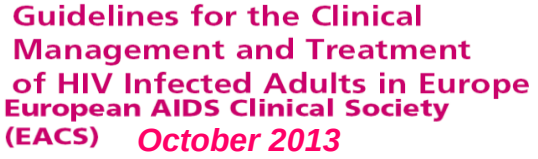
the primary goal of antiretroviral therapy

is to suppress HIV RNA maximally

(<20–75 copies/mL, depending on the assay used)

in order to preserve immunologic function and increase disease-free survival





Prognosis in HIV-1 Infection Predicted by the Quantity of Virus in Plasma

John W. Mellors,* Charles R. Rinaldo Jr., Phalguni Gupta, Roseanne M. White, John A. Todd, Lawrence A. Kingsley

The relation between viremia and clinical outcome in individuals infected with human immunodeficiency virus–type 1 (HIV-1) has important implications for therapeutic research and clinical care. HIV-1 RNA in plasma was quantified with a branched-DNA signal amplification assay as a measure of viral load in a cohort of 180 seropositive men studied for more than 10 years. The risk of acquired immunodeficiency syndrome (AIDS) and death in study subjects, including those with normal numbers of $CD4^+$ T cells, was directly related to plasma viral load at study entry. Plasma viral load was a better predictor of progression to AIDS and death than was the number of $CD4^+$ T cells.

Science 1996

Viral load monitoring and CD4 monitoring should be used together **to monitor disease progression**, **response to therapy**, and **guide opportunistic infection prophylaxis**.

Highlight from the XI International AIDS Conference Vancouver July 7–12, 1996.

Plasma HIV-1 RNA (Viral Load) Monitoring

Pre-treatment viral load level is also an important factor in the selection of an initial ARV regimen because several currently approved ARV drugs or regimens have been associated with poorer responses in patients with high baseline viral load.

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents – May 2014

Plasma HIV-1 RNA (Viral Load) Monitoring

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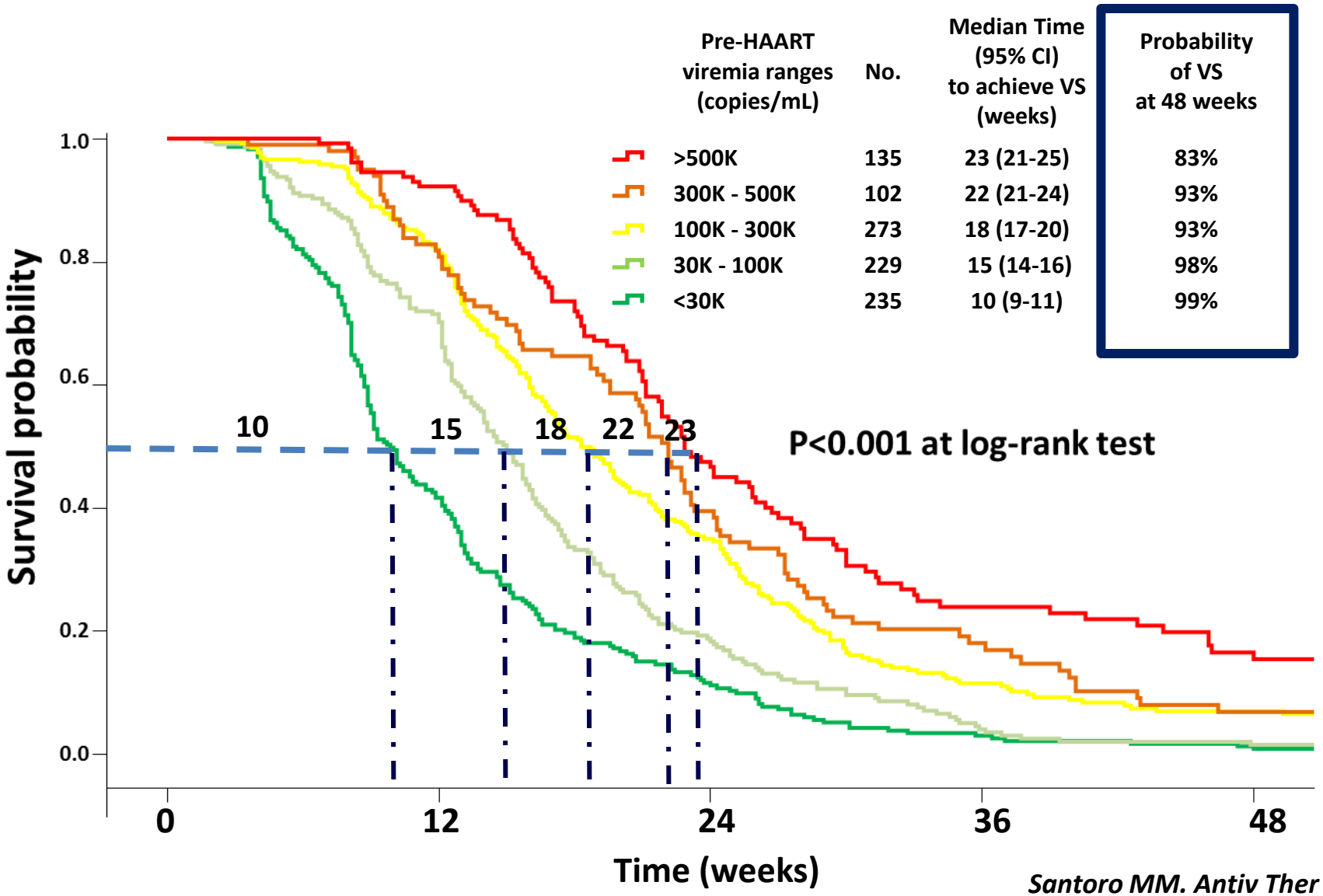
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents – May 2014

La **viremia pre-terapia** ha un **ruolo importante nel raggiungimento della soppressione virologica**. In **presenza di valori di viremie pre-terapia particolarmente elevati**, il **raggiungimento della soppressione virologica può richiedere un tempo più lungo** (a volte superiore alle 24 settimane attese), **e/o è meno frequente**.

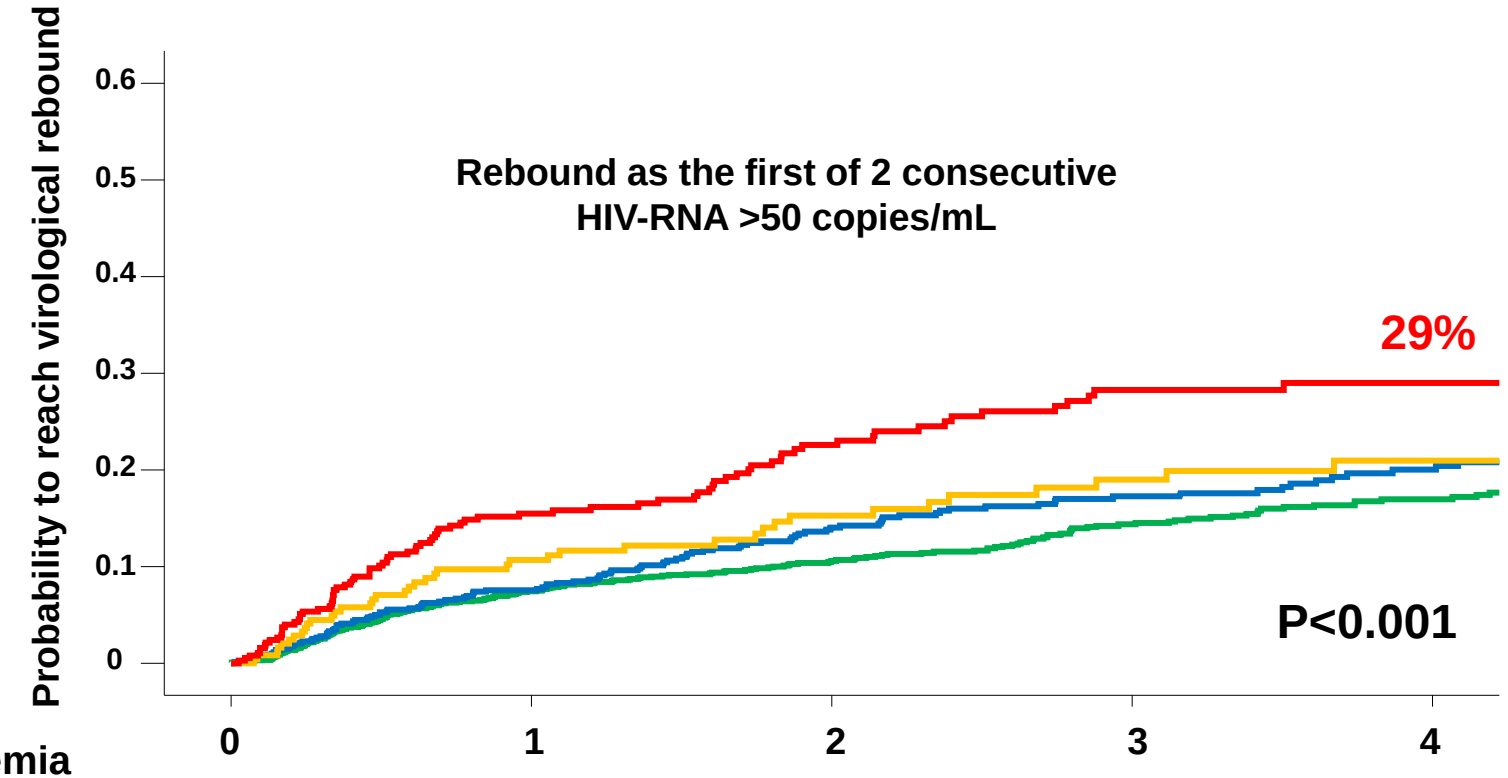
Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1 – Novembre 2013

The time to achieve virological undectability and the rate of success at 48 weeks are pre-HAART viremia dependent



Santoro MM. Antiv Ther 2013

Patients having pre-HAART viremia >500K copies/mL showed the highest probability of virological rebound (VL>50 copies/mL) by 4 years from the achievement of virological suppression.



