

# THE LANCET

## **Supplementary webappendix**

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# Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected people: a collaborative analysis of 18 HIV cohort studies

## When To Start Consortium

### Web appendix

#### The When to Start Consortium Study Group

#### French Hospital Database on HIV (ANRS CO4 FHDH)

**Scientific committee:** S Abgrall, F Barin, M Bentata, E Billaud, F Boué, C Burty, A Cabié, D Costagliola, L Cotte, P De Truchis, X Duval, C Duvivier, P Enel, L Fredouille-Heripret, J Gasnault, C Gaud, J Gilquin, S Grabar, C Katlama, MA Khuong, JM Lang, AS Lascaux, O Launay, A Mahamat, M Mary-Krause, S Matheron, JL Meynard, J Pavie, G Pialoux, F Pilorgé, I Poizot-Martin, C Pradier, J Reynes, E Rouveix, A Simon, P Tattevin, H Tissot-Dupont, JP Viard, N Viget.

**DMI2 coordinating center:** French Ministry of Health (Valérie Salomon), Technical Hospitalization Information Agency, ATIH (N Jacquemet).

**Statistical analysis center:** U943 INSERM et UPMC (S Abgrall, D Costagliola, S Grabar, M Guiguet, E Lanoy, L Lièvre, M Mary-Krause, H Selinger-Leneman), INSERM Transfert (JM Lacombe, V Potard)

**COREVIH: Paris area:** *Corevih Ile de France Centre* (GH Pitié-Salpêtrière: F Bricaire, S Herson, C Katlama, A Simon; Hôpital Saint-Antoine: N Desplanque, PM Girard, JL Meynard, MC Meyohas, O Picard; Hôpital Tenon: J Cadranet, C Mayaud, G Pialoux), *Corevih Ile de France Est* (Hôpital Saint-Louis: JP Clauvel, JM Decazes, L Gerard, JM Molina; GH Lariboisière-Fernand Widal: M Diemer, P Sellier; Hôpital Avicenne: M Bentata, P Honoré; Hôpital Jean Verdier: V Jeantils, S Tassi; Hôpital Delafontaine: D Mechali, B Taverne), *Corevih Ile de France Nord* (Hôpital Bichat-Claude Bernard: E Bouvet, B Crickx, JL Ecobichon, S Matheron, C Picard-Dahan, P Yeni), *Corevih Ile de France Ouest* (Hôpital Ambroise Paré: H Berthé, C Dupont; Hôpital Louis Mourier: C Chandemerle, E Mortier; Hôpital Raymond Poincaré: P de Truchis), *Corevih Ile de France Sud* (Hôpital Européen Georges Pompidou: D Tisne-Dessus, L Weiss; GH Tarnier-Cochin: D Salmon; Hôpital Saint-Joseph: I Auferin, J Gilquin; Hôpital Necker adultes: L Roudière, JP Viard; Hôpital Antoine Bécclère: F Boué, R Fior; Hôpital de Bicêtre: JF Delfraissy, C Goujard; Hôpital Henri Mondor: C Jung, Ph Lesprit; Hôpital Paul Brousse: D Vittecoq).

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**Overseas:** *Corevih Guadeloupe* (CHRU de Pointe-à-Pitre: M Strobel; CH Saint-Martin: F Bissuel), *Corevih Guyane* (CHG de Cayenne: R Pradinaud, M Sobesky), *Corevih Martinique* (CHRU de Fort-de-France: A Cabié), *Corevih de La Réunion* (CHD Félix Guyon: C Gaud, M Contant).

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### **Statistical And Monitoring Team**

A Cozzi-Lepri, I Fanti, T Formenti, M Prosperi

### **Participating Physicians And Centers**

**Italy** M. Montroni, A. Giacometti, A Costantini, A. Riva (Ancona); U. Tirelli, F. Martellotta (Aviano-PN); G. Pastore, N. Ladisa, (Bari); F. Suter, F. Maggiolo (Bergamo); F. Chiodo, G. Verucchi, C. Fiorini, (Bologna); G. Carosi, G. Cristini, C. Torti, C. Minardi, D. Bertelli (Brescia); T. Quirino, C Abeli (Busto Arsizio); P.E. Manconi, P. Piano (Cagliari); J Vecchiet, M. Farenga (Chieti); G Carnevale, S Lorenzotti (Cremona); F. Ghinelli, L. Sighinolfi (Ferrara); F. Leoncini, F. Mazzotta, M. Pozzi, S. Lo Caputo (Firenze); G. Pagano, G. Cassola, G Viscoli, A. Alessandrini, R. Piscopo (Genova); F. Soscia, L. Tacconi (Latina); A. Orani, R. Rossotto (Lecco); D Tommasi, P Congedo (Lecce); A. Chiopera, P. Castelli (Macerata); M Galli, A. Lazzarin, G. Rizzardini, I Schlacht, A. d'Arminio Monforte, AL Ridolfo, A Foschi, A Castagna, S Salpietro, S. Merli, S. Melzi, M.C. Moioli, P Cicconi, T Formenti (Milano); R. Esposito, C. Mussini (Modena); A Gori (Monza), N. Abrescia, A. Chirianni, CM Izzo, M. De Marco, R. Viglietti, E Manzillo (Napoli); C. Ferrari, P. Pizzaferrri (Parma); F Baldelli, G Camanni (Perugia); G. Magnani, M.A. Ursitti (Reggio Emilia); M. Arlotti, P. Ortolani (Rimini); R. Cauda, M Andreoni, A. Antinori, G. Antonucci, P. Narciso, V Tozzi, V. Vullo, A. De Luca, M. Zaccarelli, R. Acinapura, P. De Longis, M.P. Trotta, M. Lichtner, F. Carletti, (Roma); M.S. Mura, G Madeddu (Sassari); P. Caramello, G. Di Perri, G.C. Orofino, (Torino); E. Raise, F. Ebo (Venezia); G. Pellizzer, D. Buonfrate (Vicenza).

## **Swiss HIV Cohort Study (SHCS)**

M. Battegay, E. Bernasconi, J. Böni, HC Bucher, Ph. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösl, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.

