Virological response and retention in care according to time of starting ART in Italy: data from the Icona Foundation Study cohort.

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Running Head: Early ART and retention in care

Synopsis

Objectives: To describe (i) factors associated with rapid and delayed ART initiation, (ii) rates of 12-week virological response and (iii) virologically controlled retention in care by 1 year from ART initiation according to timing of start in a real-life setting.

Methods: All individuals in Icona cohort diagnosed with HIV in 2016-2017 who initiated ART analysed. They were grouped according to the time elapsed between HIV diagnosis and ART initiation: Group 1 (G1): ≤7 days; G2: 8-14 days; G3: 15-30 days; G4: 31-120 days; G5: >120 days. Multivariable logistic regression models were used to identify factors associated with: (i) the probability of rapid (G1) and very delayed (G5) ART initiation; (ii) the 12-week virological response (VR) (by modified snap-shot algorithm); (iii) the probability of retention in care at one year (i.e. on ART with HIV-RNA <50 copies/mL).

Results: 1,247 individuals included; 82 (6.6%) in G1, 115 (9.2%) in G2, 267 (21.4%) in G3, 641 (51.4%) in G4 and 142 (11.4%) in G5. Main predictors of rapid ART start (G1) were low CD4 count (Adjusted Odds Ratio (AOR)=4.71 for CD4<200 versus CD4>500 cells/mmc; p<0.001) and high HIV-RNA (AOR=2.31 for HIV-RNA ≥100.000 versus HIV-RNA<100.000 copies/mL; p=0.002) at first ID contact. Unemployed individuals were at risk of late ART start (G5). There was no association between probability of VR and timing of ART initiation. Overall, 90% of individuals remained on ART by one-year, 91% with undetectable HIV-RNA. Participants of Italian nationality, those with higher CD4 count and lower HIV-RNA at ART initiation were more likely to be retained in care by 1 year.

Conclusions: In our high-income observational setting, we did not observe differences in 1-year rate of virological response and retention in care according to timing of ART initiation.

Introduction

The initiation of ART is associated both with the control of HIV transmission, as undetectable virus means untrasmittable virus,[1] and with life expectancy and health state in people living with HIV (PLHIV); for these reasons universal ART coverage is strongly needed.

In this context, although it was established that antiretroviral therapy should be initiated in any person with HIV regardless of CD4 cells count,[2,3] there is still debate on how quickly ART should be started after HIV diagnosis, particularly in chronic asymptomatic patients. Accelerated or even immediate, so called "same day" initiation of ART has been advocated in order to reduce the probability of onward transmission of the infection and to address the issue of a possible disengagement from care occurring between HIV diagnosis and initiation of ART. On the other hand, starting treatment before the availability of laboratory test results may limit the therapeutic options, mainly because of risk of transmitted drug resistance. Moreover, it requires substantial resources to ensure availability of counselling, clinical evaluation, drug provision in a very short time-frame.[2,3]

A recent systematic review identified several randomized controlled trials which compared health outcomes of rapid initiation of ART within 14 days from HIV diagnosis with standard of care.[4] In all the studies,[5-9] other interventions aimed to improve uptake and adherence to ART were offered alongside with the rapid ART, and most of individuals in control groups started ART several weeks after HIV diagnosis. These studies provide moderate evidence of a greater viral suppression and a better retention in care at 12 months from ART initiation.[4]

Similar results have been reported in observational studies in which accelerated ART initiation (same day start or ART start within 7-14 days from HIV diagnosis) was compared with standard of care.[10-14] All these studies however included also patients with primary HIV infection and pregnant women, two categories that need urgent treatment and are highly committed to

85 treatment itself. Furthermore, they were generated in low-to-middle income countries. Therefore,
86 results could not be directly transferred to high-income countries with free of charge access to
87 care, where generally HIV is diagnosed in earlier stages, with relatively high CD4 counts, and
88 where health system is more efficient and better organised.

89 Some evidence of the potential benefit of starting ART early in the setting of high-income
90 countries comes from the RAPID study in San Francisco, an interventional study including patients
91 with acute or recent infection or with CD4 <200/cmm, belonging to a population of vulnerable
92 PLHIV.[15,16] Same-day ART initiation and an intensive social and medical evaluation and support was
93 provided within this program. Compared with the historical standard of care control group, RAPID
94 shortened the time from referral to viral suppression by 3 months, although during the first 18-
95 months loss to follow-up was similar in the RAPID and the standard of care group.