Viremia Ranks (cps/mL)	No. at risk				
0-100K	1664	1286	903	601	386
100-300K	793	607	418	289	209
300-500K	247	184	129	96	70
>500K	379	259	172	120	79

Armenia et al., V ICAR 2013

Fatal and nonfatal AIDS and non-AIDS events in HIV-1-positive individuals with high CD4 cell counts according to viral load strata

Background: This study compared the incidence of fatal and nonfatal AIDS and non-AIDS events in HIV-positive individuals with a CD4 cell count more than 350 cells/μl among viral load strata: low (<500 copies/ml), intermediate (500–9999.9 copies/ml) and high (≥10000 copies/ml).

Methods: Individuals contributed person-years at risk if their most recent CD4 cell count was more than 350 cells/μl. Follow-up was censored if their CD4 cell count dropped below 350 cells/μl. Poisson regression analysis investigated the relationship between viraemia and the incidence of AIDS and non-AIDS events.

Results: Three hundred and fifty-four AIDS events occurred during 51 732 person-years of follow-up (PYFU), crude incidence rate of AIDS across the three strata was 0.53, 0.90 and 2.12 per 100 PYFU, respectively. After adjustment, a higher rate of AIDS was observed in individuals with moderate [incidence rate ratio (IRR) 1.44, 1.02–2.05, $P = 0.03$] and high viraemia had a higher rate (IRR 3.91, 2.89–5.89, $P < 0.0001$) compared with low viraemia. Five hundred and seventy-two non-AIDS events occurred during 43 784 PYFU, the crude incidence rates were 1.28, 1.52, and 1.38 per 100 PYFU, respectively. After adjustment, particularly for age, region of Europe and starting combination antiretroviral therapy, there was a 61% (IRR 1.61, 1.21–2.14, $P = 0.001$) and 66% (IRR 1.66, 1.17–2.32, $P = 0.004$) higher rate of non-AIDS in individuals with intermediate and high viraemia compared with low viraemia.

Conclusion: In individuals with a CD4 cell count more than 350 cells/μl, an increased incidence of AIDS and a slightly increased incidence of non-AIDS was found in those with uncontrolled viral replication. The association with AIDS was clear and consistent. However, the association with non-AIDS was only apparent after adjustment and no differences were observed between intermediate and high viraemia.

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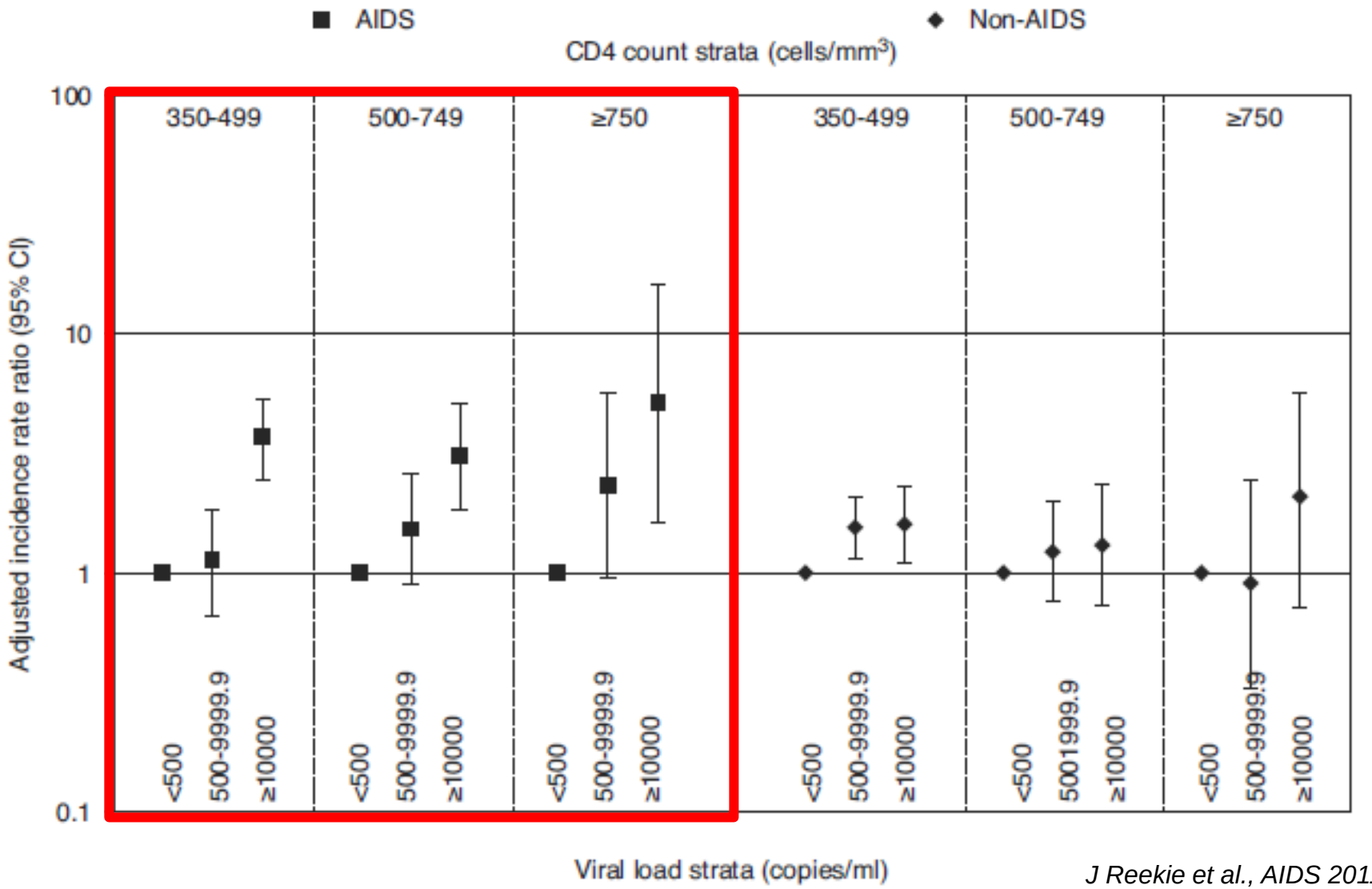
AIDS 2011, **25**:2259–2268

Reekie et al., AIDS 2011

Adjusted incidence rate ratios for AIDS and non-AIDS events by viral load strata stratified by current CD4 cell count.



J Reekie et al., AIDS 2011

Value of viremia copy years in deciding optimal timing of ART initiation in adults with HIV

Ashley D. Olson[1]; Sarah Walker[1]; Amitabh B. Suthar[2]; Caroline Sabin[1]; Heiner C. Bucher[3]; Inma Jarrin[4,5]; Santiago Moreno[6]; Santiago Perez-Hoyos[7]; Kholoud Porter[1]; Deborah Ford[1] on behalf of CASCADE Collaboration in EuroCoord

1 University College London, London, UK; 2 Geneva, Switzerland; 3 Basel Institute for Clinical Epidemiology University hospital Basel, Switzerland; 4 Instituto de Salud Carlos III, Madrid, Spain; 5 CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain; 7 Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain; 7 Unitat Suport Metodològic a l'Investigació Biomedica (USMIB- Vall d'Hebron Institut de Recerca (VHIR), Universidad Autónoma de Barcelona, Spain

EuroCoord

ABSTRACT

Background: Time updated VL levels and CD4 counts are routinely used to monitor HIV positive adults but fail to capture cumulative HIV exposure. Viremia copy years (VCY) is such a measure and has been shown to be predictive of AIDS/death, although it is unclear of its use in deciding when to start ART. We aimed to assess the impact of initiating vs. deferring ART on risk of AIDS/death by levels of VCY both independent of and within two CD4 strata, <350 and ≥350 cells/mm³.

Methodology: Using CASCADE data on HIV seroconverters, we created a series of nested cohorts corresponding to consecutive months starting month 5 post seroconversion (SC) for individuals ≥16 years at SC after 1997, had ≥1 VL measured 4-12 months post SC, were ART naïve and AIDS free prior to end of baseline month. Time to AIDS/death was compared in those initiating vs. deferring ART in the baseline month using Cox models adjusted for time independent factors: country, sex, risk group, SC year; and time dependent factors prior to the baseline month: age, time since last VL, and current CD4, VCY and VL (excluding the first 4 months post SC) and mean number of previous CD4/VL measurements/year. Robust variance was used to adjust for individuals contributing ≥1 baseline visit. We repeated analyses using CD4 strata <500 and ≥500 cells/mm³.

Results: Of 6497 individuals contributing ≥1 baseline month, 3089 (48%) initiated ART and 293 (5%) acquired AIDS/died. Median (IQR) CD4 at ART initiation was 322 (249, 419) cells/mm3. Pooling CD4 strata, hazard ratios (HR) of AIDS/death associated with initiating vs. deferring ART reduced as VCY increased, suggesting a stronger benefit of ART in those with higher VCY. Trends by VCY were different when stratifying by CD4; in patients with CD4<350 cells/mm³, there was an overall reduction in the HR of AIDS/death in all VCY groups (all HR < 1) with no evidence that this benefit varied by VCY (p=0.78). At CD4 ≥ 350 there was a trend for increasing benefit of initiation with increasing VCY, with the largest benefit seen in the VCY ≥ 100,000 c/mL group (HR, 95% CI= 0.56, 0.35-0.90); no evidence of benefit if VCY was < 20,000 c/mL. Results were qualitatively similar for CD4 strata ≥ 500 cells/mm³.

Conclusions: Although we cannot rule out the possibility of unmeasured confounding, it appears that limiting the cumulative HIV burden to < 100,000 VCY in individuals with CD4 ≥ 350 cells/mm³ through ART reduces the hazard of clinical outcomes by 44%.