## **AIDS Therapy Evaluation project Netherlands (ATHENA)**

L.A.Gras (bio-statistician), A.I. van Sighem (senior researcher), C. Smit (epidemiologist), F. de Wolf (director)

### **Treating physicians**

(\*Site coordinating physicians) Academisch Medisch Centrum bij de Universiteit van Amsterdam - Amsterdam: Dr. J.M. Prins\*, Drs. J.C. Bos, Dr. J.K.M. Eeftinck-Schattenkerk, Dr. S.E. Geerlings, Dr. M.H. Godfried, Prof. dr. J.M.A. Lange, Dr. J.T.M. van der Meer, Dr. F.J.B. Nellen, Drs. D.P. Olszyna, Dr. T. van der Poll, Prof. dr. P. Reiss, Drs. S.U.C. Sankatsing, Drs. M. van der Valk, Drs. J.N. Vermeulen, Drs. S.M.E. Vrouwenraets, Dr. M. van Vugt, Dr. F.W.M.N. Wit. Academisch Ziekenhuis Maastricht - Maastricht: Dr. G. Schreij\*, Dr. S. van der Geest, Dr. A. Oude Lashof, Dr. S. Lowe, Dr. A. Verbon. Catharina Ziekenhuis - Eindhoven: Dr. B. Bravenboer\*, Drs. M.J.H. Pronk. Emma Kinderziekenhuis - AMC Amsterdam: Prof. dr. T.W. Kuijpers, Drs. D. Pajkrt, Dr. H.J. Scherpbier. Erasmus MC - Rotterdam: Dr. M.E. van der Ende\*, Drs. H. Bax, Drs. M. van der Feltz, Dr. L.B.S. Gelinck, Drs. Mendoca de Melo, Dr. J.L. Nouwen, Dr. B.J.A. Rijnders, Dr. E.D. de Ruiter, Dr. L. Slobbe, Drs. C.A.M. Schurink, Dr. T.E.M.S.

de Vries. Erasmus MC - Sophia - Rotterdam: Dr. G. Driessen, Dr. M. van der Flier, Dr. N.G. Hartwig.  
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 Dr. E.F. Schippers. Isala Klinieken - Zwolle: Dr. P.H.P. Groeneveld\*, Dr. M.A. Alleman. Kennemer Gasthuis -  
 Haarlem: Prof. dr. R.W. ten Kate\*, Dr. R. Soetekouw. Leids Universitair Medisch Centrum - Leiden: Dr. F.P.  
 Kroon\*, Dr. S.M. Arend, Drs. M.G.J. de Boer, Prof. dr. P.J. van den Broek, Prof. dr. J.T. van Dissel, Drs. C. van  
 Nieuwkoop. Maasstadziekenhuis - locatie Clara - Rotterdam: Dr. J.G. den Hollander\*. Medisch Centrum Alkmaar -  
 Alkmaar: Dr. W. Bronsveld\*, Drs. K. Pogány. Medisch Centrum Haaglanden -locatie Westeinde - Den Haag: Dr. R.  
 Vriesendorp\*, Dr. F.J.F. Jeurissen, Dr. E.M.S. Leyten. Medisch Centrum Leeuwarden - Leeuwarden: Dr. D. van  
 Houte\*, Dr. M.B. Polée, Dr. M. van Vonderen. Medisch Spectrum Twente - Enschede: Dr. C.H.H. ten Napel\*, Dr.  
 G.J. Kootstra. Onze Lieve Vrouwe Gasthuis - Amsterdam. Prof. dr. K. Brinkman\*, Drs. G.E.L. van den Berk, Dr.  
 W.L. Blok, Dr. P.H.J. Frissen, Drs. W.E.M. Schouten. St. Medisch Centrum Jan van Goyen - Amsterdam: Dr. A.  
 van Eeden\*, Dr. D.W.M. Verhagen. Slotervaart Ziekenhuis - Amsterdam: Dr. J.W. Mulder\*, Dr. E.C.M. van Gorp,  
 Dr. A.T.A. Mairuhu Drs. R. Steingrover, Dr. J. Wagenaar. St. Elisabeth Ziekenhuis - Tilburg: Dr. J.R. Juttman\*,  
 Dr. M.E.E. van Kasteren. St. Lucas Andreas Ziekenhuis - Amsterdam: Dr. J. Veenstra\*, Dr. W.L.E. Vasmel (until  
 January, 2008). Dr. K.D. Lettinga. Universitair Medisch Centrum St. Radboud - Nijmegen: Dr. P.P. Koopmans\*,  
 Drs. A.M. Brouwer, Dr. A.S.M. Dofferhoff, Prof. dr. R. de Groot, Drs. H.J.M. ter Hofstede, Dr. M. Keuter, Dr.  
 A.J.A.M. van der Ven. Universitair Medisch Centrum Groningen - Groningen: Dr. H.G. Sprenger\*, Dr. S. van  
 Assen, Dr. C.J. Stek. Universitair Medisch Centrum Groningen - Beatrix Kliniek - Groningen: Dr. R. Doedens, Dr.  
 E.H. Scholvinck. Universitair Medisch Centrum Utrecht - Utrecht: Prof. dr. I.M. Hoepelman\*, Dr. M.M.E.  
 Schneider, Prof. dr. M.J.M. Bonten, Dr. P.M. Ellerbroek, Drs. C.A.J.J. Jaspers, Drs. L.J. Maarschalk-Ellebroek, Dr.  
 J.J. Oosterheert, Dr. E.J.G. Peters, Dr. T. Mudrikova, Drs. M.W.M. Wassenberg, Dr. S. Weijer, Drs. M.H.  
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 Geelen, Dr. T.F.W. Wolfs. VU Medisch Centrum - Amsterdam: Prof. dr. S.A. Danner\*, Dr. M.A. van Agtmael, Drs.  
 W.F.W. Bierman, Drs. F.A.P. Claessen, Drs. M.E. Hillebrand, Drs. E.V. de Jong, Drs. W. Kortmann, Dr. R.M.  
 Perenboom, Drs. E.A. bij de Vaate. Ziekenhuis Rijnstate - Arnhem: Dr. C. Richter\*, Drs. J. van der Berg, Dr. E.H.  
 Gisolf. Ziekenhuis Walcheren - Vlissingen: Dr. A.A. Tanis\*. St. Elisabeth Hospitaal/Stichting Rode Kruis  
 Bloedbank - Willemstad, Curaçao: Dr. A.J. Duits, Dr. K. Winkel.