96 In general, there is no consensus on what is the definition of rapid ART (same day, within 7
97 or 14 days from diagnosis), and WHO guidelines suggest as definition of rapid ART to use the
98 cutoff of 7 days from the diagnosis.[17]

99 Taking these studies altogether, further evidence is needed in order to establish the
100 optimal timing of ART initiation in routine clinical practice in asymptomatic subjects diagnosed
101 with HIV in high-income countries. Moreover, a rapid approach to ART initiation may have
102 different consequences in countries with healthcare reimbursement systems as in Europe.

103 In this paper we aim to analyse the rates and predictors of early and very delayed ART
104 initiation in individuals from the Icona cohort recently diagnosed with HIV and initiating ART; we
105 also aim to analyse the rates and predictors of 12-week virological response and of virologically
106 controlled retention in care by 1 year from ART initiation, according to the timing of ART initiation.
107 We believe that these data are relevant to inform the design of future experimental studies
108 addressing this question.

Patients and Methods

The present analysis was conducted on the data of a subset of the HIV-infected individuals enrolled the Icona Foundation cohort. The Italian Cohort Naive Antiretrovirals Foundation Study (ICONA) is a multi-center, observational cohort study, recruiting ART-naïve PLHIV since 1997. ICONA study has been approved by Institutional Review Boards of all the participating centers. Data are collected prospectively from the date of entry in the cohort till last available follow-up for all patients who agree to participate and sign consent forms, in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration. Demographic, clinical, laboratory data and information on therapies are prospectively collected and recorded in anonymous form. Details of the cohort are described elsewhere.[18]

Patients from the cohort were included in this analysis if: - had been diagnosed with HIV between January 2016 (year of already available universal treatment guidelines)[2,3] and December 2017 (to allow at least one-year follow-up after HIV diagnosis); and had initiated ART. Patients with acute HIV infection and with AIDS at HIV diagnosis and pregnant women were excluded because rapid ART is universally recommended for these sub-populations. Follow-up accrued from the date of HIV diagnosis (even if before the first contact with the infectious diseases –ID- center) to last clinical visit or death. The database was locked and data extracted on May 2019.

Patients were divided into 5 groups according to the time elapsed between HIV diagnosis and ART start:

Group 1 (G1): ≤ 7 days

Group 2 (G2): 8-14 days

Group 3 (G3): 15-30 days

Group 4 (G4): 31-120 days

Group 5 (G5): >120 days.

Prevalence of the 5 groups was calculated. The median time (and IQR) from HIV diagnosis to first visit at the ID center (i.e. enrolment in Icona) and from the date of enrolment to start ART were calculated for the whole population on study and according to the elapse time groups.

We defined the following outcomes:

- rapid initiation (within ≤ 7 days from HIV diagnosis);
- very delayed initiation (>120 days from HIV diagnosis);
- early virological response (VR) (defined as HIV-RNA <50 copies/mL) by 12 (9-15) weeks from starting ART
- Retention in care with undetectable HIV-RNA (<50 copies/mL) by 1-year from ART start.

Factors associated with a rapid initiation (e.g ≤7 days versus >7 days from the date of first HIV-pos test) and those associated with very delayed ART initiation (>120 days versus ≤ 120 days) were identified in separate logistic regression models. Variables considered in the multivariable model were: age 30, 31-49, ≥50 years), sex, Italian nationality, mode of HIV transmission, calendar year of HIV diagnosis, education, employment, CD4 count strata and HIV RNA strata at first contact with infectious diseases clinic (ID).

The early virological suppression outcome was defined using a modified FDA-Snapshot analysis,[19] with an intent-to-treat (ITT) missing=failure approach and a time window of 9-15 weeks. The definition uses viral load values measured before and after the window for those whose window VL was missing to classify participants as success/failure (see supplementary Table S1 for details).