CROI 2014, abstr # 558

Value of viremia copy years in deciding optimal timing of ART initiation in adults with HIV

Ashley D. Olson[1]; Sarah Walker[1]; Amitabh B. Suthar[2]; Caroline Sabin[1]; Heiner C. Bucher[3]; Inma Jarrin[4,5]; Santiago Moreno[6]; Santiago Perez-Hoyos[7]; Kholoud Porter[1]; Deborah Ford[1] on behalf of CASCADE Collaboration in EuroCoord

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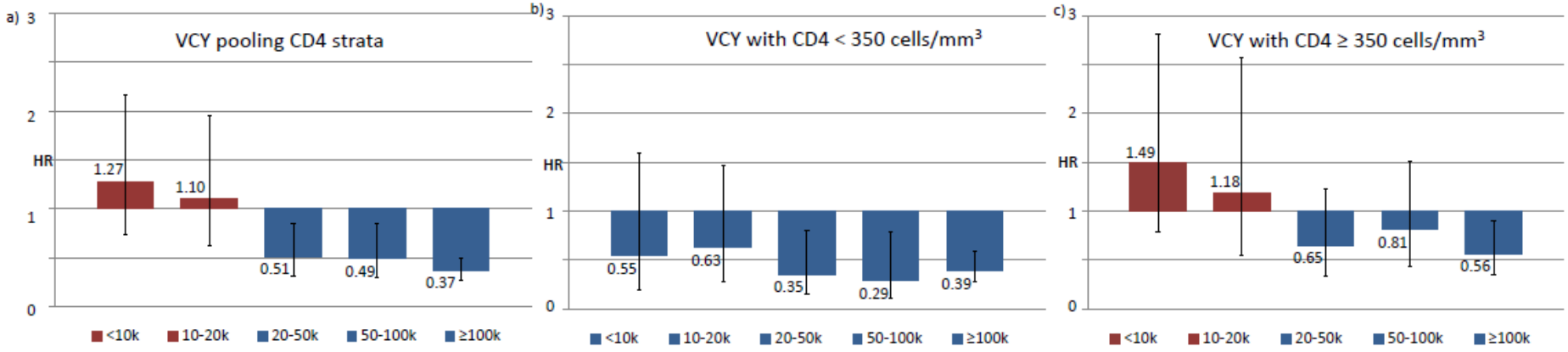
Adjusted hazard ratios for the effect of initiation vs. deferring ART on time from seroconversion (SC) to AIDS/death by a) viremia copy years pooling CD4 stratum, b) viremia copy years with CD4<350 cells/mm^{3}and c) viremia copy years with CD4≥350 cells/mm^3



Pooling CD4 strata, hazard ratios for the effect of initiating ART on time from seroconversion to AIDS/death decreased as VCYyear increased, with a 63% reduced risk of AIDS/death for those initiating ART when VCY exceeded 100,000. At CD4<350 cells/mm^3, there was an overall reduction in the risk of AIDS/death in all VCY groups (all HR < 1) for those initiating vs. deferring ART with no evidence that this benefit varied by VCY (p=0.78). At CD4 ≥ 350 there was a trend for increasing benefit of initiation vs. deferral with increasing VCY, with the largest benefit seen in the VCY ≥ 100,000 c/mL group (HR, 95% CI= 0.56, 0.35-0.90, p(heterogeneity) = 0.16). Results were qualitatively similar for CD4 strata ≥ 500 cells/mm^3.

CROI 2014, abstr # 558

Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

CID 2011;53:927–935

Michael J. Mugavero,[1,a] Sonia Napravnik,[2,3,a] Stephen R. Cole,[3] Joseph J. Eron,[2,3] Bryan Lau,[4] Heidi M. Crane,[5] Mari M. Kitahata,[5] James H. Willig,[1] Richard D. Moore,[6] Steven G. Deeks,[7] Michael S. Saag,[1] and on behalf of the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort Study

Background. Cross-sectional plasma human immunodeficiency virus (HIV) viral load (VL) measures have proven invaluable for clinical and research purposes. However, cross-sectional VL measures fail to capture cumulative plasma HIV burden longitudinally. We evaluated the cumulative effect of exposure to HIV replication on mortality following initiation of combination antiretroviral therapy (ART).

Methods. We included treatment-naive HIV-infected patients starting ART from 2000 to 2008 at 8 Center for AIDS Research Network of Integrated Clinical Systems sites. Viremia copy-years, a time-varying measure of cumulative plasma HIV exposure, were determined for each patient using the area under the VL curve. Multivariable Cox models were used to evaluate the independent association of viremia copy-years for all-cause mortality.

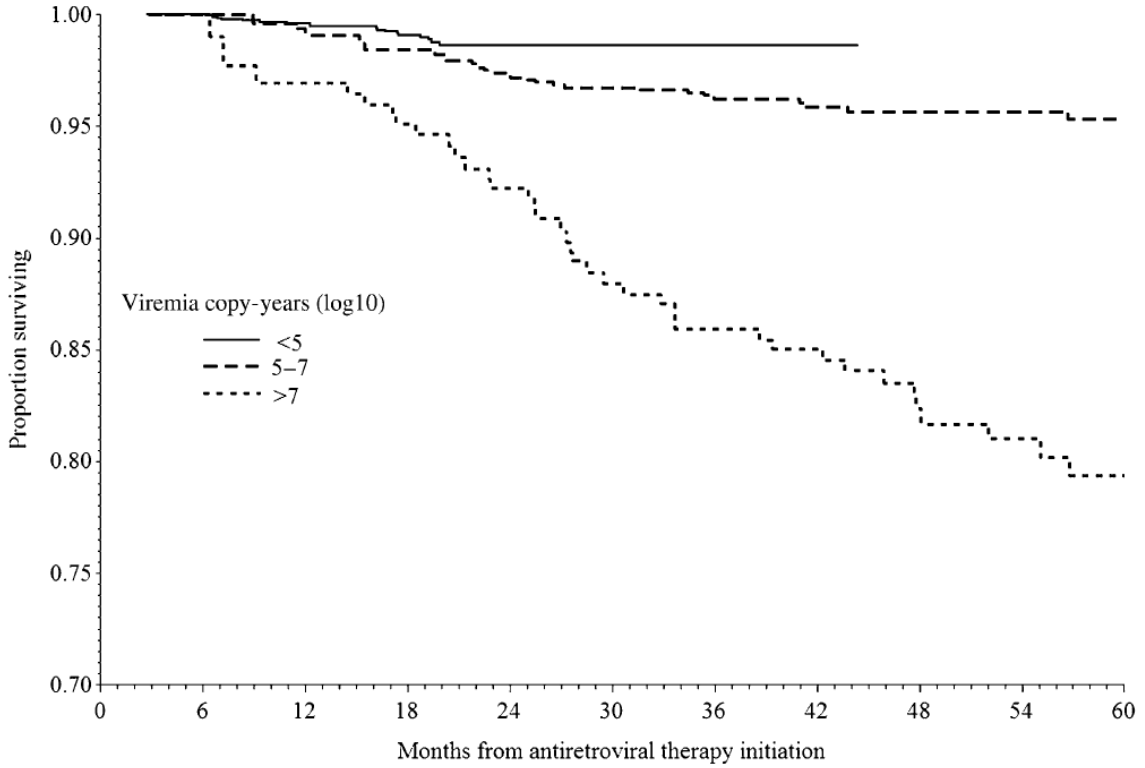
Results. Among 2027 patients contributing 6579 person-years of follow-up, the median viremia copy-years was 5.3 $\log_{10}$ copy × y/mL (interquartile range: 4.9–6.3 $\log_{10}$ copy × y/mL), and 85 patients (4.2%) died. When evaluated separately, viremia copy-years (hazard ratio [HR] = 1.81 per $\log_{10}$ copy × y/mL; 95% confidence interval [CI], 1.51–2.18 per $\log_{10}$ copy × y/mL), 24-week VL (1.74 per $\log_{10}$ copies/mL; 95% CI, 1.48–2.04 per $\log_{10}$ copies/mL), and most recent VL (HR = 1.89 per $\log_{10}$ copies/mL; 95% CI: 1.63–2.20 per $\log_{10}$ copies/mL) were associated with increased mortality. When simultaneously evaluating VL measures and controlling for other covariates, viremia copy-years increased mortality risk (HR = 1.44 per $\log_{10}$ copy × y/mL; 95% CI, 1.07–1.94 per $\log_{10}$ copy × y/mL), whereas no cross-sectional VL measure was independently associated with mortality.

Conclusions. Viremia copy-years predicted all-cause mortality independent of traditional, cross-sectional VL measures and time-updated CD4+ T-lymphocyte count in ART-treated patients, suggesting cumulative HIV replication causes harm independent of its effect on the degree of immunodeficiency.

Viremia Copy-Years Predicts Mortality Among Treatment-Naive HIV-Infected Patients Initiating Antiretroviral Therapy

Cumulative plasma HIV burden, demonstrated prognostic value for all-cause mortality among 2027 HIV-infected patients following ART

(viral load values prior to 24 weeks of ART initiation were excluded)



Viremia copy-years (log_{10})	Number at risk									
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
<5	1692	1414	1105	317	79	18	2			
5–7	245	289	332	833	851	727	606	509	414	316
>7	90	135	181	192	183	169	152	132	122	108

Mugavero et al., CID 2011;53:927–935

The Clinical Impact of Viral Load Copy Years in Antiretroviral-Naïve HIV Seroconverters

Matthias an der Heiden[1], Alexander Zoufaly[2], Caroline Sabin[3], Jan van Lunzen[4], Hans-Jürgen Stellbrink[5], Barbara Gunsenheimer-Bartmeyer[1], Philippe Vanhems[6], Santiago Perez-Hoyos[7], Geneviève Chêne[8] and Osamah Hamouda[1], on behalf of CASCADE Collaboration in EuroCoord

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METHODS

Data

- CASCADE - cohort collaboration of HIV-1 seroconverters

Inclusion criteria

- ART-naïve patients >15 years
- seroconversion (SC) dates after 1997
- viral load and CD4 measured within 4-12 months following SC

Patient follow-up

- began 4 months after SC
- censored at earliest of
  - ART start
  - CD4 <200 cells/µl
  - no VL and CD4 measurements for >12 months
  - 6 years after SC

Viral load (VL) variables

- current VL: last VL measurement carried forward in time
- Viral load copy years (VCY): time updated area under the VL curve (trapezoid rule)
- average VL: VCY divided by (time since SC)