#### **Virologists**

Academisch Medisch Centrum bij de Universiteit van Amsterdam – Amsterdam: Dr. N.K.T. Back, Dr. M.E.G.  
 Bakker, Dr. H.L. Zaaijer. Prof. dr. B. Berkhout, Dr. S. Jurriaans. CLB Stichting Sanquin Bloedvoorziening -  
 Amsterdam: Dr. Th. Cuijpers. Onze Lieve Vrouwe Gasthuis - Amsterdam: Dr. P.J.G.M. Rietra, Dr. K.J.  
 Roozendaal. Slotervaart Ziekenhuis - Amsterdam: Drs. W. Pauw, Drs. P.H.M. Smits, Dr. A.P. van Zanten. VU  
 Medisch Centrum – Amsterdam: Dr. B.M.E. von Blomberg, Dr. A. Pettersson, Dr. P. Savelkoul. Ziekenhuis  
 Rijnstate – Arnhem: Dr. C.M.A. Swanink. HAGA, ziekenhuis, locatie Leyenburg - Den Haag: Dr. P.F.H. Franck,  
 Dr. A.S. Lampe. Medisch Centrum Haaglanden, locatie Westeinde - Den Haag: Drs. C.L. Jansen.  
 Streeklaboratorium Twente - Enschede: Dr. R. Hendriks. Streeklaboratorium Groningen - Groningen: Dr. C.A.  
 Benne. Streeklaboratorium Volksgezondheid Kennemerland - Haarlem: Dr. J. Schirm, Dr. D. Veenendaal.  
 Laboratorium voor de Volksgezondheid in Friesland - Leeuwarden: Dr. H. Storm, Drs. J. Weel, Drs. J.H. van Zeijl.  
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 Dr. G.J.J. van Doornum, Dr. H.G.M. Niesters, Prof. dr. A.D.M.E. Osterhaus, Dr. M. Schutten. St. Elisabeth  
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 Dr. E. Boel, Dr. R. Schuurman. Catharina Ziekenhuis - Eindhoven: Dr. A.F. Jansz, Drs. M. Wulf.

#### **Pharmacologists**

Medisch Centrum Alkmaar - Alkmaar: Dr. A. Veldkamp. Slotervaart Ziekenhuis - Amsterdam: Prof. dr. J.H.  
 Beijnen, Dr. A.D.R. Huitema. Universitair Medisch Centrum St. Radboud - Nijmegen: Dr. D.M. Burger.  
 Academisch Medisch Centrum bij de Universiteit van Amsterdam – Amsterdam: Drs. H.J.M. van Kan.

## **The The EuroSIDA Study Group**

### **The multi-center Study Group on EuroSIDA (national coordinators in parentheses)**

Argentina: (M Losso), C Elias, 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; O  
 Suetnov, Regional AIDS Centre, Svetlogorsk. Belgium: (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital,

Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; (L Vandekerckhove) University Ziekenhuis Gent, Gent. Bosnia: (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) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Denmark: (J Nielsen) G Kronborg, T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus. Estonia: (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. Finland: (M Ristola), Helsinki University Central Hospital, Helsinki. France: (C Katlama) Hôpital de la Pitié-Salpêtrière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux. Germany: (J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Greece: (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambatakou, Ippokration Genereal Hospital, Athens. Hungary: (D Banhegyi) Szent László Hospital, Budapest. Ireland: (F Mulcahy) St. James's Hospital, Dublin. Israel: (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem. Italy: (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, C Vlasi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d' Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. Latvia: (B Rozentale) P Aldins, Infectology Centre of Latvia, Riga. Lithuania: (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. Luxembourg: (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. Netherlands: (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. Poland: (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarek, M Pynka, Medical University, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; (E Jablonowska) E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. Portugal: (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. Romania: (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucurest. Russia: (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; A Vinogradova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: (M Mokráš) D Staneková, Dérer Hospital, Bratislava. Slovenia: (J Tomazic) University Clinical Centre Ljubljana, Ljubljana. Spain: (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; (S Moreno) Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sarnat, Hospital Sant Pau, Barcelona. Sweden: (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö. Switzerland: (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. Ukraine: (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev; (G Kutsyna) Luhansk AIDS Center, Luhansk; (S Servitskiy), Odessa Region AIDS Center, Odessa; (S Antoniuk) Kiev; (M Krasnov) Kharkov State Medical University, Kharkov. United Kingdom: (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, UCL Medical School, London (University College Campus); A Phillips, MA Johnson, A Mcroft, UCL Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

**Virology group:** B Clotet, R Paredes (Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study.

**Steering Committee:** F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D'Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh  
**Coordinating Centre Staff:** J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska

### **Collaborations in HIV Outcomes Research US (CHORUS)**

Stephen Raffanti, Douglas Dieterch, Amy Justice, Stephen Becker, Anthony Scarsella, Gregory Fusco, Bernard Most, Rukmini Balu, Rashida Rana, Robin Beckerman, Theodore Ising, Jennifer Fusco, Renae Irek, Bernadette Johnson, Ashwin Hirani, Edwin DeJesus, Gerald Pierone, Philip Lackey, Chip Irek, Alison Johnson, John Burdick, Saul Leon, Joseph Arch.

### **Frankfurt HIV Cohort, Germany**

Schlomo Staszewski, Eilke B. Helm, Amina Carlebach, Axel Müller, Annette Haberl, Gabi Nisius, Tessa Lennemann, Christoph Stephan, Markus Bickel, Manfred Mösch, Peter Gute, Leo Locher, Thomas Lutz, Stephan Klauke, Gabi Knecht, Pavel Khaykin (Clinical Group); Hans W. Doerr, Martin Stürmer (Virology Group); Errol Babacan (Scientific Advisor and Data Management); Nils von Hentig (Pharmacology Group).

### **ANRS CO3 Aquitaine Cohort, France**

#### **Epidemiology, Methodology**

M. Bruyand, G. Chêne, F. Dabis (Principal Investigator), S. Lawson-Ayayi, R. Thiébaud.

#### **Infectious diseases, Internal Medicine**

M. Bonarek, F. Bonnal, F. Bonnet, N. Bernard, O. Caubet, L. Caunègre, C. Cazanave, J. Ceccaldi, FA Dauchy, C. De La Taille, S. De Witte, M. Dupon, P. Duffau, H. Dutronc, S. Farbos, C. Greib, D. Lacoste, S. Lafarie, P. Lose, D. Malvy, P. Mercié, P. Morlat, D. Neau, A. Ochoa, JL. Pellegrin, JM. Ragnaud, S. Tchamgoué, JF. Viillard.

#### **Immunology, Virology, Pharmacology, Pharmacovigilance**

Immunology: P. Blanco, JF. Moreau. Virology: H. Fleury, ME. Lafon, B. Masquelier, I. Pellegrin. Pharmacology: D. Breilh. Pharmacovigilance: G. Miremont-Salamé.