In addition, we analyzed the probability of being retained in care on ART with HIV-RNA <50 copies/mL by one year from starting ART. This analysis was performed only in patients initiating ART by the end of 2017, so that everybody had the potential for being followed-up for an entire year. Predictors of this end-point were analyzed by logistic regression according to an ITT missing=failure principle. Variables considered in multivariable models for the early virological

suppression and the retention in care virologically suppressed at 1-year outcomes were: age, sex, Italian nationality, mode of HIV transmission, calendar year of HIV diagnosis, ART regimen, CD4 count strata and HIV RNA strata at first ID contact.

Results

Out of a total of 1,581 patients with a HIV diagnosis in 2016-2017, 259 (16.5%) were excluded because of presentation with an AIDS-defining illness (n=157) or with primary infection (n=102) and 75 (4.8%) were excluded because never initiated ART. The remaining 1,247 PLHIV who satisfied the above mentioned criteria were included. The 75 PLHIV who never started ART, compared to the 1,247 included patients, were younger (34 years old (IQR: 27-45) versus 38 years (29-47); p=0.048), more frequently migrants (40% versus 27%; p=0.011) with higher CD4 count at first ID contact (median CD4 count 572 cells/cmm (439-768) versus 367 cells/mmc (213-566); p<0.001) and with lower HIV viral load (>100,000 copies/mL: 16.7% versus 36.7%; p<0.001).

Overall, the median time from HIV diagnosis to ART initiation was 40 (interquartile range-IQR: 21-73) days. In detail, 82 (6.6%) PLHIV were classified as Group 1, 115 (9.2%) as Group 2, 267 (21.4%) as Group 3, 641 (51.4%) as Group 4 and 142 (11.4%) as Group 5.

The baseline characteristics of the patients according to the timing of ART initiation are shown in Table 1. There were differences in demographics and clinical parameters according to time of ART initiation. In particular, participants initiating within 7 days from HIV diagnosis were more often severely immunosuppressed (CD4 counts <200/cmm: 48% in G1, 45% in G2, 31% in G3, 17% in G4 and 9% in G5, p<0.001) and highly viremic (HIV RNA >100,000 copies/mL: 65% in G1, 60% in G2, 42% in G3, 31% in G4 and 18% in G5, p<0.001) than those initiating later.

We also disentangled time from HIV diagnosis to ART start into two different time periods: time from HIV diagnosis to enrolment in Icona, and time from enrolment to ART start. These two

periods were strictly related: subjects initiating ART earlier showed both a shorter time from HIV diagnosis to referral to ID center and a shorter time from referral to ART initiation than those initiating later (Table 1).

Conditioning on having started ART, lower CD4 counts and higher HIV-RNA at first ID contact were associated with a more rapid time of initiation. After adjusting for age, sex, risk factors for HIV, calendar year of HIV diagnosis, Italian nationality, employment status, education and Italian geographical region, compared to PLHIV with CD4 counts>500/cmm, those with CD4 counts <200/cmm had 4.71-fold (95%CI: 2.03-10.95), those with CD4 200-350/cmm had a 2.58-fold (95%CI: 1.08-6.16) and those with CD4 350-500/cmm had a 2.16-fold (95%CI: 0.88-5.28) higher probability to initiate within 7 days from HIV diagnosis rather than later than 7 days. Also, PLHIV with HIV RNA ≥100,000 copies/mL had a 2.31-fold higher probability (95%CI:1.37-3.92) to initiate within 7 days than PLHIV with HIV RNA <100,000 copies/mL (Figure 1a).

CD4 count and viral load were also independent predictors of very late ART initiation (i.e., >120 days since the first HIV-pos test). In addition, being unemployed was independently associated with a 2.32-fold higher risk of starting ART >120 days after HIV diagnosis (95% CI: 1.34-4.02) (Figure 1b).

The 12-week VR (i.e. snapshot endpoint HIV RNA≤50 copies/mL) occurred overall in 747/1,247 (59.9%) PLHIV: 45/82 (54.9%) of G1; 63/115 (54.8%) of G2; 149/267 (55.8%) of G3, 403/641 (62.9%) of G4 and 87/142 (61.3%) of G5 (p=.168). The time elapsed from HIV diagnosis to ART start was not associated with the probability of 12-week VR; independent predictors of this outcome were Italian nationality (1.39 higher probability -95%CI: 1.04-1.87- versus migrants) and having started ART with integrase inhibitors (INSTI)-containing regimens: both PLHIV initiating boosted PI (bPI)-containing regimens and PLHIV initiating NNRTI-containing regimens had a lower probability (bPI: AOR 0.40, 95%CI: 0.28-0.58; NNRTI: AOR 0.42, 95% CI: 0.30-0.60) of obtaining

205 virological success at 12 weeks of ART as compared to PLHIV initiating INSTI-containing regimens,
206 after adjusting for demographic and viro-immunological variables. Moreover, as expected, both
207 CD4 counts and HIV-RNA at first ID contact were independent predictors of achieving 12 week-
208 virological success (Figure 2).