→ **VCY = average VL * (time since SC)**

interaction between average VL and time since SC

CROI 2014, abstr # 291

The Clinical Impact of Viral Load Copy Years in Antiretroviral-Naïve HIV Seroconverters

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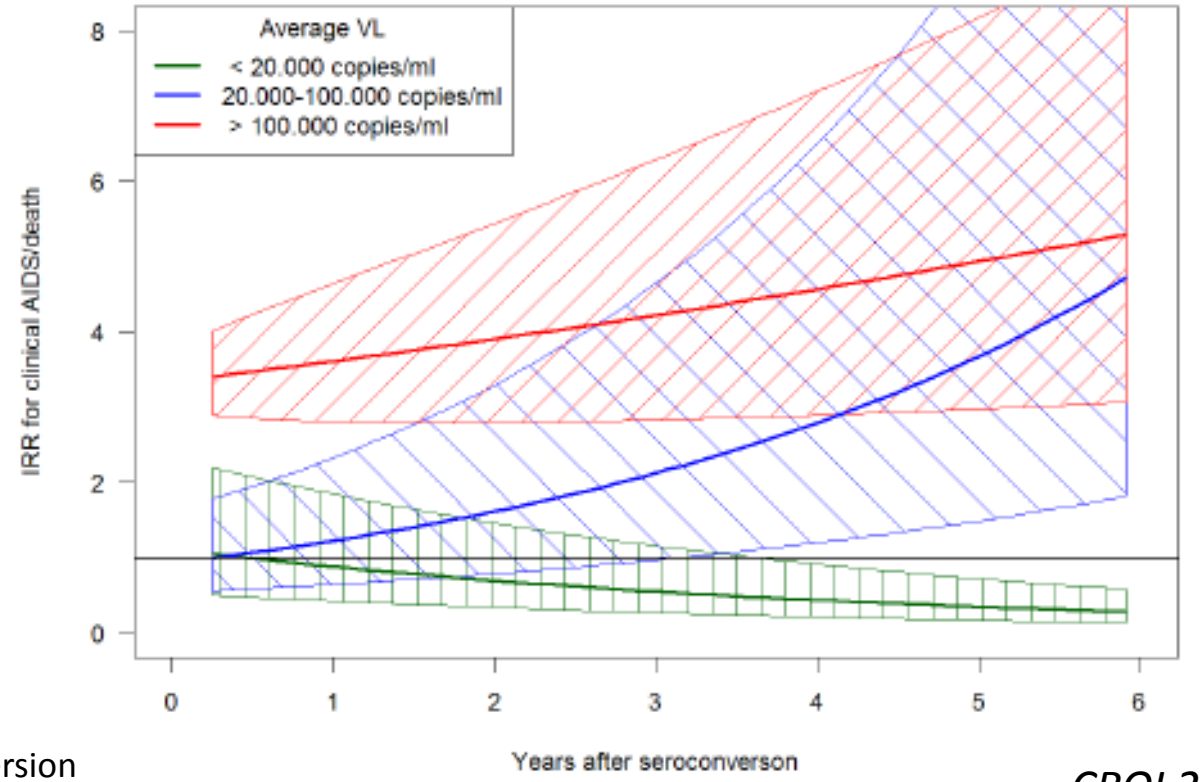
Higher average VL is associated with a higher risk of clinical AIDS/death.

Impact of average VL on rate of clinical AIDS/death changing with time after SC



SC: seroconversion

CROI 2014, abstr # 291

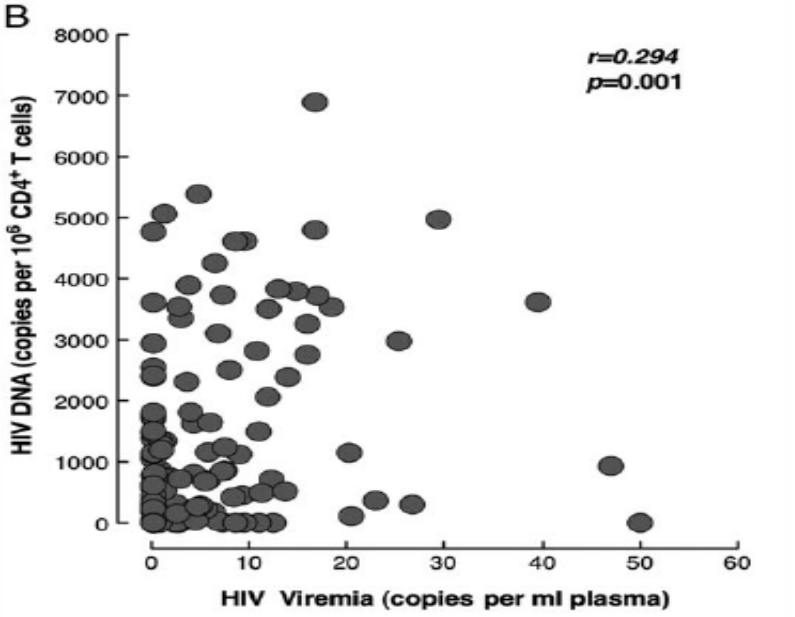
Transient **low level viremias**, with plasma HIV-1 RNA levels in the range of **50 to 400** copies/ml, have been reported to occur in **25 to 40%** of adults in whom viral replication appeared to have been suppressed by HAART

Greub, G., A. et al. Intermittent and sustained low-level HIV viral rebound in patients receiving potent antiretroviral therapy. *AIDS* **2002**

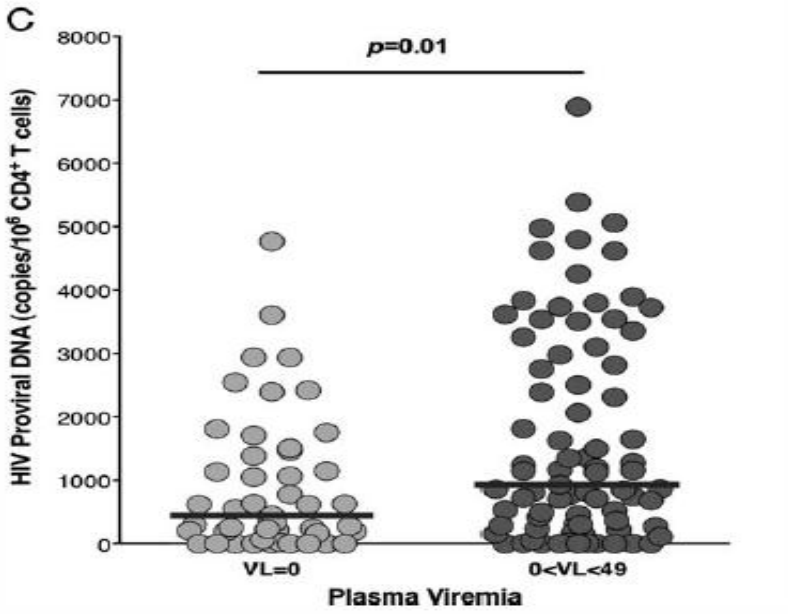
Havlir, D. V., et al. Prevalence and predictive value of intermittent viremia with combination HIV therapy. *JAMA* **2001**

Sklar, et al . Prevalence and clinical correlates of HIV viremia (‘blips’) in patients with previous suppression below the limits of quantification. *AIDS* **2002**

Residual viremia reflects the size of the viral reservoir (CD4-associated HIV DNA) during suppressive HAART



Relationship between residual plasma viremia and cell-associated HIV DNA



Frequencies of $CD4^+$ T cells carrying HIV proviral DNA based on plasma viremia

Chun T et al. J Infect Dis. 2011

Clinical Infectious Diseases Advance Access published September 6, 2013

MAJOR ARTICLE HIV/AIDS

Virologic Failure Following Persistent Low-level Viremia in a Cohort of HIV-Positive Patients: Results From 12 Years of Observation

Claudie Laprise,[1] Alexandra de Pokomandy,[2,3] Jean-Guy Baril,[4] Serge Dufresne,[4] and Helen Trottier[1]

[1]Department of Social and Preventive Medicine, University of Montreal, Sainte-Justine Hospital Research Center, [2]Department of Family Medicine, McGill University, [3]Chronic Viral Illnesses Service, McGill University Health Center, and [4]Clinique Médicale du Quartier Latin, Montreal, Canada

Background. The current goal of antiretroviral therapy (ART) is to maintain a suppressed human immunodeficiency virus (HIV) viral load below limits of assay detection. When viral loads remain in low-level viremia (LLV), especially between 50 and 200 copies/mL, the best management and clinical consequences remain unknown. Our objective was to study the long-term **impact of persistent LLV on the subsequent risk of virologic failure** in a cohort of people living with HIV in Montreal, Canada.

Methods. We compared the cumulative **incidence of subsequent virologic failure** (defined as an HIV RNA viral load of >1000 copies/mL) in patients receiving ART for at least 12 months by following **4 persistence categories (<50, 50–199, 200–499, and 500–999 copies/mL)** for 6, 9, or 12 months, using Kaplan-Meier analysis. The association between subsequent virologic failure and persistence status were estimated using a Cox proportional hazards model.