#### **Data collection**

MJ. Blaizeau, M. Decoin, S. Delveaux, C. Hannapier, S. Labarrère, V. Lavignolle-Aurillac, B. Uwamaliya-Nziyumvira.

#### **Data management**

S. Geffard, G. Palmer, D. Touchard.

#### **Scientific committee**

M. Dupon, M. Longy-Boursier, P. Morlat, JL. Pellegrin, JM. Ragnaud and F. Dabis.

### **British Columbia Centre for Excellence in HIV (BCCfE-HIV), Canada**

Linda Akagi, Eirikka Brandson, Eric Druyts, Kim Fernandes Nada Gataric, P Richard Harrigan, Marriane Harris, Anna Hayden, Robert Hogg, Viviane Lima, Julio Montaner, David Moore, Evan Wood, Benita Yip, and Wen Zhang.

### **Royal Free Hospital Cohort, London UK**

**Clinical:** S Bhagani, A Carroll, I Cropley, Z Cuthbertson, T Drinkwater, A Dunleavy, T Fernandez, AM Geretti, N Marshall, G Murphy, D Nair, D Ivens, M Johnson, S Kinloch-de Loes, M Lipman, S Madge, T Mahungu, B Prinz, L Swaden, A Rodger, M Tyrer, M Youle.

**Data management:** C Chaloner, J Holloway, J Puradiredja, S Scott, R Tsintas.

**Biostatistics/Epidemiology:** V Cambiano, E Harris, F Lampe, R Lodwick, A Phillips, C Smith.

**Laboratory:** E Amoah, C. Booth, G Clewley, A Garcia Diaz, B Gregory, W Labbett, J Libaste, F Tahami, M Thomas, Y Zhong

## **South Alberta Clinic, Canada**

John Gill, Ron Read, Hartmut Krentz, Brenda Beckthold

## **Köln / Bonn Cohort, Germany**

Gerd Fätkenheuer, Jürgen Rockstroh

## **PISCIS, Catalonia and Balearic islands, Spain**

### **Coordinators**

J. Casabona (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain) y JM. Miró (Hospital Clínic-Idibaps, Universitat de Barcelona)

### **Field coordinator**

Virginia Isern

### **Steering committee**

J. Casabona, A. Esteve, A. Alquézar (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM. Miró (Hospital Clínic-Idibaps, Universitat de Barcelona); D. Podzamczar (Hospital de Bellvitge de Barcelona); J. Murillas (Hospital Son Dureta de Mallorca).

### **Scientific committee**

A. Romero y C. Agustí (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); JM Gatell, F. Agüero (Hospital Clínic-Idibaps, Universitat de Barcelona); C. Tural, B. Clotet (Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona); E. Ferrer (Hospital de Bellvitge de Barcelona); M. Riera (Hospital Son Dureta de Mallorca) F. Segura G. Navarro (Corporació Parc Taulí de Sabadell); L. Force (Hospital de Mataró); J. Vilaró (Hospital de Vic); A. Masabeu (Hospital de Palamós); I García (Hospital General d' Hospitalet); M. Guadarrama (Hospital Alt Penedès de Vilafranca).

### **Data Management and statistical analysis**

A. Esteve, A. Montoliu y N. Ortega (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain), E. Lazzari (Hospital Clínic-Idibaps, Universitat de Barcelona).

### **Technical support**

E. Puchol, (CEEISCAT, CIBER Epidemiología y Salud Pública, CIBERESP, Spain); M. Sanchez (Hospital Clínic-Idibaps, Universitat de Barcelona).

### **Clinicians**

JL Blanco, F. Garcia-Alcaide, E. Martinez, J. Mallolas M. López-Dieguez, JF García-Goez, (Hospital Clínic-Idibaps, Universitat de Barcelona); G. Sirera, J. Romeu, A. Jou. E. Negro, C. Miranda, MC Capitan (Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona); M. Olmo, P. Barragan, M. Saumoy, F. Bolao, C. Cabellos, C. Peña. (Hospital Universitari de Bellvitge, L'Hospitalet, Barcelona), M. Sala, M. Cervantes, M Jose Amengual, M. Navarro y E Penelo (Corporació Sanitària Parc Taulí), P. Barrufet (Hospital de Mataró); M. Guadarrama (Hospital Alt Penedès de Vilafranca)

## **1917 Clinic Cohort, University of Alabama, Birmingham US**

### **Steering Committee**

Michael S. Saag, Michael J. Mugavero, James H. Willig, James L. Raper, Jeroan J. Allison, Mirjam-Colette Kempf, Joseph E. Schumacher, Andrew O. Westfall

### **Faculty Investigators**

Hui-Yi Lin, Maria Pisu, Linda Moneyham, David Vance, Laura Bachmann, Susan L Davies, Eta Berner, Edward Acosta, Jennifer King, Richard A. Kaslow

### **Research Support Team**

Karen Savage, Christa Nevin, Frances B. Walton, Malcolm L. Marler, Sarah Lawrence, Barbara Files-Kennedy, D. Scott Batey

### **Informatics Team**

Manoj A. Patil, Ujalva Patil, Mohit Varshney, Eugene Gibson, Alfredo Guzman, Dustin Rinehart

## **Veterans Aging Cohort Study (VACS), Connecticut, US**

**PI and Co-PI:** AC Justice, DA Fiellin. **Scientific Officer (NIAAA):** K Bryant

Data included represents entire VA national network

#### **Core Faculty**

K Mattocks (Deputy Director), S Braithwaite, C Brandt, R Cook, J Conigliaro, K Crothers, J Chang, S Crystal, N Day, J Erdos, M Freiberg, M Kozal, M Gaziano, M Gerschenson, B Good, A Gordon, J Goulet, K Kraemer, J Lim, S Maisto, P Miller, P O'Connor, R Papas, C Rinaldo, M Roberts, J Samet

#### **Validation sites**

Atlanta (D. Rimland, C Jones-Taylor), Baltimore (KA Oursler, R Titanji), Bronx (S Brown, S Garrison), Houston (M Rodriguez-Barradas, N Masozera), Los Angeles (M Goetz, D Leaf), Manhattan-Brooklyn (M Simberkoff, D Blumenthal, J Leung), Pittsburgh (A Butt, E Hoffman), and Washington DC (C Gibert, R Peck)

#### **Staff**

D Cohen, A Consorte, K Gordon, F Kidwai, F Levin, K McGinnis, M Rambo, J Rogers, M Skanderson, F Whitsett

#### **Funded by**

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### **The Multicenter AIDS Cohort Study (MACS)**

Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, John Hylton, Lisette Johnson, Shenghan Lai, Ned Sacktor, Ola Selnes, James Shepard, Chloe Thio. Chicago: Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services: John P. Phair (Principal Investigator), Joan S. Chmiel (Co-Principal Investigator), Sheila Badri, Bruce Cohen, Craig Conover, Maurice O'Gorman, David Ostrow, Frank Palella, Daina Variakojis, Steven M. Wolinsky. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal Investigator), Barbara R. Visscher (Co-Principal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, Thomas Coates, Rita Effros, John Fahey, Beth Jamieson, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (Co-Principal Investigator), James T. Becker, Robert W. Evans, John Mellors, Sharon Riddler, Anthony Silvestre. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (Principal Investigator), Alvaro Muñoz (Co-Principal Investigator), Stephen R. Cole, Christopher Cox, Gypsyamber D'Souza, Stephen J. Gange, Janet Schollenberger, Eric C. Seaberg, Sol Su. NIH: National Institute of Allergy and Infectious Diseases: Robin E. Huebner; National Cancer Institute: Geraldina Dominguez; National Heart, Lung and Blood Institute: Cheryl McDonald. U01-AI-35042, 5-MO1-RR-00722 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, U01-AI-35041. Website located at <http://www.statepi.jhsph.edu/macs/macs.html>.

### **Amsterdam Cohort Studies**

Maria Prins and Hanneke Schuitemaker for the Amsterdam Cohort Studies on HIV infection and AIDS, a collaboration between the Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht, are part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment. Website: <http://www.amsterdamcohortstudies.org/>

### **CASCADE collaboration**

**Steering Committee:** Julia Del Amo (Chair), Laurence Meyer (Vice Chair), Heiner C. Bucher, Geneviève Chêne, Deenan Pillay, Maria Prins, Magda Rosinska, Caroline Sabin, Giota Touloumi

**Co-ordinating Centre:** Kholoud Porter (Project Leader), Sara Lodi, Sarah Walker, Abdel Babiker, Janet Darbyshire  
**Clinical Advisory Board:** Heiner Bucher, Andrea de Luca, Martin Fisher, Roberto Muga

Collaborators: Australia Sydney AIDS Prospective Study and Sydney Primary HIV Infection cohort (John Kaldor, Tony Kelleher, Tim Ramacciotti, Linda Gelgor, David Cooper, Don Smith); Canada South Alberta clinic (John



Gill); Denmark Copenhagen HIV Seroconverter Cohort (Louise Bruun Jørgensen, Claus Nielsen, Court Pedersen); Estonia Tartu Ülikool (Irja Lutsar); France ANRS CO3 Aquitaine cohort (Geneviève Chêne, Francois Dabis, Rodolphe Thiebaut, Bernard Masquelier), French Hospital Database (Dominique Costagliola, Marguerite Guiguet), Lyon Primary Infection cohort (Philippe Vanhems), SEROCO cohort (Laurence Meyer, Faroudy Boufassa); Germany German cohort (Osamah Hamouda, Claudia Kucherer); Greece Greek Haemophilia cohort (Giota Touloumi, Nikos Pantazis, Angelos Hatzakis, Dimitrios Paraskevis, Anastasia Karafoulidou); Italy Italian Seroconversion Study (Giovanni Rezza, Maria Dorrucchi, Benedetta Longo, Claudia Balotta); Netherlands Amsterdam Cohort Studies among homosexual men and drug users (Maria Prins, Liselotte van Asten, Akke van der Bij, Ronald Geskus, Roel Coutinho); Norway Oslo and Ullevål Hospital cohorts (Mette Sannes, Oddbjorn Brubakk, Anne Eskild, Johan N Bruun); Poland National Institute of Hygiene (Magdalena Rosinska); Portugal Universidade Nova de Lisboa (Ricardo Camacho); Russia Pasteur Institute (Tatyana Smolskaya); Spain Badalona IDU hospital cohort (Roberto Muga, Jordi Tor), Barcelona IDU Cohort (Patricia Garcia de Olalla, Joan Cayla), Madrid cohort (Julia Del Amo, Jorge del Romero), Valencia IDU cohort (Santiago Pérez-Hoyos, Ildefonso Hernandez Aguado); Switzerland Swiss HIV Cohort Study (Heiner C. Bucher, Martin Rickenbach, Patrick Francioli); Ukraine Perinatal Prevention of AIDS Initiative (Ruslan Malyuta); United Kingdom Edinburgh Hospital cohort (Ray Brett), Health Protection Agency (Valerie Delpech, Sam Lattimore, Gary Murphy, John Parry, Noel Gill), Royal Free haemophilia cohort (Caroline Sabin, Christine Lee), UK Register of HIV Seroconverters (Kholoud Porter, Anne Johnson, Andrew Phillips, Abdel Babiker, Janet Darbyshire, Valerie Delpech), University College London (Deenan Pillay), University of Oxford (Harold Jaffe).

## Methods used to adjust for lead times and unseen AIDS and death events

Analyses were based on the 21247 adult HIV-infected patients followed during the pre-cART era. [Web appendix Table 1](#) shows characteristics of these patients according to contributing cohort. The majority of the patients (14286, 67%) were included in the French Hospital Database on HIV. Participants in the Multicenter AIDS Cohort Study and Amsterdam Cohort were restricted to men who have sex with men. The median of the first CD4 count below 550 cells/mm<sup>3</sup> was lower in the Swiss HIV Cohort than in other cohorts, indicating that patients in that study tended to be diagnosed later in the course of their disease.

For each CD4 range corresponding to a deferred initiation group, we fitted a mixture of two generalized gamma survival distributions<sup>1</sup> to simultaneously model the distribution of times from the first CD4 measurement in the upper CD4 range to the upper threshold of the lower CD4 range (i.e., lead-time) and the probability of progression to AIDS or death before reaching the upper threshold of the lower CD4 range. Patients who were censored were redistributed to the two groups (i.e., those who progressed to AIDS or death or who reached the upper threshold of the lower CD4 range) according to the proportion of uncensored patients in each group. We repeated all comparisons using death alone as the endpoint. Patients in the pre-cART dataset were considered to have become eligible for immediate treatment if they progressed to AIDS. AIDS events occurring within two weeks of the upper threshold of the lower CD4 range, and deaths occurring within two weeks of AIDS, were included as endpoints on the basis that they would not have been averted by initiation of cART. The fit of the generalized gamma distributions was checked visually by comparisons with non-parametric distributions.