209 We finally analyzed the percentage of PLHIV still attending the ID centers, on ART and with
210 a viral load <50 copies/mL at one year of therapy, according to the elapse time groups. This
211 analysis included only the 1,164 patients starting ART by the end of 2017, who had the potential
212 for being followed-up for an entire year. Overall, 90% of PLHIV were on therapy by 12 months,
213 and 91% of these had a HIV-RNA <50 copies/mL. Twelve patients (1.0%) died during the first year
214 of ART and 100 (8.5%) were no longer in care in Icona at 1 year. Of these individuals, 75 (6.4%)
215 were lost to clinical follow-up and 25 (2.1%) moved to another country or another clinical center in
216 Italy outside of the Icona cohort network.

217 A total of 957/1,164 (82.2%) PLHIV were retained in care with a viral load <50 copies/mL by
218 one year with no differences according to G1-G5 groups: 63/81 (77.8%) of G1; 89/115 (77.4%) of
219 G2; 219/259 (84.6%) of G3; 494/600 (82.3%) of G4 and 92/109 (84.4%) of G5 (p=.373). The main
220 independent predictor of retention in care with <50 copies/mL viral load was again Italian
221 nationality (versus migrants AOR=2.02, 95%CI= 1.39-2.93), while lower CD4 cell count at first ID
222 contact (<200 versus >500 cells/cmm AOR=0.56, 95%CI=0.35-0.91), higher HIV-RNA at first ID
223 contact (≥100,000 versus <100,000 copies/mL AOR=0.68, 95%CI= 0.48-0.98) and first-line ART
224 with bPI-based regimens (versus INSTI-based AOR=0.62, 95%CI=0.40-0.95) were associated with a
225 lower probability of retention in care with HIV-RNA <50 copies/mL at 1 year after ART start
226 (Figure 3). The results were confirmed by running two case control analyses with unmatched and
227 matched HIV RNA, using G1 and G4 groups (data not shown).
228

Discussion

Our analysis of observational data including more than one thousand PLHIV seen for care in a setting of free access to medical care who all initiated ART failed to show clear benefit of rapid ART initiation in terms of virological success and retention in care by one year of ART start in chronic asymptomatic PLHIV.

In our cohort, only 16% of the PLHIV initiated ART within 14 days from HIV diagnosis and only 37% initiated within 30 days. It has to be underlined that the lag time from HIV diagnosis to referral to clinical centre contributed, at least partially, to the time spent waiting for ART, and this does not relate to the ID clinic policy or organisation. Particularly in the metropolitan areas there are many testing points also outside the hospital settings, such as outpatients labs in which HIV testing is offered and, once the subject is found to be HIV positive (and may take several days for the response to arrive), he/she is referred to the ID centre, and the whole process takes time. A bit different is the setting of the community-based check points, in which the response is immediate and, after counselling, the subjects are immediately addressed to one ID centre for a confirmatory test and for care; unfortunately, only two cities in Italy, Bologna and Milan, have this community-based facility to date.

Our analysis shows that Italian clinicians tend to initiate ART more quickly in the most immunosuppressed asymptomatic PLHIV, provided that they follow all guidelines who recommend ART initiation independently from CD4 counts and HIV load.[2,3] Indeed, the group of PLHIV who started within 7 days from HIV diagnosis showed lower CD4 count and higher HIV-RNA levels. Interestingly, the group of people who started very late (e.g. >120 days from HIV test) was enriched with persons who declared to be unemployed. Considering that Italy has universal health care coverage, this indicator underlines the importance of reaching more fragile strata of population that can contribute to the spread of HIV infection. In this regard, the San Francisco