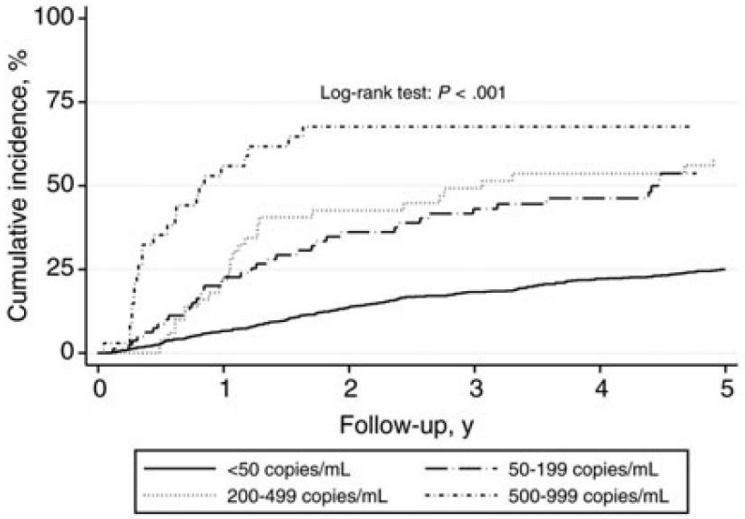
Results. The cumulative incidence of virologic failure 1 year after having maintained a LLV for 6 months was 22.7% (95% confidence interval [CI], 14.9–33.6) for 50–199 copies/mL, 24.2% (95% CI, 14.5–38.6) for 200–499 copies/mL, and 58.9% (95% CI, 43.1–75.2) for 500–999 copies/mL, compared with 6.6% (95% CI, 5.3–8.2) for an undetectable HIV RNA viral load. Even after adjustment for potential confounders, a persistent LLV of 50–199 copies/ mL for 6 months doubled the risk of virologic failure (hazard ratio, 2.22; 95% CI, 1.60–3.09), compared with undetectable viral loads for the same duration. Similar results have been found for persistent LLV of 9 or 12 months.

Conclusions. In this cohort, **all categories of persistent LLV between 50 and 999 copies/mL were associated with an increased risk of virologic failure. The results shed new light for the management of patients with LLV, especially with regard to LLV of 50–199 copies/mL.**

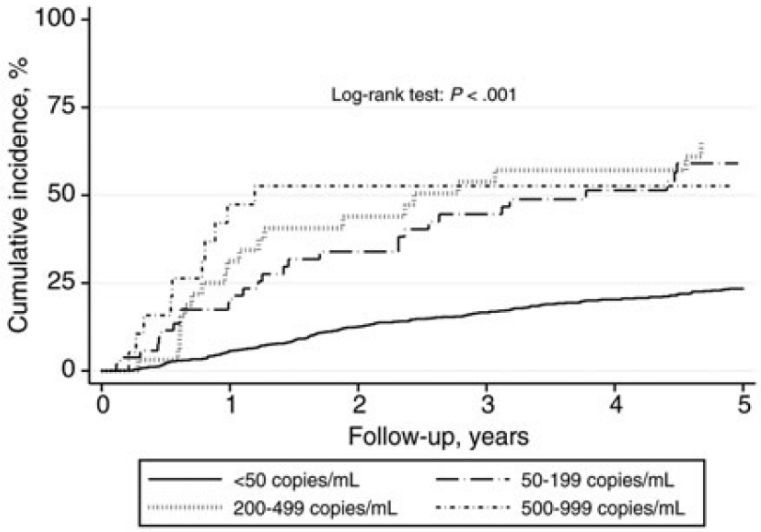
Laprise et al, CID 2013

The cumulative incidences of subsequent virologic failure (ie, > 1000 copies/mL) over 5 years, following persistence of LLV was significantly higher for all LLV strata compared to who maintained undetectable HIV load.

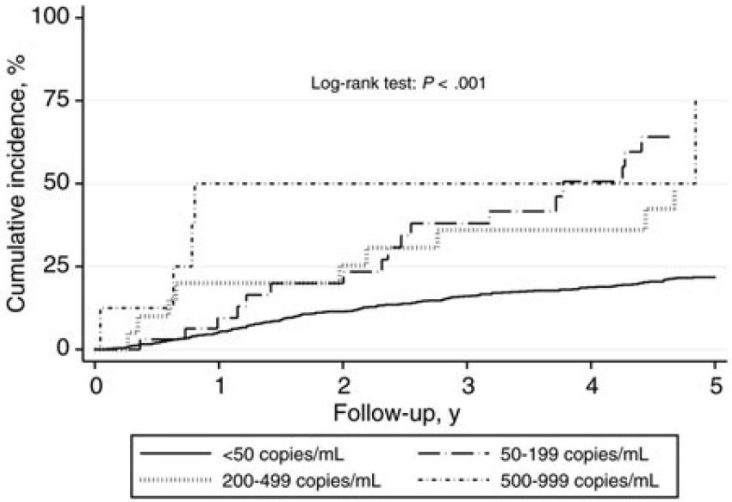
Persistent viral load status defined with a duration of 6 months



Persistent viral load status defined with a duration of 9 months



Persistent viral load status defined with a duration of 12 months



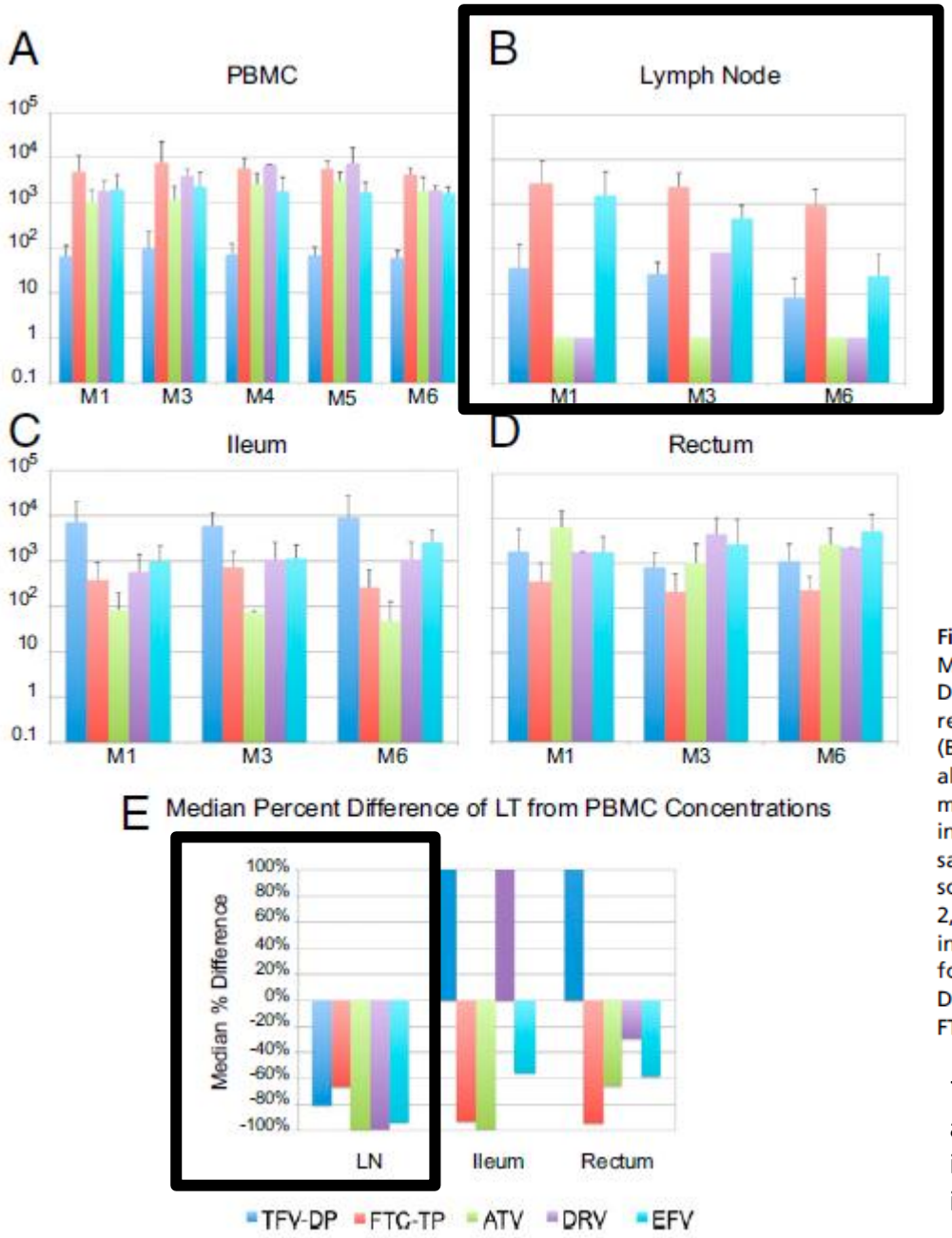
Laprise et al, CID 2013

Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues

Courtney V. Fletcher[a], Kathryn Staskus[b,1], Stephen W. Wietgrefe[b], Meghan Rothenberger[c], Cavan Reilly[d], Jeffrey G. Chipman[e], Greg J. Beilman[e], Alexander Khoruts[c], Ann Thorkelson[c], Thomas E. Schmidt[c], Jodi Anderson[c], Katherine Perkey[b], Mario Stevenson[f], Alan S. Perelson[g], Daniel C. Douek[h], Ashley T. Haase[b], and Timothy W. Schacker[c,2]

Antiretroviral therapy can reduce HIV-1 to undetectable levels in peripheral blood, but the effectiveness of treatment in suppressing replication in lymphoid tissue reservoirs has not been determined. Here we show in lymph node samples obtained before and during 6 mo of treatment that the tissue concentrations of five of the most frequently used antiretroviral drugs are much lower than in peripheral blood. These lower concentrations correlated with continued virus replication measured by the slower decay or increases in the follicular dendritic cell network pool of virions and with detection of viral RNA in productively infected cells. The evidence of persistent replication associated with apparently suboptimal drug concentrations argues for development and evaluation of novel therapeutic strategies that will fully suppress viral replication in lymphatic tissues. These strategies could avert the long-term clinical consequences of chronic immune activation driven directly or indirectly by low-level viral replication to thereby improve immune reconstitution.

PNAS 2104



Compared with concentrations in PBMCs, the **IC concentration** of **TFV-DB, FTC-TP, ATV, DRV and EFV** was **lower in the lymphatic tissue** (LT) **compartment**, particularly in the **lymph node**.