For each comparison of a lower (deferred initiation) with an upper (immediate initiation) CD4 range imputation, we created 25 completed datasets based on the fitted generalized gamma distributions, in which lead-time and unseen AIDS and death events were added to the data for individuals in the deferred initiation group in the on-cART data. We analyzed each completed dataset using Cox regression to estimate hazard ratios comparing deferred with immediate initiation of cART. Finally, estimated hazard ratios from the 25 completed datasets were combined using a standard formula for the combination of multiple imputed datasets.<sup>2</sup>

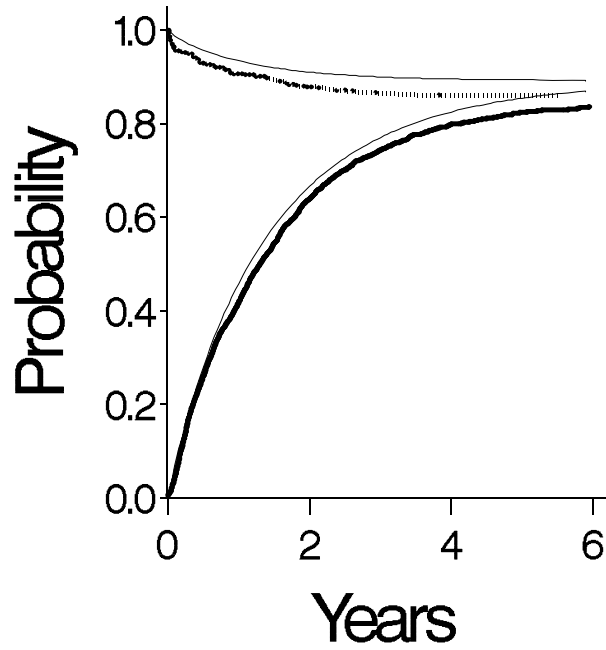
[Web appendix Figure 1](#) shows examples of non-parametric and parametric estimates of the distributions of time to progression to AIDS before crossing the upper threshold of the lower CD4 range and to crossing the upper threshold of the lower CD4 range in the absence of cART, for the ranges 151-250 and 351-450 cells/mm<sup>3</sup>. The rate of progression to AIDS before reaching the upper threshold of the lower CD4 range was greater for the lower CD4 range (AIDS before declining below 150 cells/mm<sup>3</sup>) than for the higher range (AIDS before declining below 350 cells/mm<sup>3</sup>). In the lower CD4 range, the generalized gamma mixture model appeared to somewhat underestimate the rate of progression to AIDS and death before crossing the upper threshold of the lower CD4 range, mainly due to underestimation of the number of events very soon after the first CD4 measurement in the upper range ("fast progressors"). Any bias due to underestimation of the number of fast progressors would likely be conservative because the absence of these rapid events in the deferred arm would raise the resultant survival curve to be closer to the immediate treatment arm. The fit was notably better in higher CD4 ranges. Lack of fit at lower CD4 ranges is also unlikely to be important because benefits of early initiation are clear both in the current paper and based on existing randomized evidence.<sup>3</sup>

## References

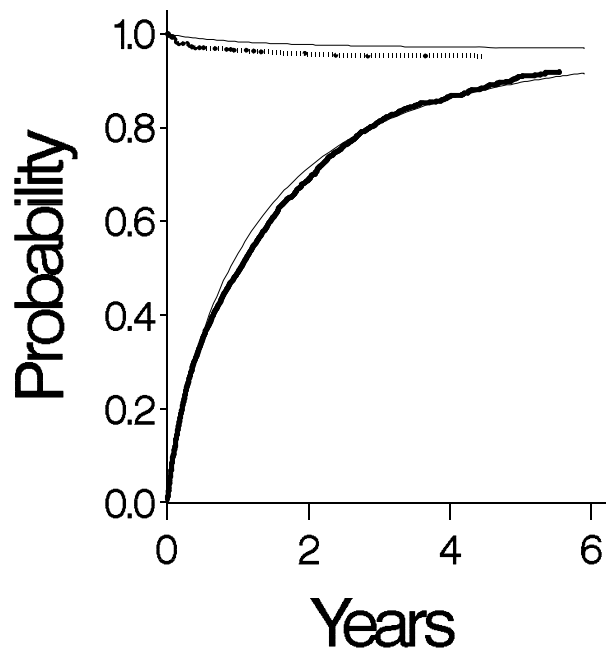
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Web appendix Figure 1: Fitted parametric estimates (thin solid lines) and non-parametric estimates (dotted line and heavy line) of cumulative proportions free of AIDS before reaching the lower CD4 threshold (upper curves) and the cumulative proportion crossing the lower CD4 threshold without AIDS diagnosis (lower curve) for (i) the range 151-250 cells/mm<sup>3</sup> and (ii) the range 351-450 cells/mm<sup>3</sup>.

(i)



(ii)



**Web appendix Table 1: Characteristics of 21,247 patients included in analyses in pre-cART cohorts.**

Cohort	Number (%) of patients	Number (%) male	Presumed mode of transmission			Median (IQR) first CD4 <550 cells/mm <sup>3</sup>	Total years follow up	Number of AIDS events	Number of deaths	Number of patients with AIDS or death
			MSM*	Het*	Other					
Swiss HIV Cohort Study	2059 (10)	1572 (76)	1134 (55)	828 (40)	97 (5)	342 (230-448)	7447	747	544	807
Multicenter AIDS Cohort Study	1324 (6)	1324 (100)	1324 (100)	0	0	387 (284-474)	5863	639	496	669
ANRS CO4 French Hospital Database on HIV	14286 (67)	10522 (74)	7044 (49)	5385 (38)	1857 (13)	347 (261-439)	41620	2873	1825	3231
ANRS CO3 Aquitaine Cohort	1238 (6)	907 (73)	579 (47)	431 (35)	228 (18)	350 (268-438)	4495	344	247	377
South Alberta Cohort	410 (2)	383 (93)	355 (87)	41 (10)	14 (3)	378 (280-465)	1598	133	85	135
Amsterdam Cohort	342 (2)	342 (100)	342 (100)	0	0	400 (310-490)	1575	140	109	150
CASCADE	1588 (7)	1386 (87)	1096 (69)	276 (17)	216 (14)	400 (298-475)	5653	480	324	524
Total	21247	16436 (77)	11874 (56)	6961 (33)	2412 (11)	354 (264-448)	68253	5356	3630	5893