253 RAPID program, addressed to vulnerable subjects, might constitute a valid example of
254 intervention.[16]
255 The fact that ART was started more quickly in participants with advanced disease could have
256 introduced a bias in our analysis and may limit the generalizability of our results. We have tried to
257 control for imbalances in key common causes of timing of ART initiation and chance of retention in
258 care but residual confounding cannot be ruled out and this could explain the discrepancies
259 between our results and those shown by randomized comparisons.
260 On the other hand, because of the differential rate of access to care and level of care provided in
261 the two settings, it is possible that the effect of early ART initiation has genuinely lower impact on
262 the probability of retention in resource-rich countries (e.g. Italy) than that seen in the setting of
263 the randomized trials (mainly conducted in Africa).
264 Our analysis also aimed at evaluating the correlation between timing of initiation and
265 short-term probability to achieve a HIV-RNA <50 copies/mL once ART was started, as this
266 condition relates to absence of HIV transmission.[1] A total of 747 out of 1,247 (60%) PLHIV
267 obtained <50 copies/mL HIV load at 12 weeks of ART; as expected both CD4 and HIV-RNA at
268 baseline were associated with the probability of achieving this outcome. Use of INSTI-based
269 regimens was also associated with a higher probability of achieving HIV-RNA suppression,
270 consistently with the results of randomized trials.[20-22] People of Italian nationality were also at
271 higher chance of achieving this outcome; this might be due to the fact that migrants often are in
272 poor and unstable socio-economic situations potentially leading to no adherence to therapies or
273 to change of residence.
274 Looking at 1 year-retention in care, our data show that once HIV-positive individuals are
275 referred to clinical centres, the large majority is retained in care, and 90% of them have <50
276 copies/mL HIV-RNA by 1 year. People who appeared to be no longer retained in care by 1 year of

ART were more likely to be those with advanced stage of HIV infection, migrants and those starting a boosted PI regimen. Migrants are often moving from one city to another or going back to their own country, and this more fragile population should be better followed in order to guarantee continuum of care. More difficult to explain is the higher risk of poor retention in care of PLHIV initiating boosted-PI including regimens. It might be the result of bias by indication, as clinicians could have offered more frequently these regimens to patients who are perceived to be less adherent, due to the high genetic barrier of PIs.[23]

Our study has several limitations. First, the analysis is restricted in individuals who have initiated ART. In order to evaluate whether the strategy of initiation ART <7 days from HIV diagnosis as opposed to other strategies in the observational context, more sophisticated methods involving the simulation of an hypothetical trial, such as RAPID for example, as well the use of counterfactuals are needed. Although only 75 people who did not start ART were excluded from this analysis, the consequences of this selection bias on the final results are difficult to predict. In addition, time-dependent confounding due to censoring of people deviating from the various timing of initiation strategies under examination have not been properly accounted for. Finally, we considered only asymptomatic patients and cannot extend our conclusions to symptomatic/AIDS patients who, according to WHO, need urgent ART initiation.[17] More in general, because of the observational nature of the study, we cannot rule out that all sources of potential confounding have been accounted for.

In conclusion, our data show that approximately 7% of recently diagnosed, asymptomatic, HIV-infected individuals in Italy initiated ART within 7 days from HIV diagnosis, 16% within 14 days, and would fit with a strategy defined as rapid ART initiation. Furthermore, in this large series of

PLHIV cared in a free of access setting, we found no evidence that the timing of ART initiation was associated with the probability of virological success and one-year retention in care. Of course, a randomized study, conducted in the resource-rich setting, to evaluate the possible benefits of this rapid initiation strategy versus a less rapid start in asymptomatic HIV pos individuals is urgently needed. The data shown in this work should be useful to better inform the design of such future studies.