Fig. 1. IC ARV concentrations by compartment and month of therapy. Mean (and SD error) IC concentrations (log scale) for TFV-DP, FTC-TP, ATV, DRV, and EFV are shown for PBMCs (*A*), LN MNCs (*B*), ileal MNCs (*C*), and rectal MNCs (*D*). For *B*, where values were below the limit of quantitation (BLQ), a value of 1 has been assigned for illustration purposes; for example, all LN samples for ATV had IC concentrations that were BLQ. (*E*) Overall median percent difference between the concentration in PBMCs and those in the LN, ileum, and rectum, respectively, for each of the five drugs from all samples obtained during the 6 mo of therapy in the individual subjects. The scale is truncated at +100%. Actual values >100% were as follows: TFV-DP, 2,229%, and DRV, 1,318% in the ileum; and TFV-DP, 599%, and DRV, 149% in the rectum. In the LN, concentrations were uniformly lower than PBMCs for all drugs: TFV-DP concentrations, –80%; FTC-TP, –66%; ATV, –100%; DRV, –99%; and EFV, –94% (all $P < 0.0001$). TFV-DP, TFV-diphosphate; FTC-TP, FTC-triphosphate.

714 determinations of ARV drug concentrations in plasma and 592 analyte determinations for IC drug concentrations in PBMCs and in mononuclear cells (MNCs) from the LN, ileum, and rectum were performed.

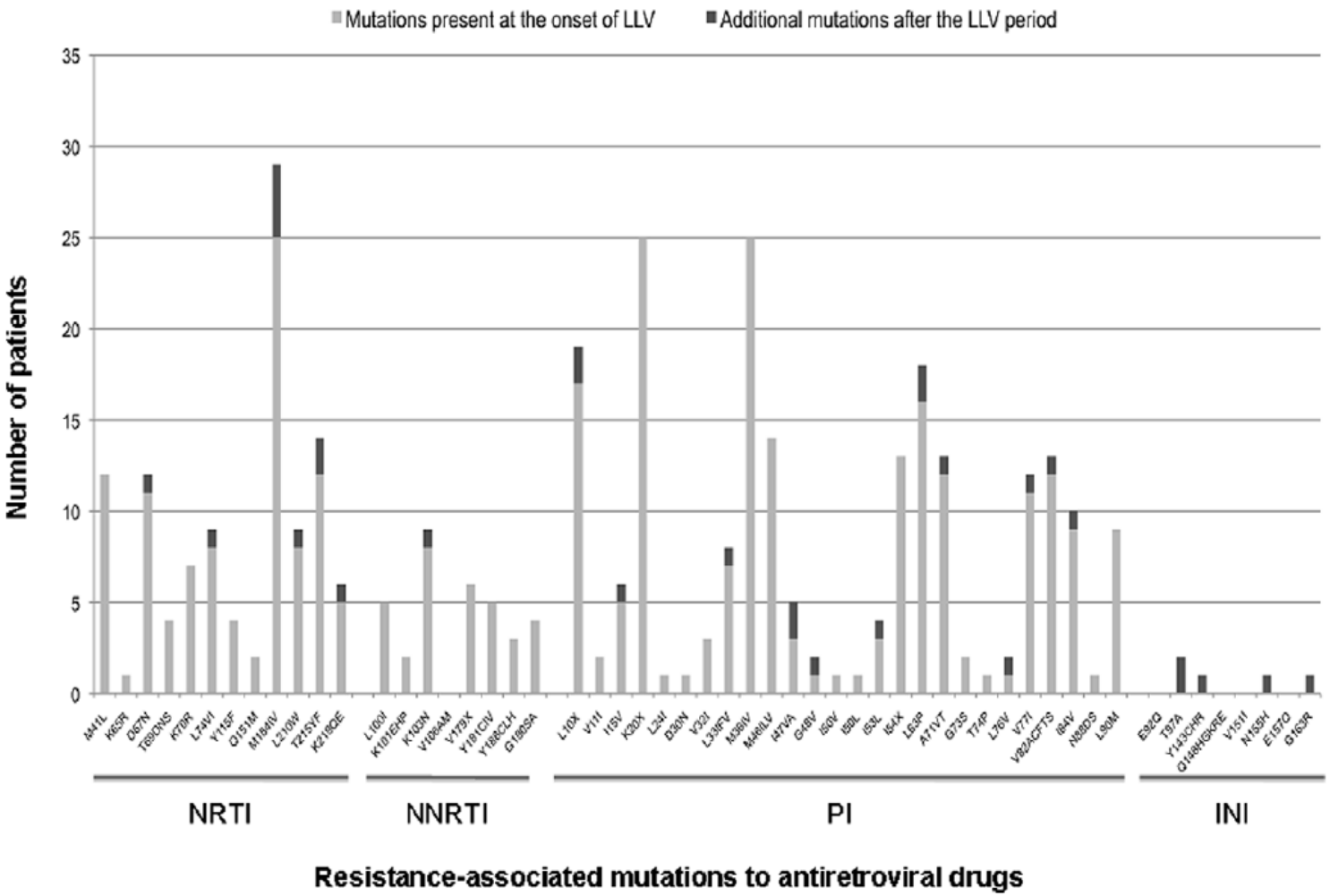
Fletcher et al., PNAS 2104

Impact of Low-Level-Viremia on HIV-1 Drug-Resistance Evolution among Antiretroviral Treated-Patients

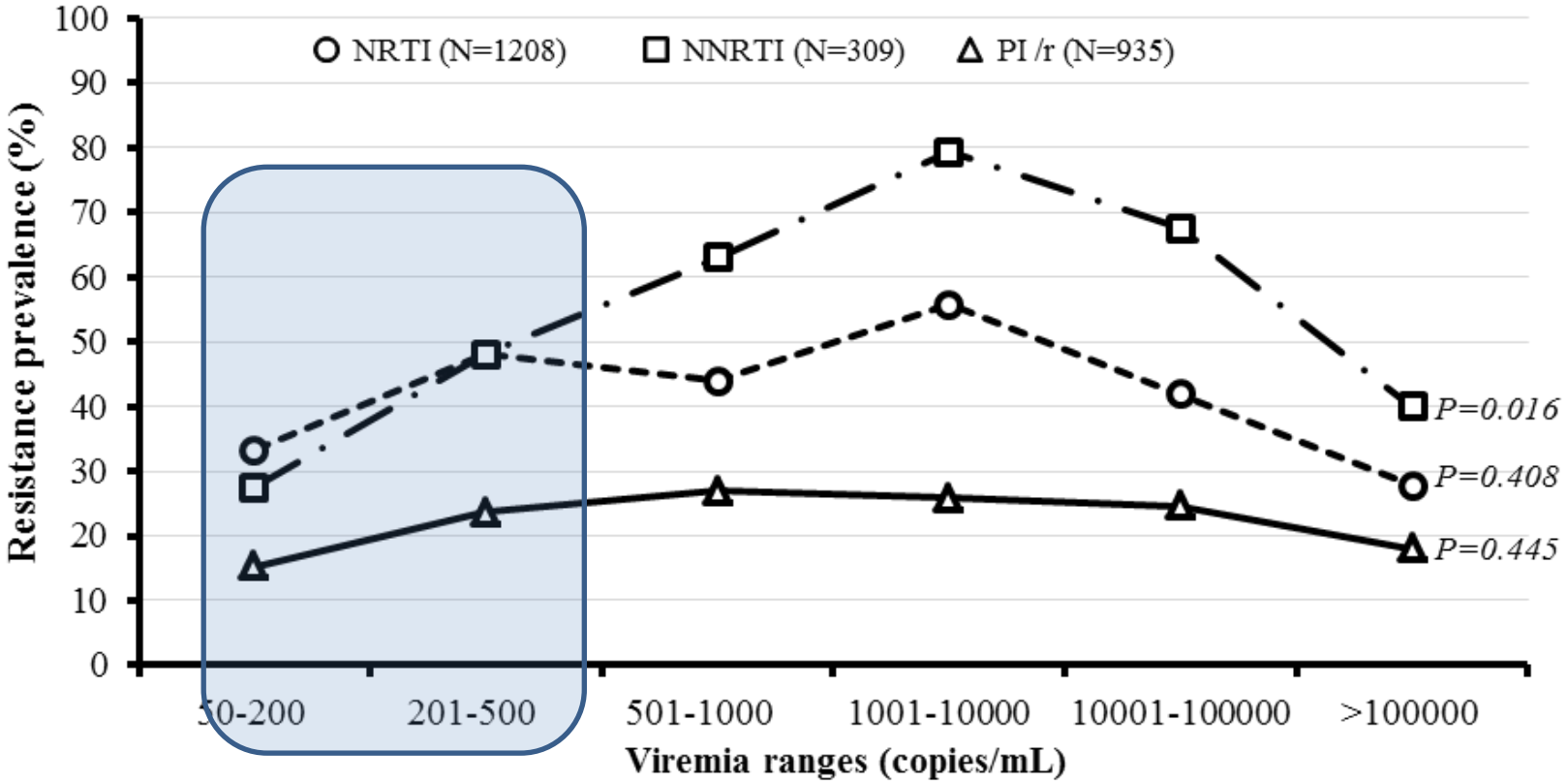
PLoS one

2012

Constance Delaugerre[1,2,3]*, Sébastien Gallien[2,3,4], Philippe Flandre[5,6], Dominique Mathez[7], Rishma Amarsy[1], Samuel Ferret[4], Julie Timsit[8], Jean-Michel Molina[2,3,4], Pierre de Truchis[9]