\* MSM: Men who have sex with men; Het: Heterosexual sex

**Web appendix Table 2: Estimated incidence rate ratios comparing the later (1992-95) with earlier (1989-91) years the pre-cART data, after adjusting for age at start of follow up, sex and risk group (MSM/other).**

CD4 range	Incidence rate ratio (95% CI)	
	AIDS or death	Death
351 - 450	1.30 (0.73,2.30)	0.99 (0.39,2.50)
251 - 350	1.01 (0.72,1.41)	0.81 (0.40,1.63)
151 - 250	1.28(1.01,1.64)	0.93 (0.57,1.53)
51 - 150	1.05 (0.88,1.26)	1.45 (0.93,2.25)
0 - 50	1.02 (0.86,1.20)	1.06 (0.70,1.62)

**Web appendix Table 3: Estimated hazard ratios comparing progression rates from the time of starting cART (naïve hazard ratios), after adjusting for age at initiation, sex and risk group (MSM/other).**

Lower CD4 range	Higher CD4 range	Adjusted hazard ratio (95% CI) for AIDS or death	Adjusted mortality hazard ratio (95% CI)
351-450	451-550	1.04 (0.81 to 1.34)	1.04 (0.68 to 1.59)
326-425	426-525	1.07 (0.85 to 1.35)	0.96 (0.65 to 1.43)
301-400	401-500	1.04 (0.84 to 1.29)	0.98 (0.66 to 1.45)
276-375	376-475	1.12 (0.92 to 1.37)	0.99 (0.68 to 1.44)
251-350	351-450	1.16 (0.96 to 1.39)	1.08 (0.76 to 1.53)
226-325	326-425	1.06 (0.89 to 1.25)	1.13 (0.83 to 1.53)
201-300	301-400	1.16 (0.98 to 1.36)	1.09 (0.82 to 1.45)
176-275	276-375	1.24 (1.07 to 1.45)	1.15 (0.80 to 1.67)
151-250	251-350	1.30 (1.13 to 1.50)	1.07 (0.82 to 1.40)
126-225	226-325	1.47 (1.28 to 1.69)	1.17 (0.89 to 1.53)
101-200	201-300	1.54 (1.35 to 1.76)	1.25 (0.97 to 1.59)
76-175	176-275	1.76 (1.55 to 2.00)	1.32 (1.07 to 1.64)
51-150	151-250	1.77 (1.57 to 2.00)	1.47 (1.19 to 1.82)
26-125	126-225	2.07 (1.85 to 2.32)	1.50 (1.23 to 1.83)
0-100	101-200	2.41 (2.17 to 2.68)	1.81 (1.47 to 2.23)

**Web appendix Table 4. Hazard ratios (adjusted for lead times and unseen AIDS and death events), split by follow up period (0-1.99 years and 2-6 years) and comparing deferring cART to a lower CD4 range with starting in a higher CD4 range. CD4 ranges have widths of 100 cells/mm<sup>3</sup>, in increments of 25 cells/mm<sup>3</sup>.**

Higher CD4 range	Lower CD4 range	AIDS or death		Death	
		Hazard ratio 0-1.99 years	Hazard ratio 2-6 years	Hazard ratio 0-1.99 years	Hazard ratio 2-6 years
451-550	351-450	0.97 (0.64,1.48)	0.99 (0.68,1.45)	0.87 (0.39,1.98)	0.97 (0.55,1.69)
426-525	326-425	1.06 (0.68,1.64)	1.17 (0.78,1.77)	1.12 (0.50,2.52)	0.83 (0.49,1.41)
401-500	301-400	1.15 (0.78,1.69)	1.00 (0.72,1.40)	1.60 (0.79,3.25)	0.77 (0.48,1.25)
376-475	276-375	1.30 (0.93,1.84)	1.05 (0.76,1.43)	1.97 (0.99,3.96)	0.69 (0.44,1.11)
351-450	251-350	1.42 (1.04,1.94)	1.11 (0.83,1.50)	1.94 (1.02,3.69)	0.87 (0.58,1.29)
326-425	226-325	1.41 (1.06,1.86)	1.02 (0.77,1.35)	1.73 (1.03,2.88)	0.98 (0.65,1.49)
301-400	201-300	1.55 (1.20,2.00)	1.14 (0.88,1.47)	1.41 (0.70,2.86)	1.03 (0.69,1.53)
276-375	176-275	1.90 (1.44,2.51)	1.29 (0.99,1.67)	1.61 (1.01,2.57)	1.13 (0.79,1.61)
251-350	151-250	1.86 (1.47,2.35)	1.52 (1.19,1.95)	1.44 (0.97,2.13)	1.06 (0.75,1.51)
226-325	126-225	2.38 (1.92,2.94)	1.63 (1.27,2.09)	1.64 (1.11,2.43)	1.08 (0.78,1.49)
201-300	101-200	2.56 (2.07,3.17)	1.77 (1.36,2.30)	1.62 (1.12,2.35)	1.13 (0.84,1.52)
176-275	76-175	2.92 (2.43,3.50)	2.01 (1.59,2.53)	1.78 (1.28,2.46)	1.28 (0.94,1.76)
151-250	51-150	2.90 (2.42,3.47)	2.00 (1.60,2.50)	1.79 (1.26,2.55)	1.42 (1.02,2.00)
126-225	26-125	3.33 (2.83,3.91)	2.26 (1.81,2.82)	1.82 (1.17,2.84)	1.54 (1.04,2.29)
101-200	0-100	3.55 (3.04,4.14)	2.89 (2.33,3.57)	2.19 (1.59,3.03)	1.88 (1.42,2.48)

**Web appendix Table 5. Hazard ratios comparing deferring cART to a lower CD4 range with starting in a higher CD4 range, among patients with presumed transmission via IDU. CD4 ranges have widths of 100 cells/ $\mu$ L, in increments of 25 cells/ $\mu$ L.**