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References

1. AJ Rodger, V Cambiano, T Bruun et al. for the PARTNER Study Group. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *The Lancet* 2019; **393**:2428–2438.
2. European AIDS Clinical Society [EACS] guidelines, version 9.0, October 2017. http://www.eacsociety.org/files/guidelines_9.0-english.pdf
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services; July 14, 2016. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf
4. Ford N, Migone C, Calmy A *et al*. Benefits and risks of rapid initiation of antiretroviral therapy. *AIDS* 2018; **32**:17-23.
5. Rosen S, Maskew M, Fox MP *et al.* Initiating antiretroviral therapy for HIV at a patient's first clinic visit: the RapIT randomized controlled trial. *PLoS Med* 2016; **13**:e1002015.
6. Amanyire G, Semitala FC, Namusobya J *et al.* Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. *Lancet HIV* 2016; **3**:e539–e548.
7. Labhardt ND, Ringera I, Lejone TI *et al.* Effect of offering same-day ART versus usual health facility referral during homebased HIV testing on linkage to care and viral suppression among adults with HIV in Lesotho: the CASCADE randomized clinical trial. *JAMA* 2018; **319**:1103–1112.
8. Koenig SP, Dorvil N, Devieux JG *et al*. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: a randomized unblinded trial.

PLoS Med 2017; **14**:e1002357.

9. Zolopa AR, Andersen J, Powderly W *et al.* Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE* 2009; **4**:e5575.
10. Langwenya N, Phillips TK, Brittain K *et al.* Same day antiretroviral therapy (ART) initiation in pregnancies is not associated with viral suppression or engagement in care: a cohort study. *J Int AIDS Soc* 2018 Jun; **21**:e25133
11. Mitiku I, Arefayne M, Mesfin Y, Gizaw M. Factors associated with loss to follow-up among women in option BR PMTCT programme in northeast Ethiopia: a retrospective cohort study. J Int AIDS Soc 2016; **19**:20662.
12. Chan AK, Kanike E, Bedell R *et al.* Same day HIV diagnosis and antiretroviral therapy initiation affects retention in option BR prevention of mother-to-child transmission services at antenatal care in Zomba District, Malawi. *J Int AIDS Soc* 2016; **19**:20672.
13. Hoenigl M, Chaillon A, Moore DJ *et al.* Rapid HIV Viral Load Suppression in those Initiating Antiretroviral Therapy at First Visit after HIV Diagnosis. *Sci Rep* 2016; **6**:32947.
14. Wu Z, Zhao Y, Ge X *et al.* Simplified HIV testing and treatment in China: analysis of mortality rates before and after a structural intervention. *PLoS Med* 2015; **12**:e1001874.
15. Pilcher CD, Ospina-Norvell C, Dasgupta A *et al.* The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting. *J Acquir Immune Defic Syndr* 2017; **74**:44–51
16. Coffey S, Bacchetti P, Sachdev D *et al.* RAPID antiretroviral therapy: high virologic suppression rates with immediate antiretroviral therapy initiation in a vulnerable urban clinic population. *AIDS* 2019; **33**:825-832.

17. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. World Health Organisation, July 2017. https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

18. d'Arminio Monforte A, Cozzi Lepri A, Rezza G *et al.* Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naıve patients. *AIDS* 2000; **14**:499–507.

19. U.S. Department of Health and Human Services, Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment guidance for industry. https://www.fda.gov/media/86284/download

20. Lennox JL, DeJesus E, Lazzarin A *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: A multicentre, double blind randomised controlled trial. *Lancet* 2009; **374**:796–806.

21. DeJesus E, Rockstroh JK, Henry K *et al.* for the GS-236-0103 Study Team: Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet* 2012; **379**:2429–38.

22. Walmsley SL, Antela A, NClumeck N *et al*. for the SINGLE Investigators: Dolutegravir plus Abacavir–Lamivudine for the Treatment of HIV-1 Infection, *N Engl J Med* 2013; **369**:1807-1818

23. Mammano F, Petit C, Clavel F. Resistance-associated loss of viral fitness in human immunodeficiency virus type 1: phenotypic analysis of protease and gag coevolution in protease inhibitor-treated patients. *J Virol* 1998; **72**:7632–7637.

Figure 1. Crude and Adjusted Odds Ratio of association between different clinical and demographic baseline characteristics and starting ART A) <=7 days from HIV diagnosis and B) >120 days from HIV diagnosis

Figure 2. Crude and Adjusted Odds Ratio of association between time from HIV diagnosis to ART start and 12-week virological success (i.e. HIV RNA <50 copies/mL) using a modified snapshot analysis from fitting a logistic regression

Figure 3. Crude and Adjusted Odds Ratio of association between time from HIV diagnosis to ART start and being in care and with virological suppression 12 months after starting ART