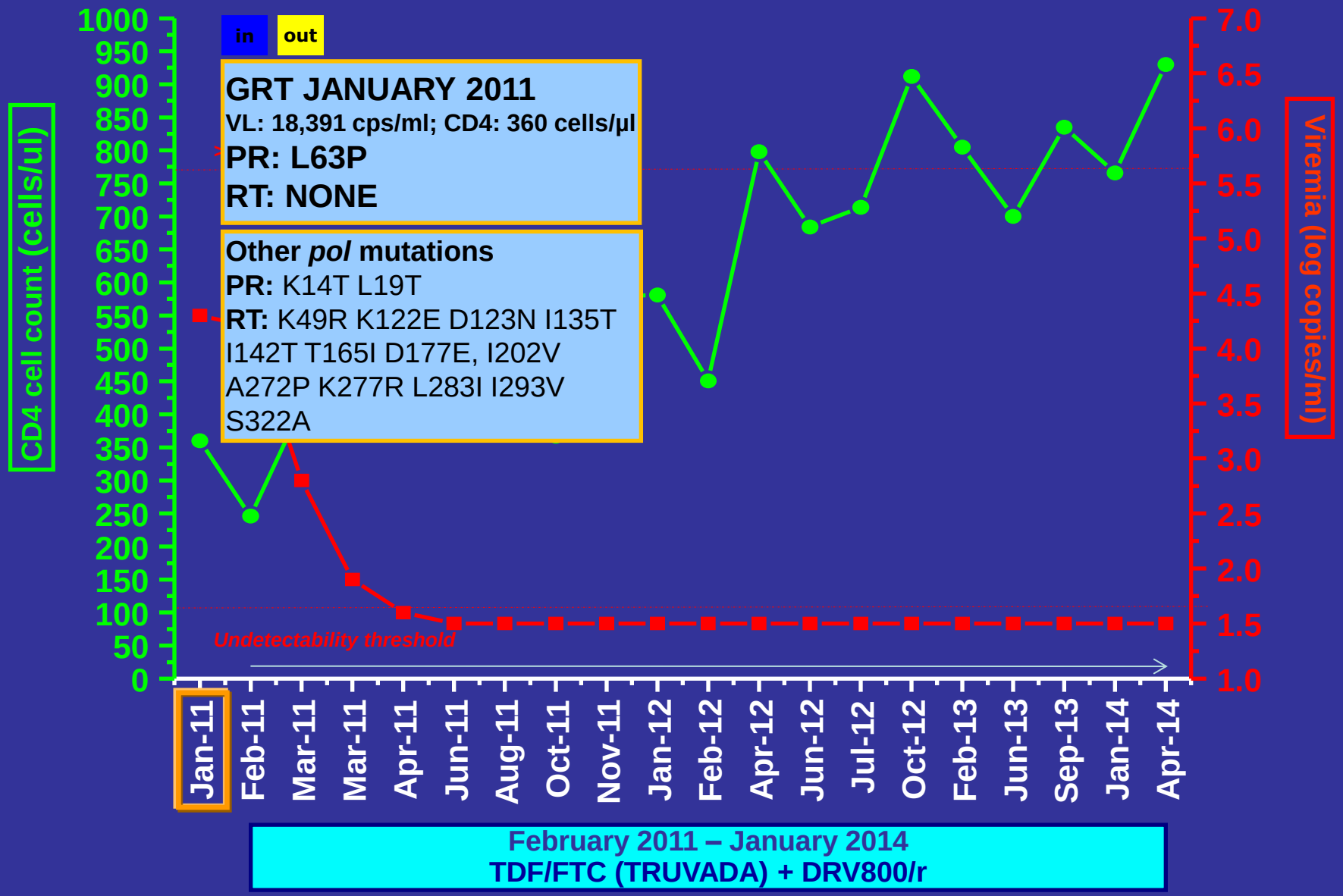
Resistance to NRTI, NNRTI or PI/r classes in samples collected from January 2008 to December 2012 stratified for plasma viremia ranges



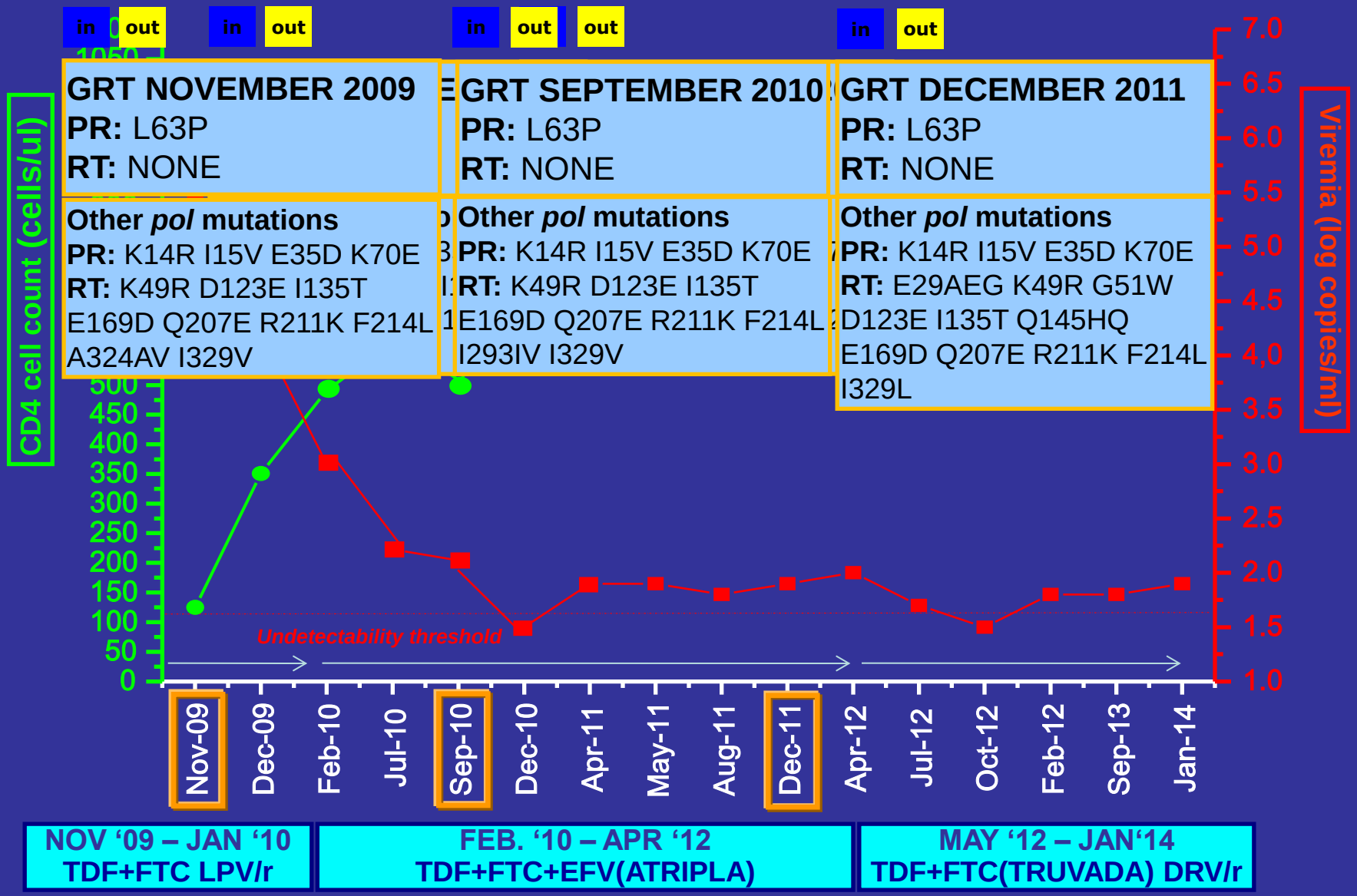
NRTI	196	123	82	283	315	209
NNRTI	40	27	27	87	83	45
PI/r	150	106	63	209	240	167

Santoro MM et al., CID 2014

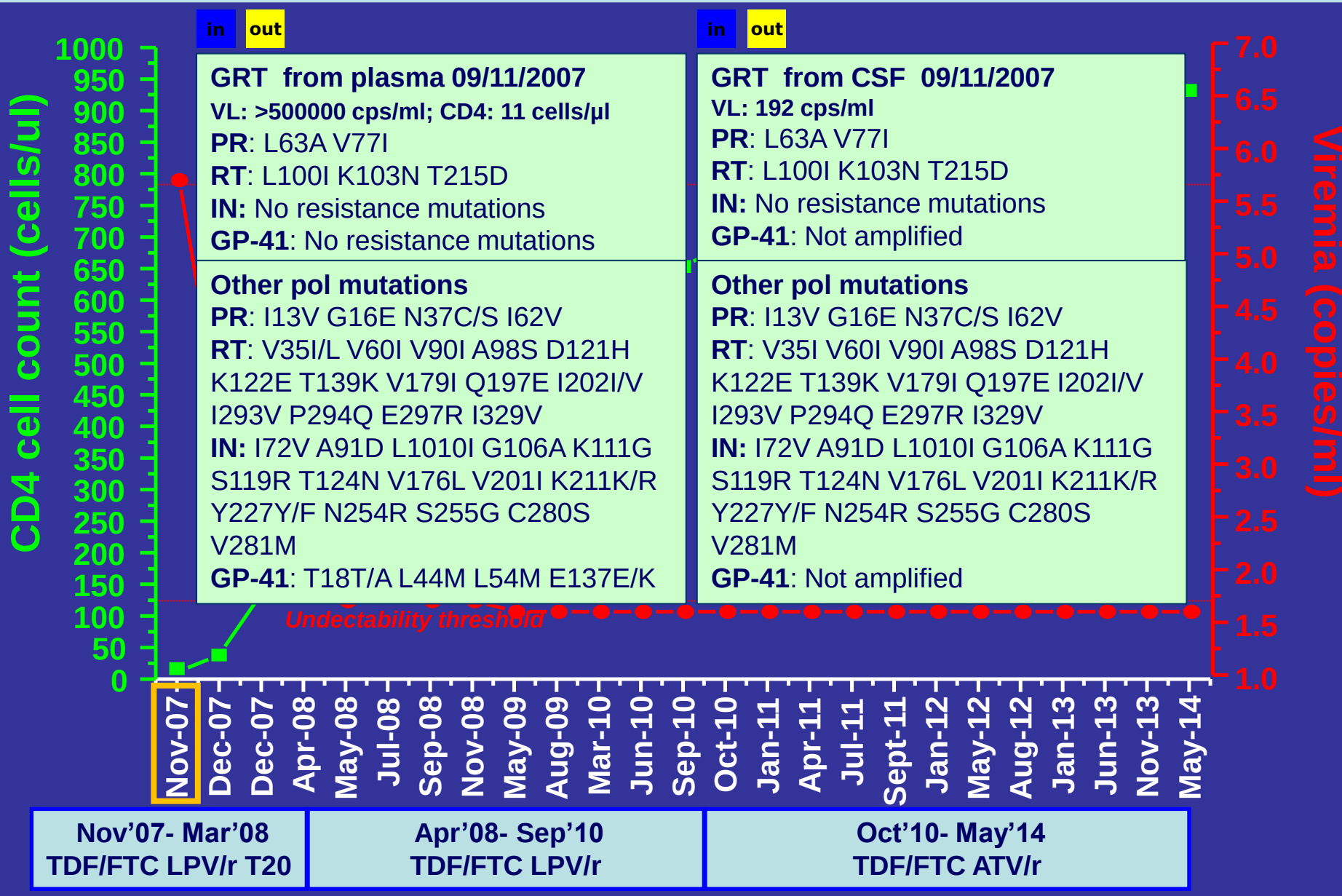
Clinical Case: ID 11922 Patient infected with HIV-1 B subtype	Age: 34	Sex: F	Risk Factor: Heterosexual	1ST Seropositivity: November 2010	CDC stage: B2