Lower CD4 range	Higher CD4 range	Hazard ratio (95% CI) for AIDS or death		Hazard ratio (95% CI) for death	
		Naïve	Adjusted for lead times and unseen AIDS and death events	Naïve	Adjusted for lead times and unseen deaths
351-450	451-550	1.13 (0.72 to 1.75)	0.90 (0.56 to 1.46)	1.20 (0.64 to 2.26)	0.99 (0.48 to 2.00)
326-425	426-525	1.31 (0.88 to 1.95)	0.94 (0.57 to 1.53)	1.23 (0.70 to 2.16)	1.11 (0.60 to 2.05)
301-400	401-500	1.49 (1.03 to 2.17)	1.28 (0.86 to 1.90)	1.49 (0.88 to 2.54)	1.28 (0.69 to 2.39)
276-375	376-475	1.23 (0.88 to 1.74)	1.18 (0.82 to 1.71)	1.26 (0.77 to 2.04)	1.24 (0.68 to 2.26)
251-350	351-450	1.33 (0.97 to 1.83)	1.35 (0.97 to 1.89)	1.41 (0.90 to 2.20)	1.42 (0.87 to 2.31)
226-325	326-425	1.28 (0.96 to 1.71)	1.22 (0.86 to 1.73)	1.54 (1.03 to 2.31)	1.35 (0.87 to 2.08)
201-300	301-400	1.31 (1.00 to 1.72)	1.20 (0.88 to 1.64)	1.50 (1.04 to 2.19)	1.22 (0.81 to 1.85)
176-275	276-375	1.56 (1.20 to 2.02)	1.36 (1.01 to 1.84)	1.63 (1.13 to 2.34)	1.29 (0.87 to 1.91)
151-250	251-350	1.39 (1.08 to 1.78)	1.21 (0.93 to 1.59)	1.38 (0.98 to 1.94)	1.17 (0.80 to 1.72)
126-225	226-325	1.36 (1.07 to 1.73)	1.34 (1.05 to 1.71)	1.20 (0.86 to 1.67)	0.91 (0.54 to 1.53)
101-200	201-300	1.25 (0.99 to 1.57)	1.31 (1.00 to 1.72)	1.10 (0.80 to 1.52)	1.05 (0.73 to 1.52)
76-175	176-275	1.14 (0.91 to 1.43)	1.25 (0.99 to 1.58)	1.11 (0.81 to 1.52)	1.07 (0.78 to 1.49)
51-150	151-250	1.21 (0.97 to 1.52)	1.28 (0.93 to 1.74)	1.13 (0.83 to 1.55)	1.16 (0.84 to 1.60)
26-125	126-225	1.29 (1.04 to 1.61)	1.62 (1.30 to 2.02)	1.21 (0.89 to 1.66)	1.29 (0.91 to 1.83)
0-100	101-200	1.49 (1.20 to 1.84)	2.00 (1.61 to 2.49)	1.32 (0.98 to 1.79)	1.54 (1.13 to 2.11)

**Web appendix Table 6. Hazard ratios for AIDS or death, (naïve, and adjusted for lead times and unseen AIDS and death events), comparing deferring cART to a lower CD4 range with starting in a higher CD4 range, restricted to four cohorts that provided both pre-cART and on-cART data.**

		Hazard ratio (95% CI) for AIDS or death	
Lower CD4 range	Higher CD4 range	Naïve	Adjusted for lead times and unseen AIDS and death events
351-450	451-550	1.00 (0.66,1.52)	0.93 (0.59,1.47)
326-425	426-525	1.09 (0.74,1.59)	1.10 (0.72,1.66)
301-400	401-500	1.11 (0.79,1.56)	1.18 (0.81,1.72)
276-375	376-475	1.22 (0.88,1.69)	1.33 (0.94,1.88)
251-350	351-450	1.33 (0.98,1.79)	1.46 (1.02,2.08)
226-325	326-425	1.26 (0.95,1.66)	1.42 (1.07,1.89)
201-300	301-400	1.11 (0.85,1.43)	1.37 (1.06,1.78)
176-275	276-375	1.15 (0.90,1.46)	1.64 (1.27,2.13)
151-250	251-350	1.20 (0.96,1.51)	1.76 (1.37,2.27)
126-225	226-325	1.39 (1.12,1.73)	2.07 (1.64,2.63)
101-200	201-300	1.69 (1.36,2.10)	2.63 (2.12,3.25)
76-175	176-275	2.02 (1.64,2.48)	3.09 (2.49,3.85)
51-150	151-250	1.85 (1.51,2.27)	3.02 (2.48,3.68)
26-125	126-225	2.04 (1.68,2.46)	3.28 (2.73,3.94)
0-100	101-200	2.17 (1.81,2.60)	3.76 (3.15,4.49)

**Web appendix Table 7. Hazard ratios (adjusted for lead times and unseen events) comparing deferring cART to a lower CD4 range with starting in a higher CD4 range, with deferral assumed to be to the first CD4 count in the lower range or to the midpoint of the range if no observation in the range was recorded. CD4 ranges have widths of 100 cells/ $\mu$ L, in increments of 25 cells/ $\mu$ L.**

		Analyses of progression to AIDS or death				Analyses of progression to death			
Lower CD4 range	Higher CD4 range	Median lead time (years)	Mean drop in CD4 count (cells per $\mu$ L)	Percent of patients progressing before reaching lower range (95% CI)	HR (95% CI)	Median lead time (years)	Mean drop in CD4 count (cells per $\mu$ L)	Percent of patients progressing before reaching lower range (95% CI)	HR (95% CI)
351-450	451-550	0.76	94	8.2 (5.5-10.8)	1.17 (0.65-2.09)	0.83	94	0.9 (0.5-1.4)	1.14 (0.72-1.82)
326-425	426-525	0.83	94	9.7 (6.5-13.0)	1.21 (0.60-2.41)	0.90	94	1.4 (0.9-1.9)	1.18 (0.72-1.94)
301-400	401-500	0.86	94	11.7 (8.5-14.9)	1.36 (0.50-3.72)	0.95	93	1.5 (0.9-2.0)	1.28 (0.80-2.06)
276-375	376-475	0.87	93	12.6 (10.0-15.3)	1.62 (1.15-2.29)	0.97	92	1.4 (0.9-2.0)	1.27 (0.86-1.88)
251-350	351-450	0.89	94	12.7 (10.2-15.2)	1.59 (1.19-2.13)	0.97	94	1.4 (0.9-1.9)	1.32 (0.83-2.11)
226-325	326-425	0.91	92	11.3 (8.8-13.8)	1.51 (1.12-2.05)	0.98	92	1.2 (0.6-1.7)	1.36 (0.94-1.98)
201-300	301-400	0.91	93	12.4 (10.1-14.7)	1.82 (1.44-2.30)	0.99	92	1.2 (0.7-1.8)	1.34 (0.98-1.85)
176-275	276-375	0.93	90	13.5 (11.2-15.8)	2.03 (1.61-2.56)	1.01	89	1.3 (0.9-1.8)	1.39 (1.06-1.82)
151-250	251-350	0.95	90	13.3 (11.0-15.6)	2.10 (1.65-2.68)	1.02	90	1.4 (0.9-1.8)	1.25 (0.95-1.63)