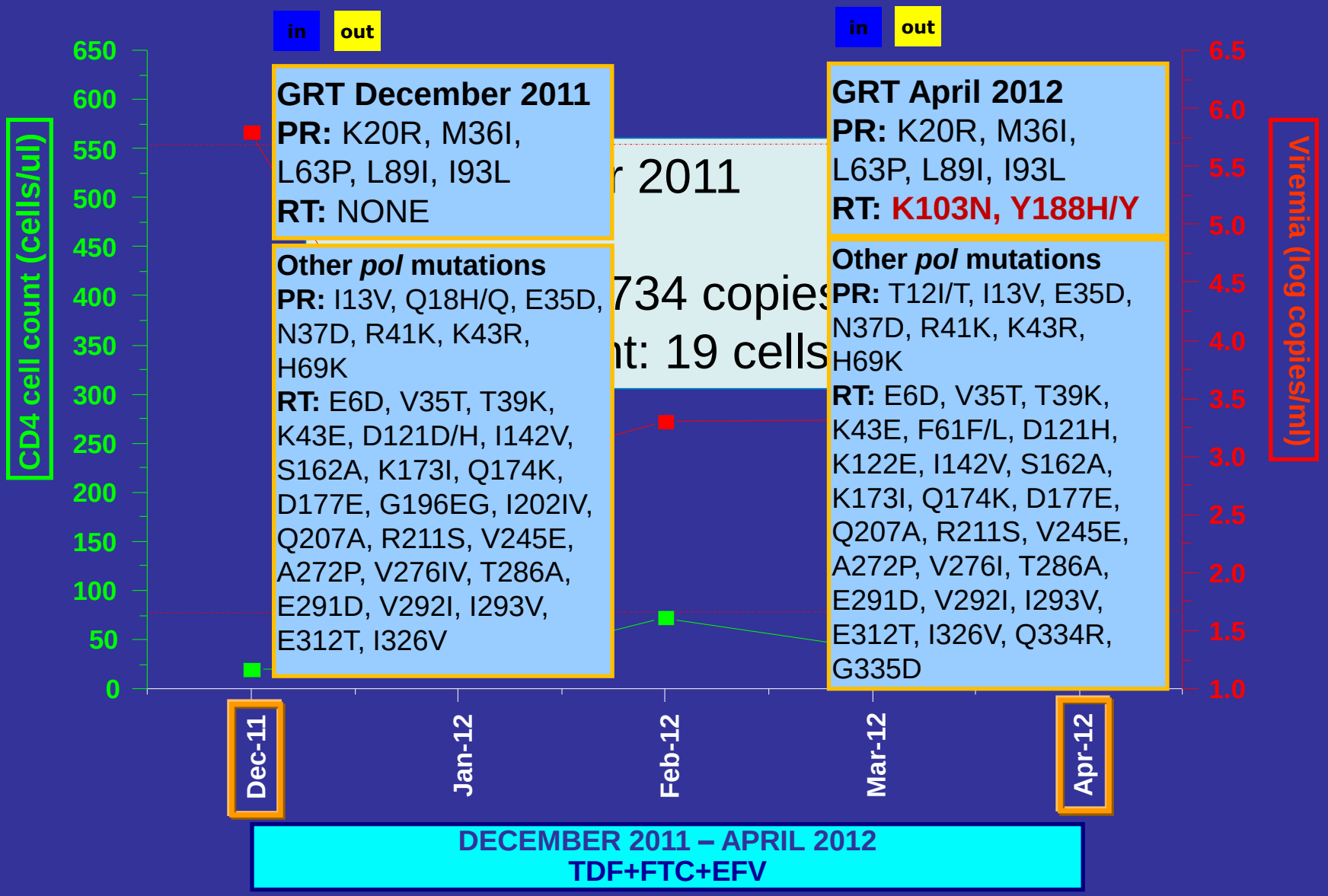
Clinical Case: ID 9964 Patient infected with HIV-1 B subtype	Age: 41	Sex: M	Risk Factor: MSM	1ST Seropositivity: December 2007	CDC stage: A



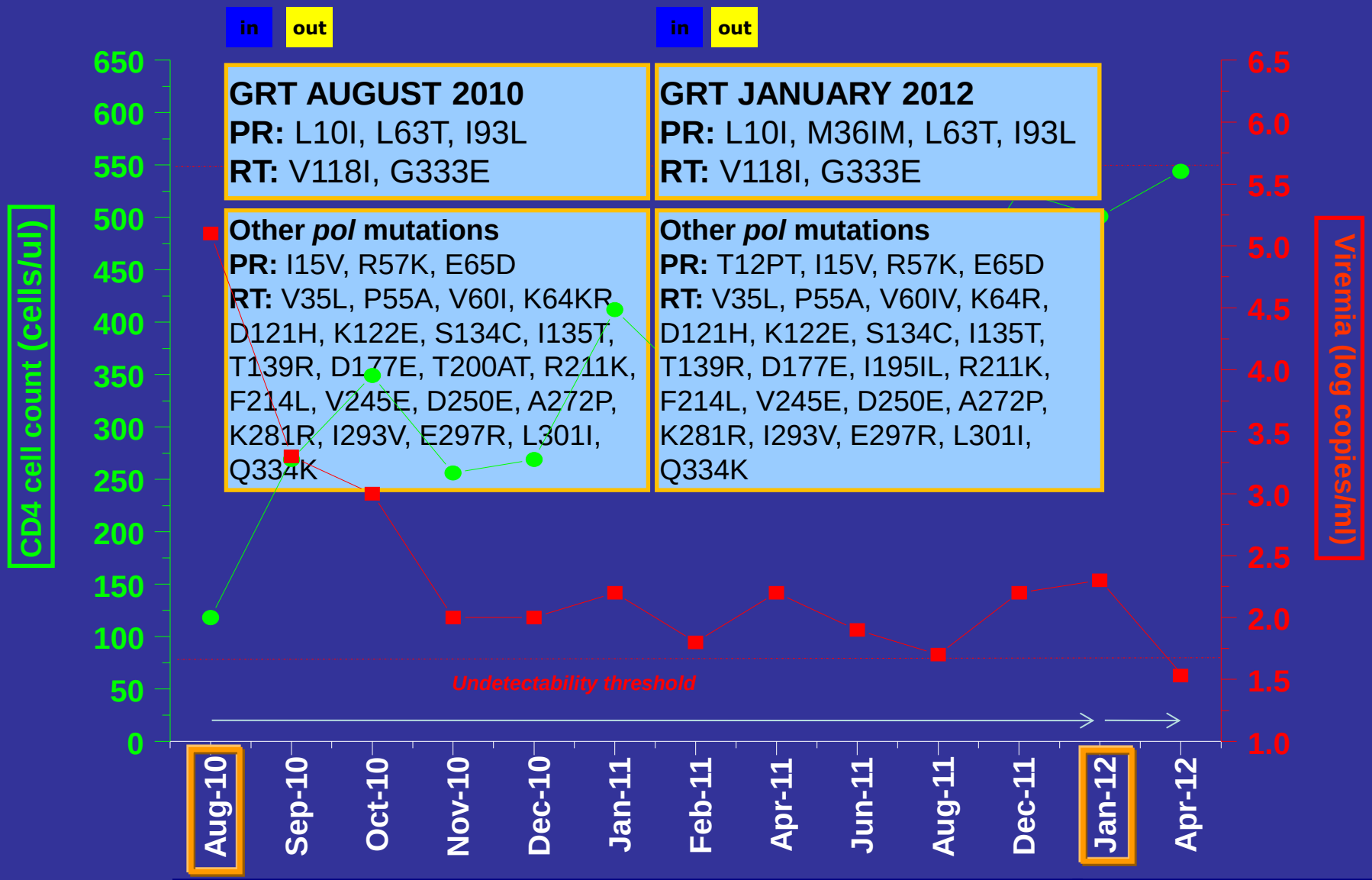
Clinical Case ID 7036 : Patient infected with HIV-1 B subtype	Age: 52	Sex: M	Risk Factor: Heterosexual	1st seropositivity: October 2007



Clinical Case: ID 13268 Patient infected with HIV-1 CRF01_AE	Age 43	Sex F	Risk Factor Heterosex	I Seropositivity December 2011	CDC stage C3



Clinical Case: ID 6784 Patient infected with HIV-1 B subtype	Age 33	Sex M	Risk Factor MSM	I Seropositivity January 2001	CDC stage B2



Conclusions (I)

- **The construction of antiretroviral therapy must be designed taking into account the long-term strategy, and not the mere control of short term viral replication.**
- **Viremia remains today a key marker of efficacy of antiviral therapy**
- **High viral load (including cumulative one) at baseline is consistently associated with higher risk of virological failure and clinical outcome ……. nevertheless….**
- **……persistent low viremia is also associated with an increased risk of virological failure, of development of resistance, and of progression of the disease, compared to patients with stable undetectable viral load**

Conclusions (II)

- **Resistance tests need to be used in clinical practice (also at low level viremia!) soon when virological failure is defined**
- **Genetic barrier still represents a key factor to be considered in a therapeutic strategy aimed at controlling the virus for long period of time, by maintaining viremia stably below the level of detection**